Pergamon

Tetrahedron 56 (2000) 1463–1468

TETRAHEDRON

Development of a Method for the Preparation of α-Azido-Masked Acyl Cyanides, Synthetic Equivalents of *N*-Protected–*C*-Activated α-Amino Acids

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Received 8 December 1999; accepted 11 January 2000

Abstract—A method for the preparation of α-azido-masked acyl cyanides as synthetic equivalents of *N*-protected–*C*-activated α-amino acids was developed using carbon–carbon bond formation between aldehydes and the *Masked Acyl Cyanide Reagents*, followed by sulfonylation and substitution by azide anion. This method was applied to the synthesis of d-threonine and l-*allo*-threonine derivatives.
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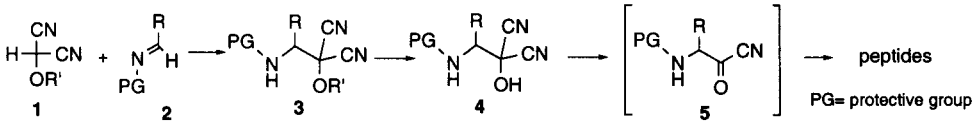
Introduction

To prepare peptides, an *N*-protected–*C*-activated α-amino acid is one of the most useful synthetic intermediates. Thus we have developed a method for the synthesis of *N*-sulfonyl-α-amino-alkoxymalononitrile **3** as a synthetic equivalent of the acyl cyanides **5**[1] using MAC[2] reagents **1** and the *N*-sulfonylimines **2** (PG=SO_2R) (Scheme 1). Since *both* the carbonyl group of **3** is masked *and* the unmasking steps from **3** to **5** via **4** can be carried under very mild conditions,[3] the epimerization of α-position of carbonyl group of **5** can be theoretically inhibited. However, the verification has not been carried out enough.[4] Furthermore *aliphatic* derivatives of **3** have not been prepared by using our method since it is difficult to prepare aliphatic aldimines **2** having electron-withdrawing groups on nitrogen. These two problems should be solved to extend the efficiency of our method.

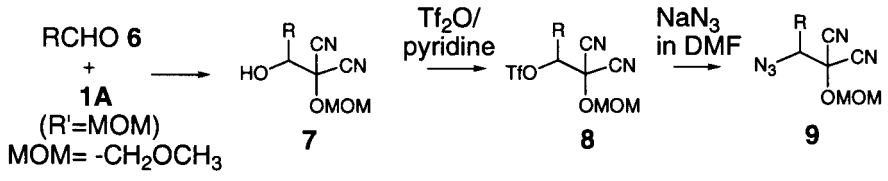
Results and Discussion

We report a new method for the preparation of the α-azido-MAC **9** (Scheme 2) as a synthetic equivalent of **3** and demonstrate the synthesis of optically active threonine derivatives from them without epimerization.

Prior to the examination of the one-pot reaction directly from the aldehyde **6** to the triflates **8**, step from **6** to **7** was optimized by using **6a** (a: R=2-phenylethyl) since **7a** is the most stable adducts of all we examined. Some of the adducts **7** were not isolated as a stable form. From **6a** and **1A**,[5] the



Scheme 1.



Scheme 2.

Keywords: cyanides; threonine; acyl anion; azides; amino acids and peptides.
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PII: S0040-4020(00)00040-5

Table 1. Reaction of aldehydes **6** with **1A**

Entry	RCHO (**6**)	**1A** (equiv.)	Catalyst (mol%)	Time (h) for **6** to **7**	Yield (%) of **8** from **6**
1	$C_6H_5CH_2CH_2CHO$ (**6a**)	2.0	$Pd(dppe)_2$ (5)	5	87
2	**6a**	2.0	Py (10)	5	94
3	**6a**	2.0	Et_3N (10)	5	79
4	**6a**	2.0	None	24	94
5	$CH_3(CH_3)_8CHO$ (**6b**)	2.0	Py (10)	5	90
6	**6b**	2.0	Et_3N (10)	5	74
7	$(CH_3)_2CHCH_2CHO$ (**6c**)	2.0	Py (10)	5	88
8	**6c**	2.0	Et_3N (10)	5	80
9	*cyclo*-$C_6H_{11}CHO$ (**6d**)	2.0	Py (10)	5	55
10	**6d**	3.0	Py (10)	5	61
11	**6d**	3.0	Et_3N (10)	5	35
12	**6d**	3.0	None	24	78
13	$(CH_3)_2CHCHO$ (**6e**)	2.0	$pd(dppe)_2$ (5)	72	20
14	**6e**	2.0	Et_3N (10)	8	46
15	**6e**	2.0	Py (10)	24	49
16	**6e**	3.0	Py (10)	24	52
17	$(CH_3)_3CCHO$ (**6f**)	3.0	[a]	>72	0
18	$C_6H_5CH{=}CHCHO$ (**6g**)	3.0	[a]	>72	0
19	*p*-$CH_3C_6H_4CHO$ (**6h**)	3.0	[a]	>72	0

[a] All the reaction conditions carried out in entries 1–16 were attempted.

