Synthetic Studies on Nogarol Anthracyclines. Enantioselective Total Synthesis of an Aminohydroxy Epoxybenzoxocin

Frank M. Hauser* and Debashis Ganguly†

Department of Chemistry, State University of New York at Albany, Albany, New York 12222

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A chiral synthesis of the aminohydroxy expoxybenzoxocin **6** is described. Enantioselective Friedel−Crafts coupling using a chiral titanium catalyst was employed to produce the optically active atrolactic ester **16a** from the phenol **11** and *l*-menthyl pyruvate (**12**). The phenolic group in **16a** was protected as the benzyl ether and the *t*-alcohol functionality as the MEM ether to give **20**, which after sequential reduction/oxidation provided the aldehyde **22**. Addition of the acetylide anion of propargyl aldehyde diethyl acetal (**23**) to aldehyde **22**, followed by oxidation of the resultant diastereoisomeric carbinols, gave the acetylenic ketone **24**. Lindlar reduction of **24** afforded the *trans*-enone **26**. Reaction of **26** with thiophenylate anion furnished **27**, which was then cyclized to the α-methyl pyranoside **29**. Oxidation of **29** to the sulfoxide and subsequent thermolysis afforded the hexenulose **30**. Sequential epoxidation of **30**, reduction of the keto epoxide **31**, and reaction of the resultant epoxycarbinol **32** with dimethylamine produced the aminohydroxy pyranose **33a**. Debenzylation of **33a** to the phenol **33b**, followed by intramolecular cyclization, completed the fabrication of the optically active aminohydroxy epoxybenzoxocin **6**. The 17-step sequence from the phenol **11** to **6** was achieved in 22% overall yield.

Introduction

Nogalamycin (**1**), reported in 1968 by Wiley and coworkers[1] at Upjohn, was the first example of an anthracycline antibiotic containing a C-aminosugar residue. (Figure 1). The antibiotic exhibited strong in vitro activity against Gram-positive bacteria, L12110 leukemia, and Kb cell lines. It also demonstrated superior antitumor activity and reduced cardiotoxicity when compared to the clinically important anthracycline antibiotics adriamycin, daunorubicin, and related compounds. The semisynthetic derivative, 7-con-*O*-methylnogarol (**2**), prepared from nogalamycin (**1**), exhibited even more substantial anticancer activity.[1g] Subsequently, other nogarol anthracycline antibiotics, arugomycin,[2] decilorubicin,[3] and viriplanin,[4] were reported, and these likewise showed significant anticancer activity.

The C-sugar residue in nogarol anthracyclines is structurally unusual in that it is present as an expoxyoxocin fragment. Moreover, in contrast to the usual attachment of C-sugars to aromatic rings at C-1′, the sugar residue in these antibiotics is connected through the C-5′ carbon. An X-ray crystallographic analysis of a

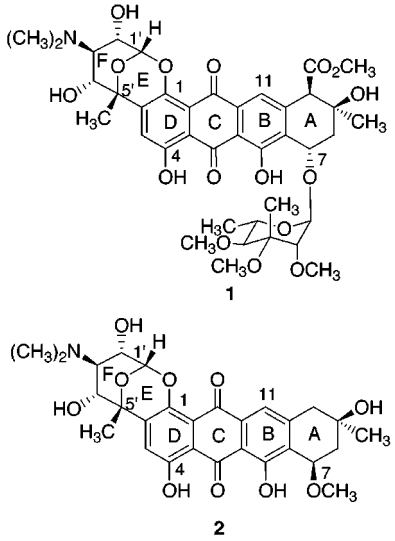

Figure 1.

DNA hexamer complexed with nogalamycin (**1**), reported by Rich et al.,[5] showed that the amine group on the epoxyoxocin is hydrogen-bonded to two sites on the DNA. This finding implies both a mechanism of action for biological activity and suggests that the amino-substituted epoxyoxocin is essential for biological activity.

The stereochemical complexity, unique structural features, and impressive anticancer activity prompted synthetic interest in these compounds. While there have been no reported preparations of nogalamycin (**1**), there have been two syntheses of 7-con-*O*-methylnogarol (**2**): a chiral route by Terashima et al.[6] and a racemic synthesis by us.[7] In addition, there have been a number

* Email: FH473@sarah.albany.edu.

† Present address: Eli Lilly & Co., Lilly Research Laboratories, Indianapolis, IN, 46285.

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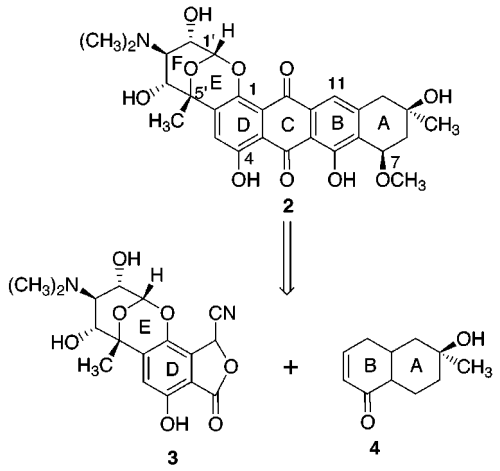
Scheme 1



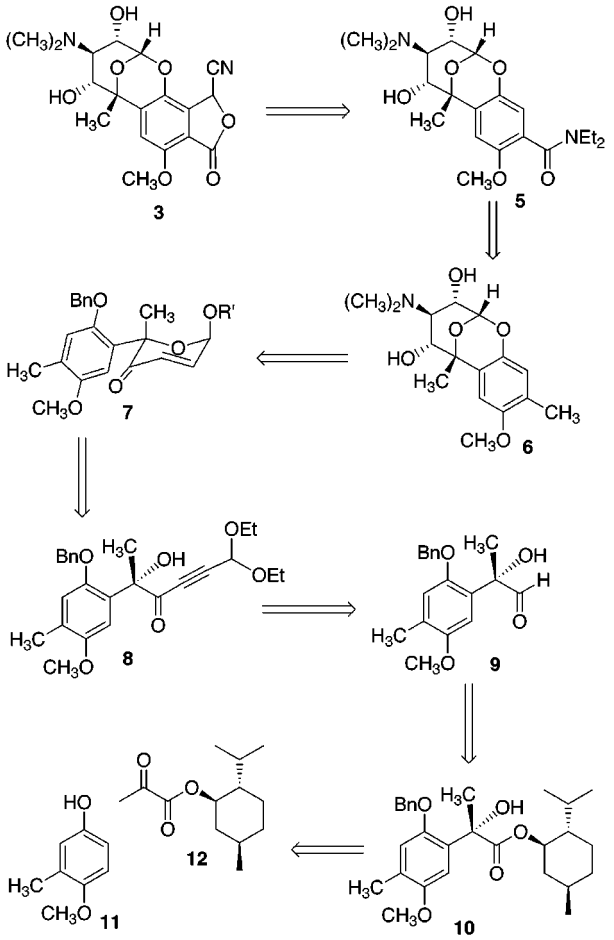
of papers describing various approaches to epoxybenzoxocins, which are potentially useful as DEF synthons to these antibiotics.[8] With the exception of the preparation by Terishma et al. that exploited a sugar starting material,[6] all of the routes to epoxyoxocins have been racemic. We describe herein a de novo route for optically active total synthesis of the epoxybenzoxocin **6** from achiral starting materials.

Results and Discussions

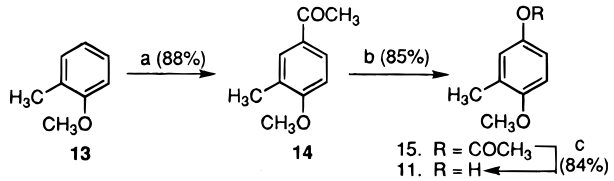
Considering the retrosynthetic analysis shown in Scheme 1, we recognized that our previous racemic preparation[7] of 7-con-*O*-methylnogarol (**2**) might be generalized to encompass an optically active total synthesis. This asymmetric preparation would be accomplished via coupling of two chiral subunits, the cyanophthalide **3** and the 1-(4*H*)-naphthaleneone **4**. We had already established methodology for brief and efficient optically active preparation of 1-(4*H*)-naphthalenones such as **4** and reported their use as AB-synthons for single enantiomer synthesis of an anthracyclinone.[9] To accomplish an optically active total synthesis of **2** that would not result in the formation of diastereoisomers, we needed a route for chiral preparation of the cyanophthalide **3**.

