δ 177.8 (s), 154.8 (s), 136.6 (d), 129.0 (s), 72.0 (d), 34.1 (t), 18.1 (q).

2-(*o*-Allylphenoxy)butanoic Acid (9a). A 5.3-g (81% yield) portion of this acid was obtained with mp 53–55 °C: IR ($CDCl_3$) 3700–2230, 1715, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.56 (s, 1 H), 7.18–6.46 (m, 4 H), 6.31–5.56 (m, 1 H), 5.21–4.95 (m, 1 H), 4.95–4.76 (m, 1 H), 4.52 (t, 1 H, J = 5.9 Hz), 3.48 (d, 2 H, J = 6 Hz), 2.00 (m, 2 H), 1.21 (t, 3 H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 177.6 (s), 155.2 (s), 136.8 (d), 129.1 (s), 76.6 (d), 34.3 (t), 26.0 (t), 9.4 (q).

General Procedure for Acid Chloride Preparation and Subsequent Intramolecular Cycloaddition. The (*o*-alkenylphenoxy)acetic acids were converted to the corresponding acid chlorides by reaction with 5–8 equiv of oxalyl chloride in benzene at ambient temperature for 3 h. The excess oxalyl chloride was removed under vacuum and the crude acid chloride was diluted with benzene and slowly added to a solution of 2 equiv of triethylamine in benzene at gentle reflux. The addition was usually over a period of 2–6 h and the total amount of solvent was 300–450 mL for a 5–10-mmol preparation. (In some instances, such as **8b** and **9b**, where the olefin functionality is not very reactive toward the cycloaddition process, it would be necessary to keep an even lower concentration of the reacting ketene.) After the addition was complete, the mixture was gently refluxed for 4–8 h. Upon cooling, the salt was removed by filtration and the solvent and excess amine were removed under reduced pressure. The crude cycloaddition product was purified by recrystallization from hexane (**5b**, **8b**) or by column chromatography using silica gel (2–7% ethyl acetate in hexane: **1b**, **2b**, **3b**, **4b**, **6b**, **7b**, **9b**).

1-Methyl-2-oxa-3,4-benzobicyclo[3.2.0]heptan-7-one (1b). A 0.54-g (60% yield) portion of **1b** was obtained from 1 g of **1a** with mp 49–50 °C: IR ($CDCl_3$) 1784, 1612, 1593 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23–6.60 (m, 4 H), 3.70–2.76 (m, 3 H), 1.58 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 207.3 (s), 160.1 (s), 128.8 (s), 128.6 (d), 125.4 (d), 121.5 (d), 109.9 (d), 102.3 (s), 53.7 (t), 39.9 (d), 15.9 (q).

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.56; H, 5.86.

6-Methyl-2-oxa-3,4-benzobicyclo[3.2.0]heptan-7-one (2b). A 0.65-g (72% yield) portion of **2b** was obtained from 1 g of **2a** with mp 65–66 °C : IR ($CDCl_3$) 1781, 1608, 1589 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15–6.58 (m, 4 H), 5.63–5.36 (m, 1 H), 4.23–3.38 (m, 2 H), 1.21 (d, exo-Me, J = 7.3 Hz), 0.84 (d, endo-Me, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 2.08.6 (s), 161.1 (s), 128.7 (d), 127.0 (d), 125.2 (s), 121.2 (d), 110.6 (d), 91.9, 59.0 (d), 39.9 (d), 8.6 (q).

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.64; H, 5.70.

1,6-Dimethyl-2-oxa-3,4-benzobicyclo[3.2.0]heptan-7-one (3b). A 0.69-g (76% yield) portion of **3b** was obtained from 1 g of **3a** with mp 69–70 °C: IR ($CDCl_3$) 1778, 1609, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.08–6.87 (m, 4 H), 3.83–3.81 (m, 2 H), 1.66 (s, 3 H), 0.96 (d, 3 H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 210.5 (s), 160.7 (s), 128.6 (d), 126.9 (d), 124.5 (s), 121.0 (d), 110.4 (d), 100.2 (s), 57.3 (d), 45.1 (d), 16.3 (q), 8.4 (q).

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.51; H, 6.39.

1-Ethyl-6-methyl-2-oxa-3,4-benzobicyclo[3.2.0]heptan-7-one (4b). A 1.31-g (71% yield) portion of a colorless oil was obtained from 2 g of **4a**: IR (Neat) 1781, 1608, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.10–6.45 (m, 4 H), 3.84–0.79 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 210.4 (s), 160.8 (s), 128.4 (d), 126.7 (d), 124.4 (s), 120.8 (d), 110.1 (d), 104.0 (s), 57.5 (d), 42.9 (d), 23.2 (t), 8.3 (q), 7.4 (q).

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 76.98; H, 6.78.

6-Methyl-1-phenyl-2-oxa-3,4-benzobicyclo[3.2.0]heptan-7-one (5b). A 1.6-g (85% yield) portion of **5b** was obtained from 2 g of **5a** with mp 95–96 °C: IR (neat) 1783, 1611, 1592 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65–6.86 (m, 9 H), 4.50–3.76 (m, 2 H), 1.19 (d, 3 H, J = 6 Hz); ^{13}C NMR ($CDCl_3$) δ 208.4 (s), 160.7 (s), 133.5 (s), 129.0 (d), 128.8 (d), 126.9 (s), 126.1 (d), 121.5 (d), 110.8 (s), 59.2 (d), 46.1 (d), 8.7 (q).

Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.40; H, 5.61.

5-Phenyl-2-oxa-3,4-benzobicyclo[3.2.0]heptan-7-one (6b). A 1.31-g (88% yield) portion of **6b** was obtained from 1.6 g of **6a** with mp 162–163 °C: IR ($CDCl_3$) δ 1789, 1608, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.32–7.41 (m, 9 H), 6.37 (t, 1 H, J = 2.5 Hz), 4.71 (dd, 1 H, J = 16.2, 2.5 Hz), 4.22 (dd, 1 H, J = 16.2, 2.5 Hz); ^{13}C NMR ($CDCl_3$) δ 203.9 (s), 142.0 (s), 131.7 (s), 129.3 (d), 128.8 (d), 127.2 (d), 126.1 (d), 125.5 (d), 122.7 (d), 111.1 (d), 99.5 (d), 59.3 (t), 50.7 (s).

