The first total synthesis of 4-deoxyannomontacin

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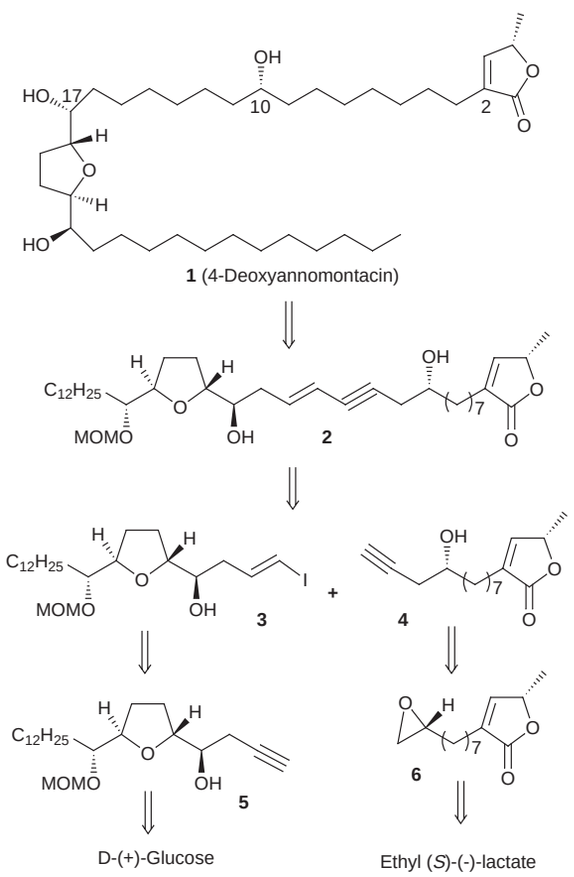
A convergent enantioselective total synthesis of 4-deoxyannomontacin, a newly isolated and characterized acetogenin compound which shows very high cytotoxicity, has been synthesized enantioselectively *via* 17 reaction steps with an overall yield of 15%. The four stereogenic centers near the ethereal link are derived from D-glucose and introduced using Sharpless asymmetric dihydroxylation. The chiral carbon in the butenolide moiety is taken from ethyl (*S*)-lactate whereas the hydroxy-group configuration is obtained from salenCo^{III}-catalyzed hydrolytic kinetic resolution.

Annonaceous acetogenins, a relatively new class of natural products so far only found in Annonaceae, have been attracting worldwide attention in recent years because of their potent biological activities, especially as growth inhibitors[1] of certain tumor cells. They have been shown[2] to function by blocking complex I in mitochondria as well as ubiquinone-linked 1,4-dihydronicotinamide adenine dinucleotide (NADH) oxidase in the cells of specific tumor cell-lines, including some multidrug-resistant ones.[3] These features make the acetogenins excellent leads for new antitumor agents. However, due to their scant natural resources, the substantial amounts[4] of enantiomerically pure samples required for further biological and clinical studies appear to be attainable only by means of chemical synthesis. Reported herein is the first enantioselective total synthesis of the recently isolated and characterized (from *Goniothalamus giganteus* by McLaughlin[5]) 4-deoxyannomontacin **1**, which shows very high (over 10^5 times more potent than adriamycin, a standard reference compound commonly used in antitumor assay of acetogenins) cytotoxicity towards the MCF-7 cell line.

The retrosynthetic strategy adopted for the current work is outlined in Scheme 1. Thus, the target **1** is planned to be derived *via* diimide reduction from enyne **2**. A key disconnection is then made at the σ-bond between C-13 and C-14, which corresponds to a synthetic step of Pd^0-catalyzed coupling between the vinyl iodide **3** and the terminal alkyne **4**. The former can be further disconnected into a known[6] alkyne **5**, while the latter (**4**) is easily accessible from the oxirane **6**, which in turn can be prepared using salenCo^{III}-catalyzed† hydrolytic kinetic resolution as described in our previous[7] communication.



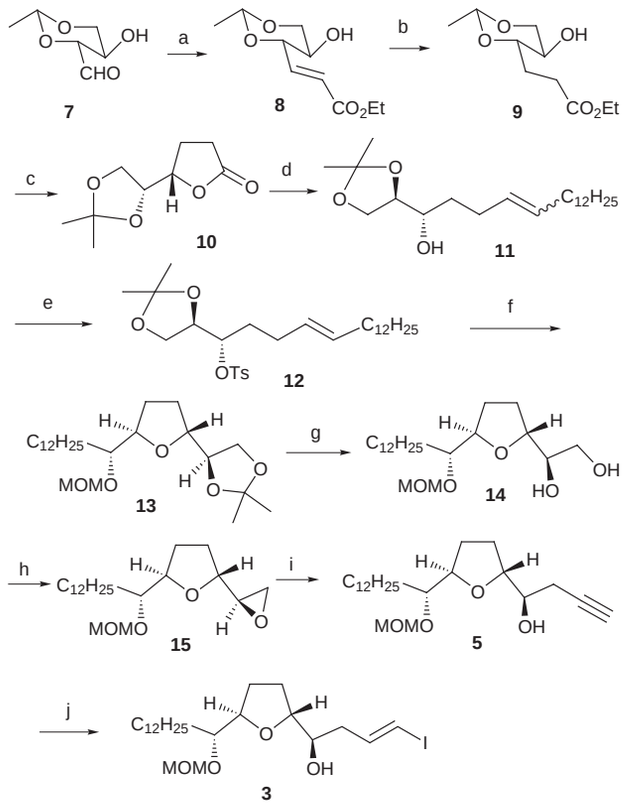
Scheme 1

Results and discussion

The synthesis started with a known aldehyde **7**, which was easily attainable from D-glucose[8] on multi-hundred-gram scales. A Wittig–Horner reaction was then used to extend the side chain, giving ester **8** in 82% yield (Scheme 2). Saturation of the carbon–carbon double bond in acrylate **8** by hydrogenation afforded propionate **9** in 95% yield. Treatment of ester **9** with propane-1,3-dithiol in the presence of boron trifluoride–diethyl ether removed the acetal protecting group and led to an intramolecular ester exchange, affording the intermediate lactone-diol, which was then remasked as acetonide **10** in a one-pot manner by subsequent treatment with 2,2-dimethoxypropane (DMOP) in 80% overall yield. The preferential formation of the five-membered lactone **10** probably resulted from the kinetic advantage over the corresponding six-membered one and the favored formation of the acetonide from the primary and secondary 1,2-diol over that of the internal *cis*-2,3-derivative.[9]

