ORIGINAL ARTICLE

Synthesis of novel sugar derived aziridines, as starting materials giving access to sugar amino acid derivatives

Cristina E. A. Sousa[1] · **Maria J. Alves**[1]

Abstract

D-Erythrosyl aziridines were obtained from D-erythrosyl triazoles either by photolysis or through diazirine intermediates. These were found to undergo rich, high yielding chemistry by reaction with protic acids (HCl, BiI_3/H_2O and trifluoroacetic acid) leading to two types of furanoid sugar α-amino acids, and polyhydroxylprolines. Based on experimental evidence, reaction mechanisms have been proposed for the syntheses.

Keywords Sugar aminoacids · Polyhydroxyprolines · D-Erythrose · Aziridines · Diazirines

Introduction

Sugar amino acids (SAAs) are hybrids of carbohydrates and amino acids, presenting somehow a nature-like and yet unnatural multifunctional scaffold anchored on a single ensemble (Chakraborty et al. 2005; Guang-Zong et al. 2015; Risseeuw et al. 2013). Compounds **1** belong to the furanoid-type of SAAs, where the glycine subunit is located at an arm. This feature is present in the natural nucleosides antibiotics nikkomycins (Isono 1988; Liao et al. 2009) and polyoxin (Fig. 1) (Isono 1988; Isono et al. 1969; Li et al. 2012). Furanoid-SAAs represents an important class of molecules that play important roles in drug design, namely with potential applications as glycomimetics and peptidomimetics (Risseeuw et al. 2013; Liao et al. 2009; Gruner et al. 2002). Furan's rigidity make SAAs ideal scaffolds for incorporation into peptidomimetics due to its ability to induce conformational restrictions, and so build enhanced metabolic stability on active peptides (Guang-Zong et al. 2015; Chapleur 1998). A great deal of glycomimetic and peptidomimetic libraries have been built on SAAs derivatization and oligomerization, since their multiple stereogenic centers can be exploited for the creation of chemical diversity (Chakraborty et al. 2005;

Risseeuw et al. 2013). For example, in compounds **1**, hydrophilicity control can be easily achieved through hydroxyl group protection. Related hydroxylated prolines **2** and **3**, also obtained in the work are azasugar-based SAAs (Risseeuw et al. 2013). This type of compounds is known to interact with carbohydrate-active enzymes and influence the secondary structure of peptides (Risseeuw et al. 2013; Takeuchi and Marshall 1998), as do their oxygen counterparts. Besides, compounds **2** are of the DMDP (2,5-dideoxy-2,5-imino-D-mannitol) type, known to be potent β-glucosidase inhibitors (Asano et al. 1998).

This work will report the acid-mediated preparation of SAAs **1–4** from D-erythrosyl fused 1,2,3-triazole 1,5-lactones **5**, previously achieved in our laboratory from D-erythrosyl lactone **6** and alkyl azides (Sousa et al. 2017).

Results and discussion

Aziridines are constrained compounds of a highly reactive nature, likely to be excellent intermediates in synthesis. D-Erythrosyl triazole-lactones obtained before in our laboratory were converted into the respective D-erythrosyl fused-aziridines **7**. These gave SAAs or SAAs-like compounds **1–4** under three different protic acids: BiI_3/H_2O, TFA, and HCl (Fig. 2). BiI_3/water was chosen with the purpose of solely cleaving the acetal group; HCl was tried to find if it would behave as HI, formed by heating BiI_3 in water at 100 °C; TFA was tried due to its bulky conjugated base which might resemble the proton donation ability of BiI_3.

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Fig. 1 Representative natural furenoid SAAs: Nikkomycin Z and Polyoxin A
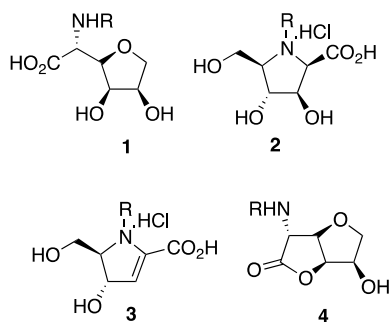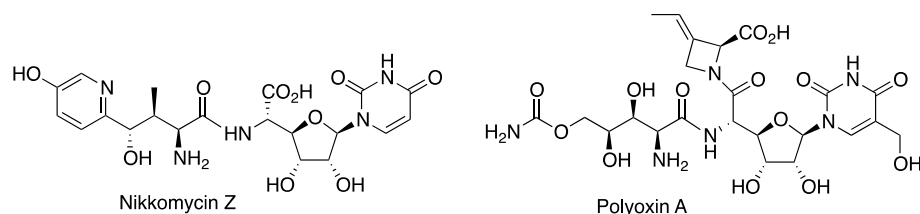
Nikkomycin Z

Polyoxin A

Fig. 2 Obtained SAAs

Aziridines **7** were refluxed in water in the presence of BiI_3 initiating a cascade of reactions ending up in tetrahydrofuran amino acids **1**. A bicyclic structure related to compounds **1**, **4**, was obtained by treating **7** with TFA at room temperature. Under hydrochloric acid treatment, aziridines **7** started a different tandem sequence of reactions leading to prolines: (2R,3R,4R,5R)-1-alkyl-3,4-dihydroxy-5-(hydroxymethyl) pyrrolidine-2-carboxylic acid (**2**), in quantitative yields. Compounds **2** further evolved to their dehydration products **3**, just by prolonging HCl treatment.
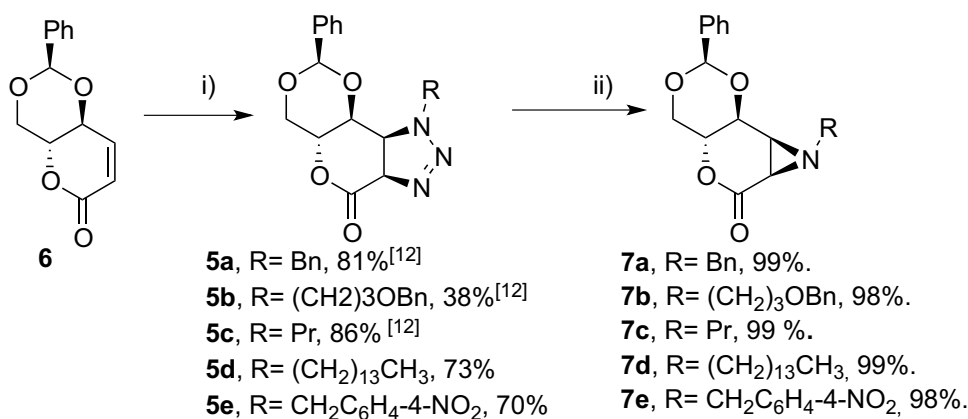
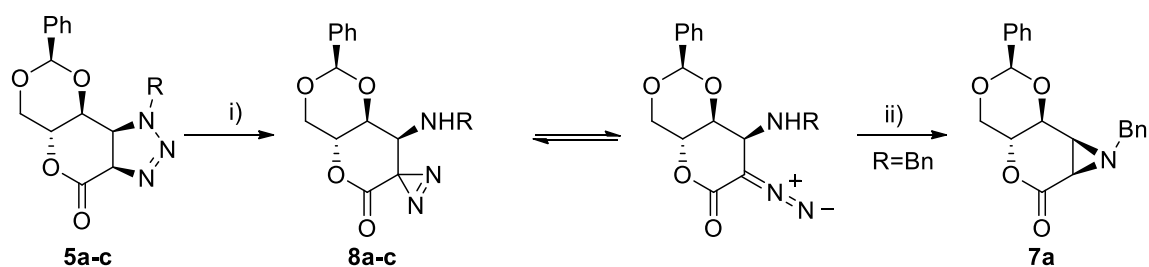## Synthesis of aziridines 7a–e

D-Erythrosyl fused-aziridine lactones **7**, the direct intermediates in the synthesis of compounds **1–4**, were obtained by nitrogen extrusion (Alves and Gilchrist 2009; Singh

et al. 2007) under photolysis from the triazole-lactones **5**. The thermo process was applied first to triazole **5a** (R = Bn), by heating a solution of **5a** in methyl orthoformate at 150 °C. After 24 h no reaction had been initiated (Scheme 1). Though very stable under thermolysis conditions, compound **5a** suffers photolysis in less than 2 h under 254 nm UV light. Initially, methanol was used as solvent to eventually trap the aziridine formed during photolysis and open the three membered ring. However, with the use of ethanol as solvent, aziridine **7a** was obtained in 86% yield after precipitation. The process was optimized when DCM was used as a solvent, giving **7a** in quantitative yield. Triazoles **5b**,**c** were also submitted to photolysis at 254 nm giving quantitative yields of the respective aziridines **7b**,**c**. Two new triazoles **5d**,**e** were obtained according to the literature (Sousa et al. 2017), and the aziridines **7d**,**e** subsequently obtained and isolated in quantitative yields.

In an attempt to cleave the acetal group of compound **5a**, a mild acidic BiI_3 (0.1 equiv.) water/acetonitrile solution of **5a** was heated at 100 °C (Bailey 2007). The diazirine compound **8a** was unexpectedly formed, with the acetal unit remaining intact. The diazirine-diazo equilibrium described in the literature (Bogdanova and Popik 2003) for diazirines was detected for compound **8a** (Scheme 2); the IR spectrum registered a diazo stretching vibration, whereas the carbon atom attached to it appears in the $^{13}C\{^1H\}$ NMR spectrum up at $\delta = 58.2$ ppm. Upon reduction with triethylsilane in the presence of diruthenium tetraacetate, the fused-aziridine **7a** formed back in

Scheme 1 Synthesis of aziridines **7a–e** from triazoles **5a–e** having the D-erythrose core structure—(i) methyl orthoformate, alkyl azide (2 equiv.), 100 °C, N_2 atmosphere, 72 h; (ii) 254 nm (UV), CH_2Cl_2, 1 h 15 min–9 h

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5a, R = Bn, 81%[12]
5b, R = (CH2)3OBn, 38%[12]
5c, R = Pr, 86% [12]
5d, R = $(CH_2)_{13}CH_3$, 73%
5e, R = $CH_2C_6H_4$-4-NO_2, 70%

7a, R = Bn, 99%.
7b, R = $(CH_2)_3OBn$, 98%.
7c, R = Pr, 99 %.
7d, R = $(CH_2)_{13}CH_3$, 99%.
7e, R = $CH_2C_6H_4$-4-NO_2, 98%.