Anal. Calcd for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 81.11; H. 4.95.

1-Methyl-5-phenyl-2-oxa-3,4-benzobicyclo[3.2.0]heptan-7-one (7b). A 2.35-g (84% yield) portion of colorless oil was obtained from 3 g of **7a**: IR (neat) 1788, 1718, 1658, 1593 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.16–7.35 (m, 9 H), 4.86 (d, 1 H, J = 16.4 Hz), 4.03 (d, 1 H, J = 16.4 Hz), 2.05 (s, 3 H); ^{13}C NMR ($CDCl_3$) 207.1 (s), 159.9 (s), 138.5 (s), 133.1 (d), 129.0 (d), 128.4 (d), 127.5 (d), 127.0 (d), 125.7 (d), 122.3 (d), 110.5 (d), 104.1 (s), 55.5 (t), 53.2 (s), 13.4 (q).

Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.35; H, 5.65.

1-Methyl-2-oxa-3,4-benzobicyclo[4.2.0]octan-8-one (8b). A 0.39-g (43% yield), of **8b** was obtained from 1 g of **8a** with mp 65–66 °C: IR ($CDCl_3$) 1777, 1610, 1591 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.07–6.84 (m, 4 H), 3.05–2.17 (m, 5 H), 1.48 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 209.9 (s), 154.6 (s), 129.1 (d), 127.5 (s), 123.8 (d), 122.2 (d), 117.3 (d), 92.6 (s), 46.9 (t), 34.4 (d), 28.2 (t), 19.5 (q).

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.65; H, 6.47.

1-Ethyl-2-oxa-3,4-benzobicyclo[4.2.0]octan-8-one (9b). A 0.45-g (49% yield) portion of a colorless oil was obtained from 1 g of **9a**; IR (neat) 1780, 1605, 1583 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.04–6.89 (m, 4 H), 2.84–2.17 (m, 5 H), 1.72 (q, 2 H, J = 4.8 Hz), 0.92 (t, 3 H, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$) 209.9 (s), 154.8 (s), 129.06 (d), 127.49 (d), 123.86 (s), 122.0 (d), 117.3 (d), 95.8 (s), 47.0 (t), 32.5 (d), 28.5 (t), 26.3 (t), 7.06 (q).

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.44; H, 7.15.

Acknowledgment. We are grateful to the Robert A. Welch Foundation for support of this work.

Stereocontrolled Synthesis of a Polyether Fragment

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Received April 2, 1985

A sequence utilizing selenolactonization of olefinic acid **4**, Ireland–Claisen rearrangement of ketal ester **9**, iodolactonization/epoxidation of olefinic acid **10**, and regioselective hydrolysis of epoxide **15b** is described for the stereocontrolled conversion of *meso*-2,4-dimethylglutaric anhydride to racemic tetrahydropyran lactone **1**.

Continued interest in the synthesis of polyether natural products has given rise of a number of strategic approaches for constructing and concatenating α,α′-disubstituted tetrahydrofuran and -pyran units.[1] For the most part,

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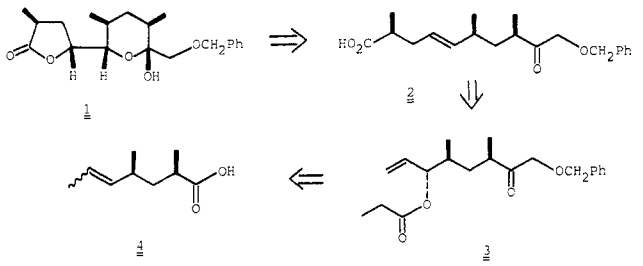
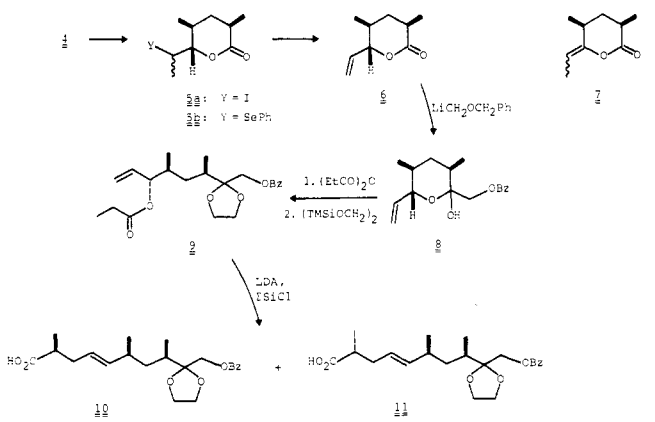
Scheme I



Scheme II



these approaches rely on the assembly of optically active precursors in a "stereochemically convergent" way, to ensure the appropriate stereorelationship between the various subunits. We have focussed recently on ether cyclization reactions which enable a "stereochemically linear" strategy to be adopted, that is, an approach in which each succeeding stereocenter is introduced with relative asymmetric induction.[2] As an illustration of this strategy we describe a route to lactone ketal **1**, a fragment representative of the A and B rings of the monensin/nigericin classes of polyether antibiotics.