adduct **7a** was produced in excellent yields for 5 h with various catalysts such as $Pd(dppe)_2$,[6] pyridine (Py), or triethylamine (Et_3N). It is noteworthy that the reaction also proceeded with *no catalyst*[7] in excellent yield although it took 24 h to convert **6a** to **7a**. According to these preliminary examinations, we carried out the one-pot reaction directly from **6a** to the triflate **8a** by the addition of trifluoromethanesulfonic anhydride (Tf_2O)[8] and Py after **6a** was sufficiently transformed to **7a**. The results are shown in entries 1–4 of Table 1. The aldehydes without bulky substituents were also transformed to the desired triflates **8** in excellent yields (entries 5–8). When the reaction of **6d** and **1A** was carried out under the similar conditions as entries 2, 5 and 7, **8d** was obtained in moderate yield (entry 9). Although 3 equiv. of **1A** was used, yield of **8d** was not increased very much (entry 10). When the reaction of **6d** is prolonged with Py or Et_3N, both MAC reagent **1A** and the adduct **7d** were gradually decreased probably due to the decomposition of **7d** and **1A** (entries 10 and 11). Finally we found that **8d** was obtained in 78% yield when the reaction of **6d** was carried out without catalyst (entry 12). In contrast, no reaction occurred when **6e** was examined without catalyst. Therefore we carefully optimized the reaction conditions using the catalysts, and the yield of **8e** was optimized to 52% (entries 13–16). The aldehyde **6f** was not converted to **8f** under the various conditions that we have mentioned above (entry 17). In entry 18, **8g** was not obtained although the adduct **7g** was observed in the crude reaction mixture by thin layer chromatography and ^1H NMR. Presumably the rate of the reverse reaction[9] (**7g→6g+1A**) is extremely high even under the weak basic conditions with Py. In entry 19, **8h**[10] was not obtained, again probably due to similar reasons. All the obtained triflates **8** were subsequently converted to the corresponding azides **9** in excellent yields (Table 2).

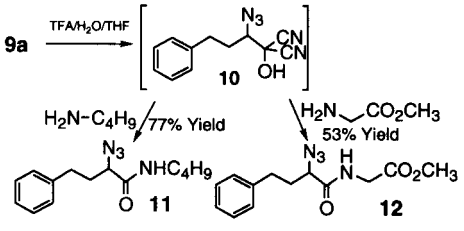
Table 2. Reaction of **8** to **9**

Entry	**8**	Yield of **9** (%)
1	**8a**	90
2	**8b**	91
3	**8c**	84
4	**8d**	91
5	**8e**	82

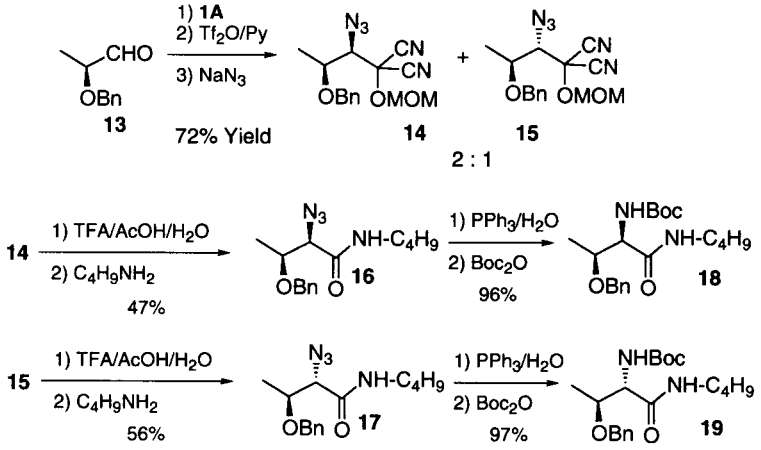
Using **9a** as a representative example, we demonstrated the transformation of the α-azido-MAC derivatives **9** into the corresponding amides via the in situ generated acyl cyanide (Scheme 3). The MOM group of **9a** was deprotected with trifluoroacetic acid (TFA)–water–tetrahydrofuran (THF) (v/v/v=4:1:1) for 24 h at rt. The resulting crude product **10** was transformed into the butylamide **11** with 1.2 equiv. of butylamine in 77% overall yield based on **9a**. Conversion of the glycine methyl ester to the dipeptide derivative **12** proceeded in 53% yield from **9a**.

Next we examined the epimerization at the α-position to the carbonyl group by synthesizing BocNH-d-Thr(Bn)-NHC_4H_9 (**18**) and BocNH-l-*allo*-Thr(Bn)-NHC_4H_9 (**19**) (Scheme 4). The key substrates **14** and **15** were prepared starting from *2S*-2-benzyloxypropionaldehyde (**13**).[11] The aldehyde **13** was reacted with 3 equiv. of **1A** in CH_2Cl_2 and the resulting adducts (the ratio of the diastereomers is ~2:1) were converted to **14** and **15** in 48 and 24% overall yields, respectively, based on conversion of **13**, 40% of which was recovered.

The carefully purified product **14** was transformed in 47% yield into the corresponding butylamide **16**, the stereochemistry of which was determined by analysis of the 300 MHz ^1H NMR of the crude product. The amide **16**



Scheme 3.



Scheme 4.

was converted to **18** in 96% yield by the reduction of the azide,[12] followed by protection using *tert*-butyl pyrocarbonate (Boc_2O). The diastereomer **15** was also transformed into **19** (via **17**) in 54% overall yield under similar conditions.

Analysis of the crude products **16** and **17** by ^1H NMR indicated that no epimerization (**14→17** or **15→16**) occurred. An authentic sample of **18** was prepared in 93% yield by condensation of commercially available Boc-NH-l-Thr(Bn) and butylamine using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) and 1-hydroxybenzotriazole (HOBt). Measurement of the $[\alpha]_d^{20}$ proved that the synthetic **18** was the d-isomer (synthetic: $[\alpha]_d^{20}=-39.22°$. authentic sample: $[\alpha]_d^{20}=+37.23°$). Compound **19** was therefore determined to be an l-*allo*-threonine derivative.

Conclusions

We have developed a new alternative method for the synthesis of *N*-protected–*C*-activated α-amino acids and have demonstrated that no epimerization occurs using optically active α-azido-MAC derivatives during the amide bond formation. By this method, aliphatic α-amino acids can be efficiently synthesized. Further studies using MAC reagents are now in progress.

