Stereoselective Transformations of (+)-Abietic Acid into (+)-Vitedoin B and (+)-Negundoin A

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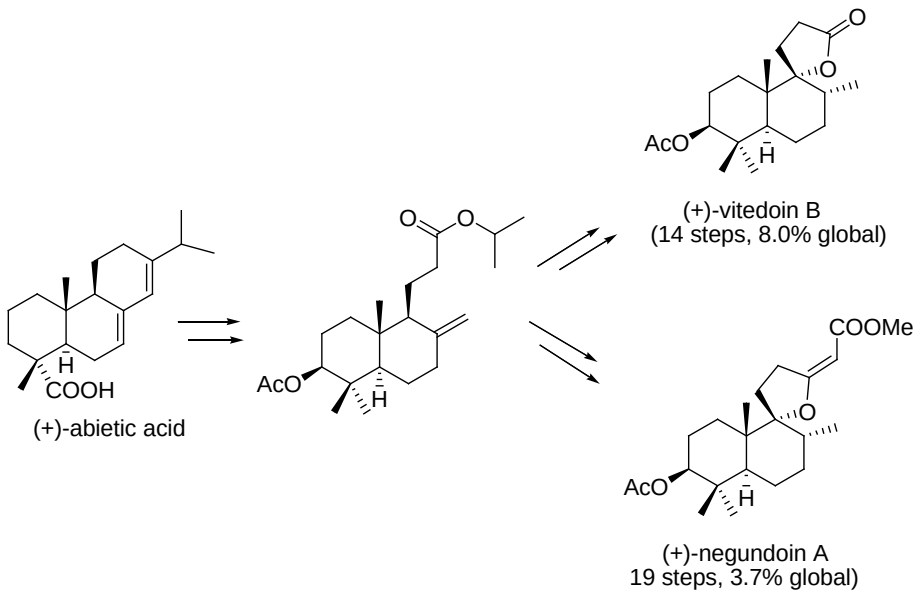


The first synthesis of spiro lactone (+)-vitedoin B (14 steps, 8.0 % global yield) and spiro enol ether (+)-negundoin A (19 steps, 3.7 % global yield), via a *nor*-labdane acetoxy ester, has been achieved starting from commercial (+)-abietic acid.

Introduction

Over recent decades, a large number of terpenoids with a spiro ether or a spiro lactone moiety in their structure have been isolated from diverse natural sources. Among the spiro ethers, spirodihydrobenzofuran derivatives, such as corallidictyal D (**1**),[1] K-76 (**2**),[2] F1839-A (**3**)[3] or stachybotrylactam (**4**),[4] must be highlighted. These compounds and other structurally related to them are characterized by a potent and diverse biological activity. Recently, some trinorlabdane-type spirolactones, such as isoambreinolide (**5**),[5] and vitedoin B (**6**),[6] whose biological activities have not yet been investigated, have been isolated from different vegetal species. A third type of spiro terpenoids includes a series of *nor*-diterpenes, with a characteristic tricyclic structure containing a spiro enol ether group with an α,β–unsaturated aldehyde, acid or ester, which have recently been isolated from different vegetal species widely used in folk medicine in some Asian countries. Representative examples are the antiinflammatory negundoin C (**7**), negundoin B (**8**) and negundoin A (**9**), isolated from *Vitex Negundo*[7] (Figure 1).

So far, only a few syntheses have been reported for some of these spirodihydrobenzofuran derivatives, such as K-76 (**2**) and stachybotrylactam (**4**); in all

cases, the spiroannulation was achieved after treatment of the suitable drimane (bicyclic sesquiterpene) phenol with a protic acid or a cationic resin.[2b, 2c, 8] Our group recently has reported efficient processes of spiro cyclization, mediated by NIS-PPh_3 and I_2-PPh_3, which allow the obtention of spirodihydrobenzofurans, such as aldehyde **1**,[9] spiro lactones, such as compounds **5** and **6**,[10] and spiro enol ethers, such as ester **9**.[11]

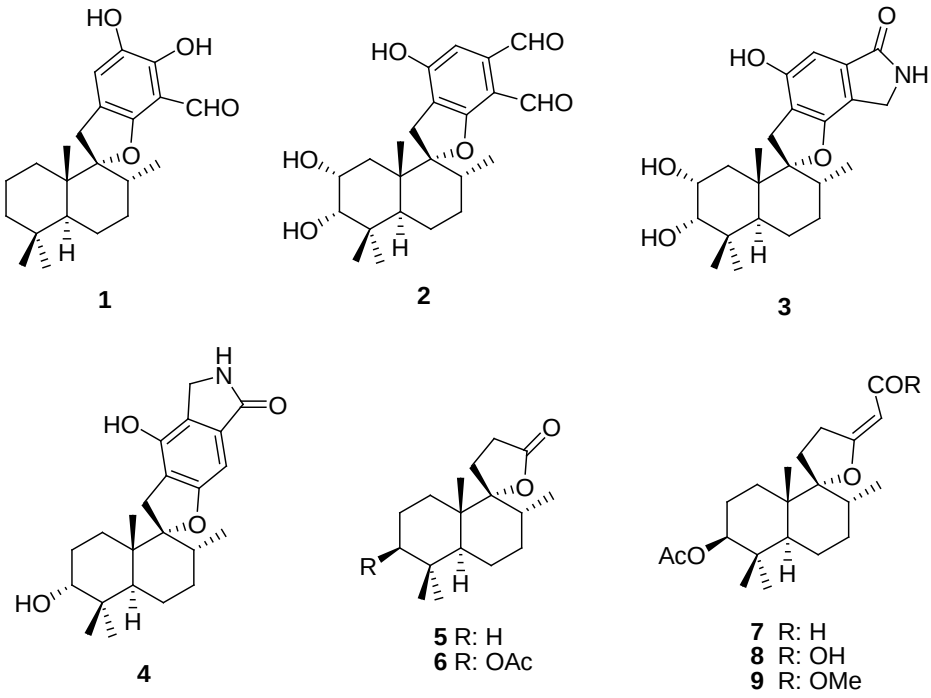


FIGURE 1. Natural spiro ethers and spiro lactones.

The important biological activities of the above mentioned metabolites makes it very interesting to consider developing synthetic routes towards these substances. Having obtained efficient methods to achieve spiroannulation processes, it is now necessary to prepare appropriate A ring functionalized synthetic precursors, which allow us to access to

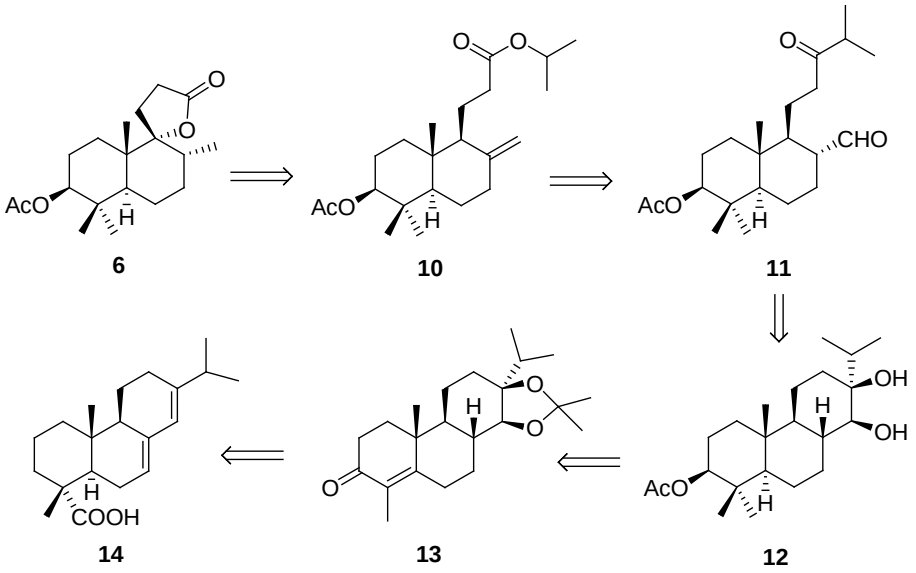
metabolites such as compounds **2-4**, **6-9** and other structurally related, with functionalities in this ring, and which possess potent biological activities.

In this paper we report the use of commercial abietic acid (**14**) to achieve this purpose, and its application to the synthesis of (+)-vitedoin B (**6**) and (+)-negundoin A (**9**).

Results and Discussion

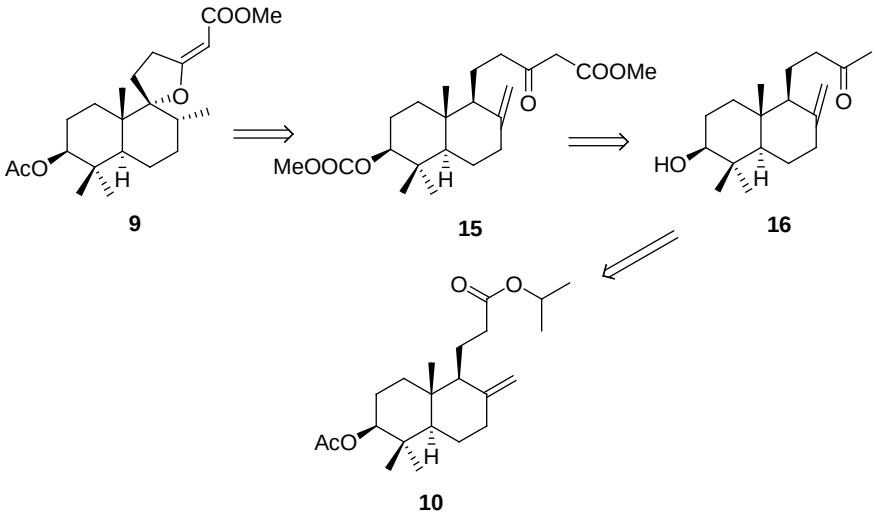
Scheme 1 shows the retrosynthesis of (+)-vitedoin B (**6**) from (+)-abietic acid (**14**). Compound **6** will be obtained directly after the I_2-PPh_3 mediated cyclization of ester **10**. This can be prepared from keto aldehyde **11**, after chemoselective reduction of aldehyde[12] and elimination of the corresponding derivative of the resulting alcohol and the Baeyer-Villiger oxidation of the isopropyl ketone. The diol **12**, the immediate precursor of compound **11**, will be formed after methylation of the enolate resulting from the Birch reduction of unsaturated ketone **13**, and hydrolysis of isopropyliden ketal. Ketone **13** can be obtained from acid **14** after the regioselective syn-dihydroxylation of the C13-C14 double bond,[13] hydrogenation of the C7-C8 double bond, oxidative decarboxylation of acid and allylic oxidation of the resulting alkene.

SCHEME 1. Retrosynthesis of (+)-vitedoin B (**6**).