Scheme 2 delineates the retrosynthetic analysis that led to the exploration of a route to the optically active epoxybenzoxocin **6**, which was to be used as an intermediate to the cyanophthalide **3**. The epoxybenzoxocin **6** was chosen as an intermediate since we have previously reported methodology for the selective oxidative transformation of methyl groups to carboxyl functionality[10] (**6** to **5**) and for the fabrication of phthalide nitriles from

Scheme 2



Scheme 3[a]



[a] a. CH_3COCl, $AlCl_3$, CH_2Cl_2, reflux, 80 °C, 2 h, 88%; b. m-CPBA, CH_2Cl_2, 0 °C to r.t., 12 h, 85%; c. THF, HCl (3 N), reflux, 10 h, 84%

diethylamides (**5** to **3**).[7] The preparation of **6** from the hexenulose **7** would parallel our earlier racemic preparation. The hexenulose **7** would be fabricated from the chiral atrolactaldehyde **9** through the intermediacy of the acetylenic ketone **8**. Planned construction of the atrolactaldehyde **9** would be from the optically active ester **10**, which would be prepared through an asymmetric Friedel–Crafts coupling[11] of the phenol **11** with *l*-menthylpyruvate (**12**).[12]

Synthesis of the phenol **11** needed to initiate the route was straightforwardly accomplished on a multigram scale as outlined in Scheme 3. Friedel–Crafts acylation of commercially available 2-methyl anisole (**13**) with CH_3COCl and $AlCl_3$ gave the acetophenone **14**, which was readily purified through distillation, in 88% yield. Following Baeyer–Villiger oxidation of **14** to **15** (85%), the acetate group was hydrolyzed (THF, 3 N HCl; 84%) to

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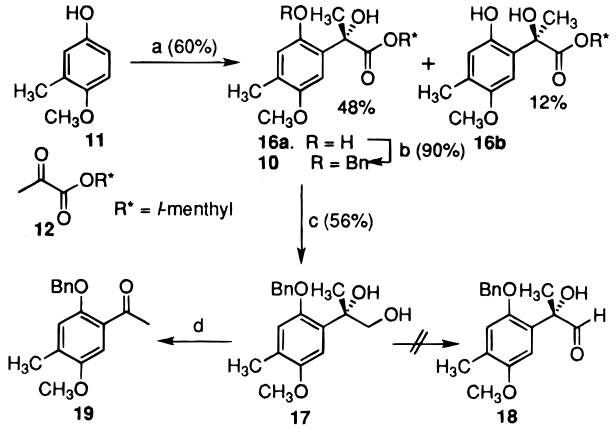
Scheme 4[a]



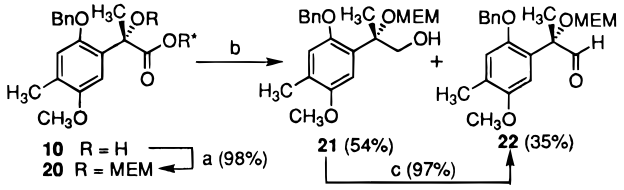
[a]a. $TiCl_4$, *l*-menthol, **12**, CH_2Cl_2, -70 °C to r.t., 60%,**16a**:**16b** = 85:15 (diastereomeric ratio); b. K_2CO_3, benzyl bromide, acetone, 90%; c. DIBAL-H/ toluene, -78 °C, 56%; d. Oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, -78 °C, 1.5 h.

the phenol **11**. The overall yield of phenol **11** for the four-step sequence was 66%.

The protocol reported by Casiraghi et al.[11] ($TiCl_4$ and *l*-menthol at −78 °C) was used to effect asymmetric coupling of phenol **11** with (−)-*l*-menthyl pyruvate (**12**),[12] (Scheme 4) and afforded the diastereoisomeric atrolactic esters **16a** and **16b** in an 86:14 ratio.[13] Purification of the atrolactic esters **16a** and **16b** proved to be challenging as a result of the small differences in their R_f values (<0.08) and streaking caused by the presence of menthol. Ultimately, the pure diastereoisomers **16a** and **16b** were obtained in 48% and 12% yield, respectively. Examination of the singlet absorptions of the tertiary C-methyl groups and the C-2 methyl doublet of the menthol ester group in the ^{1}H NMR readily established that the enantiomeric purity of the separated diatereoisomers was >99%.

Since ring closure to the oxocin at a subsequent stage of the synthesis would require that we be able to differentiate between the oxygen functionalities on the aromatic ring, protection of the phenolic group in **16a** as the benzyl ether derivative **10** was performed (K_2CO_3, $PhCH_2Br$, acetone, 90%). Attempted direct reduction of **10** to the atrolactaldehyde **18** led instead to diol **17**, even when care was taken to use exactly 1 equiv or less of DIBAL. While the yield was somewhat modest (56%), a more serious problem and one which probably contributed to the low yield was that the diol **17** was unstable. We felt that this instability was likely due to the presence of the tertiary benzylic alcohol, coupled with the fact that the aromatic ring was electron-rich. We expected that once **17** was oxidized to the atrolactaldehyde **18**, stability would return since formation of a carbocation α to the aldehyde carbonyl group would be unfavorable. Several oxidizing agents were screened in unsuccessful attempts to convert the diol **17** to the α-hydroxy aldehyde **18**. Invariably, the major product was the acetophenone **19**. Even the Swern oxidation,[14] which usually does not cleave 1,2-diols, gave principally the acetophenone **19**. Thus, it was apparent that, minimally, protection of the tertiary alcohol would be required to avoid its oxidative cleavage. Moreover, we were now mindful but not surprised that an electron-withdrawing group α to the tertiary hydroxyl group (vida infra) was necesssary to ensure stability.

Scheme 5[a]



[a]a. NaH, MEMCl, THF, 24 h, 94%; b. DIBAL-H (neat), toluene, -78 °C; c. Oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, -78 °C, 1.5 h, 97%

Various silicon groups were examined for protection of the tertiary hydroxyl group in **10**, but these proved to be too unstable for subsequent transformations. Ultimately, MEM ether protection provided an appropriate derivative. Installation of the MEM group in **20** was achieved in 97% yield through reaction of **10** with NaH and MEMCl in THF (Scheme 5). Attempted reduction of **20** with commercially available DIBAL in toluene produced a complex mixture of products that included the unreduced ester **20**, the alcohol **21**, the aldehyde **22**, and disturbingly, a substantial amount of MEM ether cleaved products. This problem was overcome through use of a freshly prepared solution of DIBAL in toluene. With this change, reduction of **20** cleanly afforded the alcohol **21** and aldehyde **22**, in 54% and 35% yield, respectively, without coproduction of cleavage products. Swern oxidation of purified **21** quantitatively furnished the aldehyde **22**. Alcohol **21** was somewhat unstable, which was not surprising because of its structural similarity to **17**. In subsequent work, the initially received diol **21**/aldehyde **22** mixture was not separated but was directly oxidized with the Swern reagent to afford an 86% overall yield of aldehyde **22** from the MEM-protected menthyl ester **20**.