Experimental

The spectra were measured with the following equipments and conditions unless otherwise noted. IR spectra were measured with Perkin–Elmer 1720 Infrared Fourier Transfer Spectrometer indicating with cm^{-1}. ^1H and ^{13}C NMR spectra were measured with JEOL JMN-AL300 Spectrometer at 300 and 75 MHz, respectively, or with JEOL GSX400 Spectrometer at 400 and 100 MHz, respectively, in chloroform-d and indicated as δ value. High Resolution Mass Spectra (HRMS) were measured with JEOL JMS-DX303. Pyridine (Py) and triethylamine (Et_3N) were distilled over potassium hydroxide. Dichloromethane (CH_2Cl_2) was distilled over phosphorous pentoxide. Acetonitrile and dimethylformamide (DMF) were distilled over calcium hydride. Tetrahydrofuran (THF), benzene and diethyl ether were distilled over sodium/benzophenone. All the reactions were carried out under nitrogen atmosphere unless otherwise noted.

(±)-(1-Hydroxy-3-phenylpropyl)(methoxymethoxy)methane-1,1-dicarbonitrile (7a). A mixture of 3-phenylpropanal (**6a**) (134 mg, 1 mmol), (methoxymethoxy)methane-1,1-dicarbonitrile (H-MAC-MOM) (**1A**) (252 mg, 2 mmol) and a catalyst (or no additive) in CH_2Cl_2 (2 mL) was stirred for 5 h (or 24 h) at rt, and was purified by silica gel column chromatography eluted with hexane–ethyl acetate (5:1) to give **7a** as a colorless oil (260 mg, 1 mmol, 100% yield). FT-IR (in $CHCl_3$): 3337, 1167, 1110, 1041, 945 cm^{-1}. ^1H NMR (400 MHz): 7.48–7.28 (m, 2H), 7.28–7.17 (m, 3H), 5.06 (d, *J*=7.1 Hz, 1H), 5.04 (d, *J*=7.1 Hz, 1H), 3.99 (dd, *J*=10.0, 1.0 Hz, 1H), 3.52 (s, 3H), 3.00 (ddd, *J*=13.7, 9.0, 4.8 Hz, 1H), 2.99 (m, 1H –O*H*), 2.78 (dt, *J*=13.7, 8.1 Hz, 1H), 2.24–2.11 (m, 1H), 2.11–1.98 (m, 1H). ^{13}C NMR (100 MHz): 140.0, 128.7, 128.5, 126.5, 112.1, 112.0, 96.5, 75.0, 70.5, 57.5, 32.3, 31.3. HRMS Calcd for $C_{14}H_{16}N_2O_3$ (M^+): 260.1161. Found 260.1158.

(±)-1-[Dicyano(methoxymethoxy)methyl]-3-phenylpropyl (trifluoromethyl)-sulfonate (8a) from 6a. A mixture of **6a** (46.2 mg, 0.35 mmol), **1A** (90.0 mg, 0.71 mmol) and catalyst (or no additive) in CH_2Cl_2 (0.8 mL) was stirred for 2–24 h at rt, then a solution of Py (163 mg, 2.1 mmol) in CH_2Cl_2 (3.5 mL) was added at 0°C. To the resulting mixture was added Tf_2O (292 mg, 1.04 mmol) dropwise slowly at 0°C. After stirred for 30 min at 0°C, the reaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with hexane–ethyl acetate (15:1) to give **8a** as a colorless oil (127.2 mg, 0.32 mmol, 94% yield). FT-IR (in $CHCl_3$): 1421, 1212, 1206, 1140 cm^{-1}. ^1H NMR (400 MHz): 7.37–7.31 (m, 2H), 7.30–7.19 (m, 3H), 5.14 (d, *J*=7.2 Hz, 1H), 5.10 (dd, *J*=6.8, 5.5 Hz, 1H), 5.09 (d, *J*=7.2 Hz, 1H), 3.57 (s, 3H), 3.00 (ddd, *J*=14.2, 7.1, 7.1 Hz 1H), 2.78 (dt, *J*=14.2, 8.2 Hz, 1H), 2.47–2.39 (m, 2H). ^{13}C NMR (100 MHz): 138.0, 129.0, 128.4, 127.2, 118.4 (q, J_{C-F}= 319.9 Hz), 110.6, 109.5, 97.0, 85.0, 67.7, 57.9, 31.8, 30.6. HRMS Calcd for $C_{15}H_{15}F_3N_2O_5S_1(M^+)$: 392.0654. Found 392.0653.

(±)-(1-Azido-3-phenylpropyl)(methoxymethoxy)methane-1,1-dicarbonitrile (9a) from 8a. A mixture of **8a** (158 mg, 0.40 mmol) and sodium azide (60 mg, 0.92 mmol) in DMF (2 mL) was stirred at 0°C for 10 min. The resulting reaction mixture was directly charged into silica gel column chromatography eluted with hexane–ethyl acetate (15:1) to give **9a** as a colorless oil (103.5 mg, 0.36 mmol, 90% yield). FT-IR (in $CHCl_3$): 2109, 1250, 1168, 1113, 1045 cm^{-1}. ^1H NMR (400 MHz): 7.48–7.41 (m, 2H), 7.28–7.18 (m, 3H), 5.10 (d, *J*=7.2 Hz, 1H), 5.07 (d, *J*=7.2 Hz, 1H), 3.73 (dd, *J*=11.2, 2.4 Hz, 1H), 3.55 (s, 3H), 3.02 (ddd, *J*=14.1, 8.3, 4.5 Hz, 1H), 2.77 (dt, *J*=14.1, 8.3 Hz, 1H), 2.27–2.16 (m, 1H), 2.07–1.94 (m, 1H). ^{13}C NMR (100 MHz): 139.0, 129.0, 128.5, 126.8, 111.6, 111.3, 96.7, 69.9, 66.4, 57.7, 31.7, 30.6. HRMS Calcd for $C_{12}H_{10}N_3O_1(M^+-N_2-CH_2OCH_3)$: 212.0824. Found 212.0854. Anal. Calcd for $C_{14}H_{15}N_5O_2$: C, 58.94; H, 5.30; N, 24.55. Found C, 58.89; H, 5.30; N, 24.43.

