Note

Total Synthesis of ($\pm$)-
Dihydronepetalactone

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The cyclopropane derivatives are one of the most attractive starting materials for synthesizing iridoid monoterpenes.¹⁾ We have previously reported the synthesis of dehydroiridodiols,^{1b)} plinolins^{1c)} and hop ether^{1e)} starting from methyl 2-oxo-6-*endo*-methylbicyclo[3.1.0]hexane-1-carboxylate (**1**), using stereoselective cleavage of the cyclopropane ring as the key step. In this paper, we report the stereoselective synthesis of ($\pm$)-dihydronepetalactone (**2**),^{2,3)} a physiologically active component for Felidae animals that was isolated from the leaves and galls of *Actinidia polygama* Mig. and from the essential oil of *Nepeta catraria*.

Bicyclo[3.1.0]hexane derivative **1** was treated with sodium cyanide in dimethyl sulfoxide at 70°C for 2 hr under a nitrogen atmosphere to give desired nitrile **3** in an 89% yield.^{1b)} Nitrile **3** was reduced with sodium borohydride in ethanol at 0°C to provide an alcohol, which was treated with methanesulfonyl chloride and triethylamine in dichloromethane at 0°C to give a methanesulfonate. The obtained methanesulfonate was transformed into unsaturated ester **4** in a 49% yield (in 3 steps) by treating with 1,8-diazabicyclo[5.4.0]-7-undecene in benzene at room temperature. Reduction of **4** with excess diisobutylaluminum hydride in toluene at room temperature and subsequent hydrolysis afforded the hemiacetal, which

was reduced with lithium aluminium hydride in ether at 0°C to provide diol **5** in a 23% yield (in 2 steps). Diol **5** was converted to α,β -unsaturated lactone **6**,^{3b)} a known precursor of dihydronepetalactone (**2**), in a 75% yield by oxidizing with manganese dioxide in dichloromethane at room temperature. The ¹H-NMR spectrum of **6** was in agreement with the values reported in the literature.^{3b)} Finally, upon treating with lithium dimethylcuprate at -10°C in ether under a nitrogen atmosphere, unsaturated lactone **6** afforded an 81% yield of ($\pm$)-dihydronepetalactone (**2**).

In addition, because enantiomeric isomers of cyclopropane **1** were readily obtained from the corresponding *l*-menthyl ester by chromatographic separation and an ester-exchange reaction,^{1b)} optically active dihydronepetalactone (**2**) can be synthesized by our process.

Experimental

Melting points (mp) are uncorrected. Infrared (IR) spectra were measured with a Hitachi 260-10 IR spectrometer in a chloroform solution. ¹H-NMR spectra were obtained from Hitachi R-600L (60 MHz) and JEOL JNM-GX 270 (270 MHz) NMR spectrometers, using tetramethylsilane as an internal standard. ¹³C-NMR spectra were obtained from a JEOL JNM-GX 270 (67.5 MHz) NMR spectrometer, and mass spectra were taken by a JEOL JMS-AX 500 mass spectrometer.

Methyl 2-(1-cyanoethyl)-5-oxocyclopentane-1-carboxylate (**3**). Cyclopropane derivative **1** (2.0 g, 11.9 mmol) was dissolved in freshly distilled dimethyl sulfoxide (40 ml) under a nitrogen atmosphere. To this solution was added sodium cyanide (710 mg, 13.1 mmol), and the reaction mixture was heated at 70°C for 2 hr before being cooled to room temperature. The reaction mixture was quenched with a 50% aqueous solution of acetic acid (30 ml) and extracted with benzene. The organic layer was washed with a saturated sodium carbonate solution and dried over magnesium sulfate. The solvent was removed *in vacuo*, and

Scheme 1. Reagents and Conditions

(a) NaCN, DMSO, 70°C; (b) NaBH₄, EtOH, 0°C; (c) MsCl, Et₃N, CH₂Cl₂, 0°C; (d) DBU, C₆H₆, rt; (e) DIBAL, PhMe, rt; (f) LiAlH₄, Et₂O, 0°C; (g) MnO₂, CH₂Cl₂, rt; (h) Me₂CuLi, Et₂O, -10°C.

the residue was purified by column chromatography on silica gel (eluting with 30% ethyl acetate in hexane) to provide cyanide **3** (2.1 g, 89%) as a colorless oil. IR $\nu_{\max}$ cm^{-1} : 2960, 2245, 1760, 1728, 1667, 1620, 1445, 1247, 1120, 998; $^1\text{H-NMR}$ δ (CDCl_3): 1.40 (3H, d, $J=7.0$ Hz), 3.14 (1H, d, $J=11.9$ Hz), 3.80 (3H, s); $^{13}\text{C-NMR}$ δ (CDCl_3): 16.0, 23.2, 29.1, 37.7, 42.9, 52.7, 59.0, 120.1, 168.4, 208.3; MS m/z (rel. intensity, %): 195 (M^+ , 5), 164 (8), 141 (51), 109 (100), 81 (17), 53 (33); HR-MS: found, m/z 195.0885 (M^+); calcd. for $\text{C}_{10}\text{H}_{13}\text{NO}_3$, 195.0886.

