

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

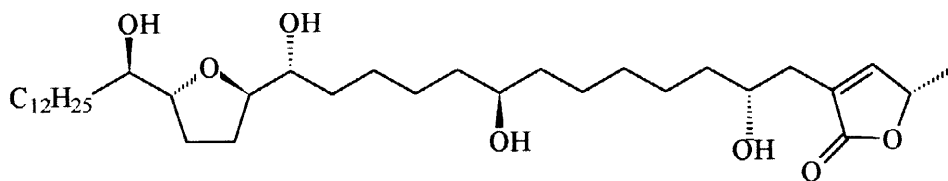
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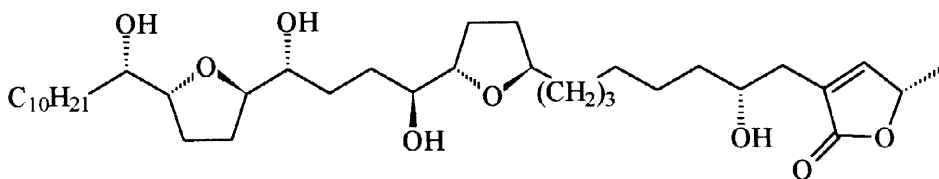
Received 28 January 1998; accepted 14 April 1998

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. © 1998 Elsevier Science Ltd. All rights reserved.

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 annonacin² and the non-adjacent bis-THF bullatalicin³ (the same situation prevails for adjacent bis-THF compounds).



Annonacin



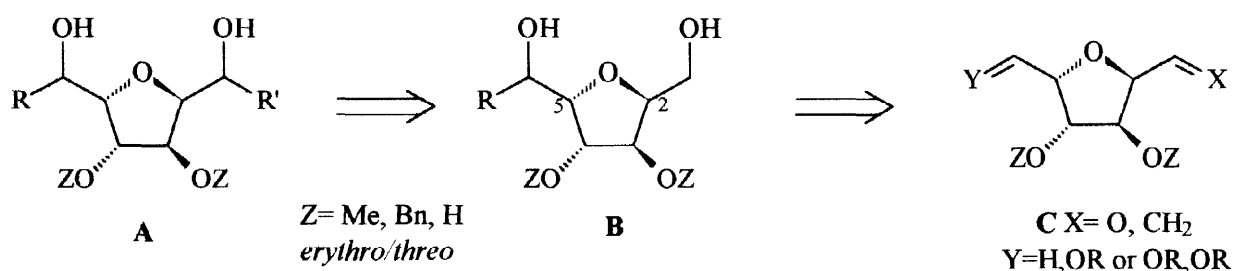
Bullatalicin

Key features which also are essential for potent bioactivity are a C₁₀-C₁₂ 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 spectrometry⁵ and ¹H NMR⁶ 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).

