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Highly stereocontrolled boron-mediated synthesis of β-hydroxy-α-amino acids and dipeptides. Part 2

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Abstract

The chiral synthons **1(a–d)** were submitted to boron-mediated asymmetric aldol condensation with acetaldehyde and benzaldehyde providing, in high diastereomeric excess (>95%), *R,R*-configured aldols **2(a–f)** which are useful intermediates to enantiomerically pure β-hydroxy-α-amino acids.

1. Introduction

Recently, we described[1] a new diastereoselective approach to β-hydroxy-α-amino acids and dipeptides through aldol reactions using the lithium enolate of an appropriate chiral synthon. In the continuation of our investigations, we focused our attention on improving the diastereoselection of aldol condensations for the synthesis of enantiomerically pure common and uncommon α-amino acids and peptides. To this aim, we performed the aldol addition reaction using the boron enolate of the chiral synthons **1(a–d)** synthesized as described in our preceding papers.[1,2]

Thus, in this paper very interesting and encouraging results are reported. The stereochemical outcome of the aldol reaction which occurred with satisfactory chemical yields and with diastereomeric excesses better than 95% (Table 1) providing aldols **2**, which are intermediates for obtaining dipeptides and/or β-hydroxy-α-amino acids, is explained.[1]

2. Results and discussion

The aldol reaction occurred with practically total conversion of the chiral synthon **1** with benzaldehyde, while with acetaldehyde the chemical yield was not higher than 70% (Scheme 1).

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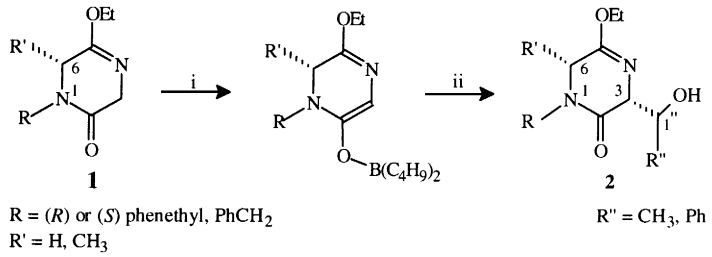
Table 1
Aldol condensation of boron enolates with acetaldehyde and benzaldehyde

Entry	1	R	R'	R''	2	(3*R*,1''*R*)-2 (a)	1,4 induction	selectivity
1	**a**	(S)-phenethyl	CH_3	CH_3	**a**	>98%	*cis*	*anti*
2	**a**	(S)-phenethyl	CH_3	Ph	**b**	>98%	*cis*	*anti*
3	**b**	(R)-phenethyl	CH_3	CH_3	**c**	95%	*cis*	*anti*
4	**c**	(S)-phenethyl	H	Ph	**d**	80% (b)	-	*anti*
5	**d**	Ph-CH_2	CH_3	CH_3	**e**	95%	*cis*	*anti*
6	**d**	Ph-CH_2	CH_3	Ph	**f**	>98%	*cis*	*anti*

(a) Yields calculated by ^{1}H-NMR on the crude reaction product; (b) 20% of the diastereomer (3*S*,1''*S*)-**2g** was obtained.



1 **2**

R = (*R*) or (*S*) phenethyl, $PhCH_2$
R' = H, CH_3
R'' = CH_3, Ph

Scheme 1. (i) Bu_2BOTf/Et_3N in CH_2Cl_2, rt; (ii) R''CHO in CH_2Cl_2, −78°C, then H_2O_2/NaOH at rt

The data reported in Table 1 show that in all the experiments performed, the reaction occurred in a highly stereocontrolled fashion: actually, except for entries 4 and 5, total 1,4-*cis* induction and *anti* stereoselection was achieved with only the isomer (3*R*,1′′*R*)-**2** being obtained. The observed stereochemical results are very different from those previously obtained by using the lithium enolates[1] which, conversely, prevalently gave *trans* induction and *anti* selectivity. Furthermore, such unsatisfactory diastereoselection has been confirmed by the results we obtained with the lithium enolates of **1**(**c**,**d**).[3]

The high stereocontrol evidenced by the boron enolates (Table 1) showed that the *Si*-face of the aldehyde approaches with a very large preference to the *Re*-face of the chiral boron enolate (Fig. 1) highly favoring relative topicity *ul*. Almost total formation of the (3*R*,1′′*R*)-**2** diastereomer was observed independent of both the substituent at N-1 (compare entries 1 and 5, 2 and 6) and its absolute configuration (compare entries 1 and 3). Moreover, it appears evident that the stereocenter on the remote C-6 influences the diastereoselectivity more than the chiral substituent on the adjacent N-1 (compare entries 4 and 6).

