Synthetic studies towards pseudopterosin A

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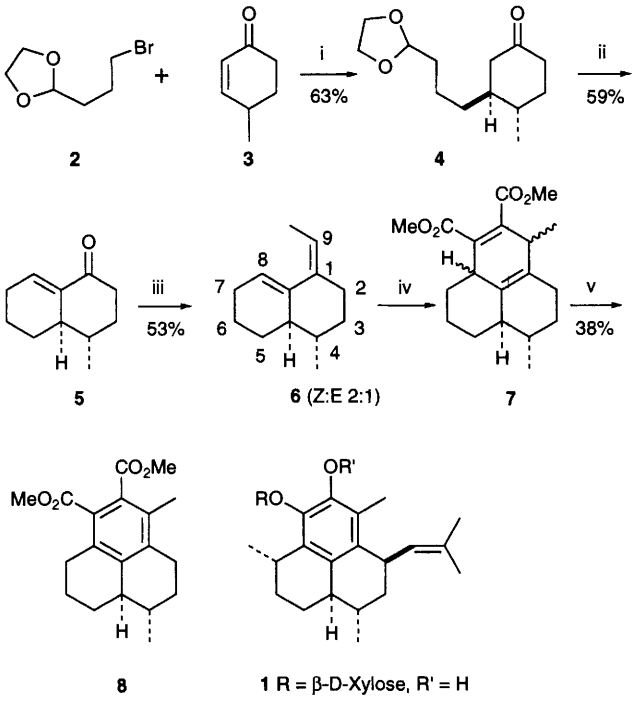
The tricyclic hexahydrophenalene derivative (±)-8, a potential precursor for the synthesis of pseudopterosins, has been prepared in 5 steps from 4-methyl-cyclohex-2-enone 3.

Pseudopterosin A, 1 (Scheme 1), a terpenoid isolated from Caribbean sea whips, has been shown to exhibit both anti-inflammatory effects, exceeding the drug industry standard



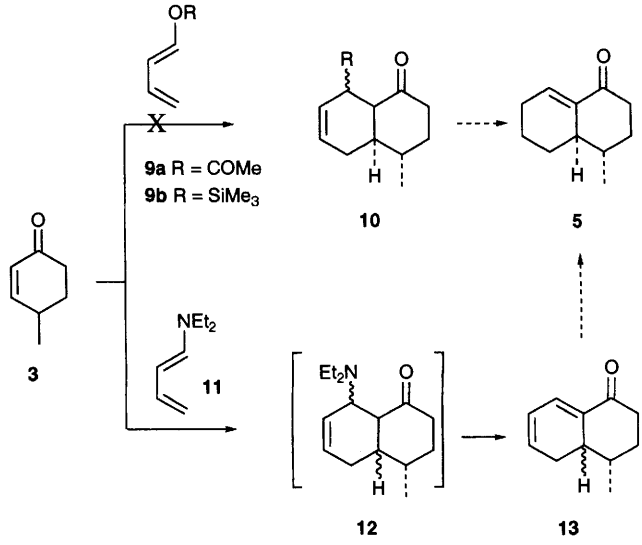
Scheme 1 *Reagents:* i, Mg, Cu^{I}Br·Me_2S; ii, HCl, THF; iii, Ph_3P=CHMe; iv, DMAD, $AlCl_3$; v, DDQ

indomethacin, and analgesic effects.[1-3] Three total syntheses of **1**[4-6] and several approaches to related tricyclic compounds[7-12] have been published. We here report a short synthetic route to the tricyclic hexahydrophenalene derivative (±)-**8**, which may serve as a starting material for synthesis of pseudopterosins and congeners.

The Cu^{I}-catalysed 1,4-addition of Grignard reagents, also carrying an acetal function, to α,β-unsaturated ketones followed by acidic aldol condensation is an efficient method for ring annulation.[13] However, the substitution patterns of the ketones used disallowed observation of the stereoselectivity of the reaction. On the other hand, it has been shown that addition of lithium dimethylcuprate[14] and Cu^{I}-catalysed[15] addition of 3-methylbut-3-enylmagnesium bromide to **3** occurs in a 1,4-fashion to give the corresponding *trans*-3,4-dialkylcyclohexanones as the major products.

