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Synthesis of (+)-(1*R*,2*S*,9*S*,9*aR*)-octahydro-1*H*-pyrrolo-[1,2-*a*]azepine-1,2,9-triol: a potential glycosidase inhibitor

Karl B. Lindsay and Stephen G. Pyne*

Department of Chemistry, University of Wollongong, New South Wales, 2522 Wollongong, Australia

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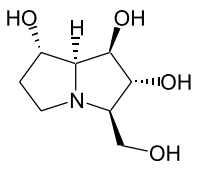
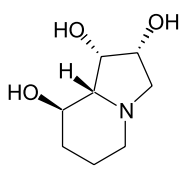
Abstract—The title compound was prepared as a potential glycosidase inhibitor. Key steps in the synthesis are vinyl epoxide aminolysis, ring-closing metathesis, *cis*-dihydroxylation and then ring closure.

1. Introduction

Polyhydroxylated pyrrolizidine [e.g., (+)-alexine (**1**)] and indolizidine [e.g., (−)-swainsonine (**2**)] alkaloids are potent glycosidase inhibitors,[1,2] making these compounds good lead compounds for the development of new drugs for the treatment of viral infections, cancer and diabetes.[3,4] Consequently a substantial volume of research has been conducted, aimed at the synthesis of these alkaloids and their analogues.[1,2,4,5] While compounds with the 5,5- and 5,6-heterocyclic ring system found in these natural products have been extensively studied, we were surprised to discover that analogues with the corresponding 5,7-heterocyclic ring system (i.e. 1*H*-pyrrolo[1,2-*a*]azepines) remain relatively unexplored. Recently we reported an asymmetric total synthesis of (−)-swainsonine (**2**) and two of its diastereomers, 1,2-*diepi*-swainsonine and 1,2,8a-*triepi*-swainsonine.[6] The non-chiral pool route used in that synthesis was very flexible, and we envisaged that it could be readily applied to polyhydroxylated systems of other ring size combinations, such as the 5,7-heterocyclic ring system of (+)-**11**, reported here (Scheme 1).



(+)-alexine (**1**)



(-)-swainsonine (**2**)

2. Results and discussion

The starting vinyl epoxide (−)-(2*S*,3*R*)-**3** was prepared from the corresponding Sharpless epoxy alcohol (92% ee) via Swern oxidation followed by a Wittig-olefination reaction.[6–9]

A solution of the vinyl epoxide (−)-**3** and allylamine (3 equiv.) in acetonitrile was heated at 120 °C in a closed teflon vessel in a microwave reactor (Milestone, ETHOS SEL), using LiOTf (1 equiv.) as a catalyst.[8] This gave only amino alcohol (−)-**4**[6,8] via an S_N2 ring opening, with no evidence of any other regio/stereoisomers. After protection of (−)-**4** as its *N*-Boc derivative, ring-closing metathesis using 5 mol% benzylidene-bis-(tricyclohexylphosphine)-dichlororuthenium (Grubbs' catalyst) in refluxing CH_2Cl_2 at high dilution (~4 mM)[6,8] for 20 h, gave the 2,5-dihydropyrrole (−)-**5** in excellent yield (85% overall for the 2 steps). Compound (−)-**5** was treated with 5 mol% $K_2OsO_4{\cdot}2H_2O$ and NMO (2.1 equiv.), to effect *cis*-dihydroxylation of the double bond, giving triol (−)-**6** also in excellent yield (96%). Only one diastereomeric product was isolated, which was expected to arise from delivery of the two hydroxyl groups to the least hindered face of the 3,4-double bond in (−)-**5**.[6] Triol (−)-**6** was then reacted with NaH and benzyl bromide, together with a catalytic amount of nBu$_4$NI.[10] This gave the desired tri-*O*-benzyl derivative (−)-**7** in 55% yield. The low yield was due primarily to the formation of an unwanted oxazolidinone (+)-**8**, which was isolated in 21% yield. No attempt was made to optimise the conditions of this reaction to lower the amount of (+)-**8** being formed, but it is likely that a higher concentration of *n*BuNI and/or benzyl bromide would improve the ratio of compounds (−)-**7** and (+)-**8** in the reaction. Compound (−)-**7** was then reacted with trifluoroacetic acid to accomplish N-deprotection. By using anisole as a cation trap, the *p*-methoxybenzyl (PMB) protecting

