

ASYMMETRIC SYNTHESIS OF β -HYDROXYACETAMIDES MEDIATED
BY ENANTIOMERICALLY PURE SULPHINYL DERIVATIVES

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Abstract. The aldol-type condensation of enantiomerically pure α -sulphinylacetamides is described. The stereochemical outcome of the reaction mainly depends on the nature of the base used to generate the enolate. Experimental evidences allow the identification of preferred reaction paths.

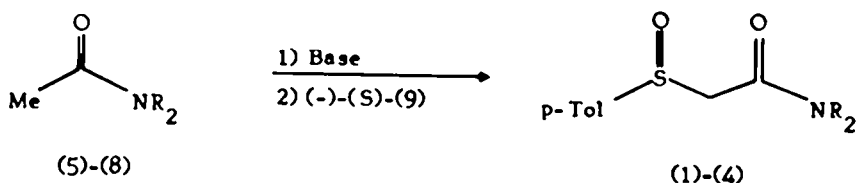
Aldol-type condensation are widely exploited as the key-step for the stereoselective construction of a number of stereocenters along an acyclic carbon backbone. While control of the relative stereochemistry of this process is well in hand, efficient reagents to secure high level of enantioselection are still the target of an impressive amount of recent research.¹⁻⁴

Good to excellent degrees of chiral discrimination have been achieved in aldol-type reactions by the use of optically active functionalized sulfoxides, such as α -sulphinyl-esters,⁵ -hydrazones,⁶ and -oxazolines.⁷ A preliminary account⁸ reported the synthesis of enantiomerically pure *p*-tolyl sulphinyl-N, N-dimethylacetamide (1) and its use as chiral acetamide enolate equivalent. In this synthon, the sulphinyl moiety represents the source of chirality, while providing the necessary substitution requirement. Indeed, both Evans¹ and Meyers⁹ have shown that only α -substituted enol acetate equivalents proved to be excellent aldehydes enantioface differentiating agents.

Stereospecific synthesis of α -sulphinylacetamides (1)-(3).

A straightforward approach to this class of compounds is represented by the reaction of α -metallated N,N-disubstituted amides¹⁰ (5)-(8) with diastereoisomerically pure, now commercially available, (-)-(S)-menthyl toluene-*p*-sulphinate (9), to afford compounds (1)-(4) in 55-83% yield. Sulphinyl derivatives (1)-(4) are stable compounds that can be prepared on a multigram scale and stored for at least 6 months in the refrigerator.

To compounds (1)-(3), obtained in optically active form, the (+)-(R) absolute configuration could be assigned on the basis of a number of data for similar Andersen type syntheses.^{6,11} The enantiomeric purity of sulfoxides (1)-(3) was checked by ¹H NMR spectroscopy in the presence of the chiral shift reagent tris [3-(heptafluoropropylhydroxymethylene)-(+)-camphorato] Europium(III), Eu(hfc)₃, and found to be $\geq 95\%$. It must be pointed out that, surprisingly, condensation of (8) with (-)-(S)-(9) resulted in practically racemic sulphinylamide (4), as further



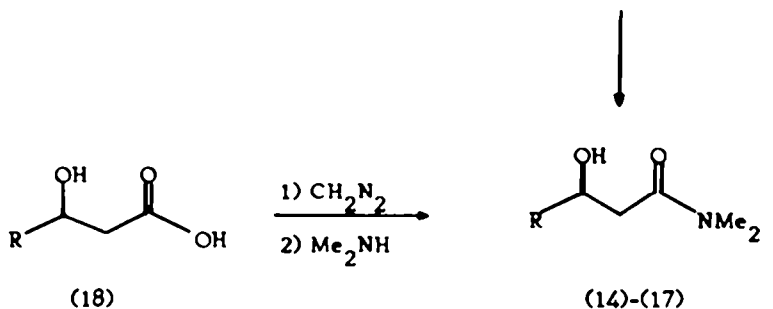
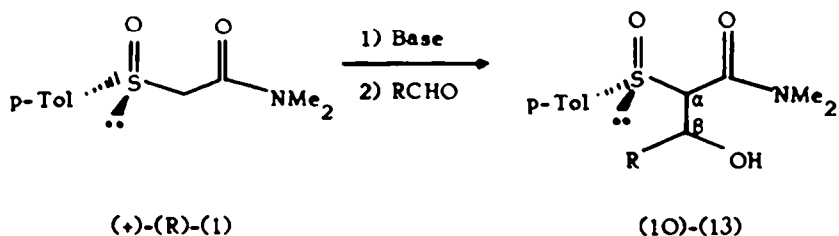
- (1), (5) R = Me
 (2), (6) R = $-(\text{CH}_2)_4-$
 (3), (7) R = *i*-Pr
 (4), (8) R = Ph

