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Nor-limonoid and homoisoanticopalane lactones from methyl isoanticopalate

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Abstract—A nor-limonoid with a γ-hydroxybutenolide group was obtained starting from the known methyl isoanticopalate. A new route for the synthesis of several lactones with a homoisoanticopalane skeleton has been opened. The stereochemistry of three intermediates was established by X-ray determination.

1. Introduction

Marine sponges are a rich source of biologically active secondary metabolites with novel chemical structure.[1] Several sesterterpenolides, isolated from marine sponges[2] show anti-inflammatory activity as the most important biological activity.

Petrosaspongiolides M(**1**), N(**2**), P(**3**), Q(**4**) and R(**5**) isolated from *Petrosaspongia nigra*[3] are a serie of novel sesterterpenes possessing a cheilanthane skeleton, that have been tested for activity against a panel of PLA2 enzymes (Fig. 1).

Recently four cheilanthane sestertepenoids **6–9** were isolated from the marine sponge *Ircinia* sp.[4] The four compounds inhibit MSK1 and MAPKAPK2, two protein kinases involved in nitrogen and stress signal transduction (Fig. 2).

Studies towards the synthesis of cheilanthane sestertepenoids have been carried out by superacidic low temperature cyclization of 13*Z*,17*Z* and 13*Z*,17*E*-bicyclogeranylfarnesoic acid methyl esters,[5] to afford 14-*epi*-cheilanthane **10** and a rearranged 14-*epi*-cheilanthane terpenoid **11** (Fig. 3).

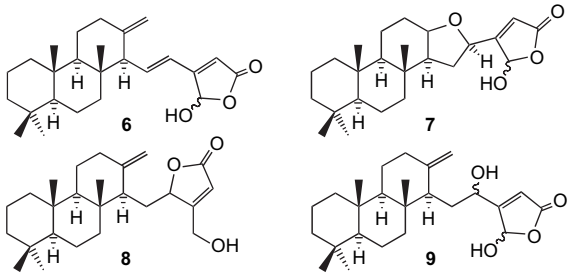

Figure 2.

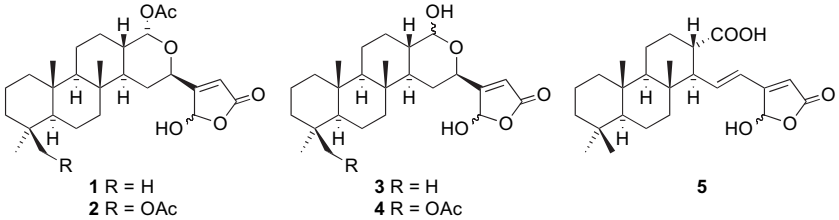

Figure 1.

Keywords: Sesterterpenolides; Petrosaspongiolides; Methyl isoanticopalate; Nor-limonoids; Homoisoanticopalane lactones.
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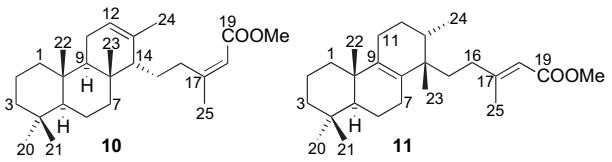
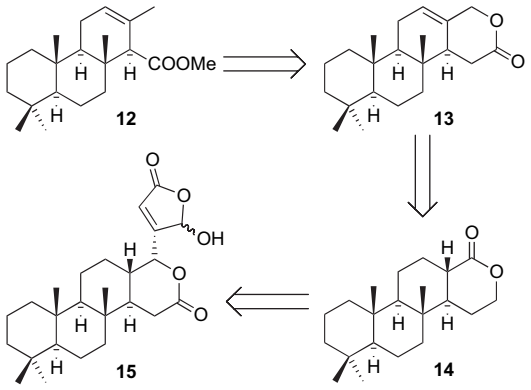


Figure 3.

In our group methyl isoanticopalate **12**, that can be obtained from sclareol,[6] has been used for the synthesis of secospongianes,[7] hyrtiosal,[8] subersic acid[9] and sesterterpenolides as luffolide.[10]

In this paper we communicate the synthesis of a nor-limonoid **15**, that can be considered as an analogue of petrosaspongiolides and several lactones, **13**, **14**, **25** and **26**, with a homoisoanticopalane skeleton, which are useful synthons for the synthesis of biological active compounds.



Scheme 1. Retrosynthetic scheme, for the synthesis of compound **15** from methyl isoanticopalate, **12**.

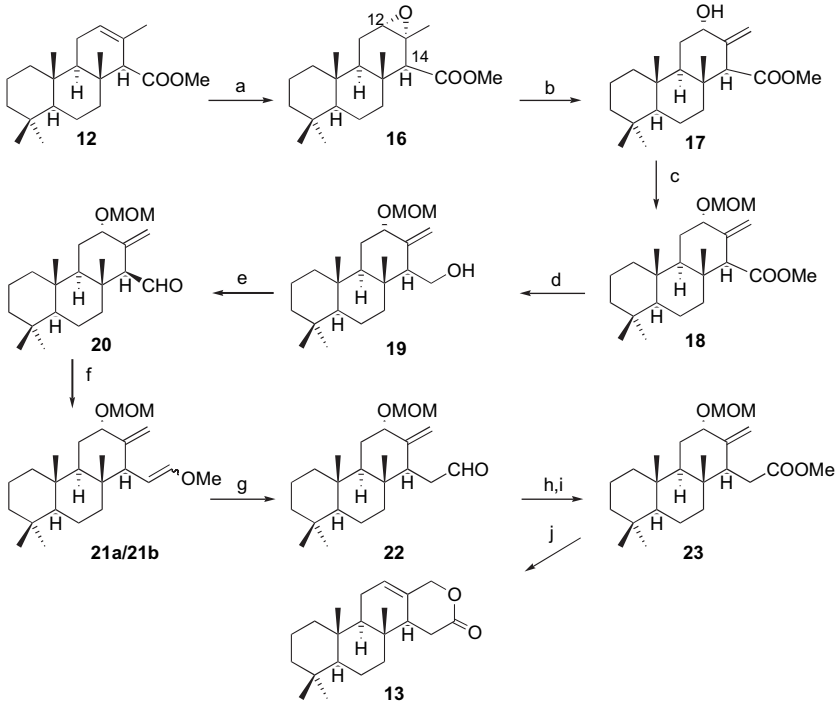
2. Results and discussion

In order to achieve these objectives we decided to obtain first of all lactone **13** from methyl isoanticopalate.

The final objective is the synthesis of the nor-limonoid **15**, in order to obtain this compound, we designed the following retrosynthetic scheme (Scheme 1). Compound **15** could proceed form lactone **14** by addition of 3-furyllithium and ulterior synthesis of the hydroxybutenolide following Faulkner methodology.[11] Compound **14** could be obtained from **13** by changing the lactone ring disposition and the last compound from methyl isoanticopalate **12**.

2.1. Synthesis of lactone 13

As first objective we decided to obtain lactone **13** as shown in Scheme 2. Epoxidation of methyl isoanticopalate, **12**, led to compound **16**, its structure being confirmed by X-ray crystallography[12] (Fig. 4). Reaction of **16** in Rúvedas conditions[13] gave the allylic alcohol **17** that was protected as its MOM derivative, **18**. Elongation of the side chain in one carbon atom was done by reduction to alcohol **19**, oxidation to the aldehyde **20** and Wittig reaction with methoxymethyltriphenyl phosphorane[14] gave mixture of enol ethers, **21**, in an excellent yield. These compounds were hydrolyzed to aldehyde **22**, which on oxidation to acid and esterification with $TMSCHN_2$ gave the methyl ester **23**. When this compound



Scheme 2. (a) *m*-CPBA, DCM, rt, 12 h, 71%; (b) $Al(^iPrO)_3$, benzene, 150 °C, 4 h, 94%; (c) DMM, P_2O_5, $CHCl_3$, 0 °C to rt, 30 min, 99%; (d) DIBAL-H, DCM, −78 °C, 30 min, 90%; (e) TPAP, NMO, DCM, sieves 4 Å, rt 10 min, 86%; (f) $(MeOCH_2PPh_3)^+Cl^-$, NaHMDS, THF, −78 °C, 45 min, 82%; (g) *p*-TsOH, acetone, rt, 7 h, 99%; (h) ^tBuOH/2-methyl-2-butene, 25% $NaH_2PO_4/NaClO_2$, rt, 99%; (i) $TMSCH_2N_2$, benzene/hexane, rt, 83% and (j) 6 N dioxane/H_2SO_4 (13/1), 90 °C, 14 h, 93%.

