Pergamon

Tetrahedron 54 (1998) 6329–6340

TETRAHEDRON

Total Synthesis of (+)-4-Deoxygigantecin

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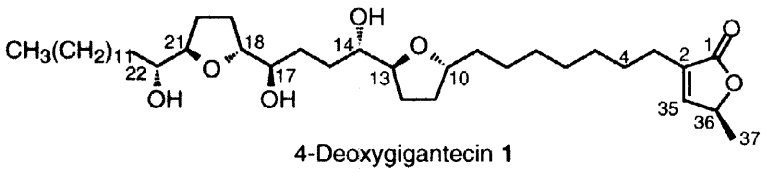
Received 12 February 1998; accepted 25 March 1998

Abstract: A total synthesis of a non-adjacent bis-tetrahydrofuranyl annonaceous acetogenin, (+)-4-deoxygigantecin (**1**) is described. Mono-tetrahydrofuran building block (**10**), of which the synthesis from (-)-muricatacin (**8**) had been described in an earlier report, was converted to bis-MOM ether (**9**) through two-step reactions. Transformation of this compound into non-adjacent bis-tetrahydrofuran unit (**5**) was carried out by a twelve-step sequence of reactions. Pd(0)-catalyzed cross coupling reaction between **5** and iodinated butenolide (**7**), which had been prepared from (*S*)-(-)-ethyl lactate, led to enyne (**4**). Finally, this compound was converted to (+)-4-deoxygigantecin (**1**) by two steps.

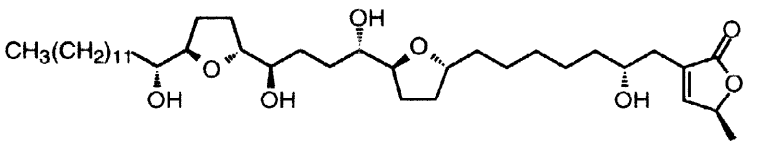
The Annonaceous acetogenins, that are a rapidly growing class of natural products, have been isolated from the limited genera of tropical or subtropical plants *Annonaceae*. These compounds have attracted much attention in recent years because of a wide variety of biological activities and thier unique structures, that are characterized by one or more tetrahydrofuran rings, together with a terminal butenolide moiety on a *C*-35 or *C*-37 carbon chain.[1] Synthetic studies have been focused mainly on the construction of mono- and adjacent bis-tetrahydrofuran ring annonaceous acetogenins to date.[2]

4-Deoxygigantecin (**1**) was isolated from *Goniothalamus giganteus* in 1992 by J. L. McLaughlin *et al.*[3] The absolute stereochemistry of natural 4-deoxygigantecin has not yet been reported. However, we assumed that **1** possessed, except for a *C*-4 carbinol center, the same absolute configuration as that of gigantecin (**2**), whose absolute stereostructure had been established by an X-ray crystallographic analysis.[4] In this paper, we describe a total synthesis of (+)-4-deoxygigantecin (**1**) *via* a convergent route.[5]

0040-4020/98/$19.00
PII: S0040-4020(98)00285-3



4-Deoxygigantecin **1**



Gigantecin **2**

Our retrosynthetic strategy is illustrated in Fig. 1. Thus, the precursor substance (**3**) or (**4**) bearing the full carbon skeleton of 4-deoxygigantecin would be synthesized by the Pd(0)-mediated cross coupling reaction of bis-tetrahydrofuran building block (**5**) with vinyl iodide (**6**) or (**7**). The compound (**5**) would be accessible from (-)-muricatacin (**8**) *via* mono-tetrahydrofuran derivative (**9**), while **6** and **7** would be prepared from (*S*)-(-)-ethyl lactate.

