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A New Conversion Method from (−)-Limonene to Nepetalactones

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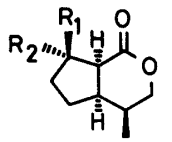
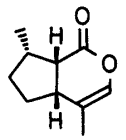
This paper describes the conversions of (−)-limonene to four nepetalactones (**1**, **2**, *ent*-**3** and **4**) in a stereocontrolled manner. The *cis*-3,4-disubstituted cyclopentanone (**5**) obtained from (−)-limonene *via* Rh(I)-catalyzed cyclization of the 4-pentenal, could be converted to the bicyclo[3.3.0]octenone (**6**). After the stereoselective conversion of **6** into the diastereomeric isomers of the ketones (**8** and **16**), a sequence of reactions involving the silyl enol ethers (**18** and **19**), ozonolysis, and subsequent lactonization afforded the target molecules.

Keywords——nepetalactone; *cis,cis*-dihydronepetalactone; dihydronepetalactone; *cis,cis*-nepetalactone; bicyclo[3.3.0]octenone; (−)-limonene

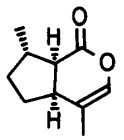
Several nepetalactones, which belong to the category of "iridoids," have been isolated from plant sources, *viz.*, *cis*, *cis*-dihydronepetalactone (**1**) from *Boschniakia rossica* HULT.,[1] dihydronepetalactone (**2**) from *Actinidia polygama* MIQ.,[2] *cis*, *cis*-nepetalactone (**3**) from *Nepeta mussini*,[3] and nepetalactone (**4**) from *Nepeta cataria* L.[4] (Chart 1). These compounds are well known to be attractive to *Felidae* animals. Recently, **4** was also found to be an aphid sex pheromone.[5] Synthetic studies of these compounds have been reported by several groups,[6] but only a few were stereocontrolled.



1: R_1 = Me, R_2 = H
cis,cis-dihydronepetalactone
2: R_1 = H, R_2 = Me
dihydronepetalactone



3: *cis,cis*-nepetalactone



4: nepetalactone

Chart 1

As a part of our synthetic studies on biologically active compounds involving a five-membered ring, we have already reported the Rh(I)-complex-catalyzed stereoselective conversion of 3,4-disubstituted 4-pentenals to *cis*-3,4-disubstituted cyclopentanones.[7] The present paper describes a conversion of (−)-limonene to the above four nepetalactones (**1**, **2**, *ent*-**3** and **4**) in a stereocontrolled fashion.

The retro synthetic analysis of these compounds is shown in Chart 2. The lactone moieties in compounds **1**, *ent*-**3** and **2**, **4** may be derived from the corresponding ketones (**8** and **16**) *via* the oxidative cleavage of the C_2–C_3 bond followed by lactonization. The ketone (**8**) may be obtained stereoselectively by catalytic hydrogenation of the enone (**6**). The C_8-epimer (**16**) of **8** may also be obtained from **6** *via* the introduction of a C_7-oxo function

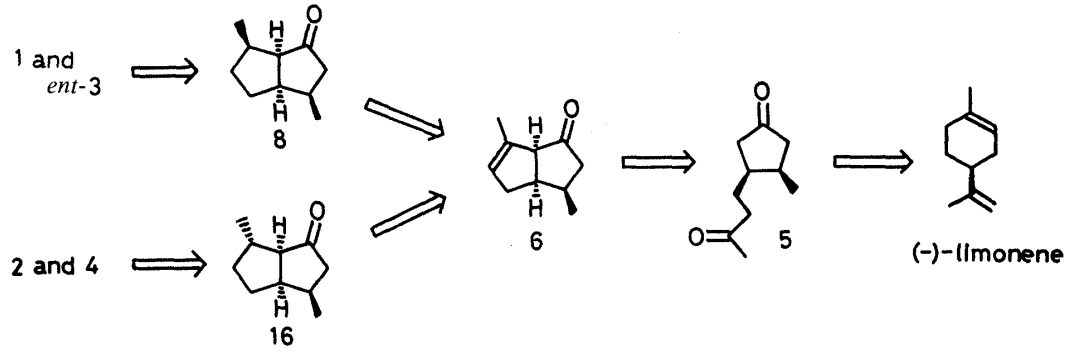


Chart 2

followed by epimerization at the C_8-position. Compound **6** may be prepared from the diketone (**5**) in the manner that we reported previously.[8] The synthetic route to **5** from (−)-limonene has been established in a stereocontrolled fashion by means of Rh(I)-catalyzed cyclization.[7] Thus, the retro synthetic analysis of **1**—**4** suggests that (−)-limonene is a favorable compound as a starting material.