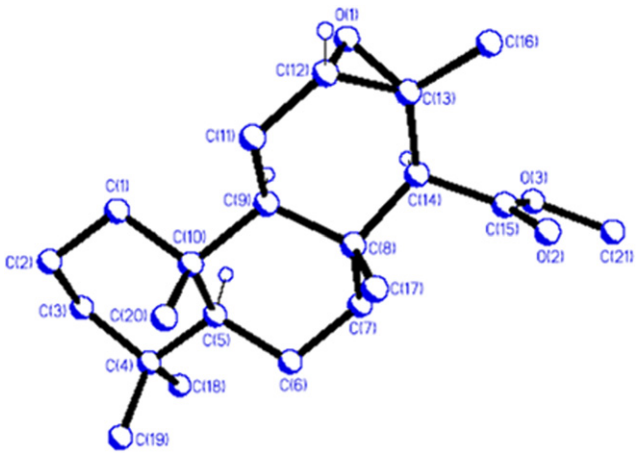


Figure 4. X-ray crystallography of compound **16**.

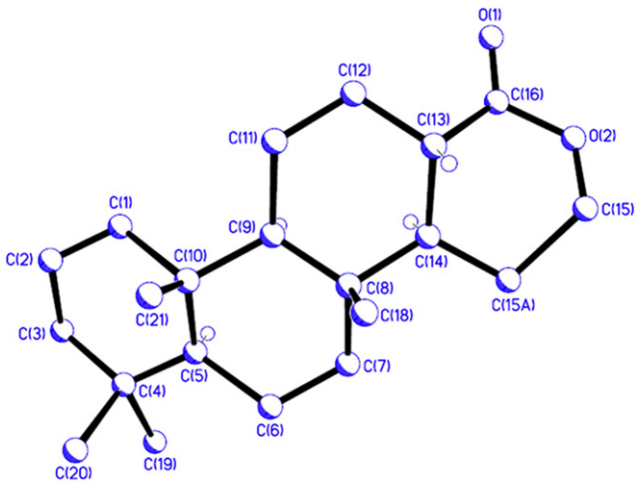


Figure 5. X-ray crystallography of compound **14**.

was treated with sulfuric acid in dioxane it produced the desired lactone **13**, in excellent global yield Scheme 2.

2.2. Transformation of lactone 13 to lactone 14

With an easy way to obtain lactone **13**, the transformation into lactone **14** was carried out as follows. Reduction of lactone **13** with LAH in THF gave diol **24**, which on TPAP oxidation[15] led to the unsaturated lactone **25** in a very good yield. Hydrogenation of **25** gave lactone **26** that shows the C/D rings union as cis. As the stereochemistry for the planned sesterterpenolide **15**, for that rings is trans, was necessary to isomerize to the *trans* lactone **14**. This was quantitatively achieved by treatment in basic conditions, obtaining lactone **14**, in nearly quantitative yield (Scheme 3).

The X-ray crystallography of **14** corroborates the structure,[16] showing the trans disposition of H-13 and H-14 (Fig. 5).

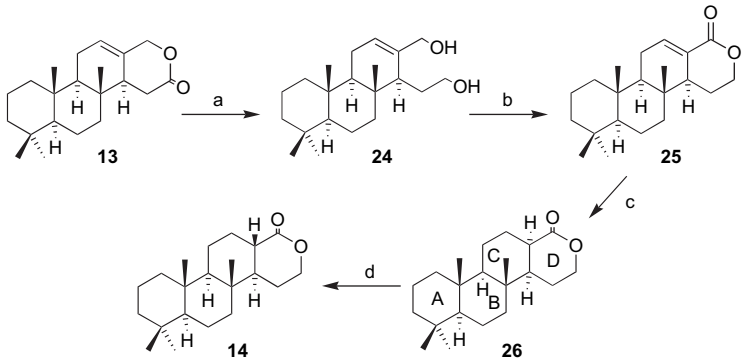
Lactones **13**, **14**, **25** and **26** are homoisoanticopalanes synthons potentially useful for future transformations into biological active compounds.

2.3. Synthesis of 15

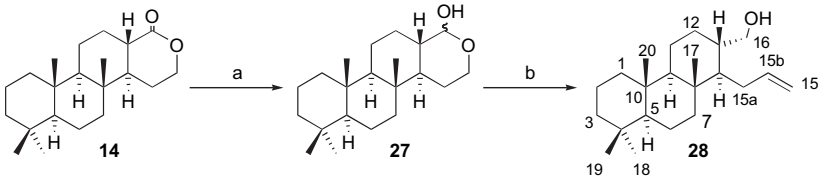
Once we obtained lactone **14**, in adequate quantities, we decided to follow to the synthesis of the nor-limonoid **15**. Lactone **14** was reduced with DIBAL[17] to the lactol **27**, and as stated previously in the retrosynthetic scheme, several attempts to add a furan ring to this lactol were tried, but were unsuccessful, so we decided to change this strategy. Lactol **27**, was treated under Wittig conditions to give olefin **28**. This unexpected result, could be understood by an 1,5 hydride transfer in an intermediate ω-hydroxyaldehyde (Scheme 4).

Compound **28** was oxidized to aldehyde **29** (Scheme 5), by treatment with TPAP under the usual conditions, in nearly quantitative yield. As can be observed this compound has an aldehyde as required for the organometalic addition. Addition of 3-furyllithium[18] to this aldehyde gave stereoselectively alcohol **30**,[19] whose stereochemistry at C-17, will be corroborated later on. The dihydroxylation of **30**, with OsO_4/NMO followed by treatment with $NaIO_4$ of the resulting diol **31**, led to lactol **32**.[20] TPAP oxidation of the last compound gave lactone **33** that shows a nor-limonoid structure. The X-ray diffraction studies[21] of **33**, confirm its structure and the stereochemistry of compound **30** at C-17 (Fig. 6).

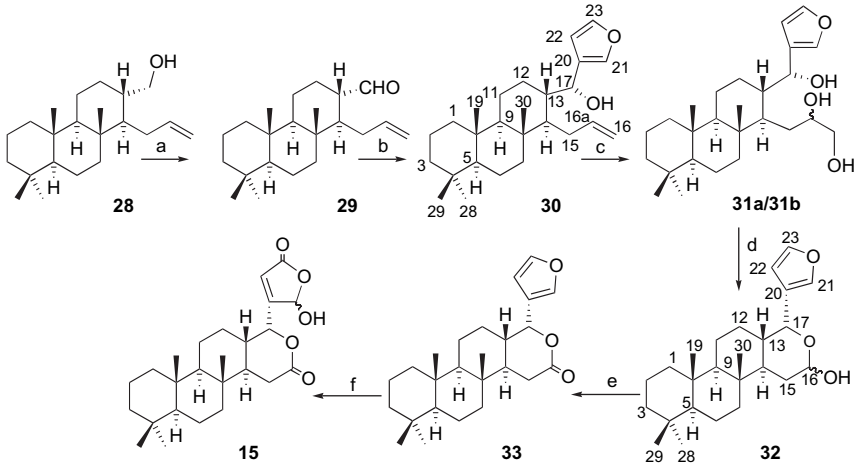
Finally compound **33** was transformed into the required γ-hydroxybutenolide **15** (68% yield) following Faulkner's methodology.[11] This functionality is present in many compounds with antitumoral activity and SAR studies will be published in due course.



Scheme 3. (a) LAH, THF, rt, 2 h, 88%; (b) MnO_2, DCM, rt, 2 h, 86%; (c) 10% H_2/Pd/C, EtOH, rt, 4 h, 98% and (d) $K^{+t}BuO^{-}$/^{t}BuOH, 70 °C, 30 min, 99%.



Scheme 4. (a) DIBAL-H, DCM, −78 °C, 30 min, 99% and (b) Ph_3PCH_2Br, NaHMDS, toluene/THF, −20 to 80 °C, 1 h, 56%.



Scheme 5. (a) TPAP, NMO, DCM, sieves 4 Å, rt, 1 h, 99%; (b) 3-bromofurane, *n*-BuLi, THF, −78 °C, 30 min, 58%; (c) OsO_4/^{t}BuOH/NMO, ^{t}BuOH/THF/H_2O (7/2/1), rt, 46 h, 58%; (d) $NaIO_4$, THF/H_2O (2/1), rt, 10 min, 65%; (e) TPAP, NMO, DCM, sieves 4 Å, rt, 1 h, 99% and (f) $^1O_2$, *hν*, Rose Bengal, DIPEA, DCM, −78 °C, 3 h, 68%.

