RSC Advances

PAPER

Cite this: *RSC Adv.*, 2015, **5**, 19455

Received 23rd January 2015
Accepted 10th February 2015

DOI: 10.1039/c5ra01340b

www.rsc.org/advances

D-Glucose based syntheses of β-hydroxy derivatives of L-glutamic acid, L-glutamine, L-proline and a dihydroxy pyrrolidine alkaloid†

K. S. Ajish Kumar* and Subrata Chattopadhyay

The β-hydroxy derivatives of L-glutamic acid, L-glutamine and L-proline, useful for peptide/protein studies, were synthesized starting from D-glucose. The C2 carbon in D-glucose provided the carboxylic acid functionality, while the amino and β-hydroxy groups of the amino acids were amenable from the C3 and C4 hydroxy groups of the sugar, respectively. The key intermediate with appropriate carbon framework of the target molecules was constructed by homologation of a suitable azido-D-glucofuranose derivative using the Arndt–Eistert reaction.

Introduction

Amino acids and monosaccharides constitute the major building blocks of the complex molecular systems that are vital for life. There has been a constant effort to understand the structures and functions of such systems by synthesizing them either chemically or biologically.[1] Hence the importance of modified amino acids as ligating agents, in the synthesis of natural proteins has received considerable attention over the years.[2] These amino acids are also the key ingredients for the synthesis of modified proteins, that help in understanding the structure–activity relationship,[3] and lantibiotic[4a,b] study of the peptides of interest, besides providing peptidomimetic drugs.[4c] Native chemical ligation (NCL) forms the basis of modern chemical synthesis of native, modified or cyclic peptides and proteins of moderate sizes,[5] and is extensively used to synthesize complex protein targets.[2,6]

Although the NCL approach has enriched peptide ligation chemistry, the required thiol/selenol-containing amino acids, which are essential, are accessible only through lengthy syntheses. The nonproteinogenic amino acids, possessing suitably placed (at the β/γ-position) hydroxy group(s) along the side chain are useful precursors of the corresponding thiol and selenol derivatives, required for NCL. A few commercially available hydroxy derivatives of natural amino acids, such as, β-hydroxy phenylalanine, β-hydroxy valine, and β-hydroxy leucine have been transformed to the corresponding thiol intermediates and used in NCL.[7] Meanwhile, the β/γ-hydroxy derivatives of glutamic acid, glutamine, lysine, arginine, and aspartic acid have also been synthesized in different laboratories, and their mercapto derivatives are proven residues for the assembly of peptides using NCL.[8] Moreover, many of these hydroxy amino acids are constituents of several natural products with intrinsic biological function.[9] Overall, both as unnatural building blocks and target compounds, the β/γ-hydroxylated amino acids are attractive synthetic targets. Consequently, several target-specific[10] as well as multi-target oriented[11] syntheses of the hydroxy amino acids have been reported.

Designing a common strategy, for various bioactive molecules has vital significance in organic synthesis. This can provide an economically accessible pathway to an array of discrete compounds from a single starting molecule.[12] The natural amino acids glutamic acid (Glu), glutamine (Gln) and proline (Pro) possess a similar five-carbon skeleton. It was hypothesized that the synthesis of suitable hydroxy derivatives of these may be realized using a common strategy. Hence, in view of our interest in modified amino acid synthesis, applicable for protein synthesis and study,[13a–c] we formulated a general strategy for synthesizing the β-hydroxy derivatives of Glu (**1a**), Gln (**1b**) and Pro (**1c**) starting from inexpensive D-glucose. The corresponding β-hydroxy azido acids were also synthesized as the masked amino acids, because similar compounds are proven candidates for Staudinger ligation in peptides/proteins syntheses.[14] In addition, several derivatives of **1a–1c**, possessing different orthogonal ester protections (Me/allyl/benzyl) were synthesized so that they can be converted to free acids under different reaction conditions. Finally, in view of our interests on iminosugars,[13d,e] we have transformed one of the intermediates into a biologically important pyrrolidine alkaloid **2**. The chemical structures of the target compounds are shown in Fig. 1. Amongst the chosen targets, L-glutamate is an important nutrient in biochemical pathways like gluconeogenesis and ammonia detoxification,[15a] and also plays a major role

Bio-organic Division, Bhabha Atomic Research Centre, Trombay, Mumbai-400085, India. E-mail: ajish@barc.gov.in

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c5ra01340b

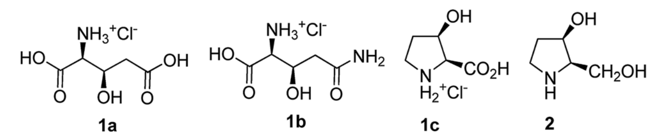


Fig. 1 Chemical structures of the synthesized compounds.

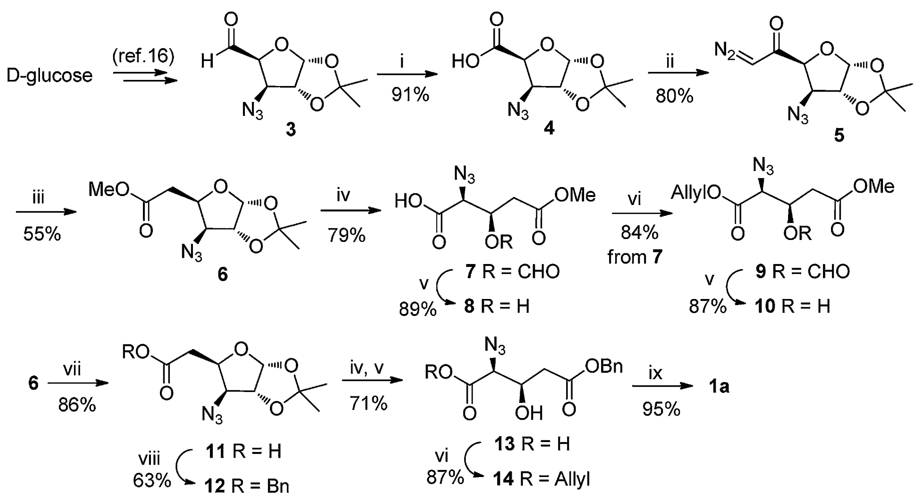
in learning, memory and neuronal development in mammalian central nervous system.[15b,c]

Results and discussion

In the retrosynthetic analysis, we conceived that the C2 carbon in D-glucose would furnish the carboxylic acid functionality, while the C3 and C4 hydroxy groups would provide the required amino/azido and β-hydroxy groups, respectively, of the targeted β-hydroxy amino acid derivatives. The synthesis commenced with the known D-glucose-derived azido aldehyde **3**,[13e,16] which was subjected to Pinnick oxidation ($NaClO_2$/NaH_2PO_4/30% H_2O_2)[17] to furnish the azido acid **4** in 91% yield. The acid **4** was activated as a mixed anhydride using ethyl chloroformate, and subsequently reacted with CH_2N_2 in Et_2O to give the α-diazo ketone **5** in 80% yield. Wolff rearrangement[18] of **5** in the presence of $PhCO_2Ag$ and Et_3N in MeOH afforded the homologated methyl ester **6** (55%) that served as the common intermediate for all the target amino acid derivatives.

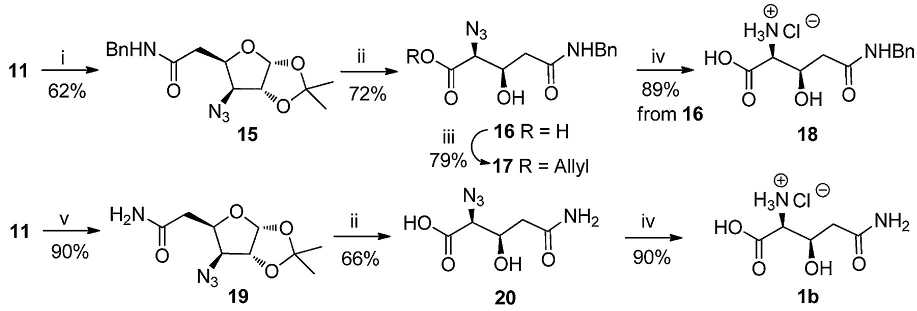
As the first application of **6**, we attempted its conversion to the β-hydroxy glutamic acid derivatives. To this end, its 1,2-acetonide group was deprotected using aqueous trifluoroacetic acid (TFA), and the resultant hemiacetal was subjected to cleavage with $NaIO_4$ to yield the intermediate azido aldehyde. This on Pinnick oxidation afforded the glutamic acid derivative **7**, containing a formylated C-3 hydroxy group (79%, over three steps). The formyl group in **7** could be selectively de-masked with aqueous saturated $NaHCO_3$ in THF to obtain the hydroxy acid **8** (89%). Compound **7** was also transformed to a fully masked Glu derivative **9** (84%) by reacting with allyl bromide in the presence of $NaHCO_3$ in anhydrous DMF. As above, the formyl group in **9** could be selectively removed with $NaHCO_3$ in THF at room temperature to obtain the β-hydroxy diester **10** in 87% yield.

