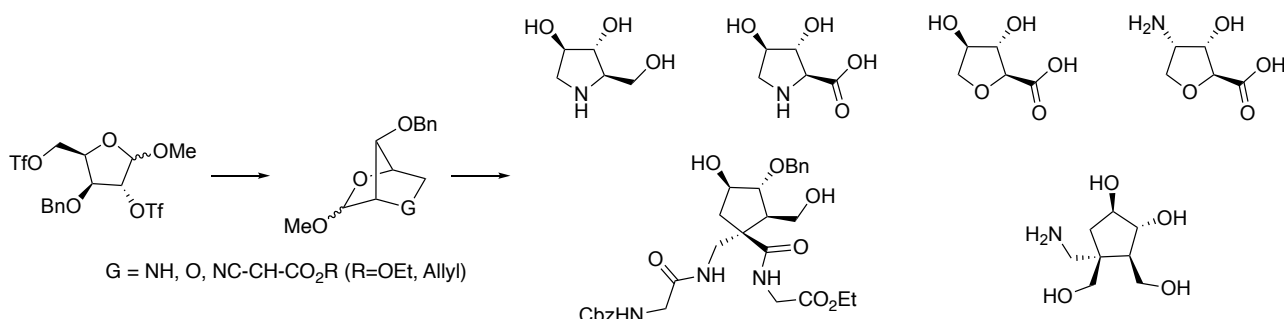# Stable D-xylose ditriflate in divergent syntheses of dihydroxy prolines, pyrrolidines, tetrahydrofuran-2-carboxylic acids, and cyclic sugar β-amino acids

Rosalino Balo,[a] Alberto G. Fernández,[a] Adam Chopdat, [a] Soufian El Ayadi,[a] Alejandro Jiménez,[a] Atsushi Kato,[c] Ramón J. Estévez,[a, b] George W. J. Fleet,[b,*] and Juan C. Estévez [a,*]

a) Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares and Departamento de Química Orgánica, Campus Vida, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, SPAIN.

b) Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Oxford, OX1 3TA, United Kingdom.

c) Department of Hospital Pharmacy, University of Toyama, Toyama 930-0194, Japan;

juancarlos.estevez@usc.es

G = NH, O, NC-CH-CO$_2$R (R=OEt, Allyl)

Double nucleophilic displacement of a sugar D-xylose ditriflate derived from diacetone-D-glucose by amines, water and alkyl cyanoacetates gave a series of bicyclic divergent intermediates for the synthesis of a wide range of highly functionalized targets, including hydroxylated prolines, pyrrolidines, THF carboxylic acids, and cyclopentanes.

1. Introduction

Carbohydrates constitute an abundant source of useful scaffolds for the synthesis of highly functionalized carbo- and heterocycles.[1] They provide the stereogenic centers bearing their OH substituents and a proper functionality for the generation of the two C-C or the two C-heteroatom bonds involved in the generation of the carbo- or heterocyclic ring. Two approaches have been developed for these purposes.[2] One of them (*approach a*) involves the cyclization of a properly functionalized open chain carbohydrate derivative and the other (*approach b*) leads to a bicyclic derivative containing the original sugar ring and the new ring, which is followed by the opening of the sugar moiety of the resulting bicycle. Both modalities have been extensively studied, with *approach b* giving the best stereochemical results. The more efficient results have been achieved by adaptation of both approaches to the simultaneous formation of critical C-C or C-heteroatom bonds. The modality based on *approach a* involves the classical functionalization of dicarbonyl sugar derivatives or the double displacement of bifunctionalised open-chain sugars by appropriate nucleophiles.[3,4,5,] The alternative based on the *approach b*, consists of the introduction of two leaving groups in a single step, followed by their double displacement by a nucleophilic reagent and the opening of the sugar moiety of the resulting bicycle.[4,6]

Sugar triflates showed to be more suitable than sugar mesylates and sugar tosylates for these purposes, due to their easy preparation and their high reactivity, that facilitates the easy and efficient formation of the new ring by intramolecular nucleophilic displacements both prior or after the opening of the sugar ring.[7,8,9] The alternative of using sugar dimesylates or sugar ditriflates for the simultaneous formation of the two key bonds leading to the new ring is particularly attractive, but has some limitations. In fact, when an open chain diol **I** is treated with methanesulfonyl chloride in pyridine, a highly selective sulfation of the primary alcohol gives the primary mesylate **II**; the alternatives for further reaction are to form the dimesylate **III** or the THF **IV**. It is usually possible by addition of diol **I** to an excess of mesyl chloride to obtain the dimesylate **III** in excellent yield, although if addition is the other way round by addition of mesyl chloride to the diol formation of the THF **IV** predominates.[3,]
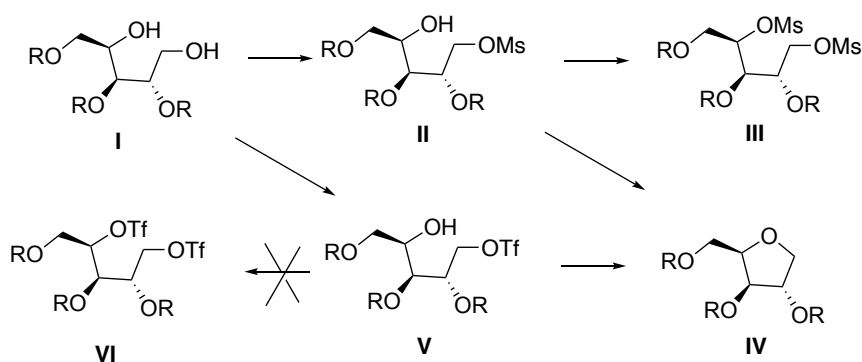
Scheme 1. *Open chain sulfonates*

In contrast, attempts to form open chain ditriflates such as **VI** invariably fail; the reaction still initially proceeds by triflation of the primary alcohol to give **V** but the very much better triflate leaving group now leads to intramolecular cyclization to **IV**.[10,11] In fact, for the formation of ditriflates from diols, it is necessary the absence of a neighboring hydroxyl group that could lead to intramolecular cyclization, particularly to a five membered ring.[11,12,13] The readily formed protected xylofuranoside **1** [as a mixture of anomers] has the diols *trans* (Scheme 2). Initial triflation of **1** gives highly regioselective formation of the primary triflates **2**; since the C_2-OH group in **1** is *trans* to the primary triflate at C_5 it is not possible to form a THF ring. Accordingly, highly yields of the ditriflates **4** [>80%] are isolated as stable intermediates. There is no evidence for the formation of the secondary triflate **3**, which undergoes efficient cyclization to dioxabicycles **5**, as shown in the THF synthesis later in the paper.
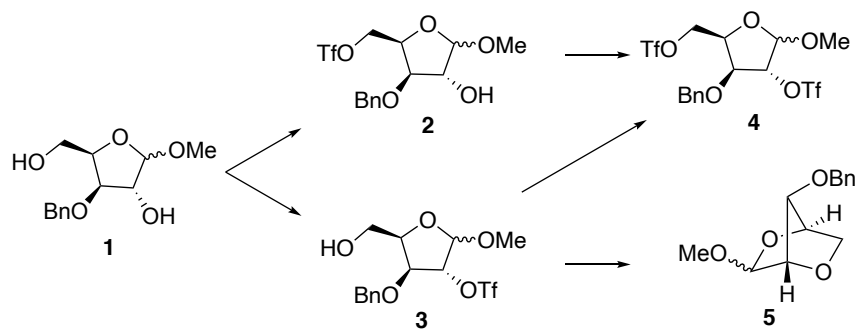

Scheme 2. *D-xylose ditriflates*

The synthesis of carbocycles and heterocycles from sugar ditriflates is at present practically limited to several synthesis of azetidines.[14,15,16,17,18,19] This article reports new chemistry on in this field. It includes new syntheses of iminocyclopentitols, 3,4-dihydroxyprolines and 3,4-dihydroxytetrahydrofuran-2-carboxylic acids, together

with preliminary studies on the extension of the cyanoacetic synthesis to sugars, which allowed access to new cyclic and bicyclic sugar $\beta^{2,2}$-amino acids.

2. **Formatión of stable sugar ditriflates 4.**

The stable anomeric xylose ditriflates **4α** and **4β** (Scheme 1) are the key intermediates for the synthesis of all the highly functionalized targets.
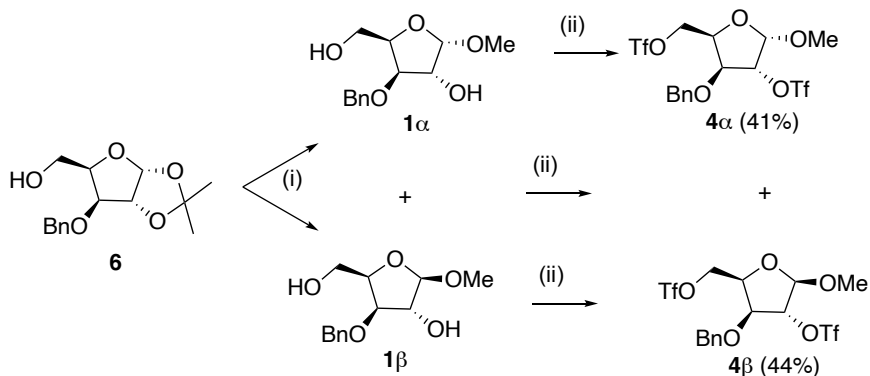
Scheme 3 – *Conditions*: i) AcCl, MeOH/H$_2$O, rt, 2 h. ii) Tf$_2$O, DIEA, CH$_2$Cl$_2$, -30 ºC, 2 h (85%)

The protected xylofuranoside **6** is readily available on a large scale in 4 steps and an overall yield of 88% from diacetone D-glucose.[20] This acetonide **6** with AcCl in methanol gave an anomeric mixture of the xylofuranosides **1α** and **1β** in 95% yield and a 1:1 ratio.[21] Treatment of the anomeric mixture **1** with triflic anhydride in dichloromethane in the presence of DIEA gave an easily separable mixture (85%) of the anomers **4α:4β** in 1:1 ratio. The configuration of the anomeric centre in **4β** is shown by the X-ray structure of **21** (Scheme 6).

Further cyclization experiments were done on the initial anomeric mixture and, in some cases, on both anomers separately.

3. **DAB and *trans,trans*-dihydroxyproline.**

Iminosugars are natural and synthetic sugar mimetics of current interest on account of their ability to interact with carbohydrate-processing enzymes. [22,23] They have shown potential for the treatment of a wide range of diseases, including diabetes, viral infections, tumor metastasis, hepatitis and lysosomal storage disorders.[24, 23] A representative example are pyrrolidine iminosugars, including the iminocyclopentitol l,4-dideoxy-l,4-imino-D-arabinitol **10** (DAB)[25], (a natural compound that has shown to be an efficient inhibitor of α-glucosidases), and its enantiomer[26] (a much more powerful inhibitor of mammalian intestinal α-glucosidases). In view of this, structurally diverse libraries of 3,4-dihydroxypyrrolidine derivatives have been screened for inhibitory activity against a variety of glycosidases.[27,28] Due to the remarkable, biological importance of this class of azasugars, concise, efficient and enantioselective syntheses of this family of sugar mimetics are highly desirable.

