Asymmetric Synthesis of (*R*)-(−)- and (*S*)-(+)-Muscone by Enantioselective Conjugate Addition of Chiral Dimethylcuprate to (*E*)-Cyclopentadec-2-en-1-one

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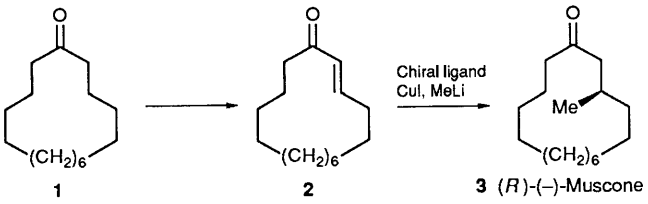
A variety of optically active secondary amino alcohols have been prepared from camphor and screened as chiral non-transferable cuprate ligands in conjugate addition reactions. The reactions of (*E*)-cyclopentadec-2-en-1-one with chiral dimethylcuprates derived from the ligand in toluene afforded muscone in enantiomeric excesses as high as 26–89%. The stereochemistry of the product correlates with the configuration of the chiral ligand used. Thus the conjugate addition using the ligand prepared from *exo*-3-monosubstituted-amino-*exo*-2-hydroxybornane gave (*S*)-(+)-muscone, while with *endo*-ligand, (*R*)-(−)-muscone was obtained in higher enantioselectivity. Muscone of essentially 100% optical purity was obtained by the addition of small amounts of THF (tetrahydrofuran) (2–10 equiv.) to the toluene solution of the chiral cuprate reagent prepared from (1*R*,2*R*,3*S*,4*S*)-3-[(1-methylpyrrol-2-yl)methylamino]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol **23** (*endo*-MPATH). The effect of the stoichiometry of the chiral ligand and the cuprate reagent on the chemical yield and enantioselectivity was briefly investigated.

Introduction

Muscone, a principal odoriferous constituent, was isolated by Walbaum in 1906 from musk pod obtained from the male musk deer *Moschus moschiferus*,[1] and its structure was determined as (−)-3-methylcyclopentadecan-1-one by Ruzicka in 1926.[2] Muscone has been the target of a number of synthetic investigators because of the importance of this unique 15-membered cyclic ketone as the ingredient of perfumes and because of its rare occurrence in Nature.† The first synthesis of racemic muscone was reported independently in 1934 by Ruzicka and Stoll,[3] and by Ziegler and Weber.[4] The absolute configuration, however, was not determined at that time. In 1951 Ställberg-Stenhagen succeeded in asymmetric synthesis of optically active muscone from methyl (*R*)-3-methyl-6-oxohexanoate as a chiral building block and established that natural muscone possessed the *R* configuration.[5] Since that time a variety of methods have been reported for the asymmetric synthesis of (*R*)-(−)-muscone.[6–12] The procedures, however, require multi-step processes starting from chiral building blocks such as (*R*)-3-methyl-*N*-phenylglutamic acid[9] and (*S*)-4-bromo-3-methylbutanenitrile.[10]



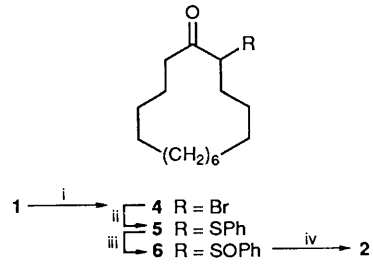
Scheme 1

The shortest route to (*R*)-muscone is the enantioselective introduction of methyl group into (*E*)-cyclopentadec-2-enone, since this unsaturated 15-membered ketone is readily prepared from commercially available cyclopentadecanone,‡ but this approach has never been developed.§ Recently the high enantioselective conjugate addition of chiral organocuprates to cyclohex-2-enone (85–97% ee) and cyclopent-2-enone (72–81% ee) has been achieved by using (1*R*,2*S*)-3,6,6-trimethyl-1-phenyl-3,6-diazahexanol,[14] (*S*)-2-methoxymethylpyrrolidine,[15] or (*S*)-*N*-methyl-1-phenyl-2-piperidinoethanamine[16] as a non-transferable chiral ligand.¶[17]

We now report the first enantioselective conjugate addition of dimethylcuprate to a macrocyclic enone, (*E*)-cyclopentadec-2-enone using the newly devised chiral ligands derived from camphor, leading to the formation of both enantiomers of muscone with high enantiomeric excesses.[18]

Results and Discussion

Although (*E*)-cyclopentadec-2-enone **2** could be prepared by bromination of the ethylene ketal of cyclopentadecanone and subsequent dehydrobromination,[3,13] this route resulted in the formation of a difficult to separate mixture of **2** and its regioisomer. In the present study we adapted a modified procedure described in Scheme 2 in order to obtain the enone **2**



Scheme 2 *Reagents and conditions*: i, Br_2, MeOH; ii, PhSNa, EtOH; iii, oxone; EtOH; iv, $CaCO_3$, benzene, reflux

of high purity. Thus, the bromide **4** was transformed into the sulphoxide **6**, which could readily be purified by silica gel chromatography because the latter possesses the lowest R_f

† Since habitat destruction and illegal poaching for the musk trade threatened the survival of this unusual deer species, they are now protected by the Convention on International Trade in Endangered Species of Wild Fauna and Flora.

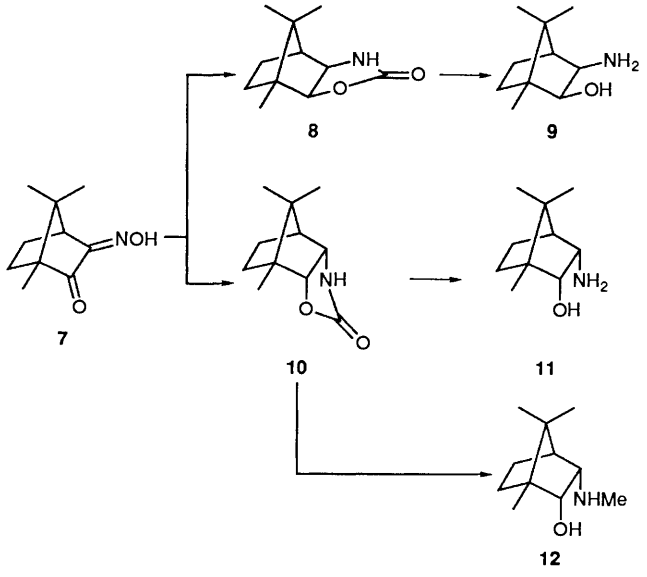
‡ Cyclopentadecanone is commercially available from Nippon Mining Co., Tokyo.

§ For a preparation of racemic muscone by conjugate addition of methylmagnesium bromide to cyclopentadec-2-enone see ref. 13.

¶ For recent development of the conjugate addition reactions using chiral non-transferable ligands see ref. 17.

value among these intermediates. Thermolysis of the sulphoxide gave the pure *trans* enone **2** in 83% yield.

