Synthesis of Bicyclic Ortho Esters by Epoxy Ester Rearrangements and Study of Their Ring-Opening Reactions

Peter Wipf* and Diana C. Aslan

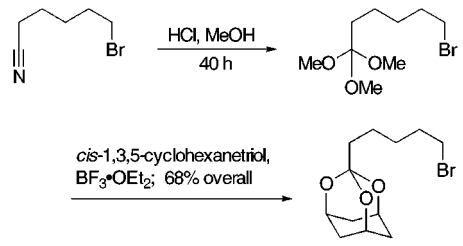
Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

pwipf+@pitt.edu

Received September 29, 2000

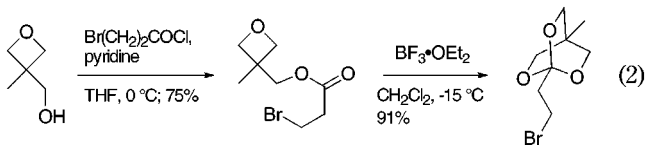
Introduction

Ortho esters represent a class of masked acid derivatives that greatly modify the reactivity pattern of the parent carboxylates and permit entry into a much broader range of nucleophilic and electrophilic transformations.[1] However, ortho esters have found surprisingly little use in organic synthesis to date, and much of their chemistry remains to be explored.[2] Since ortho esters are among the few carboxylic acid protective groups that demonstrate a high level of stability toward strong nucleophiles and bases, most current applications have been limited to protective group chemistry.[3] While a broad use of ortho esters may have been complicated by the difficulty and low yields in their preparation from acids or nitriles and alcohols, the Pinner reaction, followed by ortho ester exchange processes, represents a useful general strategy (eq 1).[4] Corey's OBO-ester pro-



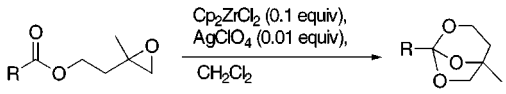
(1)

tocol, e.g., the BF_3-etherate mediated preparation of the 2,6,7-trioxabicyclo[2.2.2]octane ring system from oxetanyl esters, allows the conversion of functionalized carboxylates into ortho esters and has found wide application (eq 2).[5,6]



(2)

We have recently reported a facile synthesis of 2,7,8-trioxabicyclo[3.2.1]octanes (ABO-esters) via cationic zirconocene-catalyzed rearrangement of epoxy esters (eq 3).[2f,7,8] ABO-esters display a higher acid stability com-



(3)

pared to OBO-esters and are selectively cleaved in the presence of cationic zirconocene.[7] This orthogonal protective group profile and the possibility to cleave the five-membered ring preferentially to the six-membered ring in the [3.2.1] bicyclic framework provide new opportunities for the use of ortho esters as protective groups and in synthetic methodology.[2f] We now report new applications of the zirconocene-catalyzed epoxy ester rearrangement for the preparation of ortho ester scaffolds as well as some explorative studies for the selective ring opening with organometallic reagents.

Results and Discussion

Acylation of the enantiopure alcohol **2** derived from (*S*)-citramalate via triol **1**[9a] with hydrocinnamic acid, acetal hydrolysis, and mesylation of the primary alcohol followed by base-induced cyclization provided the epoxy ester **5** in high overall yield (Scheme 1). Addition of 0.01 equiv of $AgClO_4$ to a solution of **5** and 0.10 equiv of Cp_2ZrCl_2 in CH_2Cl_2 led to the in situ formation of a cationic zirconocene species that served as a selective Lewis acid for the rearrangement of epoxy ester into the ortho ester moiety.[7,8,10,11] Small amounts of the tetrahydrofuran ester side product formed in this transformation were removed by exposure of the crude reaction mixture to 1 M LiOH.[7] The (1*S*,5*R*)-2,7,8-trioxabicyclo[3.2.1]octane **6** was thus obtained in 24% overall yield from acetal **2**.

A shortened route was used for the preparation of racemic **6** (Scheme 2). Esterification of the commercially available homoallylic alcohol **7** with *m*-CPBA led to (±)-**5**, which was rearranged to ortho ester (±)-**6** in 82% yield. Since the latter reaction was performed on considerably larger scale, the product was formed in higher yield and did not require the purification by saponification necessary for optically active **6**.

(1) For representative recent examples, see: (a) Zhu, J.; Munn, R. J.; Nantz, M. H. *J. A*(1).For representative recent examples, see: (a) Zhu, J.; Munn, R. J.; Nantz, M. H. *J. Am. Chem. Soc.* **2000**, *122*, 2645. (b) Kanoh, S.; Nishimura, T.; Kita, Y.; Ogawa, H.; Motoi, M.; Takani, M.; Tanaka, T. *J. Org. Chem.* **2000**, *65*, 2253. (c) Oku, A.; Numata, M. *J. Org. Chem.* **2000**, *67*, 1899. (d) Andres, J. M.; de Elena, N.; Pedrosa, R. *Tetrahedron* **2000**, *56*, 1523−1531. (e) Ito, H.; Sato, A.; Kusanagi, T.; Taguchi, T. *Tetrahedron Lett.* **1999**, *40*, 3397.

(2) Reviews: (a) DeWolfe, R. H. In *Carboxylic Ortho Acid Derivatives*; Academic Press: New York, 1970. (b) DeWolfe, R. H. *Synthesis* **1974**, 153. (c) Pindur, U.; Müller, J.; Flo, C.; Witzel, H. *Chem. Soc. Rev.* **1987**, *16*, 75. (d) Kantlehner, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, p 485. (e) Scarpati, R.; Iesce, M. R.; Cermola, F.; Guitto, A. *Synlett* **1998**, 17. (f) Wipf, P.; Tsuchimoto, T.; Takahashi, H. *Pure Appl. Chem.* **1999**, *71*, 415.

(3) (a) Kocienski, P. J. *Protecting groups*; Thieme Verlag: Stuttgart, 1994. (b) Greene, T. W.; Wuts, P. G. M. *Protective groups in organic synthesis*, 3rd ed.; Wiley: New York, 1999.

(4) Voss, G.; Gerlach, H. *Helv. Chim. Acta* **1983**, *66*, 2294.

(5) Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571.

(6) (a) Luo, Y.; Blaskovich, M. A.; Lajoie, G. A. *J. Org. Chem.* **1999**, *64*, 6106. (b) Fenk, C. J. *Tetrahedron Lett.* **1999**, *40*, 7955. (c) Ducray, P.; Lamotte, H.; Rousseau, B. *Synthesis* **1997**, 404. (d) Charette, A. B.; Chua, P. *Tetrahedron Lett.* **1997**, *38*, 8499. (e) Dubé, D.; Deschenes, D.; Tweddell, J.; Gagnon, H.; Carlini, R. *Tetrahedron Lett.* **1995**, *36*, 1827.

(7) Wipf, P.; Xu, W.; Kim, H.; Takahashi, H. *Tetrahedron* **1997**, *53*, 16575.

(8) Wipf, P.; Xu, W. J. *J. Org. Chem.* **1993**, *58*, 5880.