The structurally related 3,4-dihydroxyprolines can similarly be considered as mimetics of uronic acids. Some hydroxy- and dihydroxyproline derivatives also exhibit glycosidase inhibitory activity, anti-HIV activity or immunostimulating properties,[29] and oxygenation in biological systems.[30] Specifically, (2*S*,3*R*,4*R*)-3,4-dihydroxyproline (**12**), a constituent amino acid of virotoxin in *Amantia virosa mushrooms*, has been shown to be a powerful inhibitor against β-D-glucuronidase.)[32]

This section accounts a new, stereocontrolled, divergent synthesis of iminocyclopentitol **10** and 3,4-dihydroxy-proline **12** (Scheme 4) The key step was a double nucleophilic displacement of D-xylose ditriflates **4α** and **4β** by benzylamine. This was followed by a controlled opening of the glycoside moiety of the resulting azabicyclic anomers **7α** and **7β**.
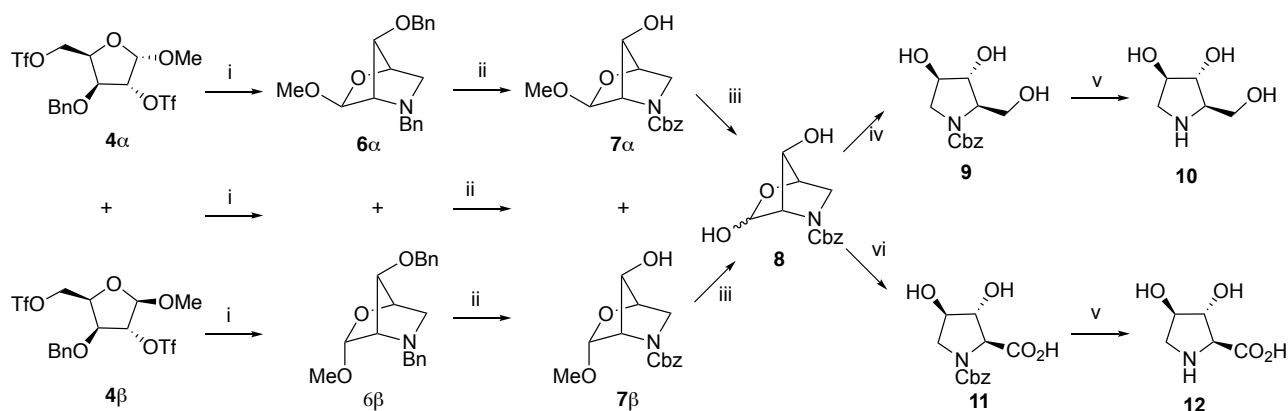
Scheme 4 – *Conditions*: i) BnNH₂, DIEA, MeCN, 45 ºC, 15 h, (85% for **6α**, 84% for **6β**, 85 % for **6α+6b**). ii) a. H₂, 10 % Pd/C, EtOH, rt, 16 h; b. CbzCl, NaHCO₃, Et₂O/H₂O (3:2) 0 ºC to rt,16 h (two steps, 79% for **7α**, 80% for **7β**, 79% for **7α+7β**). iii) TFA/H₂O 3:1, rt, 4 h. iv) NaBH₄, EtOH/H₂O 2:1, rt, 1 h (93%, two steps). v) H₂, 10% Pd/C, MeOH, rt, 4 h, quantitative vi) NaClO₂, NaH₂PO₄.H₂O, 2-methyl-2-butene, *t*BuOH/H₂O, rt,1 h (93%, two steps)

Ditriflates **4α** and **4β** were reacted separately with benzyl amine to give *exo* 6α (85% yield) and *endo* 6β (84% yield) azabicyclic glycosides, respectively. Subsequent catalytic hydrogenation of **6α** resulted in the removal of both Bn groups. The resulting compound was reacted with CbzCl, to give bicycle **7α** and compound **6β** under the same reaction conditions provided bicycle **7β**, anomer of **7α**. Compounds **6α**, **6β**, **7α** and **7β** were obtained separately, for structural characterization and the benzyl group of compounds **6** was switched to a Cbz group in order to make the final steps go in good yield. For routinary experiments the anomeric mixture **4** was transformed into the mixture **6** and this into the mixture **7**, under the same reactions conditions as for the transformation of **4α** into **7α**, via **6α**.

Hydrolysis of the glycoside moieties of the mixture **7** with aqueous trifluoroacetic acid gave the mixture of anomers **8**, which was directly converted into the *N*-protected iminocyclopentitol **9** on reaction with NaBH₄, under the conditions stated in Scheme 4. Finally, removal of the Cbz group of **9** by catalytic hydrogenation afforded the iminocyclopentitol **10** (DAB). On the other hand, oxidation of mixture **8** with NaClO₂, under the reaction conditions shown in Scheme 4, provided the *N*-protected proline **11**, which was converted into the known dihydroxylated proline **12** by removal of the Cbz group of **11** by catalytic hydrogenation.

As a whole, although many methods have been reported for the synthesis of iminocyclopentitols and 3,4-dihydroxyprolines from sugars,[29,33] only one divergent approach to these targets has previously been reported.[4] The present approach clearly improves on this former contribution.

4. **3,4-Dihydroxytetrahydrofuran-2-carboxylic acids and 4-amino-3-hydroxytetrahydrofuran-2-carboxylic acids**

As a second new synthetic application of sugar ditriflates here we report the transformation of the anomeric ditriflates **4α** and **4β** into 3,4-dihydroxytetrahydrofuran-2-carboxylic acid **15** (Scheme 5).

We hypothesized that our ditriflates **4α** and **4β** under anhydrous conditions, in dry polar solvents with traces of water (less than 0.01%) and in the presence of weak nucleophilic bases, could undergo a selective

displacement of the less sterically hindered OTf group at C_5 position by the water present in the reaction medium, giving rise to the corresponding monotriflates **13α** and **13β**, which should spontaneously cyclize to the corresponding dioxabicycles **5α** and **5β** (Scheme 5).[,34]

In the search for suitable conditions for this selective hydrolysis, the ditriflates of **4α** and **4β** were first tested with dry DMSO (%H_2O<0.01), using K_2CO_3 as a base. The results obtained (Table 1, entries 1-4) confirmed our hypothesis, poor yields were obtained and the temperature clearly influenced the reaction rate.
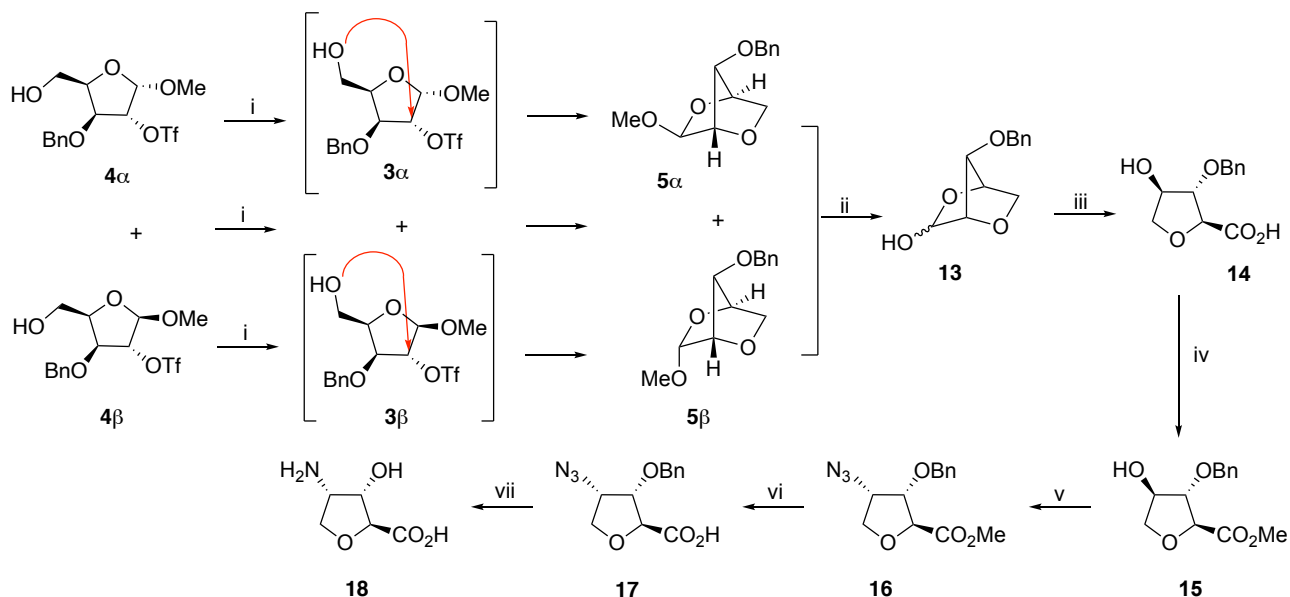
Scheme 5. *Conditions*: i) DBU, CH_3NO_2, rt, 16 h, (80% for **5α**, 65% for **5β**, 72% for **5α+5β**). ii) 2 M HCl, dioxan, 50 °C, 2h. iii) a. 2-methyl-2-butene, NaH_2PO_4, $NaClO_2$; b. 1:1 *t*BuOH/H_2O, rt, 6 h. iv) TMSCHN$_2$. 7:2 Et_2O/MeOH, rt, 1 h (70%, 3 steps). v) a. Tf$_2$O, pyr, DCM, -30 °C, 1 h; b. NaN$_3$, DMF, rt 16 h (82%, 2 steps).vi) a. 1 M LiOH, TFH, rt, 2 h; b. H$^+$, H_2O vii) H$_2$-Pd/C, MeOH, rt, 1 h (81%, 2 steps)

Table 1

Entry	Ditriflate	Solvent	Base	Temperature (°C)	ReactionTime	Dioxabicycle	% Yield
1	**4α**	DMSO	K_2CO_3	rt	16 h	**5α**	25
2	**4β**	DMSO	K_2CO_3	rt	16 h	**5β**	20
3	**4α**	DMSO	K_2CO_3	35	2 h	**5α**	25
4	**4α**	DMSO	K_2CO_3	70	0,5 h	**5α**	25
6	**4α**	MeNO$_2$	DBU	rt	16 h	**5α**	80
7	**4β**	MeNO$_2$	DBU	rt	16 h	**5β**	65

Best results were obtained when dry nitromethane was used as the solvent (%H_2O<0.01) and DBU as the base. As shown in Table 1 (entries 6 and 7), anomer **4α** gave an 80% yield of dioxabicycle **5α** and anomer **4β** gave the corresponding dioxabicycle **5β** in 65% yield. The lower yield obtained for **5β** was attributed to that the spatial orientation of its anomeric OMe makes it difficult for the OH group at C_5 to approach the C_2 carbon bearing the OTf leaving group.

