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Annonaceous Acetogenins: Preparation of New Methoxy Substituted THF Synthons from D-Glucose

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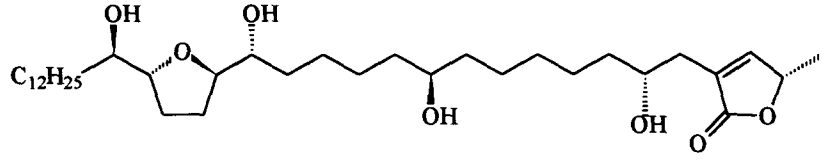
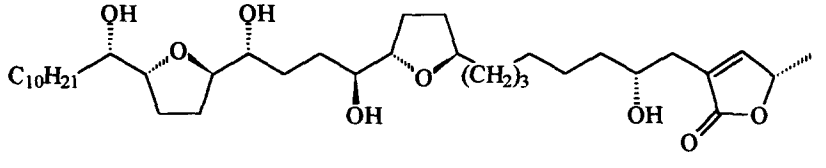
Abstract : In connection with the synthesis of cytotoxic annonaceous acetogenin analogs, enantiomerically pure *threo* (and *erythro*)-*trans* THF synthons have been prepared from D-glucose. These synthons are characterized by the presence of two methoxy (or hydroxy) groups in the THF ring, each in a *cis* configuration with respect to the vicinal side chain.

Annonaceous acetogenins, potent inhibitors of NADH:ubiquinone oxidoreductase and NADH oxidase, display interesting biological activities (cytotoxic, immunosuppressive, pesticidal,...).[1] Their fatty acid derived structures (more than 280 compounds have been isolated to date) are characterized by the presence of one to three tetrahydrofuran (THF) and/or tetrahydropyran (THP) rings and a terminal butenolide (or butanolide) moiety. *Threo* (or *erythro*)-*trans-threo* relative configurations are most common among acetogenins. Representative examples include the mono-THF annonacin[2] and the non-adjacent bis-THF bullatalicin[3] (the same situation prevails for adjacent bis-THF compounds).



Annonacin



Bullatalicin

Key features which also are essential for potent bioactivity are a C_{10}-C_{12} terminal side chain and a remote localization of the THF ring(s) and the lactone moiety. These observations suggest a possible interaction with

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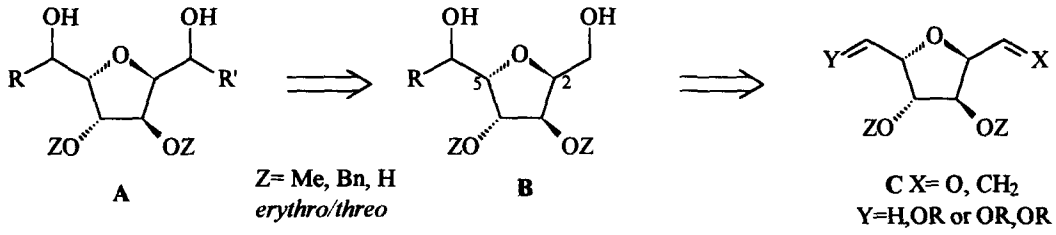
the cell membrane and with nearby localized intra- or intercellular enzymes.[4] Furthermore, the ability of these compounds to bind mono and bivalent metal ions has been demonstrated by mass spectrometry[5] and ^{1}H NMR[6] and this property may be relevant to their inhibition of NADH:ubiquinone reductase and NADH oxidase (although this has not been demonstrated). THF acetogenins are conformationally labile compounds and it seems worthwhile to prepare analogs bearing additional functional groups in the THF ring. Such compounds may exhibit enhanced and/or more specific binding and will help to determine the influence of this ionophoric property on activity and/or toxicity.

In this respect, incorporation of hydroxy or alkoxy substituents in the THF ring(s) could be of interest, especially since the THF rings seem to anchor the compounds in the hydrophobic surfaces of the membrane.[4] Enantiomerically pure **A**, analogs of annonacin and bullatalicin, should be available from carbohydrates and particularly from 2,5-anhydrosugars. Thus, 2,5-anhydro-*L*-idose derivatives **C** appear to be suitable precursors to new synthons **B** with the proper chirality at C-2 and C-5. Furthermore alkoxy (or hydroxy) groups will be in a *cis* relationship to each vicinal side chain for maximum interaction (Scheme 1).

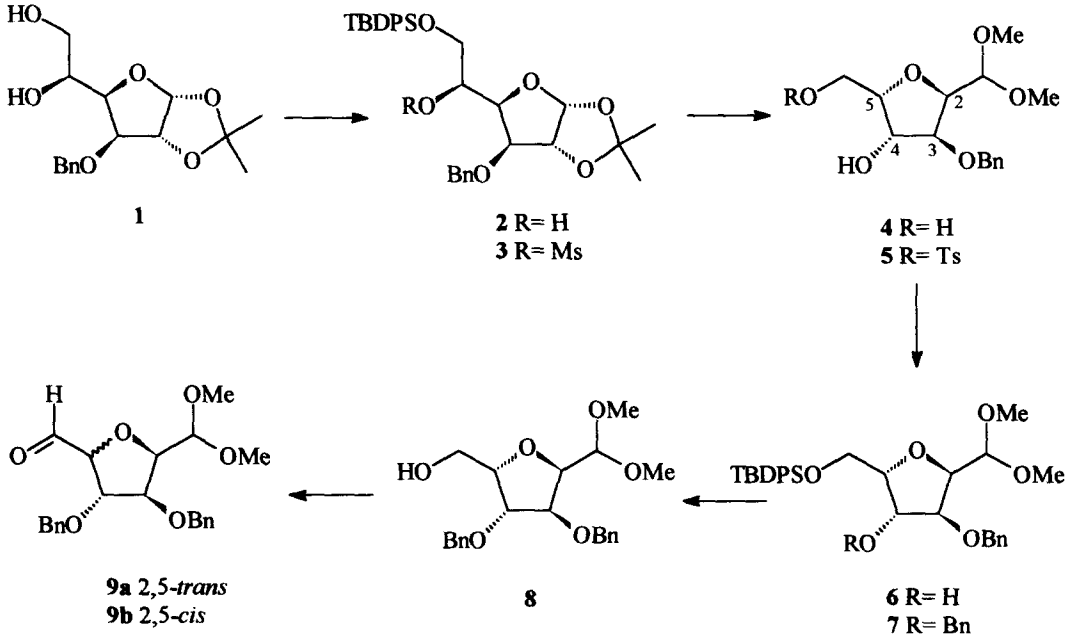


Scheme 1

Two routes were considered to prepare *erythro* or *threo* synthons **B**: Grignard condensation to a suitably protected aldehyde **C** (X=O) or epoxidation of alkene **C** (X=CH_2) followed by nucleophilic substitution with a lithioalkyne.

