Asymmetric Total Synthesis of (+)-Brefeldin A from (*S*)-Lactate by Triple Chirality Transfer Process and Nitrile Oxide Cycloaddition[†,1]

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Received July 25, 2001

A novel synthesis of (+)-brefeldin A (**1**) has been accomplished on the basis of triple chirality transfer methodology, intramolecular ester enolate alkylation, and both intra- and intermolecular nitrile oxide cycloaddition strategies.

Introduction

(+)-Brefeldin A (**1**) is a 13-membered macrolide fungal metabolite whose structure has been established by X-ray crystallography.[2] Since the first isolation of brefeldin A from the fungus *Penicillium decumbens*[3] in 1958, a diverse range of interesting biological activities has been reported for this metabolite including antibiotic, antiviral, cytostatic, antimitotic, and antitumor effects.[4] Based upon extensive studies of its mode of action, it has been found that brefeldin A causes the Golgi complex disassembly and redistribution into the endoplasmic reticulum and inhibits protein transport into post-Golgi compartments in the cell.[5] Recent significant attention toward brefeldin A stems from its ability to induce apoptosis of human cancer cells and its preclinical development status as an anticancer agent.[6]

Brefeldin A possesses five sp^3 stereogenic centers and two trans double bonds in addition to a 13-membered macrocyclic lactone unit. The challenging structural features of brefeldin A along with its unusually broad spectrum of biological activity have prompted impressive synthetic efforts to date from a number of laboratories.[7]

In this context, we describe a stereoselective synthetic approach to optically pure (+)-brefeldin A (**1**), which is unique compared to other previous syntheses[7] in that the chirality of readily available ethyl *O*-benzyl-(*S*)-lactate (**6**) [C15 in the brefeldin numbering system] controls the

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† Dedicated to Professor Steven M. Weinreb on the occasion of his 60th birthday.

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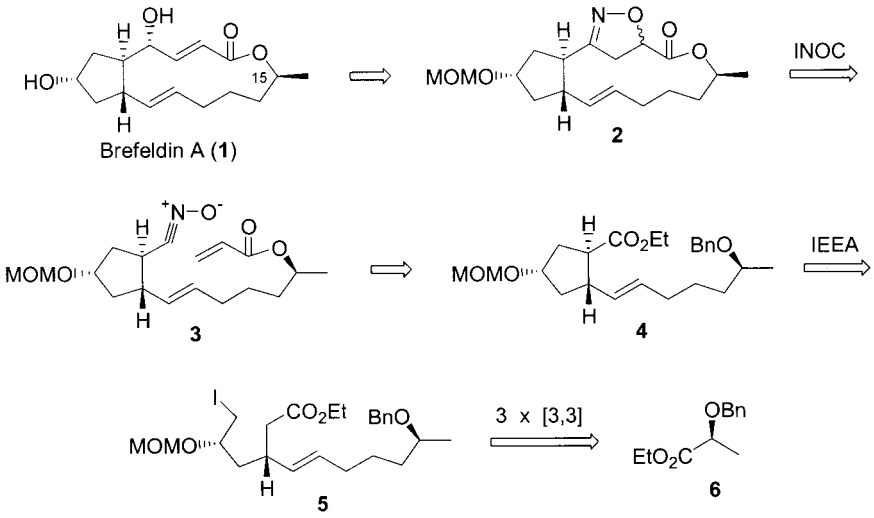
10.1021/jo010743i CCC: $22.00
Published on Web 01/15/2002

Scheme 1



relative stereochemistry of the remote stereogenic centers in the molecule.

The presence of a γ-oxygenated α,β-unsaturated macrocyclic lactone unit in brefeldin A (**1**) suggested the use of an intramolecular nitrile oxide cycloaddition (INOC) reaction as shown in the retrosynthetic analysis in Scheme 1. The successful execution of the INOC strategy hinges upon the chemoselective cleavage of the N−O bond of compound **2** in the presence of the double bond and ester functionality. Further analysis indicated Bartlett-type[7c] intermediate **4** to be an ideal synthetic precursor for the INOC substrate **3**. We envisaged the cyclopentanecarboxylate **4** might be stereoselectively constructed by an intramolecular ester enolate alkylation (IEEA)[8] of **5** and postulated that the acyclic precursor **5** could be prepared from simple lactate **6** by way of a triple chirality transfer process (vide infra).[9]

Results and Discussion

Burke's one-pot "reduction and chelation-controlled nucleophilic addition" protocol[10] on ethyl *O*-benzyl-(*S*)-lactate (**6**) yielded the desired *syn*-allylic alcohol **7** as the major component in a 6:1 ratio. Acylation of the resulting *syn*-alcohol **7** with PMB-protected glycolic acid under Steglich's DCC coupling conditions[11] to yield **8**, followed by application of the "chelation-controlled" modification[12] of the Ireland ester enolate Claisen rearrangement,[13] produced the corresponding γ,δ-unsaturated glycolate **9** after diazomethane workup in a highly stereoselective manner (Scheme 2). We were able to perform a reduction of the superfluous double bond of **9** by a catalytic hydrogenation in the presence of *n*-butylamine[14] to furnish **10** in 82% yield without hydrogenolysis of either benzylic protecting group. A reiterative three-step sequence on α-alkoxy ester **10** (i.e., one-pot reduction/chelation-controlled nucleophilic addition, followed by DCC coupling of the resulting allylic alcohol **11** with MOM-protected glycolic acid, and Ireland−Claisen rearrangement of **12**) stereoselectively furnished the elaborated glycolate **13** in good overall yield. Removal of the PMB protecting group with wet DDQ under Yonemitsu conditions,[15] followed by stereoselective Johnson ortho ester Claisen rearrangement,[16] led to the formation of diester **15** with the correct configuration at C9. Chemoselective $NaBH_4$ reduction of the α-alkoxy ester and iodination of the resulting alcohol **16** yielded the internal alkylation substrate **5**. The crucial intramolecular cyclization of ω-iodo ester **5** was successfully performed with LHMDS in THF at 0 °C to produce cyclopentanecarboxylate **4** with excellent stereoselectivity and in high yield (92%).[17]

With the desired cyclopentanecarboxylate **4** in hand, we began the second stage of our synthesis of brefeldin A by employing an INOC reaction to construct the γ-oxygenated α,β-unsaturated macrocyclic lactone moiety (Scheme 3). The requisite INOC substrate **18** was prepared from the key cyclopentanecarboxylate **4** in a straightforward five-step sequence, which entails removal of the benzyl group with concurrent reduction of the ester function by treatment with lithium in ethanol/ammonia, selective tosylation at the primary hydroxyl group, Finkelstein reaction,[18] conversion of the resulting primary iodide to nitro compound **17**,[19] and acryloylation of

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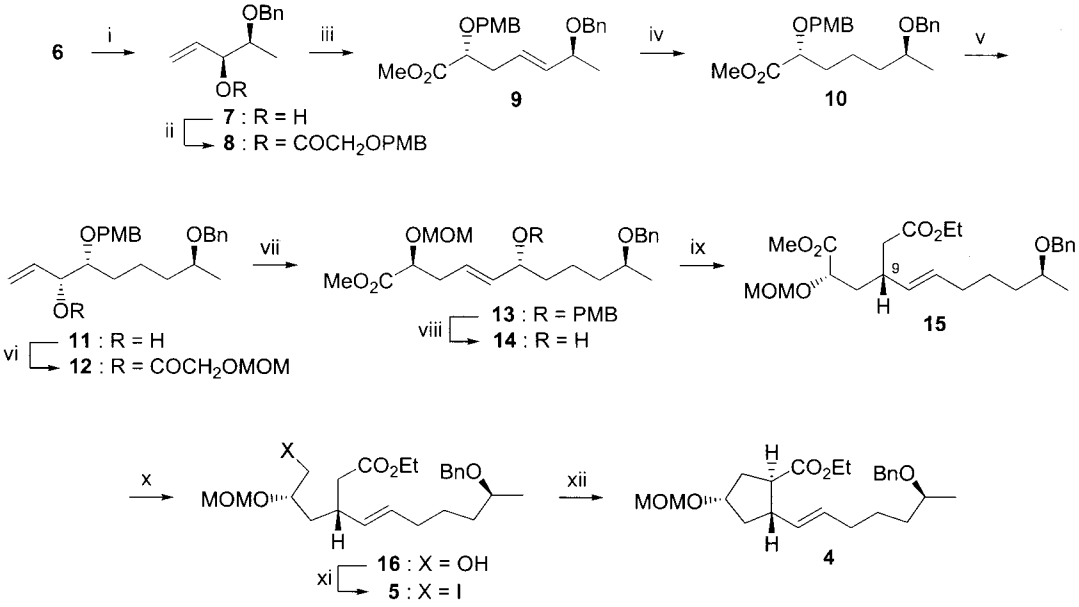
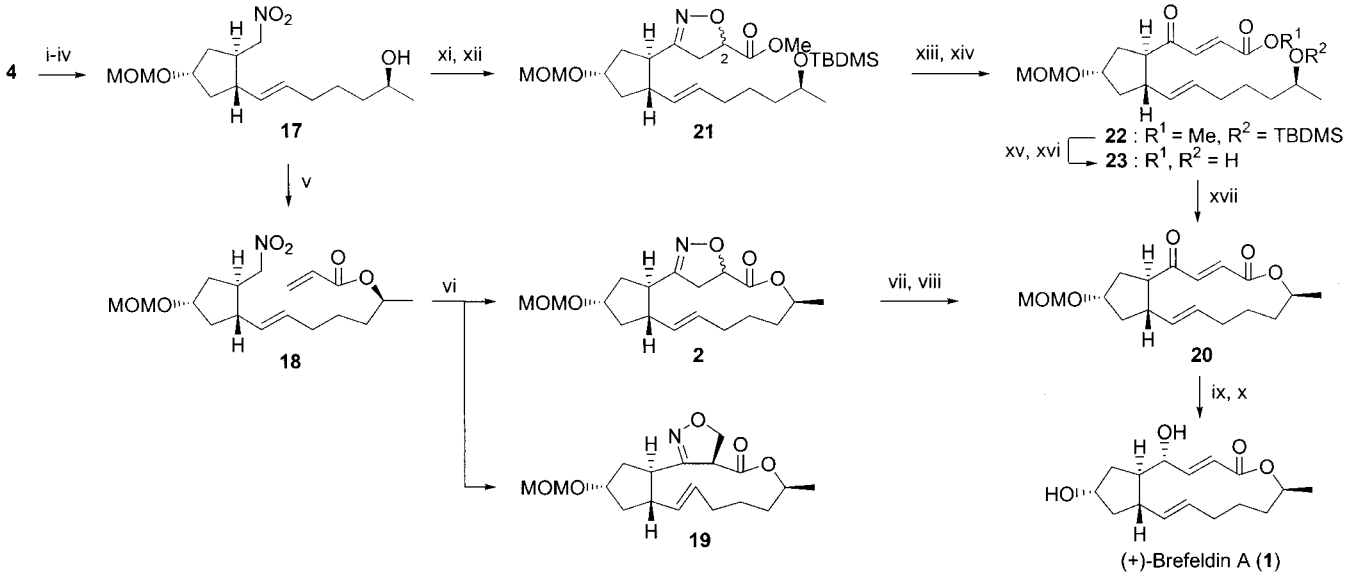
Scheme 2[a]