Keywords: 2,5-Dihydropyrroles; Vinyl epoxide; Aminolysis; Ring-closing metathesis; Dihydroxylation; Polyhydroxylated alkaloids; Azepine.
* Corresponding author. Tel.: +612-4221-3511; fax: +612-4221-4287; e-mail address: pyne@uow.edu.au

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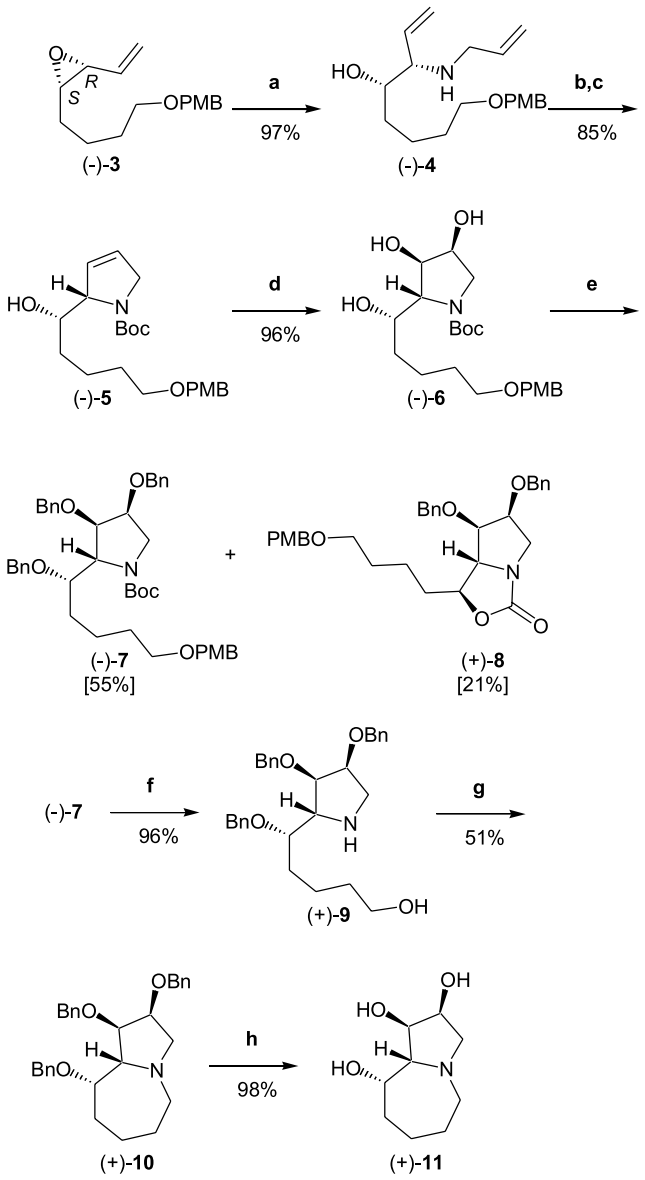

Scheme 1. Reagents and conditions: (a) allylamine (3 equiv.), LiOTf (1 equiv.), CH_3CN, 120 °C, microwave, 1 h; (b) $(Boc)_2O$ (2 equiv.), Et_3N (2 equiv.), Et_2O, rt, 18 h; (c) $Cl_2(Cy_3P)_2Ru{=}CHPh$ (5 mol%), CH_2Cl_2 reflux, 20 h; (d) $K_2OsO_4.2H_2O$ (5 mol%), NMO (2.2 equiv.), acetone, water, rt, 20 h; (e) NaH (6 equiv.), BnBr (5.5 equiv.), nBu$_4$NI (0.3 equiv.), THF, rt, 3 d; (f) TFA (10 equiv.), anisole (10 equiv.), CH_2Cl_2, rt, 2 h; (g) PPh_3 (2.5 equiv.), CBr_4 (2.5 equiv.), NEt_3 (40 equiv.) CH_2Cl_2 4 °C, 20 h; (h) $PdCl_2$ (0.9 equiv.), H_2 (1 atm), MeOH, rt, 1 h; ion-exchange.