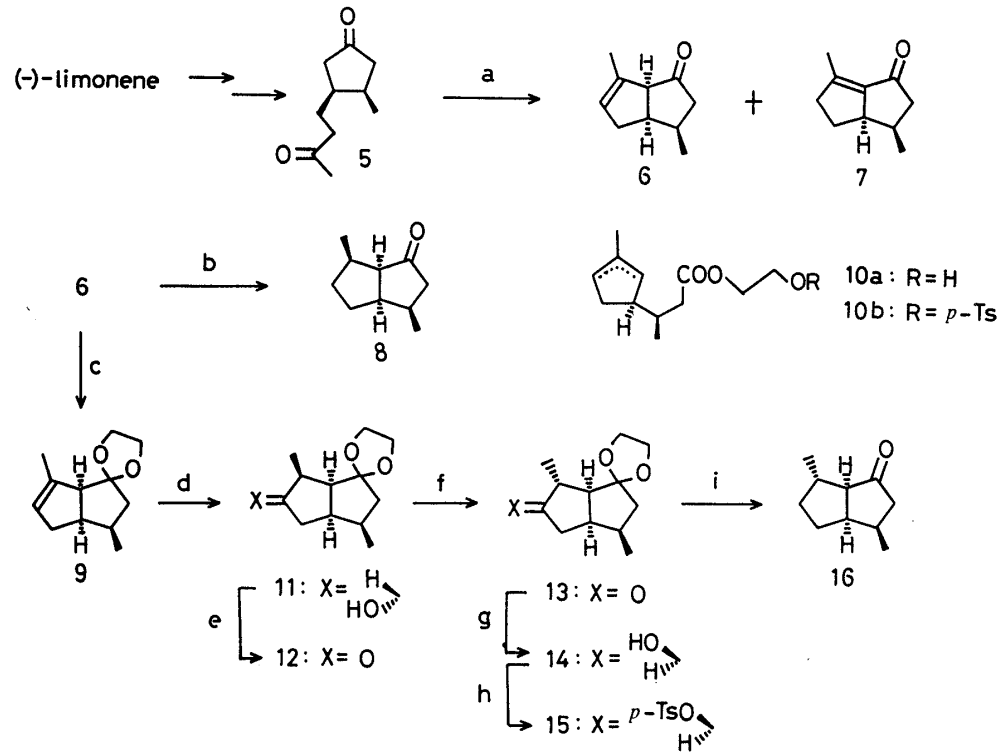
The designed sequence starts with cyclization of **5** to the bicyclo[3.3.0]octenone (**6**). Treatment of **5** with $KHSO_4$ in refluxing cyclohexane afforded **6** in 77% yield, accompanied with the isomer (**7**) in 2% yield. This reaction seems to proceed *via* the intramolecular aldol condensation of **5**, dehydration to **7**, and then deconjugation to **6**. In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **6**, the signals attributable to vinyl methyl and olefinic protons were observed at δ 1.76 (3H, s) and δ 5.37 (1H, m), respectively. In the ^{1}H-NMR spectrum of **7**, the signal of vinyl methyl protons was observed at δ 2.05 (3H, s), but no signal due to an olefinic proton could be observed. Catalytic hydrogenation of **6** with H_2/5% Pd–C in MeOH afforded the 8β-Me ketone (**8**) as a sole product in 77% yield. The configuration of the C_8-Me group was deduced to be β and *trans* relative to the hydrogen at the ring junction by taking the approach of the reagent from the convex site into consideration.

The 8α-Me ketone (**16**), required for the synthesis of compounds **2** and **4**, was prepared in the following manner. The carbonyl function in **6** was protected as the ethylene acetal in 92% yield by treatment with ethylene glycol and pyridinium *p*-toluenesulfonate (PPTS) in refluxing benzene. Interestingly, when boron trifluoride etherate or *p*-toluenesulfonic acid (*p*-TsOH) was used as a catalyst, one of the five-membered rings was cleaved to afford the cyclopentene derivatives (**10a**, **b**) in 83—85% yiled. Further details of this ring-cleavage reaction have been reported together with the results on the other ring systems.[9]

By hydroboration followed by treatment with alkaline hydroperoxide (NaOH/30% aq. H_2O_2), the ethylene acetal (**9**) was stereoselectively converted in 66% yield to the 7α-alcohol (**11**), which was submitted to Swern's oxidation to yield the 7-keto compound (**12**). The structure of **11** was determined as 7α-OH, 8β-Me by assuming the *cis*-addition of the reagent from the less hindered side of the double bond.