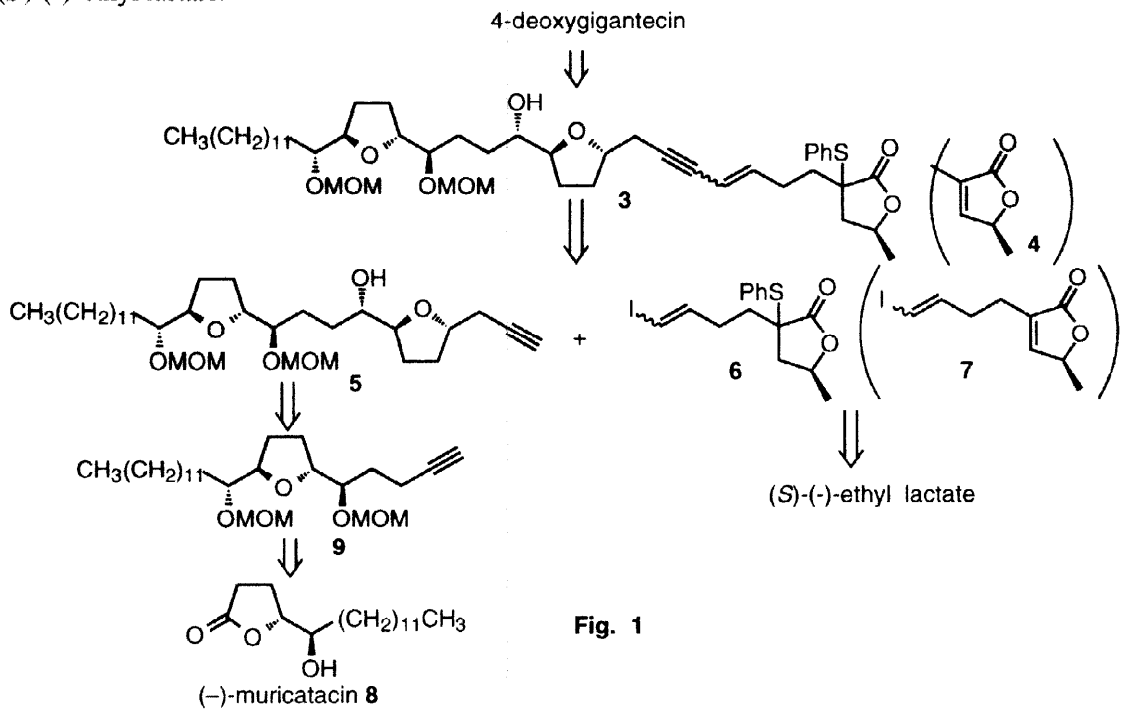
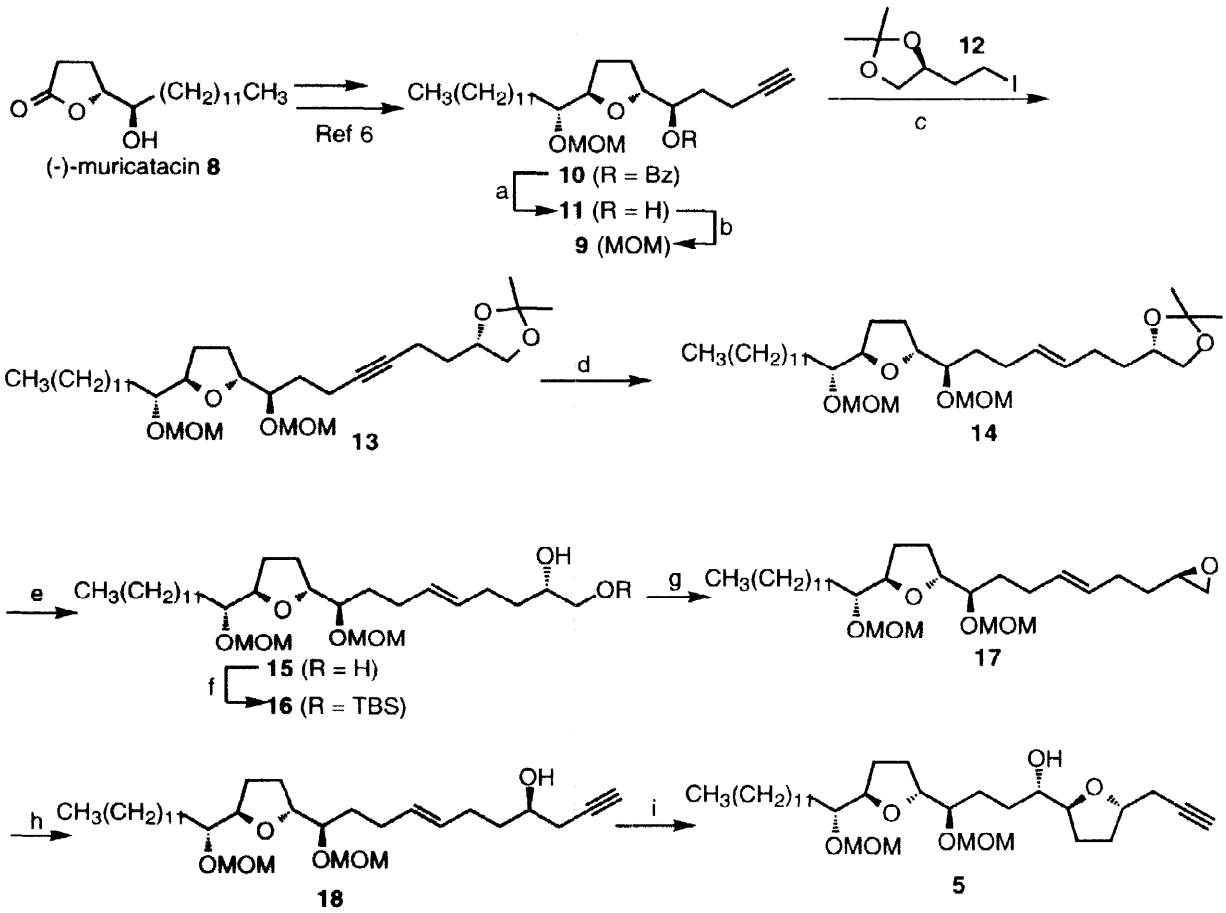


Fig. 1

Transformation of (-)-muricatacin (**8**) into **5** is depicted in Scheme 1. (-)-Muricatacin (**8**) was converted into benzoate (**10**) through the five-step reaction sequence, as reported earlier.[6] This ester (**10**) was then submitted to hydrolysis and reprotection with MOM ether to give bis-MOM ether (**9**). Alkylation of the Li salt of **9** with iodide (**12**) which had been prepared from (*S*)-(-)-malic acid[7] led to **13** in 70% yield. Reduction of **13** with Na in liquid NH_3 and subsequent removal of the acetonide group gave (*E*)-olefinic diol (**15**) in high yield. Selective protection of the primary hydroxyl group of **15** as a TBS ether and successive treatment with $MsCl/Et_3N$, TBAF and 10% aqueous NaOH afforded the desired epoxide (**17**). The coupling reaction between **17** and lithium trimethylsilylacetylide in the presence of $BF_3 \cdot Et_2O$[8] and subsequent deprotection with TBAF provided **18** in good yield. Mesylate formation from **18**, the Sharpless asymmetric dihydroxylation[9] and base-promoted cyclization with Triton B provided the key bis-