group was also removed, resulting in the formation of amino alcohol (+)-**9** in high yield (96%).[6] Formation of the 7-membered azepine ring, was achieved by treating (+)-**9** with carbon tetrabromide and triphenylphosphine in the presence of triethylamine at 4 °C for 20 h. This gave a moderate yield (51%) of the protected bicyclic compound (+)-**10**, but it should be noted that this reaction was only performed once, and higher yields may be achieved with further optimisation (e.g., longer reaction time). Finally, *O*-benzyl removal by catalytic hydrogenolysis, using $PdCl_2$ under an atmosphere of H_2 (1 atm), gave (+)-**11**.HCl in excellent yield, which was purified by ion-exchange chromatography to give the free amine (+)-**11** as a white solid (mp 100–104 °C, $[\alpha]_D^{25}$=+60.3 (*c* 0.46, MeOH)) in 98% yield.

3. Conclusions

In summary, the synthesis of a potential glycosidase inhibitor, based on a novel 1*H*-pyrrolo[1,2-*a*]azepine structure has been achieved. We believe the method is flexible enough to allow the synthesis of many analogues, including those with different stereochemistries and/or larger ring systems simply by varying the vinyl epoxide stereochemistry, and/or epoxide side-chain length. Furthermore, this method could potentially be extended to the synthesis of the key 1*H*-pyrrolo[1,2-*a*]azepine core of the stemona alkaloids.[8]

4. Experimental

4.1. General

4.1.1. (3*S*,4*S*)-8-[(4-Methoxyphenyl)methoxy]-3-(2-propenylamino)-1-octen-4-ol (4). The vinyl epoxide **3**[6–9] (500 mg, 1.90 mmol) was dissolved in CH_3CN (3 mL) then allylamine (328 mg, 5.718 mmol) and LiOTf (297 mg, 1.90 mmol) were added. The mixture was placed in a teflon tube with a 100 bar pressure cap, then heated in a microwave reactor at 120 °C for 1 h. After cooling all volatiles were removed in vacuo to give an oil. Pure product was obtained by column chromatography on flash silica gel (increasing polarity from 5 to 15% MeOH in DCM as eluant), which gave the title compound (591 mg, 1.85 mmol, 97%) as a pale yellow oil.

$[\alpha]_D^{29}$=−7 (*c* 1.3, $CHCl_3$). MS (CI+) *m*/*z* 320 (100%) (M+1), HRMS (CI+) found 320.2238, Calcd for $C_{19}H_{30}NO_3$ 320.2226 (M+1). δ_H (300 MHz, $CDCl_3$): 1.20–1.70 (6H, m, H5, H6 and H7), 2.43 (2H, br.s, NH and OH), 2.77 (1H, t, *J*=8.7 Hz, H3), 3.07 (1H, ddt, *J*=13.8. 6.3, 1.2 Hz, H1′a), 3.20–3.50 (5H, m, H4, H8, H1′b), 3.80 (3H, s, OCH_3), 4.42 (2H, s, OCH_2Ar), 5.05–5.30 (4H, m, H1 and H3′), 5.49 (1H, ddd, *J*=16.8, 10.2, 8.4 Hz, H2), 5.87 (1H, m, H2′), 6.87 (2H, dt, *J*=9.0, 2.7 Hz, 2×ArCH), 7.25 (2H, dt, *J*=9.0, 2.7 Hz, 2×ArCH). δ_C (75 MHz, $CDCl_3$): 22.3 (t, C6), 29.7, 33.4 (t, C5 and C7), 49.2 (t, C1′), 55.2 (q, OCH_3), 66.4 (d, C3), 70.0 (t, C8), 72.5 (t, OCH_2Ar), 72.6 (d, C4), 113.7 (d, 2×ArCH), 116.2, 118.5 (t, C1 and C3′), 129.2 (d, 2×ArCH), 130.6 (s, ArC), 136.4, 136.8 (d, C2 and C2′), 159.0 (s, ArC).