First, dimethylacetal **9** was prepared (Scheme 2) from D-glucose by a slight modification of the method of Defaye[7] who has converted the 5,6-di-*O*-tosylate of diol **1** to **5** (2% HCl, MeOH, reflux). The known diol **1** was selectively protected as the TBDPS ether **2** (95 %) before conversion to mesylate **3** in 89 % yield (tosylation was unsuccessful). At this stage, it was expected to find acidic conditions to carry out the Defaye reaction without cleavage of the TBDPS protecting group. However, all attempts failed using methanol or ethylene glycol in the presence of various acids (HCl, PTSA, CF_3COOH, $FeCl_3$-SiO_2) and the reaction was finally carried out under standard conditions (1% HCl, MeOH, reflux) to give diol **4** (85 %) which was then reprotected as the TBDPS ether (**6**, 91 %). The structure of diol **4** was secured by conversion to the monotosylate **5** which turned out to be identical to the compound described by Defaye.[7] This was followed by benzylation of **6** to **7** (67 %) and TBAF cleavage of the TBDPS ether to afford **8** (94 %).[8]

Alcohol **8** was then submitted to various oxidation conditions which failed to give the expected pure aldehyde **9a**. Various amounts of the epimeric aldehyde **9b** were obtained. Standard Swern oxidation using Et_3N gave a 4 to 1 mixture characterized by the presence of two CHO signals at δ 9.60 and 9.70 ppm in ^1H NMR while PCC oxidation afforded a 1/1 mixture. No attempts were made to use milder oxidation conditions to get pure aldehyde **9a**. Furthermore, condensation of $C_{12}H_{25}MgBr$ with **9a,b** (4/1 ratio) in diethyl ether gave a mixture of the 4 possible diastereoisomeric alcohols whose structures could not be firmly established.

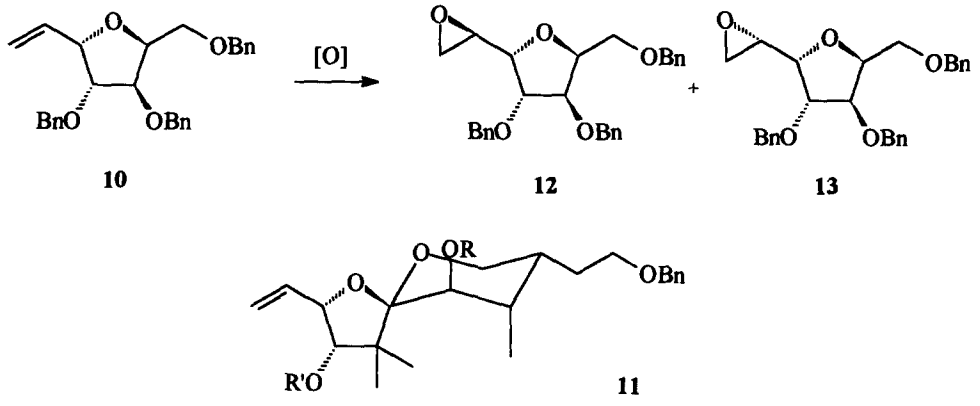


Scheme 2

This ready epimerization of aldehyde **9** led us to study the alternative preparation of synthons **C** ($X=CH_2$). To this end, alkene **10** was prepared in two steps (*i:* methylene triphenylphosphorane, DME, *ii:* Tf_2O, pyridine) from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose by the method of Martin[9] in a 50 % overall yield. Epoxidation of **10** was then studied (Scheme 3). An interesting reversal of diastereoselectivity was observed between mCPBA (*erythro/threo:* **13/12**: 3/1, 70% overall yield) and Payne conditions (*threo/erythro:* **12/13**: 5/1, 85%). This has been previously pointed out in several cases[10] and particularly by Smith[11] for the epoxidation of **11**, an intermediate toward Calyculin. We have recently proposed an hydrogen-bonded transition structure between perbenzimidic acid and an allylic ether which explains the *syn* epoxidation of cyclohexenyl derivatives under Payne conditions.[12] However, the conformational mobility of **10** precludes any safe diastereoselectivity assignment.