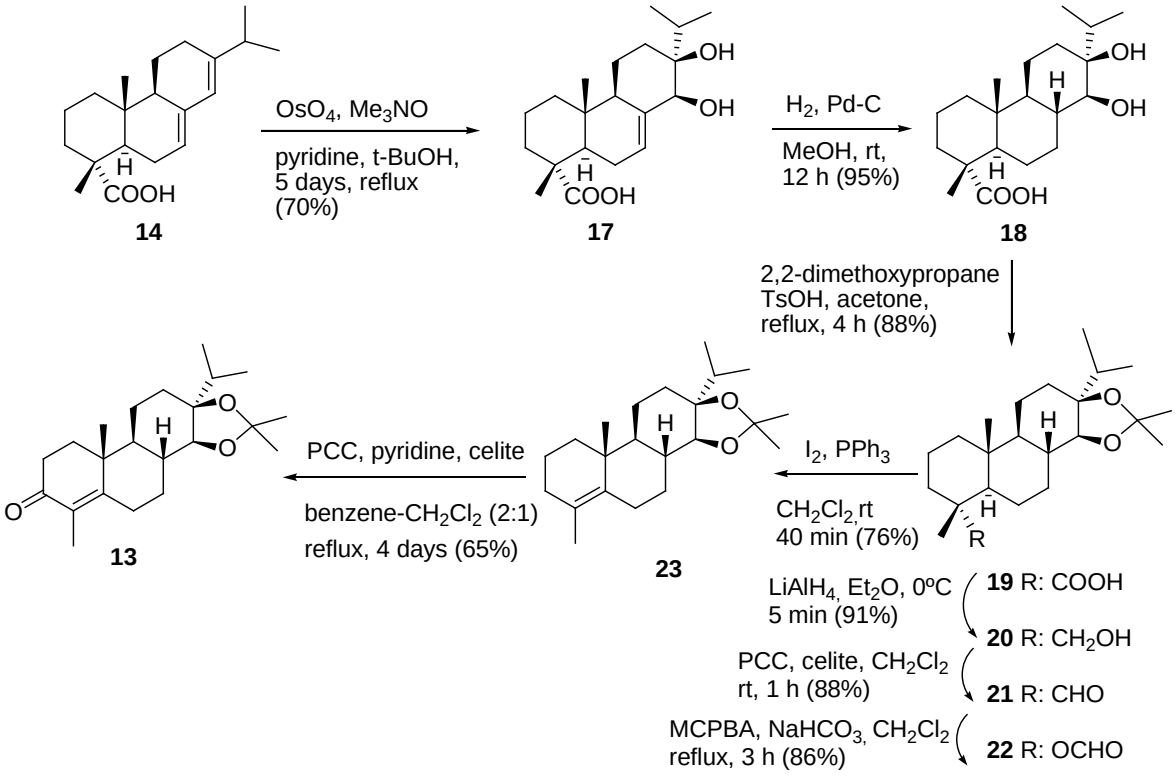
Isopropyl ester **10** is also a suitable precursor for preparing (+)-negundoin B (**9**), as shown in the retrosynthesis depicted in Scheme 2. Hydroxy ketone **16**, which as a racemic mixture has been previously transformed into the spirocompound **9**,[11] is obtained after hydrolysis of diester **10**, and further treatment with methyllithium of the resulting hydroxy acid.

SCHEME 2. Retrosynthesis of (+)-negundoin A (**9**).



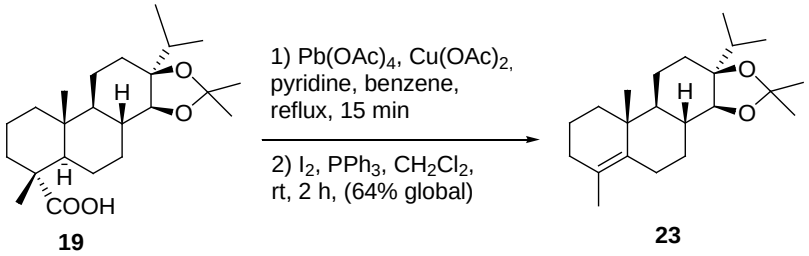
Scheme 3 shows the synthesis of unsaturated ketone **13** from abietic acid (**14**). Compound **14** underwent regioselective dihydroxylation affording diol **17**,[14] when it was treated with OsO_4, Me_3NO and pyridine in t-BuOH under reflux. Hydrogenation of this compound gave dihydroxyacid **18** as the only diastereoisomer; the observed diastereoselectivity, which led to a *trans*-fused tricyclic system, may be the result of an hydroxyl directed heterogeneous hydrogenation.[15] After protecting the diol group, the carboxylic acid was transformed into the aldehyde **21,** which was converted successively into the formate **22** and then into the alkene **23**, utilizing procedures previously developed in our laboratory.[16, 17] Treatment of compound **23** with PCC, pyridine and celite in 2:1 benzene-dichloromethane under reflux led to α,β-enone **13**.

SCHEME 3. Synthesis of ketone **13**.



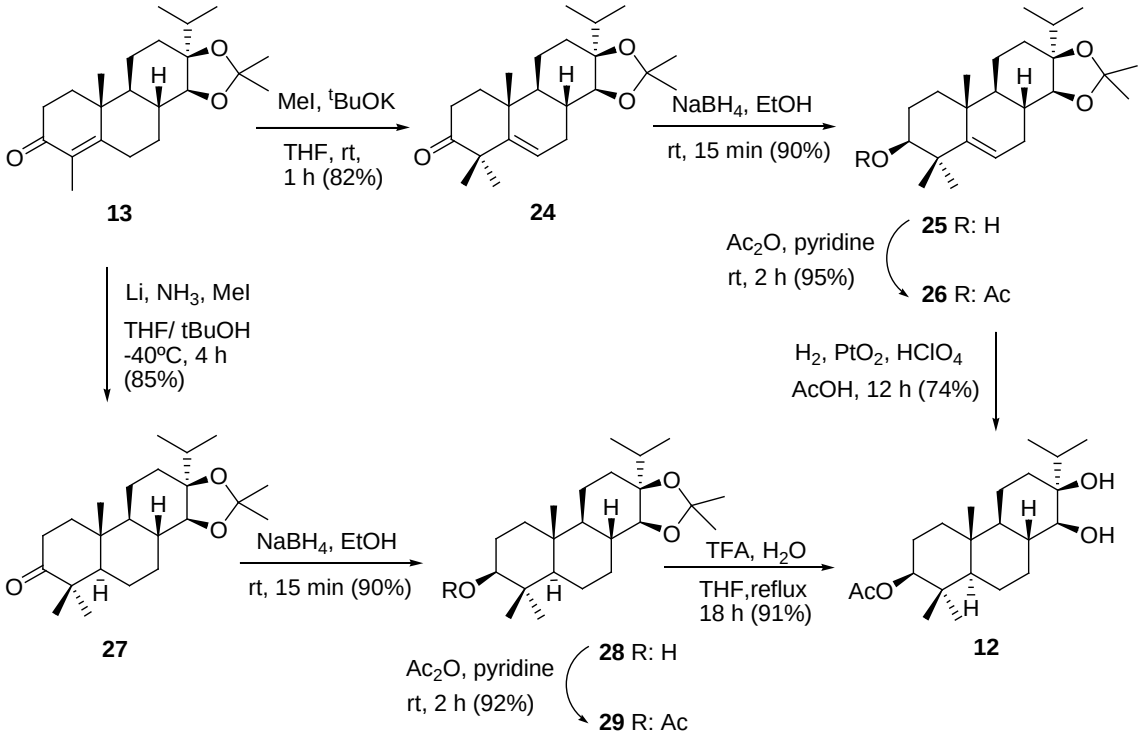
Alkene **23** was obtained in an alternative way from acid **19** (Scheme 4). Treatment of this compound with $Pb(OAc)_4$, $Cu(OAc)_2$ and pyridine in refluxing benzene gave a mixture of alkene regioisomers, which were reacted with I_2 and PPh_3 in dichloromethane affording the most stable tetrasubstituted alkene **23** in 64% global yield.

SCHEME 4. Direct transformation of acid **19** into alkene **23**.



The transformation of unsaturated ketone **13** into diol **12**, which possesses the acetyloxy and gem-dimethyl groups of the target compounds was then addressed. Scheme 5 shows two alternative procedures to achieve this purpose. Unsaturated ketone **24** resulted when ketone **13** was treated with MeI and *t*-BuOK in THF. Reduction of **24** with $NaBH_4$ and further acetylation gave the expected acetate **26**. Hydrogenation of the latter in the presence of PtO_2 and $HClO_4$ gave the simultaneous reduction of the carbon-carbon double bond and ketal deprotection, providing compound **12**.[18]

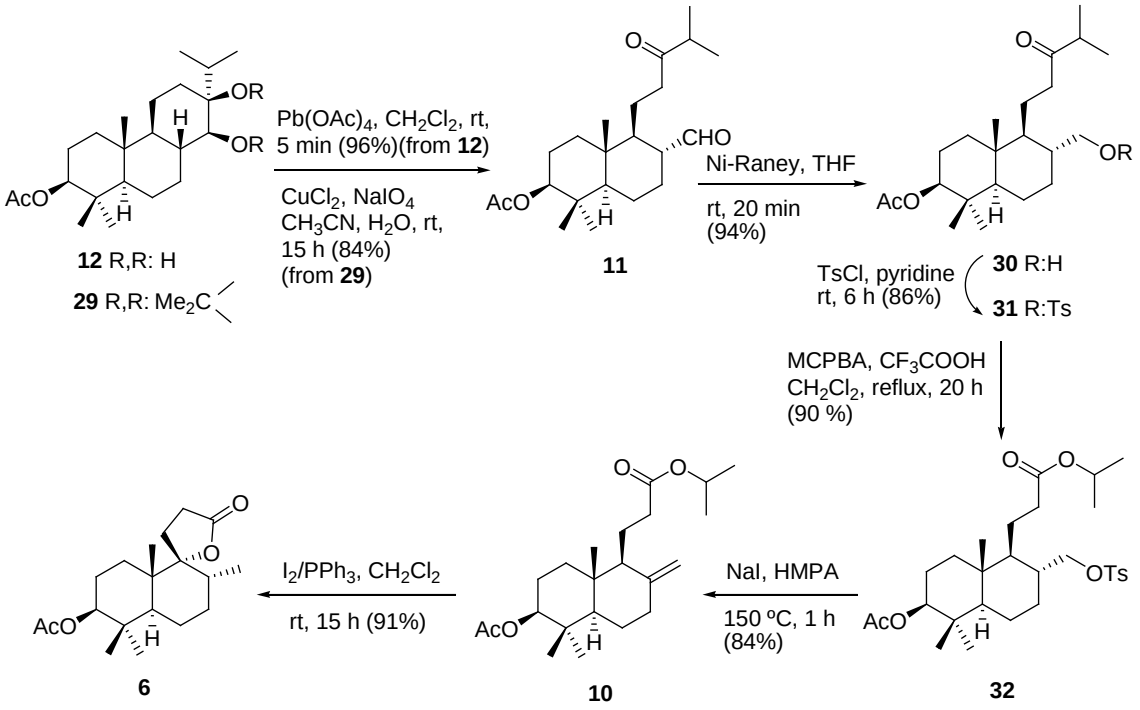
SCHEME 5. Synthesis of diol **12** from enone **13**.



Alternatively, successive treatment of a solution of enone **13** in THF-*t*-BuOH with Li and NH_3, and then with MeI gave ketone **27**. Diol **12** was obtained after reduction of the ketone group, acetylation of the resulting alcohol and ketal deprotection.