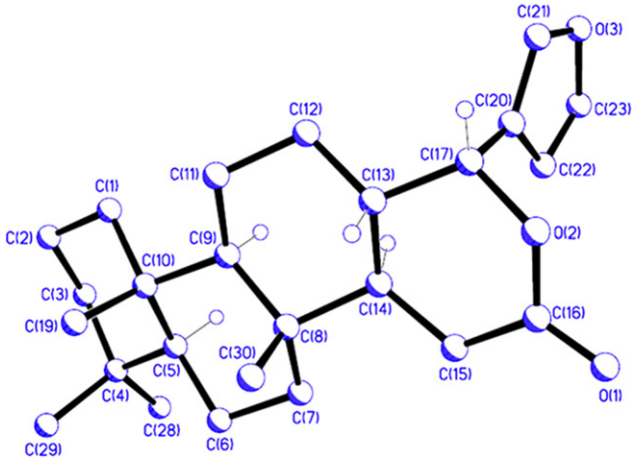


Figure 6. X-ray crystallography of compound **33**.

3. Conclusions

In conclusion, starting form methyl isoanticopalate **12**, a new route to nor-limonoids is described. Several lactones with a homoisoanticopalane skeleton have been obtained, that are useful synthons for the synthesis of biological active compounds.

4. Experimental

4.1. General

Unless otherwise stated, all chemicals were purchased with the highest purity commercially available and were used without further purification. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 200/400 and 50/75 MHz, respectively. The spectra were performed in $CDCl_3$ and referenced with respect to the residual peak of $CHCl_3$ at δ 7.26 and δ 77.0 ppm, for ^{1}H and ^{13}C, respectively. Chemical shifts are reported in parts per million and coupling constants (*J*) are given in hertz. Optical rotations were determined on a polarimetre in 1-dm cells. Diethyl ether and THF were distilled from sodium, and dichloromethane was distilled from calcium hydride under Ar atmosphere.

4.1.1. Methyl 12a,13a-epoxy-isoanticopal-15-oate 16. To an ice-cooled solution of **12** (7.0 g, 22.3 mmol) in dry CH_2Cl_2 (250 mL) was added *m*-CPBA (7.0 g, 40.6 mmol). The reaction mixture was stirred at room temperature for 1 h, diluted with water and extracted with Et_2O. The organic layer was washed successively with 10% aqueous solution of Na_2SO_3, 6% aqueous solution of $NaHCO_3$ and water. Evaporation of the dried extract gave **16** (5.3 g, 71%). Compound **16**: $[\alpha]_D^{20}$ −23.0 (*c* 0.85, $CHCl_3$), mp (hexane): 155–157 °C. IR: 1740, 1450, 1320, 1200, 1170, 1110, 1010 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.67 (3H, s, COO*Me*), 3.05 (1H, br s, H-12), 2.47 (1H, s, H-14), 1.29 (3H, s, Me-16), 1.07 (3H, s, Me-17), 0.89 (3H, s, Me-18), 0.83 (3H, s, Me-19), 0.79 (3H, s, Me-20), 2.2–0.92 (14H, m). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 172.6 (C-15), 62.1 (C-12), 60.3 (C-14), 56.9 (C-13), 56.4 (C-5), 51.0 (COO*Me*), 50.3 (C-9), 41.9 (C-3), 40,4 (C-7), 39.5 (C-1), 37.3 (C-10), 36.1 (C-8), 33.5 (C-18), 33.1 (C-4), 21.8 (C-11), 21.7 (C-19), 22.4 (C-16), 18.4 (C-2, C-6), 15.8 (C-17), 15.1 (C-20). MS: *m/z* (%) 334 (36) $[M]^+$, 319 (80), 301 (71), 205 (53), 191 (64), 177 (91), 143 (73), 123 (68), 95 (75), 81 (100), 69 (80). HRMS: calcd for $C_{21}H_{34}O_3$ $[M]^+$: 334.2508, found: 334.2564.

4.1.2. Methyl 12α-hydroxy-isoanticopal-13(16)en-15-oate 17. To a solution of **16** (2.3 g, 7.0 mmol) in toluene (50 mL) was added 398 mg (1.9 mmol) of Al(^{i}PrO)$_3$, and the mixture was stirred at 150 °C for 24 h, diluted with water and extracted with Et_2O. The organic layer was washed with 10% aqueous solution of NaOH and brine. Evaporation of the dried extract gave **17** (2.2 g, 94%). Compound **17**: $[\alpha]_D^{20}$ −32.2 (*c* 0.82, $CHCl_3$), mp (hexane): 156–158 °C. IR: 3462, 2930, 1734, 1653, 1456, 1387, 1194, 1163, 1044, 1007, 912 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.98 (1H, s, H_A-16), 4.78 (1H, s, H_B-16), 4.32 (1H, s, H-12), 3.58 (3H, s, COO*Me*), 3.29 (1H, s, H-14), 1.04 (3H, s, Me-17), 0.86, 0.84, 0.81 (9H, s each, Me-18, 19 and 20), 1.88–0.87 (14H, m). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 172.2 (C-15), 145.3 (C-13), 113.0 (C-16), 72.9 (C-12), 57.6 (C-14), 56.9 (C-5), 51.8 (C-9), 51.1 (COO*Me*), 42.2 (C-3), 40.4 (C-7), 40.2 (C-10), 39.8 (C-1), 37.4 (C-8), 33.5 (C-18), 33.4 (C-4), 29.4 (C-11), 21.6 (C-19), 18.9 (C-2), 18.6 (C-6), 16.3 (C-17), 14.4 (C-20). MS: *m*/*z* (%) 334 (12) [M]$^+$, 316 (34), 288 (6), 205 (49), 40 (92), 10 (100).

4.1.3. Methyl 12α-methoxymethoxy-isoanticopal-13(16)en-15-oate 18. To a solution of aldehyde **17** (6.6 g, 19.8 mmol) in $CHCl_3$ (118 mL), DMM (118 mL, 1.33 mol) and P_2O_5 (29.7 g, 0.21 mol) were added and the mixture was stirred for 30 min. Then, ice was added. The organic phase was separated and the aqueous phase was extracted with Et_2O. The organic layer was washed with aqueous solution of 10% $NaHCO_3$ and water, dried over Na_2SO_4 and concentrated under reduced pressure to give **18** (6.9 g, 99%). Compound **18**: $[\alpha]_D^{20}$ −3.6 (*c* 0.89, $CHCl_3$), mp (hexane): 65–67 °C. IR: 1738, 1458, 1389, 1163, 1034, 918 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.03 (1H, s, H_A-16), 4.98 (1H, s, H_B-16), 4.65 (1H, d, *J*=6.6 Hz, O*CH*$_2$OCH$_3$), 4.52 (1H, d, *J*=6.6 Hz, O*CH*$_2$OCH$_3$), 4.19 (1H, t, *J*=2.9, H-12), 3.64 (3H, s, COO*Me*), 3.35 (3H, s, OCH$_2$O*CH*$_3$), 3.16 (1H, s, H-14), 1.04 (3H, s, Me-17), 0.85, 0.83 and 0.80 (9H, s each, Me-18, 19 and 20), 1.90–0.85 (14H, m). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 172.1 (C-15), 141.7 (C-13), 113.1 (C-16), 93.2 (O*CH*$_2$OCH$_3$), 76.1 (C-12), 57.9 (C-14), 56.8 (C-5), 55.4 (OCH$_2$O*CH*$_3$), 52.5 (C-9), 51.1 (COO*Me*), 42.2 (C-3), 40.4 (C-7), 40.1 (C-10), 39.8 (C-1), 37.5 (C-8), 33.5 (C-18), 33.4 (C-4), 28.2 (C-11), 21.6 (C-19), 18.9 (C-2), 18.6 (C-6), 16.2 (C-17), 14.5 (C-20). MS: *m*/*z* (%) 378 (8) [M]$^+$, 346 (24), 333 (45), 316 (92), 191 (94), 137 (62), 69 (100). HRMS: calcd for $C_{23}H_{38}O_4$ [M]$^+$: 378.2779, found: 378.2780.