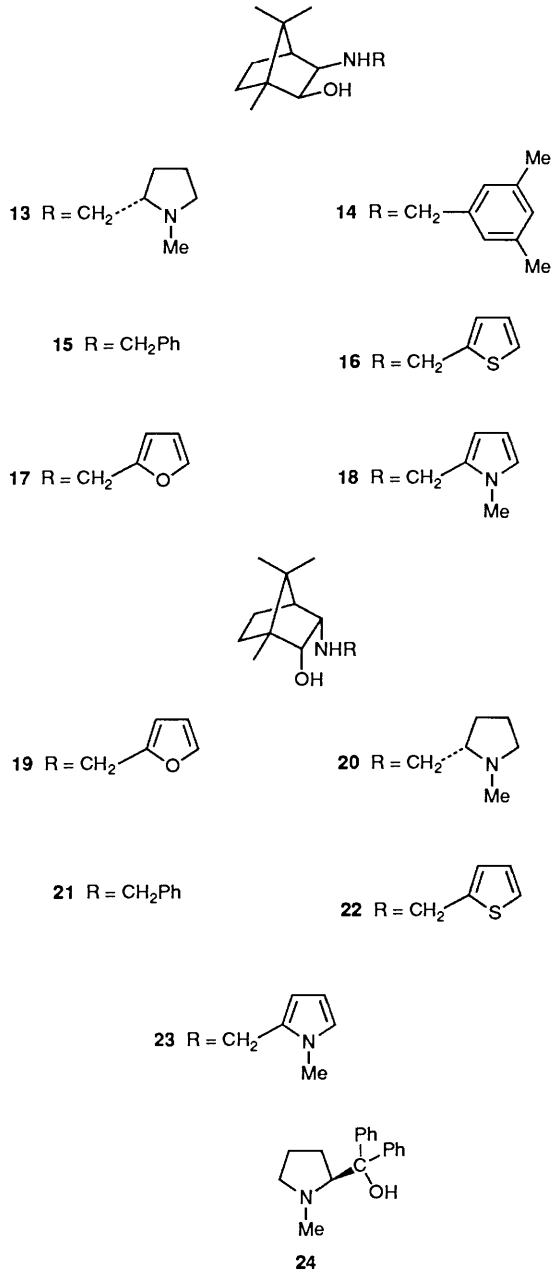
The chiral ligands needed for the conjugate addition were prepared by reduction of the corresponding amides or imines derived from *exo*-3-amino-*exo*-2-hydroxybornane and *endo*-3-amino-*endo*-2-hydroxybornane. These secondary amino alcohols were readily prepared by reduction of 3-(hydroxyimino)camphor **7** with lithium aluminium hydride (LAH) according to the reported procedure.[19–21] However NMR (400 MHz) analysis indicates that the amino alcohols contain stereoisomers. Attempts to purify these amino alcohols by recrystallization or chromatography were unsuccessful. We found that the crude *exo*-amino alcohol was readily transformed into the cyclic carbamate **8** when heated with diethyl carbonate in the presence of potassium carbonate.[21] The carbamate could easily be purified by recrystallization (hexane–ethyl acetate, 2:1) to give colourless crystals with high purity.



Scheme 3

Alkaline hydrolysis of the carbamate **8** gave the optically pure amino alcohol **9** in 98% yield. In a similar way, optically pure *endo*-3-amino-*endo*-2-hydroxybornane **11** was prepared from crude amino alcohol[22] *via* the cyclic carbamate **10**. Reduction of the latter with LAH gave *endo*-3-methylamino-2-hydroxybornane **12** in 98% yield.

The chiral methylcuprate was prepared from the corresponding secondary amino alcohol *via* sequential reactions with methyllithium, copper(I) iodide and methyllithium. We first investigated the solvent effect on the chemical yield and enantioselectivity by using the cuprate reagent prepared from *exo*-MPMTH **13**:MeLi:CuI:MeLi (1:1:1:2). The reaction in THF gave racemic muscone in 44% yield, while the reaction in toluene afforded (*S*)-muscone in 93% isolated yield with 26% enantiomeric excess (% e.e.). The % e.e. of the product was determined by comparison of the rotational data[6] after silica gel chromatography and distillation under reduced pressure. Several attempts to determine the % e.e. by using a chiral stationary phase (Chiralcel OD) or by using chiral shift reagents such as $Eu(tfc)_3$ and (+)-2,2,2-trifluoro-1-(9-anthryl)ethanol were unsuccessful. No conjugate addition reaction was observed in hydrocarbon solvents such as hexane and cyclohexane. When boron trifluoride–diethyl ether was used in this reaction, the chemical yield was the same, but the % e.e. was decreased to 14. It should be noted that the cuprate reagent, prepared from *exo*-TATH **16**:MeLi:CuI:MeLi (2:4:1:2) afforded higher optical yield (49%) than the reagent prepared



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Scheme 4

from **16**:MeLi:CuI:MeLi (1:2:1:2) (31% e.e.). The enantioselective conjugate additions using a variety of *exo*-chiral ligands in toluene are summarized in Table 1. The *exo*-ligands selectively afforded the *S*-enantiomer of muscone. In the present study the highest enantioselectivity was obtained with *exo*-MPATH **18**.

The effect of the stoichiometry of the cuprate reagent prepared from *endo*-TATH **22** in toluene on the chemical yield and selectivity was next investigated (Table 2). The use of **22**:MeLi:CuI:MeLi (1:1:1:2) afforded the *R*-configuration of muscone in 86% yield and in 32% e.e. (entry 1). In the present system, it is reasonable to assume that the formation of lithium salt **25** from **22** is fast with respect to the formation of oxygen–copper bond on treatment of the lithium salt with copper(I) iodide. When the lithium copper exchange reaction is not complete, the reagents are mixture of oxygen–copper species and the copper(I) iodide. Methyllithium (2 equiv.) added in this mixture will interact with both the oxygen–copper species **26** and copper(I) iodide and produce a mixture of chiral

Table 1 Effect of the *exo*-chiral ligand

Entry	Chiral ligand	Muscone			
		Yield (%)	$[\alpha]_D$ [T/°C, c(MeOH)]	Optical purity[a]	Configuration
1	*exo*-MPMTH **13**	93	+3.02 (22, 1.10)	26	*S*
2	*exo*-DIATH **14**	64	+4.04 (23, 5.02)	35	*S*
3	*exo*-BATH **15**	72	+4.54 (27, 5.25)	39	*S*
4	*exo*-TATH **16**	82	+5.72 (25, 5.02)	49	*S*
5	*exo*-FATH **17**	86	+5.83 (24, 5.15)	50	*S*
6	*exo*-MPATH **18**	88	+6.69 (26, 5.17)	57	*S*

[a] Based on the maximum $[\alpha]_D$ −11.7° (*c* 0.80, MeOH); see ref. 6.

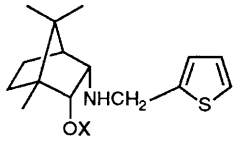
Table 2 The effect of the stoichiometry on the yield and enantioselectivity of (*R*)-muscone

Entry	Ligand[a] (equiv.)	Methyllithium (equiv.)	Cuprous iodide (equiv.)	Methyllithium (equiv.)	Enone **2** (equiv.)	Yield of (*R*)-muscone **3** (%)	Optical purity (%)
1	1	1	1	2	1	86	32
2	2	2	1	1	1	23[b]	66
3	2	2	1	2	1	84	86
4	2	2	1	2	1	39[c]	8
5	2	2	1	3	1	52[d]	18
6	2	4	1	0	1	0[e]	—
7	2	4	1	2	1	36[f]	19

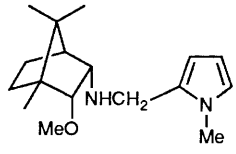
[a] *endo*-TATH **22** was used as the ligand. [b] The enone **2** was recovered in 56% yield. [c] The conjugate addition reaction was carried out at −50 °C. [d] The enone **2** was recovered in 19% yield. [e] The enone **2** was recovered in 81% yield. [f] The enone **2** was recovered in 12% yield.

dimethylcuprate **27*** and lithium dimethylcuprate (Me_2CuLi). The chiral dimethylcuprate gives (*R*)-muscone and lithium dimethylcuprate gives racemic muscone respectively. When copper(I) iodide (1 equiv.) was treated with the lithium salt **25** (2 equiv.) the oxygen–copper bond formation might be complete. Thus the addition of methyllithium (1 equiv) will produce chiral monomethylcuprate. The result indicates that the monomethylcuprate is an effective chiral species, but is less reactive to the enone **2**, giving a low yield of (*R*)-muscone (entry 2). The addition of methyllithium (2 equiv.) afforded the highest enantioselectivity and chemical yield (entry 3). This raises the interesting possibility that the structure of the copper reagent **27** is fundamentally different from those of the other heterocuprate[14–16,23] species prepared from heterocuprate (1 equiv) and organolithium reagent (1 equiv). The conjugate addition at higher temperature significantly decreases the enantioselectivity as well as the chemical yield (entry 4). The addition of methyl lithium (3 equiv.) was detrimental, resulting in low enantioselectivity (entry 5).

