Asymmetric Conjugate Addition to Unsaturated Chiral Amido Alcohols Using Grignard Reagents Co-ordinated with Tertiary Amines or DBU. Preparation of Optically Active 3-Substituted Carboxylic Acids and (*S*)-(−)-Citronellol

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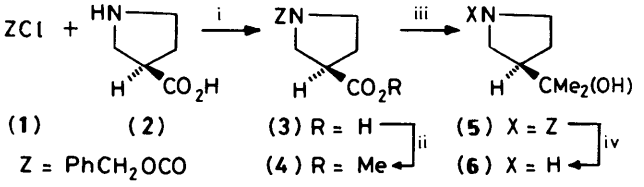
Optically active 3-substituted carboxylic acids and (*S*)-(−)-citronellol have been obtained by diastereoselective conjugate addition of Grignard reagents co-ordinated with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) to chiral amido alcohols derived from (*S*)-proline.

There has been much interest recently in developing an efficient method of asymmetric carbon–carbon bond formation and there have been a number of reports on diasteroselective conjugate additions using compounds such as oxazoline, tertiary leucine, and (−)-ephedrine derivatives *etc.*[2] In these reactions, chelation of each chiral auxiliary with the metal of an organometallic reagent is an important factor in the control of stereochemistry, as are the temperature and choice of solvent. However, the effect of amines as additives has not been fully examined.[3]

In the present study, the effect of tertiary amides and amidines on the diastereoselective conjugate addition of Grignard reagents to chiral unsaturated amines derived from (*S*)-2-(1-hydroxy-1-methylethyl)pyrrolidine or (*S*)-prolinol is examined. The presence of a tertiary-amine was found to enhance the diastereoselectivity of conjugate addition and 3-substituted optically active carboxylic acids and (*S*)-(−)-citronellol were obtained in good to high enantiomeric excesses.

Results and Discussion

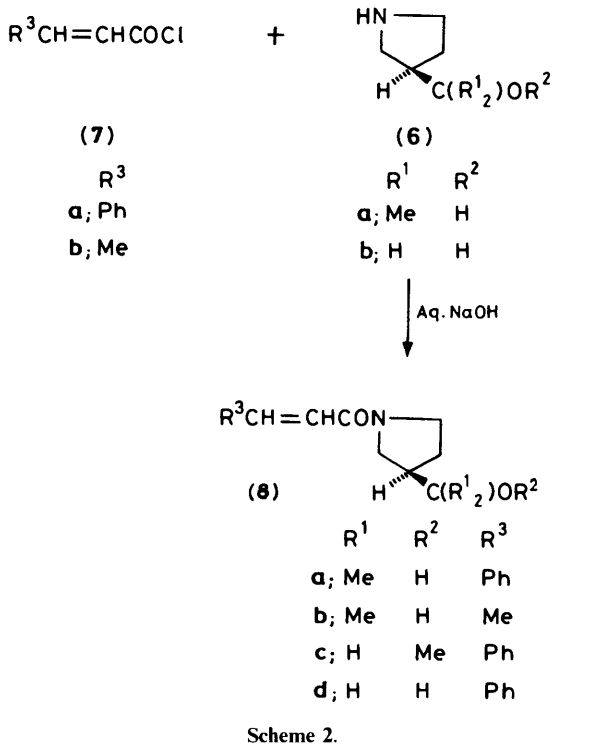
Synthesis of (S)-2-(1-*Hydroxy*-1-*methylethyl*)*pyrrolidine* (**6a**) *and Unsaturated Amides* (**8**).—(*S*)-*N*-Benzyloxycarbonylproline (*Z*-proline) (**3**),[4] was converted into (*S*)-*Z*-proline methyl ester (**4**),[5] and reaction of this with methylmagnesium bromide afforded the corresponding tertiary alcohol (**5**). Hydrogenolysis using Pd–C (10%) afforded (**6a**) in 85% yield (Scheme 1).



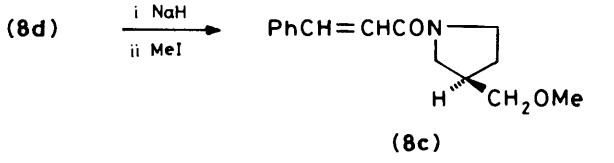
Scheme 1. *Reagents:* i, aq. NaOH; ii, MeI, DBU; iii, MeMgBr; iv, Pd (10%)–C

Unsaturated amido alcohols (**8a, b, d**) were synthesized in 81, 73, and 85% yield, respectively, from (**6a**) or (*S*)-prolinol (**6b**) and the corresponding unsaturated acyl chloride (**7a, b**) under Schotten-Baumann reaction conditions (Scheme 2). Compound (**8c**) possessing a methyl ether, was synthesized from (**8d**) by methylation of the corresponding alcohol (Scheme 3).