In further experiments, mixtures of anomers **4** were directly converted into the corresponding mixtures of glycosides **5**, which upon hydrolysis with HCl provided the corresponding anomeric mixture **13**, and this, when directly oxidized with NaClO$_2$, provided the *O*-benzylated tetrahydrofuran 2-carboxylic acid **14**, a derivative of a 3,4-dihydroxytetarhydrofuran 2-carboxylic acid not yet reported. This synthetic route constitutes a new approach for the preparation of these targets that clearly improves previous approaches, where a two C-O bonds are generated sequentially.[35,36,37] And additionally, a new contribution to the stereoselective synthesis of chiral tetrahydrofurans, an area of continuous research interest, on account of their biological importance, their presence in numerous natural products and their usefulness as scaffolds in Medicinal Chemistry.[38,39, 40]

As an application of this new chemistry, tetrahydrofuranecarboxylic acid **14** was converted into its methyl acid ester **15** and this into the known γ-azido acid ester acid **17**[41], via compound **16**, following a previous similar protocol (Scheme 5).[42]. It involved the reaction of **16** with triflic anhydride to provide its trifil derivative, from which the OTf group was replaced by azide, upon treatment with sodium azide, the result being the γ-azido acid ester **16**, with a configuration at C$_3$ opposite to those of the starting compound **16**. Finally, hydrolysis of **16** with LiOH provided the γ-azido acid **17**, which gave rise the target γ-amino acid **18** upon catalytic hydrogenation. This constitutes the first 4-amino-3-hydroxytetrahydrofuran-2-carboxylic acid reported, although some derivatives of this family of tetrahydrofuran γ-amino acids have previously been described.[43,44,45]

5. **Sugar ditriflate mediated cyanoacetic synthesis of novel sugar β^{2,2}-amino acids**

The cyanoacetic acid ester synthesis[46] showed to be a suitable approach for the synthesis of β^2- and β^{2,2}-amino acids,[47] including alicyclic and heterocyclic β^{2,2}-amino acids.[48,49] As a third contribution on synthetic applications of sugar ditriflates, we present here the application of this methodology to sugars, which allowed us to transform sugar ditriflate **4β** into compound **25** (Scheme 7), the first reported sugar β^{2,2}-amino acid derivative.

Reaction of ditriflate **4β** with ethyl cyanoacetate under the conditions shown in Scheme 6 gave the corresponding bicyclic α-cyanoacetate **21** only. Its structure was unequivocally confirmed by X-ray crystallographic analysis.

As shown in Scheme 6, formation of compound **21** could be explained assuming that selective displacement of the OTf group at C$_5$ position of **4β** by the cyanoacetic acid ester enolate should give rise to a mixture of enantiomers (*R*)-**19** and (*S*)-**19**, which are in equilibrium with their common enolate **20**. Although this enolate is theoretically able to show two ways for the intramolecular displacement of the OTf group by the enolate moiety, it was observed to favour its spontaneous transformation into the bicyclic α-cyano ester **21**, via transition state **20-A**.
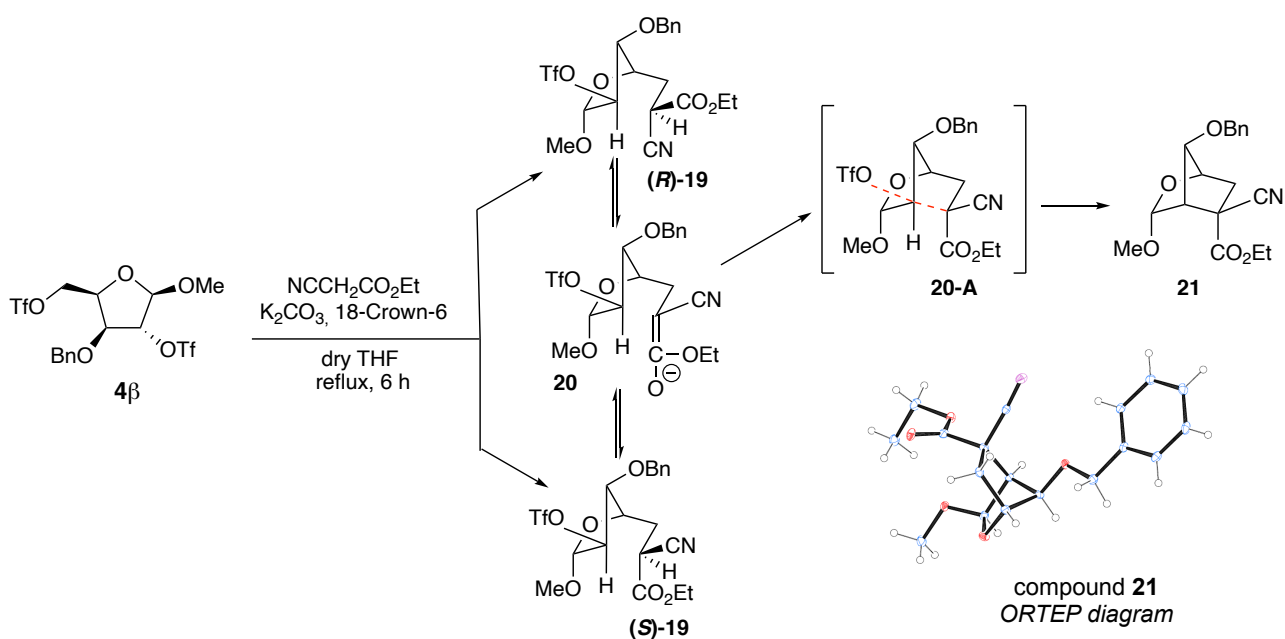
Scheme 6. *Conditions*: i) NCCH₂CO₂Et, K₂CO₃, 18-Crown-6, dry THF, reflux, 6 h (68%)

According to our plan, the ethyl α-cyano acetate **21** was transformed into the corresponding β^{2,2}-amino acid **22**, by reduction of the cyano group, by treatment with NaBH₄ in the presence of CoCl₂ (Scheme 7). And this amino acid **22** was directly reacted with CbzCl to give rise to its derivative **23**, with its NH₂ group protected as Cbz.
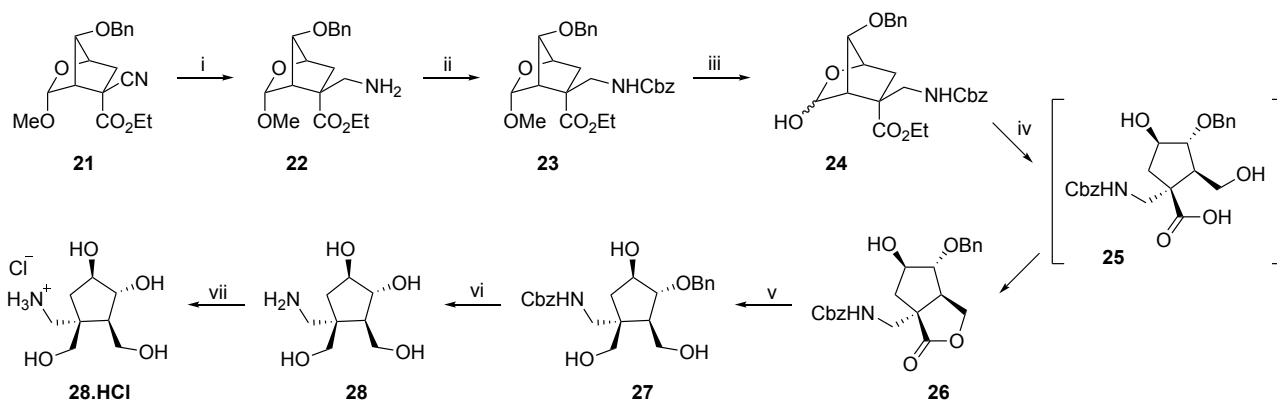
Scheme 7. *Conditions* i) NaBH₄, CoCl₂, MeOH, rt, 23 h. ii) CbzCl, 2:3 NaHCO₃/Et₂O, rt, 17 h (48%, 2 steps). iii) 2 M HCl, 50 °C, 2 h. iv) NaBH₄, EtOH/H₂O 2:1, rt, 20 min (69%, 2 steps). v) NaBH₄, THF/MeOH, 60 °C, 2 h (99%). vi) H₂, 20% Pd(OH)₂/C, MeOH, rt, 2 h. vi) aq. HCl (quantitative, 2 steps)

Acidic hydrolysis of **23** with 2 M HCl provided the anomeric mixture **24**, that was directly reacted with NaBH₄, in order to reduce its formyl group to hydroxymethyl. The resulting compound was the lactone **26**, probably arising from a spontaneous lactonization of the β^{2,2}-amino acid **26** initially formed.

As a whole, we formally have synthetized the first reported polyhydroxylated 2-aminomethylcyclopentane-carboxylic acid (compound **25**) as its γ–lactone **26**. And, as an application of these kinds of amino acids, removal of the Cbz group of its derivative **27**, by catalytic hydrogenation, provided the polyhydroxylated aminomethylcyclopentane **28**, that was isolated as its hydrochloride salt **28.HCl**, which showed poor glycosidase inhibition properties.