[a] Key: (i) (a) DIBALH, ether, −78 °C, 1.5 h; (b) $CH_2CHMgBr$, −78 °C, 20 min, then rt, 2 h, 63%; (ii) $PMBOCH_2CO_2H$, DMAP, DCC, CH_2Cl_2, 2.5 h, 93%; (iii) (a) LHMDS, TMSCl/Et_3N, THF, −78 °C, 30 min, then rt, 3 h, b) CH_2N_2, ether, rt, 30 min, 86%; (iv) H_2, 10% Pd/C, *n*-$BuNH_2$, EtOAc, rt, 3 h, 82%; (v) (a) DIBALH, ether, −78 °C, 1 h, (b) $CH_2CHMgBr$, −78 °C, 20 min, then rt, 2 h, 63%; (vi) $MOMOCH_2CO_2H$, DMAP, DCC, CH_2Cl_2, 3 h, rt, 93%; (vii) (a) LHMDS, TMSCl/Et_3N, THF, −78 °C, 30 min, then rt, 3 h, (b) CH_2N_2, ether, rt, 30 min, 86%; (viii) DDQ, H_2O/CH_2Cl_2 (1:18), rt, 40 min, 86%; (ix) $CH_3C(OEt)_3$, phenol, 125 °C, 4.5 h, 84%; (x) $NaBH_4$, EtOH, rt, 8 h, 97%; (xi) I_2, Ph_3P, imidazole, ether/CH_3CN (3:1), rt, 30 min, 85%; (xii) LHMDS, THF, 0 °C, 30 min, 92%.

Scheme 3[a]



[a] Key: (i) Li, $EtOH/NH_3$ (1:4), THF, −78 °C, 45 min, 95%; (ii) TsCl, Et_3N, DMAP, CH_2Cl_2, 1.5 h, 5 °C, 86%; (iii) NaI, 2-butanone, reflux, 1.5 h, 98%; (iv) $NaNO_2$, urea, DMSO, 15 h, rt, 75%; (v) $CH_2CHCOCl$, pyridine, CH_2Cl_2, 0 °C, 30 min, 70%; (vi) *p*-ClC_6H_4NCO, Et_3N, benzene, reflux, 20 h, 78%; (vii) $Mo(CO)_6$, H_2O/CH_3CN (1:99), reflux, 1.5 h; (viii) MsCl, Et_3N, CH_2Cl_2, rt, 2 h, 71% for the two steps; (ix) $NaBH_4$, MeOH, −78 °C, 30 min, 85%; (x) $BF_3{\cdot}Et_2O$, PhSH, rt, 30 min, 95%; (xi) TBDMSCl, imidazole, DMF, rt, 5 h, 95%; (xii) CH_2CHCO_2Me, *p*-ClC_6H_4NCO, Et_3N, benzene, reflux, 10 h, 85%; (xiii) $Mo(CO)_6$, H_2O/CH_3CN (1:99), reflux, 1.5 h; (xiv) MsCl, Et_3N, CH_2Cl_2, rt, 2 h, 65% for the two steps; (xv) PPTS, EtOH, 50 °C, 10 h, 97%; (xvi) LiOH, THF/H_2O (1:1), 5 °C, 20 min, 95%; (xvii) (a) 2,4,6-trichlorobenzoyl chloride, THF, rt, 3 h, (b) DMAP, toluene, reflux, 14 h, 53%.

secondary alcohol **17**. The nitro acrylate **18** underwent a smooth INOC reaction under the standard reaction conditions to produce a 1:1 mixture of the desired bridged isomers **2** and the unwanted fused isomer **19** (78% total yield).[20] This regiochemical outcome, to our surprise, was contrary to Asaoka's observation[21] that the bridged isomer is favored over the fused isomer in a ratio of 68:14 in the case of a simple saturated 13-membered ring cycloaddition.

For the completion of the total synthesis, chemoselective N−O bond cleavage of **2** with wet $Mo(CO)_6$,[22] followed by dehydration of the resulting *β*-hydroxy ketone by the

(20) For the structure determination of compound **2** and **19**, see the Supporting Information of the accompanying paper.[27]

action of methanesulfonyl chloride and triethylamine, yielded γ-oxo-α,β-unsaturated macrolide **20** in 71% yield for the two steps. Finally, stereoselective $NaBH_4$ reduction[7c] (85%) and removal of the MOM protecting group with thiophenol and $BF_3 \cdot Et_2O$ (95%) afforded (+)-brefeldin A (**1**), identical in all respects with the natural product.[23]

To overcome the regioselectivity problem in the INOC reaction, we turned our attention to an intermolecular version. It was necessary to protect the secondary hydroxyl group of **17** as a silyl ether to avoid urethane formation during nitrile oxide formation. As expected, the intermolecular nitrile oxide cycloaddition[24] of the silyl ether of **17**[25] with methyl acrylate proceeded in a regioselective fashion in high yield (85%) to give the desired bridged isoxazolines **21** as a 1:1 mixture of stereoisomers at C2.

The intermolecular nitrile oxide cycloaddition product was transformed into γ-oxo-α,β-unsaturated macrolide **20** as follows: chemoselective N−O bond cleavage with wet $Mo(CO)_6$ and dehydration of the resulting β-hydroxy ketone yielded the desired γ-oxo-α,β-unsaturated ester **22** in 65% yield. Removal of the silyl protecting group of **22** by mild acid hydrolysis, basic hydrolysis of ester function, and macrolactonization of the resulting hydroxy acid **23** under Yamaguchi's conditions[26] led to the formation of macrocyclic lactone **20** in 49% overall yield for the three steps.

Conclusion

In summary, a novel synthesis of (+)-brefeldin A (**1**) has been accomplished on the basis of triple chirality transfer methodology, intramolecular ester enolate alkylation, and both intra- and intermolecular nitrile oxide cycloaddition strategies. During this synthetic endeavor, we observed an unexpected result regarding the regioselectivity of the intramolecular nitrile oxide cycloaddition reaction, which is one of the main themes of the following paper.[27]

Experimental Section

General Methods. All chemicals were reagent grade and used as purchased. All moisture-sensitive reactions were performed under an inert atmosphere of N_2 or Ar using distilled dry solvents. Reactions were monitored by TLC analysis using E. Merck silica gel 60 F_{254} thin layer plates. Flash chromatography was carried out on E. Merck silica gel 60 (230−400 mesh). Optical rotations were measured using sodium light (D line 589.3 nm).

