Enantiomerically Pure Sulphinyl-4,5-dihydroisoxazoles. Part 1. Stereocontrolled Synthesis of Optically Active β-Ketols and γ-Amino Alcohols

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exo-Metallation of racemic 3-methyl-4,5-dihydroisoxazoles and reaction of the products with (−)-(*S*)-menthyl toluene-*p*-sulphinate afforded diastereoisomeric 3-sulphinylmethyl derivatives which can be separated and individually converted either into the corresponding enantio- and diastereoisomerically pure 4,5-dihydroisoxazoles or β-ketols, depending on the desulphurization conditions; furthermore, stereoselective reduction of the former provides an entry to optically active γ-amino alcohols.

Intermolecular or intramolecular cycloaddition of nitrile oxides[1] or silyl nitronates[2] to olefins affords 4,5-dihydroisoxazoles (2-isoxazolines), versatile synthons for a variety of β-ketols[3] or γ-amino alcohols.[4] The key feature of the process is the stereospecificity of the cyclization, so that the relative configuration at the stereocentres in the ring, and hence at the stereocentres of the target molecules, can be pre-determined at will by the configuration of the starting alkene. Furthermore, in the conversion of isoxazolines into γ-amino alcohols, proper choice of the reducing agent secures high levels of stereoselection at the newly formed stereocentre.[4]

Control of the absolute stereochemistry is a more elusive goal. In principle, although it can be achieved by starting either with optically active 1,3 dipoles[5] or alkenes,[6] both approaches result in only moderate degrees of chiral discrimination, severe structural requirements limiting greater success.

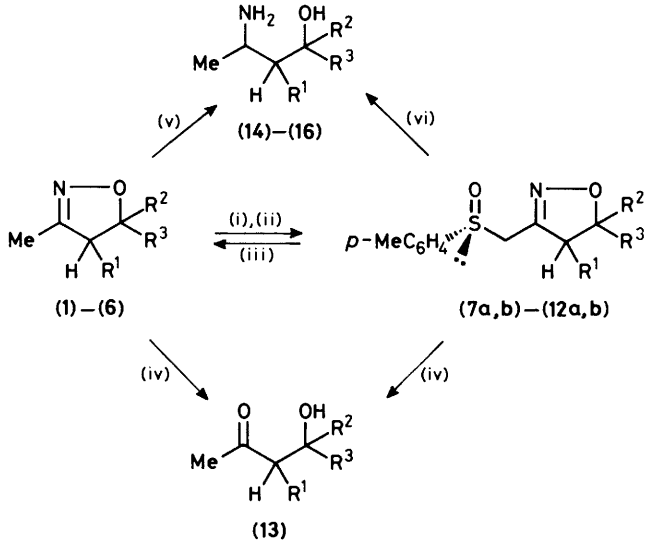
As reported in a preliminary note,[7] an alternative strategy involves the resolution of chiral but racemic 2-isoxazolines (**1**)—(**6**) *via* their sulphinyl derivatives. In our work, *exo*-metallated compounds (**1**)—(**6**) were treated with commercially available (−)-(*S*)-menthyl toluene-*p*-sulphinate to give 3-*p*-tolylsulphinylmethyl-4,5-dihydroisoxazoles (**7a,b**)—(**12a,b**). The Andersen-type synthesis, as expected, proceeded with complete inversion of chirality at sulphur and without epimerization of the stereocentre(s) in the heterocyclic ring: as a consequence, mixtures of only two diastereoisomeric sulphinylisoxazolines were generated, to which the (*R*) absolute configuration at sulphur could be assigned (Scheme 1).

In the synthesis of compounds (**7**)—(**12**), 2 equiv. of metallated 2-isoxazoline are employed, and therefore kinetic resolution of (**1**)—(**6**) is, in principle, possible. Unfortunately, the extent of stereoselection in this process was low, and the diastereoisomeric excess for (**7**)—(**12**) did not exceed a 3:2 ratio. However column chromatography or, in some instances, fractional crystallization, allowed a clean separation of the diastereoisomeric mixtures into optically pure derivatives (Table 1).

