Synthetic Study on Gymnomitrol and Related Compounds. I. Preparation and Cyclopropane Ring Opening of 1,2,6-Trimethyltetracyclo[5.3.1.$0^{2,6}$.$0^{8,11}$]undecan-9-one

Takeshi IMANISHI,* Yoshimi HIROKAWA, Masayuki YAMASHITA, Tetsuaki TANAKA, Kazuyuki MIYASHITA, and Chuzo IWATA

Faculty of Pharmaceutical Sciences, Osaka University, 1–6 Yamadaoka, Suita, Osaka 565, Japan.
Received May 18, 1992

1,2,6-Trimethyltetracyclo[5.3.1.$0^{2,6}$.$0^{8,11}$]undecan-9-one (4) was prepared from 1,5-dimethylbicyclo[3.3.0]octan-3-one (6) in fourteen steps. Its cyclopropane ring opening reaction was examined under various conditions. In all runs, 11-substituted 1,2,6-trimethyltricyclo[5.3.1.$0^{2,6}$]undecan-9-ones 20 were obtained as major products along with 7-substituted 1,2,8-trimethyltricyclo[6.3.0.$0^{2,6}$]undecan-4-ones 21 and two other products 22 and 23.

Keywords cyclopropane cleavage; tetracyclo[5.3.1.$0^{2,6}$.$0^{8,11}$]undecane; Claisen rearrangement; tricyclo[5.3.1.$0^{2,6}$]undecane; tricyclo[6.3.0.$0^{2,6}$]undecane; reductive alkylation

Gymnomitrol (**1**), one of the diquinane sesquiterpenoids, was isolated from the liverwort *Gymnomitrion obtusum* (Lindb) Pears in 1970 and its structure was assigned as **1**, which possesses the unique tricyclo[5.3.1.$0^{2,6}$]undecane framework, on the basis of chemical degradation and spectroscopic evidence.[1] Because of the interesting structure, a number of chemists conducted synthetic studies and total synthesis of **1** have been achieved by several groups.[2] In previous papers, we dealt with the behavior of cyclopropane ring opening in the tricyclo[3.3.0.$0^{2,8}$]octane compounds **2b** and showed that acid-catalyzed nucleophilic substitution reactions of **2b** gave mainly the bicyclo[3.2.1]-octane derivatives **3b** *via* a regioselective cleavage of the less reactive C(1)–C(2) bond (type B).[3] On the other hand, compounds **2a** afford the bicyclo[3.3.0]octanes **3a** predominantly *via* the C(2)–C(8) bond cleavage (type A) in the same reactions. These results can be well interpreted in terms of steric hindrance of the *gem*-dimethyl groups at C(7) and stereoelectronic requirement, as discussed below. We planned a further application of the type B cyclopropane ring cleavage of bicyclo[3.3.0.$0^{2,8}$]octanes to another ring system, *i.e.*, the tetracyclo[5.3.1.$0^{2,6}$.$0^{8,11}$]undecane framework. 1,2,6-Trimethyltetracyclo[5.3.1.$0^{2,6}$.$0^{8,11}$]undecan-9-one (**4**) is a very attractive target for the following reasons. (a) The tetracycloundecane **4**, which resembles the tricyclooctanone **2b** in steric features around the cyclopropane ring, is expected to undergo the type B cyclopropane ring opening on acid-catalyzed nucleophilic substitution reactions. (b) Since the cyclopropane ring opening reaction proceeds *via* an *SN*2-like mechanism, the relative configuration of the product should be as shown in **5**, which has the same stereochemistry as that of gymnomitrol (**1**).

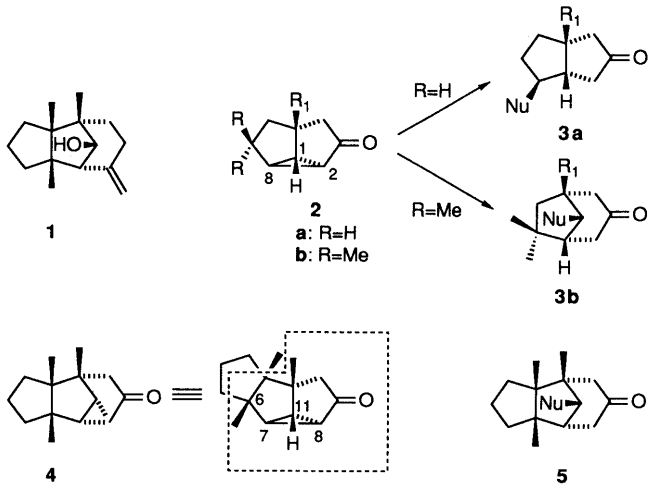
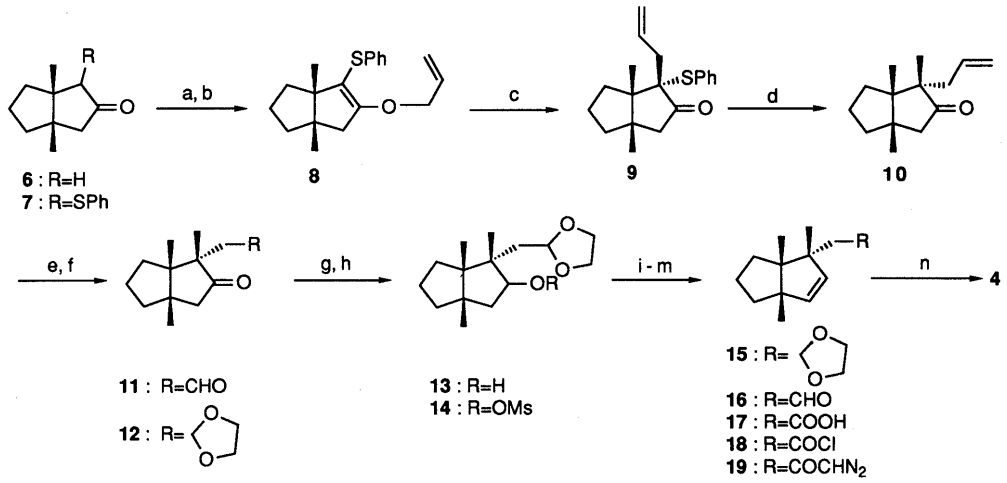


