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Tin- or magnesium-mediated diastereoselective aldol-type reactions for the asymmetric synthesis of α-substituted serines

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Abstract

Diastereoselective aldol-type reactions of ethyl (5*S*)-3,6-diethoxy-2,5-dihydro-5-isopropyl-2-pyrazinecarboxylate (5*S*)-**3** with achiral aldehydes **8a**–**d** was investigated by using $Sn(OSO_2CF_3)_2$–*N*-ethylpiperizine and $MgBr_2$–triethylamine. The reaction with Sn(II) between (5*S*)-**3** and aliphatic aldehydes **8a**,**b** proved to be quite different from that with Mg(II). On the other hand, Sn(II)- or Mg(II)-mediated aldol-type reactions of (5*S*)-**3** with benzaldehyde **8c** and 3-methyl-2-butenal **8d** each afforded the same diastereomer as the major product. These aldol products were each converted to the corresponding α-substituted serines **6** and **7** as enantiomerically pure compounds.

Recently, we have carried out extensive development of new methods for the synthesis of α-substituted serines, which should be remarkably interesting from the standpoint of pharmaceutical and bioorganic chemistry.[1,2] In earlier papers, we reported the diastereoselective aldol-type reaction and alkylation of the newly designed bislactim ether, ethyl (5*R*)- or (5*S*)-3,6-diethoxy-2,5-dihydro-5-isopropyl-2-pyrazinecarboxylate **3**, as a chiral α-substituted serine precursor.[3] Chiral α-alkylated serines can be also synthesized by utilizing a chemoenzymatic procedure.[4]

Herein we describe the diastereoselective aldol-type reaction of the bislactim ether (5*S*)-**3**, readily prepared from σ-symmetric diethyl aminomalonate **1** and L-valine (*S*)-**2**,[3b] with achiral aldehydes **8a**–**d** in conjunction with the synthesis of α-substituted serines as shown in Scheme 1. All results are shown in Table 1. The aldol-type reaction of aliphatic aldehydes **8a**,**b** with bislactim ether (5*S*)-**3** in the presence of $Sn(OSO_2CF_3)_2$ and *N*-ethylpiperidine in THF at −78°C afforded (2*R*,5*S*,1′*S*)-**4a**,**b** as their major product, respectively (entries 1 and 3). Interestingly, the similar aldol-type reaction employing $MgBr_2$ and triethylamine gave the different diastereomer (2*R*,5*S*,1′*R*)-**4a**,**b** as each major product (entries 2 and 4). In earlier papers, we also reported that the diastereoselective mode of the Sn(II)-mediated reaction differed from the Mg(II)-mediated one in the aldol-type reaction of (5*S*)-**3** with chiral aliphatic

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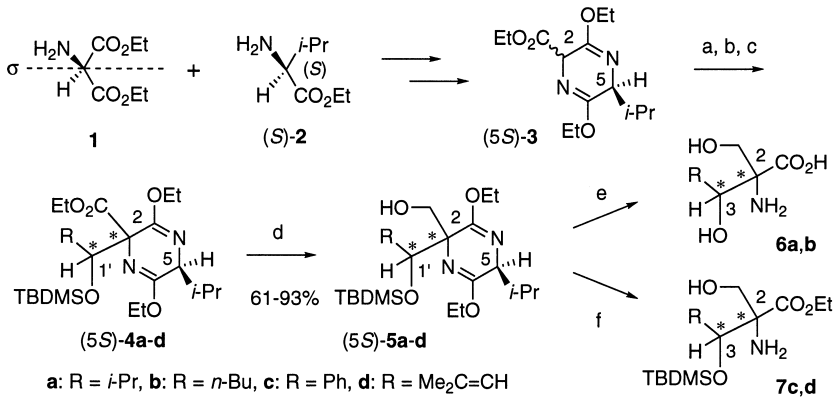


