Polycyclic framework synthesis of anominine and tubingensin A indole diterpenoids†

Ben Bradshaw, Gorka Etxebarria-Jardí and Josep Bonjoch*

Received 27th November 2007, Accepted 18th December 2007
First published as an Advance Article on the web 17th January 2008
DOI: 10.1039/b718280e

A highly congested decalin embodying an α-methylene ketone is synthesized in 11 steps from the Wieland–Miescher ketone and efficiently converted to the polycyclic frameworks of anominine and tubingensin A, which constitutes the first approach to the skeleton of these indole diterpenoids.

Introduction

Fungal sclerotia often contain unique antiinsectan metabolites that can offer protection against predation.[1] Among them, anominine (**1**),‡[2,3] isolated from *Aspergillus nomius*, shows potent activity against the crop pest *Helicoverpa zea*, and tubingensin A (**2**),[4] isolated from *A. tubingensis*, displays *in vitro* antiviral activity against the herpes simplex virus type 1 (Fig. 1). Structurally, **1** is made up of a *cis*-decalin embodying five stereogenic centres, two of which are contiguous quaternary carbons, and **2** shows a unique

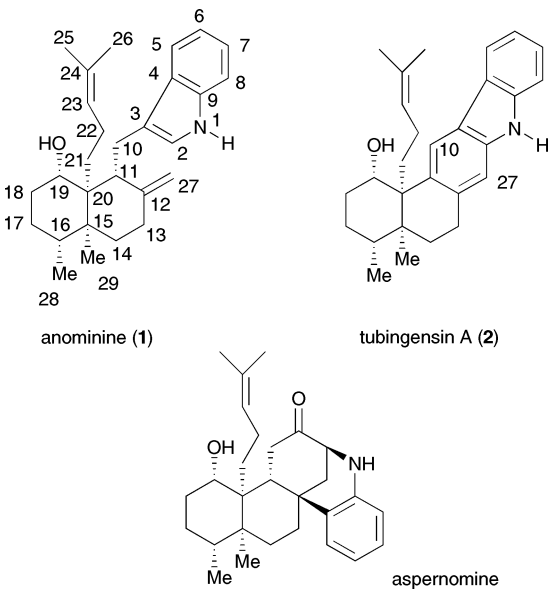


Fig. 1 Heterocyclic diterpenoids from *Aspergillus* sp.

Laboratori de Química Orgànica, Facultat de Farmàcia, Institut de Biomedicina (IBUB), Universitat de Barcelona, Av. Joan XXIII s/n, 08028-Barcelona, Spain. E-mail: josep.bonjoch@ub.edu; Fax: +34 934024539

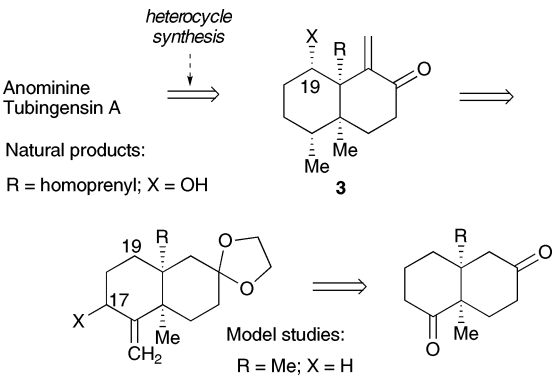
† Electronic supplementary information (ESI) available: ^{13}C NMR chemical shifts of all compounds (Table 1) and copies of selected ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/b718280e

‡ Diterpenoid **1** was named nominine when isolated in 1989. However, in 1982 the same name had been given to another natural product isolated in 1956, the hetisine-type aconite alkaloid nominine (ref. 3*a*). Furthermore, the original nominine has recently been synthesized (ref. 3*b*). After consulting Prof. Gloer (Iowa University) it was decided to change the name of the indole diterpenoid **1** to anominine. We have used Gloer's numbering of the anominine skeleton (ref. 2) throughout the discussion.

9*H*-octahydronaphtho[2,1-*b*]carbazole ring system.[5] The related compound aspernomine,[6] also isolated from *Aspergillus nomius*, contains the same decalin motif but features a novel bridged tetrahydroquinoline ring system, which may arise biogenetically from a rearrangement of an oxidized form of anominine.[7] Like anominine it is an antiinsectan metabolite and in addition exhibits significant cytotoxicity towards three human solid tumour cell lines.

Given the biological activities and the novel and synthetically challenging structures of these indole diterpenoids, possessing a prenylated sesquiterpenoid carbon skeleton, together with no previously reported approaches,[8] we embarked on a program of research to evaluate their total synthesis.

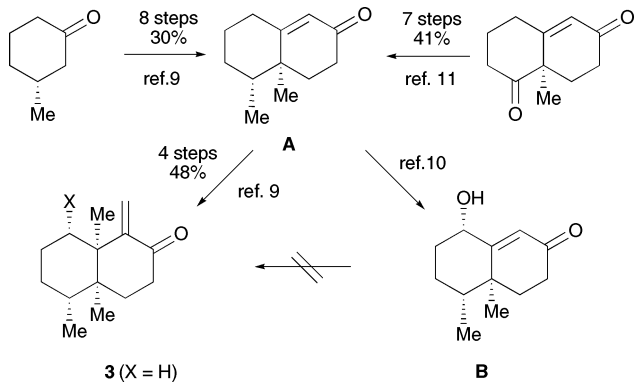
Based on our experience in the synthesis of unusual terpenoids such as nakamurol A[9] and xylarenal A,[10] we identified enone **3** (Scheme 1) as a key synthetic intermediate. We planned to explore the usefulness of its exocyclic α-methylene ketone unit for incorporating the heterocyclic ring fragment linked or fused to the decalin core of **1** and **2**.



Scheme 1 Outline of a possible synthesis of anominine and tubingensin A.

We have previously reported[9] the synthesis of **3** (R = Me, X = H) *via* a four step sequence (48%) from intermediate **A**, which in turn was prepared from (*R*)-3-methylcyclohexanone (8 steps, 30% overall yield).[11] However, our first generation synthesis of **3** did not allow the introduction of a hydroxyl group at C-19, which precluded its extension to the total synthesis of anominine and related diterpenoids. Moreover, an analogous approach (**A** → **B** → **3** R = Me, X = OH) did not allow the introduction of the quaternary centre. The installation of a hydroxyl group at

C(19) from **A** to give **B** has been previously reported by us (Scheme 2), but initial attempts to add various organometallics upon a hydroxyl-protected derivative of **B** did not result in any 1,4-addition. This was not altogether surprising given the type of compounds involved and the known effects of even remote oxygen atoms from the reactive site.[12]



Scheme 2 Previous results.

We therefore sought to design a second-generation synthesis of enone **3** to incorporate a degree of flexibility that would enable us to introduce later the C-19 hydroxyl and homoprenyl group.[13,14] In this paper we disclose our overall synthetic strategy and its successful application to the synthesis of the polycyclic frameworks of anominine and tubingensin A.

