Acetogenins of annonaceae. Part 86:† synthesis of a highly functionalized precursor of (−)-4-deoxygigantecin, an annonaceous acetogenin

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A highly functionalized precursor of (−)-4-deoxygigantecin possessing six stereogenic centers has been prepared in 14 steps from tridecanal. The key steps are (*i*) enantioselective aldolization, (*ii*) diastereoselective *C*-glycosylation and (*iii*) diastereoselective aldolization reactions, all of them using 2-trimethylsilyloxyfuran as nucleophile. This strategy would allow us to prepare squamostatin D as well, another acetogenin of *Annonaceae* possessing two nonadjacent tetrahydrofuran rings and a closely related tetrahydrofuran pattern.

Since the first isolation of uvaricin in 1982,[2] more than 300 new natural acetogenins of *Annonaceae* have been isolated from either the bark, leaves, or seeds of 30 different *Annonaceae* species,[3a,b,4a] and exclusively from this botanical family. They all are supposed to derive from lacceroic (C32) or ghedoic acids (C34), further substituted by oxygenated functions [*e.g.*, tetrahydrofuran(s), tetrahydropyran, hydroxy(s), epoxide(s), *etc.*] and possessing at one terminus a γ-methyl-γ-lactone. A tentative classification has been proposed,[5] based on biogenetic hypotheses, and recent isolation of the $\Delta^{n,n+4}$ and the $\Delta^{n,n+4,n+8}$ di- and tri-unsaturated compounds[6] (type E acetogenins) has confirmed the biogenetic hypothesis. Tetrahydropyran (THP) containing acetogenins were also isolated.[7] Insecticide, antiparasitic and immunosuppressive activities have been reported for some acetogenins,[3] but most acetogenins have displayed cytotoxicity against several cancer cells,[8] and some of them have shown *in vivo* antitumor activity.[3] The antitumor and cytotoxic activities have been rationalized as involving the inhibition of NADH oxidases both at the mitochondrial level[4b] and on the cytoplasmic membranes of cancer cells,[9] resulting in decreased biosynthesis of ATP and consequently cell proliferation, which may ultimately contribute to programmed death (apoptosis).[10] Interestingly, growth inhibition was also observed for the cancer cells expressing a multidrug resistant (MDR) phenotype.[3a,b,11,12] Because this mechanism of action has no equivalent, to our knowledge, among the anticancer chemotherapeutic agents currently in use, we have decided to synthesize natural acetogenins of *Annonaceae* and related analogs, and report herein our results concerning the preparation of a precursor of (−)-4-deoxygigantecin, **1a,b**.

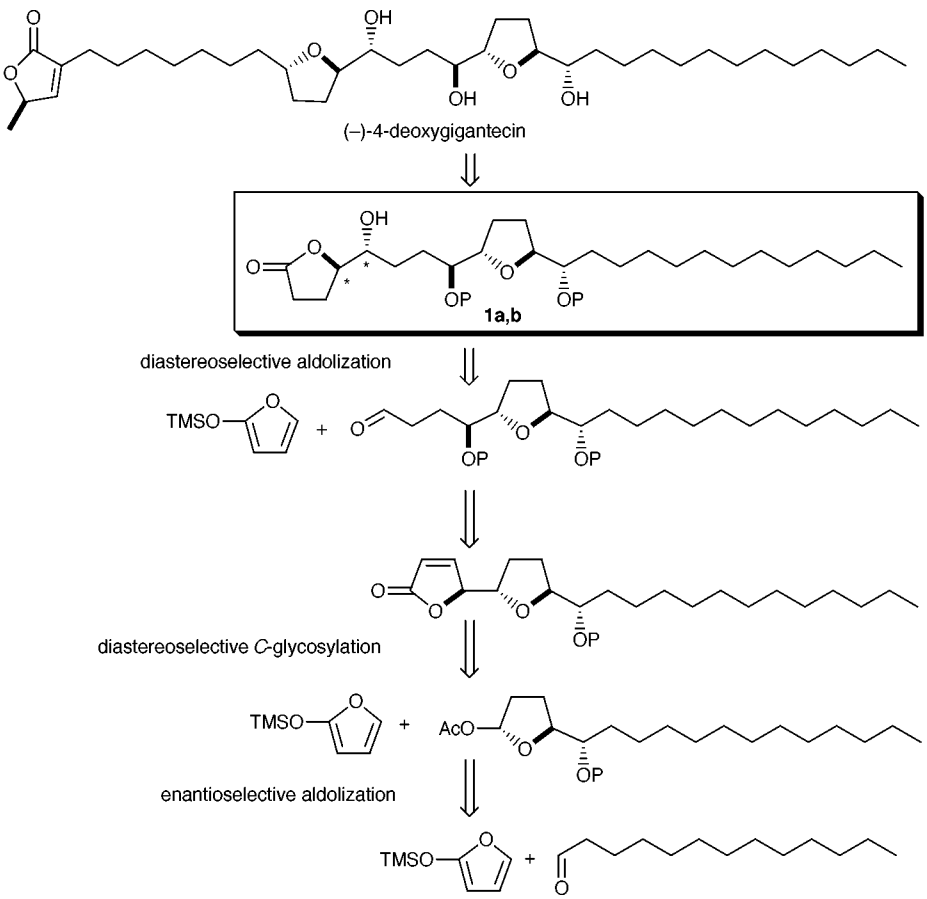
Results and discussion

Several total syntheses[13] of mono-THF,[14] adjacent bis-THF,[15] tris-THF[16] and THF-THP[17] annonaceous acetogenins have been reported, whereas only two syntheses of nonadjacent bis-THF annonaceous acetogenins, (+)-4-deoxygigantecin and (+)-squamostatin D, have been recently described in the literature.[18,19] Our retrosynthetic approach is based on the repeated use of 2-trimethylsilyloxyfuran as a four-carbon-atom building block, for chain elongation together with control of the absolute and relative configurations at the newly created chiral centers (Scheme 1).