Scheme 2 Synthesis of diazirines **8a–c** from triazoles **5a–c**, followed by transformation of **8a** into **7a**. (i) BiI$_3$ (0.1 equiv.), H$_2$O/acetonitrile (2:1), 100 °C, 2 h 30 min. (ii) HSiEt$_3$ (1 equiv.), Rh$_2$(OAc)$_4$ (0.1 equiv.), dry CH$_2$Cl$_2$, reflux, 25 h, quantitative yield
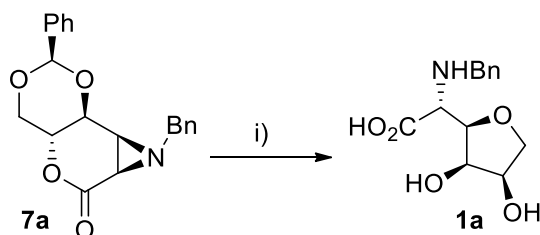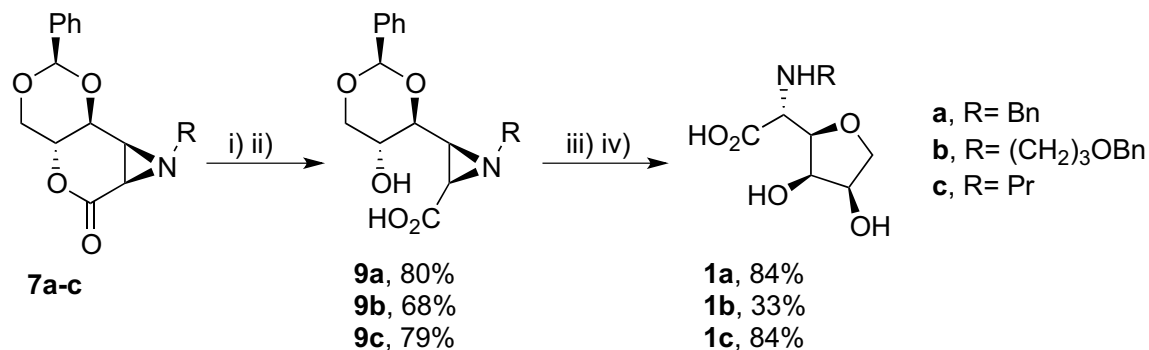

Scheme 3 Synthesis of tetrahydrofuran amino acid **1a** from compound **7a**. (i) H$_2$O/CH$_3$CN (5:2), BiI$_3$ (0.3 equiv.), 100 °C, 6 h

quantitative yield, by displacement of the silane group by the vicinal nitrogen atom, closing up the aziridine ring (Guptill et al. 2013).

Synthesis of tetrahydrofuran α-amino acids 1a-c

By heating at 100 °C a suspension of aziridine **7a** in water in the presence of BiI$_3$ (0.1 equiv.), ^{1}H NMR spectra of reaction aliquots showed formation of a mixture of products. New additions of BiI$_3$ (2 × 0.1 equiv.) led to complete disappearance of the aziridine. Heating was prolonged for 6 h and compound **1a** was isolated as the main product in 33% yield (Scheme 3).

Compound **1a**, together with analogs **1b,c** were obtained in much better yields from aziridines **9a–c**, obtained form **7a–c** by lactone ring opening under NaOH. Tetrahydrofuran α-amino acids **1a–c** were produced from aziridines **9a–c** under reflux in water in the presence of BiI$_3$ (0.1 equiv.) at a fairly good rate (2 h–2 h 30 m), and yields (Scheme 4). All three reactions were followed by ^{1}H NMR spectra, showing formation of single products. However, isolation was found difficult due to their incorporation into a gum, together with inorganic sub-products. This was especially problematic in the case of compound **1b,** were the isolated yield dropped to 33%.

Trifluoroacetic acid (TFA) was also tested as a reaction initiator. When compound **9a** was treated with TFA, compound **4a** was obtained in quantitative yield at room temperature in two days' time. Fused lactone **4a** could also be obtained in quantitative yield from **7a** under TFA, using a longer reaction time, 15 days. ^{1}H NMR spectra of reaction aliquots were taken to monitor the reaction over time. Comparing both experiments, it can be concluded that for the synthesis of compound **4a**, substrate **9a** shows a higher reactivity than compound **7a** (Scheme 5).

The structure of compounds **1** was elucidated by spectroscopic data. Key features direct to a tetrahydrofuran structure due to both the H-2 low field chemical shifts, and H-2

Scheme 4 Synthesis of aziridines **9a–c** from **7a–c**, by lactone ring opening, and their transformation into amino acids **1a–c**. (i) 1 M NaOH sol. (15 mmol, 41–70 equiv.), H$_2$O/ACN (5:1), 40 °C, 24 h; (ii) Amberlite resin IR 120 (H$^+$); (iii) BiI$_3$ (0.1 equiv.), H$_2$O, 100° C, 2 h–2 h 30 m; (iv) Dowex resin 1 × 3 (OH$^-$)

Scheme 5 Synthesis of lactone **4a**, both from **9** and **7a**, by reaction with TFA. (i) TFA (28.1 equiv.), H_2O, rt, 15 days; (ii) TFA (18.4 equiv.), H_2O, rt, 2 days

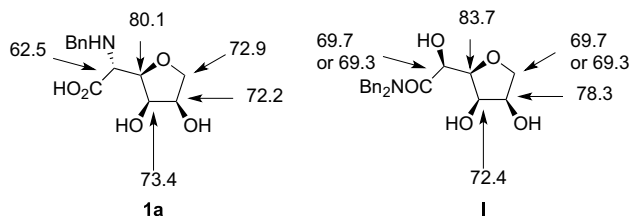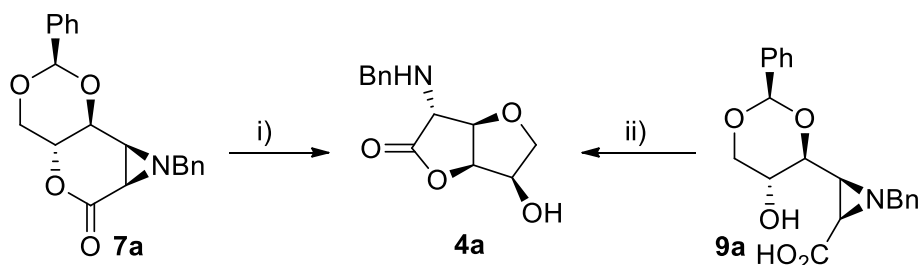**Fig. 3** $^{13}C\{^1H\}$ NMR chemical shifts for structure **1a** and its related structure **I**

peak multiplicities (doublet of doublets). In compound **1a**, H-2 appears at $\delta_H = 4.63$ ppm, and the coupling constants to vicinal Hs are $J = 8.0$ Hz, and 1.2 Hz. ^{13}C data reported in the literature for compound **I** gives additional evidence for compound **1a** (Pino-González and Noé 2008). Chemical shifts of compound **1a**, and its related compound **I** are compiled in Fig. 3.

Synthesis of pyrrolidine-2-carboxylic acids 2a,e, and 3a,e

When compounds **7a,e** were suspended and stirred in HCl-dioxane 1 M solution at room temperature, new products **2a,e** were formed in quantitative yields after 18–20 h time. These compounds are solids and were isolated in quantitative yields by simple filtration. If the reaction time is prolonged for 4 days in the case of compound **e**, and for 17 days in the case of compound **a**, products **2a,e** evolve to the respective dehydration products **3a,e** in quantitative yields (Scheme 6). Notably, the elimination process was

detected to occur in the neutralized form **2a**, kept as a solid in the freezer for a 1-year period.

These new compounds **3a,e** are α,β-unsaturated carboxylic acids, supposedly able to incorporate different nucleophiles, at the β-position, and eventually alter the stereochemistry of the carboxylic group attached to the pyrrolidine nucleus in the saturated adduct. Therefore, they are versatile intermediates in syntheses, deserving to be explored as percursors of diverse proline compounds.

Aziridine **9a** was also treated with HCl for reactivity comparison with **7a**. Aliquots of the reaction mixture were taken along the 18 h needed to full consumption of aziridine **7a**. The ^1H NMR spectra of the samples showed the formation of several products at the same time, one of which was compound **2a**.HCl (Scheme 7), that could be recognized due to the presence of a doublet at $\delta = 5.39$ ppm, $J = 7.6$ Hz assigned to H-2.

