dures. The X-ray structure determination was carried out by Dr. Kennard (Small Molecule X-Ray Diffraction Laboratory) at The University of Queensland.

Supplementary Material Available: Spectroscopic characterization of the reduction products of individual isomers of 2,8-dimethyl-1,7-dioxaspiro[5.5]undec-4-en-3-one (**23**) and of the *Z,E* and *E,Z* isomers of **3**, low-resolution mass spectral data of compounds **3**, **9**, **13**, **14**, **20**, **21**, **23–26**, **41–48**, **51–57**, and **59**, ^1H and/or ^{13}C NMR spectra for compounds **3**, **13–15**, **21–26**, **41–48**, **51**, **52**, **55–57**, and **59** and reduction product of **52** isomer **1**, and crystallography for (*E,E*)-(2*R*,6*S*,8*R*)-4-oxo-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (**49**) (59 pages). Ordering information is given on any current masthead page.

Enantioselective Synthesis of 2-Alkyl-5-methylene-1,3-dioxolan-4-ones and Exo-Selective Diels–Alder Reactions with Cyclopentadiene

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Highly stereoselective syntheses of chiral dienophiles (*R*)-**1** and (*R*)-**2** are described. Diazotization of L-serine in the presence of HCl and then treatment of the resulting β-hydroxy-α-chloropropionic acid (*S*)-**7** with KOH provides potassium glycidate ((*R*)-**8**) in good yield and high enantiomeric purity. Treatment of (*R*)-**8** with PhSH in MeOH then provides α-hydroxy acid (*S*)-**10** that can be purified by recrystallization. Condensation of (*S*)-**10** with either pivalaldehyde or cyclohexanecarboxaldehyde followed by oxidation to the sulfone and DBU-promoted elimination of benzenesulfinic acid then provides dienophiles (*R*)-**1** and (*R*)-**2**, respectively. Highly exo-selective Diels–Alder reactions of (*R*)-**1** and (*R*)-**2** with cyclopentadiene are also described. The major cycloadduct (−)-**15** (94% of total) from the Diels–Alder reaction of **1** was shown to have an enantiomeric purity of ≥99% ee. This figure defines the lower limit of enantiomeric purity of (*R*)-**1**. The diastereofacial selectivity of the Diels–Alder reactions of **1** in the exo manifold (50:1) is greater than that of **2** (20:1), as would be expected on the basis of the different steric requirements of the *tert*-butyl and cyclohexyl substituents of the two reagents. Consequently, dienophile **1** is the preferred reagent for complex synthetic applications, either as a chiral ketene equivalent or in contexts in which the α-hydroxy acid functionality will be preserved in the ultimate synthetic target. Finally, the possible role of dipole effects on the exo selectivity of the Diels–Alder reactions of these and related dienophiles are briefly discussed.

In connection with work on the synthesis of kijanolide, tetronolide, and chlorothricolide, we developed the chiral 5-methylene-1,3-dioxolan-4-ones **1** and **2** for use in asymmetric Diels–Alder constructions of the spiro tetronate top-half fragments.[1,2] We have previously reported syntheses of racemic **1** and **2** and the application of racemic **2** in a highly stereoselective synthesis of kijanolide intermediate **5** by way of the remarkable exo-selective Diels–Alder reaction with triene **3** (Scheme I).[1i,3] We report herein enantioselective syntheses of (*R*)-**1** and (*R*)-**2** and the Diels–Alder reactions with cyclopentadiene that serve to define the enantiomeric purity, the diastereofacial selectivity, and the absolute configuration of these novel, chiral dienophiles.[4]

Racemic **1** was first prepared in our laboratory in 1985 from methyl glycidate by using the sequence reported in our preliminary communication.[3,5] The exo-selective Diels–Alder reaction with cyclopentadiene was also fully characterized at that time. While further developments and synthetic applications of this Diels–Alder methodology were still in progress, Seebach described the enantioselective syntheses of (*S*)-**1** from (*S*)-lactic acid by the sequence shown below.[6] Mattay and co-workers subsequently described the Diels–Alder reactions of (*S*)-**1** with cyclopentadiene and several hetero dienes.[7] While Seebach's synthesis of **1** is very direct, it suffers in that the condensation of (*S*)-lactic acid and pivalaldehyde generates a 4:1 mixture of diastereomeric acetals from which the

(1) Studies on the synthesis of kijanolide and tetronolide: (a) Takeda, K.; Kato, H.; Sasahara, H.; Yoshii, E. *J. Chem. Soc., Chem. Commun.* **1986**, 1197. (b) Marshall, J. A.; Grote, J.; Shearer, B. *J. Org. Chem.* **1986**, *51*, 1633. (c) Takeda, K.; Urahata, M.; Yoshii, E.; Takayanagi, H.; Ogura, H. *Ibid.* **1986**, *51*, 4735. (d) Takeda, K.; Yano, S.; Sato, M.; Yoshii, E. *Ibid.* **1987**, *52*, 4135. (e) Marshall, J. A.; Grote, J.; Audia, J. E. *J. Am. Chem. Soc.* **1987**, *109*, 1186. (f) Takeda, K.; Kobayashi, T.; Saito, K.; Yoshii, E. *J. Org. Chem.* **1988**, *53*, 1092. (g) Takeda, K.; Yano, S.; Yoshii, E. *Tetrahedron Lett.* **1988**, *29*, 6951. (h) Roush, W. R.; Brown, B. B.; Drozda, S. E. *Ibid.* **1988**, *29*, 3541. (i) Roush, W. R.; Brown, B. B. *Ibid.* **1989**, *30*, 7309. (j) Marshall, J. A.; Salovich, J. M.; Shearer, B. G. *J. Org. Chem.* **1990**, *55*, 2398. (k) Boeckman, R. K., Jr.; Barta, T. F.; Nelson, S. G. *Tetrahedron Lett.* **1991**, *32*, 4091. (l) Boeckman, R. K., Jr.; Estep, K. G.; Nelson, S. G.; Walters, M. S. *Ibid.* **1991**, *32*, 4095. (j) For the first total synthesis of tetronolide: Takeda, K.; Kawanishi, E.; Nakamura, H.; Yoshii, E. *Ibid.* **1991**, *32*, 4925.

(2) Studies on the synthesis of chlorothricolide: (a) Ireland, R. E.; Thompson, W. J. *J. Org. Chem.* **1979**, *44*, 3041. (b) Ireland, R. E.; Thompson, W. J.; Srouji, G. H.; Etter, R. *Ibid.* **1981**, *46*, 4863. (c) Hall, S. E.; Roush, W. R. *J. Org. Chem.* **1982**, *47*, 4611. (d) Snider, B. B.; Burbaum, B. W. *Ibid.* **1983**, *48*, 4370. (e) Schmidt, R. R.; Hirsenkorn, R. *Tetrahedron Lett.* **1984**, *25*, 4357. (f) Marshall, J. A.; Audia, J. E.; Grote, J. *J. Org. Chem.* **1984**, *49*, 5277. (g) Boeckman, R. K., Jr.; Barta, T. E. *Ibid.* **1985**, *50*, 3421. (h) Roush, W. R.; Kageyama, M. *Tetrahedron Lett.* **1985**, *26*, 4327. (i) Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1986**, *51*, 635. (j) Marshall, J. A.; Audia, J. E.; Shearer, B. G. *Ibid.* **1986**, *51*, 1730. (k) Marshall, J. A.; Audia, J. E.; Grote, J.; Shearer, B. G. *Tetrahedron*, **1986**, *42*, 2893. (l) Marshall, J. A.; Shearer, B. G.; Crooks, S. L. *J. Org. Chem.* **1987**, *52*, 1236. (m) Roush, W. R.; Riva, R. *Ibid.* **1988**, *53*, 710. (n) Danishefsky, S. J.; Audia, J. E. *Tetrahedron Lett.* **1988**, *29*, 1371. (o) Okumura, K.; Okazaki, K.; Takeda, K.; Yoshii, E. *Ibid.* **1989**, *30*, 2233. (p) Poss, A. J.; Brodowski, M. H. *Ibid.* **1989**, *30*, 2505. (q) Roth, G. P.; Rithner, C. D.; Meyers, A. I. *Tetrahedron* **1989**, *45*, 6949. (r) Total synthesis of (±)-24-*O*-methylchlorothricolide: Takeda, K.; Igarashi, Y.; Okazaki, K.; Yoshii, E.; Yamaguchi, K. *J. Org. Chem.* **1990**, *55*, 3431. (s) Schmidt, R. R.; Hirsenkorn, R. *Liebigs Ann. Chem.* **1990**, 883. (t) Hirsenkorn, R.; Haag-Zeino, B.; Schmidt, R. R. *Tetrahedron Lett.* **1990**, *31*, 4433. (u) Roush, W. R.; Kageyama, M.; Riva, R.; Brown, B. B.; Warmus, J. S.; Moriarty, K. J. *J. Org. Chem.* **1991**, *56*, 1192.

(3) Roush, W. R.; Essenfeld, A. P.; Warmus, J. S.; Brown, B. B. *Tetrahedron Lett.* **1989**, *30*, 7305.

(4) For a review of asymmetric Diels–Alder reactions: Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876.

