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ScienceDirect
Tetrahedron 63 (2007) 11204–11212
Tetrahedron

Regioselective routes towards 14-hydroxyabietane diterpenes. A formal synthesis of immunosuppressant (−)-triptolide from (+)-abietic acid

Enrique Alvarez-Manzaneda,* Rachid Chahboun, Faouzia Bentaleb, Esteban Alvarez, M. Angeles Escobar, Said Sad-Diki, Maria José Cano and Ibtissam Messouri

Departamento de Química Orgánica, Facultad de Ciencias, Instituto de Biotecnología, Universidad de Granada, 18071 Granada, Spain

Received 24 May 2007; revised 12 July 2007; accepted 23 July 2007
Available online 31 July 2007

Abstract—Two procedures to introduce an oxygenated function into the C-14 of abietane diterpenes with complete regioselectivity have been developed. Utilizing these, the synthesis of the antileishmanial quinone (−)-12-deoxyroyleanone (**1**) and a formal synthesis of antitumour and immunosuppressant (−)-triptonide (**7**) and (−)-triptolide (**8**) from (+)-abietic acid (**13**) have been carried out.

1. Introduction

Natural abietane phenols and quinones, as well as other variously oxidized related compounds, constitute an interesting group of diterpene metabolites, due to the significant biological activities exhibited by some of them such as (−)-12-deoxyroyleanone (**1**), an antileishmanial agent,[1] and cryptoquinone (**2**) with antifungal and cytotoxic activities against mouse lymphoid neoplasm (P388) cells.[2] Other significant compounds are the antifungal (−)-deoxybuddlejone (**3**),[3] and a group of A ring modified terpenoids such as (+)-triptoquinone A (**4**), which is under study with respect to the treatment of rheumatoid arthritis,[4] the leukotriene D_4 antagonists (+)-triptinine A (**5**) and B (**6**),[5] and the lactones (−)-triptonide (**7**) and (−)-triptolide (**8**), which exhibit a variety of features, including antitumour,[6] anti-inflammatory,[7] immunosuppressive[7b,8] and antifertile activities (Fig. 1).[7b,9]

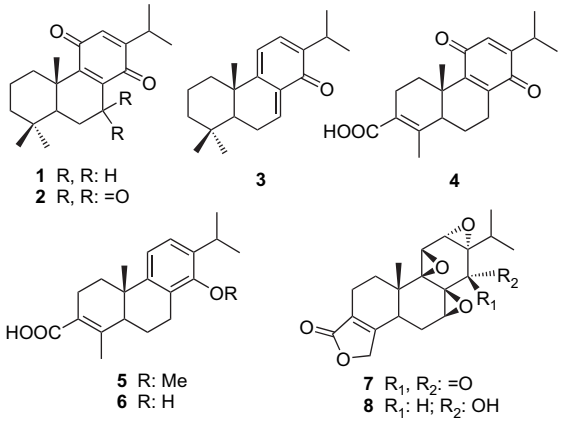


Figure 1. 12-Deoxyroyleanone (**1**) and other bioactive oxidized abietane terpenoids.

Despite the interest in these metabolites, few syntheses have been reported, and most of these have been total syntheses involving Diels–Alder cycloaddition,[10] Robinson annulation,[4] radical cyclizations[11] and electrophilic cyclizations.[12] A synthesis of lactones **7** and **8** from dehydroabietic acid has been reported by van Tamelen,[13] utilizing 14-hydroxydehydroabietic acid, prepared by electrophilic substitution,[14] as a key intermediate.

Our group recently communicated the first synthesis of quinone **1** from abietic acid, utilizing a novel methodology for introducing an oxygenated function into C-14.[15,16] Subsequently, Matsushita et al. described the synthesis of quinones **1** and **2** from dehydroabietic acid, utilizing an electrophilic substitution strategy.[17] Very recently, Yajima et al. reported an asymmetric synthesis of quinones **1** and **2**, utilizing a *B*-alkyl Suzuki–Miyaura coupling and subsequent electrophilic cyclization.[18] These authors pay special attention to the ^{13}C NMR chemical shift of aromatic carbons, which they assign incorrectly, of the phenol precursor of quinone **1**. Yajima et al. criticize our previous results on the basis of a small discrepancy with our spectroscopic data for this intermediate and their inability to reproduce our described oxidation of this phenol to quinone **1**, utilizing Fremy's salt.

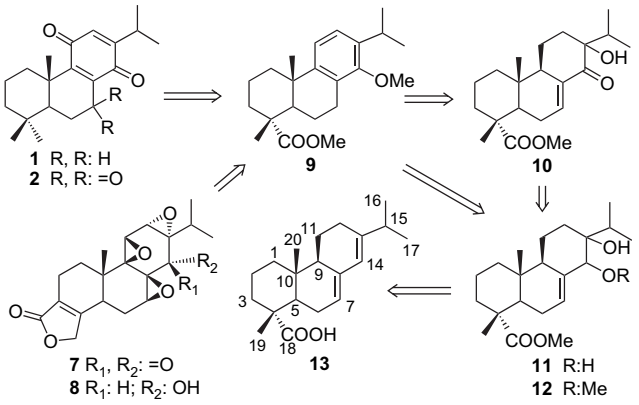
* Corresponding author. Tel./fax: +34 958 24 80 89; e-mail: eamr@ugr.es

0040–4020/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tet.2007.07.088

In this paper we report our studies on the synthesis towards 14-hydroxyabietic acid derivatives, including a very efficient alternative route to that we had previously communicated, which reaffirms our first synthesis of (−)-12-deoxyroyleanone (**1**), and a formal synthesis of (−)-triptonide (**7**) and (−)-triptolide (**8**). Moreover, we aim to end the controversy provoked by Yajima's article and correct the erroneous ^{13}C NMR assignments made in the latter.

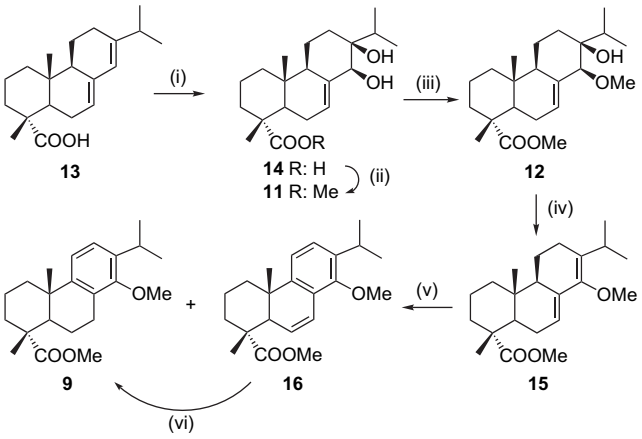
2. Results and discussion

During our research in the synthesis of bioactive compounds starting from natural diterpenes, we focused on the synthesis of this type of oxygenated terpenoids from the very accessible abietic acid (**13**). The key intermediate should be 14-hydroxydehydroabietic acid or related compounds such as **9**. The procedure based on the electrophilic substitution in dehydroabietic acid derivatives, involving nitration of the aromatic ring and the further transformation of the nitro into the hydroxyl group, could raise some problems of regio- and/or chemoselectivity. Thus, we planned an alternative method to prepare methoxy ester **9** directly from acid **13**, as depicted in the retrosynthetic Scheme 1. Compound **9** is obtained after aromatization of dienol ether resulting from the dehydration of β-methoxy alcohol **12**. Alternatively, ester **9** could be prepared from the phenol synthesized by dehydration and subsequent aromatization of hydroxy ketone **10**, resulting from the oxidation of 13,14-diol **11**, which can be synthesized by regioselective dihydroxylation of abietic acid (**13**).[19]



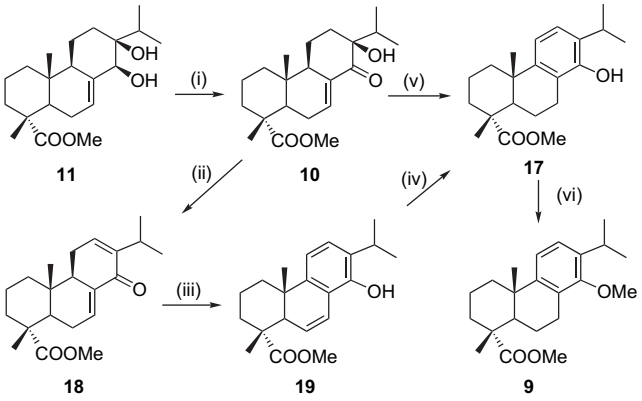
Scheme 1. Retrosynthetic analysis of 12-deoxyroyleanone (**1**) and other related terpenoids from abietic acid (**13**).

