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4-Substituted prolines as organocatalysts for aldol reactions

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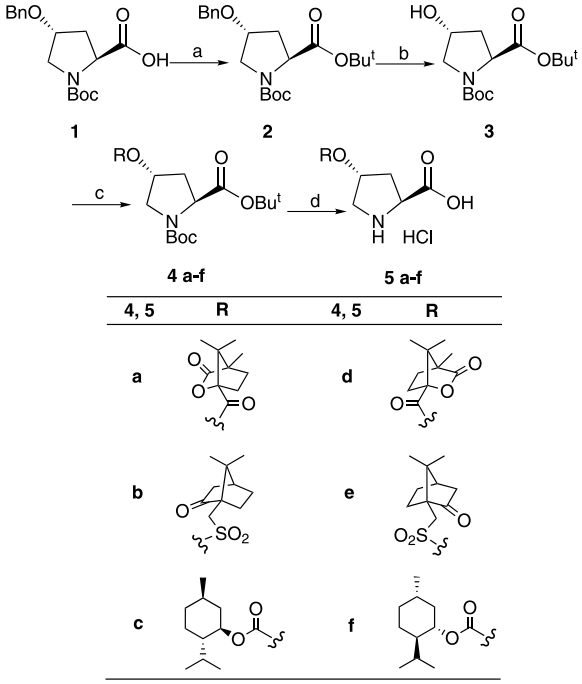
Abstract—A series of 4-substituted prolines were prepared and evaluated as organocatalysts for asymmetric aldol reactions. Using (2*S*,4*R*)-4-camphorsulfonyloxy-proline, the aldol products were obtained in much higher enantiomeric excess in comparison to that observed using proline itself. In addition, the improved solubility of these new catalysts in organic solvents permits their use in lower sub-stoichiometric amounts compared to proline.

1. Introduction

The capability of simple organic molecules from the 'chiral pool' to act like an enzyme represents a remarkable synthetic alternative to many established asymmetric transformations. Among the various enantiomerically pure small organic molecules, amino acids and peptides as well as cinchona alkaloids are extremely interesting asymmetric organocatalysts[1] demonstrating useful levels of enantioselectivity for a wide range of transformations. In particular, the natural amino acid L-proline acts as an enzyme mimic of the type I aldolase, catalysing one of the most important organic asymmetric transformations, the aldol reaction.[2] In addition, proline has shown excellent catalytic activity in catalysing a wide variety of reactions[3] such as Mannich[4] and Michael[5] reactions, Robinson annulation,[6] synthesis of amino acids,[7] α-amination of aldehydes and ketones,[8] α-oxidation[9] and α-alkylation[10] of aldehydes.

2. Results and discussion

As part of our program aimed at developing methodology for the synthesis of non-natural amino acids and exploring their applications,[11] we synthesized various 4-substituted prolines. In this article we report our study on their catalytic effect on the direct asymmetric aldol reaction.[12] To develop improved proline-based catalysts, we decided to maintain the proline backbone, since both the carboxylic acid group and the pyrrolidine group are essential for effective asymmetric induction, and to introduce a chiral bulky substituent at the 4-position. The rationale behind the design was to induce steric hindrance from one side of the pyrrolidine ring. L-4-Hydroxyproline, which has already



Scheme 1. Reagents and conditions: (a) $CCl_3C(=NH)OBu^t$, $BF_3 \cdot Et_2O$, CH_2Cl_2/C_6H_{12}, 84%; (b) H_2, 10% Pd/C, 1,4-dioxane, rt, 24 h, 84%; (c) (i) (1*S*)-(−)-camphanic acid or (1*R*)-(+)-camphanic acid, DCC, DMAP, CH_2Cl_2, rt, 24 h, 80% for **4a** and 82% for **4d**, or (ii) (1*R*)-(−)-camphor-10-sulfonyl chloride or (1*S*)-(+)-camphor-10-sulfonyl chloride, NMM, THF, 0 °C, 30 min, rt, 24 h, 85% for **4b** and 88% for **4e**, or (iii) NaH, THF, 0 °C, then rt, 30 min, and then (−)-menthyl chloroformate or (+)-menthyl chloroformate, rt, 22 h, 90% for **4c** and 93% for **4f**; (d) 5 N HCl/Et_2O, rt, 4 h, 94–96%.

Keywords: Aldol reactions; Amino acids; Asymmetric catalysis; Organocatalysts; 4-Substituted proline.
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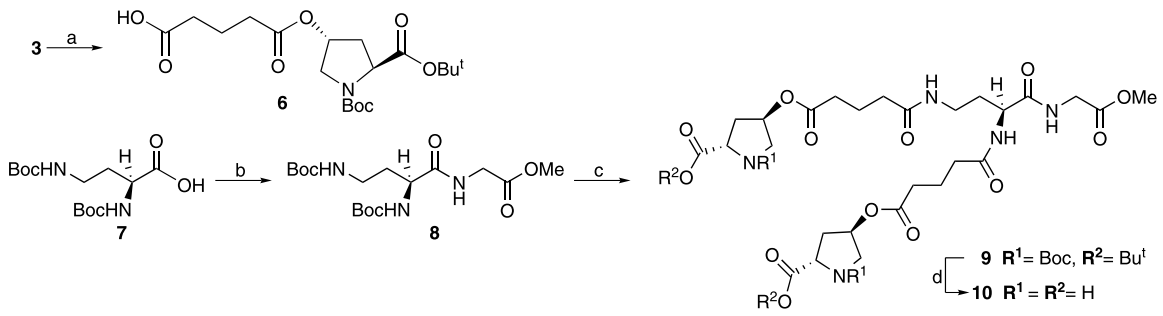
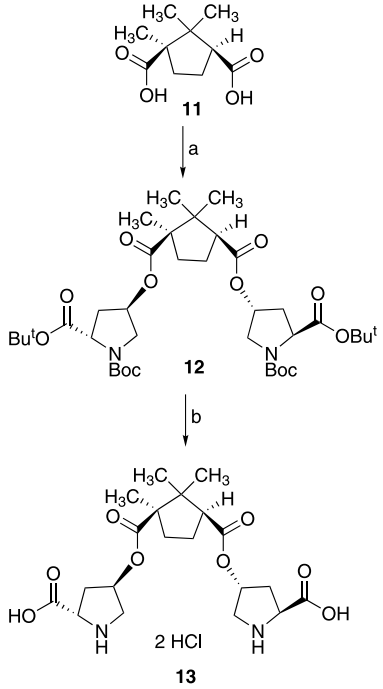