Chart 1

In this paper, we wish to describe the preparation of 1,2,6-trimethyltetracyclo[5.3.1.$0^{2,6}$.$0^{8,11}$]undecan-9-one (**4**) and the features of its cyclopropane ring opening reactions.

Preparation of 1,2,6-Trimethyltetracyclo[5.3.1.$0^{2,6}$.$0^{8,11}$]-undecan-9-one (4) The starting material for the preparation of **4** is 1,5-dimethylbicyclo[3.3.0]octan-3-one (**6**), which was also used as the common synthetic intermediate for the synthesis of **1** by Coates *et al.*,[2a] and Paquette and Han.[2e] Treatment of **6** with lithium diisopropylamide (LDA) followed by reaction with diphenyldisulfide gave **7** as a mixture of diastereoisomers in 64% yield. Due to easy enolization and steric hindrance of the C(1)-methyl group, reaction of the enolate anion generated from **7** with allyl bromide afforded the allyl vinyl ether **8** in 82% yield. Heating of the toluene solution of **8** in a sealed tube gave the Claisen rearrangement product **9** in 94% yield.[2a] This rearrangement occurred on the less hindered convex face *via* a chair form transition state affording a single product **9**. Desulfurization of **9** under the Birch reaction conditions followed by trapping of the resulting lithium enolate with methyl iodide afforded **10** in 48% yield as a single compound, through approach of the nucleophile from the less hindered side.[2a,c,e] Though this compound **10** has been already prepared as the synthetic intermediate for **1**,[2a,c,f] we have developed an alternative and efficient route to **10**. Ozonolysis of **10** followed by reductive work-up gave the aldehyde **11**, which was subjected to chemoselective acetalization with 1.1 eq of ethylene glycol to afford **12** in 72% yield. The ketone **12** was reduced with lithium aluminum hydride ($LiAlH_4$) to give **13** in nearly quantitative yield, and its mesylate **14** was converted into the olefin **15** in 86% yield. Deprotection of the acetal group in **15** and subsequent oxidation of the aldehyde **16** with chromic trioxide afforded the carboxylic acid **17** in 90% yield. The

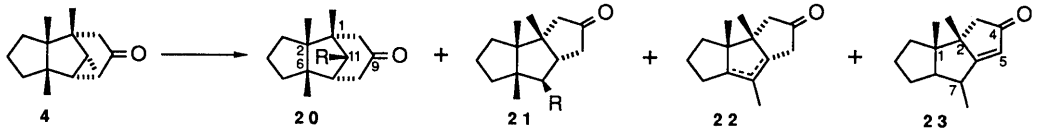


a) LDA, $(PhS)_2$ b) LDA, allyl bromide c) 180°C d) Li / liq. NH_3 then MeI e) O_3 then Me_2S f) ethylene glycol, *p*-TsOH

g) $LiAlH_4$ h) MsCl, pyridine i) NaI, DBU j) HCl-acetone k) CrO_3-H_2SO_4 l) $(COCl)_2$ m) CH_2N_2 n) $Cu(acac)_2$, reflux

Chart 2

TABLE I. Cyclopropane Ring Opening of **4**



Run	Reaction conditions	R	Yield (%)[a]			
			20	**21**	**22**	**23**
1	1) HCO_2H, 90 °C. 2) OH^-	OH	26 (29)[b]	12 (14)[b]	11 (12)[b]	4 (4)[b]
2	1) HCO_2H, *p*-TsOH, 90 °C. 2) OH^-	OH	29	13	13	34
3	1) HCO_2H, conc. H_2SO_4, 90 °C. 2) OH^-	OH	26	11	8	21
4	MeOH, *p*-TsOH, reflux	OMe	65	23	0	0
5	MeOH, conc. H_2SO_4, reflux	OMe	90	10	0	0

a) Isolated yield. *b*) Yield based on the consumed starting material **4**.

carboxylic acid **17** was transformed into the diazoketone **19** *via* the acid chloride **18** in a usual manner.[4,5] Upon treatment of **19** with copper(II) acetylacetonate ($Cu(acac)_2$) in boiling benzene, cyclopropanation smoothly took place and the expected product **4** was isolated in 64% yield.[4,5]

Its structural assignment was supported by spectral considerations. Thus the mass spectrum (MS) and elemental analysis revealed that the product has the formula $C_{14}H_{20}O$, and its infrared (IR) spectrum showed a carbonyl band absorption at 1715 cm^{-1} due to the 5-membered ring ketone adjacent to the cyclopropane ring. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum exhibited three singlet peaks at 1.02, 1.14, and 1.17 ppm due to the three methyl groups and no signal was observed below 2.70 ppm.

