Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 725–730

TETRAHEDRON: *ASYMMETRY*

Synthesis of enantiopure *N*-protected 4,5-disubstituted 3-pyrrolidinones and *N*-protected 2,5-disubstituted 3-pyrrolidinones via the Dieckmann reaction of dicarbonyl compounds derived from enantiopure β-amino esters

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Received 27 December 2000; accepted 2 March 2001

Abstract—Under the action of KHMDS in THF solvent the Dieckmann reaction of dicarbonyl compounds derived from enantiopure β-amino esters provides enantiopure *N*-protected 4,5-disubstituted 3-pyrrolidinones, whereas *N*-protected 2,5-disubstituted 3-pyrrolidinones formed in reactions mediated by *tert*-BuOK in DMF or toluene. Reduction of these pyrrolidinones afforded enantiopure polysubstituted pyrrolidines.

1. Introduction

In connection with our ongoing program into the synthesis of enantiopure β-amino acid derivatives,[1] we became interested in the intramolecular Dieckmann reaction of dicarbonyl compounds **3**, which could be prepared from *N*,*N*-disubstituted β-amino esters **1**[2] in three steps (Scheme 1). Depending on the regioselectivity of the Dieckmann reaction, enantiopure *N*-protected 4,5-disubstituted 3-pyrrolidinones **4** or *N*-protected 2,5-disubstituted 3-pyrrolidinones **5** could be obtained from these unsymmetrical dicarbonyl compounds. Both pyrrolidinones are obviously promising intermediates for preparing various synthetically challenging and medicinally important agents. For example, using **4** as starting materials we would be able to synthesize pyrrolidine glycosidase inhibitors **6**[3] and **7**,[4] and necine alkaloids such as (−)-petasinecine.[5] It is possible to transform products **5** to some natural pyrrolidine alkaloids like (−)-bulgecinine,[6] (2*R*,3*R*,5*R*)-3-hydroxy-5-methyl-2-pyrrolidinecarboxylic acid **8**,[7] as well as (+)-preussin.[8]

2. Results and discussion

With this in mind, we examined the Dieckmann reaction of diester **3a**, which was prepared from **2a** via alkylation with methyl chloroacetate and subsequent protection with $(Boc)_2O$. Treatment of **3a** with KHMDS in THF at −78°C afforded the *N*-protected 4,5-disubstituted 3-pyrrolidinone **4a** in moderate yield (Scheme 2). Other bases such as *tert*-BuOK and NaH were also applicable in this reaction. However, the yields were not improved greatly.

Inspired by Sibi's results,[9] we investigated the use of amides **9** as substrates in the Dieckmann reaction. These were synthesized by following the alkylation procedure used to form **3a** except that *N*-methoxy-*N*-methyl-chloroacetamide was used as the electrophile. At this time the condensation reaction using KHMDS in THF worked well to give the *N*-protected 4,5-disubstituted 3-pyrrolidinones **4** in good to excellent yields. The results are summarized in Table 1. It was found that both 5-alkyl-3-pyrrolidinones and 5-aryl-3-pyrrolidinones could be obtained by this method (entries 1–6). In addition, not only *N*-Boc but also *N*-alkyl substrates were suitable in this reaction (compare entries 2 and 3). Thus, this method is applicable to the preparation of a variety of enantiopure 1,4,5-trisubstituted 3-pyrrolidinones.

