7,7-Dimethyltricyclo[3.3.0.0^2,8]octan-3-ones as Synthetic Intermediates. VI.\(^1\) An Improved Formal Synthesis of (±)-Descarboxyquadrone via Highly Regioselective Cyclopropane Ring Opening of Tricyclo[3.3.0.0^2,8]octan-3-one\(^2\)

Takeshi Imanishi,\(^*\) Masayuki Yamashita, Munetaka Matsui, Tetsuaki Tanaka, Kazuyuki Miyashita, and Chuzo Iwata

Faculty of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565, Japan. Received April 27, 1992

The cyclopropane ring opening reaction of 7,7-dimethyl-3-oxotricyclo[3.3.0.0^2,8]octan-5-atomic acid (5) was examined. A regioselective C(1)-C(2) bond cleavage of 5 proceeded smoothly under acidic conditions to give a bicyclo[3.2.1]octan-3-one derivative 7 in good yield, as a result of neighboring-group participation of the carboxyl group. The lactone 7 was then successively transformed into the 1,4-diketone 9, a useful intermediate for total synthesis of (±)-descarboxyquadrone (4).

Keywords cyclopropane ring opening; bicyclo[3.2.1]octane; tricyclo[3.3.0.0^2,8]octane; 4H-3a,7-ethanobenzofuran; regioselectivity; descarboxyquadrone; neighboring-group participation

Cyclopropanes have received much attention from organic chemists from the viewpoint of their usefulness as key intermediates for the synthesis of various kinds of natural products and related compounds. Because of significant angular (Baeuerle) strain in addition to considerable torsional (Pitzer) strain, the cyclopropane readily undergoes ring cleavage under various conditions.\(^3\) Tricyclo[3.3.0.0^2,8]octan-3-one derivatives contain the cyclopropane ring as a useful convertible moiety, and have been employed as synthetic intermediates for various cyclopentadienyl natural products.\(^4\) In general, the C(2)-C(8) bond in this ring system is known to be much more easily cleaved than the C(1)-C(2) bond, because of good overlapping between the C(2)-C(8) σ-bond and the adjacent carbonyl π-orbital.\(^5\) In the preceding papers,\(^6\) we showed that an abnormal C(1)-C(2) cleavage takes place predominantly on the reaction of 7,7-dimethyltricyclo[3.3.0.0^2,8]octan-3-one (1) with HX (e.g. HCOOH, H\(^+\)–MeOH), producing the bicyclo[3.2.1]octane derivative 2 as a major product. Under the Birch reduction conditions, however, the same substrate 1 was found to afford the bicyclo[3.3.0]octan-3-one 3, exclusively via the C(2)-C(8) bond cleavage. Such products as 2 and 3 are potential synthetic intermediates for various sesquiterpenes and related compounds.\(^1,2,7\)

In this paper, we wish to report an elegant method for regioselective C(1)-C(2) cyclopropane ring cleavage in a tricyclo[3.3.0.0^2,8]octane system by the use of participation of an intramolecularly provided carboxyl group, and we also describe its application to an improved formal synthesis of descarboxyquadrone (4).\(^6,7,8\)

In acid-catalyzed nucleophilic substitution reactions, the ring cleavage in cyclopropyl ketones takes place with steric inversion at the cleaved β-carbon center.\(^9\) This means that the nucleophiles approach the β-position from antiparallel direction with respect to the C(α)-C(β) bond. When the substrate is compound 1, the attack of nucleophiles at the C(8) center from the antiparallel direction is prohibited by severe steric hindrance owing to the C(7) gem-dimethyl group and therefore the less reactive C(1)-C(2) bond cleaves more readily, resulting in predominant formation of the bicyclo[3.2.1]octane product 2.\(^5\)

In turn, a tricyclo[3.3.0.0^2,8]octanone compound bearing a nucleophilic group at the requisite position of the molecule would serve as an excellent substrate for regioselective cyclopropane ring-cleavage reactions. As a model compound for regioselective C(1)-C(2) bond cleavage, we designed 7,7-dimethyl-3-oxotricyclo[3.3.0.0^2,8]octane-5-atomic acid (5), in which the carboxyl oxygen would be easily able to approach the C(1) center but unable to attack the C(8) position as shown in Fig. 1.

The desired compound 5 was prepared from 1\(^10\) as follows. Ozonolysis of 1 in the usual manner and subsequent reductive work-up afforded the aldehyde 6 (85%), which was oxidized with chromic trioxide to give the carboxylic acid 5 in 65% yield.