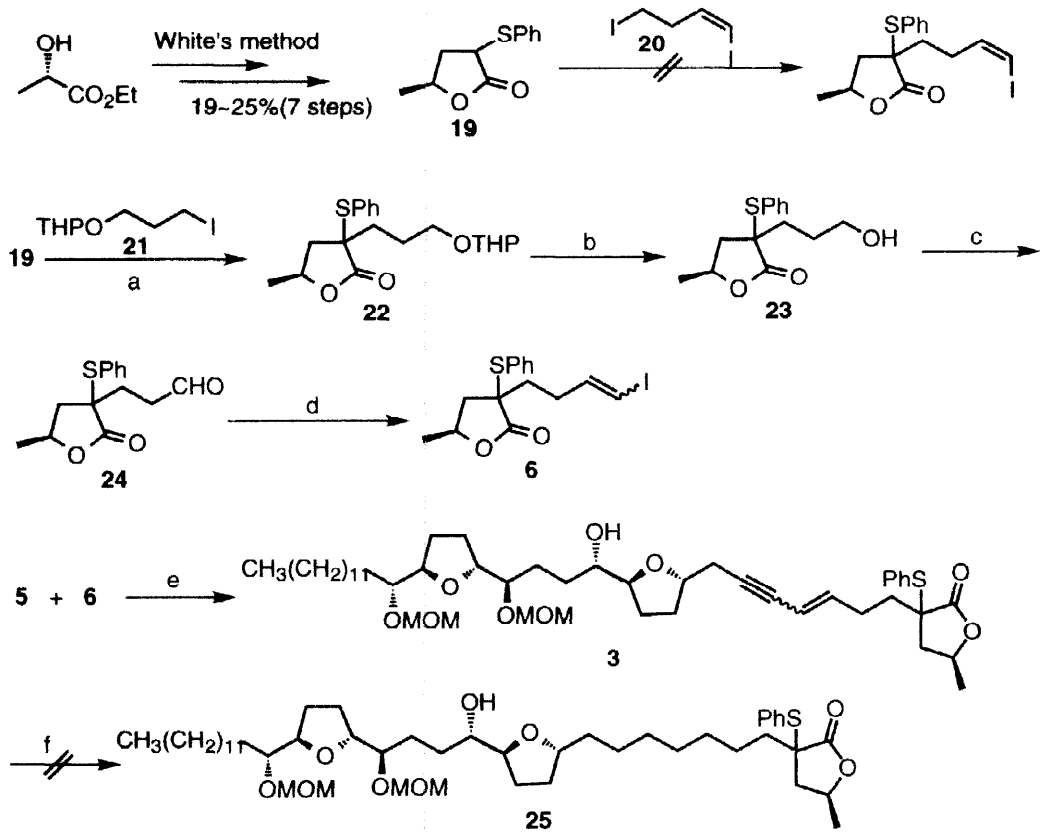


Scheme 1

Reagents and Conditions: a) NaOH, MeOH, 91%. b) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 94%. c) *n*-BuLi, THF, 70%. d) Na/NH_3, *t*-BuOH, THF, 94%. e) 60% AcOH, 96%. f) TBSCl, Et_3N, DMAP, CH_2Cl_2, 95%. g) i. MsCl, Et_3N, CH_2Cl_2. ii. TBAF, THF.iii. 10% NaOH, THF, 72%. h) i. trimethylsilylacetylene, *n*-BuLi, BF_3•Et_2O, THF.ii. TBAF, THF, 85%. i) i. MsCl, Et_3N, CH_2Cl_2. ii. AD mix α, *t*-BuOH-H_2O. iii.Triton B, MeOH, 46%.

tetrahydrofuran synthon (**5**) in 56% yield. Under the conditions using NaH instead of Triton B, the reproducibility of the reaction was poor (10~79%). The diastereomeric excess of **5** was determined to be 92% de by ^{1}H-NMR analysis of the corresponding Mosher ester derivative.

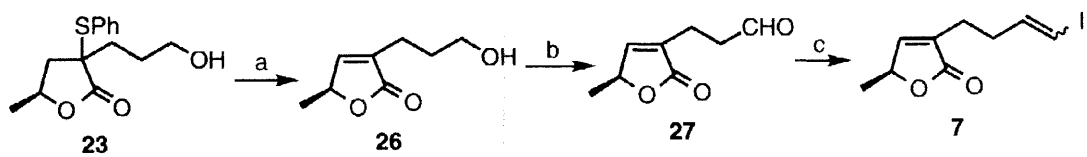
Initially, we selected vinyl iodide (**6**) as a coupling partner of **5**. Preparation of **6** is shown in Scheme 2. Firstly, we examined direct alkylation of γ-lactone (**19**)[10] derived by seven steps from (*S*)-(-)-ethyl lactate with diiodide (**20**)[11] using LDA, KHMDS and NaHMDS. All cases, however, resulted in poor yields of the product. Then, **19** was alkylated with iodo ether (**21**)[12] and NaHMDS, and the resulting lactonic ether (**22**) was deprotected with *p*-TsOH to give alcohol (**23**). Oxidation of **23** with Dess-Martin periodinane[13] and subsequent treatment with $CrCl_2/CHI_3$[14] led to the desired vinyl iodide (**6**). Pd(0)-catalyzed cross coupling reaction[15] between **5** and **6** gave enyne (**3**) in 60% yield. Unexpectedly, catalytic hydrogenation of **3** with Wilkinson's catalyst leading to saturated product (**25**) was very slow and hence, we examined an alternate approach involving the coupling reaction of **5** with iodo butenolide (**7**).



Scheme 2

Reagents and Conditions: a) NaHMDS, THF-HMPA, 89%. b) *p*-TsOH, MeOH, 96%. c) Dess-Martin periodinane, CH_2Cl_2, 91%. d) $CrCl_2$, CHI_3, THF, 70%.e) $Pd(PPh_3)_4$, Et_3N, CuI, PhH, 60%. f) H_2, $Rh(PPh_3)_3Cl$, PhH

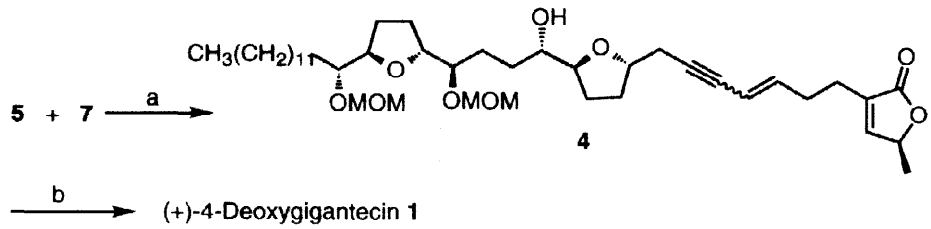
Iodobutenolide (**7**) was prepared as shown in Scheme 3. Oxidation of hydroxy lactone (**23**) with *m*CPBA and thermal elimination of the resulting sulfoxide led to hydroxy butenolide (**26**). Dess-Martin oxidation of **25** followed by treatment with $CrCl_2/CHI_3$ provided iodobutenolide (**7**). Pd(0)-mediated coupling reaction between **5** and **7** was performed as described above to give enyne (**4**) in 60% yield (Scheme 4). Finally, catalytic hydrogenation of **4** with Wilkinson's catalyst and deprotection of the MOM group with $BF_3{\cdot}Et_2O/Me_2S$[16] led to (+)-4-deoxygigantecin (**1**) in 95% overall yield. Its ^{1}H-NMR data were in good agreement with those recorded for natural **1** and the optical rotation value {$[\alpha]_D^{23}$ +16.0(*c* 0.05, MeOH)} of the synthetic sample was also consistent with that of natural product {$[\alpha]_D$ +15.5



Scheme 3

Reagents and Conditions: a) i. *m*CPBA, $ClCH_2CH_2Cl$ ii. toluene reflux, 85%. b) Dess-Martin periodinane, $ClCH_2CH_2Cl$, 95%. c) $CrCl_2$, CHI_3, THF, 85%.