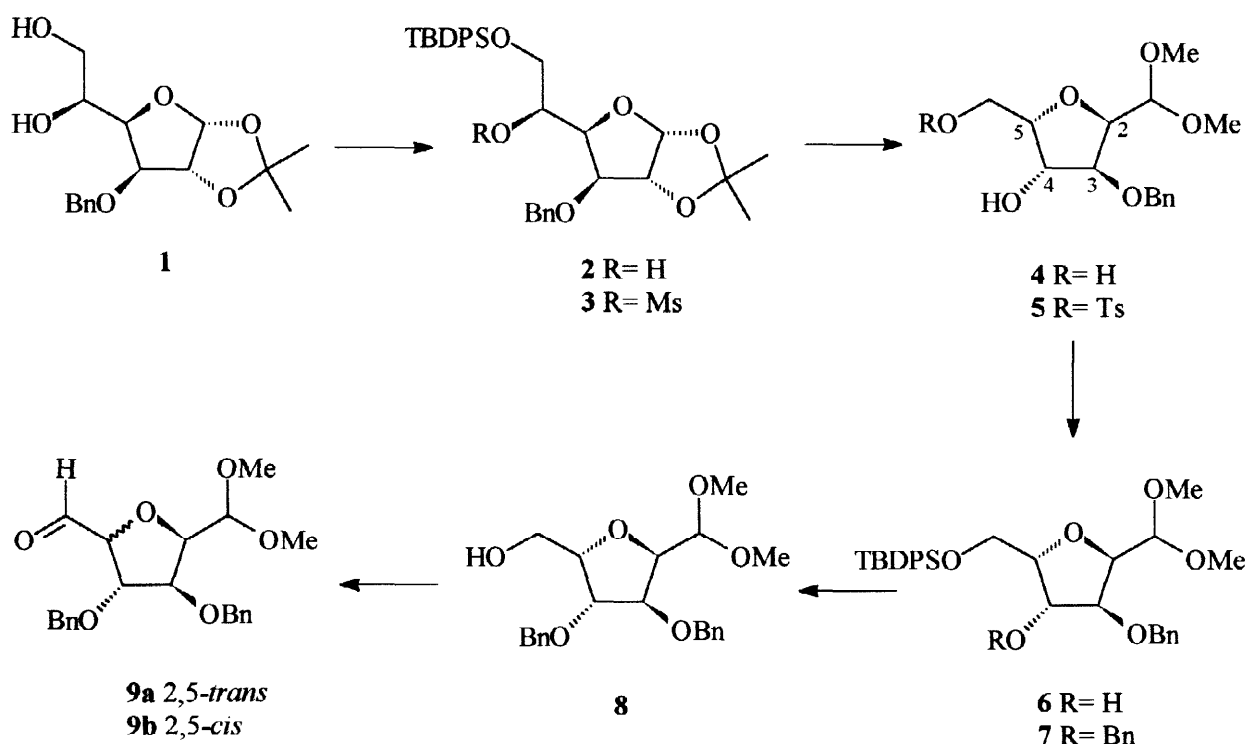


Scheme 1

Two routes were considered to prepare *erythro* or *threo* synthons **B**: Grignard condensation to a suitably protected aldehyde **C** ($\text{X}=\text{O}$) or epoxidation of alkene **C** ($\text{X}=\text{CH}_2$) 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 Defaye⁷ 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 , $\text{FeCl}_3\text{-SiO}_2$) 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 Et₃N 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 C₁₂H₂₅MgBr 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.

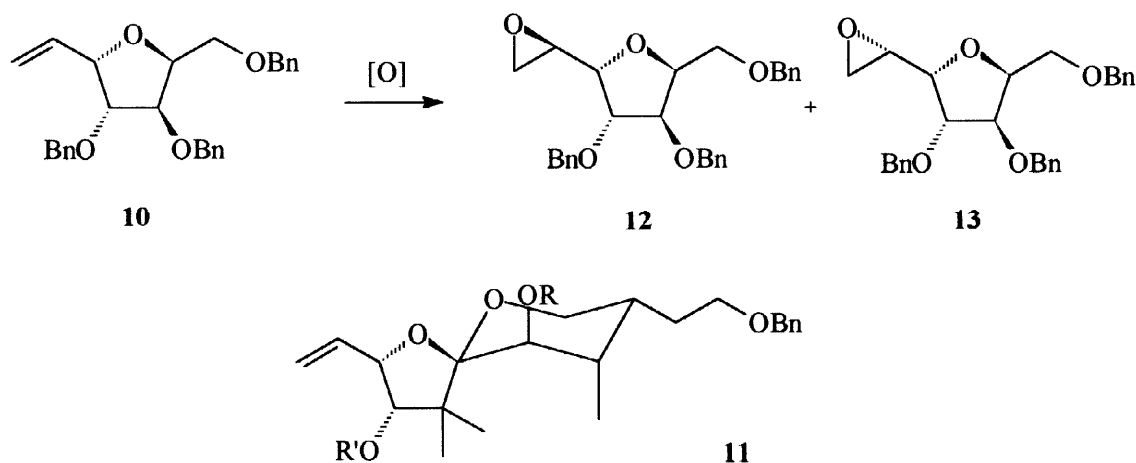


Scheme 2

This ready epimerization of aldehyde **9** led us to study the alternative preparation of synthons **C** (X=CH₂). To this end, alkene **10** was prepared in two steps (*i*: methylene triphenylphosphorane, DME, *ii*: Tf₂O, pyridine) from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose by the method of Martin⁹ 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 cases¹⁰ and particularly by Smith¹¹ 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.

