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Diastereoselective Preparation of Chiral Lithiated Allyl Amines: Application in EPC-Synthesis

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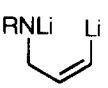
Abstract: Lithiation of chiral allylamine (*R*)-**1** with Bu^{n}Li and Bu^{t}Li leads to the formation of intermediate (*R*)-**2**, which by reaction with D_2O, Me_2CO or $(CH_2)_5CO$ affords the expected chiral compounds (*R*)-**3**, (*R*)-**4** and (*R*)-**5**, respectively. With Bu^{t}CHO the corresponding aminoalcohols (*R,R*)-**6** and (*R,S*)-**6** are separated in pure form by their transformation into the corresponding benzamides **6'**, which yield again the precursor aminoalcohols with MeLi. The carbonation of (*R*)-**2** followed by esterification affords the unexpected ester *trans*- (*R*)-**7**. The same set of reactions is carried out with (*S*)-**1** yielding the corresponding series of (*S*) derivatives. X-Ray analysis of (*S,S*)-**6'** allows the assignement of the stereochemistry for all aminoalcohols **6**. The same processes are applied to more substituted chiral amines (*R*)- and (*S*)-**11** obtaining the corresponding chiral products (*R*)- and (*S*)-**13** and (*S*)-**14**.

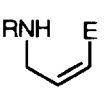
INTRODUCTION

Among the syntheses of enantiomerically pure compounds (EPC-synthesis)[1] probably the most versatile methodologies[2] use the pool of natural products as chiral precursors, so cheap and easily available molecules from nature such as carbohydrates, hydroxy and aminoacids, alkaloids and other species can be transformed into the target chiral compounds. On the other hand, we have recently described[3] the regio and stereoselective lithiation of allyl amines of type **I** to give dilithiated intermediates **II**, which after reaction with different electrophilic reagents yield the corresponding substituted allyl amines **III** in a regio and stereoselective manner. In this paper we describe the application of this methodology, which involves functionalised organolithium compounds[4], to the preparation of chiral intermediates[5] of type **II** and their application to the EPC-synthesis of functionalised chiral allyl amines.

I



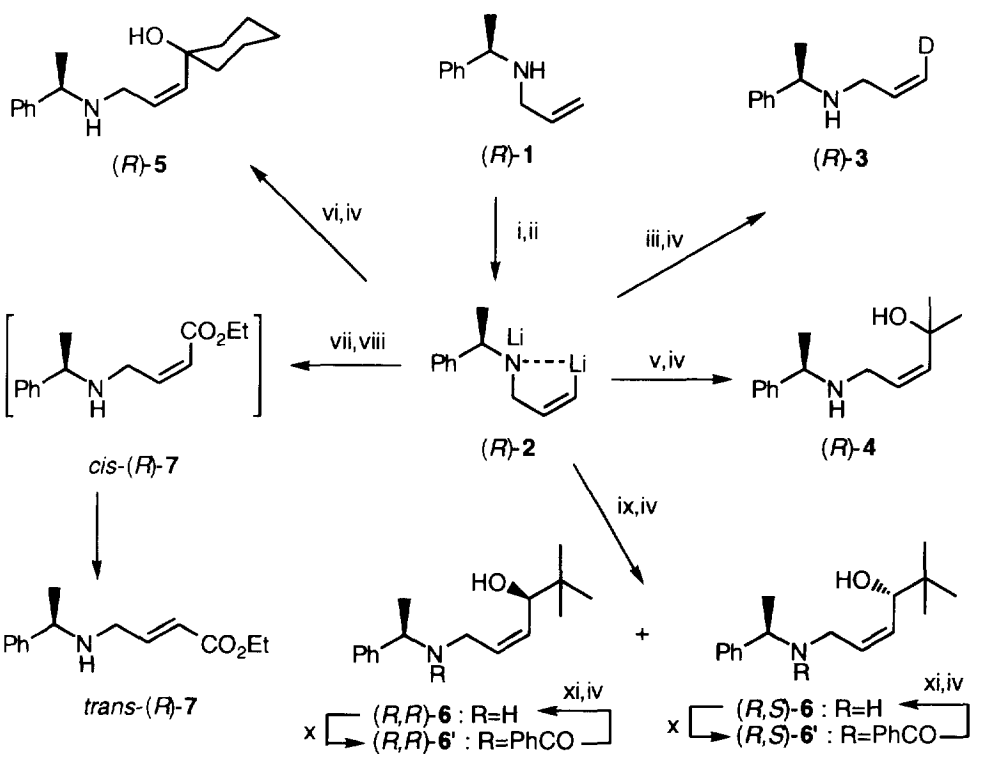
II



III

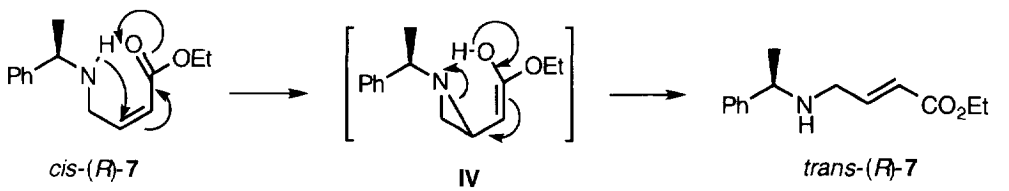
RESULTS AND DISCUSSION

The successive reaction of chiral allyl amine (*R*)-**1** with *n*-butyllithium in THF at -50°C and then with *tert*-butyllithium at temperatures ranging between -50 and 20°C[3] led to the corresponding chiral intermediate (*R*)-**2**, which by treatment with deuterium oxide afforded the deuteriated product (*R*)-**3** in a regio-, enantio- and stereoselective manner (Scheme 1 and Table 1, entry 1). The use of non-prochiral ketones, such as acetone or cyclohexanone yielded the expected chiral compounds (*R*)-**4** and (*R*)-**5**, respectively (Scheme 1 and Table 1, entries 2 and 3). In the case of using pivalaldehyde as electrophile a *ca.* 1:1 diastereoisomers mixture (300 MHz ^{1}H NMR) of the corresponding aminoalcohols (*R,R*)-**6** and (*R,S*)-**6** was obtained, which could not be separated by column chromatography under different conditions. However, the corresponding *N*-benzoylderivatives (prepared by treatment of compounds **6** with benzoyl chloride under basic conditions) were separated chromatographically affording both amides (*R,R*)-**6'** and (*R,S*)-**6'**. Recovery of aminoalcohols **6** was easily performed by treatment of their benzamides **6'** with methyllithium (3 eq) in THF, so chiral aminoalcohols (*R,R*)-**6** and (*R,S*)-**6** were obtained (Scheme 1 and Table 1, entries 4 and 5).