Effect of Tertiary Amines on Asymmetric Conjugate Addition and Examination of Reaction Conditions.—We found that tertiary amines are very effective additives in bringing about the diastereoselective conjugate addition of Grignard reagents. This



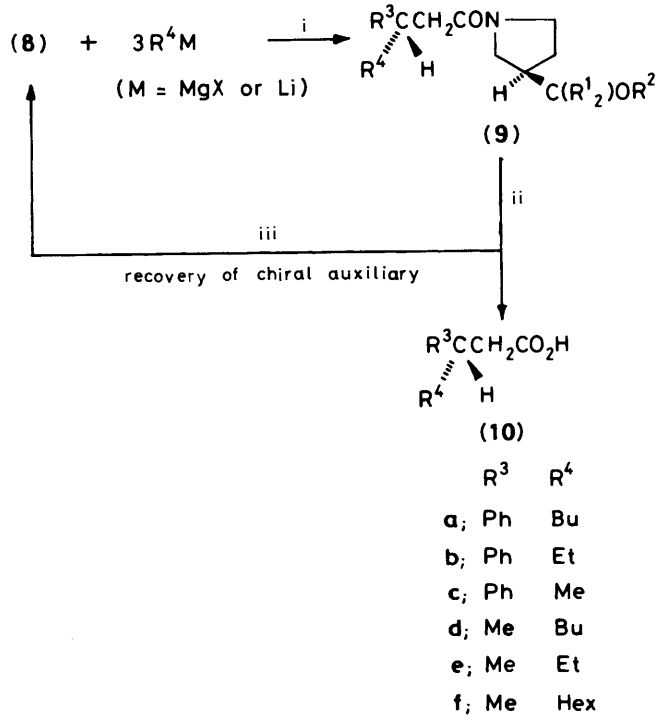
Scheme 2.



Scheme 3.

was first examined using compound (**8a**) and butylmagnesium bromide (Scheme 4). The results are summarized in Table 1. The % e.e.'s obtained for (*S*)-3-phenylheptanoic acid (**10a**) were much higher in the presence of a tertiary amine (entries 3—7) than in its absence (entries 1 and 2): of the amines examined, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was the most effective (entries 3 and 4).

Using DBU as the additive, the effect of solvent and organometallic reagents was examined. Table 2 shows the results. Tetrahydrofuran (THF, entry 1) and toluene (entry 2) showed higher asymmetric induction than diethyl ether (entry 3), with toluene affording a higher synthetic yield than THF. As



Scheme 4. *Reagents:* i, Method A or Method B; ii, 3M–HCl–dioxane (1:1, v/v); iii, (**7a**), aq. NaOH

to the effect of organometallic reagents, better results were obtained with butylmagnesium bromide (entries 1 and 2) than with butylmagnesium chloride or butyl-lithium (entries 4 and 5). As to the effect of alcohol, the tertiary alcohol showed higher asymmetric induction (entry 2) and higher synthetic yield than the primary alcohol (entry 9). When the corresponding methyl ether (**8c**) instead of the alcohol (**8d**) was used, the optical yields were low. In this case, addition of DBU did not increase the optical yield of (**10a**). Therefore, tertiary alcohols as the chiral auxiliary are considered to play an important role in asymmetric induction. Optimum reaction conditions appear to consist of a tertiary amine, especially DBU, toluene as the solvent, and alkylmagnesium bromide as the organometallic reagent (Method A). With these reaction conditions, various optically active 3-substituted carboxylic acids (**10a**—**f**) were obtained (see Table 3). Addition of DBU was also effective in other combinations of substrates (entries 6 and 7).

Recovery of Chiral Auxiliary (**6a**).—The chiral auxiliary (**6a**) was recovered in over 90% yield without racemization as the unsaturated amide (**8a**) after hydrolysis of the 1,4-adduct (**9**) (3M HCl–dioxane 1:1, v/v) followed by condensation with acyl chloride (**7a**)[6] (Scheme 4).

Preparation of Grignard Reagents Co-ordinated with DBU and their Use in the Asymmetric Synthesis of 3-Substituted Carboxylic Acids (**10**) *and* (S)-(−)-*Citronellol* (**12**).—Grignard reagents (RMgX), which have been utilized for asymmetric conjugate addition reactions, are usually prepared as a solution of diethyl ether or tetrahydrofuran (THF). RMgX is known to be co-ordinated with its solvent.[7] They can also be prepared in a hydrocarbon solvent using triethylamine as a ligand.[8] Therefore solvents or, in other words, ligands of RMgX may have an effect on asymmetric induction.[9] In the preceding paragraphs, THF solutions of Grignard reagents were utilized. Since toluene was a more suitable solvent than THF in asymmetric conjugate addition, a minimization of the amount of THF in the Grignard reagent was examined.

Table 1. Effect of tertiary amines on the synthesis of (**10a**) from (**8b**) and butylmagnesium bromide

			(**10a**)	
Entry	Tertiary amine[a]	Solvent	Yield (%)	E.e. (%)[c]
1	—	THF[b]	33	16 (*S*)
2	—	Toluene	52	37 (*S*)
3	DBU	THF	39	89 (*S*)
4	DBU	Toluene	81	88 (*S*)
5	TMEDA	THF	30	67 (*S*)
6	DBN	THF	27	50 (*S*)
7	(−)-Sparteine	THF	25	69 (*S*)

[a] DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; DBN = 1,5-diazabicyclo[4.3.0]non-5-ene. [b] THF = Tetrahydrofuran. [c] Based on the reported value of optical rotation: (**10a**), $[\alpha]_{577}$ −34.4° (*c* 8, benzene). See ref. 11.