Results and discussion

A second generation synthesis of enone 3

The new synthesis of enone **3** (Scheme 3) starts from Wieland–Miescher ketone (**4**),[15] the quaternary centre at C-20 being introduced by conjugate addition of methyl cuprate.[16] Chemoselective protection of the less hindered carbonyl of **5** was accomplished using 2-ethyl-2-methyl-1,3-dioxolane in acid medium. Wittig methylenation of the remaining carbonyl group in **6** gave the *cis*-dimethyl decalin **7**. The diastereoselectivity observed in the initial hydrogenation (H_2, Pd-C, solvent) of **7** was the opposite of what was desired, the *trans* derivative **8a** being the main compound formed (Fig. 2). However, a reversed selectivity was found when ketone **9**, obtained by hydrolysis of **7** (10% HCl aq), was used as the substrate. The *cis*–*trans* ratio was further improved by changing the catalyst from Pd to Pt and using CH_2Cl_2 as the solvent, which resulted in a 3 : 1 ratio of decalones **10** and **8b**, respectively, in quantitative yield. Hoping that an endocyclic rather than exocyclic double bond might increase the selectivity further, we attempted the hydrogenation of **11**,[17] however this failed, probably due to extreme steric hindrance. Since compounds **10** and **8b** could not be separated by chromatography, we decided to prepare the required

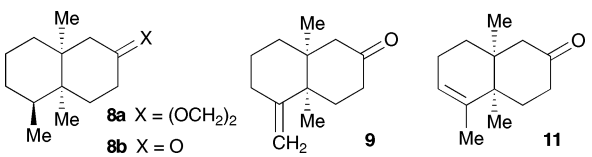
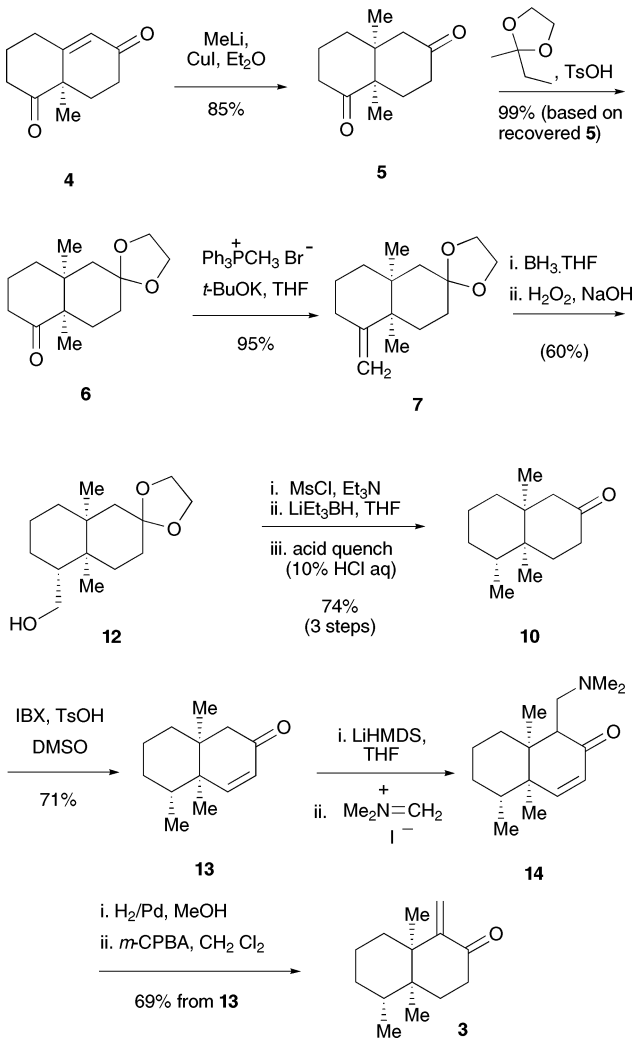


Fig. 2



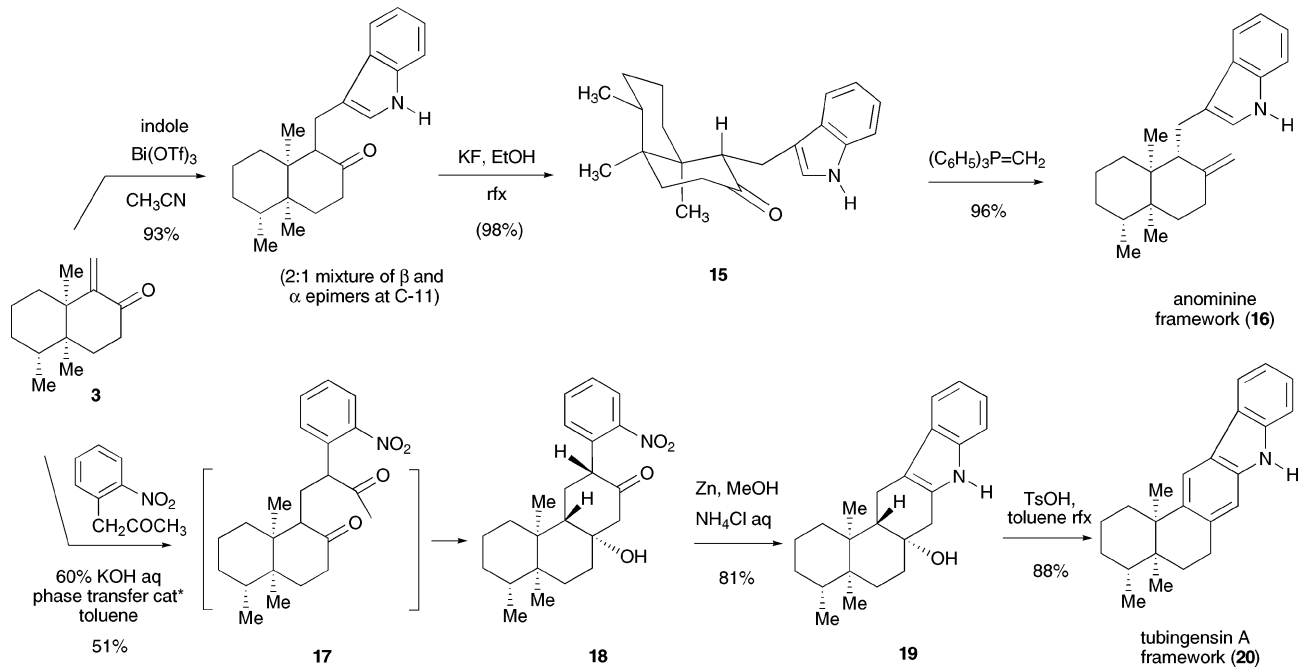
Scheme 3 A second-generation synthesis of enone **3**.

intermediate **10** by hydroboration of **7** followed by reduction of the corresponding alcohol. This gave an easily separated 4 : 1 mixture of alcohols **12** and its epimer (not shown) in 75% overall yield. Removal of the hydroxyl group was carried out efficiently by mesylation, Superhydride reduction and acid quench to give the stereochemically pure ketone **10**.

