A Synthetic Route to (±)-Tetrahydroanhydroaucubigenone

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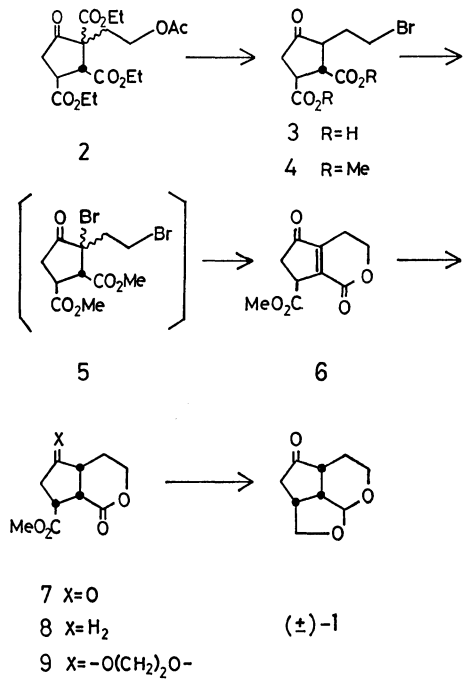
Synopsis. (±)-Tetrahydroanhydroaucubigenone was synthesized by partial reduction, followed by acid hydrolysis, of (4a*RS*,7*RS*,7a*SR*)-7-(methoxycarbonyl) octahydrocyclopenta[*c*]pyran-1,5-dione ethylene acetal, which was prepared from 2,3,4-tris(ethoxycarbonyl)cyclopentanone through 7 steps.

Tetrahydroanhydroaucubigenone (**1**),[1] a unique tricyclic acetal ketone, has been known to be one of the key compounds for the determination of aucubin.[2] Recently, we have succeeded in the synthesis of the racemate of **1** by photo-irradiation of 6-[2-(nitrosooxy)-ethyl]-3-oxabicyclo[3.3.0]octan-7-one.[3] In this paper, we wish to describe an alternative synthetic route to (±)-**1**, as shown in the following scheme.

2-(2-Acetoxyethyl)-2,3,4-tris(ethoxycarbonyl)cyclopentanone (**2**) was obtained with a small amount of an *O*-alkylated compound by the alkylation of the sodio derivative of 2,3,4-tris(ethoxycarbonyl)cyclopentanone[4] with 2-iodoethyl acetate in 36% yield. Hydrolysis and decarboxylation of **2** by heating with 47% hydrobromic acid gave *c*-3-(2-bromoethyl)-4-oxo-*r*-1, *t*-2-cyclopentanedicarboxylic acid (**3**), which was further esterified with diazomethane to give dimethyl ester **4**. Bromination of **4** with copper(II) bromide in tetrahydrofuran gave dibromide **5**, which was immediately heated with calcium carbonate in *N*,*N*-dimethylformamide to afford unsaturated lactone **6** in 26% yield.

Hydrogenation of **6** with hydrogen and 5% palladium charcoal in ethanol gave (4a*RS*,7*RS*, 7a*SR*)-7-(methoxycarbonyl) octahydrocyclopenta[*c*] pyran-1,5-dione (**7**), mp 125—126 °C, as colorless needles. (4a*RS*,7*RS*,7a*SR*)-7-(Methoxycarbonyl)octahydrocyclopenta[*c*]pyran-1-one (**8**),[5] mp 72—73 °C, was also obtained with **7** in this reaction in 36% yield.



The ethylene acetal (**9**) of **7** was partially reduced with lithium aluminum hydride in tetrahydrofuran at 0—5 °C and the resulting reduction product was warmed with 20% sulfuric acid to give (±)-tetrahydroanhydroaucubigenone, mp 56—57 °C, in 15% yield. This compound was identical in all respects with (±)-**1**, which was previously synthesized by photo-irradiation of 6-[2-(nitrosooxy)ethyl]-3-oxabicyclo[3.3.0]octan-7-one.[3]

Experimental

All the boiling and melting points are uncorrected.