Table 2. Effect of alkylating reagents (BuM) and solvent in diastereoselective synthesis of (**10a**)

				(**10a**)	
Entry[a]	Compound	BuM	Solvent	Yield (%)	E.e. (%)[c]
1	(**8a**)	BuMgBr	THF	39	89 (*S*)
2	(**8a**)	BuMgBr	Toluene	81	88 (*S*)
3	(**8a**)	BuMgBr	Et_2O	62	69 (*S*)
4	(**8a**)	BuMgCl	Toluene	60	74 (*S*)
5	(**8a**)	BuLi	THF	22	7 (*S*)
6	(**8a**)	BuLi–BuMgBr[b]	THF	21	23 (*S*)
7	(**8c**)	BuMgBr	Toluene	23	4 (*S*)
8[d]	(**8c**)	BuMgBr	Toluene	73	14 (*S*)
9	(**8d**)	BuMgBr	Toluene	29	84 (*S*)

[a] Reaction in the presence of DBU unless otherwise noted. [b] 1 equiv. of BuLi and 2 equiv. of BuMgBr were added. [c] Based on the reported value of optical rotation. See footnote *a* of Table 1. [d] Reaction without the use of DBU.

We report the preparation of RMgX co-ordinated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Scheme 5) and its use

$$RX + Mg \xrightarrow{THF} RMgX\cdot THF \xrightarrow{DBU\ toluene} RMgX\cdot DBU\cdot Toluene$$

Scheme 5.

in asymmetric conjugate addition to α,β-unsaturated amides (**8**). Our first attempt to prepare a Grignard reagent from magnesium and an alkyl halide in a mixed solvent of toluene and DBU was unsuccessful. However a Grignard reagent was prepared when THF was used as the solvent. Evaporation of THF and addition of DBU (1 equiv.) in toluene to the resulting grey solid produced a green solution which was re-evaporated to afford a residue; this was dried *in vacuo* (2 mmHg, 80 °C, 0.5 h). Further addition of toluene afforded a green solution of RMgX. The active RMgX was titrated with propan-2-ol in benzene using 1,10-phenanthroline as indicator.[10] Unlike titration in ethereal solvents, the characteristic red colour of the complex between RMgX and 1,10-phenanthroline did not appear. However, it was found that the red colour of the complex appeared with the addition of a few drops of THF.

Although the exact structure is not clear at the present stage,

Table 3. Synthesis of optically active 3-substituted carboxylic acids (**10a**—**f**) by method A

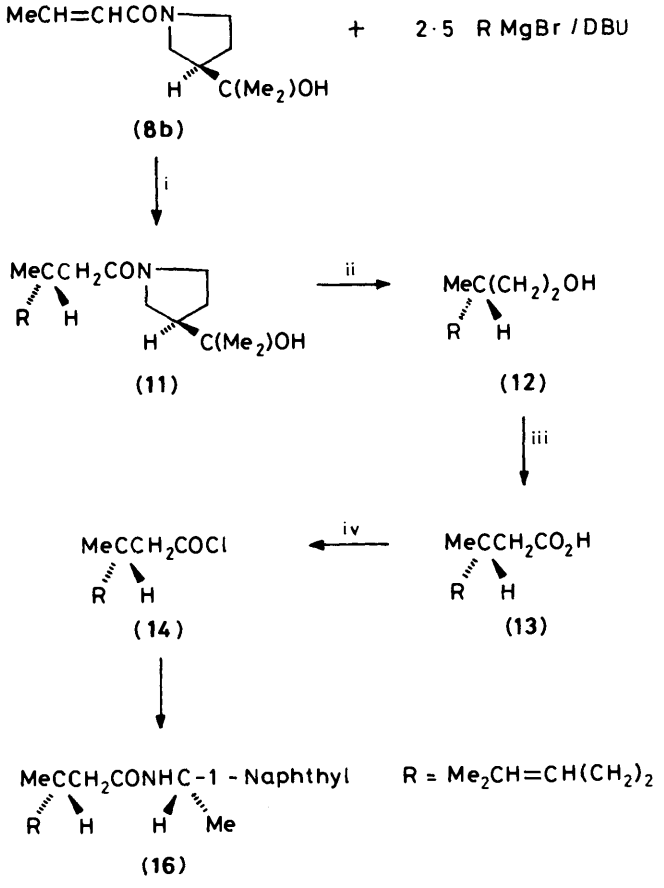
Entry	Compound	R^4MgBr	Product	Yield (%)	$[\alpha]^{20}$	E.e. (%)[b]
1	(**8a**)	BuMgBr	(**10a**)	81	$[\alpha]_{577}$ +32.23° (*c* 8.06, PhH)	88 (*S*)
2	(**8a**)	EtMgBr	(**10b**)	66	$[\alpha]_D$ +40.55° (*c* 7.04, PhH)	82 (*S*)
3	(**8a**)	MeMgBr	(**10c**)	22	$[\alpha]_D$ −36.39° (*c* 6.97, PhH)	64 (*R*)
4	(**8b**)	BuMgBr	(**10d**)	13	$[\alpha]_D$ −2.10° (neat)	50 (*S*)
5	(**8b**)	EtMgBr	(**10e**)	27	$[\alpha]_D$ +5.63° (neat)	69 (*S*)
6	(**8b**)	HexMgBr	(**10f**)	23	$[\alpha]_D$ −3.49° (neat)	68 (*S*)
7[a]	(**8b**)	HexMgBr	(**10f**)	33	$[\alpha]_D$ −2.81° (neat)	55 (*S*)