4.1.2. *N*-Boc derivative of 4 (1,1-dimethylethyl *N*-[(1*S*,2*S*)-1-ethenyl-2-hydroxy-6-[(4-methoxyphenyl)methoxy]-hexyl]-*N*-(2-propenyl)-carbamate. The amine **4** (110 mg, 0.344 mmol) was dissolved in Et_2O (10 mL), then triethylamine (75 mg, 0.776 mmol) and di-*tert*-butyldicarbonate (161 mg, 0.776 mmol) were added. The mixture was stirred at rt for under N_2 18 h then all volatiles were removed in vacuo to give an oil. Pure product was obtained by column chromatography (increasing polarity from 25% to 50% EtOAc in petroleum spirit (pet. sp.) as eluant), which gave the title compound (135 mg, 0.322 mmol, 94%) as a clear oil. $[\alpha]_D^{29}$=−15 (*c* 1.0, $CHCl_3$). MS (CI+) *m*/*z* 420 (30%) (M+1), HRMS (CI+) found 420.2745, Calcd for $C_{24}H_{38}NO_5$ 420.2750 (M+1). δ_H (300 MHz, $CDCl_3$): 1.10–1.65 (7H, m, H3, H4, H5 and OH), 1.42 (9H, s, $(CH_3)_3C$), 3.41 (2H, br. t, *J*=6.0 Hz, H6), 3.77 (3H, s,

OCH_3), 3.60–3.84 (3H, m, H2 and H1″), 3.94 (1H, br. t, J=7.5 Hz, H1), 4.40 (2H, s, OCH_2Ar), 5.02–5.22 (4H, m, H2′ and H3″), 5.72–5.96 (2H, m, H1′ and H2″), 6.84 (2H, d, J=8.7 Hz, 2×ArCH), 7.23 (2H, d, J=8.7 Hz, 2×ArCH). δ_C (75 MHz, $CDCl_3$): 22.4 (t, C4), 28.3 (q, (CH_3)$_3$C), 29.7, 34.2 (t, C3 and C5), 50.0 (br. t, C1″), 55.1 (q, OCH_3), 65.6 (d, C1), 69.9 (t, C6), 71.9 (br. d, C2), 72.4 (t, OCH_2Ar), 80.2 (s, (CH_3)$_3$$C$), 113.5 (d, 2×ArCH), 116.6, 117.8 (t, C2′ and C3″), 129.0 (d, 2×ArCH), 130.5 (s, ArCH), 134.2, 134.9 (d, C1′ and C2″), 158.0 (s, ArCH), 171.0 (br. s, CO).

4.1.3. 1,1-Dimethylethyl (2*S*)-2,5-dihydro-2-[(1*S*)-1-hydroxy-5-[(4-methoxyphenyl)methoxy]pentyl]-1*H*-pyrrole-1-carboxylate (5). The *N*-Boc derivative of **4** (500 mg, 1.193 mmol) was dissolved in dry DCM (300 mL) then benzylidene-bis-(tricyclohexlphosphine)dichlororuthenium (Grubbs' cat.) (50 mg, 0.061 mmol) was added. The mixture was heated at reflux under N_2 for 20 h, then cooled, before all solvent was removed in vacuo to give an oil. Pure product was obtained by column chromatography (increasing polarity from 25 to 50% EtOAc in pet. sp. as eluant), which gave the title compound (426 mg, 1.088 mmol, 91.2%) as a clear oil. $[\alpha]_D^{29}$=−79 (*c* 0.9, $CHCl_3$). MS (CI+) *m*/*z* 392 (37%) (M+1), HRMS (CI+) found 392.2409, Calcd for $C_{22}H_{34}NO_5$ 392.2437 (M+1). δ_H (300 MHz, $CDCl_3$): 1.48 (9H, s, (CH_3)$_3$C), 1.20–1.73 (6H, m, H2′, H3′ and H4′), 3.44 (2H, t, J=6.3 Hz, H5′), 3.56–3.66 (1H, m, H2), 3.79 (3H, s, OCH_3), 3.99 (1H, br. d, J=15.7 Hz, H5a), 4.18 (1H, br. d, J=15.6 Hz, H5b), 4.41 (2H, s, OCH_2Ar), 4.54 (1H, m, H1′), 4.96 (1H, br. s, OH), 5.60–5.90 (2H, m, H3 and H4), 6.86 (2H, dt, J=8.4, 3.0 Hz, 2×ArCH), 7.24 (2H, dt, J=8.4, 3.0 Hz, 2×ArCH). δ_C (75 MHz, $CDCl_3$): 21.7 (t, C3′), 28.4 (q, (CH_3)$_3$C), 29.7, 33.3 (C2′ and C4′), 53.9 (t, C5), 55.2 (q, OCH_3), 70.0 (t, C5′), 70.0 (d, C2), 72.4 (t, OCH_2Ar), 75.4 (d, C1′), 80.4 (s, (CH_3)$_3$$C$), 113.5 (d, 2×ArCH), 126.4, 126.7 (d, C3 and C4), 129.0 (d, 2×ArCH), 130.5 (s, ArC), 156.6 (CO), 158.8 (s, ArC).