The steps in our route which control the stereochemistry are indicated in the analytical sequence of Scheme I. The configurations of the critical stereocenters where the rings are linked are to be established during functionalization of the double bond of **2**, with control either from the ketone or the carboxyl group. The remote methyl group can in turn be introduced with the proper configuration during an Ireland–Claisen rearrangement[3] of a derivative of propanoate **3**. The requisite carbinol stereochemistry in this intermediate arises from lactonization/elimination of olefinic acid **4**, which is accessible from *meso*-2,4-dimethylglutaric anhydride.[4,5]

We have described the synthesis and various lactonization studies of olefinic acid **4** previously.[5] Both iodo- and selenocyclization proceed in good yield and with high selectivity to give the all-equatorial lactones **5**. Whereas base-induced elimination of iodolactone **5a** affords predominantly enol lactone **7**, oxidative elimination of selenide **5b** affords the desired allylic lactone **6** in excellent yield.[5] Capillary GC analysis indicated that the lactone is >95% pure stereochemically. Treatment of this material with benzyloxymethyllithium[6] provides hemiketal **8** in 92% yield (approximately 45% overall from *meso*-2,4-dimethylglutaric anhydride). Although this compound exists predominantly in the hemiketal form, as determined by NMR, the hydroxy ketone tautomer can be trapped by acylation with propanoic anhydride and thence converted to ethylene ketal **9** according to the method of Noyori[7] (86% from **8**) (see Scheme II).

The Ireland–Claisen rearrangement, carried out in the presence of HMPA to favor formation of the (*Z*)-enolsilyl ether,[3] gives acyclic acid **10** in 80% yield. The stereochemistry of the major rearrangement product was initially assigned from the extensive precedent of the Ireland–Claisen process,[3,8] although it was confirmed in subsequent transformations. The ratio of the major to the minor stereoisomers **10** and **11** is generally 10:1. The identity of the minor isomer was confirmed by its formation as the predominant product under the alternative Ireland–Claisen conditions.

To introduce the remaining stereocenters of **1**, we initially envisaged functionalizing the double bond with assistance from the ketone carbonyl (Scheme III). We anticipated that iodocyclization (**12a** → **13**), perhaps via the hydrate or a hemiketal, would provide stereocontrol of the same sort manifested by electrophilic cyclization of acid **4**.[5] The epoxide derived from **13** (e.g., **15a**), if opened in turn by the carboxyl group, would give **1**. Therefore we converted the rearrangement product **10** into the ketoester **12a** and studied its behavior under a variety of iodocyclization conditions.

In contrast to our expectation, iodocyclization of **12a** affords the lactone **14a**, even under conditions designed to facilitate hydrate formation (I_2 in 10% aqueous CH_3CN). Moreover, the stereoselectivity manifested in this lactonization is quite high: high field NMR analysis of the epoxides produced on methanolysis indicate that the ratio is 9:1. Iodolactonization of esters is well precedented, although high 1,3-relative asymmetric induction in five-membered ring formation is not.[9] When applied to the ketal ester **12b**, the iodo lactone **14b** is produced in 94% yield with the cis isomer predominating to the extent

(1) (a) Construction from carbohydrates: Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988. Ireland, R. E.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1980**, *102*, 1155. Ireland, R. E.; Courtney, L.; Fitzsimmons, B. J. *J. Org. Chem.* **1983**, *48*, 5186. Ireland, R. E.; Vevert, J. P. *Can. J. Chem.* **1981**, *59*, 572; *J. Org. Chem.* **1980**, *45*, 4259. Fraser-Reid, B.; Sun. K. M.; Tam, T. F. *Bull Soc. Chim. Fr.* **1981**, *2*, 238. (b) Oxidative cyclization reactions: Walba, D. M.; Stoudt, G. S. *Tetrahedron Lett.* **1982**, *23*, 727. Baldwin, J. E.; Crossley, M. J.; Lehtonen, E. M. M. *J. Chem. Soc., Chem. Commum.* **1979**, 918. Amouroux, R.; Folefoc, G.; Chastrette, F.; Chastrette, M. *Tetrahedron Lett.* **1981**, *22*, 2259. (c) Assembly from optically active precursors: Collum, D. B.; McDonald, J. H., III; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2117, 2118, and 2120. Ho, P.-T. *Can. J. Chem.* **1982**, *60*, 90. (d) Relative asymmetric induction: Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6789. Schmid, G.; Fukuyama, T.; Akasaka, K.; Kishi, Y. *Ibid.* **1979**, *101*, 259. Fukuyama, T.; Wang, C. L. J.; Kishi, Y. *Ibid.* **1979**, *101*, 260. Fukuyama, T.; Aksaka, K.; Karanewsky, D. S.; Wang, C. L. J.; Schmid, G. Kishi, Y. *Ibid.* **1979**, *101*, 262. Ireland, R. E.; Haebich, D. *Chem. Ber.* **1981**, *114*, 1418. Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1978**, 2745. Isobe, M.; Funabishi, Y.; Ichikawa, Y.; Mio, S.; Goto, T. *Tetrahedron Lett.* **1984**, *25*, 2021. Walba, D. M.; Wand, M. D. *Tetrahedron Lett.* **1982**, *23*, 4995; Murata, S. Noyori, R. *Tetrahedron Lett.* **1982**, *23*, 2601. Isobe, M.; Ichikawa, Y.; Masaki, H.; Goto, T. *Tetrahedron Lett.* **1984**, *25*, 3607. (e) Absolute asymmetric induction: Wuts, P. G. M.; D'Costa, R.; Butler, W. *J. Org. Chem.* **1984**, *49*, 2582.

(2) S. D. Rychnovsky; P. A. Bartlett, *J. Am. Chem. Soc.* **1981**, *103*, 3963. Bartlett, P. A.; Holmes, C. P. *Tetrahedron Lett.* **1983**, *24*, 1365. Ting, P. C.; Bartlett, P. A. *J. Am. Chem. Soc.* **1984**, *106*, 2668. Michael, J. P.; Ting, P. C.; Bartlett, P. A. *J. Org. Chem.* **1985**, *50*, 2416.

(3) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. Ireland, R. E.; Wilcox, C. S., Jr. *Tetrahedron Lett.* **1977**, 2839.

(4) Allinger, N. L. *J. Am. Chem. Soc.* **1959**, *81*, 232.