In order to check the importance of the oxygen–copper bond formation in the enantioselective conjugative addition, we prepared the *O*-methyl derivative, *endo*-**28**, from the *endo*-ligand **23**. The *O*-methyl ligand was treated with copper(I) iodide (1 equiv.) and methyllithium (2 equiv.) in toluene. Under these conditions the conjugate addition did not occur and the starting enone was recovered in 70% yield, indicating that the hydroxy function of the chiral ligand plays an important role in the enantioselective conjugate addition. Next, the lithium salt prepared from *endo*-MPATH **23** (2 equiv.) with methyllithium (2 equiv.) in toluene was treated with lithium dimethylcuprate (1 equiv.). The reaction of this mixture with (*E*)-cyclopentadec-2-enone **2** gave almost 1:1 mixture of racemic muscone (49%) and the starting enone (45%). This result shows that the simple mixing of the two reagents does not produce the chiral dimethylcuprate and that free lithium dimethylcuprate in the mixture reacted with the enone to give racemic muscone. Table 3 shows the results of the conjugate addition using chiral dimethylcuprates prepared from a variety of the *endo*-ligands. It should be emphasized that the *endo*-ligands selectively afforded natural (*R*)-muscone with higher optical purity. The ligand **24**, which had been successfully used in enantioselective addition of diethylzinc to aldehydes (up to 92% e.e.)[24] was ineffective in the conjugate addition reaction (entry 7). Quinine was also ineffective. The reagent derived from (1*R*,2*R*,3*S*,4*S*)-3-[(1-methylpyrrol-2-yl)methylamino]-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-ol (*endo*-MPATH) **23** was found to be most effective, giving (*R*)-muscone in 85% isolated yield with 89% e.e. The chiral ligands used in the reaction were easily recovered by silica gel chromatography without loss of optical purity.



25 X = Li
26 X = Cu
27 X = $CuMe_2Li_2$



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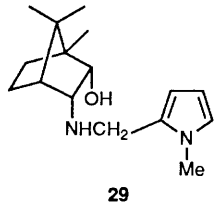

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Scheme 5

We have found that the addition of small amounts of THF to the solution of the chiral dimethylcuprate prepared at −78 °C in toluene affords (*R*)-muscone of essentially 100% optical purity.† The effect of added THF is summarized in Table 4.

* We tentatively assigned the chiral dimethylcuprate as a monomer. The structure of the chiral dimethylcuprate must await further investigation.

† In order to obtain reliable % e.e., optical rotations were measured at two wavelengths (λ 589 and 365 nm) and compared with the reported values.[6]

Table 3 Effect of the *endo*-chiral ligand

Entry	Chiral ligand	Muscone			
		Yield (%)	$[\alpha]_D$ [T/°C, c(MeOH)]	Optical purity[a]	Configuration
1	*endo*-MATH **12**	70	−4.54 (24, 5.36)	39	*R*
2	*endo*-FATH **19**	90	−3.90 (25, 5.16)	33	*R*
3	*endo*-MPMTH **20**	72	−2.43 (25, 5.46)	21	*R*
4	*endo*-BATH **21**	90	−7.52 (22, 5.09)	64	*R*
5	*endo*-TATH **22**	84	−10.09 (21, 5.06)	86	*R*
6	*endo*-MPATH **23**	85	−10.41 (22, 5.05)	89	*R*
7	**24**	59	+1.70 (24, 5.15)	15	*S*

[a] Based on the maximum $[\alpha]_D$ −11.7° (*c* 0.80, MeOH); see ref. 6.

Table 4 Effect of Additive THF

Entry	Chiral ligand	Solvent[a]	Additive	Muscone		
				Yield[b] (%)	Optical purity[c]	Configuration
1	*endo*-BATH **21**	toluene	none	90	64	R[d]
2	*endo*-BATH **21**	toluene	THF (5 eq)	36	74	R
3	*endo*-TATH **22**	toluene	none	84	86	R[d]
4	*endo*-TATH **22**	toluene	THF (5 eq)	77	93	R
5	*endo*-TATH **22**	toluene	THF (10 eq)	80	95	R[e]
6	*endo*-MPATH **23**	toluene	none	85	89	R[d]
7	*endo*-MPATH **23**	toluene	THF (2 eq)	89	100	R
8	*endo*-MPATH **23**	toluene	THF (4 eq)	94	99	R
9	*endo*-MPATH **23**	toluene	THF (10 eq)	93	100	R
10	*endo*-MPATH **23**	ether	none	57	99	R
11	*endo*-MPATH **23**	toluene	THF[f]	21	81	R[g]
12	*endo*-MPATH **29**	toluene	THF (2 eq)	90	100	S

[a] The reaction was carried out by using 11 mmol of chiral ligand, 11 mmol of MeLi, 5.5 mmol of CuI, and 11 mol of MeLi in 90 cm^3 of dry solvent, unless otherwise stated. [b] Yields are based upon isolated products purified by chromatography on silica gel. [c] Optical yields were determined from measurements of the optical rotation of the distilled product after the chromatography. [d] Reported result; see ref. 20. [e] Recovered chiral ligand **22** was used. [f] The reaction was carried out on 1.62 mmol of enone **2** in 30 cm^3 of toluene. After THF (30 cm^3) was added to the cuprate reagent at −78 °C, and the mixture was stirred for 1 h, the enone was added at −78 °C. [g] Enone **2** was recovered in 67% yield.

TATH **22** and *endo*-MPATH **23**. The increase in the enantioselectivity indicates that THF may act as an external ligand in the cuprate cluster.[15] The use of an excess of THF (entry 11) was detrimental and probably alters the composition of the cluster.[15] Under these conditions (*R*)-muscone was obtained only in 21% yield with 81% e.e. and the starting enone was recovered in 67%

In order to check the reproducibility of this high enantioselective conjugate addition, we prepared an antipodal amino alcohol **29** from L-camphor. As expected (*S*)-(+)-muscone was obtained in 90% isolated yield with 100% optical purity by using THF as additive (entry 12).

In conclusion *endo*-MPATH was found to be a very efficient chiral ligand for the conjugate addition of dimethylcuprate. Using the ligand in toluene we have been able to develop the shortest asymmetric synthesis of (*R*)-(−)- and (*S*)-(+)-muscone of essentially 100% optical purity from (*E*)-cyclopentadec-2-enone. Efforts are currently underway to clarify the structures of the organocopper species and the mechanism of the conjugate addition reaction.

