Syntheses of 11-Hydroxylated Guaianolides

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Two epimeric guaianolides, both prepared from α-santonin, were 11-hydroxylated using 2-phenylsulfonyl-3-phenoxaziridine as a reagent. Extensive use of protecting groups enabled selective acylation of the 3- and 10-hydroxy groups.

Biological activity of sesquiterpene lactones is very often associated with the presence of an α,β-unsaturated carbonyl group in the molecule.1–3 The α-methylene lactone group, often found in sesquiterpene lactones isolated from plant species belonging to the Asteraceae, in general provides the molecule with cytotoxic and allergenic properties.1–4 Some examples, however, of bioactive sesquiterpenes, which do not possess an α,β-unsaturated carbonyl group, or in which the biological activity does not depend on the presence of an α,β-unsaturated carbonyl group, have been reported. Examples of the latter sesquiterpene lactones are the palytoxins, which are believed to interfere with a binding site for the neurotransmitter GABA,5 artemisinin or QHS, which is a very promising antimalarial drug,6 and thapsigargin (1), which is a selective and very potent inhibitor of the microsomal Ca2+-pumps.7 Thapsigargin (1) has become a worldwide used tool for investigating the Ca2+-homeostasis. Structure–activity relationships have revealed that the presence of the 7,11-dihydroxy part is important for the Ca2+-pump inhibitory action of 1.5 This finding and the poor availability of 1, which only can be isolated from the Mediterranean umbrellaferous plant Thapsia garganica L.,9 focused our interest on methods for introducing hydroxy groups in the 7 and 11 positions of guaianolides. The present paper describes a method for 11-hydroxylation of guaianolides. The key reaction is an electrophilic attack of oxygen in 2-phenylsulfonyl-3-phenoxaziridine10 on a lactone enolate. Selective acylation of the different hydroxy groups in the formed hydroxy guaianolide is described.

Discussion

Isophtosantonic lactone (4a), in which the lactone and the cycloheptane rings are trans-annelated, was prepared according to literature methods by illuminating α-santonin (2) dissolved in a mixture of acetic acid and water (Scheme 1).11,12 Reduction of the ketone with sodium borohydride yielded a mixture of the desired 5a contaminated with a small amount of the tetrahydro derivative 6 (Scheme 2). The stereochemistry of the two secondary alcohols was determined from the NOESY spectra. The two alcohols, 5a and 6, were very difficult to separate. Addition of cerium(III) chloride13 to the reaction mixture increased the selectivity, but decreased the yield. The two hydroxy groups of 5a were masked as trimethylsilyl ethers (8a) before the 11-hydroxylation. This masking, however, only succeeded if lithium sulfide14 was used as a catalyst. The stereochemistry of the electrophilic attack of the oxaziridine is in general directed by the steric hindrance of the two sites of the enolate.15 In the case of the enolate

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SYNTHESES OF 11-HYDROXYLATED GUAIANOLIDES

Scheme 1.

of 8a, however, the two sites of the enolate a priori would be considered to be equally hindered. In spite of this the β-hydroxy derivative (9a) was isolated in a yield of 62% and the α-hydroxy derivative (9c) only in a yield of 2%. (Scheme 3). The stereochemistry of the introduced hydroxy groups in 9a and 9c was disclosed by the presence in the NOESY spectra of a NOE between H-13 and and H-9α and between H-13 and H-6, respectively. In order to obtain an acylation pattern of 9a similar to that of 1, the two silyl ether groups were removed to give a triol, in which the secondary hydroxy group selectively was acylated using tiglic anhydride and 4-dimethylaminopyridine as reagents. Acetylation of this product unfortunately showed that the 11-hydroxy group was acetylated faster than the 10-hydroxy group. The failure of this attempt to convert 9a into 14a forced us to use protecting groups. Thus 9a was transformed into the MEM ether 10a, which was solvolyzed to give 11a. Selective acylation of the secondary hydroxy group with tiglic anhydride afforded 12a, which was acetylated to give 13a. Removal of the MEM group with pyridinium toluene sulfonate in tert-butyl alcohol yielded the target molecule 14a. The product, however, was contaminated with the butyl ether 15, most likely formed by an ρ-Al substitution of the tiglic ester group. This side product, however, was easily avoided by running the reaction in N,N-dimethylformamide (DMF).

6-Episophoto-α-santonic lactone 4b, in which the lactone and the cycloheptane rings are cis-annelated, was in an analogous way transformed into the cis-annelated thapsigargin analogue. In addition to the allylic alcohol 5b a substantial amount of the primary alcohol 7 was formed. Reduction of lactones to primary alcohols has previously been reported. As expected from steric hindrance of the enolate of the silyl ether 8b the 11-hydroxylation of the cis-annelated guaianolide exclusively afforded formation of the α-hydroxy form 9b. Formation of the MEM ether 10b and the following two acylations to give 13b were performed analogously to the reactions on the trans-annelated guaianolides. The MEM group was removed with pyridinium toluene sulfonate in DMF.

