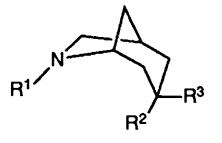
Synthesis and Stereoselective Reduction of (±)-, (+)- and (−)-6-Substituted-6-azabicyclo[3.2.1]octan-3-one

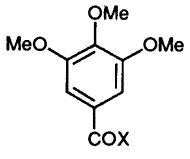
J. Bruce Pitner,[a] Philip Abraham,[a] Young J. Joo,[a] David J. Triggle[b] and F. Ivy Carroll *,[a]
[a] *Chemistry and Life Sciences, Research Triangle Institute, Research Triangle Park, North Carolina 27709, USA*
[b] *Department of Biochemical Pharmacology, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14260, USA*

Starting with 6-oxabicyclo[3.2.1]oct-3-en-7-one **6**, a three step, general synthetic route to both racemic and optically active 6-substituted 6-azabicyclo[3.2.1]octan-3-ones has been developed. Opening of the lactone ring of **6** with amines gave amides which were reduced with lithium aluminium hydride to amino alcohols. Allylic oxidation of amino alcohols **8a**, **8b**, **12** and **13** with manganese dioxide provided the bicyclic ketones **1b**, **1c**, **14** and **15**, respectively, without isolation of the intermediate monocyclic ketones. Methods for stereoselective reduction of the bicyclic ketones to the corresponding 6-substituted 6-azabicyclo[3.2.1]octan-3α-ols and -3β-ols have been developed. Displacement of the *R*-α-methylbenzyl chiral auxiliary from the diastereomeric alcohols **16**, **17**, and **20**, **21** by catalytic debenzylation followed by reductive amination provided the optically active 6-methyl-6-azabicyclo[3.2.1]octan-3-ols **1d**–**1e**, respectively. The absolute stereochemistry of all reported optically active compounds has been established by comparison of diastereoisomers **10** and **11** with the *R*-(+)-methylbenzylamine amides derived from optically enriched lactone **6**.

We have described the synthesis and biochemical properties of 6-methyl-6-azabicyclo[3.2.1]octan-3α-ol 2,2-diphenylpropionate (**1a**, azaprophen), a potent muscarinic antagonist.[1] In order to investigate the structural requirements of **1a** for acting at the muscarinic receptor, it was necessary to develop a convenient synthesis of its precursor, 6-methyl-6-azabicyclo[3.2.1]octan-3-one **1b**. Although the syntheses of this azabicyclo compound and its 6-benzyl derivative **1c** have been reported,[2,3] the syntheses were neither concise nor sufficiently versatile for use as general procedures. We now report a facile synthesis of this bicyclic system by a route that can be adapted to provide optical isomers of this ring system.[4] We also present methods for stereoselective reduction of the 3-ketone group to the 3α- and 3β-alcohols.



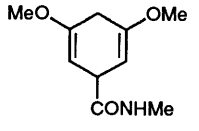
1



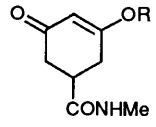
2

a; X = Cl
b; X = NHMe

a; R^1 = Me, R^2 = $(Ph)_2O(Me)CO_2$, R^3 = H
b; R^1 = Me, R^2 = R^3 = O
c; R^1 = $PhCH_2$, R^2 = R^3 = O
d; R^1 = Me, R^2 = OH, R^3 = H
e; R^1 = Me, R^2 = H, R^3 = OH
f; R^1 = $PhCH_2$, R^2 = OH, R^3 = H
g; R^1 = $PhCH_2$, R^2 = H, R^3 = OH

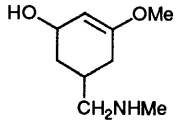


3



4

a; R = Me
b; R = H
c; R = Et



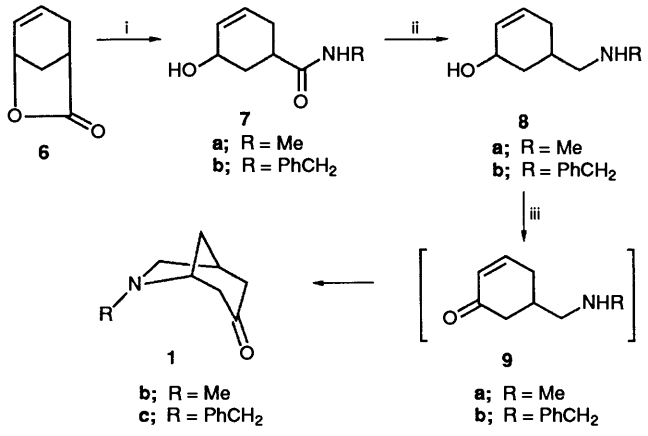
5

Results and Discussion

Initially, 6-methyl-6-azabicyclo[3.2.1]octan-3-one **1b** was prepared by a modification of the procedure reported by Furstoss and co-workers.[2] The starting point was 3,4,5-trimethoxybenzoyl chloride **2a** which, after conversion to the *N*-methylamide **2b**, could be converted by Birch reduction into 3,5-dimethoxy-1,4-dihydro-*N*-methylbenzamide **3**. We found that hydrolysis of **3** using toluene-*p*-sulphonic acid monohydrate in acetone gave the β-methoxy α,β-unsaturated ketone **4a**, thus avoiding the preparation of the enol **4b** and its conversion into **4c** as reported.[2] Reduction of **4a** with lithium aluminium hydride (LAH) gave the amino compound **5**. Exposure of **5** to hydrochloric acid followed by aqueous sodium hydrogen carbonate gave the desired azabicyclic ketone **1b**. In addition to fewer isolation steps, the major advantage of this procedure over the reported procedure[2] was that the β-methoxy α,β-unsaturated ketone **4a** could be prepared directly from **3**. Also, its purification and conversion into **1b** was much cleaner and proceeded in higher yield than the β-ethoxy α,β-unsaturated ketone used by Furstoss and co-workers.[2] Even though these improvements offered a better synthesis of **1b**, a simpler, higher-yielding, versatile method was needed.

This need led us to investigate the sequence shown in Scheme 1 which starts with the readily available lactone 6-oxabicyclo[3.2.1]oct-3-en-7-one **6**.[5,6] When lactone **6** was treated with a methanolic solution of methylamine at 100 °C, a nearly quantitative yield of the amide **7a** was obtained. LAH reduction of **7a** afforded the hydroxy amine **8a**. Allylic oxidation of **8a** using activated manganese dioxide in methylene dichloride solution gave the desired azabicyclic ketone **1b** in 78% overall yield from **6**. The intermediate **9a** was not detected by TLC or ^1H NMR analysis and apparently spontaneously cyclized to **1b**.

If benzylamine were used in place of methylamine, 6-benzyl-6-azabicyclo[3.2.1]octan-3-one **1c** was obtained in 68% overall yield. Similarly, treatment of lactone **6** with *R*-(+)-α-methylbenzylamine gave an 81% yield of a 1:1 mixture of **10** and **11** which were readily separated by flash chromatography (see



Scheme 1 All compounds are racemic. *Reagents:* i, RNH_2, MeOH or xylene; ii, LAH, Et_2O or THF; iii, MnO_2, CH_2Cl_2

Scheme 2). To establish the absolute stereochemistry of diastereoisomers **10** and **11**, the precursor racemic lactone **6** was optically enriched by enantioselective enzymatic hydrolysis of the 1*R*,5*R* isomer with pig liver esterase[7–9] to give (1*S*,5*S*)-**6** of 82% optical purity.[10,*] Treatment of this enriched lactone with R-(+)-α-methylbenzylamine gave a 9:1 mixture of **11** and **10**. This served to establish the absolute stereochemistry of **10** and **11** as 1*R*,3*R* and 1*S*,3*S*, respectively. Subjection of **10** and **11** to LAH reduction provided the optically active amines **12** and **13**. Oxidation of **12** and **13** with manganese dioxide afforded the azabicycloketones **14** and **15**, respectively (see Scheme 2).

