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Reduction of Bicyclo[3.3.1]Nonane-2,8-Diones with Baker's Yeast†

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Abstract—Reduction of bicyclo[3.3.1]nonane-2,8-dione (**1**) and its homologues **2** and **3** with baker's yeast affords (1*R*,5*S*,8*S*)-8-hydroxybicyclo[3.3.1]nonan-2-one (**4**) and its higher homologues **5** and **6** with *ca* 97 % *e.e.* in 72–86 % yields. The absolute configuration of **5** was confirmed by the X-ray crystallographic analysis of its camphanic ester **22**.

Introduction

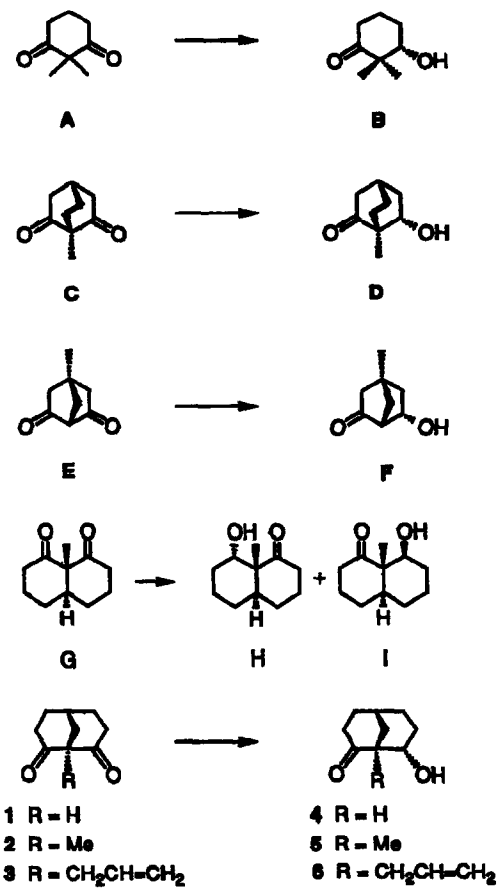
The most popular biocatalyst for asymmetric reduction is baker's yeast, *Saccharomyces cerevisiae*, as reviewed recently.[2–4] Our ongoing efforts to provide useful chiral non-racemic building blocks[5] includes reduction of prochiral diketones with baker's yeast. We have already reported the reduction of prochiral diketones such as **A**, **C**, **E** and **G** to give optically active hydroxyketones **B**,[6] **D**,[7] **F**,[8] **H**,[1] and **I**[1] (Scheme I). This paper describes the reduction of prochiral and bridged diketones **1**, **2** and **3** to give hydroxy ketones **4**, **5** and **6**. These bridged ketols may be useful in enantioselective terpene syntheses.

Results and Discussion

Preparation of the prochiral diketones 1–3

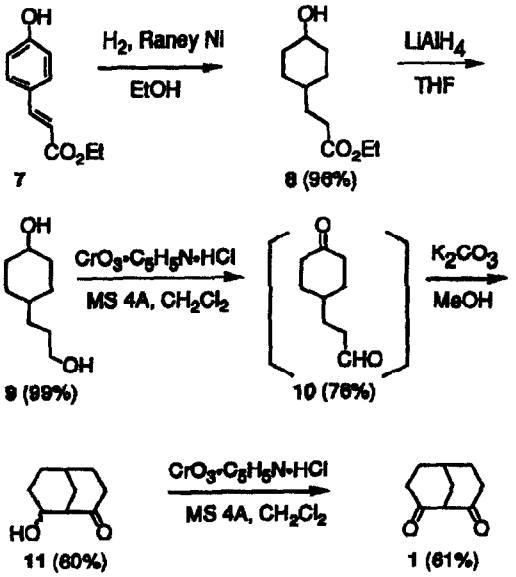
Bicyclo[3.3.1]nonane-2,8-dione (**1**) was synthesized from ethyl *p*-hydroxycinnamate (**7**) in a straightforward manner as shown in Scheme II. Catalytic hydrogenation of **7** over Raney nickel gave a saturated hydroxy ester **8**, which was reduced with lithium aluminum hydride to afford diol **9**. The crude keto aldehyde **10** obtained by oxidation of **9** with pyridinium chlorochromate (PCC) was treated with potassium carbonate in methanol to effect an aldol reaction giving **11**. Finally, PCC oxidation of **11** furnished crystalline diketone **1**. The overall yield of **1** was 26 % based on **7** in 5 steps.

Scheme III summarizes the synthesis of 1-methyl- and 1-allylbicyclo[3.3.1]nonane-2,8-diones (**2** and **3**). Oxidation of the hydroxy ester **8** with Jones' reagent yielded **12**, whose pyrrolidine enamine **13** was methylated or allylated to give **14** or **15**. Reduction of **14** or **15** with lithium aluminum hydride afforded **16** or **17**. PCC Oxidation of **16** or **17** to furnish **18** or **19** was followed by aldol reaction to give hydroxy ketone **20** or **21**. The desired crystalline diketones **2** and **3** were obtained by PCC oxidation of **20** and **21**, respectively. The overall yield of **2** from ethyl *p*-hydroxycinnamate (**7**) was 14 % (8 steps), while that of **3** was 27 % (8 steps) based on **7**.

