Enantiomerically Pure Sulphinyl-4,5-dihydroisoxazoles. Part 2.† Synthesis of Masked and Unmasked β,β′-Dihydroxy Ketones *via* Stereocontrolled Double Aldol Condensation

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Reaction of stereoisomerically pure sulphinyl-4,5-dihydroisoxazoles having one or two stereocentres at C-4 and C-5 of the heterocycle with aliphatic or aromatic aldehydes resulted in highly stereoselective formal double aldol condensation; the adducts, depending on desulphurization conditions, could be converted either into optically active β,β′-dihydroxy ketones (by Raney nickel catalyzed hydrogenation in the presence of boric acid) or hydroxyisoxazolines (by Na–Hg in buffered conditions); the latter have the heterocyclic ring available for further synthetic elaboration such as highly stereoselective lithium aluminium hydride reduction to amino diols.

The isoxazoline-based approach to the stereoselective synthesis of β-hydroxy ketones [1] has been the subject of growing interest in recent years.[2] The success of the process relies on the stereocontrolled cycloaddition of nitrile oxides (or nitrile oxide equivalents) to olefins to afford 4,5-dihydroisoxazoles (2-isoxazolines),[3] followed by their stereoconservative conversion into β-ketols by reductive ring opening.[1] A route to enantiomerically pure 2-isoxazolines, and hence to β-ketols, has been recently reported by us.[4] It involved the synthesis of optically active 3-sulphinylmethyl-4,5-dihydroisoxazoles, the separation of diastereoisomers and their reductive desulphurization to give stereoisomerically homogeneous 2-isoxazolines or β-ketols depending on reaction conditions.

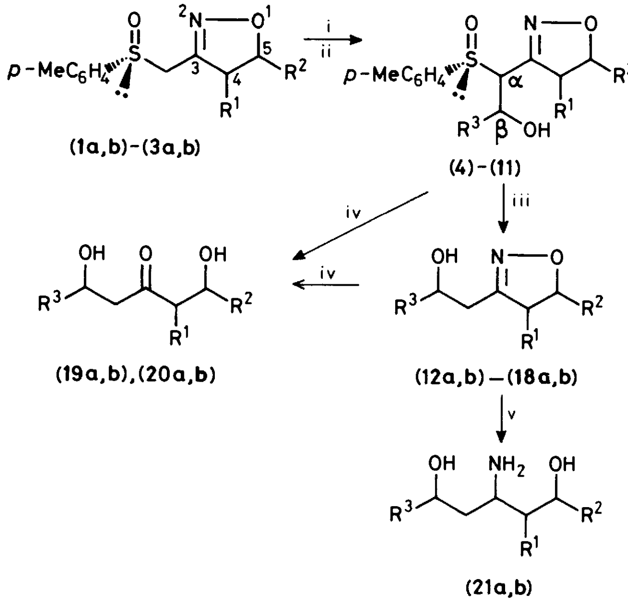
We thought, however, that in sulphinylisoxazolines the role of the sulphoxide group should not be limited to providing a 'handle' for the resolution, but might conveniently be exploited for further synthetic transformation.[5]

In line with other groups'[6] and our own work [7] on sulphoxide- mediated stereoselective carbon–carbon bond formation, we subjected sulphinylisoxazolines to an aldol condensation,[8] aiming at the stereocontrolled synthesis of polyfunctionalized carbon skeletons.

As we reported in a preliminary note,[9] enantiomerically pure 3-*p*-tolylsulphinylmethyl-4,5-dihydroisoxazoles (**1a,b**)—(**3a,b**) were α-metallated and condensed with aldehydes to give diastereoisomeric mixtures of the adducts (**4**)—(**11**), which were then transformed into either the hydroxyisoxazolines (**12a,b**)—(**18a,b**) or the β,β′-dihydroxy ketones (**19a,b**)—(**20a,b**) (Scheme 1). Therefore, this reaction sequence is equivalent to a regiospecific double aldol condensation of a ketone with two different aldehydes. Most conveniently, one of the two ketol functionalities can be kept in a latent form, available for subsequent modifications, as in compounds (**12**)—(**18**).

