An Efficient Synthesis of Cyclic β-Amino Acid Derivatives as β-Turn Mimetics

Toshio Yamanaka,*[a,b] Mitsuru Ohkubo,*[a] Masayuki Kato,[a] Yasufumi Kawamura,[b] Akinori Nishi,[b] Takahiro Hosokawa[b]

[a] Medicinal Chemistry Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 2-1-6 Kashima, Yodogawa-Ku, Osaka 532-8514, Japan

[b] Department of Environmental Systems Engineering, Kochi University of Technology, Tosayamada, Kochi 782-8502, Japan
Fax +81(6)63045435; E-mail: toshio_yamanaka@po.fujisawa.co.jp

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Abstract: Seven-, eight-, and nine-membered cyclic β-amino acids, precursors of platelet aggregation inhibitors, were synthesized for the first time starting from *N*-alkenyl amines and ethyl acrylate via ring-closing metathesis (RCM) as the key reaction. Synthesis of the corresponding enantiomerically pure β-amino acids was also accomplished in a similar manner using Evans' asymmetric allylation.

Key words: cyclic β-amino acid, β-turn mimetics, ring-closing metathesis, asymmetric allylation, platelet aggregation inhibitor

The turn structure in peptides plays a crucial role in biological molecular recognition.[1] One representative example is recognition of the β-turn structure in the RGD (Arg-Gly-Asp) peptide sequence of fibrinogen by the glycoprotein IIb/IIIa (GPIIb/IIIa) on the surface of platelets, which induces platelet aggregation. In the course of our study of non-peptide platelet aggregation inhibitors,[2,3] we designed novel RGD β-turn mimetics **1** containing cyclic β-amino acids based on the view that the ring moiety of **1** could serve as a mimetic of the β-turn of the RGD peptide (Figure 1). In order that the mimetics **1** can act as antiplatelet agents, incorporation of a carboxylic acid and an amine functional group at appropriate separation is obviously essential.

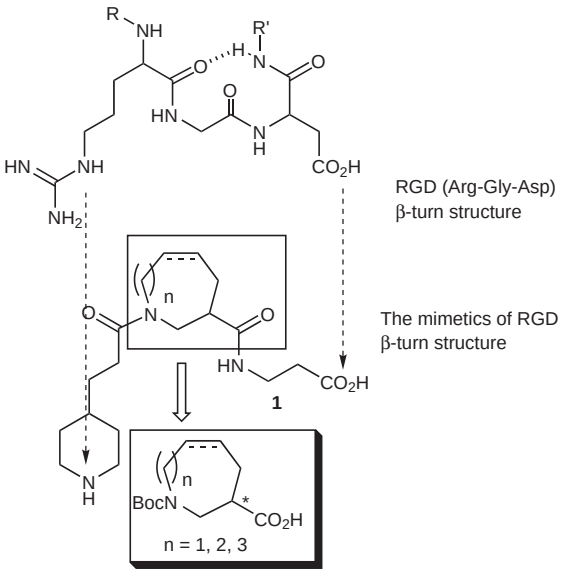

Figure 1

Although some cyclic β-amino acid derivatives have been prepared,[4] there have been no practical synthetic method of higher membered cyclic β-amino acids except for 7-membered ring ones prepared by classical manipulations.[5] In addition, there has been no document for the corresponding optically active cyclic β-amino acids or their derivatives. Under such backgrounds, we wish here to report an efficient synthesis of higher membered cyclic β-amino acid derivatives and their enantiomerically pure forms as the precursors of **1**. In this method, the ruthenium-catalyzed ring-closing metathesis (RCM)[6] and Evans' asymmetric allylation[7] serve as the key reaction. Remarkable in this approach is that the Evans' asymmetric allylation proceeds with high diastereoselectivity and predictable stereoselection. Furthermore, this strategy appears to become a general method for the synthesis of cyclic β-amino acid derivatives.