On treatment with a catalytic amount of p-toluenesulfonyl acid (TSA) in boiling benzene, the substrate 5 was converted into a single product 7. Its infrared (IR) spec-

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**Chart 1**

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**Fig. 1**

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trium exhibited two carbonyl bands at 1785 and 1720 cm⁻¹, characteristic of a 5-membered lactone and 6-membered ring ketone, respectively. In the proton nuclear magnetic resonance (¹H-NMR) spectrum, one proton singlet signal appeared at 4.65 ppm. The mass spectrum (MS) and elemental analysis data suggested its molecular formula to be C₁₃H₁₆O₃, which is the same as that of the starting material 5. From these spectral data, the structure of the product was determined to be as shown by the structure 7. From the fact that the ¹H-NMR signal of C(7a)-H in 7 appeared as a singlet peak, C(7a)-H was found to be cis to C(7)-H, indicating that the reaction proceeded in an acid-catalyzed Sₓ2-like mode as mentioned above. As expected, none of the C(2)-C(8) bond-cleaved product 8 was obtained in this reaction.

Compound 7 obtained as above was transformed into the diketone 9 by a several-step sequence of reactions. Sodium borohydride reduction of 7 in methanol gave the alcohol 10 (98% yield), which was almost diastereomerically pure and the hydroxyl group of 10 was assumed to be situated axially on the basis of its ¹H-NMR signal. The hydroxyl group of 10 was successfully replaced by hydrogen via the xanthate 11, which was obtained in 86% yield from 10 in the usual manner. Treatment of 11 with tri-n-butyltin hydride in the presence of 2,2'-azobisobutyronitrile (AIBN) aldof hydrogenated product 12. Finally, the lactone 12 was treated with methylthiyl to yield the keto alcohol 13, which, without purification, was oxidized with pyridinium chlorochromate (PCC) to give the diketone 9 in 48% overall yield from 11. Since the diketone 9 had been previously converted into descarboxy-quadron (4) in 4 steps, this new preparation of 9 provides an improved formal synthesis of descarboxy-quadron (4).

Experimental
Meling points are uncorrected. IR spectra were recorded with a Hitachi 260-10 spectrometer. ¹H-NMR spectra were measured with a Hitachi R-22 (90 MHz) or a JEOL FX-90Q (90 MHz) with tetramethylsilane as an internal standard. The mass spectra (MS) and high-resolution MS (High MS) were obtained with a Shimadzu QP-1000 or a JEOL JMS-D300 mass spectrometer. For column chromatography, silica gel 60 (E. Merck) was used. After being dried over anhydrous sodium sulfate or magnesium sulfate, organic extracts were concentrated under reduced pressure.

(1RS,2SR,5SR,8SR)-7,7-Dimethyl-3-oxotrioxocyclo[3.3.0.0²]octane-5-acetic Acid (5) The Jones reagent (S): was added dropwise to a solution of 6 (171 mg, 0.89 mmol) in purified acetone (5 ml) at 0°C until the color of the reagent persisted for more than 5 min. Excess reagent was decomposed by addition of 2-propanol, then the solvent was removed. Water was added to the residue, and the whole was extracted with AcOEt. The extract was washed with water, dried, and evaporated. The crude product was chromatographed on silica gel with hexane-AcOEt (1:2) to give 5 (120 mg, 65%) as colorless needles, mp 88.0—91.0°C (from AcOEt-hexane). IR ν (CHCl₃): cm⁻¹: 3600—3000, 1710. ¹H-NMR (CDCl₃) δ: 1.10, 1.23 (each 3H, s, 7-Me×2), 1.5—2.7 (SH, m), 1.70, 1.95 (2H, ABq, J = 12.5 Hz, 6H), 2.66 (2H, s, CH₂CO₂H), 10.31 (1H, br, CO₂H). MS m/z (%): 208 (M⁺, 24), 105 (100). Anal. Caled for C₁₃H₁₄O₄: C, 69.21; H, 7.74. Found: C, 68.92; H, 7.68.

(3RS,7RS,7aSR)-7a-Dihydro-8,8-dimethyl-4H-3a,7,7-ethanobenzofuran-2,5(3H,6H)-dione (7) A solution of 5 (120 mg, 0.58 mmol) and TSA (catalytic amount) in benzene (5 ml) was stirred at 30°C for 6 d. The mixture was washed with saturated NaHCO₃ solution and dried, and evaporated. The residue was chromatographed on silica gel with hexane-AcOEt-ChCl₃ (2:2:1) to give 7 (117 mg, 98%) as colorless needles, mp 184.0—185.5°C (from AcOEt). IR ν (CHCl₃): cm⁻¹: 1785, 1720. ¹H-NMR (CDCl₃) δ: 0.91, 1.38 (each 3H, s, 8-Me×2), 2.4—2.6 (2H, m), 3.2—2.7 (2H, m), 4.66 (1H, s, 7a-H). MS m/z (%): 208 (M⁺, 73), 69 (100). Anal. Caled for C₁₃H₁₄O₃: C, 69.21; H, 7.74. Found: C, 69.09; H, 7.88.