Since the stereochemical outcome of the process depends on many factors, let us start from the condensations carried out on sulphoxides (**1a**) and (**1b**), *i.e.* those containing a single stereocentre in the heterocyclic ring (Table 1).

The choice of the base used to generate the enolate turned out to be crucial. This was expected on the basis of previous work on related systems.[6,7] Lithium bases were less efficient than magnesium ones. Among the latter, bulkier bases promoted higher diastereoselectivity although in constantly lower chemical yields. As can be seen from Table 1, the sulphinylisoxazolines (**1a**)[4] and (**1b**)[4], which are epimeric at the C-5 stereocentre in the ring, give rise in comparable experiments



(**1a,b**)	R^1 = H; R^2 = Bu^t
(**2a,b**)	R^1 = H; R^2 = C_5H_{11}
(**3a,b**)	R^1 = *p*-$MeOC_6H_4$; R^2 = Me
(**4**),(**12a,b**)	R^1 = H; R^2 = Bu^t; R^3 = Et
(**5**),(**13a,b**),(**21a,b**)	R^1 = H; R^2 = Bu^t; R^3 = Pr^i
(**6**),(**14a,b**)	R^1 = H; R^2 = Bu^t; R^3 = Bu^t
(**7**),(**15a,b**)(**19a,b**)	R^1 = H; R^2 = C_5H_{11}; R^3 = C_5H_{11}
(**8**),(**16a,b**)	R^1 = *p*-$MeOC_6H_4$; R^2 = Me; R^3 = Et
(**9**),(**17a,b**)	R^1 = *p*-$MeOC_6H_4$; R^2 = Me; R^3 = Pr^i
(**10**),(**18a,b**)	R^1 = *p*-$MeOC_6H_4$; R^2 = Me; R^3 = Bu^t
(**11**),(**20a,b**)	R^1 = *p*-$MeOC_6H_4$; R^2 = Me; R^3 = Ph

Scheme 1. *Reagents:* i, base; ii, R^3CHO; iii, Na–Hg, NaH_2PO_4; iv, H_2, H_3BO_3, Raney nickel; v, $LiAlH_4$. With (**a**) and (**b**), diastereoisomeric products are indicated. Compounds (**3**), (**8**)—(**11**), and (**16**)—(**20**) display *trans* relative stereochemistry at C-4 and C-5 of the ring.

to different degrees of stereoselectivity, (**1a**) being always more selective. As judged by comparison of the ^1H n.m.r. spectra and the optical rotations, the hydroxyisoxazolines obtained from (**1a**) and (**1b**) are predominantly epimers, not enantiomers: since they have opposite stereochemistry at C-5, they must display the same configuration at the OH- bearing carbon (C-β).

Therefore, the sense of the enantioface differentiation on the aldehyde is determined by the sulphoxide moiety, while the

† Part 1, preceding paper.

Table 1. Stereoselective synthesis of hydroxyisoxazolines (**12a,b**)—(**14a,b**).

Sulphoxide	Adduct	R^3	Base	Yield[a] (%)	Diastereoisomeric[b] ratio a:b	α_D^{23c}
(**1a**)	(**12a,b**)	Et	MgDA	70	5:1	+74.7
(**1a**)	(**12a,b**)	Et	Bu^{t}MgBr	27	50:1	+65.5
(**1a**)	(**13a,b**)	Pr^i	MgDA	55	3.5:1	+78.8
(**1a**)	(**13a,b**)	Pr^i	Pr^{i}MgBr	80	3:1	+81.8
(**1a**)	(**13a,b**)	Pr^i	Bu^{t}MgBr	50	8:1	+68.8
(**1a**)	(**13a,b**)	Pr^i	LDA	70	1.1:1	+95.7
(**1a**)	(**14a,b**)	Bu^t	MgDA	75	2:1	+75.3
(**1b**)	(**12a,b**)	Et	MgDA	68	1:3.3	−106.6
(**1b**)	(**13a,b**)	Pr^i	MgDA	60	1:2	−96.4
(**1b**)	(**13a,b**)	Pr^i	Bu^{t}MgBr	40	1:4	−120.4
(**1b**)	(**14a,b**)	Bu^t	MgDA	60	1:1	−75.6

[a] Overall yields from (**1**). For reaction conditions see Experimental section. [b] As determined by 200 MHz ^{1}H n.m.r. spectroscopy. A 50:1 ratio indicates that a single isomer can be detected by n.m.r. [c] c = 1 in $CHCl_3$, rotation of the diastereoisomeric mixtures.

stereocentre at C-5 exerts its effect only on the extent of the stereoselectivity.