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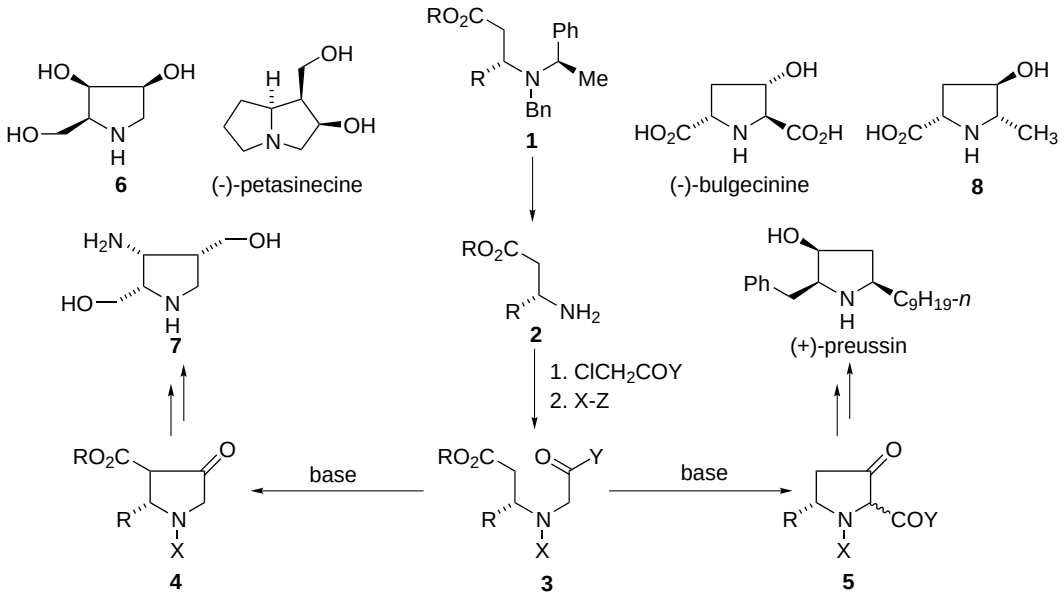
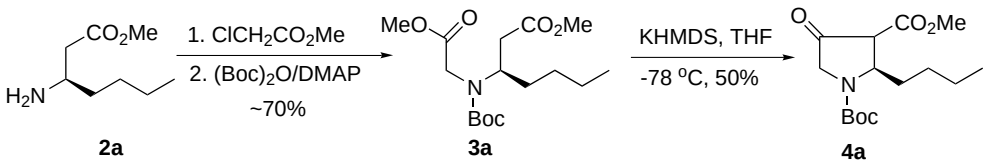
PII: S0957-4166(01)00115-X

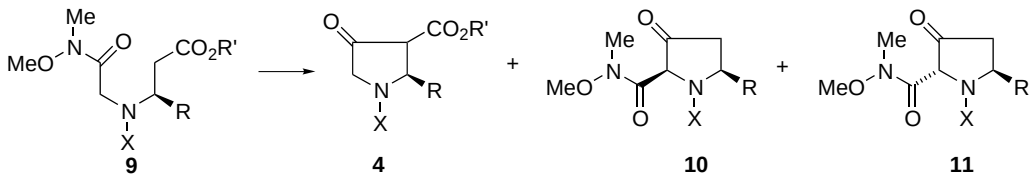


Scheme 1.



Scheme 2.

Table 1. Intramolecular Dieckmann reaction of **9**[a]



Entry	X/R/R′	Base	Solvent	*T* (°C)	*t* (min)	Yield (%)[b]		
						4	**10**	**11**
1	Boc/*n*-Bu/Me **9a**	KHMDS	THF	−78	2	89	–	–
2	Ph(Me)CH/Me/Me **9b**	KHMDS	THF	−78	2	80	–	–
3	Boc/Me/Me **9c**	KHMDS	THF	−78	2	75	–	–
4	Bn/Ph/Et **9d**	KHMDS	THF	−78	2	90	–	–
5	Boc/*p*-$CH_3OC_6H_4$/Me **9e**	KHMDS	THF	−78	2	90	–	–
6	Boc/$BnO(CH_2)_3$/Et **9f**	KHMDS	THF	−78	2	78	–	–
7	Boc/*n*-Bu/Me **9a**	KHMDS	Toluene	−20	25	–	25	–
8	Boc/*n*-Bu/Me **9a**	KOBu-*t*	Toluene	−20	25	–	20	–
9	Boc/*n*-Bu/Me **9a**	KOBu-*t*	Toluene	0	5	–	30	–
10	Boc/*n*-Bu/Me **9a**	KOBu-*t*	DMF	−78[c]	2	–	40	10
11	Boc/$BnO(CH_2)_3$/Et **9f**	KOBu-*t*	DMF	−78[c]	2	–	43	10
12	Boc/*n*-$C_{15}H_{31}$/Me **9g**	KOBu-*t*	DMF	−78[c]	2	–	37	19
13	Bn/Ph/Et **9d**	KOBu-*t*	DMF	−78[c]	2	72	–	–
14	Bn/Bu-*n*/Me **9h**	KOBu-*t*	DMF	−78[c]	2	60	–	–

[a] Reaction conditions: KHMDS (1 mmol), **9** (0.3 mmol) in THF (15 mL); or *tert*-BuOK (1 mmol), **9** (0.2 mmol) in DMF (15 mL).
[b] Isolated yield.
[c] Bath temperature.

