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Enantioselective organocatalytic conjugate addition of amines to α,β-unsaturated aldehydes: one-pot asymmetric synthesis of β-amino acids and 1,3-diamines

Jan Vesely, Ismail Ibrahem, Ramon Rios, Gui-Ling Zhao, Yongmei Xu and Armando Córdova*

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden

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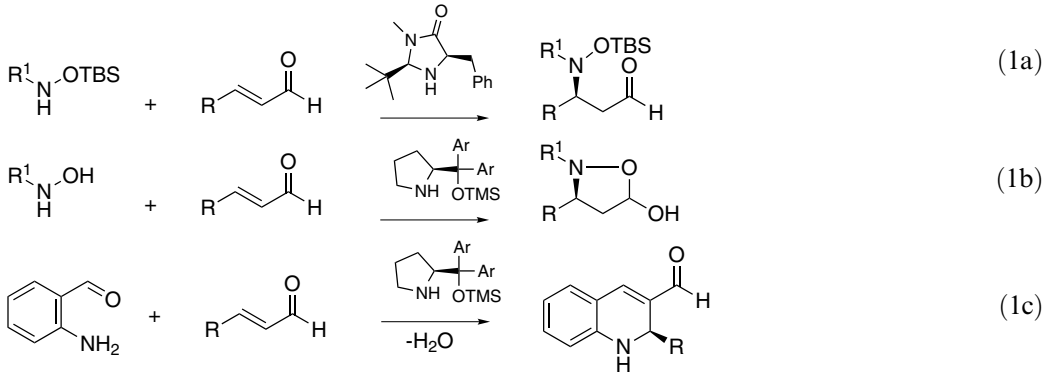
Abstract—Organocatalytic asymmetric amine conjugate additions to α,β-unsaturated aldehydes catalyzed by protected diarylprolinols are presented. The reactions proceed with high enantioselectivity and result in Cbz or Boc protected β-amino aldehydes, γ-amino alcohols, β-amino acids and 1,3-diamines with typically 82–99% ee.

The aza-Michael reaction, in which an amine is added to the β-position of a carbonyl compound, has found a multitude of applications in organic synthesis.[1] The resulting β-amino carbonyl compounds are constituents of many natural products and can be used as chiral synthons for the preparation of pharmaceutical agents. The conjugate addition of stoichiometric amounts of chiral amines to electron deficient α,β-unsaturated compounds has been the main strategy for the construction of β-amino carbonyl compounds.[2] Catalytic versions that utilize Lewis acids as catalysts have been reported.[3] Moreover, peptide derivatives mediate the asymmetric conjugate addition of TMS azide to imides.[4] Recently, MacMillan and co-workers reported the asymmetric addition of silyl protected hydroxylamines to α,β-unsaturated aldehydes in the presence of catalytic amounts of chiral imidazolidinone amines, Eq. 1a.[5] This reaction proceeds via a catalytic enantioselective iminium activation mechanism.[6] Shortly after, we reported that chiral pyrrolidine derivatives catalyze the reaction between hydroxylamines and enals to furnish 5-hydroxyisoxazolidines in one pot, Eq. 1b.[7] Furthermore, we found that chiral amines catalyze the asymmetric domino aza-Michael/aldol reaction between 2-aminobenzaldehydes and enals, Eq. 1c.[8]



* Corresponding author. Tel.: +46 8 162479; fax: +46 8 154908; e-mail addresses: acordova@organ.su.se; acordova1a@netscape.net

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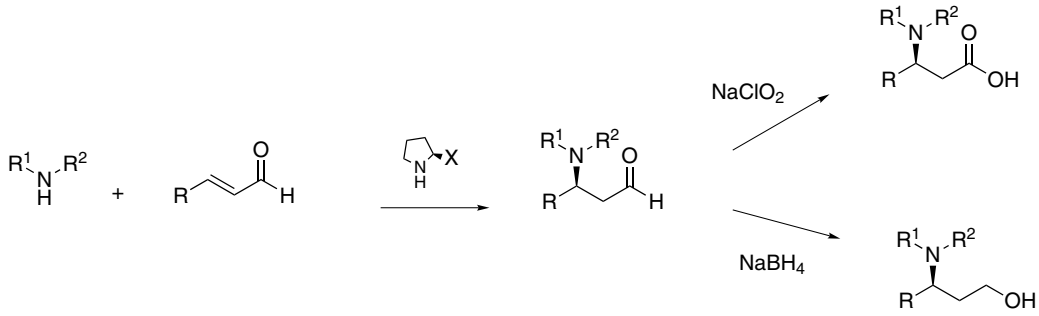
Inspired by the high chemoselectivities obtained in these reports, we became interested in whether simple chiral pyrrolidine derivatives would also be able to catalyze the conjugate addition of amines to α,β-unsaturated aldehydes. Moreover, this reaction is of high synthetic importance since it is a direct route to protected β-amino aldehydes, β-amino acids and γ-amino alcohols, Eq. 2.