Additionally, in an attempt to incorporate amino acid **23** into peptides, the hydrolysis of its ethoxycarbonyl moiety was assayed under basic conditions (1 M NaOH, MeOH, reflux, 2 h), but complex reaction mixtures resulted. This led us to design the alternative for the preparation of type **25** $\beta^{2,2}$-amino acids depicted in Scheme 8, using allyl cyanoacetate instead of ethyl cyanoacetate, in order to avoid this unsuccessful basic hydrolysis. Thus, reaction of ditriflate **4β** with allyl cyanoacetate, under the same conditions as for its previous transformation into compound **21**, provided selectively the expected bicyclic allyl α-cyanocarboxylate **29** which was directly subjected to a protocol for incorporation into peptides. It involved the hydrolysis of the allyl carboxylate of **29**, by treatment with Pd(PPh3)4 and Ph3SiH, followed by the coupling of the resulting carboxylic acid with GlyOMe, under classical peptide coupling conditions, using DIC, HOBt and DIEA. This provided the dipeptide **30**, which was reacted with NaBH4 and CoCl2, for reduction of its CN group to the methylamino group of dipeptide **31**. Treatment of **31** with CbzGlyOH, under the same peptide coupling condition as for the preparation of **30**, give rise to tripeptide **32**, where glycine subunits are linked to both the amino and carboxyl moieties of this oxabicyclic $\beta^{2,2}$-amino acid. Finally, acidic hydrolysis of the glycosidic moiety of **32** with 2 M HCl provided hemiacetal **33**, which was directly reduced to tripeptide **34**, incorporating amino acid **23** as its central subunit.
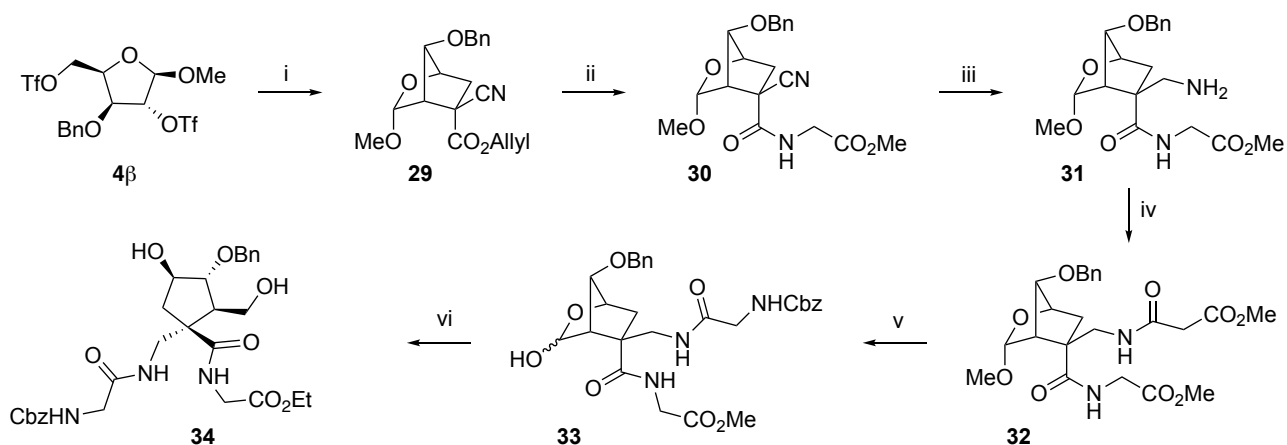
Scheme 8.- *Conditions:* i) NCCH2CO2Allyl, K2CO3, 18-Crown-6, dry THF, reflux, 5 h (75%). ii) a. Pd(PPh3)4, Ph3SiH, DCM, rt, 4 h; b. GlyOMe, DIC, HOBt, DIEA, DCM, rt, overnight (64%). iii) NaBH4, CoCl2, MeOH, rt, 3 h. iv)) CbzGlyOH, DIC, HOBt, DIEA, DCM, rt, overnight (73%, 2 steps). v) 2 M HCl, dioxan, 50 ºC, 2 h vi) NaBH4, 2:1 EtOH/H2O, rt, 20 min (96%, 2 steps)

As a whole, we have developed a protocol for the incorporation of type **22** and type **25** sugar derived $\beta^{2,2}$—amino acids into peptides.

6. **Conclusions.**

In summary, we have extended the range of the few explored synthetic applications of stable sugar ditriflates. In particular, we report here preliminary chemistry of two new, stable sugar ditriflates (the α and β anomers of methyl 2,5-di-*O*-triflil-xylofuranoside) which consists of a divergent synthesis of dihydroxy prolines, pyrrolidines, tetrahydrofuran-2-carboxylic acids and cyclic and bicyclic sugar β-amino acids. It includes the first reported example of the application of the cyanoacetic synthesis to sugars, which allowed access to the first reported polyhydroxylated cycloalkanoalkane $\beta^{2,2}$-amino acid (compound **25**) and the first reported oxabicyclic $\beta^{2,2}$-amino acid (compound **22**) and the development of a protocol for their incorporation into peptides. Additional chemistry consisted of the transformation of $\beta^{2,2}$-amino acid **25** into its aminoalcohol **28**, which showed poor glucosidase inhibition properties, as reported in the Supportig Information document.

Work is now under way to extend these studies to other pentoses and hexoses and other nucleophiles, in order to establish the scope and limitations of sugar ditriflates as synthetic tools. Further work will involve the use of polyhydroxylated cyclopentane and polyhydroxylated cyclohexane $\beta^{2,2}$-amino acids for the preparation of peptides. This is particularly interesting, because the rich functionality of these amino acids makes them useful scaffolds for accessing a variety of lipophilic or hydrophilic peptides, by protecting or deprotecting their hydroxy substituents. In addition, they can carry pharmacophore groups with well-defined spatial orientations, a property that can facilitate their interaction with biological receptors, along with the development of new materials and as peptide catalysts.

7. **Materials and Methods.**

All new compounds were characterized by NMR spectroscopy and high-resolution mass spectrometry. NMR spectra were recorded on Bruker Avance III HD 300 (Bruker, Massachusetts, USA) (^{1}H 300.13 MHz; ^{13}C 75.47 MHz) and Bruker Avance III HD 500 (Bruker, Massachusetts, USA) (^{1}H 500.13 MHz; ^{13}C 125.76 MHz) spectrometers and processed with MestreNova. The following abbreviations are used to indicate the multiplicity of signal: s—singlet, bs – broad singlet, d—doublet, t—triplet, q—quartet and sep—septet. High-Resolution Mass Spectra (HRMS) were recorded on a Hewlett Packard 5988A mass spectrometer (Hewlett Packard, Palo Alto, USA) using electrospray ionization. Specific rotations were recorded on a JASCO DIP-370 optical polarimeter (JASCO, Inc., Easton, USA). Elemental analyses were obtained from the Elemental Analysis Service at the University of Santiago de Compostela. Thin layer chromatography (TLC) was performed using Merck GF-254 type 60 (Merck KGaA, Darmstad, Germany) silica gel and ethyl acetate/hexane mixtures as eluants; the TLC spots were visualized with Hanessian mixture. Column chromatography was carried out using Merck type 9385 (Merck KGaA, Darmstad, Germany) silica gel.

Methyl 3-*O*-benzyl-α-D-xylofuranoside (1α) and methyl 3-*O*-benzyl-β-D-xylofuranoside (1β)
Acetyl chloride (12.09 mL, 170.16 mmol, 6.0 eq) was added dropwise to an ice-cooled solution (0 °C) of compound **6** (7.950 g, 28.36 mmol) in dry methanol (150 mL), controlling the internal temperature to be below 5 °C. The reaction mixture was stirred at 0 °C in an inert atmosphere for 16 h, and then was basified with solid sodium carbonate, filtered and concentrated to dryness. Purification by column chromatography (ethyl acetate/hexanes 3:1) yielded epimeric mixture **1α**+**1β** (6.850 g, 95%), in a 1 (**1α**):1.1 (**1β**) ratio, as a colorless oil.
Compound 1α: $[\alpha]_D^{24}$: +71.0 (c 1.2, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 250 MHz, ppm): 3.47 (s, 3H, -OCH$_3$), 4.42 (dt, *J*=6.8, 4.4 Hz, 1H), 4.49-4.64 (m, 4H), 4.76 (d, *J*=11.7 Hz, 1H, -C$\underline{H}_2$Ph), 5.06 (t, *J*=5.0 Hz, 1H), 5.13 (d, *J*=4.3 Hz, 1H, H-1), 7.27-7.45 (m, 5H, 5xHAr). ^{13}C NMR (CDCl$_3$, 62.5 MHz, ppm): 56.0, 73.2, 73.5, 73.7, 78.6, 87.1, 99.8, 112.2, 116.4, 120.6, 124.9,128.1, 128.6, 128.8, 135.9 (C). HRMS (ESI$^+$) calculated for C$_{15}$H$_{16}$F$_6$NaO$_9$S, [M + Na]$^+$, 541.0032. Found: 541.0032.
Compound 1β: $[\alpha]_D^{24}$: -39.6 (c 0.9, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 250 MHz, ppm): 3.46 (s, 3H, -OCH$_3$), 4.29-4.42 (m, 1H), 4.53 (d, *J*=12.0 Hz, 1H, -C$\underline{H}_2$Ph), 4.58-4.70 (m, 3H), 4.77 (d, *J*=12.0 Hz, 1H, -C$\underline{H}_2$Ph), 5.11 (s, 1H), 5.21 (s, 1H, H-1), 7.27-7.50 (m, 5H, 5xHAr). ^{13}C NMR (CDCl$_3$, 62.5 MHz, ppm): 55.9, 73.1, 75.2, 78.5, 80.5, 90.1, 106.6, 112.1, 116.3, 120.3, 124.8, 128.1, 128.7, 128.8, 135.7. HRMS (ESI$^+$) calculated for C$_{15}$H$_{16}$F$_6$NaO$_9$S, [M + Na]$^+$, 541.0032. Found: 541.0032.

Methyl 3-*O*-benzyl-2,5-di-*O*-trifluoromethanesulfonyl-α-D-xylofuranoside (4α) and methyl 3-*O*-benzyl-2,5-di-*O*-trifluoromethanesulfonyl-β-D-xylofuranoside (4β)

Trlflic anhydride (1.15 mL, 6.84 mmol) was added to a cooled (-30 ºC) solution of a recently obtained mixture **1α** and**1β** (0.610 g, 2.40 mmol) and *N,N*-diisopropylethylamine (1.13 mL, 6.84 mmol) in dichloromethane (18 mL) and the mixture was stirred at this temperature for 2 hours. Then, after reaching room temperature, the solution was washed with water (2x30 mL) and sodium bicarbonate (30 mL), dried over anhydrous magnesium sulphate and concentrated to dryness. Chromatographic column of the residue (ethyl acetate/hexanes 1:8 to 1:6) allowe to isolate compound **4α** (0.503 g, 41%) and **4β** (0.552, 44%), as yellow oils.

Compound 4α: $[\alpha]_D^{21}$: +71° (c 1.2, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 250 MHz, ppm): 3.47 (s, 3H, -OCH$_3$), 4.42 (dt, *J*=6.8, 4.4 Hz, 1H), 4.49-4.64 (m, 4H), 4.76 (d, *J*=11.7 Hz, 1H, -CH$_2$Ph), 5.06 (t, *J*=5.0 Hz, 1H), 5.13 (d, *J*=4.3 Hz, 1H, H-1), 7.27-7.45 (m, 5H, 5xAr-H). ^{13}C RMN (CDCl$_3$, 62.5 MHz, ppm): 56.0, 73.2, 73.5, 73.7, 78.6, 87.1, 99.8, 112.2, 116.4, 120.6, 124.9, 128.1, 128.6, 128.8, 135.9. EMAR (ESI$^+$): calculated for C$_{15}$H$_{16}$F$_6$NaO$_9$S, 541.0032; found, 541.0032. IR (ν, cm-1): 1418 (SO2).

Compound 4β: $[\alpha]_D^{21}$: -39.6° (c 0.9, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 250 MHz, ppm): 3.46 (s, 3H, -OCH$_3$), 4.29-4.42 (m, 1H), 4.53 (d, *J*=12.0 Hz, 1H, -CH$_2$Ph), 4.58-4.70 (m, 3H), 4.77 (d, J=12.0 Hz, 1H, -CH$_2$Ph), 5.11 (s, 1H), 5.21 (s, 1H, H-1), 7.27-7.50 (m, 5H, 5xAr-H). 13C NMR (CDCl$_3$, 62.5 MHz, ppm): 55.9, 73.1, 75.2, 78.5, 80.5, 90.1, 106.6, 112.1, 116.3, 120.3, 124.8,128.1, 128.7, 128.8, 135.7 (C). HRMS (ESI$^+$): calculated for C$_{15}$H$_{16}$F$_6$NaO$_9$S, 541.0032; found, 541.0032.