The synthetic sequences developed here are shown in Scheme 1. Thus, the substrates **4a**–**c** for RCM were firstly prepared from alkenyl amines **2a**–**c**[8] via three steps: (i) conjugate addition to ethyl acrylate, (ii) Boc protection of the NH group, and (iii) allylation at the α-position of the resulting esters **3a**–**c**. Cyclization of **4a**,**b** using Grubbs' first generation catalyst **5**[9] took place smoothly to give the corresponding 7- and 8-membered ring cyclic β-amino acid derivatives **7a**,**b** (n = 1, 2) in identical 90% yields (Table 1). However, construction of the 9-membered ring from **4c** (n = 3) was difficult, probably because of its conformational inadaptability. In addition, the cyclization of **4c** was accompanied by olefin isomerization[10] of the *N*-alkenyl moiety (Scheme 2) to yield **7b** (n = 2) via **4d** along with **7c** (n = 3) (**7c**:**7b** = 4:1, 24% yield). The use of easily handled Grubbs' second generation catalyst **6**[11] was also effective for the syntheses of **7a**,**b**. Hydrogenation of **7a**–**c** in the presence of Pd/C gave the corresponding saturated ring compounds **8a**–**c** in good yields.

Since racemic 7- and 8-membered cyclic β-amino acid derivatives **7** and **8** (n = 1 and 2) were successfully prepared, our effort was then directed towards the synthesis of optically pure cyclic β-amino acids in a similar manner. For this purpose, we prepared enantiomerically pure substrates for RCM by using Evans' asymmetric allylation.[7] Among various chiral auxiliaries,[12] we chose Evans' oxazolidinone and conducted the synthesis of **10a**,**b** as

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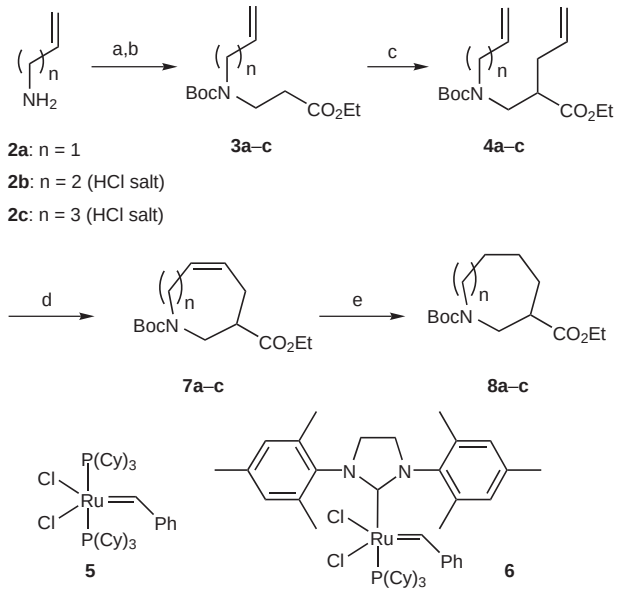
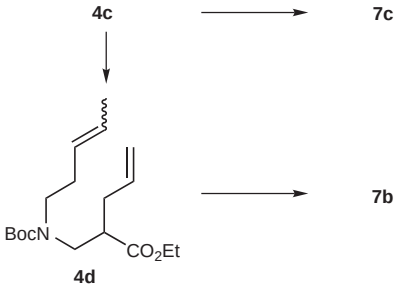


Scheme 1 *Reagents and conditions*: (a) ethyl acrylate, Et_3N (in the cases of **2b**,**c**), EtOH, r.t.; (b) $(Boc)_2O$, CH_2Cl_2, r.t., 82% for **3a**, 56% for **3b**, 40% for **3c** in 2 steps; (c) $LiN(TMS)_2$, –78 °C, THF, then allyl iodide, 67% for **4a**, 57% for **4b**, 73% for **4c**; (d) Grubbs' catalyst **5** or **6**, CH_2Cl_2, reflux (see Table 1); (e) H_2 (1 atm), Pd/C, EtOH, r.t., 90% for **8a**, 88% for **8b**, 95% for **8c**.