Mechanisms proposed

Tetrahydrofuran **1a** is generated either from aziridine **9a** and lactone-aziridine **7a**, by reflux in water/BiI$_3$. The reaction starting with **9a** was carefully followed by ^1H RNM spectra, showing a smooth transformation of **9a** into a single product, **1a**, which was isolated in 84% yield. The stereochemistry of the newly formed chiral center was proposed on the basis of a S_N2 mechanism, which would avoid the formation of a concurrent diastereomer. The regiochemistry of the nucleophilic attack occurs exclusively at C-β position, as reported in the literature in the case of a parent epoxide (Pino-González and Noé 2008). Reaction of **7a**
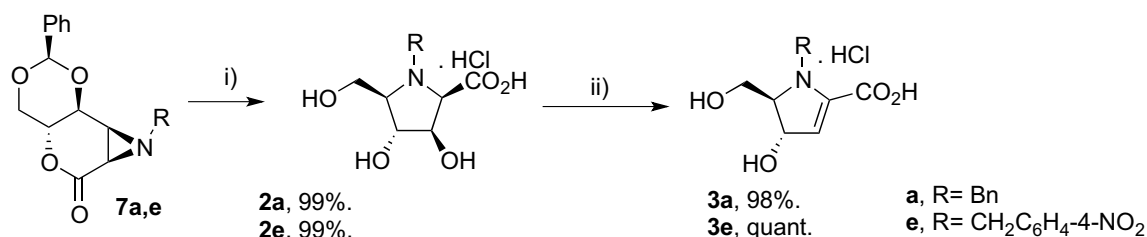

Scheme 6 Synthesis of compounds **2a,e 3a**.HCl, **3e**.HCl directly from the respective aziridines **7a,e**—(i) HCl, 37% in dioxane (43 equiv.), magnetic stirring, rt; **case a**, 20 h; **case e** 18 h; (ii) continued stirring at rt; **case a**, 17 days; **case e**, 4 days
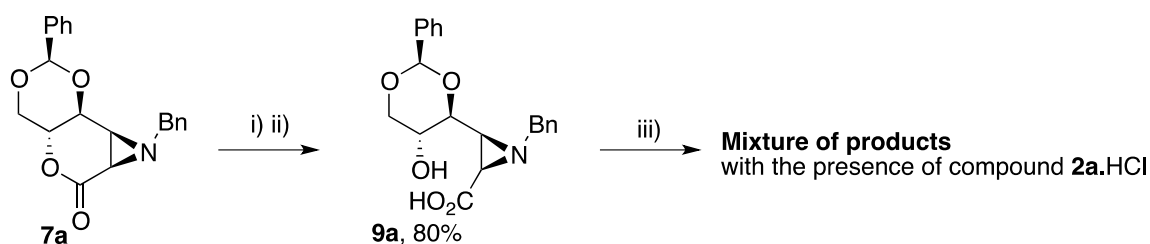
Scheme 7 Sequence of steps from **7** to **9a** for the formation of a mixture of products by HCl treatment of aziridine **2a**: (i) 1 M NaOH sol. (15 mmol, 41–70 equiv.), H₂O/ACN (5:1), 40 °C, 24 h; (ii) Amberlite resin IR 120 (H⁺); (iii) dioxane, HCl (43 equiv.), magnetic stirring, rt, 20 h

Scheme 8 Mechanism proposed for the synthesis of compound **1a** from aziridines **7a/9a** in BiI₃/H₂O
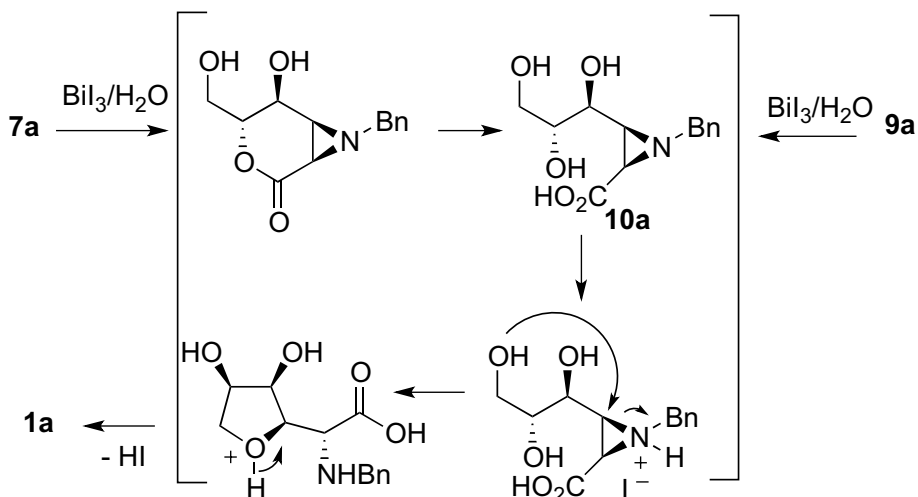
gave a mixture of products, among which was compound **1a**. Lactone cleavage of **7a** led to a common intermediate **10a** relatively to the sequence starting from **9a** (Scheme 8), but this does not seem to be an exclusive event to occur with substrate **7a**.

The bicyclic compound **4a** is the only product obtained either from **9** and **7a**, in reactions with TFA at room temperature. The reaction is quicker for **9a**, which agrees with the easier reaction of **9a** in refluxing BiI₃-H₂O compared to **7a**. The literature largely refers to the formation of bicyclic **4**-type structures from compounds as **1**, when a favored stereochemistry allows a second cyclization over the first formed 5-membered structures (Huisgen 1963). Compound **4a** probably evolves from the primary compound **1a**, as shown in Scheme 9.

Contrary to the other acids (BiI₃/H₂O and TFA), HCl gives a different outcome, with the formation of type **2** compounds, either from reactions starting with **7a** or **9a**. Based on the observation that **2a** forms in quantitative yield when **7a** is the reaction substrate, and together with other by-products when **9a** is used as substrate, different sequences of events are proposed, and condensed in Scheme 10. From **7a**, the reaction cascade mechanism
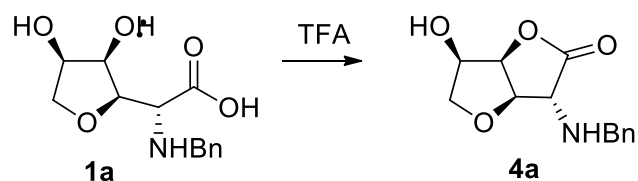
Scheme 9 Synthesis of compound **4a** from **1a** in the presence of TFA

seems to start with aziridine cleavage to give the protonated structure **11a** and then **12a**. The C–O lactone cleavage will occur later, possibly with the assistance of an epoxide formation, as represented in structure **13a**. Epoxides such as **13a** have been proposed as intermediates in six-carbon atom SAAs chemistry under concentrated HBr (Malle et al. 2008) to form proline-type **2** compounds; the five-membered ring forms in the last step by nitrogen atom attack (Malle et al. 2008). As a single product is formed from **7a** (quantitative yield), the cycloamination is proposed to occur by a S_N2 mechanism, excluding attack on both sides, that would lead to formation of two
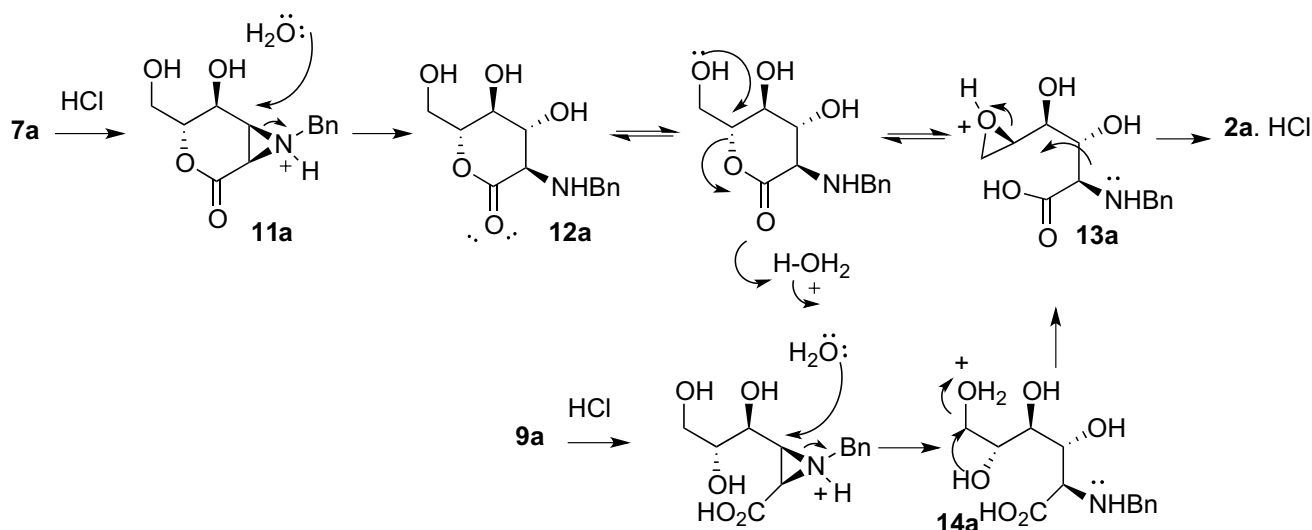
Scheme 10 Proposed sequence of events for the reaction of lactone-aziridine **7a** or aziridine **9a** in HCl to give compound **2a**.HCl

diastereomers. The mechanism described in Scheme 10 is in agreement with the multi-reactivity observed in the reaction of compound **9a**, since the open-chain intermediate **14a** directly formed from **9a** by aziridine opening, enables the formation of several products, including **2a**.

Conclusion

This work shows the versatility of the 6-carbon atom D-erythrosyl fused aziridinolactone **7** as a chiral platform in the synthesis of SAA compounds and azasugars. Two tetrahydrofuran amino acids (**1** and **4**) and two azasugars (**2** and **3**) were obtained from D-erythroyl aziridines **7**, and its derived compound **9**, with complete selectivity, and very good overall yields. Different protic acids initiate diverse mechanism pathways, notably with total selectivity, so that furane or pyrrolidine scaffolds can be produced by simply changing the nature of the acid. The fused-aziridine **7** demonstrated lower reactivity than aziridine **9**, in the syntheses of compound **1** with BiI$_3$, and its related bicyclic compound **4** with TFA. However, in the synthesis of prolines **2**, the best substrate was found to be the fused lactone-aziridine compounds **7** and not compounds **9**. This, of course, suggests that the lactone unit plays a role in the synthesis of compounds **2**.

