

A simple approach to a curved hexaquinane

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This article is dedicated to Prof. James Cook on the occasion of his 65th Birthday

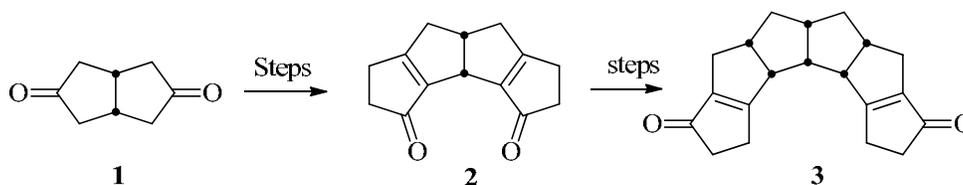
Abstract

The conversion of tetraquinane **2** to the unknown curved C₂₀-hexacyclic dione **3** is described utilizing the cyclopentane annulation strategy.

Keywords: Cyclopentane annulation, Tetraquinane, Hexaquinane

Introduction

In our attempts directed towards the synthesis of tetraquinanes and hexaquinanes,^{1,2} we observed the formation of tetraquinane **2**¹ in small amounts. This article describes our efforts to convert the tetracyclic intermediate **2** into the unknown curved C₂₀-hexacyclic dione **3** (Scheme 1).

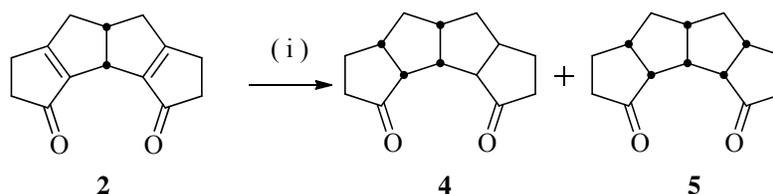


Scheme 1

Results and Discussion

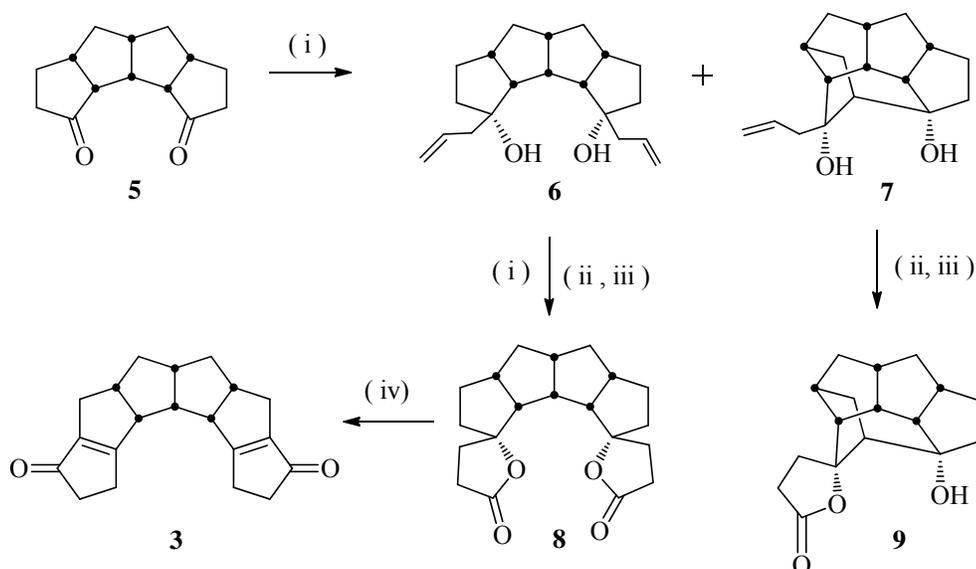
The starting material, bicyclo[3.3.0]octane 3,7-dione **1**, was obtained in a three step sequence using the Weiss-Cook reaction.³ Cyclopentane annulation of **1** provided the tetracyclic intermediate **2** as a minor product.¹ Upon reduction with hydrogen in presence of 10% Pd/C at 3 atm, the tetracyclic intermediate **2** gave a mixture of tetracyclic diones **4** and **5** in the ratio 1:4 in 76% yield (Scheme 2). The difference in the ratio can be attributed to the stability of *cis-syn-cis-*

syn-cis-fusion in isomer **5** in comparison with the *cis-syn-cis-anti-cis*-fused isomer **4**. The isomeric diones **4** and **5** were separated by column chromatography, and structural assignments are based on spectral evaluations. The minor isomer **4** exhibits fourteen resonance lines in the proton-decoupled ^{13}C NMR spectrum, which confirms its unsymmetrical nature, while the major isomer **5** shows eight lines consistent with the mirror plane symmetry in the molecule.