In the synthesis of the adducts (**4**)—(**11**) a further stereocentre is formed at the carbon α to the sulphoxide group. The stereoselectivity of its formation was determined for the adduct (**5**) from (**1a**) with Bu^{t}MgBr as base. Indeed, the adduct (**5**) was produced as a 8:1 mixture of only two isomers which were separated by flash chromatography and converted into (+)-(**13a**), α_D^{23} + 60.2 (c 1 in $CHCl_3$) and (+)-(**13b**), α_D^{23} + 137.8 (c 1 in $CHCl_3$), both enantiomerically and diastereoisomerically pure by ^{1}H n.m.r. spectroscopy. Therefore, at least in this case, the stereocentre α to the sulphoxide group is formed stereospecifically. This observation has some precedents in similar systems.[6,7] It must be noted that chromatographic separation of the isomeric components of adducts (**4**)—(**11**) and/or of their desulphurization products is generally possible. This allows the isolation of enantiomerically and diastereoisomerically pure materials.

From the data reported in Table 1 a further trend is evident: aldehydes with smaller R^3 residues produce more selective condensations, to the point that when (**1a**) is metallated with Bu^{t}MgBr and treated with propionaldehyde, the reaction is practically stereospecific. * This trend has already been reported for related systems.[6,7]

In order to rationalize the results, we decided to determine the absolute configuration at the OH-bearing carbon.

This was possible starting from compound (**2a**), α_D^{23} + 297.5 (c 1 in $CHCl_3$) for which the (R_S, R_C) absolute configuration was known from the synthesis of (+)-(S)-gingerol from (R_S,S_C)-(**2b**).[4] Metallation of (**2a**) with Bu^{t}MgBr and subsequent reaction with hexanal gave the adduct (**7**) as a 3:1 mixture of isomers. On the assumption that these were epimers at C-β (see above), they were separated by flash chromatography and individually transformed into the β, β′-dihydroxy ketones (**19a**) and (**19b**). As expected, only one of these, namely the predominant isomer (**19a**), was optically active, $\alpha^D{}_{23}$ − 40.4 (c 0.2 in $CHCl_3$) and diastereoisomerically pure by ^{1}H n.m.r. spectroscopy. On the other hand, (**29b**) was optically inactive. Therefore the (R,R) absolute configuration was assigned to dissymmetric (**19a**) and the (R,S) to *meso*-(**19b**).

The bulk of the experimental data leads us tentatively to propose for this aldol condensation the preferred attack shown in Figure 1, in which the aldehyde approaches the chiral azaenolate, made rigid by intramolecular magnesium chelation, with the hydrogen facing the sulphur lone pair.†

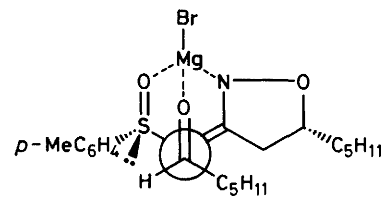


Figure 1.

This transition state is in agreement with: (a) the absolute configuration established for (**19a**); (b) the different selection observed with (**1a**) and (**1b**) that is accounted for by the steric interaction between R^3 and R^2 groups; (c) the higher stereoselectivity obtained with less sterically demanding aldehydes for which the R^3-isoxazoline ring interactions are diminished; and (d) the similar mode of attack of aldehydes on the magnesium enolates of α-sulphinyl acetates[6] and acetamides.[7]

Some of the trends observed for (**1**) hold true when the aldol condensation is extended to the sulphinylisoxazolines (**3a**)[4] and (**3b**),[4] which feature the same (R) absolute configuration at sulphur and opposite configuration at C-4 and C-5 in the heterocyclic ring, the two stereocentres having a *trans* relative stereochemistry.