Experimental

Tetrahydrofuran (THF) was distilled under argon from sodium benzophenone ketyl immediately before use. Toluene, ether, dichloromethane and hexane were distilled from calcium hydride and stored over 4 Å molecular sieves. The ether solution of methyllithium (as complex with lithium bromide, Kanto Chemicals) was titrated using diphenylacetic acid.[25]

IR spectra were recorded on a Hitachi Model 215 spectrophotometer. NMR spectra were obtained on a JEOL Model PS-100 or a JEOL Model JMN-FX-400 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. *J* values are given in Hz. Optical rotations were measured in 1 dm path length cells of 2 cm^3 or 10 cm^3 on a JASCO Model DIP-181 polarimeter. GLC was performed on a Shimadzu Model GC-8A gas chromatograph using a 0.15 cm × 120 cm glass column (20% Silicone DC-550 on Celite 545). Thin layer chromatography was performed by using Merck precoated silica gel sheets 60F-254. Silica gel (Wakogel) of the size 100–200 mesh was used for column chromatography. Mass spectra were determined on a JMS-DX-300 spectrometer at an ionization potential 70 eV. Elemental analyses were performed by the Microanalytical Laboratory, operated by the Institute for Chemical Research, Kyoto University.

Preparation of 2-(*Phenylsulphinyl*)*cyclopentadecanone* **6**.—To a stirred solution of cyclopentadecanone (10.0 g, 44.6 mmol) in methanol (60 cm^3) at 15–20 °C was added bromine (7.13 g, 44.6 mmol).[12] After being stirred for 2 h at this temperature, the solution was poured into brine covered with hexane (100 cm^3). The mixture was extracted with hexane and the extracts were washed with aqueous sodium hydrogen sulphate and water and dried ($MgSO_4$). Evaporation of the solvent gave 2-bromocyclopentadecanone **4** as an oil. A solution of the crude bromide **4** in ethanol (50 cm^3) was added, at 0 °C, to the ethanolic solution of sodium benzenethiolate prepared from sodium (1.03 g, 44.6 mmol) and benzenethiol (4.83 g, 43.8 mmol) in ethanol (150 cm^3). After the addition was complete, the mixture was heated under reflux for 5 h. The solvent was evaporated under reduced pressure and the residue diluted with water and extracted with hexane. The extracts were dried ($MgSO_4$) and evaporated under

reduced pressure to give 2-(phenylthio)cyclopentadecanone **5**. To a stirred solution of **5** in ethanol (170 cm^3) and dichloromethane (50 cm^3) at 0 °C was added a solution of oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$; 16.78 g, 27.3 mmol) in water (75 cm^3). After being stirred for 5 h at 0 °C, the mixture was quenched with aqueous Na_2SO_3, and extracted with dichloromethane. The extracts were washed with brine, dried ($MgSO_4$) and evaporated. Column chromatography (hexane–EtOAc, 3:1) of the residue gave 2-(phenylsulphinyl)cyclopentadecanone **6** as a white solid, m.p. 87–88 °C; ν_{max}(KBr)/cm^{-1} 3400, 2900, 2850, 1700, 1440 and 1050; δ_H(100 MHz) 1.24 (s, 19 H), 1.62 (m, 2 H), 1.80–2.04 (m, 4 H), 2.44 (m, 1 H), 3.68 (m, 1 H) and 7.46 (m, 5 H); *m/z* 348 (M^+ 4%), 332 (12), 223 (100) and 109 (80).

Preparation of (E)-*Cyclopentadec-2-enone* **2**.—A mixture of **6** (6.50 g, 18.7 mmol) and $CaCO_3$ (0.29 g, 2.5 mmol) in dry benzene (160 cm^3) was heated under reflux for 5 h under argon. The mixture was diluted with water and the benzene layer was separated. The organic layer was washed with brine and dried ($MgSO_4$). Evaporation of the solvent and column chromatography (silica, hexane–ethyl acetate 40:1) gave the title compound **2** (3.45 g, 83%) as a white solid, which was further purified by bulb-to-bulb distillation; ν(thin film)/cm^{-1} 2920, 1670, 1630, 1450 and 1000; δ_H(400 MHz) 1.31 (m, 16 H), 1.54 (m, 2 H), 1.68 (m, 2 H), 2.26 (m, 2 H), 2.50 (t, *J* 6.7, 2 H), 6.19 (d, *J* 15.8, 1 H) and 6.81 (dt, *J* 15.8, 7.6, 1 H).[13]

(1R,2S,3R,4S)-1,7,7-*Trimethyl*-2,3-*iminomethanoepoxybicyclo*-[2.2.1]*heptane*-9-*one* **8**.—A mixture of the crude *exo*-3-amino-*exo*-2-hydroxyborane[19,20] (22.44 g, 0.134 mol), diethyl carbonate (18.81 g, 0.159 mol) and K_2CO_3 (powdered; 1.84 g, 13.3 mmol) was heated at 150 °C for 6 h under argon.[21] The reaction mixture was cooled to room temp. and dichloromethane (200 cm^3) was added. The organic layer was washed with 10% aqueous citric acid (50 cm^3) and water and dried (Na_2SO_4). Evaporation of the solvent gave a white solid which was recrystallized from hexane–ethyl acetate (2:1) to give the *title compound* **8** (31%); m.p. 156–158 °C (Found: C, 67.5; H, 8.7; N, 7.2. $C_{11}H_{17}NO_2$ requires C, 67.6; H, 8.8; N, 7.2%); $[\alpha]_D^{22}$ −43.4° (*c* 2.02, $CHCl_3$); δ_H(400 MHz) 0.85 (s, 3 H), 1.00 (s, 3 H), 1.02 (m, 3 H), 1.06 (s, 3 H), 1.20–2.00 (m, 5 H), 3.70 (d, *J* 8, 1 H), 4.35 (d, *J* 8, 1 H) and 6.70 (m, 1 H).

(1R,2S,3R,4S)-3-*Amino*-1,7,7-*trimethylbicyclo*[2.2.1]*heptan*-2-*ol* **9**.—To a solution of **8** (20.59 g, 0.106 mol) in ethanol (230 cm^3) was added a solution of NaOH (16.90 g, 0.422 mol) in water (115 cm^3). After the mixture had been refluxed for 6 h under argon, the solvent was evaporated and the product was extracted with ether (3 × 70 cm^3). The organic layers were washed with brine, dried (Na_2SO_4) and evaporated to give the pure *exo*-3-amino-*exo*-2-hydroxybornane **9** (17.56 g, 98%) as a white solid, m.p. 200 °C; $[\alpha]_D^{24}$ −6.2° (*c* 1.01, MeOH); δ_H(400 MHz) 0.82 (s, 3 H), 0.99 (s, 3 H), 1.06 (m, 3 H), 1.10 (s, 3 H), 1.49 (m, 1 H), 1.60 (d, *J* 4.6, 1 H), 1.73 (m, 1 H), 2.50 (br s, 2 H), 3.10 (d, *J* 7.32, 1 H) and 3.42 (d, *J* 7.32, 1 H).