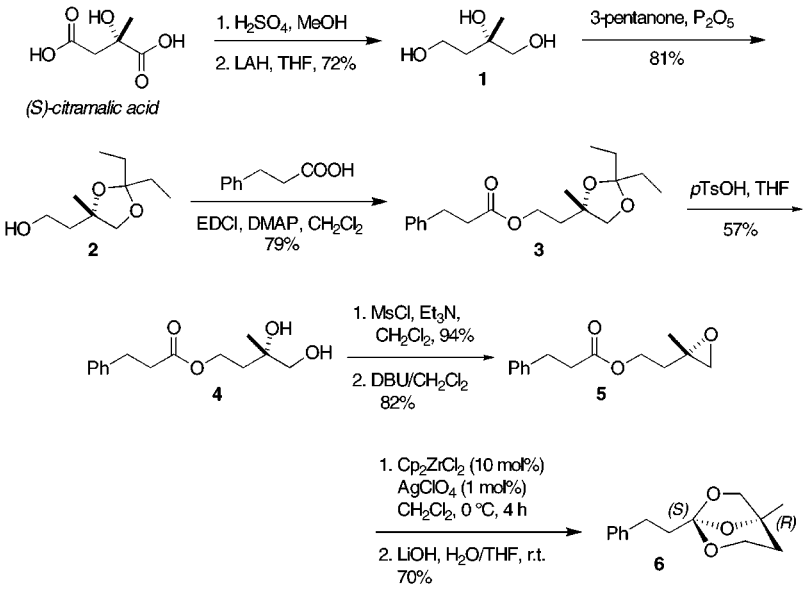
(9) (a) Barner, R.; Schmid, M. *Helv. Chim. Acta* **1979**, *62*, 2384. (b) Gill, M.; Smrdel, A. F. *Tetrahedron*: *Asymmetry* **1990**, *1*, 453.

(10) Wipf, P.; Xu, W. *J. Org. Chem.* **1993**, *58*, 825.

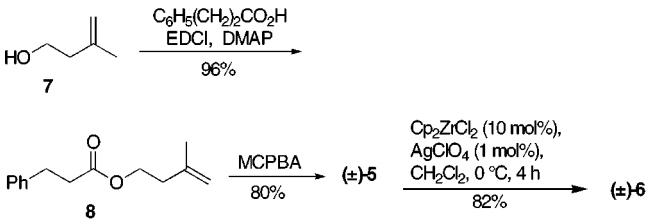
(11) Suzuki, K. *Pure Appl. Chem.* **1994**, *66*, 1557.

10.1021/jo005665y CCC: $20.00
Published on Web 12/13/2000

Scheme 1



Scheme 2



Our preliminary studies had indicated that ring opening of (±)-**6** with Grignard reagents occurred stereoselectively and a sequential conversion from ortho ester to the ketal and further to the tertiary alcohol was possible.[2f] Indeed, exposure of **6** to an excess of MeMgCl in toluene[12] at room temperature provided ketal **9** in 88% yield (Scheme 3).[13] Subsequent titanium tetrachloride assisted cleavage of **9** with ethyl, isopropyl, and phenyl Grignard reagents provided diols **11a**−**c**,[14,15] which were converted to the corresponding methyl ketones by treatment with PCC[16] and fragmented to the desired tertiary alcohols **12a**−**c** by *β*-elimination with piperidine. Ketal **9** is quite acid sensitive and rearranges to the seven-membered **10**. While this sequence proceeds with good overall yields and allows for the preparation of tertiary alcohols with three different substituents from carboxylic acid precursors, disappointingly we isolated **12a**−**c** as racemic mixtures.

While the reasons for the lack of any transfer of chirality from the enantiomerically pure **6** to the tertiary alcohol **12** are not completely clear, we speculate that the addition to twist boat conformer **9**[13] occurs via an acyclic oxocarbenium ion intermediate[14d,15] that does not provide any 1,5-stereoinduction (Figure 1). We have been unable to identify Lewis acid/nucleophile conditions that would lead to the formation of enantioenriched **11**.

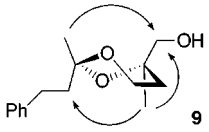
It is possible that steric hindrance between the two quaternary centers on twist boat **9** facilitates the ring-opened, extended intermediate structure **13** that lacks stereocontrol. Accordingly, we proceeded with the synthesis of ortho ester analogues **14**−**16** that were either less substituted or displayed a different substitution pattern (Figure 2). A common motif of bicycles **14** and **15** was the absence of the methyl group at C(5), which should decrease the steric hindrance for a complex formation with a Lewis acid. Fused ring system **16** provided a more rigidified scaffold that should resist relaxing into a twist boat conformation.

While the preparation of epoxy ester **18** proceeded uneventfully, we were unable to obtain the kinetically favored ortho ester **14** in the cationic zirconocene rearrangement and isolated the thermodynamically favored tetrahydrofuran **19** instead in 82% yield (Scheme 4). For the preparation of 4,4-dimethylated bicycle **15**, diol **20** was monoprotected,[17,18] oxidized, subjected to a Wittig chain extension, and deprotected in 65% overall yield (Scheme 5). After conversion to epoxy ester **22**, cationic zirconocene rearrangement at 0 °C for 30 min led to a 3:1 preference for ortho ester **15** over tetrahydrofuran **23**. If the reaction time was increased, only **23** was detected in the reaction mixture. Purification of **15** with concomitant removal of **23** was readily accomplished by treatment with 1 M LiOH solution.

A straightforward reaction sequence was developed for the preparation of ortho ester **16**. After conversion of

(12) Yeh, S.-M.; Lee, G. H.; Wang, Y.; Luh, T.-L. *J. Org. Chem.* **1997**, *62*, 8315.

(13) The structure of **9** was assigned based on COSY and NOE experiments. $CDCl_3$ was filtered through basic alumina in order to remove HCl impurities that would lead to decomposition of the sample.



^1H NOE correlations

(14) For related acetal openings, see: (a) Lindell, S. D.; Elliott, J. D.; Johnson, W. S. *Tetrahedron Lett.* **1984**, *25*, 3947. (b) Elliott, J. D.; Steele, J.; Johnson, W. S. *Tetrahedron Lett.* **1985**, *26*, 2535. (c) Alexakis, A.; Mangeney, P. *Tetrahedron Asymmetry* **1990**, *1*, 477. (d) Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1992**, *114*, 10998. (e) Luh, T. Y. *Synlett* **1996**, 201 and references therein.

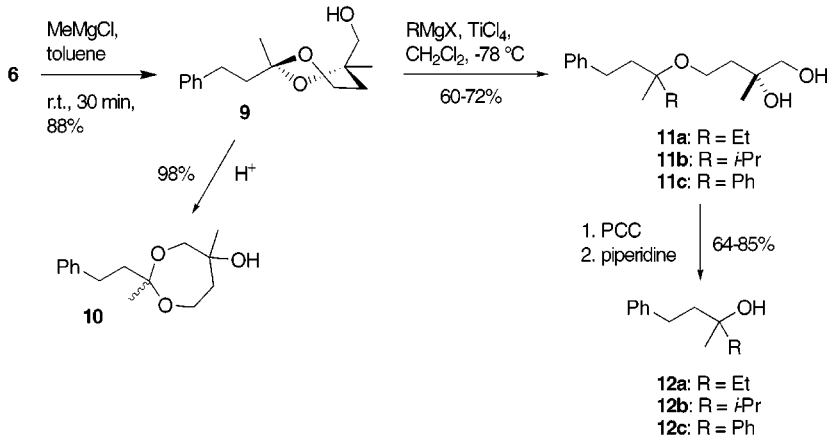
(15) For a related tandem cyclization/alkylation process with epoxy ketones and epoxy esters, see: Fotsch, C. H.; Chamberlin, A. R. *J. Org. Chem.* **1991**, *56*, 4141.

(16) Cisneros, A.; Fernandez, S.; Hernandez, J. E. *Synth. Commun.* **1982**, *12*, 833.

(17) McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388.

(18) Näf-Müller, R.; Pickenhagen, W.; Willhalm, B. *Helv. Chim. Acta* **1981**, *131*, 1424.

