flected by the number of short intermolecular contacts (Tables IV and V), particularly those involving the bacterial enzyme. A comparison of the van der Waals surface of the active site of the bacterial and avian DHFR (Figures 7 and 8) revealed that the inhibitor is less constrained in the avian enzyme.

YETI minimizations of all models relieve the shortest contacts while in general maintaining reasonable hydrogen-bonding patterns with the acidic residue. The only exception is that of DOPT in the bacterial active site (Figure 7). Despite the YETI parameterization preference to maintain hydrogen bond interactions, there is a complete reorientation of the hydrogen bonding of DOPT with Asp-26. Because DOPT occupies a different region of the active site than DAPT (Figure 2), the minimization of DOPT interactions could not simultaneously relieve its adamantyl contacts and maintain the pteridine hydrogen bonding as observed in DAPT (Figure 4).

To relieve the adamantyl short contacts, DOPT is pushed deeper into the active site causing the Asp-26 oxygens to break the O(2)···N(3) and O(1)···N(2) hydrogen bonds of the starting model. As indicated in Table VI, YETI minimization disrupts this hydrogen bonding such that the Asp-26 O(2) is more strongly hydrogen bonded to Thr-116, while the contact to N(2) is significantly weakened. The contacts to Asp-26 O(1) are no longer in hydrogen-bonding distance to its neighbors. However, a new hydrogen bond is formed involving the other N(2) amine hydrogen and a water molecule, previously too far away. The most interesting result of the movements of the Asp-26 side chain and DOPT is that the Asp-26 backbone keto function, O(26), is now involved in close contacts to N(3) and O(4) of DOPT. Data in Table VI suggest that a hydroxy resonance at O(4) of DOPT would enhance its hydrogen-bonding geometry to O(26).

A similar analysis of chicken liver DHFR (Table VI) reveals that the Glu-30 contacts to Thr-136 are outside hydrogen-bonding contact, and the hydrogen bonds are weaker in general. This is a reflection of the difference in the size of the active site of bacterial and avian DHFR (Figures 7 and 8).

Thus, these YETI modeling studies have shown that the antifolates DAMP and DAPT can be accommodated better in the active site of the avian DHFR than in the bacterial enzyme, in agreement with activity data. In addition, modeling studies with DOPT in the folate orientation show unexpected enzyme interactions in the bacterial enzyme which suggest that it is unlikely to function as a folate in this system.

Acknowledgment. The authors thank Drs. Sigmond Zakrzewski and Sue Opitz for providing samples of DAPT. This research was supported in part by research Grants NCI-34714 and FRA-287 (V.C.) from the American Cancer Society Faculty Research Award.

Supplementary Material Available: Tables of atomic partial charges, anisotropic thermal parameters, hydrogen atom parameters and geometry (7 pages); table of structure factor amplitudes (50 pages). Ordering information is given on any current masthead page.

Cyclopentane Construction with Control of Side Chain Configuration: Enantioselective Synthesis of (+)-Brefeldin A

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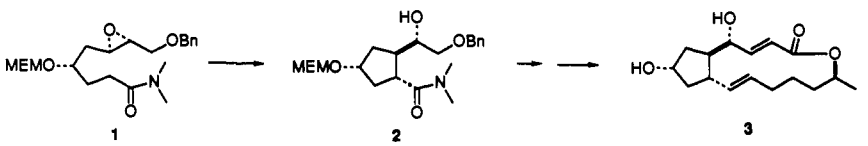
Abstract: Intramolecular opening of an enantiomerically pure epoxide by an amide enolate (**1** → **2**) is shown to be an effective method for cyclopentane construction with control of both ring and side chain absolute configuration. This opening serves as the key step in a synthesis of the Golgi apparatus-blocking macrolide (+)-brefeldin A (**3**). Other features of the synthesis include improved procedures for the enantioselective hydrogenation of a β-keto ester to the corresponding β-hydroxy ester, and for the Julia–Lythgoe reduction of a β-acetoxy sulfone to the trans alkene.



1 2 3

Introduction

(+)-Brefeldin A (**3**), first isolated in 1958 from *Penicillium decumbens*,[1] has been shown to have both antifungal and antiviral activity.[2] More recently, it has been shown that the antiviral activity of **3** is due to inhibition by **3** of the intracellular transport of secretory proteins.[3] The finding that brefelding A **3** specifically blocks the movement of proteins from the endoplasmic reticulum[4] to the Golgi apparatus[4] has made **3** a powerful tool for biochemical investigation.[5]

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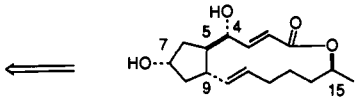
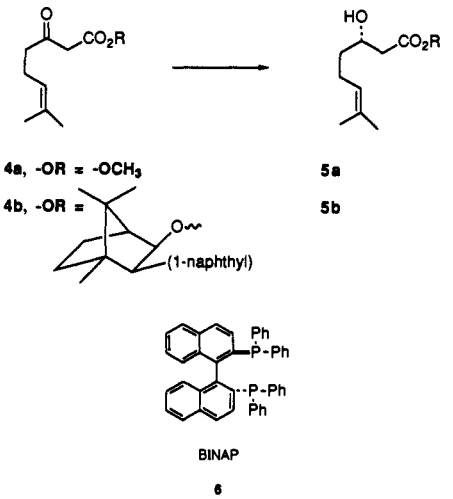
The complete structure of (+)-brefeldin A was established in 1971 by X-ray analysis.[6] Five years later, Corey and Wollenberg reported the first synthesis of racemic brefeldin A.[7] The first enantiospecific synthesis of (+)-brefeldin A was reported in 1979.[8] In the years since Corey's initial report, there have been numerous partial,[9] formal,[10] and total[11] syntheses described.

Our interest has been to develop general methods for the enantioselective construction of carbocyclic natural products.[12] The synthesis of (+)-brefeldin A (**3**) demanded a method that would allow control of absolute configuration on the pendant side chain concurrently with ring construction. The ready availability[13] of enantiomerically pure epoxides suggested intramolecular epoxide opening (**1** → **2**) as a solution to this prblem. We report an enantioselective total synthesis of (+)-brefeldin A (**3**) following this approach. A strength of the strategy outlined here is that it allows for independent control of each of the stereogenic centers of **3**.



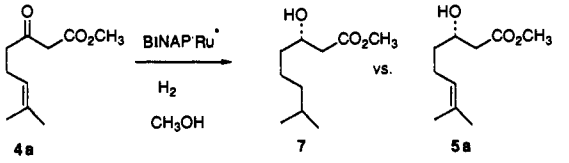
3

Substrate Preparation: Enantioselective Hydrogenation of a β-Keto Ester. At the inception of this work, we had thought to establish the requisite absolute configuration at C-7 (brefeldin numbering) by diastereoselective hydride reduction of **4b**, following the procedures we had established.[14] The early phase of this study was, in fact, based on that approach. The discovery[15-17] of the highly enantioselective BINAP·$RuCl_2$-mediated hydrogenation of β-keto esters, however, suggested that **4a** itself could be reduced to **5a**.



We first improved the catalyst preparation. The studies reported[15,16] had been carried out by dissolving BINAP·$Ru(OAc)_2$, prepared in two steps under strict anaerobic conditions (glovebox or Schlenkware) in methanolic HCl. Taking a lead from other workers in the field,[17] we found that the crude material from direct exchange of commercially available ($RuCl_2$·cyclooctadiene)$_n$ with BINAP in the presence of triethylamine is an active and highly enantioselective hydrogenation catalyst.[18]

Following the original procedure[15,16] for the hydrogenation (1500 psi of H_2, room temperature), using either catalyst, we recovered *only* the over-hydrogenated product **7**. After some exploration, we found that it is possible to dissect apart ketone reduction and alkene hydrogenation. At reduced pressure (50 psig of H_2) and elevated temperature (80 °C), **4a** is smoothly converted into the desired **5a**. Studies with enantiomerically pure shift reagents (^1H, ^{13}C NMR) demonstrated an enantiomeric ratio, using either reduction procedure, of about 99:1. We have found these conditions to be quite general.[18]



Preparation of Epoxide 1. Protection of **5a** (Scheme I) with MEM chloride and reduction of the ester with $LiAlH_4$ gives the alcohol **8**. Two-carbon homologation of **8** to **9** was found to proceed most efficiently by addition of the crude aldehyde from PCC oxidation to the phosphonoacetate anion. Reduction with DIBAL then gives the allylic alcohol **10**.