Scheme 2.
Experimental

General methods. Column chromatography separations were performed using Merck SiO$_2$ 60 (0.063–0.200 mm) or Merck SiO$_2$ 60 (0.040–0.063 mm). Reversed-phase column chromatography was performed using Merck SiO$_2$ 60 silanised (0.063–0.200 mm). Merck SiO$_2$ 60 F254 precoated aluminium sheets were used for TLC, and the spots were visualized by UV and by spraying with an ethanolic solution containing 0.1% of vanillin, 5% of H$_2$SO$_4$ and 5% of glacial acetic acid. Separations by HPLC were performed using a Waters 6000A pump, a Shimadzu SPD 6A detector ($\lambda = 230$ nm) and LiChrosorb RP-18 column (5 mm, 16 x 240 mm, flow 9.0 ml min$^{-1}$). The NMR spectra were recorded on a Bruker AMX 400 or a Bruker AC 200 F spectrometer using Me$_2$Si as an internal standard. The mass spectra (positive FAB) were obtained on a Jeol JMS-HX 110/110 A-T mass spectrometer.

Preparation of 3β,10x-dihydroxy-1zH,6βH,11zH-guai-4-enolide (5a) and 3β,10β-dihydroxy-1zH,5αH,6βH,11zH-guai-4-enolide (6). To a solution of 3-keto-10x-hydroxy-1zH,6βH,11zH-guai-4-enolide (4a, 1.0 g, 3.8 mmol), prepared by photolysis of α-santonin, in methanol (25 ml) was added sodium borohydride (500 mg, 13 mmol), and the solution was stirred at 0°C. The reaction was stopped after 10 min by addition of acetone (15 ml) and water (25 ml), and the mixture was neutralized with 4 M hydrochloric acid. The mixture was concentrated to half volume in vacuum, and the residue was saturated with NaCl and extracted with EtOAc. The EtOAc phase was dried (MgSO$_4$) and concentrated in vacuum, and the constituents of the residue were separated by column chromatography (eluent: EtOAc–acetone (7:1)) to give 5a (831 mg, 82%) and 6 (31 mg, 3%). An analytical sample of 5a was recrystallized (EtOAc–petroleum ether) to give colourless crystals, m.p. 192–195°C. Anal. for C$_{11}$H$_{16}$O$_5$ C, H. NMR data of 5a. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$: 2.93 (br t, $J = 7.7$ Hz, 1 H, H-1), 2.49 ($dt$, $J = 13.8$ and 7.7 Hz, 1H, H-2α), 1.62 (m, 1 H, H-2β), 4.54 (br t, $J = 7.7$ Hz, 1 H, H-3), 4.69 (br dq, $J = 10.9$ and 2.1 Hz, 1 H, H-6), 1.89 (m, 1 H, H-7), 1.97 (m, 2 H, H-8α and H-9β), 1.38 (m, 1 H, H-8β), 1.63 (m, 1 H, H-9α), 2.21 (dq, $J = 13.9$ and 6.9 Hz, 1 H, H-11), 1.21 (d, $J = 6.9$ Hz, 3 H, H-13), 1.05 (s, 3 H, H-14), 1.89 (s, 3 H, H-15). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$: 48.4 (C-1), 34.7 (C-2), 77.5 (C-3), 143.9 (C-4), 131.7 (C-5), 81.7 (C-6), 49.0 (C-7), 25.6 (C-8), 44.7 (C-9), 74.4 (C-10), 41.4 (C-11), 177.8 (C-12), 123.3 (C-13), 21.5 (C-14), 12.3 (C-15). NMR data of 6. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$: 2.3–2.1 (m, 1 H, H-1), 2.0–1.9 (m, 2 H, H-2α and H-4), 1.6–1.5 (m, 2 H, H-2β and H-9α), 4.06 (ddd, $J = 10.6$, 6.7 and 6.1 Hz, 1 H, H-3), 1.9–1.8 (m, 2 H, H-5 and H-8α), 4.29 (ddd, $J = 10.8$ and 10.1 Hz, 1 H, H-6), 1.74 (m, 1 H, H-7), 1.33 (m, 1 H, H-8β), 2.3–2.1 (m, 2 H, H-9β and H-11), 1.12 (d, $J = 7.1$ Hz, 3 H, H-13), 1.17 (s, 3 H, H-14), 0.88 (d, $J = 7.3$ Hz, H-15). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$: 50.3 (C-1, C-4, C-5, C-7, C-9 or C-11), 33.5 (C-2), 72.1 (C-3), 45.7 (C-1, C-4, C-5, C-7, C-9 or C-11), 39.7 (C-1, C-4, C-5, C-7, C-9 or C-11), 81.5 (C-6), 47.1 (C-1, C-4, C-5, C-7, C-9 or C-11), 25.4 (C-8), 41.2 (C-1, C-4, C-5,
Preparation of 3β,10α-bistrimethylsilyloxy-1αH,6βH,11αH-guai-4-enolide (8a). To a solution of lithium sulfide (174 mg, 3.8 mmol) in dry acetonitrile (2 ml) was added nitrogen. A mixture of trimethylsilyl chloride (1 ml, 7.4 mmol). To this solution was added 5a (53 mg, 1.2 mmol) dissolved in acetonitrile (1.5 ml), and the mixture was left under nitrogen. Trimethylsilyl chloride (0.5 ml, 3.7 mmol) and lithium sulfide (30 mg, 0.65 mmol) were added after 16 h. After an additional 16 h the mixture was concentrated under a stream of nitrogen, and to the residue was added ether (15 ml). The ether solution was washed with 2 M aqueous sodium carbonate (15 ml), water (15 ml), and brine (15 ml). The combined aqueous phases were extracted with ether, and the ether phases were dried (MgSO₄) and concentrated in vacuum. Compound 8a (198 mg, 74%) was isolated from the residue by flash column chromatography [eluent: toluene–EtOAc (9:1)] afforded 9a (464 mg) and a mixture of 9a and 9c (73 mg). Repeated chromatography of the mixture of 9a and 9c afforded 9a (a total of 498 mg, 62%), and 9c (13 mg 2%). An analytical sample of 9a was recrystallized to give colourless crystals, m.p. 127–129°C. MS of 9a: 247.2 (36, M+1), 337.1 (100, M+1-C₄H₇SiOH) Anal. for C₂₁H₂₈O₂ Si₃ C, H: 55.2 (42, M+1-C₂H₅OH), 265.1 (100, M+1-C₃H₇-O₂- C₄H₇SiOH). NMR of 9a 1H NMR (CDCl₃, 400 MHz): δ: 2.87 (br s, 1 H, H-1), 2.29 (dt, J = 14.0 and 8.0 Hz, 1 H, H-2α), 1.63 (m, 1 H, H-2β), 4.43 (br t, J = 6.5 Hz, 1 H, H-3), 5.07 (br d, q, J = 10.8 and 6.0 Hz, 1 H, H-6), 1.82 (m, 2 H, H-7 and H-8α), 1.51 (dt, J = 14.2, 10.8 and 3.4 Hz, 1 H, H-8β), 1.63 (m, 1 H, H-9α), 2.03 (dt, J = 13.2 and 2.4 Hz, 1 H, H-9β), 1.41 (s, 3 H, H-13), 1.04 (s, 3 H, H-14), 1.81 (br s, 3 H, H-15); TMS 0.15 and 0.11 (s, each 9 H) 13C NMR (CDCl₃, 100 MHz): δ: 55.6 (C-1), 45.3 (C-2), 78.1 (C-3), 130.1 (C-4), 130.5 (C-5), 79.6 (C-6), 50.9 (C-7), 21.4 (C-8), 44.8 (C-9), 77.4 (C-10), 41.6 (C-11), 178.3 (C-12), 12.5 (C-13), 22.2 (C-14), 12.5 (C-15); TMS 2.7.

