Resolution of 7,7-Dimethylbicyclo[3.2.0]hept-2-en-6-one using *Mortierella ramanniana* and 3α,20β-Hydroxy-steroid Dehydrogenase, Photochemistry of 3-Hydroxy-7,7-dimethylbicyclo[3.2.0]heptan-6-ones, and the Synthesis of (+)-Eldanolide

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The fungus *Mortierella ramanniana* reduced 7,7-dimethylbicyclo[3.2.0]hept-2-en-6-one (**1**) to give the (6*S*)-*endo*-alcohol (**9**) and the (6*S*)-*exo*-alcohol (**10**). In contrast the enzyme 3α,20β-hydroxy-steroid dehydrogenase was found to give the (6*S*)-*endo*-alcohol (**9**) and recovered optically active ketone. Both processes produced the alcohol (**9**) in high optical purity. The (6*S*)-*endo*-alcohol (**9**) was converted into the lactone (+)-(**4**) a late stage synthon for the pheromone eldanolide (+)-(**11**).

Studies by ourselves[1] and other workers[2] have shown that the photochemical retro-[2 + 2] reaction of 7,7-disubstituted bicyclo[3.2.0]heptan-6-ones to give γ-alkenyl ketenes can be an efficient process and that the ultimate product(s) (*e.g.* δ-alkenyl esters) can be obtained in synthetically useful yields. We show that this reaction can be applied to the synthesis of eldanolide,[3,4] the attractant pheromone of a West African pest, the sugar-cane borer *Eldana saccharina* (WIK).[5] In order to obtain the natural product in optically active form, the starting material for the synthesis, 7,7-dimethylbicyclo[3.2.0]hept-2-en-6-one (**1**), was resolved using a fungus and a dehydrogenase enzyme. The preparation of optically active synthons of chiral natural products using micro-organisms and/or isolated enzymes is a blossoming field of research.[6]

Preparation and Photolysis of Racemic 3-Hydroxybicyclo[3.2.0]*heptan-6-ones.*—7,7-Dimethylbicyclo[3.2.0]hept-2-en-6-one (**1**) is readily available[7] and was converted into the hydroxybicycloheptanone (**2**) in excellent yield (Scheme 1). Photolysis of this hydroxy ketone in a variety of solvents using a medium pressure mercury lamp and quartz apparatus gave mixtures of the acetal (**3**) and the lactone (**4**); the presence of triplet sensitizers and the use of pyrex apparatus had only a marginal effect on the ratio of the products (**3**):(**4**) (Table).

The lactone (**4**) arises by intramolecular trapping of the intermediate ketene by the adjacent hydroxy group, while the acetal (**3**) is formed through the intermediacy of an oxacarbene (Scheme 1). Both these processes have precedent in the literature. For example, Turro has shown that a cyclic oxacarbene can be trapped by an adjacent hydroxy group,[8] whilst the intramolecular capture of a photo-generated ketene has been a noteworthy feature in a number of studies.[9]

We reasoned that, in order to minimize the formation of the cyclic acetal (**3**), the hydroxy group should preferably occupy the *exo*-face of the bicycloheptanone system. If, as now seems likely,[2,10] the cyclobutanone/oxacarbene transformation is a reversible process then the photolysis reaction should be channelled through the γ-alkenyl ketene intermediate to give the desired lactone.

Mitsunobu transposition of the hydroxy group was effected in good yield to give the required 3-*exo*-hydroxybicycloheptan-6-one (**6**) (Scheme 1). Photolysis of this hydroxy ketone in benzene, pentane, or acetonitrile gave the lactone (**4**) as the only non-polar product. Surprisingly, the highest yield obtained was a disappointing 36%. The yield was not increased by conducting the photolysis on a very dilute solution of the substrate, suggesting that polymerisation of the intermediate ketene was not a significant problem. Despite the modest yield, this photo-transformation is synthetically useful since evaporation of the solvent and rapid filtration of the residue through a bed of silica yielded pure lactone.