Oxidation of **10** with IBX (*o*-iodoxybenzoic acid)[18] formed the enone **13**, which effectively blocked the most accessible methylene of the ketone group of **10**. Attempts to alkylate the α′-position of the ketone (*i.e.* at C-11) was problematic probably due to the extreme steric hindrance exerted by the three proximal methyl substituents, predominantly leading to *O*- rather than *C*-alkylation. Fortunately, reaction of the lithium enolate of **13** with Eschenmoser's salt, hydrogenation of the crude polar amine **14** followed by *m*-CPBA oxidation generated the exocyclic enone **3**. We were thus able to synthesize the key intermediate **3** in 11 steps and 18% overall yield from the Wieland–Miescher ketone.

Synthesis of anonimine and tubingensin A polycyclic skeletons

The remaining challenge was to elaborate the heterocyclic rings to access the polycyclic skeletons of anominine and tubingensin A. Conjugate addition of indole to enone **3** in the presence of



Scheme 4 Synthesis of anominine and tubingensin A polycyclic skeletons.

bismuth triflate[19] smoothly generated the coupled product **15** in excellent yield as a 1 : 2 mixture of diastereomers favouring the undesired stereosiomer (Scheme 4). Isomerisation of the epimeric mixture with KF in refluxing EtOH provided the all *cis* diastereomer in quantitative yield. Wittig homologation completed the synthesis of the anominine model **16**.

We then focused our attention on the tubingensin skeleton using the same common enone **3** intermediate. This enone reacted with 1-(2-nitrophenyl)propan-2-one[20] in a biphasic system (toluene/60% KOH aq) with the addition of a chiral phase transfer catalyst§ under the conditions developed by Vandewalle and Nerinckx.[21] Initially, the reaction progressed *via* a conjugate addition (*i.e.* **17**) followed by Robinson annulation to give the cyclohexanone ring as a single diastereomer **18** without elimination of the hydroxyl to form the enone. We believe that the catalyst acts only as a phase transfer agent and is not solely responsible for the stereocontrol, since we isolated intermediate **17** as a complex mixture of diastereomers. This suggests that it is the KOH that epimerises the mixture under thermodynamic control to produce the single stable diastereomer **18**. While the stereogenic centres formed in this reaction are not relevant to the synthesis of the tubingensin A framework, it should be noted that the stereochemistry at C-11 is the same as that of aspernomine. This would suggest that this ring structure could also be accessed by modifying this methodology. Reduction of **18** with Zn smoothly produced the indole **19** in 81% yield. Finally, to complete the synthesis, the tertiary alcohol was eliminated in the presence of TsOH in refluxing toluene, the dihydro intermediate formed undergoing spontaneous oxidation under the reaction conditions. We found that if the reaction was worked up too early after tlc analysis showed that no starting material remained, a mixture of **20** and dihydro derivatives analogous to 10,27-dihydrotubingensin A[5] was isolated. Stirring this mixture overnight in chloroform, exposed to the air, was sufficient to complete the oxidation.

§ *N*-(4-trifluoromethylbenzyl)cinchoninium bromide

Summary and conclusions

In summary, we have completed a synthesis of the polycyclic frameworks of anominine and tubingensin A. As a prelude to working on their total synthesis, we have demonstrated the viability of exocyclic enones as ideal molecular scaffolds for the incorporation of the heterocyclic fragments of these natural products. We have also reported a modified synthesis of the highly congested decalin **3**, which should allow the incorporation of the functionality required for the common component of these terpenoid natural products. Application of this methodology to the total synthesis of these indole diterpenoids is currently in progress and the results will be reported in due course.

Experimental section

General

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions. Analytical thin-layer chromatography was performed on SiO_2 (Merck silica gel 60 F_{254}), and the spots were located with 1% aqueous $KMnO_4$ or 2% ethanolic anisaldehyde. Chromatography refers to flash chromatography carried out on SiO_2 (SDS silica gel 60 ACC, 35–75 μm, 230–240 mesh ASTM). Drying of organic extracts during workup of reactions was performed over anhydrous $MgSO_4$, except where stated otherwise. Evaporation of solvent was accomplished with a rotatory evaporator. NMR spectra were recorded in $CDCl_3$ on a Varian Gemini 300 or Varian VNMRS 400. Chemical shifts of ^1H and ^{13}C NMR spectra are reported in ppm downfield (δ) from Me_4Si.

Terpene biogenetic numbering was used in the NMR assignation of all compounds and the IUPAC nomenclature is followed in the headings. Table 1 with all ^{13}C NMR data is found in the ESI.†

(4*aRS*,8*aSR*)-4*a*,8*a*-Dimethyl-3,4,4*a*,5,8,8*a*-hexahydro-2*H*,7*H*-naphthalene-1,6-dione 5

To a dispersion of copper iodide (32 g, 0.168 mol) in Et_2O (700 mL) at 0 °C was added MeLi (1.6 M in Et_2O, 175 mL, 0.280 mol), and the mixture was stirred for 1 h. A solution of enone **4** (10 g, 0.056 mol) in Et_2O (100 mL) was added, and the reaction was stirred at 0 °C for 30 min. The reaction was quenched with saturated aqueous NH_4Cl solution and stirred for 2 h, the aqueous layer was separated and extracted with EtOAc (5 × 100 mL), the combined organic layers were washed with saturated aqueous NH_4Cl in 20% aqueous NH_3 (5 : 1) and brine, dried, and concentrated. Purification of the residue by chromatography (10% EtOAc–hexane) gave diketone **5** (9.15 g, 85%) as a white solid; mp 129–131 °C; ^1H NMR (300 MHz, COSY) 0.98 (s, 3H, Me-29), 1.21 (s, 3H, Me-21), 1.45 (ddd, $J = 11.0, 11.0, 5.0$ Hz, 1H, H-19$_{ax}$), 1.55 (ddd, $J = 13.7, 11.1, 5.6$ Hz, 1H, H-14$_{ax}$), 1.85–1.95 (m, 3H, 2H-18, H-19$_{eq}$), 1.97 (dd, $J = 14.5, 2.1$ Hz, 1H, H-11$_{eq}$), 2.26 (dddd, $J = 15.2, 7.2, 5.6, 3.2$ Hz, 1H, H-13$_{eq}$), 2.39 (d, $J = 14.5$ Hz, 1H, H-11$_{ax}$), 2.40 (dm, $J = 14.0$ Hz, 1H, H-17$_{eq}$), 2.42 (dm, $J = 13.5$ Hz, 1H, H-14$_{eq}$), 2.57 (dddd, $J = 14.4, 11.0, 6.6, 1.5$ Hz, 1H, H-13$_{ax}$), 2.58 (m, 1H, H-17$_{ax}$); ^{13}C NMR (75 MHz, DEPT, HSQC) 21.2 (C-29), 21.9 (C-18), 23.3 (C-21), 31.5 (C-14), 34.5 (C-19), 37.1 (C-17), 38.8 (C-13), 44.8 (C-20), 50.8 (C-11), 51.8 (C-15), 211.7 (C-16), 214.9 (C-12); HRMS calcd for $C_{12}H_{19}O_2$ (MH^+) 195.1379, found 195.1381.