In order to change the regioselectivity of this Dieckmann reaction and gain access to different polysubstituted pyrrolidinones, other bases and solvents were examined. When toluene was used as solvent the reaction of **9a** mediated by KHMDS at −20°C provided 2,5-disubstituted 3-pyrrolidinone **10a** in lower yield, together with some decomposition products (entry 7). Replacement of KHMDS with *tert*-BuOK gave similar results (entries 8 and 9). However, when the reaction of **9a** was carried out in DMF at −78°C using *tert*-BuOK as a base, it afforded 2,5-disubstituted 3-pyrrolidinones **10a** and **11a** in moderate yield. The major side products were decomposition products. The ratio of **10a** and **11a** was about 4:1 and their stereochemistry was assigned by NOESY spectra. However, this regioselectivity was restricted to the substrates in which R is an alkyl group and the *N*-protecting group was Boc (entries 10–12 and 13, 14).

To further demonstrate the usage of the method presented, some pyrrolidinones were reduced to the corresponding polysubstituted pyrrolidines under different conditions. The stereochemistry of each product was established by NOESY studies. As outlined in Scheme 3, hydrogenation of **4e** catalyzed by Pd/C at 30°C and atmospheric pressure for 3 days gave **12** in 70% yield. However, reduction of **4e** with $NaBH_4$ gave **12** as a minor product and its 3,4-epimer **13** as a major product (ratio was about 1:2). Thus, different isomers could be obtained by changing the reduction conditions. The reduction of **10h** or **11h** with $NaBH_4$ is shown in Scheme 4. These reactions indicated that the stereochemistry at the 3-position was completely controlled by the 2-substituent.

3. Conclusion

In summary, we have discovered suitable reaction conditions to control the regioselectivity of the Dieckmann reaction of dicarbonyl compounds derived from enantiopure β-amino esters, which allows the synthesis of either *N*-protected 4,5-disubstituted 3-pyrrolidinones or *N*-protected 2,5-disubstituted 3-pyrrolidinones in moderate to good yields.[10] Application of this method to the synthesis of related natural alkaloids is currently underway.

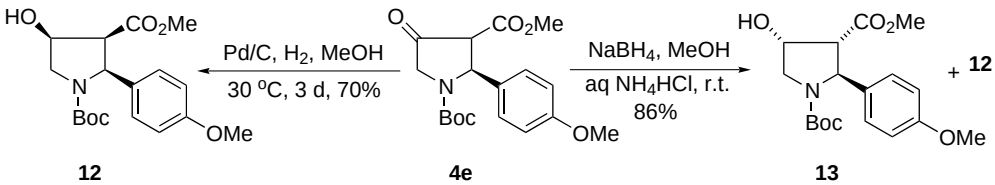
4. Experimental

4.1. General procedure for preparation of 9

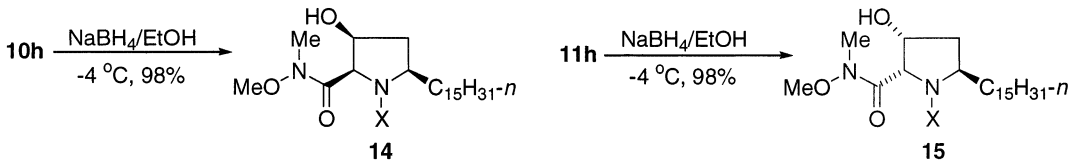
A mixture of **1** (8 mmol) and Pd/C (10%, 0.3 g) in 60 mL methanol was stirred under an atmosphere of hydrogen (70 atm) for one day. The catalyst was filtered off and washed with methanol. The filtrate was concentrated and the resulting residue was dissolved with stirring in MeCN (20 mL). To this solution was added $NaHCO_3$ (8 mmol) followed by dropwise addition of a solution of $BrCH_2CONMe(OMe)$ (6 mmol) in MeCN (10 mL). The reaction mixture was stirred for 10 h, then filtered and washed with ethyl acetate. The filtrate was concentrated in vacuo and the residue was chromatographed to afford the corresponding monoalkylated product in 60–74% yield.

4.1.1. (*R*)-3-*N*-(*tert*-Butyloxycarbonyl)-*N*-(*N*-methyl-*N*-methoxycarboamido)methylaminoheptanoic acid, methyl ester 9a. $[\alpha]_D^{20}=-15.3$ (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.26 (m, 0.5 H), 4.06 (m, 0.5 H), 4.01 (s, 1H), 3.91 (s, 1H), 3.68 (s, 1.5 H), 3.66 (s, 1.5 H), 3.61 (s, 1.5 H), 3.59 (s, 1.5H), 3.12 (s, 3H), 2.85–2.63 (m, 1H), 2.47–2.38 (m, 1H), 1.62–1.48 (m, 2H), 1.43 (s, 4.5H), 1.34 (s, 4.5H), 1.25 (m, 4H), 0.85 (m, 3H); EIMS *m*/*z* 361 (M^++H^+). Anal calcd for $C_{17}H_{32}N_2O_6$: C, 56.65; H, 8.95; N, 7.77. Found: C, 56.80; H, 8.47; N, 7.75%.