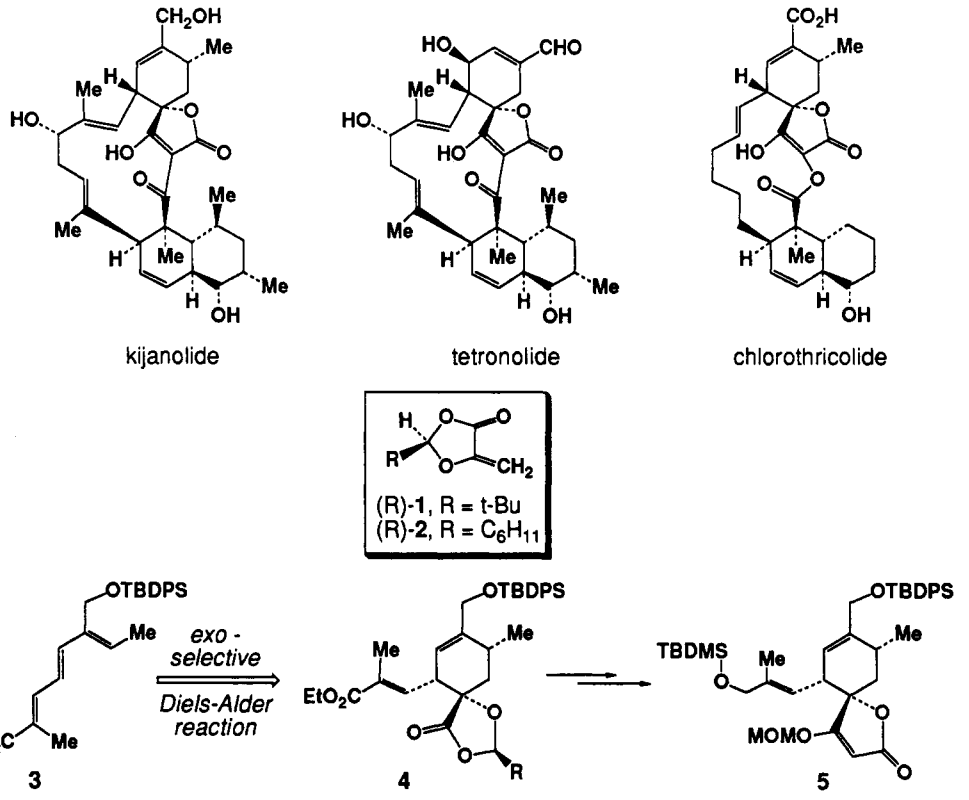
(5) The synthesis of racemic **1** and the Diels–Alder reaction with cyclopentadiene are described in the 1985 Ph.D. Thesis of A. P. Essenfeld, M.I.T., Cambridge, MA (text pages 108–119; experimental section pages 161–175).

(6) (a) Zimmermann, J.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1104. (b) Details of the preparation of **6**: Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313. (c) For an improved method of synthesis of **6** with 97:3 diastereoselectivity: Chapel, N.; Greiner, A.; Ortholand, J.-Y. *Tetrahedron Lett.* **1991**, *32*, 1441.

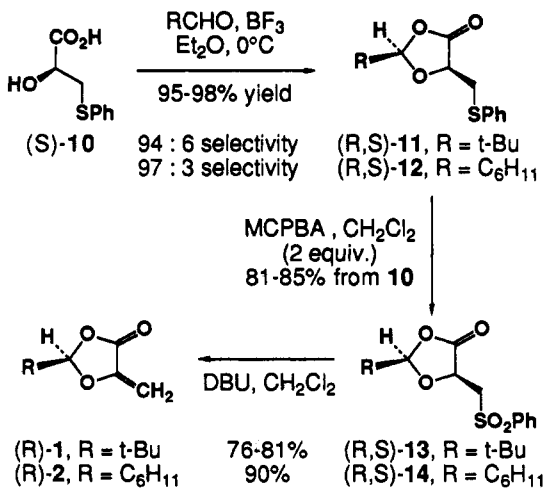
(7) (a) Mattay, J.; Mertes, J.; Maas, G. *Chem. Ber.* **1989**, *122*, 327. (b) Mattay, J.; Kneer, G.; Mertes, J. *SynLett* **1990**, 145.

0022-3263/92/1957-3380$03.00/0

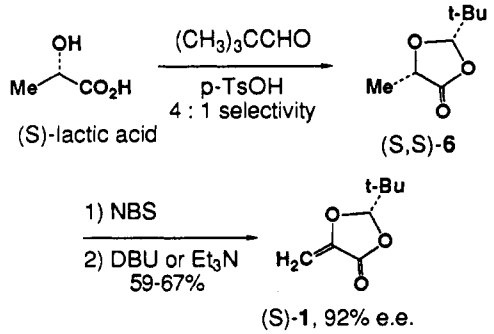
Scheme I



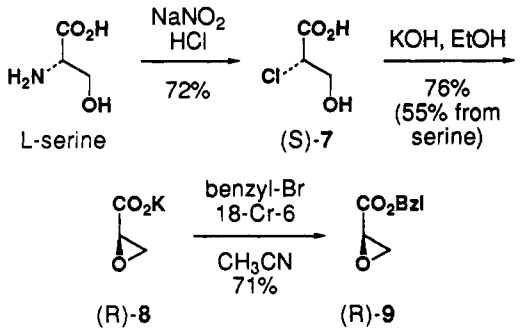
Scheme II



major isomer (*S,S*)-**6** is obtained with a purity of only 92% de following two recrystallizations from ether/hexane at −78 °C.[6b] Consequently, the enantiomeric purity of **1**, and of subsequent Diels–Alder adducts, is limited to a maximum of 92% ee when prepared by this route.[7a]



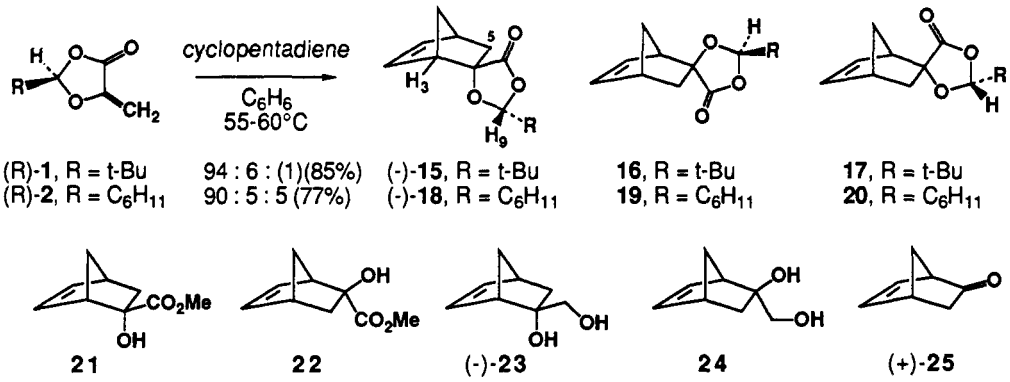
Our syntheses of (*R*)-**1** and (*R*)-**2** proceed via potassium (*R*)-glycidate (**8**), which we prepared from L-serine by adaptation of the method reported by Larchevêque and Petit.[8a] Thus, deamination of L-serine with $NaNO_2$ and HCl provided (*S*)-2-chloro-3-hydroxypropionic acid (**7**) in 72% yield.[8b] Treatment of (*S*)-**7** with KOH in ethanol at 0 °C then gave the known potassium (*R*)-glycidate (**8**) in 55% overall yield from L-serine following recrystallization from absolute methanol.[8a] In initial stages of this work, potassium salt **8** was treated with benzyl bromide and 18-crown-6 in acetonitrile to provide benzyl (*R*)-glycidate (**9**) in good yield.[8a]



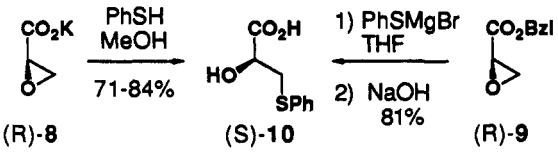
Hydroxy acid (*S*)-**10** was prepared initially by using a procedure analogous to that employed in our synthesis of racemic **1** and **2**.[3] Thus, glycidic ester (*R*)-**9** underwent regioselective (ca. 20:1) substitution when treated with in situ generated (phenylthio)magnesium bromide in THF at 0 °C. The intermediate α-hydroxy benzyl ester was then saponified with aqueous sodium hydroxide in methanol, yielding (*S*)-**10** as a white crystalline solid in 81% overall yield. Whitesides, however, reported that potassium gly-

(8) (a) Larchevêque, M.; Petit, Y. *Tetrahedron Lett.* **1987**, *28*, 1993. (b) For the diazotization of serine in the presence of HCl, see also: Lok, C. M.; Ward, J. P.; van Dorp, D. A. *Chem. Phys. Lipids* **1976**, *16*, 115.

Scheme III



cidate undergoes an analogous substitution reaction when treated with thiophenol in methanol.[9] In our hands, this reaction provided (*S*)-**10** with 7–8:1 regioselectivity. The minor regioisomer may be removed by recrystallization of **10** from benzene–hexane. However, the minor isomer does not complicate the subsequent condensation with aldehydes, and consequently it is not necessary that (*S*)-**10** be rigorously purified for preparative purposes. Accordingly, (*S*)-**10** is readily available by a simple three-step sequence from L-serine, and conversion of potassium (*R*)-glycidate (**8**) to the intermediate benzyl ester (*R*)-**9** is not necessary.