The first step consists in the autoinductive enantioselective aldolization reaction between 2-TMSOF and tridecanal[20] to afford 2,3-dehydromuricatacin, **2**, in 80% yield as a 60 : 40 diastereomeric mixture in favor of the desired *threo* derivative with >96% e.e. (*S*,*S*) (Scheme 2). The absolute configuration of the major product was deduced from comparison of the specific rotation of the hydrogenated product **3** with reported values.[21] The best result, in terms of chemical yield and e.e., was obtained when 2-TMSOF and tridecanal were added in four portions (6.5, 18.5, 25 and 50 mol%, with 30, 60 and 90 min delays, respectively, and further stirring for 180 min at −20 °C in Et_2O).[20c] Natural muricatacin **3** was then obtained after separation and quantitative hydrogenation of **2** over palladium on charcoal. The large scale preparation of **3** from L-glutamic acid,[21] in 4 steps and 50% overall yield, further confirmed the relative and absolute configurations of **3** obtained through the aldolization procedure.

Protection of the hydroxy group of **3** was then carried out by treatment with TBDMSCl in the presence of imidazole in DMF with a catalytic amount of DMAP to afford the desired silyl ether **4** in 98% yield. Reduction of **4** at −78 °C by DIBAL-H in toluene yielded the corresponding lactol **5**, which was treated with acetic anhydride in the presence of triethylamine to afford the anomeric acetates **6** in 95% yield. Then, addition at 0 °C of 2-TMSOF to an etheral solution of the acetates **6** in the presence of a catalytic amount of $TrClO_4$ led to a 60 : 40 mixture of the sole *erythro-trans-threo* and *threo-trans-threo* butenolides **7** and **8**, respectively, in 90% overall yield.[22] Interestingly, none of the *cis* isomers were isolated. Separation of both compounds was performed by column chromatography and the major undesired isomer was then treated by Et_3N at 54 °C for 12 h to give in quantitative yield a 60 : 40 mixture of **7** and **8**. Separation of both compounds allowed us to obtain the desired *threo* compound **8** in

† For Part 85, see ref. 1.



Scheme 1 Retrosynthetic scheme for the (−)-4-deoxygigantecin precursors

58% overall yield (a second epimerization of the undesired epimer could eventually further increase the total yield of **8**).

8 was then quantitatively reduced by hydrogenation over palladium on charcoal to give the corresponding butanolide **9**. LiOH treatment of the latter in DME, followed by diazotation (CH_2N_2, Et_2O, 0 °C) and protection of the hydroxyl as a silyl ether (TBDMSCl, imidazole and catalytic DMAP in DMF) afforded the corresponding ester **10** in 42% yield for the last three steps. **10** was reduced by Dibal-H in dichloromethane to the primary alcohol, which was oxidized into the corresponding aldehyde **11** by PDC treatment in the presence of a catalytic amount of PTA in 78% overall yield for the last two steps. An aldolization reaction between 2-TMSOF and the aldehyde **11** was best performed by treatment at −78 °C in CH_2Cl_2 with BF_3OEt_2 to afford an unseparable mixture of two diastereomers, **1a** and **1b**, among the four possible ones. The stereochemical relationships were determined as *threo* for both compounds, from comparison with NMR data for related products. It is worth noting that the use of $TiCl_4$ as Lewis acid afforded a more complicated mixture, whereas no reaction occured in the presence of the (*R*)-$Binol_2$–$Ti(OPr^i)_4$ complex.

Table 1 Cytotoxic activity of various compounds

Compound	KB[a] EC_{50}[b]/μM	VERO[c] EC_{50}[b]/μM
2	24.8	28.3
3	17.6	38.7
9′	14.1	19.8
Taxol[d]	1.3	<11.9
Vinblastine[d]	1.2×10^{-3}	<3.7

[a] Human epidermoid carcinoma. [b] When EC_{50} values were not precisely determined, results are expressed as the limits of the range tested. [c] African green monkey (*Cercopithecus aethiops*) kidney epithelial cells. [d] Although the modes of action are different, taxol and vinblastine were tested for comparison.