Methyl 5-(1-cyanoethyl)-1-cyclopentenecarboxylate (4). Keto ester **3** (320 mg, 1.66 mmol) was dissolved in absolute ethanol (6 ml), and the solution was cooled to 0°C . After adding sodium borohydride (0.13 g, 3.32 mmol), the reaction mixture was stirred at 0°C for 30 min. The solvent was then removed *in vacuo*, the residue being taken up in dichloromethane, and the resulting solution was acidified with 2 N hydrochloric acid. The layers were separated, the aqueous layer was extracted with dichloromethane, and the combined organic layer was dried over magnesium sulfate. The solvent was removed *in vacuo* to give a crude alcohol, which was used without being purified in the next step. IR $\nu_{\max}$ cm^{-1} : 3490, 2950, 2240, 1724, 1441, 1388, 1181.

The crude alcohol was dissolved in dry dichloromethane (5 ml) and cooled to 0°C . To this mixture was added triethylamine (150 mg, 1.52 mmol) and then methanesulfonyl chloride (170 mg, 1.52 mmol), and the reaction mixture was stirred for 1 hr at 0°C . The reaction was quenched with a saturated aqueous solution of sodium hydrogen carbonate, extracted with dichloromethane, dried over magnesium sulfate and concentrated. The obtained crude methanesulfonate was used without being purified in the next step. $^1\text{H-NMR}$ δ (CDCl_3): 2.98, 3.06 (total 3H, each s).

A solution of this crude methanesulfonate and 1,8-diazabicyclo[5.4.0]-7-undecene (290 mg, 1.89 mmol) in dry benzene (4 ml) was stirred at room temperature for 1 hr. The mixture was washed with water, dried over magnesium sulfate and evaporated to give a crude product, which was purified by column chromatography on silica gel (eluting with 20% ethyl acetate in hexane) to give unsaturated ester **4** (145 mg, 49%, in 3 steps) as a colorless liquid. IR $\nu_{\max}$ cm^{-1} : 2960, 2240, 1705, 1629, 1443, 1362, 1303, 1109; $^1\text{H-NMR}$ δ (CDCl_3): 1.35 (3H, d, $J=7.3$ Hz), 1.93–3.08 (5H, m), 3.46 (1H, dq, $J=3.7, 7.3$ Hz), 3.76 (3H, s), 6.98–7.01 (1H, m); $^{13}\text{C-NMR}$ δ (CDCl_3): 16.7, 25.4, 28.7, 32.0, 47.8, 51.4, 121.5, 135.2, 147.3, 164.7; MS m/z (%): 179 (M^+ , 2), 148 (8), 125 (70), 97 (39), 93 (73), 79 (33), 65 (100), 59 (78), 53 (40); HR-MS: found, m/z 179.0984 (M^+); calcd. for $\text{C}_{10}\text{H}_{13}\text{NO}_2$, 179.0946.

2-(Hydroxymethyl)- β -methyl-2-cyclopentene-ethanol (5). To a stirred solution of nitrile **4** (120 mg, 0.67 mmol) in dry toluene (2.5 ml) was added diisobutylaluminum hydride (a 1.5 M solution in toluene, 4.5 ml, 6.7 mmol) at 0°C . After being stirred for 2 hr at room temperature, the

reaction mixture was quenched with a saturated aqueous solution of ammonium chloride. The reaction mixture was acidified with 10% aqueous hydrochloric acid to pH 5 and stirred at room temperature for 1 hr. The mixture was then diluted with ether, washed with a saturated aqueous sodium bicarbonate solution, and dried over magnesium sulfate. The solvent was removed *in vacuo* to give a crude hemiacetal, which was used without being purified in the next reaction. IR $\nu_{\max}$ cm^{-1} : 3380, 2960, 1630, 1468, 1385, 1025.

