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Tetrahedron: *Asymmetry* 17 (2006) 2235–2239
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Improved synthesis of the valuable peptidomimetic intermediate 3-azido-4-hydroxy cyclopentanoic acid

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Received 22 June 2006; accepted 4 July 2006
Available online 27 July 2006

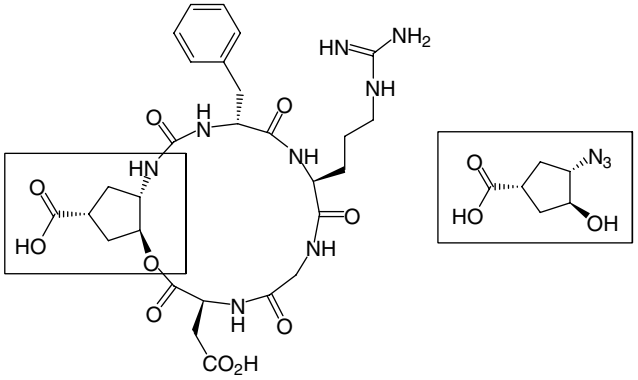
Abstract—An improved synthesis of 3-azido-4-hydroxy cyclopentanoic acid **2** is presented. This molecule is useful as a synthetic scaffold for β-turn mimetics on solid phase, with the selectivity of the turns being dependent on the diastereomer employed. A high diastereoselectivity in the synthesis of this molecule in solution is reported, which may then be attached to the solid phase for the synthesis of peptidomimetic libraries.

1. Introduction

Mimics of β-turns are important targets in medicinal chemistry.[1–3] The RGD turn associated with cell adhesion remains one of the most important motifs, with relevance to the prevention of metastasis and angiogenesis.[4] While the precise nature of the binding between an RGD turn and its integrin protein target in vivo remains unclear,[5] a critical requirement for effective peptide mimicry is the three-dimensional arrangement of the amino acid residues in the turn, which in general terms is highly dependent on the type of scaffold used as the basis for the mimic.[6]

We recently pursued the synthesis of an RGD mimic **1** reported by Jacobsen.[7] The amino acids are here built onto a core α-amino alcohol derived from an asymmetric epoxide ring opening with an azide.[8] The binding selectivity of the resultant mimics for two important integrin types was highly dependent on the diastereomer of this core unit. Control of the stereochemistry in similar reactions is also important in the synthesis of various inhibitors of HIV reverse transcriptase.[8–10]

In the original communication,[7] the asymmetric ring opening was performed on the solid phase, where the diastereomerically pure epoxide had been previously attached. We instead wished to synthesise the core 3-azido-4-hydroxy cyclopenanoic acid **2** in quantity in solution for attachment to various solid supports for library synthesis. The retrosynthetic routes to this molecule are shown (Scheme 1), and converge on the commercially available cyclopent-3-enecarboxylic acid. The first asymmetric step in the synthesis is epoxidation of the double bond. The *anti*-diastereomer is required for the present applications. To the best of our knowledge, there is no report on the epoxidation of the unprotected acid **6**, while the unprotected alcohol **7** is known to give a product *anti*:*syn* ratio of approximately 60:40.[11] Sterically the *anti*-diastereomer is favoured, but hydrogen-bonding interactions between the pendant group and the epoxidation reagent reduce the selectivity.



1 **2**

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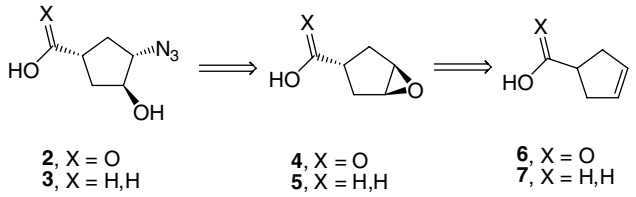
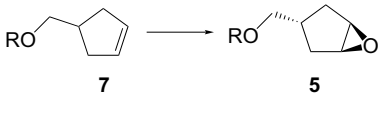
doi:10.1016/j.tetasy.2006.07.001



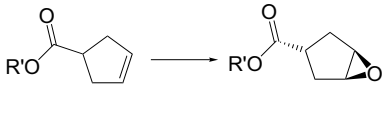
Scheme 1. Retrosynthetic analysis of 3-azido-4-hydroxy cyclopentanoic acid.