As can be seen from Table 2 the diastereoselectivities are generally excellent both with Bu^{t}MgBr and di-isopropylamide magnesium bromide (MgDA); the former gives more stereoselective condensations in lower chemical yields. A decrease in the steric requirement of the aldehyde R^3 residues is reflected by more unbalanced diastereoisomer ratios.

The sulphoxide group is still predominant in promoting the sense and the extent of the stereoselectivity, notwithstanding the presence of a bulky substituent at C-4. Indeed condensations carried out on (**3a**) and (**3b**) afford, as major products, adducts displaying the same absolute configuration at C-β.

However, the dramatic drop in selectivity observed in the synthesis of (**18a,b**; R^3 = Bu^t), from (**3b**), which from the obtained results seems to be more selective than (**3a**), is quite puzzling, and in our opinion does not allow the general

* The low reaction yield must have its influence on this result, but changing the reaction conditions to improve the yield would have prevented any meaningful comparison.

† Obviously, if the aldehyde approaches the enolate with the R^3 residue facing the p-tolyl group of the sulphoxide the outcome is the same. We think that this attack can be disregarded on steric grounds.

Table 2. Stereoselective synthesis of hydroxyisoxazolines (**16a,b**)—(**18a,b**).

Sulphoxide	Adduct	R^3	Base	Yield [a] (%)	Diastereoisomeric [b] ratio a:b	α_D^{23} [c]
(**3a**)	(**16a,b**)	Et	MgDA	80	50:1	−313.3
(**3a**)	(**17a,b**)	Pr^i	MgDA	75	16:1 [d]	*e*
(**3a**)	(**17a,b**)	Pr^i	Bu^{t}MgBr	50	20:1	*e*
(**3a**)	(**18a,b**)	Bu^t	MgDA	65	14:1	*f*
(**3b**)	(**16a,b**)	Et	MgDA	75	1:50	+178.8
(**3b**)	(**17a,b**)	Pr^i	MgDA	70	1:20	+170.0
(**3b**)	(**17a,b**)	Pr^i	Bu^{t}MgBr	40	1:50	+166.0
(**3b**)	(**18a,b**)	Bu^t	MgDA	60	1:2.2	*g*

[a] Overall yields from (3); for reaction conditions see Experimental section. [b] As determined by 200 MHz ^{1}H n.m.r. spectroscopy. A 50:1 ratio indicates that a single isomer was detected by n.m.r. [c] $c = 1$ in $CHCl_3$, rotations of diastereoisomeric mixtures. [d] Isolation of (**17a,b**) requires a fast work-up carried out at low temperature; otherwise decomposition occurs resulting in the isolation of a 9:1 diastereoisomers mixture in 50% yield.[9] [e] (−)-(**17a**), α_D^{23} − 265.8, c = 1 in $CHCl_3$; (−)-(**17b**), α_D^{23} − 169.5, c 0.5 in $CHCl_3$. [f] (−)-(**18a**), α_D^{23} − 204.3, c 1 in $CHCl_3$; (−)-(**18b**), α_D^{23} − 152.2, c 0.5 in $CHCl_3$. [g] (+)-(**18a**), α_D^{23} + 202.1, c 1 in $CHCl_3$; (+)-(**18b**), α_D^{23} − 153.0, c 1 in $CHCl_3$.

extension of the above proposed transition state to systems such as (**3a**) and (**3b**).

It must be noted that a two-step synthesis of a β,β′-dihydroxy ketone is also possible in this case. Indeed, (**3b**) was metallated with MgDA and condensed with benzaldehyde and the resulting adducts (**11**) converted directly into (**20a,b**), (diastereoisomeric ratio ⩾ 50:1, 43% overall yield).*

Finally, we wish to mention that the possibility of retaining one of the two β-ketol functions in a protected form as in (**12**)—(**18**) is particularly useful if amino polyols are the target molecules. In line with Jäger's extensive work on this topic,[10] we treated enantiomerically pure (+)-(**13a**) (see above) with $LiAlH_4$. A ⩾ 50:1 mixture of the amino diols (**21a,b**), α_D^{23} − 16.7 (c 0.5 in $CHCl_3$) was obtained in 98% yield. According to the proposed model[4,10] the major isomer should feature the *syn* relative stereochemistry at C-3 and C-5.

