TOTAL SYNTHESIS OF (8'*R*)- AND (8'*S*)-COROSSOLINE[1]

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Abstract - A convergent stereoselective total synthesis of (8'*R*)- and (8'*S*)-corossoline (**1**) has been performed *via* a multi-step process. Comparison of the mp, $[\alpha]_D$, ir and nmr data of both synthetic materials with those reported for natural corossoline did not allow for the strict determination of the configuration at the *C*-8' hydroxyl group of **1**. However, a slight chemical shift difference at the *C*-8' methine proton was observed in the ^{1}H-nmr spectra of the corresponding tris-MTPA esters of synthetic (8'*R*)- and (8'*S*)-**1**, indicating that if the tris-MTPA ester of natural **1** is available, the stereochemistry at the C-8' hydroxyl group of corossoline will be established.

The Annonaceous acetogenins, that have been isolated from a number of plants of the *Annonaceae*, have attracted much attention due to potent cytotoxic, antitumor, pesticidal, antifeedant, antiparasitic, immunosuppressive activities.[2] More than 200 compounds belonging to this family have been reported since isolation of the first in 1982.[3] Most of them possess one or more tetrahydrofuran rings, together with an α, β-unsaturated γ-lactone part on a *C*-35 or *C*-37 carbon chain.[2] Their unique structural features and their broad spectrum of potent biological activities make them an attractive target for total synthesis.[4] Corossoline (**1**), a monotetrahydrofuranyl acetogenin was isolated from the seeds of *Annona muricata* in 1991.[5] Its absolute stereochemistry except for the *C*-8' position was deduced by applying new Mosher's methodology to the monotetrahydrofuranyl annonaceous acetogenin analogs such as reticulatacin[6] and by

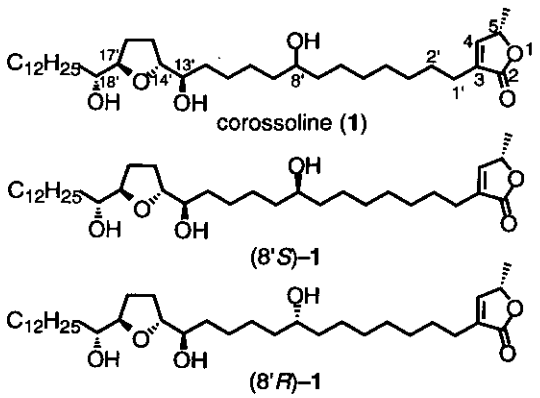
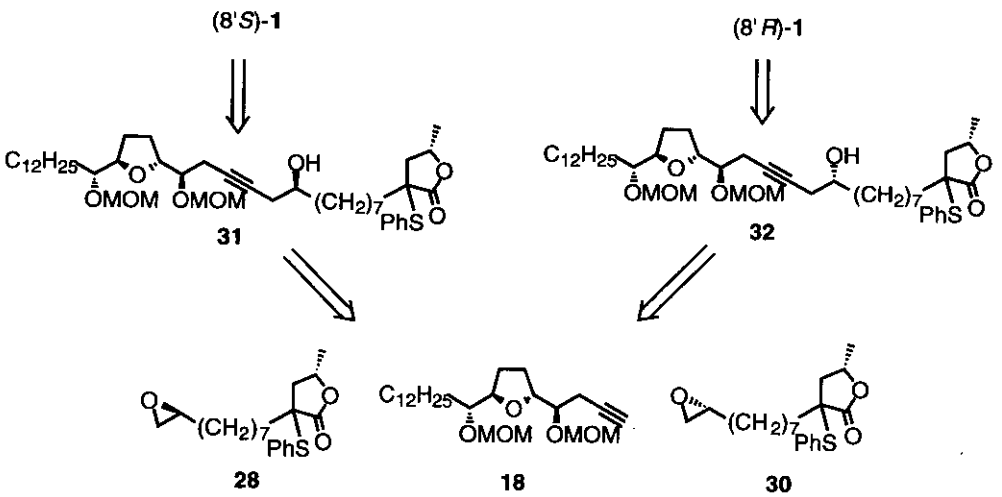


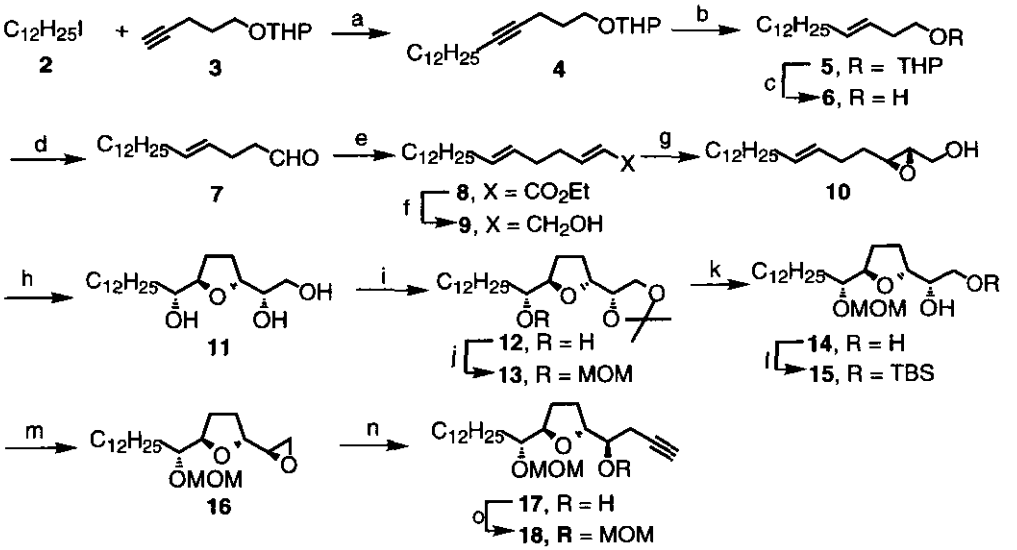
Fig. 1



Scheme 1

a total synthesis of (8'*RS*)-corossoline by Chinese group.[7] Thus, the absolute configuration of corossoline is (5*S*, 8'*R*, 13'*R*, 14'*R*, 17'*R*, 18'*R*) or (5*S*, 8'*S*, 13'*R*, 14'*R*, 17'*R*, 18'*R*). Here, we report a total synthesis of two possible diastereoisomers (8'*R*)- and (8'*S*)-**1** to confirm the stereochemistry at the *C*-8' hydroxyl group. Our synthetic strategy is outlined in Scheme 1.

As shown in Scheme 2, the tetrahydrofuran part **18** of **1** was constructed *via* a multi-step process starting from 1-iodododecane (**2**) and 5-(tetrahydro-2-pyranyloxy)pentyne (**3**). Base-promoted alkylation of **3** with **2** gave **4**, which on reduction with Na in liquid ammonia led to (*E*)-olefinic ether (**5**).[8] After removal of the tetrahydropyranyl (THP) group of **5** with *p*-TsOH and subsequent Swern oxidation, the resultant aldehyde (**7**) underwent Horner-Emmons reaction with triethyl phosphonoacetate to the chain-extended ester (**8**), which was then submitted to reduction with diisobutylaluminum hydride (DIBALH) to afford