The reduction of azabicyclic ketones has received considerable attention.[11] However, except for our earlier reports,[1,4] we are unaware of any reduction studies on the 6-azabicyclo-[3.2.1]octan-3-one ring system. Since we were interested in preparing both the 3α- and 3β-alcohols, we undertook a study to investigate possible stereoselective reduction of the ketone of this ring system. The ketone **15** was chosen for study since it was more stable than **1b** and **1c** and the resulting alcohols **16** and **17** were water-insoluble, stable products that were easily separated by chromatography. The results are summarized in Table 1 and Scheme 3.

The use of platinum catalysts for the reduction of the ketone **15**, although reported to be highly selective with some other bicyclic amino ketones,[11] gave very poor results with **15**. With platinum oxide in methanol, little of the desired alcohols were observed, and the major product was assigned structure **19** on the basis of NMR and mass spectral data analysis. A possible explanation for this result is that the catalyst promoted a ring opening retro-Michael reaction by dative-type binding to the nitrogen to give **18** which was then reduced to **19**.

In a related series of azabicyclic ketones (bicyclic 4-piperidones), House and co-workers concluded that the amine nitrogen had little effect on the reduction stereochemistry with either catalytic or hydride methods.[12] The size of the rings (and thus the steric hindrance) was largely responsible for the observed stereoselectivities. With nearly all the metal hydride reagents we examined, this appeared to be true for the 6-alkyl-6-azabicyclo[3.2.1]octan-3-one system as well. We found that bulky hydride delivery agents gave an excess of the axial α-alcohol, presumably due to a very hindered approach from the bottom face of the molecule, basically a cyclohexanone with two 1,3-diaxial interactions. L-Selectride (lithium tri-*sec*-butylborohydride) gave the greatest selectivity, a 98:2 ratio of α- to β-alcohols (entry 7). Less hindered hydride reagents were, as expected, much less selective. Reduction with sodium cyanoborohydride in acetic acid (entry 11) and catalytic reduction with platinum in acetic acid (entry 3), both methods in which the amine may be assumed to be protonated, provided poor stereoselectivity in accord with the literature reports.[11,12]

The most surprising result was found with low temperature reduction using sodium borohydride in methanol (entry 10). When the crude reaction mixture was quenched with 1 mol dm^{-3} hydrochloric acid above 0 °C, or allowed to remain for more than 12 h at 0 °C before quenching, a nearly equal proportion of α- to β-isomers was obtained. However, when the reaction mixture was quenched with hydrochloric acid at −78 °C after stirring for only 15 min at −78 °C in methanol, a high degree of stereoselectivity was obtained for the β-alcohol. One possible explanation for this could be the formation of a tertiary amine–borane complex as the protonated amine reacts with the borohydride ion.† This delivers a hydride to the carbonyl only from the bottom face of the ring to provide the β-alcohol. In support of this, we found that reduction of the *N*-benzyl ketone hydrochloride (**1c**·HCl) with sodium borohydride in methanol at −78 °C gave only the β-alcohol **1g**. In addition, intermolecular catalysis of borohydride reductions by trialkylamines has been shown not to occur under neutral conditions.[13] Moreover, the reaction of metal borohydrides with trialkylamine hydrochlorides is a known method for preparing amine–boranes,[14] and the reduction of carbonyl groups by amine–boranes is accelerated by aqueous acids.[15,16]

Reduction of the ketone **14** gave results essentially the same as **15**. Thus, reduction of **14** with L-Selectride gave **20**, whereas low temperature sodium borohydride reduction gave **21**. Similar stereoselectivity was also observed in reductions of the racemic *N*-methyl and *N*-benzyl ketones **1b** and **1c**, respectively. L-Selectride reduction provided the 3α-alcohols **1d** and **1f** and sodium borohydride reduction at −78 °C with acid quenching gave the 3β-alcohols **1e** and **1g**.

Catalytic debenzylation followed by catalytic reductive amination using paraformaldehyde of **16**, **17**, **20** and **21** gave the corresponding optically active *N*-methyl analogs of **1d** and **1e**.

Experimental

Melting points were determined on a Thomas Hoover capillary melting-point apparatus and are uncorrected. Infrared (IR) spectra were recorded on either Perkin-Elmer 267 and 467 spectrophotometers, or a Shimadzu IR-400 spectrophotometer. Proton magnetic resonance spectra were obtained on either a Varian EM390 spectrometer or a Bruker WM250 spectrometer. Chemical shifts are reported in δ values relative to tetramethylsilane and all *J* values are in Hz. Carbon-13 magnetic resonance spectra were run on the Bruker WM250 instrument using the deuterium resonance of the solvent as an internal lock. High resolution mass spectra were obtained on a VG Analytical ZAB E spectrometer. All optical rotations were determined at the sodium D line using a Rudolph Research Autopol III polarimeter (1 dm cell). HPLC was conducted on a Waters 510 Model automated gradient-controlled instrument. Elemental analyses were carried out by Atlantic Microlab, Inc., Atlanta, GA, and Galbraith Laboratories, Inc., Knoxville, TN.

N-Methyl-(3-oxo-5-methoxycyclohex-4-ene)carboxamide **4a**.—To a stirred solution of compound[2] **3** (34.0 g, 0.173 mol) in

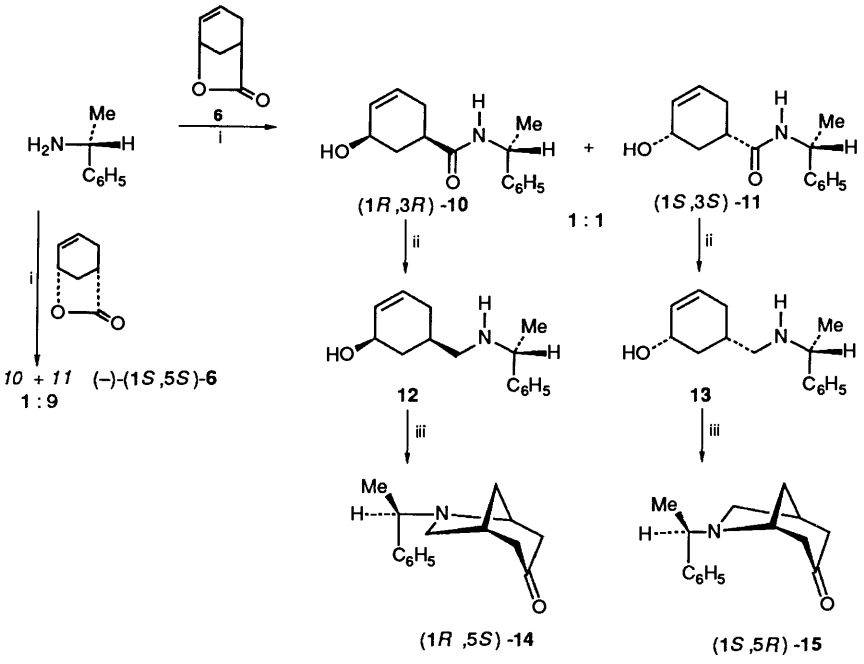
* The sample of (1*S*,5*S*)-**6** used had $[\alpha]_D^{23}$ −164.4° (*c* 2.55, $CHCl_3$). An $[\alpha]_D^{23}$ +179.2 (*c* 9.76, $CHCl_3$) is reported for a 90–95% optically pure sample of (1*R*,5*R*)-**6** (ref. 10).