Subsequent cleavage of the C–S bond by Na–Hg in the presence of NaH_2PO_4 afforded in practically quantitative yield the corresponding enantiomerically pure 3-methyl-4,5-dihydroisoxazoles (Table 2). Thus, access to both enantiomers of these compounds is secured.

According to a literature procedure,[3] Raney–nickel catalysed hydrogenation in acidic medium of the isoxazoline ring leads to β-ketols, the cycloaddition–ring opening sequence being synthetically equivalent to a stereoselective aldol condensation.

The nature of the catalyst suggested a direct conversion of stereoisomerically pure sulphinylisoxazolines into optically pure ketols in a high-yielding, one-pot procedure involving simultaneous ring opening and desulphurization. Thus,



(**1**); (**7a,b**); (**14**) $R^1 = R^2 = H$; $R^3 = Bu^t$
(**2**); (**8a,b**); $R^1 = R^2 = H$; $R^3 = n\text{-}C_5H_{11}$
(**3**); (**9a,b**); $R^1 = R^2 = (CH_2)_3$; $R^3 = H$
(**4**); (**10a,b**);(**15**) $R^1 = Me$; $R^2 = p\text{-}MeOC_6H_4$; $R^3 = H$
(**5**); (**11a,b**); (**16**) $R^1 = p\text{-}MeOC_6H_4$; $R^2 = Me$; $R^3 = H$
(**6**); (**12a,b**); (**13**) $R^1 = H$; $R^2 = Me$; $R^3 = Ph$.

Scheme. *Reagents:* i, lithium di-isopropylamide (LDA); ii, menthyl toluene-*p*-sulphinate; iii, Na–Hg, NaH_2PO_4; iv, Ni–Ra, HCl, H_2; v, $LiAlH_4$; vi, $NiCl_2$–BH_4^-. In compounds (**3**) and (**9a,b**): *cis* relative stereochemistry at C-4 and C-5 of the isoxazoline ring; in compounds (**4**), (**5**), (**10a,b**), (**11a,b**), (**15**), and (**16**): *trans* stereochemistry.

compound (**13**), $[\alpha]_D^{23}$ −5.1, $[\alpha]_D^{23}{}_{365}$ +37.8 (*c* 1 in $CHCl_3$), was obtained starting from (**12b**) or from (−)-(**6**) in 80 and 82% yield respectively.

In compounds such as (**7**)—(**12**) the presence of the sulphoxide group can be exploited for further synthetic elaboration, before unmasking of the functionalities latent in the heterocyclic ring.

The 3-step synthesis of (+)-(*S*)-gingerol from (**8b**),[7] and the highly stereoselective aldol condensations carried out on diastereoisomerically pure compounds (**7**), (**8**), and (**11**) to give, eventually, β,β′-dihydroxy ketones[8] proved the versatility of these substrates.

As mentioned above, a great deal of work has been devoted to the stereoselective conversion of 2-isoxazolines into γ-amino alcohols.[4] Jäger's pioneering work showed that in the formation

Table 1. Synthesis of 3-*p*-tolylsulphinylmethyl-4,5-dihydroisoxazoles (**7a,b**)—(**12a,b**).

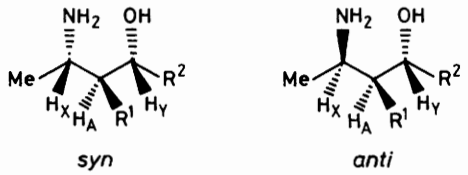
Compound	Yield (%)	Diastereoisomeric[a] ratio a:b	Diastereoisomer (a)[b] $[\alpha]_D^{23c}$	Diastereoisomer (a)[b] M.p. (°C)	Diastereoisomer (b)[b] $[\alpha]_D^{23c}$	Diastereoisomer (b)[b] M.p. (°C)
(**7a,b**)	67	46:54	+337.5	94—96	+140.3	79—81
(**8a,b**)	80	45:55	+297.5	70—72	+134.4	63—65
(**9a,b**)	84	40:60	+279.0	78—81	+79.8	82—84
(**10a,b**)	75	55:45	+328.3	130—131	*d*	
(**11a,b**)	76	46:54	+83.2	118—120	+262.2	89—91
(**12a,b**)	95	42:58	+263.8	102—104	+167.5	100—102

[a] As determined by ^{1}H n.m.r. spectroscopy. [b] Diastereoisomers (a) have higher R_f values in column chromatography than their (b) counterparts. [c] *c* 1 in $CHCl_3$. Some concentration dependence of optical rotation was observed: generally stronger molar rotations were observed for lower concentrations. [d] Compound (**10b**) could not be isolated free of (**10a**).