Preparation of 3β,10α-bistrimethylsilyloxy-11β-hydroxy-1αH,6βH-guai-4-enolide (9a) and of 3β,10α-bistrimethylsilyloxy-11α-hydroxy-1αH,6βH-guai-4-enolide (9c). To a solution of sodium bis(trimethylsilyl)amide (0.94 mmol) in tetrahydrofuran (15 ml) a solution of 8a (790 mg, 1.9 mmol) in tetrahydrofuran (20 ml) was added under argon at −78°C over 5 min. The mixture was stirred for 30 min at −78°C for 30 min at room temperature and for an additional 30 min at −78°C. Over a period of 5 min a solution of 2-phenylsulfonyl-3-phenylaziridine (520 mg, 2.0 mmol) in dry tetrahydrofuran was added to the reaction mixture. The mixture was stirred for 15 min by addition of 12 ml of a saturated aqueous solution of ammonium chloride. The reaction mixture was concentrated to 12 ml, and the residue was extracted with ether (20 ml). The ether phase was washed with water (12 ml) and brine (20 ml), dried (MgSO₄) and concentrated in vacuum. Column chromatography of the residue [eluent: toluene–MeOH (25:1)] 1H NMR (CDCl₃, 400 MHz): δ: 2.86 (br t, J = 6.5 Hz, 1 H, H-1), 2.29 (dt, J = 14.1 and 8.0 Hz, 1 H, H-2α), 1.75–1.5 (m, 3 H, H-2β, H-8β and 9α), 4.42 (br t, J = 5.9 Hz, 1 H, H-3), 5.08 (br d, q, J = 10.7 and 1.6 Hz, 1 H, H-6), 2.1–1 (m, 3 H, H-7, H-8α and H-9β), 1.40 (s, 3 H, H-13), 1.02 (s, 3 H, H-14), 1.81 (br s, 3 H, H-15); TMS 0.13 and 0.11 (s, each 9 H); MEM 4.93 (d, J = 7.1 Hz, 1 H, OCH₃-O), 4.78 (d, J = 7.1 Hz, 1 H, OCH₃-O), 3.8–3.6 (m, 2 H, OCH₂), 3.6–3.5 (m, 2 H, OCH₂)}
Preparation of 3β,10α-dihydroxy-11β-methoxyethoxy-ethoxy-12H,6βH-guai-4-eneolide (11a). A solution of 10a (118 mg, 0.23 mmol) and glacial acetic acid (200 μl) in methanol (10 ml) was heated to reflux and left without heating for 1 h. The solution was concentrated in vacuum and 11a (79 mg, 93%) was isolated from the residue by column chromatography [eluent: EtOAc]. MS: 371.2 (100, M+1). 1H NMR (CDCl₃, 200 MHz) δ: 2.91 (br t, J = 6.4 Hz, 1 H, H-1), 2.49 (dt, J = 14.0 and 8.0 Hz, 1H, H-2α), 1.75-1.5 (m, 3 H, H2-8β, H-88 and H-9β); 4.53 (br t, J = 6.6 Hz, 1 H, H-3), 5.13 (br d, J = 10.7 and 1.6 Hz, 1 H, H-6), 2.1-1.8 (m, 3 H, H-7, H-8α and H-9α), 1.40 (s, 3 H, CH3), 1.05 (s, 3 H, H-14), 1.89 (br s, 3 H, H-15); MEM 4.93 (d, J = 7.2 Hz, 1H, OCH₂O) 4.78 (d, J = 7.2, 1H, OCH₂O), 3.8-3.6 (m, 2H, OCH₂), 3.6-3.5 (m, 2H, OCH₂), 3.41 (s, 3 H, CH₃), 1.3C NMR (CDCl₃, 50 MHz) δ: 54.7 (C-1), 34.7 (C-2), 144.7 (C-4), 131.9 (C-5), 80.0 (C-6), 52.7 (C-7), 20.1 (C-8), 44.7 (C-9), 74.7 (C-10), 174.9 (C-12), 17.8 (C-13), 21.6 (C-14), 12.5 (C-15); MEM 91.1 (OCH₂O), 71.6 (CH₃O), 67.6 (OCH₂), 59.1 (CH₂O).