In future work, the dehydrated pyrrolidines **3** deserve a close look as Michael acceptors, allowing the synthesis of important types of new structures.

Experimental section

General

The solvents were used as purchased, except: dichloromethane and methanol, that were dried under CaH$_2$ and Mg/I$_2$, respectively; tetrahydrofuran, and ether, dried under Na-benzophenone, and DMF and toluene distilled with the elimination of the head distillation fractions. Petroleum ether 40–60 °C used in chromatography was submitted to distillation. D-Erythrose lactone **6** (Chakraborty et al. 2005) and 1,2,3-triazolines **5a,b** (Chakraborty et al. 2005), were obtained according to literature. All other reagents were purchased and used without further purification. Glassware was dried prior to use. Compounds were purified by dry-flash chromatography using silica 60, < 0.063 mm, and water pump vacuum or by flash chromatography using silica 60 Å 230–400 mesh as stationary phases. TLC plates (silica gel 60 F254) were visualized either with a UV lamp or in an I$_2$ chamber.

Reaction of lactone 6 with alkyl azides

To a solution of lactone **6** (~ 0.10 g; ~ 0.4 mmol) in methyl orthoformate (10 mL) was added the alkyl azide (2 equiv.). The reaction mixture was heated at 100ºC under a nitrogen atmosphere for 72 h. The solvent was evaporated, and the resulting solid residue was recrystallized from ethanol. The title compounds were obtained as white solids *c.a.* ~ 72%.

Synthesis of (3aR,5aR,8R,9aS,9bS)-8-phenyl-1-tetradecyl-1,3a,5a,6,9a,9b-hexahydro-4H-[1,3]dioxino[4′,5′:5,6]pyrano[3,4-d][1,2,3]triazol-4-one (5d)

Lactone **6** (97 mg, 0.417 mmol); $CH_3(CH_2)_{13}N_3$ (2 equiv.); obtained product (138 mg, 0.302 mmol, 73%). M.p. = 78–80 °C; $[\alpha]_D^{25} = -140.0°$ (c 0.64%, CH_2Cl_2); IR (nujol): ν_{max} 2095.8, 1772.9 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.47–7.40 (m, 5H, Ph), 5.58 (s, 1H, 8-*H*), 5.41 (d, J = 13.2 Hz, 1H, 3a-*H*), 4.48 (dd, J = 10.9, 5.5 Hz, 1H, 6-*H*), 4.29 (td, J = 14.7, 5.5 Hz, 1H, 5a-*H*), 4.12–4.08 (m, 2H, 9a-*H* e 9b-*H*), 3.87 (ddd, J = 13.7, 7.0, 1.6 Hz, 1H, CH$_2$), 3.80 (t, J = 10.5 Hz, 1H, 6-*H*), 3.66 (ddd, J = 8.5, 5.4, 3.3 Hz, 1H, CH$_2$), 1.77–1.73 (m, 2H, CH$_2$), 1.27–1.24 (m, 24H, CH$_2$), 0.89 (t, J = 6.8 Hz, 3H, CH$_3$); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 161.9(C=O), 136.3, 129.6, 128.4, 126.0 (Ph), 102.3 (8-C), 80.2 (3a-C), 76.2 (9a-C), 67.9 (6-C), 65.6 (5a-C), 54.8 (9b-C), 50.7 (1′, CH$_2$), 31.9, 29.6, 29.6, 29.6, 29.5, 29.48, 29.3, 29.2, 29.13, 28.1, 26.7, 22.66 (CH$_2$), 14.1 (CH$_3$); HRMS (ESI-TOF), found for $[C_{27}H_{41}N_3O_4 + H]^+$: 472.3176; calcd: 472.3170.

Synthesis of (3aR,5aR,8R,9aS,9bS)-1-(4-nitrobenzyl)-8-phenyl-1,3a,5a,6,9a,9b-hexahydro-4H-[1,3]dioxino[4′,5′:5,6]pyrano[3,4-d][1,2,3]triazol-4-one (5e)

Lactone **6** (100 mg, 0.430 mmol); $NO_2PHCH_2N_3$ (2 equiv.); obtained product (124 mg, 0.302 mmol, 70%). M.p. = 148–151 °C; $[\alpha]_D^{25} = -419.1°$ (c 5%, CH_2Cl_2); IR (nujol): ν_{max} 1755.6, 1517.9, 1344 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.12 (d, J = 8.7 Hz, 2H, Ar), 7.46 (m, 5H, Ph), 7.33 (d, J = 8.6 Hz, 2H, Ar), 5.60 (s, 1H, 8-*H*), 5.43 (d, J = 12.8 Hz, 1H, 3a-*H*), 5.30 (d, J = 15.2 Hz, 1H, CH$_2$), 4.86 (d, J = 15.2 Hz, 1H, CH$_2$), 4.52 (dd, J = 10.8, 5.2 Hz, 1H, 6-*H*), 4.35 (ddd, J = 10, 5.2 Hz, 1H, 5a-*H*), 4.16 (dd, J = 9.6, 3.6 Hz, 1H, 9a-*H*), 3.87–3.79 (m, 2H, 6-*H* e 9b-*H*); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 161.1 (C=O), 147.8 (Cq, Ar), 142.2 (Cq, Ar), 136.1 (Cq, Ar), 129.8 (CH, Ar), 129.6 (CH, Ar), 128.5 (CH, Ar), 125.9 (CH, Ar), 124.0 (CH, Ar), 102.3 (8-C), 81.1 (3a-C), 75.9 (9a-C), 67.8 (6-C), 65.8 (5a-C), 53.6 (CH$_2$), 53.5 (9b-C); HRMS (ESI-TOF), found for $[C_{20}H_{18}N_4O_6 + H]^+$: 411.1291; calcd: 411.1299.

N$_2$ extrusion from triazolones 5a–e

1,2,3-Triazoline **5a–e** (60–70 mg) was dissolved in CH_2Cl_2 (8 mL) introduced in a quartz tub container and irradiated at 254 nm for 1 h 15 min–9 h. Evaporation of the reaction mixture gave the title aziridine **7a–e** as white solid/thick oil in 98–99% yields.

Synthesis of (2R,4aR,6aS,7aR,7bS)-1-benzyl-2-phenyltetrahydro-4H-[1,3]dioxino(4′,5′,5,6)pyrano[3,4-b]aziridin-6(4aH)-one (7a)

Triazoline **5a** (70 mg, 0.195 mmol); 1 h 50 min. White solid; (65 mg, 0.193 mmol, 99%). M.p. = 135.8–136.9 °C; $[\alpha]_D^{25} = +32.6°$ (c 0.6%, CH_2Cl_2); IR (nujol): ν_{max} 1741.9 cm^{-1}; ^{1}H NMR (400 MHz, CD$_3$OD) δ 7.44–7.28 (m, 10H, Ph), 5.69 (s, 1H, 2-*H*), 4.74 (dt, J = 9.6, 4.8 Hz, 1H, 4a-*H*), 4.30 (dd, J = 10.0, 4.8 Hz, 1H, 4-*H*), 4.20 (dd, J = 9.2, 1.6 Hz, 1H, 7b-*H*), 3.82 (t, J = 10.4 Hz, 1H, 4-*H*), 3.76 (d, J = 13.6 Hz, 1H, 1′-*H*), 3.67 (d, J = 13.6 Hz, 1H, 1′-*H*), 2.85 (dd, J = 6.4, 1.6 Hz, 1H, 7a-*H*), 2.72 (d, J = 6.4 Hz, 1H, 6a-*H*); ^{13}C NMR (100.6 MHz, CD$_3$OD) δ 169.2 (6-C), 139.2 (Cq, Ph), 138.7 (Cq, Ph), 130.2 (CH, Ar), 129.4 (CH, Ar), 129.1 (CH, Ar), 129.0 (CH, Ar), 128.9 (CH, Ar), 128.4 (CH, Ar), 127.4 (CH, Ar), 127.2 (CH, Ar), 103.6 (2-C), 77.0 (7b-C), 69.1 (4-C), 68.3 (4a-C), 62.2 (1′-C), 42.8 (7a-C), 40.4 (6a-C); HRMS (ESI-TOF) found for $[C_{20}H_{19}NO_4 + H]^+$: 338.1390; calcd: 338.1387.

Synthesis of (2R,4aR,6aS,7aR,7bS)-1-(Propyl-3′-benzyloxy)-2-phenyltetrahydro-4H-[1,3]dioxino(4′,5′,5,6)pyrano[3,4-b]aziridin-6(4aH)-one (7b)

Triazoline **5b** (60 mg, 0.142 mmol); 1 h 15 min; thick oil; (55 mg, 0.139 mmol, 98%). $[\alpha]_D^{25} = +4.4°$ (c 0.25%, CH_2Cl_2); IR (neat): ν_{max} 1749 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.53–7.50 (m, 2H, H_{Ar}), 7.41–7.36 (m, 3H, Ph), 7.33–7.26 (m, 5H, Ph), 5.58 (s, 1H, 2-*H*), 4.70 (dt, J = 9.6, 5.2 Hz, 1H, 4a-*H*), 4.50 (s, 2H, 4′-*H*), 4.34 (dd, J = 10.0, 5.2 Hz, 1H, 4-*H*), 3.99 (dd, J = 9.2, 1.6 Hz, 1H, 7b-*H*), 3.74 (t, J = 10.6 Hz, 1H, 4-*H*), 3.64 (dt, J = 15.2, 3.2 Hz, 1H, 3′-*H*), 3.35 (d, J = 15.2 Hz, 1H, 3′-*H*), 2.70–2.64 (m, 1H, 1′-*H*), 2.51–2.47 (m, 1H, 1′-*H*), 2.37 (dd, J = 6.4, 1.2 Hz, 1H, 7a-*H*), 2.38 (d, J = 6.4 Hz, 1H, 6a-*H*), 1.92 (dd, J = 12.8, 6.2 Hz, 1H, 2′-*H*), 1.27 (t, J = 7.2 Hz, 1H, 2′-*H*); ^{13}C NMR (100.6 MHz, CD$_3$OD) δ 167.3 (6-C), 138.4 (Cq, Ph), 136.7 (Cq, Ph), 129.4 (CH, Ph), 128.4 (CH, Ph), 128.4 (CH, Ph), 127.7 (CH, Ph), 127.6 (CH, Ph), 126.2 (CH, Ph), 102.6 (2-C), 76.2 (7b-C), 72.9 (4′-C), 68.3 (4-C), 66.8 (3′-C), 66.6 (4a-C), 55.1 (1′-C), 41.3 (7a-C), 39.2 (6a-C), 29.6 (2′-C); HRMS (ESI-TOF) found for $[C_{23}H_{25}NO_5 + Na]^+$: 418.1608; calcd: 418.1625.