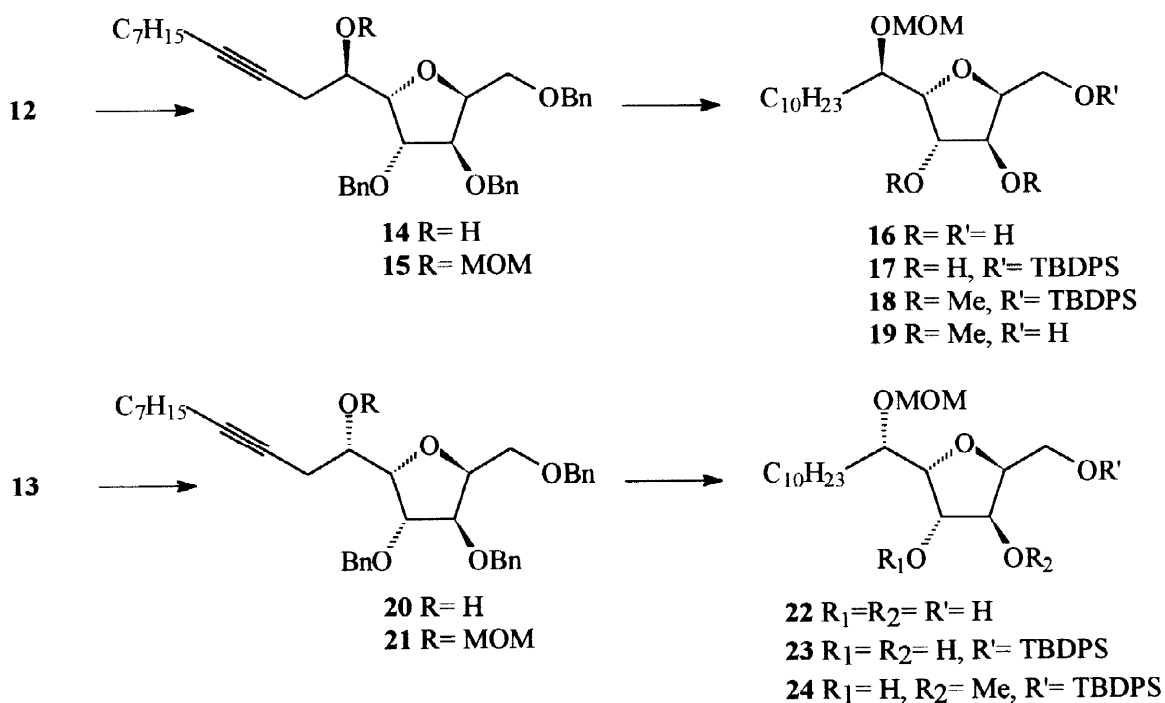
Relative configurations for epoxides **12** and **13** are, thus, proposed by comparison with Smith experiments and with the *erythro* selectivity (ca. 1.8/1) observed by Omura¹³ for the mCPBA epoxidation of

related carbohydrate derivatives. In our case, ^1H 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.

Acknowledgements. We thank the MRES for a research grant (I.T.), ADIR (Groupe Servier) and the Ligue Nationale de Recherche contre le Cancer (Comité de Charente-Maritime) for financial support. We wish to thank a referee for calling our attention to the recent paper⁴ of McLaughlin *et al.* on membrane interaction with acetogenins.

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. Assignment 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 μm) and thin layer chromatography (TLC) were performed on silica gel plates (Merck, 60GF₂₅₄).

3-*O*-benzyl-6-*O*-*tert*iobutyldiphenylsilyl-1,2-*O*-isopropylidene- α -*D*-glucofuranose **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 %). $[\alpha]_D = -29.5^\circ$ (c 0.56, CHCl₃). 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. ¹³C 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 C₃₂H₄₀O₆Si: C 70.04, H 7.35. Found: C 70.17, H 7.28.