The enantiomeric purity of hydroxy acid (*S*)-**10**, prepared either from benzyl ester (*R*)-**9** or via Whitesides' one-step conversion of potassium glycidate (*R*)-**8**, was determined to be ≥99% ee by Mosher ester analysis of the derived methyl esters (prepared by esterification of **10** with diazomethane).[10]

Treatment of isomerically pure α-hydroxy acid (*S*)-**10** with pivalaldehyde and $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at 0 °C provided a 94:6 mixture of (*R,S*)-**11** and the trans diastereomer in ≥95% yield.[11] Similarly, condensation of (*S*)-**10** with cyclohexanecarboxaldehyde provided (*R,S*)-**12** and the trans diastereomer as a 97:3 mixture, again in ≥95% yield. The yield of **11** was 85–90% from experiments in which ca. 90% isomerically pure **10** was employed (Scheme II). In our initial studies with racemic compounds, the cis isomer of **11** was separated from the minor trans diastereomer by recrystallization.[3,5] However, since purification is easily accomplished at the stage of the sulfones **13**/**14**, optically active sulfides (*R,S*)-**11** and (*R,S*)-**12** were generally converted directly to the corresponding sulfones without purification. Thus, oxidation of (*R,S*)-**11** and (*R,S*)-**12** with 2 equiv of MCPBA in CH_2Cl_2 at 25 °C provided sulfones (*R,S*)-**13** and (*R,S*)-**14** that are easily purified to ≥99% de by recrystallization from ethyl acetate/hexane.[12] The overall yield of ≥99% diastereomerically pure **13** and **14** is 69–76% yield from (*S*)-**10** (81–85% if isomerically pure **10** is used). Finally, enantiomerically pure dienophiles (*R*)-**1** and (*R*)-**2** were prepared in 76–90% yield by treating sulfones (*R,S*)-**13** and (*R,S*)-**14** with DBU in CH_2Cl_2. The variability of yield is greatest with (*R*)-**1**, which is considerably more volatile than (*R*)-**2**. We have found that dienophiles **1** and **2** are not stable to prolonged storage. Consequently, they generally are generated and then used immediately in subsequent Diels–Alder reactions.

The Diels–Alder reactions (*R*)-**1** and (*R*)-**2** with excess cyclopentadiene in benzene at 55–60 °C served to define the enantiomeric purity, diastereofacial selectivity, and absolute configuration of these dienophiles (Scheme III). The reaction of **1** provided **15** and **16** as the only detected products in a ratio of 94:6 (capillary GC analysis; the ratio is 93:7 when the Diels–Alder reaction is performed at 80 °C). The reaction with **2** also appeared to provide only two products, **18** and **19**, in a ratio of 96:4 by 300-MHz ^1H NMR analysis and 95:5 by capillary GC analysis. HPLC analysis of the crude product obtained from cyclopentadiene and **2** also revealed only two separable bands. Careful analysis of the 400-MHz ^1H NMR spectrum, however, revealed a small amount (ca. 5%) of a third diastereomer that we believe to be **20**. The olefinic resonances for **20** are observable in the 400-MHz ^1H NMR spectrum but not in spectra measured at 300 MHz since they overlap with and are obscured by the olefinic resonances of **18**. Evidence subsequently presented suggests that roughly 1–2% of **17** is also produced in the reaction with **1**. This minor diastereomer, however, escaped our direct spectroscopic detection.

The major cycloadducts **15** and **18** were shown to be exo adducts by conversion of unseparated reaction mixtures (racemic series) to corresponding mixtures of methyl esters **21** and **22** upon treatment with K_2CO_3 in MeOH (0 °C, 4 h).[13] An authentic sample of the endo diastereomer **22**, corresponding to the minor component of the **21**/**22** mixtures, was prepared by hydroxylation of the sodium enolate of methyl norbornene-4-carboxylate [$(NaN(SiMe_3)_2$, 2-(phenylsulfonyl)-3-phenyloxaziridine].[13,14] The stereochemistry of the acetal center in **15** was assigned on the basis of an NOE enhancement (12%) of H_3, but not either of the hydrogens at H_5, upon irradiation of the acetal proton H_9.[5] This analysis is in complete agreement with

(9) Hirschbein, B. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1982**, *104*, 4458.

(10) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(11) (a) For a review of the synthesis and synthetic applications of chiral 1,3-dioxalan-4-ones and related heterocycles: Seebach, D.; Imwinkelried, R.; Weber, T. *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Verlag: Berlin, 1986; Vol. 4, p 125. (b) See also ref 6b for additional examples of the condensation of aldehydes and α-hydroxy acids. (c) For the condensation of aldehydes and hydroxy acids using BF_3 etherate: Mashraqui, S. H.; Kellogg, R. M. *J. Org. Chem.* **1984**, *49*, 2513 and references therein.

(12) The cis and trans diastereomers of **13** are also easily separable by chromatography. This method has been employed by a co-worker who, in one experiment, obtained a ca. 5–6:1 mixture of the cis and trans diastereomers of **11** from the condensation of (*S*)-**10** and pivalaldehyde.

(13) These experiments were performed with racemic materials as described in refs 3 and 5.

(14) (a) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346. (b) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241.

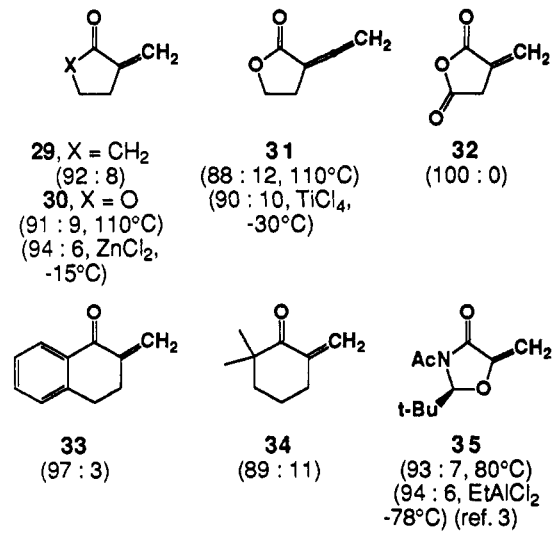
the X-ray structure reported for (+)-15 by Mattay and co-workers.[7a] The stereochemistry of the endo adducts 16/19 is assigned by analogy to 15/18.

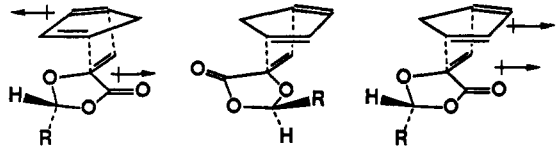
The enantioselectivity of these Diels–Alder reactions was determined following $LiAlH_4$ reduction to diol 23. Mattay and co-workers have previously established the absolute configuration of (+)-23, prepared from (+)-15 deriving from the Diels–Alder reaction with 92% ee (S)-1, by periodate cleavage to the (+)-enantiomer of the known norbornenone 25.[7a,15] The 400-MHz ^1H NMR spectrum of the Mosher ester derivative prepared from racemic 23 displays an AB pattern for the CH_2OMTPA resonance of one diastereomer (δ 4.57 and 4.46, $J_{A,B}$ = 11.3 Hz), whereas the CH_2OMTPA resonance for the second diastereomer appears as an apparent singlet at δ 4.52. Enantiomeric excesses are easily determined by integrating this region of the spectrum. Thus, reduction of chromatographically purified exo cycloadduct (−)-15 provided (−)-23 ($[\alpha]_D$ −122.2° (c = 1.67, $CHCl_3$)) that proved to have an enantiomeric purity of 99% ee according to this method of analysis. *This result indicates that dienophile 1 must have an enantiomeric purity of at least 99% ee.* The crude Diels–Alder reaction mixture was reduced and diol (−)-23 was purified chromatographically in order to assess whether the second exo diastereomer 17 was also produced but escaped spectroscopic detection. This material proved to have an enantiomeric purity of 96% ee. Consequently, we conclude that 1–2% of diastereomer 17 is probably produced in the Diels–Alder reaction of (R)-1.

A parallel set of experiments was performed with 18 and the crude mixture of cycloadducts from the reaction of (R)-2 and cyclopentadiene. Although chromatographically purified (−)-18 appears as a single band by analytical HPLC, the 400-MHz ^1H NMR spectrum of this material revealed that is contained 2% of the second diastereomer presumed to be 20. Reduction of this material provided (−)-23 in 96% ee by Mosher ester analysis. Finally, reduction of the unseparated mixture of cycloadducts provided (−)-23 with an enantiomeric purity of 90% ee.