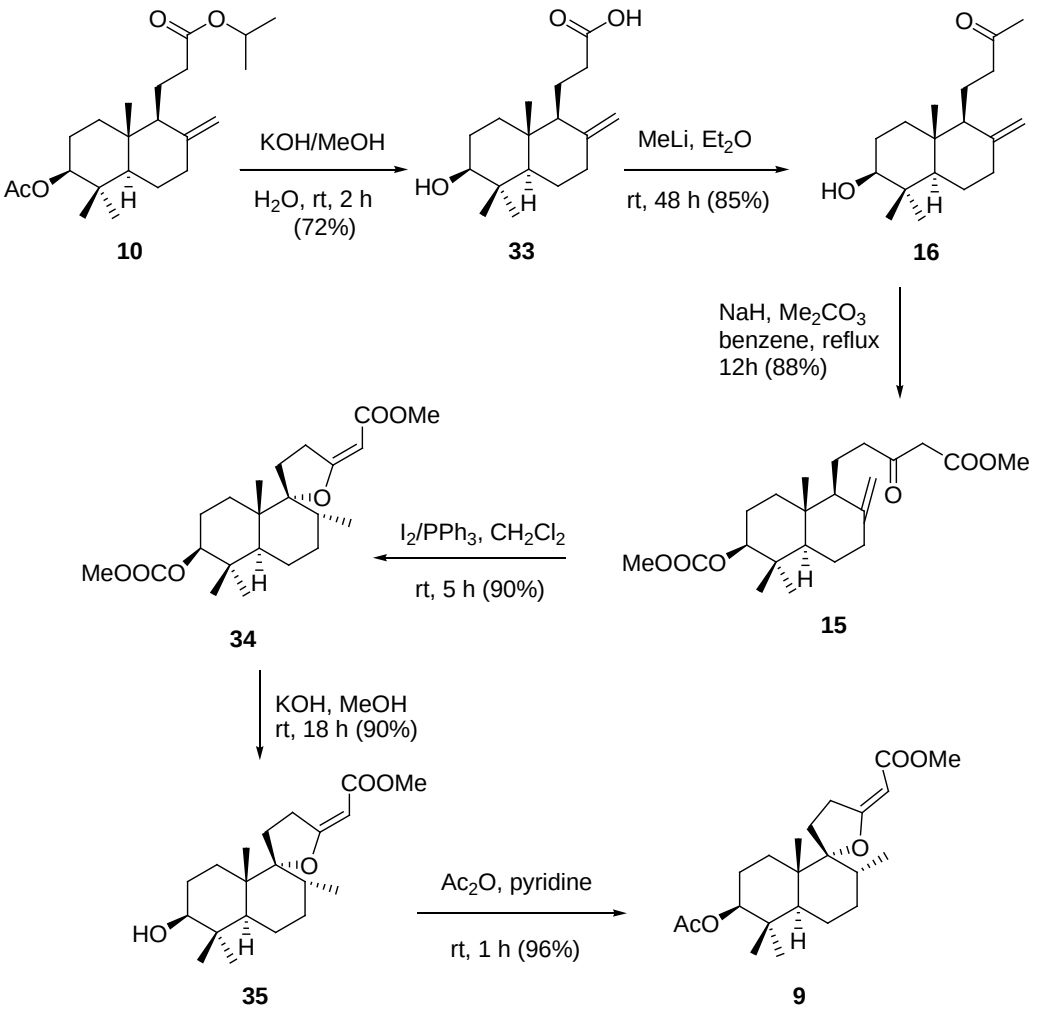
Finally, the transformation of diol **12** into (+)-vitedoin B (**6**) was undertaken (Scheme 6). Treatment of compound **12** with $Pb(OAc)_4$ in dichloromethane at room temperature gave ketoaldehyde **11** in high yield. This compound was also obtained directly from ketal **29**, when it was reacted with $CuCl_2$ and $NaIO_4$ in CH_3CN-H_2O. The ketoaldehyde **11** was chemoselectively reduced after treatment with Raney Ni[12] to the hydroxyketone **30**, which was tosylated and then subjected to Baeyer-Villiger oxidation, affording diester **32**. The latter was heated with NaI in HMPA to give the exocyclic alkene **10**, which was converted into (+)-vitedoin B (**6**) in high yield with complete stereoselectivity, after treatment with I_2-PPh_3. The spectroscopic properties of the latter were identical to those previously described for the natural compound; the optical rotation of synthetic vitedoin B (**6**) ($[\alpha]^{25}_D$: +5.2 ; c 1.0 $CHCl_3$) was similar to that reported for the natural product ($[\alpha]^{25}_D$: +4.7 ; c 0.9 $CHCl_3$).[6]

SCHEME 6. Synthesis of (+)-vitedoin B **(6)**.



The above diester **10** was also transformed into (+)-negundoin A (**9**) (Scheme 7). The treatment of hydroxy acid **33** with MeLi gave hydroxyl ketone **16**, which after methoxycarbonylation was converted into ketoester **15**. This was transformed into the spiro enol ether **34** with complete regio- and stereoselectivity when it was treated with I_2 and PPh_3. Subsequent alkaline hydrolysis of the carbonate group and acetylation of the resulting hydroxyl group finally afforded (+)-negundoin A (**9**). The optical rotation of synthetic negundoin A (**9**) ($[\alpha]^{25}_D$: +12.1; c 3.5 $CHCl_3$) was similar to that reported for the natural product ($[\alpha]^{25}_D$: +8.9; c 0.2 MeOH); the spectroscopic properties were identical to those previously described. [7]

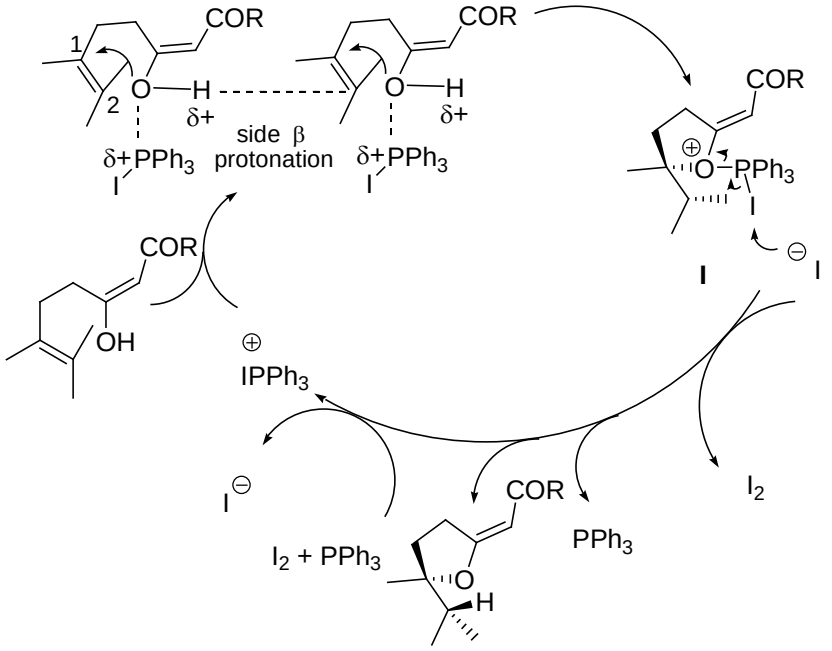
SCHEME 7. Synthesis of (+)-negundoin A **(9)**.



Scheme 8 shows a possible mechanism for the transformation of β-ketoester **15** into spiro compound **34**. The stereoselectivity observed reveals that the cyclization must take place through an *anti* concerted process. In the presence of the I_2-PPh_3 system, the exocyclic carbon-carbon double bond of compound **15** undergoes isomerization to the most stable tetrasubstituted derivative.[19] The enol hydroxyl group, activated by the phosphonium ion $^{+}PPh_3I$, acts simultaneously as a proton donor and a nucleophile. The OH group of a molecule transfers the proton by the β side on the less hindered carbon 2 of the olefinic

bond of the adjacent molecule, which simultaneously undergoes the intramolecular nucleophilic *O*-attack on the carbon 1, leading to intermediate **I**. The proton transference takes place preferably by the β side probably due to the steric hindrance exerted by the ketoester moiety on the α side.

SCHEME 8. A possible mechanism for the transformation of β-ketoester **15** into spiro enol ether **34**.



In summary, the first synthesis of spiro lactone (+)-vitedoin B (**6**) (14 steps, 8.0 % global yield) and spiro enol ether (+)-negundoin A (**9**) (19 steps, 3.7 % global yield), via acetoxy ester **10**, from commercial (+)-abietic acid (**14**) has been achieved. These results corroborate the absolute stereochemistry of these natural spiro terpenoids.

Experimental Section

(+)-Vitedoin B (6).

To a solution of triphenylphosphine (105 mg, 0.4 mmol) in dry CH_2Cl_2 (4 ml) was added iodine (51 mg, 0.4 mmol).The mixture was stirred at room temperature for 5 min and a solution of **10** (146 mg, 0.4 mmol) in dry CH_2Cl_2 (4 mL) was added. The resulting mixture was stirred at room temperature for 15 h, after which TLC showed no starting material. The solvent was removed under vacuum and the crude product was diluted with Et_2O – water (90 – 30 mL) and the phases were shaken and separated. The organic phase was washed with water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (20% ether/hexanes) to give **6** (117 mg, 91%).

Colourless solid, mp 94-95 ºC (hexane-EtOAc); $[\alpha]_D^{25}$ = + 5.2 (c = 1.0, $CHCl_3$) [lit.[7]: $[\alpha]_D^{29}$ = + 4.7 (c = 0.9, $CHCl_3$)]. ^{1}H NMR ($CDCl_3$, 500 MHz) □δ:□□ 0.85 (d, *J* = 6.6 Hz, 3H), 0.87 (s, 3H), 0.88 (s, 3H), 0.95 (s, 3H), 1.25 (br s, 2H), 1.40 - 1.47 (m, 2H), 1.50 - 1.66 (m, 5H), 1.70 - 1.84 (m, 1H), 1.86 (ddd, *J* = 13.7, 11.6, 5.0 Hz, 1H), 2.04 (s, 3H), 2.18 (ddd, *J* = 13.4, 11.8, 8.1 Hz, 1H), 2.46 (ddd, *J* = 18.7, 11.7, 5.0 Hz, 1H), 2.54 (ddd, *J* = 18.7, 11.3, 8.0 Hz, 1H), 4.48 (dd, *J* = 11.5, 4.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ:□□ 15.4 (CH_3), 15.8 (CH_3), 16.6 (CH_3), 20.9 (CH_2), 21.3 (CH_3), 23.2 (CH_2), 24.9 (CH_2), 27.8 (CH_3), 29.36 (CH_2), 29.44 (CH_2), 30.7 (CH_2), 36.7 (CH), 37.7 (C), 41.8 (C), 46.1 (CH), 80.0 (CH), 93.3 (C), 170.7 (C), 177.3 (C). IR (film) $\nu_{máx}$: 1767, 1733, 1462, 1366, 1242, 1199, 1177, 1111, 1281, 1091, 1032, 972, 954, 668 cm^{-1}. HRMS (APcI) *m/z*: calcd for $C_{19}H_{31}O_4$ ($M+H^+$) 323.2222, found: 323.2214.

(+)-Negundoin A (9).

To a solution of **35** (140 mg, 0.42 mmol) in CH_2Cl_2 (4 mL) at 0 ºC were added pyridine (0.6 mL) and acetic anhydride (0.3 mL), and the reaction mixture was stirred at room temperature for 1 h, at which time TLC showed no starting material. Then, the reaction mixture was cooled at 0 ºC, water (0.6 mL) was added to quench the reaction and the mixture was stirred for an additional 5 min. Then, it was diluted with ether (25 mL) and washed with water (3 x 5 mL), 2N HCl (3 x 6 mL), again water (3 x 5 mL), sat. aq. $NaHCO_3$ (6 mL) and brine, and the organic phase was dried over Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was purified by flash chromatography on silica gel (15 % ether/hexanes) to yield **9** (152 mg, 96%) as a colourless syrup.

$[\alpha]_D^{25}$= +12.1 (c = 3.5 $CHCl_3$). [lit.[9]: $[\alpha]_D^{29}$ = + 8.9 (c = 0.2, MeOH)]. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.77 (d, *J* = 6.6 Hz, 3H), 0.86 (s, 3H), 0.89 (s, 3H), 0.95 (s, 3H), 1.34 - 1.44 (m, 4H), 1.54 - 1.73 (m, 5H), 1.75 - 1.83 (m, 2H), 2.04 (s, 3H), 2.05 – 2.09 (m, 1H), 2.95 – 3.15 (m, 2H), 3.65 (s, 3H), 4.47 (dd, *J* = 11.7, 4.5 Hz, 1H), 5.29 (t, *J* = 1.8 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 15.5 (CH_3), 16.6 (CH_3), 16.8 (CH_3), 20.9 (CH_2), 21.3 (CH_3), 23.3 (CH_2), 26.7 (CH_2), 28.0 (CH_3), 29.3 (CH_2), 31.0 (CH_2), 31.6 (CH_2), 36.5 (CH), 37.7 (C), 42.0 (C), 46.2 (CH), 50.5 (CH_3), 80.2 (CH), 87.3 (CH), 97.7 (C), 169.5 (C), 170.8 (C), 178.5 (C). IR (film): 1735, 1707, 1633, 1365, 1244, 1127, 1033, 794, 755 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{22}H_{34}O_5Na$ ($M+Na^+$) 401.2304, found: 401.2313.