Scheme 3



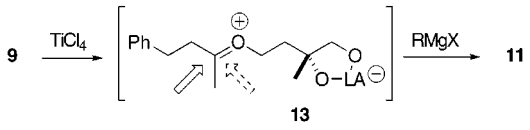


Figure 1. Mechanistic hypothesis for $TiCl_4$-(LA)-assisted opening of ketal **6**.

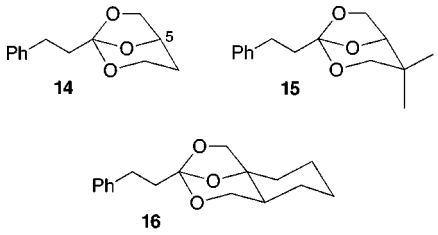
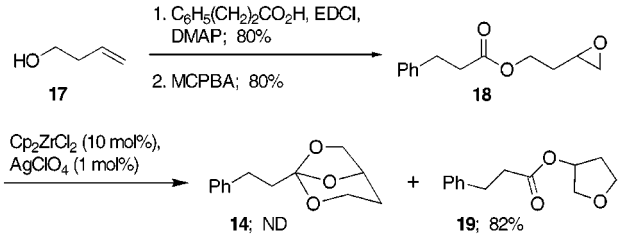


Figure 2. Analogues of bicyclic ortho ester **6** with alternative substitutions.

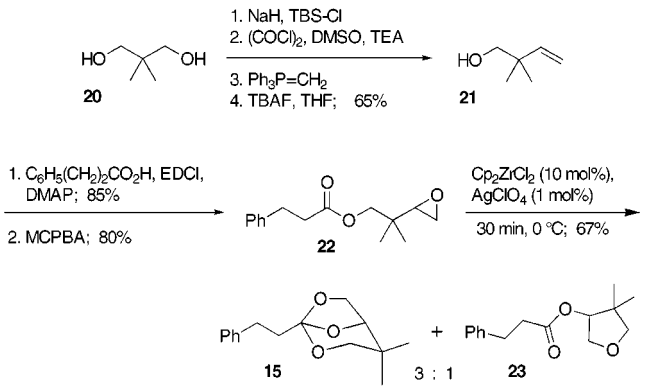
Scheme 4



cyclohexanone to the hydroxymethylene ketone **24**,[19] esterification, Wittig chain extension, and epoxidation led to ester **26**, which smoothly converted to polycyclic **16** under cationic zirconocene conditions (Scheme 6).

With ortho esters **15** and **16** in hand, we explored the ring opening reactions with Grignard reagents. Surprisingly, treatment of **15** with MeMgBr and PhMgBr resulted a 2:1 and 4:1 mixture of diastereomeric acetals **29a** and **29b**, respectively (Scheme 7). The use of cuprate reagents in place of the organomagnesium derivatives did not improve the diastereoselectivity of this substitution reaction. In addition, treatment of **29b** with allyl silane in the presence of $TiCl_4$ led to diol **30** as a 1:1 mixture of diastereomers. We believe that the mediocre diastereoselectivity in the formation of ketal **29** from ortho ester **15** is due to a combination of intramolecular nucleophilic addition through half-chair conformer **27** and intermolecular addition through half-chair **28** that display opposite facial selectivity.

Scheme 5



In contrast, the much more rigid tricyclic ortho ester **16** does not have the option of ring flipping, and indeed ketals **31a** and **31b** were obtained as single diastereomers after treatment with methyl and phenyl Grignard reagents (Scheme 8). While standard allylation of **31a** with allyl silane in the presence of $TiCl_4$ at −78 °C led to a 1:1 mixture of diastereomers of **32**, intramolecular transfer of an allylsilane according to Oshima's protocol[20] provided **32** as an 8:1 mixture of diastereomers. The major isomer was assigned based on transition state model **33**, which is in agreement with the studies by Oshima and others on the stereochemical course of Lewis acid-assisted nucleophilic opening of mixed acetals.[14] After oxidation of the diol with PCC, β-elimination of the resulting 2-alkoxymethylene cyclohexenone with piperidine led to the tertiary alcohol **12d**.

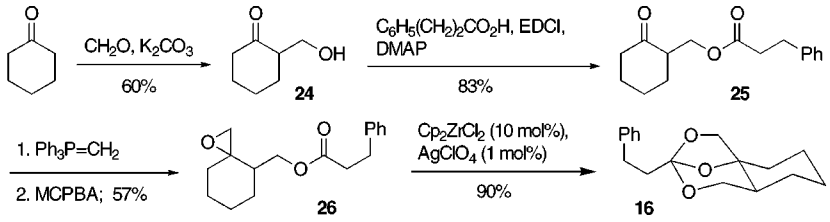
Conclusions

The formation of ortho esters with three distinctively different carbon−oxygen bonds provides an attractive manifold for selective functional group manipulations. The 2,7,8-trioxabicyclo[3.2.1]octane scaffold offers the potential for selective cleavage of C−O bonds based on ring size. We have been able to demonstrate that this strategy is feasible and can be applied for the preparation of ketals as single stereoisomers and tertiary ethers in highly diastereoenriched form. In addition, tertiary al-

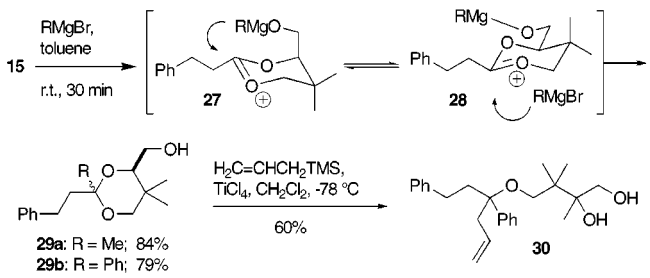
(19) Swan, G. A. *J. Chem. Soc.* **1950**, 1539.

(20) Fujita, K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Org. Lett.* **1999**, *1*, 917.

Scheme 6



Scheme 7



cohols can be obtained from the latter derivatives by a straightforward oxidation-β-elimination sequence. 2,7,8-Trioxabicyclo[3.2.1]octanes (ABO-esters) can be readily obtained by the cationic zirconocene-catalyzed rearrangement of epoxy esters. Since chiral terminal epoxides are available from the chiral pool or by asymmetric synthesis[21] and chirality is cleanly transferred to the ortho ester carbon in the rearrangement step,[2f,7] this strategy also offers the opportunity for enantioselective ortho ester, acetal, ether, and alcohol preparations. Ring-inversions and bond rotations can decrease the facial selectivity of nucleophilic additions to the cationic intermediates, and among the various substitution patterns for ortho esters that we explored, the fused ring system **16** appears to provide the most effective scaffold for highly stereoselective functionalizations.

Experimental Part

General Methods. All reactions with moisture-sensitive compounds were conducted in oven-dried glassware under an atmosphere of dry nitrogen. Solvents were dried by distillation from sodium benzophenone (THF, Et_2O) or from CaH_2 (CH_2Cl_2). *n*-Butyllithium solution was purchased from Aldrich in Sure-Seal containers. Starting materials that were commercially available were used without purification. Melting points are uncorrected and were determined either using recrystallized samples or samples which crystallized during concentration of the chromatography eluents. IR spectra were recorded neat using NaCl cells. NMR spectra were obtained at 300 MHz/75 MHz ($^1H/^{13}C$) in $CDCl_3$. Analytical thin-layer chromatography (TLC) was performed on precoated SiO_2 60 F-254 plates (particle size 0.040−0.055 mm, 230−400 mesh) and visualization was accomplished with a 254 nm UV light or by staining with a basic $KMnO_4$ solution or anisaldehyde dye.