Amino acid **10** is not suitable for Fmoc-SPPS as the side chain methyl ester is not easily cleavable under acidic/reduction condition. Hence it was thought of synthesizing a benzyl ester derivative **14** which would also serve as an ideal starting material for the various C3-substituted glutamic acid derivatives. For this, the ester function in **6** was hydrolyzed using LiOH in aqueous THF to afford the carboxylic acid **11** (86%), which on treatment with benzyl chloroformate (CbzCl) in the presence of Et_3N and 4-dimethylaminopyridine (DMAP) afforded the benzyl ester **12** in 63% yield. The ester **12** was directly transformed to the hydroxy azido acid **13** by a one-pot four-steps reaction sequence. Thus, acidic hydrolysis of the 1,2-acetonide function of **12**, $NaIO_4$ cleavage of the resultant diol to the intermediate aldehyde, followed by Pinnick oxidation and alkaline hydrolysis furnished the desired C-3 hydroxy acid **13** in 71% yield. This was esterified with allyl bromide and $NaHCO_3$ to afford another glutamic acid precursor **14** in 87% yield. Compound **14** is a template on which all the functionalities except the β-hydroxy group is protected and thus is a suitable precursor for the synthesis of C-3 substituted glutamic acid derivatives, *e.g.* β-mercapto glutamic acid. Such a transformation has already been established from similar hydroxy derivatives of various



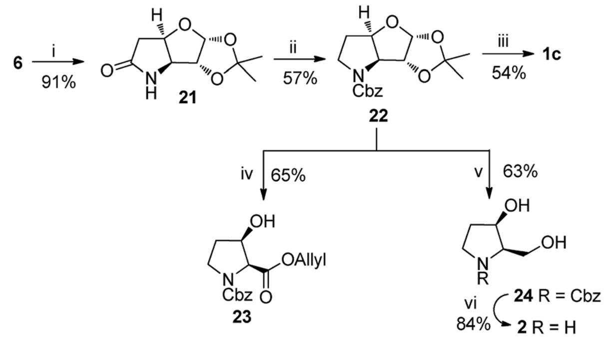
i) Aqueous $NaClO_2$, NaH_2PO_4, 30% H_2O_2, MeCN, 0 to 20 °C, 12 h; ii) (a) Ethyl chloroformate, Et_3N, 0 °C, 15 min; (b) CH_2N_2, Et_2O, 0 to 25 °C, 2.5 h; iii) $PhCO_2Ag$, Et_3N, MeOH, 25 °C, 20 min; iv) (a) TFA-H_2O (3:2), 0 °C, 6 h; (b) $NaIO_4$, 10% aqueous acetone, 0 °C, 30 min; (c) Aqueous $NaClO_2$, NaH_2PO_4, 30% H_2O_2, MeCN, 0 to 20 °C, 10 h; v) Aqueous saturated $NaHCO_3$, THF, 0 °C, 30 min; vi) Allyl bromide, $NaHCO_3$, DMF, 0 to 25 °C, 12 h; vii) Aqueous LiOH (0.3 M), THF, 0 °C, 1 h; viii) CbzCl, Et_3N, DMAP, MeCN, 25 °C, 14 h; ix) H_2 (80 psi), 10% Pd-C, MeOH-HCl, 25 °C, 12 h.

Scheme 1 Synthesis of β-hydroxy glutamic acid derivatives.



i) $BnNH_2$, HBTU, HOBt, DIEA, DMF, 25 °C, 8 h; ii) (a) TFA-H_2O (3:2), 0 °C, 2 h; (b) $NaIO_4$, 10% aqueous acetone, 0 °C, 15 min (for **16**) /40 min (for **20**); (c) Aqueous $NaClO_2$, NaH_2PO_4, 30% H_2O_2, MeCN, 0 to 20 °C, 10 h; (d) Aqueous saturated $NaHCO_3$, THF, 0 °C, 20 min; iii) Allyl bromide, $NaHCO_3$, DMF, 0 to 25 °C, 12 h; iv) H_2 (80 psi), 10% Pd-C, MeOH-HCl, 50 °C, 12 h; v) $(Boc)_2O$, $(NH_4)HCO_3.NH_2CO_2NH_4$, pyridine, MeCN, 25 °C, 5 h.

Scheme 2 Synthesis of β-hydroxy glutamine derivatives.



i) $HCOONH_4$, 10% Pd-C, MeOH, reflux, 2 h; ii) (a) $LiAlH_4$, THF, reflux, 2 h; (b) CbzCl, $NaHCO_3$, MeOH-H_2O (3:1), 0 °C, 3 h; iii) ref.11i; iv) (a) TFA-H_2O (3:2), 0 °C, 2 h; (b) $NaIO_4$, 10% aqueous acetone, 0 °C, 30 min; (c) Aqueous $NaClO_2$, NaH_2PO_4, 30% H_2O_2, MeCN, 0 to 20 °C, 10 h; (d) Aqueous saturated $NaHCO_3$, THF, 0 °C, 15 min; (e) Allyl bromide, $NaHCO_3$, DMF, 0 to 25 °C, 12 h; v) (a) TFA-H_2O (3:2), 0 °C, 3 h; (b) $NaIO_4$, 10% aqueous acetone, 0 °C, 30 min; (c) $NaBH_4$, THF-H_2O (4:1), 5 °C, 30 min; vi) H_2 (80 psi), 10% Pd/C, MeOH, 12 h.

Scheme 3 Synthesis of β-hydroxy proline derivatives and a pyrrolidine alkaloid.

amino acids.[7,8] Next, to confirm the stereochemistry at α and β-carbon in **14** it is necessary to convert it to a known derivative of β-hydroxy glutamic acid. For this azido acid **13** was opted as suitable substrate thus, a one pot reduction of azide functionality and debenzylation of ester using 10% Pd/C in MeOH–HCl afforded the fully unmasked β-hydroxy glutamic acid **1a** in 95% yield (Scheme 1). The spectral and analytical data of **1a** wherein agreement with that reported.[10q]

For the synthesis of the β-hydroxy glutamine **1b**, the benzyl amide of compound **11** was envisaged to serve as the masked amino equivalent of glutamine. Hence, compound **11** was coupled with benzylamine using HBTU and HOBt in the presence of diisopropylethylamine (DIEA) in DMF to afford the desired amide **15** (62%). This was transformed to the acid **16** (72%, over 4 steps), following the same sequence of reactions used to transform **12** to **13**. The acid **16** was converted to the *N*-benzyl azido analogue of β-hydroxy glutamine ester **17** (79%) by a base-catalyzed reaction with allyl bromide. However, catalytic hydrogenation of **16** over 10% Pd–C in MeOH even under a pressurized (80 psi H_2) condition led to reduction of the azide functionality only, and furnished the hydrochloride of β-hydroxy glutamyl benzamide **18** instead of the fully unprotected β-hydroxy glutamine hydrochloride **1b**. Our attempts to transform **16** to the desired product **1b** with HCO_2NH_4/10% Pd–C/MeOH at room temperature as well as under reflux were also unsuccessful.

In an alternative method, the acid **11** was converted to the amide **19** (90%) with di-*tert*-butyl dicarbonate ($(Boc)_2O$), $(NH_4)HCO_3 \cdot NH_2CO_2NH_4$ and pyridine in MeCN. This was converted to the acid **20** (*vide supra*), which on catalytic hydrogenation afforded **1b** in 90% yield. Azido acids, similar to **13**, **16**, and **20** are reported to be candidates for Staudinger ligation[14] in peptide/protein synthesis (Scheme 2).

Next, we focused our attention to the synthesis of the β-hydroxy proline hydrochloride **1c** and its derivative **23**. It was also realized that the intermediates, generated in the process may be transformed to the pyrrolidine derivatives such as **2** that are of our own interest as bioactive iminosugars.[13d,e] In this direction, compound **6** was subjected to a catalytic transfer hydrogenation (HCO_2NH_4/10% Pd–C/MeOH) to afford the bicyclic lactam **21** in 91% yield *via* a tandem azide reduction and cyclization. The lactam **21** was reduced with $LiAlH_4$ in THF under refluxing conditions, and the resultant amine functionality protected with CbzCl to furnish the *N*-Cbz protected bicyclic intermediate **22** in 57% yield (over two steps). The carbamate **22** was subsequently transformed to **1c** as reported earlier.[10i] We also synthesized the allyl ester of β-hydroxy proline from **22** without any purification of the intermediates. For this, compound **22** was sequentially subjected to an acid-catalyzed ketal hydrolysis, $NaIO_4$ cleavage, Pinnick oxidation and alkaline hydrolysis to obtain the crude acid. After drying *in vacuo*, the acid was subjected to a base-catalyzed allylation to furnish the β-hydroxy proline allyl ester **23** in 65% yield (over five steps). It is worth noting that the β-hydroxy esters **14**, and **23** could also serve as precursors for functional group transformations at the free hydroxy group, because the subsequent deallylation can be accomplished under neutral and non-reducing conditions using a Pd(II) catalyst (Scheme 3).

For the synthesis of the pyrrolidine iminosugar **2**, the carbamate **22** was treated with aqueous TFA to unmask the acetonide group, and the resultant diol cleaved with $NaIO_4$ to yield an aldehyde, which on $NaBH_4$ reduction afforded the *N*-Cbz protected pyrrolidine **24**. In the final step, the amino functionality in **24** was deprotected by catalytic hydrogenation over 10% Pd–C in MeOH to afford the desired dihydroxypyrrolidine **2** in 84% yield. Compound **2** is a versatile precursor for the 3,4-*cis*-substituted aza-sugars that show a wide range of biological activity. To our surprise unlike its enantiomer, only a few synthesis of **2** have been reported.[19]

Conclusions

In summary, we have devised an important strategy for the synthesis of β-hydroxy derivatives of glutamic acid, proline, glutamine, and a dihydroxy pyrrolidine alkaloid. Using this pathway different orthogonally protected hydroxy equivalent of glutamic acid, glutamine and proline are achievable. Noticeably, similar hydroxy amino acids with their functionalities protected as in **14**, and **23** have been used for the synthesis of corresponding thiol derivatives and has been used for peptide ligation (NCL). Inexpensive reagents, cheap starting materials, and simple chemical transformations make this strategy a useful one for the synthesis of various protecting group variants of glutamine, glutamic acid and proline. Our efforts to transform the hydroxy derivatives to mercapto variants and their application in peptide synthesis are in progress and will be reported elsewhere.