On treatment of **12** with potassium carbonate in MeOH, the C_8-position was epimerized to give the sterically more stable 8α-Me compound (**13**). However, it was found by monitoring this reaction process with thin layer chromatography (TLC) that the employed reaction conditions did not result in complete epimerization, even on prolongation of the reaction time. After chromatography of the crude products on silica gel, the recovered **12** was submitted to re-epimerization under the same reaction conditions. Thus, the pure **13** was obtained in 89% yield from **11**. This epimerization reaction also supported the stereochemistry at the C_8-position of **11**, **12** and **13**.

For removal of the carbonyl function in **13**, the following reactions were performed.



a) $KHSO_4$ b) H_2/5% Pd–C c) $HOCH_2CH_2OH$, PPTS d) i) $BH_3 \cdot THF$; ii) 30% H_2O_2, NaOH
e) $(COCl)_2$, DMSO f) K_2CO_3/MeOH g) $NaBH_4$/EtOH h) *p*-TsCl, Py i) i) $LiAlH_4$; ii) aq. HCl

Chart 3

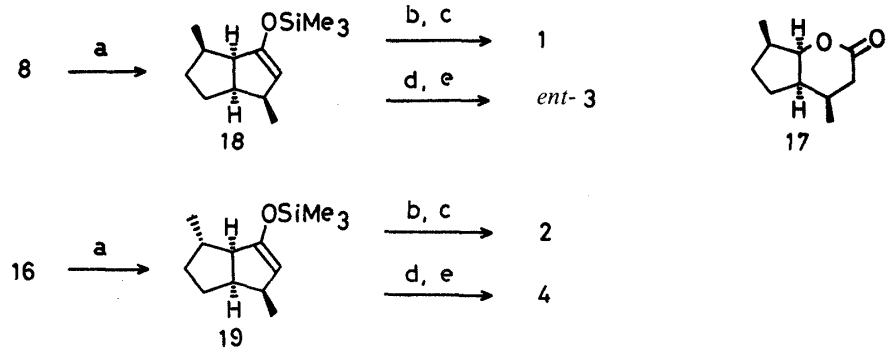
Reduction of **13** with $NaBH_4$ in EtOH at 0 °C afforded the 7β-alcohol (**14**) in 98% yield as a sole product. The structure of **14** was deduced by assuming the approach of the reagent from the convex site. Compound **14** was converted in 99% yield to the *p*-toluenesulfonate (**15**), which was subjected to reduction with $LiAlH_4$ in refluxing tetrahydrofuran (THF) followed by deacetalization to give the 8α-Me ketone (**16**) in 74% yield (Chart 3). For the same purpose, the alternative method *via* the *p*-toluenesulfonyl hydrazone of **13**, $NaBH_4$ reduction, and thermolysis resulted in the formation of a complex mixture.

Now, we could prepare the two diastereomeric ketones (**8** and **16**), which possess the desired stereochemistry for the synthesis of target molecules. The remaining problem was the regioselective cleavage of the C_2–C_3 bonds in **8** and **16**.

Preliminary Baeyer–Villiger oxidation of **8** with *m*-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 afforded the undesired C_1–C_2 bond oxidized product (**17**) in 40% yield. The structure of **17** was supported by the signal of C_1-H at δ4.54 (1H, dd, J=4, 4 Hz) in the ^{1}H-NMR spectrum.

Then, a sequence of reactions involving the silyl enol ether of the carbonyl function under kinetically controlled conditions followed by ozonolysis was performed.[10] Compounds **8** and **16** were treated with lithium diisopropylamide (LDA) and trimethylsilyl chloride in THF at −78 °C to yield the trimethylsilyl enol ethers (**18** and **19**) in 98% and 96% yields, respectively. The structures of **18** and **19** were supported by the signals of the olefinic C_3-H at δ4.45 (1H, m) in **18** and δ4.28 (1H, m) in **19** in the ^{1}H-NMR spectra, in addition to the absorption band at 1640 (C=C) cm^{-1} in the infrared (IR) spectra.