Scheme 2. Reagents and conditions: (a) glutaric anhydride, DMAP, CH_2Cl_2, rt, 36 h, 75%; (b) $HCl \cdot H_2NCH_2COOCH_3$, EDC, HOBt, Et_3N, 0 °C, 1 h, rt, 16 h, 75%; (c) (i) 5 N HCl/Et_2O, rt, 1 h, (ii) **6**, EDC, HOBt, Et_3N, 0 °C, 1 h, rt, 30 h, 70% (overall); (d) 5 N HCl/Et_2O, rt, 4 h, 96%.

been used successfully as a catalyst of the aldol reaction,[2b] seemed an ideal template. Furthermore, it has been recently reported that *trans*-4-*tert*-butyldimethylsiloxy-L-proline efficiently catalyses α-aminoxylation of carbonyl compounds, as well as *O*-nitroso-aldol/Michael, and Mannich reactions.[13]

Thus, commercially available (2*S*,4*R*)-*N*-(*tert*-butoxycarbonyl)-4-benzyloxy-proline (**1**) was converted into compound **3** (Scheme 1). Compounds **4a**,**d** were prepared by coupling **3** with (1*R*)-(+)- and (1*S*)-(−)-camphanic acid using *N*,*N*′-dicyclohexylcarbodiimide (DCC) as coupling agent in the presence of 4-dimethylamino-pyridine (DMAP).[14] Sulfonates **4b**,**e** were prepared by treatment of **3** with the corresponding sulfonyl chlorides in the presence of *N*-methyl-morpholine (NMM) in dry THF and carbonates **4c**,**f** were prepared by treatment of **3** with the corresponding chloroformates, as depicted in Scheme 1. Deprotected derivatives **5a–f** were prepared by treatment of **4a–f** with 5 N HCl/Et_2O.

Derivative **3** was glutarylated and coupled with methyl



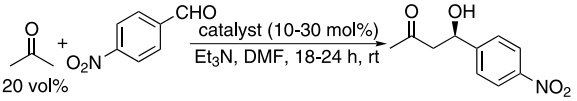
Scheme 3. Reagents and conditions: (a) **3**, DCC, DMAP, CH_2Cl_2, rt, 36 h, 74%; (b) 5 N HCl/Et_2O, rt, 4 h, 98%.

α,γ-diaminobutyryl-glycinate using 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide (EDC) in the presence of 1-hydroxybenzotriazole (HOBt) (Scheme 2). Dendron-like derivative **10** was obtained by deprotection of compound **9**. As depicted in Scheme 3 (1*R*,3*S*)-(+)-camphoric acid (**11**) was coupled with compound **3**, using the DCC/DMAP method, and deprotected to produce compound **13**.

The aldol reaction is one of the most important carbon–carbon bond-forming reactions in organic synthesis. List and Barbas have extensively studied the direct asymmetric aldol reaction of both acyclic and cyclic ketones as aldol donors with aromatic and aliphatic aldehydes and they have demonstrated that the most powerful catalysts are L-proline and 5,5′-dimethyl thiazolidinium-4-carboxylate.[2b] We have chosen in our preliminary investigations the reaction between acetone and 4-nitro-benzaldehyde and we have studied the catalytic effect of derivatives **5a–f**, **10** and **13** on this reaction. The results of our studies are summarized in Table 1.

The substituents at the 4-position have a significant effect on

Table 1. Direct asymmetric aldol reaction of acetone and 4-nitrobenzaldehyde using various proline-based catalysts



Entry[a]	Catalyst	Catalyst loading (%)	Yield (%)[b]	ee (%)[c]
1	**5a**	30	62	80
2	**5a**	20	58	73
3	**5b**	30	62	75
4	**5b**	20	60	81
5	**5c**	30	65	77
6	**5d**	30	66	44
7	**5e**	30	61	82
8	**5e**	20	59	84
9	**5e**	10	71	90
10	**5f**	30	65	71
11	**10**	30	61	68
12	**10**	15	64	70
13	**13**	30	60	69
14	**13**	15	62	71
15	L-Pro·HCl	20	60	63
16	L-Pro[d]	20	63	69
17	L-HyPro[d]	30	71	70

[a] Reactions carried out for 16–18 h at rt.
[b] Isolated yields after column chromatography.
[c] The ee was determined by HPLC on a Daicel Chiralpak AD-RH column.
[d] In the absence of Et_3N.

both the enantioselectivity and yield of the reaction. Under the conditions used (Table 1) the aldol product was obtained in 69 and 70% ee, when L-proline and L-4-hydroxyproline were used as catalysts (entries 16 and 17, respectively). However, when camphanic acid derivative **5a** was used ee values up to 80% were observed (entry 1). A decrease in the catalyst loading of **5a** led to decrease of both chemical yield and ee value (entry 2). It is interesting to note that (1*S*)-(−)-camphanic acid derivative (**5a**) led to high enantioselectivity, while the (1*R*)-(+)-camphanic acid derivative (**5d**) led to much lower enantioselectivity (entries 1 and 6, respectively). Menthyl derivatives **5c** and **5f** (entries 5 and 10, respectively), gave comparable ee values and the result for **5f** was almost similar to those acquired when proline and L-4-hydroxyproline were used as catalysts. The application of the camphorsulfonyl derivatives **5b** and **5e** led to very interesting results. The camphorsulfonyl derivative **5e** produced the aldol product in high ee (90%) when used in 10 mol% catalyst loading (entry 9). It should be noticed that although the loading of the catalyst (30 and 20%) did not considerably influence both the enantioselectivity (82 and 84%, entries 7 and 8, respectively), and the chemical yield (61 and 59%, entries 7 and 8, respectively), better chemical yield (71%) was obtained when derivative **5e** was employed in 10 mol% loading (entry 9). Dendron-like derivatives **10** and **13** containing two pyrrolidine rings per molecule led to chemical yields and ee values almost similar to those obtained by proline itself, probably because proline residues act as non interacting moieties and their catalytic potencies are neither enhanced nor cancelled out by each other.

In an attempt to test the efficacy of catalyst **5e**, we submitted 4-bromo-benzaldehyde and 2-chloro-benzaldehyde as acceptor substrates to the aldol process. The results are presented in Table 2. When proline was used as catalyst in the reaction between acetone and 4-bromo-benzaldehyde in 20 mol% loading, the aldol product was obtained in moderate ee values (62%), whilst in 10 mol% proline loading practically no aldol product was acquired (entry 2). However, when catalyst **5e** was employed in 10 mol% catalyst loading, the aldol product was isolated in much higher enantiomeric excess (80%) (entry 2). In a similar manner, in the reaction between acetone and 2-chloro-benzaldehyde, catalyst **5e** in 10 mol% loading led to a higher ee value (74%) in comparison to that observed by using proline itself (64% ee for 20 mol% proline and almost no aldol product for 10 mol%) and in a comparable chemical yield (entry 3).