Several protecting groups have been previously employed on **6** and **7** to increase the *anti*:*syn* ratio (Scheme 2).[8–10,12–15] For the protected alcohol, it is known that large silyl-protecting groups give good diastereoselectivities for the epoxidation. In our hands, the TBDMS-protected alcohol gave a 78:22 *anti*:*syn* diastereomeric ratio, and even though we and others[9] have been unable to effect their separation, a report has appeared in which the diastereomeric alcohols **5** are separable.[15] Ultimately we did not want to proceed via the alcohol series, mainly because the eventual ring-opened product **3** of the sequence would require oxidation of the primary alcohol to give a carboxylic acid in the presence of a secondary alcohol (i.e., **3** to **2**), and we have been unsuccessful in identifying suitable conditions for this transformation. The epoxidation of protected cyclopent-3-ene carboxylic esters has been less well studied. Jacobsen found that the ethyl ester gave a 75:25 *anti*:*syn* ratio with *m*-CPBA;[8] higher selectivities of 92:8 were possible with molybdenum-catalysed epoxidation with hydroperoxides, but competing decomposition of the products gave diminished yields. Earlier reports on the methyl ester gave selectivities of between 75:25 and 87:13 in favour of the *anti*-diastereomer depending on the conditions employed.



7 **5**

	R	*anti*:*syn* ratio	Ref
7a	Bz	70:30; 75:25	12;14
7b	Fmoc	75:25	12
7c	Ph_3Si	80:20	12
7d	TBDMS	89:11; 75:25	12;10;15



6 **4**

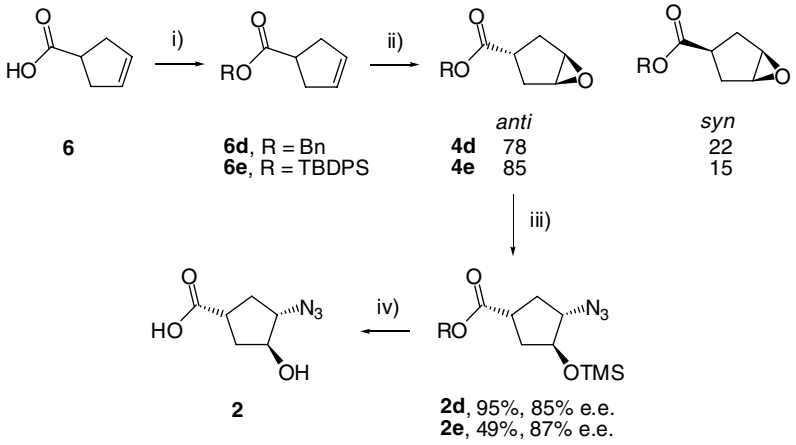
	R	*anti*:*syn* ratio	Ref
6a	Me	75:25; 87:13	13;14;9;13
6b	Et	75:25	8
6c	Pinanoyl	75:25	14

Scheme 2. Literature diastereoselectivity for epoxidation of protected cyclopent-3-ene carboxylic acid and cyclopent-3-enylmethanol.

2. Results and discussion

We have explored two alternative protecting groups for the carboxylic acid as a means to access diastereomerically pure 3-azido-4-hydroxy cyclopentanoic acid (Scheme 3). Benzyl ester **6d** gave a reasonable *anti*:*syn* selectivity of 78:22 in the epoxidation reaction, while the TBDPS ester gave a superior 85:15 ratio. These compare favourably with the best literature values. It is surprising to note that these large groups give a similar selectivity to the literature report for the epoxidation of the far less bulky methyl ester. We found that TBDMS and trityl esters of **6** are too labile for the purification of the epoxidation reaction products.