It was quickly apparent that MEM ether **10** (Scheme I) is not a good substrate for Sharpless epoxidation.[13] The reaction, slow even with the most reactive allylic alcohols, is very sluggish. The chelating protecting group may well be competing with the alcohol for key Lewis acidic reactive intermediates. Continuing addition of reagents and molecular sieves eventually led to acceptable conversion and diastereomeric ratio (established by ^{13}C NMR). If Sharpless epoxidation is to reach its full potential for the enantioselective preparation of polyoxygenated products, it will be important to uncover alternative simple, durable alcohol protecting groups that do not interfere in this way.

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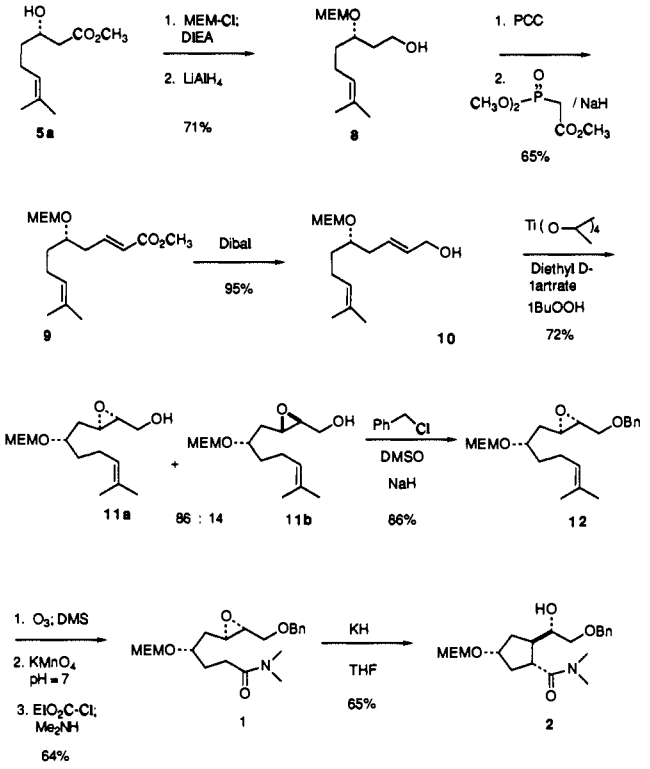
Scheme I. Cyclization of Epoxy Amide **1**

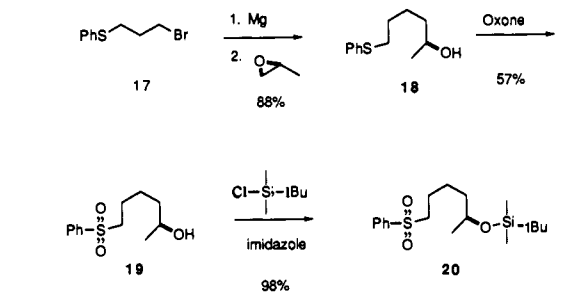


Benzylation of alcohol **11** in DMSO[19] proceeds smoothly. Ozonolysis[20] of **12** then gives the aldehyde, which is oxidized with $KMnO_4$ in pH 7 buffer[21] to the acid. In contrast to the original report,[21] we note that, under these conditions, excess $KMnO_4$ quickly oxidizes the benzylic methylene to the benzoate. The amide **1** is secured by exposure of the crude acid to ethyl chloroformate, followed by aqueous dimethylamine.[22]

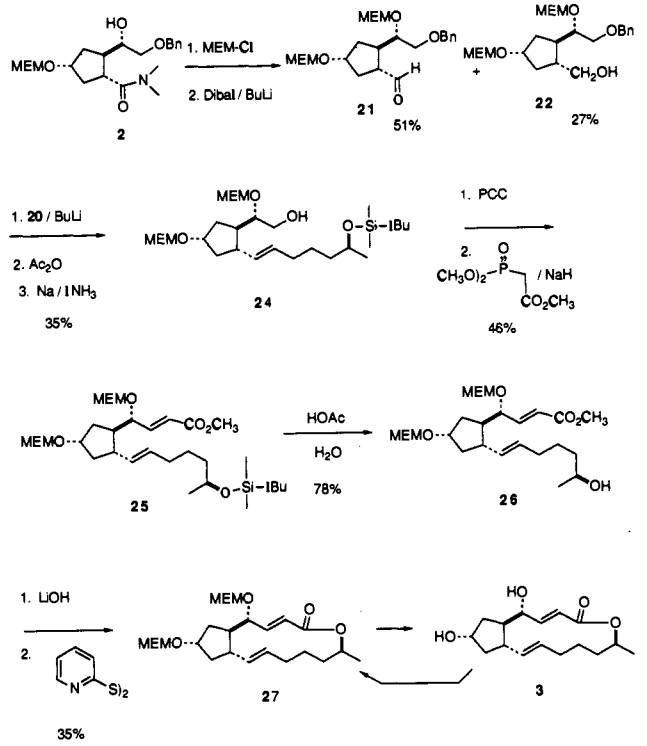
Cyclization of 1 to 2. As we began this project, carbocyclic ring construction by intramolecular epoxide opening (e.g., **1** → **2**, Scheme I) using nitrile anions[23] and sulfone anions[24] had been reported. Our objective was to develop conditions for the use of simple enolate anions,[25,26] which are stereoelectronically more demanding, in such cyclizations. If successful, cyclization could be coupled with the Sharpless epoxidation[13] to establish a general new method for enantioselective ring construction with concomitant control of side chain configuration.

Since the inception of this work, three alternative approaches have been reported for enantioselective cycloalkane construction by intramolecular opening of Sharpless-derived epoxides. Levine[28]

Scheme II



Scheme III



has demonstrated that the previously established nitrile anion opening[23] is effective in this context. Nucleophilic allylic silanes have been employed, under acid-catalyzed conditions,[11n,27,29] in intramolecular epoxide openings. Finally, Stork[30] has shown that ketone and ester enolates can be used to open *allylic* epoxides, to form cyclohexane derivatives. The only other enolate-based opening of an epoxide has been that reported by Negishi.[31]

In model studies,[32] we have demonstrated that both aldehyde and amide enolates can successfully open an epoxide intramolecularly to form a cyclopentane. With this encouragement, we turned our attention to the cyclization of **1**.

In the event, we were pleased to find that exposure of **1** (Scheme I) to excess KH in THF gives smooth cyclization to amide **2**. In contrast, no base/solvent combination could be found that would effect clean cyclization of either aldehyde **15** or ester **16**. It may

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(25) (a) In a sterically constrained case, a ketone enolate will open an epoxide intramolecularly: Nagaoka, H.; Ohsawa, K.; Takata, T.; Yamada, Y. *Tetrahedron Lett.* **1984**, *25*, 5389. (b) Intramolecular epoxide opening with a simple enolate fails: Semmelhack, M. F.; Zask, A. *J. Am. Chem. Soc.* **1983**, *105*, 2034.
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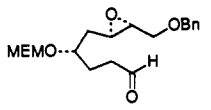
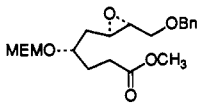
well be that failure in these cases stems from the instability of the cyclized products under the reaction conditions.



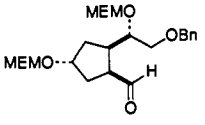
15



16

Preparation of the Lower Side Chain. The Julia–Lythgoe synthesis had been used previously to assemble the lower side chain of brefeldin A.[9d,11i,k] We have developed a simple route to the requisite enantiomerically pure alcohol **18** (Scheme II), by the opening of commercially available (*S*)-propylene oxide with the Grignard reagent prepared, following the procedure of Bakuzis,[34] from bromo sulfide **17**. Oxidation[35] and silylation then provides **20**.

Synthesis of (+)-Brefeldin A. The reduction[36] of amide **2** (Scheme III) proceeds to give aldehyde **21**, with varying amounts of alcohol **22**. In one run, we isolated an additional aldehyde product (**23**). Under equilibrating conditions (CH_3OH/K_2CO_3), **23** was converted to **21**, while **21** developed (TLC) a trace of **23**. The conclusion that **21** is in fact the desired trans diasteromer was further supported by subsequent conversion of **21** to (+)-brefeldin A (**3**).