† We intend to study this reaction in greater detail and determine the extent to which solvent interactions and other variables influence the stereoselectivity.

Table 1 Reduction of *N*-(1-phenylethyl) ketone **15**

Experiment	Reagent	Conditions	Yield[a] (%)	Ratio[b,c] **16**–**17** α:β
1	PtO_2	MeOH, 1 atm H_2, 6 h	4 **16** 71 **19**	—
2	10% Pt/C	40 psi H_2, THF, 24 h	30 20 **19**	29:71
3	10% Pt/C	40 psi H_2, AcOH, 24 h	35	43:57
4	LAH	0 °C→reflux, THF, 3 h	89	33:67
5	DIBAL-H	−78 °C, THF, 2 h	95	73:27
6	$NaEt_3BH$	−78 °C, THF, 1.25 h	89	96:4
7	L-Selectride	−78 °C, THF, 2 h	94	98:2
8	$NaBH_4$	reflux, THF, 14 h	93	35:65
9	$NaBH_4/CeCl_3$	0 °C→rt, MeOH, 3 h	87	14:86
10	$NaBH_4$	−78 °C, MeOH, 15 min[d]	94	2:98
11	$NaCNBH_3$	rt, AcOH, 3 h	75	79:21

[a] All reactions were performed on a 0.2–0.5 mmol scale. The yields reported are isolated yields. [b] The α and β isomers were separated by flash chromatography. [c] The structures of the α- and β-alcohols were established by NMR analysis. [d] The reaction was quenched at −78 °C using hydrochloric acid (1 mol dm^{-3}).



Scheme 2 Structures with wedged and dotted bonds are optically active. *Reagents:* i, xylene; ii, LAH, THF; iii, MnO_2, CH_2Cl_2

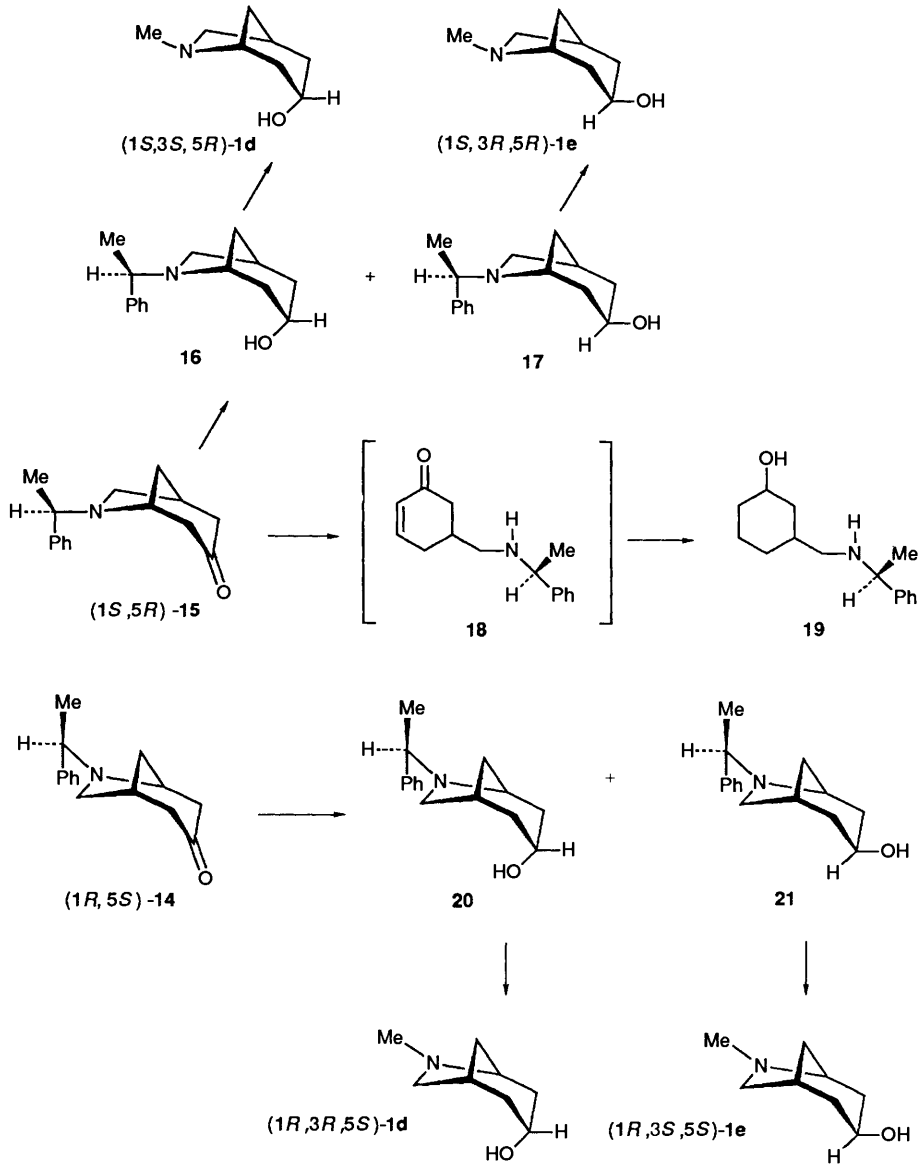
acetone (325 cm^3) and water (6 cm^3) was added toluene-*p*-sulphonic acid (70 mg). After 24 h at 25 °C, the mixture was cooled and filtered. The solid was washed with a small amount of chilled acetone and dried to give **4a** (26.84 g). An additional quantity (0.85 g) of **4a** was obtained from the mother liquor on cooling to give **4a** (27.69 g, 87%), m.p. 168–170 °C. The analytical sample was recrystallized from MeOH, m.p. 170–171 °C; $\delta_H(CDCl_3)$ 2.71 (3 H, d, NMe), 3.68 (3 H, s, OMe), 5.33 (1 H, s, 4-H) and 6.3 (1 H, br s, NH) (Found: C, 59.05; H, 7.15; N, 7.65. $C_9H_{13}NO_3$ requires C, 59.00; H, 7.15; N, 7.65%).

N-*Methyl*-(3-*hydroxycyclohex*-4-*ene*)*carboxamide* **7a**.—A solution of the lactone[5,6] **6** (5.13 g, 0.041 mol) in MeOH (7 cm^3) was placed in a bomb reactor and cooled in a dry ice–acetone bath. Methylamine (2.6 g, 0.083 mol) was added and the reactor sealed. The reaction mixture was heated at 110 °C in an oil bath for 5 h. The contents of the reactor were removed and the volatiles removed to give pure **7a** (6.29 g, 98%) as a pale yellow oil; $\delta_H(CDCl_3)$ 2.75 (3 H, d, NMe), 4.26 (1 H, dd, CHO) and 5.70 (2 H, s, olefinic); $\delta_C(CDCl_3)$ 25.3, 27.6 (C-2 and C-3), 34.1 (C-1), 39.0 (NMe), 65.3 (C-3), 126.0 and 130.6 (C-5 and C-4) and 175.9 (C=O).

An analytical sample was prepared by silica gel chromatography using 10% MeOH–CH_2Cl_2 as the eluent (Found: 61.85; H, 8.45; N, 8.95. $C_8H_{13}NO_2$ requires C, 61.91; H, 8.44; N, 9.03%).

