Tetrahedron Vol 47, No 24, pp 4195-4210, 1991
Printed in Great Britain

0040-4020/91 $3 00+ 00

CHIRAL SYNTHESIS OF 6,7-BENZOMORPHANS· SYNTHESIS OF (-)1(*S*),2(*S*),4(*R*),6(*R*)-1,2,3,4,5,6-HEXAHYDRO-2,6-METHANO-8-METHOXY -1,3,4,6-TETRAMETHYL-3-BENZAZOCINE THROUGH THE CHROMIUM HEXACARBONYL MEDIATED CYCLISATION OF 1(*S*),1′(*R*)-1,2-DIHYDRO-7-METHOXY-1,4-DIMETHYL -1-(*N*-METHYL-*N*-TRIFLUOROACETAMIDO-1′-METHYLETHAN-2′-YL)NAPHTHALENE

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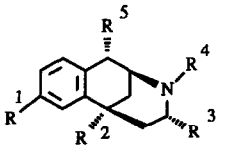
(*Received in UK* 6 *February* 1991)

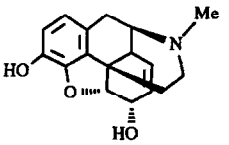
SUMMARY (-)1(*S*),2(*S*),4(*R*),6(*R*)-1,2,3,4,5,6-Hexahydro- 2,6-methano-8-methoxy- 1,3,4,6-tetramethyl-3-benzazocine has been synthesised in 86 % enantiomeric excess from the α-(η^6-chromium tricarbonyl) complex of 1(*S*),1′(*R*)-1,2-dihydro-7-methoxy-1,4-dimethyl-1-(*N*-methyl-*N*-trifluoroacetamido-1′-methylethan-2′-yl)naphthalene A precursor of this compound is 2(*R*),4(*S*)-4-(3-methoxyphenyl)-2,4-dimethylcyclohexanone which was obtained through an Enders' type *C*-methylation reaction of 4-(3-methoxyphenyl)4-methylcyclohexanone using SAMP as the reagent

6,7-Benzomorphans (1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines) (1) represent an important class of drugs some of which exhibit analgesic properties The synthesis of the 6,7-benzomorphans has attracted the attention of many organic chemists[1], and this interest is maintained today as more refined knowledge of the biological receptor sites at which these drugs interact[2] becomes available It is hoped that information of this type will lead to the design of drugs exhibiting more selective biological responses Apart from a few notable examples,[3] routes to benzomorphans take little account of stereochemical control, and lead to racemic products It is known, however, that small changes in stereochemistry initiate wide fluctuations in pharmacology[4], and that the *laevo* antipodes, related to morphine (2), are significantly more potent than their enantiomers.[5]

We now describe synthesis of the benzomorphan (19)[6], which has the morphine absolute stereochemistry, utilising a η^6-chromium complex to promote ***both*** an unusual intramolecular cyclisation of the dihydronaphthalene (17), and to control the stereoselectivity of the reaction

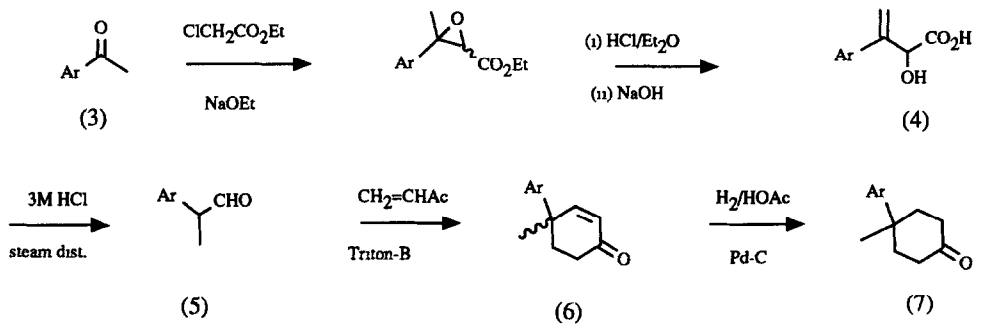


(1)



(2)

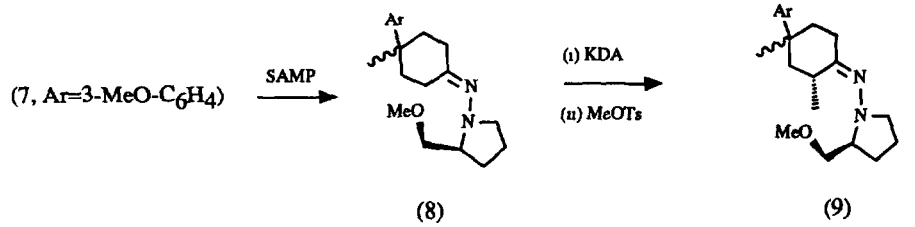
The initial starting material for the synthesis was 3-methoxyacetophenone (3)[7] which was elaborated by a Darzen's glycidic ester reaction, followed by hydrolysis to give the unsaturated acid (4) This, upon steam distillation, underwent decarboxylation to the aldehyde (5) A Robinson ring annulation with methyl vinyl ketone and catalytic hydrogenation of the resultant cyclohexenone (6) afforded the cyclohexanone (7)



The cyclohexanone (7) was reacted with SAMP[8] at 60°C, to give the hydrazones (8) in 93% These were treated with potassium diisopropylamide (KDA) and methyl tosylate in dry diethyl ether at -100°C to afford the diastereomeric hydrazones (9) which, without purification, were then converted into the corresponding methiodide salts and hydrolysed by reaction with a mixture of 3M HCl and n-pentane (the biphasic system was adopted to minimise exposure of the product ketones to aqueous acid) Column chromatography on silica of the hydrolysis products gave the *trans*-methylcyclohexanone (10), the *cis*-isomer (11) and a mixture of the two isomers in 40%, 13%, and 12% yields respectively A series of ^{1}H NMR studies using (*R*)(-)-2,2,2-trifluoro-1-(9-anthryl) ethanol (TFAE) as a chiral solvating reagent, show that the *trans*-compound was formed in an enantiomeric excess of 70%

Both *trans*- and *cis*- ketones were converted into their respective oximes (12 and 13) and ^{1}H n m r studies show that the C-2 methyl group in both of these products occupies a pseudo equatorial site Interestingly, in both cases a significant n O e enhancement (*ca* 4%) was noted between the resonance of the C-methyl hydrogen atoms and that of the oximino hydroxyl proton We expected, however, that these oximes should have *E*- stereochemistry, thereby minimising steric interactions between the C-2 methyl groups and the oximino hydroxyl units The apparent anomaly was resolved

when an X-ray determination of the *cis*-oxime revealed that it exists as a hydrogen bonded "dimer" (14) Presumably this also occurs in the *trans*-oxime, and the associated states persist in the liquid phase. This acquired geometry enforces a close spacial intermolecular relationship between the methyl groups and the hydroxyl functions of the two monomeric units



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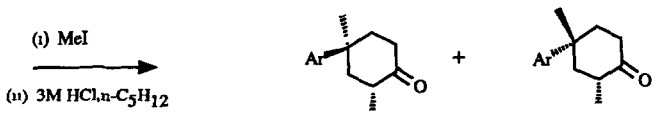
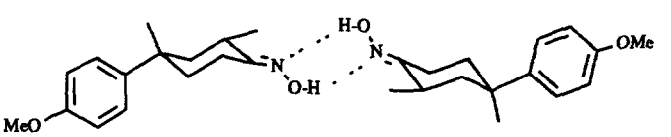


(10) (11)

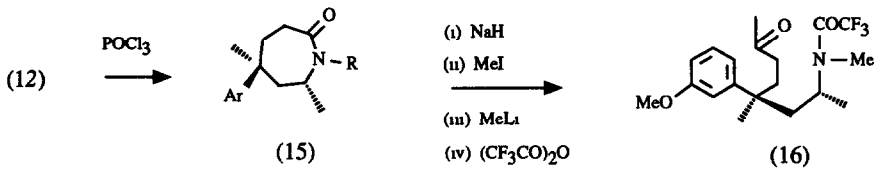
(12) *E-Trans* (13) *E-Cis*

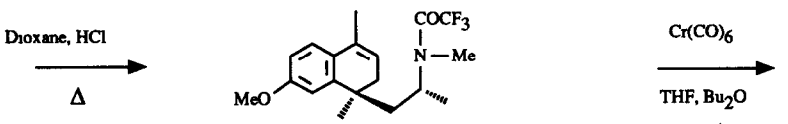


(14)

