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First synthesis of antitumoral dasyscyphin B†

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The first synthesis of dasyscyphin B, an antitumoral metabolite obtained from the ascomycete *Dasyscyphus niveus*, has been achieved starting from commercial abietic acid. The key steps of the synthetic sequence are the diastereoselective α-methylation of a ketoaldehyde, followed by an intramolecular aldol condensation and the further Diels–Alder cycloaddition of a dienol ester. The procedure reported will allow the synthesis of related metabolites functionalized in the A ring.

Introduction

During the last few years, a new type of merosesquiterpene (a natural product of mixed biosynthetic origin) with a tetracyclic structure, including a cyclopentane ring, has been isolated from vegetable species, marine sponges and terrestrial fungi. Examples of this are pelorol (**1**), first isolated from *Dactylospongia elegans*,[1] akaol A (**2**), found in a Micronesian sponge of the genus *Aka*,[2] and dasyscyphins A–E (**3–7**), metabolites from the ascomycete *Dasyscyphus niveus* (Fig. 1).[3,4] Even though the bioactivities of this family of compounds are yet to be examined comprehensively, preliminary studies have revealed that pelorol (**1**) is an activator of the inositol 5-phosphatase SHIP,[5] whereas dasyscyphin B (**4**) and C (**5**) show potent cytotoxic activities in several human cell lines,[3a] and dasyscyphin D (**6**) and E (**7**) exhibit antifungal properties.[4]

Despite the significant biological activities and the interesting tetracyclic structure of the above mentioned compounds, only a few syntheses have been reported. A total synthesis of dasyscyphin D (**6**) was recently described by She *et al.*, including a $PtCl_2$-catalyzed pentannulation reaction and acid-catalyzed Robinson annulations as key steps.[6] Andersen *et al.* previously reported the first synthesis of pelorol (**1**) starting from (+)-sclareolide, after condensation of an aryllithium with a drimane hydroxy aldehyde and a further difficult intramolecular Friedel–Crafts alkylation to create the cyclopentane C ring; the success of the latter process required a sufficiently activated aromatic moiety.[7] The results reported by Andersen's group in their enantiospecific synthesis of pelorol (**1**), corroborated by our preliminary studies, revealed that the two-synthon strategy[8] followed by intramolecular Friedel–Crafts alkylation led to the tetracyclic intermediate bearing a C8β methyl group as the major diastereoisomer, but this is not applicable for synthesizing sesquiterpene quinols such as compounds **2–7**, bearing a B/C *cis* fused system. Considering the above arguments, we recently developed a new strategy to access this type of compound, based on the Diels–Alder cycloaddition of a tricyclic diene, having a cyclopentane C ring with a C8α methyl group. Utilizing this, the first enantiospecific synthesis of akaol A (**2**) from commercial (−)-sclareol was achieved.[9]

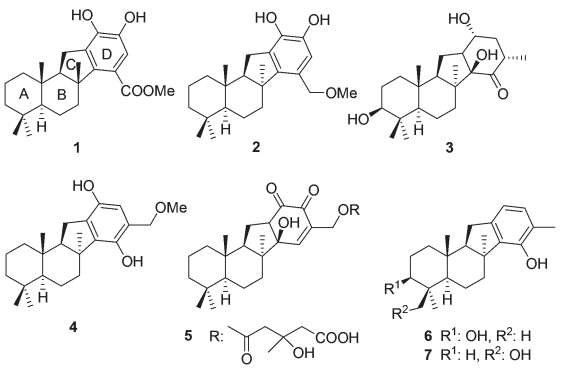

Fig. 1 Representative sesquiterpene quinols.

Results and discussion

Continuing our investigations of this new strategy to access dasyscyphins and related compounds, we explored the use of other terpenes, such as abietic acid (**12**), as the starting

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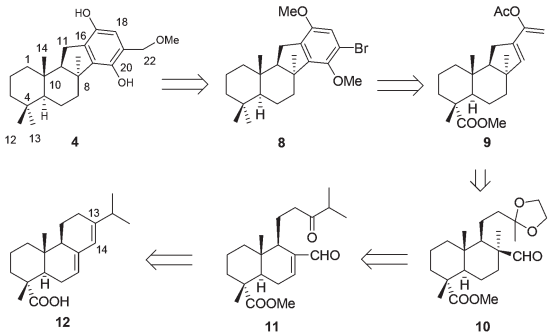
†Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR spectra for compounds **4**, **8–10** and **15–33**. See DOI: 10.1039/c3ob41290c

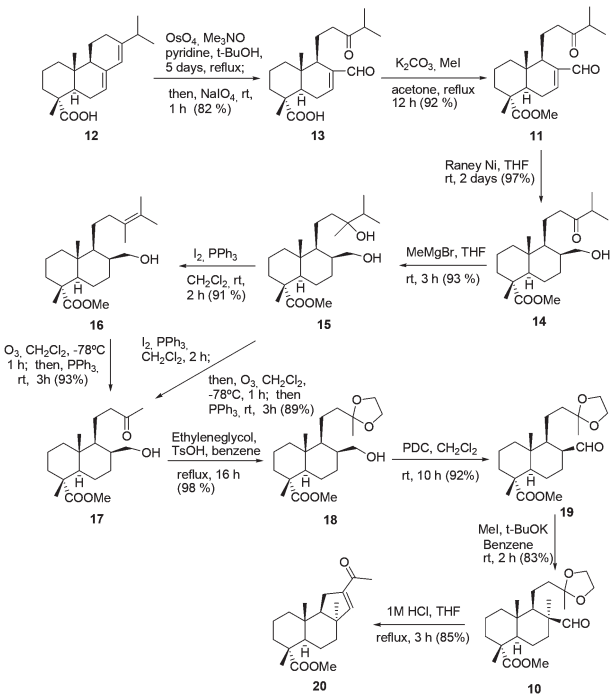


Scheme 1 Retrosynthesis of dasyscyphin B (**4**).

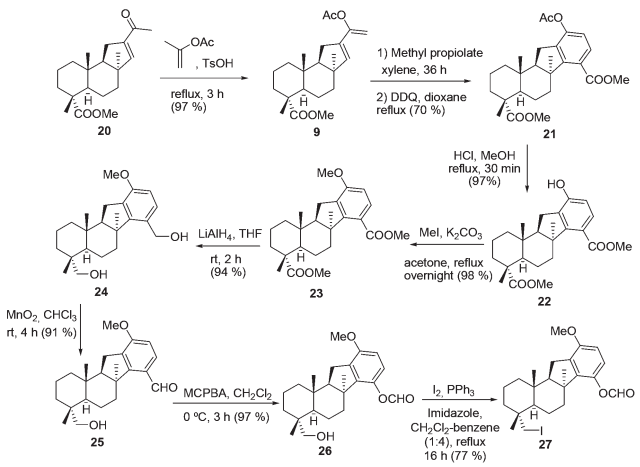
material. This, as well as being a very cheap commercial compound, will make it possible to synthesize natural dasyscyphins bearing a function in the A ring, such as dasyscyphins A (**3**), D (**6**) or E (**7**), which could be difficult to prepare by alternative methods.[6] The synthesis starting from acid **12** will also enable the preparation of unnatural analogues of these compounds functionalized in the A ring, in order to investigate the structure–activity relationship. Thus, we planned the preparation of dasyscyphin B (**4**), which had not previously been synthesized, starting from abietic acid (**12**).

Scheme 1 shows the retrosynthesis of metabolite **4**. The cyclopentane C ring of the target compound will be obtained through the intramolecular aldol condensation of a ketoaldehyde. The aromatic D ring will be elaborated after the Diels–Alder cycloaddition of dienol ester **9**, obtained from the α,β-enone resulting from the intramolecular aldol condensation of ketoaldehyde derived from ketal **10**. The C8α methyl group of compound **4** will be introduced after the diastereoselective *C*-methylation of enol derived from the corresponding ketal aldehyde. This will be prepared from ketoaldehyde **11**, after the chemoselective reduction of the enal group and the subsequent oxidative degradation of the $(CH_3)_2CH$–CO bond. Compound **11** will be synthesized after the regioselective oxidation of the C_{13}–C_{14} bond of abietic acid.

Scheme 2 shows the preparation of tricyclic intermediate **20**, which contains the cyclopentane C ring and the methyl group in the appropriate C8α arrangement. The regioselective oxidative rupture of the C_{13}–C_{14} double bond of acid **12**, affording ketoaldehyde **13**[10] in good yield, was achieved after successive treatments with OsO_4 and $NaIO_4$, without isolating the intermediate diol. The α,β-unsaturated aldehyde **11**[11] was chemoselectively reduced to ketoalcohol **14**[12] by reaction with RANEY® Ni.[13] The diol **15**, obtained as a mixture of distereoisomers, was regioselectively dehydrated after treatment with I_2 and PPh_3[14] to give the corresponding tetrasubstituted alkene **16**, without iodination, which was transformed into the hydroxy ketone **17** by ozonolysis. In an improved procedure, the diol **15** was directly converted into the hydroxy ketone **17** without isolating the intermediate alkene **16**, after the treatment of a solution of diol **15** in dichloromethane with I_2 and PPh_3 and further bubbling of this solution with an O_3/O_2 mixture. After protecting the ketone carbonyl group of



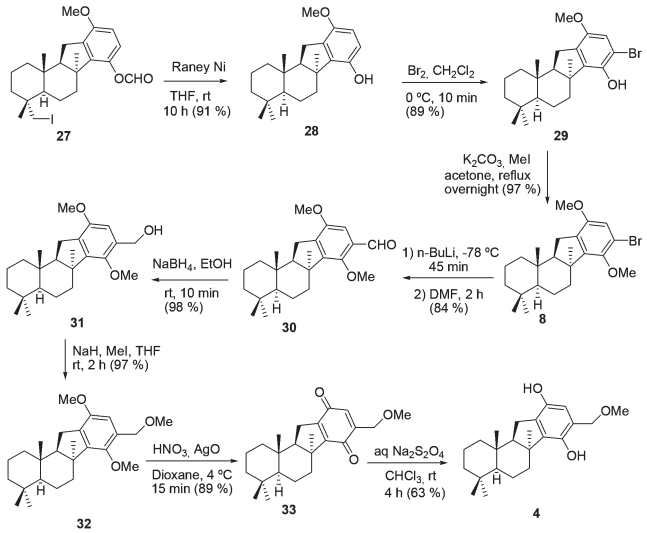
Scheme 2 Synthesis of tricyclic intermediate **20**.