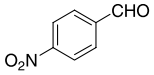
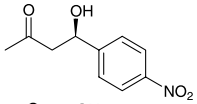
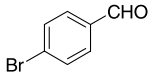
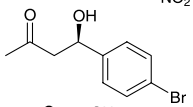
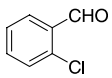
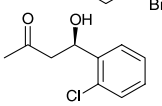
In conclusion, the results of our study indicate that for high enantioselectivity the catalyst should possess a chiral bulky group at the 4-position of the pyrrolidine ring in addition to carboxylic acid and secondary amine groups. In particular, 4-camphorsulfonyloxy-proline derivative **5e**, easily synthesized from proline derivative **1**, compares favourably to proline for the direct asymmetric aldol reaction offering: (a) higher enantioselectivity in comparison to proline and (b) a decrease of the required amount (10%) in comparison to proline (20–30%).

3. Experimental

3.1. General

Melting points were determined on a melting point apparatus and are uncorrected. Specific rotations were measured on a polarimeter using a 10 cm cell. NMR spectra were recorded on 200 and 300 MHz Varian spectrometers. Where applicable, structural assignments were based on COSY experiments. Where rotamers are apparent peaks for major and minor rotamers are reported, when resolved. IR spectra were recorded on a Perkin-Elmer 841 Spectrophotometer. Analytical TLC plates (silica gel 60 F_{254}) and silica gel 60 (70–230 or 230–400 mesh) for column chromatography were purchased from Merck. Visualisation of spots was effected with UV light and/or phosphomolybdic acid and/or ninhydrin both in ethanol stain. THF and 1, 4-dioxane were freshly distilled from sodium-benzophenone ketyl radical under an argon atmosphere immediately prior to use. Et_2O was treated with calcium chloride and stored over Na. DMF was stirred in the presence of P_2O_5 for 15 h and distilled under reduced pressure. Acetone was dried overnight over 3 Å activated molecular sieves (10% w/v) and then distilled. All other solvents and chemicals were of reagent grade and used without further purification. The samples for elemental analyses were dried over P_2O_5 under high vacuum for 48 h.

Table 2. Comparison between proline and catalyst **5e** in the direct asymmetric aldol reaction

Entry[a]	Substrate	Product	Proline (10 mol%)		Proline (20 mol%)		**5e** (10 mol%)	
			Yield (%)[b]	ee (%)	Yield (%)[b]	ee (%)[c]	Yield (%)[b]	Ee (%)[c]
1			<5	n.d.[d]	63	69	71	90
2			<5	n.d.[d]	71	62	74	80
3			<5	n.d.[d]	80	64	78	74

[a] Reactions carried out for 16–18 h at rt.
[b] Isolated yields after column chromatography.
[c] The ee was determined by HPLC on a Daicel Chiralpak AD-RH column.
[d] Not determined.

3.1.1. (2*S*,4*R*)-Di-*tert*-butyl 4-(benzyloxy)pyrrolidine-1,2-dicarboxylate (2). To a stirred solution of Boc-L-Pro(Bn)–OH (322 mg, 1.00 mmol) in CH_2Cl_2 (1 mL), a solution of *tert*-butyl-2,2,2-trichloroacetimidate (440 mg, 2.00 mmol) in C_6H_{12} (2 mL) was added, followed by $BF_3 \cdot Et_2O$ (20 μL). The stirring was continued for 24 h at rt. Work-up involved filtration of the reaction mixture through a pad of Celite® to remove trichloroacetamide and removal of the solvent under reduced pressure. The residue was purified by column chromatography using a mixture of $CHCl_3$/MeOH 95:5 as eluent to afford **2**. Yellowish oil (315 mg, 84%); $[\alpha]_D$ −23.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45 [br, 18H, 2×C$(CH_3)_3$], 2.05 (m, 1H, C*H*HCHN), 2.35 (m, 1H, CH*H*CHN), 3.45–3.75 (m, 2H, CH_2N), 4.10–4.38 (m, 2H, CHN, OCH), 4.42–4.60 (m, 2H, CH_2Ph), 7.25–7.42 (m, 5H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.9, 28.3, 35.4, 36.7, 51.2, 51.8, 58.6, 71.1, 75.7, 76.7, 79.7, 79.9, 81.0, 127.6, 127.7, 128.4, 137.7, 154.0, 172.1; IR [film, (cm^{-1})]: 1730 and 1698 (C=O); MS (ESI): *m*/*z* (%): 378 (23) [M+H$^+$], 400 (100) [M+Na$^+$]. Anal. Calcd for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28; N, 3.71. Found: C, 66.59; H, 8.38; N, 3.68.

3.1.2. (2*S*,4*R*)-Di-*tert*-butyl 4-hydroxypyrrolidine-1,2-dicarboxylate (3). To a stirred solution of **2** (380 mg, 1.00 mmol) in anhydrous 1,4-dioxane (10 mL), 10% Pd/C (40 mg) was added. The reaction mixture was stirred under H_2 for 24 h at rt. After filtration through a pad of Celite®, the solvent was removed and the residue was purified by column chromatography using EtOAc as eluent to give **3**. Colourless oil (240 mg, 84%); $[\alpha]_D$ −68.0 (*c* 1.0, MeOH); [Lit.[15] $[\alpha]_D^{21}$ −68.9 (*c* 1.06, MeOH)]; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45 [br, 18H, 2×C$(CH_3)_3$], 2.01 (m, 1H, C*H*HCHN), 2.25 (m, 1H, CH*H*CHN), 2.92 (br, 1H, OH), 3.33–3.68 (m, 2H, CH_2N), 4.28 (m, 1H, CHN), 4.45 (m, 1H, OCH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.9, 28.3, 38.3, 39.1, 54.5, 58.5, 69.1, 70.0, 79.9, 80.2, 81.1, 154.3, 172.2; IR [film, (cm^{-1})]: 1745 and 1690 (C=O); MS (FAB): *m*/*z* (%): 288 (100) [M+H$^+$]. Anal. Calcd for $C_{14}H_{25}NO_5$: C, 58.52; H, 8.77; N, 4.87. Found: C, 58.65; H, 7.69; N, 4.88.

3.2. General procedure for the preparation of the carboxylates 4a,d

To a solution of **3** (290 mg, 1.00 mmol) in dichloromethane (8 mL) was added (1*S*)-(−)-camphanic acid or (1*R*)-(+)-camphanic acid (200 mg, 1.00 mmol) followed by DCC (227 mg, 1.10 mmol) and DMAP (12 mg, 0.10 mmol). The mixture was stirred for 24 h. The dicyclohexylurea was filtered off, the solvent was removed, water (5 mL) was added and the product was then extracted with EtOAc (3× 10 mL). The combined organic layers were washed consecutively with 1 M $KHSO_4$ (1×25 mL), H_2O (1× 30 mL), $NaHCO_3$ 10% (1×25 mL), H_2O (1×30 mL) and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography using a mixture of EtOAc/petroleum ether 40–60 1:1 as eluent to give **4a**,**d**.