Scheme 1. (a) Sn(II) or Mg(II): see footnote for Table 1, (b) RCHO (**8a**–**d**), (c) $Me_2(t\text{-Bu})SiOSO_2CF_3$/2,6-lutidine/$CH_2Cl_2$/−45°C, (d) DIBAL/toluene/0°C, (e) 12 N HCl:CF_3CO_2H:*i*-PrOH (2:1:1)/170°C, (f) 0.2 N HCl:THF (1:1)/rt

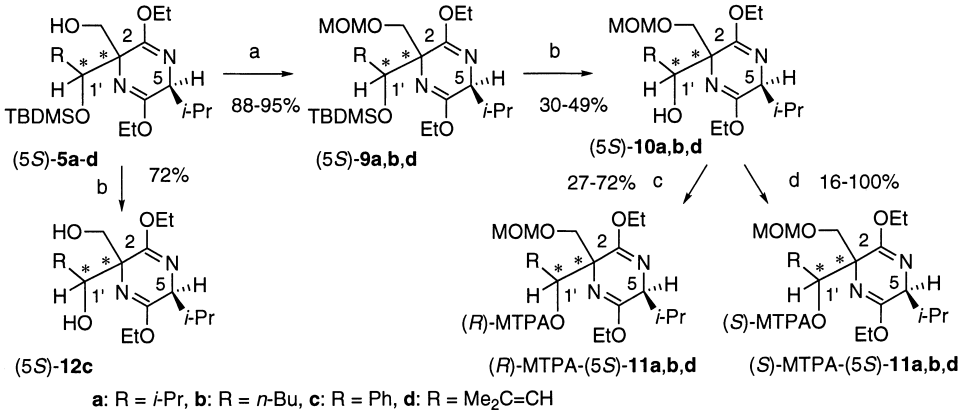
aldehydes.[3a,b] However, each major product proved to be the same diastereomer (2*R*,5*S*,1′*R*)-**4c**,**d** in the aldol-type reaction of (5*S*)-**3** with benzaldehyde **8c** and 3-methyl-2-butenal **8d** whether Sn(II) or Mg(II) was employed (entries 5–8). The diastereomer ratios of **4a**–**d** were determined by exploiting ^{1}H NMR analysis (400 MHz, $CDCl_3$). The absolute configuration of the newly formed C2 stereogenic center in the separable diastereomers **4a**–**d** was determined by the ^{1}H–^{1}H NOE (400 MHz, $CDCl_3$) experiments of **4a**–**d** and/or of the corresponding derivatives **10a**,**b**,**d** (Scheme 2). ^{1}H NMR analysis (400 MHz, $CDCl_3$) of the Mosher ester [(*R*)- and (*S*)-methoxy(trifluoromethyl)phenylacetate (MTPA)] derivatives **11a**,**b**,**d** and X-ray crystallographic analysis of diol **12c** (Fig. 1) and (*S*)-MTPA-**11d** were utilized in order to determine the absolute configuration of the chiral C1′ atom in the 10 kinds of aldol products **4a**–**d** (Scheme 2).[5]

The separable diastereoisomers **4a**–**d** were isolated by column chromatography on silica gel. Reduction of the major diastereoisomers of **4a**–**d** with DIBAL in toluene at 0°C [(2*R*,5*S*,1′*S*)-**5a**: 93%, (2*R*,5*S*,1′*R*)-**5b**: 61%, (2*R*,5*S*,1′*R*)-**5c**: 80%, and (2*R*,5*S*,1′*R*)-**5d**: 83% yields] followed by hydrolysis

Table 1
Diastereoselective aldol-type reaction of bislactim ether (5*S*)-**3** with aldehydes **8a**–**d**