Cyclopropane Ring Opening of 1,2,6-Trimethyltetracyclo[5.3.1.$0^{2,6}$.$0^{8,11}$]undecan-9-one (4) There have been many reports concerning cyclopropane ring opening.[6] In rigid cyclopropyl ketone systems, the C–C σ-bond which is well overlapped with the adjacent C=O π-orbital is known to be cleaved more easily than the other two C–C bonds.[5] Thus, in the case of **2a**, the C(2)–C(8) bond (the external bond) is cleaved more easily to afford the bicyclo[3.3.0]-octanone **3a**.[5] On the other hand, we have found that, in the case of **2b**, C(1)–C(2) bond (the internal bond) cleavage occurs exclusively or predominantly. This phenomenon is attributable to the steric hindrance of the *gem*-dimethyl groups at the C(7) position, because this opening proceeds *via* an *S*N2-like mechanism.[3] In the case of **4**, the C(6)-methyl group would prevent nucleophilic attack at the C(7) position. Therefore, it is expected that the nucleophilic attack would occur at the C(11) position and the C(8)–C(11) bond (the internal bond) would be cleaved to afford the tricyclo[5.3.1.$0^{2,6}$]undecane skeleton **5**. Furthermore, C(11) of **5** would have the same stereochemistry as that of **1**.

Cleavage of the cyclopropane ring of **4** was examined under various conditions and the results are summarized in Table I. As expected, moderate amounts of the tricyclo[5.3.1.$0^{2,6}$]octanones **20** were obtained along with **21**, **22**, and **23** in all runs. In particular, when methanol was used as a nucleophile, the C(8)–C(11) bond-cleaved product **20** (R=OMe) was selectively obtained without any **22** or **23** (see runs 4 and 5).

Structural assignments of the products **20**—**23** were based on spectral considerations. IR spectra showed a carbonyl band at 1705 cm^{-1} characteristic of a 6-membered ring ketone for **20** or at 1740 cm^{-1} due to a 5-membered ring ketone for **21**. MS and ^{1}H-NMR spectra, and other evidence were consistent with the proposed structures. The

stereochemistries of **20** and **21** were confirmed to be as shown in Table I on the basis of spectral considerations and the reaction mechanism. In the ^{1}H-NMR spectrum of **20**, the C(11) proton appeared as a singlet at 4.20 ppm, since the dihedral angle between the carbinol proton and C(7) proton is close to 90°.[1] On the other hand, IR spectrum of **22** showed a 5-membered ring ketone band at 1735 cm^{-1} and its ^{1}H-NMR spectrum exhibited a doublet (3H, J=1 Hz) at 1.53 ppm due to the vinylic methyl group. The IR spectrum of **23** showed absorption bands at 1695 and 1625 cm^{-1} due to an unsaturated 5-membered ring ketone moiety and its ^{1}H-NMR spectrum exhibited a doublet (3H, J=7.5 Hz) at 1.27 ppm due to the C(7) methyl protons. In the ultraviolet (UV) spectrum, the absorption maximum due to a 5-membered ring enone system was observed at 233 nm (ε=11800).

A tentative reaction mechanism is depicted in Chart 3. The protonated compound **24** should be the common starting species of this reaction. Nucleophilic attack on the less hindered C(11) carbon of **24** affords the tricyclo[5.3.1.0^{2,6}]octanone derivative **20** *via* **25** (path a), while nucleophilic attack on the hindered C(7) carbon affords the tricyclo[6.3.0.0^{2,6}]undecane derivative **21** *via* **27** (path b). The cation **26**, which could be formed by acid-catalyzed cyclopropane ring opening at the C(7)–C(8) bond, may also be an intermediate for **27** (path c).[5] The formation of the olefinic derivatives **22** and **23** are clearly explained as a result of the Wagner–Meerwein rearrangement of **26**. Migration of the C(6) methyl group to the cationic center gives **28** (path d), which affords **22** and **23** *via* **29**.

As described above, preparation of 1,2,6-trimethyltetracyclo[5.3.1.0^{2,6}.0^{8,11}]undecan-9-one (**4**) and its cyclopropane ring opening reaction to the tricyclo[5.3.1.0^{2,6}]-octanone derivative **20**, having the basic skeleton of gymnomitrol and the same stereochemistry of the C(11) substituent, were achieved. This methodology could serve as a novel and efficient route for the synthesis of gymnomitrol (**1**).

