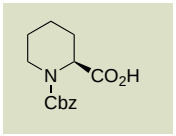
Aldrichimica Acta
Volume 32, Number 1, 1999

Chiral Heterosubstituted 1,3-Butadienes: Synthesis and [4+2] Cycloaddition Reactions

Serine Derivatives in Organic Synthesis

New Products

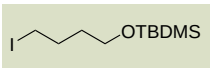
Peptides and pharmacologically active peptide mimetics have been prepared from this protected amino acid.[1,2]



(1) Benedetti, E. et al. *Protein Pept. Lett.* **1996**, *3*, 283. (2) Hauske, J. R. et al. *J. Med. Chem.* **1992**, *35*, 4284.

49,958-7 (*S*)-(–)-1-(Carbobenzyloxy)-2-piperidine-carboxylic acid, 97%

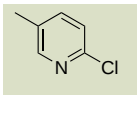
This versatile building block has been used to alkylate acetylenes, ester enolates, and allenes.[1-3]

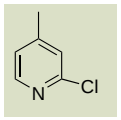


(1) Hermitage, S. A. et al. *Tetrahedron Lett.* **1998**, *39*, 3567. (2) Schostarez, H. J.; Schwartz, T. M. *J. Org. Chem.* **1996**, *61*, 8701. (3) Llerena, D. et al. *Tetrahedron* **1998**, *54*, 9373.

51,202-8 *tert*-Butyl(4-iodobutoxy)dimethylsilane, 95%

2-Substituted picolines have been prepared from these compounds. Examples include (2-pyridyl)indoles and endothelin receptors.[1,2]



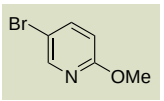


(1) Amat, M. et al. *J. Org. Chem.* **1997**, *62*, 3158. (2) Kourounakis, A. et al. *Biorg. Med. Chem. Lett.* **1997**, *7*, 2223.

49,532-8 2-Chloro-5-methylpyridine, 98%

11,632-7 2-Chloro-4-methylpyridine, 98%

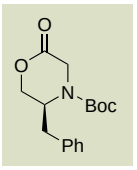
5-Substituted-2-hydroxypyridines can be prepared from this compound through lithiation in the 5-position followed by acid cleavage of the methyl ether.[1-3]



(1) Windscheif, P-M; Voegtle, F. *Synthesis* **1994**, 87. (2) Comins, D. L.; Killpack, M.O. *J. Org. Chem.* **1990**, *55*, 69. (3) Butora, G. et al. *J. Am. Chem. Soc.* **1997**, *119*, 7694.

51,029-7 5-Bromo-2-methoxypyridine, 95%

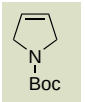
Chiral starting material for the preparation of enantiomerically pure α-amino acids.[1,2]



(1) Baker, W.R. et al. *Tetrahedron Lett.* **1992**, *33*, 1573. (2) Baker, W.R. et al. *ibid.* **1992**, *33*, 1577.

47,992-6 *tert*-Butyl (*S*)-(–)-5-benzyl-2-oxo-4-morpholinecarboxylate, 99%

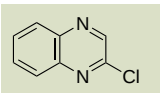
Important precursor for 3-substituted or 3,4-disubstituted pyrrolines.[1,2]



(1) Francke, W. et al. *Liebigs Ann. Chem.* **1995**, 965. (2) Okada, T. et al. *Chem. Pharm. Bull.* **1993**, *41*, 132.

47,751-6 *tert*-Butyl 2,5-dihydro-1*H*-pyrrole-1-carboxylate, 97%

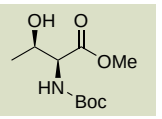
The chlorine in this compound is easily displaced by alcohols, amines, or amides.



Castle, R.N.; Masayuki, O. *J. Org. Chem.* **1961**, *26*, 954.

13,630-1 2-Chloroquinoxaline, 98%

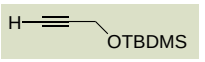
Isosteres of β-D-galactosyl-L-asparagine, 4-amino-4,6-dideoxygulopyranoside, and *N-allo*-threonine have all been prepared from this amino acid derivative.[1-3]



(1) Dondoni, A. et al. *Tetrahedron Lett.* **1998**, *39*, 6601. (2) Koskinen, A.M.P.; Otsomaa, L.A. *Tetrahedron* **1997**, *53*, 6473. (3) Williams, L. et al. *Heterocycl. Commun.* **1996**, *2*, 55.

46,565-8 *N*-(*tert*-Butoxycarbonyl)-L-threonine methyl ester, 95%

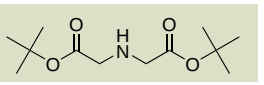
This silyl ether has been used to prepare 1-aryl-2-propyn-1-ols via palladium-catalyzed coupling of the acetylene with aryl iodides, bromides, or triflates.[1,2]



(1) Cliff, M.D.; Pyne, S.G. *Tetrahedron* **1996**, *52*, 13703. (2) Takahashi, S. et al. *Synthesis* **1980**, 627.

49,549-2 *tert*-Butyldimethyl(2-propynyloxy)silane, 97%

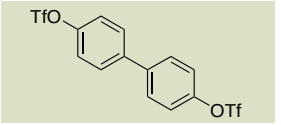
This iminodiacetate is an important precursor to europium(III) and terbium(III) chelating agents with luminescence properties.[1-3]



(1) Mukkala, V. et al. *Helv. Chim. Acta* **1992**, *75*, 1621. (2) Takalo, H. et al. *ibid.* **1996**, *79*, 789. (3) Remuinan, M.J. et al. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1099.

51,132-3 Di-*tert*-butyl iminodiacetate, 98%

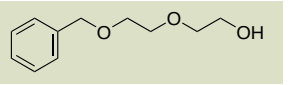
4,4'-Disubstituted biphenyls can be prepared from this ditriflate using palladium-catalyzed coupling methods.



Dolle, R.E. *J. Chem. Soc., Chem. Commun.* **1987**, 904.

51,131-5 4,4′-Biphenol bis(trifluoromethanesulfonate), 98%

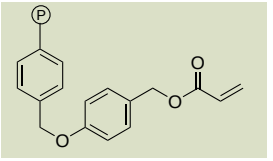
Monobenzylated di(ethylene)glycol has been used to prepare crown ethers bearing polymerizable side chains.[1-3]



(1) Collie, L. et al. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1747. (2) Peeters, E. et al. *Acta Polym.* **1996**, *47*, 485. (3) Houghton, R.P.; Southby, D.T. *Synth. Commun.* **1989**, *19*, 3199.

49,963-3 Di(ethylene glycol) benzyl ether, 97%

Solid-phase synthesis of β-peptoids using the Wang acrylate resin has been accomplished through Michael addition of amines. The peptoids are formed by further reaction of the resulting β-amine with acryloyl chloride followed by Michael addition of another amine. The peptoid is cleaved from the resin with trifluoroacetic acid.



Hamper, B.C. et al. *J. Org. Chem.* **1998**, *63*, 708.

51,017-3 Wang acrylate resin

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About Our Cover

A Farm in the Sunlight (oil on canvas, 32¼ in. x 26⅛ in.), painted by the Dutch artist Meindert Hobbema in 1668, is regarded as one of this artist's finest paintings. The focus of the picture is the farm buildings near the center of the composition, which are highlighted in the bright patch of sun in the middle ground. Typically, the artist draws the viewer's attention back into the space of the painting by means of pools of light which accent distantly seen objects and against which the trees closer to the foreground are silhouetted.

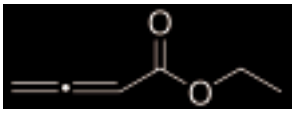
Hobbema lived and worked in Amsterdam, but his paintings almost all represent rural scenes which include farm buildings characteristic of the eastern provinces of the Netherlands, with their high-peaked roofs and half-timbered construction. Few specific sites have been identified in Hobbema's paintings, and in fact they are almost never direct observations of actual places, but usually are pure inventions of his imagination, made up of generic elements commonly found in his works. Despite this, they seem real to us and we are convinced of their fidelity to nature by the believable flow of the soft landscape, the attention to both architectural and natural details, and the careful and wonderful observation of light.

This painting is in the Andrew W. Mellon Collection at the National Gallery of Art.

"Please Bother Us."

by Jai Nagarkatti

Jai Nagarkatti, President



Dr. C. Edgar Cook (Research Triangle Institute) kindly suggested that we make ethyl 2,3-butadienoate. This acceptor-substituted allene is useful for the synthesis of β-methyleneamino acids, which constitute a class of enzyme inhibitors.[1] 1,3-Dipolar cycloadditions,[2] [3+2] cycloadditions,[3,4] and palladium-catalyzed reactions[5] have been performed with this building block.

(1) Paik, Y.H.; Dowd, P. *J. Org. Chem.* **1986**, *51*, 2910. (2) Zhao, B.-X.; Eguchi, S. *Tetrahedron* **1997**, *53*, 9575. (3) Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 3836. (4) Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906. (5) Okuro, K.; Alper, H. *J. Org. Chem.* **1997**, *62*, 1566.

49,499-2 Ethyl 2,3-butadienoate, 95%

Naturally, we made this useful allene. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on the preceding page.

Lab Notes

IR Studies of Liquids Using Accessories for Solid Samples

We have found a convenient and inexpensive way of recording IR/FTIR spectra of liquids and mulls using IR sampling accessories for solids. For liquids, one normally uses either demountable or fixed cells in which the sample is pressed as a film between two factory-built rock salt plates, together with spacers (optional), and the entire contraption is placed in the cell holder. However, the windows are prone to fogging due to their hygroscopic nature (KBr, NaCl, and CsI), or to getting scratched due to their soft nature (KRS-5). The windows can be expensive and require frequent polishing, further decreasing their life spans.

We have overcome these problems by preparing two pellets of spectroscopic grade KBr using a hydraulic press, as is usual for solid samples. The liquid/mull is then spread as a film between the two pellets and the entire arrangement mounted in the solid sample holder. After recording the spectrum, the lab-made windows can be cleaned and examined. If any damage is detected, the pellets are discarded and another set is conveniently prepared for a fresh experiment.

The technique is not useful for quantitative studies but is simple and elegant for qualitative IR studies of liquids and mulls.

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Preventing the Clogging of Solvent Inlet Filters in Reversed-Phase HPLC

In a reversed-phase HPLC system, it is recommended that the solvent inlet filter that carries the mobile phase to the pump be cleaned by back flushing. However, our hands-on experience has shown that this is not always possible with inlet filters which are used in HPLC-grade water. In this case, the blockage or clogging that usually causes high pressure occurs mainly due to fungi formed on the porous filter element.

We wish to report a safe and efficient procedure for the elimination of deposition of fungi in the porous filter. After the completion of everyday work, transfer the inlet filter from the water to a spare reservoir containing 100% methanol, purge the system, and leave in methanol until reuse. To use the system again, transfer the inlet filter to a small beaker containing deionized HPLC-grade water, purge the line, and then transfer the inlet filter to the water reservoir.

S. Massil, Ph.D., **and L. Fuss**
Analytical Lab., R&D Division
Makhteshim Chemical Works, Ltd.
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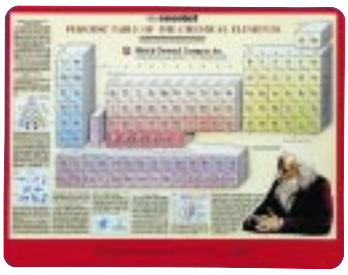

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Chiral Heterosubstituted 1,3-Butadienes: Synthesis and [4+2] Cycloaddition Reactions

José Barluenga, Angel Suárez-Sobrino, and Luis A. López*
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Outline

1. Introduction

Since its discovery in 1928,[1] the Diels–Alder reaction has evolved into a dominant method in organic synthesis. It enables, in a one-step inter- or intramolecular reaction, the rapid preparation of cyclic compounds having a six-membered ring. During the course of the [4+2] cycloaddition, up to four new stereocenters can be introduced directly and their configurations controlled to a large extent. This stereocontrol is a topic of major interest in modern synthetic chemistry. In order to perform the enantioselective version of this process a source of chirality is required. Basically, there are three possibilities: the use of (i) a chiral catalyst, (ii) a chirally modified dienophile, or (iii) a chirally modified diene. Although the use of chiral Lewis acids as catalysts has recently been demonstrated to be an attractive strategy to achieve asymmetric induction,[2] the majority of the investigations in this area have been concerned with the stoichiometric approach using chiral dienophiles (mostly derivatives of acrylic acid esters).[3] In contrast, studies dealing with chiral dienes are much less common. The slow development of this specific topic may be ascribed to the difficulty of preparing these dienes. Only recently have a number of syntheses of chiral dienes been reported and their usefulness in asymmetric synthesis demonstrated.

The present review deals with the synthesis and applications of chiral (nonracemic) heterosubstituted 1,3-butadienes in enantioselective Diels–Alder reactions. There are two major advantages to using the chiral heterosubstituted dienes over those having a carbon–carbon linkage between the diene and the auxiliary:[4] (i) the easier removal of the chiral auxiliary by carbon–heteroatom bond cleavage, and (ii) the greater reactivity of the heterosubstituted derivatives due to charge donation of the heteroatom through its lone electron pair.

The dienes discussed in this review have been classified according to the position of the heterosubstituent relative to the 1,3-diene system. For each class, a further division based on the nature of the heteroatom bonded to the diene is also made. The chemistry of chiral 2-amino-1,3-butadienes[5] and chiral sulfinyldienes[6] has been reviewed recently, and, therefore, only their general features and the most recent contributions to these two topics will be outlined.

2. Synthesis and [4+2] Cycloaddition Reactions of Chiral 1-Heterosubstituted-1,3-butadienes

2.1. Synthesis of Chiral 1-Acyloxy- and 1-Alkoxy-1,3-butadienes

The simplicity of their preparation as well as the accessibility of the chiral appendage (i.e., sugars, chiral alcohols, or chiral acid derivatives) make chiral 1-alkoxydienes and 1-acyloxydienes the most abundant type of chiral heterosubstituted dienes that have appeared in the literature (**Figure 1**).

In 1980, Trost et al. reported the synthesis of (*S*)-(*E*)-1-(*O*-methylmandeloyloxy)butadiene (**4**) (**eq 1**).[7] Although some approaches to chiral dienes had been described earlier,[8]

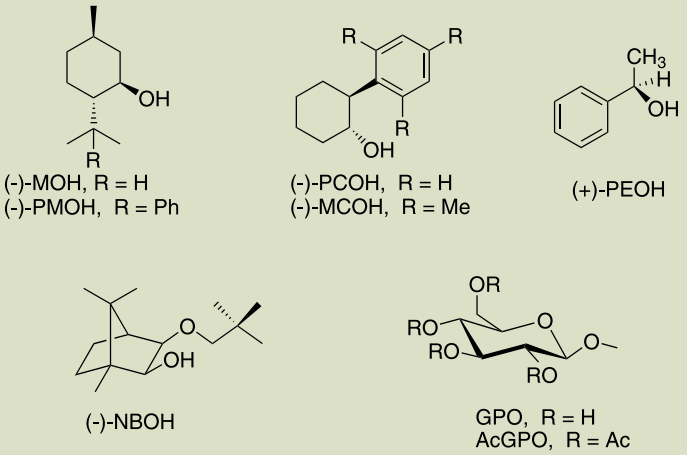
the 'Trost diene' was recognized as the first synthetically useful chiral 1,3-butadiene in terms of its high levels of diastereoselectivity towards various dienophiles. Its original synthesis involved a seven-step route from the cycloadduct of cyclopentadiene and maleic anhydride.[7] Its preparation was simplified very recently by the same author by employing a two-step synthesis from crotonaldehyde (**1**); the lithium enolate of crotonaldehyde is then generated from silyl enol ether **2** and quenched with (*S*)-*O*-methylmandeloyl chloride (**3**) (**eq 1**).[9]

Previous work directed toward the synthesis of a variety of oligosaccharides by the cycloaddition of dienyl ethers of protected sugars with activated carbonyl compounds was reported in a number of papers by David's group.[8] Some of the required dienes in these studies were prepared by the Wittig reaction of β-alkoxy-α,β-unsaturated carbonyl compounds **5** (**eq 2**).[8b] Later, the same approach was used by other authors for the synthesis of a range of chiral 1-alkoxy-1,3-dienes. In this context, the syntheses of chiral 1-alkoxy-1,3-butadienes **6**, derived from chiral alcohols, by Breitmaier and coworkers,[10] the C4-substituted diene **7** by Stoodley's group,[11] and the water-soluble diene **8** by Lubineau et al.[12] may be cited (**eq 2**).

Many efforts in this field have been centered on the synthesis of enantiopure 1-alkoxy-3-silyloxy-1,3-butadienes (chiral Danishefsky-type dienes). The achiral Danishefsky diene represents one of the most attractive 4π-edducts in [4+2] cycloadditions because of its great reactivity with different dienophiles, especially heterodienophiles.[13] In 1983, Danishefsky et al. reported the synthesis of chiral 1-alkoxy-3-trimethylsilyloxy-1,3-butadienes **11**. The key steps in the preparation of these systems are the acid- or base-catalyzed exchange reactions of β-methoxyenones **9** with the corresponding chiral alcohols, followed by enol silylation of the resulting chiral enones **10** (**eq 3**).[14]

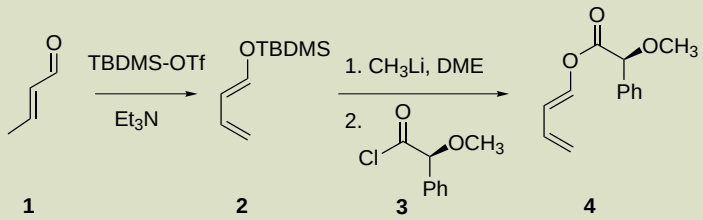
A related route for the synthesis of 1-glucopyrano-3-silyloxy-1,3-butadienes was described by Stoodley. It involved treating 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide with the sodium salt of substituted (*E*)-4-hydroxybut-3-en-2-ones followed by silylation with various silyl chlorides and zinc chloride.[15]

Pericàs's group has recently reported a different strategy that consists of coupling the C1=C2 to the C3=C4 diene fragment.[16] Chiral alkoxyacetylenes **12** undergo a completely regio- and stereoselective hydrozirconation leading to **13**, which are

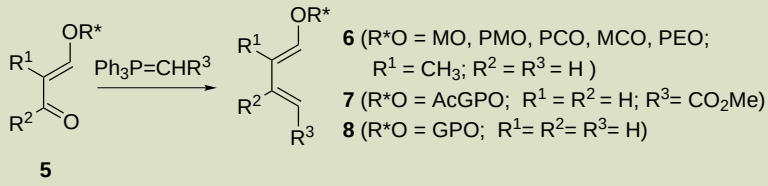


MOH = menthol
PMOH = 8-phenylmenthol
PCOH = *trans*-2-phenylcyclohexanol
MCOH = *trans*-2-mesitylcyclohexanol
PEOH =1-phenylethanol
NBOH = 3-*exo*-neopentyloxyisoborneol
GPO = β-D-glucopyranosyloxy
AcGPO = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy

Figure 1



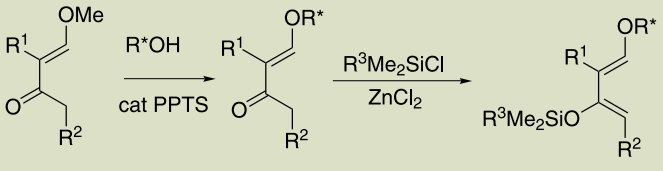
1 **2** **3** **4** **eq 1**



5

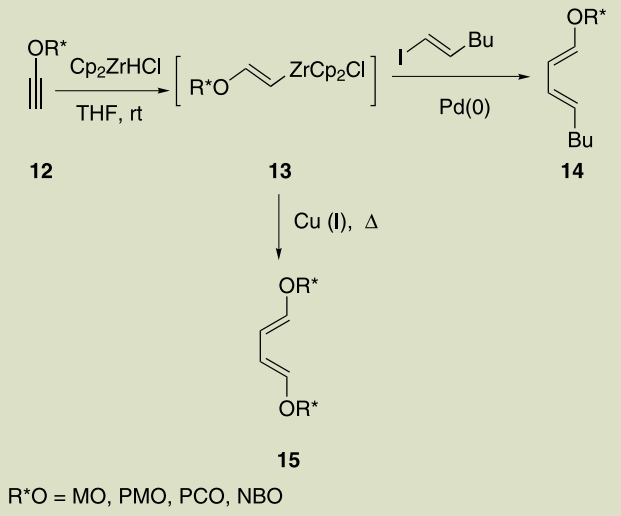
6 (R*O = MO, PMO, PCO, MCO, PEO; $R^1 = CH_3$; $R^2 = R^3 = H$)
7 (R*O = AcGPO; $R^1 = R^2 = H$; $R^3 = CO_2Me$)
8 (R*O = GPO; $R^1 = R^2 = R^3 = H$)

eq 2

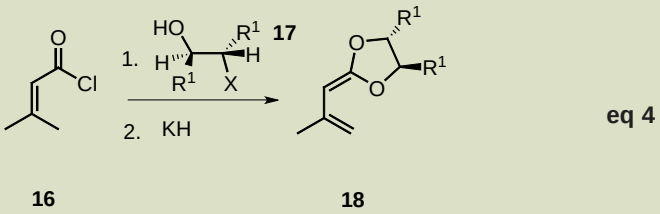


9 **10** **11** **eq 3**

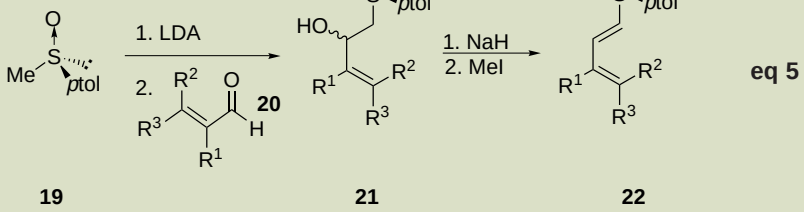
R*OH = (+)- and (–)-MOH; (–)-PMOH; (+)- and (–)-PEOH
PPTS = Pyridinium *p*-toluenesulfonate



Scheme 1



eq 4



eq 5

converted into dienes **14** by Pd(0)-catalyzed coupling with (*E*)-1-iodo-1-hexene (**Scheme 1**).[16b] Thermal dimerization of **13** in the presence of Cu(I) gives rise to chiral 1,4-dialkoxydienes **15**.[16a]

Maddaluno and co-workers have recently described the stereoselective synthesis of chiral (1*Z*,3*E*)-1,4-dialkoxy-1,3-dienes by a base-induced conjugated elimination reaction on γ-alkoxy-α,β-unsaturated acetals.[17]

Acid derivatives are suitable precursors of chiral vinylketene acetals. Thus, Konopelski's group has reported the synthesis of enantiopure dienes **18** in good yields by esterification of 3,3-dimethylacryloyl chloride (**16**) with chiral 2-chloroethanol derivatives **17**, followed by base treatment of the resulting ester derivative (**eq 4**).[18]

2.2. Synthesis of Chiral 1-Sulfinyl-1,3-butadienes

Three different approaches have been used for the synthesis of chiral 1-sulfinyl-1,3-butadienes: (i) C1=C2 bond formation by an aldol-type condensation of an enantiomerically pure sulfinyl carbanion with a carbonyl compound, (ii) C1=C2 or C3=C4 bond formation via a Wittig-type reaction, and (iii) C2–C3 bond formation by a Pd(0)-mediated coupling methodology.

The first approach was developed by Solladié's group in France and García Ruano's group in Spain.[19] For instance, they synthesized chiral 1-sulfinyldienes **22** with excellent *E* selectivity by addition of (R_s)-methyl *p*-tolyl sulfoxide (**19**)[20] to α,β-unsaturated aldehydes **20** to yield **21**, which were then dehydrated with NaH/MeI (**eq 5**).[19a,c,d]

Several syntheses of chiral 1-sulfinyl-1,3-dienes based on the Horner–Wittig or Horner–Wadsworth–Emmons reactions have been described. Although most of them employ chiral sulfinyl diaryl phosphine oxides or sulfinyl phosphonates to form the C1=C2 bond, the reactions proceed in general with only modest *E/Z* stereoselectivity.[21,22] Based on the C3=C4 bond formation by the Horner–Wadsworth–Emmons reaction, García Ruano and co-workers have recently reported an efficient *E,E*-selective synthesis of 4-substituted 1-*p*-tolylsulfinyl-1,3-butadienes.[23]

Using the Pd(0)-catalyzed coupling methodology, Paley and collaborators prepared three classes of stereoisomeric chiral 1-sulfinyldienes (**Scheme 2**).[24] (R_s)-(1*E*)- and (R_s)-(1*Z*)-sulfinyldienes **25** and **27** were synthesized by Stille coupling[25] of vinylstannanes **23** with chiral (R_s)-(*E*)- or (R_s)-(*Z*)-halovinyl sulfoxides **24** and **26**. On the other hand, the synthesis of (R_s)-(1*E*,3*Z*)-1-sulfinyldienes **30** was achieved via the Sonogashira–Schreiber methodology[26] by coupling an alkyne **28** with the enantiopure (R_s)-*trans*-2-bromovinyl sulfoxide **29** and further catalytic hydrogenation.

2.3. Synthesis of Chiral 1-Amido- and 1-Amino-1,3-butadienes

Examples of 1,3-dienes bearing an amido or amino group at C-1 are very few in number. Based on a previously reported synthesis of *N*-dienyllactams,[27] Smith and co-workers obtained ethyl *N*-dienylpyroglutamate (**32**) by heating ethyl (*S*)-pyroglutamate (**31**) with 2-butenal derivatives in the presence of *p*-TsOH (**eq 6**).[28] Recently, Stevenson's team used this methodology to attach other chiral auxiliaries such as (*S*)-(+)-3-methyl-2,3-dihydroisoindol-1-one and (*R*)-(–)-4-phenyloxazolidinone.[29]

A unique, chiral 1-aminodiene was very recently described by Kozmin and Rawal. The reaction of the C_2-symmetric (+)-*trans*-diphenylpyrrolidine (**33**) with methoxybutenone gave rise to aminoenone **34**, which was readily converted into **35** by silylation of the potassium enolate (**eq 7**).[30]

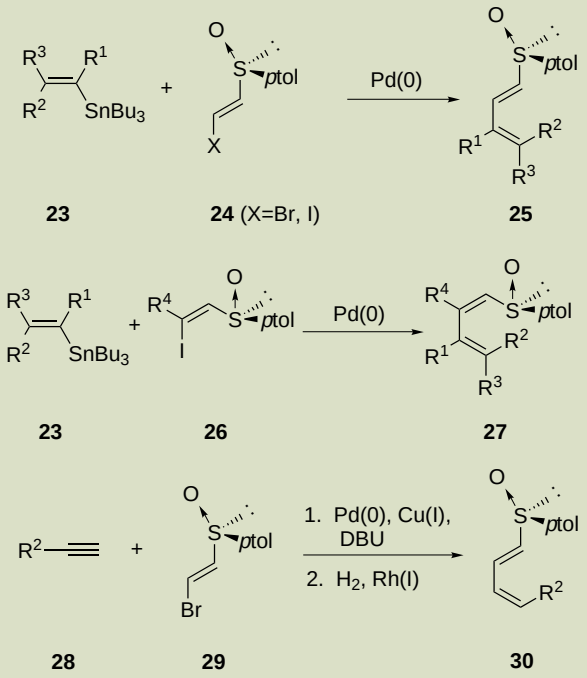
2.4. Diastereoselective [4+2] Cycloaddition Reactions of 1-Heterosubstituted-1,3-butadienes

The first study on facial selectivity in [4+2] cycloaddition reactions using chiral dienes was made by Trost et al. For instance, they found that (*S*)-(*E*)-1-(*O*-methylmandeloyloxy)butadiene (**4**) reacts with juglone (**36**)—and with acrolein as well—under Lewis acid catalysis to furnish cycloadduct **37** with complete endo and very high facial selectivities (**eq 8**).[7]

In order to explain these results, Trost proposed a π-stacking model (**Figure 2, conformation I**). Thus, the preferred conformation of **4** would have the two unsaturated moieties in a face-to-face arrangement in which the steric interactions between the diene CH groups and the methoxy group are minimized.

However, further studies have demonstrated that the π-stacking hypothesis[31] does not account well for this reaction. Thus, Masamune,[32] and later Thornton,[33] observed that replacing the phenyl group in **4** by the cyclohexyl group does not greatly reduce the facial selectivity. Further conformational studies and analysis of the crystal structures of the Diels–Alder adducts prompted Thornton to propose a perpendicular model (**Figure 2, conformation II**). In this model, the diene adopts a conformation in which the dienyl and carbonyloxy groups are in a coplanar arrangement, while the phenyl group is in a nearly perpendicular plane blocking the bottom face of the diene toward approach by the dienophile.[33] This model was later supported by ab initio calculations performed by Houk[34] and by Giessner-Prettre.[35]

Thornton's group also found that diene **4** reacted with acrolein or benzoquinone in the presence of Lewis acids at low temperatures with high facial selectivities (78–96% de). However, these results were improved by appropriate modification of the stereogenic center of **4**.[36] Thus, uncatalyzed [4+2] cycloaddition reactions of modified diene **38** (**Figure 3**) showed an enhancement and reversal of the π-facial selectivity, even at room temperature. Moreover, this selectivity was highly dependent on solvent polarity (for instance, 19:1 versus 3.3:1 for the cycloaddition of **38** with *N*-ethylmaleimide in toluene and DMF, respectively). To explain these results, the authors proposed a diene–dienophile hydrogen–bonding control model in which diene **38** adopts preferentially the more stable conformation II (**Figure 3**).

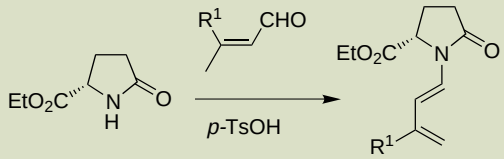


23 **24** (X=Br, I) **25**

23 **26** **27**

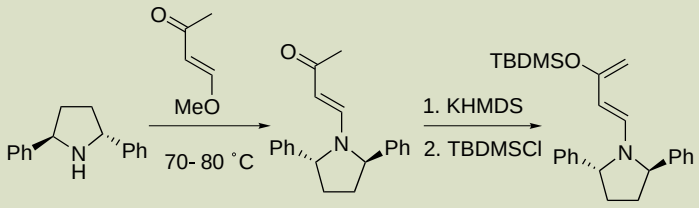
28 **29** **30**

Scheme 2



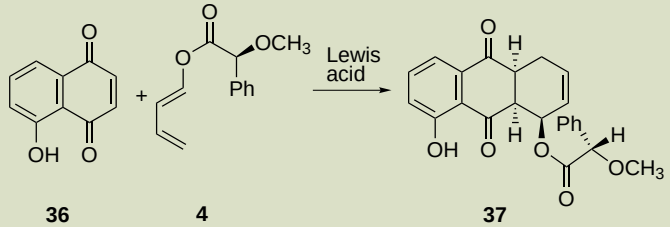
31 **32**

eq 6



33 **34** **35**

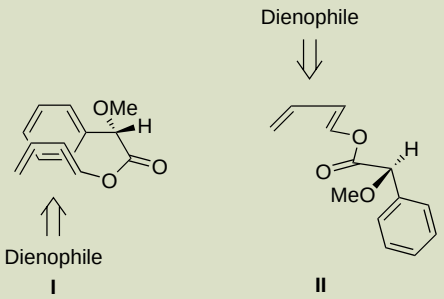
eq 7



36 **4** **37**

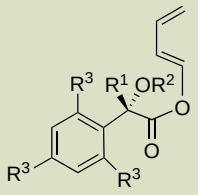
de = 97%

eq 8

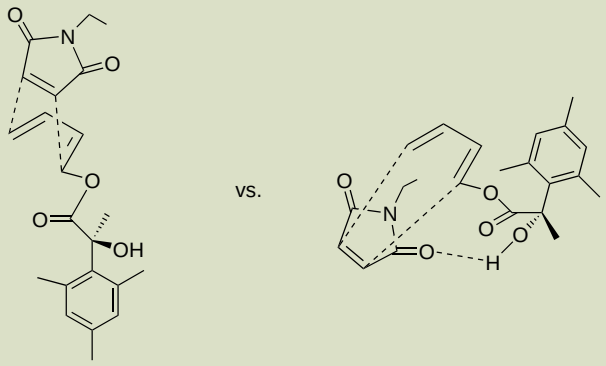


I II

Figure 2

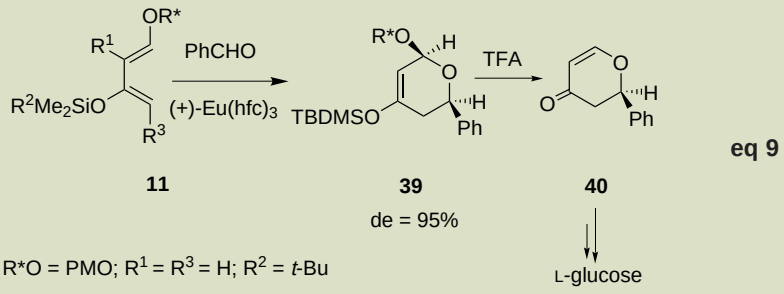


4 R^1 = H, R^2 = Me, R^3 = H
38 R^1 = Me, R^2 = H, R^3 = Me



I II

Figure 3



11 **39** **40**

de = 95%

R*O = PMO; R^1 = R^3 = H; R^2 = *t*-Bu

eq 9

Chiral 1-alkoxydienes **6** (see **eq 2**), derived from chiral alcohols, were found to cycloadd to electron-poor dienophiles with moderate to high facial selectivity.[10,37] A π-stacking model was also proposed to explain the asymmetric induction for dienes **6** bearing an aromatic ring at the stereogenic center;[10b] however, this hypothesis has not been demonstrated as yet. On the other hand, diene **14** (R*O = NBO) (see **Scheme 1**), bearing a 3-*exo*-neopentyloxyisobornyloxy auxiliary, underwent [4+2] cycloaddition reactions with very high π-facial selectivity.[16b]

A remarkable result was obtained by Danishefsky's group during the investigation of the cycloaddition of chiral 1-alkoxy-3-silyloxy-1,3-butadienes **11** with aldehydes.[14a,c] First, the authors observed only modest selectivity in the reaction of several chiral dienes **11** (R*O = MO) with benzaldehyde in the presence of $Eu(fod)_3$. However, the combination of enantiopure diene and the chiral catalyst (+)-$Eu(hfc)_3$ resulted in a diastereofacial excess of 95%. The fact that the chiral dienes exhibited opposite diastereoselectivities in the presence of achiral or chiral catalyst was attributed by the authors to a specific diene–catalyst interaction rather than to a simple double diastereoselection. These results have found application in the synthesis of optically active pyrans, L-glycolipids, and L-glucose (**eq 9**).[14c]

Sugar-derived 1-alkoxydienes have been used in [4+2] cycloaddition reactions with a number of electron-poor dienophiles, resulting in moderate to high π-facial selectivity;[11,12,15,38] some synthetic applications have also been described. Thus, Stoodley and co-workers have described the enantioselective synthesis of dehydropiperazic acid, a nonproteinogenic amino acid, by the cycloaddition of **7** with di-*tert*-butyl azodicarboxylate as the key step.[11]

Cycloaddition reactions in water of 1-alkoxydienes bearing an unprotected sugar, **8**, showed rate and stereoselectivity enhancements as compared with those of the analogous peracetylated dienes in organic solvents. Enzymatic hydrolysis of the glycopyranoside moiety of the cycloadducts yielded highly functionalized chiral cyclohexane derivatives with moderate enantioselectivity.[12]

Regarding chiral 1-sulfinyldienes, García Ruano's group conducted an extensive study on (R_s)-1-*p*-tolylsulfinyl-1,3-butadienes (**22**), and demonstrated their effectiveness toward some electron-poor dienophiles.[19c,d,39] Thus, the reaction of **22** with *N*-methylmaleimide (NMM) leads solely to the endo cycloadduct **41** with high facial selectivity (>95% de). Compound **41** was easily elaborated into the allylic alcohol **42** by a [2,3] sigmatropic rearrangement (**eq 10**).[19d]

The authors explain the face selectivity exerted by the sulfoxide auxiliary by assuming an *s*-trans conformation for the C_2=C_1–S=O moiety of the diene. In this approach, minimum steric and electrostatic repulsion between the carbonyl oxygen of NMM and the sulfinyl oxygen occurs (**Figure 4**). The authors do not rule out a chelation-controlled model in the presence of the Lewis acid. On the other hand, low reactivity and selectivity were observed for the cycloaddition of chiral 1-sulfinyldienes with electron-rich dienophiles such as enamines.[39b]

Highly remarkable results were recently reported by Rawal for chiral 1-amino-3-silyloxy-1,3-dienes. Thus, diene **35** reacted with methacrolein to give the endo cycloadduct, **43**, which, upon reduction and hydrolysis, furnished cyclohexenone **44** with 85% ee. Further transformations led to the enantioselective synthesis of (–)-α-2-elemene (**Scheme 3**).[30] In a similar way, differently substituted cyclohexenones were obtained with high enantioselectivity (92–98% ee) from **35** and α,β-unsaturated esters.

N-Dienylpyroglutamates **32** (see **eq 6**) cycloadded readily to electron-poor carbon dienophiles with excellent endo and facial selectivities (>95% de).[28] However, poor or moderate diastereoselectivity (12–84% de) resulted when heterodienophiles such as acylnitroso derivatives were employed.[40]

3. Synthesis and [4+2] Cycloaddition Reactions of Chiral 2-Heterosubstituted-1,3-butadienes

3.1. Synthesis of Chiral 2-Alkoxy-1,3-butadienes

Surprisingly, and in contrast to the case of 1-substituted alkoxydienes, no reports on the synthesis of chiral 2-alkoxydienes appeared until recently, when we described various approaches to these systems.[41] One of these approaches involves the formation of the C3=C4 bond and follows the procedure developed for the preparation of 2-amino-1,3-dienes.[42] First, the phosphonium salts **46** were prepared in nearly quantitative yield by heating chiral alcohols and commercially available prop-2-ynyltriphenylphosphonium bromide (**45**) (**eq 11**). Compounds **46** were then treated with KHMDS to generate the corresponding 2-alkoxyallylidenephosphoranes, which were subjected to Wittig olefination to give 2-alkoxydienes **47** in good yields and complete *E*-selectivity. This synthesis proved to be versatile with respect to both the chiral auxiliary [(–)-menthol, (–)-8-phenylmenthol, (±)-, (+)-, and (–)-*trans*-2-phenylcyclohexanol, and (±)-*trans*-2-mesitylcyclohexanol] and the aldehyde counterpart (aliphatic, aromatic, and heteroaromatic aldehydes, as well as formaldehyde).

A second approach to 2-alkoxy-1,3-dienes involves the formation of the C1=C2 bond, and makes use of the well-known ability of some titanium-based reagents to effect methylenation of carboxylic acid derivatives.[41b] Thus, the reaction of α,β-unsaturated esters **48**, derived from chiral alcohols, with the easy-to-handle dimethyltitanocene[43] in toluene at 70 °C gave the corresponding 2-alkoxydienes **47** and **49** (**eq 12**). Although yields were lower than those obtained in the Wittig protocol, the titanium-mediated methylenation of α,β-unsaturated esters enabled the preparation of C3-substituted derivatives, which would otherwise be unavailable.

Chiral 2-alkoxydienes with additional functionality were synthesized by a third method that employed the Wittig olefination of chiral α-alkoxyacroleins **50** with

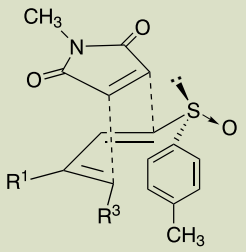
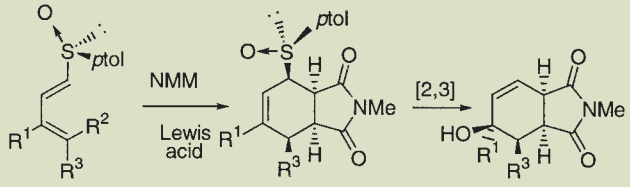
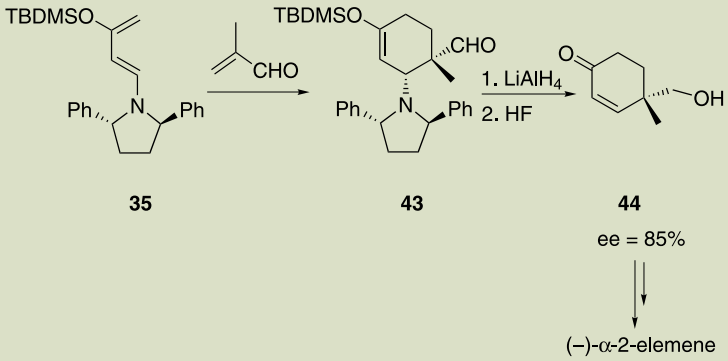


Figure 4

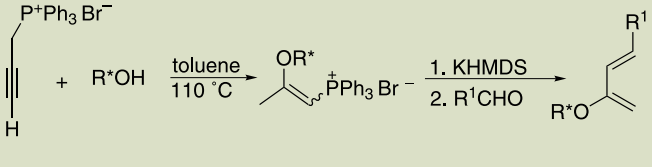


22 (R^2=H) **41** de>95% **42** **eq 10**



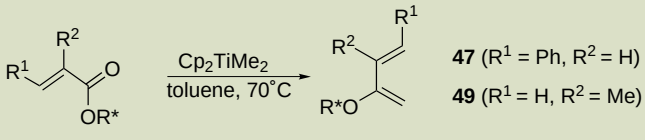
35 **43** **44** ee = 85% (–)-α-2-elemene

Scheme 3

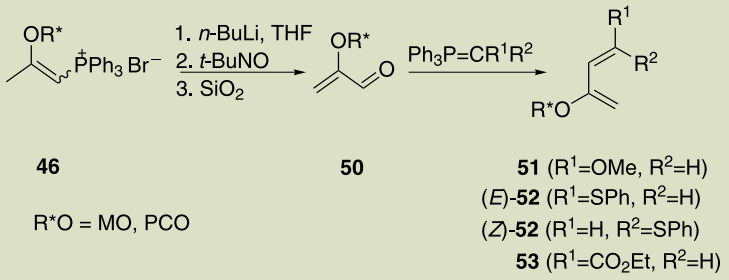


45 **46** **47** **eq 11**

R*OH =(–)-MOH; (–)-PMOH; (–)-, (+)-, and (±)-PCOH; (±)-MCOH



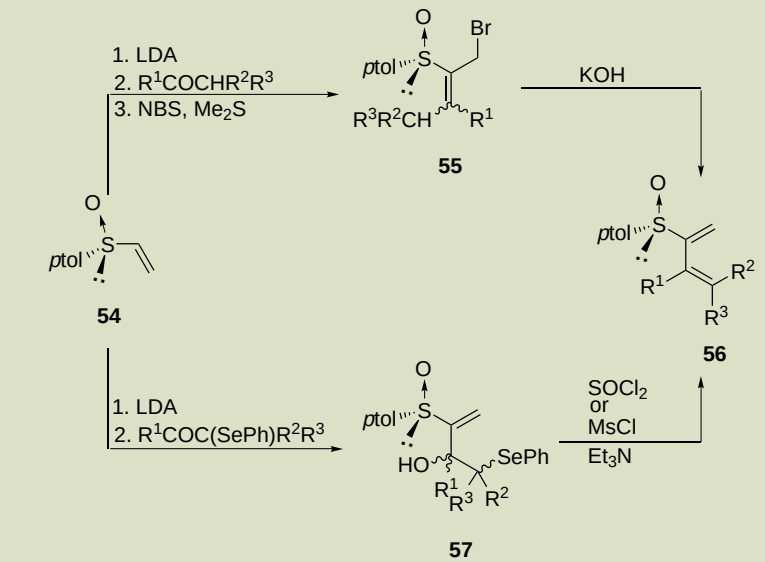
48 **47** (R^1 = Ph, R^2 = H) **49** (R^1 = H, R^2 = Me) **eq 12**



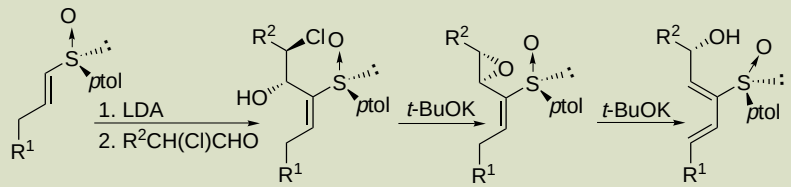
46 **50** **51** (R^1=OMe, R^2=H)
(*E*)-**52** (R^1=SPh, R^2=H)
(*Z*)-**52** (R^1=H, R^2=SPh)
53 (R^1=CO_2Et, R^2=H)

R*O = MO, PCO

eq 13

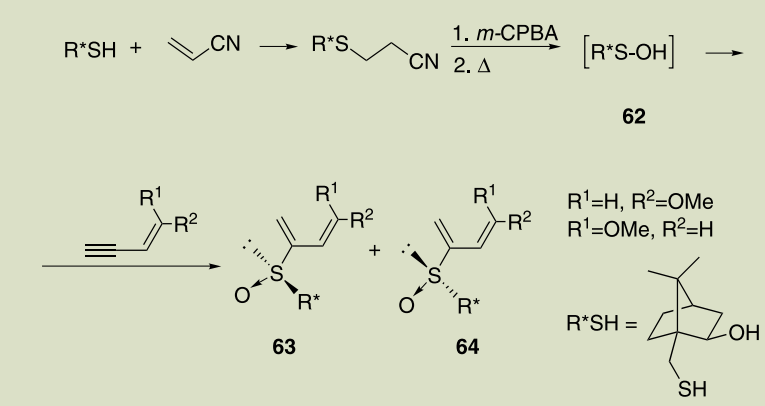


Scheme 4



58 **59** **60** **61**

eq 14



Scheme 5

phosphorus ylides.[41b] The synthesis of chiral captodative olefins **50** required two steps: (i) an aza-Wittig reaction of 2-alkoxyallylidenephosphoranes—generated in situ from phosphonium salts **46** and *n*-butyllithium—with dimethylnitrosoethane, and (ii) selective hydrolysis of the imine function. The acrolein derivatives **50** were then reacted with various types of ylides to yield the doubly activated dienes **51** and **52**, as well as the mixed diene **53** (**eq 13**).

3.2. Synthesis of Chiral 2-Sulfinyl-1,3-butadienes

The coupling of vinyl sulfoxides with carbonyl or functionalized olefinic compounds represents the most versatile approach to 2-sulfinyldienes. Both enantiomers of *p*-tolyl vinyl sulfoxide (**54**) are available in a pure form from vinylmagnesium chloride and chiral commercially available sulfinates. Thus, the sequential treatment of the anion of vinyl sulfoxide **54** with ketones and *N*-bromosuccinimide gives allylic bromides **55**, which, upon treatment with base, lead to dienes **56** (**Scheme 4**).[44] A modification of this method has also been reported; thus, the reaction of the lithium salt of vinyl sulfoxide **54** with α-selenylcarbonyl compounds gives the corresponding β-hydroxyselenides, **57**, which undergo elimination leading to enantiomerically pure mono-, di-, and trisubstituted 2-sulfinyl-1,3-butadienes **56** (**Scheme 4**).[45]

Very recently, de la Pradilla[46] synthesized enantiopure 1-hydroxyalkyl-2-sulfinyldienes **61** by a base-induced rearrangement of epoxy vinyl sulfoxides **60**. Compounds **60** were prepared in situ from chlorohydrins **59**, which, in turn, were formed by condensation of lithiated enantiomerically pure β-substituted vinyl sulfoxides **58** with α-chloro aldehydes (**eq 14**).

A different approach to 2-sulfinyldienes was reported by Paley et al. in their preparations of enantiopure (1*E*)- and (1*Z*)-2-sulfinyldienes via Pd-catalyzed Stille coupling of 1-iodovinyl sulfoxides and vinylstannanes.[24c,47]

Another entry to chiral 2-sulfinyldienes is based on the ability of sulfenic acids to add regiospecifically to 1-alkynes.[48] Aversa et al.[49] generated the required chiral sulfenic acids **62** by base-catalyzed addition of chiral thiols to acrylonitrile, followed by *m*-CPBA oxidation and thermal elimination. When species **62** were generated in the presence of an enyne, a separable diastereomeric mixture of chiral 2-sulfinylbutadienes **63** and **64** was obtained (**Scheme 5**). The best result in terms of yield, ease of separation, and stereochemical control was reached when

(1*S*)-10-mercaptoisoborneol was used as the starting thiol.

Finally, chiral 2-sulfinyldienes were generated in situ by thermally promoted loss of SO_2 from chiral 3-sulfolenes.[50]

3.3. Synthesis of Chiral 2-Amino-1,3-butadienes

In contrast to 1-aminodienes, there exist a number of synthetic methods leading to chiral 2-aminodienes. Based on the catalytic amination of alkynes, our group described the first synthesis of a chiral 2-amino-1,3-diene.[51] Thus, (*S*)-2-(methoxymethyl)pyrrolidine (SMP) (**66**) adds to 3-alken-1-ynes **65** in the presence of Hg(II) salts and Et_3N to give chiral 2-aminodienes **67** in good yields (**eq 15**).

Another route to 2-aminodienes bearing an SMP group was reported by Enders et al.,[52] and involves condensation of the amine with 2,3-butanedione in the presence of arsenic(III) choride, followed by Wittig methylenation.

Taking advantage of the ability of amines to add to propargylphosphonium salts,[42] Enders synthesized 2-amino-1,3-butadienes bearing the C_2-symmetric (*S,S*)-3,5-dimethylmorpholine (**68**).[53] Addition of the amine to propargyltriphenylphosphonium bromide (**45**) gave rise to the β-enaminophosphonium salt, **69**, which afforded the desired aminodienes **70** upon treatment with base and aldehydes (**eq 16**).

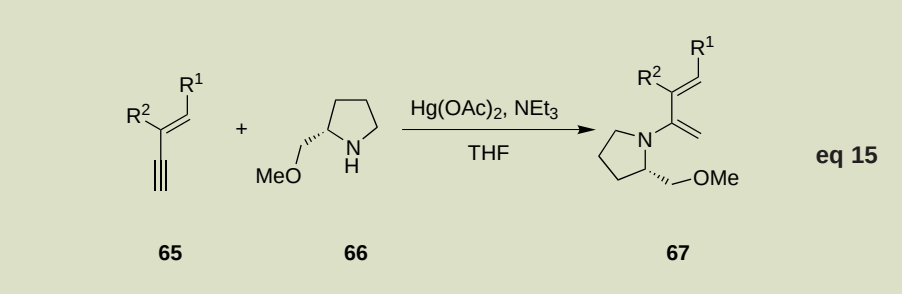
Recently, Enders's group[54] synthesized 2-aminodienes derived from SMP and (*S*)-2-(1-methoxy-1-methylethyl)pyrrolidine (SDP) by coupling α-chloroenamines with alkenyllithium reagents.

3.4. Diastereoselective [4+2] Cycloaddition Reactions of Chiral 2-Heterosubstituted-1,3-butadienes

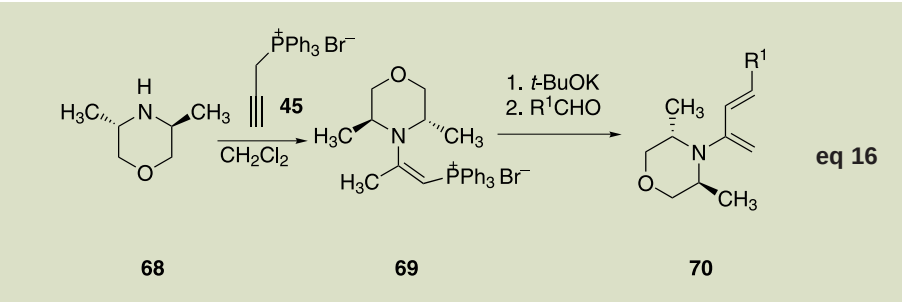
Although chiral 2-heterosubstituted dienes appear to be more attractive than 1-substituted dienes in terms of ease of removal of the chiral auxiliary and facial selectivity, there are fewer reports on the diastereoselective cycloadditions of the former dienes.

The isolated examples concerning 2-alkoxydienes came from our laboratory and dealt with the cycloadditions of dienes **47** to electron-poor carbo- and heterodienophiles, such as phenyltriazolinedione (PTAD), *N*-phenylmaleimide (NPM), and tetracyanoethylene (TCNE) (**eq 17**).[41a] We found that, whereas dienes from either (–)-menthol or (–)-8-phenylmenthol gave rather low facial selectivity (de <43%), dienes derived from *trans*-2-phenylcyclohexanol and *trans*-2-mesitylcyclohexanol underwent cycloaddition with complete endo selectivity and high face selectivity. Thus, reaction of dienes **47** (R*O = PCO, MCO) with NPM and PTAD produced cycloadducts *cis, cis*-**71** (X=CH) and **72** (X=N) with a diastereomeric excess of 71% to 92%. The Diels–Alder reaction with TCNE led to **73** highly selectively (89–90% de) using either *trans*-2-phenylcyclohexanol or *trans*-2-mesitylcyclohexanol as a chiral auxiliary (**eq 17**). Acid hydrolysis with dilute HCl converted cycloadducts **71** and **72** into the corresponding enantiopure cyclohexanone derivatives and allowed the racemization-free removal of the chiral auxiliary.

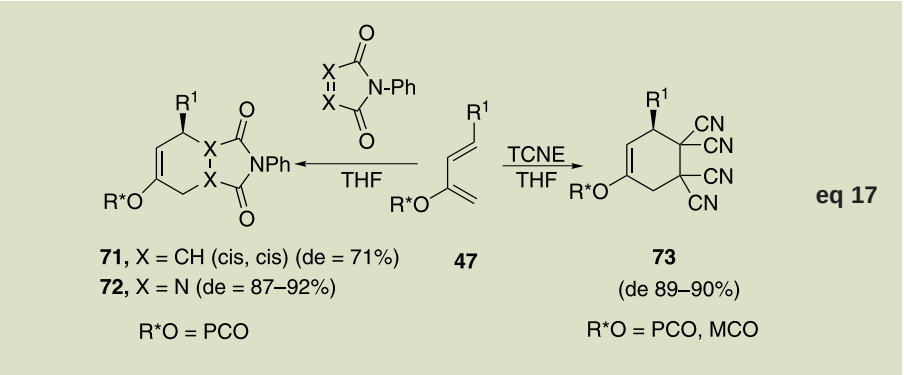
Chiral 2-sulfinyldienes induce good selectivity in [4+2] cycloaddition reactions. Maignan observed that the reaction of (R_s)-(*E*)-2-*p*-tolylsulfinyl-1,3-pentadiene (**74**) with maleimide afforded cycloadduct **76** as a single diastereoisomer,[55] while a 4:1 mixture of diastereoisomeric cycloadducts was obtained from diene **75** and maleic anhydride[56] (**eq 18**). In the latter case, the major isomer, **77**, was found to be a suitable precursor of the Karahana ether. The stereochemical course of these cycloadditions was



65 **66** **67** **eq 15**



68 **69** **70** **eq 16**

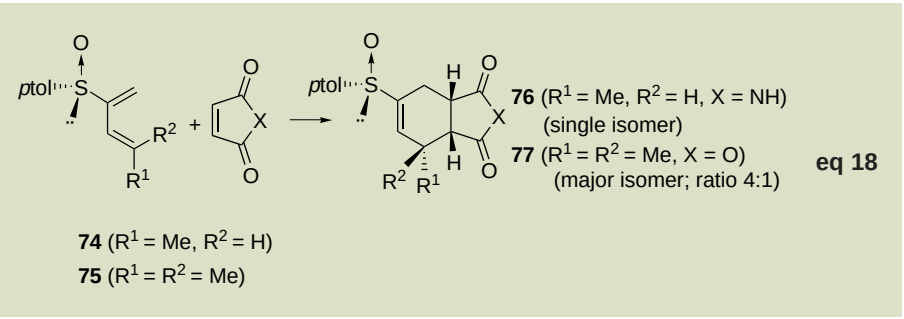


71, X = CH (cis, cis) (de = 71%)
72, X = N (de = 87–92%)
R*O = PCO

47

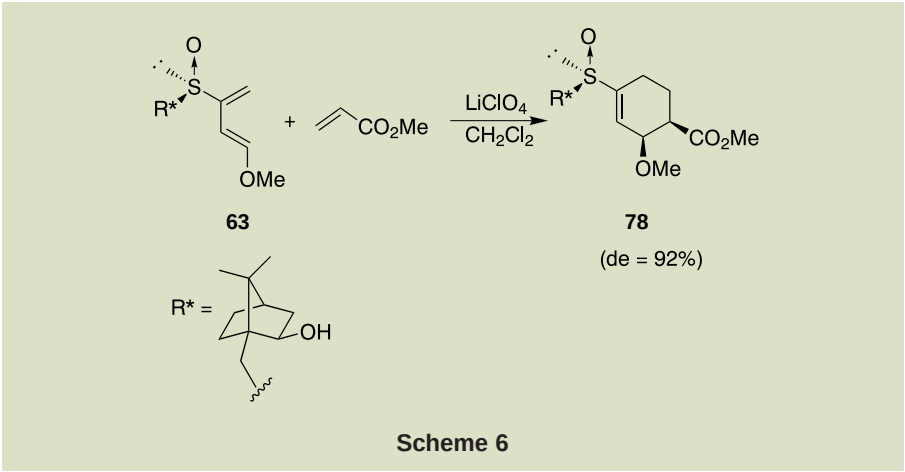
73
(de 89–90%)
R*O = PCO, MCO

eq 17



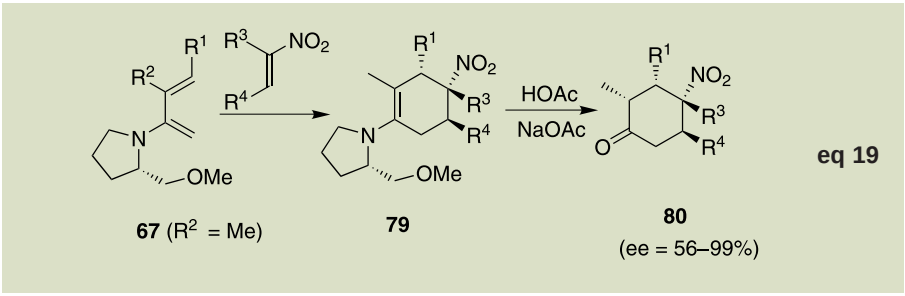
74 (R^1 = Me, R^2 = H)
75 (R^1 = R^2 = Me)

eq 18

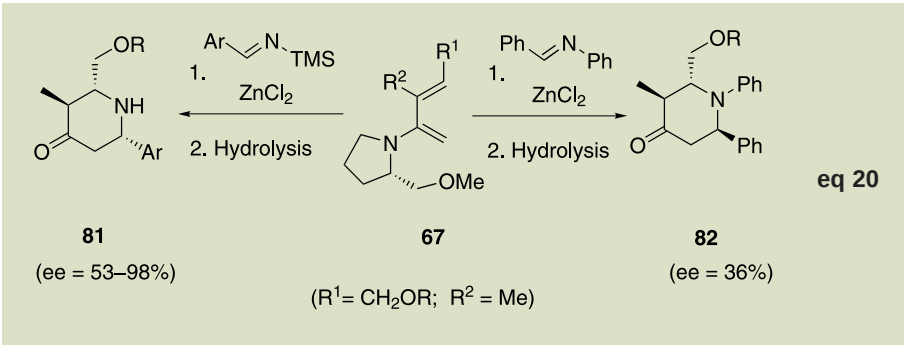


63 **78** (de = 92%)

Scheme 6



67 (R^2 = Me) **79** **80** (ee = 56–99%) **eq 19**



81 (ee = 53–98%) **67** (R^1= CH_2OR; R^2 = Me) **82** (ee = 36%) **eq 20**

explained by postulating a transition state resulting from endo approach of the dienophile to the less hindered face of the diene according to an *s*-trans conformation of the C=C–S=O moiety.

Very recently, de la Pradilla[57] has studied the stereocontrol in Diels–Alder cycloadditions of enantiopure 1-hydroxyalkyl-2-sulfinylbutadienes **61** (see **eq 14**), and has found complete face selectivity toward NPM and PTAD. The author states that the stereocontrol is due exclusively to the chiral sulfur atom. Interestingly, if the sulfur chirality is removed by oxidation to the sulfonyl derivative prior to cycloaddition, a complete reversal of facial selectivity is observed.

The influence of Lewis acid catalysts on the selectivity of [4+2] cycloadditions involving chiral 2-sulfinyldienes has been addressed. Aversa and collaborators[49b,c,58] have reported that the cycloadditions of methyl acrylate to (R_s)-(*E*)- and (S_s)-(*E*)-3-alkylsulfinyl-1-methoxybutadienes **63** and **64** (see **Scheme 5**), catalyzed by $LiClO_4$, proceed under mild conditions with complete regioselectivity and very high stereoselectivity. For instance, the enantiopure diene **63** reacts with methyl acrylate in the presence of $LiClO_4$ to give endo adduct **78** with very good facial diastereoselection (92% de) (**Scheme 6**). These authors have stated that the stereochemical control is exerted by the chiral sulfur configuration and may be rationalized in terms of mutual coordination of the metal cation to the sulfinyl oxygen of the diene and the carbonyl oxygen of the dienophile.

Further studies that confirm the efficiency of $LiClO_4$ as catalyst in enhancing facial diastereoselectivity with other electron-poor dienophiles have been carried out by the same authors.[59] The $LiClO_4$-catalyzed reaction of 2-sulfinyldienes, derived from sulfolenes, with NPM takes place also with high diastereoselectivity, as reported recently by Yang.[50]

Preliminary studies by Valentin's group,[60] and later by our group,[61] established that 2-amino-1,3-dienes react smoothly with nitroalkenes to give open-chain 4-nitroketones by a Michael-type addition of the enamine moiety to the nitroolefin, or 4-nitrocyclohexenones by a formal [4+2] cycloaddition. The product distribution was found to be solvent-dependent. Polar solvents, such as MeOH, favored the cyclization process giving rise to a single cycloadduct, while mixtures of cyclic and open-chain adducts were formed in less polar solvents, such as THF or chloroform.

Continuing these studies, the chiral version of the reaction was carried out by our group.[62] Chiral 2-aminodienes **67** were reacted with aliphatic and aromatic nitroalkenes to give cycloadducts **79** that were not isolated, but were hydrolyzed to 4-nitrocyclohexanones **80** (**eq 19**). Both the cyclization and the hydrolysis steps were highly diastereoselective, and the enantiomeric excesses ranged from good to excellent. We also observed that the substituents in both diene and nitroalkene exerted notable influence on the diastereoselectivity of the cycloaddition—very good ee's (92–95%) being reached with aliphatic nitroalkenes. Enders also investigated the [4+2] cycloaddition of aromatic nitroalkenes with related chiral 2-aminodienes and made similar observations.[52] We have recently used cycloadducts **80** in the synthesis of cyclic β-amino acids.[63]

Chiral 2-aminodienes are also capable of cycloadding to nonactivated imines in the presence of Lewis acids.[62a,64] For instance, chiral, SMP-derived 2-aminodienes **67** (R^1 = CH_2OR) react with aromatic *N*-trimethylsilylaldimines and *N*-phenylaldimines in the presence of $ZnCl_2$ to give 4-piperidones **81** and **82**, respectively, with moderate to very high enantiomeric excess (**eq 20**). It was found that the nature of the substituent at the imine nitrogen plays a crucial role in the stereochemical course of the reaction. Thus, the endo cycloadduct, **81**, and the exo cycloadduct, **82**, are exclusively produced from *N*-trimethylsilyl- and *N*-phenylaldimines, respectively.

This reaction has had interesting synthetic applications.[65] Very recently, our group reported the elaboration of piperidones **81** into enantiopure D- and L-pipecolic acid derivatives **83** and **84**.[65a] Compounds **81** were also employed as starting materials in the total synthesis of Nuphar alkaloids, such as (–)-(*5S, 8R, 9S*)-5-(3-furyl)-8-methyloctahydroindolizidine (**85**) and (–)-nupharamine (**86**) (**Figure 5**).[65b]

Enders and co-workers investigated the heterocyclizations of 2-aminodienes **70** (see **eq 16**), derived from (*S,S*)-3,5-dimethylmorpholine, with PTAD and methyltriazolinedione.[53] The cycloadducts were formed at low temperature with high selectivity (87–96% de); the chiral auxiliary was then removed by acid hydrolysis to give the corresponding carbonyl derivatives (90–91% ee).

The reactivity of 2-aminodienes toward alkenes activated by a metal pentacarbonylmethoxycarbene group—α,β-unsaturated Fischer carbene complexes—was also investigated by our group. Thus, the reaction of chiral 2-aminodienes **67** with alkenylchromium carbene complexes **87** afforded cycloheptanediones **88** through a formal [4+3] diastereoselective cycloaddition (**eq 21**).[62a,66] However, the use of tungsten Fischer alkenylcarbene complexes **89** resulted in the formation of a mixture of the diastereomeric [4+2] cycloadducts, which were hydrolyzed to the corresponding carbonyl compounds **90** and **91** (**eq 22**).[67] The endo/exo selectivity ranged from 2:1 to 15:1, and the ee of the exo isomer was much higher (82–99%) than that of the endo isomer (18–90%). Moreover, oxidation of the metal carbene group to the ester functionality was effected with $Ce(NH_4)_2(NO_3)_6$.

Our group also found that cyclic BF_2 adducts of a functionalized Fischer vinylcarbene complex, **93**, undergo exo-selective [4+2] cyclization with chiral 2-aminodienes **67** and **92** (**eq 23**).[68] The enantiomeric excesses of the cyclohexanone products, **94**, were excellent (90–93%). Surprisingly, the sense of the diastereofacial selectivity resulted apparently from the addition of the dienophile to the more hindered face of the diene. To explain this observation, the possibility of a stepwise mechanism involving zwitterionic species was taken into account. Treatment of **94** with $Ce(NH_4)_2(NO_3)_6$ followed by methanolysis allowed the removal of the metal fragment and the BF_2 group.

4. Concluding Remarks

This review has summarized the methods available for the preparation of chiral heterosubstituted 1,3-butadienes, as well as their utility as chiral 4π-components in diastereoselective [4+2] cycloadditions. Although the results obtained by Trost and co-workers in this field have remained unique for more than a decade, at least in terms of enantioselectivity, the efforts of a number of researchers in the last few years have culminated in the elaboration of a number of chiral dienic systems that show high levels of relative and absolute diastereocontrol. This research has opened a door for the enantioselective synthesis of a number of organic

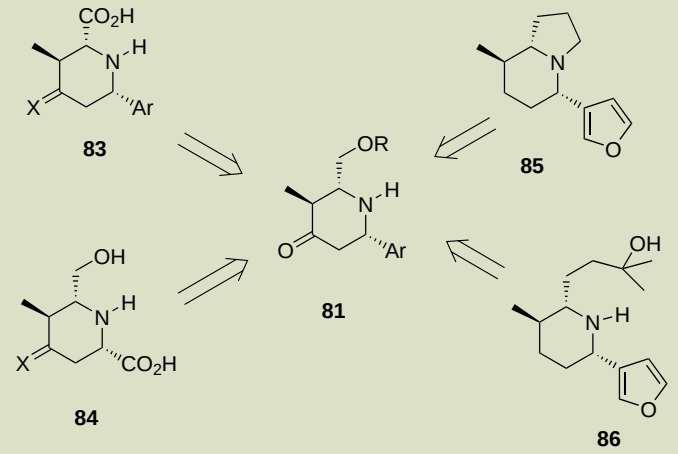
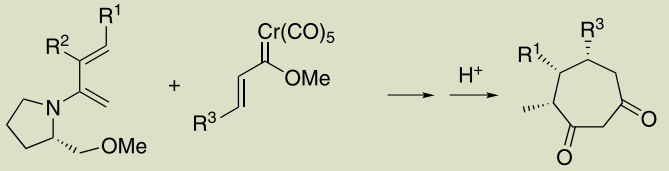
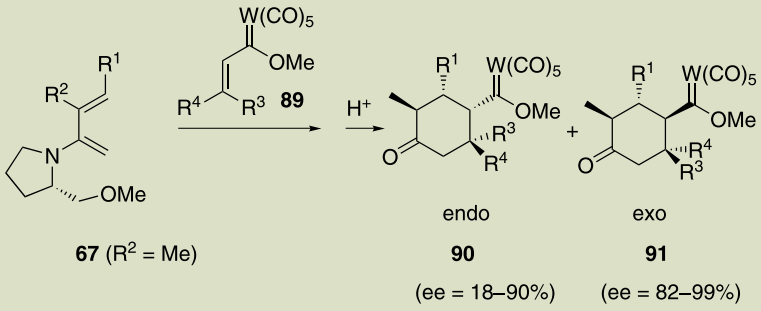


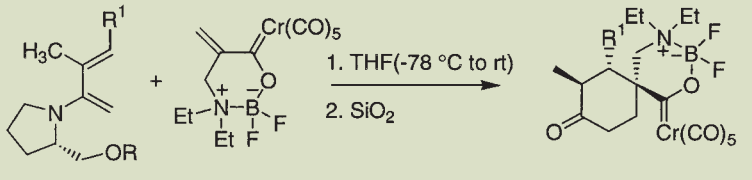
Figure 5



eq 21



eq 22



eq 23

compounds, including natural products. Our feeling is that substantially more work is necessary to fully explore and exploit the utility of these systems in organic synthesis.

5. Acknowledgments

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6. References

(1) (a) Diels, O.; Alder, K. *Justus Liebigs Ann. Chem*. **1928**, *460*, 98. For reviews, see (b) Fringelli, F.; Tatichi, A. *Dienes in the Diels–Alder Reaction;* Wiley: New York, NY, 1990. (c) Mulzer, J.; Altenbach, H.-J.; Braun, M.; Krohn, K.; Reissig, H.-U. *Organic Synthesis Highlights*; VCH: Weinheim, Germany, 1991; p 54.

(2) (a) For a review on catalytic asymmetric Diels–Alder reactions, see Kagan, B.H.; Riant, O. *Chem. Rev*. **1992**, *92*, 1007. For a few leading articles, see: (b) Evans, D.A.; Murry, J.A.; von Matt, P.; Norcross, R.D.; Miller, S.J. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 798. (c) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 3049. (d) Hayashi, Y.; Rohde, J.J.; Corey, E.J. *J. Am. Chem. Soc*. **1996**, *118*, 5502. (e) Schaus, S.E.; Branalt, J.; Jacobsen, E.N. *J. Org. Chem.* **1998**, *63*, 403.

(3) (a) For a review, see Oppolzer, W. *Angew. Chem., Int. Ed. Engl*. **1984**, *23*, 876. For leading references, see: (b) Evans, D.A.; Chapman, K.T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238. (c) Oppolzer, W.; Wills, M.; Kelly, M.J.; Signer, M.; Blagg, J. *Tetrahedron Lett.* **1990**, *31*, 5015. (d) Carretero, J.C.; Garcia Ruano, J.L.; Martín Cabrejas, L.M. *Tetrahedron: Asymmetry* **1997**, *8*, 2215, and references therein.

(4) (a) For a review on chiral C-substituted dienes, see Winterfeldt, E. *Chem. Rev.* **1993**, *93*, 827. For leading references, see (b) Tripathy, R.; Franck, R.W.; Onan, K.D. *J. Am. Chem. Soc.* **1988**, *110*, 3257. (c) Hatakeyama, S.; Sugawara, K.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1992**, 953. (d) Bloch, R.; Chaptal-Gradoz, N. *J. Org. Chem.* **1994**, *59*, 4162. (e) Crisp, G.T.; Gebauer, M.G. *J. Org. Chem.* **1996**, *61*, 8425.

(5) (a) Krohn, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1582. (b) Enders, D.; Meyer, O. *Liebigs Ann. Chem.* **1996**, 1023.

(6) Aversa, M.A.; Barattucci, A.; Bonaccorsi, P.; Giannetto, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1339.

(7) Trost, B.M.; O'Krongly, D.; Belletire, J.L. *J. Am. Chem. Soc.* **1980**, *102*, 7595.

(8) (a) David, S.; Lubineau, A.; Vatèle, J.-M. *J. Chem. Soc., Chem. Commun.* **1978**, 535. (b) David, S.; Eustache, J. *J. Chem. Soc., Perkin Trans. I* **1979**, 2521, and references therein.

(9) Trost, B.M.; Chupak, L.S.; Lübbers, T. *J. Org. Chem.* **1997**, *62*, 736.

(10) (a) Thiem R.; Rotscheidt, K.; Breitmaier, E. *Synthesis* **1989**, 836. (b) Rieger, R.; Breitmaier, E. *Synthesis* **1990**, 697.

(11) Aspinall I.H.; Cowley, P.M.; Mitchell, G.; Stoodley, R.J. *J. Chem. Soc., Chem. Commun.* **1993**, 1179.

(12) (a) Lubineau, A.; Queneau, Y. *Tetrahedron Lett.* **1985**, *26*, 2653. (b) Lubineau, A.; Queneau, Y. *J. Org. Chem*. **1987**, *52*, 1001.

(13) For reviews, see: (a) Danishefsky, S.J. *Aldrichimica Acta*, **1986**, *19*, 59. (b) Danishefsky, S.J.; DeNinno, M.P. *Angew. Chem., Int. Ed. Engl*. **1987**, *26*, 15. (c) Danishefsky, S.J. *Chemtracts—Org. Chem.* **1989**, *2*, 273.

(14) (a) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 6968. (b) Danishefsky, S.; Bednarski, M.; Izawa, T.; Maring, C. *J. Org. Chem*. **1984**, *49*, 2290. (c) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc*. **1986**, *108*, 7060.

(15) (a) Gupta, R.C; Harland, P.A.; Stoodley, R.J. *J. Chem. Soc., Chem. Commun*. **1983**, 754. (b) Gupta, R.C; Harland, P.A.; Stoodley, R.J. *Tetrahedron* **1984**, *40*, 4657. (c) Larsen, D.S.; Stoodley, R.J. *J. Chem. Soc., Perkin Trans. I* **1989**, 1841.

(16) (a) Virgili, M.; Moyano, A.; Pericàs, M.A.; Riera, A. *Tetrahedron Lett.* **1997**, *38*, 6921. (b) Virgili, M.; Pericàs, M.A.; Moyano, A.; Riera, A. *Tetrahedron* **1997**, *53*, 13427.

(17) Guillam, A.; Toupet, L.; Maddaluno, J. *J. Org. Chem.* **1998**, *63*, 5110.

(18) (a) Konopelski, J.P.; Boehler, M.A. *J. Am. Chem. Soc.* **1989**, *111*, 4515. (b) Boehler, M.A.; Konopelski, J.P. *Tetrahedron* **1991**, *47*, 4519.

(19) (a) Solladié, G.; Ruiz, P.; Colobert, F.; Carreño, M.C.; García Ruano, J.L. *Synthesis* **1991**, 1011. (b) Solladié, G.; Maugein, N.; Morreno, I.; Almario, A.; Carreño, M.C.; García Ruano, J.L. *Tetrahedron Lett.* **1992**, *33*, 4561. (c) Carreño, M.C.; Cid, M.B.; Colobert, F.; García Ruano, J.L.; Solladié, G. *Tetrahedron: Asymmetry* **1994**, *5*, 1439. (d) Arce, E.; Carreño, M.C.; Cid, M.B.; García Ruano, J.L. *J. Org. Chem.* **1994**, *59*, 3421.