Scheme 2 shows the synthesis of ester **9** from acid **13** via the β-methoxy alcohol **12**. Abietic acid (**13**) was efficiently converted into diol **14**, utilizing a modification of the method reported in the literature.[19] Compound **12**, which is obtained after methylation of dihydroxy ester **11**, underwent regioselective dehydration by treating with $SOCl_2$ and Et_3N to give the dienol ether **15**. This compound was then transformed into the corresponding dehydroabietic acid derivative by treating with Br_2 in CCl_4 under reflux. It should be noted that the desired compound **9** resulted when 1 equiv of Br_2 was utilized; however, the use of Br_2 in excess afforded a mixture of ester **9** and the Δ^6 derivative **16**, which can easily be converted into **9** after hydrogenation or by treating with Et_3SiH and CF_3COOH.



Scheme 2. Synthesis of ester **9** from acid **13** via methoxyalcohol **12**. Reagents, conditions and yields: (i) OsO_4, Me_3NO, pyridine, *t*-BuOH, reflux, seven days; (ii) MeI, K_2CO_3, acetone, reflux, 24 h; (iii) NaH, THF, MeI, rt, 2 h (96%); (iv) $SOCl_2$, Et_3N, CH_2Cl_2, −78 °C, 20 min (74%); (v) Br_2, CCl_4, $CaCO_3$, reflux, 12 h (70%); (vi) H_2, Pd–C, MeOH, 24 h (94%) or Et_3SiH, CF_3COOH, CH_2Cl_2, −40 °C, 16 h (93%).

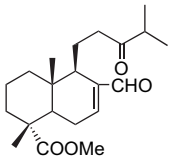
The alternative sequence from acid **13** to key intermediate **9**, via hydroxy ketone **10**, is depicted in Scheme 3. After esterification of carboxylic acid **14**, oxidation of the secondary hydroxyl group was undertaken. The transformation of diol **11** into ketone **10** was assayed under different oxidizing conditions, as shown in Table 1.



Scheme 3. Synthesis of ester **9** via hydroxy ketone **10**. Reagents, conditions and yields: (i) PhSeSePh, *t*-BuOOH, CCl_4, reflux, 2 h (92%); (ii) TsOH, benzene, reflux, 36 h (78%); (iii) K_2CO_3, MeOH, reflux, three days (70%); (iv) H_2, Pd–C; MeOH, 24 h (96%); (v) TsOH, toluene, reflux, 10 h (91%); (vi) MeI, K_2CO_3, acetone, reflux, 15 h (91%).

Diol **11** remained unaltered after treatment with MnO_2 at room temperature; however, keto aldehyde **20** was obtained in good yield when the mixture was refluxed for 16 h. Small quantities of this compound, together with aromatic esters **21** and **22** resulted when Jones reagent was utilized. Diol **11** was recovered unaltered after treatment with IBX in DMSO at room temperature; nevertheless, keto aldehyde **20**[20] resulted when the reaction was carried out in THF under reflux.[21] Treatment with PCC in CH_2Cl_2 gave the desired hydroxy ketone **10**, together with the keto aldehyde **20**. Utilization of Swern reagent gave compounds **10** and **18** in low yields. Oxidation with DDQ and TsOH in benzene gave similar results. Treatment with PDC and *t*-BuOOH in benzene gave only hydroxy ketone **10**, but in low yield. A successful

Table 1. Reaction of diol **11** under different oxidizing conditions



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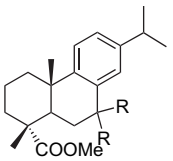


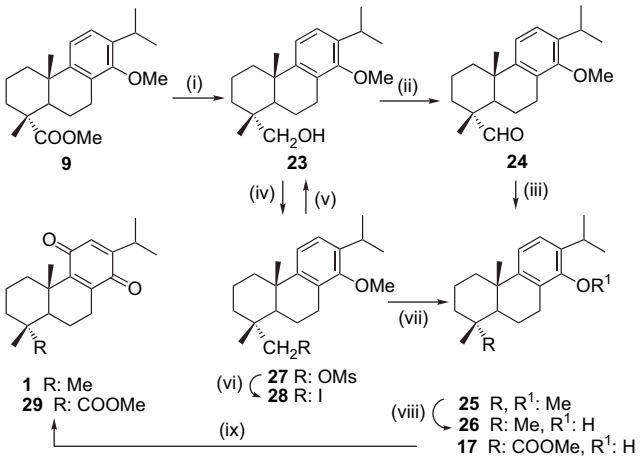
21 R, R: H
22 R, R: =O

Entry	Conditions	Product(s) (%)
1	MnO_2, benzene, rt, 24 h	No reaction
	MnO_2, benzene, reflux, 16 h	**20** (75)
2	Jones reagent, acetone, rt, 20 h	**20** (5), **21** (20), **22** (11)
3	IBX, DMSO, rt, 16 h	No reaction
4	IBX, THF, reflux, 48 h	**20** (72)
5	PCC, CH_2Cl_2, 4 Å molecular sieves, 0 °C, 30 min	**20** (37), **10** (30)
6	$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, rt, 24 h	**10** (15), **18** (5)
7	DDQ, TsOH, benzene, rt, 48 h	**10** (18), **18** (12)
8	PDC, *t*-BuOOH, benzene, rt, 3 h	**10** (36)
9	PhSeSePh, *t*-BuOOH, CCl_4, reflux, 2 h	**10** (92)

oxidation of diol **11** was attained after reaction with PhSeSePh and *t*-BuOOH in CCl_4 under reflux:[22] the desired compound **10** was obtained in 92% yield (entry 9). This ketone was converted into enone **18** by refluxing with TsOH in benzene; this compound could be a suitable intermediate for synthesizing compounds such as deoxybuddlejone (**3**). Treatment of enone **18** with K_2CO_3 in MeOH under reflux led to phenol **19**,[23] which was then hydrogenated to give phenol **17**. This compound was directly obtained in high yield when the enone **10** was refluxed with TsOH in toluene. Finally, this phenol was transformed into the desired methoxy ester **9**. Compound **17**, which has also been synthesized by Matsushita et al.,[17] had the same spectroscopic properties as those reported by these authors.

Ester **9**, which as indicated is a suitable precursor of bioactive metabolites such as **1**,**2** and **4**–**8**, was then transformed into 12-deoxyroyleanone (**1**) (Scheme 4). First, the methyl ester was converted into methyl group. Treatment of **9** with $LiAlH_4$ gave alcohol **23**, which was oxidized to aldehyde **24** and this transformed into compound **25** under the Wolff–Kishner conditions. Alternative transformations of **23** into **25**, via mesyl derivative **27**, were investigated. The treatment of **27** with $LiAlH_4$ regenerated alcohol **23**; nevertheless, compound **25** was obtained after treating mesylate **27** with Zn and NaI.[24] It should be noted that the yield of this reaction depends upon the quantity of mesylate; a more suitable procedure applicable to large amounts of compound **27** involves its conversion into iodide **28**, by treating with NaI in HMPA under reflux, and further reduction with $LiAlH_4$. Deprotection of methyl ether with BBr_3 led to phenol **26**.