N-*Methyl*-(3-*hydroxycyclohex*-4-*enyl*)*methylamine* **8a**.—A solution of the carboxamide **7a** (6.33 g, 0.041 mol) in THF (15 cm^3) was added to a suspension of $LiAlH_4$ (3.1 g, 0.082 mol) in THF (100 cm^3). After 7 h under reflux, the excess of $LiAlH_4$ was decomposed by adding water (3.1 cm^3), aqueous NaOH (3 mol dm^3, 3.1 cm^3) and water (9.3 cm^3) in succession. The precipitate was separated by filtration and washed with THF. The filtrate and the washings were evaporated to dryness to give **8a** (5.78 g, 100%) as a waxy solid. Trituration with Et_2O gave crystalline material, m.p. 74.5–75 °C; $\delta_H(CDCl_3)$ 2.41 (3 H, s, NMe), 4.18 (1 H, m, CH–O) and 5.74 (2 H, s, olefinic); $\delta_C(CDCl_3)$ 29.4, 31.5 (C-2 and C-6), 36.2 and 36.3 (C-1 and NMe), 57.6 (CH_2N), 64.7 (C-3), and 127.1 and 131.15 (C-5 and C-4) (Found: C, 67.95; H, 10.75; N, 9.9. $C_8H_{15}NO$ requires C, 68.04; H, 10.71; N, 9.92%).

6-*Methyl*-6-*azabicyclo*[3.2.1]*octan*-3-*one* **1b**.—(*a*) *From* **4a**.



Scheme 3 Structures with wedged and dotted bonds are optically active

To a suspension of $LiAlH_4$ (19 g, 0.5 mol) in THF (250 cm^3) under an atmosphere of argon, was added a solution of **4a** (28.87 g, 0.158 mol) in THF (250 cm^3) dropwise. After the addition, the mixture was heated at reflux for 4 h. The reaction mixture was cooled in an ice bath, and the excess of $LiAlH_4$ was decomposed by sequential addition of water (20 cm^3), 15% NaOH (20 cm^3) and water (60 cm^3). The white precipitate formed after 30 min was separated by filtration and washed with THF. The filtrate and washings were evaporated to dryness under reduced pressure. The residue was dissolved in CH_2Cl_2 and dried (Na_2SO_4). The CH_2Cl_2 solution was evaporated to dryness to give the amino derivative **5** (26.16 g, 97%) as a pale yellow solid.

A solution of **5** (3.56 g, 0.021 mol) in methanol (50 cm^3) containing 5% dry hydrogen chloride was stirred overnight. After the mixture was evaporated to dryness, the residue was treated with aqueous Na_2CO_3 until the mixture remained basic (1.5 cm^3). The aqueous solution was stirred for 30 min and $CHCl_3$ (100 cm^3) was added. The $CHCl_3$ solution was separated and evaporated to dryness to give **1b** (2.79 g, 96%). The sample was chromatographed on alumina (Activity III), eluting with 1% MeOH–CH_2Cl_2 to give **1b** as a pale yellow oil (1.56 g, 54%), $\delta_H(CDCl_3)$ 1.85 (1 H, d), 2.11 (1 H, m), 2.26 (1 H, m), 2.40 (3 H, s, NMe), 2.65 (3 H, m), 2.85 (1 H, m) and 3.25 (1 H, m); $\delta_C(CDCl_3)$ 34.5, 34.9, 40.5, 46.9, 48.0, 59.4, 60.0 and 209.5.

The sample was converted into the HCl salt and recrystallized from MeOH–EtOAc to give **1b**·HCl, m.p. 157–158 °C; $\delta_H(CDCl_3)$ 2.33 (1 H, m), 2.81 (8 H, m), 3.27 (1 H, m), 4.04 (1 H, m) and 4.22 (3 H, s, NMe) (Found: C, 54.8; H, 8.05; N, 8.0. $C_8H_{14}ClNO$ requires C, 54.70; H, 8.03; N, 7.97%).

(*b*) *From* **8a**. A mixture of amine **8a** (4.27 g, 0.03 mol) and activated MnO_2 (21.06 g, 0.24 mol) in CH_2Cl_2 (100 cm^3) was stirred for 20 h at room temperature. The catalyst was separated by filtration and washed with CH_2Cl_2. The filtrate and washings were evaporated to give an oily product which was purified by column chromatography on alumina (Activity III) eluting with 1% MeOH–CH_2Cl_2. The product fractions gave **1b** as a pale yellow oil (3.37 g, 80%): the ^1H NMR spectrum was identical with the spectrum of **1b** prepared from **4a**.

The sample was converted into the HCl salt and recrystallized from MeOH–EtOAc to give **1b**·HCl (3.60 g, 84%), m.p. 157–158 °C. The ^1H NMR was identical to the spectrum of **1b**·HCl prepared from **4a**.

N-*Benzyl*-(3-*hydroxycyclohex*-4-*ene*)*carboxamide* **7b**.—A solution of benzylamine (2.6 g, 0.024 mol) and lactone **6** (2.0 g, 0.016 mol) in xylene (20 cm^3) was heated at reflux for 12 h. When the reaction mixture had cooled to room temperature, the crude product precipitated as a white solid which was collected and recrystallized from CH_2Cl_2–hexane to give **7b** (2.76 g, 75%) as a fluffy white solid, m.p. 128–129 °C; $\delta_H(CDCl_3)$ 1.85 (1 H, m), 2.20 (4 H, m), 2.60 (1 H, m), 4.23 (1 H, t, CHOH), 4.40 (2 H, d, $PhCH_2$) 5.73 (2 H, br s, HC=CH), 6.05 (1 H, br s, NH) and 7.28 (5 H, m, Ph) (Found: C, 72.55; H, 7.4; N, 6.0. $C_{14}H_{17}NO_2$ requires C, 72.20; H, 7.41; N, 6.06%).

6-*Benzyl*-6-*azabicyclo*[3.2.1]*octan*-3-*one* **1c**.—A solution of the amide **7b** (2.60 g, 0.011 mol) in THF (100 cm^3) was added dropwise to a stirred suspension of LAH (0.84 g, 0.022 mol) in THF (50 cm^3) maintained at 0 to 5 °C. After the addition was complete, the mixture was heated at reflux for 16 h. The reaction was quenched at 0 °C by successive addition of water (1 cm^3), aqueous NaOH (3 mol dm^3, 1 cm^3) and water (3 cm^3), and stirred at 25 °C for an additional 45 min. The precipitated salts were removed by filtration and washed with diethyl ether (3 × 50 cm^3). The combined filtrates were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give the crude amine **8b** as a clear oil, TLC (silica, ethyl acetate) R_f 0.05; $\delta_H(CDCl_3)$ 1.48 (1 H, m), 1.78 (2 H, m), 2.12 (4 H, m), 2.65 (2 H, m), 3.78 (2 H, s, CH_2Ph), 4.17 (1 H, m, CHOH), 5.75 (2 H, br s, HC=CH) and 7.30 (5 H, m, Ph).

Activated manganese dioxide (12.0 g) was added to a solution of amine **8b** (from the above reaction) in CH_2Cl_2 (80 cm^3) and the mixture was stirred at room temperature for 2.2 h. The catalyst was removed by filtration through Celite and the solvent was removed by rotary evaporation to give the ketone **1c** (2.19 g, 90% from **7b**) as white crystals, m.p. 78–79 °C (lit.,[3] 80–81 °C); TLC (silica, 10% methanol in CH_2Cl_2) R_f 0.60; $\delta_H(CDCl_3)$ 1.80 (1 H, d, *J* 11.5), 2.10 (1 H, m), 2.18 (1 H, dd, *J* 1.5, 16.5), 2.45 (2 H, br s), 2.60 (2 H, m), 2.82 (2 H, m), 3.34 (1 H, br s), 3.75 (2 H, d, CH_2Ph) and 7.28 (5 H, m, Ph).