(3RS,7RS,7aSR)-5,6,7,7a-Tetrahydro-5-hydroxy-8,8-dimethyl-4H-3a,7-ethanobenzofuran-2(3H)-one (10) NaH (39.0 mg, 1.0 mmol) was added portionwise to a stirred solution of 7 (85.0 mg, 0.44 mmol) in MeOH (5 ml) at 0°C and the whole was stirred at 0°C for 30 min. The MeOH was evaporated off, and water was added to the residue. The mixture was extracted with CHCl₃. The extract was washed with brine, dried, and evaporated. The residue was chromatographed on silica gel with hexane-AcOEt (2:3) to give 10 (84.5 mg, 98%) as colorless needles, mp 104.5—106.5°C (from AcOEt-hexane). IR ν (CHCl₃): cm⁻¹: 3590, 3470, 3330, 1770, 1710, 1650, 1150, 1050, 780, 740, 730, 650. ¹H-NMR (CDCl₃) δ: 1.2—2.0 (1OH, m), 4.0—4.3 (1H, m, 5-H), 4.10 (1H, s, 7a-H). MS m/z (%): 210 (M⁺, 18), 55 (100). Anal. Caled for C₁₃H₁₄O₃: C, 68.47; H, 8.63. Found: C, 68.37; H, 8.87.

O-(1,3aRS,7aSR)-2,3,5,6,7,7a-Hexahydro-8,8-dimethyl-2-oxo-
4H-3a,7-ethano-benzofuran-5-yl] S-Methyl Dithiocarbonate (11) A stirred solution of 10 (84.5 mg, 0.40 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (305 mg, 2.0 mmol), and carbon disulfide (0.5 ml) in dimethylformamide (DMF) (1.5 ml) was warmed at 50–60 °C for 3 h, then allowed to cool. Methyl iodide (0.5 ml) was added to the reaction mixture at 0 °C and the whole was stirred at room temperature for an additional 30 min. After addition of water, the mixture was extracted with AcOEt. The combined extracts were washed with 1N HCl and brine, dried, and evaporated. The residue was chromatographed on silica gel with hexane-AcOEt (3:1) to give 11 (104 mg, 86%) as colorless needles, mp 125.0–126.0 °C (from benzene-hexane). IR ν (CHCl₃ cm⁻¹): 1775. ¹H-NMR (CDCl₃, δ): 1.20, 1.21 (each 3H, s, 8-Me × 2), 1.3–2.7 (9H, m), 2.56 (3H, s, S-CH₃), 4.17 (1H, s, 7a-H), 5.60–5.90 (1H, m, 5-H). MS m/z (%): 300 (M⁺, 1.2), 91 (100). Anal. Calcd for C₁₄H₁₆O₃S₂: C, 55.97; H, 6.71; S, 21.34. Found: C, 55.95; H, 6.87; S, 21.31.

(3aRS,7S,7aRS)-5,6,7a-Tetrahydroy-8,8-dimethyl-4H-3a,7-ethano-benzofuran-2(3H)-one (12) A solution of 11 (103 mg, 0.34 mmol), n-Bu₃SnH (119 mg, 0.41 mmol), and AIBN (catalytic amount) in benzene (5 ml) was refluxed for 4 h. After removal of the solvent, the residue was chromatographed on silica gel with hexane-AcOEt (5:1). The crude product 12 was contaminated by a small amount of n-Bu₃SnH, but was used for the next step without further purification. To obtain a spectral sample, an aliquot of the product was recrystallized from hexane to give colorless needles, mp 50.5–52.0 °C. IR ν (CCl₃ cm⁻¹): 1785. ¹H-NMR (CDCl₃, δ): 1.12, 1.16 (each 3H, s, 8-Me × 2), 1.2–2.2 (9H, m), 2.06 (1H, brs), 2.28 (2H, s, S-CH₃), 4.01 (1H, s, 7a-H). MS m/z (%): 194 (M⁺, 2.8), 134 (100). Anal. Calcd for C₁₂H₁₄O₂: C, 74.19; H, 9.57. Found: C, 73.78; H, 9.57.

(1R,3S,5R)-6,6-Dimethyl-1-(2-oxopropyl) bicyclo[3.2.1]octan-8-one (9) Methyl lithium (1.4M solution in hexane) was added to a solution of the crude 12 in tetrahydrofuran (THF) (2 ml) at 0 °C until the starting material was no longer detectable on thin layer chromatography (TLC). After addition of saturated NH₄Cl solution, the mixture was extracted with AcOEt. The extract was washed with brine, dried, and evaporated. The residue was dissolved in dichloromethane (2 ml) and 300 ml of PCC (2400 mg, 1.1 mmol) was added to the solution at 0 °C. The whole was stirred at room temperature for 2 h and diluted with ether. The dilute solution was passed through a pad of Florisor. The filtrate was concentrated to leave the crude product, which was chromatographed on silica gel with benzene-AcOEt (5:1) to give 9 (34.5 mg, 49% from 11) as a colorless oil, which was identical with an authentic sample.⁷⁹

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