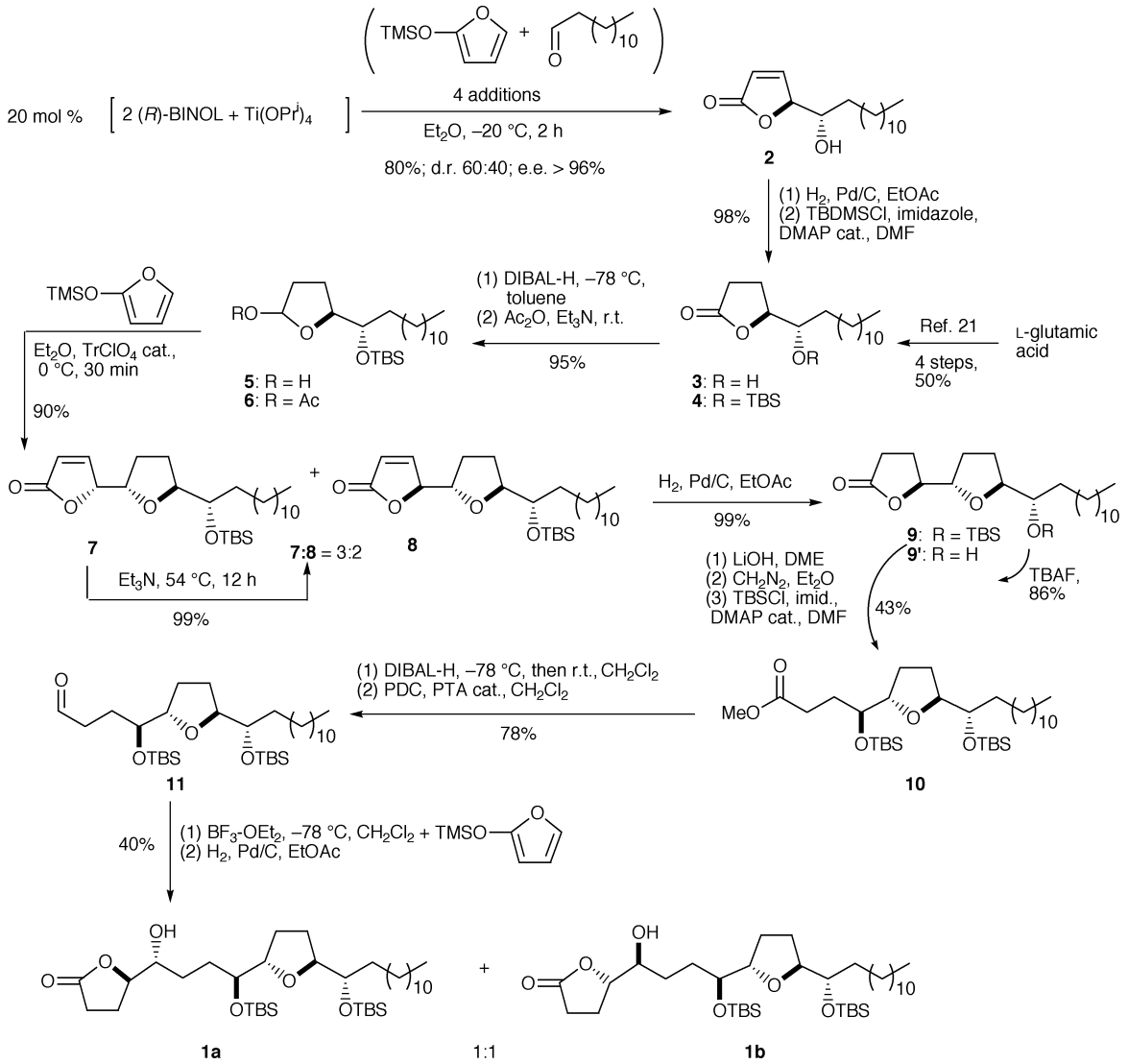
Separation of both diastereomers is expected to be accomplished in a later stage of the synthesis, based on our knowledge of natural acetogenin isolation processes (*e.g.*, by HPLC and CPC methods).[1,3,6] Furthermore, completion of the synthesis with the undesired isomer would allow us to prepare an unnatural acetogenin, whose biological activity will be evaluated and compared with the natural one. Thus, in order to gain some information on the structure-cytotoxicity relationship, several intermediates were tested against two cell lines[23] and the results are reported in Table 1.

Interestingly, compounds **3** and **9′** (obtained from **9** after TBAF deprotection of the hydroxy group) showed similar activity against cancer cells (KB) in the μM range, whereas **3** is much less active against normal cells. Moreover, compound **2** showed lower activity against cancer cells, compared to the known natural muricatacin **3**. For comparison, natural (+)-4-deoxygigantecin shows a cytotoxicity against three different cancer cell lines[24] in the range of 0.04 to 8.6 μM, indicating that our intermediates exhibit a biological activity closely related to the natural acetogenins, even though they do not possess the terminal α,β-unsaturated γ-methyl-γ-lactone.

In conclusion, we have succeeded in the synthesis, from tridecanal, of a highly functionalized precursor of (−)-4-deoxygigantecin, as a 1 : 1 bis-epimeric mixture, in 14 steps and 1.4% overall yield (and thus 78% yield per step). 2-TMSOF was used in enantioselective and diastereoselective reactions to demonstrate the versatility this reagent. Further *C*-glycosylation and introduction of the unsaturated butyrolactone through known procedures[25] should lead to the target molecule in a limited number of chemical steps. The biological activity of some of our intermediates may positively contribute to the study of the structure-activity relationship in the acetogenins of *Annonaceae*.

Experimental

Solvents were purified according to the procedures previously



Scheme 2 Synthesis of the (−)-4-deoxygigantecin precursors **1a,b**

described.[26] Infrared spectra were recorded on a Perkin–Elmer 257 apparatus (ν expressed in cm^{-1}). ^1H and ^{13}C NMR spectra were recorded with Bruker AC-200 (200 MHz) and Bruker AM-400 (400 MHz) spectrometers. Chemical shifts (δ) are referenced to the protonated solvent. Patterns are described according to Hoye *et al.*[27] and coupling constants (J) are given in Hz. Mass spectra (MS) have been recorded on a Nermag–Sidar R10-10C apparatus in either CI mode with CH_4 or NH_3 or EI mode at 70 eV. Electrospray ionization (ESI) mass spectra were recorded on a Bruker Esquire spectrometer. Flash chromatography was performed with silica gel 60 (9385 Merck), silica gel S (31607 Riedel-de-Haën), and silica gel 60H (7736 Merck). TLC was performed on plates coated with silica gel $60F_{254}$ (554 Merck).

Synthesis and characterization

(1′*S*,5*S*)-5-(1′-Hydroxydodecanyl)furan-2-(5*H*)-one, (2). To a solution of (*R*)-Binol (57 mg, 0.2 mmol) in Et_2O (2 mL), under N_2 atmosphere was added at room temperature Ti(OPr^i)$_4$ (29.5 µl, 0.1 mmol), leading to an intense orange-colored solution. After stirring for 1 h at room temperature, the solution was cooled to −20 °C and the first addition of aldehyde (6.5 mol%, 0.0325 mmol), followed by TMSOF (6.5 mol%, 0.048 75 mmol) was made. After 30 min, the second addition of aldehyde (18.5 mol%, 0.0925 mmol) and TMSOF (18.5 mol%, 0.138 mmol) was made. Then again after 60 min, the third addition of aldehyde (25 mol%, 0.125 mmol) and TMSOF (25 mol%, 0.1875 mmol) was made. After 90 min, the last addition of aldehyde (50 mol%, 0.25 mmol) and TMSOF (50 mol%, 0.375 mmol) was made. After stirring an additional 180 min, the reaction was hydrolyzed by addition of a saturated aqueous NH_4Cl solution and the organic layer extracted by EtOAc (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered then concentrated. Flash column chromatography on silica gel (cyclohexane–EtOAc 70 : 30) led to 113 mg of the two *threo* and *erythro* diastereomers in a 60 : 40 ratio (80% yield). IR ($CHCl_3$) ν: 3905–3510, 1730 cm^{-1}. CI-MS (CH_4) m/z: 283 ($MH^{\cdot+}$, 100%), 265 (27%), 199 (21%). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.54 (1H, dd, J = 5.8, J = 1.5, H_4 *erythro*), 7.45 (1H, dd, J = 5.8, J = 1.5, H_4 *threo*), 6.15 (1H, m, H_3), 4.99 (1H, m, H_5 *threo*), 4.97 (1H, m, H_5 *erythro*), 4.50 (1H, m, OH), 3.85 (1H, m, $H_{1'}$ *erythro*), 3.75 (1H, m, $H_{1'}$ *threo*), 1.55 (2H, m, $H_{2'}$), 1.25 (20H, m, CH_2), 0.87, (3H, t, J = 6.5, $H_{13'}$). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.97 (C_2), 153.85 (*threo*), 153.56 (*erythro*), 122.76 (*erythro*), 122.62 (*threo*) 86.16 (C_5), 71.73 (*threo*), 71.48 (*erythro*), 33.19, 31.87, 29.59, 29.30, 25.46, 22.64, 14.06 ($C_{13'}$). Anal. $C_{17}H_{30}O_3$: calcd C 67.89, H 9.49%; found C 68.01, H 9.54%. Analysis of the major (*threo*) diastereomer by ^1H NMR in the presence of the chiral shift reagent, europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] (Eu(hfc)$_3$), showed >96% e.e. and 90% for the *erythro* isomer.