(*c* 0.2, MeOH)}. Consequently, the absolute configuration of natural 4-deoxygigantecin is as shown in **1**.



Scheme 4

Reagents and Conditions: a) $Pd(PPh_3)_4$, Et_3N, CuI, PhH, 66%.
b) i. H_2, $Rh(PPh_3)_3Cl$,PhH ii. $BF_3{\bullet}Et_2O$, Me_2S, 95%.

EXPERIMENTAL

All melting point (mp) data are uncorrected. Column and thin layer chromatography were conducted using silica gel. Optical resolutions were measured with a JASCO DIP-4 spectrometer. IR spectra were taken with a JASCO IR-810 infrared spectrometer. ^{1}H-NMR spectra were measured with JEOL GSX-270, GSX-400 and Varian GEMINI 2000/300. Mass spectra were recorded with JEOL HX-105, JMS-DX 303 and JMS DX-303 instruments.

(2*R*,5*R*,1'*R*,1"*R*)-2-(1'-Hydroxy-4'-butynyl)-5-(1"-methoxymethoxytridecyl)tetrahydrofuran (11). To a solution of benzoate (**10**, 392mg, 0.78 mmol) in MeOH (5 ml) were added NaOH (40 mg, 1 mmol) at room temperature. After stirring 8 h, the solvent was evaporated and the resulting mixture was extracted with ether. The organic layer was washed with water, brine and dried over $MgSO_4$. Concentration and column chromatography (hexane:ethyl acetate =5:1) gave 257 mg (91%) of the title compound (**11**). $[\alpha]_D^{22}$+28.6 (*c* 1.0, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3450, 3320, 2930, 2850, 2120, 1460, 1140, 1100, 1040, 920. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, *J* = 6.8 Hz), 1.26 (18H, s), 1.35~1.50 (5H, m), 1.59~1.67 (4H, m), 1.95 (1H, t, *J* = 2.5 Hz), 1.98 (2H, m), 2.37 (2H, m), 3.41 (3H, s), 3.48 (1H, m), 3.53 (1H, m), 3.84 (1H, m), 3.96 (1H, m), 4.69 (1H, d, *J* = 6.6 Hz), 4.80 (1H, d, *J* = 6.6 Hz). *Anal*. Calcd. for $C_{24}H_{44}O_4$: C, 72.68; H, 11.18. Found: C, 72.69; H, 11.19.

(2*R*,5*R*,1'*R*,1''*R*)-2-(1'-Methoxymethoxy-4'-butynyl)-5-(1''-methoxymethoxytridecyl)-tetrahydrofuran (9). To a mixture of alcohol (**11**, 198 mg, 0.5 mmol) and i-Pr_2NEt (129 mg, 1 mmol) in CH_2Cl_2 (1 ml) was added MOMCl (60 mg, 0.75 mmol). After stirring for 12 h, the reaction mixture was quenched with 0.1N HCl and the resulting aqueous solution was extracted with ether. The organic layer was washed with sat. $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (hexane:ethyl acetate=10:1) to give the title compound (**9**, 207mg, 94%) as a colorless oil. $[\alpha]_D^{22}$+34.9 (*c* 1.0, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3300, 2920, 2850, 2100, 1460, 1140, 1100, 1030, 910. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, *J* = 6.6 Hz), 1.26 (18H, m), 1.39~1.46 (4H, m), 1.62~1.76 (4H, m), 1.94 (2H, m), 1.95 (1H, t, *J* = 2.5 Hz), 2.35 (2H, m), 3.39 (3H, s), 3.41 (3H, s), 3.46 (1H,

m), 3.61 (1H, m), 3.99 (2H,m), 4.66 (1H, d, J = 6.6 Hz), 4.70 (1H, d, J = 6.6 Hz), 4.83 (1H, d, J = 6.6 Hz), 4.84 (1H, d, J = 6.6 Hz). *Anal.* Calcd. for $C_{26}H_{48}O_5$: C, 70.87; H, 10.98. Found: C, 70.62; H, 10.69.

(2*R*,5*R*,1'*R*,8'*S*,1''*R*)-2-[8',9'-(1-Methylethylidene)dioxy-1'-methoxymethoxy-4'-nonynyl]-5-(1''-methoxymethoxytridecyl)terahydrofuran (13). To a solution of bis MOM ether (**9**, 243 mg, 0.55 mmol) in THF (3 ml) was added *n*-BuLi (1.56M solution in hexane, 0.35 ml) at -10 °C and after stirring at 0 °C for 1 h, (*S*)-iodo-3,4-(1-methylethylidene)dioxybutane (**12**, 141 mg) was added over 1 h. After being stirred at 0 °C for 1 h and at room temperature for 1 h, the reaction mixture was quenched with sat. NH_4Cl. The resulting aqueous solution was extracted with ether, the ethereal layer being dried and concentrated to afford a crude product. Purification by column chromatography using hexane-AcOEt (5:1) gave pure **13** (219 mg, 70%). $[\alpha]_D^{23}$+42.9 (*c* 1.47, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 2930, 2850, 1465, 1460, 1380, 1370, 1150, 1100, 1080, 1040, 920. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 7.0 Hz), 1.20~2.00 (30H, m), 1.35 (3H, s), 1.40 (3H, s), 2.26 (4H, m), 3.39 (6H, s), 3.44 (1H, m), 3.57 (2H, m), 3.97 (2H, m), 4.07 (1H, m), 4.17 (1H, m), 4.66 (1H, d, J = 6.6 Hz), 4.68 (1H, d, J = 6.6 Hz), 4.82 (1H, d, J = 6.6 Hz), 4.83 (1H, d, J = 6.6 Hz). HRFABMS(M+Na^+): Calcd. for $C_{33}H_{60}O_7Na$: 591.4237. Found: 591.4249.