(4*aRS*,8*aSR*)-4*a*,8*a*-Dimethyl-3,4,4*a*,5,8,8*a*-hexahydro-2*H*,7*H*-naphthalene-1,6-dione 6-monoethylene acetal 6

A solution of diketone **5** (3.3 g, 16.99 mmol) and *p*-toluenesulfonic acid monohydrate (162 mg, 0.85 mmol) in 2-ethyl-2-methyl-1,3-dioxolane (10.6 mL, 85 mmol) was stirred at room temperature for 1 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with Et_2O (3 × 100 mL), the combined organic layers were washed with brine, dried and concentrated. Purification of the residue by chromatography (5% EtOAc) gave **6** (2.7 g, 68%) as a clear oil, followed by recovered starting material **5** (1.05 g): overall yield 99% based on recovered starting material: ^1H NMR (300 MHz) 0.97 (s, 3H), 1.03 (s, 3H), 1.35–1.45 (m, 2H), 1.50–1.70 (m, 5H), 1.75–1.85 (m, 2H), 2.10 (m, 1H), 2.35 (m, 2H), 3.88 (s, 4H); ^{13}C NMR (75 MHz, DEPT) 20.5 (C-29), 21.7 (C-18), 24.8 (C-21), 30.0 (C-19), 31.6 (C-14), 34.8 (C-13), 37.7 (C-17), 41.0 (C-20), 43.6 (C-11), 51.9 (C-15), 64.2 and 64.4 (OCH_2), 109.6 (C-12), 216.2 (C-16); HRMS calcd for $C_{14}H_{23}O_3$ (MH^+) 239.1641, found 239.1642.

(4*aRS*,8*aSR*)-4*a*,8*a*-Dimethyl-5-methylene-3,4,4*a*,5,6,7,8,8*a*-octahydro-1*H*-naphthalen-2-one ethylene acetal 7

A solution of methyltriphenylphosphonium bromide (20.0 g, 56.5 mmol) and potassium *tert*-butoxide (6.3 g, 56.5 mmol) in toluene (120 mL) was stirred at reflux for 1 h. Ketone **6** (2.7 g, 11.25 mmol) in toluene (40 mL) and was then added dropwise to the above solution and the resulting mixture was stirred at reflux for 4 h. The reaction was quenched by the addition of acetone (3 mL), stirring at 100 °C for 30 min and then by the addition of water (100 mL). The reaction mixture was extracted with Et_2O (3 × 200 mL), the combined organic layers were washed with brine, dried and concentrated. Purification of the residue by chromatography (1% EtOAc–hexane) gave alkene **7** (2.5 g, 95%) as a clear oil: ^1H NMR (300 MHz)¶ 0.90 (br s, 3H), 1.08 (s, 3H), 1.43–1.84 (m, 8H), 2.12–2.37 (m, 4H), 3.83–4.06 (m, 4H), 4.73 and 4.78 (2 s, 1H each); ^{13}C NMR (75 MHz, DEPT) 20.1 (Me), 22.5 (C-18), 23.2 (Me), 27.3 (C-19), 31.2 (C-14), 32.3 (C-15), 32.9 (C-17), 35.8 (C-13), 38.3 (C-20), 41.8 (C-11), 63.5 and 63.7 (OCH_2), 107.9 (C-28), 108.1 (C-12), 132.1 (C-16); HRMS calcd for $C_{15}H_{25}O_2$ (MH^+) 237.1849, found 237.1853.

Hydrogenation of 9

Platinum(IV) oxide hydrate (20 mg, 0.06 mmol) was added to a stirred solution of ketone **9** (100 mg, 0.57 mmol) in CH_2Cl_2 (10 mL). The mixture was flushed with hydrogen and stirred under pressure (450 psi) in a sealed apparatus at room temperature for 16 h. The mixture was filtered through Celite, dried and concentrated to give ~100 mg of material. The composition of the mixture was 3 : 1 in favour of the all-*syn* epimer as found by ^1H NMR spectroscopy. The products had identical R_f values and were not separable by chromatography.

(4*aRS*,8*aSR*)-Trimethyl-3,4,4*a*,7,8,8*a*-hexahydro-1*H*-naphthalen-2-one 11

p-Toluenesulfonic acid monohydrate (149 mg, 0.78 mmol) was added to a solution of **9** (100 mg, 0.52 mmol) in AcOH (2 mL) and the resulting mixture was stirred at room temperature for 48 h. The reaction was quenched with water, and extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$, dried and concentrated. Purification of the residue by chromatography (10% EtOAc–hexane) gave **11** (98 mg, 98%) as a colourless oil: ^1H NMR (400 MHz) 0.92 (s, 3H, Me), 1.05 (s, 3H, Me), 1.25 (m, 1H, H-19), 1.65 (m, 1H, H-19), 1.73 (s, 3H, Me-28), 1.80 (m, 1H, H-14), 1.91 (d, $J = 13.0$ Hz, 1H, H-11), 1.95–2.05 (m, 3H, 2 H-18 and H-14), 2.20 (m, 2H, 2 H-13), 2.59 (d, $J = 13.4$ Hz, 1H, H-11), 5.43 (s, 1H, H-17); ^{13}C NMR (100 MHz, DEPT, HSQC) 19.4 (Me), 22.1 (br Me), 22.6 (C-18), 23.4 (C-21), 31.6 (C-19), 33.2 (br C-14), 38.9 (C-13), 39.9 (br C-15), 40.6 (C-20), 49.6 (C-11), 122.9 (C-17), 137.9 (C-16), 212.8 (C-12); HRMS calcd for $C_{13}H_{21}O$ (MH^+) 193.1592, found 193.1592.