(4*S*,5*S*)-5-Hydroxyheptadecan-4-olide [(+)-muricatacin], (3). Palladium on charcoal (6.5 mg) was added to a solution of **2** (65 mg, 0.23 mmol) in 2 mL of toluene. The solution was then vigorously stirred under H_2 atmosphere for 10 h. The

crude reaction mixture was then passed through a short pad of celite, the solvents evaporated and the crude purified by flash chromatography on silica gel (cyclohexane–AcOEt 70 : 30) to afford **3** (65 mg, 99%). $[\alpha]_D^{20}$: +24.6 (c = 1.7, MeOH); lit:[21] +23.6 (c = 1.50, $CHCl_3$). IR ($CHCl_3$) ν: 3580–3440, 2920, 2840, 1770, 1460, 1375, 1260, 1170, 980, 910 cm^{-1}. EI-MS m/z: 199 (1%), 125 (4%), 97 (6%), 87 (11%), 86 (100%), 85 (13%), 69 (16%), 57 (13%), 55 (11%), 43 (15%), 41 (17%). CI-MS (NH_3) m/z: 285 (MH^+, 31%), 268 (23%), 267 (100%), 265 (18%), 249 (7%), 239 (32%), 199 (25%), 143 (9%), 130 (23%), 125 (36%), 123 (11%), 115 (21%), 113 (26%), 112 (26%), 111 (49%), 109 (16%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.41 (1H, td, J = 4.6, J = 7.4, H_4), 3.66–3.47 (1H, m, H_5), 2.72–2.44 (2H, m, H_2), 2.33–1.88 (3H, m, H_3, OH), 1.64–1.45 (2H, m, H_6), 1.45–1.15 (20H, br s, CH_2), 0.87 (3H, t, J = 6.4, H_{17}). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.4 (C_1), 83.0 (C_4), 73.5 (C_5), 32.9, 31.6, 29.6, 29.5, 29.3, 28.6, 25.4, 24.0, 22.6, 14.0 (C_{17}). Anal. $C_{17}H_{32}O_3$: calcd C 71.78, H 11.33%; found C 71.64, H 11.40%.

(4*S*,5*S*)-5-*tert*-Butyldimethylsilyloxyheptadecan-4-olide, (4). **3** (0.811 g, 2.85 mmol) was poured into anhydrous DMF (15 mL) under N_2 atmophere. Then at room temperature imidazole (10 equiv., 28.5 mmol, 1.94 g) was added, followed by TBDMSCl (5 equiv., 14.25 mmol, 2.15 g) and a catalytic amount of DMAP. The reaction mixture was stirred at 25 °C for 12 h prior to addition of water (30 mL), followed by organic layer extraction with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude was purified by flash chromatography on silica gel (cyclohexane–AcOEt 90 : 10) to afford **4** (1.11 g, 98%). $[\alpha]_D^{20}$: +22.7 (c = 1.72, MeOH). IR ($CHCl_3$) ν: 2920, 2850, 1780, 1555, 1460, 1250, 1175, 1130 cm^{-1}. EI-MS m/z: 383 (1%), 342 (20%), 341 (77%), 323 (18%), 313 (42%), 297 (60%), 143 (25%), 75 (84%), 73 (100%), 55 (30%). CI-MS (NH_3) m/z: 400 ($MH^{\cdot+}$, 10%), 399 (22%), 383 (14%), 342 (30%), 341 (100%), 297 (68%), 267 (18%), 143 (37%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.47 (1H, ddd, J = 13.9, J = 4.4, J = 1.3, H_4), 3.77–3.59 (1H, m, H_5), 2.68–2.26 (2H, m, H_2), 2.25–1.97 (2H, m, H_3), 1.69–1.50 (2H, m, H_6), 1.49–1.12 (20H, br s, CH_2), 1.00–0.53 (12H, m, Bu^t and H_{17}), 0.08 and 0.07 [6H, 2s, $(CH_3)_2Si$)]. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.2 (C_1), 81.4 (C_4), 74.2 (C_5), 32.6, 31.8, 29.6, 29.3, 28.5, 25.7 (Bu^t), 25.2, 23.6, 22.6 (C_2 or C_3), 18.0 (C–Bu^t), 14.0 (C_{17}), −4.5 (CH_3Si).