In order to explain the stereochemical outcome of the condensation, a molecular modeling investigation[4] was carried out on the simplified model **3** of the boron enolate (Fig. 2). Energy calculations have shown that in the minimum energy conformation the atoms (N-1)–(C-2)–(C-3)–(N-4)–(C-5) are almost planar, while the C-6 is slightly out of the plane. The C-1′ is not coplanar with the heterocyclic ring with the dihedral angle (C-3)–(C-2)–(N-1)–(C-1′) being 45°. In addition, the boron enolate, independent of the C-1′ stereocenter configuration, adopts a preferential conformation

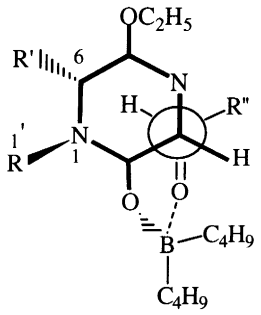


Fig. 1.

with the chiral phenethyl group *trans* with respect to both the substituent at C-6 and the boron atom which lies about 80° out of the plane and *cis* to the (C-6)-CH_3 (Fig. 1). Conformational analysis (using AM1 calculations) revealed that the isomer in which the boron atom and (C-6)-CH_3 lie *cis* is 3.5 and 4.4 kcal/mol more stable than the *trans*-isomer when the phenethyl group possesses *R*- or *S*-configuration, respectively. Such a strongly preferred arrangement would favor the *cis* attack of the aldehyde with respect to the (C-6)-CH_3 (see Fig. 1): effectively, the experimental results are consistent with the molecular modeling studies. These results suggest that the phenethyl moiety most probably acts to transfer through space the chiral information of the C-6 stereocenter to the C-3, i.e. the point of electrophilic attack. Thus, the (C-6)-CH_3 would direct the adjacent phenethyl group into the *anti* position which in turn directs the boron atom *syn* to the (C-6)-CH_3. These findings are consistent with the 'chiral relay network' already proposed.[5]

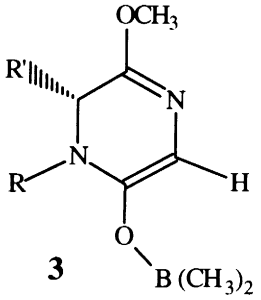


Fig. 2.

In order to confirm such a 'chirality transfer' we performed a conformational analysis of boron enolate **1d** in which the chiral phenethyl group was changed to Ph-CH_2^-. Also for this substrate in the preferred conformation, the boron is arranged *cis* with respect to the (C-6)-CH_3 and *trans* with respect to the (N-1)-CH_2Ph. AM1 calculations[4] showed that the preferred *cis* arrangement between B and CH_3 is about 1.7 kcal/mol more stable than the *trans*. Thus, it can be asserted that the chiral substituent at N-1 does not act as a chiral inductor, but more simply as a chirality transfer group, relaying the chirality from the remote chiral group at C-6.

In this context, it is interesting to point out that the substrate **1c** (entry 4), even if it gives total *anti* selectivity, in addition to diastereomer **2d** (80%) also furnished the diastereomer **2g** (20%) due to an attack of the *Si*-face of the chiral boron enolate of **1c** on the *Re*-face of benzaldehyde. The observed diastereoselection can be rationalized on the basis of the model used by d'Angelo and co-workers[6] to explain the diastereofacial differentiation in the alkylation of chiral enamine derived from (*R*)- or (*S*)-phenethylamine. These authors demonstrated that the phenethyl C–H bond preferentially eclipses the single C–C bond rather than the C=C, so that the enamine olefinic face *syn* to the phenyl ring is sterically

more hindered. A similar model, outlined in Fig. 3, could explain the observed facial stereoselection for the substrate **1c**. Indeed, because the phenethyl C–H bond preferentially eclipses the (C-5)–(C-6) bond, the phenyl ring causes greater steric hindrance on the *Si* face of the enolate, and the boron atom is then forced *trans* with respect to the aromatic ring favoring the approach of benzaldehyde from the *Re* face, i.e. the less hindered side.

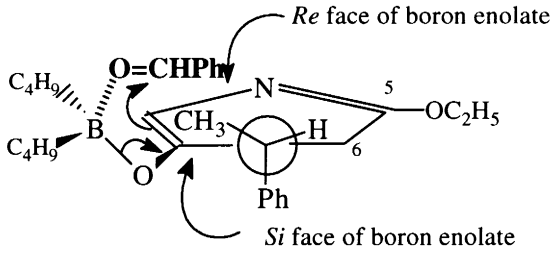


Fig. 3.