Scheme 3 Construction of the tetracyclic skeleton of dasyscyphins. Synthesis of intermediate **27**.

compound **17** as ethylene ketal, the hydroxymethyl group was converted into the formyl group, thus obtaining the aldehyde **19**. The diastereoselective α-methylation of the latter was efficiently achieved by treatment with MeI and *t*-BuOK in benzene, affording compound **10**. The ketal aldehyde **10** after treatment with 1 M HCl in THF under reflux for 3 h underwent simultaneous ketone deprotection and intramolecular aldol condensation, leading to tricyclic α,β-enone **20**.

The next step was to address the construction of the aromatic D ring of the target compound (Scheme 3). Heating of dienol ester **9** with methyl propiolate in xylene in a sealed tube, and further oxidation with DDQ in dioxane at reflux,



Scheme 4 Synthesis of dasyscyphin B (**4**).

yielded the tetracyclic acetoxy ester **21**, together with its regioisomer (ratio 6 : 1). Compound **21** was obtained almost pure after careful column chromatography. Treatment of diester **23** with $LiAlH_4$ gave diol **24**, which after benzylic oxidation followed by Baeyer–Villiger rearrangement led to hydroxy formate **26**. When this was reacted with I_2 and PPh_3, iodide **27** was obtained.

After completing the reduction of the C4-ester group and performing an appropriate functionalization of the aromatic D ring, dasyscyphin B (**4**) was obtained (Scheme 4). The successive treatment of iodo formate **27** with RANEY® Ni and bromine gave the bromophenol **29**, which was converted into the dimethyl ether **8**. Reaction of this with anh. DMF and *n*-BuLi afforded aldehyde **30**, whose formyl group was easily transformed into the methoxymethyl group of compound **32**. Oxidation of the latter with AgO and nitric acid gave quinone **33**, which was finally converted into dasyscyphin B (**4**) by treatment with aq. $Na_2S_2O_4$ in chloroform. The optical rotation of synthetic dasyscyphin B (**4**) ($[\alpha]_D^{25}$: −12; *c* 0.2, $CHCl_3$) was similar to that reported for the natural product ($[\alpha]_D^{25}$: −19; *c* 0.5, $CHCl_3$); the spectroscopic properties were identical to those previously described.[3a]

Conclusions

In conclusion, the first synthesis of antitumoral dasyscyphin B (**4**) starting from commercial abietic acid (**12**) is reported. The optical rotation of the synthetic product, similar to that of the natural compound, confirms its absolute stereochemistry. The C ring of the starting material was efficiently transformed, utilizing conventional reactions realizable at a multigram scale, providing the intermediate alcohol **17**. The appropriate configuration on C-8 was obtained after the diastereoselective α-methylation of aldehyde **19**. The cyclopentane C ring of the target compound was obtained after intramolecular aldol condensation, and the aromatic D ring was constructed *via* a Diels–Alder cycloaddition involving dienol ester **9**. The procedure reported here could also allow us to achieve the enantiospecific synthesis of dasyscyphins functionalized at the A ring, such as dasyscyphins A (**3**), D (**6**) or E (**7**).

Experimental section

General methods

Dichloromethane (DCM) was dried over calcium hydride. Benzene and tetrahydrofuran were dried over sodium–benzophenone. Chromatography separations were carried out by flash column chromatography on silica gel 60 (230–400 mesh), utilizing hexane–methyl *tert*-butyl ether (H–E) mixtures as an eluent.

Instrumentation: Infrared (IR) spectra were obtained with samples between sodium chloride plates. Data are presented as the frequency of absorption (cm^{-1}). Only selected absorbances (ν_{max}) are reported. Proton and carbon-13 nuclear magnetic resonance (^1H NMR or ^{13}C NMR) spectra were recorded at 400 or 500 MHz, for ^1H, and at 100 or 125 MHz, for ^{13}C, as indicated in each case; 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 = double, br d = broad double, t = triplet, m = multiplet), *J* = coupling constant in hertz (Hz) and the signals of the ^{13}C NMR were assigned utilizing DEPT experiments and on the basis of heteronuclear correlations. High resolution mass spectra (HRMS) were recorded using a Q-TOF spectrometer, utilizing the APcI ionization technique.

(1*R*,4a*R*,5*R*,8a*R*)-6-Formyl-1,4a-dimethyl-5-(4-methyl-3-oxopentyl)-1,2,3,4,4a,5,8,8a-octahydronaphthalene-1-carboxylic acid (13).[10] To a solution of **12** (13 g, 43 mmol) in strictly deoxygenated *t*-BuOH (150 mL) were added trimethylamine *N*-oxide dihydrate (6.2 g, 51.6 mmol) and pyridine (1 mL) under an argon atmosphere. The solution was stirred for 10 min at room temperature and 2% aq. OsO_4 (20 mL, 0.2%, 1.5 mmol) was added and the reaction mixture was further stirred under an argon atmosphere at reflux for 5 days, at which time TLC indicated no remaining starting material. Then $NaIO_4$ (12 g, 56.1 mmol) was added, and the mixture was stirred for 1 h at room temperature. After filtering and removing the solvent, the crude product was directly purified by flash chromatography on silica gel (20% ether–hexanes) to yield pure **13** (11.8 g, 82%) as a colorless syrup. $[\alpha]_D^{25}$ = +42.1 (*c* 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ: 9.35 (s, 1H), 6.76 (t, *J* = 2.7 Hz, 1H), 3.10 (ddd, *J* = 17.2, 10.8, 4.7 Hz, 1H), 2.62 (h, *J* = 6.9 Hz, 1H), 2.43 (ddd, *J* = 17.0, 10.8, 5.7 Hz, 1H), 2.35–2.07 (m, 2H), 2.05–1.81 (m, 4H), 1.79–1.45 (m, 6H), 1.26 (s, 3H), 1.09 (d, *J* = 6.9 Hz, 6H), 0.82 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 215.6 (C), 195.0 (CH), 184.4 (C), 152.3 (CH), 144.4 (C), 50.0 (CH), 46.1 (C), 44.0 (CH), 42.6 (CH_2), 40.8 (CH), 37.8 (CH_2), 37.1 (CH_2), 36.4 (C), 26.8 (CH_2), 20.9 (CH_2), 18.5 (CH_3), 18.4 (CH_3), 17.7 (CH_2), 16.9 (CH_3), 14.3 (CH_3). HRMS (APcI) *m*/*z*: calcd for $C_{20}H_{30}O_4Na$ ($M + Na^+$) 357.2042, found: 357.2037.

(1*R*,4a*R*,5*R*,8a*R*)-Methyl-6-formyl-1,4a-dimethyl-5-(4-methyl-3-oxopentyl)-1,2,3,4,4a,5,8,8a-octahydronaphthalene-1-carboxylate (11).[11] Potassium carbonate (538 mg, 3.89 mmol) and methyl iodide were added to a stirred solution of **13** (1 g, 2.99 mmol) in acetone (30 mL) and the reaction mixture was stirred at reflux for 12 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 (50–20 mL) 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 purified by flash chromatography on silica gel (10% ether–hexanes) affording pure **11** (957 mg, 92%) as a colorless syrup. $[\alpha]_D^{25}$ = +9.0 (*c* = 12.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 0.83 (s, 3H), 0.88 (m, 1H), 1.09 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.26 (s, 3H), 1.47–1.77 (m, 5H), 1.88 (m, 1H), 1.93–2.10 (m, 3H), 2.29 (m, 1H), 2.43 (ddd, *J* = 17.0, 10.6, 5.7 Hz, 1H), 2.62 (h, *J* = 6.9 Hz, 1H), 3.11 (ddd, *J* = 17.1, 10.9, 4.7 Hz, 1H), 3.65 (s, 3H), 6.75 (br s, 1H), 9.36 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 14.0 (CH_3), 214.9 (C), 194.5 (CH), 178.2 (C), 152.0 (CH), 144.0 (C), 51.8 (CH_3), 49.6 (CH), 45.9 (C), 43.9 (CH), 42.2 (CH_2), 40.4 (CH), 37.5 (CH_2), 36.8 (CH_2), 36.1 (C), 26.5 (CH_2), 20.5 (CH_2), 18.1 (CH_3), 18.0 (CH_3), 17.4 (CH_2), 16.8 (CH_3), 14.0 (CH_3). IR (film): 1724, 1688, 1461, 1245, 1187, 1144, 1008, 727, 671 cm^{-1}. HRMS (APcI) *m*/*z*: calcd for $C_{21}H_{32}O_4Na$ (M + Na^+) 371.2198, found: 371.2206.

(1*R*,4a*R*,5*S*,6*S*,8a*R*)-Methyl-6-(hydroxymethyl)-1,4a-dimethyl-5-(4-methyl-3-oxopentyl)-decahydronaphthalene-1-carboxylate (14).[12] To a solution of **11** (1.00 g, 2.87 mmol) in THF (20 mL) was added a 50% aqueous solution of RANEY® Nickel (4 mL), and the mixture was stirred at room temperature for 2 days, at which time TLC showed no **11**. Then, the reaction mixture was filtered through silica gel–Na_2SO_4 (15 : 3 g), washed with acetone (20 mL) and concentrated to give pure **14** (0.98 g, 97%) as a colorless syrup. $[\alpha]_D^{25}$ = +33.8 (*c* = 71.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 0.73 (s, 3H), 0.93–1.05 (m, 2H), 1.08 (d, *J* = 6.9 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H), 1.13 (s, 3H), 1.29 (m, 1H), 1.39–1.62 (m, 7H), 1.67–1.85 (m, 5H), 1.96 (m, 1H), 2.40 (ddd, *J* = 17.1, 9.1, 6.1 Hz, 1H), 2.53 (ddd, *J* = 15.2, 10.0, 6.1 Hz, 1H), 2.59 (h, *J* = 6.9 Hz, 1H), 3.54 (dd, *J* = 10.1, 10.1 Hz, 1H), 3.64 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 215.1 (C), 179.3 (C), 61.3 (CH_2), 52.7 (CH), 51.9 (CH_3), 50.8 (CH), 47.7 (C), 41.0 (CH), 39.7 (CH), 38.9 (CH_2), 38.2 (CH_2), 37.6 (C), 36.8 (CH_2), 28.8 (CH_2), 20.6 (CH_2), 19.2 (CH_2), 19.2 (CH_2), 18.4 (CH_3), 18.3 (CH_3), 17.8 (CH_2), 16.4 (CH_3), 15.9 (CH_3). IR (film): 3472, 1712, 1459, 1386, 1248, 1141, 1023, 752 cm^{-1}. HRMS (APcI) *m*/*z*: calcd for $C_{21}H_{36}O_4Na$ (M + Na^+) 375.2511, found: 375.2504.