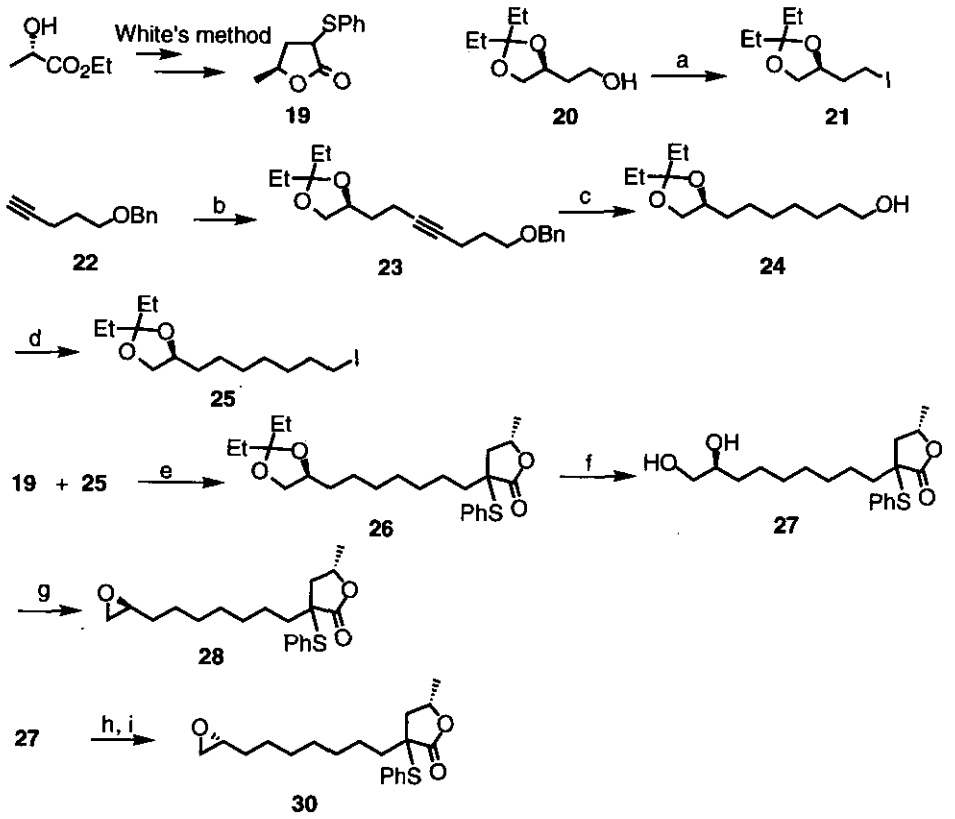
Scheme 2

Reagents and conditions: a) *n*-BuLi, THF–HMPA, 68%. b) Na/NH_3, *t*-BuOH, THF, 94%. c) *p*-TsOH/MeOH, 94%. d) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, 80%. e) triethyl phosphonoacetate, NaH, THF, 86%. f) DIBALH, CH_2Cl_2, 95%. g) i: $Ti(Oi\text{-}Pr)_4$, L–(+)–DET, TBHP, CH_2Cl_2, 94% (96%ee), ii: recrystallization, 80% (>99%ee). h) i: AD mix β, *t*-BuOH–H_2O. ii: CSA, CH_2Cl_2, 92% (96%de). iii: recrystallization, 85%(>99%de). i) 2,2–dimethoxypropane, *p*-TsOH, 95%. j) MOMCl, i-Pr_2NEt, CH_2Cl_2, 99%. k) 60%AcOH, 96%. l) TBSCl, Et_3N, DMAP, CH_2Cl_2, 97%. m) i: MsCl, Et_3N, CH_2Cl_2 ii: TBAF, THF iii:15%NaOH, THF, 85%. n) i: trimethylsilylacetylene, *n*-BuLi, $BF_3{\bullet}Et_2O$, THF, ii: TBAF, 85%. o) MOMCl, i-Pr_2NEt, CH_2Cl_2, 96%.

(*E*)-allylic alcohol (**9**). At this stage, four asymmetric centers were introduced by a consecutive sequence consisting of Sharpless asymmetric epoxidation and dihydroxylation procedures. Asymmetric epoxidation[9] of compound (**9**) with *L*-(+)-diethyl tartrate gave epoxy alcohol (**10**), which showed a 96% ee by a ^{1}H-nmr analysis of the corresponding Mosher ester derivative. Recrystallization of this sample from hexane gave enantiomerically pure **10**. Asymmetric dihydroxylation with AD-mixβ [10] and subsequent acid-catalyzed cyclization with camphorsulfonic acid (CSA) resulted in tetrahydrofuran ring-containing building block (**11**). The diastereomeric purity of this material proved to be a 96% de based on a ^{1}H-nmr analysis of the corresponding Mosher ester after conversion of **11** to acetonide (**12**). Recrystallization of **11** from AcOEt gave diastereomerically pure **11**. The secondary hydroxyl moiety of **12** was protected as a methoxymethyl (MOM) ether to afford **13**. Selective deprotection of the acetonide group of **13** with 60% AcOH was followed by silylation of the primary hydroxyl group of **14** to **15** with *t*-butyldimethylchlorosilane (TBSCl), Et_3N, and 4-dimethylaminopyridine (DMAP). Successive treatment with methanesulfonyl chloride (MsCl), tetrabutylammonium fluoride (TBAF) and 15% aq. NaOH furnished terminal

epoxide (**16**). Coupling reaction with lithium (trimethylsilyl)acetylide in the presence of boron trifluoride etherate[11] and subsequent treatment with TBAF afforded alkyne (**18**), after protection of the resulting hydroxyl group of **17** as a MOM ether.

As shown in Scheme 3, the γ-lactone parts (**28**) and (**30**) of (8'*S*)- and (8'*R*)-**1** were constructed as follows.

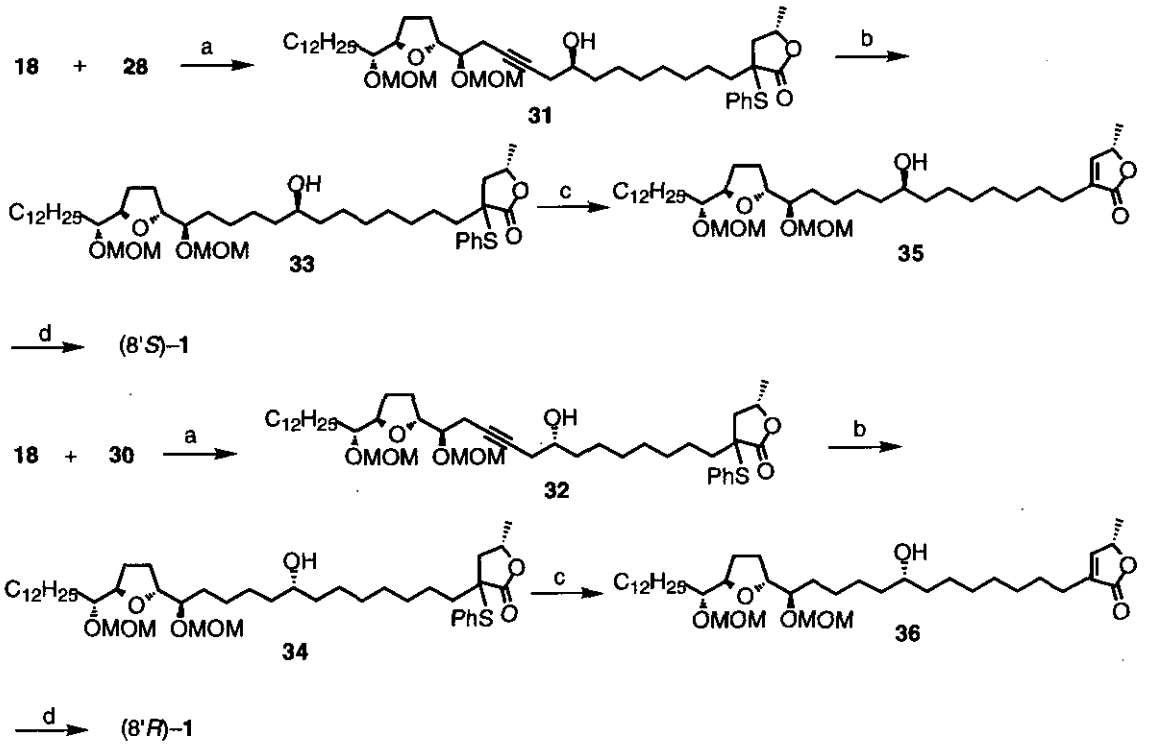


Scheme 3

Reagents and conditions : a) i: *p*-TsCl, pyridine ii: NaI, $NaHCO_3$, acetone, 87%. b) **21**, *n*-BuLi, THF–HMPA, 59%. c) H_2, 10%Pd–C, AcOEt, 96%. d) i: *p*-TsCl, pyridine ii: NaI, $NaHCO_3$, acetone, 91%. e) NaHMDS, THF–HMPA, 88%. f) *p*-TsOH, MeOH, 99%. g) i: *p*-TsCl, pyridine ii: powdered KOH, THF, 69%. h) TBSCl, Et_3N, DMAP, CH_2Cl_2, 82%. i) i: MsCl, Et_3N, CH_2Cl_2 ii: HF MeCN, iii: NaH, THF, 47%.

The substituted γ-lactone (**19**) was prepared by White's method,[12] starting from (*S*)-(-)-ethyl lactate. The synthon (**25**) corresponding to terminal epoxide part of **28** and **30** was prepared from 5-benzyloxy-1-pentyne (**22**) and (*S*)-[3,4-(1-ethylpropylidene)dioxy]-1-iodobutane (**21**), which had been derived from alcohol (**20**)[13] *via* a two-step process. Thus, base-promoted alkylation of **22** with **21** afforded **23**, which

on hydrogenation over 10% Pd-C underwent saturation of the triple bond and hydrogenolysis of the benzyl group to give **24**. Transformation of **24** into iodide (**25**) was effected in two steps through tosylate. Iodide (**25**) thus obtained was then subjected to alkylation with the sodium enolate of **19** to afford **26** in good yield.[14] The following three-step reactions leading to the requisite terminal epoxide (**28**) was effected *via* hydrolysis of the acetonide group of **26**, selective tosylation of the primary hydroxyl group of **27** and oxirane ring closure with powdered KOH. Transformation of **27** into another target molecule (**30**) was carried out as follows. Selective protection of the primary hydroxyl group of **27** with TBSCl was followed by formation of the sulfonate with MsCl, desilylation with aq. HF and epoxy ring closure with NaH to **30**.