(2*S*)-2-Methyl-butane-1,2,4-triol (1) was prepared in 72% yield from (*S*)-citramalic acid according to a literature procedure.[9]

(4*S*)-2-(2,2-Diethyl-4-methyl-[1,3]dioxolan-4-yl)ethanol (2). To a solution of triol **1** (1.20 g, 1.00 mmol) in 3-pentanone (20 mL) was added at room temperature P_2O_5 (2.84 g, 20.0 mmol, 2 equiv). The reaction mixture was stirred at room temperature for 5 h, another portion of P_2O_5 (2.84 g, 20.0 mmol, 2 equiv) was added and stirring was continued for 10 h. The reaction mixture was neutralized with saturated $NaHCO_3$ and extracted with Et_2O, the organic layer was dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (CH_2Cl_2/MeOH, 10:1) to give pure **2** (1.54 g, 81%) as an oil: IR (neat) 3399, 2919, 1435, 1350, 1255, 1051 cm^{-1}; ^1H NMR δ 3.96−3.88 (m, 1 H), 3.84−3.72 (m, 3 H), 2.81 (bs, 1 H), 2.00−1.91 (m, 1 H), 1.77−1.62 (m, 5 H), 1.35 (s, 3 H), 0.91 (t, J = 7.5 Hz, 3 H), 0.91 (t, J = 7.5 Hz, 3 H); ^{13}C NMR δ 114.0, 81.0, 75.1, 59.5, 41.2, 29.4, 29.2, 24.8, 8.5, 8.4; HRMS (EI) calcd. for $C_{10}H_{20}O_3$ 188.1412, found 188.1408.

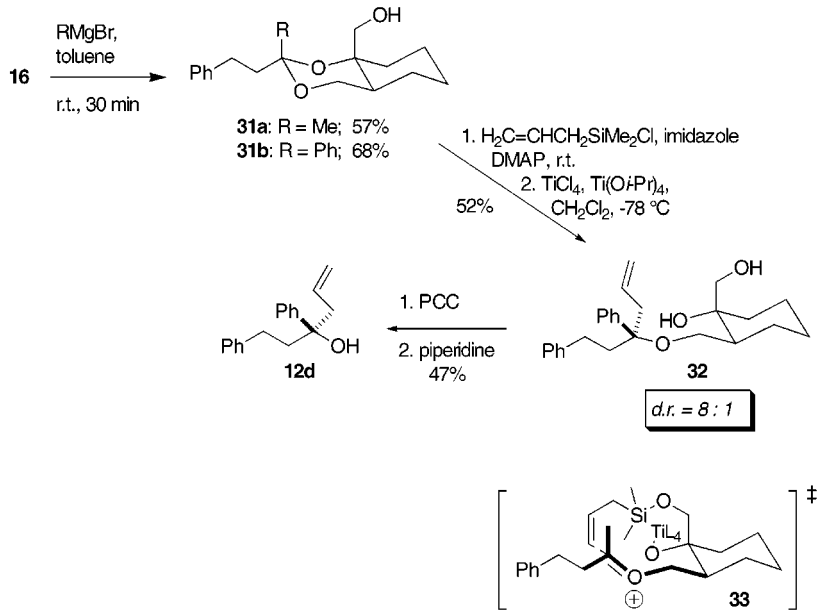
3-Phenylpropionic Acid (4*S*)-2-(2,2-Diethyl-4-methyl[1,3]-dioxolan-4-yl)ethyl Ester (3). A mixture of **2** (1.00 g, 5.32 mmol), hydrocinnamic acid (1.60 g, 10.6 mmol, 2 equiv), and DMAP (*N*,*N*-(dimethylamino)pyridine, 0.19 g, 1.60 mmol, 0.3 equiv) in 25 mL of CH_2Cl_2 was treated at 0 °C with EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 1.22 g, 6.38 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 15 h, quenched with water, and extracted with Et_2O. The organic layer was washed with 1 N HCl, water, and brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the crude residue by chromatography on SiO_2 (hexanes/Et_2O, 2:1) gave pure **3** (1.34 g, 79%) as an oil: IR (neat) 2973, 1736, 1168, 1074 cm^{-1}; ^1H NMR δ 7.27−7.15 (m, 5 H), 4.26−4.10 (m, 2 H), 3.75, 3.43 (AB, J = 8.2 Hz, 2 H), 2.92 (t, J = 7.7 Hz, 2 H), 2.58 (t, J = 7.7 Hz, 2 H), 1.95−1.76 (m, 2 H), 1.66−1.56 (m, 4 H), 1.25 (s, 3 H), 0.89 (t, J = 7.4 Hz, 6 H); ^{13}C NMR δ 172.8, 140.6, 128.7, 128.5, 126.5, 113.4, 79.4, 74.8, 61.3, 38.9, 36.1, 31.1, 29.8, 29.6, 25.2, 8.7; HRMS (EI) calcd for $C_{15}H_{18}O_4$ (M − C_2H_5) 291.1596, found 291.1593.

3-Phenylpropionic Acid (3*S*)-3,4-Dihydroxy-3-methyl-butyl Ester (4). A solution of **3** (4.40 g, 13.7 mmol) in 20 mL of THF/H_2O (9:1) was treated with *p*TsOH (*p*-toluenesulfonic acid, 0.261 g, 1.38 mmol, 0.1 equiv) and heated at reflux for 4 h. The reaction mixture was cooled to room temperature and neutralized with saturated aqueous $NaHCO_3$, the precipitate was filtered off, and the filtrate was extracted with Et_2O. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give **4** (1.97 g, 57%) as a yellow oil: IR (neat) 3409, 2927, 1731, 1161 cm^{-1}; ^1H NMR δ 7.32−7.19 (m, 5 H), 4.25 (t, J = 6.7 Hz, 2 H), 3.45, 3.40 (AB, J = 11.0 Hz, 2 H), 2.96 (t, J = 7.7 Hz, 2 H), 2.64 (t, J = 7.8 Hz, 2 H), 2.17 (bs, 2 H), 1.93−1.73 (m, 2 H), 1.18 (s, 3 H); ^{13}C NMR δ 173.0, 140.4, 128.6, 128.3, 126.4, 72.0, 69.9, 61.1, 36.9, 36.0, 31.0, 23.7; HRMS (EI) calcd for $C_{14}H_{20}O_4$ 252.1362, found 252.1360.

3-Phenylpropionic Acid (2*S*)-2-(2-Methyloxiranyl)ethyl Ester (5). A solution of diol **4** (2.1 g, 8.3 mmol) in CH_2Cl_2 was treated at −10 °C with Et_3N (1.7 mL, 9.9 mmol, 1.2 equiv) and CH_3SO_2Cl (0.7 mL, 9.1 mmol, 1.1 equiv). After 20 min, the mixture was diluted with Et_2O (40 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$, 1 N HCl, and brine, dried ($MgSO_4$), and concentrated under reduced pressure to give 2.6 g (94%) of mesylated intermediate. A solution of this compound (0.8 g, 2.7 mmol) in 10 mL of CH_2Cl_2 was treated at room temperature with a solution of DBU (1,8-diazabicyclo[5.4.0]-undec-7-ene, 0.4 mL, 1.1 equiv) in 10 mL of CH_2Cl_2. The reaction mixture was stirred at room temperature for 4 h, diluted with Et_2O, and washed with cold (0 °C) 1 N HCl, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and purified by chromatography on SiO_2 (EtOAc/hexanes, 1:1) to give **5** (0.47 g, 82%) as an oil: IR (neat) 2965, 1736, 1163 cm^{-1}; ^1H NMR δ 7.31−7.19 (m, 5 H), 4.23−4.12 (m, 2 H), 2.96 (t, J = 7.7 Hz, 2 H), 2.64 (t, J = 7.7 Hz, 2 H), 2.59, 2.54 (AB, J = 4.8 Hz, 2 H),1.95−1.79 (m, 2 H), 1.32 (s, 3 H); ^{13}C NMR δ 172.8, 140.5, 128.6, 128.3, 126.4, 61.0, 54.9, 53.6, 35.9, 35.6, 30.9, 21.2; HRMS (EI) calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1249.