(1R,3S,4S,7R)-5-Benzyl-7-(benzyloxy)-3-methoxy-2-oxa-5-azabicyclo[2.2.1]heptane (6α) and (1R,3R,4S,7R)-5-benzyl-7-(benzyloxy)-3-methoxy-2-oxa-5-azabicyclo[2.2.1]heptane (6β).

A solution of **4α** (0.292 g,0.56 mmol), *N,N*-diisopropylethylamine (0.25 mL,1.41 mmol, 2.50 eq) and benzylamine (0.07 mL, 0.62 mmol, 1.10 eq) in acetonitrile (4.5 mL) was warmed up to 45 °C for 15 h. The reaction mixture was concentrated to dryness and purified by column chromatography (ethy acetate/hexanes 1;3), to yield **6α** (0.155 g, 85%) as a yellow oil.

Compound **4β** (0.550 g, 1.06 mmol) was subjected to the same reaction conditions as for its anomer **4α**. Column chromatography of the reaction residue (ethyl acetate/hexanes 1:4), afforded **6β** (0.290 g, 84%) as a yellow oil. On the other hand, a recently prepared mixture of ditriflates **4α** and **4β** (0.292 g, 0.56 mmol) was directly subjected to the conditions for the preparation of **6β**. Purification of the reaction mixture by column chromatography (ethyl acetate/hexanes 1:4) provided a mixture of bicycles **6α** and **6β** (0.159 g, 85%).

Compound 6α: $[\alpha]_D^{24}$: +63.8 (c 2.5, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 250 MHz, ppm): 2.83 (d, *J*=9.8 Hz, 1H, H-6), 2.96 (dd, *J*=9.8, 1.3 Hz, 1H, H-6'), 3.21 (s, 1H, H-4), 3.34 (s, 3H, -OCH$_3$), 4.00 (ABq, *J*=13.5 Hz, 2H, -N-C<u>H</u>$_2$Ph), 4.20-4.27 (m, 2H, H-1, H-7), 4.59 (ABq, *J*=11.7 Hz, 2H, -O-C<u>H</u>$_2$Ph), 4.80 (s, 1H, H-3), 7.20-7.42 (m, 10H, 10xH-Ar). ^{13}C NMR (CDCl$_3$, 62.5 MHz, ppm): 55.0, 56.9, 59.1, 63.6, 72.2, 76.1, 80.0, 106.3, 126.8, 127.6, 127.8, 128.3 (4xCH), 128.5, 137.9, 140.1 (C). HRMS (ESI$^+$) calculated for C$_{20}$H$_{24}$NO$_3$, [M + H]$^+$, 326.1751. Found: 326.1744.

Compound 6β: $[\alpha]_D^{24}$: -10.3 (c 1.0, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 250 MHz, ppm): 3.05-3.17 (m, 2H, H-6, H-6'), 3.25-3.36 (m, 1H, H-4), 3.43 (s, 3H, -OCH$_3$), 4.01 (d, *J*=2.3 Hz, 1H, H-7), 4.16 (ABq, *J*=14.0 Hz, 2H, -N-C<u>H</u>$_2$Ph), 4.27-4.33 (m, 1H, H-1), 4.56 (ABq, *J*=11.7 Hz, 2H, -O-C<u>H</u>$_2$Ph), 4.95 (d, *J*=1.5 Hz, 1H, H-3), 7.20-7.42 (m, 10H, 10xH-Ar). ^{13}C NMR (CDCl$_3$, 62.5 MHz, ppm): 56.1, 57.5, 59.0, 62.1, 71.7, 79.3, 80.9, 107.1, 126.6, 127.6, 127.8, 128.1 (4xCH), 128.5, 137.7, 140.5 (C). HRMS (ESI$^+$) calculated for C$_{20}$H$_{24}$NO$_3$, [M + H]$^+$, 326.1751. Found: 326.1751.

Benzyl (1R,3S,4S,7R)-7-hydroxy-3-methoxy-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate (7α).and benzyl (1R,3R,4S,7R)-7-hydroxy-3-methoxy-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate (7β).

10% Pd/C (0.203 g) was added to a deoxygenated solution of **7α** (0.203 g, 0.62 mmol) in ethanol (10 mL) and the mixture was stirred at room temperature under a hydrogen atmosphere (1 atm) for 22 h. The reaction

mixture was filtered over a pad of celite and concentrated to dryness. The crude was purified by column chromatography (15% methanol/dichorometane) to yield an amorphous white solid (0.089 g, 99%), which was added to a cooled (0 °C) mixture of diethyl ether (22 mL) and saturated aqueous sodium bicarbonate (15 mL). Benzyl chloroformate (1.09 mL, 7.74 mmol, 3.0 eq) was then added and the mixture was stirred at room temperature for 16 h, and then was extracted with diethyl ether (4x20 mL). The combined organic layers were dried with anhydrous sodium sulfate, filtered and concentrated to dryness. The crude residue was purified by column chromatography (ethyl acetate/hexanes 1:1) to afford **7α** (0.599 g, 83%) as an amorphous white solid.

When a solution of compound **6β** (0.203 g, 0.62 mmol) in ethanol (10 mL) was subjected to the conditions for the preparation of compound **7α** and the crude residue was purified by column chromatography (ethyl acetate/hexanes 3:1), compound **7β** (0.188 g, 81%) was obtained (0.086 g, 96%) as an amorphous white solid.

When a recently obtained mixture of compounds **6α** and **6β** (0.203 g, 0.62 mmol) was subjected to the method for the preparation of **7α** and the resulting mixture was purified by column chromatography (75% erhyl acetate/hexanes 3:1), a mixture of bicycles **7α** and **7β** was isolated (0,580 g, 82%) as an amorphous white solid.

Compound 7α.- $[\alpha]_D^{24}$: +13.2 (c 1.2, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 250 MHz, ppm): 2.45 (s, 0.5H, -OH), 2.73 (s, 0.5H, -OH), 3.29 (s, 1H, H-6), 3.36 (s, 3H, -OCH$_3$), 3.59 (m, 1H, H-6'), 4.04-4.22 (m, 1H), 4.25 (s, 1H), 4.54 (s, 1H), 4.72 (m, 1H), 5.09-5.21 (m, 2H, -CH$_2$Ph), 7.28-7.41 (m, 5H, 5xH-Ar) (Two rotamers). ^{13}C NMR (CDCl$_3$, 62.5 MHz, ppm): 50.2, 55.0, 55.2, 62.0, 62.2, 67.1, 70.9, 71.5, 76.0, 76.3, 105.4, 105.7, 127.6, 127.8, 127.9, 128.4, 136.1, 155.8 (CO) (Two rotamers). HRMS (ESI$^+$) calculated for C$_{14}$H$_{17}$NNaO$_5$, [M + Na]$^+$, 302.0999. Found: 302.0994.

Compound 7β $[\alpha]_D^{24}$: -79.9 (c 1.2, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 250 MHz, ppm): 3.35 (s, 3H, -OCH$_3$), 3.39 (s, 3H, -OCH$_3$), 3.48-3.56 (m, 4H), 4.21-4.36 (m, 6H), 5.02-5.26 (m, 6H), 7.28-7.40 (m, 10H, 10xAr-H) (Two rotamers). ^{13}C NMR (CDCl$_3$, 62.5 MHz, ppm): 50.7, 50.8, 55.7, 55.9, 62.2, 62.5, 67.0, 67.1, 72.4, 73.1, 78.6, 79.1, 104.5, 104.9, 127.5, 127.7, 128.0, 128.5, 136.6, 136.8, 156.7, 157.0 (CO) (Two rotamers). HRMS (ESI+) calculated for C$_{14}$H$_{18}$NO$_5$, [M + H]$^+$, 280.1179. Found: 280.1180.

Benzyl (2R,3R,4R)-3,4-dihydroxy-2-(hydroxymethyl)pyrrolidine-1-carboxylate (9).

A solution of a recently obtained mixture of compounds **7α** and **7β** (0.170 g, 0.61 mmol) in a 3:1 mixture of trifluoroacetic acid/water (6 mL) was stirred at room temperature for 4 h. The reaction mixture was concentrated to dryness and dissolved in a 2:1 mixture of ethanol/water (6 mL), sodium bofohydride (0.046 g, 1.22 mmol, 2.0 eq) was added and the resulting mixture was stirred at room temperature for 1 h, quenched with phosphate buffer (pH 7.0), concentrated to dryness and purified by column chromatography (ethyl acetate), to afford compound **9** (0.151 g, 93%) as an amorphous white solid. $[\alpha]_D^{24}$: -23.4 (c 3.6, CHCl$_3$). ^{1}H NMR (CD$_3$OD, 250 MHz, ppm): 3.35-3.45 (m, 2H, H-5, H-5'), 3.71-3.98 (m, 3H, H-2, H-6, H-6'), 4.02-4.11 (m, 1H), 4.16 (m, 1H), 5.0.8-5.25 (m, 2H, -CH$_2$Ph), 7.28-7.46 (m, 5H, 5xAr-H). ^{13}C NMR (CD$_3$OD, 62.5 MHz, ppm): 54.3, 54.7, 61.6, 61.7, 67.9, 68.0, 68.2, 68.4, 75.5, 76.0, 78.6, 79.3, 128.7, 128.9, 129.0, 129.1, 129.5, 137.8, 137.9, 157.1, 157.2 (CO) (Two rotamers). HRMS (ESI$^+$) calculated for C$_{13}$H$_{17}$NNaO, [M + Na]$^+$, 290.0999. Found: 290.0998.

(2R,3R,4R)-2-(Hydroxymethyl)pyrrolidine-3,4-diol (DAB) (10)

10% Pd/C (0.089 g) was added to a deoxygenated solution of compound **9** ((0.089 g, 0.239 mmol) en methanol (6 mL) and the suspension was stirred for 4 hours under a hydrogen atmosphere, filetered over a celite pad and concentrated to dryness. The residue was dissolved in 1 M hydrochloric acid, ethylic ether was added and

the precipitate was filtered off, to provide the hydrochloride of compound 10 (0.035 g, 0.24 mmol, white, hygroscopic hydrochloride). $[\alpha]_D^{24}$: +35.4 (c 1.1, H_2O). ^{1}H NMR (D_2O, 300 MHz, ppm): 3.33-3.46 (m, 1H), 3.55-3.71 (m, 2H), 3.86 (dd, J=12.2, 8.1 Hz, 1H), 3.99 (dd, J=12.2, 4.8 Hz, 1H), 4.13 (t, J=3.5 Hz, 1H), 4.37 (dt, J=5.1, 2.8 Hz, 1H). ^{13}C NMR (D_2O, 75 MHz, ppm): 50.8, 59.7, 67.4, 75.1, 76.4 (CH). HRMS (ESI$^+$) calculated for $C_5H_{12}NO_3$, [M + H]$^+$, 134.0812. Found: 134.0821.