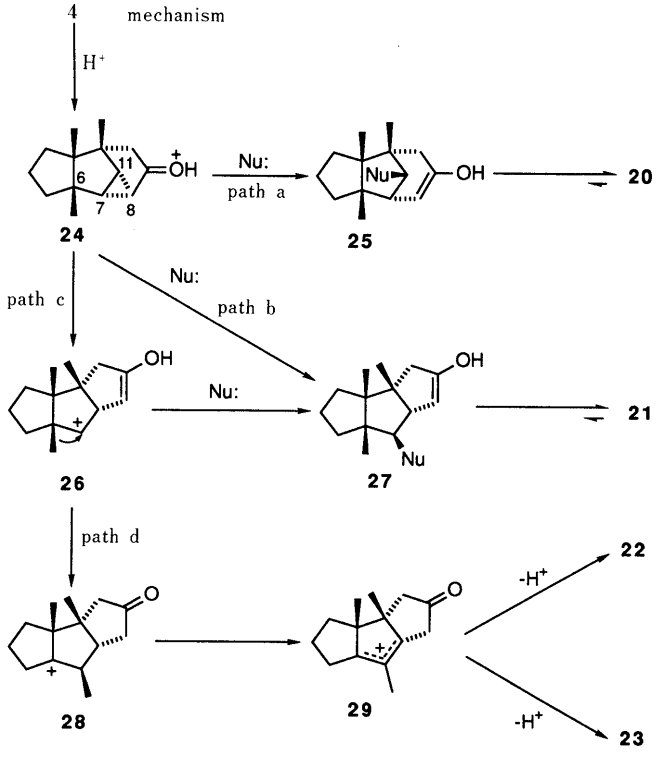


Chart 3

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. MS and high-resolution MS (High MS) were obtained with a Shimadzu QP-1000 or a JEOL JMS-D300 mass spectrometer. UV spectra were recorded with a Hitachi 124 spectrometer in 95% ethanol. For column chromatography, Silica gel 60 (E. Merck) was used. After drying over anhydrous sodium sulfate or magnesium sulfate, all organic extracts were concentrated under reduced pressure.

(1*RS*,5*RS*)-1,5-Dimethyl-2-phenylthiobicyclo[3.3.0]octan-3-one (7) Under a nitrogen atmosphere, hexamethylphosphoramide (HMPA: 1.55 g, 8.65 mmol) was added dropwise to a solution of LDA, generated from diisopropylamine (740 mg, 7.33 mmol) and *n*-butyllithium (1.28 M in hexane, 5.8 ml, 7.40 mmol) in tetrahydrofuran (THF, 7 ml) at −78 °C, and the mixture was stirred for 1 h at the same temperature. A solution of **6** (748 mg, 4.92 mmol) in THF (5 ml) and a solution of diphenyldisulfide (1.60 g, 7.33 mmol) in THF (10 ml) were successively added dropwise to the mixture at −78 °C. The whole was stirred for 1 h at the same temperature and then for an additional 12 h, during which time the reaction mixture was gradually warmed to room temperature. After addition of saturated NH_4Cl solution, the mixture was extracted with ether (25 ml × 3). The combined extracts were successively washed with 10% HCl solution, water, saturated $NaHCO_3$ solution, and brine, then dried, and evaporated. The residue was chromatographed on silica gel with benzene–hexane (3 : 2) to give **7** (824 mg, 64%) as a pale yellow oil. IR (CCl_4) cm^{-1}: 3060, 1740, 1590. ^{1}H-NMR (CCl_4) δ: 1.01, 1.05, 1.12 (total 6H, each s, 1-Me, 5-Me), 0.8—2.0 (6H, m), 2.0—2.3 (2H, m, 4-H), 3.29, 3.35 (total 1H, each s, 2-H), 7.0—7.5 (5H, m, aromatic H). MS *m/z* (%): 260 (M$^+$, 43), 95 (100). High MS Calcd for $C_{16}H_{20}OS$: 260.1234. Found: 260.1244.

(1*RS*,5*RS*)-1,5-Dimethyl-2-phenylthio-3-(2-propenyloxy)bicyclo[3.3.0]-oct-2-ene (8) Under a nitrogen atmosphere, HMPA (309 mg, 1.72 mmol) was added dropwise to a solution of LDA, prepared from diisopropylamine (178 mg, 1.76 mmol) and *n*-buthyllithium (1.6 M in hexane, 1.1 ml, 1.80 mmol) in THF (3 ml) at −78 °C, and the whole was stirred for 15 min at the same temperature. A solution of **7** (380 mg, 1.46 mmol) in THF (2 ml) was added dropwise to the mixture at −78 °C. The whole was stirred for 10 min at the same temperature and then for 20 min at 0 °C. Allyl bromide (212 mg, 1.75 mmol) was added dropwise to the mixture at 0 °C. The whole was stirred for 1 h at 0 °C and 20 h at room temperature. After addition of saturated NH_4Cl solution, the mixture was extracted with ether (10 ml × 3). The combined extracts were washed with brine, dried, and evaporated. The residue was chromatographed on silica gel with hexane–ethyl acetate (AcOEt) (20 : 1) to give **8** (360 mg, 82%) as a pale yellow oil. IR ($CHCl_3$) cm^{-1}: 3060, 1630, 1585. ^{1}H-NMR ($CDCl_3$) δ: 0.99, 1.07 (each 3H, each s, 1-Me, 5-Me), 1.2—2.0 (6H, m), 2.48 (2H, s, 4-H), 4.35—4.6 (2H, m, $OC\underline{H}_2C{=}C$), 5.0—5.4 (2H, m, $-CH{=}C\underline{H}_2$), 5.6—6.1 (1H, m, $-C\underline{H}{=}CH_2$), 6.9—7.4 (5H, m, aromatic H). MS *m/z* (%): 300 (M$^+$, 35), 259 (32), 217 (100). High MS Calcd for $C_{19}H_{24}OS$: 300.1545. Found: 300.1539.

(1*RS*,2*RS*,5*RS*)-1,5-Dimethyl-2-phenylthio-2-(2-propenyl)bicyclo[3.3.0]-octan-3-one (9) A solution of **8** (222 mg, 0.740 mmol) in toluene (10 ml) was heated in a sealed tube at 180 °C for 20 h. After the solution had cooled, the solvent was evaporated off. The residue was chromatographed on silica gel with hexane–AcOEt (10 : 1) to give **9** (209 mg, 94%) as a pale yellow oil. IR ($CHCl_3$) cm^{-1}: 3070, 1720, 1640, 1580, 920. ^{1}H-NMR (CCl_4) δ: 0.96, 1.04 (each 3H, each s, 1-Me, 5-Me), 1.2—2.6 (8H, m), 2.00, 2.90 (2H, AB-q, J=18 Hz, 4-H), 4.8—5.2 (2H, m, $-CH{=}C\underline{H}_2$), 5.8—6.4 (1H, m, $-C\underline{H}{=}CH_2$), 7.0—7.5 (5H, m, aromatic H). MS *m/z* (%): 300 (M$^+$, 25), 259 (27), 191 (25), 95 (100). High MS Calcd for $C_{19}H_{24}OS$: 300.1545. Found: 300.1551.

