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 aakaol 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,3 a 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 PtCl2-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 trimane 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 strategy8 followed by intramolecular Friedel–Crafts alkylation led to the tetracyclic intermediate bearing a Cββ 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 C8β methyl group. Utilizing this, the first enantiospecific synthesis of aakaol A (2) from commercial (−)-sclareol was achieved.9

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...
This, as well as being a very cheap commercial compound, will make it possible to synthesize natural dasycyphins bearing a function in the A ring, such as dasycyphins A (3), D (6) or E (7), which could be difficult to prepare by alternative methods. 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 dasycyphin 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-eneone 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 (CH3)2CH–CO bond. Compound 11 will be synthesized after the regioselective oxidation of the C13–C14 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 C13–C14 double bond of acid 12, affording ketoaldehyde 13 in good yield, was achieved after successive treatments with OsO4 and NaIO4, without isolating the intermediate diol. The α,β-unsaturated aldehyde 11 was chemoselectively reduced to ketoalcohol 14 by reaction with RANEY® Ni. The diol 15, obtained as a mixture of distereoisomers, was regioselectively dehydrated after treatment with I2 and PPh3 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 I2 and PPh3 and further bubbling of this solution with an O3/O2 mixture. After protecting the ketone carbonyl group of 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 tricylic α,β-eneone 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,
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 LiAlH₄ gave diol 24, which after benzylic oxidation followed by Baeyer–Villiger rearrangement led to hydroxy formate 25. When this was reacted with I₂ and PPh₃, 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 bromophenone 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 12. Oxidation of the latter with AgO and nitric acid gave quinone 33, which was finally converted into dasyscyphin B (4) by treatment with aq. Na₂S₂O₄ in chloroform. The optical rotation of synthetic dasyscyphin B (4) ([α]D²⁵: −12; ε 0.2, CHCl₃) was similar to that reported for the natural product ([α]D²⁵: −19; ε 0.5, CHCl₃); the spectroscopic properties were identical to those previously described.³

Conclusions

In conclusion, the first synthesis of antimonial 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 enantio-specific 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–benzenophenone. 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 (ε_max) are reported. Proton and carbon-13 nuclear magnetic resonance (¹H NMR or ¹³C NMR) spectra were recorded at 400 or 500 MHz, for ¹H, and at 100 or 125 MHz, for ¹³C, 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 ¹³C 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.

(1R,4aR,5R,8aR)-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 argon atmosphere. The solution was stirred for 10 min at room temperature and 2% aq. OsO₄ (20 mL, 0.2%, 1.5 mmol) was added and the reaction mixture was further stirred under argon atmosphere at reflux for 5 days, at which time TLC indicated no remaining starting material. Then NaIO₄ (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. [α]D²⁵ = +42.1 (c 1.1, CHCl₃). ¹H NMR (CDCl₃, 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 (br, J = 6.9 Hz, 1H), 2.24 (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). ¹³C NMR (CDCl₃, 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 (CH₂), 40.8 (CH), 37.8 (CH₂), 37.1 (CH₃), 36.4 (C), 26.8 (CH₃), 20.9 (CH₃), 18.5 (CH₃), 18.4 (CH₃), 17.7 (CH₃), 16.9 (CH₃), 14.3 (CH₂). HRMS (APCI) m/z: calcd for C₂₆H₂₆O₂Na (M + Na⁺) 357.2042, found: 357.2037.
(1R,4aR,5R,8aR)-Methyl 6-formyl-1,4a-dimethyl-5-(4-methyl-3-oxopentyl)-1,2,3,4,4a,5,8,8a-octahydroanaphthalene-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 (50–20 mL) and the phases were shaken and separated. The organic phase was washed with water and brine and dried over anhydrous Na2SO4. 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. [α]D25 = +9.0° (c = 12.5, CHCl3). 1H NMR (CDCl3, 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 (dd, J = 17.0, 10.6, 5.7 Hz, 1H), 2.62 (h, J = 6.9 Hz, 1H), 3.11 (dd, J = 17.1, 10.9, 4.7 Hz, 1H), 3.65 (s, 3H), 6.75 (br s, 1H). 13C NMR (CDCl3, 125 MHz) δ: 14.0 (CH3), 214.9 (C), 194.5 (CH), 178.2 (C), 152.0 (CH), 144.0 (C), 51.8 (CH3), 49.6 (CH), 45.9 (C), 43.9 (CH), 42.2 (CH2), 40.4 (CH), 37.5 (CH2), 36.8 (CH3), 36.1 (CH3), 26.5 (CH2), 20.5 (CH3), 18.1 (CH), 18.0 (CH3), 17.4 (CH2), 16.8 (CH2), 14.0 (CH3). IR (film): 1724, 1688, 1461, 1245, 1187, 1144, 1008, 727, 671 cm−1. HRMS (Apel) m/z: calcd for C23H23O4Na (M + Na+) 371.2198, found: 371.2206.