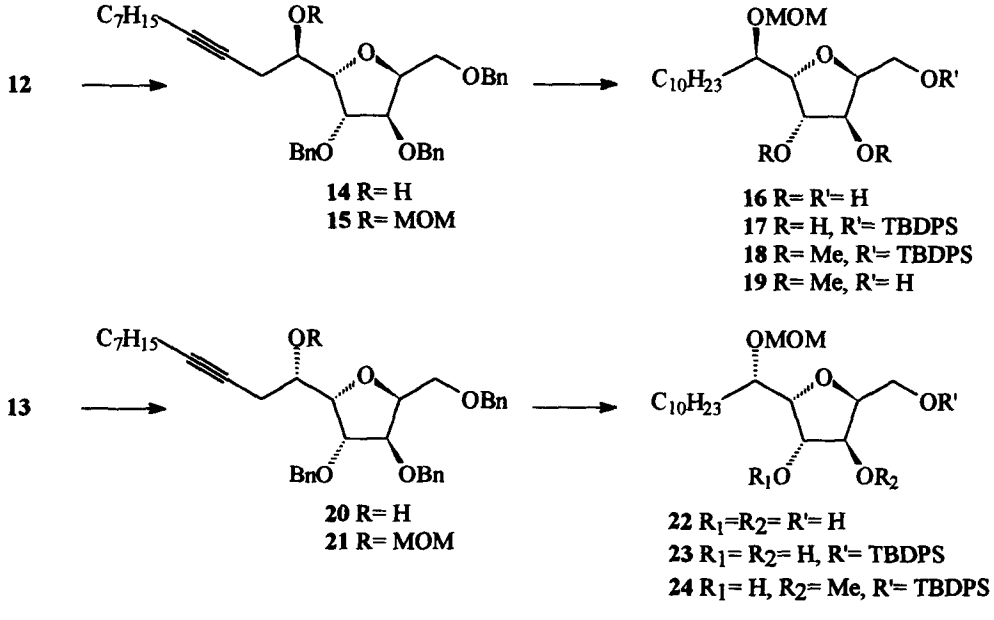
Relative configurations for epoxides **12** and **13** are, thus, proposed by comparison with Smith experiments and with the *erythro* selectivity (ca. *1.8/1)* observed by Omura[13] for the mCPBA epoxidation of

related carbohydrate derivatives. In our case, ^{1}H and ^{13}C NMR spectra of both epoxides exhibit no significant variations. For example, the coupling constant between the vicinal methyne protons of the epoxide and the THF ring is only slightly smaller (J 3.9 Hz) for **12** compared to **13** (J 4.9 Hz).



Scheme 3

Addition of 1-lithiononyne to **12** afforded **14** (92 % isolated yield, 70 % conversion) which was then converted to alcohol **17** in 3 steps: *i:* MOM protection to **15** (70 %), *ii:* quantitative alkyne reduction and hydrogenolysis of the benzyl groups to triol **16** (H_2, Pd/C) and *iii:* selective protection of the primary hydroxyl group as a TBDPS ether (70 %). The same reaction sequence was applied to **13** to give **23** in similar overall



Scheme 4

yield (Scheme 4).

At this stage, conversion of diols **17** and **23** to the corresponding dimethylethers was considered. The permethylation of **17** to **18** required prolonged heating (CH_3I, Ag_2O, CH_3CN, reflux, 4 days, 72 %) to reach completion. Obviously, steric hindrance from both side chains slowed the reaction. This was even more true in the *erythro* series since only a monomethylated compound (tentatively assigned as **24)** could be obtained after prolonged heating.

In conclusion, the synthesis of several enantiomerically pure *threo* or *erythro* THF synthons (**17-19** and **22-23)** has been completed in only 7 to 9 steps from commercially available 2,3,4,6-tetra-*O*-benzyl-*D*-glucose. Such selectively protected intermediates are amenable for further transformation. For example, Swern oxidation of **19** afforded the corresponding aldehyde (80 %) as a single diastereoisomer as shown by ^1H NMR (δ 9.62 ppm for the aldehydic proton). In contrary to **9,** no epimerisation was detected in this case. The preparation of new ring substituted analogs of annonaceous acetogenins is pursued from these intermediates and this will be reported in due course.

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Experimental Section

Melting points are uncorrected. ^1H NMR and ^{13}C NMR were recorded on a 200 (Bruker WP200SY) or 300 MHz (Bruker Advance DPX300) spectrometer, using $CDCl_3$ as solvent with TMS as internal standard. Assigmnent of ^1H and ^{13}C NMR spectra were achieved using 2D (HETCOR) methods. IR spectra were recorded on a Nicolet Magna 750 FT-IR spectrophotometer. Optical rotations were measured with a Perkin Elmer 141 polarimeter. Elemental analyses and high resolution MS were performed by the "Service Central de Microanalyse" (CNRS, Lyon). All reactions were run under an inert atmosphere. THF was dried over and distilled from sodium/benzophenone and CH_2Cl_2 was distilled from P_2O_5. Organic extract mixtures were dried over anhydrous Na_2SO_4, filtered and the solvent was then removed under reduced pressure. All separations were done under flash chromatography conditions on silica gel (Matrex, 25-40 mμ) and thin layer chromatography (TLC) were performed on silica gel plates (Merck, $60GF_{254}$).

3-*O*-benzyl-6-*O*-*tertio*butyldiphenylsilyl-1,2-*O*-isopropylidene-α-*D*-*gluco*furanose **2.**

Imidazole (0.68 g, 10 mmol) and TBDPSCl (1.14 mL, 4.4 mmol) were added to a solution of diol **1** (1.245 g, 4 mmol) in DMF (8.8 mL). Stirring was continued for 1 h at rt, followed by hydrolysis and CH_2Cl_2 extraction.

Flash chromatography using AcOEt/Pet. ether (5/95 then 15/85) afforded **2** as a colorless oil (2.097 g, 95 %). $[\alpha]_D$ = -29.5° (c 0.56, $CHCl_3$). ^1H NMR: δ 1.07 (m, 9 H, *t*BuSi), 1.29 and 1.46 (2 s, 6 H, 2 Me), 2.79 (d, *J* 12 Hz, 1 H, OH), 3.86 (m, 1 H, H-3), 4.13 (m, 2 H, H-4 and H-5), 4.33 (dd, *J* 3 and 12 Hz, 2 H, H-6), 4.59 (d, *J* 6 Hz, 1 H, H-2), 4.57 (d, *J* 12 Hz, 1 H, O-CH-Ph), 4.67 (d, *J* 12 Hz, 1 H, O-CH-Ph), 5.91 (d, *J* 6 Hz, 1 H, H-1), 7.34 (m, 10 H, H-arom), 7.67 (m, 5 H, H-arom) ppm. ^{13}C NMR: δ 19.1, 26.7, 26.75, 65.3, 68.7, 72.1, 79.3, 81.7, 82.0, 105.4 and 111.3 ppm. IR (film): 1110, 1223, 1380, 1560, 2859, 2934 and 3572 cm^{-1}. Anal.Calcd for $C_{32}H_{40}O_6Si$: C 70.04, H 7.35. Found: C 70.17, H 7.28.

