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Synthesis of methyl 3-amino-2-hydroxy-4-phenylbutanoates, important core intermediates for peptide mimics possessing biological activities

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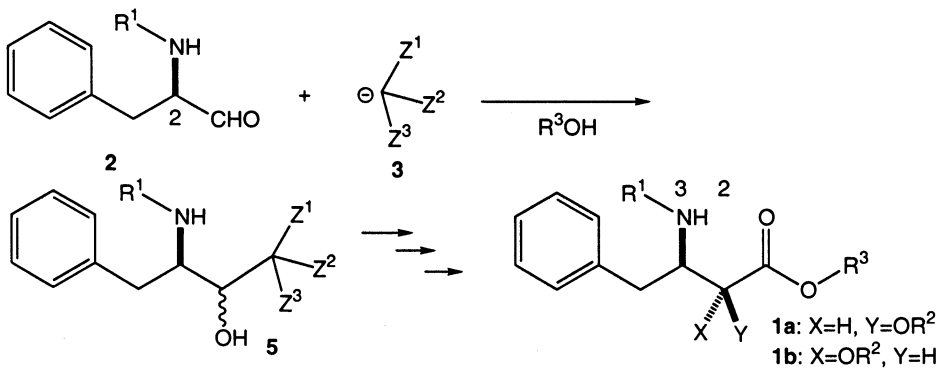
Abstract—Core intermediates for the synthesis of anti-cancer agents, inhibitors of aminopeptidases and HIV proteases, 3-amino-2-hydroxy-4-phenylbutanoates were synthesized by using H-C(CN)$_2$O-SiR$_3$ as a key reagent.

An unusual amino acid **1a**, (2*S*,3*R*)-*N*,*O*-protected-3-amino-2-hydroxy-4-phenylbutanoate as well as its 2*R*-diastereomer **1b**, is one of the important core intermediates[1] of several naturally occurring or artificially synthesized anti-cancer agents, inhibitors of aminopeptidases and HIV proteases[2] (Scheme 1). To synthesize **1** or the related compounds, several methods including the nucleophilic addition reaction to the *N*-protected-2-amino-3-phenylpropionaldehydes **2** by a masked formyl anion **3**[3] have been reported. Although the reaction is one of the most straightforward synthetic routes, the methods generally consisted of *several steps* including an unmasking procedure under vigorous conditions.

We report the synthesis of the methyl (2*S*,3*R*)-*N*,*O*-protected-3-amino-2-hydroxy-4-phenylbutanates **9a**–**11a** as shown in Scheme 2 by using 2-(*tert*-butyldimethylsiloxy)malononitrile (H-MAC-TBS,[4] **4m**) or 2-(triisopropylsiloxy)malononitrile (H-MAC-TIPS, **4n**) *in a one-portion manipulation* directly from **2Z** or **2B**.[5]

We first attempted the reaction of **2Z** with H-MAC-MOM (**4l**) in acetonitrile with various catalysts or promoters in the presence of trapping reagents such as acetic anhydride or diketene.[6] However, no *O*-acylated derivatives of the adducts **6** (R^1=Cbz, R^2=MOM) were obtained, and more than 50% of the starting material **2Z** was recovered probably because of a reversible reaction (Scheme 3). Therefore, we examined **4m** instead of **4l** since a silyl group could be migrated to generate **7** or **8**, which inhibits the reversible reaction.



Scheme 1.

Keywords: amino acids and derivatives; amino aldehydes; acyl cyanides; acyl anion equivalents; biologically active compounds.
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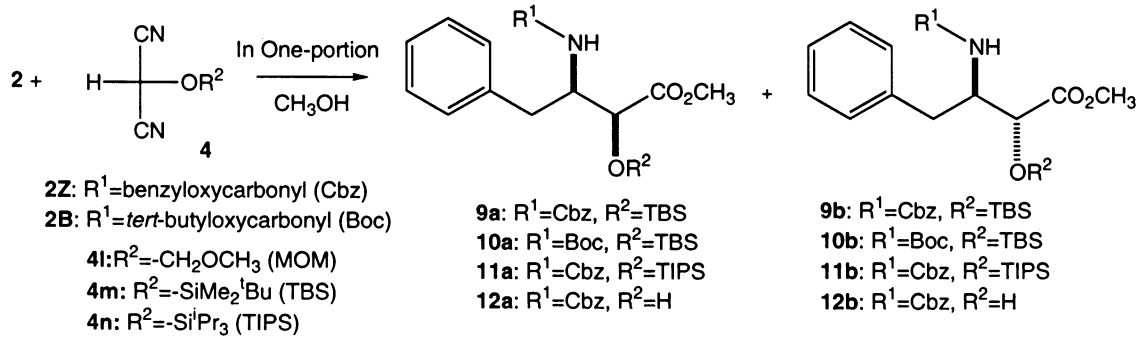
We first carried out the *one-pot but stepwise manipulation* as follows. Anticipating the generation of **7** or **8**, a mixture of DL-**2Z** and **4m** in acetonitrile was stirred for 10 minutes, then pyridine and methanol were added. However, the *stepwise manipulation* under various conditions did not give the corresponding methyl esters DL-**9**.