3.2.1. (2*S*,4*R*)-Di-*tert*-butyl 4-[(1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-carbonylox]pyrrolidine-1,2-dicarboxylate (4a). Pale yellow solid (374 mg, 80%); mp 173–175 °C; $[\alpha]_D$ −61.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.44 [br, 18H, 2×C$(CH_3)_3$], 1.50–2.50 (series of m, 6H, 2×CH_2, CH_2CHN), 3.40–3.80 (m, 2H, CH_2N), 4.23 (m, 1H, CHN), 5.28 (m, 1H, OCH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 9.5, 16.5, 16.6, 27.8, 28.1, 28.2, 28.7, 29.9, 30.2, 31.9, 32.0, 32.1, 32.6, 35.2, 36.2, 52.0, 54.3, 54.7, 58.1, 73.4, 74.1, 80.1, 80.3, 81.4, 90.6, 153.6, 166.9, 171.2, 178.0; IR [KBr, (cm^{-1})]: 1795, 1738 and 1704 (C=O); MS (FAB): *m*/*z* (%): 468 (5) [M+H$^+$]. Anal. Calcd for $C_{24}H_{37}NO_8$: C, 61.65; H, 7.98; N, 3.00. Found: C, 61.80; H, 8.32; N, 3.21.

3.2.2. (2*S*,4*R*)-Di-*tert*-butyl 4-[(1*R*,4*S*)-4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-carbonyloxy]pyrrolidine-1,2-dicarboxylate (4d). White solid (384 mg, 82%); mp 153–155 °C; $[\alpha]_D$ −18.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.44 [br, 18H, 2×C$(CH_3)_3$], 1.50–2.48 (series of m, 6H, 2×CH_2, CH_2CHN), 3.49–3.78 (m, 2H, CH_2N), 4.11 (m, 1H, CHN), 5.34 (m, 1H, OCH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 9.5, 16.5, 16.6, 27.8, 28.1, 28.8, 29.9, 30.4, 31.9, 32.0, 32.1, 32.5, 35.2, 36.3, 52.0, 52.1, 54.1, 54.6, 58.2, 73.2, 74.1, 80.3, 81.4, 90.5, 153.5, 166.7, 171.2, 177.8; MS (ESI): *m*/*z* (%): 490 (100) [M+Na$^+$]. Anal. Calcd for $C_{24}H_{37}NO_8$: C, 61.65; H, 7.98; N, 3.00. Found: C, 61.78; H, 8.30; N, 3.26.

3.3. General procedure for the preparation of the sulfonates 4b,e

To a stirred solution of **3** (290 mg, 1.00 mmol) in anhydrous THF (8 mL) were added NMM (0.14 mL, 1.25 mmol) and (1*R*)-(−)-camphor-10-sulfonyl chloride or (1*S*)-(+)-camphor-10-sulfonyl chloride (315 mg, 1.25 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and at rt for 24 h. The solvent was removed, water (15 mL) was added and the product was then extracted with EtOAc (3×10 mL). The combined organic layers were washed consecutively with 1 M $KHSO_4$ (1×25 mL), H_2O (1×30 mL), $NaHCO_3$ 10% (1×25 mL), H_2O (1×30 mL) and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography using initially a mixture of EtOAc/petroleum ether 40–60 1:1 and finally EtOAc as eluents to give **4b**,**e**.

3.3.1. (2*S*,4*R*)-Di-*tert*-butyl 4-{[(1*R*,4*S*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl]methylsulfonyloxy}pyrrolidine-1,2-dicarboxylate (4b). Colourless oil (426 mg, 85%); $[\alpha]_D$ −44.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.80–2.56 (series of m, 35H, 2×CH_3, 2×C$(CH_3)_3$, 3×CH_2, CH, CH_2CHN, CH_2SO_2) 3.40–3.80 (m, 2H, CH_2N), 4.30 (m, 1H, CHN), 5.29 (m, 1H, OCH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.6, 19.7, 25.2, 26.8, 27.9, 28.0, 28.3, 33.1, 35.5, 36.6, 42.3, 42.7, 51.9, 52.1, 58.4, 64.2, 71.9, 72.8, 80.1, 80.3, 81.4, 153.8, 171.6, 172.3, 212.8; MS (ESI): *m*/*z* (%): 524 (100) [M+Na$^+$]. Anal. Calcd for $C_{24}H_{39}NO_8S$: C, 57.46; H, 7.84; N, 2.79. Found: C, 57.70; H, 7.55; N, 2.76.

3.3.2. (2*S*,4*R*)-Di-*tert*-butyl 4-{[(1*S*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl]methylsulfonyloxy}pyrrolidine-1,2-dicarboxylate (4e). White solid (442 mg, 88%); mp 93–95 °C; $[\alpha]_D$ −10.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.76 (s, 3H, CH_3), 0.96 (s, 3H, CH_3),

1.37 [br, 18H, 2×C(CH$_3$)$_3$], 1.40–2.60 (series of m, 9H, 3×CH$_2$, CH, C*H*$_2$CHN), 2.91 (d, *J*=14.9 Hz, 1H, C*H*HSO$_2$), 3.40–3.83 (m, 3H, CH$_2$N, CH*H*SO$_2$), 4.16 (m, 1H, CHN), 5.17 (m, 1H, OCH); ^{13}C NMR (50 MHz, CDCl$_3$) δ 19.2, 19.3, 24.5, 24.6, 26.5, 27.6, 27.9, 35.9, 37.2, 42.1, 42.3, 47.7, 52.1, 52.4, 57.6, 57.7, 57.8, 78.2, 78.9, 80.0, 81.2, 153.2, 170.8, 170.9, 213.8; IR [KBr, (cm^{-1})]: 1749, 1728 and 1700 (C=O), 1365 and 1160 (S=O); MS (ESI): *m/z* (%): 524 (100) [M+Na$^+$]. Anal. Calcd for C$_{24}$H$_{39}$NO$_8$S: C, 57.46; H, 7.84; N, 2.79. Found: C, 57.71; H, 7.60; N, 2.74.