Scheme 1. *Reagents and conditions*: i, Bu^{n}Li, THF, -50°C; ii, Bu^{t}Li, -50 to 20°C; iii, D_2O; iv, H_2O; v, Me_2CO; vi, $(CH_2)_5CO$; vii, CO_2 exc., -50 to 20°C; viii, EtOH, HCl (g); ix, Bu^{t}CHO; x, PhCOCl, NaOH; xi, MeLi (3 eq), THF.

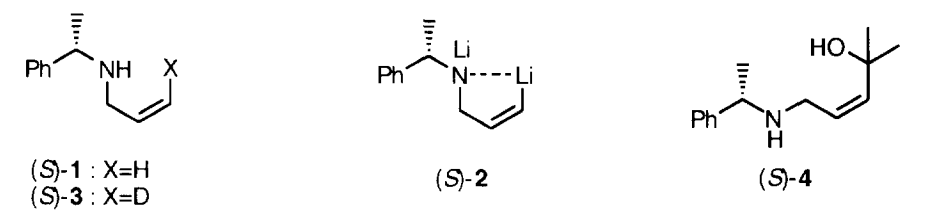
The carbonation of intermediate (*R*)-**2** with carbon dioxide (-50 to 20°C) followed by esterification (ethanol, hydrogen chloride) afforded initially the expected compound *cis*-(*R*)-**7** ($J_{HC=CH}$=11.5 Hz), which upon standing or in $CDCl_3$ solution (NMR sample) underwent *spontaneously* (12 to 24 h) complete isomerisation giving the corresponding *trans*-(*R*)-**7** ($J_{HC=CH}$=15.6 Hz) (Scheme 1 and Table 1, entry 6). Since this transformation does not take place under acidic conditions (esterification step) we think that a possible mechanistic pathway would involve a Michael/retro-Michael reaction through the corresponding aziridine intermediate **IV** shown in Scheme 2.



cis-(*R*)-**7** **IV** *trans*-(*R*)-**7**

Scheme 2.

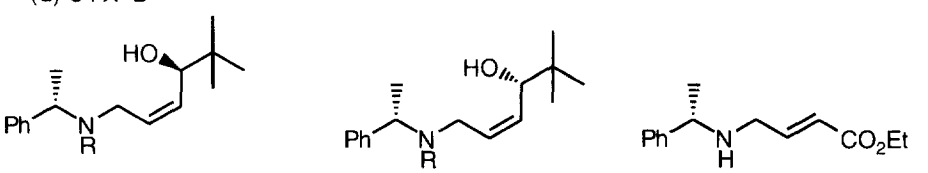
In order to prove the validity of the methodology described in Scheme 1 in the field of EPC-synthesis we carried out the same reactions starting from the enantiomeric allyl amine (*S*)-**1**, so through the corresponding intermediate (*S*)-**2** we isolated the expected products (*S*)-**3**, (*S*)-**4**, (*S,R*)-**6**, (*S,S*)-**6** [and the corresponding benzamides (*S,R*)-**6'** and (*S,S*)-**6'**] and *trans*-(*S*)-**7** [through the unstable *cis*-(*S*)-**7**] (Table 1, entries 7-11).



(*S*)-**1** : X=H
(*S*)-**3** : X=D

(*S*)-**2**

(*S*)-**4**



(*S,R*)-**6** : R=H
(*S,R*)-**6'** : R=PhCO

(*S,S*)-**6** : R=H
(*S,S*)-**6'** : R=PhCO

trans-(*R*)-**7**

The unequivocal assignement of the stereochemistry of aminoalcohols **6** was done by single-crystal analysis of compound (*S,S*)-**6'** (Figure 1)[6].

Table 1. Preparation of Chiral Amines **3-7**.

Entry	Starting material	Electrophile E+	Product[a] No.	Yield (%)[b]	R_f [c]	$[\alpha]_D^{22}$ (c)[d]	$J_{HC=CH}$(Hz)[e]
1	(*R*)-**1**	D_2O	(*R*)-**3**	91	0.32	+50.2 (0.98)	10.4
2	(*R*)-**1**	Me_2CO	(*R*)-**4**	58	0.09	+13.2 (0.70)	12.2
3	(*R*)-**1**	$(CH_2)_5CO$	(*R*)-**5**	45	0.16	+5.25 (1.22)	12.2
4	(*R*)-**1**	Bu^{t}CHO	(*R,R*)-**6**	61[f]	0.17	-13.2 (0.97)	9.5
5			(*R,S*)-**6**		0.17	+12.1 (1.06)	7.9
6	(*R*)-**1**	CO_2	*trans*-(*R*)-**7**	51[g]	0.36	+39.6 (1.05)	15.6
7	(*S*)-**1**	D_2O	(*S*)-**3**	90	0.32	-49.6 (1.08)	10.4
8	(*S*)-**1**	Me_2CO	(*S*)-**4**	65	0.09	-15.1 (1.32)	12.2
9	(*S*)-**1**	Bu^{t}CHO	(*S,R*)-**6**	53[f]	0.09	-13.1 (1.22)	7.9
10			(*S,S*)-**6**		0.17	+14.2 (0.84)	9.5
11	(*S*)-**1**	CO_2	*trans*-(*S*)-**7**	48[g]	0.36	-37.4 (1.23)	15.6

[a] All products **3-7** were >95% pure (GLC and/or 300 MHz ^{1}H NMR). [b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting material **1**. [c] Silica gel, hexane/ethyl acetate 1/1. [d] Dichloromethane; c given in g/100 ml. [e] From 300 MHz ^{1}H NMR, in deuteriochloroform. [f] A *ca.* 1:1 diastereoisomers mixture (300 MHz ^{1}H NMR) was obtained. [g] After esterification with ethanol/hydrogen chloride (see text).

