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Synthesis of *t*-2, *t*-3-Dicarboxy-*r*-1-cyclopentylacetic Acid

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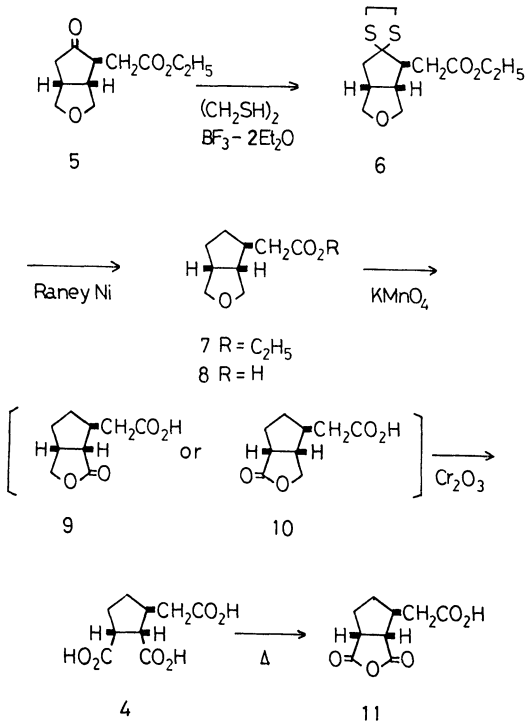
Synopsis. One of the four stereoisomers of 2,3-dicarboxycyclopentylacetic acid, the *t*-2, *t*-3, *r*-1-isomer, has been synthesized from (1*RS*, 5*SR*, 6*SR*)-6-ethoxycarbonylmethyl-3-oxabicyclo[3.3.0]octan-7-one in five steps.

The three stereoisomers of 2,3-dicarboxycyclopentylacetic acid, *c*-2, *c*-3, *r*-1-, *c*-2, *t*-3, *r*-1-, and *t*-2, *c*-3, *r*-1-isomers (**1**, **2**, and **3**), have been synthesized as the key compounds in the determination of the carbon skeleton of aucubin.[1,2] Attempts to synthesize the *t*-2, *t*-3, *r*-1-isomer (**4**) have however been unsuccessful. In this paper, the synthesis of **4** from (1*RS*,5*SR*,6*SR*)-6-ethoxycarbonylmethyl-3-oxabicyclo[3.3.0]octan-7-one (**5**)[3,4] will be reported according to the following scheme.



Scheme 1.

(1*RS*,5*SR*,6*SR*)-6-Ethoxycarbonylmethyl-3-oxabicyclo-[3.3.0]octan-7-one (**5**) was converted into thioacetal **6** with 1,2-ethanedithiol in the presence of boron trifluoride etherate, and **6** was desulfurized with Raney Nickel in dilute ethanol to give ethyl (1*RS*, 5*SR*, 6*RS*)-3-oxabicyclo[3.3.0]octane-6-acetate (**7**). The ester (**7**) was hydrolyzed to the carboxylic acid **8** by heating with 2 M hydrochloric acid. Oxidation of **8** with potassium permanganate gave the lactone carboxylic acid **9** or **10**, which was further oxidized with chromium trioxide to give *t*-2, *t*-3-dicarboxy-*r*-1-cyclopentylacetic acid (**4**). The overall yield of **4** based on the ester (**5**) was 20%.

The structure of **4** was confirmed by elemental analysis and by conversion into the anhydride **11**.[5] Compound **4** showed a melting point depression in agreement with those of the other three stereoisomers, (**1**, **2**, and **3**). The synthesis of the four stereoisomers of 2,3-dicarboxycyclopentylacetic acid (**1**, **2**, **3**, and **4**) is now completed.

Experimental

All boiling and melting points are uncorrected. The IR spectra and mass spectra were recorded with a Hitachi 135 spectrophotometer and a Hitachi RMU-6M mass spectrometer, respectively. The PMR spectrum was recorded with a Hitachi R-22 spectrometer (90 MHz), using tetramethylsilane as an internal standard.

*(1*RS,5*SR,6*SR)-6-Ethoxycarbonylmethyl-3-oxabicyclo[3.3.0]-octan-7-one (5).* The keto ester was prepared as conducted in a previous report.[4] Bp 140—144 °C/4 mmHg, IR (neat) 1730 cm^{-1} (C=O). Found: C, 61.89; H, 7.44%; M^+, 212. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60%; M, 212.