[a] Reaction without the addition of DBU. [b] Based on the reported values of optical rotations: (**10a**), see footnote *a* of Table 1; (**10b**), $[\alpha]_D$ −49.66° (*c* 7, benzene). See ref. 13; (**10c**), $[\alpha]_D$ +57.23° (*c* 9, benzene), see ref. 14; (**10d**), $[\alpha]_D^{27}$ −4.21° (neat), See ref. 15; (**10e**), $[\alpha]_D$ −8.15° (neat), see ref. 16; (**10f**), $[\alpha]_D^{23}$ +5.10° (neat), see ref. 17.

Table 4. Asymmetric synthesis of optically active 3-substituted carboxylic acids (**10a**—**e**) by method B

				Compound (**10**)		
Entry	Compound	R^4MgBr	Amine		Yield	E.e(%)[c]
1	(**8a**)	BuMgBr	DBU	(**10a**)	49	100 (82[b]) (*S*)
2	(**8a**)	BuMgBr	DBU[a]	(**10a**)	45	96 (81[b]) (*S*)
3	(**8a**)	BuMgBr	Et_3N	(**10a**)	23	75 (*S*)
4	(**8a**)	EtMgBr	DBU	(**10b**)	51	88 (*S*)
5	(**8b**)	BuMgBr	DBU	(**10d**)	45	60 (*S*)
6	(**8b**)	EtMgBr	DBU	(**10e**)	21	53 (*S*)
7	(**8b**)	PhMgBr	DBU	(**10c**)	47	67 (*S*)

[a] BuMgBr (1 equiv.)–DBU–toluene then BuMgBr–toluene were added. [b] Carboxylic acid (**10**) was reduced to alcohol. The % e.e. was then determined by n.m.r. analysis of the (−)-α-methoxy-α-(trifluoromethyl)phenyl acetic acid (MTPA) ester, see ref. 18. [c] Based on the reported values of optical rotations, see footnote *b* of Table 3.



Scheme 6. *Reagents and conditions:* i, Toluene, −40 °C ⟶ room temp.; ii, $LiBHEt_3$; iii, pyridinium dichromate, DMF; iv, $(COCl)_2$; v, (*R*)-1-naphthyl-$CH(NH_2)Me$, (**15**), pyridine

RMgX prepared as described above was found to be more effective for the asymmetric conjugate addition to α,β-unsaturated amido alcohols (**8**) (Method B). The results are summarized in Table 4.

In a typical experiment, butylmagnesium bromide (BuMgBr) prepared as described was added to a toluene solution of compound (**8a**). Subsequent hydrolysis in 6M sulphuric acid–acetic acid gave (*S*)-(+)-(**10a**) {45% overall yield; $[\alpha]_{577}^{23}$ +34.69° (*c* 5.3, benzene), 100% o.p. based on lit. value of $[\alpha]_{577}$ −34.4° (*c* 8, benzene),[11] 82% e.e. by MTPA method. This optical purity (o.p.) is higher than that obtained from BuMgBr in THF solution (88% o.p., Table 1, entry 4). DBU as the ligand was more effective than triethylamine (entries 1 and 3). BuMgBr prepared in triethylamine[8] and toluene afforded compound (**10a**) of 75% o.p. These results show that the ligands of RMgX have a considerable effect on the asymmetric conjugate addition.

(*S*)-(−)-Citronellol (**12**), a sweet smelling perfume, is an important synthetic intermediate for complex natural products, and its asymmetric synthesis has been reported.[12] The present method was applied to the diastereoselective synthesis of (*S*)-(−)-(**12**) using a Grignard reagent co-ordinated with DBU (Scheme 6). Diastereoselective addition of 4-methylpent-3-enylmagnesium bromide co-ordinated with DBU to (**8b**) gave the 1,4-adduct (**11**) in high yields. Compound (*S*)-(−)-(**12**) was obtained directly in moderate e.e. (60—63%) by the reduction of the adduct (**11**) with lithium triethylborohydride. The e.e. of (**12**) was determined by oxidizing it to (*S*)-(−)-citronellic acid (**13**) and converting this into the acid chloride (**14**). Compound (**14**) was treated with (*R*)-1-(1-naphthyl)ethylamine (**15**) to afford the diastereoisomeric amide (**16**).[12] The e.e. of (**12**) was determined (63% e.e.) by h.p.l.c. analysis of (**16**).