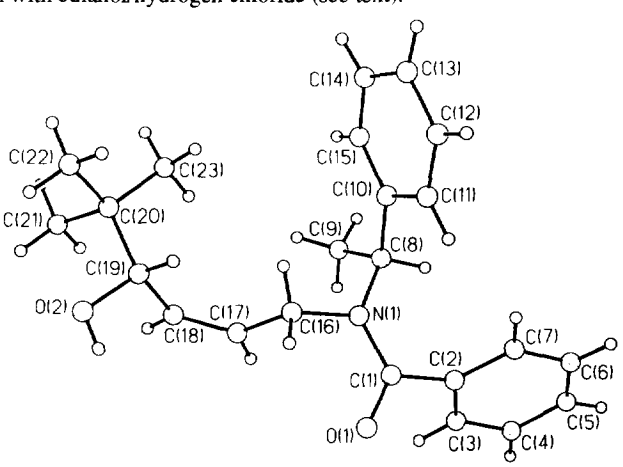
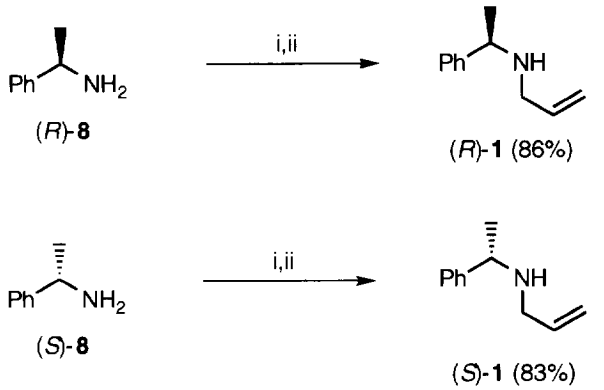


Figure 1. Ball-and-stick representation of the solid state structure of (*S,S*)-**6'**.

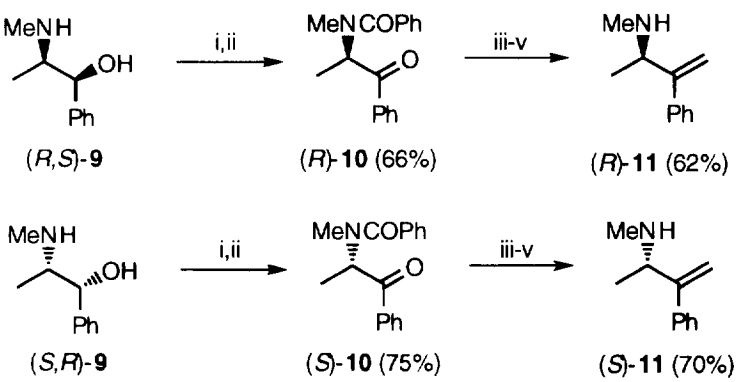
Starting amines **1** were prepared by allylation of the corresponding commercially available (*R*)- and (*S*)-α-methylbenzylamine (**8**)[7] in 83-86 isolated yield (Scheme 3).



Scheme 3. *Reagents and conditions*: i, Bu^{n}Li, THF, -50°C; ii, CH_2=$CHCH_2Br$, -50 to 20°C.

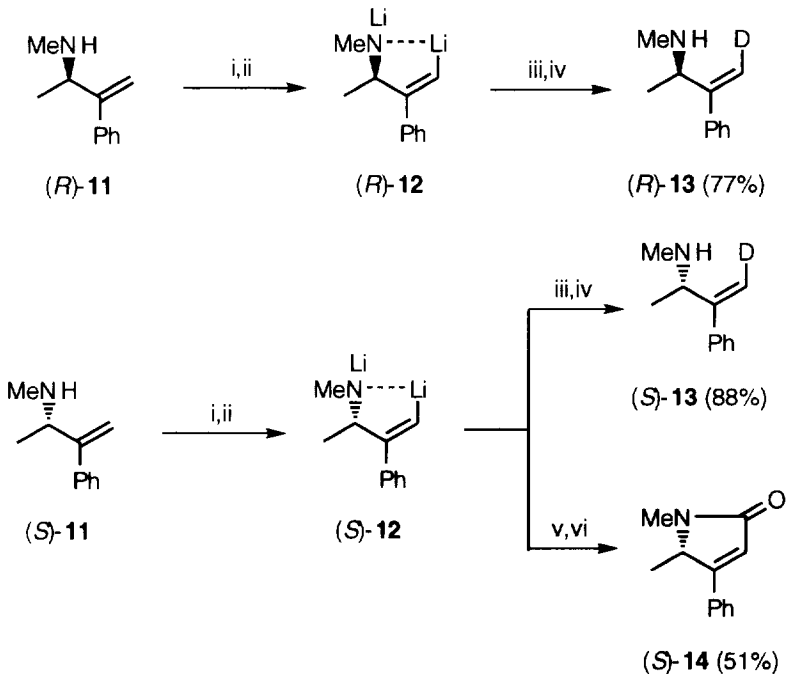
The optical purity of the products described in this paper is related to the starting chiral amines (**1**). The absence of any racemisation during the tandem lithiation/reaction with the electrophile was confirmed by transforming the chiral amine (*S*)-**3** into the corresponding (*R*)-*O*-(4-chloro-2-methylphenyl)lactic acid ammonium salt and further 300 MHz ^{1}H NMR analysis (≥96% e.e.)[8].

In the final part of this study we considered other type of chiral allylamines bearing substituents at the allylic moiety. Thus, starting amines **11** were prepared from commercially available aminoalcohols **9**[9] by the methodology described in Scheme 4: benzoylation of the amino group followed by PCC oxidation yielded compunds **10**, which after Wittig reaction with methylidene phosphorane and final treatment with an excess of methyllithium gave, after hydrolysis with water, the corresponding amines **11** (Scheme 4).



Scheme 4. *Reagents and conditions*: i, PhCOCl, NaOH, 0°C; ii, PCC, celite, CH_2Cl_2; iii, Ph_3P=CH_2, THF; iv 2.2 MeLi, -78°C; v, H_2O, -78 to 20°C.

The dilithiation of amines **11** as it was above described in Scheme 1 yielded the corresponding intermediates **12**, which upon deuterolysis with deuterium oxide afforded the expected chiral amines **13**. In the case of the starting material (*S*)-**11** the carbonation reaction followed by esterification -performed under the same reaction conditions shown in Scheme 1- led directly to the lactam (*S*)-**14**, this behaviour being completely different than those observed in the case of amines **1**. The presence of the substituents in the allyl group should play an important role to explain this difference.



Scheme 5. *Reagents and conditions*: i, Bu^{n}Li, THF, -50°C; ii, Bu^{t}Li, -50 to 20°C; iii, D_2O; iv, H_2O; v, CO_2 exc., -50 to 20°C; vi, EtOH, HCl (g).

From the results described in this paper we conclude that the possibility of preparing functionalised chiral organolithium intermediates opens a way to achive polyfunctionalised chiral molecules, since the organometallic component transfers not only the functionality but also the chiral information to the electrophile. Unfortunatly with prochiral electrophiles (carbonyl compounds) no induction was obtained due, probably, to the high reactivity of the mentioned intermediates; however, the chromatographic separation of the diastereoisomeric products allows the preparation of all possible enantiomerically pure products.