(20) Solladié, G.; Hutt, J.; Girardin, A. *Synthesis* **1987**, 173.

(21) Burke, S.D.; Shankaran, K.; Helber, M.J. *Tetrahedron Lett*. **1991**, *32*, 4655.

(22) Pindur, U.; Lutz, G.; Rogge, M. *J. Heterocycl. Chem.* **1995**, *32*, 201.

(23) Arce, E.; Carreño, M.C.; Cid, M.B.; García Ruano, J.L. *Tetrahedron: Asymmetry* **1995**, *6*, 1757.

(24) (a) Paley, R.S.; de Dios, A.; Fernandez de la Pradilla, R. *Tetrahedron Lett.* **1993**, *34*, 2429. (b) Paley, R.S.; Lafontaine, J.A.; Ventura, M.P. *Tetrahedron Lett.* **1993**, *34*, 3663. (c) Paley, R.S.; de Dios, A.; Estroff, L.A.; Lafontaine, J.A.; Montero, C.; McCulley, D.J.; Rubio, M.B.; Ventura, M.P.; Weers, H.L.; Fernandez de la Pradilla, R.; Castro, S.; Dorado, R.; Morente, M. *J. Org. Chem*. **1997**, *62*, 6326.

(25) Stille, J.K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

(26) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett*. **1975**, 4467.

(27) Zezza, C.A.; Smith, M.B. *J. Org. Chem.* **1988**, *53*, 1161.

(28) Menezes, R.F.; Zezza, C.A.; Sheu, J.; Smith, M.B. *Tetrahedron Lett.* **1989**, *30*, 3295.

(29) Murphy, J.P.; Nieuwenhuyzen, M.; Reynolds, K.; Sarma, P.K.S.; Stevenson, P.J. *Tetrahedron Lett.* **1995**, *36*, 9533.

(30) Kozmin, S.A.; Rawal, V.H. *J. Am. Chem. Soc.* **1997**, *119*, 7165.

(31) (a) Corey, E.J.; Becker, K.B.; Varma, R.K. *J. Am. Chem. Soc.* **1972**, *94*, 8616. (b) Whitesell, J.K. *Chem. Rev.* **1992**, *92*, 953. For an interesting discussion of the π-stacking effect, see also reference 34 below.

(32) Masamune, S.; Choy, W.; Petersen, J.S.; Sita, L.R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. See footnote on page 12.

(33) (a) Siegel, C.; Thornton, E.R. *Tetrahedron Lett.* **1988**, *29*, 5225. (b) Siegel, C.; Thornton, E.R. *Tetrahedron: Asymmetry* **1991**, *2*, 1413.

(34) Tucker, J.A.; Houk, K.N.; Trost, B.M. *J. Am. Chem. Soc.* **1990**, *112*, 5465.

(35) Maddaluno, J.F.; Gresh, N.; Giessner-Prettre, C. *J. Org. Chem.* **1994**, *59*, 793.

(36) (a) Tripathy, R.; Carroll, P.J.; Thornton, E.R. *J. Am. Chem. Soc.* **1990**, *112*, 6743. (b) Tripathy, R.; Carroll, P.J.; Thornton, E.R. *J. Am. Chem. Soc.* **1991**, *113*, 7630.

(37) (a) Zadel, G.; Rieger, R.; Breitmaier, E. *Liebigs Ann. Chem.* **1991**, 1343. (b) Flock, M.; Nieger, M.; Breitmaier, E. *Liebigs Ann. Chem.* **1993**, 451. (c) Lehmler, H.-J.; Nieger, M.; Breitmaier, E. *Synthesis* **1996**, 105.

(38) (a) Gupta, R.C.; Slawin, A.M.Z.; Stoodley, R.J.; Williams, D.J. *J. Chem. Soc., Chem. Commun.* **1986**, 668. (b) Gupta, R.C.; Raynor, C.M.; Stoodley, R.J.; Slawin, A.M.Z.; Williams, D.J. *J. Chem. Soc., Perkin Trans. I* **1988**, 1773. (c) Gupta, R.C.; Larsen, D.S.; Stoodley, R.J.; Slawin, A.M.Z.; Williams, D.J. *J. Chem. Soc., Perkin Trans. I* **1989**, 739. (d) Larsen, D.S.; Stoodley, R.J. *J. Chem. Soc., Perkin Trans. I* **1990**, 1339. (e) Beagley, B.; Larsen, D.S.; Pritchard, R.G.; Stoodley, R.J. *J. Chem. Soc., Perkin Trans. I* **1990**, 3113. (f) Lowe R.F.; Stoodley, R.J. *Tetrahedron Lett.* **1994**, *35*, 6351.

(39) (a) Carreño, M.C.; Cid, M.B.; García Ruano, J.L. *Tetrahedron: Asymmetry* **1996**, *7*, 2151. (b) Carreño, M.C.; Cid, M.B.; García Ruano, J.L.; Santos, M. *Tetrahedron: Asymmetry* **1997**, *8*, 2093. (c) Carreño, M.C.; Cid, M.B.; García Ruano, J.L.; Santos, M. *Tetrahedron Lett.* **1998**, *39*, 1405.

(40) Defoin, A.; Pires, J.; Streith, J. *Synlett* **1991**, 417.

(41) (a) Barluenga, J.; Tomás, M.; Suárez-Sobrino, A.; López, L.A. *J. Chem. Soc., Chem. Commun.* **1995**, 1785. (b) Barluenga, J.; Tomás, M.; López, L.A.; Suárez-Sobrino, A. *Synthesis* **1997**, 967.

(42) Barluenga, J.; Merino, I.; Palacios, F. *Tetrahedron Lett.* **1990**, *31*, 6713.

(43) This compound was introduced as a methylenating reagent by Petasis in Petasis, N.A.; Bzowej, E.I. *J. Am. Chem. Soc*. **1990**, *112*, 6392.

(44) (a) Bonfand, E.; Gosselin, P.; Maignan, C. *Tetrahedron: Asymmetry* **1993**, *4*, 1667.

(b) For an earlier report by the same group, see Bonfand, E.; Gosselin, P.; Maignan, C. *Tetrahedron Lett*. **1992**, *33*, 2347.
(45) Gosselin, P.; Bonfand, E.; Maignan, C. *Synthesis* **1996**, 1079.
(46) Fernández de la Pradilla, R.; Martínez, M.V.; Montero, C.; Viso, A. *Tetrahedron Lett.* **1997**, *38*, 7773.
(47) Paley, R.S.; Weers, H.L.; Fernández, P.; Fernández de la Pradilla, R.; Castro, S. *Tetrahedron Lett*. **1995**, *36*, 3605.
(48) Jones, D.N.; Cottam, P.D.; Davies, J. *Tetrahedron Lett.* **1979**, 4977.
(49) (a) Aversa, M.C.; Bonaccorsi, P.; Giannetto, P.; Jafari, S.M.A.; Jones, D.N. *Tetrahedron: Asymmetry* **1992**, *3*, 701. (b) Aversa, M.C.; Bonaccorsi, P.; Giannetto, P.; Jones, D.N. *Tetrahedron: Asymmetry* **1994**, *5*, 805. (c) Aversa, M.C.; Barattucci, A.; Bonaccorsi, P.; Giannetto, P.; Jones, D.N. *J. Org. Chem.* **1997**, *62*, 4376.
(50) Yang, T.-K.; Chu, H.-Y.; Lee, D.-S.; Jiang, Y.-Z.; Chou, T.-S. *Tetrahedron Lett.* **1996**, *37*, 4537.
(51) Barluenga, J.; Aznar, F.; Valdés, C.; Cabal, M.-P. *J. Org. Chem.* **1991**, *56*, 6166.
(52) Enders, D.; Meyer, O.; Raabe, G. *Synthesis* **1992**, 1242.
(53) Enders, D.; Meyer, O.; Raabe, G.; Runsink, J. *Synthesis* **1994**, 66.
(54) Enders, D.; Hecker, P.; Meyer, O. *Tetrahedron* **1996**, *52*, 2909.
(55) Gosselin, P.; Bonfand, E.; Hayes, P.; Retoux, R.; Maignan, C. *Tetrahedron: Asymmetry* **1994**, *5*, 781.
(56) Gosselin, P.; Bonfand, E.; Maignan, C. *J. Org. Chem.* **1996**, *61*, 9049.
(57) Fernández de la Pradilla, R.; Montero, C.; Viso, A. *Chem. Commun.* **1998**, 409.
(58) Adams, H.; Jones, D.N.; Aversa, M.C.; Bonaccorsi, P.; Giannetto, P. *Tetrahedron Lett.* **1993**, *34*, 6481.
(59) (a) Aversa, M.C.; Barattucci, A.; Bonaccorsi, P.; Bruno, G.; Giannetto, P.; Panzalorto, M. *Tetrahedron: Asymmetry* **1997**, *8*, 2989. (b) Aversa, M.C.; Barattucci, A.; Bonaccorsi, P.; Giannetto, P.; Panzalorto, M.; Rizzo, S. *Tetrahedron: Asymmetry* **1998**, *9*, 1577.
(60) (a) Pitacco, G.; Risaliti, A.; Trevisan, M.L.; Valentin, E. *Tetrahedron* **1977**, *33*, 3145. (b) Ferri, R.A.; Pitacco, G.; Valentin, E. *Tetrahedron* **1978**, *34*, 2537. (c) Benedetti, F.; Pitacco, G.; Valentin, E. *Tetrahedron* **1979**, *35*, 2293.
(61) (a) Barluenga, J. *Bull. Soc. Chim. Belg.* **1988**, *97*, 545. (b) Barluenga, J.; Aznar, F.; Cabal, M.-P.; Valdés, C. *J. Chem. Soc., Perkin Trans. 1* **1990**, 633.
(62) (a) Barluenga, J.; Aznar, F.; Valdés, C.; Martín, A.; García-Granda, S.; Martín, E. *J. Am. Chem. Soc.* **1993**, *115*, 4403. (b) Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C. *J. Org. Chem*. **1997**, *62*, 6746.
(63) Barluenga, J.; Aznar, F.; Valdés, C.; Ribas, C. *J. Org. Chem*. **1998**, *63*, 10052.
(64) Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C.; Fernández, M.; Cabal, M.-P.; Trujillo, J. *Chem. Eur. J*. **1996**, *2*, 805.
(65) (a) Barluenga, J.; Aznar, F.; Valdés, C.; Ribas, C. *J. Org. Chem*. **1998**, *63*, 3918. (b) Barluenga, J.; Aznar, F.; Valdés, C.; Ribas, C. submitted for publication in *J. Org. Chem*.
(66) Barluenga, J.; Aznar, F.; Martín, A.; Vázquez, J.T. *J. Am. Chem. Soc*. **1995**, *117*, 9419.
(67) (a) Barluenga, J.; Aznar, F.; Martín, A.; Barluenga, S.; García-Granda, S.; Paneque-Quevedo, A.A. *J. Chem. Soc., Chem. Commun.* **1994**, 843. (b) Barluenga, J.; Aznar, F.; Martín, A.; Barluenga, S. *Tetrahedron* **1997**, *53*, 9323.
(68) (a) Barluenga, J.; Canteli, R.-M.; Flórez, J.; García-Granda, S.; Gutiérrez-Rodriguez, A. *J. Am. Chem. Soc.* **1994**, *116*, 6949. (b) Barluenga, J.; Canteli, R.-M.; Flórez, J.; García-Granda, S.; Gutiérrez-Rodriguez, A.; Martín, E. *J. Am. Chem. Soc*. **1998**, *120*, 2514.

About the Authors

José Barluenga (middle in the picture) has been Professor of Organic Chemistry at the University of Oviedo since 1975, where he is now Director of the Instituto Universitario de Química Organometálica "E. Moles". He was born in 1940 in Tardienta, Spain. He obtained his Ph.D. degree at the University of Zaragoza in 1966 under the direction of Prof. Gómez Aranda. Following this, he spent three and a half years as a postdoctoral research fellow working on aluminium chemistry in the group of Prof. H. Hoberg at the Max Planck Gesellschaft of the Max Planck Institut für Kohlenforschung, Mülheim a.d. Ruhr, Germany. In 1970, he took a position as a Research Associate at the University of Zaragoza, where he was promoted to Associate Professor in 1972. In 1975, he moved to the University of Oviedo as Professor of Organic Chemistry. His major research interest is focused on various topics related to selective organic synthesis and organometallic chemistry.

Angel Suárez-Sobrino (right in the picture) was born in 1961 in Oviedo, Spain. He obtained his B.S. degree from the University of Oviedo and his Ph.D., in 1990, from the same University under the direction of Professor Barluenga. In 1991, he became a postdoctoral Fulbright fellow in the research group of Professor Paul A. Wender at Stanford University, California, where he spent two years working on the synthesis of natural products. In 1993, he rejoined Professor Barluenga's group in Oviedo as a Research Associate.

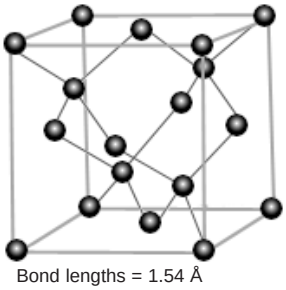
Luis A. López (left in the picture) was born in 1961 in Gijón, Spain. He studied chemistry at the University of Oviedo, where he received his Ph.D. degree in 1990 for a thesis on heterocyclic chemistry under the direction of Professor Barluenga. He spent two years at the University of Münster, Germany, as an Alexander von Humboldt postdoctoral fellow working on zirconium chemistry in Prof. G. Erker's group. In 1993, he accepted a position as a Research Associate in Professor Barluenga's group in Oviedo.

The Many Forms of Carbon

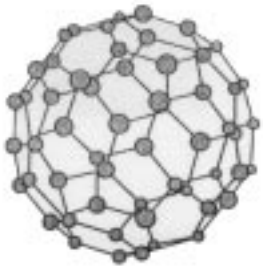
Carbon is one of the most abundant elements in the universe, and the element on which the atomic weight system is based. ($^{12}C = 12.0000$). Although C_{60} was later found to exist in space, the laboratory production and documentation of the fullerenes, combined with the interest in the production of diamond films for materials applications, spurred the current interest in the many research uses of carbon and its various forms.

Here are a few examples of the carbon forms offered by Aldrich at very competitive prices. Contact your local office today to place your order!

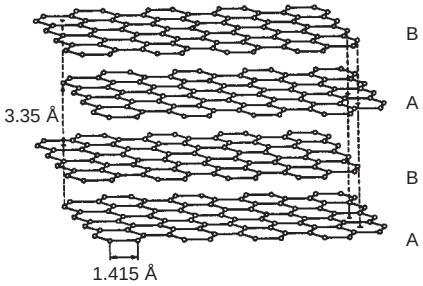
Check out our Web site at **www.sigma-aldrich.com** and send us your suggestions for other new materials if you do not find what you need through our searchable online catalog. We welcome your input and ideas! "Please bother us!"



Diamond



Buckminsterfullerene (C_{60})



Graphite

Diamond

48,357-5	Natural, monocrystalline, powder, ~1 µm, 99.9%
48,359-1	Synthetic, monocrystalline, powder, ~1 µm, 99.9%
48,360-5	Synthetic, monocrystalline, powder, ~50 µm, 99.9%
48,358-3	Synthetic, polycrystalline, powder, ~1 µm, 99.9%

Glassy Carbon

48,416-4	Spherical powder, 2–12 µm, 99.99+%
48,415-6	Spherical powder, 10–40 µm, 99.99+%

Graphite

49,653-7	Rod, 3mm diam. x 150mm length, 99.999%, low density
49,655-3	Rod, 6mm diam. x 150mm length, 99.999%, low density
28,286-3	Powder, 1–2 µm, synthetic

Fullerenes

37,964-6	**Buckminsterfullerene**, (C_{60}), 99.5%
48,303-6	**Buckminsterfullerene**, (C_{60}), 98%
48,299-4	**[5,6]-Fullerene-C_{70}**, 99%
37,965-4	**[5,6]-Fullerene-C_{70}**, 96%
48,295-1	**Fullerene-C_{76}**, 98%
48,297-8	**Fullerene-C_{78}**, 98%
48,298-6	**Fullerene-C_{84}**, 98%

Carbon Nanotubes

41,298-8	**Bucky tubes, as-produced cylinders**
41,299-6	**Bucky tubes, powdered as-produced cylinders**
41,300-3	**Bucky tubes, cylinder cores, shell removed**
40,607-4	**Bucky tubes, powdered cylinder cores**

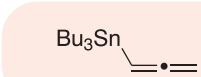
Organotin Reagents

Frankland and Löwig synthesized the first organotin compounds in 1852 by reacting alkyl halides with tin–sodium amalgam.[1,2] It was not until about one hundred years later that the commercial development of organotin compounds—used as polyvinyl chloride (PVC) stabilizers, catalysts, and marine antifouling agents—led to renewed interest in this area. Today, several hundred organotin compounds are known. Listed below are some interesting organotin reagents that are used in a variety of organic transformations. For more information or to inquire about products not listed below, please contact our Technical Services Department at **(800) 231-8327** (USA), your local Sigma-Aldrich office, or visit our Web site at **www.sigma-aldrich.com**.

49,985-4 Allenyltributyltin, tech., 80%

NEW!

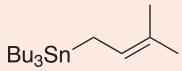
Reacts with aldehydes, often in the presence of Ti(IV) complexes, to give propargylic alcohols in high yields;[3-5] also used in the preparation of allene-substituted lactams that undergo palladium-catalyzed cyclization reactions.[6]



49,984-6 Tributyl(3-methyl-2-butenyl)tin, 90%

NEW!

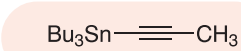
Utilized in the total synthesis of tryprostatin B via a dimethylallylboron reagent that is generated in situ by reaction with BCl_3;[7] also reacts with aldehydes to give chiral secondary alcohols.[8]



49,986-2 Tributyl(1-propynyl)tin, 95%

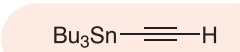
NEW!

Employed as a reagent in the total synthesis of (±)-stemoamide;[9] also reacts with bicycloalkenylbis(phenyliodonium) triflates to give bicyclic enediynes.[10]



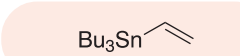
27,506-9 Tributyl(ethynyl)tin, 96%

Serves as a versatile reagent in the palladium-catalyzed reaction with carbon electrophiles, commonly referred to as Stille coupling.[11]



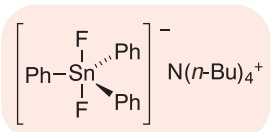
27,143-8 Tributyl(vinyl)tin, 97%

Extensively used in Stille coupling reactions; for example, several enantiomerically pure 1- and 2-sulfinyldienes have been synthesized via the reaction of halovinyl sulfoxides and tributyl(vinyl)tin.[12] Its applications in solid-phase synthesis include the preparation of dienes on a polystyrene support.[13]



41,862-5 Tetrabutylammonium difluorotriphenylstannate, 97%

Also known as Gingras' Reagent or TBAF-Sn, it is an anhydrous synthetic equivalent to tetrabutylammonium fluoride (TBAF).[14] It is useful as a fluoride source for nucleophilic displacement reactions,[15,16] and as a phenyl transfer agent in coupling reactions.[17]



References: (1) Frankland, E. *Phil. Trans.* **1852**, *142*, 417. (2) Löwig, C. *Liebigs Ann. Chem.* **1852**, *84*, 308. (3) Footnote 22 in Haruta, J. et al. *J. Org. Chem.* **1990**, *55*, 4853. (4) Suzuki, M. et al. *ibid.* **1990**, *55*, 441. (5) Yu, C-M. et al. *Chem. Commun.* **1997**, 763. (6) Karstens, W. F. J. et al. *Tetrahedron Lett.* **1997**, *38*, 6275. (7) Depew, K. M. et al. *J. Am. Chem. Soc.* **1996**, *118*, 12463. (8) Breitfelder, S. et al. *Synthesis* **1998**, 468. (9) Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **1997**, *119*, 3409. (10) Ryan, J. H.; Stang, P. J. *J. Org. Chem.* **1996**, *61*, 6162. (11) Farina, F. et al. *The Stille Reaction*; John Wiley and Sons, Inc.: New York, 1998. (12) Paley, R. S. et al. *J. Org. Chem.* **1997**, *62*, 6326. (13) Blaskovich, M. A.; Kahn, M. *ibid.* **1998**, *63*, 1119. (14) Gingras, M. *Tetrahedron Lett.* **1991**, *32*, 7381. (15) García Martínez, A. et al. *Synlett* **1993**, 587. (16) Idem *Tetrahedron Lett.* **1992**, *33*, 7787. (17) García Martínez, A. et al. *Synlett* **1994**, 1047.

Serine Derivatives in Organic Synthesis

This review is dedicated to my parents, Kamal and Shripad, for their unending support and blessings.

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Outline

1. Introduction

Since the interesting discovery of serine as a component of serecine, a silk protein,[1] it has been found in numerous biomolecules and has been extensively employed as a building block for peptides and proteins.

To the organic chemist, serine represents an attractive synthetic template for several reasons: (1) It is a naturally occurring, chiral amino acid, both isomers of which are readily available and economical raw materials; (2) each of the three carbons bears a functionality that can be selectively protected and/or elaborated; (3) a number of transformations can be carried out while maintaining optical integrity; (4) finally, the skeletons of the corresponding 2-amino-1,3-diol or α-amino acid, alanine, are part of many naturally occurring substances, allowing researchers to make use of the whole or a part of the skeleton by exploiting the "handle" that serine (and threonine) possess.

This review highlights the recent synthetic applications of serine and, to a lesser extent, those of threonine.[2] Since a majority of the applications reported in the literature involve functionalities at the terminal carbons, emphasis will be placed on the utility of these functionalities. **Figure 1** shows some of the more frequently employed serine-derived building blocks.

2. Protection and Functionalization of the Termini

In general, a key aspect of synthetic elaboration is the judicious selection of protecting and activating groups. A variety of protecting and activating groups have been employed for all three serine termini. For example, the nitrogen terminus is most commonly protected as a carbamate (Boc,[3a,3b] Cbz,[3b] or Fmoc[3e]) using standard chemistry.[3] The trityl group has been employed to a lesser extent and is introduced by reacting serine with trityl chloride after the oxygen sites have been blocked with TMS.[3c] More recently, the *N,N*-dibenzyl group has been added to the repertoire of N-protecting groups (**eq 1**).[3d]

Activation of the nitrogen as a sulfonamide or carbamate is required in certain reactions (vide infra). Tosyl,[3b] Boc,[3b] Cbz,[3b] and Pmc (2,2,5,7,8-pentamethylchroman-6-sulfonyl)[4] groups are most commonly employed for this purpose.

A variety of groups have been employed for protecting the primary alcohol in serine: Benzyl,[5] *tert*-butyldimethylsilyl (TBDMS),[6] trityl,[7] and *tert*-butyl[5b,8] are the most common ones. In this case, however, preprotection of the carboxylic and/or amino group may be necessary.

Wang and co-workers[5b] have reported an interesting preparation of *O*-benzyl- or *O*-*tert*-butylserine. Serine (or threonine) is first treated with boron trifluoride to form a cyclic oxazaborolidinone. The crude oxazaborolidinone is reacted either with isobutylene under acid catalysis or with benzyl trichloroacetimidate/BF_3 to form the corresponding O-protected oxazaborolidinone. Workup with 1 M sodium hydroxide liberates the O-protected acid (**Scheme 1**).

Simultaneous nitrogen and oxygen protection with an isopropylidene group[9] or as an oxazolidinone[4g,10] obviates the need for an independent hydroxyl protection. Boc and isopropylidene groups can be removed either simultaneously[11] or in a stepwise manner,[11b,12] whereas the oxazolidinone may be hydrolyzed under suitable conditions.[10b]

Alcohol group *activation* may be accomplished in a variety of ways as well. Conversion to good leaving groups, such as halides and sulfonate esters,[13] and to aziridines,[14] β-lactones,[15] and β-lactams[16] are two methods that have been employed most frequently.

Protection/activation of the carboxyl group as a suitable ester is most common. In the majority of the reactions at this carbon, the carboxylate group is reduced to the corresponding aldehyde or alcohol. Consequently, the ester functionality provides sufficient activation.

3. Reactions at the Hydroxyl-Bearing Carbon (C-3)

In a majority of the reactions at the C-3 carbon, the hydroxyl group is activated to function either as an electrophile or as a nucleophile. Serine may thus be viewed as an alanine cation or anion equivalent.

3.1. Reactions of 3-Halo- and 3-Sulfonyloxyalanines

Leaving groups such as halogens or sulfonate esters are the simplest hydroxyl group activators. Jacquier, Viallefont, and co-workers studied the nucleophilic displacement reactions of organocuprates with serine-derived β-iodoalanine or β-tosyloxyalanine (**Scheme 2**).[13a] Extensive elimination was observed with β-tosyloxyalanine for all but the most "non-basic" cuprates. Displacement products were obtained in good yield (up to 75%) and high optical purity (>95% ee by ^{1}H NMR) when β-iodoalanine was employed and the

reactions carried out in ether. Other nucleophiles were successfully reacted and include thiolate,[17] selenolate,[18] and tellurolate[18b] anions.

More recently, Dugave and Menez[19] successfully displaced the iodide with malonates and other active methylene compounds (**Scheme 3**), including O'Donnell's Schiff bases.[20] Nitrogen blocking with the bulky trityl or 9-phenylfluorenyl[21] group allowed these researchers to effectively prevent α-proton abstraction, and to protect the α-ester against saponification. It was thus possible to prepare γ-carboxyglutamate and other γ-functionalized amino acids by this method. Dugave and co-workers illustrated the utility of this approach further by synthesizing lanthionines, major constituents of lantibiotics.[22]

Motherwell's use of a radical chemistry approach (tributyltin hydride/AIBN) to prepare a serine glycopeptide analog provides an interesting twist to the use of 3-haloalanines in synthesis (**eq 2**).[23]

3.2. Reactions of Aziridines

Another approach for the activation of the hydroxyl group involves the conversion of serine and threonine to N-substituted aziridine derivatives. An electron-withdrawing group on the nitrogen, e.g., sulfonate or carbamate, or Lewis acid catalysis provides the driving force for efficient ring opening. Regioselectivity of ring opening, potential for a nucleophilic attack on the carboxylate functionality (in the case of aziridine carboxylates), conservation of optical integrity during preparation and/or reactions, and efficient introduction and removal of protecting groups are some of the challenges faced by researchers utilizing this approach.

Nakajima and co-workers[2g,14,24b,c] have converted serine and threonine to highly reactive, optically pure aziridine derivatives following the protocol in **Scheme 4**. Reactions of these aziridine derivatives with a variety of noncarbon[2g,14,24,25] and carbon[26] nucleophiles have been reported.

Baldwin and co-workers[27] studied the ring-opening of aziridinecarboxylates with carbon nucleophiles. As expected, organolithiums and Grignard reagents preferentially attacked the carboxylate carbon. Use of a bulky *tert*-butyl ester did not change the outcome. However, higher-order organocuprates or copper-catalyzed Grignard reactions provided significantly better selectivity. Still, in most of the reactions, product mixtures arising from attack on C-3 (desired), C-2 (undesired), and/or the carboxylate carbon resulted (**eq 3**). Optical integrity was maintained in essentially all

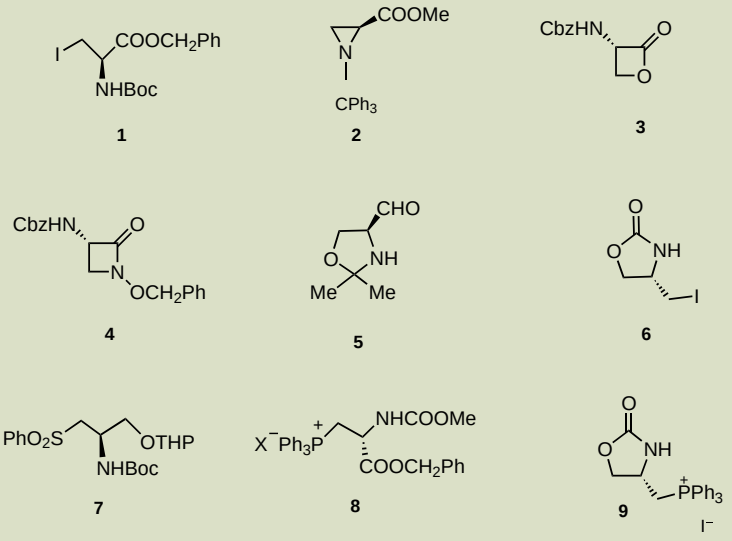
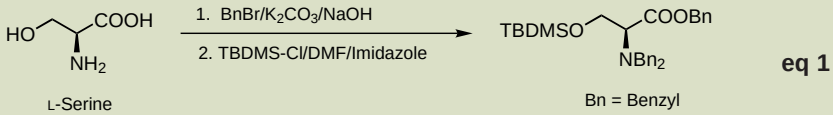
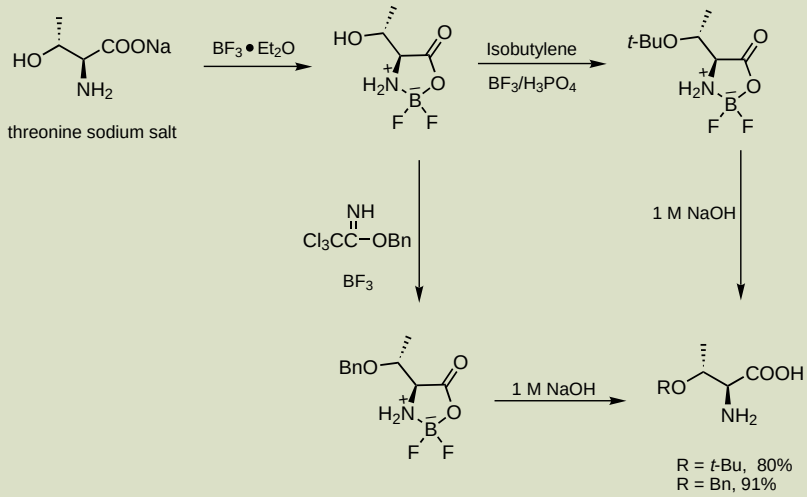


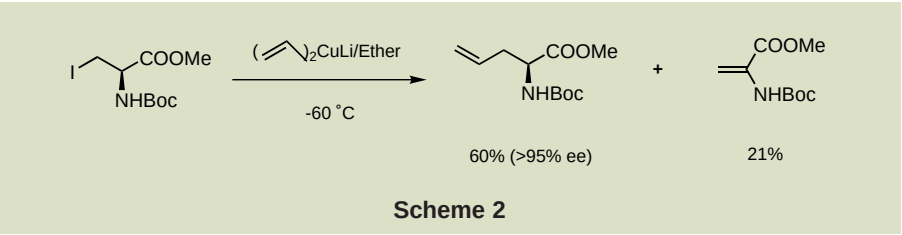
Figure 1



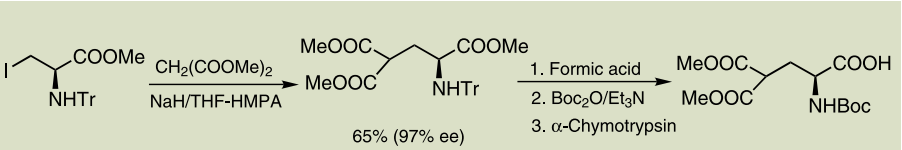
eq 1



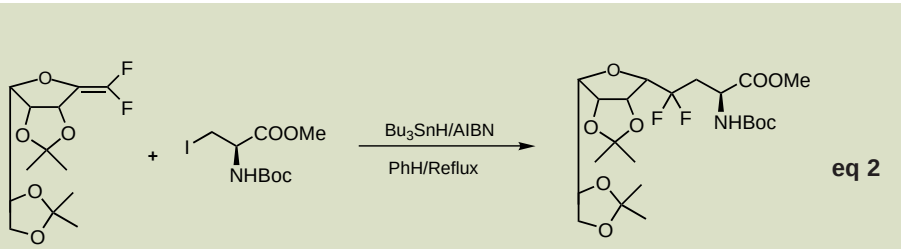
Scheme 1



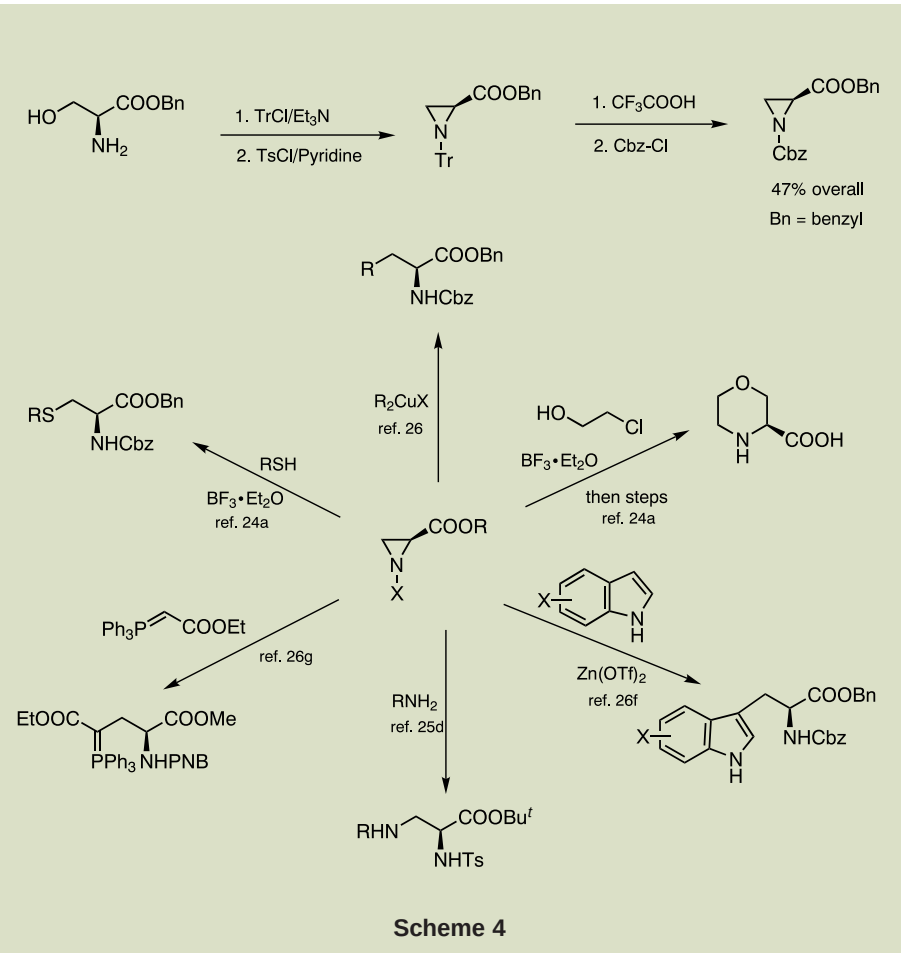
Scheme 2



Scheme 3



eq 2



Scheme 4

cases (comparison of optical rotations with those of authentic samples), confirming that little or no racemization occurred during the preparation or reactions of the aziridines. Removal of the tosyl protecting group proved to be a major challenge in molecules bearing sensitive functionality.

A variety of solutions to the preceding problems have been developed. For example, a diphenylphosphinoyl[28] group or a Pmc group[4] has been employed in place of the tosyl group to make it easier to remove the protecting group at the end of the sequence. Church and Young discovered that the free carboxylic acid reacts smoothly with carbon nucleophiles, including organocuprate[4] and organolithium[26a] species, and leads to products arising from a C-3 attack (**Scheme 5**).

van Boom[29] discovered that diethoxytriphenylphosphorane[30] converts serine benzyl ester efficiently into the corresponding aziridine. Threonine benzyl ester, however, did not provide the requisite aziridine with the same reagent. It was possible to prepare this latter aziridine efficiently using a modification of Baldwin's sulfamidate chemistry (**Scheme 6**).[31a] These two modifications allow easier access to appropriately functionalized aziridine nuclei.

Baldwin's group prepared *tert*-butyl *N*-Boc-aziridinecarboxylate using the above approach. This ester and the *tert*-butyl amide (prepared by conventional Mitsunobu chemistry) both reacted smoothly at C-3 with copper-"catalyzed" Grignard reagents at low temperature (–20 to –50 °C) to provide the desired products in high yield and optical purity. Higher temperatures resulted in increased by-product formation (**eq 4**).[26d]

An interesting example of the application of aziridine carboxylates in synthesis is found in Harada's preparation of chiral diazepines possessing highly potent 5-HT_3 receptor antagonist activity (**Scheme 7**).[25b] The synthesis of D-labeled propargylglycine (**Scheme 5**), a suicide substrate, further illustrates the utility of this approach.[26a]

Aziridines, in which the carboxylate functionality of serine has been reduced, have also been prepared and utilized in synthesis,[26b,32] as illustrated by the report from Bergmeier and Seth.[26b] When treated with a variety of organocuprates, serine-derived *N,O*-ditosylaziridinemethanol underwent a ring-opening/ring-closing sequence (similar to Sharpless's glycidyl tosylate chemistry[33]), thus providing ready access to scalemic aziridines (**Scheme 8**).

3.3. Reactions of β-Lactones

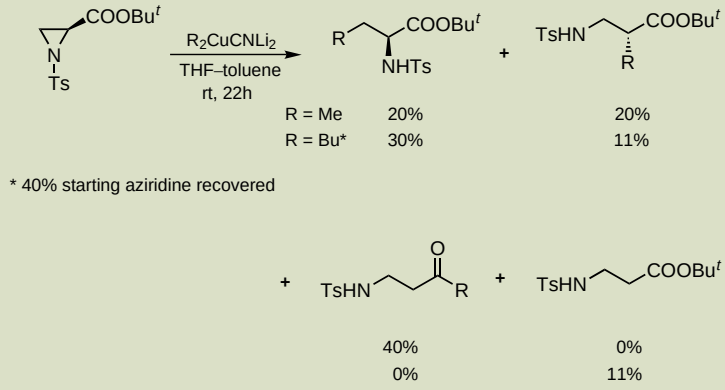
Vederas and co-workers took advantage of the β-hydroxycarboxylate moiety of serine to convert it to a highly reactive β-lactone derivative.[15,34] In this approach, Boc-, Cbz-, or Fmoc-serine are subjected to the Mitsunobu reaction conditions.[35] The resulting crystalline lactones are stable when cold (-20 °C) or can be reacted in situ. They are valuable building blocks that react readily with nitrogen,[36] sulfur,[37] carbon,[38] selenium,[39a] and phosphorus[39b,c] nucleophiles to provide the corresponding amino acid analogs (**Scheme 9**). Other approaches for the preparation of these lactones had been employed previously with limited success.[40]

Except with "hard" nucleophiles such as ammonia and alkoxide, lactone ring opening preferably occurs via attack on the β-carbon. A number of preparative modifications and improved reaction conditions, introduced since the original report, have facilitated the preparation of the lactones and have resulted in significantly less by-products. For example, use of polymer-supported dimethyl azodicarboxylate simplifies purification of the β-lactones.[34d] For substrates containing a functionality that is sensitive to the deprotection protocol, the trifluoroacetate or *p*-toluenesulfonate salt of the unprotected lactone has been prepared and reacted in a manner similar to that of the protected lactone.[34c] The problem of amide formation via attack of amines on the carbonyl carbon has been controlled by using silylated amines as nucleophiles.[34a] Lastly, a recent preparative modification by Liskamp and co-workers, which utilizes conventional peptide chemistry (BOP-Cl/HOBT in dichloromethane) for the cyclization of trityl serine and threonine,[41] is likely to further enhance the utility of this important serine derivative. Schreiber's trapoxin synthesis (**Scheme 10**)[38a] and Poulter's synthesis of a farnesyltransferase analog[42] serve as illustrative examples.

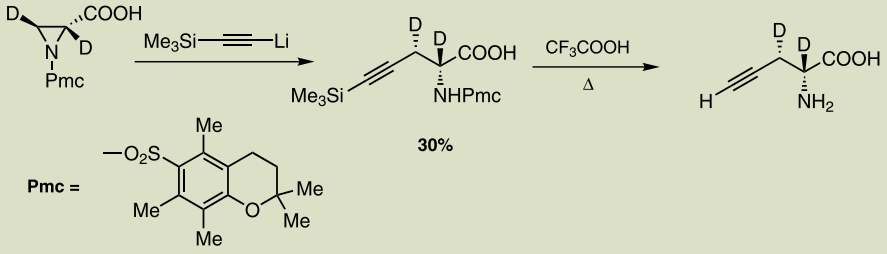
3.4. Reactions of β-Lactams and Sulfamidates

Miller and co-workers converted serine and threonine to the corresponding β-lactams via a two-step process.[2h,16] These lactams are stable, crystalline solids and may be used either as building blocks or may be incorporated as intact lactam units. Miller's synthesis of a mycobactin analog[43] (**Scheme 11**) and Kahn's synthesis of a prolylazetidinone[44] exemplify the utility of these lactams in synthesis.

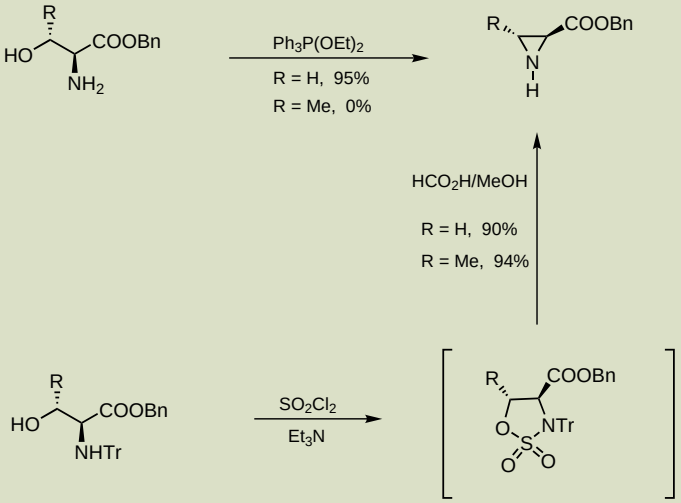
In 1990, Baldwin reported the conversion of serine to a sulfamidate intermediate[31a] (analogous to Sharpless's cyclic sulfate



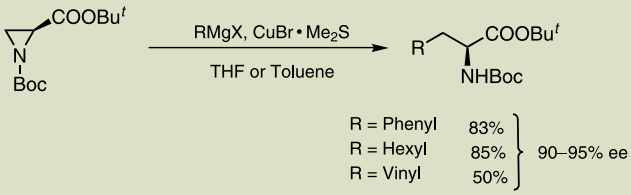
eq 3



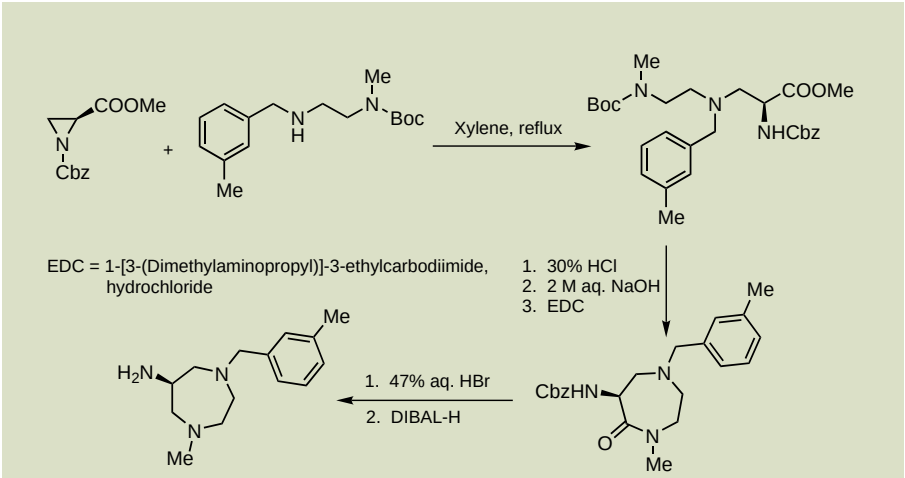
Scheme 5



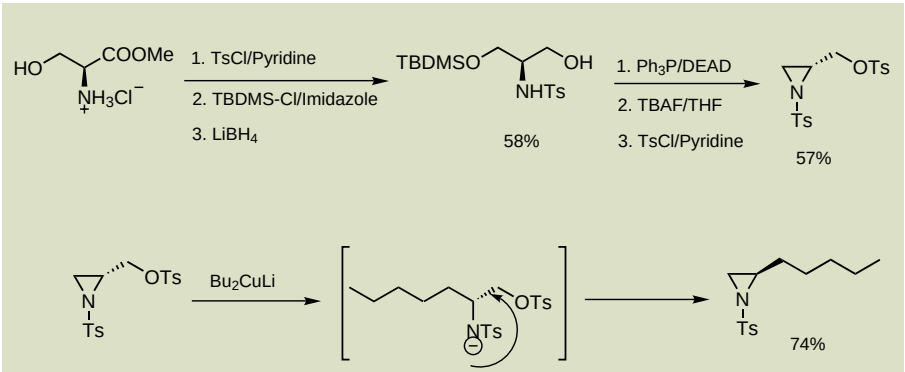
Scheme 6



eq 4



Scheme 7



Scheme 8

intermediate[45]) and the reactions of the latter with nucleophiles. The sulfamidate was readily prepared by reacting *N*-benzylserine *tert*-butyl ester with thionyl chloride, followed by oxidation. This intermediate reacted readily with noncarbon nucleophiles under acidic or neutral conditions giving products that resulted from β-substitution. Products arising from α-substitution were completely absent. However, only a limited success was achieved with carbon nucleophiles (**Scheme 12**). van Boom has since modified the two-step preparation protocol to a single-step condensation with sulfuryl chloride (**Scheme 6**).[29]

3.5. Alanine Anion Equivalents

Relatively few applications of serine-based alanine or alaninol anion equivalents (e.g., **7-9**) have been reported.[46-49]

A good example of this class of serine derivatives is the organozinc reagent **10** (**Scheme 13**) developed by Jackson and co-workers.[50,51] The iodoalanine derivative **1** was converted to a nucleophilic zinc species by reacting it with a zinc–copper couple under sonication. Pd^0- or Pd^{2+}-catalyzed coupling with acid chlorides and aryl iodides resulted in the formation of the corresponding γ-keto-α-amino acids and substituted phenylalanines, respectively. Moderate to high yields were realized in most cases, and the products were formed with high optical purity (by ^{1}H NMR of MTPA amides). Zinc-mediated dehalogenation was observed as a minor side reaction. *o*-Substituted aryl and heteroaromatic iodides reacted poorly (**Scheme 13**).[51c]

More recently, the same group extended this method to include condensation of allylic and propargylic halides with the alanine anion equivalent, providing an efficient entry into alkenyl and allenyl α-amino acids. A more reactive zinc–copper reagent was employed in these reactions.[51b] Walker's synthesis of all three regioisomers of pyridylalanine serves as an example of the synthetic utility of the organozinc intermediate (**eq 5**).[52]

4. Reactions at the Carboxylic Carbon (C-1)

In most of the reactions at the carboxylic terminus, the acid or ester is typically reduced to the alcohol or aldehyde. These are then subjected to appropriate reactions in order to incorporate the serine moiety in target molecules. Incorporation of the serinol moiety in a PNA derivative (**Scheme 14**),[53] Ernst's diastereoselective synthesis of 1,2-diamines by a palladium-catalyzed aza-Claisen rearrangement,[54] Corey's synthesis of a lactacystin analog,[55] conversion of serine derivatives into chiral, substituted pyrrolidines (**Scheme 15**),[56] sphingosine synthesis,[57] and Dondoni's synthesis of asparagine isosteres,[58] are just a few examples of the elaboration of the carboxylic carbon.

4.1. Serinal Formation

A number of serine and threonine aldehydes differing in the hydroxyl and nitrogen group protection have been prepared and used in a variety of reactions.[2i,57c,59] These aldehydes are prepared by selective reduction of the ester,[59e] by oxidation of the alcohol derived from the ester,[60] or by LAH reduction of *N*-methoxy-*N*-methylserinamide.[59a] For example, Reetz has successfully used an *N,N*-dibenzyl and *O*-TBDMS protection and alcohol oxidation sequence to prepare a serinal derivative in high yield and optical purity (**eqs 1 and 6**).[3d]

Of all the serinals introduced, Garner's aldehyde has been utilized the most for a variety of reasons. It is readily prepared on a large scale with reasonably high optical purity (93–95% ee by NMR/HPLC), it offers excellent stereoselectivity in many of its reactions, and is readily deprotected under mild conditions. In addition, since its introduction by Professor Garner's group in 1984, many groups have modified its preparation;[11b,60-63] both isomers of this product are now available commercially.[64] Merino's interesting approach to α,β-diamino acids utilizes Garner's aldehyde as a key starting material (**Scheme 16**),[65] whereas Nakagawa and co-workers have utilized Garner's aldehyde in a stereoselective preparation of PPMP (**Scheme 17**).[66]

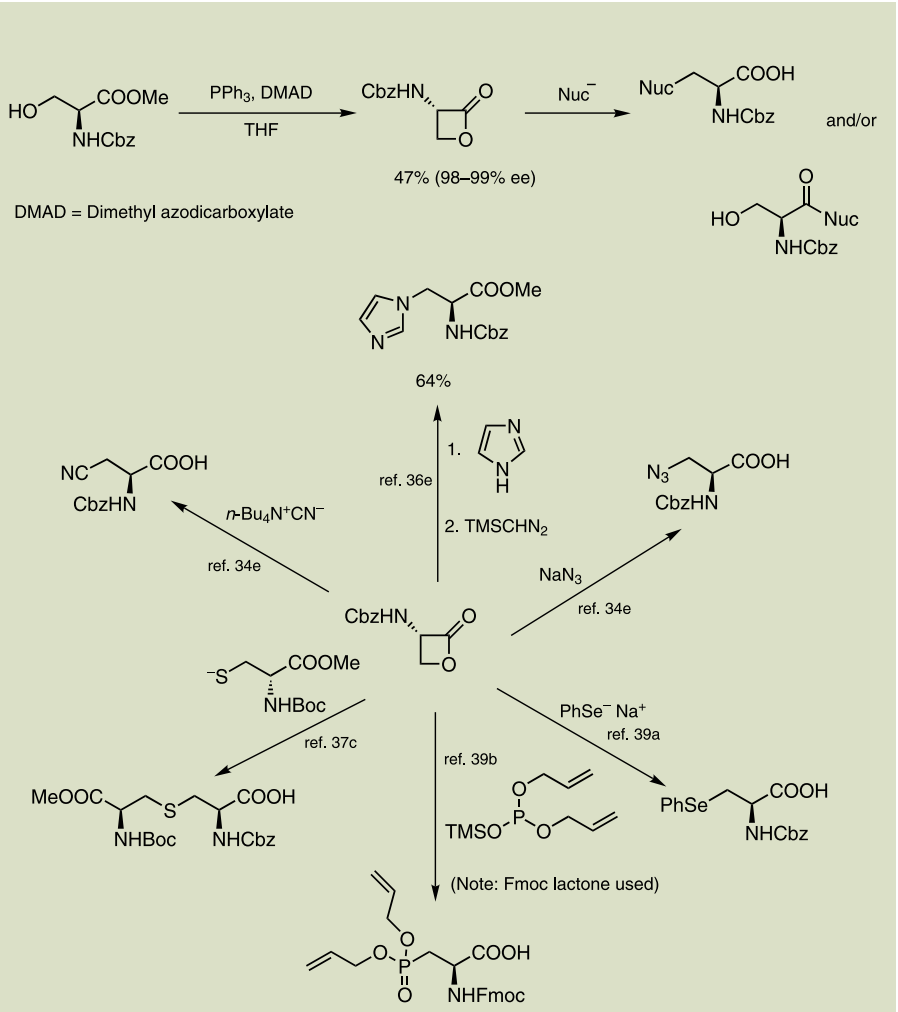
Joullié and co-workers found that increasing the steric bulk on the oxazolidine ring (e.g., replacement of the methyl substituents with a cyclohexyl ring) resulted in improved diastereoselection in the reactions of Grignard reagents with Garner's aldehyde.[11b] Rama Rao and co-workers took advantage of this observation in their studies directed at vancomycin synthesis. The addition of a substituted phenyl Grignard

reagent proceeded with high anti:syn selectivity (8:1) and chemical yield (75%). The resulting adduct was elaborated into the E ring phenylalanine component of vancomycin.[67]

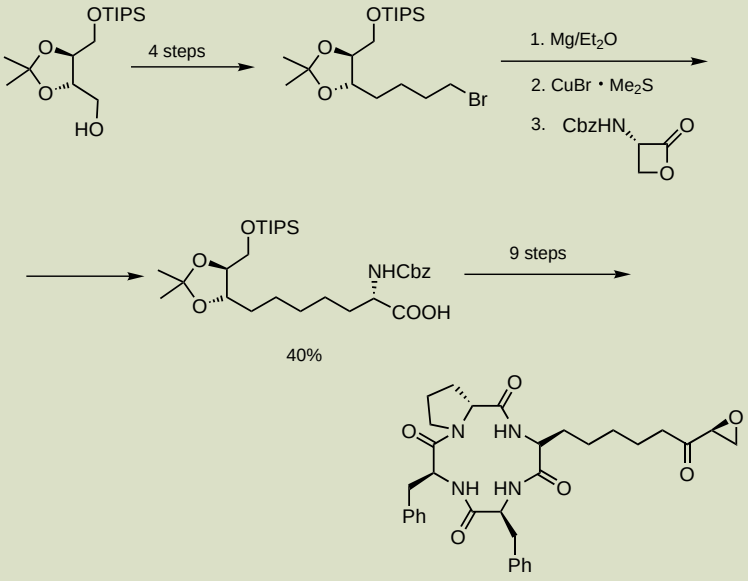
4.2. Alaninol Equivalents

Sibi and co-workers have exploited the carboxylate terminus to develop alaninol cation and anion equivalents.[48,68] Oxazolidinone **12** serves as a key intermediate in this approach. This intermediate was prepared from serine methyl ester in two steps and relatively high optical purity (93–95% by NMR and optical rotation).[48] Iodide **6**, derived from **12**, was converted to Wittig reagent **14**, which was used in slaframine synthesis.[68c] On the other hand, tosylate **13** underwent nucleophilic displacement with Gilman cuprates and copper-complexed Grignard reagents to provide chiral oxazolidinones (and unnatural amino alcohols and α-amino acids by extrapolation) in high yield and optical purity.[68d] Knochel and co-workers reported a similar study with cuprate **15**.[47] The ester intermediate **11** was also converted to a diphenylmethyloxazolidinone,[68c] which was employed successfully in Evans-type chemistry. An interesting recent report from the Sibi group highlights organotin Lewis acid catalyzed radical cyclizations of *N*-enoyloxazolidinones to bicyclic products in high yield and diastereoselectivity (**Scheme 18**).[68a]

Finally, Sasaki and co-workers have utilized alaninol anion equivalent **7** to prepare a variety of unnatural amino acids in high yield and purity (**Scheme 19**).[46,69]



Scheme 9



Scheme 10

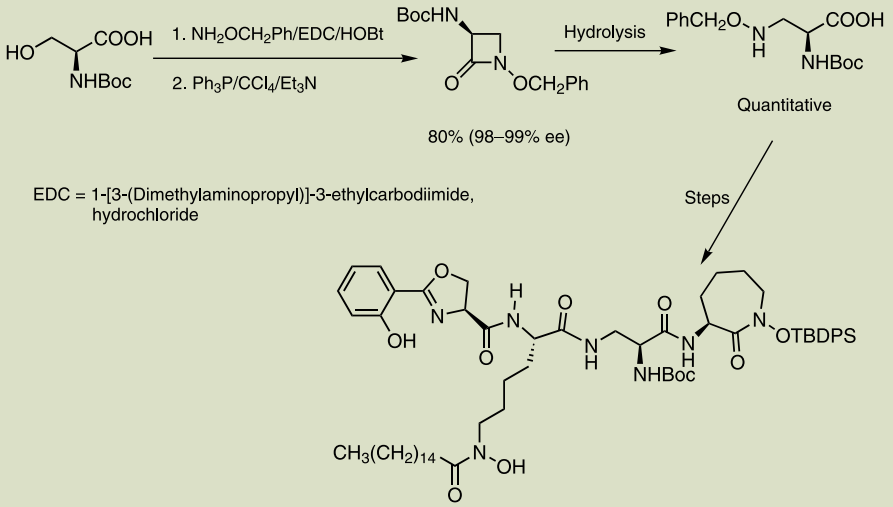
5. Conclusion

Over the last few decades, an increasing number of researchers have exploited serine and threonine—two valuable members of the chiral amino acid pool—in a variety of approaches that have resulted in elegant manipulations of their basic skeletons. As new ideas on how to exploit serine and threonine in synthesis emerge, the importance of these two compounds to synthetic chemists will steadily increase.

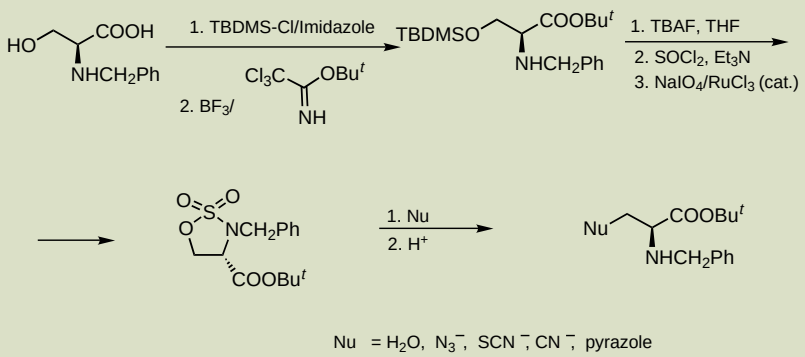
6. References and Notes

(1) *Chemistry of the Amino Acids*; Greenstein, J. P., Winitz, M., Eds.; Robert E. Krieger Publishing Company: Malabar, FL, 1984; p 2203.

(2) For general reviews of α-amino acid synthesis, see: (a) Williams R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford, U.K., 1989. (b) Duthaler, R.O. *Tetrahedron* **1994**, *50*, 1539. (c) O'Donnell, M.J.; Bennett, W.D. *Tetrahedron* **1988**, *44*,



Scheme 11



Scheme 12

5389. For reviews of β-amino acid synthesis, see: (d) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley–VCH: New York, NY, 1996. (e) Cole, D.C. *Tetrahedron* **1994**, *50*, 9517. For reviews of aziridine chemistry, see: (f) Tanner, D. *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 591. (g) Okawa, K.; Nakajima, K.; Tanaka, T. *J. Synth. Org. Chem. (Japan)* **1984**, *42*, 390. For a review of β-lactam chemistry, see: (h) Miller, M.J. *Acc. Chem. Res*. **1986**, *19*, 49. For reviews of chiral amino aldehydes in synthesis, see: (i) Reetz, M.T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531. (j) Jurczak, J.; Golebiowski, A. *The Synthesis of Antibiotic Amino Sugars from α-Amino Aldehydes, in Antibiotics and Antiviral Compounds, Chemical Synthesis and Modification*; VCH: Weinheim, Germany, 1993. (k) Jurczak, J.; Golebiowski, A. *Chem. Rev*. **1989**, *89*, 149.

(3) (a) Okawa, K. *Bull. Chem. Soc. Jpn*. **1956**, *29*, 486. (b) Jurczak, J.; Gryko, D.; Kobrzycka, E.; Gruza, H.; Prokopowicz, P. *Tetrahedron* **1998**, *54*, 6051. (c) Barlos, K.; Papaioannou, D.; Theodoropoulos, D. *J. Org. Chem.* **1982**, *47*, 1324. (d) Reetz, M.T.; Drewes, M.W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141. (e) Schon, I.; Kisfaludy, L. *Synthesis* **1986**, 303.

(4) Church, N.J.; Young, D.W. *Tetrahedron Lett.* **1995**, *36*, 151.

(5) (a) Sugano, H.; Miyoshi, M. *J. Org. Chem*. **1976**, *41*, 2352. (b) Wang, J.; Okada, Y.; Li, W.; Yokoi, T.; Zhu, J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 621.

(6) Orsini, F.; Pelizzoni, F.; Sisti, M.; Verotta, L. *Org. Prep. Proc. Intl.* **1989**, *21*, 505.

(7) Barlos, K.; Gatos, D.; Koutsogianni, S.; Schafer, H.; Stavropolous, G.; Wenguing, Y. *Tetrahedron Lett*. **1991**, *32*, 471.

(8) Wuensch, E.; Jentsch, J. *Chem. Ber.* **1964**, *97*, 2490.

(9) Garner, P.; Park, J.M. *J. Org. Chem*. **1987**, *52*, 2361.

(10) Herborn, C.; Zietlow, A.; Steckhan, E. *Angew. Chem., Int. Ed. Engl*. **1989**, *28*, 1399.

(11) (a) Villard, R.; Fotiadu, F.; Buono, G. *Tetrahedron: Asymmetry* **1998**, *9*, 607. (b) Williams, L.; Zhang, Z.; Shao, F.; Carroll, P. J.; Joullie´, M.M. *Tetrahedron* **1996**, *52*, 11673.

(12) Imashiro, R.; Sakurai, O.; Yamashita, T.; Horikawa, H. *Tetrahedron* **1998**, *54*, 10657.

(13) (a) Bajgrowicz, J.A.; El Hallaoui, A.; Jacquier, R.; Pigiere, Ch.; Viallefont, Ph. *Tetrahedron Lett*. **1984**, *25*, 2759. (b) Bajgrowicz, J.A.; El Hallaoui, A.; Jacquier, A.; Pigiere, Ch.; Viallenfont, Ph. *Tetrahedron* **1985**, *41*, 1833.

(14) Nakajima, K.; Takai, F.; Tanaka, T.; Okawa, K. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1577.

(15) Arnold, L.D.; Kalantar, T.H.; Vederas, J.C. *J. Am. Chem. Soc.* **1985**, *107*, 7105.

(16) Miller, M.J.; Mattingly, P.G.; Morrison, M.A.; Kerwin, J.F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 7026.

(17) Zioudrou, C.; Wilchek, M.; Patchornik, A. *Biochemistry* **1965**, *4*, 1811.

(18) (a) Theodoropoulos, D.; Schwartz, I.L.; Walter, R. *Biochemistry* **1967**, *6*, 3927. (b) Stocking, E.M.; Schwarz, J.N.; Senn, H.; Salzmann, M.; Silks, L.A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2443.

(19) Dugave, C.; Menez, A. *J. Org. Chem.* **1996**, *61*, 6067.

(20) Aldrich Chemical Co., catalog numbers **22,254-2**, **36,448-7** and **25,265-4.**

(21) Koskinen, A.M.P.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1859. Note: 9-Bromo-9-phenylfluorene employed for the introduction of the 9-phenylfluorenyl group is available from Aldrich (cat. no. **36,887-3**).

(22) Dugave, C; Menez, A. *Tetrahedron: Asymmetry* **1997**, *8*, 1453.

(23) Herpin, T.F.; Motherwell, W.B.; Weibel, J.-M. *Chem. Commun*. **1997**, 923.

(24) (a) Kogami, Y.; Okawa, K. *Bull. Chem. Soc. Jpn*. **1987**, *60*, 2963. (b) Nakajima K.; Okawa, K. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1565. (c) Nakajima, K. *Bull Chem. Soc. Jpn.* **1982**, *55*, 3878; and references cited therein.

(25) (a) Harada, H.; Morie, T.; Suzuki, T.; Yoshida, T.; Kato, S. *Tetrahedron* **1998**, *54*, 10671. (b) Kato, S.; Harada, H.; Morie, T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3219. (c) Farthing, C.N.; Baldwin, J.E.; Russell, A.T.; Schofield, C.J.; Spivey, A.C. *Tetrahedron Lett.* **1996**, *37*, 5225; and references cited therein. (d) Solomon, M.E.; Lynch, C.L.; Rich, D.H. *Tetrahedron Lett.* **1995**, *36*, 4955; and references cited therein. (e) Imae, K.; Kamachi, H.; Yamashita, H.; Okita, T.; Okuyama, S.; Tsuno, T.; Yamasaki, T.; Sawada, Y.; Ohbayashi, M. *J. Antibiot*. **1991**, *44*, 76. (f) See references 2–20 cited in reference 4.

(26) (a) Church, N.J.; Young, D.W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1475. (b) Bergmeier, S. C.; Seth, P.P. *J. Org. Chem*. **1997**, *62*, 2671. (c) Funaki, I.; Bell, R.P.L.; Thijs, L.; Zwanenberg, B. *Tetrahedron* **1996**, *52*, 12253. (d) Baldwin, J.E.; Farthing, C.N.; Russell, A.T.; Schofield, C.J.; Spivey, A.C. *Tetrahedron Lett*. **1996**, *37*, 3761; and references cited therein. (e) Shima, I.; Shimazaki,N.; Imai, K.; Hemmi, K.; Hashimoto, M. *Chem. Pharm. Bull.* **1990**, *38*, 564. (f) Sato, K.; Kozikowski, A.P. *Tetrahedron Lett.* **1989**, *30*, 4073. (g) Baldwin, J.E.; Adlington, R.M.; Robinson, N.G. *J. Chem. Soc., Chem. Commun.* **1987**, 153.

(27) Baldwin, J.E.; Spivey, A.C.; Schofield, C.J.; Sweeney, J.B. *Tetrahedron* **1993**, *49*, 6309.

(28) Osborn, H.M.I.; Sweeney, J.B.; Howson, W. *Tetrahedron Lett.* **1994**, *35*, 2739. Note: This protecting group did not work well in reactions of aziridinecarboxylates.

(29) (a) Kuyl-Yeheskiely, E.; Dreef-Tromp, C.M.; van der Marel, G.A.; van Boom, J.H. *Recl. Trav. Chim. Pay-Bas* **1989**, *108*, 314. (b) Kuyl-Yeheskiely, E.; Lodder, M.; van der Marel, G.A.; van Boom, J.H. *Tetrahedron Lett.* **1992**, *33*, 3013.

(30) (a) Chang, B.C.; Conrad, W.E.; Denney, D.B.; Denney, D.Z.; Edelman, R.; Powell, R.L.; White, D.W. *J. Am. Chem. Soc.* **1971**, *93*, 4004. (b) Robinson, P.L.; Barry, C.N.; Bass, S.W.; Jarvis, S.E.; Evans, S.A., Jr. *J. Org. Chem.* **1983**, *48*, 5396.

(31) (a) Baldwin, J.E.; Spivey, A.C.; Schofield, C.J. *Tetrahedron: Asymmetry* **1990**, *1*, 881. (b) For an updated study of this reaction, see Pilkington, M.; Wallis, J.D. *J. Chem. Soc., Chem. Commun.* **1993**, 1857.

(32) (a) Lim, Y.; Lee, W.K. *Tetrahedron Lett.* **1995**, *36*, 8431. (b) Ho, M.; Chung, J.K.K.; Tang, N. *Tetrahedron Lett.* **1993**, *34*, 6513.

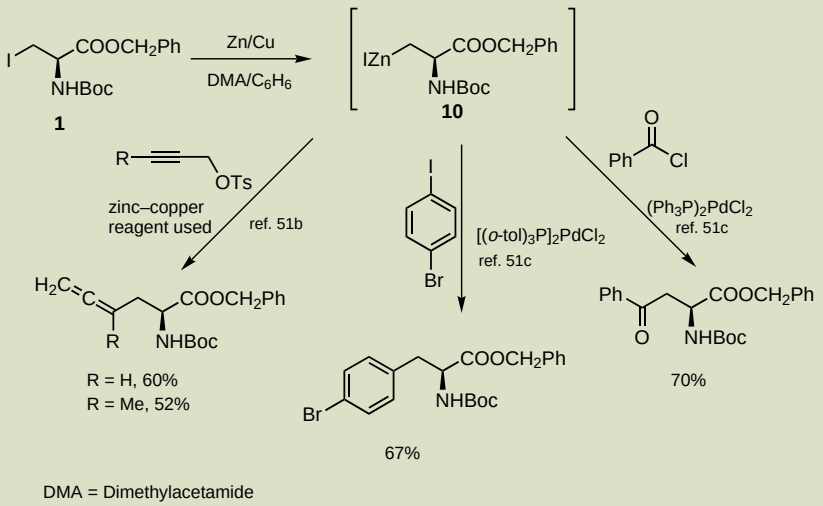
(33) Klunder, J.M.; Onami, T.; Sharpless, K.B. *J. Org. Chem.* **1989**, *54*, 1295.

(34) (a) Ratemi, E.S.; Vederas, J.C. *Tetrahedron Lett.* **1994**, *35*, 7605. (b) Pansare, S.V.; Huyer, G.; Arnold, L.D.; Vederas, J.C. *Org. Synth*. **1992**, *70*, 1. (c) Pansare, S.V.; Arnold, L.D.; Vederas, J.C. *Org. Synth*. **1992**, *70*, 10 (d) Arnold, L.D.; Assil, H.I.; Vederas, J.C. *J. Am. Chem. Soc.* **1989**, *111*, 3973. (e) Arnold, L.D.; May, R.G.; Vederas, J.C. *J. Am. Chem. Soc.* **1988**, *110*, 2237.

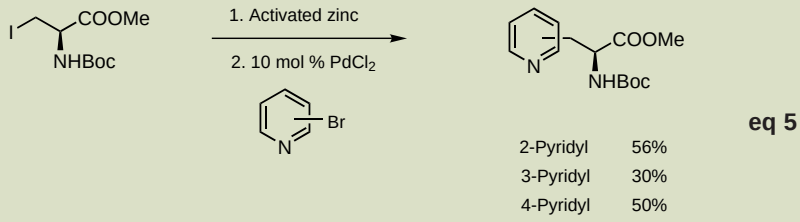
(35) Mitsunobu, O. *Synthesis* **1981**, 1.

(36) (a) Sun, G.; Uretsky, N.J.; Wallace, L.J.; Shams, G.; Weinstein, D.M.; Miller, D.D. *J. Med. Chem.* **1996**, *39*, 4430. (b) Diederichsen. U. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1886. (c) Jane, D.E.; Hoo, K.; Kamboj, R.; Deverill, M.; Bleakman, D.; Mandelzys, A. *J. Med. Chem.* **1997**, *40*, 3645. (d) Warshawsky, A.M.; Patel, M.V.; Chen, T.-M. *J. Org. Chem.* **1997**, *62*, 6439. (e) Tohdo, K.; Hamada, Y.; Shioiri, T. *Synlett* **1994**, 247.

(37) (a) Epstein, W.W.; Wang, Z. *Chem. Commun*. **1997**, 863. (b) Jungheim, L.N.; Shepherd, T.A.; Baxter, A.J.; Burgess, J.; Hatch, S.D.; Lubbehusen, P.; Wiskerchen, M.;



Scheme 13



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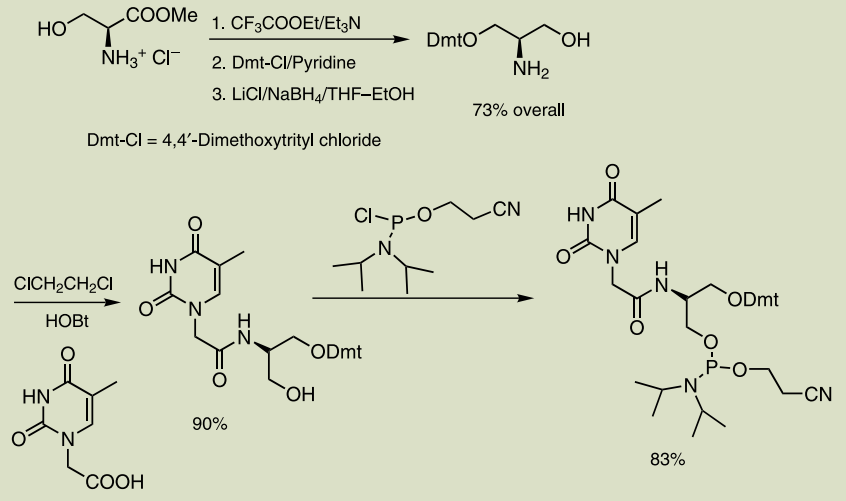
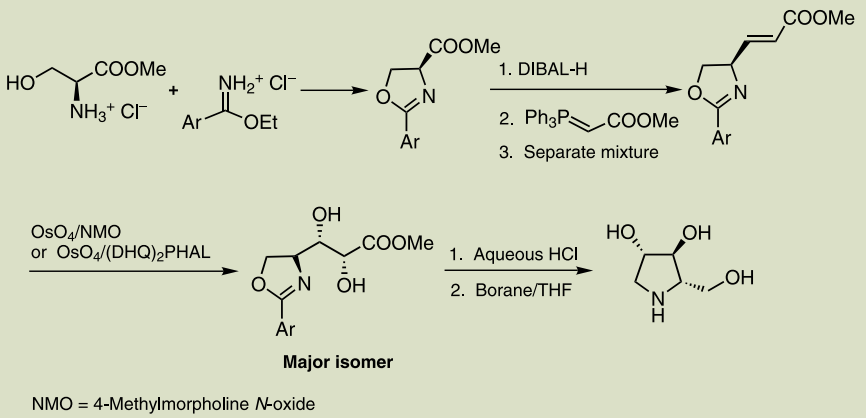
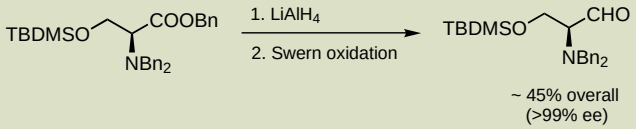


Scheme 14



Scheme 15



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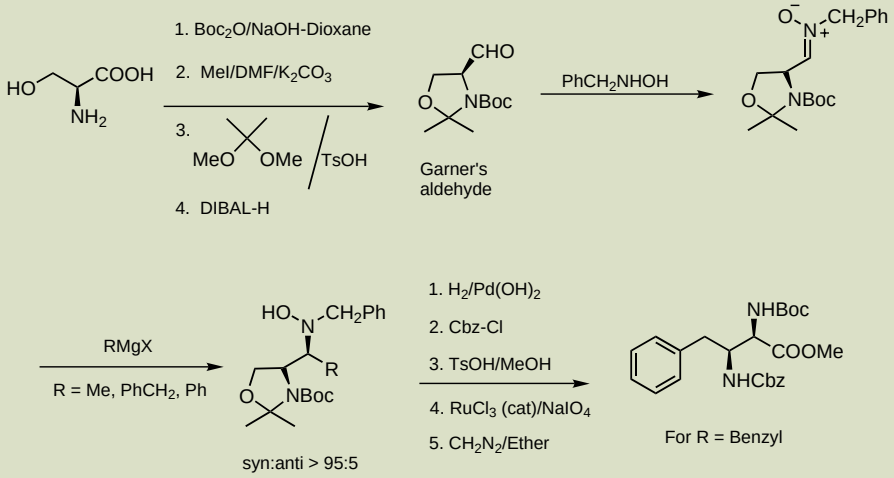


Scheme 16

Muesing, M.A. *J. Med. Chem.* **1996**, *39*, 96. (c) Shao, H.; Wang, S.H.H.; Lee, C.-W.; Oesapay, G.; Goodman, M. *J. Org. Chem.* **1995**, *60*, 2956. (d) Wolf, S.; Zhang, C.; Johnston, B.D.; Kim, C.-K. *Can. J. Chem.* **1994**, *72*, 1066.