(4*aRS*,5*SR*,8*aRS*)-5-Hydroxymethyl-4*a*,8*a*-dimethyloctahydronaphthalen-2-one ethylene acetal 12

BH_3 (1 M in THF, 25.4 mL, 25.4 mmol) was added dropwise to a cooled (0 °C) solution of alkene **7** (2.0 g, 8.5 mmol) in THF (10 mL). The resulting mixture was warmed to room temperature, stirred for 2 h. The mixture was then cooled to −78 °C, and a premixed solution of 4 mL of 30% aqueous H_2O_2 and 4 mL of 3 M NaOH was added. After stirring the mixture overnight at room temperature, the aqueous layer was extracted with Et_2O (3 × 100 mL), and the combined organic layers were washed

¶ Broad signals due to the conformational inversion of the decalin ring.

with saturated aqueous $NaHCO_3$, brine, dried and concentrated *in vacuo*. Purification by chromatography (25% EtOAc–hexane) gave the alcohol **12** (1.1 g, 60%) followed by its epimer (220 mg, 12%) as clear oils: ^{1}H NMR (400 MHz, COSY) 0.76 (s, 3H, Me-29), 0.96 (s, 3H, Me-21), 1.10 (dd, J = 14.0, 2.0 Hz, 2H, H-11$_{ax}$, H-13$_{eq}$), 1.15 (m, 1H, H-19$_{ax}$), 1.42–1.60 (m, 5H, H-13$_{ax}$, H-17$_{eq}$, H-14$_{eq}$, 2 H-18), 1.65 (td, J = 13.8, 2.8 Hz, 1H, H-14$_{ax}$), 1.75 (m, 1H, H-17$_{ax}$), 1.83 (dm, J = 11.9 Hz, 1H, H-19$_{eq}$), 1.95 (dddd, J = 12.0, 7.7, 4.0, 3.3 Hz, 1H, H-16$_{ax}$), 2.22 (d, J = 14.0 Hz, 1H, H-11$_{eq}$), 3.30 (dd, J = 10.4, 8.8 Hz, 1H, H-28), 3.79 (dd, J = 10.4, 3.3 Hz, 1H, H-28), 3.87–3.96 (m, 4H, OCH_2); ^{13}C NMR (100 MHz, DEPT, HSQC) 17.1 (C-29), 21.3 (C-18), 25.0 (C-21), 25.2 (C-19), 29.5 (C-14), 30.3 (C-17), 37.0 (C-13), 37.0 (C-20), 37.5 (C-15), 39.2 (C-16), 40.6 (C-11), 63.4 (OCH_2), 64.2 (C-28), 64.3 (OCH_2), 110.0 (C-12); HRMS calcd for $C_{15}H_{27}O_3$ (MH^+) 255.1960, found 255.1954.

(4*aRS*,5*SR*,8*aRS*)-4*a*,5,8*a*-Trimethyl-3,4,4*a*,5,6,7,8,8*a*-octahydro-1*H*-naphthalen-2-one 10

A cooled (0 °C) solution of alcohol **12** (800 mg, 3.14 mmol) in CH_2Cl_2 (25 mL) was treated sequentially with Et_3N (0.95 mL, 6.57 mmol) and methanesulfonyl chloride (270 mL, 3.46 mmol). After being stirred at room temperature for 1.5 h, the mixture was diluted with CH_2Cl_2 and washed with H_2O (15 mL), brine (2 × 5 mL), dried, and concentrated to give the mesylate, which was used in the next step without additional purification: ^{1}H NMR (300 MHz) 0.80 (s, 3H, Me-21), 0.98 (s, 3H, Me-29), 1.12 (dd, J = 14.2, 2.2 Hz, 2H, H-11$_{eq}$, H-13$_{eq}$), 1.24–1.40 (m, 1H, H-18$_{eq}$), 1.41–1.62 (m, 5H, H-13$_{ax}$, H-17$_{eq}$, H-14$_{eq}$, H-19$_{eq,ax}$), 1.63–1.86 (m, 3H, H-14$_{ax,}$ H-17$_{ax,}$ H-18$_{ax}$), 2.09–2.32 (m, 2H, H-11$_{ax,}$ H-16), 2.99 (s, 3H, –O_3S*Me*), 3.78–4.06 (m, 5H, H-28, O*C*H_2), 4.35 (dd, J = 9.52, 3.65 Hz, 1H, H-28). A solution of the above mesylate in THF (12 mL) was treated with Superhydride (1 M in THF, 9.42 mL, 9.42 mmol) and the resulting mixture was stirred at room temperature for 16 h. The reaction was quenched with 10% aqueous HCl (20 mL), stirred for 2 h and then extracted with Et_2O (3 × 20 mL), dried and concentrated. Purification by chromatography (10% EtOAc–hexane) gave **10** (450 mg, 74% from alcohol **12**) as a white solid. All data were in accordance to those previously reported.[9] For ^{13}C NMR data, see Table 1 in the ESI.†

(4*aRS*,5*RS*,8*aSR*)-Trimethyl-4*a*,5,6,7,8,8*a*-hexahydro-1*H*-naphthalen-2-one 13

To a solution of ketone **10** (400 mg, 2.06 mmol) in DMSO (6 mL) was added *o*-iodoxybenzoic acid (IBX, 1.44 g, 5.15 mmol) and *p*-toluenesulfonic acid monohydrate (118 mg, 0.62 mmol), and the mixture was heated to 70 °C for 16 h. The reaction mixture was cooled to room temperature and partitioned between EtOAc (40 mL) and H_2O (10 mL). The aqueous layer was separated and extracted with EtOAc (5 × 40 mL), the combined organic layers were washed with saturated $NaHCO_3$, saturated sodium thiosulfate solution, brine, dried and concentrated. Purification by chromatography (10% EtOAc–hexane) gave **13** (281 mg, 71%) as a colourless oil: ^{1}H NMR (300 MHz) 0.91 (d, J = 6.8 Hz, 3H, Me-28), 0.92 and 1.01 (s, 3H each, Me-29 and Me-21), 1.15 (m, 2H), 1.40–1.64 (m, 4H), 1.82 (d, J = 16.9 Hz, 1H, H-11), 1.91 (ddd, J = 12.3, 6.7, 3.5 Hz, 1H, H-16), 3.06 (d, J = 16.9 Hz, 1H, H-11), 5.91 (d, J = 10.2 Hz, 1H, H-13), 6.68 (d, J = 10.2 Hz, 1H, H-14); ^{13}C NMR (75 MHz, DEPT) 13.3 (Me), 16.9 (C-28), 21.7 (C-18), 24.9 (Me), 30.1 (C-17), 35.4 (C-19), 37.8 (C-16), 39.3 (C-15), 42.1 (C-20), 46.1 (C-11), 126.3 (C-13), 159.4 (C-14), 200.2 (C-12); HRMS calcd for $C_{13}H_{21}O$ (MH^+) 193.1592, found 193.1601.