Ozonolysis of **18** and **19** in CH_2Cl_2 at −78 °C, followed by treatment with $NaBH_4$ and subsequent lactonization with *p*-TsOH afforded the targets **1** and **2** in 42% and 62% yields, respectively. The aldehyde-carboxylic acids obtained from the ozonides of **18** and **19** by reduction with dimethylsulfide could be converted to the enol lactones *ent*-**3** and **4** by refluxing



a) LDA, Me_3SiCl b) i) O_3; ii) $NaBH_4$ c) *p*-TsOH/CH_2Cl_2
d) i) O_3; ii) Me_2S e) *p*-TsOH/cyclohexane

Chart 4

in cyclohexane with *p*-TsOH in 44% and 52% yields, respectively (Chart 4).

The ^{1}H-NMR and IR spectra, and the specific rotations of **1**—**4** were identical with the reported values.[3c,6a,c]

Experimental

IR spectra were measured with a JASCO A-202 spectrometer. ^{1}H-NMR spectra were measured on a JEOL JNM-PS-100 spectrometer. Mass spectra (MS) were taken on a JEOL JMS-D 300 spectrometer. Specific rotations were measured on a JASCO DIP-4 polarimeter. For column chromatography, silica gel (Merck, Kieselgel 60, 70—230 mesh) was used. TLC was performed on Silica gel 60 F_{254} plates (Merck). All organic solvent extracts were washed with saturated brine and dried over anhydrous sodium sulfate.

(1*S*,4*R*,5*R*)-4,8-Dimethylbicyclo[3.3.0]oct-7-en-2-one (6)——A solution of **5** (4.26 g) in cyclohexane (200 ml) was refluxed in the presence of $KHSO_4$ (6.9 g) for 6 h with vigorous stirring. The $KHSO_4$ was filtered off and washed with ether (200 ml). The combined organic solution was washed with 5% aqueous $NaHCO_3$ and brine, then dried. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel (50 g). The fraction eluted with 1% AcOEt in hexane (v/v) afforded **6** (2.94 g, 77%) as a colorless oil. Then, the fraction eluted with 5% AcOEt in hexane (v/v) afforded **7** (90 mg, 2%) as a colorless oil. **6**: $[\alpha]_D^{17}$ −704° (*c*=0.103, $CHCl_3$). IR (neat): 1740, 1660, 1380, 1160 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.09 (3H, d, *J*=6 Hz, C_4-CH_3). 1.76 (3H, m, C_8-CH_3), 5.37 (1H, m, C_7-H). MS *m/z*: 150 (M^+), 107, 80. **7**: IR (neat): 1715, 1660, 1420, 1380 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, d, *J*=7.5 Hz, C_4-CH_3), 2.05 (3H, m, C_8-CH_3), 3.48 (1H, m, C_5-H).

(1*R*,4*R*,5*R*,8*R*)-4,8-Dimethylbicyclo[3.3.0]octan-2-one (8)——A solution of **6** (826 mg) in MeOH (20 ml) was hydrogenated in the presence of 5% Pd–C (500 mg) under an H_2 atmosphere for 2 h at room temperature. The catalyst was filtered off, and the filtrate was concentrated *in vacuo* to afford an oily residue, which was purified by column chromatography on silica gel (12 g). The fraction eluted with 1% AcOEt in hexane (v/v) afforded **8** (644 mg, 77%) as a colorless oil. $[\alpha]_D^{17}$ −243° (*c*=0.113, $CHCl_3$). IR (neat): 1740, 1455, 1380, 1160 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, d, *J*=7 Hz, C_8-CH_3), 1.10 (3H, d, *J*=6 Hz, C_4-CH_3), 1.56—2.82 (10H, m). MS *m/z*: 152 (M^+), 137, 123.

(1*S*,4*R*,5*R*)-4,8-Dimethyl-2,2-ethylenedioxybicyclo[3.3.0]oct-7-ene (9)——A solution of **6** (441 mg) and ethylene glycol (520 mg) in benzene (20 ml) was refluxed for 25 h in the presence of PPTS (150 mg) with azeotropic removal of H_2O. After removal of the solvent *in vacuo*, the residue was diluted with ether (200 ml), washed with brine, and dried. Removal of the solvent *in vacuo* afforded an oily residue, which was distilled under reduced pressure to afford **9** (523 mg, 92%) as a colorless oil. bp 80—90 °C (bath temp.)/1.00 mmHg. $[\alpha]_D^{24}$ −93.5° (*c*=0.955, $CHCl_3$). IR (neat): 1655, 1310, 1110, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, d, *J*=7 Hz, C_4-CH_3), 1.78 (3H, m, C_8-CH_3), 3.92 (4H, m, OCH_2CH_2O), 5.39 (1H, br s, C_7-H). MS *m/z*: 194 (M^+), 113, 99.

