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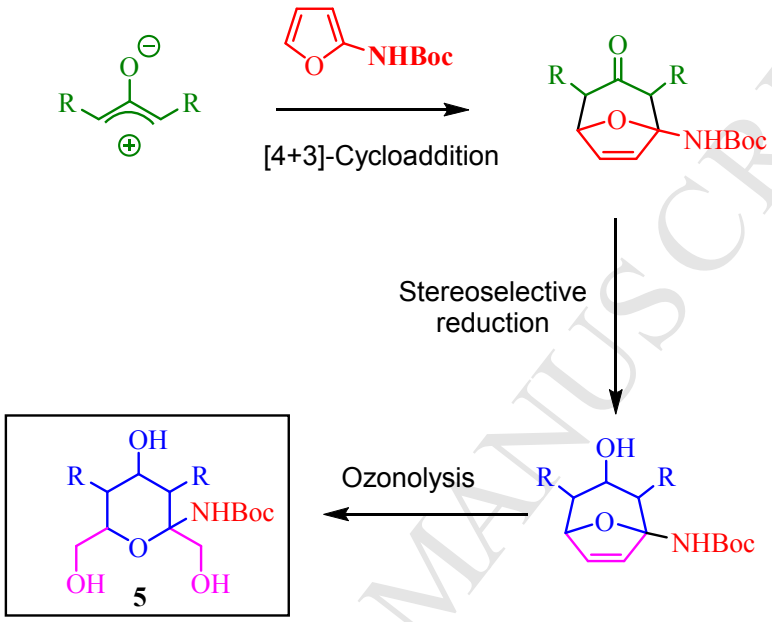

SYNTHETIC METHODOLOGY TO PREPARE POLYSUBSTITUTED 2-AMINOPYRANS. SYNTHESIS OF THE C32-C38 SUBUNIT OF IMMUNOSUPPRESSANT SANGLIFEHRIN A

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ABSTRACT:

Pyranic hemiaminal synthons are present in natural and unnatural products with biological activity. Here a synthetic pathway to prepare this type of intermediates is presented. The methodology is based on three main steps: a) The [4+3] cycloaddition reaction of an α,α'-dihaloketone and a conveniently protected 2-aminofuran diene. b) Chemical modification of the resulting oxabicyclic cycloadduct and orthogonal protection of organic functions, and c) Reductive ozonolysis of the C6-C7 double bond of the modified cycloadduct to afford a pentasusbtituted polyfunctionalized pyranic hemiaminal ester with up to 94% yield. When working with 2,4-dibromo-3-pentanone and 2-*tert*-butoxycarbonylaminofuran as starting materials, the C32-C38 subunit of immunosuppressant sanglifehrin A was obtained with excellent yield.

Keywords: [4+3]-Cycloaddition, oxyallyl cation, pyran, hemiaminal, ozonolysis.

1. Introduction

The immunosuppressant agents such as FK506, cyclosporine A and sanglifehrin A (Figure 1) have afforded an important therapeutic tool to make successful organ and bone marrow transplantation and to understand the molecular basis of signal transduction pathways at the cell level.[1] The first two compounds, even though they have very different structures, form two different drug-protein complexes that inhibit the phosphatase activity of the intracellular signaling molecule calcineurin,[2] blocking T-cell activation and preventing host rejection of transplants. The importance of sanglifehrin A is due to its action mechanism because it interferes with signaling molecules other than calcineurin and binds to cyclophilin inhibiting both T-cell and B-

cell proliferation.[3] Thus, sanglifehrin A, like cyclosporine A, exerts its immunosuppressive action by binding to cyclophilin A, but at a different site from cyclosporine A, and unlike the latter, sanglifehrin A does not inhibit calcineurin activity. Moreover, interesting applications of sanglifehrin family of natural products is been studied for the treatment of hepatitis C virus, with promising results.[4]

The biological relevance of this molecule has propitiated important synthetic efforts to afford synthetic methodologies that make available derivatives with high molecular diversity in order to carry out structure-activity relationships.[5]