Preparation of 3β-tigloyloxy-10α-hydroxy-11β-methoxyethoxy-ethoxy-12H,6βH-guai-4-eneolide (12a). A solution of 11a (75 mg, 0.20 mmol), 4-dimethylaminopyridine (80 mg, 0.66 mmol) and tiglic anhydride (250 μl, 1.4 mmol) in dry dichloromethane (6 ml) was left for 5 h at room temperature and concentrated in vacuum. Compound 12a (77 mg, 84%) was obtained by column chromatography [eluent: EtOAc-EtOAc (1:1)]. 1H NMR (CDCl₃, 200 MHz) δ: 2.99 (br s, 1 H, H-1), 2.58 (dt, J = 16.0 and 7.0 Hz, 1H, H-2α), 2.1-1.6 (m, 6 H, H-2β, H-7, H-8α, H-8β, H-9α and H-9β); 5.03 (br s, 1 H, H-3), 5.13 (br d, J = 10.6 and 1.6 Hz, 1 H, H-6), 1.46 (s, 3 H, H-13), 1.02 (s, 3 H, H-14), 1.81 (br s, 3 H, H-15); MEM 4.95 (d, J = 7.1 Hz, 1H, OCH₂O) 4.81 (d, J = 7.1, 1H, OCH₂O), 3.8-3.6 (m, 2H, OCH₂), 3.6-3.5 (m, 2H, OCH₂), 3.29 (s, 3 H, CH₃); tigloyl: 6.87 (qq, J = 1.4 Hz and 1.4 Hz, 1 H, H-β), 1.84 (br d, J = 1.4 Hz, 3 H, α-Me), 1.78 (br d, J = 7.2 Hz, 3 H, H-γ); 13C NMR (CDCl₃, 50 MHz) δ: 55.3 (C-1), 31.9 (C-2), 79.9 (C-3 or C-6), 141.7 (C-4), 134.3 (C-5), 79.6 (C-6 or C-3), 52.6 (C-7), 20.4 (C-8), 44.7 (C-9), 74.6 (C-10), 77.7 (C-11), 174.8 (C-12), 17.8 (C-13), 21.4 (C-14), 12.1 (C-15); MEM 91.1 (OCH₂O), 71.6 (CH₃O), 67.6 (OCH₂), 59.1 (CH₂O); tigloyl 167.8 (C = O), 128.7 (C-α) 137.3 (C-β), 14.4 (Me), 12.8 (Me).