(1*RS*,2*RS*,5*RS*)-1,2,5-Trimethyl-(2-propenyl)bicyclo[3.3.0]octan-3-one (10)[2a,c,f] A solution of **9** (33 mg, 0.11 mmol) in THF (1 ml) was added to a solution of lithium (5.0 mg, 0.72 mmol) in liquid ammonia (10 ml) at −78 °C. The mixture was stirred for 5 min, then HMPA (0.5 ml, 2.9 mmol) and methyl iodide (0.10 ml, 1.6 mmol) were successively added at −78 °C. The ammonia was evaporated off. After addition of water, the mixture was extracted with ether (10 ml × 3). The combined extracts were washed with brine, dried, and evaporated. The residue was chromatographed on

silica gel with hexane–AcOEt (20 : 1) to afford **10** (11 mg, 48%) as a pale yellow oil.[2a,c] IR (CCl_4) cm^{-1}: 3070, 1735, 1640, 995, 915. ^{1}H-NMR (CCl_4) δ: 0.95, 0.99, 1.16 (each 3H, each s, 1-Me, 2-Me, 5-Me), 0.9—1.9 (6H, m), 2.10, 2.22 (2H, AB-q, J=18 Hz, 4-H), 2.0—2.4 (2H, m, $-C\underline{H}_2C=C$), 4.7—5.3 (2H, m, $-C=C\underline{H}_2$), 5.5—6.2 (1H, m, $-C\underline{H}=CH_2$). MS m/z (%): 206 (M^+, 5.6), 95 (100). High MS Calcd for $C_{14}H_{22}O$: 206.1668. Found: 206.1661.

(1*RS*,2*RS*,5*RS*)-2-(1,3-Dioxolan-2-yl)methyl-1,2,5-trimethylbicyclo-[3.3.0]octan-3-one (12) Dry ozone was passed into a solution of **10** (1.70 g, 8.25 mmol) in dichloromethane (10 ml) and methanol (15 ml) for 4 h at −78 °C. After removal of the excess ozone by flushing the reaction mixture with dry N_2, dimethylsulfide (1.2 ml) was added and the whole mixture was stirred for 6 h at room temperature. Evaporation of the solvents gave crude **11** as a colorless oil. IR (CCl_4) cm^{-1}: 2840, 1740, 1725. ^{1}H-NMR (CCl_4) δ: 1.00, 1.18, 1.23 (each 3H, each s, 1-Me, 2-Me, 5-Me), 1.5—1.9 (6H, m), 2.12 (1H, dd, J=15, 4 Hz, $C\underline{H}_2CHO$), 2.20, 2.36 (2H, AB-q, J=18 Hz, 4-H), 2.51 (1H, dd, J=15, 2 Hz, $C\underline{H}_2CHO$), 10.10 (1H, dd, J=4, 2 Hz, $-C\underline{H}O$). MS m/z (%): 208 (M^+, 3.6), 60 (100). High MS Calcd for $C_{13}H_{20}O_2$: 208.1463. Found: 208.1486. The mixture of the crude **11**, ethylene glycol (557 ml, 8.96 mmol) and a catalytic amount of *p*-TsOH in benzene (20 ml) was refluxed for 2.5 h, during which time the generated water was removed with a Dean–Stark trap. After being cooled, the mixture was washed with water, saturated $NaHCO_3$ solution, and brine, dried, and evaporated. The residue was chromatographed on silica gel with hexane–AcOEt (7 : 1) to give **12** (1.50 g, 72%) as a colorless solid. IR (CCl_4) cm^{-1}: 1735, 1140, 1110, 1085, 1050. ^{1}H-NMR (CCl_4) δ: 1.00, 1.07, 1.18 (each 3H, each s, 1-Me, 2-Me, 5-Me), 1.3—2.0 (6H, m), 1.50 (1H, dd, J=15, 6 Hz, 2-$C\underline{H}_2O$), 1.82 (1H, dd, J=15, 4 Hz, 2-$C\underline{H}_2O$), 2.10, 2.26 (2H, AB-q, J=18 Hz, 4-H), 3.5—4.0 (4H, m, $OC\underline{H}_2C\underline{H}_2O$), 5.02 (1H, dd, J=6, 4 Hz, $-C\underline{H}(OCH_2)_2$). MS m/z (%): 252 (M^+, 0.6), 73 (100). High MS Calcd for $C_{15}H_{24}O_3$: 252.1726. Found: 252.1734.