* Careful chromatographic separation of the reaction mixture allowed the isolation together with (**20a,b**) of 5-hydroxy-4-(*p*-methoxyphenyl)-1-phenylhexan-3-one in 7% yield. On the basis of ^{1}H n.m.r. analysis of the mixture before chromatography this product was erroneously reported[9] to be the minor component of (**20a,b**).

Experimental

^{1}H and ^{13}C N.m.r. spectra were recorded on a Varian XL 200 instrument, 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 (diethyl ether) and tetrahydrofuran (THF) were distilled from $LiAlH_4$, di-isopropylamine from CaH_2, and methanol from Mg turnings. All reactions employing 'dry' solvents were run under argon atmosphere.

Compounds (**1a**), α_D^{23} + 337.5 (c 1 in $CHCl_3$) (**1b**), α_D^{23} + 140.3 (c 1 in $CHCl_3$), (**2a**), α_D^{23} + 297.5 (c 1 in $CHCl_3$), (**3a**), α_D^{23} + 83.2 (c 1 in $CHCl_3$), and (**3b**), α_D^{23} + 262.2 (c 1 in $CHCl_3$) were prepared as previously described.[4]

Synthesis of Hydroxy Isoxazolines (**12a,b**)—(**18a,b**).—*With Grignard reagent as base.* To a stirred solution of 3-*p*-tolylsulphinylmethyl-4,5-dihydroisoxazole (1 mmol) in THF (20 ml) cooled at −90 °C, the appropriate base (3 mmol for Bu^{t}MgBr, 1.1 mmol for Pr^{i}MgBr) as a *ca.* 0.5M-solution in ether was added dropwise. After 30 min at −90 °C, freshly distilled aldehyde (3 mmol) was added at once and the reaction mixture was stirred for an additional 3 min (10 min if Pr^{i}MgBr is the base). The reaction was then quenched by addition of saturated aqueous ammonium chloride and warmed to room temperature. The organic layer was separated and the aqueous phase extracted twice with dichloromethane; the combined organic solvents were dried and concentrated under reduced pressure. The resulting oil was then dissolved in methanol (15 ml), the solution cooled at 0 °C, and anhydrous NaH_2PO_4 (1.2 g) and 8% Na–Hg (1.5 g) added sequentially. The mixture was vigorously stirred at 0 °C for 30 min and then filtered through Celite. Saturated aqueous ammonium chloride was added to the filtrate. The organic solvents were evaporated under reduced pressure and the aqueous layer extracted twice with dichloromethane. The organic phase was dried and concentrated under reduced pressure to give a crude oil which was purified by flash chromatography on silica gel with ether–hexane as eluant. Generally diastereoisomers were not separated, and analytical and spectral data were collected on the purified diastereoisomeric mixtures. Yields, isomer ratios, and optical rotations are reported in Tables 1 and 2.

With di-isopropylamide magnesium bromide (MgDA) *as base.* MgDA was prepared (*ca.* 0.5M in ether) as previously described.[11] To the MgDA (3 mmol) suspension cooled at −90 °C, 3-*p*-tolylsulphinylmethyl-4,5-dihydroisoxazole (1 mmol) in THF (20 ml) was added dropwise. After 30 min at −90 °C, freshly distilled aldehyde (3 mmol) was added at once and the reaction mixture stirred for an additional 10 min. Work-up and desulphurization as described above gave the product.

With LDA as base. A 1.1:1 base: substrate molar ratio was used in THF at −90 °C. Metallation time was 30 min, and condensation time was 3 min. Work-up and desulphurization were carried out as described above.