3.4. General procedure for the preparation of the carbonates 4c,f

To an ice-cold solution of **3** (290 mg, 1.00 mmol) in dry THF (5 mL), NaH (24 mg, 1.00 mmol) was added. The mixture was warmed up to rt and stirred for 30 min, after which (−)- or (+)-menthyl chloroformate (240 mg, 235 μL, 1.10 mmol) was added. The stirring was continued at rt for 22 h. The solvent was removed under reduced pressure, water (7 mL) was added and the product was then extracted with EtOAc (3×6 mL). The combined organic layers were washed consecutively with 1 M KHSO$_4$ (1×20 mL), H$_2$O (1×25 mL), NaHCO$_3$ 10% (1×20 mL), H$_2$O (1×25 mL) and dried over Na$_2$SO$_4$. The solvent was evaporated and the residue was purified by column chromatography using a mixture of EtOAc/petroleum ether 40–60 1:1 as eluent to give **4c**,**f**.

3.4.1. (2*S*,4*R*)-Di-*tert*-butyl 4-{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy]carbonyloxy}pyrrolidine-1,2-dicarboxylate (4c). Pale yellow oil (423 mg, 90%); [α]$_D$ −66.0 (*c* 1.0, CHCl$_3$); ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.70–2.50 (series of m, 38H, 3×CH$_3$, 2×C(CH$_3$)$_3$, 3×CH$_2$, 3×CH, C*H*$_2$CHN), 3.50–3.80 (m, 2H, CH$_2$N), 4.22 (m, 1H, CHN), 4.48 (m, 1H, CHC*H*O), 5.17 (m, 1H, OCH); ^{13}C NMR (50 MHz, CDCl$_3$) δ 16.1, 20.6, 21.8, 23.1, 25.9, 27.8, 27.9, 28.2, 31.3, 33.9, 35.4, 36.5, 40.6, 46.8, 51.9, 58.2, 75.0, 75.8, 78.8, 80.0, 80.2, 81.3, 153.5, 154.0, 171.5; MS (ESI): *m/z* (%): 470 (45) [M+H$^+$], 492 (100) [M+Na$^+$]. Anal. Calcd for C$_{25}$H$_{43}$NO$_7$: C, 63.94; H, 9.23; N, 2.98. Found: C, 64.10; H, 9.45; N, 2.79.

3.4.2. (2*S*,4*R*)-Di-*tert*-butyl 4-{[(1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyloxy]carbonyloxy}pyrrolidine-1,2-dicarboxylate (4f). Pale yellow oil (437 mg, 95%); [α]$_D$ +25.0 (*c* 1.0, CHCl$_3$); ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.68–2.53 (series of m, 38H, 3×CH$_3$, 2×C(CH$_3$)$_3$, 3×CH$_2$, 3×CH, C*H*$_2$CHN), 3.50–3.77 (m, 2H, CH$_2$N), 4.25 (m, 1H, CHN), 4.50 (m, 1H, CHC*H*O), 5.12 (m, 1H, OCH); ^{13}C NMR (50 MHz, CDCl$_3$) δ 16.1, 20.6, 21.8, 23.1, 25.9, 27.8, 28.2, 31.3, 33.9, 35.4, 36.5, 40.6, 46.9, 51.8, 52.0, 58.1, 74.9, 75.8, 78.7, 79.9, 80.1, 81.2, 153.5, 154.0, 171.4, 171.5; IR [film, (cm^{-1})]: 1742 and 1709 (C=O); MS (ESI): *m/z* (%): 470 (40) [M+H$^+$], 492 (100) [M+Na$^+$]. Anal. Calcd for C$_{25}$H$_{43}$NO$_7$: C, 63.94; H, 9.23; N, 2.98. Found: C, 64.08; H, 9.45; N, 2.76.

3.4.3. 5-[(3*R*,5*S*)-1,5-Bis(*tert*-butoxycarbonyl)pyrrolidin-3-yloxy]-5-oxopentanoic acid (6). To a stirred solution of **3** (287 mg, 1.00 mmol) in CH$_2$Cl$_2$ (7 mL), a solution of glutaric anhydride (224 mg, 2.00 mmol) in CH$_2$Cl$_2$ (3 mL) was added, followed by DMAP (16 mg, 0.13 mmol). The stirring was continued for 36 h at rt. The solvent was then removed under reduced pressure, water (8 mL) was added and the product was extracted with EtOAc (3×8 mL). The combined organic layers were washed consecutively with 1 M KHSO$_4$ (1×20 mL) and H$_2$O (1×25 mL) and dried over Na$_2$SO$_4$. The solvent was evaporated and the residue was purified by column chromatography using EtOAc as eluent to give **6**. Light yellowish oil (300 mg, 75%); [α]$_D$ −37.3 (*c* 1.1, CHCl$_3$); ^{1}H NMR (200 MHz, CDCl$_3$) δ 1.47 [br, 18H, 2×C(CH$_3$)$_3$], 1.92–2.08 (m, 2H, CH$_2$C*H*$_2$CH$_2$), 2.17 (m, 1H, C*H*HCHN), 2.27–2.51 (m, 5H, CH*H*CHN, C*H*$_2$-CH$_2$C*H*$_2$), 3.40–3.78 (m, 2H, CH$_2$N), 4.25 (m, 1H, CHN), 5.27 (m, 1H, OCH); ^{13}C NMR (50 MHz, CDCl$_3$) δ 19.6, 27.8, 27.9, 28.2, 29.6, 32.8, 33.1, 35.5, 36.5, 51.9, 52.1, 58.4, 71.9, 72.8, 80.3, 80.5, 81.5, 153.9, 171.6, 172.3, 177.9; IR [film, (cm^{-1})]: 1738 and 1705 (C=O); MS (FAB): *m/z* (%): 402 (10) [M+H$^+$], 424 (2.5) [M+Na$^+$]. Anal. Calcd for C$_{19}$H$_{31}$NO$_8$: C, 56.84; H, 7.78; N, 3.49. Found: C, 56.65; H, 7.69; N, 3.48.