4.1.4. 1,1-Dimethylethyl (2*R*,3*R*,4*S*)-2-[(1*S*)-1-hydroxypentyl-5-[(4-methoxyphenyl)methoxy]]-3,4-dihydroxy-1-pyrrolidinecarboxylate (6). The 2,5-dihydropyrrole **5** (426 mg, 1.088 mmol) was dissolved in acetone (6 mL), then water (4 mL), *N*-methyl-morpholine-*N*-oxide (269 mg, 2.32 mmol) and $K_2OsO_4.2H_2O$ (20 mg, 0.0544 mmol) were added. The mixture was stirred at rt for 20 h, then all volatiles were removed in vacuo to give a brown oil. Pure product was obtained by column chromatography (increasing polarity from 2.5 to 10% MeOH in DCM as eluant), which gave the title compound (442 mg, 1.039 mmol, 95.5%) as a clear oil. $[\alpha]_D^{27}$=−28 (*c* 1.0, $CHCl_3$). MS (CI+) *m*/*z* 426 (100%) (M+1), HRMS (CI+) found 426.2482, Calcd for $C_{22}H_{36}NO_7$ 426.2492 (M+1). δ_H (300 MHz, $CDCl_3$): 1.40 (9H, s, (CH_3)$_3$C), 1.30–1.70 (8H, m, H2′, H3′, H4′ and 2×OH), 3.30–4.30 (9H, m, H2, H3, H4, H5, H1′, H5′ and OH), 3.78 (3H, s, OCH_3), 4.40 (2H, s, OCH_2Ar), 6.84 (2H, d, J=8.4 Hz, 2×ArCH), 7.23 (2H, d, J=8.4 Hz, 2×ArCH). δ_C (75 MHz, $CDCl_3$): 22.0 (br. t, C3′), 28.1 (q, (CH_3)$_3$C), 29.2, 32.7 (t, C2′ and C4′), 51.3 (br. t, C5), 54.9 (q, OCH_3), 67.0 (br. d, C2), 69.5 (br. d, C4), 69.7 (t, C5′), 72.2 (t, OCH_2ArCH), 72.9 (br. d, C3), 76.4 (d, C1′), 80.3 (s, (CH_3)$_3$$C$), 113.5 (d, 2×ArCH), 129.0 (d, 2×ArCH), 130.1 (s, ArC), 156.8 (br. s, CO), 158.8 (s, ArC).

4.1.5. 1,1-Dimethylethyl (2*R*,3*R*,4*S*)-2-[(1*S*)-5-[(4-methoxyphenyl)methoxyoxy)]-1-(phenylmethoxy)pentyl]-3,4-bis(phenylmethoxy)-1-pyrrolidinecarboxylate (7) and (1*S*,6*S*,7*R*,7*aR*)-tetrahydro-1-[4-[(4-methoxyphenyl)-methoxy]butyl]-6,7-bis(phenylmethoxy)-1*H*,3*H*-pyrrolo-[1,2-*c*]oxazol-3-one (8). The triol **6** (440 mg, 1.034 mmol) was dissolved in THF (60 mL) then NaH (302 mg, 6.024 mmol, 50% dispersion in wax), benzylbromide (0.64 mL, 5.50 mmol) and nBu$_4$NI (112 mg, 0.30 mmol) were added. The mixture was stirred at rt under N_2 for 3 d then poured into water (50 mL) and extracted with DCM (3×40 mL). The combined organic portions were dried ($MgSO_4$), filtered and evaporated in vacuo to give an oil. Pure products were obtained by column chromatography (increasing polarity from 20 to 100% EtOAc in pet. sp. as eluant), which gave the title compound (396 mg, 0.569 mmol, 55%), and the oxazolidinone (116 mg, 0.218 mmol, 21%) as clear oils.