(21) See, for example: (a) Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847. (b) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.

Scheme 8



(1*S*,5*R*)-5-Methyl-1-phenethyl-2,7,8-trioxabicyclo[3.2.1]-octane (6). A solution of epoxy ester **5** (0.23 g, 1.0 mmol) in 20 mL of CH_2Cl_2 was treated at 0 °C with Cp_2ZrCl_2 (bicyclopentadienylzirconium dichloride, 29 mg, 0.1 mmol, 0.1 equiv) and after 5 min with $AgClO_4$ (2.0 mg, 0.01 mmol, 0.01 equiv). The reaction mixture was stirred at 0 °C and monitored by TLC (SiO_2, C_6H_6/CH_2Cl_2/EtOAc, 10:2:1), until the formation of the product **6** was complete (4 h). The reaction mixture was quenched with saturated aqueous $NaHCO_3$, the aqueous layer was extracted with Et_2O, and the combined organic layers were dried (K_2CO_3) and concentrated under reduced pressure. For purification purposes a solution of the crude ortho ester in 10 mL of THF was treated with aqueous 1 M LiOH at room temperature for 10 h. The reaction mixture was extracted with Et_2O, dried (K_2CO_3), and concentrated under reduced pressure. The crude residue was eluted on basic alumina with Et_2O to give pure **6** (0.16 g, 70%) as an oil: IR (neat) 2938, 1485, 1372, 1003 cm^{-1}; ^1H NMR δ 7.30−7.17 (m, 5 H), 4.16−4.04 (m, 2 H), 3.89 (dd, J = 6.6, 11.4 Hz, 1 H), 3.54 (dd, J = 2.3, 7.1 Hz, 1 H), 2.84−2.78 (m, 2 H), 2.18−2.00 (m, 3 H), 1.47 (dd, J = 4.1,13.5 Hz, 1 H), 1.40 (s, 3 H); ^{13}C NMR δ 141.7, 128.3, 125.7, 120.3, 78.7, 73.8, 59.1, 37.2, 33.8, 29.6, 22.0; HRMS (EI) calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1266.

3-Phenylpropionic Acid 3-Methylbut-3-enyl Ester (8). A mixture of 3-methylbut-3-en-1-ol (**7**, 0.50 mL, 5.0 mmol), hydrocinnamic acid (0.90 g, 6.0 mmol, 1.2 equiv), and DMAP (0.18 g, 1.5 mmol, 0.3 equiv) in 25 mL of CH_2Cl_2 was treated at 0 °C with EDCI (1.2 g, 6.0 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 4 h, quenched with water, and extracted with Et_2O. The organic layer was washed with 1 N HCl, water, and brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the crude residue by chromatography on SiO_2 (hexanes/Et_2O, 2:1) gave ester **8** (1.1 g, 96%) as an oil: IR (neat) 2968, 1736, 1454, 1162 cm^{-1}; ^1H NMR δ 7.33−7.20 (m, 5 H), 4.81 (bs, 1 H), 4.73 (bs, 1 H), 4.21 (t, J = 6.8 Hz, 2 H), 3.00 (t, J = 7.8 Hz, 2 H), 2.64 (t, J = 7.8 Hz, 2 H), 2.33 (t, J = 6.8 Hz, 2 H), 1.76 (s, 3 H); ^{13}C NMR δ 173.0, 141.8, 140.7, 128.6, 128.4, 126.4, 112.4, 62.8, 36.8, 36.0, 31.1, 22.6; HRMS (EI) calcd for $C_{14}H_{18}O_2$ 234.1307, found 234.1302.

3-Phenylpropionic Acid 2-(2-Methyloxiranyl)ethyl Ester (±-5). A solution of ester **8** (1.1 g, 4.2 mmol) in 100 mL of CH_2Cl_2 was treated at 0 °C with *m*-CPBA (*m*-chloroperoxybenzoic acid, 1.1 g, 6.3 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C until the ester was consumed (4 h), diluted with Et_2O, washed with saturated aqueous $NaHCO_3$, 10% aqueous $Na_2S_2O_3$, and again saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the crude residue by chromatography on SiO_2 (hexanes/Et_2O, 1:1) gave (±)-**5** (0.90 g, 80%) as an oil.

5-Methyl-1-phenethyl-2,7,8-trioxabicyclo[3.2.1]octane (±6). Prepared in 82% yield (3.28 g) from (±)-**5** (4.00 g, 17.1 mmol), Cp_2ZrCl_2 (0.499 g, 1.71 mmol, 0.1 equiv), and $AgClO_4$ (35.4 mg, 0.171 mmol, 0.01 equiv) according to the procedure described for **6**.

(2*R*,4*S*)-(2,4-Dimethyl-2-phenethyl[1,3]dioxan-4-yl)methanol (9). CH_3MgBr (3 M solution in Et_2O, 1.0 mL, 3.0 mmol, 3 equiv) was added dropwise at room temperature to a solution of ortho ester **6** (0.23 g, 1.0 mmol) in 15 mL of toluene. The reaction mixture was stirred at room temperature until the starting material was fully consumed (30 min), diluted with Et_2O and quenched with NH_4Cl. The aqueous layer was extracted with Et_2O, and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The oily residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to give acetal **9** (0.22 g, 88%) as an oil: IR (neat) 3358, 2936, 1379, 1054 cm^{-1}; ^1H NMR δ 7.31−7.19 (m, 5 H), 4.00−3.84 (m, 2 H), 3.39 (d, J = 6.1 Hz, 2 H), 2.73−2.67 (m, 2 H), 2.15−1.99 (m, 4 H), 1.44−1.40 (m, 1 H), 1.43 (s, 3 H), 1.31 (s, 3 H); ^{13}C NMR δ 142.3, 128.5, 128.4, 125.9, 99.5, 72.9, 70.1, 56.3, 41.3, 30.8, 29.5, 26.8, 24.9; HRMS (EI) calcd for $C_{14}H_{19}O_2$ (M-CH_3O) 219.1385, found 219.1380. NOESY studies showed a correlation between the methyl group from position 4 and the methylene from position 2 of the acetal ring suggesting the conformation depicted in Scheme 3.

