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Diastereoselective alkylation of a newly designed bislactim ether towards the asymmetric synthesis of α-alkylated serines

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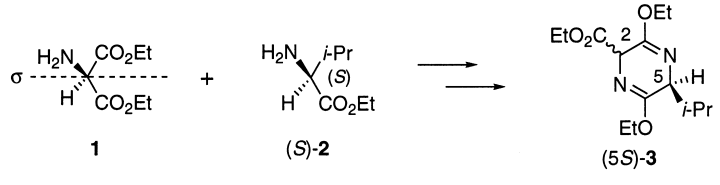
Abstract

Diastereoselective alkylation of ethyl (5*S*)-3,6-diethoxy-2,5-dihydro-5-isopropyl-2-pyrazinecarboxylate (5*S*)-**3** with alkyl halides was investigated by using NaH and *n*-BuLi. These alkylated products (2*R*,5*S*)-**4b**–**d** were converted to the corresponding α-alkylated serines (*S*)-**6b**–**d**. © 1998 Elsevier Science Ltd. All rights reserved.

Nonproteinogenic amino acids, such as α-substituted α-amino acids, have attracted our attention because of their biological activity.[1] Specifically, the construction of enantiomerically pure α-substituted serines is of considerable interest from the standpoint of synthetic and pharmaceutical chemistry.[2] In previous work, we reported the diastereoselective aldol-type reaction of a newly designed bislactim ether, ethyl (5*R*)- or (5*S*)-3,6-diethoxy-2,5-dihydro-5-isopropyl-2-pyrazinecarboxylate **3**, as the chiral α-substituted serines precursor.[3]



1 (*S*)-**2** (5*S*)-**3**

Herein we describe diastereoselective alkylation of the chiral bislactim ether **3** with alkyl halides towards the enantioselective construction of α-alkylated serines as shown in Scheme 1. Bislactim ether (5*S*)-**3** was readily prepared from σ-symmetric diethyl aminomalonate **1** and L-valine (*S*)-**2** according to the previously reported procedure.[3b] Diastereoselective alkylation of the bislactim ether (5*S*)-**3** with alkyl halides was examined by employing NaH or *n*-BuLi under suitable conditions as shown in Table 1. The reaction of the sodium enolate of (5*S*)-**3** with 2 mol equiv. of alkyl halides gave alkylated products (2*R*,5*S*)-**4a**–**d** as colorless oils in reasonable yields and 52–92% diastereomeric excess (de), respectively (entries 1–4 in Table 1). Similar treatment of the lithium enolate of (5*S*)-**3** with 2 mol equiv. of alkyl halides afforded (2*R*,5*S*)-**4a**–**c** in 68–84% yields and 34–97% de (entries 5–7), but poor reactivity was

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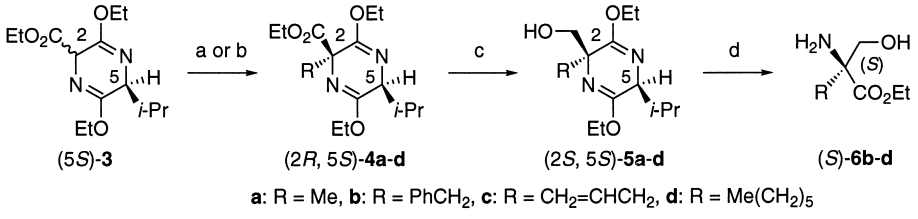
observed in the reaction with *n*-hexyl bromide (entry 8). The absolute configuration and de of (2*R*,5*S*)-**4a**–**c** were determined by ^{1}H–^{1}H NOE (400 MHz, $CDCl_3$) experiments and by comparison with the absolute configuration of each corresponding diastereomer, (2*S*,5*S*)-**4a**–**c**. When C2–Me protons of (2*R*,5*S*)-**4a** were irradiated, an NOE enhancement of C5–H was recognized (Fig. 1). On the other hand, irradiation of C2–Me protons of (2*S*,5*S*)-**4a** caused no NOE enhancement of C5–H. In the case of (2*R*,5*S*)-**4b**,**c**, a similar NOE enhancement was observed [(2*R*,5*S*)-**4b**: between C5–H and phenyl protons, (2*R*,5*S*)-**4c**: between C5–H and an allyl proton] as shown in Fig. 1. These alkyl substituents must be introduced in a *cis*-relation manner to the proton at C5 due to the steric hindrance between the alkyl halides and the *i*-propyl group at C5. Based on the reaction mechanism described above, the absolute configuration of the major product obtained from the reaction of (5*S*)-**3** with *n*-hexyl bromide was speculated to be (2*R*,5*S*)-**4d**.