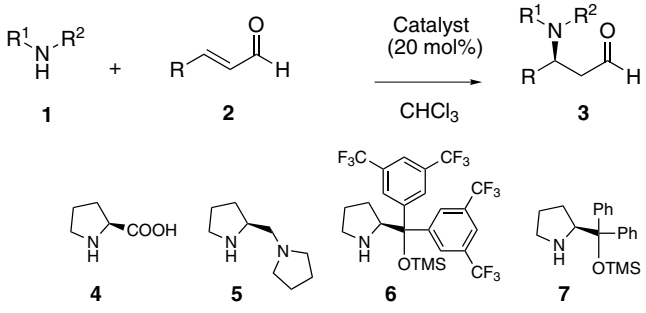
(2)

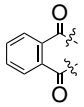
Herein, we report that simple chiral pyrrolidine derivatives catalyze highly enantioselective conjugate additions of protected *N*-methoxycarbamates to α,β-unsaturated aldehydes. The reaction gives access to the corresponding β-amino aldehydes, γ-amino alcohols and β-amino acids in good yields and 82–99% ee. Moreover, the reaction was linked in cascade with organocatalytic Mannich reactions to give the corresponding orthogonally protected chiral diamines with high enantioselectivity.

In an initial catalyst and solvent screen, we found that chiral pyrrolidines **5**–**7** catalyzed the reaction between Cbz protected methoxyamine **1a** (0.30 mmol) and enal **2a** (0.25 mmol) with high chemoselectivity in $CHCl_3$ (1 mL) to give the corresponding β-amino aldehyde **3a** with low to high conversion and up to 98% ee. (Table 1).[9] Notably, no β-amino aldehyde products arising from 1,4-catalyst incorporation were observed.

The chiral TMS protected pyrrolidine **7** was the most efficient catalyst and mediated the formation of β-amino aldehyde **3a** with the highest ee. Moreover, catalyst **7**

Table 1. Catalyst screen for the enantioselective reactions between amines **1** and enals **2**[a]



Entry	R^1	R^2	Amine	R	Product	Catalyst	Temperature (°C)	Time (h)	Conv[b] (%)	ee[c] (%)
1	Cbz	OMe	**1a**	CO_2Et	**3a**	**4**	rt	24	0	—
2	Cbz	OMe	**1a**	CO_2Et	**3a**	**5**	rt	5	>99 (49)[d]	45
3	Cbz	OMe	**1a**	CO_2Et	**3a**	**6**	rt	24	22 (18)[d]	90
4	Cbz	OMe	**1a**	CO_2Et	**3a**	**7**	rt	1	>99 (65)[d]	96
5	Cbz	OMe	**1a**	CO_2Et	**3a**	**7**	4	3	>99 (66)[d]	98
6	Cbz	OTBS	**1b**	CO_2Et	**3b**	**7**	rt	5	60 (45)[d]	99
7	Cbz	OTBS	**1b**	CO_2Et	**3b**	**7**	rt	3.5[d]	70 (55)[d,e]	99[e]
8			**1c**	*n*-Bu	**3c**	**7**	4	14	>99 (89)[f]	62

[a] Experimental conditions: A mixture of **1** (0.30 mmol), enal **2** (0.25 mmol) and catalyst (20 mol %) in 1.0 mL $CHCl_3$ was stirred under the conditions displayed in Table 1.
[b] Determined by ^1H NMR analysis.
[c] Determined by chiral-phase HPLC analysis.
[d] Isolated yield of pure alcohol **11** obtained after in situ reduction of **3**.
[e] 20 mol % acetic acid was added.
[f] Isolated yield of pure aldehyde **3c**.