To a stirred solution of lithium aluminium hydride (25 mg, 0.67 mmol) in dry ether (2 ml) was added dropwise this crude hemiacetal in ether (1 ml) at 0°C , and the reaction mixture was stirred at room temperature for 1 hr. The excess hydride was quenched by the dropwise addition of water. Finally, a saturated aqueous solution of ammonium chloride was added, and the two layers were separated. The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo*. The residual oil was purified by preparative TLC (eluting with 50% ethyl acetate in hexane) to give diol **5** (24.4 mg, 23%, in 2 steps) as colorless liquid. IR $\nu_{\max}$ cm^{-1} : 3350, 2930, 1635, 1460, 1375, 1080, 1025, 812; $^1\text{H-NMR}$ δ (CDCl_3): 0.69 (3H, d, $J=6.7$ Hz), 1.57–2.32 (6H, m), 3.39–3.53 (2H, m), 3.89 (2H, 2 br. s), 4.06–4.19 (2H, m), 5.66 (1H, br. s); $^{13}\text{C-NMR}$ δ (CDCl_3): 10.5, 23.1, 31.4, 35.9, 44.5, 59.9, 66.6, 127.3, 144.9; MS m/z (%): 156 (M^+ , 2), 138 (12), 107 (69), 97 (64), 79 (100), 67 (77), 55 (35); HR-MS: found, m/z 156.1038 (M^+); calcd. for $\text{C}_9\text{H}_{16}\text{O}_2$, 156.1150. Di-benzoate mp 122 – 123°C , colorless prisms. Anal. Found: C, 75.95; H, 6.82%. Calcd. for $\text{C}_{23}\text{H}_{24}\text{O}_4$: C, 75.80; H, 6.64%.

5-Methyl-3-oxabicyclo[4.3.0]non-9-en-2-one (6). To a solution of alcohol **5** (24 mg, 0.15 mmol) in dry dichloromethane (1 ml) was added manganese dioxide (39 mg, 0.45 mmol). The resulting mixture was stirred at room temperature for 3 hr and then filtered through a pad of Florisil. The solvent was removed under reduced pressure to give a crude product. Preparative TLC (eluting with 50% ethyl acetate in hexane) provided unsaturated lactone **6** (17 mg, 75%) as a colorless liquid. IR $\nu_{\max}$ cm^{-1} : 2965, 1707, 1631, 1401, 1382, 1254, 1169, 1118, 1028, 987, 917; $^1\text{H-NMR}$ δ (CDCl_3): 0.97 (3H, d, $J=7.3$ Hz), 1.70–3.30 (6H, m), 4.24 (1H, dd, $J=2.0, 11.1$ Hz), 4.41 (1H, dd, $J=2.6, 11.1$ Hz), 6.94–7.13 (1H, m); $^{13}\text{C-NMR}$ δ (CDCl_3): 10.8, 27.8, 30.0, 31.8, 45.9, 75.7, 132.5, 146.4, 163.5; MS m/z (%): 152 (M^+ , 20), 122 (20), 108 (11), 93 (50), 79 (100), 66 (53), 51 (11); HR-MS: found, m/z 152.0770 (M^+); calcd. for $\text{C}_9\text{H}_{12}\text{O}_2$, 152.0837.

($\pm$)-Dihydronepetalactone (2). Methyl-lithium in ether (a 1.6 M solution in ether, 0.37 ml, 0.59 mmol) was added to a suspension of cuprous iodide (56 mg, 0.30 mmol) in dry ether (3 ml) at -10°C . A solution of **6** (15 mg, 0.10 mmol) in ether (0.5 ml) was added dropwise with

stirring, and stirring was continued for 2 hr at -10°C . After having been quenched with a 10% aqueous solution of acetic acid (3 ml), the mixture was added to water and extracted with ether. Removal of the solvent from the dried (magnesium sulfate) mixture afforded a crude product, which was purified by preparative TLC (eluting with 30% ethyl acetate in hexane) to give (±)-dihydronepetalactone (**2**: 13 mg, 81%) as a colorless liquid. IR ν_{max} cm^{-1} : 2970, 1725, 1465, 1385, 1331, 1187, 1101, 1058; $^1\text{H-NMR}$ δ (CDCl_3): 1.00 (3H, d, $J=6.7$ Hz), 1.21 (3H, d, $J=6.4$ Hz), 1.10–2.40 (8H, m), 3.88 (1H, t, $J=10.7$ Hz), 4.16 (1H, dd, $J=3.5, 10.7$ Hz); $^{13}\text{C-NMR}$ δ (CDCl_3): 15.7, 20.3, 31.8, 34.4, 35.2, 38.8, 44.7, 49.0, 72.9, 175.0; MS m/z (%): 168 (M^+ , 9), 153 (40), 139 (3), 126 (17), 113 (94), 100 (7), 95 (24), 81 (100), 67 (70), 55 (29); HR-MS: found, m/z 168.1133 (M^+); calcd. for $\text{C}_{10}\text{H}_{16}\text{O}_2$, 168.1151.

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