A Stereoselective Synthesis of Five- and Six-Membered Cyclic β-Amino Acids

Patrick Perlmutter,*[a] Mark Rose,[a] and Filisaty Vounatsos[a]

Keywords: Amino acids / Ring-closing metathesis / Asymmetric synthesis / Thioester

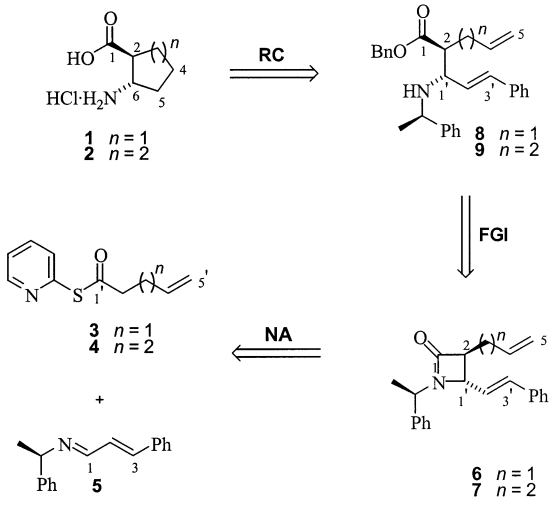
The cyclic β-amino acids **1** and **2** have been prepared in a short and stereoselective manner. The synthesis features a diastereoselective thioester enolate/imine condensation reaction and a ring-closing metathesis as key processes.

Introduction

There has been considerable interest in cyclic β-amino acids **1** and **2** because of their potential use as therapeutic agents[1] and their role as structure-forming elements in β-peptides.[2] Their ability to adopt compact, stable secondary structures within peptides[3] adds to their appeal as targets for chemical synthesis.[4] As such, there has been an extensive effort by many research groups to access these compounds, resulting in the development of a number of new methods for their synthesis.[5]

Although a number of elegant approaches exist for constructing cyclic β-amino acids, very few of these offer access to unsaturated analogues of **1** and **2**. It is against this background that we chose to investigate the use of a NARC[6] sequence for the development of a general method towards the synthesis of cyclic β-amino acids. In the NARC approach, hetero- and carbocyclic compounds[7] are formed by a nucleophilic addition (NA) followed by a ring closure (RC).

In the retrosynthetic analysis (Scheme 1) of the target compounds, it was anticipated that **1** and **2** could be accessed from β-amino esters **8** and **9**, respectively, through the application of ring-closing metathesis (RCM).[8] Compounds **8** and **9** could be elaborated from **6** and **7**, via enolate/imine condensation of imine **5** with pyridyl thioesters **3** and **4**. Herein, we give full details of this approach by presenting the stereoselective syntheses of the five- and six-membered cyclic β-amino acids **1** and **2**.



Scheme 1. Retrosynthetic analysis

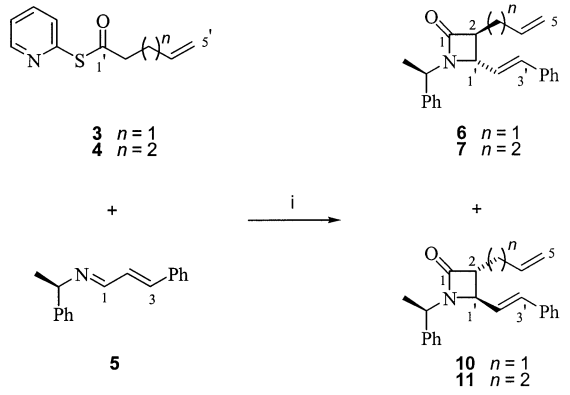
Results and Discussion

Both **3** and **5** undergo diastereoselective condensation readily under Lewis acid conditions.[9,10] Accordingly, freshly prepared pyridyl thioester[11] **3** was precomplexed with $SnCl_4$ at −78 °C and then treated with triethylamine and the enantiopure imine[12,13] **5**, yielding a 3:1 mixture of the readily separable β-lactam[14,15] diastereomers **6** {34%, $[\alpha]_D$ = +25.2 (*c* = 1, MeOH)} and **10** (Scheme 2). Similar condensation of thioester **4** with imine **5** gave a 2:1 mixture of **7** {25%, $[\alpha]_D$ = +36.7 (*c* = 1, MeOH)} and **11**, which were obtained as oils after chromatographic separation (Scheme 2).

