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Diastereoselective aldol reaction of an α-alkoxycarbonylamino aldehyde with a silyl enol ether

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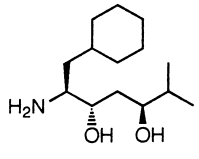
Abstract

The aldol reaction of optically active α-alkoxycarbonylamino aldehydes with a silyl enol ether in the presence of a Lewis acid afforded γ-amino-β-hydroxyketones diastereoselectively. The effect of the α-amide proton on the diastereoselectivity is discussed. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

Optically active β-amino alcohols are biologically interesting compounds which are widely used in the inhibitors of aspartic proteases such as renin and HIV-proteases.[1] We have already reported a series of potent renin inhibitors which contain a (2*S*,3*S*,5*S*)-2-amino-1-cyclohexyl-6-methyl-3,5-heptanediol fragment (**1**) as a transition state mimic in the renin-catalyzed reaction.[2]



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Since aminodiol **1** could be prepared from *syn*-γ-amino-β-hydroxyketone **4a** with a high stereoselectivity by use of the Evans' reduction method,[3] the diastereoselective synthesis of **4a** was explored for the preparation of **1**. Thus, we proposed the reaction of optically active α-alkoxycarbonylamino aldehyde **2a** with silyl enol ether **3** in the presence of a Lewis acid, which was obtained from the Mukaiyama stereoselective aldol reaction,[4] as shown in Scheme 1. Here we report the stereoselective aldol reaction, and we also discuss a mechanism to explain the stereoselectivity.

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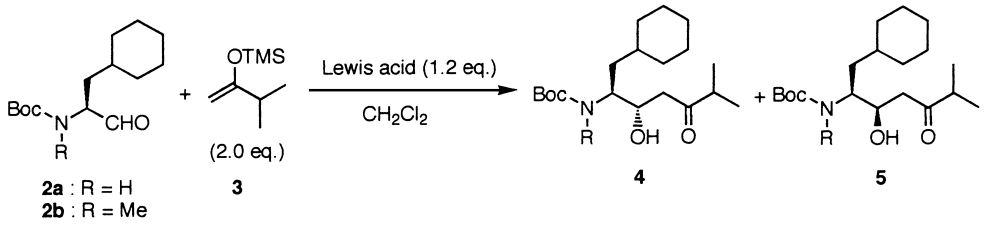


Scheme 1.

2. Results and discussion

The results of the reaction of *N-tert*-butoxycarbonyl-L-cyclohexylalaninal **2a**[5] with *O*-trimethylsilyl enolate **3**[6] in the presence of various Lewis acids (1.2 equiv.) are summarized in Table 1. The aldol reaction of **2a** with **3** in dichloromethane at −78°C using titanium(IV) chloride ($TiCl_4$) as the Lewis acid afforded the desired *syn*-adduct **4a** along with the *anti*-isomer **5a** in a ratio of 80 to 20 (run 1).[7] The use of tin(IV) chloride ($SnCl_4$) also gave similar stereoselectivity as $TiCl_4$ (run 2).[8] When boron trifluoride etherate ($BF_3 \cdot OEt_2$) was used as a Lewis acid, both the stereoselectivity and yield increased (runs 3 and 4).

Table 1
The aldol reaction of aldehyde **2** with *O*-trimethylsilyl enol ether **3** in the presence of a Lewis acid

Run	Aldehyde	Lewis acid	Temp. (°C)	Yield (%)	Ratio of **4** to **5**
1	**2a**	$TiCl_4$	-78	51[a]	80 : 20[a]
2	**2a**	$SnCl_4$	-78	56[a]	80 : 20[a]
3	**2a**	$BF_3 \cdot Et_2O$	-78	66[a]	93 : 7[a]
4	**2a**	$BF_3 \cdot Et_2O$	-40	73[a]	90 : 10[a]
5	**2b**	$BF_3 \cdot Et_2O$	-78	38	20 : 80[b]
6	**2b**	$SnCl_4$	-78	27	20 : 80[b]

[a] Determined by HPLC analysis using (D)-diethyl tartarate as an internal standard.
[b] Determined by ^{1}H-NMR as the corresponding acetate.