(1R,4aR,5S,6S,8aR)-Methyl 5-(3,4-dimethylpent-3-enyl)-1,4a-dimethyl-decahydroanaphthalene-1-carboxylate (15). 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–Na2SO4 (15:3 g), washed with acetone (20 mL) and concentrated to give pure 15 (0.98 g, 97%) as a colorless syrup. [α]D25 = +33.8° (c = 71.5, CHCl3). 1H NMR (CDCl3, 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, 5H), 1.67–1.85 (m, 5H), 1.96 (m, 1H), 2.40 (dd, J = 17.1, 9.1, 6.1 Hz, 1H), 2.53 (dd, 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). 13C NMR (CDCl3, 125 MHz) δ: 215.1 (C), 179.3 (C), 61.3 (CH3), 52.7 (CH), 51.9 (CH3), 50.8 (CH), 47.7 (C), 41.0 (CH), 39.7 (CH), 38.9 (CH3), 38.2 (CH2), 37.6 (C), 36.8 (CH2), 28.8 (CH2), 20.6 (CH3), 19.2 (CH2), 19.2 (CH3), 18.4 (CH3), 18.3 (CH), 17.8 (CH3), 16.4 (CH3). IR (film): 3472, 1712, 1459, 1586, 1248, 1141, 1023, 752 cm−1. HRMS (Apel) m/z: calcd for C22H22O4Na (M + Na+) 397.2564, found: 397.2504.

(1R,4aR,5S,6S,8aR)-Methyl 5-(3-hydroxy-3,4-dimethylpentyl)-6-(hydroxymethyl)-1,4a-dimethyl-decahydroanaphthalene-1-carboxylate (16). Iodine (9.35 g, 36.86 mmol) was slowly added to a solution of triphenylphosphine (PPh3) (9.67 g, 36.86 mmol) in THF (70 mL) 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, the reaction 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% NaHSO3 (120–30 mL) was added and the resulting mixture was washed with water and brine, and dried over anhydrous Na2SO4. 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. [α]D25 = +28.7° (c 4.0, CHCl3). 1H NMR (CDCl3, 500 MHz) δ: 3.71 (d br, J = 9.3 Hz, 1H), 3.56 (dd, J = 10.3, 10.3 Hz, 1H), 3.65 (s, 3H), 2.10 (dd, 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). 13C NMR (CDCl3, 125 MHz) δ: 179.5 (C), 128.1 (C), 124.1 (C), 61.6 (CH3), 53.5 (CH), 52.0 (CH2), 51.0 (CH), 47.9 (C), 40.0 (CH), 38.3 (CH2), 37.6 (C), 37.0 (CH3), 33.4 (CH2), 28.8 (CH2), 23.8 (CH3), 20.8 (CH2), 20.7 (CH2), 20.2 (CH3), 18.6 (CH3), 18.0 (CH2), 16.5 (CH2), 16.2 (CH3). IR (film): 3428, 1726, 1456, 1386, 1247, 1192, 1143, 1020, 773 cm−1. HRMS (Apel) m/z: calcd for C22H22O5Na (M + H+) 351.2899, found: 351.2907.
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. [α]D25 = +24.3 (c 23.1, CHCl3).1H NMR (CDCl3, 500 MHz): δ: 3.64 (s, 3H), 3.63 (zd, δ = 10.1 Hz, 1H), 3.52 (zd, δ = 10.1, 1H, 1H), 2.55 (zd, δ = 10.7, 6.3 Hz, 1H), 2.51 (zd, δ = 10.0, 5.6 Hz, 1H), 2.38 (zd, δ = 9.5, 6.0 Hz, 1H), 2.34 (zd, δ = 10.3, 6.7 Hz, 1H), 2.13 (s, 3H), 1.95 (zd, δ = 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).13C NMR (CDCl3, 125 MHz): δ: 209.45 (C), 179.39 (C), 61.34 (CH3), 52.71 (CH), 50.02 (CH2), 48.87 (CH3), 42.45 (CH3), 39.76 (CH2), 38.33 (CH2), 37.63 (C), 36.94 (CH2), 30.19 (CH2), 28.89 (CH2), 20.75 (CH2), 19.35 (CH2), 17.93 (CH2), 16.50 (CH2), 16.05 (CH2). IR (film): 3437, 1720, 1680, 1546, 1457, 1377, 1246, 1061, 857, 756 cm−1.

