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TETRAHEDRON: *ASYMMETRY*

A practical, two-stage preparation of benzyl (3*R*)-3-amino-2-oxo-1-pyrrolidinecarboxylate (2*S*,3*S*)-2,3-bis[(4-methylbenzoyl)oxy]butanediote (2:1)

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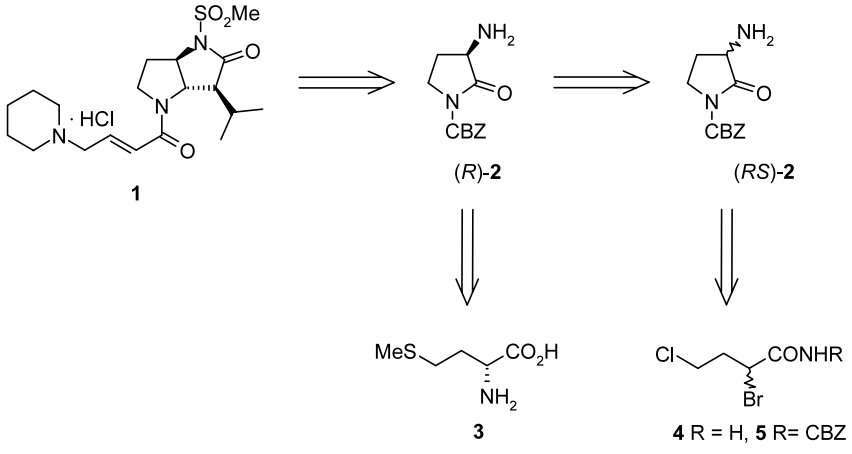
Abstract—A convenient, efficient and cost-effective two-stage synthesis of benzyl (3*R*)-3-amino-2-oxo-1-pyrrolidinecarboxylate (2*S*,3*S*)-2,3-bis[(4-methylbenzoyl)oxy]butanediote (2:1) via a crystallisation-induced dynamic resolution process is reported.

1. Introduction

Pyrrolidine-*trans*-lactams have emerged recently as attractive templates around which selective serine protease inhibitors can be developed.[1–3] A recent example is the potent, human neutrophil elastase inhibitor **1**,[4] which is of interest as a potential therapy for respiratory diseases such as cystic fibrosis and chronic bronchitis. A key intermediate in the preparation of these compounds is benzyl (3*R*)-3-amino-2-oxo-1-pyrrolidinecarboxylate (*R*)-**2** (Scheme 1).[5] Herein we report the development of a cost-effective synthesis of this protected 3-aminopyrrolidinone as its (2*S*,3*S*)-2,3-bis[(4-methylbenzoyl)oxy]-butanedioc acid (di-*p*-toluoyltartarate) salt.

Previous work has described the preparation of (*R*)-**2** from the expensive unnatural amino acid (*R*)-methionine **3**.[6] Our strategy for preparing (*R*)-**2** is based around introducing the 3-amino substituent towards the end of the synthesis, relying on a final dynamic resolution step



Scheme 1.

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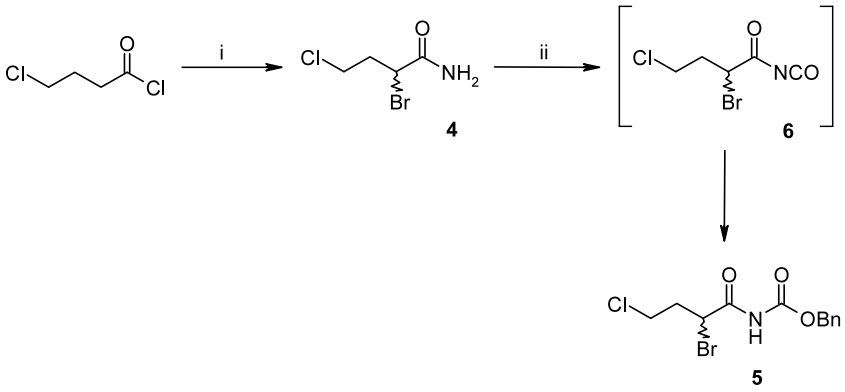