(38) Taunton, J.; Collins, J.L.; Schreiber, S.L. *J. Am. Chem. Soc.* **1996**, *118*, 10412.

(39) (a) Sakai, M.; Hashimoto, K.; Shirama, H. *Heterocycles* **1997**, *44*, 319. (b) Lohse, P.A.; Felber, R. *Tetrahedron Lett.* **1998**, *39*, 2067. (c) Ross, F.G.; Botting, N.P.; Leeson, P.D. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2643.

(40) See references 7–9 cited in reference 15.

(41) Sliedregt, K.M.; Schouten, A.; Kroon, J.; Liskamp, R.M.J. *Tetrahedron Lett.* **1996**, *37*, 4237.

(42) Cassidy, P.B.; Poulter, C.D. *J. Am. Chem. Soc.* **1996**, *118*, 8761.

(43) Xu, Y.; Miller, M.J. *J. Org. Chem.* **1998**, *63*, 4314.

(44) Qabar, M.N.; Kahn, M. *Tetrahedron Lett.* **1996**, *37*, 965.

(45) Gao, Y.; Sharpless, K.B. *J. Am. Chem. Soc.* **1988**, *110*, 7538.

(46) Sasaki, N.A.; Dockner, M.; Chiaroni, A.; Riche, C.; Potier, P. *J. Org. Chem.* **1997**, *62*, 765; and references cited therein.

(47) Duddu, R.; Eckhardt, M.; Furlong, M.; Knoess, H.P.; Berger, S.; Knochel, P. *Tetrahedron* **1994**, *50*, 2415.

(48) (a) Sibi, M.P.; Renhowe, P.A. *Tetrahedron Lett.* **1990**, *31*, 7407. (b) Bertozzi, C.R.; Hoeprich, P.D., Jr.; Bednarski, M.D. *J. Org. Chem.* **1992**, *57*, 6092.

(49) Itaya, T.; Mizutani, A.; Iida, T. *Chem. Pharm. Bull.* **1991**, *39*, 1407.

(50) Dexter, C.S.; Jackson, R.F.W. *Chem. Commun.* **1998**, 75; and references cited therein.

(51) (a) Gair, S.; Jackson, R.F.W.; Brown, P.A. *Tetrahedron Lett.* **1997**, *38*, 3059. (b) Dunn, M.J.; Jackson, R.F.W.; Pietruszka, J.; Turner, D. *J. Org. Chem.* **1995**, *60*, 2210. (c) Jackson, R.F.W.; Wishart, N.; Wood, A.; James, K.; Wythes, M.J. *J. Org. Chem.* **1992**, *57*, 3397. (d) Jackson, R.F.W.; James, K.; Wythes, M.J.; Wood, A. *J. Chem. Soc., Chem. Commun.* **1989**, 644.

(52) (a) Walker, M.A.; Kaplita, K.P.; Chen, T.; King, H.D. *Synlett* **1997**, 169. For similar reports, see (b) Ye, B.; Burke, T.R., Jr. *J. Org. Chem.* **1995**, *60*, 2640. (c) Schmidt, B.; Ehlert, D.K. *Tetrahedron Lett*. **1998**, *39*, 3999.

(53) Benhida, R.; Devys, M.; Fourrey, J.-L.; Lecubin, F.; Sun, J.-S. *Tetrahedron Lett.* **1998**, *39*, 6167.

(54) Gonda, J.; Helland, A.-C.; Ernst, B.; Bellus, D. *Synthesis* **1993**, 729.

(55) Corey, E.J.; Li, W.-D.Z. *Tetrahedron Lett.* **1998**, *39*, 7475.

(56) (a) Huang, Y.; Dalton, D.R.; Carroll, P.J. *J. Org. Chem.* **1997**, *62*, 372. (b) Hashimoto, K.; Ohfune, Y.; Shirahama, H. *Tetrahedron Lett.* **1995**, *36*, 6235. (c) Heffner, R.J.; Joullié, M.M. *Tetrahedron Lett.* **1989**, *30*, 7021.

(57) (a) Hoffman, R.V.; Tao, J. *Tetrahedron Lett.* **1998**, *39*, 3953. (b) Hoffman, R.V.; Tao, J. *J. Org. Chem.* **1998**, *63*, 3979. (c) Andrés, J.M.; Pedrosa, R. *Tetrahedron: Asymmetry* **1998**, *9*, 2493.

(58) Dondoni, A.; Massi, A.; Marra, A. *Tetrahedron Lett.* **1998**, *39*, 6601.

(59) (a) Franciotti, M.; Mordini, A.; Taddei, M. *Synlett* **1992**, 137. (b) Reetz, M.T.; Lauterbach, L.H. *Heterocycles* **1993**, *35*, 627. (c) Endo, Y.; Masaaki, D.; Driedger, P. E.; Stabel, S.; Shudo, K. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2997. (d) Bussolari, J.C.; Beers, K.; Lalan, P.; Murray, W.V.; Gauthier, D.; McDonnell, P. *Chem. Lett.* **1998**, 787. (e) Garner, P.; Park, J.M. *J. Org. Chem.* **1987**, *52*, 2361; and references cited therein.

(60) Dondoni, A.; Perrone, D. *Synthesis* **1997**, 527.

(61) Garner, P.; Pak, J.M. *Org. Synth.* **1992**, *70*, 18.

(62) McKillop, A.; Taylor, R.J.K.; Watson, R.J.; Lewis, N. *Synthesis* **1994**, 31.

(63) For an interesting synthesis of the antipode from L-serine, see Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J.M.; Zurbano, M.M. *Synthesis* **1997**, 1146.

(64) Aldrich Chemical Co., catalog numbers **43,274-1** and **46,206-3**.

(65) (a) Merino, P.; Lanaspa, A.; Merchan, F.L.; Tejero, T. *Tetrahedron: Asymmetry* **1998**, *9*, 629. (b) Merino, P.; Franco, S.; Tejero, T. *J. Org. Chem*. **1998**, *63*, 5627.

(66) Nishida, A.; Sorimachi, H.; Iwaida, M.; Matsumizu, M.; Kawate, T.; Nakagawa, M. *Synlett* **1998**, 389.

(67) Rama Rao, A.V.; Gurjar, M.K.; Lakshmipathi, P.; Reddy, M.M.; Nagarajan, M.; Pal, S.; Sarma, B.V.N.B.S.; Tripathy, N.K. *Tetrahedron Lett.* **1997**, *38*, 7433.

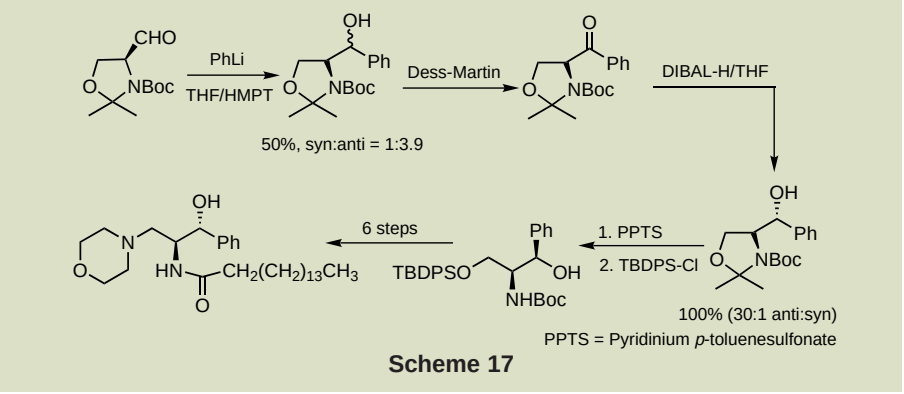
(68) (a) Sibi, M.P.; Ji, J. *J. Am. Chem. Soc.* **1996**, *118*, 3063. (b) Sibi, M.P.; Deshpande, P.K.; LaLoggia, A.J.; Christensen, J.W. *Tetrahedron Lett.* **1995**, *36*, 8961. (c) Sibi, M.P; Deshpande, P.K.; Ji, J. *Tetrahedron Lett.* **1995**, *36*, 8965. (d) Sibi, M.P.; Rutherford, D.; Sharma, R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1675. (e) Sibi, M.P.; Christensen, J.W.; Li, B.; Renhowe, P.A. *J. Org. Chem.* **1992**, *57*, 4329.

(69) For selected Sasaki work, see: (a) Sagnard, I.; Sasaki, N.A.; Chiaroni, A.; Riche, C.; Potier, P. *Tetrahedron Lett.* **1995**, *36*, 3149. (b) Sasaki, N.A.; Pauly, R.; Fontaine, C.; Chiaroni, A.; Riche, C.; Potier, P. *Tetrahedron Lett.* **1994**, *35*, 241. (c) Sasaki, N.A.; Hashimoto, C.; Potier, P. *Tetrahedron Lett.* **1987**, *28*, 6069.

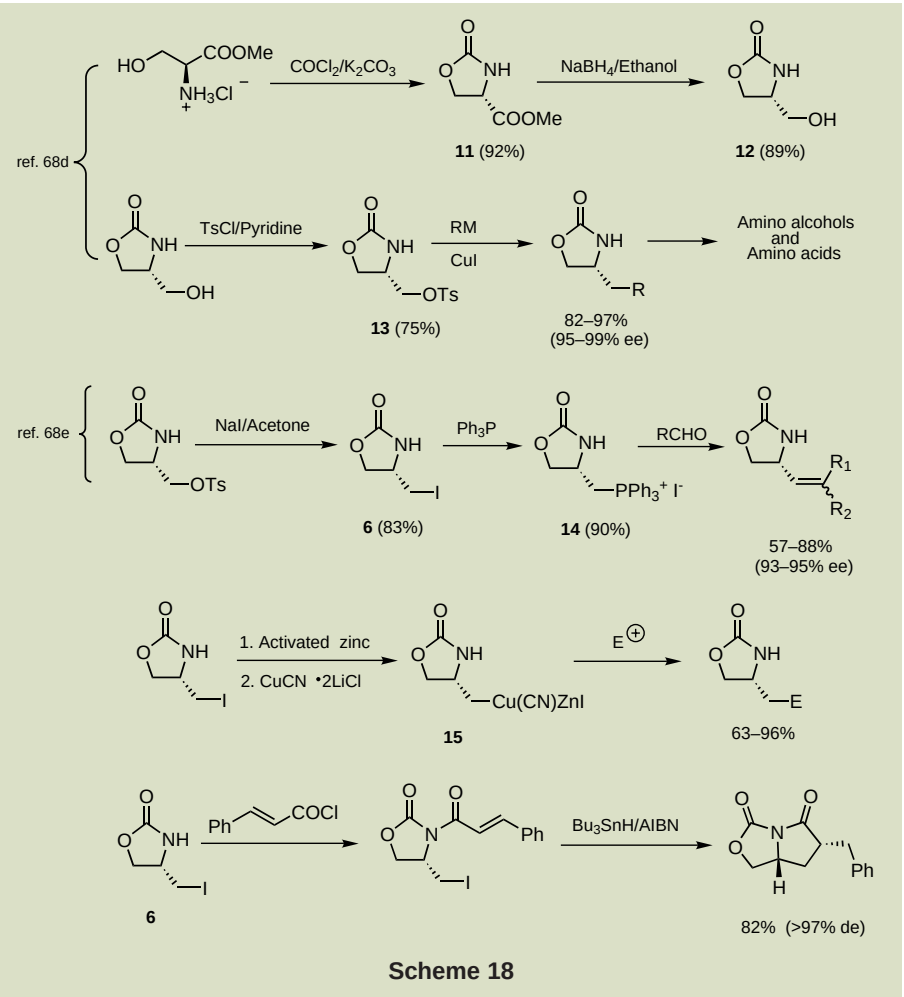
About the Author

After completing undergraduate education and a brief stay at Ciba Geigy Research Center in Mumbai (India), Dr. Kulkarni joined Professor Al Padwa's group for a Ph.D. Following graduation, he moved to Rensselaer Polytechnic Institute for postdoctoral research with Professor Art Schultz. After a second postdoc with Professor Barry Snider at Brandeis, Yash joined Aldrich as a Scientist (Cancer Research Contracts) in July 1985. He has worn many different hats during his 13+ year career at Aldrich. For example, he was Supervisor of two National Cancer Research Contracts at Aldrich for four years before becoming Supervisor of R&D in 1991. In 1993, he was promoted to Manager, R&D/Stable Isotopes. In his current position as a Senior Scientist (Process Development), Yash assists Sigma-Aldrich in developing syntheses of pharmaceutical intermediates and bulk/custom-synthesis candidates.

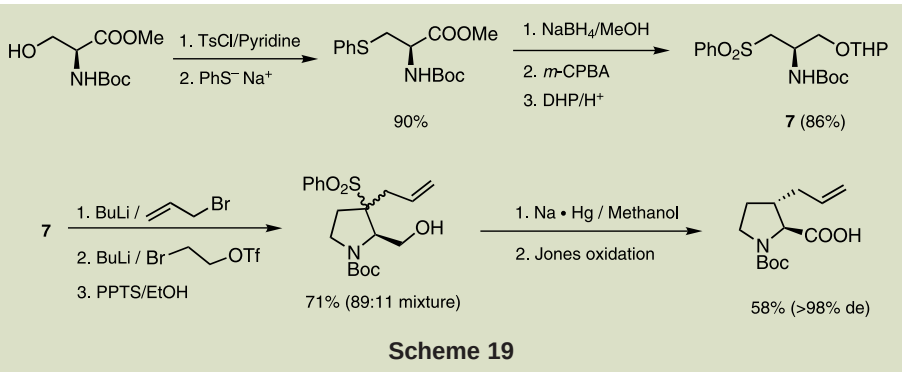
Yash has co-authored nearly two dozen publications in a variety of areas and has developed many new (unpublished) syntheses for Sigma-Aldrich. During his academic and industrial careers, he has gained expertise in many different areas, and particularly enjoys the chemistry of amino acids, nucleosides, and chiral products.



Scheme 17



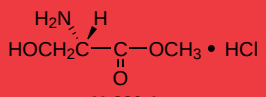
Scheme 18



Scheme 19

Serine Derivatives

The preceding review highlights the importance of serine derivatives as templates for the construction of more complex medicinal products. To take advantage of some of the exciting chemistry described, take a look at the following list of reagents and serine-derived building blocks that Aldrich offers and are mentioned in the review. For further information, visit our Web site at **www.sigma-aldrich.com** or contact our Technical Services department at **(800) 231-8327** (USA).



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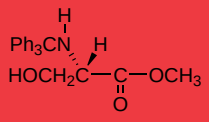
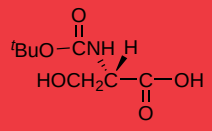
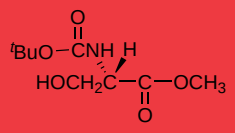


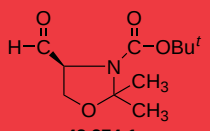
41,134-5



15500F



41,048-9



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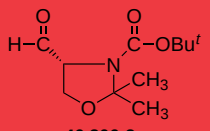

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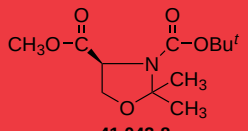
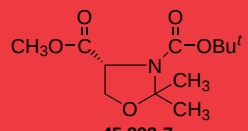
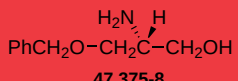


41,043-8



45,893-7



47,375-8

Amino acid based products:

41,220-1 **L-Serine methyl ester hydrochloride**, 98%

41,134-5 ***N*-Trityl-L-serine methyl ester**, 99%

15500F ***N*-(*tert*-Butoxycarbonyl)-L-serine**, 99%

41,048-9 ***N*-(*tert*-Butoxycarbonyl)-L-serine methyl ester**, 95%

43,274-1 ***tert*-Butyl (*S*)-(–)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate**, 95%

46,206-3 ***tert*-Butyl (*R*)-(+)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate**, 96%

41,043-8 **Methyl (*S*)-(–)-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-4-oxazolidinecarboxylate**, 98%

45,893-7 **Methyl (*R*)-(+)-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-4-oxazolidinecarboxylate**, 98%

47,375-8 **(*R*)-(+)-2-Amino-3-benzyloxy-1-propanol**, 97%

40,626-0 ***N*-(*tert*-Butoxycarbonyl)-3-iodo-D-alanine benzyl ester**, 99%

Some of the reagents cited:

D9,000-8 **Diethyl azodicarboxylate**

19,913-3 **Di-*tert*-butyl dicarbonate**, 97%

16,146-2 **1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride**,98+%

15,726-0 **1-Hydroxybenzotriazole hydrate**

14,033-3 **Benzyl 2,2,2-trichloroacetimidate**, 99%

27280F **α-Chymotrypsin**

21,817-0 **(Trimethylsilyl)acetylene**, 98%

86843F **Tetrabutylammonium fluoride trihydrate**

36,283-2 **(Trimethylsilyl)diazomethane**, 2.0 *M* solution in hexane

91077F ***tert*-Butyl 2,2,2-trichloroacetimidate**, 96%

10,001-3 **4,4'-Dimethoxytrityl chloride**, 95%

36,887-3 **9-Bromo-9-phenylfluorene**, 97%

22,051-5 **Methyl benzimidate hydrochloride**, 97%

36,518-1 ***N*-Benzylhydroxylamine hydrochloride**, 97%

30,230-9 **2-Cyanoethyl diisopropylchlorophosphoramidite**

23,809-0 **1-Bromo-4-iodobenzene**, 98%

For comprehensive information on the manipulation of protecting groups, see *Protective Groups in Organic Synthesis, 2nd ed., by T.W. Greene and P. Wuts* (**Z22,155-4**) or *Protecting Groups* by P.J. Kociénski (**Z27,283-3**).

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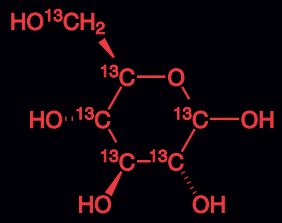
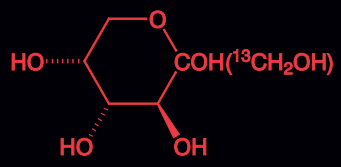
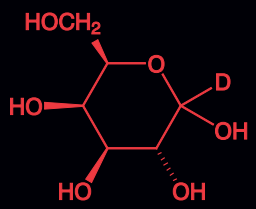


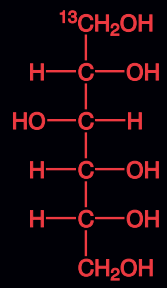
38,937-4



41,555-3



49,507-7



48,918-2

38,937-4 **D-Glucose-$^{13}C_6$**, 99 atom % ^{13}C

- Starting material in the enzymatic conversion of labeled glucose to ribonucleosides and the corresponding RNA and DNA monomers and oligomers.[1,2]
- Source of ^{13}C label in the study of the formation pathway of isopentenyl diphosphate in *Streptomyces aeriouvifer*.[3]
- Starting material in the solid-phase chemical synthesis of selectively labeled oligomers, which cannot be synthesized by enzymatic reactions.[4]

28,265-0 **D-Glucose-*6,6-d*$_2$**, 98 atom % D

- Used in a study of the biosynthetic pathway of Aristeromycin and Neplanocin A in *Streptomyces citricolor*.[5]

29,704-6 **D-Glucose-*1*-^{13}C**, 99 atom % ^{13}C

31,079-4 **D-Glucose-*2*-^{13}C**, 99 atom % ^{13}C

31,080-8 **D-Glucose-*6*-^{13}C**, 99 atom % ^{13}C

49,216-7 **D-Glucose-$^{12}C_6$, ^{13}C-depleted**, 99.9 atom % ^{12}C

41,555-3 **D-Fructose-*1*-^{13}C**, 99 atom % ^{13}C

49,214-0 **D-Fructose-*2*-^{13}C**, 99 atom % ^{13}C

49,215-9 **D-Fructose-*6*-^{13}C**, 99 atom % ^{13}C

48,872-0 **D-Fructose-*6,6-d*$_2$**, 98 atom % D

49,507-7 **D-Galactose-*1-d***, 98 atom % D

48,918-2 **D-Sorbitol-*1*-^{13}C**, 99 atom % ^{13}C

References: (1) Tolbert, T.J.; Williamson, J.R. *J. Am. Chem. Soc.* **1997**, *119*, 12100. (2) Quant, S. et al. *Tetrahedron Lett.* **1994**, *35*, 6649. (3) Seto, H. et al. *ibid.* **1996**, *37*, 7979. (4) Ono, A. et al. *ibid.* **1998**, *39*, 2793. (5) Hill, J.M. et al. *J. Am. Chem. Soc.* **1995**, *117*, 5391.

From the Aldrich Bookshelf

Organic Reactions

Leo A. Paquette, Editor-in-Chief, John Wiley & Sons, New York, NY. Presented from a preparative viewpoint, each volume in this series covers a single reaction or definitive phase of a reaction. Chapters are written by experts, and contain tables of all known examples of the reaction under consideration.

Vol. 53 *1998, 672pp.* The Oxidation of Alcohols by Modified Oxochromium(VI)–Amine Reagents. The Retro-Diels–Alder Reaction, Part II. Dienophiles with One or More Heteroatom.

Z41,029-2

Vol. 52 *1998, 600pp.* The Retro-Diels–Alder Reaction, Part I: C–C Dienophiles. Enantioselective Reduction of Ketones.

Z41,028-4

Vol. 51 *1997, 502pp.* Asymmetric Aldol Reactions Using Boron Enolates. The Catalyzed α-Hydroxyalkylation and α-Aminoalkylation of Activated Olefins (The Morita-Baylis-Hillman Reaction). [4+3] Cycloaddition Reactions.

Z40,227-3

Organic Syntheses

Collective Volumes, Vol. 9. *Jeremiah P. Freeman, Editor-in-Chief, John Wiley & Sons, New York, NY, 1998, 840pp.* This series serves as a single-source compendium of the most up-to-date and significant procedures currently in use. Volume 9 consists of checked procedures previously published in annual volumes 70–74, revised and updated.

Z41,165-5

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The Organic Chemistry of Drug Synthesis, Vol. 6

Daniel Lednicer, John Wiley & Sons, New York, NY, 1998, 244pp. Covering the literature from 1994 to 1998, the book provides a quick overview of the synthetic routes to access specific classes of therapeutic agents.

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Combinatorial Chemistry and Molecular Diversity in Drug Discovery

E.M. Gordon and J.F. Kerwin, Eds., Wiley-Liss, New York, NY 1998, 516pp. Applies combinatorial techniques and molecular diversity to drug discovery and development. Highlights the critical concepts and issues that are entailed in implementing combinatorial chemistry. Covers techniques and tools used in the field as well as the organizational and strategic questions faced by pharmaceutical managers as they implement and exploit combinatorial technologies.

Z41,160-4

Hawley's Condensed Chemical Dictionary

13th ed., R.J. Lewis, Sr., Van Nostrand Reinhold, New York, NY, 1997, 1,229pp. New significant data about flammable and explosive materials, poisons, pesticides, carcinogens, radioactive wastes, and corrosive agents. More than 20,000 entries are organized alphabetically for easy use. Each chemical substance entry is identified by name, physical properties, source of occurrence, CAS No., chemical formula, hazard, derivation, synonym, and use.

Z40,228-1

Strategies for Organic Drug Synthesis and Design

D. Lednicer, John Wiley & Sons, New York, NY, 1997, 500pp. Ideal for anyone learning or working in organic, medicinal, or pharmaceutical chemistry today, this work offers a clear examination of the synthetic routes followed to prepare a range of compounds with assigned generic names. With drugs selected for the illustrative value of the chemistry used for synthesis, the book illustrates a great variety of organic transformations and structural classes of compounds.

Z40,856-5

Named Organic Reactions

T. Laue and A. Plagens, Eds., John Wiley & Sons, New York, NY, 1998, 298pp. Hardcover. The definitive guide to 134 key reactions. The chapters are ordered alphabetically and are each treated systematically, giving the name of the reaction, followed by an explanatory subtitle, scheme for the overall reaction together with introductory sentences.

Z41,030-6

Introduction to Ionomers

A. Eisenberg and J.S. Kim, John Wiley & Sons, New York, NY, 1998, 325pp. Hardcover. First book in twenty years to survey the field of ionomers for the nonspecialist. Written by one of the founders of the field, the book relates the molecular structure of ionomers to their physical properties and interactions, including concepts such as the glass transition and mechanical properties of random styrene-based and other polymers.

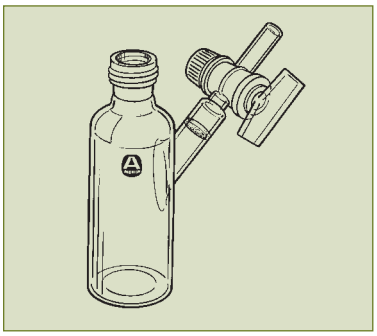
Z41,033-0

The Borane, Carborane, and Carbocation Continuum

J. Casanova, Ed., John Wiley & Sons, New York, NY, 1998, 437pp. Hardcover. Covers all aspects of the research on carbocations, boranes, and carboranes, including the most recent advances in the field. Contains contributions from experts in the field, including two Nobel Prize winners: George Olah (USC) and William Lipscomb (Harvard).

Z41,032-2

SCHLAKER REACTION TUBES



The "Schlaker" tube (derived from "Schlenk" and peptide "shaker") is designed for running oxygen-sensitive reactions on a solid-phase resin. The glass frit in the sidearm permits filtration of excess reagents and solvent removal with complete recovery of the resin for the next reaction. Made of heavy-wall glass, with glass stopcock and frit (porosity 25 to 50 µm) on sidearm, and a plain or threaded ⅀14/20 top joint. Compatible with Schlenk glassware.

Directions for use. Place the resin in the tube. With a rubber septum or a septum-inlet adapter (available separately at right) in the top joint, evacuate and purge with N_2 to remove oxygen. Stir gently while heating in an oil bath for high temperatures, or place on a shaker for room-temperature reactions. When the reaction is complete, apply positive N_2 pressure through the septum in the top joint, and vacuum to the sidearm. Tilt the Schlaker tube on its side to allow solvent and excess reagents to flow out, leaving the resin behind.

Schlaker reaction tubes

Cap. (mL)	*Plain joint* Cat. No.	*Screw-thread joint* Cat. No.
10	**Z40,923-5**	**Z40,929-4**
25	**Z40,924-3**	**Z40,930-8**
50	**Z40,925-1**	**Z40,931-6**
100	**Z40,927-8**	**Z40,932-4**
250	**Z40,928-6**	**Z40,933-2**

Male joint cap, glass, with screw-thread ⅀14/20 joint.

Z23,085-5

Septum-inlet adapters, with ⅀14/20 joint. Use with rubber septum **Z10,072-2** or **Z12,435-4**.

Z10,224-5

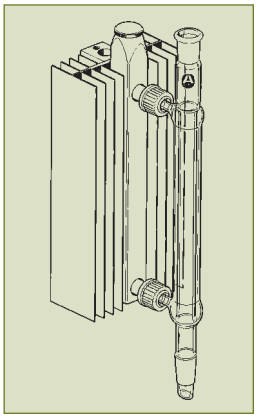
Z22,352-2

Rubber septa, fit ⅀14/20 joints.

White rubber	*Red rubber*
Z10,074-9	**Z12,437-0**

ALDRICH AIRFLUX CONDENSER APPARATUS

Closed coolant system eliminates wastewater and accidental laboratory flooding



Efficient aluminum heat sink disperses heat. Remove plastic cap on heat sink to fill with distilled water. Water passes through to glass condenser. Complete apparatus includes Airflux aluminum heat sink, removable glass condenser, and boiling flask.

- Ideal for solvents boiling between 60 and 150 °C
- Use with flasks up to 250mL in size and heating mantles with 60W max. output
- Condensers can be mounted in tandem* for flask sizes up to 1L and 300W heating mantles with a controller for steady reflux rates
- Mounts to ½ in. lattice rods or support stands via built-in clamp on heat sink

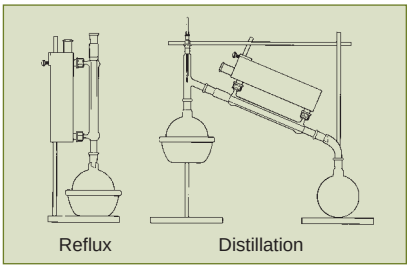
Airflux size	Flask cap. (mL)	*24/40 joints* Cat. No.	*24/29 joints* Cat. No.	*29/32 joints* Cat. No.
Small	100	**Z41,036-5**	**Z41,038-1**	**Z41,041-1**
Large	250	**Z41,037-3**	**Z41,040-3**	**Z41,043-8**

*Do not use tandem-mounted, water-cooled Airflux units to condense solvents boiling over 100 °C. Alternative coolants such as ethylene glycol may be suitable. Tests should be carried out to determine satisfactory performance.

Replacement Airflux condensers

Condenser size	*24/40 joints* Cat. No.	*24/29 joints* Cat. No.	*29/32 joints* Cat. No.
Small	**Z41,048-9**	**Z41,050-0**	**Z41,052-7**
Large	**Z41,049-7**	**Z41,051-9**	**Z41,053-5**

Typical operations, distillation and reflux, shown below.



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β-Amino acids are used in structural biology and as building blocks for the design of new peptidomimetics.

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We also encourage inquiries about custom synthesis in the field of protected specialty amino acids and building blocks.

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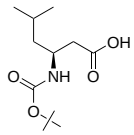
N-BOC-protected unnatural amino acids



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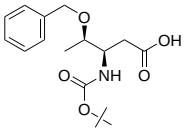

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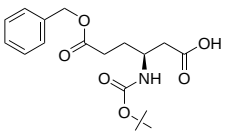

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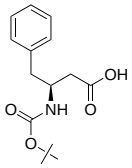

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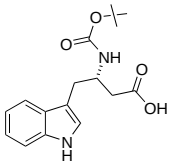

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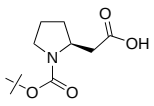
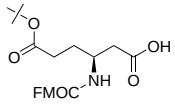


14982

14975	**BOC-L-β-homoleucine**
14976	**BOC-*O*-benzyl-L-β-homothreonine**
14977	**BOC-L-β-homoglutamic acid 6-benzyl ester**
14979	**BOC-L-β-homophenylalanine**
14981	**N_β-BOC-L-β-homotryptophan**
14982	**(*S*)-2-(1-BOC-2-pyrrolidinyl)acetic acid**

N-FMOC-protected unnatural amino acids



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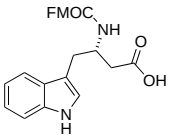

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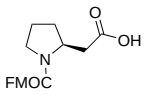

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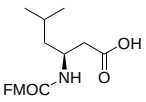

47946

47834	**FMOC-4-(trifluoromethyl)-D-phenylalanine**
47835	**FMOC-4-(trifluoromethyl)-L-phenylalanine**
47837	**FMOC-L-β-homoglutamic acid 6-*tert*-butyl ester**
47901	**N_β-FMOC-L-β-homotryptophan**
47912	**(*S*)-2-(1-FMOC-2-pyrrolidinyl)acetic acid**
47946	**FMOC-L-β-homoleucine**

N-Z-protected unnatural amino acids

96065	***N*-Z-D-α-cyclohexylglycine**
96075	**Z-dehydroalanine**
96077	**Z-dehydroalanine methyl ester**
96079	**Z-*N*,2-dimethylalanine**
96083	**N_α-Z-L-2,4-diaminobutyric acid**
96084	**N_α-Z-D-2,3-diaminopropionic acid**

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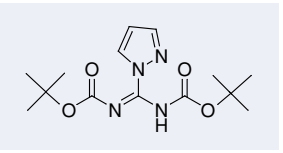
Aldrichimica Acta

Volume 32, Number 2, 1999

Enzymatic Dihydroxylation of Aromatics in Enantioselective Synthesis: Expanding Asymmetric Methodology

New Products

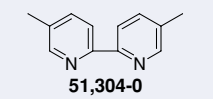
Both the solution- and solid-phase synthesis of guanidines have been accomplished with this reagent.[1-3]



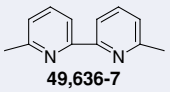
(1) Wu, Y. et al. *Synth. Commun*. **1993**, *23*, 3055. (2) An, H. et al. *Tetrahedron* **1998**, *54*, 3999. (3) Robinson, S.; Roskamp, E.J. *ibid*. **1997**, *53*, 6697.

43,416-7 ***N,N′*-Bis(*tert*-butoxycarbonyl)-1*H*-pyrazole-1-carboxamidine**, 98%

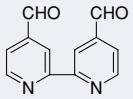
A variety of highly functional bipyridines, useful as organometallic ligands, have been prepared from these compounds. The methyl groups can be easily oxidized to the acid[1] or converted to the bromomethyl derivatives.[2,3] A number of alkenyl-substituted bipyridines have been prepared from the dicarboxaldehyde.[4,5]



51,304-0



49,636-7



47,466-5

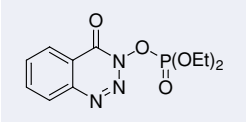
(1) Odobel, F. et al. *Tetrahedron Lett*. **1998**, *39*, 3689. (2) Schubert, U.S. et al. *ibid*. **1998**, *39*, 8643. (3) Ebmeyer, F.; Voegtle, F *Chem. Ber*. **1989**, *122*, 1725. (4) Kocian, O. et al. *Tetrahedron Lett*. **1990**, *31*, 5069. (5) Della, C. et al. *J. Heterocycl. Chem*. **1990**, *27*, 163.

51,304-0 **5,5′-Dimethyl-2,2′-dipyridyl**, 98%

49,636-7 **6,6′-Dimethyl-2,2′-dipyridyl**, 98%

47,466-5 **2,2′-Bipyridine-4,4′-dicarboxaldehyde**, 95%

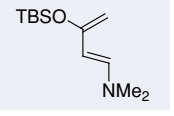
This peptide coupling agent is a stable crystalline solid, and is suitable for both solution- and solid-phase synthesis. No additives are needed to prevent racemization when using this reagent.



Fan, C-X. et al. *Synth. Commun*. **1996**, *26*, 1455.

49,596-4 **3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one**, 98%

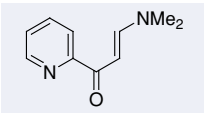
This diene has been reported to be significantly more reactive than Danishefsky's diene (1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene).



Kozmin, S.A.; Rawal, V.H. *J. Org. Chem*. **1997**, *62*, 5252.

49,595-6 ***trans*-3-(*tert*-Butyldimethylsilyloxy)-*N,N*-dimethyl-1,3-butadien-1-amine**, 90%

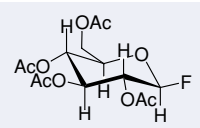
A variety of 2,2':6',2"-terpyridines can be prepared from this reagent.



Jameson, D. L.; Guise, L. E. *Tetrahedron Lett*. **1991**, *32*, 1999.

51,167-6 **3-(Dimethylamino)-1-(2-pyridyl)-2-propen-1-one**, 95%

Glycosyl fluorides are widely utilized intermediates for C-, O-, N-, or S-glycosylations.[1,2]



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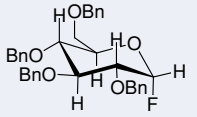


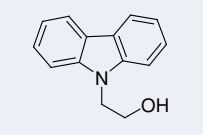
51,172-2

(1) Drew, K. N.; Gross, P. H. *J. Org. Chem*. **1991**, *56*, 509. (2) Jegou, A. et al. *Tetrahedron* **1998**, *54*, 14779.

51,054-8 **β-D-Glucopyranosyl fluoride tetraacetate**, 97%

51,172-2 **2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl fluoride**, 97%, predominantly α

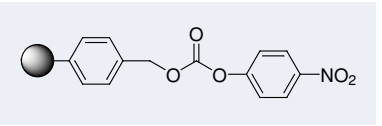
Monomers for the synthesis of azo-aromatic photoconductive polymers have been prepared from this compound.[1-3]



(1) Ho, M.S. et al. *Macromolecules* **1996**, *29*, 4613. (2) Toru, Y.; Tokuji, M. *J. Phys. Chem*. **1995**, *99*, 16047. (3) Zhao, C. et al. *Chem. Mater*. **1995**, *7*, 1237.

47,974-8 **9*H*-Carbazole-9-ethanol**, 97%

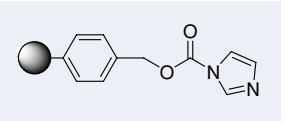
This carbonate resin is used to bind amines or amino acids as urethanes. Dipeptides and hydantoins have been prepared from these polymer-bound urethanes.[1-3]



(1) Dixit, D.M.; Leznoff, C.C. *J. Chem. Soc., Chem. Commun*. **1977**, 798. (2) Dressman, B.A. et al. *Tetrahedron Lett*. **1996**, *37*, 937. (3) Gouilleux, L. et al. *ibid*. **1996**, *37*, 7031.

49,483-6 **4-Nitrophenyl carbonate, polymer-bound**

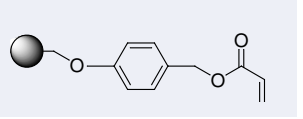
Solid-phase synthesis of peptides and peptidomimetics has been accomplished using polymer-bound carbonylimidazole. Carbamates are formed by reaction with unprotected amines. The carbamates are cleaved using trifluoroacetic acid.[1,2]



(1) Hauske, J.R.; Dorff, P. *Tetrahedron Lett*. **1995**, *36*, 1589. (2) Rotella, D.P. *J. Am. Chem. Soc*. **1996**, *118*, 12246.

49,823-8 **Carbonylimidazole, polymer-bound**

Solid-phase synthesis of β-peptoids using the Wang acrylate resin has been accomplished through Michael addition of amines. The peptoids are formed by further reaction of the resulting β-amine with acryloyl chloride followed by Michael addition of another amine. The peptoid is cleaved from the resin with trifluoroacetic acid.



Hamper, B.C. et al. *J. Org. Chem*. **1998**, *63*, 708.

51,017-3 **Wang acrylate resin**

Aldrichimica Acta

Volume 32, Number 2, 1999

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About Our Cover

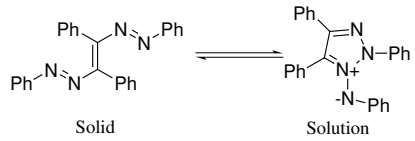
Alexander the Great Threatened by His Father (oil on canvas, 51in. x 37⅛in.) was painted by the Italian artist Donato Creti probably between 1700 and 1705. It represents a famous confrontation between Alexander and his father, King Philip of Macedon, as recorded by the ancient Greek historian Plutarch. Alexander was angered by his father's philandering and divorce from his mother, Olympia. Feelings came to a head at the banquet Philip hosted to celebrate his marriage to Cleopatra, a maiden much younger than he. Her uncle Attalus called upon the people present to pray that a legitimate heir to the Macedonian throne might be born from this union. Alexander flew into a rage, hurled his cup at Attalus, and shouted, "What about me?" Philip rose angrily and drew his sword as if to strike his son, but stumbled drunkenly and fell.

The artist chose to depict the most dramatic moment of this story, when the wedding guests are reacting to Philip's brash action. The cup Alexander has thrown lies on the step to the right. The frightened young woman wearing a diadem at the left is Cleopatra, and the astounded old man beneath the protagonists' outstreched hands is Attalus. The drama of the event is expressed not only through the emotion-charged gestures and expressions, but also by the sharply foreshortened view of the servant who has been knocked down on the left, the fluttering drapery at the upper right, the fantastic palace opening behind the banquet scene, and even the low vantage point from which we witness the action. A dynamic use of light also pervades the painting, accentuating the main actors, revealing the luxurious materials and rich colors, and illuminating distant chambers glimpsed through grand colonnades and courtyards.

This painting is part of the Samuel H. Kress Collection at the National Gallery of Art, Washington, D.C.

"Please Bother Us."

by Jai Nagarkatti, President



Professor Richard N. Butler of the National University of Ireland, Galway, kindly suggested that we make 1,2-bis(phenylazo)stilbene. This compound functions as an azolium 1,3-dipole and is useful for the preparation of triazolium salts. These salts can be easily converted to triazines, oxatriazines, or thiatriazines.

Butler, R. N.; O'Shea, D. F. *Heterocycles* **1994**, *37*, 571.

51,578-7 **α,β-Bis(phenylazo)stilbene**, mixture of isomers

Naturally, we made this useful reagent. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page or on the inside back cover.

Lab Notes

Safe Transfer of Air- and Moisture-Sensitive Reagents in the Laboratory

Advances in organometallic chemistry in the last few decades have brought pyrophoric and moisture-sensitive reagents, especially those of organolithium and aluminum, into common usage in organic chemistry laboratories. The commercial availability and high selectivity of these reagents have made them indispensable in the modern chemistry laboratory, despite their highly reactive nature and the risks associated with their handling. In laboratory settings, these reagents are most conveniently transferred from commercial containers to reaction vessels by using either a syringe–needle combination or cannulation techniques,[1,2] without resorting to the use of a glove box or the Schlenk line of dedicated glassware.[3,4]

However, it is almost inevitable that small amounts of the pyrophoric liquid being transferred, e.g., *t*-BuLi solutions and Me_3Al, are exposed to the atmosphere on the tip of the needle or cannula, often causing sparks or small fires. While in most cases the fire is localized and burns out quickly, it always makes one apprehensive, considering the possibility that the sparks or fire may spread to other flammable materials abundant in organic chemistry laboratories. A simple device and a procedure to minimize such risks are described here.

A piece of glass tubing of approximately 6 mm ID and 4 cm in length is capped with rubber septa at both ends and the septa secured with copper wires. This tube is purged with inert gas and serves to protect the needle tip from being exposed to air. When withdrawing air-sensitive reagents, the needle is allowed to protrude through both septa and into the reservoir (**Figure 1**). Once the desired amount of reagent is removed, the tip of the needle or cannula is withdrawn from the reservoir and slid into the glass tubing filled with inert atmosphere, while the lower septum is kept in close contact with the cap of the reservoir to minimize exposure by the needle tip to the air during the process. The syringe or cannula is then safely transported (**Figure 2**) to the reaction flask and the sequence reversed to dispense the reagent (**Figure 3**). After the transfer is finished, the same procedure is followed to withdraw inert solvent to rinse the residual reagent from the syringe needle or cannula or to effect final quenching and cleaning. This simple device has virtually eliminated sparks associated with the transfer of pyrophoric reagents in the author's laboratory.

References: (1) Kramer, G. W.; Levy, A. B.; Midland, M. M. In *Organic Syntheses via Boranes*; Brown, H.C., Ed.; Wiley–Interscience: New York, NY, 1975. (2) Lane, C. F.; Kramer, G. W. *Aldrichimica Acta* **1977**, *10*, 11. (3) Capka, M. *Chem. Listy* **1973**, *67*, 1104. (4) Shriver, D. F. *The Manipulation of Air-Sensitive Compounds*; McGraw–Hill: New York, NY, 1969.

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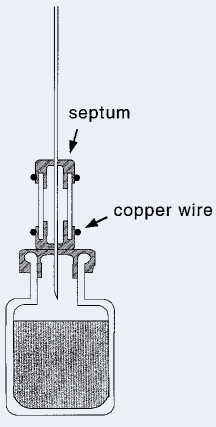

Figure 1

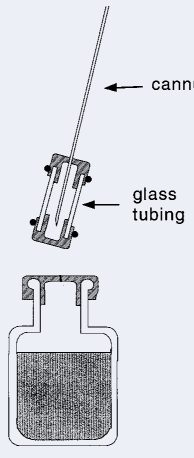

Figure 2

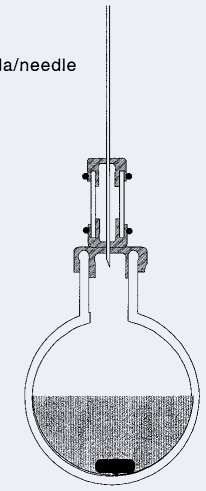
Figure 3

Maintaining a Constant Water Level in an Open, Warm-Water Bath

In our laboratories, we are required, for safety reasons, to use a steam bath to heat large-scale reactions (22-L or 50-L flask size) that contain flammable solvents (bp ≤ 80 °C, e.g., ethanol). This is accomplished by heating a water bath with steam coils that are immersed in the water. Extended periods of heating result in significant evaporation of the water, and lead to a reduction of the water level in the bath.

To maintain a constant water level in the bath during extended periods of heating, we cover the entire surface of the water with mineral oil (Aldrich cat. no. **33,077-9**). This greatly reduces the evaporation of the water, and little, if any, decomposition of the mineral oil occurs during a 72-hour period. For example, we have heated in this way a 12-L flask—in which an aldehyde deprotection step was carried out in acetone for 72 h—and observed no reduction of the water level in the bath. However, heating for more than 72 hours tends to accelerate decomposition of the oil. If longer heating times are required, the mineral oil can simply be decanted and replaced with a fresh batch.

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Enzymatic Dihydroxylation of Aromatics in Enantioselective Synthesis: Expanding Asymmetric Methodology†

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[#]Department of Chemistry, University of Florida, Gainesville, FL 32611-7200, USA
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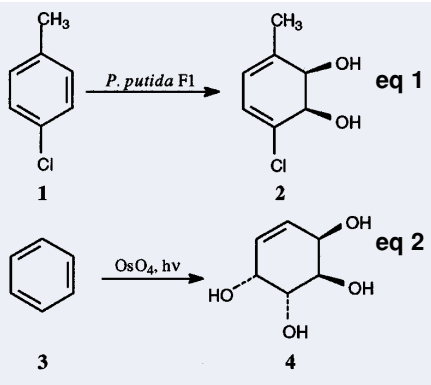
1. Introduction

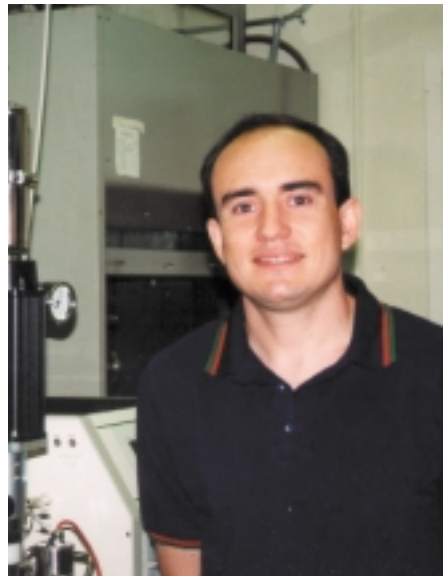
Studies of the microbial oxidation of aromatic hydrocarbons by soil bacteria led, in 1968, to the isolation of the first stable *cis*-cyclohexadienediol, **2** (**eq 1**).[1] Twenty-seven years later, Motherwell and Williams[2] reported the chemical equivalent of this reaction in their synthesis of racemic conduritol E (**4**) (**eq 2**).

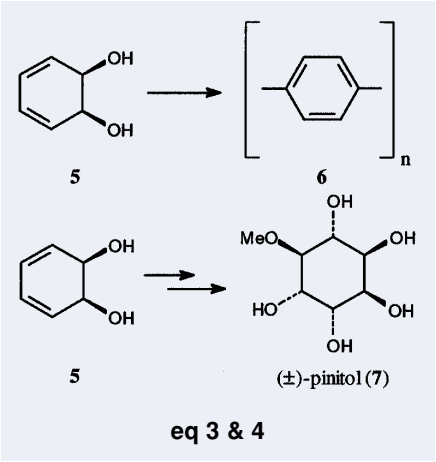


Prior to 1983, the *cis*-cyclohexadienediols produced by bacteria elicited little interest from synthetic chemists in industry and academia. In that year, however, chemists from Imperial Chemical Industries in England reported the use of the biocatalytically generated *meso-cis*-diol **5**—derived from benzene—as a monomer for the synthesis of polyphenylene (**6**) on an industrial scale (**eq 3**).[3,4]

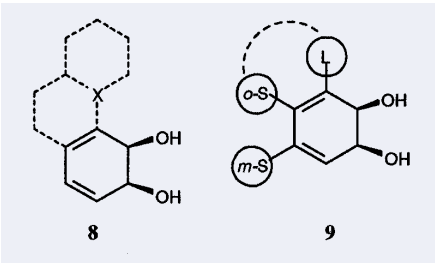
In the late eighties, an expansion of the use of these diols in synthetic ventures took place, and the *meso-cis*-diol **5** served as the starting material for many of the early syntheses. The first academic disclosure was Ley´s synthesis of racemic pinitol (**7**) in 1987 (**eq 4**),[5] and this milestone was followed by many applications reported by several groups worldwide.[6]

The synthetic achievements in this area have been reviewed previously on several occasions.[7-18] This review will focus on selected synthetic applications and the categories of reactions that can be used to exploit the array of functionalities available in the general structure **8**. The drawing represents the three major classes of aromatics: single-ring, fused, and biphenyls. For all such substrates, there have evolved the corresponding enzymes of slightly different topologies: toluene, naphthalene, and biphenyl dioxygenases. A recently published review[18] lists most of the diols for which accurate characterization data ($[\alpha]_D$, ee) are available. In this review, Boyd advances the idea of directing effects for the oxidation, as depicted in **9**, to explain the remarkable regio- and enantioselectivity of the dioxygenases.



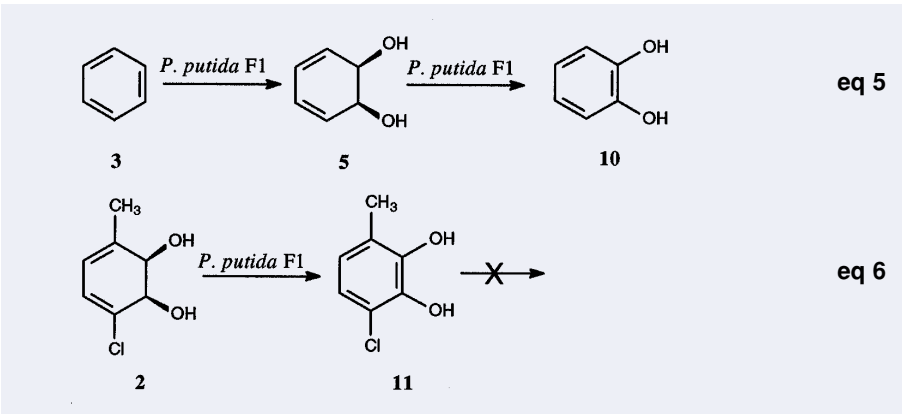


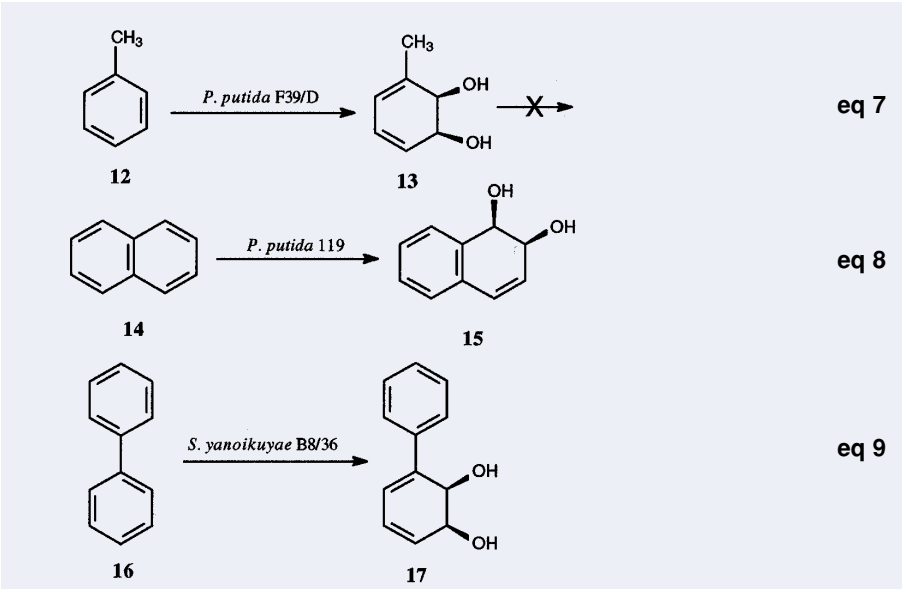
eq 3 & 4



Some of the reactive modes that are possible with these diols have already been reduced to practice, some are self-evident from the analysis of the reactive manifolds, and some undoubtedly await discovery. Most of the synthetic accomplishments originate in the use of only a few of the hundreds of diol metabolites isolated to date, and we include, at the end of this review, the full listing of diol metabolites known as of this writing (see Tables 1-5).

Such a list of actual structures before the eyes of a synthetic chemist should stimulate new thinking and the development of more complex strategies for advanced synthetic applications. Thus, this particular treatise contains, in addition to a historical overview, three areas of focus: production of metabolites, rationale for synthetic design, and applications according to the reaction type. The authors hope that this area will continue to expand, and that new and imaginative synthetic ventures from existing, as well as newly discovered, metabolites will be forthcoming.





2. Historical Perspective

In 1968, a strain of *Pseudomonas putida* (now designated as strain Fl), which grew with ethylbenzene as the sole source of carbon and energy, was isolated.[19] The organism also grew on benzene and toluene, and initial oxidation studies were conducted with toluene-grown cells. Oxygen uptake experiments showed that *P. putida* Fl rapidly oxidized benzene (**3**), *cis*-l,2-dihydroxycyclohexa-3,5-diene (*cis*-dihydrobenzenediol) (**5**), and catechol (**10**).[19] *trans*-Dihydrobenzenediol, the product of oxidative metabolism in mammalian systems,[20] was not oxidized. Toluene-grown cells did not accumulate detectable amounts of *cis*-dihydrobenzenediol, and evidence for its formation from benzene was provided by isotope experiments with cell extracts. The same cell extracts oxidized synthetic *cis*-dihydrobenzenediol to catechol (**10**) when NAD^+ was provided as an electron acceptor (**eq 5**).

The oxidation of fluorobenzene, chlorobenzene, bromobenzene, and iodobenzene by toluene-grown cells led to the formation of their respective 3-halogenated catechols which were resistant to further oxidation. The major product formed from *p*-chlorotoluene (**1**) was identified as 4-chloro-2,3-dihydroxy-l-methylbenzene (**11**), and extraction of 25 liters of a culture filtrate yielded 38 mg of (+)-*cis*-4-chloro-2,3-dihydroxy-1-methylcyclohexa-4,6-diene (**2**), the first stable *cis*-cyclohexadienediol.[1] A *cis*-diol dehydrogenase in the cell extracts oxidized **2** to **11** (**eq 6**).[1]

Subsequent studies led to the isolation of a mutant strain of *P. putida* Fl (strain 39/D, now designated F39/D) that was devoid of *cis*-diol dehydrogenase activity. Benzene-induced cells of strain F39/D oxidized benzene to *cis*-dihydrobenzenediol. Experiments with $^{18}O_2$ showed that both oxygen atoms in the dihydrodiol were derived from dioxygen,[21] stimulating initial thoughts that the intermediate in the transformation might be a dioxetane. Such an intermediate is unlikely to be formed from triplet oxygen species, however.

P. putida F39/D oxidized toluene (**12**) to enantiomerically pure *cis*-(1*S*,2*R*)-dihydroxy-3-methylcyclohexa-3,5-diene (**13**) (**eq 7**).[22,23] Other substrates oxidized to *cis*-dihydrodiols by strain F39/D were ethylbenzene,[24,25] *p*-fluorotoluene,[25] *p*-chlorotoluene,[25] *p*-bromotoluene,[25] chlorobenzene,[25] *p*-xylene,[26] and 3-methylcyclohexene.[27]

The identification of *cis*-dihydrodiols as intermediates in the degradation of benzene, toluene, and ethylbenzene led to studies of the reactions used by bacteria to initiate the degradation of aromatic hydrocarbons containing fused aromatic rings. Prior to 1971, it was generally believed that bacteria oxidize

naphthalene to *trans*-1,2-dihydroxy-1,2-dihydronaphthalene (*trans*-dihydronaphthalenediol).[28] However, the techniques used at that time did not differentiate between cis and trans isomers and a mutant strain of *Pseudomonas putida* (strain 119) was isolated that oxidized naphthalene (**14**) to *cis*-(1*R*,2*S*)-dihydroxy-1,2-dihydronaphthalene (**15**) (*cis*-dihydronaphthalenediol) (**eq 8**).[29,30] Both oxygen atoms in the *cis*-dihydrodiol were derived from a single molecule of dioxygen.[30]

Interest in the biodegradation of polychlorinated biphenyls led to the isolation of a *Beijerinckia* species strain B1[31] (now named *Sphingomonas yanoikuyae* strain B1)[32] that would grow with biphenyl (**16**) as the sole source of carbon. A mutant strain of this organism (strain B8/36) oxidized biphenyl to *cis*-(1*S*,2*R*)-dihydroxy-3-phenylcyclohexa-3,5-diene (**17**) (*cis*-dihydrobiphenyldiol) (**eq 9**).[31] Strain B8/36 oxidized anthracene and phenanthrene to *cis*-(1*R*,2*S*)-dihydroxy-1,2-dihydroanthracene and *cis*-(3*S*,4*R*)-dihydroxy-3,4-dihydrophenanthrene, respectively.[33,34] The major products formed from benzo[*a*]pyrene [BP] and benzo[*a*]anthracene [BA] were *cis*-9,10-dihydroxy-9,10-dihydro-BP and *cis*-1,2-dihydroxy-1,2-dihydro-BA, respectively.[35] In subsequent experiments, it was shown that *S. yanoikuyae* B8/36 oxidizes BA to *cis*-1,2-, *cis*-5,6-, *cis*-8,9-, and *cis*-10,11-dihydrodiols. With the exception of the 5,6-dihydrodiol, which was formed in trace quantities, the *cis*-dihydrodiols have an *R* absolute configuration at the hydroxylated benzylic centers. More recently, *S. yanoikuyae* B8/36 has been reported to oxidize chrysene to *cis*-(3*S*,4*R*)-dihydroxy-3,4-dihydrochrysene.[36]

Although *cis*-cyclohexadienediols are common intermediates in the bacterial oxidation of aromatic hydrocarbons, they are not formed exclusively from this class of compounds. In 1971, Reiner and Hegeman isolated a mutant strain of *Alcaligenes eutrophus* (strain B9) that oxidized benzoic acid (**18**) to (–)-*cis*-cyclohexadiene-l,2-diol-1-carboxylic acid (**19**) (**eq 10**).[37]

Subsequent studies by Reineke and colleagues showed that *A. eutrophus* strain B9 and *Pseudomonas sp*. strain B13 oxidize a variety of halogenated and methyl-substituted benzoic acids to *cis*-diol carboxylic acids.[38,39] In contrast to "ipso" dioxygenation, other *Pseudomonas* strains oxidize substituted benzoates to dihydrodiols, as Ribbons has shown in the case of the oxidation of cumic acid (**20**) to 2,3-dihydroxy-4-isopropylcyclohexa-4,6-dienoic acid (**21**) (**eq 11**).[40,41] (Note that the stereochemistry of the diol is the opposite of that in **2** with respect to the alkyl substituent.) Recently, the absolute stereochemistry and the reactive tendencies of the *cis*-diol **21** have been reported.[42]

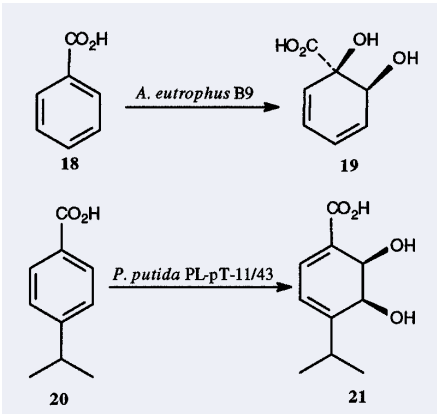
It is evident from the tables at the end of this review that some element of predictability exists with respect to the regio- and stereochemical outcome of the enzymatic dioxygenation of aromatic compounds. It should be noted that the trends in oxidation patterns (specificities) are unique and sometimes complementary for individual oxygenases.[43] These aspects, combined with the description of experimental needs in the next section, allow the nonspecialist access to this technology in order to enhance the art of asymmetric synthesis.

3. Whole-Cell Oxidation of Aromatics—Diol Formation

Several reviews are available in the area of microbial degradation of aromatic compounds[44-46] and these should be consulted by the nonspecialist before he/she begins preparative biotransformations.

Most of our current knowledge of the products formed by toluene (TDO), naphthalene (NDO), and biphenyl (BPDO) dioxygenases has been obtained with mutants that do not express their respective *cis*-dihydrodiol dehydrogenases. A laboratory procedure for the oxidation of chlorobenzene to 1-chloro-(2*S*,3*S*)-dihydroxycyclohexa-4,6-diene by *P. putida* F39/D has been described.[47] In practice, this procedure can be used for other volatile substrates. Solid substrates such as naphthalene and biphenyl can be added directly to the culture flask. Under these conditions, the aromatic hydrocarbons induce the synthesis of their respective dioxygenases. The induced cells can be harvested, resuspended in a mineral salts medium or buffer, and examined for their ability to oxidize different substrates. In such cases, pyruvate is usually added to provide the NADH necessary for the dioxygenase reaction. Constitutive mutants, such as *P. putida* UV4,[3] do not require an inducer, since the dioxygenase is present under all growth conditions.

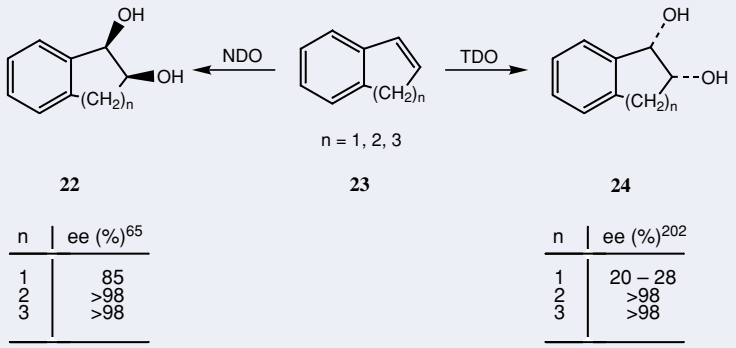
Inducers are not always the substrates used for the isolation of the wild type strains. For example, salicylate and anthranilate induce the synthesis of NDO in *Pseudomonas sp*. NCIB 9816,[48] and *m*-xylene induces BPDO in *Sphingomonas yanoikuyae* B8/36.[49] Care must be taken in the interpretation of results provided by blocked mutants, since other enzymes may be present that can affect the final distribution and stereochemistry of the isolated products.[50,51] In addition, it is advisable to examine each mutant for reversion to the wild type strain. For example, *P. putida* 119, the strain first used to isolate *cis*-dihydronaphthalenediol,[29] produced revertants when the cells reached the stationary growth phase. This was accompanied by the rapid disappearance of *cis*-dihydronaphthalenediol from the culture medium.[52] The subsequent use of the stable dihydrodiol dehydrogenase mutant *Pseudomonas sp*. 9816/11 alleviated this problem.[53]



eq 10 & 11

The genes encoding TDO,[54] NDO,[55] and BPDO[56] have been cloned and expressed in *Escherichia coli*. There are several advantages to using recombinant strains for the production of *cis*-dihydrodiols. These include the control of dioxygenase synthesis by the isopropyl-β-D-thiogalactoside (IPTG)-inducible promoters, the use of multicopy plasmids for the synthesis of increased amounts of enzyme, and the use of vector controls to identify host background activity. A major drawback often encountered in the synthesis of large amounts of proteins by recombinant strains is the production of the desired enzyme in the form of inactive inclusion bodies. One way to minimize the formation of inclusion bodies is to lower the temperature of the culture at the start of dioxygenase synthesis.

TDO, NDO, and BPDO are related multicomponent enzyme systems with overlapping substrate specificities. Each system uses a short electron transport chain to transfer electrons from NAD(P)H to their oxygenase components that consist of dissimilar (αβ) subunits.[57] The dioxygenation reaction is believed to occur at a mononuclear iron site in the α subunit. This is supported by recent X-ray structural data on the NDO oxygenase component;[58] however, the precise mechanism of dioxygenation, which involves the highly endothermic disruption of aromaticity, is unknown. The components of the TDO, NDO, and BPDO oxygenase systems have been purified and used in substrate specificity studies. Although such experiments are time-consuming and labor-intensive, they provide unequivocal evidence for the identification of the initial oxidation products formed from specific substrates. They have been particularly useful in demonstrating that NDO can catalyze monohydroxylation, desaturation (dehydrogenation), O- and N-dealkylation, and sulfoxidation reactions.[43]



n	ee (%)[65]
1	85
2	>98
3	>98

n	ee (%)[202]
1	20 – 28
2	>98
3	>98

Figure 1. Antipodal specificity of toluene and naphthalene dioxygenases.

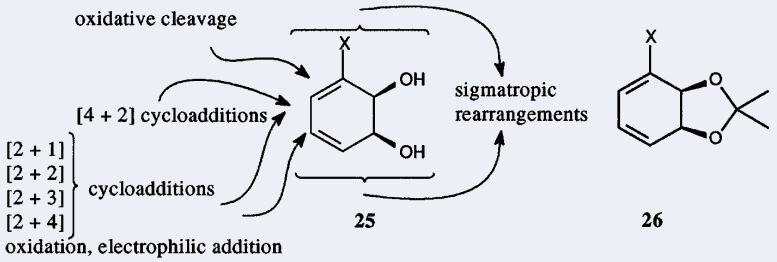


Figure 2. Local bond-forming sites in the *cis*-dienediols.

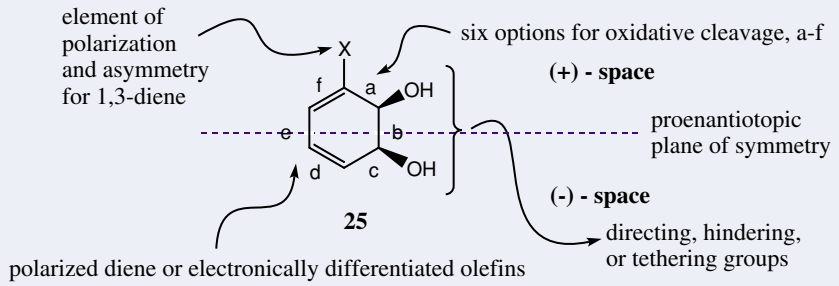
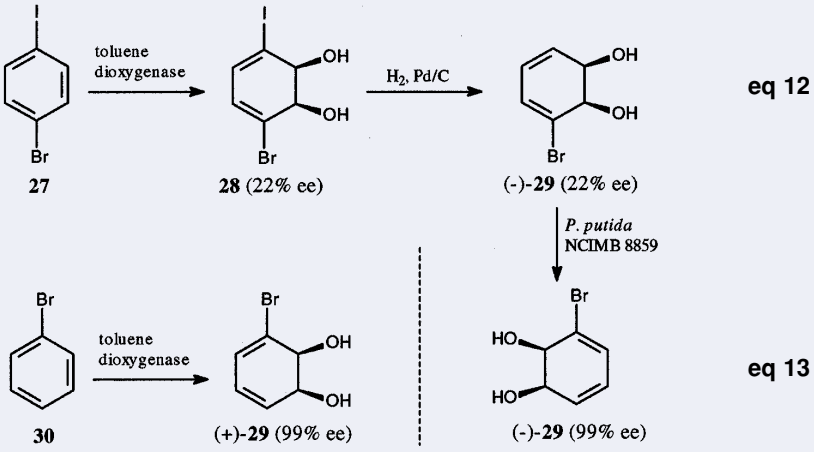


Figure 3. Global elements for stereomanipulation and enantiodivergence in the *cis*-dienediols [(+) and (–) space are assigned arbitrarily].



The discovery of the enzymatic asymmetric dihydroxylation of aromatic compounds by toluene, naphthalene, and biphenyl dioxygenases, and the availability of mutant and recombinant bacterial strains that express these enzymes, provided the community of organic chemists with the opportunity to use these biocatalysts in the preparation of useful synthetic intermediates. The following discussion aids the chemist not yet acquainted with these powerful tools.

There are generally two types of bacteria that are used to oxidize aromatic compounds to *cis*-cyclohexadienediols. From the point of view of a nonspecialist, the following narrative reiterates the principles mentioned above and should serve as a guide to those wishing to learn the technique. The organisms most commonly used are mutants of the wild type strain that have lost the ability to dehydrogenate *cis*-diols and recombinant strains of *Escherichia coli* that contain the cloned dioxygenase genes. Consequently, there are two procedures to be followed in terms of utilizing these organisms to produce *cis*-cyclohexadienediols. Both procedures can be easily performed with minimal skills in microbiology.

The first procedure involves the use of blocked mutants in which the enzyme synthesis must be induced by a known aromatic inducer (for *P. putida* F39/D this might be toluene, chlorobenzene, bromobenzene, or several other monocyclic aromatic compounds). If the inducer is also the substrate to be converted to a *cis*-cyclohexadienediol, the procedure is simple. The mutant is grown in a mineral salts medium, which provides the requisite inorganic elements (N, P, Mg, Fe, etc.), and an organic substrate that does not repress the synthesis of the dioxygenase (usually pyruvate or glucose). The aromatic compound can usually be added at the start of the growth. The accumulation of *cis*-cyclohexadienediol is monitored spectrophotometrically until the biotransformation ceases. Variations of this procedure are used when the substrate does not induce dioxygenase synthesis. The mutant is grown in a mineral salts medium with pyruvate or glucose in the presence of an inducing substrate as described above. Following the induction period, a new substrate is added, which, if recognized by the enzyme, is oxidized to the corresponding diol. The final fermentation broth contains the metabolites derived from the inducer and the substrate; thus, such a process necessitates a separation. Alternatively, the cells may be separated from the broth after induction and resuspended in a fresh medium before addition of the second substrate. The bacterial cells are then removed and the clear supernatant extracted with acid-free ethyl acetate.

The second procedure is slightly more complex to execute, but leads to potentially higher cell and product yields, and is ideal for testing new compounds as substrates for oxidation. It relies on the use of a recombinant organism in which transcription of the genes encoding the dioxygenase is initiated by exposure to a known nonaromatic inducer, in most cases isopropyl-β-D-thiogalactoside (IPTG). The cells are allowed to grow and synthesize the dioxygenase before the introduction of the substrate to be oxidized. Separation problems are avoided, but the procedure requires the use of a fermentor with carefully regulated oxygen levels, temperature, pH, CO_2 release, and nutrient/substrate feeds. Quite recently, an attempt has been made to transfer the genes encoding TDO from *E. coli* JM109 (pDTG601) to yeast cells[59] by a procedure successfully implemented by Stewart for cyclohexanone monooxygenase from *Acinetobacter*.[60] This particular enzyme has been successfully used in both isolated and whole-cell fermentations, with applications in organic synthesis by Furstoss,[61] Taschner,[62] and Stewart.[60] If the genetic information for the biosynthesis of the more complex dioxygenase enzyme systems can be transferred to yeast also, it will no doubt greatly enhance the attractiveness of this methodology to the traditionally trained synthetic practitioner.

The diols produced from aromatic substrates vary in stability and are usually isolated by extraction. They are then crystallized and stored at low temperature. They are more stable as free diols than in the protected forms (see section on cycloadditions). For shipping or long-term storage, it is best to store them as frozen suspensions in pH 8.5 phosphate buffer. So far, with very few exceptions, they are produced with the absolute stereochemistry as shown, and, in most cases, absolute enantiomeric purity— except for the diol derived from fluorobenzene,[63] the *meso*-diols originating from symmetrical substrates, and diols from several more highly substituted aromatic rings. As noted earlier, the enantiomeric specificities of individual dioxygenases are often unique and in some cases complementary; thus, both enantiomers of certain oxidation products can be accessed through the use of different oxygenase systems.[43] For example, naphthalene dioxygenase and toluene dioxygenase oxidize some hydrocarbons related to indene to the antipodal *cis*-diols, albeit in diverse enantiopurities (**Figure 1**). However, recent studies have identified organisms capable of generating several enantiopure *cis*-diols of opposite chirality to that of previously identified metabolites. It has been shown that a carbazole-utilizing strain oxidizes biphenyl, biphenylene, and 9-fluorenone to previously unobserved *cis*-diol enantiomers.[64] Thus, both enantiomers of several *cis*-diols can be generated through either subsequent chemical conversion of the diols,[65] enantioselective enzymatic resolution,[66] symmetry-driven design,[67,68] or the use of strains expressing dioxygenases with different specificities as mentioned above.

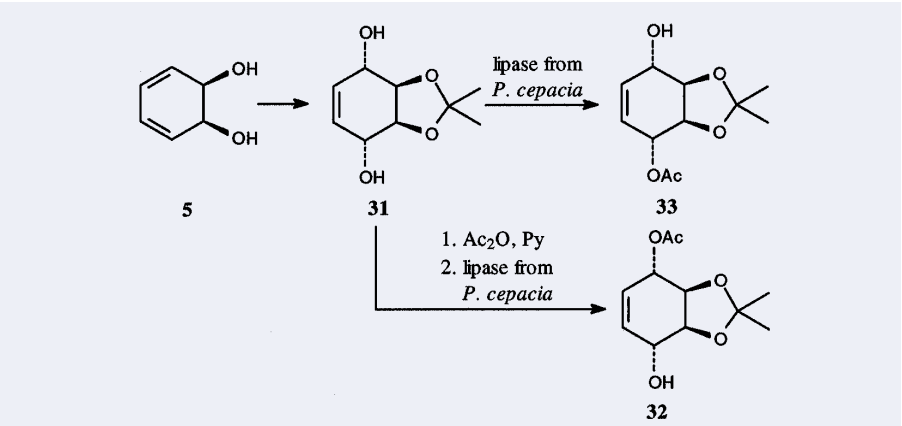


Figure 4. Enantiodivergence by lipase resolution.

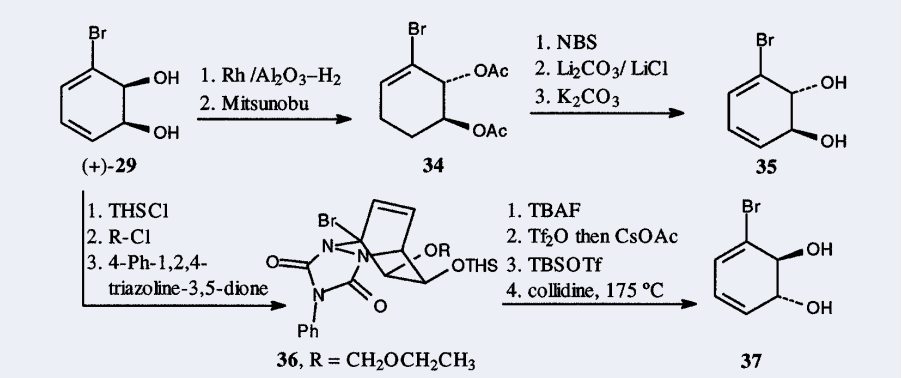


Figure 5. Two approaches to the "diastereomeric switch" of diols.

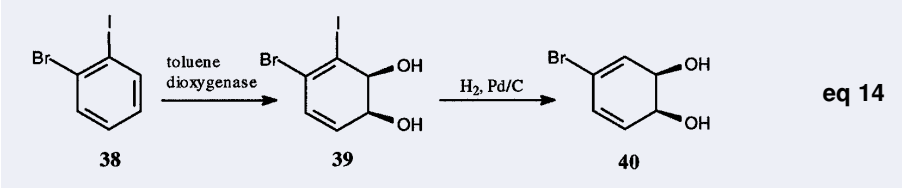
4. Synthetic Design Rationale

cis-Dihydroarenediols of the general structure **25**, and their acetonides **26** contain an amazing combination of mutually intertwined functionalities and, therefore, many possibilities for further use. The intellectual analysis of these possibilities can be summarized in two separate ways: first, various "local" bond-forming reactions as divided by class and shown in **Figure 2**; second, the "global" implications that address the enantio-, stereo-, and regioselectivities that can be expected from the manipulation of these compounds (**Figure 3**).