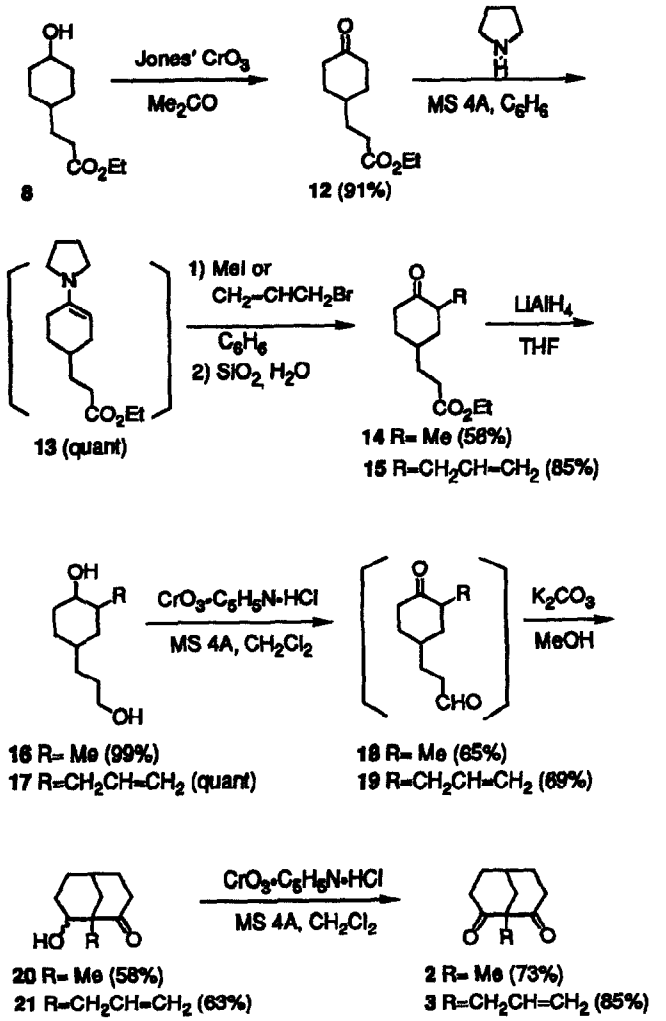


Scheme I. Reduction of prochiral diketones with baker's yeast.

†Dedicated to Professor J. Bryan Jones in honor of his 60th birthday.
Preparative Bioorganic Chemistry, Part 18. For Part 17, see Ref 1.



Scheme II. Synthesis of bicyclo[3.3.1]nonane-2,8-dione (1).



Scheme III. Synthesis of 1-methyl- and 1-allylbicyclo[3.3.1]nonane-2,8-diones (2 and 3).

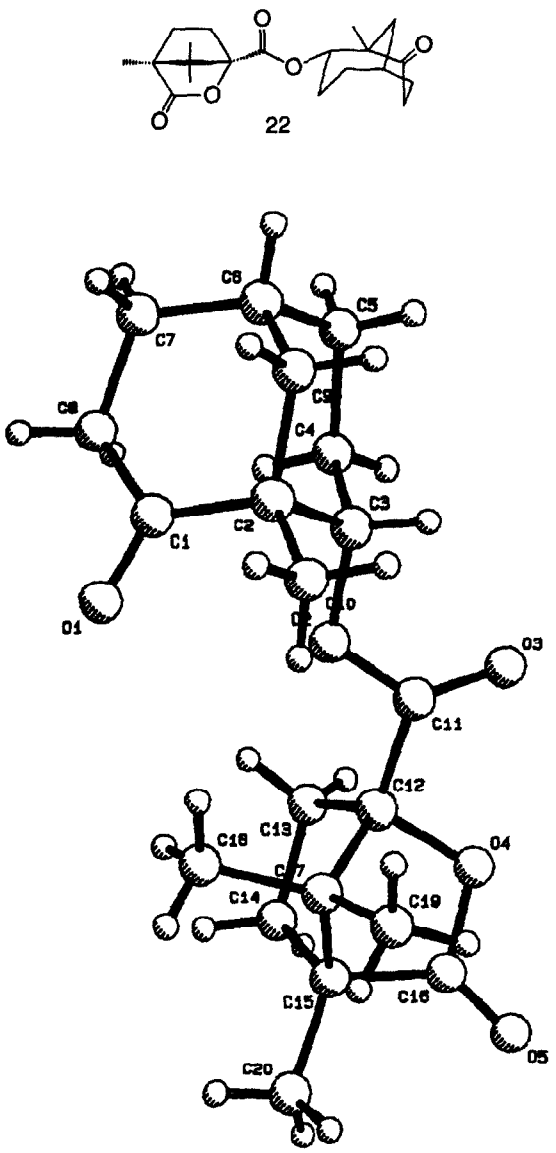


Figure 1. The Perspective view of **22**. Selected bond lengths [pm], bond angles [°] and torsion angles [°] with their e.s.d.'s in parentheses: O(1)–C(1) 119.2(9); C(1)–C(2) 150(1); C(1)–C(8) 152(2); C(2)–C(3) 153(1); C(2)–C(9) 156(1); C(3)–C(4) 150(1); O(2)–C(3) 146.2(8); C(2)–C(1)–C(8) 119.1(8); C(1)–C(2)–(3) 111.4(7); C(2)–C(3)–C(4) 115.4(7); C(3)–O(2)–C(11) 116.9(5); O(2)–C(3)–C(2)–C(1) –57.1(9); O(2)–C(11)–C(12)–O(4) –176.9(6); O(5)–C(16)–C(15)–C(20) 17(1).