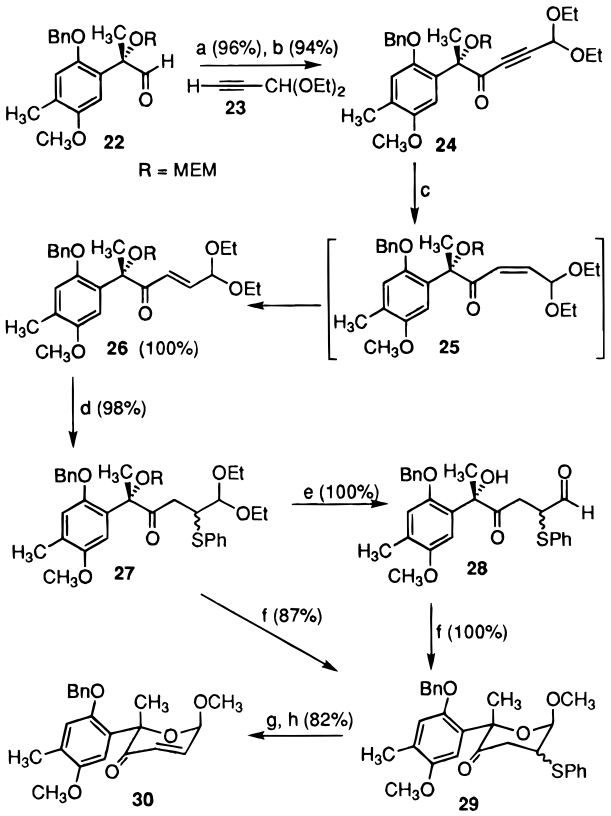
Planned introduction of the remaining three carbons that were needed for elaboration of the pyranose ring was based on addition of the acetylene **23** to the aldehyde **22** (Scheme 6). The acetylide anion generated from reaction of *n*-BuLi with commercially available propargyl aldehyde diethylacetal (**23**) was reacted with the aldehyde **22** to afford a diastereoisomeric mixture of alcohols (70:30 ratio) in 96% yield. Because conversion of the alcohols to the ketone **24** would both destroy the newly created chiral center and enhance stability of the intermediate by introducing an electron-withdrawing group α to the labile tertiary hydroxyl group, the mixture was not separated but was directly oxidized with excess MnO_2 to the ketone **24** in 94% yield.

The plan was to effect Lindlar hydrogenation of **24** to the *Z*-olefinic product **25**, because this olefin geometry would allow direct cyclization to the ethyl glycoside of the hexenulose **30**. Unexpectedly, Lindlar reduction of **24** provided a quantitative yield of the *E*-olefinic isomer **26**, apparently from rapid in situ isomerization of the *Z*-isomer **25**. Because the olefin geometry in **26** prohibited direct cyclization, an alternative pathway to the hexenulose **30** would need to be established. Although conjugate addition of a nucleophile to **26**, cyclization of the adduct to the pyranose, and then elimination of the introduced nucleophile appeared to be a reasonable solution to this

(13) We repeated the procedure originally reported by Casiraghi et al.[11] and found that the yield (84%) and diastereoselectivity (92%) is substantially higher when α-naphthol is used in the reaction.

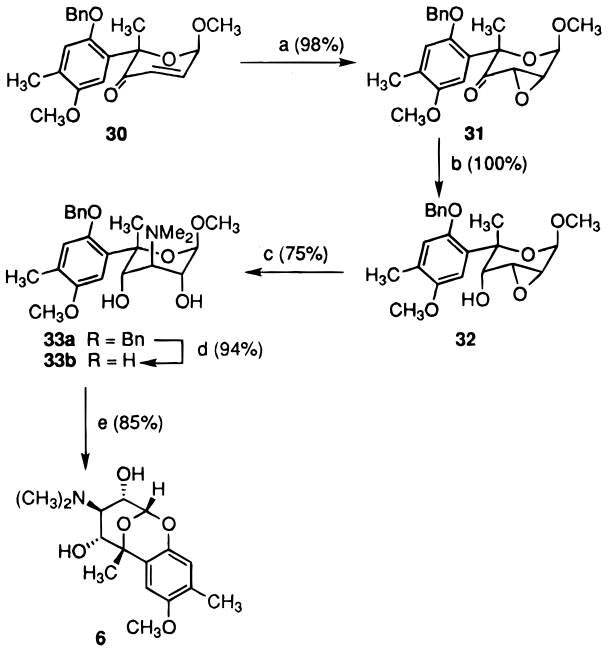
(14) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957−962. Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651−1660.

Scheme 6[a]



[a]Reagents and Conditions: a. **23**, n-BuLi, then **22**, THF, 0 °C to r.t., 96%; b. MnO_2, CH_2Cl_2, r.t., 12 h, 94%; c. Lindlar catalyst, quinoline, EtOAc, 24 h, 100%; d. PhSH, Et_3N, $CHCl_3$, 98%. e. TFA, THF, H_2O (100%); f. MeOH, $CHCl_3$, TsOH, TFA, Δ, 12 h, 87%; g. m-CPBA, CH_2Cl_2, r.t., 4 h. 100%; h. Toluene, $CaCO_3$, K_2CO_3, 48 h, 110 °C, 82%.

Scheme 7[a]



[a]a. ^tBuOOH, triton-B, CH_2Cl_2, r.t., 98%; b. $NaBH_4$, i-PrOH, r.t., 24 h, 100%; c. $(CH_3)_2NH$, sealed tube, 140 °C, 24 h, 75%; d. 10% Pd-C, ammonium formate, EtOH, 94%; e. AcOH, HCl (3 N), 3 h., 70 °C, 85%

problem, it would undoubtedly require working with a mixture of diastereoisomers. A thiolate was chosen as the nucleophile since the incorporated sulfur-containing group might be eliminated as either the sulfoxide or sulfone. As expected, Et_3N-catalyzed conjugate addition of PhSH to **26** produced a diastereoisomeric mixture of sulfides **27** in 98% yield.

An issue that had to be addressed at this point was formation of the α-glycoside. In earlier work we had found that this anomer is essential for introduction of functionality on the pyranose ring with the correct regio- and stereochemistry.[15] Although intramolecular cyclization of **27** furnished predominantly the α-ethyl glycoside, problems were encountered with this derivative,[16] which necessitated that **27** be converted to the α-methyl glycoside **30**.

Treatment of **27** with TFA in THF/H_2O concomitantly hydrolyzed the acetal and cleaved the MEM ether giving a quantitative yield of the keto aldehyde **28**. It was apparent from inspection of the ^1H NMR spectrum of the product that it consisted solely of aldehyde diastereoisomers and that none of the pyranose form was present. Initially, problems were encountered with the conversion of **28**, but ultimately conditions ($CHCl_3$, MeOH, 2:1; TFA, PPTS, TsOH) were found for selective transformation to the α-methyl pyranoside **29** (95:5 mixture of anomers) in nearly quantitatively yield. With further study, it was found that the three-step sequence used to convert the diethylacetal **27** to the α-methyl pyranoside **29** could be accomplished in one pot through reaction with excess methanol in the presence of TsOH/CF_3CO_2H. Under these conditions, a 93:7 ratio of anomeric methyl glycosides was produced, in which the desired anomer **29** predominated. The anomeric, diastereoisomeric sulfide mixture **29** was oxidized with *m*-CPBA (1 equiv) to the sulfoxide, which without purification was thermolyzed (toluene, $CaCO_3$, K_2CO_3, 48 h) to afford the hexenulose **30** after separation of the minor anomer (82% yield).[17]

The sequence employed in our racemic synthesis of 7-con-*O*-methylnogarol was used to functionalize the pyranose ring (Scheme 7). Epoxidation[18] of the double bond in **30** with *tert*-butyl hydroperoxide and Triton-B produced the epoxide **31** as the sole product of reaction in 98% yield. Reduction of the epoxyketone **31** with $NaBH_4$ stereospecifically furnished the alcohol **32** in quantitative yield, and subsequent reaction of **32** with dimethylamine[19] (sealed tube, 140 °C, 24 h, 75%) regio- and stereospecifically opened the epoxide to produce the amino sugar **33a**. Debenzylation of **33a** with 10% Pd/C and ammonium formate in ethanol[20] gave the phenol **33b**, which without purification was cyclized with acetic acid/HCl to the aminoexpoxybenzoxocin **6** in 85% overall yield from **33a**.

(15) Unpublished results, Ph.D. dissertation; Ellenberger, W. P., Oregon Graduate Center, 1987.

(16) The ethyl glycoside analogue of the epoxy alcohol **32** unexpectedly proved to be unstable to the conditions (sealed tube, 140 °C) needed to open the epoxide ring with dimethylamine.

(17) The undesired β-anomer was recycled to the desired α-anomer **20** in 50% yield through treatment with TFA and MeOH.

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Summary. The developed sequence provides a route for optically active total synthesis of the epoxybenzoxocin **6** from achiral starting materials in 22% overall yield over 17 steps. Additional studies are in progress to find a more enantioselective protocol for construction of the tertiary carbinol and to modify the route to avoid formation of unstable intermediates.

