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Lateral lithiation in terpenes: synthesis of (+)-ferruginol and (+)-sugiol

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ABSTRACT

This paper describes the use of (−)-sclareol in the synthesis of the tricyclic diterpenes of abietane skeleton, such as (+)-ferruginol and (+)-sugiol, using as key step the lateral lithiation of a dinorditerpene derivative.

1. Introduction

The diterpene tricyclic of abietane skeleton, are one of the natural product groups widely distributed in nature some of which display an interesting range of biological activities.[1] A major part of these compounds have ring C aromatic. In Figure 1, are shown the most common variation of known derivatives with aromatic ring C and C-15 and/or C-16 functionality or not.

Diterpene abietanes as (+)-ferruginol **1** and (+)-sugiol **2**, isolated from *Podocarpus ferruginenus*[2] and *Juniperus communis* L.,[3] respectively, are widely distributed in nature.[4] Recently it has been found that (+)-ferruginol has a potent activity as gastric protector in animals,[5] while, (+)-sugiol shows antiinflamatory,[6] antitumoral,[7] antioxidant and antimicrobiane properties.[8] Other interesting abietanes are more functionalized as incanone **3**, that shows cytotoxic activity against human leukemia cells[9] or cyrtophyllone B **4**[10] (Fig. 2).

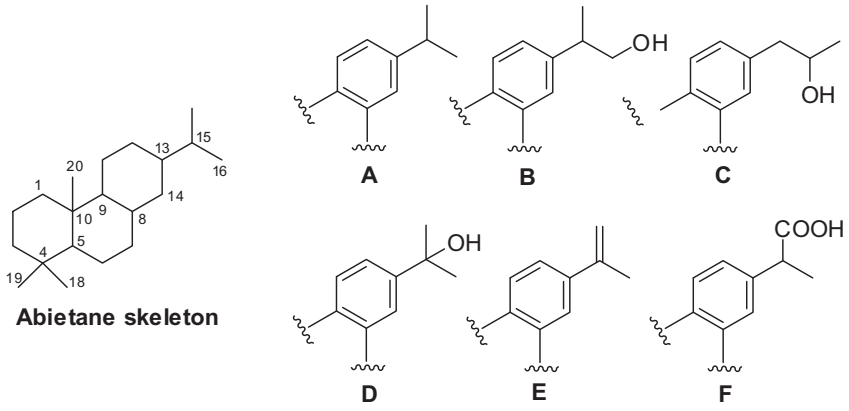

Figure 1. Abietane skeleton structure types differently substituted on the side chain.

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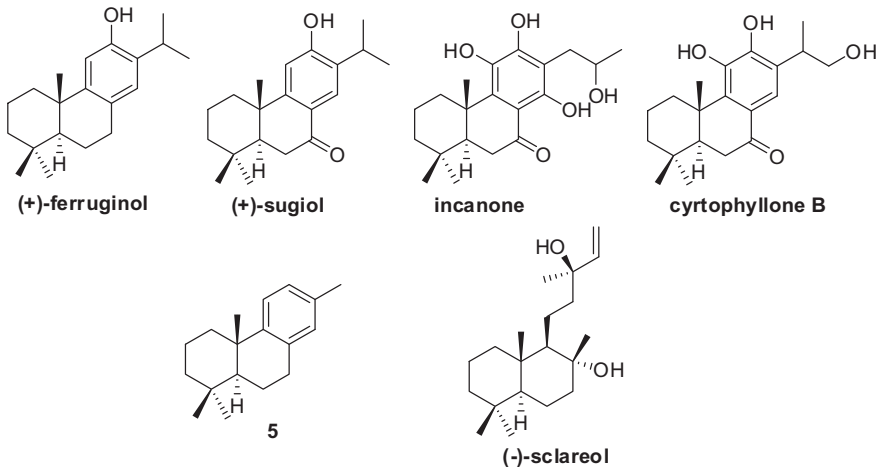
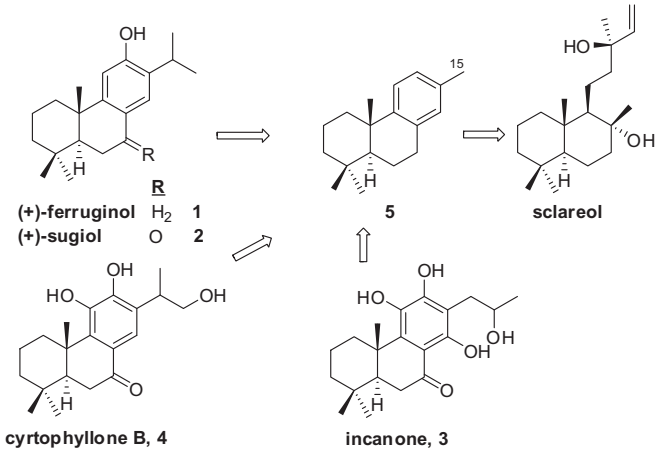


Figure 2. Diterpenes with abietane and *abeo*-abietane skeletons, accesibles from (−)-sclareol through norditerpene **5**.

Recently our group has synthesised the dinorpimarane **5** from (−)-sclareol, Figure 2, in three steps in good yield.[11] In this paper it is shown that **5**, is an excellent starting material for the synthesis of abietanes with different side chain. The methodology will be applied to the synthesis of the natural products (+)-ferruginol **1** and (+)-sugiol **2** and analogues of incanone **3** and cyrtophyllone B, **4**.

2. Results and discussion

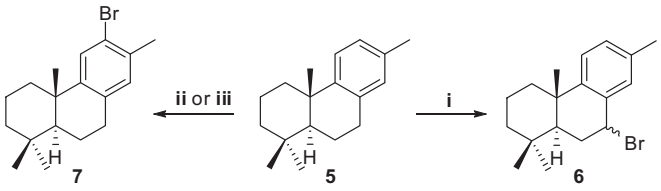
In Scheme 1, it is shown the retrosynthetic analysis for the synthesis of (+)-ferruginol **1**, (+)-sugiol **2** and analogues of incanone, **3** and cyrtophyllone B, **4** from (−)-sclareol using the dinorpimarane **5** as the key intermediate.



Scheme 1. Retrosynthetic analysis for access the abietane skeleton from (−)-sclareol.

The transformation of **5** into abietane diterpenes requires functionalization at C-15 or alkylation at this carbon. The direct functionalization of C-15 of compound **5**, first attempted under radical conditions. However treatment of **5** with NBS and catalytic AIBN in CCl_4 at 70 °C,[12] gave **6** (72%), while reaction with NBS/AIBN under irradiation with a lamp of 200 W in THF/H_2O (Scheme 2),[13] gave **7** (66%) and the reaction with NBS/AIBN in ionic solvent as [bmim]PF_6, led again to **7** with in lower yield 46 %.