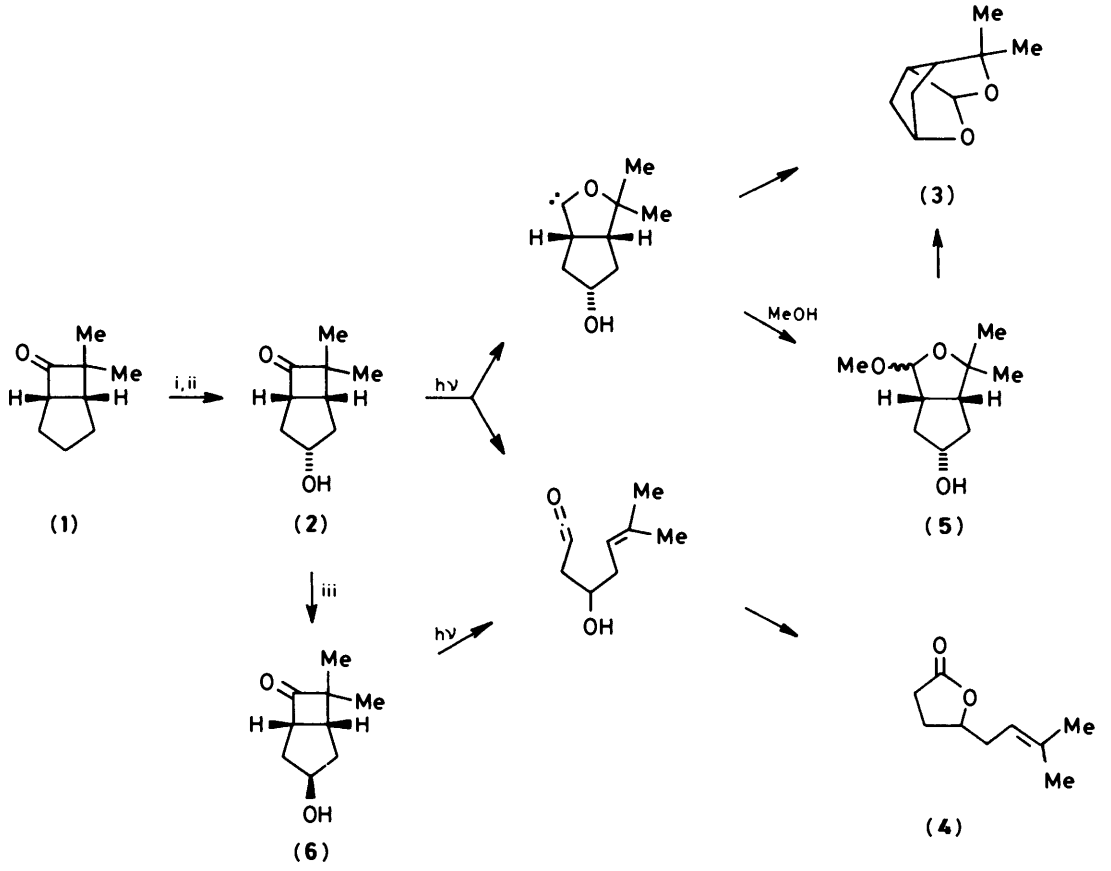
Table. Photolyses of 3-hydroxybicyclo[3.2.0]heptan-6-ones

Substrate	Solvent (additive)	Products: Lactone (**4**) (%)	Products: Cyclic acetal (**3**) (%)
(**2**)	Methanol	41	5[a]
(**2**)	Benzene	42	18
(**2**)	Benzene (2,5-dimethylhexa-2,4-diene)	35	40
(**2**)	Acetonitrile	37	43
(**2**)	Pentane	43	19
(**2**)	Pentane (benzophenone)	35	19
(**2**)	Pentane (methyl benzoate)	39	28
(**6**)	Benzene	36	
(**6**)	Pentane	32	
(**6**)	Pentane (2,5-dimethylhexa-2,4-diene)[b]	28	
(**6**)	Acetonitrile	29	

[a] Plus the acetal (**5**) (30%) which rearranged to the acetal (**3**) on standing. [b] Photolysis conducted at 0—5 °C.