(1*S*,4*R*,5*R*,7*S*,8*S*)-4,8-Dimethyl-2,2-ethylenedioxy-7-hydroxybicyclo[3.3.0]octane (11)——Borane–THF complex (0.96 ml, 1.0 M solution in THF) was added to a stirred solution of **9** (198 mg) in THF (1 ml) at 0 °C. After 2 h, H_2O (0.1 ml), 3 N aqueous KOH (0.15 ml) and 30% H_2O_2 (0.25 ml) were successively added. After being stirred for 2 h at 0 °C, the reaction mixture was diluted with ether (100 ml) and washed with brine, then dried. After removal of the solvent *in vacuo*, the residue was purified by column chromatography on silica gel (3 g). The fraction eluted with 10% AcOEt in hexane (v/v) afforded **11** (143 mg, 66%) as colorless needles. mp 75—79 °C (hexane–ether). $[\alpha]_D^{26}$ +23.7° (*c*=1.14, $CHCl_3$). IR (nujol): 3400, 1285, 1110, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, d, *J*=6.5 Hz, C_4-CH_3), 1.12 (3H, d, *J*=7 Hz, C_8-CH_3), 3.82 (4H, s, OCH_2CH_2O), 3.88 (1H, m, C_7-H). MS *m/z*: 212 (M^+), 169, 113. *Anal.* Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.73; H, 9.58.

(1*S*,4*R*,5*R*,8*S*)-4,8-Dimethyl-2,2-ethylenedioxybicyclo[3.3.0]octan-7-one (13) and (1*S*,4*R*,5*R*,8*R*)-4,8-Dimethyl-2,2-ethylenedioxybicyclo[3.3.0]octan-7-one (12)——Dimethyl sulfoxide (DMSO) (0.9 ml) in CH_2Cl_2 (3 ml) was added to a stirred solution of oxalyl chloride (0.52 ml) in CH_2Cl_2 (15 ml) at −60 °C under an Ar atmosphere. After 5 min, **11** (1.11 g) in CH_2Cl_2 (5 ml) was added, and the whole was stirred for 15 min, then triethylamine (3.7 ml) was added at −60 °C. After 10 min, the reaction mixture was brought to room temperature, diluted with brine (25 ml), and then extracted with ether. The ether extract was successively washed with 1% aqueous HCl, 5% aqueous $NaHCO_3$, and brine, then dried. Removal of the solvent afforded crude **12** (1.09 g), which was dissolved in MeOH (50 ml). K_2CO_3 (51 mg) was added to the stirred solution at 0 °C. After 12 h, a solution of $(NH_4)_2SO_4$ (48 mg) in H_2O (10 ml) was added, and the MeOH was evaporated off *in vacuo*. The aqueous residue was extracted with ether, and the ether extract was dried. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel (12 g). The fraction eluted with 5% AcOEt in hexane (v/v) afforded pure **13** (884 mg) and a mixture (104 mg) of **12** and **13**. The latter was submitted to re-epimerization under the same reaction conditions. Thus, compound **13** (978 mg) was obtained as a colorless oil in 89% yield. $[\alpha]_D^{26}$ +11.4° (*c*=0.98, $CHCl_3$). IR (neat): 1740, 1270, 1110, 1080 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, d, *J*=7 Hz, C_4-CH_3), 1.10 (3H, d, *J*=6 Hz, C_8-CH_3), 3.89 (4H, m, OCH_2CH_2O). MS *m/z*: 210 (M^+), 195, 113.

An analytical sample of **12** was obtained as colorless needles by purification of crude **12** by column chromatography on silica gel. **12**: mp 79—83 °C (hexane–ether). $[\alpha]_D^{25}$ +123° (*c*=0.98, $CHCl_3$). IR (Nujol): 1735, 1280, 1110, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, d, *J*=7 Hz, C_4-CH_3), 1.14 (3H, d, *J*=6.5 Hz, C_8-CH_3), 3.82 (4H, m, OCH_2CH_2O). MS *m/z*: 210 (M^+), 195, 113. *Anal.* Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.67; H, 8.52.