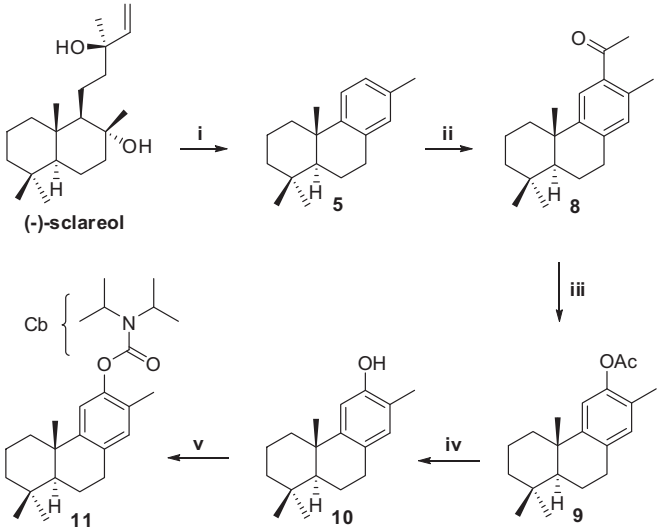
As the direct functionalization did not gave the expected results, it was decided the use of lateral lithiation for the activation of C-15. *ortho*-Lithiation[14] and lateral lithiation,[15] are two excellent methodologies for the regioselective synthesis of natural products.[16] Several groups, such as methoxyls,[17] *N*,*N*-alquilamides,[18] *N*,*N*′-diarylureas,[19] oxazolines,[20] carbamates[21] and toluensulfonamides[22] are capable of



Scheme 2. (i) NBS, AIBN cat., CCl_4, 70 °C, 2 h, 62%; (ii) NBS, AIBN cat., TFH/H_2O, hν (200 W), 10 min, 46%; (iii) NBS, AIBN cat., [bmim]PF_6, 80 °C, 2 h 30 min, 46%.

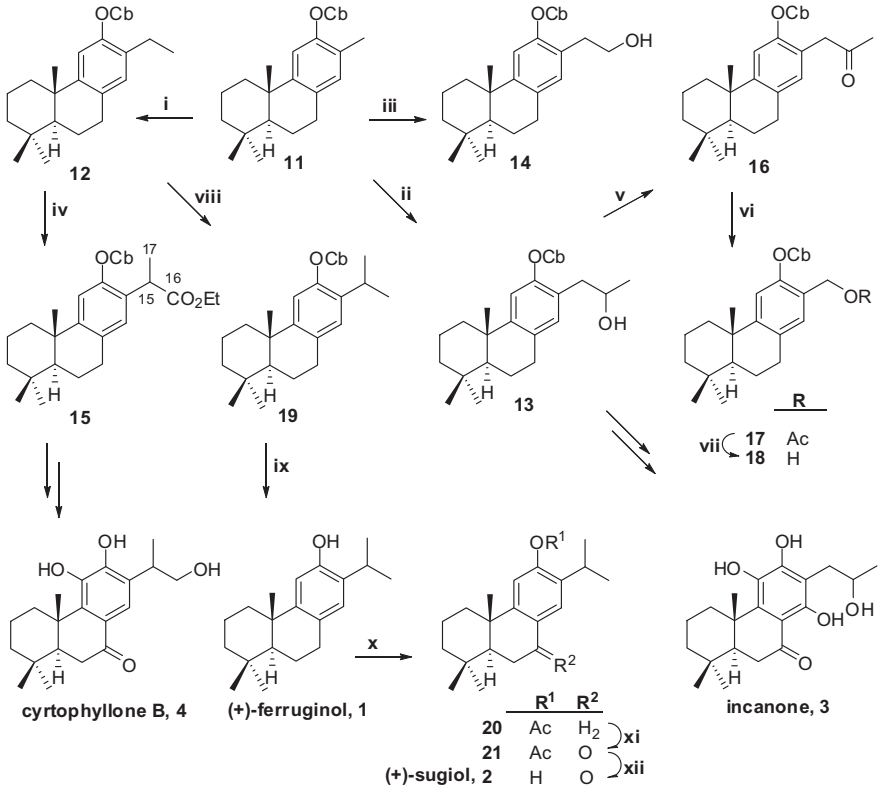
directing regioselectively the addition or substitution of aromatic compounds differently substituted with different electrofiles.

Considering that the objective of this work is the synthesis of (+)-ferruginol **1**, (+)-sugiol **2**, analogues of incanone **3** and of cyrtophyllone B **4**, that present and oxygenated function in C-12, the carbamoyl was chosen group as the one for directing the lateral lithiation. For this reason first of all will be synthesised compound **11** (Scheme 3). Friedel–Crafts acylation of **5** gave the acylderivative **8**, that by Baeyer–Villiger oxidation gave **9** in 80% yield for the two steps. The hydrolysis of the last compound gave phenol **10**, that by treatment with *N*,*N*-diisopropilcarbamoyl chloride in presence NaH (Scheme 3) gave the required **11** in good yield.



Scheme 3. (i) Ref. 11, 71%; (ii) AcCl, $SnCl_4$ 85 °C, 45 min, 90%; (iii) UHP, TFAA, rt, 24 h, 91%; (iv) K_2CO_3, MeOH, H_2O, 3%, rt, 30 min, 98%, (v) (1) NaH 60%, THF, 0 °C→rt, 15 min; (2) (*i*-Pr)$_2$NCOCl, 2 h, rt, 92%.

With compound **11** in hand, several conditions for the lateral lithiation were tested. (Scheme 4). Compound **11** was treated with



Scheme 4. (i) (1) 10 equiv sec-BuLi, −78 °C, 10 min; (2) 10 equiv MeI, −78 °C→rt 20 min, 94%; (ii) (1) 10 equiv sec-BuLi, −78 °C, 10 min; (2) 10 equiv CH_3CHO, −78 °C→rt 20 min, 87%; (iii) (1) 32 equiv sec-BuLi, −78 °C, 10 min; (2) 5 equiv HCHO, −78 °C→rt 20 min, 68%. (iv) (1) 10 equiv sec-BuLi, −78 °C, 10 min; (2) 10 equiv $ClCO_2Et$, −78 °C→rt,74%; (v) TPAP/NMO, DCM, rt, 10 min, 99%; (vi) *m*-CPBA, DCM, rt, 16 h, 74%; (vii) K_2CO_3, MeOH, rt, 45 min, 97%; (viii) (1) 10 equiv sec-BuLi, −78 °C, 10 min; (2) 10 equiv MeI, −78 °C→rt, 20 min, 82%; (ix) $LiAlH_4$, Et_2O, reflux 16 h, 93%; (x) Ac_2O, py, 6 h, rt, 98%; (xi) Na_2CrO_4, NaOAc, AcOH/Ac_2O, 65 °C, 45 min, 77%; (xii) K_2CO_3, MeOH, rt, 96%.

a big excess of sec-BuLi (10 equiv) at −78 °C and the lithiated species were made to react with different electrophiles as MeI, acetaldehyde and formaldehyde, obtaining compounds **12**, **13** and **14**, in good yield, not being found the products of *ortho*-lithiation (Scheme 4). Compounds **12** and **14** are norpimaranes and the side chain of **13**, correspond to a 17(15→16)-*abeo*-abietane, partial structure **C** in Figure 1, as the natural product incanone **3**.[9]

In order to prove the interest of compounds **12** and **13**, they have been transformed into more complex abietanes. Reaction of **12** with sec-BuLi and ethyl chloroformiate gave ester **15**, a very interesting intermediate for the synthesis of cyrtophyllone B type abietanes and other compounds of partial structure as **B** and **F** in Figure 1.

Oxidation of **13** with TPAP/NMO in DCM afforded ketone **16**, Scheme 4. Baeyer–Villiger oxidation of **16**, gave **17** that treated with K_2CO_3/MeOH led to the hydroxyderivative **18**. This compound can be used for the synthesis of abietanes differently substituted at C-15, of type D and E, Figure 1.

