Synthesis and characterisation of a suite of four chiral pyridyl alcohols derived from (−)-menthol

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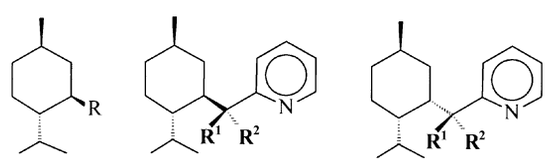
Reaction of menthylmagnesium chloride with pyridine-2-carbaldehyde gives a mixture of four isomeric chiral menthyl- and neomenthyl-substituted pyridylcarbinols which were fully characterised by a combination of spectroscopic and X-ray crystallographic methods. All of these alcohols catalyse the addition of diethylzinc to benzaldehyde, but with disappointing enantioselectivities.

Recently, much effort has been expended on the synthesis of chiral pyridylcarbinol derivatives with a view to their application as enantioselective catalysts or auxiliaries. A diversity of reactions are amenable to catalysis which involves the intervention of pyridylcarbinol ligands. These processes include, for example, the epoxidation of allylic alcohols,[1] the conjugate addition of dialkylzinc reagents to α,β-unsaturated ketones[2] and, especially, the nucleophilic addition of dialkylzinc reagents to aldehydes.[3] The latter process is of particular interest in that a positive, non-linear relationship between the optical purity of the catalyst and that of the addition product is often observed.[4]

In this paper, we describe the synthesis from (−)-menthol **1** of the suite of four chiral pyridyl alcohols **2a**–**2d**. We chose the monoterpenoid **1** to provide the major element of asymmetry in the target molecules on the basis of its ready availability in both enantiomeric forms, and also in the expectation that incorporation of its equatorially trisubstituted cyclohexane ring into the alcohols **2a** and **2b** would restrict the conformational freedom of these compounds in a beneficial way when they were applied as chiral auxiliaries or as catalysts.[5]



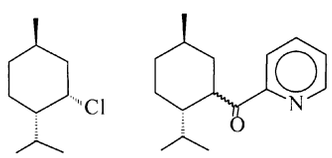
1 R = OH
3 R = Cl

2a R^1 = H; R^2 = OH
2b R^1 = OH; R^2 = H

2c R^1 = OH; R^2 = H
2d R^1 = H; R^2 = OH

(−)-Menthyl chloride **3** was obtained according to Huckel and Pietrzok's[6] method by reacting (−)-menthol **1** with phosphorus pentachloride in the presence of a small amount of ferric chloride. The product contained variable but relatively small (generally <10%) amounts of its axial neomenthyl isomer **4**. The derived Grignard reagent, prepared in tetrahydrofuran solution, reacted with pyridine-2-carbaldehyde to yield a mixture containing all four of the possible product alcohols **2a**–**2d**.

The ratio of the equatorial "menthyl" alcohols **2a** and **2b** to the axial "neomenthyl" alcohols **2c** and **2d** that was obtained from this reaction was typically 2 : 1 even when a 32 : 1 mixture of menthyl chloride **3** and neomenthyl chloride **4** was used to form the Grignard reagent. We discuss this observation in more detail below.



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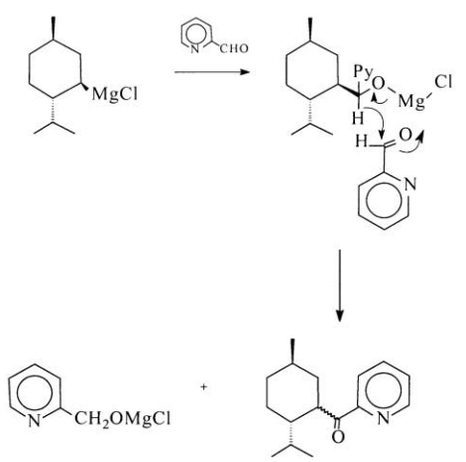
5a α-bond
5b β-bond

Unexpectedly, significant amounts of the equatorial ketone **5a** and of the axial ketone **5b** were also obtained as products of the reaction between menthylmagnesium chloride and pyridine-2-carbaldehyde. The formation of these ketones can reasonably be accounted for by invoking the Cannizzaro-like mechanism outlined in Scheme 1 where an initially formed chloro-



Scheme 1

magnesium alkoxide transfers a hydride ion to the strongly electrophilic pyridine-2-carbaldehyde.

The more basic alcohols **2a**–**2d** could be easily separated from the ketones **5a** and **5b** *via* extraction into aqueous hydrochloric acid followed by later release from their salts. The

† To receive any correspondence regarding the X-ray crystallographic structure of **6**

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combined yield of the alcohols **2a**–**2d** was 65%. Overlapping resonances made it impossible to obtain reliable ratios for these alcohols using ^{1}H NMR spectroscopy, but "integration" of the ^{13}C signals for their α-carbinyl carbon atoms suggested the relative proportions of **2a** : **2b** : **2c** : **2d** to be 1.8 : 2.3 : 1 : 1. By careful chromatography over silica gel it was possible to obtain pure samples of each of these four alcohols.

The menthyl alcohol (−)-(1*R*)-**2a** was obtained as an oil which was laevorotatory in chloroform solution but dextrorotatory in ethanol, suggesting the possibility of intramolecular hydrogen bonding in the former solvent. Its methyl ether **6** was crystalline, enabling both the stereochemistry at C-1 of the menthyl ring and the relative configuration of the secondary carbinol centre to be obtained by X-ray crystallographic analysis (Fig. 1). The absolute configurations of **6** and of

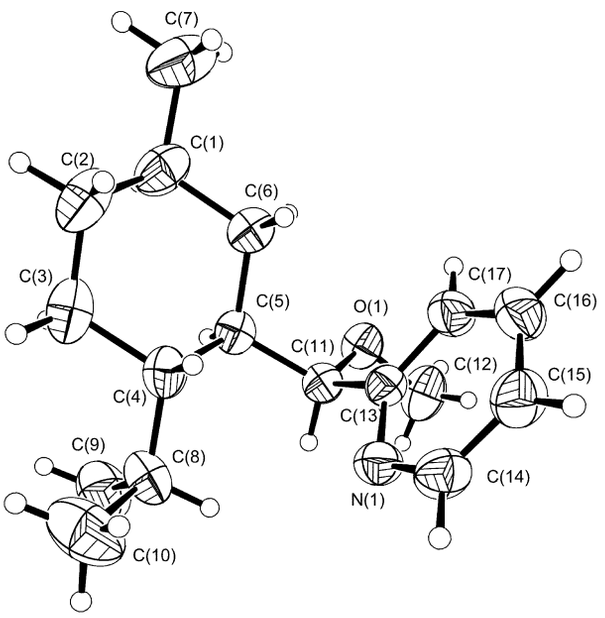
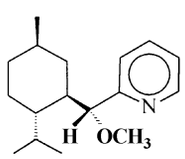


Fig. 1

compound **2c** discussed below were not determined by X-ray analysis but follow from the known absolute configuration of the (−)-(1*R*,3*R*,4*S*)-menthol **1** used for their synthesis.