(5) Bartlett, P. A.; Richardson, D. P.; Myerson, J. *Tetrahedron* **1984** *40*, 2317. See also: Collum, D. B.; McDonald, J. H., III; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2118.

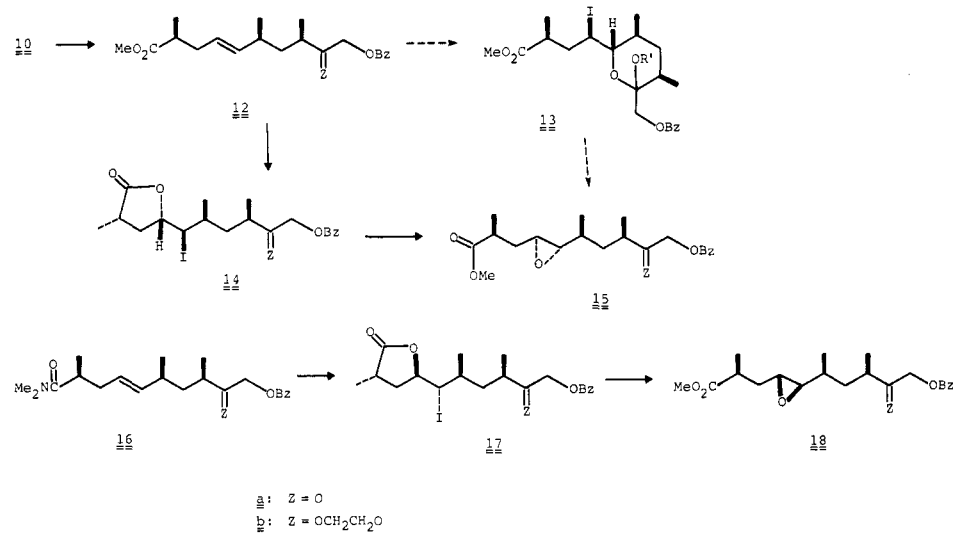
(6) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.

(7) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

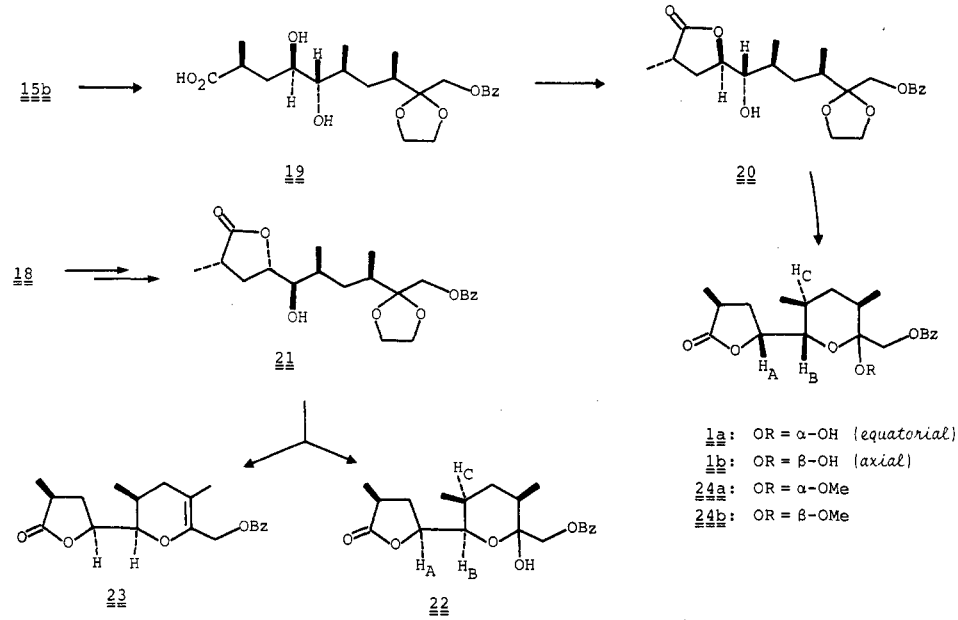
(8) Hill, R. K. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press, Orlando, FL, 1984; Vol. 3, p 503.

(9) Jäger, V.; Günther, H. J. *Tetrahedron Lett.* **1977**, 2543. Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* **1978**, *100*, 3950.

Scheme III



Scheme IV

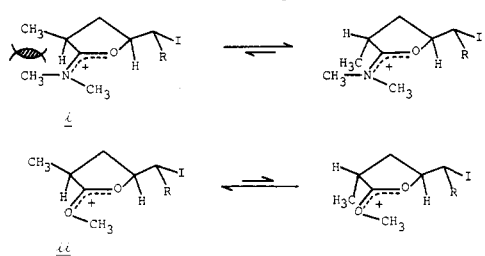


of 80%.[10] To assign the configuration of iodolactones **14** and the major epoxides **15**, we prepared the diastereomers **17a** and **18a** by iodolactonizing the dimethylamide **16a**. As Yoshida has demonstrated, such amides afford very selectively the *trans*-α-methyl γ-lactones.[11] Although arrived at in a serendipitous manner, an efficient route to the desired epoxides was in hand.

With the α-configuration of the epoxide established, it was necessary to engineer its hydrolysis at the position γ to the carboxyl group. The epoxy esters **15** were exposed to guanidine in ethanol, conditions designed to facilitate hydrolysis of the methyl ester and subsequent intramolecular opening of the epoxide. In the case of ketone **15a**, a complex mixture of products is produced, among which are no γ-lactones (IR evidence). These undesired products arise from participation of the ketone before hydrolysis of the ester occurs, since treatment of the ketal **15b** under identical conditions affords cleanly, at room temperature over 24 hours, a more polar intermediate presumed to be diol acid **19** (Scheme IV); when the solvent is replaced with THF and the mixture is acidified, lactone **20** is obtained in 95% crude yield (77% stereochemical purity). Sulfuric acid-catalyzed cyclization of this material in acetone at reflux in turn affords in 93% yield the desired tetrahydropyran lactone **1** as a 54:23:23 mixture of the β- and α-anomers (**1b** and **1a**) and other isomers, respectively. From this mixture, simple crystallization from hexane provides a purified mixture of the desired stereoisomers

(10) The major isomer **12a** (90% of the mixture), affords a 9:1 ratio of epoxides **15a** and **18a**; the minor isomer in **12a** accounts for the remaining diastereomers.