2.1. Synthesis of (+)-ferruginol 1 and (+)-sugiol 2

To put in value the lateral lithiation, we decided to synthesis two abietanes, such as (+)-ferruginol **1** and (+)-sugiol **2** from **12**, Scheme 4. Reaction of **12** with an excess of sec-BuLi followed by the addition of MeI, abietane **19** was obtained in good yield, Scheme 4. Reduction of **19** with LAH in refluxing ether for 16 h, gave **1**, $[\alpha]_D^{20}$ +42.9 (*c* 0.2, $CHCl_3$), which physical properties were coincident with the ones of natural (+)-ferruginol, $[\alpha]_D^{25}$ +55.7 (*c* 0.5, $CHCl_3$).[23]

Acetylation of **1** with Ac_2O in the usual conditions gave the acetyl derivative **20**, which by oxidation with Na_2CrO_4 led to ketone **21** (Scheme 4). Hydrolysis of **21** with K_2CO_3/MeOH gave **2** whose spectroscopical properties, $[\alpha]_D^{20}$ +15.3 (*c* 0.3, $CHCl_3$) and mp 284–286 °C, were coincident with the ones of the natural (+)-sugiol **2**, $[\alpha]_D^{25}$ +12.3 (*c* 0.1, $CHCl_3$) and mp 282–285 °C.[9]

3. Conclusions

It has been shown, that lateral lithiation reaction is a direct an easy way to accede to the tricyclic diterpenes with abietane (i.e., cyrtophyllone B) and *abeo*-abietane (i.e., incanone) skeletons. This methodology has been applied in the synthesis of the natural compounds (+)-ferruginol **1** and (+)-sugiol **2** from (−)-sclareol with 37% and 27% overall yields, respectively.

4. Experimental

4.1. General

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification. IR spectra were recorded on a BOMEM 100 FT-IR or an AVATAR 370 FT-IR Thermo Nicolet spectrophotometers. ^1H and ^{13}C NMR spectra were performed in $CDCl_3$ and referenced to the residual peak of $CHCl_3$ at δ 7.26 ppm and δ 77.0 ppm, for ^1H and ^{13}C, respectively, using Varian 200 VX and Bruker DRX 400 instruments. Chemical shifts are reported in δ parts per million and coupling constants (*J*) are given in hertz. MS were performed at a VG-TS 250 spectrometer at 70 eV ionising voltage. Mass spectra are presented as *m*/*z* (% rel int.). HRMS were recorded on a VG Platform (Fisons) spectrometer using chemical ionisation (ammonia as gas) or Fast Atom Bombardment (FAB) technique. For some of the samples, QSTAR XL spectrometer was employed for electrospray ionisation (ESI). Optical rotations were determined on a Perkin–Elmer 241 polarimeter in 1 dm cells. Diethyl ether and THF

were distilled from sodium, and dichloromethane was distilled from calcium hydride under argon atmosphere.

4.2. Reaction of 5 with NBS/AIBN to yield 6

To a solution of **5** (50 mg, 0.20 mmol) in CCl_4 (0.8 mL), NBS (35 mg, 0.20 mmol) and AIBN (2 mg) were added. The mixture was heated at 70 °C for 2 h and after that, diluted with Et_2O, washed with H_2O and brine, the organic phase was dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. After column chromatography on silica gel compounds **5** (15 mg, 30%) and **6** (39 mg, 62%) were obtained.

*4.2.1. 7-Bromo-16,17-dinor-pymara-8,11,13-triene (**6**).* R_f 0.12 (*n*-Hex/EtOAc 9/1); $[\alpha]_D^{20}$ +7.6 (*c* 0.6, $CHCl_3$); IR ν_{max} (film): 2928, 1402, 1378, 1203, 997, 818, 767 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 7.22 (2H, d, *J*=2.2 Hz, H-11), 7.17 (2H, d, *J*=2.2 Hz, H-12), 7.13 (2H, s, H-14), 4.95–4.90 (1H, m, H-7), 4.75 (1H, t, *J*=1.8 Hz, H-7), 2.33 (6H, s, Me-15), 2.31–1.05 (18H, m,), 1.63 (6H, s, Me-20), 1.26 (6H, s, Me-18), 1.08 (6H, s, Me-19); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 145.8 (C-9), 136.1 (C-13), 132.2 (C-8), 131.3 (C-14), 130.3 (C-12), 126.3 (C-11), 75.8 (C-7), 50.7 (C-5), 47.7 (C-6), 43.8 (C-1), 43.5 (C-3), 39.1 (C-10), 34.7 (C-4), 33.5 (C-18), 25.7 (C-20), 22.8 (C-19), 21.0 (C-15), 19.7 (C-2); EIHRMS: calcd for $C_{18}H_{25}BrNa$ ($M+Na^+$): 343.1036, found: 343.1040.

4.3. Reaction of 5 with NBS/hν to yield 7

To a solution of **5** (20 mg, 0.08 mmol) in H_2O (0.5 mL) and THF (0.1 mL), NBS (34 mg, 0.2 mmol) and AIBN (1 mg) were added at room temperature. The reaction was allowed to stir for 10 min under 200 W lamp. After this time, the mixture was diluted with Et_2O and the organic phase washed with H_2O and brine, dried over Na_2SO_4, filtered and the solvent was evaporated. By column chromatography over silica gel in *n*-Hex/EtOAc (9/1), compounds **5** (9 mg, 45%) and **7** (12 mg, 46%) were separated.

*4.3.1. 12-Bromo-16,17-dinor-pymara-8,11,13-triene (**7**).* R_f 0.59 (*n*-Hex); $[\alpha]_D^{20}$ +51.4 (*c* 0.8, $CHCl_3$); IR ν_{max} (film): 2925, 2865, 1472, 1388, 1314, 1211, 1145, 1083, 974, 874 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.38 (1H, s, H-11), 6.90 (1H, s, H-14), 2.85 (1H, dd, *J*=10.7 and 4.0 Hz, H_A-7), 2.76 (1H, dd, *J*=10.7 and 4.0 Hz, H_B-7), 2.30 (3H, s, Me-15), 2.20–2.19 (1H, m, H-1), 1.80–1.74 (4H, m, H-2 and H-6), 1.50–1.49 (m, 1H, H-3), 1.29–1.27 (1H, m, H-1), 1.28–1.26 (1H, m, H-5), 1.21–1.19 (1H, m, H-3), 1.16 (3H, s, Me-20), 0.94 (3H, s, Me-18), 0.92 (3H, s, Me-19); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.8 (C-9), 134.4 (C-8), 131.2 (C-14), 128.2 (C-11), 123.1 (C-12), 121.9 (C-13), 50.1 (C-5), 41.5 (C-3), 38.8 (C-1), 37.6 (C-10), 33.4 (C-4), 33.2 (C-18), 29.7 (C-7), 24.8 (C-20), 22.2 (C-19), 21.5 (C-15), 19.1 (C-2), 18.8 (C-6); EIHRMS: calcd for $C_{18}H_{25}BrNa$ ($M+Na^+$): 343.1042, found: 343.1045.

4.4. Reaction of 5 with NBS/[bmim]PF_6 to yield 7

In a 5 mL round-bottom flask containing compound **5** (20 mg, 0.08 mmol), [bmim]PF_6 (0.01 mL), NBS (16 mg, 0.09 mmol) and AIBN (1 mg) were added at room temperature. The reaction mixture was heated at 80 °C for 2 h 30 min, after that, the mixture was diluted with Et_2O and the organic phase washed with H_2O and brine, dried over Na_2SO_4, filtered and the solvent evaporated. By column chromatography on silica gel compound **7** (11 mg, 45%) was separated.

4.5. Reaction of 5 with AcCl/$SnCl_4$ to yield 8

To a stirred solution of **5** (47 mg, 0.19 mmol) and acetyl chloride (0.05 mL, 0.76 mmol) in dichloromethane (2.0 mL) at 0 °C, a solution 1 M of $SnCl_4$ in heptane (0.3 mL, 0.3 mmol) was added under argon atmosphere. The reaction mixture was heated at 70 °C for 1 h. Then, the reaction was cooled to room temperature and ice was added. The reaction mixture was extracted with ether. The organic phase was washed with aqueous 6% $NaHCO_3$ and H_2O, dried over Na_2SO_4, filtered and the solvent evaporated to afford **8** (48 mg, 90%).