Preparation of 3β-tigloyloxy-10α-acetoxy-11β-methoxyethoxy-ethoxy-12H,6βH-guai-4-eneolide (13a). A solution of 12a (77 mg, 0.17 mmol), 4-dimethylaminopyridine (80 mg, 0.66 mmol) and acetic anhydride (600 μl, 5.9 mmol) in dry dichloromethane (3 ml) was left for 5 h at room temperature and concentrated in vacuum. Compound 13a (70 mg, 83%) was isolated by column chromatography [eluent: toluene-EtOAc (5:1)]; MS: 495.1 (100, M+1). 1H NMR (CDCl₃, 400 MHz) δ: 3.84 (br s, 1 H, H-1), 2.52 (dt, J = 14.9 and 8.4 Hz, 1H, H-2α), 1.65 (m, 1 H, H-2β), 5.53 (br s, 1 H, H-3), 5.12 (br dq, J = 10.7 and 1.4 Hz, 1 H, H-6), 2.01 (br t, J = 10.6 Hz, 1 H, H-7); 1.88 (m, 1 H, H-8α), 1.59 (m, 1 H, H-8β); 2.41 (dt, J = 13.6 and 4.2 Hz, 1H, H-9α); 2.19 (dt, J = 13.6 and 3.8 Hz, 1 H, H-9β); 1.44 (s, 3 H, H-13), 1.17 (s, 3 H, H-14); 1.85 (br s, 3 H, H-15); MEM 4.93 (d, J = 7.1 Hz, 1H, OCH₂O) 4.79 (d, J = 7.1, 1H, OCH₂O), 3.75-3.6 (m, 2 H, OCH₂), 3.7-3.5 (m, 2 H, OCH₂), 3.39 (s, 3 H, CH₃); tigloyl: 6.87 (qq, J = 1.4 Hz and 1.4 Hz, 1H, H-β); 1.85 (br d, J = 1.4 Hz, 3 H, α-Me); 1.81 (br d, J = 7.1 Hz, 3 H, H-γ); acetyl 1.96 (s, 3 H, H-3). 13C NMR (CDCl₃, 100 MHz) δ: 51.9 (C-1), 31.9 (C-2), 79.9 (C-3), 142.0 (C-4), 133.6 (C-5), 79.3 (C-6), 52.4 (C-7), 20.6 (C-8), 37.7 (C-9), 86.5 (C-10), 77.7 (C-11), 174.7 (C-12), 17.8 (C-13), 20.0 (C-14), 12.1 (C-15); MEM 91.2 (OCH₂O) 71.7 (CH₂O), 67.6 (CH₂O), 59.1 (CH₂O); tigloyl 167.8 (C = O), 128.7 (C-α) 137.4 (C-β), 14.4 (Me), 12.9 (Me); acetyl 170.3 (C = O).
Preparation of 3β,10α-dihydroxy-1αH,6βH,11βH-guai-4-enolide (5b) and 3β,6β,10α,12-tetrahydroxy-1αH,6αH,11βH-guai-4-enolide (4b). To a solution of 3-keto-10α-hydroxy-1αH,6αH,11βH-guai-4-enolide (4b, 6.5 g, 24 mmol), prepared by photohydration of 6-epi-α-santonin, in methanol (200 ml) was added sodium borohydride (3.0 g, 78 mmol), and the solution was stirred at 0°C. The reaction was stopped after 20 min by addition of acetone (60 ml) and water (100 ml). The mixture was concentrated to half volume in vacuum, and the residue was saturated with NaCl and extracted with EtOAc. The EtOAc phase was dried (MgSO4), concentrated in vacuum, and the constituents of the residue were separated by column chromatography [eluent: EtOAc-acetone (7:1)] to give 5b (1.2 g, 60%, 7 (1.2 g, 18%). An analytical sample of 5b was recrystallized (EtOAc-hexane) to give colourless crystals, m.p. 73–75°C. Anal. for C33H52O8: C, 67.15; H, 10.24; NMR data of 5b: 1H NMR (CDCl3, 400 MHz) δ: 2.63 (br t, J = 6.3 Hz), 2.38 (dt, J = 13.7 and 6.3 Hz, 1H, H-2xx), 1.7–1.5 (m, 4 H, H-2β, H-8x, H-8β and H-9β), 4.49 (br t, J = 6.3 Hz, 1 H, H-3), 5.50 (br d, J = 8.0, 1 H, H-6), 2.43 (m, 1 H, H-7), 1.92 (m, 1 H, H-9β), 2.17 (p, J = 7.3 Hz, 1 H, H-11), 1.28 (d, J = 7.3 Hz, 3 H, H-13), 1.18 (s, 3 H, H-14), 1.81 (br s, 3 H, H-15). 13C NMR (CDCl3, 100 MHz) δ: 56.4 (C-1), 35.8 (C-2), 79.0 (C-3), 140.4 (C-4), 133.7 (C-5), 79.7 (C-6), 45.7 (C-7), 27.1 (C-8), 39.9 (C-9), 73.8 (C-10), 42.6 (C-11), 179.7 (C-12), 14.3 (C-13 or C-15), 26.3 (C-14), 12.3 (C-15 or C-13). NMR data of 7: 1H NMR (DMSO-d6, 400 MHz) δ: 2.55 (m, 1 H, H-1), 2.13 (dt, J = 13.3 and 7.7 Hz, 1H, H-2xx), 1.9–1.3 (m, 6 H, H-2β, H-8x, H-9x, H-9β and H-11), 4.19 (br q, J = 6.9 Hz, 1 H, H-3), 4.36 (br d, J = 5.0, 1 H, H-6), 1.13 (m, 1H, H-8β), 3.29 (m, 1 H, H-12), 0.88 (d, J = 7.0 Hz, 3 H, H-13), 1.03 (s, 3 H, H-14), 1.61 (s, 1 H, H-15). 13C NMR (DMSO-d6, 100 MHz) δ: 55.6 (C-1), 35.5 (C-2), 76.0 (C-3), 141.1 (C-4), 139.8 (C-5), 66.9 (C-6), 43.2 (C-7), 20.3 (C-8), 46.7 (C-9), 72.9 (C-10), 41.1 (C-11), 63.6 (C-12), 14.7 (C-13 or C-15), 20.8 (C-14), 11.7 (C-15 or C-13).