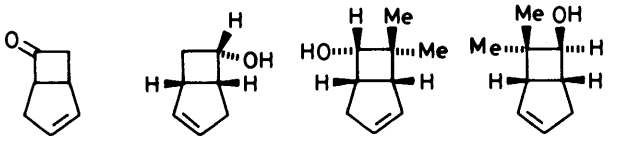
Resolution of (±)-7,7-*Dimethylbicyclo*[3.2.0]*hept-2-en-6-one* (**1**) *using* Mortierella ramanniana.—It has been reported previously[11] that bicyclo[3.2.0]hept-2-en-6-one (**7**) is reduced with very high substrate enantioselectivity using the fungus *Mortierella ramanniana* to give only the (6*S*)-*endo*-alcohol (**8**) and recovered optically active ketone. Incubation of the 7,7-dimethyl derivative (**1**) with the same micro-organism gave very different results.[12]

At substrate concentrations of 1—2 g l^{-1}, reduction of 7,7-dimethylbicycloheptenone (**1**) occurred at a rate approximately



Scheme 1. *Reagents:* i, MeCONHBr, Me_2CO, H_2O (ref. 18); ii, Bu_3SnH, PhMe, heat, AIBN; iii, DEAD, Ph_3P, $PhCO_2H$ then K_2CO_3, MeOH.

half of that for the unsubstituted bicycloheptenone (**7**). Reduction of the dimethylbicycloheptenone (**1**) was more susceptible to inhibition at higher substrate concentrations (≥ 5 g l^{-1}).

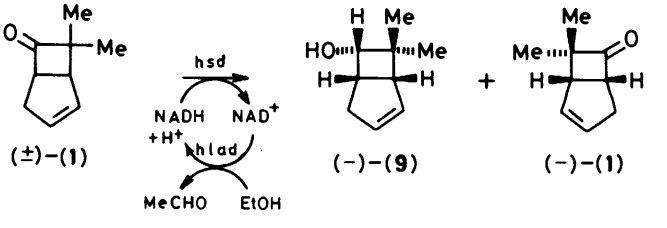


(±)-(**7**) (-)-(**8**) (-)-(**9**) (+)-(**10**)

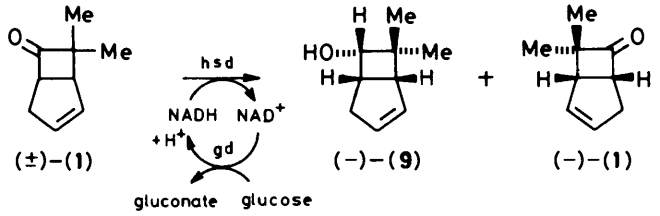
With the ketone (**1**) both 6-*exo*- and 6-*endo*-alcohols were detected at the lower substrate concentrations. A large scale run involving the reduction of the ketone (**1**) (15 g) in three 5-l fermentations gave after 21 h, 6-*endo*-ol (3.8 g), 6-*exo*-ol (3.4 g), and starting material (0.2 g). The two alcohols were obtained pure by chromatography over silica. Gas chromatography of the 6-*endo*-alcohol (derivatised as the isopropylurethane using isopropyl isocyanate) over a Chirasil-valine stationary phase showed that the enantiomer ratio was 91:9. The major enantiomer was subsequently shown to be the (6*S*)-*endo*-alcohol (**9**) (*vide infra*). Analysis of the 6-*exo*-alcohol in the same way showed an enantiomer ratio of >97:<3. The major enantiomer was shown to be the (6*S*)-*exo*-alcohol (**10**).