Reduction of lactone **10** with Dibal-H afforded the corresponding lactol, which was treated with (bromotridecylidene)-triphenylphosphorane to give the alcohol **11** in 70% overall yield as a mixture of the *Z* and *E* isomers. Photo-isomerization[10] of *Z*/*E*-alkene **11** converted practically all the *Z* isomer into the *E* one. The latter was then transformed into tosylester **12** in 94% yield. Asymmetric dihydroxylation[11] using AD-mix-β established the desired stereogenic centers at C-21 and

† salen = bis(salicylidene)ethylenediaminato(2−).

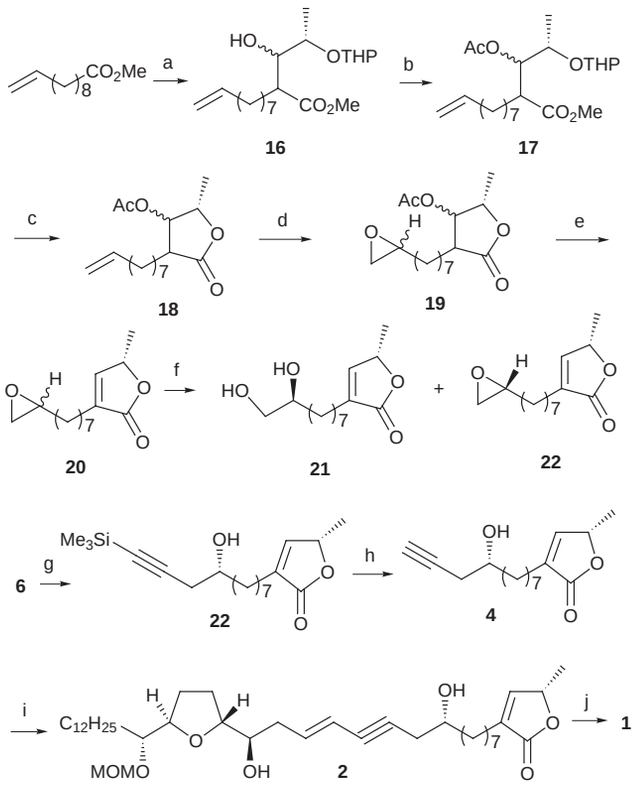


Scheme 2 *Reagents and conditions* (*and yields*): (a) Ph_3PCHCO_2Et, THF, rt (82%); (b) 10% Pd–C, H_2 (95%); (c) propane-1,3-dithiol, $BF_3{\cdot}Et_2O$; then DMOP, CH_2Cl_2 (80%); (d) Dibal-H, CH_2Cl_2, −78 °C (91%); $C_{13}H_{27}\overset{+}{P}Ph_3Br^-$, *n*-BuLi, −20 °C to rt (77%); (e) *hv*, PhSSPh, Cyclohexane–1,4-dioxane (90%); then 60% NaH, *N*-TsIm, THF_2 (94%); (f) AD-mix-β, Bu′OH–water; then MeOH, K_2CO_3; then MOMCl, $^iPr_2NEt$, CH_2Cl_2 (90%); (g) 50% AcOH, 60 °C (80%); (h) 60% NaH, *N*-TsIm (92%); (i) trimethylsilylacetylene, *n*-BuLi, $BF_3{\cdot}OEt_2$, **15**, THF; then *n*-Bu_4NF, THF (90%); (j) Bu_3SnH, AIBN, 130 °C; then I_2, ether (95%).

C-22. An intramolecular Williamson etherification was then used to construct the THF ring with concurrent configurational inversion at C-18. Up to this point, all four stereogenic centers of correct configuration in moiety **3** are already securely established. The remaining free hydroxy group was protected as its MOM ether **13** (90% for three steps) before the masked terminal diol functionality was converted into epoxide **15** *via* hydrolysis of the acetonide **13** (80%, along with 15% of the triol due to loss of the MOM group, which could recycled to diol **14**) followed by treatment with *N*-tosylimidazole (*N*-TsIm). Compared with other routes to epoxide **15**[6] or its equivalent,[12] the present one is substantially improved, in terms of both overall yield and the number of reaction steps involved.

Chain elongation was achieved by nucleophilic attack of lithium trimethylsilylacetylide as reported by Tanaka[6] but the yield was now somewhat improved (90%). Conversion of the terminal alkyne **5** into the vinyl iodide **3** using[13] tributyltin hydride (TBTH) followed by iodine went smoothly, giving a 4:1 mixture of *E*/*Z* isomers. Since the olefinic bond would be saturated later, the mixture could be used in the next coupling step as such without further purification. Thus, iodide **3** was obtained in 13 steps and 22% overall yield (*cf*. 17 steps and 16.9% overall yield in ref. 6).