Experimental Section

All reactions were run under N_2 or Ar unless otherwise noted. Glassware for air-sensitive reactions was oven dried, assembled while hot, and cooled under a nitrogen purge. Solvents were predried and distilled unless otherwise stated. THF, PhH, and toluene were distilled from sodium−benzophenone ketyl prior to use. CH_2Cl_2 was distilled from anhydrous P_2O_5, and DMF, CH_3CN, DMSO, TEA, TMEDA, and hexanes were distilled from CaH_2 and stored over 4 Å molecular sieves. Pyridine and quinoline were distilled from CaH_2 and stored over KOH. Melting points were taken on a Koffler hot-stage melting point apparatus and are uncorrected. Flash chromatography was performed according to the literature procedure,[21] using Baker flash silica gel 60 (40 mm). Preparative TLC and TLC utilized EM Kieselgel 60 F-254 (0.25 mm thickness) precoated plates.

4-Methoxy-3-methylacetophenone (14). To a mechanically stirred mixture of anhydrous $AlCl_3$ (55.98 g, 0.71 mol) in CH_2Cl_2 (50 mL) was added slowly a solution of 2-methyl anisole **3** (79.20 g, 0.65 mol) in CH_2Cl_2 (40 mL), followed by acetyl chloride (51 mL, 0.71 mol) in CH_2Cl_2 (30 mL). The reaction was heated on a steam bath for 2 h, then cooled to room temperature, quenched with HCl (3 N, 30 mL), and extracted with Et_2O (125 mL). The organic layer was washed with brine, then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Vacuum distillation of the residue afforded 93.65 g (88%) of pure **14** with bp 132−134 °C (7 mm). ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 3 H); 2.55 (s, 3 H); 3.89 (s, 3 H); 6.74 (s, 1 H); 6.89 (s, 1 H); 7.77 (s, 1 H).

4-Acetoxy-2-methylanisole (15). To a magnetically stirred mixture of the acetophenone **14** (66.35 g, 0.40 mol) in CH_2Cl_2 (150 mL) at 0 °C was added *m*-CPBA (252.5 g, 0.73 mol). The mixture was warmed to room temperature and then heated at reflux for 16 h, at which point TLC analysis indicated disappearance of the starting material. The reaction was quenched with saturated $Na_2S_2O_3$ (70 mL) and extracted with Et_2O (200 mL). The organic layer was washed successively with a saturated solution of $Na_2S_2O_3$, Na_2CO_3, H_2O, and brine, then dried (Na_2SO_4), filtered, and evaporated under reduced pressure. Vacuum distillation of the residue gave 61.90 g (85%) of **15** with bp 136−138 °C (20 mm). ^{1}H NMR ($CDCl_3$) δ 2.20 (s, 3 H); 2.26 (s, 3 H); 3.81 (s, 3 H); 6.82 (m, 3 H).

4-Hydroxy-3-methylanisole (11). A magnetically stirred solution of **15** (65.0 g, 0.36 mol) in THF (100 mL) and HCl (3 N, 30 mL) was heated at reflux overnight. The reaction was cooled to room temperature, quenched with saturated Na_2CO_3 (80 mL) and extracted with Et_2O (120 mL). The organic layer was washed with H_2O and brine, then dried (Na_2SO_4), filtered and evaporated under reduced pressure. Vacuum distillation of the residue gave 41.7 g (84%) of **11** with bp 136−138 °C (20 mm). IR (film) 3380, 1599 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 3 H); 3.77 (s, 3 H); 4.70 (s, 3 H); 6.65 (m, 3 H).

(2*S)-2-Hydroxy-2-(2′-hydroxy-5′-methoxy-4′-methylphenyl)-propionic acid-(−)-menthyl Esters (16a) and the (2*R**)-Isomer (16b).** To a precooled (−70 °C) 1-L three-necked round-bottom flask fitted with an addition funnel were added successively CH_2Cl_2 (60 mL), $TiCl_4$ (10 mL, 0.09 mol), and menthol (14.1 g, 92 mmol) in CH_2Cl_2 (60 mL). The mixture was stirred for 50 min, and then a solution of 4-hydroxy-3-methylanisole **11** (11.7 g, 85 mmol) in CH_2Cl_2 (70 mL) was added dropwise. The deep red solution was stirred for 5 h, and then menthyl pyruvate **12** (20.45 g, 904 mmol) in CH_2Cl_2 (60 mL) solution was added dropwise. The reaction was stirred initially at −70 °C for 24 h, then subsequently warmed to −40, −20, and 0 °C, with 24 h of stirring at each interval, and finally was stirred at room temperature for 48 h. The reaction was quenched with saturated NH_4Cl solution (200 mL), and the solvent was evaporated under reduced pressure. The residue was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine, then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash chromatography of the residue (silica gel, 200 g, 13% EtOAc/hexanes) provided 14.8 g (48%) of C-2*S* **16a** and 3.70 g (12%) of C-3*R* **16b** as light yellow oils.

16a: $[a]^{23}_D = -16.8°$ (*c* 16.12, CH_2Cl_2); IR (film) 3363, 1721, 1627 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.77 (d, J = 7.2 Hz, 3 H); 0.89−0.90 (m, 7 H); 0.96−1.15 (m, 2 H); 1.35−1.57 (m, 2 H); 1.60−1.77 (m, 2 H); 1.79 (s, 3 H); 1.84−1.93 (m, 1 H); 2.01−2.12 (m, 1 H); 2.15 (s, 3 H); 3.75 (s, 3 H); 4.35 (s, 1 H); 4.83 (dt, J = 10.9, 4.5 Hz, 1 H); 6.70 (overlap, 2 H); 8.15 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.8, 16, 20.7, 21.8, 23.1, 26.2, 26.4, 33.9, 34, 40.5, 47.0, 56.0, 77.3, 78.0, 108.5, 120.1, 122.6, 128.4, 148.8, 150.8, 174.3. Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.28; H, 8.82.

16b: $[a]^{23}_D = +57.9°$ (*c* 3.45, CH_2Cl_2); IR (film) 3363, 1721, 1627 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.62 (d, J = 7.2 Hz, 3 H); O.74 (d, 3 H); 0.89−0.90 (m, 5 H); 0.96−1.15 (m, 2 H); 1.35−1.57 (m, 2 H); 1.60−1.77 (m, 2 H); 1.82 (s, 3 H); 2.01−2.12 (m, 1 H); 2.17 (s, 3 H); 3.75 (s, 3 H); 4.20 (s, 1 H); 4.72 (dt, J = 10.8, 4.3 Hz, 1 H); 6.62 (1 H); 6.68 (1 H); 7.92 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.6, 15.8, 20.5, 21.9, 23.1, 25.7, 26.0, 31.3, 34, 40.4, 47.0, 56.2, 71.3, 77.3, 109.5, 119.6, 122.6, 128.5, 149.0, 151.0, 174.2.

(2*S)-2-Hydroxy-2-(2′-benzyloxy-5′-methoxy-4′-methylphenyl)-propionic acid-(−)-menthyl Ester (10).** To a magnetically stirred mixture of the α-hydroxy menthyl ester **16a** (15.79 g, 43.3 mmol) and anhydrous K_2CO_3 (24.8 g, 180 mmol) in acetone (400 mL) was added dropwise benzyl bromide (8.1 mL, 67 mmol). The mixture was heated at reflux for 15 h, at which point TLC analysis indicated the disappearance of the starting material. The reaction was cooled to the room temperature and filtered, and the K_2CO_3 cake was washed with excess CH_2Cl_2 (3 × 70 mL). Evaporation of the solvent and chromatography of the residue (silica gel, 200 g, 8% EtOAc/hexanes) provided 17.68 g (90%) of the benzyl ether **10** as a thick brown oil. $[a]^{23}_D = -43.5°$ (*c* 1.55, CH_2Cl_2); IR (film) 3359, 1715, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.77 (d, J = 7.2 Hz, 3 H); 0.89−0.90 (m, 7 H); 0.96−1.15 (m, 2 H); 1.35−1.57 (m, 2 H); 1.60−1.77 (m, 2 H); 1.79 (s, 3 H); 1.84−1.93 (m, 1 H); 2.01−2.12 (m, 1 H); 2.20 (s, 3 H); 3.83 (s, 3 H); 4.21 (s, 1 H); 4.65 (dt, J = 10.7, 4.5 Hz, 1 H); 5.08 (d, J = 12.3 Hz, 1 H); 5.04 (d, J = 12.3 Hz, 1 H); 6.75 (s, 1 H); 6.96 (s, 1 H); 7.29−7.49 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 15.9, 16.1, 20.7, 21.9, 23.0, 24.6, 25.8, 25.9, 31.1, 34.1, 39.9, 46.5, 56.1, 70.8, 70.9, 74.3, 75.6, 109.2, 115.3, 126.9, 127.7, 128.5, 136.5, 149.5, 151.5, 174.2. Anal. Calcd for $C_{28}H_{38}O_5$: C, 73.97; H, 8.42. Found: C, 74.07; H, 8.31.