2,5-Dimethyl-2-phenethyl[1,3]-dioxepan-5-ol (10). Treatment of acetal **9** (0.10 g, 0.40 mmol) with $CDCl_3$ containing traces of acid led to **10** (98 mg, 98%) as a 1:1 mixture of two diastereomers, which were separated by chromatography on SiO_2 (Et_2O/hexanes, 1:1): IR (neat) 3380, 2936, 1052 cm^{-1}; diastereomer A ^1H NMR δ 7.29−7.19 (m, 5 H), 3.91−3.73 (m, 4 H), 2.76−2.70 (m, 2 H), 2.57 (bs, 1 H), 2.00−1.91 (m, 3 H), 1.81−1.73 (m, 1 H), 1.45 (s, 3 H), 1.40 (s, 3 H); ^{13}C NMR δ 141.9, 128.5, 128.3, 125.9, 110.9, 81.4, 75.1, 59.5. 42.1, 41.2, 30.9, 25.0; diastereomer B ^1H NMR δ 7.30−7.20 (m, 5 H), 3.98−3.74 (m, 2 H), 3.91, 3.82 (AB, J = 8.4 Hz, 2H), 2.77−2.71 (m, 3 H), 2.01−1.95 (m, 3 H), 1.82−1.74 (m, 1 H), 1.45 (s, 3 H), 1.37 (s, 3 H);^{13}C NMR δ 142.0, 128.5, 128.3, 125.9, 110.9, 81.5, 75.0, 59.6. 42.0, 41.3, 30.8, 25.0, 24.8; HRMS (EI) calcd for $C_{14}H_{19}O_3$ (M − CH_3) 235.1334, found 235.1338.

4-(1-Ethyl-1-methyl-3-phenylpropoxy)-2-methylbutane-1,2-diol (11a). $TiCl_4$ (0.22 mL, 2.0 mmol, 2 equiv) was added dropwise at −78 °C to a solution of acetal **9** (0.25 g, 1.0 mmol) in 10 mL of CH_2Cl_2, followed by the dropwise addition of EtMgBr (1 M solution in Et_2O, 4.0 mL). After the starting material was consumed (15 min), the reaction was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. Purification by chromatography on SiO_2

(hexanes/Et_2O, 1:1) gave **11a** (0.17 g, 60%) as an oil: IR (neat) 3419, 2972, 1366, 1075 cm^{-1}; ^1H NMR δ 7.31−7.17 (m, 5 H), 3.80 (bs, 2 H), 3.70−3.40 (m, 4 H), 2.98 (bs, 2 H), 2.63−2.57 (m, 2 H), 2.01−1.88 (m, 1 H), 1.84−1.55 (m, 5 H), 1.21 (s, 3 H), 1.19 (s, 3 H), 0.90 (t, J = 7.5 Hz, 3 H); ^{13}C NMR δ 142.5, 128.6, 128.4, 125.9, 78.0, 72.7, 70.3, 57.5, 39.5, 38.2, 30.3, 30.2, 24.5, 22.6, 8.2; HRMS (EI) calcd for $C_{15}H_{23}O_3$ (M − C_2H_5) 251.1647, found 251.1640.

3-Methyl-1-phenylpentan-3-ol (12a).[22] A solution of tertiary ether **11a** (56 mg, 0.20 mmol) in 3 mL of CH_2Cl_2 was treated at room temperature with pyridinium chlorochromate (0.34 g, 1.6 mmol, 8 equiv) and 4 Å molecular sieves (0.30 g). After being stirred at room temperature for 2 h, the reaction mixture was filtered through SiO_2 and eluted with Et_2O, and the filtrate was evaporated to give the corresponding ketone. A solution of the ketone (0.2 mmol) in 3.6 mL (9 equiv) of 0.5 M solution of piperidinium acetate in benzene was heated at reflux for 2 h. After being cooled to room temperature, the reaction mixture was filtered through SiO_2 (hexanes/Et_2O, 1:1). The solvent was removed under reduced pressure, and the crude residue was purified by chromatography on SiO_2 (hexanes/Et_2O, 4:1) to give pure **12a** (23 mg, 64%) as an oil: ^1H NMR δ 7.31−7.16 (m, 5 H), 2.71−2.65 (m, 2 H), 1.79−1.73 (m, 2 H), 1.57 (q, J = 7.5 Hz, 2H),1.23 (s, 3 H), 0.94 (t, J = 7.5 Hz, 3 H).

3-Phenylpropionic Acid 2-Oxiranylethyl Ester (18). A mixture of but-3-en-1-ol (**17**, 0.43 mL, 5.0 mmol), hydrocinnamic acid (0.90 g, 6.0 mmol, 1.2 equiv), and DMAP (0.18 g, 1.5 mmol, 0.3 equiv) in 25 mL of CH_2Cl_2 was treated at 0 °C with EDCI (1.2 g, 6.0 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 4 h, quenched with water, and extracted with Et_2O. The organic layer was washed with 1N HCl, water, and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the crude residue by chromatography on SiO_2 (hexanes/Et_2O, 2:1) gave the ester (0.82 g, 80%) as an oil. A solution of this ester (0.82 g, 4.0 mmol) in 100 mL of CH_2Cl_2 was treated at 0 °C with *m*-CPBA (1.0 g, 6.0 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C until the ester was consumed (6 h), diluted with Et_2O, washed with saturated aqueous $NaHCO_3$, 10% aqueous $Na_2S_2O_3$ and again with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the crude residue by chromatography on SiO_2 (hexanes/Et_2O, 1:1) gave epoxy ester **18** (0.70 g, 80%) as an oil: IR (neat) 2934, 1736, 1453, 1159 cm^{-1}; ^1H NMR δ 7.32−7.21 (m, 5 H), 4.23 (t, J = 6.3 Hz, 2 H), 3.00−2.95 (m, 3 H), 2.77−2.74 (m, 1 H), 2.66 (t, J = 7.7 Hz, 2 H), 2.48−2.46 (m, 1 H), 1.93−1.75 (m, 2 H); ^{13}C NMR δ 172.8, 140.5, 128.6, 128.3, 126.4, 61.4, 49.6, 46.9, 35.9, 31.9, 31.0; HRMS (EI) calcd. for $C_{13}H_{16}O_3$ 220.1099, found 220.1099.

3-Phenylpropionic Acid Tetrahydrofuran-3-yl Ester (19). According to the procedure described for compound **6**, oily **19** (0.18 g, 82%) was obtained from the epoxy ester **18** (0.22 g, 1.0 mmol). In this case, no trace of the desired ortho ester **14** was observed and the reaction was stopped when the epoxy ester **18** was fully converted to **19** (4 h). The crude residue was eluted on basic alumina with Et_2O to give pure **19**: IR (neat) 3410, 2933, 1733, 1163, 1079 cm^{-1}; ^1H NMR δ 7.32−7.20 (m, 5 H), 5.32−5.27 (m, 1 H), 3.91−3.75 (m, 4 H), 2.96 (t, J = 7.6 Hz, 2 H), 2.65 (t, J = 7.5 Hz, 2 H), 2.18−2.08 (m, 1 H), 1.97−1.91 (m, 1 H); ^{13}C NMR δ 172.7, 140.3, 128.6, 128.4, 126.4, 74.9, 73.1, 67.0, 35.9, 32.8, 30.9; HRMS (EI) calcd for $C_{13}H_{16}O_3$ 220.1099, found 220.1099.