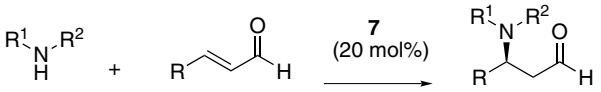
catalyzed the reaction with high enantioselectivity in several of the other solvents tested. Changing the amine nucleophile to *N*-silyloxycarbamate **1b** improved the enantioselectivity of the reaction but reduced the reaction rate (entries 6 and 7). For instance, β-amino aldehyde **3b** was formed in 70% conversion after 3.5 h in 99% ee in the presence of a catalytic amount of **7**. Phthalimide **1c** could also be used as a nucleophile and the corresponding β-amino aldehyde **3c** was isolated in 89% yield with 62% ee (entry 8). Based on our preliminary results, we decided to investigate the catalytic asymmetric conjugate additions of protected hydroxylamines **1a**, **b**, **d** and phthalimide **1c** to different enals **2** with (*S*)-diphenylprolinol **7** as the organocatalyst (Table 2).[10]

The catalytic conjugate additions of Cbz or Boc protected methoxyamines **1a** and **1d** to enals **2** proceeded with high chemo- and enantioselectivity and the corresponding β-amino aldehydes **3a**, **3d**–**h** were obtained in good to high yields with 92–99% ee. For example, diarylprolinol **7** catalyzed the asymmetric conjugate addition between amine **1a** and crotonaldehyde with high chemoselectivity to give β-amino aldehyde **3g** in 86% yield with 92% ee (entry 5). The organocatalytic conjugate addition between TBS protected hydroxylamine **1b** and 2-hexenal at −20 °C gave the corresponding β-amino aldehyde **3i** in 59% yield with 93% ee (entry 7). Moreover, the reactions were operationally simple and readily scaled up. However, catalyst **7** was unable to catalyze the conjugate addition of protected hydroxylamines **1a**, **b** and **d** to cinnamic aldehydes (e.g., entry 9). Notably, the addition of a small amount of an organic acid (20 mol %) enabled these reactions to take place. For example, the use of 3,5-dinitrobenzoic acid (20 mol %) as an additive made it possible for chiral pyrrolidine **7** to catalyze the reaction between amine **1a** and 4-nitrocinnamic aldehyde to give the corresponding β-amino aldehyde **3k** in 40% yield with 82% ee (entry 10). Thus, the presence of an acid additive pushes the equilibrium towards product formation. Moreover, phthalimide **1c** was also added to cinnamic aldehyde and the corresponding aldehyde **3j** was isolated in 69% yield, but with 45% ee when benzoic acid (20 mol %) was added (entry 8). The same reaction without the acid additive in $CHCl_3$–EtOH 6:1 increased the yield to 80% and slightly decreased the ee to 40%.

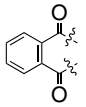
We next decided to link the organocatalytic asymmetric aza-Michael reactions in a cascade with a three-component proline-catalyzed asymmetric Mannich reaction in one pot.[11–13] This should be possible due to the complete difference in reactivity between chiral pyrrolidine **7** and proline in the separate reactions. To our delight, the novel cascade reaction gave direct access to orthogonally protected chiral diamine derivatives with excellent chemo- and enantioselectivities (Scheme 1). In fact, the proline catalyzed Mannich reaction kinetically resolved the β-amino aldehyde intermediate **3f** to give diamines **8a** and **8b** with 98% and 99% ee, respectively.

The organocatalytic asymmetric amine conjugate reactions were also useful for the one-pot synthesis of the corresponding β-amino acids **9** or γ-amino alcohols **11** by in situ oxidation and reduction, respectively (Scheme 2).

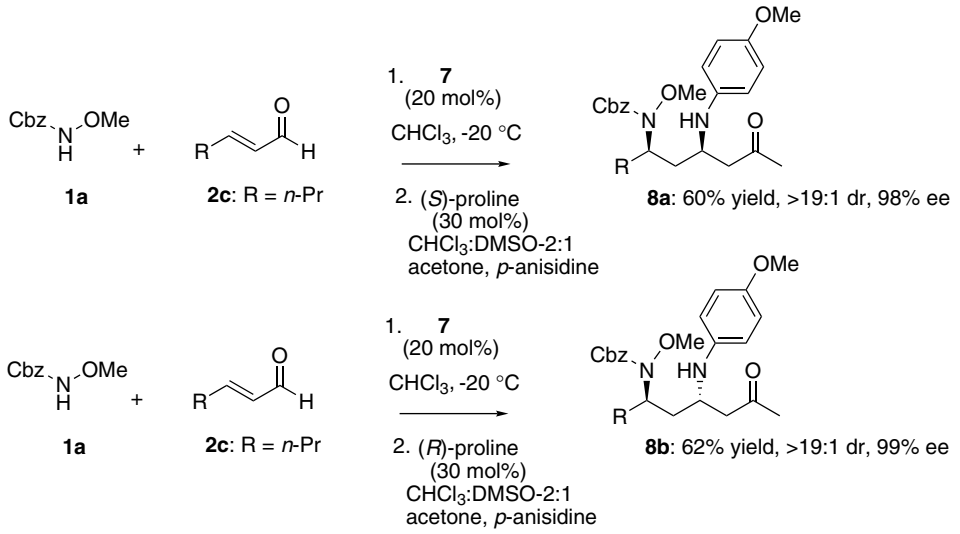
Table 2. Direct organocatalytic asymmetric conjugate addition reactions between amines **1** and aldehydes **2**[a]