Experimental

General.—I.r. spectra, high resolution mass spectra, and optical rotations were recorded with a Hitachi 260-10

spectrophotometer, a Hitachi M-80 mass spectrometer, and a JASCO DIP-181 polarimeter respectively. ^{1}H N.m.r. spectra were recorded with either a Varian EM-360A, a JEOL JNM-PMX-60, or a JEOL JNM-FX100 spectrometer. Bulb-to-bulb distillation was carried out with a Shibata Glass Tube Oven GTO-250. Tetrahydrofuran (THF), diethyl ether (ether), and toluene were distilled over lithium aluminium hydride. All the reactions were performed under an argon atmosphere. (*S*)-*N*-Benzyloxycarbonylproline (**3**) was synthesized according to the literature procedure,[4] as was (*S*)-*N*-benzyloxycarbonylproline methyl ester (**4**),[5] $[\alpha]_D^{20}$ −57.7° (*c* 1, MeOH) {lit.,[5] $[\alpha]_D$ −59.1° (*c* 1, MeOH)}.

(S)-2-(1-*Hydroxy*-1-*methylethyl*)*pyrrolidine* (**6a**).—Methylmagnesium bromide (225 mmol) in THF (248 ml, 0.91M) was added to a THF solution (210 ml) of compound (**4**) (23.7 g, 90 mmol) with ice cooling. After the mixture had been stirred for 1 h, the reaction was quenched by the addition of saturated aqueous ammonium chloride. The precipitate was filtered off and the filtrate was washed with 1M HCl (50 ml × 2), dried (Na_2SO_4) and evaporated under reduced pressure to afford the crude tertiary alcohol (**5**) {23.2 g as a yellow oil, $[\alpha]_D^{20}$ −69.3° (*c* 3, $CHCl_3$)}. Compound (**5**) was dissolved in EtOH (150 ml), and Pd–C (2.4 g, 10%) was added. The mixture was refluxed and hydrogen gas was bubbled into the mixture for 5 h. The catalyst was filtered off, the solvent was evaporated, and the resulting oily residue purified by distillation. Compound (**6a**) was obtained as colourless needles (9.50 g, 86%), m.p. 32.5—33.5 °C; b.p. 84 °C/19 mmHg; $[\alpha]_D^{20}$ −20.1° (*c* 3.00, $CHCl_3$); δ($CDCl_3$) 1.00—1.40 (6 H, s), 1.45—2.00 (4 H, m), 2.15—2.54 (2 H, m), and 2.70—3.20 (3 H, m); $\nu_{max.}$ 2 980, 2 870, 1 455, 1 370, 1 190, 1 160, 1 000, and 670 cm^{-1}; *m/z* (e.i.m.s.) 129.1175 (M^+ requires 129.1155) (HCl salt) (Found: C, 50.8; H, 9.85; N, 8.5. $C_7H_{16}NClO$ requires C, 50.75; H, 9.74; N, 8.46%).

(S)-1-*Cinnamoyl*-2-(1-*hydroxy*-1-*methylethyl*)*pyrrolidine* (**8a**).—1M NaOH was added to compound (**6a**) (8.55 g, 66.2 mmol), water (50 ml), followed by cinnamoyl chloride (**7a**) (11.2 g, 67 mmol) in ether (100 ml) at 0 °C. The mixture was stirred vigorously for 1.5 h at room temperature, extracted with $CHCl_3$, and the extract dried (Na_2SO_4) and evaporated under reduced pressure. Recrystallization of the residue from hexane–ethyl acetate afforded compound (**8a**) as colourless needles (13.94 g, 81%), m.p. 113—114.5 °C, $[\alpha]_D^{20}$ −90.04° (*c* 2.008, $CHCl_3$); $\nu_{max.}$ 3 220, 2 985, 1 658, 1 590, 1 425, 1 312, 1 170, and 780 cm^{-1}; δ($CDCl_3$) 1.10—1.50 (6 H, d), 1.50—2.55 (4 H, m), 3.30—4.53 (3 H, m), 6.20—6.42 (1 H, s), and 6.60—8.00 (7 H, m) (Found: C, 74.1; H, 8.2; N, 5.4. $C_{16}H_{21}NO_2$ requires C, 74.10; H, 8.16; N, 5.40%).