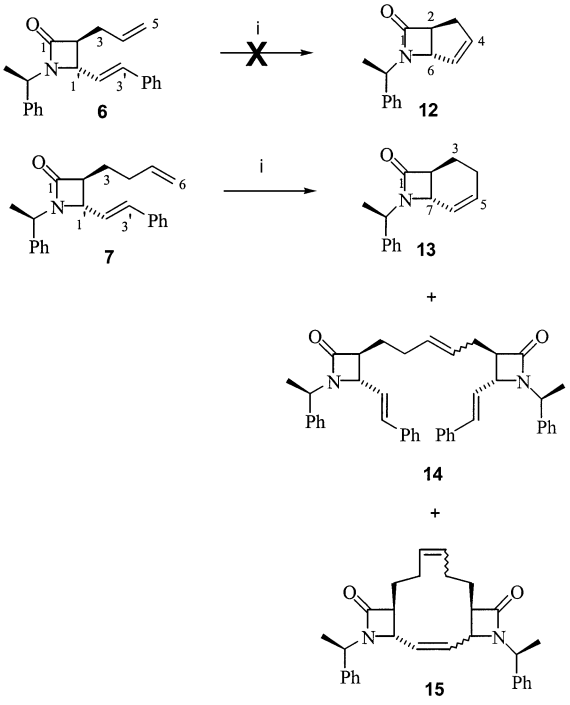
With these intermediates in hand, we briefly investigated the direct ring-closing metathesis of substrates **6** and **7** to form the *trans*-fused bicycles **12** and **13** as shown in Scheme 3.

Attempted ring closure of **6** to give **12** under standard RCM conditions was unsuccessful, presumably because of the inherent ring strain associated with a 4,5-*trans*-substituted bicyclic structure (Scheme 3). Reaction of a dilute solution of **7** in toluene at 55 °C with 10 mol % Grubbs' catalyst[16] gave, in poor conversion, an inseparable mixture of the target compound **13**, as well as the cross metathesis product **14**, and the β-lactam dimer **15**.[17]

[a] Monash University, School of Chemistry,
P. O. Box 23, Victoria 3800, Australia
Fax: (internat.) + 61-3/9905-4597
E-mail: patrick.perlmutter@sci.monash.edu.au



Scheme 2

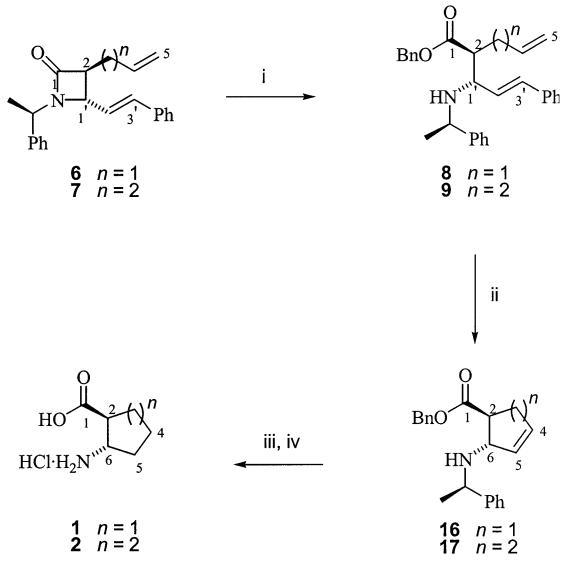


Scheme 3

Treatment of β-lactams **6** and **7** with chlorotrimethylsilane in the presence of benzyl alcohol gave the desired ring-closing metathesis substrates, β-amino esters **8** {from **6**, 63%, $[\alpha]_D = +20.8$ ($c = 1$, MeOH)} and **9** {from **7**, 84%, $[\alpha]_D = +54.5$ ($c = 1$, MeOH)} (Scheme 4). Gratifyingly, subjecting this material to Grubbs' catalyst[16–18] under high-dilution conditions afforded the cyclic β-amino esters **16** {from **8**, 56%, $[\alpha]_D = +61.2$ ($c = 1$, MeOH)} and **17** {from **9**, 46%, $[\alpha]_D = +39.3$ ($c = 1$, MeOH)}.

Hydrogenation of **16** and **17** gave, after treatment with an ethereal solution of HCl, the target compounds **1** {from **16**, 79%, $[\alpha]_D = +62.0$ ($c = 0.6$, H_2O)} and **2** {from **17**, 68%, $[\alpha]_D = +45.8$ ($c = 0.5$, H_2O)} as their hydrochloride salts (Scheme 4).

Comparison of the optical rotations of **1** and **2** with literature values established the absolute stereochemistry of



Scheme 4

both **1**[5a] and **2**[19] as (1*S*,2*S*). These values serve also to confirm the stereochemistries of all the new compounds described in this work.

Conclusion

In conclusion, we have demonstrated that the nucleophilic addition/ring closure sequence provides a new approach to the stereoselective preparation of cyclic β-amino acids. The extension of this approach to larger ring cyclic β-amino acids, as well as more highly functionalised derivatives, is currently under development in our laboratories.