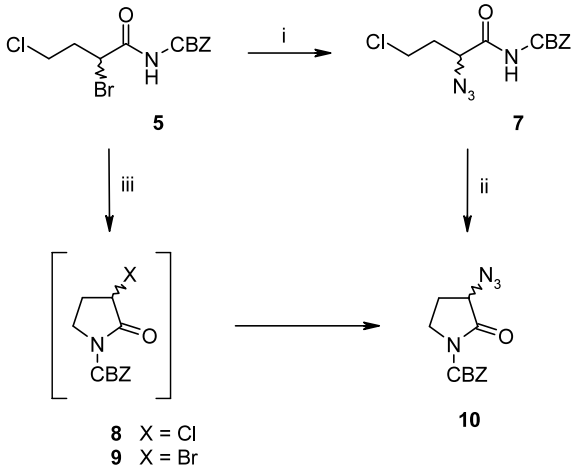
Scheme 2. *Reagents and conditions*: (i) (1) Br_2, 100°C, (2) Aq. NH_3, CH_2Cl_2; (ii) (1) $(COCl)_2$, CH_2Cl_2, (2) PhMe, 60°C, (3) benzyl alcohol.

to impart the requisite homochirality. The route described relies on the intramolecular cyclisation of a CBZ-protected amide and avoids amino acid starting materials.[6–8] Apart from using inexpensive, readily available starting materials, a key feature of this approach is that the labile stereogenic centre is established at a late stage in the synthesis.

2. Results and discussion

Bromine was added to 4-chlorobutanoyl chloride at ca. 100°C (Scheme 2). At this temperature, in the absence of solvent, the reaction was addition rate controlled.[9] The crude reaction mixture was cooled and added directly to a mixture of aqueous ammonia and dichloromethane to provide amide **4**. Under these conditions, displacement of the 4-chloro or 2-bromo substituents by ammonia was not observed and so the product was isolated in an excellent yield (100%). The required CBZ protecting group was introduced at this point. Introducing this group post cyclisation to 3-bromo-2-oxopyrrolidine[10] proved difficult, so acidic conditions[11] were used to introduce the CBZ group early to avoid premature cyclisation that can occur under basic conditions. Thus treatment of **4** with oxalyl chloride, followed by warming of solution to ca. 60°C in toluene, generated the putative acyl isocyanate **6**, which on addition of benzyl alcohol provided diimide **5**. One approach to improving throughput and efficiency is to minimise the number of isolated intermediates. Hence, we established that **5** could be prepared directly from 4-chlorobutanoyl chloride, without needing to isolate **4**, in 68% yield overall. Isolation at this point was attractive, as this proved to be the last crystalline intermediate before the final product.

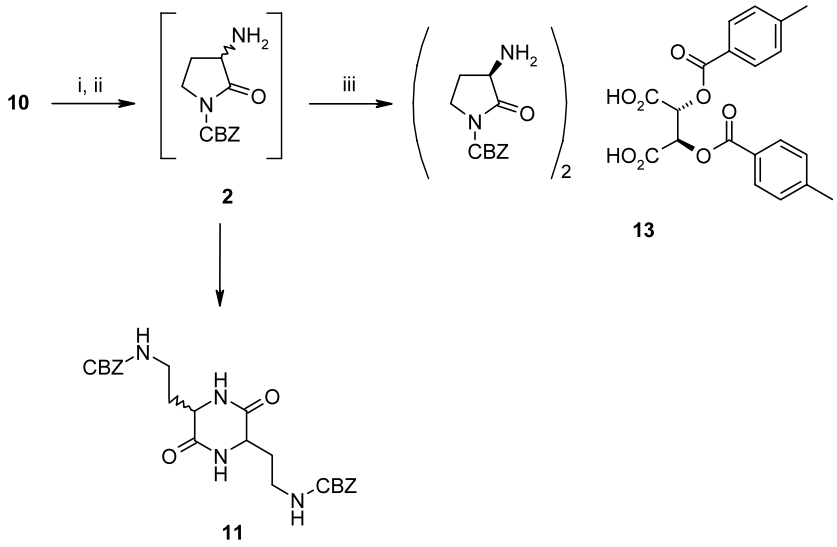
With the pivotal intermediate **5** in hand, we turned our attention to the later stages. Treatment of **5** with sodium azide led cleanly to chloroazide **7**, which, on addition of Na_2CO_3, cyclised readily to the desired azidolactam **10** (Scheme 3). However, to avoid a potential thermal runaway on scale-up [the process is exothermic and **7** decomposes thermally with a relatively low onset temperature (46°C)], we investigated an



Scheme 3. *Reagents and conditions*: (i) NaN_3, DMF; (ii) Na_2CO_3, DMF; (iii) Aq. Na_2CO_3, NaN_3, cat. $BnBu_3NBr$, EtOAc.

alternative reaction sequence. Treatment of **5** with base (e.g. K_2CO_3, $^iPr_2NEt$, $^tBuNH_2$) in DMF induced rapid cyclisation to provide a mixture of halolactams **8** and **9**. Both **8** and **9** react with azide, but the displacement of chloride from **8** was unacceptably slow.[12] Remarkably, we were able to circumvent this issue by introducing a phase transfer catalyst (benzyltributylammonium bromide). Under these conditions, using a mixture of Na_2CO_3 and NaN_3 in EtOAc/water, **8** was not observed during the cyclisation step and introduction of the azide to produce **10** proceeded smoothly.