3-*O*-benzyl-6-*O*-*tertio*butyldiphenylsilyl-1,2-*O*-isopropylidene-5-*O*-mesyl-α-*D*-*gluco*furanose **3.**

MsCl (1. 1 mL, 13.6 mmol) and a catalytic amount of DMAP were added to a solution of **23** (5.34 g, 9.74 mmol) in pyridine (13.5 mL). Stirring was continued for 6 h at rt, followed by hydrolysis and extraction with CH_2Cl_2,. There was obtained **3** (5.45 g, 89 %) as a white powder, m.p. 95-96°C, after recrystallisation from MeOH.

$[\alpha]_D$ = -36.5° (c 0.09, $CHCl_3$). ^1H NMR: δ 1.07 (m, 9 H, *t*BuSi), 1.28 and 1.46 (2 s, 6 H, 2 Me), 2,88 (s, 3H, SO_2Me), 4.06 (m, 4 H, H-3, H-4 and H-6), 4.59 (m, OCH_2Ph and H-2), 5.15 (m, 1 H, H-5), 5.84 (d, *J* 6 Hz, H-1), 7.36 (m, 10 H, H-arom) and 7.67 (m, 5 H, H-arom) ppm. ^{13}C NMR: δ 18.8, 25.8, 26.3, 38.45, 62.8, 71.7, 77.2, 78.2, 80.9, 81.2, 104.7, 111.4, 127.8-136.9 ppm. IR (film): 930, 1122, 1187, 1368, 2868 and 2932 cm^{-1}.Anal. Calcd for $C_{33}H_{43}SO_8Si$: C 63.23, H 6,76. Found: C 63.34, H 6.58.

(2*R*,3*S*,4*S*,5*S*)-3-benzyloxy-4-hydroxy-5-hydroxymethyl-2-dimethoxymethyl-tetrahydrofuran **4.**

A suspension of **3** (5 g, 7.98 mmol) in 0.5 % HCl-MeOH (50 mL) was heated at reflux for 8 h. After cooling and neutralisation with a cold saturated solution of $NaHCO_3$ the crude mixture was extracted with ether. Flash chromatography using AcOEt/Pet. ether as eluent (30/70 to 90/10) afforded **4** as a colorless oil (2 g, 85%).

$[\alpha]_D$ = +26° (c 0.23, $CHCl_3$). ^1H NMR: δ 3.36 and 3.40 (2 s, 6 H, 2 Me), 3.95 (m, 4 H, 2 OH and CH_2OH), 4.16 (m, 2 H, H-3 and H-4), 4.26 (m, 1 H, H-2), 4.37 (m, 1 H, H-5), 4.59 (m, 3 H, $CH(OMe)_2$, OCH_2Ph), 7.30 (m, 5 H, H-arom) ppm. ^{13}C NMR: δ 53.0, 54.8, 60.9, 72.1, 75.1, 79.0, 79.95, 84.6, 102.4 and 127-138 ppm. IR (film): 1111, 2943, 3475 and 3548 cm^{-1}. HRMS: calcd for $C_{15}H_{22}O_6$, 298.1416, found, 298.1418.

(2*R*,3*S*,4*S*,5*S*)-3-benzyloxy-4-hydroxy-5-*tertio*butyldiphenylsilyloxymethyl-2-dimethoxymethyl-tetrahydrofuran **6.**

A mixture of **4** (1.44 g, 4.8 mmol), imidazole (0.817 g, 12 mmol) and TBDPSCl (19 mL, 7.24 mmol) in DMF (10 mL) was stirred for 3 h at rt. After hydrolysis, extraction with ether and flash-chromatography using AcOEt/Pet. ether as eluent (15/85), **6** was isolated as a colorless oil (2.35 g, 91 %).

^1H NMR: δ 1.04 (m, 9 H, *t*BuSi), 3.38 and 3.43 (2 s, 6 H, 2 OMe), 4.05 (m, 3 H, CH_2OSi and OH),

4.15 (d, *J* 2 Hz, 1 H, H-3), 4.21 (d, *J* 3 Hz, 1 H, H-4), 4,33 (dd, *J* 4 and 8 Hz, 1 H, H-2), 4.47 (m, 1 H, H-5), 4.63 (m, 3H, $CH(OMe)_2$ and OCH_2Ph) and 7.3-7.8 (m, 15 H, H-arom) ppm. ^{13}C NMR: δ 19.0, 26.7, 52.4, 54.7, 63.4, 72.4, 76.3, 79.25, 79.4, 85.1, 102.25 and 127-139 ppm. IR (film): 982, 1083, 1562, 2940 and 3462 cm^{-1}. HRMS: calcd for $C_{31}H_{40}O_6Si$, 536.2594, found, 536.2569.

(2*R*,3*S*,4*S*,5*S*)-3,4-dibenzyloxy-5-*tertio*butyldiphenylsilyloxymethyl-2-dimethoxymethyl-tetrahydrofuran **7**.
Freshly prepared Ag_2O (230 mg, 0.99 mmol) was added to a solution of **6** (0.354 g, 0.66 mmol) and benzyl bromide (0.2 mL, 1.65 mmol) in DMF (1 mL). Stirring was continued for 3 h at rt with protection from light. After addition of $CHCl_3$ and filtration over Celite®, flash chromatography using AcOEt/Pet. ether as eluent (5/95 to 10/90) afforded **7** as a colorless oil (0.280 g, 67 %).
$[\alpha]_D$ = + 11.6° (c 0.3, $CHCl_3$). ^1H NMR: δ 1.05 (m, 9 H, *t*BuSi), 3.63 (s, 6 H, 2 OMe), 3.90 (m, 2 H, CH_2OSi), 4.03 (d, *J* 3.7 Hz, 1 H, H-3), 4.06 (d, *J* 3.7 Hz, 1 H, H-4), 4.13 (dd, *J* 3.7 and 8 Hz, 1 H, H-2), 4.37 (m, 1 H, H-5), 4.53 (m, 4 H, 2 OCH_2Ph), 4.63 (d, *J* 8 Hz, 1 H, $CH(OMe)_2$) and 7.28-7.66 (m, 20 H, H-arom) ppm. ^{13}C NMR: δ 19.2, 26.85, 52.4, 55.0, 61.1, 72.5, 72.55, 78.9, 80.9, 81,0, 81,95, 102.1 and 127-138 ppm. IR (film): 982, 1083, 1562, 2940 and 3462 cm^{-1}. HRMS: calcd for $C_{38}H_{46}O_6Si$, 626.3063, found, 626.3089.