The issues of enantioselectivity are addressed by manipulating the *order* of reactions to a given target in such a manner as to elaborate specifically only one terminus (or apex) of the cyclohexadienediol, with the crucial enantiodifferentiation step performed in either "D" or "L" space in relation to the final absolute stereochemistry of the target (note: +/- and D/L are arbitrarily assigned). The appropriate "switch" is made following the removal of the differentiating group X. These strategies have already been elucidated and described in several disclosures and need not be discussed here.[10,11,13-17,67,68]

Another means by which enantiodivergence is achieved was reported by Boyd.[65] It relies first on the directing effect of the larger C-1 substituent in the enzymatic oxidation step of **27**, and, then, on the greater reactivity of the iodine in the Pd/C hydrogenolysis of **28** as shown in **eq 12**. In this way, the enantiomeric pair of diols **29** is obtained (**eq 13**).

The efficiency of this method relies on the ability of the enzyme to completely differentiate between the iodine and bromine atoms in the aromatic substrate. Unfortunately, **28** is obtained in very low optical purity, and this is translated into optically impure **29**. Boyd overcame this problem by exposing the scalemic mixture of **29** to a second fermentation step using a nonblocked strain of *Pseudomonas*, which is able to completely metabolize the undesired enantiomer (in this case the (2*S*,3*S*)-(+)-enantiomer)



eq 14

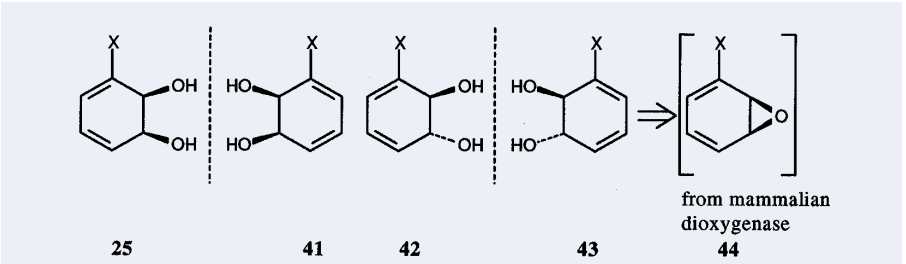


Figure 6. Enantio- and diastereodifferentiation strategy.

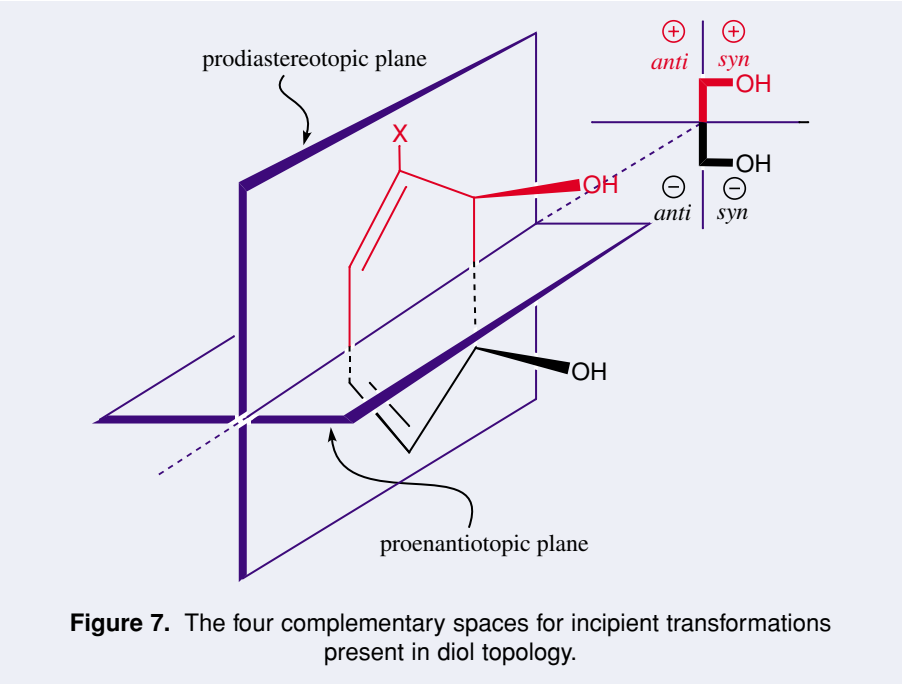


Figure 7. The four complementary spaces for incipient transformations present in diol topology.

leaving (–)-**29** to accumulate. This approach has the obvious disadvantage that a considerable amount of valuable (+)-**29** has to be created and then destroyed to attain the target.

A completely different approach to enantiodifferentiation of the dienediol residue was developed by Johnson.[66] The *meso*-diol **5** was functionalized to the conduritol derivative **31**, which was enzymatically resolved into either of the enantiomers **32** or **33**, as shown in **Figure 4**, to allow for the enantiodifferentiation of the projected targets.

The issue of enantiodivergence is crucial to the credibility of chemoenzymatic synthesis: too frequently the traditionalists in the synthetic organic community criticize the use of enzymatic reactions, and justify the rather inefficient chiral-auxiliary approach to asymmetric synthesis by pointing out that *ent*-enzymes are unavailable. The above result and the symmetry-based approach[13,14,67] clearly rebuff such criticism.

Boyd[69] has also addressed the "diastereomeric switch" between the cis diols and their trans isomers. Boyd's method for the conversion of cis diols to the trans isomers is accomplished as shown in **Figure 5**. In this process, the reactive diene needs to be reduced to the alkene to avoid aromatization during the Mitsunobu inversion of the proximal hydroxyl group. The diene is restored later by a bromination–elimination process to furnish **35**. Independently, an alternative procedure for the preparation of trans diols was reported (also shown in Figure 5).[70] In this case, the diene system was "protected" by a reversible Diels–Alder reaction with the active dienophile, 4-phenyl-1,2,4-triazoline-3,5-dione, and the inversion performed with **36** to ultimately yield **37**. Interestingly, these two approaches become complementary, since they do not involve the inversion of the same stereocenter.

In addition, Boyd's method has also been successfully applied to the synthesis of 3,4-diols such as **40** from *o*-iodobromobenzene (**eq 14**). All combinations of enantio- and diastereomeric ventures are now possible from diol pairs **25**/**41** and **42**/**43** (**Figure 6**). The latter pair corresponds to diols that would be formed by the hydrolytic opening of arene oxides of type **44**, which are produced by the action of more highly evolved eukaryotic enzymes on aromatics.[20,33] Thus, the issues concerning the availability of metabolites in both enantiomeric constitutions and the approach to targets in both absolute configurations are addressed.

The summary of all design principles based on symmetry[11,13,14,67,68] is offered by the drawing in **Figure 7**. Diastereoselectivity issues are controlled by either directing or hindering effects of the biochemically installed diol, whereas the regioselectivity of the first functionalization is controlled by the polarization of the diene system. This regioselectivity also determines the commitment to a specific enantiomeric space, here arbitrarily assigned as "+" for the "upper domain" and "–" for the "lower domain". There are four possibilities for the configuration of the next chiral center to be constructed: syn or anti to the diol in either "+" or "–" space as configured in the enantiomer of the final product (see projection in Figure 7). These operations are relatively easy to control and lead to a fully exhaustive design of a particular class of compounds.[11,13,14,67,68]

There are a number of bond-forming reactions possible from the multiple functionalities of these types of compounds. The diene undergoes a variety of regioselective [4+2] cycloadditions, including its intramolecular variants. Separate cycloaddition chemistry can be initiated singly at the disubstituted olefin. The presence of a polarized diene unit allows for controlled interaction with electrophilic reagents. The allylic alcohol functionalities are amenable for use in Claisen-type rearrangements, as was proposed in the very first publication from our laboratory in 1988[71] and reduced to practice in 1997.[72] Since every carbon atom in these molecules is either unsaturated or oxygenated, the preparation of polyoxygenated compounds, such as cyclitols and carbohydrates, starting from *cis*-dihydroarenediols, is convenient. The logic of this design flows from these considerations and is discussed in the following sections. The oxidation of the periphery of the dienediol and subsequent cleavage of any one

of the six bonds provide access to acyclic chains with defined stereochemistry, as in the case of carbohydrates. Their carbon content is addressed by the controlled oxidative loss of either 0, 1, or 2 carbon atoms from the dienediol unit. The following section briefly outlines the diversity of chemical operations possible with *cis*-dihydroarenediols, and provides examples of specific synthetic applications.

5. Applications to Synthesis

Peripheral oxidative functionalization of dienediols yields the first level of synthons with increased complexity, here shown as "primary synthons" in **Figure 8**. The materials are then further functionalized to "secondary synthons" (**Figure 9**) before a decision is made with regard to the cleavage of the cyclohexane ring. The oxidative functionalization of acetonides **26**, derived from **25**, yields *anti*-epoxides **45**, diols **46**, or aziridines **47**. The unusual production of chloroepoxide **48** seems to be the consequence of 1,4-addition of $KMnO_4$ across the polarized diene. Singlet oxygen and acylnitroso compounds yield cyclic peroxides **49** and oxazines **50**, the latter regiospecifically, and both with the expected anti stereochemistry. Boronate esters[73] and acetals derived from benzaldehyde[74] and other aldehydes[75] have been reported as protecting and directing groups, although the most common protective group remains the acetonide. The functionalization of free diols has been limited to monoprotection as in **51**. In most instances (except for epoxidation in the case of **52**), the stereoselectivity in the transformations of free diols is poor. The details of these reactions can be found in several reviews.[7-11]

These primary synthons can be manipulated further into the secondary synthons shown in Figure 9. The most common transformations involve the removal of the halogen that directed the primary functionalization to the more electron-rich olefin and functioned to preserve the asymmetry. Both primary and secondary synthons (some of which are now commercially available) have been used primarily in cyclitol and sugar syntheses (see the corresponding sections for examples).

The reactivity of the dienediols (free or protected) has been exploited in cycloadditions, leading to C–C, C–O, or C–N bond formation; peripheral oxidation; and further functionalization, as well as partial or full oxidative cleavage. The latter two aspects find use in the general design of carbohydrates.

Interesting applications emerged from Stephenson's group.[76,77] A derivative of the iron complex **55** (**Figure 9**) undergoes nucleophilic addition with sodium malonate, leading to stereospecific C–C bond formation.[77] The epoxyaziridine **64** results from a rearrangement of oxazines of type **50**.[78]

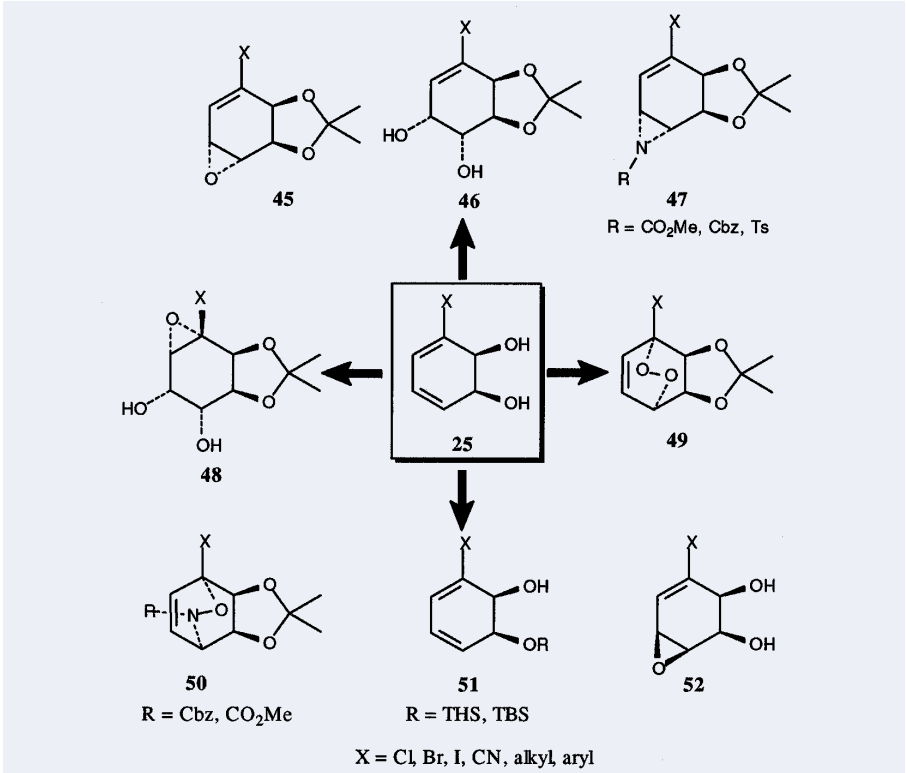


Figure 8. Examples of primary synthons.

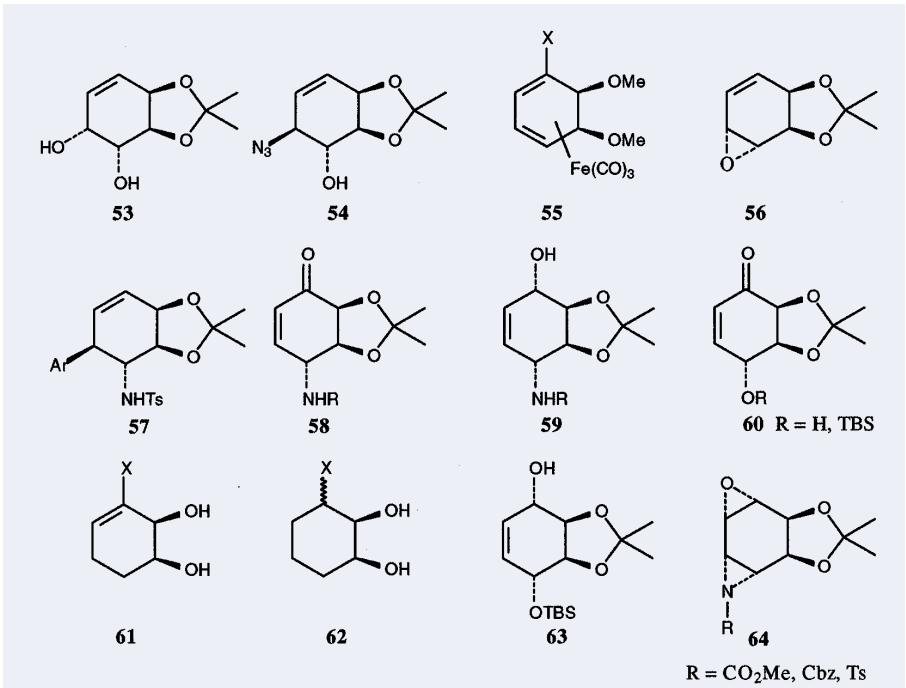


Figure 9. Examples of secondary synthons.

5.1. Cycloadditions

cis-Cyclohexadienediols derived from monocyclic aromatics are reactive towards cycloadditions; the halodienes (X = Cl, Br, I, F), where the diene functionality is quite polarized, are especially reactive. In fact, acetonides **26** dimerize readily, even at (or below) room temperature,[79-81] although the free diols are reasonably stable in the crystalline state. The acetonide of dihydrostyrenediol, **66**, dimerizes to three different Diels–Alder products[82] with spectacular regio- and stereoselectivity, as shown in **Figure 10**.

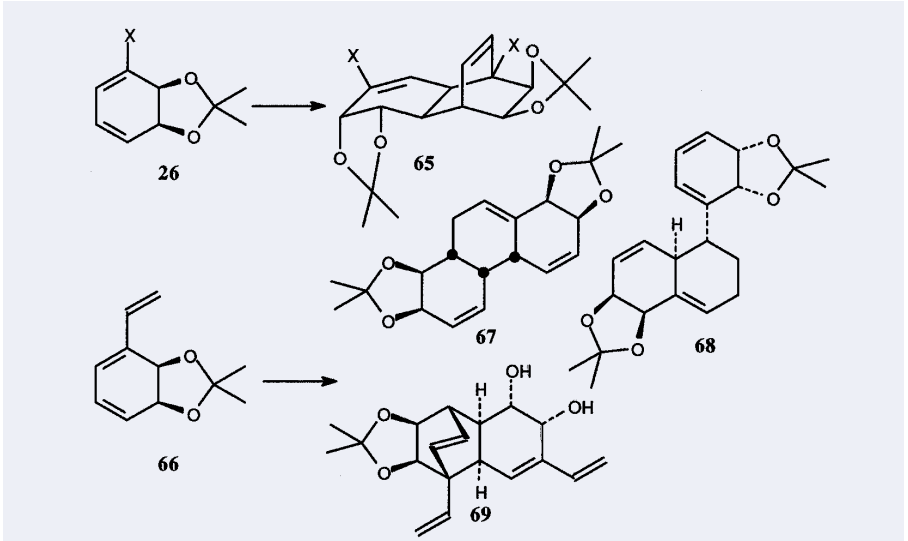


Figure 10. Diels–Alder adducts of some dienediol acetonides.

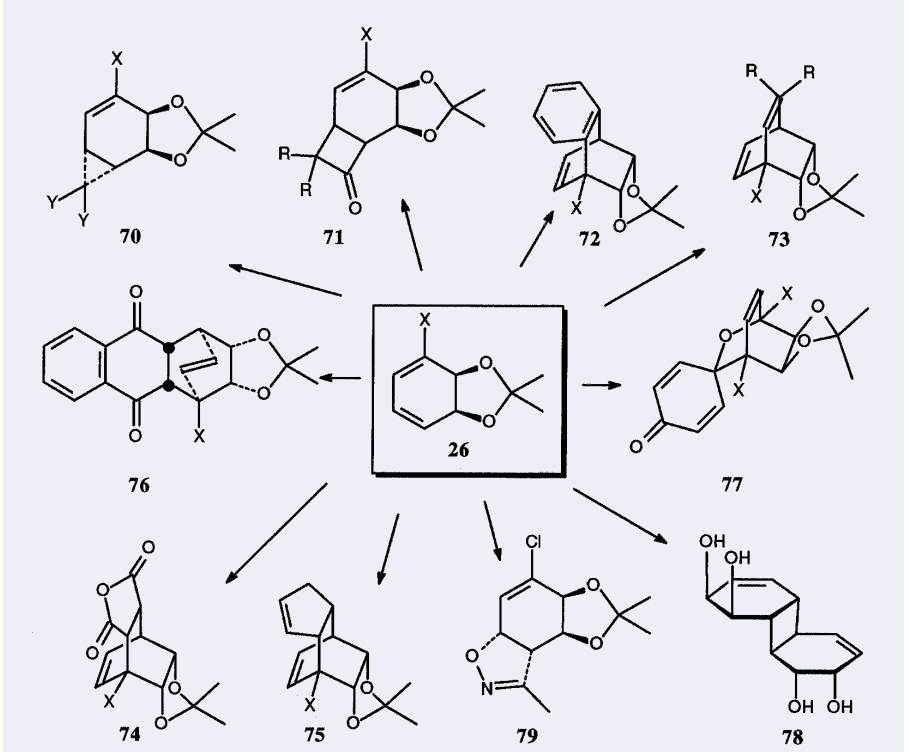


Figure 11. Cycloadditions of some dienediols and their acetonides.

The electronic parameters of *cis*-cyclohexadienediols have been investigated both experimentally[79-87] and by calculations.[83,87] Complete regioselectivity is expected for cycloadditions with polarized dienophiles, such as acylnitroso compounds. Other types of cycloadditions also exhibit preference for the more electron-rich olefin. These parameters have been exploited in many cycloadditions, as indicated in **Figure 11**. The selectivity of cycloadditions of dienediols and their derivatives, where X is not a halogen, is, as expected, much lower. Cyclopropanation;[88-92] ketene addition;[93] benzyne cycloaddition;[84-85] benzo- and naphthoquinone additions ([4+2] and photo [2+2]);[85] a variety of acrylate,[87] propiolate,[87] and maleic anhydride[85] Diels–Alder additions; singlet-oxygen,[68,71,83,94] and acylnitroso cycloadditions[68,78,83,87,95,96] have all been exploited. The *cis*-diol derived from benzene undergoes a photosensitized [2+2] cycloaddition to produce dimer **78** (**Figure 11**).[97] The singlet-oxygen and acylnitroso cycloadditions have found applications in the synthesis of conduritols and conduramines (see examples in the next section and in recent reviews).[8,10,11,13,18,98,99]

Advanced intermediates with applications in natural product synthesis have been obtained by means of simple cycloaddition processes. For example, the lower portion of morphine, with all five contiguous stereogenic centers, has been synthesized by the intramolecular Diels–Alder reaction from dihydrotoluene- and β-azidoethyldihydrobenzenediols, respectively. In the first model study, the diene was partially reduced; this allowed the remaining olefin to function as a dienophile and lead to **82** (**Figure 12**). The more advanced intermediate, **85**, was similarly synthesized from **83**. With diene **86**, the initial cycloaddition produced **87**, which underwent a Cope rearrangement to furnish **88**, possessing the same skeleton as **82**, albeit with a different stereochemistry.[100] Adduct **82** was originally reported with the wrong stereochemistry;[100] the correct stereochemical assignment[101] was made in 1998 by X-ray analysis when discrepancies were noted in the spectra of **82** and **85**. The stereochemistry of **88** was obtained as shown by a Diels–Alder/Cope sequence, but the correlation of the two routes was not chemically confirmed.[100] Banwell has also applied the tandem Diels–Alder/Cope sequence to the synthesis of octalins **91**,[86] and later to intermediates such as **92**, that are used in taxane synthesis.[74]

5.2. Cyclitols, Conduritols, Conduramines, Inositols, and Derivatives

Conduritols A–F, as well as some of the inositols—all shown in **Figure 13**—have been synthesized from either epoxide **45** or **52**,[102] diol **46**, or the singlet-oxygen adduct **49**. Because the details of their syntheses have been reviewed in several instances,[11,15,98,99] only the generalized approaches are shown here.

The *cis*-dihydroarenediols, as well as the primary synthons shown in Figure 8, are ideally suited for the synthesis of this simple class of cyclitols (**Figure 14**).[68,103] Conduramines become available by cleaving the nitrosyl Diels–Alder adducts **50** to ketoamines **58** and hydroxyamines **59**, or by opening epoxides with nitrogen nucleophiles to **54**. Lipase desymmetrization of meso conduramines has been used by Johnson in enantiodivergent syntheses of conduramine A-1.[104] All of the sequences leading to cyclitols begin with the protected cis diol **26** (X = Cl, Br), except the conduritol C synthesis by Carless, which employed the syn epoxide **52**.[102] Inositol synthesis becomes possible by careful peripheral oxidation of the dienediols.

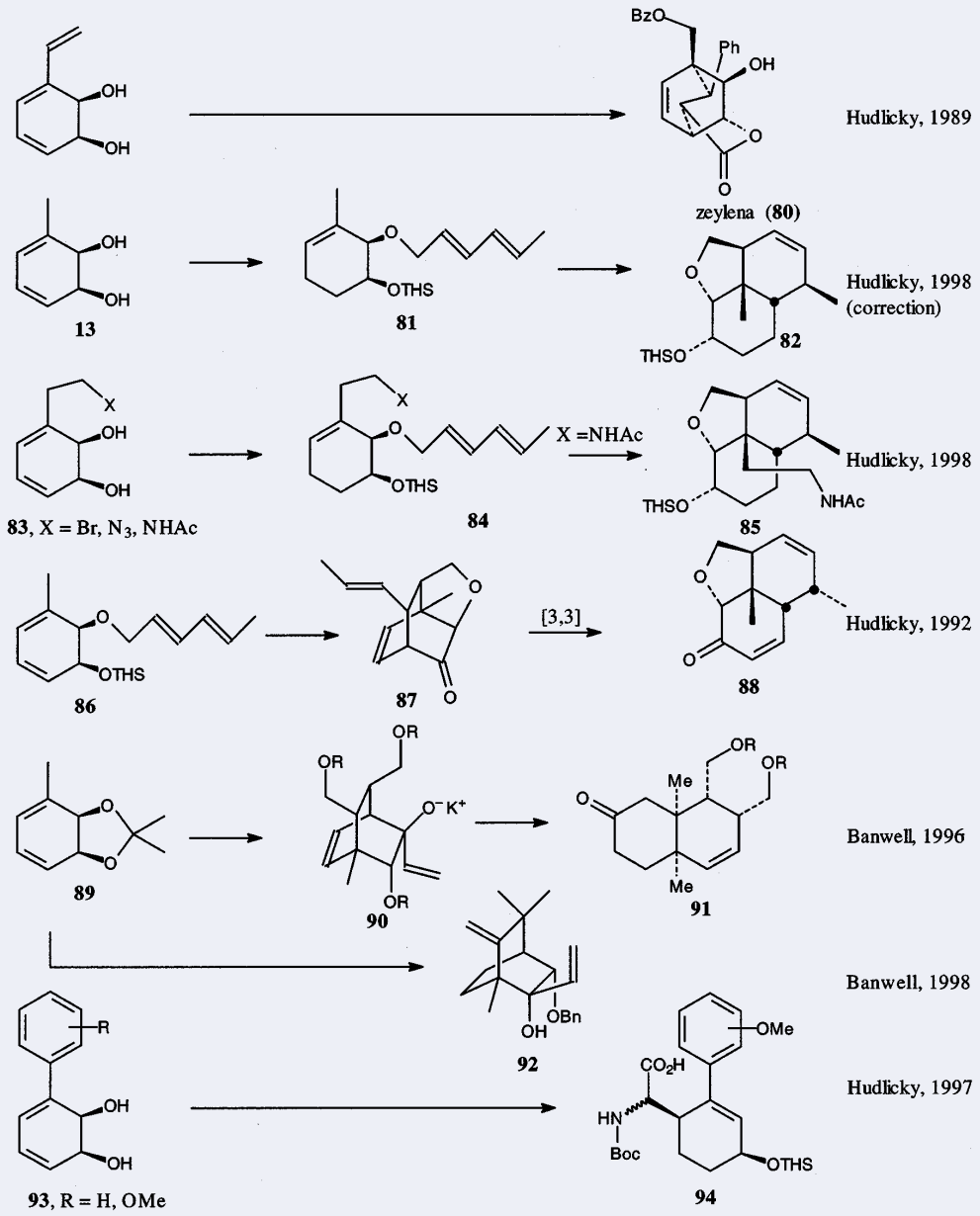


Figure 12. Examples of cycloadditions and sigmatropic processes aimed at natural product synthesis.

Following Ley's pioneering preparation of racemic **7**,[5] a resolution using (–)-menthoxyacetyl chloride[105] produced both enantiomers, as shown in Figure 15. Hudlicky's group accomplished the enantiodivergent preparation of both pinitols (**Figure 15**) by employing the symmetry principles discussed in the previous section.[67,68]

In 1990, we reported two enantiodivergent syntheses of (+)- and (–)-pinitol from optically pure, protected diol **26** (**Figure 15**). The concept of "proenantiotopic symmetry" was first reported in connection with this synthesis, whereby identical sets of reagents were used in a different order to attain enantiodivergence.[67,68]

Of the nine isomeric inositols portrayed in Figure 13, D-*chiro*-, L-*chiro*-, *allo*-, *neo*-, and *muco*-inositols have been synthesized from bromobenzene. D-*chiro*- and *allo*-inositols have also been prepared from the unique chloroepoxide **48**.[106,107] Recently, the preparation of some of these inositols has been optimized to medium scale.[108,109] A recently published handbook compiles structures and includes references to the synthesis of major cyclitols and derivatives.[110]

Amino inositols, fluorodeoxyinositols, and fluorodeoxyamino inositols have also been synthesized, as shown in **Figure 16**. In all of these preparations, careful planning with respect to the placement of the electrophilic epoxides (the recipients of F^-, N_3^-, NHR, OH, etc.) is the key to efficient synthesis. Recently, 3-deoxy-3-fluoro-L-*chiro*-inositol (**117**) has been made, via fluorohydrin **116**, by the selective opening of vinyloxirane **45** with fluoride.[111] Fortamine (**118**) was prepared by Vandewalle from the meso diol derived from benzene.[112] The fluoroamino inositol **119**, along with its enantiomer, were synthesized recently in our laboratories because of its structural resemblance to the antibiotic L-*myo* inosamine.[113] Conduritol analogs such as **120**[114] and **121**[115] led to investigations of "unnatural" derivatives that contain the cyclitol or conduramine motifs.

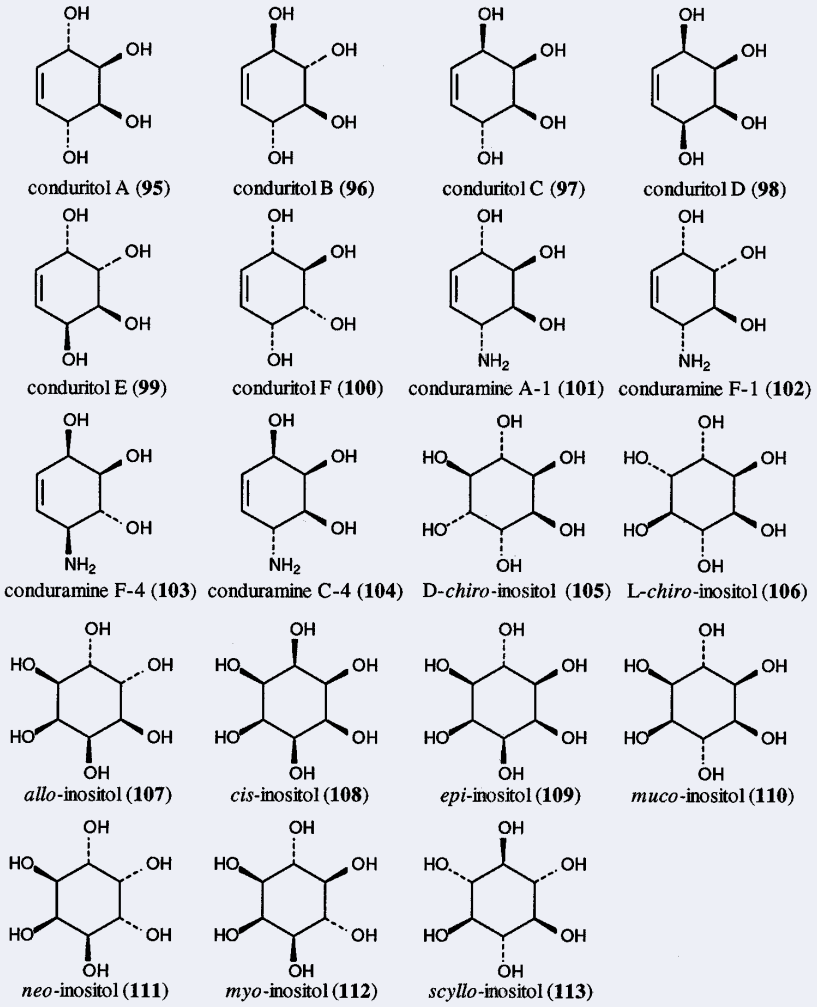


Figure 13. All conduritols, conduramines, and inositols.

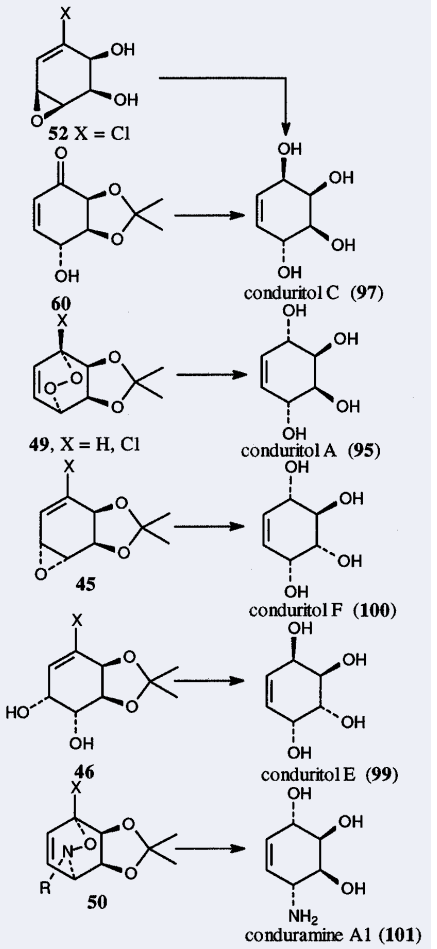


Figure 14. Conduritol and conduramine synthesis.

As the field of inositol and cyclitol synthesis matured, more complex structures were targeted. Dihydronaphthalenediol-derived analogs such as **123** were synthesized from the epoxydiol **122**, and were shown to have interesting molecular and biological properties.[116] Dimeric ethers and amines of type **124** (**Figure 17**) were also recently prepared via *cis*-dihydronaphthalenediol, and were shown to have interesting solid-state properties.[117,118]

The oligomers of L-*chiro*-inositols such as **127** are made by iterative coupling of primary synthons **125** with vinyl oxiranes **45**. Compound **127** possesses a natural β-turn in its secondary structure.[119,120] The amino cyclitol dimeric ether **128**, prepared similarly, chelates calcium ions and forms helical assemblies in the solid state (**Figure 17**).[120] The chemistry of the higher inositol conjugates (an octamer has recently been synthesized) and their derivatives is likely to have a major impact on medicinal and materials chemistry in the near future.

5.3. Carbohydrates

To execute a general and exhaustive design of carbohydrates, it is necessary that the cyclohexene ring be cleaved at a selected location and the resulting compound reductively cyclized in a premeditated fashion. The placement of heteroatoms other than oxygen onto the periphery of the dienediol also provides access to heterosugars. By simple oxidation of the periphery of the dienediol, followed by selective reductive cyclizations, many permutations of hexoses become possible, as shown in **Figure 18**. Notice that, even though there are two options for 6- and 5-membered-ring closures, the resulting sugars will be diastereomeric, depending on the definition of peripheral stereochemistry prior to cleavage and recyclization. Thus, all 16 isomers of single hexoses are available from a single precursor as a function of detailed planning, usually from primary synthons such as epoxides or diols.

A detailed analysis of this strategy has been published,[11,13-17] and most examples have been reduced to practice. The first application involved the two-carbon oxidative scission of **26** to provide protected erythruronolactone **135** in 51% yield in just 3 steps from bromo- or chlorobenzene.[121,122] A periodate cleavage of chloroepoxide diol **48** gave lactone **135**, a synthon with a proenantiotopic plane of symmetry, in 38% overall yield (**Figure 19**).[123]

Both enantiomers of erythrose (**136**), as well as L-ribonolactone (**137**), have been made from **135**. Because of its symmetry, the latter compound was found to be a useful synthon for pyrrolizidine alkaloid synthesis (see Figure 24).

Azasugars were synthesized from azido alcohols of type **138** (all four diastereomers of this synthon were prepared[124]) by oxidative cleavage of C6–C1 followed by recyclization of the reduced nitrogenous function, as in the synthesis of mannojirimycin (**139**) (**Figure 20**).[125]

Reductive cyclization employing different hydroxyl groups results in the selective

syntheses of 2-, 3-, or 4-aminosugars, the latter made from the isomeric azidohydrin **140**. Glucosamine (**141**) and deoxyaminomannose **142** are prepared in this fashion.[126] Sphingosines **143** (all four isomers) have been prepared via azidoerythroses **144** by successive cleavage of C6–C1 and C2–C3 in intermediates **138** and **140**, after the stereochemistry of the alcohol and azido groups had been defined (**Figure 20**).[124,127] Deuteromannose derivative **145** was prepared from pentadeuterobromobenzene by this strategy.[128]

Following the principal strategy of first precisely defining the peripheral substitution and then applying oxidative cleavage/reductive cyclization, deoxyfluorosugars also become available, as exemplified by the glucose and mannose derivatives **147** and **148**, respectively.[129]

Deoxysugars such as *pseudo*-β-D-altropyranose (**149**)[130] and a pseudosugar-inositol conjugate, **150**,[131] were prepared as shown in **Figure 21**. These examples demonstrate the enormous power of the reductive cyclization technology as a fully exhaustive method of synthesis for *any* carbohydrate derivative. The technique relies on the definition of stereochemistry on the cyclic precursor prior to oxidative cleavage. Its various iterations have since been used by Banwell to construct sugars such as nonulosonic acid derivative **152** from chlorobenzene,[132] and by Johnson in the synthesis of azasugars and analogs.[133,134] The rationale for the exhaustive strategy for carbohydrate synthesis has been delineated in detail on several occasions.[11,14,15,17]

Cleavage and reductive cyclization of conduramines, such as **59**, obtained by lipase-mediated resolution, led to 1-deoxygalactonojirimycin (**153**), as reported by Johnson (**Figure 22**).[133]

A combination of Suzuki-type coupling with oxidoreductive recyclization strategy has been exploited by Johnson in the preparation of various glycomimetics, e.g., aza-*C*-disaccharides (**Figure 22**).[134] It is expected that applications such as these will grow as the complexity of the targets that are attained increases.

5.4. Alkaloid Synthesis

Certain oxygenated alkaloids lend themselves quite naturally to considerations involving the incorporation of *cis*-dihydroarenediols into their design. In addition, the enantiodivergent design that furnished both enantiomers of pinitol has also been found to be applicable to erythruronolactone, which possesses the same proenantiotopic plane of symmetry.

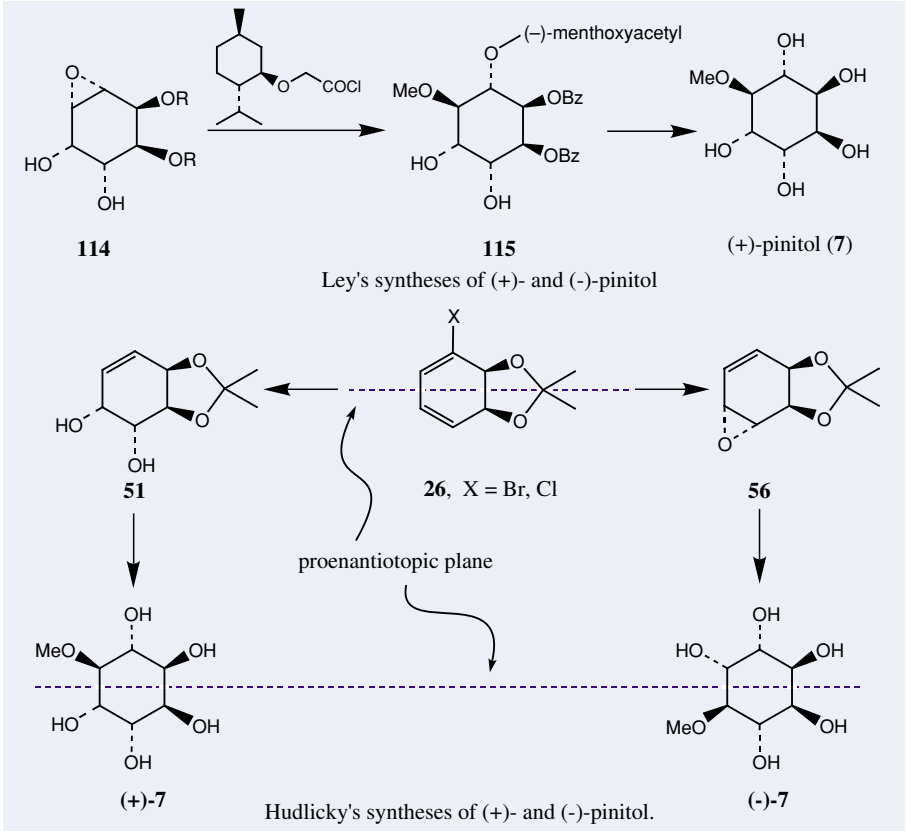


Figure 15. Enantiodivergent syntheses of pinitols.

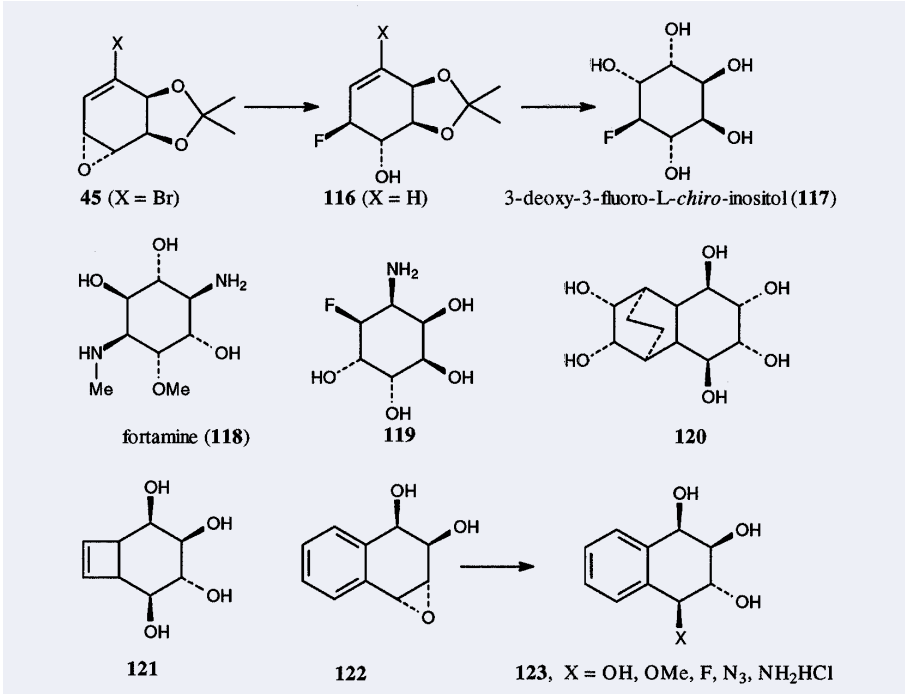


Figure 16. Analogs of conduritols, conduramines, and inositols.

Thus, either conduramine **58**, cyclitol **60**, or erythruronolactone **135** can be manipulated directly into both enantiomers of a target compound by principles of the commutative law of algebra (**Figure 23**). This law states that the summation of a set of numbers is independent

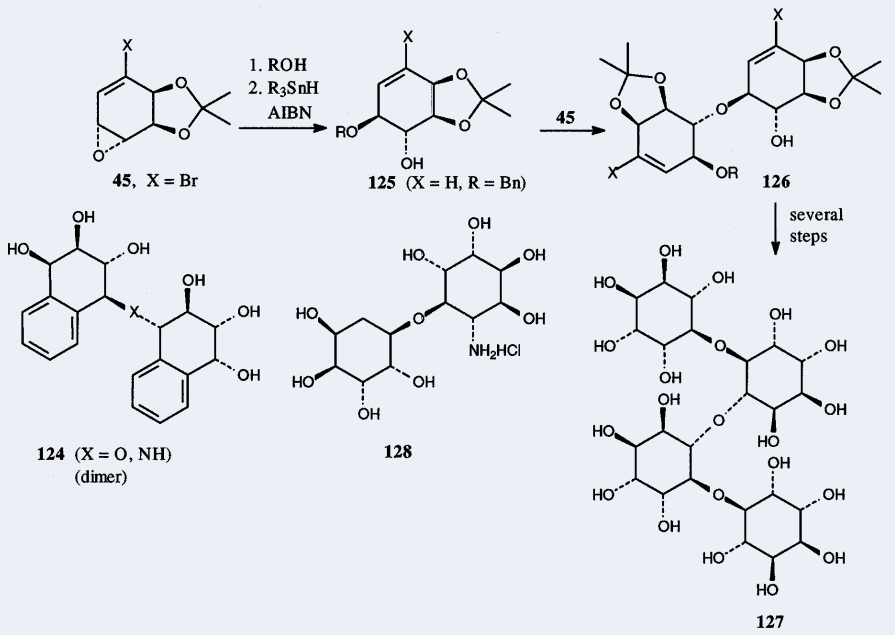


Figure 17. Inositol oligomers synthesized via iterative coupling.

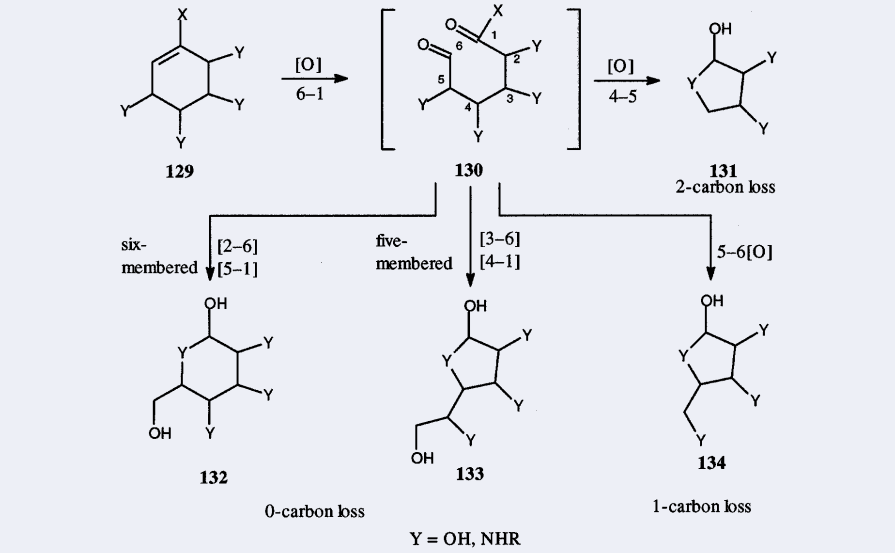
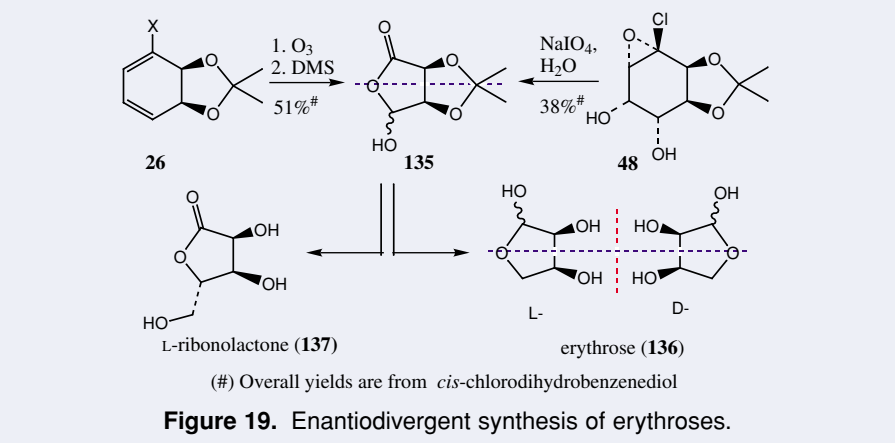


Figure 18. Examples of permutations in oxidoreductive cyclizations for carbohydrates.



(#) Overall yields are from *cis*-chlorodihydrobenzenediol

Figure 19. Enantiodivergent synthesis of erythroses.

of the order of addition of individual numbers. Thus, it is the precise ordering of chemical events (otherwise identical in the pathways to each enantiomer) that determines the symmetry of the product.

Figure 24 displays another application of this principle to the synthesis of trihydroxyheliotridanes.[122,135] Erythruronolactone (**135**) was converted to D- and L-erythroses by taking advantage of different rates of reaction at the carboxylate vs. aldehyde termini.[121,122] Wittig synthesis of the diene, followed by conversion of the remaining alcohol to the azide, allowed the formation of vinylaziridines **158** in both enantiomeric series. In both series, these were formed as diastereoisomeric pairs from *E/Z* dienes in a 5:1 ratio. Thermolysis generated the pyrrolizidines in an overall [4+1] intramolecular pyrrolizine annulation,[136] whose development and history have been reviewed.[110] Pyrrolizidine alkaloids synthesized by this method in our laboratory in the racemic series included platynecine, hastanecine, turneforcidine, dihydroxyheliotridane, supinidine, isoretronecanol, and trachelanthimidine, validating the [4+1] pyrrolizine annulation as a fully general method of synthesis.[135,136] Because of the endo mode of cyclization of the intermediate ylide, **160**, that is generated by thermolysis, the diastereomers of vinylaziridines converged stereoselectively to single isomers of pyrrolizidines in each series.

In 1992, taking advantage of the rapid generation of conduramines by the acylnitroso Diels–Alder reaction, we synthesized lycoricidine from bromobenzene in nine steps (**Figure 25**).[87,95] Oxazine **50** was reduced and acylated to the functionalized conduramine derivative **161**. The abnormal Heck cyclization followed by deprotection yielded (+)-lycoricidine **162**. The racemate of the natural product was also synthesized by Martin along a similar pathway from *cis*-dihydrobenzenediol.[137]

Kifunensine (**165**), an unusual indolizidine alkaloid, which also classifies as a hydroxylated piperidine (or azasugar), has been obtained in conjunction with our projects in carbohydrate chemistry involving oxidative cleavage of the functionalized cyclohexene **163** and its appropriate reductive cyclization (**Figure 26**).[138,139] Azido alcohol **163** was selectively transformed first to the azamannosolactone or mannojirimycin intermediate **139**, whose cyclization with oxalylamide did not yield kifunensine; however, the furanose form of azidomannose **164** was successfully transformed to kifunensine[138,139] by a known literature procedure.[140]

Our interest in amaryllidaceae alkaloids led us to the first asymmetric synthesis of pancratistatin (**169**), attained in 13 steps from bromobenzene via the addition of arylcuprate

166 to vinylaziridine **47** (**Figure 27**). In this first-generation synthesis,[141] the robust aryl amide and tosyl amide moieties had to be manipulated to intermediate **168**, whose treatment in refluxing water under pH controlled conditions (catalytic amount of sodium benzoate) furnished the target alkaloid in a remarkable sequence of five consecutive reactions.[141-143]

In the second-generation attempt,[142] aimed at 7-deoxypancratistatin (**173**), some major improvements were realized by taking advantage of the potential electrophilicity of the carbamate group in aziridines **171** in order to avoid using the robust benzamide moiety. The modified Bischler–Napieralski cyclization of **172** under the conditions reported by Banwell[144] gave the cyclic amide and eventually led to an 11-step synthesis of 7-deoxypancratistatin (**Figure 27**).[142,143] The enantiomers of both alkaloids can be prepared from 4-substituted iododiols **26** by the application of the "racemic switch" method of Boyd.[65] *ent*-7-Deoxypancratistatin has recently been synthesized from **26** via an additional lipase-catalyzed enrichment procedure.[145]

The recognition that amaryllidaceae alkaloids as well as morphine alkaloids may be viewed as oxygenated biphenyls (**Figure 28**) led us to consider a design in which synthons such as **177** would be made by either direct enzymatic oxidation of the corresponding biphenyls, or by a Suzuki-type coupling of *cis*-halodihydrobenzenediols with the appropriate aryl fragment. Such thinking led us to design the synthesis of narciclasine (**Figure 29**).[146]

The synthesis took advantage of the unique symmetry found in **178**—the metabolite obtained by biooxidation of *m*-dibromobenzene—and its subsequent cycloaddition with acylnitroso carbamate to oxazine **179**. Suzuki coupling of **179** with arylboronic acid followed by reductive cleavage of **180** did not generate the expected hydroxycarbamate. Instead, the unsaturated ketone **181** was formed and then transformed into the anti alcohol by means of directed hydride reduction, or standard reduction followed by Mitsunobu inversion (**Figure 29**). Finally, closure of the B ring was made through the Bischler–Napieralski-type reaction as in the case of 7-deoxypancratistatin synthesis.[142,146]

The enzymatic dioxygenation of biphenyls was pursued, and a number of metabolites have been identified, among them the desired diol **182** that is derived from 2,3-dimethoxybiphenyl.[147] An approach to morphine was envisioned, where the stereochemistry of the C–14 and C–9 centers would be controlled by the outcome of a sigmatropic process, which would transfer the configuration of one of the OH groups to a carbon center. Ideally suited

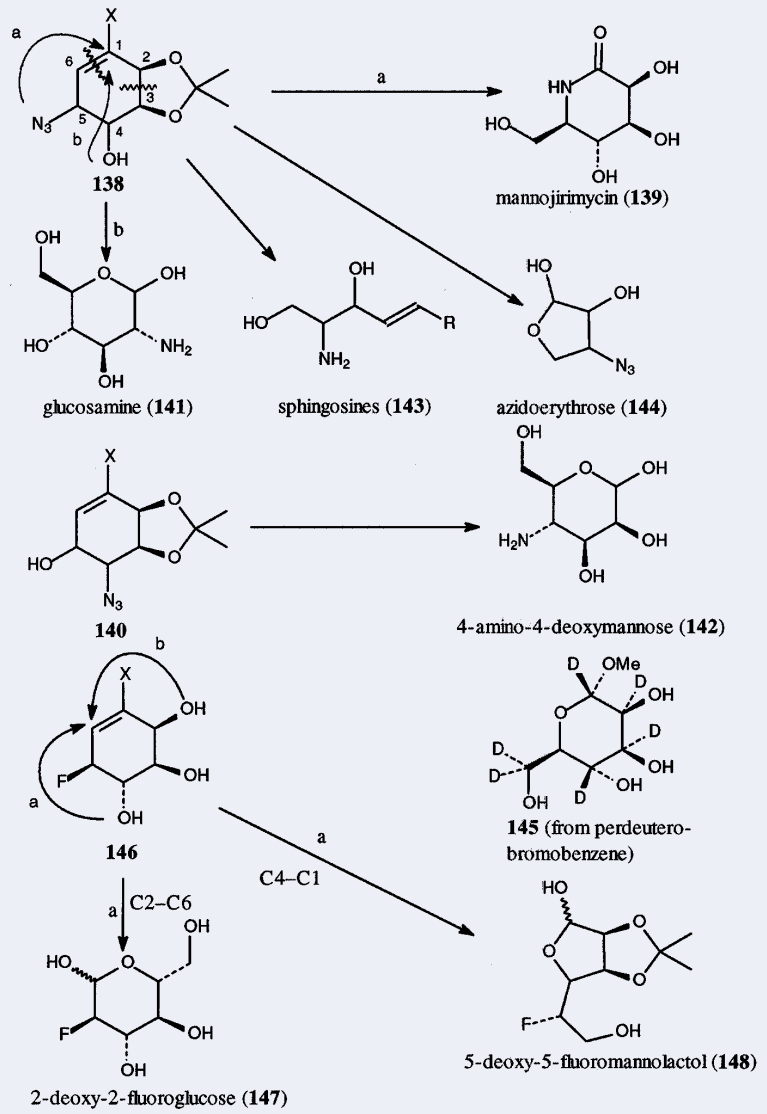


Figure 20. Design of aza-, amino-, fluorodeoxy-, and perdeuterosugars by oxidative cleavage–reductive cyclization strategy.

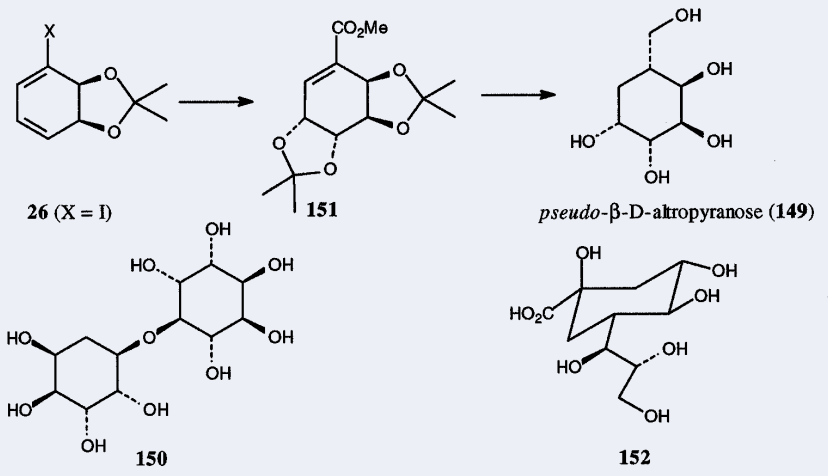


Figure 21. Synthesis of deoxysugar analogs.

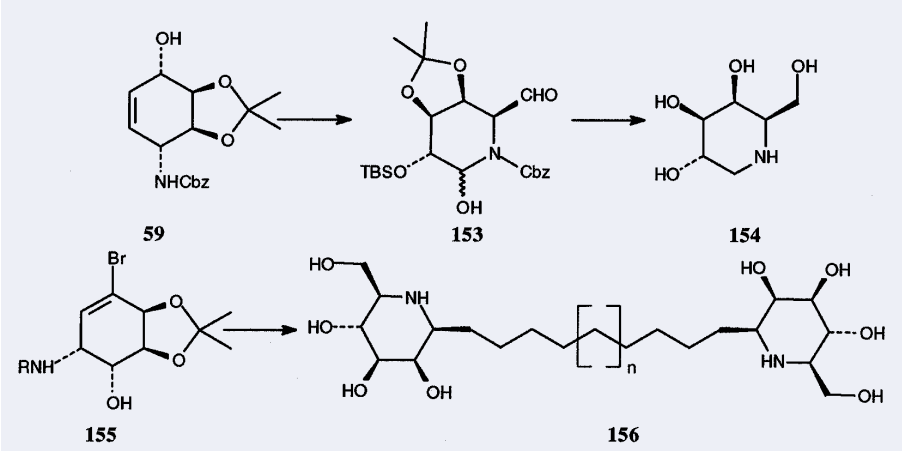


Figure 22. Syntheses of nojirimycin analogs and carbon-tethered glycomimetics.

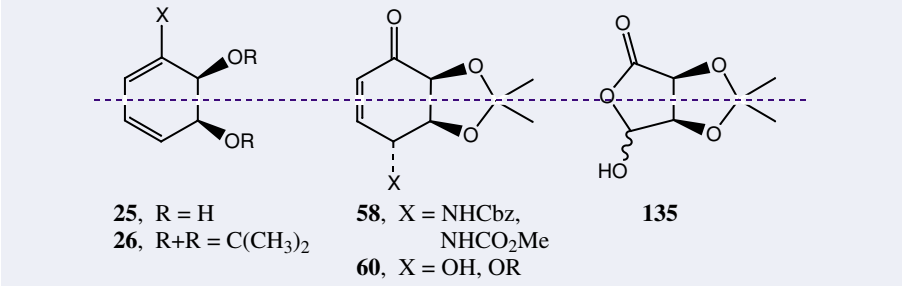


Figure 23. Synthons containing a proenantiotopic plane.

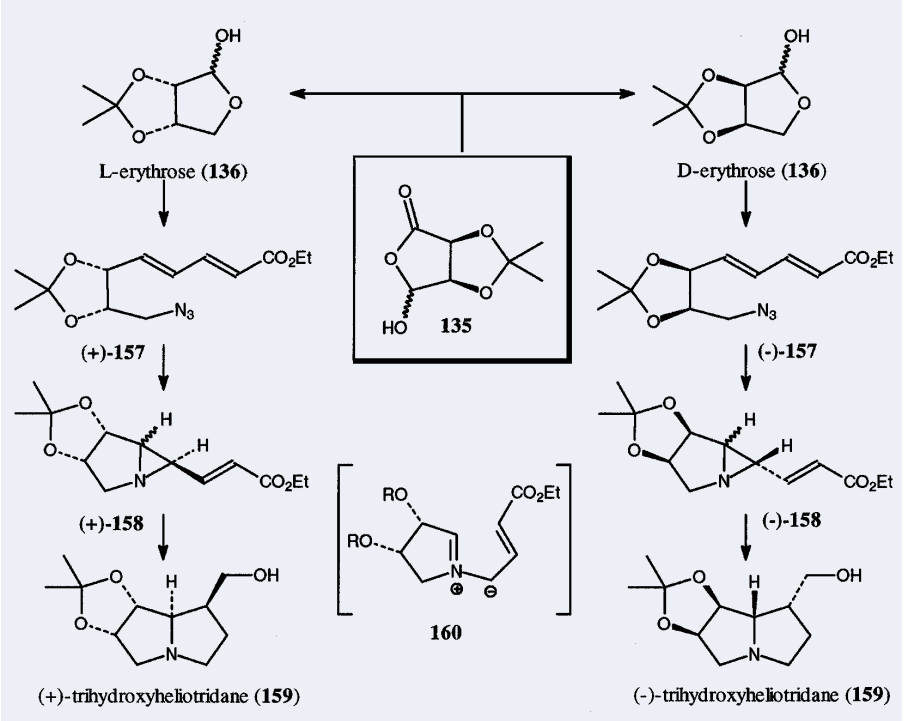


Figure 24. Enantiodivergent synthesis of oxygenated pyrrolizidine alkaloids.

for this purpose is the Kazmaier modification[148] of the Claisen rearrangement of the corresponding glycine enolates, and we have applied it to glycinate **183** (**Figure 30**).[72] Amino acid esters generally fail to rearrange under standard Ireland conditions, but react successfully in the presence of a Lewis acid, such as $ZnCl_2$ or $SnCl_4$. To fully control the relative stereochemistry of C–9 and C–14, **184**, which was generated as a 4:1 mixture of stereoisomers, was transformed into lactone **185** in which the bulky NHBoc group would be epimerized to the exo surface of the bicyclic ring system.

Diols **186**, derived from β-bromoethyl and *o*-bromo-β-bromoethylbenzene, comprised the starting point for a tandem radical cyclization approach to morphine in the former case and a stepwise cyclization in the latter (**Figure 31**). In the tandem as well as the stepwise approach, the bromocatechol unit required for the aromatic ring of morphine was made enzymatically from bromobenzene with an organism that also expressed the second enzyme in the pathway, namely, the diol dehydrogenase.[149,150]

The tandem process, modeled after Parker's approach,[151] provided low yields of the pentacyclic precursor **188**, with the epi configuration at C–14 (**Figure 31**).[149,150] When *o*-bromo-β-bromoethylbenzene was first converted to the isoquinoline derivative **189**, through a single radical cyclization followed by attachment of the bromocatechol (in an ent configuration), *ent*-morphinan (**190**) was attained.[150] The isoquinoline formation was nonstereospecific with respect to C–9 (morphine numbering) and resulted in a 2:1 mixture of isomers (α/β). However, the isoquinoline in the correct enantiomeric series was obtained selectively via acid-catalyzed cyclization of the acyliminium salt **191**.[152] Dibenzoate **191** yields **192** stereospecifically, and the trans isomer of **191** gives accordingly the α-isomer of **192**, thus providing for a fully enantiodivergent approach to morphine. The mechanistic details of the acid-catalyzed cyclization of **191** and its trans isomer have recently been published.[153] Further refinements in this multigeneration process are ongoing and include the generation of precursors for **191** by electrochemical oxidations.[152] Additional routes to morphine are being pursued via Diels–Alder cycloadditions of compounds related to **85** and **88**, but containing the required elements of the aromatic ring of morphine.

5.5. Miscellaneous Natural Products

The incorporation of certain *cis*-dihydroarenediols into synthetic sequences results almost always in a significant shortening of the routes to the desired targets. We recognized such advantages in our pursuit of the total syntheses of natural products, even during the very first project that we undertook in this area.[71] The protected dihydroxylated

cyclopentenone **194** has been used by Johnson in a triply convergent synthesis of prostaglandin $PGE_2\alpha$ (**195**) (**Figure 32**).[154,155] The starting enone itself is available in several steps from arabinose by published methods,[156-158] only two of which employ the diols derived from either chlorobenzene[158] or toluene.[71,158] Ozonolysis of the diol derived from toluene provides ketoaldehyde **193**, which is dehydrated with alumina to provide the important enone, **194**, in just three operations from toluene.[71] An alternative to this process (sometimes not easily reproduced because of the nature of the aluminum oxide catalyst) has been developed by using the diol derived from chlorobenzene and its high-yielding ozonolysis to erythruronolactone (**135**); intermediate **135** was converted to **194** by the method of Borchardt (**Figure 32**).[156]

The bicyclic enone, **194**, is a very useful five-carbon synthon (every carbon is differentially functionalized), and we have used it in a synthesis of specionin (**200**), an antifeedant for the spruce budworm.[159] This particular approach relied on the [2+3] intermolecular cyclopentene annulation developed in our laboratories,[160] and provided specionin via vinylcyclopropane **197** and its rearrangement (thermal or fluoride ion-catalyzed)[160] products, cyclopentenes **198** or **199** (**Figure 33**). Noteworthy in this synthesis is the fact that the initial biochemically installed asymmetry is propagated through the synthesis and is later destroyed in the final elaboration to the bisacetal ring in **200**.

The unusual natural product zeylena (**80**), containing a *trans*-diol unit, has been investigated in connection with the antitumor properties of related cyclohexene oxides. We approached its synthesis from the diol derived from styrene by "protecting" the reactive triene unit via its Diels–Alder reaction with diethyl azodicarboxylate (DEAD) (**Figure 34**).

Following the Mitsunobu inversion of the distal hydroxyl with cinnamic acid, the triene was liberated; intramolecular Diels–Alder reaction with cinnamate set the required bicyclo[2.2.2]octane framework. Further oxidative adjustments of the styrene double bond led to the synthesis of zeylena.[161]

Methyl shikimate (**206**) was synthesized by Johnson[104,162] from the meso diol of benzene via lipase resolution (**Figure 35**).

Both enantiomers have been obtained by transforming the resolved conduritol A derivative, **204**, into the iodoenone **207**. Vandewalle[163] reported a synthesis of shikimate as portrayed in Figure 35. In this synthesis, the protected conduritol **209** was transformed via Mitsunobu elimination and subsequent epoxide opening to dithiane **210** and further to methyl shikimate (**206**).

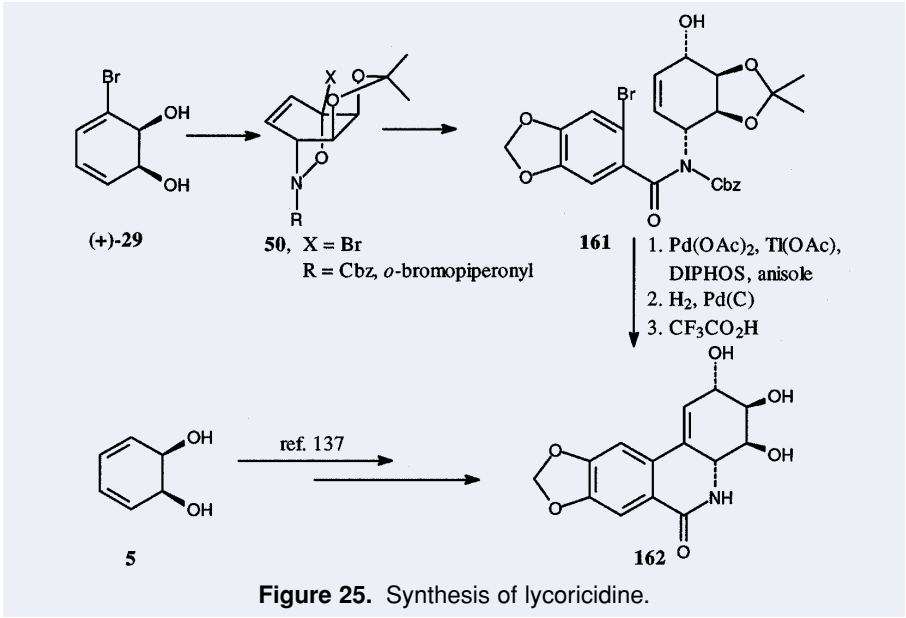


Figure 25. Synthesis of lycoricidine.

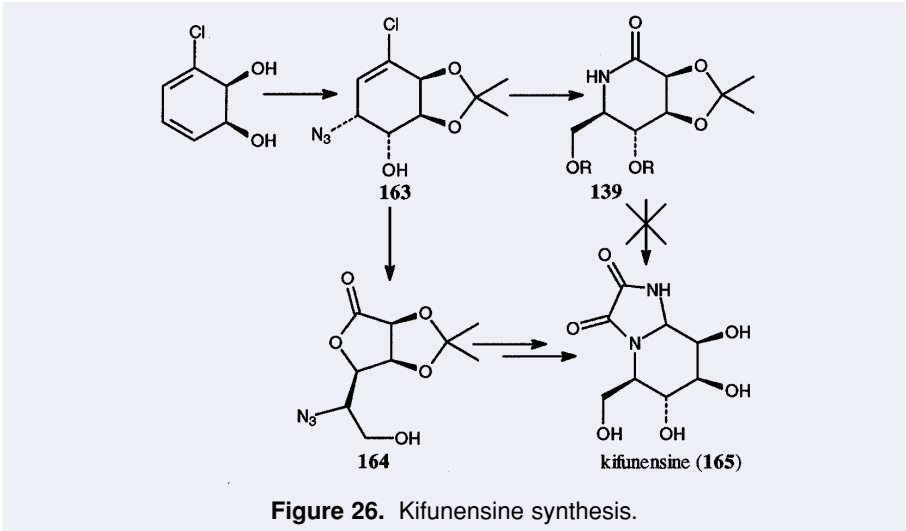


Figure 26. Kifunensine synthesis.

Coupling of synthons derived from **25** to C_2-symmetric derivatives and preparation of phenanthrene-type ring systems has been reported recently.[164]

Banwell synthesized tropolones from dihydrobenzene- or dihydrotoluenediols[88] by taking advantage of the cyclopropanation of the double bonds in the dienediol (**Figure 36**).

The *meso*-diol **25** (X = H) was cyclopropanated, the diol unit deprotected, oxidized, and rearranged with Lewis acid to tropolone **213**. In the case of dihydrotoluenediol, the selectivity of the cyclopropanation favored the more electron-rich (i.e., methyl-bearing) olefin; this was also the case with bromodihydrobenzenediol (**214**). This particular application, followed by the two-carbon oxidative-scission strategy outlined earlier, gave a differentially functionalized cyclopropane suitable for elaboration into chrysanthemates or other pyrethroids, such as deltamethrin (**219**).[89]

Banwell applied the anion-accelerated oxy-Cope rearrangement of bicyclo[2.2.2]-octanes, derived from *cis*-dihydrotoluene-diol, to the synthesis of the taxane AB ring system (**Figure 37**). The required bicyclo[2.2.2]octane framework was generated by iminoketene addition to yield **220**. The Cope rearrangement generated the oxygenated core of the AB ring system of taxol, **222**. In a more advanced study, the initial adduct, **224**, was subjected to transannular cyclization to provide the tricyclic skeleton **225**, the fragmentation of which, modeled after Holton's taxane synthesis, furnished the ring A allylic alcohol, **226**.[74]

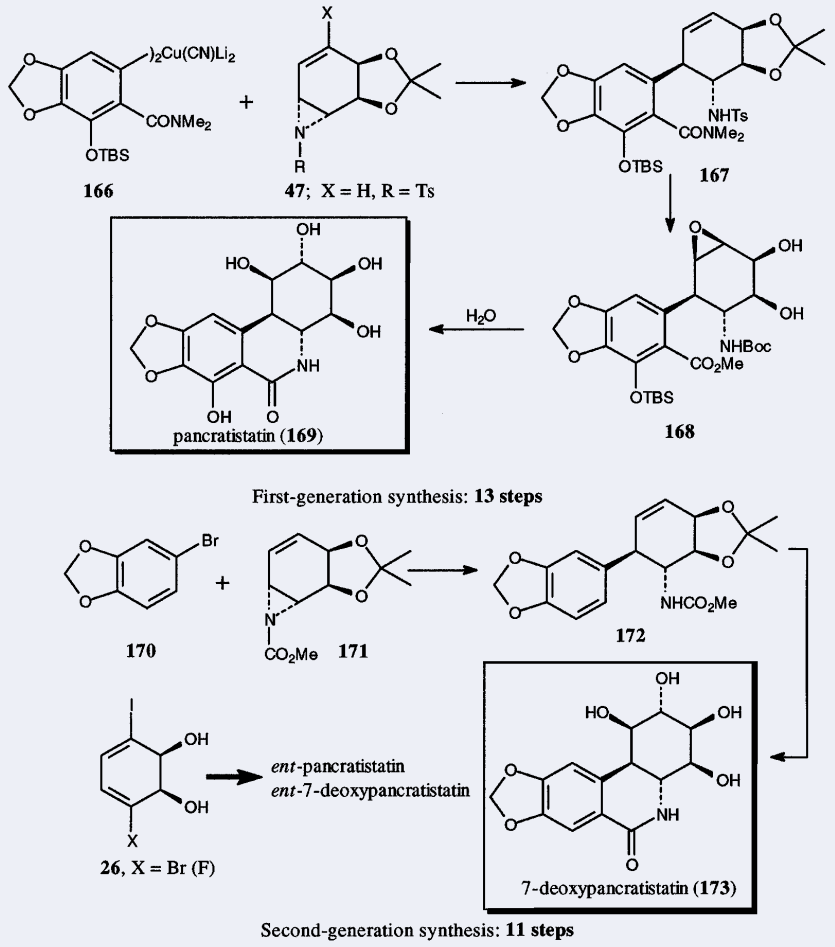


Figure 27. First asymmetric synthesis of pancratistatin and second-generation synthesis of (+)- and (–)-7-deoxypancratistatin

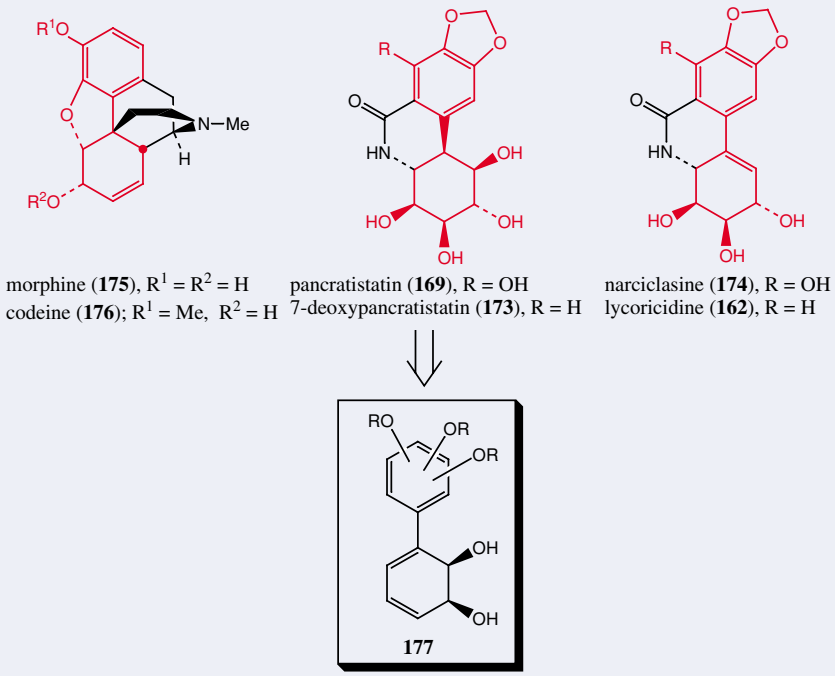


Figure 28. Disconnection of morphine and amaryllidaceae alkaloids to oxygenated biphenyls.

5.6. Recent Applications of Commercial Significance

Several applications of commercial value of the *cis*-cyclohexadienediols have already been reduced to practice. In addition to the pioneering work of ICI (now Zeneca) on the commercial synthesis of polyphenylene[3,4] from benzene via the corresponding meso diol, and the medium-scale preparation of several inositols (D-*chiro*-, L-*chiro*-, *allo*-, *muco*-, and *neo*-) published by our group, there are other examples as shown in **Figure 38**.