A Staudinger reduction[13] of **10** readily provided **2**, though careful control of the hydrolysis conditions was required. The critical parameters were water content and temperature, as under the slightly basic conditions of this reaction, formation of the insoluble dimer **11** was facile (Scheme 4).[14] The final step was a crystallisation-induced dynamic resolution.[15,16] Key to the efficiency of this process is a large difference in solubility between the diastereomeric salt pairs. We screened the salts formed between **2** and a wide range of chiral acids, selected on the basis of their low cost and bulk availability. Rather than measure solubility directly, we



Scheme 4. *Reagents and conditions*: (i) PPh_3, THF; (ii) EtOAc, THF, water; (iii) (+)-di-*p*-toluoyltartaric acid **12**, cat. 3,5-dichlorosalicylaldehyde, EtOAc, water, 60°C.

looked initially for a marked difference in melting point between the pairs. A large difference in melting point infers a large difference in solubility with the higher melting salt being least soluble.[17] For each acid, the melting point of the solid formed from a 1:1 mixture (and 1:2 for bifunctional acids) of the acid and the individual enantiomers of **2**[18] was determined (Table 1); a range of solvents was used in the screen to improve the probability that crystalline salts would be obtained. (+)-Di-*p*-toluoyltartaric acid **12**, with a melting point difference of 44°C between the pair of salts was selected for further work.

The dynamic resolution process was developed using **12** and a catalytic quantity of 3,5-dichlorosalicylaldehyde. EtOAc was chosen as the solvent to avoid isolation of **10** and, attractively, deliver a single organic solvent for the entire stage. Initially, a designed experiment was performed to identify factors (water, tributylamine and **12**) that were critical for high diastereomeric purity of the bulk reaction mixture.[19] From this study, additional water and to a lesser extent excess **12** were identified as the factors that had a significant positive effect. In contrast, tributylamine had little effect on diastereomeric purity, but caused some degradation, with a markedly improved resolution rate. Fortunately, it was found that a similar rate enhancement could be achieved by raising the reaction temperature from 20 to 60°C, so the process was further developed without including the additional base. From this work, a simple process from **7** to **13** was readily identified that produced **13** in 67% yield [(*R*)-**2** of 98% ee].[20]

Table 1. Melting points of the diastereomeric salts

Chiral acid	Mp (°C)	
	(*R*)-**2**	(*S*)-**2**
(−)-Camphorsulphonic acid[a]	154	162
(+)-Dibenzoyltartaric acid[a]	168	175
(+)-Di-*p*-toluoyltartaric acid **12**[a]	184	140
(−)-Malic acid	171	167
(−)-Mandelic acid[a]	132	113
(−)-Pyrrolidone-5-carboxylic acid	108	144
(−)-Tartaric acid[a]	193	168

[a] Both enantiomers available at low cost.

In summary, a convenient, efficient, two-stage process for the preparation of **13**, a key intermediate in the synthesis of pyrrolidine-*trans*-lactams, has been developed from inexpensive starting materials.

3. Experimental

3.1. General procedure

Melting points were measured using an Electrothermal A1 8102 Digital Melting Point Apparatus in open capillary tubes and are uncorrected. Differential scanning calorimetry (DSC) screening tests were carried out on a Mettler 12E calorimeter in a high-pressure gold plated pan with a 5°C/min ramp rate. NMR spectra were recorded on a Bruker DPX250 spectrometer; ^{1}H NMR spectra at 250 MHz (chemical shifts are expressed in ppm relative to internal TMS, coupling constants in Hz) and ^{13}C at 100 MHz. Infrared spectra were recorded in Nujol mull on a Nicolet 20SXC FTIR spectrophotometer. Mass spectra were obtained on a Micromass Q-TOF hybrid quadrupole time of flight mass spectrometer using +ve ion electrospray and erythromycin as lock mass. Elemental analyses were performed by Butterworth Laboratories Limited. HPLC was carried out using the following method: a gradient from 100% A to 95% B over 8 min (A = water:TFA 1000:0.5. B = acetonitrile:TFA 1000:0.5); column 50 mm×2.0 mm Luna C18(2), 3 μm; flow rate 1.0 mL/min; temperature 40°C; UV detection at 220 nm. Chiral

HPLC was carried out using the following method: isocratic with heptane/ethanol mixtures, column Chiralcel AD or OD-H 250×4.6 mm, 5 μm; flow rate 1.0 mL/min; temperature ambient–50°C; UV detection at 215 nm. Reagents and solvents were obtained from commercial suppliers and used without further purification.