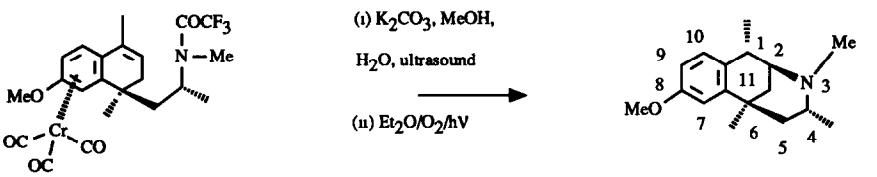
A Beckmann rearrangement of the *trans*-oxime with phosphorus oxychloride in pyridine at 0°C then afforded the caprolactam (15, R=H), which was *N*-alkylated by reaction with sodium hydride, followed by the addition of methyl iodide, to give the *N*-methylcaprolactam (15, R=Me) Further reaction with methyl lithium and then entrapment of the anion so formed with trifluoroacetic anhydride gave the trifluoroacetamide (16) in 42% yield, for four steps Cyclisation to the dihydronaphthylamide (17) was achieved by heating (16) with 5M hydrogen chloride in dry dioxane at 70°C (yield 88%) Finally (17) was activated by complexation with chromium hexacarbonyl to give a mixture of the α- and β- chromium tricarbonyl complexes (10·1 ratio) These were separated

by column chromatography, and the α-isomer (18) cyclised to the corresponding chromium derivative of the benzomorphan (19) through reaction with potassium carbonate in aqueous methanol and ultra-sonification over a period of 76 hours The product was then decomplexed and the required tricycle (19) purified by flash chromatography The yield for the cyclisation step was 40% (based on recovered starting material), the specific rotation of the microcrystalline product is $[\alpha]_D^{18}$ -59° (c 1 9 $CHCl_3$), and the enantiomeric excess is 86% (determined as before)





(17)



Hydrolysis of the dihydronaphthylamide (17) affords the corresponding amine (20), and we note that complexation of this compound with chromium hexacarbonyl gives an α β product ratio of only 2 1, compared to 10·1 for (17) An X-ray structure determination of (17) reveals that the carbonyl group of the amide lies over the top of the benzene ring (see figure 1) Initially we thought that this was the result of π-stacking, and if sustained in solution this could reduce the accessibility of the reagent to the β-face of the aromatic ring and hence explain the high selectivity of the complexation reaction However, the angle as determined by the least squares method, between the plane containing the trifluoroacetamido group and the plane of the aromatic ring is 27 6°, and the distances between the aryl ring and the oxygen atom, the carbonyl carbon atom, and the nitrogen atom of the amide are 3.23, 3.42, and 3 16 Å respectively These data do not support this argument, and it seems likely that the structure shown by the X-ray study is simply the result of preferred crystal packing This is supported by the fact that the ^{1}H n m r spectrum of (17) shows it to be a mobile molecule and to exist in solution as a mixture of rotamers

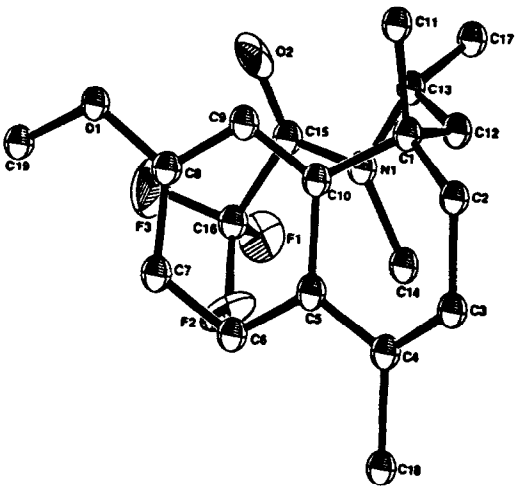
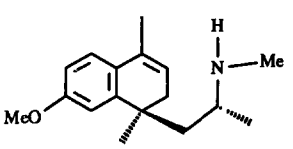


Figure 1 Crystal structure of the naphthylamide (17)

It is known[9] that for the α-hydroxytetrahydronaphthalene (21) the sole product of complexation is the chromium tricarbonyl derivative (22) Here it appears that the lone pair electrons of the α-orientated hydroxyl group chelate the chromium reagent and direct it exclusively to the proximal face of the aromatic ring other related examples have been reported [10] In the case of the free amine the lone pair electrons on the nitrogen atom may play similar role, but here there is a competing steric effect engendered by the presence of the β-aminoalkyl side chain Where lone pair electrons are less unavailable, as in the naphthylamide (17), no reagent approach control is exerted and now the α β ratio of complexed products reflects the influence of steric effects only



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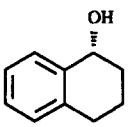

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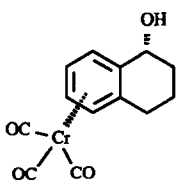
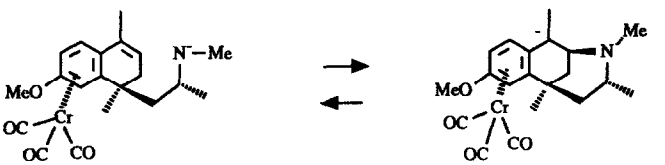


(22)

In some preliminary experiments the α-chromium tricarbonyl complex of the amine (20) was reacted with ^{t}butyl lithium to form the anion (23), which we assumed would equilibrate with the tricyclic carbanion (24) However, attempts to trap the carbanion by protonation, or by reactions with methyl iodide or with dimethyl disulphide failed, and in the case of protonation starting material was recovered A literature precedent for this type of behaviour is known[11] and it appears that carbanion formation is only favoured at low temperature Repetition of our experiments at temperatures as low as -100°C were also unsuccessful, and these failures caused us to devise the reaction conditions, recorded above, which ensure that anion formation and hence equilibration do not occur Thus in the protic medium cyclisation to the benzomorphan derivative (26) proceeds through the intermediacy of the complex (25). The amine function of which attacks the electron depleted double bond prior to stereoselective protonation *anti* to the metal atom The importance of chromium complexation is shown by the fact that treatment of the uncomplexed naphthylamide (17) with potassium carbonate in aqueous methanol leads only to the formation of the amine (20) This is to be expected, of course, since it is the presence of the electron withdrawing chromium unit which activates an otherwise electron rich double bond towards nucleophilic attack by the amino group



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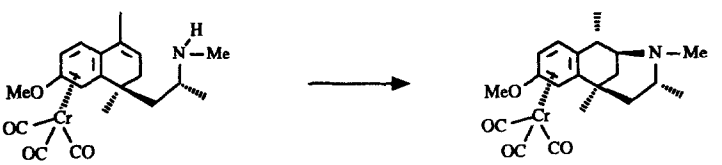

(25) (26)

EXPERIMENTAL

GENERAL

Column chromatography was carried out using silica gel 60 GF7736 or 9385 (E Merck), or alumina (Camag, Fisons 100-250 mesh) Thin-layer chromatography (t l c) was with silica gel 60 GF254 (E. Merck) Ether refers to diethyl ether and petrol to 60-80°C boiling range petroleum ether ^{1}H and ^{13}C N M R. spectra were recorded at 270 MHz and 68 MHz respectively with a JEOL FX270 instrument The solvent was deuteriated chloroform solutions unless stated otherwise Chemical

shifts are expressed in p p.m (δ) downfield from tetramethylsilane (TMS) as an internal standard. Electronic spectra were recorded for 95% ethanolic solutions on a Perkin-Elmer Lambda-3 spectrophotometer Infra-red spectra were measured on a Perkin-Elmer 1310 instrument. Mass spectra were recorded with a V.G mass spectrometer in the electron ionisation mode at 70 eV unless otherwise stated.