(1*R*,4a*R*,5*S*,8a*R*)-Methyl 5-(3-hydroxy-3,4-dimethylpentyl)-6-(hydroxymethyl)-1,4a-dimethyl-decahydronaphthalene-1-carboxylate (15). To a solution of **14** (10 g, 28.37 mmol) in anhydrous THF (70 mL) was added dropwise a solution of methylmagnesium bromide (50.7 mL of a 1.4 M solution in toluene–THF, 70.92 mmol) at 0 °C. The mixture was stirred under an argon atmosphere at room temperature for 3 h, at which time TLC showed no starting material. Then, 5% aqueous NH_4Cl (15 mL) was added slowly at 0 °C and the mixture was extracted with ether (3 × 100 mL). The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4 and concentrated in vacuum. Purification by flash column chromatography on silica gel (15% ether–hexanes) gave 9.72 g of **15** (93%) (a 1 : 1 mixture of diastereomers) as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 3.74–3.66 (m, 2H), 3.65 (s, 6H), 3.55–3.47 (m, 2H), 2.00–1.85 (m, 4H), 1.79–1.64 (m, 8H), 1.61–1.39 (m, 12H), 1.36–1.22 (m, 8H), 1.14 (s, 6H), 1.07 (s, 6H), 0.99–0.92 (m, 4H), 0.91 (d, *J* = 6.7 Hz, 6H), 0.88 (d, *J* = 6.7 Hz, 6H), 0.74 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 179.3 (2C), 77.2 (C), 74.9 (C), 61.7 (CH_2), 61.6 (CH_2), 53.8 (CH), 53.7 (CH), 51.8 ($2CH_3$), 50.8 (2CH), 47.7 (2C), 39.7 (2CH), 38.5 (CH_2), 38.2 (CH_2), 38.0 (CH_2), 37.6 (2C), 37.0 (CH), 36.9 (CH_2), 36.1 (CH), 29.7 (CH_2), 29.2 ($2CH_2$), 29.0 (CH_2), 23.2 (CH_3), 22.7 (CH_3), 20.8 (CH_2), 20.7 (CH_2), 18.4 (CH_2), 18.3 (CH_2), 17.8 ($2CH_2$), 17.6 ($2CH_3$), 16.9 ($2CH_3$), 16.4 ($2CH_3$), 16.1 ($2CH_3$). IR (film): 3370, 1726, 1457, 1386, 1250, 1195, 1145, 1018, 914, 733 cm^{-1}. HRMS (APcI) *m*/*z*: calcd for $C_{22}H_{41}O_4$ (M + H^+) 369.3005, found: 369.3012.

(1*R*,4a*R*,5*S*,6*S*,8a*R*)-Methyl 5-(3,4-dimethylpent-3-enyl)-6-(hydroxymethyl)-1,4a-dimethyl-decahydronaphthalene-1-carboxylate (16). Iodine (9.35 g, 36.86 mmol) was slowly added to a solution of triphenylphosphine (PPh_3) (9.67 g, 36.86 mmol) in CH_2Cl_2 (80 mL) at 0 °C and the mixture was stirred at room temperature for 10 min. A solution of **15** (12.35 g, 33.51 mmol) in CH_2Cl_2 (40 mL) was then added and the resulting mixture was further stirred at room temperature for 2 h, at which time TLC showed no **15**. Then the solvent was removed under vacuum and ether–5% $NaHSO_3$ (120–30 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 purified by flash chromatography on silica gel (15% ether–hexanes) affording pure **16** (10.67 g, 91%) as a colorless syrup. $[\alpha]_D^{25}$ = +28.7 (*c* 4.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 3.71 (d br, *J* = 9.3 Hz, 1H), 3.56 (dd, *J* = 10.3 Hz, 10.3 Hz, 1H), 3.65 (s, 3H), 2.10 (ddd, *J* = 12.4, 12.4, 5.1 Hz, 1H), 2.02–1.83 (m, 3H), 1.79–1.66 (m, 2H), 1.64 (s, 3H), 1.63 (s, 6H), 1.61–1.36 (m, 4H), 1.35–1.26 (m, 2H), 1.13 (s, 3H), 1.07–0.93 (m, 3H), 0.79–0.72 (m, 2H), 0.71 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 179.5 (C), 128.1 (C), 124.1 (C), 61.6 (CH_2), 53.5 (CH), 52.0 (CH_3), 51.0 (CH), 47.9 (C), 40.0 (CH), 38.3 (CH_2), 37.6 (C), 37.0 (CH_2), 33.4 (CH_2), 28.8 (CH_2), 23.8 (CH_2), 20.8 (CH_2), 20.7 (CH_3), 20.2 (CH_3), 18.6 (CH_3), 18.0 (CH_2), 16.5 (CH_3), 16.2 (CH_3). IR (film): 3428, 1726, 1456, 1386, 1247, 1192, 1143, 1020, 773 cm^{-1}. HRMS (APcI) *m*/*z*: calcd for $C_{22}H_{39}O_3$ (M + H^+) 351.2899, found: 351.2907.

(1*R*,4a*R*,5*S*,6*S*,8a*R*)-Methyl 6-(hydroxymethyl)-1,4a-dimethyl-5-(3-oxobutyl)-decahydronaphthalene-1-carboxylate (17). A solution of **16** (2 g, 5.71 mmol) in CH_2Cl_2 (30 mL) was cooled to −78 °C and it was slowly bubbled with an O_3/O_2 mixture; the course of the reaction was monitored by TLC. When the starting material was consumed (1 h), the solution was flushed with argon, and triphenylphosphine (1.5 g, 5.72 mmol) was added. The reaction mixture was then warmed to room

temperature over 15 min and further stirred for 4 h. The solvent was removed, and the crude product was purified by flash column chromatography on silica gel (20% ether–hexanes) to give 1.72 g of **17** (93%) as a colourless oil. $[\alpha]_D^{25}$ = +24.3 (*c* 23.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 3.64 (s, 3H), 3.63 (d, *J* = 10.1 Hz, 1H), 3.52 (dd, *J* = 10.1, 10.1 Hz, 1H), 2.55 (dd, *J* = 10.7, 6.3 Hz, 1H), 2.51 (dd, *J* = 10.0, 5.6 Hz, 1H), 2.38 (dd, *J* = 9.5, 6.0 Hz, 1H), 2.34 (dd, *J* = 10.3, 6.7 Hz, 1H), 2.13 (s, 3H), 1.95 (dd, *J* = 9.0, 3.2 Hz, 1H), 1.83–1.66 (m, 4H), 1.58–1.38 (m, 4H), 1.31–1.22 (m, 2H), 1.12 (s, 3H), 1.01–0.93 (m, 2H), 0.72 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 209.45 (C), 179.39 (C), 61.34 (CH_2), 52.71 (CH), 52.01 (CH_3), 50.87 (CH), 47.83 (C), 42.45 (CH_2), 39.76 (CH), 38.33 (CH_2), 37.63 (C), 36.94 (CH_2), 30.19 (CH_3), 28.89 (CH_2), 20.75 (CH_2), 19.35 (CH_2), 17.93 (CH_2), 16.50 (CH_3), 16.05 (CH_3). IR (film) 3437, 1720, 1449, 1387, 1363, 1248, 1140, 1104, 1020 cm^{-1}. HRMS (APcI) *m*/*z*: calcd for $C_{19}H_{33}O_4$ ($M + H^+$) 325.2379, found: 325.2371.

(1*R*,4a*R*,5*S*,6*S*,8a*R*)-Methyl 6-(hydroxymethyl)-1,4a-dimethyl-5-(3-oxobutyl)-decahydronaphthalene-1-carboxylate (17) from 15. Iodine (2.10 g, 8.26 mmol) was added to a solution of triphenylphosphine (2.17 g, 2.28 mmol) in CH_2Cl_2 (15 mL) at 0 °C and the mixture was stirred at room temperature for 10 min. A solution of **15** (3 g, 8.15 mmol) in CH_2Cl_2 (20 mL) was then added and the resulting mixture was further stirred at room temperature for 2 h, at which time TLC showed no **15**. Then, the mixture was cooled to −78 °C and it was slowly bubbled with an O_3/O_2 mixture; the course of the reaction was monitored by TLC. When the starting material was consumed (70 min), the solution was flushed with argon, and triphenylphosphine (2.2 g, 8.39 mmol) was added. Following the same work-up used for **17** from **16**, 2.35 g of **17** (89%) was obtained as a colourless oil.

(1*R*,4a*R*,5*S*,8a*R*)-Methyl 6-(hydroxymethyl)-1,4a-dimethyl-5-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-decahydronaphthalene-1-carboxylate (18). Ethylene glycol (2.7 mL, 49.01 mmol) followed by toluene *p*-toluenesulfonic acid (15 mg) was added to **17** (10.6 g, 32.67 mmol) in benzene (40 mL) and the mixture was heated under reflux for 16 h using a Dean Stark trap. After cooling to room temperature and concentrating under reduced pressure, ether (100 mL) was added and the solution was washed with saturated aqueous $NaHCO_3$ (3 × 30 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound **18** (11.80 g, 98%) as a colourless oil. $[\alpha]_D^{25}$ = +16.8 (*c* 17.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 3.97–3.87 (m, 4H), 3.67 (dd, *J* = 10.3, 10.3 Hz, 1H), 3.64 (s, 3H), 3.52 (dd, *J* = 10.3, 10.3 Hz, 1H), 2.15 (d, *J* = 9.5 Hz, 1H), 1.96 (d, *J* = 7.4 Hz, 1H), 1.87 (d, *J* = 9.4 Hz, 1H), 1.80–1.67 (m, 4H), 1.60–1.47 (m, 4H), 1.46–1.38 (m, 2H), 1.31 (s, 3H), 1.30–1.22 (m, 2H), 1.13 (s, 3H), 1.03–0.93 (m, 2H), 0.73 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 179.4 (C), 110.4 (C), 64.8 ($2CH_2$), 61.5 (CH_2), 53.3 (CH), 52.0 (CH_3), 51.0 (CH), 47.9 (C), 39.9 (CH), 38.4 (CH_2), 37.7 (CH_2), 37.7 (C), 37.0 (CH_2), 28.9 (CH_2), 27.1 (CH_3), 23.9 (CH_3), 20.8 (CH_2), 19.5 (CH_2), 18.0 (CH_2), 16.6 (CH_3), 16.2 (CH_3). IR (film): 3498, 1783, 1724, 1580, 1451, 1389, 1247, 1187 cm^{-1}. HRMS (APcI) *m*/*z*: calcd for $C_{21}H_{37}O_5$ ($M + H^+$) 369.2641, found: 369.2653.