3.1.1. 2-Bromo-4-chlorobutanamide, 4. Bromine (191 g, 1.20 mol) was added to 4-chlorobutanoyl chloride (100 g, 0.70 mol) stirred at 95–110°C over 3 h. After a further 15 min, the solution was cooled to <30°C, diluted with CH_2Cl_2 (400 mL) and added to a rapidly stirred mixture of aqueous ammonia (0.88 specific gravity, 60 g, 3.5 mol), water (180 mL) and CH_2Cl_2 (600 mL) maintained at 20–30°C. The phases were separated, the aqueous phase extracted with CH_2Cl_2 (250 mL) and the combined organic phases washed with saturated brine (370 mL, containing 3 g of sodium metabisulphite). CH_2Cl_2 (240 mL) was added, the solution concentrated and dried in vacuo at 45°C to give **4** as a pale brown solid (114 g, 100%).

Whilst this material was sufficiently pure to use in subsequent process investigation, a sample was recrystallised from *tert*-butylmethylether:isooctane to provided **4** as a white solid; mp 88–89°C. IR: $\nu = 1664$, 3184, 3344 cm^{-1}. ^1H NMR (D_6-DMSO): $\delta = 2.25$–2.33 (m, 2H), 3.64–3.77 (m, 2H), 4.47–4.53 (m, 1H), 7.35 (br s, 1H), 7.82 (br s, 1H). ^{13}C NMR (D_6-DMSO): $\delta = 36.5$, 42.6, 45.9, 169.4. HRMS: m/z calcd for $C_4H_7BrClNO$ (M+H$^+$): 199.9478. Found: 199.9490.

3.1.2. Benzyl 2-bromo-4-chlorobutanoylcarbamate, 5. Bromine (55 mL, 1.07 mol) was added to 4-chlorobutanoyl chloride (100 mL, 0.89 mol) stirred at 105–110°C over 1 h. After a further 40 min, the solution was cooled to <30°C. CH_2Cl_2 (150 mL) was added and the solution added to a rapidly stirred mixture of aqueous ammonia (0.88 specific gravity, 230 mL), water (230 mL) and CH_2Cl_2 (750 mL) maintained at 20–30°C. The aqueous phase was separated and extracted with CH_2Cl_2 (400 mL). The combined organic phases were washed with aqueous sodium chloride (23% w/w, 390 g), and concentrated in vacuo. Toluene (450 mL) was added, followed by oxalyl chloride (73 mL, 0.84 mol) at <30°C over 15 min. The mixture was heated at 50–60°C for 135 min, cooled to 20°C and benzyl alcohol (88 mL, 0.85 mol) added at 20–30°C. The solution was cooled to 5°C to initiate crystallisation. Isooctane (500 mL) was added over 20 min, the precipitate collected by filtration, washed with isooctane (2×150 mL) and dried to give **5** (204 g, 68%) as an off-white solid.[21]

Whilst this material was sufficiently pure to use in subsequent chemistry, a sample was recrystallised from *tert*-butylmethylether:isooctane to provide **5** as a white solid; mp 91–92°C. IR: $\nu = 1703$, 1752, 3254 cm^{-1}. ^1H NMR (D_6-DMSO): $\delta = 2.27$–2.46 (m, 2H), 3.64–3.81 (m, 2H), 4.87 (br s, 1H), 5.18 (s, 2H), 7.34–7.44 (m, 5H), 11.15 (s, 1H). ^{13}C NMR (D_6-DMSO): $\delta = 35.7$, 42.9, 45.2, 67.1, 128.6, 128.7, 128.8, 128.9, 135.9, 151.3. HRMS: m/z calcd for $C_{12}H_{13}BrClNO_3$ (M+H$^+$): 333.9846. Found: 333.9827.