The different behaviour of the ketone (**1**) compared to the parent compound (**7**) is rationally explained by assuming that (at least) two enzymes are involved in the reduction process and that one (or more) of these enzymes is inhibited by bicycloheptenone (**7**).[13] The difference in the absolute configurations of the 6-*endo*-alcohols (**8**) and (**9**) is not surprising in view of Prelog's rule concerning the selectivity of dehydrogenase enzymes.[14]

Resolution of (±)-7,7-*Dimethylbicyclo*[3.2.0]*hept*-2-*en*-6-*one* (**1**) *using Isolated Enzymes.*—The utilisation of enzymes to resolve racemic ketones is becoming well established.[15] The ketone (**1**) was not reduced by horse liver alcohol dehydrogenase (hlad) (e.c.1.1.1.1) or the commercially available alcohol dehydrogenase from the organism *Thermoanaerobium brockii*, under the appropriate reaction conditions. However, 3α,20β-hydroxy steroid dehydrogenase (hsd) (e.c.1.1.1.53) catalysed the reduction of the ketone (**1**) by NADH to give the 6-*endo*-alcohol. The cofactor was recycled by coupling the reduction of the ketone (**1**) by hsd to either the oxidation of ethanol catalysed by hlad or yeast alcohol dehydrogenase yad (Scheme 2) or the oxidation of glucose catalysed by glucose dehydrogenase (gd) (e.c.1.1.1.47) (Scheme 3). The 7,7-dimethylbicyclo[3.2.0]hept-2-en-6-*endo*-ol was obtained from the reaction mixture by extraction and column chromatography. A sample of the alcohol obtained in this way was shown, by g.c. over the chiral column, to be optically pure (6*S*)-alcohol (**9**).

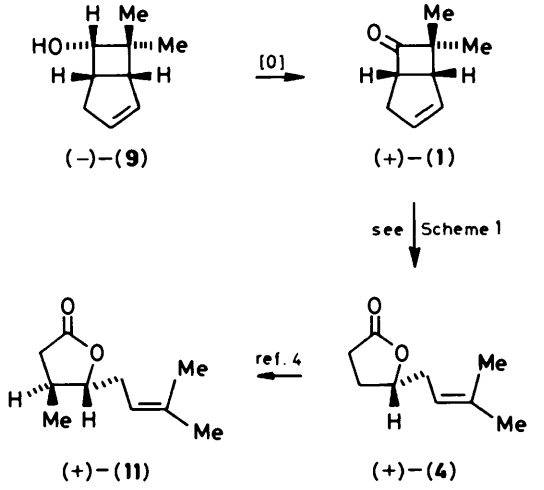


Scheme 2.



Scheme 3.

Preparation of Optically Active Eldanolide (**11**).—Pyridinium dichromate oxidation of the bicycloheptenol (−)-(**9**) gave the optically active ketone (+)-(**1**) and this compound was converted into the lactone (**4**) {$[\alpha]_D$ 20.4° (*c* 1.2 MeOH); lit.,[4] $[\alpha]_D$ 20° (*c* 1.2 MeOH)} by the route shown in Scheme 4. This lactone can be converted into the natural product eldanolide (+)-(**11**) with the correct absolute stereochemistry using a previously documented[4] sequence involving phenylselenation, oxidative elimination of the phenylselenyl moiety to give an α,β-unsaturated lactone, and conjugate addition of a methyl group using lithium dimethylcuprate.



Scheme 4.

The conversion of the *endo*-alcohol (−)-(**9**) into the ketone (+)-(**1**) and then by further reactions into the lactone (+)-(**4**) established the absolute stereochemistry of the alcohol and the ketone. Oxidation of the *exo*-alcohol gave the ketone (−)-(**1**). Thus the fungal reductions and the free enzyme reductions all give the *S*-stereochemistry at the reduction site.