(4*aRS*,5*SR*,8*aSR*)- 4*a*,5,8*a*-Trimethyl-1-methylene-3,4,4*a*,5,6,7,8,8*a*-octahydro-1*H*-naphthalen-2-one 3

Enone **13** (506 mg, 2.64 mmol) in THF (10 mL) was added dropwise to a cooled (−78 °C) solution of LiHMDS (1 M in THF, 5.27 mL, 5.27 mmol) in THF (7.5 mL). The resulting solution was stirred for 5 min at −78 °C, warmed to 0 °C, stirred for 1 h, recooled to −78 °C then transferred *via* cannula over 15 min to a stirred suspension of Eschenmoser's salt (1.47 g, 7.92 mmol,) in 15 mL of THF at −78 °C. The resulting mixture was stirred for 10 min at −78 °C, then for 10 min in a room temperature water bath, and then transferred to a separatory funnel with ether (50 mL) and saturated $NaHCO_3$ solution (10 mL). The aqueous layer was separated, diluted with 50 mL of water, and extracted with 50 mL of CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated at reduced pressure to give a yellow-orange oil **14**. The residue was dissolved in MeOH (50 mL), Pd/C (100 mg) was added, and the mixture was stirred under hydrogen (1 atm) for 16 h. The mixture was filtered through Celite, dried and concentrated. This crude material was partitioned between CH_2Cl_2 (25 mL) and saturated $NaHCO_3$ solution (12.5 mL), and *m*-CPBA (Aldrich, 57–86%, 911 mg, 5.28 mmol, 1.5–2.3 equiv) was added in one portion. The resulting mixture was stirred vigorously for 20 min, then transferred to a separatory funnel and separated. The aqueous layer was extracted with CH_2Cl_2 (25 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure *at room temperature* to avoid undesired polymerisation. Purification by chromatography (5% EtOAc–hexane) gave **3** as a clear oil (350 mg, 69%). All spectroscopic data were identical to that previously reported.[9] For ^{13}C NMR data, see Table 1 in the ESI.†

(1*RS*,4*aRS*,5*SR*,8*aRS*)-1-(1*H*-Indol-3-ylmethyl)-4*a*,5,8*a*-trimethyl-3,4,4*a*,5,6,7,8,8*a*-octahydro-1*H*-naphthalen-2-one 15

To a solution of indole (37 mg, 0.32 mmol), and the enone **3** (65 mg, 0.32 mmol) in CH_3CN (1 ml) was added bismuth triflate (6 mg, 0.01 mmol, 3 mol%) and the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with CH_2Cl_2 and absorbed onto silica. Purification by column chromatography (5% EtOAc–hexane) gave ketoindole (95 mg, 93%) as a mixture of epimers. The mixture was dissolved in EtOH (10 mL), potassium fluoride (255 mg, 4.40 mmol) was added, and the resulting mixture was heated at reflux for 48 h. After the reaction was cooled to room temperature, the mixture was partitioned between water and CH_2Cl_2, and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were washed with brine, dried, and concentrated. Purification of the residue by chromatography (25% EtOAc–hexane) gave **15** (93 mg, 98%) as a white solid: mp 173–175 °C; ^{1}H NMR (400 MHz, COSY) 0.82 (s, 3H, Me), 0.83 (d, J = 6.8 Hz, 3H, Me-28), 0.86 (s, 3H, Me), 1.40 (qd, J = 12.8, 4.8 Hz, 1H, H-17$_{ax}$), 1.51 (dm, J = 12.5 Hz, 1H, H-17$_{eq}$), 1.55-1–70 (m, 3H, H-14$_{ax}$, 2 H-18), 1.71 (td, J = 14.0, 4,5 Hz, 1H, H-19$_{ax}$), 1.87 (dm, J = 14.0 Hz, 1H, H-14$_{eq}$), 1.90 (ddd, J = 14.0, 6.0, 2.4 Hz,

1H, H-19$_{eq}$), 2.14 (ddd, J = 12.9, 4.4, 2.4 Hz, 1H, H-13$_{eq}$), 2.31 (m, 1H, H-16$_{ax}$), 2.37 (td, J = 14.0, 6.0 Hz, 1H, H-13$_{ax}$), 2.62 (d, J = 13.5 Hz, 1H, H-10), 3.25 (dd, J = 13.5, 9.5 Hz, 1H, H-10), 3.30 (d, J = 9.5 Hz, 1H, H-11), 7.05 (d, J = 2.2 Hz, 1H, H-2), 7.10 (t, J = 7.8 Hz, 1H, H-6), 7.16 (t, J = 7.8 Hz, 1H, H-7), 7.31 (d, J = 8.0 Hz, 1H, H-8), 7.59 (d, J = 7.8 Hz, 1H, H-5), 7.94 (br s, 1H, NH); ^{13}C NMR (100 MHz, DEPT, HSQC) 16.0 (C-28), 16.3 (C-29), 17.4 (C-10), 18.8 (C-21), 21.9 (C-18), 30.6 (C-17), 30.9 (C-16), 32.5 (C-14), 33.5 (C-13), 38.7 (C-15), 39.6 (C-19), 47.0 (C-20), 53.6 (C-11), 111.0 (C-8), 115.9 (C-3), 118.5 (C-5), 119.1 (C-6), 121.6 (C-7), 123.5 (C-2), 127.5 (C-4), 135.9 (C-9), 213.6 (C-12); HRMS calcd for $C_{22}H_{29}NO$ (M^+) 323.2249, found 323.2260.

3-[(1*RS*,4*aSR*,5*RS*,8*aSR*)-4*a*,5,8*a*-Trimethyl-2-methylenedecahydronaphthalen-1-ylmethyl]-1*H*-indole 16

A solution of methyltriphenylphosphonium bromide (200 mg, 0.56 mmol) and potassium *tert*-butoxide (55 mg, 0.49 mmol) in toluene (5 mL) was stirred at 90 °C for 30 min. A solution of ketone **15** (40 mg, 0.12 mmol) in toluene (3 mL) was added, and the reaction was heated at 90 °C for 2 h. After the mixture was cooled to room temperature, the reaction was quenched with water, and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were washed with brine, dried, and concentrated. Purification of the residue by column chromatography (2.5% EtOAc–hexane) gave **16** (38 mg, 96%) as a white solid: mp 83–85 °C; ^{1}H NMR (400 MHz, COSY) 0.80 and 0.81 (2 s, 3H each, Me-21, Me-29), 0.81 (d, J = 6.8 Hz, 3H, Me-28), 1.20–1.55 (m, 6H, 2 H-18, 2 H-17, H-14$_{ax}$, H-19$_{ax}$), 1.64 (dm, J = 14.0 Hz, 1H, H-14$_{eq}$), 1.77 (dm, J = 12.0 Hz, 1H, H-19$_{eq}$), 2.08 (ddd, J = 13.9, 4.4, 2.6 Hz, 1H, H-13$_{eq}$), 2.25 (dt, J = 13.9, 13.7, 5.2 Hz, 1H, H-13$_{ax}$), 2.40 (ddd, J = 10.8, 6.5, 3.9 Hz, 1H, H-16), 2.83 (dd, J = 16.0, 10.3 Hz, 1H, H-10), 2.94 (d, J = 16.0 Hz, 1H, H-10), 3.24 (d, J = 10.3 Hz, 1H, H-11), 4.65 (d, 1H, H-27), 4.83 (d, J = 1.6 Hz, 1H, H-27), 6.96 (s, 1H, H-2), 7.11 (ddd, J = 7.6, 7.2, 1.1 Hz, 1H, H-6), 7.17 (t, J = 7.6 Hz, 1H, H-7), 7.33 (d, J = 8.0 Hz, 1H, H-8), 7.65 (d, J = 7.9 Hz, 1H, H-5), 7.86 (br s, 1H, NH); ^{13}C NMR (100 MHz, DEPT, HSQC) 16.3 (C-29), 16.5 (C-28), 18.3 (C-21), 19.9 (C-10), 21.6 (C-18), 30.5 (C-16), 31.1 (C-17), 32.1 (C-19), 32.9 (C-13), 33.9 (C-14), 39.7 (C-15), 42.5 (C-11), 42.8 (C-20), 107.7 (C-27), 111.0 (C-8), 116.7 (C-3), 118.7 (C-5), 119.0 (C-6), 121.5 (C-7), 121.7 (C-2), 128.0 (C-4), 135.9 (C-9), 149.5 (C-12); HRMS calcd for $C_{23}H_{31}N$ (M^+) 321.2456, found 321.2457.