Table 1 Ring-Closing Metathesis (RCM) of **4a**–**c**[a]

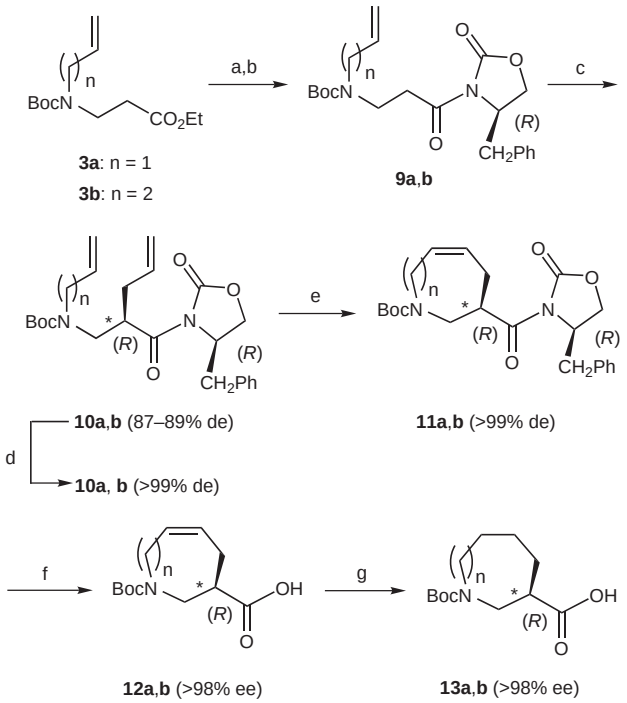
Substrate	n	Catalyst	Product	Yield (%)[b]
4a	1	**5**	**7a**	90
4a	1	**6**	**7a**	97
4b	2	**5**	**7b**	90
4b	2	**6**	**7b**	98
4c	3	**5**[c]	**7c**	24[d]
4c	3	**6**	**7c**	0[e]

[a] Reaction conditions: **4a**–**c** (1.0 mmol), catalyst **5** or **6** (10 mol%), dry CH_2Cl_2 (40 mL), reflux, 2 h, under N_2 atmosphere.
[b] Isolated yields after purification by silica gel column chromatography.
[c] 20 mol% of catalyst **5** was used.
[d] Isolated as a mixture of **7c** and **7b** (**7c**:**7b** = 4:1).
[e] Compound **7b** was isolated in 5% yield.