demonstrated by ^1H NMR spectroscopy in the presence of $\text{Eu}(\text{hfc})_3$. Reaction of α -metallated N,N-diphenylacetamide (8) is sluggish and much slower than that of N,N-dialkyl derivatives (5)-(7). This could result in a competitive attack of produced lithium menthoxide on (-)-(S)-(9) leading to racemization. A precedent of this observation was found in the synthesis of β -ketosulphoxides.¹² It is worth mentioning that a different approach to optically active α -sulphonylamides has been very

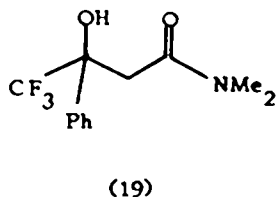
recently reported,¹³ via carbodiimide mediated condensation of a secondary amine with optically active (p-tolyl sulphonyl) acetic acid.

Aldol condensation of sulphonylamides.

As already reported,⁸ aldehydes react smoothly with the enolates derived from (+)-(R)-(1) at -78°C in THF. Several factors affect the stereochemical outcome of the process, the most important being the nature of the base.



- (10)-(14) R = Me
 (11)-(15) R = *i*-Bu
 (12)-(16) R = *i*-Pr
 (13)-(17) R = *t*-Bu



Indeed, condensation of lithium enolate derived from (+)-(R)-(1) followed by reductive desulphurization of the crude adducts (10)-(13), afforded (+)- β -hydroxyamides (14)-(17) in low to medium enantiomeric excess (e.e.) (Table 1).

On the other hand, the corresponding magnesium enolates gave (-)- β -hydroxyamides (14)-(17) with strikingly higher e.e. (Table 2).

In both cases several experimental conditions were screened in order to achieve top levels of enantioselections. As far as lithium enolates are concerned, they can be generated either by n -BuLi or by lithium diisopropylamide (LDA), without substantial variations of both chemical and optical yields (entries 5, 9). The optimum substrate: base molar

ratio is 1:1.1 (entries 3,5,6,8). Addition of hexamethylphosphoramide (HMPA) reversed and lowered at the mean time the degree of enantioselection (entries 3,7). Finally longer condensation times did not improve chemical yields, leaving the e.e. practically unchanged (entries 3,5).

As mentioned above, we investigate also the condensation of the magnesium enolates of (+)-(R)-(1) on the hypothesis that the strongly chelating magnesium counter-ion should provide a more rigid and stereodiscriminating transition state. Indeed, excellent stereoselections were observed in the best conditions, which involve the use of 0.55 molar equivalents t -BuMgBr, with a condensation time of 60 min. (entries 10-13, Table 2). Shorter

Table 1. Enantioselective synthesis^a of β -hydroxyacetamides (14)-(17) from lithium enolate of (+)-(R)-(1) and RCHO.