Yeast reduction of the diketones 1–3 to hydroxy ketones 4–6

To briskly fermenting baker's yeast in an aqueous solution of sucrose, the diketone **1** in 95 % ethanol and a 0.2 % aqueous solution of Triton X-100 were added, and the mixture was shaken at 30 °C for 2.5 h. The product was isolated by extraction in 72 % yield, and found to be the crystalline ketol **4** with an equatorially oriented hydroxy group as revealed by its IR (ν_{O-H} = 3,520 cm^{-1}) and ^{1}H-NMR (δ = 3.60–3.98, $W_{1/2}$ = 20 Hz, CH_{ax}OH) spectra. At this stage, the absolute configuration of the ketol as depicted in **4** was assumed on the basis of the known enantioselectivity of the yeast reduction of prochiral

ketones to give (*S*)-alcohols.[2–4] Similarly, the diketones **2** and **3** were also reduced with baker's yeast to give ketols **5** and **6** in 86 and 72 % yield, respectively. The enantiomeric purities of **4**, **5** and **6** were estimated by the 300 MHz ^{1}H-NMR analysis of the corresponding (*S*)-α-methoxy-α-trifluoromethylphenylacetates (MTPA esters),[9] and found to be 97 % *e.e.* in each case.

The absolute configuration of the ketols **4–6** was determined in the following manner. Treatment of **5** with (–)-camphanic chloride gave its camphanic ester **22** as crystals. The structure of **22** was solved by a single-crystal X-ray analysis. The perspective view of **22** and its selected structural parameters are given in Figure 1. The perspective view of **22** clearly indicates that the ketol **5** possesses (1*R*,5*S*,8*S*)-stereochemistry as expected. In addition, the ORD measurements of **4**, **5** and **6** revealed all of them to exhibit positive Cotton effects at 308–315 nm, supporting their common (1*R*,5*S*,8*S*)-stereochemistry. It should be added that the application of the octant rule[10] to the structures **4–6** predicts positive Cotton effects in their ORD spectra.

In conclusion, three new chiral and non-racemic building blocks **4–6** were prepared by the yeast reduction of **1–3**. The use of the ketols **4–6** in terpene syntheses will be reported in due course.

Experimental Section

All mps and bps are uncorrected. ^{1}H-NMR spectra were recorded with $CDCl_3$ or TMS as an internal standard at 90 MHz on a Jeol JNM EX-90 spectrometer or at 300 MHz on a Bruker AC-300 spectrometer. ^{13}C-NMR spectra were recorded with $CDCl_3$ as an internal standard at 22.4 MHz on a Jeol JNM EX-90 spectrometer or at 75 MHz on a Bruker AC-300 spectrometer. Optical rotations were measured on a Jasco DIP-371 polarimeter. The optical rotary dispersion was measured on a Jasco J-20C spectropolarimeter. Column chromatography was carried out on columns packed with Merck Kieselgel 60, Art. Nr. 7734 or with Nacalai Tesque Florisil, 100–200 mesh.

Ethyl 3-(4-hydroxycyclohexyl)propionate 8

A mixture of ethyl 4-hydroxycinnamate (111.1 g, 578.2 mmol) and W-7 Raney Ni (22 g) in EtOH (44 mL) was shaken under a hydrogen pressure of 100 kg/cm^2 at 150 °C for 3 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was diluted with Et_2O and this solution was washed with saturated sodium hydrogen carbonate solution, H_2O and brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with *n*-hexane/Et_2O (2:1) gave **8** (110.8 g, 96 %) as an oil. An analytical sample was distilled; bp 116–117 °C/1 Torr ; n_D^{20} = 1.4668; IR (film): ν = 3400 cm^{-1} (s, O–H), 1735 (s, C=O), 1175 (s, CO_2Et); ^{1}H-NMR ($CDCl_3$, 90 MHz): δ = 1.24 (t, 3H, *J* = 7.2 Hz, -$CO_2CH_2CH_3$), 0.80–2.1 (m, 12H), 2.30 (t, 2H, *J* = 7.5 Hz, -CH_2CO_2-), 3.30–3.72 (m, 0.6H, $W_{1/2}$ = 20 Hz, 4'-H_{ax}), 3.82–4.25 (m, 0.4H, 4'-H_{eq}), 4.11 (q, 2H, *J* = 7.2 Hz, -$CO_2CH_2CH_3$); Found: C, 65.89; H, 10.09; Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07.

3-(4-Hydroxycyclohexyl)propan-1-ol 9

A solution of **8** (1.96 g, 9.8 mmol) in dry THF (10 mL) was added dropwise to a stirred and ice-cooled suspension of $LiAlH_4$ (0.31 g, 8.1 mmol) in dry THF (30 mL). This mixture was stirred for 3 h at room temperature, after which a few drops of water were added to quench the excess reducing agent followed by the addition of dilute hydrochloric acid. The organic phase was then separated and the aqueous layer was extracted several times with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate, filtered through Florisil and concentrated *in vacuo* to give **9** (1.53 g, 99 %) as a solid. This was used in the next step without further purification. An analytical sample was recrystallized from Et_2O/*n*-hexane/ethyl acetate; mp 90–91 °C; IR (nujol): ν = 3270 cm^{-1} (s, OH), 1060 (s, C–O); ^{1}H-NMR ($CDCl_3$, 90 MHz): δ = 0.65–2.15 (m,15H), 3.3–3.8 (m, 1H, 4'-H), 3.63 (t, 2H, *J* = 6.3 Hz, 1-H); Found: C, 68.43; H, 11.37; Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.47.