Table 2. Synthesis of enantiomerically pure 2-isoxazolines.

Compound	Yield (%)	$[\alpha]_D^{23a}$
(+)-(**1**)	*b*	+119.5
(−)-(**1**)	*b*	−121.0
(+)-(**4**)	90	+208.0
(−)-(**5**)	91	−269.5
(+)-(**5**)	89	+270.6
(−)-(**6**)	98	−40.0

[a] *c* 0.2 in $CHCl_3$. [b] Volatile product, chromatographic yield 90%.



(**14**)—(**16**)

Figure

of the new stereocentre the sense and the extent of the stereoselection depend on several factors, the most important being the nature of the reducing species, as well as the stereochemistry and the relative steric requirements of the substituents at C-5. Having in hand a reliable entry to enantiomerically pure 2-isoxazolines, we studied their conversion into optically active γ-amino alcohols (Table 3).

In agreement with Jäger's conclusion[9] we observed that in the $LiAlH_4$ reduction of (**1**) and (**4**) the extent of diastereoselection depends on the bulkiness of the substituent at C-5. Indeed racemic (**1**) and (**4**) gave the corresponding γ-amino alcohols in *syn*:*anti*[10,*] diastereoisomer ratios, of 25:1 and 5.5:1 respectively. However, in compound (**5**) the presence, in a *trans* arrangement, of a much bulkier substituent at C-4 than at C-5, resulted in preferential attack of the reducing species from the side opposite to the aromatic ring, leading to a 2.5:1 isomer ratio, in favour of the product having the *anti* relative stereochemistry shown in the Figure (as demonstrated by n.O.e. measurements, see Experimental section).

When the reaction was repeated on enantiomerically pure compounds (−)-(**4**), (+)-(**5**), and (−)-(**5**), the corresponding γ-amino alcohols (−)-(**15**), $[\alpha]_D^{23}$ −12.3 (*c* 1 in $CHCl_3$), (+)-(**16**), $[\alpha]_D^{23}$ +14.7 (*c* 1 in $CHCl_3$), and (−)-(**16**), $[\alpha]_D^{23}$ −14.5 (*c* 1 in $CHCl_3$) were obtained, respectively, in the above reported isomer ratios and in ≥ 90% yield.

Also, in this case, we thought that a one-step conversion of sulphinylisoxazoline into γ-amino alcohols would have been valuable. Since cleavage of C–S bonds† by borohydrides in the presence of nickel(II) salts has been reported[11] and borohydrides are known to open the isoxazoline ring,[9] we extended this method to our substrates. Indeed reduction of compounds (**7a**) and (**7b**) with $Zn(BH_4)_2$–$NiCl_2$ in methanol afforded compound (**14**) in quantitative yield. Unfortunately, stereoselections were poor, the *syn*:*anti* ratios being 7:3 and 2:1 starting from compounds (**7a**) and (**7b**), respectively. Sodium borohydride proved to be even less selective giving a 3:2 ratio from (**7b**). It must be noted that for Ni^{II}–BH_4^- reduction, a work-up with NH_4OH is essential for a high-yielding recovery of amino alcohols; if this is omitted, yields are in the range of 50%. It is puzzling that under these conditions the recovered product shows substantially higher diastereoisomeric ratios: for instance $Zn(BH_4)_2$–$NiCl_2$ reduction of compound (**7b**) affords (**14**) in 45% yield as a 9:1 *syn*:*anti* mixture.