3.4.4. (*S*)-Methyl 2-[2,4-bis(*tert*-butoxycarbonyl)butanamido]acetate (8). To a stirred solution of (*S*)-2,4-bis(*tert*-butoxycarbonyl)butanoic acid (**7**) (318 mg, 1.00 mmol) in CH$_2$Cl$_2$ (10 mL) were added methyl glycinate hydrochloride (126 mg, 1.00 mmol), 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride (211 mg, 1.10 mmol), 1-hydroxybenzotriazole (135 mg, 1.00 mmol) and Et$_3$N (0.16 mL, 1.10 mmol). The reaction mixture was stirred for 1 h at 0 °C and for 16 h at rt. The solvent was removed, water (8 mL) was added and the product was extracted with EtOAc (3×8 mL). The combined organic layers were washed consecutively with 1 M KHSO$_4$ (1×10 mL), H$_2$O (1×10 mL), 5% aqueous NaHCO$_3$ (1×10 mL), H$_2$O (1×10 mL), dried (Na$_2$SO$_4$), and the solvent was evaporated to give **8**. White solid (292 mg, 75%); mp 100–101 °C; [α]$_D$ −29.4 (*c* 1.0, CHCl$_3$); ^{1}H NMR (200 MHz, CDCl$_3$) δ 1.40 [br, 18H, 2×C(CH$_3$)$_3$], 1.70–2.00 (m, 2H, CHC*H*$_2$), 3.05 (m, 1H, C*H*HNHOCO), 3.45 (m, 1H, CH*H*NHOCO), 3.69 (s, 3H, OCH$_3$), 3.85–4.35 (m, 3H, CH, C*H*$_2$COOCH$_3$), 5.22 (m, 1H, CH$_2$N*H*OCO), 5.50 (d, *J*=8 Hz, 1H, CHN*H*OCO), 8.64 (m, 1H, NHCO); ^{13}C NMR (50 MHz, CDCl$_3$) δ 28.2, 28.3, 34.2, 36.7, 41.1, 51.6, 52.2, 79.5, 79.9, 155.6, 156.7, 170.1, 172.1; IR [KBr, (cm^{-1})]: 3331 (N–H), 1754, 1705 and 1689 (C=O), 1519 (N–H); MS (ESI): *m/z* (%): 389 (25) [M$^+$]. Anal. Calcd for C$_{17}$H$_{31}$N$_3$O$_7$: C, 52.43; H, 8.02; N, 10.79. Found: C, 52.56; H, 7.98; N, 10.80.

3.4.5. (2*S*,4*R*)-Di-*tert*-butyl 4-(5-((*S*)-3-(5-((3*R*,5*S*)-1,5-bis(*tert*-butoxycarbonyl)pyrrolidin-3-yloxy)-5-oxopentanamido)-4-(2-methoxy-2-oxoethylamino)-4-oxobutylamino)-5-oxopentanoyloxy)pyrrolidine-1,2-dicarboxylate (9). The *tert*-butoxycarbonyl groups of **8** (390 mg, 1.00 mmol) were removed by treatment with 5 N HCl in Et$_2$O (14 mL) for 1 h at rt. After evaporation, Et$_2$O was added and the product was filtered and recrystallised from MeOH/Et$_2$O. The product was suspended in CH$_2$Cl$_2$ (8 mL) and to the solution were added **6** (802 mg, 2.00 mmol), EDC (422 mg, 2.20 mmol), HOBt (270 mg, 2.00 mmol) and Et$_3$N (0.70 mL, 5.00 mmol). The reaction mixture was stirred for 1 h at 0 °C and for 30 h at rt. The solvent was removed, water (15 mL) was added and the product was extracted with EtOAc (3×10 mL). The combined organic layers were

washed consecutively with 1 M $KHSO_4$ (1×25 mL), H_2O (1×30 mL), 5% aqueous $NaHCO_3$ (1×25 mL), H_2O (1×30 mL), dried (Na_2SO_4), and the solvent was evaporated to give a residue, which was further purified by column chromatography using initially $CHCl_3$ and finally $CHCl_3$/MeOH 95:5 as eluents to give **9**. Colourless oil (670 mg, 70%); $[\alpha]_D$ −48.0 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.48 [br, 36H, 4×$C(CH_3)_3$], 1.68–2.75 (m, 18H, 2×$CH_2CH_2CH_2$, $CHCH_2CH_2$, 2×$OCHCH_2CHN$), 2.92 (m, 1H, $CHCH_2CHH$), 3.40–4.08 (m, 9H, $CHCH_2CHH$, 2×CH_2N, OCH_3, $CHHCOOCH_3$), 4.10–4.35 (m, 3H, $CHHCOOCH_3$, 2×$OCHCH_2CHN$), 4.47 (m, 1H, $CHCH_2$-CH_2), 5.17–5.35 (m, 2H, 2×OCH), 6.68–7.00 (m, 2H, 2×NHCO), 8.26 (m, 1H, NHCO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.4, 20.8, 28.0, 28.3, 33.3, 33.5, 34.2, 35.2, 35.3, 35.5, 35.7, 36.3, 36.5, 41.1, 49.9, 51.8, 52.0, 52.1, 52.3, 58.4, 71.7, 72.0, 72.7, 80.4, 81.5, 153.9, 170.1, 171.6, 171.7, 171.9, 172.5, 172.9, 173.7; IR [film, (cm^{-1})]: 3315 (N–H), 1735, 1696, 1683 and 1650 (C=O), 1535 (N–H); MS (FAB): *m/z* (%): 956 (47) [M+H$^+$]. Anal. Calcd for $C_{45}H_{73}N_5O_{17}$: C, 56.53; H, 7.70; N, 7.33. Found: C, 56.55; H, 7.71; N, 7.35.

3.4.6. Compound 12. To a solution of **3** (575 mg, 2.00 mmol), in dichloromethane (10 mL), (1*R*,3*S*)-(+)-camphoric acid (200 mg, 1.00 mmol) was added, followed by DCC (454 mg, 2.20 mmol) and DMAP (24 mg, 0.20 mmol). The mixture was stirred for 36 h at rt. The dicyclohexylurea was filtered off, the solvent was removed, water (12 mL) was added and the product was then extracted with EtOAc (3×10 mL). The combined organic layers were washed consecutively with 1 M $KHSO_4$ (1×25 mL), H_2O (1×30 mL), $NaHCO_3$ 10% (1×25 mL), H_2O (1×30 mL) and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography using a mixture of EtOAc/petroleum ether 40–60 1:1 as eluent to give **12**. Colourless oil (547 mg, 74%); $[\alpha]_D$ −32.8 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 0.92 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.38 [br, 36H, 4×$C(CH_3)_3$], 1.75–2.40 (series of m, 8H, 2×CH_2, 2×CH_2CHN), 2.75 (m, 1H, CHCO), 3.30–3.70 (m, 4H, 2×CH_2N), 4.10–4.26 (m, 2H, 2×CHN), 5.10–5.25 (m, 2H, 2×OCH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.9, 19.5, 19.9, 20.5, 24.2, 27.6, 27.7, 28.0, 28.1, 32.8, 33.2, 35.2, 36.3, 43.4, 51.7, 51.9, 54.0, 58.1, 71.7, 72.5, 79.8, 80.0, 81.1, 153.6, 153.8, 171.2, 171.3, 172.0; IR [film, (cm^{-1})]: 1806, 1762, 1741 and 1703 (C=O); MS (ESI): *m/z* (%): 739 (15) [M+H$^+$]. Anal. Calcd for $C_{38}H_{62}N_2O_{12}$: C, 61.77; H, 8.46; N, 3.79. Found: C, 61.90; H, 8.50; N, 3.82.