General procedures for 9 from 6

A mixture of **6** (1 mmol), **1A** (252 mg, 2 mmol), and a catalyst (or no catalyst) in CH_2Cl_2 (2 mL) was stirred for 5–24 h at rt. The resulting solution was diluted with CH_2Cl_2 (5 mL), cooled to 0°C, and Py (6 mmol) was added. Then a solution of Tf_2O (3 mmol) in CH_2Cl_2 (2 mL) was slowly added dropwise. The reaction mixture was stirred for 30 min at 0°C. The residue was briefly purified by short silica gel column chromatography eluted with hexane–ethyl acetate (15:1) to give **8**, which was used in the next reaction without further purification. A mixture of **9** (1 mmol) and sodium azide (195 mg, 3 mmol) in DMF (5 mL) was stirred at 0°C for 10 min. The resulting reaction mixture was directly charged into silica gel column chromatography eluted with hexane–ethyl acetate (15:1) to give **9** as a colorless oil.

(±)-(Azidodecyl)(methoxymethoxy)methane-1,1-dicarbonitrile (9b). FT-IR (in $CHCl_3$): 2929, 2116, 1168, 1040, 937 cm^{-1}; ^1H NMR (400 MHz): 5.13 (d, *J*=7.2 Hz, 1H), 5.10 (d, *J*=7.2 Hz, 1H), 3.78 (dd, *J*=10.4, 2.8 Hz, 1H), 3.58 (s, 3H), 1.94–1.83 (m, 1H), 1.78–1.60 (m, 3H), 1.53–1.20 (m, 12H), 0.89 (t, *J*=6.8 Hz, 3H). ^{13}C NMR (100 MHz): 111.7, 111.4, 96.7, 70.0, 67.5, 57.6, 31.9, 29.4, 29.3, 29.2, 29.1, 29.0, 26.0, 22.7, 14.1. Anal. Calcd for $C_{15}H_{25}N_5O_2$: C, 58.61; H, 8.20; N, 22.78. Found C, 58.85; H, 8.24; N, 22.61.

(±)-(1-Azido-3-methylbutyl)(methoxymethoxy)methane-1,1-dicarbonitrile (9c). FT-IR (in $CHCl_3$): 2964, 2120, 1469, 1251, 1168, 1057, 1036, 970, 928 cm^{-1}; ^1H NMR (400 MHz): 5.13 (d, *J*=7.2 Hz, 1H), 5.10 (d, *J*=7.2 Hz, 1H), 3.85 (dd, *J*=11.4, 2.4 Hz, 1H), 3.58 (s, 3H), 1.98–1.87 (m, 1H), 1.75 (ddd, *J*=13.8, 11.4, 3.9 Hz, 1H), 1.61 (ddd, *J*=13.8, 10.0, 2.4 Hz, 1H), 1.04 (d, *J*=6.4 Hz, 3H), 1.00 (d, *J*=6.4 Hz, 3H). ^{13}C NMR (100 MHz): 111.8, 111.4, 96.7, 70.2, 65.9, 57.6, 37.6, 25.0, 23.3, 21.0. Anal. Calcd for $C_{10}H_{15}N_5O_2$: C, 50.62; H, 6.37; N, 29.52. Found C, 50.82; H, 6.48; N, 29.43.

(±)-(Azidocyclohexylmethyl)(methoxymethoxy)methane-1,1-dicarbonitrile (9d). FT-IR (in $CHCl_3$): 2937, 2113, 1168, 1015, 928 cm^{-1}; ^1H NMR (400 MHz): 5.15 (d, *J*=7.2 Hz, 1H), 5.10 (d, *J*=7.2 Hz, 1H), 3.73 (d, *J*=4.0 Hz, 1H), 2.02–1.89 (m, 2H), 1.89–1.64 (m, 4H), 1.48–1.04 (m, 5H). ^{13}C NMR (100 MHz): 111.8, 111.6, 96.4, 72.7, 68.9, 39.2, 31.3, 29.7, 27.2, 26.0, 25.6, 25.6. Anal. Calcd for $C_{12}H_{17}N_5O_2$: C, 54.74; H, 6.51; N, 26.60. Found C, 54.80; H, 6.60; N, 26.47.

(±)-(1-Azido-2-methylpropyl)(methoxymethoxy)methane-1,1-dicarbonitrile (9e). FT-IR (in $CHCl_3$): 2973, 2115, 1168, 1021 cm^{-1}; ^1H NMR (400 MHz): 5.16 (d, *J*=6.8 Hz, 1H), 5.10 (d, *J*=6.8 Hz, 1H), 3.77 (d, *J*=4.0 Hz, 1H), 3.58 (s, 3H), 2.40–2.28 (m, 1H), 1.18 (d, *J*=6.8 Hz, 3H), 1.12 (d, *J*=6.8 Hz, 3H). ^{13}C NMR (100 MHz): 111.8, 111.6, 96.4, 72.8, 69.1, 57.7, 29.7, 21.5, 16.7. Anal. Calcd for $C_9H_{13}N_5O_2$: C, 48.42; H, 5.87; N, 31.37. Found C, 48.58; H, 5.96; N, 31.15.