Experimental

Where necessary, solvents were dried and purified according to recommended procedures.[16] Light petroleum refers to the fraction boiling in the range 40—60 °C. Ether is diethyl ether. Organic solvents were dried over magnesium sulphate or sodium sulphate and evaporation refers to solvent removal on a rotary evaporator under reduced pressure. T.l.c. was performed on precoated plates (Merck silica gel 60F 354). Flash chromatography refers to the method of Still *et al.*[17] M.p.s were determined on a Kofler block and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 297 grating spectrophotometer. ^{1}H N.m.r. spectra were recorded on a Bruker WM250 MHz spectrometer and a Perkin-Elmer 200 MHz spectrometer. ^{13}C N.m.r. spectra were recorded on a JEOL FX100 spectrometer. Electron impact (e.i.) mass spectra and accurate mass determinations were obtained on Varian 311A and Finnigan 4500 machines. G.c. was performed on a Perkin-Elmer 8310 Gas Chromatograph using a 2 m × 3 mm column packed with 10—15% Carbowax 20 M on Chromsorb W (80—100 mesh or 100—200 mesh). The oven temperature was 150 °C and the helium flow rate was 20—30 ml min^{-1}. The optical purities of the urethanes were determined by g.c. employing a Chirasil-L-Val stationary phase.

Mortierella ramanniana CMI35044A was maintained and grown in 4 l or 40 l batch cultures as described previously.[11]

All enzymes and nucleotides were purchased from the Sigma Chemical Company Ltd.

(±)-3-endo-*Hydroxy*-7,7-*dimethylbicyclo*[3.2.0]*heptan*-6-*one* (**2**).—7,7-Dimethylbicyclo[3.2.0]hept-2-en-6-one (**1**) (49.0 g, 360 mmol) was dissolved in acetone (300 ml) and water (60 ml). *N*-Bromoacetamide (62.1 g, 450 mmol, 1.25 equiv.) was added with stirring. After 22 h at room temperature water (60 ml) was added and the acetone was removed under reduced pressure. Ether (300 ml) was added and the organic phase was separated and washed with water (6 × 200 ml). The aqueous washes were back-extracted with ether (2 × 200 ml). The combined organic fractions were dried and evaporated to yield a thick brown oil (83.4 g). Chromatography [ethyl acetate–light petroleum (1:6 v/v)] gave 2-*exo*-bromo-3-*endo*-hydroxybicyclo[3.2.0]heptan-6-one (72.1 g, 86%) as an oil after being dried *in vacuo* over phosphorus pentaoxide. The clear oil was dissolved in light petroleum (250 ml) and kept at −10 °C overnight to give the bromohydrin (67.9 g, 81%) as white needles, m.p. 67—69 °C (lit.,[18] m.p. 66—69 °C).

The bromohydrin (5 g, 21.5 mmol), tributyltin hydride (9.4 g, 32.3 mmol, 1.5 equiv.) and a catalytic amount of 2,2′-azo(2-methylpropiononitrile) (AIBN) (106 mg, 0.65 mmol, 2 mol%) were dissolved in anhydrous toluene (215 ml) and the resulting solution was deoxygenated with argon. The reaction vessel was sealed and stirred at room temperature for 0.5 h. The solvent was removed and the residue was partitioned between hexane and acetonitrile.[19] The acetonitrile was washed with hexane and concentrated under reduced pressure to give a white solid. Flash chromatography [acetone–dichloromethane (1:19 v/v, followed by 1:9 v/v)] gave the *title compound* (**2**) (2.7 g, 82%) as white needles, m.p. 64—66 °C (from ethyl acetate–light petroleum) (Found: C, 69.9; H, 9.2. $C_9H_{14}O_2$ requires C, 70.1; H, 9.15%); $\nu_{max.}$(neat) 3 450, and 1 765 cm^{-1}; δ($CDCl_3$), 4.47 (1 H, br s, 3-H), 3.61 (1 H, ddd, 5-H), 2.55 (1 H, ddd, 1-H), 2.15—1.68 (5 H, m, 2 × 2-H, 2 × 4-H, and OH), and 1.29 and 1.17 (6 H, 2 s, 2 × Me); *m/z* 154 (M^+) and 126 (M^+ − CO).