(2*R*,5*R*,1'*R*,8'*S*,1''*R*,*E*)-2-[8',9'-(1-Methylethylidene)dioxy-1'-methoxymethoxy-4'-nonenyl]-5-(1''-methoxymethoxytridecyl)terahydrofuran (14). To a solution of Na (23 mg, 1 mmol) in liq. NH_3 (20 ml) was added a solution of **13** (147 mg, 0.26 mmol) in THF (1 ml) containing *t*-BuOH (0.14 ml) at -40 °C and stirring was continued for 8 h. Saturated NH_4Cl was added and the resulting aqueous solution was extracted with ether. Drying and concentrating the ethereal solution gave a crude product, which was purified by column chromatography (hexane:AcOEt = 5:1) to yield pure **14** (140 mg, 94%). $[\alpha]_D^{23}$+45.7 (*c* 1.26, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 2930, 2850, 1455, 1380, 1370, 1210, 1150, 1100, 1030, 965, 920. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 6.8 Hz), 1.20~2.00 (32H, m), 1.35 (3H, s), 1.40 (3H, s), 2.08 (4H, m), 3.39 (6H, s), 3.50 (3H, m), 4.00 (4H, m), 4.66 (1H, d, J = 6.6 Hz), 4.67 (1H, d, J = 6.6 Hz), 4.82 (1H, d, J = 6.6 Hz), 4.84 (1H, d, J = 6.6 Hz). HRFABMS (M+Na^+): Calcd. for $C_{33}H_{62}O_7Na$: 593.4393. Found: 593.4395.

(2*R*,5*R*,1'*R*,8'*S*,1''*R*,*E*)-2-(8',9'-Dihydroxy-1'-methoxymethoxy-4'-nonenyl)-5-(1''-methoxymethoxytridecyl)terahydrofuran (15). A solution of **14** (126 mg, 0.22 mmol) in 60% aqueous AcOH (1 ml) was heated at 60 °C for 1 h and concentrated to give a crude product, which was purified by TLC (hexane:AcOEt = 2:1) to afford pure **15** (112 mg, 96%). $[\alpha]_D^{23}$+41.7 (*c* 1.00, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3450, 2930, 2850, 1470, 1460, 1210, 1150, 1100, 1030, 965, 920. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 6.8 Hz), 1.20~2.00 (30H, m), 1.90 (1H, d, J = 5.3 Hz, OH), 2.11 (1H, br. OH), 2.17 (4H, m), 3.39 (6H, s), 3.45 (3H, m), 3.63 (1H, m), 3.72 (1H, m), 3.99 (2H, m), 4.66 (1H, d, J = 6.6 Hz), 4.67 (1H, d, J = 6.6 Hz), 4.81 (1H, d, J = 6.6 Hz), 4.83 (1H, d, J = 6.6 Hz), 5.45 (2H, m). HRFABMS (M+Na^+): Calcd. for $C_{30}H_{58}O_7Na$: 553.4080. Found: 553.4093.

(2*R*,5*R*,1'*R*,8'*S*,1''*R*,*E*)-2-(9'-*tert*-Butyldimethylsilyloxy-8'-hydroxy-1'-methoxymetho-

xy-4'-nonenyl)-5-(1''-methoxymethoxytridecyl)terahydrofuran (16). A solution of **15** (112 mg, 0.21 mmol), DMAP (10 mg) and Et_3N (0.04 ml, 0.28 mmol) in CH_2Cl_2 (2 ml) was treated with TBSCl (41 mg, 0.27 mmol) and stirring was continued for 12 h. The reaction mixture was then diluted with ether, washed successively with sat. $NaHCO_3$, saturated NH_4Cl and saturated NaCl. Drying and concentrating the ethereal solution provided a crude product, which, on purification by TLC (hexane:AcOEt = 5:1), afforded pure **16** (129 mg, 95%). $[\alpha]_D^{23}$+36.3 (*c* 1.09, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3500, 2930, 2850, 1460, 1250, 1150, 1100, 1040, 965, 920, 840, 780. ^{1}H-NMR ($CDCl_3$) δ: 0.07 (6H, s), 0.88 (3H, t, *J* = 6.8 Hz), 0.90 (9H, s), 1.20~1.93 (30H, m), 2.15 (4H,m), 2.40 (1H, d, *J* = 3.7 Hz), 3.39 (6H, s), 3.41~3.46 (3H, m), 3.60 (2H, m), 3.99 (2H, m), 4.66 (1H, d, *J* = 6.6 Hz), 4.68 (1H, d, *J* = 6.6 Hz), 4.82 (1H, d, *J* = 6.6 Hz), 4.84 (1H, d, *J* = 6.6 Hz), 5.44 (2H, m). HRFABMS (M+Na$^+$): Calcd. for $C_{36}H_{72}O_7NaSi$: 667.4945. Found: 667.4945.

(2*R*,5*R*,1'*R*,8'*S*,1''*R*,*E*)-2-(8',9'-Epoxy-1'-methoxymethoxy-4'-nonenyl)-5-(1''-methoxymethoxytridecyl)terahydrofuran (17). To a solution of **16** (112 mg, 0.17 mmol), Et_3N (0.04 ml, 0.28 mmol) in CH_2Cl_2 (1 ml) was added MsCl (0.015 ml, 0.19 mmol) at -10 °C and after 10 min, ether (10 ml) was added, the resulting ethereal solution being washed with 0.1 N HCl and saturated $NaHCO_3$. Drying and concentrating the ethereal solution provided a crude product, which was then dissolved in THF (1 ml) and the mixture was treated with TBAF (1 M solution in THF, 0.2 ml) at 0 °C. After being stirred at room temperature for 10 h, the reaction mixture was treated with 20% NaOH (2 ml, 1.0 mmol) at 0 °C and stirring was continued for 2 h. Ether (10 ml) was added and the solution was washed with H_2O and saturated NaCl. Drying and concentrating the ethereal solution provided a crude product, which, on purification by TLC (hexane:AcOEt = 5:1), afforded pure **17** (77 mg, 72%). $[\alpha]_D^{22}$+45.5 (*c* 0.77, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 2930, 2850, 1460, 1150, 1100, 1030, 965, 920. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, *J* = 6.8 Hz), 1.20~1.95 (30H, m), 2.15 (4H,m), 2.47 (1H, dd, *J* = 4.8, 2.7 Hz), 2.75 (1H, dd, *J* = 4.8, 4.2 Hz), 2.92 (1H, m), 3.39 (6H, s), 3.46 (2H, m), 3.99 (2H, m), 4.65 (1H, d, *J* = 6.6 Hz), 4.66 (1H, d, *J* = 6.6 Hz), 4.82 (1H, d, *J* = 6.6 Hz), 4.84 (1H, d, *J* = 6.6 Hz), 5.46 (2H, m). HRFABMS (M+Na$^+$): Calcd. for $C_{30}H_{56}O_6Na$: 535.3975. Found:535.3990.