Thus, treatment of **3** with the Grignard reagent prepared from bromodioxolane **2**[16,17] at −78 °C in the presence of CuBr·Me_2S afforded the protected keto aldehyde **4** (*trans*:*cis*, 97:3 as determined by GLC/MS analysis) (Scheme 1). Evidently the *trans* adduct was the major isomer as later shown by NOESY measurements on the end product **8**. Subsequent acidic hydrolysis of **4** induced the aldol condensation to give the methyloctalone **5** which, on treatment with ethylphosphorane, afforded the diene **6** as a mixture of isomers (*Z*:*E*, 2:1). This isomeric composition was determined by NOESY measurements on the pure isomers, which were separated by preparative GLC. We also observed that the minor isomer, having a more favourable geometry for the Diels–Alder reaction, was more rapidly consumed in the reaction with dimethyl acetylenedicarboxylate (DMAD). By conducting the Diels–Alder reaction in the presence of $AlCl_3$ at 0 °C both isomers were smoothly converted into the diester **7**. Aromatization of **7** was performed with dichlorodicyanobenzoquinone (DDQ) in dimethylformamide (DMF) at 140 °C to give the diester **8** in 38% yield over the last two steps. In toluene this reaction was very slow, produced many side products and gave a much lower yield. The better result in the more polar solvent agrees with the suggestion of a hydride ion transfer in the initial rate-determining step.[18] We also noticed that the product mixture after the Diels–Alder reaction aromatized spontaneously during silica gel chromatography. This observation will be further developed in our work towards a practical synthesis of **1**.

A key intermediate in our approach is the unsaturated ketone **5**. At first it seemed reasonable that **5** could be synthesized by a Diels–Alder reaction between the diene **9a** or **9b** and **3** followed by hydrogenation of the adduct **10** and elimination of the β-substituent (Scheme 2). Although the butadienes **9a** and **9b** have been used in Diels–Alder cyclizations with α,β-unsaturated carbonyl compounds[19-22] they failed to react with **3** even under forcing conditions. An equimolar solution of **9a** or **9b** and **3** when heated in refluxing toluene for several days or when



Scheme 2 Unsuccessful Diels–Alder reactions to the octalone system **5**

heated neat in a sealed tube at 160 °C failed to afford the product **10**. The alternative diene **11**[23] has also been reported to react with α,β-unsaturated carbonyl compounds in a Diels–Alder fashion.[23–25] Compound **11** when heated with **3** in toluene at 100 °C gave the adduct **12** but the reaction was, unfortunately, accompanied by sluggish elimination of diethylamine to give the conjugated ketodiene **13**. Although selective saturation of the γ,δ-double bond[25] in **13** would give **5**, the yield of **13** (3:1 mixture of diastereoisomers) was too low and the material was too difficult to purify to be synthetically useful.

In conclusion, we have developed a five-step synthesis of compound **8**, which seems well suited as an intermediate for the preparation of pseudopterosins and congeners. In particular, the possibility of obtaining optically active material is well provided for by using (*S*)-**3**.[26] Work along these lines is in progress.

Experimental

NMR spectra were recorded on a Varian XL 300, Bruker ACP 250 or Bruker ARX 500 NMR spectrometer using tetramethylsilane as internal standard; *J* values are recorded in Hz. IR spectra were recorded on a Perkin-Elmer 681 spectrometer. GC analyses were performed on a Perkin-Elmer AutoSystem fitted with a Supelco SPB-20 fused silica capillary column (30 m × 0.25 mm i.d.; 0.25 μm film thickness). GC/MS analyses were performed on an HP 5890 Gas Chromatograph coupled to an HP 5970 mass selective detector or a Varian 3400 Gas Chromatograph coupled to a Finnigan Incos 50B/500E mass spectrometer. Mps were determined using glass capillaries in a Büchi apparatus and are uncorrected. TLC analyses were performed on Merck Silica Gel F-254 (0.25 mm) pre-coated plates and column chromatographic purifications were performed using Matrex (Amicon) silica gel, particle size 0.035–0.070 mm. The ketone **3** was prepared from 4-methylcyclohexanone (Acros Chimica) by literature methods.[27] Butyllithium (1.6 mol dm^{-3} in hexane), Cu(I)Br·Me_2S and DDQ were purchased from Acros Chimica and used as delivered. Magnesium turnings were washed several times with diethyl ether and oven dried at 150 °C prior to use. THF was distilled from potassium and diethyl ether was distilled from sodium wire. DMF was pre-dried over molecular sieves (3 Å), distilled under reduced pressure and stored over molecular sieves (3 Å). Glassware was dried in an oven at 150 °C for several hours prior to use and the reactions were performed under a nitrogen atmosphere.

