Effective Cleavage of 7-Alkoxytricyclo[6.4.0.0^{2,7}]dodecan-3-one System

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Several effective methods for the cleavage of the cyclobutane ring in 7-alkoxytricyclo[6.4.0.0^{2,7}]dodecan-3-one system are described. These involve reactions with hydriodic acid, with trimethylsilyl trifluoromethanesulfonate, and with KOH in H_2O-DMSO *via* a lactone derivative.

Among various naturally occuring materials, taxane (**1**)[1] and ophiobolane (**2**)[2] are interesting from a synthetic view point, for they have a unique carbon skeleton, that of an 8-membered ring condensed with a 6- or 5-membered ring.

In the course of our synthetic study to the taxane skeleton, the combination of regio- and stereo-controlled intramolecular enone-olefin cycloaddition with subsequent cyclobutane cleavage[3] has been employed as a key reaction. We described previously that the irradiation of 5,5-dimethyl-3-(3-methyl-2-cyclohexenylmethoxy)-2-cyclohexenone afforded a cyclobutane derivative **3**.[4] The remaining problem was how to cleave the cyclobutane ring to a bicyclo[6.4.0]dodecane derivative. In the present study, we will report several effective methods for the cleavage of the cyclobutane system.

The starting cyclobutane **6** was prepared from **3** *via* reaction sequences in Scheme 1. Allylation of the photocycloadduct **3** afforded a mixture of 2-allyl ketones **5** and an enol ether **4**; the mixture on heating underwent a Claisen rearrangement, providing a stereoisomeric mixture of **5a** (73%) and **5b** (9%). The stereochemistry of the allyl group in **5a** was confirmed by the pseudocontact shifts on the addition of Eu-FOD to the alcohol **7a** (see Experimental). The allyl group of **5a** was hydrogenated over PtO_2 to afford the 2-propyl ketone **6**.

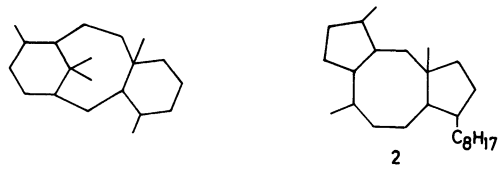
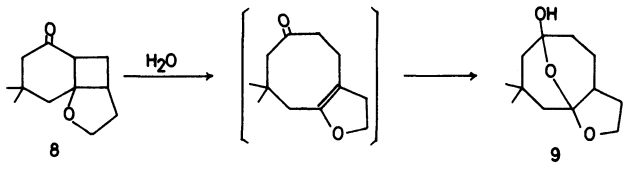


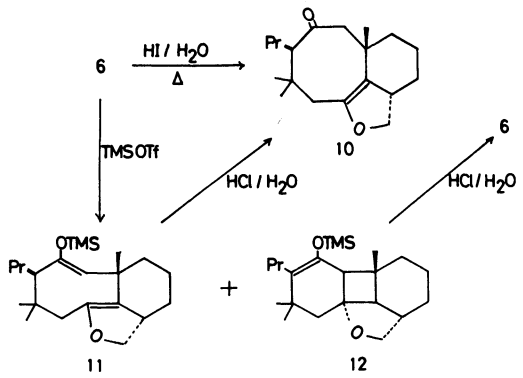
Fig. 1.

In 1973, Tamura and co-workers reported that the photoadduct **8** could be cleaved into a cyclooctane derivative **9** in 53% yield by refluxing **8** in water.[5]

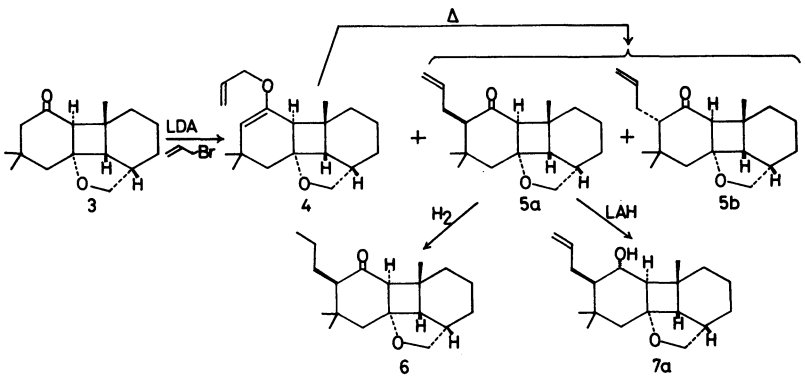


Scheme 2.

