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Lewis Acid- and Cationic Lithium-Mediated Diastereoselective Aldol-Type Reaction Based on a Double Chiral Recognition Manner for the Asymmetric Synthesis of α-Substituted Serines

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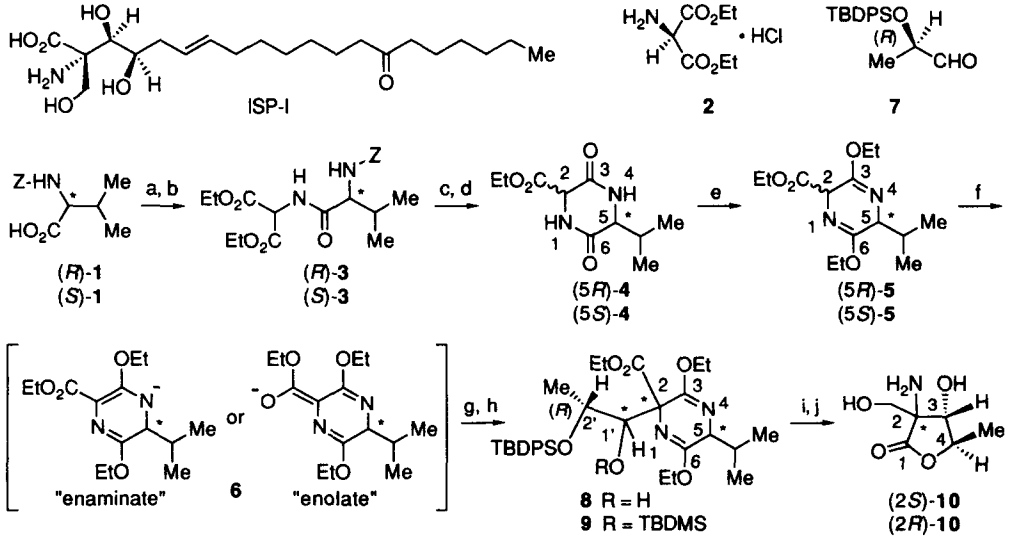
Abstract: Diastereoselective aldol-type reaction of ethyl (5*R* or 5*S*)-3,6-diethoxy-2,5-dihydro-5-isopropyl-2-pyrazinecarboxylate (**5**) with chiral aldehyde **7** was investigated by using $Sn(OSO_2CF_3)_2$-*N*-ethylpiperizine, $MgBr_2$-Et_3N, *n*-butyllithium, and lithium diisopropylamide. The mediation mode with Sn(II) between (5*R* or 5*S*)-**5** and **7** proved to be quite different from that with Mg(II). The two aldol products were converted to the corresponding γ-lactonic α-substituted serines (2*S*)- and (2*R*)-**10**.

α-Chiral carbon-substituted ("α-substituted") α-amino acids must be of great interest to us from the viewpoints of investigation of their biological activities[1] and also of potential modification of the original enzymatic function by chemicoenzymatic exchange for the natural amino acid residue in the active center domain of enzymes.[2] Among syntheses of α-substituted α-amino acids, there have been a few reports on



Scheme 1. a) *N*-methylmorpholine / *i*-BuOCOCl / THF, b) compound **2** / DMF, c) H_2 / Pd-C / EtOH, d) hot EtOH, e) Et_3OBF_4 / CH_2Cl_2, f) Lewis acid - *tert.* amine or base: see foot note of Table 1., g) compound **7**, h) $Me_2(t\text{-Bu})SiOSO_2CF_3$ / 2,6-lutidine / CH_2Cl_2, i) *i*-Bu_2AlH / CH_2Cl_2, j) 12N HCl / *i*-PrOH

