Double Aldol Condensation: Stereoselective Synthesis of Masked and Un-masked β,β'-Dihydroxyketones

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Aldol condensations of stereoisomerically pure 3-sulphinylmethyl-4,5-dihydroisoxazoles allow a highly stereocontrolled entry to optically active masked and un-masked β,β'-dihydroxyketones.

4,5-Dihydroisoxazoles (Δ^2-isoxazolines), which can be obtained by regioselective and stereocontrolled cycloadditions of nitrile oxides to olefins,[1,2] provide a straightforward approach to the preparation of stereoisomerically homogeneous β-hydroxyketones.[2]

We recently reported the synthesis of diastereoisomerically and enantiomerically pure 3-sulphinylmethyl-4,5-dihydroisoxazoles (**4**)—(**6**) *via exo*-metallation of racemic (**1**)—(**3**), subsequent reaction with (−)-(*S*)-menthyl toluene-*p*-sulphinate, and separation of the resulting diastereoisomers, all of which display the same (*R*) absolute configuration at sulphur.[3] These were then converted into the corresponding enantiomerically pure 4,5-dihydroisoxazoles or β-hydroxy ketones.[3] Since this method can control both relative and absolute stereochemistry at C-4 and C-5 in the isoxazoline ring, we exploited the ability of the sulphinyl moiety in promoting stereoselective carbon–carbon bond formation in aldol and related reaction.[4,5]

Sulphoxides (**4**)—(**6**) were α-metallated and condensed with aldehydes to afford adducts (**7**)—(**12**) as mixtures of diastereoisomers, which were either desulphurized (Na–Hg, NaH_2PO_4) to hydroxyisoxazolines (**13a, b**)—(**17a, b**), or directly converted (H_2, H_3BO_3, Raney-nickel) into β,β'-dihydroxyketones (**18a, b**)—(**19a, b**). Both these derivatives represent the products of a formal regiospecific double aldol condensation of a ketone with two different aldehydes, one of the two ketol moieties being selectively preserved in the case of the hydroxy isoxazolines (**13a, b**)—(**17a, b**) (Scheme 1).

Good to excellent degrees of stereoselection in C–C bond formation were obtained when bulky magnesium bases were used (Tables 1 and 2). t-Butylmagnesium bromide gave better stereochemical results although somewhat lower chemical yields with respect to di-isopropylamide–magnesium bromide (MgDA).[6]

Condensation of sulphinyl isoxazolines (**4a**), $[\alpha]_D^{23}$ +337.5,[3] and (**4b**), $[\alpha]_D^{23}$ +140.3,[3] epimeric at C-5, afforded

Table 1. Stereoselective synthesis of hydroxyisoxazolines (**13a, b**).[a]

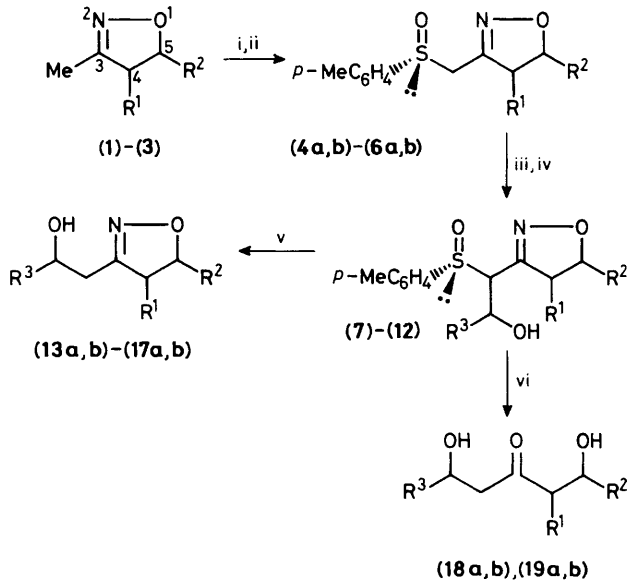
Sulphoxide	Adduct	Base	Yields/%[b]	Diastereoisomeric[c] ratio **a** : **b**	$[\alpha]_D^{23}$[d]
(**4a**)	(**13a, b**)	LDA[e,f]	70	1.1 : 1	+95.7
(**4a**)	(**13a, b**)	Pr^iMgBr[e,g]	80	3 : 1	+81.8
(**4a**)	(**13a, b**)	Bu^tMgBr[f,h]	50	8 : 1	+68.8
(**4a**)	(**13a, b**)	MgDA[g,h]	55	3.5 : 1	+78.8
(**4b**)	(**13a, b**)	Bu^tMgBr[f,h]	40	1 : 4	−120.4
(**4b**)	(**13a, b**)	MgDA[g,h]	60	1 : 2	−96.4