The other moiety needed for Pd^0-catalyzed coupling, *i.e.*, compound **4**, was obtained in 83% yield by desilylation of alkyne **22**,[7] an intermediate readily attainable from salenCo^{III}-catalyzed hydrolytic kinetic resolution of a racemic epoxide (Scheme 3) as reported[7] by us earlier in a communication. The cross-coupling of the vinyl iodide **3** with terminal alkyne **4** occurred easily under Hoye's conditions [$PdCl_2(PPh_3)_2$–CuI–NEt_3][14] to yield the desired enyne **2** in 82% yield, providing the



Scheme 3 *Reagents and conditions* (*and yields*): (a) see ref. 12*b*; (b) Ac_2O, Py (91%); (c) 10% H_2SO_4, THF (83%); (d) MCPBA, CH_2Cl_2 (91%); (e) DBU, THF, 2 h (96%); (f) 2% mol (*R,R*)-salenCo(OAc), water, 40 h (44% for **21**, 46% for **6**); (g) *n*-BuLi, trimethylsilylacetylene, $BF_3{\cdot}OEt_2$, −78 °C (60–85%, 99.0% de); (h) *n*-Bu_4NF, THF (83%); (i) **3**, $Pd(PPh_3)_2Cl_2$, Et_3N, CuI (82%); (j) $TsNHNH_2$, NaOAc, DME–water, reflux; then $BF_3{\cdot}OEt_2$, DMS (88%).

first example using a C-10 oxygenated butenolide in the Pd^0-catalyzed coupling in the syntheses of acetogenins. Subsequent selective reduction with diimide generated *in situ* from tosylhydrazine as reported[15] by Marshall, followed by removal of the MOM protecting group, gave title compound **1** in 88% yield; the physical and spectroscopic data of the synthetic product **1** were consistent with the natural product. The whole synthesis consists of 17 steps with an overall yield of 15%.

Experimental

Mps were measured on a ZMD-2 melting-point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 MC autopol polarimeter, and are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were obtained on a Shimadzu IR-440 or a Perkin-Elmer 983 spectrophotometer. ^1H NMR spectra were taken on a Varian EM-390, AMX-300 or AMX-600 spectrometer. *J*-Values are in Hz. Mass spectra were measured on an HP 5989A spectrometer. Microanalyses were carried out in the Microanalytic Laboratory of this Institute. Flash column chromatography was performed on silica gel H (10–40 μ). Light petroleum refers to the fraction with distillation range 60–90 °C. Ether refers to diethyl ether.

(2*R*,4*S*,5*R*)-4-[2-(Ethoxycarbonyl)vinyl]-5-hydroxy-2-methyl-1,3-dioxane 8

To a solution of aldehyde **7** (1.2 g, 8.21 mmol) in 20 cm^3 of dry THF was added PPh_3CHCO_2Et (3 g, 8.62 mmol). Stirring was then continued at rt. When TLC (eluent light petroleum–EtOAc 1:1) showed the completion of the reaction, the mixture was concentrated and chromatographed on a silica gel column to afford *title compound* **8** (1.464 g, 82%) as a mixture of *Z* and *E* isomers (~2:1). The *Z* olefin is an oil and the *E* one is a solid, ν_{max}(film)/cm^{-1} 3400, 1720, 1660, 1410; δ_H(300 MHz;

$CDCl_3$) for the *Z* isomer: 1.24 (6H, m), 3.40 (3H, m), 4.02 (1H, ddd, *J* 9.6, 4.0 and 1.5), 4.14 (2H, q, *J* 7.1), 4.73 (1H, q, *J* 5.1), 5.02 (1H, dt, *J* 8.3 and 0.8), 5.99 (1H, dd, *J* 11.7 and 1.0), 6.13 (1H, dd, *J* 11.7 and 8.4); δ_H(300 MHz, $CDCl_3$) for the *E* isomer: 1.26 (6H, m), 3.38 (3H, m), 4.03 (2H, m), 4.15 (2H, q, *J* 7.1), 4.77 (1H, q, *J* 5.0), 6.04 (1H, dd, *J* 15.8 and 1.8), 7.08 (1H, dd, *J* 15.8 and 4.1); *m*/*z* (EI) 217 (M + 1, 100%), 199 (M + 1 − H_2O, 34) (Found: C, 55.6; H, 7.3. $C_{10}H_{16}O_5$ requires C, 55.55; H, 7.46%).

(2*R*,4*S*,5*R*)-4-[2-Ethoxycarbonyl)ethyl]-5-hydroxy-2-methyl-1,3-dioxane 9

In the presence of 10% Pd–C (0.2 g), a solution of acrylate **8** (1.9 g, 8.79 mmol) in 95% EtOH (30 cm^3) was hydrogenated under 1 atm of hydrogen at rt for 2 h. The catalyst was filtered off and the filtrate was concentrated. Chromatography on silica gel gave *title compound* **9** (1.814 g, 95%) as an oil, $[\alpha]_D$ −36.0 (*c* 1.1, $CHCl_3$); ν_{max}(film)/cm^{-1} 3450, 1725, 1450; δ_H(300 MHz, $CDCl_3$) 1.19 (6H, m), 1.67 (1H, m), 2.15 (1H, m), 2.38 (2H, m), 3.29 (4H, m), 3.95 (1H, m), 4.06 (2H, q, *J* 7.1), 4.62 (1H, q, *J* 5.0); *m*/*z* (EI) 219 (M + 1, 14%), 201 (M + 1 − H_2O, 4) (Found: C, 55.0; H, 8.4. $C_{10}H_{18}O_5$ requires C, 55.03; H, 8.31%).

(4′*R*, 5*S*)- 5-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)tetrahydrofuran-2-one 10

To a solution of hydroxy ester **9** (19.00 g, 87.16 mmol) in CH_2Cl_2 (100 cm^3) was added boron trifluoride–diethyl ether (2.5 cm^3, 19.73 mmol) followed by propane-1,3-dithiol (8.8 cm^3, 87.65 mmol). The mixture was stirred for 2 h. When TLC showed the disappearance of the starting material, DMOP, (14 cm^3, 113.86 mmol) was introduced and the stirring was continued for another hour. The reaction mixture was washed successively with saturated aq. $NaHCO_3$ and brine, dried over Na_2SO_4, and then concentrated to give a residue, which was purified by column chromatography on silica gel to give lactone **10** (12.89 g, 80%) as an oil, $[\alpha]_D$ +6.9 (*c* 0.69, $CHCl_3$); ν_{max}(film)/cm^{-1} 1780, 1460; δ_H(300 MHz, $CDCl_3$) 1.34 (3H, s), 1.47 (3H, s), 2.33 (2H, m), 2.50 (2H, m), 3.82 (1H, m), 4.12 (2H, m), 4.39 (1H, m): *m*/*z* (EI) 187 (M + 1, 90%), 171 (M − CH_3, 100) (Found: M^+, 186.0901. $C_9H_{14}O_4$ requires *M*, 186.0888).