(1*R*,4a*R*,5*S*,6*S*,8a*R*)-Methyl 6-formyl-1,4a-dimethyl-5-(2-(2-methyl-1,3-dioxolan-2-yl))-decahydronaphthalene-1-carboxylate (19). Pyridinium dichromate (PDC; 5.33 g, 14.16 mmol) was added to a stirred solution of **18** (2.61 g, 7.08 mmol) in dry CH_2Cl_2 (40 mL) and the mixture was stirred at room temperature under an argon atmosphere for 10 h, at which time TLC showed no remaining starting material. Then, the reaction mixture was worked up by the addition of ether (40 mL), and the resulting mixture was filtered through a silica gel pad and washed with a mixture of ether (20 mL). The filtrate was washed with a 1 N HCl solution (20 mL) and brine and dried over anhydrous Na_2SO_4. The solvent was evaporated to yield 2.39 g of aldehyde **19** (92%) as a colourless syrup. $[\alpha]_D^{25}$ = +23.7 (*c* 39.4, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 9.97 (s, 1H), 3.99–3.86 (m, 4H), 3.65 (s, 3H), 2.51 (t, *J* = 4.9 Hz, 1H), 2.31 (br d, *J* = 14.6 Hz, 1H), 1.97–1.86 (m, 1H), 1.81–1.68 (m, 5H), 1.65–1.51 (m, 5H), 1.46 (ddd, *J* = 12.9, 12.9, 3.6 Hz, 1H), 1.34 (s, 3H), 1.25 (d, *J* = 3.2 Hz, 1H), 1.18 (m, 1H), 1.12 (s, 3H), 1.05 (m, 1H), 0.76 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 204.8 (CH), 179.3 (C), 110.2 (C), 64.8 ($2CH_2$), 53.9 (CH), 52.1 (CH_3), 50.2 (CH), 47.7 (C), 47.6 (CH), 38.3 (C), 38.0 ($2CH_2$), 37.1 (CH_2), 26.0 (CH_2), 23.9 (CH_3), 21.8 (CH_2), 19.3 (CH_2), 18.0 (CH_2), 16.5 (CH_3), 15.5 (CH_3). IR (film): 1724, 1448, 1388, 1248, 1061, 754 cm^{-1}. HRMS (APcI) *m*/*z*: calcd for $C_{21}H_{34}O_5Na$ ($M + Na^+$) 389.2304, found: 389.2306.

(1*R*,4a*R*,5*R*,6*S*,8a*R*)-Methyl 6-formyl-1,4a,6-trimethyl-5-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-decahydronaphthalene-1-carboxylate (10). Potassium *tert*-butoxide (252 mg, 2.249 mmol) was added to a stirred solution of **19** (633 mg, 1.73 mmol) in dry benzene (30 mL) under an argon atmosphere. After 5 min methyl iodide (0.4 mL, 5.19 mmol) was added and the reaction mixture was stirred at room temperature for 2 h, at which time TLC showed no starting material. The mixture was concentrated *in vacuo* to give a crude product, which was dissolved in ether (40 mL) and washed with brine (2 × 10 mL). The organic phase was dried over anhydrous Na_2SO_4 and the solvent was evaporated to give a crude product, which was purified by flash chromatography on silica gel (15% ether–hexanes), affording 545 mg of **10** (83%) as colourless syrups. $[\alpha]_D^{25}$ = +2.7 (*c* 16.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 9.80 (d, *J* = 1.2 Hz, 1H), 4.01–3.89 (m, 4H), 3.64 (s, 3H), 2.16 (dt, *J* = 13.4, 3.1 Hz, 1H), 1.85–1.65 (m, 5H), 1.62–1.37 (m, 5H), 1.32 (s, 3H), 1.26–1.11 (m, 3H), 1.09 (s, 3H), 1.04 (m, 1H), 1.01 (s, 3H), 0.98 (d, *J* = 6.4 Hz, 1H), 0.74 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 206.3 (CH), 179.3 (C), 109.8 (C), 64.8 ($2CH_2$), 60.9 (CH), 52.0 (CH_3), 50.3 (CH), 50.1 (C), 47.6 (C), 43.3 (CH_2), 38.9 (C), 37.9 (CH_2), 37.1 (CH_2), 35.1 (CH_2), 24.2 (CH_3), 23.8 (CH_3), 22.1 (CH_2), 18.8 (CH_2), 17.8 (CH_2), 16.5 (CH_3), 15.5 (CH_3). IR (film): 1725, 1457, 1377, 1246, 1061, 857, 756 cm^{-1}. HRMS (APcI) *m*/*z*: calcd for $C_{22}H_{36}O_5Na$ ($M + Na^+$) 403.2460, found: 403.2454.

(3a*R*,5a*R*,6*R*,9a*R*,9b*S*)-Methyl 2-acetyl-3a,6,9a-trimethyl-3a,4,5,5a,6,7,8,9,9a,9b-decahydro-1*H*-cyclopenta[*a*]naphthalene-6-carboxylate (20). HCl (4 mL, 1 M) was added to a stirred solution of **10** (300 mg, 0.79 mmol) in THF (25 mL). The reaction mixture was heated under reflux for 3 h, at which time TLC showed no **10**. The reaction was allowed to cool to room

temperature and the solvent was evaporated *in vacuo*. Then, the residue was dissolved in ether (30 mL) and washed with water (2 × 10 mL) and brine (2 × 10 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography (15% ether–hexanes) to give 213 mg (85%) of methyl ketone **20** as a colourless syrup. $[\alpha]_D^{25}$ = +7.7 (*c* 10.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.46 (d, *J* = 2.1 Hz, 1H), 3.66 (s, 3H), 2.61 (ddd, *J* = 17.1, 7.8, 2.4 Hz, 1H), 2.46 (d, *J* = 16.9 Hz, 1H), 2.28 (s, 3H), 1.88 (dt, *J* = 13.7, 6.0 Hz, 1H), 1.75 (dd, *J* = 11.2, 4.7 Hz, 1H), 1.71–1.64 (m, 3H), 1.62–1.56 (m, 2H), 1.55–1.44 (m, 2H), 1.39 (m, 1H), 1.26 (m, 1H), 1.18 (s, 3H), 1.08 (s, 3H), 0.97 (ddd, *J* = 12.9, 12.9, 4.3 Hz, 1H), 0.71 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 197.3 (C), 179.3 (C), 154.7 (CH), 143.1 (C), 59.8 (CH), 52.0 (CH_3), 48.8 (C), 47.1 (C), 45.6 (CH), 40.5 (CH_2), 37.1 (CH_2), 36.3 (C), 33.6 (CH_2), 31.2 (CH_2), 30.5 (CH_3), 26.7 (CH_3), 21.4 (CH_2), 17.7 (CH_2), 17.0 (CH_3), 16.0 (CH_3). IR (film): 1726, 1667, 1457, 1366, 1245, 1175, 1137, 1068, 603 cm^{-1}. HRMS (APcI) *m*/*z*: calcd for $C_{20}H_{31}O_3$ (M + H$^+$) 319.2273, found: 319.2271.

(3a*R*,5a*R*,6*R*,9a*R*,9b*S*)-Methyl 2-(1-acetoxyvinyl)-3a,6,9a-trimethyl-3a,4,5,5a,6,7,8,9,9a,9b-decahydro-1*H*-cyclopenta[*a*]naphthalene-6-carboxylate (9). *p*-Toluenesulfonic acid (15 mg) was added to a stirred solution of **20** (450 mg, 1.41 mmol) in isopropenyl acetate (15 mL). The reaction mixture was heated under reflux for 3 h, at which time TLC showed no **20**. The reaction was allowed to cool to room temperature and ether (30 mL) was added. Then, the solution was washed with saturated aqueous $NaHCO_3$ (3 × 10 mL). The organic phase was dried over anhydrous Na_2SO_4 and the solvent was evaporated to give a crude product, which was purified by flash chromatography on silica gel (5% ether–hexanes), affording 494 mg of **9** (97%) as a colourless syrup. $[\alpha]_D^{25}$ = +25.7 (*c* 16.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.52 (d, *J* = 1.7 Hz, 1H), 4.90 (d, *J* = 1.3 Hz, 1H), 4.79 (d, *J* = 1.5 Hz, 1H), 3.65 (s, 3H), 2.64 (ddd, *J* = 16.1, 7.9, 2.3 Hz, 1H), 2.26 (d, *J* = 16.0 Hz, 1H), 2.19 (s, 3H), 1.79 (dd, *J* = 13.4, 6.0 Hz, 1H), 1.74 (dd, 10.9, 4.8 Hz, 1H), 1.71–1.63 (m, 3H), 1.61–1.52 (m, 2H), 1.51–1.34 (m, 3H), 1.22 (m, 1H), 1.18 (s, 3H), 1.02 (s, 3H), 0.98 (ddd, *J* = 12.9, 12.9, 3.9 Hz, 1H), 0.78 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 179.4 (C), 169.0 (C), 150.8 (C), 140.2 (CH), 134.8 (C), 102.4 (CH_2), 60.3 (CH), 52.0 (CH_3), 47.9 (C), 47.1 (C), 45.7 (CH), 40.8 (CH_2), 37.1 (CH_2), 36.3 (C), 33.9 (CH_2), 32.8 (CH_2), 31.0 (CH_3), 21.4 (CH_2), 21.1 (CH_3), 17.8 (CH_2), 17.0 (CH_3), 15.8 (CH_3). IR (film): 1765, 1725, 1447, 1370, 1204, 1069, 1020, 858 cm^{-1}. HRMS (APcI) *m*/*z*: calcd for $C_{22}H_{32}O_4Na$ (M + Na$^+$) 383.2198, found: 383.2206.