(2*R*,5*R*,1'*R*,8'*S*,1''*R*,*E*)-2-(8'-Hydroxy-1'-methoxymethoxy-4'-undecen-10'-ynyl)-5-(1''-methoxymethoxytridecyl)terahydrofuran (18). To a solution of trimethylsilylacetylene (29 mg, 0.3 mmol) in THF (0.5 ml) was added *n*-BuLi (1.56 M solution in hexane, 0.2 ml) at -78 °C and after 30 min, BF_3•Et_2O (43 mg, 0.3 mmol) was added, stirring being continued for 20 min. To this mixture was then added a solution of **17** (77 mg, 0.15 mmol) in THF (0.5 ml) and the reaction mixture was stirred for 1 h. Saturated NH_4Cl was added and the aqueous solution was extracted with ether, the ethereal layer being washed with H_2O and sat. NaCl. Drying and concentrating the ethereal solution provided a crude product, which was then dissolved in THF (0.5 ml) and the mixture was treated with TBAF (1 M solution in THF, 0.2 ml) at 0 °C. After being stirred at room temperature for 5 h, the reaction mixture was diluted with ether (10 ml) and the ethereal solution was washed with H_2O and saturated NaCl. Drying and concentrating the ethereal solution provided a crude product, which, on purification by TLC (hexane:AcOEt = 3:1), afforded pure **18** (69 mg, 85%). $[\alpha]_D^{22}$+38.8 (*c* 0.69, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3450, 3300, 2920, 2850, 1455, 1150, 1100, 1030, 960, 920. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, *J* = 6.8 Hz), 1.20~1.96 (30H, m), 1.92 (1H,

d, J = 5.2 Hz, OH), 2.06 (1H, t, J = 2.7 Hz), 2.16 (4H, m), 2.33 (1H, ddd, J = 16.7, 6.8, 2.7 Hz), 2.44 (1H, ddd, J = 16.7, 4.8, 2.7 Hz), 3.39 (6H, s), 3.47 (2H, m), 3.80 (1H, m), 3.99 (2H, m), 4.66 (1H, d, J = 6.6 Hz), 4.67 (1H, d, J = 6.6 Hz), 4.82 (1H, d, J = 6.6 Hz), 4.84 (1H, d, J = 6.6 Hz), 5.46 (2H, m). HRFABMS (M+Na$^+$): Calcd. for $C_{32}H_{58}O_6Na$: 561.4131. Found: 561.4134.

(2*R*,5*R*,1'*R*,4'*S*,5'*S*,8'*S*,1''*R*)-2-(5',8'-Epoxy-4'-hydroxy-1'-methoxymethoxy-10'-undecynyl)-5-(1''-methoxymethoxytridecyl)terahydrofuran (5). To a solution of **18** (34 mg, 0.07 mmol), Et_3N (0.02 ml, 0.14 mmol) in CH_2Cl_2 (1 ml) was added MsCl (0.008 ml, 0.1 mmol) at -10 °C and after 10 min, the reaction mixture was diluted with ether (10 ml), the ethereal layer being washed with 0.1 N HCl and saturated NaCl. Drying and concentrating the ethereal solution provided a crude product, which was then added at 0 °C to a suspension of AD mix α (0.08 g) in *t*-BuOH/H_2O (1:1, 1 ml) containing methanesulfonamide (3 mg). After stirring at 0 °C for 48 h, half-saturated Na_2SO_3 was added and the aqueous solution was extracted with ethyl acetate. The organic layer was washed with saturated NaCl and dried. Concentration gave a crude product, which was then dissolved in MeOH (0.5 ml) and treated with Triton B (40% in MeOH, 0.29 ml, 0.7 mmol), stirring being continued for 24 h. The mixture was diluted with ether (10 ml) and washed with H_2O and saturated NaCl. Drying and concentrating the ethereal solution afforded a crude product, which, on purification by TLC (hexane:AcOEt = 1:1), afforded pure **5** (18 mg, 46%). $[\alpha]_D^{22}$+17.2 (*c* 0.18, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3450, 3300, 2930, 2850, 1150, 1100, 1030, 920. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 6.7 Hz), 1.20~2.10 (35H, m), 1.97 (1H, t, J = 2.8 Hz), 2.33 (1H, ddd, J = 16.7, 6.8, 2.8 Hz), 2.44 (1H, ddd, J = 16.7, 5.0, 2.8 Hz), 3.39 (1H, m), 3.40 (6H, s), 3.52 (2H, m), 3.85 (1H, m), 3.95 (2H, m), 4.07 (1H, 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), 4.85 (1H, d, J = 6.6 Hz). HRFABMS (M+Na$^+$): Calcd. for $C_{32}H_{58}O_7Na$: 577.4080. Found: 577.4091.

(3*RS*,5*S*)-3-[3'-(Tetrahydro-2-pyranyloxy)propyl]-5-methyl-3-(phenylsulfanyl)tetrahydrofuran-2-one (21). To a solution of **19** (1.17 g, 5.9 mmol) in THF (15 ml) was added slowly NaHMDS (0.6 M solution in toluene, 10 ml) at 0 °C and after 30 min, a solution of 1-iodo-3-(tetrahydro-2-pyranyloxy)propane (**20**, 1.59 g, 6.9 mmol) in THF/HMPA (1:1, 10 ml) was added over 1 h. The mixture was stirred at room temperature for 5 h and the reaction was quenched with saturated NH_4Cl. The aqueous solution was extracted with ether and the ethereal layer was washed with saturated NaCl. Drying and concentrating the ethereal solution afforded a crude product, which, on purification by column chromatography (hexane:AcOEt = 1:1), afforded pure **21** (1.84 g, 89%). IR (film) ν_{max} cm^{-1}: 3050, 2940, 2860, 1760, 1440, 1340, 1180, 1120, 1070, 1030, 980, 750, 695. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (2.4H, d, J= 6.3 Hz), 1.39 (0.6H, d, J = 6.3 Hz), 1.46~2.01 (11H, m), 2.30~2.60 (1H, m), 3.35 (1H, m), 3.50 (1H, m), 3.80 (2H, m), 4.50 (2H, m), 7.35 (3H, m), 7.55 (2H, m). *Anal.* Calcd. for $C_{19}H_{26}O_4S$: C, 65.11; H, 7.48. Found: C, 64.65; H, 7.53.