Preparation of 3β,10α-bistrimethylsilylxyloxy-1αH,6αH,11βH-guai-4-enolide (8b). Compound 5b (3.0 g, 11 mmol) was silylated as described above for preparation of 8a using lithium sulfide (2 g, 43 mmol) and chlorotrimethylsilane (15 ml) dissolved in dry acetonitrile (20 ml) to give after flash chromatography over silica gel [eluent: toluene-EtOAc (25:1)] 8b (3.6 g, 80%, as a viscous colourless oil, which quickly became yellowish. Owing to instability the product was quickly converted into 9b. 1H NMR of 8b (CDCl3, 200 MHz) δ: 2.61 (br t, J = 7.3 Hz), 2.15 (m, 1H, H-2xx), 1.70 (m, 1 H, H-2β), 4.39 (br t, J = 6.7 Hz, 1 H, H-3), 5.55 (br d, J = 8.0 Hz, 1 H, H-6), 2.44 (m, 1 H, H-7) 1.70 (m, 2H, H-8x and H-9x), 1.43 (m, 1H, H-8β), 1.85 (m, 1 H, H-9β), 2.15 (m, 1 H, H-11), 1.27 (d, J = 6.7 Hz, 3 H, H-13), 1.18 (s, 3 H, H-14), 1.69 (br s, 3 H, H-15); TMS 0.15 (s, 9 H) 13C NMR (CDCl3, 100 MHz) δ: 56.5 (C-1), 37.1 (C-2), 78.3 (C-3), 139.1 (C-4), 132.9 (C-5), 79.9 (C-6), 45.2 (C-7), 27.2 (C-8 or C-14), 39.0 (C-9), 77.0 (C-10), 42.0 (C-11), 179.6 (C-12), 14.4 (C-13 or C-15), 27.0 (C-14 or C-8), 11.9 (C-15 or C-13); TMS 2.5.

Preparation of 3β,10α-bistrimethylsilylxyloxy-1α-hydroxy-1αH,6αH,11βH-guai-4-enolide (9b). Compound 8b (2.3 g, 5.6 mmol) was hydroxylated as described above for preparation of 9a using sodium bis(trimethylsilyl)amide (10 mmol) and 2-phenylsulfonyl)-3-phenyloxaziridine (1.4 g, 5.4 mmol) dissolved in tetrahydrofuran (115 ml) to give 9b (1.7 g, 71%) after column chromatography over silica gel [eluent: toluene-EtOAc (9:1)]. 1H NMR (CDCl3, 400 MHz) δ: 2.63 (m, 1 H, H-1), 2.19 (dt, J = 13.4 and 7.7 Hz, 1H, H-2xx), 1.56 (ddd, J = 13.4, 6.4 and 4.8 Hz, 1 H, H-2β), 4.35 (br t, J = 6.0 Hz, 1 H, H-3), 5.65 (br d, J = 7.2 Hz, 1 H, H-6), 2.63 (m, 1 H, H-17), 1.62 (m, 1 H, H-8x), 1.46 (m, 1 H, H-8β), 1.68 (m, 1 H, H-9x), 1.95 (ddd, J = 14.4, 5.3 and 4.1 Hz, 1 H, H-9β), 1.37 (s, 3 H, H-13), 1.17 (s, 3 H, H-14), 1.75 (br s, 3 H, H-15); TMS 0.16 and 0.13 (s, each 9H) 13C NMR (CDCl3, 100 MHz) δ:57.3 (C-1 or C-7), 36.5 (C-2), 78.5 (C-3) 142.1 (C-4), 131.9 (C-5), 79.5 (C-6), 48.4 (C-7 or C-1), 21.5 (C-8), 41.3 (C-9), 77.2 (C-10), 76.0 (C-11), 178.7 (C-12), 21.0 (C-13), 24.9 (C-14), 12.8 (C-15); TMS 2.5.