3-(3-[1,3]Dioxolan-2-ylpropyl)-4-methylcyclohexanone 4

A solution of the bromide **2**[16] (20.6 g, 0.106 mol) in THF (50 cm^3) was added in one portion to magnesium turnings (2.58 g, 0.106 mol) covered with THF (10 cm^3) and the mixture was placed in an ultrasound bath for 50 min. Further THF (100 cm^3) was added to the reaction mixture which was then cooled to −78 °C and treated with $Cu^IBr{\cdot}Me_2S$ (1.6 g, 7.6 mmol) in Me_2S (7 cm^3), added during 10 min. This mixture was stirred at −78 °C for 1 h after which a solution of **3** (5.8 g, 53 mmol) in THF (10 cm^3) was added dropwise to it over 10 min. Stirring was continued at −78 °C for 9 h and then at room temperature for 1 h. The reaction was quenched by the addition of 2 mol dm^{-3} aqueous NH_4Cl (adjusted to pH 8 with aqueous ammonia; 30 cm^3) to the mixture. The resulting deep blue solution was stirred for 1.5 h after which it was filtered and diluted with diethyl ether (50 cm^3). The water phase was separated and the organic phase was washed with aqueous NH_4Cl (pH 8; 2 × 30 cm^3), water (2 × 30 cm^3) and brine (2 × 30 cm^3) and dried ($MgSO_4$). The mixture was concentrated by removal of solvent on a rotary evaporator and the residue starting material was distilled off by bulb-to-bulb distillation (100 °C, 10 mmHg). Chromatography of the residue [SiO_2, EtOAc–heptane (1:3), TLC R_F 0.19] gave pure **4** (2.22 g, 63%) [Found: C, 69.3; H, 9.8%; *M* (mass spectrum CI, methane), 226. $C_{13}H_{22}O_3$ requires C 69.0; H 9.8%; *M*, 226]; ν_{max}/cm^{-1} (neat) 1712 (C=O); δ_H(300 MHz, $CDCl_3$), 4.84 (1 H, t, *J* 5.0), 4.02–3.80 (4 H, m, OCH_2CH_2O), 2.48–2.24 (3 H, m), 2.10–1.93 (2 H, m), 1.7–1.2 (9 H, m) and 1.1 (3 H, d, *J* 6.5); δ_C(75 MHz, $CDCl_3$) 212.28, 104.36, 64.90, 64.83, 45.77, 44.24, 40.97, 35.16, 34.27, 34.02, 33.65, 20.08 and 18.91.

4-Methyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-1-one 5

A solution of the ketone **4** (5.3 g, 23.5 mmol) in ether (20 cm^3) was added to a mixture of hydrochloric acid (6 mol dm^{-3}, 10 cm^3) and THF (200 cm^3) heated at 80 °C. After the mixture had been stirred for 6 h, it was cooled to room temperature, concentrated under reduced pressure to 1/5 of its volume, neutralized with saturated aqueous $NaHCO_3$ and diluted with diethyl ether (100 cm^3). The organic phase was separated and washed with water (3 × 30 cm^3) and brine (1 × 30 cm^3) and the aqueous washings were back extracted with diethyl ether (50 cm^3). The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure and the residue was chromatographed [SiO_2, EtOAc–heptane (1:9); TLC R_F 0.2] to give **5** (2.26 g, 59%) (Found: C, 80.0; H, 9.4. $C_{11}H_{16}O$ requires C, 80.4; H, 9.8%); ν_{max}/cm^{-1} (neat) 1685 (C=O) and 1622 (C=C); δ_H(500 MHz, $CDCl_3$)† 6.72 (1 H, 5 lines with small splittings, 8-H), 2.54 (1 H, ddd, *J* 17.3, 4.8, 2.4, 2′-H), 2.33 (1 H, dt, *J* 17.3, 6.5, 2″-H), 2.27–2.10 (2 H, m, 7′-H, 7″-H), 2.10–2.03 (1 H, m, 5′-H), 1.98–1.91 (1 H, m, 4a-H) 1.88 (1 H, ddt, *J* 13.0, 6.4, 2.2, 3′-H), 1.83–1.80 (1 H, m, 6′-H) 1.60–1.38 (3 H, m, 3″-H, 4-H, 6″-H) 1.13–1.05 (1 H, m, 5″-H) and 1.03 (3 H, d, *J* 6.3, CH_3); δ_C(75 MHz, $CDCl_3$) 201.30 (CO), 139.23, 136.42 (=CH), 43.82 (CH), 39.80 (CH_2), 36.25 (CH), 31.71 (CH_2), 27.94 (CH_2), 25.95 (CH_2), 21.39 (CH_2) and 19.58 (CH_3).