4.1.2. (*R*)-3-*N*-(*R*)-1-Phenylethyl)-*N*-(*N*-methyl-*N*-methoxycarboamido)methylaminobutanoic acid, methyl ester 9b. $[\alpha]_D^{20}=-5.1$ (*c* 2.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.20 (m, 5H), 4.21 (q, $J=6.7$ Hz, 1H), 3.60 (s, 3H), 3.55 (s, 3H), 3.54–3.45 (m, 3H), 3.11 (s, 3H), 2.58 (dd, $J=14.6$, 5.8 Hz, 1H), 2.15 (dd, $J=14.6$, 8.4 Hz, 1H), 1.35 (d, $J=6.7$ Hz, 3H), 1.08 (d,



Scheme 3.



Scheme 4.

$J=6.6$ Hz, 3H); EIMS m/z 323 (M^++H^+). Anal calcd for $C_{17}H_{26}N_2O_4$: C, 63.33; H, 8.13; N, 8.69. Found: C, 63.16; H, 8.20; N, 8.61%.

4.1.3. (*R*)-3-*N*-(*tert*-Butyloxycarbonyl)-*N*-(*N*-methyl-*N*-methoxycarboamido)methylaminobutanoic acid, methyl ester 9c. $[\alpha]_D^{20}=-10.7$ (c 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.41 (q, $J=6.9$ Hz, 0.5H), 4.12 (q, $J=6.9$ Hz, 0.5H), 4.08 (s, 1H), 3.92 (s, 1H), 3.68 (s, 1.5H), 3.66 (s, 1.5H), 3.62 (s, 1.5H), 3.60 (s, 1.5H), 3.12 (s, 3H), 2.79–2.61 (m, 1H), 2.43–2.36 (m, 1H), 1.43 (s, 4.5H), 1.34 (s, 4.5H), 1.21 (d, $J=6.8$ Hz, 1.5H), 1.17 (d, $J=6.8$ Hz, 1.5H); EIMS m/z 319 (M^++H^+). Anal calcd for $C_{14}H_{26}N_2O_6$: C, 52.82; H, 8.23; N, 8.80. Found: C, 52.62; H, 8.51; N, 8.72%.

4.1.4. (*S*)-3-*N*-Benzyl-*N*-(*N*-methyl-*N*-methoxycarboamido)methylamino-3-phenylpropanoic acid, ethyl ester 9d. $[\alpha]_D^{20}=-16.4$ (c 2.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61–7.20 (m, 10H), 4.62 (t, $J=6.9$ Hz, 1H), 4.03 (q, $J=6.7$ Hz, 2H), 3.90 (d, $J=13.8$ Hz, 1H), 3.65 (m, 1H), 3.51–3.22 (m, 5H), 3.13–3.02 (m, 4H), 2.75 (dd, $J=14.4$, 8.8 Hz, 1H), 1.11 (t, $J=7.1$ Hz, 3H); EIMS m/z 385 (M^++H^+). Anal calcd for $C_{22}H_{28}N_2O_4$: C, 68.73; H, 7.34; N, 7.29. Found: C, 68.67; H, 7.19; N, 7.10%.

4.1.5. (*S*)-3-*N*-(*tert*-Butyloxycarbonyl)-*N*-(*N*-methyl-*N*-methoxycarboamido)methylamino-3-(4′-methoxyphenyl)-propanoic acid, methyl ester 9e. $[\alpha]_D^{20}=-52.4$ (c 2.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, $J=7.8$ Hz, 2H), 6.84 (d, $J=7.8$ Hz, 2H), 5.81 (dd, $J=9.5$, 5.9 Hz, 0.5H), 5.54 (dd, $J=9.5$, 5.9 Hz, 0.5H), 4.11 (d, $J=17.8$ Hz, 0.5H), 3.95 (d, $J=17.8$ Hz, 0.5H), 3.80 (s, 3H), 3.78–3.54 (m, 7H), 3.23–2.91 (m, 2H), 3.13 (s, 3H), 1.48 (s, 4.5H), 1.43 (s, 4.5H); EIMS m/z 354 (M^+−Bu-t+H^+). Anal calcd for $C_{20}H_{30}N_2O_7$: C, 58.52; H, 7.37; N, 6.82. Found: C, 58.48; H, 7.42; N, 6.96%.