(1R,2R,3S,4S)-1,7,7-*Trimethyl*-2,3-*iminomethanoepoxybicyclo*[2.2.1]*heptan*-9-*one* **10**.—By a similar procedure described for **8**, the *title compound* was prepared in 75% yield by heating a mixture of crude *endo*-3-amino-*endo*-2-hydroxybornane (26.26 g, 0.155 mol),[22] diethyl carbonate (43.3 cm^3, 0.357 mol) and powdered K_2CO_3), (2.15 g, 0.016 mol) at 145–150 °C for 3 h; m.p. 167.5–168.5 °C (Found: C, 67.6; H, 8.8; N, 7.1. $C_{11}H_{17}NO_2$ requires C, 67.6; H, 8.8; N, 7.2%); $[\alpha]_D^{26}$ +81.8° (*c* 2.21, $CHCl_3$); ν(KBr)/cm^{-1} 2950, 1760, 1715, 1250 and 1055; δ_H(100 MHz) 0.96 (s, 9 H), 1.22–1.46 (m, 1 H), 1.46–1.83 (m, 3 H), 1.82–1.96 (m, 1 H), 4.20 (dt, *J* 6, 12, 1 H) and 6.50 (br s, 1 H).

(1R,2R,3S,4S)-3-*Amino*-1,7,7-*trimethylbicyclo*[2.2.1]*heptan*-2-*ol* **11**.—By a similar procedure to that described for **9**, alkaline hydrolysis of **10** gave the title compound **11** in 97% yield; m.p. 163 °C; $[\alpha]_D^{25}$ +36.0° (*c* 1.04, MeOH) (lit., $[\alpha]_D^{20}$ +35.8° (*c* 1, MeOH); δ_H(400 MHz) 0.92 (s, 3 H), 0.95 (s, 6 H), 1.02 (m, 1 H), 1.17 (m, 1 H), 1.45 (m, 2 H), 1.80 (m, 3 H), 3.55 (dd, *J* 4.6, 9.2, 1 H) and 3.61 (d, *J* 9.2, 1 H).

(1R,2R,3S,4S)-3-*Methylamino*-1,7,7-*trimethylbicyclo*[2.2.1]-*heptan*-2-*ol* (*endo-MATH*) **12**.—To a suspension of LAH (5.58 g, 147 mmol) in dry THF (90 cm^3) was added a solution of **10** (7.17 g, 36.8 mmol) in dry THF (50 cm^3) at room temp. under argon. The mixture was refluxed for 3 h and quenched by sequential addition of water (5.6 cm^3), 15% aqueous sodium hydroxide (5.6 cm^3) and water (16.8 cm^3) at 0 °C. The resulting suspension was filtered through a Hyflo Super-Cel. The organic layer was dried ($MgSO_4$) and evaporated to give the *title compound* **12** as a white solid (98%); m.p. 88–90 °C (Found: C, 78.7; H, 9.7; N, 5.4. $C_{17}H_{25}NO$ requires C, 78.7; H, 9.7; N, 5.4%); $[\alpha]_D^{23}$ +26.4° (*c* 2.00, $CHCl_3$); ν(KBr)/cm^{-1} 3265, 2905, 1450, 1070 and 740; δ_H(400 MHz) 0.82 (s, 3 H), 1.10 (m, 1 H), 1.35 (m, 2 H), 2.95 (dd, *J* 4.3, 9.2, 1 H) and 3.62 (dd, *J* 1.8, 9.2, 1 H).

N-{(1R,2S,3R,4S)-2-*Hydroxy*-1,7,7-*trimethylbicyclo*[2.2.1]-*heptan*-3-*yl*}-2-[(S)-1-*benzyloxycarbonyl*]*prolinamide*.—To a stirred mixture of (*S*)-*N*-benzyloxycarbonylproline (14.76 g, 59.2 mmol) in dry dichloromethane (50 cm^3) at 0 °C was added dicyclohexylcarbodiimide (12.21 g, 59.2 mmol). The resulting suspension was then stirred at 0 °C for 15 min after which a solution of **9** (10.0 g, 59.2 mmol) in dichloromethane (50 cm^3) was added at 0 °C for 3 h. The reaction mixture was filtered to remove dicyclohexylurea. The filtrate was extracted with 10% aqueous citric acid, brine, 4% aqueous sodium hydrogen carbonate and again brine. The organic layer was dried (Na_2SO_4) and concentrated and the crude product was chromatographed (silica, hexane–ethyl acetate, 1:1) to give the title compound in 75% yield as a viscous oil; $[\alpha]_D^{25}$ −28.2° (*c* 2.23, $CHCl_3$) ν(KBr)/cm^{-1} 3375, 2950, 1710, 1650 and 1420; δ_H(100 MHz) 0.76, 0.84, 0.98 (s, 10 H), 1.40–1.76 (m, 4 H), 1.76–2.20 (m, 4 H), 1.80 (m, 1 H), 3.46 (m, 2 H), 3.72 (m, 2 H), 4.28 (m, 1 H), 5.14 (s, 2 H), 6.80 (br s, 1 H) and 7.28 (m, 5 H). The amide was directly subjected to reduction.

(1R,2S,3R,4S)-3-[(S)-1-*Methylpyrrolidin*-2-*yl*]*methylamino*-1,7,7-*trimethylbicyclo*[2.2.1]*heptan*-2-*ol* (exo-*MPMTH*) **13**.—Reduction of the above amide with LAH (3 equiv.) in refluxing THF gave the *title compound* **13** in 69% yield as a pale yellow oil; b.p. 151–156 °C/1 mmHg (Found: C, 72.2; H, 11.5; N, 10.9. $C_{16}H_{30}N_2O$ requires C, 72.1; H, 11.4; N, 11.0%); $[\alpha]_D^{24}$ −26.4° (*c* 2.10, $CHCl_3$); ν(thin film)/cm^{-1} 3275, 2930, 1475, 1395 and 1105; δ_H(100 MHz) 0.84, 1.02, 1.16 (s, 10 H), 1.26–1.64 (m, 2), 1.88 (m, 6 H), 2.04–2.32 (m, 2 H), 2.48 (s, 4 H), 2.84 (m, 3 H), 3.24 (m, 2 H) and 3.64 (d, *J* 8.0, 1 H).

(1R,2S,3R,4S)-3-(3,5-*Dimethylbenzylamino*)-1,7,7-*trimethylbicyclo*[2.2.1]*heptan*-2-*ol* (exo-*DATH*) **14**.—The reduction of the amide prepared from **9** and 3,5-dimethylbenzoyl chloride with LAH (3 equiv.) in refluxing THF for 6 h gave the *title compound* **14** as a viscous oil (88%) (Found: C, 79.3; H, 10.1; N, 4.8. $C_{19}H_{29}NO$ requires C, 79.4; H, 10.2; N, 4.9%); $[\alpha]_D^{23}$ +20.9° (*c* 2.18, $CHCl_3$); δ_H(400 MHz) 0.80 (s, 3 H), 0.99 (s, 3 H), 1.05 (m, 2 H), 1.08 (s, 3 H), 1.45 (m, 1 H), 1.62 (m, 1 H), 1.72 (m, 1 H), 2.33 (s, 6 H), 2.84 (d, *J* 7.3, 1 H), 3.48 (d, *J* 7.3, 1 H), 3.73 (d, *J* 5.2, 2 H) and 6.95 (m, 3 H).