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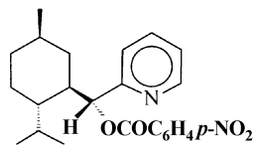
The alcohol **2a** could be obtained more conveniently by oxidation of the entire mixture of alcohols **2a**–**2d** which was obtained from the Grignard reaction to give a mixture (76%) of (NMR) both the equatorial ketone **5a** and the axial ketone **5b**. Base-catalysed equilibration of this mixture using potassium *tert*-butoxide in DMSO led to almost complete (>20 : 1) formation of the thermodynamically more stable equatorial ketone **5a**. Reduction of **5a** in tetrahydrofuran solution using sodium borohydride or lithium aluminium hydride proceeded with relatively poor diastereoselectivity, but the more hindered reagent lithium tri-*tert*-butoxyaluminium hydride gave a 14 : 1 mixture of **2a** and its oily anti-Cram (−)-(1*S*)-epimer **2b** in 93% yield. These alcohols were readily separable by column chromatography.

The structure of **2b** was confirmed by its oxidation to the menthyl ketone (−)-**5a**, easily identified from its NMR spectrum which exhibited a typical double triplet at δ 4.14 ppm due to the axial proton on C-1 of the menthyl ring.

The anti-Cram alcohol **2b** could also be accessed *via* Mitsunobu inversion of the alcohol **2a**. Thus, employing conditions recommended[7] for the inversion of sterically hindered alcohols, the (1*R*)-alcohol **2a** was efficiently converted into the (1*S*)-4-nitrobenzoate **7** which could then be hydrolysed to provide **2b** in 69% overall yield from **2a**.



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X-Ray crystallography was used to reveal the (1*S*)-configuration of the crystalline neomenthyl alcohol (−)-**2c**, mp 68 °C, and clearly indicated that its hydroxy group did not engage in intramolecular hydrogen-bonding with the adjacent pyridyl nitrogen atom (Fig. 2).

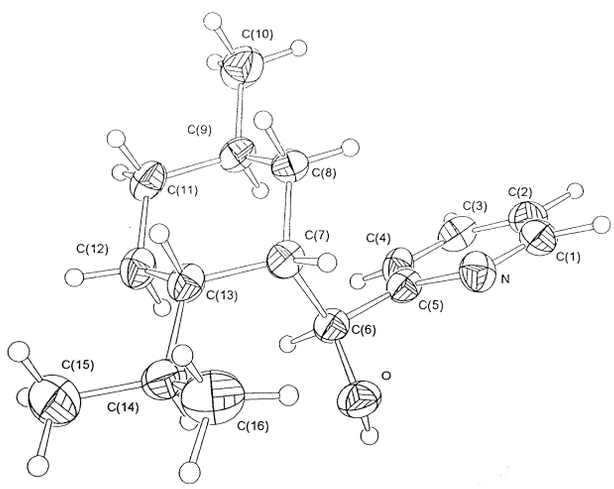


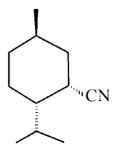
Fig. 2

The epimeric anti-Cram alcohol (+)-**2d** was obtained as crystals, mp 33 °C, which were not suitable for X-ray analysis. However, this compound could be oxidised with chromic acid under two-phase conditions to give the neomenthyl ketone (+)-**5b** which showed a characteristic narrow multiplet for its C-1 equatorial proton at δ 4.59 ppm with $W_{1/2}$ = 11.4 Hz.

Appropriate 2D ^{1}H NMR experiments revealed the equatorial nature of H-1 on the cyclohexyl ring for both of the neomenthyl systems **2c** and **2d**, confirming that the bulky pyridylcarbinol substituent remains axial in each of these compounds.

The alcohols **2c** and **2d** have been claimed by Adolfsson *et al.*,[8] who obtained them by small-scale reaction of 2-lithiopyridine with neomenthyl carbonitrile **8** (synthesised from (−)-menthol **1**), followed by reduction of the derived ketone **5b** with sodium borohydride. However, these authors do not report either of the alcohols **2c** or **2d** as being crystalline. Furthermore, whilst the ^{1}H and ^{13}C NMR data which we have recorded for **2c** and **2d** are generally in good agreement with that provided by Adolfsson *et al.*, we have obtained a specific rotation for **2c** which conflicts in both sign and magnitude with that reported by Adolfsson[8] (see Experimental section). The configurations for the carbinol centres of **2c** and **2d** that were suggested by Adolfsson *et al.* relied on experiments with Mosher esters, and our crystallographic results are in agreement with these assignments.

The relative proportions of the equatorial alcohols **2a** and **2b** and of the axial alcohols **2c** and **2d** which are formed by reaction of menthylmagnesium chloride with pyridine-2-



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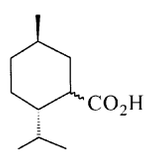
carbaldehyde are of interest in that a far greater proportion of the product mixture than would be expected consists of the neomenthyl derivatives **2c** and **2d**. Indeed, since neomenthyl chloride **4** readily undergoes base-catalysed *trans*-diaxial elimination of hydrogen chloride to yield menthenes, the total absence of the neomenthyl compounds **2c** and **2d** from the reaction mixture would not have been surprising.

It has been reported[9] that menthylmagnesium chloride reacts with carbon dioxide to give *exclusively* the equatorial carboxylic acid **9**. We have confirmed this result, obtaining unrecrystallised acid **9** in 88% yield and in >100 : 1 ratio with the epimeric neomenthyl acid **10**. The possibility that dynamic interconversion of menthyl- and neomenthylmagnesium chlorides takes place in solution cannot be ruled out as an explanation for the ratio of axial to equatorial products **2a**–**2d** which we have observed for the reaction with pyridine-2-carbaldehyde, but the result of the carbonation experiment suggests that this does not occur.[10] It seems more likely that the menthyl ketone **5a**, formed (*vide supra*) as a secondary product when the Grignard reagent derived from menthyl chloride **3** is reacted with pyridine-2-carbaldehyde, subsequently equilibrates with its neomenthyl isomer **5b**, and that this latter ketone then enters into an Oppenauer-like redox equilibrium with the menthyl-configured chloromagnesium alkoxides which are the primary products of the reaction. This can then lead to the mixture of equatorial **2a** + **2b** and axial **2c** + **2d** products which is obtained.



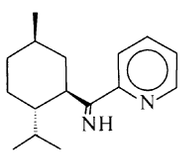
9 β-bond
10 α-bond

We briefly investigated a number of alternative routes to the alcohols **2a**–**2d** and to the ketones **5a**–**5b**. Thus, one-pot Barbier reaction[11] between (−)-menthyl chloride **3** and pyridine-2-carbaldehyde in the presence of lithium metal gave modest amounts of the alcohols **2a**–**2d**. Reaction of menthylmagnesium chloride with pyridine-2-carbonitrile was more successful, yielding a mixture containing the imine **11** which was hydrolysed using concentrated aqueous hydrochloric acid to give exclusively the menthyl ketone **5a**. By contrast with the facile base-catalysed isomerisation described above, prolonged treatment with strong acid does not epimerise the axial neomenthyl ketone **5b** to its equatorial isomer **5a**, and we therefore conclude that the only imine formed as a product of the Grignard reaction is the equatorial isomer **11**.

