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Stereoselective preparation of mono- and bis-derivatives of pentacyclo[6.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$] undecane (D_3-trishomocubane)

Research Article

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Abstract: The rearrangement of easily accessible Cookson's diketone with chlorosulfonic acid in chloroform followed by the acidic hydrolysis gave 6-chloro-7-hydroxy-dichloropentacyclo[6.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-4-one, whose *syn*-stereochemistry was assigned through the X-ray crystal structure analysis. This key structure was used for the stereoselective synthesis of the D_3-trishomocubane derivatives as well as for the preparation of potential drugs bearing hydroxy- and amino- functional groups. A new multigram preparative synthesis of D_3-trishomocubane was developed.

Keywords: *D_3-trishomocubane • Aminoalcohol • Propeller chirality • Hydroxyketone*

1. Introduction

Pentacyclo[6.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane (D_3-trishomocubane), one of the few known molecules that possess propeller chirality, combines high lipophilicity with conformational rigidity, and attracts growing attention of theoreticians and experimentalists specialized in drug design and catalysis [1]. Recent report describes the 3D-QSAR studies of a new generation of potential M2 inhibitors based on a combination of the lipophilic D_3-trishomocubane moiety and polar groups (hydroxy, carboxy, urea/thiourea) separated from cage with the one-carbon-atom bridge [2]. A number of homological cubylamines that topologically relate to the neuroprotector 3,5-dimethyl-1-aminoadamantane (Memantine) were also reported to serve as fast, voltage-dependent NMDA receptor antagonists [3].

D_3-Trishomocubane is a $C_{11}H_{14}$ stabilomer [4], and was obtained under harsh reaction conditions through the acid-promoted cationic rearrangements of mono- and dihydroxy substituted pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane (C_s-trishomocubane) derivatives [5-7]. Ketones and alcohols of D_3-trishomocubane series were obtained in optically-active forms. The enantioseparation of D_3-trishomocubanol is possible through the reaction with phthalic anhydride and crystallization of salts with (+)-2-(1-aminoethyl)naphthalene [8] or, alternatively, through the reaction of amino-acetal of D_3-trishomocubanone with l-ephedrine [9] that are difficult to perform even at the gram scale. Biochemical methods of the synthesis of enantiopure D_3-trishomocubane derivatives display only moderate enatioselectivities [10]. Current lack of multigram preparative methods for the selective synthesis of D_3-trishomocubanes hampers further applications of this promising class of molecules in medicine and makes the development of new stereoselective methods particularly important.

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2. Experimental procedure

The ^{1}H NMR (400.13 MHz) and ^{13}C NMR (100.61 MHz) spectra were recorded on a Bruker DPX-400 spectrometer; solvent – $CDCl_3$, internal standard – TMS. GC/MS measurements were performed on Hewlett-Packard 5971A (EI 70 eV, mass-selective detector), chromatograph HP 5890, column HP-5 (5% phenylmethyl silicone), evaporator temperature 250°C, column oven temperature 60–250°C, temperature gradient 20°C min^{-1}. GLC-analyses were performed on Shimadzu GC-14B chromatograph with a flame ionization detector, column Optima-1, evaporator temperature 275°C, oven temperature 80–250°C, temperature gradient 20°C min^{-1}. The X-Ray study was carried out on an automatic diffractometer STOE IPDS, equipped with graphitic monochromator, utilizing standard procedure [20]. The structure was solved by the direct method and refined according to full-frame anisotropic approximation for all carbon atoms. All H-atoms could be found in the difference fourier syntheses and were refined isotropically. Calculations were performed using SHELX97 software [20,21]. The results of the crystal structure analysis of 6-chloro-7-hydroxypentacyclo-[6.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-4-one ethyleneketal (**8**) were deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 930939. Tetrahydrofurane was refluxed before use with sodium metal in presence of benzophenone and was distilled under argon flow.