Compounds (**12a,b**) (Found: C, 66.5; H, 10.5; N, 6.9. $C_{11}H_{21}NO_2$ requires C, 66.3; H, 10.6; N, 7.0%); δ 4.17—4.29 (1 H, dd and dd, CHON), 3.75—3.95 (1 H, m, C*H*OH), 2.90—2.60 (3 H, m, CH_2 inside the ring and OH), 2.35—2.45 (2 H, m, HOCHCH_2CN), 1.45—1.60 (2 H, m, CH_2Me), 0.95 (3 H, t, $MeCH_2$), and 0.87 (9 H, s, Me_3C). Diastereoisomers were distinguished by expansion of the CHON signals. (**12a**) features a dd at δ 4.18—4.29; (**12b**) features a dd at δ 4.17—4.28.

Compounds (**13a,b**) (Found: C, 67.6; H, 10.7; N, 6.5. $C_{12}H_{23}NO_2$ requires C, 67.6; H, 10.9; N, 6.6%); (**13a**), δ 4.19—4.29 (1 H, dd, CHON), 3.62—3.75 (1 H, m, C*H*OH), 2.65—2.95 (2 H, AB part of an ABX system, CH_2 inside the ring), 2.35—

2.53 (3 H, m, *H*OCHC*H*$_2$CN), 1.75 (1 H, m, C*H*Me$_2$), 0.98 (6 H, dd, *Me*$_2$CH), and 0.95 (9 H, s, Me$_3$C); (**13b**), δ 4.20—4.30 (1 H, dd, CHON), 3.65—3.77 (1 H, m, C*H*OH), 2.64—2.96 (2 H, AB part of an ABX system, CH$_2$ inside the ring), 2.30—2.55 (3 H, m, *H*OCHC*H*$_2$CN), 1.75 (1 H, m, C*H*Me$_2$), 0.96 (6 H, dd, Me$_2$CH), and 0.94 (9 H, s, Me$_3$C).

Compounds (**14a,b**) (Found: C, 68.9; H, 11.0; N, 6.05. $C_{13}H_{25}NO_2$ requires C, 68.7; H, 11.1; N, 6.2%); δ 4.16—4.27 (1 H, dd and dd, CHON), 3.48—3.60 (1 H, m, C*H*OH), 2.60—2.95 (2 H, m, CH$_2$ inside the ring), 2.21—2.49 (3 H, m, *H*OCHC*H*$_2$CN), and 0.87 and 0.92 (18 H, 2s, Me$_3$C). Diastereoisomers were distinguished by expansion of the CHON signals. (**12a**) features a dd at δ 4.17—4.27; (**12b**) features a dd at δ 4.16—4.26.

Compound (**15a**) had α_D^{23} + 50.0 (*c* 0.2 in CHCl$_3$) (Found: C, 70.4; H, 11.4; N, 5.4. $C_{15}H_{29}NO_2$ requires C, 70.5; H, 11.4; N, 5.5%); δ 4.15—4.50 (1 H, m, CHON), 3.65—3.90 (1 H, m, C*H*OH), 2.18—3.02 (5 H, m, *H*OCHC*H*$_2$CNC*H*$_2$), 0.90—1.70 [16 H, m, (CH$_2$)$_4$], and 0.65—0.90 (6 H, m, Me).

Compound (**15b**) had α_D^{23} + 74.6 (*c* 0.2 in CHCl$_3$); δ 4.22—4.75 (1 H, m, CHON), 3.65—4.15 (1 H, m, C*H*OH), 2.25—3.20 (5 H, m, *H*OCHC*H*$_2$CNC*H*$_2$), 1.0—1.8 [16 H, m, (CH$_2$)$_4$], and 0.65—1.0 (6 H, m, Me).