Experimental Section

General Remarks: Optical rotations were recorded with a Perkin–Elmer 141 polarimeter at the sodium D-line (589 nm) using spectroscopic-grade solvents at the temperature specified. Infrared (IR) spectra were recorded with a Perkin–Elmer 1600 Series Fourier Transform spectrometer and refer to thin films of liquids (neat) or dichloromethane (CH_2Cl_2) films. Infrared band intensities of each frequency of absorption are expressed as follows: s (strong), m (medium), w (weak) or b (broad). ^{1}H NMR spectra were recorded at 300 MHz with a Varian Mercury spectrometer and at 400 MHz with a Bruker Avance DRX 400 spectrometer. Chemical shifts were recorded on the δ scale in ppm. Spectra were acquired in deuteriochloroform ($CDCl_3$) at 20 °C unless otherwise stated. For ^{1}H NMR spectra recorded in $CDCl_3$, the peak due to residual $CHCl_3$ (δ = 7.26 ppm) was used as the internal reference. ^{13}C NMR spectra were recorded at 75 MHz with a Varian Mercury spectrometer and are referenced using the central peak (δ = 77.0 ppm) of the $CDCl_3$ triplet for proton-decoupled spectra. ^{13}C NMR chemical shifts and assignments for identifiable carbon atoms are given. The assignment of signals observed in various NMR spectra was often assisted by conducting attached proton test (APT) or homonuclear (^{1}H/^{1}H) correlation spectroscopy (COSY) experiments. Mass spectrometry (MS ESI) was performed

using samples in MeOH with a Micromass Platform QMS spectrometer. High resolution mass spectra (HRMS) for accurate mass determinations were recorded with a Bruker BioApex 47e FTMS fitted with an analytical electrospray source using NaI for accurate mass calibration. The principal ion peaks (*m*/*z*) are reported along with their intensities, expressed as a percentage of the base peak (100%). [M^+]refers to the molecular ion. Elemental microanalyses were performed by the University of Otago, Dunedin, New Zealand. Silica gel used for chromatography was 40−63 μm (230−400 mesh) silica gel 60 (Merck no. 9385). Preparative thin layer chromatography (TLC) was performed on glass plates (20 × 20 cm), coated with 0.5 mm of silica gel (Merck 70−230 mesh, no. 7747) that had been activated at 100 °C for at least 1 h prior to use. Analytical thin layer chromatography (TLC) was performed on Polygram Sil G/UV_{254} fluorescent indicator and inspected under ultraviolet light or dipped in an ammonium molybdate/cerium sulfate solution followed by heating. All reactions requiring anhydrous conditions were performed in flame-dried glassware under N_2 or Ar. Many starting materials and reagents were available from the Aldrich Chemical Company and were used as supplied. Bis(tricyclohexylphosphane)benzylideneruthenium(IV) dichloride (Grubbs' catalyst) was purchased from Strem Chemicals Inc., USA. Solvents were purified as follows. Anhydrous diethyl ether and tetrahydrofuran (THF) were distilled from sodium metal/benzophenone ketyl prior to use. Toluene and dichloromethane were dried with, and freshly distilled from, calcium hydride. Hexanes refer to the hydrocarbon fraction boiling between 40 and 60 °C and was distilled before use. Organic solutions were concentrated under reduced pressure in a rotary evaporator with the water bath generally not exceeding 80 °C.

Thioester 3: Oxalyl chloride (3 mL, 34 mmol) was added dropwise to a stirred solution of 4-pentenoic acid (3.08 g, 31 mmol) at 0 °C under N_2. The reaction mixture was stirred at 0 °C for 1 h and then warmed to room temperature over 2 h. The crude 4-pentenoyl chloride was taken up in CH_2Cl_2 (50 mL) then added to a solution of thiopyridine (3.11 g, 28 mmol) and triethylamine (3 mL, 28 mmol) in CH_2Cl_2 (60 mL) at 0 °C. After stirring for 30 min, the mixture was poured into ice-cold water (75 mL), the organic phase was separated and washed with ice-chilled KOH solution (5%, 150 mL) and water (75 mL). The organic phase was separated, dried (Na_2SO_4), filtered, and concentrated under reduced pressure, to give thioester **3** in quantitative yield as a dark brown oil. This material was used immediately without further purification. IR (neat): $\tilde{\nu}_{max}$ = 1713 s, 1642 s, 1618 s, 1582 s, 1498 s, 1420 m, 1258 w, 1110 s, 1086 s, 992 s, 916 s, 757 s cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.51 (m, 2 H, 3′-H), 2.80 (t, *J* = 6.5 Hz, 2 H, 2′-H), 5.01 (ddt, *J* = 10.2, 1.8, 1.3 Hz, 1 H, 5′-H, H_{cis}), 5.07 (ddt, *J* = 17.3, 1.8, 1.3 Hz, 1 H, 5′-H, H_{trans}), 5.80 (ddt, *J* = 17.1, 10.2, 6.5 Hz, 1 H, 4′-H), 7.20−8.60 (m, 4 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 29.5 (C-3′), 43.6 (C-2′), 116.3 (C-5′), 123.7 (C-5), 130.2 (C-3), 135.9 (C-4), 137.3 (C-4′), 150.4, (C-2), 151.9 (C-6), 196.9 (C-1′) ppm. HRMS: calcd. for $C_{10}H_{12}NSO^+$ 194.063; found 194.063. $C_{10}H_{11}NSO$ (193.056): calcd. C 62.15, H 5.74, N 7.25; found C 62.73, H 5.81, N 7.25.