(2*S)-2-(2′-Benzyloxy-5′-methoxy-4′-methylphenyl)-2-(methoxy ethoxy methyloxy)-propionic acid-(−)-menthyl Ester (20).** A solution of the benzyloxy α-hydroxy menthyl ester **10** (15.59 g, 34.3 mmol) in THF (30 mL) was added dropwise to a magnetically stirred suspension of NaH (11.35 g, 0.28 mol, 60% in mineral oil, prerinsed twice with dry hexanes) at 0 °C. The reaction was warmed to room temperature and stirred for 1.5 h, then MEMCl (10.0 mL, 81 mmol) was added, and the reaction was stirred for 24 h. The reaction was quenched with H_2O (20 mL) and extracted with Et_2O (60 mL). The organic layer was washed with brine, then dried (Na_2SO_4), filtered, and evaporated under reduced pressure. Chromatography of the residue (silica gel, 150 g, 5%, 10%, 15% EtOAc/hexanes) provided 18.02 g (97%) of the MEM ether **20** as a viscous pale yellow oil. $[a]^{23}_D = -57.6°$ (*c* 3.87, CH_2Cl_2); IR (film) 1734 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.77 (d, J = 7.2 Hz, 3 H); 0.89−0.90 (m, 7 H); 0.96−1.15 (m, 2 H); 1.35−1.57 (m, 2 H); 1.60−1.77 (m, 2 H); 1.85 (s, 3 H); 1.84−1.93 (m, 1 H); 2.01−2.12 (m, 1 H); 2.18 (s, 3 H); 3.31 (s, 3 H); 3.43−3.57 (m, 2 H); 3.66−3.81 (m, 2 H); 3.80 (s, 3 H); 4.55 (dt, J =

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10.7, 4.5 Hz, 1 H); 4.74−5.04 (m, 4 H); 6.71 (s, 1 H); 7.16 (s, 1 H); 7.20−7.43 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 15.5, 15.8, 20.5, 21.6, 22.6, 22.8, 25.1, 30.8, 33.8, 39.6, 46.3, 55.5, 58.5, 67, 70.1, 71.4, 74.8, 79.3, 90.8, 109.1, 114.7, 126.2, 126.3, 127.1, 128, 132.8, 148.4, 151.2, 171.2. Anal. Calcd for $C_{32}H_{45}O_7$: C, 70.95; H, 8.37. Found: C, 71.20; H, 7.92.

(2*S)-2-(2′-Benzyloxy-5′-methoxy-4′-methylphenyl)-2-(methoxy ethoxy methyloxy)-propionic Aldehyde (22) and (2*S**)-2-(2′-Benzyloxy-5′-methoxy-4′-methylphenyl)-2-(methoxy ethoxy methyloxy)-propionic Alcohol (21).** To a magnetically stirred mixture of the MEM-protected menthyl ester **20** (14.62 g, 27.0 mmol) and powdered 4 Å molecular sieves (650 mg) in toluene (50 mL) at −78 °C was added dropwise neat DIBAL (9.1 mL, 51 mmol). The reaction was monitored by TLC until the starting material disappeared and then slowly brought to room temperature. Rochelle salt (sodium potassium tartrate, 700 mg) was added, followed by H_2O and 10% NaOH solution (7:1 v/v; 14 mL, 2 mL) and stirred until a solid formed. The mixture was filtered through florisil, and the residue was washed with excess CH_2Cl_2. The solvent was evaporated under reduced pressure, and the residue was taken up in Et_2O (60 mL). The organic phase was washed with brine, then dried (Na_2SO_4), filtered, and evaporated under reduced pressure. Chromatography of the residue (silica gel, 150 g, 15%, 20%, and finally 30% EtOAc/hexanes) provided 3.62 g (35%) of the MEM-protected aldehyde **22** and 5.69 g (54%) of the MEM-protected alcohol **21** as a thick pale yellow oil. **21:** $[a]^{23}_D = -45.6°$ (*c* 2.75, CH_2Cl_2); IR (film) 1724, 1665, 1608 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.62 (s, 3 H); 2.18 (s, 3H); 2.99 (b s, 1 H); 3.37 (s, 3 H); 3.56 (t, J = 4.6 Hz, 2 H); 3.79 (s, 3 H); 3.80−3.90 (m, 3 H); 4.04 (d, J = 3.8 Hz, 1 H); 4.07 (d, J = 3.8 Hz, 1 H); 4.80 (d, J = 7.7 Hz, 2 H); 4.91 (d, J = 7.7 Hz, 2 H); 5.02 (s, 2 H); 6.78 (s, 1 H); 7.03 (s, 1 H); 7.25−7.43 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.8, 22.2, 56, 58.8, 66.4, 67.6, 70.9, 71.5, 82.4, 90.6, 110.6, 116.1, 126.4, 127.3, 127.7, 128.5, 129.1, 137.1, 149.3, 151.7. Anal. Calcd for $C_{22}H_{30}O_6$: C, 67.71; H, 7.69. Found: C, 67.78; H, 7.66.

(2*S)-2-(2′-Benzyloxy-5′-methoxy-4′-methylphenyl)-2-(methoxy ethoxy methyloxy)-propionic Aldehyde (22).** To a stirred solution of $(COCl)_2$, (3.7 mL, 42 mmol) in CH_2Cl_2 (17 mL) was added DMSO (6.6 mL, 92 mmol) in CH_2Cl_2 (10 mL), and the pale yellow solution was stirred for 15 min. A solution of MEM-protected alcohol **11** (3.38 g, 8.7 mmol) in CH_2Cl_2 (15 mL) was added dropwise, and the mixture was stirred for 0.5 h. Trimethylamine (22 mL, 0.16 mmol) in CH_2Cl_2 (15 mL) was added, the cold bath was removed, and the reaction was stirred for 20 min. TLC analysis indicated the disappearance of the starting material. The reaction was quenched with saturated NH_4Cl solution (15 mL), warmed to room temperature, and extracted with Et_2O (60 mL). The organic layer was washed with brine, then dried (Na_2SO_4), filtered ,and evaporated under reduced pressure. Chromatography of the residue (silica gel, 50 g, 15% EtOAc/$CHCl_3$) provided 3.27 g (97%) of the MEM-protected aldehyde **22** as a greenish yellow oil. $[a]^{23}_D = +13.5°$ (*c* 10.27, CH_2Cl_2); IR (film) 1735, 1608 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.68 (s, 3 H); 3.83 (s, 3 H); 4.83 (s, 2 H); 4.98 (s, 2 H); 6.77 (s, 1 H); 7.04 (s, 1 H); 7.25−7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 16.2, 20, 55.9, 58.8, 67.1, 70.9, 71.2, 81.3, 90.6, 110, 115.7, 126.5, 127.2, 127.7, 127.9, 128.4, 136.5, 148.6, 151.8, 199.5. Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 67.74; H, 8.25.