X-RAY DATA COLLECTION AND PROCESSING

A Hilger and Watts Y290 4-circle diffractometer was used with graphite monochromated Mo-K_α radiation Full details of the data recorded have been deposited at the Cambridge Data Base

Cis/trans-Ethyl 2-(3-methoxyphenyl)-2-methyl-1-oxirane-1-carboxylate

Sodium (46 g, 2.0 mol) was added portionwise over a period of 4 h to well stirred absolute ethanol (750 cm^3) maintained at 0°C and protected by a nitrogen atmosphere The mixture was stirred at room temperature for 12 h, to ensure that all the sodium had dissolved, and then cooled to 0°C again A mixture of 3-methoxyacetophenone (150 2 g) and ethyl chloroacetate (245 1 g) in benzene (250 cm^3) was added at 0°C over a period of 1 h, and the resultant mixture was stirred at 0°C for 1 h, and at room temperature for a further 3 h The reaction mixture was quenched by adding it to a slurry of ice (1000 g) and glacial acetic acid (100 cm^3), it was then extracted with dichloromethane (4x500 cm^3) The combined extracts were washed with saturated aqueous sodium bicarbonate solution (200 cm^3), then with saturated brine (100 cm^3), and then evaporated under reduced pressure to give an orange oil. Distillation gave the title compound as a yellow oil (223 1 g, 94%), b p 140.0-145 0°C (0 1 mm Hg). $\nu_{max}cm^{-1}$ 1730 (CO), *m/z* (%) 236 (M^+, 31), 163 (100) and 162 (100).

δ_H (Isomer I) 7 20 (1 H, t, J 7.9 Hz, 5′-H), 6 94-6 88 (1 H, m, 6′-H), 6 85 (1 H, t, J 2 6 Hz, 2′-H), 6 77 (1 H, ddd, J 7 9, 2 6 and 0 9 Hz, 4′-H), 4 24 (2 H, ABX_3, J_{AB} 10 8 Hz, J_{AX} 7 3 Hz, J_{BX} 7 2 Hz, $OC\underline{H}_2CH_3$), 3 76 (3 H, s, OCH_3), 3 34 (1 H, s, 1-H), 1 72 (3 H, s, 2-CH_3) and 1 31 (3 H, t, J 7.1 Hz, $OCH_2C\underline{H}_3$); δ_C 166 8 (CO), 159 6 (3′-C), 141 7 (1′-C), 129 2, 117 3, 113 3 and 110 4 (4xAr-CH), 61 3 (2-C), 60.9 (1-C), 60 9 ($O\underline{C}H_2CH_3$), 54 7 (OCH_3), 16 7 and 14.0 (2xCH_3)

δ_H (Isomer II) 7 18 (1 H, t, J 8.2 Hz, 5′-H), 6 94-6 90 (2 H, m, 2′- and 6′-H), 6.76 (1 H, ddd, *J* 8 2, 2 6 and 1 1 Hz, 4′-H), 3 90 (2 H, ABX_3, J_{AB} 14 3 Hz, $J_{AX,BX}$ 7 1 Hz, $OC\underline{H}_2CH_3$), 3 78 (3 H, s, OCH_3), 3 59 (1 H, s, 1-H), 1 72 (3 H, s, 2-CH_3) and 0 92 (3 H, t, J 7 1 Hz, $OCH_2C\underline{H}_3$); δ_C 166 6 (CO), 159 1 (3′-C), 138 6 (1′-C), 128 8, 118 5, 113 7 and 111 5 (4xAr-CH), 63.4 (2-C), 60 5 ($O\underline{C}H_2CH_3$), 60 4 (1-C), 54 9 (OCH_3), 24 4 and 13.7 (2xCH_3)

Ethyl 2-hydroxy-3-(3-methoxyphenyl)-3-butenoate

Concentrated sulphuric acid (3 cm^3) was added dropwise to a stirred solution of the mixed *cis*- and *trans*-oxirane esters (115 g, 0.49 mol) in ether (500 cm^3) at 0°C and the mixture was stirred at room temperature for 30 min It was then washed with water (50 cm^3), saturated aqueous sodium bicarbonate solution (2x100 cm^3), and saturated brine (50 cm^3), dried (Na_2SO_4), and evaporated under reduced pressure to give the title compound as an orange oil (95 9 g, 83%), b.p 127.0-130 0 °C (0.1 mm Hg); υ_{max} 3500 (OH), 1740 (CO) cm^{-1}, δ_H 7.23 (1 H, dd, J 8.0 and 2 5Hz, 5′-H), 7 01-6 95 (2 H, m, 6′- and 2′-H), 6 84 (1 H, ddd, J 8 0, 2 5 and 0.9 Hz, 4′-H), 5.49 (1 H, s, 4-H), 5.44 (1 H, s, 4- H), 5 02 (1 H, s, 2-H), 4 26-4 06 (2 H, m, ABX_3 J_{AB} 10.7 Hz and $J_{AX,BX}$ 7.1 Hz, CH_2), 3.79 (3 H, s, CH_3O), 3 44 (1 H, br s, OH) and 1.12 (3 H, t, J 7.1 Hz, CH_3); δ_C 173 3, 159.3, 145.8,

139.9, 129.2, 119 3, 117 2, 113 3, 112 6, 73 6, 62 0, 55.1, 13 8, m/z (%) 236 (M^+, 43), 163 (100), 150 (25), 135 (73) [Found: C, 65 9, H, 6 8 $C_{13}H_{16}O_4$ requires C, 66 1, H, 6 8%]

2-Hydroxy-3-(3-methoxyphenyl)-3-butenoic acid (4)

A mixture of the butenoate ester (95 9 g, 0 41 mol) and 2M aqueous sodium hydroxide (500cm^3), was stirred at room temperature for 12 h The orange solution formed was extracted with dichloromethane (100 cm^3) and the aqueous layer acidified to pH 2 with concentrated hydrochloric acid. The aqueous layer was then extracted with dichloromethane (4x300cm^3) and the organic washings from the acid layer combined This organic portion was washed with saturated brine (50 cm^3), dried and evaporated to give the title compound as a yellow waxy solid (81 3 g, 96%) υ_{max}cm^{-1}(liquid) 3400-2900br (OH), 1700 (CO), 1590 (C=C), δ_H 8.0-6 6 (2 H, br s, CHOH and COOH), 7 19 (1 H, t, J 7.9 Hz, 5′-H), 6 99-6 94 (2 H, m, 2′- and 6′-H), 6 81 (1 H, dd, J 7.9 and 2 0 Hz, 4′-H), 5 49 (1 H, s, 4-H), 5.41 (1 H, s, 4-H), 5 07 (1 H, s, 2-H) and 3 81 (3 H, s, CH_3), δ_C176 5, 159 2, 144 9, 139 4, 129 3, 119 3, 117 7, 113 4, 112 6, 73 2, and 55 1; m/z (%) 208 (M^+ 25%), 163 (25) and 135 (55) [Acc mass 208 0733 $C_{11}H_{12}O_4$ requires 208 0734]

2-(3-Methoxyphenyl)propanal (5)

A mixture of the butenoic acid (4) (81 2 g, 0.49 mol) and 3 M hydrochloric acid (250 cm^3), was placed in a two necked round bottomed flask (500 cm^3) fitted with an inlet tube connected to a steam generator and a splash head fitted with a water condenser The contents of the flask was then steam distilled until no further product was visible by tlc in the distillate The aqueous distillate was extracted with dichloromethane (3x1000 cm^3) and the combined organic portions were washed with saturated aqueous sodium bicarbonate solution (250 cm^3), dried, and evaporated under reduced pressure to give a colourless oil (36 3 g). Distillation gave the title compound as a colourless oil (32 2 g, 40%). b p 122 0-123 5°C (8 mm Hg) υ_{max}cm^{-1} (neat) 2960, 2920 (CH), 1710 (CHO), δ_H 9 67 (1 H, d, J 1 3 Hz, CHO), 7 30 (1 H, t, J 7 9 Hz, 5′-H), 6 86-6 78 (2 H, m, 4′- and 6′-H), 6 76 (1 H, t, J 2 0 Hz, 2′-H), 3 81 (3 H, s, CH_3O), 3 60 (1 H, qd, J 7 0 and 1 3 Hz, 2-H) and 1 43 (3 H, d, J 7 0 Hz, 3-H), δ_C 200 8, 160 1, 139 2, 130 0, 120 5, 114.0, 112 6, 55 1, 52 9, and 14 4, *m/z* (%) 164 (M^+ 83%), 150 (18) and 135 (100) [Acc mass· 164 0831 M^+, calc for $C_{10}H_{12}O_2$ 164.0837]