8-Hydroxybicyclo[3.3.1]nonan-2-one 11

Diol **9** (2.97 g, 18.8 mmol) was added portionwise to a stirred and ice-cooled suspension of pyridinium chlorochromate (16.2 g, 75.1 mmol) and molecular sieves 4 Å (20 g) in dichloromethane (100 mL). The mixture was stirred for 1 h at room temperature after which Et_2O and Florisil were added. This whole mixture was filtered through Florisil and concentrated *in vacuo*. The residue was chromatographed over Florisil. Elution with *n*-hexane/ethyl acetate (1:1) gave crude **10** (2.20 g, 76 %). Methanol (80 mL), H_2O (0.2 mL), and K_2CO_3 (176 mg) were then added to crude **10** (1.89 g,12.3 mmol) and the mixture was stirred for 1 h at room temperature. The mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with *n*-hexane/Et_2O (1:1) gave **11** (1.14 g, 60 %) as a solid. An analytical sample was recrystallized from diisopropyl ether/*n*-hexane; mp 130–133 °C; IR (nujol): ν = 3425 cm^{-1} (s, OH), 1700 (s, C=O); ^{1}H-NMR ($CDCl_3$, 90 MHz): δ = 1.15–2.87 (m, 13H), 3.60–3.98 (m, 0.5H, $W_{1/2}$ = 20 Hz, 8-H_{ax}), 3.98–4.16 (m, 0.5H, $W_{1/2}$ = 9 Hz, 8-H_{eq}); Found: C, 69.46; H, 9.18; Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15; HRMS: m/z 154.0968; Calcd for $C_9H_{14}O_2$ (M^+): 154.0993.

Bicyclo[3.3.1]nonane-2,8-dione 1

A solution of **11** (0.20 g, 1.3 mmol) in dichloromethane (5 mL) was added dropwise to a stirred and ice-cooled suspension of pyridinium chlorochromate (0.86 g, 4.0 mmol) and molecular sieves 4 Å (2.5 g) in dichloromethane (10 mL). The mixture was stirred for 3 h at room temperature after which Et_2O and Florisil were added. This whole mixture was filtered through Florisil and concentrated *in vacuo* to afford a solid. This was

recrystallized from diisopropyl ether to afford **1** (0.12 g, 61 %) as crystals; mp 132–134 °C; IR (nujol): ν = 1720 cm^{-1} (s, C=O), 1695 (s, C=O); ^{1}H-NMR ($CDCl_3$, 90 MHz): δ = 1.80–2.75 (m, 11H), 3.33–3.50 (m, 1H, 1-H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 25.4, 30.0, 33.7, 37.8, 65.3, 204.6; Found: C, 70.96; H, 7.94; Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95.

Ethyl 3-(4-oxocyclohexyl)propionate ***12***

A stirred and ice-cooled solution of **8** (41.4 g, 207 mmol) in acetone (1 L) was treated with Jones' chromic acid (*ca* 100 mL) until the mixture turned red-brown. The excessive chromic acid was destroyed by the addition of 2-propanol, and the mixture was concentrated *in vacuo*. The residue was dissolved in water and the resulting mixture was saturated with ammonium sulfate and extracted several times with Et_2O. The combined organic layers were washed with water, saturated sodium hydrogen carbonate solution and brine, dried with anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with *n*-hexane/ethyl acetate (20:1–4:1) gave **12** (37.3 g, 91 %). This was used in the next step without any further purification. However, a portion of it was distilled to give an analytical sample; bp 94 °C/0.2 Torr; n_D^{19} = 1.4633; IR (film): ν = 1735 cm^{-1} (s, CO_2Et), 1720 (s, C=O), 1190 (s, CO_2Et); ^{1}H-NMR ($CDCl_3$, 90 MHz): δ = 1.24 (t, 3H, *J* = 7.2 Hz, -OCH_2CH_3), 1.08–2.46 (m, 13H), 4.12 (q, 2H, *J* = 7.2 Hz, -OCH_2CH_3); Found: C, 66.64; H, 8.97; Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15.

Ethyl 3-(3-methyl-4-oxocyclohexyl)propionate ***14***

A mixture of **12** (5.28 g, 26.6 mmol) and pyrrolidine (2.67 g, 37.5 mmol) in dry benzene (80 mL) was refluxed with removal of water using molecular sieves 4 Å as a water trap for 6 h. After cooling, the solvent and excess amine were removed *in vacuo* to give crude **13**. Dry benzene (40 mL) and iodomethane (1.70 mL, 27.3 mmol) were added to this and the mixture was heated under reflux for 15 h. After the addition of water (20 mL) and silica gel (2 g), stirring was continued for 3 h at room temperature. This mixture was then poured into water and extracted several times with Et_2O. The combined organic layers were washed with saturated sodium hydrogen carbonate solution, saturated sodium thiosulfate solution, again with sodium hydrogen carbonate solution, then with brine, dried with anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with *n*-hexane/ethyl acetate (20:1–10:1) gave **14** (2.16 g, 38 %, or 58 % based on consumed **12**) and recovered **12** (1.82 g, 35 %). This **14** was used in the next step without further purification. However, an analytical sample was distilled to give pure **14**; bp 117–118 °C/3.8 Torr; n_D^{18} = 1.4620; IR (film): ν = 1735 cm^{-1} (s, CO_2Et), 1715 (s, C=O), 1180 (s, CO_2Et); ^{1}H-NMR ($CDCl_3$, 90 MHz): δ = 1.01 and 1.08 (each d, total 3H, *J* = 6.3 and 7.2 Hz, CH_{3eq} and CH_{3ax}), 1.26 (t, 3H, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 1.40–2.70 (m, 12H), 4.14 (q, 2H, *J* = 7.2 Hz, $CO_2CH_2CH_3$); Found C, 67.80; H, 9.49; Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50.