Experimental

^{1}H and ^{13}C N.m.r. spectra were recorded on Varian XL 200 or XL 300 instruments, using tetramethylsilane as internal standard and $CDCl_3$ as solvent. I.r. 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, preparative, and column chromatography. Organic extracts were dried over Na_2SO_4 and filtered before removal of the solvent under reduced pressure. 'Dry' solvents were distilled under a dry N_2 atmosphere before use: ether and tetrahydrofuran (THF) were distilled from $LiAlH_4$, di-isopropylamine from CaH_2, methanol from Mg turnings. All reactions employing 'dry' solvents were run under argon atmosphere. (−)-(*S*)-Menthyl toluene-*p*-sulphinate and alkenes were commercial products and were used without further purification. Ether refers to diethyl ether.

Synthesis of Racemic Compounds (**1**)—(**6**).—Racemic 3-methyl-4,5-dihydroisoxazoles were synthesized following the method described by Mukaiyama.[12]

Compound (**1**), 80%, had b.p. 70—73 °C at 10 mmHg (Found: C, 68.2; H, 10.8; N, 9.8. $C_8H_{15}NO$ requires C, 68.05; H, 10.7; N, 9.9%); δ 4.15 (1 H, t, CHO), 2.5—3.0 (2 H, m, CH_2), 1.9 (3 H, s, MeCN), and 0.95 (9 H, s, Me_3C).

Compound (**2**), 90%, had b.p. 48—50 °C at 2 mmHg (Found: C, 69.8; H, 11.2; N, 8.9. $C_9H_{17}NO$ requires C, 69.6; H, 11.05; N, 9.0%); δ 4.45 (1 H, m, CHO), 2.35—3.15 (2 H, m, CH_2CN), 1.95

* With *syn* and *anti* we refer to the relative stereochemistry of the two nitrogen and oxygen bearing carbon atoms.

† This reaction has been applied so far only to S^{II} and not to S^{IV} derivatives.

Table 3. Stereoselective synthesis of γ-amino alcohols (**14**)—(**16**).

Starting material	Reducing[a] species	Product	Yield (%)	Diastereoisomeric[b] ratio	$[\alpha]_D^{23}$[c]
(**1**)	$LiAlH_4$	(**14**)	96	≥25:1	
(**4**)	$LiAlH_4$	(**15**)	93	5.5:1	
(**5**)	$LiAlH_4$	(**16**)	95	1:2.5	
(−)-(**4**)	$LiAlH_4$	(−)-(**15**)	95	5.5:1	−12.3[d]
(+)-(**5**)	$LiAlH_4$	(+)-(**16**)	95	1:2.5	+14.7[d]
(−)-(**5**)	$LiAlH_4$	(−)-(**16**)	94	1:2.5	−14.5[d]
(**7a**)	$Zn(BH_4)_2$–$NiCl_2$	(**14**)	98	2.3:1[e]	*e,f*
(**7b**)	$Zn(BH_4)_2$–$NiCl_2$	(**14**)	98	2:1[e]	*e,g*
(**7b**)	$NaBH_4$–$NiCl_2$	(**14**)	93	1.5:1[e]	
(**7b**)	$Zn(BH_4)_2$–$NiCl_2$	(**14**)	45[h]	9:1[e]	

[a] For reaction conditions see Experimental. [b] As determined by 200 MHz ^1H or ^{13}C n.m.r. [c] *c* 1 in $CHCl_3$. [d] Rotation of isomer mixtures. [e] As determined on the O,N-trifluoroacetylderivatives. [f] *Syn* isomer: $[\alpha]_D^{23}$ −20.5 (*c* 1 in $CHCl_3$); *anti* isomer: $[\alpha]_D^{23}$ +2.9 (*c* 1 in $CHCl_3$). [g] *Syn* isomer: $[\alpha]_D^{23}$ +20.8 (*c* 1 in $CHCl_3$); *anti* isomer: $[\alpha]_D^{23}$ −2.3 (*c* 1 in $CHCl_3$). [h] Work-up carried out without NH_4OH (see Experimental).

Table 4. ^1H n.m.r. data for γ-amino alcohols (**14**)—(**16**) (Figure).