Synthesis of (2R,4aR,7bS)-2-phenyl-7-propyltetrahydro-4H (Chakraborty et al. 2005; Risseeuw et al. 2013) dioxino[4′,5′:5,6]pyrano[3,4-b]azirin-6(4aH)-one (7c)

Triazoline **5c** (70 mg, 0.221 mmol); 1 h 57 m; thick oil; (63 mg, 0.218 mmol, 99%). $[\alpha]_D^{25} = +10.5°$ (c 0.8%, CH$_2$Cl$_2$); IR (neat): ν_{max} 1749 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.52–7.44 (m, 2H, Ph), 7.42–7.34 (m, 2H, Ph), 5.55 (s, 1H, 2-H), 4.72 (dt, J = 10.2, 4.7 Hz, 1H, 4a-H), 4.31 (dd, J = 10.0, 4.8 Hz, 1H, 4-H), 3.96 (br d, J = 9.2 Hz, 1H, 7b-H), 3.71 (t, J = 10.6 Hz, 1H, 4-H), 2.47 (br d, J = 6.4 Hz, 1H, 7a-H), 2.45–2.32 (m, 2H, 1′-H), 2.38 (d, J = 6.0 Hz, 1H, 6a-H), 1.61 (q, J = 7.2 Hz, 2H, 2′-H), 0.99 (t, J = 7.4 Hz, 3H, 3′-H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 167.3 (6-C), 136.6 (Cq, Ph), 129.2 (CH, Ph), 128.2 (CH, Ph), 126.1 (CH, Ph), 102.4 (2-C), 76.0 (7b-C), 68.1 (4-C), 66.5 (4a-C), 60.3 (1′-C), 41.0 (7a-C), 39.1 (6a-C), 22.6 (2′-C), 11.4 (3′-C); HRMS (ESI-TOF) found for [C$_{16}$H$_{19}$NO$_4$ + H]$^+$: 290.1382; calcd: 290.1387.

Synthesis of (2R,4aR,7bS)-2-phenyl-7-tetradecyltetrahydro-4H-[1,3]dioxino[4′,5′:5,6]pyrano[3,4-b]azirin-6(4aH)-one (7d)

Triazoline **5d** (70 mg, 0.148 mmol); 3 h 30 m; thick oil; (65 mg, 0.147 mmol, 99%). $[\alpha]_D^{25} = +79.49°$ (c 0.78%, CH$_2$Cl$_2$); IR (neat): ν_{max} 1745.4 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.52–7.39 (m, 5H, Ph), 5.56 (s, 1H, 2-H), 4.73 (dt, J = 10.4, 4.9 Hz, 1H, 4a-H), 4.33 (dd, J = 10.4, 4.9 Hz, 1H, 4-H), 3.98 (dd, J = 9.3, 1.2 Hz, 1H, 7b-H), 3.73 (t, J = 10.6 Hz, 1H, 4-H), 2.50–2.45 (m, 2H, CH$_2$ e 7a-H), 2.42–2.37(m, 2H, CH$_2$ e 6a-H), 1.61–1.57 (m, 2H, CH$_2$), 1.43–1.40 (m, 2H, CH$_2$), 1.26 (sl, 24H, CH$_2$), 0.88 (t, J = 6.7 Hz, 3H, CH$_3$); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 167.5 (6-C), 136.7 (Cq, Ph), 129.3 (CH, Ph), 128.3 (CH, Ph), 126.2 (CH, Ph), 102.5 (2-C), 76.2 (7b-C), 68.3 (4-C), 66.6 (4a-C), 58.8 (1′, CH$_2$), 41.3 (7a-C), 39.2 (6a-C), 31.9, 29.6, 29.6, 29.6, 29.5, 29.5, 29.4, 29.3, 27.0, 22.6 (CH$_2$), 14.1 (CH$_3$). HRMS (ESI-TOF) found for [C$_{27}$H$_{41}$NO$_4$ + H]$^+$: 444.3123; calcd: 444.3114.

Synthesis of (2R,4aR,7bS)-7-(4-nitrobenzyl)-2-phenyltetrahydro-4H-[1,3]dioxino[4′,5′:5,6]pyrano[3,4-b]azirin-6(4aH)-one (7e)

Triazoline **5e** (70 mg, 0.170 mmol); 9 h; thick oil; (64 mg, 0.167 mmol, 98%). $[\alpha]_D^{25} = +96.97°$ (c 0.99%, CH$_2$Cl$_2$); IR (neat): ν_{max} 1750.6, 1513.8, 1341.2 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.21(d, J = 2.9 Hz, 2H, Ar), 7.60(d, J = 8.8 Hz, 2H, Ar), 7.52–7.39 (m, 5H, Ph), 5.60 (s, 1H, 2-H), 4.85 (ddt, J = 10.6, 4.8, 1.3 Hz, 1H, 4a-H), 4.39 (dd, J = 10.4, 4.8 Hz, 1H, 4-H), 4.09(d, J = 9.5 Hz, 1H, 7b-H),

3.99 (d, J = 14.9 Hz, 1H, 1′-H), 3.80(t, J = 10.6 Hz, 1H, 4-H), 3.63 (d, J = 14.9 Hz, 1H, 1′-H), 2.69 (br s, 2H, 7a-H e 6a-H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 166.2 (6-C), 147.3 (Cq, Ar), 144.5 (Cq, Ar), 136.4 (Cq, Ar), 129.7 (CH, Ar), 128.4 (CH, Ar), 128.0 (CH, Ar), 126.1 (CH, Ar), 123.7 (CH, Ar), 102.6 (2-C), 75.6 (7b-C), 68.2 (4-C), 66.8 (4a-C), 60.6 (1′-C), 41.5 (7a-C), 39.6 (6a-C); HRMS (ESI-TOF) found for [C$_{20}$H$_{18}$N$_2$O$_6$ + H]$^+$: 383.1243; calcd: 383.1238.

Synthesis of diazirines compounds

To a solution of 1,2,3-triazoline **5a–c** (70–110 mg, 0.166–0.300 mmol, 1 equiv.) in H$_2$O/ACN (8:4 mL) heated for 20 min at 100–110 °C, BiI$_3$ (0.1 equiv.) was added. The reaction mixture was kept under heating for 2 h 30 min. After this time, the reaction mixture was allowed to reach room temperature, and activated basic resin added (Dowex 1×3, $^-$OH). The resin was filtered off, washed with H$_2$O (2×5 mL), and the filtrate evaporated to give as pure products, the diazirine compounds (η = 46–64%).

Synthesis of (2′R,4a′R,8′S,8a′S)-8′-(benzylamino)-2′-phenyl-8′,8a′-dihydro-4H-spiro[diazirine-3,7′-pyrano [3,2-d][1,3]dioxin]-6′ (4a′H)-one (8a)

1,2,3-Triazoline **5a** (110 mg, 0.300 mmol); compound **8a** (50 mg, 0.137 mmol, 46%). $[\alpha]_D^{25} = +24.7°$ (c 0.55%, CH$_2$Cl$_2$); IR (neat): ν_{max} 3372, 2109, 1688 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.47–7.27 (m, 10H, Ph), 5.63 (s, 1H, 2-H), 4.85 (td, J = 10, 5.2 Hz, 1H, 4a-H), 4.50 (dd, J = 10.8, 5.2 Hz, 1H, 4-H), 4.25 (d, J = 4 Hz, 1H, 8-H), 4.04 (dd, J = 9.6, 4.4 Hz, 1H, 9-H), 3.99 (d, J = 13.2 Hz, 1H, 1′-H), 3.90 (d, J = 13.2 Hz, 1H, 1′-H), 3.85 (t, J = 10.6 Hz, 1H, 4-H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 163.8 (6-C), 139.2 (Cq, Ar), 138.9 (Cq, Ar), 136.4 (CH, Ar), 129.5 (CH, Ar), 128.7 (CH, Ar), 128.4 (CH, Ar), 127.9 (CH, Ar), 127.5 (CH, Ar), 126.1 (CH, Ar), 101.9 (2-C), 75.6 (9-C), 68.3 (4-C), 65.6 (4a-C), 58.2 (7-C), 52.9 (8-C), 51.3 (1′-C). HRMS (ESI) found for [C$_{20}$H$_{19}$N$_3$O$_4$ + H]$^+$: 366.1437; calcd: 366.1448.