(2*R*,3*S*,4*S*,5*S*)-3,4-dibenzyloxy-5-hydroxymethyl-2-dimethoxymethyl-tetrahydrofuran **8.**
A solution of **7** (1.246 g, 2 mmol) and TBAF (0. 95 g, 3 mmol) in THF (10 mL) was stirred at rt for 18 h. After hydrolysis with a saturated solution of NH_4Cl and extraction with ether, flash chromatography using AcOEt/Pet. ether as eluent (30/70) gave **8** (0.73 g, 94 %) as a colorless oil.
$[\alpha]_D$ = +40.5° (c 0.58, $CHCl_3$). ^1H NMR: δ 2.88 (m, 1 H, OH), 3.40 and 3.43 (2 s, 6 H, 2 OMe), 3.83 (m, 2 H, CH_2OH), 4.02 (dd, *J* 1 and 4.4 Hz, 1 H, H-4), 4.06 (d, *J* 3.7 Hz, 1 H, H-3), 4.20 (dd, *J* 3.7 and 7.7 Hz, 1 H, H-2), 4.31 (m, 3 H, H-5 and OCH_2Ph), 4.53 (m, 2 H, OCH_2Ph), 4.64 (d, *J* 7.7 Hz, 1H, $C\underline{H}(OMe)_2$) and 7.32 (m, 10 H, H-arom) ppm. ^{13}C NMR: δ 52.8, 54.8, 61.3, 72.1, 72.4, 79.0, 80.7, 81.2, 82.05, 102.25 and 127-138 ppm. IR (film): 1084, 2938 and 3487 cm^{-1}. HRMS: calcd for $C_{22}H_{28}O_6$, 388.1858, found, 358.1881.

(2*R*,3*S*,4*S*,5*R*,*S*)-3,4-dibenzyloxy-5-hydroxymethyl-2-dimethoxymethyl-tetrahydrofuran **9a,b.**
A solution of DMSO (0.06 mL, 0.87 mmol) in CH_2Cl_2 (0.3 mL) was slowly added to a cold (-78°C) solution of oxalyl chloride (0.03 mL, 0.44 mmol) in CH_2Cl_2 (0.2 mL). After 5 min, alcohol **8** (0.150 g, 0.39 rnmol) in CH_2Cl_2 (0.25 mL) was added and the reaction mixture was stirred at -78°C for 15 min before addition of Et_3N (0.3 mL). The reaction mixture was stirred up to rt, hydrolyzed with water (2 mL) and extracted with CH_2Cl_2. An unseparable 4/1 mixture of **9a,b** was obtained as a colorless oil (0,144 g, 95 %).
^1H NMR: δ 3.40 and 3.47 (2 s, 6 H, 2 Me), 4.0-4.5 (m, 8 H, H-2, H-3, H-4, H-5 and OCH_2Ph), 4.69 (d, *J* 7.4 Hz, 1 H, $CH(OMe)_2$), 7.31 (m, 10 H, H-arom), 9.60 (s, 0.75 H, CHO) and 9.70 (s, 0.25 H, CHO) ppm.

(2*R*,3*S*,4*S*,5*S*)-2-benzyloxymethyl-3,4-dibenzyloxy-5-(*R*-oxacyclopropyl)-tetrahydrofuran **12** and (2*R*,3*S*,4*S*,5*S*)-2-benzyloxymethyl-3,4-dibenzyloxy-5-(*S*-oxacyclopropyl)-tetrahydrofuran **13.**

mCPBA epoxidation. A solution of **10** (0.261 g, 0.6 mmol) and mCPBA (0.155 g, 0.9 mmol) in CH_2Cl_2 (2 mL) was stirred for 72 h at rt. After hydrolysis with a saturated solution of Na_2SO_4 and extraction with CH_2Cl_2, the epoxide mixture was separated by flash chromatography using AcOEt/Pet. ether as eluent (10/90) to give **12** and **13** in a 1/3 ratio (70 %).

Payne epoxidation. To a solution of **10** (1.9 g, 4.32 mmol) in MeOH (3 mL) was added benzonitrile (0.68 mL, 6.63 mmol), $KHCO_3$ (0.110 g, 1.1 mmol) and then (dropwise) 30 % H_2O_2 (0.68 mL, 6.63 mmol). The white suspension was stirred for 48 h at rt, hydrolysed with a saturated solution of Na_2SO_3 and extracted with CH_2Cl_2. Flash chromatography afforded **12** and **13** in a 5/1 ratio (85 %).

12: $[\alpha]_D$ = + 12° (c 0. 25, $CHCl_3$). ^1H NMR: δ 2.55 (dd, J 2.7 and 5 Hz, 1 H, CH_2 epoxide), 2.76 (t, *J* 5 Hz, 1 H, CH_2 epoxide), 3.24 (m, 1 H, CH epoxide), 3.69 (m, 2 H, CH_2OBn.) 3.80 (t, *J* 4.7 Hz, 1 H, H-5), 4.04 (dd, *J* 2.1 and 4.7 Hz, 1 H, H-4), 4.13 (dd, *J* 2.1 and 4.3 Hz, 1 H, H-3), 4.43 (m, 1 H, H-2), 4.53 (m, 6 H, 3 OCH_2Ph) and 7.33 (m, 15 H, H-arom) ppm. ^{13}C NMR: δ 43.3 (C-7), 51.1 (CH_2 epoxide), 68.3 (CH epoxide), 72.1, 72.4, 73.4 (3 CH_2OBn), 79.25 (C-2), 81.05 (C-5), 81.25 (C-3), 82.6 (C-4) and 125-139 (C-arom) ppm. IR (film): 1076 and 2997 cm^{-1}. HRMS: calcd for $C_{28}H_{30}O_5$, 446.2093, found, 446.2076.