Compound	H_X	H_A	H_Y	Me	J_{AY}	J_{AX}	J_{MeH_X}
syn-(**14**)[a,b]	2.87	1.05	3.32	1.05	10	10	6.3
syn-(**15**)[c,d]	2.85	1.45	4.28	1.20	9.6	12	6.4
anti-(**15**)[c,e]	3.12	1.70	4.51	1.15	6.0	*f*	6.4
anti-(**16**)[c]	3.37	2.47	4.43	1.04	13	5.6	6.3
syn-(**16**)[c]	3.20	2.04	4.07	0.81	14	14	6.3

[a] At 200 MHz. [b] R^1 = H_B; δ 1.45; J_{AB} 14; J_{BX} 2.5; J_{BY} 2.3. [c] At 300 MHz. [d] R^1 = Me, δ 0.55. [e] R^1 = Me, δ 0.75. [f] Undetectable.

(3 H, s, MeCN), 1.1—1.8 [8 H, m, $(CH_2)_4$], and 0.8—1.1 (3 H, m, *Me*CH_2).

Compound (**3**) had b.p. 75—80 °C at 5 mmHg (lit.,[13] b.p. 61 °C at 2 mmHg).

Compounds (**4**) and (**5**) were obtained in 7:3 ratio and 55% yield from the cycloaddition of acetonitrile oxide to *E*-1-*p*-methoxyphenylpropene. They were purified by column chromatography on silica gel with ether–hexane (1:9) as eluant.

Compound (**4**) had n_D^{23} 1.5402 (Found: C, 70.3; H, 7.2; N, 6.7. $C_{12}H_{15}NO_2$ requires C, 70.2; H, 7.4; N, 6.8%); δ 6.6—7.2 (4 H, m, C_6H_4), 4.7 (1 H, d, CHO), 3.7 (3 H, s, MeO), 2.9 (1 H, m, C*H*Me), 1.9 (3 H, s, MeCN), and 1.2 (3 H, d, *Me*CH).

Compound (**5**) had m.p. 48—50 °C (Found: C, 70.3; H, 7.2; N, 6.7. $C_{12}H_{15}NO_2$ requires C, 70.2; H, 7.4; N, 6.8%); δ 6.6—7.1 (4 H, m, C_6H_4), 4.25 (1 H, m, CHO), 3.7 (3 H, s, MeO), 3.55 (1 H, d, CHCN), 1.9 (3 H, s, MeCN), and 1.3 (3 H, d, *Me*CH).

Compound (**6**), 87%, had b.p. 135—140 °C at 9 mmHg (Found: C, 75.4; H, 7.5; N, 7.9. $C_{11}H_{13}NO$ requires C, 75.4; H, 7.5; N, 8.0%); δ 7.0—7.3 (5 H, m, Ph), 2.85 (2 H, s, CH_2), 1.8 (3 H, s, MeCN), and 1.55 (3 H, s, MeCO).

Synthesis of 3-p-*Tolylsulphinylmethyl*-4,5-*dihydroisoxazoles* (**7a,b**)—(**12a,b**).—To a stirred solution of LDA (10 mmol) in THF (10 ml) cooled at −95 °C, 3-methyl-4,5-dihydroisoxazole (10 mmol) in THF (20 ml) was added over 5 min. The mixture was stirred for 30 min, and menthyl toluene-*p*-sulphinate (5 mmol) in THF (20 ml) was then added in 5 min. After being stirred at −95 °C for 30 min the reaction mixture was quenched with saturated aqueous ammonium chloride. The organic layer was separated and the aqueous phase extracted twice with dichloromethane. The combined organic solutions were dried and concentrated under reduced pressure. The resulting thick oils were purified by flash or gravity chromatography with ether–hexane as eluant. Generally two successive chromatographies were performed: the first one to afford compounds (**7**)—(**12**) as a mixture of diastereoisomers, whose ratio was determined by ^1H n.m.r. analysis, and the analytical data of which were collected. These mixtures were then separated by a second column chromatography into the individual components. Yields, diastereoisomeric ratios and optical rotations of the single isomers are reported in Table 1.