It was clear, however, that only a part of the product mixture that was obtained *via* reaction of menthylmagnesium chloride with pyridine-2-carbonitrile had been successfully hydrolysed by aqueous hydrochloric acid. Careful chromatography of the remaining material, or of a sample of the crude product mixture obtained from the Grignard reaction, led to the isolation of a fraction that was identified as being the novel amidine **12**. This exhibited spectroscopic data that clearly established its gross structure and confirmed that it was not the isomeric compound **13**. The amidine **12** was resistant to acid-catalysed hydrolysis, being recovered unchanged after boiling with concentrated hydrochloric acid. We rationalise the formation of **12** as outlined in Scheme 2, but are unable to confidently assign a

Table 1 Enantioselective addition of diethylizinc to benzaldehyde catalysed by the alcohols **2a**–**2d**

Catalyst	Yield of **14** (%)	Configuration	$[\alpha]_D$	Ee (%)
2a	96	(*R*)	+5.5	12.12
2b	80	(*R*)	+4.0	8.8
2c	94	(*R*)	+10.2	22.5
2d	84	(*R*)	+4.0	8.8



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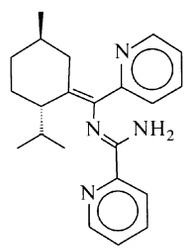

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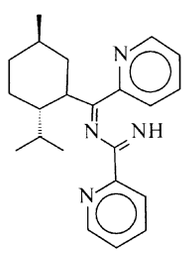

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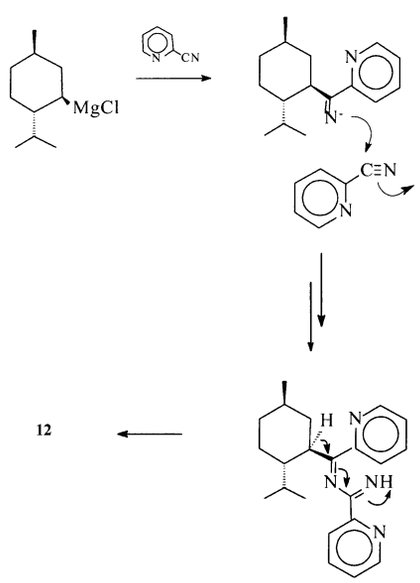
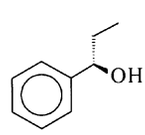


Scheme 2

configuration to the double bond which is exocyclic to the menthyl ring.

Each of the pyridyl alcohols **2a**–**2d** proved to be an active catalyst for the enantioselective addition of diethylzinc to benzaldehyde to give optically active 2-phenylpropanol (Table 1). The results obtained were somewhat disappointing in terms of the ee values of the phenylpropanol **14** produced, but it is noteworthy that the (*R*)-alcohol was always favoured, regardless of the configuration at C-1 of the catalyst that was employed.



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Further applications of the alcohols **2a**–**2d** and of their methyl ethers are under investigation.

Experimental

^{1}H NMR spectra were recorded for solutions in $CDCl_3$ using Bruker MSL-300 or Bruker AVANCE DPX-400 spectrometers. *J* values are given in Hz. Assignments were verified by appropriate H–H COSY, C–H COSY and ^{13}C-DEPT experiments. IR spectra were recorded for Nujol mulls (N) or for liquid films (L) between sodium chloride plates using Perkin Elmer 883 or Paragon-FT spectrometers. High-resolution mass spectra were obtained using a VG Alto Spec instrument. Melting points (uncorrected) were measured in unsealed capillary tubes using a Stuart Scientific SMP2 digital apparatus. Optical rotations were measured for solutions in a 1 dm cell using a Perkin-Elmer 141 polarimeter; specific optical rotations are given in units of 10^{-1} deg cm^2 g^{-1}. Thin layer chromatography was carried out using Merck Kieselgel 60 F_{254} 0.2 mm silica gel plates. Column chromatography was carried out using Merck Keiselgel 60 (70–230 mesh) silica gel. All solvents were distilled before use. The (−)-menthol **2** used in this work had $[\alpha]_D$ − 51.3 (*c* 2.38 in EtOH).

Crystal data for 2c

$C_{16}H_{25}NO$, M = 247.37. Monoclinic, a = 10.460(2), b = 5.5610(4), c = 13.412(2) Å, $\alpha = 90°$, $\beta = 110.951(7)°$, $\gamma = 90°$, V = 728.5(2) Å^3, space group $P2_1$, Z = 2, D (calculated) = 1.128 g cm^3, crystal dimensions 0.5 × 0.5 × 0.15 mm.

Data collection and processing. Enraf-Nonius CAD-4 diffractometer, temperature 293(2) K, wavelength 0.71703 Å, absorption coefficient 0.069 mm^{-1}, theta range for data collection 1.64 to 25.21°, 1476 reflections collected, index ranges $-12 \le h \le 11$; $0 \le k \le 6$; $0 \le l \le 14$, 1413 independent reflections [R(int) = 0.0392].

Structure analysis and refinement. The structure was solved by direct methods, SHELXS-86,[12] and refined to a final R value of 0.0540 for $I > 2\sigma(I)$ by full matrix least squares analysis on $|F|^2$ (236 parameters) using SHELXL-93.[13] All the non-hydrogen atoms were refined anisotropically. The hydrogens, with the exception of the hydroxy hydrogen which was located from the difference map, were fixed geometrically and those in similar environments were given common temperature factors (CH 0.03651, CH_2 0.3295, CH_3 0.07375). The hydroxy hydrogen was isotropically refined with an independent temperature factor. All calculations were carried out using a VAX-1 mainframe computer. Figures were drawn using SCHAKAL.[14]

Crystal data for 6

$C_{17}H_{27}NO$, M = 261.40. Orthorhombic, a = 10.8957(1), b = 11.2627(9), c = 13.3035(1) Å, V = 1632.5(2) Å^3, space group $P2_12_12_1$, Z = 4, D (calculated) = 1.064 g cm^3, crystal dimensions 0.5 × 0.5 × 0.5 mm.

Data collection and processing. Enraf-Nonius CAD-4 diffractometer, temperature 293(2) K, wavelength 0.71069 Å, absorption coefficient 0.065 mm^{-1}, theta range for data collection 2.37 to 25.96°, 1904 reflections collected, index ranges $0 \le h \le 13$; $0 \le k \le 13$; $0 \le l \le 1838$ independent reflections [R(int) = 0.0168], 1523 reflections observed (>2σ).

Structure analysis and refinement. The structure was solved by direct methods, SHELXS-86,[12] and refined by full matrix least squares analysis using SHELXL-93.[13] Data were corrected for Lorentz and polarisation effects but not for absorption. Hydrogen atoms were included in calculated positions with thermal parameters 30% larger than the atom to which they were attached. The non-hydrogen atoms were refined anisotropically. Final R indices [$I > 2\sigma(I)$] were R_1 = 0.0350 and wR_2 = 0.1081. All calculations were performed on a Silicon Graphics R4000 computer. The ORTEX program was used to obtain the drawings.[15]

Additional data available for structures **2c** and **6** includes tables of atomic coordinates and of bond lengths and angles (CCDC reference numbers 186677 and 186678, respectively). See http://www.rsc.org/suppdata/p1/b2/b205872n/ for these files in electronic format.