(±)-3-exo-*Hydroxy*-7,7-*dimethylbicyclo*[3.2.0]*heptan*-6-*one* (**6**).—A solution of diethyl azodicarboxylate (DEAD) (6.1 g, 35 mmol) in anhydrous tetrahydrofuran (20 ml) was added dropwise over a period of 5 min to a stirred solution of triphenylphosphine (9.2 g, 35 mmol), the hydroxybicycloheptanone (**2**) (3.6 g, 23.3 mmol), and benzoic acid (4.3 g, 35.0 mmol) in anhydrous tetrahydrofuran (250 ml) at room temperature. The mixture was stirred at room temperature overnight and the solvent was removed under reduced pressure. Ether was added to the residue and a crystal of diethyl hydrazinedicarboxylate added to precipitate triphenylphosphine oxide and diethyl hydrazinedicarboxylate which were filtered off. The filtrate was evaporated to give an orange oil. Flash chromatography [dichloromethane–light petroleum (1:1 v/v)] gave the 3-*exo*-benzoyloxybicyclo[3.2.0]heptan-6-one (4.7 g, 78%), m.p. 84—85 °C (from ethyl acetate) (Found: C, 74.15; H, 7.0. $C_{16}H_{18}O_3$ requires C, 74.4; H, 7.0%); $\nu_{max.}$($CHBr_3$) 1 770, and 1 730 cm^{-1}; δ($CDCl_3$), 8.02 (2 H, m, ArH), 7.62—7.35 (3 H, m, ArH), 5.34 (1 H, dddd, *J* 8, 8, 2, and 2 Hz, 3-H), 3.84 (1 H, t, *J* 8 Hz, 5-H), 2.69 (1 H, ddd, *J* 8, 8, and 2 Hz, 1-H), 2.45 (1 H, m, 4-*endo*-H), 2.32 (1 H, m, 2-*endo*-H), 2.02—1.78 (2 H, m, 2-*exo*-H, 4-*exo*-H),

1.30 (3 H, s, 7-*exo*-Me), and 1.10 (3 H, s, 7-*endo*-Me); *m/z* 259 ($M^+ + 1$).

To a stirred solution of 3-*exo*-benzoyloxybicyclo[3.2.0]-heptan-6-one (222 mg, 0.86 mmol) in methanol at room temperature was added potassium carbonate (235 mg, 1.7 mmol). After 2 h the mixture was filtered through a sinter (porosity 4) and the solvent was removed under reduced pressure to give a clear oil. Flash chromatography [dichloromethane–acetone (8:1,v/v)] gave the *title compound* (**6**) (126 mg, 95%) (Found: C, 69.9; H, 9.15. $C_9H_{14}O_2$ requires C, 70.1; H, 9.15%); $\nu_{max.}(CHBr_3)$ 3 600 and 1 765 cm^{-1}; $\delta(CDCl_3)$ 4.26 (1 H, m, 3-H), 3.72 (1 H, dd, *J* 8.5 and 8 Hz, 5-H), 2.55 (1 H, ddd, 8, 8, and 2 Hz, 1-H), 2.22 (2 H, m, 4-*endo*-H and 2-*endo*-H), 2.05 (1 H, m, 2-*exo*-H), 1.80—1.46 (2 H, m, 4-*exo*-H and OH), 1.22 (3 H, s, 7-*exo*-Me) and 0.98 (3 H, s, 7-*endo*-Me); *m/z* 154 (M^+) and 126 ($M^+ - CO$).