*4.5.1. 12-Acetyl-15,16-dinor-pymara-8,11,13-triene (**8**).* R_f 0.65; $[\alpha]_D^{20}$ +13.3 (*c* 2.8, $CHCl_3$); IR ν_{max} (film): 2925, 1707, 1679, 1458, 1375, 1262, 1212, 1162, 1039, 893 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 7.63 (1H, s, H-11), 6.91 (1H, s, H-14), 2.86–2.81 (2H, m, H-7), 2.56 (3H, s, *Me*CO–), 2.46 (3H, s, Me-17), 2.34–1.12 (9H, m), 1.19 (3H, s, Me-20), 0.96 (3H, s, Me-18), 0.94 (3H, s, Me-19); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 201.7 (Me*C*O–), 147.9 (C-9), 140.1 (C-8), 135.5 (C-12), 135.2 (C-13), 132.8 (C-14), 126.4 (C-11), 50.6 (C-5), 41.8 (C-3), 39.0 (C-1), 37.7 (C-10), 33.7 (C-4), 33.5 (C-18), 30.5 (C-7), 29.6 (*Me*CO–), 25.2 (C-20), 21.8 (C-19), 21.5 (C-17), 19.4 (C-2), 19.0 (C-6); EIHRMS: calcd for $C_{20}H_{28}ONa$ ($M+Na^+$): 307.2038, found: 307.2035.

4.6. Baeyer–Villiger oxidation of 8 to yield 9

To a solution of **8** (105 mg, 0.37 mmol) in dichloromethane (4.0 mL), UHP (122 mg, 1.3 mmol) was added at 0 °C, then TFAA (0.21 mL, 1.48 mmol) was added under argon atmosphere. The reaction was allowed at room temperature for 1 h 30 min. After the work-up with Na_2SO_3 the reaction was left at room temperature for 20 min. The organic phase was washed with aqueous 6% $NaHCO_3$, 6% K_2CO_3, 10% Na_2SO_3, H_2O and brine, dried over anhydrous Na_2SO_4, filtered and evaporated the solvent, **9** (100 mg, 91%) was obtained.

*4.6.1. 12-Acetoxy-15,16-dinor-pymara-8,11,13-triene (**9**).* R_f 0.56; $[\alpha]_D^{20}$ +44.2 (*c* 0.74, $CHCl_3$); IR ν_{max} (film): 2926, 1761, 1700, 1498, 1458, 1367, 1206, 1171, 1024, 915, 665 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 6.89 (1H, s, H-14), 6.85 (1H, s, H-11), 2.86–2.80 (2H, m, H-7), 2.30 (3H, s, *Me*COO–), 2.09 (3H, s, Me-17), 2.34–1.22 (9H, m), 1.17 (3H, s, Me-20), 0.94 (3H, s, Me-18), 0.91 (3H, s, Me-19); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 169.9 (Me*C*OO–), 149.4 (C-9), 147.5 (C-12), 133.3 (C-13), 131.6 (C-14), 126.8 (C-8), 117.7 (C-11), 50.3 (C-5), 41.8 (C-3), 39.0 (C-1), 37.8 (C-10), 33.6 (C-4), 33.5 (C-18), 29.9 (C-7), 25.1 (C-20), 21.8 (C-19), 21.1 (*Me*COO–), 19.4 (C-2), 19.2 (C-6), 15.9 (C-17); EIHRMS: calcd for $C_{20}H_{28}O_2$ ($M+Na^+$): 323.1987, found: 323.1986.

4.7. Reaction of 9 with K_2CO_3 to yield 10

To a solution of **9** (21 mg, 0.07 mmol) in MeOH (1 mL), K_2CO_3 (50 mg, 0.36 mmol) was added and stirred at room temperature for 30 min. Then, water was added and extracted with ether. The organic phase was washed with H_2O and brine. After dried over Na_2SO_4, filtered and evaporated the solvent **10** (18 mg, 98%) was obtained.

*4.7.1. 15,16-Dinor-pymara-8,11,13-trien-12-ol (**10**).* R_f 0.58; mp 241 °C; $[\alpha]_D^{20}$ +39.3 (*c* 1.4, $CHCl_3$); IR ν_{max} (film): 3397, 2925, 2865, 1717, 1684, 1507, 1458, 1375, 1265, 1193, 1135, 1013, 889, 665 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 6.80 (1H, s, H-14), 6.68 (1H, s, H-11), 4.62 (1H, br s, –OH), 2.82–2.77 (2H, m, H-7), 1.84–1.22 (9H, m), 2.18 (3H, s, Me-17), 1.17 (3H, s, Me-20), 0.94 (3H, s, Me-18), 0.92 (3H, s, Me-19); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 152.0 (C-9), 149.5 (C-12), 131.5 (C-14), 127.5 (C-13), 121.1 (C-8), 110.9 (C-11), 50.7 (C-5), 41.9 (C-3), 39.1 (C-1), 37.8 (C-10), 33.7 (C-4), 33.6 (C-18), 29.8 (C-7), 25.0 (C-20), 21.9 (C-19), 19.6 (C-2), 19.4 (C-6), 15.5 (C-17); EIHRMS: calcd for $C_{18}H_{26}O$ ($M+Na^+$): 281.1882, found: 281.1880.

4.8. Reaction of 8 with *N*,*N*-diisopropyl carbamoyl chloride to yield 11

In a 25 mL round-bottom flask equipped with magnetic stirring, NaH 60% in mineral oil (48 mg, 2.0 mmol) was washed with THF

(3×2 mL), then, a solution of compound **8** (50 mg, 0.19 mmol) in THF (0.7 mL) was added at 0 °C under argon atmosphere via cannula. The reaction was stirred for 15 min at 0 °C. Then, a solution of *N,N*-diispropil carbamoyl chloride (33 mg, 0.20 mmol) in THF (0.8 mL) was added and the mixture was left to stir for 2 h. After this time, the reaction was quenched with EtOAc saturated in water. The crude was extract with EtOAc, and washed with HCl 2 M, H_2O and brine. After that, the crude mixture was dried over Na_2SO_4, filtered and the solvent evaporated. After column chromatography on silica gel compound **9** (67 mg, 92%) was separated.

*4.8.1. 16,17-Dinor-pymara-8,11,13-trien-12-ol N,N-diisopropilcarbamate (**11**).* R_f 0.51 (*n*-Hex/EtOAc 9/1); $[\alpha]_D^{20}$ +38.0 (*c* 0.8, $CHCl_3$); IR ν_{max} (film): 2929, 1713, 1460, 1433, 1314, 1271, 1202, 1136, 1028, 796 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.87 (1H, s, H-14), 6.86 (1H, s, H-11), 4.16–3.96 (2H, m, −OCON(C*H*Me_2)$_2$), 2.85 (1H, dd, *J*=12.5 and 4.9 Hz, H_A-7), 2.78 (1H, dd, *J*=8.7 and 4.9 Hz, H_B-7), 2.21–2.09 (2H, m, H-6), 2.11 (3H, s, Me-15), 1.88–1.22 (7H, m), 1.32–1.29 (12H, m, −OCON(CH*Me*$_2$)$_2$), 1.18 (3H, s, Me-20), 0.94 (3H, s, Me-18), 0.92 (3H, s, Me-19); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.4 (−*O*CON(CH(Me)$_2$)$_2$), 148.9 (C-9), 147.9 (C-12), 132.0 (C-8), 131.1 (C-14), 127.2 (C-13), 117.8 (C-11), 50.2 (C-5), 46.6 (−OCON(*C*H(Me)$_2$)$_2$), 41.7 (C-3), 38.8 (C-1), 37.5 (C-10), 33.4 (C-4), 33.2 (C-18), 29.7 (C-7), 24.7 (C-20), 21.2 (C-19), 21.5 (−OCON(CH(*Me*)$_2$)$_2$), 19.2 (C-2), 19.0 (C-6), 16.0 (C-15); EIHRMS: calcd for $C_{25}H_{40}NO_2$ (M+H^+): 386.3070, found: 386.3069.