4-Ethyleneketal 6,7-dichloropentacyclo[6.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-4-one (7). To a cold stirred solution of Cookson's diketone (**1**) (10 g, 0.0574 mol) in 20 mL of chloroform, freshly distilled chlorosulfonic acid (20 mL, 0.3 mol) was added dropwise. After 24 h of stirring, the reaction mixture was poured onto ice, and extracted with chloroform. The combined organic layers were washed with water to pH=6, dried over anhydrous Na_2SO_4, and the solvent was evaporated *in vacuo*. To the resulting yellow solid (15.2 g) a solution of sodium bicarbonate (10% 150 mL) was added. The reaction mixture was heated under reflux for 4 h and extracted with chloroform after cooling. The combined extracts were dried over anhydrous Na_2SO_4, and the solvent was removed *in vacuo* to give 10.85 g of the mixture of chloro ketol **3** and dichloroketone **4** in 4.5:1 ratio (GLC). The mixture was dissolved in 200 mL of dry benzene; ethylene glycol (10 g, 0.16 mol) and *p*-toluenesulfonic acid monohydrate (0.2 g) were added. The reaction mixture was refluxed with the Dean-Stark receiver for 6 h, and the benzene solution was washed with a 10%-solution of sodium bicarbonate, water and brine,. Organic layer was dried over Na_2SO_4, the solvent was removed *in vacuo* to give 12.4 g of the mixture of ethylene ketals **7** and **8** as a viscous oil, which crystallized on storing. This mixture was stirred under reflux with triphenylphosphine (13.3 g, 0.05 mol) in 120 mL of carbon tetrachloride for 5 h, 1 mL of MeOH was added and the mixture refluxed for additional 1 h. After cooling of the reaction the precipitate of triphenylphosphine oxide was separated by filtration, carbon tetrachloride was removed *in vacuo* from the filtrate, the residue was treated with 100 mL of diethyl ether.The undissolved precipitate of triphenylphosphine oxide was filtered off, 4-5 g of finely dispersed lithium iodide monohydrate was added to the filtrate and the mixture was stirred for 1.5–2 h at room temperature. The formed precipitate was filtered through silica gel, the solvent was removed *in vacuo* yielding ethylene ketal of dichloroketone **7** (11.8 g, 75 %), m.p. 103–105 °C (ethanol). ^{1}H NMR ($CDCl_3$), δ, ppm: 1.38–1.57 m (2H, CH_2), 1.91–2.02 m (1H, CH), 2.02–2.15 m (1H, CH), 2.26–2.39 m (1H, CH), 2.39–2.56 m (2H, CH), 2.56–2.64 m (1H, CH), 3.04–3.11 br s (1H, CHCl), 3.8–4.09 m (4H, CH_2), 4.09–4.17 m (1H, CH). ^{13}C NMR ($CDCl_3$), δ, ppm: 33.8 (1C, CH_2), 41.9 (1C, CH), 43.1 (1C, CH), 48.0 (1C, CH), 49.4 (1C, CH), 50.8 (1C, CH), 51.3 (1C, CH), 51.9 (1C, CH), 64.1 (1C, CH_2), 65.4 (1C, CH_2), 68.8 (1C, CCl), 78.4 (1C, CHCl), 118.9 (1C, COO). MS *m/z*, (I_r, %): 276 (0.6) [M(^{37}Cl)]$^+$, 274 (3.6) [M(^{37}Cl^{35}Cl)]$^+$, 272 (6.2) [M(^{35}Cl)]$^+$, 239 (37.2) [M – Cl(^{37}Cl)], 237 (100) [M – Cl(^{35}Cl)], 137 (48.7), 129 (48.0), 115 (47.6), 99 (48.7), 91 (19.5) [C_7H_7], 89 (23.8), 77 (78.9) [C_6H_5], 73 (66.8) [$C_3H_5O_2$], 66 (99.2) [C_5H_6], 65 (71.5) [C_5H_5], 51 (50.0). Found, %: C, 57.14; H, 5.21. $C_{13}H_{14}Cl_2O_2$.Calc. %: C, 57.16; H, 5.17.

4-Ethyleneketal pentacyclo[6.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$] undecane-4-one (9). To a solution of dichloride **7** (9.4 g, 0.0344 mol) in 200 mL of dry THF and 20 mL *t*-BuOH, thin lithium wire (7.2 g, 1.02 mol) was added. The mixture was refluxed with condenser for 2 h, additional 6 mL of *t*-BuOH were added and mixture was refluxed for 2–3 h. Any excess of lithium was decomposed by addition of water. The water solution was extracted with methylene chloride, the extract was dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Yield 6.67 g (95%), b.p. 138–144 °C (13 mm. Hg). ^{1}H NMR ($CDCl_3$), δ, ppm.: 1.33 d and 1.39 d (AB system, 4H, CH_2, J_{AB} = 12 Hz), 1.69–1.72 m (2H, CH), 2.10–2.16 m (4H, CH), 2.40–2.45 m (2H, CH), 3.90–3.94 m (4H, CH_2).^{13}C NMR ($CDCl_3$), δ, ppm.: 33.8 (2C, CH_2), 41.5 (2C, CH), 44.1 (2C, CH), 47.2 (2C, CH), 51.0 (2C, CH), 64.7 (2C, CH_2O), 120.1 (1C, COO). MS, *m/z*, (I_r, %): 204 (33.3) [M]$^+$, 149 (11.8), 139 (8.8) [M – C_5H_5], 138 (43.7) [M – C_5H_6], 137 (45.7), 117 (23.4), 99 (32.3), 91 (35.8) [C_7H_7], 79 (28.1), 78 (33.5), 77 (33.3) [C_6H_5], 73 (47.3) [$C_3H_5O_2$],

66 (100) [C_5H_6], 65 (42.2)[C_5H_5], 51 (23.3). Found,%: C, 76.43; H, 7.93. $C_{13}H_{16}O_2$. Calc.,%: C, 76.44; H, 7.90.

Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-4-one (10). To a solution of ketal **9** (1.2 g, 0.0055 mol) in 10 mL of THF 40 mL of the water solution of 10%-sulfuric acid was added, the mixture was heated to 80°C and stirred for 5 h. The sulfuric acid was neutralized by adding of solid sodium hydroxide until pH=7–8, the product was extracted with methylene chloride, extract was dried over anhydrous Na_2SO_4, the solvent was removed *in vacuo*. Yield 0.96 g (98%), m.p. 163–164°C (after sublimation). The spectroscopic properties are identical to those described previously [22].

6-Chloro-7-hydroxypentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]-undecane-4-one (4). To 7.5 g of the mixture obtained after reaction of Cookson's diketone (5 g, 0.0287 mol) with chlorosulfonic acid, according to method as described above for substance (**10**), a water solution of sulfuric acid 10%, 150 mL was added, the mixture was stirred under reflux for 7-8 h. The reaction mixture was cooled, dried over anhydrous Na_2SO_4, the solvent removed *in vacuo*. Yield 5.1 g (85%), m.p. 183–184°C (ethanol) (lit. 183–185°C). The spectroscopic properties are identical to those described previously [13].

4-Ethyleneketal *syn*-6-chloro-7-hydroxypentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-4-one (8) was synthesized from chloroketol **4** (5 g, 0.0238 mol) according to procedure as described above for **7**, crystallized from mixture of hexane : 2–propanol = 7:3. Yield 4.92 g (81%), m.p. 111–112°C. ^{1}H NMR ($CDCl_3$), *δ*, ppm.: 1.32 d and 1.42 d (AB system, 2H, CH_2, J_{AB} = 12 Hz), 1.82–1.92 m (1H, CH), 1.92–2.02 м (1H, CH), 2.02–2.13 m (1H, CH), 2.25–2.56 m (4H, CH), 2.91–3.02 br s (1H, CH), 3.75–4.05 m (4H, CH_2; 1H, OH). ^{13}C NMR ($CDCl_3$), *δ*, ppm.: 34.4 (1C, CH_2), 40.7 (1C, CH), 42.1 (1C, CH), 46.7 (1C, CH), 47.1 (1C, CH), 50.1 (1C, CH), 50.7 (1C, CH), 51.7 (1C, CH), 64.1 (1C, CH_2), 65.4 (1C, CH_2), 77.8 (1C, CCl), 78.9 (1C, CHOH), 118.9 (1C, OCO). MS *m/z*, (I_r, %): 256 (5.9) [*M*(^{37}Cl)]$^+$ 254 (10.4) [*M*(^{35}Cl)]$^+$, 219 (13.3) [*M* – Cl], 183 (29.4), 137 (72.8), 128 (37.2), 115 (100), 112 (64.7), 91 (75.0) [C_7H_7], 77 (63.6) [C_6H_5], 73 (31.7) [$C_3H_5O_2$], 66 (47.1) [C_5H_6], 65 (55.6) [C_5H_5], 51 (27.1). Found%: C, 61.33; H, 5.92. $C_{13}H_{15}ClO_3$. Calc.,%: C, 61.30; H, 5.94.

4-Ethyleneketal *syn*-7-hydroxypentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-4-one (11) was obtained from compound **8** (6.5 g, 0,0255 mol) according to procedure, as described above for the preparation of **9**. Yield 4.79 g (85.4%), m.p. 91–92 °C (hexane 2–propanol = 7:3). ^{1}H NMR ($CDCl_3$), *δ*, ppm.: 1.35–1.45 м (2H, CH_2), 1.7–1.85 m (2H, CH), 2.02 s (1H, CH), 2.1–2.4 m (3H, CH), 2.48 s (1H, CH), 2.71 s (1H, CH), 3.71 m (1H, OH), 3.77–4.05 m (4H, CH_2O), 4.06 s (1H, CHOH). ^{13}C NMR ($CDCl_3$), *δ*, ppm.: 33.6 (1C, CH_2), 40.5 (1C, CH), 40.6 (1C, CH), 43.8 (1C, CH), 44.0 (1C, CH), 46.4 (1C, CH), 49.7 (1C, CH), 50.7 (1C, CH), 51.6 (1C, CH_2), 64.7 (2C, CH_2O), 77.1 (1C, CH), 119.9 (1C, COO). MS, *m/z*, (I_r, %): 220 (97.3) [*M*]$^+$, 192 (14.6), 154 (43.7) [*M* – C_5H_6], 137 (91.0), 125 (39.5), 112 (43.7), 99 (43.2), 91 (64.1) [C_7H_7], 78 (41.0) [C_6H_6], 77 (56.5) [C_6H_5], 73 (100) [$C_3H_5O_2$], 66 (58.7) [C_5H_6], 65 (47.9) [C_5H_5], 51 (29.6). Found,%: C, 70.88; H, 7.32. $C_{13}H_{16}O_3$. Calc.,%: C, 70.89; H, 7.32.