(1R,4aR,5S,6S,8aR)-Methyl 6-(hydroxymethyl)-1,4a-dimethyl-5-(3-oxobutylidene)decahydronaphthalene-1-carboxylate (17). Iodine (2.10 g, 8.26 mmol) was added to a solution of triphenylphosphine (2.17 g, 2.28 mmol) in CH2Cl2 (15 mL) at room temperature, and the mixture was stirred at room temperature for 10 min. A solution of 15 (3 g, 8.15 mmol) in CH2Cl2 (20 mL) was then added and the resulting mixture was further stirred at room temperature for 2 h, at which time TLC showed no mixture. Then, the mixture was cooled to −78 °C and it was slowly bubbled with an O2/O3 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.

(1R,4aR,5R,6S,8aR)-Methyl 6-formyl-1,4a,6-trimethyl-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-toluensulfonic acid (15 mg) was added to a solution of 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 NaHCO3 (3 × 30 mL). The organic phase was dried (MgSO4) and concentrated under reduced pressure to give the title compound 18 (11.80 g, 98%) as a colourless oil. [α]D25 = +16.8 (c 17.5, CHCl3).1H NMR (CDCl3, 500 MHz): δ: 3.97–3.87 (m, 4H), 3.67 (zd, δ = 10.3, 10.3 Hz, 1H), 3.64 (s, 3H), 3.52 (zd, δ = 10.3, 10.3 Hz, 1H), 2.15 (d, δ = 9.5 Hz, 1H), 1.96 (d, δ = 7.4 Hz, 1H), 1.87 (zd, δ = 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).13C NMR (CDCl3, 125 MHz): δ: 179.4 (C), 110.4 (C), 64.8 (CH2), 61.5 (CH2), 53.3 (CH), 52.0 (CH2), 51.0 (CH), 47.9 (C), 39.9 (CH), 38.4 (CH), 37.7 (CH2), 37.7 (C), 37.0 (CH2), 28.9 (CH2), 27.1 (CH2), 23.9 (CH2), 20.8 (CH2), 19.5 (CH2), 18.0 (CH2), 16.6 (CH2), 16.2 (CH2). IR (film): 3498, 1783, 1724, 1580, 1451, 1389, 1247, 1187 cm−1. HRMS (Apel) m/z: calculated for C21H17O2 (M + H)+ 369.2641, found: 369.2653.