(1R,2S,3R,4S)-3-*Benzylamino*-1,7,7-*trimethylbicyclo*[2.2.1]-*heptan*-2-*ol* (exo-*BATH*) **15**.—The reduction of the amide

prepared from **9** and benzoyl chloride with LAH (3 equiv.) in refluxing THF for 5 h gave the *title compound* **15** (69%) as white needles; m.p. 88.5 °C (Found: C, 78.6; H, 9.6; N, 5.3. $C_{17}H_{25}NO$ requires C, 78.7; H, 9.7; N, 5.4%) $[\alpha]_D^{23}$ +22.4° (*c* 2.03, $CHCl_3$); ν(KBr)/cm^{-1} 3100, 2950, 1500, 1110 and 730; δ_H(400 MHz) 0.76 (s, 3 H), 0.95 (s, 3 H), 1.00 (m, 2 H), 1.41 (m, 1 H), 1.58 (d, *J* 4.6, 1 H), 2.79 (d, *J* 7.0, 1 H), 3.41 (d, *J* 7.3, 1 H), 3.78 (s, 2 H), 4.50 (br s, 1 H) and 7.30 (m, 5 H).

N-{(1R,2S,3R,4S)-2-*Hydroxy*-1,7,7-*trimethylbicyclo*[2.2.1]-*heptan*-3-*yl*}*thiophene*-2-*carboxamide*.—To a solution of **9** (11.55 g, 68.2 mmol) in dry dichloromethane (100 cm^3) containing dry pyridine (6.62 cm^3, 81.8 mmol) and 4,-*N*,*N*-dimethylaminopyridine (DMAP) (2.50 g, 20.5 mmol) at 0 °C was added a solution of thenoyl chloride (10.0 g, 68.2 mmol) in dry dichloromethane (30 cm^3). The mixture was stirred at 0 °C for 3 h, and then at room temp. overnight. The reaction was poured into a cold dilute hydrochloric acid. The organic layer was separated, and washed with brine, dried (Na_2SO_4) and concentrated. The residue was crystallized from ethyl acetate to give the *title compound* (14.46 g, 76%); m.p. 164.5 °C (Found: C, 64.5; H, 7.6; N, 4.8. $C_{15}H_{21}NO_2S$ requires C, 64.5; H, 7.6; N, 5.0%) $[\alpha]_D^{24}$ +52.9° (*c* 2.24, $CHCl_3$); ν(KBr)/cm^{-1} 3310, 2940, 1615, 1535, 1495 and 725; δ_H(100 MHz) 0.66 (s, 3 H), 0.92, 1.08 (s, 8 H), 1.30–1.76 (m, 2 H), 1.93 (m, 1 H), 3.80 (m, 2 H), 4.12 (br s, 1 H), 6.96 (m, 1 H), 7.16 (br s, 1 H) and 7.36 (m, 2 H).

(1R,2S,3R,4S)-1,7,7-*Trimethyl*-3-*thenylaminobicyclo*[2.2.1]-*heptan*-2-*ol* (exo-*TATH*) **16**.—The reduction of the above amide with LAH (3 equiv.) in refluxing THF gave the *title compound* **16** as white crystals; m.p. 95–96 °C (Found: C, 67.8; H, 8.9; N, 5.3. $C_{15}H_{23}NOS$ requires C, 67.9; H, 8.7; N, 5.3%); $[\alpha]_D^{24}$ +34.4° (*c* 2.16, $CHCl_3$); ν(KBr)/cm^{-1} 3260, 2920, 1100, 860 and 720; δ_H(400 MHz) 0.77 (s, 3 H), 0.95 (s, 3 H), 1.01 (m, 2 H), 1.05 (s, 3 H), 1.42 (m, 2 H), 1.56 (d, *J* 4.6, 1 H), 1.69 (m, 1 H), 2.82 (d, *J* 7.3, 1 H), 3.42 (d, *J* 7.3, 1 H), 4.01 (d, *J* 14, 1 H), 4.34 (br s, 1 H), 6.93 (m, 2 H) and 7.20 (m, 1 H).

N-{(1R,2S,3R,4S)-2-*Hydroxy*-1,7,7-*trimethylbicyclo*[2.2.1]-*heptan*-3-*yl*}*furan*-2-*carboxamide*.—To a solution of **9** (5.00 g, 29.6 mmol) in dry dichloromethane (80 cm^3) containing dry pyridine (2.87 cm^3, 35.5 mmol) and DMAP (0.72 g, 5.92 mmol) at 0 °C was added a solution of 2-furoyl chloride (3.86 g, 29.6 mmol) in dry dichloromethane (30 cm^3). The mixture was stirred at 0 °C for 3 h, and then at room temp. overnight. The reaction was poured into a cold dilute hydrochloric acid. The organic layer was separated, and washed with brine, dried (Na_2SO_4) and concentrated. The residue was crystallized from ethyl acetate to give the *title compound* (6.67 g, 86%); m.p. 181.0–181.5 °C (Found: C, 68.5; H, 8.0; N, 5.3. $C_{15}H_{21}NO_3$ requires C, 68.4; H, 8.0; N, 5.3%); $[\alpha]_D^{23}$ +68.4° (*c* 2.24, $CHCl_3$); δ_H(400 MHz) 0.84 (s, 3 H), 0.96, 1.14 (s, 8 H), 1.50–1.84 (m, 2 H), 1.92 (m, 1 H), 2.80 (br s, 1 H), 3.90 (m, 2 H), 6.46 (m, 1 H), 7.02 (m, 2 H) and 7.36 (m, 1 H).

(1R,2S,3R,4S)-3-*Furfurylamino*-1,7,7-*trimethylbicyclo*[2.2.1]-*heptan*-2-*ol* (exo-*FATH*) **17**.—The reduction of the above amide with LAH (3 equiv.) in refluxing THF gave the *title compound* **17** (79%) as a solid; m.p. 100–101 °C (Found: C, 72.3; H, 9.3; N, 5.7. $C_{15}H_{23}NO_2$ requires C, 72.3; H, 9.3; N, 5.6%); $[\alpha]_D^{23}$ +42.9° (*c* 1.95, $CHCl_3$); ν(KBr)/cm^{-1} 3325, 3100, 2920, 1455, 1115 and 760; δ_H(400 MHz) 0.76 (s, 3 H), 0.94 (s, 3 H), 1.00 (m, 2 H), 1.04 (s, 3 H), 1.10–1.88 (m, 4 H), 2.75 (d, *J* 10, 1 H), 3.40 (d, *J* 10, 1 H), 3.74 (s, 2 H), 4.32 (br s, 1 H), 6.28 (m, 2 H) and 7.36 (m, 1 H).

(1R,2S,3R,4S)-3-[(1-*Methylpyrrol*-2-*yl*)*methylamino*]-1,7,7-*trimethylbicyclo*[2.2.1]*heptan*-2-*ol* (exo-*MPATH*) **18**.—A mixture of 1-methylpyrrole-2-carbaldehyde (2.50 g, 22.9 mmol), **9** (3.87 g, 22.9 mmol) and Na_2SO_4 (9.76 g, 68.7 mmol) in dry benzene was stirred for 5 d at room temp. under argon. The mixture was filtered and the solvent was evaporated under reduced pressure to give the imine as a white solid. Into a suspension of LAH (1.74 g, 45.8 mmol) in dry ether (85 cm^3) was added a solution of the imine in dry ether (45 cm^3). After the addition was complete, the mixture was heated under reflux for 10 h. The reaction mixture was quenched by sequential addition of water (1.7 cm^3), 15% aqueous sodium hydroxide, (1.7 cm^3) and water (5.1 cm^3). The solid was filtered off, and the filtrate was dried (Na_2SO_4) and exaporated. The resulting solid was chromatographed (silica, hexane–ethyl acetate, 1:1) to give the product (2.91 g, 48%). Crystallization of this from hexane gave the *title compound* **18** (2.91 g, 48%); m.p. 103–104 °C (Found: C, 73.1; H, 9.8; N, 10.7. $C_{16}H_{26}N_2O$ requires C, 73.2; H, 10.0; N, 10.7%); $[\alpha]_D^{21}$ +36.4° (*c* 2.12, $CHCl_3$); ν(KBr)/cm^{-1} 3310, 3100, 2950, 1500, 1110 and 730; δ_H (400 MHz) 0.75 (s, 3 H), 0.94 (s, 3 H), 1.02 (m, 6 H), 1.43 (m, 1 H), 1.60 (d, *J* 4.6, 1 H), 1.72 (m, 1 H), 2.81 (d, *J* 7.3, 1 H), 3.43 (d, *J* 7.3, 1 H), 3.61 (s, 3 H), 3.65 (d, *J* 14, 1 H), 3.80 (d, *J* 14, 1 H), 6.04 (m, 2 H) and 6.60 (m, 1 H).