(1*RS*,2*RS*,5*RS*)-2-(1,3-Dioxolan-2-yl)methyl-1,2,5-trimethylbicyclo-[3.3.0]octan-3-ol (13) $LiAlH_4$ (79 mg, 2.1 mmol) was added portionwise to a solution of **12** (263 mg, 1.04 mmol) in ether (10 ml) at 0 °C and the whole was stirred for 30 min at 0 °C. After addition of saturated potassium sodium tartrate solution, the precipitate was filtered off. The filtrate was dried, and evaporated to give **13** (258 mg, 97%) as a colorless oil. IR (CCl_4) cm^{-1}: 3550, 3520. ^{1}H-NMR (CCl_4) δ: 0.79, 0.82, 0.84, 1.00, 1.02 (total 9H, each s, 1-Me, 2-Me, 5-Me), 1.20—2.25 (8H, m), 2.80, 3.07 (total 1H, br, $O\underline{H}$), 3.6—4.1 (5H, m, $OC\underline{H}_2C\underline{H}_2O$, and 3-$\underline{H}$), 4.98 (1H, m, $C\underline{H}(OCH_2)_2$). MS m/z (%): 254 (M^+, 0.4), 236 (2.5), 221 (1.7), 73 (100). High MS Calcd for $C_{15}H_{26}O_3$: 254.1882. Found: 254.1893.

(1*RS*,2*SR*,5*RS*)-2-(1,3-Dioxolan-2-yl)methyl-1,2,5-trimethylbicyclo-[3.3.0]oct-3-ene (15) Methanesulfonyl chloride (27 mg, 0.24 mmol) was added to a solution of **13** (30 mg, 0.12 mmol) in pyridine (2 ml) at 0 °C and the whole was stirred for 10 h at room temperature. After addition of water, the mixture was extracted with ether (7 ml × 3). The combined extracts were washed with saturated copper(II) sulfate solution (10 ml × 3), water, and brine, dried, and evaporated to give the crude mesylate **14**. The mixture of **14** and a catalytic amount of NaI in 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU, 2 ml) was heated at 100—120 °C for 20 h. After addition of water, the mixture was extracted with ether (10 ml × 3). The combined extracts were washed with 1.2 N HCl solution (5 ml × 2), saturated $NaHCO_3$ solution, and brine, then dried, and evaporated. The residue was chromatographed on silica gel with hexane–AcOEt (20 : 1) to afford **15** (24 mg, 86%) as a colorless oil. IR (CCl_4) cm^{-1}: 3040, 1620. ^{1}H-NMR (CCl_4) δ: 0.91, 0.98, 1.04 (each 3H, each s, 1-Me, 2-Me, 5-Me), 1.65 (2H, d, J=5 Hz, 4-$C\underline{H}_2$), 1.15—1.8 (6H, m), 3.6—4.0 (4H, m, $OC\underline{H}_2C\underline{H}_2O$), 4.85 (1H, t, J=5 Hz, $C\underline{H}(OCH_2)_2$), 5.28, 5.47 (2H, AB-q, J=6 Hz, 3-H, 4-H). MS m/z (%): 236 (M^+, 2.8), 73 (100). High MS Calcd for $C_{15}H_{24}O_2$: 236.1776. Found: 236.1777.

(1*RS*,2*SR*,5*RS*)-1,2,5,-Trimethylbicyclo[3.3.0]oct-3-ene-2-acetic Acid (17) A mixture of **15** (464 mg, 1.97 mmol) in acetone (20 ml) and 1.2 N HCl solution (5 ml) was refluxed for 6 h. After removal of the acetone, the mixture was extracted with ether (10 ml × 3). The combined extracts were washed with saturated $NaHCO_3$ solution and brine, dried, and evaporated to leave the crude aldehyde **16** as a colorless oil. IR ($CHCl_3$) cm^{-1}: 3040, 2730, 1720, 1620. ^{1}H-NMR ($CDCl_3$) δ: 0.94, 1.05, 1.08 (each 3H, each s, 1-Me, 2-Me, 5-Me), 1.15—2.0 (6H, m), 2.42 (2H, d, J=4 Hz, $C\underline{H}_2CHO$), 5.46 (2H, s, 3-H, 4-H), 10.06 (1H, t, J=4 Hz, $C\underline{H}O$). MS m/z (%): 192 (M^+, 1.3), 177 (1.1), 149 (100). High MS Calcd for $C_{13}H_{20}O$: 192.1514. Found: 192.1514. The Jones reagent (8 N) was added dropwise to the solution of **16** in purified acetone (10 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, and then the solvent was removed. Water was added to the residue, and the whole was extracted with chloroform (15 ml × 3). The combined $CHCl_3$ layers were extracted with 10% NaOH solution (15 ml × 2). The aqueous layers were acidified with concentrated HCl solution and the mixture was extracted with $CHCl_3$. The combined organic extracts were washed with brine, dried, and evaporated to give **17** (368 mg, 90%) as colorless crystals, mp 64—65 °C. IR (CCl_4) cm^{-1}: 3500—2400, 3040, 1715. ^{1}H-NMR (CCl_4) δ: 0.97, 1.05, 1.07 (each 3H, each s, 1-Me, 2-Me, 5-Me), 1.2—1.9 (6H, m), 2.34 (2H, d, J=2 Hz, $C\underline{H}_2COOH$), 5.38, 5.62 (2H, AB-q, J=6 Hz, 3-H, 4-H), 11.75 (1H, br, $COO\underline{H}$). MS m/z (%): 208 (M^+, 17.2), 193 (100). High MS Calcd for $C_{13}H_{20}O_2$: 208.1462. Found: 208.1462.