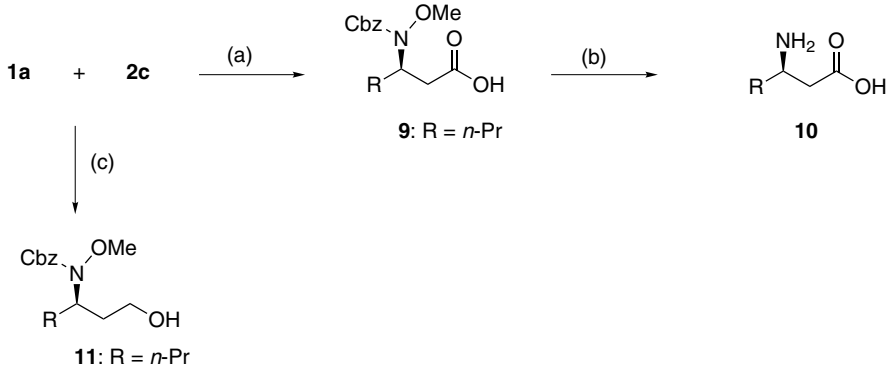
1 **2** **3**

Entry	R^1	R^2	Amine	R	Product	Temperature (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	Cbz	OMe	**1a**	CO_2Et	**3a**	4	3	66	98
2	Boc	OMe	**1d**	CO_2Et	**3d**	rt	24	56	99
3	Cbz	OMe	**1a**	*n*-Pr	**3e**	−20	12	62	96
4	Cbz	OMe	**1a**	*n*-Bu	**3f**	−20	14	65	95
5	Cbz	OMe	**1a**	Me	**3g**	−20	18	86[d]	92[d]
6	Cbz	OMe	**1a**	$BnOCH_2$	**3h**	−20	16	64	98
7	Cbz	OTBS	**1b**	*n*-Pr	**3i**	−20	24	59	93
8			**1c**	Ph	**3j**	−20	24	80[e,h] (69)[f,h]	40[e] (45)[f]
9	Cbz	OMe	**1a**	$4\text{-}NO_2C_6H_4$	**3k**	rt	48	0	—
10	Cbz	OMe	**1a**	$4\text{-}NO_2C_6H_4$	**3k**	rt	6	40[g]	82[g]

[a] Experimental conditions: A mixture of **1** (0.30 mmol), enal **2** (0.25 mmol) and catalyst **7** (20 mol %) in 1.0 mL $CHCl_3$ was stirred under the conditions displayed in Table 2.
[b] Isolated yield of pure alcohol **11** obtained by in situ reduction of compound **3** with $NaBH_4$.
[c] Determined by chiral-phase HPLC analysis.
[d] 3 equiv of crotonaldehyde used.
[e] The reaction was run in $CHCl_3$–EtOH 6:1.
[f] 20 mol % of benzoic acid was added, $CHCl_3$–EtOH 6:1.
[g] 20 mol % of 3,5-dinitrobenzoic acid was added.
[h] Isolated yield of pure compound **3j**.



Scheme 1. One-pot asymmetric cascade aza-Michael/Mannich reactions using a combination of **7** and (*S*)-proline or (*R*)-proline as the catalysts, respectively.



Scheme 2. Reagents and conditions: (a) (i) (*S*)-**7** (20 mol %), $CHCl_3$, −20 °C, 14 h; (ii) $NaClO_2$, *iso*-butene, KH_2PO_4, *t*-BuOH–H_2O 2:1, 54% (overall); (b) H_2 (90 MPa), Pd/C (10 mol %), MeOH, rt, 48 h, 90%; (c) (i) (*S*)-**7** (20 mol %), $CHCl_3$, −20 °C, 14 h; (ii) $NaBH_4$, MeOH, 0 °C, 5 min, 62% (overall).