*Ethyl (1*RS,5*SR,6*RS)-3-oxabicyclo[3.3.0]octane-6-acetate (7).* To a mixture of 1,2-ethanedithiol (5 ml) and boron trifluoride etherate (5 ml) was added **5** (3.0 g), and the reaction mixture stirred for 20 min. After removal of the excess reagents *in vacuo*, the resulting thioacetal (**6**) was refluxed in 70% ethanol (300 ml) for 14 h in the presence of Raney Nickel prepared from 90 g of alloy. The reaction mixture was filtered and the filtrate evaporated *in vacuo*. The remaining oil was extracted with ether and the solvent removed. After drying over anhydrous Na_2SO_4, the yield of **7** was 0.7 g (35%); bp 82—83 °C/3 mmHg, MS *m/e* 198 (M^+), IR (neat) 1730 cm^{-1} (C=O). PMR ($CDCl_3$) δ 1.22 (3H, t, J=7.6 Hz, $-CH_2\underline{CH_3}$), 1.70—2.90 (9H, m), 3.67 (4H, m, $-CH_2OCH_2-$), 4.18 (2H, q, J=7.6 Hz, $-\underline{CH_2}CH_3$).

t-2,t-3-Dicarboxy-r-1-cyclopentylacetic Acid (4). A mixture of **7** (0.4 g) and 2 M hydrochloric acid (10 ml) was refluxed for 3 h. The reaction mixture was evaporated *in vacuo* to yield (1*RS*,5*SR*,6*RS*)-3-oxabicyclo[3.3.0]octane-6-acetic acid (**8**). The compound **8** was used in the subsequent reaction without purification.

To a solution of **8** (0.32 g) in water (10 ml) was added dropwise and with stirring $KMnO_4$ (0.6 g) dissolved in water (20 ml) over a period of 9 h at room temperature. After decomposition of the excess $KMnO_4$ with ethanol, the reaction mixture was heated at 80 °C and filtered using a glass filter packed with Celite-545 (Johns-Manville Sales Corp). The filtrate was acidified with 6 M hydrochloric acid and extracted several times with hot ethyl acetate. The ethyl acetate solution was washed with water, dried over anhydrous Na_2SO_4, and freed from ethyl acetate to give the lactone carboxylic acid (**9** or **10**) (0.3 g, 84%) as a viscous oil. IR (neat) 1710 and 1755 cm^{-1} (C=O).

To a solution of the above oxidation product (0.3 g) in acetic acid (50 ml) was added a mixed solution of chromic anhydride (0.4 g), concd H_2SO_4 (0.7 ml), and water (1.4 ml) over a period of 1 h cooling by ice-cold water. The reaction mixture was allowed to stand for 5 days and the remaining

chromium trioxide decomposed with methanol (2 ml). After removal of the solvent *in vacuo*, the residue was extracted with ethyl acetate. The ethyl acetate solution was dried over anhydrous Na_2SO_4 and freed from ethyl acetate to give crude crystals (0.26 g). Recrystallization from ethyl acetate gave **4** (115 mg, 42% yield from **7**) as colorless prisms; mp 167—168 °C. IR (KBr) 3230, 1710, 1422, 1223, 1187, 923, and 780 cm^{-1}. Found: C, 49.70; H, 5.70%; M^+, 216. Calcd for $C_9H_{12}O_6$: C, 50.00; H, 5.56%; M, 216. The carboxylic acid **4** showed melting point depression with the other three stereoisomers (**1**, **2**, and **3**), respectively.

t-*3-(Carboxymethyl)*-r-*2*,c-*3-cyclopentanedicarboxylic Anhydride (11)*. Tricarboxylic acid **4** (16 mg) was heated in an oil bath at 175—195 °C under reduced pressure (3 mmHg) to yield the anhydride **11** (14 mg); mp 141—142 °C (benzene–petroleum ether). IR (KBr) 2940, 1852, 1784, 1682, 1438, 1417, 1343, 1280, 1226, 1103, 1072, 1032, 978, 928, and 812 cm^{-1}. Found: C, 54.28; H, 5.25%; M^+, 198. Calcd for $C_9H_{10}O_5$: C, 54.54; H, 5.05%; M, 198.

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References

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4) H. Obara, H. Kimura, M. Suzuki, and J. Onodera, *Bull. Chem. Soc. Jpn.*, **51**, 3610 (1978).

5) The ease of such anhydride formation indicates that the two carboxyl groups at the 2 and 3 positions in **4** are *cis*, similar to that for the *c*-2, *c*-3, *r*-1-isomer **1**.[6]

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