(11) Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.-I.; Yoshida, Z.-I., Yanagi, K.; Kazunori, Y.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079. The trans selectivity in the amide cyclizations is attributed to steric interactions between the β-substitutent and one of the *N*-methyl groups in the cis intermediate i. The analogous intermediate in the ester



cyclization (ii) lacks this potential interaction, which may explain the predominance of cis material from this lactonization.

1b and **1a**.

The structures of the tetrahydropyran lactones **1**, in particular the configurations at the stereocenters which link the rings, were assigned straightforwardly by NMR decoupling experiments. In the major, β-anomer **1b**, irradiation of the resonance for H_B (see structure) [δ 3.88 (dd, 1, J = 2.3, 9.8 Hz)] results in simplification of that for H_A [δ 4.65 (ddd, 1, J = 2.3, 2.4, 8.9 Hz)] to a double doublet with J = 2.4 and 8.9 Hz, indicating that the 9.8-Hz coupling of H_B arises from a trans-diaxial relationship with H_C. A 10.6-Hz coupling was similarly shown for the α-anomer **1a**. The anomeric configuration of the predominant isomer was assigned as β (axial) on the basis of known steric and electronic effects.

In contrast to its unfavorable behavior under basic conditions, the epoxy ketone **15a** is neatly converted to the tetrahydropyran **1** with perchloric acid in 10% aqueous THF (81% chromatographed yield as 77:19:4 mixture of β/α/other isomers). Similar treatment of epoxy ketal **15b** gives the ketal lactone intermediate **20** and subsequently **1**. Direct conversion of **15b** to **1** appears to produce a higher proportion of stereoisomers than the two-step methods, although the reasons for this are not clear.

Cyclization of the stereoisomeric epoxide **18b** was also explored briefly. Compound **18b** is produced by mesylation of hydroxy lactone **20** followed by Na_2CO_3 in methanol. The inverted hydroxy lactone **21** is formed with H_2SO_4 in aqueous THF at room temperature. Under the same conditions which convert **20** cleanly to **1** (H_2SO_4 in refluxing acetone), the isomer **21** affords a mixture of tetrahydropyran lactone **22** (46% chromatographed yield) and the dihydropyran **23** (31%). The propensity for **21** to give enol ether **23** is a reflection of the steric congestion present in either of the chair forms of hemiketal **22**. The NMR spectrum of **22** reveals a coupling constant J_{BC} = 8.6 Hz. Although this is higher than normally encountered for an axial–equatorial relationship, it is likely that distortion of the tetrahydropyran ring with resulting reduction in the dihedral angle between the hydrogens is responsible.

We also explored the protection of the hemiketal moiety of the hydroxytetrahydropyran **1** by conversion to the methyl ketals **24**. This was readily accomplished with H_2SO_4 in dry methanol at room temperature, with formation of the anomeric methyl ketals as a 4:1 mixture of anomers. Separation of the anomers and resubmission of the minor component to the reaction conditions can be used to increase the overall yield of the β material. These compounds are also produced directly on treatment of the ketal lactone **20** with acid in methanol.

Experimental Section[12]

(3*R,5*S**)-5-[(2*R**,3*R**,5*S**,6*S**)-6-Hydroxy-3,5-dimethyl-6-(phenylmethoxy)-2,3,4,5-tetrahydropyran-2-yl]-3-methyl-4,5-dihydro-2(3*H*)-furanone (1b) and the 6*R** Anomer, 1a.** A solution of 1.57 g (4.0 mmol) of the lactone ketal mixture **20** described below and 2.0 mL of 2 M H_2SO_4 in 100 mL of acetone was heated at reflux for 4 h. The mixture was cooled, 20 mL of saturated $NaHCO_3$ was added, and most of the acetone was removed on a rotary evaporator. Water and brine were added and the mixture was extracted several times with ethyl acetate. Workup afforded 1.45 g of crude tetrahydropyran lactone **1**, which was purified by chromatography (1:2 EtOAc/hexane) to give 1.29 g (93% yield) of the product as a 54:23:23 mixture of **1b**/**1a**/other isomers. Recrystallization twice from hexane afforded a sample with the ratio of 73:20:7. Final purification of **1b** was achieved by HPLC (Partisil 10, 1:2 EtOAc/hexane): mp 83 °C (hexane); IR (KBr) 3400 br, 2940, 1760, 1170, 1080, 1000 cm^{-1}; ^1H NMR δ 0.89 (d, 6, J = 6.5), 1.23 (d, 3, J = 7.3), 1.38–1.72 (m, 4), 1.82 (ddd, 1, J = 8.9, 9.4, 12.4), 2.47 (ddd, 1, J = 2.4, 9.7, 12.4; on irradiation of resonance at δ 1.82 collapses to dd, J = 2.4, 9.7), 2.68–2.87 (m, 1), 3.14 (d, 1, J = 1.3), 3.33 (d, 1, J = 9.9), 3.50 (d, 1, J = 9.9), 3.88 (dd, 1, J = 2.3, 9.8), 4.56 (d, 1, J = 12.2), 4.62 (d, 1, J = 12.2), 4.65 (ddd, 1, J = 2.3, 2.4, 8.9; on irradiation of resonance at 3.88 collapses to dd, J = 2.4, 8.9), 7.20–7.45 (m, 5). Anal. Calcd. for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.77; H, 8.08.