4.1.4. 12α-Methoxymethoxy-isoanticopal-13(16)en-15-ol 19. To a solution of **18** (434 mg, 1.1 mmol) in dry methylene chloride (27 mL) was added a solution of DIBAL-H in toluene (1.6 M, 1.68 mL, 2.4 mmol) under argon at −78 °C. The solution stirred for 30 min, was quenched by addition of MeOH (5 mL) and water (5 mL) and extracted with Et_2O (3×100 mL). The organic layer was washed with water (3×30 mL) and dried over Na_2SO_4. Evaporation of the solvent followed by chromatography on silica gel (hexane/EtOAc 9/1) yielded the alcohol **19** (362 mg, 90%). Compound **19**: $[\alpha]_D^{20}$ +1.6 (*c* 1.1, $CHCl_3$). IR: 3428, 1719, 1649, 1387, 1209, 1099, 907 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.09 (1H, s, H_A-16), 4.84 (1H, s, H_B-16), 4.61 (1H, d, *J*=6.6 Hz, O*CH*$_2$OCH$_3$), 4.51 (1H, d, *J*=6.6 Hz, O*CH*$_2$OCH$_3$), 4.15 (1H, s, H-12), 3.77 (2H, m, H-15), 3.32 (3H, s, OCH$_2$O*CH*$_3$), 0.85 (3H, s, Me-17), 0.82, 0.76 and 0.68 (9H, s each, Me-18, 19 and 20), 2.35–0.86 (15H, m). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 145.9 (C-13), 111.0 (C-16), 93.8 (O*CH*$_2$OCH$_3$), 77.9 (C-12), 58.6 (C-15), 56.5 (C-5), 55.5 (OCH$_2$O*CH*$_3$), 54.1 (C-14), 52.8 (C-9), 42.1(C-3), 40.6 (C-7), 39.9 (C-1), 39.5 (C-10), 37.5 (C-8), 33.5 (C-18), 33.4 (C-4), 28.7 (C-11), 19.2 (C-2), 18.7 (C-6), 16.2 (C-17), 15.7 (C-20). MS: *m*/*z* (%) 350 (1) [M]$^+$, 288 (11), 191 (18), 115 (14), 99 (100), 85 (68), 83 (37). HRMS: calcd for $C_{22}H_{38}O_3$ [M]$^+$: 350.2821, found: 350.2812.

4.1.5. 12α-Methoxymethoxy-isoanticopal-13(16)en-15-al 20. To a mixture of **19** (362 mg, 1.03 mmol), *N*-methylmorpholine *N*-oxide (NMO) (262 mg, 1.9 mmol) and molecular sieves (515 mg, 500 mg/mmol) in anhydrous CH_2Cl_2 (10.4 mL) under argon at room temperature and TPAP (32 mg, 0.1 mmol) were added. The reaction mixture was stirred for 1 h and then filtered through a short pad of silica gel and Celite, eluting with EtOAc. Evaporation of the solvent yielded the aldehyde **20** (309 mg, 86%). Compound **20**: $[\alpha]_D^{20}$ +23.0 (*c* 0.88, $CHCl_3$). IR: 2947, 2731, 1717, 1669, 1464, 1387, 1148, 1096, 1034, 918 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.84 (1H, d, *J*=3.8 Hz, H-15), 5.09 (1H, s, H_A-16), 4.84 (1H, s, H_B-16), 4.61 (1H, d, *J*=6.6 Hz, O*CH*$_2$OCH$_3$), 4.51 (1H, d, *J*=6.6 Hz, O*CH*$_2$OCH$_3$), 4.14 (1H, s, H-12), 3.30 (3H, s, OCH$_2$O*CH*$_3$), 2.79 (1H, s, H-14), 1.08 (3H, s, Me-17), 0.82, 0.81 and 0.76 (3×3H, s, Me-18, 19 and 20), 2–0.83 (14H, m). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 205.0 (C-15), 142.8 (C-13), 113.6 (C-16), 93.1 (O*CH*$_2$OCH$_3$), 76.2 (C-12), 63.3 (C-14), 56.7 (C-5), 55.4 (OCH$_2$O*CH*$_3$), 51.8 (C-9), 42.1 (C-3), 40.9 (C-7), 40.0 (C-10), 39.7 (C-1), 37.6 (C-8), 33.5 (C-18), 33.4 (C-4), 28.2 (C-11), 21.6 (C-19), 18.7 (C-2), 18.6 (C-6), 16.4 (C-17), 16.3 (C-20). MS: *m*/*z* (%) 348 (11) [M]$^+$, 316 (25), 286 (35), 191 (18), 115 (59), 57 (100). HRMS: calcd for $C_{22}H_{36}O_3$ [M]$^+$: 348.2664, found: 348.2667.

4.1.6. 12α-Methoxymethoxy-15a-homo-isoanticopal-13(16),15a(15)-dienil-15-methylether. To a suspension of methoxymethyltriphenylphosphonium chloride (MeO CH_2PPh_3Cl) (4.4 g, 12.8 mmol) in THF (6 mL) at −78 °C under an argon atmosphere, a 1.0 M solution of NaHMDS in THF (11.3 mL, 11.3 mmol) was added dropwise and the solution stirred for 20 min. A solution of the aldehyde **20** (4.5 g, 12.9 mmol) in THF (14.5 mL) was added dropwise and the mixture stirred for 1 h. It was allowed to warm to room temperature, quenched with aqueous NH_4Cl and extracted with Et_2O. The organic layer was washed with water and dried over Na_2SO_4. The residue obtained after removing the solvent was purified by column chromatography (hexane/EtOAc 9/1) to afford a mixture **21a/21b** (3.03 g, 82%) (7/3, *Z*/*E*). Compound **21a/21b**: IR: 2932, 1665, 1460, 1387, 1269, 1244, 1206, 1148, 1115, 1094, 1036 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ *isomer Z* (major): 5.96 (1H, d, *J*=6.6 Hz, H-15), 4.87 (1H, br s, H_A-16), 4.79 (1H, br s, H_B-16), 4.64 (1H, d, *J*=6.6 Hz, O*CH*$_2$OCH$_3$), 4.48 (1H, d, *J*=6.6 Hz, O*CH*$_2$OCH$_3$), 4.32 (1H, dd, J_1=10.2 and J_2=6.6 Hz, H-15a), 4.17 (1H, s, H-12), 3.51 (3H, s, O*Me*), 3.34 (3H, s, OCH$_2$O*CH*$_3$), 3.24 (1H, d, *J*=10.2 Hz, H-14), 2.5–0.9 (14H, m), 0.81, 0.79, 0.77 and 0.68 (4×3H, s, Me-17, 18, 19 and 20); *isomer E* (minor): 6.16 (1H, d, *J*=12.6 Hz, H-15), 4.91 (1H, br s, H_A-16), 4.79 (1H, br s, H_B-16), 4.72 (1H, dd, J_1=12.6 and J_2=2.4 Hz, H-15a), 4.60 (1H, d, *J*=6.6 Hz, O*CH*$_2$OCH$_3$), 4.45 (1H, d, *J*=6.6 Hz,

O*CH*$_2$OCH$_3$), 4.19 (1H, s, H-12), 3.54 (3H, s, O*Me*), 3.33 (3H, s, OCH$_2$O*CH*$_3$), 3.32–3.28 (1H, m, H-14), 2.5–0.9 (14H, m), 0.81, 0.79, 0.77 and 0.69 (4×3H, s, Me-17, 18, 19 and 20). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 148.6 (C-13), 147.4 (C-15), 112.2 (C-16), 103.6 (C-15a), 93.1 (O*CH*$_2$OCH$_3$), 76.7 (C-12), 59.6 (O*Me*), 56.7 (C-5), 55.3 (OCH$_2$O*CH*$_3$), 52.4 (C-9), 47.0 (C-14), 42.3 (C-3), 40.9 (C-7), 39.9 (C-1), 39.5 (C-10), 37.5 (C-8), 33.6 (C-19), 33.5 (C-4), 28.4 (C-11), 21.7 (C-18), 19.1 (C-2), 18.8 (C-6), 16.3 (C-17) 14.6 (C-20). MS: *m/z* (%) 376 (8) [M]$^+$, 344 (36), 331 (37), 299 (29), 191 (74), 179 (75), 71 (100). HRMS: calcd for $C_{24}H_{40}O_3$ [M]$^+$: 376.2977, found: 376.2968.