Experimental section

(3a*R*,5*S*,6*R*,6a*R*)-6-Azido-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]-dioxole-5-carboxylic acid 4

To a stirred solution of **3** (3.31 g, 15.52 mmol) in MeCN (50 mL) were added NaH_2PO_4 (0.484 g, 3.10 mmol) in H_2O (5 mL) and aqueous 30% H_2O_2 (2.3 mL, 17.1 mmol). The mixture was cooled to 0 °C, $NaClO_2$ (2.24 g, 24.84 mmol) in H_2O (6 mL) was dropwise added in 0.5 h and stirred at 20 °C till completion of the reaction (*cf.* 12 h, monitored by gas evolution). The reaction mixture was treated with sodium sulphate (1.00 g), and extracted with EtOAc (3 × 30 mL). Evaporation of solvent and column chromatography (silica gel, 10% MeOH/$CHCl_3$) of the residue gave **4** (3.25 g, 91%) as a thick liquid. $R_f = 0.30$ (30% MeOH/$CHCl_3$); $[\alpha]_D^{25}$ −31.3 (*c* 1.08, $CHCl_3$); ν_{max}/cm^{-1}: 3430, 2108, 1683 cm^{-1}; ^1H NMR: δ 8.19 (broad s, D_2O exchangeable, 1H), 6.01 (d, $J = 3.4$ Hz, 1H), 4.86 (d, $J = 3.7$ Hz, 1H), 4.67 (d, $J = 3.4$ Hz, 1H), 4.33 (d, $J = 3.7$ Hz, 1H), 1.48 (s, 3H), 1.32 (s, 3H); ^{13}C NMR: δ 171.2, 113.1, 105.2, 82.9, 78.1, 66.5, 26.6, 26.2. Anal. calcd for $C_8H_{11}N_3O_5$: C, 41.92; H, 4.84; N, 18.33%. Found: C, 41.99; H, 4.90; N, 18.42%.

3-Azido-6-diazo-3,6-dideoxy-1,2-*O*-isopropylidine-5-keto-α-D-*xylo*-1,4-furanose 5

To a cooled (0 °C) and stirred solution of **4** (3.12 g, 13.62 mmol) in THF (45 mL) was sequentially added Et_3N (2.27 mL, 16.33 mmol) and ethyl chloroformate (1.43 mL, 14.97 mmol). After 15 min, the mixture was brought to room temperature and filtered through Celite-545. CH_2N_2 [prepared from *N*-nitrosomethyl urea (2.00 g, 19.40 mmol) and KOH (5 g)] in Et_2O (50 mL) was dropwise added to the filtrate at 0 °C in 0.5 h. After stirring at room temperature for 2 h, the mixture was concentrated *in vacuo*, and the residue purified by column chromatography (silica gel, 10% EtOAc/hexane) gave **5** (2.78 g, 80%) as a thick liquid. $R_f = 0.35$ (20% EtOAc/hexane); $[\alpha]_D^{25}$ −90.3 (*c* 1.14, $CHCl_3$); ν_{max}/cm^{-1}: 2105, 1720 cm^{-1}; ^1H NMR: δ 5.95 (d, $J = 3.3$ Hz, 1H), 5.81 (s, 1H), 4.71 (d, $J = 3.1$ Hz, 1H), 4.62 (d, $J = 3.3$ Hz, 1H), 4.35 (d, $J = 3.1$ Hz, 1H), 1.48 (s, 3H), 1.32 (s, 3H); ^{13}C NMR: δ 191.1, 112.7, 105.1, 82.8, 82.5, 66.7, 54.7, 26.4, 26.0. Anal. calcd for $C_9H_{11}N_5O_4$: C, 42.69; H, 4.38; N, 27.66%. Found: C, 42.75; H, 4.44; N, 27.74%.

Methyl[(3a*R*,5*R*,6*S*,6a*R*)-6-azido-2,2-dimethyltetrahydrofuro-[2,3-*d*][1,3]dioxol-5-yfl]acetate 6

To a stirred solution of **5** (1.00 g, 3.95 mmol) in anhydrous MeOH (15 mL) was dropwise added silver benzoate (0.290 g, 1.26 mmol) in Et_3N (3 mL). After stirring at 25 °C for 20 min, the mixture was concentrated *in vacuo*, and the residue purified by column chromatography (silica gel, 5% EtOAc/hexane) to obtain **6** (0.560 g, 55%) as a thick liquid. $R_f = 0.52$ (20% EtOAc/hexane); $[\alpha]_D^{25}$ −59.1 (*c* 1.17, $CHCl_3$); ν_{max}/cm^{-1}: 2105, 1737, 1208 cm^{-1}; ^1H NMR: δ 5.81 (d, $J = 3.7$ Hz, 1H), 4.63 (d, $J = 3.7$ Hz, 1H), 4.60–4.44 (m, 1H), 4.08 (d, $J = 3.2$ Hz, 1H), 3.67 (s, 3H), 2.87–2.59 (m, 2H), 1.47 (s, 3H), 1.28 (s, 3H); ^{13}C NMR: δ 170.6, 112.1, 104.1, 83.5, 75.4, 66.7, 51.9, 33.5, 26.5, 26.1; ESI-MS: calcd for $[C_{10}H_{15}N_3O_5 + Na]^+$: 280.09 Da. Found: 279.88 Da. Anal. calcd for $C_{10}H_{15}N_3O_5$: C, 46.69; H, 5.88; N, 16.33%. Found: C, 46.67; H, 5.93; N, 16.43%.

(2*S*,3*R*)-2-Azido-3-(formyloxy)-5-methoxy-5-oxopentanoic acid 7

A solution of **6** (0.702 g, 2.73 mmol) in TFA–H_2O (3.00 mL, 3 : 2) was stirred at 0 °C for 6 h. Azeotropic removal of TFA with toluene *in vacuo* afforded the intermediate hemiacetal (0.700 g, thick liquid), which was taken in acetone/water (10 mL, 9 : 1), cooled to 0 °C and $NaIO_4$ (0.640 g, 2.99 mmol) added. After stirring for 0.5 h, the reaction mixture was concentrated *in vacuo*, the residue extracted with $CHCl_3$ (3 × 10 mL), and the extract concentrated *in vacuo* to get the crude α-azido aldehyde (0.503 g, thick liquid). This was dissolved in MeCN (5 mL), treated successively with NaH_2PO_4 (0.08 g, 0.53 mmol) in H_2O (1 mL) and 30% H_2O_2 (0.40 mL, 2.95 mmol), cooled to 0 °C, and $NaClO_2$ (0.39 g, 4.36 mmol) in H_2O (1.5 mL) added into it in 20 min. After stirring at 20 °C till completion of the reaction (~10 h, monitored by gas evolution), the reaction mixture was treated with sodium sulphate (0.20 g), and extracted with EtOAc (3 × 15 mL). Concentration of the extract *in vacuo* followed by column chromatography (silica gel, 10% MeOH/$CHCl_3$) of the residue gave **7** (0.500 g, 79% in three steps) as a thick liquid. $R_f = 0.30$ (30% MeOH/$CHCl_3$); $[\alpha]_D^{25}$ −6.00 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1}: 2111, 1701 cm^{-1}; ^{1}H NMR: δ 9.31–8.71 (broad m, 1H, D_2O exchangeable), 8.00 (s, 1H), 5.84–5.65 (m, 1H), 4.31 (d, J = 2.2 Hz, 1H), 3.68 (s, 3H), 2.84 (dd, J = 6.8, 1.2 Hz, 2H); ^{13}C NMR: δ 171.6, 170.2, 159.9, 69.5, 62.3, 52.3, 35.2. Anal. calcd for $C_7H_9N_3O_6$: C, 36.37; H, 3.92; N, 18.18%. Found: C, 36.42; H, 3.98; N, 18.28%.

(2*S*,3*R*)-2-Azido-3-hydroxy-5-methoxy-5-oxopentanoic acid 8

To a cooled (0 °C) and stirred solution of **7** (0.141 g, 0.61 mmol) in THF (3 mL) was added aqueous saturated $NaHCO_3$ (1 mL). After stirring for 0.5 h, the reaction mixture was concentrated *in vacuo*, the residue acidified to pH 1 with aqueous 1 N HCl, and extracted with EtOAc (6 × 10 mL). The combined organic extracts were dried, concentrated *in vacuo* to obtain a residue, which on column chromatography (silica gel, 20% MeOH/$CHCl_3$) gave **8** (0.110 g, 89%) as a thick liquid. $R_f = 0.30$ (30% MeOH/$CHCl_3$); $[\alpha]_D^{25}$ −26.0 (*c* 1.10, $CHCl_3$); ν_{max}/cm^{-1}: 3510, 2105, 1713, 1206 cm^{-1}; ^{1}H NMR: δ 6.64 (broad s, D_2O exchangeable, 2H), 4.72–4.55 (m, 1H), 4.00 (d, J = 2.3 Hz, 1H), 3.71 (s, 3H), 2.78 (dd, J = 16.6, 8.3 Hz, 1H), 2.63 (dd, J = 16.6, 4.8 Hz, 1H); ^{13}C NMR: δ 172.4, 68.7, 64.7, 52.3, 37.8. Anal. calcd for $C_6H_9N_3O_5$: C, 35.47; H, 4.47; N, 20.68%. Found: C, 35.44; H, 4.52; N, 20.77.

5-Methyl 1-prop-2-en-1-yl(2*S*,3*R*)-2-azido-3-(formyloxy)-pentanedioate 9

To a solution of **7** (0.500 g, 2.16 mmol) in DMF (3 mL) at 0 °C was added $NaHCO_3$ (0.45 g, 5.40 mmol) followed by allyl bromide (0.23 mL, 2.70 mmol). The reaction mixture was stirred to 25 °C for 12 h, DMF was removed *in vacuo*, the residue extracted with EtOAc (3 × 10 mL), the organic extract dried and concentrated *in vacuo*. The product was purified by column chromatography (silica gel, 10% EtOAc/hexane) to afford **9** (0.493 g, 84%) as a viscous liquid. $R_f = 0.40$ (20% EtOAc/hexane); $[\alpha]_D^{25}$ −11.0 (*c* 1.16, $CHCl_3$); ν_{max}/cm^{-1}: 3524, 2109, 1721, 1211 cm^{-1}; ^{1}H NMR: δ 7.96 (s, 1H), 6.00–5.70 (m, 2H), 5.43–5.21 (m, 2H), 4.69–4.63 (m, 2H), 4.23 (d, J = 2.9 Hz, 1H), 3.67 (s, 3H), 2.80 (d, J = 6.9 Hz, 2H); ^{13}C NMR: δ 169.6, 167.2, 159.1, 130.8, 119.8, 69.3, 66.9, 62.3, 52.1, 35.1. Anal. calcd for $C_{10}H_{13}N_3O_6$: C, 44.28; H, 4.83; N, 15.49%. Found: C, 44.25; H, 4.80; N, 15.61%.