(1*S*,4*R*,5*R*,7*R*,8*R*)-4,8-Dimethyl-2,2-ethylenedioxy-7-hydroxybicyclo[3.3.0]octane (14)——$NaBH_4$ (210 mg) was added portionwise to a stirred solution of **13** (884 mg) in EtOH (20 ml) at 0 °C. After 0.5 h, the reaction mixture was diluted with brine (20 ml), and the EtOH was evaporated off *in vacuo*. The aqueous residue was extracted with ether. The ether extract was washed and dried. Removal of the solvent *in vacuo* gave an oily residue, which was chromatographed on silica gel (15 g). The fraction eluted with 20% AcOEt in hexane (v/v) afforded **14** (882 mg, 98%) as a colorless oil. $[\alpha]_D^{27}$ −6.1° (*c*=0.985, $CHCl_3$). IR (neat): 3400, 1300, 1200, 1110, 1045 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, d, *J*=7 Hz, C_4-CH_3), 1.05 (3H, d, *J*=6 Hz, C_8-CH_3), 3.51 (1H, m, C_7-H), 3.86 (4H, m, OCH_2CH_2O). MS *m/z*: 212 (M^+), 169, 113.

(1*S*,4*R*,5*R*,7*R*,8*R*)-4,8-Dimethyl-2,2-ethylenedioxy-7-*p*-toluenesulfonyloxybicyclo[3.3.0]octane (15)——*p*-TsCl (358 mg) was added to a stirred solution of **14** (300 mg) in pyridine (1 ml) at 0 °C. After being stirred for 13 h at room temperature, the reaction mixture was poured into ice-water (20 ml), and extracted with AcOEt. The AcOEt extract was successively washed with 1% aqueous HCl, 5% aqueous $NaHCO_3$, and brine, then dried. Removal of the solvent *in vacuo* gave a colorless solid, which was chromatographed on silica gel (6 g). The fraction eluted with 10% AcOEt in hexane (v/v) afforded **15** as colorless needles. mp 101—104 °C (hexane–AcOEt). $[\alpha]_D^{23}$ −33.9° (*c*=0.905, $CHCl_3$). IR (Nujol): 1600, 1355, 1180, 1060 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.87, 0.88 (3H each, d, *J*=6.5, 7 Hz, C_4- and C_8-CH_3), 2.45 (3H, s, aromatic CH_3), 3.83 (4H, m, OCH_2CH_2O), 4.16 (1H, m, C_7-H), 7.32, 7.79 (2H each, d, *J*=8 Hz, aromatic H). MS *m/z*: 366 (M^+), 351, 211, 194. *Anal.* Calcd for $C_{19}H_{26}O_5S$: C, 62.28; H, 7.15. Found: C, 62.21; H, 7.08.

(1*R*,4*R*,5*R*,8*S*)-4,8-Dimethylbicyclo[3.3.0]octan-2-one (16)——A solution of **15** (472 mg) in THF (2 ml) was added dropwise to a refluxing suspension of $LiAlH_4$ (213 mg) in THF (10 ml). After 2 h, the reaction mixture was cooled to 0 °C, and acidified with 10% aqueous HCl (10 ml). The whole was stirred at room temperature for 8 h, then extracted with ether. The ether extract was washed with 5% aqueous $NaHCO_3$, and brine, then dried. Removal of the solvent *in vacuo* gave an oily residue, which was chromatographed on silica gel (8 g). Distillation of the fraction eluted with 5% ether in pentane (v/v) afforded **16** (146 mg, 74%) as a colorless oil. bp 70—80 °C (bath temp.)/1.0 mmHg. $[\alpha]_D^{21}$ −183° (*c*=0.244, $CHCl_3$). IR (neat): 1740, 1380, 1350, 1250, 1160 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.09, 1.12 (3H each, d, *J*=6.5, 7 Hz, C_4- and C_8-CH_3), 1.10—2.80 (10H, m). MS *m/z*: 152 (M^+), 137, 123, 110.

Baeyer–Villiger Reaction of 8——MCPBA (340 mg) was added to a stirred solution of **8** (180 mg) in CH_2Cl_2 (5 ml) at room temperature. After 5 h, the reaction mixture was diluted with CH_2Cl_2 (30 ml), and washed with 5% $NaHCO_3$, and brine, then dried. Removal of the solvent *in vacuo* gave an oily residue, which was chromatographed on silica gel (5 g). The fraction eluted with 5% AcOEt in hexane (v/v) afforded **17** (80 mg, 40%) as a colorless oil. IR (CCl_4): 1745, 1450, 1245, 1080 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.93, 1.10 (3H each, d, *J*=6.5 Hz, C_5- and C_9-CH_3), 4.54 (1H, dd, *J*=4, 4 Hz, C_1-H). MS *m/z*: 168 (M^+), 153, 140.