4-(3-Methoxyphenyl)-4-methyl-2-cyclohexen-1-one (6)

A 40% methanolic solution of benzyltrimethylammonium hydroxide (24 5 g, 59 mmol) was added over 1 h to a stirred solution of the aldehyde (5) (32 2 g, 196 mmol) and methyl vinyl ketone (15 1 g, 216 mmol) in *t*- butanol (150 cm^3 at 0 °C under a nitrogen atmosphere The reaction was stirred at room temperature for 2 h, then poured on to ice (300 g), and extracted with ether (3x300 cm^3) The organic portions were combined, washed with saturated brine (50 cm^3), dried and evaporated under reduced pressure to give a pale yellow oil Distillation gave the title compound as a colourless oil (30.0 g, 71%). b p 124 0-131.0°C (0 05mm Hg) υ_{max}cm^{-1}(neat) 1670 (CO), 1590 (C=C), δ_H 7 27 (1 H, t, J 8 2 Hz, 5′-H), 6 93-6 87 (3 H, m, 2-H, 2′-H and 6′-H), 6 79 (1 H, dd, J 8.2 and 2 5 Hz, 4′-H), 6 11 (1 H, d, J 10 1 Hz, 3-H), 3 80 (3 H, s, CH_3O), 2 45-2 05 (4 H, m, 5- and 6-H) and 1 54 (3 H, s, 4-CH_3, δ_C 199 4, 159 7, 156 9, 146 9, 129 6, 118 6, 112 9 and 111 2, 55 2, 40 6, 37 9, 34 6 and 27 6, m/z (%) 216 (M^+,100%), 201 (29), 188 (35), 174 (32), 173 (37) and 158 (50) [Acc mass found.

216.1141 $C_{14}H_{16}O_2$ requires: 216.1148].

4-(3-Methoxyphenyl)-4-methylcyclohexanone (7)

A solution of the cyclohexenone (6) (20.0 g, 92 4 mmol) in glacial acetic acid (200 cm^3) was hydrogenated in the presence of 10% palladium on charcoal catalyst (1.0 g), at atmospheric pressure, until hydrogen uptake ceased The reaction mixture was filtered through a bed of celite to remove the catalyst, and the filter bed washed with ethyl acetate (4x100 cm^3) Water (500 cm^3) was added to the combined filtrates and the organic layer separated. The aqueous layer was extracted with ethyl acetate (3x100 cm^3). All the organic layers were combined, washed with water (100 cm^3), saturated brine (50 cm^3, dried and evaporated under reduced pressure to give a colourless oil Crystallization from petrol gave the title compound as colourless needles or plates (18 3 g, 91%) m.p. 66.5-67.5°C $\upsilon_{max}cm^{-1}$(liquid) 1710 (CO); δ_H 7.31 (1 H, t, J 8.0 Hz, 5'-H), 7.03 (1 H, ddd, J 8.0, 2.1 and 0.9 Hz, 6'-H), 6 99 (1 H, t, J 2.1 Hz, 2'-H), 6.79 (1 H, ddd, J 8.0, 2.1 and 0 9 Hz, 4'-H), 3 83 (3 H, s, CH_3O), 2.55-1 85 (8 H, m, 4xCH_2) and 1.31 (3 H, 4-CH_3), δ_C 211 5, 159.8, 147 6, 129.6, 117 9, 112.5, 110 2, 55 0, 37 7, 38 2, 37.0, and 31.0, *m/z* (%) 218 (M^+ 73%), 161 (73) and 148 (100)[Found· C, 76 8, H, 8 45, $C_{14}H_{18}O_2$ requires: C, 77.0; H, 8.3%].

2(S)-2-Methoxymethyl-N-[4'-(3-methoxyphenyl)-4'-methylcyclohexylidene]-1-pyrrolidinamine (8)

A mixture of (S)-1-amino-2-methoxymethylpyrrolidine (SAMP) (10 g, 77 mmol) and the cyclohexanone (7) (16 g, 73 mmol) was heated at 60 °C for 18 h, with stirring, under an argon atmosphere The reaction mixture was allowed to cool and then dissolved in ether (200 cm^3). This solution was washed with water (30 cm^3), saturated brine (10 cm^3), dried and evaporated under reduced pressure to give a yellow oil. Distillation gave the title compound as a colourless oil (21 8 g, 90%), b.p 176 0-178.0°C at 0.05 mmHg. $[\alpha]_D^{18}$ +175.3 (c 0.5 $CHCl_3$); δ_H (mixture of diastereoisomers - all signals doubled) 7 28 (1 H, 2xt, J 8 0 Hz, 5''-H), 7 03-6.94 (2 H, m, 2''- and 6''-H), 6 79-6 73 (1 H, m, 4''-H), 3 82 and 3.81 (3 H, 2xs, Ar OH3, 3 48-2 90 (5 H, m, 2-CH_2, 2-H and 5-H), 3 37 and 2.20 (3 H, 2xs, CH_2OCH_3), 2.58-1 59 (12 H, m, 6xCH_2), 1.30 and 1.22 (3 H, 2xs, 4'-CH_3); δ_C 169.1 and 168.3, 159.9 and 159.7, 150.1 and 148.5, 129.5 and 129.3, 118.4 and 118.0, 112.9 and 112.5, 110 1 and 110.0, 75.5 and 75.3, 66.0 and 65.9, 55 1, 55 1 and 54 7, 38 3, 38 1, 37 8, 37 3, 36 9, 31 9 and 26 6, 32.2 and 28 6, 25.8 and 25 7, and 22.0 and 21 9, *m/z* (%) 330 (M^+ 51%) and 285 (100) [Found C, 72 3%; H, 9.15, N, 8 6, $C_{20}H_{30}N_2O_2$ requires C, 72.7, H, 9 2, N, 8.5%].

(+)-*Cis/trans*-2(R),4(R,S)-4-(3-methoxyphenyl)-2,4-dimethylcyclohexa none (11 and 10)

Butyl lithium (1.6 M, 45 5 cm^3 was added dropwise over a period of 1 h to a stirred slurry of potassium *t*- butoxide (8 2 g, 73 1 mmol) and dry diisopropylamine (7 4 g, 72.8 mmol), at -78 °C and under an argon atmosphere. The suspension was then stirred at -78 °C for 1 h. A solution of the hydrazone (9) (21.8 g, 65.9 mmol) in dry ether (50 cm^3) was added over a period of 30 min, at -78°C. After stirring at -78°C for 10 h, the suspension was cooled to -100°C and a solution of methyl tosylate (14 77 g, 79 3 mmol) in dry ether (30cm^3) was added over a period of 30 min. Stirring was continued at -100°C for 2 h, before the reaction was allowed to warm to room temperature overnight. The suspension was poured into a mixture of water (200 cm^3 and ether (500 cm^3), separated, and the aqueous phase extracted with ether (3x200 cm^3) The combined organic layers were washed with

saturated brine (100 cm^3), dried and evaporated under reduced pressure to give a pale yellow oil This residue was dissolved in iodomethane (25 cm^3) and heated at 40°C in a sealed tube for 16 h After cooling, the solution was evaporated under reduced pressure to give a brown oil The brown oil was stirred vigorously with a mixture of pentane (400 cm^3) and 2 5 M hydrochloric acid (250 cm^3) for 15 min The pentane was then separated and replaced with a fresh portion of pentane (400 cm^3), and the mixture stirred vigorously for a further 15 min. This process was repeated twice more and the combined pentane fractions were dried, and evaporated under reduced pressure to give a colourless oil. Purification by "suction flash" column chromatography on silica gel, eluting with ethyl acetate/ petrol (3·47) gave *trans*- 2(R),4(S)-4-(3-methoxyphenyl)-2,4-dimethylcyclohexanone (10) (5 74 g, 37%), *cis*- 2(R),4(R)-4-(3-methoxyphenyl)-2,4-dimethylcyclohexanone (11) (1 91 g, 13%) and a mixture of the two (1.68 g, 11%) as colourless oils.