[a] Reactions carried out at −90 °C under argon in tetrahydrofuran (THF); metallation time 30 min. All bases *ca.* 0.5 M in diethyl ether except LDA(THF). All compounds gave analytical and spectral data in agreement with the proposed structures. [b] Overall yields from (**4**); products isolated by flash chromatography (diethyl ether–hexane). [c] As determined by 200 MHz ^1H n.m.r. spectroscopy. [d] *c* 1 in $CHCl_3$. [e] 1.1 mol equiv. [f] Condensation time 3 min. [g] Condensation time 10 min. [h] 3.0 mol equiv.

as major products epimeric and not enantiomeric hydroxyisoxazolines, thus showing that the enantioface differentiation on the aldehyde is determined by the sulphoxide group.† Chiral discrimination by the stereocentre at C-5 appears to operate synergistically, with better stereochemical results being obtained in the case of (**4a**) than with (**4b**).

The absolute configuration of the newly formed exocyclic stereocentre was established starting from sulphoxide (**5a**), $[\alpha]_D^{23}$ +297.5, of known (*R,R*) absolute configuration.[3] Generation of the enolate with Bu^tMgBr and condensation with n-hexanal afforded (**8**) as a 3 : 1 mixture of diastereoisomers. These were separated and individually converted into the corresponding ketols (**19a**) and (**19b**), respectively. Only (**19a**), derived from the predominant adduct, was optically active, $[\alpha]_D^{23}$ −40.4 (*c* 0.2 in $CHCl_3$), and diastereoisomerically pure, as shown by ^1H. n.m.r. spectroscopy. Therefore the (*R,R*) absolute configuration was assigned to (**19a**). As expected for a *meso* compound (**19b**) was optically inactive. To account for this stereochemical outcome, we tentatively propose that the major product of the aldol condensation derives from the transition state shown in Figure 1. This is in agreement with previous results[4] obtained in related systems, and with different stereoselectivities observed with the epimeric sulphinyl isoxazolines (**4a**) and (**4b**), probably because of steric interactions between the R^3 group of the aldehydes and the substituent at C-5 in the heterocyclic ring.‡

These reactions have been extended to sulphinyl isoxazolines (**6a**), $[\alpha]_D^{23}$ +83.2,[3] and (**6b**) +262.2,[3] in which a substituent is also present at C-4. As mentioned above, (**6a**) and (**6b**) have the same configuration at sulphur; they both feature a *trans* arrangement of the substituents at C-4 and C-5, and opposite configurations at these two stereocentres. Excellent stereoselection is generally achieved (Table 2).



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

Scheme 1. *Reagents:* i, lithium di-isopropylamide (LDA); ii, menthyl toluene-*p*-sulphinate; iii, base; iv, R^3CHO; v, 8% Na–Hg, NaH_2PO_4; vi, H_2, H_3BO_3, · Raney nickel. With **a** and **b** diastereoisomeric products are indicated.

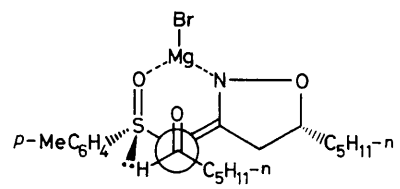


Figure 1

Although the relative influence of the groups at C-4 and C-5 and of the aldehyde R^3 residue is unclear at present, the presence of the sulphoxide group is essential in determining the extent and direction of the chiral discrimination. Aldol

† Metallation of (**4a**) with Bu^tMgBr and condensation with isobutyraldehyde afforded adduct (**7**) as a 8 : 1 mixture of only two diastereoisomers. They were separated by flash chromatography and individually converted into (+)-(**13a**), $[\alpha]_D^{23}$ + 60.2 (*c* 1 in $CHCl_3$) and (+)-(**13b**), $[\alpha]_D^{23}$ +137.8 (*c* 1 in $CHCl_3$), respectively. Chromatographic separation of the diastereoisomeric mixtures (**7**)—(**12**) and/or of their desulphurization products is possible in most cases, thus ensuring the isolation of enantiomerically and diastereoisomerically pure materials. The reaction, at least in the case of adducts (**7**) and (**8**) is, not unprecedentally,[2,7] stereospecific at the carbon α to the sulphoxide; however desulphurization destroys the stereocentre thus created.

‡ Further attack would lead to the same result, namely the one in the aldehyde approaches the enolate with the R^3 group facing the *p*-tolyl residue of the sulphoxide. We think that it can be disregarded on steric grounds.