Ethyl 3-(3-allyl-4-oxocyclohexyl)propionate ***15***

A mixture of **12** (30.0 g, 151 mmol) and pyrrolidine (17.8 g, 250 mmol) in dry benzene (100 mL) was refluxed with removal of water using a Dean–Stark water separator for 12 h. After cooling, the solvent and excess amine were removed *in vacuo* to give crude **13**. Dry acetonitrile (140 mL) and allyl bromide (12.0 mL, 139 mmol) were added to this and refluxing was performed for 15 h. After the addition of water (100 mL) and silica gel (3 g), stirring was continued for 10 h at room temperature. This mixture was then poured into water and extracted several times with Et_2O. The combined organic layers were washed with brine, dried with anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with *n*-hexane/ethyl acetate (15:1) gave **15** (24.8 g, 69 %, or 85 % based on consumed **12**) and recovered **12** (5.8 g, 19 %). This **15** was used in the next step without further purification. An analytical sample was distilled to give pure **15**; bp 118.5 °C/0.5 Torr; n_D^{19} = 1.4742; IR (film): ν = 3100 cm^{-1} (w, $CH{=}CH_2$), 1735 (s, CO_2Et), 1715 (s, C=O), 1640 (m, $CH{=}CH_2$), 1180 (s, CO_2Et); ^{1}H-NMR ($CDCl_3$, 90 MHz): δ = 1.27 (t, 3H, *J* = 7.0 Hz, $CO_2CH_2CH_3$), 1.43–2.70 (m, 14H), 4.15 (q, 2H, *J* = 7.0 Hz, $CO_2CH_2CH_3$), 4.89–5.19 (m, 2H, $C{=}CH_2$), 5.47–6.00 (m, 1H, CH=C); Found: C, 70.32; H, 9.32; Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30.

3-(4-Hydroxy-3-methylcyclohexyl)propan-1-ol ***16***

A solution of **14** (1.87 g, 8.81 mmol) in dry THF (10 mL) was added dropwise to a stirred and ice-cooled suspension of $LiAlH_4$ (0.84 g, 22 mmol) in dry THF (35 mL). This mixture was stirred for 17 h at room temperature. The usual alkaline work-up gave an oil. This was chromatographed over silica gel. Elution with *n*-hexane/ethyl acetate (2:1–1:1) gave **16** (1.50 g, 99 %). This was used in the next step without further purification. However, an analytical sample was distilled; bp 146 °C/0.5 Torr; n_D^{18} = 1.4863; IR (film): ν = 3350 cm^{-1} (s, OH), 1055 (s, C–O); ^{1}H-NMR ($CDCl_3$, 90 MHz): δ = 0.45–2.10 (m, 17H), 2.93–3.86 (m, 1H, C*H*OH), 3.62 (t, 2H, *J* = 6.4 Hz, CH_2OH); Found: C, 69.29; H, 11.75; Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70.

3-(4-Hydroxy-3-allylcyclohexyl)propan-1-ol ***17***

A solution of **15** (17.7 g, 74.4 mmol) in dry THF (100 mL) was added dropwise to a stirred and ice-cooled suspension of $LiAlH_4$ (3.79 g, 100 mmol) in dry THF (300 mL). This mixture was stirred for 16 h at room temperature. The usual alkaline work-up gave an oil. This was chromatographed over silica gel. Elution with *n*-hexane/ethyl acetate (2:1–1:1) gave **17** (15.6 g, quant.). This was used in the next step without further purification. However, an analytical sample was distilled; bp 145 °C/0.6 Torr; n_D^{19} = 1.4966; IR (film): ν = 3350 cm^{-1} (s, OH), 3090 (m, $CH{=}CH_2$), 1640 (m, C=C), 1055 (s, C–O), 915 (m, $CH{=}CH_2$); ^{1}H-NMR ($CDCl_3$, 90 MHz): δ = 0.86–2.53 (m, 16H), 3.30–3.92 (m, 1H, C*H*OH), 3.63 (t, 2H, *J* = 5.9 Hz, CH_2OH), 4.86–5.20 (m, 2H, $C{=}CH_2$), 5.56–6.12 (m, 1H, CH=C); Found: C, 72.44; H, 11.22; Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18.

8-Hydroxy-1-methylbicyclo[3.3.1]nonan-2-one **20**

A solution of **16** (1.41 g, 8.18 mmol) in dichloromethane (10 mL) was added dropwise to a stirred and ice-cooled suspension of pyridinium chlorochromate (7.65 g, 35.5 mmol) and molecular sieves 4 Å (10 g) in dichloromethane (50 mL). The mixture was stirred for 1 h at room temperature after which Et_2O and Florisil were added. This whole mixture was filtered through Florisil and concentrated *in vacuo* to afford crude **18** (0.89 g, 5.29 mmol, 65 %). Methanol (20 mL), and K_2CO_3 (150 mg) were then added to this and the mixture was stirred for 2 h at room temperature. The mixture was poured into water and extracted several times with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with *n*-hexane/Et_2O (1:1) gave **20** (0.52 g, 58 %) as a solid. An analytical sample was recrystallized from diisopropyl ether/*n*-hexane; mp 86–88 °C; IR (nujol): ν = 3450 cm^{-1} (s, OH), 1690 (s, C=O); ^{1}H-NMR ($CDCl_3$, 90 MHz): δ = 1.06 (s, 1.5H, CH_3 of the isomer with an axial OH), 1.18 (s, 1.5H, CH_3 of the isomer with an equatorial OH), 1.22–2.82 (m, 12H), 3.20–3.54 (m, 0.5H, $W_{1/2}$ = 22 Hz, $CH_{ax}OH$), 3.68–3.82 (m, 0.5H, $W_{1/2}$ = 6 Hz, $CH_{eq}OH$); Found: C, 70.87; H, 9.58; Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59; HRMS: m/z 168.1134; Calcd for $C_{10}H_{16}O_2$ (M^+): 168.1150.