(3*RS*,4*aSR*,8*RS*,8*aSR*,10*aSR*)-10*a*-Hydroxy-4*b*,8,8*a*-trimethyl-3-(2-nitrophenyl)dodecahydro-1*H*-phenanthren-2-one 18

To a solution of 1-(2-nitrophenyl)propan-2-one (93 mg, 0.52 mmol), *N*-(4-trifluoromethylbenzyl)cinchoninium bromide (27 mg, 0.05 mmol) and 60% (w/v) KOH (0.25 mL) in toluene (2 mL) was added enone **3** (100 mg, 0.52 mmol) in toluene (3 mL) and the mixture was stirred at room temperature for 48 h. The mixture was partitioned between water and CH_2Cl_2, and the aqueous layer extracted with CH_2Cl_2 (2 × 20 mL). The organic extracts were washed with brine, dried, and concentrated. Purification of the residue by column chromatography (20% EtOAc–hexane) gave **18** (94 mg, 51%) as a bright yellow solid: 166–168 °C; ^{1}H NMR (400 MHz, COSY) 0.83 (d, J = 6.4 Hz, 6H, Me-28, Me-29), 0.98 (s, 3H, Me-21), 1.20–1.40 (m, 5H, H-13$_{eq}$, H-14$_{eq}$, H-17, H-19), 1.45–1.60 (m, 4H, H-17, 2 H-18, H-19), 1.78 (td, J = 14.0, 4.0 Hz, 1H, H-13$_{ax}$), 1.90 (td, J = 14.0, 4.0 Hz, 1H, H-14$_{ax}$), 2.15 (m, 2H, H-10$_{eq}$, H-16), 2.39 (q, J = 12.5 Hz, 1H, H-10$_{ax}$), 2.43 (d, J = 14.0 Hz, 1H, H-27$_{eq}$), 2.68 (dd, J = 11.9, 2.4 Hz, 1H, H-11), 2.75 (d, 1H, H-27$_{ax}$), 4.40 (dd, J = 12.4, 5.3 Hz, 1H, H-3$_{ax}$), 7.42 (t, J = 7.7 Hz, 1H, H-7), 7.47 (d, J = 7.7 Hz, 1H, H-5), 7.61 (t, J = 7.7 Hz, 1H, H-6), 7.95 (d, J = 7.7 Hz, 1H, H-8); ^{13}C NMR (100 MHz, DEPT, HSQC) 16.0 (C-28), 16.3 (C-29), 20.5 (C-21), 21.6 (C-18), 27.0 (C-14), 29.9 (C-10), 30.2 (C-16), 30.7 (C-17), 33.1 (C-19), 35.0 (C-13), 39.1 (C-15), 39.2 (C-20), 41.4 (C-11), 52.8 (C-3), 57.7 (C-27), 76.4 (C-12), 124.6 (C-8), 127.7 (C-7), 130.6 (C-6), 132.9 (C-5), 133.6 (C-4), 149.5 (C-9), 206.4 (C-2); HRMS calcd for $C_{23}H_{32}NO_4$ (MH^+) 386.2331, found 386.2330.

(4*RS*,4*aRS*,6*aRS*,13*aRS*,13*bRS*)-4,4*a*,13*b*-Trimethyl-2,3,4,4*a*,5,6,6*a*,7,8,13,13*a*,13*b*-dodecahydro-1*H*-naptho[2,1-*b*]carbazol-6*a*-ol 19

To a solution of **18** (27 mg, 0.07 mmol) in MeOH (2 mL) were added sequentially sat. aq. NH_4Cl (0.7 mL), Zn dust (460 mg, 7.0 mmol) and the mixture was stirred at room temperature for 3 h. The reaction was quenched by the addition of sat. aq. $NaHCO_3$, filtered through Celite and washed with EtOAc. The combined organic layers were washed with $NaHCO_3$, brine, dried and concentrated. Purification of the residue by chromatography (20% EtOAc–hexane) gave alkene **19** (19 mg, 81%) as a light yellow solid: mp >220 °C; ^{1}H NMR (400 MHz, COSY) 0.81 (d, J = 6.8 Hz, 3H, Me-28), 0.86 (s, 3H, Me-29), 1.11 (s, 3H, Me-21), 1.26–1.48 (m, 7H, 2 H-14, 2 H-17, 2 H-18, H-19$_{ax}$), 1.60 (dm, J = 12.0 Hz, 1H, H-19$_{eq}$), 1.72–1.92 (m, 2H, 2 H-13), 2.10 (m, 1H, H-16), 2.55 (dd, J = 12.0, 5.5 Hz, 1H, H-11$_{ax}$), 2.70 (dd, J = 14.5, 13.0 Hz, 1H, H-10$_{ax}$), 2.71 (d, J = 16.0 Hz, 1H, H-27), 2.81 (dd, J = 14.5, 6.0 Hz, 1H, H-10$_{eq}$), 2.91 (d, J = 16.0 Hz, 1H, H-27), 7.11 (ddd, J = 7.7, 7.5, 1.2 Hz, 1H, H-7), 7.13 (ddd, J = 7.7, 7.1, 1.3 Hz 1H, H-6), 7.30 (d, J = 7.5 Hz, 1H, H-8), 7.50 (d, J = 7.5 Hz, 1H, H-5), 7.68 (s, 1H, NH); ^{13}C NMR (100 MHz, DEPT, HSQC) 15.9 (C-28), 16.6 (C-29), 17.5 (C-10), 20.0 (C-21), 21.5 (C-18), 27.3 (C-14), 30.0 (C-16), 30.6 (C-17), 32.6 (C-19), 33.9 (C-13), 38.1 (C-11), 39.1 (C-15), 39.2 (C-20), 41.4 (C-27), 71.8 (C-12), 108.9 (C-3), 110.6 (C-8), 117.9 (C-5), 119.3 (C-7), 121.4 (C-6), 127.6 (C-2), 130.9 (C-4), 136.4 (C-9); HRMS calcd for $C_{23}H_{31}NO$ (M^+) 337.2406, found 337.2408.