Entry	R	Base	Yield ^b (%)	$[\alpha]_D^{23}$ ^c	e.e. ^d (%)
1	Me	BuLi ^{e,f}	65	+ 30.3	47
2	Bu ⁱ	BuLi ^{e,f}	77	+ 14.3	45
3	Pr ⁱ	BuLi ^{e,f}	77	+ 21.6	34
4	Bu ^t	BuLi ^{e,f}	20	+ 6.6	8
5	Pr ⁱ	BuLi ^{e,g}	78	+ 19.4	31
6	Pr ⁱ	BuLi ^{h,f}	40	+ 10.6	17
7	Pr ⁱ	BuLi ^{e,f,i}	78	- 11.9	19
8	Pr ⁱ	BuLi ^{g,j}	74	+ 17.1	27
9	Pr ⁱ	LDA ^{e,g}	70	+ 21.6	34

^a For general condensation procedure see Experimental.

^b Overall yield of (14)-(17) from (+)-(R)-(1).

^c 1, CHCl₃.

^d As determined by ¹H NMR spectroscopy with the aid of Eu(hfc)₃.

^e 1.1 mol. equiv. of base.

^f Condensation time 3 min.

^g Condensation time 60 min.

^h 2.0 mol. equiv. of base.

ⁱ In the presence of 3.0 mol. equiv. of HMPA.

^j 0.55 mol. equiv. of base.

reaction times resulted in slightly lower e.e. (entries 12,14). Higher base: substrate molar ratio did not improve substantially chemical yields, while producing a small decrease of enantioselections (entries 14,16). A dramatic drop of both synthetic and optical yields was observed with a 1:0.1 substrate:base molar ratio or by working in the presence of HMPA, which is likely to prevent a strong chelation of magnesium by the sulphinyl oxygen (entries 12,17,18). A further comment is needed on the influence of the R residue of aldehyde. Independently on the nature of the counter-ion of the enolate, less sterically demanding

aldehydes undergo more efficient enantioface differentiation. In the case of lithium enolates e.e. range from 8 to 47% on passing from $R = Bu^t$ to $R = Me$ (Table 1). A similar trend holds also for magnesium enolates although at different and much satisfactory levels of enantioselections (e.e. 90-99%, Table 2). Unfortunately, several attempts to condense (+)-(R)-(1) with a variety of ketones ($PhCOCH_3$, Bu^tCOCH_3 , Pr^iCOCH_3) were disappointing. The only exception is represented by trifluoromethyl acetophenone, which affords the corresponding β -hydroxy amide (19) in 55% yield and in 67% e.e.

Table 2. Enantioselective synthesis^a of β -hydroxyacetamides (14)-(17) from magnesium enolate of (+)-(R)-(1) and $RCHO$.

Entry	R	Base	Yield ^b (%)	$[\alpha]_D^{23}$ ^c	e.e. ^d (%)
10	Me	$Bu^tMgBr^{e,f}$	68	-65.0	>99
11	Bu^i	$Bu^tMgBr^{e,f}$	71	-31.3	98
12	Pr^i	$Bu^tMgBr^{e,f}$	66	-59.7	95
13	Bu^t	$Bu^tMgBr^{e,f}$	56	-70.9	90
14	Pr^i	$Bu^tMgBr^{e,g}$	62	-53.5	85
15	Bu^i	$Bu^tMgBr^{g,h}$	73	-28.4	89
16	Pr^i	$Bu^tMgBr^{g,h}$	63	-43.3	69
17	Pr^i	$Bu^tMgBr^{f,i}$	31	-12.6	20
18	Pr^i	$Bu^tMgBr^{e,f,j}$	31	-32.9	52

^a For general condensation procedure see Experimental.

^b Overall yield of (14)-(17) from (+)-(R)-(1).

^c c 1, $CHCl_3$.

^d As determined by 1H NMR spectroscopy with the aid of $Eu(hfc)_3$.

^e 0.55 mol. equiv. of base.

^f Condensation time 60 min.

^g Condensation time 3 min.

^h 1.1 mol. equiv. of base.

ⁱ 0.1 mol. equiv. of base.

^j In the presence of 3.0 mol. equiv. of HMPA.

Stereochemical outcomes.