Scheme 4

Reagents and conditions: a) *n*-BuLi, BF_3•Et_2O, THF, 92% (99%). b) H_2, $Rh(PPh_3)_3Cl$, benzene, 92% (99%). c) i:*m*CPBA, CH_2Cl_2 ii: toluene, reflux, 87%. d) BF_3•Et_2O, dimethyl sulfide, 98%. [Yields in parentheses are for (8'*R*)–series]

As shown in Scheme 4, completion of the carbon skeleton to give the coupled products (**31**) and (**32**) was achieved by the application of Wu's method.[7] Coupling reaction between the lithium salt of **18** and **28** (or **30**) in the presence of boron trifloride etherate afforded **31** (or **32**), which was converted to saturated product **33** (or **34**) by catalytic hydrogenation of **31** (or **32**) using Wilkinson's catalyst. Oxidation with

*m*CPBA followed by thermal elimination afforded **35** (or **36**). Finally, deprotection of the MOM group with boron trifloride etherate in the presence of dimethyl sulfide[15] gave (8'*S*)- and (8'*R*)-**1**. Their ir and ^{1}H-nmr spectral data were almost consistent with those reported for natural **1** by French group, and the optical rotation values (+22.2° and +21.0°) of (8'*S*)-and (8'*R*)-**1** were also very close to that of natural **1** (+19°), whereas the melting point data [56.5-58°C for (8'*S*)-**1** and 66-69°C for (8'*R*)-**1**] were considerably different from that (45-50°C) of natural **1**. Very recently, C.-J. Chang *et al*. isolated corossoline possessing the mp of 62°C and the $[\alpha]_D$ of +64° from *Goniothalamus amuyon*.[15] This indicated the difficulty of strictly determining the stereochemistry at the *C*-8' position of natural corossoline by comparison of the data accessible from natural and synthetic **1**. However, the ^{1}H-nmr spectra of the corresponding tris-(*S*)-MTPA esters of synthetic (8'*R*)- and (8'*S*)-**1** showed a slight chemical shift difference for the *C*-8' methine proton. Thus, the *C*-8' proton of 8'*R* ester resonated at higher field (0.04ppm) relative to that of 8'*S* ester. This indicated that if the tris-(*S*)-MTPA ester of natural **1** is available, the stereochemistry of corossoline will be established.

EXPERIMENTAL

All melting points (mp) are uncorrected. Optical rotation was measured with a JASCO DIP-4 spectrometer. Ir spectra were taken with a JASCO ir-810 infrared spectrophotometer. ^{1}H- and ^{13}C-nmr spectra were measured with JEOL GSX-270 (270 MHz) and GSX-400 (400 MHz) spectrometers. Ms spectra were recorded with a JEOL JMS-HX-105 and JMS-DX-303 instruments.

1-(Tetrahydro-2-pyranyloxy)-4-heptadecyne (4). To a solution of 5-(tetrahydro-2-pyranyloxy)-4-pentyne (**3**) (3.34 g, 20 mmol) in THF (20 ml) was added *n*-BuLi (1.56 M solution in hexane, 12.8 ml) at -40°C. After stirring for 40 min at 0°C, 1-iodododecane (**2**) (6.51 g, 22 mmol) in HMPA (10 ml) was added to the mixture over 1 h. The mixture was stirred for 1 h at 0°C and then for 1 h at room temperature. The reaction mixture was quenched with sat. aq. NH_4Cl and extracted with ether. The extract was washed with brine and dried over $MgSO_4$. After removal of the solvents, the residue was purified by silica gel column chromatography, eluted with hexane-AcOEt (20:1) to give compound (**4**) (4.57 g, 68%) as a colorless oil. Ir (film) ν_{max} cm^{-1}: 2930, 2850, 1470, 1460, 1205, 1120, 1140, 1040. ^{1}H-Nmr ($CDCl_3$) δ: 0.88 (3H, t, J = 6.6 Hz), 1.25-1.90 (28H, m), 2.13 (2H, tt, J = 7.0, 2.2 Hz), 2.27 (2H, tt,

J = 7.0, 2.2 Hz), 3.50 (2H, m), 3.82 (2H, m), 4.60 (1H, dd, J = 3.9, 2.7 Hz). *Anal.* Calcd for $C_{22}H_{40}O_2$: C, 78.51; H, 11.98. Found: C, 78.21; H, 11.75.

(*E*)-1-(Tetrahydro-2-pyranyloxy)-4-heptadecene (5). Anhydrous liq. ammonia (100 ml) was condensed in a 300 ml four-necked flask. Sodium metal (1.5 g, 65 mmol) was added, producing a deep blue color. THF (20 ml) and dry *t*-BuOH (6 ml) followed by a solution of **4** (3.7 g, 11 mmol) in THF (10 ml) were added. After being stirred for 8 h at -40°C, the reaction mixture was quenched with NH_4Cl. The mixture was extracted with ether and the extract was washed with brine. Drying over $MgSO_4$ and concentration gave crude **5**, which was purified by silica gel chromatography, eluted with hexane-AcOEt (20:1) to give compound (**5**) (3.50 g, 94%) as a colorless oil. Ir (film) ν_{max} cm^{-1}: 3020, 2930, 2850, 1465, 1455, 1200, 1140, 1120, 1035, 965. ^{1}H-Nmr ($CDCl_3$) δ: 0.88 (3H, t, J = 6.7 Hz), 1.25-1.90 (28H, m), 1.97 (2H, m), 2.05 (2H, m), 3.37 (1H, m), 3.40 (1H, m), 3.72 (1H, m), 3.87 (1H, m), 4.58 (1H, dd, J = 2.9, 2.9 Hz), 5.41 (2H, m). *Anal.* Calcd for $C_{22}H_{42}O_2$: C, 78.04; H, 12.50. Found: C, 77.82; H, 12.04.

(*E*)-4-Heptadecen-1-ol (6). To a solution of **5** (3.00 g, 8.9 mmol) in MeOH (20 ml) was added *p*-TsOH (10 mg). After the mixture had been stirred for 6 h, the solvent was evaporated and the crude product was chromatographed over silica gel with hexane-AcOEt (10:1 ~ 5:1) as eluent to give compound (**6**) (2.13 g, 94%) as a colorless oil. Ir (film) ν_{max} cm^{-1}: 3350, 3020, 2930, 2850, 1465, 1460, 1060, 965. ^{1}H-Nmr ($CDCl_3$) δ: 0.88 (3H, t, J = 6.5 Hz), 1.20-1.40 (21H, m), 1.62 (2H, m), 1.97 (2H, m), 2.07 (2H, m), 3.66 (2H, dt, J = 5.4, 6.6 Hz), 5.43 (2H, m). *Anal.* Calcd for $C_{17}H_{34}O$: C, 80.24; H, 13.47. Found: C, 79.86; H, 13.68.

(*E*)-4-Heptadecenal (7). A solution of alcohol **6** (1.27 g, 5.0 mmol) in CH_2Cl_2 (15 ml) was added dropwise to a mixture of oxalyl chloride (0.87 ml, 10 ml) and DMSO (0.94 ml, 13.3 mmol) in CH_2Cl_2 (20 ml) at -78°C over 30 min. After 40 min, Et_3N (5.21 ml, 36.5 mmol) was added slowly and the temperature was raised to 0°C. The reaction mixture was quenched with sat. aq. NH_4Cl and extracted with ether. Drying over $MgSO_4$ and evaporation of the solvent gave crude aldehyde (**7**) (1.01 g, 80%), which was taken to the next step without purification. Ir (film) ν_{max} cm^{-1}: 3020, 2930, 2850, 2720, 1730, 1460, 970. ^{1}H-Nmr ($CDCl_3$) δ: 0.88 (3H, t, J = 6.9 Hz), 1.20-1.40 (20H, m), 1.96 (2H, m), 2.34 (2H, m),

2.49 (2H, m), 5.43 (2H, m), 9.76 (1H, s).

(2*E*,6*E*)-Ethyl Nonadeca-2,6-dienoate (8). To a suspension of NaH (60% in mineral oil, 400 mg, 10 mmol) in THF (20 ml) was added triethyl phosphonoacetate (2.24 g, 10 mmol) at 0°C. The mixture was stirred for 30 min at 0°C and then for 1 h at room temperature. The mixture was cooled to -78°C, and a solution of aldehyde (**7**) (1.51 g, 6 mmol) in THF (5 ml) was then added. After being stirred for 2 h, the reaction mixture was quenched with sat. aq. NH_4Cl. The mixture was extracted with ether, the ethereal solution being washed with brine and dried over $MgSO_4$ and concentrated. Silica gel column chromatography of the residue (hexane-AcOEt = 20:1) gave **8** (1.67 g, 86%) as a colorless oil. Ir (film) ν_{max} cm^{-1}: 2930, 2850, 1725, 1655, 1260, 1145, 970. ^{1}H-Nmr ($CDCl_3$) δ: 0.88 (3H, t, *J* = 6.7 Hz), 1.20-1.40 (23H, m), 1.97 (2H, m), 2.16 (2H, m), 2.25 (2H, m), 4.17 (2H, q, *J* = 7.1 Hz), 5.40 (2H, m), 5.82 (1H, dt, *J* = 15.6, 1.5 Hz), 6.96 (1H, dt, *J* = 15.6, 6.7 Hz). *Anal.* Calcd for $C_{21}H_{38}O_2$: C, 78.20; H, 11.88. Found: C, 78.47; H, 12.13.