(1*RS*,2*SR*,6*SR*,7*RS*,8*SR*,11*SR*)-1,2,6-Trimethyltetracyclo[5.3.1.-$0^{2,6}$.$0^{8,11}$]undecan-9-one (4) Oxalyl chloride (1.04 g, 8.19 mmol) was added dropwise to a solution of **17** (855 mg, 4.11 mmol) in benzene (5 ml) at 0 °C and the whole was stirred for 1 h at 0 °C. Removal of the volatile components left the crude acid chloride **18**. The solution of **18** in benzene (5 ml) was added dropwise to a solution of an excess of diazomethane in ether at 0 °C and the whole was stirred for an additional 30 min at 0 °C. Removal of the solvents and excess diazomethane afforded the crude diazoketone **19**. The solution of **19** in benzene (20 ml) was added dropwise to a refluxing solution of $Cu(acac)_2$ (108 mg, 0.41 mmol) in benzene (50 ml) and the whole was refluxed for 4 h. After evaporation of the solvent, the residue was diluted with ether and 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 hexane–AcOEt (20 : 1) to give **4** (540 mg, 64%) as colorless crystals, mp 46.0—47.5 °C. IR ($CHCl_3$) cm^{-1}: 3035, 1715. ^{1}H-NMR ($CDCl_3$) δ: 1.02, 1.14, 1.17 (each 3H, each s, 1-Me, 2-Me, 6-Me), 0.8—2.70 (11H, m). MS m/z (%): 204 (M^+, 2.3), 96 (100). *Anal.* Calcd for $C_{14}H_{20}O$: C, 82.06; H, 10.05. Found: C, 82.30; H, 9.87.

The Reaction of 4 with Formic Acid (Run 1) A solution of **4** (250 mg, 1.23 mmol) in 98—100% formic acid (5 ml) was heated for 12 h. After removal of the formic acid, methanol (3 ml) was added to the residue and the mixture was basified with 5% NaOH solution. The whole was stirred for 30 min at room temperature. After removal of the solvents, the mixture was extracted with $CHCl_3$ (10 ml × 3). The combined extracts were washed with brine, dried, and evaporated. The residue was chromatographed on silica gel with hexane–AcOEt (4 : 1) to give **20** (R = OH) (71 mg, 26%), **21** (R = OH) (34 mg, 12%), **22** (27 mg, 11%), **23** (10 mg, 4%), and recovered **4** (25 mg, 10%).

(1*RS*,2*RS*,6*RS*,7*SR*,11*RS*)-11-Hydroxy-1,2,6-trimethyltricyclo[5.3.-$1.0^{2,6}$]undecan-9-one (**20**; R = OH): Colorless crystals. mp 115—116 °C. IR ($CHCl_3$) cm^{-1}: 3600, 3450, 1705. ^{1}H-NMR ($CDCl_3$) δ: 1.00, 1.11, 1.23 (each 3H, each s, 1-Me, 2-Me, 6-Me), 1.3—2.8 (11H, m), 4.20 (1H, s, 11-H). MS m/z (%): 222 (M^+,4.3), 204 (8.5), 189 (6.0), 96 (100). *Anal.* Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.43, H; 10.21.

(1*RS*,2*RS*,6*SR*,7*RS*,8*RS*)-7-Hydroxy-1,2,8-trimethyltricyclo[6.3.0.$0^{2,6}$]-undecan-4-one (**21**; R = OH): A colorless oil. IR ($CHCl_3$) cm^{-1}: 3600, 3450, 1740. ^{1}H-NMR ($CDCl_3$) δ: 0.94, 0.97, 1.15 (each 3H, each s, 1-Me, 2-Me, 8-Me), 0.7—2.8 (11H, m), 3.50 (1H, d, J=10 Hz, 7-H). MS m/z (%): 222 (M^+, 12), 207 (9.6), 126 (100). High MS Calcd for $C_{14}H_{22}O_2$: 222.1620. Found: 222.1640.

(1*RS*,2*RS*)-1,2,7-Trimethyltricyclo[6.3.0.$0^{2,6}$]undecen-4-one (**22**): A colorless oil. IR ($CHCl_3$) cm^{-1}: 1735. ^{1}H-NMR ($CDCl_3$) δ: 1.03, 1.13 (each 3H, each s, 1-Me, 2-Me), 1.53 (3H, d, J=1 Hz, 7-Me), 1.20—2.8 (11H, m). MS m/z (%): 204 (M^+, 30), 189 (26), 97 (100). High MS Calcd for $C_{14}H_{20}O$: 204.1512. Found: 204.1506.

(1*RS*,2*RS*,7*RS*)-1,2,7-Trimethyltricyclo[6.3.0.$0^{2,6}$]undec-5-en-4-one (**23**): A colorless oil. IR ($CHCl_3$) cm^{-1}: 1695, 1625. ^{1}H-NMR ($CDCl_3$) δ: 1.03, 1.23 (each 3H, each s, 1-Me, 2-Me), 1.30 (3H, d, J=7.5 Hz, 7-Me), 1.4—2.5 (10H, m), 5.80 (1H, d, J=1.5 Hz, 5-H). UV λ_{max} nm (ε): 233 (11800). MS m/z (%): 204 (M^+, 3.4), 189 (5.7), 179 (100). High MS Calcd for $C_{14}H_{20}O$: 204.1515. Found: 204.1525.

The Reaction of 4 with Formic Acid and *p*-TsOH (Run 2) A mixture of **4** (32 mg, 0.16 mmol), *p*-TsOH (trace), and 98—100% formic acid (5 ml) was heated with stirring at 90 °C for 5.5 h. The usual work-up afforded an oil, which was subjected to alkaline hydrolysis as described above to give a crude oily product. Column chromatography of the product on silica gel afforded **20** (R = OH) (10 mg, 29%), **21** (R = OH) (4.5 mg, 13%), **22** (4.0 mg, 12%), and **23** (11 mg, 34%).