Isopropyl-3-((1S,4aR,6S,8aR)-6-acetoxy-5,5,8a-trimethyl-2-methylene-decahydronaphthalen-1-yl)propanoate (10).

To a solution of **32** (367 mg, 0.68 mmol) in HMPA (5 mL) was added NaI (123 mg, 0.82 mmol) and the reaction mixture was stirred at 150 ºC for 1 h, at which time TLC showed no starting material. Then, ether (40 mL) was added and the organic phase was washed with brine (8 x 15 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (10 % ether/hexanes) to yield **10** (209 mg, 84%) as a colorless syrup.

$[\alpha]_D^{25}$= +22.0 (c = 7.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.71 (s, 3H), 0.84 (s, 3H), 0.86 (s, 3H), 1.13 - 1.45 (m, 3H), 1.22 (d, *J* = 6.2 Hz, 3H), 1.22 (d, *J* = 6.2 Hz, 3H), 1.52 - 1.68 (m, 2H), 1.68 - 1.77 (m, 2H), 1.77 - 1.89 (m, 2H), 1.90 – 2.00 (m, 1H), 2.04 (s, 3H), 2.02-2.15 (m, 2H), 2.35 - 2.45 (m, 2H), 4.51 (s, 1H), 4.52 – 4.54 (m, 1H), 4.86 (s, 1H), 4.99 (h, *J* = 6.2 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.4 (CH_3), 16.5 (CH_3), 19.2 (CH_2), 21.3 (CH_3), 21.87 (CH_3), 21.91 (CH_3), 23.8 (CH_2), 24.3 (CH_2), 28.2 (CH_3), 33.4 (CH_2), 36.6 (CH_2), 37.9 (CH_2), 38.0 (C), 39.2 (C), 54.7 (CH), 55.8 (CH), 67.4 (CH), 80.6 (CH), 107.0 (CH_2), 147.2 (C), 170.9 (C), 173.5 (C). IR (film): 1732, 1372, 1243, 1109, 1029, 773, 669 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{22}H_{36}O_4Na$ ($M+Na^+$) 387.2511, found: 387.2509.

(2S,4aR,5S,8aR)-6-formyl-1,1,4a-trimethyl-5-(4-methyl-3-oxopentyl)-decahydronaphthalen-2-yl acetate (11).

Lead (IV) acetate (598 mg, 1.35 mmol) was added to a solution of **12** (415 mg, 1.13 mmol) in dry CH_2Cl_2 (15 mL) and the mixture was stirred at room temperature for 5 min, at which

time TLC showed no **12**. The reaction was filtered through a silica gel pad and washed with ether (30 mL). The organic phase was then washed with 5% aq. $NaHSO_3$ (10 mL), sat. aq. $NaHCO_3$ (3 x 10 mL) and brine, and dried over Na_2SO_4. Removal of the solvent in vacuum gave a crude product which was directly purified by flash chromatography on silica gel (15 % ether/hexanes) to yield **11** (396 mg, 96%) as a colorless oil.

$[\alpha]_D^{25}$= +7.9 (c = 33.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.80 - 0.98 (m, 3H), 0.85 (s, 6H), 0.86 (s, 3H), 1.00 - 1.07 (m, 2H), 1.04 (d, *J* = 6.9 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 1.10 - 1.47 (m, 3H), 1.60 (ddd, *J* = 25.1, 13.2, 3.5 Hz, 1H), 1.62 - 1.87 (m, 3H), 2.03 (s, 3H), 2.25 - 2.39 (m, 2H), 2.45 - 2.57 (m, 2H), 4.47 (dd, *J* = 11.8, 4.5 Hz, 1H), 9.54 (d, *J* = 4.0 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.0 (CH_3), 16.5 (CH_3), 18.1 (CH_3), 18.2 (CH_3), 19.8 (CH_2), 21.2 (CH_3), 22.9 (CH_2), 23.5 (CH_2), 26.8 (CH_2), 28.1 (CH_3), 36.4 (CH_2), 37.6 (C), 37.7 (C), 40.7 (CH), 41.0 (CH_2), 50.0 (CH), 53.5 (CH), 53.8 (CH), 80.4 (CH), 170.8 (C), 204.8 (CH), 213.8 (C). IR (film): 1731, 1711, 1465, 1369, 1246, 1032, 751 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{22}H_{36}O_4Na$ ($M+Na^+$) 387.2511, found: 387.2508.

Synthesis of 11 from 29.

$CuCl_2$ (62 mg, 0.46 mmol) and $NaIO_4$ (98mg, 0.46 mmol), dissolved in water, were added to a solution of **29 (**150mg, 0.37 mmol**)** in acetonitrile (10 mL) and the mixture was stirred at room temperature for 15 h, at which time TLC showed no **29**. Then, the solvent was removed under vacuum and ether – water (40 : 10 mL) was added. The phases were shaken, separated and the organic phase was washed with brine (3 x 10 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (10 % ether/hexanes) to yield **11** (112 mg, 84%) as a colorless syrup.

(2S,4aR,4bS,7S,8S,10aR)-7,8-dihydroxy-7-isopropyl-1,1,4a-trimethyl-tetradecahydrophenanthren-2-yl acetate (12).

PtO_2 (80 mg, 0.35 mmol) and $HClO_4$ (1.5 mL, 22.9 mmol) were added to a solution of **26** (650 mg, 1.61 mmol) in dry AcOH (8 mL), and the mixture was stirred at room temperature for 12 h, under an hydrogen atmosphere (3 atm). Then, it was filtered through a silicagel pad and washed with ether (60 mL). The filtrate was washed with water (5 x 15 mL), aq. $NaHCO_3$ (5 x 15 mL) and (3 x 10 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (25 % ether/hexanes) to yield **12** (418 mg, 74%) as a colorless syrup.

$[\alpha]_D^{25}$= - 15.5 (c = 14.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.66 (ddd, *J* = 11.7, 11.7, 3.4 Hz, 1H), 0.76 - 1.04 (m, 2H), 0.86 (s, 3H), 0.87 (s, 3H), 0.87 (d, *J* = 6.9 Hz, 3H) 0.88 (s, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 1.10 (ddd, *J* = 13.6, 13.6, 4.0 Hz, 1H), 1.17 (ddd, *J* = 13.4, 4.1 Hz, 1H), 1.24 - 1.47 (m, 3H), 1.48 - 1.72 (m, 7H), 1.75 (ddd, *J* = 13.2, 3.5, 3.5 Hz, 1H), 2.04 (s, 3H), 2.05 – 2.10 (m, 1H), 2.22 (ddd, *J* = 12.7, 7.0, 3.7 Hz, 1H), 3.16 (d, *J* = 9.6 Hz, 1H), 4.48 (dd, *J* = 11.7, 4.6 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.3 (CH_3), 16.3 (CH_3), 16.7 (CH_3), 17.7 (CH_3), 18.8 (CH_2), 20.9 (CH_2), 21.3 (CH_3), 23.9 (CH_2), 27.1 (CH_2), 28.2 (CH_3), 31.4 (CH_2), 33.5 (CH), 36.4 (C), 37.0 (CH_2), 37.8 (C), 38.6 (CH), 53.1 (CH), 54.3 (CH), 75.0 (CH), 77.1 (C), 81.0 (CH), 171.0 (C). IR (film): 3475, 1731, 1457, 1368, 1247, 1031, 977 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{22}H_{38}O_4Na$ ($M+Na^+$) 389.2668, found: 389.2670.

Synthesis of 12 from 29.

To a solution of **29** (127 mg, 0.31 mmol) in THF (8 mL) were added trifluoroacetic acid (1 mL, 13.5 mmol) and water (1 mL) and the reaction mixture was stirred under reflux for 18 h, at which time TLC showed no starting material. Then, the solvent was removed under vacuum and ether – water (40 : 10 mL) was added. The phases were shaken, separated and the organic phase was washed with brine (3 x 10 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (20 % ether/hexanes) to yield **12** (104 mg, 91%) as a colorless syrup.

(3aS,9aR,9bS,11aS)-11a-isopropyl-2,2,6,9a-tetramethyl-4,5,9,9a,9b,10,11,11a-octahydrophenanthro[2,1-d][1,3]dioxol-7(3aH,3bH,8H)-one (13).

Pyridinium chlorochromate (PCC) (1.55 g, 7.20 mmol), pyridine (0.62 g, 7.80 mmol) and celite (1 g) were added to a stirred solution of **23** (0.4 g, 1.20 mmol) in benzene – CH_2Cl_2 (30 – 15 mL) and the mixture was kept stirring at reflux under argon atmosphere for 4 days, at which time TLC showed no remaining starting material. Following the same work-up used to prepare **21**, a crude product, was obtained which by chromatography on silica gel (30% ether/hexanes) gave **13** (270 mg, 65%) as a colorless syrup.

$[\alpha]_D^{25}$= +5.6 (c = 7.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.85 – 0.87 (m, 1H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 1.07 – 1.09 (m, 1H), 1.13 (s, 3H), 1.33 – 1.35 (m, 1H), 1.46 (s, 3H), 1.52 – 1. 54 (m, 2H), 1.53 (s, 3H), 1.68 (ddd, *J* = 13.1, 13.1, 5.5 Hz, 1H), 1.78 (s, 3H), 1.79 - 1.93 (m, 2H), 1.97 - 2.06 (m, 2H), 2.12 (ddd, *J* = 14.3, 14.3, 4.3 Hz,

1H), 2.27 (ddd, *J* = 12.8, 7.0, 2.8 Hz, 1H), 2.35 - 2.47 (m, 2H), 2.77 (ddd, *J* = 14.7, 3.3, 3.3 Hz, 1H), 3.59 (d, *J* = 8.2 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 11.1 (CH_3), 15.7 (CH_3), 17.9 (CH_3), 19.2 (CH_3), 20.1 (CH_2), 25.7 (CH_2), 27.4 (CH_2), 29.6 (CH_3), 30.3 (CH_3), 32.0 (CH_2), 33.6 (CH_2), 33.7 (CH), 34.7 (CH_2), 39.0 (C), 40.4 (CH), 48.8 (CH), 84.1 (CH), 85.4 (C), 108.5 (C), 128.4 (C), 162.4 (C), 198.7 (C). IR (film): 1669, 1376, 1366, 1237, 1214, 1039, 772, 668 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{22}H_{34}O_3Na$ ($M+Na^+$) 369.2406, found: 369.2411.

Methyl 5-((1S,4aR,6S,8aR)-6-(methoxycarbonyloxy)-5,5,8a-trimethyl-2-methylene-decahydronaphthalen-1-yl)-3-oxopentanoate (15).

NaH (60%, 130 mg, 3.2 mmol) and dimethyl carbonate (1.2 mg, 13 mmol) were added to a stirred solution of **16** (186 mg, 0.65 mmol) in benzene (17 mL) and the mixture was kept stirring at reflux under argon atmosphere overnight, at which time TLC showed no remaining starting material. Then, water (2 ml) was slowly added at 0 °C and ether –water (50 : 20 mL) was added, and the phases were shaken and separated. The organic phase was washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (15% ether/hexanes) to give pure **15** (218 mg, 88 %) as a colourless syrup.