(1R,3R)-*and*(1S,3S)-N-[(R)-1-*Phenylethyl*]-(3-*hydroxycyclohex*-4-*ene*)*carboxamide* **10** *and* **11**.—A mixture of (R)-(+)-α-methylbenzylamine (37.6 g, 0.310 mol) and racemic lactone **6** (19.3 g, 0.16 mol) in xylene (100 cm^3) was heated at reflux for 20 h. The reaction mixture was allowed to cool to room temperature and the crude product precipitated as a white solid. This was collected and recrystallized from CH_2Cl_2–hexane to give **10** and **11** as a mixture (24.1 g) of diastereoisomers. A further quantity (5.7 g) of **10** and **11** was obtained from the mother liquor (81% total yield).

A sample (11.9 g) of the diastereoisomeric mixture of **10** and **11** was separated by flash chromatography on 550 g of silica gel using a gradient elution technique (20:1 to 5:1 diethyl ether–ethyl acetate) and the pure fractions were combined. After recrystallization from CH_2Cl_2–hexane, 3.86 g of the less polar 1*R*,3*S* amide **10** and 4.12 g of the more polar 1*R*,3*S* amide **11** were obtained as fluffy white solids. Analysis by HPLC (ethyl acetate, Dynamax 60A silica column, 2 cm^3/min flow rate, 256 nm UV detection) indicated each amide to be of greater than 98% diastereoisomeric purity.

Physical data for **10**, m.p. 163–164 °C; TLC (silica, 5:1 ethyl ether–ethyl acetate) R_f 0.29; $\delta_H(CDCl_3)$ 1.50 (3 H, d, *J* 7, Me), 1.78 (1 H, m), 2.00–2.40 (3 H, m), 2.55 (1 H, m), 2.91 (1 H, d, *J* 8), 4.22 (1 H, m, CHOH), 5.12 (1 H, q, NCHMe), 5.83 (2 H, br s, HC=CH), 5.92 (1 H, m, NH) and 7.31 (5 H, m, Ph); $[\alpha]_D^{24}$ +98.0° (*c* 1, $CHCl_3$) (Found: C, 73.35; H, 7.85; N, 5.75. $C_{15}H_{19}NO_2$ requires C, 73.44; H, 7.81; N, 5.71%).

Physical data for **11**, m.p. 155.5–157 °C; TLC (silica, 5:1 diethyl ether–ethyl acetate) R_f 0.25; $\delta_H(CDCl_3)$ 1.49 (3 H, d, *J* 7, Me), 1.85 (1 H, m), 2.12–2.35 (3 H, m), 2.53 (1 H, m), 3.00 (1 H, d, *J* 8), 4.23 (1 H, m, CHOH), 5.11 (1 H, q, NCHMe), 5.75 (2 H, br s, HC=CH), 5.97 (1 H, m, NH) and 7.32 (5 H, m, Ph); $[\alpha]_D^{24}$ +81.6° (*c* 1, $CHCl_3$) (Found: C, 73.55; H, 7.85; N, 5.7. $C_{15}H_{19}NO_2$ requires C, 73.44; H, 7.81; N, 5.71%).

Determination of Absolute Stereochemistry of **10** *and* **11**.—To a stirred solution of 2000 units of pig liver esterase in phosphate buffer (0.1 mol dm^{-3}, 80 cm^3, pH 8) at room temperature (23 °C) was added a solution of racemic **6** (4.25 g, 0.034 mol) in MeOH (5 cm^3). The pH was maintained at 8 by adding 1 mol dm^{-3} NaOH. After the addition of approximately 34 cm^3 of NaOH (about 25 h), the pH of the reaction was raised to 10, and the mixture was extracted with CH_2Cl_2. The dried (Na_2SO_4) CH_2Cl_2 extracts were concentrated and the residue purified by column chromatography on silica gel, eluting with solvent mixture of EtOAc–hexane (1:3) to give (1*S*,5*S*)-**6** [1.85 g, 43.5% or 87% of the (−)-isomer], $[\alpha]_D^{23}$ −164.4° (*c* 2.55, $CHCl_3$).

A solution of the lactone (1*S*,5*S*) **6** (1.24 g, 0.01 mol) and (*R*)-(+)-α-methylbenzylamine (1.33 g, 0.011 mol) toluene (10 cm^3) was heated to reflux for 8 h. The precipitate obtained upon cooling was separated, washed with light petroleum and dried to give a product which was mainly **11** (1.8 g, 74%), m.p. 154–156 °C; $[\alpha]_D^{23}$ +75.8° (*c* 0.78, $CHCl_3$). HPLC analysis (EtOAc–hexane, 7:3, Dynamax 60A, silica gel column, 2 cm^3/min flow rate, 256 nm UV detector) showed the mixture to contain 90% of **11** and 10% of **10**.

(1R,3R)-N-[(R)-1-*Phenylethyl*]-(3-*hydroxycyclohex*-4-*enyl*)-*methylamine* **12**.—A solution of amide **10** (4.00 g, 0.016 mol) in THF (150 cm^3) was added dropwise to a stirred suspension of LAH (1.24 g, 0.033 mol) in THF (80 cm^3) maintained at 0 to 5 °C. After the addition was complete, the mixture was heated at reflux for 16 h. The reaction was quenched at 0 °C by successive addition of water (1.5 cm^3), aqueous NaOH (3 mol dm^{-3}, 1.5 cm^3) and water (4.5 cm^3). The mixture was stirred for 45 min at room temperature, the precipitated salts were removed by filtration and washed with ethyl ether (3 × 75 cm^3). The combined filtrates were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give the amine **12** (3.81 g, 100%) as a clear oil and of sufficient purity to be used in the next reaction: TLC (silica, ethyl acetate) R_f 0.10; $\delta_H(CDCl_3)$ 1.36 (3 H, d, *J* 6.5, Me), 1.46 (1 H, m), 1.70 (1 H, m), 1.94 (1 H, m), 2.13 (2 H, m), 2.51 (2 H, m), 2.80 (2 H, br s), 3.71 (1 H, q, *J* 6.5, CHMe), 4.18 (1 H, m, CHOH), 5.74 (2 H, m, HC=CH) and 7.28 (5 H, m, Ph).

An analytical sample of **12**·HCl recrystallized from methanol–diethyl ether had m.p. 176–177 °C (Found: C, 67.1; H, 8.3; Cl, 13.35; N, 5.2. $C_{15}H_{22}ClNO$ requires C, 67.28; H, 8.28; Cl, 13.24; N, 5.23%).

(1S,3S)-N-[(R)-1-*Phenylethyl*]-(3-*hydroxycyclohex*-4-*enyl*)-*methylamine* **13**.—A similar procedure provided the diastereoisomeric 1*S*,3*S* amine **13** from amide **11**: TLC (silica, ethyl acetate) R_f 0.10; $\delta_H(CDCl_3)$ 1.41 (3 H, d, *J* 6.5, Me), 1.45 (1 H, m), 1.82 (1 H, dd), 1.92 (1 H, m), 2.06 (1 H, m), 2.19 (1 H, m), 2.42 (1 H, dd), 2.56 (1 H, dd), 3.38 (2 H, br s), 3.77 (1 H, q, *J* 6.5, CHMe), 4.18 (1 H, m, CHOH), 5.74 (2 H, m, HC=CH) and 7.31 (5 H, m, Ph).

An analytical sample of **13**·HCl recrystallized from MeOH and ether had m.p. 108–110 °C (Found: C, 66.05; H, 8.4; N, 5.1. $C_{15}H_{22}ClNO \cdot \frac{1}{4}H_2O$ requires C, 66.16; H, 8.33; N, 5.14%).