Preparation of 3β,10α-bistrimethylsilylxyloxy-1α-methoxyethoxyethoxymethoxy-1αH,6αH,11βH-guai-4-enolide (10b). Compound 9b was methoxymethoxyethylated as described above for preparation of compound 10a using 9b (740 mg, 1.74 mmol), sodium bis(trimethylsilyl)amide (3.5 mmol) and β-methoxyethoxymethyl chloride (400 µl, 3.2 mmol) dissolved in tetrahydrofuran (6 ml). A mixture of starting material (9b) and 10b (800 mg) in the ratio 1:11 was obtained by column chromatography [eluent: toluene-MeOH (25:1)]. 1H NMR (CDCl3, 400 MHz) δ: 2.63 (m, 1 H, H-1), 2.18
Preparation of 3β,10α-dihydroxy-11α-methoxyethoxy-methoxy-1αH,6αH-guai-4-en-olide (11b). Compound 10b (800 mg, 1.60 mmol) was desilylated as described above for preparation of compound 11a with treatment of glycolic acid (1 ml) in MeOH (8 ml) to give 11b (480 mg, 83%) after column chromatography (eluents: EtOAc: MeOH: 3:1). $^1$H NMR (CDCl$_3$, 200 MHz) δ: 2.69 (brs, 1 H, H-1), 2.56 (dt, J = 14.6 and 8.4 Hz, 1H, H-2z), 1.75 (dt, J = 14.6 and 3.8 Hz, 1 H, H-2b), 4.44 (br d, J = 5.9 Hz, 1 H, H-3), 5.62 (br d, J = 4.9 Hz, 1 H, H-6), 2.57 (ddd, J = 12.8, 4.9 and 3.0 Hz, 1 H, H-7), 1.62 (m, 2 H, H-8 and H-9z), 1.23 (m, 1 H, H-8b), 1.95 (m, 1 H, H-9b), 1.38 (s, 3 H, H-13), 1.10 (s, 3 H, H-14), 1.86 (brs, 3 H, H-15); MEM 4.90 (d, J = 7.4 Hz, 1 H, OCH$_3$) 4.83 (d, J = 7.4, 1 H, OCH$_3$), 3.75-3.65 (m, 2 H, OCH$_3$), 3.65-3.5 (m, 2 H, OCH$_3$), 3.35 (s, 3 H, CH$_3$). $^{13}$C NMR (CDCl$_3$, 100 MHz) δ: 56.8 (C-1), 34.8 (C-2), 78.8 (C-3 or C-6), 145.2 (C-4), 132.5 (C-5), 78.2 (C-6 or C-3), 49.8 (C-7), 21.0 (C-8), 43.2 (C-9), 73.8 (C-10), 81.1 (C-11), 175.4 (C-12), 16.7 (C-13), 22.7 (C-14), 13.4 (C-15); MEM 91.2 (OCH$_3$), 71.6 (CH$_2$O), 67.7 (CH$_2$O), 59.1 (CH$_3$O).}