(1*S*,4′*R*)-1-(2′,2′-Dimethyl-1′,3′-dioxolane-4′-yl)heptadec-4-en-1-ol 11

To a solution of lactone **10** (3.422 g, 18.39 mmol) in CH_2Cl_2 (30 cm^3) stirred at −78 °C under N_2 was added dropwise Dibal-H (1.12 M; 33 cm^3, 36.96 mmol). After 1 h of stirring, MeOH (15 cm^3) was added slowly. The mixture was allowed to warm to rt (becoming a transparent colloid) before being filtered, and washed with ether several times. The filtrate was dried over $MgSO_4$ and concentrated. Drying under vacuum afforded the corresponding lactol (3.147 g, 91%) as an oil.

A mixture of *n*-$C_{13}H_{27}Br$ (13.49 g, 51.21 mmol) and PPh_3 (13.44 g, 51.21 mmol) was heated to 130 °C for 5 h and was then cooled to 70 °C. Dry ether (10 cm^3) was added. The resulting mixture was then refluxed for another hour. After removal of the ether by decantation, the residue was dried *in vacuo*. To the solution (stirred at −30 °C under N_2) of the residue in 100 cm^3 of dry THF was added dropwise *n*-BuLi (2.5 M; 20.0 cm^3, 50 mmol). After another hour of stirring, a solution of the crude lactol (5.01 g, 26.92 mmol) in 15 cm^3 of THF was introduced. Stirring was continued for 30 min before the mixture was allowed to warm to rt and was stirred at that temperature for 2 h. The reaction mixture was then poured into ice-cooled brine, extracted with ether, and the extract was dried over $MgSO_4$. After removal of the solvent and chromatography, *alcohol* **11** (7.28 g, 77%, from lactone **10**, total 70%) was obtained as a mixture of *Z*/*E* isomers. $[\alpha]_D$ +10.7 (*c* 0.6, $CHCl_3$); ν_{max}(film) cm^{-1} 3466, 1458; δ_H(300 MHz, CD_3COCD_3) 0.85 (3H, t, *J* 6.4), 1.29 (28H, m), 1.63 (2H, m), 2.19 (2H, m), 2.93 (1H, OH), 3.49 (1H, m), 3.86 (2H, m), 3.99 (1H, m), 5.36 (2H, m): *m*/*z* (EI) 354 (M^+, 4%), 339 (M − CH_3, 4) (Found: C, 74.35; H, 12.3. $C_{22}H_{42}O_3$ requires C, 74.52; H, 11.94%).

(1*S*,4′*R*)-1-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)heptadec-4-en-1-ol tosyl ester 12

To a solution of alcohol **11** (2.49 g, 7.02 mmol) in purified cyclohexane–1,4-dioxane (19 : 1; 63.2 cm^3) was added PhSSPh (300 mg, 1.38 mmol). The mixture was irradiated by a 500 W high-pressure mercury lamp under N_2 for 4 h. The mixture was concentrated, and purified by column chromatography (light petroleum–EtOAc 20 : 1) to afford the *E* olefin (2.24 g, 90%). Data for the *Z* isomer: $[\alpha]_D$ +12.2 (*c* 1.4, $CHCl_3$); δ_H(600 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.0), 1.33 (27H, m), 1.50 (1H, m), 2.04 (2H, q, *J* 7.0), 2.19 (2H, m), 3.79 (1H, dt, *J* 9.1 and 4.0), 3.90 (1H, dd, *J* 8.1 and 7.0), 3.97 (1H, dd, *J* 8.1 and 6.7), 4.03 (1H, dt, *J* 6.8 and 4.0), 5.35 (1H, m), 5.41 (1H, m). The *Z* configuration of the double bond was established by double-resonance spectroscopy: Irradiation at δ 2.04 revealed 5.42 (1H, d, *J* 10.9) and 5.36 (1H, dt, *J* 10.9 and 5.9). Irradiation at δ 2.19 led to 5.42 (1H, dt, *J* 10.5, 5.9) and 5.36 (1H, d, *J* 10.9); ν_{max}(film)/cm^{-1} 3500, 1460. Data for *E* isomer: $[\alpha]_D$ +9.4 (*c* 1.2, $CHCl_3$); δ_H(600 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.0), 1.33 (27H, m), 1.52 (1H, m), 1.97 (2H, q, *J* 6.9), 2.10 (1H, m), 2.20 (1H, m), 3.79 (1H, dt, *J* 9.1 and 4.1), 3.91 (1H, dd, *J* 8.0 and 7.2), 3.97 (1H, dd, *J* 8.1 and 6.3), 4.02 (1H, dt, *J* 6.7 and 4.2), 5.40 (1H, dt, *J* 14.6 and 6.8), 5.47 (1H, dt, *J* 14.8 and 6.7). The *E* configuration of the double bond was established also by double-resonance spectroscopy: Irradiation at δ 1.97 revealed 5.47 (1H, d, *J* 15.1) and 5.40 (1H, dt, *J* 15.1 and 5.6). Similarly, irradiation at δ 2.11 led to 5.47 (1H, dt, *J* 15.1 and 4.5) and 5.40 (1H, dd, *J* 15.1 and 3.3); ν_{max}(film)/cm^{-1} 3500, 2900, 1460, 1370, 1060, 968.