5-Methyl 1-prop-2-en-1-yl(2*S*,3*R*)-2-azido-3-hydroxypentanedioate 10

Following the procedure used for **8**, deformylation of **9** (0.230 g, 0.84 mmol) with aqueous saturated $NaHCO_3$ (1.5 mL) in THF (5 mL) followed by usual work up and column chromatography (silica gel, 10% EtOAc/hexane) afforded **10** (0.180 g, 87%) as a thick liquid. $R_f = 0.30$ (20% EtOAc/hexane); $[\alpha]_D^{25}$ −17.0 (*c* 1.74, $CHCl_3$); ν_{max}/cm^{-1}: 3611, 2102, 1716, 1202 cm^{-1}; ^{1}H NMR: δ 6.08–5.82 (m, 1H), 5.50–5.21 (m, 2H), 4.82–4.69 (m, 2H), 4.65–4.49 (m, 1H), 3.88 (d, J = 2.6 Hz, 1H), 3.71 (s, 3H), 2.76 (dd, J = 16.3, 7.6 Hz, 1H), 2.75–2.25 (broad s, D_2O exchangeable, 1H), 2.58 (dd, J = 16.3, 4.5 Hz, 1H); ^{13}C NMR: δ 172.1, 168.3, 131.0, 119.5, 68.9, 66.7, 64.9, 52.1, 37.8. Anal. calcd for $C_9H_{13}N_3O_5$: C, 44.44; H, 5.39; N, 17.28%. Found: C, 44.51; H, 5.46; N, 17.36%.

[(3a*R*,5*R*,6*S*,6a*R*)-6-Azido-2,2-dimethyltetrahydrofuro[2,3-*d*]-[1,3]dioxol-5-yl]acetic acid 11

To a cooled (0 °C) solution of **6** (1.20 g, 4.66 mmol) in THF (40 mL) was dropwise added an aqueous 0.3 M solution of LiOH (0.58 g, 13.99 mmol) over 30 min. After completion of reaction (*cf.* TLC, 30 min), the pH of the mixture was adjusted to 5–6 with aqueous saturated citric acid (20 mL), and extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried, concentrated, and the residue purified by column chromatography (silica gel, 10% MeOH/$CHCl_3$) to give **11** (0.980 g, 86%) as a thick liquid. $R_f = 0.30$ (30% MeOH/$CHCl_3$); $[\alpha]_D^{25}$ −31.4 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1}: 3584, 2102, 1742 cm^{-1}; ^{1}H NMR: δ 9.00–7.81 (broad s, D_2O exchangeable, 1H), 5.86 (d, J = 3.7 Hz, 1H), 4.68 (d, J = 3.7 Hz, 1H), 4.62–4.50 (m, 1H), 4.10 (d, J = 3.2 Hz, 1H), 2.94–2.65 (m, 2H), 1.51 (s, 3H), 1.31 (s, 3H); ^{13}C NMR: δ 175.8, 112.3, 104.2, 83.5, 75.1, 66.7, 33.6, 26.5, 26.2. Anal. calcd for $C_9H_{13}N_3O_5$: C, 44.44; H, 5.39; N, 17.28%. Found: C, 44.40; H, 5.41; N, 17.39%.

Benzyl[(3a*R*,5*R*,6*S*,6a*R*)-6-azido-2,2-dimethyltetrahydrofuro-[2,3-*d*][1,3]dioxol-5-yl]acetate 12

To a solution of **11** (0.210 g, 0.86 mmol) in CH_3CN (5 mL) was added Et_3N (0.27 mL, 1.93 mmol), CbzCl (0.245 mL, 1.72 mmol) and DMAP (0.05 g, 0.43 mmol). After stirring for 2 h at 25 °C, another portion of CbzCl (0.120 mL, 0.86 mmol) and DMAP (0.03 g, 0.22 mmol) were added and the mixture stirred overnight. It was concentrated *in vacuo* and extracted with EtOAc (3 × 15 mL). The combined organic extracts were sequentially washed with aqueous $NaHCO_3$ (5 mL) and water (5 mL), and dried. Concentration of extract and column chromatography (silica gel, 5% EtOAc/hexane) of the residue afforded **12** (0.180 g, 63%) as a viscous liquid. $R_f = 0.51$ (10% EtOAc/hexane); $[\alpha]_D^{25}$ −28.5 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1}: 2110, 1734 cm^{-1}; ^{1}H NMR: δ 7.34 (s, 5H), 5.84 (d, J = 3.7 Hz, 1H), 5.14 (s, 2H), 4.65 (d, J = 3.7 Hz, 1H), 4.59 (ddd, J = 8.2, 6.3, 3.3 Hz, 1H), 4.09 (d, J = 3.3 Hz, 1H), 2.96–2.66 (m, 2H), 1.49 (s, 3H), 1.31 (s, 3H); ^{13}C NMR: δ 170.0, 135.5, 128.6, 128.4, 128.2, 112.2, 104.2, 83.6, 75.5, 66.8, 66.7, 33.9, 26.5, 26.2; ESI-MS: calcd for $[C_{16}H_{19}N_3O_5 + Na]^+$: 356.12 Da. Found: 355.89 Da. Anal. calcd for $C_{16}H_{19}N_3O_5$: C, 57.65; H, 5.75; N, 12.61%. Found: C, 57.63; H, 5.78; N, 12.70%.

(2*S*,3*R*)-2-Azido-5-(benzyloxy)-3-hydroxy-5-oxopentanoic acid 13

As described earlier, **12** (0.100 g, 0.30 mmol) was deacetalized with TFA–H_2O (3 mL, 3 : 2), the resultant diol cleaved with $NaIO_4$ (0.072 g, 0.33 mmol) in 10% aqueous acetone (5 mL) followed by oxidation with NaH_2PO_4 (0.01 g, 0.06 mmol), 30% H_2O_2 (50 µL, 0.30 mmol) and $NaClO_2$ (0.05 g, 0.49 mmol). The product was finally deformylated with aqueous saturated $NaHCO_3$ (1 mL). Usual workup and column chromatography (silica gel, 2% MeOH/$CHCl_3$) of the residue afforded **13** (0.060 g, 71% over four steps) as a thick liquid. $R_f = 0.31$ (10% MeOH/$CHCl_3$); $[\alpha]_D^{25}$ −20.0 (*c* 1.01, $CHCl_3$); ν_{max}/cm^{-1}: 2112, 1725 cm^{-1}; ^{1}H NMR: δ 7.33 (s, 5H), 6.91 (broad s, D_2O exchangeable, 2H), 5.13 (s, 2H), 4.71–4.60 (m, 1H), 3.96 (d, $J = 2.1$ Hz, 1H), 2.80 (dd, $J = 16.6, 8.3$ Hz, 1H), 2.64 (dd, $J = 16.6, 4.7$ Hz, 1H); ^{13}C NMR: δ 172.4, 171.7, 135.1, 128.6, 128.5, 128.3, 68.7, 67.0, 64.8, 38.0. Anal. calcd for $C_{12}H_{13}N_3O_5$: C, 51.61; H, 4.69; N, 15.05%. Found: C, 51.58; H, 4.72; N, 15.13%.

5-Benzyl 1-prop-2-en-1-yl(2*S*,3*R*)-2-azido-3-hydroxypentanedioate 14

Following the procedure used for **9**, the acid **13** (0.078 g, 0.27 mmol) was subjected to allylation using allyl bromide (29.0 μL) and $NaHCO_3$ (0.056 g) in DMF (1 mL). Usual workup and column chromatography (silica gel, 5% EtOAc/hexane) of the residue afforded **14** (0.075 g, 87%) as a thick liquid. $R_f = 0.38$ (20% EtOAc/hexane); $[\alpha]_D^{25}$ −24.3 (*c* 1.08, $CHCl_3$); ν_{max}/cm^{-1}: 2108, 1742 cm^{-1}; ^1H NMR: δ 7.34 (s, 5H), 6.05–5.80 (m, 1H), 5.42–5.29 (m, 2H), 5.15 (s, 2H), 4.72 (broad d, $J = 5.8$ Hz, 2H), 4.65–4.53 (m, 1H), 3.87 (d, $J = 3.1$ Hz, 1H), 3.14 (s, D_2O exchangeable, 1H), 2.79 (dd, $J = 16.7, 8.4$ Hz, 1H), 2.62 (dd, $J = 16.7, 4.5$ Hz, 1H); ^{13}C NMR: δ 171.5, 168.2, 135.2, 131.0, 128.7, 128.5, 128.3, 119.4, 68.9, 66.9, 66.7, 64.9, 38.0; ESI-MS: calcd for $[C_{15}H_{17}N_3O_5 + Na]^+$: 342.10 Da. Found: 341.85 Da. Anal. calcd for $C_{15}H_{17}N_3O_5$: C, 56.42; H, 5.37; N, 13.16%. Found: C, 56.48; H, 5.43; N, 13.23%.

(2*S*,3*R*)-3-Hydroxy-L-glutamic acid hydrochloride 1a

A mixture of **13** (0.085 g, 0.31 mmol) and 10% Pd–C (0.02 g) in methanolic HCl (10 mL) was stirred for 12 h under H_2 (80 psi). The catalyst was filtered through Celite-545 and washed with MeOH (3 × 10 mL), concentrated and the residue dried *in vacuo* to afford **1a** (0.048 g, 95%) as a semisolid. $[\alpha]_D^{25}$ +14.7 (*c* 1.02, H_2O); ν_{max}/cm^{-1}: 3577, 1737 cm^{-1}; ^1H NMR: δ 4.66–4.58 (m, 1H), 4.10 (d, $J = 3.3$ Hz, 1H), 2.87 (dd, $J = 16.4, 4.0$ Hz, 1H), 2.72 (dd, $J = 16.4, 8.7$ Hz, 1H); ^{13}C NMR: δ 174.1, 170.3, 65.5, 57.3, 38.4; ESI-MS: calcd for $[C_5H_9NO_5 + Na]^+$: 186.04 Da. Found: 186.10 Da. Anal. calcd for $C_5H_{10}ClNO_5$: C, 30.09; H, 5.05; N, 7.02%. Found: C, 30.13; H, 5.10; N, 7.13%.