N-{(1R,2R,3S,4S)-2-*Hydroxy*-1,7,7-*trimethylbicyclo*[2.2.1]-*heptan*-3-*yl*}*furan*-2-*carboxamide*.—By a similar procedure to that described for the *exo* amide, the *title compound* was prepared in 78% yield from **11** and 2-furoyl chloride; m.p. 139.2–140.0 °C (Found: C, 68.6; H, 8.0; N, 5.3. $C_{15}H_{21}NO_3$ requires C, 68.4; H, 8.0; N, 5.3%); $[\alpha]_D^{23}$ +63.1° (*c* 1.98, $CHCl_3$); ν(KBr)/cm^{-1} 3350, 2940, 1625, 1520, 1020 and 775; δ_H(100 MHz) 0.90, 0.94, 0.98 (s, 9 H), 1.08–1.64 (m, 3 H), 1.80–2.18 (m, 2 H), 3.16 (br s, 1 H), 4.16 (dd, *J* 12, 6, 1 H), 4.42 (m, 1 H), 6.60 (m, 1 H), 7.22 (m, 2 H) and 7.58 (m, 1 H).

(1R,2R,3S,4S)-3-*Furfurylamino*-1,7,7-*trimethylbicyclo*[2.2.1]-*heptan*-2-*ol* (endo-*FATH*) **19**.—The reduction of the above amide with LAH (3 equiv.) in refluxing THF gave the *title compound* **19** (82%) as white crystals; m.p. 71 °C (Found: C, 72.2; H, 9.4; N, 5.7. $C_{15}H_{23}NO_2$ requires C, 72.3; H, 9.3; N, 5.6%); $[\alpha]_D^{23}$ +11.3° (*c* 2.19, $CHCl_3$); ν(KBr)/cm^{-1} 3330, 2925, 1160, 765 and 755; δ_H(400 MHz) 0.86, 0.88 (s, 9 H), 1.12 (m, 1 H), 1.40 (m, 2 H), 1.43–1.69 (br s, 1 H), 1.70 (t, *J* 4.1, 1 H), 1.76 (m, 1 H), 3.15 (dd, *J* 8.9, 4.3, 1 H), 3.64 (d, *J* 8.9, 1 H), 3.66–3.76 (m, 3 H), 6.17 (m, 1 H), 6.30 (m, 1 H) and 7.35 (m, 1 H).

N-{(1R,2R,3S,4S)-2-*Hydroxy*-1,7,7-*trimethylbicyclo*[2.2.1]-*heptan*-3-*yl*}-2-[(S)-1-(*benzyloxycarbonyl*]*prolinamide*.—By a similar procedure to that described for the *exo* amide, the *title compound* was prepared from (*S*)-*N*-benzyloxycarbonylproline and **11** as a solid (56%, 6.57 g); m.p. 130 °C (Found: C, 68.9; H, 8.1; N, 6.9. $C_{23}H_{32}N_2O_4$ requires C, 69.0; H, 8.1; N, 7.0%); $[\alpha]_D^{25}$ −43.5° (*c* 2.07, $CHCl_3$); δ_H(100 MHz) 0.80, 0.84, (s, 10 H), 1.24 (m, 2 H), 1.94 (m, 6 H), 2.88 (m, 2 H), 3.48 (m, 2 H), 3.92 (m, 2 H), 4.28 (m, 1 H), 5.16 (m, 2 H), 6.80 (m, 1 H) and 7.24 (m, 5 H).

(1R,2R,3S,4S)-3-[(S)-1-*Methylpyrrolidin*-2-*yl*]*methylamino*-1,7,7-*trimethylbicyclo*[2.2.1]*heptan*-2-*ol* **20**.—To a suspension of LAH (2.42 g, 63.6 mmol) in THF (100 cm^3) was added, at room temp., a solution of the above amide (8.50 g, 21.2 mmol) in THF (100 cm^3). The mixture was refluxed for 8 h, and quenched with sequential addition of water (2.4 cm^3), 15% aqueous sodium hydroxide (2.4 cm^3) and water (7.2 cm^3) at 0 °C. The mixture was filtered, concentrated under reduced pressure and extracted with ether. The ethereal solution was extracted with 10% aqueous HCl. The acid extracts were made alkaline by addition of 15% aqueous NaOH and again extracted with ether. The organic layer was washed with brine, dried ($NaSO_4$) and distilled to give the *title compound* (3.08 g, 54%) as a pale yellow

oil; b.p. 159–164 °C/0.1 mmHg; $[\alpha]_D^{22}$ +44.6° (*c* 1.68, $CHCl_3$); *v*(thin film)/cm^{-1} 3275, 2930, 1475, 1395 and 1105; δ_H(100 MHz) 0.88 (s, 9 H), 1.20–1.48 (m, 4 H), 1.76 (m, 6 H), 2.32 (s, 1 H), 2.52 (m, 3 H), 2.64–2.92 (m, 2 H), 3.08 (m, 3 H) and 3.60 (m, 2 H).

N-{(1R,2R,3S,4S)-2-*Hydroxy*-1,7,7-*trimethylbicyclo*[2.2.1]-*heptan*-3-*yl*}-*benzamide*.—By a similar procedure described for the *exo* amide, the *title compound* was prepared in 79% yield from **11** and benzoyl chloride; m.p. 135 °C (Found: C, 74.7; H, 8.6; N, 5.1. $C_{17}H_{23}NO_2$ requires C, 74.7; H, 8.5; N, 5.1%) $[\alpha]_D^{25}$ +65.4° (*c* 2.04, $CHCl_3$).

(1R,2R,3S,4S)-3-*Benzylamino*-1,7,7-*trimethylbicyclo*[2.2.1]-*heptan*-2-*ol* (endo-*BATH*) **21**.—The reduction of the above amide with LAH (3 equiv.) in refluxing THF gave the *title compound* (85%), which was crystallized from hexane; m.p. 65–66 °C (Found: C, 78.7; H, 9.7; N, 5.4. $C_{17}H_{25}NO$ requires C, 78.7; H, 9.7; N, 5.4%); $[\alpha]_D^{24}$ +27.9° (*c* 2.03, $CHCl_3$) *v*(KBr)/cm^{-1} 3265, 2905, 1450, 1070 and 740; δ_H(400 MHz) 0.85 (m, 10 H), 1.00–1.80 (m, 5 H), 2.60 (m, 2 H), 3.20 (m, 1 H), 3.68 (m, 2 H), 6.56 (m, 1 H) and 7.26 (m, 5 H).