(2*E*,6*E*)-Nonadeca-2,6-dien-1-ol (9). To a solution of **8** (650 mg, 2.0 mmol) in CH_2Cl_2 (6 ml) cooled to -78°C was added DIBALH (1.0 M solution in hexane, 4 ml). After being stirred for 1 h at this temperature, the reaction mixture was quenched with MeOH (2 ml) and warmed to room temperature. The mixture was filtered through a Celite pad and the filtrate was concentrated. Silica gel column chromatography of the residue (hexane-AcOEt = 10:1 ~ 5:1) gave **9** (0.53 g, 95%) as a colorless solid, mp 34~36°C. Ir (KBr) ν_{max} cm^{-1}: 3350, 3020, 2930, 2850, 1465, 1455, 1165, 965. ^{1}H-Nmr ($CDCl_3$) δ: 0.88 (3H, t, *J* = 6.6 Hz), 1.21 (1H, br OH), 1.22-1.40 (20H, m), 1.97 (2H, m), 2.10 (4H, m), 4.09 (2H, m), 5.40 (2H, m), 5.67 (2H, m). *Anal.* Calcd for $C_{19}H_{36}O$: C, 81.36; H, 12.94. Found: C, 81.00; H, 12.95.

(2*S*,3*S*,6*E*)-2,3-Epoxynonadec-6-en-1-ol (10). To a suspension of $Ti(Oi\text{-}Pr)_4$ (2.12 g, 7.5 mmol) and 4A molecular sieves in CH_2Cl_2 (30 ml) were added *L*-(+)-diethyl tartrate (1.55 g, 7.5 mmol) at -25°C. After stirring for 10 min, a solution of allyl alcohol (**9**) (1.90 g, 6.8 mmol) in CH_2Cl_2 (5 ml) and *t*-butyl hydroperoxide (5.2 M solution in toluene, 2.86 ml) were added to the mixture at the same temperature, stirring being continued for 20 h. The mixture was quenched with a 10% aq. solution of tartaric acid (17 ml), and allowed to warm to room temperature. The mixture was extracted with CH_2Cl_2, the organic layer being washed with water and concentrated. The residue was dissolved in ether (50 ml) and to this solution

was added 1M NaOH (22 ml) at 0°C. After vigorous stirring for 30 min, the mixture was extracted with ether, the ethereal solution being washed with brine and dried over $MgSO_4$ and concentrated. Silica gel column chromatography of the residue (hexane-AcOEt = 6:1) gave **10** as a colorless solid [2.00 g, 94%, 96% ee by a ^{1}H-nmr analysis of the ester derived from (*R*)-(-)-MTPA chloride], which upon recrystallization from hexane gave optically pure **10** (>99% ee) as colorless needles (1.70 g, 80%), mp 69~70°C. $[\alpha]_D^{23}$ -20.0° (*c* 1.14, $CHCl_3$). Ir (KBr) ν_{max} cm^{-1}: 3300, 3150, 2920, 2850, 1460, 960, 870. ^{1}H-Nmr ($CDCl_3$) δ: (3H, t, *J* = 6.6 Hz), 1.20-1.40 (20H, m), 1.60 (1H, br, OH), 1.62 (2H, m), 1.98 (2H, m), 2.15 (2H, m), 2.95 (2H, m), 3.58-3.67 (1H, ddd, *J* = 12.5, 7.3, 4.2 Hz), 3.87-3.95 (1H, ddd, *J* = 12.5, 5.6, 2.4 Hz), 5.41-5.52 (2H, m). *Anal.* Calcd for $C_{19}H_{36}O_2$: C,76.97; H, 12.94. Found: C, 76.72; H, 12.17.

(2*R*,5*R*,1'*S*,1''*R*)-2-(1',2'-Dihydroxyethyl)-5-(1''-hydroxytridecyl)tetrahydrofuran (11) . A solution of **10** (1.49 g, 5.0 mmol) in *t*-BuOH/H_2O (20 ml, 1:1) was added to a mixture of AD-mix β (8.50 g) and methanesulfonamide (0.30 g, 3.2 mmol) in *t*-BuOH/H_2O (50 ml, 1/1) at 0°C. The resulting heterogeneous mixture was stirred for 24 h at 0°C. This reaction mixture was directly extracted with three 50 ml portions of AcOEt. The combined organic extract was washed with half-saturated aq. Na_2SO_3 and dried with $MgSO_4$. Subsequent concentration of the extract gave a colorless solid, which was dissolved in CH_2Cl_2 (30 ml) and to the solution was added camphorsulfonic acid (50 mg) at 0°C. After the mixture had been stirred for 2 h at this temperature, it was treated with sat. aq. $NaHCO_3$ and extracted with AcOEt. The extract was dried with $MgSO_4$ and concentrated to afford crude **11** as a colorless solid [1.45 g, 96% de by a ^{1}H-nmr analysis of the ester derived from (*R*)-(-)-MTPA chloride after conversion to acetonide (**12**)], which upon recrystallization from AcOEt gave optically pure **11** (>99% de) as colorless needles (1.34 g, 85%), mp 108~109°C. $[\alpha]_D^{24}$ +11.0° (*c* 0.20, EtOH). Ir (KBr) ν_{max} cm^{-1}: 3400, 2930, 2850, 1460, 1120, 1030, 880. ^{1}H-Nmr ($CDCl_3$) δ: 0.88 (3H, t, *J* = 6.7 Hz), 1.20-1.70 (22H, m), 1.80-2.10 (4H, m), 2.00 (1H, br OH), 2.26 (1H, br OH), 2.36 (1H, br OH), 3.39 (1H, m), 3.60-4.00 (5H, m). *Anal.* Calcd for $C_{19}H_{38}O_4$: C, 69.04; H, 11.59. Found: C, 69.08; H, 11.86.

(2*R*,5*R*,1'*S*,1''*R*)-2-[1',2'-(1-Methyethylidene)dioxy]-5-(1''-hydroxytridecyl)tetrahydrofuran (12). To a solution of compound (**11**) (140 mg, 0.45 mmol) and 2,2-dimethoxypropane (1.0 ml) was added *p*-TsOH (10 mg). After the mixture had been stirred for 2 h, it was diluted with ether and washed with sat.

aq. $NaHCO_3$ and brine. Drying with $MgSO_4$ and concentration gave crude **12**, which was purified by silica gel column chromatography, eluted with hexane-AcOEt (5:1) to give **12** (156 mg, 95%) as a colorless oil. $[\alpha]_D^{24}$+3.5° (*c* 1.00, $CHCl_3$). Ir (film) ν_{max} cm^{-1}: 3500, 2930, 2850, 1470, 1460, 1380, 1370, 1250, 1210, 1060, 850. ^{1}H-Nmr ($CDCl_3$) δ: 0.88 (3H, t, *J* = 6.6 Hz), 1.20-1.60 (22H, m), 1.35 (3H, s), 1.41 (3H, s), 1.60-2.20 (4H, m), 2.27 (1H, d, *J* = 3.9 Hz, OH), 3.36 (1H, m), 3.77-4.12 (5H, m). *Anal.* Calcd for $C_{22}H_{42}O_4$: C, 71.30; H, 11.42. Found: C, 71.31; H, 11.52.

(2*R*,5*R*,1'*S*,1''*R*)-2-[1',2'-(1-Methylethylidene)dioxy]-5-(1''-methoxymethoxytridecyl)tetrahydrofuran (13). An ice-cooled mixture of **12** (4.64 g, 12.6 mmol) and chloromethyl methyl ether (**CAUTION; carcinogen**) (1.84 ml, 24 mmol) in CH_2Cl_2 (20 ml) was treated with i-Pr_2NEt (4.52 ml, 26 mmol) and the resultant mixture was warmed to room temperature and stirred for 24 h. After completion of the reaction, the reaction mixture was cooled to 0°C and sat. aq. NH_4Cl (10 ml) was added to it. The mixture was extracted with ether and the organic layer was washed with brine. The extract was dried over $MgSO_4$ and concentrated to give crude **13**, which was purified by silica gel column chromatography, eluted with hexane-AcOEt (15:1), to give **13** (5.18 g, 99%) as a colorless oil. $[\alpha]_D^{24}$+16.9° (*c* 1.00, $CHCl_3$). Ir (film) ν_{max} cm^{-1}: 2930, 2850, 1470, 1460, 1380, 1370, 1260, 1215, 1150, 1100, 1060, 1040. ^{1}H-Nmr ($CDCl_3$) δ: 0.88 (3H, t, *J* = 6.5 Hz), 1.20-1.50 (22H, m), 1.35 (3H, s), 1.40 (3H, s), 1.60-2.10 (4H, m), 3.39 (3H, s), 3.45 (1H, m), 3.81-4.11 (5H, m), 4.67 (1H, d, *J* = 6.8 Hz), 4.80 (1H, d, *J* = 6.8 Hz). *Anal.* Calcd for $C_{24}H_{46}O_5$: C, 69.52; H, 11.18. Found: C, 69.62; H, 11.17.