(1R,5S)-6-[(R)-1-*Phenylethyl*]-6-*azabicyclo*[3.2.1]*octan*-3-*one* **14**.—Activated manganese dioxide (22.0 g, 0.25 mol) was added to a stirred solution of **12** (3.80 g, 0.016 mol) in CH_2Cl_2 (100 cm^3). After 2 h, the manganese dioxide was removed by

filtration through Celite and the solvent was removed by rotary evaporation to give a light brown oil. After being dried under reduced pressure and set aside overnight in the freezer a waxy solid formed. Recrystallization from diethyl ether–hexane gave **14** (3.22 g, 86%), m.p. 65–66 °C; TLC (silica, 10% methanol in CH_2Cl_2) R_f 0.63; ν_{max}(KBr)/cm^{-1} 1711; δ_H($CDCl_3$) 1.26 (3 H, d, *J* 6.5, Me), 1.74 (1 H, d, *J* 7.5), 2.05 (2 H, m), 2.44 (3 H, m), 2.62 (1 H, m), 2.77 (2 H, m), 3.30 (1 H, m), 3.57 (1 H, q, *J* 6.5, CHMe) and 7.24 (5 H, m, Ph); $[\alpha]_D^{24}$ +17.7° (*c* 1, $CHCl_3$) (Found: C, 78.65; H, 8.4; N, 6.15. $C_{15}H_{19}NO$ requires C, 78.56; H, 8.35; N, 6.11%).

(1S,5R)-6-[(R)-1-*Phenylethyl*]-6-*azabicyclo*[3.2.1]*octan*-3-*one* **15**.—An analogous procedure provided the ketone **15** (3.12 g, 96%) as a waxy solid from reaction of **13** (3.29 g, 0.014 mol) and manganese dioxide (26.0 g). An analytical sample was recrystallized from diethyl ether–hexane, m.p. 60–61 °C; TLC (silica, 10% methanol in CH_2Cl_2) R_f 0.63; IR (KBr)/cm^{-1} 1710; δ_H($CDCl_3$) 1.31 (3 H, d, *J* 6.5, Me), 1.79 (1 H, d), 2.04 (1 H, m), 2.15 (1 H, d), 2.43 (2 H, br s), 2.52 (3 H, m), 2.89 (1 H, dd), 3.41 (1 H, m), 3.65 (1 H, q, *J* 6.5, CHMe) and 7.28 (5 H, m, Ph); $[\alpha]_D^{24}$ +9.5° (*c* 1, $CHCl_3$) (Found: C, 78.65; H, 8.4; N, 6.1. $C_{15}H_{19}NO$ requires C, 78.56; H, 8.35; N, 6.11%).

Catalytic Hydrogenation of **15**.—Reduction of ketone **15** with platinum catalysts (see Table 1) gave varying amounts of **19**, TLC (silica, 90:9:1, $CHCl_3$–MeOH–NH_4OH) R_f 0.39; δ_H($CDCl_3$) 0.86 (2 H, m), 1.27 (2 H, m), 1.31 (3 H, d, CH*Me*), 1.58 (3 H, m), 1.72 (2 H, m), 1.97 (2 H, m), 2.36 (2 H, m), 3.54 (1 H, m, CHOH), 3.71 (1 H, q, C*H*Me) and 7.31 (5 H, m, Ph); *m*/*z* (EI) 233 (M^+, 5), 218 (M − Me, 30), 134 (68), 106 (22) and 105 (100); ν_{max}(film, NaCl)/cm^{-1} 3345br (OH), 3020, 2920, 2850 and 1450.

A HCl salt of **19** was recrystallized from methanol–diethyl ether, m.p. 153–155 °C (Found: C, 64.1; H, 9.05; Cl, 12.65; N, 5.00. $C_{15}H_{21}ClNO{\cdot}\frac{2}{3}H_2O$ requires C, 63.93; H, 9.06; Cl, 12.58; N, 4.97%).

(1R,3R,5S)-6-[(R)-1-*Phenylethyl*]-6-*azabicyclo*[3.2.1]*octan*-3α-*ol* **20**.—The ketone **14** (3.22 g, 0.014 mol) was dissolved in THF (75 cm^3) and cooled to −78 °C with stirring. L-Selectride (21.1 cm^3) of a 1.0 mol dm^{-3} solution in THF) was added dropwise *via* a syringe (10 min), and the reaction mixture was stirred for 3 h at −78 °C, then allowed to warm to 0 °C. The reaction was quenched by addition of NaOH (3 mol dm^{-3}) and 30% aqueous H_2O_2 and stirred for 2 h. The mixture was filtered, the filtrate was evaporated and the resulting residue was partitioned between CH_2Cl_2 and 10% NH_4OH. The aqueous layer was extracted with three further portions of CH_2Cl_2, and the combined organic fractions (200 cm^3) was dried ($NaSO_4$) and the solvent was evaporated to give an oil. During storage in the freezer this solidified to give **20** (2.72 g, 84%) as off-white crystals of sufficient purity to be used in the next step. An analytical sample was recrystallized from methanol, m.p. 125–126 °C; TLC (90:9:1 $CHCl_3$–MeOH–NH_4OH) R_f 0.75; δ_H($CDCl_3$) 1.40 (3 H, d, CHMe), 1.45 (2 H, m), 1.75 (2 H, m), 1.90 (3 H, m), 2.65 (2 H, m), 3.10 (1 H, t), 3.44 (2 H, m), 3.90 (1 H, m, $W_{\frac{1}{2}}$ 12 Hz, CHOH) and 7.25 (5 H, m, Ph); $[\alpha]_D^{23}$ −4.4° (*c* 0.75, $CHCl_3$) (Found: C, 77.75; H, 9.2; N, 6.05. $C_{15}H_{21}NO$ requires C, 77.88; H, 9.15; N, 6.05%).

(1S,3S,5R)-6-[(R)-1-*Phenylethyl*]-6-*azabicyclo*[3.2.1]*octan*-3α-*ol* **16**.—A similar procedure yielded **16** (2.48 g, 98%) as a waxy yellow solid from **15** (2.50 g, 0.011 mol). An analytical sample was recrystallized from MeOH–ethyl ether, m.p. 78.5–80 °C; TLC (90:9:1 $CHCl_3$–MeOH–NH_4OH) R_f 0.75; δ_H($CDCl_3$) 1.42 (3 H, d, CHMe), 1.43 (1 H, m), 1.61–2.12 (6 H, m), 2.33 (2 H, m), 2.91 (1 H, d, *J* 9), 3.52 (1 H, t), 3.59 (1 H, q, CHMe), 3.94 (1 H, m, $W_{\frac{1}{2}}$ 10.5 Hz, CHOH) and 7.27 (5 H, m, Ph); $[\alpha]_D^{23}$ +20.3° (*c* 0.75, $CHCl_3$) (Found: C, 77.7; H, 9.2; N, 6.0. $C_{15}H_{21}NO$ requires C, 77.88; H, 9.15; N, 6.05%).