Entry	Aldehyde	Conditions [a]	Time	Diastereomer Ratio [b] (2*R*,1′*S*) : (2*R*,1′*R*) : (2*S*,1′*R*) : (2*S*,1′*S*)	Yield (%) of **4**
1	**8a**	**A**	2 h	66 : 8 : 25 : 1	84
2	**8a**	**B**	2.5 h	7 : 83 : 1 : 9	86
3	**8b**	**A**	2 h	55 : 25 : 17 [c] : 3 [c]	84
4	**8b**	**B**	30 min	7 : 75 : 2 [c] : 16 [c]	75
5	**8c**	**A**	30 min	10 : 88 : 0 [c] : 2 [c]	86
6	**8c**	**B**	10 min	18 : 72 : 0 [c] : 10 [c]	70
7	**8d**	**A**	30 min	34 : 52 : 8 [c] : 6 [c]	80
8	**8d**	**B**	10 min	16 : 64 : 3 [c] : 17 [c]	74

a) **A**: THF, -78 °C, (5*S*)-**3** / $Sn(OSO_2CF_3)_2$ / *N*-ethylpiperidine / **8** (1 : 1.5 : 1.6 : 2); **B**: MeCN, -20 °C, (5*S*)-**3** / $MgBr_2$ / triethylamine / **8** (1 : 2 : 4 : 2). b) ^{1}H NMR analysis (400 MHz NMR, $CDCl_3$). c) Configuration of C1' was assigned arbitrarily



Scheme 2. (a) MOMCl/*i*-Pr_2NEt/CH_2Cl_2/rt, (b) TBAF/THF/rt, (c) (*S*)-MTPACl/DMAP/Et_3N/CH_2Cl_2/rt, (d) (*R*)-MTPACl/DMAP/Et_3N/CH_2Cl_2/rt

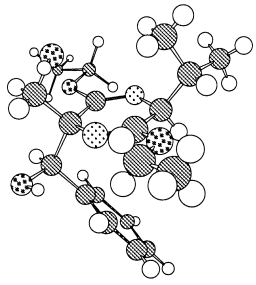
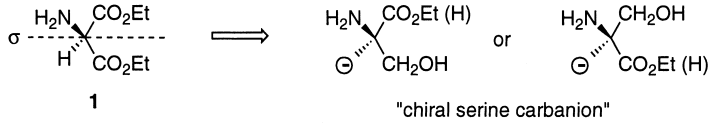


Fig. 1. Computer-generated drawing of (2*R*,5*S*,1′*R*)-**12c** derived from the X-ray coordinates

with 12 N HCl:CF_3CO_2H:*i*-PrOH (2:1:1) or 0.2 N HCl:THF (1:1) afforded the corresponding α-substituted serines **6a**,**b** and **7c**,**d** [(2*R*,3*S*)-**6a**: 26%, (2*R*,3*R*)-**6b**: 37%, (2*R*,3*R*)-**7c**: 35%, and (2*R*,3*R*)-**7d**: 28% yields], respectively.[6]

The different stereochemical outcome in the Sn(II)- or Mg(II)-mediated aldol-type reaction of (5*S*)-**3** with aliphatic aldehydes **8a**,**b** can be rationalized in terms of the corresponding six-membered transition states as we previously proposed.[3a,b] In contrast, unsaturated aldehydes such as benzaldehyde **8c** and 3-methyl-2-butenal **8d** may change the common transition state in the Sn(II)-mediated aldol-type reaction owing to plausible π–π stacking between the bislactim ring of (5*S*)-**3** and the unsaturated (or aromatic) moiety of aldehydes **8c**,**d**. Interestingly, the crystal structure of (2*R*,5*S*,1′*R*)-**12c** was shown to be a folded conformation with two stacked rings, the bislactim ring and the benzene ring (Fig. 1).[3c]

In conclusion, α-substituted serines were synthesized as each enantiomerically pure form by using the aldol-type reactions of (5*S*)-**3** with achiral aldehydes. Thus, we demonstrated that σ-symmetric diethyl aminomalonate **1** could be utilized as the chiral serine carbanion synthon.