$[\alpha]_D^{25}$= + 33.7 (c = 8.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.71 (s, 3H), 0.85 (s, 3H), 0.93 (s, 3H), 1.13 - 1.46 (m, 3H), 1.51 – 1.75 (m, 3H), 1.80 - 2.02 (m, 4H), 2.36 - 2.48 (m, 2H), 2.64 - 2.80 (m, 2H), 3.41 (s, 2H), 3.73 (s, 3H), 3.77 (s, 3H), 4.36 (dd, *J* = 12.0, 4.2 Hz, 1H), 4.45 (brs, 1H), 4.85 (brs, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.3 (CH_3), 16.4 (CH_3),

17.4 (CH_2), 23.7 (CH_2), 24.2 (CH_2), 28.1 (CH_3), 36.5 (CH_2), 37.9 (CH_2), 38.2 (C), 39.3 (C), 42.0 (CH_2), 49.1 (CH_2), 52.3 (CH_3), 54.5 (CH_3), 54.6 (CH), 55.5 (CH), 85.1 (CH), 107.0 (CH_2), 147.2 (C), 155.7 (C), 167.6 (C), 202.8 (C). IR (film): 1745, 1718, 1442, 1271, 974, 793 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{22}H_{34}O_6Na$ ($M+Na^+$) 417.2253, found: 417.2244.

4-((1S,4aR,6S,8aR)-6-hydroxy-5,5,8a-trimethyl-2-methylene-decahydronaphthalen-1-yl)butan-2-one (16).

To a solution of **33** (100 mg, 0.36 mmol) in dry Et_2O (10 mL) was added MeLi in dimethoxymethane (3.0M, 0.5mL, 1.5 mmol) and the reaction mixture was stirred at room temperature for 48 h, at which time TLC showed no starting material. Then water (0.5 mL) was slowly added at 0 °C, later Et_2O –water (30 : 15 mL) was added and the phases were shaken and separated. The organic phase was washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (20% ether/hexanes) to give pure **16** (84 mg, 85%) as a colorless syrup.

$[\alpha]_D^{25}$= +5.0 (c = 3.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.69 (s, 3H), 0.77 (s, 3H), 0.99 (s, 3H), 1.08 (dd, *J* = 12.5, 2.8 Hz, 1H), 1.15 - 1.34 (m, 3H), 1.39 (ddd, *J* = 25.9, 13.0, 4.4 Hz, 1H), 1.53 - 1.77 (m, 3H), 1.77 - 1.88 (m, 2H), 1.95 (ddd, *J* = 12.9, 12.9, 4.2 Hz, 1H), 2.10 (s, 3H), 2.28 – 2.32 (m, 1H), 2.40 (ddd, *J* = 12.8, 4.2, 2.4 Hz, 1H), 2.56 – 2.60 (m, 1H), 3.24 – 3.26 (m, 1H), 4.45 (s, 1H), 4.84 (s, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.3 (CH_3), 15.4 (CH_3), 17.5 (CH_2), 24.0 (CH_2), 27.9 (CH_2), 28.3 (CH_3), 30.1 (CH_3), 36.9 (CH_2), 38.1 (CH_2), 39.1 (C), 39.5 (C), 42.7 (CH_2), 54.6 (CH), 55.9 (CH), 78.8 (CH), 106.7

(CH_2), 147.7 (C), 209.2 (C). IR (film): 3422, 1712, 1456, 1363, 1163, 889, 670 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{18}H_{30}O_2Na$ ($M+Na^+$) 301.2143, found: 301.2139.

(1R,4aR,4bS,7S,8S,8aS,10aR)-7,8-dihydroxy-7-isopropyl-1,4a-dimethyl-tetradecahydrophenanthrene-1-carboxylic acid (18).

To a solution of **17** (10 g, 29.72 mmol) in dry AcOH (100 mL) was added 10% Pd/C (1 g) and the mixture was stirred at room temperature under hydrogen atmosphere (3 atm) for 12 h. Then, the mixture was filtered through a silica gel pad and washed with ether (150 mL). The filtrate was washed with water (5 x 30 mL), aq. 5% $NaHCO_3$ (5 x 30 mL) and brine. The solvent was evaporated to yield **18** (9.56 g, 95 %) as a white solid.

Mp: 148 ºC. $[\alpha]_D^{25}$ = - 9.8 (c = 17.9, MeOH). ^{1}H RMN (CD_3COCD_3, 500 MHz) δ: 0.76 – 0.78 (m, 1H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 3H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.93 - 1.04 (m, 2H), 1.16 (s, 3H), 1.16 – 1.18 (m, 1H), 1.22 - 1.30 (m, 2H), 1.35 - 1.44 (m, 2H), 1.48 - 1.69 (m, 4H), 1.70 - 1.83 (m, 4H), 2.05 – 2.09 (m, 1H), 2.22 – 2.24 (m, 1H), 2.84 (br s, 2H), 3.13 (d, *J* = 9.6 Hz, 1H). ^{13}C RMN (CD_3COCD_3, 125 MHz) δ: 15.1 (CH_3), 16.9 (CH_3), 17.4 (CH_3), 18.2 (CH_3), 19.0 (CH_2), 19.6 (CH_2), 24.9 (CH_2), 27.8 (CH_2), 32.3 (CH_2), 34.3 (CH), 37.0 (C), 37.9 (CH_2), 39.4 (CH_2), 39.8 (CH), 47.8 (C), 52.6 (CH), 54.9 (CH), 75.3 (C), 77.4 (CH), 180.1 (C). IR (KBr): 3389, 1695, 1455, 1386, 1261, 692 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{20}H_{34}O_4Na$ ($M+Na^+$) 361.2355, found: 361.2362.

(3aS,3bS,5aR,6R,9aR,9bS,11aS)-11a-isopropyl-2,2,6,9a-tetramethyl-tetradecahydrophenanthro[2,1-d][1,3]dioxole-6-carboxylic acid (19).

To a solution of **18** (3.85 g, 11.37 mmol) in dry acetone (40 mL) were added 2,2-dimethoxypropane (2.54 g, 24.4 mmol) and *p*-toluenesulphonic acid (95 mg, 0.5 mmol) and the reaction mixture was stirred under reflux for 4 h, at which time TLC showed no starting material. Then, the solvent was removed under vacuum and ether – water (90 : 20 mL) was added. The phases were shaken, separated and the organic phase was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (20 % ether/hexanes) to yield **19** (3.79 g, 88%) as a colorless syrup.

$[\alpha]_D^{25}$ = + 34.1 (c = 10.6, $CHCl_3$). ^{1}H RMN ($CDCl_3$, 500 MHz) δ: 0.69 (ddd, *J* = 12.3, 12.3, 3.5 Hz, 1H), 0.87 (s, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.96 - 1.11 (m, 2H), 0.94 (d, *J* = 6.9 Hz, 3H), 1.17 (s, 3H), 1.18 - 1.31 (m, 2H), 1.39 - 1.54 (m, 2H), 1.43 (s, 3H), 1.47 (s, 3H), 1.54 - 1.66 (m, 5H), 1.67-1.84 (m, 4H), 1.98 (h, *J* = 6.8 Hz, 1H), 2.12 – 2.16 (m, 1H), 3.56 (d, *J* = 8.2 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.1 (CH_3), 15.8 (CH_3), 16.5 (CH_3), 17.9 (CH_2), 19.2 (CH_3), 19.3 (CH_2), 24.1 (CH_2), 25.7 (CH_2), 29.5 (CH_3), 30.1 (CH_3), 33.1 (CH_2), 33.7 (CH), 36.3 (C), 37.1 (CH_2), 38.1 (CH_2), 40.3 (CH), 47.2 (C), 48.9 (CH), 51.2 (CH), 85.0 (CH), 85.6 (C), 108.3 (C), 184.8 (C). IR (film): 1695, 1368, 1236, 1215, 1038, 757 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{23}H_{38}O_4Na$ ($M+Na^+$) 401.2668, found: 401.2676.

((3aS,5aR,6R,9aR,9bS,11aS)-11a-isopropyl-2,2,6,9a-tetramethyl-tetradecahydrophenanthro[2,1-d][1,3]dioxol-6-yl)methanol (20).

$LiAlH_4$ (0.53 g, 14.04 mmol) was added at 0 °C to a stirred solution of **19** (4.43 g, 11.70 mmol) in dry diethyl ether (60 mL) and the mixture was stirred at room temperature under an argon atmosphere for 5 min, at which time TLC showed no compound **19**. Then, acetone (0.5 mL) was slowly added at 0 °C and Et_2O –water (50 : 15 mL) was added, and the phases were shaken and separated. The organic phase was washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (20% ether/hexanes) to give pure **20** (3.74 g, 91%) as a colorless syrup.

$[\alpha]_D^{25}$ = -18.6 (c = 10.8, $CHCl_3$). ^{1}H RMN ($CDCl_3$, 500 MHz) δ: 0.64 (ddd, *J* = 12.4, 12.4, 3.5 Hz, 1H), 0.77 (s, 3H), 0.80 - 1.07 (m, 2H), 0.87 (s, 3H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 1.10 - 1.35 (m, 4H), 1.36 - 1.67 (m, 7H) 1.43 (s, 3H), 1.48 (s, 3H), 1.74 (br d, *J* = 13.0 Hz, 1H), 1.78 – 1.82 (m, 1H), 1.98 (h, *J* = 6.9 Hz, 1H), 2.16 – 2.18 (m, 1H), 3.09 (d, *J* = 10.8 Hz, 1H), 3.41 (d, *J* = 10.8 Hz, 1H), 3.54 (d, *J* = 8.3 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.4 (CH_3), 15.8 (CH_3), 17.8 (CH_3), 18.1 (CH_2), 19.2 (CH_3), 19.5 (CH_2), 21.1 (CH_2), 25.9 (CH_2), 29.5 (CH_3), 30.2 (CH_3), 33.3 (CH_2), 33.7 (CH), 35.4 (CH_2), 36.7 (C), 37.6 (C), 38.7 (CH_2), 40.1 (CH), 47.6 (CH), 51.0 (CH), 71.9 (CH_2), 85.2 (CH), 85.5 (C), 108.2 (C). IR (film): 3453, 1716, 1457, 1381, 1239, 1038, 771 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{23}H_{40}O_3Na$ ($M+Na^+$) 387.2875, found: 387.2869.

(3aS,5aR,6R,9aR,9bS,11aS)-11a-isopropyl-2,2,6,9a-tetramethyl-tetradecahydrophenanthro[2,1-d][1,3]dioxole-6-carbaldehyde (21).

Pyridinium chlorochromate (PCC) (5 g, 13.29 mmol) and celite (4 g) was added to a stirred solution of **20** (3.71 g, 10.18 mmol) in dry CH_2Cl_2 (70 mL) and the mixture was stirred at room temperature under an argon atmosphere for 1 h, at which time TLC showed no remaining starting material. Then, the reaction was worked up by the addition of ether (40 mL) and the resulting mixture was filtered through a silica gel pad and washed with ether (60 mL). The filtrate was washed with 2N HCl (3 x 30 mL) and brine. The solvent was evaporated to yield a crude product, which was chromatographed on silica gel (10% ether/hexanes) to yield **21** (3.02 g, 88%) as a colorless syrup.