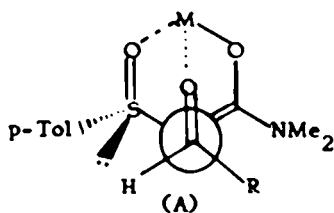
The absolute configuration of N,N-dimethyl- β -3-hydroxy-4-methylpentanamide (16) was unambiguously established as (-)-(S) by chemical correlation with the corresponding (-)-(S) acid (18).^{1,7} The latter was converted into the methylester (diazomethane in diethyl ether) which was then transformed into (-)-(S)-(16) (excess dimethyl amine in methanol). By a likely extension the (R),(R), and (S) absolute configuration can be tentatively assigned to (-)-(14), (-)-(15), and (-)-(17), respectively.⁷

In principle four diastereoisomeric transition states A-D are possible for the condensation of the enolate of α -sulphinylacetamides with aldehydes, assuming the commonly accepted Z geometry for amide enolates.¹ Such enolate configuration should receive further support by chelation between the metal and the sulphinyl oxygen.

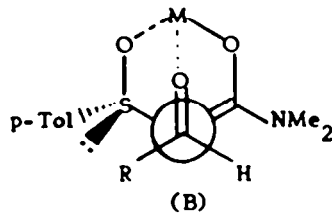
Transition states A and D (M = MgBr) both lead to β -hydroxyamides with the experimentally observed absolute configuration.

However, careful inspection of space filling CPK molecular models indicate that D can be disregarded because of heavy steric interactions between the p-tolyl group and the aldehyde R residue. Other experimental evidences in favour of transition state A are: *i*, the observed decrease in stereoselection met with when R residue becomes more sterically requiring (Table 2); and: *ii*, a similar trend found in condensation carried out on sulphonylamides (2)-(4) which display different ligands at nitrogen. Indeed, in ancillary experiments good degrees of chiral discrimination (66% e.e.) were maintained in the condensation of sulfoxide (2) with isobutyraldehyde, while (3) and (4) proved to be definitely less selective. A transition state similar to A was proposed by Solladie⁵ for the aldol type condensation of α -sulphinylesters.

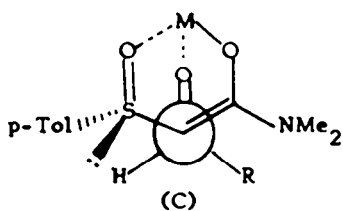
In the case of lithium enolates of (+)-(R)-(1) transition state B and C (M = Li) must be taken into account as the ones leading to β -hydroxyamides (+)-(14)-(17). Since



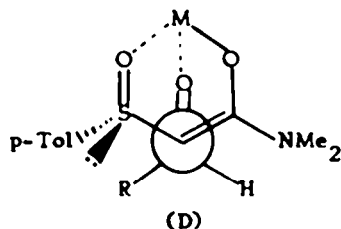
R, R, R



R, R, S



R, S, S



R, S, R

also in this case the larger is the aldehyde R residue the lower are the e.e., transition state C ($M = 1.1$) should be favoured. To substantiate this working hypothesis we isolated by flash chromatography the diastereoisomeric adduct (12) obtained from magnesium and lithium enolate of (+)-(R)-(1).

When the reaction was carried out with *t*-BuMgBr as base (0.55 mol. equiv.) only two out of four diastereoisomeric adducts (12a), $[\alpha]_D^{23} = +288.1^\circ$ (c 1, CHCl₃) and (12b), $[\alpha]_D^{23} = +54.0^\circ$ (c 0.2, CHCl₃) were isolated in $\sim 35:1$ ratio: (12a) and (12b) feature the same (R) absolute configuration at sulphur and, as shown by 200 MHz ¹H NMR spectroscopy, the same syn^{1,4} relative configuration at C_α and C_β.

The absolute configuration at C_β of the predominant isomer (12a) can be inferred as (R) from that (S) of desulphurized (-)-(16). Thus the (RRR) and (RSS) stereochemistry can be assigned to (12a) and (12b) respectively.