In the aldol reaction of **2a** mediated by $TiCl_4$ or $SnCl_4$, the observed *syn*-selectivity can be rationalized in terms of the chelation-controlled mechanism (Fig. 1, (A)) as suggested by Terashima et al.[8] However, $BF_3 \cdot OEt_2$, which is incapable of chelation,[9] gave **4a** with a higher stereoselectivity. We propose that this selectivity is explained by the hydrogen bonding interaction between the carbonyl oxygen of the aldehyde and the α-NH proton (Fig. 1, (B)).[10] Thus, nucleophile **3** approaches from the less hindered side of the hydrogen bonded five-membered ring, giving the *syn*-adduct **4a**. To confirm the effect of the α-NH proton on the diastereoselectivity, we examined the aldol reaction of *N*-methylated aldehyde

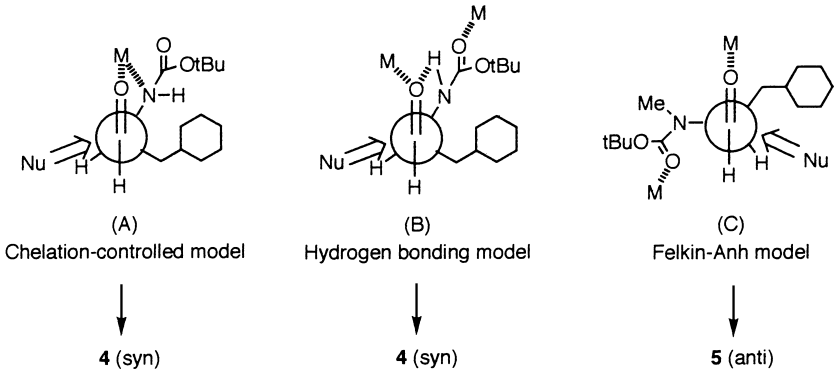


Figure 1.

2b mediated by $BF_3 \cdot OEt_2$, and found an inversion of the stereoselectivity (run 5).[11] This result can be rationalized by the Felkin–Anh model (Fig. 1, (C)). Interestingly, in the aldol reaction of **2b** with $SnCl_4$, the 'Felkin–Anh' product **5b** was obtained in preference to the 'chelation-controlled' product **4b** (run 6).

To gain more insight into the hydrogen bonding model described above, we observed the conformational changes in aldehydes **2a** and **2b** induced by the addition of $BF_3 \cdot OEt_2$ at −78°C in CD_2Cl_2 with NMR spectroscopy. The ^1H and ^{13}C NMR data are summarized in Table 2. By addition of 1 equiv. of $BF_3 \cdot OEt_2$, the carbamate (N*C*(=O)O) and the *tert*-butyl (O*C*$(CH_3)_3$) carbon signals were shifted to downfield, and the signals derived from noncomplexed ether (14.0, 65.0 ppm in ^{13}C NMR) appeared in both the NMR spectra of **2a** and **2b**. These results suggest that 1 equiv. of BF_3 is quantitatively coordinated by the carbamate oxygen of the substrate. From our experimental results, the aldol reaction of **2a** with less than 1 equiv. of $BF_3 \cdot OEt_2$ did not take place at all: the activation of the aldehyde carbonyl group by excess BF_3 is thought to be required to promote the reaction. However, the downfield shifts of the aldehyde proton or carbon signals implying the complexation of the aldehyde oxygen of **2a** with BF_3 were not detected even after addition of 2 equiv. of $BF_3 \cdot OEt_2$ in the NMR experiment. The life-time of the transition state, in which the aldehyde oxygen of **2a** coordinates with BF_3, may be too short to be detected by NMR. Instead, the different behavior of the aldehyde group was observed between **2a** and **2b** in the NMR studies. By exposure of *N*-methylated substrate **2b** to $BF_3 \cdot OEt_2$, the proton and carbon signals of aldehyde disappeared, and the signals corresponding to an acetal function appeared. This result indicates that BF_3 promoted the conversion of **2b** to its trimer, paraldehyde.[12] The low yield observed in the aldol reaction of **2b** (Table 1) may be due to this paraldehyde formation. In contrast, no trimerization was observed in the mixture of **2a** and $BF_3 \cdot OEt_2$. From these results, it is suggested that the aldehyde carbonyl group of **2a** is reluctant to be converted to its trimer since it forms a hydrogen bond with the α-NH proton.

Aminodiol **1** was prepared as shown in Scheme 2. The reduction of hydroxyketone **4a** using tetramethylammonium borohydride in propionic acid afforded *anti*-diol **6** with a high stereoselectivity (84% de).[3] After recrystallization, enantiomerically pure **6** was obtained in 34% yield starting from the crude mixture of **4a** and **5a** produced under the conditions of run 3 in Table 1. The Boc group of **6** was removed by treatment with trifluoroacetic acid to give aminodiol **1**.