Photolysis of (±)-3-endo-*Hydroxy*-7,7-*dimethylbicyclo*-[3.2.0]*heptan*-6-*one* (**2**).—(a) *In benzene.* To a stirred solution of the hydroxy ketone (**2**) (602 mg, 4.0 mmol) in dry benzene (60 ml) was added 2,5-dimethylhexa-2,4-diene (882 mg, 8.0 mmol, 2 equiv.). The solution was deoxygenated using a stream of argon for 0.5 h. Irradiation at room temperature under an atmosphere of argon using a medium pressure lamp through a quartz filter for 4 h gave a solution containing two major non-polar components. The solvent was removed to give a yellow oil. Flash chromatography (dichloromethane) gave the γ-*lactone* (**4**) (211 mg, 35%) as an oil (Found: C, 70.15; H, 9.35. $C_9H_{14}O_2$ requires C, 70.1; H, 9.15%); $\nu_{max.}(CHBr_3)$ 1 779 cm^{-1}; $\delta(CDCl_3)$, 5.13 (1 H, m, C=CH), 4.51 (1 H, quintet, *J* 6 Hz, CHO), 2.6—1.75 (6 H, m, 2 × 2-H, 2 × 3-H, and 2 × 5-H) and 1.68 (6 H, m, Me_2C=C); *m/z* 154 (M^+) and the *tricyclic acetal* (**3**) (241 mg, 40%) as an oil, $\nu_{max.}(CHBr_3)$ 1 068, and 1 055 cm^{-1}; $\delta(CDCl_3)$, 5.33 (1 H, d, *J* 3 Hz, 2-H), 4.29 (1 H, s, 7-H), 3.01 (1 H, br s, 1-H), 2.18 (1 H, m, 5-H), 1.98—154 (4 H, m, 2 × 6-H and 2 × 8-H) and 1.3 (6 H, 2 s, 2 × Me); $\delta_C(CDCl_3)$ 105.1 (d, C-2), 83.0 (s, C-4), 74.5 (d, C-7), 46.9 and 44.6 (2 d, C-1 and -5), 37.6 and 33.5 (2 t, C-6 and -8), and 29.4 and 25.5 (q, 2 × Me).

(b) *In methanol.*—A stirred solution of the 3-*endo*-hydroxybicyclo[3.2.0]heptan-6-one (**2**) (500 mg, 3.2 mmol) in dry methanol (120 ml) was deoxygenated using a stream of argon for 0.5 h. Irradiation at room temperature under an argon atmosphere using a medium pressure lamp through a Pyrex filter for 9 h gave a solution containing three components. The solvent was evaporated to give a clear oil. Flash chromatography [acetone–dichloromethane (1:19 v/v followed by 1:6 v/v)] gave the γ-lactone (**4**) (203 mg, 41%), the tricyclic acetal (**3**) (24 mg, 5%) and the *acetal* (**5**) (179 mg, 30%); $\delta(CDCl_3)$, 4.80 (1 H, s, 2-H), 4.12 (1 H, q, 7-H), 3.31 (3 H, s, OMe), 2.82—2.68 (1 H, m, 1-H), 2.43 (1 H, q, 5-H), 2.23—1.53 (5 H, m, 2 × 6-H, 2 × 8-H and OH), 1.36 and 1.29 (6 H, 2 s, 2 × 4-Me) which rearranged to the tricyclic acetal (**3**) with time.

Photolysis of (±)-3-exo-*Hydroxy*-7,7-*dimethylbicyclo*[3.2.0]-*heptan*-6-*one* (**6**).—To a stirred solution of the 3-*exo*-hydroxybicyclo[3.2.0]heptan-6-one (**6**) (650 mg, 4.2 mmol) in dry pentane (65 ml) was added 2,5-dimethylhexa-2,4-diene (926 mg, 8.4 mmol, 2 equiv.). The solution was deoxygenated using a stream of argon for 0.5 h. Irradiation at room temperature under an argon atmosphere using a medium pressure lamp through a quartz filter for 5 h gave a solution containing one non-polar component plus baseline material. The solvent was removed to give a yellow oil. Flash chromatography (dichloromethane) gave the γ-lactone (**4**) (182 mg, 28%).