Therefore (12a) is produced via transition state A, and (12b) via transition state C.

When the reaction was carried out with *n*-BuLi as base (1.1 mol. equiv.) three out of four possible diastereoisomeric adducts (12a), $[\alpha]_D^{23} = +284.0^\circ$ (c 1, CHCl₃), (12b), $[\alpha]_D^{23} = +55.0^\circ$ (c 1, CHCl₃), and (12c)^{*} were obtained in 2.7:4.6:1 ratio.

The nice agreement between the optical rotation and the melting point values (see Experimental), together with superposable 200 MHz ¹H NMR spectra showed that the two major products deriving from the lithium enolate are identical to the two isolated from magnesium enolate. On the base of ¹H NMR spectroscopy anti relative configuration at C_α and

C_β could be assigned to (12c). Since the experimentally found e.e. for (+)-(R)-(16) is 31%, this can be obtained only if (12b) and (12c) display the same (S) configuration at C_β. Therefore the (RRS) absolute configuration can be assigned to (12c), which should be generated through transition state B. In conclusion, for magnesium enolate of (+)-(R)-(1) the major reaction path involves aldehyde approach with the hydrogen facing the sulphur lone pair (transition state A), and the minor path features aldehyde attack with the hydrogen facing the *p*-tolyl group (transition state C). The latter is the favoured attack in the case of lithium enolate and is accompanied by minor amount of product deriving from transition state A and B.

Therefore both enantiomers of β-hydroxyacetamides in good or excellent enantiomeric purities are obtained from a single chiral precursor.

EXPERIMENTAL

¹H, ¹³C NMR spectra were recorded on a Varian XL 200 instrument, using tetramethylsilane as internal standard and CDCl₃ as solvent. Infrared spectra were recorded with a Perkin Elmer 457 spectrometer. Optical rotations were measured on a Perkin Elmer 241 spectrometer. Elemental analyses were performed with a Perkin Elmer 240 instrument. Silica gel was used for analytical and column chromatography. Organic extracts were dried over sodium sulphate and filtered before removal of the solvent under reduced pressure. Anhydrous solvents were distilled under a nitrogen atmosphere before use: THF and diethylether from lithium aluminum hydride, HMPA and diisopropylamine from CaH₂, methanol from magnesium turnings. All reactions employing anhydrous solvent were run under argon. Aldehydes and ketones were commercial products and were distilled before use, as it was N,N-dimethylacetamide. Acetamides (6)-(8) were prepared from the corresponding amines and acetyl chloride; they had physical and spectral data in agreement with those reported in literature. Compound (6) had b.p. 80°C at 10 mmHg (Lit.¹⁴ b.p. 196°C); compound (7) had b.p. 110°C at 20 mmHg (Lit.¹⁵ b.p. 108°C at

^{*} (12c) was obtained together with (12b) as a 6:1 mixture of the two diastereoisomeric adducts. This mixture had $[\alpha]_D^{23} = +142.3^\circ$ (c 0.3, CHCl₃). The (12c):(12b) isomer ratio was determined by ¹H NMR spectroscopy.

15 mmHg): compound (8) had m.p. 101°C (Lit.¹⁶ m.p. 100°C). (-)-(S)-p-Toluene methyl sulphinate (9), now commercially available from Fluka, had $[\alpha]_D^{25} = -202.5^\circ$ (c 1, acetone).⁵

Synthesis of sulphinylacetamides (1)-(4).