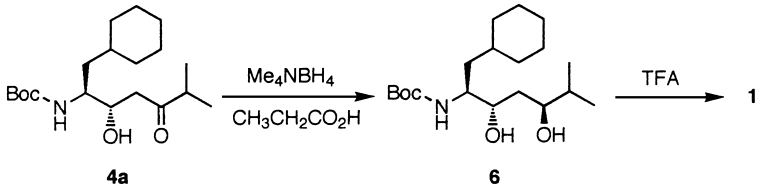
3. Conclusions

The aldol reaction of optically active α-alkoxycarbonylamino aldehyde **2a** with silyl enol ether in the presence of a Lewis acid afforded *syn*-γ-amino-β-hydroxyketone **4a** diastereoselectively. The

Table 2
^{1}H and ^{13}C NMR data of **2a** and **2b** and their complexes with $BF_3 \cdot OEt_2$

substrate	$BF_3 \bullet OEt_2$	^{1}H ∂ (ppm)	^{13}C ∂ (ppm)		
		C<u>H</u>O	<u>C</u>HO	N<u>C</u>(=O)O	O<u>C</u>$(CH_3)_3$
2a	none	9.42	200.7	155.0	79.4
2a	1 equiv.	9.42	195.8	156.8	91.1
2a	2 equiv.	9.42	195.8	156.8	91.1
2b	none	9.49, 9.53[a]	202.1	154.1, 155.0[a]	79.3, 79.8[a]
2b	1 equiv.	6.11, 6.18[a,b]	109.2, 110.1[a,b]	158.1, 158.9[a]	96.3, 97.9[a]
2b	2 equiv.	6.11, 6.18[a,b]	109.2, 110.1[a,b]	158.1, 158.9[a]	96.3, 97.9[a]

[a] Two peaks due to rotamers.
[b] Paraldehyde



Scheme 2.

syn-selectivity with $BF_3 \cdot OEt_2$ as a Lewis acid can be explained by the transition state model of the intramolecular hydrogen bonding formed between the α-amide proton and the aldehyde oxygen of **2a**.

4. Experimental

4.1. General

Melting points were determined on a Buchi 535 melting point apparatus. Infrared (IR) spectra were recorded on a Jasco IR700 IR spectrometer or on a Perkin–Elmer 1650 FT-IR spectrometer. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. Nuclear magnetic resonance (NMR) spectra were measured on Bruker AMX300 (300 MHz), ARX400 (400 MHz) and Jeol JNMA300 (300 MHz) instruments. Chemical shifts are reported as δ values (parts per million relative to tetramethylsilane as an internal standard. Fast atom bombardment mass spectra (FABMS) were obtained with a Finnigan MAT TSQ700 mass spectrometer or with a Jeol SX102 mass spectrometer. Elemental analyses were performed by the Analytical Group, Central Pharmaceutical Research Institute, Japan Tobacco Inc. Thin-layer chromatography (TLC) was carried out using Merck precoated silica gel 60 F-254 plates (thickness

0.25 mm). Preparative TLC was carried out using Merck precoated silica gel 60 F-254 plates (thickness 0.5–1.0 mm). Column chromatography was carried out using Merck silica gel 60 (70–230 mesh or 230–400 mesh).

4.2. General procedure for the aldol reactions

A solution of *N*-Boc-cyclohexylalaninal **2a** (1.0 mmol) in CH_2Cl_2 (10 ml) was treated with a Lewis acid (1.2 mmol). After being stirred for 10 min, silyl enolate **3** (2.0 mmol) was added and the mixture was stirred for 1 h. The mixture was poured into a mixture of ice and saturated aqueous $NaHCO_3$, and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was separated by silica gel chromatography with a mixture of AcOEt and hexane (1:9) to give the analytical samples of hydroxyketone **4a** and **5a**.

4.2.1. (5S,6S)-6-(tert-Butoxycarbonyl)amino-7-cyclohexyl-2-methyl-5-hydroxy-3-heptanone **4a**

A pale yellow oil. R_f 0.40 (AcOEt:hexane=3:7). ^{1}H NMR ($CDCl_3$) δ: 0.8–1.9 (m, 13H), 1.11 (d, 6H, *J*=6.9 Hz, -CH(C*H*$_3$)$_2$), 1.45 (s, 9H, -C(C*H*$_3$)$_3$), 2.5–2.8 (m, 3H), 3.40 (d, 1H, *J*=2.3 Hz), 3.61 (m, 1H), 4.02 (m, 1H), 4.70 (br d, 1H, *J*=9.9 Hz, -CON*H*-). FABMS m/z: $[M+H]^+$ calcd for $C_{19}H_{36}NO_4$: 342.2646. Found: 342.2649.