13: $[\alpha]_D$ = -28° (c 0.1, $CHCl_3$). ^1H NMR: δ 2.77 (dd, *J* 2.6 Hz, 1 H, CH_2 epoxide), 2.93 (m, 1 H, CH_2 epoxide), 3.33 (m, 1 H, CH epoxide), 3.76 (m, 3 H, H-5 and CH_2OBn), 4.09 (dd, *J* 1.2 and 3.7 Hz, 1 H, H-3), 4.16 (dd, *J* 1.2 and 3.9 Hz, 1 H, H-4), 4.47 (m, 1 H, H-2), 4.53 (m, 6 H, 3 OCH_2Ph) and 7.34 (m, 15 H, H-arom) ppm. ^{13}C NMR: δ 46.9 (CH_2 epoxide), 48.85 (CH epoxide), 68.2 (CH_2OBn), 72.05 (2 C) and 73.35 (3 CH_2OBn), 79.65 (C-2), 81.2 (C-3), 81.4 (C-4), 81.65 (C-5) and 127-138 (C-arom) ppm. IR (film): 1083 and 2925 cm^{-1}. HRMS: calcd for $C_{28}H_{30}O_5$ 446.2093, found, 446.2084.

(2*R*,3*S*,4*S*,5*S*)-2-benzyloxymethyl-3,4-dibenzyloxy-5-(1*R*-hydroxy-undec-3-ynyl)-tetrahydrofuran **14.**

nBuLi (15 mL of a 1.6 M solution, 23.4 mmol) was added to a cold (-78°C) solution of 1-nonyne (3.5 mL, 23.4 mmol) in anhydrous THF (150 mL). After stirring for 20 min, freshly distilled $BF_3.Et_2O$ (3 mL) was added and the reaction mixture was stirred at -78°C for 15 min before the dropwise addition of a solution of **12** (5.8 g, 13 mmol) in THF (52 mL). After stirring for 5.5 h at -78°C, a cold saturated solution of NH_4Cl (16 mL) was added. Extraction with ether and flash chromatography (AcOEt/pet. ether: 15/85) afforded **14** as a colorless oil.

$[\alpha]_D$ = -24.7° (c 0.92, $CHCl_3$). ^1H NMR: δ 0.88 (t, *J* 7 Hz, 3 H, Me), 1.30 (m, 10 H, 5 CH_2), 2.11 (m, 2 H, CH_2-C≡C), 2.42 (m, 2 H, $OCCH_2$-C≡C), 3.03 (s, 1 H, OH), 3.75, (m, 2 H, CH_2OBn), 3.99 (m, 1, H, C<u>H</u>OH), 4.06 (d, *J* 4.4 Hz, 1 H, H-4), 4.09 (d, *J* 4 Hz, 1 H, H-3), 4.22 (t, *J* 4.4 Hz, 1 H, H-5), 4.36 (m, 1 H, H-2), 4.53

(m, 6 H, 3 OCH_2Ph) and 7.31 (m, 5 H, H-arom) ppm. ^{13}C NMR: δ 14.0 (Me), 18.7-31.6 (7 C), 67.9 (CH_2OBn), 69.5 (CHOH), 72.0, 72.25, 73.3 (3 OCH_2Ph), 75.95 (C≡), 79.0 (C-2), 80.5 (C-5), 80.95 (C-3), 82.85 (C≡), 82.8 (C-4) and 125.7-138 (C-arom) ppm. IR (film): 1110, 2929 and 3541 cm^{-1}. HRMS: calcd for $C_{37}H_{46}O_5$, 570.3345, found, 570.3353.

(2*R*,3*S*,4*S*,5*S*)-2-benzyloxymethyl-3,4-dibenzyloxy-5-(1*R*-methoxymethyloxy-undec-3-ynyl)-tetrahydrofuran **15.**

MOMCl (6 mL, 80 mmol) and *i*PrNEt$_2$ (1.4 mL, 80 mmol) were added to a stirred solution of **14** (4.6 g, 8 mmol) in CH_2Cl_2 (24 mL) at 0°C. After stirring for 48 h at rt, hydrolysis with NH_4Cl, extraction with ether and flash chromatography (AcOEt/Pet. ether: 10/90) gave **15** as a colorless oil (3.68 g, 75 %).

$[\alpha]_D$ = +32.9° (c 0.43, $CHCl_3$). ^1H NMR: δ 0.88 (t, *J* 7 Hz, 3 H, Me), 1.23 (m, 10 H, 5 CH_2), 2.11 (m, 2 H, CH_2-C≡C), 2.40 (m, 2 H, $OCCH_2$-C≡C), 3.40 (s, 3 H, OMe), 3.74 (m, 2 H, CH_2OBn), 3.92 (m, 1 H, CHOMOM), 4. 00 (d, *J* 2.6 Hz, 1 H, H-4), 4.08 (d, *J* 4 Hz, 1 H, H-3), 4.3 4 (m, 1 H, H-5), 4.46 (m, 1 H, H-2), 4.55 (m, 6 H, 3 OCH_2Ph), 4.73 (d, *J* 6.8 Hz, OCHOMe), 4.85 (d, *J* 6.8 Hz, OCHOMe) and 7.30 (m, 5 H, H-arom) ppm. ^{13}C NMR: δ 73.3(3 OCH_2Ph), 74.8 (COMOM), 75.94 (C≡), 78.8 (C-2), 80.4 (C-3), 81.7 (C-5), 81.7 (C-4), 81.85 (C≡), 96.4 (OCOMe) and 137-138 (C-arom) ppm. IR (film): 1102, 2929 and 3032 cm^{-1}. HRMS: calcd for $C_{39}H_{50}O_6$, 614.3607, found, 614.3621.