The major *anti*-diastereomer of the epoxide benzyl ester **4d** may be deprotected to give **4** under standard hydrogenolysis conditions (H_2, Pd/C, 1 atm) quantitatively. We



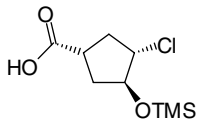
6 **6d**, R = Bn; **6e**, R = TBDPS

	anti	*syn*
4d	78	22
4e	85	15

2 **2d**, 95%, 85% e.e.; **2e**, 49%, 87% e.e.

Scheme 3. Synthesis of 3-azido-4-hydroxy cyclopentanoic acid via benzyl- and TBDPS-protection of the carboxylic acid. Reagents and conditions: (i) for **6d**: BnBr, TBAI, $NaHCO_3$, H_2O/CH_2Cl_2, 70%; for **6e**: TBDPSCl, DIPEA, DMAP, CH_2Cl_2, 71%; (ii) *m*-CPBA, CH_2Cl_2, 81%; (iii) $TMSN_3$, (1*R*,2*R*)-(−)-[1,2-cyclohexanediamino-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)]chromium(III) chloride (2–5 mol %), Et_2O; (iv) from **2d**, NaOH/THF, 82%; from **2e**, TBAF/THF, 70%.

attempted the asymmetric ring-opening reaction on this free acid, with disappointing results. At low catalytic loadings (4 mol %) of Jacobsen's chromium(III) salen catalyst, the ring-opening reaction was extremely slow and after 40 h, epoxide **4** clearly remained. Extending the reaction times and increasing catalyst loading (to 8 mol %) also proved ineffective with complex reaction mixtures being formed (as judged by the ^{1}H NMR of the crude reaction mixture). We attempted to purify the reaction mixture by attaching the crude material onto a 2-chlorotrityl chloride-based resin, reasoning that TFA cleavage would then yield pure carboxylic acid **2**. Unfortunately, this procedure resulted in a mixture of two materials being isolated, the target carboxylic acid **2** and a second similar material which we believe to be chloride **2f**. Jacobsen has previously noted competing chloride incorporation as a minor contaminant in a high yielding ring-opening reaction and attributed this to the presence of the chloride anion in the pre-catalyst.[16] Presumably, due to the lower overall yield observed herein and the much higher catalyst loading required, the contamination is more significant here.



2f

Thus asymmetric ring opening with the Cr-salen catalyst and TMS-azide of the major diastereomers of epoxides **4d** and **4e** was investigated and found to give good enantiomeric excesses in both cases. Ring opening of the benzyl-protected ester **4d** proceeded more smoothly, however, giving **2d** in nearly quantitative yield and 85% ee. Removal of the protecting groups in both cases was facile and **2** was most conveniently obtained by sodium hydroxide-mediated cleavage of both benzyl and TMS protecting groups.

Attachment of 3-azido-4-hydroxy cyclopentanoic acid (Scheme 4) to a solid support can be achieved with a 2-chlorotrityl chloride-based resin, **8**. The supported azido alcohol **9** was loaded with an Fmoc-protected amino acid to give ester **10**. The overall yield of the loading steps (cyclopentanoic acid and amino acid) was found to be ca. 40%, as determined by a combination of Fmoc cleavage and quantitation, mass gain of the two resin-bound species and chlorine elemental analysis.

3. Conclusion

In conclusion we have described short, new routes to diastereomerically pure 3-azido-4-hydroxy cyclopentanoic acid **2**, which should be of wide use in the preparation of β-turn mimics on solid phase, and for the synthesis of nucleoside analogues.