Next, we examined the *one-portion manipulation*. In methanol in the presence of pyridine, the desired methyl esters **9** were obtained directly from **2Z** in 36% yield (entry 1 in Table 1). Encouraged by this result, further various conditions were examined. When 4-(*N*,*N*-dimethylamino)pyridine (DMAP) was used as base

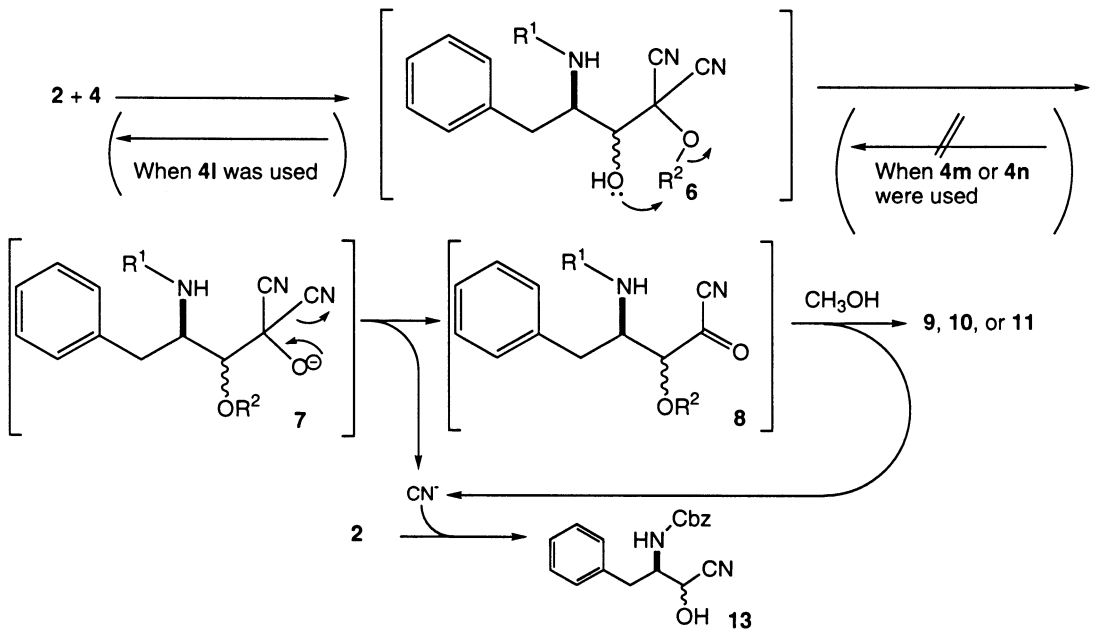


Scheme 2.

Table 1. Reaction of (±)-**2Z** and **4m**

Entry	Solvent	Base	Temp. (°C)	Period (h)	**9**		**13**
					Yield	**9a**:**9b**	Yield
1	MeOH	Pyridine	rt	2	36	72:28	63
2	MeOH	DMAP	−25	12	45	63:37	51
3	Et_2O	Pyridine	rt	48	Trace	–	–
4	Et_2O	Imidazole	rt	2	67	78:22	20
5	Et_2O	DMAP	0	5	83	79:21	Trace
6	Et_2O	PPY	rt	2	80	78:22	Trace
7	Et_2O	PPY	0	5	86[8]	79:21	Trace
8	Et_2O	PPY	−25	12	65	79:21	Trace

A representative procedure (entry 7): A mixture of DL-**2Z** (23.4 mg, 0.083 mmol), **4m** (32.4 mg, 0.165 mmol), PPY (12.2 mg, 0.083 mmol) and methanol (10 μl, 0.247 mmol) in ether (2 ml) was stirred at 0°C for 5 h. The resulting mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 4:1) to afford **9a** and **9b** (total 32.4 mg, 0.071 mmol, 86% yield).



Scheme 3.

instead of pyridine, the yield was slightly increased (entry 2). Since the cyanohydrin DL-**13** was obtained in briefly 50–60% yield as a major byproduct in entries 1 and 2, we considered that the formation of **13** could be inhibited in less polar solvent than in methanol. Therefore, we used ether[7] as a solvent with 3 equivalents of methanol with various bases. Using 4-pyrrolidinopyridine (PPY) gave the best result (entry 6) of all the four examinations (entries 3, 4, 5, and 6). Next, we carried out the reactions with PPY at room temperature (rt), 0°C and −25°C (entries 6, 7 and 8, respectively). As shown in entry 7, DL-**9** was obtained at 0°C in satisfactory yield. The distereomeric ratio of DL-**9a** and DL-**9b** was 79:21.[8,9] We also carried out the reaction of the optically active compound D-**2Z** under the same conditions as entry 7. No epimerization of the C_3 position of either **9a** or **9b** occurred in this experiment.[10]

The syntheses of **10** and **11** having alternative protecting groups were also examined under similar conditions to entry 7. Both were obtained in 80 and 85% yields, respectively, with similar diastereoselectivity (**10a**:**10b** = **11a**:**11b** = 79:21). Stereochemistry of the compounds **9**–**11** was determined by well-known protection/deprotection procedures to convert them to the known compounds **12a** and **12b**.[1,11]

In conclusion, we have synthesized methyl *N*-protected-3-amino-2-siloxy-4-phenylbutanoates including optically active ones in a one-portion manipulation in high yields with good diastereoselectivity. Further synthetic studies for biologically active compounds are now in progress.