(S)-1-*Crotonoyl*-2-(1-*hydroxy*-1-*methylethyl*)*pyrrolidine* (**8b**).—Compound (**8b**) was synthesized from (**6a**) (0.695 g, 5.4 mmol) and crotonoyl chloride (**7b**) (0.52 ml, 5.43 mmol) by the same procedure described for (**8a**). Purification by t.l.c. on silica gel using CH_2Cl_2–MeOH (20:1) as eluant afforded (**8b**) (0.769 g, 73%), m.p. 50—50.5 °C; b.p. 2 mmHg/138 °C (bath temperature); $[\alpha]_D^{20}$ −95.81° (*c* 2.006, $CHCl_3$); $\nu_{max.}$ 3 290, 2 995, 1 670, 1 600, 1 427, 1 322, 1 215, 1 175, 970, 900, 835, and 690 cm^{-1}; δ($CDCl_3$) 0.90—1.45 (6 H, d), 1.45—2.30 (7 H, m), 3.15—3.97 (2 H, m), 3.97—4.35 (1 H, t), and 5.90—7.40 (3 H, m) (Found: C, 67.0; H, 9.7; N, 6.9. $C_{11}H_{19}NO_2$ requires C, 66.97; H, 9.71; N, 7.10%).

(S)-1-*Cinnamoylprolinol* (**8d**).—1M Aqueous NaOH (30 ml) was added to a mixture of (*S*)-prolinol (**6b**) (2.28 g, 22.6 mmol) and water (20 ml). The mixture was cooled in an ice-bath and (**7a**) (3.87 g, 23.2 mmol) in ether (30 ml) was added. The mixture was stirred at room temperature for 3 h and extracted with ethyl acetate; the extract was then dried (Na_2SO_4), and evaporated under reduced pressure. Purification of the residue by silica gel column chromatography (eluant, ethyl acetate) afforded (**8d**) as crystals (4.46 g, 85%), m.p. 84.5—85.5 °C; $[\alpha]_D^{20}$ −33.0° (*c* 2, $CHCl_3$); $\nu_{max.}$ 3 350, 2 950, 2 380, 1 650, 1 580, 1 430, 1 260, 1 200, 1 050, 980, 905, 860, 770, and 680 cm^{-1}; δ($CDCl_3$) 1.50—2.30 (4 H, m), 3.39—3.85 (4 H, m), 4.00—4.70 (1 H, m), 5.00—5.50 (1 H, m), and 6.40—8.00 (7 H, m) (Found: C, 72.7; H, 7.35; N, 6.1. $C_{14}H_{17}NO_2$ requires C, 72.70; H, 7.41; N, 6.06%).

(S)-1-*Cinnamoyl*-2-*methoxymethylpyrrolidine* (**8c**).—Compound (**8d**) (3.81 g, 16.5 mmol) in THF (33 ml) was added to sodium hydride (50% dispersion in mineral oil, 2.7 g) which had been washed with THF (15 ml). The mixture was stirred for 10 min at room temperature, after which methyl iodide (8.2 ml) was added, and the mixture stirred for a further 1 h. Water was added to quench the reaction after which the mixture was evaporated under reduced pressure, diluted with ether (100 ml), and washed with water (2 × 35 ml). The organic layer was dried (Na_2SO_4), evaporated under reduced pressure and the residue purified by silica gel column chromatography using $CHCl_3$–AcOEt (10:1) as eluant to afford compound (**8c**) (3.84 g, 95%); $[\alpha]_D^{20}$ −34.25° (*c* 4, $CHCl_3$); $\nu_{max.}$ 3 450, 2 940, 2 890, 1 650, 1 600, 1 500, 1 458, 1 420, 1 200, 1 115, 980, 770, and 705 cm^{-1}; δ($CDCl_3$) 1.70—2.29 (4 H, m), 3.20—3.85 (7 H, m), 4.00—4.60 (1 H, m), and 6.50—7.90 (7 H, m); *m/z* (e.i.m.s.) 245.1402 (M^+, requires 245.1417).

Typical Procedure for the Synthesis of Compound (**10**) *in the Presence of* DBU *or Tertiary Amine*.—(S)-3-*Phenylheptanoic acid* (**10a**) *by method A*. DBU (2.02 ml, 13.5 mmol) was added to a solution of compound (**8a**) (0.781 g, 3.01 mmol) in toluene (8 ml) and the mixture was cooled to −40 °C; butylmagnesium bromide (0.82M THF solution; 9.03 mmol, 11 ml) was added over a period of 30 min. The temperature was allowed to rise to room temperature, after which the reaction was quenched with saturated aqueous NH_4Cl (11 ml) and extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated under reduced pressure and the oily residue was dissolved in 3M HCl–dioxane [1:1 (v/v); 30 ml] and the mixture refluxed for 40 h. The mixture was extracted with $CHCl_3$ and the extract dried (Na_2SO_4), and evaporated. The residue was purified by silica gel t.l.c. using CH_2Cl_2–MeOH (50:1) as eluant to afford (**10a**) (0.503 g, 81%), b.p. 140 °C/2 mmHg (bath temperature); $[\alpha]_{577}^{20}$ +30.23° (*c* 8.055, PhH), 88% e.e. {lit.,[11] $[\alpha]_{577}$ −34.4° (*c* 8, PhH)}; $\nu_{max.}$ 2 940, 1 717, 1 500, 1 460, 1 300, 1 192, 765, and 700 cm^{-1}; δ($CDCl_3$) 0.58—1.90 (9 H, m), 2.40—3.36 (3 H, m), 6.86—7.40 (5 H, s), and 11.6—11.8 (1 H, s).