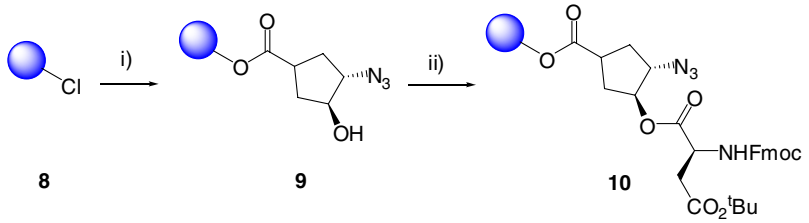
4. Experimental

4.1. Cyclopent-3-enecarboxylic acid benzyl ester 6d

A solution of 3-cyclopenten-1-carboxylic acid (1 mmol, 112 mg) in saturated $NaHCO_3$ (2 mL) was added to a solution of benzyl bromide (1.1 equiv, 1.1 mmol, 188 mg) and tetrabutylammonium iodide (TBAI) (20 mol %, 74 mg) in DCM (2 mL). The mixture was vigorously stirred at rt for 16 h, washed with water and the aqueous phase extracted with DCM (2 × 10 mL). The organic phases were collected, dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc, 9:1) to give **6d** as a colourless liquid (141 mg, 70%). TLC (*n*-hexane/EtOAc 9:1), $R_f = 0.56$; IR (thin film): 1732, 1419 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.34$ (m, 5H), 5.65 (s, 2H), 5.13 (s, 2H), 3.16 (tt, $J = 9.1$, 7.3 Hz, 1H), 2.96–2.64 (m, 4H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): $\delta = 175.6$, 136.5, 129.1, 128.6, 128.2 (2C), 66.3, 41.6, 36.4. HRMS (ESI) calcd for $[M+NH_4]^+$, $(C_{13}H_{18}O_2N)^+$ 220.1332, found 220.1332.

4.2. *trans*-3,4-Epoxycyclopentanecarboxylic acid benzyl ester *anti*-4d

To a cooled solution (0 °C) of **6d** (1 mmol, 202 mg) in DCM (10 mL) was added *m*-CPBA (1.3 equiv, 224 mg) in three portions. The solution was allowed to warm to room temperature and stirred at the same temperature for 4 h. The white precipitate formed was filtered and the solid residue washed with DCM. The organic layer was washed with saturated $NaHCO_3$ solution and 10% Na_2SO_4 solution. The organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. The two diastereoisomers were separated by flash column chromatography on silica gel (*n*-hexane/EtOAc, 9:1 to 7:3) to give the *anti*- and *syn*-epoxides as colourless liquids in 81% overall yield and diastereomeric ratio (*anti*:*syn*) 78:22.



8 **9** **10**

Scheme 4. Attachment of aspartic acid to solid-supported 3-azido-4-hydroxy cyclopentanoic acid. Reagents and conditions: (i) **2**, DIPEA, DCM/DMF; (ii) Fmoc-Asp(O^{t}Bu)–OH, EDC, DMAP, DMF.

4.2.1. *anti*-4d (major diastereoisomer). TLC (*n*-hexane/EtOAc 8:2), $R_f = 0.54$; IR (thin film) 1732, 1496, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz): $\delta = 7.22$ (m, 5H), 5.02 (s, 2H), 3.34 (s, 2H), 2.60 (app. quin, $J = 8.1$ Hz, 1H), 2.22 (dd, $J = 13.8$ and 8.1 Hz, 2H), 1.77 (dd, $J = 13.8$ and 9.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): $\delta = 174.5$, 136.2, 128.6, 128.2, 128.0, 66.2, 56.0, 37.5, 31.2. HRMS (ESI) calcd for $[M+Na]^+$, $(C_{13}H_{14}O_3Na)^+$ 241.0835, found 241.0832.

4.2.2. *syn*-4d (minor diastereoisomer). TLC (*n*-hexane/EtOAc 8:2), $R_f = 0.38$; IR (thin film) 1732, 1496, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz): $\delta = 7.33$ (m, 5H), 5.11 (s, 2H), 3.46 (s, 2H), 2.78–2.69 (m, 3H), 1.85 (dd, $J = 14.6$ and 9.1 Hz, 2H).