Scheme 2. (i) H_2 , 10% Pd-C, EtOAc, 3 atm.

Upon reaction with allylmagnesium bromide, the tetracyclic dione **5** furnished diol **6** and the *trans*-annular product **7** (45% and 30%, respectively; Scheme 3). In agreement with the proposed structures, the proton decoupled ^{13}C NMR spectrum of **6** shows 11 lines; **7** exhibits well-resolved resonances for 17 carbon atoms, and the structure was further confirmed by X-ray diffraction studies.⁴ Formation of **7** is envisaged by the transformation of one carbonyl group of **5** into an enolate, which reacts in a *trans*-annular manner with the other carbonyl group. The resulting ketol reacts with a second molecule of the Grignard reagent to produce the monoallylic diol **7**. The symmetrical diallylic diol **6** and the monoallylic diol **7** were converted into the corresponding lactones **8** and **9** by hydroboration-oxidation sequences. Methanesulphonic acid/ P_2O_5 caused the symmetrical lactone **8** to rearrange and form the curved hexacyclic enone **3**.



Scheme 3. (i) Allylmagnesium bromide/ether, THF. (ii) NaBH_4 , $\text{BF}_3 \cdot \text{Et}_2\text{O}$, THF, (iii) Jones reagent. (iv) Methanesulphonic acid, P_2O_5 .

Conclusions

The cyclopentane annulation strategy developed in our laboratory was utilized to convert the tetracyclic compound **2** to the hitherto unknown curved hexaquinane dione **3**. In view of limitations associated with cyclopentane annulation strategies, the methodology demonstrated here may find useful application in the synthesis of various natural and non-natural products having the cyclopentane rings fused together.

Experimental Section

General. Melting points were recorded on Labhosp or Veego melting point apparatus. Infrared (IR) spectra were recorded on Nicolet Impact-400 FT IR spectrometer. Solid samples were recorded as KBr wafers and liquid samples as film between NaCl plates. Ultraviolet spectra were recorded on Shimadzu UV-260 instruments. NMR spectra were recorded with Varian VXR 300 spectrometers (^1H at 300 MHz, ^{13}C NMR at 75.4 MHz) using CDCl_3 or $\text{CDCl}_3/\text{CCl}_4$ solutions, and chemical shifts were referenced to TMS. Mass spectral measurements were carried out on GCD 1800 Hewlett-Packard GS-MS spectrometer. The high-resolution mass measurements were carried out using JEOL JMS-DX 303 GC-MS instrument. Accurate mass measurement by CI ionization method was carried out using Autospec X instrument. Elemental analysis was performed on Carlo-Erba MOD 1106 CHN analyzer. Analytical thin-layer chromatography (TLC) was performed on glass plates (10 × 5 cm) coated with Acme's silica gel G or GF 254 (containing 13% calcium sulfate as a binder). Silica gel was coated on glass plate using the 'Sandwich Technique'. All reactions were monitored employing TLC technique using appropriate solvent system for development. Transfer of moisture sensitive materials were carried out in a glove box, using standard syringe-septum techniques, and the reactions were carried out under nitrogen or argon atmosphere until work up.

Compounds (4) and (5). The tetracyclic enone **2**¹ (525 mg, 2.45 mmol) in ethyl acetate (40 mL) was treated with hydrogen in the presence of 10% Pd/C (24 mg) at 3 atm pressure for 4 h. The reaction mixture was filtered and the solvent was removed under reduced pressure on a rotary evaporator. The mixture of products obtained was purified by chromatography (silica gel; petroleum ether/ethyl acetate 4:1) furnishing the minor saturated tetracyclic diketone **4** (85 mg, 16%) as off-white solid; mp 88–89 °C. R_f 0.62 (ethyl acetate/petroleum ether 1:4). IR (KBr): ν_{max} 2945, 2917, 2878, 1726, 1457, 1175, 1017 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 3.26 (1H, d, $J = 9$ Hz), 3.03 (1H, t, $J = 9$ Hz), 1.43–2.82 (14H, m), 0.94–1.24 (2H, m). ^{13}C NMR (75 MHz, $\text{CDCl}_3/\text{CCl}_4$): δ 220.8, 220.6, 54.4, 53.6, 49.0, 46.7, 44.0, 39.9, 37.5, 36.0, 35.9, 34.8, 23.2, 23.1. Anal. calcd. for $\text{C}_{14}\text{H}_{18}\text{O}_2$: C, 77.03; H, 8.31. Found: C, 77.04; H, 8.60.