Synthesis of (2′R,4a′R,8′S,8a′S)-8′-(3-(benzyloxi)propylamine)-2′-phenyl-8′,8a′-dihydro-4′H-spiro[diazirine-3,7′-pyrano[3,2-d][1,3]dioxin]-6′ (4a′H)-one (8b)

1,2,3-Triazoline **5b** (70 mg, 0,166 mmol); compound **8b** (32 mg, 0.076 mmol, 46%). $[\alpha]^D_{25} = +102.48°$ (c 0.51%, CH$_2$Cl$_2$); IR (neat): ν_{max} 3326, 2108, 1689 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.49–7.27 (m, 10H, HAr), 5.62 (s, 1H, 2-H), 4.75 (td, J = 10, 5.2 Hz, 1H, 4a-H), 4.50–4.45(m, 2H, 4′-H), 4.46 (dd, J = 10.8, 5.2 Hz, 1H, 4-H), 4.17 (d,

$J = 4.4$ Hz, 1H, 8-H), 4.00 (dd, $J = 9.6$, 4.4 Hz, 1H, 9-H), 3.82 (t, $J = 10.6$ Hz, 1H, 4-H), 3.55 (dt, $J = 11.6$, 5.6 Hz, 2H, 3'-H), 2.91–2.85 (m, 1H, 1'-H), 2.88–2.76 (m, 1H, 1'-H), 1.87–1.82 (m, 3H, 2'-H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 163.6 (6-C), 138.1 (Cq, Ar), 136.8 (CH, Ar), 129.5 (CH, Ar), 128.4 (CH, Ar), 127.7 (CH, Ar), 126.1 (CH, Ar), 101.8 (2-C), 75.2 (9-C), 73.0 (4'-C), 68.4 (3'-C), 68.2 (4-C), 65.4 (4a-C), 57.9 (7-C), 53.4 (8-C), 45.4 (1'-C), 29.7 (2'-C). HRMS (ESI) found for $[C_{23}H_{25}N_3O_5 + H]^+$: 424.1850; calcd: 424.1867.

Synthesis of (2'R,4a'R,8'S,8a'S)-2'-phenyl-8'-(propylamine) -8',8a'-dihydro-4'H-spiro[diazirine-3,7'-pyrano[3,2-d][1,3] dioxin]-6' (4a'H)-one (8c)

1,2,3-Triazoline **5c** (70 mg, 0.220 mmol); compound **8c** (45 mg, 0.141 mmol, 64%). $[\alpha]_D^{25} = +43.2°$ (c 0.5%, ethyl acetate); IR (neat): ν_{max} 3335, 2107, 1692 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.47–7.27 (m, 5H, AR), 5.62 (s, 1H, 2-H), 4.81 (td, $J = 10.2$, 5.2 Hz, 1H, 4a-H), 4.48 (dd, $J = 10.8$, 5.2 Hz, 1H, 4-H), 4.17 (d, $J = 4.4$ Hz, 1H, 8-H), 4.01 (dd, $J = 9.6$, 4 Hz, 1H, 9-H), 3.82 (t, $J = 10.6$ Hz, 1H, 4-H), 2.71–2.59 (m, 2H, 1'-H), 1.61–1.50 (m, 2H, 2'-H), 0.95 (t, $J = 7.4$ Hz, 3H, 3'-H); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 164.0 (6-C), 13.5 (Cq, Ar), 129.5 (CH. Ar), 128.4 (CH. Ar), 126.1 (CH, Ar), 125.5 (CH, Ar), 101.8 (2-C), 75.5 (9-C), 68.3 (4-C), 65.5 (4a-C), 58.0 (7-C), 53.9 (8-C), 49.4 (1'-C), 23.3 (2'-C), 11.8 (3'-C). HRMS (ESI) found for $[C_{16}H_{19}N_3O_4 + H]^+$: 318.1447; calcd: 318.1448.

Synthesis of (2S,3R)-1-substituted-3-((2R,4S,5R)-5-hydroxy-2-phenyl-1,3-dioxan-4-yl)aziridine-2-carboxylic acid (9a-c)

General procedure

To a solution of (2R,4aR,6aS,7aR,7bS)-1-substituted-2-phenyltetrahydro-4H-[1,3]dioxino(4',5',5,6)pyrano[3,4-b] aziridin-6(4aH)-one **7a–c** (90–120 mg, 0.22–0.37 mmol, 1 equiv.) in H$_2$O/CH$_3$CN (20/4 mL) under magnetic stirring at 40 °C 1 M NaOH sol. (600 mL, 15 mmol, 41–70 equiv.) was added. The reaction mixture was left stirring for 24 h and then allowed to reach room temperature. Activated acid resin [Amberlite resin IR 120 (H$^+$)] was added for neutralization, washed with H$_2$O (2×5 mL) and filtered off. Evaporation of the filtrate to dryness gave title products as oils (68–80%).

(2S,3R)-1-benzyl-3-((2R,4S,5R)-5-hydroxy-2-phenyl-1,3-dioxan-4-yl)aziridine-2-carboxylic acid (9a)

Compound **7a** (120 mg, 0.355 mmol), compound **9a** (100 mg, 0.284 mmol, 80%); $[\alpha]_D^{25} = +4.4°$ (c 3%, CH$_3$CH$_2$OH); IR (neat): ν_{max} 3362, 1633 cm^{-1}; ^{1}H NMR (400 MHz, D$_2$O) δ 7.53–7.39 (m, 10H, H_{Ar}), 5.57 (s, 1H, 3''-H), 4.26 (dd, $J = 10.2$, 3.8 Hz, 1H, 5''-H), 3.79–3.76 (m, 2H, 1''-H + 6''-H), 3.73 (d, $J = 13.6$ Hz, 1H, 1'-H), 3.72 (dd, $J = 10.4$, 6.4 Hz, 1H, 5''-H), 3.57 (d, $J = 13.2$ Hz, 1H, 1'-H); 2.41 (d, $J = 7.2$ Hz, 1H, 2-H); 2.31 (t, $J = 7.2$ Hz, 1H, 3-H); ^{13}C NMR (100.6 MHz, D$_2$O) δ 175.6 (C=O), 137.4 (Cq, Ar), 136.0 (Cq, Ar), 129.1 (CH, Ar), 128.2 (CH, Ar), 128.1 (CH, Ar), 128.1 (CH, Ar), 127.1 (CH, Ar), 125.5 (CH, Ar), 100.3 (3''-C), 78.9 (1''-C), 69.7 (5''-C), 65.0 (6''-C), 61.6 (1'-C), 44.9 (3-C), 42.8 (2-C); HRMS (ESI-TOF) found for $[C_{20}H_{21}NO_5 + H]^+$: 356.1489; calcd: 356.1493.

(2S,3R)-1-Propyl-3'-benzyloxy-3-((2R,4S,5R)-5-hydroxy-2-ph enyl-1,3-dioxan-4-yl)aziridine-2-carboxylic acid (9b)

Compound **7b** (90 mg, 0. 228 mmol), compound **9b** (64 mg, 0.155 mmol, 68%); $[\alpha]_D^{25} = +23.5°$ (c 0.5%, CH$_3$CH$_2$OH); IR (neat): ν_{max} 3387, 1668 cm^{-1}; ^{1}H NMR (400 MHz, D$_2$O) δ 7.56–7.31 (m, 10H, H_{Ar}), 5.50 (s, 1H, 1''-H), 4.53 (d, $J = 2.3$ Hz, 2H, 5'-H), 4.24 (dd, $J = 10.4$, 4.8 Hz, 1H, 5''-H), 3.77 (dt, $J = 9.6$, 4.7 Hz, 1H, 6''-H), 3.70 (t, $J = 10.0$ Hz, 1H, 1''-H), 3.69 (t, $J = 8.8$ Hz, 1H, 5''-H), 3.63 (td, $J = 6.4$, 1.6 Hz, 1H, 3'-H), 2.57 (dt, $J = 13.4$, 6.8 Hz, 1H, 1'-H), 2.39–2.28 (m, 1H, 1'-H), 2.17–2.10 (m, 1H, 2-H), 2.02 (dd, $J = 15.0$, 7.7 Hz, 1H, 3-H), 1.90–1.83 (m, 2H, 2'-H); ^{13}C NMR (100.6 MHz, D$_2$O) δ 176.29 (C=O), 137.4 (Cq), 136.6 (Cq), 129.5 (CH, Ar), 128.7 (CH, Ar), 128.6 (CH, Ar), 128.3 (CH, Ar), 126.0 (CH, Ar), 100.7 (3''-C), 79.9 (1''-C), 72.6 (5'-C), 70.8 (5''-C), 68.2 (3'-C), 65.7 (6''-C), 55.8 (1'-C), 45.7 (3-C), 43.2 (2-C), 28.5 (2'-C); HRMS (ESI-TOF) found for $[C_{23}H_{27}NO_6 + H]^+$: 414.1911; calcd: 414.1911.

(2S,3R)-1-Propyl-3-((2R,4S,5R)-5-hydroxy-2-phenyl-1,3-dioxan-4-yl)aziridine-2-carboxylic acid (9c)

Compound **7c** (107 mg, 0.369 mmol), compound **9c** (90 mg, 0.292 mmol, 79%); IR (neat): ν_{max} 3409, 1665 cm^{-1}; $[\alpha]_D^{25} = +6.6°$ (c 0.6%, CH$_3$CH$_2$OH); ^{1}H NMR (400 MHz, D$_2$O) δ 7.48–7.43 (m, 5H, H_{Ar}), 5.54 (s, 1H, 3''-H), 4.27 (dd, $J = 10.6$, 5.0 Hz, 1H, 5''-H), 3.85 (dt, $J = 10$, 4.8 Hz, 1H, 6''-H), 3.75 (t, $J = 8$ Hz, 1H, 1''-H), 3.70 (t, $J = 10.8$ Hz, 1H, 5''-H), 2.55 (dt, $J = 11.8$, 7.0 Hz, 1H, 1'-H), 2.21–2.14 (m, 2H, 1'-H and 2-H), 2.04 (t, $J = 7.2$ Hz, 1H, 3-H), 1.58 (h, $J = 7.4$ Hz, 2H, 2'-H), 0.90 (t, $J = 7.5$ Hz, 3H, 3'-H); ^{13}C NMR (100.6 MHz, D$_2$O) δ 176.0 (C=O), 136.1 (Cq, Ar), 129.0 (Cq, Ar), 128.1 (CH, Ar), 125.5 (CH, Ar), 100.2 (3''-C), 79.4 (1''-C), 70.3 (5''-C), 65.3 (6''-C), 60.6 (1'-C), 45.0 (3-C), 42.8 (2-C), 21.3 (2'-C), 10.7 (3'-C); HRMS (ESI-TOF) found for $[C_{16}H_{21}NO_5 + Na]^+$: 330.1308; calcd: 330.1312.