***syn*-7-Hydroxypentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-4-one (12)** was obtained from hydroxy ketal **11** (3.19 g, 0.015 mol) according to procedure, as described above for the preparation of (**10**). Yield 2.46 g (98%), as a viscous colourless liquid. ^{1}H NMR ($CDCl_3$), *δ*, ppm.: 1.45 d and 1.56 d (AB system, 2H, CH_2, J_{AB} = 10 Hz), 1.7–1.85 m (2H, CH), 2.1–2.55 m (5H, CH), 2.88 s (1H, CH), 3.64 m (1H, OH), 4.07 s (1H, CHOH). ^{13}C NMR ($CDCl_3$), δ, ppm.: 35.3 (1C, CH_2), 39.0 (1C, CH), 39.7 (1C, CH), 41.2 (1C, CH), 44.8 (1C, CH), 45.6 (1C, CH), 45.8 (1C, CH), 49.6 (1C, CH), 51.3 (1C, CH), 77.8 (1C, CH), 216.4 (1C, C=O). MS is identical to spectrum described previously [17].

***syn*-7-(Hydroxyimino)pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-4-ol (15).** To **a** solution of 1.2 g (0,018 mol) of hydroxylamine hydrochloride in 4.2 mL of water and 4.2 mL of solution of sodium hydroxide 10% a solution of 0.5 g (2.84 mmol) hydroxy ketone **12** in 6.2 mL of ethanol was added. The resulting mixture was refluxed for 30 h, ethanol was evaporated on an oil bath, the residue was diluted with 10 mL of water and left for crystallization overnight. The precipitate was filtered off and washed twice with water. Yield 0.45 g (83%), as a white crystalline substance with mp. 149–150°C (aqueous ethanol). ^{1}H NMR (DMSO)–d_6) *δ*, ppm.: 1.31–1.47 m (2H, CH_2), 1.84–2.01 m (2H, CH), 2.02–2.34 m (4H, CH), 2.62–2.79 m (2H, CH), 3.95 br.s. (1H, OH), 4.82 d (1H, CHOH), ~8.00 s (1H, N-OH). ^{13}C NMR ($CDCl_3$), *δ*, ppm.: 33.6 (CH_2), 37.8 (CH), 40.0 (CH), 41.1 (CH), 43.8 (CH), 44.3 (CH), 46.4 (CH), 49.1 (CH), 50.6 (CH), 75.7 (CHOH), 165.4 (C=NOH). MS, *m/z*,(I_r, %): 191 (26.8) [*M*]$^+$, 174 (42.8) [*M* – NH_3] 156 (11.9) [*M* – (NH_3+H_2O)], 144 (25.6), 125 (78.0) [*M* – C_5H_6], 115 (29.8), 104 (16.8), 97 (91.9), 91 (53.8) [C_7H_7], 80 (55.1) [C_6H_8], 79 (68), 78 (52.7), 77 (78.3) [C_6H_5], 67 (51.8), 66 (100), 65 (71.4) [C_5H_5], 53 (61.8), 52 (50.9), 51 (69.7). Found,%: C, 69.12; H, 6.82. $C_{11}H_{13}NO_2$. Calc.,%: C, 69.09; H, 6.85.

7-Aminopentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-4-ol (16). To a solution of oxime **15** (0.1 g, 0.52 mmol) in 30 mL of anhydrous methanol in a high pressure reactor was added 0.1 g of 5% palladium on carbon. High pressure reactor was filled several times with hydrogen

and left under excessive pressure 1.0–1.2 MPa overnight at room temperature for 24 h. The reaction mixture was separated from catalyst by filtration through fine silica gel, the methanol was removed in vacuo, the residue was dissolved in a minimum amount of diethyl ether and the amine was precipitated by stepwise addition of diethyl ether saturated with gaseous hydrogen chloride yielding 0.08 g (82%) of hygroscopic white crystals. Obtained amine hydrochloride was treated with 10% water solution of KOH, extracted with diethyl ether, extract was dried over anhydrous KOH, the solvent removed *in vacuo*. ^{1}H NMR (DMSO-d_6) δ, ppm.: 1.3–1.5 m (2H, CH_2), 1.7–2.35 m (8H, CH), 3.26, 3.35 d (1H, $CHNH_2$, J_W=2 Hz), 3.95, 4.0 s (1H, CHOH), 4.77 s, 4.78 s (1H, OH), ~8.25 br s (2H, NH_2). ^{13}C NMR (DMSO-d_6) δ, ppm.: 32.2, 32.3, 32.5, 32.6 (1C, CH_2), 51.3, 51.4, 55.0, 55.1 (1C, $CHNH_2$), also carbon atoms connected to hydroxyl group, δ, ppm.: 74.4, 74.5, 74.8, 74.9 (1C, CHOH), carbon atoms of the cage have chemical shift in intervals 39.0–40.7, 42.5–45.5, 46.3–49.9 (8C, CH). MS, *m/z*, (I_r, %): 177 (16.8) $[M]^+$, 160 (22.6) [M – NH_3], 144 (11.2), 104 (62.8), 91 (8.8) [C_7H_7], 79 (12), 78 (22.4), 77 (78.3) [C_6H_5], 70 (100), 65 (35.4) [C_5H_5], 53 (40.8), 52 (26.9), 51 (91.7). Found,%: C, 74.52; H, 8.51. $C_{11}H_{15}NO$. Calc.,%: C, 74.54; H, 8.53.

Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-4,7-dione (14). To a stirred and cooled 20 mL of pyridine chromium trioxide (1.5 g, 15 mmol) was added in small portions. To the resulting solution the hydroxy ketone **12** (1 g, 5.7 mmol) in 7.5 mL of dry pyridin was added dropwise. The reaction mixture was stirred for 14–15 h at temperature 25°C, then 25 mL of diethyl ether was added and the mixture filtered through a glass filter. Precipitate was washed thoroughly 4 times with 15 mL of diethyl ether. The ethereal filtrate was washed twice with 20 mL of 5% hydrochloric acid, 2 times with 15 mL of saturated solution of sodium bicarbonate, twice with 15 mL of brine, and was dried over anhydrous Na_2SO_4, the solvent was removed *in vacuo* to give 0.8 g (81%) of white solid, m.p. 213–214°C (after sublimation). The spectroscopic properties are identical to those described previously [23].

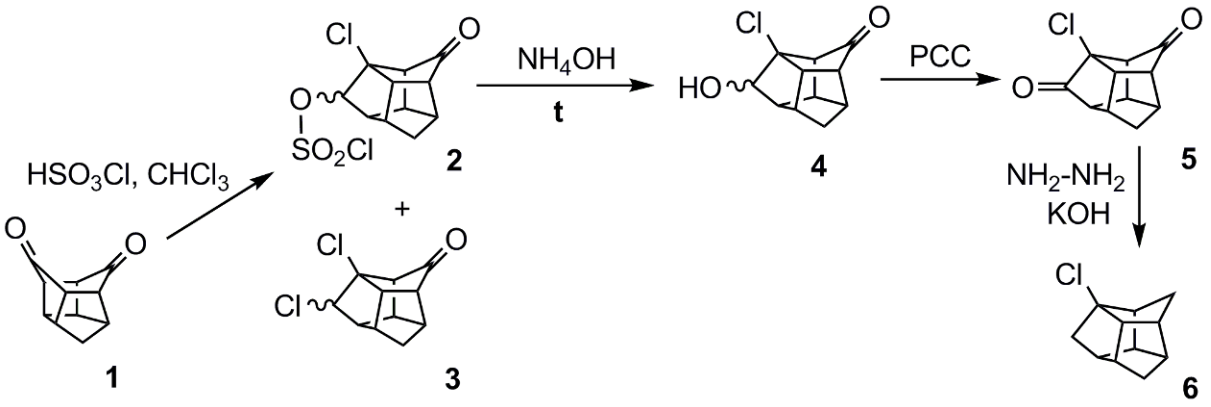
Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-4-ol (13). To a solution of 1.43 g 85% of KOH in 5.6 mL of the diethylene glycol hydroxy ketone **12** (1 g, 5.7 mmol) and 2 mL of 98–100% hydrazine monohydrate was added. The reaction mixture was left overnight and then stirred under heating on an oil bath to 180–190°C. An alcohol condensed in the reflux condenser was washed with diethyl ether in the separate bulb. After the end of the reaction (6–8 h), combined ether layers were washed with water, dried over anhydrous Na_2SO_4, and the solvent was removed *in vacuo*. Yield 0.71 g (78%), m.p. 85–86°C (hexane). The spectroscopic properties are identical to those described previously [4].