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6. The conditions we first examined were referred from our previous publications. (a) Nemoto, H.; Kubota, Y.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 1665–1666. (b) Nemoto, H.; Ma, R.; Ibaragi, T.; Suzuki, I.; Shibuya, M. *Tetrahedron* **2000**, *41*, 1463–1468.
7. The reaction rates of both MAC anion and cyanide anion to **2Z** could be strongly affected by the polarity of solvents. In fact, we observed that the aldehyde **2Z** was consumed within a short period in acetonitrile as well as in methanol. In hexane or toluene as a representative non-polar solvent, more than 10 hours were required to finish the reaction. However, the ratio of the desired compound **9a** to the cyanohydrin **13** was independent from the polarity of solvent. We chose ether since the ratio in ether was higher than the ratios in other solvents.
8. According to the following publications, the major isomer **9a** is the product by non-chelation control. (a) Herrantz, R.; Castro-Pichel, J.; Vinuesa, S.; Garcia-Lopez, M. T. *J. Org. Chem.* **1990**, *55*, 2232–2234. (b) Reetz, M. T.; Drewes, M. W.; Harms, K.; Reif, W. *Tetrahedron Lett.* **1988**, *29*, 3295–3598.
9. We also carried out the reaction based on entry 7 in the presence of several Lewis acids such as zinc chloride, magnesium bromide, triisobutylalminium and tin(II) triflate. However, the diastereoselectivity of **9a** was not optimized. Furthermore, chemical yields were dramatically decreased in some cases.
10. No epimerization was confirmed by HPLC analysis of the desilylated derivatives (+)-**12a** and (+)-**12b** (Daicel OD chiral column 4.6 mm Φ×250 mm length, hexane/ethanol = 15:1, flow rate = 0.7 ml/min. (+)-**12a**: rt = 24.7 min, (−)-**12a**: rt = 30.6 min, (+)-**12b**: rt = 34.3 min, (−)-**12b**: rt = 31.9 min).
11. To determine the relative stereochemistry of all the compounds, we carried out the following reactions.
9a or **9b**→**12a** or **12b** (Bu_4NF in THF at 0°C for 30 min, 88% yield)
9a or **9b**→**10a** or **10b** ($Pd(OH)_2/H_2$, Boc_2O, in MeOH at rt for 2 h, 91% yield)
11a or **11b**→**12a** or **12b** (Bu_4NF in THF at 0°C for 30 min, 91% yield)
9a: colorless oil; FT-IR ($CHCl_3$): 3437, 2953, 1753, 1717, 1504, 1146, 840 cm^{-1}; ^1H NMR (300 MHz): δ 7.40–7.10 (m, 10H), 5.17 (brd, J = 8.5 Hz, NH), 5.01 (d, J = 12.3 Hz, 1H), 4.97 (d, J = 12.3 Hz, 1H), 4.41–4.29 (m, 1H), 4.23 (d, J = 1.4 Hz, 1H), 3.64 (s, 3H), 2.87 (d, J = 7.5 Hz, 2H), 0.96 (s, 9H), 0.10 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (75 MHz): δ 172.2, 155.7, 137.5, 136.5, 129.2, 128.5, 128.5, 128.1, 128.0, 126.6, 72.1, 66.6, 55.5, 52.0, 38.1, 25.8, 18.4, −4.7, −5.3; EI-HRMS calcd for $C_{25}H_{35}NO_5Si$ (M^+): 457.2285. Found 457.2302.
9b: colorless oil; FT-IR ($CHCl_3$): 3443, 2954, 1753, 1719, 1507, 1254, 1150, 838 cm^{-1}; ^1H NMR (300 MHz): δ 7.39–7.10 (m, 10H), 5.03 (s, 2H), 4.86 (brd, J = 7.6 Hz, NH), 4.45 (d, J = 3.1 Hz, 1H), 4.50–4.25 (m, 1H), 3.64 (s, 3H), 2.87–2.62 (m, 2H), 0.93 (s, 9H), 0.08 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (75 MHz): δ 171.7, 155.6, 137.3, 136.4, 129.4, 128.5, 128.4, 128.1, 128.0, 126.7, 73.3, 66.7, 55.0, 51.8, 35.5, 25.7, 18.3, −5.0, −5.5; EI-HRMS calcd for $C_{25}H_{35}NO_5Si$ (M^+): 457.2285. Found 457.2249.