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SHORT COMMUNICATIONS

Preparative Synthesis of Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-4-one (D_3-Trishomocubanone)

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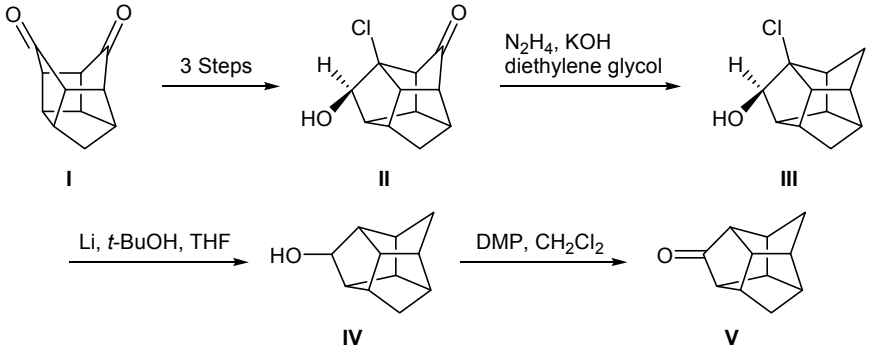
Highly symmetrical chiral structure of the pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (D_3-trishomocubane) molecule combines high lipophilicity and conformational rigidity, which makes its derivatives promising as medicinal agents [1]. Some amino derivatives of D_3-trishomocubane exhibit biological activity, and they can be used as building blocks for a new generation of NMDA antagonists [2] and neuroprotectors [3, 4].

The key intermediate product in the synthesis of various D_3-trishomocubane derivatives is D_3-trishomocubanone whose preparation was described in [5, 6]. D_3-Trishomocubane is the $C_{11}H_{14}$ stabilomer [7], and its carbon skeleton is constructed under harsh conditions via acid-catalyzed rearrangement of secondary mono- and dihydroxypentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes. This approach implies preliminary reduction of accessible Cookson's diketone, pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione (**I**), to the corresponding diol, which elongates the synthetic scheme and reduces the preparative yield to 25–30% [8–11]. Alternatively, it was proposed to build up D_3-structure by rearrangement of diketone **I** in chlorosulfonic acid [12], which allows one to avoid the reduction step. The rearrangement procedure described in [13] improved the yield of **II** to 70%, and the proposed workup procedure made chloro hydroxy ketone **II** readily accessible.

We now describe a new method of synthesis of D_3-trishomocubanone (**V**), which includes Wolff–Kishner reduction of **II** to *syn*-1-chloropentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-11-ol (**III**) (yield 80%). The subsequent dehalogenation of **III** with Li/*t*-BuOH in THF gives D_3-trishomocuban-4-ol (**IV**) in 90% yield. The conversion of **III** was monitored by capillary column GLC, and an additional amount of *tert*-butyl alcohol was added (if necessary). Alcohol **IV** without additional purification was oxidized with Dess–Martin periodinane (DMP) to target pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-4-one (**V**, 90%) [14]. Compound **V** can be subjected to enantiomeric resolution [15] or further transformations to obtain various functional derivatives.

Thus we have proposed a convenient procedure for the synthesis of D_3-trishomocubanone from commercially available diketone **I** in an overall yield of 55%.

***syn*-6-Chloro-7-hydroxypentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-4-one (II).** A 7.5-g por-



tion of the mixture obtained by reaction of Cookson's diketone (**I**) with chlorosulfonic acid according to the procedure described in [13] was treated with 150 mL of 10% aqueous sulfuric acid. The mixture was heated for 8 h under reflux with stirring, cooled, and extracted with methylene chloride. The organic phase was washed with water and dried over sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was recrystallized twice from hexane–propan-2-ol (7:3). Yield 3.8 g (83%), mp 183–184°C (from hexane). ^{1}H NMR spectrum, δ, ppm: 1.68 s (2H, CH), 2.08 d (2H, CH_2), 2.33 s (1H, CH), 2.53 m (4H, CH), 3.25 s (1H, OH), 4.12 s (1H, C**H**OH). ^{13}C NMR spectrum, δ_C, ppm: 36.5 (CH_2), 37.7 (CH), 39.9 (CH), 46.6 (CH), 48.2 (CH), 49.7 (CH), 50.5 (CH), 51.6 (CH), 72.8 (CCl), 78.7 (CHOH), 212.2 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 212/210 (5/10) $[M]^+$, 175 (7) $[M - Cl]^+$, 164 (25), 146 (28), 129 (46), 116 (40), 82 (80), 66 (100). Found, %: C 62.87; H 5.21. $C_{11}H_{13}ClO$. Calculated, %: C 62.91; H 5.54.