(±)-2-Azido-*N*-butyl-4-phenylbutanamide (11). A solution of **9a** (285 mg, 1 mmol) in TFA–THF–water (4:1:1) (6 mL) was stirred for 24 h at rt. The reaction mixture was concentrated in vacuo to remove the solvent. The residue was dissolved in CH_2Cl_2 (2 mL), and then butylamine (365 mg, 5 mmol) was added. The mixture was stirred for 15 min at rt, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with hexane–ethyl acetate (5:1) to give **11** as a colorless oil (200 mg, 0.77 mmol, 77% yield). FT-IR (in $CHCl_3$): 3422, 2111, 1673 cm^{-1}. ^1H NMR (400 MHz): 7.33–7.27 (m. 2H), 7.25–7.17 (m, 3H), 6.34 (br, 1H, –N*H*), 3.95 (dd, *J*=7.6, 4.8 Hz, 1H), 3.35–3.20 (m, 2H), 2.82–2.67 (m, 2H), 2.30–2.18 (m, 1H), 2.17–2.06 (m, 1H), 1.56–1.44 (m, 2H), 1.40–1.38 (m, 2H), 0.93 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz): 169.0, 140.3, 128.6, 128.5, 126.3, 63.8, 39.2, 33.9, 31.5, 31.5, 20.0, 13.7. EI-HRMS Calcd for $C_{14}H_{21}N_4O$ (M^++1): 261.1715. Found 261.1716.

(±)-Methyl 2-(2-azido-4-phenylbutanoylamino)acetate (12). A solution of **9a** (285 mg, 1 mmol) in TFA–THF–water (4:1:1) (6 mL) was stirred for 24 h at rt. The reaction mixture was concentrated in vacuo to remove the solvent. To the residue in CH_2Cl_2 (2 mL) were added Et_3N (505.5 mg, 5 mmol) and glycine methyl ester hydrochloride (151 mg, 1.2 mmol). The mixture was stirred for 2 h at rt, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with hexane–ethyl acetate (4:1) to give **12** as a colorless oil (150 mg, 0.53 mmol, 53% yield). FT-IR (in $CHCl_3$): 3417, 2113, 1749, 1685 cm^{-1}; ^1H NMR (400 MHz): 7.32–7.19 (m, 5H), 6.82 (brt, *J*=5.2 Hz, 1H), 4.06 (d, *J*=5.2 Hz, 2H), 4.01 (dd, *J*=7.2, 5.2 Hz, 1H), 3.78 (s, 3H), 2.85–2.70 (m, 2H), 2.32–2.09 (m, 2H). ^{13}C NMR (100 MHz): 169.8, 169.5, 140.2, 128.6, 128.5, 126.3, 63.4, 52.5, 41.1, 33.7, 31.3; EI-HRMS Calcd for $C_{13}H_{17}N_4O_3(M^++1)$: 277.1301. Found 277.1299.

1*S*,2*R*-(14) and 1*R*,2*R*-[1-Azido-2-(phenylmethoxy)propyl](methoxymethoxy)methane-1,1-dicarbonitrile (15). A mixture of **13** (62.0 mg, 0.376 mmol) and **1A** (142 mg, 1.128 mmol) in CH_2Cl_2 (0.5 mL) was stirred for 2 h at rt. The resulting mixture was concentrated in vacuo and the residue was treated by silica gel short column chromatography to remove the remaining **13** (25.0 mg, 0.152 mmol, 40% recovered) and **1A**. The eluent was concentrated and dissolved in CH_2Cl_2 (0.5 mL). To the solution was added Py (261 mg, 3.3 mmol) at 0°C, then was added Tf_2O (0.1 mL,

d=1.487, 0.621 mmol), and the resulting mixture was stirred for 10 min at 0°C. The mixture was directly poured into silica gel column chromatography to give a mixture of diastereomers (67:33, briefly 68.0 mg, 0.161 mmol, 72% yield based on conversion of **13**), which was used in the next step without further purification.

To the crude mixture of diastereomers in DMF (5 mL) was added sodium azide (31.4 mg, 0.483 mmol), and the mixture was stirred for 40 min at rt. The resulting mixture was poured into water and extracted with three portions of ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with hexane–ethyl acetate (3:1) to give **14** (34.1 mg, 0.108 mmol, 48% yield based on conversion of **13**) and **15** as colorless oils (16.8 mg, 0.053 mmol, 24% yield), respectively.

14: $[\alpha]_d^{20}$ −5.28 (*c*=0.11, $CHCl_3$). IR (neat): 2925, 2360, 2114 cm^{-1}. ^1H NMR: 7.40–7.30 (m, 5H, C_6H_5–), 5.14 (d, *J*=7.0 Hz, 1H, one of –OCH_2O–), 5.08 (d, *J*=7.0 Hz, 1H, one of –OCH_2O–), 4.65 (d, *J*=11.5 Hz, 1H, one of $C_6H_5CH_2O$–), 4.56 (d, *J*=11.5 Hz, 1H, one of $C_6H_5CH_2O$–), 3.96 (d, *J*=7.5 Hz, 1H, –CH(OBn)C*H*N_3–), 3.77 (dq, *J*=7.5, 6.0 Hz, 1H, CH_3CH(OBn)–), 3.56 (s, 3H, –OCH_3), 1.42 (d, *J*=6.0 Hz, 3H, CH_3CH(OBn)–). ^{13}C NMR: 136.8 (C of C_6H_5–), 128.6 (two CH of C_6H_5), 128.5 (two CH of C_6H_5), 128.3 (one CH of C_6H_5–), 111.6 (*C*N), 111.3 (*C*N), 96.3 (–OCH_2O–), 72.0 (–*C*H–OBn), 71.5 (C_6H_5–*C*H_2O–), 70.8 (–*C*H–N_3), 68.0 (–*C*$(CN)_2$OMOM), 57.6 (–OCH_3), 16.3 (*C*H_3CH(OBn)–). HRMS: *m*/*z* calcd for $C_{15}H_{17}N_5O_3$: 315.1331, Found: 315.1365.