However, a similar attempt with **6** was unsuccessful. A more drastic conditions such as refluxing with aqueous hydriodic acid was required and, in this case, a fused 8-membered ring derivative **10** was obtained in 70% yield. The structure of **10** was confirmed by spectroscopic evidence. Besides the carbonyl group (1705 cm^{-1} in IR and δ 214.5 in ^{13}C NMR), an enol ether group is recognized in ^{13}C NMR spectrum at δ 115.6 and 145.4. The disappearance of eight-carbon signals in ^{13}C NMR spectrum suggests the conforma-



Scheme 3.

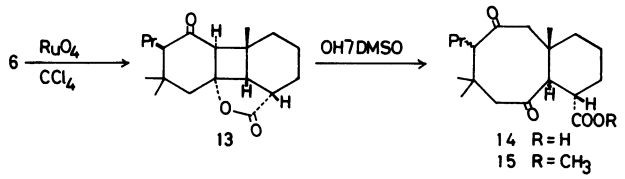


Scheme 1.

tional mobility of the cyclooctane ring.

In searching for milder conditions, we found that trimethylsilyl trifluoromethanesulfonate (TMSOTf)[6] would be effectively employed for the cleavage of the cyclobutane system under neutral conditions. Treatment of the ketone **6** with freshly prepared TMSOTf in purified carbon tetrachloride under an argon atmosphere gave a ring-opened compound **11** in 84% yield, accompanied by a small amount of a simple enol silyl ether **12** (11%) and recovered starting material **6** (5%). In ^{1}H NMR spectrum of **11**, the methylene protons attached to oxygen appear at δ 3.80 (1H, dd, J=9 and 3 Hz) and 4.23 (1H, t, J=9 Hz), and a vinyl proton at 4.53 (1H, s); four vinylic carbons are recognized in ^{13}C NMR spectrum at δ 115.2 (d), 115.9 (s), 145.1 (s), and 152.2 (s). The enol silyl ether **11** was quantitatively converted into the ketone **10** on aqueous hydrochloric acid in THF. This is the first example of the cleavage of the cyclobutane ring by means of TMSOTf.

An alternative procedure for the preparation of an 8-membered ring system *via* a lactone **13** is as follows.



Scheme 4.

The oxidation of **6** was successful by using a stoichiometric amount of RuO_4[7] in purified carbon tetrachloride for only several minutes at room temperature. The γ-lactone **13** (1765 cm^{-1} in IR) was obtained in 86% yield. Saponification of **13** in DMSO gave a diketo acid **14** in 80% yield. The ^{13}C NMR spectrum of the methyl ester **15** (214.2, C=O; 213.6, C=O; 176.0, ester) and mass spectrum [m/z 336 (M^+), 321 (M^+-CH_3), and 305 (M^+-OCH_3)] indicate that the cyclobutane ring is cleaved to an cyclooctane ring system.

In summary, the preparation of the fused 8-membered ring system can now be achieved not only under acidic or basic but also under neutral conditions.

Experimental

All the melting points are uncorrected. IR spectra were recorded on a Hitachi 215 grating spectrophotometer. ^{1}H NMR spectra were measured on JEOL MH-100 and LMN-FX90Q spectrometers and ^{13}C NMR on a JEOL LMN-FX90Q, using TMS as the internal standard. Mass spectra were obtained on a Hitachi RMU-6MG analyzer. High resolution mass spectra were performed at Nippon Roche Research Center, Kamakura.

4-Allyl-1,5,5-trimethyl-8-oxatetracyclo[8.3.1.0^{2,7}.0^{7,14}]tetradecan-3-one (5). To 5 ml of a dry THF solution of lithium diisopropylamide (LDA, 8.75 mmol), were added 5 ml of hexamethylphosphoric triamide (HMPA) at −78°C and then 424 mg (1.71 mmol) of 1,5,5-trimethyl-8-oxatetracyclo-[8.3.1.0^{2,7}.0^{7,14}]tetradecan-3-one (**3**)[4] in 3 ml of dry THF. The mixture was stirred for 30 min, then allyl bromide was added at a once and the whole allowed to warm to room temperature. After 3 h, the mixture was poured into a saturated ammonium chloride solution, and extracted with ether. The ether layer was washed with water and brine, and dried over anhyd Na_2SO_4. Evaporation of the solvent gave an oil. Flash-chromatography on silica gel (elution with hexane–ethyl acetate=30:1—20:1) afforded 432 mg of an enol ether **4** and 88 mg of a mixture of **5a** and **5b**.