2,2-Dimethyl-but-3-en-1-ol (21). Prepared according to a literature protocol in 65% yield from diol **20**.[18]

3-Phenylpropionic Acid 2-Methyl-2-oxiranylpropyl ester (22). A mixture of 2,2-dimethylbut-3-en-1-ol (**21**, 0.50 g, 5.0 mmol), hydrocinnamic acid (0.90 g, 6.0 mmol, 1.2 equiv), and DMAP (0.18 g, 1.5 mmol, 0.3 equiv) in 25 mL of CH_2Cl_2 was treated at 0 °C with EDCI (1.2 g, 6.0 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 4 h, quenched with water and extracted with Et_2O. The organic layer was washed with 1 N HCl, water, and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification of the crude residue by chromatography on SiO_2 (hexanes/Et_2O, 2:1) gave the ester (0.99 g, 85%) as an oil. A solution of this ester (0.99 g, 4.3 mmol) in 100 mL of CH_2Cl_2 was treated at 0 °C with *m*-CPBA (1.1 g, 6.4 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C until the ester was consumed (4 h), diluted with Et_2O, washed with saturated aqueous $NaHCO_3$, 10% aqueous $Na_2S_2O_3$, and again saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the crude residue by chromatography on SiO_2 (hexanes/Et_2O, 1:1) gave epoxy ester **22** (0.84 g, 80%) as an oil: IR (neat) 2972, 1735, 1160 cm^{-1}; ^1H NMR δ 7.32−7.20 (m, 5 H), 3.96, 3.89 (AB, J = 11.1 Hz, 2 H), 2.98 (t, J = 7.8 Hz, 2 H), 2.82−2.80 (m, 1 H), 2.68 (t, J = 7.7 Hz, 2 H), 2.73−2.57 (m, 2 H), 0.90 (s, 3 H), 0.87 (s, 3 H); ^{13}C NMR δ 172.7, 140.5, 128.6, 128.4, 126.4, 70.4, 56.8, 43.7, 35.9, 34.5, 31.0, 20.4, 20.1; HRMS (EI) calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1409.

4,4-Dimethyl-1-phenethyl-2,7,8-trioxabicyclo[3.2.1]-octane (15) and 3-Phenylpropionic Acid 5,5-Dimethyltetrahydrofuran-2-yl Ester (23). According to the procedure described for **6**, oily **15** (0.13 g, 50%) and oily **23** (0.04 g, 17%) were obtained from the epoxy ester **22** (0.25 g, 1.0 mmol). In this case, the reaction mixture was quenched with 10% aqueous KOH solution. **15**: IR (neat) 3054, 2965, 2900, 1471, 1456, 4265, 1064, 738 cm^{-1}; ^1H NMR δ 7.38−7.25 (m, 5 H), 4.21 (d, J = 7.7 Hz, 1 H), 4.10−4.08 (m, 1 H), 3.86−3.82 (m, 1 H), 3.80 (d, J = 11.1 Hz, 1 H), 3.42 (d, J = 11.0, 1 H), 2.96−2.90 (m, 2 H), 2.30−2.24 (m, 2 H), 1.36 (s, 3 H), 0.84 (s, 3 H); ^{13}C NMR δ 142.1, 128.7, 126.1. 119.3, 81.6, 69.9, 66.3, 37.1, 32.2, 30.1, 24.4, 22.1; HRMS (EI) calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1412. **23**: IR (neat) 2966, 1736, 1162, 1081 cm^{-1}; ^1H NMR δ 7.32−7.18 (m, 5 H), 4.88 (dd, J = 2.1, 3.0 Hz, 1 H), 4.20 (dd, J = 5.0,10.7 Hz, 1 H), 3.65 (dd, J = 1.8, 8.7 Hz, 1 H), 3.55, 3.56 (AB, J = 5.6 Hz, 2 H), 2.97 (t, J = 7.7 Hz, 2 H), 2.68 (t, J = 7.7 Hz, 2 H), 1.08 (s, 3 H), 0.97 (s, 3 H);^{13}C NMR δ 172.7, 104.5, 128.7, 128.5, 126.6, 80.9, 78.8, 73.4, 42.5, 36.1, 31.1, 25.2, 18.9; HRMS (EI) calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1413.

3-Phenylpropionic Acid 2-Oxocyclohexylmethyl Ester (25). A mixture of cyclohexanone (25.0 mL, 0.242 mol) and K_2CO_3 (0.502 g, 3.64 mmol, 0.015 equiv) in 50 mL of water was stirred vigorously at 40 °C while formaldehyde (37.5 mL, 0.460 mol, 1.9 equiv, 37% aqueous solution) was added during 1 h. Stirring was continued for 1 h; the cooled reaction mixture was extracted with Et_2O, and the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by chromatography on SiO_2 (EtOAc/hexanes, 1:1) to give oily α-hydroxymethyl cyclohexanone **24**[18] (18.6 g, 60%). A mixture of **24** (1.28 g, 10.0 mmol), hydrocinnamic acid (1.65 g, 11.0 mmol, 1.1 equiv), and DMAP (0.366 g, 3.00 mmol, 0.3 equiv) in 25 mL of CH_2Cl_2 was treated at 0 °C with EDCI (2.29 g, 12.0 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 15 h, quenched with water, and extracted with Et_2O. The organic layer was washed with 1 N HCl, water, and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the crude residue by chromatography on SiO_2 (hexanes/Et_2O, 2:1) gave **25** (2.29 g, 83%) as an oil: IR (neat) 2938, 1735, 1164 cm^{-1}; ^1H NMR δ 7.29−7.15 (m, 5 H), 4.41−4.35 (m, 1 H), 4.07−4.01 (m, 1 H), 2.93 (t, J = 7.6 Hz, 2 H), 2.62 (t, J = 7.6 Hz, 2 H), 2.64−2.56 (m, 1 H), 2.41−2.23 (m, 2 H), 2.13−1.98 (m, 2 H), 1.85 (bs, 1 H), 1.70−1.60 (m, 2 H), 1.42−1.26 (m, 1 H); ^{13}C NMR δ 210.4, 172.8, 140.5, 128.5, 128.3, 126.3, 63.3, 49.5, 42.1, 35.8, 31.0, 27.7, 24.7; HRMS (EI) calcd for $C_{16}H_{20}O_3$ 260.1412, found 260.1423.

3-Phenylpropionic Acid 1-Oxaspiro[2.5]oct-4-ylmethyl Ester (26). To a suspension of Ph_3PCH_3I (1.6 g, 4.4 mmol) in THF (100 mL) was added dropwise at 0 °C *n*-BuLi (2.8 mL, 4.4 mmol, 1.6 M in hexanes). The reaction mixture was stirred at 0 °C for 30 min and cooled to −78 °C, and a solution of ketone **25** (1.1 g, 4.0 mmol) in THF (20 mL) was added. After 1 h, the reaction mixture was warmed to room temperature, quenched with NH_4Cl and extracted with Et_2O. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure, and the crude residue was filtered through a layer of SiO_2 providing the crude ester that was used in the next step without further purification. A solution of this ester (0.65 g, 2.5 mmol) in 100 mL of CH_2Cl_2 was treated at 0 °C with *m*-CPBA (0.65 g, 3.8 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C until the ester was consumed (4 h), diluted with Et_2O, and washed with saturated aqueous $NaHCO_3$, 10% aqueous $Na_2S_2O_3$, and again with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and

(22) Khalaf, A. A.; Roberts, R. M. *J. Org. Chem.* **1972**, *37*, 2384.

concentrated under reduced pressure. Purification of the crude residue by chromatography on SiO_2 (hexanes/Et_2O, 1:1) gave the epoxy ester **26** (0.62 g, 57% after two steps) as an oil: IR (neat) 2934, 1736, 1454, 1290 cm^{-1}; ^1H NMR δ 7.31−7.18 (m, 5 H) 4.20−4.14 and 4.01−3.86 (2m, 2 H), 2.94 (t, J = 7.7 Hz, 2 H), 2.73 (d, J = 4.5 Hz, 1 H), 2.75−2.55 (m, 2 H), 2.48 (d, J = 4.4 Hz, 1 H), 1.95−1.42 (m, 9 H);^{13}C NMR δ 173.0, 172.9, 140.6, 128.7, 128.5, 126.5, 64.0, 63.8, 59.2, 59.1, 53.3, 52.4, 40.7, 39.6, 36.1, 33.4, 32.7, 31.2, 27.8, 27.6, 24.9, 24.5, 23.8, 23.0; HRMS (EI) calcd for $C_{17}H_{22}O_3$ 274.1569, found 274.1582.