(4*S*,3*S*)-4-Benzyloxypent-1-en-3-ol (7). To a cooled (−78 °C) solution of ethyl *O*-benzyl (*S*)-lactate (**6**) (5.00 g, 24.00 mmol) in dry ether (2.1 L) was added dropwise DIBALH (31 mL, 1.0 M solution in hexane). After 1.5 h, vinylmagnesium bromide (108 mL, 1.0 M solution in THF) was added to the reaction mixture at −78 °C, and the mixture was stirred for 20 min at the same temperature. The reaction mixture was warmed to room temperature, stirred for 2 h, and quenched with saturated aqueous citric acid solution. The separated organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated at reduced pressure. The resulting residue was purified by column chromatography on silica gel (acetone/$CHCl_3$, 1:99) to afford *syn*-allylic alcohol **7** (2.91 g, 63%) and *anti*-allylic alcohol (476 mg, 10%). *syn*-Allylic alcohol **7**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38−7.26 (m, 5H), 5.83 (ddd, J = 17.1, 10.7, 6.3 Hz, 1H), 5.37 (dd, J = 17.0, 1.0 Hz, 1H), 5.23 (dd, J = 10.4, 0.8 Hz, 1H), 4.68 (d, J = 11.2 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 3.95 (br t, J = 6.2 Hz, 1H), 3.44 (quintet, J = 6.2 Hz, 1H), 2.75 (d, J = 2.8 Hz, 1H), 1.19 (d, J = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 138.2, 136.9, 128.4, 127.7, 117.3, 78.2, 76.5, 71.1, 15.4; IR (neat) 3434, 1092 cm^{-1}; $[\alpha]^{18}_D$ = −23.3 (c = 1.00, CH_3OH); HRMS (EI) calcd for $C_{12}H_{16}O_2$ (M^+) 192.1150, found 192.1168. *anti*-Allylic alcohol: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37−7.26 (m, 5H), 5.86 (ddd, J = 17.1, 10.7, 6.1 Hz, 1H), 5.32 (ddd, J = 17.2, 1.4, 1.4 Hz, 1H), 5.22 (ddd, J = 10.8, 1.4, 1.4 Hz, 1H), 4.64 (d, J = 11.6 Hz, 1H), 4.54 (d, J = 11.6 Hz, 1H), 4.26−4.24 (m, 1H), 3.65−3.60 (m, 1H), 2.25 (br s, 1H), 1.16 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 138.4, 136.5, 128.4, 127.7, 127.6, 116.5, 77.4, 74.6, 70.8, 14.0; IR (neat) 3435, 1092 cm^{-1}; $[\alpha]^{18}_D$ = +4 (c = 0.10, CH_3OH).

(4-Methoxybenzyloxy)acetic Acid (1*S*)-1-[(1*S*)-(1-Benzyloxyethyl)]allyl Ester (8). To a mixture of *syn*-allylic alcohol **7** (1.89 g, 9.83 mmol), *O*-(*p*-methoxybenzyl)glycolic acid (4.30 g, 21.92 mmol), and DMAP (110 mg, 0.90 mmol) in dry CH_2Cl_2 (150 mL) was added DCC (3.10 g, 15.02 mmol) at room temperature. After 2.5 h, methanol (2.0 mL) and acetic acid (2.0 mL) were added to the reaction mixture. The mixture was stirred for 20 min and neutralized with saturated aqueous $NaHCO_3$ solution. The organic layer was separated and diluted with hexane (100 mL). The white precipitate was filtered off using a short pad of Celite, and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:6) to give ester **8** (3.39 g, 93%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.26 (m, 7H), 6.87 (d, J = 8.0 Hz, 2H), 5.86 (ddd, J = 17.2, 10.6, 6.5 Hz, 1H), 5.45 (t, J = 6.2 Hz, 1H), 5.33 (ddd, J = 17.4, 1.5, 1.5 Hz, 1H), 5.28 (ddd, J = 10.8, 1.6, 1.6 Hz, 1H), 4.63 (d, J = 11.6 Hz, 1H), 4.55 (s, 2H), 4.54 (d, J = 11.6 Hz, 1H), 4.08 (s, 2H), 3.81 (s, 3H), 3.66 (quintet, J = 6.2 Hz, 1H), 1.16 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.4, 159.3, 138.3, 132.6, 129.6, 129.1, 128.2, 127.4, 118.6, 113.7, 76.7, 75.2, 72.7, 71.2, 66.7, 55.1, 15.5; IR (neat) 1755, 1250 cm^{-1}; $[\alpha]^{18}_D$ = −7.3 (c = 1.0, CH_3OH); HRMS (EI) calcd for $C_{22}H_{26}O_5$ (M^+) 370.1780, found 370.1784.

(2*R*,4*E*,6*S*)-6-Benzyloxy-2-(4-methoxybenzyloxy)hept-4-enoic Acid Methyl Ester (9). To a cooled (−78 °C) solution of LHMDS (100 mL, 0.24 M in THF) were added TMSCl/Et_3N (1:1, 13.3 mL) and ester **8** (2.18 g, 5.89 mmol) in THF (20 mL). After 30 min at the same temperature, the reaction mixture was warmed to room temperature and stirred for 3 h. The solvent (about 60%) was evaporated at reduced pressure, and 2 N NaOH solution (33.8 mL) and water (23.0 mL) were added to the mixture. After 20 min, the mixture was acidified with *d*-HCl (pH 2) and extracted with ether (100 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. After excess ethereal CH_2N_2 was added to the resulting residue, the mixture was stirred for 30 min at room temperature and concentrated at reduced pressure. The residue was purified by column chromatography on silica gel (acetone/$CHCl_3$, 1:99) to give α-alkoxy ester **9** (1.95 g, 86%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.24 (m, 7H), 6.85 (d, J = 8.4 Hz, 2H), 5.63 (ddd, J = 15.6, 7.0, 7.0 Hz, 1H), 5.46 (dd, J = 15.6, 7.6 Hz, 1H), 4.64 (d, J = 11.2 Hz, 1H), 4.50 (d, J = 12.0 Hz, 1H), 4.37 (d, J = 11.2 Hz, 1H), 4.32 (d, J = 11.6 Hz, 1H), 4.00 (t, J = 6.0 Hz, 1H), 3.87 (quintet, J = 7.0 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 2.56−2.48 (m, 2H), 1.25 (d, J = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.5, 159.4, 138.8, 135.5,

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(23) Natural brefeldin A: $[\alpha]^{16}_D$ = + 92.6 (c = 0.1, MeOH). Synthetic brefeldin A: $[\alpha]^{16}_D$ = +92.2 (c = 0.1, MeOH).

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129.6, 129.4, 128.2, 127.6, 127.3, 126.9, 113.8, 77.5, 75.4, 71.9, 69.7, 55.2, 51.7, 35.8, 21.6; IR (neat) 1752, 1250 cm^{-1}; $[\alpha]^{18}_D$ = +39.2 (*c* = 1.0, CH_3OH); HRMS (EI) calcd for $C_{16}H_{20}O_4$ (M^+ − BnOH) 276.1362, found 276.1355.

(2*R*,6*S*)-6-Benzyloxy-2-(4-methoxybenzyloxy)heptanoic Acid Methyl Ester (10). A mixture of α-alkoxy ester **9** (1.00 g, 2.60 mmol), *n*-$BuNH_2$ (0.25 mL), and 10% Pd/C (60 mg) in EtOAc (25 mL) was stirred for 3 h at room temperature under a hydrogen atmosphere (30 psi). The mixture was filtered through a pad of Celite, and the filtrate was concentrated at reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:6) to give saturated ester **10** (820 mg, 82%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33−7.26 (m, 7H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.62 (d, *J* = 11.2 Hz, 1H), 4.54 (d, *J* = 11.6 Hz, 1H), 4.42 (d, *J* = 11.6 Hz, 1H), 4.34 (d, *J* = 11.6 Hz, 1H), 3.91 (dd, *J* = 7.0, 5.8 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.50−3.44 (m, 1H), 1.75−1.71 (m, 2H), 1.62−1.39 (m, 4H), 1.17 (d, *J* = 5.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 173.4, 159.4, 139.0, 129.7, 128.3, 127.6, 127.3, 113.8, 113.6, 77.6, 74.6, 72.0, 70.3, 55.2, 51.7, 36.2, 33.0, 21.3, 19.6; IR (neat) 1750, 1514, 1250 cm^{-1}; $[\alpha]^{18}_D$ = +4.9 (*c* = 1.0, CH_3OH); HRMS (EI) calcd for $C_{16}H_{23}O_5$ (M^+ − Bn) 295.1546, found 295.1540.

(3*R*,4*R*,8*S*)-8-Benzyloxy-4-(4-methoxybenzyloxy)non-1-en-3-ol (11). To a cooled (−78 °C) solution of ester **10** (1.02 g, 2.64 mmol) in anhydrous ether (190 mL) was added DIBALH (4.9 mL, 1.0 M solution in hexane). After 1 h, vinylmagnesium bromide (10.6 mL, 1.0 M solution in THF) was added to the mixture at −78 °C. The mixture was stirred for 20 min at the same temperature and warmed to room temperature. After 2 h, the mixture was quenched with *d*-HCl and washed with saturated $NaHCO_3$ solution. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (acetone/$CHCl_3$, 1:49) to give *syn*-allylic alcohol **11** (639 mg, 63%) and *anti*-allylic alcohol (107 mg, 11%) as colorless oils. *syn*-Allylic alcohol **11**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33−7.23 (m, 5H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.86 (m, 1H), 5.36−5.19 (m, 2H), 4.58−4.42 (m, 4H), 4.04 (br t, 1H), 3.79 (s, 3H), 3.50 (m, 1H), 3.33 (m, 1H), 2.04−1.42 (m, 6H), 1.19 (d, *J* = 5.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.3, 139.0, 137.7, 130.3, 129.5, 128.3, 127.6, 127.3, 116.6, 113.8, 81.9, 74.6, 74.4, 72.4, 70.3, 55.2, 36.6, 30.6, 21.2, 19.6; IR (neat) 3439, 1514 cm^{-1}; $[\alpha]^{18}_D$ = +41.8 (*c* = 1.0, CH_3OH); HRMS (EI) calcd for $C_{17}H_{25}O_4$ (M^+ − Bn) calcd 293.1753, found 293.1741. *anti*-Allylic alcohol: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35−7.25 (m, 5H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.86 (m, 1H), 5.33−5.19 (m, 2H), 4.57−4.42 (m, 4H), 4.30 (m, 1H), 3.79 (s, 3H), 3.49 (m, 1H), 3.42 (m, 1H), 1.59−1.39 (m, 6H), 1.18 (d, *J* = 5.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.3, 139.1, 136.7, 130.5, 129.4, 128.3, 127.6, 127.3, 116.4, 113.8, 81.7, 74.7, 73.4, 71.9, 70.3, 55.2, 36.7, 29.3, 21.8, 19.6; IR (neat) 3453, 1514 cm^{-1}; $[\alpha]^{18}_D$ = +26 (*c* = 0.20, CH_3OH).