(4*RS*,4*aSR*,13*bRS*)-4,4*a*,13*b*-Trimethyl-2,3,4,4*a*,5,6,8,13*b*-octahydro-1*H*-naptho[2,1-*b*]carbazole 20

To a solution of **19** (12 mg, 0.04 mmol) in toluene (10 mL) was added *p*-toluenesulfonic acid (7 mg, 0.04 mmol) and the mixture was stirred at reflux for 3 h. The reaction mixture was diluted with CH_2Cl_2 (40 mL), washed with sat. aq. $NaHCO_3$, H_2O, brine, dried and concentrated. Purification of the residue by column chromatography (5% EtOAc–hexane) gave carbazole **20** (10 mg, 88%) as a light yellow gum: ^{1}H NMR (400 MHz) 0.84 (d, J = 6.8 Hz, 3H, Me-28), 0.98 (s, 3H, Me-29), 1.18 (s, 3H, Me-21), 1.22–1.28 (m, 1H), 1.45–1.57 (m, 2H), 1.61–1.77 (m, 3H), 1.79–2.11 (m, 2H), 2.25 (m, 1H), 2.87 (dd, J = 17.5, 6.4 Hz, 1H, H-13$_{eq}$), 3.02 (ddd, J = 17.5, 13.0, 7.3 Hz, 1H, H-13$_{ax}$), 7.12 (s, 1H, H-27), 7.18 (ddd, J = 8.0, 5.7, 2.5 Hz, 1H, H-6), 7.35 (m, Hz, 2H, H-7, H-8), 7.79 (br s, 1H, NH), 8.02 (s, 1H, H-10), 8.02 (d, J = 7.6 Hz, 1H,

H-5); ^{13}C NMR (100 MHz, DEPT) 16.3 (C-28 and C-29), 22.7 (C-18), 26.6 (C-13), 28.6 (C-14), 29.7 (C-17), 30.9 (C-21), 32.1 (C-16), 33.6 (C-19), 37.8 (C-15), 42.1 (C-20), 110.1 (C-8), 110.3 (C-27), 117.5 (C-10), 119.0 (C-6), 119.9 (C-5), 122.4 (C-3), 123.7 (C-4), 125.2 (C-7), 135.0 (C-11), 136.2 (C-12), 137.7 (C-2), 140.0 (C-9).

Acknowledgements

This research was supported by the Ministry of Education and Science (Spain)-FEDER through project CTQ2007-61338/BQU. Thanks are also due to the DURSI (Catalonia) for Grant 2005SGR-00442 and the MEC for a fellowship to G.E.

Notes and references

1 J. B. Gloer, *Acc. Chem. Res.*, 1995, **28**, 343.
2 B. L. Rinderknecht, J. B. Gloer, P. F. Dowd and D. T. Wicklow, *J. Org. Chem.*, 1989, **54**, 2530.
3 (*a*) S. Sakai, I. Yamamoto, K. Yamaguchi, H. Takayama, M. Ito and T. Okamoto, *Chem. Pharm. Bull.*, 1982, **30**, 4579; (*b*) H. Muratake and M. Natsume, *Angew. Chem., Int. Ed.*, 2004, **43**, 4646; H. Muratake, M. Natsume and H. Nakai, *Tetrahedron*, 2006, **62**, 7093.
4 M. R. TePaske, J. B. Gloer, P. F. Dowd and D. T. Wicklow, *J. Org. Chem.*, 1989, **54**, 4743.
5 For the isolation of the 10,27-dihydrotubingensin A, see: H. L. Sings, G. H. Harris and A. W. Dombrowski, *J. Nat. Prod.*, 2001, **64**, 836.
6 G. M. Staub, J. B. Gloer, D. T. Wicklow and P. F. Dowd, *J. Am. Chem. Soc.*, 1992, **114**, 1015.
7 Y. Liu, W. W. McWhorter, Jr. and C. E. Hadden, *Org. Lett.*, 2003, **5**, 333.
8 For a synthesis of the related 12-demethylaflavinine, see: S. Danishefsky, S. Chackalamannil, P. Harrison, M. Silvestri and P. Cole, *J. Am. Chem. Soc.*, 1985, **107**, 2474.
9 S. Díaz, J. Cuesta, A. González and J. Bonjoch, *J. Org. Chem.*, 2003, **68**, 7400.
10 S. Díaz, A. González, B. Bradshaw, J. Cuesta and J. Bonjoch, *J. Org. Chem.*, 2005, **70**, 3749.
11 For the synthesis of *ent*-**A** from the Wieland–Miescher ketone see: L. A. Paquette, T.-Z. Wang, C. M. G. Philippo and S. Wang, *J. Am. Chem. Soc.*, 1994, **116**, 3367.
12 S. Vellekoop and R. A. J. Smith, *Tetrahedron*, 1998, **54**, 11971.
13 For a review on stereoselective construction of the decalin skeleton with multiple contiguous stereocenters, see: T. Tookoroyama, *Synthesis*, 2000, 611.
14 For other recent approaches leading to highly substituted decalins, see: (*a*) T. Tricotet and R. Brückner, *Tetrahedron Lett.*, 2006, **47**, 8499; (*b*) M. E. Jung and M. Murakami, *Org. Lett.*, 2007, **9**, 461; (*c*) S. Marchart, J. Mulzer and V. S. Enev, *Org. Lett.*, 2007, **9**, 813.
15 In this model study, we used the almost totally racemic Wieland–Miescher ketone isolated in the enantiomeric purification of (−)-**4**: N. Harada, T. Sugioka, H. Uda and T. Kuriki, *Synthesis*, 1990, 53.
16 (*a*) R. A. J. Smith and D. J. Hannah, *Tetrahedron*, 1979, **35**, 1183; (*b*) G. Hirai, H. Oguri, M. Hayashi, K. Koyama, Y. Koizumi, S. M. Moharram and M. Hirama, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2647.
17 Isomerization of **7** to **11** was achieved by acid treatment using TsOH and AcOH.
18 K. C. Nicolaou, T. Montagnon, P. S. Baran and Y. L. Zhong, *J. Am. Chem. Soc.*, 2002, **124**, 2245.
19 A. V. Reddy, K. Ravinder, T. V. Goud, P. Krishnaiah, T. V. Raju and Y. Venkateswarlu, *Tetrahedron Lett.*, 2003, **44**, 6257.
20 C. Molinaro, J. Mowat, F. Gosselin, P. D. O'Shea, J.-F. Marcoux, R. Angelaud and I. W. Davies, *J. Org. Chem.*, 2007, **72**, 1856.
21 W. Nerinckx and M. Vandewalle, *Tetrahedron: Asymmetry*, 1990, **1**, 265.