***syn*-1-Chloropentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-11-ol (III).** Ketone **II**, 1 g (4.76 mmol), was added to a solution of 1.43 g of 85% potassium hydroxide in 5.6 mL of diethylene glycol, 2 mL of 98–100% hydrazine hydrate was added, and the mixture was left overnight. The mixture was then heated on an oil bath (180–190°C) under stirring until the reaction was complete (6–8 h), cooled, diluted with water, and extracted with methylene chloride. The extract was washed with water and dried over Na_2SO_4, and the solvent was distilled off under reduced pressure. Yield 0.73 g (78%), mp 195–196°C (from hexane). ^{1}H NMR spectrum, δ, ppm: 1.33–1.53 m (2H, CH_2), 1.57–1.83 m (2H, CH_2), 2.05 s (1H, CH), 2.09–2.19 m (3H, CH), 2.15 s (1H, CH), 2.28 s (1H, CH), 2.55 s (1H, CH), 2.87 br.s (1H, OH), 4.07 s (1H, CH). ^{13}C NMR spectrum, δ, ppm: 31.9 (CH_2), 34.1 (CH_2), 40.3 (CH), 45.8 (CH), 46.2 (CH), 47.3 (CH), 47.9 (CH), 49.2 (CH), 50.7 (CH), 77.3 (CCl), 78.3 (CHOH). Mass spectrum, *m*/*z* (I_{rel}, %): 198/196 (9/18) $[M]^+$, 180 (10), 161 (100) $[M - Cl]^+$, 143 (23), 130 (22), 128 (23), 115 (20), 95 (60), 91 (46), 79 (69), 66 (71), 51 (34). Found, %: C 67.17; H 6.61. $C_{11}H_{13}ClO$. Calculated, %: C 67.19; H 6.63.

Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-4-ol (IV). Thin lithium wire, 7.2 g (1.02 mol), was added to a solution of 4.4 g (2.24 mmol) of compound **III** and 8 mL of *tert*-butyl alcohol in 200 mL of anhydrous THF. The mixture was heated for 2 h under reflux, an additional 4 mL of *tert*-butyl alcohol was added, and the mixture was heated for 2–3 h more. Excess lithium was quenched by adding water on cooling. The aqueous phase was extracted with methylene chloride, the extract was dried over Na_2SO_4, and the solvent was distilled off under reduced pressure. Yield 3.31 g (91%), mp 85–86°C (from hexane). ^{1}H NMR spectrum, δ, ppm: 1.22–2.91 m (8H, CH), 1.59–1.43 d.d (2H, CH_2), 2.11–1.92 d.d (2H, CH_2), 4.17 s (1H, C**H**OH). Mass spectrum, *m*/*z* (I_{rel}, %): 162 (15), 144 (75), 129 (22), 116 (15), 95 (100), 91 (35), 79 (85), 66 (55). Found, %: C 81.47; H 9.25. $C_{11}H_{14}O$. Calculated, %: C 81.39; H 9.33.

Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-4-one (V). A solution of 11.66 g (2.75 mmol) of DMP in 120 mL of methylene chloride was added to a solution of 4 g (2.5 mmol) of compound **IV** in 80 mL of methylene chloride. The mixture was stirred for 30 min at room temperature and diluted with 300 mL of diethyl ether, 150 mL of 5% aqueous sodium hydroxide was added, and the mixture was stirred for 10 min. The organic phase was separated, washed with three portions of water until neutral reaction, and dried over Na_2SO_4, and the solvent was distilled under reduced pressure. Yield 3.71 g (91%), mp 163–164°C (from hexane). ^{1}H NMR spectrum, δ, ppm: 1.53–1.57 d.d (4H, CH_2), 1.60–2.90 m (8H, CH). ^{13}C NMR spectrum, δ_C, ppm: 33.00 (CH_2), 33.68 (CH_2), 40.67 (CH), 41.23 (CH), 43.14 (CH), 44.21 (CH), 47.14 (CH), 47.45 (CH), 52.22 (CH), 53.49 (CH), 77.45 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 162 (25), 132 (20), 91 (15), 66 (100). Found, %: C 82.52; H 7.45. $C_{11}H_{12}O$. Calculated, %: C 82.49; H 7.51.

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer at 400.13 and 100.61 MHz, respectively, using $CDCl_3$ as solvent and tetramethylsilane as internal reference. The mass spectra (electron impact, 70 eV) were obtained on a Hewlett Packard 5971A mass-selective detector coupled with an HP 5890 gas chromatograph (HP-5 capillary column, injector temperature 250°C, oven temperature programming from 60 to 250°C at a rate of 20 deg/min). GLC analysis was performed on a Shimadzu GC-14B chromatograph equipped with a flame ionization detector (Optima-1 column, injector temperature 275°C, oven temperature programming from 80 to 250°C at a rate of 20 deg/min).

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