Even though the structure of this phenol is quite evident, given that a simple inspection of the ^1H NMR spectrum reveals two doublets (J=8.2 Hz) at 6.85 and 7.01 ppm, characteristic of the H-11 and H-12 *ortho* protons, Yajima et al.[18] pay special attention to the ^{13}C NMR signals for the aromatic carbons of this compound. In their article, these authors announce a good agreement between the aromatic ^{13}C NMR chemical shifts for the phenol they synthesized and those

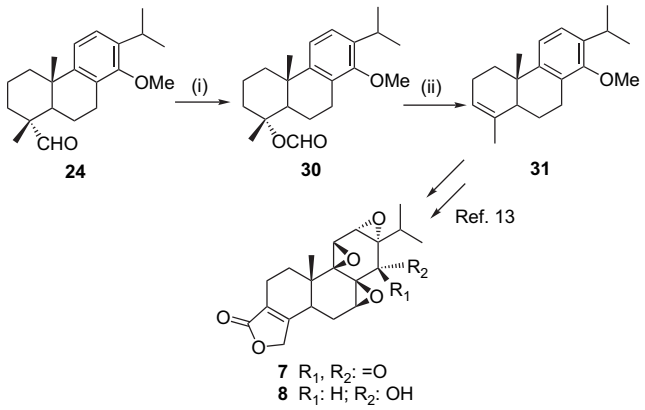


Scheme 4. Synthesis of 12-deoxyroyleanone (**1**) from ester **9**. Reagents, conditions and yields: (i) $LiAlH_4$, THF, rt, 3 h (95%); (ii) PCC, CH_2Cl_2, rt, 1 h (70%); (iii) N_2H_4, KOH, ethyleneglycol–ethyleneglycol dimethylether (3:2), 180 °C, three days (70%); (iv) MsCl, Et_3N, CH_2Cl_2, 0 °C–rt, 4 h (93%); (v) $LiAlH_4$, THF, reflux, 24 h (95%); (vi) NaI, HMPA, reflux, three days (90%); (vii) Zn, NaI, HMPA, 110 °C, three days (75%) for **27**, or $LiAlH_4$, THF, reflux, 24 h (96%) for **28**; (viii) BBr_3, CH_2Cl_2, −10 °C, 30 min (95%); (ix) Fremy's salt, MeOH–H_2O, rt (91% for **26** and 83% for **17**).

reported by Matsushita et al.,[17] and emphasize a small discrepancy with our previously reported data.[15] However, Yajima et al. make a wrong assignment, which they also attribute unfoundedly to Matsushita et al. The signal at 123.24 ppm, assigned to C-8 by Yajima et al. is due to a methine carbon, as the DEPT experiment revealed, and therefore it would be attributed to C-12. On the other hand, the signal at 120.62 ppm, which they assigned to C-12, and which as the DEPT indicated is a quaternary carbon, would be attributed to C-8. Then, a tentative assignation for the aromatic ring carbons, in accordance with the chemical shift pattern observed in similar structures, is δ 116.5 (C-11), 120.7 (C-8), 123.3 (C-12), 130.1 (C-13), 149.1 (C-9), 150.3 (C-14). This assignation agrees with that of Yajima et al., but interchanging the assignations for C-8 and C-12.

Finally, phenol **26** was transformed into 12-deoxyroyleanone (**1**) by treating with potassium nitrosodisulfonate. It should be noted that Yajima et al. indicate that they also assayed this oxidation unsuccessfully. However, we insist on the total reproducibility of this reaction. In fact, before synthesizing compound **1**, we assayed this oxidation over the less elaborated phenol **17**, which under the same reaction conditions afforded quinone **29**, which had also been prepared by Matsushita et al.;[17] our spectroscopic data and those reported by these authors were identical.

As we initially postulated, ester **9** is a suitable precursor of the A ring functionalized bioactive compounds **4**–**8**. Thus, aldehyde **24** was efficiently transformed into alkene **31**, utilizing novel procedures developed by our group (Scheme 5). The treatment of compound **24** with MCPBA gave in good yield formate **30**,[25] which was converted with complete regioselectivity into the trisubstituted alkene **31** by treating with I_2 and PPh_3.[26] Compound **31** has previously been transformed into (−)-triptonide (**7**) and (−)-triptolide (**8**),[13] and therefore the sequence reported herein involves a formal synthesis of these bioactive compounds from (+)-abietic acid (**13**).



Scheme 5. Synthesis of alkene **31**, precursor of bioactive compounds **7** and **8**, from aldehyde **24**. Reagents, conditions and yields: (i) MCPBA, $NaHCO_3$, CH_2Cl_2, reflux, 3 h (93%); (ii) I_2, PPh_3, CH_2Cl_2, rt, 12 h (91%).

3. Conclusion

In summary, two efficient procedures to prepare 14-hydroxyabietic acid and related compounds, from abietic acid (**13**) are reported. Utilizing these, the synthesis of the antileishmanial 12-deoxyroyleanone (**1**) and a formal synthesis of antitumour and immunosuppressant (−)-triptonide (**7**) and (−)-triptolide (**8**) from this diterpenic acid are described.

4. Experimental

4.1. General

Dichloromethane (DCM) was dried over calcium hydride, while toluene, tetrahydrofuran (THF) and benzene were dried over sodium-benzophenone. Methanol was distilled from magnesium at 760 Torr. Dimethylformamide (DMF) and ethanol were dried over 4 Å molecular sieves. Chromatography separations were carried out by conventional column on silica gel 60 (230–400 mesh) using hexane–MeO*t*-Bu (H–E) mixtures of increasing polarity. Infrared (IR) spectra were obtained using Perkin Elmer Spectrum Models 782 and 983G spectrophotometers with samples between sodium chloride plates or as potassium bromide pellets. Data are presented as the frequency of absorption (cm^{-1}). Proton and carbon-13 nuclear magnetic resonance (^1H NMR and ^{13}C NMR) spectra were recorded on Varian 300 and 400 spectrometers, chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane. Data are presented as follows: chemical shift, multiplicity (s=singlet, br s=broad singlet, d=doublet, br d=broad doublet, t=triplet, m=multiplet), *J*=coupling constant in hertz (Hz). The signals of the ^{13}C NMR were assigned utilizing DEPT experiments and on the basis of literature data. HRMS were obtained on a trisector WG AutoSpecQ spectrometer. FAB spectra acquisition was performed with a 10,000 resolution and a relative error of 5 ppm.

4.1.1. 13β,14β-Dihydroxyabieta-7-en-18-oic acid (14). To a solution of abietic acid (**13**) (10.01 g, 33.11 mmol) in *t*-BuOH (50 mL) were added trimethylamine-*N*-oxide dihydrate (4.42 g, 39.8 mmol) and pyridine (0.3 mL) under argon atmosphere. After stirring for 5 min at room temperature, a 2% aqueous solution of OsO_4 (14 mL) was added and the reaction mixture was further stirred under an atmosphere of argon at reflux for seven days. $NaHSO_3$ (10 mL) was added and the solvent was evaporated, then AcOEt (100 mL) was added and the mixture was washed with 5% HCl (2×20 mL), water (3×20 mL) and brine. The organic phase was dried over Na_2SO_4 and concentrated to give a crude product, which was chromatographed on silica gel (H–E, 3:7) to give pure **14** (6.5 g, 58%) as a colourless solid. Mp 156–157 °C [lit.:[19a] 154–155 °C]; $[\alpha]_D^{25}$ −3.75 (*c* 0.8, $CHCl_3$); IR (KBr) ν 3441, 2924, 1693, 1462, 1262, 1023, 801 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.83 (3H, s), 0.87 (3H, d, *J*=6.9 Hz), 0.93 (3H, d, *J*=6.9 Hz), 1.32 (3H, s), 1.43 (1H, dd, *J*=11.6, 2.9 Hz), 1.91 (1H, m), 2.17 (1H, h, *J*=6.9 Hz), 3.68 (3H, s, COOMe), 4.02 (1H, br s), 5.88 (1H, d, *J*=4.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 36.8 (C-1), 19.2 (C-2), 39.1 (C-3), 46.2 (C-4), 51.2 (C-5), 26.5 (C-6), 119.9 (C-7), 137.8 (C-8), 44.5 (C-9), 35.2 (C-10), 19.2 (C-11), 24.9 (C-12), 76.4 (C-13), 73.1 (C-14), 33.12 (C-15), 17.8 (C-16), 18.0 (C-17), 183.9 (C-18), 15.1 (C-19), 19.2 (C-20); HRMS (FAB) *m/z* calcd for $C_{20}H_{32}O_4Na$, 359.2198; found, 359.2202.