The results presented above establish that dienophiles (R)-1 and (R)-2 prepared from L-serine have enantiomeric purities of ≥99% ee and that ≤1% racemization of 1 and 2 occurs during the Diels–Alder reactions with cyclopentadiene. The absolute stereostructures established for (−)-15 and (−)-18 indicate that exo transition state 26 is the lowest energy transition structure available to this system. The greater diastereofacial selectivity of (R)-1 (≥50:1) compared to (R)-2 (20:1) is consistent with the different steric requirements of the "R" substituents in the pair of exo transition states 26 and 27.[11] Erosion of exo-diastereofacial selectivity has also been observed in Diels–Alder reactions leading to the top-half fragments of kijanolide, tetronolide, and chlorothricolide when 2, but not 1, is employed as the chiral dienophile.[16] Consequently, *tert*-butyl-substituted dienophile 1 is the preferred reagent for synthetic applications owing to its greater diastereofacial selectivity.

Chart I. Exo-Selective Diels–Alder Reactions with Cyclopentadiene: Ratios of Exo to Endo Cycloadducts (ref 19)





An extremely interesting aspect of the Diels–Alder reactions of 1 and 2 is the significant preference for exo cycloaddition. We have observed excellent selectivity with 1 and 2 and several classes of dienes including highly functionalized trienes like 3.[1i,3] While several *conformational flexible* α-oxygenated and other α-substituted dienophiles are known to display a modest preference for the exo cycloadduct,[17,18] the level of exo selectivity almost always falls significantly below the level observed with 1 and 2.[1i,3,7,16] The very high preference for exo cycloaddition with 1, 2, and related dienophiles[3,19,20] appears to correlate with the *conformationally restricted* (S)-*cis enone*. Indeed, Buono and co-workers have recently summarized data for the Diels–Alder reactions of cyclopentadiene and several α-methylene lactones and α-methylene cyclic ketones 29–34 (Chart I), each of which provides excellent exo selectivity under thermal *or* Lewis acid catalyzed conditions.[19,20] Lewis acid catalyzed Diels–Alder reactions of 1 and 35 are also known to proceed with excellent exo selectivity.[3,7a] These observations are significant, indicating that increased secondary orbital interactions in the Lewis acid catalyzed reactions are incapable of increasing the preference for the endo products. It is perhaps necessary to reopen the question of whether secondary orbital effects are solely responsible for the observed stereoselectivity in Diels–Alder reactions.

We speculate that the preference for exo cycloaddition with these dienophiles (1, 2, 29–35) may be due to the

(15) For other syntheses of 25 and the confirmation of absolute stereochemistry: (a) Oppolzer, W.; Chapius, C.; Dupuis, D.; Guo, M. *Helv. Chim. Acta* **1985**, *68*, 2100. (b) Le Drian, C.; Greene, A. E. *J. Am. Chem. Soc.* **1982**, *104*, 5473 and references therein.

(16) We previously reported that the Diels–Alder reaction of racemic 2 and triene 3 provided an 8–9:1 mixture of 4 (R = C_6H_{11}, deriving from exo transition state 26) and the corresponding endo cycloadduct assumed to derive from TS 28. In fact, however, the minor product is the second exo diastereomer arising via a TS analogous to 27. Repetition of this experiment with the optically active dienophile (R)-1, however, provided a 13–14:1 mixture of 4 (R = *t*-Bu) and the endo cycloadduct. The second exo cycloadduct, deriving from *exo*-27, has not been observed in this reaction. Similar results have been observed in Diels–Alder reactions leading to the top halves of chlorothricolide and tetronolide. Details of these observations will be reported in due course (Roush, W. R.; Brown, B. B.; Sciotti, R. J. Unpublished research).

(17) Creary, X.; Inocencio, P. A.; Underiner, T. L.; Kostromin, R. *J. Org. Chem.* **1985**, *50*, 1932, and references 5–7 cited therein.

(18) Berson, J. A.; Hamlet, J.; Mueller, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 297.

(19) Fotiadu, F.; Michel, F.; Buono, G. *Tetrahedron Lett.* **1990**, *31*, 4863.

(20) α-Methylene β-lactones have also recently been observed to undergo exo-selective Diels–Alder reactions with cyclopentadiene: Adam, W.; Albert, R.; Hasemann, L.; Nava Salgado, V. O.; Nestler, B.; Peters, E.-M.; Peters, K.; Prechtl, F.; von Schnering, H. G. *J. Org. Chem.* **1991**, *56*, 5782.

difference in dipole moment in the exo vs the endo transition states.[21] Such arguments were presented nearly 20 years ago by Berson and co-workers in their detailed analysis of the stereoselectivity and solvent dependence of the Diels–Alder reactions of cyclopentadiene and methyl acrylate, methyl methacrylate, and methyl crotonate.[18] They concluded that "the permanent dipole moment of the endo transition state is greater than that of the exo" and established a new solvent polarity constant based on the solvent dependence of the exo/endo ratio (increased exo selectivity in low polarity media). Buono's data for the Diels–Alder reactions of **31** and cyclopentadiene are consistent with this hypothesis: 88:12 exo:endo in toluene; 87:13 in CH_2Cl_2; and 79:21 in water.[19]

If the dipole moment hypothesis is correct, it follows that the exo transition state **26** is lower in energy than *endo*-**28** since the dipoles associated with the diene and dienophile are aligned in **28**, leading to a much larger net dipole than in *exo*-**26** where the two dipoles cancel to a large extent since they are more or less anti-parallel. Exo stereoselectivity is less dramatic with dienophiles like α-methoxy or α-acetoxy acrylates,[17] or even methacrylates,[18] since both the s-cis and the s-trans enoate rotamers should be reactive and the dipole contribution of each rotamer to the respective transition states will probably be different. That is, the product distribution for Diels–Alder reactions of a conformationally unconstrained α-substituted dienophile will be the result of four transition states (s-cis-exo; s-trans-exo; s-cis-endo and s-trans-endo) and not simply two as is the case with **1**, **2**, and **29–35**.

In conclusion, highly stereoselective syntheses of chiral dienophiles (*R*)-**1** and (*R*)-**2** have been developed. The reagents undergo remarkably exo-selective Diels–Alder reactions with cyclopentadiene, as well as several more highly functionalized dienes and trienes,[1i,3,7a,16] The major cycloadduct (−)-**15** (94% of total) from the Diels–Alder reaction of **1** has an enantiomeric purity of ≥99% ee. The diastereofacial selectivity of the Diels–Alder reactions of **1** in the exo manifold (50:1) is greater than that of **2** (20:1), as would be expected on the basis of the different steric requirements of the *tert*-butyl and cyclohexyl substituents of the two reagents. Consequently, dienophile **1**, prepared from pivalaldehyde and hydroxy acid (*S*)-**10**, is the preferred reagent for synthetic applications, either as a chiral ketene equivalent[22] or in contexts in which the α-hydroxy acid functionality will be utilized in the ultimate synthetic target.[1,2]

Experimental Section

General. All reactions were conducted in oven-dried (125 °C) or flame-dried glassware under atmospheres of dry Ar or N_2. All solvents were purified before use. Ether, THF, and toluene were distilled from sodium benzophenone ketyl. CH_2Cl_2 and CH_3CN were distilled from CaH_2.

^1H NMR spectra were measured at 300, 400, and 500 MHz on commercially available instruments. Residual $CHCl_3$ (δ 7.26 ppm) was used as internal reference for spectra measured in $CDCl_3$. Low and high resolution mass spectra were measured at 70 eV.

Analytical TLC was performed by using 2.5-cm × 10-cm plates coated with a 0.25-mm thickness of silica gel containing PF 254 indicator (Analtech). Preparative TLC was performed by using 20-cm × 20-cm plates coated with a 0.25- or 0.5-mm thickness of silica gel containing PF254 indicator (Analtech). Flash chromatography was performed as described by Still using Kieselgel 60 (230–400 mesh) or Kieselgel 60 (70–230 mesh).[23] Unless otherwise noted, all compounds purified by chromatography are sufficiently pure (by ^1H NMR analysis) for use in subsequent reactions.

Potassium D-Glycidate (8).[8] To a vigorously stirred, 0 °C solution of L-serine (100.0 g, 0.95 mol) in 6 N HCl (1.21, 7.10 mol) was added freshly pulverized $NaNO_2$ (105.5 g, 1.10 mol) in small portions at such a rate that the reaction temperature remained between 0 and 5 °C. This addition required approximately 2.5 h on this scale. The mixture was stirred for an additional 4 h at 0 °C and then was extracted with Et_2O (4 × 500 mL). The ethereal extracts were dried over $CaCl_2$ and the solvent was removed by evaporation to give 85.2 g (72%) of crude (*S*)-2-chloro-3-hydroxypropionic acid (**7**) as a yellow liquid.

Crushed KOH (77.5 g, 1.38 mol) was then added slowly to a 0 °C solution of **7** (85.2 g, 0.68 mol) in 300 mL of absolute ethanol. The resulting slurry was brought to 25 °C after 3 h and stirred for an additional 14 h. KCl was removed by filtration and washed with cold methanol (3 × 300 mL). The combined alcoholic filtrates were concentrated in vacuo to give a viscous oil which was recrystallized from absolute methanol, giving 65.2 g (55% overall from L-serine) of the previously reported glycidate **8**:[8,9] mp 164–166 °C; $[\alpha]^{26}_D$ +17.7° (*c* 2.65, MeOH); ^1H NMR (400 MHz, D_2O; referenced by using DSS) δ 3.20 (dd, *J* = 4.8, 2.7 Hz, 1 H), 2.78 (dd, *J* = 5.6, 4.8 Hz, 1 H), 2.62 (dd, *J* = 5.6, 2.7 Hz, 1 H).