$[\alpha]_D^{25}$ = -34.5 (c = 51.6, $CHCl_3$). ^{1}H RMN ($CDCl_3$, 500 MHz) δ: 0.68 (ddd, *J* = 11.6, 11.6, 6.0 Hz, 1H), 0.80 - 1.14 (m, 2H), 0.88 (s, 3H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 1.06 (s, 3H), 1.17 - 1.28 (m, 2H), 1.33 - 1.54 (m, 6H), 1.42 (s, 3H), 1.46 (s, 3H), 1.55 - 1.68 (m, 3H), 1.76 - 1.86 (m, 2H), 1.98 (h, *J* = 6.9 Hz, 1H), 2.10 - 2.14 (m, 1H), 3.55 (d, *J* = 8.3 Hz, 1H), 9.20 (s, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.2 (CH_3), 14.4 (CH_3), 15.8 (CH_3), 17.1 (CH_2), 19.2 (CH_3), 19.4 (CH_2), 23.9 (CH_2), 25.7 (CH_2), 29.5 (CH_3), 30.2 (CH_3), 32.4 (CH_2), 32.9 (CH_2), 33.7 (CH), 35.8 (C), 38.1 (CH_2), 40.3 (CH), 46.8 (CH), 49.6 (C), 50.9 (CH), 84.9 (CH), 85.5 (C), 108.3 (C), 206.5 (CH). IR (film): 1727, 1455, 1235, 1216, 1040, 864, 758 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{23}H_{38}O_3Na$ ($M+Na^+$) 385.2719, found: 385.2723.

(3aS,5aR,6R,9aR,9bS,11aS)-11a-isopropyl-2,2,6,9a-tetramethyl-tetradecahydrophenanthro[2,1-d][1,3]dioxol-6-yl formate (22).

m-Chloroperoxybenzoic acid (MCPBA, 70%; 7.38 g, 29.94 mmol), and $NaHCO_3$ (2.51 g, 29.94 mmol) were added to a stirred solution of **21** (3.62 g, 9.98 mmol) in CH_2Cl_2 (300 mL) and the reaction was stirred under reflux for 3 h, at which time TLC indicated no starting material remaining. The reaction was quenched with sat. aq. Na_2SO_3 (30 mL) and stirred for an additional 15 min. Then, the organic solvent was removed under vacuum and ether (100 mL) was added. The organic phase was washed with sat. aq. $NaHCO_3$ (8 x 30 mL) and brine, dried over Na_2SO_4 and concentrated to give **22** (3.25 g, 86%) as a colorless syrup. $[\alpha]_D^{25}$ = -52.8 (c = 20.3, $CHCl_3$). ^{1}H RMN ($CDCl_3$, 500 MHz) δ: 0.68 (ddd, *J* = 12.1, 12.1, 3.3 Hz, 1H), 0.84 (s, 3H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.93 - 1.07 (m, 2H), 0.94 (d, *J* = 6.9 Hz, 3H), 1.20 – 1.24 (m, 1H), 1.33 (ddd, *J* = 25.6, 12.9, 3.9 Hz, 1H), 1.39 - 1.75 (m, 8H), 1.43 (s, 3H), 1.46 (s, 3H), 1.47 (s, 3H), 1.76 - 1.85 (m, 2H), 1.99 (h, *J* = 6.8 Hz, 1H), 2.20 (ddd, *J* = 12.8, 6.9, 3.7 Hz, 1H), 2.50 (br d, *J* = 12.4 Hz, 1H), 3.55 (d, *J* = 8.3 Hz, 1H), 8.02 (s, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 13.7 (CH_3), 15.8 (CH_3), 19.2 (CH_3), 19.4 (CH_2), 19.5 (CH_2), 20.3 (CH_3), 20.7 (CH_2), 25.7 (CH_2), 29.5 (CH_3), 30.2 (CH_3), 32.7 (CH_2), 33.7 (CH), 37.7 (CH_2), 37.8 (C), 38.2 (CH_2), 40.1 (CH), 51.0 (CH), 53.1 (CH), 84.9 (CH), 85.5 (C), 87.3 (C), 108.3 (C), 160.5 (CH). IR (film): 1721, 1448, 1385, 1189, 1040, 861, 772 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{23}H_{38}O_4Na$ ($M+Na^+$) 401.2668, found: 401.2677.

(3aS,9aR,9bS,11aS)-11a-isopropyl-2,2,6,9a-tetramethyl-3a,3b,4,5,7,8,9,9a,9b,10,11,11a-dodecahydrophenanthro[2,1-d][1,3]dioxole (23).

To a solution of triphenylphosphine (1.61 g, 6.16 mmol) in dry CH_2Cl_2 (30 mL) was added iodine (1.56 g, 6.16 mmol) and the mixture was stirred at room temperature for 5 min. Then, a solution of **22** (2.12 g, 5.60 mmol) in dry CH_2Cl_2 (20 mL) was added and the resulting mixture was stirred at room temperature for 40 min. Then, aq. 5% $NaHSO_3$ (5 mL) was added and the mixture was stirred for 5 min. The solvent was removed under vacuum, and the crude product was diluted with ether – water (90 – 30 mL).The phases were shaken and separated and the organic phase was washed with water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was directly purified by flash chromatography on silica gel (5% ether/hexanes) to give **23** (1.34 g, 76 %) as a colorless syrup.

$[\alpha]_D^{25}$= +12.5 (c = 29.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.71 – 0.73 (m, 1H), 0.86 - 1.00 (m, 2H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.96 (s, 3H), 1.19 - 1.30 (m, 2H), 1.44 (s, 3H), 1.45 - 1.60 (m, 2H), 1.52 (s, 3H), 1.61 (s, 3H), 1.68 - 1.78 (m, 2H), 1.80 - 1.90 (m, 4H), 1.93 – 1.97 (m, 1H), 1.99 (h, *J* = 6.9 Hz, 1H), 2.12 (ddd, *J* = 12.6, 6.9, 3.7 Hz, 1H), 2.56 (ddd, *J* = 14.2, 3.4, 3.4 Hz, 1H), 3.55 (d, *J* = 8.3 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 15.9 (CH_3), 19.2 (CH_2), 19.3 (CH_3), 19.7 (CH_3), 19.9 (CH_3), 20.7 (CH_2), 25.0 (CH_2), 26.0 (CH_2), 29.7 (CH_3), 30.3 (CH_3), 33.0 (CH_2), 33.2 (CH_2), 33.8 (CH), 37.5 (C), 37.9 (CH_2), 41.0 (CH), 49.3 (CH), 84.9 (CH), 85.6 (C), 108.2 (C), 124.4 (C), 136.0 (C). IR (film): 1457, 1377, 1367, 1236, 1038, 773 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{22}H_{36}O_2Na$ ($M+Na^+$) 355.2613, found: 355.2621.

Synthesis of 23 from 19.

To a solution of **19** (840 mg, 2.22 mmol) in benzene (25 mL) were added lead (IV) acetate (1.28 mg, 2.89 mmol), cooper (II) acetate (22 mg, 0.11 mmol) and pyridine (668 mg, 8.44 mmol), and the reaction mixture was stirred under reflux for 15 min, at which time TLC showed no **19**. Then, it was diluted with ether (40 mL) and washed with 2N HCl (3 x 10 mL), water (10 mL), sat. aq. $NaHCO_3$ (3 x 10 mL), brine, and the organic phase was dried over Na_2SO_4. Removal of the solvent under vacuum afforded a crude product (837 mg) which was used in the next step without purification.

To a stirred solution of this crude (837 mg) in dry CH_2Cl_2 (15 mL), was added a solution of triphenylphosphine (755 mg, 2.88 mmol) and iodine (731 mg, 2.88 mmol) in dry CH_2Cl_2 (30 mL) and the resulting mixture was stirred at room temperature for 2 h. Following the same work-up used for **23** from **22**, a crude product was obtained which was directly purified by flash chromatography on silica gel (5% ether/hexanes) to give **23** (472 mg, 64 %) as a colorless syrup.

(3aS,3bS,9aR,9bS,11aS)-11a-isopropyl-2,2,6,6,9a-pentamethyl-3b,4,9,9a,9b,10,11,11a-octahydrophenanthro[2,1-d][1,3]dioxol-7(3aH,6H,8H)-one (24).

Potassium *tert*-butoxide (155 mg, 1.38 mmol) was added to a stirred solution of **13** (400 mg, 1.15 mmol) in dry THF (20 mL) under an argon atmosphere and the reaction mixture was stirred at room temperature for 20 min. Then, methyl iodide (0.072 mL, 1.38 mmol) was added and the reaction mixture was stirred at room temperature for an additional 1 h, at which time TLC showed no starting material. The mixture was concentrated in vacuo to

give a crude product, which was diluted with ether – water (40 : 10 mL) and the phases were shaken and separated. The organic phase was washed with water, brine and dried over anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was purified by flash chromatography on silica gel(5% ether/hexanes), affording 340 mg of **24** (82%), as colorless syrup.

$[\alpha]_D^{25}$ = -19.9 (c = 22.6, $CHCl_3$). ^{1}H RMN ($CDCl_3$, 500 MHz) δ: 0.81 (s, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 1.22 (s, 3H), 1.24 (s, 3H), 1.35 - 1.59 (m, 4H), 1.45 (s, 3H), 1.49 (s, 3H), 1.68 (ddd, *J* = 13.5, 11.3, 8.5 Hz, 1H), 1.75 - 1.91 (m, 4H), 1.97 - 2.08 (m, 2H), 2.43 - 2.61 (m, 2H), 3.70 (d, *J* = 7.3 Hz, 1H), 5.60 (dd, *J* = 4.9, 2.0 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 15.8 (CH_3), 18.8 (CH_3), 19.3 (CH_3), 20.1 (CH_2), 25.5 (CH_2), 27.2 (CH_3), 29.5 (CH_3), 30.07 (CH_3), 30.09 (CH_3), 31.8 (CH_2), 32.6 (CH_2), 33.7(CH_2), 34.1 (CH), 36.3 (CH), 37.4 (C), 44.9 (CH), 48.6 (C), 85.3 (CH), 85.9 (C), 108.7 (C), 119.8 (CH), 149.1 (C), 216.2 (C). IR (film): 2961, 2873, 1710, 1464, 1380, 1238, 1040, 668 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{23}H_{36}O_3Na$ ($M+Na^+$) 383.2562, found: 383.2555.

(3aS,3bS,7S,9aR,9bS,11aS)-11a-isopropyl-2,2,6,6,9a-pentamethyl-3a,3b,4,6,7,8,9,9a,9b,10,11,11a-dodecahydrophenanthro[2,1-d][1,3]dioxol-7-ol (25).

Sodium borohydride (84 mg, 2.22 mmol) was added to a stirred solution of **24** (323 mg, 0.90 mmol) in EtOH (5 mL) and the reaction mixture was stirred at room temperature for 15 min, at which time TLC showed no **24**. The reaction mixture was quenched with water (1 mL), and the solvent was evaporated. The crude product was diluted with ether – water (30 : 10 mL) and the phases were shaken and separated. The organic phase was washed

with water and brine and the organic phase was dried over Na_2SO_4 and concentrated to give **25** (292 mg, 90%) as a colorless syrup.

$[\alpha]_D^{25}$ = -84.0 (c = 20.6, $CHCl_3$). ^{1}H RMN ($CDCl_3$, 500 MHz) δ: 0.89 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 1.04 (s, 3H), 1.06 (s, 3H), 1.09 – 1.11 (m, 1H), 1.15 (s, 3H), 1.35 - 1.60 (m, 2H), 1.44 (s, 3H), 1.49 (s, 3H), 1.66 - 1.92 (m, 8H), 1.99 (h, *J* = 6.9 Hz, 1H), 2.50 – 2.58 (m, 1H), 3.23 (dd, *J* = 11.1, 5.0 Hz, 1H), 3.66 (d, *J* = 7.1 Hz, 1H), 5.62 (dd, *J* = 4.4, 2.4 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 15.8 (CH_3), 19.1 (CH_3), 19.3 (CH_2), 20.8 (CH_3), 23.5 (CH_3), 25.9 (CH_2), 27.22 (CH_2), 27.24 (CH_3), 29.3 (CH_3), 29.9 (CH_3), 33.4 (CH_2), 34.1 (CH), 35.6 (CH), 36.3 (CH_2), 37.2 (C), 41.5 (C), 47.1 (CH), 77.4 (CH), 85.8 (C), 85.9 (CH), 108.5 (C), 120.0 (CH), 149.1 (C). IR (film): 3470, 1467, 1367, 1238, 1040, 866, 756 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{23}H_{38}O_3Na$ ($M+Na^+$) 385.2719, found: 385.2724.