3. Stereochemical assignments

While the absolute configuration of the new introduced stereogenic centers of **2**(**a**,**b**,**c**) was already established,[1] the stereochemistry of **2**(**d**,**f**) and **2g** was assigned by comparison of the specific rotation value of the corresponding (2*R*,3*R*)- and (2*S*,3*S*)-methyl phenylserinate with that reported in the literature[7] obtained from the respective aldols by following the simple procedure previously reported.[1] The configuration of **2e** was assigned on the basis of ^{1}H NMR spectroscopic data by using the approach previously employed for analogous compounds[1] and confirmed by the agreement of the measured specific rotation value of the corresponding (2*R*,3*R*)-threonine, obtained from **2e**,[1] with that reported in the literature.[8]

4. Experimental

4.1. General information

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 MHz. Coupling constants (J) are in hertz. Optical rotation values were measured at 25°C on a Perkin–Elmer 343 polarimeter. The reactions involving organometallic reagents were carried out under an argon atmosphere in dry solvent. Bu_2BOTf was used as a commercially available 1 M solution in CH_2Cl_2. Et_3N was distilled from CaH_2 prior to use. The aldehydes employed were distilled prior to use.

4.2. (1′S)-5-Ethoxy-1-(1′-phenethyl)-3,6-dihydro-1H-pyrazine-2-one **1c**

The product was synthesized following the procedure we described for **1a**[2b] by using the ethyl ester of bromoacetic instead of bromopropionic acid. ^{1}H NMR: δ 1.2 (t, 3H, J=7.1), 1.52 (d, 3H, J=7.1), 3.38 (ddd, 1H, J=2.6, 2.6, 17), 3.74 (ddd, 1H, J=2.6, 2.6, 17), 4.06 (m, 2H), 4.2 (dd, 1H, J=2.6, 2.6), 6.1 (q, 1H, J=7.1), 7.3 (m, 5ArH). ^{13}C NMR: δ 13.9, 14.6, 40.2, 49.2, 50.6, 61.2, 127.1, 127.5, 128.4, 138.4, 157.6, 165.7. Anal. calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37. Found: C, 68.46; H, 7.35.

4.3. General procedure for the aldol reaction of **1(a–d)** with aldehydes

To 10 mmol of the lactime **1(a–d)** dissolved in 20 ml of dry CH_2Cl_2 under an argon atmosphere, 2.8 ml (20 mmol) of dry Et_3N and 18 ml (18 mmol) of Bu_2BOTf were added. The reaction was stirred 1 h at rt, then the bath was cooled to −78°C and 20 mmol of aldehyde were slowly added. After 30 min the reaction was quenched with phosphate buffer (pH=7) and extracted with ethyl acetate. The organic solution was evaporated in vacuo and 10 ml of 1N NaOH were added to the residue dissolved in 40 ml of methanol, then 10 ml of 30% H_2O_2 were added dropwise to the solution. After 1 h water was added, the methanol removed in vacuo and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with water and dried. After evaporation of the organic solvent, the residue was subjected to ^{1}H NMR analysis.

4.4. (3R,6R,1′S,1′′R)-5-Ethoxy-3-(1′′-hydroxyethyl)-6-methyl-1-(1′-phenethyl)-3,6-dihydro-1H-pyrazine-2-one **2a**

See the literature for details.[1]

4.5. (3R,6R,1′S,1′′R)-5-Ethoxy-3-(1′′-hydroxybenzyl)-6-methyl-1-(1′-phenethyl)-3,6-dihydro-1H-pyrazine-2-one **2b**

See the literature for details.[1]

4.6. (3R,6R,1′R,1′′R)-5-Ethoxy-3-(1′′-hydroxyethyl)-6-methyl-1-(1′-phenethyl)-3,6-dihydro-1H-pyrazine-2-one **2c**

See the literature for details.[1]

4.7. (3R,1′S,1′′R)-5-Ethoxy-3-(1′′-hydroxybenzyl)-1-(1′-phenethyl)-3,6-dihydro-1H-pyrazine-2-one **2d**

^{1}H NMR: δ 1.2 (t, 3H, J=7.1), 1.42 (d, 3H, J=7.1), 2.65 (dd, 1H, J=2.4, 17.1), 3.47 (dd, 1H, J=2.7, 17.1), 3.97 (d, 1H, J=7.3), 4.12 (m, 2H), 4.59 (m, 1H), 5.3 (dd, 1H, J=5.5, 7.3), 5.95 (q, 1H, J=7.1), 6.95 (m, 2ArH), 7.25 (m, 8ArH). ^{13}C NMR: δ 13.6, 14.4, 39.6, 48.8, 60.9, 63.6, 74, 126.4, 127, 127.3, 127.6, 128, 128.5, 137, 138.8, 159, 166. $[\alpha]_D$=−90.2 (*c* 2.54, $CHCl_3$). Anal. calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86. Found: C, 71.8; H, 6.84.