23

In conjunction with this work, we have uncovered a convenient variation of the Julia–Lythgoe synthesis. The dianion of **20** adds smoothly to **21** to give, after acetylation, the acetoxy sulfone as a diastereomeric mixture. Reduction of this mixture with Na(Hg), following the usual procedure,[33] is quite sluggish. Since the next step was to be, in any case, dissolving metal cleavage of the benzyl ether, we submitted the mixture of acetoxy sulfones to reduction with sodium in liquid ammonia. We were pleased to find that this reaction indeed proceeded to give alcohol **24** directly. An exploration of the generality of this procedure is currently underway in our laboratory. We note that the Keck group has previously reported lithium/ammonia reduction of β-acetoxy sulfones to alkenes.[37]

At this point, the synthetic scheme converged with that recently reported by Corey.[11m] Oxidation and homologation of **24** (Scheme II) gave **25**, which is identical (^{1}H NMR, optical rotation) with the material they reported.[11m,38] Congruence was also established for synthetic **26** and **27**, as well as with natural (+)-brefeldin A (**3**), and with bis(MEM) ether **27** prepared from natural **3**.

Directions for the Future. (+)-Brefeldin A (**3**), with the unique capability of blocking transport of proteins from the endoplasmic reticulum, is a powerful tool for biomedical investigation. The approach outlined here, allowing for independent control of each of the stereogenic centers of **3**, should open the way for detailed structure/activity studies in this series.

Experimental Section

General Procedure. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AM-250 spectrometer. Chemical shifts are based on the setting of tetramethylsilane as chemical shift of 0 ppm. Infrared spectra were determined on a Nicolet 5DXB System FT IR and are reported in wavenumbers (cm^{-1}). High-resolution mass spectrometry (HRMS) was performed by Gordon Nicol on a VG 70-70 mass spectrometer. Low-resolution mass spectra (LRMS) were obtained on a Hewlett-Packard 5890 gas chromatograph–mass spectrometer (GC–MS). Optical rotations were measured on a Rudolph Research Autopol III polarimeter, using concentrations expressed in grams per 100 mL. Ultraviolet–visible (UV/vis) spectra were scanned by using a Perkin-Elmer 553 fast-scan UV/vis spectrophotometer. Thin-layer chromatographies (TLC) were run by using Analtech, Inc. 2.5 × 10 cm, 250 micron analytical plates coated with silica gel GF. Column chromatography was done under air pressure on TLC grade 60-Å silica gel.[39] The solvent mixtures indicated for TLC are volume/volume mixtures. Ozone was generated by a Welsbach ozonator.

Tetrahydrofuran (THF) and ether were distilled daily from sodium metal/benzophenone under nitrogen. Methylene chloride (CH_2Cl_2) was distilled daily from calcium hydride under nitrogen. Xylene (mixture of isomers) was distilled from calcium hydride under nitrogen and stored over 4-Å molecular sieves. Dimethyl sulfoxide (DMSO) was distilled from molecular sieves under nitrogen and stored over molecular sieves. Methanol was distilled immediately prior to use from methyl benzoate/sodium methoxide under nitrogen. All reactions were run in flame-dried glassware under a nitrogen atmosphere, except those involving water in the reaction mixture.

Methyl 7-Methyl-3-oxo-6-octenoate (4a). Methanol (1.36 mL) was added dropwise to 60% sodium hydride in mineral oil (65.39 g, 1.635 mol; washed twice with petroleum ether) in THF (400 mL) at 0 °C. Dimethyl carbonate (152.6 mL, 1.81 mol) was added slowly dropwise, additional THF (100 mL) was added, and the mixture was heated to reflux. 6-Methyl-5-hepten-2-one (96.6 mL, 0.65 mol) in THF (102 mL) was added slowly dropwise over a period of 6.5 h. After an additional 11.5 h, the mixture was cooled in ice, diluted with ether (250 mL), quenched by slow addition of water (100 mL), and acidified with 10% aqueous HCl (500 mL). The mixture was partitioned between ether and, sequentially, saturated aqueous $NaHCO_3$ and brine. The extract was dried (Na_2SO_4), concentrated, and bulb to bulb distilled (bath, 90–100 °C) to yield **4a** as a colorless oil (114.1 g, 95%): R_f (18% EtOAc/petroleum ether) = 0.61; ^{1}H NMR ($CDCl_3$) δ 5.05 (t, J = 7.1 Hz, 1 H), 3.71 (s, 3 H), 3.46 (s, 2 H), 2.55 (m, 2 H), 2.25 (m, 2 H), 1.66 (s, 3 H), 1.61 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 202.3, 167.5, 132.9, 122.1, 52.1, 48.9, 42.9, 25.5, 22.1, 17.4; IR (CCl_4) 3090–2780, 1752, 1722, 1449, 1434, 1239 cm^{-1}; HRMS *m/e* 184.1075, calcd 184.1088.

Preparation of the Ruthenium Catalyst. All manipulations were carried out in a N_2 atmosphere. Following a modification of the published procedures,[15-17] 39 mg of $(RuCl_2$-cyclooctadiene$)_n$, 100 mg of (*S*)-(−)-**2**, 2′-bis(diphenylphosphino)-1,1′-binaphthyl, 4.5 mL of toluene, and 0.0275 mL of triethylamine was sealed in a 5-mL reactivial. Stirring was continued at 140 °C until the solution was a clear homogeneous red (2–4 h). Solvent was removed in vacuo, and the residue was taken up in 10 mL of THF. The resultant orange-brown suspension was divided into five equal portions, each of which was stored in a stoppered vial under N_2 until use.

Methyl (*S*)-3-Hydroxy-7-methyl-6-octenoate (5a). Keto ester **4a** (6.0 g, 32.6 mmol), methanol (22.5 mL), and catalyst as prepared above (4 mL; from 40 mg of BINAP) were combined in a modified[18] Parr bottle. The resulting solution was clear dark green. Hydrogenation was carried out at 50 psig and 80 °C for 6 h. After solvent evaporation, the residue was distilled bulb to bulb (bath, 100 °C; 0.5 mm) to give 6.08 g of colorless oil. A portion of this oil (0.501 g) was chromatographed to give recovered starting material (0.066 g) followed by product **5a** (0.414 g, 2.23 mmol, 96% yield from **4a** at 87% conversion): $[\alpha]_D$ −2.59°, EtOH; ^{1}H NMR δ 5.11 (br t, J = 10.2 Hz, 1 H), 4.00 (septet, J = 4.1 Hz, 1 H), 3.71 (s, 3 H), 3.1 (br s, 1 H), 2.37–2.55 (m, 2 H), 2.06 (q, J = 7.4 Hz, 2 H), 1.68 (s, 3 H), 1.62 (s, 3 H), 1.3–1.7 (m, 2 H); ^{13}C NMR δ 173.3, 132.2, 123.6, 67.5, 51.6, 41.2, 36.4, 25.6, 24.0, 17.5; IR 3451 (br), 2952, 2924, 2861, 1736, 1441, 1377, 1300, 1268, 1202, 1173, 1110, 1075, 1005, 843 cm^{-1}; MS *m/e* calcd 186.1255; found 186.1246.

(*S*)-3-[(2-Methoxyethoxy)methoxy]-7-methyl-6-octen-1-ol (8). MEM chloride (1.13 mL, 9.66 mmol) was added dropwise to a solution of 1.200 g (6.44 mmol) of alcohol **5a**, dry CH_2Cl_2 (12 mL), and *N*,*N*-diisopropylethylamine (1.68 mL, 9.66 mmol). After 18 h, the mixture was evaporated and directly chromatographed and then distilled bulb to bulb (bath, 0.5 mm, 100–110 °C) to give the MEM ester as a colorless oil (1.269 g, 72%): R_f (20% EtOAc/petroleum ether) = 0.42, R_f (25% DME/petroleum ether) = 0.63; ^{1}H NMR ($CDCl_3$) δ 5.09 (tt, J = 1.37, 8.37 Hz, 1 H), 4.76 (d, J = 1.37 Hz, 2 H), 4.04 (quintet, J = 6.57 Hz, 1 H), 3.73–3.66 (m, 2 H), 3.68 (s, 3 H), 3.55 (m, 2 H), 3.395 (s, 3 H), 2.54 (dq, 2 H), 2.04 (q, J = 7.33 Hz, 2 H), 1.68 (s, 3 H), 1.60 (s, 3 H), 1.68 (m, 2 H); ^{13}C δ 171.6, 131.8, 123.5, 94.8, 74.2, 71.6, 67.0, 58.8, 51.3, 39.8, 34.6, 25.5, 23.6, 17.5; IR (neat) 2980–2819 (br), 2249, 1743, 1623, 1441, 1377, 920, 850 cm^{-1}.