To a stirred solution of diisopropylamine (2.9 ml, 20 mmol) in THF (50 ml) at 0°C, a 1.35 normal solution of n-BuLi in hexane (15 ml) is added. The mixture is stirred at 0°C for 15 min., then cooled at -78°C and the proper acetamide (20 mmol) in THF (20 ml) is added dropwise. The reaction mixture is warmed up at -40°C, cooled again at -78°C and a solution of (-)-(S)-(9) (2.94 g, 10 mmol) in THF (20 ml) is added and stirring is continued at -78°C for 15 min (in the case of compound (4) the reaction is much slower and overnight stirring at 0°C is required). The reaction is quenched with saturated ammonium chloride solution (30 ml) and the organic phase separated. The aqueous phase is extracted twice with dichloromethane (100 ml), and the combined organic phases dried and evaporated in vacuo. The resulting oil is washed with pentane and then with diisopropylether, which makes compounds (1), (2), and (4) solids, while (3) remains a thick oil. Compound (1), 83% yield, had m.p. 64-66°C; $[\alpha]_D^{25} = +192.2^\circ$ (c 1, CHCl₃). Found: C% 58.57; H% 6.69; N% 6.24. C₁₁H₁₅NO₂S requires: C% 58.63; H% 6.71; N% 6.21. ¹H NMR: δ 7.51-7.20 (AA'BB' system, 4H, aromatic protons); 3.92-3.60 (AB system, 2H, CH₂); 2.82, 2.80 (2s, 6H, N(CH₃)₂); 2.28 (s, 3H, CH₃-Ar).

Compound (2), 75% yield, had m.p. 103-105°C $[\alpha]_D^{25} = +173.3^\circ$ (c 1, CHCl₃). Found: C% 62.20; H% 6.85; N% 5.52. C₁₃H₁₇NO₂S requires: C% 62.12; H% 6.81; N% 5.57. ¹H NMR: δ 7.64-7.33 (AA'BB' system, 4H, aromatic protons); 4.00-3.64 (AB system, 2H, CH₂); 3.58-3.05 (m, 4H, CH₂-N-CH₂); 2.40 (s, 3H, CH₃Ar); 2.00-1.64 (m, 4H, CH₂-CH₂N).

Compound (3), 77.5% yield, had $n_D^{27} = 1.5378$; $[\alpha]_D^{27} = +90.5^\circ$ (c 1, CHCl₃). Found: C% 63.94; H% 8.20; N% 5.03. C₁₅H₂₃NO₂S requires: C% 64.02; H% 8.24; N% 4.98. ¹H NMR: δ 7.40-7.10 (AA'BB' system, 4H, aromatic protons); 3.85-3.40 (AB system, 2H, CH₂); 3.30 (m, 2H, CH(CH₃)₂); 2.20 (s, 3H, CH₃-Ar); 1.30-0.60 (m, 12H, (CH₃)₂CH).

Compound (4), 55% yield, had m.p. 165-166°C. Found: C% 72.09; H% 5.47; N% 4.03. C₂₁H₁₉NO₂S requires: C% 72.17; H% 5.48; N% 4.01. ¹H NMR: δ 7.60-7.35 (AA'BB' system, 4H, C₆H₄SO); 7.40-7.00 (m, 10H, N(C₆H₅)₂); 4.06-3.72 (AB system, 2H, CH₂); 2.48 (s, 3H, CH₃-Ar).

Synthesis of (14)-(17) via lithium enolates.

The procedure for (+)-(16) is typical: to a stirred solution of (+)-(R)-(1) (225.3 mg, 1 mmol) in THF (50 ml) at -78°C, a 1.35 normal

solution of n-BuLi in hexane is added (see Table 1 for substrate: base molar ratios). After 30 min at -78°C isobutyraldehyde (0.28 ml, 3 mmol) is added at once. After the required condensation time (see Table 1) the reaction is quenched by addition of saturated ammonium chloride solution (5 ml) and the organic phase separated. The aqueous layer is extracted twice with dichloromethane (25 ml), the combined organic phases dried and evaporated in vacuo. The crude residue is taken into dry methanol (15 ml) and anhydrous sodium dihydrogen phosphate (1.2 g) is added. To the resulting slurry, cooled at -15°C, 8% sodium amalgam (1.5 g) is added in one portion. The mixture is stirred at -15°C for 1h, then filtered and added of saturated ammonium chloride solution (5 ml). The organic solvent is evaporated in vacuo and the resulting aqueous phase extracted twice with dichloromethane (20 ml). The organic phase is dried and concentrated to give a crude oil which is purified by flash chromatography (diethylether as eluent) to give (+)-(16). Compounds (14)-(17) are thick oils that become solids when stored in the refrigerator at -20°C. β -Hydroxyacetamide (14) had ¹H NMR spectral data in agreement with those reported for its racemic analogue.¹⁰