the chiral serine derivatives possessing the hydroxymethyl group.[3] Very recently, we have achieved an asymmetric total synthesis of ISP-I (a potent immunosuppressive principle in the *Isaria sinclairii* metabolite) bearing the chiral α-substituted serine moiety.[4] In order to construct the serine moiety, we utilized the successfully modified Schöllkopf bislactim ether procedure[5] which is herein described (Scheme 1). We designed a new bislactim ether derivative, ethyl (5*R*) or (5*S*)-3,6-diethoxy-2,5-dihydro-5-isopropyl-2-pyrazinecarboxylate (**5**) for the chiral serine precursor. The chiral heterocycle **5** can be readily derived from *N*-benzyloxycarbonyl-D- or L-valine (*R*-**1** or *S*-**1**) and diethyl aminomalonate hydrochloride (**2**). Namely, (*R*)- or (*S*)-**1** was treated with *i*-BuOCOCl in the presence of *N*-methylmorpholine in THF at -18 °C followed by amide formation with a solution of **2** in DMF to give each corresponding compound (*R*)-**3** (83%) or (*S*)-**3** (81%), respectively. The amide (*R*)- or (*S*)-**3** was submitted to hydrogenolytic debenzyloxycarbonylation over Pd-C followed by heating in EtOH to afford the diketopiperazine (5*R*)-**4** (92%) or (5*S*)-**4** (87%). Their treatment with Et_3OBF_4 in CH_2Cl_2 gave readily the corresponding chiral bislactim diethyl ether (5*R*)-**5** (77%) or (5*S*)-**5** (88%) as a diastereomeric mixture due to the ethoxycarbonyl group. Diastereoselective aldol-type reactions of the chiral heterocycle (5*R*)- or (5*S*)-**5** with the chiral aldehyde **7**[6] were examined by employing $Sn(OSO_2CF_3)_2$-*N*-ethylpiperidine, $MgBr_2$-Et_3N, *n*-butyllithium (*n*-BuLi), and lithium diisopropylamide (LDA) under the suitable conditions as shown in Table 1. The Lewis acid- and cationic lithium-mediated reactions between enaminate or enolate **6** and **7** proceeded in a double chiral recognition manner to afford aldol products **8** with various diastereomeric ratios respectively. Since undesirable retro-aldol reactions of the diastereomeric products **8** occurred during their purification, the crude compounds **8** in each reaction were treated with *tert*-butyldimethylsilyl (TBDMS) trifluoromethanesulfonate in the presence of 2,6-lutidine to give the corresponding TBDMS ethers **9**. The compounds **9** were submitted to the ^1H NMR (400 MHz, $CDCl_3$) analysis to determine their diastereomeric ratios. Among the possible eight diastereomeric products, seven pure compounds **9** were obtained by chromatographic separation of each reaction mixture on a silica gel plate. All results are listed in Table 1. The absolute configuration of newly formed chiral carbon atoms of four products **9** [(5*R*, 2*S*, 1'*S*), (5*R*, 2*S*, 1'*R*), (5*S*, 2*S*, 1'*S*), and (5*S*, 2*R*, 1'*S*)] was established by their X-ray crystallographic analysis respectively.[7] Stereochemistry of the compound (5*S*, 2*R*, 1'*R*)-**9** was determined on the basis of its ^1H-^1H NOE experiment (400 MHz, $CDCl_3$, 5 H ↔ *t*-Bu protons of TBDMS group) in comparison with that (The same ^1H-^1H NOE must be impossible.) of another possible product (5*S*, 2*S*, 1'*R*)-**9**. Unfortunately, we

Table 1. Aldol-Type Reaction of (5*R*)- and (5*S*)-**5** with Chiral Aldehyde **7**.

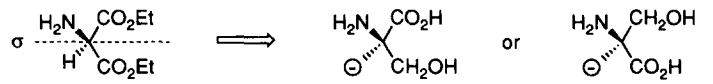
Run	**5**	Base or LA-Amine[a)]	Solv	Temp (°C)	Time (h)	Yield (%) of **9**	Diastereomer Ratio[b)] (2*S*, 1'*S*) : (2*S*, 1'*R*) : (2*R*, 1'*R*) : (2*R*, 1'*S*)
1	5*R*	A	THF	-78	4	70	100 : — : — : —
2	〃	B	MeCN	-20	3	51	35 : 39 : 26[c)] : —
3	〃	B'	〃	〃	2.5	83	24 : 48 : 28[c)] : —
4	〃	C	THF	-78	7.5	72	63 : 27 : 6[c)] : 4[c)]
5	〃	D	〃	〃	6.5	74	88 : 4 : 6[c)] : 2[c)]
6	5*S*	A	〃	〃	5	79	46 : — : 17 : 37
7	〃	B	MeCN	-20	3	59	— : — : — : 100
8	〃	B'	〃	〃	3.5	81	— : — : — : 100
9	〃	C	THF	-78	7	62	48 : — : 18 : 34
10	〃	D	〃	〃	6.5	61	61 : — : — : 39

[a] LA = Lewis Acid, A: $Sn(OSO_2CF_3)_2$ (1.5 mol eq) - *N*-ethylpiperidine (1.6 mol eq), B: $MgBr_2$ (1.5 mol eq) - Et_3N (1.6 mol eq), B': $MgBr_2$ (2 mol eq) - Et_3N (4 mol eq), C: *n*-BuLi (1.1 mol eq), D: LDA (1.1 mol eq). [b] Determined by ^1H NMR (400 MHz, $CDCl_3$) analysis. [c] The configuration of C1' was arbitrarily assigned.

could not determine the stereochemistry of the remaining two products **9** of which one should be (5*R*, 2*R*, 1'*R*) or (5*R*, 2*R*, 1'*S*) configuration.