4.1.6. (*R*)-3-*N*-(*tert*-Butyloxycarbonyl)-*N*-(*N*-methyl-*N*-methoxycarboamido)methylamino - 6 - benzoxyhexanoic acid, ethyl ester 9f. $[\alpha]_D^{20}=+1.6$ (c 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 5H), 4.49 (s, 2H), 4.44 (m, 0.5H), 4.20–3.95 (m, 4.5H), 3.71 (s, 1.5H), 3.67 (s, 1.5H), 3.50 (s, 2H), 3.20 (s, 3H), 2.90–2.70 (m, 1H), 2.52–2.40 (m, 1H), 1.85–1.55 (m, 4H), 1.47 (s, 4.5H), 1.40 (s, 4.5H), 1.23 (m, 3H); EIMS m/z 467 (M^++H^+). Anal calcd for $C_{24}H_{38}N_2O_7$: C, 61.78; H, 8.21; N, 6.00. Found: C, 61.63; H, 7.97; N, 6.10%.

4.1.7. (*R*)-3-*N*-(*tert*-Butyloxycarbonyl)-*N*-(*N*-methyl-*N*-methoxycarboamido)methylaminooctadecanoic acid, methyl ester 9g. $[\alpha]_D^{20}=-1.2$ (c 2.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30 (m, 0.5H), 4.10 (m, 0.5H), 4.07 (s, 1H), 3.95 (s, 1H), 3.72 (s, 1.5H), 3.70 (s, 1.5H), 3.66 (s, 1.5H), 3.64 (s, 1.5H), 3.16 (s, 3H), 2.85 (dd, $J=15.7$, 6.3 Hz, 0.5H), 2.78 (dd, $J=15.5$, 6.7 Hz, 0.5H), 2.49 (dd, $J=7.5$, 2.0 Hz, 0.5H), 2.43 (dd, $J=7.2$, 1.9 Hz, 0.5H), 1.64–1.49 (m, 2H), 1.47 (s, 4.5H), 1.38 (s, 4.5H), 1.26 (m, 26H), 0.85 (t, $J=6.5$ Hz, 3H); EIMS m/z 413 (M^+−Boc). Anal calcd for $C_{28}H_{54}N_2O_6$: C, 65.33; H, 10.57; N, 5.44. Found: C, 65.47; H, 10.61; N, 5.46%.

4.1.8. (*R*)-3-*N*-Benzyl-*N*-(*N*-methyl-*N*-methoxycarboamido)methylamino-3-heptanoic acid, methyl ester 9h. $[\alpha]_D^{20}=-5.4$ (c 2.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, $J=7.4$ Hz, 2H), 7.30 (t, $J=7.5$ Hz, 2H), 7.25 (m, 1H), 3.78 (m, 2H), 3.61 (s, 3H), 3.52 (s, 3H), 3.43 (s, 2H), 3.27 (m, 1H), 3.12 (s, 3H), 2.74 (dd, $J=14.4$, 6.5 Hz, 1H), 2.34 (dd, $J=14.3$, 7.3 Hz, 1H), 1.67 (m, 1H), 1.47 (m, 1H), 1.36 (m, 4H), 0.90 (t, $J=6.7$ Hz, 3H); EIMS m/z 319 (M^+−OMe). Anal calcd for $C_{19}H_{30}N_2O_4$: C, 65.12; H, 8.63; N, 7.99. Found: C, 65.42; H, 8.31; N, 7.73%.

4.2. General procedure for condensation of 9 catalyzed by KHMDS

To a stirred solution of **9** (0.3 mmol) in dry THF (15 mL) was added dropwise KHMDS (0.5 M in THF, 2 mL) at −78°C. After the solution was stirred for 2 min at the same temperature, HCl (1N, 1 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate three times and the combined organic layers were washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed to afford **4**.

4.2.1. (4*RS*,5*R*)-1-(*tert*-Butyloxycarbonyl)-4-methoxycarbonyl-5-*n*-butyl-3-pyrrolidinone 4a. $[\alpha]_D^{20}=+2.3$ (c 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.80–4.51 (m, 1H), 4.30–4.02 (m, 2H), 3.88–3.60 (m, 3.5H), 3.18 (m, 0.5H), 1.95 (m, 1H), 1.67 (m, 1H), 1.45 (s, 9H), 1.25 (m, 4H), 0.85 (m, 3H); EIMS m/z 299 (M^+); HRMS found m/z 242.1043 (M^+− Bu); $C_{11}H_{16}NO_5$ requires 242.1031.