4.1.2. Methyl 13β,14β-dihydroxyabieta-7-en-18-oate (11).

4.1.2.1. Synthesis of diol 11 from 14. K_2CO_3 (5.7 g, 41.97 mmol) was added to a solution of **14** (5.59 g, 16.79 mmol) in acetone (75 mL) and the reaction mixture was kept stirring at room temperature for 15 min. Then, iodomethane (3.1 mL, 51 mmol) was added and the reaction mixture was stirred at reflux for 24 h. The solvent was evaporated and the crude reaction mixture was poured into ether–water (60:10 mL) and it was extracted with ether (2× 30 mL). The organic phase was washed with brine, dried over Na_2SO_4 and the solvent evaporated to give **11** (5 g, 94%) as a colourless solid. Mp 107–107.1 °C; $[\alpha]_D^{25}$ −0.57 (*c* 0.7, $CHCl_3$). The MS, IR, ^1H and ^{13}C NMR data agreed with the literature data.[27]

4.1.2.2. Synthesis of diol 11 from 13. To a solution of abietic acid (**13**) (5.00 g, 16.55 mmol) in *t*-BuOH (25 mL) were added trimethylamine-*N*-oxide dihydrate (2.21 g, 19.9 mmol) and pyridine (0.1 mL) under argon atmosphere. After stirring for 5 min at room temperature, a 2% aqueous solution of OsO_4 (7 mL) was added and the reaction mixture was further stirred under an atmosphere of argon at reflux for seven days. Following the same workup described for **14**, 5.54 g of the crude product was obtained. This was dissolved in acetone (75 mL) and K_2CO_3 (5.4 g, 39.76 mmol) was added; after stirring for 10 min at room temperature, iodomethane was added (3.5 mL, 57.59 mmol) and the reaction mixture was stirred at reflux for 24 h. Following the same workup described above, a crude product (5.3 g) was obtained. The chromatography of this crude on silica gel (H–E, 7:3) gave pure **11** (5.2 g, 90%) as a colourless oil.

4.1.3. Methyl 13β-hydroxy-14β-methoxyabieta-7-en-18-oate (12). NaH (60% dispersion in mineral oil) (170 mg, 4.26 mmol) was carefully added to a cold (0 °C) solution of **11** (0.5 mg, 1.43 mmol) in dry THF (10 mL) under argon atmosphere and the mixture was stirred at this temperature for 5 min. MeI (0.6 mL) was added and the resulting reaction

mixture was stirred at room temperature for 2 h, at which time TLC showed the disappearance of starting material. The reaction mixture was poured into ice-water and it was extracted with ether (2×20 mL). The organic phase was washed with brine, dried over Na_2SO_4 and the solvent evaporated to give a crude product, which was purified by column chromatography on silica gel (H–E, 85:15) affording pure **12** (0.51 g, 96%) as a colourless oil. $[\alpha]_D^{25}$ +5.13 (*c* 0.91, $CHCl_3$); IR (film) ν 3519, 2944, 1726, 1460, 1371, 1242, 1146 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{22}H_{36}O_4Na$, 387.2511; found, 387.2507. The ^1H and ^{13}C NMR data agreed with the literature data.[15]

4.1.4. Methyl 14-methoxyabieta-7,13-dien-18-oate (15). $SOCl_2$ (1 mL, 13.7 mmol) was added slowly to a solution of **12** (1.7 mg, 4.67 mmol) and triethylamine (5 mL) in dry CH_2Cl_2 (50 mL) at −78 °C. The reaction mixture was stirred at this temperature under argon atmosphere for 20 min, at which time TLC showed no starting material. The reaction mixture was quenched with satd aq $NaHCO_3$ (6 mL) and the cooling bath was removed. The mixture was poured into ether–water (60:20 mL) and it was extracted with ether (2×30 mL). The organic phase was washed with 2 N HCl (3×20 mL), brine (3×20 mL), dried over Na_2SO_4 and the solvent evaporated to give a crude product, which was purified by flash chromatography on silica gel (H–E, 95:5) affording pure **15** (1.2 g, 74%) as a colourless oil. $[\alpha]_D^{25}$ −11.0 (*c* 0.85, $CHCl_3$); IR (film) ν 2836, 1726, 1624, 1385, 738 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{22}H_{34}O_3Na$, 369.2405; found, 369.2412. The ^1H and ^{13}C NMR data agreed with the literature data.[15]

4.1.5. Methyl 14-methoxyabieta-6,8,11,13-tetraen-18-oate (16). A solution of bromine (0.18 mL, 3.51 mmol) in CCl_4 (15 mL) was added to a suspension of **15** (0.96 g, 2.90 mmol) and $CaCO_3$ (0.79 g, 7.89 mmol) in CCl_4 (20 mL), and the reaction mixture was stirred at reflux for 12 h, at which time TLC showed no **15**. Then the precipitated solid was filtered, the filtrate was washed with ether (10 mL) and the solvent was evaporated to give a crude product, which was purified by flash chromatography to give pure **16** (0.69 g, 70%) as a colourless oil. $[\alpha]_D^{25}$ +22.2 (*c* 1.0, $CHCl_3$); IR (film) ν 2947, 1726, 1447, 1245, 816 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{22}H_{30}O_3Na$, 395.2092; found, 365.2094. The ^1H and ^{13}C NMR data agreed with the literature data.[15]

4.1.6. Methyl 14-methoxyabieta-8,11,13-trien-18-oate (9).

4.1.6.1. Treatment of 16 with H_2/Pd–C. To a solution of **16** (0.50 g, 1.46 mmol) in methanol (30 mL), 10% Pd–C (100 mg) was added and the reaction mixture was stirred at room temperature under hydrogen atmosphere for 24 h. Filtration and concentration gave **9** (472 mg, 94%) as a colourless solid. Mp 97 °C; $[\alpha]_D^{25}$ +38.2 (*c* 0.71, $CHCl_3$); IR (KBr) ν 2956, 1726, 1620, 1448, 1246, 817 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{22}H_{32}O_3Na$, 367.2249; found, 367.2254. The ^1H and ^{13}C NMR data agreed with the literature data.[15]

4.1.6.2. Treatment of 16 with Et_3SiH/CF_3COOH. To a solution of **16** (0.87 g, 2.56 mmol) in dichloromethane (20 mL), triethylsilane (0.6 mL) and trifluoroacetic acid (0.4 mL) were successively added at −40 °C, and the resulting mixture was stirred for 16 h. Then, the mixture was diluted with ether (50 mL) and washed with satd aq $NaHCO_3$ (2×10 mL), water (2×10 mL) and brine (2×10 mL). The organic phase was dried over Na_2SO_4 and the solvent evaporated to give **9** (819 mg, 93%).

4.1.7. Oxidation of diol 11.

4.1.7.1. Treatment of 11 with MnO_2. To a stirred solution of **11** (100 mg, 0.285 mmol) in dry benzene (10 mL) was added MnO_2 (0.49 g, 5.71 mmol). After stirring at reflux for 48 h, TLC showed no **11**, then the reaction was worked up by the addition of ether (10 mL), and the resulting mixture was filtered through a silica gel pad and washed with ether (10 mL). The solvent was evaporated to yield **20** (74 mg, 75%) as a colourless oil.

*Methyl 13,14-dioxo-13-secoabieta-7,13-dien-18-oate (**20**).* IR (film) ν 3500, 2951, 1714, 1652, 1631, 1462, 1386, 1246, 1187 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.78 (3H, s), 1.03 (3H, d, *J*=6.9 Hz), 1.05 (3H, d, *J*=6.9 Hz), 1.21 (3H, s), 2.21 (1H, m), 2.40 (1H, m), 2.57 (1H, h, *J*=6.9 Hz), 3.05 (1H, m), 3.6 (3H, s, COOMe), 6.7 (1H, q, *J*=2.7 Hz, H-7), 9.3 (1H, s, H-CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 42.4 (C-1), 20.7 (C-2), 37.7 (C-3), 46.9 (C-4), 49.9 (C-5), 26.7 (C-6), 152.2 (C-7), 144.2 (C-8), 44.1 (C-9), 36.3 (C-10), 18.3 (C-11), 37.0 (C-12), 215.2 (C-13), 194.7 (C-14), 40.6 (C-15), 17.4 (C-16), 17.6 (C-17), 178.4 (C-18), 14.1 (C-19), 18.2 (C-20), 52.0 (C-COOMe); HRMS (FAB) *m/z* calcd for $C_{21}H_{32}O_4Na$, 371.2198; found, 371.2191.