2-[(3a*R*,5*R*,6*S*,6a*R*)-6-Azido-2,2-dimethyltetrahydrofuro[2,3-*d*]-[1,3]dioxol-5-yl]-*N*-benzylacetamide 15

To a solution of **11** (0.080 g, 0.33 mmol) in DMF at 25 °C was added HBTU (0.14 g, 0.37 mmol), HOBt monohydrate (0.06 g, 0.37 mmol) and DIEA (0.17 mL, 0.99 mmol). After stirring for 5 min, benzylamine (0.04 mL, 0.38 mmol) in DMF (0.40 mL) was added, and the mixture stirred for an additional 8 h. The mixture was concentrated *in vacuo*, the residue extracted with EtOAc (3 × 20 mL), the organic extract washed with water (3 × 5 mL) and brine (1 × 5 mL), and dried. Concentration of the extract *in vacuo*, and column chromatography (silica gel, 12% EtOAc/hexane) of the residue yielded **15** (0.068 g, 62%) as a thick liquid. $R_f = 0.55$ (50% EtOAc/hexane); $[\alpha]_D^{25}$ −24.0 (*c* 1.05, $CHCl_3$); ν_{max}/cm^{-1}: 2103, 1689 cm^{-1}; ^1H NMR: δ 7.31–7.23 (m, 2H), 7.22–7.17 (m, 3H), 6.29 (broad s, D_2O exchangeable, 1H), 5.79 (d, $J = 3.7$ Hz, 1H), 4.59 (d, $J = 3.7$ Hz, 1H), 4.56–4.49 (m, 1H), 4.41 (dd, $J = 14.8, 5.8$ Hz, 1H), 4.34 (dd, $J = 14.8, 5.6$ Hz, 1H), 3.98 (d, $J = 3.0$ Hz, 1H), 2.62 (dd, $J = 15.2, 7.7$ Hz, 1H), 2.53 (dd, $J = 15.2, 5.8$ Hz, 1H), 1.43 (s, 3H), 1.25 (s, 3H); ^{13}C NMR: δ 170.0, 137.7, 128.7, 127.6, 127.5, 112.4, 104.3, 83.4, 76.0, 67.1, 43.7, 36.2, 26.5, 26.2; ESI-MS: calcd for $[C_{16}H_{20}N_4O_4 + Na]^+$: 355.13 Da. Found: 354.93 Da. Anal. calcd for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.07; N, 16.86%. Found: C, 57.80; H, 6.05; N, 16.93%.

(2*S*,3*R*)-2-Azido-5-(benzylamino)-3-hydroxy-5-oxopentanoic acid 16

Following the procedure used for the synthesis of **13**, compound **15** (0.110 g, 0.33 mmol) was deacetalized with TFA–H_2O (3 mL, 3 : 2), the resultant diol cleaved with $NaIO_4$ (0.08 g, 0.37 mmol) in 10% aqueous acetone (5 mL) followed by oxidation with NaH_2PO_4 (0.01 g), 30% H_2O_2 (35 μL) and $NaClO_2$ (0.05 g). The product was finally deformylated with aqueous saturated $NaHCO_3$ (1 mL). Usual workup and column chromatography (silica gel, 10% MeOH/$CHCl_3$) of the residue afforded **16** (0.067 g, 72% in four steps) as a thick liquid. $R_f = 0.35$ (30% MeOH/$CHCl_3$); $[\alpha]_D^{25}$ −19.0 (*c* 1.04, $CHCl_3$); ν_{max}/cm^{-1}: 3570, 2107, 1737, 1685 cm^{-1}; ^1H NMR: δ 7.34–7.23 (m, 5H), 7.18 (broad s, D_2O exchangeable, 1H), 4.43 (s, 1H), 4.34 (s, 2H), 3.74 (s, 1H), 2.49 (s, 2H); ^{13}C NMR: δ 173.9, 172.0, 138.4, 128.1, 127.1, 126.7, 69.4, 67.5, 42.7, 39.9. Anal. calcd for $C_{12}H_{14}N_4O_4$: C, 51.80; H, 5.07; N, 20.13%. Found: C, 51.87; H, 5.13; N, 20.25%.

Prop-2-en-1-yl(2*S*,3*R*)-2-azido-5-(benzylamino)-3-hydroxy-5-oxopentanoate 17

Following the procedure described earlier, **16** (0.06 g, 0.22 mmol) was reacted with allyl bromide (20 μL) in the presence of $NaHCO_3$ (0.04 g) in DMF (2 mL). Usual workup and column chromatography (silica gel, 8% EtOAc/hexane) of the residue gave **17** (0.055 g, 79%) as a thick liquid. $R_f = 0.41$ (30% EtOAc/hexane); $[\alpha]_D^{25}$ −16.4 (*c* 0.55, $CHCl_3$); ν_{max}/cm^{-1}: 2105, 1744 cm^{-1}; ^1H NMR: δ 7.38–7.17 (m, 5H), 6.13–5.69 (m, partially D_2O exchangeable, 2H), 5.44–5.15 (m, 2H), 4.67 (broad d, $J = 5.8$ Hz, 2H), 4.62–4.46 (m, 1H), 4.38 (d, $J = 5.7$ Hz, 2H), 3.75 (d, $J = 3.2$ Hz, 1H), 2.58 (dd, $J = 15.4, 8.9$ Hz, 1H), 2.37 (dd, $J = 15.4, 3.8$ Hz, 1H), 1.58 (broad s, D_2O exchangeable, 1H); ^{13}C NMR: δ 170.8, 168.4, 137.6, 131.1, 128.8, 127.8, 127.7, 119.4, 69.6, 66.7, 65.1, 43.7, 39.1; ESI-MS: calcd for $[C_{15}H_{18}N_4O_4 + Na]^+$: 341.12 Da. Found: 340.92 Da. Anal. calcd for $C_{15}H_{18}N_4O_4$: C, 56.60; H, 5.70; N, 17.60%. Found: C, 56.55; H, 5.68; N, 17.69%.

(1*S*,2*R*)-4-(Benzylamino)-1-carboxy-2-hydroxy-4-oxobutan-1-aminium chloride 18

Catalytic hydrogenation of **16** (0.048 g, 0.17 mmol) over 10% Pd–C (0.015 g) in MeOH (5 mL) using H_2 (80 psi) gave **18** (0.044 g, 89%) as a semi-solid. $[\alpha]_D^{25}$ +22.0 (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1}: 1713, 1406 cm^{-1}; ^1H NMR: δ 7.44 (d, $J = 3.9$ Hz, 2H), 7.38 (s, 3H), 4.72–4.64 (m, 1H), 4.44 (s, 2H), 4.19 (d, $J = 3.7$ Hz, 1H), 2.82–2.76 (m, 1H), 2.70 (dd, $J = 14.8, 8.8$ Hz, 1H); ^{13}C NMR: δ 173.6, 171.7, 139.5, 130.5, 129.2, 129.0, 67.8, 59.0, 44.8, 41.8; ESI-MS: calcd for $[C_{12}H_{16}N_2O_4 + H]^+$: 253.11 Da. Obsd: 253.90 Da. Anal. calcd for $C_{12}H_{17}ClN_2O_4$: C, 49.92; H, 5.93; N, 9.70%. Found: C, 49.88; H, 5.96; N, 9.78%.

2-[(3a*R*,5*R*,6*S*,6a*R*)-6-Azido-2,2-dimethyltetrahydrofuro[2,3-*d*]-[1,3]dioxol-5-yl]acetamide 19

To a solution of **11** (0.210 g, 0.87 mmol) in CH_3CN (10 mL) was added $(Boc)_2O$ (0.246 g, 1.13 mmol), and NH_4HCO_3 (0.161 g, 2.04 mmol) to give a cloudy mixture. After adding pyridine (0.05 mL, 0.60 mmol), the mixture was stirred at room temperature till completion of the reaction (~for 5 h, *cf.* TLC). The mixture was concentrated *in vacuo*, the residue extracted with EtOAc (3 × 15 mL), the organic extract washed with water (5 mL) and dried. Concentration of the extract *in vacuo*, and column chromatography (silica gel, 30% EtOAc/hexane) of the residue afforded **19** (0.189 g, 90%) as colorless crystals. mp: 122–125 °C; $R_f = 0.45$ (80% EtOAc/hexane); $[\alpha]_D^{25}$ −23.1 (*c* 1.18, MeOH); ν_{max}/cm^{-1}: 2111, 1665 cm^{-1}; ^{1}H NMR: δ 5.81 (d, J = 3.7 Hz, 1H), 4.72 (d, J = 3.7 Hz, 1H), 4.56 (td, J = 6.9, 3.1 Hz, 1H), 4.04 (d, J = 3.1 Hz, 1H), 2.63 (dd, J = 15.2, 7.3 Hz, 1H), 2.55 (dd, J = 15.2, 6.6 Hz, 1H), 1.45 (s, 3H), 1.29 (s, 3H); ^{13}C NMR: δ 172.1, 110.2, 102.7, 81.9, 74.6, 65.6, 33.0, 23.8, 23.4; ESI-MS: calcd for $[C_9H_{14}N_4O_4 + Na]^+$: 265.09 Da. Found: 265.90 Da. Anal. calcd for $C_9H_{14}N_4O_4$: C, 44.63; H, 5.83; N, 23.13%. Found: C, 44.59; H, 5.87; N, 23.25%.