4.9. Reaction of 11 with sec-BuLi/MeI to yield 12

To a solution of compound **11** (10 mg, 0.03 mmol) in THF (0.3 mL) at −78 °C under argon atmosphere, a solution of sec-BuLi 1.4 M in THF (0.34 mL) was added dropwise and the reaction mixture was stirred for 10 min. Then, MeI (0.02 mL, 0.3 mmol) was added slowly and the mixture was left to stir for another 30 min. After this time, the reaction was allowed to reach room temperature and then, NH_4Cl was added dropwise carefully. The mixture was extracted with Et_2O and the combined extracts were washed with H_2O and brine, dried over Na_2SO_4 and the solvent evaporated. After column chromatography over silica gel compound **12** (10 mg, 94%) was separated.

*4.9.1. 17-Nor-pymara-8,11,13-trien-12-ol N,N-diisopropylcarbamate (**12**).* R_f 0.48 (*n*-Hex/EtOAc 9/1); $[\alpha]_D^{20}$ +41.1 (*c* 0.5, $CHCl_3$); IR ν_{max} (film): 2964, 2928, 2870, 1716, 1460, 1432, 1375, 1313, 1258, 1214, 1135, 1044, 804 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 6.88 (1H, s, H-14), 6.87 (1H, s, H-11), 4.11–3.99 (2H, m, −OCON(C*H*Me_2)$_2$), 2.89–2.82 (2H, m, H-7), 2.49 (2H, c, *J*=7.5 Hz, H-15), 2.21–1.22 (9H, m), 1.31–1.26 (12H, m, −OCON(CH*Me*$_2$)$_2$), 1.19 (3H, s, Me-20), 1.17 (3H, t, *J*=7.5 Hz, Me-16), 0.93 (3H, s, Me-18), 0.91 (3H, s, Me-19); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 154.2 (−*O*CON(CHMe$_2$)$_2$), 149.0 (C-9), 147.6 (C-12), 133.1 (C-13), 132.4 (C-8), 129.6 (C-14), 118.4 (C-11), 50.4 (C-5), 46.6/46.0 (−OCON(*C*HMe$_2$)$_2$), 41.9 (C-3), 39.0 (C-1), 37.8 (C-10), 33.7 (C-18), 33.5 (C-4), 30.0 (C-7), 25.0 (C-20), 23.1 (C-15), 21.8 (−OCON(CH*Me*$_2$)$_2$), 20.8 (C-19), 19.4 (C-6), 19.3 (C-2), 14.5 (C-16); EIHRMS: calcd for $C_{26}H_{41}NO_2Na$ (M+Na^+): 422.3028, found: 422.3026.

4.10. Reaction of 11 with sec-BuLi/CH_3CHO to yield 13

To a solution of compound **9** (20 mg, 0.06 mmol) in THF (0.2 mL) at −78 °C under argon atmosphere, a solution of sec-BuLi 1.4 M in THF (0.42 mL) was added dropwise carefully. Then, CH_3CHO (0.03 mL, 0.6 mmol) was added and the reaction was stirred for 30 min. After this time, the mixture was allowed to reach room temperature and NH_4Cl was added slowly to quench the reaction. The reaction mixture was extracted with Et_2O and the organic layer was washed with H_2O and brine. The crude was dried over Na_2SO_4, filtered and solvent evaporated to give a crude oil, which was chromatographed on silica to afford compound **13** (22 mg, 87%).

*4.10.1. 12-N,N-diisopropylcarbamoyloxy-17(15→16)-abeo-abieta-8,11,13-trien-16-ol (**13**).* R_f 0.15 (*n*-Hex/EtOAc 8/2); $[\alpha]_D^{20}$ +35.8 (*c* 0.9, $CHCl_3$); IR ν_{max} (film): 3420 (broad), 2928, 1696, 1436, 1375, 1318, 1257, 1135, 1049, 902, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.92 (2H, s, H-14), 6.86 (2H, s, H-11), 4.05–3.98 (6H, m, H-16 and -OCON(C*H*Me_2)$_2$), 2.87 (2H, dd, *J*=18.0 and 7.2 Hz, H_A-7), 2.83 (2H, ddd, *J*=18.0, 10.8 and 7.2 Hz, H_B-7), 2.68 and 2.65 (1H, dd each, *J*=14.0 and 3.2 Hz, H_A-15), 2.52 and 2.49 (1H, dd each, *J*=14.0 and 7.2 Hz, H_B-15), 2.21–2.18 (6H, m, H-1 and H-5), 1.48–1.46 (2H, m, H-3), 1.39–1.33 (24H, m, −OCON(CH*Me*$_2$)$_2$), 1.27–1.24 (4H, m, H-2), 1.26–1.23 (4H, m, H-6), 1.24 (3H, d each, *J*=6.8 Hz, Me-17), 1.18 (6H, s, Me-20), 1.14–1.12 (2H, m, H-3), 0.94 (6H, s, Me-18), 0.92 (6H, s, Me-19); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.5 (−*O*CON(CHMe$_2$)$_2$), 149.9 (C-9), 147.8 (C-12), 132.5 (C-8), 131.3 (C-14), 127.9 (C-13), 118.5 (C-11), 67.9 (C-16), 50.1 (C-5), 46.7/46.2 (−OCON(*C*HMe$_2$)$_2$), 41.6 (C-3), 39.8 (C-15), 38.7 (C-1), 37.6 (C-10), 33.4 (C-4), 33.2 (C-18), 29.6 (C-7), 24.7 (C-20), 23.4 (C-17), 21.6 (−OCON(CH*Me*$_2$)$_2$), 20.5 (C-19), 19.1 (C-2), 18.9 (C-6); EIHRMS: calcd for $C_{27}H_{43}NO_3Na$ (M+Na^+): 452.3131, found: 452.3129.

4.11. Reaction of 11 with sec-BuLi/CH_2O to yield 14

To a solution of compound **9** (20 mg, 0.05 mmol) in THF (0.2 mL) at −78 °C under argon atmosphere, a solution of sec-BuLi 1.4 M in THF (0.62 mL) was added and the reaction stirred for 10 min. Then, CH_2O (10 μL, 37 wt % aqueous solution) was added and the reaction was left with stirring for another 30 min. After this time, the reaction was allowed to warm to room temperature and then NH_4Cl was added. The mixture was extracted with Et_2O and washed with H_2O and brine, dried over Na_2SO_4 and the solvent evaporated. By column chromatography on silica gel compound **14** (15 mg, 68%) was separated.