Thioester 4: Oxalyl chloride (3 mL, 34 mmol) was added dropwise to 5-hexenoic acid (3.6 g, 31 mmol), stirred at 0 °C under N_2. The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for a further 2 h. The crude 5-hexenoyl chloride was taken up in CH_2Cl_2 (50 mL) then added to a solution of thiopyridine (3.11 g, 28 mmol) and triethylamine (3 mL, 28 mmol) in dichloromethane (60 mL) at 0 °C. After stirring for 30 min, the mixture was poured into ice-cold water (75 mL), the organic phase was separated and washed with ice-chilled KOH solution (5%, 150 mL) and water (75 mL). The organic phase was separated, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The thioester **4** was obtained in quantitative yield as a dark brown oil. This material was used immediately without further purification. IR (neat): $\tilde{\nu}_{max}$ = 1711 s, 1640 s, 1573 s, 1582 s, 1450 s, 1421 s, 1120 s, 915 m, 766 m, 734 m cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.77 (m, 2 H, 4′-H), 2.09 (m, 2 H, 3′-H), 2.67 (t, *J* = 7.4 Hz, 2 H, 2′-H), 5.03 (m, 2 H, 6′-H), 5.71 (m, 1 H, 5′-H), 7.24−8.61 (m, 4 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.3 (C-4′), 32.6 (C-3′), 43.2 (C-2′), 115.5 (C-6′), 123.2 (C-5), 129.8 (C-5′), 136.8 (C-3), 136.9 (C-4), 149.9 (C-2), 151.1 (C-6), 195.8 (C-1′) ppm. HRMS: calcd. for $C_{11}H_{13}NSONa^+$ 230.061; found 230.061.

Imine 5: Cinnamaldehyde (1.8 mL, 14 mmol) was added in one portion to α-methylbenzylamine (1.8 mL, 14 mmol) at 0 °C. After stirring for 20 min, the product was dissolved in diethyl ether (20 mL), dried (Na_2SO_4), filtered, and the solution concentrated under reduced pressure, to afford the title compound **5** (ca. 3.3 g) as a pale-yellow oil. The imine **5** was used without further purification in the next step of the reaction sequence. IR (neat): $\tilde{\nu}_{max}$ = 3082 s, 2924 m, 2842 m, 1640 s, 1620 s, 1493 m, 1376 m, 1063 s, 978 s, 910 s, 748 s, 691 s, 640 m cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.62 (d, *J* = 6.5 Hz, 3 H, CH_3), 4.46 (q, *J* = 6.5 Hz, 1 H, C*H*CH_3), 6.99 (d, *J* = 7.4 Hz, 1 H, 2-H), 7.23−7.50 (m, 11 H, 2 × Ph, 3-H), 8.13 (d, *J* = 7.4 Hz, 1 H, 1-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.9 (CH*C*H_3Ph), 70.0 (*C*HCH_3), 126.8, 127.1, 127.4, 128.5, 128.7, 129.0, 129.3 (Ph), 135.9 (C-2), 142.0 (Ph), 144.9 (C-3), 161.5 (C-1) ppm. ESI MS: *m*/*z* (%) = 236.30 (100) [M + 1].

β-Lactam 6: A solution of the thioester **3** (5.40 g, 28 mmol) in CH_2Cl_2 (300 mL) was cooled to −78 °C under N_2. A solution of $SnCl_4$ (3.2 mL, 28 mmol) in CH_2Cl_2 (30 mL) was added, followed by triethylamine (3.9 mL, 28 mmol). After stirring for 30 min, a solution of the imine **5** (14 mmol) in CH_2Cl_2 (30 mL) was added and the reaction mixture stirred for a further 30 min. The reaction mixture was warmed to room temperature and stirred overnight. Following addition of sat. aqueous $NaHCO_3$ (100 mL) the entire mixture was filtered through Celite™. The organic phase was separated, dried (Na_2SO_4), filtered, and concentrated under reduced pressure, to give a mixture (3:1) of β-lactams (1.93 g, 44%). Subjecting this material to flash chromatography (silica, hexane/EtOAc, 5:1) afforded the major isomer **6** (1.47 g, 34%) as an oil. $[\alpha]_D^{30.5}$ = +25.2 (*c* = 1, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2958 s, 2928 s, 2864 s, 1750 s, 1638 m, 1460 m, 1174 m, 823 m, 767 m cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.72 (d, *J* = 7.2 Hz, 3 H, CHCH_3), 2.39−2.61 (m, 2 H, 3-H), 2.97 (ddd, *J* = 9.0, 5.0, 2.1 Hz, 1 H, 2-H), 3.78 (dd, *J* = 9.0, 2.6 Hz, 1 H, 1′-H), 4.80 (q, *J* = 7.2 Hz, 1 H, C*H*CH_3), 5.01 (ddt, *J* = 10.2, 1.8, 1.3 Hz, 1 H, 5-H, H_{cis}), 5.07 (ddt, *J* = 17.3, 1.8, 1.3 Hz, 1 H, 5-H, H_{trans}), 5.83 (ddt, *J* = 17.1, 10.2, 6.5 Hz, 1 H, 4-H), 5.90 (dd, *J* = 15.7, 9.0 Hz, 1 H, 2′-H), 6.42 (d, *J* = 15.7 Hz, 1 H, 3′-H), 7.21−7.33 (m, 10 H, 2 × Ph) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.6 (CH_3), 32.4 (C-3), 53.4 (C-1′), 55.8 (*C*HCH_3), 58.9 (C-2), 117.3 (C-2′), 126.6 (C-3′), 127.2 (C-4), 127.7 (C-5), 127.9, 128.3, 128.8, 134.8, 134.4, 135.7, 141.8, 142.4 (2 × Ph), 169.5 (C-1) ppm. HRMS: calcd. for $C_{22}H_{23}ONNa^+$ 340.167; found 340.166. $C_{22}H_{23}NO$ (317.177): calcd. C 83.51, H 7.01, N 4.43; found C 83.71, H 7.37, N 4.42.