4.1.7. 12α-Methoxymethoxy-15a-homo-isoanticopal-13(16)en-15-al 22. To a solution of **21a/21b** (470 mg, 1.49 mmol) in acetone (247 mL) and water (3 mL), *p*-TsOH (360 mg, 1.9 mmol) was added at room temperature. After being stirred for 7 h, the reaction mixture was diluted with water and extracted with Et_2O. The extracts were washed with 6% aqueous $NaHCO_3$ solution and water. Evaporation of the solvent yielded the aldehyde **22** (449 mg, 99%). Compound **22**: $[\alpha]_D^{20}$ +3.5 (*c* 0.79, $CHCl_3$). IR: 1728, 1647, 1462, 1387, 1258, 1208, 1148, 1096, 1032, 918, 733 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.53 (1H, t, *J*=2.2, H-15), 4.95 (1H, s, H$_A$-16), 4.57 (1H, s, H$_B$-16), 4.55 (1H, d, *J*=6.6 Hz, O*CH*$_2$OCH$_3$), 4.44 (1H, d, *J*=6.6 Hz, O*CH*$_2$OCH$_3$), 4.13 (1H, s, H-12), 3.31 (3H, s, OCH$_2$O*CH*$_3$), 2.68 (1H, t, *J*=7.4 Hz, H-14), 2.37 (2H, dd, J_1=7.4 and J_2=2.2 Hz, H-15a), 1.98–1.05 (14H, m), 0.82 (3H, s), 0.78 (6H, s), 0.66 (3H, s). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 203.3 (C-15), 146.7 (C-13), 112.6 (C-16), 99.3 (O*CH*$_2$OCH$_3$), 76.8 (C-12), 56.5 (C-5), 55.4 (OCH$_2$O*CH*$_3$), 52.8 (C-9), 46.2 (C-14), 42.1 (C-15a), 40.9 (C-3), 39.9 (C-7), 39.5 (C-1), 39.4 (C-10), 37.5 (C-8), 33.5 (C-19), 33.4 (C-4), 28.5 (C-11), 21.6 (C-18), 19.2 (C-2), 18.7 (C-6), 16.2 (C-17), 15.0 (C-20). MS: *m/z* (%) 362 (12) [M]$^+$, 300 (28), 191 (78), 157 (32), 123 (35), 69 (100). HRMS: calcd for $C_{23}H_{38}O_3$ [M]$^+$: 362.2821, found: 362.2816.

4.1.8. Methyl 12α-methoxymethoxy-15a-homo-isoanticopal-13(16)en-15-oate 23. To a solution of **22** (2.8 g, 8.16 mmol) in ^{t}BuOH (97 mmL), a solution of 25% NaH_2PO_4/$NaClO_2$ in water was added at room temperature. The reaction mixture was stirred for 12 h, diluted with water and 2 N HCl and extracted with Et_2O. The organic layer was washed with water and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated to give the acid (3.05 g). To a solution of the acid (1.5 g, 4.05 mmol) in benzene and methanol, $TMSCHN_2$ was added under an argon atmosphere at 0 °C. After 10 min of vigorous stirring the solvent was evaporated to give a residue, which was purified by silica gel column chromatography (hexane/EtOAc 9/1) to yield **23** (1.3 g, 83%). Compound **23**: $[\alpha]_D^{20}$ −8.1 (*c* 0.68, $CHCl_3$). IR: 1738, 1651, 1441, 1387, 1329, 1157, 1096, 1032, 918 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.93 (1H, s, H$_A$-16), 4.70 (1H, s, H$_B$-16), 4.59 (1H, d, *J*=6.6 Hz, O*CH*$_2$OCH$_3$), 4.45 (1H, d, *J*=6.6 Hz, O*CH*$_2$OCH$_3$), 4.15 (1H, s, H-12), 3.60 (3H, s, COO*Me*), 3.33 (3H, s, OCH$_2$O*CH*$_3$), 2.62 (1H, dd, J_{BX}=11.0 and J_{AX}=4.0 Hz, H-14), 2.43 (1H, dd, J_{AB}=15.8 and J_{AX}=4.0 Hz, H$_A$-15a), 2.30 (1H, dd, J_{AB}=15.8 and J_{BX}=11.0 Hz, H$_B$-15a), 1.68–0.87 (14H, m), 0.81 (3H, s), 0.76 (2×H, s), 0.64 (3H, s). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 174.1 (C-15), 146.9 (C-13), 111.4 (C-16), 92.8 (O*CH*$_2$OCH$_3$), 76.2 (C-12), 56.4 (C-5), 55.3 (OCH$_2$O*CH*$_3$), 52.4 (C-9), 51.6 (COO*Me*), 47.8 (C-14), 42.1 (C-3), 40.4 (C-7), 39.5 (C-1), 39.2 (C-8), 37.4 (C-10), 33.5 (C-18), 33.4 (C-4), 30.4 (C-15a), 28.7 (C-11), 21.6 (C-19), 19.2 (C-2), 18.8 (C-6), 16.2 (C-17), 14.8 (C-20). MS: *m/z* (%) 392 (12) [M]$^+$, 347 (35), 315 (32), 191 (100), 123 (48), 69 (92). HRMS: calcd for $C_{24}H_{40}O_4$ [M]$^+$: 392.2927, found: 392.2934.

4.1.9. 15a-Homo-isoanticopal-12en-15,16-olide 13. To a solution of **23** (1 g, 2.6 mmol) in dioxane (149 mL) was added a solution of 6 N H_2SO_4 (115 mL) at 85 °C. The solution was stirred for 24 h, quenched by addition of ice and brine and extracted with EtOAc (3×100 mL). The organic layer was washed with water (3×30 mL) and dried over Na_2SO_4. Evaporation of the solvent followed by chromatography on silica gel ($CHCl_3$) yielded the lactone **13** (781 mg, 93%). Compound **13**: $[\alpha]_D^{20}$ −45.8 (*c* 0.53, $CHCl_3$). IR: 1748, 1464, 1387, 1258, 1036, 1017 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.70 (1H, br s, H-12), 4.65 (1H, d, *J*=13.2 Hz, H$_A$-16), 4.56 (1H, d, *J*=13.2 Hz, H$_B$-16), 2.80–2.22 (3H, m), 2.20–0.98 (14H, m), 0.85, 0.83, 0.79 and 0.70 (4×3H, s, Me-17, 18, 19 and 20). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 174.3 (C-15), 129.4 (C-13), 70.9 (C-16), 123.9 (C-12), 56.6 (C-5), 54.5 (C-9), 47.6 (C-14), 42.0 (C-3), 39.9 (C-7), 39.9 (C-1), 35.7 (C-8), 37.5 (C-10), 33.6 (C-18), 33.4 (C-4), 30.0 (C-15a), 23.2 (C-11), 21.8 (C-19), 18.7 (C-2), 18.6 (C-6), 15.4 (C-17), 14.2 (C-20). EIMS *m/z* (%) 316 (M$^+$) (1), 256 (2), 192 (3), 137 (4), 86 (100), 69 (26). HRMS: calcd for $C_{21}H_{32}O_2$ [M]$^+$: 316.2402, found: 316.2432.

4.1.10. 15a-Homo-isoanticopal-12-en-15,16-diol 24. To a solution of **13** (500 mg, 1.6 mmol) in THF (40 mL), at 0 °C under an argon atmosphere, LAH (200 mg) was added. The mixture was stirred for 1 h. It was allowed to warm to room temperature, quenched with aqueous EtOAc and dried over Na_2SO_4. Evaporation of the solvent yielded the compound **24** (449 mg, 99%). Compound **24**: $[\alpha]_D^{20}$ +12.2 (*c* 0.1, $CHCl_3$). IR: 3380, 1458, 1439, 1387, 1364, 1209, 1049, 988, 839 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.71 (1H, br s, H-12), 4.27 (1H, d, *J*=12.0 Hz, H$_A$-16), 3.87 (1H, d, *J*=12.0 Hz, H$_B$-16), 3.86–3.79 (1H, m, H$_A$-15), 3.71–3.61 (1H, m, H$_B$-15), 1.70–1.52 and 0.87–0.70 (2H, m, H-1), 1.67–1.51 (2H, m, H-2), 1.43–1.29, 1.18–1.03 (2H, m, H-3), 0.90–0.75 (1H, m, H-5), 1.48–1.36 (2H, m, H-6), 1.95–1.80, 1.21–1.05 (2H, m, H-7), 1.28–1.13 (1H, m, H-9), 1.80–1.63 (2H, m, H-11), 2.12–2.00 (1H, m, H-14), 2.22–1.86 (2H, m, H-15a), 0.89 (3H, s, Me-17), 0.86 (3H, s, Me-18), 0.82 (3H, s, Me-19), 0.74 (3H, s, Me-20). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 138.5 (C-13), 126.8 (C-12), 66.5 (C-16), 64.5 (C-15), 56.5 (C-5), 55.0 (C-9), 49.3 (C-14), 42.1 (C-3), 40.8 (C-7), 40.0 (C-1), 37.4 (C-8), 37.1 (C-10), 33.6 (C-18), 33.3 (C-4), 28.3 (C-11), 23.0 (C-15a), 21.9 (C-19), 18.9 (C-2), 18.7 (C-6), 15.6 (C-17), 14.5 (C-20). EIMS *m/z* (%) 302 (M−18$^+$) (3), 257 (4), 192 (12), 107 (38), 85 (100). HRMS: calcd for $C_{21}H_{36}O_2$ [M−18]$^+$: 302.2610, found: 302.2620.