Methoxymethoxyacetic Acid (1*R*)-1-[(1*R*,5*S*)-5-Benzyloxy-1-(4-methoxybenzyloxy)hexyl]allyl Ester (12). To a mixture of *syn*-allylic alcohol **11** (541 mg, 1.41 mmol), *O*-(methoxymethyl)glycolic acid (254 mg, 2.12 mmol), and DMAP (30 mg, 0.25 mmol) in dry CH_2Cl_2 (20 mL) was added DCC (494 mg, 2.39 mmol) at room temperature. After 3 h, the reaction mixture was diluted with hexane and filtered through a pad of Celite. Concentration of the filtrate in vacuo and purification of the resulting residue by column chromatography on silica gel (EtOAc/hexane, 1:2) gave ester **12** (637 mg) in 93% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26−7.16 (m, 7H), 6.78 (d, *J* = 8.8 Hz, 2H), 5.78 (ddd, *J* = 17.2, 10.8, 6.4 Hz, 1H), 5.42 (t, *J* = 5.8 Hz, 1H), 5.24 (d, *J* = 17.6 Hz, 1H), 5.19 (d, *J* = 10.8 Hz, 1H), 4.63 (s, 2H), 4.52 (d, *J* = 11.6 Hz, 1H), 4.48 (d, *J* = 11.6 Hz, 1H), 4.43 (d, *J* = 11.2 Hz, 1H), 4.35 (d, *J* = 11.6 Hz, 1H), 4.15−4.05 (m, 2H), 3.71 (s, 3H), 3.43−3.35 (m, 2H), 3.32 (s, 3H), 1.52−1.30 (m, 6H), 1.10 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.2, 159.2, 139.0, 132.6, 130.3, 129.4, 128.2, 127.5, 127.3, 116.4, 113.7, 96.3, 79.1, 75.8, 74.7, 72.4, 70.3, 64.2, 55.7, 55.2, 36.6, 30.5, 21.5, 19.6; IR (neat) 1757, 1514, 1063 cm^{-1}; $[\alpha]^{18}_D$ = +37.9 (*c* = 1.0, CH_3OH); HRMS (EI) calcd for $C_{28}H_{38}O_7$ (M^+) 486.2618, found 486.2640.

(2*S*,4*E*,6*R*,10*S*)-10-Benzyloxy-6-(4-methoxybenzyloxy)-2-methoxymethoxyundec-4-enoic Acid Methyl Ester (13). To a cooled (−78 °C) solution of LHMDS (30 mL, 0.09 M in THF) were added TMSCl/Et_3N(1:1, 1.45 mL) and ester **12** (313 mg, 0.64 mmol) in THF (4 mL). After 20 min, the reaction mixture was warmed to room temperature and stirred for 3 h. The solvent (about 60%) was removed at reduced pressure, and 2 N NaOH (3.7 mL) and water (1.3 mL) were added to the mixture. After 20 min, the mixture was acidified with *d*-HCl (pH 2−3) and extracted with ether (50 mL × 5). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. After excess ethereal CH_2N_2 was added to the resulting residue, the mixture was stirred for 30 min at room temperature and concentrated at reduced pressure. The resulting residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to give ester **13** (277 mg, 86%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26−7.16 (m, 7H), 6.78 (d, *J* = 8.8 Hz, 2H), 6.55 (ddd, *J* = 15.6, 7.8, 7.8 Hz, 1H), 6.39 (dd, *J* = 15.6, 8.0 Hz, 1H), 4.64 (d, *J* = 6.8 Hz, 1H), 4.61 (d, *J* = 6.8 Hz, 1H), 4.47 (d, *J* = 11.6 Hz, 1H), 4.42 (d, *J* = 11.2 Hz, 1H), 4.36 (d, *J* = 12.0 Hz, 1H), 4.17 (d, *J* = 11.6 Hz, 1H), 4.13 (t, *J* = 6.4 Hz, 1H), 3.72 (s, 3H), 3.66 (s, 3H), 3.63−3.57 (m, 1H), 3.43−3.38 (m, 1H), 3.31 (s, 3H), 2.55−2.42 (m, 2H), 1.59−1.47 (m, 2H), 1.40−1.28 (m, 4H), 1.10 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.2, 158.9, 139.0, 134.8, 130.8, 129.2, 128.2, 127.5, 127.3, 127.2, 113.6, 96.1, 79.1, 75.4, 74.7, 70.2, 69.4, 55.9, 55.1, 51.6, 36.4, 35.7, 35.7, 21.4, 19.5; IR(neat) 1752, 1514, 1034 cm^{-1}; $[\alpha]^{18}_D$ = +24.3 (*c* = 1.0, CH_3OH); HRMS (EI) calcd for $C_{27}H_{35}O_6$ (M^+ − MOM) calcd 455.2434, found 455.2437.

(2*S*,4*E*,6*R*,10*S*)-10-Benzyloxy-6-hydroxy-2-methoxymethoxyundec-4-enoic Acid Methyl Ester (14). A mixture of ester **13** (281 mg, 0.56 mmol) and DDQ (154 mg, 0.68 mmol) in CH_2Cl_2/water (18:1, 15 mL) was stirred for 40 min at room temperature. The mixture was filtered through a short pad of Celite, and the filtrate was concentrated at reduced pressure. The resulting residue was purified by column chromatography on silica gel (EtOAc/hexane, 2:3) to give allylic alcohol **14** (183 mg, 86%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27−7.18 (m, 5H), 5.58 (ddd, *J* = 15.6, 6.4, 6.4 Hz, 1H), 5.51 (dd, *J* = 15.6, 6.0 Hz, 1H), 4.62 (d, *J* = 7.6 Hz, 1H), 4.59 (d, *J* = 7.2 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.37 (d, *J* = 11.6 Hz, 1H), 4.11 (t, *J* = 6.0 Hz, 1H), 4.10−3.96 (m, 1H), 3.66 (s, 3H), 3.49−3.41 (m, 1H), 3.30 (s, 3H), 2.50−2.39 (m, 2H), 1.59−1.33 (m, 6H), 1.12 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.2, 138.9, 136.9, 128.2, 127.5, 127.3, 125.1, 96.0, 75.2, 74.7, 72.3, 70.2, 55.9, 51.8, 37.1, 36.4, 35.5, 21.3, 19.5; IR (neat) 3447, 1752 cm^{-1}; $[\alpha]^{18}_D$ = −3.2 (*c* = 0.50, CH_3OH); HRMS (EI) calcd for $C_{19}H_{27}O_5$ (M^+ − MOM) 335.1859, found 335.1861.

(2*S*,4*R*)-4-[(6*S*)-6-Benzyloxyhept-1-enyl]-2-methoxymethoxyhexanedioic Acid 6-Ethyl Ester 1-Methyl Ester (15). A mixture of allylic alcohol **14** (131 mg, 0.344 mmol), triethyl orthoacetate (12 mL), and phenol (3 mg, 0.032 mmol) was stirred for 4.5 h at 125 °C. The mixture was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to give diester **15** (130 mg, 84%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27−7.17 (m, 5H), 5.42 (ddd, *J* = 15.2, 6.8, 6.8 Hz, 1H), 5.17 (dd, *J* = 15.4, 8.6 Hz, 1H), 4.60 (d, *J* = 6.8 Hz, 1H), 4.58 (d, *J* = 6.8 Hz, 1H), 4.49 (d, *J* = 11.6 Hz, 1H), 4.37 (d, *J* = 12.0 Hz, 1H), 4.06 (t, *J* = 6.6 Hz, 1H), 4.03 (q, *J* = 7.2 Hz, 2H), 3.66 (s, 3H), 3.45−3.40 (m, 1H), 3.31 (s, 3H), 2.68−2.59 (m, 1H), 2.35 (dd, *J* = 14.6, 5.4 Hz, 1H), 2.19 (dd, *J* = 14.6, 9.0 Hz, 1H), 1.90 (q, *J* = 6.7 Hz, 2H), 1.77−1.73 (m, 2H), 1.52−1.26 (m, 4H), 1.15 (t, *J* = 7.0 Hz, 3H), 1.11 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.8, 171.9, 139.1, 131.9, 131.4, 128.2, 127.5, 127.3, 98.2, 74.6, 73.8, 70.2, 60.1, 56.1, 51.8, 39.8, 37.7, 36.0, 35.6, 32.4, 25.2, 19.5, 14.2; IR (neat) 1736, 1028 cm^{-1}; $[\alpha]^{18}_D$ = +2.3 (*c* = 1.0, CH_3OH); HRMS (EI) calcd for $C_{23}H_{33}O_6$ (M^+ − MOM) calcd 405. 2277, found 405. 2261.