Compound (**7**) (Found: C, 64.6; H, 7.8; N, 4.9. $C_{15}H_{21}NO_2S$ requires C, 64.5; H, 7.6; N, 5.0%). (**7a**): δ 7.2—7.5 (4 H, m, C_6H_4), 4.15 (1 H, t, CHO), 3.4—3.8 (2 H, AB system, CH_2SO), 2.85 (2 H, d, CH_2CN), 2.5 (3 H, s, *Me*Ar), and 1.0 (9 H, s, Me_3C). (**7b**): δ 7.2—7.5 (4 H, m, C_6H_4); 4.22 (1 H, t, CHO), 3.5—3.9 (2 H, AB system, CH_2SO), 2.6—3.2 (2 H, AB part of an ABX system, CH_2CN), 2.45 (3 H, s, *Me*Ar), and 0.9 (9 H, s, Me_3C).

Compound (**8**). (Found: C, 65.7; H, 7.9; N, 4.6. $C_{16}H_{23}NO_2S$ requires C, 65.5; H, 7.9; N, 4.8%). (**8a**): δ 7.2—7.6 (4 H, m, C_6H_4), 4.2—4.65 (1 H, m, CHO), 3.5—3.9 (2 H, AB system, CH_2SO), 2.55—3.1 (2 H, AB part of an ABX system, CH_2CN), 2.45 (3 H, s, *Me*Ar), 1.2—1.9 [8 H, m, $(CH_2)_4$], and 0.95 (3 H, m, *Me*CH_2). (**8b**): δ 7.2—7.6 (4 H, m, C_6H_4), 4.2—4.65 (1 H, m, CHO), 3.5—3.9 (2 H, AB system, CH_2SO), 2.4—3.2 (2 H, AB part of an ABX system, CH_2CN), 2.46 (3 H, s, *Me*Ar), 1.1—1.7 [8 H, m, $(CH_2)_4$], and 0.95 (3 H, m, *Me*CH_2).

Compound (**9**) (Found: C, 64.0; H, 6.4; N, 5.1. $C_{14}H_{17}NO_2S$ requires C, 63.85; H, 6.5; N, 5.3%). (**9a**): δ 7.25—7.55 (4 H, m, C_6H_4), 4.8—5.1 (1 H, m, CHO), 3.73 (2 H, s, CH_2SO), 3.4—3.6 (1 H, m, CHCN), 2.45 (3 H, s, *Me*Ar), and 1.4—2.3 [6 H, m, $(CH_2)_3$]. (**9b**): δ 7.1—7.4 (4 H, m, C_6H_4), 4.85—5.1 (1 H, m, CHO), 3.6—3.9 (1 H, m, CHCN), 3.25—3.7 (2 H, AB system, CH_2SO), 2.4 (3 H, s, *Me*Ar), and 1.3—2.15 [6 H, m, $(CH_2)_3$].

Compound (**10**). (Found: C, 66.6; H, 6.2; N, 4.1. $C_{19}H_{21}NO_3S$ requires C, 66.45; H, 6.2; N, 4.2%). (**10a**): δ 6.75—7.55 (4 H, m, C_6H_4O), 7.1—7.4 (4 H, m, C_6H_4SO), 4.95 (1 H, d, CHO), 3.8 (3 H, s, MeO and 2 H, s, CH_2SO), 3.25 (1 H, m, CHCN), 2.4 (3 H, s, *Me*Ar), and 1.2 (3 H, d, *Me*CH). (**10b**): δ 6.7—7.5 (4 H, m, C_6H_4O), 7.1—7.4 (4 H, m, C_6H_4SO), 4.90 (1 H, d, CHO), 3.80 (2 H, s, CH_2SO), 3.75 (3 H, s, MeO), 3.15 (1 H, m, CHCN), 2.42 (3 H, s, *Me*Ar), and 1.3 (3 H, d, *Me*CH).