3.5. General procedure for the removal of Boc and Bu^t protecting groups

Boc and Bu^t groups of **4a–f**, **9**, **12** (1.00 mmol) were removed by treatment with 5 N HCl in Et_2O (14 mL, 70 mmol) for 4 h at rt. After evaporation under reduced pressure to a small volume (1 mL), anhydrous Et_2O was added (5 mL) and the precipitated product was afforded through decantation.

3.5.1. (2*S*,4*R*)-4-[(1*S*,4*R*)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carbonyloxy]pyrrolidine-2-carboxylic acid hydrochloride (5a). White solid (334 mg, 96%); mp 219–221 °C; $[\alpha]_D$ −6.4 (*c* 1.0, DMF); ^1H NMR (200 MHz, CD_3OD) δ 0.97 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.57–2.75 (series of m, 6H, 2×CH_2, CH_2CHN), 3.58 (m, 1H, $CHHN$), 3.83 (dd, *J*=5.0, 13.6 Hz, 1H, $CHHN$), 4.63 (m, 1H, CHN), 5.67 (m, 1H, OCH); ^{13}C NMR (50 MHz, CD_3OD) δ 9.9, 17.0, 17.2, 28.1, 29.8, 31.6, 35.9, 52.2, 55.6, 56.1, 59.7, 75.3, 92.4, 167.9, 170.2, 179.9; MS (ESI): *m/z* (%): 312 (100) [M+H$^+$]. Anal. Calcd for $C_{15}H_{21}NO_6 \cdot HCl$: C, 51.80; H, 6.38; N, 4.03. Found: C, 52.01; H, 6.47; N, 4.11.

3.5.2. (2*S*,4*R*)-4-{[(1*R*,4*S*)-7,7-Dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl]methylsulfonyloxy}pyrrolidine-2-carboxylic acid hydrochloride (5b). White solid (363 mg, 95%); mp 164–166 °C; $[\alpha]_D$ −26.2 (*c* 1.0, MeOH); ^1H NMR (200 MHz, CD_3OD) δ 0.91 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.47–2.90 (series of m, 9H, 3×CH_2, CH_2CHN, CH), 3.35 (m, 1H, $CHHSO_2$), 3.62–3.87 (m, 3H, CH_2N, $CHHSO_2$), 4.64 (m, 1H, CHN), 5.59 (m, 1H, OCH); ^{13}C NMR (50 MHz, CD_3OD) δ 19.7, 19.9, 26.3, 27.7, 37.0, 43.4, 44.1, 49.1, 53.0, 59.2, 59.4, 80.8, 170.3, 216.6; MS (ESI): *m/z* (%): 346 (100) [M+H$^+$]. Anal. Calcd for $C_{15}H_{23}NO_6S \cdot HCl$: C, 47.18; H, 6.33; N, 3.67. Found: C, 47.02; H, 6.48; N, 3.85.

3.5.3. (2*S*,4*R*)-4-{[(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyloxy]carbonyloxy}pyrrolidine-2-carboxylic acid hydrochloride (5c). White solid (330 mg, 94%); mp 195–197 °C (dec); $[\alpha]_D$ −22.0 (*c* 1.0, H_2O); ^1H NMR (200 MHz, CD_3OD) δ 0.75–2.15 (series of m, 18H, 3×CH_3, 3×CH_2, 2×CH, $CHHCHN$), 2.35–2.72 (m, 2H, CH, $CHHCHN$), 3.58 (m, 1H, $CHHN$), 3.74 (dd, *J*=4.4, 13.6 Hz, 1H, $CHHN$), 4.45–4.66 (m, 2H, CHN, $CHCHO$), 5.37 (m, 1H, OCH); ^{13}C NMR (50 MHz, CD_3OD) δ 16.7, 21.0, 22.4, 24.4, 27.4, 32.6, 35.2, 35.8, 41.8, 48.4, 52.3, 59.5, 77.1, 80.3, 155.1, 170.4; MS (ESI): *m/z* (%): 314 (100) [M+H$^+$]. Anal. Calcd for $C_{16}H_{27}NO_5 \cdot HCl$: C, 54.93; H, 8.07; N, 4.00. Found: C, 54.80; H, 8.15; N, 4.15.

3.5.4. (2*S*,4*R*)-4-[(1*R*,4*S*)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carbonyloxy]pyrrolidine-2-carboxylic acid hydrochloride (5d). White solid (330 mg, 95%); mp 234–235 °C (dec); $[\alpha]_D$ −15.0 (*c* 1.0, DMF); ^1H NMR (200 MHz, CD_3OD) δ 0.96 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.58–2.70 (series of m, 6H, 2×CH_2, CH_2CHN), 3.56 (m, 1H, $CHHN$), 3.80 (dd, *J*=4.8, 13.6 Hz, 1H, $CHHN$), 4.53 (m, 1H, CHN), 5.62 (m, 1H, OCH); ^{13}C NMR (50 MHz, CD_3OD) δ 9.8, 17.0, 17.1, 28.1, 29.8, 31.6, 36.0, 52.2, 55.7, 56.1, 60.2, 75.3, 92.4, 168.0, 168.3, 179.9; MS (FAB): *m/z* (%): 312 (97) [M+H$^+$]. Anal. Calcd for $C_{15}H_{21}NO_6 \cdot HCl$: C, 51.80; H, 6.38; N, 4.03. Found: C, 52.08; H, 6.50; N, 4.09.

3.5.5. (2*S*,4*R*)-4-{[(1*S*,4*R*)-7,7-Dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl]methylsulfonyloxy}pyrrolidine-2-carboxylic acid hydrochloride (5e). White solid (363 mg, 95%); mp 184–186 °C; $[\alpha]_D$ +15.2 (*c* 1.0, DMF); ^1H NMR (200 MHz, CD_3OD) δ 0.91 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.42–2.87 (series of m, 9H, 3×CH_2, CH_2CHN, CH), 3.35 (m, 1H, $CHHSO_2$), 3.64–3.83 (m, 3H, $CHHSO_2$, CH_2N), 4.65 (m, 1H, CHN), 5.59 (m, 1H, OCH); ^{13}C NMR (50 MHz, CD_3OD) δ 19.7, 19.9, 26.4, 27.7, 36.7, 43.4,

44.1, 49.2, 53.1, 59.3, 59.4, 80.7, 170.3, 216.4; MS (FAB): *m/z* (%): 346 (100) [M+H$^+$]. Anal. Calcd for $C_{15}H_{23}NO_6S\cdot HCl$: C, 47.18; H, 6.33; N, 3.67. Found: C, 46.98; H, 6.42; N, 3.81.