3.1.3. Benzyl 2-azido-4-chlorobutanoylcarbamate, 7. Sodium azide (0.70 g, 10.8 mmol) was added to a mixture of **5** (3.0 g, 9.0 mmol), sodium bicarbonate (1.5 g, 17.9 mmol) and benzyltributylammonium bromide (0.12 g, 0.3 mmol) in ethyl acetate (30 mL) and water (30 mL) vigorously stirred at 20°C. After 5 h, the organic phase was separated, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash column chromatography using a gradient of ethyl acetate and isooctane (1:10–3:7) as eluant gave **7** (1.3 g, 47%) as a colourless oil. IR: $\nu = 1713$, 1770, 2113, 3276 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 2.12$–2.22 (m, 1H), 2.34–2.43 (m, 1H), 3.65–3.75 (m, 2H), 4.59–4.67 (m, 1H), 5.22 (s, 2H), 7.34–7.42 (m, 5H), 8.16 (br s, 1H). ^{13}C NMR ($CDCl_3$): $\delta = 34.3$, 40.4, 60.5, 68.5, 127.1, 127.5, 128.9, 134.5, 150.4. HRMS: m/z calcd for $C_{12}H_{13}ClN_4O_3$ (M+H$^+$): 297.0754. Found: 297.0752. DSC: exotherm range 46–168°C, 132 kJ with rapid gas evolution; 168–257°C, 56 kJ.

3.1.4. Benzyl 3-chloro-2-oxopyrrolidine-1-carboxylate, 8. A solution of **5** (5.0 g, 14.9 mmol) and diisopropylethylamine (3.0 mL, 17.2 mmol) in DMF (20 mL) was stirred at 20°C. After 15 h, the aqueous sulphuric acid (2 M, 100 mL) was added. The mixture was extracted with CH_2Cl_2 (2×50 mL), the combined organic phases washed with water (3×50 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to give a mixture of **8** and **9** (6:1, 3.98 g) as an orange oil. A sample (3.5 g) was purified by flash column chromatography using ethyl acetate and isooctane (1:9–2:3) as eluant to give **8** (1.2 g, 34%) as a colourless oil. IR: $\nu = 1726$, 1761, 1795 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 2.19$–2.28 (m, 1H), 2.50–2.60 (m, 1H), 3.78–3.84 (m, 1H), 3.92–3.98 (m, 1H), 4.42 (dd, $J = 6$, 8 Hz, 1H), 5.31 (s, 2H), 7.31–7.45 (m, 5H). ^{13}C NMR ($CDCl_3$): $\delta = 29.4$, 44.2, 55.5, 69.0, 128.7, 128.9, 129.0, 135.3, 151.6, 169.0. HRMS: m/z calcd for $C_{12}H_{12}ClNO_3$ (M+H$^+$): 254.0584. Found: 254.0588.

3.1.5. Benzyl 3-bromo-2-oxopyrrolidine-1-carboxylate, 9. A mixture of **5** (3.0 g, 9.0 mmol), sodium carbonate (1.14 g, 10.8 mmol) and benzyltributylammonium bromide (0.12 g, 0.3 mmol) in ethyl acetate (30 mL) and water (30 mL) was vigorously stirred at 50°C. After 1.5 h, the mixture was cooled to 25°C. The organic phase was separated, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash column chromatography using a gradient of ethyl acetate and isooctane (1:9–2:3) as eluant gave **9** (1.1 g, 42%) as a colourless oil. IR: $\nu = 1725$, 1756, 1791 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 2.25$–2.34 (m, 1H), 2.52–2.61 (m, 1H), 3.84–3.97 (m, 2H), 4.21 (dd, $J = 4$, 8 Hz, 1H), 5.31 (s, 2H), 7.32–7.46 (m, 5H). ^{13}C NMR ($CDCl_3$): $\delta = 29.3$, 43.7, 44.4, 68.6, 128.3, 128.5, 128.6, 134.9, 169.1. HRMS: m/z calcd for $C_{12}H_{12}BrNO_3$ (M+H$^+$): 298.0079. Found: 289.0085.