(3*R,5*S**,6*R**)-6-Ethenyl-3,5-dimethyl-3,4,5,6-tetrahydro-2-pyrone (6).** A mixture of 12.45 g (40 mmol) of selenolactone **5b**,[5] 28.17 g (0.01 mol) of chloramine-T, 0.91 g (4 mmol) of triethylbenzylammonium chloride,[13] 400 mL of benzene, and 400 mL of 1 M phosphate buffer, pH 7.5, was stirred vigorously at 21 °C for 3 h. The aqueous layer was extracted with two portions of petroleum ether, the combined organic layer was dried, and the solvent was removed by distillation through a 20-cm Vigreux column and then under vacuum. Sublimation (60 °C/0.05 mmHg) of the residue gave 5.71 g (93% yield) of lactone **6**, >99% pure by NMR: mp 57–8 °C; IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR δ 0.98 (d, 3), 1.30 (d, 3), 1.40 (q, 1), 1.74–1.90 (m, 1), 1.93–2.05 (m, 1), 2.49–2.63 (m, 1), 4.36 (dd, 1), 5.26–5.36 (m, 2), 5.73–5.89 (m, 1); ^{13}C NMR δ 16.83, 16.95, 33.73, 36.01, 37.12, 75.72, 87.66, 118.37, 135.28, 173.47. Exact mass calcd for $C_9H_{14}O_2$: m/z 154.0994. Found: 154.0999.

(2*R,3*R**,5*S**,6*R**)-2-[((Benzyloxy)methyl]-6-ethenyl-3,5-dimethyl-3,4,5,6-tetrahydropyran-2-ol (8).** To a stirring solution of 16.98 g (41.3 mmol) of [(benzyloxy)methyl]tributyltin in 150 mL of dry THF at −78 °C was added 25.0 mL of 1.61 M butyllithium/hexane (40.3 mmol) over a 2-min period.[6] After 4 min, a solution of 3.86 g (25 mmol) of lactone **6** in a total of 70 mL of THF was added. After 5 min, the reaction was quenched by the addition of 50 mL of aqueous saturated NH_4Cl, then partitioned between petroleum ether and water. The crude product obtained on workup was purified by chromatography (1:9 → 1:3 EtOAc/hexane) to give 6.375 g (92% yield) of hemiacetal **8**: IR 3350 cm^{-1}; ^1H NMR δ 0.82 (d, 3), 0.89 (d, 3), 1.35–1.78 (m, 4), 3.09 (br s, 1), 3.49 (ABq, 2, J = 10.1), 3.93 (t, 1, J = 8.4), 4.67 (ABq, 2, J = 12.1), 5.13–5.29 (m, 2), 5.74–5.8 (m, 1), 7.25–7.35 (m, 5). Exact mass calcd for $C_{17}H_{22}O_2$ (M−H_2O): 258.1620. Found: 258.1618.

(1*R,2*S**,4*R**)-1-Ethenyl-5,5-(ethylenedioxy)-2,4-dimethyl-6-(phenylmethoxy)hexyl Propanoate (9).** A mixture of 8.44 g (32.0 mmol) of hemiacetal **8**, 4.89 g (40 mmol) of 4-(dimethylamino)pyridine, and 20 mL (156 mmol) of propanoic anhydride was kept at 21 °C for 30 min, and then partitioned between 300 mL of hexane and 60 mL of 1 N HCl. The aqueous phase was extracted with another portion of hexane, and the combined organic layer was washed with 1 N HCl and then with successive 30-mL portions of 2 N NaOH until the aqueous phase remained basic. Workup afforded 11.45 g of a thick oil which was purified by chromatography (1:8 EtOAc/hexane) to give 9.82 g (92% yield) of the acyclic keto ester: IR 1740, 1460, 1200 cm^{-1}; ^1H NMR δ 0.88 (d, 3), 1.10 (d, 3), 1.15 (t, 3), 1.6–2.0 (m, 3), 2.34 (q, 2), 2.86 (m, 1), 4.11 (ABq, 2), 4.60 (s, 2), 5.2 (m, 3), 5.7 (m, 1), 7.3 (m, 5). A solution of 3.32 g (10.0 mmol) of this material in a total of 6 mL of dry CH_2Cl_2 was added over a 2-min period to a stirring solution of 2.68 g (13 mmol) of 1,2-bis(trimethylsilyloxy)ethane and 120 mg (0.54 mmol) of trimethylsilyl triflate in 4 mL of CH_2Cl_2 at −78 °C. After 1 h at −78 °C, the mixture was warmed to 0 °C over a 6-h period, then quenched by the addition of 0.25 mL of pyridine. The reaction mixture was partitioned between ether and saturated $NaHCO_3$, the aqueous layer was extracted with an additional portion of ether, and the combined organic phase was worked up to give 4.34 g of crude material. Chromatography (1:5 EtOAc/hexane) provided 3.53 g (94% yield) of pure ketal ester **9**: IR 2980, 1740, 1190, 1100 cm^{-1}; ^1H NMR δ 0.90 (d, 3), 0.98 (d, 3), 1.14 (t, 3), 1.6–2.15 (m, 4), 2.34 (q, 2),

(12) General. Unless otherwise indicated, all reaction workup culminated in washing the organic layer with water and brine, drying over $MgSO_4$ or $CaSO_4$, and removing the solvent on a rotary evaporator and finally under high vacuum. IR spectra were obtained on liquid films and NMR spectra in $CDCl_3$ as solvent, unless otherwise indicated.

(13) Sharpless, K. B.; Gordon, K. M.; Lauer, R. F.; Patrick D. W.; Singer S. P.; Young, M. W. *Chem. Scr.* **1975**, *8A*, 9.

3.44 (s, 2), 4.00 (m, 4), 4.57 (ABq, 2), 5.2 (m, 3), 5.75 (m, 1), 7.30 (m, 5).