(1R,3S,5S)-6-[(R)-1-*Phenylethyl*]-6-*azabicyclo*[3.2.1]*octan*-3β-*ol* **21**.—The ketone **14** (1.65 g, 0.007 mol) was dissolved in methanol (40 cm^3) and cooled with stirring to −78 °C. An excess of sodium borohydride (1.65 g) was added in three portions, and the mixture was stirred for 30 min at −78 °C. The reaction was quenched at −78 °C by dropwise addition of HCl (1 mol dm^{-3}) until bubbling ceased. The volume of the mixture was reduced to *ca.* 5 cm^3 by rotary evaporation, and the residue was partitioned between 20% NH_4OH and CH_2Cl_2. The aqueous layer was extracted with three further portions of CH_2Cl_2, and the combined fractions were reduced under reduced pressure to an oil. This was subjected to flash chromatography (silica, 94:5:1 $CHCl_3$–MeOH–NH_4OH) to give **21** (1.60 g, 96%) as a clear oil which crystallized during storage. The sample was recrystallized from CH_2Cl_2–light petroleum, m.p. 65–68 °C; TLC (90:9:1 $CHCl_3$–MeOH–NH_4OH) R_f 0.45; δ_H(90 MHz, $CDCl_3$) 1.15 (1 H, t), 1.32 (3 H, d, CHMe), 1.45 (1 H, m), 1.73–2.58 (6 H, m), 2.72 (2 H, br s), 3.12 (1 H, t), 3.55 (1 H, q, CHMe), 4.15 (1 H, m, $W_{\frac{1}{2}}$ 20 Hz, CHOH) and 7.28 (5 H, m, Ph); $[\alpha]_D^{23}$ −15.95 (*c* 0.81, $CHCl_3$) (Found: M^+, 231.1621. $C_{15}H_{21}NO$ requires M^+, 231.1623) (Found: C, 76.5; H, 9.15; N, 5.9. $C_{15}H_{21}NO{\cdot}0.25\ H_2O$ requires C, 76.39; H, 9.19; N, 5.94%).

(1S,3R,5R)-N-[(R)-1-*Phenylethyl*]-6-*azabicyclo*[3.2.1]*octan*-3β-*ol* **17**.—The diastereoisomer **17** was obtained in a similar manner from reduction of ketone **15** as a clear oil which solidified on trituration with light petroleum, m.p. 120–123 °C; TLC (90:9:1 $CHCl_3$–MeOH–NH_4OH) R_f 0.42; δ_H(250 MHz, $CDCl_3$) 1.16 (1 H, t), 1.30 (2 H, m), 1.31 (3 H, d, CHMe), 1.72 (2 H, m), 1.96 (1 H, m), 2.04 (1 H, m), 2.36 (1 H, m), 2.57 (1 H, d), 2.84 (1 H, dd), 3.22 (1 H, t), 3.67 (1 H, q, CHMe), 4.17 (1 H, m, $W_{\frac{1}{2}}$ 21, CHOH) and 7.28 (5 H, m, Ph); $[\alpha]_D^{23}$ +5.87 (*c* 0.749, $CHCl_3$) (Found: M^+, 231.1625. $C_{15}H_{21}NO$ requires M^+, 231.1623) (Found: C, 76.45; H, 9.2; N, 5.95. $C_{15}H_{21}NO{\cdot}0.25\ H_2O$ requires C, 76.39; H, 9.19; N, 5.94%).

(1R,3R,5S)-6-*Methyl*-6-*azabicyclo*[3.2.1]*octan*-3α-*ol* [(1R,3R,5S)-**1d**].—The α-alcohol **20** (6.5 g, 0.028 mol) and 1.8 g of 10% Pd/C in methanol (150 cm^3) were stirred under a hydrogen atmosphere for 24 h. The catalyst was removed by filtration through Celite and washed with three 100 cm^3 portions of methanol. Evaporation of solvent from the filtrate yielded a yellow solid. This solid was dissolved in 200 cm^3 of methanol, and paraformaldehyde (1.5 g, 0.05 mol) was added. The mixture was stirred for 10 min, 0.5 g 10% Pd/C was added and the suspension was stirred under hydrogen (1 atm) for 6 h. The catalyst was removed by filtration through Celite, the solvent evaporated, and the resulting residue was purified by chromatography (alumina). Elution with $CHCl_3$ removed nonpolar impurities. Elution with $CHCl_3$–MeOH–NH_4OH (40:9:1) gave the 6-methyl alcohol (1*R*,3*R*,5*S*)-**1d** (3.1 g, 79%) as a clear oil: TLC (silica, 40:9:1 $CHCl_3$–MeOH–NH_4OH) R_f 0.05; δ_H($CDCl_3$) 1.40 (1 H, d, *J* 11), 1.51 (1 H, dd, *J* 0.7, 4.5), 1.78–2.01 (4 H, m), 2.28–2.40 (2 H, m), 2.40 (3 H, s, NMe), 3.04 (1 H, t), 3.34 (1 H, dd), 3.89 (1 H, br s, $W_{\frac{1}{2}}$ 12, CHOH) and 5.50–6.50 (1 H, br s, OH, concentration dependent) (Found: M^+, 141.1152. $C_8H_{15}NO$ requires M^+, 141.1154).

(1S,3S,5R)-6-*Methyl*-6-*azabicyclo*[3.2.1]*octan*-3α-*ol* [(1S,3S,5R)-**1d**].—The enantiomer (1*S*,3*S*,5*R*)-**1d** was prepared by the same procedure as (1*R*,3*R*,5*S*)-**1d** and possessed identical TLC and NMR properties (Found: M^+, 141.1152. $C_8H_{15}NO$ requires M^+, 141.1154).

(1S,3R,5R)-6-*Methyl*-6-*azabicyclo*[3.2.1]*octan*-3β-*ol* [(1S,3R,5R)-**1e**].—The β-isomer (1*S*,3*R*,5*R*)-**1e** was prepared by a procedure similar to that described for (1*R*,3*R*,5*S*)-**1d**. Thus, **17** (1.65 g, 0.007 mol) was hydrogenated with 0.15 g Pd/C for 20 h under 1 atm of hydrogen. After removal of the catalyst, the solution was mixed with paraformaldehyde (0.75 g, 0.025 mol) and Pd/C (0.15 g) and again hydrogenated under 1 atm of H_2 for 10 h. The catalyst was removed, and the residue, after evaporation of the MeOH, was purified by column chromatography on alumina (Activity III) eluting with a solvent mixture of $CHCl_3$–CH_3OH–NH_4OH (90:9:1) to give (1*S*,3*R*,5*R*)-**1e** (1.0 g, 100%) as a clear oil: $\delta_H(CDCl_3)$ 1.22 (1 H, d, *J* 10.8), 1.32 (1 H, d, *J* 11.5), 1.40 (1 H, d, *J* 11.0), 1.78 (1 H, m), 1.97 (1 H, m), 2.18 (1 H, m), 2.35 (m, 1 H), 2.40 (3 H, s, NMe), 2.68 (2 H, m), 3.05 (1 H, m), 3.43 (1 H, m), 3.98 (1 H, m, $W_{\frac{1}{2}}$ 23 Hz, CHOH) (Found: M^+, 141.1152. $C_8H_{15}NO$ requires M^+, 141.1154).

(1R,3S,5S)-6-*Methyl*-6-*azabicyclo*[3.2.1]*octan*-3β-*ol* [(1R,3S,5S)-**1e**]. The 6-methyl β-alcohol (1*R*,3*S*,5*S*)-**1e** was prepared from **21** as a clear oil: ^1H NMR and TLC were identical with the (1*S*,3*R*,5*R*)-**1e** isomer (Found: M^+, 141.1152. $C_8H_{15}NO$ requires M^+, 141.1154).