(3*R*,4*R*)-*N*-((Benzyloxy)carbonyl)-3,4-dihydroxy-*L*-proline (11)

A solution of a mixture of compounds **7α** and **7β** (0.162 g, 0.58 mmol) in a 3:1 mixture of trifluoroacetic acid/water (6 mL) was stirred at room temperature for 4 h, and then was concentrated to dryness and dissolved in a 1:1 mixture of *t*-butanol/water (9 mL). 2-Methyl-2-butene (0.62 mL, 5.80 mmol, 46 eq), sodium dihydrogen phosphate monohydrate (0.136 g, 0.87 mmol, 1.5 eq) and sodium chlorite (0.079 g, 0.87 mmol, 1.5 eq) were added to the solution. The reaction mixture was then stirred at room temperature for 1 h, concentrated to dryness and purified by column chromatography (15% metanol/dichloromethane) to afford **11** (0.151 g, 93%) as an amorphous white solid. $[\alpha]_D^{24}$: -2.8 (c 3.8, MeOH). ^{1}H NMR (CD$_3$OD, 250 MHz, ppm): 3.36 (dt, J=11.6, 2.6 Hz, 1H, H-5), 3.66 (ddd, J=11.6, 5.0, 1.7 Hz, 1H, H-5'), 3.93-4.01 (m, 1H, H-2), 4.15 (d, J=1.7 Hz, 1H, H-4), 4.19 (d, J=2.1 Hz, 1H, H-3), 4.95-5.08 (m, 2H, -CH$_2$Ph), 7.12-7.33 (m, 5H, 5xH-Ar) (Two rotamers). ^{13}C NMR (CD$_3$OD, 62.5 MHz, ppm): 53.4, 53.6, 67.3, 67.6, 68.3, 75.2, 75.9, 80.0, 80.9, 128.6, 128.8, 128.9, 129.1, 129.4, 129.5 (5xCH), 137.9, 156.9, 157.2, 173.1,173.4 (two rotamers). HRMS (ESI$^+$) calculated for $C_{13}H_{15}NNaO_6$, [M + Na]$^+$, 304.0792. Found: 304.0796.

(3*R*,4*R*))-3,4-Dihydroxy-*L*-proline (12)

10% Pd/C w/w (0.005 g) was added to a deoxygenated solution of **11** (0.050 g, 0.18 mmol) in methanol (6 mL) and reaction mixture was stirred at room temperature under a hydrogen atmosphere (1 atm) for 4 h. The reaction mixture was filtered over a pad of celite and concentrated to dryness. The crude was dissolved in the minimal amount of 1 M hydrochloric acid, ethylic ehter was added until precipitation and the precipitate was filtered off, to afford **12** (0.032 g, 99%) as a white, hygroscopic hydrochloride salt. $[\alpha]_D^{24}$: +1.6 (c 1.1, H_2O). ^{1}H NMR (D_2O, 300 MHz, ppm): 3.57 (d, J=12.7 Hz, 1H, H-5), 3.67-3.76 (m, 1H, H-5'), 4.44-4.39 (m, 1H), 4.47 (s, 1H), 4.69 (s, 1H). ^{13}C NMR (D_2O, 75 MHz, ppm): 53.9, 68.5, 76.2, 80.4, 171.9. HRMS (ESI$^+$) calculated for $C_5H_{10}NO_4$, [M + H]$^+$, 148.0605. Found: 148.0611.

(1*R*,3*S*,4*S*,7*S*)-7-(Benzyloxy)-3-methoxy-2,5-dioxabicyclo[2.2.1]heptane (5α) and (1*R*,3*S*,4*S*,7*S*)-7-(benzyloxy)-3-methoxy-2,5-dioxabicyclo[2.2.1]heptane (5β).

DBU (0.024 mL, 0.16 mmol, 1.50 eq.) was added to a solution of **4α** (0.054 g, 0.11 mmol) in nitromethane (2.5 mL). The reaction mixture was stirred at room temperature for 17 h, poured into ethyl acetate (20 mL), washed with water (3x5 mL), dried over anhydrous sodium sulpahte, filtered and concentrated to dryness. The residue was purified by silica gel column chromatography (ethyl acetate/hexanes 1:5) to give **5α** (19 mg, 80 %) as a pale orange oil.

Compound **4β** (0.130 g, 0.25 mmol) was subjected to the procedure for the transformation of **4α** into **5α**. Work-up of the reaction mixture provided a residue, which was purified by silica gel column chromatography (ethyl acetate/hexanes 1:2) to give **5β** (38 mg, 65 %) as a pale brown oil.

A solution of a recently obtained mixture of **4α** and **4β** (0.130 g, 0.25 mmol) was subjected to the conditions used for the transformation of **4α** into **5α**. Silica gel column chromatography (ethyl acetate/hexanes 1:2) of the reaction residue gave a mixture of **5α** and **5β** (0,330 g, 72 %).

Compound **5α**.- $[\alpha]_D^{24}$: +60.5 (c 1.48, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 300 MHz, ppm): 3.36 (s, 3H, OCH3), 3.70 (d, J = 7.9 Hz, 1H, H-6), 4.00 (d, J = 7.9 Hz, 1H, H-6), 4.11 (s, 1H, CH-O), 4.21 – 4.27 (m, 2H, 2xCH-O), 4.60 (ABq, J = 11.8 Hz, 2H, CH$_2$-Ar), 4.75 (s, 1H, CH-OMe), 7.29 – 7.41 (m, 5H, Ar).^{13}C NMR (CDCl$_3$, 75 MHz, ppm): 55.4, 70.8, 72.4, 74.9, 76.6, 78.5, 106.1, 127.8, 128.0, 128.5, 137.6. HRMS (ESI$^+$): calculated for C$_{13}$H$_{16}$NaO$_4$, [M + H]$^+$, 259.0941, found: 259.0938.

Compound **5β**.- $[\alpha]_D^{24}$: +8.2 (c 1.45, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 300 MHz, ppm): 3.44 (s, 3H, OCH$_3$), 3.96 (d, J = 8.0 Hz, 1H, H-6), 4.03 (d, J = 2.8 Hz, 2H, CH-O, H-6), 4.20 (s, 1H, CH-O), 4.26 (s, 1H, CH-O), 4.60 (ABq, J = 11.9 Hz, 2H, CH2-Ar), 4.95 (s, 1H, CH-OMe), 7.26 – 7.40 (m, 5H, Ar).^{13}C NMR (CDCl$_3$, 75 MHz, ppm): 56.1, 71.6, 72.2, 76.7, 78.5, 79.5, 105.5, 128.0, 128.2, 128.6, 137.4. HRMS (ESI$^+$): calculated for C$_{13}$H$_{16}$NaO$_4$, [M + H]$^+$, 259.0941, found: 259.0939.

Methyl (2*S*,3*S*,4*R*)-3-(benzyloxy)-4-hydroxytetrahydrofuran-2-carboxylate (15)

A solution of a recently obtained mixture of **5α** and **5β** (0.288 g, 1.22 mmol) was solved in 1,4-dioxane (17 mL), 1 M hydrochloric acid (17 mL) added and the mixture was warmed up to 50 °C for 2 h and then was concentrated to dryness. The residue was redissolved in a mixture of *tert*-butanol/water (18 mL, 1:1), 2-metil-2-butene (0.129 mL, 1.22 mmol, 1.0 eq), sodium dihydrogen phospate (0.286 g, 1.83 mmol, 1.5 eq) and sodium chlorite(0.165 g, 1.83 mmol, 1.5 eq) were added, and the resulting mixture was stirred at room temperature for 6 h. The reaction mixture was poured into water (30 mL) and extracted with ethyl acetate (4x10 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated to dryness. The crude product was dissolved in a 7:2 mixture of ethanol/water (4 mL) and trimethylsilyldiazomethane (2 M in ethyl ether, 0.73 mL, 1.46 mmol, 1.2 eq) was added dropwise. After stirring at room temperature for 1 hour, the reaction mixture was concentrated to dryness and purified by silica gel column chromatography (ethyl acetate/hexanes 1:2), to afford compound **15** (0.216 g, 70 %) as a white solid. $[\alpha]_D^{24}$: +43.0 (c 1.66, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 300 MHz, ppm): 3.10 (bs, 1H, -OH), 3.74 (s, 3H, -OCH$_3$), 4.04 (d, *J* = 9.9 Hz, 1H, H-5), 4.10 (dd, *J* = 9.9, 3.3 Hz, 1H, H-5), 4.15 (s, 1H, H-3), 4.27 (dd, *J* = 3.3, 1.6 Hz, 1H, H-4), 4.50 (d, J = 1.6 Hz, 1H, H-2), 4.63 (ABq, *J* = 11.8 Hz, 2H, CH$_2$-Ph), 7.30 –7.37 (m, 5H, Ar). ^{13}C NMR (CDCl$_3$, 75 MHz, ppm): 52.5, 71.8, 74.8, 75.2, 81.4, 87.7, 127.8, 128.0, 128.5, 137.2, 172.3. HRMS (ESI$^+$): calculated for C$_{13}$H$_{16}$NaO$_5$, [M + H]$^+$, 275.0890, found: 275.0889.

Methyl (2*S*,3*S*,4*S*)-4-azido-3-(benzyloxy)tetrahydrofuran-2-carboxylate (16)

Pyridine (48.3 mL) and triflici anhydride (67 mL (0.40 mmol, 2.00 eq) were added to a stirred, cooled (-30 ºC) solution of compound **15** (50.3 mg, 0.20 mmol) in dry dichoromethane and the stirring was continued for 1 h. The reaction mixture was then washed with saturated aqueous sodium chloride (2x5 mL) and the organic layer with dried (anhydrous sodium sulphate), filtered and concentrated to dryness. The crude product was solved in dry *N*,*N*-dimethylformaide (1.5 mL), sodium azide (51.7 mg, 0.80 mmol) was added and the mixture was stirred at room temperature for 16.5 hours and then concentrated to dryness. Column chromatography of the residue (ethy acetate/hexanes 1:4) provided compound compound **16** (41.5 mg, 82%), as a colorless oil. $[\alpha]_D^{23}$: +47.3 (c 1.16, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 300 MHz, ppm): 3.75 (s, 3H, OCH$_3$), 3.91 (ddd, *J* = 5.0, 5.0, 4.9 Hz, 1H, H-4), 3.99 (dd, *J* = 9.4, 4.4 Hz, 1H, H-5), 4.14 (dd, *J* = 9.5, 5.2 Hz, 1H, H-5), 4.30 (t, $_J$ = 5.0, 5.0 Hz, 1H, H-3), 4.51 (d, *J* = 4.8 Hz, 1H, H-2), 4.71 (s, 2H, CH$_2$-Ph), 7.28 - 7.47 (m, 5H, Ar). ^{13}C NMR (CDCl$_3$, 75 MHz, ppm): 52.6, 60.8, 71.1, 72.9, 80.2, 82.3, 128.0, 128.3, 128.6, 136.8, 171.4. EMAR (ESI+): calculated for C$_{13}$H$_{15}$N$_3$NaO$_4$, 300.0955; foundo, 300.0791.