Compound **7**. $[\alpha]_D^{30}$=−29 (*c* 3.96, $CHCl_3$). MS (ES+) *m*/*z* 696.4 (100%) (M+1), HRMS (ES+) found 696.3895, Calcd for $C_{43}H_{54}NO_7$ 696.3900 (M+1). δ_H (300 MHz, $CDCl_3$): 1.45 (9H, s, (CH_3)$_3$C), 1.20–1.70 (6H, m, H2′, H3′ and H4′), 3.28–3.43 (3H, m, H5a and H5′), 3.52 (1H, br. d, J=6.3 Hz, H5b), 3.78 (3H, s, OCH_3), 3.75–3.87 (1H, m, H1′), 3.87–4.06 (2H, m, H3 and H4), 4.17–4.74 (7H, m, H2 and 3×OCH_2Ph), 4.40 (2H, s, OCH_2Ar), 6.86 (2H, d, J=9.0 Hz 2×ArCH), 7.21–7.36 (17H, m, 2×ArCH and 3×OCH$_2$*Ph*). δ_C (75 MHz, $CDCl_3$): two rotamers were evident in equal intensity 22.9/23.2 (t, C3′), 28.4 (q, (CH_3)$_3$C), 29.6 (t, C4′), 30.0/30.4 (t, C2′), 48.8/49.5 (t, C5), 55.2 (q, OCH_3), 62.5/63.6 (d, C2), 69.9 (t, C5′), 71.2, 71.3/71.8, 72.4, 72.3/72.6 (t, OCH_2Ar and 3×OCH_2Ph), 75.3/76.3, 76.5/77.8, 78.4/78.6 (d, C3, C4 and C1′), 79.7/80.0 (s, (CH_3)$_3$$C$), 113.7 (d, ArCH), 127.6, 127.7, 127.7, 128.0, 128.0, 128.2, 128.2, 128.3, 128.3 (d, 3×OCH$_2$*Ph*), 129.1 (d, 2×ArCH), 130.6 (s, ArCH), 137.6, 138.0, 138.4 (s, 3×OCH$_2$*Ph*), 159.0 (s, 2×ArCH), 164.0 (s, CO).

Compound **8**. $[\alpha]_D^{30}$=+28 (*c* 1.03, $CHCl_3$). MS (ES+) *m*/*z* 532.3 (47%) (M+1), HRMS (ES+) found 532.2698, Calcd for $C_{32}H_{37}NO_6$ 532.2699 (M+1). δ_H (300 MHz, $CDCl_3$): 1.40–1.86 (6H, m, H1′, H2′ and H3′), 3.37 (1H, dd, J=12.9, 1.5 Hz, H5a), 3.42 (2H, t, J=6.3 Hz, H4′), 3.53 (1H, dd, 9.0, 4.8 Hz, H7), 3.70–3.80 (2H, m, H5b and H7*a*), 3.77 (3H, s, OCH_3), 4.09 (1H, td, J=5.1, 1.5 Hz, H6), 4.22 (1H, ddd, J=7.2, 5.4, 3.6 Hz, H1), 4.39 (1H, d, J=12.0 Hz, OCH_2Ph), 4.41 (2H, s, OCH_2Ar), 4.59 (2H, AB system, J=12.0 Hz, OCH_2Ph), 4.65 (1H, d, J=12.0 Hz, OCH_2Ph), 6.86 (2H, dt, J=8.4, 3.0 Hz, 2×ArCH), 7.22–7.38 (12H, m, 2×ArCH and 2×OCH$_2$*Ph*). δ_C (75 MHz, $CDCl_3$): 21.1 (t, C2′), 29.2 (C3′), 35.0 (t, C1′), 50.8 (t, C5), 55.1 (q, OCH_3), 65.0 (d, C7*a*), 69.4 (t, C4′), 71.9, 72.2, 72.4 (t, OCH_2Ar and 2×OCH_2Ph), 75.8, 79.0 (C6 and C7), 81.5 (d, C1), 113.6 (d, 2×ArCH), 127.7, 127.9, 127.9, 128.1, 128.4, 128.5 (d, 2×OCH$_2$*Ph*), 129.1 (d, 2×ArCH), 130.4 (s, ArC), 137.0, 137.2 (s, 2×OCH$_2$*Ph*), 159.0 (s, ArC), 160.9 (s, C3).