4.1.7.2. Treatment of 11 with *Jones reagent*. To a stirred solution of **11** (0.32 g, 0.91 mmol) in acetone (15 mL) was added at 0 °C *Jones reagent*[28] (0.5 mL) and the reaction mixture was stirred for 30 min, at which time TLC showed no **11**. Then the solvent was evaporated and the crude product was diluted with ether (30 mL), washed with water (6×10 mL), brine, dried over anhyd Na_2SO_4 and concentrated to give a crude product, which was chromatographed on silica gel (H–E, 9:1) to give **20** (15 mg, 5%), **21** (58 g, 20%) and **22** (32 mg, 11%).

*Methyl 7-oxoabieta-8,11,13-trien-18-oate (**22**).* IR (film) ν 2952, 1726, 1682, 1460, 1249 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.11 (3H, s), 1.16 (3H, d, *J*=6.9 Hz), 1.18 (3H, d, *J*=6.9 Hz), 1.27 (3H, s), 2.65 (1H, dd, *J*=6.9, 3.5 Hz), 2.85 (1H, h), 3.56 (3H, s, COOMe), 7.21 (1H, d, *J*= 8.2 Hz), 7.34 (1H, dd, *J*=8.2, 2.1 Hz), 7.79 (1H, d, *J*= 2.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.4 (CH_3), 18.2 (CH_2), 23.8 (CH_3), 23.9 (CH_3), 24.0 (CH), 33.5 (CH_3), 36.6 (CH_2), 37.2 (CH_2), 37.4 (C), 37.9 (CH_2), 43.8 (CH), 52.2 (CH_3), 123.5 (CH), 125.1 (CH), 132.6 (CH), 146.9 (C), 153.0 (C), 177.8 (C), 198.6 (C); HRMS (FAB) *m/z* calcd for $C_{21}H_{28}O_3Na$, 351.1936; found, 351.1928.

4.1.7.3. Treatment of 11 with IBX in DMSO. IBX (0.3 g, 1.07 mmol) was added to a solution of diol **11** (0.20 g, 0.57 mmol) in DMSO (6 mL) and the reaction mixture was stirred at room temperature for 16 h. Then the reaction mixture was diluted with ether (20 mL), washed with satd aq Na_2CO_3 (2×6 mL), dried over Na_2SO_4 and the solvent evaporated to give the unaltered **11** (194 mg).

4.1.7.4. Treatment of 11 with IBX in THF. IBX (0.3 g, 1.07 mmol) was added to a solution of diol **11** (0.20 g,

0.57 mmol) in dry THF (10 mL) and the reaction mixture was stirred at reflux for 48 h. Then the solvent was evaporated and the residue was extracted with ether (2×15 mL), the organic phase was washed with satd aq Na_2CO_3 (2×10 mL), dried over Na_2SO_4 and the solvent evaporated to give a crude product, which was purified by flash chromatography on silica gel (H–E, 7:3), affording **20** (143 mg, 72%) as a colourless oil.

4.1.7.5. Treatment of 11 with PCC. Pyridinium chlorochromate (PCC) (1.28 g, 5.49 mmol) and molecular sieves 3 Å (3.75 g) were added to a stirred solution of **11** (0.50 g, 1.43 mmol) in dry CH_2Cl_2 (20 mL) and the mixture was kept stirring at room temperature under argon atmosphere for 30 min, at which time TLC showed no remaining starting material. Then, the reaction was worked up by the addition of CH_2Cl_2 (10 mL) and the resulting mixture was filtered through a silica gel pad and washed with a mixture of ether–CH_2Cl_2 (20:30 mL). The solvent was evaporated to yield a crude product, which was chromatographed on silica gel (H–E, 7:3) to yield **10** (150 mg, 30%) and **20** (184 mg, 37%).

4.1.7.6. Swern oxidation of 11. To a stirred solution of $(COCl)_2$ (1.79 mL, 20.57 mmol) in dry dichloromethane (17 mL) was added DMSO (2.5 mL) at −78 °C, the reaction mixture was stirred for 2 min and the cooling bath was removed for 5 min. Then a solution of **11** (3.0 g, 8.57 mmol) in dichloromethane (35 mL) was added at −78 °C and the reaction mixture was stirred at this temperature for an additional 15 min. Then, triethylamine (5 mL) was added and the cooling bath was removed. After stirring for 15 min, the reaction mixture was diluted with ether (80 mL) and washed with 2 N HCl (3×20 mL), water and brine. The organic phase was dried over Na_2SO_4 and concentrated to give a crude product (2.9 g), which was purified by column chromatography on silica gel (H–E, 3:2), to give **10** (447 mg, 15%) and **18** (142 mg, 5%).

4.1.7.7. Treatment of 11 with DDQ. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 113 mg, 0.49 mmol) and *p*-toluenesulfonic acid (15 mg, 0.079 mmol) were added to a stirred solution of **14** (95 mg, 0.271 mmol) in dry benzene (6 mL) and the reaction mixture was stirred at room temperature for 48 h, at which time TLC showed no **14**. Then it was diluted with ether (25 mL), washed with water, satd aq $NaHCO_3$ and brine to give a crude product, which was purified by column chromatography on silica gel (H–E, 9:1), to give **10** (17 mg, 18%) and **18** (11 mg, 12%).

4.1.7.8. Treatment of 11 with PDC. Pyridinium dichromate (PDC; 13.9 g, 36.25 mmol) and 6 M *t*-BuOOH in decane (7.32 mL, 43.92 mmol) were added to a stirred solution of **11** (3.14 g, 8.97 mmol) and Celite (10.78 g) in dry benzene (114 mL). The reaction mixture was stirred at room temperature under argon atmosphere for 3 h 15 min, at which time TLC showed no **11**. The resulting mixture was filtered through a silica gel pad and washed with a 1:1 mixture of hexane–ether (50 mL) and the solvent was evaporated to give a crude product (3.5 g). The chromatography of this crude on silica gel (H–E, 7:3) gave **10** (1.13 g, 36%) as a colourless oil.

*Methyl 13β-hydroxy-14-oxoabieta-7-en-18-oate (**10**).* $[\alpha]_D^{25}$ +16.85 (*c* 0.94, $CHCl_3$); IR (film) ν 3500, 2951, 1714, 1652, 1631, 1462, 1386, 1246, 1187 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{21}H_{32}O_4Na$, 371.2198; found, 371.2192. The ^1H and ^{13}C NMR data agreed with the literature data.[15]

4.1.7.9. Treatment of 11 with PhSeSePh/*t*-BuOOH. Diphenyl diselenide (0.60 g, 1.92 mmol) and 6 M *t*-BuOOH in decane (0.65 mL, 3.9 mmol) were added to a stirred solution of **11** (0.50 g, 1.43 mmol) in dry CCl_4 (20 mL) and the mixture was kept stirring at reflux under argon atmosphere for 2 h, at which time TLC showed no remaining starting material. Then, the solvent was evaporated and the residue was purified by flash chromatography on silica gel (H–E, 7:3) affording **10** (457 mg, 92%) as a colourless oil.

4.1.8. Methyl 7-oxoabieta-7,12-dien-18-oate (18). Hydroxy ketone **10** (0.30 g, 0.862 mmol) and *p*-toluenesulfonic acid (140 mg, 0.736 mmol) in dry benzene (15 mL) were heated at reflux for 36 h, at which time TLC showed the disappearance of starting material. Then the solvent was evaporated to give a crude product, which was purified by flash chromatography on silica gel (H–E, 7:3) affording **18** (0.22 g, 78%) as a colourless oil. $[\alpha]_D^{25}$ −0.66 (*c* 0.91, $CHCl_3$); IR (film) ν 2870, 1724, 1667, 1612, 1460, 1424, 1385, 1302, 1005, 911, 827, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.86 (3H, s), 0.97 (3H, d, *J*=6.9 Hz), 1.03 (3H, d, *J*=6.9 Hz), 1.24 (3H, s), 2.90 (1H, h, *J*=6.9 Hz), 3.63 (3H, s, COOMe), 6.69 (1H, d, *J*=8.3 Hz), 7.00 (1H, q, *J*=2.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 36.9 (C-1), 18.2 (C-2), 38.1 (C-3), 46.1 (C-4), 43.6 (C-5), 26.0 (C-6), 135.7 (C-7), 135.0 (C-8), 49.6 (C-9), 37.0 (C-10), 23.1 (C-11), 140.6 (C-12), 145.7 (C-13), 186.3 (C-14), 26.7 (C-15), 22.3 (C-16), 23.1 (C-17), 178.5 (C-18), 14.9 (C-19), 16.9 (C-20), 52.0 (C-COO*Me*); HRMS (FAB) *m/z* calcd for $C_{21}H_{30}O_3Na$, 353.2092; found, 353.2091.