4.3. (1*R*,3*S*,4*S*)-3-Azido-4-trimethylsilanyloxy-cyclopentane-1-carboxylic acid benzyl ester 2d

To a solution of (1*R*,2*R*)-(−)-[1,2-cyclohexanediamino-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)]chromium(III) chloride (0.02 mol, 13 mg) in dry Et_2O was added *anti*-**4d** (1 mmol, 218 mg) under N_2. After 15 min, $TMSN_3$ (1.1 mmol, 127 mg) was added and the brown solution stirred at room temperature for 30 h. The solvent was removed in vacuo and the residue filtered through a plug of silica gel with *n*-hexane/EtOAc (8:2) to provide **2d** as a pale yellow oil (95% yield, 85% ee). The ee was determined by chiral HPLC (*n*-hexane/*i*-PrOH 99.7:0.3 CHIRACEL OD 0.45 × 25 cm, 1 mL/min). $R_t = 13.867$ min (minor enantiomer) and 15.527 min (major enantiomer). The other enantiomer was prepared following the same procedure using (1*S*,2*S*) catalyst ($R_t = 13.867$ min). Assignment of absolute stereochemistry is based on the assignments previously reported.[7] TLC (*n*-hexane/EtOAc 8:2), $R_f = 0.79$; IR (thin film) 2106, 1732, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz): $\delta = 7.34$ (m, 5H), 5.13 (s, 2H), 4.07 (dd, $J = 11.1$ and 5.4 Hz, 1H), 3.68 (dd, $J = 11.8$ and 6.9 Hz, 1H), 3.06 (app. quin, $J = 7.4$ Hz, 1H), 2.36–2.15 (m, 2H), 1.93–1.82 (m, 2H), 0.13 (s, 9H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): $\delta = 174.9$, 136.0, 128.7, 128.3, 128.2, 76.9, 68.0, 66.7, 39.1, 35.8, 31.8, 0.04. HRMS (ESI) calcd for $[M+H]^+$, $(C_{16}H_{24}N_3O_3Si)^+$ 334.1581, found 334.1581.

4.4. (1*R*,3*S*,4*S*)-3-Azido-4-hydroxy-cyclopentane-1-carboxylic acid 2

To a solution of **2d** (1 mmol, 333 mg) in THF (10 mL) was added 1 M NaOH (4 mL). The mixture was stirred at rt for 4 h. THF was evaporated and the aqueous phase extracted with DCM (three times). The aqueous phase was acidified with 10% HCl to pH 4 and concentrated. The residue was taken up with DCM and the precipitate filtered. The solid was rinsed with DCM, and the organic phase dried over $MgSO_4$ and concentrated in vacuo to give **2** as a pale yellow oil (82% yield). IR (thin film) 3700–2400 (broad), 3348, 2110, 1708, 1419 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz): $\delta = 6.50$ (br s, 1H), 4.17 (m, 1H), 3.76 (m, 1H), 3.18–2.98 (m, 1H), 2.49–2.10 (m, 2H), 2.10–1.84 (m, 2H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): $\delta = 180.6$, 76.6, 67.7, 39.1, 35.2, 32.0. HRMS (ESI) calcd for $[M+Na]^+$, $(C_6H_9N_3O_3Na)^+$ 194.0536, found 194.0535.

4.5. Cyclopent-3-enecarboxylic acid *tert*-butyldiphenylsilyl ester 6e

TBDPSCl (1.1 mmol, 306 mg) was added to a solution of 3-cyclopenten-1-carboxylic acid (1 mmol, 211 mg), DIPEA (2 mmol, 258 mg) and DMAP (10 mol %) in DCM (10 mL), and the mixture stirred overnight at rt. The reaction mixture was washed with brine and the aqueous layer extracted with DCM (3 × 20 mL). The organic phases were collected, dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash-chromatography on silica gel (*n*-hexane 100% to *n*-hexane/EtOAc, 7:3) to give **6e** as a clear liquid (248 mg, 71%). TLC (*n*-hexane/EtOAc 8:2), $R_f = 0.74$; IR (thin film): 1724, 1473, 1427 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz): $\delta = 7.66$ (m, 4H), 7.37 (m, 6H), 5.68 (s, 2H), 3.26 (m, 1H), 2.72 (m, 4H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): $\delta = 175.1$, 135.5, 132.2, 130.3, 129.3, 127.9, 43.6, 36.5, 27.2, 19.4. HRMS (ESI) calcd for $[M+Na]^+$, $(C_{22}H_{26}O_2SiNa)^+$ 373.1594, found 373.1593.