EXPERIMENTAL PART

General.- For general information see reference 5b.

Preparation of Starting Chiral Allylamines **1**. *General Procedure.*-To a cooled (-50°C) solution of the corresponding chiral amine **8** (1.28 ml, 10.0 mmol) in THF (100 ml) under argon was added a 1.6 M hexane

solution (11.0 mmol) of Bu^nLi, and to the resulting mixture allyl bromide (1.21ml, 11.0 mmol) was added. The temperature was allowed to rise to 20°C during *ca.* 3 h and stirring was continued for 15 h at the same temperature. The resulting mixture was hydrolysed with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated (15 mmHg). The resulting residue was purified by distillation under reduced pressure to give the title compounds (*R*)-**1** and (*S*)-**1**. Yields are given in Scheme 3; physical and spectroscopic data follow.

(R) N-*Allyl* -α-m*ethylbenzylamine* [(*R*)-**1**]: bp 58-59°C (1 mmHg); ν_{max} (film) 3300 (NH), 1640, 1600 cm^{-1}; δ_H 1.35 (3H, d, J = 6.4, CH_3), 1.62 (1H, br s, NH), 3.10 (2H, dd, J = 5.5, 1.2, CH_2N), 3.79 (1H, q, J = 6.4, CHN), 5.06 (1H, dt, J = 11.8, 1.2, CH*H*=CH), 5.12 (1H, d, J = 18.1, C*H*H=CH), 5.82-5.89 (1H, m, C*H*=CH_2), 7.20-7.35 (5H, m, ArH); δ_C 24.2 (CH_3), 50.2 (CH_2N), 57.5 (CHN), 115.6 (*C*H_2=CH), 126.6, 126.9, 128.4, 136.9, 145.5 (ArC, *C*H=CH_2); m/z 161 (M^+, 4%), 146 (71), 105 (76), 104 (43), 103 (28), 91 (24), 84 (16), 79 (25), 78 (51), 77 (83), 76 (12), 68 (10), 65 (14), 63 (23), 54 (61), 51 (98), 41 (100) (Found: M^+, 161.1209. $C_{11}H_{15}N$ requires M, 161.1204); $[\alpha]_D^{25}$ = +49.3 [c = 1.12 (CH_2Cl_2)].

(R) N-*Allyl* -α-*methylbenzylamine* [(*S*)-**1**]: boiling point and spectroscopic data were found to be the same than for (*R*)-**1**; (Found: M^+, 161.1182. $C_{11}H_{15}N$ requires M, 161.1204); $[\alpha]_D^{25}$ = -53.8 [c = 1.04 (CH_2Cl_2)].

Preparation of Chiral Amines **3-7**. *General Procedure.*- To a cooled (-50°C) solution of the corresponding chiral allyl amine **1** (0.16 ml, 1.0 mmol) was added succesively a 1.6 M hexane solution (1.1 mmol) of Bu^nLi and 1.6 M hexane solution (1.2 mmol) of Bu^tLi. The resulting mixture was allowed to rise to 20°C during *ca.* 2 h. Then the mixture was cooled at -78°C and the corresponding electrophile (1.2 mmol; 0.5 ml in the case of deuterium oxide; CO_2 was bubbled for 1 h) was added and the mixture was stirred at the same temperature for 1 h. When CO_2 was used as electrophile, the reaction solvents were evaporated (15 mmHg) and the resulting residue was treated with a 5 M ethanol solution (5 ml) of hydrogen chloride for 10 h before hydrolysis. The reaction mixture was hydrolysed with water, acidified with 2 M hydrochloric acid and extracted with ethyl acetate. The aqueous layer was then basified with 2 M sodium hydroxide and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated (15 mmHg). The resulting residue was purified by column chromatography (silica gel; hexane/ethyl acetate) and/or recrystallised or distilled (Kugelrohr) to yield pure products **3-7**. Compounds **6** could not be separated by column chromatography under different conditions, but the corresponding benzoyl derivatives **6'** were separated chromatographically. Benzoyl derivatives **6'** were prepared by benzoylation of aminoalcohols **6** with benzoyl chloride under basic conditions (2 M sodium hydroxide, 0°C, 2 h)[5c]. Debenzoylation of amidoalcohols **6'** was carried out by addition of a 1.6 M hexane solution (3 eq) of MeLi to a cooled (-78°C) solution of amidoalcohols **6'**. Stirring was continued for 1 h and then the reaction mixture was quenched as above to yield pure products **6**. Yields and physical data (R_f) are included in Table 1; other physical, analytical and spectroscopic data follow.

(R,Z)-N-*3-Deuterioallyl-α-methylbenzylamine* [(*R*)-**3**]: bp 58-59°C (1 mmHg); ν_{max} 3300 (NH), 1640, 1600 cm^{-1}; δ_H 1.35 (3H, d, J = 6.4, CH_3), 1.57 (1H, br s, NH), 3.10 (2H, dd, J = 5.5, 1.2, CH_2N), 3.83 (1H, q, J = 6.4, CHN), 5.06 (1H, dt, J = 10.4, 1.2, C*H*D=CH), 5.82-5.89 (1H, m, C*H*=CHD), 7.20-7.35 (5H, m, ArH); δ_C 24.1 (CH_3), 50.1 (CH_2N), 57.4 (CHN), 115.3 (t, J_{CD} = 23.8, *C*HD=CH), 126.5, 126.8, 128.3, 136.7, 145.4 (ArC, *C*H=CHD); m/z : 162 (M^+, 3%), 147 (94), 105 (52), 104 (21), 103 (13), 91 (28), 85 (33), 79 (28), 78 (18), 77 (54), 57 (13), 51 (35), 42 (100) (Found: M^+, 162.1272. $C_{11}H_{14}DN$ requires M, 162.1267).

(S,Z)-N-*3-Deuterioallyl-α-methylbenzylamine* [(*S*)-**3**]: boiling point and spectroscopic data were found to be the same than for (*R*)-**3**; (Found: M+, 162.1257. $C_{11}H_{15}N$ requires M, 162.1267).