(3*R*,4*E*,9*S*)-9-Benzyloxy-3-[(2*S*)-3-hydroxy-2-methoxymethoxypropyl]dec-4-enoic Acid Ethyl Ester (16). To a solution of diester **15** (119 mg, 0.26 mmol) in absolute ethanol (8.0 mL) was added $NaBH_4$ (100 mg, 2.64 mmol) at 0 °C. The

reaction mixture was warmed to room temperature and stirred for 8 h. After water (0.5 mL) was added to the mixture, the mixture was concentrated in vacuo. The residue was dissolved in EtOAc and washed with water. The aqueous phase was reextracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:1) to afford alcohol **16** (108 mg, 97%) as a thick syrup: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27−7.18 (m, 5H), 5.40 (ddd, J = 15.2, 6.8, 6.8 Hz, 1H), 5.17 (dd, J = 15.6, 8.4 Hz, 1H), 4.63 (d, J = 6.8 Hz, 1H), 4.58 (d, J = 6.8 Hz, 1H), 4.49 (d, J = 11.6 Hz, 1H), 4.37 (d, J = 11.6 Hz, 1H), 4.03 (q, J = 7.1 Hz, 2H), 3.57−3.36 (m, 4H), 3.34 (s, 3H), 2.96 (br s, 1H), 2.55−2.45 (m, 1H), 2.29 (dd, J = 14.6, 6.2 Hz, 1H), 2.18 (dd, J = 15.0, 8.2 Hz, 1H), 1.91 (q, J = 6.5 Hz, 2H), 1.53−1.29 (m, 6H), 1.16 (t, J = 7.2 Hz, 3H), 1.11 (d, J = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.1, 139.0, 132.4, 131.5, 128.2, 127.5, 127.3, 96.6, 79.5, 74.6, 70.2, 64.9, 60.2, 55.5, 40.4, 36.5, 36.1, 36.0, 32.3, 25.2, 19.5, 14.2; IR (neat) 3468, 1732, 1036 cm^{-1}; $[\alpha]^{18}_D$ = +10.0 (c = 0.50, CH_3OH); HRMS (EI) calcd for $C_{16}H_{27}O_5$ (M^+ − Bn, MeOH) calcd 299.1854, found 299.1852.

(3*R*,4*E*,9*S*)-9-Benzyloxy-3-[(2*S*)-3-iodo-2-methoxymethoxypropyl]dec-4-enoic Acid Ethyl Ester (5). To a solution of alcohol **16** (482 mg, 1.14 mmol) in ether/acetonitrile (3:1, 11 mL) were added imidazole (201 mg, 2.96 mmol), Ph_3P (388 mg, 1.48 mmol), and iodine (375 mg, 1.48 mmol) at room temperature. After 30 min, the mixture was diluted with hexane and filtered through a short pad of silica gel. Concentration of the filtrate in vacuo and purification of the residue by column chromatography on silica gel (EtOAc/hexane, 1:20) gave ω-iodo ester **5** (516 mg, 85%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.33−7.24 (m, 5H), 5.55−5.18 (m, 2H), 4.65 (s, 2H), 4.55 (d, J = 11.8 Hz, 1H), 4.42 (d, J = 11.8 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.55−3.24 (m, 4H), 3.36 (s, 3H), 2.65−2.45 (m, 1H), 2.44−2.18 (m, 2H), 1.96 (q, J = 6.5 Hz, 2H), 1.68−1.39 (m, 6H), 1.22 (t, J = 7.0 Hz, 3H), 1.17 (d, J = 5.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.0, 139.1, 131.9, 131.7, 128.3, 127.6, 127.3, 95.8, 74.6, 74.2, 70.3, 60.3, 56.1, 40.6, 40.1, 36.1, 32.4, 25.3, 19.6, 14.3, 11.2; IR (neat) 1734, 1038 cm^{-1}; $[\alpha]^{18}_D$ = +6.9 (c = 1.0, CH_3OH).

(1*R*,2*S*,4*S*)-2-[(1*E*,6*S*)-6-Benzyloxyhept-1-enyl]-4-methoxymethoxycyclopentanecarboxylic Acid Ethyl Ester (4). To a solution of iodide **5** (124 mg, 0.233 mmol) in anhydrous THF (12 mL) was added LHMDS (9.3 mL, 1 M solution in THF) at 0 °C. After 50 min at the same temperature, the reaction mixture was quenched with saturated NH_4-Cl solution and concentrated in vacuo. The residue was dissolved in EtOAc, and the solution was washed with water. The aqueous layer was reextracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to give cyclopentanecarboxylate **4** (87 mg, 92%) as a thick syrup: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28−7.18 (m, 5H), 5.42−5.30 (m, 2H), 4.56 (s, 2H), 4.49 (d, J = 12.0 Hz, 1H), 4.38 (d, J = 12.0 Hz, 1H), 4.17−4.12 (m, 1H), 4.09−4.01 (m, 2H), 3.46−3.40 (m, 1H), 3.30 (s, 3H), 2.63−2.55 (m, 2H), 2.24−2.18 (m, 1H), 2.00−1.89 (m, 4H), 1.54−1.28 (m, 5H), 1.16 (t, J = 7.2 Hz, 3H), 1.12 (d, J = 5.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 175.3, 139.1, 132.2, 130.7, 128.3, 127.6, 127.3, 95.3, 77.1, 74.7, 70.3, 60.3, 55.3, 48,7, 45.7, 40.0, 36.9, 36.1, 32.4, 25.3, 19.6, 14.3; IR (neat) 1732, 1040 cm^{-1}; $[\alpha]^{18}_D$ = −23.3 (c = 0.50, CH_3OH); HRMS (EI) calcd for $C_{24}H_{36}O_5$ (M^+) 404.2563, found 404.2541.

(2*S*,6*E*)-7-[(1*S*,2*R*,4*S*)-4-Methoxymethoxy-2-nitromethylcyclopentyl]hept-6-en-2-ol (17). (1) Reduction of Ester Group and Debenzylation. To a solution of cyclopentanecarboxylate **4** (705 mg, 1.74 mmol) in dry THF (4.7 mL) were added ethanol (4.7 mL) and liquid ammonia (19 mL) at −78 °C. Li wire (122 mg, 17.58 mmol) was then added portionwise to the mixture over 15 min at −78 °C. After 30 min, the reaction mixture was quenched with saturated NH_4Cl solution and warmed to room temperature. The mixture was diluted with EtOAc and washed with water. The aqueous layer was reextracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (MeOH/$CHCl_3$, 1:9) to give the diol (450 mg, 95%) as a thick syrup: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.40−5.32 (m, 2H), 4.55 (s, 2H), 4.08−4.05 (m, 1H), 3.75−3.69 (m, 1H), 3.58 (dd, J = 10.7, 5.3 Hz, 1H), 3.44 (dd, J = 10.7, 6.2 Hz, 1H), 3.29 (s, 3H), 2.17−2.03 (m, 2H), 1.98−1.90 (m, 3H), 1.83 (ddd, J = 12.9, 8.3, 3.8 Hz, 1H), 1.56 (ddd, J = 13.4, 9.2, 7.1 Hz, 1H), 1.47−1.29 (m, 5H), 1.11 (d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 134.19, 130.29, 95.30, 67.92, 65.57, 55.24, 46.12, 44.55, 40.61, 38.72, 35.97, 32.28, 25.56, 23.47; IR (neat) 3403, 1042 cm^{-1}; $[\alpha]^{18}_D$ = −32.8 (c = 0.50, CH_3OH); HRMS (EI) calcd for $C_{14}H_{24}O_3$ (M^+ − MeOH) 240.1725, found 240.1725.

(2) Monotosylation. To a solution of the above diol (230 mg, 0.84 mmol) in dry CH_2Cl_2 (5.0 mL) were added *p*-toluenesulfonyl chloride (1.62 g, 8.50 mmol), Et_3N (3.6 mL, 25.83 mmol), and DMAP (103 mg, 0.84 mmol) at 5 °C. After 1.5 h at room temperature, the mixture was poured into ice−water and extracted with CH_2Cl_2 (30 mL × 3). The combined organic layers were washed with *d*-HCl, saturated $NaHCO_3$ solution, and brine, dried over anhydrous $MgSO_4$, and concentrated at reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to give the monotosylate (308 mg, 86%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 5.24−5.15 (m, 2H), 4.51 (s, 2H), 4.04−3.98 (m, 2H), 3.81 (dd, J = 9.6, 6.1 Hz, 1H), 3.74−3.68 (m, 1H), 3.26 (s, 3H), 2.38 (s, 3H), 2.14−1.97 (m, 3H), 1.90−1.86 (m, 2H), 1.79 (ddd, J = 13.2, 7.8, 3.5 Hz, 1H), 1.56−1.50 (m, 2H), 1.44−1.23 (m, 4H), 1.11 (d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 144.6, 133.0, 132.4, 131.1, 129.7, 127.8, 95.1, 76.4, 71.6, 67.7, 55.1, 43.4, 42.8, 40.0, 38.6, 35.7, 32.1, 25.3, 23.3, 21.5; IR (neat) 3435, 1177 cm^{-1}; $[\alpha]^{18}_D$ = −30.8 (c = 0.50, CH_3OH); HRMS (EI) calcd for $C_{21}H_{30}O_5S$ (M^+ − MeOH) 394.1814, found 394.1818.