3.5.6. (2*S*,4*R*)-4-{[(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyloxy]carbonyloxy}pyrrolidine-2-carboxylic acid hydrochloride (5f). White solid (333 mg, 95%); mp 120–122 °C; $[\alpha]_D$ −22.0 (*c* 1.0, H_2O); ^{1}H NMR (200 MHz, CD_3OD) δ 0.70–2.15 (series of m, 18H, 3×CH_3, 3×CH_2, 2×CH, C*H*HCHN), 2.35–2.74 (m, 2H, CH, CH*H*CHN), 3.53 (m, 1H, C*H*HN), 3.74 (dd, *J*=4.4, 13.6 Hz, 1H, CH*H*N), 4.44–4.65 (m, 2H, CHN, CHC*H*O), 5.38 (m, 1H, OCH); ^{13}C NMR (50 MHz, CD_3OD) δ 16.6, 21.1, 22.4, 24.3, 27.2, 32.6, 35.2, 35.9, 41.7, 48.4, 52.3, 59.6, 77.1, 80.3, 155.1, 170.6; MS (FAB): *m/z* (%): 314 (60) [M+H$^+$]. Anal. Calcd for $C_{16}H_{27}NO_5\cdot HCl$: C, 54.93; H, 8.07; N, 4.00. Found: C, 54.83; H, 8.17; N, 4.19.

3.5.7. (2*S*,4*R*)-4-(5-((*S*)-3-(5-((3*R*,5*S*)-5-Carboxypyrrolidin-3-yloxy)-5-oxopentanamido)-4-(2-methoxy-2-oxoethylamino)-4-oxobutylamino)-5-oxopentanoyloxy)pyrrolidine-2-carboxylic acid dihydrochloride (10). Colourless viscous oil (690 mg, 96%); $[\alpha]_D$ −24.5 (*c* 1.0, H_2O); ^{1}H NMR (200 MHz, D_2O) δ 1.75–2.10 (m, 6H, 2×$CH_2CH_2CH_2$, CH_2CH_2CH), 2.17–2.50 (m, 10H, 2×$CH_2CH_2CH_2$, 2×OCHC*H*HCHN), 2.50–2.74 (m, 2H, 2×OCHCH*H*CHN), 3.20–3.75 (series of m, 9H, CH_2CH_2CH, CH_3O, 2×$OCHCH_2N$), 3.94–4.05 (m, 2H, CH_2COOCH_3), 4.35 (m, 1H, CH_2CH_2CH), 4.49–4.65 (m, 2H, 2×$OCHCH_2CHN$), 5.44–5.50 (m, 2H, 2×OCH); ^{13}C NMR (50 MHz, D_2O) δ 22.9, 23.1, 33.1, 35.5, 37.0, 37.3, 37.5, 38.3, 39.7, 43.8, 53.7, 54.0, 56.0, 61.5, 72.4, 76.1, 174.3, 175.7, 177.0, 177.1, 178.6, 178.8. Anal. Calcd for $C_{27}H_{41}N_5O_{13}\cdot 2HCl$: C, 45.26; H, 6.05; N, 9.77. Found: C, 45.27; H, 6.12; N, 9.80.

3.5.8. Compound 13. White solid (490 mg, 98%); mp 115–117 °C; $[\alpha]_D$ −4.1 (*c* 1.0, MeOH); ^{1}H NMR (200 MHz, CD_3OD) δ 1.03 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.70–2.90 (series of m, 9H, 2×CH_2, 2×CH_2CHN, CHCO), 3.50–3.75 (m, 4H, 2×CH_2N), 4.60 (m, 2H, 2×CHN), 5.45 (m, 2H, 2×OCH); ^{13}C NMR (50 MHz, CD_3OD) δ 14.4, 20.3, 20.6, 20.8, 25.3, 33.8, 34.6, 34.7, 35.8, 52.3, 55.6, 59.7, 74.1, 170.7, 173.7; MS (FAB): *m/z* (%): 411 (100) [M$^+$ −CH_3]. Anal. Calcd for $C_{20}H_{30}N_2O_8\cdot 2HCl$: C, 48.10; H, 6.46; N, 5.61. Found: C, 47.99; H, 6.52; N, 5.81.

3.6. General procedure for the preparation of aldol products

To a mixture of anhydrous DMF (1.60 mL) and anhydrous acetone (0.40 mL) was added the corresponding aldehyde (0.20 mmol) followed by the catalysts **5a–f** or **10** or **13** (10–30 mol%) and an equivalent amount of Et_3N. The resulting mixture was stirred at rt for 18–24 h. Following aqueous workup with saturated ammonium chloride solution and extraction several times with EtOAc, the combined organic layers were dried (Na_2SO_4), and the solvent was evaporated. The pure aldol products were obtained by column chromatography using a mixture of EtOAc/petroleum ether 40–60 1:1 as eluent.

3.6.1. (4*R*)-(4-Nitrophenyl)-4-hydroxy-2-butanone[2b] (14) ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.21 (s, 3H, CH_3), 2.83 (m, 2H, CH_2), 3.56 (d, *J*=3.2 Hz, 1H, OH), 5.25 (m, 1H, CH), 7.52 (d, *J*=7.0 Hz, 2H, C_6H_4), 8.20 (d, *J*=7.0 Hz, 2H, C_6H_4); HPLC (Daicel Chiralpak AD-RH, CH_3CN/H_2O 30:70, flow rate 0.5 mL/min, λ=254 nm): t_R (major)= 16.58 min, t_R (minor)=20.26 min.

3.6.2. (4*R*)-(4-Bromophenyl)-4-hydroxy-2-butanone[2b] (15) ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H, CH_3), 2.82 (m, 2H, CH_2), 3.40 (d, *J*=3.0 Hz, 1H, OH), 5.12 (m, 1H, CH), 7.24 (d, *J*=8.4 Hz, 2H, C_6H_4), 7.47 (d, *J*=8.4 Hz, 2H, C_6H_4); HPLC (Daicel Chiralpak AD-RH, CH_3CN/H_2O 30:70, flow rate 0.5 mL/min, λ=254 nm): t_R (major)= 27.31 min, t_R (minor)=30.77 min.

3.6.3. (4*R*)-(2-Chlorophenyl)-4-hydroxy-2-butanone[2b] (16) ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22 (s, 3H, CH_3), 2.64–3.03 (m, 2H, CH_2), 3.61 (br, 1H, OH), 5.56 (m, 1H, CH), 7.19–7.34 (m, 3H, C_6H_4), 7.64 (d, *J*=7.7 Hz, 1H, C_6H_4); HPLC (Daicel Chiralpak AD-RH, CH_3CN/H_2O 30:70, flow rate 0.5 mL/min, λ=254 nm): t_R (major)= 15.63 min, t_R (minor)=18.07 min.

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