(−)-(1*R*,3*R*,4*S*)-3-Chloro-4-isopropyl-1-methylcyclohexane 3[6]

A mixture of phosphorus pentachloride (40 g) and anhydrous ferric chloride (1.0 g) suspended in hexane (55 cm^3) was stirred vigorously at 0 °C. A solution of (−)-menthol **2** (30 g) in hexane (75 cm^3) was added dropwise during 40 min. After a further 90 min, ice was added to quench the reaction. The hexane extract was washed with water and with aqueous sodium hydrogen carbonate solution, dried over anhydrous magnesium sulfate, and evaporated to yield the derived chlorides **3** and **4** (30.3 g) which were distilled at reduced pressure, bp 94–96 °C/15 mmHg, $[\alpha]_D$ − 44 (*c* 14.12 in MeOH). ^{1}H NMR analysis by integration of the signals for the axial and equatorial protons on C-3 indicated a menthyl : neomenthyl ratio of 93 : 7. δ_H (400 MHz) 0.70 (3H, d, *J* 6.8), 0.86 (6H, d, *J* 6.3), 0.9 (2H, m), 1.4 (2H, m), 1.65 (2H, m), 1.80 (1H, m), 2.19 (1H, m), 2.35 (1H, m) and 3.77 (0.93H, apparent dt, *J* 11.0, 11.0 and 4.2) and 4.44 (0.07 H, m) ppm; δ_C 15.1 (CH_3), 20.95 (CH_3), 21.88 (CH_3), 24.23 (CH_2), 27.09 (CH), 33.34 (CH), 34.21 (CH_2), 46.71 (CH_2), 50.40 (CH) and 63.81 (CH) ppm.

Occasionally, menthyl : neomenthyl ratios up to 87 : 13 were observed, but this did not affect the stereochemical outcome of any later reactions.

Menthylmagnesium chloride

Magnesium turnings (5.56 g) were covered by dry THF and stirred vigorously under an atmosphere of nitrogen. A small crystal of iodine and/or one drop of 1,2-dibromoethane were added, followed by freshly-distilled menthyl chloride **3** (12 g) which had previously been dried over anhydrous sodium carbonate to remove traces of hydrogen chloride. The mixture was heated to induce reaction, and further menthyl chloride (28 g) in THF (200 cm^3) was added at such a rate that the solution continued to reflux. Further THF was added when the reaction was complete in order to adjust the Grignard reagent concentration to *ca*. 0.5 M. Solutions of reagent were assayed by titration in the usual way.

Reaction of menthylmagnesium chloride with pyridine-2-carbaldehyde: formation of the ketones 5a and 5b, and of the alcohols 2a–2d

Freshly distilled pyridine-2-carbaldehyde (15.33 g) was added slowly to an ice-cold solution of menthylmagnesium chloride in tetrahydrofuran (0.53 M; 270 cm^3). The mixture was allowed to reach room temperature and then refluxed during 12 h, after which time the reaction mixture was cooled and quenched with water. Extraction with ether yielded a crude oily product (36 g). This was dissolved in ether and shaken with 1 M HCl, and the organic layer was washed with water, dried over magnesium sulfate, and evaporated to give a mixture (9 g) containing hydrocarbons (NMR suggested the presence of bimenthyls) together with a 3 : 1 mixture of the ketones **5a** and **5b**. The acidic aqueous layer was then basified using sodium carbonate and extracted with ether. The ethereal extract was dried over anhydrous potassium carbonate and evaporated to yield a mixture (23 g) of the isomeric alcohols **2a**–**2d**. The latter were separated by chromatography on silica gel using an ethyl acetate : hexane gradient as eluant. The alcohols were eluted in the order **2d**, **2b**, **2a** and **2c**.

(−)-(*R*)-[(1′*R*,2′*S*,5′*R*)-2′-Isopropyl-5′-methylcyclohexyl]-(2″-pyridyl)methanol 2a. Obtained as an *oil* which had $[\alpha]_D$ −12.5 (*c*. 3.10 in $CHCl_3$) or $[\alpha]_D$ +14.6 (*c* 1.30 in EtOH); ν_{max} (L) 3406, 3063, 3012, 2953, 2917, 2869, 1592, 1570, 1471, 1454, 1434, 1409, 1385, 1367, 1347, 1308, 1263, 1237, 1211, 1180, 1149, 1115, 1097, 1040, 1014, 993, 982, 967, 913, 876, 849, 812, 806, 777, 762, 750, 734, 678, 668, 646 and 621 cm^{-1}; δ_H 0.13 (1H, apparent q, *J* 12.3), 0.55 (1H, m), 0.66 (3H, d, *J* 6.8), 0.69 (3H, d, *J* 6.7), 0.84 (3H, d, *J* 6.8), 0.8–1.1 (2H, overlapping ms), 1.21 (1H, br m), 1.54 (2H, m), 1.79 (2H, m), 2.16 (1H, m, -C*H*Me_2), 4.85 (1H, br s, exch. D_2O, -O*H*), 4.90 (1H, s, -C*H*OH), 7.04–7.10 (2H, overlapping ms, *H*-3′ and *H*-5′), 7.54 (1H, dt, *J* 7.9 and 1.7, *H*-4′) and 8.41 (1H, dd, *J* 4.8 and 0.9, *H*-6′) ppm; δ_C 15.22 (CH_3), 21.39 (CH_3), 22.59 (CH_3), 24.21 (CH_2), 26.73 (CH), 26.84 (CH), 32.59 (CH), 34.88 (CH_2), 35.87 (CH_2), 43.37 (CH), 46.25 (CH), 72.02 (-*C*HOH), 120.96 (CH), 121.98 (CH), 135.97 (CH), 147.67 (CH) and 160.08 (quat) ppm. HRMS (EI) *m*/*z* 247.1944. *Calculated* for $C_{16}H_{25}NO$ 247.1936.

(−)-(*S*)-[(1′*R*,2′*S*,5′*R*)-2′-Isopropyl-5′-methylcyclohexyl]-(2″-pyridyl)methanol 2b. Obtained as an *oil* which had $[\alpha]_D$ −25 (*c* 1.16 in $CHCl_3$); ν_{max} (L) 3425, 2955, 2919, 2869, 1594, 1570, 1467, 1436, 1406, 1386, 1368, 1345, 1308, 1261, 1179, 1149, 1112, 1095, 1065, 1036, 900, 872, 841, 804, 779, 762, 748 and 679 cm^{-1}; δ_H 0.7–1.2 (5H, overlapping ms), 0.73 (3H, d, *J* 6.4), 0.91 (3H, d, *J* 6.8), 1.00 (3H, d, *J* 6.8),1.5–1.8 (4H, overlapping ms), 2.37 (1H, m, -C*H*Me_2), 4.56 (1H, br s, exch. D_2O, -O*H*), 5.07 (1H, s, -C*H*OH), 7.16–7.21 (2H, overlapping ms, *H*-3′ and *H*-5′), 7.68 (1H, dt, *J* 7.9 and 1.7, *H*-4′) and 8.53 (1H, dd, *J* 4.6 and 1.5, *H*-6′) ppm; δ_C 15.58 (CH_3), 21.59 (CH_3), 22.72 (CH_3), 24.32 (CH_2), 26.37 (CH), 32.55 (CH), 32.79 (CH_2), 35.08 (CH_2), 43.01 (CH), 45.87 (CH), 70.47 (-*C*HOH), 120.0 (CH), 121.77 (CH), 136.52 (CH), 147.6 (CH) and 161.7 (quat) ppm. HRMS (EI) *m*/*z* 247.1922. *Calculated* for $C_{16}H_{25}NO$ 247.1936.