4.6. *anti*-3,4-Epoxycyclopentanecarboxylic acid *tert*-butyldiphenylsilyl ester *anti*-4e

To a cooled solution (0 °C) of **6e** (1 mmol, 366 mg) in DCM (10 mL) was added *m*-CPBA (1.3 equiv, 224 mg) in three portions. The solution was allowed to warm to room temperature and stirred at the same temperature for 4 h. The white precipitate formed was filtered and the solid residue rinsed with DCM. The organic layer was then washed with a saturated $NaHCO_3$ solution and 10% Na_2SO_4 solution. The organic phase was dried over $MgSO_4$ and concentrated. The two diastereoisomers were separated by flash column chromatography on silica gel (*n*-hexane/EtOAc 9:1 to 7:3) to give *anti*- and *syn*-epoxides as white solids in 81% overall yield and diastereomeric ratio (*anti*:*syn*) 85:15.

4.6.1. *anti*-4e (major diastereoisomer). TLC (*n*-hexane/EtOAc 8:2), $R_f = 0.53$; Mp: 82–83 °C; IR (thin film) 1716, 1427, 1330 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz): $\delta = 7.64$ (m, 4H), 7.39 (m, 6H), 3.52 (s, 2H), 2.83 (m, 1H), 2.42 (dd, $J = 14.1$ and 7.9 Hz, 2H), 1.92 (dd, $J = 14.1$ and 9.9 Hz, 2H), 1.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): $\delta = 173.9$, 135.4, 131.8, 130.3, 127.9, 56.4, 39.3, 31.3, 27.0, 19.3. HRMS (ESI) calcd for $[M+Na]^+$, $(C_{22}H_{26}O_3SiNa)^+$ 389.1543, found 389.1546.

4.6.2. *syn*-4e (minor diastereoisomer). TLC (*n*-hexane/EtOAc 8:2), $R_f = 0.40$; Mp: 93–95 °C; IR (thin film) 1716, 1427, 1330 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz): $\delta = 7.69$ (m, 4H), 7.37 (m, 6H), 3.50 (s, 2H), 2.80 (m, 3H), 1.88 (dd, $J = 14.6$ and 8.9 Hz, 2H), 1.11 (s, 9H).

4.7. (1*R*,3*S*,4*S*)-3-Azido-4-trimethylsilanyloxy-cyclopentane-1-carboxylic acid *tert*-butyldiphenylsilyl ester 2e

To a solution of (1*R*,2*R*)-(−)-[1,2-cyclohexanediamino-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)]chromium(III) chloride (0.05 mol, 33 mg) in dry Et_2O (5 mL) was added *anti*-**4e** (1 mmol, 366 mg) under N_2. After 15 min, $TMSN_3$ (3 mmol, 346 mg) was added and the brown solution stir-