The ester (1.107 g, 4.037 mmol) in ether (5 mL) was added dropwise to $LiAlH_4$ (0.153 g, 4.037 mmol) in ether (20 mL) at 0 °C. The ice bath was removed, and the solution was stirred for 1 h. The mixture was cooled to 0 °C and then quenched by slow addition of water (1 mL), then

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aqueous 10% NaOH (1 mL), and then water again (5 mL). The layers were separated, and the aqueous layer was diluted with 10% aqueous HCl (3 mL) and extracted with ether (3 × 10 mL). The combined organics were washed with brine, dried (Na_2SO_4), concentrated, and bulb to bulb distilled (bath, 0.5 mm, 120–130 °C) to yield **8** as a colorless oil (0.977 g, 71% from **5a**): R_f (18% EtOAc/petroleum ether) = 0.11; ^{1}H NMR ($CDCl_3$) δ 5.1 (tt, J = 1.42, 7.64 Hz, 1 H), 4.78 (ABq, J = 7.1, 9.1 Hz, 2 H), 3.85 (m, 3 H), 3.7 (m, 2 H), 3.6 (m, 2 H), 3.40 (s, 3 H), 2.85 (t, J = 6.04 Hz, 1 H), 2.05 (q, J = 7.6 Hz, 2 H), 1.85 (m, 2 H), 1.68 (s, 3 H), 1.60 (s, 3 H), 1.6–1.5 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 131.9, 123.9, 94.3, 75.0, 71.7, 67.2, 59.2, 59.0, 36.8, 34.4, 25.7, 23.7, 17.7; IR (CCl_4) 3600–3400, 3020–2780, 1454, 1317, 1104, 1038 cm^{-1}.

Methyl (*S*)-5-[(2-Methoxyethoxy)methoxy]-9-methyl-2,8-decadienoate (9). Alcohol **8** (0.500 g, 2.03 mmol) in CH_2Cl_2 (5 mL) was added to a suspension of pyridinium chlorochromate (1.313 g, 6.09 mmol), sodium acetate (1.313 g), and CH_2Cl_2 (15 mL). After 2 h, the mixture was diluted with ether (10 mL) and filtered through Florisil (5 g) on a thin bed of Celite. The solution was concentrated to a brown oil: R_f (40% EtOAc/petroleum ether) = 0.52. Trimethyl phosphonoacetate (0.5545 g, 3.045 mmol) in THF (4 mL) was added dropwise to 60% NaH in mineral oil (0.114 g, 2.842 mmol; washed with petroleum ether three times) in THF (3 mL) at 0 °C. After 1 h at 0 °C, the crude aldehyde in THF (3.15 mL, total 10.15 mL, 0.2 M) was added dropwise. After 20 h, since the reaction was not complete, a new batch of anion was prepared separately from trimethyl phosphonoacetate (0.555 g), 60% NaH (0.114 g) and THF (9 mL). The solution was added to the reaction mixture after cooling to 0 °C. After an additional 15 min at room temperature, the reaction was quenched by addition of 5% aqueous HCl (2 mL). The mixture was partitioned between ether and, sequentially, saturated aqueous $NaHCO_3$ and brine. The solution was dried (Na_2SO_4), concentrated, and chromatographed to yield **9** as an oil (0.3964 g, 65% from the alcohol): R_f (40% EtOAc/petroleum ether) = 0.60; ^{1}H NMR ($CDCl_3$) δ 7.02 (m, J = 15.7 Hz, 1 H), 5.89 (d, J = 15.7 Hz, 1 H), 5.08 (tt, J = 7.1 Hz, 1 H), 4.75 (s, 2 H), 3.73 (s, 3 H), 3.7 (m, 3 H), 3.55 (t, J = 4.4 Hz, 2 H), 3.39 (s, 3 H), 2.45 (m, 2 H), 2.05 (m, 2 H), 1.68 (s, 3 H), 1.59 (s, 3 H), 1.68–1.4 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 166.8, 145.7, 132.2, 123.7, 123.2, 94.6, 75.9, 71.8, 67.2, 59.1, 51.5, 37.4, 34.5, 25.8, 23.9, 17.8; IR (CCl_4) 3070–2780, 1726, 1658, 1438, 1271, 1107, 1043 cm^{-1}.

(*S*)-5-[(2-Methoxyethoxy)methoxy]-9-methyl-2,8-decadien-1-ol (10). Ester **9** (3.46 g, 11.52 mmol) in dry THF (21.2 mL) was added dropwise to a solution of 1 M diisobutylaluminum hydride (DIBAL) in toluene (28.9 mmol) and dry THF (25 mL) at 0 °C. After another 10 min, NaF (1.94 g, 46.2 mmol) was added, the reaction mixture was stirred vigorously, and water (0.62 mL) was added slowly. After 30 min, 10% aqueous HCl was added. The solution became warm, and a white solid precipitated. The mixture was filtered through Celite with ether. The filtrate was partitioned between ether and, sequentially, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), concentrated, and chromatographed to yield **10** as a colorless oil (2.975 g, 95%): R_f (40% EtOAc/petroleum ether) = 0.19; $[\alpha]_D$ −13.2° (*c* 1.0, EtOH); ^{1}H NMR ($CDCl_3$) δ 5.71 (m, 2 H), 5.10 (t, 1 H), 4.74 (s, 2 H), 4.08 (br s, 2 H), 3.85–3.50 (m, 6 H), 3.40 (s, 3 H), 2.25 (m, 2 H), 2.05 (m, 2 H), 1.68 (s, 3 H), 1.60 (s, 3 H), 1.6–1.45 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 145.6, 131.8, 128.5, 124.0, 94.4, 76.7, 71.9, 67.1, 63.4, 59.1, 37.3, 34.4, 25.7, 23.9, 17.7; IR (CCl_4) 3580–3330, 3020–2780, 1450, 1380, 1110, 1044 cm^{-1}.

(1*R*,2*S*)-2-[2-[(*S*)-(2-Methoxyethoxy)methoxy]-6-methyl-5-heptenyl]oxiranemethanol (11a). Titanium(IV) isopropoxide (54.6 μL, 0.050 equiv) was added to a suspension of 4-Å powdered molecular sieves (0.20 g, 20 wt %), CH_2Cl_2 (4.5 mL), and diethyl D-tartrate (0.0567 g, 0.075 equiv) at −23 °C. After 20 min at −23 °C, 3.35 M anhydrous *tert*-butyl hydroperoxide (1.1 mL, 3.685 mmol) in CH_2Cl_2 was added. After another 20 min at −23 °C, the alcohol **10** (0.99977 g, 3.67 mmol) in CH_2Cl_2 (1.6 ml, total 6.1 mL, 0.6 M) was added slowly by syringe. The mixture was stirred for 15 min at −23 °C, and then the flask was sealed and placed in the freezer (−18 °C) for 15 h. TLC showed about $^2/_3$ conversion at this point. A mixture of D-(−)-DET (0.0567 g), Ti(*o*-iPr)$_4$ (54.6 μL), and CH_2Cl_2 (0.8 mL) was added at −23 °C. After 20 min, the flask was placed back in the freezer for 3 h. More 3.35 M *t*-BuOOH (0.55 mL) was added, and after 6 h, more powdered sieves (0.2 g) were added. After 13 h, the reaction seemed to be closer to completion, so it was quenched with water (2.08 mL, 20 × wt of Ti(*o*-iPr)$_4$ used) and allowed to warm to room temperature. Aqueous NaOH (30%) saturated with NaCl (0.5 mL) was added. After 13 min, the mixture was filtered through glass wool. The layers were separated, and the aqueous layer was extracted twice with EtOAc. The combined organics were dried ($MgSO_4$), vacuum filtered through Celite, concentrated, and chromatographed to give recovered starting material **10** (0.201 g, 20% recovery), followed by a mixture of **11a** and **11b** as an oil (0.610 g, 57.5%). Thus, at 80% conversion, the corrected yield was 72%. The diastereomeric ratio was determined to be 86:14 by cutting and weighing the ^{13}C NMR peaks at 34–35 ppm, which had been shown to be equal in the product from stereorandom epoxidation: R_f (EtOAc) = 0.42; ^{1}H NMR ($CDCl_3$) δ 5.09 (t, J = 6.9 Hz, 1 H), 4.78 (s, 2 H), 3.91–3.62 (m, 5 H), 3.57 (t, J = 4.5 Hz, 2 H), 3.39 (s, 3 H), 3.09 (m, 1 H), 2.95 (m, 1 H), 2.3 (br s, 1 H), 2.03 (m, 2 H), 1.9–1.5 (m, 4 H), 1.68 (s, 3 H), 1.60 (s, 3 H); ^{13}C NMR ($CDCl_3$) (major diastereomer) δ 131.5, 123.7, 94.4, 75.0, 71.6, 66.9, 61.6, 58.7, 58.6, 53.1, 36.8, 34.7, 25.2, 23.5, 17.3.