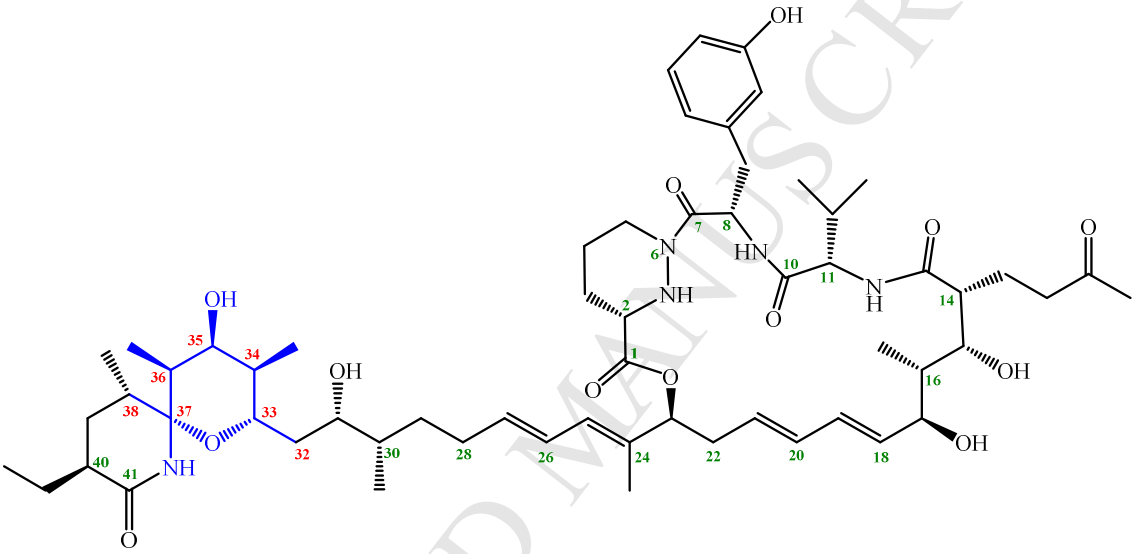
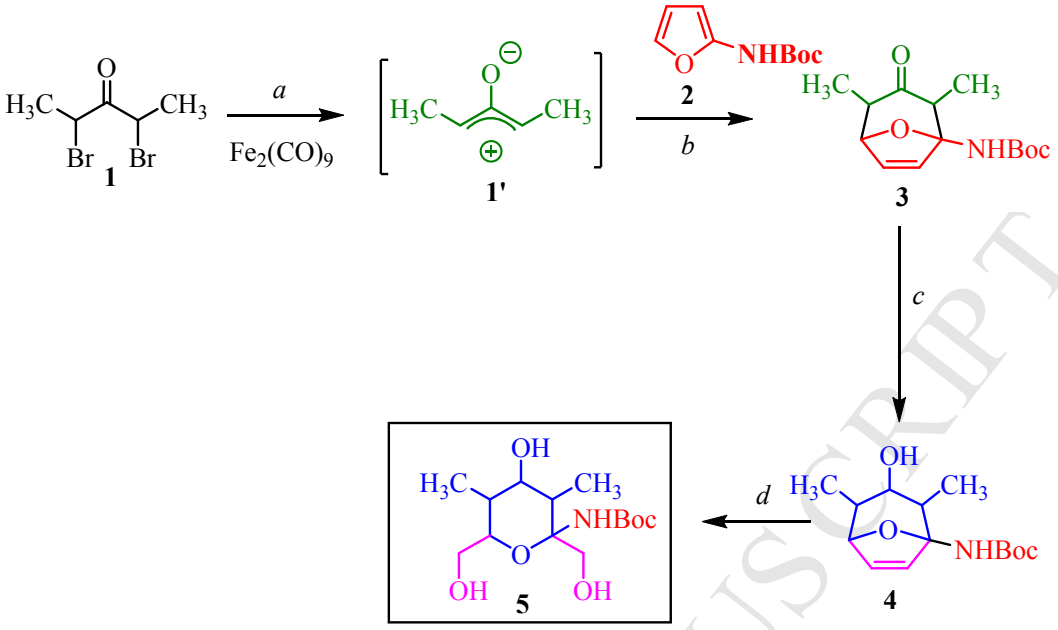


Figure 1. Structure of sanglifehrin A.