4.2.2. (4*RS*,5*R*)-1-((*R*)-1-Phenylethyl)-4-methoxycarbonyl-5-methyl-3-pyrrolidinone 4b. $[\alpha]_D^{20}=-6.2$ (c 8.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.22 (m, 5H), 4.17 (q, $J=6.6$ Hz, 1H), 3.75 (s, 3H), 3.61 (m, 1H), 3.11 (d, $J=8.7$ Hz, 1H), 3.03 (s, 2H), 1.37 (d, $J=6.8$ Hz, 3H), 1.27 (d, $J=6.7$ Hz, 3H); EIMS m/z 261 (M^+); HRMS found m/z 261.1387 (M^+); $C_{15}H_{19}NO_3$ requires 261.1367.

4.2.3. (4*RS*,5*R*)-1-(*tert*-Butyloxycarbonyl)-4-methoxycarbonyl-5-methyl-3-pyrrolidinone 4c. $[\alpha]_D^{20}=-15.1$ (c 6.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.72–4.60 (m, 1H), 4.30–4.03 (m, 2H), 3.78–3.56 (m, 4H), 1.47 (s, 9H), 1.38–1.28 (m, 3H); EIMS m/z 258 (M^++H^+); HRMS found m/z 226.1095 (M^+–OMe); $C_{11}H_{16}NO_4$ requires 226.1081.

4.2.4. (4*RS*,5*R*)-1-Benzyl-4-methoxycarbonyl-5-phenyl-3-pyrrolidinone 4d. $[\alpha]_D^{20}=-32.4$ (c 2.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, $J=7.5$ Hz, 2H), 7.47–7.21 (m, 8H), 4.32 (d, $J=10.6$ Hz, 1H), 4.17 (m, 2H), 4.02 (d, $J=13.1$ Hz, 1H), 3.59 (d, $J=17.6$ Hz, 1H), 3.46 (d, $J=10.5$ Hz, 1H), 3.21 (d, $J=13.1$ Hz, 1H), 2.94 (d, $J=17.6$ Hz, 1H), 1.26 (t, $J=7.3$ Hz, 3H); EIMS m/z 323 (M^+); HRMS found m/z 323.1566 (M^+); $C_{20}H_{21}NO_3$ requires 323.1523.

4.2.5. (4*RS*,5*R*)-1-(*tert*-Butyloxycarbonyl)-4-methoxycarbonyl-5-(4′-methoxyphenyl)-3-pyrrolidinone 4e. $[\alpha]_D^{20}=-13.2$ (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ

7.25–7.06 (m, 3H), 6.86–6.77 (m, 2H), 5.53 (m, 0.5H), 5.40 (m, 0.5H), 4.41–4.30 (m, 1H), 4.29–3.70 (m, 1H), 3.67 (s, 3H), 3.68–3.12 (m, 4H), 1.46–1.20 (m, 9H); EIMS m/z 349 (M^+); HRMS found m/z 349.1541 (M^+); $C_{18}H_{23}NO_6$ requires 349.1526.

4.2.6. (4*RS*,5*R*)-1-(*tert*-Butyloxycarbonyl)-4-ethoxycarbonyl-5-(3′-benzoxypropanyl)-3-pyrrolidinone 4f. $[\alpha]_D^{20}=+25.3$ (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5H), 4.87–4.48 (m, 3H), 4.44–4.00 (m, 4H), 3.70–2.85 (m, 4H), 1.90–1.40 (m, 9H), 1.30 (m, 3H); EIMS m/z 405 (M^+); HRMS found m/z 405.2171 (M^+); $C_{22}H_{31}NO_6$ requires 405.2151.

4.3. General procedure for condensation of 9 catalyzed by *tert*-BuOK

To a dry flask containing *tert*-BuOK (110 mg, 0.982 mmol) was added a pre-cooled (−78°C) solution of **9** (0.2 mmol) in DMF (15 mL) under argon at −78°C. The solution was stirred for 2 min at the same temperature, then aqueous HCl (1N, 1 mL) was added to quench the reaction. The mixture was neutralized with $NaHCO_3$ and extracted three times with ethyl acetate. The combined organic extract was washed with brine, dried over $MgSO_4$ and filtered. After removal of the solvent from the filtrate, the residue was chromatographed to afford **10** and **11**.

4.3.1. (2*R*,5*R*)-1-(*tert*-Butyoxycarbonyl)-2-(*N*-methyl-*N*-methoxycarboamido)-5-*n*-butyl-3-pyrrolidinone 10a. $[\alpha]_D^{20}=+41.5$ (c 3.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.28 (m, 1H), 4.23 (m, 1H), 3.82 (s, 3H), 3.23 (s, 3H), 2.79 (m, 1H), 2.37 (d, $J=18.5$ Hz, 1H), 2.01 (m, 1H), 1.78–1.24 (m, 12H), 0.88 (t, $J=6.7$ Hz, 3H); EIMS m/z 328 (M^+); HRMS found m/z 328.2036 (M^+); $C_{16}H_{28}N_2O_5$ requires 328.2004.