15: $[\alpha]_d^{20}$ −3.97 (*c*=0.25, $CHCl_3$): R (neat): 2925, 2360, 2114 cm^{-1}. ^1H NMR: 7.40–7.30 (m, 5H, C_6H_5–), 5.11 (d, *J*=7.0 Hz, 1H, one of –OCH_2O–), 5.03 (d, *J*=7.0 Hz, 1H, one of –OCH_2O–), 4.68 (d, *J*=10.0 Hz, 1H, one of $C_6H_5CH_2O$–), 4.53 (d, *J*=10.0 Hz, 1H, one of $C_6H_5CH_2O$–), 4.16 (dq, *J*=3.0, 6.0 Hz, 1H, CH_3CH(OBn)–), 3.74 (d, *J*=3.0 Hz, 1H, –CH(OBn)C*H*N_3–), 3.54 (s, 3H, –OCH_3), 1.41 (d, *J*=6.0 Hz, 3H, CH_3CH(OBn)–). ^{13}C NMR: 136.7 (C of C_6H_5–), 128.5 (two CH of C_6H_5–), 128.2 (two CH of C_6H_5–), 128.1 (one CH of C_6H_5–), 111.6 (*C*N), 111.4 (*C*N), 96.3 (–OCH_2O–), 73.7 (–*C*H–OBn), 71.7 (C_6H_5–*C*H_2O–), 70.7 (–*C*H–N_3), 67.6 (–*C*$(CN)_2$OMOM), 57.6 (–OCH_3), 16.7 (*C*H_3CH(OBn)–). HRMS: *m*/*z* calcd for $C_{15}H_{17}N_5O_3$: 315.1331, Found: 315.1365.

2*S*,3*R*-2-Azido-*N*-butyl-3-(phenylmethoxy)butanamide (16). A solution of **14** (6.6 mg, 0.021 mmol) in TFA–water–THF (4:1:1, 1 mL) was stirred for 10 h at rt. The resulting mixture was concentrated in vacuo and the residue was dissolved in CH_2Cl_2 (1 mL). To the solution, butylamine (0.02 mL, *d*=0.740, 0.222 mmol) was added, and the mixture was stirred for 10 min at rt. The resulting solution was concentrated in vacuo and the residue was purified by silica gel column chromatography eluted with hexane–ethyl acetate (3:1) to give **16** as a colorless oil (3.1 mg, 0.0107 mmol, 47% yield). $[\alpha]_d^{20}$ −1.41 (*c*=0.43, $CHCl_3$): R (neat): 3326, 1652, 735, 696 cm^{-1}. ^1H NMR: 7.40–7.25 (m, 5H, C_6H_5–), 6.46 (brt, *J*=6.5 Hz, 1H, –N*H*–), 4.60 (d, *J*=11.5 Hz, one of $C_6H_5CH_2O$–), 4.47 (d, *J*=11.5 Hz, one of $C_6H_5CH_2O$–), 4.09 (dq, *J*=3.0, 6.0 Hz, 1H, CH_3CH–(OBn)–), 3.91 (d, *J*=3.0 Hz, 1H, –CH(OBn)C*H*N_3–), 3.27 (dt, *J*=6.5, 6.5 Hz, –NHCH_2–), 1.34 (d, *J*=6.0 Hz, 3H, CH_3CH(OBn)–), 1.64–1.23 (m, 4H, –NHCH_2(CH_2)$_2$CH_3), 0.90 (t, *J*=7.0 Hz, 3H, –NH$(CH_2)_3CH_3$). ^{13}C NMR: 167.7 (–*C*=O), 137.7 (C of C_6H_5–), 128.4 (two CH of C_6H_5–), 127.8 (one CH of C_6H_5–), 127.8 (two CH of C_6H_5–), 75.7 (–*C*H–OBn), 71.9 (C_6H_5–CH_2O–), 68.6 (–*C*H–N_3), 39.3 (–NH*C*H_2–), 31.5 (–*C*H_2–), 20.0 (–*C*H_2–), 16.7 (*C*H_3CH(OBn)–), 13.7 (–NH$(CH_2)_3CH_3$). HRMS: *m*/*z* calcd. for $C_{15}H_{22}N_4O_2$: 290.1743, Found: 290.1776.