Physical data for (10) $[\alpha]_D^{18}$ +18 1 (c 1 3 $CHCl_3$), δ_H 7 33 (1 H, t, J 8 0 Hz, 5′-H), 7 07 (1 H, ddd, J 8 0, 2 2 and 0 7 Hz, 6′-H), 7 02 (1 H, t, J 2 2 Hz, 2′-H), 6 80 (1 H, ddd, J 8 0, 2 2 and 0 7 Hz, 4′-H), 3 83 (3 H, s, CH_3O), 2 65- 2 53 (2 H, m, 2-H_{ax} and 6-H_{ax}), 2 41-2 27 (3 H, m, 6-H_{eq}, 5-H_{eq} and 3-H_{eq}), 1.84 (1 H, td, J 13 4 and 5 3 Hz, 5-H_{ax}), 1.60 (1 H, t, J 13 4 Hz, 3-H_{ax}), 1 21 (3 H, s, 4-CH3) and 1 01 (3 H, d, J 6 6 Hz, 2-CH_3), δ_C 212 8, 160 1, 147 2, 129 8, 118 1, 112 9, 110 2, 55 1, 46.7, 41 3, 39.2, 38 6, 37 9, 33.6, and 14 3, *m/z* (%) 232 (M^+ 36%) and 148 (100) [Found: C, 77 4; H, 8 85, $C_{15}H_{20}O_2$ requires C, 77.5, H, 8 7%]

Physical data for (11) $[\alpha]_D^{18}$ +4 0 (c 0 3, $CHCl_3$); δ_H 7 26 (1 H, t, J 8 0 Hz, 5′-H), 7 00-6.97 (1 H, m, 6′-H), 6 94 (1 H, t, J 2.2 Hz, 2′-H), 6 76 (1 H, dd, J 8 0 and 2 2 Hz, 4′-H), 3 81 (3 H, s, CH_3O), 2 75-2 59 (2 H, m, 2-H_{ax} and 6-H_{ax}), 2 41 (1 H, ddd, J 14 6, 4 6 and 2 8 Hz, 6-H_{eq}), 2 23-2 09 (3 H, m, 5-H_{ax}, 5-H_{eq} and 3-H_{eq}), 1 80 (1 H, t, J 13 3 Hz, 3-H_{ax}), 1 59 (3 H, s, 4-CH_3) and 1 06 (3 H, d, J 6 4 Hz, 2-CH_3), δ_C 212 8, 159 6, 151 4, 129 2, 117 4, 111 9, 110 4,,55 1, 47 4, 40 8, 38 3, 38 4, 38 0, 24 4, and 14 5, *m/z* (%) 232 (M^+ 73%), 175 (21), 161 (38) and 148 (100) [Found C, 77 3; H, 8 8, $C_{15}H_{20}O_2$ requires· C, 77 5, H, 8 7%]

(+)-E-*Trans*-2(R),4(S)-4-(3-methoxyphenyl)-2,4-dimethylcyclohexanone oxime (12)

A mixture of the dimethylcyclohexanone (10) (5 68 g, 24 4 mmol), hydroxylamine hydrochloride (6 79 g, 97 7 mmol) and sodium acetate (8 02 g, 97 7mmol) in 80% methanol (50 cm^3) was stirred at room temperature for 18 h The reaction mixture was poured into water (100 cm^3) and extracted with ethyl acetate (4x50 cm^3) The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (30 cm^3), saturated brine (25 cm^3), dried, and evaporated under reduced pressure to give a coloourless solid Crystallization from ether/ petrol gave the title compound as a prisms (5 13 g, 85%), m p 94 0-95 0 °C, $[\alpha]_D^{18}$ +3 5 (c 1 1 $CHCl_3$), $\upsilon_{max}cm^{-1}$(Nujol mull) 3250br (OH), 1610 (C=N), δ_H 9 80 (1 H, br s, OH), 7 29 (1 H, t, J 8 0 Hz, 5′-H), 7 00 (1 H, d, J 8 0 Hz, 6′-H), 6 96 (1 H, d, J 2 2 Hz, 2′-H), 6 75 (1 H, dd, J 8 0 and 2 2 Hz, 4′-H), 3 81 (3 H, s, CH_3O), 3 27 (1 H, dt, J 14 1 and 2.8 Hz, 6-H_{eq}), 2 50-2 38 (2 H, m, 3-H_{eq} and 5-H_{eq}), 2 38-2.20 (1 H, m, 2-H_{ax}), 1 82-1 49 (2 H, m, 5-H_{ax} and 6-H_{ax}), 1 43 (1 H, t, J 13.3 Hz, 3-H_{ax}), 1 15 (3 H, s, 4-CH_3) and 1 09 (3 H, d, J 6.4 Hz, 2-CH_3), δ_C 162 5 159 9, 147 8, 129 6, 118.4, 113.0, 110 0, 55 1, 47 0, 39 0, 36 4, 34 1, 33 5, 21 3, and 16 3, *m/z* (%) 247 (M^+ 52), 230 (25), 149 (56) and 148 (28) [Found C, 72 4, H, 8 54, N, 5 81, $C_{15}H_{21}NO_2$ requires C, 72 8; H, 8 6, N, 5 7%]

(+)-E-Cis-2(R),4(R)-4-(3-methoxyphenyl)-2,4-dimethylcyclohexanoneoxime (13)

A mixture of the dimethylcyclohexanone (11) (1 40 g, 6 0 mmol), hydroxylamine hydrochloride (1 47 g, 21 2 mmol) and sodium acetate (2.48 g, 30.2mmol) in 80% methanol (25 cm^3) was stirred at room temperature for 18 h The reaction mixture was poured into water (25 cm^3) and extracted with ethyl acetate (4x30 cm^3). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (15 cm^3), saturated brine (15 cm^3), dried, and evaporated under reduced pressure to give a solid. Crystallization from ether/ petrol gave the title compound as colourless needles (1.25 g, 84%). m.p 105 0- 106 0 °C, $[\alpha]_D$ +48 4 (c 1.0 $CHCl_3$), $\upsilon_{max}cm^{-1}$(Nujol mull) 3200br (OH), 1600 (C=N); δ_H 9.10 (1 H, br s, OH), 7.25 (1 H, t, J 8 0 Hz, 5′- H), 6 97 (1 H, m, 6′-H), 6 92 (1 H, t, J 2 2 Hz, 2′-H), 6.74 (1 H, dd, J 8 0 and 2 2 Hz, 4′-H), 3 81 (3 H, s, CH_3O), 3 39 (1 H, m, 6-H_{eq}), 2.68-2.58 (1 H, m, 2-H_{ax}), 2.10-1.75 (4 H, m, 3-H_{eq}, 5- H_{ax}, 5-H_{eq} and 6-H_{ax}), 1 64 (1 H, t, J 13 0 Hz, 3-H_{ax}), 1.44 (3 H, s, 4-CH_3) and 1.14 (3 H, d, J 6.5 Hz, 2-CH_3), δ_C 162.3, 159 5, 152 3, 129 1, 117 5, 111 8, 110 4, 55 1, 47 4, 37 4, 36 7, 33 1, 24 4, 20 8, and 16 5, *m/z* (%) 247 (M^+ 100), 230 (28), 205 (20), 148 (33) and 121 (31) [Found C, 72 7; H, 8 6, N, 5 6, $C_{15}H_{21}NO_2$ requires C, 72 8, H, 8 6, N, 5 7%]

Crystal data. $C_{15}H_{21}O_2N$, M = 247.37 Triclinic, a = 6 437(2), b = 10 830(2), c = 11.366(2)Å, α = 113.47(1), β = 98.99(2), γ = 101 65(2)°, V = 686 75 $Å^3$ (by least squares refinement on diffractometer angles for 12 automatically centred reflections, λ = 0 71069 Å), space group $P\bar{1}$, Z = 2, D_x = 1 19 gcm^{-3} Colourless rods Crystal dimensions 0 3 x 0 3 x 0.3 mm, μ(Mo-K_α) = 0.44 cm^{-1}. 1837 reflections were measured ($2<\theta<22^\circ$), 1741 unique and 1151 observed with $I>3\sigma(I)$ The structure was solved (direct methods) and refined using the SHELX suite of programs Final R and R_w were 0.071 and 0 074 with a weighting scheme of w = 8 1764[$\sigma^2(F_o)$ + 0 08$(F_o)^2$]