Benzyl (2*R*)-Glycidate (9).[8] To a solution of D-**8** (30.0 g, 0.24 mol) in anhydrous CH_3CN (500 mL) were added 18-crown-6 (8.0 g, 0.03 mol) and 98% benzyl bromide (33.4 mL, 0.28 mol). This solution was heated at 40 °C for 16 h under N_2. The solution was filtered, and the resulting KBr was washed repeatedly with dry CH_3CN. Concentration of the combined filtrates produced a red viscous oil which was extracted with 95% hexane–ether (6 × 100 mL). The combined extracts were concentrated in vacuo, yielding a yellow oil that was triturated with hexane (10 mL) to remove residual benzyl bromide. This produced 35.1 g (71%) of **9** that was sufficiently pure for use in the next step: R_f 0.31 (2:1 hexane–ether); $[\alpha]^{26}_D$ +22.1° (*c* 6.5, $CHCl_3$); lit.[8a] for (*S*)-**9** prepared from D-serine, $[\alpha]^{22}_D$ −22.9°; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (s, 5 H), 5.25 and 5.19 (AB dd, *J* = 12.1 Hz, 2 H), 3.48 (dd, *J* = 2.2, 4.4 Hz, 1 H), 3.00–2.94 (m, 2 H); IR (neat) 3065, 3039, 3002, 1756, 1498, 1457, 1405, 1366, 1282, 1251, 1194, 1141, 1022, 873, 748, 697 cm^{-1}; MS *m/z* 179 (M^+ + H); HRMS for $C_{10}H_{11}O_3$ calcd 179.0705, found 179.0699. Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.44; H, 5.66. Found: C, 67.24; H, 5.77.

2(*S*)-Hydroxy-3-(phenylthio)propanoic Acid (10). Method A: Via Benzyl 2(*S*)-Hydroxy-3-(phenylthio)propionate. A solution of 99% thiophenol (2.3 mL, 21.9 mmol) in anhydrous THF (5 mL) was slowly added to a 0 °C solution of ethylmagnesium bromide (5.0 mL, 21.1 mmol, 2.0 M in Et_2O) in anhydrous THF (32 mL). This mixture was stirred for 30 min, and then a solution of **9** (2.9 g, 16.3 mmol) in anhydrous THF (5 mL) was added dropwise over a 1-h period. This reaction was allowed to stir under N_2 at 25 °C for 3 h before being quenched with H_2O (10 mL) and diluted with Et_2O (50 mL). The aqueous layer was acidified to pH = 5 with 1 N HCl and extracted with Et_2O (3 × 100 mL). The combined extracts were washed with 10% aqueous NaOH, H_2O, and brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by silica gel chromatography (1:1 ether–hexane), giving 4.44 g (95%) of benzyl 2(*S*)-hydroxy-3-(phenylthio)propionate that contained ca. 5% of the regioisomeric thiophenol substitution product: R_f 0.32 (1:1 hexane–ether); $[\alpha]^{26}_D$ −10.2° (*c* 2.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.44–7.21 (m, 10 H), 5.12 and 4.93 (AB dd, *J* = 12.1 Hz, 2 H), 4.48–4.42 (m, 1 H), 3.41 (A′ of A′B′X, *J* = 15.2, 4.0 Hz, 1 H), 3.29 (B′ of A′B′X, *J* = 15.2, 5.6 Hz, 1 H), 3.14 (d, *J* = 6.1 Hz, 1 H); IR (neat) 3465, 3055, 3022, 1751, 1582, 1479, 1453, 1438, 1188, 1089, 749, 693 cm^{-1}; HRMS for $C_{16}H_{16}O_3S$ (parent ion) calcd 288.0816, found 288.0807. The enantiomeric purity of this intermediate was determined to be ≥99% ee by the Mosher ester analysis. The (*S*)-MTPA derivative of benzyl 2(*S*)-hydroxy-3-(phenylthio)propionate showed, among others, ^1H NMR signals at δ 5.14 (s, 3 H), and 3.53 (s, 3 H). The (*R*)-MTPA derivative, however, showed corresponding resonances only at δ 5.17 (s, 3 H) and 3.57 (s, 3 H).

To a solution of benzyl (*S*)-2-hydroxy-3-(phenylthio)propionate (2.7 g, 9.4 mmol) in MeOH (20 mL) was added 3 N NaOH (9.4 mL, 28.2 mmol) over a 1-h period. The resulting slurry was briskly stirred for 16 h before being taken to pH = 8 with 1 N HCl and

(21) We thank Professor R. Gandour of LSU for suggesting this idea to us.

(22) For a review of ketene equivalents: Ranganathan, S.; Ranganathan, D.; Mehrotra, A. K. *Synthesis* **1977**, *5*, 289.

(23) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

extracted with Et_2O (1 × 100 mL). The aqueous solution was further acidified to pH = 3 and extracted with EtOAc (3 × 100 mL). The EtOAc layers were combined and washed with H_2O and brine and then dried ($MgSO_4$) and concentrated in vacuo to give crude **10** as a white solid. Recrystallization of this material from benzene–hexane afforded 1.68 g (94%) of (*S*)-**10** that was >97% pure by ^1H NMR.

Method B: Via the Reaction of D-8 and Thiophenol. To a 25 °C solution of 99% thiophenol (0.89 mL, 8.72 mmol) in anhydrous MeOH (13 mL) was added D-glycidate **8** (1.00 g, 7.93 mmol) under N_2. The mixture was stirred for 60 h and then was concentrated to ca. 20% of the original volume. This solution was diluted with 1:1 H_2O and EtOAc, acidified to pH = 3 with 1 N HCl and extracted with EtOAc (3 × 75 mL). The combined extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crystalline crude product, an 8:1 mixture of **10** and the regioisomeric α-phenylthio β-hydroxy acid, was recrystallized from benzene–hexane to give 1.11 g (71%) of (*S*)-**10** that had an isomeric purity of 10–11:1. Characteristic ^1H NMR signals (acetone-d_6) attributed to the minor regisomer are δ 3.94 (q, *J* = 10.1 Hz, 1 H) and δ 3.89 (m, 2 H). This material was further purified by additional recrystallizations for analytical characterization. For preparative purposes, however, once recyrstallized (*S*)-**10** with ≥90% purity was used directly in condensations with aldehydes. Data for isomerically pure **10**: mp 84–85 °C; $[\alpha]^{26}_D$ −22.3° (*c* 5.1, MeOH); ^1H NMR (300 MHz, acetone-d_6) δ 7.48–7.23 (m, 5 H), 4.40 (dd, *J* = 6.5, 4.1 Hz, 1 H), 3.45 (dd, *J* = 14.1, 4.1 Hz, 1 H), 3.26 (dd, *J* = 14.1, 6.5 Hz, 1 H); IR (neat) 3460, 1720, 1585, 1090 cm^{-1}; MS *m/z* 198 (parent ion). Anal. Calcd for $C_9H_{10}O_3S$: C, 54.43; H, 5.09. Found: C, 54.70; H, 5.13.

Enantiomeric Purity Determination of (*S*)-10. A 0 °C solution of (*S*)-**10** (0.20 g, 1.0 mmol), prepared either by method A or B, in anhydrous Et_2O (5.0 mL) was treated with a 0 °C solution of diazomethane [generated from *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (0.46 g, 3.0 mmol)] in anhydrous Et_2O (5.0 mL). The reaction was allowed to warm to 25 °C (15 min) and was stirred for an additional 30 min before being concentrated in vacuo. Purification of the crude mixture by silica gel chromatography (2:1 hexane–ether) provided 0.16 g (75%) of the known[9] methyl (*S*)-2-hydroxy-3-(phenylthio)propionate [methyl β-(thiophenoxy)lactate]: R_f 0.31 (2:1 hexane–ether); ^1H NMR (300 MHz, $CDCl_3$) δ 7.44–7.21 (m, 5 H), 4.40 (m, 1 H), 3.61 (s, 3 H), 3.40 (dd, *J* = 14.1, 4.2 Hz, 1 H), 3.24 (dd, *J* = 14.1, 5.4 Hz, 1 H), 3.16 (d, *J* = 6.8 Hz, 1 H). A solution of this lactate ester (0.05 g, 0.23 mmol) in anhydrous CH_2Cl_2 (1.0 mL) was treated with either (*S*)-(−)-MTPA-Cl or (*R*)-(+)-MTPA-Cl (58 μL, 0.28 mmol), Et_3N (98 μL, 0.69 mmol) and catalytic DMAP under N_2. The mixture was diluted with Et_2O (5 mL) when judged complete by TLC analysis, producing a precipitate that was filtered through glass wool. Concentration of the organic layer in vacuo yielded the crude Mosher ester derivatives that were purified by preparative TLC (2:1 hexane–ether; the diastereomeric MTPA derivatives do not separate). The purified esters (>95% yield) were examined by high field ^1H NMR analysis. The (*S*)-(−)-MTPA derivative showed, among others, signals at δ 3.71 (s, 3 H) and 3.60 (s, 3 H). The (*R*)-(+)-MTPA derivative, however, showed resonances only at δ 3.74 (s, 3 H) and 3.66 (s, 3 H), thus indicating the enantiomeric purity of optically active **10** to be ≥99% ee when prepared by either method A or B.