3.1.6. Benzyl 3-azido-2-oxopyrrolidine-1-carboxylate, 10. A mixture of **5** (50.0 g, 149 mmol), sodium azide (11.5 g, 177 mmol), sodium carbonate (19.0 g, 179 mmol) and benzyltributylammonium bromide (2.0 g, 6.4 mmol) in ethyl acetate (200 mL) and water (400 mL) was vigorously stirred at 50°C. After 2.5 h, the mixture was cooled to 25°C. The organic phase was separated and the aqueous

phase back-extracted with ethyl acetate (2×200 ml). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo to give **10** as a purple oil. A sample of **10** was purified by flash chromatography using dichloromethane as eluant to give **10** as a colourless oil that solidified on standing. IR: $\nu = 1786$, 2104 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 1.81$–1.92 (m, 1H), 2.29–2.38 (m, 1H), 3.59–3.66 (m, 1H), 3.82–3.87 (m, 1H), 4.21 (t, $J = 9$ Hz, 1H), 5.28 (s, 2H), 7.31–7.44 (m, 5H). ^{13}C NMR ($CDCl_3$): $\delta = 24.7$, 43.0, 60.1, 68.5, 128.2, 128.5, 128.7, 134.9, 151.1, 170.1. HRMS: m/z calcd for $C_{12}H_{12}N_4O_3$ ($M+H^+$): 261.0988. Found: 261.0994.

3.1.7. Benzyl (3*R*)-3-amino-2-oxopyrrolidine-1-carboxylate (2*S*,3*S*)-2,3-bis[(4-methylbenzoyl)oxy]butanedioate (2:1), 13. A mixture of **5** (50 g, 149 mmol), sodium carbonate (19 g, 179 mmol), sodium azide (11.5 g, 177 mmol) and benzyltributylammonium bromide (2.0 g, 6.4 mmol) in ethyl acetate (200 mL) and water (400 mL) was stirred vigorously at 50°C. After 2.5 h, the mixture was cooled to 25°C. The organic phase was separated and the aqueous phase back-extracted with ethyl acetate (2×200 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. Ethyl acetate (500 mL) was added, followed by a solution of triphenylphosphine (40 g, 153 mmol) in ethyl acetate (100 mL) over 15 min, whilst the temperature rose to 40°C. After a further 15 min at ca. 40°C, water (10 mL) was added. After 3.5 h, **12** (45 g, 116 mmol), 3,5-dichloro-salicylaldehyde (1.0 g, 5.2 mmol) and water (25 mL) were added. The reaction mixture was heated at 60–66°C for 3.5 h, before cooling to 20°C overnight. The product was filtered off, washed with ethyl acetate (200 mL) and dried to give **13** (42.5 g, 67%) as a white solid;[21] mp 178–179°C (dec.). Chiral HPLC: 5.31 min [(*S*)-**2**, 1.1% a/a], 7.40 min [(*R*)-**2**, 98.9% a/a]. IR: $\nu = 1721$, 1773 cm^{-1}. ^1H NMR (D_6-DMSO): $\delta = 1.70$–1.82 (m, 2H), 2.22–2.29 (m, 2H), 2.34 (s, 6H), 3.49–3.57 (m, 2H), 3.69–3.75 (m, 2H), 3.77–3.82 (dd, $J = 8$, 11 Hz, 2H), 5.24 (s, 2H), 5.59 (s, 2H), 7.29 (d, $J = 8$ Hz, 4H), 7.32–7.44 (m, 10H), 7.80 (d, $J = 8$ Hz, 4H). ^{13}C NMR (D_6-DMSO): $\delta = 21.5$, 25.6, 43.0, 57.5, 71.6, 127.2, 128.1, 128.5, 128.8, 129.6, 129.6, 136.0, 165.1, 168.3. HRMS: m/z calcd for $C_{12}H_{15}N_2O_3$ ($M+H^+$): 235.1083. Found: 235.1090. m/z calcd for $C_{20}H_{22}NO_8$ ($M+NH_4^+$): 404.1345. Found: 404.1325. Anal. calcd for $C_{44}H_{46}N_4O_{14}$: C, 61.8; H, 5.42; N, 6.55. Found: C, 61.5; H, 5.40; N, 6.40%.

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18. Samples of (*R*)-**2** and (*S*)-**2** were prepared from (*R*)- and (*S*)-methionine, respectively, using the methodology outlined in Ref. 6.
19. Design of experiments (DOE) analysis was performed using Design-Expert® (Stat-Ease, Inc., Minneapolis, MN, 1.800.801.7191, www.statease.com).
20. A solution of (*R*)-**2** in EtOAc was readily prepared by treating **13** with aqueous sodium carbonate followed by extraction into ethyl acetate. However, **11** was rapidly formed when the extract was heated and/or concentrated.
21. Formal stability studies have not been performed on either **5** or **13**. However, samples showed no change in either appearance or impurity profile after storage for one year in amber coloured glass bottles at <30°C.