To an ice-cooled solution of the *E* olefin (259 mg, 0.725 mmol) in dry THF (10 cm^3) was added NaH (60% dispersion in mineral oil; 58 mg, 1.45 mmol). After stirring of the mixture for 1 h, *N*-tosylimidazole (*N*-TsIm) (180 mg, 0.81 mmol) was added and the stirring was continued for another 2 h before the reaction was quenched by the addition of saturated aq. NH_4Cl. The mixture was extracted with ether, and the extract was washed with saturated aq. NaCl, and then dried with $NaSO_4$. Evaporation of the solvent afforded the crude product, which was chromatographed to afford tosyl ester **12** (370 mg, 94%). $[\alpha]_D$ −7.7 (*c* 1.8, $CHCl_3$); ν_{max}(film)/cm^{-1} 2991, 2920, 2851, 1598, 1334, 1190, 1174, 927, 905; δ_H(300 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.7), 1.36 (26H, m), 1.70 (2H, m), 1.96 (4H, m), 2.45 (3H, s), 3.74 (2H, dd, *J* 8.6 and 6.1), 3.97 (1H, dd, *J* 8.6 and 6.5), 4.62 (1H, dd, *J* 10.8 and 6.2), 5.29 (2H, m), 7.31 (2H, d, *J* 8.3), 7.80 (2H, d, *J* 8.3); *m*/*z* (EI) 508 (M^+, trace), 353 (M − Ts, 4%).

(4*R*,2′*R*,5′*R*,1″*R*)-4-{5′-[1″-Methoxymethoxy)tridecyl]tetrahydrofuran-2-yl}-2,2-dimethyl-1,3-dioxolane 13

A mixture of K_2CO_3 (3.21 g, 23.25 mmol), $K_3Fe(CN)_6$ (7.655 g, 23.25 mmol), $NaHCO_3$ (1.953 g, 23.25 mmol) and $CH_3SO_2NH_2$ (0.738 g, 7.75 mmol) was dissolved in *t*-BuOH–water (77.5 cm^3, 1 : 1) with stirring. To the resulting mixture were added $K_2OsO_2(OH)_4$ (28.5 mg, 0.077 mmol) and $(DHQD)_2PHAL$[11] (302 mg, 0.39 mmol). After the solution became clear, tosyl ester **12** (4.2 g, 7.75 mmol) was added to the reaction mixture. The mixture was stirred at rt overnight. Na_2SO_3 (11.6 g) was added and the mixture was stirred for another 30 min before being extracted with EtOAc (25 cm^3 × 4) and the organic layers were washed successively with 5% HCl and brine. The extract was dried over Na_2SO_4 and concentrated. To a solution of the residue in MeOH (20 cm^3) was added K_2CO_3 (3.4 g) and the mixture was stirred at rt. After completion of the reaction, most of the solvent was evaporated off. The residue was dissolved in water and extracted with EtOAc (25 cm^3 × 4). The combined organic layer was washed with brine, dried over

Na_2SO_4, then concentrated to give the *hydroxytridecyl THF compound* as an oil, $[\alpha]_D$ +3.3 (*c* 0.9, $CHCl_3$); ν_{max}(film)/cm^{-1} 3491; δ_H(300 MHz, $CDCl_3$) 0.87 (3H, t, *J* 6.7), 1.24 (20H, m), 1.38 (3H, s), 1.41 (3H, s), 1.65 (2H, m), 1.99 (4H, m), 3.40 (1H, m), 3.68 (1H, t, *J* 7.5), 3.85 (1H, t, *J* 6.5), 4.02 (3H, m); *m*/*z* (EI) 371 (M + 1, 45%), 353 (M + 1 − H_2O, 38) (Found: C, 71.2; H, 11.7. $C_{22}H_{42}O_4$ requires C, 71.31; H, 11.42%).

To the solution of the obtained THF compound in CH_2Cl_2 were added MOMCl (1.2 cm^3, 15.8 mmol) and Pr^i_2NEt (3 cm^3, 17.2 mmol). The resulting mixture was warmed to rt and stirred for 24 h. After completion of the reaction, the mixture was cooled to 0 °C and saturated aq. NH_4Cl (10 cm^3) was added. The mixture was extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give the crude product, which was chromatographed to give the MOM compound **13** (2.88 g, 90% for 2 steps) as an oil, $[\alpha]_D$ +30.1 (*c* 0.17, $CHCl_3$); ν_{max}(film)/cm^{-1} 2924, 2853, 1466, 1370, 1218, 1155, 1043; δ_H(300 MHz, $CDCl_3$) 0.87 (3H, t, *J* 6.7), 1.24 (22H, m), 1.36 (3H, s), 1.41 (3H, s), 1.68 (2H, m), 1.95 (2H, m), 3.38 (3H, s), 3.51 (1H, m), 3.74 (1H, t, *J* 7.5), 3.99 (2H, m), 4.08 (2H, m), 4.66 (1H, d, *J* 6.9), 4.80 (1H, d, *J* 6.9); *m*/*z* (EI) 383 (M − CH_3O, 10%), 353 (M − MOM, 14).

(1*R*,2′*R*,5′*R*,1″*R*)-1-{5′-[1″-(Methoxymethoxy)tridecyl]tetrahydrofuran-2-yl}ethane-1,2-diol 14

A solution of compound **13** (2.88 g, 6.95 mmol) in 50% aq. AcOH (30 cm^3) was stirred at 60 °C for 5 h. The solvent was evaporated off and the crude product was purified by column chromatography to give diol **14** (2.07 g, 80%) and the triol compound (with the MOM group removed) (340 mg, 15%). For diol **14**: mp 36–37 °C; $[\alpha]_D$ +12.6 (*c* 0.74, $CHCl_3$); ν_{max}(film)/cm^{-1} 3389, 1464; δ_H(300 MHz, CD_3COCD_3) 0.88 (3H, t, *J* 6.7), 1.28 (20H, m), 1.60 (2H, m), 1.90 (4H, m), 3.32 (3H, s), 3.44 (2H, m), 3.54 (2H, m), 3.96 (2H, m), 4.59 (1H, d, *J* 6.7), 4.78 (1H, d, *J* 6.8); *m*/*z* (EI) 356 (M − H_2O, 2%), 343 (M − CH_3O, 76), 313 (M − MOM, 100) (Found: C, 67.1; H, 11.6. $C_{21}H_{42}O_5$ requires C, 67.34; H, 11.30%).