4.8. (3R,6R,1′R)-1-Benzyl-5-ethoxy-3-(1′-hydroxyethyl)-6-methyl-3,6-dihydro-1H-pyrazine-2-one **2e**

^{1}H NMR: δ 1.24 (t, 3H, J=7.1), 1.31 (d, 3H, J=6.1), 1.43 (d, 3H, J=6.8), 3.82 (dq, 1H, J=1.9, 6.8), 4 (d, 1H, J=15), 4.15 (m, 4H), 5.34 (d, 1H, J=15), 7.3 (m, 5ArH). ^{13}C NMR: δ 14, 19.2, 20, 45.9, 51.2, 61.5, 64.1, 70.1, 127.7, 128, 128.6, 131.5, 160.4, 168.1. $[\alpha]_D$=22.6 (*c* 0.61, $CHCl_3$). Anal. calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64. Found: C, 66.32; H, 7.65.

4.9. (3R,6R,1′R)-1-Benzyl-5-ethoxy-3-(1′-hydroxybenzyl)-6-methyl-3,6-dihydro-1H-pyrazine-2-one **2f**

^{1}H NMR: δ 0.5 (d, 3H, J=7), 1.2 (t, 3H, J=7.1), 3.6 (dq, 1H, J=2.1, 7), 3.78 (d, 1H, J=14.9), 3.82 (d, 1H, J=7.3), 4.1 (q, 2H, J=7.1), 4.64 (dd, 1H, J=2.1, 5.4), 5.3 (d, 1H, J=14.9), 5.3 (dd, 1H, J=5.4, 7.3),

7.25 (m, 10ArH). ^{13}C NMR: δ 14.1, 17.6, 45.6, 50.9, 61.5, 64.6, 74.9, 126.9, 127.6, 127.7, 128.2, 128.6, 135.4, 140, 160.8, 166.4. $[\alpha]_D$=−34 (*c* 1.95, $CHCl_3$). Anal. calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86. Found: C, 71.45; H, 6.88.

*4.10. (3*S*,1′*S*,1′′*S*)-5-Ethoxy-3-(1′′-hydroxybenzyl)-1-(1′-phenethyl)-3,6-dihydro-1*H*-pyrazine-2-one* ***2g***

^{1}H NMR: δ 1.2 (d, 3H, J=7.1), 1.22 (t, 3H, J=7.1), 2.7 (dd, 1H, J=2.3, 16.9), 3.04 (dd, 1H, J=2.2, 16.9), 3.82 (d, 1H, J=7.1), 4.1 (m, 2H), 4.6 (m, 1H), 5.34 (dd, 1H, J=5.4, 7.1), 5.97 (q, 1H, J=7.1), 7.3 (m, 10ArH). ^{13}C NMR: δ 14.1, 14.4, 39.8, 49.3, 61.8, 64.6, 75.1, 126.9, 127.3, 127.6, 127.8, 138.4, 139.8, 159.2, 165.9. $[\alpha]_D$=−57.6 (*c* 1, $CHCl_3$). Anal. calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86. Found: C, 71.45; H, 6.84.

Acknowledgements

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3. The following diastereomeric distribution was observed:

1	Aldehyde	(3R,1′′R) **2**	(3S,1′′S) **2**	(3S,1′′R) **2**	(3R,1′′S) **2**	*trans/cis* ratio	*Anti/syn* Ratio
c	PhCHO	9%	8%	28%	55%	-	17:83
d	PhCHO	19%	37%	25%	19%	62:38	56:44
d	CH_3CHO	24%	49%	27%	-	76:24	73:27

4. Energy calculations were performed by the AM1 method (HyperChem Program, 1994) by using the ‘Polak-Ribiere’ algorithm (RMS gradient 0.01 kcal).
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8. *Beil*. *4*(3), 1629: $[\alpha]_D$=−9 (*c* 2, H_2O).