(2*R*,5*S*)-2-*tert*-Butyl-5-[(phenylthio)methyl]-1,3-dioxolan-4-one (11). Method A: Via >97% Pure (*S*)-10. To a 0 °C solution of 97% pivalaldehyde (1.43 mL, 12.8 mmol) and α-hydroxy acid (*S*)-**10** (2.30 g, 11.6 mmol; >97% purity) in anhydrous Et_2O (40 mL) was added 2.03 mL of BF_3·Et_2O (2.34 g, 34.8 mmol) dropwise over a 30-min period. The reaction was stirred for 4 h at 0 °C under N_2 and then was diluted with saturated aqueous $NaHCO_3$ and extracted with Et_2O (3 × 50 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product (3.08 g, 99% yield) consisted of a 94:6 mixture of the *cis*- and *trans*-dioxalanones, as determined by ^1H NMR analysis. Diastereomerically enriched *cis*-**11** was obtained in 85–90% yield by silica gel chromatography (2:1 hexane–ether) from reactions performed on scales less than 10 mmol. The crude product from the specific experiment described here, however, was directly oxidized to sulfone **13** without prior purification. Data for *cis*-**11**: mp 45–46 °C; R_f 0.75 (2:1 ether–hexane); $[\alpha]^{26}_D$ + 34.50° (*c* 2.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.17 (m, 5 H), 5.13 (s, 1 H), 4.47 (dd, *J* = 7.1, 3.5 Hz, 1 H), 3.48 and 3.18 (AB dd of ABX, *J* = 14.5, 7.1 Hz, 2 H), 0.92 (s, 9 H); IR (CH_2Cl_2) 3082, 2980, 2927, 2895, 1797, 1570, 1481, 1430, 1402, 1363, 1340, 1288, 1223, 1115, 1057, 982, 930 cm^{-1}; HRMS for $C_{14}H_{18}O_3S$ (parent ion) calcd 266.0983, found 266.0979. Anal. Calcd for $C_{14}H_{18}O_3S$: C, 63.13; H, 6.81; S, 12.04. Found: C, 63.13; H, 6.84; S, 12.08.

The minor trans (2*S*,5*S*)-diastereomer of **11** was not isolated. The following data for *trans*-**11** were obtained from mixtures with the cis isomer **11** as the major component: ^1H NMR (250 MHz, $CDCl_3$) δ 7.43–7.17 (m, 5 H), 5.28 (s, 1 H), 4.62 (dd, *J* = 5.1, 4.0 Hz, 1 H), 3.44 and 3.22 (AB dd of ABX, *J* = 14.5, 5.1 Hz, 2 H), 0.89 (s, 9 H).

Method B: Via 90% Pure (*S*)-10 (from the Reaction of D-8 and Thiophenol). To a 0 °C solution of 97% pivalaldehyde (0.41 mL, 3.7 mmol) and α-hydroxy acid (*S*)-**10** (0.66 g, 3.3 mmol; 90–91% isomeric purity) in anhydrous Et_2O (20 mL) was added 1.23 mL of BF_3·Et_2O (10 mmol) dropwise over a 30-min period. The reaction was then processed as described above in method A. The crude product was purified by silica gel chromatography (2:1 hexane–ether), giving 745 mg (85%) of ≥95% isomerically pure **11**. Products deriving from the β-hydroxy α-phenylthio regioisomer of **10** were not observed.

(2*R*,5*S*)-2-Cyclohexyl-5-[(phenylthio)methyl]-1,3-dioxolan-4-one (12). A 0 °C solution of cyclohexanecarboxaldehyde (11.0 mL, 84.0 mmol) and α-hydroxy acid (*S*)-**10** (15.0 g, 76.0 mmol; >97% purity) in anhydrous Et_2O (300 mL) was treated with BF_3·Et_2O (28.0 mL, 32.3 g, 228 mmol), using the procedure described for the preparation of (*R*,*S*)-**11**. The crude sulfide **12** (22.0 g, 99% yield) consisted of a 97:3 mixture of the cis and trans acetal diastereomers (^1H NMR analysis). This material was directly oxidized to sulfone **14** as described subsequently. On smaller reaction scales (≤10 mmol), sulfide **12** was purified by silica gel chromatography (2:1 hexane–ether) and obtained in 85–90% yield with improved diastereomeric purity. Data for purified **12**: R_f 0.41 (1:1 hexane–ether); $[\alpha]^{26}_D$ + 53.7° (*c* 3.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.44–7.20 (m, 5 H), 5.25 (d, *J* = 5.1 Hz, 1 H), 4.47 (dd, *J* = 6.7, 3.5 Hz, 1 H), 3.52 and 3.18 (AB dd of ABX, *J* = 14.4, 6.7 Hz, 2 H), 1.80–1.65 (m, 6 H), 1.54–1.02 (m, 5 H); IR ($CHCl_3$) 3020, 2935, 2859, 1794, 1582, 1481, 1452, 1404, 1355, 1300, 1178, 1125, 1021, 950, 891 cm^{-1}; HRMS for $C_{16}H_{20}O_3S$ (parent ion) calcd 292.1128, found 292.1118. Anal. Calcd for $C_{16}H_{20}O_3S$: C, 65.72; H, 6.89. Found: C, 65.68; H, 6.68.

The minor trans (2*S*,5*S*)-diastereomer of **12** was not isolated. The following data for *trans*-**12** were obtained from mixtures with the cis isomer **12** as the major component: ^1H NMR (300 MHz, $CDCl_3$) δ 7.44–7.20 (m, 5 H), 5.21 (d, *J* = 4.9 Hz, 1 H), 4.42 (dd, *J* = 6.5, 4.0 Hz, 1 H), 3.42 and 3.14 (AB dd of ABX, *J* = 14.5, 6.5 Hz, 2 H), 1.80–1.65 (m, 6 H), 1.54–1.02 (m, 5 H).

(2*R*,5*S*)-2-*tert*-Butyl-5-[(phenylsulfonyl)methyl]-1,3-dioxolan-4-one (13). A solution of 50% MCPBA (8.16 g, 23.6 mmol, Aldrich) in dry CH_2Cl_2 (25 mL) was added dropwise over a 30-min period to a 0 °C solution of sulfide **11** (2.13 g, 10.7 mmol; a 94:6 mixture of diastereomers from the preceding experiment) in CH_2Cl_2 (20 mL). The mixture was stirred under N_2 at room temperature for 16 h before being quenched with saturated aqueous $NaHSO_3$ and extracted with anhydrous Et_2O (3 × 100 mL). The extracts were carefully washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated in vacuo. This produced a white solid that was recrystallized from ethyl acetate–hexane, yielding 2.75 g (86% yield) of **13** that had a diastereomeric purity of ≥99 de: mp 106–107 °C; R_f 0.40 (1:1 ether–hexane); $[\alpha]^{26}_D$ +44.5° (*c* 1.20, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.95–7.54 (m, 5 H), 5.10 (s, 1 H), 4.81 (dd, *J* = 10.2, 1.9 Hz, 1 H), 3.67 and 3.40 (AB dd of ABX, *J* = 15.1, 10.2 Hz, 2 H), 0.75 (s, 9 H); IR ($CHCl_3$) 3020, 2979, 2903, 1798, 1583, 1482, 1459, 1408, 1339, 1310, 1172, 1148, 1129, 1085, 1042, 970, 840, 685 cm^{-1}; HRMS for $C_{14}H_{19}O_5S$ (M^+ + H) calcd 299.0948, found 299.0949. Anal. Calcd for $C_{14}H_{18}O_5S$: C, 56.36; H, 6.08. Found: C, 56.31; H, 6.09.

Data for (2*S*,5*S*)-2-*tert*-butyl-5-[(phenylsulfonyl)methyl]-1,3-dioxolan-4-one, the minor diastereomeric sulfone:[12] R_f 0.35 (1:1 ether–hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.95–7.54 (m, 5 H), 5.16 (s, 1 H), 4.83 (dd, *J* = 10.2, 1.9 Hz, 1

H), 3.60 and 3.52 (AB dd of ABX, J = 15.1, 10.2 Hz, 2 H), 0.87 (s, 9 H); IR ($CHCl_3$) 2965, 2931, 1802, 1483, 1449, 1410, 1342, 1328, 1310, 1212, 1169, 1149, 1126, 1086, 1036, 981, 686 cm^{-1}; HRMS for $C_{14}H_{19}O_5S$ (M^+ + H) calcd 299.0948, found 299.0956.