(4*R*,4a*R*,6a*S*,11a*R*,11b*R*)-Dimethyl 10-acetoxy-4,6a,11b-trimethyl-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1*H*-benzo[*a*]fluorene-4,7-dicarboxylate (21). Methyl propiolate (262 mg, 3.12 mmol) was added to a solution of diene **9** (450 mg, 1.25 mmol) in xylene (5 mL), and the mixture was heated at 170 °C for 36 h in a sealed tube. At this time, TLC showed no remaining starting material. The reaction was allowed to cool to room temperature and then concentrated *in vacuo* to give an unresolvable mixture of adducts. To a solution of this crude product in 1,4-dioxane (15 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 567 mg, 2.5 mmol), and the reaction mixture was stirred at 100 °C for 1 h. Then the solvent was evaporated *in vacuo*, and the residue was dissolved in ether (50 mL), washed with water (5 × 15 mL) and brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated to give a crude product which was chromatographed on silica gel (10% ether–hexanes) to give 552 mg of a 6 : 1 mixture of compound **21** and its regioisomer (92%) as a colourless syrup. A further chromatography of this mixture on silica gel (5% ether–hexanes) provided 420 mg of the pure regioisomer **21** (70%). $[\alpha]_D^{25}$ = +21.0 (*c* 13.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.35 (d, *J* = 8.3 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 3.86 (s, 3H), 3.66 (s, 3H), 2.87 (dd, *J* = 16.7, 7.1 Hz, 1H), 2.57 (d, *J* = 16.6 Hz, 1H), 2.40 (dt, *J* = 14.9, 4.0 Hz, 1H), 2.31 (s, 3H), 1.82 (d, *J* = 7.1 Hz, 1H), 1.78 (dd, *J* = 11.7, 2.8 Hz, 1H), 1.75–1.66 (m, 3H), 1.66–1.51 (m, 3H), 1.48 (dt, *J* = 17.5, 6.5 Hz, 1H), 1.34 (s, 3H), 1.24 (m, 1H), 1.08 (s, 3H), 1.00 (ddd, *J* = 12.5, 12.5, 4.9 Hz, 1H), 0.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 179.5 (C), 169.5 (C), 168.5 (C), 151.8 (C), 148.6 (C), 137.4 (C), 128.7 (CH), 125.9 (C), 119.5 (CH), 63.1 (CH), 52.2 (CH_3), 52.0 (CH_3), 49.5 (C), 48.0 (CH), 47.3 (C), 39.7 (CH_2), 37.0 (CH_2), 36.8 (C), 33.7 (CH_2), 31.8 (CH_3), 28.4 (CH_2), 22.1 (CH_2), 21.0 (CH_3), 17.7 (CH_2), 17.1 (CH_3), 15.6 (CH_3). IR (film): 1768, 1725, 1448, 1252, 1207, 1162, 986, 755 cm^{-1}. HRMS (APcI) *m*/*z*: calcd for $C_{26}H_{34}O_6Na$ (M + Na$^+$) 465.2253, found: 465.2246.

(4*R*,4a*R*,6a*S*,11a*R*,11b*R*)-Dimethyl 10-hydroxy-4,6a,11b-trimethyl-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1*H*-benzo[*a*]fluorene-4,7-dicarboxylate (22). Conc. hydrochloric acid (1 mL) was added to a stirred solution of **21** (440 mg, 0.99 mmol) in MeOH (10 mL) and the reaction mixture was refluxed for 30 min, at which time TLC showed no starting material remaining. Then, the solvent was removed under vacuum and ether–water (30 : 10 mL) was added. 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 (35% ether–hexanes) to yield 386 mg of **22** (97%) as a colourless syrup. $[\alpha]_D^{25}$ = +17.8 (*c* 11.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.35 (d, *J* = 8.3 Hz, 1H), 6.60 (d, *J* = 8.3 Hz, 1H), 5.31 (s, 1H), 3.84 (s, 3H), 3.66 (s, 3H), 2.87 (dd, *J* = 16.1, 7.1 Hz, 1H), 2.67 (d, *J* = 16.1 Hz, 1H), 2.45 (dt, *J* = 14.8, 4.3 Hz, 1H), 1.84 (d, *J* = 7.1 Hz, 1H), 1.79 (dd, *J* = 11.5, 3.1 Hz, 1H), 1.77–1.69 (m, 3H), 1.68–1.60 (m, 2H), 1.55 (m, 1H), 1.49 (dt, *J* = 10.1, 3.1 Hz, 1H), 1.37 (s, 3H), 1.24 (m, 1H), 1.08 (s, 3H), 1.02 (ddd, *J* = 12.7, 12.7, 5.2 Hz, 1H), 0.31 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 179.6 (C), 169.6 (C), 153.9 (C), 152.6 (C), 130.4 (C), 130.1 (CH), 120.8 (C), 112.9 (CH), 63.5 (CH), 52.1 (CH_3), 51.9 (CH_3), 49.6 (C), 48.0 (CH), 47.3 (C), 39.9 (CH_2), 37.0 (CH_2), 36.9 (C), 33.4 (CH_2), 31.5 (CH_3), 27.4 (CH_2), 22.2 (CH_2), 17.8 (CH_2), 17.1 (CH_3), 15.7 (CH_3). IR (film): 3413, 1721, 1700, 1583, 1434, 1258, 1134, 757 cm^{-1}. HRMS (APcI) *m*/*z*: calcd for $C_{24}H_{33}O_5$ (M + H$^+$) 401.2328, found: 401.2331.

(4*R*,4a*R*,6a*S*,11a*R*,11b*R*)-Dimethyl 10-methoxy-4,6a,11b-trimethyl-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1*H*-benzo[*a*]fluorene-4,7-dicarboxylate (23). Methyl iodide (160 mg, 1.13 mmol)

was added to a stirred suspension of **22** (350 mg, 0.87 mmol) and K_2CO_3 (180 mg, 1.30 mmol) in acetone (10 mL) under an argon atmosphere. The mixture was heated under reflux overnight. Then, the solvent was evaporated *in vacuo*, ether (40 mL) was added and the mixture was washed with water (2 × 10 mL) and brine (1 × 10 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated to give a crude product which was purified by flash chromatography (10% ether–hexanes) to give 355 mg (98%) of **23** as a colourless syrup. $[\alpha]_D^{25}$ = +21.1 (*c* 13.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.45 (d, *J* = 8.5 Hz, 1H), 6.65 (d, *J* = 8.5 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.66 (s, 3H), 2.84 (dd, *J* = 17.0, 6.8 Hz, 1H), 2.72 (d, *J* = 16.7 Hz, 1H), 2.43 (dt, *J* = 14.8, 4.4 Hz, 1H), 1.83–1.76 (m, 2H), 1.68 (ddd, *J* = 14.0, 13.5, 8.2 Hz, 2H), 1.57–1.44 (m, 3H), 1.37 (s, 3H), 1.30–1.21 (m, 2H), 1.12 (m, 1H), 1.08 (s, 3H), 1.02 (m, 1H), 0.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 179.6 (C), 169.6 (C), 157.6 (C), 151.9 (C), 132.8 (C), 130.1 (CH), 120.6 (C), 107.7 (CH), 63.4 (CH), 55.4 (CH_3), 52.0 (CH_3), 51.9 (CH_3), 49.6 (C), 47.9 (CH), 47.3 (C), 39.8 (CH_2), 37.0 (C), 36.9 (CH_2), 33.3 (CH_2), 31.4 (CH_3), 28.0 (CH_2), 22.1 (CH_2), 17.8 (CH_2), 17.1 (CH_3), 15.7 (CH_3). IR (film): 1727, 1457, 1434, 1259, 1188, 1138, 755 cm^{-1}. HRMS (APcI) *m*/*z*: calcd for $C_{25}H_{34}O_5Na$ (M + Na^+) 437.2304, found: 437.2297.

((4*R*,4a*R*,6a*S*,11a*R*,11b*R*)-10-Methoxy-4,6a,11b-trimethyl-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1*H*-benzo[*a*]fluorene-4,7-diyl)dimethanol (24). $LiAlH_4$ (40 mg, 1.05 mmol) was added to a stirred solution of **23** (175 mg, 0.42 mmol) in dry THF (10 mL) cooled to 0 °C and the reaction mixture was stirred under an argon atmosphere for 2 h, at which time TLC showed no remaining starting material. Then 2 N HCl (0.5 mL) was added slowly at 0 °C, and the mixture was extracted with ether (2 × 20 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and the solvent was evaporated to give 153 mg of pure **24** (94%) as a colourless syrup. $[\alpha]_D^{25}$ = +4.2 (*c* 8.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.10 (d, *J* = 8.1 Hz, 1H), 6.64 (d, *J* = 8.3 Hz, 1H), 4.71 (s, 2H), 3.82 (s, 3H), 3.41 (d, *J* = 10.3 Hz, 1H), 3.13 (d, *J* = 10.6 Hz, 1H), 2.85 (dd, *J* = 16.9, 7.5 Hz, 1H), 2.73 (d, *J* = 17.0 Hz, 1H), 2.59 (d, *J* = 14.5 Hz, 1H), 1.81–1.67 (m, 3H), 1.66–1.35 (m, 5H), 1.25 (s, 3H), 1.03–0.80 (m, 3H), 0.73 (s, 3H), 0.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 155.4 (C), 151.0 (C), 132.0 (C), 129.3 (CH), 127.9 (C), 108.0 (CH), 72.2 (CH_2), 63.1 (CH_2), 62.4 (CH), 55.3 (CH_3), 49.6 (C), 46.1 (CH), 40.4 (CH_2), 37.7 (C), 37.2 (C), 35.5 (CH_2), 34.8 (CH_2), 32.6 (CH_3), 28.3 (CH_2), 19.7 (CH_2), 17.9 (CH_2), 17.9 (CH_3), 16.1 (CH_3). IR (film): 3357, 1605, 1493, 1462, 1385, 1249, 1056, 757, 668 cm^{-1}. HRMS (APcI) *m*/*z*: calcd for $C_{23}H_{35}O_3$ (M + H^+) 359.2586, found: 359.2588.