4: IR (CCl_4) 1650, 1145, 1050, 990, and 920 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.06 (3H, s), 1.08 (6H, s), 1.78 (2H, s), 2.75 (1H, br s), 3.75 (1H, t, J=9 Hz), 4.04 (1H, t, J=9 Hz), 4.13 (2H, m), 4.55 (1H, s), and 5.0—6.3 (3H, m); MS m/z 288 (M^+).

The enol ether **4** was heated in a sealed tube at 195°C for 2 h. The combined mixture of **5a** and **5b** was flash-chromatographed on silica gel (elution with hexane–ethyl acetate=100:1—20:1) to give 359 mg of **5a** (73%) as crystals and 44 mg of **5b** (9%) as an oil.

5a: mp 70—71°C (pentane); IR (CCl_4) 1685, 1635, 1170, 1040, 990, and 905 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.82 (3H, s), 1.05 (3H, s), 1.08 (3H, s), 1.94 (2H, AB center, J=16 Hz), 2.4 (2H, m), 2.74 (1H, s), 3.63 (1H, dd, J=10 and 9 Hz), 3.93 (1H, t, J=9 Hz), 4.7—4.9 (2H, m), and 5.6—6.1 (1H, m); MS m/z 288 (M^+, 2%) and 109 (100%).

Found: C, 79.09; H, 9.83%. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78%.

5b: oil; IR (CCl_4) 1710, 1045, 995, and 915 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.83 (3H, s), 1.17 (3H, s), 1.20 (3H, s), 2.74 (1H, br s), 3.76 (1H, t, J=9 Hz), 4.09 (1H, t, J=9 Hz), and 4.8—6.0 (3H, m); MS m/z 288 (M^+, 4%) and 109 (100%).

4-Allyl-1,5,5-trimethyl-8-oxatetracyclo[8.3.1.0^{2,7}.0^{7,14}]tetradecan-3-ol (7a). To a suspension of 20 mg of lithium aluminum hydride in 1 ml of dry THF, was added 21 mg of **5a** in 0.5 ml of dry THF at 0°C. The mixture was stirred at that temperature for 15 min and then at room temperature for 30 min. Work up as usual and flash chromatography on silica gel with hexane–ethyl acetate (10:1) gave **7a** (71%) and **7b** (28%).

7a: mp 93—94°C (hexane, 0°C); IR (CCl_4) 3600, 1045, 980, and 920 cm^{-1}; ^{1}H NMR (CCl_4) δ (the Δ values show the pseudocontact shift upon the addition of 0.23 equiv of Eu-FOD)=0.76 (3H, s, Δ0.44), 0.95 (3H, s, Δ0.44), 1.27 (3H, s, Δ0.98), 2.65 (1H, br d, J=9 Hz, Δ2.57), 3.60 (1H, t, J=9 Hz, Δ0.30), 3.80 (1H, t, J=9 Hz, Δ2.34), 3.89 (1H, t, J=9 Hz, Δ0.29), and 4.8—6.2 (3H, m).

Found: C, 78.60; H, 10.41%. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.42%.

7b (an epimeric alcohol of **7a**): oil; IR (CCl_4) 3300br, 1050, 1000, and 920 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.91 (3H, s), 0.92 (3H, s), 1.02 (3H, s), 3.62 (1H, br d, J=5 Hz), 3.70 (1H, t, J=9 Hz), 3.93 (1H, t, J=9 Hz), and 4.8—6.0 (3H, m).

4-Propyl-1,5,5-trimethyl-8-oxatetracyclo[8.3.1.0^{2,7}.0^{7,14}]tetradecan-3-one (6). An ethanolic solution (5 ml) of **5a** (25 mg) was hydrogenated over PtO_2 under hydrogen at ordinary pressure. After 2 h, the catalysts were removed by filtration and the filtrate was evaporated to give an oil. Chromatography on silica gel with chloroform afforded 22 mg (88%) of **6**.