Compound (**11**). (Found: C, 66.5; H, 6.2; N, 4.05. $C_{19}H_{21}NO_3S$ requires C, 66.45; H, 6.2; N, 4.2%). (**11a**): δ 6.75—7.05 (4 H, m, C_6H_4O), 7.2—7.5 (4 H, m, C_6H_4SO), 4.5 (1 H, m, CHO), 3.8 (1 H, d, CHCN), 3.73 (3 H, s, MeO), 3.41, 3.70 (2 H, AB system, CH_2SO), 2.40 (3 H, s, *Me*Ar), and 1.2 (3 H, d, *Me*CH). (**11b**): δ 6.7—7.0 (4 H, m, C_6H_4O), 7.2—7.5 (4 H, m, C_6H_4SO), 4.6 (1 H, m, CHO), 3.87 (1 H, d, CHCN), 3.33—3.73 (2 H, AB system, CH_2SO), 2.45 (3 H, s, *Me*Ar), and 1.4 (3 H, d, MeCH).

Compound (**12**). (Found: C, 69.1; H, 6.2; N, 4.4. $C_{18}H_{19}NO_2S$

requires C, 69.0; H, 6.1; N, 4.5%). (**12a**): δ 7.2—7.4 (9 H, 2m, C_6H_4SO and Ph), 3.8 (2 H, s, CH_2SO), 3.15 (2 H, s, CH_2CN), 2.4 (3 H, s, *Me*Ar), 1.6 (3 H, s, MeCO). (**12b**): δ 7.1—7.5 (9 H, 2m, C_6H_4SO and Ph), 3.5—3.95 (2 H, AB system, CH_2SO), 3.25 (2 H, s, CH_2CN), 2.38 (3 H, s, *Me*Ar), and 1.7 (3 H, s, MeCO).

Synthesis of Optically Active 2-Isoxazolines.—To a stirred suspension of sulphinylisoxazoline (1 mmol) and anhydrous NaH_2PO_4 (1.2 g) in MeOH (15 ml) at 0 °C, 8% NaHg (1.5 g) was added in one portion. After being stirred at 0 °C for 30 min the reaction mixture was filtered through Celite and saturated aqueous ammonium chloride (10 ml) added. The organic solvent was evaporated under reduced pressure and the aqueous layer extracted twice with dichloromethane. The organic phase was dried and concentrated to give a crude oil which was purified by flash chromatography (ether–hexane as eluant). Yields and optical rotations are reported in Table 2. The products thus obtained give ^{1}H n.m.r. spectra identical to those of their racemic counterparts.

Synthesis of 4-Hydroxy-4-phenylpentan-2-one (**13**).—From (**12b**): in a hydrogenation vessel were placed (**12b**) (1 mmol, 313 mg), Raney nickel (300 mg), MeOH (15 ml), water (3 ml), and concentrated HCl (0.3 ml). The vessel was mechanically shaken for 3 h under a hydrogen atmosphere after which the reaction mixture was filtered through Celite. The filtrate was added to aqueous sodium hydrogen carbonate and extracted twice with dichloromethane. The combined organic solvents were dried and concentrated under reduced pressure to give an oil, column chromatography of which afforded (**13**) $[\alpha]_D^{23}$ −5.1, $[\alpha]_{365}^{23}$ +37.8 (*c* 1 in $CHCl_3$) in 80% yield; the spectral data are in agreement with those reported.[14] From (−)-(**6**) following the described procedure,[3] (**13**) was obtained in 82% yield.

Synthesis of γ-Amino Alcohols (**14**)—(**16**).—Reductions with $LiAlH_4$ were carried out as described by Jäger,[9] with a 3:1 reducing agent: substrate molar ratio in ether. Yields, isomer ratios and optical rotations are reported in Table 3. Reductions with zinc or sodium borohydride in the presence of nickel(II) chloride were carried out as follows. To a methanol (15 ml) solution of $NiCl_2 \cdot 6H_2O$ (0.475 g, 2 mmol) and sulphinylisoxazoline (1 mmol), $Zn(BH_4)_2$ (0.16 M in ether; 4 mmol, 25 ml) or $NaBH_4$ (0.190 g, 5 mmol) was added portionwise at −30 °C. After being stirred for 3 h the reaction mixture was concentrated under reduced pressure. To the resulting residue concentrated aqueous ammonium hydroxide (20 ml) was added and the aqueous layer extracted twice with dichloromethane. Evaporation of the organic solvent gave the crude products which were then converted into the corresponding *O,N*-trifluoroacetyl derivatives by a standard procedure. The latter were purified by flash chromatography (ether–hexane as eluant). As mentioned in the text omission of ammonium hydroxide from the work-up gave lower yields and higher *syn–anti* isomer ratios. Analytically satisfactory samples of γ-amino alcohols were obtained only with $LiAlH_4$ reduction which allows an 'anhydrous' work-up.