β-Lactam 7: A solution of the thioester **4** (5.79 g, 28 mmol) in CH_2Cl_2 (300 mL) was cooled to −78 °C under N_2. A solution of $SnCl_4$ (3.2 mL, 28 mmol) in CH_2Cl_2 (30 mL) was added dropwise, followed by triethylamine (3.9 mL, 28 mmol). After stirring for 30 min, a solution of the imine **5** (14 mmol) in CH_2Cl_2 (30 mL) was added and the reaction mixture stirred for a further 30 min. The

reaction mixture was warmed to room temperature and stirred overnight. Following addition of sat. aqueous $NaHCO_3$ (100 mL) the entire mixture was filtered through Celite™. The organic phase was separated, dried (Na_2SO_4), filtered, and concentrated under reduced pressure, to give a mixture (2:1) of β-lactams (2.87 g, 63%). Subjecting this material to flash chromatography (silica, hexane/EtOAc, 5:1) afforded a major pure fraction containing isomer **7** (1.14 g, 25%) as an oil. $[\alpha]_D^{30.5} = +36.7$ ($c = 1$, CH_3OH). IR (CH_2Cl_2 film): $\tilde{\nu}_{max} = 2977$ s, 2932 s, 1745 s, 1676 m, 1641 m, 1494 s, 1450 s, 1376 m, 967 s, 913 s, 747 s, 699 s cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.64 (d, $J = 7.2$ Hz, 3 H, CH_3), 2.00−2.22 (br. m, 4 H, 3-H and 4-H), 2.84 (m, 1 H, 2-H), 3.68 (dd, $J = 9.0$, 1.9 Hz, 1 H, 1′-H), 4.53 (q, $J = 7.2$ Hz, 1 H, C*H*CH_3), 4.80−5.00 (m, 2 H, 6-H), 5.68 (ddt, $J = 17.1$, 10.2, 6.5 Hz, 1 H, 5-H), 5.84 (dd, $J = 15.8$, 9.0 Hz, 1 H, 2′-H), 6.38 (d, $J = 15.8$ Hz, 1 H, 3′-H), 7.00−7.30 (m, 10 H, 2 × Ph) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.3 (CH_3), 27.7 (C-3), 31.3 (C-4), 53.0 (C-2), 56.1 (C-1′), 59.6 (*C*HCH$_3$), 115.5 (C-6), 126.4, 126.8, 127.4 (Ph), 127.8 (C-5), 128.0, 128.5, 128.5 (Ph), 133.3 (C-2′), 135.8 (Ph), 137.3 (C-3′), 141.6 (Ph), 169.3 (C-1) ppm. HRMS: calcd. for $C_{23}H_{25}ONNa^+$ 354.183; found 354.183.

β-Amino Ester 8: A mixture of the β-lactam **6** (412 mg, 1.3 mmol), chlorotrimethylsilane (305 μL, 2.4 mmol) and a solution of benzyl alcohol in CH_2Cl_2 (1 M, 4 mL) was stirred at room temperature for 48 h. The reaction mixture was taken up in EtOAc (20 mL) and washed with sat. aqueous $NaHCO_3$ (20 mL). The organic phase was separated, dried (Na2SO4), filtered, and concentrated under reduced pressure. Subjection of this material to flash chromatography (silica, hexane/ethyl acetateEtOAc, 7:1) afforded the title compound **8** (346 mg, 63%) as an oil. $[\alpha]_D^{30.5} = +20.8$ ($c = 1$, CH_3OH). IR (neat): $\tilde{\nu}_{max} = 3320$ w, 1734 s, 1494 s, 1450 s, 1156 w, 969 s, 915 s, 750 m, 698 s cm^{-1}. 1H NMR ($CDCl_3$, 300 MHz): δ = 1.22 (d, $J = 6.6$ Hz, 3 H, CH_3), 1.50 (br. s, 1 H, NH), 2.27 (t, $J = 6.9$ Hz, 2 H, 3-H), 2.52 (t, $J = 8.1$ Hz, 1 H, 2-H), 3.08 (t, $J = 8.8$ Hz, 1 H, 1-H), 3.83 (q, $J = 6.6$ Hz, 1 H, C*H*CH_3), 4.90 (m, 2 H, 5-H), 5.05 and 5.29 (AB system, 2 H, $J = 12.3$ Hz, CH_2Ph), 5.64 (ddt, $J = 16.9$, 10.1, 6.8 Hz, 1 H, 4-H), 5.82 (dd, $J = 15.8$, 9.1 Hz, 1 H, 2′-H), 6.20 (d, $J = 15.8$ Hz, 1 H, 3′-H), 7.10−7.40 (m, 15 H, 3 × Ph) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 25.2 (CH_3), 34.1 (C-3), 51.6 (C-2), 54.5 (C-1′), 59.7 (*C*HCH$_3$), 66.2 (*C*H$_2$Ph), 116.7 (C-5), 126.4, 126.8, 127.0 (Ph), 127.8 (C-3′), 128.2, 128.3, 128.4, 128.5, 128.6, 129.9 (Ph), 133.2, 135.3 (C-2′ and C-3′), 173.8 (C-1) ppm. HRMS: calcd. for $C_{29}H_{31}NO_2Na^+$ 448.225; found 448.225.