(+)-Cis-5(R),7(R)-hexahydro-5-(3-methoxyphenyl)-5,7-dimethyl-2H-azepine-2-one

Phosphorus oxychloride (3 4 cm^3) was added dropwise to a stirred solution of the *cis*-oxime (13) (1 14 g, 4 6mmol) in dry pyridine (7 5 cm^3) at 0 °C, under a nitrogen atmosphere After stirring at 0 °C for 5 h, the solution was carefully poured onto ice (50 g) and left for 1 h Concentrated hydrochloric acid (8 cm^3) was added slowly and the resulting mixture extracted with ethyl acetate (4x30 cm^3) The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (10 cm^3), saturated brine (10 cm^3), dried, and evaporated under reduced pressure to give a yellow oil This crystallized from pentane to give the title compound as a colourless solid (8 83 g, 73%), m p 113 0-114 0°C $[\alpha]_D^{18}$ +1 1 (c 1 2 $CHCl_3$), $\upsilon_{max}cm^{-1}$(Nujol mull) 3200,3080 (NH), 1640 (CO), δ_H 7 25 (1 H, t J 8 0 Hz, 5′-H), 6 97 (1 H, d, J 7 9 Hz, 6′-H), 6 92 (1 H, t, J 2 0 Hz, 2′-H), 6 75 (1 H, dd, J 8 0 and 2.0 Hz, 4′-H), 6 55 (1 H, br s, NH), 3 80 (4 H, s, 7-H and CH_3O), 2.75 (1 H, t, J 13 6 Hz, 3-H_{ax}), 2 38 (1 H, dd, J 13 6 and 7 7 Hz, 3-H_{eq}), 2 06 (1 H, t, J 13.6 Hz, 4- H_{ax}), 1 87 (1 H, dd, J 14 5 and 10 2 Hz, 6-H_{ax}), 1 81 (1 H, dd, J 13 6 and 7.7 Hz, 4-H_{eq}), 1 69 (1 H, d, J 14 5 Hz, 6-H_{eq}), 1.43 (3 H, s, 5-CH_3) and 1 25 (3 H, d, J 6 6 Hz, 7-CH_3), δ_C 177 2, 159 5, 152 0, 129.1, 117.5, 112 0, 110 5, 55 1, 49.7, 44 2, 39.6, 34 7, 32.1, 23 8, and 22 7; *m/z* (%) 247 (M^+ 79%), 204 (30) and 189 (24) [Found· C, 73 0, H, 8 7, N, 5 7, $C_{15}H_{21}NO_2$ requires. C, 72 8, H, 8 6, N, 5 7%].

(-)-*Trans*-5(S),7(R)-hexahydro-5-(3-methoxyphenyl)-5,7-dimethyl-2H-azepine-2-one (15, R=H)

This compound was prepared in identical manner to that of the *cis*-isomer, but starting from the oxime (12) Compound (15) is a colourless crystalline solid. Yield 82%, m p 133 0-134°C [ethyl acetate/petrol (4 1)], $[\alpha]_D^{18}$ -29 6 (c 1 2 $CHCl_3$), $\upsilon_{max}cm^{-1}$(Nujol mull) 3200 (NH), 3080 (NH), 1670 (CO), δ_H 7.33 (1 H, t J 8 0 Hz, 5'-H), 6 85 (1 H, d, J 8 0 Hz, 6'-H), 6 83-6 75 (2 H, m, 2'- and 4'-H), 6 29 (1 H, br s, NH), 3 82 (3 H, s, CH_3O), 3 56-3 40 (1 H, m, 7- H_{ax}), 2 54-2 24 (4 H, m, 3-H_{ax}, 3-H_{eq}, 4-H_{ax} and 6-H_{ax}), 1 82- 1 66 (1 H, m, 4-H_{eq}), 1.59 (1 H, dd, J 14 8 and 9 5 Hz, 6-H_{eq}), 1 24 (3 H, d, J 6 8 Hz, 7-CH_3) and 1 14 (3 H, s, 5-CH_3), δ_C 177 3, 159.9, 147 4, 129 7, 118 5, 113.3, 110 1, 55 1, 48 3, 45 0, 41 7, 35 3, 33 5, 32.7, and 22 3, m/z (%) 247 (M^+ 36%), 148 (30) and 99 (100) [Found C, 72 9, H, 8 7, N, 5 6, $C_{15}H_{21}NO_2$ requires· C, 72 8, H, 8 6, N, 5 7%]

Enantiomeric excess 80% (±4%) as determined by ^{1}H n m r spectroscopy TFAE (0 030g) added to sample (0.010g) dissolved in $CDCl_3$

(-)-Trans-5(S),7(R)-hexahydro-5-(3-methoxyphenyl)-1,5,7-trimethyl-2-azepinone (15, R=Me)

Dry tetrahydrofuran (50 cm^3) was added to a mixture of the *trans*-caprolactam (15, R=H) (6 05 g, 24 5 mmol) and sodium hydride (97% oil dispersion, 1 21 g, 48 9 mmol), and the suspension was stirred at room temperature for 18 h, under a nitrogen atmosphere Iodomethane (7 6 cm^3, 17 4 g, 122 mmol) was added dropwise and the suspension was stirred at room temperature for a further 48 h After quenching with ice (100 g), the mixture was extracted with ethyl acetate (4x50 cm^3) The combined, extracts were washed with saturated brine (30 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the title compound as a pale yellow oil (6 35 g, 99%). $[\alpha]_D^{18}$ -1 8 (c 4.3 $CHCl_3$), δ_H 7 31 (1 H, t, J 8 0 Hz, 5'-H), 6 90 (1 H, ddd, J 8 0, 2 0 and 0 8 Hz, 6'-H), 6 84 (1 H, t, J 2 0 Hz, 2'-H), 6 78 (1 H, ddd, J 8 0, 2 0 and 0 8 Hz, 4'-H), 3 82 (3 H, s, OCH_3), 3 67 (1 H, p, J 8 0 Hz, 7-H), 2 86 (3 H, s, NCH_3), 2 62 (1 H, t, J 12 8 Hz, 3-H), 2 56-2 37 (2 H, m, 3- and 4-H), 2 21 (1 H, dd, J 14 8 and 1 8 Hz, 6-H), 1 70-1 56 (2 H, m, 6- and 4-H), 1 30 (3 H, d, J 8 0 Hz, 7-CH_3) and 1.12 (3 H, s, 5-CH_3), δ_C 175 6 (CO), 159 9 (3'-C), 147 5 (1'-C), 129 7 (Ar-CH), 118 5 (Ar-CH), 113 1 (Ar-CH), 110 2 (Ar-CH), 55 0 (OCH_3), 49 8 (7-C), 45 9 (CH_2), 41 5 (5-C), 34 6 (CH_3), 34 3 (CH_2), 33.0 (CH_2), 27 3 (CH_3) and 20 5 (CH_3); *m/z* (%) 261 (M^+, 33), 246 (2, M-CH_3) and 113 (100) [Acc mass found 261 1737 $C_{16}H_{23}NO_2$ requires 261 1727]

(+)-5(S),7(R)-5-(3-Methoxyphenyl)-5-methyl-7-(N-methyltrifluoroacetamido)octan-2-one (16)

Methyl lithium (1 4 M, 14 2 cm^3, 19 9 mmol) was added dropwise to a stirred solution of the methylcaprolactam (15, R=Me)(5 2 g, 19 9 mmol) in dry tetrahydrofuran (100 cm^3) at 0°C, under a nitrogen atmosphere, and the mixture was stirred at room temperature for 2 h After cooling to -23°C, trifluoroacetic anhydride (8 4 cm^3, 12 5 g, 59 7 mmol) was added dropwise and the solution was then allowed to warm to room temperature over the period of 1 h The reaction was poured onto ice (200 g) and then extracted with ethyl acetate (4x75 cm^3) The combined organic layers were washed with water (50 cm^3), saturated brine (40 cm^3), dried and evaporated under reduced pressure to give a brown oil (12 5 g) Purification by "suction flash" column chromatography on silica gel, eluting with chloroform, gave the title compound as a pale yellow waxy solid (4 11 g, 55%) m p 79 0-80 0°C, and the starting compound (15, R=Me) as a yellow oil (0 67 g, 13%) $[\alpha]_D^{18}$ +89 4 (c 1 3, $CHCl_3$) $\nu_{max}cm^{-1}$ 1680 (CO); δ_H (9·1 rotameric mixture) 7 19 (1 H, t, J 7 9 Hz, 5'-H), 6 82-6 69