Scheme 1. (a) NaH/RX/THF/rt, (b) *n*-BuLi/RX/THF 0°C, (c) DIBAL/CH_2Cl_2/0°C or 0°C→rt, (d) 0.2 N HCl/MeCN/rt

Reduction of each diastereomeric mixture of **4a**–**d** with 2.5 mol equiv. of DIBAL in CH_2Cl_2 at 0°C to room temperature followed by chromatographic separation of the resultant two diastereoisomers on a silica gel column gave the corresponding primary alcohols (2*S*,5*S*)-**5a**–**d** as the enantiomerically pure compound in various yields (**5a**: 56%, **5b**: 84%, **5c**: 76%, and **5d**: 77%). Interestingly, a considerable upfield shift of C5–H (δ 2.91 ppm in $CDCl_3$, 2.92 ppm in THF-d_8, 2.92 ppm in methanol-d_4, and 3.13 ppm in benzene-d_6) of (2*S*,5*S*)-**5b** was evidently recognized when compared with the chemical shift (δ 3.72 ppm in $CDCl_3$, 3.70 ppm in THF-d_8, 3.78 ppm in methanol-d_4, and 3.90 ppm in benzene-d_6) of (2*R*,5*S*)-**5b** in the ^{1}H NMR (200 MHz) spectrum.[4] In addition, one of the Me protons (δ −0.05 ppm in $CDCl_3$, −0.14 ppm in THF-d_8, −0.04 ppm in methanol-d_4, and 0.35 ppm in benzene-d_6) of

Table 1
Diastereoselective alkylation of bislactim ether (5*S*)-**3**

Entry	RX	Conditions [a]	Time	Product	Yield (%)	De (%) [b]
1	MeI	**A**	50 min	(2*R*, 5*S*)-**4a**	69	52
2	$PhCH_2Br$	**A**	1.5 h	(2*R*, 5*S*)-**4b**	82	92
3	CH_2=$CHCH_2Br$	**A**	45 min	(2*R*, 5*S*)-**4c**	58	82
4	$Me(CH_2)_5Br$	**A**	7.75 h	(2*R*, 5*S*)-**4d**	71	70
5	MeI	**B**	2.5 h	(2*R*, 5*S*)-**4a**	68	34
6	$PhCH_2Br$	**B**	40 min	(2*R*, 5*S*)-**4b**	84	97
7	CH_2=$CHCH_2Br$	**B**	2.75 h	(2*R*, 5*S*)-**4c**	74	88
8	$Me(CH_2)_5Br$	**B**	2.5 h	—	— [c]	—

a) Conditions **A**: THF, rt, (5*S*)-**3** / NaH / RX (1 : 1.5 : 2); **B**: THF, 0 °C, (5*S*)-**3** / *n*-BuLi / RX (1 : 1.1 : 2). b) ^{1}H NMR analysis (400 MHz, $CDCl_3$). c) No reaction. 76% recovery of (5*S*)-**3**.

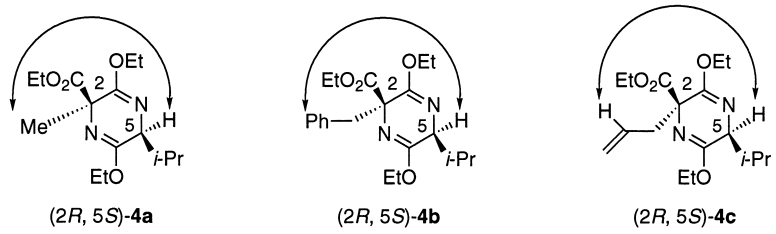
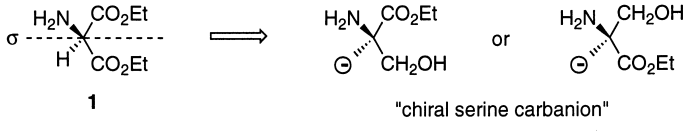


Fig. 1. Selected ^{1}H–^{1}H NOE enhancements (400 MHz ^{1}H NMR, $CDCl_3$) for (2*R*,5*S*)-**4a**–**c**

(2*R*,5*S*)-**5b** exhibited a significant upfield shift in comparison with the chemical shift (δ 0.58 or 0.87 ppm in $CDCl_3$, 0.59 or 0.89 ppm in THF-d_8, 0.69 or 0.95 ppm in methanol-d_4, and 0.71 or 1.01 ppm in benzene-d_6) of (2*S*,5*S*)-**5b**.[4] Such a phenomenon seems to be rationalized in terms of the shielding effect of the phenyl moiety, which probably adopts a folded conformation with the bislactim ether moiety.[5,6] Hydrolysis of (2*S*,5*S*)-**5b**–**d** with 2 mol equiv. of 0.2 N HCl in MeCN at room temperature afforded the corresponding α-alkylated serines (*S*)-**6b**–**d** as each enantiomerically pure compound (**6b**: 58%, **6c**: 16%, and **6d**: 31% yields).[7] Unfortunately, (*S*)-**6a** was not obtained after hydrolysis of (2*S*,5*S*)-**5a** under the acidic conditions.[8]

In conclusion, some α-alkylated serines were synthesized, each in enantiomerically pure form, by using chiral bislactim ether (5*S*)-**3**. Thus, we demonstrated that σ-symmetric diethyl aminomalonate **1** could be utilized as the chiral serine carbanion synthon.