4.3.2. (2*S*,5*R*)-1-(*tert*-Butyoxycarbonyl)-2-(*N*-methyl-*N*-methoxycarboamido)-5-*n*-butyl-3-pyrrolidinone 11a. $[\alpha]_D^{20}=+16.9$ (c 2.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.10 (s, 0.4H), 5.06 (s, 0.6H), 4.45 (m, 0.6H), 4.42 (m, 0.4H), 3.85 (s, 3H), 3.27 (s, 3H), 2.97 (dd, $J=19.5$, 9.5 H, 0.4H), 2.91 (dd, $J=17.9$, 9.4 Hz, 0.6H), 2.37 (d, $J=17.8$ Hz, 1H), 1.95–1.20 (m, 15H), 0.89 (m, 3H); EIMS m/z 328 (M^+); HRMS found m/z 328.2035 (M^+); $C_{16}H_{28}N_2O_5$ requires 328.2004.

4.3.3. (2*R*,5*R*)-1-(*tert*-Butyoxycarbonyl)-2-(*N*-methyl-*N*-methoxycarboamido)-5-(3′-benzoxypropyl)-3-pyrrolinone 10f. $[\alpha]_D^{20}=+40.3$ (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 5H), 5.34 (m, 1H), 4.50 (s, 2H), 4.30 (m, 1H), 3.85 (s, 3H), 3.51 (m, 2H), 3.25 (s, 3H), 2.85 (m, 1H), 2.45 (d, $J=18.8$ Hz, 1H), 2.01–1.28 (m, 13H); EIMS m/z 420 (M^+); HRMS found m/z 420.2298 (M^+); $C_{12}H_{32}N_2O_6$ requires 420.2265.

4.3.4. (2*S*,5*R*)-1-(*tert*-Butyoxycarbonyl)-2-(*N*-methyl-*N*-methoxycarboamido)-5-(3′-benzoxypropyl)-3-pyrrolidinone 11f. $[\alpha]_D^{20}=+10.4$ (c 0.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 5H), 5.12 (m, 1H), 4.48 (s, 2H), 4.26 (m, 1H), 3.83 (s, 3H), 3.47 (s, 2H), 3.21 (s, 3H), 2.92 (dd, $J=17.6$, 9.4 Hz, 1H), 2.36 (d, $J=17.6$ Hz, 1H), 1.78–1.28 (m, 13H); EIMS m/z 420 (M^+); HRMS found m/z 420.2298 (M^+); $C_{12}H_{32}N_2O_6$ requires 420.2265.

4.3.5. (2*R*,5*R*)-1-(*tert*-Butyoxycarbonyl)-2-(*N*-methyl-*N*-methoxycarboamido)-5-*n*-pentadecyl-3-pyrrolidinone 10g. $[\alpha]_D^{20}=+44.0$ (c 2.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.31 (m, 1H), 4.23 (m, 1H), 3.85 (s, 3H), 3.26 (s, 3H), 2.79 (m, 1H), 2.40 (d, $J=17.9$ Hz, 1H), 2.01–1.25 (m, 38H), 0.88 (t, $J=6.5$ Hz, 3H); EIMS m/z 482 (M^+); HRMS found m/z 381.3132 (M^+−Boc); $C_{22}H_{41}N_2O_3$ requires 381.3121.

4.3.6. (2*S*,5*R*)-1-(*tert*-Butyoxycarbonyl)-2-(*N*-methyl-*N*-methoxycarboamido)-5-*n*-pentadecyl-3-pyrrolidinone 11g. $[\alpha]_D^{20}=+16.9$ (c 2.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.08 (m, 1H), 4.42 (m, 1H), 3.85 (s, 3H), 3.23 (s, 3H), 2.95 (m, 1H), 2.36 (d, $J=17.9$ Hz, 1H), 1.90–1.28 (m, 38H), 0.88 (t, $J=6.5$ Hz, 3H); EIMS m/z 482 (M^+); HRMS found m/z 381.3132 (M^+−Boc); $C_{22}H_{41}N_2O_3$ requires 381.3121.