(1*SR*,4*S*,5*S*)-1-Hydroxy-5-*tert*-butyldimethylsilyloxy-1,4-epoxyheptadecane, (5). **4** (obtained from L-glutamic acid through the procedure described in ref. 21) (4.65 g, 11.65 mmol) was poured into CH_2Cl_2 (20 mL) under N_2 atmosphere. At −78 °C Dibal-H (1 M in toluene, 12.8 mL, 1.1 equiv.) was then added dropwise. Stirring was maintained for 40 min, then saturated aqueous NH_4Cl solution (3 mL) was added and the solution was allowed to reach room temperature. The solution was filtered on silica gel and the solid washed with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Flash chromatography (cyclohexane–AcOEt 90 : 10) purification of the crude material afforded **5** (4.40 g, 95%). IR ($CHCl_3$) ν: 3600–3100, 2920, 2930, 2840, 1460, 1255, 1245, 1190 cm^{-1}. EI-MS m/z: 367 (2%), 343 (9%), 326 (14%), 325 (52%), 313 (52%), 115 (27%), 75 (92%), 73 (100%). CI-MS (NH_3) m/z: 399 (1%), 384 (21%), 383 ($M^{\cdot+} - H_2O$, 50%), 381 (11%), 367 (9%), 343 (36%), 326 (22%), 325 (83%), 314 (18%), 313 (62%), 299 (10%), 251 (15%), 233 (11%), 171 (59%), 145 (32%), 131 (100%), 121 (31%), 115 (48%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.60–5.48 (0.5H, m, H_{1a}), 5.38 (0.5H, dd, J = 10.0, J = 3.5, H_{1b}), 4.22 (1H, m, H_4), 3.96 (0.5H, d, J = 10.0, OH), 3.53 (1H, m, H_5), 2.65 (0.5H, m, OH), 2.12–1.60 (6H, m, H_2, H_3, H_6), 1.58–1.01 (20H, m, CH_2), 0.98–0.78 (12H, m, Bu^t and H_{17}), 0.12 [0.5 · 6H, s, $(CH_3)_2Si$ *cis* or *trans*], 0.06 and 0.05 [0.5 · 6H, 2s, $(CH_3)_2Si$ *cis* or *trans*]. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 98.8 (C_{1a}), 98.3 (C_{1b}), 80.7 (C_4), 74.7 (C_{5a}), 74.2 (C_{5b}), 34.9, 34.3, 33.2, 32.7, 31.9, 29.8, 29.6, 29.3, 25.9 (Bu^t), 25.5, 24.7, 24.1, 22.7, 18.2 (C–Bu^t), 14.1 (C_{17}), −4.3 (CH_3Si), −4.5 (CH_3Si).

(1*SR*,4*S*,5*S*)-1-Acetoxy-5-*tert*-butyldimethylsilyloxy-1,4-epoxy-heptadecane, (6). **5** (4.0 g, 10 mmol) was poured into anhydrous triethylamine (Et_3N, 30 mL) under N_2 atmosphere. Then at room temperature acetic anhydride (9.45 mL, 10 equiv.) was added, followed by a catalytic amount of DMAP. After 12 h of stirring, solvents were evaporated. Flash chromatography (CH_2Cl_2–Et_3N 90 : 10) purification on silica gel led to **6** (4.25 g, 95%). IR ($CHCl_3$) ν: 2930, 2845, 1730, 1440, 1360, 1240, 1120 cm^{-1}. EI-MS m/z: 383 (4%), 326 (22%), 325 (100%), 117 (70%), 75 (64%), 73 (70%). CI-MS (NH_3) m/z: 460, ($M^{\cdot} + NH_4^+$, 23%), 401 (36%), 400 ($MH^{\cdot+}$ − acetyl, 100%), 383 (35%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.39–6.18 (1H, m, H_1), 4.30–4.12 (0.5H, m, H_{4a}), 4.08–3.98 (0.5H, m, H_{4b}), 3.74–3.51 (1H, m, H_5), 2.22–1.67 (4H, m, H_2, H_3), 2.05 and 2.01 (3H, 2s, CH_3 acetyl α or β), 1.25 (22H, m, CH_2), 1.01–0.74 (12H, m, Bu^t and H_{17}), 0.17 [3H, s, $(CH_3)_2Si$], 0.12 [3H, s, $(CH_3)_2Si$], 0.07 [6H, s, $(CH_3)_2Si$]. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 170.4 (CO, acetyl), 170.1 (CO, acetyl), 99.3 (C_{1a}), 98.5 (C_{1b}), 85.0 (C_{4a}), 82.3 (C_{4b}), 75.2 (C_{5a}), 73.8 (C_{5b}), 32.9, 32.8, 32.1, 31.9, 29.6, 29.3, 25.9 (Bu^t), 25.7, 25.2, 24.5, 23.9, 22.6, 21.3 (CH_3, acetyl), 18.1 (C, Bu^t), 14.1 (C_{17}), −4.3 (CH_3Si), −4.8(CH_3Si).

(4*R*,5*S*,8*S*,9*S*)- and (4*S*,5*S*,8*S*,9*S*)-9-*tert*-Butyldimethylsilyloxy-5,8-epoxyhenicos-2-en-4-olide, (7) and (8). **6** (0.509 g, 1.15 mmol) was poured into Et_2O (10 mL) under N_2 atmosphere. The solution was cooled to 0 °C and $TrClO_4$ (39.4 mg, 0.115 mmol) was added, followed by 2-trimethylsilyloxyfuran (TMSOF, 0.386 mL, 2 equiv.). After 30 min at 0 °C a saturated aqueous $NaHCO_3$ solution (10 mL) was added. After extraction with EtOAc, the combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography on silica gel (cyclohexane–AcOEt 85 : 15) afforded **7** (285 mg) and **8** (189 mg) (90% overall yield, *erythro* (**7**): *threo* (**8**) = 60 : 40).