4.1.6. (1′*S*,2*R*,3*R*,4*S*)-1′,3,4-*tris*(Phenylmethoxy)-2-pyrrolidinepentanol (9). The carbamate **7** (396 mg, 0.569 mmol) was dissolved in DCM (5 mL), then TFA (5 mL) and anisole (0.60 mL, 5.44 mmol) were added. The mixture was stirred at rt for 2 h, then all volatiles were removed in vacuo.

The residue was dissolved in $CHCl_3$ then poured into sat. Na_2CO_3 solution (5 mL), and extracted with $CHCl_3$ (3×25 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated in vacuo to give an oil. Pure product was obtained by column chromatography (increasing polarity from 5 to 15% MeOH in DCM as eluant), which gave the title compound (260 mg, 0.547 mmol, 96%) as a clear oil. $[\alpha]_D^{26}$=+81 (*c* 2.60, $CHCl_3$). MS (ES+) *m/z* 476.7 (100%) (M+1), HRMS (ES+) found 476.2808, Calcd for $C_{30}H_{38}NO_4$ 476.2801 (M+1).

δ_H (300 MHz, $CDCl_3$): 1.26–1.90 (6H, m, H2′, H3′ and H4′), 2.96–3.15 (4H, m, H5, NH and OH), 3.31 (1H, dd, *J*=7.5, 2.4 Hz, H2), 3.50 (1H, td, *J*=7.2, 2.4 Hz, H5′), 3.58 (2H, t, *J*=6.3 Hz, H1′), 3.70 (1H, dd, *J*=7.5, 5.1 Hz, H3), 3.90 (1H, q, *J*=4.5 Hz, H4), 4.23 (1H, d, *J*=11.1 Hz OC*H*$_2$Ph), 4.32 (1H, d, *J*=11.7 Hz, OC*H*$_2$Ph), 4.50 (1H, d, *J*=12.0 Hz, OC*H*$_2$Ph), 4.55 (1H, d, *J*=11.4 Hz, OC*H*$_2$Ph), 4.60 (1H, d, *J*=12.0 Hz, OC*H*$_2$Ph), 4.62 (1H, d, *J*=12.0 Hz, OC*H*$_2$Ph), 7.15–7.40 (15H, m, 3×OCH$_2$*Ph*). δ_C (75 MHz, $CDCl_3$): 21.4 (t, C3′), 30.6, 32.5 (t, C2′ and C4′), 49.3 (t, C5), 61.6 (t, C1′), 63.0 (d, C2), 71.2, 71.9, 72.0 (t, 3×O*C*H$_2$Ph), 76.4, 77.5, 79.6 (C3, C4 and C5′), 127.5, 127.6, 127.6, 127.7, 127.9, 128.0, 128.2, 128.2, 128.2 (d, 3×OCH$_2$*Ph*), 137.9, 138.0, 138.3 (s, 3×OCH$_2$*Ph*).