Merck considered the biocatalytic production of dihydroindenediol for incorporation into the AIDS drug indinavir.[165] Genencor manufactures indigo by a combination of metabolic engineering of the aromatic amino acid pathway and naphthalene dioxygenase-mediated oxidation of indole to *cis*-dihydroindolediol, which dehydrates to indoxyl, the precursor of indigo.[166,167] The preparation of D-*chiro*-inositol and other inositols has been performed on a medium scale (50–100 g) and can be considered easily scalable to multikilogram quantities.[108] It is expected that other targets of commercial significance will soon employ some of the metabolites discussed in this review in their synthetic sequences.

Quite recently, both chloro- and bromodihydrobenzenediols have been used in reactions on polymer supports.[168] Ketalization was accomplished on polystyrene resin via benzyl ether linkers, as depicted in Figure 38. Many diverse structures have been generated by these methods and freed from the resin by CF_3CO_2H. The yields reported are comparable to those from the solution-phase synthesis of similar compounds.

6. Conclusion and Outlook

It is evident that a tremendous amount of work has been accomplished in the utilization of metabolites derived from aromatics. The pioneering work of Gibson, Ribbons, and the EPA group in Pensacola (associated with the University of Minnesota) made it possible to lay the groundwork for the synthetic community to take full advantage of the rich potential of these compounds. Yet, the expansion of chemoenzymatic methods in general, and the use of *cis*-dihydroarenediols in particular, has hardly begun, as evidenced by the relatively few groups worldwide involved in this area.[6,14] The applications to synthesis have so far originated in only a few of the diols listed in the tables. More complex strategies, as well as the use of tandem reaction sequences and an expanded reservoir of polyfunctional metabolites, should support further growth of this discipline. Without a single exception, all

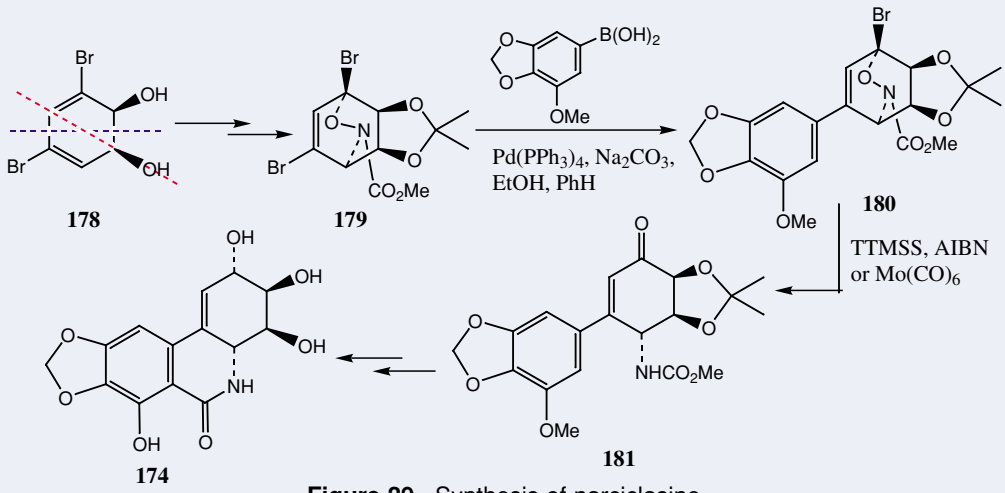


Figure 29. Synthesis of narciclasine.

total syntheses (certainly those from our laboratory) that incorporate a *cis*-diol in the sequence toward the target molecule are considerably shorter than the traditional approaches in the literature. This trend will no doubt continue with new applications. The readers are invited to view the collection of structures in the tables and apply them in their own innovative designs.

7. Acknowledgments

The authors are grateful to the many coworkers who participated in the ventures described in this review during the period 1988–1998, and whose names are listed in the citations. The generous financial support for this work came from NSF (CHE-9315684, CHE-9521489 and CHE-9615112), EPA R82613, Genencor International, Mallinckrodt Specialty Chemicals, Jeffress Trust Fund, TDC Research, Inc., TDC Research Foundation, and NIH (support of Gibson's work only). Several outside postdoctoral fellowships (Michel Desjardins, Kurt Konigsberger, and Jacques Rouden) are also acknowledged. Logistical help from Dr. Gregg Whited, from Genencor International, Inc., is greatly appreciated. The authors are also in debt to Prof. Gustavo Seoane (Universidad de la República, Montevideo, Uruguay) for his initial input. Careful proofreading and many suggestions for the final draft were provided by Dr. Josie Reed, Prof. Douglas Ribbons, and Dr. Sol Resnick. To all these individuals go our heartfelt thanks. Last, but not least, one of us (TH) is indebted to Dr. Larry Kwart, whose convincing arguments and practical advice led to the establishment of microbial oxidation technology in the group. Without his initial input, none of the work described in this review would have ever come to fruition.

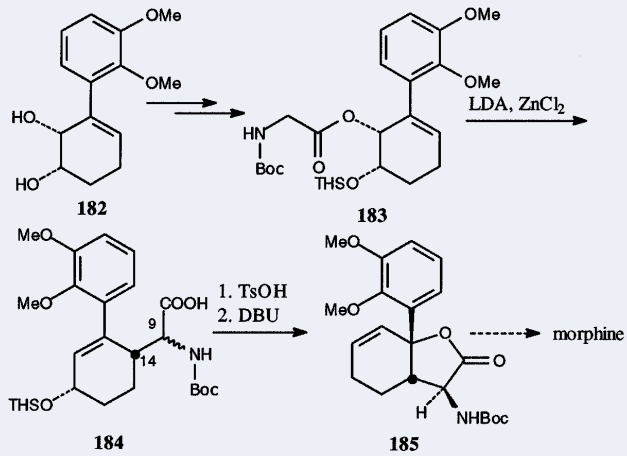


Figure 30. Claisen rearrangement approach to morphine.

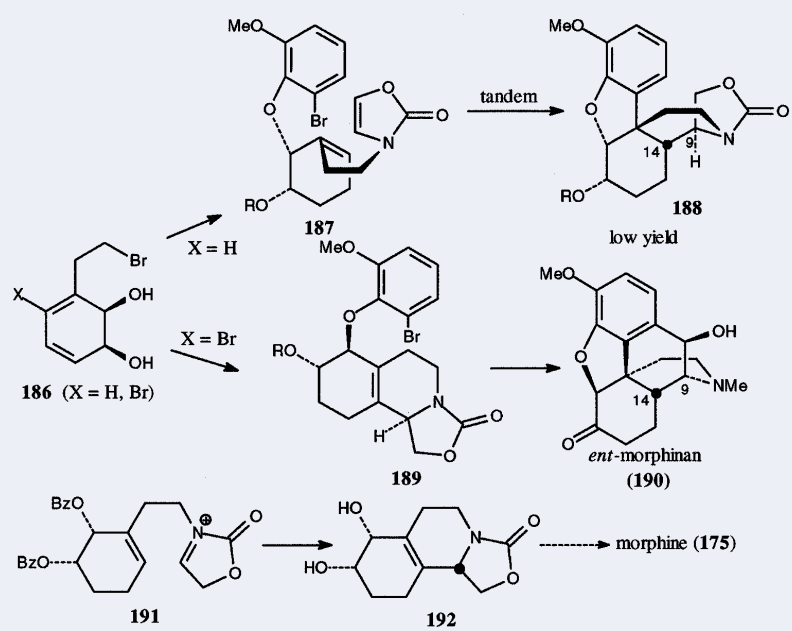


Figure 31. Tandem vs. stepwise radical cyclization approach to morphine.

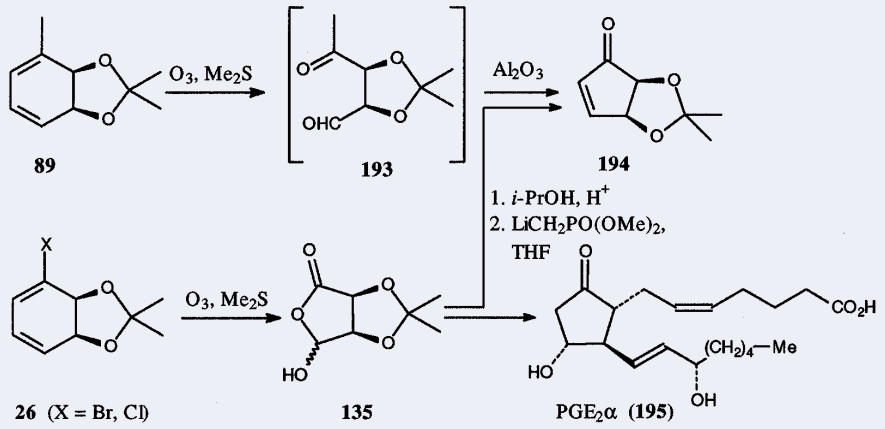


Figure 32. Two approaches to a prostaglandin intermediate.

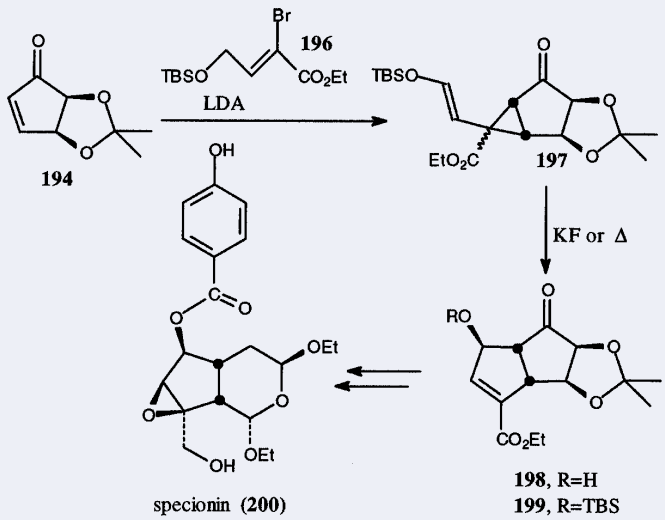


Figure 33. Synthesis of specionin.

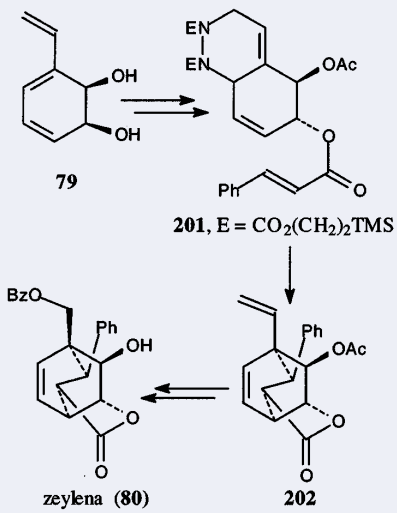


Figure 34. Synthesis of zeylena.

8. References and Notes

(†) In Tables 1–5, compounds are pictured exactly as reported in the literature. In some cases, the absolute stereochemistry is inferred but not necessarily proven beyond doubt. Compounds in brackets imply that the actual diol has not been isolated. Compounds in color are those that have been exploited in synthetic ventures.

1. Gibson, D. T.; Koch, J. R.; Schuld, C. L.; Kallio, R.E. *Biochemistry* **1968**, *7*, 3795.
2. Motherwell, W. B.; Williams, A. S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2031.
3. Ballard, D. G. H.; Courtis, A.; Shirley, I. M.; Taylor, S. C. *J. Chem. Soc., Chem. Commun.* **1983**, 954.
4. Ballard, D. G. H.; Courtis, A.; Shirley, I. M.; Taylor, S.C. *Macromolecules* **1988**, *21*, 294.
5. Ley, S. V.; Sternfeld, F.; Taylor, S. *Tetrahedron Lett.* **1987**, *28*, 225.
6. The latest count revealed the following groups actively participating in this field: **Australia:** Banwell; **Austria:** Griengl; **Japan:** Suemone; **India:** Mereyala; **Italy:** Bossetti, Di Gennaro, Nicolosi, Orsini, Sello; **Spain:** Noheda; **UK:** Boyd, Carless, Carnell, Crout, Dalton, Ley, Page, Ribbons, Roberts, Stephenson, Widdowson; **Uruguay:** Seoane; **U.S.:** Chapman, Eaton, Gibson, Grubbs, Gunsalus, Hudlicky, Johnson, Martin, Olivo, Selifonov, Wackett, Whited, Wiest, Ziffer.
7. Widdowson, D. A.; Ribbons, D. W.; Thomas, S. D. *Janssen Chimica Acta* **1990**, *8*, 3.
8. Carless, H. A. J. *Tetrahedron: Asymmetry* **1992**, *3*, 795.
9. Sheldrake, G. N. In *Chirality and Industry*; Collins, A. N., Sheldrake, G. N., Crosby, J., Eds.; John Wiley and Sons, Ltd.: Chichester, U.K., 1992; p 127.
10. Brown, S. M.; Hudlicky, T. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 2, p 113.
11. Hudlicky, T.; Reed, J.W. In *Advances in Asymmetric Synthesis*; Hassner, A., Ed.; JAI Press: Greenwich, CT, 1995; p 271.
12. Grund, A.D. *SIM News* **1995**, *45*, 59.
13. Hudlicky, T.; Thorpe, A. J. *Chem. Commun.* **1996**, 1993.
14. Hudlicky, T. *Chem. Rev.* **1996**, *96*, 3.
15. Hudlicky, T.; Entwistle, D. A.; Pitzer, K. K.; Thorpe, A. J. *Chem. Rev.* **1996**, *96*, 1195.
16. Hudlicky, T. In *Green Chemistry: Designing Chemistry for the Environment*; Anastas, P. T., Williamson, T. C., Eds.; ACS Symposium Series; American Chemical Society: Washington, DC, 1996; Vol. 626, p 180.
17. Hudlicky, T. In *Green Chemistry: Frontiers in Benign Chemical Syntheses and Processes*; Anastas, P. T., Williamson, T. C., Eds.; Oxford University Press: Oxford, UK, 1998; Chapter 10, p 166.
18. Boyd, D. R.; Sheldrake, G. N. *Nat. Prod. Rep.* **1998**, 309.
19. Gibson, D. T.; Koch, J. R.; Kallio, R. E. *Biochemistry* **1968**, *7*, 2653.
20. Jerina, D. M.; Daly, J. W. B.; Zaltzman-Niremberg, P.; Udenfriend, S. *Arch. Biochem.* **1968**, *128*, 176.
21. Gibson, D. T.; Cardini, G. E.; Maseles, F. C.; Kallio, R. E. *Biochemistry* **1970**, *9*, 1631.

22. Gibson, D. T.; Hensley, M.; Yoshioka, H.; Mabry, T. J. *Biochemistry* **1970**, *9*, 1626.
23. Ziffer, H.; Jerina, D. M.; Gibson, D. T.; Kobal, V. M. *J. Am. Chem. Soc*. **1973**, *95*, 4048.
24. Gibson, D. T.; Gschwendt, B.; Yeh, W. K.; Kobal, V. M. *Biochemistry* **1973**, *12*, 1520.
25. Ziffer, H.; Kabuto, K.; Gibson, D. T.; Kobal, V. M.; Jerina, D. M. *Tetrahedron* **1977**, *33*, 2491.
26. Gibson, D. T.; Mahadevan, V.; Davey, J. F. *J. Bacteriol*. **1974**, *119*, 930.
27. Ziffer, H.; Gibson, D. T. *Tetrahedron Lett*. **1975**, 2137.
28. Gibson, D. T. *Crit. Rev. Microbiol*. **1971**, *1*, 199.
29. Jerina, D. M.; Daly, J. W.; Jeffrey, A. M.; Gibson, D. T. *Arch. Biochem. Biophys*. **1971**, *142*, 394.
30. Jeffrey, A. M.; Yeh, H. J. C.; Jerina, D. M.; Patel, T. R.; Davey, J. F.; Gibson, D. T. *Biochemistry* **1975**, *14*, 575.
31. Gibson, D. T.; Roberts, R. L.; Wells, M. C.; Kobal, V. M. *Biochem. Biophys. Res. Commun*. **1973**, *50*, 211.
32. Khan, A. A.; Wang, R.-F.; Cao, W.-W.; Franklin, W.; Cerniglia, C. E. *Int. J. Syst. Bacteriol*. **1996**, *46*, 466.
33. Akhtar, M. N.; Boyd, D. R.; Thompson, N. J.; Koreeda, M.; Gibson, D. T.; Mahadevan, V.; Jerina, D. M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2506.
34. Koreeda, M.; Akhtar, M. N.; Boyd, D. R.; Neill, J. D.; Gibson, D. T.; Jerina, D. M. *J. Org. Chem*. **1978**, *43*, 1023.
35. Jerina, D. M.; van Bladeren, P. J.; Yagi, H.; Gibson, D. T.; Mahadevan, V.; Neese, A. S.; Koreeda, M.; Sharma, N. D.; Boyd, D. R. *J. Org. Chem*. **1984**, *49*, 3621.
36. Boyd, D. R.; Sharma, N. D.; Agarwal, R.; Resnick, S. M.; Schocken, M. J.; Gibson, D. T.; Sayer, J. M.; Yagi, H.; Jerina, D. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1715.
37. Reiner, A. M.; Hegeman, G. D. *Biochemistry* **1971**, *10*, 2530.
38. Reineke, W.; Otting, W.; Knackmuss, H.-J. *Tetrahedron* **1978**, *34*, 1707.
39. Reineke, W.; Knackmuss, H.-J. *Biochim. Biophys. Acta* **1978**, *542*, 412.
40. DeFrank, J. J.; Ribbons, D. W. *J. Bacteriol*. **1977**, *129*, 1356.
41. DeFrank, J. J.; Ribbons, D. W. *J. Bacteriol*. **1977**, *129*, 1365.
42. Jenkins, G. N.; Ribbons, D. W.; Widdowson, D. A.; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2647.
43. Resnick, S. M.; Lee, K.; Gibson, D. T. *J. Ind. Microbiol*. **1996**, *17*, 438.
44. Gibson, D. T.; Subramanian, V. In *Microbial Degradation of Organic Compounds*; Gibson, D. T., Ed.; Marcel Dekker: New York, NY 1984; Vol. 13, p 181.
45. Gibson, D. T. In *Microbial Metabolism and the Carbon Cycle*; Hagedorn, S. R., Hanson, S. H., Kunz, D. A., Eds.; Hardwood Academic Publisher: New York, NY, 1988; p 33.
46. Gibson, D. T. In *Degradation of Synthetic Organic Molecules in the Biosphere*; National Academy of Sciences: Washington, DC, 1971; p 117.
47. Hudlicky, T.; Stabile, M. S.; Whited, G. Gibson, D. T. *Org. Synth*. **1999**, *76*, 77.
48. Barnsley, E. A. *J. Gen. Microbiol*. **1975**, *88*, 193.

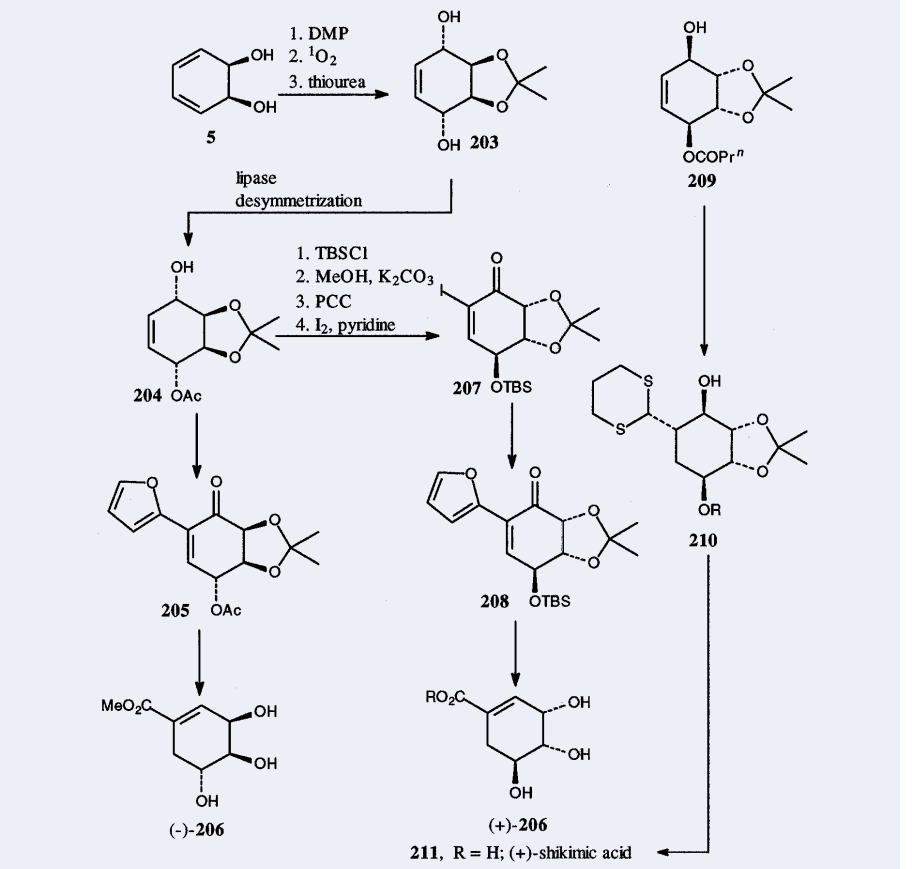


Figure 35. Synthesis of methyl shikimate and shikimic acid.

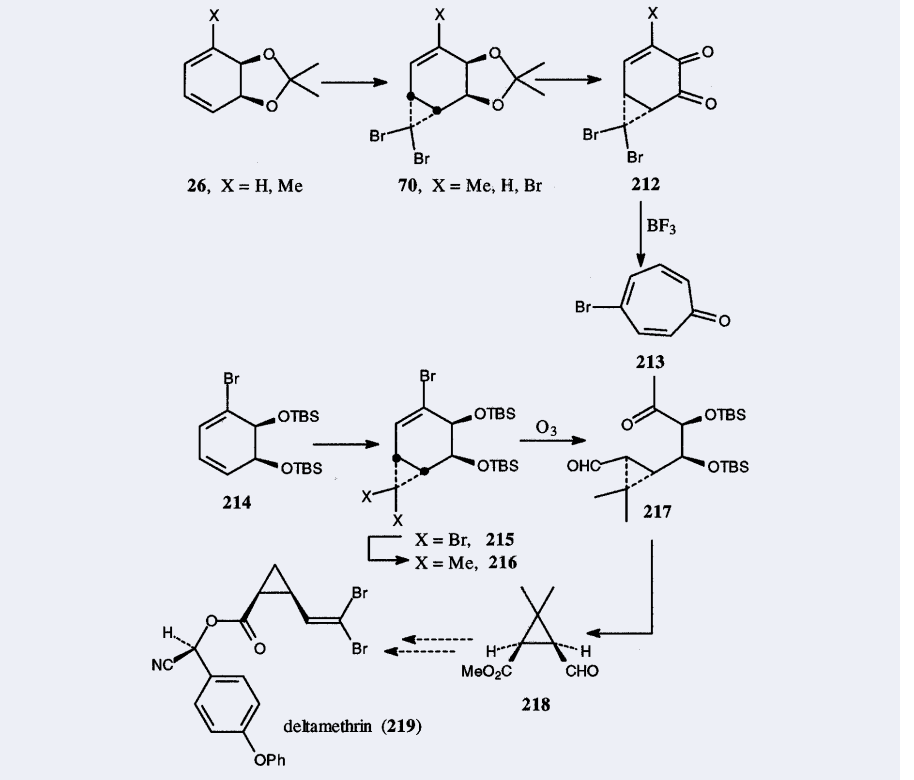


Figure 36. Synthesis of tropolones and synthons for chrysanthemates.

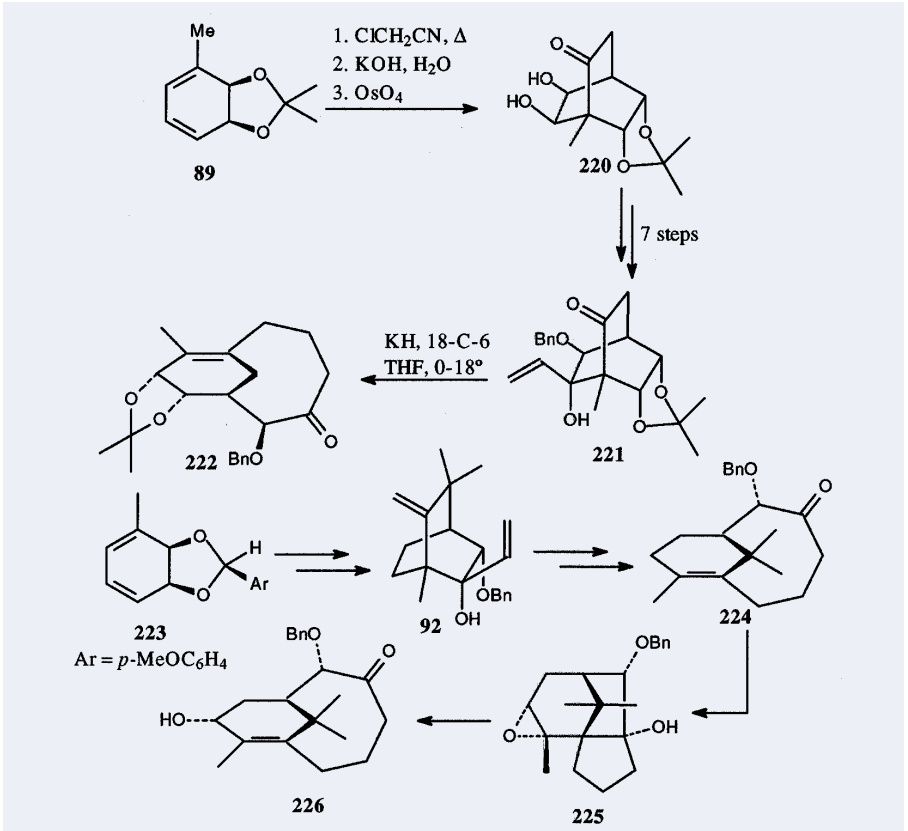


Figure 37. Approaches to taxanes.

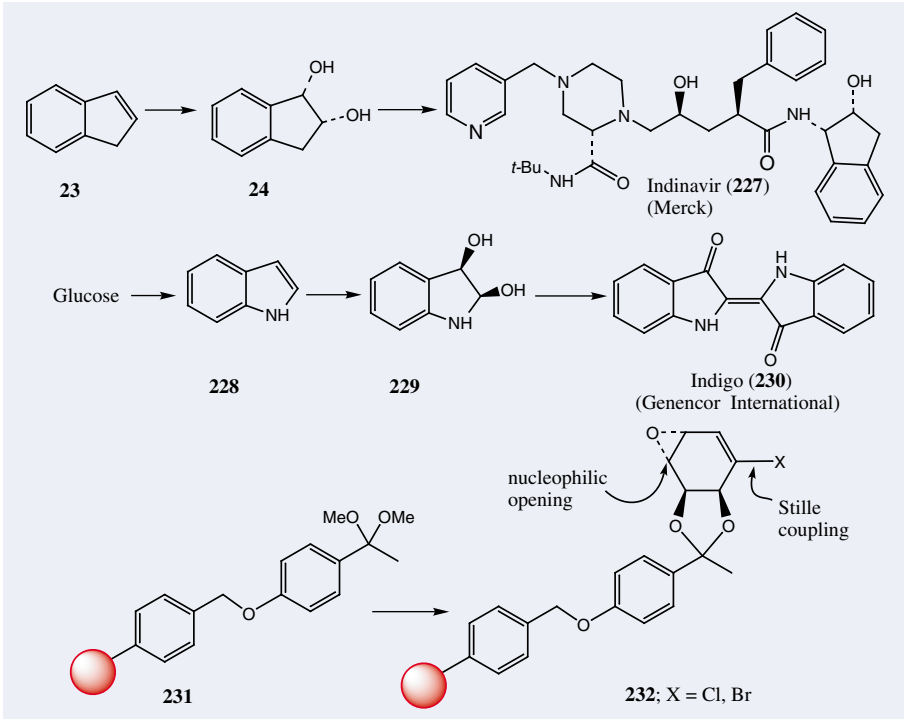
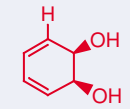


Figure 38. Potential commercial applications of *cis*-dihydroarenediols.

49. Mahaffey, W. R.; Gibson, D. T.; Cerniglia, C. E. *Appl. Environ. Microbiol*. **1988**, *54*, 2415.
50. Gibson, D. T.; Resnick, S. M.; Lee, K.; Brand, J. M.; Torok, D. S.; Wackett, L. P.; Schocken, M. J.; Haigler, B. E. *J. Bacteriol*. **1995**, *177*, 2615.
51. Lee, K.; Gibson, D. T. *Appl. Environ. Microbiol*. **1996**, *62*, 3101.
52. Gibson, D. T.; Klečka, G. M. Unpublished results.
53. Klečka, G. M.; Gibson, D. T. *Biochem. J*. **1979**, *180*, 639.
54. Zylstra, G. J.; Gibson D. T. *J. Biol. Chem*. **1989**, *264*, 14940.
55. Simon, M. J.; Osslund, T. D.; Saunders, R.; Ensley, B. D.; Suggs, S.; Harcourt, A.; Suen, W. C.; Cruden, D. L.; Gibson, D. T.; Zylstra, G. J. *Gene* **1993**, *127*, 31.
56. Mondello, F. J. *J. Bacteriol*. **1989**, *171*, 1725.
57. Butler, C. S.; Mason, J. R. *Adv. Microbiol. Phys*. **1997**, *38*, 47.
58. Kauppi, B.; Lee, K.; Carredano, E.; Parales, R. E.; Gibson, D. T.; Eklund, H.; Ramaswamy, S. *Structure* **1998**, *6*, 571.
59. Stewart, J. D.; Hudlicky, T.; Novak, B. H. Unpublished results, 1996.
60. Stewart J. D.; Reed, K. W.; Kayser, M. M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 755.
61. Furstoss, R. Use of Biooxygenation in Fine Organic Synthesis. In *Microbial Reagents in Organic Synthesis*; Servi, S., Ed.; Kluwer Academic Publishers: Dordretch, Netherlands, 1992; p 333.
62. Taschner, M. J.; Peddada, L.; Cyr, P.; Chen, Q.-Z.; Black, D. J. The Enzymatic Baeyer–Villiger Oxidation. In *Microbial Reagents in Organic Synthesis*; Servi, S., Ed.; Kluwer Academic Publishers: Dordretch, Netherlands, 1992; p 347.
63. Boyd, D. R.; Dorrity, M. R. J.; Hand, M. V.; Malone, J. F.; Sharma, N. D.; Dalton, H.; Gray, D. J.; Sheldrake, G. N. *J. Am. Chem. Soc*. **1991**, *113*, 666.
64. Resnick, S. M.; Gibson, D. T. In *Abstr. of the 96th Gen. Meet. of the Am. Soc. For Microbiol*, 1996.
65. Allen, C. C. R.; Boyd, D. R.; Dalton, H.; Sharma, N. D.; Brannigan, I.; Kerley, N. A.; Sheldrake, G. N.; Taylor, S. C. *J. Chem. Soc., Chem. Commun*. **1995**, 117.
66. Johnson, C. R.; Adams, J. P.; Collins, M. A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1.
67. Hudlicky, T.; Price, J. D.; Rulin, F.; Tsunoda, T. *J. Am. Chem. Soc*. **1990**, *112*, 9439.
68. Hudlicky, T.; Rulin, F.; Tsunoda, T.; Luna, H.; Andersen, C.; Price, J. D. *Isr. J. Chem*. **1991**, *31*, 229.
69. Boyd, D. R.; Sharma, N. D.; Dalton, H.; Clarke, D. A. *Chem. Commun*. **1996**, 45.
70. McKibben, B. P.; Barnosky, G. S.; Hudlicky, T. *Synlett* **1995**, 806.
71. Hudlicky, T.; Luna, H.; Barbieri, G.; Kwart, L. D. *J. Am. Chem. Soc*. **1988**, *110*, 4735.
72. Gonzalez, D.; Schapiro, V.; Seoane, G.; Hudlicky, T.; Abboud, K. *J. Org. Chem*. **1997**, *62*, 1194.
73. Resnick, S. M.; Torok, D. S.; Gibson, D. T. *J. Org. Chem*. **1995**, *60*, 3546.
74. Banwell, M. G.; Darmos, P.; McLeod, M. D.; Hockless, D. C. R. *Synlett* **1998**, 897.
75. Hudlicky, T.; McKibben, B. P. Unpublished results, 1994: Pivalic aldehyde has been used as a protective group.
76. Stephenson, G. R.; Howard, P. W.; Taylor, S. C. *J. Chem. Soc., Chem. Commun*. **1991**, 127.
77. Howard, P. W.; Stephenson, G. R.; Taylor, S. C. *J. Chem. Soc., Chem. Commun*. **1988**, 1603.
78. Braun, H.; Burger, W.; Kresze, G.;

Table 1. Diols Derived from Monocyclic Aromatics



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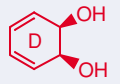
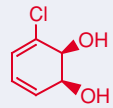
(ref. 19,21)



E. coli JM109(pDTG601A)
(ref. 218)



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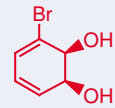
P. putida UV4
(ref. 25,63,184)



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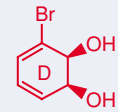

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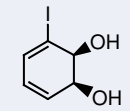

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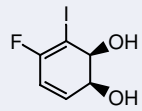

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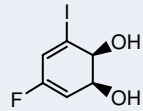

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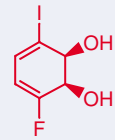

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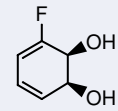

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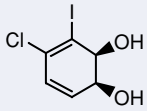

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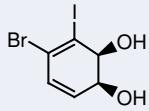

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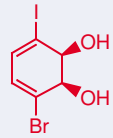

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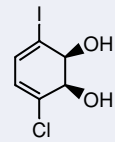
E. coli JM109(pDTG601A)
(ref. 145,169)



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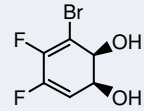

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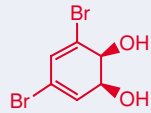

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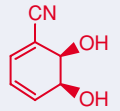
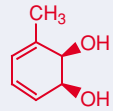
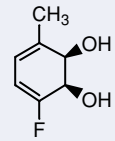


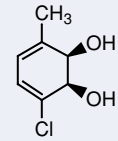
P. putida 39/D
P. putida UV4
(ref. 161,184)



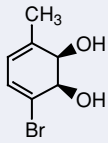
P. putida 39/D
P. putida UV4
(ref. 22,63,180)



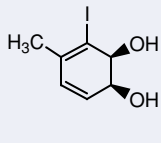
P. putida 39/D
P. putida UV4
(ref. 25,169)



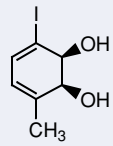
P. putida 39/D
(ref. 1,25)



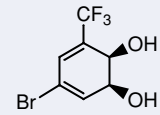
P. putida
(ref. 25,39)



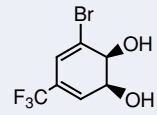
P. putida UV4
E. coli JM109(pDTG601A)
(ref. 170)



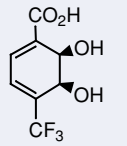
P. putida UV4
E. coli JM109(pDTG601A)
(ref. 169, 170)



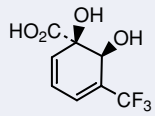
P. putida 39/D
E. coli JM109(pDTG601A)
(ref. 219)



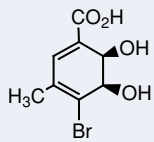
P. putida 39/D
E. coli JM109(pDTG601A)
(ref. 219)



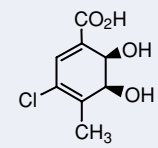
P. putida JT107
(ref. 177)



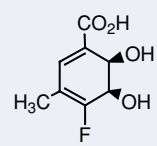
P. putida mt-2 +
A. eutrophus B9
(ref. 183)



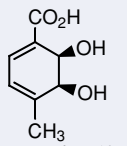
P. putida JT107
(ref.40)



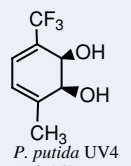
P. putida JT107
(ref. 40)



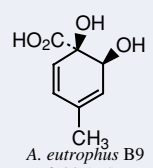
P. putida JT107
(ref. 40)



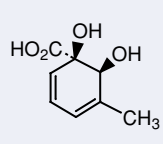
P. putida JT107
(ref. 40)



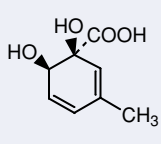
P. putida UV4
(ref. 169)



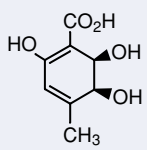
A. eutrophus B9
(ref. 38,175)



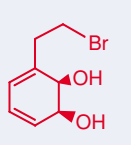
A. eutrophus B9
Pseudomonas sp. B13
(ref. 38,39,175)



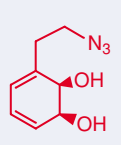
Pseudomonas sp. B13
(ref. 39,175)



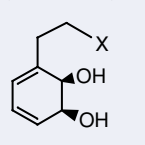
P. putida JT107
(ref. 40)



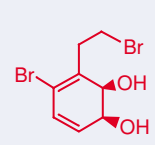
P. putida 39/D
E. coli JM109(pDTG601A)
(ref. 192)



E. coli JM109(pDTG601A)
(ref. 242)

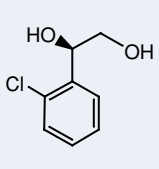


X = CN, SCN, NCS, OAc, OH
E. coli JM109(pDTG601A)
(ref. 242)

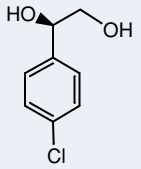


P. putida 39/D
E. coli JM109(pDTG601A)
(ref. 193)

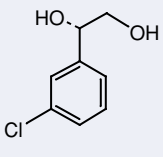
Table 1. Diols Derived from Monocyclic Aromatics (cont.)



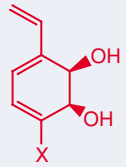
P. putida 39/D
(ref. 186,187)



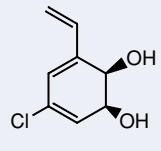
P. putida 39/D
(ref. 187)



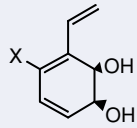
P. putida 39/D
(ref. 187)



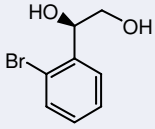
X = H, Cl
P. putida 39/D
(ref. 71,135,187)



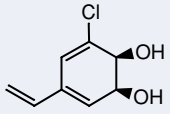
P. putida 39/D
(ref. 187)



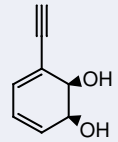
X = Cl, Br
P. putida 39/D
(ref. 187-189)



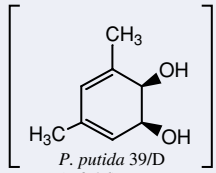
P. putida 39/D
(ref. 189)



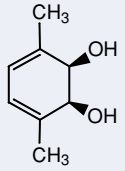
P. putida 39/D
(ref.187)



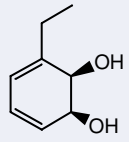
P. putida 39/D
(ref. 71,192)



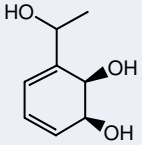
P. putida 39/D
(ref. 26)



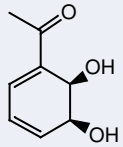
P. putida 39/D
(ref. 26)



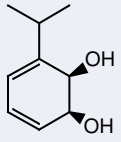
P. putida 39/D
(ref. 24)



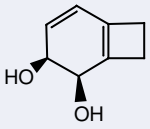
P. putida 39/D
(ref. 24)



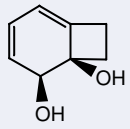
P. putida 39/D
(ref. 24)



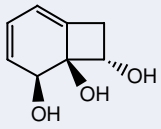
P. desmolytica
P.convexa
(ref. 175,196)



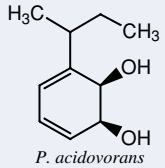
P. putida UV4
(ref. 191,231)



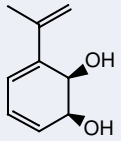
P. putida UV4
(ref. 191,231)



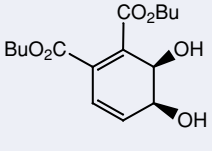
P. putida UV4
(ref. 231)



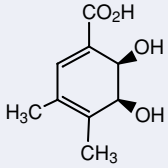
P. acidovorans
(ref. 203)



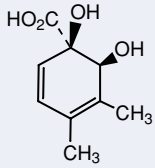
P. putida
(ref. 194, 196)



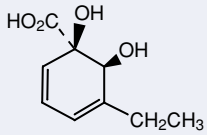
Micrococcus sp. 12B
(ref. 186)



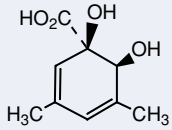
P. putida JT107
(ref. 40)



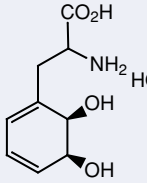
P. putida
(ref. 181)



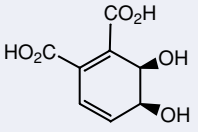
P. putida
(ref. 181)



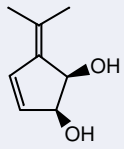
Pseudomonas sp. B1
(ref. 175)



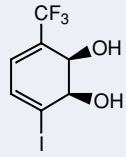
unidentified strain
(ref. 195)



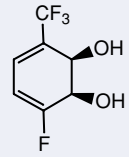
Micrococcus sp. 12B
(ref. 186)



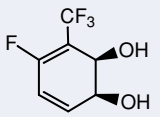
P. putida RE213
(ref. 232)



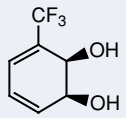
P. putida UV4
(ref. 169)



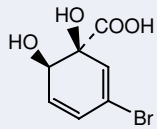
P. putida NCIB12190
(ref. 174)



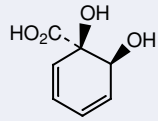
P. putida NCIB12190
(ref. 174)



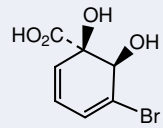
P. putida UV4
P. putida 39/D
(ref. 63,174,229)



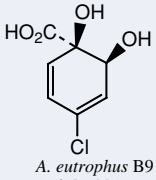
A. eutrophus B9
(ref. 38,39)



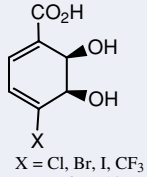
P. putida,
A. eutrophus B9
(ref. 37-39,175,181)



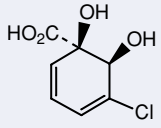
A. eutrophus B9
Pseudomonas sp. B13
(ref. 38,39)



A. eutrophus B9
(ref. 37,38)

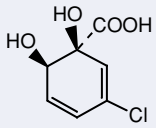


X = Cl, Br, I, CF_3
P. putida JT107
(ref. 40,177)

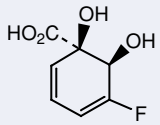


P. fluorescens
A. eutrophus B9
(ref. 37,38,175,178)

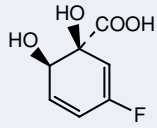
Table 1. Diols Derived from Monocyclic Aromatics (cont.)



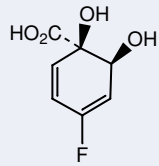
Pseudomonas sp. WR91
A. eutrophus B9
(ref. 37,179)



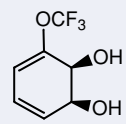
A. eutrophus B9
(ref. 37,38,39)



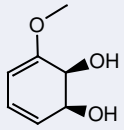
A. eutrophus B9
(ref. 37,38)



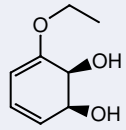
A. eutrophus B9
(ref. 38)



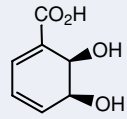
P. putida 39/D
E. coli JM109(pDTG601A)
(ref. 227)



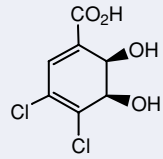
P. putida UV4
P. putida 39/D
E. coli JM109(pDTG601A)
(ref. 63,184,228)



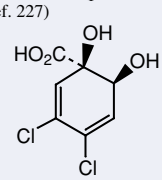
P. putida 39/D
E. coli JM109(pDTG601A)
P. putida UV4
(ref. 184,220,228)



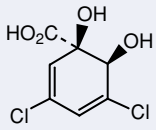
P. putida JT107
(ref. 40)



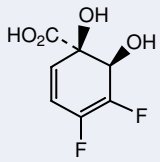
P. putida JT107
(ref. 40)



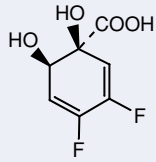
Pseudomonas sp. B13
(ref. 175)



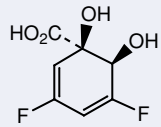
A. eutrophus B9
(ref. 38,175)



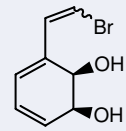
P. putida JT103
(ref. 176)



P. putida JT103
(ref. 176)

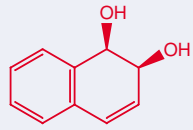


P. putida JT103
(ref. 173,176)

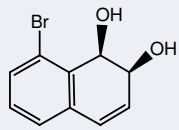


E. coli JM109(pDTG601A)
(ref. 241)

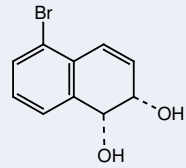
Table 2. Diols Derived from Fused Aromatic Systems



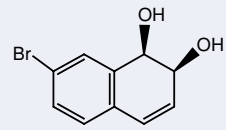
P.putida UV4, *P. putida* 119
P. putida NCIB 9816/11
A. quadruplicatum
E. coli JM109(pDTG601A)
(ref. 29,30,117,198,199,200,234)



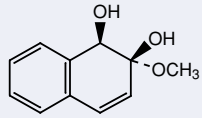
P. putida NCIB 9816/11
(ref. 197)



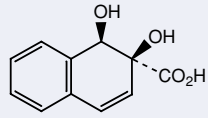
P. putida NCIB 9816/11
(ref.197)



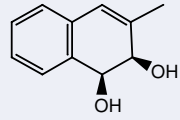
P. putida NCIB 9816/11
(ref. 197)



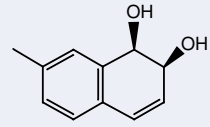
P. testosteroni
(ref. 201)



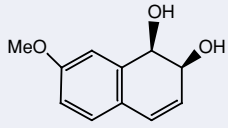
P. testosteroni
(ref. 201)



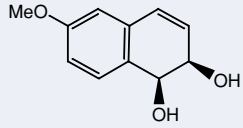
P. putida NCIB 9816/11
(ref. 222)



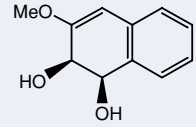
P. putida NCIB 9816/11
(ref. 222)



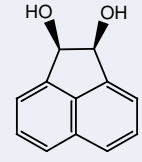
P. putida 39/D
P. putida NCIB 9816/11
E. coli JM109 (pDTG601A)
E. coli JM109 (pDTG141)
S. yanoikuyae B8/36
(ref. 223)



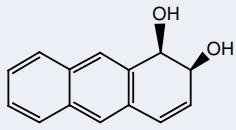
P. putida 39/D
P. putida NCIB 9816/11
E. coli JM109 (pDTG601A)
E. coli JM109 (pDTG141)
S. yanoikuyae B8/36
(ref. 223)



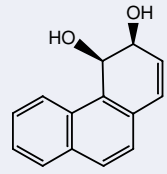
P. putida 39/D
E. coli JM109 (pDTG601A)
(ref. 223)



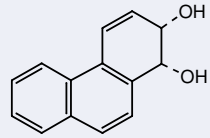
Beijerinckia sp.
(ref. 205)



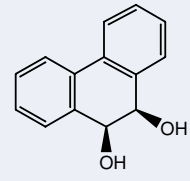
P. putida 119
S. yanoikuyae B8/36
(ref. 33,212)



P. putida 119
S. yanoikuyae B8/36
(ref. 34,212)

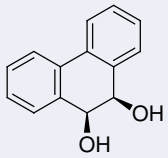


P. putida 119
S. yanoikuyae B8/36
(ref. 34,212)

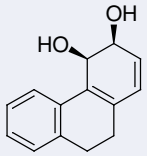


A. quadruplicatum PR/6
(ref. 213)

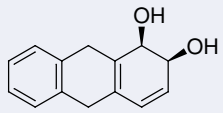
Table 2. Diols Derived from Fused Aromatic Systems (cont.)



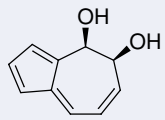
P. putida NCIB 9816/11
E. coli JM109(pDTG141)
(ref. 235)



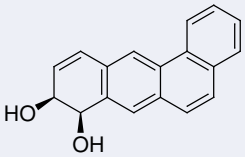
P. putida NCIB 9816/11
E. coli JM109(pDTG141)
(ref. 235)



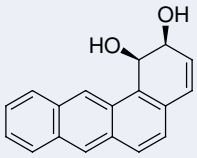
P. putida NCIB 9816/11
E. coli JM109(pDTG141)
(ref. 235)



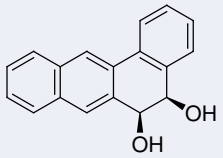
P. putida UV4
(ref. 238)



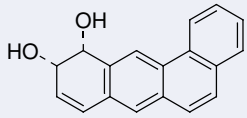
S. yanoikuyae B8/36
(ref. 35,214)



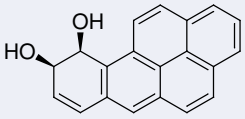
S. yanoikuyae B8/36
(ref. 35,214)



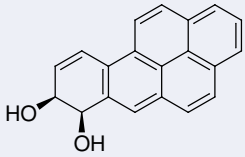
S. yanoikuyae B8/36
(ref. 35,214)



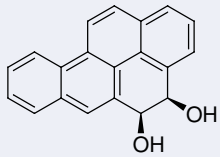
S. yanoikuyae B8/36
(ref. 35,214)



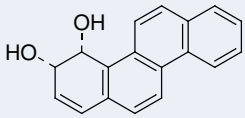
S. yanoikuyae B8/36
(ref. 35,214)



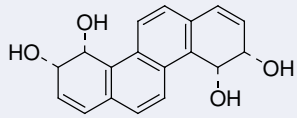
S. yanoikuyae B8/36
S. capricornicum (green algae)
(ref. 35,214,216)



S. yanoikuyae B8/36
S. capricornicum (green algae)
(ref. 35,214,216)



S. yanoikuyae B8/36
(ref. 243)

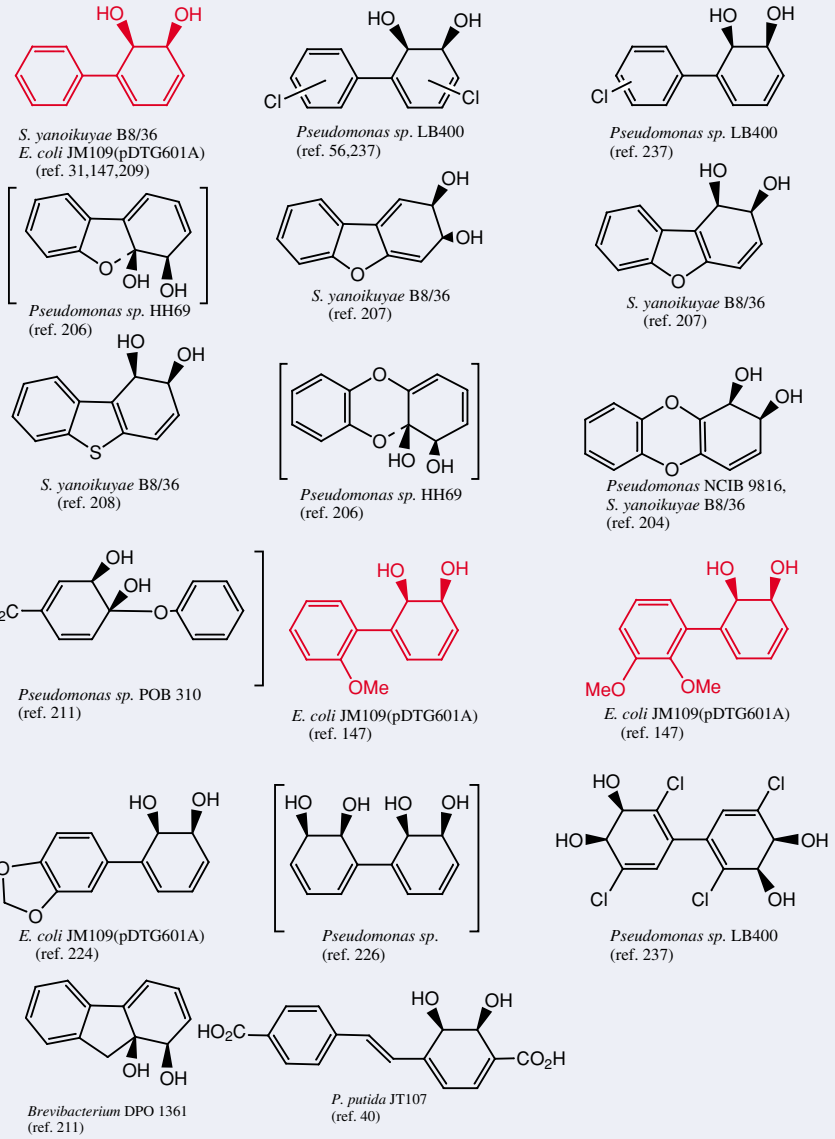


S. yanoikuyae B8/36
(ref. 243, 244)

Schmidtchen, F. P.; Vaerman, J. L.; Viehe, H. G. *Tetrahedron: Asymmetry* **1990**, *1*, 403.

79. Hudlicky, T.; Boros, E. E.; Olivo, H. F.; Merola, J. S. *J. Org. Chem*. **1992**, *57*, 1026.
80. Pittol, C. A.; Pryce, R. J.; Roberts, S. M.; Ryback, G.; Sik, V.; Williams, J. O. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1160.
81. Ley, S. V.; Redgrave, A. J.; Taylor, S. C.; Ahmed, S.; Ribbons, D. W. *Synlett* **1991**, 741.
82. Hudlicky, T.; Boros, C. H. *Tetrahedron Lett*. **1993**, *34*, 2557.
83. Hudlicky, T.; Luna, H.; Olivo, H. F.; Andersen, C.; Nugent, T.; Price, J. D. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2907.
84. Banwell, M. G.; Dupuche, J. R.; Gable, R. W. *Aust. J. Chem*. **1996**, *49*, 639.
85. Hudlicky, T.; McKibben, B. P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 485.
86. Banwell, M. G.; Dupuche, J. R. *Chem. Commun*. **1996**, 869.
87. Hudlicky, T.; Olivo, H. F.; McKibben, B. *J. Am. Chem. Soc*. **1994**, *116*, 5108.
88. Banwell, M. G.; Collis, M. P. *J. Chem. Soc., Chem. Commun*. **1991**, 1343.
89. Banwell, M. G.; Forman, G. S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2565.
90. Banwell, M. G.; Collis, M. P; Mackay, M. F.; Richards, S. L. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1913.
91. Banwell, M. G.; Corbett, M.; Mackay, M. F.; Richards, S. L. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1329.
92. Banwell, M. G.; Bridges, V. S.; Dupuche, J. R.; Richards, S. L.; Walter, J. M. *J. Org. Chem*. **1994**, *59*, 6338.
93. Cotterill, I. C.; Finch, H.; Reynolds, D. P.; Roberts, S. M.; Rzepa, H. S.; Short, K. M.; Slawin, A. M. Z.; Wallis, C. J.; Williams, D. J. *J. Chem. Soc., Chem. Commun*. **1988**, 470.
94. Carless, H. A. J.; Oak, O. Z. *Tetrahedron Lett*. **1989**, *30*, 1719.
95. Hudlicky, T.; Olivo, H. F. *J. Am. Chem. Soc*. **1992**, *114*, 9694.
96. Olivo, H. F., Ph.D. Dissertation, Virginia Tech., Blacksburg, VA, 1992. *Diss. Abstr*. Vol. 53 07B, p 3487.
97. Yang, N. C.; Noh, T.; Gan, H.; Halfon, S.; Hrnjez, B. J. *J. Am. Chem. Soc*. **1988**, *110*, 5919.
98. Balci, M.; Sütbeyaz, Y.; Seçen, H. *Tetrahedron* **1990**, *46*, 3715.
99. Balci, M. *Pure Appl. Chem*. **1997**, *69*, 97.
100. Hudlicky, T.; Boros, C. H.; Boros, E. E. *Synthesis* **1992**, 174.
101. Butora, G.; Gum, A. G.; Hudlicky, T.; Abboud, K. A. *Synthesis* **1998**, 275.
102. Carless, H. A. J. *J. Chem. Soc., Chem. Commun*. **1992**, 234.
103. Hudlicky, T.; Price, J. D. *Synlett* **1990**, 159.
104. Johnson, C. R.; Ple, P. A.; Su, L.; Heeg, M. J.; Adams, J. P. *Synlett* **1992**, 388.
105. Ley, S. V.; Sternfeld, F. *Tetrahedron* **1989**, *45*, 3463.
106. Mandel, M.; Hudlicky, T.; Kwart, L. D.; Whited, G. M. *J. Org. Chem*. **1993**, *58*, 2331.
107. Hudlicky, T.; Mandel, M.; Rouden, J.; Lee, R. S.; Bachmann, B.; Dudding, T.; Yost, K. J.; Merola, J. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1553.
108. Brammer, L. E., Jr.; Hudlicky, T. *Tetrahedron: Asymmetry* **1998**, *9*, 2011.
109 Desjardins, M.; Brammer, L. E., Jr.; Hudlicky, T. *Carbohydr. Res*. **1997**, *304*, 39.
110. Hudlicky, T.; Cebulak, M. *Cyclitols and Their Derivatives: A Handbook of Physical, Spectral, and Synthetic Data*, VCH Publisher: Weinheim, Germany, 1993.
111. Nguyen, B. V.; York, C.; Hudlicky, T. *Tetrahedron* **1997**, *53*, 8807.
112. Pingli, L.; Vandewalle, M. *Tetrahedron* **1994**, *50*, 7061.
113. Oppong, K. A.; Hudlicky, T.; Yan, F.; York, C.; Nguyen, B. V. *Tetrahedron* **1999**, *55*, 2875.
114. Billington, D. C.; Perrou-Sierra, F.; Picard, I.;

Table 3. Diols Derived from Linked Aromatic Systems



S. yanoikuyae B8/36
E. coli JM109(pDTG601A)
(ref. 31,147,209)

Pseudomonas sp. LB400
(ref. 56,237)

Pseudomonas sp. LB400
(ref. 237)

Pseudomonas sp. HH69
(ref. 206)

S. yanoikuyae B8/36
(ref. 207)

S. yanoikuyae B8/36
(ref. 207)

S. yanoikuyae B8/36
(ref. 208)

Pseudomonas sp. HH69
(ref. 206)

Pseudomonas NCIB 9816,
S. yanoikuyae B8/36
(ref. 204)

Pseudomonas sp. POB 310
(ref. 211)

E. coli JM109(pDTG601A)
(ref. 147)

E. coli JM109(pDTG601A)
(ref. 147)

E. coli JM109(pDTG601A)
(ref. 224)

Pseudomonas sp.
(ref. 226)

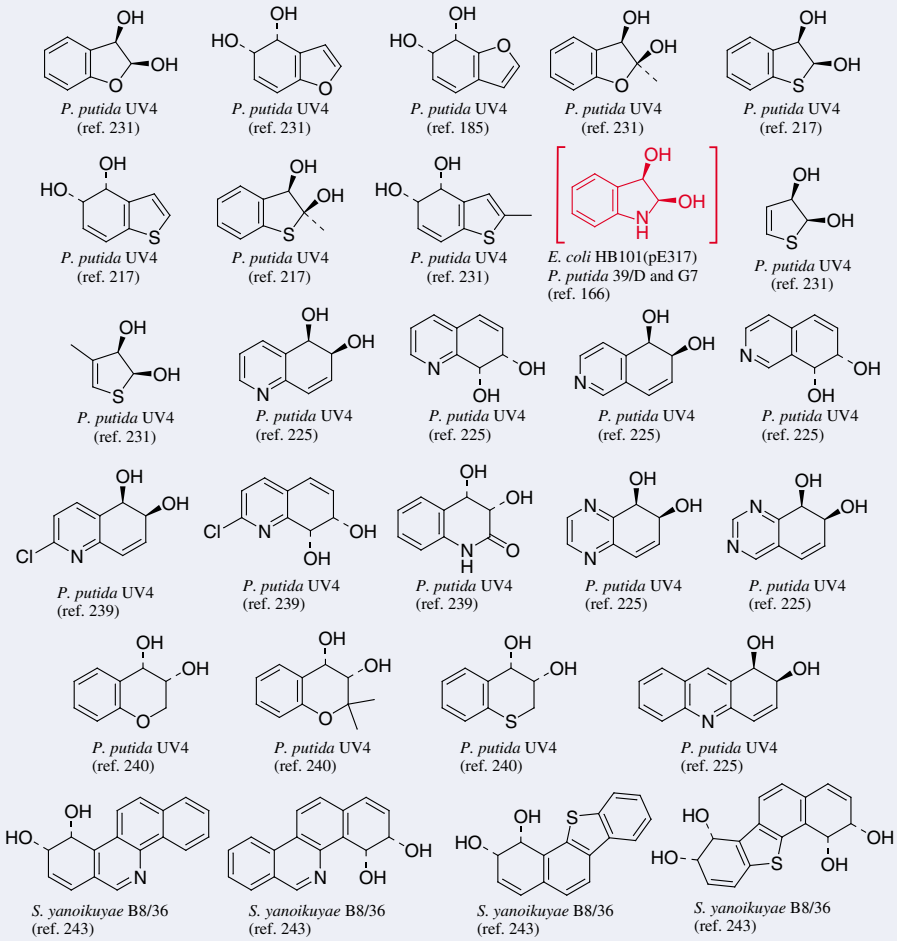
Pseudomonas sp. LB400
(ref. 237)

Brevibacterium DPO 1361
(ref. 211)

P. putida JT107
(ref. 40)

Beaubras, S.; Duhault, J.; Espinal, J.; Challal, S. *Bioorg. Med. Chem. Lett*. **1994**, *4*, 2307.
115. Kara, Y.; Balci, M.; Bourne, S. A.; Watson, W. H. *Tetrahedron Lett*. **1994**, *35*, 3349.
116. Lallemand, M.-C.; Desjardins, M.; Freeman, S.; Hudlicky, T. *Tetrahedron Lett*. **1997**, *38*, 7693.
117. Desjardins, M.; Lallemand, M.-C.; Hudlicky, T.; Abboud, K. A. *Synlett* **1997**, 728.
118. Desjardins, M.; Lallemand, M.-C.; Freeman, S.; Hudlicky, T.; Abboud, K. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 621.
119. Hudlicky, T.; Abboud, K. A.; Bolonick, J.; Maurya, R.; Stanton, M. L.; Thorpe, A. J. *Chem. Commun*. **1996**, 1717.
120. Hudlicky, T.; Abboud, K. A.; Entwistle, D. A.; Fan, R.; Maurya, R.; Thorpe, A. J.; Bolonick, J.; Myers, B. *Synthesis* **1996**, 897.
121. Hudlicky, T.; Luna, H.; Price, J. D.; Rulin, F. *Tetrahedron Lett*. **1989**, *30*, 4053.
122. Hudlicky, T.; Luna, H.; Price, J. D.; Rulin, F. *J. Org. Chem*. **1990**, *55*, 4683.
123. Mandel, M.; Hudlicky, T.; Kwart, L. D.; Whited, G. M. *Collect. Czech. Chem. Commun*. **1993**, *58*, 2517.
124. Nugent, T. C.; Hudlicky, T. *J. Org. Chem*. **1998**, *63*, 510.
125. Hudlicky, T.; Rouden, J.; Luna, H. *J. Org. Chem*. **1993**, *58*, 985.
126. Pitzer, K.; Hudlicky, T. *Synlett* **1995**, 803.
127. Hudlicky, T.; Nugent, T.; Griffith, W. *J. Org. Chem*. **1994**, *59*, 7944.
128. Hudlicky, T.; Pitzer, K. K.; Stabile, M. R.; Thorpe, A. J.; Whited, G. M. *J. Org. Chem*. **1996**, *61*, 4151.
129. Yan, F.; Nguyen, B. V.; York, C.; Hudlicky, T. *Tetrahedron* **1997**, *53*, 11541.
130. Entwistle, D. A.; Hudlicky, T. *Tetrahedron Lett*. **1995**, *36*, 2591.
131. Hudlicky, T.; Thorpe, A. J. *Synlett* **1994**, 899.
132. Banwell, M. G.; De Savi, C.; Watson, K. *Chem. Commun*. **1998**, 1189.
133. Johnson, C. R.; Golebiowski, A.; Sundram, H.; Miller, M. W.; Dwaihy, R. L. *Tetrahedron Lett*. **1995**, *36*, 653.
134. Johns, B. A.; Pan, Y. T.; Elbein, A. D.; Johnson, C. R. *J. Am. Chem. Soc*. **1997**, *119*, 4856.
135. Hudlicky, T.; Seoane, G.; Price, J. D.; Gadamasetti, K. G. *Synlett* **1990**, 433.
136. Hudlicky, T.; Frazier, J. O.; Seoane, G.; Tiedje, M.; Seoane, A.; Kwart, L. D.; Beal, C. *J. Am. Chem. Soc*. **1986**, *108*, 3755.
137. Martin, S. F.; Tso, H.-H. *Heterocycles* **1993**, *35*, 85.
138. Rouden, J.; Hudlicky, T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1095.
139. Hudlicky, T.; Rouden, J.; Luna, H.; Allen, S. *J. Am. Chem. Soc*. **1994**, *116*, 5099.
140. Kayakiri, H.; Kasahara, C.; Nakamura, K.; Oku, T.; Hashimoto, M. *Chem. Pharm. Bull*. **1991**, *39*, 1392.
141. Tian, X.; Hudlicky, T.; Konigsberger, K. *J. Am. Chem. Soc*. **1995**, *117*, 3643.
142. Tian, X.; Maurya, R.; Konigsberger, K.; Hudlicky, T. *Synlett* **1995**, 1125.
143. Hudlicky, T.; Tian, X.; Konigsberger, K.; Maurya, R.; Rouden, J.; Fan, B. *J. Am. Chem. Soc*. **1996**, *118*, 10752.
144. Banwell, M. G.; Bissett, B. D.; Busato, S.; Cowden, C. J.; Hockless, D. C. R.; Holman, J. W.; Read, R. W.; Wu, A. W. *J. Chem. Soc., Chem. Commun*. **1995**, 2551.
145. Hudlicky, T.; Akgun, H., *Tetrahedron Lett*. **1999**, 308.
146. Hudlicky, T.; Gonzalez, D.; Martinot, T. *Tetrahedron Lett*. **1999**, 3077.
147. Gonzalez, D.; Schapiro, V.; Seoane, G.; Hudlicky, T. *Tetrahedron: Asymmetry* **1997**, *8*, 975.
148. Kazmaier, U. *Liebigs Ann./Recl*. **1997**, 285; and references cited therein.
149. Butora, G.; Hudlicky, T.; Fearnley, S. P.; Gum, A. G.; Stabile, M. R.; Abboud, K. A. *Tetrahedron Lett*. **1996**, *37*, 8155.
150. Butora, G.; Hudlicky, T.; Fearnley, S. P.; Stabile, M. R.; Gum, A. G.; Gonzalez, D. *Synthesis* **1998**, 665.
151. Parker, K. A.; Fokas, D. *J. Org. Chem*. **1994**, *59*, 3933.
152. Endoma, M. A.; Butora, G.; Claeboe, C. D.; Hudlicky, T.; Abboud, K. A. *Tetrahedron Lett*. **1997**, *38*, 8833.
153. Bottari, P.; Endoma, M. A.; Hudlicky, T.; Ghiviringa, I.; Abboud, K. A. *Coll. Czech. Chem. Commun*. **1999**, *64*, 203.
154. Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc*. **1986**, *108*, 5655.
155. Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc*. **1988**, *110*, 4726.
156. Borcherding, D. R.; Scholtz, S. A.; Borchardt, R. T. *J. Org. Chem*. **1987**, *52*, 5457.
157. Bestmann, H. J.; Roth, D. *Synlett* **1990**, 751.
158. Hudlicky, T.; Natchus, M. G.; Nugent, T. C. *Synth. Commun*. **1992**, *22*, 151.

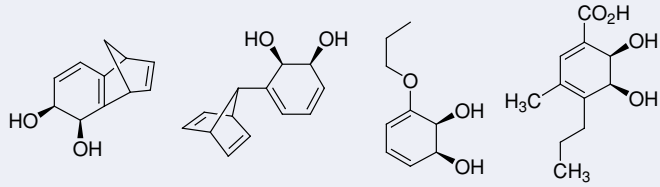
Table 4. Diols Derived from Aromatic Heterocycles



159. Hudlicky, T.; Natchus, M. *J. Org. Chem*. **1992**, *57*, 4740.
160. For details of this methodology, see: Hudlicky, T.; Heard, N. E.; Fleming, A. *J. Org. Chem*. **1990**, *55*, 2570.
161. Hudlicky, T.; Seoane, G.; Pettus, T. *J. Org. Chem*. **1989**, *54*, 4239.
162. Johnson, C. R.; Ple, P. A.; Adams, J. P. *J. Chem. Soc., Chem. Commun*. **1991**, 1006.
163. Dumortier, L.; Van der Eycken, J.; Vandewalle, M. *Synlett* **1992**, 245.
164. Noheda, P.; Garcia-Ruiz, G.; Pozuelo, M. C.; Abbassi, K.; Pascual-Alfonso, E.; Alonso, J. M; Jimenez-Barbero, J. *J. Org. Chem*. **1998**, *63*, 6772.
165. (a) Davies, I. W.; Senanayake, C. H.; Castonguay, L.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett*. **1995**, *36*, 7619. (b) See also: Davies I. W.; Reider P. J. *Chem. Ind. (London)* **1996**, 412.
166. Ensley, B. D.; Ratzkin, B. J.; Osslund, T. D.; Simon, M. J.; Wackett, L. P.; Gibson, D. T. *Science* **1983**, *222*, 167.
167. Whited, G. Presented at Biotrans '95, University of Warwick, 1995.
168. Wendeborn, S.; De Mesmaeker, A.; Brill, W. K. D. *Synlett* **1998**, 865.
169. Boyd, D. R.; Sharma, N. D.; Hand, M. V.; Garza, A. *J. Am. Chem. Soc*. **1973**, *95*, 4420.
181. Whited, G. M.; McCombie, W. R.; Kwart, L. D.; Gibson, D. T. *J. Bacteriol*. **1986**, *166*, 1028.
182. Geary, P. J.; Pryce, R. J.; Roberts, S. M.; Ryback, G.; Winders, J. A. *J. Chem. Soc., Chem. Commun*. **1990**, 204.
183. Engesser, K. H.; Cain, R. B.; Knackmuss, H.-J. *Arch. Microbiol*. **1988**, *149*, 188.
184. Boyd, D. R.; Sharma, N. D.; Byrne, B.; Hand, M. V.; Malone, J. F.; Sheldrake, G. N.; Blacker, J.; Dalton, H. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1935.
185. Boyd, D. R.; Sharma, N. D.; Boyle, R.; McMordie, R. A. S.; Chima, J.; Dalton, H. *Tetrahedron Lett*. **1992**, *33*, 1241.
186. Eaton, R. W.; Ribbons, D. W. *J. Bacteriol*. **1982**, *151*, 48.
187. Hudlicky, T.; Boros, E. E.; Boros, C. H. *Tetrahedron: Asymmetry* **1993**, *4*, 1365.
188. Hudlicky, T.; Boros, E. E.; Boros, C. H. *Synlett* **1992**, 391.
189. Konigsberger, K.; Hudlicky, T. *Tetrahedron: Asymmetry* **1993**, *4*, 2469.
190. Bestetti, G.; Galli, E.; Benigni, C.; Orsini, F.; Pellizzoni, F. *Appl. Microbiol. Biotechnol*. **1989**, *30*, 252.
191. Boyd, D. R.; Sharma, N. D.; Stevenson, P. J.; Chima, J.; Gray, D. J.; Dalton, H. *Tetrahedron Lett*. **1991**, *32*, 3887.
192. Stabile, M. R.; Hudlicky, T.; Meisels, M. L. *Tetrahedron: Asymmetry* **1995**, *6*, 537.
193. Stabile, M. R.; Hudlicky, T.; Meisels, M. L.; Butora, G.; Gum, A. G.; Fearnley, S. P.; Thorpe, A. J.; Ellis, M. R. *Chirality* **1995**, *7*, 556.
194. Omori, T.; Jigami, Y.; Minoda, Y. *Agr. Biol. Chem*. **1974**, *38*, 409.
195. Buck, R.; Eberspacher, J.; Lingens, F. *Hoppe-Seyler's Z. Physiol. Chem*. **1979**, *360*, 957.
196. Omori, T.; Jigami, Y.; Minoda, Y. *Agr. Biol. Chem*. **1975**, *39*, 1781.
197. Hudlicky, T.; Endoma, M. A. A.; Butora, G. *Tetrahedron: Asymmetry* **1996**, *7*, 61.
198. Cerniglia, C. E.; Gibson, D. T.; Van Baalen, C. *J. Gen. Microbiol*. **1980**, *116*, 485.
199. Cerniglia, C. E.; Gibson, D. T.; Van Baalen, C. *J. Gen. Microbiol*. **1980**, *116*, 495.
200. Cerniglia, C. E.; Gibson, D. T.; Van Baalen, C. *Biochem. Biophys. Res. Commun*. **1979**, *88*, 50.
201. Knackmuss, H.-J.; Beckmann, W.; Otting, W. *Angew. Chem., Int. Ed. Engl*. **1976**, *15*, 549.
202. Boyd, D. R.; McMordie, R. A. S.; Sharma, N. D.; Dalton, H.; Williams, P.; Jenkins, R. O. *J. Chem. Soc., Chem. Commun*. **1989**, 339.
203. Baaggi, G.; Castelani, D.; Galli, E.; Treccani, V. *Biochem. J*. **1972**, *126*, 1091.
204. Klečka, G. M.; Gibson, D. T. *Appl. Environ. Microbiol*. **1980**, *39*, 288.
205. Shocken, M. J.; Gibson, D. T. *Appl. Environ. Microbiol*. **1976**, *48*, 10.
206. Fortnagel, P.; Harms, H.; Wittich, R. M.; Krohn, S.; Meyer, H.; Sinwell, V.; Wilkes, H.; Francke, W. *Appl. Environ. Microbiol*. **1990**, *56*, 1148.
207. Cerniglia, C. E.; Morgan, J. C.; Gibson, D. T. *Biochem. J*. **1979**, *180*, 175.
208. Laborde, A. L.; Gibson, D. T. *Appl. Environ. Microbiol*. **1977**, *34*, 783.
209. Catelani, D.; Sorlini, C.; Treccani, V.