β-Amino Ester 9: A mixture of the β-lactam **7** (190 mg, 0.6 mmol), chlorotrimethylsilane (140 μL, 1.1 mmol) and a solution of benzyl alcohol in CH_2Cl_2 (1 M, 2 mL) was stirred at room temperature for 48 h. The reaction mixture was taken up in EtOAc (10 mL) and washed with sat. aqueous $NaHCO_3$ (10 mL). The organic phase was separated, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Subjection of this material to flash chromatography (silica, hexane/EtOAc, 8:1) afforded the title compound **9** (203 mg, 84%) as an oil. $[\alpha]_D^{30.5} = +54.5$ ($c = 1$, CH_3OH). IR (neat): $\tilde{\nu}_{max} = 3030$ w, 2931 s, 1735 s, 1640 s, 1601 s, 1495 m, 1451 m, 749 m, 696 m cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.23 (d, $J = 6.4$ Hz, 3 H, CH_3), 1.40−1.70 (br. m, 3 H, 3-H and NH), 1.95 (br. m, 2 H, 4-H), 2.46 (dq, $J = 9.8$, 4.9 Hz, 1 H, 2-H), 3.07 (t, $J = 8.8$ Hz, 1 H, 1′-H), 3.84 (q, $J = 6.4$ Hz, 1 H, C*H*CH_3), 4.87 (m, 1 H, 6-H), 4.92 (m, 1 H, 5-H), 5.07 and 5.33 (AB system, 2 H, $J = 12.3$ Hz, CH_2Ph), 5.65 (ddt, $J = 17.1$, 10.2, 6.5 Hz, 1 H, 5-H), 5.82 (dd, $J = 15.8$, 9.1 Hz, 1 H, 2′-H), 6.20 (d, $J = 15.8$ Hz, 1 H, 3′-H), 7.30 (m, 15 H, 3 × Ph) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 25.5 (CH_3), 29.0 (C-4), 31.6 (C-3), 51.2 (C-2), 54.1 (C-1), 59.9 (*C*HCH$_3$), 66.1 (CH$_2$Ph), 115.2 (C-6), 126.3, 126.8, 126.9 (Ph), 127.7 (C-5), 128.2, 128.3, 128.4, 128.5, 128.6, 130.0 (Ph), 133.0, 137.6 (C-2′ and C-3′), 174.4 (CO) ppm. HRMS: calcd. for $C_{30}H_{33}NO_2Na^+$ 462.240; found 462.241.

Cyclic β-Amino Ester 16: The β-amino ester **8** (256 mg, 0.6 mmol) was dissolved in degassed toluene (150 mL) and a solution of Grubbs' catalyst (97 mg, 0.1 mmol) in toluene (10 mL) was added under Ar. The reaction mixture was kept under Ar and warmed at 55 °C for 48 h. The solvent was removed to give a dark brown oil that was subjected to flash chromatography (alumina, hexane/EtOAc, 6:1) to yield the title compound **16** (108 mg, 56%) as a dark oil. Further chromatography gave a sample suitable for analysis. $[\alpha]_D^{30.5} = +61.2$ ($c = 1.0$, CH_3OH). IR (CH_2Cl_2): $\tilde{\nu}_{max} = 3030$ w, 1730 s, 1494 s, 1452 s, 1351 m, 1263 m, 1158 m, 736 m, 699 s cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.30 (d, $J = 6.6$ Hz, 3 H, CH_3), 1.55 (br. s, 1 H, NH), 2.63 (m, 2 H, 5-H), 2.83 (m, 1 H, 1-H), 3.92 (q, $J = 6.6$ Hz, 1 H, C*H*CH_3), 4.02 (br. d, $J = 5.8$ Hz, 1 H, 2-H), 5.08 (s, 2 H, CH_2Ph), 5.70 (s, 2 H, 3-H and 4-H), 7.20−7.47 (m, 10 H, 2 × Ph) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.4 (CH_3), 35.05 (C-5), 50.4 (C-2), 56.2(*C*HCH$_3$), 66.0 (C-1), 66.4 (*C*H$_2$Ph), 126.5, 126.8, 128.1, 128.3, 128.4 (Ph), 130.3 (C-4), 131.4 (C-3), 135.8, 145.3 (Ph), 174.7 (CO) ppm. HRMS: calcd. for $C_{21}H_{23}NO_2Na^+$ 344.162; found 344.162.