(4*R*,4a*R*,6a*S*,11a*R*,11b*R*)-4-(Hydroxymethyl)-10-methoxy-4,6a,-11b-trimethyl-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1*H*-benzo[*a*]-fluorene-7-carbaldehyde (25). To a solution of **24** (275 mg, 0.71 mmol) in chloroform (15 mL) was added manganese(IV) oxide (371 mg, 4.26 mmol) and the reaction mixture was stirred at room temperature for 4 h. The inorganic solid was removed by filtration of the mixture through a silica gel pad (10 g) and washed with ether (10 mL). The combined filtrates were evaporated to yield 246 mg (91%) of compound **25** as a colourless syrup. $[\alpha]_D^{25}$ = −23.8 (*c* 6.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 10.33 (s, 1H), 7.78 (d, *J* = 8.5 Hz, 1H), 6.76 (d, *J* = 8.5 Hz, 1H), 3.90 (s, 3H), 3.40 (d, *J* = 10.7 Hz, 1H), 3.15 (d, *J* = 10.6 Hz, 1H), 2.91 (dd, *J* = 17.3, 8.7 Hz, 1H), 2.79 (d, *J* = 17.3 Hz, 1H), 2.37 (dd, *J* = 14.3, 6.3 Hz, 1H), 2.06 (dd, *J* = 14.1, 6.8 Hz, 1H), 1.81 (d, *J* = 8.7 Hz, 1H), 1.72 (d, *J* = 13.1 Hz, 1H), 1.65 (m, 1H), 1.60–1.45 (m, 2H), 1.42 (s, 3H), 1.41–1.25 (m, 4H), 0.95 (ddd, *J* = 13.0, 13.0, 3.4 Hz, 1H), 0.78 (s, 3H), 0.56 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 190.4 (CH), 160.1 (C), 156.5 (C), 132.1 (C), 132.0 (CH), 126.4 (C), 108.2 (CH), 71.9 (CH_2), 62.3 (CH), 55.6 (CH_3), 50.1 (C), 44.3 (CH), 41.1 (CH_2), 38.0 (C), 37.1 (C), 35.5 (CH_2), 34.6 (CH_2), 32.5 (CH_3), 28.8 (CH_2), 19.1 (CH_2), 17.9 (CH_2), 17.4 (CH_3), 16.3 (CH_3). IR (film): 3481, 1675, 1593, 1462, 1273, 1251, 1050, 757 cm^{-1}. HRMS (APcI) *m*/*z*: calcd for $C_{23}H_{33}O_3$ (M + H^+) 357.2430, found: 357.2422.

(4*R*,4a*R*,6a*S*,11a*R*,11b*R*)-4-(Hydroxymethyl)-10-methoxy-4,6a,11b-trimethyl-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1*H*-benzo[*a*]fluoren-7-yl formate (26). *m*-Chloroperoxybenzoic acid (MCPBA, 75%; 106 mg, 0.46 mmol) was added at 0 °C to a stirred solution of **25** (147 mg, 0.38 mmol) in CH_2Cl_2 (10 mL) and the reaction was stirred for 3 h, at which time TLC indicated no starting material remaining. The reaction was quenched with sat. aq. Na_2SO_3 (0.5 mL) and stirred for an additional 10 min. Then, it was poured into ether–water (20 : 7 mL), and the organic phase was washed with sat. aq. $NaHCO_3$ (5 × 8 mL) and brine, dried over Na_2SO_4 and concentrated to give **26** (148 mg, 97%) as a colourless oil. $[\alpha]_D^{25}$ = −4.3 (*c* 9.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 8.30 (s, 1H), 6.78 (d, *J* = 8.7 Hz, 1H), 6.64 (d, *J* = 8.7 Hz, 1H), 3.82 (s, 3H), 3.39 (d, *J* = 10.8 Hz, 1H), 3.12 (d, *J* = 10.8 Hz, 1H), 2.87 (dd, *J* = 17.2, 7.8 Hz, 1H), 2.76 (d, *J* = 16.3 Hz, 1H), 2.43 (dt, *J* = 16.3, 5.1 Hz, 1H), 1.74 (d, *J* = 6.3 Hz, 1H), 1.67 (m, 1H), 1.57 (m, 1H), 1.55–1.41 (m, 2H), 1.38 (dd, *J* = 13.2, 4.0 Hz, 1H), 1.33–1.24 (m, 4H), 1.20 (s, 3H), 0.92 (ddd, *J* = 12.9, 12.9, 3.5 Hz, 1H), 0.74 (s, 3H), 0.50 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 160.5 (CH), 153.7 (C), 143.4 (C), 139.6 (C), 133.5 (C), 121.1 (CH), 109.0 (CH), 72.1 (CH_2), 62.1 (CH), 55.6 (CH_3), 48.6 (C), 45.2 (CH), 40.8 (CH_2), 37.8 (C), 37.1 (C), 35.5 (CH_2), 33.5 (CH_2), 31.5 (CH_3), 29.0 (CH_2), 19.2 (CH_2), 17.8 (CH_2), 17.8 (CH_3), 16.2 (CH_3). IR (film): 3455, 1740, 1591, 1485, 1465, 1221, 1129, 1056, 757 cm^{-1}. HRMS (APcI) *m*/*z*: calcd for $C_{23}H_{33}O_4$ (M + H^+) 373.2379, found: 373.2386.

(4*R*,4a*R*,6a*S*,11a*R*,11b*R*)-4-(Iodomethyl)-10-methoxy-4,6a,11b-trimethyl-2,3,4,4a,5,6,6a,7,10,11,11a,11b-dodecahydro-1*H*-benzo[*a*]fluoren-7-yl formate (27). To a solution of triphenylphosphine (487 mg, 1.86 mmol) in dry CH_2Cl_2 (10 mL) was added successively iodine (503 mg, 1.98 mmol) and imidazole (253 mg, 3.72 mmol). The mixture was stirred at room temperature for 5 min and a solution of alcohol **26** (230 mg, 0.62 mmol) in dry benzene (40 mL) was added. The resulting mixture was stirred at reflux for 16 h; at this time TLC showed no **26**. 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 Et_2O–water (50–15 mL) 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 (5% ether–hexanes) to give **27** (229 mg, 77%) as a colourless oil. $[\alpha]_D^{25} = -32.8$ (*c* 11.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.30 (s, 1H), 6.79 (d, *J* = 8.6 Hz, 1H), 6.65 (d, *J* = 8.7 Hz, 1H), 3.82 (s, 3H), 3.28 (d, *J* = 9.9 Hz, 1H), 3.15 (d, *J* = 9.9 Hz, 1H), 2.91 (dd, *J* = 17.4, 8.2 Hz, 1H), 2.76 (dd, *J* = 17.3, 2.0 Hz, 1H), 2.32 (dt, *J* = 14.4, 6.2 Hz, 1H), 1.78 (dd, *J* = 8.3, 1.9 Hz, 1H), 1.75 (m, 1H), 1.70 (dt, *J* = 12.9, 3.0 Hz, 1H), 1.54–1.42 (m, 2H), 1.37–1.30 (m, 3H), 1.24 (s, 3H), 1.18 (d, *J* = 4.9 Hz, 1H), 1.11 (d, *J* = 12.3 Hz, 1H), 0.97 (s, 3H), 0.93 (m, 1H), 0.53 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 160.4 (CH), 153.7 (C), 143.5 (C), 139.6 (C), 133.1 (C), 121.1 (CH), 108.9 (CH), 62.1 (CH), 55.6 (CH_3), 48.6 (C), 48.1 (CH), 40.9 (CH_2), 39.3 (CH_2), 37.2 (C), 35.8 (C), 32.8 (CH_2), 31.2 (CH_3), 29.2 (CH_2), 28.7 (CH_2), 18.7 (CH_2), 18.6 (CH_3), 18.2 (CH_2), 15.6 (CH_3). IR (film): 1740, 1485, 1220, 1126, 1054, 756 cm^{-1}. HRMS (APcI) *m*/*z*: calcd for $C_{23}H_{31}O_3INa$ ($M + Na^+$) 505.1216, found: 505.1208.

(4a*S*,6a*S*,11a*R*,11b*S*)-10-Methoxy-4,4,6a,11b-tetramethyl-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1*H*-benzo[*a*]fluoren-7-ol (28). To a solution of **27** (250 mg, 0.52 mmol) in THF (10 mL) was added 50% aqueous solution of RANEY® Nickel (5 mL) and the mixture was stirred at room temperature for 10 h; at this time TLC showed no **27**. Then, the reaction mixture was filtered through a silica gel–Na_2SO_4 pad (20 : 5 g), washed with acetone (20 mL) and concentrated to give pure **28** (150 mg, 91%) as a colourless syrup. $[\alpha]_D^{25} = -7.5$ (*c* 13.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.50 (d, *J* = 8.5 Hz, 1H), 6.46 (d, *J* = 8.5 Hz, 1H), 4.31 (s, 1H), 3.77 (s, 3H), 2.86 (dd, *J* = 17.1, 8.1 Hz, 1H), 2.73 (dd, *J* = 17.1, 2.0 Hz, 1H), 2.60 (dt, *J* = 13.8, 6.2 Hz, 1H), 1.78 (d, *J* = 14.5 Hz, 1H), 1.77 (dd, *J* = 14.0, 1.9 Hz, 1H), 1.75–1.70 (m, 2H), 1.50 (m, 1H), 1.44–1.29 (m, 4H), 1.26 (s, 3H), 1.16 (ddd, *J* = 13.8, 13.8, 4.3 Hz, 1H), 1.01 (dd, *J* = 11.2, 5.0 Hz, 1H), 0.88 (s, 3H), 0.81 (s, 3H), 0.52 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 149.9 (C), 146.0 (C), 138.7 (C), 133.0 (C), 114.3 (CH), 109.0 (CH), 62.1 (CH), 55.8 (CH_3), 51.7 (CH), 48.3 (C), 42.4 (CH_2), 41.6 (CH_2), 37.3 (C), 33.5 (C), 33.4 (CH_2), 33.4 (CH_3), 30.8 (CH_3), 29.2 (CH_2), 21.9 (CH_3), 19.6 (CH_2), 18.6 (CH_2), 15.7 (CH_3). IR (film): 3419, 1493, 1452, 1264, 1247, 1060, 795 cm^{-1}. HRMS (APcI) *m*/*z*: calcd for $C_{22}H_{33}O_2$ ($M + H^+$) 329.2481, found: 329.2484.