4.1.11. 15a-Homo-isoanticopal-12-en-16,15-olide 25. To a solution of **24** (200 mg, 0.62 mmol) in DCM (25 mL), at room temperature under anhydrous atmosphere, MnO_2 (200 mg) was added. The mixture was stirred for 1 h. After filtration, the solvent was evaporated to yield the compound

25 (170 mg, 86%). Compound **25**: $[\alpha]_D^{20}$ +8.3 (*c* 0.64, $CHCl_3$). IR: 2959, 1717, 1643, 1458, 1389, 1262, 1088, 932, 733 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.30–7.25 (1H, m, H-12), 4.41 (1H, ddd, J_1=5.5, J_2=2 and J_3= 1.2 Hz, H_A-15), 4.20 (1H, ddd, J_1=6.6, J_2=5.5 and J_3= 1.2 Hz, H_B-15), 2.33–2.01 (3H, m), 1.90–1.10 (14H, m), 0.90, 0.87, 0.83 and 0.75 (4×3H, s, Me-17, 18, 19 and 20). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 165.6 (C-16), 143.0 (C-12), 126,3 (C-13), 68.4 (C-15), 56.3 (C-5), 53.7 (C-9), 42.2 (C-14), 41.7 (C-3), 40.1 (C-1), 39.5 (C-7), 37.0 (C-8), 34.8 (C-10), 33.3 (C-18), 33.1 (C-4), 24.2 (C-15a), 22.6 (C-11), 21.6 (C-19), 18.5 (C-2), 18.3 (C-6), 15.3 (C17), 14.1 (C-20). EIMS *m/z* (%) 316 (M^+) (18), 301 (11), 192 (100), 177 (53), 125 (71), 69 (42).

4.1.12. (13*R*)-15a-Homo-isoanticopal-16,15-olide 26. To a solution of **25** (274 mg, 0.85 mmol) in EtOH (17 mL), at room temperature under hydrogen atmosphere, Pd/C 10% (83 mg) was added. The mixture was stirred for 1 h. After filtration with Celite® and silica, the solvent was evaporate to yield the compound **26** (276 mg, 98%). Compound **26**: $[\alpha]_D^{20}$ −43.3 (*c* 0.55, $CHCl_3$). IR: 2947, 2845, 1734, 1697, 1458, 1385, 1248, 1024, 801 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 4.30 (1H, ddd, J_1=11.5, J_2=6.6 and J_3=1.3 Hz, H_A-15), 4.12 (1H, dt, J_1=11.5 and J_2=7.4 Hz, H_B-15), 2.60 (1H, t, *J*=6.6 Hz, H-13), 2.04–1.93 (1H, m, H_A-15a), 1.88–1.70 (1H, m, H_B-15a), 1.68–1.57 and 1.00–0.85 (2H, m, H-1), 1.70–1.20 (2H, m, H-2), 1.44–1.25 and 1.20–1.00 (2H, m, H-3), 0.84–0.68 (1H, m, H-5), 1.70–1.20 (2H, m, H-6), 1.77–1.65 and 0.80–0.68 (2H, m, H-7), 0.86–0.68 (1H, m, H-9), 1.70–1.20 (2H, m, H-11), 2.49–2.30 and 1.51–1.40 (2H, m, H-12), 1.91–2.08 (1H, m, H-14), 0.84 (3H, s, Me-18), 0.81 (3H, s, Me-17), 0.80 (3H, s, Me-20), 0.78 (3H, s,Me-19). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 176.5 (C-16), 65.5 (C-15), 59.5 (C-5), 56.6 (C-9), 45.4 (C-14), 42.0 (C-3), 40.5 (C-1), 39.4 (C-7), 38.7(C-8), 37.3 (C-10), 36.3 (C-13), 33.3 (C-4), 33.2 (C-18), 25.2 (C-12), 22.2(C-15a), 21.4 (C-19), 18.2 (C-2), 17.8 (C-6), 17.0 (C-11), 16.3 (C-17), 13.8 (C-20). EIMS *m/z* (%) 318 (M^+) (18), 217 (15), 191 (50), 163 (99), 123 (100), 99 (72), 81 (45).

4.1.13. (13*S*)-15a-Homo-isoanticopal-16,15-olide 14. To a solution of **26** (128 mg, 0.40 mmol) in ^{t}BuOH (4.0 mL), at room temperature under anhydrous atmosphere, 1 M ^{t}BuO$^-$K$^+$ in THF (1.8 mL, 1.8 mmol) was added. The mixture was heating and stirring in reflux at 70 °C for 30 min. Then, saturated water and 2 N HCl were added. The organic phase was separated and the aqueous phase was extracted with EtOAc. Extracts were washed with water and dried. Evaporation of the solvent yielded the lactone **14** (131 mg, 99%) as a crystalline colourless solid. Compound **14**: $[\alpha]_D^{20}$ −27.5 (*c* 0.36, $CHCl_3$), mp: 199–201 °C. IR: 2932, 2845, 1728, 1699, 1439, 1385, 1177 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 4.37–4.12 (2H, m, H-15), 2.45–2.20 (2H, m, H_A-15a and H-13), 1.40–1.30 (1H, m, H_B-15a), 1.79–1.68 and 1.11–0.98 (2H, m, H-1), 1.74–1.30 (2H, m, H-2), 1.43–1.30 and 1.18–1.03 (2H, m, H-3), 0.87–0.71 (1H, m, H-5), 1.74–1.30 (2H, m, H-6), 1.70–1.60 and 0.87–0.73 (2H, m, H-7), 0.85–0.73 (1H, m, H-9), 0.74–1.30 (2H, m, H-11), 2.36–2.23 and 1.42–1.28 (2H, m, H-12), 1.40–1.20 (1H, m, H-14), 0.88 (3H, s, Me-20), 0.86 (3H, s, Me-18), 0.83 (3H, s, Me-17), 0.81 (3H, s, Me-19). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 175.0 (C-16), 67.7 (C-15), 58.9 (C-5), 56.5 (C-9), 49.1 (C-14), 41.2 (C-3), 40.1 (C-1), 39.8 (C-7), 39.4 (C-13), 37.4 (C-8), 37.3 (C-10), 33.3 (C-4), 33.3 (C-18), 28.0 (C-12), 22.5 (C-15a), 21.4 (C-19), 19.8 (C-2), 18.5 (C-6), 18.3 (C-11), 16.2 (C-17), 14.2 (C-20). EIMS *m/z* (%) 318 (M^+) (35), 191 (34), 123 (28), 94 (100). HRMS: calcd for $C_{21}H_{34}O_2$ $[M]^+$: 318.2559, found: 318.2560.

4.1.14. (13*S*)-15a-Homo-isoanticopal-16,15-epoxy-16*R*/*S*-ol 27. To a solution of **14** (137 mg, 0.43 mmol) in dry methylene chloride (6 mL) was added a solution of DIBAL-H in toluene (1.6 M, 0.6 mL, 0.9 mmol) under argon at −78 °C. The solution was stirred for 30 min, quenched by addition of MeOH (1.6 mL) and Na^+ and K^+ tartrate (3 mL) and extracted with EtAcO. The organic layer was washed with water and dried over Na_2SO_4. Evaporation of the solvent yielded the lactol **27** (16*S*/16*R* 8/2) (136 mg, 99%). Compound **27**: IR: 3366, 2932, 2845, 1458, 1385, 1127, 1074, 976 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 4.98 (1H, d, *J*=2 Hz, H-16*R*), 4.22 (1H, d, *J*=6.2 Hz, H-16S), 4.01 (1H, ddd, J_1=11.4, J_2=4.0 and J_3=2.2 Hz, H_A-15 major), 3.95 (1H, ddd, J_1=10.0, J_2=9.0 and J_3=3.6 Hz, H_A-15 minor), 3.61 (1H, dt, J_1=10.0 and J_2=3.2 Hz, H_B-15 minor), 3.44 (1H, dt, J_1=11.4 and J_2=2.8 Hz, H_B-15 major), 2.08–2.02 (1H, m, H-13), 1.65–0.90 (19H, m), 0.85 (6H, s), 0.83 (3H, s), 0.79 (3H, s). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 100.9 (C-16), 65.8 (C-15), 59.5 (C-5), 56.6 (C-9), 52.7 (C-14), 42.2 (C-13), 42.1 (C-3), 39.9 (C-1), 40.6 (C-7), 37.5 (C-8), 36.4 (C-10), 33.2 (C-4), 33.3 (C-18), 28.6 (C-15), 24.3 (C-15a), 21.4 (C-19), 19.5 (C-11), 18.6 (C-2), 18.5 (C-6), 16.4 (C-17), 15.0 (C-20). EIMS *m/z* (%) 320 (M^+) (64), 287 (9), 259 (10), 191 (100), 123 (35), 69 (38). HRMS: calcd for $C_{21}H_{36}O_2$ $[M]^+$: 320.2715, found: 320.2725.