(5*S)-5-(2′-Benzyloxy-5′-methoxy-4′-methylphenyl)-5-(methoxy ethoxy methyloxy)-4-oxo-hex-2-yne-1-diethyl Acetal (24).** To a magnetically stirred solution of the propargyl aldehyde diethyl acetal (**23**) (9.4 mL, 65 mmol) at room temperature was added dropwise *n*-BuLi (2.15 M in hexanes, 26.6 mL, 57.2 mmol), and the solution was stirred for 1.5 h. The MEM-protected aldehyde **22** (5.18 g, 13.3 mmol) in THF (30 mL) was added dropwise, and the reaction was stirred until disappearance of the starting material was indicated by TLC (24 h). The reaction was quenched with saturated NH_4Cl solution and extracted with Et_2O (50 mL). The organic layer was washed with brine, then dried (Na_2SO_4), filtered, and evaporated under reduced pressure. Chromatography of the residue (silica gel, 30 g, 20% EtOAc/hexanes) provided the diastereomeric alcohols **a** (1.98 g, 29%) and **b** (4.63 g, 67%) as light yellow oils. **a:** $[a]^{23}_D = +20.1°$ (*c* 5.51, CH_2Cl_2); IR (film) 3410, 2975, 2930 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.08 (t, J = 7.1 Hz, 6 H); 1.77 (s, 3 H); 2.21 (s, 3 H); 3.31−3.40 (m, 3 H); 3.42 (s, 3 H); 3.57−3.70 (m, 3 H); 3.80 (s, 3 H); 4.01−4.12 (m, 1 H); 4.24 (d, J = 9.3 Hz, 1 H); 5.01−5.16 (m, 6 H); 6.77 (s, 1 H); 7.13 (s, 1 H); 7.27−7.43 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.8, 15.9, 20.2, 55.9, 60.4, 60.5, 67.0, 67.9, 70.9, 71.2, 80.3, 83.3, 85.3, 90.6, 91.2, 110.8, 115.6, 126.4, 127.3, 127.9, 128.6, 136.9, 148.9, 151.6.

b: $[a]^{23}_D = +8.7°$ (*c* 10.38, CH_2Cl_2); IR (film) 3410, 2973, 2932 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.17 (t, J = 7.2 Hz, 6 H); 1.85 (s, 3 H); 2.18 (s, 3 H); 3.32 (d, J = 7.2 Hz, 1 H); 3.37 (s, 3 H); 3.45−3.65 (m, 7 H); 3.80 (s, 3 H); 3.87−3.95 (m, 1 H); 4.83 (s, 2 H); 5.05 (s, 2 H); 5.20 (d, J = 7.1 Hz, 1 H); 5.24 (d, J = 1.1 Hz, 1 H); 6.79 (s, 1 H); 6.99 s, 1 H); 7.27−7.43 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.9, 15.9, 20.8, 55.8, 58.8, 60.5, 60.6, 67.4, 67.6, 70.7, 71.6, 81.0, 82.9, 84.2, 91.2, 111.6, 116.0, 126.8, 127.0, 127.7, 128.5, 137.0, 149.6, 151.5.

A mixture of the diastereoisomeric alcohols (7.57 g, 14.7 mmol) and MnO_2 (28.76 g, 331 mmol) in CH_2Cl_2 (70 mL) was stirred at the room temperature for 16 h. The mixture was filtered, the residue was washed with excess CH_2Cl_2, and the filtrate was evaporated under reduced pressure. Chromatography of the residue (silica gel, 30 g, 15% EtOAc/hexanes) provided 7.09 g (94%) of the ketone **24**. $[a]^{23}_D = -11.9°$ (*c* 10.25, CH_2Cl_2); IR (film) 2929, 2250, 1686 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.08 (t, J = 7.0 Hz, 6 H); 1.77 (s, 3 H); 2.20 (s, 3 H); 3.35 (s, 3 H); 3.32−3.42 (m, 5 H); 3.49−3.54 (m, 2 H); 3.67−3.75 (m, 1 H); 3.82 (s, 3 H); 4.81 (d, J = 5.7 Hz, 1 H); 4.89 (d, J = 5.7 Hz, 1 H); 5.0 (s, 2 H); 5.18 (s, 1 H); 6.71 (s, 1 H); 7.16 (s, 1 H); 7.26−7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.7, 16.0, 20.3, 55.7, 60.8, 60.9, 67.3, 70.7, 71.4, 81.6, 82.2, 85.6, 90.5, 90.7, 109.4, 115.2, 126.9, 127.1, 127.4, 127.6, 128.1, 136.6, 148.6, 151.7, 185.4. Anal. Calcd for $C_{29}H_{38}O_8$: C, 67.69; H, 7.44. Found: C, 67.79; H, 7.44.

(5*S)-5-(2′-Benzyloxy-5′-methoxy-4′-methylphenyl)-5-(methoxy ethoxy methyloxy)-4-oxo-hex-2-en-1-diethyl Acetal (26).** A mixture of the ketone **24** (6.56 g, 12.7 mmol) in EtOAc (25 mL), Lindlar catalyst (2.35 g), and quinoline (7 mL) was stirred under a hydrogen atmosphere for 24 h. The reaction mixture was filtered through Celite, and the filtrate was diluted with Et_2O (50 mL). The solution was successively washed with 10% HCl, H_2O, and brine, then dried (Na_2SO_4), filtered ,and evaporated under reduced pressure to provide 6.58 g (100%) of the α,β-unsaturated ketone **26**. $[a]^{23}_D = -23.4°$ (*c* 2.52, CH_2Cl_2); IR (film) 3053, 2976, 2927, 2304, 1705, 1638 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.06 (t, J = 7.1 Hz, 3 H); 1.18 (t, J = 7.1 Hz, 3 H); 1.73 (s, 3 H); 2.19 (s, 3 H); 3.17−3.28 (m, 1 H); 3.34 (s, 3 H); 3.46−3.55 (m, 4 H); 3.61−3.76 (m, 3 H); 3.84 (s, 3 H); 4.83 (s, 2 H); 4.83 (d, J = 12.0 Hz, 1 H); 4.95 (d, J = 12.0 Hz, 1 H); 5.81 (q, J = 13.7 Hz, 2 H); 6.29 (d, J = 18.7 Hz, 1 H); 6.67 (s, 1 H); 7.22 (s, 1 H); 7.25−7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 15.2, 15.3, 16.2, 20.3, 55.9, 58.9, 62.4, 62.6, 67.4, 70.4, 71.5, 82.2, 90.3, 96.9, 109.4, 115.0, 124.7, 126.6, 126.7, 127.1, 127.4, 128.3, 136.9, 142.1, 148.4, 151.9, 197.2. Anal. Calcd for $C_{29}H_{40}O_8$: C, 67.42; H, 7.80 Found: C, 67.42; H, 7.75.

(5*S,2*R**)-5-(2′-Benzyloxy-5′-methoxy-4′-methylphenyl)-5-(methoxy ethoxy methyloxy)-4-oxo-2-phenylthio-hexane-1-diethyl Acetal and the (5*S**,2*S**)-Isomer (27).** To a stirred solution of the α,β-unsaturated ketone **15** (7.44 g, 14.4 mmol) in $CHCl_3$ (25 mL, reagent grade) at 0 °C was added Et_3N (3.7 mL, 21 mmol) followed by PhSH (2.1 mL, 17 mmol). The reaction was warmed slowly to room temperature for 24 h, at which point TLC analysis indicated disappearance of the starting material. The reaction was quenched with 10% NaOH (10 mL) and extracted with Et_2O (30 mL). The organic layer was washed successively with H_2O and brine, then dried (Na_2SO_4), filtered, and evaporated under reduced pressure. Chromatography of the residue (silica gel, 30 g, 12% EtOAc/hexanes) provided a diastereomeric mixture of thiophenylated ketones **27a** (3.87 g, 43%) and **27b** (5.05 g, 56%).

27a: IR (film) 3418, 1719, 1583 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.99 (t, J = 6.9 Hz, 3 H); 1.02 (t, J = 7.2 Hz, 3 H); 1.70 (s, 3 H); 2.16 (s, 3 H); 2.77−3.12 (m, 2 H); 3.27−3.82 (m, 9 H); 3.33

(s, 3 H); 3.79 (s, 3 H); 4.35 (d, J = 4.1 Hz, 1 H); 4.68 (d, J = 3.7 Hz, 1 H); 4.78 (d, J = 3.7 Hz, 1 H); 4.94 (s, 2 H); 6.69 (s, 1 H); 7.11−7.48 (m, 9 H); 7.51 (d, J = 2.47 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 15.0, 15.1, 16.2, 21.0, 29.6, 37.4, 47.3, 55.9, 58.9, 63.4, 67.2, 70.6, 71.7, 83.1, 90.9, 104.4, 110.4, 115.5, 126.5, 126.8, 127.3, 127.5, 128.4, 128.6, 131.4, 135.8, 136.9, 148.4, 148.7, 206.7.