(2*R*,5*R*,1'*S*,1''*R*)-2-(1',2'-Dihydroxyethyl)-5-(1''-methoxymethoxytridecyl)tetrahydrofuran (14). A solution of compound (**13**) (1.64 g, 3.96 mmol) in 60% aq. AcOH (20 ml) was stirred at 60°C . After the mixture had been stirred for 6 h, the solvent was evaporated and the crude product was chromatographed over silica gel with hexane-AcOEt (2:1) as eluent to give compound (**14**) (1.42 g, 96%) as colorless needles, mp 61~61.5°C. $[\alpha]_D^{24}$+24.1° (*c* 1.00, $CHCl_3$). Ir (KBr) ν_{max} cm^{-1}: 3350, 2920, 2850, 1460, 1145, 1060, 1030. ^{1}H-Nmr ($CDCl_3$) δ: 0.88 (3H, t, *J* = 6.7 Hz), 1.20-1.50 (22H, m), 1.60-2.04 (4H, m), 2.28 (1H, br OH), 2.43 (1H, br OH), 3.40 (3H, s), 3.42-4.04 (6H, m), 4.68 (1H, d, *J* = 6.8 Hz), 4.79 (1H, d, *J* = 6.8 Hz). *Anal.* Calcd for $C_{21}H_{42}O_5$: C, 67.34; H, 11.30. Found: C, 67.06; H, 11.17.

(2*R*,5*R*,1'*S*,1''*R*)-2-[2'-(*tert*-Butyldimethylsilyl)oxy-1'-hydroxyethyl]-5-(1''-methoxymethoxytri-

decyl)tetrahydrofuran (15). To a mixture of **14** (265 mg, 0.70 mmol) and Et_3N (0.12 ml, 0.85 mmol) and DMAP (20 mg) was added *t*-butyldimethylchlorosilane (128 mg, 0.80 mmol). After the mixture had been stirred for 12 h, it was diluted with ether and washed with sat. aq. $NaHCO_3$, sat. aq. NH_4Cl and brine. Drying with $MgSO_4$ and concentration gave crude **15**, which was chromatographed over silica gel, eluted with hexane-AcOEt (10:1), to give compound (**15**) (330 mg, 97%) as a colorless oil. $[\alpha]_D^{24}$+16.9°(*c* 1.00, $CHCl_3$). Ir (film) ν_{max} cm^{-1}: 3470, 2920, 2850, 1460, 1250, 1100, 1040, 840, 780. ^{1}H-Nmr ($CDCl_3$) δ: 0.07 (6H, s), 0.90 (12H, br.), 1.20-1.60 (22H, m), 1.60-2.05 (4H, m), 2.45 (1H, d, *J* = 4.2 Hz, OH), 3.40 (3H, s), 3.41-4.01 (6H, m), 4.68 (1H, d, *J* = 6.8 Hz), 4.80 (1H, d, *J* = 6.8 Hz). *Anal.* Calcd for $C_{27}H_{56}O_5Si$: C, 66.34; H, 11.55. Found: C, 66.31; H, 11.26.

(2*R*,5*R*,1'*R*,1''*R*)-2-(1',2'-Epoxyethyl)-5-(1''-methoxymethoxytridecyl)tetrahydrofuran (16). To a mixture of **15** (330 mg, 0.68 mmol) and Et_3N (0.18 ml, 1.28 mmol) in CH_2Cl_2 (3 ml) was added methanesulfonyl chloride (0.075 ml, 0.97 mmol) at -10°C. After the reaction had been completed, the mixture was diluted with ether and washed with 0.1N HCl and brine. Drying with $MgSO_4$ and evaporation provided an oil, which was dissolved in THF (3 ml) and treated with *n*-Bu_4NF (1.0 M solution in THF, 0.75 ml) at 0°C. After the mixture had been stirred for 12 h, 15% aq. NaOH (0.6 ml) was added to it at 0°C. After being stirred in an ice-bath for 30 min and then at room temperature for 5 h, the mixture was diluted with ether and washed with water and brine. Drying with $MgSO_4$ and concentration gave crude **16**. Purification by silica gel column chromatography (hexane-AcOEt = 7:1) gave **16** (205 mg, 85%) as a colorless wax, mp 39~41°C. $[\alpha]_D^{24}$+20.9° (*c* 2.48, $CHCl_3$). Ir (film) ν_{max} cm^{-1}: 2920, 2850, 1460, 1145, 1100, 1040, 910. ^{1}H-Nmr ($CDCl_3$) δ: 0.88 (3H, t, *J* = 6.6 Hz), 1.20-1.55 (22H, m), 1.60-2.10 (4H, m), 2.71 (1H, dd, *J* = 5.1, 2.6 Hz), 2.75 (1H, dd, J = 5.1, 4.2 Hz), 3.00 (1H, ddd, J = 6.8, 4.2, 2.6 Hz), 3.40 (3H, s), 3.45 (1H, m), 3.92 (1H, m), 4.05 (1H, m), 4.68 (1H, d, *J* = 6.8 Hz), 4.79 (1H, d, *J* = 6.8 Hz). *Anal.* Calcd for $C_{21}H_{40}O_4$: C, 70.74; H, 11.31. Found: C, 70.30; H, 11.19.

(2*R*,5*R*,1'*R*,1''*R*)-2-(1'-Hydroxy-3'-butynyl)-5-(1''-methoxymethoxytridecyl)tetrahydrofuran (17). To a solution of trimethylsilylacetylene (1.46 ml, 15 mmol) in THF (15 ml) was added a solution of *n*-BuLi (1.56 M solution in hexane, 9.6 ml) at -78°C. After the mixture had been stirred for 20 min, boron trifluoride etherate (1.84 ml, 15 mol) was added at this temperature and stirred for 30 min. The resulting

mixture was treated with epoxide **16** (2.40 g, 6.7 mmol), then stirred for 2 h, and then quenched by addition of sat. aq. NH_4Cl. The mixture was stirred for 5 min, warmed to room temperature, and extracted with ether. The organic extract was washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in THF (15 ml) and treated with *n*-Bu_4NF (1.0 M solution in THF, 6.9 ml) at 0°C. The mixture was allowed to warm to room temperature and stirred for a further 5 h. After completion of the reaction, the mixture was diluted with ether (50 ml) and washed with water and brine. Drying ($MgSO_4$) and evaporation of the solvent afforded crude **17**, which was chromatographed over silica gel (hexane:AcOEt = 6:1) to afford pure **17** (2.41 g, 85%) as a colorless oil. $[\alpha]_D^{24}$+12.9° (*c* 1.10, $CHCl_3$). Ir (film) ν_{max} cm^{-1}: 3450, 3320, 2930, 2850, 2120, 1460, 1150, 1100, 1040, 920. ^{1}H-Nmr ($CDCl_3$) δ: 0.88 (3H, t, *J* = 7.0 Hz), 1.20-2.00 (26H, m), 2.01 (1H, t, *J* = 2.6 Hz), 2.43 (2H, dd, *J* = 6.2, 2.6 Hz), 2.53 (1H, d, *J* = 5.5 Hz, OH), 3.41 (3H, s), 3.51 (1H, m), 3.63 (1H, m), 4.00 (2H, m), 4.70 (1H, d, *J* = 7.0 Hz), 4.80 (1H, d, *J* = 6.6 Hz). *Anal.* Calcd for $C_{23}H_{42}O_4$: C, 72.21; H, 11.06. Found: C, 71.91; H, 11.08.

(2*R*,5*R*,1'*R*,1''*R*)-2-(1'-Methoxymethoxy-3'-butynyl)-5-(1''-methoxymethoxytridecyl)tetrahydrofuran (18). An ice-cooled mixture of alcohol (**17**) (2.16 g, 5.65 mmol) and chloromethyl methyl ether (**CAUTION; carcinogen**) (0.92 ml, 12.0 mmol) in CH_2Cl_2 (20 ml) was treated with i-Pr_2NEt (2.26 ml, 13.0 mmol) and the resulting mixture was allowed to warm to room temperature and stirred for 25 h. After completion of the reaction, the reaction mixture was cooled to 0°C and sat. aq. NH_4Cl was added to it. The mixture was extracted with ether and the extract was washed with brine, dried with $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (hexane-AcOEt = 15:1) afforded **18** (2.55 g, 96%) as a colorless oil. $[\alpha]_D^{24}$+20.9° (*c* 1.02, $CHCl_3$). Ir (film) ν_{max} cm^{-1}: 3320, 2930, 2850, 2130, 1470, 1150, 1100, 1040, 920. ^{1}H-Nmr ($CDCl_3$) δ: 0.88 (3H, t, *J* = 6.7 Hz), 1.20-1.60 (22H, m), 1.61-1.80 (2H, m), 1.92-2.05 (2H, m), 1.98 (1H, t, *J* = 2.7 Hz), 2.38-2.60 (2H, ddd, *J* = 17.2, 6.0, 2.7 Hz), 3.40 (3H, s), 3.42 (3H, s), 3.47 (1H, m), 3.66 (1H, m), 4.00 (1H, m), 4.16 (1H, m), 4.67 (1H, d, *J* = 6.6 Hz), 4.78 (2H, s), 4.84 (1H, d, *J* = 6.6 Hz). *Anal.* Calcd for $C_{25}H_{46}O_5$: C, 70.38; H, 10.87. Found : C, 70.24; H, 11.22.