Synthesis of amino acids 1a-c

General procedure for method 1

A solution of (2*S*,3*R*)-1-substituted-3-((2*R*,4*S*,5*R*)-5-hydroxy-2-phenyl-1,3-dioxan-4-yl)aziridine-2-carboxylic acid **9a–c** (65–100 mg, 0.169–0.282 mmol, 1 equiv.) in H_2O (10–15 mL) at 115 °C temperature was added BiI_3 (0.1 equiv.). The reaction mixture was left for 2 h–2 h 30 m. After this time, it was allowed to reach room temperature, and activated basic resin (Dowex 1×3, $^-$OH). The resin was filtered off, washed with H_2O (2×5 mL), and the filtrate evaporated to yield a crude product, which purified by dry-flash chromatography (ethanol, 5% NH_3 aq. sol.) to give pure products **1a-c** (33–84%).

2-(Benzyl)-2-((3*R*,4*R*)-3,4-dihydroxytetrahydrofuran-2-yl) acetic acid (1a)

Method 1 Compound **9a** (100 mg, 0.281 mmol); H_2O (15 mL); 2 h. Compound **1a**: viscous oil (63 mg, 0.236 mmol, 84%); $[\alpha]_D^{25} = +86.7°$ (c 0.15%, CH_3CH_2OH); IR (neat): ν_{max} 3307, 1646 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.52–7.43 (m, 5H, H_{Ar}), 4.63 (dd, $J = 8.0$, 1.2 Hz, 1H, 2a-*H*), 4.57 (dd, $J = 7.8$, 4.3 Hz, 1H, 3-*H*), 4.28 (d, $J = 12.8$ Hz, 1H, 1′-H), 4.23 (d, $J = 12.0$ Hz, 1H, 1′-H), 4.23–4.20 (m, 1H, 4-*H*), 3.81 (dd, $J = 10.0$, 1.5 Hz, 1H, 5-*H*), 3.72 (dd, $J = 10.0$, 3.2 Hz, 1H, 5-*H*), 3.64 (d, $J = 1.4$ Hz, 1H, 2-*H*); ^{13}C NMR (100.6 MHz, CD_3OD) δ 172.0 (C=O), 133.5 (Cq, Ar), 131.0 (CH, Ar), 130.4 (CH, Ar), 130.2 (CH, Ar), 80.1 (2a-C), 73.4 (3-C), 72.9 (5-C), 72.2 (4-C), 62.5 (2-C), 52.6 (1′-C). HRMS (ESI-TOF) found for $[C_{13}H_{17}NO_5+H]^+$: 268.1175; calcd: 268.1180.

Method 2 To a solution of (2*R*,4a*R*,6a*S*,7a*R*,7b*S*)-7-benzyl-2-phenyltetrahydro-4*H*[1,3]dioxino[4′,5′:5,6]pyrano[3,4-b]azirin-6(4a*H*)-one **7a** (31 mg, 0.092 mmol, 1 equiv.) in H_2O/CH_3CN (10:4 mL) heated at 100 °C was added BiI_3 (0.3 equiv.). The reaction mixture was left heating for 6 h, allowed to reach room temperature, and activated basic resin (Dowex 1×3, OH$^-$) added. The resin was filtered off, washed with H_2O (2×5 mL), and the filtrates combined and evaporated to yield product **1a** (8 mg, 0.03 mmol, 33%) as an oil.

2-(Propyl-3′-benzyloxy)-2-((3*R*,4*R*)-3,4-dihydroxytetrahydro furan-2-yl)acetic acid (1b)

Compound **9b** (70 mg, 0.169 mmol); H_2O (10 mL); 2 h. Compound **1b**: viscous oil (18 mg, 0.056 mmol, 33%); $[\alpha]_D^{25} = +80°$ (c 0.15%, CH_3CH_2OH); IR (neat): ν_{max} 3394, 1680 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.41–7.27 (m, 5H, H_{Ar}), 4.62 (d, $J = 11.7$ Hz, 1H, 5′-*H*), 4.58 (dd, $J = 7.8$,

1.7 Hz, 1H, 2a-*H*), 4.55 (t, $J = 3.5$ Hz, 1H, 3-*H*), 4.53 (d, $J = 11.7$ Hz, 1H, 5′-*H*), 4.21 (ddd, $J = 4.1$, 3.4, 1.8 Hz, 1H, 4-*H*), 3.78 (dd, $J = 10.0$, 1.8 Hz, 1H, 5-*H*), 3.71 (dd, $J = 10.0$, 3.3 Hz, 1H, 5-*H*), 3.68 (dd, $J = 6.3$, 1.8 Hz, 1H, 3′-*H*), 3.67 (dd, $J = 4.8$, 2.4 Hz, 1H, 3′-*H*), 3.55 (d, $J = 1.5$ Hz, 1H, 2-*H*), 3.24 (t, $J = 6.6$ Hz, 2H, 1′-*H*), 2.05–1.97 (m, 2H, 2′-*H*). ^{13}C NMR (100.6 MHz, CD_3OD) δ 172.5 (C=O), 139.4 (Cq, Ar), 129.4 (CH, Ar), 129.0 (CH, Ar), 128.9(CH, Ar), 128.7 (CH, Ar), 80.1 (2a-C), 74.3 (5′-C), 73.4 (3-C), 72.9 (5-C), 72.2 (4-C), 69.5 (3′-C), 63.2 (2-C), 48.3 (1′-C), 28.0 (2′-C); HRMS (ESI-TOF) found for $[C_{16}H_{23}NO_6{}^+H]^+$: 326.1604; calcd: 326.1598.

2-(Propyl)-2-((3*R*,4*R*)-3,4-dihydroxytetrahydrofuran-2-yl) acetic acid (1c)

Compound **9c** (65 mg, 0.211 mmol); H_2O (15 mL); 2 h 30 min. Compound **1c**: viscous oil (39 mg, 0.178 mmol, 84%); $[\alpha]_D^{25} = +50°$ (c 0.2%, CH_3CH_2OH); IR (neat): ν_{max} 3412, 1632 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 4.57 (dd, $J = 7.2$, 4.4 Hz, 1H, 2a-*H*), 4.38 (dd, $J = 7.2$, 2.2 Hz, 1H, 3-*H*), 4.24 (h, $J = 2.8$ Hz, 1H, 4-*H*), 3.91 (dd, $J = 9.8$, 4.2 Hz, 1H, 5-*H*), 3.84 (dd, $J = 9.8$, 2.6 Hz, 1H, 5-*H*), 3.29 (d, $J = 2$ Hz, 1H, 2-*H*), 2.72 (dt, $J = 11.4$, 6.9 Hz, 1H, 1′-*H*), 2.57 (dt, $J = 11.6$, 7.2 Hz, 1H, 1′-*H*), 1.56 (h, $J = 7.3$ Hz, 2H, 2′-*H*), 0.96 (t, $J = 7.4$ Hz, 3H, 3′-*H*); ^{13}C NMR (100.6 MHz, CD_3OD) δ 178.3 (C=O), 80.0 (2a-C), 72.6 (5-C), 72.0 (3-C), 70.5 (4-C), 61.5 (2-C), 49.6 (1′-C), 21.8 (2′-C), 10.9 (3′-C). HRMS (ESI-TOF) found for $[C_9H_{17}NO_5+H]^+$: 220.1182; calcd: 220.1180.

Synthesis of *(3R,6R)*-3-(benzylamino)-6-hydroxytetr ahydrofuro[3,2-*b*]furan-2(3*H*)-one (4a)

Method 1

To a solution of compound **9a** (30 mg, 0.085 mmol, 1 equiv.) in H_2O (6 mL) at rt TFA (120 μL, 1.56 mmol, 18.4 equiv.) was added. The reaction mixture was left stirring for 2 days. Then, solid $NaHCO_3$ (35 mg) and MeOH (5 mL) were added to the mixture, concentrated, and extracted with ethanol (5 mL). The solvent was removed in the rotary evaporator to give the pure product **4a** (thick oil; 20 mg, 0.080 mmol, 94%).