3-*O*-benzyl-6-*O*-*tert*iobutyldiphenylsilyl-1,2-*O*-isopropylidene-5-*O*-mesyl- α -*D*-glucofuranose **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 CH₂Cl₂. There was obtained **3** (5.45 g, 89 %) as a white powder, m.p. 95–96°C, after recrystallisation from MeOH.

$[\alpha]_D = -36.5^\circ$ (c 0.09, CHCl₃). 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, SO₂Me), 4.06 (m, 4 H, H-3, H-4 and H-6), 4.59 (m, OCH₂Ph 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. ¹³C 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 C₃₃H₄₃SO₈Si: 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 NaHCO₃ 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%).

$[\alpha]_D = +26^\circ$ (c 0.23, CHCl₃). ¹H NMR: δ 3.36 and 3.40 (2 s, 6 H, 2 Me), 3.95 (m, 4 H, 2 OH and CH₂OH), 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, OCH₂Ph), 7.30 (m, 5 H, H-arom) ppm. ¹³C 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 C₁₅H₂₂O₆, 298.1416, found, 298.1418.

(2*R*,3*S*,4*S*,5*S*)-3-benzyloxy-4-hydroxy-5-*tert*iobutyldiphenylsilyloxymethyl-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, CH₂OSi 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 OCH₂Ph) and 7.3–7.8 (m, 15 H, H-arom) ppm. ¹³C 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 C₃₁H₄₀O₆Si, 536.2594, found, 536.2569.

(2*R*,3*S*,4*S*,5*S*)-3,4-dibenzyloxy-5-*tert*butyldiphenylsilyloxymethyl-2-dimethoxymethyl-tetrahydrofuran **7**.

Freshly prepared Ag₂O (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 CHCl₃ 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 %).

$[\alpha]_D = +11.6^\circ$ (c 0.3, CHCl₃). ¹H NMR: δ 1.05 (m, 9 H, *t*BuSi), 3.63 (s, 6 H, 2 OMe), 3.90 (m, 2 H, CH₂OSi), 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 OCH₂Ph), 4.63 (d, J 8 Hz, 1 H, CH(OMe)₂) and 7.28–7.66 (m, 20 H, H-arom) ppm. ¹³C 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 C₃₈H₄₆O₆Si, 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 NH₄Cl and extraction with ether, flash chromatography using AcOEt/Pet. ether as eluent (30/70) gave **8** (0.73 g, 94 %) as a colorless oil.

$[\alpha]_D = +40.5^\circ$ (c 0.58, CHCl₃). 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, CH₂OH), 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 OCH₂Ph), 4.53 (m, 2 H, OCH₂Ph), 4.64 (d, J 7.7 Hz, 1H, CH(OMe)₂) and 7.32 (m, 10 H, H-arom) ppm. ¹³C 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 C₂₂H₂₈O₆, 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 CH₂Cl₂ (0.3 mL) was slowly added to a cold (-78°C) solution of oxalyl chloride (0.03 mL, 0.44 mmol) in CH₂Cl₂ (0.2 mL). After 5 min, alcohol **8** (0.150 g, 0.39 mmol) in CH₂Cl₂ (0.25 mL) was added and the reaction mixture was stirred at -78°C for 15 min before addition of Et₃N (0.3 mL). The reaction mixture was stirred up to rt, hydrolyzed with water (2 mL) and extracted with CH₂Cl₂. 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 OCH₂Ph), 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 CH₂Cl₂ (2 mL) was stirred for 72 h at rt. After hydrolysis with a saturated solution of Na₂SO₄ and extraction with CH₂Cl₂, 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), KHCO₃ (0.110 g, 1.1 mmol) and then (dropwise) 30 % H₂O₂ (0.68 mL, 6.63 mmol). The white suspension was stirred for 48 h at rt, hydrolysed with a saturated solution of Na₂SO₃ and extracted with CH₂Cl₂. Flash chromatography afforded **12** and **13** in a 5/1 ratio (85 %).