Compounds (**10b—f**) *by method* A. (*S*)-3-Phenylpentanoic acid (**10b**). Yield 66%, b.p. 190 °C/3 mmHg (bath temp.); $[\alpha]_D^{20}$ +40.55° (*c* 7.04, PhH) {lit.,[13] $[\alpha]_D$ −49.66° (*c* 7, PhH)}; $\nu_{max.}$ 3 030, 2 975, 1 710, 1 500, 1 460, 1 420, 1 290, 1 100, 960, 762, and 707 cm^{-1}; δ($CDCl_3$) 0.55—1.1 (3 H, t), 1.35—2.05 (2 H, m), 2.40—3.30 (3 H, m), 6.90—7.50 (5 H, s), and 10.50—10.75 (1 H, s).

(*R*)-3-Phenylbutanoic acid (**10c**). Yield 22%, b.p. 140 °C/2 mmHg (bath temp.); $[\alpha]_D^{20}$ −36.39° (*c* 6.97, PhH) {lit.,[14] $[\alpha]_D$ +57.23° (*c* 9, PhH)}; $\nu_{max.}$ 2 980, 1 705, 1 500, 1 460, 1 420, 1 300, 1 220, 1 195, 1 090, 1 022, 930, 770, and 707 cm^{-1}; δ($CDCl_3$) 1.35—1.50 (3 H, d), 2.38—2.90 (2 H, m), 3.00—3.50 (1 H, m), 7.00—7.45 (5 H, s), and 10.45—10.98 (1 H, br).

(*S*)-3-Methylheptanoic acid (**10d**). This was synthesized from compound (**8b**) by the same procedure used for the synthesis of (**10a**). Yield 13%, b.p. 140 °C/2 mmHg (bath temp.); $[\alpha]_D^{20}$ −2.10° (neat), {lit.,[15] $[\alpha]_D^{27}$ −4.21° (neat)}; $\nu_{max.}$ 2 950, 1 710, 1 460, 1 410, 1 380, 1 290, 1 230, 1 190, and 930 cm^{-1}; δ($CDCl_3$) 0.60—1.50 (11 H, m), 1.50—2.50 (3 H, m), 11.4—11.8 (1 H, s).

(*S*)-3-Methylpentanoic acid (**10e**). Yield 27%, $[\alpha]_D^{20}$ +5.63°

(neat) {lit.,[16] $[\alpha]_D$ −8.15° (neat)}; $\nu_{max.}$ 2 970, 1 710, 1 460, 1 415, 1 390, 1 300, 1 210, and 930 cm^{-1}; δ($CDCl_3$) 0.70—1.15 (6 H, m), 1.15—2.14 (3 H, m), 2.14—2.60 (2 H, m), and 10.7—11.2 (1 H, s).

(*S*)-3-Methylnonanoic acid (**10f**). Yield 23%, $[\alpha]_D^{20}$ −3.49° (neat) {lit.,[17] $[\alpha]_D^{23}$ +5.10° (neat)}; $\nu_{max.}$ 2 950, 2 870, 1 715, 1 470, 1 420, 1 390, 1 300, 1 230, and 940 cm^{-1}; δ($CDCl_3$) 0.60—1.10 (6 H, m), 1.10—1.60 (10 H, s), 1.70—2.60 (3 H, m), and 11.1—11.6 (1 H, br).

Preparation of Grignard Reagents Co-ordinated with DBU, and their Titration.—Butyl bromide (3.3 ml, 30.7 mmol) in THF (12 ml) was slowly added to a mixture of Mg (0.745 g, 30.8 mmol) in THF (5 ml). The mixture was stirred for 1 h, after which the THF was evaporated off under reduced pressure. Toluene (5 ml) and DBU (4.6 ml, 30.7 mmol) were added successively to the resulting grey solid to give a dark green solution. Evaporation of the latter under reduced pressure gave a residue which was dried *in vacuo* (80 °C/2 mmHg) for 30 min and then dissolved in toluene (17 ml) to afford a dark green solution of the Grignard reagent.

Titration. A trace quantity of 1,10-phenanthroline[10] and a few drops of THF were added to the Grignard solution to give a red solution; the colour disappeared on addition of propan-2-ol (0.50M benzene solution). Thus the concentration of the above prepared Grignard solution was determined to be 0.802M.

Preparation of a Grignard Reagent Co-ordinated with Triethylamine.—This was prepared according to the literature procedure[8] and was titrated as described above.

Typical Procedure for the Synthesis of Compound (**10**) *using Grignard Reagents Co-ordinated with DBU.*—(*S*)-3-*Phenylheptanoic acid* (**10a**) *by method B.* Compound (**8a**) (0.774 g, 2.96 mmol) was dissolved in toluene (8 ml) and the solution cooled to −40 °C. Butylmagnesium bromide co-ordinated with DBU (8.95 mmol, 12.6 ml, 0.71M toluene solution) was then added over 30 min. The reaction mixture was allowed to warm to room temperature after which the reaction was quenched by the addition of saturated aqueous NH_4Cl (11 ml). Work-up as described in method A afforded (**10a**) (49%), $[\alpha]_{577}^{23}$ +34.69° (*c* 5.3, benzene).