(2*R*,5*S*)-2-Cyclohexyl-5-[(phenylsulfonyl)methyl]-1,3-dioxolan-4-one (14). A solution of 50% MCPBA (57.0 g, 165 mmol, Aldrich) in dry CH_2Cl_2 (100 mL) was added dropwise over a 30-min period to a 0 °C solution of crude sulfide **12** (22.0 g, 75 mmol; a 97:3 mixture of diastereomers) in CH_2Cl_2 (250 mL). The mixture was stirred for 16 h under N_2 before being worked up as described for the preparation of **13**. The crude product was recrystallized from ethyl acetate–hexane, giving 19.9 g of (*R*,*S*)-**14** with a diastereomeric purity of ≥98% de. The yield was 82% for the two steps from (*S*)-**10**: mp 70–71 °C; R_f 0.39 (3:1 ether–hexane); $[\alpha]^{26}_D$ +23.5° (*c* 14.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.95–7.45 (m, 5 H), 5.24 (d, J = 4.6 Hz, 1 H), 4.76 (dd, J = 7.7, 1.8 Hz, 1 H), 3.66 and 3.42 (AB dd of ABX, J = 15.1, 7.7 Hz, 2 H), 1.73–1.50 (m, 6 H), 1.19–0.84 (m, 5 H); IR ($CHCl_3$) 3020, 2945, 2860, 1800, 1585, 1450, 1390, 1340, 1320, 1170, 1150, 1125, 1085, 1020, 970, 955, 890, 835, 675 cm^{-1}; MS m/z 241 ($M^+ - C_6H_{11}$); HRMS for $C_{10}H_9O_5S$ calcd 241.0168, found 241.0169. Anal. Calcd for $C_{16}H_{20}O_5S$: C, 59.18; H, 6.21. Found: C, 59.05; H, 6.03.

(2*R*)-2-*tert*-Butyl-5-methylene-1,3-dioxolan-4-one (1). 1,8-Diazabicyclo[5.4.0]undec-7-ene (2.28 mL, 15.2 mmol) was slowly added to a 0 °C solution of sulfone **13** (3.50 g, 11.7 mmol) in anhydrous CH_2Cl_2 (80 mL) under N_2. After 2 h the reaction was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and carefully concentrated in vacuo (25 °C bath; ≥30 mmHg). Purification of the crude mixture by silica gel chromatography (20:1 hexane–ether) produced 1.40 g (76%) of (*R*)-**1**: lit.[7a] bp 59–60 °C/6 Torr; R_f 0.35 (15:1 hexane–ether); $[\alpha]^{26}_D$ +14.2° (*c* 1.65, $CHCl_3$); lit.[7a] $[\alpha]^{27}_D$ −14.9° (*c* 1.52, $CHCl_3$) for (*S*)-**1** prepared from (*S*)-lactate; ^1H NMR (400 MHz, $CDCl_3$) δ 5.43 (s, 1 H), 5.12 (d, J = 2.7 Hz, 1 H), 4.85 (d, J = 2.7 Hz, 1 H), 0.97 (s, 9 H); IR (CH_2Cl_2) 3005, 2966, 2903, 1798, 1671, 1475, 1308, 1128, 1035, 990, 882 cm^{-1}; MS m/z (parent ion) 156.

(2*R*)-2-Cyclohexyl-5-methylene-1,3-dioxolan-4-one (2). 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.90 mL, 6.02 mmol) was slowly added to a 0 °C solution of sulfone **14** (1.50 g, 4.63 mmol) in anhydrous CH_2Cl_2 (45 mL) under N_2. After 2 h the reaction was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine and then dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of crude **2** by silica gel chromatography (20:1 hexane–ether) produced 0.76 g of **2** as a semisolid in 90% yield: R_f 0.40 (15:1 hexane–ether); $[\alpha]^{26}_D$ +18.9° (*c* 2.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.57 (d, J = 4.3 Hz, 1 H), 5.12 (d, J = 2.5 Hz, 1 H), 4.84 (d, J = 2.5 Hz, 1 H), 1.81–1.18 (m, 11 H); IR ($CHCl_3$) 3015, 2938, 2860, 1798, 1722, 1659, 1454, 1300, 1122, 1053, 975, 860 cm^{-1}; HRMS for $C_{10}H_{14}O_3$ (parent ion) calcd 182.0939, found 182.0942. Dienophile **2** prepared in this way contained a small amount (ca. 10%) of $C_6H_{11}CHO$ that was not separated during the chromatographic purification.

Diels–Alder Reaction of Cyclopentadiene and (*R*)-1. A solution of freshly prepared (*R*)-**1** (0.08 g, 0.51 mmol) in dry benzene (0.5 mL) was placed in a Carius tube and degassed with a stream of Ar. Excess cyclopentadiene (0.42 mL, 5.12 mmol) was added via syringe and the tube sealed under N_2. The Carius tube was placed in a 55 °C oil bath and stirred for 15 h. The mixture was then cooled and concentrated in vacuo. The crude product consisted of a 94:6 ratio of **15** and **16** as determined by analysis of the olefinic region of the ^1H NMR spectrum. This diastereoselectivity was confirmed by capillary gas chromatography analysis (SE-54, 50 m, 100–175 °C, 10°/min); t(**15**) = 10.50, t(**16**) = 10.88). A sample of the crude product (0.04 g) was removed for use in the subsequently described $LiAlH_4$ reduction. The remainder was purified by silica gel chromatography (20:1 hexane–ether), giving 0.05 g of diastereomerically enriched exo adduct **15**: mp 52–53 °C; R_f 0.32 (24:1 pentane–ether); $[\alpha]^{26}_D$ −147.9° (*c* 2.4, $CHCl_3$); $[\alpha]^{24}_D$ +148.6° (*c* 0.87, $CHCl_3$) has been reported for the enantiomer;[7a] ^1H NMR (400 MHz, $CDCl_3$) δ 6.44 (dd, J = 5.6, 3.0 Hz, 1 H), 6.06 (dd, J = 5.6, 3.0 Hz, 1 H), 5.14 (s, 1 H), 3.15 (br s, 1 H), 2.97 (br s, 1 H), 2.29 (dd, J = 12.5, 3.5 Hz, 1 H), 1.94 (br d, J = 9.1 Hz, 1 H), 1.49 (dt, J = 2.0, 9.1 Hz, 1 H), 1.32 (dd, J = 12.5, 3.5 Hz, 1 H), 0.91 (s, 9 H); IR (CH_2Cl_2) 2990, 2903, 1783, 1720, 1491, 1412, 1367, 1344, 1238, 1210, 1165, 1131, 1107, 1065, 965 cm^{-1}; HRMS for $C_{13}H_{18}O_3$ (parent ion) calcd 222.1256, found 222.1256.

Partial Data for Endo Cycloadduct 16. Endo cycloadduct **16** was not isolated. The following NMR data for **16** were obtained on mixtures with the exo diastereomer **15**: ^1H NMR (250 MHz, $CDCl_3$) δ 6.39 (dd, J = 5.5, 3.0 Hz, 1 H), 5.97 (dd, J = 5.5, 3.0 Hz, 1 H), 5.18 (s, 1 H), 3.18 (br s, 1 H).

Diels–Alder Reaction of Cyclopentadiene and (*R*)-2. The Diels–Alder reaction of freshly prepared (*R*)-**2** (0.20 g, 1.10 mmol) and excess cyclopentadiene (0.90 mL, 11.0 mmol) was performed in benzene (1.1 mL) at 55–60 °C using the procedure described for the Diels–Alder reaction with (*R*)-**1**. Analysis of the crude product by 300-MHz ^1H NMR revealed only two products, **18** and **19**, in a ratio of 96:4. This ratio was confirmed by capillary GC and analytical HPLC [4.6- × 250-mm Chemcopak column packed with 3-μm Chemcosorb silica gel; 95% hexane–ethyl acetate, 1 mL/min; t(**18**) = 22.0, t(**19**) = 22.9]; only two peaks were detected by these methods. Careful analysis of the 400-MHz ^1H NMR spectrum, however, revealed a small amount (ca. 5%) of a third diastereomer believed to be **20**. The olefinic resonances of **20** overlap with those of **18** at 300 MHz. Silica gel purification (20:1 hexane–ether) yielded 0.18 g of enriched exo adduct **18** (a 98:2 mixture of **18** and **20** by NMR, but a single band by HPLC) and 0.03 g of a 1:1 mixture of exo **18** and endo **19**; 0.07 g of the crude product was removed for use in the subsequently described reduction experiment.

Data for 18: R_f 0.24 (15:1 hexane–ether); $[\alpha]^{26}_D$ −94.1° (*c* 1.70, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.46 (dd, J = 5.0, 3.6 Hz, 1 H), 6.08 (dd, J = 5.0, 3.6 Hz, 1 H), 5.29 (d, J = 4.3 Hz, 1 H), 3.16 (br s, 1 H), 2.98 (br s, 1 H), 2.30 (dd, J = 12.3, 3.8 Hz, 1 H), 1.96 (br d, J = 9.1 Hz, 1 H), 1.77–1.61 (m, 6 H), 1.51 (dd, J = 9.1, 1.6 Hz, 1 H), 1.49 (dd, J = 12.3, 3.8 Hz, 1 H), 1.23–1.07 (m, 5 H); IR ($CHCl_3$) 2991, 2949, 2860, 1782, 1451, 1395, 1354, 1338, 1277, 1242, 1171, 1138, 1060, 973 cm^{-1}; HRMS for $C_{15}H_{20}O_3$ (parent ion) calcd 248.1407, found 248.1413. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.44; H, 8.16.

Partial data for endo cycloadduct 19 (obtained on a 1:1 mixture with exo diastereomer **18**): ^1H NMR (400 MHz, $CDCl_3$) δ 6.39 (dd, J = 5.4, 2.9 Hz, 1 H), 6.18 (dd, J = 5.4, 2.9 Hz, 1 H), 5.33 (d, J = 4.3 Hz, 1 H), 3.18 (br s, 1 H).