(2*S*,3*R*)-5-Amino-2-azido-3-hydroxy-5-oxopentanoic acid 20

Following the procedure used for the synthesis of **16**, compound **19** (0.08, 0.33 mmol) was deacetalized with TFA–H_2O (3 mL, 3 : 2), the resultant diol subjected to oxidative cleavage with $NaIO_4$ (0.08 g, 0.37 mmol) followed by oxidation with NaH_2PO_4 (0.01 g), 30% H_2O_2 (35 μL) and $NaClO_2$ (0.05 g). The product was deformylated using $NaHCO_3$ (1 mL) in THF (5 mL). Usual workup and purification by column chromatography (silica gel, 10% MeOH/$CHCl_3$) of the residue gave **20** (0.04 g, 66% over four steps) as a thick liquid. $R_f = 0.45$ (30% MeOH/$CHCl_3$); $[\alpha]_D^{25}$ −14.4 (*c* 1.00, MeOH); ν_{max}/cm^{-1}: 2110, 1690 cm^{-1}; ^{1}H NMR: δ 4.50 (broad s, 1H), 3.85 (d, J = 1.5 Hz, 1H), 2.49 (dd, J = 14.7, 8.2 Hz, 1H), 2.42 (dd, J = 14.7, 5.0 Hz, 1H); ^{13}C NMR: δ 174.5, 170.6, 69.0, 65.3, 39.4. Anal. calcd for $C_5H_8N_4O_4$: C, 31.92; H, 4.29; N, 29.78%. Found: C, 31.95; H, 4.26; N, 29.87%.

(2*S*,3*R*)-3-Hydroxy-L-glutamine hydrochloride 1b

The procedure for transforming **13** to **1a** was followed for the catalytic hydrogenation of **20** (0.02, 0.11 mmol) using 10% Pd/C (0.015 g) and H_2 (80 psi) to give **1b** as a semisolid (0.019 g, 90%). $[\alpha]_D^{25}$ +9.1 (*c* 1.08, H_2O); ν_{max}/cm^{-1}: 3440, 1708 cm^{-1}; ^{1}H NMR: δ 4.71–4.60 (m, 1H), 4.20 (d, J = 3.8 Hz, 1H), 2.77 (dd, J = 15.1, 4.1 Hz, 1H), 2.67 (dd, J = 15.1, 8.8 Hz, 1H); ^{13}C NMR: δ 174.8, 169.9, 65.8, 57.1, 39.3; ESI-MS: calcd for $[C_5H_{10}N_2O_4 + Na]^+$: 185.05 Da. Found: 185.00 Da. Anal. calcd for $C_5H_{11}ClN_2O_4$: C, 30.24; H, 5.58; N, 14.11%. Found: C, 30.29; H, 5.64; N, 14.23%.

(3a*R*,4a*R*,7a*S*,7b*R*)-2,2-Dimethylhexahydro-6*H*-[1,3]dioxolo-[4,5]furo[3,2-*b*]pyrrol-6-one 21

A mixture of **6** (0.300 g, 1.16 mmol), 10% Pd/C (0.03 g) and HCO_2NH_4 (0.220 g, 3.50 mmol) in MeOH (15 mL) was refluxed for 2 h till completion of the reaction (*cf.* TLC). The mixture was filtered through Celite-545, the residue washed with MeOH (10 mL) and concentrated *in vacuo*. Column chromatography (silica gel, EtOAc) of the residue yielded **21** (0.210 g, 91%) as a white solid. mp: 174–176 °C; $R_f = 0.30$ (EtOAc); $[\alpha]_D^{25}$ +24.8 (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1}: 1658, 1413 cm^{-1}; ^{1}H NMR: δ 7.45 (broad s, D_2O exchangeable, 1H), 5.88 (d, J = 3.8 Hz, 1H), 4.90 (t, J = 3.8 Hz, 1H), 4.58 (d, J = 3.8 Hz, 1H), 4.08 (d, J = 4.2 Hz, 1H), 2.60–2.32 (m, 2H), 1.46 (s, 3H), 1.27 (s, 3H); ^{13}C NMR: δ 177.0, 112.1, 106.0, 83.2, 77.9, 63.9, 38.0, 26.9, 26.4. Anal. calcd for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03%. Found: C, 54.29; H, 6.63; N, 7.10%.

(3a*R*,4a*R*,7a*S*,7b*R*)-2,2-Dimethylhexahydro-3a*H*-[1,3]dioxolo-[4,5]furo[3,2-*b*]-*N*-carboxybenzylpyrrole 22

To a stirred and ice-cold suspension of $LiAlH_4$ (0.071 g, 1.88 mmol) in dry THF (5 mL) was added **21** (0.150 g, 0.75 mmol) in dry THF (10 mL) in 5 min. The mixture was stirred further for 15 min at 0 °C, allowed to attain room temperature (25 °C), and then refluxed. After 3 h, the mixture was cooled to 25 °C, EtOAc (7 mL) added into it slowly followed by aqueous saturated NH_4Cl (1 mL) and stirred for 1 h. It was filtered through Celite-545 by washing with 20% MeOH–EtOAc, and the filtrate evaporated *in vacuo* to give the corresponding amine. The amine was dissolved in MeOH–water (3 : 1, 10 mL), cooled to 0 °C, $NaHCO_3$ (0.176 g, 2.10 mmol) and CbzCl (0.25 mL, 1.75 mmol) were successively added into it. After 3 h, the mixture was concentrated *in vacuo*, and the residue extracted with CH_2Cl_2 (3 × 10 mL). The organic extract was dried, concentrated *in vacuo*, and the residue purified by column chromatography (silica gel, 7% EtOAc/hexane) to give **22** (0.136 g, 57% over two steps) as a colorless thick liquid. $R_f = 0.50$ (20% EtOAc/hexane); $[\alpha]_D^{25}$ −55.6 (*c* 1.06, $CHCl_3$); ν_{max}/cm^{-1}: 1671, 1420 cm^{-1}; ^{1}H NMR: δ 7.49–7.25 (m, 5H), 5.80 (s, 1H), 5.20–5.01 (m, 2H), 4.92–4.60 (m, 2H), 4.20 (s, 1H), 3.77–3.60 (m, 1H), 3.40–3.23 (m, 1H), 2.06 (dd, J = 13.6, 6.0 Hz, 1H), 1.91–1.69 (m, 1H), 1.49 (s, 3H), 1.28 (s, 3H); ^{13}C NMR: δ 154.4, 136.6, 128.5, 128.0, 127.9, 111.8, 106.0, 84.5, 82.2, 67.6, 67.0, 45.5, 30.0, 27.1, 26.5; ESI-MS: calcd for $[C_{17}H_{21}NO_5 + Na]^+$: 342.13 Da. Found: 341.93 Da. Anal. calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39%. Found: C, 63.89; H, 6.67; N, 4.47%.

(2*S*,3*R*)-3-Hydroxyproline hydrochloride 1c

Following the procedure used for the synthesis of **16**, compound **22** (0.160 g, 0.50 mmol) was deacetalized with TFA–H_2O (3 mL, 3 : 2), the resultant diol subjected to oxidative cleavage with $NaIO_4$ (0.110 g, 0.50 mmol), followed by oxidation with NaH_2PO_4 (0.01 g), 30% H_2O_2 (35 μL), $NaClO_2$ (0.05 g) and subsequent deformylation with aqueous saturated $NaHCO_3$ (1 mL) in THF (5 mL). The resultant acid was hydrogenated with H_2 (80 psi) over 10% Pd–C (0.015 g) to afford **1c** (0.045 g, 54% over five steps) as a pale-yellow semi-solid. $[\alpha]_D^{25}$ −12.3 (*c* 1.04, H_2O); ν_{max}/cm^{-1}: 3576, 1715 cm^{-1}; ^{1}H NMR: δ 4.86 (t, J = 4.0 Hz, 1H), 4.44 (d, J = 4.0 Hz, 1H), 3.50–3.71 (m, 2H), 2.39–2.29 (m, 1H), 2.26–2.18 (m, 1H); ^{13}C NMR: δ 169.2, 70.8, 66.3, 44.0, 32.9. Anal. calcd for $C_5H_{10}ClNO_3$: C, 35.83; H, 6.01; N, 8.36%. Found: C, 35.80; H, 6.07; N, 8.44%.

Prop-2-en-1-yl(2*S*,3*R*)-*N*-carboxybenzyl-3-hydroxypyrrolidine-2-carboxylate 23

As described before, **22** (0.064 g, 0.20 mmol) was deacetalized using TFA–H_2O (3 mL, 3 : 2), the resultant diol oxidatively cleaved with $NaIO_4$ (0.047 g, 0.22 mmol) followed by oxidation with NaH_2PO_4 (0.006 g), 30% H_2O_2 (21 μL), $NaClO_2$ (0.03 g), and the formyl group unmasked with aqueous $NaHCO_3$ (1 mL) in THF (5 mL). The resultant crude acid was dried *in vacuo* and allylated with allyl bromide (21.6 μL) and $NaHCO_3$ (0.04 g) in DMF (3 mL). The mixture was concentrated *in vacuo*, the residue extracted with EtOAc (3 × 10 mL), the organic extract washed with water (2 × 5 mL) and dried. Concentration of the extract *in vacuo*, and column chromatography of the residue (silica gel, 15% EtOAc/hexane) gave **23** (0.040 g, 65% over five steps) as a thick liquid. R_f = 0.36 (50% EtOAc/*n*-hexane); $[\alpha]_D^{25}$ +28.00 (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1}: 1715, 1215 cm^{-1}; ^1H NMR: δ 7.45–7.22 (m, 5H), 6.08–5.60 (m, 1H), 5.48–4.91 (m, 4H), 4.86–4.34 (m, 4H), 3.81–3.40 (m, 2H), 2.84 (broad s, D_2O exchangeable, 1H), 2.24–1.82 (m, 2H); ^{13}C NMR: δ 169.8, 154.4, 136.2, 131.8, 128.4, 128.0, 127.8, 118.5, 72.2, 67.2, 65.9, 63.8, 44.4, 32.0; ESI-MS: calcd for $[C_{16}H_{19}NO_5 + Na]^+$: 328.11 Da. Found: 327.96 Da. Anal. calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59%. Found: C, 63.01; H, 6.25; N, 4.66%.