(1*S*,2*R*)-1-[2-[(*S*)-(2-Methoxyethoxy)methoxy]-6-methyl-5-heptenyl]-2-[(phenylmethoxy)methyl]oxirane (12). Alcohol **11** (3.388 g, 1.75 mmol) in DMSO (19.5 mL, total 34.5 mL, 10 × wt alcohol) was added rapidly to a brownish suspension (stirred 13 min) of unwashed 60% NaH in mineral oil (0.719 g, 18.0 mmol) in dry DMSO (15 mL). Benzyl chloride (2.07 mL, 18.0 mmol) was added almost immediately. After 1 h at room temperature, the solution was diluted with ether (20 mL), cooled in an ice bath, and quenched by addition of a few pieces of ice. The mixture was acidified carefully with 3% aqueous HCl, and extracted four times with ether. The organic layer was washed once with water, dried ($MgSO_4$), concentrated, and chromatographed to yield **12** as a pale green oil (3.810 g, 86%): R_f (40% EtOAc/petroleum ether) = 0.50; ^{1}H NMR ($CDCl_3$) δ 7.34 (s, 5 H), 5.09 (br t, 1 H), 4.78 (s, 2 H), 4.56 (ABq, J = 5.5 Hz, 2 H), 3.83–3.70 (m, 4 H), 3.55–3.43 (m, 3 H), 3.38 (s, 3 H), 2.96 (m, 2 H), 2.01 (m, 2 H), 1.81–1.52 (m, 4 H), 1.68 (s, 3 H), 1.59 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 137.9, 131.9, 128.3, 127.6, 123.8, 94.6, 75.0, 73.2, 71.7, 70.3, 67.0, 58.9, 57.3, 53.2, 37.0, 34.8, 25.5, 23.7, 17.6.

***N*,*N*-Dimethyl-(1*S*,2*R*)-β-[(*S*)-(2-methoxyethoxy)methoxy]-2-[(phenylmethoxy)methyl]oxiranepentanamide (1).** Ozone in oxygen was passed through a solution of alkene **12** (1.00 g, 2.64 mmol) in 13.2 mL of CH_2Cl_2 and 0.43 mL of methanol containing pyridine (2 drops) and a crystal of Sudan III red indicator at −78 °C until the red color was discharged (3.76 min). N_2 was bubbled through for 10 min, and then dimethyl sulfide (1.5 eq) was added. After 3 h at room temperature, the mixture was concentrated and chromatographed to give the aldehyde **15** as a yellow oil (0.862 g, 93%): R_f (EtOAc) = 0.54; ^{1}H NMR ($CDCl_3$) δ 9.76 (s, 1 H), 7.33 (s, 5 H), 4.75 (m, 2 H), 4.56 (ABq, J = 4.5, 12.0 Hz, 2 H), 3.84 (br t, 1 H), 3.69 (m, 3 H), 3.53 (m, 3 H), 3.37 (s, 3 H), 2.95 (br s, 1 H), 2.53 (t, J = 6.0 Hz, 1 H), 2.04–1.50 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 201.8, 128.4, 127.7, 94.7, 74.7, 73.3, 71.7, 70.1, 67.4, 59.0, 57.1, 53.0, 39.6, 36.9, 27.1.

Aqueous $KMnO_4$ (0.5 M, 1.537 mL, 0.6 equiv) was added to a solution of aldehyde **15** (0.451 g, 1.28 mmol), *tert*-butyl alcohol (7.67 mL, 0.167 M), and 1.25 M aqueous pH 7 phosphate buffer (5.12 mL, 6.4 mmol). The reaction was followed by TLC for disappearance of starting material, and thus additional $KMnO_4$ solution was added after 10 min (0.100 mL), 17 min (0.07 mL), 27 min (0.05 mL), 38 min (0.05 mL), and 46 min (0.05 mL). The reaction was quenched after 55 min of total reaction time by addition of saturated aqueous $NaHSO_3$. The solution was acidified with 10% aqueous HCl until the color disappeared and then extracted with EtOAc. The organic layers were dried (Na_2SO_4) and concentrated to a viscous oil (0.435 g), of which half (0.226 g, 0.614 mmol if pure) was diluted with dry THF (1.23 mL) and cooled to −40 °C. Triethylamine (94 μL, 0.675 mmol) was added, followed by ethyl chloroformate (58.6 μL, 0.613 mmol). Nothing visible happened, so more Et_3N (90 μL) and ethyl chloroformate (30 μL) were added 15 min later. After 22 min at −40 °C (TLC showed mixed anhydride, R_f (50% acetone/methylene chloride) = 0.78), 40% aqueous dimethylamine (0.154 mL, 1.227 mmol) was added. The cooling bath was removed, and after 20 min, additional 40% aqueous dimethylamine (0.05 mL) was added. After 2.5 h, the mixture was partitioned between EtOAc and water. The organic layers were dried (Na_2SO_4, K_2CO_3), concentrated, and chromatographed to produce **1** as a colorless oil (0.1818 g, 65% from 12): R_f (50% acetone/CH_2Cl_2) = 0.55, R_f (20% acetone/CH_2Cl_2) = 0.36; ^{1}H NMR ($CDCl_3$) δ 7.33 (s, 3 H), 4.77 (m, 2 H), 4.56 (ABq, J = 5.2, 11.9 Hz, 2 H), 3.86 (m, 1 H), 3.69 (m, 3 H), 3.55–3.42 (m, 4 H), 3.36 (s, 3 H), 2.99 (s, 3 H), 2.96 (m, 1 H), 2.93 (s, 3 H), 2.4 (m, 2 H), 2.0–1.6 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 172.4, 137.9, 128.3, 127.6, 94.7, 74.8, 73.2, 71.7, 70.3, 67.2, 58.9, 57.2, 53.0, 37.0, 35.3, 29.8, 28.6; IR (neat) 3480 (br), 3121–2685 (br s), 1652, 1497, 1455, 1398, 1363, 1265, 1202, 1152–1012 (br), 920, 850, 737.5, 702 cm^{-1}.

***N*,*N*-Dimethyl-(1*R*,2*R*,4*R*)-2-[(*S*)-1-hydroxy-2-(phenylmethoxy)-ethyl]-4-[(2-methoxyethoxy)methoxy]cyclopentanecarboxamide (2).** Amide **1** (0.75 g, 1.897 mmol) in THF (7 mL) was added dropwise to 35% KH in mineral oil (2.61 g, 22.3 mmol; washed several times with ether) in THF (3 mL). After 13 h, the mixture was cooled in ice and quenched carefully with water (1.5 mL) and then partitioned between ether and, sequentially, 3% aqueous HCl, saturated aqueous $NaHCO_3$, and brine. The organic layers were dried (Na_2SO_4), concentrated, and chromatographed to yield **2** as an oil (0.484 g, 65%): R_f (20% acetone/CH_2Cl_2) = 0.29, R_f (EtOAc) = 0.51; ^{1}H NMR ($CDCl_3$) δ 7.33 (m,

5 H), 4.71 (s, 2 H), 4.52 (ABq, J = 3.3 Hz, 2 H), 4.22 (m, 1 H), 3.82 (m, 1 H), 3.69 (m, 2 H), 3.6–3.4 (m, 3 H), 3.38 (s, 3 H), 3.4–3.3 (m, 1 H), 3.01 (s, 3 H), 2.94 (s, 3 H), 2.7 (br q, 1 H), 2.35–2.25 (m, 1 H), 2.0–1.7 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 174.3, 137.9, 128.4, 127.7, 94.25, 77.25, 73.9, 73.3, 71.8, 69.9, 66.8, 58.9, 42.9, 41.6, 37.1, 37.0, 35.7, 32.0; IR (neat) 3423 (br), 2931, 2889, 1637, 1497, 1455, 1398, 1363, 1258, 1202, 1138–1019 (br), 850, 745, 702 cm^{-1}.