6: mp 63—64°C (methanol, −20°C); IR ($CHCl_3$) 1690 sh and 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.75 (3H, s), 0.83 (3H, t, J=6.5 Hz), 0.98 (3H, s), 1.05 (3H, s), 1.94 (1H, d, J=15 Hz), 2.00 (1H, d, J=10 Hz), 2.06 (1H, d, J=15 Hz), 2.46 (1H, m), 2.79 (1H, br s), 3.65 (1H, t, J=9 Hz), and 3.98 (1H, t, J=9 Hz); ^{13}C NMR ($CDCl_3$) δ=14.3 (q), 16.2 (t), 22.4 (t), 22.9 (t),24.1

(t), 26.3 (q), 26.7 (q), 29.6 (q), 32.0 (s), 33.7(d), 35.8 (t), 36.4 (s), 49.2 (t), 50.6 (d), 51.6 (d), 61.4(d), 71.1 (t), 82.0 (s), and 212.9 (s); MS *m/z* 290 (M^+, 4%) and 109 (100%).

Found: C, 78.55; H, 10.44%. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.42%.

11-Propyl-8,12,12-trimethyl-2-oxatricyclo[6.5.1.0^{4,14}]tetradec-1(14)-en-10-one (10). *Procedure A*: To a vigorously stirred suspension of **6** (10 mg) in 5 ml of water, 5 drops of hydriodic acid were added, and the mixture was refluxed for 4 h. The products were extracted in ether and chromatographed on silica gel with chloroform–hexane (2:1—3:1) to give a ketone **10** (7 mg, 70%) as crystals.

10: mp 68—70 °C; IR (CCl_4) 1705, 1685, 1460, 1365, and 1206 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.76 (6H, s), 1.00 (3H, s), 2.0—4.0 (several broad signals), and 4.27 (1H, t, J=9 Hz); ^{13}C NMR ($CDCl_3$) δ (sharp signals only at)=14.6, 21.6, 22.2, 28.6, 36.8, 41.0, 42.7, 73.3, 115.6, 145.4, and 214.5.

Found: *m/z* 290.2245. Calcd for $C_{19}H_{30}O_2$: M 290.2247.

Procedure B: To a solution of **11** (7 mg, see below) in 5 ml of THF, were added 2 drops of a 10% hydrochloric acid. The solution was stirred for 2 h at room temperature. The whole was poured into water, extracted with ether, and the ether extract was dried over anhyd $MgSO_4$. Evaporation of the solvent gave the ketone **10** (6 mg, 100%).

11-Propyl-8,12,12-trimethyl-10-trimethylsiloxy-2-oxatricyclo-[6.5.1.0^{4,14}]tetradeca-1(14),9-diene (11). In a 5 ml flask, containing a solution of the ketone **6** (20 mg, 7×10^{-2} mmol) in 0.5 ml of dry CCl_4 (washed with concd H_2SO_4, dil KOH, H_2O, dried over P_2O_5; fractionally distilled) and a spinning bar, was added 27 mg (2.4×10^{-1} mmol) of triethylamine. After stirring for 5 min, was added drop by drop 47 mg (2.1×10^{-1} mmol) of TMSOTf at 0 °C, under a dry argon atmosphere. The whole was allowed to warm to room temperature and stirred for 24 h. If some of the starting ketone **6** still remained 1 mol equivalents of Et_3N and TMSOTf were added to the solution, and the whole was again stirred over night. The resulting solution was passed through a short silica-gel column with CH_2Cl_2 to remove triethylammonium triflate. The crude products, obtained by evaporation of the solvent, were chromatographed on silica gel (with hexane–benzene=5:1) to give an 8-membered enol trimethylsilyl ether **11** (22 mg, 84%) as crystals, a simple enol trimethylsilyl ether **12** (3 mg, 11%), and **6** (1 mg, 5%).

11: IR (CCl_4) 1670, 1635, 1365, 1245, 1200, and 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.19 (9H, s), 0.83 (3H, s), 0.88 (3H, s), 1.23 (3H, s), 3.80 (1H, dd, J=9 and 3 Hz), 4.23 (1H, t, J=9 Hz), and 4.53 (1H, s); ^{13}C NMR ($CDCl_3$) δ=0.4 (q, ×3), 14.9 (q), 21.9 (t, ×2), 24.3 (q), 25.4 (q), 26.3 (q), 27.5 (t), 34.8 (s, ×2), 40.8 (t), 43.3 (d), 44.0 (t), 48.1 (d), 72.3 (t), 115.7 (d), 115.9 (s), 145.1 (s), and 152.7 (s); MS *m/z* 362 (M^+, 8%) and 347 ($M^+ - CH_3$, 100%).