(3) Iodination. A mixture of the above tosylate (107 mg, 0.25 mmol) and sodium iodide (753 mg, 5.02 mmol) in 2-butanone (12 mL) was refluxed for 1.5 h. After removal of the solvent, cold water was added to the residue. The mixture was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with saturated $Na_2S_2O_3$ solution, saturated $NaHCO_3$ solution, and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc/hexane, 2:3) to give the iodo compound (94 mg, 98%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.53−5.21 (m, 2H), 4.59 (s, 2H), 4.19−4.05 (m, 1H), 3.85−3.37 (m, 1H), 3.40−3.30 (m, 1H), 3.33 (s, 3H), 3.08 (dd, J = 9.7, 7.0 Hz, 1H), 2.38−2.22 (m, 1H), 2.16−1.95 (m, 4H), 1.91−1.33 (m, 7H), 1.17 (d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 132.3, 131.4, 95.2, 75.8, 67.9, 55.2, 47.7, 45.1, 40.8, 40.0, 38.7, 32.3, 25.5, 23.5, 12.7; IR (neat) 3408, 1044 cm^{-1}; $[\alpha]^{18}_D$ = −38.0 (c = 0.50, CH_3OH); HRMS (EI) calcd for $C_{14}H_{23}IO_2$ (M^+ − MeOH) calcd 350.0743, found 350.0737.

(4) Conversion to Nitro Compound. To a solution of the above iodo compound (93 mg, 0.24 mmol) in DMSO (4 mL) were added urea (101 mg, 1.68 mmol) and sodium nitrite (83 mg, 1.20 mmol) at room temperature. After 15 h, the mixture was poured into water and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with water, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc/hexane, 2:3) to give nitro compound **17** (54 mg, 75%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.38 (ddd, J = 15.2, 6.7, 6.7 Hz, 1H), 5.26 (dd, J = 15.2, 8.6 Hz, 1H), 4.54 (s, 2H), 4.37 (dd, J = 12.1, 5.0 Hz, 1H), 4.15−4.08 (m, 2H), 3.76−3.70 (m, 1H), 3.28 (s, 3H), 2.50−2.42 (m, 1H), 2.21 (ddd, J = 14.3, 7.8, 6.4 Hz, 1H), 2.07−1.93 (m, 4H), 1.58−1.49 (m, 2H), 1.45−1.30 (m, 4H), 1.24 (br s, 1H), 1.12 (d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 132.2, 131.6, 95.2, 78.7, 76.0, 67.9, 55.3, 45.7, 42.1, 40.2, 38.6, 37.4, 32.2, 25.4, 23.5; IR (neat) 3412, 1553, 1040 cm^{-1}; $[\alpha]^{18}_D$ = −21.6 (c = 0.50, CH_3OH); HRMS (EI) calcd for $C_{14}H_{24}NO_4$ (M^+ − OMe) 270.1705, found 270.1702.

Acrylic Acid (1*S*,5*E*)-6-[(1*S*,2*R*,4*S*)-4-Methoxymethoxy-2-nitromethylcyclopentyl]-1-methylhex-5-enyl Ester (18). To a mixture of alcohol **17** (46 mg, 0.15 mmol) and pyridine (0.12 mL, 1.48 mmol) in dry CH_2Cl_2 (10 mL) was added acryloyl chloride (0.11 mL, 1.35 mmol) at 0 °C. After 30 min, the mixture was diluted with CH_2Cl_2 and washed with *d*-HCl, $NaHCO_3$ solution, and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated at reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to give acrylate **18** (38 mg, 70%) as a thick syrup: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.31 (dd, J = 17.3, 1.5 Hz, 1H), 6.03 (dd, J = 17.8, 10.4 Hz, 1H), 5.72 (dd, J = 10.4, 1.4 Hz, 1H), 5.36 (ddd, J = 15.2, 6.6, 6.6 Hz, 1H), 5.26 (dd, J = 15.2, 8.6 Hz, 1H), 4.93−4.90 (m, 1H), 4.54 (s, 2H), 4.37 (dd, J = 12.1, 4.8 Hz, 1H), 4.14−4.08 (m, 2H), 3.28 (s, 3H), 2.50−2.42 (m, 1H), 2.21 (ddd, J = 13.9, 8.0, 6.3 Hz, 1H), 2.06−1.92 (m, 4H), 1.59−1.42 (m, 4H), 1.40−1.28 (m, 2H), 1.18 (d, J = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.9, 132.0, 131.8, 130.2, 129.1, 95.3, 78.7, 76.0, 71.0, 55.3, 45.6, 42.1, 40.2, 37.4, 35.3, 32.0, 25.0, 19.9; IR (neat) 1721, 1553 cm^{-1}; $[\alpha]^{20}_D$ = −6.1 (c = 0.10, CH_3OH); HRMS (EI) calcd for $C_{17}H_{26}NO_5$ (M^+ − OMe) 324.1811, found 324.1818.

Intramolecular Nitrile Oxide Cycloaddition of Acrylate 18. A mixture of acrylate **18** (52 mg, 0.15 mmol), *p*-chlorophenyl isocyanate (246 mg, 1.60 mmol), and Et_3N (0.22 mL, 1.60 mmol) in benzene (49 mL) was refluxed for 18 h. The reaction mixture was filtered through a short pad of Celite and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4). The first fraction was collected and rechromatographed (EtOAc/hexane, 1:5) to give fused isomer **19** (21 mg, 38%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.44 (ddd, J = 15.3, 9.7, 5.0 Hz, 1H), 5.19 (dd, J = 15.3, 7.2 Hz, 1H), 5.12−5.07 (m, 1H), 4.62 (dd, J = 8.8, 8.1 Hz, 1H), 4.61 (s, 2H), 4.39 (dd, J = 10.9, 8.8 Hz, 1H), 4.28−4.23 (m, 1H), 3.96 (dd, J = 10.9, 8.1 Hz, 1H), 3.36 (s, 3H), 2.84−2.77 (m, 2H), 2.37 (ddd, J = 13.8, 7.0, 7.0 Hz, 1H), 2.22−2.15 (m, 2H), 1.89−1.82 (m, 1H), 1.63−1.49 (m, 5H), 1.25−1.15 (m, 1H), 1.21 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.6, 157.3, 132.2, 132.1, 95.2, 76.8, 71.7, 70.6, 58.3, 55.4, 48.1, 41.6, 40.4, 39.6, 31.7, 30.2, 20.4, 17.9; IR (neat) 1721 cm^{-1}; $[\alpha]^{18}_D$ = +99 (c = 0.10, CH_3OH); HRMS (EI) calcd for $C_{18}H_{27}NO_5$ (M^+) 337.1889, found 337.1873.

The second fraction was collected and rechromatographed (EtOAc/hexane, 1:4) to give C2-(*R*) bridged isomer **2** (10 mg, 19%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.77 (ddd, J = 15.0, 10.2, 5.0 Hz, 1H), 5.27 (dd, J = 15.0, 9.0 Hz, 1H), 4.94 (dd, J = 11.8, 4.6 Hz, 1H), 4.92−4.86 (m, 1H), 4.61 (s, 2H), 4.30−4.26 (m, 1H), 3.41 (dd, J = 17.3, 11.8 Hz, 1H), 3.35 (s, 3H), 3.01 (dd, J = 17.3, 4.6 Hz, 1H), 2.70−2.62 (m, 1H), 2.55 (ddd, J = 11.8, 11.8, 5.0 Hz, 1H), 2.40 (ddd, J = 13.9, 7.2, 7.2 Hz, 1H), 2.12−1.98 (m, 2H), 1.98−1.86 (m, 2H), 1.82−1.74 (m, 1H), 1.68−1.58 (m, 2H), 1.53−1.47 (m, 1H), 1.28 (d, J = 6.3 Hz, 3H), 1.04−0.96 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.5, 159.2, 132.8, 131.4, 95.1, 77.2, 76.0, 73.3, 55.4, 51.1, 46.1, 42.7, 40.0, 39.0, 32.7, 31.0, 26.2, 20.1; IR (neat) 1728 cm^{-1}; $[\alpha]^{18}_D$ = −62 (c = 0.10, CH_3OH); HRMS (EI) calcd for $C_{18}H_{27}NO_5$ (M^+) 337.1889, found 337.1888.

The third fraction was collected and rechromatographed (EtOAc/hexane, 1:2) to give C2-(*S*) bridged isomer **2** (12 mg, 21%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.70 (ddd, J = 15.1, 10.1, 4.9 Hz, 1H), 5.27 (dd, J = 15.1, 8.6 Hz, 1H), 4.99 (dd, J = 11.1, 2.7 Hz, 1H), 4.94−4.88 (m, 1H), 4.61 (d, J = 6.8 Hz, 1H), 4.60 (d, J = 6.8 Hz, 1H), 4.27−4.22 (m, 1H), 3.35 (s, 3H), 3.33 (dd, J = 16.9, 2.7 Hz, 1H), 3.10 (dd, J = 16.9, 11.1 Hz, 1H), 3.11−3.04 (m, 1H), 2.41−2.29 (m, 2H), 2.05−1.97 (m, 2H), 1.81−1.51 (m, 6H), 1.27 (d, J = 6.5 Hz, 3H), 1.09−1.02 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.6, 160.1, 132.5, 130.8, 95.3, 77.2, 75.7, 74.4, 55.4, 48.7, 41.6, 40.0, 37.1, 35.8, 33.2, 31.2, 26.1, 20.4; IR (neat) 1734 cm^{-1}; $[\alpha]^{18}_D$ = +88 (c = 0.10, CH_3OH); HRMS (EI) calcd for $C_{18}H_{27}NO_5$ (M^+) 337.1889, found 337.1888.