3. Results and discussion

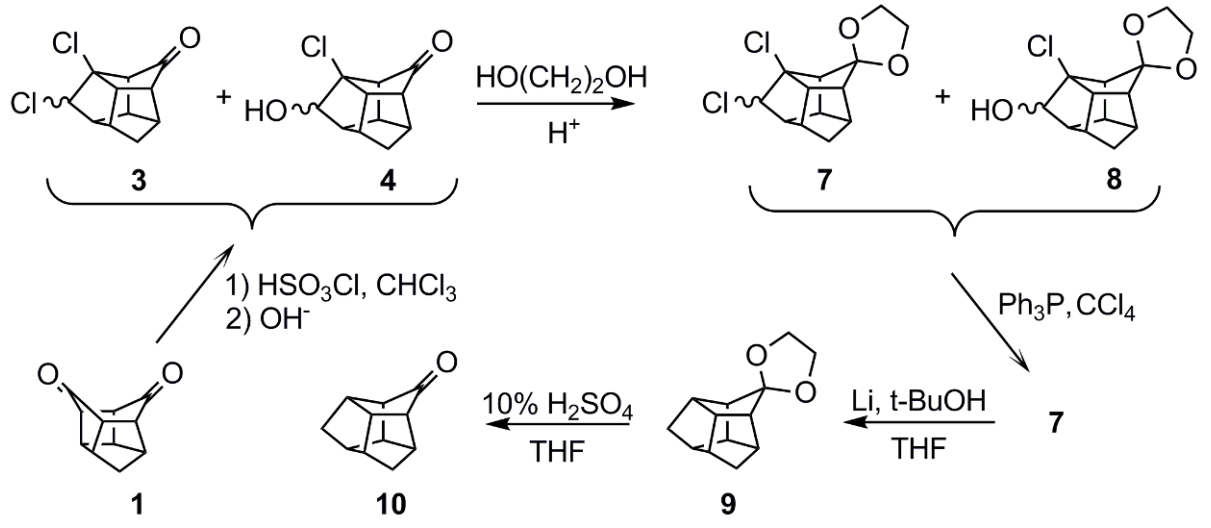
The precursor of D_3-trishomocubane, Cookson's diketone (pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione, **1**) [11] is easily available from inexpensive 1,4-benzoquinone and cyclopentadiene in two steps with quantitative yield. Previously, the rearrangement of **1** was performed in chlorosulfonic acid and resulted in 6-chloro-7-chlorosulfonylhydroxypentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-4-one (**2**) in 64% preparative yield [12]. Chloroketone (**3**) was further hydrolyzed to 6-chloro-7-hydroxypentacyclo-[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-4-one (**4**). Alternatively, the preparation of 1-chloropentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]-undecane (**6**) through the rearrangement of **1** in the mixture of chlorosulfonic acid with chloroform was described (Scheme 1) [13]. Under milder reaction conditions the yield of **4** increases substantially, however this causes an increase of the by-product formation (up to 20%). This approach allows direct rearrangement of **1** with increase of the preparative yields however the preparative potential of this reaction still remains undisclosed.

We have found that the rearrangement of **1** in chlorosulfonic acid gave ketones **3** and **4** without the admixtures of chlorosulfonic derivative after the workup of the reaction mixture with 10% sodium bicarbonate solution (Scheme 2).

Ketones **3** and **4** are separable by column chromatography, but such separation was omitted and the keto-groups were protected by reflux with ethylene glycol in benzene in the presence of *p*-toluensulfonic acid to give a mixture of the respective ethylene ketals **7** and **8**. Chlorohydroxylation of thus obtained mixture in the PPh_3–CCl_4 system gave **7** in 80% preparative yield. Dichloride **7** was reduced to pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-4-one 4-ethyleneketal (**9**) in the lithium–*tert*-butanol system under the GC control, which allows monitoring the completion of the reaction by adding new portions of *tert*-butanol, if necessary. Hydrolysis of the D_3-trishomocubanone ethylene ketal (**9**) gave the respective ketone **10** in 80 % yield. We thus developed a simple procedure for the preparation of ketone **10** directly from Cookson diketone with total yield ca 50% avoiding column chromatography separations. This is in contrast to the methods of synthesis of D_3-trishomocubanone described in literature that involve reduction of Cookson's diketone to pentacy-



Scheme 1. Chlorosulfonation of Cookson's diketone (**1**).



Scheme 2. Multigram synthesis of D_3-trishomocubanone (**10**).

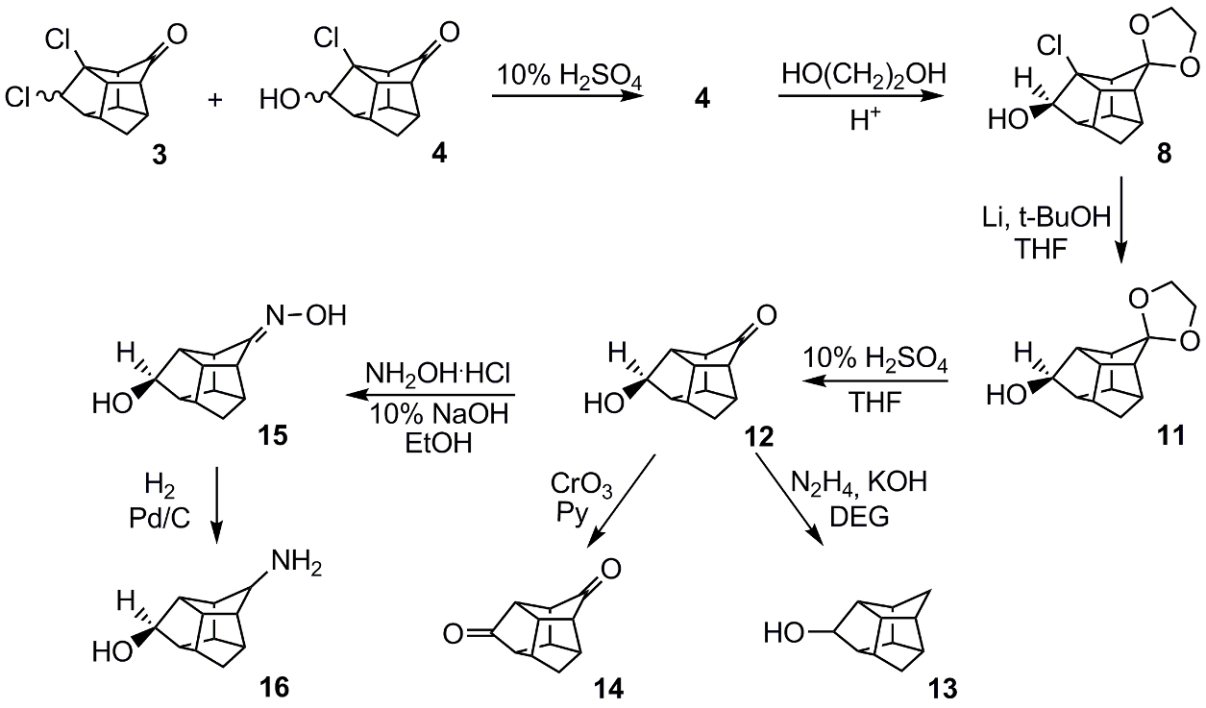
clo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-diol, which further undergoes skeleton rearrangement with formation of D_3-trishomocubane structure [4,8,14].