(2*R*,3*S*,4*S*,5*S*)-2-hydroxymethyl-3,4-dihydroxy-5-(1*R*-methoxymethyloxy-undecyl)-tetrahydrofuran **16.**

A suspension of **15** (3.58 g, 6.8 mmol) and 10 % Pd/C in MeOH (5.8 mL) was stirred under H_2 (1 atm) for 48 h. After filtration over celite, there was obtained crude **16** (1.98 g, quant) which was used without further purification in the next step.

^1H NMR: δ 0.88 (t, *J* 7 Hz, 3 H, Me), 1.26 (m, 18 H, 9 CH_2), 3.21 (s, 3 H, OMe), 3.40 (m, 9 H, H-2, H-3, H-4, H-5, CH_2O, CHOMOM, 2 OH), 4.68 (d, *J* 6.3 Hz, 1 H, OCHOMe) and 4.86 (d, *J* 6.3 Hz, 1 H, OCHOMe) ppm.

(2*R*,3*S*,4*S*,5*S*)-3,4-dihydroxy-5-(1*R*-methoxymethyloxy-undecyl)-2-tertbutyldimethylsilyloxymethyl-tetrahydrofuran **17**.

Crude triol **16** (1.98 g, 5.68 mmol) was dissolved in DMF (13 mL) and then imidazole (1.16 g, 17 mmol) and TBDPSCl (3 mL, 11.3 mL) were added before stirring for 5 h at rt. Hydrolysis, extraction with CH_2Cl_2 and flash chromatography (AcOEt/Pet. ether 20/80) afforded **17** a yellow oil (2.3 g, 70 %).

$[\alpha]_D$ = -20.1° (c 0.41, $CHCl_3$). ^1H NMR: δ 0.85-1.15 (m, 30 H, Me, 10 CH_2 and *t*BuSi), 3.41 (s, 3 H, OMe), 3.75 (m, 1 H, OH), 3.95 (m, 1 H, CHOMOM), 4.05 (m, 2 H, CH_2OSi), 4.25 (m, 3 H, H-2, H-3 and H-5), 4.37 (m, 2 H, H-4 and OH), 4.76 (d, *J* 6.6 Hz, 1 H, OCHOMe), 4.86 (d, *J* 6.6 Hz, 1 H, OCHOMe) and 7.38-7,80 (m, 10 H, H-arom) ppm. ^{13}C NMR: δ 14-32 (Me, 9 CH_2 and *t*BuSi), 56.05 (OMe), 63.8 (CH_2OSi), 76.5

(COMOM), 78.3 (C-2), 79.0 (C-5), 79.75 (C-4), 81.2 (C-3), 95.9 (OCH_2O) and 127-136 (C-arom) ppm. IR (film): 1114, 2929 and 3461 cm^{-1}. HRMS: calcd for $C_{34}H_{54}O_6Si$, 586.3689, found, 586.3658.

(2*R*,3*S*,4*S*,5*S*)-3,4-dimethoxy-5-(1*R*-methoxymethyloxy-undecyl)-2-*tertio*butyldimethylsilyloxymethyl tetrahydrofuran **18.**

To a solution of diol **17** (1.816 g, 3.1 mmol) in CH_3CN (3 mL) was added freshly prepared Ag_2O (1.5 g, 6.8 mmol) and CH_3I (2.8 mL, 45 mmol, 15 eq). After stirring at reflux for 96 h in the dark, the crude mixture was filtered over celite®. Flash chromatography afforded **18** (1.37 g, 72 %) together with trace amounts of starting material and of an unknown monomethyl derivative.

$[\alpha]_D$ = +79.4° (c 0.3, $CHCl_3$). ^1H NMR: δ 0.85-1.46 (m, 30 H, Me, 9 CH_2 and *t*BuSi), 3.36 (m, 9 H, 3 OMe), 3.63 (d, *J* 3.6 Hz, 1 H, H-4), 3.82 (m, 3 H, CH_2OSi and CHOMOM), 3.88 (m, 1 H, H-3), 3.97 (dd, *J* 3.6 and 8.4 Hz, H-6), 4.32 (td, *J* 6 and 10 Hz, 1 H, H-2), 4.64 (d, *J* 6.6 Hz, 1 H, OCHOMe), 4.92 (d, *J* 6.6 Hz, 1H, OCHOMe) and 7.35-7.73 (m, 10 H, H-arom) ppm. ^{13}C NMR: δ 14-32 (Me, 9 CH_2, and *t*BuSi), 55.6, 57.4 and 58.1 (3 OMe), 61.65 (CH_2OSi), 76.1 (COMOM), 80.4 (C-2), 82.2 (C-3), 83.35 (C-5), 83.6 (C-4), 96.9 (OCH_2O) and 125-136 (C-arom) ppm. HRMS: calcd for $C_{36}H_{58}O_6Si$, 614.4002, found, 614.4005.

(2*R*,3*S*,4*S*,5*S*)-2-hydroxymethyl-3,4-dimethoxy-5-(1*R*-methoxymethyloxy-undecyl)-tetrahydrofuran **19.**

Procedure: The reaction was carried out in a manner similar to the preparation of **8**.