9-Phenethyl-8,10,12-trioxatricyclo[7.2.1.00,0]dodecane (16). According to the procedure described for **6**, **16** (0.24 g, 90%) was obtained from the epoxy ester **26** (0.27 g, 1.0 mmol) as a colorless solid: mp 49−50 °C (hexanes); IR (neat) 2936, 1447, 1299, 1180, 1016 cm^{-1}; ^1H NMR δ 7.32−7.17 (m, 5 H), 4.27 (dd, J = 4.5, 11.3 Hz, 1 H), 4.04 (d, J = 7.0 Hz, 1 H), 3.52−2.48 (m, 2 H), 2.88−2.82 (m, 2 H), 2.20−2.15 (m, 2 H), 2.10−1.94 (m, 1 H), 1.88−1.42 (m, 6 H), 1.42−1.20 (m, 2 H);^{13}C NMR δ 141.9, 128.5, 128.4, 125.8, 120.5, 80.1, 74.8, 65.0, 38.5, 37.3, 31.9, 29.8, 26.9, 25.2, 22.0; HRMS (EI) calcd for $C_{17}H_{22}O_3$ 274.1569, found 274.1570.

3,3-Dimethyl-4-(1-phenethyl-1-phenylbut-3-enyloxy)butane-1,2-diol (30). A solution of $Ti(O^iPr)_4$ (1.2 mL, 4.0 mmol, 4 equiv) and $TiCl_4$ (0.44 mL, 4.0 mmol, 4 equiv) in 10 mL of CH_2Cl_2 was added dropwise at −78 °C to a solution of acetal **29b** (0.33 g, 1.0 mmol) and allyl trimethylsilane (0.59 mL, 3.7 mmol, 3.7 equiv) in 10 mL of CH_2Cl_2. After the starting material was consumed (1 h) the reaction mixture was quenched with aqueous saturated NH_4Cl (10 mL), extracted with Et_2O, and the combined organic layers were dried ($MgSO_4$). Purification of the crude residue by chromatography on SiO_2 (hexanes/Et_2O, 1:1) gave oily **30** (0.22 g, 60%) as a 1:1 mixture of diastereomers: IR (neat) 3422, 2918, 1458, 1265, 1069, 740, 739 cm^{-1}; ^1H NMR δ 7.43−7.09 (m, 10 H), 5.66−5.57 (m, 1 H), 5.21−5.10 (m, 2 H), 3.67−3.63 (m, 3 H), 3.17−3.10 (m, 2 H), 2.96 (bs, 2 H), 2.79 (d, J = 7.0 Hz, 2 H), 2.49−2.40 (m, 2 H), 2.24−2.16 (m, 2 H), 0.98 (s, 3 H), 0.96 (s, 3 H); ^{13}C NMR δ 142.4, 142.0, 133.2, 133.0, 128.5, 128.4, 128.3, 127.4, 126.4, 126.0, 118.4, 80.7, 78.5, 78.2, 70.2, 69.9, 63.1, 63.0, 40.9, 40.7, 38.5, 37.4, 37.3, 29.5, 23.3, 20.4, 20.3; HRMS (EI) calcd for $C_{21}H_{27}O_3$ 327.1960, found 327.1971.

1-Hydroxymethyl-2-(1-phenethyl-1-phenylbut-3-enyloxymethyl)cyclohexanol (32). To a solution of **31b** (0.25 g, 0.7 mmol) in CH_2Cl_2 (20 mL) at room temperature were added successively imidazole (48 mg, 0.7 mmol, 1 equiv), DMAP (9.0 mg, 0.07 mmol, 0.1 equiv) and dimethylallylchlorosilane (0.13 mL, 0.90 mmol, 1.2 equiv), and the reaction mixture was stirred at room temperature for 1 h. The solution was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the silylated derivative of **31b**, which was used in the next step without purification. This product (0.10 g, 0.20 mmol) was dissolved in 3 mL of CH_2Cl_2 at −78 °C and a solution of $Ti(O^iPr)_4$ (0.26 mL, 0.9 mmol, 4 equiv) and $TiCl_4$ (98 μL, 0.90 mmol, 4 equiv) in 2 mL of CH_2Cl_2 were added dropwise. After 15 min, the reaction mixture was quenched with saturated aqueous NH_4Cl and worked up as described for **30** to give **32** (46 mg, 52% from **31b**) as a 8:1 mixture of diastereomers. Major isomer: IR (neat) 3424, 2933, 1447, 1061 cm^{-1}; ^1H NMR (500 MHz) δ 7.41−7.38 (m, 4 H), 7.33−7.24 (m, 3 H), 7.20−7.08 (m, 3 H), 5.63−5.55 (m, 1 H), 5.31−5.10 (m, 2 H), 3.67 (d, J = 10.0 Hz, 1 H), 3.46−3.33 (m, 4 H), 2.82−2.72 (m, 2 H), 2.54−2.38 (m, 2 H), 2.29−2.14 (m, 2 H), 1.73−1.54 (m, 6 H), 1.34−1.24 (m, 4 H); ^{13}C NMR δ 142.7, 142.0, 132.9, 128.5, 128.4, 128.3, 127.5, 126.4, 126.0, 118.5, 81.5, 72.6, 70.1, 63.8, 53.5, 42.7, 41.3, 38.2, 35.1, 29.6, 26.3, 25.7, 21.4; HRMS (EI) calcd for $C_{23}H_{29}O_3$ (M − C_3H_5) 353.2117, found 353.2104.

(3*R*)-1,3-Diphenylhex-5-en-3-ol (12d). A solution of tertiary ether **32** (20 mg, 51 μmol) in 2 mL of CH_2Cl_2 was treated at room temperature with pyridinium chlorochromate (90 mg, 0.41 mmol) and 4 Å molecular sieves (0.10 g). After stirring at room temperature for 2 h, the reaction mixture was filtered through SiO_2 (Et_2O) and the filtrate was evaporated to give the corresponding ketone. A solution of this ketone in 3 mL of toluene was treated with piperidine (0.05 mL, 0.5 mmol) and was heated at reflux for 48 h. After being cooled to room temperature, the reaction mixture was filtered through SiO_2 (hexanes/Et_2O, 1:1). The solvent was removed under reduced pressure and the crude residue was purified by chromatography on SiO_2 (hexanes/Et_2O, 4:1) to give **12d** (6.0 mg, 47%) as an oil: IR (neat) 3559, 3026, 1495, 1446, 701 cm^{-1}; ^1H NMR δ 7.58−7.46 (m, 4 H), 7.40−7.21 (m, 6 H), 5.74−5.63 (m, 1 H), 5.30−5.22 (m, 2 H), 2.90−2.78 (m, 2 H), 2.69−2.62 (m, 1 H), 2.54−2.40 (m, 1 H), 2.31−2.22 (m, 3 H);^{13}C NMR δ 145.9, 142.8, 133.6, 128.7, 128.6, 126.9, 126.0, 125.6, 120.2, 76.0, 48.0, 44.9, 30.3; HRMS (EI) calcd for $C_{18}H_{18}$ (M − H_2O) 234.1409, found 234.1414.

Acknowledgment. This work was supported by the National Science Foundation (CHE-9453461). We thank Dr. Teruhisa Tsuchimoto for obtaining preliminary data on the nucleophilic substitution of ortho esters with Grignard reagents.

Supporting Information Available: Experimental protocols and spectral characterization for **11b**,**c**, **12b**,**c**, **29a**,**b**, and **31a**,**b**; ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO005665Y