Continued elution of the column with petroleum ether/ethyl acetate (7:3) gave isomer **5** (322 mg, 60%) as off-white solid; mp 156–158 °C. R_f 0.32 (ethyl acetate/petroleum ether 1:4). IR (KBr):

ν_{\max} 2942, 2874, 1735, 1458, 1150, 1091, 947 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 2.00–2.88 (14H, m), 1.49–1.74 (2H, m), 0.87–0.98 (2H, m). ^{13}C NMR (75 MHz, $\text{CDCl}_3/\text{CCl}_4$): δ 219.9, 52.7, 50.3, 49.6, 44.2, 39.3, 39.1, 25.9. Anal. calcd. for $\text{C}_{14}\text{H}_{18}\text{O}_2$: C, 77.03; H, 8.31. Found: C, 77.52; H, 8.19.

Compounds (6) and (7). To activated magnesium turnings (400 mg, 16.45 mmol), allyl bromide (0.8 mL, 9.2 mmol) in dry ether (5 mL) was added at 0 °C; stirring was continued at room temperature for 2 h. To the Grignard reagent at 0 °C was then added a solution of dione **5** (0.108 g, 0.50 mmol) in dry THF (25 mL) and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured onto saturated ammonium chloride solution (100 mL), and the solvent was removed under reduced pressure on a rotary evaporator. The reaction mixture was extracted with ethyl acetate (200 mL) and the organic layer was washed with water (100 mL), brine (100 mL) and dried. Removal of the solvent on a rotary evaporator under reduced pressure gave a crude product, which was separated and purified by column chromatography (silica gel, petroleum ether/ethyl acetate 9:1) furnishing the symmetric diol **6** (63 mg, 45%) as a colorless liquid. R_f 0.63 (petroleum ether/ethyl acetate 1:2.3). IR (neat): ν_{\max} 3424, 3075, 2935, 2864, 1639, 1452, 1051, 911 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 5.85–5.99 (2H, m), 5.08–5.19 (4H, m), 2.53–2.70 (2H, m), 2.25–2.38 (4H, m), 2.02–2.06 (2H, m), 1.56–1.78 (10H, m), 1.25–1.44 (4H, m), 0.82–0.96 (2H, m). ^{13}C NMR (75 MHz, CDCl_3): δ 134.6, 118.4, 82.0, 60.3, 46.9, 46.2, 45.6, 43.9, 39.8, 38.2, 29.9. HRMS: calcd. for $\text{C}_{20}\text{H}_{30}\text{O}_2 - \text{H}_2\text{O}$: 284.2140; found: 284.2137.

Continued elution of the column with the same solvent furnished the *trans*-annular diol **7** (43 mg, 30%) as a white solid; mp 105–107 °C. R_f 0.55 (petroleum ether/ethyl acetate 1:2.3). IR (KBr): ν_{\max} 3373, 3075, 2930, 2861, 1643, 1456, 1153, 1090, 912 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 5.90–6.04 (1H, m), 5.08–5.23 (2H, m), 2.97 (1H, s), 2.88 (1H, s), 2.21–2.85 (7H, m), 1.86–2.13 (4H, m), 1.32–1.65 (7H, m), 1.05–1.28 (1H, m). ^{13}C NMR (75 MHz, CDCl_3): 133.8, 119.1, 87.7, 82.3, 55.7, 53.0, 50.3, 48.7, 47.2, 46.4, 44.3, 40.9, 39.6, 39.5, 37.4, 31.0, 29.4. HRMS: calcd. for $\text{C}_{17}\text{H}_{24}\text{O}_2 - \text{H}_2\text{O}$: 242.1670; found: 242.1669.