4.1.15. (13*S*)-15a,15b-Dihomo-isoanticopal-15b(15)en-16-ol 28. To a suspension of Ph_3PCH_2Br (1.5 g, 4.25 mmol) in toluene (3.7 mL) at −20 °C under an argon atmosphere, 0.6 M NaHMDS in toluene (7.4 mL, 4.44 mmol) was added dropwise and the solution stirred for 30 min. A solution of the lactol **27** (136 mg, 0.42 mmol) in benzene (4 mL) was added dropwise and the mixture stirred for 1 h at 80 °C. It was allowed to warm to room temperature, quenched with aqueous NH_4Cl and extracted with Et_2O. The organic layer was washed with water and dried over Na_2SO_4. The residue, obtained after the solvent was removed was purified by column chromatography (benzene) to afford **28** (76 mg, 56%). Compound **28**: $[\alpha]_D^{20}$ +5 (*c* 0.1, $CHCl_3$). IR: 3401, 2926, 2851, 1653, 1559, 1458, 1387, 1262, 1101, 1044, 907, 801 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 5.87 (1H, dddd, J_1=17.2, J_2=10.2, J_3=8.4 and J_4=5.0 Hz, H-15b), 5.05 (1H, d, *J*=17.2 Hz, H_A-15), 4.96 (1H, d, *J*=10.2 Hz, H_B-15), 3.61 (1H, dd, J_1=11.4 and J_2=4.0 Hz, H_A-16), 3.55 (1H, dd, J_1=11.4 and J_2=3.0 Hz, H_B-16), 2.29 (1H, ddd, J_1=17.6, J_2=5.0 and J_3=2.4 Hz, H_A-15a), 1.85–1.75 (1H, m, H_B-15a), 1.74–1.59 and 0.87–0.70 (2H, m, H-1), 1.18–1.66 (2H, m, H-2), 1.41–1.29 and 1.19–1.05 (2H, m, H-3), 0.90–0.75 (1H, m, H-5), 1.18–1.66 (2H, m, H-6), 1.98–1.85 and 1.11–0.96 (2H, m, H-7), 0.89–0.75 (1H, m, H-9), 1.67–1.60 and 1.30–1.23 (2H, m, H-11), 1.74–1.87 (2H, m, H-12), 1.41–1.29 (1H, m, H-13), 1.05–0.89 (1H, m, H-14), 0.88 (3H, s, Me-20), 0.86 (3H, s, Me-18), 0.83 (3H, s, Me-17), 0.81 (3H, s, Me-19). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 141.2 (C-15b), 114.0 (C-15), 65.5 (C-16), 59.6 (C-5), 56.4 (C-9), 52.2 (C-14), 42.0 (C-3), 41.7 (C-13), 40.7 (C-7), 39.9

(C-1), 38.3 (C-8), 37.5 (C-10), 33.3 (C-18), 33.2 (C-4), 32.3 (C-15a), 30.9 (C-12), 21.4 (C-19), 20.1 (C-11), 18.6 (C-2), 18.5 (C-6), 16.2 (C-17), 15.1 (C-20). EIMS *m/z* (%) 318 (M^+) (20), 277 (10), 191 (100), 109 (30), 95 (43), 69 (62). HRMS: calcd for $C_{22}H_{38}O$ $[M]^+$: 318.2923, found: 318.2923.

4.1.16. (13*S*)-15a,15b-Dihomo-isoanticopal-15b(15)en-16-al 29. To a mixture of **28** (59 mg, 0.18 mmol), *N*-methylmorpholine *N*-oxide (NMO) (38 mg, 0.28 mmol) and molecular sieves (90 mg, 500 mg/mmol) in anhydrous DCM (2 mL) under argon and at room temperature and TPAP (5.3 mg, 0.015 mmol) were added. The reaction mixture was stirred for 1 h and then filtered through a short pad of silica gel and Celite®, eluting with EtOAc. Evaporation of the solvent yielded the aldehyde **29** (61 mg, 100%). Compound **29**: $[\alpha]_D^{20}$ +7.0 (*c* 0.1, $CHCl_3$). IR: 2932, 2851, 1724, 1458, 1387, 1262, 1103, 1028, 914, 802 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.42 (1H, d, J=4.8 Hz, H-16), 5.67 (1H, dddd, J_1=16.0, J_2=10.0, J_3=8.4 and J_4=6.0 Hz, H-15b), 4.97 (1H, d, J=10.0 Hz, H_A-15), 4.94 (1H, d, J= 16 Hz, H_B-15), 2.38–2.20 (2H, m, H-15a), 1.74–1.60 and 0.85–0.70 (2H, m, H-1), 1.75–1.27 (2H, m, H-2), 1.46–1.30 and 1.20–1.05 (2H, m, H-3), 0.94–0.78 (1H, m, H-5), 1.75–1.27 (2H, m, H-6), 1.94–1.86 and 1.14–0.97 (2H, m, H-7), 0.97–0.72 (1H, m, H-9), 1.75–1.27 (2H, m, H-11), 1.71–1.63 and 1.37–1.29 (2H, m, H-12), 2.35–2.26 (1H, m, H-13), 1.45–1.31 (1H, m, H-14), 0.88 (3H, s, Me-20), 0.86 (3H, s, Me-18), 0.83 (3H, s, Me-17), 0.81 (3H, s, Me-19). ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.3 (C-16), 138.5 (C-15b), 116.6 (C-15), 59.2 (C-5), 56.4 (C-9), 53.6 (C-14), 51.1 (C-13), 41.9 (C-3), 40.6 (C-7), 39.9 (C-1), 37.7 (C-8), 37.5 (C-10), 33.2 (C-18), 33.1 (C-4), 33.1 (C-15a), 27.2 (C-12), 21.4 (C-19), 19.0 (C-11), 18.6 (C-2), 18.4 (C-6), 16.2 (C-17), 15.0 (C-20). EIMS *m/z* (%) 316 (M^+) (13), 301 (17), 191 (100), 123 (38), 95 (49), 69 (68). HRMS: calcd for $C_{22}H_{36}O$ $[M]^+$: 316.2766, found: 316.2746.

4.1.17. (13*S*,17*R*)-16a-Homo-18-nor-16-seco-meliac-16a(16)en-17-ol 30. A solution of 3-bromofurane (69 μL, 0.767 mmol) in THF (1.75 mL) was treated dropwise with *n*-BuLi (1.6 M in hexane, 0.5 mL, 0.77 mmol) at −78 °C. After the reaction mixture was stirred for 10 min at this temperature, a solution of aldehyde **29** (60.6 mg, 0.192 mmol) in dry THF (1 mL) was added and stirred for an additional 30 min. The reaction mixture was treated with saturated NH_4Cl aqueous solution, warmed to room temperature and extracted with Et_2O. The organic layer was washed with brine and water and dried over Na_2SO_4. The residue obtained after removal of the solvent was purified by chromatography (benzene) to yield the alcohol **30** (42.4 mg, 58%,). Compound **30**: $[\alpha]_D^{20}$ +16.6 (*c* 0.2, $CHCl_3$). IR: 3484, 2930, 2853, 1636, 1464, 1387, 1262, 1161, 1028, 909, 876, 797, 723 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (1H, s, H-23), 7.33 (1H, s, H-21), 6.26 (1H, s, H-22), 5.99 (1H, dddd, J_1=16.8, J_2=10.1, J_3=9.2 and J_4=5.1 Hz, H-16a), 5.12 (1H, d, J=16.8 Hz, H_A-16), 5.06–4.95 (2H, m, H_B-16 and H-17), 2.45–2.35 and 1.28–1.25 (2H, m, H-15), 1.70–1.59 and 0.82–0.70 (2H, m, H-1), 1.60–1.54 and 1.40–1.37 (2H, m, H-2), 1.40–1.30 and 1.18–1.06 (2H, m, H-3), 0.94–0.78 (1H, m, H-5), 1.64–1.59 (2H, m, H-6), 2.00–1.90 and 1.16–1.04 (2H, m, H-7), 0.97–0.72 (1H, m, H-9), 1.62–1.58 and 1.22–1.20 (2H, m, H-11), 1.50–1.45 (2H, m, H-12), 1.30–1.20 (1H, m, H-13), 1.51–1.41 (1H, m, H-14), 0.86 (3H, s, Me-28), 0.83 (3H, s, Me-19), 0.81 (3H, s, Me-29), 0.80 (3H, s, Me-30). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8 (C-23), 141.3 (C-16a), 138.9 (C-21), 128.5 (C-20), 114.3 (C-16), 108.6 (C-22), 66.6 (C-17), 59.5 (C-5), 56.4 (C-9), 51.9 (C-14), 45.0 (C-13), 42.0 (C-3), 40.9 (C-7), 39.9 (C-1), 38.5 (C-8), 37.5 (C-10), 33.3 (C-28), 33.2 (C-4), 32.2 (C-15), 24.9 (C-12), 21.4 (C-29), 19.8 (C-11), 18.6 (C-2), 18.5 (C-6), 16.1 (C-30), 15.1 (C-19). EIMS *m/z* (%) 384 (M^+) (8), 297 (19), 269 (20), 243 (10), 191 (18), 143 (100). HRMS: calcd for $C_{26}H_{40}O_2$ $[M]^+$: 384.3028, found: 384.3032.