4.1.9. Methyl 7-hydroxyabieta-8,11,13-trien-18-oate (17). Ketone **10** (0.2 mg, 0.575 mmol) and *p*-toluenesulfonic acid (0.1 mg, 0.526 mmol) in dry toluene (10 mL) were heated at reflux for 10 h. Then the solvent was evaporated to give a crude product, which was purified by flash chromatography on silica gel (H–E, 85:15) affording **17** (172 mg, 91%) as a colourless oil. $[\alpha]_D^{25}$ +7.7 (*c* 1.0, $CHCl_3$) [lit.:[17] +51.7 (*c* 0.5, $CHCl_3$)]. The MS, IR, ^1H and ^{13}C NMR data agreed with the literature data.[17]

4.1.10. Methyl 14-hydroxyabieta-6,8,11,13-tetraen-18-oate (19). K_2CO_3 (0.39 g, 2.85 mmol) was added to a solution of **18** (92 mg, 0.28 mmol) in MeOH (6 mL), and the reaction mixture was kept stirring at reflux for three days, at which time TLC showed the disappearance of compound **18**. The reaction was quenched with 2 N HCl (1 mL). The mixture was poured into ether–water (20:5 mL) and it was extracted with ether (2×15 mL). The organic phase was washed with brine, dried over Na_2SO_4 and the solvent evaporated to give **19** (70 mg, 70%) as a colourless oil. IR (film) ν 3583, 2948, 2923, 2869, 1724, 1627, 1566, 1433, 1386, 1123, 1002, 762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.05 (3H, s), 1.21 (3H, d, *J*=6.9 Hz), 1.24 (3H, d, *J*=6.9 Hz), 1.38 (3H, s), 2.16 (1H, m), 2.86 (1H, t, *J*=3.0 Hz), 3.10 (1H, h, *J*=6.9 Hz), 3.65 (3H, s, COOMe), 5.77 (1H, dd, *J*=9.8, 2.9 Hz), 6.73 (1H, d, *J*=8.3 Hz), 6.77 (1H, dd, *J*=9.8,

3.1 Hz), 7.03 (1H, d, J=8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 35.5 (C-1), 18.4 (C-2), 35.6 (C-3), 46.3 (C-4), 46.2 (C-5), 129.6 (C-6), 125.2 (C-7), 119.8 (C-8), 146.6 (C-9), 37.6 (C-10), 114.2 (C-11), 121.0 (C-12), 131.8 (C-13), 148.4 (C-14), 26.9 (C-15), 22.5 (C-16), 22.8 (C-17), 17.9 (C-19), 20.5 (C-20), 52.0 (C-COO*Me*); HRMS (FAB) *m/z* calcd for $C_{21}H_{28}O_3Na$, 351.1936; found, 351.1929.

4.1.11. Treatment of 19 with H_2/Pd–C. To a solution of **19** (0.5 g, 1.52 mmol) in methanol (30 mL), 10% Pd–C (100 mg) was added and the reaction mixture was stirred at room temperature under hydrogen atmosphere for 24 h. Filtration and concentration gave **17** (0.48 g, 96%) as a colourless oil.

4.1.12. Methylation of 17. K_2CO_3 (0.60 g, 4.35 mmol) was added to a solution of **17** (575 mg, 1.74 mmol) in acetone (15 mL) and the reaction mixture was kept stirring at room temperature for 15 min. Then iodomethane (0.54 mL, 8.71 mmol) was added and the reaction mixture was stirred at reflux for 15 h. The solvent was evaporated and the crude reaction mixture was poured into ether–water (30:10 mL) and it was extracted with ether (2×10 mL). The organic phase was washed with brine, dried over Na_2SO_4 and the solvent evaporated to give **9** (545 mg, 91%) as a colourless oil.

4.1.13. 14-Methoxyabieta-8,11,13-trien-18-ol (23). $LiAlH_4$ (0.5 g, 13.16 mmol) was added to a stirred solution of **9** (1.0 g, 3.01 mmol) in dry THF (10 mL) cooled to 0 °C, and the reaction mixture was kept stirring at room temperature under argon atmosphere for 3 h, at which time TLC showed the disappearance of starting material. Then, 2 N HCl (0.5 mL) was added slowly at 0 °C and the mixture was extracted with ether (2×25 mL). The organic phase was washed with brine, dried over Na_2SO_4 and the solvent evaporated to give **23** (0.9 g, 95%) as a colourless solid. Mp 102 °C; $[\alpha]_D^{25}$ +5.7 (*c* 0.04, $CHCl_3$); IR (KBr) ν 3401, 1484, 1410, 1329, 1263, 1212, 1031, 817 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.88 (3H, s), 1.18 (3H, d, J=6.9 Hz), 1.20 (3H, d, J=6.9 Hz), 1.22–1.95 (8H, m), 2.25 (1H, br d, J=12.7 Hz), 2.74 (1H, ddd, J=17.6, 11.3, 6.2 Hz), 2.98 (1H, dd, J=17.6, 6.2 Hz), 3.23 (1H, d, J=10.8 Hz), 3.27 (1H, h, J=6.9 Hz), 3.48 (1H, d, J=10.8 Hz), 3.70 (3H, s), 7.01 (1H, d, J=8.1 Hz), 7.04 (1H, d, J=8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.4 (CH_3), 18.4 (CH_2), 18.7 (CH_2), 23.9 (CH_3), 24.0 (CH_3), 24.6 (CH_2), 25.3 (CH_3), 26.1 (CH), 35.0 (CH_2), 37.6 (C), 37.9 (C), 38.6 (CH_2), 43.6 (CH), 60.5 (CH_3), 72.2 (CH_2), 120.3 (CH), 123.6 (CH), 128.6 (C), 137.9 (C), 149.1 (C), 154.8 (C); HRMS (FAB) *m/z* calcd for $C_{21}H_{32}O_2Na$, 339.2300; found, 339.2304.

4.1.14. 14-Methoxyabieta-8,11,13-trien-18-al (24). Pyridinium chlorochromate (PCC) (0.50 g, 2.32 mmol) was added to a stirred solution of **22** (0.50 g, 1.58 mmol) in dry CH_2Cl_2 (25 mL) and the mixture was kept stirring at room temperature under argon atmosphere for 1 h, at which time TLC showed no remaining starting material. Then, the reaction was worked up by the addition of CH_2Cl_2 (20 mL) and the resulting mixture was filtered through a silica gel pad and washed with a mixture of ether–CH_2Cl_2 (15:30 mL). The solvent was evaporated to yield **23** (0.35 g, 70%), as a colourless oil. $[\alpha]_D^{25}$ +7.13 (*c* 1.1, $CHCl_3$); IR (film) ν 1725, 1449, 1410, 1330, 1219, 1152, 1029, 872, 818, 757 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.15 (3H, s), 1.18 (6H, d, J=6.9 Hz), 1.21 (3H, s), 1.31–1.90 (8H, m), 2.31 (1H, br d, J=12.7 Hz), 2.73 (1H, ddd, J=17.6, 11.3, 6.2 Hz), 2.96 (1H, dd, J=17.6, 6.2 Hz), 3.27 (1H, h, J=6.9 Hz), 3.69 (3H, s), 7.01 (1H, d, J=8.1 Hz), 7.06 (1H, d, J=8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1 (CH_3), 17.8 (CH_2), 20.9 (CH_2), 23.9 (CH_3), 24.0 (CH_3), 24.3 (CH_2), 25.2 (CH), 26.1 (CH), 32.0 (CH_2), 36.5 (C), 38.0 (CH_2), 42.5 (CH), 49.8 (C), 60.5 (CH), 120.2 (CH), 123.9 (CH), 128.3 (C), 138.4 (C), 147.9 (C), 155.0 (C), 206.2 (C); HRMS (FAB) *m/z* calcd for $C_{21}H_{30}O_2Na$, 337.2143; found, 337.2138.