Partial data for exo-diastereofacial isomer 20 (obtained from mixtures with **18**): ^1H NMR (400 MHz, $CDCl_3$) δ 6.42 (dd, 1 H), 6.05 (dd, 1 H), 5.25 (d, 1 H), 3.14 (br s, 1 H), 2.98 (br s, 1 H).

(1*S*,2*S*)-2-Hydroxybicyclo[2.2.1]hept-5-ene-2-methanol (23). This experiment was performed by using purified cycloadducts exo **15** (*tert*-butyl dienophile series) or **18** (cyclohexyl dienophile series), as well as the crude, unseparated mixtures of cycloadducts from the previously described Diels–Alder reactions with cyclopentadiene. Thus, excess $LiAlH_4$ was added to a 0 °C solution of the substrate (**16**, **19**, or crude reaction mixtures) in anhydrous Et_2O (0.2 M). The mixtures were stirred at 25 °C for 1 h before being quenched with H_2O. The mixtures were washed with 15% aqueous NaOH, filtered, dried ($MgSO_4$), and concentrated in vacuo. Purification of the crude product by silica gel chromatography (1:1 ether–ethyl acetate) yielded the known diol **23** in 85–90% yield: R_f 0.25 (1:1 ether–ethyl acetate); mp 46–47 °C; lit.[7a] mp 46.5 °C; $[\alpha]^{26}_D$ −122.2° (*c* 1.67, $CHCl_3$); lit.[7a] $[\alpha]^{22}_D$ 127.8° (*c* 2.75, $CHCl_3$) for the enantiomer; ^1H NMR (400 MHz, $CDCl_3$) δ 6.47 (dd, J = 5.9, 3.0 Hz, 1 H), 6.16 (dd, J = 5.9, 3.0 Hz, 1 H), 3.76 and 3.69 (AB dd, J = 11.4 Hz, 2 H), 2.92 (br s, 1 H), 2.85 (br s, 1 H), 2.48 (br s, 1 H (OH)), 1.91 (br s, 1 H (OH)), 1.77 (dd, J = 12.4, 3.8 Hz, 1 H), 1.58 (dm, J = 9.0 Hz, 1 H), 1.43 (br d, J = 9.0 Hz, 1 H), 1.07 (dd, J = 12.4, 3.8 Hz, 1 H); IR ($CHCl_3$) 3700–3150 (br), 3060, 2985, 2875, 1463, 1451, 1343, 1276, 1064, 1051, 1033, 991, 909 cm^{-1}; HRMS for $C_8H_{12}O_2$ (parent ion) calcd 140.0834, found 140.0838.

Endo diol **24**[15a] was not isolated but was detected in the NMR spectra of the diols produced upon reduction of crude mixtures of Diels–Alder adducts: ^1H NMR (400 MHz, $CDCl_3$) δ 6.17 (dd, J = 5.6, 3.0 Hz, 1 H), 6.08 (dd, J = 5.6, 3.0 Hz, 1 H), 3.46 and 3.45 (AB dd of ABX, J = 10.9, 4.6 Hz, 2 H), 2.86 (br s, 1 H), 2.71

(br s, 1 H), 1.92 (d, J = 8.6 Hz, 1 H), 1.89 (t, J = 4.6 Hz, 1 H), 1.72 (br s, 1 H), 1.64 (d, J = 8.6 Hz, 1 H), 1.62 (dd, J = 12.4, 2.7 Hz, 1 H), 1.18 (dd, J = 12.4, 2.7 Hz, 1 H).

Mosher Ester Analysis of 23. This analysis was performed using diol **23** prepared by the $LiAlH_4$ reductions of purified cycloadducts **15** (racemic and optically active) and (−)-**18**, as well as the crude, unseparated mixtures of cycloadducts obtained from the Diels–Alder reactions of (*R*)-**1** and (*R*)-**2**. Thus, to a solution of **23** in anhydrous CH_2Cl_2 (0.1 M) were added (*R*)-(+)-MTPA-Cl (1.2 equiv), Et_3N (1.1 equiv), and catalytic DMAP. This mixture was stirred for 12 h at 23 °C under N_2. The Mosher ester derivatives were purified by preparative TLC [R_f 0.55 (2:1 ether–hexane); the diastereomeric MTPA derivatives do not separate], and the purified esters (>95% yield) were examined by high field ^1H NMR analysis. The 500-MHz ^1H NMR spectrum of Mosher ester derivative prepared from racemic **23** displays an AB pattern for the CH_2OMTPA resonance of one diastereomer (δ 4.57 and 4.46, J_{AB} = 11.3 Hz) whereas the CH_2OMTPA resonance for the second diastereomer appears as an apparent singlet at δ 4.52. The MTPA derivative of **23** prepared from purified cycloadduct (−)-**15**, however, showed essentially only the resonances at δ 4.57 and 4.46, indicating the enantiomeric purity of **15**, and hence dienophile (*R*)-**1**, to be ≥99% ee. The Mosher ester analysis of **23** prepared from the unseparated mixture of Diels–Alder adducts prepared with (*R*)-**1** had an enantiomeric purity of 96% ee, indicating that up to 2% of exo cycloadduct **17** was also produced in the Diels–Alder reaction. Parallel analyses performed with **23** deriving from purified (−)-**18** (a 98:2 mixture of **18** and **20**) as well as from the unseparated mixture of cycloadducts obtained from the Diels–Alder reaction with (*R*)-**2** indicated enantiomeric purities of 96% and 90% ee, respectively.

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Supplementary Material Available: ^1H NMR spectra of **2**, **13**, the trans diastereomer of **13**, **21**, and **22** and procedures for the synthesis of **21** and **22** (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Synthesis of 2,5-Furanocycles through Intraannular Cyclization of Macrocyclic Allenones

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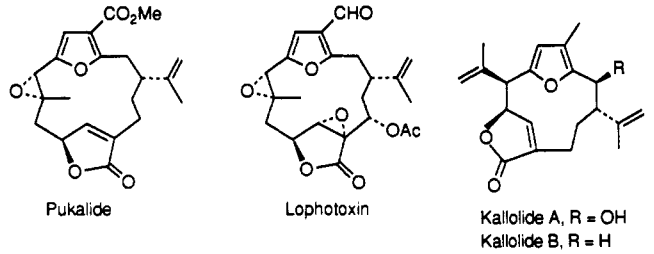
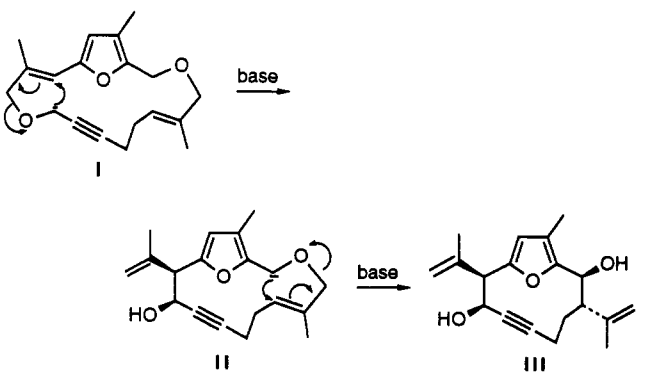
A new approach to 2,5-bridged furanocyclic compounds was demonstrated for rings of 12–14 members. Accordingly, allenylstannyl aldehydes **1.16**, **2.11**, **3.12a**, **3.12b**, **4.12**, **5.15**, and **6.12**, upon treatment with $BF_3{\cdot}OEt_2$ at −78 °C, smoothly cyclized to the homopropargylic alcohols **1.17**, **2.12**, **3.13a**, **3.13b**, **4.13**, **5.16**, and **6.13** in 87–94% yield. Oxidation and basic isomerization afforded the allenones **1.19**, **2.14**, **3.15a**, **3.15b**, **4.14**, **5.18**, and **6.15** in high yield. Intraannular cyclization to the furanocycles **1.21**, **2.15**, **3.16a**, **3.16b**, **4.16**, **5.19**, and **6.16** was effected with catalytic $AgNO_3$ and $CaCO_3$ in aqueous acetone. Furanocycles **1.21**, **2.15**, **3.16a**, and **3.16b**, with an appropriately disposed transannular (*Z*)-double bond, underwent facile intramolecular Diels–Alder cyclization in over 90% yield. The 12-membered furanocycles **4.16** and **5.19** with a transannular (*E*) double bond did not cyclize but instead were oxidized by the $AgNO_3$ catalyst to macrocyclic enediones **4.17** and **5.20**. These unusual furan reactions are presumably facilitated by ring strain (furan bending) in accord with molecular mechanics calculations.

Pukalide,[1] lophotoxin,[2] and the kallolides[3] are representative examples of marine natural products possessing a 12- or 14-membered 2,5-furanocyclic structure.[4] In connection with a program on the synthesis of biologically active cembranoid natural products we became interested in developing routes to such 2,5-furanocycles. In our initial approach we prepared the macrocyclic diether **I** hoping to effect sequential [2,3] Wittig ring contractions via **II** to the carbocyclic intermediate **III**, or a stereoisomer thereof.[5a] The conversion of **III** to kallolide A finds





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