27b: IR (film) 3516, 1721, 1583 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10 (t, J = 6.9 Hz, 3 H); 1.16 (t, J = 7.2 Hz, 3 H); 1.73 (s, 3 H); 2.16 (s, 3 H); 2.75 (dd, J = 13.5, 5.7 Hz, 1 H); 3.27−3.45 (m, 1 H); 3.51 (s, 3 H); 3.53−3.80 (m, 9 H); 3.79 (s, 3 H); 4.51 (d, J = 3.6 Hz, 1 H); 4.67 (d, J = 3.2 Hz, 1 H); 4.76 (d, J = 3.2 Hz, 1 H); 4.84 (s, 2 H); 6.61 (s, 1 H); 7.01−7.19 (m, 3 H); 7.20−7.35 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 15.0, 15.1, 16.1, 21.2, 29.6, 37.7, 46.2, 55.6, 58.5, 63.4, 63.7, 67.1, 70.3, 71.6, 83.3, 90.5, 103.5, 110.0, 115.1, 126.2, 126.6, 127.3, 127.4, 128.2, 128.5, 130.9, 136.1, 137.1, 148.7, 151.5, 207.4.

(5*S)-α-Methyl-5-(2′-Benzyloxy-5′-methoxy-4′-methylphenyl)-2-phenylthio-2,3,6-trideoxy-hex-4-ulose (29a) and the *β*-Anomer (29b).** To a magnetically stirred solution of **27a** and **27b** (2.52 g, 4.0 mmol) in MeOH/$CHCl_3$ (2:7 v/v; 8 mL, 28 mL) at 0 °C was added TsOH (20 mg) in TFA (4 mL). The reaction was warmed to room temperature and then heated at reflux. (The compound at the same R_f of the starting material **16a** and **16b** was found to be the transacetalized MEM-cleaved tertiary alcohol (240 mg, 12% yield), which was subjected to further cyclization in the same condition to provide the desired product **19a** and **19b**). The reaction was cooled to room temperature, quenched with Na_2CO_3 solution (30 mL), and extracted with Et_2O (30 mL). The organic layer was washed with H_2O and brine, then dried (Na_2SO_4), filtered, and evaporated under reduced pressure. Chromatography of this residue (silica gel, 15 g, 10% EtOAc/hexanes) provided 1.60 g (83%) of the diastereomeric cyclized products **29a** and **29b**. As a diastereomeric mixture of **29a** and **29b:** IR (film) 3057, 1731, 1583 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.70 (s, 3 H); 1.85 (s, 3 H); 2.20 (s, 3 H); 2.21 (s, 3 H); 2.32−2.62 (m, 2 H); 2.82 (m, 1 H); 3.32−3.40 (m, 2 H); 3.43 (s, 3 H); 3.54 (s, 3 H); 3.71−3.78 (m, 1 H); 3.85 (s, 6 H); 4.69 (d, J = 8.2 Hz, 1 H); 4.71−5.09 (m,4 H); 6.81 (s, 2 H); 6.97 (s, 1 H); 7.01 (s, 1 H); 7.18−7.82 (m, 20 H); ^{13}C NMR ($CDCl_3$) δ 16.1, 17.9, 23.3, 24.5, 29.3, 37.0, 38.5, 41.1, 44.7, 45.3, 55.9, 71.4, 72.0, 80.6, 81.2, 99.3, 101.8, 106.3, 109.7, 110.0, 114.9, 116.1, 116.8, 126.6, 126.7, 127.0, 127.5, 127.8, 128.1, 128.2, 128.4, 128.5, 128.6, 128.7, 128.9, 131.3, 131.8, 132.3, 133.1, 133.6, 135.9, 136.1, 148.4, 148.5, 151.8, 152.0, 206.6, 206.8.

(5*S)-α-Methyl-5-(2′-benzyloxy-5′-methoxy-4′-methylphenyl)-6-deoxyhex-2-en-4-ulose (30a) and (5*S**)-Methyl-*β*-5-(2′-benzyloxy-5′-methoxy-4′-methylphenyl)-6-deoxyhex-2-en-4-ulose (30b).** To a magnetically stirred solution of the anomeric methyl pyranosides **29a** and **29b** (2.01 g, 4.2 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added *m*-CPBA (1.15 g, 6.7 mmol), and the reaction was warmed to room temperature. The reaction was stirred for 4 h, then quenched with saturated $Na_2S_2O_3$ (15 mL) solution, and extracted with Et_2O (30 mL). The organic layer was washed successively with Na_2CO_3 solution (20 mL), H_2O (15 mL), and brine (15 mL), then dried (Na_2SO_4), filtered ,and evaporated under reduced pressure to afford a pale yellow solid. Without further purification, the diastereomeric sulfoxide mixture was heated at reflux in toluene (15 mL), in the presence of $CaCO_3$ (30 mg) and K_2CO_3 (20 mg) for 48 h. The reaction was cooled to room temperature and filtered, and the filtrate was diluted with Et_2O (25 mL). The organic layer was washed with brine, then dried (Na_2SO_4), filtered, and evaporated under reduced pressure. Chromatography of the residue (silica gel, 15 g, 13% EtOAc/hexanes) provided 1.18 g (93%) of the α-anomer **29a** and 0.09 g (7%) of the *β*-anomer **29b**. The *β*-anomer **29b** was converted to the α-anomer **29a** in 50% yield by heating in MeOH (5 mL) and TFA (2−3 drops) for 24 h.

30a: mp 105−107 °C; $[a]^{23}_D$ = +7.9° (c 6.3, CH_2Cl_2); IR (CH_2Cl_2) 3053, 1692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.86 (s, 3 H); 2.20 (s, 3 H); 3.46 (s, 3 H); 3.82 (s, 3 H); 4.79 (d, J = 11.3 Hz, 1 H); 4.90 (d, J = 11.3 Hz, 1 H); 5.09 (dd, J = 2.9, 1.2 Hz, 1 H); 5.87 (dd, J = 10.4, 2.9 Hz, 1 H); 6.44 (dd, J = 10.4, 2.9 Hz, 1 H); 6.79 (s, 1 H); 6.95 (s, 1 H); 7.29−7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 16.2, 24.4, 29.6, 55.6, 55.9, 77.6, 80.6, 94.7, 110.1, 116.7,127.1, 127.8, 128.0, 128.2, 128.3, 136.7, 141.1, 149.7, 151.8, 197.3. Anal. Calcd for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57 Found: C, 71.62; H, 6.63.

30b: mp 123−127 °C; $[a]^{23}_D$ = +15.8° (c 4.05, CH_2Cl_2); IR (CH_2Cl_2) 2925, 1693 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.77 (s, 3 H); 2.18 (s, 3 H); 3.28 (s, 3 H); 3.81 (s, 3 H); 4.81 (d, J = 11.3 Hz, 1 H); 5.08 (d, J = 11.3 Hz, 1 H); 5.34 (t, J = 1.6 Hz, 1 H); 5.89 (dd, J = 10.4, 1.7 Hz, 1 H); 6.53 (dd, J = 10.4, 1.7 Hz, 1 H); 6.76 (s, 1 H); 6.92 (s, 1 H); 7.35−7.49 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 16.2, 21.6, 54.7, 54.8, 56.1, 71.9, 79.9, 94.1, 94.2, 110.4, 110.7, 116.8, 117.1, 128.2, 128.5, 128.6, 128.8, 136.9, 143.2, 149.7, 151.8, 197.2. Anal. Calcd for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57 Found: C, 71.79; H, 6.65.