4.1.7. (1*R*,2*S*,9*S*,9*aR*)-Octahydro-1,2,9-*tris*(phenylmethoxy)-1*H*-pyrrolo[1,2-*a*]azepine (10). The amino alcohol **9** (240 mg, 0.505 mmol) was dissolved in DCM (20 mL) then the solution was cooled to 0 °C. Carbontetrabromide (419 mg, 1.263 mmol), and triphenylphosphine (331 mg, 1.263 mmol) were added, then the mixture was stirred under N_2 for 5 min. Triethylamine (2.8 mL, 20.09 mmol) was added, then the mixture was stirred at 0 °C for 2 h, before being left to stand at 4 °C for 18 h. The mixture was poured into water (50 mL), then extracted with DCM (3×40 mL). The combined organic portions were dried ($MgSO_4$), filtered and evaporated in vacuo to give a black semi solid. Pure product was obtained by column chromatography (increasing polarity from 1 to 5% MeOH in DCM as eluant), which gave the title compound (118 mg, 0.258 mmol, 51%) as a clear oil. $[\alpha]_D^{27}$=+64 (*c* 1.15, $CHCl_3$). MS (ES+) *m/z* 458.5 (100%) (M+1), HRMS (ES+) found 458.2694, Calcd for $C_{30}H_{36}NO_3$ 458.2695 (M+1). δ_H (300 MHz, $CDCl_3$): 1.30–1.46 (1H, m, H7a), 1.56–1.94 (5H, m, H6, H7b, H8), 2.51 (1H, ddd, *J*=11.7, 8.4, 4.8 Hz, H5a), 2.84 (1H, dd, *J*=9.3, 7.5 Hz, H3a), 2.90 (1H, dd, *J*=3.9, 2.4 Hz, H9*a*), 3.03 (1H, dt, *J*=11.7, 5.7 Hz, H5b), 3.22 (1H, dd, *J*=9.3, 5.1 Hz, H3b), 3.56 (1H, td, *J*=5.1, 2.4 Hz, H9), 3.85 (1H, t, *J*=4.5 Hz, H1), 4.02 (1H, dt, *J*=7.5, 5.1 Hz, H2), 4.22 (1H, d, *J*=12.0 Hz OC*H*$_2$Ph), 4.35 (1H, d, *J*=12.0 Hz OC*H*$_2$Ph), 4.53 (1H, d, *J*=12.3 Hz OC*H*$_2$Ph), 4.56 (1H, d, *J*=12.0 Hz OC*H*$_2$Ph), 4.58 (1H, d, *J*=12.3 Hz OC*H*$_2$Ph), 4.59 (1H, d, *J*=12.0 Hz OC*H*$_2$Ph), 7.17–7.42 (15H, m, 3×OCH$_2$*Ph*). δ_C (75 MHz, $CDCl_3$): 21.7 (t, C7), 30.0, 31.9 (t, C6 and C8), 56.5, 57.9 (t, C3 and C5), 70.5, 71.6, 72.3 (t, 3×O*C*H$_2$Ph), 72.3 (d, C9*a*), 75.9, 76.8 (d, C1 and C2), 80.4 (d, C9), 127.5, 127.5, 127.7, 127.9, 128.2, 128.2, 128.2, 128.3, 128.3 (d, 3×OCH$_2$*Ph*), 138.5, 138.5, 138.5 (s, 3×OCH$_2$*Ph*).

4.1.8. (1*R*,2*S*,9*S*,9*aR*)-Octahydro-1*H*-pyrrolo[1,2-*a*]azepine-1,2,9-triol (11). The tri-*O*-benzyl compound **10** (115 mg, 0.251 mmol) was dissolved in MeOH (4 mL) then $PdCl_2$ (40 mg, 0.226 mmol) was added and the flask flushed with H_2 (g). The mixture was stirred at rt under an atmosphere of H_2 for 1 h, then the flask was flushed with N_2, before the mixture was filtered through celite. The solids were washed with MeOH (2×10 mL), and the combined filtrates were evaporated in vacuo. The residue was dissolved in water (2 mL) and applied to Dowex-1 basic ion exchange resin (OH− form). Elution with water (50 mL), followed by evaporation of the eluant in vacuo gave the title compound (46 mg, 0.246 mmol, 97.9%) as a white solid. mp. 100–104 °C. $[\alpha]_D^{25}$=+60.3 (*c* 0.46, MeOH). MS (CI+) *m/z* 188 (100%) (M+1), HRMS (ES+) found 188.1301, Calcd for $C_9H_{18}NO_3$ 188.1287 (M+1). δ_H (300 MHz, D_2O): 1.22–1.38 (1H, m, H7a), 1.42–4.62 (4H, m, H6, H7b and H8a), 1.76–1.88 (1H, m, H8b), 2.34 (1H, dt, *J*=12.0, 6.3 Hz, H5a), 2.46 (1H, dd, *J*=10.2, 6.6 Hz, H3a), 2.63–2.70 (1H, m, H9*a*), 2.84 (1H, dt, *J*=11.7, 5.7 Hz, H5b), 3.00 (1H, dd, *J*=10.5, 5.4 Hz, H3b), 3.86–3.97 (3H, m, H1, H2 and H9). δ_C (75 MHz, D_2O ref CH_3CN): 21.4 (t, C7), 29.4, 36.1 (t, C6 and C8), 56.5, 59.7 (t, C3 and C5), 69.6 (d, C9*a*), 70.8 (d, C9), 73.6, 74.9 (d, C1 and C2).

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