N-{(1R,2R,3S,4S)-2-*Hydroxy*-1,7,7-*trimethylbicyclo*[2.2.1]-*heptan*-3-*yl*}*thiophene*-2-*carboxamide*.—By a similar procedure to that described for the *exo* amide, the *title compound* was prepared in 82% yield; m.p. 152.8–153.8 °C (Found: C, 64.4; H, 7.6; N, 5.0. $C_{15}H_{21}NO_2S$ requires C, 64.5; H, 7.6; N, 5.0%); $[\alpha]_D^{22}$ +68.3° (*c* 2.04, $CHCl_3$) *v*(KBr)/cm^{-1} 3300, 2940, 1620, 1530, 1395 and 730; δ_H(100 MHz) 0.92, 0.96 (s, 9 H), 1.08–1.60 (m, 3 H), 1.90 (m, 1 H), 2.16 (m, 1 H), 3.42 (br s, 1 H), 4.16 (dd, *J* 16, 8, 1 H), 4.36 (m, 1 H), 7.06 (br s, 1 H), 7.16 (br s, 1 H) and 7.62 (m, 2 H).

(1R,2R,3S,4S)-1,7,7-*Trimethyl*-3-*thenylaminobicyclo*[2.2.1]-*heptan*-2-*ol* (endo-*TATH*) **22**.—The reduction of the above amide with LAH (3 equiv.) in refluxing THF gave the crude product as a white solid (60%), which was chromatographed (silica, hexane–ethyl acetate, 2:1) to give the *title compound* **22**; m.p. 109–110 °C (Found: C, 68.0; H, 8.8; N, 5.4. $C_{15}H_{23}NOS$ requires C, 67.9; H, 8.7; N, 5.3%); $[\alpha]_D^{21}$ +14.4° (*c* 2.00, $CHCl_3$); *v*(KBr)/cm^{-1} 3320, 3150, 2925, 1115, 1070 and 725; δ_H(400 MHz) 0.86, 0.89 (s, 9 H), 1.13 (m, 1 H), 1.39 (m, 2 H), 1.45–1.74 (br s, 2 H), 1.75 (m, 1 H), 3.23 (dd, *J* 8.9, 4.3), 3.67 (d, *J* 8.9), 3.68–3.88 (br s, 1 H), 3.91 (s, 2 H), 6.93 (m, 2 H) and 7.19 (m, 1 H).

(1R,2R,3S,4S)-3-[(1-*Methylpyrrol*-2-*yl*)*methylamino*]-1,7,7-*trimethylbicyclo*[2.2.1]*heptan*-2-*ol* (endo-*MPATH*) **23**.—A mixture of 1-methylpyrrole-2-carbaldehyde (4.98 g, 45.6 mmol), *endo*-3-amino-*endo*-2-hydroxybornane **11** and Na_2SO_4 (19.4 g, 137 mmol) in dry benzene was stirred for 4 d at room temp. The mixture was filtered and evaporated under reduced pressure to give imine as a white solid. Into a suspension of LAH (3.46 g, 91.2 mmol) in dry ether (180 cm^3) was added a solution of the imine in dry ether (180 cm^3) at room temp. After the addition, the mixture was refluxed for 4 h. The reaction mixture was quenched, filtered, dried (Na_2SO_4) and evaporated. The resulting solid was recrystallized from hexane to give the *title compound* **23** as a white solid (9.65 g, 81%); m.p. 82.5–83.5 °C (Found: C, 73.1; H, 10.0; N, 10.7. $C_{16}H_{26}N_2O$ requires C, 73.2; H, 10.0; N, 10.7%); $[\alpha]_D^{26}$ +18.6° (*c* 1.95, $CHCl_3$); *v*(KBr)/cm^{-1} 3300, 3100, 2940, 1500, 1110 and 730; δ_H 0.86, (400 MHz) 0.90 (s, 9 H), 1.12 (dt, *J* 12.4, 2.8, 1 H), 1.31–1.47 (m, 3 H), 1.74 (m, 1 H), 1.80 (t, *J* 4.3, 1 H), 3.20 (dd, *J* 9.0, 4.3, 1 H), 3.64 (m, 7 H), 6.05 (m, 2 H) and 6.59 (m, 1 H).

(1S,2S,3R,4R)-3-[(1-*Methylpyrrol*-2-*yl*)*methylamino*]-1,7,7-*trimethylbicyclo*[2.2.1]*heptan*-2-*ol* (endo-*MPATH*) **29**.—The reduction of the imine, prepared from (1*S*,2*S*,3*R*,4*R*)-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol and 1-methylpyrrole-2-carbaldehyde, with LAH in refluxing THF gave the *title compound* **29** (86%) as a white solid, m.p. 82 °C (Found: C, 73.0; H, 10.1; N, 10.5. $C_{16}H_{26}N_2O$ requires C, 73.2; H, 10.0; N, 10.7%) $[\alpha]_D^{21}$ −18.3° (*c* 2.60, $CHCl_3$).

Procedures for Conjugate Addition of Chiral Organocuprate to (E)-*Cyclopentadec*-2-*enone* **2**.—Methyllithium (1.00 mol dm^{-3} ether solution; 2.2 equiv.) was added at 0 °C to a solution of chiral amine (11.0 mmol) and toluene (90 cm^3) in a septum-sealed 100 cm^3 two-necked round bottomed flask under argon atmosphere. After 30 min at this temperature, the resulting solution was cooled to −20 °C, and copper(I) iodide was added; the mixture was then warmed to −5 °C during 2.5 h. The resulting grey suspension was cooled to −78 °C and methyllithium (2.2 equiv.) was added. The mixture was stirred for 30 min at −78 °C and warmed to −5 °C during 2.0 h. After recooling to −78 °C, a solution of **2** (1.11 g, 5.0 mmol) in toluene (10 cm^3) was added along the wall of the reaction flask. The mixture was stirred for 15–16 h at −78 °C, and quenched with saturated aqueous ammonium chloride–30% aqueous ammonium hydroxide (12 cm^3). The mixture was extracted with ether and the organic layers were washed with brine and dried ($MgSO_4$). Column chromatography (silica, hexane–ethyl acetate, 45 : 1) gave muscone as a colourless oil. The enantiomeric excess of muscone was determined after bulb-to-bulb distillation by comparison of its optical rotation with a reported value (lit.,[6] $[\alpha]_D$ −11.7° (*c* 0.80, methanol). Further elution [hexane–ethyl acetate (2:1–1:1)] gave the chiral ligand. The measurement of the specific rotation showed that no racemization took place during these manipulations.

Preparation of Muscone of 100% *Optical Purity*.—The following experimental procedure was used for the preparation of (*R*)-muscone of essentially 100% optical purity in gram amounts. To a solution of chiral methylcuprate prepared from *endo*-MPATH **23** (2.89 g, 11.0 mmol), methyllithium (11.0 mmol), copper(I) iodide (1.05 g, 5.50 mmol) and methyllithium (11.0 mmol) in dry toluene (90 cm^3) at −78 °C by the procedure described above was added dry THF (4.1 cm^3, 50 mmol) and the solution was stirred for 15 min at −78 °C. A solution of **2** (1.11 g, 5.0 mmol) in dry toluene was added dropwise at −78 °C and the mixture was stirred overnight at −78 °C. After quenching at −78 °C by the addition of 1:1 mixture of saturated aqueous ammonium chloride–30% aqueous ammonium hydroxide (12 cm^3). The mixture was extracted with ether, and the combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Chromatography (silica, hexane–ethyl acetate, 45:1) gave (*R*)-(−)-muscone (1.11 g, 93%) as a colourless oil. Distillation of the oil gave 1.05 g (88%) of muscone; $[\alpha]_D^{18}$ −12.5° (*c* 5.00, methanol).

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