(±)-6-*Methyl*-6-*azabicyclo*[3.2.1]*octan*-3α-*ol* **1d**.—The racemic alcohol **1d** was obtained by reduction of the 6-methyl ketone **1b** with L-Selectride, followed by a non-oxidative, non-aqueous work-up. The ketone **1b** (750 mg, 0.005 mol) was dissolved in THF (25 cm^3) and cooled to −78 °C with stirring. L-Selectride (8.1 cm^3 of a 1.0 mol dm^{-3} solution in THF) was added dropwise *via* a syringe (5 min), and the reaction mixture was stirred for 2 h at −78 °C. The reaction was quenched by addition of aqueous NaOH (3 mol dm^{-3}, 0.8 cm^3) at −78 °C and allowed to warm slowly to room temperature. After dilution with diethyl ether and filtration through a sintered glass funnel, the filtrate was concentrated by rotary evaporation. The resulting residue was purified by flash chromatography (alumina, Activity III, gradient of 95:5 to 80:20 $CHCl_3$–MeOH with 0.5% NH_4OH) to yield the racemic alcohol **1d** (651 mg, 85%) as an oil. None of the β-alcohol **1e** could be detected in the 250 MHz ^1H NMR spectrum of **1d**.

(±)-6-*Benzyl*-6-*azabicyclo*[3.2.1]*octan*-3α-*ol* **1f**.—The ketone **1c** gave the α-alcohol **1f** after reduction with L-Selectride in a manner analogous to preparation of alcohol **1d**. Data for α-alcohol **1f**: $\delta_H(CDCl_3)$ 1.45 (2 H, m), 1.98 (4 H, m), 2.45 (2 H, m), 3.28 (2 H, m), 3.72 (2 H, s, CH_2Ph), 3.85 (1 H, br s, $W_{\frac{1}{2}}$ 12 Hz, CHOH), 5.80 (br s, OH) and 7.30 (5 H, m, Ph) (Found: C, 76.45; H, 8.95; N, 6.3%; M^+, 217.1468. $C_{14}H_{19}NO$ requires C, 77.01; H, 8.88; N, 6.45%; M^+, 217.1467).

(±)-6-*Benzyl*-6-*azabicyclo*[3.2.1]*octan*-3β-*ol* **1g**.—*Method A from* **1c**. The ketone **1c** (50 mg, 0.23 mmol) was dissolved in methanol (5 cm^3) and cooled with stirring to −78 °C. An excess of sodium borohydride (50 mg) was added and the mixture was stirred for 15 min at −78 °C. The reaction was quenched at −78 °C by dropwise addition of 1 mol dm^{-3} HCl until bubbling ceased. The volume of the mixture was reduced to *ca.* 2 cm^3 by rotary evaporation and the residue was partitioned between 20% NH_4OH and CH_2Cl_2. The aqueous layer was extracted with three further portions of CH_2Cl_2 and the combined fractions were evaporated under reduced pressure to an oil. This was subjected to flash chromatography (silica, 94:5:1 $CHCl_3$–MeOH–NH_4OH) to give **1g** (48 mg, 96%) as a clear oil: $\delta_H(CDCl_3)$ 1.32 (3 H, m), 1.90 (3 H, m), 2.45 (2 H, m), 2.72 (2 H, d), 3.18 (1 H, t), 3.75 (2 H, s, CH_2Ph), 4.15 (1 H, m, $W_{\frac{1}{2}}$ 23 Hz, CHOH) and 7.28 (5 H, m, Ph) (Found: C, 76.7; H, 8.9; N, 6.4%; M^+, 217.1468. $C_{14}H_{19}NO$ requires C, 77.01; H, 8.88; N, 6.45%; M^+, 217.1467).

Method B from **1c**·HCl. The ketone **1c** (329 mg, 1.53 mmol) was dissolved in 5% methanolic HCl (50 cm^3) and evaporated to dryness under reduced pressure and dried *in vacuo*. The **1c**·HCl thus formed was dissolved in MeOH (5 cm^3) and cooled in dry ice (acetone bath). A solution of $NABH_4$ (110 mg, 3 mmol) in MeOH (5 cm^3) was added dropwise over a period of 10 min. The mixture was diluted with water (10 cm^3), and the pH was brought to 1–2 with dilute HCl, stirred for 5 min at room temperature, and basified with concentrated NH_4OH. The mixture was extracted with CH_2Cl (3 × 20 cm^3), dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel. Eluting with a solvent mixture (90:9:2, $CHCl_3$–MeOH–NH_4OH) gave **1g** (0.26 g, 80%) as a clear oil. The physical characteristics were identical with the sample obtained in Method A.

(±)-6-*Methyl*-6-*azabicyclo*[3.2.1]*octan*-3β-*ol* **1e**.—The ketone **1b** was reduced to the β-alcohol **1e** with sodium borohydride in a manner similar to the preparation of the alcohol **1g** (Method A). After chromatography (Alumina, Activity III, $CHCl_3$–CH_3OH–NH_4OH 90:9:1), the clear oil was converted into the hydrochloride salt. The hydrochloride salt was recrystallized from MeOH–Et_2O, m.p. 234–236 °C (lit.,[1] 235–236 °C). TLC and NMR spectra were identical with those described earlier.[1]

Acknowledgements

This research was supported by Grant AG-07418 from the National Institute on Aging.

References

1 F. I. Carroll, P. Abraham, K. Parham, R. C. Griffith, A Ahmad, M. M. Richard, F. N. Padilla, J. M. Witkin and P. C. Chiang, *J. Med. Chem.*, 1987, **30**, 805.
2 (*a*) R. Furstoss, P. Teissier and B. Waegell, *J. Chem. Soc., Chem. Commun.*, 1970, 384; (*b*) R. Furstoss, G. Esposito, P. Teissier and B. Waegell, *Bull. Soc. Chim. Fr.*, 1974, 2485.
3 W. J. Gensler, C. D. Gatsonis and Q. A. Ahmed, *J. Org. Chem.*, 1968, **33**, 2968.
4 P. Abraham, J. B. Pitner, Y. J. Joo, D. J. Triggle and F. I. Carroll, *J. Chem. Soc., Chem. Commun.*, 1990, 984.
5 P. A. Bartlett and L. A. McQuaid, *J. Am. Chem. Soc.*, 1984, **106**, 7854.
6 T. Inukae and M. Kasai, *J. Org. Chem.*, 1965, **30**, 3567.
7 P. Mohr, N. Waespe-Sarcevic, C. Tamm, K. Gawronska and J. K. Yawronski, *Helv. Chim. Acta*, 1983, **66**, 2501.
8 H. M. Schwartz, W. Wu, P. W. Marr and J. B. Jones, *J. Am. Chem. Soc.*, 1978, **100**, 5199.
9 T. Kuhn, C. Tamm, A. Riesen and M. Zehnder, *Tetrahedron Lett.*, 1989, **30**, 693.
10 S. F. Martin, M. S. Dappen, B. Dupre, C. J. Murphy and J. A. Colapret, *J. Org. Chem.*, 1989, **54**, 2209.
11 M. Tramontini, *Synthesis*, 1982, 605.
12 (*a*) H. O. House, H. C. Muller, C. G. Pitt and P. P. Wickham, *J. Org. Chem.*, 1963, **28**, 2407; (*b*) H. O. House and W. M. Bryant, *J. Org. Chem.*, 1965, **30**, 3634.
13 H. C. Brown and K. Ichikawa, *J. Am. Chem. Soc.*, 1961, **83**, 4372.
14 A. Hajos, *Complex Hydrides and Related Reducing Agents in Organic Synthesis*, Elsevier, 1979, p. 30.
15 S. S. White, Jr. and H. C. Kelly, *J. Am. Chem. Soc.*, 1970, **92**, 4203.
16 H. C. Kelly, M. B. Giusto and F. R. Marchelli, *J. Am. Chem. Soc.*, 1964, **86**, 3882.

Paper 1/00123J
Received 10*th January* 1991
Accepted 7*th February* 1991