Compound (8). To a stirred solution of diol **6** (55 mg, 0.18 mmol) and NaBH_4 (120 mg, 3.17 mmol) in dry THF (30 mL), freshly distilled $\text{BF}_3 \cdot \text{OEt}_2$ (0.7 mL, 5.69 mmol) in dry THF (5 mL) was added at 0 °C over a period of 30 min. The reaction was stirred at room temperature for 1 h and then cooled to 0 °C. Freshly prepared Jones reagent (4 mL) was added dropwise. The solution was stirred at room temperature for 4 h, and THF was removed on a rotary evaporator under reduced pressure. The reaction mixture was extracted with ethyl acetate (150 mL), the organic layer was washed with water (25 mL), brine (25 mL), and dried. Removal of the solvent gave the crude lactone **8**, which was purified by column chromatography (silica gel, hexane/ethyl acetate 1:1) to furnish pure lactone **8** (40 mg, 66%) as a white solid; mp 123–124 °C. R_f 0.53 (petroleum ether/ethyl acetate 1:4). IR (KBr): ν_{\max} 2925, 2855, 1755, 1459, 1421, 1167, 921 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 2.53–2.72 (4H, m), 2.12–2.22 (2H, m), 2.04–2.08 (4H, m), 1.60–1.81 (2H, m), 1.25–1.58 (14H, m). ^{13}C NMR (75 MHz, $\text{CDCl}_3/\text{CCl}_4$): δ 176.6, 94.4, 59.7, 48.8, 46.5, 42.5, 38.4, 37.8, 33.1, 30.1, 29.0. MS [GC-MS]: m/z 294 ($[\text{M} - 2\text{H}_2\text{O}]^+$).

Compound (9). To a stirred solution of diol **7** (35 mg, 0.1346 mmol) and NaBH₄ (72 mg, 1.9 mmol) in dry THF (25 mL), freshly distilled BF₃·OEt₂ (0.4 mL, 3.25 mmol) in dry THF (5 mL) was added at 0 °C over a period of 45 min. The reaction was stirred at room temperature for 2 h and then cooled to 0 °C. Freshly prepared Jones reagent (5 mL) was added dropwise. The solution was stirred at room temperature for 3 h, and then THF was removed on a rotary evaporator under reduced pressure. The reaction mixture was extracted with ethyl acetate (150 mL) and the organic extract was washed with water (50 mL), brine (50 mL), and dried. Removal of the solvent gave the crude lactone **9**, which was purified by column chromatography (silica gel, petroleum ether/ethyl acetate 2:3) to furnish pure lactone **9** (20 mg, 54%) as a white solid; mp 79–80 °C. *R_f* 0.37 (ethyl acetate). IR (KBr): ν_{\max} 2928, 2859, 1759, 1456, 1108, 1047, 912 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 3.26 (1H, bs), 2.80–2.86 (1H, m), 2.01–2.63 (15H, m), 1.13–1.25 (5H, m). ¹³C NMR (75 MHz, CDCl₃/CCl₄): δ 176.0, 150.7, 122.5, 94.0, 52.0, 51.6, 50.4, 46.5, 45.1, 45.0, 44.0, 42.8, 41.7, 40.0, 39.9, 32.4, 28.3. MS [GC-MS]: *m/z* 256 ([M–H₂O]⁺).

Compound (3). Lactone **8** (25 mg, 0.07 mmol) was dissolved in methanesulphonic acid (5 mL) and P₂O₅ (approximately 10 mg) was added. The reaction mixture was heated at 50–55 °C for 4 h, cooled to 0 °C, and diluted with water (50 mL). The reaction mixture was extracted with chloroform (100 mL), and the organic layer was washed with saturated sodium bicarbonate solution (75 mL), brine (75 mL), and dried. Evaporation of the solvent at reduced pressure gave the crude hexacyclic enone **3**, which was purified by column chromatography (silica gel, petroleum ether/ethyl acetate 7:3) to furnish dione **3** (12 mg, 54%) as a white solid; mp 134 °C. *R_f* 0.43 (ethyl acetate). IR (KBr): ν_{\max} 2926, 2857, 1700, 1630, 1458, 1351, 1173, 1026 cm⁻¹. UV (CH₃OH): λ_{\max} (ϵ) 246.4 nm (3,107). ¹H NMR (400 MHz, CDCl₃): δ 3.34–3.50 (2H, m), 3.08–3.16 (2H, m), 2.72–2.82 (4H, m), 2.46–2.66 (8H, m), 2.14–2.24 (1H, m), 2.02–2.12 (2H, m), 1.80–1.94 (2H, m), 1.48–1.60 (1H, m). ¹³C NMR (75 MHz, CDCl₃): δ 204.4, 187.1, 147.1, 57.3, 52.4, 47.9, 46.4, 41.0, 38.6, 31.9, 24.3. HRMS: calcd. for C₂₀H₂₂O₂: 294.1619; Found: 294.1616.

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