(−)-(*S*)-[1′*S*,2′*S*,5′*R*)-2′-Isopropyl-5′-methylcyclohexyl]-(2″-pyridyl)methanol 2c. Obtained as *plates*, mp 68 °C (pentane) which had $[\alpha]_D$ −42 (*c* 1.08 in $CHCl_3$) or $[\alpha]_D$ −20 (*c* 0.24 in EtOH) {*lit.*[8] an oil, $[\alpha]_D$ + 5.3 (*c* 0.79 in EtOH)}; ν_{max} (N) 3277, 3055, 3021, 2928, 2865, 1594, 1573, 1456, 1436, 1378, 1366, 1343, 1284, 1258, 1242, 1216, 1170, 1150, 1092, 1044, 1028, 1013, 1001, 990, 960, 935, 916, 892, 866, 806, 786, 751, 723, 678 and 625 cm^{-1}; δ_H 0.64 (3H, d, *J* 7.9), 0.75–1.15 (4H, overlapping ms), 0.90 (3H, d, *J* 6.4), 1.02 (3H, d, *J* 6.4), 1.48 (2H, m, including -C*H*Me), 1.79 (2H, m), 2.07 (1H, m, -C*H*Me_2), 2.35 (1H, m, *H*-1), 3.40 (1H, br s, exch. D_2O, -O*H*), 4.94 (1H, d, *J* 8.8, -C*H*OH), 7.15 (1H, m, *H*-5′), 7.24 (1H, d, *J* 8.1, *H*-3′), 7.61 (1H, dt, *J* 7.7 and 1.8, *H*-4′) and 8.50 (1H, dd, *J* 4.2 and 0.9, *H*-6′) ppm; δ_C 22.22 (CH_3), 22.48 (CH_3), 22.68 (CH_3), 24.97 (CH_2), 27.05 (CH), 29.98 (CH), 36.01 (CH_2), 39.09 (CH_2), 42.34 (CH), 49.90 (CH), 74.63 (-*C*HOH), 121.68 (CH), 122.25 (CH), 136.13 (CH), 148.85 (CH) and 163.38 (quat) ppm [*Calculated* for $C_{16}H_{25}NO$: C 77.73, H 10.12, N 5.67; *found* C 77.69, H 10.40, H 5.63%].

(+)-(*R*)-[1′*S*,2′*S*,5′*R*)-2′-Isopropyl-5′-methylcyclohexyl]-(2″-pyridyl)methanol 2d. Obtained as *needles*, mp 33 °C (chloroform) which had $[\alpha]_D$ +30.5 (*c* 1.51 in $CHCl_3$) or $[\alpha]_D$ +30 (*c* 0.8 in EtOH) {*lit.*[8] an oil, $[\alpha]_D$ +10 (*c* 0.8 in EtOH)}; ν_{max} (N) 3396, 2954, 2923, 2853, 1594, 1570, 1456, 1407, 1377, 1260, 1225, 1148, 1101, 1062, 1028, 865, 800, 748, 724 and 668 cm^{-1}; δ_H 0.68 (3H, d, *J* 6.6), 0.7–1.2 (5H, overlapping ms), 0.99 (3H, d, *J* 6.4), 1.01 (3H, d, *J* 6.4), 1.7–1.9 (3H, overlapping ms), 1.95 (1H, m, -C*H*Me_2), 2.17 (1H, m, *H-1*), 4.5 (1H, br s, exch. D_2O, -O*H*), 5.09 (1H, d, *J* 2.2, -C*H*OH), 7.18 (1H, m, *H*-5′), 7.21 (1H, d, *J* 7.9, *H*-3′), 7.64 (1H, dt, *J* 7.9 and 1.8, *H*-4′) and 8.53 (1H, d, *J* 4.8, *H*-6′) ppm; δ_C 21.58 (CH_3), 21.74 (CH_3), 23.39 (CH_3), 26.27 (CH_2), 28.12 (CH), 29.36 (CH), 35.78 (CH_2), 35.95 (CH_2), 40.88 (CH), 47.83 (CH), 72.87 (-*C*HOH), 120.24 (CH), 121.74 (CH), 136.47 (CH), 147.55 (CH) and 162.68 (quat) ppm. HRMS (EI) *m*/*z* 247.1919. *Calculated* for $C_{16}H_{25}NO$ 247.1936.

(−)-[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl] 2′-pyridyl ketone 5a and (+)-[(1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl] 2′-pyridyl ketone 5b *via* oxidation of a mixture of the alcohols 2a–2d

A mixture of the crude alcohols **2a**–**2d** (6 g), obtained as described above, was dissolved in ether (60 cm^3) at 0 °C. A solution of sodium dichromate dihydrate (4.2 g) in water (60 cm^3) containing sulfuric acid (2.9 cm^3) was added dropwise with stirring and the resulting mixture was stirred during a further 12 h. Ethanol (10 cm^3) was added to break down the sticky chromium complexes which had formed, and the reaction mixture was extracted with ether. The ethereal extract was washed, dried, and evaporated to give (NMR) an oily 3 : 1 mixture of the ketones **5a** and **5b** (4.5 g; 76%), bp 165 °C at 0.5 mmHg.

(−)-[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl] 2′-pyridyl ketone 5a *via* base-catalysed isomerisation of a mixture of 5a and 5b

A 3 : 1 mixture of the ketones **5a** and **5b** (1.4 g) was dissolved under nitrogen in DMSO (13 cm^3) with a catalytic amount of potassium *tert*-butoxide (50 mg). The mixture was stirred during 12 h and then diluted with water and extracted with ether. The extract was dried over magnesium sulfate and evaporated to give an oil (1.3 g) which (NMR) was a 20 : 1 mixture of **5a** and **5b**.

(−)-[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl] 2′-pyridyl ketone 5a and *N*-[(2′*S*,5′*R*)-2′-isopropyl-5′-methylcyclohex-2′-enylidene(2″-pyridyl)methyl]pyridine-2-carboxamidine 12 *via* reaction of menthylmagnesium chloride with pyridine-2-carbonitrile

Pyridine-2-carbonitrile (2.73 g) was added to a solution of menthylmagnesium chloride in THF (1.03 M; 25 cm^3). After the exothermic reaction had subsided, the mixture was refluxed during 8 h, cooled and poured onto ice. Extraction using ether gave a thick brown oil (2.8 g) from which hydrocarbons (menthenes, bimenthyls) were removed by vacuum distillation to leave a non-volatile residue (1.9 g). This (NMR) did not contain any of the ketones **5a** or **5b**.