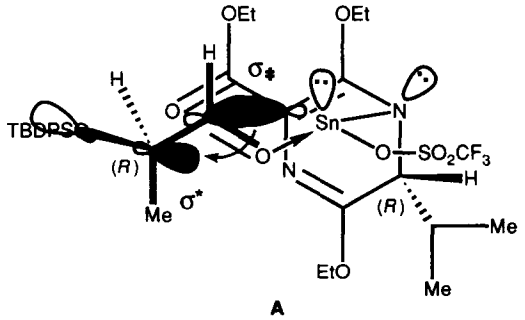
The aldol-type reaction of (5*R*)-**5** with **7** in the presence of $Sn(OSO_2CF_3)_2$ and *N*-ethylpiperidine afforded exclusively a compound (5*R*, 2*S*, 1'*S*)-**9** in 70% yield (Run 1). In this reaction, $Sn(OSO_2CF_3)_2$ must be an excellent mediator. Interestingly, the similar aldol-type reaction employing $MgBr_2$ and Et_3N gave its diastereomer (5*R*, 2*S*, 1'*R*)-**9** as the major product in a moderate diastereoselective manner (Runs 2 and 3). In the cases of *n*-BuLi and LDA, four possible diastereomers **9** were furnished. The major product proved to be the same compound (5*R*, 2*S*, 1'*S*)-**9** as the reaction with $Sn(OSO_2CF_3)_2$ and *N*-ethylpiperidine has been done as described above (Runs 4 and 5).

The excellent Lewis acid mediator in the diastereoselective aldol-type reaction using (5*S*)-**5** and the chiral aldehyde **7** proved to be $MgBr_2$. The reaction in the presence of Et_3N proceeded smoothly to give an exclusive product (5*S*, 2*R*, 1'*S*)-**9** in 81% yield (Run 8). On the other hand, the similar reaction of (5*S*)-**5** with **7** using $Sn(OSO_2CF_3)_2$-*N*-ethylpiperidine, *n*-BuLi, or LDA gave a compound (5*S*, 2*S*, 1'*S*)-**9** as the major product together with other diastereomer(s) (Runs 6, 9, and 10). Reduction of (5*R*, 2*S*, 1'*S*)- and (5*S*, 2*R*, 1'*S*)-**9** with diisobutylaluminum hydride (DIBAL) followed by hydrolysis with 12N HCl in *i*-PrOH afforded the corresponding γ-lactonic α-substituted serines (2*S*)-**10** [68% yield from **9**, colorless powder, mp 152-153 °C, $[\alpha]_D^{22}$ +38.6 ° (*c* 0.57, MeOH)] and (2*R*)-**10** [51% yield from **9**, colorless oil, $[\alpha]_D^{22}$ +62.1 ° (*c* 0.37, MeOH)], respectively. Thus, we demonstrated that σ-symmetric diethyl aminomalonate is utilized as the chiral serine carbanion synthons based on the synthetic operation as illustrated in Scheme 1.



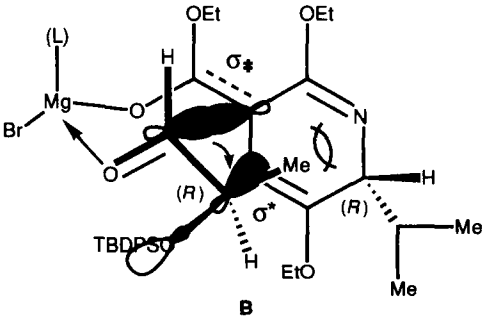
"chiral serine carbanion"