*4.11.1. 12-N,N-Diisopropylcarbamoyloxy-17-nor-pymara-8,11,13-trien-16-ol (**14**).* R_f 0.35 (*n*-Hex/EtOAc 7/3); $[\alpha]_D^{20}$ +28.7 (*c* 0.5, $CHCl_3$); IR ν_{max} (film): 3411 (broad), 2927, 1712, 1438, 1375, 1316, 1253, 1134, 1044, 900 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.93 (1H, s, H-14), 6.86 (1H, s, H-11), 4.07–4.01 (2H, m, −OCON(C*H*Me_2)$_2$), 3.82 (2H, t, *J*=6.0 Hz, H-16), 2.88 (1H, dd, *J*=7.8 and 4.6 Hz, H_A-7), 2.81 (1H, dd, *J*=7.8 and 4.6 Hz, H_B-7), 2.73 (2H, t, *J*=6.0 Hz, H-15), 2.22–2.20 (2H, m, H-1 and H-5), 1.49–1.48 (1H, m, H-1), 1.48–1.46 (1H, m, H-3), 1.42–1.38 (12H, m, −OCON(CH*Me*$_2$)$_2$), 1.33–1.30 (4H, m, H-2 and H-6), 1.23–1.22 (1H, m, H-3), 1.18 (3H, s, Me-20), 0.94 (3H, s, Me-19), 0.92 (3H, s, Me-18); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.7 (−*O*CON(CHMe$_2$)$_2$), 149.9 (C-9), 147.9 (C-12), 132.6 (C-8), 130.9 (C-14), 128.0 (C-13), 118.4 (C-11), 62.7 (C-16), 50.0 (C-5), 46.8/46.1 (−OCON(*C*HMe$_2$)$_2$), 41.6 (C-3), 38.9 (C-1), 37.6 (C-10), 33.7 (C-4), 33.4 (C-18), 33.2 (C-15), 29.6 (C-7), 24.7 (C-20), 21.8 (−OCON(CH*Me*$_2$)$_2$), 20.5 (C-19), 19.1 (C-2), 18.9 (C-6); EIHRMS: calcd for $C_{26}H_{41}NO_3Na$ (M+Na^+): 438.2964, found: 438.2958.

4.12. Reaction of 12 with $EtCO_2Cl$ /sec-BuLi to yield 15

To a solution of **12** (38 mg, 0.1 mmol) in THF (0.6 mL) at −78 °C under argon atmosphere, a solution of sec-BuLi 1.4 M in THF (0.6 mL) was added dropwise. The mixture was stirred for 10 min. After this time, ethyl chloroformate (57 μL, 0.6 mmol) was added, and the mixture was left to stir for 30 min. Then, EtOAc saturated in water was added slowly to quench the reaction. The mixture was extracted with EtOAc and washed with H_2O and brine. After dried over Na_2SO_4 and filtered, the solvent was evaporated, to give

a crude oil, which was chromatographed on silica gel to afford compound **15** (35 mg, 74%).

*4.12.1. Ethyl 12-N,N-diisopropylcarbamoyloxy-abieta-8,11,13-trien-16-oate (**15**).* R_f 0.74 (*n*-Hex/EtOAc 8/2); $[\alpha]_D^{20}$ +5.9 (*c* 1.0, $CHCl_3$); IR ν_{max} (film): 2964, 2874, 1744, 1712, 1462, 1370, 1257, 1155 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 6.87 (2H, s, H-14), 6.77 (2H, s, H-11), 4.35–4.08 (4H, m, $-OCON(CHMe_2)_2$), 4.18 (4H, c, *J*=7.3 Hz, $-CO_2CH_2CH_3$), 2.88–2.78 (4H, m, H-7), 2.68 and 2.49 (1H, c each, *J*=7.2 Hz, H-15), 2.21–1.24 (18H, m), 1.33–1.29 (24H, m, $-OCON(CHMe_2)_2$), 1.28 (6H d, *J*=7.2 Hz, Me-17), 1.05 and 1.02 (3H, s each, Me-20), 0.93 (6H, s, Me-18), 0.91 (6H, s, Me-19), 0.86 and 0.85 (3H, t each, *J*=7.3 Hz, $-CO_2CH_2CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 175.3 (C-16), 153.7 ($-OCON(CHMe_2)_2$), 147.1 (C-12), 140.0 (C-9), 132.6 (C-13), 132.5 (C-8), 129.9 (C-14), 118.6 (C-11), 61.3 ($-CO_2CH_2CH_3$), 43.9 (C-5), 41.9 (C-3), 41.4/41.0 ($-OCON(CHMe_2)_2$), 40.5 (C-15), 39.0 (C-10), 38.9 (C-1), 33.6 (C-4), 33.5 (C-18), 27.7 (C-7), 21.8 (C-20), 19.4 (C-6), 18.3 (C-2), 17.7 (C-19), 14.6/14.5 ($-OCON(CHMe_2)_2$), 14.3 ($-CO_2CH_2CH_3$), 11.9 (C-17); EIHRMS: calcd for $C_{29}H_{45}NO_4Na$ ($M+Na^+$): 494.3245, found: 494.3247.

4.13. Oxidation of 13 with TPAP/NMO to yield 16

To a solution of compound **13** (10 mg, 0.02 mmol) in DCM (0.4 mL), NMO (8.0 mg, 0.06 mmol) and TPAP (1 mg) were added at room temperature, and the mixture was stirred for 10 min. After this time, the crude was filtered through a column packed with Celite® and washed with EtOAc and Et_2O. Then, the solvent was evaporated to afford compound **16** (9 mg, 99%).

*4.13.1. 12-N,N-Diisopropylcarbamoyloxy-17(15→16)-abeo-abieta-8,11,13-trien-16-one (**16**).* R_f 0.42 (*n*-Hex/EtOAc 8/2); $[\alpha]_D^{20}$ +38.0 (*c* 0.7, $CHCl_3$); IR ν_{max} (film): 2927, 1716, 1432, 1315, 1253, 1135, 1043, 900, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.91 (1H, s, H-14), 6.87 (1H, s, H-11), 4.02–3.98 (2H, m, $-OCON(CHMe_2)_2$), 3.52 (2H, s, H-15), 2.88–2.81 (2H, m, H-7), 2.24–1.21 (9H, m), 2.10 (3H, s, Me-17), 1.30 (6H, d, *J*=2.4 Hz, $-OCON(CHMe_2)_2$), 1.26 (6H, d, *J*=2.4 Hz, $-OCON(CHMe_2)_2$), 1.23 (3H, s, Me-20), 0.94 (3H, s, Me-18), 0.92 (3H, s, Me-19); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.4 (C-16), 153.3 ($-OCON(CHMe_2)_2$), 150.5 (C-9), 147.7 (C-12), 132.6 (C-13), 131.3 (C-14), 124.2 (C-8), 118.5 (C-11), 50.0 (C-5), 46.6/46.3 ($-OCON(CHMe_2)_2$), 45.6 (C-15), 41.6 (C-3), 38.6 (C-1), 37.7 (C-10), 33.4 (C-4), 33.0 (C-18), 30.0 (C-17), 29.6 (C-7), 24.7 (C-20), 21.6 ($-OCON(CHMe_2)_2$), 20.4 (C-19), 19.1 (C-2), 18.9 (C-6); EIHRMS: calcd for $C_{27}H_{41}NO_3Na$ ($M+Na^+$): 450.2984, found: 450.2986.

4.14. Baeyer–Villiger's reaction of 16 with *m*-CPBA to yield 17

To a solution of compound **16** (20 mg, 0.05 mmol) in DCM (1 mL), *m*-CPBA (26 mg, 0.15 mmol) was added at 0 °C. The reaction was stirred at room temperature for 16 h. After this time, Na_2SO_3 was added carefully at 0 °C and the mixture was left with stirring for another 20 min. Then the reaction mixture was extracted with Et_2O and washed successively with aqueous 10% Na_2SO_3, 6% $NaHCO_3$, H_2O and brine, dried (Na_2SO_4), filtered and the solvent evaporated to yield compound **17** (15 mg, 74%).