(2*S*,3*S*,4*S*)-4-amino-3-hydroxytetrahydrofuran-2-carboxylic acid (18)

1 N Aqueous lithium hydroxide was added to a solution of compound **16** (42.7 mg, 0.15 mmol) in tetrahydrofuran (3 mL) and the mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure, water (10 mL) was added and the pH was adjusted at 3-4 by adding 1 M aqueous hydrochloric acid. The mixture was extracted with dichoromethane (3x7 mL) and the pooled organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated to dryness. Then 10% Pd/C was added to a deoxygenated solution of the crude residue in methanol (4.5 mL) and the mixture was stirred, under a hydrogen atmosphere (1 atm), for 1 hour. The suspension was filtered through a celite pad and the filtrate was concentrated to dryness. This provided compound compound **18** (18.3 mg, 81%) as a white solid. [α]$_D^{23}$: +28.4 (c 1.1, CHCl$_3$). ^{1}H NMR (D$_2$O, 300 MHz, ppm): 3.34 - 3.41 (m, 1H, H-5), 3.50 (dd, *J* = 8.9, 7.7 Hz, 1H, H-5), 4.02 (dd, *J* = 8.8, 6.9 Hz, 1H, H-4), 4.08 (d, *J* = 2.8 Hz, 1H, H-2), 4.14 (dd, *J* = 5.1, 2.7 Hz, 1H, H-3). EMAR (ESI$^+$): calculated for C$_5$H$_{10}$NO$_4$, 148.0604; found, 148.0604.

Ethyl (1*R*,3*R*,4*S*,5*S*,7*R*)-7-(benzyloxy)-5-cyano-3-methoxy-2-oxabicyclo[2.2.1]heptane-5-carboxylate (21).

Ethyl cyanoacetate (0.029 mL, xx mmol, 1.1 eq), potassium carbonate (0.138 g, xx, mmol, 4.0 eq) and 18-crown-6 ether(0.007 g, xx mmol, 0.1 eq) were added to a solution of **4β** (0.129 g, 0.249 mmol) in dry tetrahydrofuran (2 mL). After stirring at reflux for 6 h, the reaction mixture was concentrated to dryness and the residue was partitioned with ethyl ether and water. The organic layer was washed twice with water, dried over anhydrous sodium sulphate, filtered and concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (ethyl acetate/hexanes 1:5) to afford compound **21** (0.046 g, 68%) as a colorless oil. [α]$_D^{22}$:-64.9 (c 1.0, CH$_3$CN). IR (ATR, cm^{-1}): 2240, 2208, 1748. ^{1}H NMR (CDCl$_3$, 300 MHz, ppm): 1.32 (t, *J* = 7.1 Hz, 3H), 2.44 (d, *J* = 14.1 Hz, 1H), 2.92 (d, *J* = 14.1 Hz, 1H), 3.26 (s, 3H, CH$_3$), 3.28 – 3.36 (m, 1H), 4.18 – 4.32 (m, 4H), 4.48 (d, *J* = 11.8 Hz, 1H), 4.83 (d, *J* = 11.8 Hz, 1H), 4.99 (d, *J* = 2.5 Hz, 1H), 7.28 – 7.47 (m, 5H). ^{13}C NMR (CDCl$_3$, 75 MHz, ppm): 14.0, 37.4, 43.5, 50.7, 55.7, 62.7, 72.1, 77.7, 83.0, 102.6, 120.5, 128.2, 128.2, 128.7, 136.9, 166.9. HRMS (ESI+): calculated for C$_{18}$H$_{21}$NNaO$_5$ (M+Na)$^+$ 354.1312, found 354.1320.

Ethyl (1*R*,3*R*,4*S*,5*S*,7*R*)-7-(benzyloxy)-5-((((benzyloxy)carbonyl)amino)methyl)-3-methoxy-2-oxabicyclo[2.2.1]heptane-5-carboxylate (23).

Cobalt dichloride$_2$ (0.367 g, 2.823 mmol) and sodium borohydride (0.675 g, 17.856 mmol) were added to a solution of **21** (0.275 g, 0.8305 mmol) in methanol (40) was stirred at room temperature for 18 h. The methanol was removed under vacuum and the residue was suspended in water and extracted twice with dichoromethane. The combined organic layers were dried over anhydrous sodium sulphate, filtered, and concentrated to dryness under vacuum. The crude residue was redissolved in a 2:3 mixture of saturated aqueous solution of sodium bicarbonate and ethyl ether (11.6 mL) and benzyloxycarbonyl chloride (0.350 mL, 2.49 mmol) was added. After stirring overnight at room temperature, the reaction mixture was diluted with 10 mL of saturated aqueous solution of sodium bicarbonate (10 mL) and extracted with ethyl ether (4x10mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered, and evaporated. The crude residue was purified by silica gel column chromatography (ethyl acetate/hexanes 1:2) to afford **23** (0.249 g, 64%) as a colorless oil. [α]$_D^{22}$ +11.6 (c 2.2, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 300 MHz, ppm): 1.25 (t, *J* = 7.2 Hz, 3H), 1.79 – 2.13 (m, 2H), 2.59 – 2.85 (m, 2H), 3.24 (s, 3H), 3.72 (dd, *J* = 13.3, 6.6 Hz, 1H), 3.90 – 4.24 (m, 4H), 4.40 – 4.67 (m, 2H), 4.94 (d, *J* = 2.3 Hz, 1H), 4.99 – 5.18 (m, 2H), 7.26 – 7.48 (m, 10H). ^{13}C NMR (CDCl$_3$, 75 MHz, ppm): 14.1,

36.0, 48.0, 49.0, 50.4, 55.5, 60.8, 66.6, 72.4, 78.2, 83.8, 103.6, 127.9, 128.0, 128.5, 128.6, 136.7, 137.2, 156.4, 174.4. HRMS (ESI+): calculated for $C_{26}H_{31}NNaO_7$ (M+Na)$^+$ 492.1993, found 492.1992.

Benzyl ((3a*R*,5*R*,6*R*,6a*R*)-6-(benzyloxy)-5-hydroxy-3-oxotetrahydro-1*H*-cyclopenta[*c*]furan-3a(3*H*)-yl)carbamate (26)

To a solution of **23** (0.213 g, 0.469 mmol) in dioxane (15 mL) 2M hydrochloric acid (15 mL) was added, the mixture was stirred at 50 ºC for 2 h and the liquids were evaporated. The residue was dissolved in ethanol (15 mL) and water (10 mL), and sodium borohydride (0.036 g, 2 eq) was added. After stirring for 20 min, the ethanol was removed, and residue was redissolved in water and extracted three times with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulphate, filtered, and evaporated. The crude was purified by silica gel column chromatography (ethyl acetate/hexanes2:1) to afford compound compound **26** (0.133 g, 69%) as a colorless oil. $[\alpha]_D^{22}$ +16 (c 3.5, CHCl₃). ^{1}H NMR (CDCl₃, 300 MHz, ppm): 1.99 – 2.20 (m, 2H), 2.42 (s, 1H), 2.95 (dd, *J* = 9.8, 3.9 Hz, 1H), 3.47 (dd, *J* = 6.4, 2.4 Hz, 2H), 3.75 (s, 1H), 4.14 (dd, *J* = 9.4, 3.9 Hz, 1H), 4.23 – 4.40 (m, 2H), 4.43 – 4.61 (m, 2H), 5.10 (m, 2H), 5.42 (t, *J* = 6.4 Hz, 1H), 7.27 – 7.44 (m, 10H). ^{13}C NMR (CDCl₃, 75 MHz, ppm): 41.6, 46.2, 47.5, 54.9, 67.1, 70.3, 71.4, 75.8, 90.3, 127.7, 128.0, 128.0, 128.1, 128.3, 128.6, 136.4, 137.7, 157.0, 181.9. HRMS (ESI+): calculated for $C_{23}H_{26}NO_6$ (M+H)$^+$ 412.1755, found 412.1756.

Benzyl (((1*S*,2*R*,3*R*,4*R*)-3-(benzyloxy)-4-hydroxy-1,2-bis(hydroxymethyl)cyclopentyl)methyl)carbamate (27).

Sodium borohydride (0.013 g, 0.340 mmol) was added, under stirring, to a solution of **26** (0.070 g, 0.170 mmol) in dry tetrahydrofuran (1.7 mL) and the reaction mixture was heated at 60 °C for 15 min. Then, metahnol (0.340 mL) and sodium borohydride (0.004 g, 0.085 mmol) were added and the stirring was continued at rt for 2 h. The reaction mixture was quenched with saturated aqueous solution of ammonium chloride and was extracted with ethyl acetate mL). The combined organic layers were dried over anhydrous sodium sulphante, filtered, and evaporated. The crude was purified by silica gel column chromatography (ethyl acetate) to afford compound **27** (0.070 g, 99%) as a colorless oil. $[\alpha]_D^{22}$ +0.6 (c 6.7, CHCl₃). ^{1}H NMR (CDCl₃, 300 MHz, ppm): 1.12 – 1.36 (m, 1H), 1.69 – 1.94 (m, 2H), 3.01 (d, *J* = 14.2 Hz, 1H), 3.29 (d, *J* = 14.2 Hz, 1H), 3.42 (d, *J* = 12.1 Hz, 1H), 3.53 (d, *J* = 12.1 Hz, 1H), 3.60 (dd, *J* = 8.8, 5.0 Hz, 1H), 3.73 – 3.81 (m, 2H), 3.94 – 4.17 (m, 4H), 4.57 (d, *J* = 11.6 Hz, 1H), 4.70 (d, *J* = 11.6 Hz, 1H), 5.06 (s, 2H), 5.74 (s, 1H), 7.23 – 7.38 (m, 10H). ^{13}C NMR (CDCl₃, 75 MHz, ppm): 39.3, 46.8, 47.3, 51.5, 60.5, 64.2, 67.2, 72.5, 75.2, 87.8, 127.8, 128.1, 128.3, 128.5, 128.6, 136.1, 138.3, 158.1. HRMS (ESI+): calculated for $C_{23}H_{30}NO_6$ (M+H)$^+$ 416.2068, found 416.2068.

((1*S*,2*R*,3*R*,4*R*)-3,4-dihydroxy-1,2-bis(hydroxymethyl)cyclopentyl)methanaminium chloride (28.HCl).