(1R,4aR,5S,6S,8aR)-Methyl 6-formyl-1,4a-dimethyl-5-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-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 CH2Cl2 (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 Na2SO4. The solvent was evaporated to yield 2.39 g of aldehyde 19 (92%) as a colourless syrup. [α]D25 = +23.7 (c 39.4, CHCl3).1H NMR (CDCl3, 500 MHz): δ: 9.97 (s, 1H), 3.99–3.86 (m, 4H), 3.65 (s, 3H), 2.51 (m, 1H, δ = 14.6 Hz, 1H), 1.97–1.86 (m, 1H), 1.81–1.68 (m, 5H), 1.65–1.51 (m, 5H), 1.46 (zd, δ = 12.9, 12.9, 3.6 Hz, 1H), 1.34 (zd, 3H), 1.25 (zd, δ = 3.2 Hz, 1H), 1.18 (m, 1H), 1.12 (s, 3H), 1.05 (m, 1H), 0.76 (s, 3H).13C NMR (CDCl3, 125 MHz): δ: 204.8 (CH), 179.3 (C), 110.2 (C), 64.8 (2CH2), 53.9 (CH), 52.1 (CH2), 50.2 (CH), 47.7 (C), 47.6 (CH3), 38.3 (C), 38.0 (2CH2), 37.1 (CH2), 26.0 (CH3), 23.9 (CH2), 21.8 (CH3), 19.3 (CH2), 18.0 (CH2), 16.5 (CH2), 15.5 (CH2). IR (film): 1724, 1448, 1388, 1284, 1061, 754 cm−1. HRMS (Apel) m/z: calculated for C21H16O3N (M + Na)+ 389.2304, found: 389.2306.
temperature and the solvent was evaporated in vacuo. Then, the residue was dissolved in ether (30 mL) and washed with water (2 x 10 mL) and brine (2 x 10 mL). The organic phase was dried over anhydrous Na2SO4 and concentrated under vacuum. The organic phase was washed with saturated aqueous NaHCO3 (3 x 10 mL). The organic phase was dried over anhydrous Na2SO4 and the solvent was evaporated to give a crude product, which was purified by flash chromatography on silica gel (5% ether–hexanes) to give 552 mg of the pure regioisomer (92%) as a colourless syrup. 

Methyl propiolate (262 mg, 0.97 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. Then, the solvent was removed under vacuum and the residue was dissolved in ether (50 mL), washed with water (5 x 15 mL) and brine. The organic phase was dried over anhydrous Na2SO4 and concentrated to give a crude product which was chromatographed on silica gel (10% ether–hexanes) to give 525 mg of the 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%).

α,β-Methyl 2-(1-acetoxyvinyl)-3α,6,9α-trimethyl-3a,4,5,5a,6,7,8,9,9a,9b-decahydro-1δ-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 NaHCO3 (3 x 10 mL). The organic phase was washed with dioxane-4,6a,11b-tricyclo[3.3.3.04,7]tetradecane (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 x 15 mL) and brine. The organic phase was dried over anhydrous Na2SO4 and concentrated to give a crude product which was chromatographed on silica gel (10% ether–hexanes) to give 552 mg of the 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%).
was added to a stirred suspension of 22 (350 mg, 0.87 mmol) and K₂CO₃ (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 Na₂SO₄ and concentrated to give a crude product which was purified by flash chromatography (10% ether–hexanes) to give 353 mg (98%) of 23 as a colourless syrup. [α]D²⁵ = +21.1 (c 13.1, CHCl₃). ¹H NMR (CDCl₃, 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, 8.5, 2.2 Hz), 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), 0.91 (s, 3H). ¹³C NMR (CDCl₃, 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 (CH₂), 52.0 (CH₃), 51.9 (CH), 49.6 (C), 47.9 (CH), 47.3 (C), 39.8 (CH₂), 37.0 (C), 36.9 (CH₃), 33.3 (CH₃), 31.4 (CH₄), 28.0 (CH₂), 22.1 (CH₂), 17.8 (CH₃), 17.1 (CH₃), IR (film): 3481, 1740, 1591, 1485, 1465, 1221, 1129, 1056, 757 cm⁻¹. HRMS (Apel) m/z: calculated for C₂₃H₃₅O₃Na (M + Na⁺) 437.2304, found: 437.2297.