Compound (**14**). (Found: C, 66.3; H, 13.0; N, 9.45. $C_8H_{19}NO$ requires C, 66.15; H, 13.2; N, 9.6%). *Compound* (**15**). (Found: C, 69.1; H, 9.15; N, 6.5. $C_{12}H_{19}NO_2$ requires C, 68.9; H, 9.15; N, 6.7%). *Compound* (**16**). (Found: C, 69.05; H, 9.3; N, 6.5. $C_{12}H_{19}NO_2$ requires C, 68.9; H, 9.15; N, 6.7%).

The ^{1}H n.m.r. data for compounds (**14**)—(**16**) are reported in Table 4. Assignment of relative stereochemistry in compounds (**16**) is in agreement with n.O.e. measurements obtained by irradiation of H_γ (Figure): an increase in the Me_3CN signal was observed only for *anti*-(**16**).

References

1 C. Grundmann and P. Grünanger, 'The Nitrile Oxides,' Springer Verlag, Berlin, 1971; M. Christl and R. Huisgen, *Chem. Ber.* 1973, **106**, 3345, and references therein; Z. P. Kozikowski and P. D. Stein, *J. Org. Chem.*, 1984, **49**, 2301, and references therein.
2 S. H. Andersen, N. B. Das, R. D. Jorgensen, G. Kjeldsen, J. S. Knudsen, S. C. Sharma, and K. B. G. Torssell, *Acta Chem. Scand. Ser. B*, 1982, **36**, 1.
3 D. P. Curran, *J. Am. Chem. Soc.*, 1983, **105**, 5826; A. P. Kozikowski and M. Adamczyk, *Tetrahedron Lett.*, 1982, 3123.
4 V. Jäger, H. Grund, V. Buss, W. Schwab, I. Muller, R. Schohe, R. Franz, and R. Ehrler, *Bull. Soc. Chim. Belg.*, 1983, **92**, 1039, and references therein.
5 A. P. Kozikowski, Y. Kitagawa, and J. P. Springer, *J. Chem. Soc., Chem. Commun.*, 1983, 1460, and references therein.
6 K. N. Houk, S. R. Moses, Y. D. Wu, N. G. Rondan, V. Jäger, R. Schohe, and F. R. Fronczek, *J. Am. Chem. Soc.*, 1984, **106**, 3880, and references therein; A. P. Kozikowski and K. Ghosh, *J. Org. Chem.*, 1984, **49**, 2762.
7 M. Cinquini, F. Cozzi, and A. Gilardi, *J. Chem. Soc., Chem. Commun.*, 1984, 551.
8 R. Annunziata, M. Cinquini, F. Cozzi, and A. Restelli, *J. Chem. Soc., Chem. Commun.*, 1984, 1253.
9 V. Jäger, V. Buss, and W. Schwab, *Liebigs Ann. Chem.*, 1980, 122.
10 S. Masamune, *Heterocycles*, 1984, **21**, 107.
11 M. R. Euerby and R. D. Waigh, *J. Chem. Soc., Chem. Commun.*, 1984, 127.
12 T. Mukaiyama and T. Hoshino, *J. Am. Chem. Soc.*, 1960, **82**, 5339.
13 H. Grund and V. Jäger, *Liebigs Ann. Chem.*, 1980, 80.
14 T. J. Leitereg and D. J. Cram, *J. Am. Chem. Soc.*, 1968, **90**, 4019.

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