12: [α]_D = +12° (c 0.25, CHCl₃). ¹H NMR: δ 2.55 (dd, *J* 2.7 and 5 Hz, 1 H, CH₂ epoxide), 2.76 (t, *J* 5 Hz, 1 H, CH₂ epoxide), 3.24 (m, 1 H, CH epoxide), 3.69 (m, 2 H, CH₂OBn), 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 OCH₂Ph) and 7.33 (m, 15 H, H-arom) ppm. ¹³C NMR: δ 43.3 (C-7), 51.1 (CH₂ epoxide), 68.3 (CH epoxide), 72.1, 72.4, 73.4 (3 CH₂OBn), 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 C₂₈H₃₀O₅, 446.2093, found, 446.2076.

13: [α]_D = -28° (c 0.1, CHCl₃). ¹H NMR: δ 2.77 (dd, *J* 2.6 Hz, 1 H, CH₂ epoxide), 2.93 (m, 1 H, CH₂ epoxide), 3.33 (m, 1 H, CH epoxide), 3.76 (m, 3 H, H-5 and CH₂OBn), 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 OCH₂Ph) and 7.34 (m, 15 H, H-arom) ppm. ¹³C NMR: δ 46.9 (CH₂ epoxide), 48.85 (CH epoxide), 68.2 (CH₂OBn), 72.05 (2 C) and 73.35 (3 CH₂OBn), 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 C₂₈H₃₀O₅, 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 BF₃·Et₂O (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 NH₄Cl (16 mL) was added. Extraction with ether and flash chromatography (AcOEt/pet. ether: 15/85) afforded **14** as a colorless oil.

[α]_D = -24.7° (c 0.92, CHCl₃). ¹H NMR: δ 0.88 (t, *J* 7 Hz, 3 H, Me), 1.30 (m, 10 H, 5 CH₂), 2.11 (m, 2 H, CH₂-C \equiv C), 2.42 (m, 2 H, OCCH₂-C \equiv C), 3.03 (s, 1 H, OH), 3.75 (m, 2 H, CH₂OBn), 3.99 (m, 1 H, CHOH), 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 OCH₂Ph) and 7.31 (m, 5 H, H-arom) ppm. ¹³C NMR: δ 14.0 (Me), 18.7–31.6 (7 C), 67.9 (CH₂OBn), 69.5 (CHOH), 72.0, 72.25, 73.3 (3 OCH₂Ph), 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 C₃₇H₄₆O₅, 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*PrNEt₂ (1.4 mL, 80 mmol) were added to a stirred solution of **14** (4.6 g, 8 mmol) in CH₂Cl₂ (24 mL) at 0°C. After stirring for 48 h at rt, hydrolysis with NH₄Cl, extraction with ether and flash chromatography (AcOEt/Pet. ether: 10/90) gave **15** as a colorless oil (3.68 g, 75 %).

[α]_D = +32.9° (c 0.43, CHCl₃). ¹H NMR: δ 0.88 (t, *J* 7 Hz, 3 H, Me), 1.23 (m, 10 H, 5 CH₂), 2.11 (m, 2 H, CH₂-C≡C), 2.40 (m, 2 H, OCCH₂-C≡C), 3.40 (s, 3 H, OMe), 3.74 (m, 2 H, CH₂OBn), 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), 4.34 (m, 1 H, H-5), 4.46 (m, 1 H, H-2), 4.55 (m, 6 H, 3 OCH₂Ph), 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. ¹³C NMR: δ 73.3 (3 OCH₂Ph), 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 C₃₉H₅₀O₆, 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 H₂ (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 CH₂), 3.21 (s, 3 H, OMe), 3.40 (m, 9 H, H-2, H-3, H-4, H-5, CH₂O, 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 CH₂Cl₂ and flash chromatography (AcOEt/Pet. ether 20/80) afforded **17** a yellow oil (2.3 g, 70 %).

[α]_D = -20.1° (c 0.41, CHCl₃). ¹H NMR: δ 0.85–1.15 (m, 30 H, Me, 10 CH₂ 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, CH₂OSi), 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. ¹³C NMR: δ 14–32 (Me, 9 CH₂ and *t*BuSi), 56.05 (OMe), 63.8 (CH₂OSi), 76.5

(COMOM), 78.3 (C-2), 79.0 (C-5), 79.75 (C-4), 81.2 (C-3), 95.9 (OCH₂O) and 127–136 (C-arom) ppm. IR (film): 1114, 2929 and 3461 cm⁻¹. HRMS: calcd for C₃₄H₅₄O₆Si, 586.3689, found, 586.3658.