(R,Z)-*2-Methyl-5-(*N-*α-methylbenzylamino)-3-penten-2-ol* [(*R*)-**4**][10]: ν_{max} 3600-3200 cm^{-1} (NH, OH); δ_H 1.23, 1.26 [6H, 2 s, $C(CH_3)_2$], 1.35 (3H, d, *J* = 6.4, $CHCH_3$), 3.08 (1H, ddd, *J* = 12.8, 6.1, 1.2, C*H*HN), 3.16 (1H, ddd, *J* = 12.8, 6.1, 1.2, CH*H*N), 3.64 (2H, br s, NOH, OH), 3.72 (1H, q, *J* = 6.4, CHN), 5.30-5.37 (1H, m, CH_2CH=CH), 5.58 (1H, dt, *J* = 12.2, 1.2, CH_2CH=C*H*), 7.18-7.36 (5H, m, ArH); δ_C 23.0 ($CHCH_3$), 31.3 [$C(CH_3)_2$], 44.0 (CH_2N), 58.0 (CHN), 70.7 (COH), 126.6, 126.6, 127.4, 128.7, 138.1, 143.5 (ArC, CH=CH); m/z : 204 (M+-CH_3, 14%), 201 (20), 106 (26), 105 (60), 103 (12), 93 (13), 82 (20), 81 (23), 79 (30), 77 (36), 59 (24), 56 (12), 51 (13), 43 (100).

(S,Z)-*2-Methyl-5-(*N-*α-methylbenzylamino)-3-penten-2-ol* [(*S*)-**4**][10]: spectroscopic data were found to be the same than for (*R*)-**4**.

(R,Z)-*1-[3-(*N-*α-methylbenzylamino)-1-propenyl]cyclopentanol* [(*R*)-**5**][10]: ν_{max} 3600-3200 cm^{-1} (NH, OH); δ_H 1.25-1.74 (10H, m, 5 x ring CH_2), 1.35 (3H, d, *J* = 6.4, $CHCH_3$), 3.11 (1H, ddd, *J* = 13.1, 6.1, 1.2, C*H*HN), 3.23 (1H, ddd, *J* = 13.1, 6.1, 0.9, CH*H*N), 3.78 (1H, q, *J* = 6.4, CHN), 4.11 (2H, br s, NOH, OH), 5.41-5.49 (1H, m, CH_2CH=CH), 5.68 (1H, dt, *J* = 12.2, CH_2CH=C*H*), 7.22-7.36 (5H, m, ArH); δ_C 22.1, 22.1 (2 x ring CH_2), 23.0 (CH_3), 25.6, 39.0, 39.2 (3 x ring CH_2), 44.1 (CH_2N), 57.9 (CHN), 71.4 (COH), 123.6, 126.5, 127.3, 128.6, 142.9, 143.9 (ArC, CH=CH); m/z 241 (M+-H_2O, 7%), 106 (18), 105 (84), 104 (17), 103 (25), 79 (37), 78 (19), 77 (56), 56 (58), 55 (38), 53 (15), 51 (17), 43 (39), 41 (100).

(3R,αR,Z)-*2,2-Dimethyl-6-(*N-*α-methylbenzylamino)-3-hexen-3-ol* [(*R,R*)-**6**][10]: ν_{max} 3500-3150 cm^{-1} (NH, OH); δ_H 0.87 [9H, s, $C(CH_3)_3$], 1.38 (3H, d, *J* = 6.7, $CHCH_3$), 2.56 (2H, br s, NOH, OH), 3.02 (1H, dd, *J* = 13.5, 4.9, C*H*HN), 3.24 (1H, dd, *J* = 13.5, 6.1, CH*H*N), 3.79 (1H, q, *J* = 6.7, CHN), 3.91 (1H, d, *J* = 6.4, CHO), 5.65-5.71 (2H, m, CH=CH), 7.22-7.36 (5H, m, ArH); δ_C 23.0 ($CHCH_3$), 25.6 [$C(CH_3)_3$], 34.9 [$C(CH_3)_3$], 44.2 (CH_2N), 57.9 (CHN), 75.5 (CHOH), 126.1, 127.2, 128.5, 129.6, 133.9, 144.6 (ArC, CH=CH); m/z : 232 (M+-CH_3, 2%), 106 (12), 105 (37), 79 (18), 77 (24), 69 (12), 57 (96), 43 (26), 41 (100).

(3S,αS,Z)-*2,2-Dimethyl-6-(*N-*α-methylbenzylamino)-3-hexen-3-ol* [(*S,S*)-**6**][10]: spectroscopic data were found to be the same than for (*R,R*)-**6**.

(3S,αR,Z)-*2,2-Dimethyl-6-(*N-*α-methylbenzylamino)-3-hexen-3-ol* [(*R,S*)-**6**]: mp 76-77°C (hexane/dichloromethane); ν_{max} 3500-3150 cm^{-1} (NH, OH); δ_H 0.88 [9H, s, $C(CH_3)_3$], 1.35 (3H, d, *J* = 6.7, $CHCH_3$), 2.78 (2H, br s, NOH, OH), 3.02 (1H, dd, *J* = 13.8, 2.3, C*H*HN), 3.16 (1H, dd, *J* = 13.8, 5.4, CH*H*N), 3.76 (1H, q, *J* = 6.7, CHN), 3.86 (1H, d, *J* = 6.3, CHO), 5.68-5.71 (2H, m, CH=CH), 7.23-7.32 (5H, m, ArH); δ_C 24.0 ($CHCH_3$), 25.5 [$C(CH_3)_3$], 34.7 [$C(CH_3)_3$], 44.1 (CH_2N), 58.2 (CHN), 75.2 (CHOH), 126.7, 127.2, 128.5, 129.6, 134.4, 144.4 (ArC, CH=CH); m/z : 232 (M+-CH_3, 1%), 106 (16), 105 (51), 79 (15), 77 (24), 69 (16), 57 (84), 55(10), 43 (21), 41 (100). Anal.Calcd. for $C_{16}H_{25}NO$: C, 77.67; H, 10.19; N, 5.66. Found: C, 77.21; H, 10.41; N, 5.30.

(3R,αS,Z)-*2,2-Dimethyl-6-(*N-*α-methylbenzylamino)-3-hexen-3-ol* [(*S,R*)-**6**]: analytical and spectroscopic data

were found to be the same than for (*R,S*)-**6**.