(1″*R*,2*R*,2′*R*,5*R*)-2-[1″-(Methoxymethoxy)tridecyl]-5-(oxiran-2′-yl)tetrahydrofuran[6] 15

An ice-cooled solution of diol **14** (375 mg, 1 mmol) in dry THF (20 cm^3) was treated with NaH (60%; 120 mg, 3 mmol). After being stirred for 30 min, the mixture was cooled and *N*-tosylimidazole (228 mg, 1.03 mmol) was added. The resulting mixture was stirred at −20 °C for another 8 h before being quenched with cold saturated aq. NH_4Cl and extracted with ether. The ethereal solution was washed with brine, dried over Na_2SO_4, and concentrated. Column chromatography of the residue gave *title compound* **15** (328 mg, 92%) as a solid, mp 39–40 °C; $[\alpha]_D$ +19.3 (*c* 1.7, $CHCl_3$) {lit.[6] $[\alpha]_D^{24}$ +20.9 (*c* 2.48, $CHCl_3$)}; ν_{max}(KBr)/cm^{-1} 2920, 2850, 1464, 1146; δ_H(300 MHz, $CDCl_3$) 0.86 (3H, t, *J* 6.7), 1.36 (20H, m), 1.67 (2H, m), 1.82 (2H, m), 2.02 (2H, m), 2.72 (2H, m), 2.96 (1H, m), 3.38 (3H, s), 3.45 (1H, m), 3.92 (1H, dt, *J* 4.4 and 7.1), 4.02 (1H, dt, *J* 7.2 and 5.2), 4.66 (1H, d, *J* 6.9), 4.78 (1H, d, *J* 6.9); *m*/*z* (EI) 325 (M − CH_3O, 8%), 295 (M − MOMO, 100).

(1*R*,1″*R*,2′*R*,5′*R*)-1-{5′-[1″-Methoxymethoxy)tridecyl]tetrahydrofuran-2-yl}but-3-yn-1-ol[6] 5

To a solution of trimethylsilylacetylene (0.15 cm^3, 1.54 mmol) in THF at −78 °C was added a solution of *n*-BuLi (2.7 M; 0.6 mmol). After stirring of the mixture for 20 min, $BF_3{\cdot}OEt_2$ (0.18 cm^3, 1.5 mmol) was added at the same temperature and the stirring was continued for another 30 min. Compound **15** (232 mg, 0.65 mmol) was added and the mixture was stirred for 2 h before being quenched with saturated aq. NH_4Cl. The mixture was then stirred and warmed to rt during 5 min and extracted with ether. The extract was washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was dissolved in THF (2 cm^3) and treated with *n*-Bu_4NF (1.0 M solution in THF, 0.7 cm^3) at 0 °C. The mixture was allowed to warm to rt and was stirred for a further 5 h, diluted with ether, and washed successively with water and brine. Drying ($MgSO_4$) and evaporation afforded the crude product, which was chromatographed to afford the alcohol **5** (224 mg, 90%) as an oil, $[\alpha]_D$ +13.2 (*c* 0.43, $CHCl_3$) {lit.,[6] $[\alpha]_D^{24}$ +12.9 (*c* 1.10, $CHCl_3$}; ν_{max}(film)/cm^{-1} 3446, 1459; δ_H(300 MHz, CD_3COCD_3) 0.87 (3H, t, *J* 6.7), 1.38 (22H, m), 1.90–1.67 (4H, m), 2.38 (3H, m), 3.32 (3H, s), 3.44 (1H, m), 3.52 (1H, m), 4.02 (2H, m), 4.62 (1H, d, *J* 6.7), 4.80 (1H, d, *J* 6.7); *m*/*z* (EI) 351 (M − OCH_3, 0.4%), 321 (M − MOM, trace).

(1*R*,1″*R*,2′*R*,5′*R*)-4-Iodo-1-{5′-[1″-(methoxymethoxy)tridecyl]-tetrahydrofuran-2′-yl}but-3-en-1-ol 3

TBTH (325 mg, 1.120 mmol) was added to a mixture of alkynol **15** (289 mg, 0.755 mmol) and a catalytic amount of 1,1-azocyclohexanecarbonitrile (AIBN). The mixture was heated at 130 °C for 2 h and then cooled to rt. Excess of TBTH was removed by distillation under reduced pressure. The residue was dissolved in ether (2.1 cm^3). Iodine (210 mg, 0.827 mmol) was added slowly at 0 °C over a period of 1 h. The solvent was removed and the residue was purified by column chromatography to give *enol* **3** (367 mg, *E*:*Z* = 4:1, 95%) as a liquid, ν_{max}(film)/cm^{-1} 3450, 1608, 1466; δ_H(300 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.7), 1.26 (22H, m), 1.65 (2H, m), 1.95 (2H, m), 2.22 (2H, m), 3.41 (3H, s), 3.44 (2H, m), 3.82 (1H, m), 3.88 (1H, m), 4.70 (1H, m), 4.80 (1H, m), 6.12 (0.8H, d, *J* 14.6), 6.36 (0.4H, m), 6.61 (0.8H, dt, *J* 14.5 and 7.3); *m*/*z* (ESI) 534 (M + 1+Na) (Found: C, 54.05; H, 8.8. $C_{23}H_{43}IO_4$ requires C, 54.12; H, 8.49%).