Cyclic β-Amino Ester 17: The β-amino ester **9** (110 mg, 0.25 mmol) was dissolved in degassed toluene (60 mL) and a solution of Grubbs' catalyst (40 mg, 0.05 mmol) in toluene (10 mL) was added under Ar. The reaction mixture was kept under Ar and warmed at 55 °C for 48 h. The solvent was removed under reduced pressure to give a dark brown oil. Subjection of this material to flash chromatography (alumina, hexane/EtOAc 4:1) afforded recovered starting material (20 mg, 19%) and the title compound **17** (39 mg, 46%) as a dark oil. Further chromatography gave a sample suitable for analysis. $[\alpha]_D^{30.5} = +39.3$ ($c = 1$, CH_3OH). IR (neat): $\tilde{\nu}_{max} = 3027$ w, 1732 s, 1494 s, 1453 s, 1386 m, 1263 s, 1152 s, 736 m, 699 s cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.31 (d, $J = 6.5$ Hz, 3 H, CH_3), 1.52 (m, 1 H, 6-H), 1.90 (m, 1 H, 7-H), 2.05 (m, 2 H, 5-H), 2.43 (ddd, $J = 11.7$, 8.8, 3.1 Hz, 1 H, 1-H), 3.32 (dt, $J = 8.8$, 2.2 Hz, 1 H, 2-H), 4.01 (q, $J = 6.5$ Hz, 1 H, C*H*CH_3), 5.00 and 5.20 (AB system, 2 H, $J = 12.4$ Hz, CH_2Ph), 5.72 (m, 1 H, 4-H), 5.85 (dq, $J = 8.1$, 2.2 Hz, 1 H, 3-H), 7.08−7.39 (m, 10 H, 2 × Ph). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.3 (C-6), 24.6 (C-5), 25.3 (CH_3), 47.6 (C-1), 52.6 (*C*HCH$_3$), 54.8 (C-2), 66.0 (CH_2Ph), 126.8, 126.9 (Ph), 127.3 (C-4), 127.9 (C-3), 127.9, 128.0, 128.2, 128.4, 136.2, 145.3 (Ph), 174.7 (CO) ppm. HRMS: calcd. for $C_{22}H_{25}NO_2Na^+$ 358.178; found 358.177.

Cyclic β-Amino Acid 1: A stirred solution of **16** (60 mg, 0.18 mmol) and palladium hydroxide on carbon (20%, 60 mg) in EtOH (7 mL) was hydrogenated at 60 psi at room temperature for 48 h. The reaction mixture was filtered through a short pad of Celite™, which was then washed with EtOAc (2 × 10 mL). The combined filtrates were concentrated under reduced pressure, then taken up in EtOH (1 mL) and treated with an ethereal solution of HCl. Concentration of the solvent under reduced pressure gave the title compound (19 mg, 79%) as a colourless solid. $[\alpha]_D^{30.5} = +62.0$ ($c = 0.6$, H_2O) {ref.[5a] $[\alpha]_D = +51.8$ ($c = 1$, H_2O)}. ^1H NMR (CD_3OD, 300 MHz,): δ = 1.55−1.90 (br. m, 4 H, 2 × CH_2), 2.05−2.20 (br. m, 2 H, CH_2), 2.57 (q, $J = 8.5$ Hz, 1 H, 1-H), 3.65 (q, $J = 7.8$ Hz, 1 H, 2-H) ppm. HRMS: calcd. for $C_6H_{11}NO_2Na^+$ 152.068; found 152.068.

Cyclic β-Amino Acid 2: A stirred solution of compound **17** (22 mg, 0.07 mmol) and palladium hydroxide on carbon (20%, 25 mg) in

EtOH (7 mL) was hydrogenated at 60 psi at room temperature for 48 h. The reaction mixture was filtered through a short pad of Celite™, which was then washed with ethyl acetate (2 × 10 mL). The combined filtrates were concentrated under reduced pressure, then taken up in EtOH (1 mL) and treated with an ethereal solution of HCl. Concentration of the solution under reduced pressure gave the title compound (8 mg, 68%) as a colourless solid. $[\alpha]_D^{30.5}$ = +45.8 (c = 0.5, H_2O) {ref.[5a] $[\alpha]_D$ = +47.4 (c = 1.14, H_2O)}. ^1H NMR (CD_3OD, 400 MHz,): δ = 1.30 (m, 4 H, 2 × CH_2), 1.75 (m, 2 H, CH_2), 2.05 (m, 1 H, *H*CH), 2.15 (m, 1 H, *H*CH), 2.25 (m, 1 H, 1-H), 3.10 (m, 1 H, 2-H) ppm. HRMS: calcd. for $C_7H_{13}NO_2Na^+$ 166.084; found 166.084.