(1*R*,4*S*,5*R*,8*R*)-4,8-Dimethyl-2-trimethylsilyloxybicyclo[3.3.0]oct-2-ene (18) and (1*R*,4*S*,5*R*,8*S*)-4,8-Dimethyl-2-trimethylsilyloxybicyclo[3.3.0]oct-2-ene (19)——Butyl lithium (1.3 ml of 1.2 M solution in hexane) was added dropwise to a solution of diisopropylamine (0.24 ml) in THF (3 ml) at −78 °C under an Ar atmosphere. The reaction mixture was stirred for 20 min at −78 °C, and for 15 min at 0 °C, then cooled to −78 °C. Trimethylsilyl chloride (1.0 ml) in THF (2 ml) and **8** (197 mg) in THF (4 ml) were successively added at −78 °C. The whole was stirred for 15 min, then triethylamine (2 ml) was added. Stirring was continued for 20 min, and the reaction mixture was diluted with pentane (150 ml). The organic solution was washed with water (20 ml), then dried. Removal of the solvent *in vacuo* gave an oily residue, which was distilled under reduced pressure to afford **18** (287 mg, 98%) as a colorless oil. bp 85—90 °C (bath temp.)/1.2 mmHg. IR (neat): 3050, 1640, 1260 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.19 (9H, s, $OSi(CH_3)_3$),

0.92, 1.11 (3H each, d, $J=6.5$, 7 Hz, C_4- and C_8-CH_3), 4.45 (1H, m, C_3-H).

In a similar manner, **16** (217 mg) afforded **19** (312 mg, 96%) as a colorless oil. IR (neat): 3050, 1640, 1260 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.19 (9H, s, $OSi(CH_3)_3$), 0.93, 1.00 (3H each, d, $J=6.5$ Hz, C_4- and C_8-CH_3), 4.28 (1H, m, C_3-H).

***cis,cis*-Dihydronepetalactone (1) and Dihydronepetalactone (2)**——Ozone gas[11] was bubbled into a solution of **18** (287 mg) in a mixture of MeOH (10 ml) and CH_2Cl_2 (2 ml) at -78 °C until a blue solution was obtained. The resulting ozonide was decomposed with $NaBH_4$ (212 mg) at -78 °C. The mixture was stirred for 1 h, $NaBH_4$ (100 mg) was added, and then stirring was continued for 20 min at 0 °C. After removal of the solvent *in vacuo*, the residue was diluted with 10% aqueous HCl, then extracted with ether. The ether extract was dried. After removal of the solvent, the residue was dissolved in CH_2Cl_2 (2 ml), and this solution was stirred for 16 h at room temperature in the presence of *p*-TsOH·H_2O (30 mg). The reaction mixture was diluted with ether, and successively washed with 5% aqueous $NaHCO_3$, and brine, then dried. Removal of the solvent *in vacuo* gave an oily residue, which was chromatographed on silica gel (3 g). The fraction eluted with 10% AcOEt in hexane (v/v) afforded **1** (92 mg, 42%) as a colorless oil. $[\alpha]_D^{22}$ -21.1 ° ($c=1.20$, $CHCl_3$) (reported value: -15.6 °).[6a] IR (neat): 1725, 1380, 1200, 1105, 1050 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, d, $J=7.5$ Hz, C_5-CH_3), 0.98 (3H, d, $J=6$ Hz, C_9-CH_3), 3.11 (1H, dd, $J=9$, 10 Hz, C_1-H), 4.01, 4.02 (1H each, d, $J=7$, 8 Hz, C_4-H). MS *m/z*: 168 (M^+), 126, 113. High-MS for $C_{10}H_{16}O_2$ (M^+): Calcd *m/z* 168.1150. Found 168.1138.

Similar treatment of **19** (190 mg) gave **2** (91 mg, 62%) as a colorless oil. $[\alpha]_D^{17}$ $+58.3$ ° ($c=1.03$, CCl_4) (reported value: $+66.2$ °).[6c] IR (neat): 1730, 1380, 1250, 1210, 1110, 1060 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, d, $J=7$ Hz, C_5-CH_3), 1.19 (3H, d, $J=7$ Hz, C_9-CH_3), 4.04, 4.05 (1H each, d, $J=6$, 9 Hz, C_4-H). MS *m/z*: 168 (M^+), 153, 125, 113. High-MS for $C_{10}H_{16}O_2$ (M^+): Calcd *m/z* 168.1150. Found 168.1154.