2*R*,3*R*-2-Azido-*N*-butyl-3-(phenylmethoxy)butanamide (17). A solution of **15** (11.7 mg, 0.037 mmol) in TFA–water–THF (4:1:1, 0.5 mL) was stirred for 10 h at rt. The resulting mixture was concentrated in vacuo and the residue was dissolved in CH_2Cl_2 (1 mL). To the solution, butylamine (0.02 mL, *d*=0.740, 0.222 mmol) in CH_2Cl_2 (1 mL) was added, and the mixture was stirred for 10 min at rt. The resulting solution was concentrated in vacuo and the residue was purified by silica gel column chromatography eluted with hexane–ethyl acetate (3:1) to give **17** as a colorless oil (6.0 mg, 0.021 mmol, 56% yield). $[\alpha]_d^{20}$ −5.76 (*c*=0.31, $CHCl_3$): R (neat): 2933, 2360, 1658 cm^{-1}. ^1H NMR: 7.40–7.25 (m, 5H, C_6H_5–), 6.48 (brt, *J*=6.5 Hz, 1H, –N*H*–), 6.43 (d, *J*=12.0 Hz, one of $C_6H_5CH_2O$–), 4.60 (d, *J*=12.0 Hz, one of $C_6H_5CH_2O$–), 4.34 (d, *J*=3.0 Hz, 1H, –CH(OBn)C*H*N_3–), 4.23 (dq, *J*=3.0, 6.5 Hz, 1H, CH_3CH(OBn)–), 3.27 (dt, *J*=6.5, 6.5 Hz, 2H, –NHCH_2–), 1.18 (d, *J*=6.5 Hz, 3H, CH_3CH(OBn)–), 1.64–1.23 (m, 4H, –NHCH_2(CH_2)$_2$CH_3), 0.92 (t, *J*=7.0 Hz, 3H, –NH$(CH_2)_3CH_3$). ^{13}C NMR: 167.1 (–*C*=O), 138.1 (C of C_6H_5–), 129.1 (two CH of C_6H_5), 127.9 (one CH of C_6H_5), 127.8 (two CH of C_6H_5), 76.6 (–*C*H–OBn), 71.3 ($C_6H_5CH_2O$–), 66.5 (–*C*H–N_3), 39.3 (–NH*C*H_2–), 31.6 (–*C*H_2–), 20.1 (–*C*H_2–), 14.6 (*C*H_3CH(OBn)–), 13.8 (–NH$(CH_2)_3CH_3$). HRMS: *m*/*z* calcd for $C_{15}H_{22}N_4O_2$: 290.1743, Found: 290.1774.

2*S*,3*R*-2-[(*tert*-Butoxy)carbonylamino]-*N*-butyl-3-(phenylmethoxy)-butanamide ((−)-18). To a solution of **16** (2.9 mg, 0.010 mmol) in THF–water (20:1, 1.05 mL) was added triphenylphosphine (10.9 mg, 0.041 mmol) and the mixture was stirred for 10 h at rt. The mixture was concentrated in vacuo and the residue was dissolved in CH_2Cl_2 (0.5 mL). To the solution, Boc_2O (7.0 mg, 0.032 mmol) was added. The mixture was stirred for 10 h at rt, poured into water, extracted with ethyl acetate and washed with brine. The extract was concentrated in vacuo and the residue was purified by silica gel column chromatography eluted with hexane–ethyl acetate (3:1) to give **18** as a colorless oil (3.5 mg, 0.0096 mmol, 96% yield). $[\alpha]_d^{20}$ −39.22 (*c*=0.056, $CHCl_3$). FT-IR (neat) 3326, 1652, 765, 696 cm^{-1}. ^1H NMR: 7.40–7.25 (m, 5H, C_6H_5–), 6.48 (brt, *J*=6.5 Hz, 1H, –N*H*CH_2–), 5.51 (brd, *J*=5.5 Hz, 1H, –N*H*Boc–), 4.61 (d, *J*=11.0 Hz, 1H, one of $C_6H_5CH_2O$–), 4.56 (d, *J*=11.0 Hz, 1H, one of $C_6H_5CH_2O$–), 4.24 (brd, *J*=5.5 Hz, 1H, –C*H*NHBoc–), 4.18 (dq, *J*=3.0, 6.0 Hz, 1H, CH_3CH(OBn)–), 3.26 (m, 2H, –NHCH_2–), 1.52–1.20 (m, 4H, –NHCH_2(CH_2)$_2$–), 1.45 (s, 9H, –C(CH_3)$_3$), 1.17 (d, *J*=6.0 Hz, 3H, CH_3CH(OBn)–), 0.88 (t, *J*=7.0 Hz, –NH$(CH_2)_2CH_3$). ^{13}C NMR: 169.7 (–*C*=O of the amide), 155.9 (–*C*=O of the carbamate), 138.2 (C of C_6H_5–), 128.5

(two CH of C_6H_5–), 127.9 (one CH of C_6H_5–), 127.9 (two CH of C_6H_5–), 80.1 (–$C(CH_3)_3$), 75.0 (CH_3CH(OBn)–), 71.7 ($C_6H_5CH_2O$–), 57.6 (–CHNHBoc–), 39.3 (–$NHCH_2$–), 31.6 (–CH_2–), 28.4 (–$C(CH_3)_3$), 20.1 (–CH_2–), 15.6 (CH_3CH(OBn)–), 13.8 (–$NH(CH_2)_3CH_3$). HRMS: *m*/*z* calcd for $C_{20}H_{32}N_2O_4$: 364.2362, Found: 364.2378.