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4. (2*S*,5*S*)-**5b**: colorless needles (CH_2Cl_2–*n*-hexane), mp 63–64°C, $[\alpha]_D^{21}$ −79.7 (*c* 1.00, MeOH), ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.58 (3H, d, *J*=6.8 Hz), 0.87 (3H, d, *J*=6.8 Hz), 1.28 (3H, t, *J*=7.1 Hz), 1.34 (3H, t, *J*=7.1 Hz), 2.14 (1H, dsept, *J*=3.2, 6.8 Hz), 2.28 (1H, X of ABX, t, J_{AX}=J_{BX}=6.7 Hz), 2.85 (1H, A′ of A′B′, d, *J*=13.0 Hz), 2.91 (1H, d, *J*=3.2 Hz), 3.06 (1H, B′ of A′B′, d, *J*=13.0 Hz), 3.71 (1H, A of ABX, dd, J_{AX}=6.7, J_{AB}=7.2 Hz), 3.79 (1H, B of ABX, dd, J_{BX}=6.7, J_{AB}=7.2 Hz), 3.97–4.27 (4H, m), 6.97–7.02 (2H, m), 7.14–7.20 (3H, m); IR ($CHCl_3$) 3600, 1693, 1384, 1367, 1215 cm^{-1}; HREI-MS calcd for $C_{19}H_{28}N_2O_3$ MW 332.2099, found *m/e* 332.2097 (M^+). Anal. calcd for $C_{19}H_{28}N_2O_3$: C, 68.65; H, 8.49; N, 8.43. Found: C, 68.32; H, 8.51; N, 8.33. (2*R*,5*S*)-**5b**: colorless needles (CH_2Cl_2–*n*-hexane), mp 91–92°C, $[\alpha]_D^{21}$ +91.9 (*c* 0.51, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$) δ −0.05 (3H, d, *J*=6.8 Hz), 0.81 (3H, d, *J*=6.8 Hz), 1.28 (3H, t, *J*=7.1 Hz), 1.36 (3H, t, *J*=7.1 Hz), 1.76 (1H, dsept, *J*=4.2, 6.8 Hz), 1.92–2.08 (1H, brs), 2.84 (1H, A of AB, d, *J*=12.6 Hz), 3.18 (1H, B of AB, d, *J*=12.6 Hz), 3.61 (1H, A′ of A′B′, d, *J*=10.6 Hz), 3.72 (1H, d, *J*=4.2 Hz), 3.78 (1H, B′ of A′B′, d,

J=10.6 Hz), 4.01–4.28 (4H, m), 7.07–7.25 (5H, m); IR ($CHCl_3$) 3600, 1691, 1307, 1225, 1212 cm^{-1}; HREI-MS calcd for $C_{19}H_{28}N_2O_3$ MW 332.2099, found *m*/*e* 332.2081 (M^+). Anal. calcd for $C_{19}H_{28}N_2O_3$: C, 68.65; H, 8.49; N, 8.43. Found: C, 68.38; H, 8.59; N, 8.29.

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7. (*S*)-**6b**: white powder, mp 47.5–49.5°C, $[\alpha]_D^{24}$ +4.5 (*c* 0.69, MeOH), ^1H NMR (200 MHz, $CDCl_3$) δ 1.26 (3H, t, *J*=7.1 Hz), 2.14 (3H, brs), 2.81 (1H, A of AB, d, *J*=13.4 Hz), 3.10 (1H, B of AB, d, *J*=13.4 Hz), 3.58 (1H, A′ of A′B′, d, *J*=10.6 Hz), 3.84 (1H, B′ of A′B′, d, *J*=10.6 Hz), 4.18 (2H, q, *J*=7.1 Hz), 7.11–7.16 (2H, m), 7.23–7.29 (3H, m); IR ($CHCl_3$) 3572, 3032, 2931, 1693, 1306, 1243, 1225, 1220 cm^{-1}; HRFAB-MS calcd for $C_{12}H_{18}NO_3$ M^++H 224.1286, found *m*/*e* 224.1292 (M^++H).
8. For the chemoenzymatic synthesis of both enantiomers of α-methylserine, see: Sano, S.; Hayashi, K.; Miwa, T.; Ishii, T.; Fujii, M.; Mima, H.; Nagao, Y. *Tetrahedron Lett*. **1998**, *39*, 5571–5574.