(4a*S*,6a*S*,11a*R*,11b*S*)-8-Bromo-10-methoxy-4,4,6a,11b-tetramethyl-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1*H*-benzo[*a*]fluoren-7-ol (29). A solution of bromine (0.09 mL, 1.72 mmol) in CH_2Cl_2 (3 mL) was added to a solution of **28** (283 mg, 0.86 mmol) in CH_2Cl_2 (10 mL) at 0 °C, and the reaction mixture was stirred for 10 min. A 5% $NaHSO_3$ solution (1 mL) was added to quench the reaction and the mixture was stirred for an additional 5 min. Then ether (25 mL) was added and the organic phase was washed with water (6 × 10 mL) and brine and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the crude product was purified by flash column chromatography on silica gel (15% ether–hexanes) to give 312 mg of **29** (89%) as a yellow syrup. $[\alpha]_D^{25} = +4.6$ (*c* 8.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.72 (s, 1H), 5.09 (s, 1H), 3.75 (s, 3H), 2.80 (dd, *J* = 17.2, 8.0 Hz, 1H), 2.69 (dd, *J* = 17.5, 2.3 Hz, 1H), 2.65 (dt, *J* = 12.0, 5.6 Hz, 1H), 2.64 (dd, *J* = 10.0, 4.0 Hz, 1H), 1.75 (dd, *J* = 8.6, 6.2 Hz, 1H), 1.72 (dd, *J* = 5.4, 3.1 Hz, 1H), 1.70–1.59 (m, 2H), 1.50 (m, 1H), 1.44–1.25 (m, 2H), 1.23 (s, 3H), 1.15 (m, 1H), 0.98 (dd, *J* = 11.2, 4.8 Hz, 1H), 0.91 (dd, *J* = 13.0, 3.5 Hz, 1H), 0.88 (s, 3H), 0.81 (s, 3H), 0.50 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 149.5 (C), 142.7 (C), 139.1 (C), 133.1 (C), 111.7 (CH), 107.8 (C), 62.0 (CH), 56.0 (CH_3), 51.8 (CH), 49.2 (C), 42.3 (CH_2), 41.5 (CH_2), 37.3 (C), 33.4 (CH_3), 33.4(C), 32.9 (CH_2), 30.5 (CH_3), 29.1 (CH_2), 21.9 (CH_3), 19.6 (CH_2), 18.6 (CH_2), 15.7 (CH_3). IR (film): 3525, 1474, 1451, 1268, 1224, 1175, 1061, 1013, 771, 669 cm^{-1}. HRMS (APcI) *m*/*z*: calcd for $C_{22}H_{32}BrO_2$ ($M + H^+$) 407.1586, found: 407.1586.

(4a*S*,6a*S*,11a*R*,11b*S*)-8-Bromo-7,10-dimethoxy-4,4,6a,11b-tetramethyl-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1*H*-benzo[*a*]-fluorene (8). Methyl iodide (139 mg, 0.98 mmol) was added to a stirred suspension of **29** (305 mg, 0.75 mmol) and K_2CO_3 (155 mg, 1.13 mmol) in acetone (25 mL) under an argon atmosphere. The mixture was heated under reflux overnight. Then, the solvent was evaporated *in vacuo*, ether (40 mL) was added and the mixture was washed with water (2 × 10 mL) and brine (1 × 10 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated to give a crude product which was purified by flash chromatography (5% ether–hexanes) to give 306 mg (97%) of **8** as a colorless syrup. $[\alpha]_D^{25} = +0.2$ (*c* 8.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.82 (s, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 2.76 (ddd, *J* = 10.4, 8.3, 4.2 Hz, 1H), 2.65 (d, *J* = 16.8 Hz, 1H), 1.71 (br d, *J* = 11.3 Hz, 1H), 1.67–1.57 (m, 3H), 1.48 (m, 1H), 1.43–1.24 (m, 5H), 1.15 (ddd, *J* = 13.1, 13.1, 4.0 Hz, 1H), 0.95 (dd, *J* = 11.5, 3.3 Hz, 1H), 1.22 (s, 3H), 0.88 (s, 3H), 0.78 (s, 3H), 0.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 152.0 (C), 147.4 (C), 145.7 (C), 132.6 (C), 114.9 (C), 113.6 (CH), 62.3 (CH), 61.6 (CH), 55.8 (CH_3), 52.8 (CH_3), 49.4 (C), 42.2 (CH_2), 41.0 (CH_2), 37.4 (C), 34.2 (CH_2), 33.6 (CH_3), 33.3 (C), 32.7 (CH_3), 28.6 (CH_2), 22.1 (CH_3), 20.0 (CH_2), 18.6 (CH_2), 15.5 (CH_3). IR (film): 1595, 1472, 1427, 1224, 1052, 966, 828, 770 cm^{-1}. HRMS (APcI) *m*/*z*: calcd for $C_{23}H_{33}BrO_2Na$ ($M + Na^+$) 443.1562, found: 443.1557.

(4a*S*,6a*S*,11a*R*,11b*S*)-7,10-Dimethoxy-4,4,6a,11b-tetramethyl-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1*H*-benzo[*a*]fluorene-8-carbaldehyde (30). To a solution of **8** (310 mg, 0.73 mmol) in THF (20 mL) was added *n*-butyllithium (2.4 M, 0.9 mL, 2.19 mmol) at −78 °C under an argon atmosphere, and the reaction mixture was stirred at this temperature for 45 min. Freshly distilled DMF (0.17 mL, 2.19 mmol) was then added and the mixture was stirred for a further 2 h, at which time TLC showed no starting material. Then the mixture was quenched with water (0.3 mL) and the solvent was removed, and ether–water (40–10 mL) were added to the crude product. The phases were shaken and 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 that was directly purified by flash chromatography (7% ether–hexanes) to give 229 mg of aldehyde **30** (84%) as a colorless syrup. $[\alpha]_D^{25} = -29.5$ (*c* 14.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$,

500 MHz) δ: 10.29 (s, 1H), 7.13 (s, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 2.83 (ddd, J = 15.7, 14.5, 6.9 Hz, 1H), 2.76 (d, J = 17.8 Hz, 1H), 1.76–1.59 (m, 4H), 1.54–1.43 (m, 2H), 1.43–1.28 (m, 4H), 1.26 (s, 3H), 1.16 (dd, J = 13.2, 13.2, 4.2 Hz, 1H), 0.97 (dd, J = 11.5, 3.2 Hz, 1H), 0.89 (s, 3H), 0.78 (s, 3H), 0.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 189.7 (CH), 154.9 (C), 152.3 (C), 145.4 (C), 142.1 (C), 129.0 (C), 107.6 (CH), 65.8 (CH), 62.4 (CH), 55.7 (CH_3), 52.7 (CH_3), 48.8 (C), 42.2 (CH_2), 40.9 (CH_2), 37.4 (C), 34.2 (CH_2), 33.6 (CH_3), 33.3 (C), 32.6 (CH_3), 29.4 (CH_2), 22.1 (CH_3), 20.0 (CH_2), 18.5 (CH_2), 15.5 (CH_3). IR (film): 1683, 1590, 1474, 1389, 1303, 1217, 1114, 1052 cm^{-1}. HRMS (APcI) m/z: calcd for $C_{24}H_{34}O_3Na$ (M + Na^+) 393.2406, found: 393.2409.

((4a*S*,6a*S*,11a*R*,11b*S*)-7,10-Dimethoxy-4,4,6a,11b-tetramethyl-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1*H*-benzo[*a*]fluoren-8-yl)-methanol (31). Sodium borohydride (31 mg, 0.82 mmol) was added to a stirred solution of **30** (190 mg, 0.51 mmol) in EtOH (8 mL), and the reaction mixture was stirred at room temperature for 10 min at which time TLC showed no **30**. The reaction mixture was quenched at 0 °C with water (1 mL), the solvent was evaporated, and the crude product was diluted with ether (20 mL) and washed with water and brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated to give 187 mg of **31** (98%) as a colorless syrup. $[\alpha]_D^{25}$ = −4.4 (*c* 7.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.68 (s, 1H), 4.73 (d, J = 12.4 Hz, 1H), 4.69 (d, J = 12.4 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 2.82 (dd, J = 10.7, 6.3 Hz, 1H), 2.79 (m, 1H), 2.69 (d, J = 16.8 Hz, 1H), 2.03 (br s, 1H), 1.73 (br d, J = 12.7 Hz, 1H), 1.66–1.54 (m, 5H), 1.54–1.44 (m, 2H), 1.42–1.24 (m, 4H), 1.23 (s, 3H), 1.15 (ddd, J = 14.1, 14.1, 4.6 Hz, 1H), 0.95 (dd, J = 11.5, 3.2 Hz, 1H), 0.88 (s, 3H), 0.77 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 151.9 (C), 148.5 (C), 144.6 (C), 133.2 (C), 132.9 (C), 109.5 (CH), 62.7 (CH), 62.5 (CH), 61.6 (CH_2), 55.6 (CH_3), 53.0 (CH_3), 48.9 (C), 42.3 (CH_2), 41.0 (CH_2), 37.4 (C), 34.4 (CH_2), 33.7 (CH_3), 33.3 (C), 32.9 (CH_3), 28.5 (CH_2), 22.1 (CH_3), 20.2 (CH_2), 18.6 (CH_2), 15.5 (CH_3). IR (film): 3407, 1595, 1464, 1218, 1110, 1053 cm^{-1}. HRMS (APcI) m/z: calcd for $C_{24}H_{37}O_3$ (M + H^+) 373.2743, found: 373.2738.

(4a*S*,6a*S*,11a*R*,11b*S*)-7,10-Dimethoxy-8-(methoxymethyl)-4,4,6a,11b-tetramethyl-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1*H*-benzo[*a*]fluorene (32). Sodium hydride 60% dispersion in mineral oil (100 mg, 2.5 mmol) was added to a stirred solution of **31** (142 mg, 0.38 mmol) in dry THF (12 mL) cooled to 0 °C under an argon atmosphere. After 5 min, methyl iodide (0.2 mL, 3.21 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. The reaction was poured over ice (4 g) and concentrated *in vacuo* to give a crude product, which was dissolved in ether (40 mL) and washed with brine. The organic phase was dried over anhydrous Na_2SO_4 and the solvent was evaporated to give a crude product which was purified by flash chromatography on silica gel (5% ether–hexanes) affording 143 mg of pure **32** (97%) as a colorless syrup. $[\alpha]_D^{25}$ = −5.9 (*c* 7.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.70 (s, 1H), 4.46 (s, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.44 (s, 3H), 2.81 (dd, J = 16.5, 7.1 Hz, 1H), 2.68 (d, J = 16.8 Hz, 1H), 1.72 (br d, J = 12.4 Hz, 1H), 1.66–1.54 (m, 3H), 1.48 (m, 1H), 1.42–1.32 (m, 3H), 1.32–1.24 (m, 2H), 1.22 (s, 3H), 1.15 (ddd, J = 13.2, 13.2, 4.0 Hz, 1H), 0.95 (dd, J = 11.4, 3.1 Hz, 1H), 0.88 (s, 3H), 0.77 (s, 3H), 0.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 151.8 (C), 148.9 (C), 144.3 (C), 132.8 (C), 130.4 (C), 110.1 (CH), 69.9 (CH_2), 62.9 (CH), 62.6 (CH), 58.5 (CH_3), 55.6 (CH_3), 52.9 (CH_3), 48.9 (C), 42.3 (CH_2), 41.1 (CH_2), 37.4 (C), 34.4 (CH_2), 33.7 (CH_3), 33.3 (C), 32.8 (CH_3), 28.6 (CH_2), 22.1 (CH_3), 20.2 (CH_2), 18.6 (CH_2), 15.5 (CH_3). IR (film): 1595, 1464, 1378, 1319, 1218, 1191, 1117, 1054, 990 cm^{-1}. HRMS (APcI) m/z: calcd for $C_{25}H_{38}O_3Na$ (M + Na^+) 409.2719, found: 409.2726.