4.1.15. 14-Methoxyabieta-8,11,13-triene (25). Hydrazine hydrate (0.5 mL) and KOH (0.20 g) were added to a solution of aldehyde **24** (0.40 g, 1.27 mmol) in ethyleneglycol–ethylenglycol dimethylether (3:2, 15 mL) and the reaction mixture was heated at 180 °C for three days, at which time TLC showed no **24**. The reaction mixture was allowed to cool to room temperature and was diluted with water (5 mL) and extracted with ether (2×20 mL). The combined organic phases were washed with water and brine, dried over Na_2SO_4 and the solvent evaporated to give a crude product, which was purified by column chromatography on silica gel (H–E, 95:5), affording **25** (267 mg, 70%) as a colourless syrup. $[\alpha]_D^{25}$ +15.1 (*c* 1.0, $CHCl_3$); IR (film) ν 2963, 2945, 1605, 1452, 1378, 1050, 1018, 980 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.93 (3H, s), 0.96 (3H, s), 1.18 (3H, s), 1.21 (3H, d, J=6.8 Hz), 1.20 (3H, d, J=6.8 Hz), 1.32 (1H, dd, J=12.5, 2.1 Hz), 1.39 (1H, ddd, J=13.1, 13.1, 3.6 Hz), 1.48 (1H, br d, J=13.1 Hz), 1.55–1.85 (8H, m), 1.93 (1H, dd, J=13.2, 7.8 Hz), 2.26 (1H, br d, J=12.7 Hz), 2.73 (ddd, J=17.7, 11.4, 7.7 Hz), 3.01 (1H, dd, J=17.6, 7.7 Hz), 3.28 (1H, h, J=6.9 Hz), 3.72 (3H, s), 7.02 (1H, d, J=8.4 Hz), 7.05 (1H, d, J=8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.7 (CH_2), 19.4 (CH_2), 21.7 (CH_3), 23.4 (CH_3), 24.0 (CH_3), 25.0 (CH_3), 29.5 (CH_2), 26.1 (CH), 33.4 (CH_3), 33.4 (C), 37.8 (C), 39.0 (CH_2), 41.7 (CH_2), 50.2 (CH), 60.5 (CH_3), 120.4 (CH), 123.7 (CH), 128.7 (C), 137.8 (C), 149.4 (C), 154.0 (C); HRMS (FAB) *m/z* calcd for $C_{21}H_{32}ONa$, 323.2351; found, 323.2347.

4.1.16. 14-Methoxy-18-mesyloxyabieta-8,11,13-triene (27). Mesyl chloride (0.7 mL) was added to a solution of **23** (0.40 g, 1.26 mmol) and triethylamine (1 mL) in dichloromethane (15 mL) at 0 °C and the reaction mixture was stirred at room temperature for 4 h, at which time TLC showed no **23**. The reaction mixture was quenched with water (1 mL) and it was diluted with ether (40 mL) and washed with 2 M aq HCl, water and brine. The organic phase was dried over anhyd Na_2SO_4 and concentrated under vacuum to yield **27** (461 mg, 93%) as a colourless oil. $[\alpha]_D^{25}$ +13.5 (*c* 1.06, $CHCl_3$); IR (film) ν 1495, 1355, 1175, 1028, 956, 847, 755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.95 (3H, s), 1.16 (3H, s), 1.18 (3H, d, J=6.9 Hz), 1.21 (6H, d, J=6.9 Hz), 1.45–1.90 (8H, m), 2.26 (1H, br d, J=12.7 Hz), 2.70 (1H, ddd, J=16.5, 11.5, 6.2 Hz), 2.96 (3H, s), 3.00 (1H, dd, J=16.5, 6.2 Hz), 3.27 (1H, h, J=6.9 Hz), 3.69 (3H, s), 3.79 (1H, d, J=9.4 Hz), 4.05 (1H, d, J=9.4 Hz), 6.99 (1H, d, J=8.1 Hz), 7.01 (1H, d, J=8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.1 (CH_3), 18.4 (CH_2), 18.5 (CH_2), 23.9 (CH_3), 24.0 (CH_3), 24.4 (CH_2), 25.3 (CH_3), 26.1 (CH), 35.1 (CH_2), 37.2 (CH_3), 37.2 (C), 37.6 (C), 38.2

(CH_2), 43.4 (CH), 60.5 (CH_3), 77.1 (CH_2), 120.3 (CH), 123.8 (CH), 128.3 (C), 138.1 (C), 148.4 (C), 154.8 (C); HRMS (FAB) *m/z* calcd for $C_{22}H_{34}O_4SNa$, 417.2075; found, 417.2081.

4.1.17. Treatment of 27 with NaI/Zn. NaI (160 mg, 0.81 mmol) and zinc (105 mg, 1.59 mmol) were added to a solution of **27** (120 mg, 0.30 mmol) in HMPA (5 mL) and the reaction mixture was stirred at 110 °C for three days, at which time TLC showed no **27**. The reaction mixture was quenched with water (2 mL), diluted with ether (30 mL) and washed with water (6×10 mL) and brine. The organic phase was dried over anhyd Na_2SO_4 and concentrated under vacuum to yield **25** (68 mg, 75%).

4.1.18. 14-Methoxy-18-iodoabieta-8,11,13-triene (28). NaI (560 mg, 2.83 mmol) was added to a solution of **27** (420 mg, 1.06 mmol) in HMPA (8 mL) and the reaction mixture was stirred at reflux for three days, at which time TLC showed no **27**. The reaction mixture was quenched with water (2 mL), diluted with ether (30 mL) and washed with water (6×10 mL) and brine. The organic phase was dried over Na_2SO_4 and concentrated under vacuum to yield **28** (407 mg, 90%) as a yellow oil. $[\alpha]_D^{25}$ −7.6 (*c* 1.1, $CHCl_3$); IR (film) ν 1456, 1381, 1260, 1212, 1030, 979, 819 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.10 (3H, s), 1.20 (3H, s), 1.21 (3H, d, *J*=6.9 Hz), 1.21 (3H, d, *J*=6.9 Hz), 1.30–1.82 (7H, m), 2.24 (1H, ddd, *J*=12.8, 12.8, 3.1 Hz), 2.79 (1H, ddd, *J*=17.7, 11.0, 7.5 Hz), 3.01 (1H, ddd, *J*=17.7, 6.2, 1.4 Hz), 3.25 (1H, d, *J*=10.0 Hz), 3.29 (1H, h, *J*=6.9 Hz), 3.38 (1H, d, *J*=10.0 Hz), 3.72 (3H, s), 7.02 (1H, d, *J*=8.4 Hz), 7.06 (1H, d, *J*=8.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 18.5 (CH_2), 18.8 (CH_3), 19.2 (CH_2), 24.1 (CH_3), 24.1 (CH_3), 24.8 (CH_2), 24.9 (CH_3), 26.3 (CH), 38.3 (CH_2), 35.9 (C), 38.1 (C), 38.7 (CH_2), 47.2 (CH), 60.7 (CH_3), 120.7 (CH), 124.0 (CH), 128.7 (C), 138.2 (C), 148.9 (C), 155.0 (C).

4.1.19. Treatment of 28 with $LiAlH_4$. $LiAlH_4$ (0.3 g, 7.9 mmol) was added to a stirred solution of **28** (0.75 g, 1.76 mmol) in dry THF (15 mL) cooled to 0 °C, and the reaction mixture was kept stirring under argon atmosphere at reflux for 24 h, at which time TLC showed the disappearance of starting material. Then, 2 N HCl (0.5 mL) was added slowly and the mixture was extracted with ether (3×20 mL). The organic phase was washed with brine, dried over Na_2SO_4 and the solvent evaporated to give **25** (507 mg, 96%) as a colourless oil.