4.3.7. (2*R*,3*S*,4*S*)-1-(*tert*-Butyloxycarbonyl)-4-hydroxy-3-methoxycarbonyl-2-(4′-methoxyphenyl)-pyrrolidine 12. A suspension of **4e** (20 mg, 0.057 mmol) and 10% Pd/C (5 mg) in of MeCN (1 mL) was stirred under hydrogen (1 atm.) at 30°C for 3 days. The catalyst was removed by filtration and the filtrate was concentrated. The residue was chromatographed to afford **12** (14 mg, 70%). $[\alpha]_D^{20}=-10.5$ (c 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, $J=8.3$ Hz, 2H), 6.78 (d, $J=8.5$ Hz, 2H), 5.08 (m, 1H), 4.61 (br s, 1H), 3.90 (m, 1H), 3.74 (s, 3H), 3.67 (m, 1H), 3.51 (s, 3H), 3.38 (m, 1H), 1.43–1.16 (m, 9H); EIMS m/z 351 (M^+); HRMS found m/z 351.1649 (M^+); $C_{18}H_{25}NO_6$ requires 351.1683.

4.3.8. (2*R*,3*R*,4*R*)-1-(*tert*-Butyloxycarbonyl)-4-hydroxy-3-methoxycarbonyl-2-(4′-methoxyphenyl)-pyrrolidine 13. To a solution of **4e** (28 mg, 0.08 mmol) in ethanol (3 mL) and saturated aqueous NH_4Cl (1 mL) was added sodium borohydride (10 mg, 0.26 mmol). The solution was stirred at room temperature for 20 min, and partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer was extracted further with ethyl acetate. The combined organic extract was dried over $MgSO_4$ and concentrated. The residue was chromatographed to afford **13** (16 mg, 59%) and **12** (8 mg, 29%). $[\alpha]_D^{20}=+7.8$ (c 1.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, $J=8.1$ Hz, 2H), 6.85 (d, $J=8.6$ Hz, 2H), 4.98 (br s, 1H), 4.53 (dd, $J=14.8$, 6.3 Hz, 1H), 4.11 (dd, $J=11.0$, 6.8 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.48 (dd, $J=11.0$, 7.7 Hz, 1H), 3.00 (t, $J=7.8$ Hz, 1H), 1.25–1.09 (m, 9H); EIMS m/z 352 (M^++H^+); HRMS found m/z 351.1649 (M^+); $C_{18}H_{25}NO_6$ requires 351.1683.

4.3.9. (2*R*,3*S*,5*R*)-1-(*tert*-butyoxycarbonyl)-2-(*N*-methyl-*N*-methoxycarboamido)-3-hydroxy-5-*n*-pentadecyl-pyrrolidine 14. To a solution of **10h** (15 mg, 0.03 mmol) in EtOH (1 mL) cooled with an ice-salt bath was added sodium borohydride (4 mg, 0.1 mmol). The solution was stirred for 20 min before it was partitioned between ethyl acetate and water. The organic layer was sepa-

rated and the aqueous layer was extracted with ethyl acetate. The combined extracts were dried over $MgSO_4$ and concentrated. The residue was chromatographed to afford **14** (15 mg, 98%). $[\alpha]_D^{20} = -19.6$ (*c* 1.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.94 (m, 1H), 4.55 (m, 1H), 3.85–3.73 (m 4H), 3.23 (s, 3H), 2.47–2.13 (m, 3H), 1.85–1.20 (m, 37H), 0.88 (t, $J = 7.6$ Hz, 3H); EIMS m/z 383 (M^+–Boc); HRMS found m/z 383.3231 (M^+–Boc); $C_{22}H_{43}N_2O_3$ requires 383.3277.

4.3.10. (2*S*,3*R*,5*R*) - 1 - (*tert* - Butyoxycarbonyl) - 2 - (*N* - methyl-*N*-methoxycarboamido)-3-hydroxy-5-*n*-pentadecyl-pyrrolidine 15. Following the procedure from **10h** to **14**, pyrrolidine **15** was obtained from **11h** in 98% yield. $[\alpha]_D^{20} = +3.1$ (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.90 (d, $J = 8.0$ Hz, 0.5H), 4.83 (d, $J = 8.0$ Hz, 0.5H), 4.70 (m, 1H), 4.05 (m, 0.5H), 3.95 (m, 0.5H), 3.83 (s, 1.5H), 3.78 (s, 1.5H), 3.22 (s, 3H), 2.05 (m, 2H), 1.74 (m, 2H), 1.46 (s, 4.5H), 1.43 (s, 4.5H), 1.21 (m, 26H), 0.88 (t, $J = 6.7$ Hz, 3H); EIMS m/z 383 (M^+–Boc); HRMS found m/z 383.3231 (M^+–Boc); $C_{22}H_{43}N_2O_3$ requires 383.3277.

Acknowledgements

The authors are grateful to the Chinese Academy of Sciences and National Natural Science Foundation of China (grants 29725205 and 29972049), and Qiu Shi Science & Technologies Foundation for financial support.

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