***ent-cis,cis*-Nepetalactone (*ent*-3) and Nepetalactone (4)**——Ozone gas was bubbled into a solution of **18** (445 mg) in a mixture of MeOH (15 ml) and CH_2Cl_2 (3 ml) at -78 °C until a blue solution was obtained. The resulting ozonide was decomposed with dimethyl sulfide (1 ml). After 0.5 h at -78 °C, the reaction mixture was stirred at room temperature for 3 h. Removal of the solvent *in vacuo* gave an oily residue, which was chromatographed on silica gel (5 g). The fraction eluted with 20% AcOEt in hexane (v/v) afforded the crude aldehyde-carboxylic acid (266 mg), which was dissolved in cyclohexane (60 ml). The solution was refluxed for 6 h in the presence of *p*-TsOH·H_2O (120 mg). The reaction mixture was diluted with ether, and successively washed with 5% aqueous $NaHCO_3$ and brine, then dried. Removal of the solvent *in vacuo* gave an oily residue, which was chromatographed on silica gel (6 g). The fraction eluted with 2—4% AcOEt in hexane (v/v) afforded *ent*-**3** (141 mg, 59%) as a colorless oil. $[\alpha]_D^{21}$ -77.6 ° ($c=1.34$, $CHCl_3$) (reported value of **3**: $+81.0$ °).[3b] IR (neat): 1755, 1685, 1340, 1125, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.99 (3H, d, $J=7$ Hz, C_9-CH_3), 1.60 (3H, m, C_5-CH_3), 3.10 (1H, dd, $J=9.5$, 9.5 Hz, C_1-H), 6.17 (1H, m, C_4-H). MS *m/z*: 166 (M^+), 151, 138, 123. High-MS for $C_{10}H_{14}O_2$ (M^+): Calcd *m/z* 166.0994. Found 166.0993.

Similar treatment of **19** (178 mg) gave **4** (68 mg, 52%) as a colorless oil. $[\alpha]_D^{20}$ $+2.7$ ° ($c=2.0$, $CHCl_3$) (reported value: $+3.7$ °).[3b] IR (neat): 1755, 1690, 1340, 1205, 1130 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, d, $J=7$ Hz, C_9-CH_3), 1.64 (3H, m, C_5-CH_3), 6.17 (1H, m, C_4-H). MS *m/z*: 166 (M^+), 151, 138, 123. High-MS for $C_{10}H_{14}O_2$ (M^+): Calcd *m/z* 166.0994. Found 166.0998.

References and Notes

1) T. Sakan, F. Murai, S. Isoe, S. B. Hyeon, and Y. Hayashi, *Nippon Kagaku Zasshi*, **90**, 507 (1969).
2) T. Sakan, S. Isoe, S. B. Hyeon, R. Katsumura, T. Maeda, J. Wolinsky, D. Dickerson, M. Slabaugh, and D. Nelson, *Tetrahedron Lett.*, **1965**, 4097.
3) *a*) F. E. Regnier, G. R. Waller, and E. J. Eisenbraun, *Phytochemistry*, **6**, 1281 (1967); *b*) E. J. Eisenbraun, C. E. Brown, R. L. Irvin-Willis, D. J. McGurk, E. L. Eliel, and D. L. Harris, *J. Org. Chem.*, **45**, 3811 (1980).
4) *a*) J. Meinwald, *J. Am. Chem. Soc.*, **76**, 4571 (1954); *b*) S. M. McElvain and E. J. Eisenbraun, *ibid.*, **77**, 1599 (1955).
5) G. W. Dawson, D. C. Griffiths, N. F. Janes, A. Mudd, J. A. Pickett, L. G. Wadhams, and C. M. Woodcock, *Nature* (London), **325**, 614 (1987).
6) *a*) J. Wolinsky and E. J. Eustace, *J. Org. Chem.*, **37**, 3376 (1972); *b*) I. Fleming and N. K. Terrett, *Tetrahedron Lett.*, **25**, 5103 (1984); *c*) J. Wolinsky and D. Nelson, *Tetrahedron*, **25**, 3767 (1969); *d*) R. Trave, A. Marchesini, and G. Luisa, *Gazz. Chim. Ital.*, **98**, 1132 (1968).
7) K. Sakai, Y. Ishiguro, K. Funakoshi, K. Ueno, and H. Suemune, *Tetrahedron Lett.*, **25**, 961 (1984).
8) H. Suemune, H. Maruoka, S. Saeki, and K. Sakai, *Chem. Pharm. Bull.*, **34**, 4629 (1986).
9) H. Suemune, K. Oda, and K. Sakai, *Tetrahedron Lett.*, **28**, 3373 (1987).
10) R. D. Clark and C. H. Heathcock, *J. Org. Chem.*, **41**, 1396 (1976).
11) An Ishii ozone generator was used for O_3 oxidation.