Our results are in full agreement with the fact that the rearrangement of **1** with formation of the D_3-trishomocubane skeleton [15] occurs with the participation of only one keto-group that gives *anti*-7-chlorosulfonate-6-chloropentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]-undecane-4-one (**2**) stereoselectively. This is also in accord with the stereoselectivity of the rearrangement of the substituted tertiary C_S–trishomocubane alcohols [16]. As only one diastereomer dominates in the mixture of chlorohydroxy ketones **4**, we attempted to isolate it and characterized it individually taking into account that this molecule is seen to be a good precursor for further enantioseparations.

We found that the treatment of dichloro ketone **3** with 10%-sulfuric acid quantitatively gives chlorohydroxyketone **4**. In order to develop simple method for preparation of **4** we replaced the basic hydrolysis of the reaction mixture after the isomerization of **1** in chlorosulfonic acid for acidic one (Scheme 3).

The stereochemistry of thus obtained 4–ethylen-eketal- 6-chloro-7-hydroxypentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}] undecane-4-one (**8**) was defined through the X-ray crystal structure analysis (Fig. 1, see Supplementary Information for further details). It confirms an almost ideal D_3-propeller structure of the cage and *syn*-substitution stereochemistry. This is in contrast to *anti*-substitution pattern of the 7-chlorosulfonate-6-chloro-pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-4-one (**2**) [15] and reveals the inversion of stereochemistry at the ^{7}C-position under hydrolysis.

The epimer **8** was converted into the individual *syn*-stereoisomer of 7-hydroxypentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}] undecane-4-one (**12**) through the effective reduction-deprotection procedure. The epimeric ketone **12** was available previously only through a cumbersome



Scheme 3. Preparation of individual epimers of 4,7- disubstituted D_3-trishomocubane derivatives.

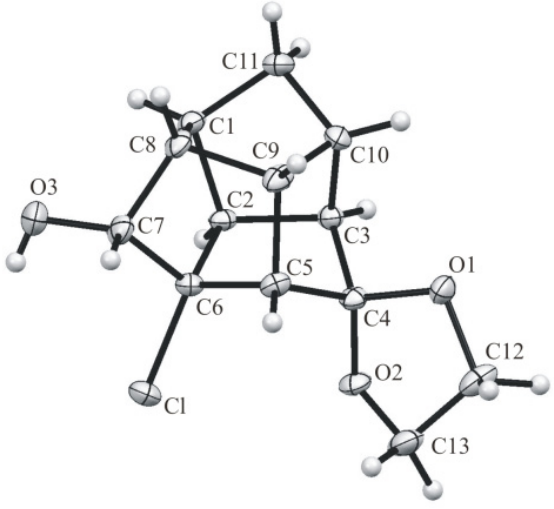


Figure 1. The X-ray crystal structure of 6-chloro-7-hydroxypentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-4- one ethylene ketal (**8**).

pyrolysis of the Rh-complex of *anti*-octahydro-1,2,4-metheno-lH-cyclobuta[cd]pentalen-1-ol [17] and may be useful for enantioseparations. Its oxidation gave pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-4,7-dione (**14**), which is a useful building block for H-bonded ladderanes [18] the reduction of **12** gave pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]-undecane-4-ol (**13**) – a useful precursor for optical resolution as well as for further functionalizations.