red at rt for 72 h. The solvent was removed in vacuo and the residue filtered through a plug of silica gel with *n*-hexane/EtOAc (8:2) to provide **2e** as a pale yellow oil (49% yield, 87% ee). The ee was determined by chiral HPLC (*n*-hexane/*i*-PrOH 99.8:0.2 Chiracel OD 0.45 × 25 cm, 1 mL/min). $R_t = 13.837$ min (minor enantiomer) and 14.377 min (major enantiomer). The other enantiomer was prepared following the same procedure using (1*S*,2*S*) catalyst ($R_t = 13.837$ min). TLC (*n*-hexane/EtOAc 8:2), $R_f = 0.73$; IR (thin film) 2106, 1724, 1473 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz): $\delta = 7.67$ (m, 4H), 7.40 (m, 6H), 4.07 (m, 1H), 3.70 (m, 1H), 3.14 (m, 1H) 2.40–2.21 (m, 2H), 1.97–1.80 (m, 2H), 1.11 (s, 9H), 0.14 (s, 9H); ^{13}C NMR ($CDCl_3$, 67.5 MHz): $\delta = 174.2$, 135.4, 131.8, 130.4, 127.8, 77.8, 68.1, 40.9, 35.8, 32.0, 27.1, 19.4, 0.25. HRMS (ESI) calcd for $[M+Na]^+$, $(C_{25}H_{35}N_3O_3Si_2Na)^+$ 504.2109, found 504.2114.

4.8. (1*R*,3*S*,4*S*)-3-Azido-4-hydroxy-cyclopentane-1-carboxylic acid 2

To a solution of **2e** (0.54 mmol, 260 mg) in THF (5 mL) was added TBAF (2 equiv, 1.08 mmol, 341 mg) and the resulting solution stirred for 1 h at room temperature. The solvent was removed and the crude purified by flash column chromatography (EtOAc/MeOH, 9:1) to give **2** as a colourless liquid (65 mg, 70%). Spectroscopic data as above.

4.9. 2-Chlorotrityl-(1*R*,3*S*,4*S*)-3-azido-4-hydroxy-cyclopentane-1-carboxylate polystyrene 9

A solution of (1*R*,3*S*,4*S*)-3-azido-4-hydroxy-cyclopentane-1-carboxylic acid **2** (0.35 mmol, 60 mg) in DCM (5 mL) and DMF (1 mL) containing DIPEA (4 equiv, 1.4 mmol, 243 μL) was added to 2-chlorotrityl chloride resin **8** (207 mg, loading = 1.4 mmol g^{-1}) and the suspension gently stirred for 3 h. The resin was filtered and washed with DCM (3 × 10 mL) and then subjected to a second coupling under the same conditions. After 3 h, the resin was filtered and washed with DCM (3 × 10 mL) and dried in vacuo overnight to give **9** as a straw powder (241 mg, 87% yield by mass, implies[17] product resin loading is 1.18 mmol g^{-1} × 0.87 = 1.02 mmol g^{-1}). IR (suspension in DCM): 3500, 2110, 1732, 1708 cm^{-1}.

4.10. Coupling of aspartic acid to solid-supported azido alcohol 10

A solution of Fmoc–Asp(O^{t}Bu)–OH (3 equiv, 0.45 mmol, 189 mg), EDC (3 equiv, 0.45 mmol, 86 mg) and DMAP (3 equiv, 0.45 mmol, 55 mg) in DMF (5 mL) was added to a suspension of **9** (150 mg, ca. 0.15 mmol reactive sites) in DMF (1 mL). The mixture was bubbled in a flow of N_2 for 3 h. The resin was then filtered, washed with DMF (3 × 10 mL) and DCM (3 × 10 mL) and then dried in vacuo overnight to give **10** as a straw powder (174 mg, 40% by mass). IR (suspension in DCM): 2106, 1728, 1643, 1600 cm^{-1}.

The substitution level was determined spectrophotometrically by Fmoc cleavage: in a volumetric flask, a solution of piperidine (20%) in DMF (0.5 mL) was added to resin **10** (11.6 mg) and the mixture shaken for 15 min. DMF was then added to bring the volume to 50 mL. The reference solution was prepared in the same manner without the addition of the resin. The blank was used to zero the UV spectrophotometer. The absorbance of the sample solution at 301 nm was 0.428255. The substitution level was calculated from the equation:[18] ($Abs_{301\ nm}$ × vol (mL)/7800 × *m* (g)) and determined to be 0.236 mmol/g.

Acknowledgements

We would like to thank the EPSRC for funding (GR/T17014/01). We wish to acknowledge the use of the EPSRC's Chemical Database Service at Daresbury.[19]

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