Method 2

To a solution of compound **7a** (47 mg, 0.139 mmol) in H_2O (10 mL) TFA (300 μL, 3.9 mmol, 28.1 equiv.) was added at rt. The reaction mixture was left stirring for 15 days. Then, solid $NaHCO_3$ (35 mg) and MeOH (5 mL) were added to the mixture, concentrated, and extracted with ethanol (5 mL). The solvent was removed in the rotary evaporator to give

the pure product **4a** (thick oil; quant.). $[\alpha]_D^{25} = +17.5°$ (c 0.4%, MeOH); IR (neat): ν_{max} 3412, 1683.4 cm^{-1}; ^{1}H NMR (400 MHz, D$_2$O) δ 7.38–7.25 (m, 5H, H$_{Ar}$), 4.35 (dd, J = 4.8, 5.6 Hz, 1H, 6a-H), 4.26 (dd J = 2.4, 6 Hz, 1H, 3a-H), 4.15 (q, J = 4.8 Hz, 1H, 6-H), 3.87–3.82 (m, 1H, 5-H), 3.84 (d, J = 12.4 Hz, 1H, 1′-H), 3.75 (dd, J = 9.2, 4.4 Hz, 1H, 5-H), 3.63 (d, J = 12.4 Hz, 1H, 1′-H), 3.37–3.15(m, 1H, 3-H); ^{13}C NMR (100.6 MHz, D$_2$O) δ 161.3 (C=O), 140.5 (Cq$_{Ar}$), 129.6 (CH, Ar), 129.5 (CH, Ar), 128.2 (CH, Ar), 81.8 (3a-C), 74.2 (6a-C), 73.4 (5-C), 72.6 (6-C), 63.4 (3-C), 53.3 (1′-C). HRMS (ESI) found for [C$_{13}$H$_{14}$NO$_4$ + H$_3$O$^+$]: 266.1022; calcd: 266.1033.

Synthesis of (2*R*,3*R*,4*R*,5*R*)-1-substituted-2-carboxy-3,4-dihydroxy-5-(hydroxymethyl)pyrrolidin-1-ia (2a.HCl, 2e.HCl)

N-Benzyl substituted compound (2a.HCl)

Method 1—from aziridinolactone 7a To a solution of compound **7a** (28 mg, 0.083 mmol, 1 equiv.) in dioxane (2.70 mL), HCl 37% (295 µL, 3.6 mmol, 43.4 equiv.) was added at rt. The reaction mixture was maintained under magnetic stirring for 20 h. The solvent was removed in the rotary evaporator to give the pure product **2a**.HCl (thick oil; 25 mg, 0.082 mmol, 99%). $[\alpha]_D^{25} = +96.6°$ (c 0.2%, MeOH); IR (neat): ν_{max} 3329.2, 1797.6 cm^{-1}; ^{1}H NMR (400 MHz, D$_2$O) δ 7.49–7.44 (m, 5H, Ph), 5.39 (d, J = 7.6 Hz, 1H, 2-H), 4.90 (dd J = 4.4, 6.8 Hz, 1H, 4-H), 4.59 (d, J = 13.2 Hz, 1H, 1′-H), 4.50 (dd, J = 6.8, 7.6 Hz, 1H, 3-H), 4.44 (d, J = 13.2 Hz, 1H, 1′-H), 4.12 (dd, J = 7.8, 3.4 Hz, 1H, 5-H), 3.82 (dd, J = 12.0, 3.2 Hz, 1H, 6-H), 3.76 (dd, J = 12.0, 3.6 Hz, 1H, 6-H); ^{13}C NMR (100 MHz, D$_2$O)$^{a)}$ δ 170.6 (C=O), 130.0 (Cq, Ph), 130.0 (CH, Ph), 129.8 (CH, Ph), 129.6 (CH, Ph), 129.4 (CH, Ph), 79.8 (4-C), 69.7 (5-C), 61.8 (6-C), 60.4 (3-C), 51.9 (2-C), 50.4 (1′-C); HRMS (ESI) found for [C$_{13}$H$_{18}$ClNO$_5$ + H]$^+$: 304.0946; calcd: 304.0952.

Method 2—from aziridine 9a

(1) The aziridine **9a** (29 mg; 0.082 mmol) was dissolved in dioxane (2.70 mL), and conc. HCl was added (295 µL, 3.6 mmol, 43.9 equiv.). The mixture was stirred for 18 h. Evaporation of the reaction mixture to dryness gave a mixture of compounds with no starting material present. The ^{1}H NMR spectrum showed the presence of compound **2a**.HCl$^{(a)}$. The reaction was left to stand for a longer period being monitored daily by NMR. No evolution was observed during this time. No purification was followed to obtain pure **2a**.HCl.

   (a) ^{1}H NMR of the reaction mixture showed a signal that was assigned to H-2 of compound **2a**.HCl.

The signal appears at δ = 5.43 ppm, as a doublet with J = 7.6 Hz.

N-(4-Nitrobenzyl) compound (2e.HCl)

Method 1 To a solution of compound **7e** (32 mg, 0.084 mmol, 1 equiv.) in dioxane (2.70 mL) HCl 37% (295 µL, 3.6 mmol, 42.9 equiv.) was added at room temperature. The reaction mixture was maintained under magnetic stirring for 18 h. The mixture was evaporated to dryness in the rotary evaporator to give the pure product **2e**.HCl, as a thick oil (26 mg, 0.083 mmol, 99%); $[\alpha]_D^{25} = -177.5°$ (c 0.4%, MeOH); IR (neat): ν_{max} 3326.3, 1798.1, 1524.1, 1349.3 cm^{-1}; ^{1}H NMR (400 MHz, D$_2$O) δ 8.37–8.33 (m, 2H, Ar), 7.80–7.77 (m, 2H, Ar), 5.46 (dd J = 7.6 Hz, 1H, 2-H), 4.93 (dd, J = 6.4, 4.4 Hz, 1H, 4-H), 4.77 (d, J = 13.2 Hz, 1H, 1′-H), 4.64 (d, J = 13.2 Hz, 1H, 1′-H), 4.57 (dd, J = 7.4, 6.6 Hz, 1H, 3-H), 4.21–4.10 (m, 1H, 5-H), 3.84 (dt, J = 13.2, 3.2 Hz, 2H, 6-H); ^{13}C NMR (100 MHz, D$_2$O) δ 170.6 (C=O), 148.5 (Cq, Ar), 137.0 (Cq, Ar), 131.0 (CH, Ar), 124.3 (CH, Ar), 79.8 (4-C), 69.8 (5-C), 61.9 (6-C), 60.9 (3-C), 52.1 (2-C), 49.4 (1′-C). HRMS (ESI) found for C$_{13}$H$_{16}$N$_2$O$_6$Cl (M + H$^+$-H$_2$O): 331.0693; calcd: 331.0692 and found for [C$_{13}$H$_{16}$N$_2$O$_7$ + H]$^+$: 313.1026; calcd: 313.1030.

Dehydration of pyrrolidin-1-ia 2a.HCl, 2e.HCl

Synthesis of (2*R*,3*S*)-1-benzyl-5-carboxy-3-hydroxy-2-(hydroxymethyl)-2,3-dihydro-1*H*-pyrrol-1-ium (3a.HCl)

To a solution of **7a** (28 mg, 0.083 mmol, 1 equiv.) in dioxane (2.70 mL) HCl 37% (295 µL, 3.6 mmol, 43.4 equiv.) was added at room temperature. The reaction mixture was stirred for 17 days at room temperature. Thick oil **3a** (23 mg, 0.081 mmol, 98%); $[\alpha]_D^{25} = +10°$ (c 0.2%, MeOH); ^{1}H NMR (400 MHz, D$_2$O) δ 7.71 (s, 1H, 3-H), 7.48 -7.740 (m, 5H, Ph), 5.29 (d, J = 3.2 Hz, 1H, 4-H), 4.15 (s, 2H, 1′-H), 4.04 (ddd, J = 4.8, 5.6, 3.2 Hz, 1H, 5-H), 3.72 (dd, J = 12.0, 4.0 Hz, 1H, 6-H), 3.65 (dd, J = 12.0, 5.6 Hz, 1H, 6-H); ^{13}C NMR (100 MHz, D$_2$O) δ 170.6 (C=O), 147.6 (3-C), 132.5 (Cq, Ph), 129.8 (CH$_{Ar}$), 129.1 (CH$_{Ar}$), 128.7 (CH$_{Ar}$), 129.8 (2-C), 82.7 (4-C), 70.9 (5-C), 61.7 (6-C), 43.0 (1′-C). HRMS (ESI) found for [C$_{13}$H$_{16}$NO$_4$Cl + H]$^+$: 286.0843; calcd: 286.0841.

Synthesis of (2*R*,3*S*)-1-benzyl-5-carboxy-3-hydroxy-2-(hydroxymethyl)-2,3-dihydro-1*H*-pyrrol-1-ium (3e.HCl)

To a solution of **7e** (32 mg, 0.084 mmol) in dioxane (2.70 mL) HCl 37% (295 µL, 3.6 mmol, 42.9 equiv.) was added at room temperature. The reaction mixture was stirred

for 92 h at room temperature. Thick oil (28 mg, quant.); $[\alpha]_D^{25} = -1.69°$ (c 0.2%, MeOH); IR (neat): ν_{max} 3427.5, 1643.8, 1521.8, 1349.7 cm^{-1}; ^{1}H NMR (400 MHz, D$_2$O) δ 8.36–8.34 (m, 2H, Ar), 7.79 (d, $J = 2.0$ Hz, 1H, 3-*H*), 7.72–7.70 (m, 2H, Ar), 5.37 (dd, $J = 4.4$, 1.6 Hz, 1H, 4-*H*), 4.36 (s, 2H, 1′-*H*), 4.16 (dd, $J = 14.4$, 7.2 Hz, 1H, 6-*H*), 4.15-4.11 (m, 1H, 5-*H*), 3.81–3.72 (m, 1H, 6-*H*); ^{13}C NMR (100 MHz, D$_2$O) δ 171.0 (C=O), 147.7 (3-C), 139.8 (Cq, Ar), 129.8 (CH, Ar), 124.2 (CH, Ar), 124.1 (2-C), 82.8 (4-C), 71.0 (5-C), 61.8 (6-C), 42.3 (1′-C). HRMS (ESI) found for $[C_{13}H_{15}N_2O_6Cl+H]^+$: 331.0699; calcd: 331.0691.

Declarations

Conflict of interest The authors declare that there is no competing interests exist.

Consent for publication The authors declare that there is no duality of interest associated with this manuscript, and all the authors consent to publish this manuscript.

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