In this paper, we present our contribution to this synthetic objective, the diastereoselective preparation of pyranic hemiaminal synthons, present in natural and unnatural products with biological activity, in particular in sanglifehrin A molecule. Our synthetic methodology to prepare this type of intermediates is based on three key steps (Scheme 1): a) The [4+3] cycloaddition reaction of an oxyallyl cation, generated *in situ* from an α,α'-dihaloketone, and a conveniently protected 2-aminofuran diene. b) Chemical modification of the resulting oxabicyclic cycloadduct and orthogonal protection of organic functions, and c) Reductive ozonolysis of the C6-C7 double bond of the modified cycloadduct to afford a pentasusbtituted polyfunctionalized pyranic hemiaminal with five stereocenters. In the present work we used 2,4-dibromo-3-pentanone and 2-*tert*-butoxycarbonylaminofuran as starting materials to afford the C32-C38 subunit of immunosuppressant Sanglifehrin A with excellent yield.



Scheme 1. *(a)* Generation of oxyallyl cation **1'**. *(b)* [4+3] cycloaddition. *(c)* Reduction of the carbonyl group on C3. *(d)* Reductive ozonolysis.

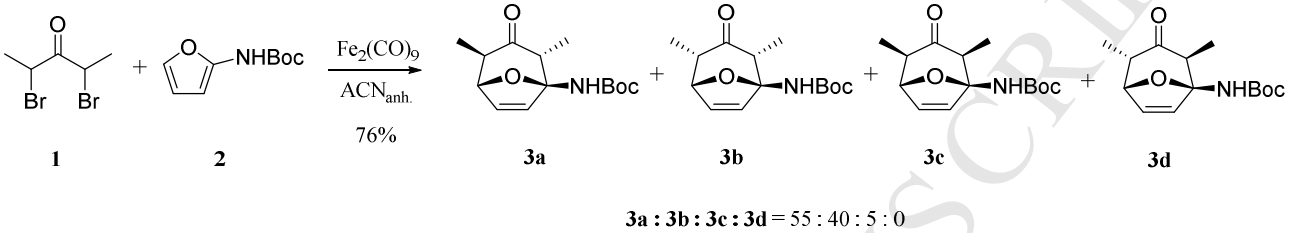
This methodology is very versatile because: a) Many different haloketones and heterosubstituted precursors of oxyallyl cations may be used. b) 2-Aminofurans with different degree of substitution and/or functionalization on C3, C4 or C5 may be used as dienes. c) Diene and dienophile are easily available from the synthetic point of view. d) The oxabicyclic cycloadduct could be transformed in very different ways in order to get molecular diversity. e) The ozonolysis step affords, in the reductive version, a 2-aminopyran synthon with 2,6-bis(hydroxymethyl) substituents that can be used to connect it to other subunits in a total synthetic process. Moreover, ozonolysis could be also performed under oxidative conditions, opening the way to formyl, carboxyl or epoxide connecting terminal functions.

2. Results and discussion

2.1. [4+3]-Cycloaddition reaction

The oxabicyclic structures 1-*tert*-butoxycarbonylamino-8-oxabicyclo[3.2.1]oct-6-en-3-ones **3a-c** were prepared by a [4+3]-cycloaddition reaction[6] between a furan derivative, functionalized at C-2 by a protected amino group, **2,** and an oxyallyl cation **1'**,

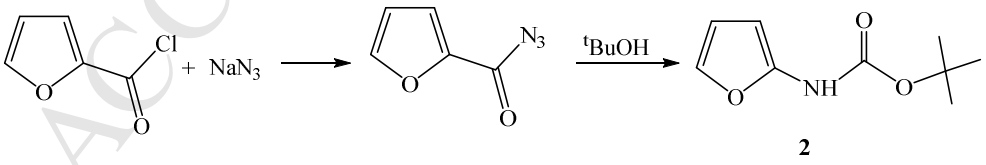
generated *in situ* from 2,4-dibromo-3-pentanone **1**, in the presence of $Fe_2(CO)_9$ as a reducing agent (Scheme 2).[7] This [4C(4π) + 3C(2π)] cycloaddition reaction has been widely studied and optimized by us[8] and other authors [9] and it has been demonstrated to be an straightforward and scalable method to afford a wide variety of versatile bicyclic intermediates with the formation of four chiral stereocenters in only one step.[10]



Scheme 2. Synthesis of 8-oxabicyclo[3.2.1]oct-6-en-3-one by a [4+3] cycloaddition reaction.