19: colorless oil (92%). $[\alpha]_D$ = +62.1° (c 0.28, $CHCl_3$). ^1H NMR: δ 0.88 (t, *J* 7 Hz, 3 H, Me), 1.24 (m, 18 H, 9 CH_2), 3.15 (m, 1 H, OH), 3.41 (m, 9 H, 3 OMe), 3.66 (d, *J* 3.1 Hz, 1 H, H-4), 3.73 (m 3 H, CH_2OSi and CHOMOM), 3.88 (d, *J* 4.7 Hz, 1 H, H-3), 3.97 (dd, *J* 3.9 and 8 Hz, H-5), 4.21 (dd, *J* 5 and 10.6 Hz, 1 H, H-2), 4.64 (d, *J* 6.7 Hz, 1 H, OCHOMe) and 4.86 (d, *J* 6.7 Hz, 1 H, OCHOMe) ppm. ^{13}C NMR: δ 13-32 (Me, 9 CH_2), 55.2, 56.95 and 57.7 (3 OMe), 60.45 (CH_2OSi), 76,0 (COMOM), 79.655 (C-2), 82.45 (C-5), 82.95 (C-3), 85.5 (C-4) and 96.5 (OCH_2O) ppm. HRMS: calcd for $C_{20}H_{40}O_6$, 376.2820, found, 376.2820.

(2*R*,3*S*,4*S*,5*S*)-2-benzyloxymethyl-3,4-dibenzyloxy-5-(1*S*-hydroxy-undec-3-ynyl)-tetrahydrofuran **20.**

Procedure: The reaction was carried out in a manner similar to the preparation of **14.**

20: colorless oil (92 %). $[\alpha]_D$ = +25.8° (c 0.3, $CHCl_3$). ^1H NMR: δ 0.88 (t, *J* 7 Hz, 3 H, Me), 1.25 (m, 10 H, 5 CH_2), 2.13 (m, 2 H, CH_2-C≡C), 2.49 (m, 2 H, $OCCH_2$-C≡C), 3.70 (m, 2 H, CH_2O), 4.02 (m, 1 H, CHOBn), 4. 0 7 (d, *J* 3.9 Hz, 1 H, H-3), 4.09 (d, *J* 3.9 Hz, 1 H, H-5), 4.15 (t, *J* 3.8 Hz, 1 H, H-4), 4.35 (m, 1 H, H-2), 4.51 (m, 6 H, 3 OCH_2Ph) and 7.30 (m, 5 H, H-arom) ppm. IR (film): 1073, 2929 and 3557 cm^{-1}. HRMS: calcd for $C_{37}H_{46}O_5$, 570.3345, found, 570.3365.

(2*R*,3*S*,4*S*,5*S*)-2-benzyloxymethyl-3,4-dibenzyloxy-5-(1*S*-methoxymethyloxy-undec-3-ynyl)-tetrahydrofuran **21.**

Procedure: The reaction was carried out in a manner similar to the preparation of **15.**

21: colorless oil (96 %). $[\alpha]_D$ = +32.9° (c 0.43, $CHCl_3$). ^1H NMR: δ 0.88 (t, *J* 7 Hz, 3 H, Me), 1.24 (m, 10 H, 5 CH_2), 2.14 (m, 2 H, CH_2-C=C), 2.65 (m, 2 H, $OCCH_2$-C=C), 3.38 (s, 3 H, OMe), 3.70 (m, 2 H, H-1), 3.89 (m, 1 H, CHOMOM), 4.01 (d, *J* 3.5 Hz, 1 H, H-3), 4.08 (d, *J* 3 Hz, 1 H, H-4), 4.26 (dd, *J* 3 and 9 Hz, 1 H, H-5), 4.33 (m, 1 H, H-2), 4.54 (m, 8 H, 3 OCH_2Ph and OCH_2OMe) and 7.33 (m, 5 H, H-arom) ppm. ^{13}C NMR: δ 14-32 (8 C), 55.8 (OMe), 72.0, 72.2, 73.4 (3 OCH_2Ph), 74.35. (C-6), 76.35 (C≡), 79.55 (C-2), 80.3 (C-5), 80.85 (C-3), 81.25 (C-4), 81.8 (C≡), 97.05 (OCOMe) and 125-139 (C-arom) ppm. IR (film): 1109, 2929 and 3031 cm^{-1}.

(2*R*,3*S*,4*S*,5*S*)-2-hydroxymethyl-3,4-dihydroxy-5-(1*S*-methoxymethyloxy-undecyl)-tetrahydrofuran **22.**

Procedure: The reaction was carried out in a manner similar to the preparation of **16.**

22: colorless oil (quant). ^1H NMR; δ 0.88 (t, *J* 7 Hz, 3 H, Me), 1.26 (m, 18 H, 9 CH_2), 3.21 (s, 3 H, OMe), 3.40 (m, 9 H, H-2, H-3, H-4, H-5, H-1,H-6, 2 OH), 4.62 (m, 1 H, OH), 4.68 (d, *J* 6.3 Hz, 1 H, OCHOMe) and 4.86 (d, *J* 6.3 Hz, 1 H, OCHOMe) ppm.

(2*R*,3*S*,4*S*,5*S*)-3,4-dihydroxy-5-(1*S*-methoxymethyloxy-undecyl)-2-*tertio*butyldimethylsilyloxymethyl-tetrahydrofuran **23**.

Procedure: The reaction was carried out in a manner similar to the preparation of **17**.

$[\alpha]_D$ = 0° (c 0.25, $CHCl_3$). ^1H NMR: δ 0.85-1.50 (m, 32 H, Me, 10 CH_2 and *t*BuSi), 3.42 (s, 3 H, OMe), 3.85 (m, 1 H, CHOMOM), 4.06 (m, 2 H, CH_2OSi), 4.12 (m, 1 H, H-5), 4.19 (m, 1 H, H-4), 4.21 (m, 1 H, H-2), 4.29 (m, 1 H, OH), 4.39 (m, 2 H, H-3 and OH), 4.75 (m, 2 H, OCH_2OMe) and 7.38-7.80 (m, 10 H, H-arom) ppm. ^{13}C NMR: δ 14-32 (Me, 9 CH_2, and *t*BuSi), 56.05 (OMe), 63.7 (CH_2OSi), 76.75 (C-2), 78.3 (COMOM), 78.9 (C-5), 79.3 (C-3), 82.3 (C-4), 97.95 (OCH_2O) and 127-136 (C-arom) ppm. IR (film): 1113, 2929 and 3472 cm^{-1}. HRMS: calcd for $C_{34}H_{54}O_6Si$, 586.3689, found 586.3675.

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