Methyl (1*RS*,1′*RS*,2′*S*)-2-[1′-acetoxy-2′-(tetrahydropyran-2″-yl)propyl]undec-10-enoate 17

To an ice-cooled solution of compound **16**[12b] (1.34 g, 3.76 mmol) in pyridine (5 cm^3) was added Ac_2O (1.0 cm^3, 10.58 mmol). The reaction mixture was warmed to rt and stirred for 24 h. Et_2O was added and the organic phase was washed in turn with 3 M HCl, saturated aq. $NaHCO_3$ and brine. After drying and concentration, the residue was chromatographed to give 1.36 g of *acetoxy ester* **17** (91%), ν_{max}(film)/cm^{-1} 3074, 1740, 1439; δ_H(300 MHz, $CDCl_3$, the characteristic peaks only) 2.10 (3H, s, OAc), 2.64 (1H, m), 3.69 (3H, s, CO_2Me), 4.94 (1H, m), 5.80 (1H, ddt, *J* 16.9, 10.3 and 6.7); *m*/*z* (EI) (relative intensity) 297 (M − OTHP, 4%), 238 (M − OTHP − OAc, 2.44) (Found: C, 66.3; H, 10.0. $C_{22}H_{38}O_6$ requires C, 66.30; H, 9.61%).

(3*RS*,4*RS*,5*S*)-4-Acetoxy-5-methyl-3-(non-8′-enyl)tetrahydrofuran-2-one 18

An ice-cooled solution of ester **17** (350 mg, 0.88 mmol) in THF (5 cm^3) was treated with 10% H_2SO_4 (0.8 cm^3). The solution was saturated by adding NaCl, then was extracted with ether. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated. Silica gel column chromatography gave lactone **18** (205 mg, 83%), ν_{max}(film)/cm^{-1} 1773, 1740; δ_H(300 MHz, $CDCl_3$) 1.32 (10H, m), 1.45 (3H, d, *J* 6.6), 1.58 (2H, m), 1.81 (2H, m), 2.09 (3H, s), 2.69 (1H, m), 4.49–4.37 (1H, m), 4.90 (0.5H, m), 4.94 (1H, m), 5.00 (1H, m), 5.14 (0.5H, m), 5.78 (1H, ddt, *J* 17.0, 10.3 and 6.7); *m*/*z* (EI) 283 (M + 1, 100%), 223 (M − OAc, 76) (Found: C, 67.8; H, 9.5. $C_{16}H_{26}O_4$ requires C, 68.06; H, 9.28%).

(3*RS*,4*RS*,5*S*,8′*RS*)-4-Acetoxy-3-(8′,9′-epoxynonanyl)-5-methyltetrahydrofuran-2-one 19

To an ice-cooled solution of ene **18** (205 mg, 0.727 mmol) in CH_2Cl_2 (6 cm^3) was added MCPBA (70% v/v; 214 mg). The mixture was stirred at rt overnight. Na_2SO_3 (120 mg) was added

and stirring was continued for another 30 min. The mixture was diluted with ether and washed with brine, dried over Na_2SO_4, concentrated, and chromatographed on silica gel to give epoxide **19** (198 mg, 91%), ν_{max}(film)/cm^{-1} 1777, 1740, 1460; δ_H(300 MHz, $CDCl_3$) 1.36–1.80 (17H, m), 2.10 (3H, s), 2.46 (1H, dd, *J* 4.9 and 2.7), 2.68 (1H, m), 2.75 (1H, t, *J* 4.5), 2.9 (1H, m), 4.49–4.38 (1H, m), 4.91 (2/3H, m), 5.13 (1/3H, m); *m*/*z* (EI) 299 (M + 1, 56%), 239 (M − OAc, 51).

(5*S*,8′*RS*)-3-(8′,9′-Epoxynonanyl)-5-methyl-2,5-dihydrofuran-2-one 20

An ice-cooled solution of acetoxy lactone **19** (1.115 g, 3.74 mmol) in dry THF (12 cm^3) was treated with DBU (0.3 cm^3, 2.0 mmol). The mixture was stirred at rt for 2 h before being neutralized with several drops of HOAc. Concentration followed by chromatography on silica gel gave *unsaturated lactone* **20** (854 mg, 96%), ν_{max}(film)/cm^{-1} 1748; δ_H(300 MHz, $CDCl_3$) 1.32–1.53 (15H, m), 2.25 (2H, t, *J* 7.0), 2.45 (1H, dd, *J* 5.1 and 2.8), 2.73 (1H, t, *J* 4.5), 2.89 (1H, m), 4.98 (1H, m), 6.97 (1H, s); *m*/*z* (EI) 239 (M + 1, 4%) (Found: C, 70.3; H, 9.6. $C_{14}H_{22}O_3$ requires C, 70.56; H, 9.30%).

Hydrolytic kinetic resolution reaction of compound 20

(5*S*,8′*R*)-3-(8′,9′-Epoxynonanyl)-5-methyl-2,5-dihydrofuran-2-one 6. A solution of compound **20** (162 mg, 0.681 mmol) in DME (0.8 cm^3) was treated with (*R,R*)-salen-Co(OAc) (9 mg, 2% mol) and distilled water (0.007 cm^3, 0.55 equiv). The mixture was stirred at rt for 40 h, then purified by chromatography to give diastereoisomer **6** (74 mg, 46%) and diol **21** (76 mg, 44%). The IR, ^{1}H NMR and EIMS data of compound **6** were the same as for diastereoisomeric mixture **20**.