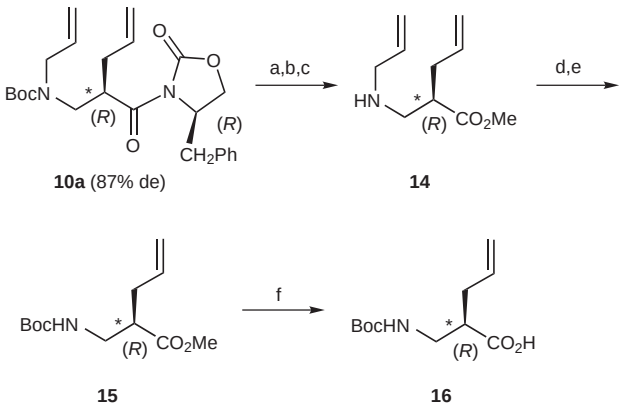
Scheme 2

outlined in Scheme 3. Thus, hydrolysis of *N*-alkenyl β-amino esters **3a**,**b** followed by treatment with *t*-BuCOCl in the presence of Et_3N gave the corresponding acid anhydrides which were reacted with *N*-lithium (*R*)-4-benzyl-2-oxazolidinone generated in situ to give **9a** and **9b** in 78% and 79% yield, respectively. The oxazolidinones **9a**,**b** were then allowed to react with allyl iodide (3.5 equiv) in the presence of $NaN(TMS)_2$ (1.1 equiv) at –78 °C to 0 °C in THF. In this reaction, allyl iodide must approach the diastereoface of the enolate formed in situ avoiding the steric bulkiness of the (4*R*)-benzyl group in the oxazolidinone auxiliary. This process results in the *R*-configuration at the 2′-position. Indeed, the 2′-*R*-configuration products **10a**,**b** were obtained in 68% and 71% yields with 87% and 89% de, respectively. Purification of crude products **10a**,**b** by column chromatography gave diastereomerically pure **10a**,**b** in 64% and 57% yield, respectively. The stereochemical assignment of the 2′-*R*-configuration in **10a** is described later. The ring-closing metathesis of **10a**,**b** using **6** (reflux in CH_2Cl_2) took place smoothly to give **11a**,**b** in good yields with no loss of optical purity.[13] Removal of the oxazolidinone auxiliary by LiOOH[14,15] at 0 °C in THF provided the cyclic β-amino acids **12a**,**b** in good yields.[16] Subsequent hydrogenation with Pd/C gave the corresponding saturated cyclic compounds **13a**,**b** quantitatively.[17] The enantiomeric excesses of **12** and **13** were >98% by HPLC analysis.



Scheme 3 *Reagents and conditions*: (a) 1 *N* aq NaOH, THF, EtOH, r.t.; (b) *t*-BuCOCl, Et_3N, THF, then (*R*)-4-benzyl-2-oxazolidinone, *n*-BuLi, 78% for **9a**, 79% for **9b** in 2 steps; (c) $NaN(TMS)_2$, THF, –78 °C, then allyl iodide allowed to warm to 0 °C, 71% for **10a**, 68% for **10b**; (d) medium pressure column chromatography on silica gel, 64% for **10a**, 57% for **10b** from **9a**,**b**; (e) **6** (10 mol%), CH_2Cl_2, reflux, 97% for **11a**, 96% for **11b**; (f) LiOOH, THF, 0 °C, 87% for **12a**, 93% for **12b**; (g) H_2 (1 atm), Pd/C, EtOH, r.t., 100% for **13a**, 100% for **13b**.

The stereochemical assignment of the 2′-*R*-configuration in **10a** was determined as follows: the oxazolidinone auxiliary of **10a** was removed by LiOOH, and subsequent esterification by (trimethylsilyl)diazomethane[18] and deprotection of the Boc group by trifluoroacetic acid (TFA) gave allyl amine **14**. The *N*-allyl group in **14** was then removed by $Pd(PPh_3)_4$ catalyst in the presence of 3,5-dimethylbarbituric acid[19] to give **15** via Boc-protection of the resulting NH_2 group. Hydrolysis of **15** yielded α-allyl-β-amino acid **16**, the optical rotation of which was found to be '+'. Comparison with the reported data[20] allowed us to assign the configuration as *R* (Scheme 4).



Scheme 4 *Reagents and conditions*: (a) LiOOH, THF, 0 °C, 87%; (b) $TMSCHN_2$, CH_2Cl_2, MeOH, r.t.; (c) TFA, CH_2Cl_2, r.t., 32% in 3 steps; (d) cat. $Pd(PPh_3)_4$, 3,5-dimethylbarbituric acid, CH_2Cl_2, r.t.; (e) $(Boc)_2O$, 63% in 2 steps; (f) LiOH, THF, MeOH, r.t., 82%; **16**: $[\alpha]_D^{26}$ +11.0 (*c* 1.09, CH_2Cl_2).

Starting from the β-amino acid derivatives **7** and **8**, we prepared the RGD β-turn mimetics **1** shown in Figure 1 and measured the effect on platelet aggregation. As a result, the compound derived from 7-membered β-amino acid ester **8a** showed good efficacy.[21] The details of these results, including the structure–activity relationships, will be reported in the near future.