Experientia **1971**, *27*, 1173.
210. Selifonov, S. A.; Grifoll, M.; Gurst, J. E.; Chapman, P. J. *Biochem. Biophys. Res. Commun*. **1993**, *193*, 67.
211. Engesser, K. H.; Fietz, W.; Fischer, R.; Schulte, P.; Knackmuss, H.-J. *FEMS Microbiol. Lett*. **1990**, *69*, 317.
212. Jerina, D. M.; Selander, H.; Yagi, H.; Wells, M. C.; Davey, J. F.; Mahadevan, V.; Gibson, D. T. *J. Am. Chem. Soc*. **1976**, *98*, 5988.
213. Narro, M. L.; Cerniglia, C. E.; Van Baalen, C.; Gibson, D. T. *Appl. Environ. Microbiol*. **1992**, *58*, 1351.
214. Gibson, D. T.; Mahadevan, V.; Jerina, D. M.; Yagi, H.; Yeh, H. J. C. *Science* **1975**, *189*, 295.
215. Eaton, S. L.; Resnick, S. M.; Gibson, D. T. *Appl. Environ. Microbiol*. **1996**, *62*, 4388.
216. Lindquist, B.; Warshawsky, D. *Experientia* **1985**, *41*, 767.
217. Boyd, D. R.; Sharma, N. D.; Boyle, R.; McMurray, B. T.; Evans, T. A.; Malone, J. F.; Dalton, H.; Chima, J.; Sheldrake, G. N. *J. Chem. Soc., Chem. Commun*. **1993**, 49.
218. Reddy, G. D.; Wiest, O.; Hudlicky, T.; Schapiro, V.; Gonzalez, D. *J. Org. Chem*. **1999**, *64*, 2860.
219. Hudlicky, T.; Gonzalez, D.; Stabile, M.; Endoma, M. A.; Deluca, M.; Parker, D.; Gibson, D. T.; Resnick, S. M.; Whited, G. M. *J. Fluor. Chem*. **1998**, *89*, 23.
220. Astley, S. T.; Meyer, M.; Stephenson, G. R. *Tetrahedron Lett*. **1993**, *34*, 2035.
221. Allen, C. C. R.; Boyd, D. R.; Dalton, H.; Sharma, N. D.; Haughey, S. A.; McMordie, R. A. S.; McMurray, B. T.; Sheldrake, G. N.; Sproule, K. *J. Chem. Soc., Chem. Commun*. **1995**, 119.
222. Deluca, M. E.; Hudlicky, T. *Tetrahedron Lett*. **1990**, *31*, 13.
223. Whited, G. M.; Downie, J. C.; Hudlicky, T.; Fearnley, S. P.; Dudding, T. C.; Olivo, H. F.; Parker, D. *Bioorg. Med. Chem*. **1994**, *2*, 727.
224. Hudlicky, T.; Gonzalez, D.; Schilling, S. Unpublished results, 1997.
225. Boyd, D. R.; Sharma, N. D.; Dorrity, M. R. J.; Hand, M. V.; McMordie, R. A. S.; Malone, J. F.; Porter, H. P.; Dalton, H.; Chima, J.; Sheldrake, G. N. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1065.
226. Kimura, K.; Kato, H.; Nishi, A.; Furukawa, K. *Biosci. Biotech. Biochem*. **1996**, *60*, 220.
227. Resnick, S. M.; Gibson, D. T. Unpublished results.
228. Resnick, S. M.; Gibson, D. T. *Biodegradation* **1993**, *4*, 195.
229. Nadeau, L. J.; Sayler, G. S.; Spain, J. C. *Arch. Microbiol*. **1998**, *171*, 44.
230. Boyd, D. R.; Dorrity, M. R. J.; Malone, J. F.; McMordie, R. A. S.; Sharma, N. D.; Dalton, H.; Williams, P. *J. Chem. Soc., Perkin Trans. 1* **1990**, 489.
231. Boyd, D. R.; Sharma, N. D.; Brannigan, I. F.; Haughey, S. A.; Malone, J. F.; Clarke, D. A.; Dalton, H. *Chem. Commun*. **1996**, 2361.
232. Eaton, R. W.; Selifonov, S. A. *Appl. Environ. Microbiol*. **1996**, *62*, 756.
233. Resnick, S. M.; Gibson, D. T. *Appl. Environ. Microbiol*. **1996**, *62*, 1364.

Table 5. Miscellaneous Diols

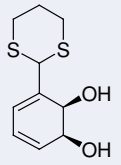


P. putida BM2 (ref. 182)

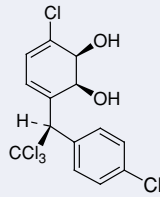
P. putida BM2 (ref. 182)

P. putida 39/D (ref. 135)

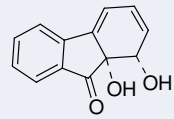
P. putida JT107 (ref. 40)



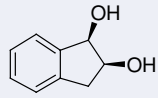
P. putida UV4 (ref. 221)



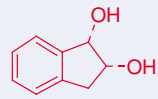
A. eutrophus A5 (ref. 229)



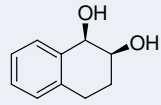
Pseudomonas sp. F274 (ref. 210)



P. putida NCIB 9816/11
P. putida NCIMB 8859
(ref. 50,65)



P. putida UV4
P. putida 39/D
(ref. 65,202,236)



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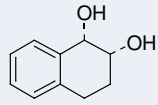
S. yanoikuyae B8/36
(ref. 65,171,215)



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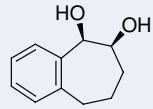

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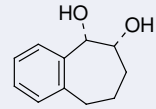

P. putida UV4
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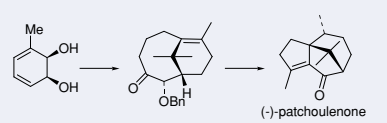
(ref. 65,202,230,233)

234. Boyd, D. R.; Sharma, N. D.; Kerley, N. A.; McMordie, R. A. S.; Sheldrake, G. N.; Williams, P.; Dalton, H. *J. Chem. Soc., Perkin Trans. 1* **1996**, 67.
235. Resnick, S. M.; Gibson, D. T. *Appl. Environ. Microbiol*. **1996**, *62*, 3355.
236. Wackett, L. P.; Kwart, L. D.; Gibson, D. T. *Biochemistry* **1988**, *27*, 1360.
237. Haddock, J. D.; Horton, J. R.; Gibson, D. T. *J. Bacteriol*. **1995**, *177*, 20.
238. Bowers, N. I.; Boyd, D. R.; Sharma, N. D.; Kennedy, M. A.; Sheldrake, G. N.; Dalton, H. *Tetrahedron: Asymmetry* **1998**, *9*, 1831.
239. Boyd, D. R.; Sharma, N. D.; Carroll, J. G.; Malone, J. F.; Mackerracher, D. G.; Allen, C. C. R. *Chem. Commun*. **1998**, 683.
240. Boyd, D. R.; Sharma, N. D.; Boyle, R.; Evans, T. A.; Malone, J. F.; McCombe, K. M.; Dalton, H.; Chima, J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1757.
241. Novak, B. H.; Hudlicky, T. *Tetrahedron: Asymmetry* **1999**, *10*, in press.
242. Hudlicky, T.; Endoma, M. A. A.; Butora, G. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2187.
243. Boyd, D. R.; Sharma, N. D.; Hempestall, F.; Kennedy, M. A.; Malone, J. F.; Allen, C. C. R.; Resnick, S. M.; Gibson, D. T. *J. Org. Chem*. **1999**, *64*, 4005.

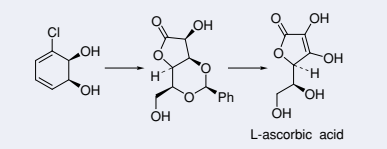
Note Added in Proof

Total Syntheses

1. Banwell, M.; McLeod, M. Chemoenzymatic total synthesis of the sesquiterpene (–)-patchoulenone *Chem. Commun*. **1998**, 1851.



2. Banwell, M.; Blakey, S.; Harfoot, G.; Longmore, R. W. First synthesis of L-ascorbic acid (vitamin C) from a non-carbohydrate source. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3141.



3. Banwell, M. G.; Blakey, S.; Harfoot, G.; Longmore, R. W. *cis*-1,2-Dihydrocatechols in chemical synthesis: First synthesis of L-ascorbic acid (vitamin C) from a non-carbohydrate source. *Aust. J. Chem*. **1999**, *52*, 137.

4. Boyd, D. R.; Sharma, N. D.; Byrne, B.; Hand, M. V.; Malone, J. F.; Sheldrake, G. N.; Blacker, J.; Dalton, H. Enzymatic and chemoenzymatic synthesis and stereochemical assignment of *cis*-dihydrodiol derivatives of monosubstituted benzenes. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1935.
5. Boyd, D. R.; Sharma, N. D.; Carroll, J. G.; Malone, J. F.; Mackerracher, D. G.; Allen, C. C. R. Dioxygenase-catalysed *cis*-dihydrodiol formation in the carbo- and heterocyclic rings of quinolines. *Chem. Commun*. **1998**, 683.
6. Barr, S. A.; Bowers, N.; Boyd, D. R.; Sharma, N. D.; Hamilton, L.; Austin, R.; McMordie, S.; Dalton, H. The potential role of *cis*-dihydrodiol intermediates in bacterial aromatic hydroxylation and the NIH Shift. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3443.
7. O'Dowd, C. R.; Boyd, D. R.; Sharma, N. D. Enantiopure synthesis of syn and anti arene dioxides. *Abstr. Pap.—Am. Chem. Soc*. **1998**, *216*, U470.
8. Lakshman, M. K.; Chaturvedi, S.; Zajc, B.; Gibson, D. T.; Resnick, S. M. A general chemoenzymatic synthesis of enantiopure *cis*-β-amino alcohols from microbially derived *cis*-glycols. *Synthesis* **1998**, 1352.
9. Parales, R. E.; Emig, M. D.; Lynch, N. A.; Gibson, D. T. Substrate specificities of hybrid naphthalene and 2,4-dinitrotoluene dioxygenase enzyme systems. *J. Bacteriol*. **1998**, *180*, 2337.
10. Parales, J. V.; Parales, R. E.; Resnick, S. M.; Gibson, D. T. Enzyme specificity of 2-nitrotoluene 2,3-dioxygenase from *Pseudomonas sp*. strain JS42 is determined by the C-terminal region of the α subunit of the oxygenase component. *J. Bacteriol*. **1998**, *180*, 1194.
11. Allen, C. C. R.; Boyd, D. R.; Hempestall, F.; Larkin, M. J.; Sharma, N. D. Contrasting effects of a nonionic surfactant on the biotransformation of polycyclic aromatic hydrocarbons to *cis*-dihydrodiols by soil bacteria. *Appl. Environ. Microbiol*. **1999**, *65*, 1335.
12. Brovetto, M.; Schapiro, V.; Cavalli, G.; Padilla, P.; Sierra, A.; Seoane, G.; Suescun, L.; Mariezcurrena, R. Osmylation of chiral *cis*-cyclohexadienediols. *New J. Chem*. **1999**, *23*, 549.
13. Jiang, H. Y.; Parales, R. E.; Gibson, D. T. The α subunit of toluene dioxygenase from *Pseudomonas putida* F1 can accept electrons from reduced Ferredoxin(TOL) but is catalytically inactive in the absence of the β subunit. *Appl. Environ. Microbiol*. **1999**, *65*, 315.
14. Nojiri, H.; Nam, J. W.; Kosaka, M.; Morii, K. I.; Takemura, T.; Furihata, K.; Yamane, H.; Omori, T. Diverse oxygenations catalyzed by carbazole 1,9a-dioxygenase from *Pseudomonas sp.* strain CA10. *J. Bacteriol*. **1999**, *181*, 3105.
15. Parales, R. E.; Parales, J. V.; Gibson, D. T. Aspartate 205 in the catalytic domain of naphthalene dioxygenase is essential for activity. *J. Bacteriol*. **1999**, *181*, 1831.

About the Authors

Tomas Hudlicky was born in 1949 in Prague, Czechoslovakia, where he received his elementary and middle school education. After several years of working as a process chemist apprentice and in other odd jobs in pharmaceutical chemistry, it became apparent that higher education opportunities were closed to him. In 1968, he emigrated to the U.S. with his parents and sister. Hudlicky's educational experience continued at Blacksburg High School, from which he dropped out in the spring of 1969. Accepted as a probational student at Virginia Tech the following autumn, he received his B.S. in chemistry in 1973, and went on to pursue graduate studies at Rice University under the direction of Professor Ernest Wenkert in the field of indole alkaloid total synthesis, earning his Ph.D. in 1977. He then spent a year at the University of Geneva working under the late Professor Wolfgang Oppolzer on the synthesis of isocomene. In 1978, he joined the faculty at the Illinois Institute of Technology as an Assistant Professor, and began the first phase of his research career in the field of general methods of synthesis for triquinane terpenes and other natural products containing five-membered rings by [4+1] cyclopentene, pyrroline, and dihydrofuran annulation methodologies. He returned to his alma mater, Virginia Tech, in 1982, and rose to the rank of Professor in 1988. One year later, at the 20-year class reunion of the Blacksburg High School class of 1969, he received his High School Diploma. The next phase of his research involved the investigation of *cis*-cyclohexadienediols in enantioselective synthesis, as summarized in this review.

In 1995, he moved to his present position at the University of Florida in Gainesville. His current research interests include the development of enantioselective synthetic methods, bacterial dioxygenase-mediated degradation of aromatics, design and synthesis of fluorinated inhalation anesthetic agents, synthesis of morphine and amaryllidaceae alkaloids, and design of unnatural oligosaccharide conjugates with new molecular properties. His hobbies include skiing, hockey, martial arts, and music.

David Gonzalez was born in Montevideo, Uruguay in 1965. He attended elementary and middle school at Instituto Crandon, and received his undergraduate education at the School of Chemistry of the Uruguayan public University (Universidad de la República). He performed undergraduate research in the Natural Products laboratory of Professor Patrick Moyna, where he later worked as a lab technician. In 1994, with the aid of a grant from SAREC and a master's fellowship from CONICYT, he obtained his master's degree in the area of bioactive marine natural products under the orientation of Professor Eduardo Manta. He was later accepted as a graduate student at the University of Florida, where he completed his doctoral degree in Professor Tomas Hudlicky's group. His current research interests involve the use of microbial biotransformations as a tool in organic synthesis. The results of his research have been presented at several meetings and have led to seven publications.

Dr. David T. Gibson was born in Wakefield, Yorkshire, England. He received a B.Sc. degree (First Class Honors) in Biochemistry in 1961 from the University of Leeds, England. He obtained his Ph.D. in 1964 in the same department under the guidance of the late Stanley Dagley. His dissertation research played a major role in the elucidation of the meta ring-fission pathway used by bacteria to degrade aromatic compounds. Dr. Gibson's initial postdoctoral studies were conducted in the laboratory of Dr. Charles J. Sih in the College of Pharmacy at the University of Wisconsin, where he worked on the microbial degradation of the steroid A ring. He then began studies on the bacterial oxidation of hydrocarbons with the late Dr. Reino E. Kallio in the Department of Microbiology at the University of Illinois. In 1967, he joined the faculty of the Department of Microbiology at the University of Texas at Austin as an assistant professor. The following year, he worked as a Research Biochemist in the Pharmaceuticals Division of Imperial Chemical Industries at Alderly Edge, Cheshire, England. In 1969, he returned to the Department of Microbiology at the University of Texas, rising through the ranks to Professor of Microbiology in 1975, and Director of the Center for Applied Microbiology in 1981. During this period, he studied the chemistry and enzymology of the reactions used by bacteria, fungi, and algae to initiate the degradation of aromatic hydrocarbons. In 1988, he was appointed to his current position as Foundation Professor in Microbiology and Biocatalysis at the University of Iowa. Dr. Gibson's current interests focus on the structure and function of bacterial enzymes that catalyze the asymmetric dihydroxylation of aromatic hydrocarbons. He is the author of more than 150 publications and the mentor of 22 graduate students. He has served on the editorial boards of the Journal of Biological Chemistry, the Journal of Bacteriology, and Biodegradation. From 1981–1988, he was a member of the Scientific Advisory Board of AMGEN. In 1997, he received the Proctor and Gamble Award in Applied and Environmental Microbiology from the American Society for Microbiology.

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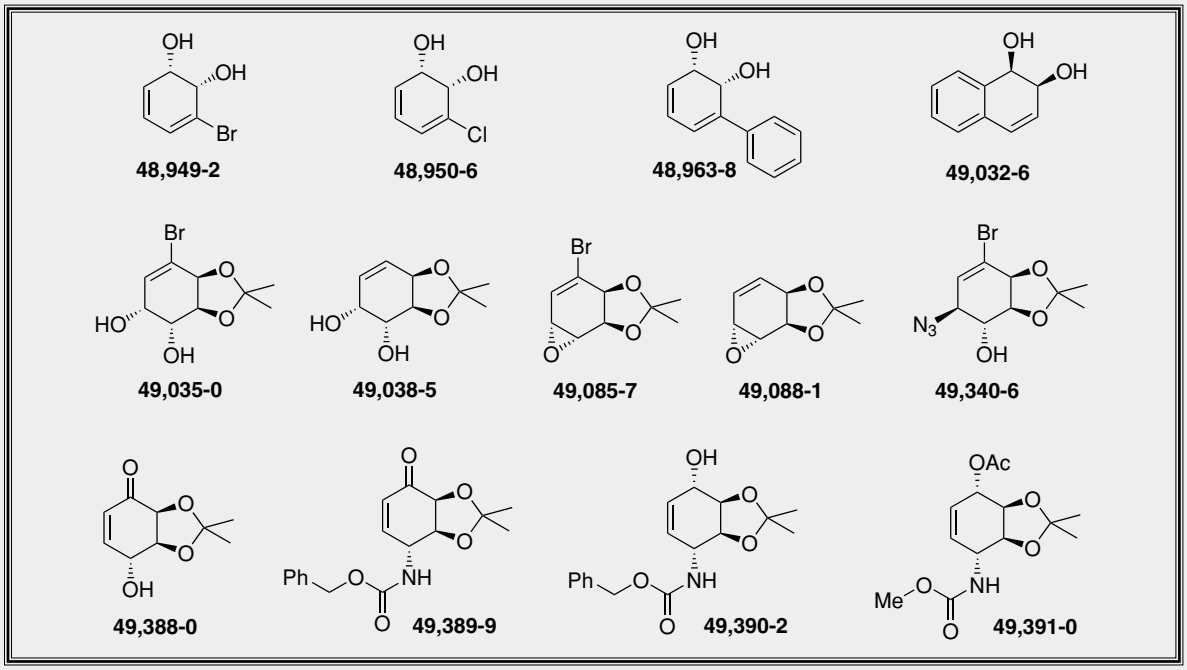

48,949-2 **(1*S-cis*)-3-Bromo-3,5-cyclohexadiene-1,2-diol**, 96%

48,950-6* **(1*S-cis*)-3-Chloro-3,5-cyclohexadiene-1,2-diol**, 98%

48,963-8* **(1*S-cis*)-3-Phenyl-3,5-cyclohexadiene-1,2-diol**, 98%

49,032-6* **(1*R-cis*)-1,2-Dihydro-1,2-naphthalenediol**, 98%

49,035-0 **[3a*S*-(3aα,4α,5α,7aα)]-7-Bromo-3a,4,5,7a-tetrahydro-2,2-dimethyl-1,3-benzodioxole-4,5-diol**, 99%

49,038-5 **[3a*S*-(3aα,4α,5α,7aα)]-3a,4,5,7a-Tetrahydro-2,2-dimethyl-1,3-benzodioxole-4,5-diol**, 98%

49,085-7 **[3a*S*-(3aα,5aβ,6aβ,6bα)]-4-Bromo-3a,5a,6a,6b-tetrahydro-2,2-dimethyloxireno[*e*]-1,3-benzodioxole**, 98%

49,088-1 **[3a*R*-(3aα,5aβ,6aβ,6bα)]-3a,5a,6a,6b-Tetrahydro-2,2-dimethyloxireno[*e*]-1,3-benzodioxole**, 96%

49,340-6 **[3a*S*-(3aα,4α,5β,7aα)]-5-Azido-7-bromo-3a,4,5,7a-tetrahydro-2,2-dimethyl-1,3-benzodioxol-4-ol**, 99%

49,388-0 **(3a*S*,7*R*,7a*S*)-7,7a-Dihydro-7-hydroxy-2,2-dimethyl-1,3-benzodioxol-4(3a*H*)-one**, 98%

49,389-9 **(3a*S*,7*R*,7a*S*)-7-(Carbobenzyloxyamino)-7,7a-dihydro-2,2-dimethyl-1,3-benzodioxol-4(3a*H*)-one**, 98%

49,390-2 **(3a*R*,4*S*,7*R*,7a*S*)-7-(Carbobenzyloxyamino)-3a,4,7,7a-tetrahydro-2,2-dimethyl-1,3-benzodioxol-4-ol**, 98%

49,391-0 **(3a*R*,4*S*,7*R*,7a*S*)-3a,4,7,7a-Tetrahydro-7-(methoxycarbonylamino)-2,2-dimethyl-1,3-benzodioxol-4-ol 4-acetate**, 98%

* All these products are offered as a suspension in phosphate buffer. The unit size corresponds to the actual amount of product and not the total volume. The label provides simple instructions on how to extract the product from the suspension prior to use. The chemical purity of each product was determined on the pure crystals prior to suspending them in the phosphate buffer.

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49,766-5	**5-Bromo-2-thienylzinc bromide**
49,775-4	***tert*-Butylzinc bromide**
49,776-2	**4-Chlorobenzylzinc chloride**
49,777-0	**4-Chlorobutylzinc bromide**
49,779-7	**6-Chlorohexylzinc bromide**
49,781-9	**5-Chloropentylzinc bromide**
49,783-5	**4-Chlorophenylzinc iodide**
49,789-4	**4-Cyanobutylzinc bromide**
49,790-8	**2-Cyanoethylzinc bromide**
49,796-7	**3-Cyanopropylzinc bromide**
49,803-3	**Cyclohexylzinc bromide**
49,804-1	**Cyclopentylzinc bromide**
49,807-6	**3,5-Dichlorophenylzinc iodide**
49,842-4	**3,5-Dimethylphenylzinc iodide**
49,944-7	**2-Ethoxybenzylzinc chloride**
49,945-5	**4-Ethoxybenzylzinc chloride**
49,846-7	**3-(Ethoxycarbonyl)phenylzinc iodide**
49,847-5	**4-(Ethoxycarbonyl)phenylzinc iodide**
49,849-1	**4-Ethoxy-4-oxobutylzinc bromide**
49,850-5	**6-Ethoxy-6-oxohexylzinc bromide**
49,851-3	**5-Ethoxy-5-oxopentylzinc bromide**
49,852-1	**3-Ethoxy-3-oxopropylzinc bromide**
49,855-6	**2-Ethylhexylzinc bromide**
49,857-2	**4-Ethylphenylzinc iodide**
49,860-2	**4-Fluorobenzylzinc chloride**
49,896-3	**Isobutylzinc bromide**
49,878-5	**2-Methoxybenzylzinc chloride**
49,883-1	**3-Methoxyphenylzinc iodide**
49,885-8	**4-Methoxyphenylzinc iodide**
49,905-6	***exo*-2-Norbornylzinc bromide**
49,907-2	**4-Pentenylzinc bromide**
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49,937-4	**Propylzinc bromide**

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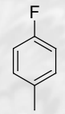
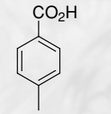
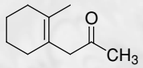
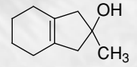
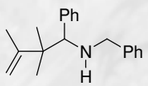
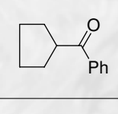
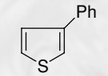
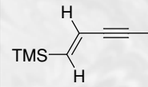
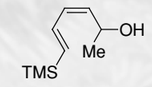
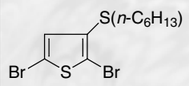
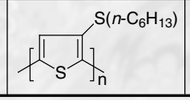
Uses of Mg*

Reactant	Product	Ref.
		13
		10
		10
		14

Uses of Zn*

Reactant	Product	Ref.
		13
		9
		12
		11

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References: (1) Erdik, E. *Organozinc Reagents in Organic Synthesis*; CRC Press, Inc.: Boca Raton, FL, 1996; Aldrich Catalog Number Z28,012-7. (2) Rieke, R. D.; Hanson, M. V. *Tetrahedron* **1997**, *53*, 1925. (3) Hanson, M. V.; Brown, J. D.; Rieke, R. D.; Niu, Q.J. *Tetrahedron Lett.* **1994**, *35*, 7205. (4) Cintas, P. *Activated Metals in Organic Synthesis*; CRC Press, Inc.: Boca Raton, FL, 1993; Aldrich Catalog Number Z24,607-7. (5) Miller, J. A.; Farrell, R. P. *Tetrahedron Lett.* **1998**, *39*, 7275. (6) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445. (7) Negishi, E.; King, A. O.; Okukado, N. *ibid.* **1977**, *42*, 1821. (8) Velarde-Ortiz, R.; Guijarro, A.; Rieke, R. D. *Tetrahedron Lett.* **1998**, *39*, 9157. (9) Rieke, R.D.; Kim, S-H.; Wu, X. *J. Org. Chem.* **1997**, *62*, 6921. (10) Rieke, R.D.; Sell, M.S.; Xiong, H. *J. Am. Chem. Soc.* **1995**, *117*, 5429. (11) Wu, X.; Chen, T-A.; Rieke, R.D. *Macromolecules* **1995**, *28*, 2101. (12) Chou, W-N.; Clark, D.L.; White, J.B. *Tetrahedron Lett.* **1991**, *32*, 299. (13) Rieke, R.D.; Hanson, M.V. *Tetrahedron* **1997**, *53*, 1925; and references cited therein. (14) Sell, M.S.; Klein, W.R.; Rieke, R.D. *J. Org. Chem.* **1995**, *60*, 1077.

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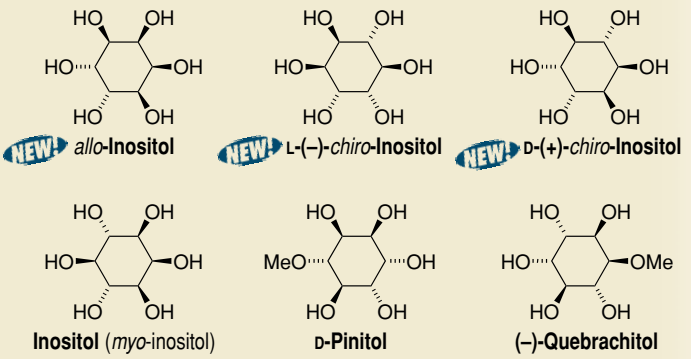
References: (1) Potter, B.V.L. *Nat. Prod. Rep.* **1990**, *7*, 1. (2) Bellington, D.C. *Chem. Soc. Rev.* **1989**, *18*, 83. (3) Berridge, M.J.; Irvine, R.F. *Nature* **1989**, *341*, 197. (4) Hudlicky, T.; Cebulak, M. *Cyclitols and Their Derivatives. A Handbook of Physical, Spectral, and Synthetic Data*; VCH: New York, 1993. (5) Hudlicky, T. et al. *Chem. Rev.* **1996**, *96*, 1195. (6) Hudlicky, T. et al. *Synthesis* **1996**, 897.



46,808-8	*allo*-**Inositol**, 97%
46,805-3	L-(–)-*chiro*-**Inositol**, 95%
46,804-5	D-(+)-*chiro*-**Inositol**, 95%
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44,125-2	D-**Pinitol**, 95%
36,060-0	**(–)-Quebrachitol**, 97%
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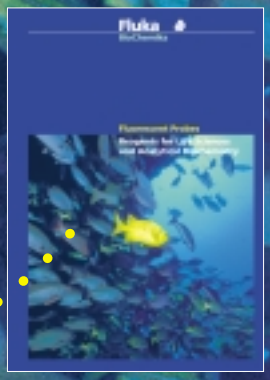

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30,697-5	***tert*-Butyl methyl ether,** 99.8%	**30 ppm**
28,911-6	**Carbon tetrachloride,** 99.5+%	**20 ppm**
28,830-6	**Chloroform,** 99+%	**10 ppm**
27,099-7	**Dichloromethane,** 99.8%	**10 ppm**
29,630-9	**1,4-Dioxane,** 99.8%	**30 ppm**
45,984-4	**Ethyl alcohol,** 99.5%, non-denatured (TAX-PAID)	**30 ppm**
27,764-9	**Ethyl alcohol,** reagent, denatured	**30 ppm**
25,952-7	**Ethylene glycol dimethyl ether,** 99.5%	**30 ppm**
24,665-4	**Heptane**, 99%	**10 ppm**
22,706-4	**Hexanes**	**20 ppm**
29,699-6	**Methyl acetate,** 99.5%	**30 ppm**
32,241-5	**Methyl alcohol,** 99.8%	**20 ppm**
27,438-0	**Methyl sulfide,** 99+%	**30 ppm**
31,032-8	**Propylene carbonate,** 99.7%	**30 ppm**
27,097-0	**Pyridine,** 99.8%	**30 ppm**
18,656-2	**Tetrahydrofuran,** 99.9%	**30 ppm**
24,451-1	**Toluene,** 99.8%	**20 ppm**

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A Symposium sponsored by the Inorganic and Organic Divisions of the American Chemical Society

218th National Meeting, New Orleans, LA
August 22–25, 1999

Organizer: Professor P. V. Ramachandran – Purdue University

Sunday, August 22, 1999

INORGANIC DIVISION SYMPOSIUM
(ORGN, CO-SPONSOR)

AM Session Chair: L. Barton

9:00 AM
S. Strauss
Selective Fluorination of B–H Bonds

9:30 AM
R. Grimes
Small Metallacarboranes in Synthesis: Beyond Metallocenes

10:00 AM
F. Hawthorne
Synthetic Challenges and Structural Victories in Polyhedral Borane Chemistry

10:30 AM
L. Sneddon
Metal-Catalyzed Syntheses of New Polyborane Monomers and Polymers

11:00 AM
T. Fehlner
Utilization of Monoboranes in the Syntheses of Metallaboranes of Groups 5–9

11:30 AM
K. Wade
Recent Studies of Icosahedral Carboranes

PM Session Chair: S. Krishnamurthy

1:30 PM
H. C. Brown
Organoboranes for Organic Syntheses: Recent Advances in the Syntheses of Amines

2:00 PM
P. Knochel
Stereoselective Rearrangement of Organoboranes: A New Method of Cyclic and Acyclic Stereocontrol of Adjacent Carbon Centers

2:30 PM
A. Suzuki
Cross-Coupling Reactions of Organoboron Compounds with Organic Electrophiles

3:00 PM
D. Matteson
A Mystery Story of Ligand Transfer on Boron

3:30 PM
K. Smith
Selective Polymeric Organoborohydride Agents—Synthesis and Applications

4:00 PM
P. K. Jadhav
Enantioselective Allylboration Reaction with Diisopinocampheylborane Reagents

4:30 PM
M. Zaidlewicz
Organoborane Dienophiles as 1-Alkene Equivalents, Terpenylboranes and Catalytic Hydroboration of Dienes and Enynes

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Monday, August 23, 1999

INORGANIC DIVISION SYMPOSIUM
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AM Session Chair: K. Wade

8:30 AM
S. Shore
Cyclic Organohydroborate Metallocene Complexes

9:00 AM
H. Noth
N- and *B*-Metalated Borazines: Will There Be a Renaissance in Borazine Chemistry?

9:30 AM
R. Contreras
Boron in Optically Active Heterocycles

10:00 AM
L. Barton
Reactions of Metallaboranes: From Cluster Degradation to the Formation of Linked Clusters

10:30 AM
N. Hosmane
Organometallics Derived from Carboranes and Boranes

11:00 AM
W. Siebert
Hydroboration and Diboration of Unsaturated Compounds

11:30 AM
R. B. King
Analogies Between the Chemical Bonding in Deltahedral Boranes and Planar Aromatic Hydrobcarbons

PM Session Chair: C. Recatto

1:30 PM
M. Cook
Borane Chemistries through Sodium Borohydride

2:00 PM
J. Bruening
Borane Reagents for the Pharmaceutical Industry: CalSelect™ Reducing Agents

2:30 PM
C. Goralski
Lithium Aminoborohydrides: Reagents with Multiple Personalities

3:00 PM
M. Srebnik
The Chemistry and Applications of C-1 Bridged Phosphorus Boronates

3:30 PM
M. Periasamy
New Organic Synthetic Methods Using Sodium Borohydride/Iodine System

4:00 PM
J. S. Cha
Alkylboranes as Selective Reducing and Hydroborating Agents

4:30 PM
N. N. Joshi
Oxazaborolidine-Catalyzed Reduction of Functionalized Ketones

Wednesday, August 25, 1999

ORGANIC DIVISION SYMPOSIUM
(INOR, CO-SPONSOR)

AM Session Chair: P. V. Ramachandran

8:30 AM
A. Pelter
Some Alkene Syntheses via Organoboranes

9:00 AM
N. Miyaura
Rhodium-Catalyzed Addition of Organoboronic Acids to Aldehydes and Enones

9:30 AM
H. Yamamoto
Designer Lewis Acid Catalysts of Boron

10:00 AM
I. Paterson
Stereocontrolled Synthesis of Concanamycin F Using Chiral Boron Enolates

10:30 AM
R. Hoffmann
Synthesis of Heterocyclic Compounds by Domino-Hydroformylation-Allylboration-Hydroformylation Reactions

11:00 AM
E. I. Negishi
Hydrometalation and Carbometalation of Alkynyl- and Alkenylboranes and Hydroboration of Alkynyl- and Alkenylmetals

11:30 AM
A. Soloway
Boranes in Developing of Tumor Targeting Agents for Boron Neutron Capture Therapy

PM Session Chair: D. Matteson

1:00 PM
N. Petasis
Synthesis of Amine Derivatives from Organoboronic Acids

1:30 PM
G. Kabalka
Solventless Suzuki Coupling Reactions on Alumina

2:00 PM
J. Soderquist
New Asymmetric Organoborane Conversions with 10-TMS-9-BBD Systems

2:30 PM
K. K. Wang
Synthesis of Conjugated Dienes, Diene-allenes, Ene-diynes, Enyne-allenes, and Related Compounds via Organoboranes

3:00 PM
Y. Yamamoto
Tris(pentafluorophenyl)boron-Catalyzed Reduction of Alcohols and Ethers with Hydrosilanes

3:30 PM
T. Cho
Catalytic Asymmetric Reduction of α-Functionalized Ketones

4:00 PM
P. V. Ramachandran
Organoboranes for Fluoro-Organic Synthesis: Transition Metal Catalyzed Hydroboration of Perfluoroalkyl(aryl)ethylenes

4:30 PM
N. M. Yoon
Borohydride Exchange Resin–Nickel Boride, A Versatile Reagent for Organic Synthesis

5:00 PM **Concluding Remarks**

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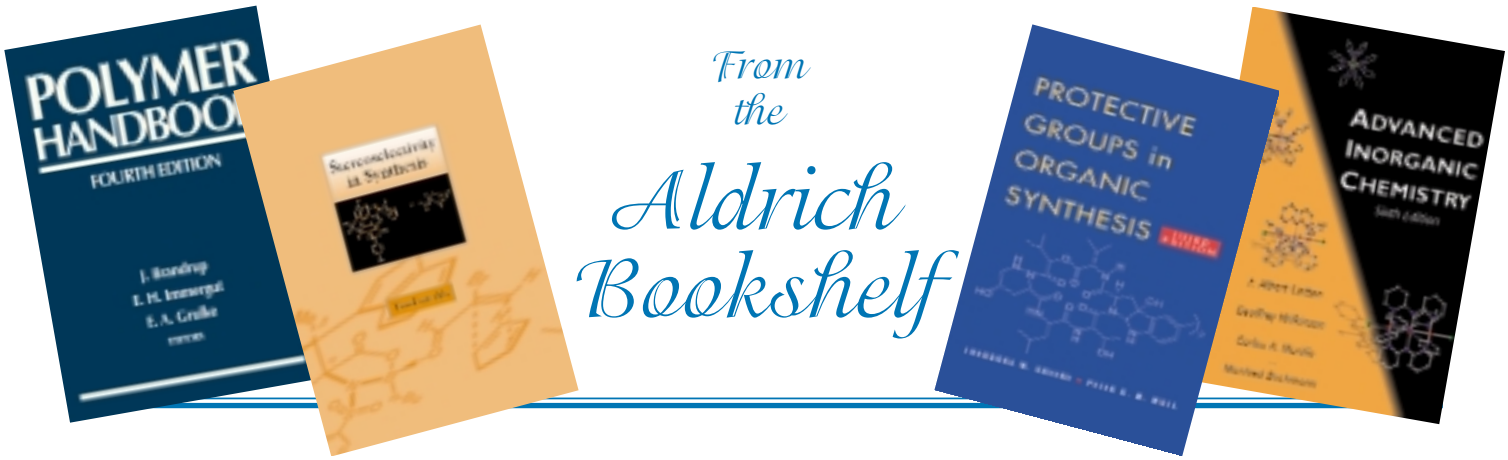
49,166-7	**Acetone-**$^{13}C_3$, 99 atom % ^{13}C
48,516-0	**Acetonitrile-***1*-^{13}C, 99 atom % ^{13}C
48,517-9	**Acetonitrile-***1*-^{13}C-^{15}N, 99 atom % ^{13}C, 99 atom % ^{15}N
48,521-7	**Acetonitrile-**$^{13}C_2$, 99 atom % ^{13}C
49,167-5	**Acetonitrile-**$^{13}C_2$-^{15}N, 99 atom % ^{13}C, 99 atom % ^{15}N
49,168-3	**Acetonitrile-***2*-^{13}C-^{15}N, 99 atom % ^{13}C, 99 atom % ^{15}N
48,533-0	**Benzene-**d_5, 99 atom % D
48,563-2	**Benzene-**^{13}C, 99 atom % ^{13}C
48,540-3	**Chloroform-**^{13}C, 99 atom % ^{13}C
49,218-3	**Dichloromethane-**^{13}C, 99 atom % ^{13}C
49,219-1	**Dichloromethane-***d*, 95 atom % D
48,551-9	**Methyl-**^{13}C **sulfoxide**, 99 atom % ^{13}C
48,618-3	**Pyridine-**^{15}N, 99 atom % ^{15}N
48,621-3	**Toluene-***2,3,4,5,6*-d_5, 98 atom % D
48,707-4	**Toluene-**α,α,α-d_3, 99 atom % D
48,708-2	**Toluene-**α-^{13}C, 99 atom % ^{13}C



From the Aldrich Bookshelf

Protective Groups in Organic Synthesis

3rd ed., T.W. Greene and P.M. Wuts, John Wiley & Sons, New York, NY, 784pp. Hardcover. Details the use of protecting groups in synthetic organic chemistry. Expanded by more than 50%, provides readers with a compendium of 1,050 of the most useful protective groups as well as 5,350 references to original publications.

Z41,242-2

Stereoselectivity in Synthesis

T. Ho, John Wiley & Sons, New York, NY, 1999. Hardcover. Shows how to choose the best method for a given synthesis. Provides readers with a thorough understanding of stereoselectivity in organic and medicinal chemistry as well as the pharmaceutical, agricultural, and food industries.

Z41,243-0

Organic Coatings: Science and Technology

2nd ed., Z.W. Wicks, F.N. Jones, and S.P. Pappas, John Wiley & Sons, New York, NY, 1999, 630pp. Hardcover. Combines a presentation of contemporary scientific knowledge in the field of organic coatings with a summary of its applied technology. This new self-contained volume is more accessible and contains new developments in the field since the publication of the first edition.

Z41,244-9

Flavourings

E. Ziegler and H. Ziegler, Eds., Wiley-VCH, Weinheim, Germany, 1998, 710pp. Hardcover. Provides a comprehensive insight into the production, processing, and applications of various food flavourings. Focuses on the conventional and new analytical methods employed in the field. Covers food legislation as well as quality control.

Z41,253-8

Kirk-Othmer Encyclopedia of Chemical Technology

4th ed., Concise, M. Grayson and D. Eckroth, Eds., John Wiley & Sons, New York, NY, 1999. Hardcover. This abridged version of a 28-volume set contains information about 1,100 topics of interest to chemists.

Z41,246-5

Polymer Handbook

4th ed., J. Brandrup, E. Immergut and E.A. Grulk, Eds., John Wiley & Sons, Somerset, NJ, 1999, 2336pp. Hardcover. Contains information pertaining to polymerization, depolymerization, and characterization in solution or in the solid state. Explores developments in the field since 1989, such as new PVT relationships and new copolymer reactivity parameters.

Z41,247-3

Measure for Measure

R. Young and T. Glover, Blue Willow, Inc., Littleton, CO, 1996, 864pp. Softbound. A comprehesive conversion factor reference that contains over 39,000 conversions for over 5100 different units. Designed specifically for engineers, scientists, students, and teachers. Comes in a convenient size (4in. W x 6in. H x 1in. D) with a durable white Lexotone® cover.

Z41,248-1

Advanced Inorganic Chemistry

6th ed., F.A. Cotton and G. Wilkinson, John Wiley & Sons, New York, NY, 1999. Hardcover. Incorporates many new chemical developments, particularly recent theoretical advances in the interpretation of bonding and reactivity in inorganic compounds. As in previous editions, the chapters devoted to the elements form the core and are covered in periodic table sequence.

Z41,245-7

Chemistry of Advanced Materials: An Overview

L.V. Interrante and M.J. Hampden-Smith, Eds., Wiley-VCH, New York, NY, 1998, 580pp. Hardcover. Advanced materials are substances such as composites (tennis rackets are graphite composites), super alloys (used in the aerospace industry), and advanced ceramics (used in semi-conductors, superconductors in the levitating bullet train, and tiles in the space shuttle). This is the first volume in a new series, Chemistry of Advanced Materials, devoted to providing a broad perspective about materials chemistry and helping scientists and engineers understand the importance of chemistry in materials science and engineering.

Z40,863-8

The Systematic Identification of Organic Compounds

7th ed., R.L. Shriner, C.F. Hermann, T.C. Morrill, D.Y. Curtin, and R.C. Fuson, John Wiley & Sons, New York, NY, 1997, 669pp. Hardcover. Updated edition explores the fundamentals of organic qualitative analysis. Provides protocols for both wet and spectroscopic methods of analysis. Includes one chapter of identification exercises.

Z40,642-2

Fragrances: Beneficial and Adverse Effects

P.J. Frosch, J.D. Johansen, and I.R. White, Eds., Springer-Verlag, New York, NY, 1998, 234pp. Hardcover. Presents numerous aspects of fragrance use and safety in a comprehensive form. Provides detailed information about recent neuropharmacological and psychosocial findings, chemistry and identification of sensitizers by various assays, skin absorption studies, and environmental issues. International guidelines for manufacturers are provided and commented upon.

Z40,866-2

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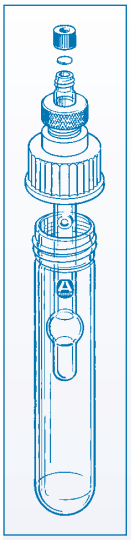
ALDRICH MNNG DIAZOMETHANE GENERATOR WITH SYSTEM 45 CONNECTION



MNNG (1-methyl-3-nitro-1-nitrosoguanidine; cat. no. **12,994-1**) is probably the most convenient precursor to diazomethane, because it is stable and crystalline, and generates diazomethane upon treatment with aqueous alkali.

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The screw thread closure and PTFE adapter provide an efficient, gas-tight connection between the inner tube and the outer body section. For storage, simply remove the inner tube assembly from the threaded outer section and screw on the PTFE lined screw cap. Access to the material is made through the open-top septum cap with a syringe. Supplied complete with threaded body, threaded inner tube, PTFE adapter, 32mm cap, O-ring, lock nut, septum, and 8mm open-top cap.

Typical Generator Setup

- 1mmol (133mg) or less of MNNG reagent is placed in the inside tube through the 8mm open-top screw cap along with 0.5mL of water to dissipate any heat generated.
- Ether (~3mL) is placed in the outside tube and the two parts are assembled and held together by tightening the 32mm screw cap.
- Immerse the lower part in an ice bath and inject (dropwise, very slowly to prevent frothing or possible buildup of back pressure) about 0.6mL of 5*N* sodium hydroxide through the PTFE-faced silicone septum via a syringe with a narrow gauge needle (No. 22) to prevent diazomethane leakage around the shank. (See below for syringe ordering information.)
- Diazomethane collects in the ether ready for use.

Diazoethane, despite its lower volatility, can be generated similarly from ENNG (1-ethyl-3-nitro-1-nitrosoguanidine; cat. no. **E4,160-5**). This apparatus is also useful for the generation of radioactive or deuterated diazomethane because it is a closed system.

WARNING: MNNG is mutagenic and exposure may cause skin sensitivity. While MNNG is more convenient for the generation of small quantities of diazomethane, Diazald is the preferred reagent for large-scale production of diazomethane. However, it has recently been reported that Diazald can be used in place of MNNG in the above apparatus. See: F. Ngan and M. Toofan *Journal of Chromatographic Science* **1991**, *29*, 8. Diazomethane has been reported to be explosive, particularly on contact with ground-glass joints during distillation.

Description	Cat. No.
MNNG diazomethane generator	**Z41,173-6**
Replacement parts	
O-ring seal	**Z41,174-4**
PTFE-faced silicone septum, 32mm	**Z41,175-2**
PTFE-faced silicone septum, 8mm	**Z41,176-0**
Screw cap with hole, 8mm	**Z41,177-9**
Disposable syringes	
All PE/PP, 1mL (order needles below)	**Z23,072-3**
Disposable needles, 22 gauge, 1in. L	**Z11,806-0**

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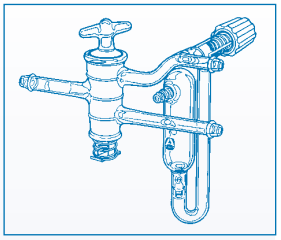

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- Sturdy, high-performance construction

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Z22,532-0

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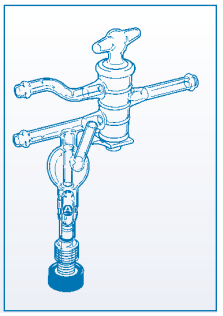
Z10,361-6



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Aldrichimica Acta

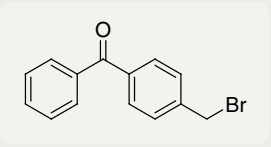
Volume 32, Number 3, 1999 (*Last issue in 1999*)

Ring-Closing Metathesis of Nitrogen-Containing Compounds: Applications to Heterocycles, Alkaloids, and Peptidomimetics

Are Two Phenyls Better than One? Synthesis and Applications of (R)-4-Diphenylmethyl-2-oxazolidinone

NewProducts

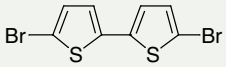
This benzophenone has been used to prepare several photoinitiators, including tetraalkylammonium salts, for acrylate polymerization.[1] It is also used to prepare photocleavable protein cross-linking agents.[2]



(1) Zhang, W. et al. *J. Org. Chem.* **1999**, *64*, 458. (2) Oatis, J.E., Jr.; Knapp, D.R. *Tetrahedron Lett.* **1998**, *39*, 1665.

44,938-5 **4-(Bromomethyl)benzophenone**, 97%

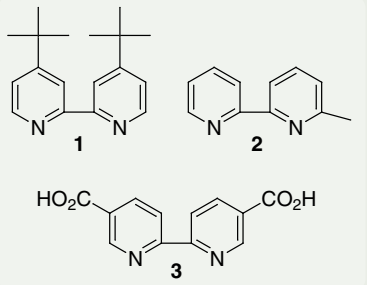
Oligothiophenes, with nonlinear optic and electrochemical applications, have been prepared from this brominated bithiophene.[1,2]



(1) Nakanishi, H. et al. *J. Org. Chem.* **1998**, *63*, 8632. (2) Roncali, J. *Chem. Rev.* **1992**, *92*, 711.

51,549-3 **5,5'-Dibromo-2,2'-bithiophene**, 99%

A variety of organometallic complexes have been prepared from these bipyridines. Compounds **1** and **2** are useful for the preparation of ruthenium complexes with increased solubility in organic solvents and modified redox properties relative to those of the complexes with unsubstituted bipyridine analogs.[1,2] Compound **3** has been utilized to prepare highly functionalized bipyridines.[3]



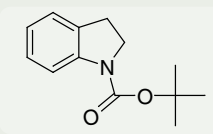
(1) Hadda, T.B.; Bozec, H.L. *Polyhedron* **1988**, 575. (2) Fabian, R.H. et al. *Inorg. Chem.* **1980**, *19*, 1977. (3) Penicaud, V. et al. *Tetrahedron Lett.* **1998**, *39*, 3689.

51,547-7 **4,4'-Di-*tert*-butyl-2,2'-dipyridyl**, 98% (**1**)

51,614-7 **6-Methyl-2,2'-dipyridyl**, 97% (**2**)

51,776-3 **2,2'-Bipyridine-5,5'-dicarboxylic acid**, 97% (**3**)

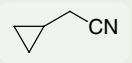
This compound is readily lithiated at C-7 using *sec*-butyllithium, and has been used to prepare a variety of 7-substituted indolines.



Meyers, A.I.; Milot, G. *J. Org. Chem.* **1993**, *58*, 6538.

51,014-9 ***tert*-Butyl indoline-1-carboxylate**, 98%

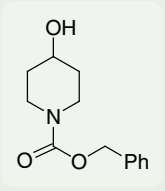
Important starting material for the preparation of cyclopropane-substituted heterocycles.[1,2]



(1) Li, Q. et al. *J. Med. Chem.* **1996**, *39*, 3070. (2) Kim, D.-K. et al. *ibid.* **1997**, *40*, 2363.

51,611-2 **Cyclopropylacetonitrile**, 97%

Useful synthon for the synthesis of biologically active quinolones[1] and fibrinogen receptor antagonists.[2]



(1) Cooper, C.S. et al. *J. Med. Chem.* **1992**, *35*, 1392. (2) Alig, L. et al. *ibid.* **1992**, *35*, 4393.

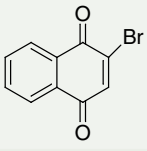
51,390-3 **Benzyl 4-hydroxy-1-piperidinecarboxylate**, 97%

This cyclopentadiene has been used as a diene in Diels–Alder reactions,[1] and for the preparation of fulvenes[2] and metallocenes.[3]

(1) Riemshneider, R.; Nehring, R. *Monatsh. Chem.* **1959**, *90*, 568. (2) Miyake, S. et al. *Macromolecules* **1995**, *28*, 3074. (3) Drewitt, M.J. *Chem. Commun.* **1996**, 2153.

49,498-4 ***tert*-Butylcyclopentadiene**, mixture of isomers

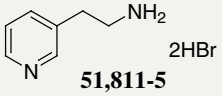
A number of anthraquinones and naphthoquinones have been prepared from this compound.[1,2]



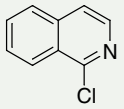
(1) Kesteleyn, B. et al. *J. Org. Chem.* **1999**, *64*, 1173. (2) Joshi, B.S. et al. *ibid.* **1994**, *59*, 8220.

51,030-0 **2-Bromo-1,4-naphthoquinone**, 98%

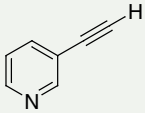
These heterocyclic synthons are widely used starting materials in medicinal chemistry.[1-4]



51,811-5



15,674-4



52,044-6

(1) Tucker, T.J. et al. *J. Med. Chem.* **1994**, *37*, 2437. (2) Moltzen, E.K. et al. *ibid.* **1994**, *37*, 4085. (3) Zhang, H. et al. *J. Org. Chem.* **1998**, *63*, 6886. (4) Hoffman, J.M. et al. *J. Med. Chem.* **1992**, *35*, 3784.

51,811-5 **3-(2-Aminoethyl)pyridine dihydrobromide**, 98%

15,674-4 **1-Chloroisoquinoline**, 95%

52,044-6 **3-Ethynylpyridine**, 98%

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About Our Cover

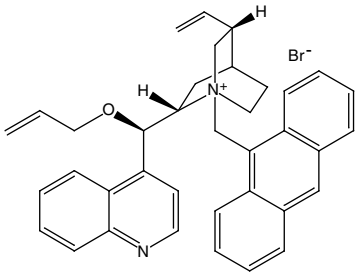
Jan Davidsz. de Heem's *Vase of Flowers* (oil on canvas, 27⅜ in. x 22¼ in.), painted about 1660, is a beautiful example of the delight that Dutch and Flemish seventeenth-century artists took in the natural world. The brilliant color, the soft texture of flower petals, the moist gleam of dew on leaves, and the detailed delineation of insects and small animals all contribute to the extraordinary illusionism of the painting. Moreover, the dynamic rhythms of the leaves, wheat stalks, peas, and flowers, and the small creatures crawling and fluttering in the air surpass mere description to make the objects represented seem almost to break through the surface of the picture. One can almost imagine the sweet scents of the flowers. The painting is far more than simply an extraordinary literal record of reality, however. It is an important expression of the imagination of the artist, who has overcome the laws of nature. Normally, this combination of flowers, fruits, and vegetables could not be in the same bouquet because they mature at different seasons of the year. Furthermore, these flowers will continue to bloom long after those in nature have withered and died. *Ars longa, vita brevis.* The painting is also filled with symbolic associations that would have been well understood in the seventeenth century. Insects and snails represent forces that are destructive of the beauties of nature. The transient loveliness of flowers is a reminder of the temporality of life. The morning glory, which opens at dawn and closes at dusk, symbolizes the light of truth.

This painting is part of the Andrew W. Mellon Collection at the National Gallery of Art, Washington, D. C.

"Please Bother Us."

by Jai Nagarkatti

Jai Nagarkatti, President



Dr. Martin J. O'Donnell (IUPUI, Indianapolis) kindly suggested that we make *O*-allyl-*N*-(9-anthracenylmethyl)-cinchonidinium bromide. This phase-transfer catalyst is useful for the enantioselective synthesis of α-amino acid derivatives.[1-3] A key step in the synthesis is the enantioselective alkylation of the enolate derived from *N*-(diphenylmethylene)glycine *tert*-butyl ester.

(1) O'Donnell, M.J. et al. *Tetrahedron* **1999**, *55*, 6347.
(2) O'Donnell, M.J. et al. *Tetrahedron Lett.* **1998**, *39*, 8775.
(3) Corey, E.J. et al. *J. Am. Chem. Soc.* **1997**, *119*, 12414.

49,961-7 ***O*-Allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide**, 95%

36,448-7 ***N*-(Diphenylmethylene)-glycine *tert*-butyl ester**, 98%

Naturally, we made this useful catalyst. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page or on the inside back cover.

Lab Notes

A Simple, Inexpensive Apparatus for Parallel Synthesis

In recent years, combinatorial chemistry[1] has emerged as an important component in drug discovery and as a technology that can increase the productivity of pharmaceutical research tremendously. Numerous synthesizers with varying degrees of automation are available commercially, both for solution- and solid-phase synthesis. Moreover, synthesis carried out in multiwell plates requires a liquid handling system and generates only a few milligrams of products.

In an attempt to increase the number of compounds synthesized, keeping in mind the cost, we designed a simple piece of equipment that is a modification of a vacuum manifold. Initially, we used a manifold with five arms (**Figure A**). Each arm is about 7 inches in length and serves as an air condenser; a reflux condenser is attached to the top of the manifold. The apparatus can be comfortably used for higher boiling solvents, especially when a common solvent is in use, with no overflow or drying of any flask. Later on, this apparatus was modified to accommodate a larger number (10) of reaction vessels (**Figure B**). Using this apparatus in an oil bath heated on a laboratory stirrer/hotplate, we carried out a series of solution-phase ester, amide, and guanidine syntheses in both 10-mL and 15-mL flasks. Each of the reaction flasks was charged with only 5–7 mL of reaction solution, and rigorous reflux was avoided to permit the refluxing solvent (e.g., xylenes) to condense completely in the 7-in. arm and thus avoid cross-contamination. We isolated a few hundred milligrams of each product in a relatively pure form (HPLC purity of guanidine derivatives >93%) with no cross-contamination. In the absence of fancier and more costly equipment, this apparatus can be used effectively for the synthesis of analogs with a common chemistry. It does not require any additional laboratory space and may also be suitable for solid-phase synthesis.

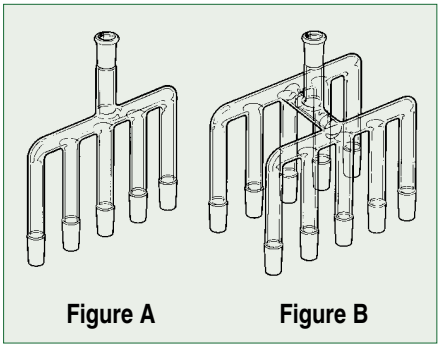


Figure A Figure B

References: (1) *Combinatorial Chemistry: Synthesis and Application*; Wilson, S.R., Czarnik, A.W., Eds.; John Wiley & Sons, Inc.: New York, NY, 1997 (**Z28,759-8**).

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A Simple and Efficient Apparatus for Growing Crystals by Diffusion of Reacting Solutions

Growing crystals for X-ray diffraction analysis is often a challenging task. Several methods and techniques have been developed to grow good-quality crystals. Among them are the slow evaporation of saturated solutions,[1] cooling of saturated solutions, liquid diffusion, vapor diffusion, diffusion of reacting solutions,[2] and other more sophisticated methods such as crystal growing in gels.[3] In our research, we encountered difficulties growing suitable crystals of an organic host–guest complex using conventional methods. Layering one reacting solution on the other in a tube[2] gave crystals of some quality, but were too small for X-ray diffraction analysis. To overcome this problem, we designed a simple apparatus, which allows growing crystals of the complex during its formation reaction.

If compound **A** readily forms a crystalline complex with compound **B**, the size and quality of the crystals of the complex **AB** can be significantly improved by performing the reaction slowly. The apparatus shown in **Figure 1** is capable of extending the reaction time up to several weeks. The whole system is an easily made, single-piece glassware consisting of several parts:

Continued on page 90.

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Ring-Closing Metathesis of Nitrogen-Containing Compounds: Applications to Heterocycles, Alkaloids, and Peptidomimetics§

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Outline

1. Introduction

Olefin metathesis, a process by which alkylidene groups on alkenes are exchanged (**Figure 1**), was first reported in 1955 by Anderson and Merckling. Their seminal report described the polymerization of norbornene by titanium(II) species.[1] Despite its widespread use in industry as a method for producing higher olefins and polymers, it is only in recent times that the process has become more generally utilized. The generalization into synthetic organic chemistry has been driven primarily by the discovery of well-defined and functional-group-tolerant catalysts independently by Schrock and Grubbs.[2,3] The functional-group tolerance and reasonable stability of these catalysts have allowed their widespread use for ring formation. This review describes the applications of olefin metathesis to systems containing nitrogen functionality such as peptides, peptidomimetics, and azasugars, and covers the literature from January 1990 to December 1998. Recent reviews by Blechert, Armstrong, and Grubbs have surveyed other aspects of olefin metathesis in synthesis.[3]

2. Catalysts and Mechanism

At the present time there are two main types of catalyst in use (**Figure 2**). These are the molybdenum-based complex **1**, developed by Schrock and co-workers,[2] and the ruthenium-based complexes **2**, and in particular **3**, developed by Grubbs and co-workers.[4] Complex **1** has the major disadvantage of being particularly air- and moisture-sensitive, whereas **3** is not significantly affected by air, moisture, or other reaction impurities. Both catalysts are commercially available and details for their synthesis have been reported.[4d] It is worth noting that complex **3** is readily prepared by a short, one-pot sequence that is readily scalable to amounts as large as 10 g.[5] A number of other catalysts are also illustrated in Figure 2. Titanium carbenes such as **4** (presumably formed under the reaction conditions), which are more commonly utilized in olefination reactions, find occasional use.[6] Hoveyda and co-workers have recently reported the synthesis and some applications of ruthenium alkylidene **5**.[7] Although its scope has yet to be defined, this catalyst may well offer some advantages since it is stable to silica chromatography and thus can be recycled. It is worth noting that, although its rate of initiation is some 30-fold slower than that of carbene **3**, its rate of propagation is fourfold faster. Further investigations of carbenes that contain other nonphosphine ligands may yield even more useful catalysts.[8] In a similar vein, Grubbs and Nguyen have also reported the preparation of polystyrene–divinylbenzene-supported ruthenium carbenes and examined their activity and reuse.[9]

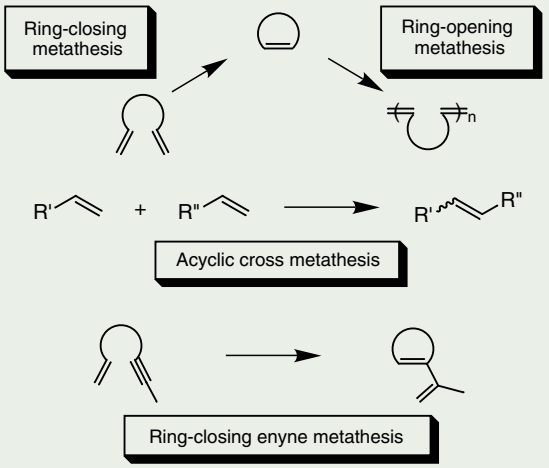


Figure 1. General types of olefin metathesis reactions.

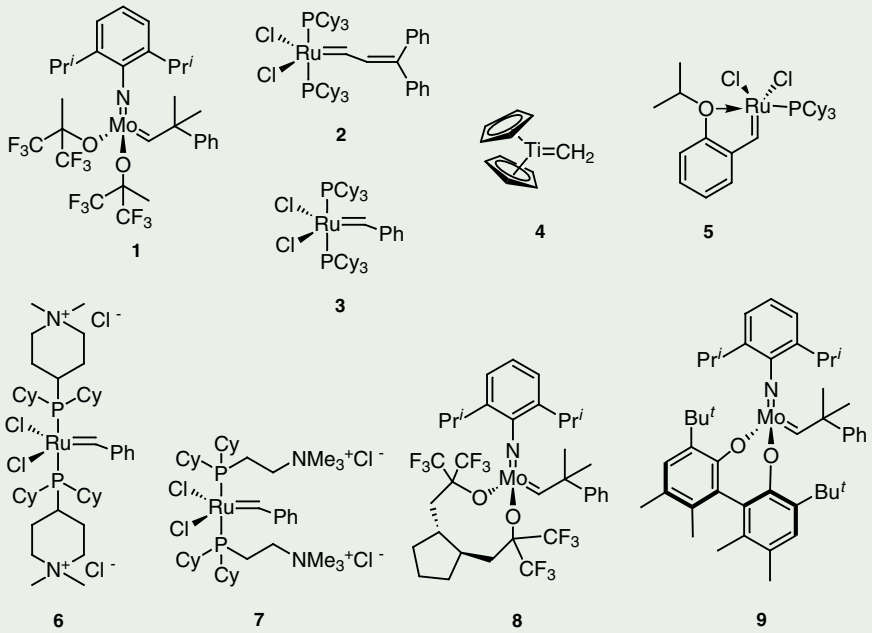


Figure 2. Catalysts used for olefin metathesis.

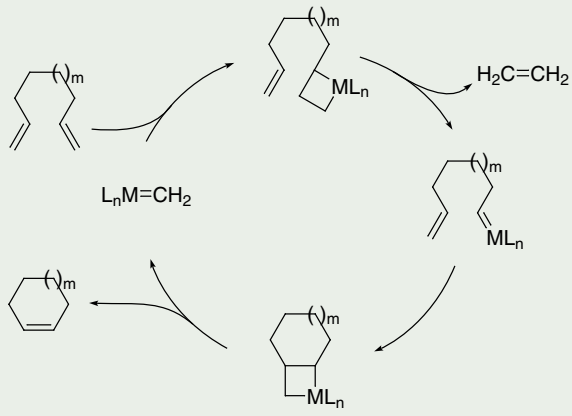


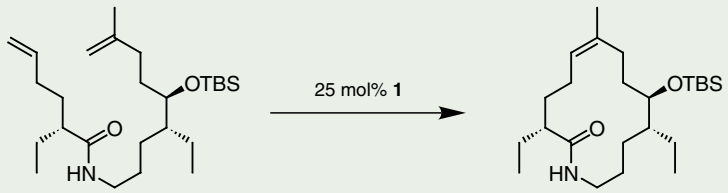
Figure 3. Schematic mechanism for ring-closing metathesis of acyclic dienes.

Catalysts that allow ring-closing metathesis (RCM) in methanol and water (complexes **6** and **7**) have recently been reported by Grubbs and co-workers.[10] The phosphine ligands of these catalysts contain quaternary ammonium salts, which confer enhanced solubility (and hence activity) in protic solvents. This study also revealed that the nature of the substrate has an important influence on the ease of cyclization. Phenyl-substituted substrates are claimed to be the best suited to cyclizations, since, as opposed to simple alkylidenes, they yield more stable benzylidene systems upon turnover. The exceptional activity of these catalysts in protic solvents should allow their ready application to systems of biological significance. Asymmetric ring-closing metathesis with chiral molybdenum carbenes **8**[11] and **9**[12] has been described but has yet to see widespread use. Several tungsten-based catalysts have also been described but have not been widely applied.[13] The preparation of imines by molybdenum-mediated metathesis has been reported recently.[14]

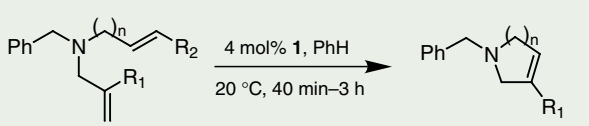
Most of the early work in olefin metathesis was performed using poorly defined catalyst systems and, even today, mechanistic studies on the ring-closing metathesis reaction remain scarce. This is primarily because of the difficulties involved in characterizing the species in these "classical" metathesis systems. However, there is some evidence that the reaction proceeds via metallacyclobutanes (**Figure 3**).[15] With the availability of well-defined catalysts, progress should now be more rapid on this front. In light of this, Grubbs has recently investigated the ring-closure of diethyl diallylmalonate by $H_2C{=}Ru(PCy_3)_2Cl_2$.[16] This study revealed that the major mechanistic pathway for this catalyst was via phosphine loss before metallacyclobutane formation.[17] Although this report is informative, care must be exercised in extending the results of this study to other catalyst systems. For the purpose of this review, the general mechanism illustrated in Figure 3 is adequate.

3. Scope and Functionality Tolerance

The body of literature that has emerged over the past three years has provided enough information to allow some guidelines to be formulated with respect to both ring size and compatible functionality. Catalysts **1–3** are all capable of catalyzing the formation of simple five-, six-, and seven-membered mono- and bicyclic rings. Eight-membered rings, as is the case for so many methods, remain more difficult to access by metathesis chemistry.[18] Nonetheless, examples do exist.[19] The formation of macrocycles is facile, and

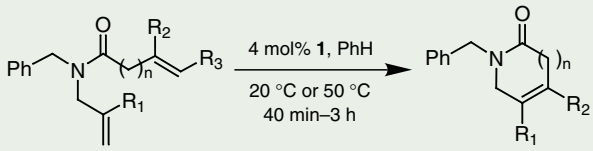


eq 1



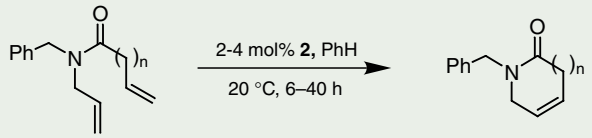
n	R_1	R_2	Yield (%)
1	H	H	86
1	Me	H	85
2	Me	Et	86
3	Me	H	73

eq 2



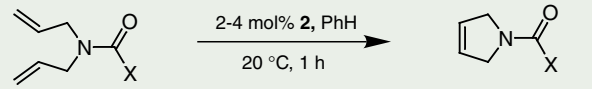
n	R_1	R_2	R_3	Yield (%)
0	H	H	Me	74
0	H	Me	Me	77
1	H	H	Et	80
2	H	H	H	87
2	Me	H	H	81

eq 3



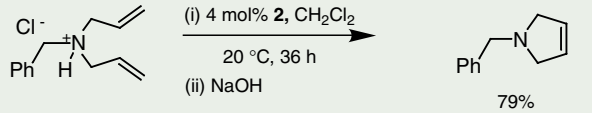
n = 0, 1, 2; 78-93%

eq 4



X = CF_3, 93%
X = *t*-BuO, 91%

eq 5



79%

eq 6

catalysts **1–3** have all been utilized in total syntheses of macrolides. Examples include the Hoveyda synthesis of fluvirucin (**eq 1**)[20] and the Danishefsky,[21] Nicolaou,[22] or Schinzer[23] syntheses of epothilones. In general, ruthenium alkylidenes **2** and **3** are less active than **1** with respect to the formation of trisubstituted alkenes, and incapable of cyclizations that form tetrasubstituted alkenes.[24] In contrast, **1** is capable of catalyzing the formation of tri- and tetrasubstituted bonds. Although appreciably sensitive to oxygen and water, molybdenum catalyst **1** is relatively tolerant of functionality in the substrate. At least in simple systems, this catalyst will tolerate ketones, esters, amides, epoxides, acetals, silyl ethers, some amines, and sulfides. Ruthenium catalysts **2** and **3** are remarkably tolerant of oxygen and moisture, and they will also tolerate substrates containing free alcohols, as well as the functional groups listed above for **1**. With catalysts **2** and **3**, some authors have noted difficulties in cyclizing substrates in which functional groups, that can potentially coordinate the metal center, are adjacent to the initially metathesized alkene. As a solution to this problem, Fürstner and Langemann have reported a procedure that involves the addition of Ti(*i*-PrO)$_4$ to these reactions.[25] Significant differences in the rates and yields of these reactions were noted.

The functional-group tolerance and ability of catalysts **5–8** to form cyclic structures of various sizes have yet to be fully explored. It is reasonable to assume that their compatibility with various functional groups will be similar to those of the original ruthenium and molybdenum catalysts. Their ability to form rings of various sizes is also expected to be similar, although the asymmetric processes may prove less efficient with some substrates.

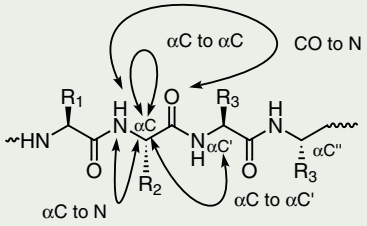
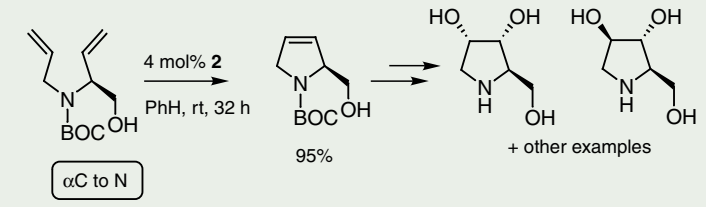
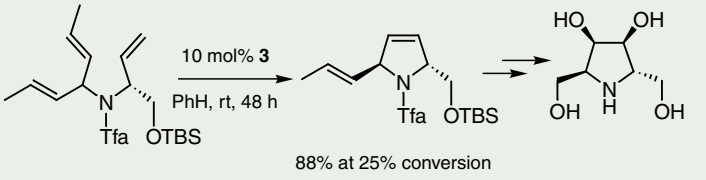


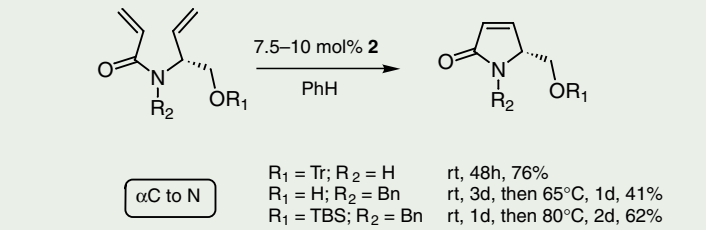
Figure 4. Nomenclature used to describe the cyclizations of peptidomimetics.



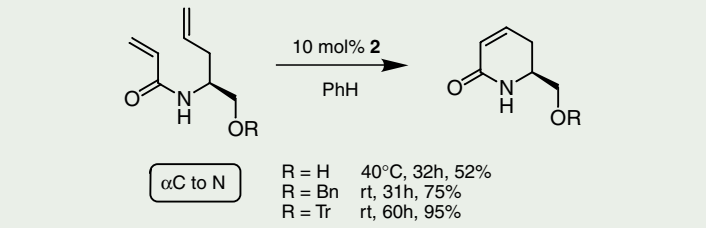
eq 7



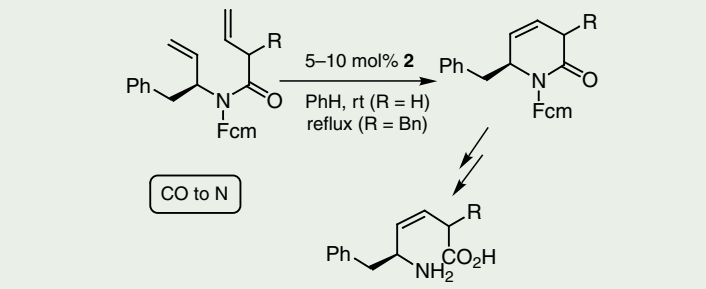
eq 8



eq 9



eq 10



eq 11

4. Applications to the Synthesis of Nitrogen-Containing Systems

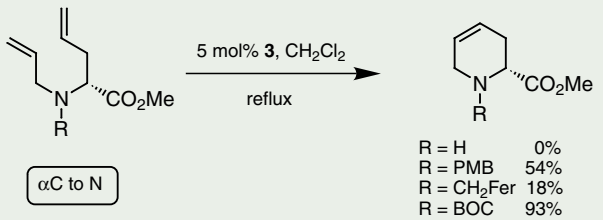
Due to their high catalytic activity and functional-group tolerance, catalysts **1–9** seem ideally suited to applications involving nitrogen. Many reports have appeared recently detailing ready access to a diverse range of compounds including peptidomimetics, peptide tertiary structure mimics, and azasugars. This growth of ring-closing metathesis (RCM) as a synthetic method for the preparation of nitrogen-containing compounds can probably be traced to 1992 and 1993 when several papers were published by Grubbs and co-workers on the synthesis of heterocycles by RCM.[26] In these papers, Fu, Grubbs, and Nguyen delineated the nitrogen-functional-group compatibility of catalysts **1** and **2**, along with their ability to form five-, six-, and seven-membered rings (**eq 2–6**). The remainder of this review will be devoted to presenting illustrative examples of the application of RCM to a number of these and related classes of compounds. For organizational purposes, we have classed the examples into three main groups that are defined by what the dienes are attached to:

(i) Cyclizations leading to heterocyclic structures. Here, the diene chain contains one or more nitrogen atom(s) such that cyclization gives rise to heterocycles, including pyrrolidines, piperidines, lactams, azasugars, and alkaloids. Systems that contain rings of 10 or more atoms are discussed under macrocyclic systems in part (iii).

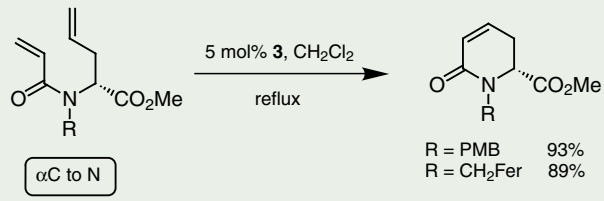
(ii) Cyclizations leading to carbocycles. Examples in this class give rise to carbocycles that contain a pendant nitrogen functionality.

(iii) Miscellaneous cyclizations. This section includes macrocyclizations, solid-phase methods, and various other applications.

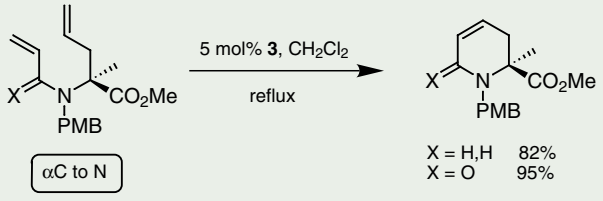
For some examples of peptidomimetics, we have tried to point out the relationship of the peptidomimetic to the peptide by denoting the atoms between which cyclization occurs relative to those of a simple peptide substrate.[27] This approach should prove useful to researchers working with peptidomimetics, whereby it is important to have systematic and documented methods for restraining the conformations of peptides and pseudopeptides. The nomenclature used is illustrated in **Figure 4**.