Addition of lithium trimethylsilylacetylide to oxirane 6 to give silyl alcohol 22

To a solution of trimethylsilylacetylene (0.12 cm^3, 0.85 mmol) stirred at −78 °C under N_2 was added *n*-BuLi (2.5 M; 0.34 cm^3, 0.85 mmol). After stirring of the mixture for 20 min, $BF_3{\cdot}OEt_2$ (0.105 cm^3) was added. Stirring was continued for 30 min before a solution of the oxirane **6** (100 mg, 0.42 mmol) in THF (1 cm^3) was added dropwise. The mixture was stirred for 2.5 h. Saturated aq. NH_4Cl was added to quench the reaction. After being stirred for 5 min, the mixture was warmed to rt and extracted with ether. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography of the residue yielded the silyl alcohol **22** (135 mg, 85%), ν_{max}(film)/cm^{-1} 3447, 2174, 1747; δ_H(60 MHz, $CDCl_3$) 0 (9H, s), 1.2 (14H, m), 1.9 (2H, m), 2.3 (4H, m), 3.6 (1H, m), 4.9 (1H, m), 6.9 (1H, s); *m*/*z* (EI) 337 (M + 1, 10%), 319 (M + 1 − H_2O, 9).

(5*S*,8′*R*)-3-(8′-Hydroxyundec-10′-ynyl)-5-methyl-2,5-dihydrofuran-2-one 4

To an ice-cooled solution of compound **22**[7] (430 mg, 1.278 mmol) in dry THF (10 cm^3) was slowly added *n*-Bu_4NF (1.0 M; 1.5 cm^3). The mixture was stirred for 2 h before being diluted with ether, washed successively with water and brine, and dried over $MgSO_4$. Concentration followed by column chromatography gave the *title alcohol* **4** (280 mg, 83%) as a liquid, $[\alpha]_D$ +30.1 (*c* 0.61, $CHCl_3$); ν_{max}(film)/cm^{-1} 3446, 3300, 1747, 1458; δ_H(300 MHz, $CDCl_3$) 1.40 (15H, m), 2.05 (1H, m), 2.26 (2H, tt, *J* 7.6 and 1.5), 2.34 (1H, dd, *J* 6.6 and 2.7), 2.43 (1H, m), 3.75 (1H, m), 4.99 (1H, m), 6.98 (1H, m); *m*/*z* (EI) 247 (M + 1 − H_2O, 1%); *m*/*z* (ESI) 287 (M + Na) (Found: M$^+$, 264.1724. $C_{16}H_{24}O_3$ requires *M*, 264.1725).

Coupling of iodide 3 with alkyne 4 to give diol 2

$PdCl_2(PPh_3)_2$ (5.6 mg) and CuI (4.8 mg) were added to a solution of iodide **3** (56 mg, 0.11 mmol) in Et_3N (4 cm^3) stirred under N_2. A solution of alkyne **4** (29 mg, 0.11 mmol) in Et_3N (0.5 cm^3) was then added. The resulting mixture was stirred for 2 h before saturated aq. NH_4Cl (3 cm^3) was added. The mixture was then extracted with ether twice. The organic phase was washed with saturated aq. NaCl and dried over $MgSO_4$. Purification on silica gel gave diol **2** (58 mg, 82%), $[\alpha]_D$ +19.3 (*c* 0.39, $CHCl_3$); ν_{max}(film)/cm^{-1} 3455, 1757, 1466; δ_H(300 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.6), 1.39 (39H, m), 1.67 (2H, m), 1.98 (2H, m), 2.27 (2H, t, *J* 7.6), 2.47 (2H, m), 3.41 (3H, s), 3.50 (2H, m), 3.73 (1H, m), 3.85 (1H, m), 3.97 (1H, m), 4.70 (1H, d, *J* 6.6), 4.80 (1H, m), 5.00 (1H, dq, *J* 1.5 and 6.7), 5.54 (1H, d, *J* 14.8), 6.16 (1H, dt, *J* 15.0), 6.99 (1H, d, *J* 1.4).

4-Deoxyannomontacin 1

To a stirred solution of enyne **2** (80 mg, 0.124 mmol) and toluene-*p*-sulfonyl hydrazide (1.59 g, 8.48 mmol) in DME (14 cm^3) at reflux was added a solution of NaOAc (0.79 g, 9.61 mmol) in water (13.2 cm^3) over a 5.5 h period. The mixture was then cooled to rt, poured into water, and extracted with ether. The organic phases were dried and concentrated. The residue was dissolved in 4 cm^3 of DMS and cooled to 0 °C. Boron trifluoride–diethyl ether (0.6 cm^3, 4.8 mmol) was added. The mixture was stirred for 30 min before being quenched with saturated aq. $NaHCO_3$ and diluted with AcOEt. The mixture was washed successively with water and brine. Drying over $MgSO_4$ and evaporation of the solvent gave a solid, which was purified by chromatography to give title compound **1** (66 mg, 88%) as a solid, mp 66.9–67.5 °C; $[\alpha]_D$ +17.0 (*c* 0.38, $CHCl_3$) {lit.,[5] $[\alpha]_D^{25}$ +10.9 (c 0.060, $CHCl_3$)}; ν_{max}(film)/cm^{-1} 3444, 3338, 1741, 1468; δ_H(600 MHz, $CDCl_3$) *inter alia* 0.88 (3H, t, *J* 6.9), 1.29 (36H, m), 1.40 (3H, d, *J* 7.2), 1.54 (2H, m), 1.98 (2H, m), 2.27 (2H, t, *J* 7.5), 2.47 (2H, m), 3.41 (2H, m), 3.58 (1H, m), 3.80 (2H, m), 4.99 (1H, q, *J* 6.6), 6.98 (1H, s); δ_C (150 MHz, $CDCl_3$) 173.83, 148.85, 134.30, 82.65, 82.59, 74.05, 71.93, 37.47, 37.42, 33.46, 33.48, 29.62–29.24, 29.09, 28.73, 27.38, 25.58–25.49, 25.15, 22.66, 19.20, 14.09; *m*/*z* (ESI) 631.6 (M + Na), 1239.7 (2M + Na); *m*/*z* (SCI) 610 (M + 1), 556 (M + 1 − 3H_2O) (Found: [MH]$^+$, 609.5089. $C_{37}H_{69}O_6$ requires *m*/*z*, 609.5089).

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