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(13) **Procedure for the Preparation of 11a.**
To a solution of **10a** (735 mg, 1.72 mmol, >99% de) in anhyd CH_2Cl_2 (70 mL) was added Grubbs' catalyst **6** (146 mg, 0.172 mmol). The mixture was refluxed under nitrogen atmosphere for 1.5 h. After cooling to r.t., solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc–hexane = 1:4) to give **11a** (664 mg, 97%) as an amorphous solid. The diastereomeric purity of purified **11a** was >99% de determined by HPLC analysis using CHIRALPAK AD (DAICEL) with hexane–*i*-PrOH (85:15). IR (KBr): 2976, 2929, 1772, 1697, 1684, 1456, 1051, 1020, 702 cm^{-1}. ^1H NMR ($CDCl_3$; major rotamer): δ = 1.47 (s, 9 H), 2.38–2.58 (m, 2 H), 2.73–2.79 (m, 1 H), 3.28 (dd, *J* = 13.2, 3.3 Hz, 1 H), 3.65 (dd, *J* = 13.9, 8.0 Hz, 1 H), 3.79 (dd, *J* = 13.9, 6.8 Hz, 1 H), 3.85–4.06 (m, 2 H), 4.10–4.27 (m, 3 H), 4.58–4.82 (m, 1 H), 5.62–5.89 (m, 2 H), 7.20–7.36 (m, 5 H). HRMS: *m*/*z* calcd for $C_{22}H_{29}N_2O_5$ $[M + H]^+$: 401.2076; found: 401.2069. $[\alpha]_D^{27}$ –42.0 (*c* 0.525, $CHCl_3$).
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(16) **Procedure for the Preparation of 12a.**
To a solution of **11a** (560 mg, 1.40 mmol) in THF (28 mL) and H_2O (9 mL) were added 30% H_2O_2 (1.27 mL, 11.2 mmol, 8.0 equiv) and then 1 *N* aq LiOH solution (2.8 mL, 2.8 mmol, 2.0 equiv) under ice cooling. The reaction mixture was stirred at the same temperature for 30 min, then treated with 20% aq $Na_2S_2O_3$ solution (55 mL) and stirred for further 5 min. It was extracted with Et_2O. The aqueous phase was acidified to pH 2 with 10% aq $KHSO_4$, and extracted with EtOAc twice. The extracts were combined and dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified with silica gel short column chromatography on silica gel (CH_2Cl_2–EtOAc = 1:1) to give **12a** (295 mg, 87%)

as an oil. The enantiomeric purity of purified **12a** was >98% ee determined by HPLC analysis using CHIRALPAK AD column (DAICEL) (hexane–EtOH–TFA = 98:2:0.1). IR (neat): 2978, 2933, 2866, 1734, 1697, 1419, 1367, 1269, 1252, 1167, 891 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.47 (s, 9 H), 2.43–2.47 (m, 2 H), 2.80–3.15 (m, 1 H), 3.55–4.30 (m, 4 H), 5.55–5.85 (m, 2 H). HRMS: *m*/*z* calcd for $C_{12}H_{20}NO_4$ [M + H]$^+$: 242.1392; found: 242.1387. $[\alpha]_D^{26}$ –23.2 (*c* 1.01, $CHCl_3$).

(17) **Procedure for the Preparation of 13a.**
To a solution of **12a** (48 mg, 0.20 mmol) in MeOH (1.5 mL) was added 10% Pd/C (24 mg), and the mixture was stirred under H_2 atmosphere (1 atm) at r.t. for 3 h. The catalyst was filtered off, and the filtrate was evaporated off to give **13a** (48 mg, 100%) as a solid. The enantiomeric purity of purified **13a** was >98% ee determined by HPLC analysis using CHIRALPAK AD column (DAICEL) with (hexane–EtOH–TFA = 98:2:0.1). IR (KBr): 2976, 2933, 2866, 1732, 1695, 1481, 1423, 1367, 1163 cm^{-1}. ^1H NMR ($CDCl_3$; major rotamer): δ = 1.31–1.96 (m, 5 H), 1.48 (s, 9 H), 2.01–2.08 (m, 1 H), 2.86–2.93 (m, 1 H), 3.13–3.27 (m, 1 H), 3.52 (dt, *J* = 13.9, 5.1 Hz, 1 H), 3.60–3.70 (m, 2 H). HRMS: *m*/*z* calcd for $C_{12}H_{22}NO_4$ [M + H]$^+$: 244.1549; found: 244.1542. $[\alpha]_D^{26}$ –7.7 (*c* 0.74, $CHCl_3$).

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