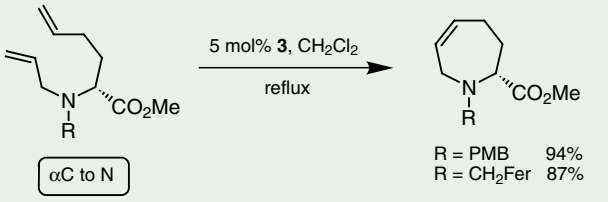
eq 12



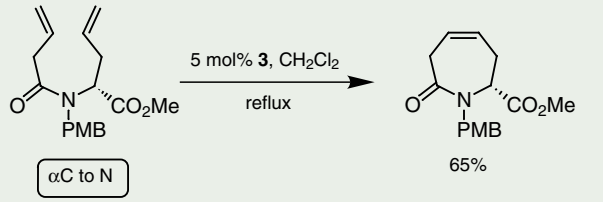
eq 13



eq 14



eq 15



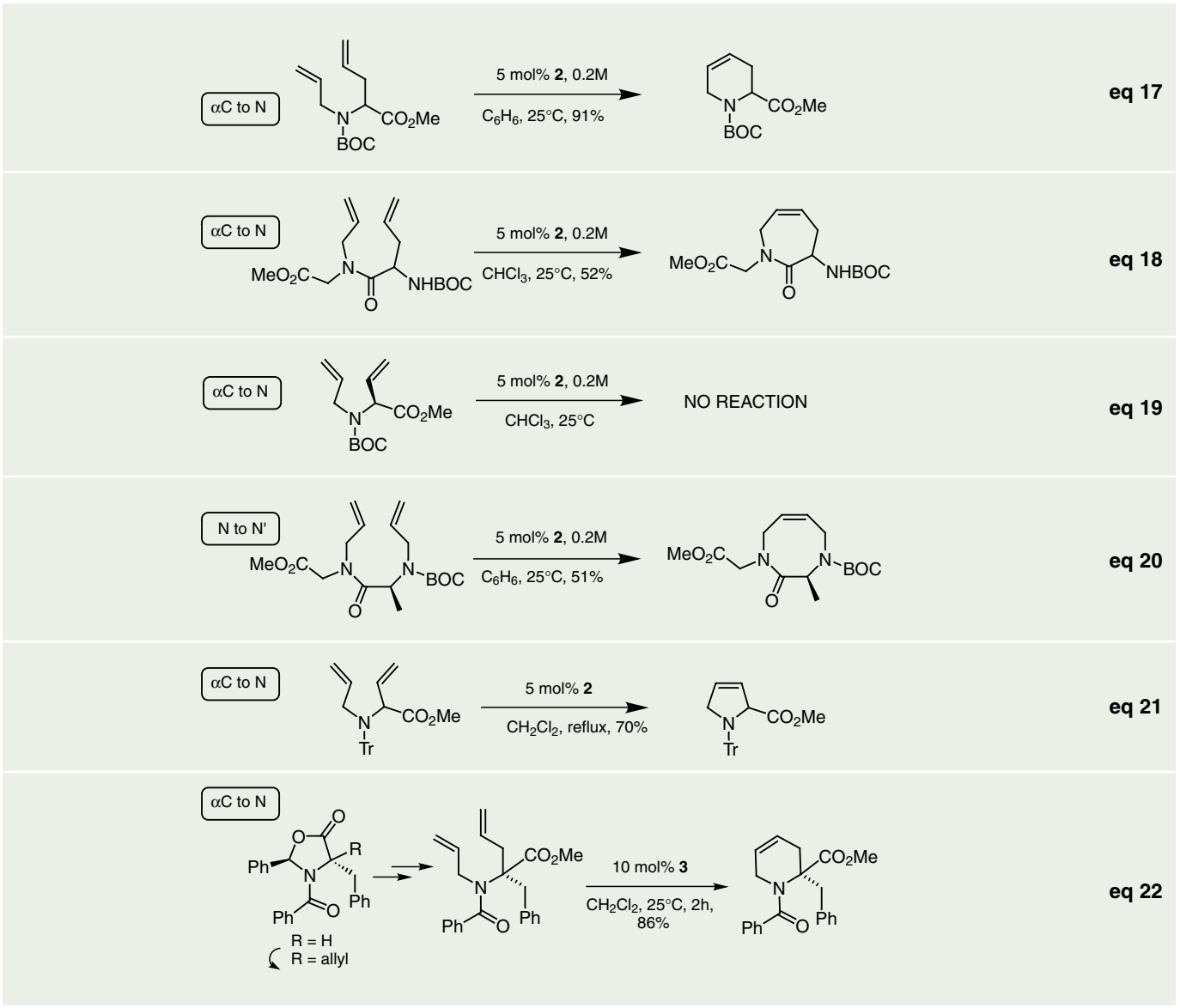
eq 16

4.1. Cyclizations Leading to Heterocycles: Pyrrolidines, Piperidines, Lactams, Azasugars, Alkaloids, and Related Compounds

There are a large number of examples of RCM involving substrates in which the diene linker contains a nitrogen atom. These types of cyclizations give access to a number of useful classes of compounds such as mono- and bicyclic pyrrolidine, pyrrolidinone, piperidine, and piperidinone ring systems. Many of these heterocycles are derived from amino acids, and offer a significant potential as peptidomimetics in which the torsion angle between the α carbon and the nitrogen of the amino acid is defined by the ring size and the position of the alkene. Some of these compounds are also important intermediates for the synthesis of azasugars and alkaloids.

A flexible synthesis of azasugars and homoazasugars has been reported by Blechert and Huwe (**eq 7** and **8**).[28] RCM of a vinyl glycine methyl ester derived diene, followed by stereoselective functionalization of the double bond, gave the desired sugar derivatives in good yields. The same group has also synthesized a number of five- and six-membered lactams using carbene **2** (**eq 9** and **10**).[29] Like many examples of metathesis cyclizations of this type, the yield of the cyclic product is dependent on the nature of the protecting group on nitrogen. In some cases, however, protection of the nitrogen is not necessary (**eq 10**). It is also interesting to note that increasing steric demand of the oxygen substituent in the example shown in eq 10 led to a marked increase in yield of the cyclic product (compare R = H, Bn, and Tr). The precursors in the pyrrolidinone series (**eq 9**) and the piperidinone series (**eq 10**) were synthesized from vinylglycine and allylglycine, respectively. Garro-Hélion and Guibé have reported an efficient sequence to *Z*-ethylenic peptidomimetics based on a related RCM chemistry.[30] Treatment of the acyclic dienes with **2** resulted in a smooth cyclization to the desired piperidinones; however, reflux in benzene was required in the case where R = Bn (**eq 11**). These compounds were then hydrolyzed to give the deprotected peptide isosteres.

Related work by Rutjes and Schoemaker has also resulted in the synthesis of a series of six- and seven-membered lactams and heterocycles (**eq 12–16**).[31] The yields of the RCM-derived tetrahydropyridines shown in **eq 12** were dependent on the nature of the

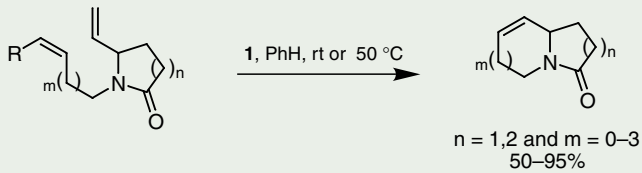


protecting group (R) on nitrogen. Without protection (R = H), ring closure was not observed, while BOC protection resulted in an excellent yield. The ease of cyclization of the acyclic amides shown in **eq 13** also proved to be dependent on the nature of the protecting group. The free amide (R = H) was sluggish, while the N-protected counterparts cyclized readily and in excellent yields. It has been suggested that an increase in steric bulk around the nitrogen leads to a more favorable transition state for ring closure.[31] The introduction of a methyl substituent α to the carboxyl group resulted in a marked increase in the ease of RCM (**eq 14**). The trifluoromethyl analogs have also been reported recently by Osipov, Dixneuf, and co-workers.[32] The homoallylglycine-derived acyclic systems shown in **eq 15** and **16** gave the corresponding seven-membered-ring heterocycles. The nature of N-protection proved to be less critical in these examples. A sequence based on the Ireland–Claisen rearrangement, followed by RCM, has been reported as a convenient means to construct similar systems.[33] The products shown in equations 12–16 are non-natural cyclic amino acid derivatives that deserve further study because of their interesting properties.

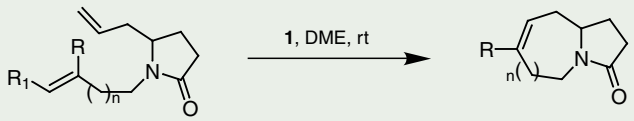
Grubbs and co-workers have also reported a number of applications of their Ru carbenes to peptide and heterocyclic chemistry. In a seminal paper, the application of carbene **2** to the synthesis of cyclic amino acids was reported (**eq 17–20**).[34] While six- and seven-membered cyclic amino acids were readily synthesized (**eq 17** and **18**), attempts to prepare a dehydroproline system were unsuccessful (**eq 19**). This was attributed to the acidity of the α hydrogen, although conformational effects and/or internal complexation of the carbene by the carbonyl group may also play a role. Recent work by Campagne and Ghosez[35] has shown that dehydroproline systems can be prepared, provided a triphenylmethyl (trityl) group is used as the protecting group on the nitrogen (**eq 21**). The original report by Grubbs and co-workers also included the synthesis of an eight-membered Ala–Gly dipeptide (**eq 20**).

The chemistry shown in **eq 12** and **eq 17** was recently extended by Abell and co-workers, who used a combination of Seebach's oxazolidinone chemistry and RCM in the synthesis of a phenylalanine mimic (**eq 22**).[36] This tetrahydropyridine system was designed to probe the constraints imposed by the six-membered ring on the torsion angle between the α carbon and the nitrogen. X-ray analysis demonstrated that this type of system has potential as a β-turn mimic.

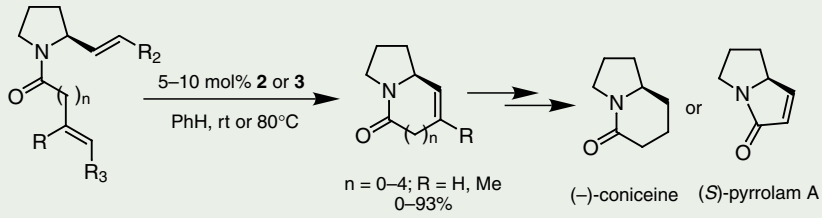
A number of groups have investigated the use of metathesis chemistry to form bicyclic systems. Martin and co-workers have shown the potential of RCM to form the ring systems found in a number of alkaloids (**eq 23** and



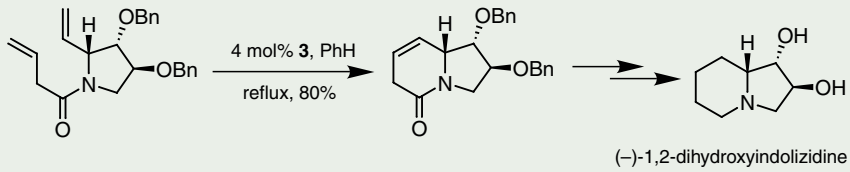
eq 23



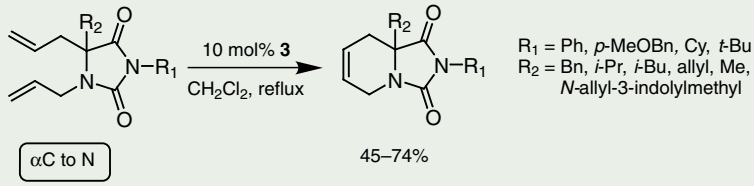
eq 24



eq 25



eq 26



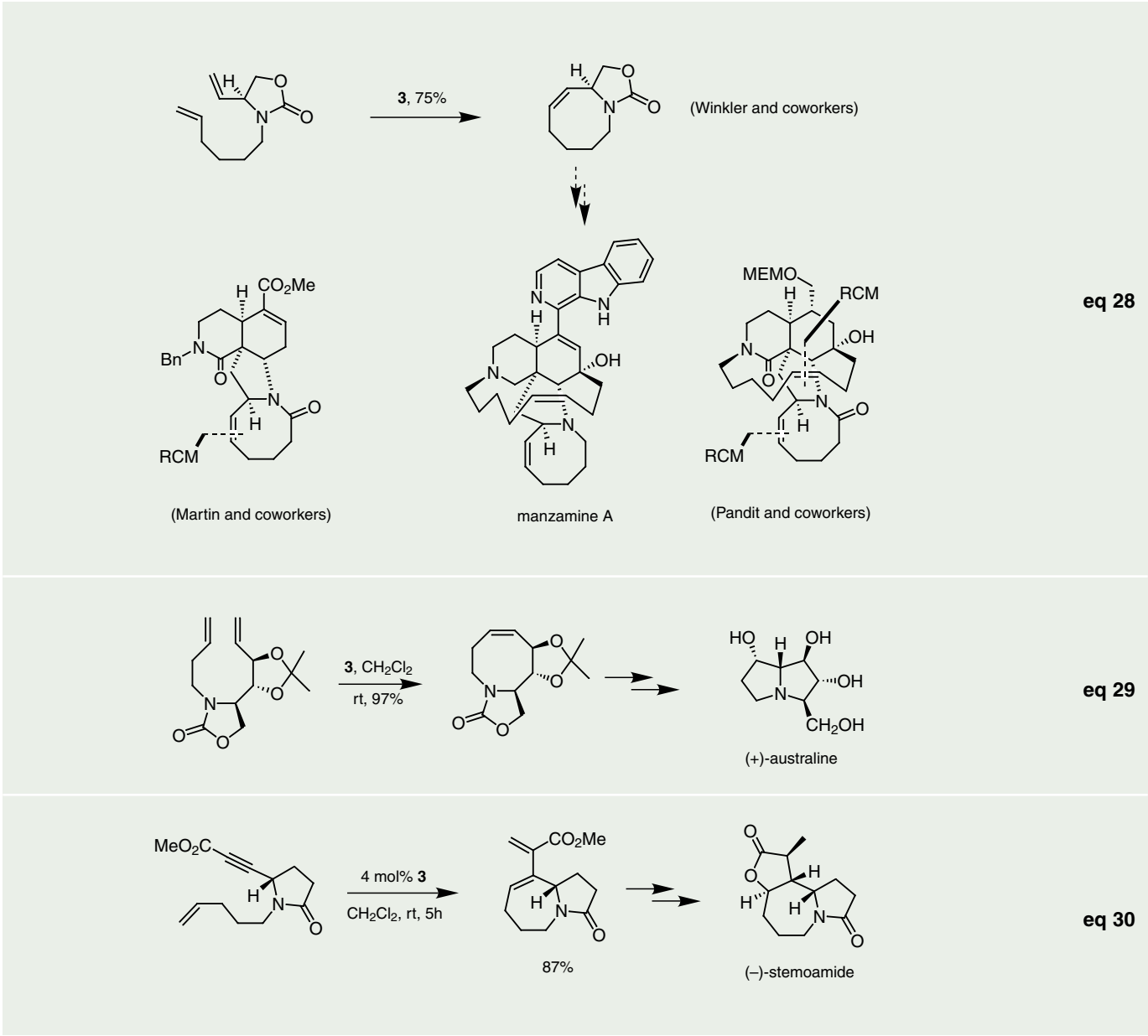
eq 27

24).[37] This work has demonstrated that a number of fused nitrogen heterocycles, including pyrrolizidines, indolizidines, and quinolizidines, can be readily prepared. Further examples of related bicyclic systems that have been synthesized using RCM are shown in **eq 25–27**.[38] Several of these examples have been used in the synthesis of simple alkaloids.

A number of medium-sized rings have been synthesized by RCM (**eq 28–30**). Seven-membered heterocyclic rings can be readily formed by RCM (see for example eq 15–16). However, reported syntheses of eight-membered rings tend to be on dienes attached or fused to other ring systems, i.e., the acyclic precursor is 'pre-organized' into a conformation that favors cyclization.[39] Early studies in this area by Grubbs and co-workers demonstrated the application of RCM to structures suitable for mitomycin and FR-900482 synthesis.[40] As part of studies directed toward the manzamine class of alkaloids, Winkler and co-workers investigated the synthesis of azocine rings by RCM (**eq 28**).[41] Advanced intermediates en route to manzamine A have been similarly cyclized by Martin's group using Mo carbene **1**, and by Pandit and co-workers using Ru carbene **2** (**eq 28**).[42] Magnier and Langlois have recently reported similar results.[43] An elegant synthesis of (+)-australine, utilizing RCM as the key step to form an eight-membered ring, has been reported by White and co-workers (**eq 29**).[44] As a further example, ring-closing enyne metathesis has been employed with impressive strategic gain in a concise synthesis of a key intermediate en route to (–)-stemoamide (**eq 30**).[45]

Some examples of diastereoselective RCM have recently been reported by Blechert and co-workers (**eq 31–33**).[46] The existing stereogenic center is used to control the cyclization of a diastereotopic diene. Control of which alkene is metathesized first is important, and the use of *trans*-disubstituted alkenes allows the initial reaction to be directed to the monosubstituted alkene. Levels of diastereoselection are modest when forming six-membered rings (**eq 31** and **32**), but are >70% with five-membered rings (**eq 33**). Interestingly, changing the catalyst from Mo carbene **1** to Ru carbene **3** allows some control of the relative diastereoselection (**eq 33**). This is probably related to the different spatial arrangements of various ligands around the different metal centers.

Pandit and co-workers have explored the applications of RCM of dienes appended to polysubstituted pyrrolidinones and piperidinones (**eq 34** and **35**).[47] In one such case (**eq 34**), a demanding five-membered-ring



cyclization was performed by using 50 mol% of catalyst **2**. These studies have expanded on an earlier report by the same group on a concise synthesis of castanospermine (**eq 36**), which demonstrated that, in some systems, α,β-unsaturated esters may be suitable substrates for metathesis.[48]

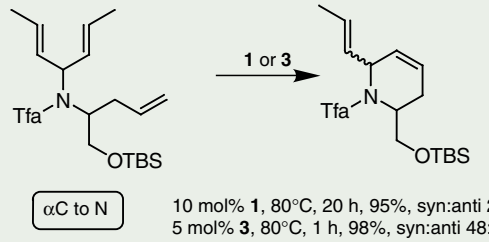
A number of other substrates, such as β-lactam-based dienes, have also been used to prepare interesting heterocycles by RCM (**eq 37** and **38**).[49]

4.2. Cyclizations Leading to Carbocycles

Although widely utilized for the synthesis of heterocycles, RCM has only been applied to a handful of systems that lead to carbocycles. This will undoubtedly be an area of growth over the next few years as more research groups employ RCM in carbocycle synthesis.

Hammer and Undheim have applied RCM to the synthesis of a number of five-, six-, and seven-membered carbocycles derived from (2*R*)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (enantiomer of Schöllkopf's bislactim ether; see **eq 39** and **40**).[50,51] The results detailed in eq 39 indicate that, not surprisingly, the reaction is sensitive to steric interaction between the isopropyl group and the alkylidene. For example, the authors note that an allyl group syn to the isopropyl group is less reactive than when it is in the anti position. It is also worth noting that in these studies, five-membered rings were more difficult to form than either six- or seven-membered rings. The bislactims are readily hydrolyzed by dilute acid (0.2 M TFA, MeCN) to give an amino ester, where the α carbon is incorporated into a five-, six-, or seven-membered ring. Two recent reports have demonstrated the use of enones and hydroxymethylated dienes related to those in eq 39 and 40 as suitable RCM substrates within this strategy.[52] Further studies by Hammer and Undheim have also explored the applications of ruthenium-catalyzed, ring-closing enyne metathesis to systems derived from Schöllkopf's bislactim ether (**eq 41**).[53]

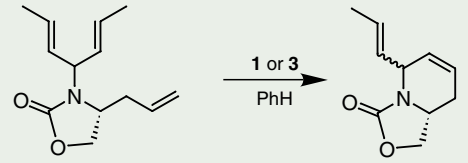
Kotha and Sreenivasachary have applied RCM to the synthesis of simple carbocyclic amino acids (**eq 42** and **43**).[54] Recently, Maier and Lapeva reported a synthesis of cyclohexenylamines that relies on RCM as the key step (**eq 44**).[55]



αC to N

10 mol% **1**, 80°C, 20 h, 95%, syn:anti 26:74
5 mol% **3**, 80°C, 1 h, 98%, syn:anti 48:52

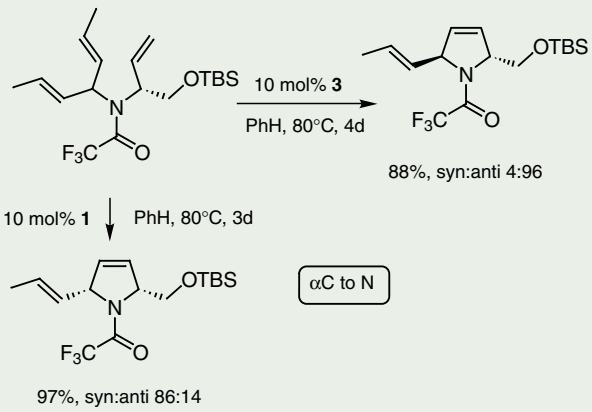
eq 31



αC to N

5 mol% **1**, rt, 24h, 88%, syn:anti 36:64
5 mol% **3**, rt, 2h, 90%, syn:anti 50:50

eq 32



88%, syn:anti 4:96

97%, syn:anti 86:14

eq 33

4.3. Miscellaneous Cyclizations: Macrocyclic Peptides, Solid-Phase Methods, and Other Applications

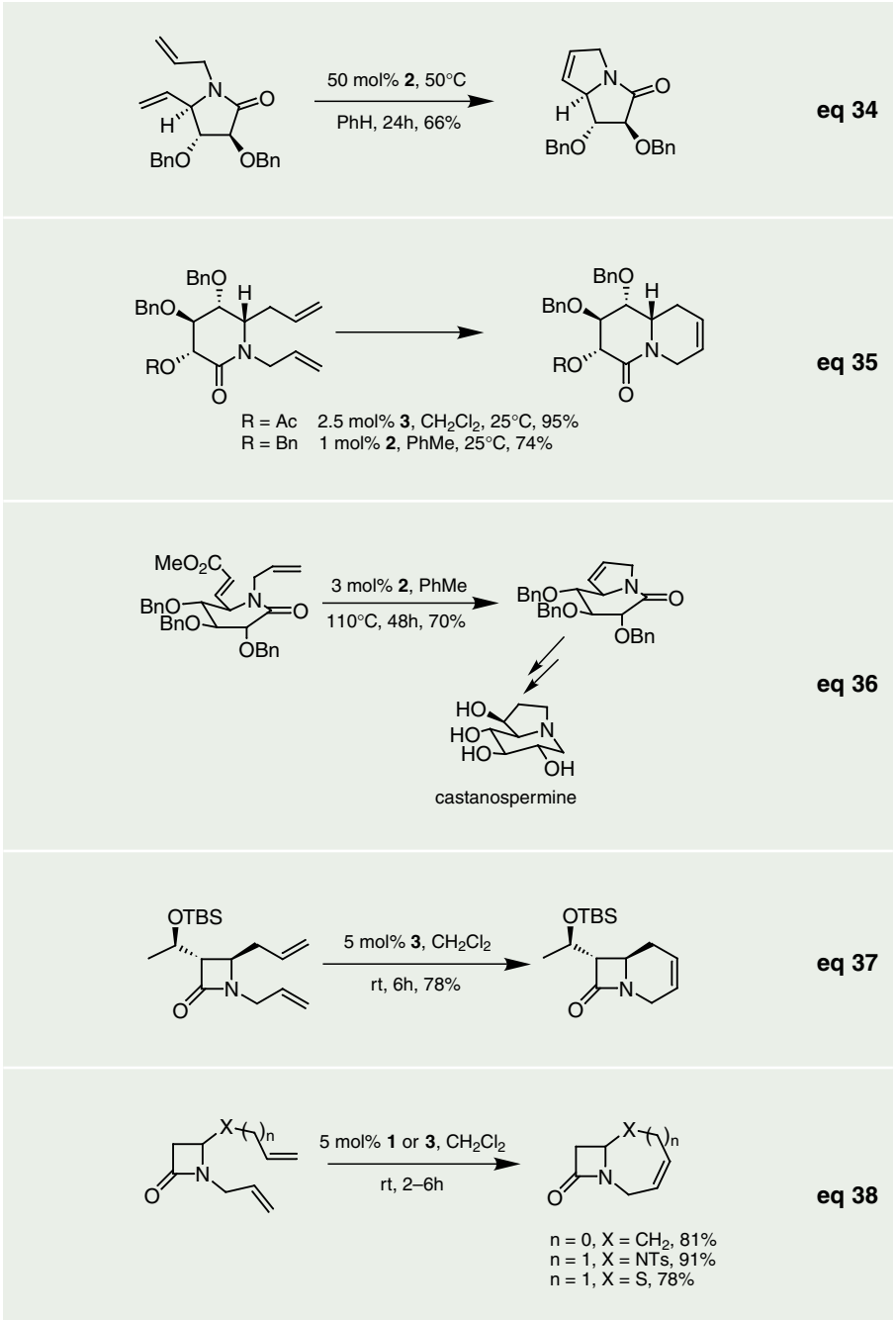
Miller, Blackwell, and Grubbs have described a number of applications of RCM to give rigid amino acids and macrocyclic peptides.[34] In this work (**eq 45** and **46**), a number of acyclic polypeptides were cyclized under high dilution to give 14- and 20-membered macrocycles. Several other polypeptides were cyclized, including a 14-membered tetrapeptide designed as a 'dicarba' analog of a disulfide β-turn motif (**eq 47**).[34] Initially, it had been thought that pre-existing conformational restrictions in the peptide backbone would be necessary to induce RCM cyclization.[56] However, the success of the cyclization shown in eq 47 demonstrates that this may not strictly be the case.

Williams and Liu have reported related studies in which a differentially protected 2,7-diaminosuberic acid derivative was prepared by RCM (**eq 48**).[57] Vederas and coworkers concurrently developed a similar route (**eq 49**).[58] 2,7-Diaminosuberic acids have been utilized in the synthesis of dicarba analogs of naturally occurring biologically active peptides.[59]

Several other research groups have utilized RCM in the synthesis of macrocyclic peptides. Katzenellenbogen and co-workers employed RCM as part of studies on a proposed Type 1 β-turn mimic (**eq 50**).[60] Here, the use of RCM on a dipeptide allowed the convenient synthesis of the 10-membered lactam in six steps. By comparison, a more traditional macrolactamization route to this compound required nine steps, and the RCM route had the added advantage of providing access to the (3*S*,10*S*) diastereoisomer, which was unobtainable by the original route.

Rich and co-workers have also reported a related synthesis of a macrocyclic pepsin inhibitor by RCM of a tripeptide-derived diene (**eq 51**).[61] The macrocyclic alkene and the fully saturated analog (derived from this compound by reduction) proved to be good inhibitors of *Rhizopus chinensis* pepsin (K_i 1.31 μM and 0.34 μM, respectively).

Acyclic dienes that are not derived from amino acids have also been shown to undergo macrocyclization by RCM. For example, Fuchs and co-workers reported such a macrocyclization in their synthesis of the tricyclic *ansa*-bridged core of roseophilin (**eq 52**).[62]



This reaction required very dilute conditions (0.5 mM) to avoid the formation of macrocyclic dimers.

In an impressive example of what the authors describe as 'supramolecular design by covalent capture', Clark and Ghadiri have synthesized a macromolecular peptide by an intermolecular RCM (**eq 53**).[63] Here, the two precursors are held in close proximity by hydrogen bonding between the amino acid side chains of the *N*-methyl cyclic peptides such that intermolecular RCM gives the macrocycle in an impressive yield of 65%. Another example of the use of RCM to give peptidic supramolecular structures was recently provided by Blackwell and Grubbs with the preparation of helical polypeptides.[64] Here, carbene **3** was used to prepare examples of heptapeptides in which the *i* and (*i* + 4) residues of the peptide are linked by RCM (**eq 54**). As noted by the authors, "The relative ease of introducing carbon–carbon bonds into peptide secondary structures by RCM and the predicted metabolic stability of the bonds renders olefin metathesis an exceptional methodology for the synthesis of rigidified peptide architectures". This area is one of exceptional promise given the compatibility of **3** with functional groups and solvents commonly found in peptide chemistry.

The products of RCM of amino acid based substrates have also been reported as key intermediates of important isosteric units. For example, Ghosh and co-workers have reported the cyclization of amino acid derived acrylate esters as part of a synthesis of hydroxyethylene isosteres that form the core units of an important class of HIV protease inhibitors (**eq 55**).[65] This work further demonstrates the usefulness of Fürstner and Langemann's procedure, which involves the addition of Ti(*i*-PrO)$_4$, in the case of substrates that may form stable, chelated carbene intermediates.

Although yet to be clearly defined, a substantial amount of the chemistry described in this review is applicable to solid-phase methods. Amongst the most impressive examples of the potential of this adaptation is the recent report by Nicolaou and co-workers of the synthesis of a library of epothilone analogs by a solid-phase RCM–cleavage strategy.[66] In the area of nitrogen-containing substrates, a number of groups have reported solid-phase adaptations of their syntheses using RCM. Blechert and co-workers have reported that their previous synthesis of five- and six-membered nitrogen heterocycles (**eq 9–11**) can be performed on solid-phase resins, such as Tentagel S and tritylpolystyrol (**eq 56–59**).[67] Examples have been reported where the resin is attached through either nitrogen or carbon, and, in all cases, the cyclizations appear to be slower than the corresponding solution-phase cyclizations.

An RCM–cleavage strategy for the synthesis of cyclic lactams has also been reported by van Maarseveen and co-workers (**eq 60**).[68] An essential feature of this work is the cleaving of the lactams from the resin in the course of RCM. The rate of RCM is, however, slow under relatively standard reaction conditions, a feature that the authors attribute to the immobilization of the carbene on the resin. This problem can be partly overcome by the addition of a terminal olefin such as 1-octene, although the yields are still modest. Piscopio and co-workers have reported a similar RCM–cleavage strategy for the solid-phase synthesis of pipecolinic acids and Freidinger lactams (**eq 61**).[69] In this report, the use of a cinnamyl alcohol resin appears to aid the cyclization–cleavage reaction. Further developments of this work have recently been reported.[70]

The synthesis of hexahydroisoindoles has been carried out on solid phase using Wang resin (**eq 62**).[71] Although no yields were reported, the authors described the synthesis of a library of 4200 (theoretical) compounds by this methodology. The equivalent solution-phase chemistry was also reported.

Grubbs and co-workers have demonstrated that RCM cyclization of polypeptides can also be performed on solid phase.[34] As noted by the authors, peptides of >5 residues in length

usually suffer from low solubility in solvents commonly used for RCM. However, the synthesis and RCM of these substrates was readily performed on a PEG/PS resin (**eq 63**).

5. Conclusions

Ring-closing metathesis has clearly reached the point where it is a reliable and relatively mature technique for the formation of a diverse range of ring structures. The mild conditions under which most reactions can be performed, along with the high functional-group tolerance of the current catalysts, mean that it is clearly of immense value in many areas of chemistry. The synthesis of N-containing compounds such as heterocycles and peptides has benefited from these features. Ring-closing metathesis also offers a new potential for strategic disconnections as is clearly evidenced by the synthesis of macrolides, where it provides a powerful alternative to traditional macrocyclization techniques. The future of ring-closing metathesis can almost certainly be bright as new catalysts and applications are discovered.

6. Acknowledgments

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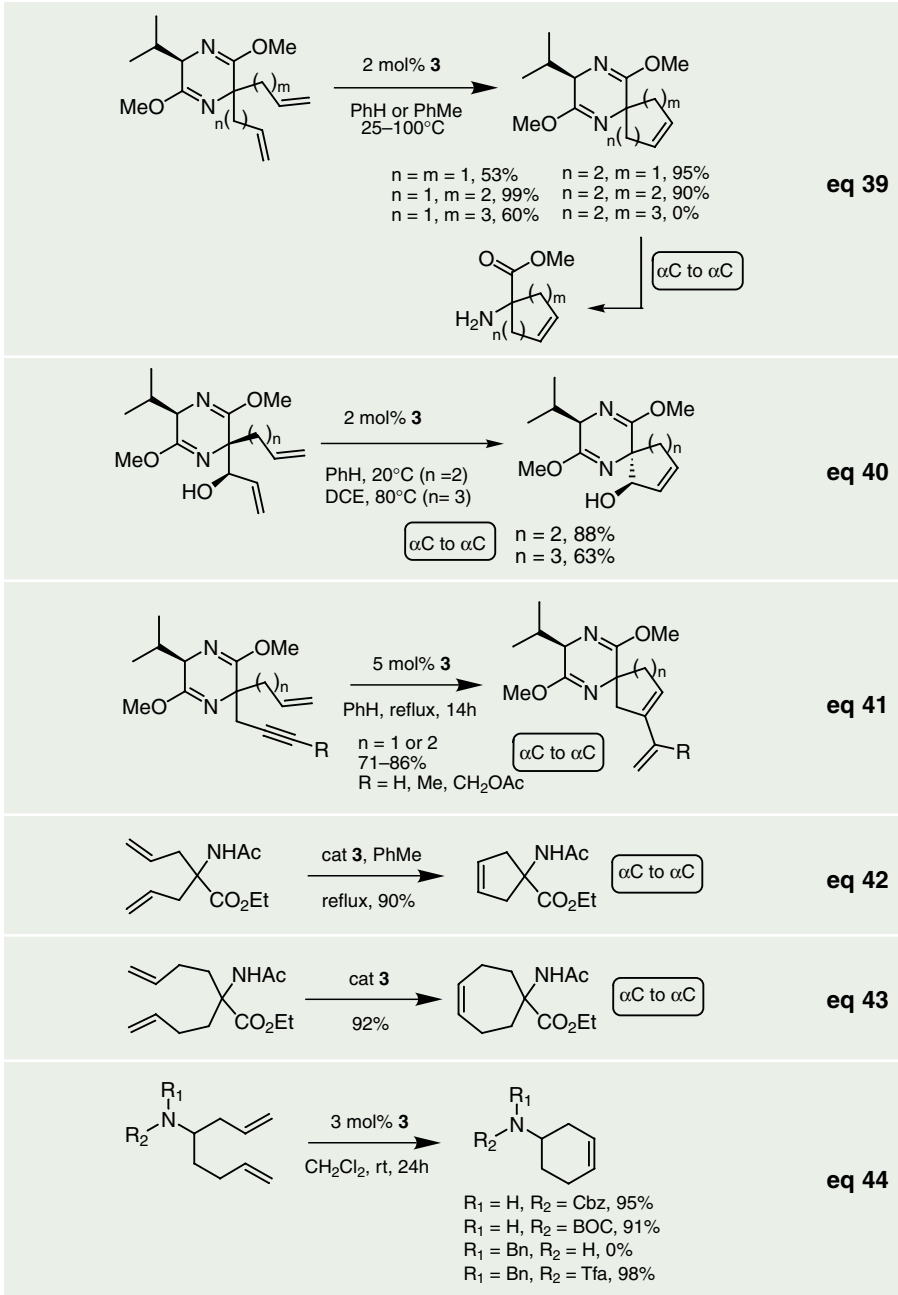


7. References and Notes

§ Abbreviations: Ac, acetyl; BOC, *tert*-butoxycarbonyl; Bn, benzyl; Cbz, benzyloxycarbonyl; DCE, dichloroethane; Fcm, ferrocenylmethyl; Fer, ferrocenyl; FMOC, 9-fluorenylmethoxycarbonyl; MEM, (2-methoxyethoxy)methyl; PCy_3, tricyclohexylphosphine; PMB, 4-methoxybenzyl; TBS, *tert*-butyldimethylsilyl; TFA, trifluoroacetic acid; Tfa, trifluoroacetyl; TIPS, triisopropylsilyl; Tr, triphenylmethyl; Ts, 4-methylphenylsulfonyl.

(1) Anderson, A.W.; Merckling, N.G. U.S. Patent 2,721,189, 1955; *Chem. Abstr*. **1956**, *50*, 3008i.

(2) (a) Schrock, R.R.; Murdzek, J.S.; Bazan, G.C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc*. **1990**, *112*, 3875. (b) Bazan, G.C.; Khosravi, E.; Schrock, R.R.; Feast, W.J.; Gibson, V.C.; O'Regan, M.B.; Thomas, J.K.; Davis, W.M. *J. Am. Chem. Soc*. **1990**, *112*, 8378. (c) Bazan, G.C.; Oskam, J.H.; Cho, H.-N.; Park, L.Y.; Schrock, R.R. *J. Am. Chem. Soc*. **1991**, *113*, 6899.

(3) (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl*. **1997**, *37*, 2036. (b) Armstrong, S.K. *J. Chem. Soc., Perkin Trans.1* **1998**, 371. (c) Grubbs, R.H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (d) Grubbs, R.H.; Miller, S.J.; Fu, G.C. *Acc. Chem. Res*. **1995**, *28*, 446.

(4) (a) Nguyen, S.T.; Johnson, L.K.; Grubbs, R.H.; Ziller, J.W. *J. Am. Chem. Soc*. **1992**, *114*, 3974. (b) Nguyen, S.T.; Grubbs, R.H.; Ziller, J.W. *J. Am. Chem. Soc*. **1993**, *115*, 9858. (c) Schwab, P.; France, M.B.; Ziller, J.W.; Grubbs, R.H. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 2039. (d) Schwab, P.; Grubbs, R.H.; Ziller, J.W. *J. Am. Chem. Soc*. **1996**, *118*, 100.

(5) Grubbs, R. H. Personal communication.

(6) See for example: Nicolaou, K.C.; Postema, M.H.D.; Yue, E.W.; Nadin, A. *J. Am. Chem. Soc*. **1996**, *118*, 10335.

(7) Kingsbury, J.S.; Harrity, J.P.A.; Bonitatebus, P.J., Jr.; Hoveyda, A.H. *J. Am. Chem. Soc*. **1999**, *121*, 791.

(8) For recent investigations, see: (a) Fürstner, A.; Picquet, M.; Bruneau, C.; Dixneuf, P.H. *Chem. Commun*. **1998**, 1315. (b) Dias, E.L.; Grubbs, R.H. *Organometallics* **1998**, *17*, 2758.

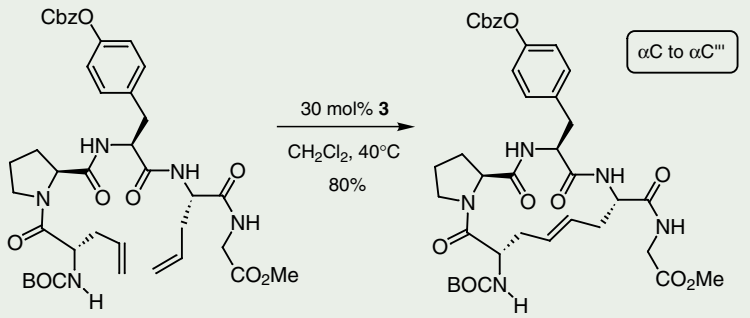
(9) Nguyen, S.T.; Grubbs, R.H. *J. Organomet. Chem*. **1995**, *497*, 195.

(10) Kirkland, T.A.; Lynn, D.M.; Grubbs, R.H. *J. Org. Chem*. **1998**, *63*, 9904.

(11) (a) Fujimura, O.; Grubbs, R.H. *J. Am. Chem. Soc*. **1996**, *118*, 2499. (b) Fujimura, O.; Grubbs, R.H. *J. Org. Chem*. **1998**, *63*, 824.

(12) (a) Alexander, J.B.; La, D.S.; Cefalo, D.R.; Hoveyda, A.H.; Schrock, R.R. *J. Am. Chem. Soc*. **1998**, *120*, 4041. (b) La, D.S.; Alexander, J.B.; Cefalo, D.R.; Graf, D.D.; Hoveyda, A.H.; Schrock, R.R. *J. Am. Chem. Soc*. **1998**, *120*, 9720.

(13) (a) Couturier, J.–L.; Paillet, C.; Leconte, M.; Basset, J.–M. *Angew. Chem., Int. Ed. Engl*. **1993**, *32*, 112. (b) Nugent, W.A.; Feldman, J.;



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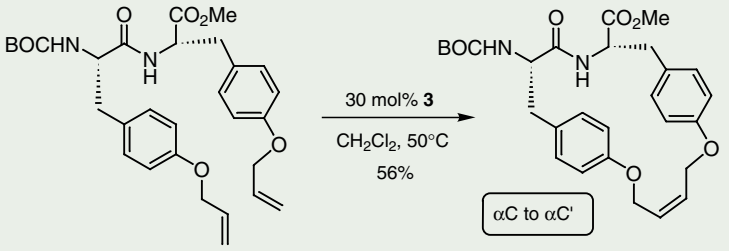

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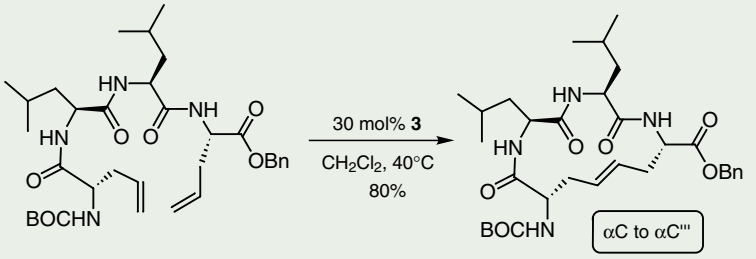

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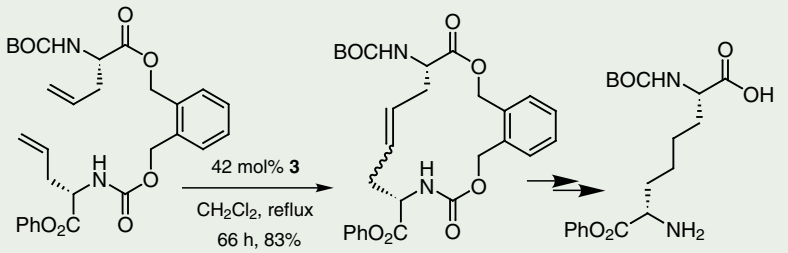

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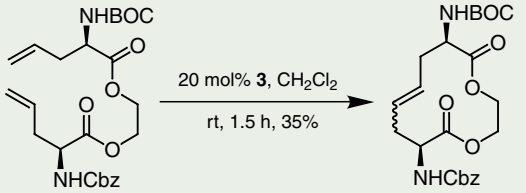

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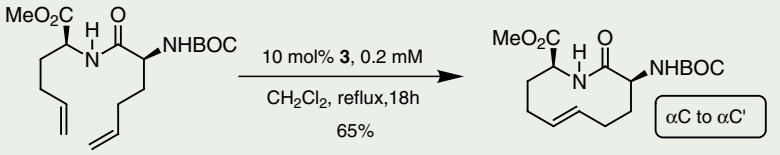

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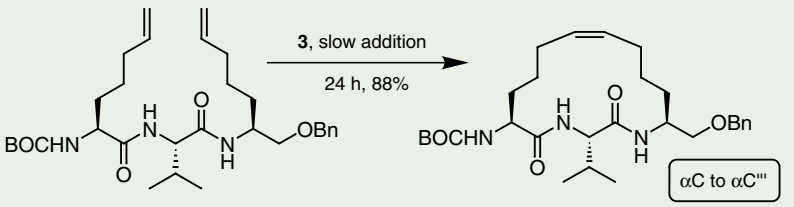

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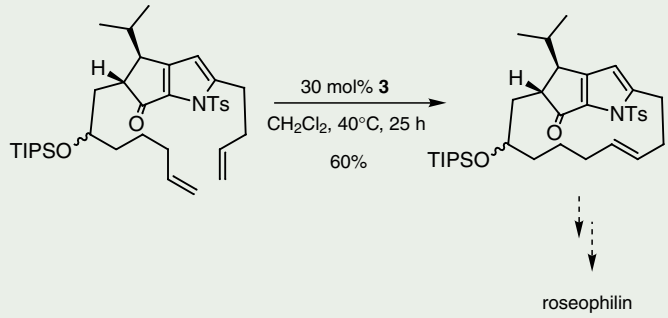
Calabrese, J.C. *J. Am. Chem. Soc*. **1995**, *117*, 8992.
(14) Cantrell, G.K.; Meyer, T.Y. *J. Am. Chem. Soc*. **1998**, *120*, 8035.
(15) Hérrison, J.–P.; Chauvin, Y. *Makromol. Chem*. **1970**, *141*, 161.
(16) Dias, E.L.; Nguyen, S.T.; Grubbs, R.H. *J. Am. Chem. Soc*. **1997**, *119*, 3887.
(17) An X-ray structure of a reaction 'intermediate' obtained recently by Snapper and co-workers supports this postulate. Tallarico, J.A.; Bonitatebus, P.J., Jr.; Snapper, M.L. *J. Am. Chem. Soc*. **1997**, *119*, 7157.
(18) Phillips, A.J.; Abell, A.D. Unpublished results directed towards taxane synthesis, University of Canterbury, 1997–1998.
(19) (a) Miller, S.J.; Kim, S.–H.; Chen, Z.-R.; Grubbs, R.H. *J. Am. Chem. Soc*. **1995**, *117*, 2108. (b) Fürstner, A.; Langemann, K. *J. Org. Chem*. **1996**, *61*, 8746.
(20) Houri, A.F.; Xu, Z.; Cogan, D.A.; Hoveyda, A.H. *J. Am. Chem. Soc*. **1995**, *117*, 2943.
(21) Balog, A.; Meng, D.; Kamenecka, T.; Bertinato, P.; Su, D.–S.; Sorensen, E.J.; Danishefsky, S.J. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 2801.
(22) Yang, Z.; He, Y.; Vourloumis, D.; Vallberg, H.; Nicolaou, K.C. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 166.
(23) Schinzer, D.; Limberg, A.; Böhm, O.M. *Chem.—Eur. J*. **1996**, *2*, 1477.
(24) Kirkland, T.A.; Grubbs, R.H. *J. Org. Chem*. **1997**, *62*, 7310. For further examples of trisubstituted systems, see: (a) Maier, M.E.; Langenbacher, D.; Rebien, F. *Liebigs Ann. Chem*. **1995**, 1843. (b) Hölder, S.; Blechert, S. *Synlett* **1996**, 505. (c) Chang, S.; Grubbs, R.H. *J. Org. Chem*. **1998**, *63*, 864.
(25) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc*. **1997**, *119*, 9130.
(26) (a) Fu, G.C.; Grubbs, R.H. *J. Am. Chem. Soc*. **1992**, *114*, 5426. (b) Fu, G.C.; Grubbs, R.H. *J. Am. Chem. Soc*. **1992**, *114*, 7324. (c) Fu, G.C.; Nguyen, S.T.; Grubbs, R.H. *J. Am. Chem. Soc*. **1993**, *115*, 9856.
(27) For the genesis of this nomenclature system, see Toniolo, C. *Int. J. Peptide Protein Res*. **1990**, *35*, 287.
(28) (a) Huwe, C.M.; Blechert, S. *Tetrahedron Lett*. **1995**, *36*, 1621. (b) Huwe, C.M.; Blechert, S. *Synthesis* **1997**, 61.
(29) Huwe, C.M.; Kiehl, O.C.; Blechert, S. *Synlett* **1996**, 65.
(30) (a) Garro-Hélion, F.; Guibé, F. *Chem. Commun*. **1996**, 641. (b) Sauriat-Dorizon, H.; Guibé, F. *Tetrahedron Lett*. **1998**, *39*, 6711.
(31) Rutjes, F.P.J.T.; Schoemaker, H.E. *Tetrahedron Lett*. **1997**, *38*, 677.
(32) Osipov, S.N.; Bruneau, C.; Picquet, M.; Kolomiets, A.F.; Dixneuf, P.H. *Chem. Commun*. **1998**, 2053.
(33) Miller, J.F.; Termin, A.; Koch, K.; Piscopio, A.D. *J. Org. Chem*. **1998**, *63*, 3158.
(34) Miller, S.J.; Blackwell, H.E.; Grubbs, R.H. *J. Am. Chem. Soc*. **1996**, *118*, 9606.
(35) Campagne, J.-M.; Ghosez, L. *Tetrahedron Lett*. **1998**, *39*, 6175.
(36) Abell, A.D.; Gardiner, J.; Phillips, A.J.; Robinson, W.T. *Tetrahedron Lett*. **1998**, *39*, 9563.
(37) Martin, S.F.; Chen, H.-J.; Courtney, A.K.;



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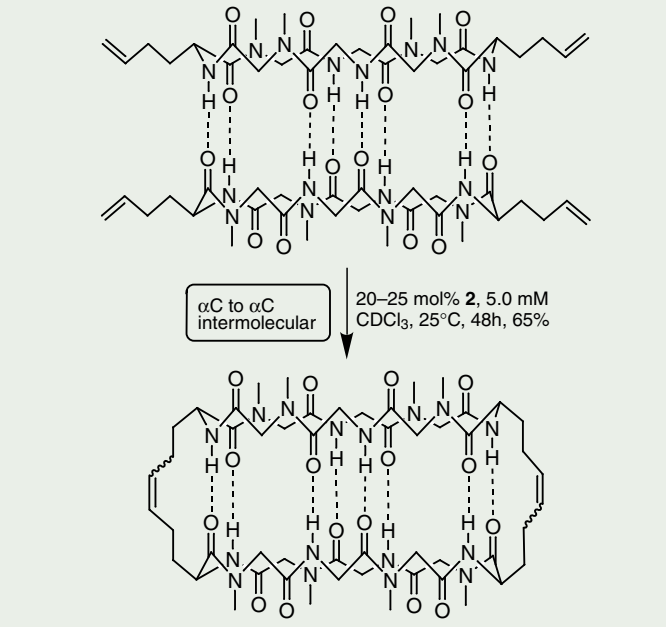

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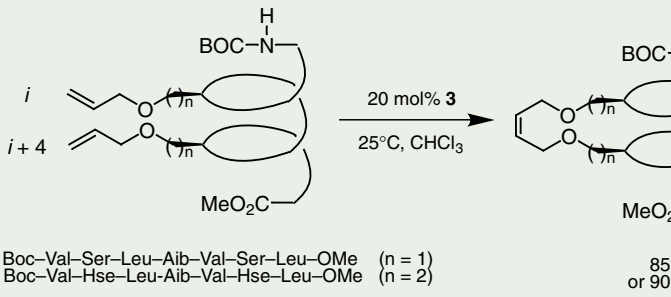

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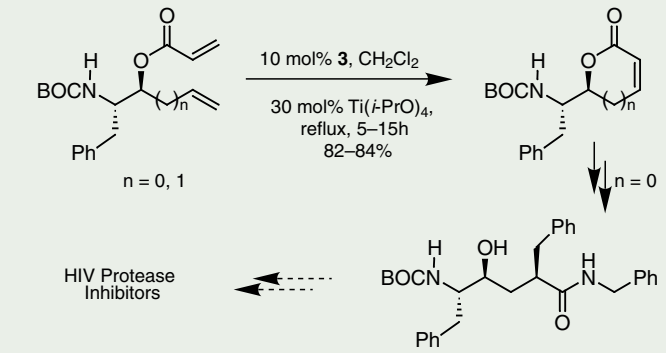

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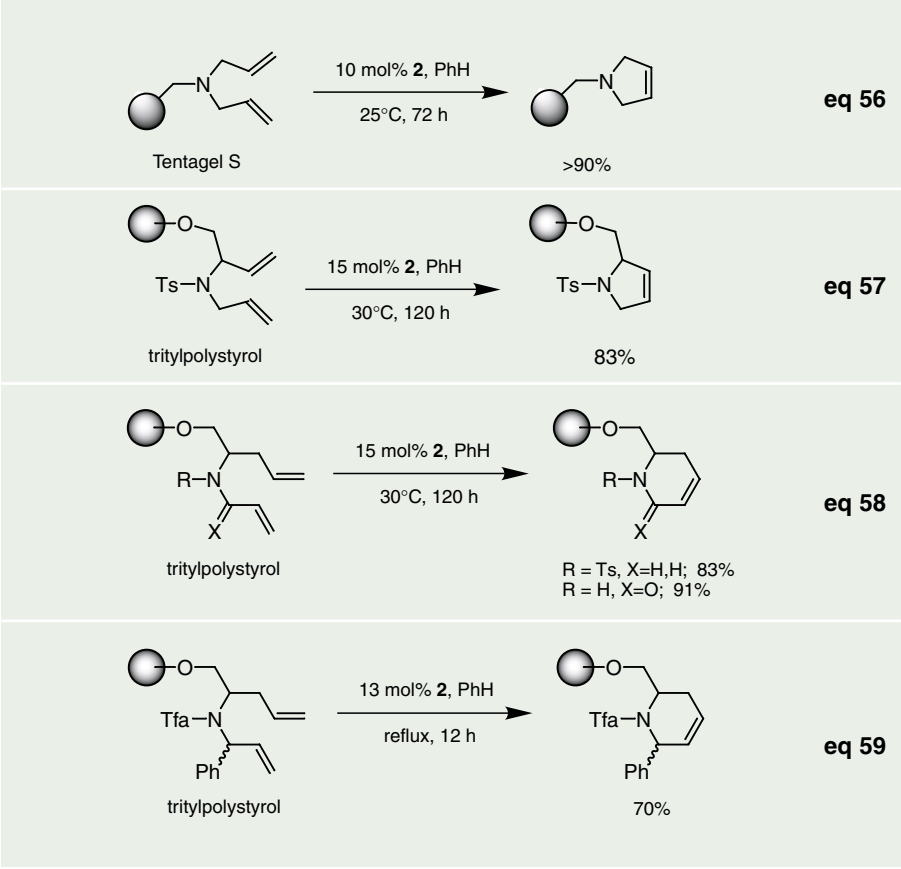


Liao, Y.; Pätzel, M.; Ramser, M.N.; Wagman, A.S. *Tetrahedron* **1996**, *52*, 7251.

(38) (a) Arisawa, M.; Takezawa, E.; Nishida, A.; Mori, M.; Nakagawa, M. *Synlett* **1997**, 1179. (b) Paolucci, C.; Musiani, L.; Venturelli, F.; Fava, A. *Synthesis* **1997**, 1415. (c) Dyatkin, A.B. *Tetrahedron Lett*. **1997**, *38*, 2065.

(39) Illuminati, G.; Mandolini, L. *Acc. Chem. Res*. **1981**, *14*, 95.

(40) Miller, S.J.; Kim., S.-H.; Chen, Z.-R.; Grubbs, R.H. *J. Am. Chem. Soc*. **1995**, *117*, 2108. Related concurrent studies have been reported by Martin and co-workers. See reference 37.

(41) Winkler, J.D.; Stelmach, J.E.; Axten, J. *Tetrahedron Lett*. **1996**, *37*, 4317.

(42) (a) Martin, S.F.; Liao, Y.; Wong, Y.; Rein, T. *Tetrahedron Lett*. **1994**, *35*, 691. (b) Pandit, U.K.; Borer, B.C.; Bieräugel, H. *Pure Appl. Chem*. **1996**, *68*, 659.

(43) Magnier, E.; Langlois, Y. *Tetrahedron Lett*. **1998**, *39*, 837.

(44) White, J.D.; Hrnciar, P.; Yokochi, A.F.T. *J. Am. Chem. Soc*. **1998**, *120*, 7359.

(45) Kinoshita, A.; Mori, M. *J. Org. Chem*. **1996**, *61*, 8356.

(46) Huwe, C.M.; Velder, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 2376.

(47) Overkleeft, H.S.; Bruggeman, P.; Pandit, U.K. *Tetrahedron Lett*. **1998**, *39*, 3869.

(48) Overkleeft, H.S.; Pandit, U.K. *Tetrahedron Lett*. **1996**, *37*, 547.

(49) Barrett, A.G.M.; Baugh, S.P.D.; Gibson, V.C.; Giles, M.R.; Marshall, E.L.; Procopiou, P.A. *Chem. Commun*. **1997**, 155.

(50) Hammer, K.; Undheim, K. *Tetrahedron* **1997**, *53*, 2309.

(51) Hammer, K.; Undheim, K. *Tetrahedron* **1997**, *53*, 5925.

(52) (a) Krikstolaitytè, S.; Hammer, K.; Undheim, K. *Tetrahedron Lett*. **1998**, *39*, 7595. (b) Hammer, K.; Undheim, K. *Tetrahedron: Asymmetry* **1998**, *9*, 2359.

(53) Hammer, K.; Undheim, K. *Tetrahedron* **1997**, *53*, 10603.

(54) Kotha, S.; Sreenivasachary, N. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 257.

(55) Maier, M.E.; Lapeva, T. *Synlett* **1998**, 891.

(56) Miller, S.J.; Grubbs, R.H. *J. Am. Chem. Soc*. **1995**, *117*, 5855.

(57) Williams, R.M.; Liu, J. *J. Org. Chem*. **1998**, *63*, 2130.

(58) Gao, Y.; Lane-Bell, P.; Vederas, J.C. *J. Org. Chem*. **1998**, *63*, 2133.

(59) See for example: (a) Walker, R.; Yamanaka, T.; Sakakibara, S. *Proc. Natl. Acad. Sci. U.S.A*. **1974**, *71*, 1901. (b) Veber, D.F.; Strachan, R.G.; Bergstrand, S.J.; Holly, F.W.; Homnick, C.F.; Hirschmann, R.; Torchiana, M.; Saperstein, R. *J. Am. Chem. Soc*. **1976**, *98*, 2367.

(60) Fink, B.E.; Kym, P.R.; Katzenellenbogen, J.A. *J. Am. Chem. Soc*. **1998**, *120*, 4334.

(61) Ripka, A.S.; Bohacek, R.S.; Rich, D.H. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 357.

(62) Kim, S.H.; Figueroa, I.; Fuchs, P.L. *Tetrahedron Lett*. **1997**, *38*, 2601.

(63) Clark, T.D.; Ghadiri, M.R. *J. Am. Chem. Soc*. **1995**, *117*, 12364.

(64) Blackwell, H.E.; Grubbs, R.H. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 3281.

(65) Ghosh, A.K.; Cappiello, J.; Shin, D. *Tetrahedron Lett*. **1998**, *39*, 4651.

(66) Nicolaou, K.C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E. *Nature* **1997**, *387*, 268.

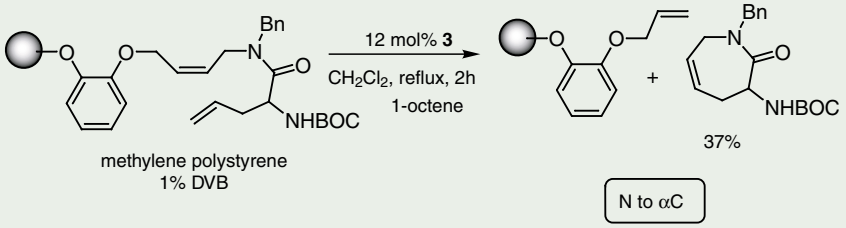
(67) Schuster, M.; Pernerstorfer, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 1979.

(68) van Maarseveen, J.H.; den Hartog, J.A.J.; Engelen, V.; Finner, E.; Visser, G.; Kruse, C. G. *Tetrahedron Lett*. **1996**, *37*, 8249.

(69) Piscopio, A.D.; Miller, J.F.; Koch, K. *Tetrahedron Lett*. **1997**, *38*, 7143.

(70) Piscopio, A.D.; Miller, J.F.; Koch, K. *Tetrahedron Lett*. **1998**, *39*, 2667.

(71) Heerding, D.A.; Takata, D.T.; Kwon, C.; Huffman, W.F.; Samanen, J. *Tetrahedron Lett*. **1998**, *39*, 6815.



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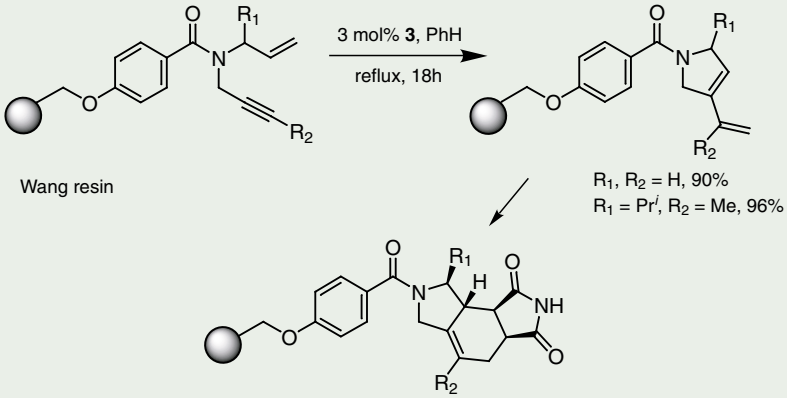

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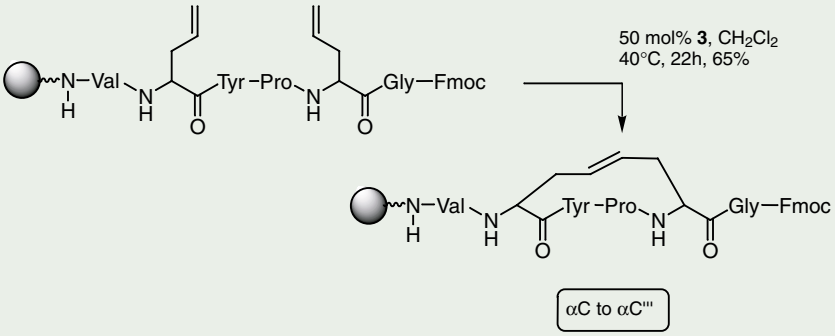

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About the Authors

Dr. Andrew Abell was born in 1960 in Adelaide, South Australia. He obtained a Bachelor of Science with First Class Honours in Organic Chemistry from the University of Adelaide in 1982. Dr. Abell received his Ph.D. from the same university in 1986 working with Dr. Ralph Massy-Westropp on aspects of terpenoid chemistry. Two years were then spent working as a postdoctoral fellow with Professor Sir Alan Battersby at the University of Cambridge, Cambridge, UK. In 1987, he took a position as a lecturer in chemistry at the University of Canterbury, where he is currently employed as a senior lecturer. Dr. Abell was awarded the New Zealand Institute of Chemistry Easterfield Medal in 1995 and a Senior Fulbright Fellowship in 1994, which was spent working at SmithKline Beecham Pharmaceuticals, King of Prussia, USA. He is also a recent recipient of a Royal Society of Chemistry Travel award for international authors. Dr. Abell has authored more than sixty publications and trained 15 Ph.D. students and 6 M.S. students. His current research interests include the design, synthesis, and biological properties of peptidomimetics.

Dr. Andrew Phillips was born in 1970 in Kawerau, New Zealand. In 1995, he obtained a Bachelor of Science with First Class Honours in Biochemistry from the University of Canterbury. The following year, he began a Ph.D. research program with Andrew Abell on the possible applications of ring-closing metathesis to the synthesis of the taxane diterpenoids. He is presently a postdoctoral associate with Professor Peter Wipf at the University of Pittsburgh. His current research interests include the applications of transition metals in organic synthesis, the synthesis of natural products, and the applications of organic synthesis to the investigation of biological processes such as cell signaling.

Lab Notes (continued from page 74).

(1) a crystallization chamber where crystal growth occurs; (2) curved tubes, which serve as gates that prevent the free flow of solutions into the crystallization chamber (as a result of the density difference between the two solutions and the pure solvent); and (3) side arms, which serve as reservoirs for the reacting solutions. Best results are obtained by using a seed crystal of the complex as follows: A small crystal seed is placed into the crystallization chamber. This chamber and the curved tubes are then filled with the pure solvent used in the reaction. The pure solvent serves as a buffer layer preventing the immediate mixing of the two reacting solutions. Separately prepared solutions of reactants **A** and **B** are carefully and simultaneously poured into the corresponding side arms. A smooth addition can be accomplished with the aid of disposable pipettes. The side arms are closed with rubber or plastic stoppers and the system is kept undisturbed for the period of time required for the complete mixing of the two components. Thus, mixing of the solutions occurs slowly in the reaction chamber only due to diffusion.

We used this system to prepare crystals of several complexes of organic hosts with guanidinium and alkylguanidinium salts.[4] The crystals grown in our apparatus, even without crystal seed, were about ten times larger in the edge dimensions (0.3 mm the smallest edge) than the crystals obtained in the vertical tube by layering the reacting solutions. For the apparatus with inner diameters of side arms and curved tubes of 12 mm and 4 mm, respectively, and a total volume of 7 mL, the whole crystal growing process takes about 2 to 3 weeks. After crystal growth has stopped, the stoppers are removed, and the crystals collected by pouring the solution into a beaker. If some crystals remain attached to the glass surface, they can be detached by gentle tapping with a piece of wood.

Our design can be very useful for growing crystals by diffusion of reacting solutions. Compared to the simple layering technique, it provides several advanced features such as smooth and independent-of-density gradient diffusion of the solutions leading to the formation of larger crystals, and the ability to use a crystal seed, since it can be simply placed into the crystallization chamber without special attachment techniques. The crystal growth and the major diffusion interface occur in the same chamber providing the shortest path between regions of local supersaturation and crystallization, thus minimizing the undesired spontaneous formation of many other nucleation sites.

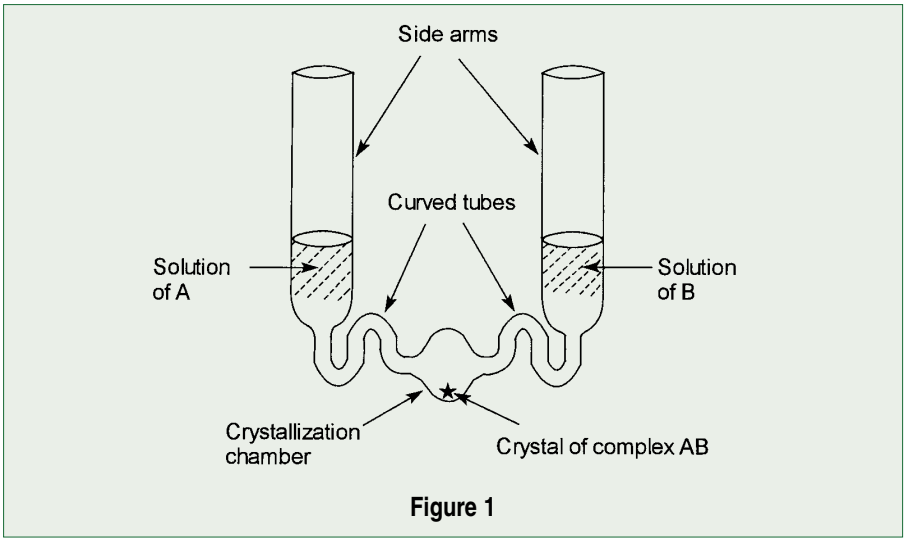

Figure 1

References: (1) Fischinger, A.J. A Flotation Method for Growing Large Single Crystals. *J. Chem. Ed.* **1969**, *46*, 486. (2) Jones, P.G. Crystal Growing. *Chem. Br.* **1981**, *17*, 222. (3) Suib, S.L. Crystal Growth in Gels. *J. Chem. Ed.* **1985**, *62*, 81. (4) Bell, T.W.; Khasanov, A.B.; Drew, M.G.B.; Filikov, A.; James, T.L. A Small-Molecule Guanidinium Receptor: The Arginine Cork. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2543.

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Editor's Note: Following publication of the lab note, *Maintaining a Constant Water Level in an Open, Warm-Water Bath* (*Aldrichimica Acta* **1999**, *32(2)*, 34), we received other suggestions on accomplishing the same thing. Chester J. Opalka of Albany Molecular Research, Inc. wrote to recommend the use of paraffin wax (e.g., **32,720-4**), which, he states, is easier to separate from the water after the bath has cooled. Jim Brien of Aldrich Techware recommends the use of polypropylene floating balls (**Z37,593-4**). Each of these three ideas, as well as the one recommending the use of polystyrene chips (Stronski, R.E. *J. Chem. Educ.* **1967**, *44*, 767), has its merits and drawbacks; for example the paraffin wax cannot be used if the bath temperature is lower than 56–80 °C. However, each is a lot simpler to carry out than some of the more complicated setups and devices recommended elsewhere in the literature.

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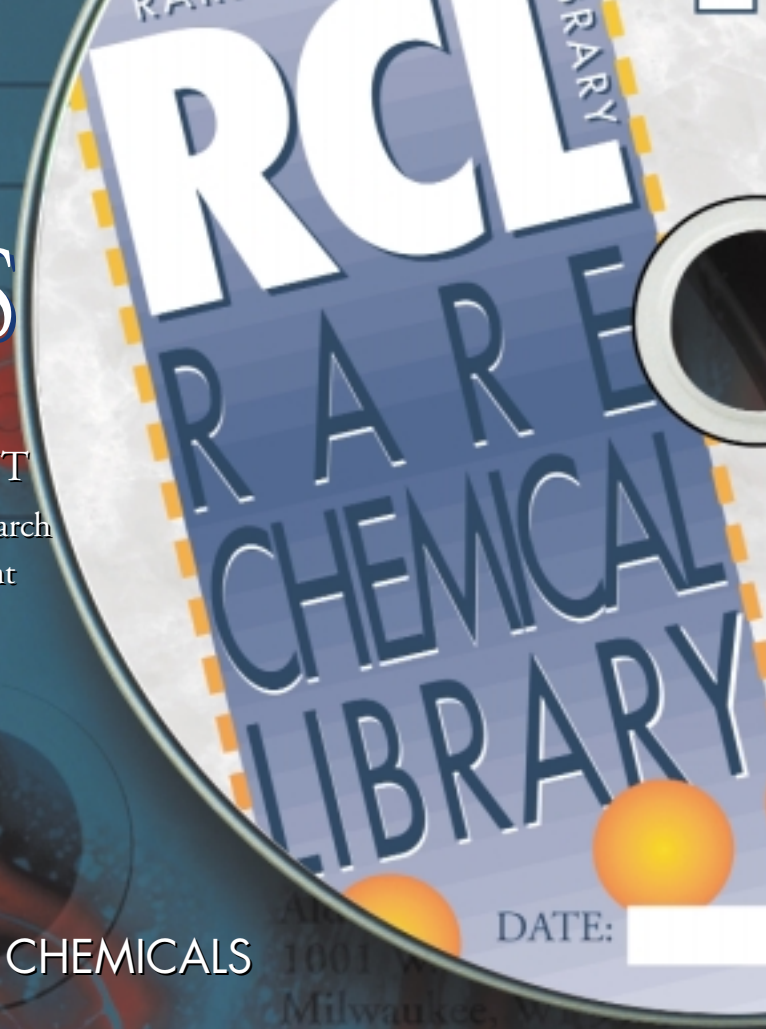

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Year 2000 ACS Award Recipients

Aldrich, a proud sponsor of three separate ACS awards, congratulates the following year 2000 recipients for their outstanding contributions to chemistry.

ACS Award for Creative Work in Synthetic Organic Chemistry

Professor Dennis P. Curran
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Professor Curran has been selected to receive this award in recognition of his lasting impact and outstanding pioneering contributions to such wide-ranging research areas as synthetic radical chemistry, natural product synthesis, stereoselective organic reactions, fluorous chemistry, and others. To paraphrase a recent statement by an admiring colleague, Dennis is one of the most prominent synthetic organic chemists not only in the US, but also in the rest of the world. His loyalty to the University of Pittsburgh has given its chemistry department a top ranking.

ACS Award in Inorganic Chemistry

Dr. Edward I. Stiefel
Exxon Research and Engineering Co.

This award is a fitting tribute to Dr. Stiefel's pioneering research and outstanding achievements in Inorganic Chemistry. In the words of an enthusiastic colleague, Ed has made "significant and original contributions to Co-ordination Chemistry, Bioinorganic Chemistry, Inorganic Materials, and Catalysis", and is regarded as a "leading international authority" in these areas. Most noteworthy are his studies of transition metal sulfide complexes that have important biological and industrial applications, his synthesis of the first isolated metal complexes of the anti-Parkinsonism drug L-DOPA, and his discovery and development of the remarkable "induced internal electron transfer reactions" in which the addition of an external oxidant leads to reduction of the metal center.

Herbert C. Brown Award for Creative Research in Synthetic Methods

Professor Samuel J. Danishefsky
Sloan–Kettering Institute for Cancer Research and Columbia University

One of the leading synthetic organic chemists of the twentieth century, Professor Danishefsky was chosen for this award on the basis of his seminal contributions to the twin areas of synthetic methodology and total synthesis of complex molecules of biological significance. Notable examples of the former include the glycal assembly method for the synthesis of oligosaccharides and glycoconjugates, the Diels—Alder reaction of siloxydienes, and Lewis acid catalyzed cyclocondensation reactions. His accomplishments in the latter area include the total synthesis of paclitaxel, camptothecin, coriolin, and pancratistatin, to name only a few.

Congratulations to each and all!

Are Two Phenyls Better than One? Synthesis and Applications of (*R*)-4-Diphenylmethyl-2-oxazolidinone

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Outline

1. Introduction

Chiral auxiliaries have played a key role in the development of efficient and elegant routes to a variety of enantiomerically pure compounds (**Figure 1**).[1] Academics as well as the chemical industry have made extensive use of chiral auxiliaries in the synthesis of target molecules. The more commonly used auxiliaries are derived from either amino acids or terpenes. The availability of these naturally occurring materials in both enantiomeric forms makes them ideal starting materials. Oxazolidinones, readily available from chiral amino alcohols, have been the more popular auxiliaries.[2] Pioneering work from Professor David Evans's group has firmly established the utility of oxazolidinones as superior auxiliaries for a variety of bond constructions.[3]

Compounds **2–5** are generally successful in providing high levels of selectivity in a large number of transformations (alkylation, aldol, Diels–Alder, etc.). However, there are reactions in which they do not provide adequate selectivity. A notable transformation in this category is the conjugate addition reaction. While working on the preparation of unnatural amino acids from serine, we came upon an oxazolidinone which, we thought, was worth looking into as a chiral auxiliary. Our hypothesis was that, by placing a large group at the oxazolidinone 4 position, which extends its bulk to the β carbon in enoates, there was the potential for achieving a higher selectivity in transformations in which the traditional chiral auxiliaries did not perform satisfactorily. This account describes the preparation and utilization of a new oxazolidinone auxiliary, **1**, that is derived from diphenylalaninol. The chemistry described here is work from our laboratory only. Wherever possible, the advantages and disadvantages of the new auxiliary and its efficiency, as compared to that of the traditional compounds, will be highlighted.

2. Synthesis of (*R*)-4-Diphenylmethyl-2-oxazolidinone

Chiral oxazolidinones can be readily prepared from the corresponding amino alcohols. However, there are only a few enantioselective routes to the parent amino acid, diphenylalanine,[4] and most of these require several steps. We have prepared **1** in three steps from serine methyl ester hydrochloride (**Scheme 1**). Treatment of **12** with triphosgene and triethylamine provides oxazolidinone **13** in 95% yield. The desired aryl groups are introduced by reaction of **13** with phenylmagnesium bromide to furnish tertiary alcohol **14**,

which is then deoxygenated with Na/NH_3. The synthesis of **1** {mp: 135–137 °C, $[\alpha]_D^{20}$ = +37.1° (c = 1.0, CH_2Cl_2)} is amenable to scaleup, and we have typically prepared **1** in 25–50-g quantities.[5] Having reasonable quantities of the auxiliary on hand, we set out to evaluate its utility by examining three major types of reactions: alkylation, aldol condensation, and conjugate addition.