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

To a solution of diol **17** (1.816 g, 3.1 mmol) in CH₃CN (3 mL) was added freshly prepared Ag₂O (1.5 g, 6.8 mmol) and CH₃I (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.

[α]_D = +79.4° (c 0.3, CHCl₃). ¹H NMR: δ 0.85–1.46 (m, 30 H, Me, 9 CH₂ 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, CH₂OSi 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. ¹³C NMR: δ 14–32 (Me, 9 CH₂, and *t*BuSi), 55.6, 57.4 and 58.1 (3 OMe), 61.65 (CH₂OSi), 76.1 (COMOM), 80.4 (C-2), 82.2 (C-3), 83.35 (C-5), 83.6 (C-4), 96.9 (OCH₂O) and 125–136 (C-arom) ppm. HRMS: calcd for C₃₆H₅₈O₆Si, 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%). [α]_D = +62.1° (c 0.28, CHCl₃). ¹H NMR: δ 0.88 (t, *J* 7 Hz, 3 H, Me), 1.24 (m, 18 H, 9 CH₂), 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, CH₂OSi 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. ¹³C NMR: δ 13–32 (Me, 9 CH₂), 55.2, 56.95 and 57.7 (3 OMe), 60.45 (CH₂OSi), 76.0 (COMOM), 79.655 (C-2), 82.45 (C-5), 82.95 (C-3), 85.5 (C-4) and 96.5 (OCH₂O) ppm. HRMS: calcd for C₂₀H₄₀O₆, 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 %). [α]_D = +25.8° (c 0.3, CHCl₃). ¹H NMR: δ 0.88 (t, *J* 7 Hz, 3 H, Me), 1.25 (m, 10 H, 5 CH₂), 2.13 (m, 2 H, CH₂-C≡C), 2.49 (m, 2 H, OCCH₂-C≡C), 3.70 (m, 2 H, CH₂O), 4.02 (m, 1 H, CHOBn), 4.07 (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 OCH₂Ph) and 7.30 (m, 5 H, H-arom) ppm. IR (film): 1073, 2929 and 3557 cm⁻¹. HRMS: calcd for C₃₇H₄₆O₅, 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 %). $[\alpha]_D = +32.9^\circ$ (c 0.43, CHCl₃). ¹H NMR: δ 0.88 (t, *J* 7 Hz, 3 H, Me), 1.24 (m, 10 H, 5 CH₂), 2.14 (m, 2 H, CH₂-C=C), 2.65 (m, 2 H, OCCH₂-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 OCH₂Ph and OCH₂OMe) and 7.33 (m, 5 H, H-arom) ppm. ¹³C NMR: δ 14-32 (8 C), 55.8 (OMe), 72.0, 72.2, 73.4 (3 OCH₂Ph), 74.35. (C-6), 76.35 (C \equiv), 79.55 (C-2), 80.3 (C-5), 80.85 (C-3), 81.25 (C-4), 81.8 (C \equiv), 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 CH₂), 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-*tert*iobutyldimethylsilyloxymethyl-tetrahydrofuran **23**.

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

$[\alpha]_D = 0^\circ$ (c 0.25, CHCl₃). ¹H NMR: δ 0.85-1.50 (m, 32 H, Me, 10 CH₂ and *t*BuSi), 3.42 (s, 3 H, OMe), 3.85 (m, 1 H, CHOMOM), 4.06 (m, 2 H, CH₂OSi), 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, OCH₂OMe) and 7.38-7.80 (m, 10 H, H-arom) ppm. ¹³C NMR: δ 14-32 (Me, 9 CH₂, and *t*BuSi), 56.05 (OMe), 63.7 (CH₂OSi), 76.75 (C-2), 78.3 (COMOM), 78.9 (C-5), 79.3 (C-3), 82.3 (C-4), 97.95 (OCH₂O) and 127-136 (C-arom) ppm. IR (film): 1113, 2929 and 3472 cm⁻¹. HRMS: calcd for C₃₄H₅₄O₆Si, 586.3689, found 586.3675.