(2*S*,3a*R*,5*E*,9*S*,13*E*,14a*S*)-2-Methoxymethoxy-9-methyl-2,3,3a,9,10,11,12,14a-octahydro-1*H*-8-oxa-cyclopentacyclotridecene-4,7-dione (20). To a mixture of the two bridged isomers **2** (8 mg, 0.024 mmol and 9.5 mg, 0.028 mmol) in H_2O/CH_3CN (1:99, 4 mL) was added $Mo(CO)_6$ (14 mg, 0.053 mmol) at room temperature. The mixture was refluxed for 1.5 h, and the solvent was removed in vacuo. The resulting residue was dissolved in EtOAc, and the solution was washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo to afford the crude β-hydroxy ketone (15.9 mg). This crude alcohol was dissolved in CH_2Cl_2 (5.0 mL), and Et_3N (0.13 mL, 0.93 mmol) and methanesulfonyl chloride (0.04 mL, 0.52 mmol) were added to the solution. After 2 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with saturated citric acid, saturated $NaHCO_3$ solution and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to give lactone **20** (12 mg, 65% for the two steps): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.76 (d, J = 16.0 Hz, 1H), 6.44 (d, J = 15.8 Hz, 1H), 5.86 (ddd, J = 15.1, 10.9, 4.1 Hz, 1H), 5.52 (ddd, J = 15.2, 9.6, 1.3 Hz, 1H), 4.70−4.61 (m, 1H), 4.63 (s, 2H), 4.12−4.07 (m, 1H), 3.36 (s, 3H), 2.88 (q, J = 9.1 Hz, 1H), 2.56 (quintet, J = 9.1 Hz, 1H), 2.30−2.21 (m, 2H), 2.18−2.11 (m, 1H), 2.05−1.98 (m, 1H), 1.96−1.88 (m, 2H), 1.84−1.77 (m, 1H), 1.68−1.58 (m, 2H), 1.33 (d, J = 6.1 Hz, 3H), 1.27−1.16 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.5, 166.1, 140.2, 135.7, 132.9, 128.3, 95.2, 77.2, 73.7, 56.0, 55.3, 45.2, 40.3, 34.2, 32.7, 32.2, 25.6, 20.2; IR (neat) 1725, 1042 cm^{-1}; $[\alpha]^{18}_D$ = −18.5 (c = 0.50, CH_3OH); HRMS (EI) calcd for $C_{17}H_{22}O_4$ (M^+ − MeOH) 290.1518, found 290.1541.

3-[(1*R*,2*S*,4*S*)-2-[(1*E*,6*S*)-6-(*tert*-Butyl-dimethylsilanyloxy)hept-1-enyl]-4-methoxymethoxycyclopentyl]-4,5-dihydroisoxazole-5-carboxylic Acid Methyl Ester (21). (1) Protection of Hydroxyl Group. A mixture of alcohol **17** (54 mg, 0.18 mmol), TBDMSCl (35 mg, 0.23 mmol), and imidazole (18 mg, 0.26 mmol) in DMF (3.0 mL) was stirred for 5 h at room temperature. The mixture was diluted with EtOAc and washed with water. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:7) to give the silyl ether (71 mg, 95%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.45 (ddd, J = 15.2, 6.7, 6.7 Hz, 1H), 5.31 (dd, J = 15.2, 8.6 Hz, 1H), 4.61 (s, 2H), 4.45 (dd, J = 12.1, 4.7 Hz, 1H), 4.20−4.15 (m, 2H), 3.78 (dddd, J = 11.9, 5.9, 5.9, 5.9 Hz, 1H), 3.35 (s, 3H), 2.56−2.48 (m, 1H), 2.28 (ddd, J = 13.9, 7.8, 6.4 Hz, 1H), 2.12−2.05 (m, 2H), 2.00−1.94 (m, 2H), 1.66−1.54 (m, 3H), 1.46−1.31 (m, 3H), 1.11 (d, J = 6.1 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 132.6, 131.3, 95.3, 78.7, 76.0, 68.4, 55.3, 45.7, 42.2, 40.2, 39.1, 37.4, 32.3, 25.9, 25.5, 23.8, 18.1, −4.4, −4.7; IR (neat) 1553, 1044 cm^{-1}; $[\alpha]^{17}_D$ = −13.2 (c = 1.5, CH_3OH); HRMS (EI) calcd for $C_{21}H_{40}NO_5Si$ (M^+ − C_4H_9) 358.2050, found 358.2061.

(2) Intermolecular Nitrile Oxide Cycloadditon. A mixture of the above silyl ether (60 mg, 0.14 mmol), methyl acrylate (0.25 mL, 2.78 mmol), *p*-chlorophenyl isocyanate (236 mg, 1.54 mmol) and Et_3N (0.22 mL, 1.58 mmol) in benzene (20 mL) was refluxed for 10 h. The mixture was cooled to room temperature. The white precipitate was filtered off through a pad of Celite and the filtrate was concentrated in vacuo. The resulting residue was dissolved in EtOAc/hexane (1:3) and insoluble material was removed by filtration. Concentration of the filtrate and purification of the residue by column chromatography on silica gel (EtOAc/hexane, 2:3) afforded a 1:1 mixture of isoxazoles **21** (58 mg, 85%) as a thick syrup: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.47−5.35 (m, 2H), 4.96 (ddd, J = 11.4, 6.3, 2.5 Hz, 1H), 4.62 (s, 2H), 4.23−4.19 (m, 1H), 3.79−3.74 (m, 4H), 3.35 (s, 3H), [3.28 (dd, J = 17.1, 6.3 Hz) and 3.24 (dd, J = 17.1, 11.1 Hz), 1H], [3.13 (dd, J = 16.9, 6.7 Hz) and 3.10 (dd, J = 16.9, 11.3 Hz), 1H], 2.81 (quintet, J = 9.3 Hz, 1H), 2.45 (dddd, J = 18.4, 9.1, 9.1, 9.1 Hz, 1H), 2.30 (ddd, J = 14.0, 8.1, 6.2 Hz, 1H), 2.09−1.94 (m, 4H), 1.61−1.55 (m, 1H), 1.45−1.31 (m, 3H), 1.11 (d, J = 6.1 Hz, 3H), 0.88 (s, 9H), 0.87−0.80 (m, 1H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9, 160.04, 159.95, 132.18, 132.16, 131.6, 95.24, 95.22, 77.17, 77.14, 76.9, 76.48, 76.45, 68.48, 68.46, 55.4, 52.7, 46.5, 46.4, 42.4, 42.2, 40.4, 40.2, 39.7, 39.2, 37.2, 37.1, 32.4, 29.7, 25.9, 25.53, 25.50, 23.8, 18.2, −4.4, −4.7; IR (neat) 1744 cm^{-1};

$[\alpha]^{18}_D = -27.0$ ($c = 0.10$, CH_3OH); HRMS (CI) calcd for (MH^+) 484.3094, found 484.3105.

(2*E*)-4-[(1*R*,2*S*,4*S*)-2-[(1*E*,6*S*)-6-(*tert*-Butyldimethylsilanyloxy)hept-1-enyl]-4-methoxymethoxycyclopentyl]-4-oxobut-2-enoic Acid Methyl Ester (22). A mixture of isoxazoles **21** (56 mg, 0.12 mmol), water (0.8 mL), and $Mo(CO)_6$ (31 mg, 0.12 mmol) in acetonitrile (8.0 mL) was refluxed for 1.5 h. The solvent was evaporated and the residue was dissolved in EtOAc. The mixture was washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated at reduced pressure to give the crude hydroxy ketone which was dissolved in CH_2Cl_2 (10 mL). To the solution were added methanesulfonyl chloride (0.14 mL, 1.81 mmol) and Et_3N (0.33 mL, 2.37 mmol) at 0 °C. After 2 h at room temperature, the mixture was diluted with CH_2Cl_2 and washed with saturated citric acid solution, saturated $NaHCO_3$ solution, and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:7) to give ketone **22** (35 mg, 65%) as a thick syrup: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.11 (d, J = 15.8 Hz, 1H), 6.67 (d, J = 15.8 Hz, 1H), 5.43−5.37 (m, 2H), 4.63 (s, 2H), 4.23−4.16 (m, 1H), 3.80 (s, 3H), 3.79−3.75 (m, 1H), 3.36 (s, 3H), 3.14 (q, J = 8.8 Hz, 1H), 2.76−2.64 (m, 1H), 2.26 (ddd, J = 13.9, 8.0, 5.9 Hz, 1H), 2.11−1.95 (m, 4H), 1.64−1.55 (m, 1H), 1.45−1.26 (m, 4H), 1.10 (d, J = 6.1 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.9, 166.0, 139.5, 132.3, 131.5, 130.6, 95.4, 77.2, 68.5, 55.4, 54.6, 52.3, 44.8, 40.2, 39.2, 36.1, 32.3, 25.9, 25.4, 23.8, 18.1, −4.4, −4.7; IR (neat) 1732 cm^{-1}; $[\alpha]^{18}_D = -23.0$ (c = 0.10, CH_3OH); HRMS (CI) calcd for $C_{25}H_{45}O_6Si$ (MH^+) 469.2985, found 469.2987.