A part of this residue was stirred with dilute hydrochloric acid and then extracted with ether to give an oil which now (NMR, IR) consisted partly of the ketone **5a**. This was isolated by distillation; it had bp 135 °C/0.5 mmHg; $[\alpha]_D$ −48.27 (*c* 0.959 in $CHCl_3$); ν_{max} (L) 3053, 2953, 2921, 2869, 1690, 1583, 1568, 1508, 1456, 1435, 1385, 1368, 1338, 1294, 1273, 1237, 1208, 1183, 1137, 1088, 1044, 1016, 995, 974, 928, 866, 818, 802, 744, 702, 685, 668 and 618 cm^{-1}; δ_H 0.68 (3H, d, *J* 6.9), 0.7–1.2 (3H, overlapping ms), 0.84 (3H, d, *J* 6.9), 0.86 (3H, d, *J* 6.6), 1.4–1.8 (6H, overlapping ms), 4.14 (1H, apparent dt, *J* 11.2, 11.2 and 3.4, -C*H*C=O), 7.41 (1H, ddd, *J* 6.5, 4.8 and 1.3, *H*-5′), 7.80 (1H, dt, *J* 7.9 and 1.8, *H*-4′), 8.03 (1H, d, *J* 7,9, *H*-3′) and 8.68 (1H, dd, *J* 4.8 and 1.0, *H*-6′) ppm; δ_C 16.51 (CH_3), 21.45 (CH_3), 22.36 (CH_3), 24.22 (CH_2), 29.12 (CH), 32.40 (CH), 34.72 (CH_2), 39.33 (CH_2), 44.17 (CH), 45.87 (CH), 122.2 (CH), 126.9 (CH), 136.8 (CH), 148.9 (quat) and 205.9 (C=O) ppm [*Calculated* for $C_{16}H_{23}NO$: C 78.37, H 9.39, N 5.71; *found* C 78.65, H 9.63, N 5.67%].

A further portion (1.3 g) of the non-volatile residue obtained as described above was subjected to chromatography on silica gel using 10% ethyl acetate : 85% hexane : 5% triethylamine as eluant to give the following fractions: *(a)* the menthyl ketone **5a** (150 mg; 11.5%), *(b)* a fraction (143 mg; 11%) containing several components which yielded the ketone **5a** on treatment with hydrochloric acid, and *(c)* the oily *amidine* **12** (260 mg; 20%) which was unaffected by treatment with hydrochloric acid

and which had ν_{max}(L) 3460, 3378, 3056, 2955, 2927, 2867, 1739, 1640, 1586, 1566, 1508, 1469, 1442, 1426, 1374, 1242, 1169, 1147, 1112, 1091, 1047, 997, 979, 958, 938, 921, 884, 847, 802, 792, 748, 695 and 668 cm^{-1}; δ_H (400 MHz) 0.77 (6H, overlapping ds, 2 × Me groups), 0.86 (2H, m), 1.04 (3H, d, *J* 7.0, Me group), 1.18 (2H, m), 1.57–2.10 (4H, overlapping ms), 2.48 (1H, d, *J* 12.7), 6.29 (2H, br s, exch. D_20, -N*H*$_2$), 7.10 (1H, dd, *J* 7.6 and 4.6, 5′-*H*), 7.27 (1H, dd, *J* 7.5 and 4.7, 5″-*H*), 7.48 (1H, d, *J* 7.3, 3′-*H*), 7.59 (1H, dt, *J* 7.4, 7.4 and 1.3, 4′-*H*), 7.71 (1, dt, *J* 7.5, 7.5 and 1.8, 4″-*H*), 8.34 (1H, dd, *J* 7.9 and 1.1, 3″-*H*), 8.46 (1H, dd, *J* 4.6 and 0.9, 6″-*H*) and 8.54 (1H, dd, *J* 4.7 and 0.9, 6′-*H*) ppm; δ_C (100 MHz) 18.47 (CH_3), 20.82 (CH_3), 21.71 (CH_3), 23.95 (CH_2), 26.60 (CH), 26.84 (CH_2), 29.70 (CH), 30.20 (CH_2), 44.15 (CH), 121.40 and 121.60 (CH), 124.59 and 124.87 (CH), 126.87 (quat.), 136.03 (CH), 136.43 (CH), 136.75 (quat.), 139.82 (quat.), 147.65 (CH), 148.09 (CH), 152.04 (quat.) and 152.83 (quat.) ppm, *m*/*z* 348 (M^+), 331 ($M - NH_3$), 316, 305, 263, 227, 212 (100%), 201, 184, 168, 157, 143, 132, 122, 105, 92 and 78 amu. HRMS: $C_{22}H_{28}N_4$ (M); found: *m*/*z* 348.2318. Calc. *m*/*z* 348.2314.

(+)-[(1*S*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl] 2′-pyridyl ketone 5b. Obtained as an *oil* by careful column chromatography of a small portion of the crude reaction mixture obtained from pyridine-2-carbaldehyde as described above. It had bp 165 °C/0.6 mmHg; $[\alpha]_D$ +12.75 (*c* 1.96 in $CHCl_3$); ν_{max} (L) 3053, 2949, 2867, 2843, 1689, 1583, 1569, 1472, 1456, 1434, 1386, 1368, 1339, 1298, 1274, 1260, 1226, 1195, 1169, 1148, 1123, 1088, 1045, 1025, 1017, 994, 982, 945, 928, 900, 884, 858, 826, 813, 778, 760, 743, 709, 668 and 618 cm^{-1}; δ_H 0.76 (6H, d, *J* 6.5), 0.89 (3H, d, *J* 6.6), 0.82–0.97 (1H, m), 1.08–1.20 (1H, m), 1.25–1.50 (2H, ms), 1.60 (1H, m, -C*H*Me$_2$), 1.72–2.04 (4H, overlapping ms), 4.59 (1H, m, $W_{1/2}$ 11.4 Hz, -C*H*C=O), 7.42 (1H, ddd, *J* 7.6, 4.8 and 1.3, *H*-5′), 7.81 (1H, dt, *J* 7.7 and 1.7, *H*-4′), 7.99 (1H, d, *J* 7.9, *H*-3′) and 8.65 (1H, d, *J* 4.0, *H*-6′) ppm; δ_C 21.56 (2 × CH_3), 22.28 (CH_3), 26.34 (CH_2), 27.12 (CH), 30.07 (CH), 35.46 (CH_2), 37.37 (CH_2), 40.51 (*C*HC=O), 46.86 (CH), 122.04 (CH), 126.6 (CH), 136.9 (CH), 148.8 (CH), 153.7 (quat) and 204.4 (C=O) ppm. HRMS (EI) *m*/*z* 245.11774. *Calculated* for $C_{16}H_{23}NO$ 245.1779.

Oxidation of (−)-(*S*)-[(1′*R*,2′*S*,5′*R*)-2′-isopropyl-5′-methylcyclohexyl](2″-pyridyl)methanol 2b to (−)-[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl] 2′-pyridyl ketone 5a

The alcohol **2b** (40 mg) was dissolved in ether (1 cm^3) and stirred with a solution of sodium dichromate dihydrate (28 mg) and sulfuric acid (0.2 cm^3) in water 0.4 cm^3) until oxidation was complete. The reaction mixture was diluted with further ether, washed sequentially with water and with sodium hydrogen carbonate solution, dried and evaporated to give the ketone **5a** (32 mg; 81%), identical in every respect with material isolated as described above.