(4R,4aR,6aS,11aR,11bR)-10-Methoxy-4,6a,11b-trimethyl-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1H-benzo[a]fluorene-7-yl formate (26). 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 CH₂Cl₂ (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. Na₂SO₄ (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. NaHCO₃ (5 × 8 mL) and brine, dried over Na₂SO₄ and concentrated to give 26 (148 mg, 97%) as a colourless oil. [α]D²⁵ = +4.3 (c 9.6, CHCl₃). ¹H NMR (CDCl₃, 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 = 13.0, 4.0 Hz, 1H), 1.33–1.24 (m, 4H), 1.20 (s, 3H), 0.92 (ddd, J = 12.9, 3.5 Hz, 1H), 0.74 (s, 3H), 0.50 (s, 3H). ¹³C NMR (CDCl₃, 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 (CH₂), 62.1 (CH₂), 55.6 (CH₂), 48.6 (C), 45.2 (CH₂), 40.8 (CH₂), 37.8 (C), 37.1 (C), 35.5 (CH₃), 33.5 (CH₃), 31.5 (CH₃), 29.0 (CH₂), 19.2 (CH₂), 17.8 (CH₂), 17.8 (CH₃), 16.2 (CH₃), IR (film): 3455, 1740, 1451, 1455, 1212, 1129, 1056, 757 cm⁻¹. HRMS (Apel) m/z: calculated for C₂₃H₃₅O₃Na (M + Na⁺) 373.2379, found: 373.2386.

(4R,4aR,6aS,11aR,11bR)-1-Hydroxy-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1H-benzo[a]fluorene-7-yl formate (27). To a solution of triphenylphosphine (487 mg, 1.86 mmol) in dry CH₂Cl₂ (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% NaHSO₃ (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 Et₂O–water (50–15 mL) and the phases were shaken and separated. The organic phase was washed with water and brine, and dried
over anhydrous Na2SO4. 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. [α]D25 = −32.8 (c 11.9, CHCl3).

1H NMR (CDCl3, 500 MHz) δ: 8.30 (s, 1H), 6.79 (d, J = 8.6 Hz, 1H), 6.65 (d, J = 8.7 Hz, 1H), 3.92 (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), 1.76 (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). 13C NMR (CDCl3, 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 (CH3), 48.6 (C), 48.1 (CH), 40.9 (CH2), 39.3 (CH2), 37.2 (C), 35.8 (C), 32.8 (CH2), 31.2 (CH3), 29.2 (CH2), 28.7 (CH2), 18.7 (CH2), 18.6 (CH2), 18.2 (CH3), 15.6 (CH3).

IR (film): 1740, 1485, 1220, 1126, 1054, 756 cm−1.


(4α,6αS,11αR,11βS)-10-Methoxy-4,4,6α,11b-tetramethyldibenz[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 g) 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–Na2SO4 pad (20 g), washed with acetone (20 mL) and concentrated to give pure 28 (150 mg, 91%) as a colourless syrup. [α]D25 = −7.5 (c 13.7, CHCl3).

1H NMR (CDCl3, 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 (ddd, 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). 13C NMR (CDCl3, 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 (CH3), 51.7 (CH), 48.3 (C), 42.4 (CH2), 41.6 (CH2), 37.3 (C), 33.5 (C), 33.4 (CH3), 33.4 (CH2), 29.2 (CH2), 21.9 (CH3), 19.6 (CH2), 18.6 (CH3), 15.7 (CH3).

IR (film): 3419, 1493, 1452, 1246, 1247, 1060, 795 cm−1. HRMS (APCI) m/z: calculated for C22H12O3Na+ (M + Na)+ 432.2481, found: 432.2484.

(4α,6αS,11αR,11βS)-8-Bromo-10-methoxy-4,4,6α,11b-tetramethyl-2,3,4α,5,6α,11,11a,11b-decahydro-1H-benzo[a][fluoren-7-carboxaldehyde (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 water (6 × 10 mL) and brine and dried over anhydrous Na2SO4. The solvent was removed under vacuum and the crude product was purified by flash column chromatography on silica gel (15% ether–hexanes) to give 32 mg of 29 (89%) as a yellow syrup. [α]D25 = +4.6 (c 8.3, CHCl3).