8-Hydroxy-1-allylbicyclo[3.3.1]nonan-2-one **21**

A solution of **17** (10.1 g, 50.9 mmol) in dichloromethane (100 mL) was added dropwise to a stirred and ice-cooled suspension of pyridinium chlorochromate (35.5 g, 162 mmol) and molecular sieves 4 Å (55 g) in dichloromethane (250 mL). The mixture was stirred for 2 h at room temperature after which Et_2O and Florisil were added. This whole mixture was filtered through Florisil and concentrated *in vacuo* to afford crude **19** (6.82 g, 35.1 mmol, 69 %). Methanol (100 mL), water (0.1 mL) and K_2CO_3 (750 mg) were then added to a portion of this crude **10** (5.7 g, 29.3 mmol) and the mixture was stirred for 2.5 h at room temperature. The mixture was poured into brine and extracted several times with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with *n*-hexane/ethyl acetate (10:1) gave **21** (3.6 g, 63 %) as an oil. This was used in the next step without further purification. However, an analytical sample was distilled; bp 121 °C/4 Torr; n_D^{20}= 1.5145; IR (film): ν = 3470 cm^{-1} (s, OH), 3095 (w, $CH=CH_2$), 1695 (s, C=O), 1640 (m, C=C); ^{1}H-NMR ($CDCl_3$, 90 MHz): δ = 0.83–3.06 (m, 14H), 3.21–3.56 (m, 0.6H, $W_{1/2}$ = 19 Hz, $CH_{ax}OH$), 3.74–3.89 (m, 0.4H, $W_{1/2}$ = 6 Hz, $CH_{eq}OH$), 4.89–5.22 (m, 2H, $C=CH_2$), 5.43–6.00 (m, 1H, -CH=C); Found: C, 74.11; H, 9.37; Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34.

1-Methylbicyclo[3.3.1]nonane-2,8-dione **2**

A solution of **20** (0.46 g, 2.71 mmol) in dichloromethane (3 mL) was added dropwise to a stirred and ice-cooled suspension of pyridinium chlorochromate (1.1 g, 5.1 mmol) and molecular sieves 4 Å (2 g) in dichloromethane (15 mL). The mixture was stirred for 3 h at room temperature after which Et_2O and Florisil were added. This whole mixture was filtered through Florisil and concentrated *in vacuo* to afford a solid. This was recrystallized from diisopropyl ether/*n*-hexane to afford pure **2** (0.33 g, 73 %) as crystals; mp 74.5–75.5 °C; IR (nujol): ν = 1715 cm^{-1} (s, C=O), 1685 (s, C=O); ^{1}H-NMR ($CDCl_3$, 90 MHz): δ = 1.16 (s, 3H, CH_3), 1.74–2.71 (m, 11H); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 18.2, 26.3, 30.4, 37.8, 41.1, 62.7, 207.4; Found: C, 72.34; H, 8.53; Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49.

1-Allylbicyclo[3.3.1]nonane-2,8-dione **3**

A solution of **21** (3.00 g, 15.4 mmol) in dichloromethane (30 mL) was added dropwise to a stirred and ice-cooled suspension of pyridinium chlorochromate (6.5 g, 30 mmol) and molecular sieves 4 Å (10.5 g) in dichloromethane (50 mL). The mixture was stirred for 2.5 h at room temperature after which Et_2O and Florisil were added. This whole mixture was filtered through Florisil and concentrated *in vacuo* to afford an oil. This was recrystallized from diisopropyl ether/*n*-hexane to afford pure **3** (2.52 g, 85 %) as crystals; mp 34–35 °C; IR (film): ν = 3100 cm^{-1} (w, $CH=CH_2$), 1730 (s, C=O), 1700 (s, C=O), 1640 (m, C=C); ^{1}H-NMR ($CDCl_3$, 90 MHz): δ = 1.67–2.65 (m, 13H), 4.87–5.19 (m, 2H, $-C=CH_2$), 5.38–5.90 (m, 1H, -CH=C); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 25.6, 29.7, 35.9, 36.5, 38.0, 64.9, 118.9, 133.1, 207.2; Found: C, 75.29, H, 8.43; Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39.

Reduction with baker's yeast

Reduction was carried out with dry baker's yeast purchased from the Oriental Yeast Co. (Tokyo).