2*R*,3*R*-2-[(*tert*-Butoxy)carbonylamino]-*N*-butyl-3-(phenylmethoxy)butanamide ((+)-19). To a solution of **17** (6.0 mg, 0.021 mmol) in THF–water (20:1, 1.05 mL) was added triphenylphosphine (10.9 mg, 0.041 mmol) and the mixture was stirred for 10 h at rt. The mixture was concentrated in vacuo and the residue was dissolved in CH_2Cl_2 (0.5 mL). To the solution, Boc_2O (7.0 mg, 0.032 mmol) was added. The mixture was stirred for 10 h at rt, poured into water, extracted with ethyl acetate, washed with brine and dried over magnesium sulfate. The extract was concentrated in vacuo and the residue was purified by silica gel column chromatography eluted with hexane–ethyl acetate (3:1) to give **18** as a colorless oil (7.3 mg, 0.020 mmol, 97% yield). $[\alpha]_d^{20}$ +12.80 (*c*=0.063, $CHCl_3$). FT-IR (neat) 3328, 1650, 667, 606 cm^{-1}. ^1H NMR: 7.40–7.25 (m, 5H, C_6H_5–), 6.10 (brt, *J*=6.5 Hz, 1H, –N*H*CH_2–), 5.14 (brd, *J*=6.0 Hz, 1H, –N*H*Boc–), 4.59 (d, *J*=11.5 Hz, 1H, one of $C_6H_5CH_2O$–), 4.47 (d, *J*=11.5 Hz, 1H, one of $C_6H_5CH_2O$–), 4.18 (t, *J*=6.0 Hz, 1H, –C*H*NHBoc–), 3.82 (dq, *J*=6.0, 6.0 Hz, 1H, CH_3CH(OBn)–), 3.25 (quintet, *J*=6.0 Hz 2H, –NHCH_2–), 1.50–1.20 (m, 4H, –$NHCH_2(CH_2)_2$–), 1.45 (s, 9H, –$C(CH_3)_3$), 1.25 (d, *J*=6.0 Hz, 3H, CH_3CH(OBn)–), 0.89 (t, *J*=7.0 Hz, –$NH(CH_2)_2CH_3$). ^{13}C NMR: 169.7 (*C*=O of the amide), 155.9 (*C*=O of the carbamate), 138.2 (C of C_6H_5–), 128.5 (two CH of C_6H_5–), 127.9 (one CH of C_6H_5–), 127.8 (two CH of C_6H_5–), 80.1 (–$C(CH_3)_3$), 76.8 (CH_3CH(OBn)–), 75.0 ($C_6H_5CH_2O$–), 57.6 (–CHNHBoc–), 39.3 (–$NHCH_2$–), 31.6 (–CH_2–), 28.4 (–$C(CH_3)_3$), 20.1 (–CH_2–), 15.5 (CH_3CH(OBn)–), 13.8 (–$NH(CH_2)_3CH_3$). HRMS: *m*/*z* calcd for $C_{20}H_{32}N_2O_4$: 364.2362, Found: 364.2338.

Preparation of authentic sample for (2*R*,3*S*-2-[(*tert*-butoxy)carbonyl- amino]-*N*-butyl-3-(phenylmethoxy)butanamide) ((+)-18)

A mixture of 2*R*,3*S*-2-[(*tert*-butyloxy)carbonylamino]-3-phenylmethoxybutanoic acid (Boc-l-Thr(OBn)) (200 mg, 0.646 mmol), butylamine (0.06 mL, 0.647 mmol), HOBt (198 mg, 1.293 mmol), EDC (186 mg, 0.907 mmol) in CH_2Cl_2 (5 mL) was stirred for 20 min at rt, poured into water, extracted with CH_2Cl_2, washed with brine and dried over magnesium sulfate. The extract was concentrated in vacuo and the residue was purified by silica gel column chromatography eluted with hexane–ethyl acetate (1:1) to give (+)-**18** as a colorless oil (220 mg, 0.604 mmol, 93% yield). $[\alpha]_d^{20}$ +37.23 (*c*=0.059, $CHCl_3$).

Acknowledgements

We thank the JSPS (Japan Society for the Promotion of Science) for the foreign student scholarship awarded to R. Ma.

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2. MAC is an abbreviation of –[$C(CN)_2O$]–. 'MAC reagent' means 'H–[$C(CN)_2O$]–R'. Nemoto, H.; Ibaragi, T.; Kido, M.; Bando, M.; Shibuya, M. *Tetrahedron Lett.* **1999**, *40*, 1319–1322.

3. Some unstable carbonyl compounds have been effectively synthesized using the transformation from HO–C–CN to –C=O. For example, *β-hydroxycyclopentanone*: (a) Stork, G.; Takahashi, T.; Kawamoto, I.; Suzuki, T. *J. Am. Chem. Soc.* **1978**, *100*, 8272–8273.; *β,γ-unsaturated ketone*: (b) Takahashi, T.; Nemoto, H.; Kanda, Y.; Tsuji, J.; Fukazawa, Y.; Okajima, T.; Fujise, Y. *Tetrahedron* **1987**, *43*, 5499–5520.

4. Although we have demonstrated the suppression of epimerization, the synthesized compound is not an α-amino acid derivative.[2]

5. By using the MAC reagent **1B** (R′=1-ethoxyethyl) instead of **1A**, **6a** was also converted to the desired adduct in high yield. However, the adduct cannot be used in further steps since the corresponding sulfonates were not obtained in reproducible yields. NMR analysis of the crude product indicated that the 1-ethoxyethyl moiety of the adduct was lost. Thus we focused on using **1A** for further optimization.

6. We previously reported the preparation of acylated derivatives of **7** using aldehydes **6** and **1A** with $Pd(dppe)_2$. Nemoto, H.; Kubota, Y.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 1665–1666.

7. Ionic carbon–carbon bond formation between malononitrile and benzaldehyde has been reported without the use of any additive. Corson, B. B.; Stoughton, R. W. *J. Am. Chem. Soc.* **1928**, *50*, 2825–2837.

8. Although sulfonylation reactions of **7a** were also attempted using *p*-toluenesulfonyl chloride, *p*-toluenesulfonic anhydride, methanesulfonyl chloride, and methanesulfonic anhydride, Tf_2O gave the best results.

9. The fact that the reverse reaction occurs is supported by the kinetics of the hydrolysis of benzylidenemalononitrile. Bernasconi, C. F.; Howard, K. A.; Kanavarioti, A. *J. Am. Chem. Soc.* **1984**, *106*, 6827–6835.

10. In contrast to **7g**, **7h** was not observed at all by either ^1H NMR or TLC presumably because the reverse reaction is extremely fast even under neutral conditions. However, when H-MAC-$SiMe_2{}^tBu$ is used instead of **1A**, migration of the $SiMe_2{}^tBu$ prevents the reverse reaction. Therefore, all the aldehyde **6h** was consumed and a product was isolated after a short period. This result will be published after further optimization.

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