Oxidation of (+)-(*S*)-[(1′*S*,2′*S*,5′*R*)-2′-isopropyl-5′-methylcyclohexyl](2″-pyridyl)methanol 2d to (+)-[(1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl] 2′-pyridyl ketone 5b

The alcohol **2** (30 mg) was dissolved in ether (1 cm^3) and stirred with a solution of sodium dichromate dihydrate (21 mg) and sulfuric acid (0.15 cm^3) in water 0.3 cm^3) until oxidation was complete. The reaction mixture was diluted with further ether, washed sequentially with water and with sodium hydrogen carbonate solution, dried and evaporated to give the ketone **5b** (23 mg; 77%), identical in every respect with material isolated as described above.

Reduction of [(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl] 2′-pyridyl ketone 5a by lithium tri-*tert*-butoxyaluminium hydride

The pure ketone **5a** (1.17 g) was dissolved, under nitrogen, in anhydrous tetrahydrofuran (12.5 cm^3) at 0 °C. Lithium tri-*tert*-butoxyaluminium hydride (1.45 g) was added to the stirred solution, the ice-bath was removed, and the mixture was stirred for 16 h. It was then diluted with water and extracted with ether to give a mixture of the alcohols **2a** and **2b** (1.08 g) in the ratio (^{1}H NMR) 14 : 1 as judged by integration of their -C*H*OH resonances.

(−)-(*S*)-[(1′*R*,2′*S*,5′*R*)-2′-Isopropyl-5′-methylcyclohexyl]-(2″-pyridyl)methanol 2b *via* Mitsunobu inversion[7] of (−)-(*R*)-[(1′*R*,2′*S*,5′*R*)-2′-isopropyl-5′-methylcyclohexyl](2″-pyridyl)-methanol 2a

The alcohol **2a** (100 mg), triphenylphosphine (410 mg) and 4-nitrobenzoic acid (270 mg) in dry THF (7.5 cm^3) were stirred together at 0 °C under nitrogen. Diethyl azidodicarboxylate (278 mg) was added dropwise, and the reaction mixture was then stirred at room temperature during 12 h followed by 3 h at 40 °C. The mixture was cooled, diluted with ether and washed with sodium hydrogen carbonate solution. Ether was removed under reduced pressure and the ester **7** was purified by chromatography over silica gel using ethyl acetate–hexane 10 : 90 as eluant from which it was obtained as an *oil* (120 mg; 75%) which had ν_{max} (L) 2923, 1732, 1609, 1591, 1573, 1531, 1470, 1436, 1410, 1388, 1348, 1266, 1171, 1148, 1102, 1016, 999, 976, 873, 854, 833, 802, 784, 761, 720 and 665 cm^{-1}; δ_H (400 MHz) 0.77 (3H, d, *J* 6.4), 0.82 (3H, d, *J* 6.8), 0.89 (3H, d, *J* 6.8), 1.04 (2H, m), 1.17 (2H, m), 1.27 (2H, m), 1.66 (2H, m), 2.07 (2H, m), 6.30 (1H, s, -C*H*OCOAr), 7.11 (2H, m, H-2-*py* and H-5-*py*), 7.55 (1H, t, *J* 7.8, H-4-*py*), 8.25 (4H, m, *Ar*-H) and 8.52 (1H, d, *J* 3.3, H-6-*py*) ppm; δ_C 15.45 (CH_3), 21.38 (CH_3), 22.56 (CH_3), 24.19 (CH_2), 26.55 (CH), 32.55 (CH), 34.53 (CH_2), 35.04 (CH_2), 43.53 (CH), 43.70 (CH), 76.75 (CH), 119.78 (*py*-CH), 121.97 (*py*-CH), 123.62 (*Ar*-CH), 130.73 (*Ar*-CH), 135 (*Ar*-C), 136.06 (*py*-CH), 149.28 (*py*-CH), 150 (*Ar*-C), 158.9 (*py*-C) and 164 (C=O) ppm. HRMS (EI) *m*/*z* 396.2048. *Calculated* for $C_{23}H_{28}N_2O_4$ 396.2049.

This ester **7** (120 mg) was refluxed during 4 h with aqueous sodium hydroxide solution (10%; 5 cm^3). The mixture was then cooled and extracted with ether. The ether extract was dried and evaporated to give the alcohol **2b** (65 mg; 92%), identical in every respect with material obtained as described above.

(+)-(*R*)-[(1′*R*,2′*S*,5′*R*)-2′-Isopropyl-5′-methylcyclohexyl]-(2″-pyridyl)methyl methyl ether 6

The alcohol **2a** (1.04 g) was dissolved in DMSO (10 cm^3). Sodium hydride (60% dispersion in oil; 0.25 g) was added. After evolution of hydrogen had ceased, iodomethane (0.9 g) was added and the mixture was stirred at rt during 13 h. Excess sodium hydride was quenched using ethanol, and the mixture was diluted with water and extracted with ether to give a brown semi-crystalline mass (1.3 g). TLC indicated that a single product had been formed, and chromatography over silica gel using 1% ether : 99% hexane afforded the pure *ether* **6** as *plates*, mp 77 °C (pentane) which had $[\alpha]_D$ +50.78 (*c* 0.128 in $CHCl_3$) or $[\alpha]_D$ +40.17 (*c* 1.17 in EtOH]; ν_{max} (N) 3052, 2955, 2859, 2825, 1589, 1571, 1460, 1433, 1377, 1364, 1351, 1345, 1260, 1197, 1178, 1151, 1109, 1086, 1048, 1022, 994, 975, 930, 917, 873, 854, 811, 782, 756, 720 and 685 cm^{-1}; δ_H 0.3–0.7 (2H, ms), 0.78 (3H, d, *J* 6.9), 0.79 (3H, d, *J* 6.6), 0.87 (3H, d, *J* 6.9), 0.9–1.05 (1H, m), 1.22–1.38 (1H, m), 1.55–1.68 (2H, m), 1.77–1.84 (1H, m), 1.87–1.97 (1H, m), 2.50–2.59 (1H, d of septets, *J* 6.9 and 3.0, -C*H*Me$_2$), 3.28 (3H, s, -OC*H*$_3$), 4.54 (1H, d, *J* 4.0, -C*H*(OCH$_3$)), 7.15 (1H, ddd, *J* 8.6, 4.8 and 1.2, *H*-5′), 7.34 (1H, d, *J* 7.9, *H*-3′), 7.66 (1H, dt, *J* 7.8, 7.8 and 1.7, *H*-4′) and 8.53 (1H, ddd, *J* 4.8, 1.9 and 1.0, *H*-6′) ppm; δ_C 15.09 (CH_3), 21.43 (CH_3), 22.68 (CH_3), 24.11 (CH_2), 26.56 (CH), 32.57 (CH), 34.90 (CH_2), 35.76 (CH_2), 43.61 (CH), 44.59 (CH), 57.32 (-O*C*H$_3$), 85.07 (-C*H*OCH$_3$), 121.8 (2 × CH), 135.6 (CH), 148.5 (CH) and 160.3 (quat) ppm. HRMS (EI) *m*/*z* 261.2087. *Calculated* for $C_{17}H_{27}NO$ 261.2093.

Barbier reaction of menthyllithium with pyridine-2-carbaldehyde

A mixture of menthyl chloride **3** (8.7 g) and pyridine-2-carbaldehyde (5.4 g) was slowly added to a stirred suspension of small pieces of lithium (1.4 g) in dry THF (200 cm^3) at 0 °C under nitrogen. A dark red colour slowly developed. After a further 4 h the mixture was decanted from the remaining lithium into dilute sulfuric acid. The mixture was neutralised using sodium carbonate and extracted with ethyl acetate. Evaporation yielded a dark red oil (10.2 g) which was further processed as described above for the Grignard reaction between menthylmagnesium chloride and pyridine-2-carbaldehyde to give a mixture of the alcohols **2a**–**2d** (*ca*. 3 g).