Products (**10**) were prepared according to method B. (*S*)-3-Phenylpentanoic acid (**10b**): yield 51%, $[\alpha]_D^{26}$ +43.4° (*c* 7, benzene); (*S*)-3-methylheptanoic acid (**10d**), yield 45%, $[\alpha]_D^{26}$ −2.54° (neat); (*S*)-3-methylpentanoic acid (**10e**), yield 21%, $[\alpha]_D^{26}$ +4.33° (neat); (*S*)-3-phenylbutanoic acid (**10c**), yield 47%, $[\alpha]_D^{25}$ −38.30° (*c* 5.9, benzene).

Determination of Enantiomeric Excess by N.m.r.—$LiAlH_4$ (0.047 g, 1.24 mmol) was added to a solution of compound (**10a**) (0.0966 g, 0.468 mmol; obtained from Table 4, entry 1) in THF (3 ml) and the mixture was refluxed for 30 min. After the reaction had been quenched by addition of 1M HCl, the mixture was extracted with $CHCl_3$ and the extract dried (Na_2SO_4), and evaporated. Purification by silica gel t.l.c. using $CHCl_3$–AcOEt (10:1) as eluant afforded (*S*)-3-phenylheptanol (0.089 g, 99% yield). This was treated with (−)-α-methoxy-α-(trifluoromethyl)-phenylacetyl (MTPA) chloride.[18] The e.e. was determined by ^1H n.m.r. (100 MHz) analysis of the corresponding (−)-MTPA ester. The methoxy signal (δ 3.58 p.p.m.) split into two sets of singlet peaks (δ 3.80 and 3.88 p.p.m.) on addition of the chiral shift reagent [Eu(hfc)$_3$]. From the integration of these peaks, the e.e. of (**10a**) was determined to be 82%.

In a similar manner, the e.e. of acid (**10b**) was determined to be 81%.

Recovery of Chiral Auxiliary and its Conversion into (**8a**).—Dioxane–3M HCl [1:1 (v/v); 40 ml] was added to the 1,4-adduct (**9**) (0.678 g, 2.14 mmol) obtained from compound (**8a**) and BuMgBr, and the mixture was refluxed for 40 h. The carboxylic acid (**10a**) was extracted with $CHCl_3$. The aqueous layer was made alkaline (pH 12), and cinnamoyl chloride (**7a**) (0.356 g, 2.14 mmol) in ether was added. The mixture was stirred vigorously for 1 h at room temperature and then extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated and the residue purified by silica gel column chromatography (eluant AcOEt), to give compound (**8a**) (0.50 g, 90%); $[\alpha]_D^{26}$ −89.8° (*c* 2.00, $CHCl_3$).

(S)-(−)-*Citronellol* (**12**).—To a solution of (**8b**) (1.100 g, 5.57 mmol) in toluene (19 ml) was added 4-methylpent-3-enylmagnesium bromide (0.87M toluene solution, co-ordinated with DBU; 16 ml) over a period of 30 min at −40 °C. The mixture was allowed to warm to room temperature gradually (20 h) with stirring, after which saturated aqueous NH_4Cl (4 ml) was added to the mixture. The mixture was neutralized with 3M HCl (13 ml) and the aqueous layer was extracted with chloroform; the extract was then dried (Na_2SO_4) and evaporated under reduced pressure and the residue purified by silica gel column chromatography using ($CHCl_3$–AcOEt (10:7) as eluant to give the 1,4-adduct (**11**) (1.07 g, 3.79 mmol, 68.1%). This adduct (0.934 g, 3.31 mmol) was dissolved in THF (2 ml), and $LiBEt_3H$ (0.375M THF solution; 30 ml, 11.22 mmol) was added at room temperature. The reaction mixture was stirred overnight after which it was quenched with water and neutralized with 3M HCl (5 ml). The aqueous layer was extracted with Et_2O and the extract was dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using $CHCl_3$–AcOEt (10:1) as eluant to give (*S*)-(−)-(**12**) as an oil (4.04 g, 2.56 mmol, 77.6%), $[\alpha]_D^{20}$ −2.83° (neat). The oxidation of (**12**) by pyridinium dichromate gave citronellic acid (**13**)[19] (51%), $[\alpha]_D^{24}$ −4.16° (neat), which was converted into (*R*)-1-(1-naphthyl)ethylamide (**16**) by the reaction of the corresponding carboxylic acid chloride (**14**) and (*R*)-1-(1-naphthyl)ethylamine (**15**). The enantiomeric excess was then determined by analysis of (**16**) using h.p.l.c. (Unisil Q CN, 1.0 × 300 mm, BQ362, hexane–THF (5:1, v/v) as eluant, 20 kg cm^{-2}, 1.15 ml min^{-1}, R_t for (*R,R*)-(**16**), 9.2 min; (*S,R*)-(**16**), 11.0 min; 63% e.e.

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