7: $[\alpha]_D^{20}$: +22 (c = 0.3, MeOH). IR ($CHCl_3$) ν: 2930, 2855, 1755, 1380, 1255, 1185 cm^{-1}. EI-MS m/z: 466 ($M^{\cdot+}$, 2%), 422 (5%), 409 (65%), 383 (50%), 313(100%), 269 (10%), 153 (90%), 115 (50%), 83 (30%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.58 (1H, dd, J = 5.60, J = 1.35, H_3), 6.15 (1H, dd, J = 5.60, J = 1.80, H_2), 4.85 (1H, dt, J = 7.0, J = 1.75, H_4), 3.95 (1H, m, H_8), 3.88 (1H, m, H_5), 3.53 (1H, m, H_9), 2.20–1.60 (6H, m, H_6, H_7, H_{10}), 1.32 (20H, br s, CH_2), 0.80 (12H, br s, Bu^{t}Si, H_{21}), 0.05 and 0.04 [6H, 2s, $(CH_3)_2Si$]. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.83 (C_1), 155.00 (C_3), 122.10 (C_2), 85.20 (C_4), 83.12 (C_8), 79.32 (C_5), 75.00 (C_9), 33.24, 32.00, 29.80, 29.60, 29.33, 29.19, 27.46, 25.92, 25.41, 22.67, 18.23 (C–Bu^t), 14.11 (C_{21}), −4.20 (CH_3Si), −4.57 (CH_3Si).

8: $[\alpha]_D^{20}$: +14 (c = 0.5, MeOH). IR ($CHCl_3$) ν: 2930, 2855, 1760, 1465, 1380, 1255, 1185 cm^{-1}. EI-MS m/z: 466 ($M^{\cdot+}$, 5%), 422 (10%), 409 (30%), 383 (20%), 313 (60%), 269 (40%), 243 (50%), 153(100%), 115 (60%), 83 (20%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.39 (1H, dd, J = 5.7, J = 1.5, H_3), 6.15 (1H, dd, J = 5.0, J = 2.0, H_2), 5.05 (1H, dt, J = 4.0, J = 6.8, H_4), 4.23 (1H, ddd, J = 4, J = 6.8, J = 7, H_5), 3.88 (1H, m, H_8), 3.52 (1H, m, H_9), 2.20–1.58 (6H, m, H_6, H_7, H_{10}), 1.25 (20H, br s, CH_2), 1.00–0.75 (12H, br s, Bu^{t}Si, H_{21}), 0.03 [6H, s, $(CH_3)_2Si$]. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 173.50 (C_1), 153.56 (C_3), 122.61 (C_2), 84.72 (C_4), 83.26 (C_8), 77.50 (C_5), 74.79 (C_9), 32.98, 31.85, 29.75, 29.57, 29.28, 27.71, 27.33, 25.88, 25.48, 22.61, 18.19 (C–Bu^t), 14.05 (C_{21}), −4.30 (CH_3Si), −4.63 (CH_3Si).

(4*S*,5*S*,8*S*,9*S*)-9-*tert*-Butyldimethylsilyloxy-5,8-epoxy-henicosan-4-olide, (9). **8** (obtained from several previous experiments) (1 g, 2.15 mmol) was poured into EtOAc (15 mL). Palladium on charcoal (0.1 g) was then added and the

reaction mixture was stirred 18 h under a hydrogen atmosphere at room temperature. The solution was then filtered on celite and the solid washed with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford the corresponding butanolide **9** (1 g, 99%). $[\alpha]_D^{20}$: +20 ($c = 0.5$, MeOH). IR ($CHCl_3$) ν: 2930, 2855, 1785, 1465, 1360, 1175, 1110 cm^{-1}. EI-MS m/z: 468 ($M^{\cdot+}$, 5%), 410 (70%), 383 (20%), 313 (100%), 243 (90%), 155 (40%), 115 (70%), 85 (80%). ^1H NMR (200 MHz, $CDCl_3$) δ: 4.45 (1H, ddd, $J = 7.40$, $J = 5.85$, $J = 2.50$, H_4), 4.04 (1H, ddd, $J = 10.0$, $J = 7.40$, $J = 2.50$, H_5), 3.95 (1H, m, H_8), 3.52 (1H, dt, $J = 5.0$, $J = 2.50$, H_9), 2.70–2.41 (2H, m, H_2), 2.20 (2H, m, H_3), 1.95 (2H, m, H_7), 1.66 (2H, m, H_6), 1.25 (22H, br s, CH_2), 0.88 (12H, br s, Bu^tSi, H_{21}), 0.05 [6H, s, $(CH_3)_2Si$]. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.47 (C_1), 82.76 (C_8), 81.25 (C_4), 80.58 (C_5), 74.81 (C_9), 33.25, 31.85, 29.83, 29.60, 29.57, 29.53, 29.50, 29.27, 28.11, 27.87, 27.63, 25.88, 24.52, 22.60, 18.13 (C–Bu^t), 14.02 (C_{21}), −4.36 (CH_3Si), −4.60 (CH_3Si).

(4*S*,5*S*,8*S*,9*S*)-9-Hydroxy-5,8-epoxyhenicosan-4-olide, (9′). 9 (0.05 g, 0.106 mmol) was poured into anhydrous THF (3 mL) under N_2 atmosphere. After the temperature was brought to 0 °C, 0.21 mL of 1 M tetrabutylammoniun fluoride solution was added and the mixture stirred for 2 h. Then water (5 mL) was added and the solution extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography (cyclohexane–EtOAc 50 : 50) to afford **9′** (32 mg, 86%). $[\alpha]_D^{20}$: +8.3 ($c = 1.33$, $CHCl_3$). IR ($CHCl_3$) ν: 3700–3500, 2930, 2855, 1775, 1180, 1075 cm^{-1}. CI-MS (NH_3) m/z: 372 ($M^{\cdot} + NH_4^+$, 100%), 337 (15%), 269 (16%), 174 (16%), 138 (44%), 130 (25%), 111 (18%). EI-MS m/z: 269 (20%), 155 (54%), 138 (100%), 111 (55%), 97 (24%), 83 (34%). ^1H NMR (200 MHz, $CDCl_3$) δ: 4.47 (1H, ddd, $J = 8.0$, $J = 5.0$, $J = 3.0$, H_4), 4.05 (1H, dt, $J = 7.5$, $J = 3.0$, H_5), 3.84 (1H, dt, $J = 7.5$, $J = 5.5$, H_8), 3.39 (1H, m, H_9), 2.65 (2H, m, H_2), 2.45–2.30 (3H, br m, H_3 and OH), 2.25–2.00 (2H, m, H_7), 1.72–1.60 (2H, m, H_6), 1.25 (22H, br s, CH_2), 0.86 (3H, t, $J = 6.8$, H_{21}). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.35 (C_1), 83.50 (C_8), 81.20 (C_4), 80.77 (C_5), 73.64 (C_9), 33.77, 31.90, 29.33, 28.17, 25.58, 24.65, 22.67, 14.10.