References and Notes

1. Cavé, A.; Figadère, B.; Laurens, A.; Cortes, D. Acetogenins from Annonaceae. In *Progress in the Chemistry of Organic Natural Products*, Vol 70, Herz, W.; Kirby, G. W.; Moore, R. E.; Steglich, W.; Tamm, Ch. Eds., Springer: Wien, New-York, 1997, pp 81-288. Zeng, L.; Ye, Q.; Oberlies, N.H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J.L. *Nat. Prod. Reports*, **1996**, *13*, 275-306. Gu, Z.-M.; Zhao, G.X.; Oberlies, N.H.; Zeng, L.; McLaughlin, J.L. *Recent Advances in Phytochemistry*, Arnason, J.T.; Mata, R.; Romeo, J.T. Eds., Plenum Press: New-York, 1995, pp 249-310.

2. McCloud, T.G.; Smith, D.L.; Chang C.-J.; McLaughlin, J.L. *Experientia*, **1987**, *43*, 947; Alkofahi, A.; Rupprecht, J.K.; Smith, D.L.; Chang, C.-J.; McLaughlin, J.L. *Experientia*, **1988**, *44*, 83; Lieb, F.; Nonfon, M.; Wachendorff-Neumann, U.; Wendisch, D. *Planta Med.*, **1990**, *56*, 317.
3. Hui, Y.-H.; Rupprecht, J.K.; Anderson, J.E.; Liu, Y.-M.; Smith, D.L.; Chang C.-J.; McLaughlin, J.L. *Tetrahedron*, **1989**, *45*, 6948.
4. Shimada, H.; Grutzner, J.B.; Kozlowski, J.F.; McLaughlin, J.L. *Biochem.* **1998**, *37*, 854.
5. Laprévote, O.; Das, B. *Tetrahedron*, **1994**, *50*, 8479.
6. Sasaki, S.; Naito, H.; Maruta, K.; Kawahara, E.; Maeda, M. *Tetrahedron Lett.*, **1994**, *35*, 3337. Peyrat, J.-F.; Figadère, B.; Cavé, A.; Mahuteau, J. *Tetrahedron Lett.*, **1995**, *36*, 7653. Peyrat, J.-F.; Mahuteau, J.; Figadère, B.; Cavé, A. *J. Org. Chem.*, **1997**, *62*, 4811.
7. Defaye, J. *Adv. Carbohydr. Chem. Biochem.* **1970**, *25*, 181. Defaye, J.; Ratovelomanana, V. *Carbohydr. Res.* **1971**, *17*, 57.
8. It should be noticed that this route gives the opportunity to introduce other alkoxy groups in the THF ring from **6**.
9. Martin, O.R.; Yang F.; Xie, F. *Tetrahedron Lett.*, **1995**, *36*, 47.
10. Woodward, R.B.; Gosteli, J.; Ernest, I.; Friary, R.J.; Nestler, G.; Raman, H.; Sitrin, R.; Suter, C.; Whitesell, J.K. *J. Am. Chem. Soc.*, **1973**, *95*, 6853. Achmatowicz, O.; Szechner, B. *Carbohydr. Res.*, **1976**, *50*, 23. Gagnieu, C.H.; Grouiller, A.V. *J. Chem. Soc. Perkin I*, **1982**, 1009. Bowles, J.; Campbell, M.M.; Sainsbury, M.S.; Davies, G.M. *Tetrahedron Lett.*, **1989**, *30*, 3711.
11. Smith, A.B. III; Salvatore, B.A. *Tetrahedron Lett.*, **1994**, *35*, 6051.
12. Bachmann, C.; Gesson, J.-P.; Renoux, B.; Tranoy, I. *Tetrahedron Lett.* **1998**, *39*, 379.
13. Kawahata, Y.; Takatsuto, S.; Ikekawa, N.; Murata, M. and Omura, S. *Chem. Pharm. Bull.* **1986**, *34*, 3102.