4.1.18. (13*S*,17*R*)-16a-Homo-18-nor-16-seco-meliaca-16a*R*/*S*,16,17-triol 31a/31b. To a solution of **30** (137 mg, 0.43 mmol) in a mixture of ^{t}BuOH/THF/H_2O 7/2/1 (1 mL) was added NMO (5.8 mg, 0.043 mmol) and OsO_4 in ^{t}BuOH under an argon atmosphere. The solution was stirred for 46 h. Then was added Na_2SO_3 (0.3 mL) and was stirred for 30 min more and extracted with EtAcO. The organic layer was washed with water, 10% $Na_2S_2O_3$, 2 N HCl, H_2O and brine and dried over Na_2SO_4. The residue obtained after removal of the solvent was purified by chromatography (hexane/EtOAc 7/3) to yield the isomeric triols **31a** (50 mg, 28%) and **31b** (100 mg, 56%). Compound **31a**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (1H, s, H-23), 7.36 (1H, s, H-21), 6.25 (1H, s, H-22), 5.07 (1H, s, H-17), 3.78–3.67 (2H, m, H-16a and H_A-16), 3.42 (1H, dd, J_1=17.2 and J_2=9.5 Hz, H_B-16), 1.98–0.79 (20H, m), 0.85, 0.81, 0.80 and 0.79 (3H, s each, Me-19, 28, 29 and 30). Compound **31b**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (1H, s, H-23), 7.33 (1H, s, H-21), 6.26 (1H, s, H-22), 4.96 (1H, s, H-17), 3.94–3.91 (1H, m, H-16a), 3.65 (1H, dd, J_1=12.4 and J_2=3.2 Hz, H_A-16), 3.55 (1H, dd, J_1=12.4 and J_2=7.4 Hz, H_B-16), 1.98–0.79 (20H, m), 0.85, 0.81, 0.80 and 0.79 (4×3H, s, Me-19, 28, 29 and 30).

4.1.19. (13*S*,16*R*/*S*)-Hydroxy-18-nor-limonoid 32. To a solution of **31a/31b** (30 mg, 0.072 mmol) in a mixture of THF/H_2O 2/1 (0.36 mL) was added slowly $NaIO_4$ (29 mg, 0.134 mmol). The solution was stirred for 10 min and Et_2O (2 mL) was added. The organic layer was washed with 4% $NaHCO_3$, H_2O and brine and dried over Na_2SO_4. The residue obtained after removal of the solvent was purified by chromatography (benzene/EtAcO 9/1) to yield the lactol **32** (18 mg, 65%). Compound **32**: IR: 3394, 2928, 2866, 1740, 1458, 1387, 1262, 1132, 1032, 874, 797 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.41 (1H, s, H-23), 7.39 (1H, s, H-21), 6.40 (1H, s, H-22), 4.83 (1H, d, J=6.0 Hz, H-17), 4.98–4.93 (1H, m, H-16), 1.98–0.81 (20H, m), 0.88, 0.85, 0.83 and 0.80 (4×3H, s, Me-19, 28, 29 and 30).

4.1.20. (13*S*)-18-Nor-limonoid 33. To a mixture of **32** (18 mg, 0.05 mmol), *N*-methylmorpholine *N*-oxide (NMO) (12 mg, 0.085 mmol) and molecular sieves (25 mg, 500 mg/mmol) in anhydrous CH_2Cl_2 (0.5 mL) under argon and at room temperature and TPAP (2 mg, 0.005 mmol) were added. The reaction mixture was stirred for 1 h and then filtered through a short pad of silica gel and Celite®, eluting with EtOAc. Evaporation of the solvent yielded the lactone **33** (195 mg, 98%). Compound **33**: $[\alpha]_D^{20}$ −48.6 (*c* 0.15, $CHCl_3$). IR: 2932, 2864, 1734, 1717,1458, 1387, 1262, 1194, 1032, 801 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (1H, s, H-23), 7.29 (1H, s, H-21), 6.24 (1H, s, H-22), 5.32 (1H, d, J=6.0 Hz, H-17), 2.59 (1H, dd, J_1=18.8 and

J_2=7.6 Hz, H_A-15), 2.41 (1H, dd, J_1=18.8 and J_2=7.6 Hz, H_B-15), 1.69–1.54 (2H, m, H-1), 1.62–1.25 (2H, m, H-2), 1.42–1.28 and 1.15–1.01 (2H, m, H-3), 0.73–0.61 (1H, m, H-5), 1.62–1.25 (2H, m, H-6), 1.07–0.91 and 0.87–0.67 (2H, m, H-7), 0.84–0.69 (1H, m, H-9), 1.62–1.25 (2H, m, H-11), 1.82–1.70 and 0.94–0.88 (2H, m, H-12), 1.43–1.28 (1H, m, H-13), 1.52–1.38 (1H, m, H-14), 0.88 (3H, s, Me-19), 0.84 (3H, s, Me-30), 0.82 (3H, s, Me-28), 0.79 (3H, s, Me-29). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9 (C-16), 143.3 (C-23), 140.2 (C-21), 122.5 (C-20), 109.5 (C-22), 78.0 (C-17), 59.1 (C-5), 56.4 (C-9), 43.9 (C-14), 41.9 (C-3), 39.8 (C-7), 39.7 (C-1), 37.4 (C-8), 36.8 (C-10), 35.9 (C-13), 33.2 (C-4), 33.2 (C-28), 29.5 (C-15), 28.7 (C-12), 21.4 (C-29), 19.5 (C-11), 18.5 (C-2), 18.1 (C-6), 16.4 (C-30), 14.3 (C-19). EIMS *m/z* (%)384 (M^+) (37), 317 (18), 287 (51), 246 (100), 191 (40), 137 (45). HRMS: calcd for $C_{25}H_{36}O_3$ $[M]^+$: 384.2664, found: 384.2655.

4.1.21. (13*S*,21*R*/*S*)-21-Hydroxy-23,21-olide-18-nor-20(22)en-limonoid 15. Rose Bengal (2 mg) was added to a solution of **33** (10 mg, 0.026 mmol) and DIPEA (0.05 mL, 0.27 mmol) in dry DCM (3.2 mL) at room temperature. Anhydrous oxygen was bubbled in for 10 min, and after that the solution was placed under oxygen atmosphere at −78 °C and irradiated with a 200 W lamp. After 6 h irradiation was stopped, the pink solution was allowed to warm to room temperature, and saturated aqueous oxalic acid (1 mL) was added. After 30 min of vigorous stirring, the mixture was diluted with water and extracted with DCM. The combined organic extracts were washed with water and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated to give a residue, which was purified by silica gel column chromatography (benzene/EtOAc 8/2) to yield **15** (8 mg, 68%). $[\alpha]_D^{20}$ −26.1 (*c* 0.28, $CHCl_3$). IR: 3339, 2924, 2855, 1738, 1462, 1053 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.20 (1H, s, H-22), 5.98 (1H, s, H-21), 5.35 (1H, d, J=6.0 Hz, H-17), 2.58 (1H, dd, J_1=18.4 and J_2=7.0 Hz, H_A-15), 2.33 (1H, dd, J_1=18.4 and J_2=10.6 Hz, H_B-15), 2.20–1.02 (18H, m), 0.88 (3H, s), 0.84 (6H, s), 0.80 (3H, s). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 171.9 (C-16), 169.2 (C-23), 164.1 (C-20), 121.6 (C-22), 98.2 (C-21), 78.0 (C-17), 59.1 (C-5), 56.4 (C-9), 43.9 (C-14), 41.9 (C-3), 39.8 (C-7), 39.7 (C-1), 37.4 (C-8), 36.8 (C-10), 35.9 (C-13), 33.2 (C-4), 33.2 (C-28), 29.5 (C-15), 28.7 (C-12), 21.4 (C-29), 19.5 (C-11), 18.5 (C-2), 18.1 (C-6), 16.4 (C-30), 14.3 (C-19); EIMS *m/z* (%) 417 (M^++1) (25), 307 (12), 154 (100), 107 (31), 84 (33). HRMS: calcd for $C_{25}H_{37}O_5$ $[MH]^+$: 417.2641, found: 417.2635.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.06.004.

References and notes

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20. Numbering of **32** has been considered as a nor-limonoid skeleton.
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