(4*S*,5*S*,8*S*,9*S*)-Methyl-4,9-di-*tert*-butyldimethylsilyloxy-5,8-epoxyhenicosanoate, (10). 9 (0.090 g, 0.191 mmol) was poured into dimethoxyethane (DME, 1.5 mL) and an aqueous LiOH solution (1 M, 0.96 mL, 0.96 mmol) was added at room temperature. After 35 min of stirring a 10% molar aqueous citric acid solution was added and organic layer extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was poured into Et_2O (2 mL) and CH_2N_2 in Et_2O (0.1 g per 100 mL, 8 mL, 0.195 mmol) was added dropwise at 0 °C. After 30 min of stirring, a 10% aqueous citric acid solution was added and the organic layer extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was poured into DMF and imidazole (0.130 g, 1.9 mmol) was added, followed by TBDMSCl (0.144 g, 0.95 mmol) and a catalytic amount of DMAP. After 15 h of stirring at room temperature, water was added and the organic layer extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification of the crude mixture by flash chromatogtaphy on silica gel (cyclohexane–EtOAc 90 : 10) afforded **10** (0.05 g, 42% from **9**). $[\alpha]_D^{20}$: −10 ($c = 0.4$, $CHCl_3$). IR ($CHCl_3$) ν: 3655–3465, 2960, 2930, 2855, 1775, 1730 1685, 1460, 1360, 1250 cm^{-1}. CI-MS (CH_4) m/z: 615 ($MH^{\cdot+}$, 39%), 614 ($M^{\cdot+}$, 17%), 599 ($M^{\cdot+}$ − Me, 58%), 557 ($M^{\cdot+}$ − Bu^t, 100%), 483 (79%), 465 (20%), 425 (21%), 383 (11%) 313 (20%), 255 (9%), 231 (23%), 171 (10%), 149 (16%), 84 (18%). ^1H NMR (200 MHz, $CDCl_3$) δ: 3.90 (2H, m, H_5, H_8), 3.65 (3H, s, Me), 3.58 (2H, m, H_4, H_9), 2.40 (2H, m, AB system, H_1), 1.90–1.56 (8H, m, H_3, H_6, H_7, H_{10}), 1.24 (20H, br s, CH_2), 0.86 (21H, br s, 2 Bu^tSi, H_{21}), 0.05 and 0.03 [12H, 2s, $(CH_3)_2Si$]. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 174.25 (C_1), 81.80 (C_8, C_5), 74.61 (C_9), 73.76 (C_4), 51.42 (Me), 32.74, 31.92, 30.35, 29.83, 29.61, 29.35, 27.83, 27.35, 27.16, 26.76, 25.92, 23.45, 23.21, 22.68, 22.34, 21.94, 21.09, 20.83, 19.77, 18.15 (C–Bu^t), 14.10 (C_{21}), 7.39, 1.00, −3.95 (CH_3Si), −4.31 (CH_3Si), −4.52 (CH_3Si), −4.73 (CH_3Si).

(4*S*,5*S*,8*S*,9*S*)-4,9-Di-*tert*-butyldimethylsilyloxy-5,8-epoxyhenicosanal, (11). 10 (0.043 g, 0.068 mmol) was poured into CH_2Cl_2, under N_2 atmosphere. The temperature was brought to −40 °C and Dibal-H (1 M in toluene, 0.4 mL, 0.4 mmol) was added. After 1 h of stirring at room temperature, an aqueous NH_4Cl solution was added to form a gel. The reaction mixture was filtered over a short pad of silica gel and the solid washed with a cyclohexane–EtOAc (90 : 10) mixture. The combined organic layers were then dried over $MgSO_4$, filtered and concentrated to afford the expected primary alcohol (0.035 g, 88%). $[\alpha]_D^{20}$: −11.5 ($c = 1.04$, $CHCl_3$). IR ($CHCl_3$) ν: 3685–3130, 2935, 2860, 1715, 1645, 1460, 1360, 1255 cm^{-1}. CI-MS (CH_4) m/z: 587 ($MH^{\cdot+}$, 100%), 571 (51%), 529 ($M^{\cdot+}$ − Bu^t, 71%), 397 (74%), 323 (65%), 133 (20%), 115 (31%), 97 (35%). ^1H NMR (200 MHz, $CDCl_3$) δ: 3.97 (2H, m, H_5, H_8), 3.65 (4H, m, H_1, H_4, H_9), 1.77–1.54 (10H, m, H_2, H_3, H_6, H_7, H_{10}), 1.27 (20H, br s, CH_2), 0.89 (21H, br s, 2 Bu^tSi, H_{21}), 0.08 and 0.06 [12H, 2s, $(CH_3)_2Si$]. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 81.79 (C_8, C_5), 74.67 (C_9, C_4) 63.12 (C_1), 32.70, 31.92, 29.85, 29.64, 29.34, 29.07, 27.36, 27.24, 25.94, 25.70, 22.67, 20.97, 18.17 (C–Bu^t), 14.09 (C_{21}), 7.56, 0.98, −3.06 (CH_3Si), −4.42 (CH_3Si), −4.69 (CH_3Si).