Compound (**16**) (Found: C, 68.6; H, 7.9; N, 5.3. $C_{15}H_{21}NO_3$ requires C, 68.4; H, 8.0; N, 5.3%); (**16a**), δ 6.83—7.09 (4 H, m, C$_6$H$_4$), 4.38—4.52 (1 H, dq, C*H*Me), 3.79 (3 H, s, MeO), 3.77 (1 H, d, CHCN), 2.77 (1 H, br s, OH), 2.05—2.31 (2 H, AB part of an ABX system, CH$_2$CN), 1.42 (2 H, m, C*H*$_2$Me), 1.36 (3 H, d, *Me*CH), and 0.87 (3 H, t, CH$_2$*Me*). (**16b**), δ 6.82—7.10 (4 H, m, C$_6$H$_4$), 4.40—4.54 (1 H, dq, C*H*Me), 3.81 (1 H, d, CHCN), 3.77 (3 H, s, MeO), 2.6 (1 H, br s, OH), 2.14—2.32 (2 H, AB part of an ABX system, CH$_2$CN), 1.46 (2 H, m, C*H*$_2$Me), 1.39 (3 H, d, *Me*CH), and 0.87 (3 H, t, CH$_2$Me). The two isomers can be distinguished from the CH$_2$CN signal. By iterative computer analysis with the Laocoon 3 program[12] we found for (**16a**): J_{AB} 16 Hz, J_{AX} 1 Hz, and J_{BX} 7 Hz; and for (**16b**): J_{AB} 16 Hz, J_{AX} 8 Hz, and J_{BX} 1.5 Hz.

Compound (**17**) (Found: C, 69.1; H, 8.6; N, 4.9. $C_{16}H_{23}NO_3$ requires C, 69.3; H, 8.4; N, 5.05%); (**17a**), δ 6.88—7.14 (4 H, m, C$_6$H$_4$), 4.43—4.58 (1 H, dq, C*H*Me), 3.83 (3 H, s, MeO), 3.86 (1 H, d, CHCN), 3.70 (1 H, m, C*H*OH), 2.66 (1 H, br s, OH), 2.10—2.36 (2 H, AB part of an ABX system, CH$_2$CN), 1.67 (1 H, m, C*H*Me$_2$), 1.42 (3 H, d, *Me*CH), and 0.90 and 0.84 (6 H, 2d, CH*Me*$_2$). (**17b**), δ 6.85—7.12 (4 H, m, C$_6$H$_4$), 4.41—4.56 (1 H, dq, C*H*Me), 3.83 (1 H, d, CHCN), 3.81 (3 H, s, MeO), 3.65 (1 H, m, CHOH), 2.49 (1 H, br s, OH), 2.14—2.37 (2 H, AB part of an ABX system, CH$_2$CN), 1.67 (1 H, m, C*H*Me$_2$), 1.41 (3 H, d, *Me*CH), and 0.85 and 0.84 (6 H, 2d, CH*Me*$_2$).

Compound (**18**). (Found: C, 70.4; H, 8.5; N, 4.8. $C_{17}H_{25}NO_3$ requires C, 70.1; H, 8.65; N, 4.8%). (**18a**), δ 6.81—7.06 (4 H, m, C$_6$H$_4$), 4.35—4.51 (1 H, dq, C*H*Me), 3.81 (1 H, d, CHCN), 3.76 (3 H, s, MeO), 3.49 (1 H, dd, C*H*OH), 2.59 (1 H, br s, OH), 1.95—2.31 (2 H, AB part of an ABX system, CH$_2$CN), 1.34 (3 H, d, *Me*CH), 0.78 (9 H, s, Me$_3$C). (**18b**), δ 6.83—7.08 (4 H, m, C$_6$H$_4$); 4.40—4.54 (1 H, dq, C*H*Me), 3.83 (1 H, d, CHCN), 3.78 (3 H, s, MeO), 3.56 (1 H, dd, C*H*OH), 2.14—2.35 (2 H, AB part of an ABX system, CH$_2$CN), 1.38 (3 H, d, *Me*CH), and 0.81 (9 H, s, Me$_3$C). The diastereoisomeric components of mixtures (**17a,b**) and (**18a,b**) were separated by flash chromatography on silica gel with a 3:1 ether–hexane mixture as eluant.