(*S*)-1-Iodo-[3,4-(1-ethylpropylidene)dioxy]butane (21). To an ice-cooled solution of (*S*)-3,4-(1-ethylpropylidene)dioxybutan-1-ol (**20**) (5.8 g, 33.3 mmol) in pyridine (20 ml) was added *p*-TsCl (7.6 g, 39.9

mmol). After being stirred in an ice-bath for 1 h and then at room temperature for 5 h, the mixture was extracted with ether. The extract was washed 0.1 N HCl (50 ml) and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was dissolved in acetone (50 ml), and $NaHCO_3$ (13.0 g, 155 mmol) and NaI (12.5 g, 83.4 mmol) were added to the solution. After being stirred for 6 h, the mixture was extracted with ether. The extract was washed with sat. aq. $Na_2S_2O_3$, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-AcOEt = 20:1) to give **21** (8.26 g, 87%) as a colorless oil. $[\alpha]_D^{22}$ -20.6° (*c* 4.61, $CHCl_3$). Ir (film) ν_{max} cm^{-1}: 2975, 2940, 2840, 1460, 1350, 1200, 1170, 1080, 920, 770. ^{1}H-Nmr ($CDCl_3$) δ: 0.89 (3H, t, *J* = 6.7 Hz), 0.90 (3H, t, *J* = 6.7 Hz), 1.62 (4H, m), 2.08 (2H, m), 3.26 (2H, m), 3.52 (1H, dd, *J* = 7.5, 7.5 Hz), 4.10 (1H, dd, *J* = 7.5, 7.5 Hz), 4.15 (1H, m). *Anal.* Calcd for $C_9H_{17}I$: C, 38.04; H, 6.03. Found : C, 38.23; H, 5.89.

(*S*)-8,9-(1-Ethylpropylidene)dioxy-1-benzyloxy-4-nonyne (23). To a solution of 5-benzyloxy-1-pentyne (**22**) (6.50 g, 36.0 mmol) in THF (50 ml) was added *n*-BuLi (1.56 M solution in hexane, 25 ml) at -40°C. After stirring for 40 min at 0°C, **21** (10.0 g, 36 mmol) in HMPA (15 ml) was added to the mixture over 1 h. The mixture was stirred for 1 h at 0°C and then for 1 h at room temperature. The reaction mixture was quenched by addition of sat. aq. NH_4Cl and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-AcOEt = 20:1) to give **23** (6.46 g, 59%) as a colorless oil. $[\alpha]_D^{24}$ -3.9° (*c* 1.48, $CHCl_3$). Ir (film) ν_{max} cm^{-1}: 3060, 3030, 2970, 2930, 2870, 1450, 1200, 1170, 1100, 1080, 920, 730, 695. ^{1}H-Nmr ($CDCl_3$) δ: 0.89 (3H, t, *J* = 6.6 Hz), 0.90 (3H, t, *J* = 6.6 Hz), 1.52-1.84 (8H, m), 2.27 (4H, m), 3.55 (3H, m), 4.04-4.21 (2H, m), 4.51 (2H, s), 7.28-7.35 (5H, m). *Anal.* Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found : C, 76.12; H, 9.36.

(*S*)-8,9-(1-Ethylpropylidene)dioxynonan-1-ol (24). To a solution of **23** (5.46 g, 16.6 mmol) in AcOEt (50 ml) was added 10% Pd-C (540 mg) at room temperature, and the suspension was vigorously stirred under a hydrogen atmosphere. After being stirred for 12 h, the reaction mixture was filtered through a Celite pad and concentrated *in vacuo*. Silica gel column chromatography of the residue (hexane-AcOEt = 5:1) gave **24** (3.90 g, 96%) as a colorless oil. $[\alpha]_D^{24}$+13.8° (*c* 1.00, $CHCl_3$). Ir (film) ν_{max} cm^{-1}: 3400, 2970, 2930, 2850, 1460, 1350, 1200, 1170, 1075, 920. ^{1}H-Nmr ($CDCl_3$) δ: 0.89 (3H, t, *J* = 7.5 Hz), 0.90 (3H,

t, J = 7.5 Hz), 1.24 (1H, br OH), 1.30-1.68 (16H, m), 3.45 (1H, m), 3.63 (2H, m), 4.06 (2H, m). *Anal.* Calcd for $C_{14}H_{28}O_3$: C, 68.81; H, 11.55. Found : C, 69.24; H, 11.40.

(*S*)-1-Iodo-8,9-(1-ethylpropylidene)dioxynonane (25). To an ice-cooled of **24** (2.65 g, 10.8 mmol) in pyridine (15 ml) was added *p*-TsCl (2.54 g, 13.0 mmol). After being stirred for 1 h at 0°C and then for 5 h at room temperature, the mixture was diluted with ether and washed with water, 0.1 N HCl and brine. Drying over $MgSO_4$ and subsequent concentration gave an oil, which was dissolved in acetone (15 ml) and treated with $NaHCO_3$ (4.0 g, 47.6 mmol) and NaI (4.0 g, 25.5 mmol). After being stirred for 8 h, the mixture was extracted with ether and the extract was washed with water, sat. aq. $Na_2S_2O_3$, brine, and dried over $MgSO_4$. Removal of the solvent and silica gel column chromatography (hexane-AcOEt = 20:1) afforded **25** (3.51 g, 91%) as a colorless oil, $[\alpha]_D^{22}$ +9.2° (*c* 1.68, $CHCl_3$). Ir (film) ν_{max} cm^{-1}: 2980, 2940, 2860, 2850, 1460, 1080, 920. ^{1}H-Nmr ($CDCl_3$) δ: 0.89 (3H, t, J = 7.5 Hz), 0.90 (3H, t, J = 7.5 Hz), 1.20-1.87 (16H, m), 3.19 (2H, t, J = 7.1 Hz), 3.45 (1H, m), 4.04 (2H, m). *Anal.* Calcd for $C_{14}H_{27}O_2I$: C, 47.47; H, 7.68. Found : C, 47.83; H, 7.77.

(3*RS*,5*S*,8'*S*)-3-[8',9'-(1-Ethylpropylidene)dioxynonyl]-5-methyl-3-(phenylsulfanyl)tetrahydrofuran-2-one (26). To an ice-cooled solution of lactone (**19**)(1.80 g, 8.97 mmol) in THF (20 ml) was added NaHMDS (0.6 M solution in toluene, 15 ml). After the mixture had been stirred at 0°C for 30 min, **25** (3.18 g, 8.97 mmol) in HMPA (10 ml) was added to it and the whole was allowed to warm to room temperature. The reaction mixture was quenched by addition of sat. aq. NH_4Cl and extracted with ether. Drying over $MgSO_4$ and subsequent concentration gave crude **26**, which was chromatographed over silica gel (hexane-AcOEt = 10:1) to afford pure **26** (3.42 g, 88%) as a colorless oil. Ir (film) ν_{max} cm^{-1}: 3050, 2970, 2930, 2850, 1765, 1460, 1440, 1340, 1180, 1175, 920, 750, 695. ^{1}H-Nmr ($CDCl_3$) δ: 0.89 (3H, t, J = 6.5 Hz), 0.90 (3H, t, J = 6.5 Hz), 1.19 (2.4 H, d, J = 6.2 Hz), 1.38 (0.6H, d, J = 6.2 Hz), 1.23-1.83 (18H, m), 1.98 (1H, m), 2.35 (0.2H, dd, J = 13.9, 5.5 Hz), 2.45 (1H, m), 2.50 (0.8H, dd, J = 13.9, 7.7 Hz), 4.05 (2H, m), 4.48 (0.8H, m), 4.52 (0.2H, m), 7.35 (3H, m), 7.54 (2H, m). *Anal.* Calcd for $C_{25}H_{38}O_4S$: C, 69.09; H, 8.81. Found: C, 69.22; H, 8.58.

(3*RS*,5*S*,8'*S*)-3-(8',9'-Dihydroxy)nonyl-5-methyl-3-(phenylsulfanyl)tetrahydrofuran-2-one (27).