*4.14.1. 15-Acetoxy-16,17-dinor-pymara-8,11,13-trien-12-ol N,N-diisopropylcarbamate (**17**).* R_f 0.43 (*n*-Hex/EtOAc 8/2); $[\alpha]_D^{20}$ +35.0 (*c* 2.1, $CHCl_3$); IR ν_{max} (film): 2965, 1742, 1716, 1432, 1376, 1314, 1226, 1043, 900, 732 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 7.05 (1H, s, H-14), 6.96 (1H, s, H-11), 4.98 (2H, s, H-15), 4.14–3.88 (2H, m, $-OCON(CHMe_2)_2$), 2.91–2.82 (2H, m, H-7), 2.21–1.18 (9H, m), 2.05 (3H, s, $-OCOMe$), 1.34–1.26 (12H, m, $-OCON(CHMe_2)_2$), 1.18 (3H, s, Me-20), 0.94 (3H, s, Me-18), 0.92 (3H, s, Me-19); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 171.1 ($-OCOMe$), 153.9 ($-OCON(CHMe_2)_2$), 152.1 (C-12), 148.0 (C-9), 132.8 (C-13), 131.1 (C-14), 125.2 (C-8), 119.0 (C-11), 62.3 (C-15), 50.2 (C-5), 47.3/46.5 ($-OCON(CHMe_2)_2$), 41.8 (C-3), 38.9 (C-1), 38.1 (C-10), 33.7 (C-18), 33.5 (C-4), 29.9 (C-7), 24.9 (C-20), 21.8 ($-OCOMe$), 21.3 ($-OCON(CHMe_2)_2$), 20.7 (C-19), 19.4 (C-6), 19.1 (C-2); EIHRMS: calcd for $C_{27}H_{41}NO_4Na$ ($M+Na^+$): 466.2904, found: 466.2905.

4.15. Hydrolysis of 17 with K_2CO_3/MeOH to yield 18

To a solution of **17** (70 mg, 0.12 mmol) in MeOH (0.8 mL), K_2CO_3 (88 mg, 0.64 mmol) was added at room temperature and the reaction was left to stir for 45 min. After this time, the mixture was diluted in Et_2O and washed with H_2O and brine. The organic phase was dried over Na_2SO_4, filtered and the solvent evaporated to afford **18** (48 mg, 97%).

*4.15.1. 12-N,N-Diisopropylcarbamoyloxy-16,17-dinor-pymara-8,11,13-trien-15-ol (**18**).* R_f 0.31 (*n*-Hex/EtOAc 8/2); $[\alpha]_D^{20}$ +35.9 (*c* 1.9, $CHCl_3$); IR ν_{max} (film): 3447 (broad), 2929, 1695, 1435, 1370, 1314, 1150, 1136, 1044, 903, 733 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 7.13 (1H, s, H-14), 6.89 (1H, s, H-11), 4.42 (2H, s, H-15), 4.18–3.98 (2H, m, $-OCON(CHMe_2)_2$), 3.15 (1H, s, –OH), 2.96–2.86 (2H, m, H-7), 2.22–1.18 (9H, m), 1.36 (6H, d, *J*=3.8 Hz, $-OCON(CHMe_2)_2$), 1.27 (6H, d, *J*=3.8 Hz, $-OCON(CHMe_2)_2$), 1.18 (3H, s, Me-20), 0.94 (3H, s, Me-18), 0.92 (3H, s, Me-19); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 155.5 ($-OCON(CHMe_2)_2$), 151.8 (C-12), 147.4 (C-9), 133.5 (C-13), 131.5 (C-14), 130.4 (C-8), 118.0 (C-11), 60.7 (C-15), 50.2 (C-5), 47.3/46.5 ($-OCON(CHMe_2)_2$), 41.8 (C-3), 39.0 (C-1), 38.0 (C-10), 33.7 (C-18), 33.5 (C-4), 29.9 (C-7), 25.0 (C-20), 21.7 ($-OCON(CHMe_2)_2$), 20.7 (C-19), 19.4 (C-6), 19.1 (C-2); EIHRMS: calcd for $C_{25}H_{39}NO_3Na$ ($M+Na^+$): 424.2828, found: 424.2826.

4.16. Reaction of 12 with sec-BuLi/MeI to yield 19

To a solution of compound **12** (24 mg, 0.06 mmol) in THF (0.2 mL), a solution of sec-BuLi 1.4 M in THF (0.43 mL) was added dropwise at −78 °C, and after that, the mixture was left to stir for 10 min. Subsequent, MeI (0.04 mL, 0.60 mmol) was added and left stirring for 30 additional minutes. After this time, the reaction was allowed to reach room temperature and NH_4Cl was added slowly. The mixture was then extracted with Et_2O and washed with H_2O and brine. The crude mixture was dried over Na_2SO_4, filtered and the solvent was evaporated. By column chromatography on silica gel compound **19** (20 mg, 82%) was separated.

*4.16.1. Abieta-8,11,13-trien-12-ol N,N-diisopropylcarbamate (**19**).* R_f 0.40 (*n*-Hex); $[\alpha]_D^{20}$ +33.8 (*c* 2.23, $CHCl_3$); IR ν_{max} (film): 2964, 2870, 1716, 1460, 1431, 1375, 1312, 1248, 1153, 1044, 899, 758 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 6.92 (1H, s, H-14), 6.84 (1H, s, H-11), 4.18–4.01 (2H, m, $-OCON(CHMe_2)_2$), 2.99 (1H, sep, *J*=6.5 Hz, H-15), 2.98–2.81 (2H, m, H-7), 2.24–1.22 (9H, m), 1.35–1.26 (12H, m, $-OCON(CHMe_2)_2$), 1.21 (3H, d, *J*=6.5 Hz, Me-16), 1.17 (3H, d, *J*=6.5 Hz, Me-17), 1.19 (3H, s, Me-20), 0.94 (3H, s, Me-19), 0.92 (3H, s, Me-18); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 154.2 ($-OCON(CHMe_2)_2$), 148.7 (C-9), 146.9 (C-12), 137.4 (C-13), 132.3 (C-8), 126.7 (C-14), 118.5 (C-11), 50.3 (C-5), 46.6/46.4 ($-OCON(CHMe_2)_2$), 41.9 (C-3), 39.0 (C-1), 37.8 (C-10), 33.7 (C-4), 33.5 (C-18), 30.2 (C-7), 27.2 (C-15), 23.4 (C-20), 23.1 (C-19), 21.8 ($-OCON(CHMe_2)_2$), 20.8 (C-16), 20.1 (C-17), 19.4 (C-2), 19.3 (C-6); EIHRMS: calcd for $C_{27}H_{43}NO_2Na$ ($M+Na^+$): 436.3178, found: 436.3174.

4.17. Reduction of 19 with $LiAlH_4$ to yield 1

To a solution of compound **19** (22 mg, 0.05 mmol) in Et_2O (0.4 mL), LAH (19 mg, 0.5 mmol) was added at 0 °C. Subsequent, the mixture was heated to boil during 16 h. After this time, the reaction

was allowed to reach room temperature and then, EtOAc saturated in water was added dropwise carefully. The mixture was extracted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, filtered and the solvent was evaporated to afford compound **1** (14 mg, 93%).

*4.17.1. Abieta-8,11,13-trien-12-ol (**1**).* R_f 0.34 (*n*-Hex); $[\alpha]_D^{20}$ +42.9 (*c* 0.2, $CHCl_3$); IR ν_{max} (film): 3388 (broad), 2925, 2866, 1508, 1460, 1417, 1375, 1002, 892, 733 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 6.83 (1H, s, H-14), 6.63 (1H, s, H-11), 4.48 (1H, s, −OH), 3.16 (1H, sep, *J*=6.5 Hz, H-15), 2.84–2.79 (2H, m, H-7), 2.21–1.22 (9H, m), 1.24 (3H, d, *J*=6.5 Hz, Me-16), 1.21 (3H, d, *J*=6.5 Hz, Me-17), 1.17 (3H, s, Me-20), 0.93 (3H, s, Me-19), 0.91 (3H, s, Me-18); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 150.4 (C-12), 148.4 (C-9), 131.1 (C-13), 127.0 (C-8), 126.3 (C-14), 110.7 (C-11), 50.1 (C-5), 41.4 (C-3), 38.6 (C-1), 37.2 (C-10), 33.1 (C-4), 33.0 (C-18), 29.5 (C-7), 26.5 (C-15), 24.5 (C-20), 22.5 (C-19), 22.3 (C-16), 21.3 (C-17), 19.0 (C-2), 18.9 (C-6); EIHRMS: calcd for $C_{20}H_{30}ONa$ (M+Na^+): 309.2195, found: 309.2190.