4.2.2. (5R,6S)-6-(tert-Butoxycarbonyl)amino-7-cyclohexyl-2-methyl-5-hydroxy-3-heptanone **5a**

White solid. R_f 0.34 (AcOEt:hexane=3:7). Mp 94–96°C. ^{1}H NMR ($CDCl_3$) δ: 0.7–2.0 (m, 13H), 1.10 (d, 6H, *J*=6.9 Hz, -CH(C*H*$_3$)$_2$), 1.44 (s, 9H, -C(C*H*$_3$)$_3$), 2.5–2.8 (m, 3H), 3.40 (br d, 1H), 3.63 (m, 1H), 3.97 (m, 1H), 4.55 (br d, 1H, -CON*H*-). Anal. calcd for $C_{19}H_{35}NO_4$: C, 66.83; H, 10.33; N, 4.10. Found: C, 66.96; H, 10.49; N, 4.11.

4.3. (2S,3S,5S)-2-(tert-Butoxycarbonyl)amino-1-cyclohexyl-6-methyl-3,5-heptanediol **6**

To propionic acid (200 ml) was added tetramethylammonium borohydride (10 g, 113 mmol) by portions at 0°C, and the mixture was stirred for 1 h. To the mixture was added dropwise a solution of crude **4a** (9.62 g, 28 mmol), which was prepared under the conditions of run 3 in Table 1, in propionic acid (50 ml). After being stirred for 2 h at 0°C, the mixture was poured into a mixture of ice and saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (500 ml). The organic layer was washed with aqueous 2N NaOH (200 ml×3) and brine (300 ml×2), dried over $MgSO_4$, then evaporated. The residue was recrystallized from hexane:AcOEt (10:1) to give **6** (3.3 g, 34%) as white crystals. R_f 0.63 (AcOEt:hexane=1:1). Mp 148–150°C. IR (KBr) cm^{-1}: 1716. $[\alpha]_D^{25}$ −54.3 (c=1.05, MeOH). ^{1}H NMR ($CDCl_3$) δ: 0.8–1.9 (m, 16H), 0.90 (d, 3H, *J*=6.8 Hz, -CH(C*H*$_3$)$_2$), 0.94 (d, 3H, *J*=6.7 Hz, -CH(C*H*$_3$)$_2$), 1.45 (s, 9H, -C(C*H*$_3$)$_3$), 2.47 (br d, 1H, -O*H*), 2.68 (br d, 1H, -OH), 3.59 (m, 1H), 3.69 (m, 1H), 3.83 (m, 1H), 4.64 (br d, 1H, *J*=9.1 Hz, -CON*H*-). Anal. calcd for $C_{19}H_{37}NO_4$: C, 66.44; H, 10.86; N, 4.08. Found: C, 66.55; H, 11.09; N, 4.31.

4.4. (2S,3S,5S)-2-Amino-1-cyclohexyl-6-methyl-3,5-heptanediol **1**

A solution of **6** (2.44 g, 7.1 mmol) in trifluoroacetic acid (50 ml) was stirred for 30 min at room temperature, then concentrated. Saturated aqueous $NaHCO_3$ (50 ml) was added to the residue, and the mixture was extracted with $CHCl_3$ (50 ml×3). The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by silica gel chromatography with a mixture of $CHCl_3$, MeOH

and NH_4OH (95:5:0.5) to give **1** (1.59 g, 92%) as white crystals. Mp 88–90°C. $[\alpha]_D^{25}$ −53.3 (c=1.02, MeOH). ^1H NMR ($CDCl_3$) δ: 0.8–1.9 (m, 16H), 0.91 (d, 3H, *J*=6.8 Hz, -CH(CH_3)$_2$), 0.95 (d, 3H, *J*=6.7 Hz, -CH(CH_3)$_2$), 2.75 (ddd, 1H, *J*=3.3, 6.6, 9.9 Hz, $NH_2CH<$), 3.51 (dt, 1H, *J*=3.8, 7.0 Hz), 3.61 (ddd, 1H, *J*=2.8, 6.1, 8.9 Hz). Anal. calcd for $C_{14}H_{29}NO_2$: C, 69.09; H, 12.01; N, 5.75. Found: C, 69.08; H, 11.99; N, 5.96.

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