(3*RS*,5*S*)-3-(3'-Hydroxypropyl)-5-methyl-3-(phenylsulfanyl)tetrahydrofuran-2-one (22). A solution of **21** (175 mg, 0.5 mmol) and *p*-TsOH•H_2O (20 mg) in MeOH (3 ml) was stirred at room temperature for 8 h. Evaporation of the solvent left a crude product, which, after column chromatography (hexane:AcOEt = 1:1), afforded pure **22** (128 mg, 96%). IR (film) ν_{max} cm^{-1}: 3400, 3050, 2940, 2860,

1760, 1440, 1340, 1180, 1050, 980, 750, 695. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (2.4H, d, J = 6.3 Hz), 1.39 (0.6H, d, J = 6.3 Hz), 1.60~2.00 (5H, m), 1.95 (1H, br. OH), 2.33 (0.2H, dd, J = 13.9, 5.5 Hz), 2.54 (0.8H, dd, J = 13.9, 7.7 Hz), 3.64 (2H, m), 4.58 (0.8H, m), 4.68 (0.2H, m), 7.35 (3H, m), 7.55 (2H, m). *Anal.* Calcd. for $C_{14}H_{18}O_3S$: C, 63.13; H, 6.81. Found: C, 62.60; H,6.89.

(3*RS*,5*S*)-3-(3'-Formylethyl)-5-methyl-3-(phenylsulfanyl)tetrahydrofuran-2-one (23). A solution of **22** (100 mg, 0.38 mmol) in CH_2Cl_2 (2 ml) was stirred with Dess-Martin periodinane (211 mg, 0.5 mmol) at room temperature for 5 h. After completion of the reaction, the whole solution was passed through a short silica gel plug and the eluate was concentrated to give **23** (91 mg, 91%), which was used in the next reaction without further purification. IR (film) ν_{max} cm^{-1}: 3050, 2980, 2930, 2830, 2720, 1760, 1720, 1440, 1380, 1340, 1180, 750, 695. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (2.4H, d, J = 6.3 Hz), 1.39 (0.6H, d, J = 6.3 Hz), 1.80~3.00 (6H, m), 4.58 (0.8H, m), 4.68 (0.2H, m), 7.35 (3H, m), 7.55 (2H, m), 9.80 (1H, s).

(3*RS*,5*S*,3'*EZ*)-3-(4'-Iodo-3'-butenyl)-5-methyl-3-(phenylsulfanyl)tetrahydrofuran-2-one (6). A solution of **23** (56 mg, 0.21 mmol), $CrCl_2$ (0.28 g, 2.3 mmol) and $CHCl_3$ (0.3 g, 0.76 mmol) in THF (2 ml) was stirred at room temperature for 8 h. H_2O was added and the aqueous solution was extracted with ether, the ethereal layer being washed and dried. Evaporation of the solvent gave a crude product, which, on purification by column chromatography (hexane:AcOEt = 5:1), afforded pure **6** (56 mg, 70%). IR (film) ν_{max} cm^{-1}: 3050, 2940, 2920, 1760, 1600, 1440, 1340, 1185, 750, 695. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (2.4H, d, J = 6.3 Hz), 1.40 (0.6H, d, J = 6.3 Hz), 1.80~2.70 (6H, m), 4.51 (1H, m), 6.10 (0.9H, dt, J = 14.3, 1.3 Hz, *E*), 6.30 (0.2H, m, *Z*), 6.40 (0.9H, dt, J = 14.3, 7.1 Hz, *E*), 7.35 (3H, m), 7.55 (2H, m). HREIMS (M^+-I): Calcd. for $C_{15}H_{17}O_2S$: 261.0949. Found: 261.0961.

(3*RS*,5*S*,8'*S*,11'*S*,12'*S*,15'*R*,16'*R*,19'*R*,20'*R*,*EZ*)-3-[8',11':16',19'-Diepoxy-12'-hydroxy-15',20'-bis(methoxymethoxy)-3'-dotriaconten-5'-ynyl]-5-methyl-3-(phenylsulfanyl)tetrahydrofuran-2-one (3). A mixture of **6** (12 mg, 0.032 mmol), Et_3N (4 mg, 0.04 mmol), $Pd(PPh_3)_4$ (2 mg, 0.0016 mmol) in benzene (0.5 ml) was stirred at at room temperature for 8 h. To this mixture was then added a solution of **5**(18 mg, 0.032 mmol) in THF (0.1 ml) and CuI (0.5 mg). After stirring for 2 h, saturated NH_4Cl was added and the aqueous solution was extracted with ether, the ethereal layer being washed with saturated NaCl and dried. Concentration of the solution provided a crude product, which, on purification by TLC (hexane:AcOEt = 2:1), afforded pure **3** (15 mg, 60%). IR (film) ν_{max} cm^{-1}: 3450, 3050, 2920, 2850, 1760, 1180, 1100, 1030, 750, 695. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J = 6.7 Hz), 1.20~2.05 (47H, m), 3.39 (6H, s), 3.44 (3H, m), 3.85 (1H, m), 3.96 (2H, m), 4.10 (1H, m), 4.67 (1H, d, J = 6.6 Hz), 4.83 (1H, d, J = 6.6 Hz), 4.84 (1H, d, J = 6.6 Hz), 5.40 (1H, m), 6.00 (1H, m), 7.35 (3H, m), 7.55 (2H, m). HRFABMS ($M+Na^+$): Calcd. for $C_{47}H_{74}O_9SNa$: 837.4951. Found: 837.4970.

(*S*)-3-(3'-Hydroxypropyl)-5-methyl-2,5-dihydrofuran-2-one (25). To a solution of **22** (1.45 g, 5.4 mmol) in 1,2-dichloroethane (20 ml) was added *m*CPBA (1.16 g, 5.4 mmol) at 0 °C and after 15 min, saturated $Na_2S_2O_3$ and saturated $NaHCO_3$ were added, stirring being continued for 2 h. The aqueous

solution was extracted with ether, the ethereal layer being washed with saturated NaCl and dried. Concentration of the solution provided a crude product, which was dissolved in toluene (5 ml) and the mixture was refluxed for 0.5 h. Concentration and purification of the residue by column chromatography (hexane:AcOEt = 2:1) afforded pure **25** (720 mg, 85%). $[\alpha]_D^{22}$+54 (*c* 0.84, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3450, 3080, 2930, 2855, 1750, 1650, 1440, 1320, 1200, 1100, 1080, 1020, 950. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, d, *J* = 6.6 Hz), 1.72 (1H, t, *J* = 5.5 Hz, OH), 1.80 (2H, m), 2.30 (2H, tt, *J* = 7.3, 1.4 Hz), 3.68 (2H, dt, *J* = 5.5, 6.3 Hz), 5.00 (1H, qd, *J* = 6.6, 1.6 Hz), 7.05 (1H, d, *J* = 1.4 Hz). *Anal.* Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.09; H,7.88.