Reduction of bicyclo[3.3.1]nonane-2,8-dione **1** *to give (1R,5S,8S)-8-hydroxybicyclo[3.3.1]nonan-2-one* **4**

Diketone **1** (0.15 g, 0.99 mmol) was reduced using a 500 mL-Sakaguchi (flat-bottomed) flask containing a 20 % (w/v) aqueous sucrose solution (100 mL) and dry baker's yeast (8 g). The flask was shaken at 30 °C for 0.5 h, and then a mixture of **1** in 95 % ethanol (2 mL) and 0.2 % aqueous solution of Triton X-100 (2 mL) was added. The flask was shaken at 30 °C for an additional 2.5 h. Subsequently, the content of the flask was filtered through Celite. The filter cake was thoroughly washed with ethyl acetate. The filtrate was saturated with sodium chloride after which the organic layer was separated and the aqueous portion extracted several times with ethyl acetate. The combined organic solution was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with *n*-hexane/ethyl acetate (6:1) gave **4** as a solid. This could be recrystallized from diisopropyl ether/*n*-hexane to give pure **4** (0.11 g, 72 %) as fine needles; mp 130–132 °C; $[\alpha]_D^{20}$ = –3.6 ° ($CHCl_3$, *c* = 0.65) (97 % *e.e.* as estimated by the 300-MHz NMR analysis of its (*S*)-MTPA ester); IR (CCl_4

solution): ν = 3520 cm^{-1} (m, OH), 1700 (s, C=O), 1085 (s, C–O); ^{1}H-NMR ($CDCl_3$, 90 MHz): δ = 1.10–2.90 (m, 13H), 3.60–3.98 (m, 1H, $W_{1/2}$ = 20 Hz, $CH_{ax}OH$); ^{13}C-NMR ($CDCl_3$, 22.4 MHz): δ = 24.8, 26.3, 29.7, 30.5, 31.2, 38.9, 51.3, 71.8, 216.8; ORD (*c* = 0.07, 1,4-dioxane): $[\alpha]_{500}$ = –1050 °, $[\alpha]_{462}$ = 0 °, $[\alpha]_{313}$ = +1150 ° (max), $[\alpha]_{290}$ = 0 °, $[\alpha]_{256}$ = –2210 ° (min), $[\alpha]_{250}$ = –2190 °; Found: C, 69.94, H, 9.35; Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.08.

Reduction of 1-methylbicyclo[3.3.1]nonane-2,8-dione 2 to give (1R,5S,8S)-1-methyl-8-hydroxybicyclo[3.3.1]nonan-2-one 5

In the same manner as described above, diketone **2** (0.22 g, 1.3 mmol) in 95 % ethanol (2 mL) and 0.2 % aqueous solution of Triton X-100 (2 mL) was reduced with baker's yeast (8 g) in 100 mL of 20 % (w/v) aqueous sucrose solution at 30 °C for 4 h. Subsequent work-up followed by chromatography gave crude **5** as a solid. This could be recrystallized from diisopropyl ether/*n*-hexane to give pure **5** (0.19 g, 86 %) as colorless plates; mp 77–78 °C; $[\alpha]_D^{21}$ = –24 ° ($CHCl_3$, *c* = 0.97) (97 % *e.e.* as estimated by the 300-MHz NMR analysis of its (*S*)-MTPA ester); IR (CCl_4 solution): ν = 3530 cm^{-1} (m, OH), 1695 (C=O), 1070 (s, C–O); ^{1}H-NMR ($CDCl_3$, 90 MHz): δ = 1.17 (s, 3H, CH_3), 1.22–2.78 (m, 12H), 3.20–3.54 (m, 1H, $W_{1/2}$ = 21 Hz, $CH_{ax}OH$); ^{13}C-NMR($CDCl_3/CD_3OD$ (3/2), 75 MHz): δ = 21.2, 26.2, 27.4, 29.8, 31.2, 38.87, 38.93, 50.3, 76.55, 218.3; ORD (*c* = 0.07, 1,4-dioxane): $[\alpha]_{500}$ = –590 °, $[\alpha]_{470}$ = 0 °, $[\alpha]_{308}$ = +1330 ° (max), $[\alpha]_{284}$ = 0 °, $[\alpha]_{250}$ = –1330 °; Found; C, 71.43; H, 9.50; Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59.

Reduction of 1-allylbicyclo[3.3.1]nonane-2,8-dione 3 to give (1R,5S,8S)-1-allyl-8-hydroxybicyclo[3.3.1]nonan-2-one 6

In the same manner as described above, diketone **3** (0.51 g, 2.7 mmol) in 95 % ethanol (2 mL) and 0.2 % aqueous solution of Triton X-100 (2 mL) was reduced with baker's yeast (8 g) in 100 mL of 20 % (w/v) aqueous sucrose solution at 30 °C for 4 h. Subsequent work-up followed by chromatography gave **6** (0.52 g, quant.) as an oil. This could be recrystallized from diisopropyl ether/*n*-hexane at low temperature to give pure **6** (0.37 g, 72 %) as colorless rods; mp 11.5–13 °C; $[\alpha]_D^{22}$ = –102 ° ($CHCl_3$, *c* = 0.96) (97 % *e.e.* as estimated by the 300-MHz NMR analysis of its (*S*)-MTPA ester); IR (film): ν = 3450 cm^{-1} (s, OH), 3100 (m, CH=CH_2), 1690 (s, C=O), 1640 (m, C=C), 1050 (s, C–O); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 1.27 (dtd, 1H, *J* = 13.5, 11.4, 7.2 Hz, 7-H_{ax}),1.39 (dd, 1H, *J* = 13.7, 2.5 Hz, 9-$H_{OH\ side}$), 1.49–1.64 (m, 3H, 6-$H_{ax,eq}$, 4-H_{eq}), 1.92 (dq, 1H, *J* = 13.3, 4.2 Hz, 7-H_{eq}), 2.09 (d, 1H, *J* = 13.7 Hz, 9-$H_{C=O\ side}$), 2.15–2.45 (m, 5H, CH–C=C, 5-H, 4-H_{ax}, 3-$H_{ax,eq}$), 2.66 (dd, 1H, *J* = 13.5, 7.1 Hz, CH–C=C), 2.87 (d, 1H, *J* = 9.7, OH), 3.40 (ddd, 1H, *J* = 12.0, 9.7, 5.1 Hz, $CH_{ax}OH$), 5.09 (d and d, 2H, *J* = 13.6 and 12.2 Hz, C=CH_2), 5.62–5.76 (m, 1H, -C*H*=CH_2); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 24.8, 25.4, 29.9, 32.0, 34.0, 38.9, 39.1, 52.9, 75.3, 118.8, 133.1, 220.7; ORD (*c* = 0.07, 1,4-dioxane): $[\alpha]_{500}$ = –1140 °, $[\alpha]_{472}$ = 0 °, $[\alpha]_{315}$ = +550 ° (max), $[\alpha]_{292}$ = 0 °, $[\alpha]_{250}$ = –1070 °; Found: C, 74.29; H, 9.34; Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34.