Acknowledgments

We gratefully acknowledge financial support from the Australian Research Council, and the Australian Government.

[1] D. C. Cole, *Tetrahedron* **1994**, *50*, 9517−9582.
[2] S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173−180.
[3] D. H. Appella, L. A. Christianson, I. L. Karle, D. R. Powell, S. H. Gellman, in *Book of Abstracts, 213th ACS National Meeting, San Francisco, April 13−17*, **1997**, p. 328.
[4] L. A. Christianson, M. J. Lucero, D. H. Appella, D. A. Klein, S. H. Gellman, *J. Comput. Chem.* **2000**, *21*, 763−773.
[5] [5a] S. G. Davies, I. Ichihara, I. Lenoir, A. S. Walters, *J. Chem. Soc., Perkin Trans. 1* **1994**, *9*, 1411−1415. [5b] W. Maison, M. Kosten, A. Charpy, J. Kintscher-Langenhagen, I. Schlemminger, A. Lutzen, O. Westerhoff, J. Martens, *Eur. J. Org. Chem.* **1999**, *9*, 2433−2441. [5c] P. O'Brien, D. W. Porter, N. M. Smith, *Synlett* **2000**, 1336−1338. [5d] P. Wipf, X. Wang, *Tetrahedron Lett.* **2000**, *41*, 8747−8751. [5e] C. Evans, R. McCague, S. M. Roberts, A. G. Sutherland, R. Wisdom, *J. Chem. Soc., Perkin Trans. 1* **1991**, *9*, 2276−2277. [5f] J. W. Tilley, W. Danho, S.-J. Shiuey, I. Kulesha, J. Swistok, R. Makofske, J. Michalewsky, J. Triscari, D. Nelson, S. Weatherford, V. Madison, D. Fry, C. Cook, *J. Med. Chem.* **1992**, *35*, 3774−3783. [5g] O. Miyata, K. Muroya, T. Kobayashi, R. Yamanaka, S. Kajisa, J. Koide, T. Naito, *Tetrahedron* **2002**, *58*, 4459−4479.
[6] For reviews of the NARC approach see: [6a] P. Perlmutter, *Stereosel. Heterocycl. Synth. II* **1997**, *190*, 87−103. [6b] P. Perlmutter, *Curr. Med. Chem.* **1996**, *2*, 139−152.
[7] [7a] G. D. Fallon, E. D. Jones, P. Perlmutter, W. Selajarern, *Tetrahedron Lett.* **1999**, *40*, 7435−7438. [7b] P. Perlmutter, W. Selajarern, *Aust. J. Chem.* **2000**, *53*, 349−353. [7c] I. Mavropoulos, P. Perlmutter, *Tetrahedron Lett.* **1996**, *37*, 3751−3754.
[8] M. E. Maier, *Angew. Chem. Int. Ed.* **2000**, *39*, 2073−2077.
[9] [9a] M. Benaglia, M. Cinquini, F. Cozzi, *Eur. J. Org. Chem.* **2000**, *4*, 563−572. [9b] R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, F. Ponzini, L. Raimondi, *Tetrahedron* **1994**, *50*, 2939−2948. [9c] R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, L. Raimondi, *Tetrahedron* **1994**, *50*, 5821−5828.
[10] For an efficient preparation of acyclic *cis*-β-amino acids by stereoselective addition of enolates to chiral sulfonyl imines see: T. P. Tang, J. A. Ellman, *J. Org. Chem.* **1999**, *64*, 12−13.
[11] R. Annunziata, M. Cinquini, F. Cozzi, P. G. Cozzi, *J. Org. Chem.* **1992**, *57*, 4155−4162.
[12] Imine **5** was prepared by condensation of cinnimaldehyde with (*R*)-α-methylbenzylamine using an adaptation of the methods described by Georg et al., see: G. I. Georg, Z. Wu, *Tetrahedron Lett.* **1994**, *35*, 381−384.
[13] The use of chiral auxiliary-modified imines in combination with the enolates derived from 2-pyridyl thioesters is described by Cozzi et al., see: R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, L. Raimondi, *Tetrahedron* **1994**, *50*, 9471− 9486.
[14] Only the major β-lactam isomers **6** and **7** were fully characterised and used in the subsequent steps. The minor β-lactam isomers **10** and **11** were assigned as having the *trans* configuration based on the 1′-H/2-H coupling constant values (J_{trans} = 2.0−2.4 Hz).
[15] For review articles on the general subject of the β-lactam route to β-amino acids see:[15a] L. Banfi, G. Guanti, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2393−2395. [15b] I. Ojima, F. Delaloge, *Chem. Soc. Rev.* **1997**, *26*, 377−386.
[16] Purchased from Strem Chemicals, Inc.
[17] The use of more reactive RCM catalysts[16] in these ring closures is currently under investigation in our laboratories.
[18] T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18−29.
[19] T. Yamazaki, Y. F. Zhu, A. Probst, R. K. Chadha, M. Goodman, *J. Org. Chem.* **1991**, *56*, 6644−6655.

Received May 21, 2002
[O02269]