Compound (15): C% 62.45; H% 11.10; N% 8.03. C₉H₁₉NO₂ requires: C% 62.39; H% 11.05; N% 8.08. ¹H NMR: δ 4.22 (bs, 1H, OH); 4.04 (X part of an ABX system, 1H, CH-O); 2.95, 2.91 (2s, 6H, N(CH₃)₂); 2.44-2.14 (AB part of an ABX system, 2H, CH₂CO); 1.90-1.66 (m, 1H, CH(CH₃)₂); 1.56-1.00 (AB part of an ABMX system, 2H, CH-CH₂-CH); 0.89 (d, 6H, (CH₃)₂CH).

Compound (16): C% 60.40; H% 10.75; N% 8.81. C₈H₁₇NO₂ requires: C% 60.34; H% 10.76; N% 8.79. ¹H NMR: δ 4.00 (bs, 1H, OH); 3.50 (X part of an ABX system, 1H, CH-O); 2.72, 2.68 (2s, 6H, NCH₃)₂); 2.24-1.90 (AB part of an ABX system, 2H, CH₂CO); 1.50-1.31 (m, 1H, CH(CH₃)₂); 0.65 (t, 6H, (CH₃)₂CH).

Compound (17): C% 62.38; H% 11.00; N% 8.12. C₉H₁₉NO₂ requires: C% 62.39; H% 11.05; N% 8.08. ¹H NMR: δ 4.16 (bs, 1H, OH); 3.64 (X part of an ABX system, 1H, CH-O); 2.97, 2.93 (2s, 6H, N(CH₃)₂); 2.33-2.08 (AB part of an ABX system, 2H, CH₂CO); 0.88 (s, 9H, (CH₃)₃C).

Synthesis of (14)-(17) via magnesium enolates.

The procedure for (-)-(16) is typical: to a stirred solution of (+)-(R)-(1) (225.3 mg, 1 mmol) in THF (50 ml) kept at -78°C, a 0.51 normal solution of t-BuMgBr in diethylether is added (see Table 2 for base:substrate molar ratios). The enolate precipitates to give a white suspension. After 30 min stirring at -78°C isobutyraldehyde (0.28 ml, 3 mmol) is added at once. After the required condensation time (see Table 2) the reaction is worked up as described above for the condensation of lithium enolates to give (14)-(17).

Synthesis of (19) from (+)-(R)-(1).

To the magnesium enolate of (+)-(R)-(1), prepared as described above (0.55 mol. equiv. of base), trifluoromethylacetophenone (0.41 ml, 3 mmol) is added at once. After 15 h at -78°C the reaction is worked up in the usual way. Compound (19) is isolated by flash chromatography (petroleum ether:diethylether 7:3 mixture as eluent) in 55% yield. It has m.p. $39-40^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{25} = +47.9^{\circ}$ (c 1, CHCl_3). Found: C% 55.04; H% 5.36; N% 5.40. $\text{C}_{12}\text{H}_{14}\text{F}_3\text{NO}_2$ requires: C% 55.16; H% 5.40; N% 5.36. ^1H NMR: δ 7.58 (bs, 1H, OH); 7.44-7.14 (m, 5H, aromatic protons); 3.14-3.02 (AB system, 2H, CH_2CO); 3.05, 2.88 (2s, 6H, $\text{N}(\text{CH}_3)_2$).

Enantiomeric excess determination.