Reaction of menthylmagnesium chloride with carbon dioxide: (−)-(1*R*,3*R*,4*S*)-4-isopropyl-1-methylcyclohexane-3-carboxylic acid 9

A solution of menthylmagnesium chloride (0.65 M in THF; 5 cm^3) was added with swirling to excess powdered carbon dioxide (4 g). The resulting mixture was poured on to ice to which concentrated hydrochloric acid (2 cm^3) had been added, and extracted with ether. The ethereal extract was washed with water and then with sodium hydroxide solution. The alkaline aqueous layer was acidified using hydrochloric acid and extracted with ether. The ether extract was dried and evaporated to give the crude acid **9** as colourless needles (0.52 g; 88%), mp 56–57 °C (*lit*.[9] mp 60–63 °C for the pure compound); $[a]_D$ −50.7 (*c* 2.13 in $CHCl_3$) {*lit*.[9] $[a]_D$ −56.1 (*c* 5.2 in EtOH)}; ν_{max} (N) 3100, 2974, 2650, 1702, 1458, 1420, 1388, 1371, 1340, 1295, 1242, 1226, 1206, 1139, 1086, 1056, 1006, 963, 879 and 700 cm^{-1}; δ_H 0.80 (3H, d, *J* 6.8), 0.90 (3H, d, *J* 6.4), 0.91 (3H, d, *J* 6.8), 0.9–1.1 (2H, overlapping ms), 1.21 (1H, m), 1.35 (1H, m, -C*H*Me_2), 1.50 (1H, tt), 1.64–1.78 (3H, overlapping ms), 1.91 (1H, m), 2.29 (1H, dt, *J* 11.5, 11.5 and 3.3, *H*-3) and 10.52 (1H, br s, exch. D_2O, -O*H*) ppm; δ_C 15.91 (CH_3), 21.24 (CH_3), 22.24 (CH_3), 23.65 (CH_2), 29.10 (CH), 31.97 (CH), 34.45 (CH_2), 38.72 (CH_2), 44.15 (CH), 47.62 (CH) and 183.21 (*C*O_2H) ppm.

Enantioselective addition of diethylzinc to benzaldehyde catalysed by alcohols 2a–2d

The general procedure described by Bolm[3d] was applied. The following paragraph gives details of a representative experiment. One of the alcohols **2a**–**2d** (24.7 mg; 5 mol%) was dissolved in dry toluene (4 cm^3) under a nitrogen atmosphere. This solution was cooled in an ice-bath and benzaldehyde (212 mg) was added. A solution of diethylzinc in hexane (1 M; 4 cm^3, 2 eq.) was then added dropwise during 5 min. The resulting pale yellow solution was stirred at 0 °C during 3 h and then at room temperature during a further 20 h. The then colourless reaction mixture was quenched by the slow addition of dilute hydrochloric acid, neutralised using solid sodium carbonate, and extracted with ether. The ethereal extract was washed with brine, dried over anhydrous sodium carbonate, and evaporated to give a crude product that was separated from any unreacted benzaldehyde and from recovered catalyst by column chromatography. The purities of the samples of (+)-(*R*)-1-phenylpropanol **14** which were thus obtained were validated by ^{1}H NMR spectroscopy, and ee values were determined by polarimetry for chloroform solutions with reference to the literature[16] value of $[a]_D$ = +45.45 (*c* 5.15 in $CHCl_3$) for material of 100% ee.

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References

1 J. M. Hawkins and K. B. Sharpless, *Tetrahedron Lett.*, 1987, **28**, 2835.
2 (*a*) C. Bolm and M. Ewald, *Tetrahedron Lett.*, 1990, **31**, 5011; (*b*) C. Bolm, *Tetrahedron: Asymmetry*, 1991, **2**, 701; (*c*) C. Bolm, M. Ewald and M. Felder, *Chem. Ber.*, 1992, **125**, 1205.
3 (*a*) M. Ishizaki, K. Fujita, M. Shimamoto and O. Hoshino, *Tetrahedron: Asymmetry*, 1994, **5**, 411; (*b*) M. Ishizaki and O. Hoshino, *Tetrahedron: Asymmetry*, 1994, **5**, 1901; (*c*) M. Ishizaki and O. Hoshino, *Chem. Lett.*, 1994, 1357; (*d*) C. Bolm, H. Schlingoff and K. Harms, *Chem. Ber.*, 1992, **125**, 1191; (*e*) G. Chelucci and F. Soccolini, *Tetrahedron: Asymmetry*, 1992, **3**, 1235.
4 (*a*) M. Kitamura, S. Suga, M. Niwa and R. Noyori, *J. Am. Chem. Soc.*, 1995, **117**, 4832 and references therein; (*b*) T. Shibata, H. Morioka, T. Hayase, K. Choji and K. Soai, *J. Am. Chem. Soc.*, 1996, **118**, 471; (*c*) C. Girard and H. Kagan, *Angew. Chem., Int. Ed.*, 1998, **37**, 2922.
5 (*a*) T. Shono, N. Kise, T. Fujimoto, A. Yamanami and R. Nomura, *J. Org. Chem.*, 1994, **59**, 1730; (*b*) M. Genov, V. Dimitrov and V. Ivanova, *Tetrahedron: Asymmetry*, 1997, **8**, 3703; (*c*) for a review of menthyl-based chiral auxiliaries see J. K. Whitesell, *Chem. Rev.*, 1992, **92**, 953.
6 W. Huckel and H. Pietrzok, *Justus Liebigs Ann. Chem.*, 1939, **540**, 250.
7 J. A. Dodge, J. S. Nissen and M. Presnell, *Org. Synth.*, 1996, **73**, 110.
8 H. Adolfsson, K. Nordstrom, K. Warnmark and C. Moberg, *Tetrahedron: Asymmetry*, 1996, **7**, 1967.
9 D. G. Rowsell, BP 1 392 907/1975 (*Chem. Abstr.,* 1975, **83**, 114682t).
10 The ratio of menthyl and neomenthyl carboxylic acids which are obtained *via* the carbonation of menthyllithium is both temperature- and solvent-dependent: W. H. Glaze and C. M. Selman, *J. Org. Chem.*, 1968, **33**, 1987.
11 (*a*) J. C. de Souza-Barboza, C. Petrier and J-L. Luche, *J. Org. Chem.*, 1988, **53**, 1212; (*b*) P. J. Pearce, D. H. Richards and N. F. Scully, *J. Chem. Soc., Perkin Trans. 1*, 1972, 1655.
12 G. M. Sheldrick, *Acta Crystallogr., Sect. A*, 1990, **46**, 467.
13 G. M. Sheldrick, *SHELXL-93, A computer program for crystal structure determination*, University of Gottingen, 1993.
14 E. Keller, University of Freiburg, Germany.
15 P. McArdle, *J. Appl. Crystallogr.*, 1995, **28**, 65.
16 R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, 1914, 1115.