(3R,αR,Z)-*2,2-Dimethyl-6-(*N-*benzoyl*-N-*α-methylbenzylamino)-3-hexen-3-ol* [(*R,R*)-**6'**]: mp 133-134°C (hexane/dichloromethane); ν_{max} : 3600-3300 (OH), 1630 cm^{-1} (C=O); δ_H 0.88 [9H, s, $C(CH_3)_3$], 1.66 (3H, d, *J* = 7.0, $CHCH_3$), 3.15 (1H, br s, OH), 3.40 (1H, d, *J* = 15.2, CHO), 4.08-4.42 (2H, m, CH_2N), 5.07-5.16 (1H, m, CHN), 5.31-5.69 (2H, m, CH=CH), 7.25-7.45 (10H, m, ArH); δ_C 17.9 ($CHCH_3$), 25.5 [$C(CH_3)_3$], 34.2 [$C(CH_3)_3$], 57.1 (CH_2N), 60.3 (CHN), 73.6 (CHOH), 126.4, 127.6, 128.6, 128.7, 129.5, 131.9, 136.6, 139.9 (ArC, CH=CH), 172.0 (C=O); m/z 294 (M^+-But, 8%), 106 (11), 105 (100), 77 (32), 68 (13), 57 (12), 41 (10). Anal.Calcd. for $C_{23}H_{29}NO_2$: C, 78.58; H, 8.32; N, 3.99. Found: C, 77.98; H, 8.71; N, 3.75. $[\alpha]_D^{25}$ = +68.2 [c = 1.12 (CH_2Cl_2)].

(3S,αS,Z)-*2,2-Dimethyl-6-(*N-*benzoyl*-N-*α-methylbenzylamino)-3-hexen-3-ol* [(*S,S*)-**6'**]: physical and spectroscopic data were found to be the same than for (*R,R*)-**6'**. Anal.Calcd. for $C_{23}H_{29}NO_2$: C, 78.58; H, 8.32; N, 3.99. Found: C, 77.85; H, 8.82; N, 3.68. $[\alpha]_D^{25}$ = -71.3 [c = 1.01 (CH_2Cl_2)].

(3S,αR,Z)-*2,2-Dimethyl-6-(*N-*benzoyl*-N-*α-methylbenzylamino)-3-hexen-3-ol* [(*R,S*)-**6'**][10]: R_f 0.13 (hexane/ethyl acetate, 5/1); ν_{max} 3600-3300 (OH), 1630 cm^{-1}(C=O); δ_H 0.89 [9H, s, $C(CH_3)_3$], 1.65 (3H, d, *J* = 6.7, $CHCH_3$), 2.11 (1H, br s, OH), 4.06-4.33 (3H, m, CH_2N, CHO), 5.10-5.18 (2H, m, CHN, C*H*=CH), 5.54-5.73 (1H, m, CH=C*H*), 7.35-7.51 (10H, m, ArH); δ_C 17.5 ($CHCH_3$), 25.4 [$C(CH_3)_3$], 34.6 [$C(CH_3)_3$], 56.9 (CH_2N), 60.3 (CHN), 74.5 (CHOH), 126.2, 127.8, 128.6, 128.9, 129.4, 132.9, 136.7, 138.5 (ArC, CH=CH), 171.9 (C=O); m/z : 294 (M^+-But, 8%), 106 (10), 105 (100), 77 (26), 68 (11), 57 (22), 43 (13), 41 (14); $[\alpha]_D^{25}$ = +92.9 [c = 0.93 (CH_2Cl_2)].

(3R,αS,Z)-*2,2-Dimethyl-6-(*N-*benzoyl*-N-*α-methylbenzylamino)-3-hexen-3-ol* [(*S,R*)-**6'**][10]: R_f and spectroscopic data were found to be the same than for (*R,R*)-**6'**. $[\alpha]_D^{25}$ = -103.9 [c = 1.07 (CH_2Cl_2)].

Ethyl (R,Z)-4-*(*N-*α-Methylbenzylamino)-2-butenoate* [*cis*-(*R*)-**7**][11]: δ_H 1.22 (3H,t, *J* = 7.0, CH_2CH_3), 1.36 (3H, d, *J* = 6.7, $CHCH_3$), 2.33 (1H, br s, NH), 3.02 (2H, dd, *J* = 5.5, 1.9, CH_2N), 3.80 (1H, q, *J* = 6.7, CHN), 4.10 (2H, q, *J* = 7.3, CH_2CH_3), 5.77 (1H, dt, *J* = 9.8, 2.1, CH_2CH=C*H*), 6.23-6.29 (1H, m, CH_2CH=CH), 7.20-7.34 (5H, m, ArH); δ_C 14.1 (CH_2CH_3), 23.9 ($CHCH_3$), 45.7 (CH_2N), 57.9 (CHN), 59.9 (OCH_2), 120.3, 126.5, 126.5, 128.3, 144.9, 148.6 (ArC, CH=CH), 166.0 (C=O).

Ethyl (S,Z)-4-*(*N-*α-Methylbenzylamino)-2-butenoate* [*cis*-(*S*)-**7**][11]: spectroscopic data were found to be the same than for *cis*-(*R*)-**7**.

Ethyl (R,E)-4-*(*N-*α-Methylbenzylamino)-2-butenoate* [*trans*-(*R*)-**7**][10]: ν_{max} 3700-3300 (NH), 1705 cm^{-1} (C=O); δ_H 1.19 (3H, t, *J* = 7.0, CH_2CH_3), 1.28 (3H, d, *J* = 6.4, $CHCH_3$), 2.00 (1H, br s, NH), 3.02 (2H, dd, *J* = 5.5, 1.5, CH_2N), 3.72 (1H, q, *J* = 6.4, CHN), 4.10 (2H, q, *J* = 7.0, CH_2CH_3), 5.88 (1H, dt, *J* = 15.6, 1.5, CH_2CH=C*H*), 6.88 (1H, dt, *J* = 15.6, 5.5, CH_2CH=CH), 7.13-7.26 (5H, m, ArH); δ_C 14.1 (CH_2CH_3), 24.1 ($CHCH_3$), 47.9 (CH_2N), 57.5 (CHN), 60.2 (OCH_2), 121.3, 126.5, 127.0, 128.4, 144.8, 146.7 (ArC, CH=CH), 166.3 (C=O); m/z : 218 (M^+-CH_3, 43%), 190 (10), 144 (19), 128 (61), 118 (21), 105

(100), 104 (29), 103 (38), 91 (17), 85 (26), 82 (15), 77 (87), 68 (43), 55 (40), 54 (27), 51 (42), 45 (32); $[\alpha]_D^{25}$ = +39.6 [c = 1.05 (CH_2Cl_2)].

Ethyl (S,E)-4-*(*N-*α-Methylbenzylamino)-2-butenoate* [*trans*-(*S*)-**7**][10]: spectroscopic data were found to be the same than for [*trans*-(*R*)-**7**]. $[\alpha]_D^{25}$ = -37.4 [c = 1.23 (CH_2Cl_2)].