The Reaction of 4 with Formic Acid and Concentrated Sulfuric Acid (Run 3) A mixture of **4** (34 mg, 0.17 mmol), concentrated H_2SO_4 (trace), and 98—100% formic acid (5 ml) was heated with stirring at 90 °C for 3 h. The usual work-up afforded an oil, which was subjected to alkaline hydrolysis as described above to give a crude oily product. Column chromatography

of the product on silica gel afforded **20** (R=OH) (9.5 mg, 26%), **21** (R=OH) (4.1 mg, 11%), **22** (2.8 mg, 8%), and **23** (7.1 mg, 21%).

The Reaction of 4 with Methanol and *p*-TsOH (Run 4) A mixture of **4** (20 mg, 0.098 mmol), *p*-TsOH (trace), and methanol (10 ml) was refluxed for 4 d. After removal of the methanol, water was added to the residue and the mixture was extracted with AcOEt (10 ml × 3). The combined extracts were washed with saturated $NaHCO_3$ solution and brine, then dried, and evaporated. The residue was chromatographed on silica gel with hexane–ether (10:1) to give **20** (R=OMe) (15 mg, 65%) and **21** (R=OMe) (5.3 mg, 23%).

(1*RS*,2*RS*,6*RS*,7*SR*,11*RS*)-11-Methoxy-1,2,6-trimethyltricyclo[5.3.1.-$0^{2,6}$]undecan-9-one (**20**; R=OMe): Colorless crystals. mp 31—32 °C. IR ($CHCl_3$) cm^{-1}: 1705. ^{1}H-NMR ($CDCl_3$) δ: 0.96, 1.03, 1.12 (each 3H, each s, 1-Me, 2-Me, 6-Me), 0.7—3.0 (11H, m), 3.34 (3H, s, $OC\underline{H}_3$), 3.64 (1H, s, 11-H). MS *m/z* (%): 236 (M^+, 19), 221 (9), 96 (100). *Anal.* Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.09; H, 10.12.

(1*RS*,2*RS*,6*SR*,7*RS*,8*RS*)-7-Methoxy-1,2,8-trimethyltricyclo[6.3.0.-$0^{2,6}$]undecan-4-one (**21**; R=OMe): A colorless oil. IR ($CHCl_3$) cm^{-1}: 1730. ^{1}H-NMR ($CDCl_3$) δ: 0.90, 0.98, 1.16 (each 3H, each s, 1-Me, 2-Me, 8-Me), 0.8—2.8 (11H, m), 3.17 (1H, d, J=8.5 Hz, 7-H), 3.40 (3H, s, $OC\underline{H}_3$). MS *m/z* (%): 236 (M^+, 9.5), 221 (12), 149 (100). High MS Calcd for $C_{15}H_{24}O_2$: 236.1777. Found: 236.1789.

The Reaction of 4 with Methanol and Concentrated Sulfuric Acid (Run 5) A mixture of **4** (22 mg, 0.11 mmol), concentrated H_2SO_4 (trace), and methanol (10 ml) was refluxed for 30 h. The usual work-up as described above afforded an oil. Column chromatography of the product on silica gel afforded **20** (R=OMe) (23 mg, 90%) and **21** (R=OMe) (2.7 mg, 10%).

Acknowledgement This work was supported in part by a Grant-in-Aid for Scientific Research (No. 63570992) from the Ministry of Education, Science, and Culture of Japan. The authors are also grateful to Shionogi Research Laboratories for financial support.

References

1) J. D. Connolly, A. E. Harding, and I. M. S. Thornton, *J. Chem. Soc., Chem. Commun.*, **1972**, 1320; *idem*, *J. Chem. Soc., Perkin Trans. 1*, **1974**, 2487.
2) *a*) R. M. Coates, S. K. Shah, and R. W. Mason, *J. Am. Chem. Soc.*, **101**, 6765 (1979); *idem*, *ibid.*, **104**, 2198 (1982); *b*) G. Büchi and P.-S. Chu, *ibid.*, **101**, 6767 (1979); *idem*, *Tetrahedron*, **37**, 4509 (1981). *c*) S. C. Welch and S. Chayabunjonglerd, *J. Am. Chem. Soc.*, **101**, 6768 (1979); S. C. Welch, S. Chayabunjonglerd, and A. S. C. P. Rao, *J. Org. Chem.*, **45**, 4086 (1980); *d*) M. Kodama, T. Kurihara, J. Sasaki, and S. Ito, *Can. J. Chem.*, **57**, 3343 (1979); *e*) L. A. Paquette and Y.-K. Han, *J. Am. Chem. Soc.*, **103**, 1831 (1981); *f*) T. Uyehara, K. Osanai, M. Sugimoto, I. Suzuki, and Y. Yamamoto, *J. Am. Chem. Soc.*, **111**, 7264 (1989).
3) T. Imanishi, M. Matsui, M. Yamashita, and C. Iwata, *Tetrahedron Lett.*, **27**, 3161 (1986); T. Imanishi, M. Yamashita, M. Matsui, F. Ninbari, T. Tanaka, and C. Iwata, *Chem. Pharm. Bull.*, **36**, 1351 (1988).
4) W. von E. Doering, E. T. Fossel, and R. L. Kaye, *Tetrahedron*, **21**, 25 (1965).
5) S. A. Monti, D. J. Bucheck, and J. C. Shepard, *J. Org. Chem.*, **34**, 3080 (1969).
6) M. Demuth and K. Schaffner, *Angew. Chem. Int. Ed. Engl.*, **21**, 820 (1982) and references cited therein.