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5. The crystallographic data are as follows. (2*R*,5*S*,1′*R*)-**12c**: $C_{19}H_{28}N_2O_4$, *M*=348.44, orthorhombic, $P2_12_12$, *a*=15.198(2) Å, *b*=24.749(3) Å, *c*=10.635(2) Å, *V*=3996.5(9) Å^3, *Z*=8, D_{cal}=1.158 g/cm^3. (*S*)-MTPA-(2*R*,5*S*,1′*R*)-**11d**: $C_{29}H_{41}F_3N_2O_7$, *M*=586.65, triclinic, P1, *a*=9.730(3) Å, *b*=9.916(3) Å, *c*=9.642(2) Å, α=108.29(2)°, β=119.45(2)°, γ=82.76(3)°, *V*=768.7(5) Å^3, *Z*=1, D_{cal}=1.267 g/cm^3.
6. (2*R*,3*S*)-**6a**: colorless powder (MeOH), mp 226–227°C (dec.), $[\alpha]_D^{27}$ −26.1 (*c* 0.12, MeOH), ^{1}H NMR (400 MHz, D_2O) δ 0.90 (3H, d, *J*=6.8 Hz), 1.00 (3H, d, *J*=6.8 Hz), 1.89 (1H, dsept, *J*=2.9, 6.8 Hz), 3.85 (1H, d, *J*=2.9 Hz), 3.86 (1H, A of AB, *J*=12.2 Hz), 4.05 (1H, B of AB, *J*=12.2 Hz); IR (KBr) 2964, 2358, 1641, 1541, 1467, 1404, 1355, 1247 cm^{-1}; HRFAB-MS calcd for $C_7H_{16}NO_4$ M$^+$+H 178.1079, found *m*/*e* 178.1087 (M$^+$+H). (2*R*,3*R*)-**6b**: colorless powder (MeOH), mp 231–232°C (dec.), $[\alpha]_D^{26}$ +36.1 (*c* 0.06, MeOH), ^{1}H NMR (400 MHz, D_2O) δ 0.88 (3H, t, *J*=6.8 Hz), 1.27–1.50 (6H, m), 3.85–3.90 (1H), 3.87 (1H, A of AB, *J*=11.7 Hz), 4.03 (1H, B of AB, *J*=11.7 Hz); IR (KBr) 2959, 1615, 1344 cm^{-1}; HRFAB-MS calcd for $C_8H_{18}NO_4$ M$^+$+H 192.1236, found *m*/*e* 192.1217 (M$^+$+H). Anal. calcd for $C_8H_{17}NO_4$: C, 50.25; H, 8.96; N, 7.32. Found: C, 50.19; H, 8.80; N, 7.23. (2*R*,3*R*)-**7c**: colorless oil, $[\alpha]_D^{26}$ −44.9 (*c* 1.00, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.25 (3H, s), 0.06 (3H, s), 0.89 (9H, s), 1.12 (3H, t, *J*=7.2 Hz), 2.04–2.18 (3H, Br), 3.66 (1H, A of AB, *J*=10.4 Hz), 3.89 (1H, B of AB, *J*=10.4 Hz), 3.92–4.06 (2H, m), 4.89 (1H, s), 7.22–7.31 (5H, m); IR (NaCl) 3382, 2931, 2888, 2858, 1740, 1585, 1472, 1363, 1255, 1217 cm^{-1}; HRCI-MS calcd for $C_{18}H_{32}NO_4Si$ M$^+$+H 354.2101, found *m*/*e* 354.2130 (M$^+$+H). (2*R*,3*R*)-**7d**: colorless oil, $[\alpha]_D^{25}$ −36.9 (*c* 1.01, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.02 (3H, s), 0.04 (3H, s), 0.86 (9H, s), 1.25 (3H, t, *J*=7.2 Hz), 1.65 (3H, s), 1.69 (3H, s), 2.00–2.09 (3H, Br), 3.55 (1H, A of AB, *J*=10.4 Hz), 3.77 (1H, B of AB, *J*=10.4 Hz), 4.01–4.10 (2H, m), 4.15–4.23 (2H, m), 4.50 (1H, d, *J*=9.6 Hz), 5.16 (1H, d, *J*=10.0 Hz); IR (NaCl) 2930, 2858, 1738, 1473, 1377, 1251, 1217 cm^{-1}; HRCI-MS calcd for $C_{16}H_{34}NO_4Si$ M$^+$+H 332.2257, found *m*/*e* 332.2247 (M$^+$+H).