(*S*)-6-(Phenylthio)-2-hexanol (18). Grignard solution prepared from sulfide **17** (5.66 g, 25.8 mmol) and Mg turnings (0.628 g, 25.8 mmol) in 20 mL of THF was added dropwise by syringe to a solution of CuI (4.916 g, 25.8 mmol) in THF (6.45 mL) at −30 °C. After 5 min, (*S*)-propylene oxide (1.00 g, 17.2 mmol) was added rapidly. The mixture was warmed to 0 °C and stirred for 2 h and then quenched by addition of saturated aqueous NH_4Cl (16 mL). The mixture was partitioned between ether and, sequentially, saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), concentrated, and chromatographed to give **18** as an oil (3.18 g, 88%): R_f (20% EtOAc/petroleum ether) = 0.33; $[\alpha]_D$ +5.1° (*c* 1.0, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.35–7.2 (m, 3 H), 7.2–7.1 (m, 2 H), 3.8–3.7 (m, 1 H), 2.93 (t, J = 7.2 Hz, 2 H), 1.75–1.6 (m, 3 H), 1.6–1.35 (m, 4 H), 1.18 (d, J = 6.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 136.8, 129.0, 128.8, 125.8, 68.0, 38.8, 33.6, 29.1, 25.0, 23.6; IR (CCl_4) 3550–3220, 3010–2780, 1481, 1120 cm^{-1}.

(*S*)-6-(Phenylsulfonyl)-2-hexanol (19). Oxone (7.02 g, 1.5 equiv) was added slowly to a solution of sulfide **18** (1.60 g, 7.61 mmol), methanol (30.4 mL), and water (70 μL, 3.8 mmol). After 21 h, the mixture was filtered through a glass frit with acetone to remove the solid, concentrated, and chromatographed to yield sulfone **19** as a colorless oil (1.05 g, 57%): R_f (EtOAc) = 0.51, R_f (50% EtOAc/petroleum ether) = 0.20; $[\alpha]_D$ +7.7° (*c* 1.0, EtOH) (lit.[11k] $[\alpha]_D$ +7.91° in $CDCl_3$); ^{1}H NMR ($CDCl_3$) 7.9 (m, 2 H), 7.7–7.5 (m, 3 H), 3.7 (m, 1 H), 3.11 (t, J = 7.7 Hz, 1 H), 2.45 (concentration-dependent br s, 1 H), 1.7 (m, 2 H), 1.5–1.3 (m, 4 H), 1.10 (d, J = 6.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 139.2, 134.1, 133.1, 129.3, 128.8, 128.0, 67.5, 56.2, 38.2, 24.5, 23.6, 22.7; IR (CCl_4) 3650–3220, 3010–2880, 1550, 1320, 1153 cm^{-1}.

(*S*)-1-(Phenylsulfonyl)-5-[(dimethylethyl)dimethylsilyl]oxy]hexane (20). Imidazole (0.742 g, 10.875 mmol) and 4-(dimethylamino)pyridine (0.133 g, 1.0875 mmol) were added to sulfone **19** (1.05 g, 4.35 mmol) in CH_2Cl_2 (6 mL) at 0 °C. After most of the solid dissolved, *tert*-butyldimethylsilyl chloride (1.31 g, 8.7 mmol) in CH_2Cl_2 (4.9 mL) was added dropwise. After 5 min at 0 °C and 18 h at room temperature, the mixture was partitioned between CH_2Cl_2 and water. The organic layers were dried ($MgSO_4$), concentrated, and chromatographed to yield **20** as a pale green oil (1.523 g, 98%): R_f (50% EtOAc/petroleum ether) = 0.75, R_f (20% EtOAc/petroleum ether) = 0.56; ^{1}H NMR ($CDCl_3$) δ 7.87 (d, J = 6.95 Hz, 2 H), 7.67–7.50 (m, 3 H), 3.70 (m, 1 H), 3.06 (t, J = 8.0 Hz, 2 H), 1.74–1.60 (m, 2 H), 1.45–1.30 (m, 4 H), 1.04 (d, J = 6.1 Hz, 3 H), 0.82 (s, 9 H), −0.03 (d, J = 5.9 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 133.5, 129.2, 128.0, 67.9, 56.3, 38.9, 25.8, 24.4, 23.7, 22.7, 18.0, −4.45, −4.84; IR (neat) 3902–3627 (br, many small peaks), 2959, 2931, 2861, 2362, 2341, 1145, 1089, 1039, 836, 773 cm^{-1}; $[\alpha]_D$ +9.27° (*c* 0.426 ethanol); HRMS *m/e* 341, 299, 257, 199, 135, 75, 45, 31, exptl 341.1570 (M − CH_3) (calcd 341.1607), exptl 299.1140 (M − C_4H_9) (calcd 299.1137).

(1*R*,2*R*,4*R*)-2-[(*S*)-1-[(2-methoxyethoxy)methoxy]-2-(phenylmethoxy)ethyl]-4-[(2-methoxyethoxy)methoxy]cyclopentanecarboxaldehyde (21). MEM chloride was added dropwise to a solution of alcohol **2** (0.423 g, 1.07 mmol), CH_2Cl_2 (2.15 mL, 0.5 M), and *N*,*N*-diisopropylethylamine (0.2795 mL, 1.5 equiv). After 23 h, the mixture was evaporated and directly chromatographed to produce the ether as an oil (0.484 g, 94%): R_f (20% acetone/CH_2Cl_2) = 0.43, R_f (EtOAc) = 0.15; ^{1}H NMR ($CDCl_3$) δ 7.31 (m, 5 H), 4.9–4.71 (m, 4 H), 4.48 (ABq, J = 3.1 Hz, 2 H), 4.18 (m, 1 H), 3.75–3.65 (m, 4 H), 3.6–3.45 (m, 5 H), 3.39 (s, 3 H), 3.36 (s, 3 H), 2.97 (s, 3 H), 2.92 (s, 3 H), 3.0–2.85 (m, 2 H), 2.35–2.25 (m, 2 H), 2.1–1.6 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 174.2, 138.3, 128.2, 127.4, 96.0, 94.3, 77.6, 77.4, 73.3, 73.1, 71.7, 67.4, 66.7, 58.8, 42.2, 41.7, 37.1, 36.9, 35.6, 32.9; IR (neat) 3600–3450 (br), 3100–2800 (br s), 1644, 1497, 1455, 1398, 1363, 1258, 1202, 1173–990 (br), 834, 850, 744, 702 cm^{-1}.