Preparation of Compounds **10**. *General Procedure.*- To a cooled (0°C) suspension of PCC (7.50 g, 35 mmol) and celite (7.50 g) in dichloromethane (100 ml) was added a solution of the corresponding *N*-benzoylephedrine [these were easily prepared by benzoylation of ephedrine chlorohydrates **9** with benzoyl chloride under basic conditions (2 M sodium hydroxide, 0°C, 2 h)][5c] in dichloromethane (15 ml). Stirring was continued at the same temperature for 3 h and the solid was filtered off and washed with dichloromethane. The organic layer was evaporated (15 mmHg) and the resulting residue was purified by column chromatography (silica gel; hexane/ethyl acetate) and recrystallised to yield pure products **10**. Yields are included in Scheme 4. Physical, analytical and spectroscopic data follow.

(R)-N-*Methyl*-N-*(1-metyl-2-oxo-2-phenyl)benzamide* [(*R*)-**10**]: mp 51-52°C (hexane/dichloromethane); ν_{max} 1690 (PhCOCH), 1640 cm^{-1} (PhCON); δ_H 1.49 (3H, d, *J* = 7.0, C*H*$_3$CH), 2.72 (3H, s, CH_3N), 6.21 (1H, q, *J* = 7.0, C*H*CH$_3$), 7.23-8.06 (10H, m, ArH); δ_C 12.8 (*C*H$_3$CH), 32.8 (CH_3N), 53.5 (CH_3*C*H), 126.6, 128.2, 128.3, 129.6, 133.4, 135.2, 135.7 (ArC), 171.0 (Ph*C*ON), 199.1 (Ph*C*OCH); m/z 267 (M^+, 0.6%), 162 (42), 106 (11), 105 (100), 77 (44), 51 (16), 44 (10). Anal.Calcd. for $C_{17}H_{17}NO_2$: C, 76.37; H, 6.41; N, 5.24. Found: C, 76.54; H, 6.44; N, 4.76. $[\alpha]_D^{25}$ = +99.7 [c = 1.22 (CH_2Cl_2)].

(S)-N-*Methyl*-N-*(1-metyl-2-oxo-2-phenyl)benzamide* [(*S*)-**10**]: physical and spectroscopic data were found to be the same than for (*R*)-**10**. Anal.Calcd. for $C_{17}H_{17}NO_2$: C, 76.37; H, 6.41; N, 5.24. Found: C, 76.75; H, 6.45; N, 4.85. $[\alpha]_D^{25}$ = -116.3 [c = 0.78 (CH_2Cl_2)].

Preparation of Starting Chiral Allylamines **11**. *General Procedure.*- To a solution of triphenylphosphine (1.56 g, 6.0 mmol) in THF (60 ml) was added iodomethane (0.85 g, 6 mmol) and the solution was stirred at 20°C for 4 h. A white solid was appearing slowly (phosphonium salt). Then, the mixture was cooled at -60°C and a 1.6 M hexane solution (6.5 mmol) of Bu^{n}Li was added, turning the reaction solution deep orange. After 30 min at the same temperature a THF solution (3 ml) of the corresponding ketobenzamide **10** (1.35 g, 5 mmol) was added dropwise. The reaction was allowed to rise to 25°C and stirring was continued for 10 h. After that the reaction mixture was cooled to -78°C and a 1.6 M hexane solution (8 mmol) of methyl lithium was added. Stirring was continued for 1 h and the resulting mixture was hydrolysed with water, acidified with 2 M hydrochloric acid and extracted with ethyl acetate. The aqueous layer was then basified with 2 M sodium hydroxide and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated (15 mmHg). The resulting residue was purified by distillation to yield pure products **11**. Yields are included in Scheme 4. Physical, analytical and spectroscopic data follow.

(R)-N-*Methyl-3-phenyl-3-buten-2-amine* [(*R*)-**11**]: bp 62-63°C (1 mmHg); ν_{max} 3280 cm^{-1} (NH); δ_H 1.25 (3H, d, *J* = 6.4, CHC*H*$_3$), 2.47 (3H, s, CH_3N), 3.65 (1H, q, *J* = 6.4, CHN), 4.17 (1H, br s, NH), 5.28 (1H, d, *J* = 1.0, C=C*H*H), 5.30 (1H, d, *J* = 1.0, C=CH*H*), 7.27-7.38 (5H, m, ArH); δ_C 20.6 (*C*HCH$_3$), 33.3 (CH_3N), 58.6 (CHN), 112.9 (C=*C*H$_2$), 126.8, 127.4, 128.2, 140.9, 150.9 (ArC, *C*=CH$_2$); m/z 161 (M^+, 12%), 146 (40), 131 (23), 115 (10), 91 (10), 77 (18), 58 (100), 51 (11), 50 (18) (Found: M^+, 161.1210.

$C_{11}H_{15}N$ requires M, 161.1204); $[\alpha]_D^{25}$ = -4.0 [c = 1.00 (CH_2Cl_2)].

(S)-N-*Methyl-3-phenyl-3-buten-2-amine* [(*S*)-**11**]: physical and spectroscopic data were found to be the same than for (*R*)-**11**. (Found: M+, 161.1201. $C_{11}H_{15}N$ requires M, 161.1204); $[\alpha]_D^{25}$ = +4.2 [c = 1.33 (CH_2Cl_2)].

Preparation of Chiral Compounds **13-14**. *General Procedure*.- To a cooled (-50°C) solution of the corresponding chiral allyl amine **11** (0.160 ml, 1.0 mmol) was added succesively a 1.6 M hexane solution (1.1 mmol) of Bu^nLi and 1.6 M hexane solution (1.2 mmol) of Bu^tLi. The resulting mixture was allowed to rise to 20°C during *ca.* 2 h. Then the mixture was cooled at -78°C and the corresponding electrophile (0.5 ml in the case of deuterium oxide; CO_2 was bubbled for 1 h) was added and the mixture was stirred at the same temperature for 1 h. When CO_2 was used as electrophile, the reaction solvents were evaporated (15 mmHg) and the resulting residue was treated with a 5 M ethanol solution (5 ml) of hydrogen chloride for 10 h before hydrolysis. The reaction mixture was hydrolysed with water, acidified with 2 M hydrochloric acid and extracted with ethyl acetate. The aqueous layer was then basified with 2 M sodium hydroxide and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated (15 mmHg). The resulting residue was purified by column chromatography (silica gel; hexane/ethyl acetate) and/or recrystallised or distilled (Kugelrohr) to yield pure products **13** and **14**. Yields are included in Table 5; other physical, analytical and spectroscopic data follow.