The enantiomeric purities of compound (1)-(4), (14)-(17), and (19) were checked by ^1H NMR spectroscopy with the aid of the chiral shift reagent $\text{Eu}(\text{hfc})_3$ in condition pre-established with their racemic counterparts. A 5:1 sample:shift reagent molar ratio generally gave satisfactory peaks separations. A good agreement between the optical rotation values and the e.e. evaluated by ^1H NMR was observed for (14)-(17).

Separation of the diastereomeric components of adduct (12).

The crude product of the condensation of isobutyraldehyde with the lithium enolate of (+)-(R)-(1) is flash chromatographed with a 93:7 diethyl ether:isopropanol mixture as eluent. Starting from 1 mmol of (+) (1), 78 mg of (12a), m.p. $91-93^{\circ}\text{C}$, 133 mg of (12b), m.p. $106-109^{\circ}\text{C}$, 29 mg of (12c) were obtained (see text). The assignment of *anti* or *syn* relative stereochemistry at C_α and C_β rests on the values of the coupling constants $\text{H}-\text{C}_\alpha-\text{C}_\beta-\text{H}$. For the *syn* isomers, (12a) and (12b), $J = 3.7$ Hz; for the *anti* isomer, (12c), $J = 7.6$ Hz. In a similar way, starting from the magnesium enolate of (+)-(R)-(1) and isobutyraldehyde, 208 mg of (12a), m.p. $92-94^{\circ}\text{C}$, and 6 mg of (12b), m.p. $107-110^{\circ}\text{C}$ were obtained (see text).

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References.

1. D.A. Evans, J.V. Nelson, and T.R. Taber, *Top. Stereochem.*, 1982, **13**, 1.
2. T. Mukaiyama, *Org. React.*, 1981, **203**.
3. C.H. Heathcock, *Science*, 1981, **214**, 395.
4. S. Masamune, *Heterocycles*, 1984, **21**, 107.
5. G. Solladié, F. Matlouhi-Moghadam, C. Luttmann, and C. Mioskowski, *Helv. Chim. Acta*, 1982, **65**, 1602.
6. L. Colombo, C. Gennari, G. Poli, C. Scolastico, R. Annunziata, M. Cinquini, and F. Cozzi, *J.C.S. Chem. Commun.*, 1983, 403; L. Colombo, C. Gennari, G. Poli, C. Scolastico, R. Annunziata, M. Cinquini, and F. Cozzi, *J.C.S. Perkin Trans. 1*, in press; R. Annunziata, S. Cardani, M. Cinquini, F. Cozzi, A. Gilardi, G. Poli, and C. Scolastico, *J.C.S. Perkin Trans. 1*, in press.
7. R. Annunziata, M. Cinquini, F. Cozzi, and A. Gilardi, *Synthesis*, 1983, 1016.
8. R. Annunziata, M. Cinquini, F. Cozzi, F. Montanari, and A. Restelli, *J.C.S. Chem. Commun.*, 1983, 1138.
9. A.I. Meyers and P.J. Reider, *J. Am. Chem. Soc.*, 1979, **101**, 2501, and references therein.
10. R.P. Woodbury and M.W. Rathke, *J. Org. Chem.*, 1977, **42**, 1688.
11. M. Mikolajczyk and J. Drabowicz, *Top. Stereochem.*, 1982, **13**, 333; G. Solladié, *Synthesis*, 1981, 185.
12. R. Annunziata, M. Cinquini, and F. Cozzi, *J.C.S. Perkin Trans. 1*, 1979, 1687.
13. P. Magnus, T. Gallagher, P. Brown, and J.C. Huffman, *J. Am. Chem. Soc.*, 1984, **106**, 2105.
14. A.W. Campbell and P.F. Tryon, *Ind. Eng. Chem.*, 1953, **45**, 125.
15. S. Komori, M. Okahara, and E. Shinsugi, *Technol. Repts. Osaka Univ.*, 1958, **8**, 497; *C.A.* 1959, **53**, 18874f.
16. S. Stephanou, C.A. VanderWerf, and H.H. Sisler, *J. Am. Chem. Soc.*, 1948, **70**, 264.