(*S*)-3-(2'-Formylethyl)-5-methyl-2,5-dihydrofuran-2-one (26). A solution of **25** (97 mg, 0.62 mmol) in 1,2-dichloroethane (10 ml) was stirred with Dess-Martin periodinane (308 mg, 0.7 mmol) at room temperature for 15 min. After completion of the reaction, the whole solution was passed through a short silica gel plug and the eluate was concentrated to give a crude product, which was purified by column chromatography (hexane:AcOEt = 2:1) to afford pure **26** (91 mg, 95%). $[\alpha]_D^{22}$+41 (*c* 0.75, $CHCl_3$) . IR (film) ν_{max} cm^{-1}: 3080, 2930, 2825, 2720, 1750, 1720, 1650, 1320, 1200, 1080, 1020, 950. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, d, *J* = 6.6 Hz), 2.65 (2H, m), 2.78 (2H, tt, *J* = 7.1, 1.1 Hz), 5.00 (1H, qd, *J* = 6.6, 1.6 Hz), 7.05 (1H, d, *J* = 1.4 Hz), 9.80 (1H, t, *J* = 1.1 Hz).

(*S,EZ*)-3-(4'-Iodo-3'-butenyl)-5-methyl-2,5-dihydrofuran-2-one (7). Ninety one mg (0.61 mmol) of **26** was submitted to the reaction described for **6**. Purification of the crude product by column chromatography (hexane:AcOEt = 5:1) afforded pure **7** (144 mg, 85%). IR (film) ν_{max} cm^{-1}: 3080, 2940, 1750, 1650, 1600, 1440, 1320, 1200, 1080, 1020, 950. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (2.67H, d, *J* = 6.8 Hz), 1.41 (0.33H, d, *J* = 6.8 Hz), 2.35 (4H, m), 5.00 (1H, qd, *J* = 6.6, 1.6 Hz), 6.08 (0.89H, dt, *J* = 14.5, 1.3 Hz, *E*), 6.30 (0.22H, m, *Z*), 6.47 (0.89H, dt, *J* = 14.3, 6.9 Hz, *E*), 7.02 (0.89H, d, *J* = 1.4 Hz), 7.07 (0.11H, d, *J* = 1.4 Hz). HREIMS (M^+): Calcd. for $C_9H_{11}O_2I$: 277.9804. Found: 277.9818.

(5*S*,8'*S*,11'*S*,12'*S*,15'*R*,16'*R*,19'*R*,20'*R*,*EZ*)-3-[8',11':16',19'-Diepoxy-12'-hydroxy-15',20'-bis(methoxymethoxy)-3'-dotriaconten-5'-ynyl]-5-methyl-2,5-dihydrofuran-2-one (4). Pd(0)-catalyzed cross-coupling reaction using 5 mg (0.018 mmol) of **5** and 9 mg (0.016 mmol) of **7** was performed according to the procedure described for **3**. Purification of the crude product by TLC (hexane:AcOEt = 2:1) afforded pure **4** (7 mg, 66%). IR (film) ν_{max} cm^{-1}: 3450, 2920, 2850, 1750, 1650, 1320, 1150, 1100, 1030, 950. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, *J* = 6.6 Hz), 1.20~2.10 (35H, m), 1.40 (3H, d, *J* = 6.8 Hz), 2.25 (6H, m), 3.39 (6H, s), 3.44 (3H, m), 3.85 (1H, m), 4.00 (2H, m), 4.10 (1H, m), 4.67 (1H, d, *J* = 6.6 Hz), 4.68 (1H, d, *J* = 6.6 Hz), 4.83 (1H, d, *J* = 6.6 Hz), 4.84 (1H, d, *J* = 6.6 Hz), 5.00 (1H, qd, *J* = 6.8, 1.6 Hz), 5.50 (0.89H, m), 5.80 (0.22H, m), 6.10 (0.89H, m), 7.02 (0.89H, d, *J* =1.4 Hz), 7.07 (0.11H, d, *J* =1.4 Hz). HRFABMS (M+Na^+): Calcd. for $C_{41}H_{68}O_9Na$: 727.4761. Found:727.4764.

4-Deoxygigantecin (1). Thoroughly deaerated (sonicated) benzene (0.1 ml) was added to $Rh(PPh_3)_3Cl$ (0.5 mg) under an H_2 atmosphere and the solution was stirred for 2 h. To this mixture was then added a solution of **4** (1.1 mg, 0.0014 mmol) in benzene (0.05 ml), stirring being continued for 8 h. After

completion of the reaction, the whole solution was passed through a silica gel plug and evaporation of the solvent gave a crude residue, which was dissolved in Me_2S (0.05 ml) and then treated with $BF_3 \cdot Et_2O$ (1 drop) at 0 ℃. After 5 min, saturated $NaHCO_3$ was added and the aqueous solution was extracted with AcOEt. Evaporation of the solvent left a crude product, which, by purification with TLC (AcOEt), afforded the desired 4-deoxygigantecin (**1**, 1.0 mg, 95%). $[\alpha]_D^{23}$+16.0 (*c* 0.05, MeOH){ lit.[3] $[\alpha]_D$+15.5 (*c* 0.2, MeOH)}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, *J* = 6.8 Hz), 1.40 (3H, d, *J* = 6.9 Hz), 1.21~1.80 (42H, m), 1.99 (4H, m), 2.15 (1H, br. OH), 2.26 (2H, tt, *J* = 7.3, 1.5 Hz), 2.40 (1H, br. OH), 2.65 (1H, br. OH),), 3.40~3.45 (3H, m), 3.80~3.89 (4H, m), 5.00 (1H, qd, *J* = 6.8, 1.5 Hz), 6.99 (1H, d, *J* =1.5 Hz).

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