Reduction of 7,7-*Dimethylbicyclo*[3.2.0]*hept*-2-*en*-6-*one* (**1**) *using* M. ramanniana.—Shake flask bioconversions were carried out as described previously.[11] Aliquots (5 ml) of the conversion mixture were salted with sodium chloride (1.0 g) and extracted with dichloromethane (5 ml). After centrifugation the organic phase was separated and dried. The quantities of alcohols and ketone in the organic phase were measured by g.c. For large-scale conversions *M. ramanniana* was harvested by filtration and resuspended in distilled water (3 × 5 l at *ca.* 200 g wet weight of fungus l^{-1}) contained in 7 l LH Engineering fermenters. Substrate (3 × 5 g) was added and the fermentations were maintained at 25 °C, agitated at 600 rev min^{-1} and aerated at 0.5 l min^{-1}. Evaporation of the substrate was minimised by the use of a condenser. After 21 h sodium chloride (1.5 kg) was added to the fermentation broth and the broth was extracted with dichloromethane (6 × 1 l). The combined organic extracts were dried. G.c. analysis showed the presence of 7,7-dimethylbicyclo[3.2.0]hept-2-en-6-one (0.2 g), 7,7-dimethylbicyclo-[3.2.0]hept-2-en-6-*endo*-ol (3.8 g) and 7,7-dimethylbicyclo-[3.2.0]hept-2-en-6-*exo*-ol (3.4 g). Evaporation of the solvent and chromatography of the residue over silica using dichloromethane–acetone (v/v 50:1) as eluant gave the pure alcohols (**9**) $[\alpha]_D^{21}$ −95° and (**10**) $[\alpha]_D^{21}$ +119°. The optical purity of the separated alcohols was shown to be 85:8 and >97:<3 for the *endo*- (**9**) and *exo*-alcohol (**10**) respectively using the chiral g.c. column after converting the alcohols into the isopropylurethane derivatives.

Reduction of 7,7-*Dimethylbicyclo*[3.2.0]*hept*-2-*en*-6-*one using* 3α,20β-*Hydroxy-steroid Dehydrogenase.*—Tris-HCl buffer (pH 8; 305 ml, 200 mM), the ketone (**1**) (1.0 g), NAD^+ (0.072 mmol), glycerol (1.09 mol) and *either* glucose (73 mmol), manganese sulphate (2.5 μmol), and glucose dehydrogenase (3 mg; 20 units) *or* ethanol (870 mmol) and alcohol dehydrogenase (from horse liver 5 mg; 10 units or from yeast 8 mg; 1 600 units) were stirred together for 10 min. 3α,20β-Hydroxy-steroid dehydrogenase (0.9 mg; 9 units) was added. Similar quantities of nucleotide and enzymes were added at intervals. After 24 h sodium chloride was added to the reaction mixture which was then extracted with dichloromethane (4 × 100 ml). The combined organic fractions were dried and evaporated. Chromatography of the residue over silica gave recovered starting material and 7,7-dimethylbicyclo[3.2.0]hept-2-en-6-*endo*-ol (**9**) (22%) (e.e. ≥95% as judged by g.c. of the *N*-isopropylurethane derivative over a chiral stationary phase).

Synthesis of the Optically Active Lactone (**4**).—(1*R*,5*S*,6*S*)-7,7-Dimethylbicyclo[3.2.0]hept-2-en-6-ol (**9**)[12] ($[\alpha]_D$ −112°, *c* 1.0 $CHCl_3$) was oxidized with pyridinium dichromate to give (1*R*,5*S*)-7,7-dimethylbicyclo[3.2.0]hept-2-en-6-one (65%) ($[\alpha]_D$ +46.3°, *c* 1.21 $CHCl_3$). This ketone was converted into (1*R*,3*S*,5*S*)-3-hydroxy-7,7-dimethylbicyclo[3.2.0]heptan-6-one ($[\alpha]_D$ +115.8°, *c* 1.47 $CHCl_3$), (1*R*,3*R*,5*S*)-3-hydroxy-7,7-dimethylbicyclo[3.2.0]heptan-6-one ($[\alpha]_D$ +110.3°, *c* 1.65 $CHCl_3$) and the lactone (**4**) ($[\alpha]_D$ +20.4°, *c* 1.2 MeOH) in the manner described above for the racemic compounds.

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