(2*R,4*E*,6*R**,8*S**)-9,9-(Ethylenedioxy)-2,6,8-trimethyl-10-(phenylmethoxy)-4-decenoic Acid (10).** A solution of lithium diisopropylamide was generated from 11.2 mL of 1.61 M (18.0 mmol) butyllithium/hexane and 3.04 mL (22 mmol) of diisopropylamine in 140 mL of dry THF at 0 °C. The solution was cooled to −75 °C, and 120 mL of a 1:1 mixture of hexamethylphosphoramide and THF was added over 10 min. After 5 min, a solution of 2.26 g (6.0 mmol) of ester **9** in a total of 10 mL of THF was added within 3 min. After 7 min, 15 mL of a 2.0 M solution (30 mmol) of *tert*-butyldimethylsilyl chloride in THF was added during 1 min. The mixture was stirred at −78 °C for 9 min, then allowed to warm to 21 °C. After 2.5 h, 20 mL of methanol was added, the mixture was partitioned between hexane and 1 N HCl, and the aqueous portion was extracted with another portion of hexane. The combined organic phase was evaporated without drying, and the residue was dissolved in 100 mL of THF and 30 mL of 1.5 N HCl. After 3 h at 21 °C, this mixture was partitioned between 1 N NaOH and ether, and the aqueous phase was washed with another portion of ether, acidified with concentrated HCl, and extracted with ether. Workup afforded 1.91 g (84% yield) of analytically pure ketal acid **10**. The NMR spectrum indicated that this material was an 9:1 mixture of stereoisomers. IR 3200, 2980, 1710, 1100, 740 cm^{-1}; ^1H NMR δ 0.86 (d, 3), 0.945 (d, 3), 1.15 (d, 3), 1.0–2.5 (m, 7), 3.42 (ABq, 2), 3.60 (m, 4), 4.62 (m, 2), 5.1–5.4 (m, 2), 7.34 (m, 5). Anal. Calcd for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 70.09; H, 8.69.

Methyl (2*R,4*E*,6*R**,8*S**)-9,9-(Ethylenedioxy)-2,6,8-trimethyl-10-(phenylmethoxy)-4-decenoate (12b).** A solution of 2.12 g (5.62 mmol) of acid **10** in 20 mL of ether was treated with excess diazomethane in the dark for 20 min at 0 °C. Acetic acid in ether (10%) was added until the solution was colorless, the solvent was evaporated, and the residue was chromatographed (14% EtOAc/hexane) to give 2.00 g (91% yield) of the methyl ester **12b**: IR 1740 cm^{-1}; ^1H NMR δ 0.87 (d, 3), 0.94 (d, 3), 1.1 (m, 1), 1.12 (d, 3), 1.4 (m, 1), 1.9 (m, 1), 2.1 (m, 2), 2.3 (m, 1), 2.5 (m, 1), 3.46 (s, 2), 3.65 (s, 3), 4.0 (m, 4), 4.57 (s, 2), 5.25 (m, 2), 7.3 (m, 5).

(3*R,5*R**)-5-[(1*S**,2*R**,4*S**)-1-Iodo-5,5-(ethylenedioxy)-2,4-dimethyl-6-(phenylmethoxy)hexyl]-3-methyl-4,5-dihydro-2(3*H*)-furanone (14b).** A solution of 4.57 g (18 mmol) of iodine in 100 mL of acetonitrile was added to a stirring solution of 2.34 g (6 mmol) of ester **12b** in a mixture of 30 mL of water and 170 mL of acetonitrile at −15 °C. An additional 9.14 g (36 mmol) of iodine was added after 3 h. After 6 h, the mixture was diluted with ether and washed with saturated, aqueous $NaHCO_3$ and $Na_2S_2O_3$. The aqueous layers were back-extracted with ether, and the combined organic fractions were dried for 5 h at 0 °C and evaporated to give 3.61 g of the iodolactone as a brown semisolid which was used directly in the next reaction: IR 2980, 1780, 1170, 1100 cm^{-1}; ^1H NMR δ 0.92 (d, 3), 0.95 (d, 3), 1.1–1.7 (m, 4), 1.28 (d, 3), 1.84–2.03 (m, 1), 2.56–2.8 3 (m, 2), 3.48 (s, 2), 3.85–4.15 (m, 5), 4.45–4.65 (m, 1), 4.55 (d, 1, J = 12.5), 4.65 (d, 1, J = 12.5), 7.15–7.50 (m, 5). Exact mass calcd for $C_{22}H_{31}O_5I$: 502.1216. Found: 502.1232.

Methyl (2*R,4*R**,5*R**,6*R**,8*S**)-4,5-Epoxy-9,9-(ethylenedioxy)-2,6,8-trimethyl-10-(phenylmethoxy)decanoate (15b).** A mixture of the iodolactone described above (<6 mmol) and 0.954 g (9.0 mmol) of Na_2CO_3 in 150 mL of methanol was stirred at 0 °C for 4 h, then at 21 °C for 2 days. The mixture was partitioned between 300 mL of 2:1 water/brine and 100 mL of ethyl acetate, the aqueous layer was extracted with another portion of ethyl acetate, and the combined organic phase was worked up to give 2.40 g of crude epoxide. This material was purified by chromatography (30% EtOAc/hexane) to give 2.30 g (94% yield) of epoxide **15b** as a 9:1 mixture of isomers: IR 2970, 1740, 1200, 1100 cm^{-1}; ^1H NMR δ 0.93 (d, 3), 0.95 (d, 3), 1.16–1.27 (m, 1), 1.23 (d, 3), 1.33–1.80 (m, 3), 1.81–1.99 (m, 1), 2.13–2.26 (m, 1), 2.45 (dd, 1, J = 2.2, 7.3), 2.54–2.69 (m, 1), 2.70 (dt, 1, J = 2.2, 6.0), 3.49 (s, 2), 3.68 (s, 3), 3.91–4.06 (m, 4), 4.58 (s, 2), 7.23–7.43 (m, 5). Exact mass calcd for $C_{23}H_{34}O_6$: 406.2356. Found: 406.2375. Calcd for $C_{15}H_{25}O_5$ (M − CH_2OBz): 285.1702. Found: 285.1703.