We thus developed a convenient preparative pathway to **12**, which is a key synthon of various D_3-trishomocubane 4,7-derivatives, including optically active ones. As hydroxyamines are among most promising bifunctional homocubane derivatives, we incorporated the amino function into the structure. The reaction of hydroxylamine with hydroxyketone **12** gave the respective oxime **15**, whose reduction on Pd gave 7-aminopentacyclo-[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-4-ol (**16**). From the analysis of the NMR ^{1}H and ^{13}C spectra amine **16** forms as two diastereomers in the 2:3 ratio (from integral intensities of *α*-hydroxy proton signals at 4.00 and 4.05 ppm). In the NMR ^{13}C spectrum the pairs of the resonances at 74.4, 74.5, 74.8, 74.9 ppm belong to the carbons attached to the CHOH fragment. Analysis of the NMR ^{13}C DEPT-spectrum of **16** allows assignment of the carbon resonances of the CH_2-fragments at 32.2, 32.3, 32.5, 32.6 ppm. The biological activity of aminoalcohol **16** is of high interest in view of high activities of many parent D_3-trishomocubylamines [18-19].

4. Conclusions

We suggest an effective and simple method for the construction of the D_3-trishomocubanone skeleton

directly from Cookson's diketone avoiding of usage of harsh reaction conditions and chromatographic separation steps. The isolation and characterization of individual epimer of the disubstituted D_3-trishomocubane cage opens new routes to stereoisomers of 4,7-disubstituted D_3-trishomocubane that are potentially useful for optical resolutions and preparation of new pharmacologically active compounds.

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References

[1] (a) G.R.Underwood, B. Ramamoorthy, Tetrahedron Lett. 11, 4125 (1970); (b) D.M. Ho, R.A. Pascal, Chem. Mater. 5, 1358 (1993)
[2] A.V. Gaidai, D.M. Volochnyuk, O.V. Shishkin, A.A. Fokin, I.A. Levandovskiy, T.E. Shubina, Synthesis 810 (2012)
[3] A. Sklyarova, V. Rodionov, C. Parsons, G. Quack, P. Schreiner, A. Fokin, Med. Chem. Res. 360 (2012)
[4] G.J. Kent, S.A. Godleski, E. Osawa, P.v.R. Schleyer, J. Org. Chem. 42, 3852 (1977)
[5] S.A. Godleski, P.v.R. Schleyer, E. Osawa, G.J. Kent, J. Chem. Soc., Chem. Commun. 976 (1974)
[6] K. Naemura, T. Fujii, H. Chikamatsu, Chem. Lett. 15, 923 (1986)
[7] D.W. Oliver, T.G. Dekker, S. Afr. J. Chem. 32, 45 (1979)
[8] M. Nakazaki, K. Naemura, N. Arashiba, J. Org. Chem. 43, 689 (1978)
[9] P.E. Eaton, B. Leipzig, J. Org. Chem. 43, 2483 (1978)
[10] M. Nakazaki, H. Chikamatsu, K. Naemura, T. Suzuki, M. Iwasaki, Y. Sasaki, T. Fujii, J. Org. Chem. 46, 2726 (1981)
[11] R. C. Cookson, E. Crundwell, R.R. Hill, J. Hudec, J. Chem. Soc. 3062 (1964)
[12] G.A. Tolstikov, B.M. Lerman, F.Z. Galin, Zh. Org. Khim. 12, 1133 (1976)
[13] D.I. Sharapa, A.V. Gayday, A.G. Mitlenko, I.A. Levandovskiy, T.E. Shubina, Eur. J. Org. Chem. 2011, 2554 (2011)
[14] G. Helmchen, G. Staiger, Angew. Chem. Int. Ed. 16, 116 (1977)
[15] G.A. Tolstikov, B.M. Lerman, F.Z. Galin, Y.T. Struchkov, V.G. Andrianov, Tetrahedron Lett. 19, 4145 (1978)
[16] (a) D.W. Oliver, T.G. Dekker, F.O. Snyckers, T.G. Fourie, J. Med. Chem. 34, 851 (1991); (b) A.J.M. Carpy, D.W. Oliver, Helv. Chim. Acta 77, 543 (1994)
[17] C. Zlotogorski, J. Blum, E. Osawa, H. Schwarz, G. Hoehne, J. Org. Chem. 49, 971 (1984).
[18] V.T. Nguyen, P.D. Ahn, R. Bishop, M.L. Scudder, D.C. Craig, Eur. J. Org. Chem. 4489 (2001)
[19] (a) C.J. Van der Schyf, W.J. Geldenhuys, Neurotherapeutics 6, 175 (2009); (b) W.J. Geldenhuys, S.F. Mala, J.R. Bloomquist, A.P. Marchand, C.J.V.d. Schyf, Med. Res. Rev. 25, 21 (2005)
[20] G.M. Sheldrick, Programs for the Solution of Crystal Structures, SHELXS97 and SHELXL97 (University of Gottingen, Germany, 1997)
[21] G. Sheldrick, Acta Crystallogr., Sect. A: Found. Crystallogr. 64, 112 (2008)
[22] G. Mehta, A.V. Reddy, A. Srikrishna, J. Chem. Soc., Perkin Trans. 291 (1986)
[23] E.C. Smith, J.C. Barborak, J. Org. Chem. 41, 1433 (1976)