(5*S)-Methyl-6-deoxy-2,3-anhydro-5-(2′-benzyloxy-5′-methoxy-4′-methylphenyl)-hexos-4-ulose (31).** To a solution of the unsaturated ketone **30** (442 mg, 1.16 mmol) in CH_2Cl_2 (20 mL) was added *t*-BuOOH (0.75 mL, 2.3 mmol) and Triton B (3 mL), and the mixture was stirred overnight at room temperature. The reaction was quenched with H_2O (5 mL) and extracted with Et_2O (50 mL). The organic layer was washed with brine, then dried (Na_2SO_4), filtered, and evaporated under reduced pressure. Chromatography of the residue (silica gel, 10 g, 20% EtOAc/hexanes) provided 458 mg (98%) of the keto epoxide **31** as a colorless oil. $[a]^{23}_D$ = −34.0° (c 4.59, CH_2Cl_2); IR (film) 2931, 1724 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.72 (s, 3 H); 2.17 (s, 3 H); 3.39 (d, J = 4.0 Hz, 1 H); 3.53 (s, 3 H); 3.58 (m, 1 H); 3.82 (s, 3 H); 4.83 (d, J = 2.7 Hz, 1 H); 4.89 (d, J = 2.7 Hz, 1 H); 5.13 (d, J = 1.1 Hz, 1 H); 6.72 (s, 1 H); 6.99 (s, 1 H); 7.26−7.49 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 15.9, 26.8, 53.8, 55.9, 56.3, 57.4, 72.0, 80.5, 96.3, 96.4, 109.8, 110.1, 116.8, 117.1, 127.3, 127, 128.0, 128.5, 137.0, 148.3, 152.3, 201.7. Anal. Calcd for $C_{22}H_{24}O_6$: C, 68.72; H, 6.29. Found: C, 68.69; H, 6.31.

(5*S)-Methyl-6-deoxy-2,3-anhydro-5-(2′-benzyloxy-5′-methoxy-4′-methylphenyl)-lyxo-hexopyranoside (32).** To a stirred solution of keto epoxide **31** (300 mg, 0.77 mmol) in 2-propanol (20 mL) was added $NaBH_4$ (60 mg, 1.5 mmol) and the mixture was stirred overnight at room temperature. The reaction was quenched with H_2O (5 mL) and diluted with Et_2O (25 mL), and the layers were separated. The organic layer was washed with H_2O and brine, then dried (Na_2SO_4), filtered, and evaporated under reduced pressure. Chromatography of the residue (silica gel, 10 g, 20% EtOAc/hexanes) gave 302 mg (99%) of pure **32** as white crystals with mp 144−146 °C. $[a]^{23}_D$ = +15.9° (c 0.75, CH_2Cl_2); IR (CH_2Cl_2) 3550, 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.59 (s, 3 H); 2.20 (s, 3 H); 2.28 (d, J = 10.6 Hz, 1 H); 3.31 (d, J = 3.8 Hz, 1 H); 3.54 (s, 3 H); 3.61 (dd, J = 6.5, 3.4 Hz, 1 H); 3.81 (s, 3 H); 4.71 (dd, J = 10.4, 6.4 Hz, 2 H); 4.96 (d, J = 11.6 Hz, 1 H); 5.21 (d, J = 11.6 Hz, 1 H); 6.78 (s, 1 H); 7.29 (s, 1 H); 7.29−7.46 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 15.7, 23.4, 51.5, 51.8, 55.5, 55.9, 64.6, 71.1, 77.8, 96.4, 109.7, 115.5, 125.8, 127.5, 127.8, 128.6, 129.8, 137.2, 148.1, 151.7. Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.23; H, 6.79.

(5*S)-Methyl-α-3−6-dideoxy-3-(dimethylamino)-5-(2′-benzyloxy-5′-methoxy-4′-methylphenyl)-gluco-hexopyranoside (33a).** A mixture of **32** (250 mg, 0.65 mmol) and dimethylamine (6 mL) was heated overnight at 140 °C in a sealed tube. The reaction mixture was cooled to room temperature, and the excess dimethylamine was evaporated. Chromatography of the residue (silica gel, 5 g, 10% MeOH/CH_2Cl_2) provided 208 mg of **33** as a yellowish solid in 75% yield with mp 171−174 °C. $[a]^{23}_D$ = −25.4° (c 1.26, CH_2Cl_2); IR (CH_2Cl_2) 3425, 1625 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.78 (s, 3 H); 2.22 (s, 3 H); 2.45 (s, 6 H); 2.94 (t, J = 10.5 Hz, 1 H); 3.35 (s, 3 H); 3.55 (t, J = 8.4 Hz, 1 H); 3.64 (d, J = 10.7 Hz, 1 H); 3.79 (s, 3 H); 4.11 (d, J = 7.4 Hz, 1 H); 5.08 (s, 2 H); 6.85 (s, 1 H); 7.26−7.52 (m, 5 H); 7.59 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 16.0, 28.1, 41.3, 55.6, 56.9, 65.6, 70.7, 71.1, 75.5, 78.8, 101.4, 111.9, 115.6, 126.7, 126.9, 127.2, 127.9, 128.6, 136.5, 149.3, 151.6. Anal. Calcd for $C_{24}H_{33}NO_6$: C, 66.80; H, 7.71 Found: C, 66.98; H, 7.90.

(5*S)-Methyl-α-3,6-dideoxy-3-(dimethylamino)-5-(2′-hydroxy-5′-methoxy-4′-methylphenyl)-gluco-hexopyranoside (33b).** A mixture of **33a** (260 mg, 0.6 mmol), 10% Pd/C

(261 mg), and ammonium formate (175 mg) in EtOH (15 mL) was stirred at room temperature for 24 h. The mixture was filtered through Celite, and the residue was washed with Et_2O (25 mL). The filtrate was evaporated under reduced pressure, and the residue was chromatographed (silica gel, 5 g, 2% MeOH/CH_2Cl_2) to afford 195 mg of the phenol **33b** as an oil in 95% yield. $[a]^{23}_D = -27.6°$ (*c* 7.08, CH_2Cl_2); IR (CH_2Cl_2) 2929, 1654, 1560 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.69 (s, 3 H); 2.17 (s, 3 H); 2.64 (s, 6 H); 3.02 (t, $J = 11.0$ Hz, 1 H); 3.59 (s, 3 H); 3.61−3.73 (m, 2 H); 3.75 (s, 3 H); 4.29 (d, $J = 7.5$ Hz, 1 H); 5.91 (br s, 1 H); 6.71 (s, 1 H); 7.14 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.8, 41.9, 59.9, 57.6, 65.1, 70.4, 71.8, 78.8, 80.0, 101.4, 109.3, 120.1, 122.0, 128.1, 161.9. Anal. Calcd for $C_{17}H_{27}NO_6$: C, 59.81; H, 7.97. Found: C, 59.69; H, 7.91.

(2*S,3*S**,4*R**,5*R**,6*S**)-4-*N*,*N*-Dimethylamino-3,5-dihydroxy-6,9-dimethyl-8-methoxy-3,4,5,6-tetrahydro-8-methoxy-2,6-epoxy-2*H*-1-benzoxocin (6).** A mixture of **33b** (55 mg, 0.16 mmol) in acetic acid (2.6 mL) and 3 N HCl (0.5 mL) was heated on a steam bath for 3 h. The reaction was cooled to room temperature and neutralized with saturated Na_2CO_3 solution (20 mL). The mixture was extracted with Et_2O (25 mL), and the organic layer was washed successively with H_2O and brine, then dried (Na_2SO_4), filtered, and evaporated under reduced pressure. Chromatography of the residue (silica gel, 5 g, 10% MeOH/CH_2Cl_2) provided 43 mg of **6** (86%; 94% based on reclaimed starting material) as white crystals with mp 42−45 °C; $[a]^{23}_D = -34.7°$ (*c* 4.29, CH_2Cl_2); IR (CH_2Cl_2) 2907, 1601 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.67 (s, 3 H); 2.19 (s, 3 H); 2.64 (s, 6 H); 3.50 (d, $J = 10.3$ Hz, 1 H); 3.80 (s, 3 H); 4.03 (m, 2 H); 5,47 (d, $J = 3.7$ Hz, 1 H); 6.57 (s, 1 H); 6.70 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.8, 40.8, 59.8, 65.1, 70.4, 78.8, 80.2, 101.4, 109.8, 120.6, 122.2. 125.6, 128.1, 150.8. Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.16; H, 7.49. Found: C, 62.23; H,7.50.

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