n-BuLi (2.5 M) in hexane (1.96 mL) was added to a solution of THF (3.04 mL) and 1 M DIBAL in toluene (5.00 mL) at 0 °C. The solution was stirred for 30 min and maintained at 0 °C thereafter. The newly created 0.5 M ate complex (0.4 mL, 0.2 mmol) was added dropwise at room temperature to a solution of the above amide (0.1003 g, 0.207 mmol) in THF (0.7 mL). The reaction was followed by TLC for disappearance of the amide. Thus, additional ate complex was added after 21 min (0.2 mL), 38 min (0.2 mL), and 52 min (0.1 mL). After a total of 56 min from the initial addition, the reaction was acidified by addition of 10% aqueous HCl and extracted three times with CH_2Cl_2. The organic layers were dried (Na_2SO_4), concentrated, and chromatographed to give the trans aldehyde **21** as a colorless oil (49 mg, 54%), followed by alcohol **22** as a colorless oil (27 mg, 29%). From one run, a small amount of the cis aldehyde **23** was recovered. **21**: R_f (EtOAc) = 0.51. **23**: R_f (EtOAc) = 0.36. **22**: R_f (EtOAc) = 0.20 **2**: R_f (EtOAc) = 0.15. **21**: ^{1}H NMR ($CDCl_3$) δ 9.6 (d, 1 H), 7.3 (m, 5 H), 4.95–4.6 (m, 4 H), 4.55–4.45 (m, 2 H), 4.25 (br s, 1 H), 3.85–3.62 (m, 6 H), 3.6–3.5 (m, 5 H), 2.2–1.65 (m, 4 H). **22**: ^{1}H NMR ($CDCl_3$) δ 7.31 (br s, 5 H), 4.94 (d, J = 7.2 Hz, 2 H), 4.73 (d, J = 7.2 Hz, 2 H), 4.69 (s, 2 H), 4.16 (m, 2 H), 3.93 (m, 2 H), 3.8 (m, 2 H), 3.66 (m, 2 H), 3.53 (m, 4 H), 3.37 (s, 3 H), 3.36 (s, 3 H), 2.95 (m, 1 H), 2.2–1.4 (m, 6 H). **23**: ^{1}H NMR ($CDCl_3$) 9.6 (d, 1 H), 7.32 (m, 5 H), 4.92–4.67 (m, 4 H), 4.5 (ABq, 2 H), 4.25 (br s, 1 H), 3.88–3.63 (m, 6 H), 3.6–3.5 (m, 5 H), 3.40 (s, 3 H), 3.38 (s, 3 H), 2.9–2.65 (m, 2 H), 2.1–1.6 (m, 4 H).

(1*R*,2*R*,4*S*)-4-[(2-Methoxyethoxy)methoxy]-2-[(*S*)-6-[[(dimethylethyl)dimethylsilyl]oxy]-1-heptenyl]-α-[(*S*)-(2-methoxyethoxy)methoxy]cyclopentaneethanol (24). *n*-Butyllithium in hexane (2.55 M, 0.394 mL, 1.005 mmol) was added to a solution of sulfone **20** (0.180 g, 0.502 mmol) and dry THF (2.5 mL, 0.2 M) at −78 °C. After 30 min, aldehyde **21** (88.4 mg, 0.201 mmol) in THF (1.005 mL, 0.2 M) was added dropwise. After 100 min at −78 °C, more dianion (0.072 g of sulfone, 1 mL of THF, and 0.079 mL of *n*-BuLi) was prepared separately and added to the reaction. The diastereomeric sulfone alcohols appeared on TLC as two spots: R_f (50% EtOAc/petroleum ether) = 0.28 and 0.37. Two hours after the addition of the aldehyde, glacial acetic acid was added (78 μL, 1.41 mmol), followed immediately by pyridine (0.804 mL, 0.25 M in aldehyde). Acetic anhydride (0.152 mL, 1.61 mmol) was then added, followed by 4-(dimethylamino)pyridine (0.050 mmol). After 5 min at −78 °C, the mixture was allowed to warm to room temperature for 13 h. The mixture was partitioned between ether and, sequentially, saturated aqueous $CuSO_4$ and saturated aqueous $NaHSO_3$. The organic layers were dried (Na_2SO_4), concentrated, and chromatographed to give first recovered sulfone **20**, followed by the diastereomeric sulfone acetates as an oil (0.124 35 g, 73%): R_f (50% EtOAc/petroleum ether) = 0.41; ^{1}H NMR ($CDCl_3$) δ 7.85 (m, 2 H), 7.51 (m, 3 H), 7.25 (m, 5 H), 5.4–5.2 (m, 1 H), 4.8–4.4 (m, 3 H), 4.0 (m, 2 H), 3.8–3.55 (m, 2 H), 3.55–3.35 (m, 13 H), 3.32 (m, 6 H), 2.0–1.0 (m, 18 H), 0.82 (m, 9 H), +0.02 to −0.07 (m, 6 H).

Liquid ammonia (15 mL) was condensed into a solution of the diastereomeric sulfone acetates (0.1234 g, 0.1467 mmol) in dry ether (1.5 mL). Sodium metal was added in small pieces until the blue color persisted. After 15 min, solid NH_4Cl was added, the condenser was removed, and the ammonia was allowed to evaporate. The residue was partitioned between EtOAc and, sequentially, water and brine. The organic layers were dried (Na_2SO_4), concentrated, and chromatographed to provide the desired product **24** as an oil (37.95 mg, 35% from **21**), followed by an additional product (R_f (EtOAc) = 0.18) (11.49 mg, 14%) that apparently results from overreduction at the newly created double bond. By ^{13}C NMR, the alkene **24** was approximately 85:15 trans/cis: R_f (EtOAc) = 0.42, R_f (50% EtOAc/petroleum ether) = 0.20; ^{1}H NMR ($CDCl_3$) δ 5.4–5.2 (m, 2 H), 4.8 (m, *x* H), 4.67 (s, (4 − *x*) H), 4.13 (m, 1 H), 3.84 (m, 2 H), 3.74 (m, 2 H), 3.64 (m, 2 H), 3.53 (m, 6 H), 3.36 (s, 6 H), 2.26–2.11 (m, 2 H), 2.0–1.7 (m, 6 H), 1.4–1.3 (m, 5 H), 1.07 (d, J = 6.07 Hz, 3 H), 0.85 (s, 9 H), 0.01 (s, 6 H); ^{13}C NMR ($CDCl)_3$ δ 133.4, 131.0, 97.0, 94.15, 83.6, 71.8, 71.6, 68.4, 67.5, 66.8, 65.7, 58.9, 46.1, 43.7, 40.0, 39.1, 33.1, 32.4, 25.8, 25.6, 23.7, −4.5, −4.8.

Methyl (1*R*,2*R*,4*S*)-4-[(2-Methoxyethoxy)methoxy]-2-[(*S*)-6-[[(dimethylethyl)dimethylsilyl]oxy]-1-heptenyl]-α-[(*S*)-(2-methoxyethoxy)-methoxy]cyclopentane-β-butenoate (25). Alcohol **24** (37.95 mg, 6.916 × 10^{-5} mol) in CH_2Cl_2 (0.4 mL, total 0.7 mL, 0.1 M) was added to a suspension of pyridinium chlorochromate (67.1 mg, 0.311 mmol), sodium acetate (67.1 mg), and CH_2Cl_2 (0.3 mL). After 3 h, the mixture was diluted with ether and then filtered through Florisil on a bed of Celite. The solution was concentrated under nitrogen: R_f (50% EtOAc/petroleum ether) = 0.40. Meanwhile, trimethyl phosphonoacetate (0.311 mL, 1.92 mmol) was added dropwise to 60% NaH in oil (0.072 g, 1.79 mmol; washed three times with petroleum ether) in THF (9.6 mL) at 0 °C. This stock solution of anion (0.2 M based on the phosphonacetate) was maintained at 0 °C. Phosphonate solution (1.13 mL, 0.207 mmol based on NaH) was added to a solution of the crude aldehyde in THF (0.8 mL) at room temperature. After 1.5 h, the mixture was diluted with ether and acidified with 5% aqueous HCl and then partitioned between EtOAc and, sequentially, saturated aqueous $NaHCO_3$ and brine. The organic layers were dried (Na_2SO_4), concentrated, and chromatographed to yield **25** as a pale green oil (19.32 mg, 46%): R_f (50% EtOAc/petroleum ether) = 0.38; ^{1}H NMR ($CDCl_3$) 6.83 (dd, J = 6.3, 15.7 Hz, 1 H), 5.93 (dd, J = 1.15, 15.76 Hz, 1 H), 5.35 (m, 2 H), 4.68 (s, 2 H), 4.66 (m, 2 H), 4.20–4.09 (m, 2 H), 3.81–3.72 (m, 1 H), 3.71 (s, 3 H), 3.67–3.64 (m, 4 H), 3.55–3.51 (m, 4 H), 3.37 (s, (6 − *y* − *x*) H), 3.36 (s, *y* H), 3.35 (s, *x* H), 2.35 (m, 1 H), 2.16 (m, 1 H), 2.0–1.6 (m, 5 H), 1.5–1.2 (m, 5 H), 1.09 (d, J = 6.0 Hz, 3 H), 0.86 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 166.5, 148.2, 133.3, 131.3, 121.3, 94.3, 94.2, 76.75, 75.6, 71.7,

68.5, 67.5, 66.8, 58.9, 48.3, 43.0, 40.2, 39.2, 32.8, 32.5, 25.9, 25.6, 23.8, 18.1, -4.4, -4.7; $[\alpha]_D$ -20.1° (c 0.318, $CHCl_3$) (lit.[11m,33] $[\alpha]_D$ -27.73° (c 1.44, $CHCl_3$)).