Preparation of 3β-tigloyloxy-10α-hydroxy-11α-methoxyethoxy-methoxy-1αH,6αH-guai-4-en-olide (12b). Compound 12b (420 mg, 1.1 mmol), 4-dimethinopyridine (250 mg, 2.0 mmol) and tiglic anhdydride (800 µl, 4.4 mmol) was dissolved in dry dichloromethane (15 ml) and left for 5 h. Compound 12b (417 mg, 81%) was isolated by column chromatography [eluents: toluene-EtOAc (1:1)] of the residue obtained by concentration of the reaction mixture in vacuo. $^1$H NMR (CDCl$_3$, 400 MHz) δ: 2.77 (br d, 1 H, H-1), 2.45 (dt, J = 15.6 and 8.7 Hz, 1 H, H-2a), 1.92 (dt, J = 15.6 and 2.5 Hz, 1 H, H-2b), 5.49 (br d, J = 8.7 Hz, 1 H, H-3), 5.64 (br s, 1 H, H-6), 2.56 (ddd, J = 12.7, 4.6 and 2.7 Hz, 1 H, H-7), 1.65 (m, 2 H, H-8a and H-9a), 1.27 (m, 1 H, H-8b), 2.00 (m, 1 H, H-9b), 1.41 (s, 3 H, H-13), 1.00 (s, 3 H, H-14), 1.85 (br s, 3 H, H-15); MEM 4.92 (d, J = 7.4 Hz, 1 H, OCH$_3$) 4.87 (d, J = 7.4, 1 H, OCH$_3$), 3.8-3.5 (m, 2 H, OCH$_3$), 3.6-3.5 (m, 2 H, OCH$_3$), 3.37 (s, 3 H, CH$_3$); tigloyl: 6.85 (qq, J = 7.2 and 1.4 Hz, H-8b), 1.84 (br d, J = 1.4 Hz, 3 H, α-Me), 1.79 (br d, J = 7.2 Hz, 3 H, H-γ). $^{13}$C NMR (CDCl$_3$, 100 MHz) δ: 57.2 (C-1), 32.1 (C-2), 80.9 (C-3), 142.1 (C-4), 135.0 (C-5), 78.2 (C-6), 50.6 (C-8), 43.9 (C-9), 74.4 (C-10), 81.0 (C-11), 175.1 (C-12), 16.5 (C-13), 21.9 (C-14), 12.1 (C-15); MEM 91.2 (OCH$_3$), 71.6 (CH$_2$O), 67.7 (CH$_2$O), 59.1 (CH$_3$O); tigloyl 168.0 (C = O), 128.7 (C-α) 137.5 (C-β), 14.4 (Me), 12.1 (Me).}

Preparation of 3β-tigloyloxy-10α-acetoxy-11α-methoxyethoxy methoxy-1αH,6αH-guai-4-en-olide (13b). Compound 12b (380 mg, 0.84 mmol), 4-dimethinopyridine (250 mg, 2.1 mmol) and acetic anhdydride (1 ml) was dissolved in dichloromethane (15 ml) and left for 5 h. The residue after concentration of the reaction mixture in vacuo was purified by column chromatography [eluents: toluene- EtOAc (2:1)] to give 13b (410 mg, 98%). MS: 495.1 (M + 1). $^{13}$H NMR (CDCl$_3$, 400 MHz) δ: 3.58 (br s, 1 H, H-1), 2.44 (br t, J = 15.6 and 8.7 Hz, 1 H, H-2x), 1.82 (m, 1 H, H-2b), 5.49 (br d, J = 8.7 Hz, 1 H, H-3), 5.63 (br s, 1 H, H-6), 2.56 (ddd, J = 13.2, 4.3 and 2.7, 1 H, H-7), 1.62 (m, 2 H, H-8x), 1.24 (m, 1 H, H-8b), 2.25 (m, 1 H, H-9a), 2.34 (ddd, J = 13.7, 6.8 and 2.5 Hz, 1 H, H-9b), 1.41 (s, 3 H, H-13), 1.28 (s, 3 H, H-14), 1.86 (br s, 3 H, H-15); MEM 4.92 (d, J = 7.4 Hz, 1 H, OCH$_3$) 4.87 (d, J = 7.4, 1 H, OCH$_3$), 3.8-3.65 (m, 2 H, OCH$_3$), 3.6-3.5 (m, 2 H, OCH$_3$), 3.37 (s, 3 H, CH$_3$); tigloyl: 6.85 (qq, J = 7.1 and 1.4 Hz, 1 H, H-β), 1.83 (br d, J = 1.4, 3 H, α-Me), 1.80 (br d, J = 7.1 Hz, 3 H, H-γ); acetyl 1.96 (s, 3 H, 3C NMR (CDCl$_3$, 100 MHz) δ: 53.8 (C-1), 31.9 (C-2), 80.9 (C-3) 143.3 (C-4), 134.2 (C-5), 77.7 (C-6), 50.8 (C-7), 20.6 (C-8), 37.6 (C-9), 86.1 (C-10), 81.2 (C-11), 175.0 (C-12), 163.3 (C-13), 19.7 (C-14), 12.1 (C-15); MEM 91.2 (OCH$_3$), 71.6 (CH$_2$O), 67.8 (CH$_2$O), 59.1 (CH$_3$O); tigloyl 167.8 (C = O), 128.6 (C-α) 137.6 (C-β), 14.4 (Me), 12.9 (Me); acetel 170.3 (C = O), 22.6 (C-α).
128.9 (C-α), 137.6 (C-β), 14.2 (Me), 12.9 (Me); acetyl
171.6 (C=O), 22.3 (C-α).

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