20% Pd(OH)₂/C (0.130 g of) was added to a deoxygenated solution of **27** (0.065 g, 0.1564 mmol) in methanol (6 mL). After another deoxygenation cycle, two drops of concentrated hydrochloric acid were added, and the reaction mixture was stirred under hydrogen (1 atm) at room temperature for 2 h, and then was filtered through Celite, washed with methanol, and the filtrate was concentrated to dryness under vacuum, to afford compound **28.HCl** (0.036 g, quantitative yield), as a highly hygroscopic white solid. $[\alpha]_D^{22}$ +4.4 (c 1.3, MeOH). ^{1}H NMR (MeOD, 300 MHz, ppm): 1.58 (dd, *J* = 13.7, 7.2 Hz, 1H), 1.68 – 1.89 (m, 2H), 2.82 (d, *J* = 11.8Hz, 1H), 3.00 (d, *J* = 11.8 Hz, 1H), 3.24 (d, *J* = 11.3 Hz, 1H), 3.44 – 3.80 (m, 4H), 3.86 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (MeOD, 75 MHz, ppm): 37.8, 43.1, 46.7, 52.9, 58.5, 63.4, 75.4, 78.7. HRMS (ESI+): calcd for $C_8H_{18}NO_4$ (M+H)$^+$ 192.1230, found 192.1226.

Allyl (1*R*,3*R*,4*S*,5*S*,7*R*)-7-(benzyloxy)-5-cyano-3-methoxy-2-oxabicyclo[2.2.1]heptane-5-carboxylate (29).

A solution of **4β** (0.324 g, 0.625 mmol), allyl cyanoacetate (0.08 mL, 1.1 eq), potassium carbonate (0.345 g, 4.0 eq) and 18-crown-6 ether (0.017 g, 0.1 eq) in dry tetrahydrofuran (5 mL) was subjected to the conditions for the preparation of **21**. The work-up provided a residue that was purified by silica gel column chromatography (ethyl acetate/hexanes 1:5) to give **29** (0.150 g, 70%) as a colorless oil. $[\alpha]_D^{22}$ -10.9 (c 0.6, CH$_3$CN). ^{1}H NMR (CDCl$_3$, 300 MHz, ppm): 2.46 (dd, *J* = 14.5, 1.9 Hz, 1H), 2.93 (d, *J* = 14.1 Hz, 1H), 3.26 (s, 3H), 3.33 (s, 1H), 4.24 – 4.28 (m, 2H), 4.48 (d, *J* = 11.8 Hz, 1H), 4.57 – 4.67 (m, 1H), 4.74 (ddt, *J* = 13.2, 5.7, 1.4 Hz, 1H), 4.83 (d, *J* = 11.8 Hz, 1H), 4.99 (d, *J* = 2.5 Hz, 1H), 5.23 – 5.32 (m, 1H), 5.35 – 5.47 (m, 1H), 5.86 – 6.05 (m, 1H), 7.28 – 7.44 (m, 5H). ^{13}C NMR (CDCl$_3$, 75 MHz, ppm): 37.4, 43.4, 50.7, 55.6, 67.0, 72.0, 77.5, 82.9, 102.4, 118.8, 120.2, 128.1, 128.1, 128.2, 128.6, 131.5, 136.8, 166.6. HRMS (ESI$^+$): calculated for C$_{19}$H$_{21}$NNaO$_5$ (M+Na)$^+$ 366.1312, found 366.1312.

Methyl ((1*R*,3*R*,4*S*,5*S*,7*R*)-7-(benzyloxy)-5-cyano-3-methoxy-2-oxabicyclo[2.2.1]heptane-5-carbonyl)glycinate (30).

Triphenylsilane (0.22 mL, 4.0 eq) and tetrakis(triphenylphosphine)palladium (0.052 g, 0.1 eq) were added to a solution of **29** (0.168 g, 0.450 mmol) in dichloromethane (10 m). After stirring at room temperature for 2 hours, dichlorometane (11 mL) were added and the mixture was washed with 1 M sodium bisulphate. The organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated to dryness under vacuum. The crude residue was dissolved in dichlormethane (4 mL) and 1-hydroxybenzotriazole(0.083 g, 1.2 eq) and *N*,*N*-diisopropylcarbodiimide (0.085 mL, 1.2 eq) were added. This mixture was added to a cooled (0 ºC) solution of glycine methyl ester hydrochloride (0.068 g, 1.2 eq) and diisopropylethylamine (0.315 mL, 4.0 eq) in dichloromethane (4 mL). After stirring at room temperature overnight, the reaction mixture was washed with 1 M hydrochloric acid, water and saturated aqueous sodium bicarbonate. The organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated to dryness. The crude residue was purified by column chromatography (ethyl acetate/hexanes 1:2) to afford **30** (0.108 g, 64%) as a colorless oil. $[\alpha]_D^{22}$ -68.6 (c 2.0, CH$_3$CN). ^{1}H NMR (CD$_3$CN, 300 MHz, ppm): 2.30 (dd, *J* = 14.6, 2.7 Hz, 1H), 2.86 (d, *J* = 14.6 Hz, 1H), 3.18 (s, 3H), 3.43 (s, 1H), 3.70 (s, 3H), 3.83 (dd, *J* = 17.5, 5.4 Hz, 1H), 4.02 (dd, *J* = 17.5, 5.6 Hz, 1H), 4.27 (s, 1H), 4.34 (d, *J* = 1.8 Hz, 1H), 4.54 (d, *J* = 11.6 Hz, 1H), 4.75 (d, *J* = 11.6 Hz, 1H), 5.00 (d, *J* = 2.5 Hz, 1H), 6.90 – 6.98 (m, 1H), 7.26 – 7.47 (m, 5H). ^{13}C NMR (CD$_3$CN, 75 MHz, ppm): 38.1, 42.6, 44.7, 50.6, 52.6, 56.2, 72.3, 77.9, 84.6, 104.0, 122.5, 128.7, 128.8, 129.2, 138.6, 167.4, 170.7. HRMS (ESI+): calculated for C$_{19}$H$_{22}$N$_2$NaO$_6$ (M+Na)$^+$ 397.1370, found 397.1373.

Methyl ((1*R*,3*R*,4*S*,5*S*,7*R*)-7-(benzyloxy)-5-((2-(((benzyloxy)carbonyl)amino)acetamido)methyl)-3-methoxy-2-oxabicyclo[2.2.1]heptane-5-carbonyl)glycinate (32).

Cobalt dichloride (0.095 g, 3.5 eq) and sodium (0.168 g, 21 eq) were added to a solution of **30** (0.079 g, 0.210 mmol) in methanol (10 mL). After being stirring at room temperature for 3 h, the reaction mixture was concentrated to dryness, redissolved in water and extracted twice with dichloromethane. The combined organic layers were dried over anhydrous sodium sulphate, filtered, and evaporated. The corresponding amine was dissolved in dichloromethane (2 mL) and was added diisopropylethylamine (0.15 mL, 4.0 eq) at 0 ºC. To this reaction was added a solution of N-carbobenzyloxyglycine (0.053 g, 1.2 eq), benzotriazole (0.039 g, 1.2 eq) and *N*,*N*-diisopropylcarbodiimide (0.039 mL, 1.21.2 eq) in dichloromethane (2 mL) at 0 ºC. After being stirring at room temperature overnight the reaction was washed with 1M hydrochloric acid, water and saturated sodium bicarbonate. The organic layer was dried over anhydrous sodium sulphate$_4$, filtered, and

evaporated. The residue was purified by silica gel column chromatography (ethyl acetate) to give **32** (0.087 g, 73%) as a colorless oil. $[\alpha]_D^{22}$ +8.5 (c 4.2, CH$_3$CN). ^{1}H NMR (CD$_3$CN, 300 MHz, ppm): 1.88 – 1.94 (m, 1H), 2.37 (d, *J* = 13.8 Hz, 1H), 2.79 (s, 1H), 3.16 (s, 3H), 3.18 – 3.26 (m, 1H), 3.64 – 3.75 (m, 5H), 3.81 (dd, *J* = 17.5, 5.6 Hz, 1H), 3.93 (dd, *J* = 17.5, 5.6 Hz, 1H), 4.14 (s, 1H), 4.21 (s, 1H), 4.51 – 4.68 (m, 3H), 4.93 (d, *J* = 2.3 Hz, 1H), 5.10 (s, 2H), 5.91 – 6.01 (m, 1H), 6.77 (t, *J* = 5.6 Hz, 1H), 7.12 – 7.24 (m, 1H), 7.27 – 7.54 (m, 10H). ^{13}C NMR (CD$_3$CN, 75 MHz, ppm): 36.8, 42.0, 45.0, 47.8, 48.9, 52.5, 52.9, 55.8, 67.2, 72.9, 78.8, 85.3, 105.1, 128.7, 128.7, 128.9, 128.9, 129.1, 129.3, 129.4, 138.1, 138.9, 157.5, 170.4, 173.2, 175.2. HRMS (ESI+): calculated for C$_{29}$H$_{35}$N$_3$NaO$_9$ (M+Na)$^+$ 592.2265, found 592.2260.

Methyl ((1*S*,2*R*,3*R*,4*R*)-3-(benzyloxy)-1-((2-(((benzyloxy)carbonyl)amino)acetamido)methyl)-4-hydroxy-2-(hydroxymethyl)cyclopentane-1-carbonyl)glycinate (34).

2 M Hydrochloric acid (3 mL) was added to a solution of **32** (0.044 g, 0.077 mmol) in dioxane (3 mL) at 50 ºC. After being stirred at 50 ºC for 2 h, the liquids was evaporated and the residue was dissolved in etanol (3 mL) and water (3 mL), and sodium borohydride$_4$ (0.006 g, 2 eq) was added. After 20 min, the ethanol was removed and the residue was redissolved in water and extracted three times with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated to dryness. The crude was purified by silica gel column chromatography (ethyl acetate/hexanes 3:1) to afford **34** (0.041 g, 96%) as a colorless oil. $[\alpha]_D^{22}$ -4.1 (c 0.9, CH$_3$CN). ^{1}H NMR (CD$_3$CN, 300 MHz, ppm): 1.80 (dd, J = 13.9, 4.1 Hz, 1H), 1.90 (d, J = 6.2 Hz, 1H), 2.34 – 2.41 (m, 1H), 3.01 (d, J = 3.9 Hz, 1H), 3.40 (q, J = 7.1, 6.6 Hz, 2H), 3.61 – 3.70 (m, 4H), 3.76 (d, J = 3.4 Hz, 1H), 3.88 – 4.02 (m, 2H), 4.12 (dt, J = 8.0, 4.4 Hz, 1H), 4.39 (d, J = 7.8 Hz, 1H), 4.60 (d, J = 1.8 Hz, 2H), 4.89 – 4.98 (m, 1H), 5.06 (d, J = 2.4 Hz, 2H), 6.00 (d, J = 6.4 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 7.24 – 7.46 (m, 10H). ^{13}C NMR (CD$_3$CN, 75 MHz, ppm): 39.9, 42.7, 45.1, 45.5, 52.9, 54.6, 55.1, 67.3, 71.9, 76.4, 86.1, 89.3, 128.5, 128.7, 128.8, 128.9, 129.3, 129.4, 137.9, 139.5, 157.7, 170.8, 170.9, 177.6. HRMS (ESI+): calculated for C$_{28}$H$_{33}$N$_3$NaO$_9$ (M+Na)$^+$ 578.2109, found 578.2106.

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