1H NMR (CDCl3, 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, 2.1 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 (ddd, 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). 13C NMR (CDCl3, 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 (CH3), 51.8 (CH), 49.2 (C), 42.3 (CH3), 41.5 (CH2), 37.3 (C), 33.4 (CH3), 33.4 (C), 32.9 (CH3), 30.5 (CH2), 29.1 (CH2), 21.9 (CH3), 19.6 (CH3), 18.6 (CH3), 15.7 (CH3). IR (film): 3525, 1474, 1451, 1268, 1224, 1175, 1061, 1013, 771, 669 cm−1. HRMS (APCI) m/z: calculated for C22H12BrO2 (M + H)+ 407.1586.
Na2SO4 and the solvent was evaporated to give a crude product.

11.5, 3.2 Hz, 1H), 0.89 (s, 3H), 0.78 (s, 3H), 0.39 (s, 3H). 13C NMR (CDCl3, 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 (CH3), 52.7 (CH2), 48.8 (C), 42.2 (CH2), 40.9 (CH3), 37.4 (C), 34.2 (C), 33.6 (CH3), 33.3 (C), 32.6 (CH2), 29.4 (CH2), 22.1 (CH), 20.0 (CH2), 18.5 (CH3). IR (film): 1683, 1590, 1474, 1389, 1303, 1217, 1114, 1052 cm⁻¹. HRMS (Apel) m/z: calc'd for C23H30O5Na (M + Na⁺) 409.2719, found: 409.2726.

14a,6a,6a,11aR,11bS)-8-(Methoxymethyl)-4,4a,6a,11b-tetramethyl-2,3,4,4a,5,6,6a,11a,11b-decahydro-1H-benzo[a][fluoren-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, HNO3 (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 H2O (60 mL) and extracted with CH2Cl2 (3 × 50 mL). The combined organic layers were dried over anhydrous Na2SO4 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. [α]D²⁵ = +15.0 (c 3.3, CHCl₃). 1H NMR (CDCl₃, 300 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 (dd, J = 14.3, 7.4 Hz, 1H), 1.80 (d, 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 (dddd, 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). 13C NMR (CDCl₃, 150 MHz) δ 187.3 (C), 186.1 (C), 153.6 (C), 147.5 (C), 146.2 (C), 131.0 (CH), 68.1 (CH2), 59.9 (CH3), 59.3 (CH), 49.9 (CH), 49.6 (C), 42.3 (CH2), 41.8 (CH3), 36.9 (C), 33.5 (C), 30.9 (CH3), 28.9 (CH2), 29.5 (CH2), 21.6 (CH), 19.6 (CH2), 18.5 (CH3), 16.0 (CH3). IR (film): 3407, 3195, 1595, 1646, 1218, 1110, 1053 cm⁻¹. HRMS (Apel) m/z: calc'd for C36H36O8Na (M + Na⁺) 779.2429, found: 779.2444.

Dasyccphin B (4). Na2S2O4 (157 mg, 0.90 mmol) was added to a suspension of quinone 33 (35 mg, 0.098 mmol) in 8 mL of CHCl₃–H2O (1:1) and the mixture was stirred at room temperature for 4 h, at which time TLC showed no starting material. Then, CHCl₃ 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 Na2SO4. 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. [α]D²⁵ = +12.0 (c 0.2, CHCl₃). 1H NMR (CDCl₃, 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). 13C NMR (CDCl₃, 150 MHz) δ 146.6 (C), 144.1 (C), 139.2 (C), 130.3 (C), 121.4 (C), 113.0 (CH), 74.4 (CH2), 62.2 (CH), 58.2 (CH2), 52.0 (CH), 48.5 (C), 42.2 (CH2), 41.5 (CH3), 37.3 (C), 33.5 (CH3), 33.3 (CH2), 30.8 (CH3), 28.3 (CH2), 22.0 (CH3),
19.7 (CH₃), 18.6 (CH₃), 15.6 (CH₃). HRMS (APCI) m/z: calcld for C₂₃H₃₅O₃ (M + H⁺) 359.2586, found: 359.2590.

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Notes and references