1-Ethylidene-4-methyl-1,2,3,4,4a,5,6,7-octahydronaphthalene 6

Butyllithium (1.6 mol dm^{-3}, 4 cm^3, 6.4 mmol) was added dropwise at −78 °C to a slurry of ethyl(triphenyl)phosphonium bromide (2.51 g, 6.75 mmol) in diethyl ether (17 cm^3). The mixture was heated to room temperature and stirred for 1 h after which it was re-cooled to −78 °C and the ketone **5** (731 mg, 4.50 mmol) in diethyl ether (3 cm^3) was added dropwise to it over 11 min. Stirring was continued at −78 °C for 4 h and then at room temperature for a further 0.5 h after which the mixture was diluted with water (30 cm^3) and stirred vigorously until clear. The organic phase was separated and washed with water (30 cm^3) and brine (30 cm^3) and the washings were back extracted with diethyl ether (30 cm^3). The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure and the residue was extracted with pentane (30 cm^3). The extract was filtered through a short silica layer and then concentrated under reduced pressure. The residue was chromatographed [SiO_2, EtOAc–heptane (5:95), TLC R_F 0.74] to give **6** (417 mg, 2.37 mmol, 53%) as a mixture of isomers (*Z*:*E*, 2:1) [Found (HRMS; EI 70 eV): 176.1540. 176.1541. $C_{13}H_{20}$ requires 176.1565]; ν_{max}/cm^{-1} (neat) 3020 (=CH), 1440. The two isomers were separated by preparative GLC (Supleco FBP 20 column). These compounds must be stored at a low temperature under argon to prevent deterioration. Major isomer (*Z*)-**6**: δ_H(500 MHz, $CDCl_3$) 5.46 (1 H, pentet, 8-H), 5.21 (1 H, dq, *J* 1.92, 6.8, 9-H), 2.17 (1 H, ddd, *J* 3.1, 3.4, 11.9, 2′-H), 2.14–1.98 (4 H, m, 7′-H, 7″-H, 5′-H, 2′-H), 1.78–1.69 (2 H, m, 3′-H, 6′-H), 1.66 (3 H, dd, *J* 2.1, 6.8, CH_3CH=), 1.63–1.55 (1 H, m, 4a-H), 1.44 (18 lines, m, *J* 2.7, 6″-H), 1.31–1.20 (1 H, m, 4-H), 1.20–1.09 (2 H, m, 3″-H, 5″-H) and 0.93 (3 H, d, *J* 6.4 CH_3);

† Single and double primes refer to the two protons at a particular locant.

δ_C(62.5 MHz, $CDCl_3$) 141.72, 137.60, 124.33 (C-8), 117.35 (C-9), 44.71 (C-4a), 39.89 (C-4), 37.31 (C-2), 36.39 (C-3), 29.02 (C-5), 25.78 (C-7), 21.92 (C-6), 20.07 (4-CH_3) and 14.54 (9-CH_3).