(3aS,3bS,7S,9aR,9bS,11aS)-11a-isopropyl-2,2,6,6,9a-pentamethyl-3a,3b,4,6,7,8,9,9a,9b,10,11,11a-dodecahydrophenanthro[2,1-d][1,3]dioxol-7-yl acetate (26).

To a solution of **25** (376 mg, 1.04 mmol) in pyridine (5 mL) at 0 ºC was added acetic anhydride (2 mL), and the reaction mixture was stirred at room temperature for 2 h, at which time TLC showed no starting material. Then, the reaction mixture was cooled at 0 ºC, water (5 mL) was added to quench the reaction and the mixture was stirred for an additional 10 min. Then, it was diluted with ether - water (40 : 10 mL) and the phases were shaken and separated. The organic phase was washed with water (10 mL), 2N HCl (4 x 10

mL), again water (10 mL), sat. aq. $NaHCO_3$ (4 x 10 mL), brine, and the organic phase was dried over Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was purified by flash chromatography on silica gel (10 % ether/hexanes) gave **26** (399 mg, 95%) as a colorless syrup.

$[\alpha]_D^{25}$ = - 46.6 (c = 32.8, $CHCl_3$). RMN ($CDCl_3$, 500 MHz) δ: 0.89 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 1.02 (s, 3H), 1.06 (s, 3H), 1.12 (s, 3H), 1.16 – 1.18 (m, 1H), 1.36 – 1.38 (m, 1H), 1.43 (s, 3H), 1.47 (s, 3H), 1.54 – 1.56 (m, 1H), 1.68 - 1.92 (m, 8H), 1.98 (h, *J* = 6.8 Hz, 1H), 2.05 (s, 3H), 2.50 – 2.55 (m, 1H), 3.66 (d, *J* = 7.2 Hz, 1H), 4.47 (dd, *J* = 11.3, 4.7 Hz, 1H), 5.61 (dd, *J* = 4.5, 2.6 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 15.9 (CH_3), 19.1 (CH_3), 19.4 (CH_2), 20.9 (CH_3), 21.3 (CH_3), 23.7 (CH_2), 24.8 (CH_3), 25.9 (CH_2), 27.2 (CH_3), 29.4 (CH_3), 30.0 (CH_3), 33.4 (CH_2), 34.1 (CH), 35.7 (CH), 35.9 (CH_2), 37.2 (C), 40.3 (C), 47.0 (CH), 79.4 (CH), 85.9 (CH), 85.9 (C), 108.6 (C), 120.6 (CH), 148.3 (C), 170.7 (C). IR (film): 1736, 1468, 1367, 1241, 1035, 757 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{25}H_{40}O_4Na$ ($M+Na^+$) 427.2824, found: 427.2831.

(3aS,9aR,9bS,11aS)-11a-isopropyl-2,2,6,6,9a-pentamethyl-decahydrophenanthro[2,1-d][1,3]dioxol-7(3aH,3bH,8H)-one (27).

A solution of enone **13** (253 mg, 0.73 mmol) in THF / tBuOH (5: 1 mL) was added under argon to liquid NH_3 at -78 ° C, and the mixture was stirred for 10 minutes. Then was added Li (51 mg, 7.3 mmol), and the mixture was stirred at - 40 ° C for 3 h, then MeI (136 μL, 2.19 mmol) was added, and the mixture was stirring 1 h. After this time the mixture was heated to room temperature to evaporate the NH_3, then the mixture was diluted with ether and water, the organic phase was washed with water (3 x 25 mL) and brine (1 x 25 mL),

and dried over Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was purified by flash chromatography on silica gel (10 % ether/hexanes) gave **27** (225 mg, 85%) as a colorless syrup.

$[\alpha]_D^{25}$= -39.8 (c = 19.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.63 (ddd, *J* = 12.1, 12.1, 3.4 Hz, 1H), 0.85 - 1.13 (m, 2H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 1.01 (s, 3H), 1.03 (s, 3H), 1.06 (s, 3H), 1.20 - 1.34 (m, 3H), 1.34 - 1.54 (m, 2H), 1.43 (s, 3H), 1.48 (s, 3H), 1.55-1.67 (m, 2H), 1.79 (ddd, *J* = 14.3, 4.5, 4.5 Hz, 1H), 1.94 - 2.07 (m, 2H), 2.23 (ddd, *J* = 11.0, 7.0, 3.5 Hz, 1H), 2.32 (ddd, *J* = 15.4, 5.1, 3.6 Hz, 1H), 2.62 (ddd, *J* = 15.3, 13.2, 6.3 Hz, 1H), 3.56 (d, *J* = 8.3 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 13.5 (CH_3), 15.8 (CH_3), 19.2 (CH_3), 19.9 (CH_2), 21.9 (CH_3), 22.3 (CH_2), 25.7 (CH_2), 25.8 (CH_3), 29.5 (CH_3), 30.2 (CH_3), 33.1 (CH_2), 33.7 (CH), 34.5 (CH_2), 36.5 (C), 37.8 (CH_2), 40.2 (CH), 47.7 (C), 50.3 (CH), 54.6 (CH), 84.8 (CH), 85.6 (C), 108.3 (C), 216.9 (C). IR (film): 1707, 1457, 1366, 1241, 1039, 667 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{23}H_{38}O_3Na$ ($M+Na^+$) 385.2719, found: 385.2724.

(3aS,7S,9aR,9bS,11aS)-11a-isopropyl-2,2,6,6,9a-pentamethyl-tetradecahydrophenanthro[2,1-d][1,3]dioxol-7-ol (28).

Sodium borohydride (89 mg, 2.36 mmol) was added to a stirred solution of **27** (345 mg, 0.95 mmol) in EtOH (5 mL) and the reaction mixture was stirred at room temperature for 15 min, at which time TLC showed no **27**. Following the same work-up used to prepare **25**, **28** (292 mg, 90%) was obtained as a colorless syrup.

$[\alpha]_D^{25}$= -32.8 (c = 4.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.55 (ddd, *J* = 12.3, 3.7 Hz, 1H), 0.76 - 1.08 (m, 2H), 0.79 (s, 3H), 0.83 (s, 3H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.98 (s, 3H), 1.20 (ddd, *J* = 24.0, 10.8, 3.5 Hz, 1H), 1.34 (ddd, *J* = 25.9, 13.1, 3.7 Hz, 1H), 1.39 - 1.68 (m, 7H), 1.43 (s, 3H), 1.47 (s, 3H), 1.74 - 1.83 (m, 2H), 1.91 (h, *J* = 6.9 Hz, 1H), 2.14 (ddd, *J* = 12.7, 7.1, 3.7 Hz, 1H), 3.14 (dd, *J* = 11.6, 4.5 Hz, 1H), 3.47 (d, *J* = 8.3 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 13.9 (CH_3), 15.5 (CH_3), 15.8 (CH_3), 19.2 (CH_3), 19.5 (CH_2), 21.1 (CH_2), 25.8 (CH_2), 27.4 (CH_2), 28.2 (CH_3), 29.5 (CH_3), 30.2 (CH_3), 33.6 (CH_2), 33.7 (CH), 36.7 (C), 37.3 (CH_2), 38.9 (C), 40.0 (CH), 51.0 (CH), 53.9 (CH), 79.0 (CH), 85.1 (CH), 85.5 (C), 108.2 (C). IR (film): 3438, 1637, 1367, 1237, 1037, 756 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{23}H_{40}O_3Na$ ($M+Na^+$) 387.2875, found: 387.2868.

(3aS,7S,9aR,9bS,11aS)-11a-isopropyl-2,2,6,6,9a-pentamethyl-tetradecahydrophenanthro[2,1-d][1,3]dioxol-7-yl acetate (29).

To a solution of **28** (376 mg, 1.03 mmol) in pyridine (5 mL) at 0 ºC was added acetic anhydride (2 mL), and the reaction mixture was stirred at room temperature for 2 h, at which time TLC showed no starting material. Following the same work-up used to prepare **26**, a crude product was obtained which was purified by chromatography on silica gel (10 % ether/hexanes) being obtained **29** (385 mg, 92%) as a colorless syrup.

$[\alpha]_D^{25}$= 26.7 (c = 4.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.57 (ddd, *J* = 12.1, 12.1, 3.5 Hz, 1H), 0.86 (s, 6H), 0.87 (s, 3H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.40 - 1.41 (m, 4H), 1.43 (s, 3H), 1.48 (s, 3H), 1.40 - 1.70 (m, 7H), 1.73 - 1.85 (m, 2H), 1.98 (h, *J* = 6.9 Hz, 1H), 2.04 (s, 3H), 2.18 – 2.22 (m, 1H), 3.54 (d, *J* = 8.2 Hz, 1H), 4.48 (dd, *J* = 11.6, 4.5 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.0 (CH_3), 15.8 (CH_3), 16.7 (CH_3), 19.2 (CH_3), 19.5 (CH_2), 21.0 (CH_2), 21.3 (CH_3), 23.8 (CH_2), 25.8 (CH_2), 28.2 (CH_3), 29.5 (CH_3),

30.2 (CH_3), 33.5 (CH_2), 33.7 (CH), 36.6 (C), 36.9 (CH_2), 37.8 (C), 40.0 (CH), 50.9 (CH), 54.0 (CH), 80.9 (CH), 85.0 (CH), 85.6 (C), 108.2 (C), 170.9 (C). IR (film): 1734, 1456, 1366, 1240, 1031 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{25}H_{42}O_4Na$ ($M+Na^+$) 429.2981, found: 429.2979.

(2S,4aR,5S,8aR)-6-(hydroxymethyl)-1,1,4a-trimethyl-5-(4-methyl-3-oxopentyl)-decahydronaphthalen-2-yl acetate (30).

To a solution of **11** (387 mg, 1.06 mmol) in THF (20 mL) was added 50% aqueous solution of Raney Nickel (2 mL) and the mixture was stirred at room temperature for 20 min, at this time TLC showed no **11**. Then, the reaction mixture was filtered through a silica gel – Na_2SO_4 pad (10 : 2 g), washed with acetone (10 mL) and concentrated to give pure **30** (366 mg, 94 %) as colorless syrup.

$[\alpha]_D^{25}$= -0.9 (c = 8.8, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.65-0.96 (m, 3H), 0.77 (s, 3H), 0.79 (s, 6H), 0.98 - 1.40 (m, 4H), 1.01 (d, *J* = 6.9 Hz, 6H), 1.46 - 1.69 (m, 4H), 1.70 - 1.81 (m, 2H), 1.97 (s, 3H), 2.36 – 2.40 (m, 1H), 2.44 - 2.57 (m, 2H), 3.48 - 3.59 (m, 2H), 4.39 (dd, *J* = 11.7, 2.5 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.1 (CH_3), 16.5 (CH_3), 18.2 (CH_3), 18.3 (CH_3), 20.9 (CH_2), 21.3 (CH_3), 21.8 (CH_2), 23.7 (CH_2), 28.1 (CH_3), 30.5 (CH_2), 37.0 (CH_2), 37.8 (C), 38.1 (C), 40.9 (CH), 41.2 (CH), 41.9 (CH_2), 51.3 (CH), 54.2 (CH), 65.6 (CH_2), 80.5 (CH), 170.9 (C), 215.3 (C). IR (film): 3490, 1733, 1715, 1458, 1367, 1246, 1031 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{22}H_{38}O_4Na$ ($M+Na^+$) 389.2668, found: 389.2673.