(2*R*,3*R*)-2-(Hydroxymethyl)-*N*-carboxybenzylpyrrolidin-3-ol 24

A solution of **22** (0.100 g, 0.31 mmol) in TFA–H_2O (3.00 mL, 3 : 2) was stirred at to 0 to 10 °C for 1.5 h. TFA was removed azeotropically with toluene *in vacuo* to afford the hemiacetal as a thick liquid. To a cooled (0 °C) solution of the crude hemiacetal in acetone–water (9 : 1, 5 mL) was added $NaIO_4$ (0.073 g, 0.34 mmol). After stirring for 30 min, the reaction mixture was concentrated *in vacuo*, and the residue extracted with $CHCl_3$ (3 × 10 mL) to get the crude aldehyde (0.09 g) as a thick liquid. This was dissolved in THF–H_2O (4 : 1, 5 mL), cooled to 5 °C and $NaBH_4$ (0.015 g, 0.40 mmol) in H_2O (0.5 mL) was added to it. After stirring for 30 min, the mixture was concentrated *in vacuo*, the residue extracted with EtOAc (2 × 10 mL), the organic extract washed with water (2 × 5 mL) and dried. Concentration of the extract *in vacuo*, and column chromatography of the residue (silica gel, 20% EtOAc/hexane) yielded **24** (0.05 g, 63% over three steps) as a thick liquid. R_f = 0.30 (60% EtOAc/hexane); $[\alpha]_D^{25}$ −11.5 (*c* 1.20, $CHCl_3$); ν_{max}/cm^{-1}: 1673, 1421 cm^{-1}; ^1H NMR: δ 7.41–7.28 (m, 5H), 5.12 (q, *J* = 12.4 Hz, 2H), 4.51 (d, *J* = 3.7 Hz, 1H), 4.09–3.80 (m, 3H), 3.54 (t, *J* = 6.3 Hz, 2H), 2.85–2.34 (m, D_2O exchangeable, 2H), 2.11–1.85 (m, 2H); ^{13}C NMR: δ 154.5, 136.4, 128.5, 128.1, 128.0, 72.8, 67.2, 61.9, 44.6, 32.9; ESI-MS: calcd for $[C_{13}H_{17}NO_4 + Na]^+$: 274.10 Da. Found: 274.11 Da. Anal. calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57%. Found: C, 62.18; H, 6.87; N, 5.66%.

(2*R*,3*R*)-2-(Hydroxymethyl)pyrrolidin-3-ol 2

A mixture of **24** (0.080 g, 0.31 mmol) and 10% Pd/C (0.02 g) in MeOH (10 mL) was stirred under H_2 (80 psi) for 6 h. The catalyst was filtered through Celite-545 by washing with MeOH (20 mL), and the filtrate concentrated *in vacuo* to afford **2** (0.030 g, 84%) as a thick liquid. R_f = 0.15 (40% MeOH/$CHCl_3$); $[\alpha]_D^{25}$ +11.5 (*c* 1.14, H_2O); ν_{max}/cm^{-1}: 3480 cm^{-1}; ^1H NMR: δ 4.57 (s, 1H), 3.99 (dd, *J* = 12.0, 5.1 Hz, 1H), 3.87 (dd, *J* = 12.0, 8.2 Hz, 1H), 3.58–3.51 (m, 1H), 3.50–3.40 (m, 1H), 3.38–3.32 (m, 1H), 2.30–2.20 (m, 1H), 2.11–2.03 (m, 1H); ^{13}C NMR: δ 70.5, 64.5, 58.6, 43.1, 33.1; ESI-MS: calcd for $[C_5H_{11}NO_2 + H]$: 118.08 Da. Found: 118.19 Da. Anal. calcd for $C_5H_{11}NO_2$: C, 51.26; H, 9.46; N, 11.96%. Found: C, 51.33; H, 9.38; N, 12.05%.

References

1 (*a*) *Amino acids, Peptides, and Proteins*, ed. R. C. Sheppard, The Chemical Society, London, 1972–1981; (*b*) *Amino acids, Peptides, and Proteins*, ed. G. T. Young, The Chemical Society, London, 1968–1971; (*c*) R. A. Dwek, *Chem. Rev.*, 1996, **96**, 683–720; (*d*) A. Varki, *Glycobiology*, 1993, **3**, 97–130; (*e*) C.-H. Wong, *Acc. Chem. Res.*, 1999, **32**, 376–385; (*f*) C. T. Walsh, *Antibiotics: Actions, Origins, Resistance*, ASM Press, Washington, DC, 2003; (*g*) C. T. Walsh, *Post Translational Modifications of Proteins: Expanding Natures Inventory*, Roberts and Company, Englewood, 2006.

2 (*a*) P. E. Dawson and S. B. H. Kent, *Annu. Rev. Biochem.*, 2000, **69**, 923–960; (*b*) S. B. H. Kent, *Chem. Soc. Rev.*, 2009, **38**, 338–351.

3 (*a*) J. K. Thottathil, J. L. Moniot, R. H. Mueller, M. K. Y. Wong and T. P. Kissick, *J. Org. Chem.*, 1986, **51**, 3140–3143; (*b*) J. K. Thottathil and J. L. Moniot, *Tetrahedron Lett.*, 1986, **27**, 151–154; (*c*) J. Krapcho, C. Turk, D. W. Cushman, J. R. Powell, J. M. DeForrest, E. R. Spitzmiller, D. S. Karanewsky, M. Duggan, G. Rovnyak, J. Schwartz, S. Natarajan, J. D. Godfrey, D. E. Ryono, R. Neubeck, K. S. Atwal and E. W. Petrillo Jr, *J. Med. Chem.*, 1988, **31**, 1148–1160; (*d*) A. M. P. Koskinen and H. Rapoport, *J. Org. Chem.*, 1989, **54**, 1859–1866; (*e*) P. Remuzon, *Tetrahedron*, 1996, **52**, 13803–13835; (*f*) K. Hashimoto, Y. Shima and H. Shirahama, *Heterocycles*, 1996, **42**, 489–492; (*g*) Q. Wang, N. A. Sasaki and P. Potier, *Tetrahedron*, 1998, **54**, 15759–15780; (*h*) T. Goodman and L. Moroder, in *Synthesis of Peptides and Peptidomimetics*, Houben-Weyl, Thieme, Stuttgart, Germany, 2003, vol. E22c, pp. 215–271.

4 (*a*) M. R. Levengood, P. J. Knerr, T. J. Oman and W. A. van der Donk, *J. Am. Chem. Soc.*, 2009, **131**, 12024–12025; (*b*) P. J. Knerr and W. A. van der Donk, *J. Am. Chem. Soc.*, 2012, **134**, 7648–7651; (*c*) J. Vagner, H. Qu and V. J. Hruby, *Curr. Opin. Chem. Biol.*, 2008, **12**, 292–296.

5 (*a*) P. E. Dawson, T. W. Muir, I. Clark-Lewis and S. B. Kent, *Science*, 1994, **266**, 776–778; (*b*) L. Z. Yan and P. E. Dawson, *J. Am. Chem. Soc.*, 2001, **123**, 526–533; (*c*) N. A. McGrath and R. T. Raines, *Chem. Res.*, 2011, **44**, 752–761.

6 (*a*) R. J. Payne and C.-H. Wong, *Chem. Commun.*, 2010, **46**, 21–43; (*b*) P. Siman and A. Brik, *Org. Biomol. Chem.*, 2012, **10**, 5684–5697; (*c*) L. Raibaut, N. Ollivier and O. Melnyk, *Chem. Soc. Rev.*, 2012, **41**, 7001–7015; (*d*) N. Metanis, E. Keinan and P. E. Dawson, *Angew. Chem., Int. Ed.*, 2010, **49**, 7049–7052; (*e*) S. D. Townsend, Z. Tan, S. Dong, S. Shang, J. A. Brailsford and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2012, **134**, 3912–3916.

7 (*a*) D. Crich and A. Banerjee, *J. Am. Chem. Soc.*, 2007, **129**, 10064–100065; (*b*) C. Haase, H. Rohde and O. Seitz, *Angew. Chem., Int. Ed.*, 2008, **47**, 6807–6810; (*c*) J. Chen, Q. Wan, Y. Yuan, J. Zhu and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 2008, **47**, 8521–8524.

8 (*a*) R. Yang, K. K. Pasunooti, F. Li, X.-W. Liu and C.-F. Liu, *J. Am. Chem. Soc.*, 2009, **131**, 13592–13593; (*b*) J. Chen, P. Wang, J. Zhu, Q. Wan and S. J. Danishefsky, *Tetrahedron*, 2010, **66**, 2277–2283; (*c*) J. Chen, P. Wang, J. Zhu, Q. Wan and S. J. Danishefsky, *Tetrahedron*, 2010, **66**, 2277–2283; (*d*) Z. Tan, S. Shang and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 2010, **49**, 9500–9503; (*e*) S. Shang, Z. Tan, S. Dong and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2011, **133**, 10784–10786; (*f*) P. Siman, S. V. Karthikeyan and A. Brik, *Org. Lett.*, 2012, **14**, 1520–1523; (*g*) L. R. Malins, K. M. Cergol and R. J. Payne, *ChemBioChem*, 2013, **14**, 559–563; (*h*) R. E. Thompson, B. Chan, L. Radom, K. A. Jolliffe and R. J. Payne, *Angew. Chem., Int. Ed.*, 2013, **52**, 9723–9727; (*i*) K. M. Cergol, R. E. Thompson, L. R. Malins, P. Turner and R. J. Payne, *Org. Lett.*, 2014, **16**, 290–293; (*j*) S. D. Townsend, Z. Tan, S. Dong, S. Shang, J. A. Brailsford and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2012, **134**, 3912–3916.