Minor isomer (*E*)-**6**: δ_H(500 MHz, $CDCl_3$) 5.61 (1 H, 5 lines, 8-H), 5.40 (1 H, dq, *J* 2.2, 7.0, 9-H), 2.67–2.57 (1 H, m, 2′-H), 2.11–1.91 (3 H, m, 5′-H, 7′-H, 7″-H), 1.83–1.67 (3 H, m, 2″-H, 3′-H, 6′-H), 1.60–1.72 (1 H, m, 4a-H), 1.60 (3 H, dd, *J* 6.8, 1.6, CH_3CH=), 1.36 (1 H, 18 lines, 6″-H), 1.30–1.19 (1 H, m, 4-H), 1.18–1.02 (2 H, m, 3″-H, 3, 5″-H) and 0.95 (3 H, d, *J* 6.4, CH_3); δ_C(125 MHz, $CDCl_3$) 143.13, 141.73, 120.34 (C-8), 116.36 (C-9), 44.75 (C-4a), 39.12 (C-4), 34.96 (C-3), 28.93 (C-5), 27.57 (C-2), 26.12 (C-7), 22.10 (C-6), 20.07 (4-CH_3) and 13.21 (9-CH_3).

Dimethyl 3,6-dimethyl-5,6,6a,7,8,9-hexahydro-4H-phenalene-1,2-dicarboxylate 8

Methylene dichloride (4 cm^3) was added to $AlCl_3$ (76 mg, 0.57 mmol) followed by dimethyl acetylenedicarboxylate (88 mg, 0.63 mmol) dissolved in CH_2Cl_2 (2 cm^3). After the mixture had been swirled for 20 min at room temperature it was cooled to 0 °C and **6** (100 mg, 0.57 mmol) in CH_2Cl_2 (2 cm^3) was added dropwise to it. After 2 h at 0 °C the solution was equilibrated between diethyl ether (30 cm^3) and 2 mol dm^{-3} HCl (30 cm^3). The ethereal phase was separated and washed with brine (30 cm^3) and the washings were back extracted with diethyl ether (30 cm^3). The combined ethereal phases were dried ($MgSO_4$), filtered and evaporated to afford **7** as a semi-solid. This was dissolved in DMF (2 cm^3) to which DDQ (129 mg, 0.57 mmol) in DMF (2 cm^3) was added. The mixture was stirred at 140 °C for 37 h, after which it was cooled to room temperature, diluted with diethyl ether (4 cm^3), filtered through diatomaceous earth (Hyflo SuperCel) and poured into water (30 cm^3). The ethereal phase was separated, washed with water (3 × 30 cm^3) and brine (3 × 30 cm^3), dried ($MgSO_4$) filtered and evaporated. Chromatography [SiO_2, EtOAc–heptane (1:9) TLC R_F 0.14) of the residue yielded **8** (68 mg, 38% over two steps) as white needles, mp 103–104 °C (hexane) (Found: C, 71.5; H, 7.6. $C_{19}H_{24}O_4$ requires C, 72.13; H, 7.65.) [Found (HR(EI)MS): 316.1682. $C_{19}H_{24}O_4$ requires 316.1674]; ν_{max}/cm^{-1} (neat) 1740 (C=O); δ_H(500 MHz, $CDCl_3$) 3.85 (3 H, s, CO_2Me), 3.84 (3 H, s, CO_2Me), 2.85–2.95 (1 H, 5 lines, 9′-H), 2.72–2.78 (1 H, m, 4′-H), 2.60–2.70 (2 H, m, 9″-H, 4″-H), 2.15–2.20 (1 H, m, 7′-H), 2.18, (3 H, s, Ar-CH_3), 2.10–2.15 (1 H, m, 6a-H), 1.88–1.93 (1 H, m, 5′-H), 1.78–1.85 (1 H, m, 8′-H), 1.65–1.70 (1 H, m, 8″-H), 1.45–1.50 (1 H, m, 5″-H), 1.35–1.45 (1 H, m, 6-H), 1.05–1.15 (1 H, m, 7″-H) and 1.10 (3 H, d, *J* 6.2, CH_3); δ_C(125 MHz, $CDCl_3$) 169.51, 168.0, 140.89, 138.35, 133.58, 131.68, 130.05, 128.94, 52.34, 52.29, 43.61 (C6a), 32.08 (C-5′ or C-6), 31.79 (C-5′ or C-6), 27.78 (C-4), 27.02 (C-7), 26.62 (C-9), 21.86 (C-8), 20.55 (CH_3) and 16.41 (Ar-CH_3).

Acknowledgements

We thank the Swedish Natural Research Council for financial support. We also thank Mr Ingemar Sethson for performing some of the NMR experiments and Mr Christher Åstot-Lundmark for HRMS measurements.

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Paper 5/06223C
Received 20*th September* 1995
Accepted 5*th October* 1995