(4a*S*,6a*S*,11a*R*,11b*S*)-8-(Methoxymethyl)-4,4,6a,11b-tetramethyl-1,2,3,4,4a,5,6,6a,11,11a-decahydro-11b*H*-benzo[*a*]fluorene-7,10-dione (33). AgO (124 mg, 1.00 mmol) was added to a stirred solution of **32** (110 mg, 0.20 mmol) in 1,4-dioxane (6 mL) at 4 °C. After 5 min, HNO_3 (4 N, 0.1 mL) was added dropwise and the mixture was stirred for a further 15 min, at which time TLC showed no starting material. Then, the reaction mixture was poured into H_2O (60 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated to give a crude product which was purified by flash chromatography on silica gel (10% ether–hexanes) affording 90 mg of pure **33** (89%) as a yellow syrup. $[\alpha]_D^{25}$ = +1.5 (*c* 3.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 6.63 (s, 1H), 4.28 (d, J = 2.2 Hz, 1H), 4.27 (d, J = 2.2 Hz, 1H), 3.45 (s, 3H), 2.73 (dd, J = 19.6, 8.9 Hz, 1H), 2.61 (dd, J = 19.6, 2.8 Hz, 1H), 2.17 (dt, J = 14.3, 7.4 Hz, 1H), 1.80 (dt, J = 14.5, 7.6 Hz, 1H), 1.73–1.63 (m, 2H), 1.60 (br d, J = 13.1 Hz, 1H), 1.46–1.30 (m, 3H), 1.25 (s, 3H), 1.15 (ddd, J = 13.2, 13.2, 3.3 Hz, 1H), 1.01 (dd, J = 10.9, 6.4 Hz, 1H), 0.97–0.87 (m, 2H), 0.86 (s, 3H), 0.85 (s, 3H), 0.71 (s, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 187.3 (C), 186.1 (C), 153.6 (C), 147.5 (C), 146.2 (C), 131.0 (CH), 68.1 (CH_2), 59.9 (CH_3), 59.3 (CH), 49.9 (CH), 49.6 (C), 42.3 (CH_2), 41.8 (CH_2), 36.9 (C), 33.5 (C), 33.0 (CH_3), 30.8 (CH_2), 29.8 (CH_3), 29.5 (CH_2), 21.6 (CH_3), 19.0 (CH_2), 18.5 (CH_2), 16.0 (CH_3). IR (film): 1732, 1651, 1456, 1107, 772, 669 cm^{-1}. HRMS (APcI) m/z: calcd for $C_{23}H_{32}O_3Na$ (M + Na^+) 379.2249, found: 379.2244.

Dasyscyphin B (4). $Na_2S_2O_4$ (157 mg, 0.90 mmol) was added to a suspension of quinone **33** (35 mg, 0.098 mmol) in 8 mL of $CHCl_3$–H_2O (1 : 1) and the mixture was stirred at room temperature for 4 h, at which time TLC showed no starting material. Then, $CHCl_3$ was removed under vacuum, and the mixture was diluted with ether (25 mL) and the phases were shaken and separated. The organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was evaporated to give a crude product which was purified by flash chromatography on silica gel (30% ether–hexanes) affording 22 mg of pure **4** (63%) as a colorless syrup. $[\alpha]_D^{25}$ = −12 (*c* 0.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 6.31 (s, 1H), 4.59 (d, J = 11.8 Hz, 1H), 4.51 (d, J = 11.8 Hz, 1H), 3.42 (s, 3H), 2.70 (m, 1H), 2.62 (d, J = 16.4, 1H), 1.75–1.67 (m, 3H), 1.64–1.52 (m, 3H), 1.42–1.25 (m, 3H), 1.24 (s, 3H), 1.20–0.90 (m, 3H), 0.88 (s, 3H), 0.80 (s, 3H), 0.51 (s, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 146.6 (C), 144.1 (C), 139.2 (C), 130.3 (C), 121.4 (C), 113.0 (CH), 74.4 (CH_2), 62.2 (CH), 58.2 (CH_3), 52.0 (CH), 48.5 (C), 42.2 (CH_2), 41.5 (CH_2), 37.3 (C), 33.5 (CH_3), 33.4 (C), 33.3 (CH_2), 30.8 (CH_3), 28.3 (CH_2), 22.0 (CH_3),

19.7 (CH_2), 18.6 (CH_2), 15.6 (CH_3). HRMS (APcI) *m*/*z*: calcd for $C_{23}H_{35}O_3$ ($M + H^+$) 359.2586, found: 359.2590.

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Notes and references

1 (*a*) E. Goclik, G. M. Koenig, A. D. Wright and R. Kamisnky, *J. Nat. Prod.*, 2000, **63**, 1150–1152; (*b*) J. H. Kwak, F. J. Schmitz and M. Kelly, *J. Nat. Prod.*, 2000, **63**, 1153–1156.

2 V. J. R. V. Mukku, R. A. Edrada, F. J. Schmitz, M. K. Shanks, B. Chandhuri and D. Fabbro, *J. Nat. Prod.*, 2003, **66**, 686–689.

3 (*a*) V. Rojas de la Parra, V. Mierau, T. Anke and O. Sterner, *Tetrahedron*, 2006, **62**, 1828–1832; (*b*) V. Mierau, V. Rojas de la Parra, O. Sterner and T. Anke, *J. Antibiot.*, 2006, **59**, 53–56.

4 J. C. Liermann, H. Kolshorn, H. Auke, E. Thines and T. Opatz, *J. Nat. Prod.*, 2008, **71**, 1654–1656.

5 (*a*) M. Kalesnikoff, L. M. Sly, M. R. Hughes, T. Buchse, M. J. Rauh, L.-P. Cao, V. Lam, A. Mui, M. Huber and G. Krystal, *Rev. Physiol. Biochem. Pharmacol.*, 2003, **149**, 87–103; (*b*) M. J. Rauh, M. Kalesnikoff, M. R. Hughes, L. M. Sly, V. Lam and G. Krystal, *Biochem. Soc. Trans.*, 2003, **31**, 286–291; (*c*) M. J. Rauh and G. Krystal, *Clin. Invest. Med.*, 2002, **25**, 68–70; (*d*) G. Krystal, *Semin. Immunol.*, 2002, **12**, 397–403.

6 L. Zhang, X. Xie, J. Liu, J. Qi, D. Ma and X. She, *Org. Lett.*, 2011, **13**, 2956–2958.

7 L. Yang, D. E. Williams, A. Mui, C. Ong, G. Krystal, R. van Soest and R. Andersen, *Org. Lett.*, 2005, **7**, 1073–1076.

8 The two-synthon strategy, involving the reaction of an aryllithium derived from a suitably protected polyphenol with a bicyclic sesquiterpene (drimane derivative) electrophile, has been widely utilized for synthesizing merosesquiterpenes. For recent examples, see: (*a*) A. F. Barrero, E. J. Alvarez-Manzaneda and R. Chahboun, *Tetrahedron Lett.*, 1997, **38**, 2325–2328; A. F. Barrero, E. J. Alvarez-Manzaneda and R. Chahboun, *Tetrahedron*, 1998, **54**, 5635–5650; (*b*) O. Arjona, M. Garranzo, J. Maluego, E. Maroto, J. Plumet and B. Sáez, *Tetrahedron Lett.*, 1997, **38**, 7249–7252; (*c*) K.-I. Takao, T. Sasaki, T. Kozaki, Y. Yaganisawa, K.-I. Tadano, A. Kawashima and H. Shinonaga, *Org. Lett.*, 2001, **3**, 4291–4294; (*d*) S. Maiti, S. Sengupta, C. Giri, B. Achari and A. K. Banerjee, *Tetrahedron Lett.*, 2001, **42**, 2389–2391; (*e*) S. Quideau, M. Lebon and A.-M. Lamidey, *Org. Lett.*, 2002, **22**, 3975–3978; (*f*) H. Ishibashi, K. Ishihara and H. Yamamoto, *J. Am. Chem. Soc.*, 2004, **126**, 11122–11123; (*g*) E. J. Alvarez-Manzaneda, R. Chahboun, I. Barranco Pérez, E. Cabrera, E. Alvarez and R. Alvarez-Manzaneda, *Org. Lett.*, 2005, **7**, 1477–1480; (*h*) E. J. Alvarez-Manzaneda, R. Chahboun, E. Cabrera, E. Alvarez, A. Haidour, J. M. Ramos, R. Alvarez-Manzaneda, M. Hmamouchi and H. Bouanou, *J. Org. Chem.*, 2007, **72**, 3332–3339.

9 E. Alvarez-Manzaneda, R. Chahboun, E. Alvarez, A. Fernández, R. Alvarez-Manzaneda, A. Haidour, J. M. Ramos and A. Akhaouzan, *Chem. Commun.*, 2012, **48**, 606–608.

10 H. Ohtsu, R. Tanaka, Y. In, S. Matsunaga, H. Tokuda and H. Nishino, *Planta Med.*, 2001, **67**, 55–60.

11 E. Alvarez-Manzaneda, R. Chahboun, F. Bentaleb, E. Alvarez, M. A. Escobar, S. Sad-Diki, M. J. Cano and I. Messouri, *Tetrahedron*, 2007, **63**, 11204–11212.

12 M. C. Costa, S. P. Alves, M. E. Correia and M. J. Marcelo-Curto, *Synthesis*, 2006, 1171–1175.

13 A. F. Barrero, E. J. Alvarez-Manzaneda, R. Chahboun and R. Meneses, *Synlett*, 1999, 1663–1666.

14 E. Alvarez-Manzaneda, R. Chahboun, E. Cabrera Torres, E. Alvarez, R. Alvarez-Manzaneda, A. Haidour and J. M. Ramos, *Tetrahedron Lett.*, 2004, **45**, 4453–4455; 2005, **46**, 1075–1077; 2005, **46**, 3755–3759.