9 (*a*) D. D. Van Slyke and A. Hiller, *Proc. Natl. Acad. Sci. U. S. A.*, 1921, **7**, 185–186; (*b*) J. C. Sheeham, K. Maeda, A. K. Sen and J. A. Stock, *J. Am. Chem. Soc.*, 1962, **84**, 1303–1305; (*c*) W. Traub and K. A. Piez, *Adv. Protein Chem.*, 1971, **25**, 243–352; (*d*) H. Maehr, C.-M. Liu, N. J. Palleroni, J. Smallheer, L. Todan, T. H. Williams and J. F. Blount, *J. Antibiot.*, 1986, **39**, 17–25; (*e*) T. A. Smitka, J. B. Deeter, A. H. Hunt, F. P. Mertz, R. M. Ellis, L. D. Boeck and R. C. Yao, *J. Antibiot.*, 1988, **41**, 726–733; (*f*) A. A. Tymiak, T. J. McCormick and S. E. Unger, *J. Org. Chem.*, 1989, **54**, 1149–1157; (*g*) S. Omura, T. Fujimoto, K. Otoguro, R. Koriguchi, H. Tanaka and Y. Sasaki, *J. Antibiot.*, 1991, **44**, 113–116; (*h*) S. Omuro, K. Matsuzaki, T. Fujimoto, K. Kosuge, T. Furuya, S. Fujita and A. Nakagawa, *J. Antibiot.*, 1991, **44**, 117–118; (*i*) S. Chatterjee, D. K. Chatterjee, R. H. Jani, J. Blumbach, B. N. Ganguli, N. Klesel, M. Limbert and G. Siebert, *J. Antibiot.*, 1992, **45**, 839–845; (*j*) For amino acids as enzyme inhibitors see: C. Walsh, *Tetrahedron*, 1982, **38**, 871–909; (*k*) A. I. Ayi and R. Guedj, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2045–2051.

10 For mono target oriented hydroxy amino acid synthesis see: For-leu: (*a*) D. Seebach, E. Juaristi, D. D. Miller, C. Schickli and T. Weber, *Helv. Chim. Acta*, 1987, **70**, 237–261; (*b*) D. A. Evans, E. B. Sjogren, A. E. Weber and R. E. Conn, *Tetrahedron Lett.*, 1987, **28**, 39–42; (*c*) M. E. Jung and Y. H. Jung, *Tetrahedron Lett.*, 1989, **48**, 6637–6640; (*d*) C. G. Cald Well and S. S. Bondy, *Synthesis*, 1990, 34–35; (*e*) E. J. Corey, D. H. Lee and S. Choi, *Tetrahedron Lett.*, 1992, **33**, 6735–6738; (*f*) J. S. Yadav, S. Chandrasekhar, R. Y. Reddy and A. V. R. Rao, *Tetrahedron*, 1995, **51**, 2749–2754; For Pro: (*g*) S. Hanessian and S. P. Sahoo, *Can. J. Chem.*, 1984, **62**, 1400–1402; (*h*) J. Cooper, P. T. Gallagher and D. W. Knight, *J. Chem. Soc., Chem. Commun.*, 1988, 509–510; (*i*) N. B. Kalamkar, V. M. Kasture and D. D. Dhavale, *Tetrahedron Lett.*, 2010, **51**, 6745–6747 and references cited therein. For a review on 5-hydroxy-lysine see: (*j*) K. R. Herbert, G. M. Williams, G. J. S. Cooper and M. A. Brimble, *Org. Biomol. Chem.*, 2012, **10**, 1137–1144; For Lys: (*k*) P. F. Hughes, S. H. Smith and J. T. Olson, *J. Org. Chem.*, 1994, **59**, 5799–5802; For Glu: (*l*) T. Kunieda, T. Ishizuka, T. Higuchi and M. Hirobe, *J. Org. Chem.*, 1988, **53**, 3381–3383; (*m*) H. Takahata, Y. Banba, M. Tajima and T. Momose, *J. Org. Chem.*, 1991, **56**, 240–245; (*n*) H. Takahata, Y. Banba, M. Tajima and T. Momose, *J. Org. Chem.*, 1991, **56**, 240–245; (*o*) S. Shiokawa, T. Ohta and S. Nozoe, *Chem. Pharm. Bull.*, 1992, **40**, 1398–1399; (*p*) N. D-Uomo, M. C. D-Giovannia, D. Misiti, G. Zappia and G. D. Monache, *Liebigs Ann. Chem.*, 1994, 641–644; (*q*) L. Tamborini, P. Conti, A. Pinto, S. Colleoni, M. Gobbi and C. D. Micheli, *Tetrahedron*, 2009, **65**, 6083–6089.

11 For multiple target oriented hydroxy amino acid synthesis see: (*a*) Y. N. Belokon, A. G. Bulychev, S. V. Vitt, Y. T. Struchkov, A. S. Batsanov, T. V. Timofeeva, V. A. Tsyryapkin, M. G. Ryzhov, L. A. Lysova, V. I. Bakhrnutov and V. M. Belikov, *J. Am. Chem. Soc.*, 1985, **107**, 4252–4259; (*b*) S. S. Norio, B. M. Inabaf, T. Moriwaket and S. Torii, *Tetrahedron Lett.*, 1985, **26**, 5309–5312; (*c*) D. A. Evans, E. B. Sjogren, A. E. Weberm and R. E. Conn, *Tetrahedron Lett.*, 1987, **28**, 39–42; (*d*) D. A. Evans and A. E. Weber, *J. Am. Chem. Soc.*, 1987, **109**, 7151–7157; (*e*) M. Hirama, H. Hioki and S. Itô, *Tetrahedron Lett.*, 1988, **29**, 3125–3128; (*f*) R. C. Roemmele and H. Rapoport, *J. Org. Chem.*, 1989, **54**, 1866–1875; (*g*) M. A. Blaskovich and G. A. Lajoie, *J. Am. Chem. Soc.*, 1993, **115**, 5021–5030; (*h*) M. A. Blaskovich and G. A. Lajoie, *J. Am. Chem. Soc.*, 1993, **115**, 5021–5030; (*i*) Y. N. Belokon, K. A. Kochetkov, N. S. Ikonnikov, T. V. Strelkova, S. R. Harutyunyan and A. S. Saghiyan, *Tetrahedron: Asymmetry*, 2001, **12**, 481–485; (*j*) B. Ma, J. L. Parkinson and S. L. Castle, *Tetrahedron Lett.*, 2007, **48**, 2083–2086; (*k*) S. G. Davies, A. M. Fletcher, A. B. Frost, J. A. Lee, P. M. Roberts and J. E. Thomson, *Tetrahedron*, 2013, **69**, 8885–8898; (*l*) S. C. Deshmukh and P. Talukdar, *J. Org. Chem.*, 2014, **79**, 11215–11225; (*m*) Y. Singjunla, J. Baudoux and J. Rouden, *Org. Lett.*, 2013, **15**, 5770–5773; (*n*) K. Makino, T. Goto, Y. Hiroki and Y. Hamada, *Angew. Chem., Int. Ed.*, 2004, **43**, 882–882.

12 (*a*) D. R. Spring, *Org. Biomol. Chem.*, 2003, **1**, 3867–3870; (*b*) D. S. Tan, *Nat. Chem. Biol.*, 2005, **1**, 74–84.

13 (*a*) K. S. A. Kumar, M. Haj-Yahya, D. Olschewski, H. A. Lashuel and A. Brik, *Angew. Chem., Int. Ed.*, 2009, **48**, 8090–8094; (*b*) Z. Harpaz, P. Siman, K. S. A. Kumar and A. Brik, *ChemBioChem*, 2010, **11**, 1232–1235; (*c*) K. S. A. Kumar, *Bioorg. Med. Chem.*, 2013, **21**, 3609–3613; (*d*) V. P. Vyavahare, C. Chakraborty, B. Maity, S. Chattopadhyay, V. G. Puranik and D. D. Dhavale, *J. Med. Chem.*, 2007, **50**, 5519–5523; (*e*) K. S. A. Kumar, J. S. Rathee, M. Subramanian and S. Chattopadhyay, *J. Org. Chem.*, 2013, **78**, 7406–7413.

14 N. Nepomniaschiy, V. Grimminger, A. Cohen, S. DiGiovanni, H. Lashuel and A. Brik, *Org. Lett.*, 2008, **11**, 5243–5524 and references cited therein.

15 (*a*) P. M. Headley and S. Grillner, *Trends Pharmacol. Sci.*, 1990, **11**, 205–211; (*b*) H. Bräuner-Osborne, J. Egebjerg, E. Ø. Nielsen, U. Madsen and P. Krogsgaard-Larsen, *J. Med. Chem.*, 2000, **43**, 2609–2645; (*c*) J. N. C. Kew and J. A. Kemp, *Psychopharmacology*, 2005, **179**, 4–29.
16 J. M. J. Tronchet, B. Gentile, J. Ojha-Poncet, G. Moret, D. Schwarzanbach and F. Barblat-Ray, *Carbohydr. Res.*, 1977, **59**, 87–93.
17 E. Dalcanale and F. Montanari, *J. Org. Chem.*, 1986, **51**, 567–569.
18 (*a*) V. Lee and M. S. Newman, *Org. Synth.*, 1970, **50**, 77; (*b*) J. Mulzer, in *Comprehensive Organic Functional Group Transformations*, ed. A. R. Katritzky, O. Meth-Cohn and C. W. Rees, Pergamon Press, Oxford, 1995, vol. 5, pp. 146 and 276; (*c*) J. Podlech and D. Seebach, *Angew. Chem., Int. Ed.*, 1995, **34**, 471–472; (*d*) J. N. Tilekar, N. T. Patil and D. D. Dhavale, *Synthesis*, 2000, **3**, 395–398; (*e*) C. W. Jefford, Q. Tang and A. Zaslona, *J. Am. Chem. Soc.*, 1991, **113**, 3513–3518.
19 (*a*) J. H. Lee, J. E. Kang, M. S. Yang, K. Y. Kang and K. H. Park, *Tetrahedron*, 2001, **57**, 10071–10076; (*b*) L. M. Mascavage, Q. Lu, J. Vey, D. R. Dalton and P. J. Carrol, *J. Org. Chem.*, 2001, **66**, 3621–3626; (*c*) E. M. Dangerfield, C. H. Plunkett, B. L. Stocker and M. S. M. Timmer, *Molecules*, 2009, **14**, 5298–5307.