Methyl (1*R*,2*R*,4*S*)-4-[(2-Methoxyethoxy)methoxy]-2-((*S*)-6-hydroxy-1-heptenyl)-α-[(*S*)-(2-methoxyethoxy)methoxy]cyclopentane-β-butenoate (26). Following the procedure of Corey and Carpino,[11m,33] 3:1 acetic acid/water (0.8 mL) was added to silyl ether **25** (9.47 mg, 1.57 × 10^{-5} mol). After 5.5 h, the solution was partitioned between ether and saturated aqueous Na_2CO_3. The organic layers were dried ($MgSO_4$), concentrated, and chromatographed to give **26** as a colorless oil (5.97 mg, 78%): R_f (50% EtOAc/petroleum ether) = 0.10, R_f (EtOAc) = 0.40; ^1H NMR ($CDCl_3$) δ 6.81 (dd, J = 6.15, 15.76 Hz, 1 H), 5.94 (dd, J = 1.0, 15.8 Hz, 1 H), 5.36 (m, 2 H), 4.68 (s, 2 H), 4.67 (s, 2 H), 4.21-4.12 (m, 2 H), 3.81-3.59 (m, 1 H), 3.72 (s, 3 H), 3.67-3.64 (m, 4 H), 3.55-3.50 (m, 4 H), 3.38 (s, 3 H), 3.37 (s, 3 H), 2.34 (m, 1 H), 2.17 (m, 1 H), 2.0-1.3 (m, 11 H), 1.17 (d, J = 6.17 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.6, 148.2, 133.6, 130.9, 121.3, 94.3, 94.2, 76.7, 75.9, 71.8, 71.7, 67.9, 67.5, 66.9, 59.0, 51.6, 48.3, 43.1, 40.3, 38.8, 33.2, 32.4, 25.6, 23.5.

Bis(MEM) Brefeldin A (27). Continuing the procedure of Corey and Carpino,[11m,33] 1 M aqueous LiOH (73.3 μL) was added to a solution of ester **26** (5.97 mg, 1.11 × 10^{-5} mol) in methanol (0.43 mL). After 21 h, the mixture was partitioned between chloroform and 10% aqueous HCl. The organic layers were dried ($MgSO_4$), concentrated, and chromatographed to give the hydroxy acid as a pale green oil (crude wt 5.47 mg): R_f (EtOAc) = 0.03; ^1H NMR ($CDCl_3$ δ 6.86 (dd, J = 6.2, 15.76 Hz, 1 H), 5.94 (d, J = 16.0 Hz, 1 H), 5.32 (m, 2 H), 4.69 (s, 2 H), 4.67 (m, 2 H), 4.15 (m, 2 H), 3.78 (m, 2 H), 3.66 (m, 4 H), 3.55 (m, 5 H), 3.38 (s, 3 H), 3.37 (s, 3 H), 2.31 (m, 1 H), 2.16 (m, 1 H), 2.0-1.2 m, 10 H), 1.18 (d, J = 6.0 Hz, 3 H).

Triphenylphosphine (9.4 mg, 3.58 × 10^{-5} mol) was added to a solution of the hydroxy acid (crude wt 5.47 mg), xylenes (0.224 mL, 0.05 M), and "Aldrithiol 2" (Aldrich) (2,2'-dipyridyl disulfide) (8.22 mg, 3.73 × 10^{-5} mol). After 7 h, the solution was diluted with xylenes (5.47 mL) and then warmed to reflux for 12 h. The solution was washed with 10% aqueous HCl, dried ($MgSO_4$), concentrated, and chromatographed to give an oil (2.54 mg), which still contained pyridyl residues. This oil was partitioned between ether and 10% aqueous HCl. The organic layers were dried ($MgSO_4$), concentrated, and chromatographed to yield **27** as an oil (1.15 mg, 21% from methyl ester **26**): R_f (EtOAc) = 0.48; ^1H NMR ($CDCl_3$) δ 7.08 (dd, J = abc, 1 H), 5.83 (d, J = abs, 1 H), 5.62 (m, 1 H), 5.21 (m, 1 H), 4.95-4.6 (m, 4 H), 4.2-4.05 (m, 2 H), 3.83 (m, 1 H), 3.66 (m, 4 H), 3.54 (m, 4 H), 3.38 (s, 6 H), 2.35-1.5 (m, 12 H), 1.24 (d, J = 6.13 Hz, 3 H).

Preparation of 27 from Natural (+)-Brefeldin A. MEM chloride (6.5 μL) was added to a solution of natural (+)-brefeldin A (Sandoz) (approximately 4 mg), CH_2Cl_2 (1.25 mL), and *N*,*N*-diisopropylamine (9.9 μL). After 45 h, the mixture was partitioned between CH_2Cl_2 and brine. The organic layers were dried (Na_2SO_4), concentrated, and chromatographed. The bis(MEM) product **27** eluted first, as a yellow oil (1.33 mg). Next eluted was the mono(MEM) product as an oil (0.61 mg). Mono(MEM): R_f(mono(MEM)) (25% acetone/ether) = 0.54; ^1H NMR ($CDCl_3$) δ 7.34 (dd, J = 3.0, 15.65 Hz, 1 H), 5.90 (dd, J = 2.0, 15.69 Hz, 1 H), 5.69 (m, 1 H), 5.245 (m, 1 H), 4.9-4.6 (m, 2 H), 4.2-4.05 (m, 2 H), 3.75-3.63 (m, 2 H), 3.57 (m, 3 H), 3.38 (d, J = 1.23 Hz, 3 H), 2.35-2.1 (m, 4 H), 2.1-1.95 (m, 2 H), 1.91-1.66 (m, 6 H), 1.25 (d, J = 6.21 Hz, 3 H). Bis(MEM): R_f(bis(MEM)) (25% acetone/ether) = 0.64, R_f (EtOAc) = 0.48; UV/vis λ 235 nm; ^1H NMR ($CDCl_3$) δ 7.09 (dd, J = 3.67, 15.75 Hz, 1 H), 5.83 (d, J = 15.63 Hz, 1 H), 5.62 (m, 1 H), 5.20 (m, 1 H), 4.95-4.6 (m, 4 H), 4.2-4.05 (m, 2 H), 3.83 (m, 1 H), 3.65 (m, 4 H), 3.54 (m, 4 H), 3.38 (s, 6 H), 2.35-1.5 (m, 12 H), 1.24 (d, J = 6.28 Hz, 3 H).

(+)-Brefeldin A (3). Concluding the procedure of Corey and Carpino,[11m,33] a 1 M solution of titanium tetrachloride in CH_2Cl_2 (0.115 mL) was added dropwise to a solution of synthetic **27** (1.15 mg, 2.52 × 10^{-6}) in CH_2Cl_2 (0.115 mL) at 0 °C. After 1.17 h at 0 °C, the reaction was quenched with saturated aqueous $NaHCO_3$. The solution was partitioned between chloroform and brine. The organic layers were dried ($MgSO_4$), concentrated, and cospotted on TLC with natural (+)-brefeldin A. The spots matched exactly. The concentrate was then chromatographed to give **3** as a white solid: R_f (25% acetone/ether) = 0.375; ^1H NMR ($CDCl_3$) (partial) δ 7.35 (dd, J = 2.99, 15.36 Hz, 1 H), 5.90 (dd, J = 1.71, 15.79 Hz, 1 H).

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Isolation and Characterization of the Duocarmycin-Adenine DNA Adduct

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Abstract: The isolation and full characterization of the duocarmycin-adenine adduct **7** derived from the duocarmycin alkylation of calf thymus DNA is detailed.

Two independent efforts have described the isolation, structure determination, assignment of absolute configuration, and preliminary evaluation of a new class of antitumor antibiotics now including duocarmycin A[2-4] (**1**), duocarmycin B_1 and B_2 (**2** and **3**),[6] duocarmycin C_1[3-5] (**4**, pyrindamycin B[7]), duocarmycin C_2[3] (**5**, pyrindamycin A[7]), and duocarmycin SA (**6**),[8] Figure 1. The structural similarity between duocarmycin A (**1**) and (+)-CC-1065 suggested that the agents may be acting by a common or related

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