For example, enal **2c** was converted in one-pot to β-amino acid **9** in 54% overall yield with 98% ee. Subsequent deprotection gave the corresponding β-amino acid **10**. Comparison with the literature established that the absolute stereochemistry of **10** ($[\alpha]_D^{25}$ −30.4 (*c* 0.1, H_2O), lit. (*ent*-**10** $[\alpha]_D^{15}$ +61 (*c* 0.4, H_2O)[15]) was (3*R*).[14] On the basis of the absolute configuration, we propose transition-state model **I** to account for the enantioselectivity of the amino acid catalyzed formation of β-amino aldehydes **3** (Fig. 1). Hence, the bulky (*S*)-diarylprolinol derivative forms an iminium intermediate with enal **2** which is attacked by the *N*-Boc or Cbz protected amines **1** from its *Re*-face (*R* = alkyl) providing the (3*R*)-β-amino acid derivatives **3**.

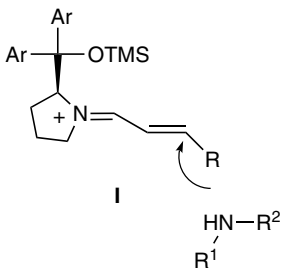


Figure 1. Transition state model evoked to account for the enantioselectivity of the (*S*)-**7** catalyzed reactions.

In summary, we have reported a simple, highly enantioselective, organocatalytic asymmetric amine conjugate addition reaction. The chiral pyrrolidine catalyzed reactions between protected *N*-methoxycarbamates and α,β-unsaturated aldehydes proceeded with high chemo- and enantioselectivity to furnish β-amino aldehydes in good to high yields with 82–99% ee. Moreover, a novel organocatalytic asymmetric cascade aza-Michael/Mannich reaction was developed. Further elaboration of amine conjugate additions, their synthetic application and mechanistic studies are ongoing in our laboratory.[16]