3. Alkylation Reactions

The synthetic utility of oxazolidinone **1** in stereoselective alkylations was explored first (**eq 1**).[6] Thus, treatment of **15**[7] with NaHMDS in THF at -78 °C produced an enolate, which, upon quenching with reactive alkyl bromides, furnished the alkylated products **16** in moderate-to-good yields and excellent diastereofacial selectivity. The stereochemical course of these reactions was established for one of the examples by $LiOH/H_2O_2$ hydrolysis of **16** (R = CH_2Ph) to afford a known carboxylic acid. In comparison, alkylation with benzyl bromide of the lithium enolate derived from the *N*-propionyl derivative of **2** proceeds in 92% yield and >99% de.[8]

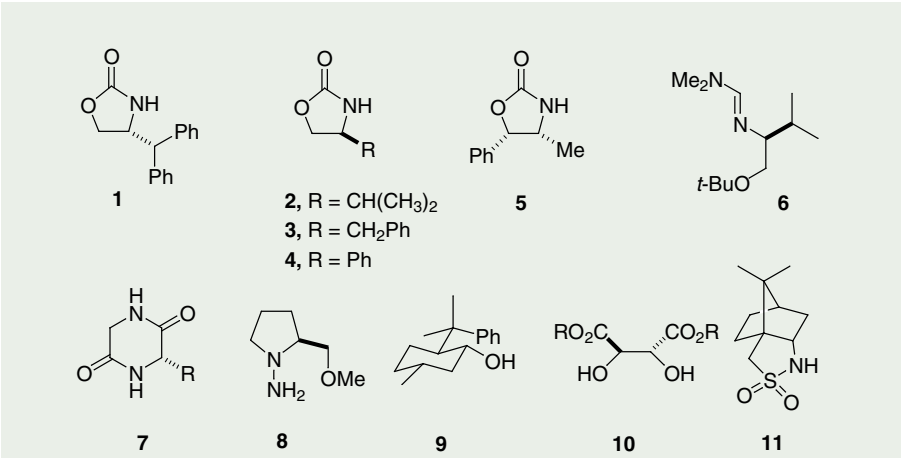
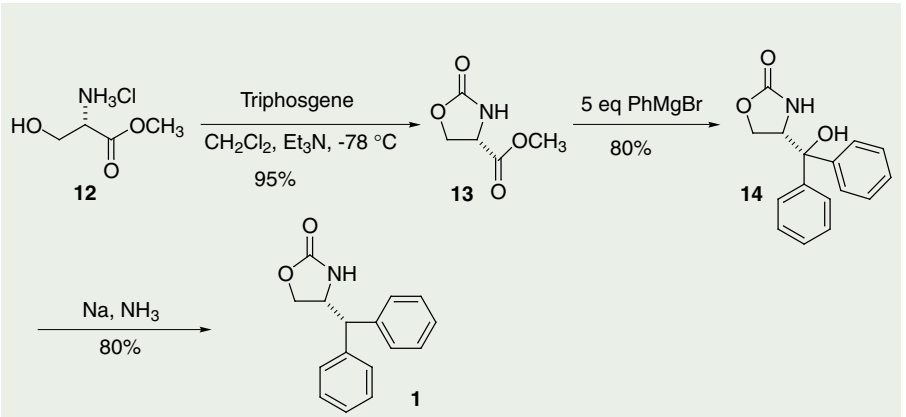
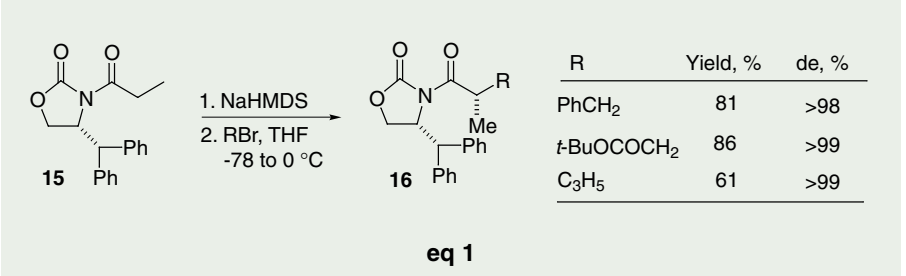


Figure 1. Some Commonly Used Chiral Auxiliaries.

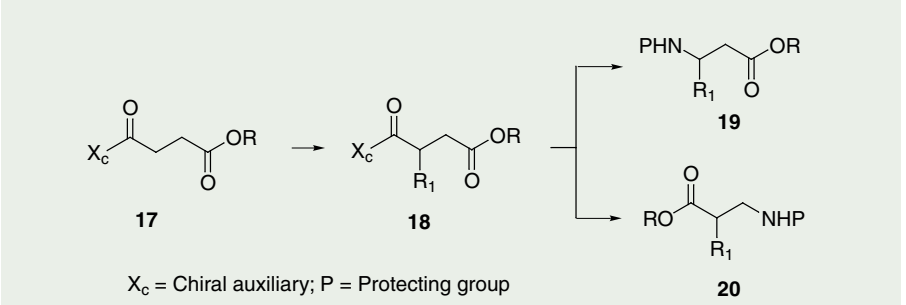


Scheme 1. Synthesis of the Chiral Auxiliary.



R	Yield, %	de, %
$PhCH_2$	81	>98
t-BuOCOCH$_2$	86	>99
C_3H_5	61	>99

eq 1



Scheme 2. Outline for the Synthesis of β-Amino Acids.

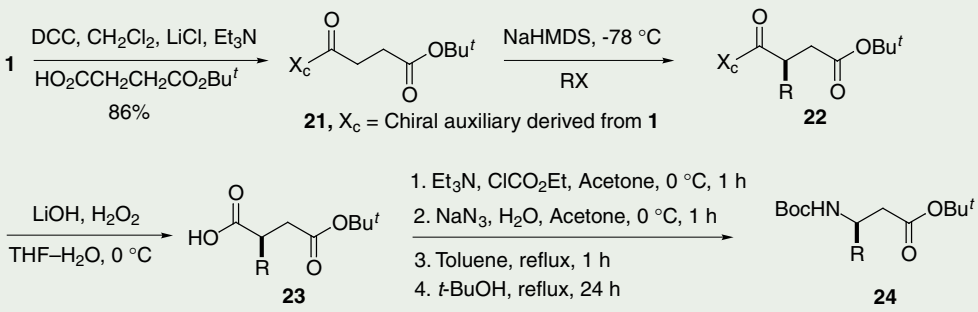
3.1. Synthesis of β-Amino Acids

Naturally occurring β-amino acids are compounds with an interesting pharmacological profile.[9] They are also found as components in a wide variety of biologically active compounds,[10] including peptides such as pepstatin.[11] β-Amino acids are also useful precursors in the synthesis of β-lactams.[12] Recently, α-substituted β-amino acids have received greater scrutiny, since they are important segments of bioactive molecules such as paclitaxel.[13]

We have evaluated the synthesis of β-amino acids in the context of a general methodology involving functionalization of linear dicarboxylic acid derivatives in a regio- and stereoselective manner. The succinate unit is an ideal fragment for the synthesis of a variety of natural products if substituents can be introduced regio- and stereoselectively onto the carbon framework.[14] Further selective conversion of one of the carboxyl groups to an amino functionality by a Curtius rearrangement provides access to β-amino acids. Alternatively, the lactonization strategy provides butyrolactone natural products (*vide infra*).

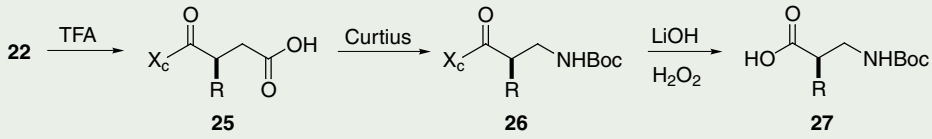
Scheme 2 illustrates our approach to β-amino acids wherein the starting material is a readily available succinate, **17**. The two carboxyl groups are differentiated by forming an ester at one end and attaching a chiral auxiliary to the other. With the two ends differentiated, the first step is a regio- and stereoselective alkylation at the carbon α to the imide functionality to furnish **18**. The second step involves the selective removal of either the imide or the ester functionality; this is then followed by a Curtius rearrangement of the free carboxyl group with retention of stereochemistry (if applicable). Thus, intermediate **18** serves as a common precursor for two different β-amino acids, **19** and **20**.[15]

Our methodology began with the attachment[16] of the mono-*tert*-butyl succinate[17] to oxazolidinone **1** (**Scheme 3**). Treatment of **21** with one equivalent of NaHMDS, followed by quenching with a reactive alkyl bromide, furnished **22** in good yield and diastereoselectivity.[18] In this reaction step, temperature and counterion played an important role in the generation of the enolate. When the reaction mixtures were warmed to above -48 °C, after sodium enolate generation, cleavage of the chiral auxiliary was observed. The regioselectivity observed for the enolate generated from **21** may be attributed to the higher acidity of the hydrogens α to the imide as compared with those α to the ester group.[19] The next step involved the selective hydrolysis of the imide functionality. This was accomplished by treating **22** with LiOH/H_2O_2 to furnish **23**.[20] The key step in our methodology was the use



RBr	Yield **22**, % (de)	Yield **23**, %	Yield **24**, %
Benzyl bromide	83 (92)	90	83
Allyl bromide	72 (92)	88	80
(*E*)-1-Bromo-3-undecene	60 (97)	87	90
Cinnamyl bromide	73 (84)	80	78
Methyl iodide	83 (81)		

Scheme 3. Synthesis of β-Amino Acids.



R	Yield **25**, %	Yield **26**, %	Yield **27**, %
CH_2Ph	93	68	87
C_3H_5	97	69	98
CH_3	55	66	83

Scheme 4. Synthesis of Isomeric β-Amino Acids.

of the Curtius rearrangement to effect the one-pot conversion of the carboxylic acid group to the protected amino group with retention of stereochemistry (**23** to **24**).[21,22] Thus, the synthesis of β-amino acids was accomplished in four steps in good overall yields and high optical purities.

Intermediate **22** also served as a useful precursor for the synthesis of isomeric β-amino acids (**Scheme 4**). Selective deprotection of the *tert*-butyl ester functionality was achieved in high yields using trifluoroacetic acid. Curtius rearrangement followed by cleavage of the imide provided the isomeric β-amino acids in good yields (**26** → **27**).

3.2. Radical Allylations

The stereoselective introduction of functional groups into acyclic systems by free radical methods is often a challenge.[23] As has been amply demonstrated in the literature, as well as by the chemistry illustrated above, oxazolidinones provide high stereoselectivities in enolate alkylations. We were intrigued by the potential of oxazolidinones in radical chemistry, and wondered whether they would be equally suited for the introduction of the allyl group under a radical chain process. However, the use of oxazolidinone auxiliaries[24] in radical reactions has been hampered by the limited rotamer control that is available in the absence of Lewis acid additives.[25] Based on literature precedents for Diels–Alder reactions using oxazolidinone auxiliaries, we surmised that a proper combination of a chelating Lewis acid and the R group in the chiral auxiliary would allow for highly diastereoselective radical reactions. This would require that the radical react from a single rotamer (**28**) out of several possible rotamers (**28**–**31**) (**Figure 2**).

Radical allylations using several mono- and multidentate Lewis acids were tested (**Table 1**).[26] As expected, poor selectivity was observed with single-point-binding Lewis acids, such as BF_3•OEt_2. Of the Lewis acids examined, scandium and magnesium reagents resulted in the highest selectivities.[27] The sense of stereoinduction in the Lewis acid mediated radical allylation was the same as that of the enolate allylation, with the two reactions providing comparable diastereoselectivities.

The effect of the substituent at C-4 of the oxazolidinone ring was also examined. The results shown in Table 1 indicate that arylalkyl substituents provide the highest selectivities, and, of these, the diphenylmethyl and tritylmethyl groups give the best results. The traditional Evans auxiliaries derived from phenylalaninol and valinol gave good and low selectivities, respectively.

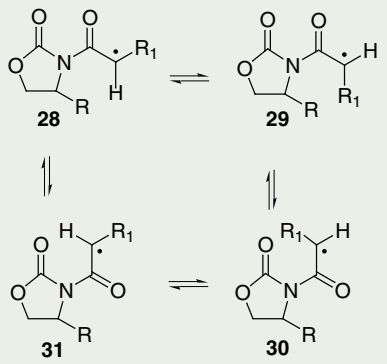
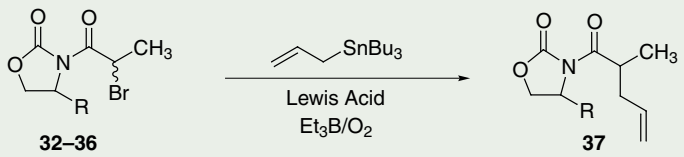


Figure 2. Rotamers of *N*-Acyloxazolidinones.

Table 1. Effect of Lewis Acid and Chiral Auxiliary on the Diastereoselectivity of Radical Allylations.



Compound (config.)	Lewis Acid	Reaction Conditions	Yield, %	Ratio (config.)[a]
32, R = $CH(Ph)_2$ (*R*)	None	-78 °C, CH_2Cl_2, 3 h	93	1:1.8 (*S*)
	$BF_3{\cdot}OEt_2$	-78 °C, CH_2Cl_2, 2.5 h	85	1:1.4
	$MgBr_2$	-78 °C, CH_2Cl_2, 2 h	94	≥100:1 (*S*)
	$Yb(OTf)_3$	-78 °C, THF, 2 h	86	5:1
	$Sc(OTf)_3$	-78 °C, ether, 2 h	94	≥100:1
33, R = CH_2CPh_3 (*R*)	$Sc(OTf)_3$	-78 °C, ether, 2 h	88	100:1 (*S*)
34, R = CH_2Ph (*R*)	$Sc(OTf)_3$	-78 °C, ether, 2 h	91	58:1 (*S*)
35, R = $CH(CH_3)_2$ (*S*)	$MgBr_2$	-78 °C, CH_2Cl_2, 2 h	85	2.8:1
36, R = Ph (*S*)	$MgBr_2$	-78 °C, CH_2Cl_2, 2 h	92	3:1

[a] The configuration of the major isomer at the newly formed chiral center.

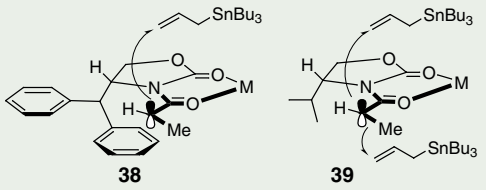


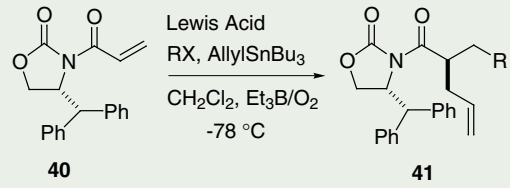
Figure 3. Models for Chiral-Auxiliary-Dependent Selectivity.

A model, **38**, that accounts for the observed selectivity is shown in **Figure 3**. In this model, the metal coordinates both carbonyl oxygens, and the allylic 1,3 strain favors the *s-cis* rotamer of the intermediate radical. Allylstannane addition to the chelated intermediate takes place from the face opposite the bulky oxazolidinone 4-substituent. The low selectivity observed for **35**, with an isopropyl substituent (see **39**), as compared to those for **32** and **34**, with diphenylmethyl and benzyl substituents, suggests that additional factors may, in conjunction with steric effects, be responsible for the high selectivities observed with these auxiliaries.[28]

Diastereoselective allylations were also achieved in a slightly different manner through radical addition to chiral oxazolidinone acrylate and trapping with allylstannane (**Scheme 5**).[29] In reactions with α,β-unsaturated substrates, the Lewis acid functions not only to control the rotamer populations, but also to increase the reactivity at the β carbon. After initial addition of the radical, an intermediate is generated at the α position and is trapped readily with allylstannane. It was found that magnesium bromide provides the highest selectivities (>100:1) in the tandem addition of isopropyl radical and trapping with allylstannane. A variety of radical precursors were employed to evaluate the scope of this methodology. Excellent diastereoselectivities resulted from alkyl radicals and acyl radicals, but the methoxymethyl radical appeared to interfere with the Lewis acid, in particular $MgBr_2$. Higher selectivities were attainable with $Yb(OTf)_3$ as a Lewis acid, presumably as a reflection of its higher coordinating ability. As in the case of the simple allylations discussed in Table 1, the highest diastereoselectivities were also obtained with auxiliary **1** in the tandem addition–trapping reactions.

4. Aldol Reactions

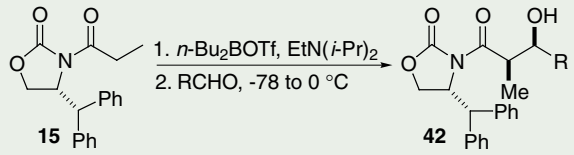
A major breakthrough in the total synthesis of complex natural products was the development of the stereoselective aldol reaction that uses boron enolates derived from *N*-acyloxazolidinones.[30] As a prelude to exploring the utility of **1** in the total synthesis of natural products, aldol reactions of **15** with representative aldehydes were examined (**eq 2**). The *Z* enolate of **15** was generated upon treatment with *n*-Bu_2BOTf followed by diisopropylethylamine in CH_2Cl_2 at 0 °C.[6] Quenching of the enolate with the appropriate aldehyde produced the syn aldol, **42**, in good yield. NMR and HPLC analyses of the crude reaction mixtures indicated that each aldol product was formed essentially as a single diastereomer. Crystallinity of all the aldol adducts was an advantage in their purification. The absolute stereochemistry of the aldol product was confirmed by hydrolysis of **42** to furnish the enantiomer of a known carboxylic acid in 90% yield, along with the chiral auxiliary (94%). In comparison, an aldol reaction of the *N*-propionyl derivative of **2** with benzaldehyde gave the product with >97% de. These results show that oxazolidinone **1** can be effectively employed in aldol reactions.



RX	Lewis Acid	Yield, %	Ratio[a]
CH_3I	$MgBr_2$	82	>100:1
i-PrI	$MgBr_2$	85	>100:1
t-BuI	$MgBr_2$	94	>100:1
$MeOCH_2Br$	$Yb(OTf)_3$	70	58:1
MeCOBr	$MgBr_2$	55	50:1

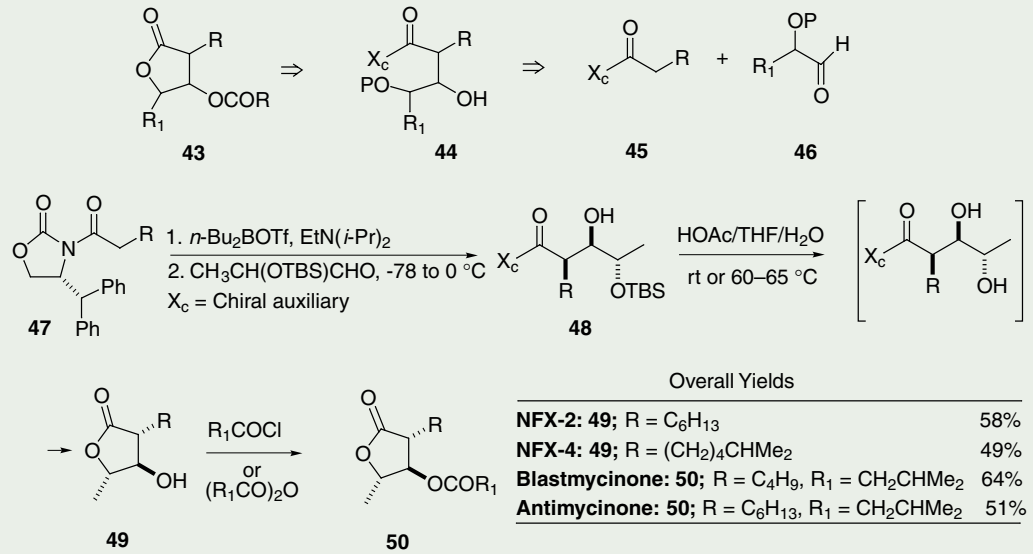
[a] Diastereomeric ratio (by ^1H NMR)

Scheme 5. Tandem Addition—Allylation.



RCHO	Product	Yield, %	de, %
PhCHO	R = Ph	83	98
Piperonal	R = $-C_6H_3(-OCH_2-O-)$	82	97
Hexanal	R = C_5H_{11}	84	97

eq 2



Overall Yields	
NFX-2: 49; R = C_6H_{13}	58%
NFX-4: 49; R = $(CH_2)_4CHMe_2$	49%
Blastmycinone: 50; R = C_4H_9, R_1 = CH_2CHMe_2	64%
Antimycinone: 50; R = C_6H_{13}, R_1 = CH_2CHMe_2	51%

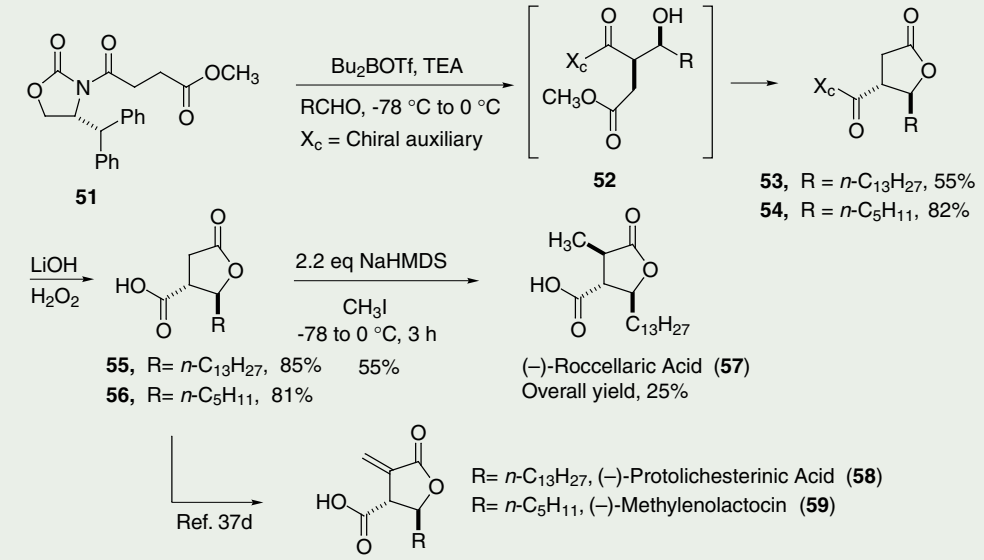
Scheme 6. Synthesis of Butyrolactone Natural Products.

4.1. Synthesis of Butyrolactone Natural Products

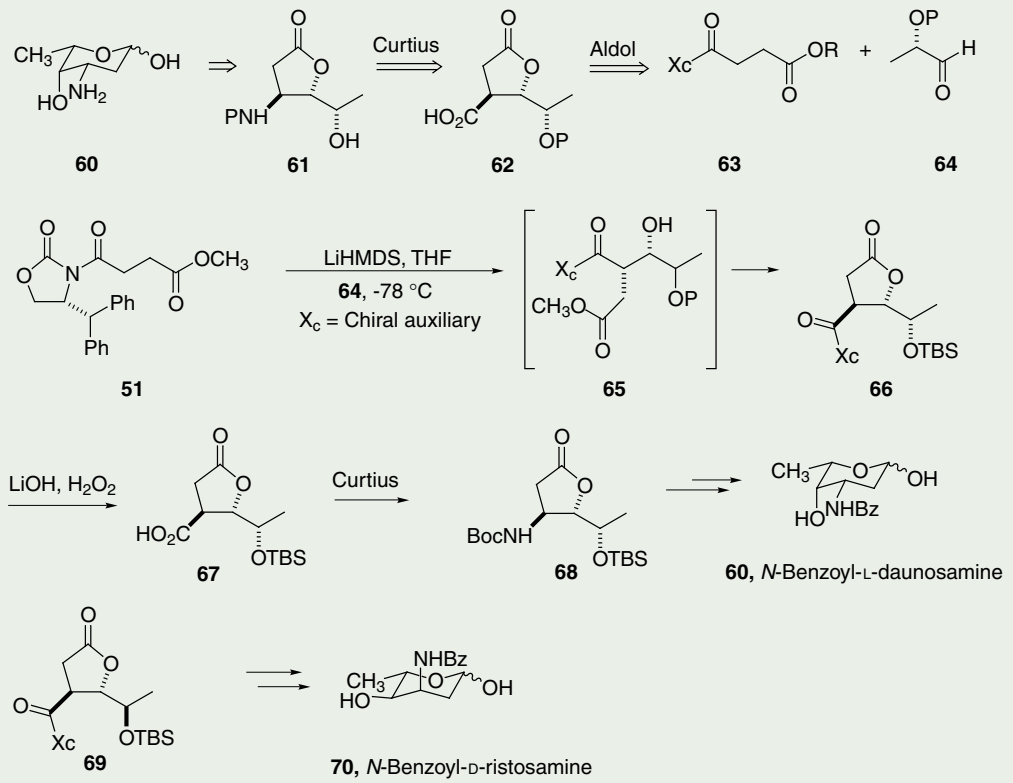
The development of new methodologies for the synthesis of butyrolactone natural products has received considerable attention.[31] The 3-alkyl-4-hydroxy-5-methyl-2(3*H*)-dihydrofuranone substructure is found in a wide variety of metabolites with very different origins.[32] Of these, the polyketide metabolites blastmycinone,[33] NFX-2,[34] antimycinone,[35] and NFX-4 contain short-to-medium-length carbon chains at the C-3 position.

The three contiguous chiral centers in blastmycinone and related compounds present a reasonable challenge for the development of new methodologies. We have been interested in exploring the aldol reaction between α-alkoxy aldehydes (**46**) and chiral *N*-acyloxazolidinones (**45**) as a method for the establishment of the stereotriad. The relative and absolute stereochemistries of the stereocenters would then be established by the nature of the aldol reaction (syn or anti) and by the resident chiralities of the auxiliary and the α-alkoxy aldehyde (**Scheme 6**).

The reaction of OTBS-lactaldehyde with the boron enolate derived from **47** gave the syn aldol product **48**.[36] Yields for the aldol product from several runs only averaged around 60%. Subsequently, enolate generation using modified conditions (Bu_2BOTf, Me_2NPh/Et_2O/0 ºC/1 h; aldehyde/-78 ºC to 0 ºC/24 h) led to a reasonable improvement in chemical yields for the aldol products. Careful deprotection of the silyl group in **48** gave the hydroxy-lactones directly in good yields. These were then converted to the natural products by acylation. This strategy to the target



Scheme 7. Synthesis of Paraconic Acid Natural Products.



Scheme 8. Synthesis of Amino Sugars.

lactones has two key attributes: high overall yields and a small number of synthetic steps.

4.2. Synthesis of Paraconic Acid Natural Products

Paraconic acids (4-carboxy-γ-butyrolactones) are a small class of biologically active butyrolactone natural products.[37] Three members from this class, methylenolactocin, protolichesterinic acid, and roccellaric acid have received attention, since they exhibit antibiotic, antitumor,[38] antifungal, and growth-regulating properties. As discussed earlier, we were interested in the utilization of linear dicarboxylic acids for the synthesis of trisubstituted lactone natural products by cyclization and carboxyl differentiation.

Our synthetic strategy for these natural products was based on the selective aldol reaction at the α carbon of the imide (**Scheme 7**).[39] Using the well-established boron triflate mediated reaction of **51** gave the syn aldol product, **52**. This product could be

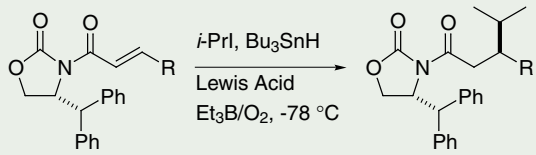
isolated prior to lactonization, but chemical yields suffered dramatically (40–45%); therefore, the cyclization was carried out without the isolation of **52**. The syn selectivity in the aldol reaction was established by converting the aldol products to compounds of known configurations. At this stage, we tried to introduce the desired methyl group at C-3 by metallation/alkylation of **53**. These experiments were unsuccessful: None of the desired products was obtained, and cleavage of the chiral auxiliary was observed along with several other unidentified products. Successful installation of the methyl group was possible with the acid derivative **55**. Treatment of **53** with in situ generated lithium hydroperoxide gave acid **55** as well as the chiral oxazolidinone **1**. Introduction of the C-3 methyl group with the desired β stereochemistry was carried out by dideprotonation followed by treatment with methyl iodide. The use of 2.2 equivalents of NaHMDS gave roccellaric acid only (β:α = >100:1) along with unreacted starting material (55% yield; 95% based on recovered starting material). The use of LiHMDS gave both diastereomers (β:α = 1:1) as well as some of the dialkylation product.[40] The overall yield of roccellaric acid was 25% over four steps.[41] Compounds **55** and **56** have been converted by Greene and co-workers to protolichesterinic acid and methylenolactocin, respectively.[37d]

4.3. Synthesis of Amino Sugars

The studies described above established two protocols for strategic bond formations: (1) selective functionalization α to the imide carbonyl in a differentially protected succinate, and (2) Curtius rearrangement in monosubstituted succinic acids with retention of configuration. We wanted to combine these two protocols for the synthesis of amino sugars. A number of clinically important anthracycline antibiotics contain a 3-amino-hexose unit as part of their structures. L-Daunosamine[42] (**60**) is the glycosidic component of naturally occurring anthracyclines daunomycin, adriamycin, and carminomycin;[43] and L-ristosamine is a component of the glycoprotein ristomycin.[44]

The key features of our synthetic strategy for daunosamine are: (1) the regio- and diastereoselective syn aldol reaction of a desymmetrized chiral succinate with an O-protected lactaldehyde (**63** + **64** to **62**), and (2) the Curtius rearrangement of the acid **62** to an advanced intermediate, **61** (**Scheme 8**). Further adjustments in the oxidation state of **61** lead to the target amino sugar. Additionally, D-ristosamine, the C-5 epimer of daunosamine, can also be prepared using the same methodology by using the O-protected (*R*)-lactaldehyde.

Table 2. Conjugate Radical Additions.



71, R = CH_3
72, R = Ph
73, R = CO_2Et

74, R = CH_3
75, R = Ph
76, R = CO_2Et

Model for the observed selectivity

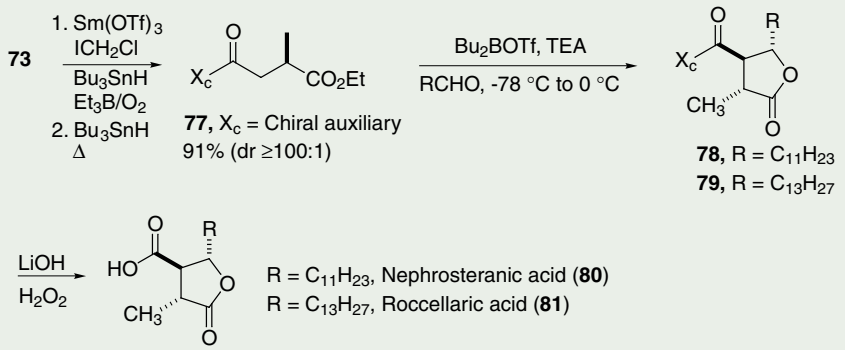
Oxazolidinone	Lewis Acid (eq)	Reaction Conditions	Yield, %[a]	Diastereomeric Ratio[b]
71	None	-78 °C, CH_2Cl_2/hexane	60	1.3:1
	$BF_3 \cdot OEt_2$ (1.0)	-78 °C, CH_2Cl_2/hexane	80	1.3:1
	$Sc(OTf)_3$ (1.0)	-78 °C, CH_2Cl_2/hexane/THF	90	15:1
	$Yb(OTf)_3$ (1.0)	-78 °C, CH_2Cl_2/hexane/THF	93[c]	25:1
72	$MgBr_2$ (1.0)	-78 °C, CH_2Cl_2/hexane/ether	90	20:1
	$Yb(OTf)_3$ (1.0)	-78 °C, CH_2Cl_2/hexane/THF	89[c]	45:1
	$Yb(OTf)_3$ (0.3)	-78 °C, CH_2Cl_2/hexane/THF	90	20:1
	$Lu(OTf)_3$ (1.0)	-78 °C, CH_2Cl_2/hexane/THF	90	50:1
73	$Mg(OTf)_2$ (1.0)	-78 °C, CH_2Cl_2	87	1:1
	$Sm(OTf)_3$ (1.0)	-78 °C, CH_2Cl_2/THF	95	29:1
	$Er(OTf)_3$ (3.0)	-78 °C, CH_2Cl_2/THF	91	71:1

[a] NMR yields. [b] Determined by 'H NMR. [c] Yield of purified material.

In contrast to the good chemical efficiency of the reactions of **51** and simple aliphatic aldehydes described above (see Scheme 7), the chemical yields in the boron-mediated aldol condensations with protected lactaldehydes were disappointing.[45] These results led us to examine reactions with lithium enolates, which have been shown to be more reactive.[46] Treatment of a THF solution of **51** with LiHMDS at -78 ºC furnished the lithium enolate, which was immediately reacted with a freshly prepared (*S*)- or (*R*)-*O*-TBS-lactaldehyde solution. We were delighted to find that these reactions gave a satisfactory chemical yield as well as high diastereoselectivity (**Scheme 8**). The aldol reactions were highly syn-selective: the absolute stereochemistry (non-Evans syn) obtained was the opposite of that observed in the boron-mediated aldol reaction (Evans syn). The diastereoselectivity in the aldol reaction was ~15:1. As has been reported in the literature,[47] ca. 14% of chiral auxiliary cleavage was observed in the lithium aldol reaction. The aldol adduct, **65**, underwent lactonization slowly, thus requiring acid catalysis. The imide could be conveniently deprotected to furnish the acid, **67**. In contrast to the Curtius rearrangement of the acyclic system **23**, the rearrangement of **67** to **68** was more facile with diphenylphosphoryl azide (DPPA). The synthesis was completed by a reduction–deprotection sequence, or by the reverse sequence. Yields of the target amino sugars by the former sequence were higher. Similarly, lactone **69**, the aldol–cyclization product from **51** and (*R*)-*O*-TBS-lactaldehyde, was converted to ristosamine. The overall yields of daunosamine and ristosamine were 18% in each case.

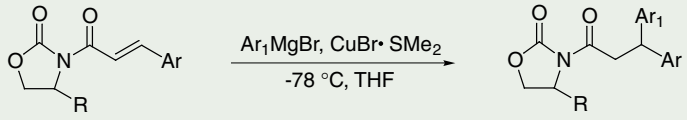
5. Conjugate Additions

Conjugate addition is one of the most important transformations in synthetic organic chemistry.[48] Diastereoselective conjugate additions to control stereochemistry at the β center have been approached in a number of ways. One approach utilizes chiral auxiliaries on the acceptor and yields products highly diastereoselectively. Another approach uses chiral nucleophiles (either chiral themselves or having chiral attachments), again highly selectively. Of the variety of chiral auxiliaries examined for conjugate addition, oxazolidinones have generally been inferior in terms of selectivity. Recently, several groups have undertaken a systematic study of various



Scheme 9. Conjugate Radical Addition to Fumarates. Synthesis of Paraconic Acid Natural Products.

Table 3. Diastereoselective Conjugate Additions. Effect of Chiral Auxiliary on Selectivity.



72, 82–86 **87–93**

Reactant	R	Ar	Prod.	Ar_1	Yield, %	de, %
72	$CH(Ph)_2$	Ph	**87**	3,4,5-$(MeO)_3C_6H_2$	85	88
82	$CH(Ph)_2$	3,4-$(OCH_2O)C_6H_3$	**88**	Ph	90	97
83	$CH(Ph)_2$	3,4,5-$(MeO)_3C_6H_2$	**89**	3,4-$(OCH_2O)C_6H_3$	88	95
83	$CH(Ph)_2$	3,4,5-$(MeO)_3C_6H_2$	**90**	3,4-(OCH_2O)-5-$MeOC_6H_2$	89	97
84	CH_2Ph	Ph	**91**	3,4-$(OCH_2O)C_6H_3$	80	28
85	CH_2Ph	3,4-$(OCH_2O)C_6H_3$	**92**	Ph	85	36
86	Ph	Ph	**93**	3,4-$(OCH_2O)C_6H_3$	90	92

auxiliaries in the addition of copper reagents to enoates.[49] Hruby has shown that the oxazolidinone derived from phenylglycinol provides high selectivity in the addition of aryl cuprates to cinnamates.[50] In the following section, we describe the use of **1** in conjugate additions to acyclic systems using radical and copper nucleophiles, and compare its effectiveness vis-à-vis the traditional oxazolidinones in controlling the stereochemistry at the β carbon.

5.1. Radical Conjugate Additions

When we initiated our study, examples of highly diastereoselective, intermolecular, conjugate radical additions in acyclic systems were rather sparse.[51] As discussed in section 3.2, we felt that, by utilizing a chelating Lewis acid and the proper choice of the C-4 substituent of the oxazolidinone, rotamer control should be feasible, and that there was potential for obtaining a high selectivity in the conjugate addition.

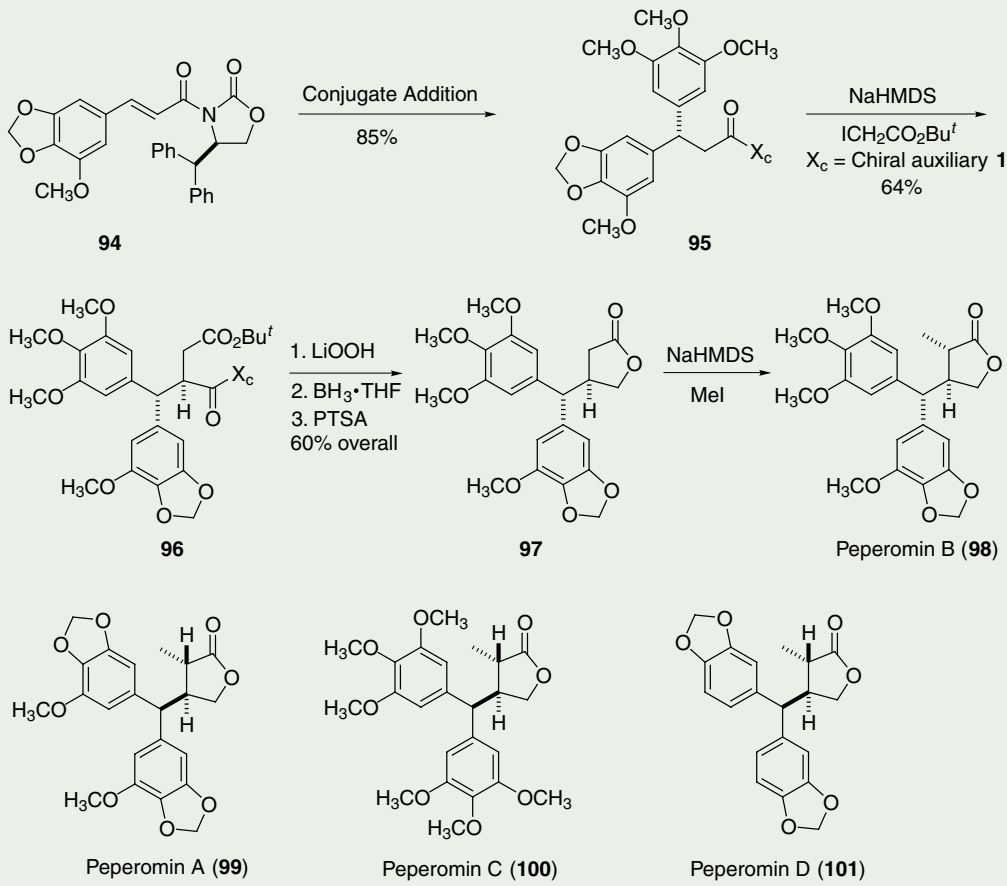
Intermolecular conjugate addition of the nucleophilic isopropyl radical to enoates **71**–**73**, derived from oxazolidinone **1**, in the absence and presence of various Lewis acids was investigated (**Table 2**).[52] After evaluating several Lewis acids, some trends emerged. Lanthanide Lewis acids provided the highest levels of selectivity, and the use of substoichiometric amounts of Lewis acids had a negligible effect on the stereoselectivity or reaction efficiency. It must be noted that the level of selectivity achieved through free radical conjugate addition to oxazolidinones rivals, if not surpasses, that obtained through ionic methodology.[50] Higher selectivities were observed for the less reactive cinnamates than for the more reactive crotonates in conjugate radical additions.

In a similar manner, conjugate radical additions to differentially protected fumarate **73** allowed access to functionalized succinates.[53] Regioselectivity in these radical additions is provided by preferential activation of the β carbon by the Lewis acid, which coordinates the imide carbonyl. These conjugate additions proceeded in excellent yields. High regio- and diastereoselectivity were observed with lanthanide and other Lewis acids, but little selectivity was seen in the absence of a chelating Lewis acid or with substoichiometric amounts of the Lewis acid. In general, the reactivity pattern was fumarate > crotonate > cinnamate. In contrast to the reactivity of crotonates and cinnamates in these reactions, where it was possible to use catalytic amounts of the Lewis acid, the fumarate substrate was orders of magnitude more reactive, and, hence, a highly selective radical addition to fumarate under catalytic Lewis acid conditions was not possible.

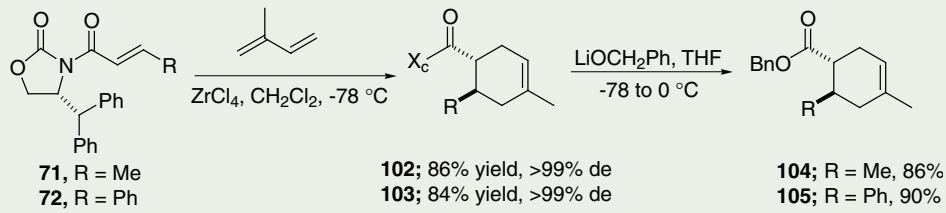
A model that accounts for the stereochemical outcome of the reaction is shown in Table 2. Upon chelation of the two carbonyls with the Lewis acid, their orientation becomes fixed. The Lewis acid also activates the β carbon toward addition of the nucleophilic radical species. A proper matching of the Lewis acid and the substrate, as well as the nucleophilicity of the radical, are the key factors in obtaining good chemical yields and high selectivities in the reaction. The stereochemistry of the product can be explained by postulating that the radical approaches from the face opposite the bulky diphenylmethyl substituent in the chelated intermediate. As was seen in the allylation experiments, replacement of the diphenylmethyl group by the smaller benzyl or isopropyl group (Evans auxiliary) results in much lower selectivities (~3:1). Similarly, the phenylglycinol-derived oxazolidinone is equally ineffective.

5.2. Synthesis of Paraconic Acid Natural Products

The difficulties we had with the introduction of the methyl group at C-3 (see section 4.2) led us to devise alternate approaches to the synthesis of paraconic acid natural products. The facile conjugate addition of nucleophilic radicals to fumarate **73** and the selective aldol reactions with succinates boded well for the new strategy. Conjugate addition of the chloromethyl radical to **73** gave the conjugate addition product in high chemical yield as a single isomer (**Scheme 9**). The chloro group was reduced at higher temperatures using radical conditions to furnish the methyl compound. Thus, we were able to install the remote chiral center in a highly selective manner. However, the direct introduction of the methyl group using methyl iodide was not possible. Boron triflate mediated, syn-selective aldol condensation of **77** with the respective aldehydes furnished **78** and **79** in high yields. Selective removal of the chiral auxiliary gave the natural products



Scheme 10. Synthesis of Peperomins.



Scheme 11. Diels–Alder Reactions.

(–)-nephrosteranic acid (**80**) and (–)-roccellaric acid (**81**). The natural products were synthesized in four steps in 53% and 42% overall yields, respectively. The key step in the total synthesis, the conjugate addition to **73**, once again illustrates the utility of **1** in controlling the stereochemistry at the β center.

5.3. Conjugate Addition of Copper Reagents

In connection with a project on the total synthesis of lignan natural products described in section 5.4, we became interested in exploring diastereoselective conjugate additions using copper reagents. To this end, we examined the addition of aryl Grignard reagents to the oxazolidinone-derived cinnamates, **72** and **82–86**, in the presence of Lewis acids and other additives (**Table 3**). The best reaction conditions involved the use of the Grignard reagent and the copper(I) bromide–dimethyl sulfide complex. NMR and HPLC analyses indicated that the diastereoselectivity was very high and was dependent on the oxazolidinone C-4 substituent: Chiral auxiliaries **1** and **4** gave the best selectivity, whereas **3** was far less selective—as reported by Hruby.[50,54] These experiments clearly show that **1** can shield the β carbon effectively in both radical and copper additions.

5.4. Synthesis of Peperomins

Recently, a novel and unusual class of lignans, peperomins, were isolated from *Peperomia japonica*[55] and from *Peperomia glabella*.[56] Using the conjugate addition protocol described in section 5.3, we have now developed an efficient route for the total synthesis of peperomins A–D.[57] This

synthesis relies on the use of functionalized succinates and their further elaboration into the target molecules.

Conjugate addition of the Grignard reagent derived from 1-bromo-3,4,5-trimethoxybenzene to **94** (Xc = **1**) in the presence of CuBr gave **95** in good yield and high selectivity (**Scheme 10**). Introduction of the acetic acid side chain was carried out by alkylation of the sodium enolate of **95** with *tert*-butyl iodoacetate to provide **96**. In this transformation, the chiral auxiliary determines the face selectivity. Selective manipulation of one of the carboxyls by hydrolysis, reduction, and lactonization furnished **97** in a good overall yield. The C-3 methyl group of the lactone was then installed by another alkylation with methyl iodide. The diastereoselectivity of this alkylation reaction was dependent on the base used and the C-4 substituent. The overall yield for the synthesis of peperomin B was ~25%. Lactones **99**–**101** were synthesized analogously in comparable overall efficiencies.

6. Diels–Alder Reactions

Another major reaction type in which oxazolidinone auxiliaries have been extensively utilized is the Diels–Alder reaction. In an excellent study, Evans[58] has shown that phenyl groups in the chiral auxiliary can participate in π stacking and lead to high diastereoselectivities. With this precedent in mind, we explored the Lewis acid mediated Diels–Alder reactions of **71** and **72** (**Scheme 11**).[6] Reaction of **71** with isoprene, using $ZrCl_4$ as a Lewis acid, furnished the cyclohexene **102** in 86% yield and >99% de. Analogous experiments reported in the literature, using **2** and **3** as chiral auxiliaries and diethylaluminum chloride as a Lewis acid, gave 68% and 91% de's, respectively.[59] Similarly, reaction of **72** with isoprene produced **103** as a single diastereomer in excellent chemical yield. The high diastereoselectivities observed in these Diels–Alder reactions indicate that the diphenyl auxiliary provides advantages similar to those of the auxiliary derived from phenylalanine in reactions where participation of the phenyl group in π-stacking interactions is important.

7. Conclusions

In answer to the question posed in the title, two phenyl groups in the auxiliary are definitely better for certain transformations. In general, they provide equal or better levels of selectivity than the traditional Evans auxiliaries (**2**–**5**). 4-Diphenylmethyl-2-oxazolidinone (**1**) is a more sterically demanding analog of **3**, provides high levels of diastereoselection, has potential for π stacking in a variety of reactions, and adds to the pool of useful chiral auxiliaries. In addition to practical advantages such as a three-step preparation, crystallinity, and ease of recovery, the new auxiliary **1** shows promise for providing high diastereoselectivity in more challenging synthetic transformations for which existing auxiliaries are unsatisfactory.[60]

8. Acknowledgements

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9. References and Notes

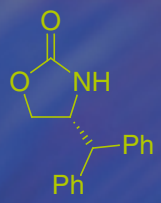
(1) *Handbook of Chiral Chemicals*; Ager, D. J., Ed.; Marcel Dekker: New York, NY, 1999.
(2) (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichimica Acta* **1997**, *30*, 3. (b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.
(3) (a) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23. (b) For a recent monograph, see: Ager, D. J.; East, M. B. *Asymmetric Synthetic Methodology*; CRC Press: Boca Raton, FL, 1996.
(4) (a) Chen, H. G.; Beylin, V. G.; Marlatt, M.; Leja, B.; Goel, O. P. *Tetrahedron Lett*. **1992**, *33*, 3293. (b) Josien, H.; Martin, A.; Chassaing, G. *Tetrahedron Lett*. **1991**, *32*, 6547. (c) Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron* **1994**, *50*, 9837. (d) Tararov, V. I.; Savel'eva, T. F.; Kuznetsov, N. Yu.; Ikonnikov, N. S.; Orlova, S. A.; Belokon, Y. N.; North, M. *Tetrahedron: Asymmetry* **1997**, *8*, 79. (e) Koskinen, A. M. P.; Hassila, H.; Myllymäki, V. T.; Rissanen, K. *Tetrahedron Lett*. **1995**, *36*, 5619.
(5) This auxiliary is now commercially available from Aldrich Chemical Company (Cat. no. **49,470-4** & **49,469-0**). For its synthesis, see Sibi, M. P.; Deshpande, P. K.; La Loggia, A. J.; Christensen, J. W. *Tetrahedron Lett*. **1995**, *36*, 8961. For an alternate synthesis via the Curtius rearrangement, see Takacs, J. M.; Jaber, M. R.; Vellekoop, A. S. *J. Org. Chem*. **1998**, *63*, 2742.
(6) Sibi, M.P.; Deshpande, P. K.; Ji, J. *Tetrahedron Lett*. **1995**, *36*, 8965.
(7) A variety of procedures can be employed for the acylation of **1** with simple acids as well as acids containing sensitive functional groups.
(8) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc*. **1982**, *104*, 1737.
(9) (a) For a discussion of the synthesis and biology of β-amino acids, see *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley–VCH: New York, NY, 1997. (b) For a comprehensive review, see Cole, D. C. *Tetrahedron* **1994**, *50*, 9517.
(10) (a) Shinagawa, S.; Kanamaru, T.; Harada, S.; Asai, M.; Okazaki, H. *J. Med. Chem*. **1987**, *30*, 1458. (b) Kabawata, N.; Inamoto, T.; Hashimoto, S. *J. Antibiot*. **1992**, *45*, 513. (c) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1994**, *50*, 11303.
(11) Iizuka, K.; Kamijo, T.; Harada, H.; Akahane, K.; Kubota, T.; Umeyama, H.; Kiso, Y. *J. Chem. Soc., Chem. Commun*. **1989**, 1678.
(12) Miyachi, N.; Shibasaki, M. *J. Org. Chem*. **1990**, *55*, 1975.
(13) Guénard, D.; Guéritte-Voegelein, F.; Potier, P. *Acc. Chem. Res*. **1993**, *26*, 160.
(14) For other selected methods for the synthesis of substituted succinates, see: (a) Xue, C-B.; He, X.; Roderick, J.; DeGrado, W. F.; Cherney, R. J.; Hardman, K. D.; Nelson, D. J.; Copeland, R. A.; Jaffee, B. D.; Decicco, C. P. *J. Med. Chem*. **1998**, *41*, 1745. (b) Beckett, R. P.; Crimmin, M. J.; Davis, M. H.; Spavold, Z. *Synlett* **1993**, 137.
(15) For the synthesis of β-amino acids using oxazolidinones, see: (a) Arvanitis, E.; Ernst, H.; Ludwig, A. A.; Robinson, A. J.; Wyatt, P. B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 521. (b) Evans, D. A.; Wu, L. D.; Wiener, J. J. M.; Johnson, J. S.; Ripin, D. H. B.; Tedrow, T. S. *J. Org. Chem*. **1999**, *64*, 6411.
(16) Ho, G.-J.; Mathre, D. J. *J. Org. Chem*. **1995**, *60*, 2271.
(17) Büchi, G.; Roberts, E. C. *J. Org. Chem*. **1968**, *33*, 460.
(18) Sibi, M. P.; Deshpande, P. K. North Dakota State University, Fargo, ND. Unpublished results, 1995.
(19) For a selective alkylation of a similar C-4 unit, see: (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc*. **1981**, *103*, 2127. (b) Evans, D. A.; Bilodeau, M. T.; Somers, T. C.; Clardy, J.; Cherry, D.; Kato, Y. *J. Org. Chem*. **1991**, *56*, 5750. (c) Oppolzer, W.; Cintas-Moreno, P.; Tamura, O.; Cardinaux, F. *Helv. Chim. Acta* **1993**, *76*, 187.
(20) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett*. **1987**, *28*, 6141.
(21) (a) Burgess, K.; Lim, D.; Ho, K.-K.; Ye, C.-Y. *J. Org. Chem*. **1994**, *59*, 2179. (b) De Kimpe, N.; Boeykens, M.; Tehrani, K. A. *J. Org. Chem*. **1994**, *59*, 8215.
(22) (a) Weinstock, J. *J. Org. Chem*. **1961**, *26*, 3511. (b) Kaiser, C.; Weinstock, J. In *Organic Syntheses*; Noland, W. E., Ed.; Wiley: New York, NY, 1988; Coll. Vol. VI, p 910.
(23) (a) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH Publishers: Weinheim, Germany, 1995. (b) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res*. **1991**, *24*, 296.
(24) For one of the first examples, see Crich, D.; Davies, J. W. *Tetrahedron Lett*. **1987**, *28*, 4205.
(25) For an excellent recent review, see Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 2562.
(26) Sibi, M. P.; Ji, J. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 190.
(27) Enolate allylation of 3-(1-oxopropyl)-4-(methylethyl)-2-oxazolidinone gave a 98:2 mixture of the allylated product (reference 8).
(28) The higher selectivity for aryl-containing auxiliaries indicates that some π stacking may be operating in these systems.
(29) Sibi, M. P.; Ji, J. *J. Org. Chem*. **1996**, *61*, 6090.
(30) For selected examples, see: (a) Lonomycin A: Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *J. Am. Chem. Soc*. **1995**, *117*, 3448. (b) Cytovaricin: Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J.

J. Am. Chem. Soc. **1990**, *112*, 7001. (c) Macbecin I: Evans, D. A.; Miller, S. J.; Ennis, M. D.; Ornstein, P. L. *J. Org. Chem*. **1992**, *57*, 1067.
(31) For selected examples of the synthesis of biologically active butyrolactones, see: (a) Berkenbusch, T.; Brückner, R. *Tetrahedron* **1998**, *54*, 11461, and references therein. (b) Brown, H. C.; Kulkarni, S. V.; Racherla, U. S. *J. Org. Chem*. **1994**, *59*, 365.
(32) (a) Ortuno, R. M.; Bigorra, J.; Font, J. *Tetrahedron* **1988**, *44*, 5139. (b) Vieira, P. C.; Yoshida, M.; Gottleib, O. R.; Filho, H. F. P.; Nagem, T. J.; Filho, R. B. *Phytochemistry* **1983**, *22*, 711.
(33) *Dictionary of Antibiotics and Related Substances*; Bycroft, B. W., Ed.; Chapman & Hall: London, UK, 1988.
(34) Li, W.; Nihira, T.; Sakuda, S.; Nishida, T.; Yamada, Y. *J. Ferment. Bioeng*. **1992**, *74*, 214.
(35) Nishida, T.; Nihira, T; Yamada, Y. *Tetrahedron* **1991**, *47*, 6623 (degradation of antimycin A_1 to antimycinone).
(36) Sibi, M. P.; Lu, J.; Talbacka, C. L. *J. Org. Chem*. **1996**, *61*, 7848.
(37) For selected recent syntheses of paraconic acids (esters), see: (a) Chandrasekharam, M.; Liu, R-S. *J. Org. Chem*. **1998**, *63*, 9122. (b) Mandal, P. K.; Maiti, G.; Roy, S. C. *J. Org. Chem*. **1998**, *63*, 2829. (c) Banks, M. R.; Dawson, I. M.; Gosney, I.; Hodgson, P. K. G.; Thorburn, P. *Tetrahedron Lett*. **1995**, *36*, 3567. (d) Murta, M. M.; de Azevedo, M. B. M.; Greene, A. E. *J. Org. Chem*. **1993**, *58*, 7537; and references cited therein. (e) Mawson, S. D.; Weavers, R. T. *Tetrahedron* **1995**, *51*, 11257.
(38) Park, B. K.; Nakagawa, M.; Hirota, A.; Nakayama, M. *J. Antibiot*. **1988**, *41*, 751.
(39) Sibi, M. P.; Deshpande, P. K.; La Loggia, A. J. *Synlett* **1996**, 343.
(40) For an example of a counterion-dependent alkylation, see Kigoshi, H.; Imamura, Y.; Yoshikawa, K.; Niwa, H.; Yamada, K. *Tetrahedron Lett*. **1991**, *32*, 4541; and references cited therein.
(41) Other reported syntheses of roccellaric acid and overall yields: (a) (–)-, 1.5% (14 steps) Mulzer, J.; Salimi, N.; Hartl, H. *Tetrahedron: Asymmetry* **1993**, *4*, 457. (b) (+)-, 18% (6 steps) Takahata, H.; Uchida, Y.; Momose, T. *J. Org. Chem*. **1995**, *60*, 5628.
(42) (a) Arcamone, F.; Franceschi, G.; Orezzi, P.; Cassinelli, G.; Barbieri, W.; Mondelli, R. *J. Am. Chem. Soc*. **1964**, *86*, 5334. (b) Arcamone, F.; Cassinelli, G.; Orezzi, P.; Franceschi, G.; Mondelli, R. *J. Am. Chem. Soc*. **1964**, *86*, 5335.
(43) Arcamone, F. *Topics in Antibiotic Chemistry;* Wiley: New York, NY, 1978; Vol. 2, pp 88–229.
(44) Gauze, G. F.; Kudrina, E. S.; Ukholina, R. S.; Gavrilina, G. V. *Antibiotiki* **1963**, *8*, 387; *Chem. Abstr*. **1965**, *62*, 5843e.
(45) Sibi, M. P.; Lu, J.; Edwards, J. *J. Org. Chem*. **1997**, *62*, 5864.
(46) (a) Bartroli, J.; Turmo, E.; Belloc, J.; Forn, J. *J. Org. Chem*. **1995**, *60*, 3000. (b) Reference 8.
(47) D'Souza, A. A.; Motevalli, M.; Robinson, A. J.; Wyatt, P. B. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1.
(48) (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, UK, 1992. (b) For a recent review, see Leonard, J.; Diez-Barra, E.; Merino, S. *Eur. J. Org. Chem*. **1998**, 2051.
(49) For a comparative study of chiral auxiliaries, see: (a) Andersson, P. G.; Schink, H. E.; Österlund, K. *J. Org. Chem*. **1998**, *63*, 8067. (b) Williams, D. R.; Kissel, W. S.; Li, J. J. *Tetrahedron Lett*. **1998**, *39*, 8593.
(50) For conjugate additions using oxazolidinone auxiliaries, see: Nicolás, E.; Russell, K. C.; Hruby, V. J. *J. Org. Chem*. **1993**, *58*, 766.
(51) (a) Stack, J. G.; Curran, D. P.; Geib, S. V.; Rebek, J., Jr.; Ballester, P. *J. Am. Chem. Soc*. **1992**, *114*, 7007. (b) Porter, N. A.; Scott, D. M.; Rosenstein, I. J.; Giese, B.; Veit, A.; Zeitz, H. G. *J. Am. Chem. Soc*. **1991**, *113*, 1791. (c) Reference 23.
(52) (a) Sibi, M. P.; Jasperse, C. P.; Ji, J. *J. Am. Chem. Soc*. **1995**, *117*, 10779. (b) Sibi, M. P.; Ji, J.; Sausker, J. B.; Jasperse, C. P. *J. Am. Chem. Soc*. **1999**, *121*, 7517.
(53) Sibi, M. P.; Ji, J. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 274.
(54) For NMR studies, see Lou, B-S.; Li, G.; Lung, F-D.; Hruby, V. J. *J. Org. Chem*. **1995**, *60*, 5509.
(55) Chen, C-M.; Jan, F-Y.; Chen, M-T.; Lee, T-J. *Heterocycles* **1989**, *29*, 411.
(56) Delle Monache, F.; Compagnone, R. S. *Phytochemistry* **1996**, *43*, 1097.
(57) Johnson, M. D. M.S. Thesis, North Dakota State University, Fargo, ND, 1999.
(58) (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc*. **1988**, *110*, 1238. (b) For a review, see Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475.
(59) Zirconium tetrachloride was shown to give inferior selectivity relative to diethylaluminum chloride. See reference 58.
(60) For another application of the auxiliary, see: Kang, H-Y.; Pae, A. N.; Cho, Y. S.; Koh, H. Y.; Chung, B. Y. *Chem. Commun*. **1997**, 821.

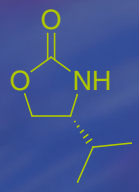
About the Author

Mukund Sibi hails from Bangalore, India. After undergraduate studies in Bangalore, he joined Hunter College, CUNY, and received his Ph.D. degree under the guidance of Prof. Robert Lichter. He carried out postdoctoral studies with Profs. Gordon Gribble (Dartmouth College), Victor Snieckus (University of Waterloo), and Robert Holton (Florida State University). He joined North Dakota State University in 1987, where he is currently Professor of Chemistry. His research interests include the development of new asymmetric processes, total synthesis of natural products, chiral catalysis, and nonfood uses of agricultural materials.

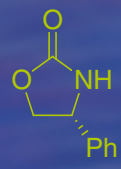
Oxazolidinone Chiral Auxiliaries



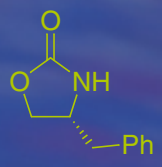
49,470-4



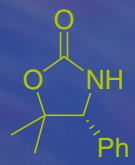
33,994-6



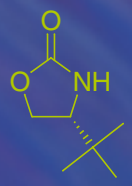
40,245-1



30,097-7



45,070-7



49,376-7

Chiral oxazolidinones similar to the one discussed by Professor Sibi in the preceding review, have found widespread use as auxiliaries in diasteroselective Michael additions, alkylations, aldol condensations, cyclopropanations, Diels–Alder, and other reactions. In addition, the auxiliaries are easily recycled under mild conditions, and most are available in bulk quantities. Aldrich offers a broad range of chiral oxazolidinones—a sampling is shown below—and amino alcohol precursors. Please call our Technical Services department at **800-231-8327** (USA) or visit us on the Web at www.sigma-aldrich.com to request your FREE copy of the *1998-99 Chiral Nonracemic Compounds* catalog.

For a recent review of the preparation, applications, and recycling of oxazolidinones, see Ager, D.J. et al. *Chem. Rev.* **1996**, *96*, 835.

49,470-4 *New!* **(*R*)-(+)-4-(Diphenylmethyl)-2-oxazolidinone**, 98%
49,469-0 *New!* **(*S*)-(−)-4-(Diphenylmethyl)-2-oxazolidinone**, 97%
33,994-6 **(*R*)-(+)-4-Isopropyl-2-oxazolidinone**, 99% (99% ee/GLC)
29,888-3 **(*S*)-(−)-4-Isopropyl-2-oxazolidinone**, 99% (98% ee/GLC)
40,245-1 **(*R*)-(−)-4-Phenyl-2-oxazolidinone**, 98%
37,669-8 **(*S*)-(+)-4-Phenyl-2-oxazolidinone**, 98%
30,097-7 **(*R*)-(+)-4-Benzyl-2-oxazolidinone**, 99%
29,464-0 **(*S*)-(−)-4-Benzyl-2-oxazolidinone**, 99%
45,070-7 **(*R*)-(−)-5,5-Dimethyl-4-phenyl-2-oxazolidinone**, 98% (99% ee/HPLC)
45,071-5 **(*S*)-(+)-5,5-Dimethyl-4-phenyl-2-oxazolidinone**, 98% (99% ee/HPLC)
49,376-7 *New!* **(*R*)-(+)-4-*tert*-Butyl-2-oxazolidinone**, 99%
44,051-5 **(*S*)-(−)-4-*tert*-Butyl-2-oxazolidinone**, 99%
29,889-1 **(4*R*,5*S*)-(+)-4-Methyl-5-phenyl-2-oxazolidinone**, 99% (99% ee/GLC)
34,052-9 **(4*S*,5*R*)-(−)-4-Methyl-5-phenyl-2-oxazolidinone**, 99% (99% ee/HPLC)
45,454-0 **(4*R*,5*S*)-(+)-*cis*-4,5-Diphenyl-2-oxazolidinone**, 98%
44,744-7 **(4*S*,5*R*)-(−)-*cis*-4,5-Diphenyl-2-oxazolidinone**, 98%
45,066-9 **(*R*)-(+)-4-Isopropyl-5,5-dimethyl-2-oxazolidinone**, 98%
45,067-7 **(*S*)-(−)-4-Isopropyl-5,5-dimethyl-2-oxazolidinone**, 98%
46,397-3 **(3a*S*-*cis*)-(−)-3,3a,8,8a-Tetrahydro-2*H*-indeno[1,2-*d*]oxazol-2-one**, 98% (99%ee/HPLC)
46,396-5 **(3a*R*-*cis*)-(+)-3,3a,8,8a-Tetrahydro-2*H*-indeno[1,2-*d*]oxazol-2-one**, 97% (99%ee/HPLC)
49,604-9 *New!* **(*S*)-(+)-4-(1*H*-Indol-3-ylmethyl)-2-oxazolidinone**, 98%
49,603-0 *New!* **(*R*)-(−)-4-(1*H*-Indol-3-ylmethyl)-2-oxazolidinone**, 98%

Some Other Products Mentioned in Professor Sibi's Review:

41,220-1 **L-Serine methyl ester hydrochloride**, 98%
12,423-0 ***tert*-Butyl bromoacetate**, 98%
19,035-7 **(*R*)-(−)-2-Phenylglycinol**, 98% (99% ee/GLC)
33,075-2 **Triphosgene**, 98%
D8,000-2 **1,3-Dicyclohexylcarbodiimide**, 99%
27,141-1 **Allyltributyltin**, 97%
26,147-5 **Dibutylboron triflate**, 1.0*M* solution in dichloromethane
23,050-2 **Copper(I) bromide-dimethyl sulfide complex**, 99%
17,875-6 **Diphenylphosphoryl azide**, 97%

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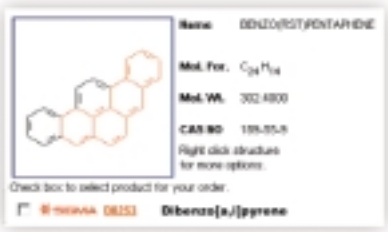

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   - ❒ Food/Beverage (FDBEV)
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   - ❒ Pharmaceutical Co. (PHARM)
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Heterocyclic Chemistry

3rd ed., J.A. Joule, K. Mills, and G. Smith, Chapman and Hall, New York, NY, 1995, 448pp. Softbound. General discussion of structures, properties and reactivity of aromatic heterocycles. Detailed review of reactions and synthesis.

Z25,750-8

Kirk-Othmer Concise Encyclopedia of Chemical Technology

4th ed., M. Grayson and D. Eckroth, Eds., John Wiley & Sons, New York, NY, 1999, 2,196pp. Hardcover. This abridged version of a 28-volume set contains information about 1,100 topics of interest to chemists.

Z41,246-5

Protective Groups in Organic Synthesis

3rd ed., T.W. Greene and P.G.M. Wuts, John Wiley & Sons, New York, NY, 1999, 784pp. Hardcover. Details the use of protecting groups in synthetic organic chemistry. Expanded by more than 50%, providing readers with a compendium of 1,050 of the most useful protective groups as well as 5,350 references to original publications.

Z41,242-2

Strategies for Organic Drug Synthesis and Design

D. Lednicer, John Wiley & Sons, New York, NY, 1997, 500pp. Hardcover. Ideal for anyone learning or working in organic, medicinal, or pharmaceutical chemistry today, this work offers a clear examination of the synthetic routes followed to prepare a range of compounds with assigned generic names. With drugs selected for the illustrative value of the chemistry used for synthesis, the book describes a great variety of organic transformations and structural classes of compounds.

Z40,856-5

Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides

M.P. Doyle, M.A. McKervey, and T. Ye, John Wiley & Sons, New York, NY, 1998, 652pp. Hardcover. This resource brings together a wealth of procedures for the synthesis and practical use of diazocarbonyl compounds. It features methods for the preparation of important catalysts and for applications of diazocarbonyl compounds within each of the main transformation categories—including in-depth coverage of cyclopropanation, C–H and X–H insertion, Wolff rearrangement, ylide formation, aromatic cycloaddition and substitution, and many other useful reactions.

Z40,857-3

Introduction to Medicinal Chemistry: How Drugs Act and Why

A. Gringauz, John Wiley & Sons, New York, NY, 1997, 736pp. Hardcover. Integrates the chemical and pharmacological aspects of drugs, and links the sciences of organic chemistry, biochemistry, and biology with the clinical areas required for a thorough understanding of modern medicinal drugs.

Z42,066-2

Fiesers' Reagents for Organic Synthesis, Vol. 19

T.-L. Ho, Ed., John Wiley & Sons, New York, NY, 2000, 504pp. Hardcover. The latest volume in this series offers an update of the reagent literature through 1996.

Z42,164-2

Chemistry and Technology of Isocyanates

H. Ulrich, John Wiley & Sons, New York, NY, 1997, 514pp. Hardcover. Highlights the syntheses, reactions, and applications of mono- and diisocyanates.

Z40,213-3

Troubleshooting HPLC Systems: A Bench Manual

P. Sadek, John Wiley & Sons, New York, NY, 1999, 320pp. Hardcover. Provides highly practical guidance on the use, maintenance, and troubleshooting of HPLC systems for all chemical analysts regardless of their levels of experience.

Z42,175-8

α-Hydroxy Acids in Enantioselective Syntheses

G.M. Coppola and H.F. Schuster, Wiley-VCH, Weinheim, Germany, 1997, 513pp. Hardcover. Chiral α-hydroxy acids available from nature's chiral pool serve as starting materials in a wide variety of enantioselective conversions leading to commercially important products. This monograph, a stimulating source of ideas and an essential reference work for research chemists, focuses on the well-known lactic, mandelic, malic, and tartaric acids. Examples show how chiral centers inherent in these simple compounds can be used to control the introduction of further stereogenic centers. Readers can directly apply new transformations in their own work, since reaction conditions are given in handy tables.

Z40,864-6

Stereoselectivity in Synthesis

T.-L. Ho, John Wiley & Sons, New York, NY, 1999, 448pp. Hardcover. Shows how to choose the best method for a given synthesis. Provides readers with a thorough understanding of stereoselectivity in organic and medicinal chemistry as well as the pharmaceutical, agricultural, and food industries.

Z41,243-0

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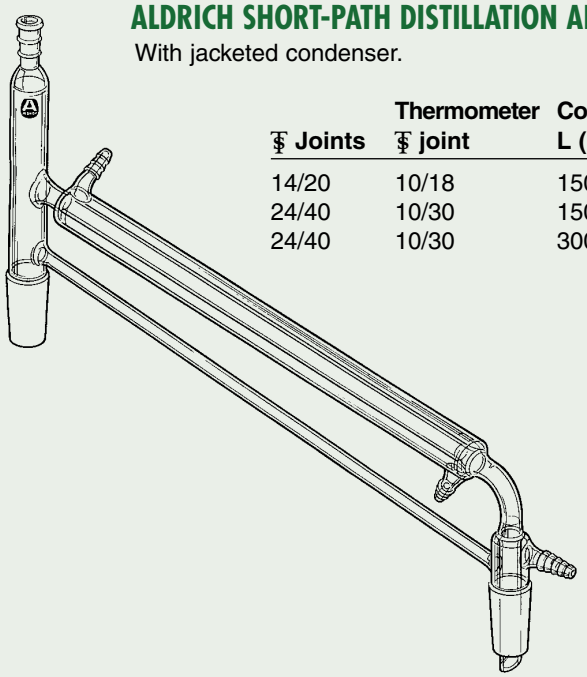
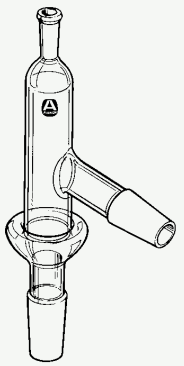
ALDRICH SHORT-PATH DISTILLATION APPARATUS

With jacketed condenser.



Joints	Thermometer joint	Condenser L (mm)	Cat. No.
14/20	10/18	150	**Z41,552-9**
24/40	10/30	150	**Z41,553-7**
24/40	10/30	300	**Z41,554-5**



ALDRICH ANTI-CREEP DISTILLATION HEADS

Prevent creeping and flooding during distillations.

Joints	Thermometer joint	Cat. No.
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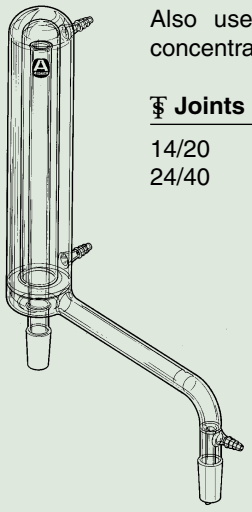
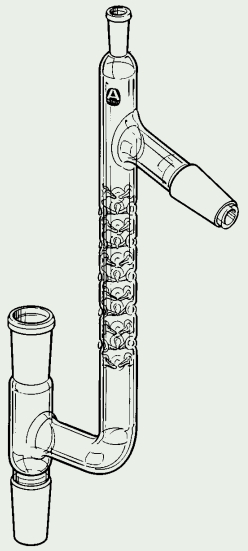
24/40	10/30	**Z41,556-1**



ALDRICH WATER-COOLED DISTILLATION HEADS

Also useful for removing solvents from reaction mixtures or concentrating solutions prior to crystallization.

Joints	Cat. No.
14/20	**Z41,548-0**
24/40	**Z41,549-9**



ALDRICH CLAISEN DISTILLATION HEADS

With Vigreux indents.

Joints	Thermometer joint	Cat. No.
14/20	10/18	**Z41,550-2**
24/40	10/30	**Z41,551-0**

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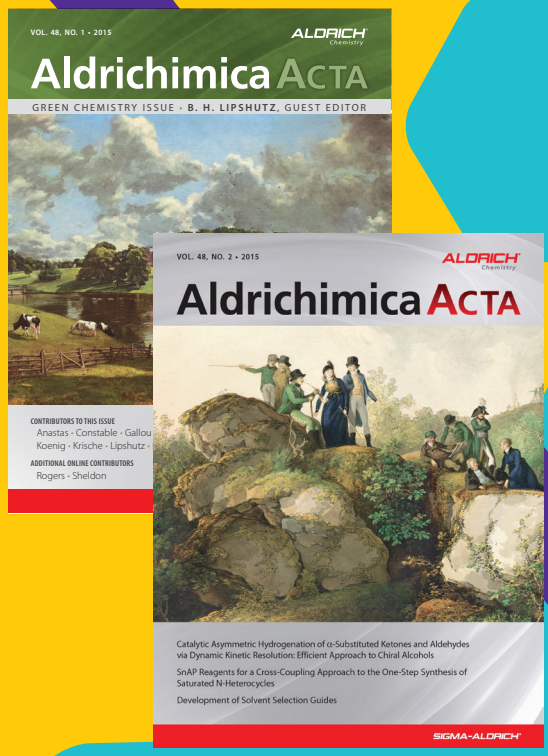

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