(3 H, m, 2′-H, 4′-H, and 6′-H), 4 77 (1H, m, 7-H), 3 78 (3 H, s, OCH_3), 2.65 (s, NCH_3, minor rotamer), 2 39(q, J=1.7Hz NCH_3, major rotamer) 2 32-1 52 (6H, m, 3-H_2, 4-H_2, and 6-H_2), 1.99 (3H, s, 1-H_3), 1 52(3H, s, 5-H_3), 1.08(3H, d, J 6 8Hz, 8-H), *m/z* (%) 373 (M^+, 28%), 175 (66), 154 (100), 148 (89) [Found C, 61 0· H, 7 05, N, 3 7 $C_{19}H_{26}F_3NO_3$ C, 61 1, H, 7 0, N, 3.75%)

(+)-1(S),1′(R)-1,2-Dihydro-7-methoxy-1,4-dimethyl-1-[1′-(N-methyltrifluoroacetamido) -1′-methylethan-2′-yl]naphthalene (17)

A solution of hydrogen chloride in dry dioxane (5 3 M, 10 cm^3) was added to a solution of the trifluoroacetamidoketone (16) (3 91 g, 10 5 mmol) in dry dioxane (40 cm^3) and the resulting solution heated at 70°C for 2 h, under a nitrogen atmosphere After cooling, the solution was treated with methanol (500 cm^3) and then evaporated under reduced pressure until only 50cm^3) remained. This process was repeated twice more to ensure that all the hydrogen chloride had been removed The remainder of the solvent was removed under reduced pressure to give a yellow oil. Purification by "suction flash" column chromatography on silica gel, eluting with ethyl acetate/ petrol (1.19), gave the starting compound as a yellow oil (1 10 g, 28%) and the title compound as a colourless crystalline solid (2 35 g, 63%), m p. 95 0-96 0°C $[\alpha]_D^{18}$ +43 9 (c 1 1 $CHCl_3$), $\nu_{max}cm^{-1}$ 1685 (CO), 1610 (C=C), δ_H (1 4 mixture of rotamers) 7 15 (1 H, d, J 8 6 Hz, 5′-H), 6 79 (1H, d, J 2 6 Hz, 8′-H), 6 71 (1H, dd, J 8 6 and 2 6 Hz, 6′-H), 5 64-5 61 (1 H, m, 3′-H), 4 86-4 73 (1 H, m, 2-H, major rotamer), 4 11-4 05 (1 H, m, 2-H, minor rotamer), 3 79 (3 H, s, OCH_3), 2 60 (3 H, s, NCH_3, minor rotamer), 2 47 (3 H, q, J 1 7 Hz, NCH_3, major rotamer), 2.31 -1 96 (3 H, m, 2x1-H and 2′-H), 2.04 (3 H, s, 4′-CH_3), 1 36 (3 H, s, 1′-CH_3), 1 26 (1 H, dd, J 15 1 and 2 6 Hz, 2′-H), 1 12 (3 H, d, J 6 4 Hz, 3-H, minor rotamer) and 1 04 (3 H, d, J 7 0 Hz, 3-H, major rotamer), *m/z* (%) 355 (M^+, 35), 188 (100), 187 (94), 186 (71) and 172 (47) [Found C, 64 5, H, 6 9, N, 3 9, $C_{19}H_{24}F_3NO_2$ requires C, 64 2, H, 6 8, N, 3 9%]

Crystal data $C_{19}H_{24}O_2NF_3$, M = 355 4 Orthorhombic, a = 8 992(3), b = 13 042(3), c = 15 511(5)Å, V = 1819 0 Å^3 (by least squares refinement on diffractometer angles for 12 automatically centred reflections, λ = 0 71069 Å), space group $P2_12_12_1$, Z = 4, D_x = 1 30 gcm^{-3}. Colourless rods. Crystal dimensions 0 3 x 0 3 x 0 33 mm, μ(Mo-K_α) = 0 64 cm^{-1}. 1837 reflections were measured ($2<\theta<24^\circ$), 1624 unique and 895 observed with $I>3\sigma(I)$ The structure was solved (direct methods) and refined using the SHELX suite of programs Final R was 0 0925 for unit weights

(+)-1(S),1′(R)-1,2-Dihydro-7-methoxy-1,4-dimethyl-1-[1′-(N-methylamino)-1′-methyl ethan-2′-yl]naphthalene (20)

A mixture of the trifluoroacetamidodihydronaphthalene (17)(0.50 g, 1 41 mmol) and anhydrous potassium bicarbonate (1 0 g, 7 24 mmol) in 80% methanol (5 cm^3) was sonicated in an ultrasonic bath for 18 h, under a nitrogen atmosphere The resulting solution was poured into water (10 cm^3) and extracted with ethyl acetate (4x10 cm^3) The combined organic layers were washed with saturated brine (5 cm^3), dried, and evaporated under reduced pressure to give the title compound as a pale yellow oil (0 36 g, 99%) $[\alpha]_D^{18}$ +40 8 (c 1 4 CH_2Cl_2), ν_{max} (liquid) cm^{-1} 3360w (NH), 1610 (C=C), δ_H 7 19 (1 H, d, J 8 4 Hz, 5′-H), 6.89 (1 H, d, J 2 6 Hz, 8′-H), 6 73 (1 H, dd, J 8 4 and 2.6 Hz, 6′-H), 5 65-5 58 (1 H, m, 3′-H), 3 82 (3 H, s, OCH_3), 2.43 (1 H, pd, J 6.4 and 3 3 Hz, 2-H), 2 32-2.23

(1 H, m, 2'-H), 2 12-2 02 (1 H, m, 2'-H), 2 03 (3 H, m, 4'-CH_3), 1 99 (3 H, s, NCH_3), 1 94 (1 H, dd, J 14.4 and 6.4 Hz, 1-H), 1.33 (3 H, s, 1'-CH_3), 1.25 (2 H, br s and dd, J 14.4 and 3.3 Hz, NH and 1-H) and 0 98 (3 H, d, J 6 4 Hz, 3-H)

1,2-Dihydro-7-methoxy-1,4-dimethyl-1-[1'-(N-methylamino)-1'-methylethan-2'-yl]naphthalene chromiumtricarbonyl

Chromium hexacarbonyl (0 12 g, 0 55 mmol) and the amino dihydronaphthalene (20) (0 13 g, 0.50 mmol) were placed in a round bottomed flask (5 cm^3) fitted with a water condenser and a nitrogen /vacuum system. After the system had been thoroughly flushed out with nitrogen, a degassed solution of di- n-butyl ether (3 cm^3) and tetrahydrofuran (0 3 cm^3) was added via a cannula and the mixture was heated under reflux for 30 h (The solution changed colour from orange to black in this time) The solution was allowed to cool before filteration through an alumina pad which had been previously flushed with nitrogen. A degassed solution of dichloromethane/ethanol/triethylamine (90 8 1) was used to wash the filter pad, and the combined filtrates were evaporated under reduced pressure to give an orange oil Purification by "flash" column chromatography on silica gel (which had been flushed with nitrogen prior to use), eluting with a degassed solution of dichloromethane/ethanol/triethylamine (180 8 1) gave the title compound as an orange oil (0 048 g, 24%), which was sensitive to both air and light δ_H (2·1 mixture of two diastereomers) 5 69-5 12 (4 H, m, 3'-, 5'-, 6'- and 8'-H), 3 72 (3 H, s, OCH_3), 2 68-2 39 (2 H, m), 2 36-2 20 (1 H, m), 2 28 major and 2 17 minor (3 H, 2xs, NCH_3), 1 88 (3 H, s, 4'-CH_3), 1 68-1 09 (3 H, m), 1 47 major and 1.16 minor (3 H, 2xs, 1'-CH_3), and 0 90 (minor) and 0 72 (major) (3 H, 2xd, J 6 Hz, 3-H)

1(S),1'(R)-1,2-Dihydro-7-methoxy-1,4-dimethyl-1-[1'-(N-methyltrifluoroacetamido)-1'-methylethan-2'-yl]naphthalenechromiumtricarbonyl (18)