Oxyallyl cation **1'** (Scheme 1) was generated *in situ* during the cycloaddition reaction by reduction of 2,4-dibromo-3-pentanone with $Fe_2(CO)_9$. This haloketone was easily obtained by bromination of the corresponding 3-pentanone, following well described procedures.[11]

The non-commercial 2-(NHBoc)-furan **2**, precursor of cycloadducts **3a**, **3b** and **3c**, was obtained following the procedure described by Lynch.[12] This procedure involves a one-pot reaction between the 2-furoyl chloride, sodium azide and an excess of *tert*-butyl alcohol. The reaction takes place by a Curtius rearrangement of the intermediate 2-furoyl azide to obtain, in 82% yield, the desired 2-aminofuran **2**. (Scheme 3).



Scheme 3. Formation of the *tert*-butyl *N*-(2-furoyl)-carbamate.

Oxabicyclic ketones **3a-c,** were separated by flash column chromatography and their stereochemistry was unequivocally established by NMR correlation studies[13] and confirmed by X-ray diffraction analysis. A certain degree of diastereoselectivity was

observed in the cycloaddition reaction, with formation of cycloadducts **3a** and **3b** as major products and a small amount of stereoisomer **3c**. Compound **3d** was not detected even by GC/MS studies of the reaction crude mixture. The low or no formation of **3c** and **3d**, respectively, having a 3*S** configuration on C2 (with Me-C2 and NHBoc in close proximity), is due to the high steric hindrance exerted by NHBoc group, which avoids the approach of the methyl group from the oxyallyl cation in its (*E, Z)* configuration,[7] along the cycloaddition process. However, the diastereoisomeric ratio may be modified by using more electrophilic oxyallyl cations[6] or taking advantage of the coordinating effects of the cationic counterion of the oxyallyl species.[14]

2.2. Stereoselective reduction of the carbonyl group on C3

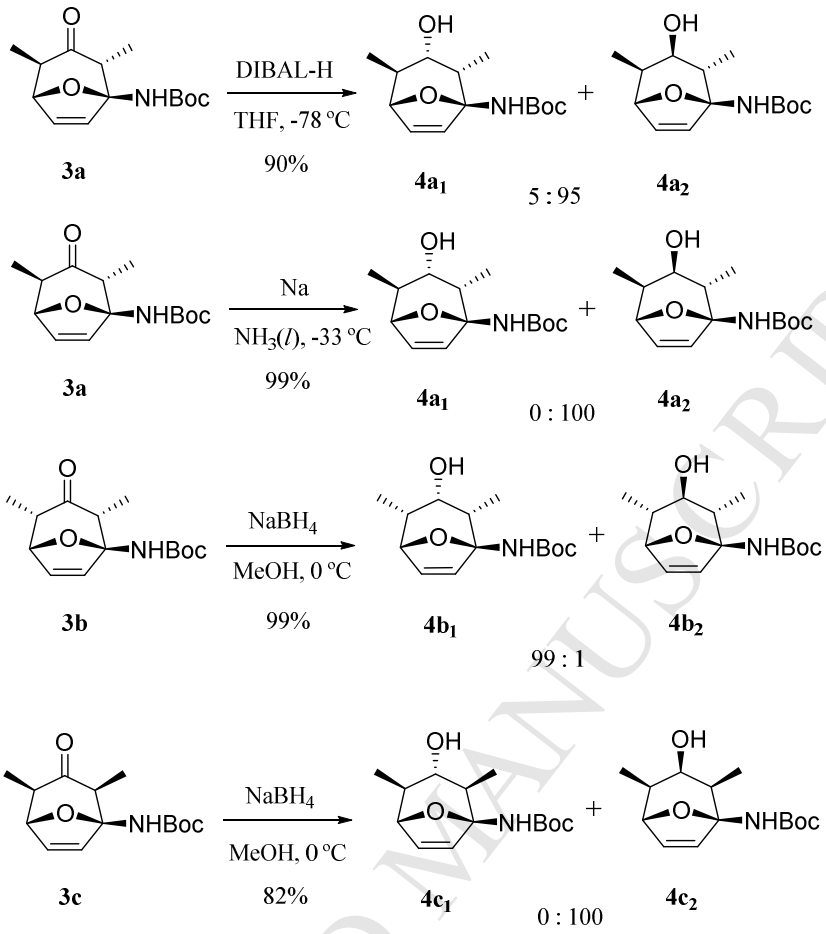
In the present work, the reduction of the ketone group on C6 was approached by using different reducing agents and different reaction conditions in order to synthesize the alcohols with high diastereoselectivity and in high yield. To exemplify this optimization study, the assays carried out with **3a** are quoted in Table 1. In addition, bibliographic references are included in the table, illustrating precedents of the synthetic methodologies used in the present work for the different reduction procedures. These reduction methodologies were evaluated for each substrate and, for preparative purposes, the most successful or adequate one was selected for each substrate (Scheme 4).

