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]

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The cyclopropane ring opening reaction of 7,7-dimethyl-3-oxotricyclo[3.3.0.0^{2,8}]octane-5-acetic 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 successfully 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; 4*H*-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 (Baeyer) 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 cyclopentanoid 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]octanone 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]octanone **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]

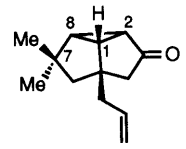
In this paper, we wish to report an elegant method for regioselective C(1)–C(2) cyclopropane ring cleavage in a tricyclo[3.3.0.0^{2,8}]octane system by the use of participation of an intramolecularly provided carboxyl group, and we also describe its application to an improved formal synthesis of descarboxyquadrone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

In acid-catalyzed nucleophilic substition 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**.[6]

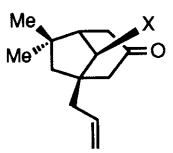
In turn, a tricyclo[3.3.0.0^{2,8}]octanone compound bearing a nucleophilic group at the requisite position of the molecule would serve as an excellent substrate for regioselective cyclopropane ring-cleavage reactions. As a model compound for regioselective C(1)–C(2) bond cleavage, we designed 7,7-dimethyl-3-oxotricyclo[3.3.0.0^{2,8}]octane-5-acetic 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**[6] 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*-toluenesulfonic acid (TSA) in boiling benzene, the substrate **5** was converted into a single product **7**. Its infrared (IR) spec-



1



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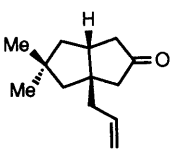

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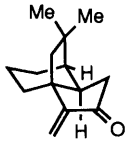

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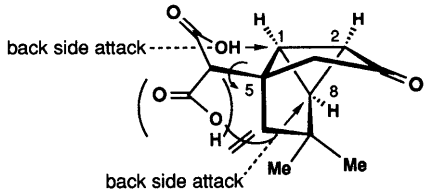
Chart 1



5

Fig. 1

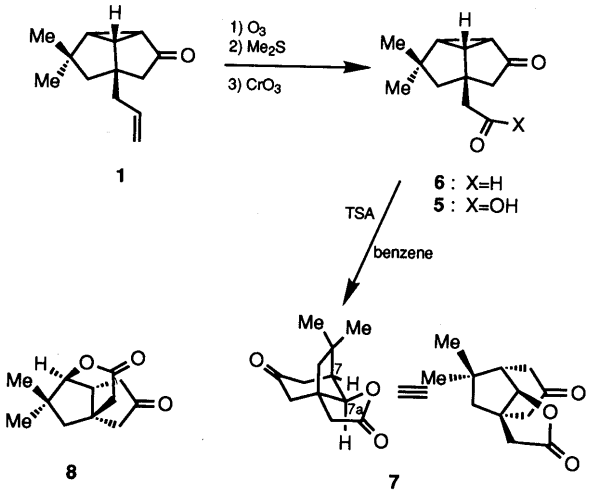


Chart 2

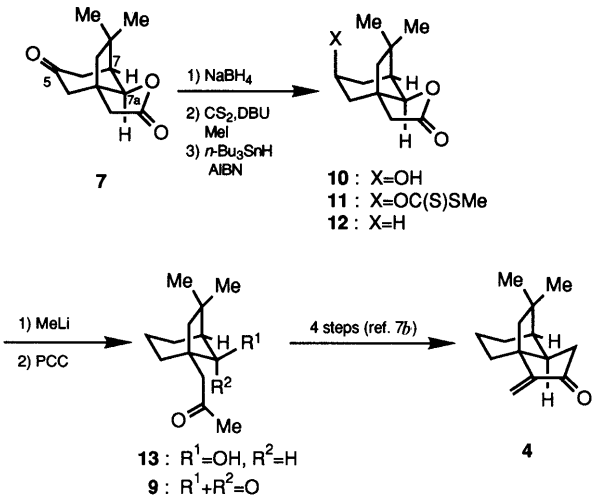


Chart 3

trum 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 (^{1}H-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 $C_{12}H_{16}O_3$, 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 ^{1}H-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 *SN*2-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 ^{1}H-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′-azobisisobutyronitrile (AIBN)[10] afforded the hydrogenated product **12**. Finally, the lactone **12** was treated with methyllithium 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 descarboxyquadrone (**4**) in 4 steps,[7b] this new preparation of **9** provides an improved formal synthesis of descarboxyquadrone (**4**).

Experimental

Melting points are uncorrected. IR spectra were recorded with a Hitachi 260-10 spectrometer. ^{1}H-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.