2-(2-Acetoxyethyl)-2,3,4-tris(ethoxycarbonyl)cyclopentanone (2). To a suspension of metallic sodium (2.3 g) in 150 ml of dry toluene was added dropwise 2,3,4-tris(ethoxycarbonyl)cyclopentanone[4] (30 g) with efficient stirring. The stirred mixture was heated on a water bath until all the sodium was consumed. Then 2-iodoethyl acetate (32 g) was added under cooling with ice water, and the mixture was left overnight at room temperature and then refluxed for 18 h. After cooling, the mixture was poured into 10% aqueous acetic acid (50 ml) and the toluene layer was separated, washed with aqueous $NaHCO_3$ solution and water, dried over Na_2SO_4, and freed from toluene to give a viscous liquid. Distillation of the residue under reduced pressure afforded **2** (14 g, 36%) containing a small amount of an *O*-alkylated by-product. Bp 153—155 °C/0.3 mmHg (1 mmHg= 133.322 Pa), MS *m/e* 386 (M^+); IR (neat) 1730 cm^{-1} (br. C=O). Additional absorption bands at 1635 and 1685 cm^{-1} can be attributed to the *O*-alkylated by-product. Found: C, 55.86; H, 6.92%. Calcd for $C_{18}H_{26}O_9$: C, 55.95; H, 6.78%.

Dimethyl c-3-(2-Bromoethyl)-4-oxo-r-1,t-2-cyclopentanedicarboxylate (4). A mixture of **2** (5.0 g) and 47% hydrobromic acid (100 ml) was gently refluxed for 2 h. The reaction mixture was evaporated *in vacuo* and the resulting crude bromo keto acid (2.7 g, 75%) was methylated with diazomethane in the usual manner. The resulting crude dimethyl ester was chromatographed on a column of silica gel using benzene–ethyl acetate (4:1) as an eluent to give **4** as a colorless oil (46%). MS *m/e* 306, 308 (M^+). Found: C, 43.37; H, 4.75%. Calcd for $C_{11}H_{15}O_5Br$: C, 43.02; H, 4.92%. *c*-3-(2-Bromoethyl)-4-oxo-*r*-1,*t*-2-cyclopentanedicarboxylic acid (**3**), mp 164—165 °C (from acetic acid), was obtained pure from the above crude bromo keto acid by silica gel column chromatography using toluene–ethyl acetate–acetic acid (25:25:4) as an eluent. Found: C, 38.79; H, 4.04%. Calcd for $C_9H_{11}O_5Br$: C, 38.73; H, 3.97%.

7-(Methoxycarbonyl)-1,3,4,5,6-hexahydrocyclopenta[c]pyran-1,5-dione (6). To a solution of **4** (4.0 g) in tetrahydrofuran (50 ml) was added copper(II) bromide (6.5 g), and the mixture was refluxed with vigorous stirring for 4 h. Then the reaction mixture was filtered and the filtrate was evaporated *in vacuo* to give crude dibromo keto ester (**5**) as an oil, which was immediately used in the next reaction without purification. To a mixture of the above dibromo keto ester in *N*,*N*-dimethylformamide (4 ml) was added calcium

carbonate (1.43 g), and the mixture was heated at 90—100 °C with stirring for 4 h. The reaction mixture was then poured into ice water and the aqueous mixture was extracted several times with ethyl acetate. The ethyl acetate was removed from the extracts *in vacuo* to give a brown oil (3.5 g). The column chromatography on silica gel using benzene–ethyl acetate (5:1) as an eluent gave 2-(2-bromoethyl)-3,4-bis(methoxycarbonyl)-2-cyclopentenone (0.55 g, 14%) as the first eluate. MS *m/e* 304, 306 (M^+), IR (neat) 1725 (br. C=O) and 1640 cm^{-1} (C=C). Found: C, 43.60; H, 4.60%. Calcd for $C_{11}H_{13}O_5Br$: C, 43.30; H, 4.29%. From the second eluate, the target unsaturated lactone **6** (0.72 g, 26%) was obtained. MS *m/e* 210 (M^+), IR (neat) 1740, 1720 (C=O), 1655 cm^{-1} (C=C). Found: C, 56.56; H, 4.85%. Calcd for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80%.