The stereochemical outcome in the cases of Runs 1, 2 and 3 in Table 1 may be understood in terms of presumed six-membered transition state A [Sn(II)-enaminate] or B [Mg(II)-enolate] based on the $\sigma_{\ddagger}$ (OC•••C) → σ* (C-OTBDPS) orbital overlap effect.[8] In the case of Runs 7 and 8, the similar presumed transition state C may be understandable for the excellent diastereoselectivity toward the sole product. The similar aldol reaction of (5*R*)-**5** with the chiral aldehyde **11** bearing an extremely bulky group employing $MgBr_2$ and Et_3N seemed to proceed *via* the possible six-membered transition state B' [Mg(II)-enolate] based on the antiperiplanar (R and C•••C) steric effect.[8] In fact, $MgBr_2$ proved to be an excellent mediator and $Sn(OSO_2CF_3)_2$ was confirmed to be an unsatisfied one for the aldol-type reaction of (5*R*)-**5** with the chiral aldehyde **12** in the course of the asymmetric total synthesis of ISP-I.[4]



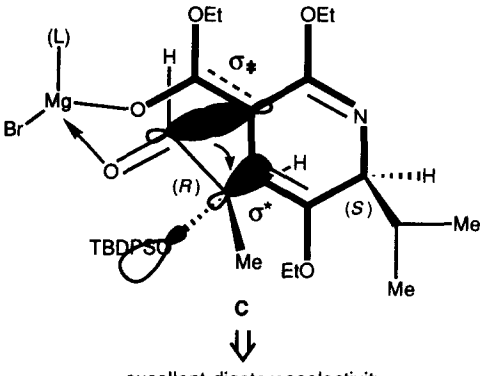
A

excellent diastereoselectivity



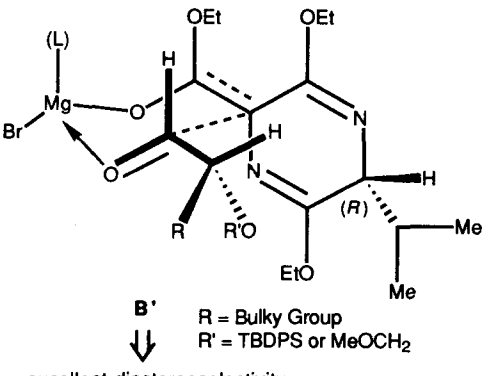
B

moderate diastereoselectivity



C

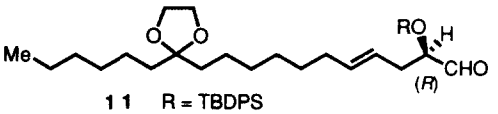
excellent diastereoselectivity



B'

R = Bulky Group
R' = TBDPS or $MeOCH_2$

excellent diastereoselectivity



11 R = TBDPS
12 R = $MeOCH_2$

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6. Chiral aldehyde **7** (99.4% de) was readily converted from commercially available (*R*)-(+)-methyl lactate.
7. The crystallographic data of four diastereomers **9** are as follows. (5*R*, 2*S*, 1'*S*)-**9**: $C_{39}H_{62}N_2O_6Si_2$, M = 711.10, monoclinic, $P2_1$, a = 8.882 (3) Å, b = 19.283 (2) Å, c = 12.599 (2) Å, β = 95.43 (2) °, V = 2148.0 (7) $Å^3$, z = 2, D_{cal} = 1.099 g/cm^3, R = 0.041. (5*R*, 2*S*, 1'*R*)-**9**: $C_{39}H_{62}N_2O_6Si_2$, M = 711.10, monoclinic, $P2_1$, a = 11.883 (4) Å, b = 16.721 (6) Å, c = 12.212 (4) Å, β = 114.47 (2) °, V = 2208 (1) $Å^3$, z = 2, D_{cal} = 1.069 g/cm^3, R = 0.049. (5*S*, 2*S*, 1'*S*)-**9**: $C_{39}H_{62}N_2O_6Si_2$, M = 711.10, monoclinic, $P2_1$, a = 10.738 (4) Å, b = 30.028 (4) Å, c = 13.719 (3) Å, β = 91.81 (2) °, V = 4421 (1) $Å^3$, z = 4, D_{cal} = 1.068 g/cm^3, R = 0.043. (5*S*, 2*R*, 1'*S*)-**9**: $C_{39}H_{62}N_2O_6Si_2$, M = 711.10, orthorhombic, $P2_12_12_1$, a = 16.685 (2) Å, b = 25.161 (2) Å, c = 10.449 (3) Å, V = 4386 (1) $Å^3$, z = 4, D_{cal} = 1.077 g/cm^3, R = 0.056.
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