(3*R,5*S**)-5-[(1*R**,2*R**,4*S**)-5,5-(Ethylenedioxy)-1-hydroxy-2,4-dimethyl-6-((phenylmethoxy)hexyl)]-3-methyl-4,5-dihydro-2(3*H*)-furanone (20).** A solution of 1.83 g (4.5 mmol) of epoxide **15b**, 1.29 g (13.5 mmol) of guanidine hydrochloride, and 10 mL of 0.9 N NaOH in 50 mL of 96% ethanol was kept at 21 °C for 20 h. The solution was brought to pH 6 with 3 N H_2SO_4, and the ethanol was removed at reduced pressure on a rotary evaporator. Water (5 mL), 75 mL of THF, and 3 mL of 3 M H_2SO_4 were added and the mixture was stirred at 21 °C for 6 h, at which point TLC analysis indicated that a single material was present. Saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL) were added, most of the THF was removed on the rotary evaporator, and the remaining solution was extracted with several portions of ethyl acetate. Workup afforded 1.89 g of crude lactone, which was purified by chromatography (2:3 EtOAc/hexane) to give 1.68 g (95% yield) of lactone **20**. ^1H NMR analysis indicated that this material consisted of a mixture of isomers, of which the major one (**20**) predominated to the extent of 77%: IR 3970 br, 2970, 1770, 1090, 1040 cm^{-1}; ^1H NMR δ 0.91 (d, 3), 0.97 (d, 3), 1.24 (d, 3), 1.65–1.97 (m, 4), 2.10–2.25 (m, 1), 2.39 (br s, 1), 2.46 (ddd, 1, J = 4.1, 9.7, 13.3), 2.68–2.86 (m, 1), 3.43, (d, 1, J = 10.8), 3.51 (d, 1, J = 10.8), 3.59 (dd, 1, J = 3.6, 7.7), 3.92–4.08 (m, 4), 4.55 (dd, 1, J = 3.6, 7.8), 4.58 (s, 2), 7.20–7.45 (m, 5). Anal. Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.06; H, 8.16.

(3*R*,5*S)-5-[(2*R**,3*R**,5*S**,6*S**)-6-Methoxy-3,5-dimethyl-6-(benzyloxymethyl)-2,3,4,5-tetrahydropyran-2-yl]-3-methyl-4,5-dihydro-2(3*H*)-furanone (24b) and the 6*R** Anomer, 24a.** A solution of 325 μL (6.0 mmol) of 98% H_2SO_4 and 1.01 g (2.90 mmol) of a mixture of hydroxytetrahydropyrans containing a 49:24:27 mixture of **1b**/**1a**/other isomers in 60 mL of methanol was kept at 21 °C for 1 h. After neutralization with 20 mL of saturated $NaHCO_3$, the methanol was removed on a rotary evaporator, water was added, and the mixture was extracted with several portions of ethyl acetate. The crude product (0.99 g) consisted of a 59:14:27 ratio of **24b**/**24a**/other isomers which were separated on HPLC (1:5 EtOAc/hexane) to give 0.51 g (48% yield) of the β-anomer **24b** of 97% purity: IR 2980, 1775, 1110 cm^{-1}; ^1H NMR δ 0.87 (d, 3, J = 6.2), 0.89 (d, 3 J = 6.8), 1.22 (d, 3, J = 7.3), 1.28–1.65 (m, 3), 1.82 (ddd, 1, J = 8.9, 9.7, 12.6), 1.94–2.11 (m, 1), 2.52 (ddd, 1, J = 2.2, 9.5, 12.6), 2.76–2.94 (m, 1), 3.17 (s, 3), 3.44 (d, 1, J = 9.9), 3.52 (d, 1, J = 9.9), 3.57 (dd, 1, J = 2.0, 10.3), 4.49 (d, 1, J = 12.3), 4.55 (d, 1, J = 12.3), 4.64 (ddd, 1, J = 2.0, 2.2, 8.9), 7.28–7.5 (m, 5). Exact mass calcd for $C_{21}H_{30}HO_5$: 362.2094. Found: 362.2079. Calcd for $C_{20}H_{27}O_4$ (M − OCH_3): 331.1909. Found: 331.1908.

Acknowledgment. This work was supported by the National Institutes of Health through grant no. GM-30141. We would also like to thank the Andrew E. and G. Norman Wigeland Fund of the American-Scandinavian Foundation for a fellowship to K.H.H. and Takeda Chemical Industries for support of A.M.

Registry No. (±)-**1a**, 99032-04-9; (±)-**1b**, 98944-62-8; **5b**, 98944-65-1; (±)-**6**, 98944-66-2; (±)-**8**, 98944-67-3; (±)-**9**, 98944-68-4; (±)-**9** (diketal), 98976-62-6; (±)-**10**, 98944-69-5; (±)-**11**, 99032-05-0; (±)-**12a**, 98944-75-3; (±)-**12b**, 98944-70-8; **13**, 98944-71-9; (±)-**14b**, 98944-72-0; (±)-**15a**, 98944-76-4; (±)-**15b**, 98944-73-1; (±)-**16b**, 98944-77-5; (±)-**17b**, 99032-07-2; (±)-**18b** (isomer 1), 99032-08-3; (±)-**18b** (isomer 2), 99032-09-4; (±)-**19**, 98944-64-0; (±)-**20**, 98944-63-9; (±)-**21** (isomer 1), 99032-10-7; (±)-**21** (isomer 2), 99032-11-8; (±)-**22**, 99032-12-9; (±)-**23**, 98944-78-6; (±)-**24a**, 99032-06-1; (±)-**24b**, 98944-74-2.

Supplementary Material Available: Experimental details and characterization of compounds reported in the text but not described in the Experimental Section (4 pages). Ordering information is given on any current masthead page.