4.1.20. Abieta-8,11,13-trien-14-ol (26). BBr_3 (0.25 mL, 2.6 mmol) was added to a solution of **25** (250 mg, 0.83 mmol) in dichloromethane (15 mL) at −10 °C and the reaction mixture was stirred for 30 min, at which time TLC showed no **25**. The reaction mixture was poured into ice-water and it was diluted with ether (30 mL) and washed with water (5×10 mL) and brine. The organic phase was dried over Na_2SO_4 and concentrated under vacuum to yield **26** (225 mg, 95%) as a yellow oil. $[\alpha]_D^{25}$ +15.1 (*c* 1.0, $CHCl_3$) [lit.:[17] +52.9 (*c* 0.5, $CHCl_3$); lit.:[18] +27.9 (*c* 0.96, $CHCl_3$)]. IR (film) ν 3500, 1569, 1491, 1420, 1381, 1216, 1177, 1103, 995, 809 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (3H, s), 1.17 (3H, s), 1.19 (3H, s), 1.22 (3H, d, *J*=6.8 Hz), 1.23 (3H, d, *J*=6.8 Hz), 1.41 (1H, dd, *J*=12.3, 1.8 Hz), 2.26 (1H, dt, *J*=12.7, 3.2 Hz), 2.59 (1H, ddd, *J*=16.5, 11.3, 6.8 Hz), 2.78 (1H, dd, *J*=16.5, 6.3 Hz), 3.12 (1H, h, *J*=6.8 Hz), 4.61 (1H, s), 6.84 (1H, d, *J*=8.2 Hz), 7.00 (1H, d, *J*=8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.3 (CH_2), 19.3 (CH_2), 21.7 (CH_3), 22.6 (CH_3), 22.8 (CH_3), 22.9 (CH_3), 24.4 (CH_3), 24.9 (CH_3), 27.1 (CH), 33.4 (CH_3), 33.4 (C), 38.8 (C), 39.0 (CH_2), 41.7 (CH_2), 49.8 (CH), 116.5 (CH), 120.7 (C), 123.3 (CH), 130.1 (C), 149.1 (C), 150.3 (C); HRMS (FAB) *m/z* calcd for $C_{20}H_{30}ONa$, 309.2194; found, 309.2187.

4.1.21. Oxidation of 17 with $(KSO_3)_2NO$. Potassium nitrosodisulfonate (0.60 g, 2.23 mmol) was added to a stirred solution of **17** (200 mg, 0.606 mmol) in methanol (60 mL) and water (6 mL). After stirring for 10 h, TLC showed no starting material. Then, the solvent was evaporated and the crude product was extracted with ether (2×20 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated to give a crude product, which was purified by flash chromatography on silica gel (H–E, 3:2) to give **29** (173 mg, 83%) as a yellow oil. The MS, IR, ^1H and ^{13}C NMR data agreed with the literature data.[17]

4.1.22. Oxidation of 26 with $(KSO_3)_2NO$. Potassium nitrosodisulfonate (0.80 g, 2.98 mmol) was added to a stirred solution of **26** (150 mg, 0.524 mmol) in methanol (50 mL) and water (5 mL). After stirring for 4 h, TLC showed no starting material. Following the same workup described for **17**, 143 mg (91%) of 12-deoxyroyleanone (**1**) was obtained as a yellow oil.

4.1.23. 4-Formyloxy-14-methoxy-18-norabieta-8,11,13-triene (30). To a stirred solution of **24** (1.0 g, 3.18 mmol) and $NaHCO_3$ (0.6 g) in CH_2Cl_2 (50 mL), *m*-chloroperbenzoic acid (MCPBA) (1.1 g, 4.78 mmol) was added at room temperature. After stirring at reflux for 3 h, TLC indicated that no starting aldehyde **24** remained. The reaction mixture was quenched with 10% aq Na_2SO_3 (5 mL) and the mixture was stirred for an additional 45 min. Then, it was poured into ether–water (80:20 mL), and the organic phase washed with satd aq $NaHCO_3$ (8×20 mL), brine and dried over Na_2SO_4. After evaporating the solvent in vacuo, **30** (0.98 g, 93%) was obtained as a colourless oil. $[\alpha]_D^{25}$ +13.2 (*c* 0.52, $CHCl_3$); IR (film) ν 1719, 1567, 1584, 1385, 1330, 1198, 1102, 1029, 861, 820, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.20 (3H, s), 1.21 (3H, d, *J*=6.9 Hz), 1.22 (3H, d, *J*=6.9 Hz), 1.59 (3H, s), 1.98 (1H, dd, *J*=12.3, 1.8 Hz), 2.12 (1H, dd, *J*=12.9, 7.6 Hz), 2.24 (1H, d, *J*=12.5 Hz), 2.64 (1H, m), 2.75 (1H, ddd, *J*=17.6, 12.9, 7.6 Hz), 3.06 (1H, dd, *J*=17.6, 5.5 Hz), 3.14 (1H, h, *J*=6.9 Hz), 3.72 (3H, s), 7.02 (1H, d, *J*=8.2 Hz), 7.07 (1H, d, *J*=8.2 Hz), 8.08 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.9 (CH_2), 18.9 (CH_3), 19.0 (CH_2), 22.9 (CH_3), 23.7 (CH_3), 25.1 (CH), 36.6 (CH_2), 36.9 (CH_2), 37.6 (C), 48.4 (CH), 59.4 (OCH_3), 119.5 (CH), 122.9 (CH), 127.4 (C), 137.3 (C), 146.6 (C), 153.9 (C), 159.5 (C); HRMS (FAB) *m/z* calcd for $C_{21}H_{30}O_3Na$, 353.2093; found, 353.2100.

4.1.24. 14-Methoxy-18-norabieta-3,8,11,13-tetraene (31).[13] Iodine (1.0 g, 3.94 mmol) was added to a solution of Ph_3P (1 g, 3.8 mmol) in CH_2Cl_2 (10 mL) and the mixture was stirred at room temperature for 5 min. A solution of **30** (1 g, 3.03 mmol) in CH_2Cl_2 (10 mL) was then added and the

reaction mixture was stirred at room temperature for 12 h, at which time TLC showed no **30**. The reaction mixture was quenched with 5% aq $NaHSO_3$ (3 mL) and the mixture was stirred for an additional 15 min. Then, it was diluted with ether (30 mL) and the organic phase was washed successively with satd aq $NaHCO_3$ (2×10 mL), brine, dried over anhyd Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography (H–E, 9:1) to give **31** (783 mg, 91%) as a colourless oil. $[\alpha]_D^{25}$ +38.4 (*c* 0.7, $CHCl_3$); IR (film) ν 1647, 1561, 1447, 1329, 1260, 1203, 1032, 820, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.21 (3H, d, *J*=6.9 Hz), 1.22 (3H, d, *J*=6.9 Hz), 1.26 (3H, s), 150–1.60 (2H, m), 1.76 (3H, s), 1.87 (1H, br d, *J*=10.7 Hz), 2.06 (1H, m), 2.61 (1H, ddd, *J*=16.8, 10.4, 5.0 Hz), 2.89 (1H, dd, *J*=16.8, 4.7 Hz), 3.30 (1H, h, *J*=6.9 Hz), 3.71 (3H, s), 5.42 (1H, br s), 7.06 (1H, d, *J*=6.8 Hz), 7.08 (1H, d, *J*=6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 22.6 (CH_3), 23.3 (CH_2), 23.9 (CH_2), 24.1 (CH_3), 24.1 (CH_3), 26.4 (CH), 27.4 (CH_3), 33.8 (CH_2), 36.6 (C), 46.8 (CH), 60.7 (OCH_3), 121.6 (CH), 123.2 (CH), 123.9 (CH), 130.1 (C), 135.5 (C), 137.8 (C), 145.1 (C), 154.5 (C); HRMS (FAB) *m/z* calcd for $C_{20}H_{28}ONa$, 307.2038; found, 307.2042.

Acknowledgements

The authors thank the Spanish Ministry of Science and Technology (Project CTQ 2006-12697) and the 'Junta de Andalucia' (PAI group FQM-348) for their financial support.

Supplementary data

Copies of ^1H NMR, ^{13}C NMR and DEPT spectra for compounds **1**, **9**, **10**, **12**, **15**–**19**, **23**–**28**, **30** and **31** are included as supplementary data. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.07.088.

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16. The present authors regret making some errors in Ref. 15. The ^{13}C NMR chemical shifts for the aromatic carbons in compound **17** should be δ 116.5 (CH), 120.7 (C), 123.3 (CH), 130.1 (C), 149.1 (C), 150.3 (C). Compounds **8**, **9** and **11** are 13β,14β-disubstituted derivatives.
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