(1*RS*,2*SR*,5*RS*,8*SR*)-7,7-Dimethyl-3-oxotricyclo[3.3.0.0^{2,8}]octane-5-acetaldehyde (6) Dry ozone was passed into a solution of **1** (200 mg, 1.1 mmol) in MeOH (10 ml) at −78 °C for 40 min. After removal of the excess ozone by flashing the reaction mixture with dry N_2, dimethyl sulfide (0.5 ml) was added and the whole was stirred at room temperature for 12 h. After evaporation of the solvents, the residue was chromatographed on silica gel with hexane–AcOEt (3:1) to give **6** (171 mg, 85%) as a colorless oil. IR ν (CCl_4) cm^{-1}: 1720. ^{1}H-NMR (CCl_4) δ: 1.12, 1.27 (each 3H, s, 7-Me×2), 0.9—2.8 (7H, m), 2.89 (2H, d, J=1.5 Hz, C$\underline{H}_2$–CHO), 9.76 (1H, t, J=1.5 Hz, CH_2–C$\underline{H}$O). MS m/z (%): 192 (M^+, 2.8), 69 (100). High MS Calcd for $C_{12}H_{16}O_2$: 192.1148. Found; 192.1133.

(1*RS*,2*SR*,5*SR*,8*SR*)-7,7-Dimethyl-3-oxotricyclo[3.3.0.0^{2,8}]octane-5-acetic Acid (5) The Jones reagent (8 N) 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 brine, 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 ($CHCl_3$) cm^{-1}: 3600—3000, 1710. ^{1}H-NMR ($CDCl_3$) δ: 1.10, 1.23 (each 3H, s, 7-Me×2), 1.5—2.7 (5H, m), 1.70, 1.95 (2H, AB-q, J=12.5 Hz, 6-H), 2.66 (2H, s, C$\underline{H}_2CO_2H$), 10.31 (1H, br, $CO_2\underline{H}$). MS m/z (%): 208 (M^+, 2.4), 105 (100). *Anal.* Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.92; H, 7.68.

(3a*RS*,7*RS*,7a*SR*)-7,7a-Dihydro-8,8-dimethyl-4*H*-3a,7-ethanobenzofuran-2,5(3*H*,6*H*)-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 $NaHCO_3$ solution and brine, dried, and evaporated. The residue was chromatographed on silica gel with hexane–AcOEt–$CHCl_3$ (2:2:1) to give **7** (117 mg, 98%) as colorless needles, mp 184.0—185.5 °C (from AcOEt). IR ν ($CHCl_3$) cm^{-1}: 1785, 1720. ^{1}H-NMR ($CDCl_3$) δ: 1.04, 1.18 (each 3H, s, 8-Me×2), 1.5—2.0 (3H, m), 2.1—2.9 (6H, m), 4.65 (1H, s, 7a-H). MS m/z (%): 208 (M^+, 73), 69 (100). *Anal.* Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.09; H, 7.88.

(3a*RS*,7*RS*,7a*SR*)-5,6,7,7a-Tetrahydro-5-hydroxy-8,8-dimethyl-4*H*-3a,7-ethanobenzofuran-2(3*H*)-one (10) $NaBH_4$ (39.0 mg, 1.0 mmol) was added portionwise to a stirred solution of **7** (85.0 mg, 0.41 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 $CHCl_3$. 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 104.0—104.5 °C (from AcOEt–hexane). IR ν ($CHCl_3$) cm^{-1}: 3590, 3470, 1770. ^{1}H-NMR ($CDCl_3$) δ: 1.15, 1.31 (each 3H, s, 8-Me×2), 1.2—2.6 (10H, m), 4.0—4.3 (1H, m, 5-H), 4.10 (1H, s, 7a-H). MS m/z (%): 210 (M^+, 1.8), 55 (100). *Anal.* Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.37; H, 8.87.

***O*-[(3a*RS*,7*RS*,7a*SR*)-2,3,5,6,7,7a-Hexahydro-8,8-dimethyl-2-oxo-**

4*H*-3a,7-ethanobenzofuran-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 1 N 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 ($CHCl_3$) cm^{-1}: 1775. ^{1}H-NMR ($CDCl_3$) δ: 1.20, 1.21 (each 3H, s, 8-Me × 2), 1.3—2.7 (9H, m), 2.56 (3H, s, S-CH_3), 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 $C_{14}H_{20}O_3S_2$: C, 55.97; H, 6.71; S, 21.34. Found; C, 55.95; H, 6.87; S, 21.31.

(3a*RS*,7*SR*,7a*RS*)-5,6,7,7a-Tetrahydro-8,8-dimethyl-4*H*-3a,7-ethanobenzofuran-2(3*H*)-one (12) A solution of **11** (103 mg, 0.34 mmol), *n*-Bu_3SnH (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*-Bu_3SnH, 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 (CCl_4) cm^{-1}: 1785. ^{1}H-NMR (CCl_4) δ: 1.12, 1.16 (each 3H, s, 8-Me × 2), 1.2—2.2 (9H, m), 2.06 (1H, br s), 2.28 (2H, s, 3-H), 4.01 (1H, s, 7a-H). MS *m/z* (%); 194 (M^+, 2.8), 134 (100). *Anal.* Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.78; H, 9.57.

(1*RS*,5*SR*)-6,6-Dimethyl-1-(2-oxopropyl)bicyclo[3.2.1]octan-8-one (9) Methyllithium (1.4 M 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 NH_4Cl 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 PCC (240 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 Florisil. 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.[7b]

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