(2S,4aR,5S,8aR)-1,1,4a-trimethyl-5-(4-methyl-3-oxopentyl)-6-(tosyloxymethyl)-decahydronaphthalen-2-yl acetate (31).

To a solution of **30** (320 mg, 0.87 mmol) in pyridine (5 ml) was added *p*- toluenesulfonyl chloride (215 mg, 1.13 mmol) and the reaction mixture was stirred at room temperature for 6 h, at which time TLC showed no starting material. Then, it was diluted with ether (40 mL) and washed with 2N HCl (3 x 20 mL) and brine, and the organic phase was dried over Na_2SO_4. Removal of the solvent under vacuum afforded a crude product which was purified by flash chromatography on silica gel (15 % ether/hexanes) to yield **31** (391 mg, 86%) as a colorless syrup.

$[\alpha]_D^{25}$= -3.5 (c = 10.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.73 - 0.91 (m, 3H), 0.80 (s, 3H), 0.825 (s, 3H), 0.833 (s, 3H), 1.03 - 1.37 (m, 2H), 1.055 (d, *J* = 6.9 Hz, 3H), 1.060 (d, *J* = 6.9 Hz, 3H), 1.49 - 1.63 (m, 4H), 1.64 - 1.75 (m, 3H), 1.78 (ddd, *J* = 13.2, 3.5, 3.5 Hz, 1H), 2.03 (s, 3H), 2.30 – 2.38 (m, 1H), 2.43 – 2.45 (m, 1H), 2.45 (s, 3H), 2.51 (h, *J* = 6.9 Hz, 1H), 3.95 (ddd, *J* = 12.5, 9.6, 4.0 Hz, 2H), 4.44 (dd, *J* = 11.8, 4.4 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 2H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 13.8 (CH_3), 16.5 (CH_3), 18.1 (CH_3), 18.2 (CH_3), 20.5 (CH_2), 21.2 (CH_3), 21.6 (CH_3), 22.0 (CH_2), 23.6 (CH_2), 28.0 (CH_3), 30.2 (CH_2), 36.5 (CH_2), 37.7 (C), 38.0 (C), 39.1 (CH), 40.8 (CH), 41.6 (CH_2), 51.0 (CH), 53.8 (CH), 73.2 (CH_2), 80.6 (CH), 127.8 (CH), 127.8 (CH), 129.8 (CH), 129.8 (CH), 133.0 (C), 144.8 (C), 170.8 (C), 214.1 (C). IR (film): 1731, 1713, 1363, 1246, 1177, 667 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{29}H_{44}O_6SNa$ ($M+Na^+$) 543.2756, found: 543.2757.

Isopropyl-3-((1S,4aR,6S,8aR)-6-acetoxy-5,5,8a-trimethyl-2-(tosyloxymethyl)-decahydronaphthalen-1-yl)propanoate (32).

m-Chloroperoxybenzoic acid (MCPBA, 70%; 555 mg, 2.25 mmol), and trifluoroacetic acid (256 mg, 2.25 mmol) were added to a stirred solution of **31** (393 mg, 0.75 mmol) in CH_2Cl_2 (20 mL) and the reaction was stirred under reflux for 20 h, at which time TLC indicated no starting material remaining. The reaction was quenched with sat. aq Na_2SO_3 (5 mL) and stirred for an additional 15 min. Then, the organic solvent was removed under vacuum and ether (40 mL) was added. The organic phase was washed with sat. aq. $NaHCO_3$ (5 x 15 mL) and brine, dried over Na_2SO_4 and concentrated to give **32** (505 mg, 90%) as a colorless syrup.

$[\alpha]_D^{25}$= - 4.5 (c = 10.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.70 – 0.72 (m, 1H), 0.79 (s, 3H), 0.81 - 0.91 (m, 2H), 0.83 (s, 6H), 1.03 - 1.38 (m, 3H), 1.22 (d, *J* = 6.3 Hz, 6H), 1.50 - 1.86 (m, 8H), 2.03 (s, 3H), 2.04 - 2.22 (m, 2H), 2.45 (s, 3H), 3.88 (dd, *J* = 9.6, 6.1 Hz, 1H), 4.07 (dd, *J* = 9.6, 3.1 Hz, 1H), 4.44 (dd, *J* = 11.7, 4.5 Hz, 1H), 4.96 (h, *J* = 6.3 Hz, 1H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 2H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 13.9 (CH_3), 16.5 (CH_3), 20.5 (CH_2), 21.2 (CH_3), 21.6 (CH_3), 21.8 (CH_3), 21.9 (CH_3), 23.5 (CH_2), 23.6 (CH_2), 28.0 (CH_3), 30.3 (CH_2), 35.8 (CH_2), 36.5 (CH_2), 37.7 (C), 37.9 (C), 39.1 (CH), 51.2 (CH), 53.8 (CH), 67.6 (CH), 73.3 (CH_2), 80.6 (CH), 127.9 (CH), 127.9 (CH), 129.8 (CH), 129.8 (CH), 133.1 (C), 144.7 (C), 170.8 (C), 172.6 (C). IR (film): 1731, 1364, 1246, 1177, 1109, 954, 816, 667 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{29}H_{44}O_7SNa$ ($M+Na^+$) 559.2705, found: 559.2698.

3-((1S,4aR,6S,8aR)-6-hydroxy-5,5,8a-trimethyl-2-methylene-decahydronaphthalen-1-yl)propanoic acid (33).

2N KOH in MeOH (1 mL) and water (0.1 mL) was added to a solution of **10** (197 mg, 0.54 mmol) in MeOH (5 mL) and the mixture was stirred at room temperature for 2 h, at which time TLC showed no remaining starting material. Then, the solvent was removed in vacuum and ether – water (30 : 10 mL) was added, and the phases were shaken and separated. 2N HCl (2 mL) was added slowly to the aqueous phase and the mixture was diluted with ether (30 mL). The organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated to afford pure **33** (109 mg, 72%) as a colourless syrup.

$[\alpha]_D^{25}$= + 26.1 (c = 4.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.70 (s, 3H), 0.77 (s, 3H), 0.99 (s, 3H), 1.09 (dd, *J* = 12.1, 2.3 Hz, 1H), 1.18 - 1.44 (m, 3H), 1.54 - 1.92 (m, 6H), 1.96 (ddd, *J* = 13.0, 13.0, 5.0 Hz, 1H), 2.10 – 2.30 (m, 1H), 2.41 (ddd, *J* = 12.8, 4.1, 2.4 Hz, 1H), 2.52 (ddd, *J* = 16.5, 8.9, 4.4 Hz, 1H), 3.26 (dd, *J* = 11.8, 4.3 Hz, 1H), 4.51 (s, 1H), 4.87 (s, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 14.3 (CH_3), 15.4 (CH_3), 18.9 (CH_2), 23.9 (CH_2), 27.8 (CH_2), 28.3 (CH_3), 32.7 (CH_2), 36.9 (CH_2), 38.0 (CH_2), 39.1 (C), 39.4 (C), 54.5(CH), 55.8 (CH), 78.8 (CH), 106.9 (CH_2), 147.2 (C), 179.2 (C). IR (film): 3446, 1704, 1652, 1457, 1029, 770, 668 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{17}H_{28}O_3$ Na ($M+Na^+$) 303.1936, found: 303.1941.

3-De-*O*-acetyl-3-*O*-methoxycarbonyl-negundoin A (34).

To a solution of triphenylphosphine (13 mg, 0.05 mmol) in dry CH_2Cl_2 (5 mL) was added iodine (13 mg, 0.05 mmol) and the mixture was stirred at room temperature for 5 min. Then, a solution of **15** (197 mg, 0.5 mmol) in dry CH_2Cl_2 (3 mL) was added and the resulting mixture was stirred at room temperature for 5 h, at which time TLC showed no remaining starting material. The solvent was removed under vacuum and the crude product

was directly purified by flash chromatography on silica gel (15% ether/hexanes) to give compound **34** (177 mg, 90%) as a colourless syrup

$[\alpha]_D^{25}$= + 23.0 (c = 6.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.77 (d, *J* = 6.6 Hz, 3H), 0.87 (s, 3H), 0.95 (s, 3H), 0.96 (s, 3H), 1.30 - 1.46 (m, 4H), 1.51 - 1.74 (m, 5H), 1.75 - 1.85 (m, 2H), 2.08 (ddd, *J* = 13.5, 11.8, 7.6 Hz, 1H), 2.99 – 3.05 (m, 1H), 3.10 – 3.16 (m, 1H), 3.65 (s, 3H), 3.77 (s, 3H), 4.31 (dd, *J* = 11.9, 4.5 Hz, 1H), 5.30 (t, *J* = 1.8 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 15.5 (CH_3), 16.4 (CH_3), 16.8 (CH_3), 20.8 (CH_2), 23.2 (CH_2), 26.7 (CH_2), 27.9 (CH_3), 29.3 (CH_2), 31.0 (CH_2), 31.5 (CH_2), 36.5 (CH), 37.9 (C), 41.9 (C), 46.2 (CH), 50.5 (CH_3), 54.6 (CH_3), 84.6 (CH), 87.3 (CH), 97.7 (C), 155.7 (C), 169.5 (C), 178.4 (C). IR (film): 1746, 1706, 1633, 1441, 1273, 1128, 1108, 968, 956, cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{22}H_{34}O_6Na$ ($M+Na^+$) 417.2253, found: 417.2262.

3-De-*O*-acetyl negundoin A (35).

2N KOH in MeOH (1.5 mL) was added to a solution of **34** (158 mg, 0.41 mmol in MeOH (12 mL) and the mixture was stirred at room temperature for 18 h, at which time TLC showed no remaining starting material. Then, the solvent was removed in vacuum and ether – water (50 : 15 mL) was added, and the phases were shaken and separated. The organic phase was washed with water and brine, dried over Na_2SO_4 and concentrated to afford a crude product which was directly purified by flash chromatography on silica gel (25% ether/hexanes) to give **35** (120 mg, 90%), as a colourless syrup.

$[\alpha]_D^{25}$= +11.5 (c = 6.7, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.77 (d, *J* = 6.6 Hz, 3H), 0.79 (s, 3H), 0.93 (s, 3H), 1.01 (s, 3H), 1.25 - 1.50 (m, 4H), 1.52 - 1.69 (m, 4H), 1.79 (ddd,

J = 13.5, 11.3, 4.6 Hz, 1H), 2.09 (ddd, *J* = 13.4, 11.7, 7.5 Hz, 1H), 3.00 (ddd, *J* = 11.4, 7.5, 2.0 Hz, 1H) 3.03 (ddd, *J* = 11.5, 7.6, 2.0 Hz, 1H), 3.11 (ddd, *J* = 11.7, 4.6, 1.7 Hz, 1H), 3.14 (ddd, *J* = 11.8, 4.6, 1.7 Hz, 1H), 3.21 (dd, *J* = 11.6, 4.5 Hz, 1H), 3.65 (s, 3H), 5.28 (t, *J* = 1.8 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ: 15.4 (CH_3), 15.5 (CH_3), 16.8 (CH_3), 21.1 (CH_2), 26.6 (CH_2), 26.8 (CH_2), 28.0 (CH_3), 29.5 (CH_2), 31.1 (CH_2), 31.6 (CH_2), 36.5 (CH), 38.8 (C), 42.1 (C), 46.0 (CH), 50.5 (CH_3), 78.3 (CH), 87.0 (CH), 98.0 (C), 169.5 (C), 178.8 (C). IR (film): 1667, 1630, 1364, 1126, 1045, 961, 815, 756 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{20}H_{32}O_4Na$ ($M+Na^+$) 359.2198, found: 359.2192.

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Supporting Information Available. ^{1}H NMR and ^{13}C NMR spectra for compounds **6**, **9**, **10-13**, **15**, **16** and **18-35.** This material is available free of charge via the internet at http://pubs.acs.org.

References and Footnotes

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