Table 2. Stereoselective synthesis of hydroxyisoxazolines (**15a, b**)—(**17a, b**).[a]

Sulphoxide	Adduct	Base	Yields/%[b]	Diastereoisomeric[c] ratio **a** : **b**	$[\alpha]_D^{23}$[d]
(**6a**)	(**15a, b**)	MgDA	80	50 : 1	−313.3
(**6a**)	(**16a, b**)	Bu^{t}MgBr	50	20 : 1	−254.3
(**6a**)	(**16a, b**)	MgDA	50	9 : 1	[e]
(**6a**)	(**17a, b**)	MgDA	60	14 : 1	[f]
(**6b**)	(**15a, b**)	MgDA	75	1 : 50	+178.8
(**6b**)	(**16a, b**)	Bu^{t}MgBr	40	1 : 50	+166.9
(**6b**)	(**16a, b**)	MgDA	70	1 : 20	+170.0
(**6b**)	(**17a, b**)	MgDA	60	1 : 2.2	[g]

[a] Reactions carried out at −90 °C under argon in THF. Metallation time 30 min; condensation time 10 min. All bases *ca.* 0.5 M in diethyl ether. All new compounds gave analytical and spectral data in agreement with the proposed structures. [b] Overall yields from (**6**), products isolated by flash chromatography (diethyl ether–hexane). [c] As determined by 200 MHz ^{1}H n.m.r. spectroscopy. [d] *c* 1 in $CHCl_3$. [e] (−)-(**16a**), $[\alpha]_D^{23}$ −265.8, *c* 1 in $CHCl_3$; (−)-(**16b**), $[\alpha]_D^{23}$ −169.5, *c* 0.5 in $CHCl_3$. [f] (−)-(**17a**), $[\alpha]_D^{23}$ −204.3, *c* 1 in $CHCl_3$; (−)-(**17b**), $[\alpha]_D^{23}$ −152.2, *c* 0.5 in $CHCl_3$. [g] (+)-(**17a**) and (+)-(**17b**) had rotations comparable to those reported above.

condensation carried out with isoxazoline (**3**) showed poor stereoselectivity. Furthermore, the hydroxyisoxazolines predominantly produced from (**6a**) and (**6b**) are diastereoisomeric: they have the same configuration at the OH-bearing carbon and opposite configuration at the centres in the ring. Accordingly, the predominant isomer obtained from (**6a**) is the enantiomer of the minor product obtained from (**6b**), and *vice versa* (see Table 2).

Aldol condensation of sulphinyl isoxazolines was also extended to aromatic aldehydes. *E.g.*, reaction of sulphoxide (**6b**) with PhCHO afforded β,β′-dihydroxyketone (**18a, b**) as a 6 : 1 mixture of diastereoisomers, $[\alpha]_D^{23}$ +71.7, in 50% overall yield from (**6b**).

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References

1 K. Bast, N. Christl, R. Huisgen, W. Mack, and R. Sustmann, *Chem. Ber.*, 1973, **106**, 3258, and references therein; S. F. Martin and B. Dupre, *Tetrahedron Lett.*, 1983, 1337; V. Jager, R. Schohe, and E. F. Paulus, *ibid.*, 1983, 5501 and references therein.

2 V. Jager, H. Grund, V. Buss, W. Schwab, I. Muller, R. Schohe, R. Franz, and R. Ehrler, *Bull. Soc. Chim. Belg.*, 1983, **92**, 1039; D. P. Curran, *J. Am. Chem. Soc.*, 1983, **105**, 5826; A. P. Kozikowski and J. G. Scripko, *ibid.*, 1984, **106**, 353.

3 M. Cinquini, F. Cozzi, and A. Gilardi, *J. Chem. Soc., Chem. Commun.*, 1984, 551.

4 G. Solladie, F. Matloubi-Moghadam, C. Luttermann, and C. Mioskowski, *Helv. Chem. Acta*, 1982, **65**, 1602, and references therein; R. Annunziata, M. Cinquini, F. Cozzi, F. Montanari, and A. Restelli, *J. Chem. Soc., Chem. Commun.*, 1983, 1138.

5 R. Annunziata, S. Cardani, M. Cinquini, F. Cozzi, A. Gilardi, G. Poli, and C. Scolastico, *J. Chem. Soc., Perkin Trans.*, in the press; R. Annunziata, M. Cinquini, F. Cozzi, and A. Gilardi, *Synthesis*, 1983, 1016.

6 T. Hiyama and K. Kobayashi, *Tetrahedron Lett.*, 1982, 1597.

7 M. Mikolajczyk and J. Drabowicz, *Top. Stereochem.*, 1982, 333.