4.18. Reaction of 1 with Ac_2O/Py to yield 20

To a solution of compound **1** (15 mg, 0.05 mmol) in Ac_2O (0.2 mL), pyridine (0.2 mL) was added at room temperature and the mixture was left to stir for 6 h. After this time, ice was added and extracted with EtOAc and washed with $NaHCO_3$ 6%, H_2O and brine, dried over Na_2SO_4, filtered and the solvent was evaporated to afford compound **20** (17 mg, 98%).

*4.18.1. Abieta-8,11,13-trien-12-ol acetate (**20**).* R_f 0.67 (*n*-Hex/EtOAc 9/1); $[\alpha]_D^{20}$ +31.0 (*c* 1.2, $CHCl_3$); IR ν_{max} (film): 2926, 2868, 1760, 1460, 1368, 1206, 1016, 914 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 6.94 (1H, s, H-14), 6.82 (1H, s, H-11), 2.93–2.82 (3H, m, H-7 and H-15), 2.30 (3H, s, −OCO*Me*), 2.50–1.24 (9H, m), 1.20 (3H, d, *J*=6.2 Hz, Me-16), 1.16 (3H, d, *J*=6.2 Hz, Me-17), 1.17 (3H, s, Me-20), 0.94 (3H, s, Me-19), 0.92 (3H, s, Me-18); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 170.2 (−*O*COMe), 149.0 (C-9), 146.3 (C-12), 136.8 (C-13), 133.4 (C-8), 127.1 (C-14), 118.2 (C-11), 50.2 (C-5), 41.9 (C-3), 39.0 (C-1), 37.8 (C-10), 33.6 (C-4), 33.5 (C-18), 30.2 (C-7), 27.4 (C-15), 25.0 (C-20), 23.3 (C-19), 23.2 (−OCO*Me*), 21.8 (C-16), 21.2 (C-17), 19.4 (C-2), 19.2 (C-6); EIHRMS: calcd for $C_{22}H_{32}O_2Na$ (M+Na^+): 351.2302, found: 351.2308.

4.19. Oxidation of 20 with Na_2CrO_4 to yield 21

To a solution of compound **20** (12 mg, 0.04 mmol) in benzene (2 mL), AcOH (0.3 mL), Ac_2O (0.3 mL), NaOAc (10 mg, 0.12 mmol) and Na_2CrO_4 (19 mg, 0.12 mmol) were added at room temperature. The mixture was heated to boil during 45 min. After this time, the reaction was allowed to reach room temperature and then, MeOH (0.5 mL) was added, and the mixture was stirred for 15 additional minutes. The reaction was extracted with Et_2O and washed with $NaHCO_3$ 6%, K_2CO_3 6%, H_2O and brine. Then, the mixture was dried over Na_2SO_4, filtered and the solvent was evaporated. After column chromatography on silica gel compound **21** (10 mg, 77%) was separated.

*4.19.1. 12-Acetoxy-abieta-8,11,13-trien-7-one (**21**).* R_f 0.55 (*n*-Hex/EtOAc 9/1); $[\alpha]_D^{20}$ +22.4 (*c* 0.3, $CHCl_3$); IR ν_{max} (film): 2962, 2930, 1766, 1683, 1610, 1368, 1199, 1166, 1014, 910 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 7.99 (1H, s, H-14), 6.98 (1H, s, H-11), 2.98 (1H, sep, *J*=6.5 Hz, H-15), 2.73 (1H, dd, *J*=18.4 and 4.4 Hz, H_A-6), 2.63 (dd, 1H, *J*=18.4 and 12.0 Hz, H_B-6), 2.35 (3H, s, −OCO*Me*), 1.90 (1H, dd, *J*=12.0 and 4.4 Hz, H-5), 1.89–1.4 (6H, m), 1.24 (3H, d, *J*=6.5 Hz, Me-16), 1.21 (3H, d, *J*=6.5 Hz, Me-17), 1.18 (3H, s, Me-20), 0.99 (3H, s, Me-19), 0.93 (3H, s, Me-18); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 199.0 (C-7), 170.0 (−*O*COMe), 155.4 (C-9), 152.9 (C-12), 138.6 (C-13), 129.3 (C-8), 126.7 (C-14), 118.1 (C-11), 49.4 (C-5), 41.5 (C-3), 38.2 (C-1), 38.1 (C-10), 36.4 (C-6), 33.5 (C-4), 32.7 (C-18), 27.5 (C-15), 23.1 (C-20), 23.0 (C-19), 22.9 (−OCO*Me*), 21.5 (C-16), 21.2 (C-17), 19.0 (C-2); EIHRMS: calcd for $C_{22}H_{30}O_3Na$ (M+Na^+): 365.2091, found: 365.2088.

4.20. Hydrolysis of 21 with K_2CO_3/MeOH to yield 2

To a solution of compound **21** (10 mg, 0.03 mmol) in MeOH (3 mL), K_2CO_3 (41 mg, 0.3 mmol) was added and the mixture left to stir at room temperature for 45 min. After this time, the mixture was diluted in Et_2O, washed with H_2O and brine, dried over Na_2SO_4, filtered and the solvent was evaporated affording compound **2** (9 mg, 96%).

*4.20.1. 12-Hidroxy-abieta-8,11,13-trien-7-one (**2**).* R_f 0.22 (*n*-Hex/EtOAc 9/1); mp 282–284 °C; $[\alpha]_D^{20}$ +15.3 (*c* 0.3, $CHCl_3$); IR ν_{max} (film): 3247 (broad), 2926, 2854, 1725, 1598, 1461, 1265, 1124, 864 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.91 (1H, s, H-14), 6.69 (1H, s, H-11), 5.54 (1H, s, −OH), 3.18 (1H, sep, *J*=6.2 Hz, H-15), 2.66 (1H, dd, *J*=18.4 and 4.4 Hz, H_A-6), 2.60 (1H, dd, *J*=18.4 and 14.0 Hz, H_B-6), 1.83 (1H, dd, *J*=14.0 and 4.4 Hz, H-5), 1.84–1.22 (6H, m), 1.27 (3H, d, *J*=6.2 Hz, Me-16), 1.24 (3H, d, *J*=6.2 Hz, Me-17), 1.22 (3H, s, Me-20), 0.98 (3H, s, Me-19), 0.92 (3H, s, Me-18); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.6 (C-7), 158.1 (C-12), 156.4 (C-9), 132.5 (C-13), 126.5 (C-14), 124.6 (C-8), 109.9 (C-11), 49.4 (C-5), 41.3 (C-3), 37.8 (C-1), 36.0 (C-10), 35.0 (C-6), 33.6 (C-4), 33.2 (C-18), 26.7 (C-15), 23.2 (C-20), 22.7 (C-19), 22.4 (C-16), 21.3 (C-17), 18.8 (C-2); EIHRMS: calcd for $C_{20}H_{28}O_2Na$ (M+Na^+): 323.1987, found: 323.1988.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.07.066.

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