12: oil; IR (CCl_4) 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.15 (9H, s), 0.89 (3H, t, J=7 Hz), 1.05 (6H, s), 1.55 (3H, s), 2.57 (1H, br s), 3.90 (1H, t, J=9 Hz), and 4.20 (1H, t, J=9 Hz); MS *m/z* 362 (M^+, 15%) and 347 ($M^+ - CH_3$, 100%).

4-Propyl-1,5,5-trimethyl-8-oxatetracyclo[8.3.1.0^{2,7}.0^{7,14}]tetradecane-3,9-dione (13). To a solution of the ketone **6** (40 mg) in 10 ml of purified CCl_4 (see above), was added drop by drop a solution of RuO_4 (Mitsuwa Kagaku Yakuhin Co. Ltd., Osaka, Japan; 61% activity, 38 mg) in 5 ml of pure CCl_4. The whole was stirred for 10 min. The remained RuO_4 was reduced to RuO_2 by addition of several drops of 2-propanol. RuO_2 was removed through a silica-gel column by elution with CH_2Cl_2 and the eluates were evaporated to give a crude γ-lactone **13** (36 mg, 86%) as crystals. This material was decomposed during recrystallization and, therefore, an analytical sample was obtained by sublimation (110 °C, 400 pa).

13: mp 152—153 °C; IR($CHCl_3$) 1765, 1695, and 1185 cm^{-1}; ^1H NMR($CDCl_3$) δ=0.87 (3H, s), 0.91 (3H, t, J=6.6 Hz), 1.08 (3H, s), 1.14 (3H, s), 2.12 (2H, AB center), 2.42 (1H, dd, J=12 and 1 Hz), 2.80 (1H, br s), and 2.92 (1H, dm, J=12 Hz); ^{13}C NMR ($CDCl_3$) δ=79.6 (C-O), 180.5 (-COO-), and 211.1 (-CO-).

Found: C, 74.92; H, 9.27%. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27%.

Methyl 4-propyl-1,5,5-trimethyl-3,7-dioxobicyclo[6.4.0]dodecane-9-carboxylate (15). The γ-lactone **13** (7 mg) was dissolved in 2 ml of DMSO and 2 ml of a 10% KOH solution was added at room temperature under an argon atmosphere. After gently refluxed for 3 h, the mixture was allowed to cool to room temperature. The whole was poured into 10 ml of ice-water, washed with benzene and then acidified with 1 M† HCl. The solution was extracted with ether. Evaporation of the solvent gave crude carboxylic acid **14** (7 mg) as crystals. A pure sample was obtained by chromatography on silica gel (with CH_2Cl_2–acetone=100:1—20:1).

14: mp 190.5—191 °C; IR ($CHCl_3$) 3500—2500br and 1695 cm^{-1}; ^1H NMR($CDCl_3$) δ=0.92 (3H, s), 0.98 (9H, s), and 1.97—3.12 (7H, m).

To a solution of the crude acid **14** in 20 ml of ether, was added drop by drop an ethereal solution of diazomethane at 0 °C. The whole was stirred for 30 min at that temperature, and evaporated to give a crude oil. Chromatography of the oil on silica gel (CH_2Cl_2) gave a pure methyl ester **15** (5 mg, 92%; 72% overall yield from **13**).

15: oil; IR ($CHCl_3$) 1715 and 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.95 (s, 3H), 1.01 (s, 6H), 2.10 and 2.78 (AB, J=12.1 Hz), 2.23 and 3.10 (AB, J=12.7 Hz), 1.9—3.3 (3H, m), and 3.58 (3H, s); ^{13}C NMR ($CDCl_3$) δ=14.3 (q), 17.3 (q), 20.1 (q), 20.6 (t), 21.6 (t), 29.5 (t), 30.7 (t), 31.9 (q), 39.4 (s), 39.5 (s), 41.5 (t), 43.1 (d), 51.9 (q), 59.2 (t, ×2), 61.8 (d), 64.6 (d), 176.0 (s), 213.6 (s), and 214.2 (s).

Found: *m/z* 336.2295. Calcd for $C_{20}H_{32}O_4$: M 336.2302.

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† 1 M=1 mol dm^{-3}.