To a solution of **26** (900 mg, 2.07 mmol) in MeOH (10 ml) was added *p*-TsOH (50 mg). After the mixture had been stirred for 48 h, the solvent was evaporated. The residue was purified by silica gel column chromatography (hexane-AcOEt = 2:1~1:1) to afford **27** (721 mg, 99%) as a colorless oil. Ir (film) ν_{max} cm^{-1}: 3400, 3060, 2940, 2850, 1760, 1460, 1440, 1340, 1190, 1070, 750, 695. ^{1}H-Nmr ($CDCl_3$) δ:1.19 (2.4H, d, *J* = 6.2 Hz), 1.37 (0.6H, d, *J* = 6.2 Hz), 1.25-1.81 (14H, m), 1.98 (1H, m), 1.90 (1H, br OH), 2.10 (1H, br OH), 2.35 (0.2H, dd, *J* = 13.8, 5.5 Hz), 2.50 (0.8H, dd, *J* = 13.9, 7.6 Hz), 3.43 (1H, m), 3.63 (2H, m), 4.47 (0.8H, m), 4.57 (0.2H, m), 7.35 (3H, m), 7.54 (2H, m). HREIms (M^+). Found: 366.1848. Calcd for $C_{20}H_{30}O_4S$: 366.1865.

(3*RS*,5*S*,8'*S*)-3-(8',9'-Epoxynonyl)-5-methyl-3-(phenylsulfanyl)tetrahydrofuran-2-one (28). To an ice-cooled solution of **27** (1.00 g, 2.74 mmol) in pyridine (10 ml) was added *p*-TsCl (574 mg, 3.01 mmol). After being stirred in an ice-bath for 1 h and then at room temperature for 5 h, the mixture was extracted with ether. The extract was washed with water, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was dissolved in dry THF (20 ml) and treated with powdered KOH (230 mg, 4.11 mmol) at 0°C. After being stirred for 2 h, the mixture was diluted with ether. The organic layer was washed with water, brine, dried over $MgSO_4$, and concentrated. The resulting residue was purified by silica gel column chromatography (hexane-AcOEt = 8:1) to give **28** (663 mg, 69%) as a colorless oil. Ir (film) ν_{max} cm^{-1}: 3050, 2980, 2850, 1765, 1440, 1340, 1185, 1110, 750, 695. ^{1}H-Nmr ($CDCl_3$) δ: 1.19 (2.4H, d, *J* = 6.2 Hz), 1.38 (0.6H, d, *J* = 6.2 Hz), 1.30-1.83 (14H, m), 1.98 (1H, m), 2.35 (0.2H, dd, *J* = 13.9, 5.5 Hz), 2.46 (1H, dd, *J* = 4.9, 2.7 Hz), 2.50 (0.8H, dd, J = 13.9, 7.7 Hz), 2.75 (1H, dd, J = 4.9, 4.0 Hz), 2.90 (1H, m), 4.47 (0.8H, m), 4.60 (0.2H, m), 7.38 (3H, m), 7.54 (2H, m). *Anal.* Calcd for $C_{20}H_{28}O_3S$: C, 68.93; H, 8.10. Found: C, 68.64; H, 7.99.

(3*RS*,5*S*,8'*S*)-3-(9'-*tert*-Butyldimethylsilyloxy-8'-hydroxy)nonyl-5-methyl-3-(phenylsulfanyl)tetrahydrofuran-2-one (29). To a mixture of **27** (500 mg, 1.37 mmol) in CH_2Cl_2 (10 ml), Et_3N (0.24 ml, 1.70 mmol) and DMAP (50 mg) was added *t*-butyldimethylchlorosilane (256 mg, 1.60 mmol). After the mixture had been stirred for 12 h, it was diluted with ether and washed with sat. aq. $NaHCO_3$, sat. aq. NH_4Cl, and brine. Drying over $MgSO_4$ and subsequent concentration gave crude **29**, which was purified by silica gel column chromatography to give **29** (538 mg, 82%) as a colorless oil. Ir (film) ν_{max} cm^{-1}: 3500,

3150, 2930, 2855, 1765, 1250, 1190, 1100, 840.^{1}H-Nmr ($CDCl_3$) δ: 0.08 (6H, s), 0.90 (9H, s), 1.19 (2.4H, d, J = 6.2 Hz), 1.38 (0.6H, d, J = 6.2 Hz), 1.20-1.81 (14H, m), 1.98 (1H, m), 2.32 (0.2H, dd, J = 13.9, 5.5 Hz), 2.43 (1H, d, J = 3.3 Hz, OH), 2.50 (0.8H, dd, J = 13.9, 7.7 Hz), 3.39 (1H, m), 3.62 (2H, m), 4.48 (0.8H, m), 4.60 (0.2H, m), 7.37 (3H, m), 7.54 (2H, m). *Anal.* Calcd for $C_{26}H_{44}O_4SSi$: C, 64.95; H, 9.22. Found: C, 64.96; H, 9.22.

(3*RS*,5*S*,8'*R*)-3-(8',9'-Epoxy)nonyl-5-methyl-3-(phenylsulfanyl)tetrahydrofuran-2-one (30). To a mixture of **29** (200 mg, 0.42 mmol) and Et_3N (0.1 ml, 0.71 mmol) was added MsCl (0.05 ml, 0.65 mmol) at -10°C. After the reaction had been completed, the mixture was diluted with ether and washed with 0.1 N HCl and brine. Drying over $MgSO_4$ and evaporation of the solvent gave an oil, which was dissolved in MeCN (0.41 ml) and treated with 55% aq. HF (21 μl, 0.58 mmol) at 0°C. After being stirred for 3 h at room temperature, the reaction mixture was quenched with sat. aq. $NaHCO_3$. The mixture was extracted with ether and the organic layer was washed with brine. Drying over $MgSO_4$ and concentration gave an oil, which was dissolved in THF and treated with NaH (20 mg, 60% in mineral oil, 0.50 mmol). After being stirred for 48 h, the reaction mixture was extracted with ether and the extract was washed with water and brine. Drying over $MgSO_4$ and concentration gave an oil, which was purified by silica gel column chromatography (hexane-AcOEt = 8:1) to afford **30** (69 mg, 47%) as a colorless oil. The ir and ^{1}H-nmr spectra were similar to those of **28**. *Anal.* Calcd for $C_{20}H_{28}O_3S$: C, 68.93; H, 8.10. Found: C, 68.72; H, 7.95.

(3*RS*,5*S*,8'*S*,13'*R*,2''*R*,5''*R*,1'''*R*)-3-{8'-Hydroxy-13'-methoxymethoxy-13'-[5''-(1'''-methoxymethoxytridecyl)tetrahydrofuran-2''-yl]tridec-10'-ynyl}-5-methyl-3-(phenylsulfanyl)tetrahydrofuran-2-one (31). To a solution of **18** (2.55 g, 5.4 mmol) in THF (30 ml) was added a solution of *n*-BuLi (1.6 M solution in hexane, 3.4 ml) at -78°C. After the mixture had been stirred for 30 min, boron trifluoride etherate (0.66 ml, 5.4 mmol) was added to the mixture and stirring was continued for further 20 min. Finally, a solution of **28** (0.94 g, 2.7 mmol) was added to the mixture. After the mixture had been stirred for 1 h, the reaction was quenched with sat. aq. NH_4Cl. The organic materials were extracted with ether and the extract was washed with brine. Drying over $MgSO_4$ and evaporation of the solvent gave an oil, which was chromatographed over silica gel (hexane-AcOEt = 3:1) to give **31** (1.93 g, 92%) as a colorless oil. Ir (film) ν_{max} cm^{-1}: 3480, 3120, 2930, 2850, 1765, 1465, 1440, 1180, 1150,

1100, 1035, 920. ^{1}H-Nmr ($CDCl_3$) δ: 0.88 (3H, t, *J* = 6.8 Hz), 1.19 (2.4 H, d, *J* = 6.2 Hz), 1.38 (0.6H, d, *J* = 6.2 Hz), 1.20-2.00 (41H, m), 2.20-2.56 (5H, m), 2.35 (1H, d, *J* = 4.8 Hz, OH), 3.40 (3H, s), 3.41 (3H, s), 3.46 (1H, m), 3.66 (2H, m), 4.01 (1H, m), 4.14 (1H, m), 4.48 (0.8H, m), 4.60 (0.2H, m), 4.66 (1H, d, *J* = 6.6 Hz), 4.75 (1H, d, *J* = 7.0 Hz), 4.79 (1H, d, *J* = 7.0 Hz), 4.87 (1H, d, *J* = 6.6 Hz), 7.38 (3H, m), 7.54 (2H, m). *Anal.* Calcd for $C_{45}H_{74}O_8S$: C, 69.73; H, 9.62. Found: C, 69.42; H, 9.18.