The thus-obtained alcohol (0.035 g, 0.059 mmol) was poured into CH_2Cl_2 and pyridinium dichromate (PDC) (0.102 g, 0.273 mmol) was added at room temperature, followed by a catalytic amount of pyridinium trifluoroacetate (PTA). After 3 h of stirring the reaction mixture was directly filtered through a short pad of silica gel and the solid washed with a cyclohexane–EtOAc (90 : 10) mixture. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford **11** (0.034 g, 97%). $[\alpha]_D^{20}$: −11 ($c = 1.46$, $CHCl_3$). IR ($CHCl_3$) ν: 3675–3370, 2960, 2930, 2855, 2735, 1720, 1605, 1460, 1360, 1255, 1210 cm^{-1}. CI-MS (CH_4) m/z: 585 ($MH^{\cdot+}$, 66%), 570 (63%), 527 ($M^{\cdot+}$ − Bu^t, 100%), 453 (79%), 383 (21%), 313 (59%), 285 (14%), 255 (4%), 201 (12%), 171 (12%), 149 (10%), 133 (36%), 115 (59%), 97 (25%). ^1H NMR (200 MHz, $CDCl_3$) δ: 9.78 (1H, br s, H_1), 3.95 (2H, m, H_5, H_8), 3.73–3.50 (3H, m, H_{2a}, H_4, H_9), 2.50 (1H, m, H_{2b}), 1.99–1.53 (8H, m, H_3, H_6, H_7, H_{10}), 1.25 (20H, br s, CH_2), 0.90 (21H, br s, 2 Bu^tSi, H_{21}), 0.06 and 0.05 [12H, 2s, $(CH_3)_2Si$]. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 202.54 (C_1), 81.74 (C_8, C_5), 74.64 (C_9), 73.71 (C_4), 32.80, 32.68, 31.92, 31.16, 30.50, 30.16, 29.65, 29.35, 29.22, 28.73, 27.32, 27.22, 26.89, 25.91, 25.55, 25.07, 22.68, 18.06 (C–Bu^t), 14.09 (C_{21}), 6.73, 0.99, −3.95 (CH_3Si), −4.11 (CH_3Si), −4.31 (CH_3Si), −4.71 (CH_3Si).

(4*SR*,5*SR*,8*S*,9*S*,12*S*,13*S*)-5-Hydroxy-8,13-di-*tert*-butyldimethylsilyl-9,12-epoxypentacosan-4-olide, (1a,b). 11 (0.034 g, 0.058 mmol) was poured into CH_2Cl_2 under N_2 atmosphere, the temperature was brought to −78 °C and TMSOF (15 μL, 0.09 mmol) was added, followed by $BF_3 \cdot Et_2O$ (7 μL, 0.058 mmol). After 4 h of stirring, an aqueous NH_4Cl solution was added and the organic layers extracted by EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification of the crude mixture by flash chromatography on silica gel (cyclohexane–EtOAc 80 : 20) afforded an unseparable mixture of the desired butenolides (0.014 g, 38.5%, with >95% of the *threo* derivatives). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.46 (0.5H, dd, $J = 4.6$, $J = 0.8$, H_4), 7.45 (0.5H, dd, $J = 4.6$, $J = 0.6$, H_4), 6.17 (1H, br d, $J = 2.8$, H_3),

5.02 (0.5H, m, H_5), 4.97 (0.5H, m, H_5), 3.93 (2H, m, $H_{5'}$, $H_{8'}$), 3.78 (1H, m, $H_{1'}$), 3.66 (1H, m, $H_{4'}$), 3.56 (1H, m, $H_{9'}$), 1.87 (2H, m, $H_{6'a}$, $H_{7'a}$) 1.77–1.47 (8H, m, $H_{2'}$, $H_{3'}$, $H_{6'b}$, $H_{7'b}$, $H_{10'}$), 1.26 (20H, br s, CH_2), 0.89 (21H, br s, Bu^tSi, $H_{21'}$), 0.09, 0.08, 0.06 and 0.05 (12H, 4s, $(CH_3)_2Si$]. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 175.65 (C_2), 154.23 (C_4), 122.67 (C_3), 86.80 (C_{5a}), 85.41 (C_{5b}), 81.61 ($C_{5'}$), 81.41 ($C_{5'}$ or $C_{8'}$), 74.62 ($C_{4'}$), 73.98 ($C_{9'}$), 71.91 ($C_{1'}$), 43.75, 37.08, 36.02, 33.28, 32.86 31.89, 31.22, 30.53, 29.85, 29.64, 29.34, 28.68, 28.50, 27.70, 27.26, 25.92, 25.49, 22.64, 18.19 (C–Bu^t), 14.09 ($C_{21'}$), 7.02, 0.87, −3.86 (CH_3Si), −4.34 (CH_3Si), −4.83 (CH_3Si). ESI-MS *m/z*: 686 ($M^{\cdot} + NH_4^+$, 60%), 669 ($MH^{\cdot +}$, 100%).

The unseparable mixture of the butenolides (0.014 g, 0.02 mmol) was then poured into EtOAc (2 mL) and palladium on charcoal (0.0014 g) was added. After 18 h of stirring at room temperature under a hydrogen atmosphere, the reaction mixture was directly filtered through a short pad of silica gel and the solid washed with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford a mixture of **1a,b** (0.014 g, 99%). ^1H NMR (200 MHz, $CDCl_3$) δ: 4.40 (1H, m, H_4), 3.90 (2H, m, H_9, H_{12}), 3.73 (1H, m, H_5), 3.68–3.48 (2H, m, H_8, H_{13}), 2.50 (3H, m, H_2, H_{3a}), 2.36 (1H, m, H_{3b}), 2.10–1.39 (10H, m, H_6, H_7, H_{10}, H_{11}, H_{14}), 1.26 (18H, br s, CH_2), 0.88 (21H, br s, 2 Bu^tSi, H_{25}), 0.07 and 0.05 [12H, 2s, $(CH_3)_2Si$]. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 176.41 (C_1), 82.77 (C_4), 82.38 (C_9 or C_{12}), 82.08 (C_9 or C_{12}) 73.55 (C_{13}), 72.95 (C_8), 68.22 (C_5), 43.11, 38.11, 34.80, 34.01, 33.44, 32.28, 31.89, 31.16, 30.00, 29.64, 29.31, 29.20, 28.01, 27.13, 25.91, 25.31, 24.43, 23.07, 22.65, 18.43 (C–Bu^t), 18.12 (C–Bu^t), 14.85 (C_{25}), 6.96, −4.09 (CH_3Si), −4.25 (CH_3Si), −4.38 (CH_3Si), −4.90 (CH_3Si). ESI-MS *m/z*: 688 ($M^{\cdot} + NH_4^+$, 59%), 671 ($MH^{\cdot +}$, 100%).

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