Chromium hexacarbonyl (0 68 g, 3 09 mmol) and the trifluoroacetamidodihydronaphthalene 29c (1 00 g, 2.81 mmol) were placed in a round bottomed flask (50 cm^3) fitted with a water condenser and a nitrogen /vacuum system After the system had been thoroughly flushed out with nitrogen, a degassed solution of di- n-butyl ether (18 cm^3) and tetrahydrofuran (2 cm^3) was added via a cannula and the mixture was heated under reflux for 40 h (The solution changed colour from orange to green in this period) The solution was allowed to cool before being filtered through an alumina pad which had been previously flushed with nitrogen A degassed solution of petrol and then ethyl acetate was used to wash the filter pad, and the filtrate was evaporated under reduced pressure to give an orange oil Purification by "flash" column chromatography on silica gel (which had been flushed with nitrogen prior to use), eluting with a gradient of degassed ethyl acetate/ petrol (3 22 to 3 17 to 1·4) gave the *trans*- isomer of the title compound as a yellow/orange microcrystalline solid (0 49 g, 36%) m p 95 0- 96 0°C, the *cis*-isomer as an orange solid (0 05 g, 4%) m p 104 5-106 0°C, and the starting material as a pale yellow crystalline solid (0.58 g, 58%)

Physical data for the *trans*-complex ν_{max} cm^{-1} 1960, 1950, 1890 and 1850 (Cr-CO), 1680 (amide CO), δ_H 5.66 (1 H, d, J 6 Hz, 3'-H), 5.58 (1 H, d, J 7 Hz, 5'-H), 5 19-5.14 (2 H, m, 6'- and 8'-H), 4 82 (1 H, br p, J 7 Hz, 2-H), 3 70 (3 H, s, OCH_3), 2 63 (4 H, m and s, NCH_3 and 1x2'-H_2), 2 24 (1 H, dd, J 14 and 9 Hz, 1x1-H_2), 2 09 (1 H, dd, J 17 and 7 Hz, 1x2'-H_2), 1 92 (3 H, s, 4'-CH_3), 1 44 (3 H, s, 1'-CH_3), 1 28 (1 H, d, J 14 Hz, 1x1-H_2) and 1 08 (3 H, d, J 7 Hz, 3-H), δ_C 233 3 (Cr-CO), 140 7

(4'-C), 128 2 (7'-C), 125 0 (3'-C), 117 7 and 97.2 (4'a- and 8'a-C), 90.0, 77 6 and 76 9 (5'-, 6'- and 8'-C), 55 3 (OCH_3), 47.0 (2-C), 41 1 and 37 4 (2'- and 1-C), 35 9 (1'-C), 32 4 (NCH_3), 23.7, 20 0 and 18 7 (3xCH_3), *m/z* (%)(CI) 492 (M+1, 18), 491 (23, M^+), 407 (16, M^+-3xCO), 356 (100), 355 (48, M-$Cr(CO)_3$), 188 (43), 187 (52) and 186 (49) [Found· C, 53 9, H, 5 05, N, 2.8, $C_{22}H_{24}CrF_3NO_5$ requires: C, 53 8; H, 4 9, N, 2.85%]

Physical data for the cis-complex. ν_{max} cm^{-1}1970, 1940, 1890, 1860 and 1840sh (Cr-CO), 1690 (amide CO), δ_H 5 69-5.59 (2 H, m, 3'- and 5'-H), 5.17-5.04 (3 H, m, 2-, 6'- and 8'-H), 3 72 (3 H, s, OCH_3), 3 05 (3 H, s, NCH_3), 2.59-2.02 (3 H, m, 2'-H_2 and 1x1-H_2), 1 88 (3 H, s, 4'-CH_3), 1.31 (3 H, d, J 7 Hz, 3-H) and 1.17-1 02 (4 H, m and s, 1x1-H_2 and 1'-CH_3), δ_C 233 5 (Cr-CO), 141.7 (4'-C), 127 3 (7'-C), 125 0 (3'-C), 118 6 and 97.3 (4'a- and 8'a-C), 90 5, 77 2 and 75 0 (5'-, 6'- and 8'-C), 55 7 (OCH_3), 47 1 (2-C), 41 6 and 33 9 (2'- and 1-C), 35 4 (1'-C), 26.5, 20 4 and 18.8 (3xCH_3); *m/z* (%) 407 (M^+-3xCO, 18), 355 (41, M-$Cr(CO)_3$), 213 (11), 201 (13), 188 (85), 187 (100) and 186 (93) [Acc mass found for fragment 407 1180 (M^+-3xCO) $C_{19}H_{24}CrF_3NO_2$ requires 407.1158]

(-)-1,2,3,4,5,6-Hexahydro-8-methoxy-1,3,4,6-tetramethyl-2,6-methano-3-benzazocine (19)

Degassed aqueous methanol (67%, 6 cm^3) was added via a cannula to a mixture of trifluoroacetamidodihydronaphthalene chromium tricarbonyl complex (18) (0.10 g, 0.2 mmol) and anhydrous potassium carbonate (0 20 g, 1 4 mmol) under an argon atmosphere. The mixture was sonicated in an ultrasonic bath for 3 days, during which time the potassium carbonate dissolved. At the end of this period three components were visible by t l c . the starting material, the amino derivative of the starting material, and the chromium tricarbonyl complex of the title compound The solution was added to water (5 cm^3) and extracted with ethyl acetate (4x5 cm^3) The combined organic portions were washed with brine (3 cm^3) and quickly dried, and evaporated under reduced pressure to give an orange oil (0 08 g) This residue was then dissolved in diethylether (5 cm^3) and placed in a sunlit position, in the presence of air, for 24 h (After this time the orange solution formed a green suspension) The suspension was evaporated under reduced pressure and the residue then purified by "flash" column chromatography on silica gel, eluting with dichloromethane/ ethanol/aqueous ammonia (100:8 1) to give a mixture of the title compound (19) and the aminodihydronaphthalene (20) Further purification by preparative t.l c on silica gel (1 mm, 60 GF254 Merck), using the same eluant as before, gave the the aminodihydronaphthalene (20) (0 030 g, 57%) and the title compound as a white waxy solid (0 009 g, 17% overall yield, 40% based on recovered aminodihydronaphthalene) m p 66 0-67 0°C, $[\alpha]_D^{18}$ -59 3 (c 2 0, CH_2Cl_2), ν_{max} cm^{-1} 2980, 1600, 1570, δ_H 7 08 (1 H, d, J 8 4 Hz, 10-H), 6 80 (1 H, d, J 2 7 Hz, 7-H), 6.73 (1 H, dd, J 8.4 and 2 7 Hz, 9-H), 3 79 (3 H, s, OCH_3), 3 12 (1 H, q, J 7 1 Hz, 1-H), 2 88 (1 H, t, J 3 1 Hz, 2-H), 2.42 (3 H, s, NCH_3), 2 13-1 92 (2 H, m, 1x4- and 1x11-H_2), 1 69 (1 H, ddd, J 12 6, 3 8 and 1 1 Hz, 1x11-H_2), 1 35 (5 H, s and m, 6-CH_3 and 5-H_2), 1 22 (3 H, J 7 1 Hz, 1-CH_3) and 0 92 (3 H, d, J 6 2 Hz, 4-CH_3), δ_C 157 7 (8-C), 145 4 and 145.6 (6a- and 10a-C), 128 9, 111 2 and 110 1 (7-, 9- and 10-C), 62 8 (CH), 55 1 (OCH_3), 50 1 (CH and CH_2), 39.7 (NCH_3), 36 0 (CH_2), 33.8 (6-C), 29 6 (1-C), 28 0, 24 9 and 20 6 (3xCH_3), *m/z* (%) 259 (M^+, 20), 244 (100, M-CH_3), and 124 (31)[Acc mass found 259 1936 (M^+, 26%), $C_{17}H_{25}NO$ requires· 259 1934] Enantiomeric excess 86% (±2%) as determined by ^1H n m r using a solution of TFAE (0 050g) and the sample (0 007g) in $CDCl_3$

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ACKNOWLEDGEMENTS

We thank the S E.R C. and Glaxo Group Research Ltd., for a C A S E. studentship to C S W.