Synthesis of 6,10-*Dihydroxydecapentan*-8-*one* (**19**).—Compounds (−)-(*R*,*R*)-(**19a**) and *meso*-(**19b**) were obtained from (+)-(**15a**) and (+)-(**15b**) respectively in *ca.* 90% yield following Curran's method. Optical rotations are reported in the text (Found: C, 69.7; H, 11.75. $C_{15}H_{30}O_3$ requires C, 69.7; H, 11.7%). (**19a**), δ 3.85—4.15 (2 H, m, C*H*OH), 2.9 (2 H, br s, OH), 2.5 (4 H, br d, CH$_2$CO), 1.0—1.6 [16 H, m, (CH$_2$)$_4$], and 0.7—0.95 (6 H, m, Me). (**19b**), δ 3.95—4.25 (2 H, m, C*H*OH), 2.2—2.8 (6 H, m, CH$_2$CO and OH), 1.05—1.60 [16 H, m, (CH$_2$)$_4$], and 0.8—1.05 (6 H, m, Me).

Synthesis of 1,5-*Dihydroxy*-4-(p-*methoxyphenyl*)-1-*phenylhexan*-3-*one* (**20**).—The adduct (**11**) prepared from (**3b**) (1 mmol), and benzaldehyde with MgDA as base, as described above, was placed in a hydrogenation vessel with methanol (10 ml), water (2 ml), Raney–Nickel (300 mg), and H$_3$BO$_3$ (310 mg, 5 mmol) under a hydrogen atmosphere. The vessel was shaken for 3 h at room temperature. The reaction mixture was filtered through Celite and MeOH evaporated under reduced pressure. The residue was extracted twice with dichloromethane. The organic layer was separated, dried, and concentrated under reduced pressure. The resulting material was purified by flash chromatography to give (**20a,b**) [43% from (**3b**)], α_D^{23} + 67.5 (*c* 0.12, in CHCl$_3$), m.p. 70—72 °C (Found: C, 72.3; H, 7.2. $C_{19}H_{22}O_4$ requires C, 72.6; H, 7.05%); δ 7.16—7.39 (5 H, m, Ph), 6.80—7.06 (4 H, m, C$_6$H$_4$), 5.08—5.18 (1 H, X part of ABX system C*H*CH$_2$), 4.74 (2 H, br s, OH), 4.30—4.45 (1 H, dq, C*H*Me), 3.78 (3 H, s, OMe), 3.53 (1 H, d, CHCN), 2.77—2.86 (2 H, AB part of ABX system, C*H*$_2$CHOH), and 0.98 (3 H, d, Me). As mentioned in the footnote on p. 2295 5-hydroxy-4-(*p*-methoxy phenyl)-1-phenylhexan-3-one was also obtained in 7% yield in the reductive desulphurization of the adduct (**11**). It has α_D^{23} + 119.4 (*c* 0.06, in CHCl$_3$), low melting material; δ 6.80—7.20 (9 H, m, ArH), 4.30—4.45 (1 H, dq, C*H*Me), 3.77 (3 H, s, OMe), 3.48 (1 H, d, CHCN), 2.58—2.95 [4 H, m, (CH$_2$)$_2$], and 0.96 (3 H, d, Me) (Found: C, 76.2; H, 7.5. $C_{19}H_{22}O_3$ requires C, 76.5; H, 7.4%).

Synthesis of 5-*Amino*-2,2,8-*trimethylnonane*-3,7-*diol* (**21a,b**).—To a stirred solution of LiAlH$_4$ (1 mmol) in ether (5 ml) cooled at 0 °C, (**13a**) [α_D^{23} + 60.2 (*c* 1 in CHCl$_3$)] (0.3 mmol, 64 mg), in ether (10 ml) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. Work-up gave (**21a,b**) (66 mg, 98%) as a ≥ 50:1 mixture of isomers (Found: C, 66.1; H, 12.6; N, 6.2. $C_{12}H_{27}NO_2$ requires C, 66.3; H, 12.5; N, 6.4%); δ 3.48—3.60 (1 H, m, C*H*OHPr^i), 3.40 (1 H, dd, C*H*OHBu^t) 3.15 (1 H, m, C*H*NH$_2$), 2.70 (4 H, br s, OH and NH$_2$), 1.50—1.70 (2 H, m, CH$_2$), 1.10—1.45 (3 H, m, CH$_2$ and C*H*Me$_2$), 0.91 and 0.89 (6 H, 2d, CH*Me*$_2$), and 0.87 (9 H, s, Bu^t).

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