*(4a*RS,7RS,*7a*SR*)-7-(Methoxycarbonyl) octahydrocyclopenta*[c]*-pyran-1,5-dione (**7**).* The unsaturated lactone **6** (0.7 g) was hydrogenated in ethanol (20 ml) using hydrogen and 5% palladium charcoal (0.5 g) as a catalyst at room temperature and atmospheric pressure. After filtration of the reaction mixture, the filtrate was evaporated *in vacuo* and the residue was chromatographed on silica gel using benzene–ethyl acetate (5:2) as an eluent. From the first eluate, (4a*RS*,7*RS*,7a*SR*)-7-(methoxycarbonyl) octahydrocyclopenta-[*c*]pyran-1-one (**8**) (240 mg, 36%) was obtained. Mp 72—73 °C, MS *m/e* 198 (M^+), IR (KBr) 1720 and 1730 cm^{-1} (br. C=O). The physical and spectral data were identical with those of an authentic sample.[5] From the second eluate, **7** (100 mg, 16%) was obtained as colorless needles. Mp 125—126 °C (from benzene), MS *m/e* 212 (M^+), IR (KBr) 1740 and 1723 cm^{-1} (C=O). Found: C, 56.69; H, 5.81%. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70%.

*(±)-Tetrahydroanhydroaucubigenone ((±)-**1**).* A mixture of **7** (80 mg), ethylene glycol (37 mg), and *p*-toluenesulfonic acid (10 mg) in dry toluene (5 ml) was refluxed for 5 h, during which time most of water was removed by azeotropic distillation at atmospheric pressure. After removal of the solvent *in vacuo*, the residue was worked up in the usual manner to give ethylene acetal **9** (98%), MS *m/e* 256 (M^+).

To a solution of **9** (50 mg) in dry tetrahydrofuran (5 ml) was added lithium aluminum hydride in small portions at 0—5 °C until disappearance of a spot of **9** has been confirmed on TLC. Into a reaction mixture was then added 20% sulfuric acid under cooling with ice water until the solution become slightly acidic. The tetrahydrofuran layer was separated by decantation and heated at 50 °C for 20 min. The tetrahydrofuran was removed *in vacuo* and the residue was dissolved in ethyl acetate, and the ethyl acetate solution was washed with aqueous $NaHCO_3$ solution and water, dried over Na_2SO_4, and freed from ethyl acetate to give a viscous oil. The resulting oil was chromatographed on silica gel using benzene–ethyl acetate (5:1) as an eluent to give crude (±)-**1**. Recrystallization from benzene–petroleum ether afforded colorless needles (10 mg, 30%). mp 56—57 °C. The IR and MS spectra of this compound was completely identical with those of an authentic sample of (±)-**1**.[3]

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References

1) P. Karrer and H. Schmid, *Helv. Chim. Acta*, **29**, 525 (1946); S. Fujise, *Nippon Kagaku Zasshi*, **74**, 725 (1953); S. Fujise, H. Obara, and H. Uda, *Chem. Ind.*, **1960**, 289.

2) J. M. Bobbitt and P. K. Segebarth, "Cyclopentanoid Terpene Derivatives," ed by W. I. Taylor and A. R. Battersby, Marcel Dekker, Inc., New York (1969), p. 25, and references cited therein.

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

4) K. Kurosawa and H. Obara, *Bull. Chem. Soc. Jpn.*, **39**, 528 (1966).

5) K. Kurosawa, H. Obara, and H. Uda, *Bull. Chem. Soc. Jpn.*, **39**, 534 (1966).