(R,Z)-*4-Deuterio*-N-*methyl-3-phenyl-3-buten-2-amine* [(*R*)-**13**]: bp 62-63°C (1 mmHg); ν_{max} 3280 cm^{-1} (NH); δ_H 1.19 (3H, d, *J* = 6.4, $CHCH_3$), 1.85 (1H, br s, NH), 2.41 (3H, s, CH_3N), 3.58 (1H, q, *J* = 6.4, CHN), 5.23 (1H, s, C=CHD), 7.26-7.37 (5H, m, ArH); δ_C 20.9 ($CHCH_3$), 33.9 (CH_3N), 58.85 (CHN), 112.1 (t, J_{CD} = 21.4, C=CHD), 126.85, 127.2, 128.1, 141.2, 151.6 (ArC, *C*=CHD); m/z 162 (M^+, 8%), 147 (24), 132 (10), 131 (12), 77 (10), 58 (100) (Found: M+, 162.1260. $C_{11}H_{14}DN$ requires M, 162.1267); $[\alpha]_D^{25}$ = -3.5 [c = 1.13 (CH_2Cl_2)].

(S,Z)-*4-Deuterio*-N-*methyl-3-phenyl-3-buten-2-amine* [(*S*)-**13**]: physycal and spectroscopic data were found to be the same than for (*R*)-**13**. (Found: M+, 16.1265. $C_{11}H_{14}DN$ requires M, 162.1267); $[\alpha]_D^{25}$ = +5.6 [c = 1.06 (CH_2Cl_2)].

(S)-*2,2,5,5-Tetrahydro-1,5-dimethyl-4-phenyl-2(1H)-pyrrolone* [(*S*)-**14**]: mp 124-125°C (hexane/dichloromethane); ν_{max} 3600-3300 (NH), 1670 cm^{-1} (C=O); δ_H 1.29 (3H, d, *J* = 6.7, $CHCH_3$), 3.01 (3H, s, CH_3N), 4.47 (1H, q, *J* = 6.7, CHN), 6.29 (1H, s, C=CH), 7.37-7.40 (5H, m, ArH); δ_C 17.4 ($CHCH_3$), 26.8 (CH_3N), 59.4 (CHN), 120.5 (C=CH), 126.7, 128.9, 129.7, 131.7, 160.2 (ArC, *C*=CH), 170.4 (C=O); m/z 187 (M^+, 5%), 56 (40), 42 (100). Anal.Calcd. for $C_{12}H_{13}NO$: C, 76.97; H, 7.00; N, 7.48. Found: C, 76.32; H, 7.12; N, 7.20. $[\alpha]_D^{25}$ = -0.7 [c = 1.31 (CH_2Cl_2)].

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REFERENCES AND NOTES

§ To whom correspondence on the X-ray structure should be addressed.

1. For the introduction of the term EPC-synthesis see: Seebach, D.; Hungerbühler, E. *Mod. Synth. Methods* **1980**, *2*, 91-173.
2. For an excellent general discussion see, for instance: Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1320-1367.
3. (a) Barluenga, J.; Fañanás, F. J.; Foubelo, F.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1988**, 1135-1136. (b) Barluenga, J.; Fañanás, F. J.; Foubelo, F.; Yus, M. *Tetrahedron Lett.* **1988**, *29*, 4859-4862. (c) Barluenga, J.; Foubelo, F.; Fañanás, F. J.; Yus, M. *J. Chem. Research (S)* **1989**, 200-201; *(M)* **1989**, 1524-1552.
4. For a review on functionalised organolithium compounds, see: Nájera, C.; Yus, M. *Trends Org. Chem.* **1991**, *2*, 155-181.
5. For recent accounts on chiral β-aminated organolithium compounds, see: (a) Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron Lett.* **1993**, *34*, 1649-1652. (b) Almena, J.; Foubelo, F.; Yus, M. *J. Org. Chem.* **1994**, *59*, 3210-3215. (c) Foubelo, F.; Yus, M. *Tetrahedron Lett.* **1994**, *35*, 4831-4834.
6. (a) Crystal data of (*S,S*)-**6'** (to be deposited with the Cambridge Crystallographic Data Centre): $C_{23}H_{29}NO_2$, M_r=351.47, monoclinic, space group $P2_1$, a=11.873(3), b=6.112(3), c=14.483(4) Å, β=105.37(2)°, V=1013.3(6) Å^3, Z=2, D=1.152 g·cm^{-3}. Data were from a CAD-4 diffractometer, MoKα radiation (graphite crystal monochromator, λ=0.71073 Å), μ=0.72 cm^{-1}, T=22-25±1°C. The structure was solved by direct methods (SHELXTL-PLUS[6b]). Hydrogen atoms were placed at idealised positions and treated as riding atoms, except for the OH group and the methyl groups, the torsion angles of which were derived from a Fourier map. The structure was refined to F^2_o, using all data (SHELXL-93[6c,d]). The enantiomorph was fixed according to the known stereochemistry at C(8). Final wR2=0.1116 for all 1476 reflections measured. R1 (for comparison purposes)=0.0802 for 625 reflections with $|F_o|>4\sigma(|F_o|)$. (b) SHELXTL-PLUS Release 4.21/V:© 1990, Siemens Analytical X-ray Instruments, Inc., Madison, Wisconsin. (c) Sheldrick, G. M., Shelxl-93: FORTRAN-77 program for the refinement of crystal structutes from diffraction data. University of Göttingen, 1993. (d) Sheldrick, G. M. *J. Appl. Cryst.* **1995**, in preparation.
7. Compounds (*R*)-**8** (98% pure, 96% ee) and (*S*)-**8** (98% pure, 99% ee) are commercially available from Aldrich.
8. Chinchilla, R.; Foubelo, F.; Nájera, C.; Yus, M. *Tetrahedron :Asymmetry*, in press.
9. These products are available from Aldrich as the corresponding hydrochlorides (see Experimental Part).
10. For products (*R*)-**4**, (*S*)-**4**, (*R*)-**5**, (*R,R*)-**6**, (*S,S*)-**6**, (*R,S*)-**6'**, (*S,R*)-**6'**, *trans*-(*R*)-**7** and *trans*-(*S*)-**7** was not possible to obtain the corresponding HRMS due to the low intensity of the M^+ signal.
11. Whole characterisation was not possible because of spontaneous decomposition to the *trans*-isomer.

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