(2*E*)-4-[(1*R*,2*S*,4*S*)-2-[(1*E*,6*S*)-6-Hydroxyhept-1-enyl]-4-methoxymethoxycyclopentyl]-4-oxobut-2-enoic Acid (23). (1) Removal of Silyl Group. A mixture of ketone **22** (16.0 mg, 0.034 mmol) and PPTS (17 mg, 0.068 mmol) in ethanol (4 mL) was stirred for 10 h at 50 °C. The mixture was diluted with EtOAc and washed with water. The aqueous layer was reextracted with EtOAc. The combined organic layers were washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 2:3) to give the hydroxy ester (12.0 mg, 97%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.12 (d, J = 15.9 Hz, 1H), 6.68 (d, J = 15.9 Hz, 1H), 5.48−5.38 (m, 2H), 4.63 (s, 2H), 4.21−4.17 (m, 1H), 3.81 (s, 3H), 3.80−3.75 (m, 1H), 3.36 (s, 3H), 3.14 (q, J = 8.8 Hz, 1H), 2.66 (quintet, J = 8.1 Hz, 1H), 2.25 (ddd, J = 13.8, 7.9, 5.8 Hz, 1H), 2.12−2.07 (m, 1H), 2.02−1.97 (m, 3H), 1.62−1.55 (m, 1H), 1.48−1.32 (m, 3H), 1.17 (d, J = 6.2 Hz, 3H), 0.89−0.80 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.8, 166.1, 139.6, 132.8, 131.4, 130.5, 95.3, 77.2, 67.9, 55.4, 54.6, 52.4, 45.1, 40.3, 38.8, 35.8, 32.2, 25.5, 23.4; IR (neat) 3439, 1730 cm^{-1}; $[\alpha]^{18}_D = -39.0$ (c = 0.10, CH_3OH); HRMS (EI) calcd for $C_{18}H_{27}O_5$ ($M^+ - OMe$) 323.1859, found 323.1861.

(2) Saponification. A mixture of the above hydroxy ester (12.0 mg, 0.03 mmol) and LiOH (4 mg, 0.17 mmol) in 50% aqueous THF (2.0 mL) was stirred for 20 min at 5 °C. The mixture was acidified with *d*-HCl (pH 1−2) and diluted with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated at reduced pressure to afford crude hydroxy acid **23** (10.9 mg, 95%) as a thick syrup that was subjected to the next step without further purification. An analytical sample of **23** was obtained by column chromatography on silica gel (MeOH/$CHCl_3$, 3:7). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.76 (d, J = 15.8 Hz, 1H), 6.64 (d, J = 15.7 Hz, 1H), 5.41 (dd, J = 15.2, 8.2 Hz, 1H), 5.33 (ddd, J = 15.0, 6.5, 6.5 Hz, 1H), 4.61 (s, 2H), 4.20−4.15 (m, 1H), 3.76−3.72 (m, 1H), 3.34 (s, 3H), 3.21−3.14 (m, 1H), 3.05 (br s, 1H), 2.52 (quintet, J = 8.5 Hz, 1H), 2.21 (ddd, J = 13.7, 7.8, 5.9 Hz, 1H), 2.10−2.05 (m, 1H), 1.97−1.93 (m, 2H), 1.88−1.83 (m, 1H), 1.55 (ddd, J = 13.6, 8.9, 5.1 Hz, 1H), 1.42−1.19 (m, 3H), 1.11 (d, J = 6.1 Hz, 3H), 0.90−0.80 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.8, 173.1, 139.1, 136.2, 133.2, 131.1, 95.2, 77.2, 67.6, 55.3, 53.4, 46.2, 40.5, 38.2, 35.8, 31.9, 25.3, 23.0; IR (neat) 3376, 1738, 1042 cm^{-1}; $[\alpha]^{18}_D = -23$ (c = 0.10, CH_3OH).

Lactone 20 from Hydroxy Acid 23. To a solution of crude hydroxy acid **23** (10.9 mg, 0.032 mmol) in THF (0.5 mL) were added Et_3N (0.0059 mL, 0.04 mmol) and 2,4,6-trichlorobenzoyl chloride (0.0055 mL, 0.035 mmol). After 3 h at room temperature, the mixture was diluted with dry toluene (11 mL) and was added slowly over 3 h to a refluxing solution of DMAP (20 mg, 0.16 mmol) in dry toluene (2 mL). The reaction mixture was refluxed for 14 h, and the solvent was removed at reduced pressure. The residue was dissolved in EtOAc, and the solution was washed with aqueous citric acid solution and saturated $NaHCO_3$ solution. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to give lactone **20** (5.5 mg, 53%) as a thick syrup.

(+)-Brefeldin A (1). (1) $NaBH_4$ Reduction of Carbonyl Group. To a solution of ketone **20** (14.8 mg, 0.046 mmol) in methanol (3 mL) was added $NaBH_4$ (5 mg, 0.13 mmol) at −78 °C. After 30 min at the same temperature, acetone (0.2 mL) was added and the mixture warmed to room temperature. The mixture was diluted with EtOAc and washed with water, saturated $NaHCO_3$ solution, and brine. The organic layer was dried over $MgSO_4$ and concentrated at reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 2:3) to give the alcohol (12.7 mg, 85%) as a thick syrup: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35 (dd, J = 15.7, 3.1 Hz, 1H), 5.91 (dd, J = 15.7, 1.9 Hz, 1H), 5.71 (ddd, J = 15.1, 10.4, 4.6 Hz, 1H), 5.25 (dd, J = 15.1, 9.6 Hz, 1H), 4.89−4.82 (m, 1H), 4.63 (s, 2H), 4.15−4.08 (m, 2H), 3.36 (s, 3H), 2.32 (quintet, J = 8.7 Hz, 1H), 2.20−2.12 (m, 2H), 2.05−1.99 (m, 1H), 1.89−1.71 (m, 5H), 1.59−1.49 (m, 2H), 1.26 (d, J = 6.3 Hz, 3H), 0.97−0.88 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.16, 151.45, 136.26, 130.55, 117.59, 95.16, 77.21, 75.97, 71.12, 55.33, 51.83, 43.99, 40.61, 38.18, 34.07, 31.82, 26.72, 20.88; IR (neat) 3412, 1713 cm^{-1}; $[\alpha]^{18}_D = +62.2$ (c = 0.50, CH_3OH); HRMS (EI) calcd for $C_{18}H_{28}O_5$ (M^+) 324.1945, found 324.1937.

(2) Removal of MOM Group. To a solution of the above alcohol (18.0 mg, 0.056 mmol) in dry CH_2Cl_2 (5.0 mL) were added $BF_3{\cdot}Et_2O$ (0.035 mL, 0.28 mmol) and thiophenol (0.029 mL, 0.28 mmol) at room temperature. The reaction mixture was stirred for 30 min at 20 °C and concentrated at reduced pressure. The resulting residue was purified by column chromatography on silica gel (EtOAc), followed by recrystallization (EtOAc), to afford (+)-brefeldin A (**1**) (14.8 mg, 95%) as white crystals: ^{1}H NMR (CD_3OD, 500 MHz) δ 7.35 (dd, J = 15.7, 3.1 Hz, 1H), 5.73 (dd, J = 15.6, 2.0 Hz, 1H), 5.65 (ddd, J = 15.1, 10.3, 4.7 Hz, 1H), 5.18 (dd, J = 15.2, 9.6 Hz, 1H), 4.73−4.67 (m, 1H), 4.11 (quintet, J = 5.2 Hz, 1H), 3.93 (ddd, J = 9.6, 3.0, 2.0 Hz, 1H), 2.29 (quintet, J = 8.6 Hz, 1H), 2.03 (ddd, J = 13.4, 8.4, 5.2 Hz, 1H), 1.94−1.88 (m, 2H), 1.80−1.63 (m, 5H), 1.52−1.45 (m, 1H), 1.34 (dddd, J = 13.4, 7.9, 5.4, 1.3 Hz, 1H), 1.14 (d, J = 6.2 Hz, 3H), 0.85−0.78 (m, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 168.4, 155.1, 138.1, 131.4, 117.8, 76.6, 73.2, 73.0, 53.2, 45.5, 44.1, 41.9, 35.0, 33.0, 28.0, 21.1; IR (KBr) 3367, 1713 cm^{-1}; mp 203−204 °C; $[\alpha]^{18}_D = +92.2$ (c = 0.10, CH_3OH); HRMS (EI) calcd for $C_{16}H_{24}O_4$ (M^+) 280.1675, found 280.1663.

Acknowledgment. This research was supported by KMOE (BSRI-97-3420), the Ministry of Health and Welfare (HMP-00-CD-02-0004), and 2001 BK21 Project for Medicine, Dentistry and Pharmacy.

Supporting Information Available: Copies of the ^{1}H NMR spectra for **1**, **4**, **5**, **18**, **20**, and **23** and ^{13}C NMR spectra for **1**, **4**, **5**, **11**, **16**, silyl ether of **17**, **18**, **20**, **21**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO010743I