Acknowledgement

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9. *Typical experimental procedure*: To a stirred solution of catalyst **7** (20 mol %) and amine **1** (1.2 equiv) in solvent (1.0 mL) at the reported temperature was added α,β-unsaturated aldehyde **2** (1.0 equiv). The reaction was vigorously stirred for the time given in Table 1. Next, MeOH (2 mL) was added and the reaction temperature cooled to 0 °C followed by addition of the excess $NaBH_4$. After 10 min, the $NaBH_4$ was quenched by addition of a saturated solution of NH_4Cl and the product extracted with EtOAc and the solvent evaporated. Silica gel column chromatography (pentane:EtOAc-mixtures or toluene:EtOAc-mixtures) furnished the corresponding amino alcohol **11**. Data for **3a**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 9.78 (t, $J = 1.2$ Hz, 1H), 7.40–7.32 (m, 5H), 5.27 (d, $J = 12.0$ Hz, 1H), 5.23 (d, $J = 12.0$ Hz, 1H), 5.16 (dd, $J = 6.0$ Hz, 7.2 Hz, 1H), 4.17 (q, $J = 7.2$ Hz, 2H), 3.72 (s, 3H), 3.17 (ddd, $J = 1.2$ Hz, 6.0 Hz, 17.6 Hz, 1H), 2.96 (ddd, $J = 1.2$ Hz, 7.2 Hz, 17.6 Hz, 1H), 1.20 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.2$, 169.1, 160.0, 135.7, 128.7, 128.6, 128.4, 68.5, 64.0, 62.3, 58.1, 42.7, 14.1. HRMS (ESI): calcd for $[M+Na]^+$ ($C_{15}H_{19}NO_6Na$) requires m/z 332.1105. Found: 332.1109. Data for **11a**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.39$–7.33 (m, 5H), 5.27 (d, $J = 12.4$ Hz, 1H), 5.23 (d, $J = 12.4$ Hz, 1H), 4.84 (dd, $J = 4.8$ Hz, 9.6Hz, 1H), 4.17 (q, $J = 7.2$ Hz, 2H), 3.82–3.77 (m, 1H), 3.79 (s, 3H), 3.73–3.67 (m, 1H), 2.32–2.23 (m, 1H), 2.17–2.07 (m, 1H), 1.82 (br s, 1H), 1.22 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.4$, 160.1, 135.8, 128.7, 128.5, 128.3, 68.3, 64.0, 61.8, 60.0, 59.3, 31.3, 14.2. $[\alpha]_D^{25}$ −40.9 (*c* 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC on Daicel Chiralpak OD–H with *iso*-hexane/*i*-PrOH (90:10) as the eluent. Flow: 0.5 mL/min; minor isomer: $t_R = 23.1$ min; major isomer: $t_R = 24.4$ min.; HRMS (ESI): calcd. for $[M+Na]^+$ ($C_{15}H_{21}NO_6Na$) requires m/z 334.1261. Found: 334.1255.
10. *Typical experimental procedure*: To a stirred solution of catalyst **7** (20 mol %) and amine **1** (1.2 equiv) in $CHCl_3$ (1.0 mL) at the reported temperature was added α,β-unsaturated aldehyde **2** (1.0 equiv). The reaction was vigorously stirred for the time given in Table 2. Next, MeOH (2 mL) was added and the reaction temperature cooled to 0 °C followed by addition of the excess $NaBH_4$. After 10 min, the $NaBH_4$ was quenched by the addition of a saturated solution of NH_4Cl and the reaction then extracted with EtOAc and the solvent evaporated. Silica gel column chromatography (pentane:EtOAc-mixtures or toluene:EtOAc-mixtures) furnished the corresponding amino alcohol **11**.
11. To a stirred solution of catalyst **7** (16 mg, 0.05 mmol) and methoxy-*N*-benzylcarbamate **1a** (54 mg, 0.30 mmol) in chloroform (1.0 mL) at −20 °C was added *trans*-hex-2-enal (29 μL, 0.25 mmol). The reaction was vigorously stirred for 14 h at the same temperature. Next, the temperature was increased to 23 °C and DMSO (0.5 mL), acetone (0.5 mL), *p*-anisidine (34 mg, 0.275 mmol) and proline (9 mg, 0.075 mmol) were added to the reaction mixture, which was stirred overnight. Silica gel column chromatography (toluene:EtOAc-mixtures) furnished the corresponding ketones **8**. Data for **8a**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.39–7.32 (m, 5H), 6.72 (d, $J = 8.9$ Hz, 2H), 6.52 (d, $J = 8.9$ Hz, 2H), 5.10 (d, $J = 12.8$ Hz, 1H), 5.00 (d, $J = 12.8$ Hz, 1H), 4.18–4.07 (m, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 2.63–2.52 (m, 2H), 2.02 (s, 3H), 1.94–1.85 (m, 1H), 1.74–1.63 (m, 2H), 1.44–1.30 (m, 4H), 0.86 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 208.5$, 158.2, 152.4, 141.0, 136.3, 129.0, 128.5, 128.3, 115.4, 115.1, 67.8, 64.3, 58.0, 56.0, 48.9, 47.3, 37.3, 34.7, 31.0, 19.7, 14.0. $[\alpha]_D^{25}$ +7.4 (*c* 1.0, $CHCl_3$). The enantiomeric excess was determined by HPLC on Daicel Chiralpak OD–H with *iso*-hexane/*i*-PrOH (95:5) as the eluent. Flow: 1.0 mL/min; minor isomers: $t_{R1} = 13.4$ min, $t_{R2} = 16.8$ min; major isomers: $t_{R3} = 21.0$ min, $t_{R4} = 47.6$ min.; HRMS (ESI): calcd. for $[M+Na]^+$ ($C_{25}H_{34}N_2O_5Na$) requires m/z 465.2360. Found: 465.2341.
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14. To a stirred solution of Cbz-protected amino acid **9** in MeOH (0.1 M) was added 10% (in weight) of Pd/C (10%). The reaction was stirred under 90 atm of hydrogen for 48 h. Then the crude reaction was filtered through a plug of Celite.The solvent was removed under reduced pressure to afford the pure β-amino acid **10**. Data for **10**: 90% yield; $[\alpha]_D^{25}$ −21.2 (*c* 1.0, MeOH); $[\alpha]_D^{25}$ −30.4 (*c* 0.1, H_2O). (lit. *ent*-**10** $[\alpha]_D^{15}$ +61 (*c* 0.4, H_2O)[15] ^{1}H NMR (400 MHz, MeOD): $\delta = 3.42$–3.30 (m, 1H), 2.52 (dd, $J = 4.5$ Hz, 18.0 Hz, 1H), 2.32 (dd, $J = 9.0$ Hz, 18.0 Hz, 1H), 1.66–1.57 (m, 2H), 1.50–1.36 (m, 2H), 0.97 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, MeOD): $\delta = 176.4$, 49.4, 37.8, 35.0, 18.5, 12.9.
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