Determination of the enantiomeric purity

4, **5** and **6** were converted into the corresponding (*S*)-MTPA esters by treatment with (*R*)-MTPA chloride in pyridine with a small amount of 4-*N*,*N*-dimethylaminopyridine as a catalyst and was analyzed by the 300-MHz ^{1}H-NMR spectroscopy in $CDCl_3$. The signals used for the analysis of the MTPA esters of **4** and **6** were the signals due to the methoxy protons of the corresponding (*S*)-MTPA ester, and the signals used for analysis of the MTPA ester of **5** were the signals due to the methyl protons of the corresponding (*S*)-MTPA ester. Chemical shifts of the peaks used were as follows; (*S*)-MTPA ester of **4**; δ = 3.57 (d, 3H, *J* = 1.2 Hz, OCH_3); (*R*)-MTPA ester of **4**: δ = 3.48 (d, 3H, *J* = 1.0 Hz, OCH_3); (*S*)-MTPA ester of **6**: δ = 3.55 (d, 3H, *J* = 1.0 Hz, OCH_3); (*R*)-MTPA ester of **6**: δ = 3.49 (s, 3H, OCH_3); (*S*)-MTPA ester of **5**: δ = 1.10 (s, 3H, CH_3); (*R*)-MTPA ester of **5**: δ = 1.00 (s, 3H, CH_3).

Camphanic ester 22 of 5

A mixture of camphanic acid (40 mg) in $SOCl_2$ (0.5 mL) and a drop of *N*,*N*-dimethylformamide was stirred for 2 h at 70 °C. After cooling, this was concentrated *in vacuo* to afford the corresponding acid chloride as a solid. Pyridine (0.5 mL), **4** (12 mg, 0.07 mmol) and a small amount of 4-*N*,*N*-dimethylaminopyridine were then added and the mixture was stirred for 20 h at room temperature. An excess of 3-*N*,*N*-diethylamino-1-propylamine was added and stirred for 5 min to destroy any acid chloride and acid anhydride. This was diluted with Et_2O and washed thoroughly with dilute hydrochloric acid, then with saturated sodium hydrogen carbonate solution and brine, dried over anhydrous magnesium sulfate, filtered through silica gel and concentrated *in vacuo* to afford crystalline **22** (24 mg, quant.). This was recrystallized from methanol to give pure **22** as plates; mp 203–204 °C; IR (nujol): ν = 1785 cm^{-1} (s, lactone carbonyl), 1750 (s, ester carbonyl), 1710 (s, ketone carbonyl); ^{1}H-NMR ($CDCl_3$, 90 MHz): δ = 0.99 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.10 (s, 6H, two CH_3), 1.50–2.65 (m, 15H), 4.92–5.20 (m, 1H, C*H*OH); Found: 348.1974; Calcd for $C_{20}H_{28}O_5$: 348.1937 (High resolution MS).

X-Ray analysis of 22

A colorless plate crystal of **22** having approximate dimensions of 0.1 x 0.3 x 0.4 mm was mounted on a Rigaku AFC5S four-circle automated diffractometer with graphite monochromated MoKα radiation. Crystal data: $C_{20}H_{28}O_5$, MF = 348.44, orthorhombic, space group $P2_12_12_1$, a = 11.211 (1)Å, b = 23.395 (2)Å, c = 7.122 (5)Å, V = 1868 (1)Å, Z = 4, Dc = 1.239 g/cm^3 and μ(MoKα) = 0.82 cm^{-1}. The data were collected using the

ω-2θ scan technique to a maximum 2θ value of 50 °. Three reference reflections monitored periodically showed no significant intensity fluctuations during the course of data collection. A total of 1953 independent reflections were collected. Azimuthal scans of several reflections indicated no need for an absorption correction. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods. The resulting E map revealed the positions of all non H-atoms. The calculated H atoms were included for the structure factor calculation. The refinement of atomic parameters was carried out by a full-matrix least-squares refinement, using anisotropic temperature factors for all non-H atoms. The final refinement was based on 1244 observed reflections ($I > 2\sigma(I)$) and 226 variable parameters and converged to R = 0.068, Rw = 0.083. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.20 and –0.33 e/A^3, respectively.

Neutral atomic scattering factors were taken from Cromer and Waber.[11] All calculations were performed using the TEXSAN crystallographic software package.[12,13]

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