(3*RS*,5*S*,8'R,13'*R*,2''*R*,5''*R*,1'''*R*)-3-{8'-Hydroxy-13'-methoxymethoxy-13'-[5''-(1'''-methoxymethoxytridecyl)tetrahydrofuran-2''-yl]tridec-10'-ynyl}-5-methyl-3-(phenylsulfanyl)tetrahydrofuran-2-one (32). In the same manner as just described, **30** (115 mg, 0.33 mmol) and **18** (306 mg, 0.65 mmol) afforded **32** (253 mg, 99%) as a colorless oil. The ir spectrum was similar to that of **31**. ^{1}H-Nmr ($CDCl_3$) δ: 0.88 (3H, t, *J* = 6.6 Hz), 1.18 (2.4H, d, *J* = 6.2 Hz), 1.38 (0.6H, d, *J* = 6.2 Hz), 1.21-2.00 (41H, m), 2.44 (1H, d, *J* = 4.8 Hz, OH), 2.20-2.54 (5H, m), 3.40 (3H, s), 3.41 (3H, s), 3.46 (1H, m), 3.66 (2H, m), 4.01 (1H, m), 4.14 (1H, m), 4.48 (0.8H, m), 4.60 (0.2H, m), 4.67 (1H, d, *J* = 6.6 Hz), 4.75 (1H, d, *J* = 6.6 Hz), 4.78 (1H, d, *J* = 6.6 Hz), 4.89 (1H, d, *J* = 6.6 Hz), 7.38 (3H, m), 7.54 (2H, m). *Anal.* Calcd for $C_{45}H_{74}O_8S$: C, 69.73; H, 9.62. Found: C, 69.16; H, 9.58.

(3*RS*,5*S*,8'*S*,13'*R*,2''*R*,5''*R*,1'''*R*)-3-{8'-Hydroxy-13'-methoxymethoxy-13'-[5''-(1'''-methoxymethoxytridecyl)tetrahydrofuran-2''-yl]tridecy}-5-methyl-3-(phenylsulfanyl)tetrahydrofuran-2-one (33). A solution of **31** (523 mg, 0.67 mmol) in benzene (5 ml) was hydrogenated over chlorotris-(triphenylphosphine)rhodium (150 mg, 0.16 mmol) for 5 h. Filtration and concentration afforded an oil, which was purified by silica gel column chromatography (hexane-AcOEt = 3:1) to give **33** (480 mg, 92%) as a colorless oil. Ir (film) ν_{max} cm^{-1}: 3500, 3050, 2930, 2850, 1765, 1460, 1440, 1340, 1180, 1150, 1100, 1030, 920, 750, 695. ^{1}H-Nmr ($CDCl_3$) δ: 0.88 (3H, t, *J* = 7.0 Hz), 1.19 (2.4H, d, *J* = 6.2 Hz), 1.37 (0.6H, d, *J* = 6.2 Hz), 1.20-1.99 (49H, m), 2.32 (0.2H, dd, *J* = 13.9, 5.5 Hz), 2.50 (0.8H, dd, *J* = 13.9, 7.3 Hz), 3.39 (6H, s), 3.46 (2H, m), 3.57 (1H, m), 3.98 (2H, m), 4.47 (0.8H, m), 4.60 (0.2H, m), 4.65 (1H, d, *J* =6.6 Hz), 4.66 (1H, d, *J* = 6.6 Hz), 4.83 (1H, d, *J* = 6.6 Hz), 4.84 (1H, d, *J* = 6.6 Hz), 7.38 (3H, m), 7.54 (2H, m). HRFABms ($M+Na^+$). Found: 801.5360. Calcd for $C_{45}H_{78}O_8NaS$: 801.5315.

(3*RS*,5*S*,8'*R*,13'*R*,2''*R*,5''*R*,1'''*R*)-3-{8'-Hydroxy-13'-methoxymethoxy-13'-[5''-(1'''-methoxymethoxytridecyl)tetrahydrofuran-2''-yl]tridecyl}-5-methyl-3-(phenylsulfanyl)tetrahydrofuran-2-one

(34). In the same manner as just described above, **32** (16 mg, 0.021 mmol) afforded **34** (16 mg, 99%) as a colorless oil. The ir and ^{1}H-nmr spectra were similar to those of **33**. HRFABms (M+Na $^+$). Found: 801.5335. Calcd for $C_{45}H_{78}O_8NaS$: 801.5315.

(3*RS*,5*S*,8'*S*,13'*R*,2''*R*,5''*R*,1'''*R*)-3-{8'-Hydroxy-13'-methoxymethoxy-13'-[5''-(1'''-methoxymethoxytridecyl)tetrahydrofuran-2''-yl]tridecyl}-5-methyl-2,5-dihydrofuran-2-one (35). To a solution of **33** (19 mg, 0.024 mmol) in CH_2Cl_2 (0.5 ml) was added *m*CPBA (80%, 5.2 mg, 0.024 mmol) at 0°C. After the mixture had been stirred at this temperature for 10 min, aq. $Na_2S_2O_3$/$NaHCO_3$ (1:1, 1.0 ml) was added. After stirring at room temperature for 1 h, the mixture was extracted with ether and the extract was washed with brine. Drying over $MgSO_4$ and subsequent concentration gave an oil, which was dissolved in toluene (2.0 ml) and the solution was refluxed for 1 h. After completion of the reaction, concentration of the mixture gave an oil, which was purified by silica gel column chromatography (hexane-AcOEt = 2:1) to afford **35** (14 mg, 87%) as a colorless oil. $[\alpha]_D^{22}$+31.4° (*c* 0.14, $CHCl_3$). Ir (film) ν_{max} cm^{-1}: 3500, 2920, 2850, 1755, 1455, 1315, 1145, 1100, 1030, 920. ^{1}H-Nmr ($CDCl_3$) δ: 0.88 (3H, t, *J* = 7.0 Hz), 1.40 (3H, d, *J* = 7.0 Hz), 1.20-1.63 (45H, m), 1.92 (2H, m), 1.95 (1H, br OH), 2.26 (2H, t, *J* = 7.7 Hz), 3.39 (6H, s), 3.46 (2H, m), 3.57 (1H, m), 3.97 (2H, m), 4.66 (2H, d, *J* = 7.0 Hz), 4.83 (1H, d, *J* = 7.0 Hz), 4.84 (1H, d, *J* = 7.0 Hz), 4.99 (1H, dq, *J* = 1.5, 6.6 Hz), 6.98 (1H, d, *J* = 1.5 Hz). HRFABms (M+Na$^+$). Found: 691.5130. Calcd for $C_{39}H_{72}O_8Na$: 691.5125.

(3*RS*,5*S*,8'*R*,13'*R*,2''*R*,5''*R*,1'''*R*)-3-{8'-Hydroxy-13'-methoxymethoxy-13'-[5''-(1'''-methoxymethoxytridecyl)tetrahydrofuran-2''-yl]tridecyl}-5-methyl-2,5-dihydrofuran-2-one (36). In the same manner as just described above, **34** (16 mg, 0.021 mmol) afforded **36** (12 mg, 87%) as a colorless oil. $[\alpha]_D^{22}$+32.5° (*c* 0.16, $CHCl_3$). The ir and ^{1}H-nmr spectra were similar to those of **35**. HRFABms (M+Na$^+$). Found: 691.5146. Calcd for $C_{39}H_{72}O_8Na$: 691.5125.

(8'*S*)-Corossoline [(8'*S*)-1]. Boron trifluoride etherate (0.1 ml, 0.8 mmol) was added dropwise to a solution of **35** (14 mg, 0.021 mmol) in dimethylsulfide (0.7 ml) at 0°C, and the mixture was stirred for 5 min at this temperature. The reaction mixture was quenched with sat. aq. $NaHCO_3$ and diluted with AcOEt. The mixture was washed with water and brine. Drying over $MgSO_4$ and evaporation of the

solvent gave a colorless solid, which was purified by preparative tlc (AcOEt) to give (8'*S*)-**1** (12 mg, 98%) as a colorless solid, mp 56.5~58°C. $[\alpha]_D^{22}$ +22.2° (*c* 0.18, MeOH). Ir (KBr) ν_{max} cm^{-1}: 3400, 2920, 2850, 1750, 1465, 1380, 1320, 1190, 1080. ^{1}H-Nmr ($CDCl_3$) δ: 0.88 (3H, t, *J* = 6.8 Hz), 1.20-1.80 (45H, m), 1.40 (3H, d, *J* = 6.6 Hz), 2.27 (2H, t, *J* = 7.3 Hz), 2.32 (1H, br OH), 2.36 (1H, br OH), 3.40 (2H, m), 3.59 (1H, m), 3.81 (2H, m), 5.00 (1H, dq, *J* = 1.5, 6.6 Hz), 6.98 (1H, d, *J* = 1.5 Hz). ^{13}C-Nmr ($CDCl_3$, 100 MHz) δ: 173.87, 148.89, 134.24, 82.68, 82.62, 77.41, 74.03, 73.84, 71.67, 37.44, 37.32, 33.42, 33.27, 31.89, 29.69-28.73, 27.35, 25.56, 25.53, 25.47, 25.13, 22.66, 19.18, 14.08. HREIms (M^+). Found: 580.4734. Calcd for $C_{35}H_{64}O_6$: 580.4703.

(8'*R*)-Corossoline [(8'*R*)-1]. In the same manner as just described, **36** (12 mg, 0.018 mmol) afforded (8'*R*)-**1** (10 mg, 98 %) as a colorless solid, mp 66~69°C. $[\alpha]_D^{22}$ +21.0° (*c* 0.20, MeOH). The ir, ^{1}H-nmr and ^{13}C-nmr spectra were similar to those of (8' *S*)-**1**. HRFABms ($M+Na^+$). Found: 603.4601. Calcd for $C_{35}H_{64}O_6Na$: 603.4601.

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