Thus, reduction of **3a** was performed with DIBAL-H in anhydrous THF at -78 ºC, obtaining the alcohol **4a** in 90% yield and 5:95 *endo /exo* diastereoisomeric ratio. The use of sodium metal in liquid NH_3 may afford also the alcohol **4a**, but with the diastereoselectivity *endo / exo*, 0:100. On the other hand, **3b** was reduced by $NaBH_4$ in anhydrous methanol at 0 ºC obtaining the alcohol **4b** in 99 % yield and 99:1 *endo/exo* diastereoisomeric ratio (Scheme 4). Finally, ketone **3c** was reduced under these last conditions affording alcohol $\mathbf{4c_2}$ (*exo*) in 82% yield and in a stereospecific manner (diastereoselectivity *endo/exo*: 0:100). In all cases, the diastereoisomeric alcohols were efficiently separated by flash column chromatography and pure samples were physically and spectroscopically characterized.

Table 1. Reduction methodologies evaluated in this work for ketone **3a**.

Entry	Reducing agent	Solvent	T (°C)	t_r (h)	C[a] (%)	Y[b] (%)	DAS[c] *endo* / *exo* (*4a*$_1$ / *4a*$_2$)	Bibliographic Reference
1	$NaBH_4$	MeOH	0	2	100	95	30 / 70	8*l*-8*o*
2	$Na(AcO)_3BH$	MeOH	0	48	0	0	-	15
3	$Li(^{s}Bu)_3BH$ *(L-Selectride®)*	THF	-78 to 25	2	100	0	-	16
4	Na^0	$NH_3(l)$	-33	0.5	100	99	0 / 100	17
5	$LiAlH_4$	THF	-78	1	100	99	67 / 33	8*l*-8*o*
6	$Li(^{t}BuO)_3AlH$ *(TTBAL-H)*	THF	25	7.5	78	65	49 / 51	18
7	$Li(^{i}Bu)_2AlH$ *(DIBAL-H)*	CH_2Cl_2	-24 to 25	4	100	80	50 / 50	19
8	$Li(^{i}Bu)_2AlH$ *(DIBAL-H)*	CH_2Cl_2	-78	4	100	82	78 / 22	19
9	$Li(^{i}Bu)_2AlH$ *(DIBAL-H)*	THF	-78	1.5	100	90	5 / 95	20
10	$(MeO\text{-}CH_2CH_2O)_2AlH_2$ *(Red-Al®)*	Toluene	25	1.5	100	0	-	21
11	SmI_2	THF	25	5	100	0	-	22
12	$HSnBu_3$ / AIBN	MeOH	Δ_{Reflux}	5	0	0	-	23
13	$HSnBu_3$ / AIBN	Tolueno	Δ_{Reflux}	20	100	0	-	22
14	$HSnBu_3$ / SiO_2	CH_2Cl_2	25	24	0	0	-	24

[a] Conversion of starting material. [b] Yield on isolated product. [c] Diastereoselectivity *endo / exo.*



Scheme 4. Reduction of the ketone group in cycloadducts **3a-c**.

The results quoted in Scheme 4 confirm the approach of the hydride H^- ion, predicted for the reaction as described in Figure 2. When the methyl substituents on C2 and C4 positions are in a *cis-exo* configuration (**3c**), the hydride attack took place by the most accessible face (*Si* face) of the carbonyl group, giving excellent diastereoisomeric ratios. When methyl groups adopt a *cis-endo* configuration (**3b**), the attack of hydride takes place by the *Re* face. However, when methyl groups are in a *trans* configuration (**3a**), the results indicate that the more hindered face is the *Re* face flanked by the axial methyl group on C4 and the NHBoc subunit. This leads the hydride attack preferentially by the *Si* face of the ketone and affords a diastereoisomeric ratio slightly lower, 5 : 95. Thus, we may conclude that the stereoselectivity observed in the reduction of the carbonyl group is conditioned by the configuration of the substituents at C2 and C4 positions of the cycloadduct at the minimum energy conformation of the oxan-4-one ring (Figure 2). Thus, methyl groups in axial position for a chair-like conformation of

the oxan-4-one ring act as umbrellas that block the attack of hydride ions by the *Re* face of carbonyl group (Figure 2).

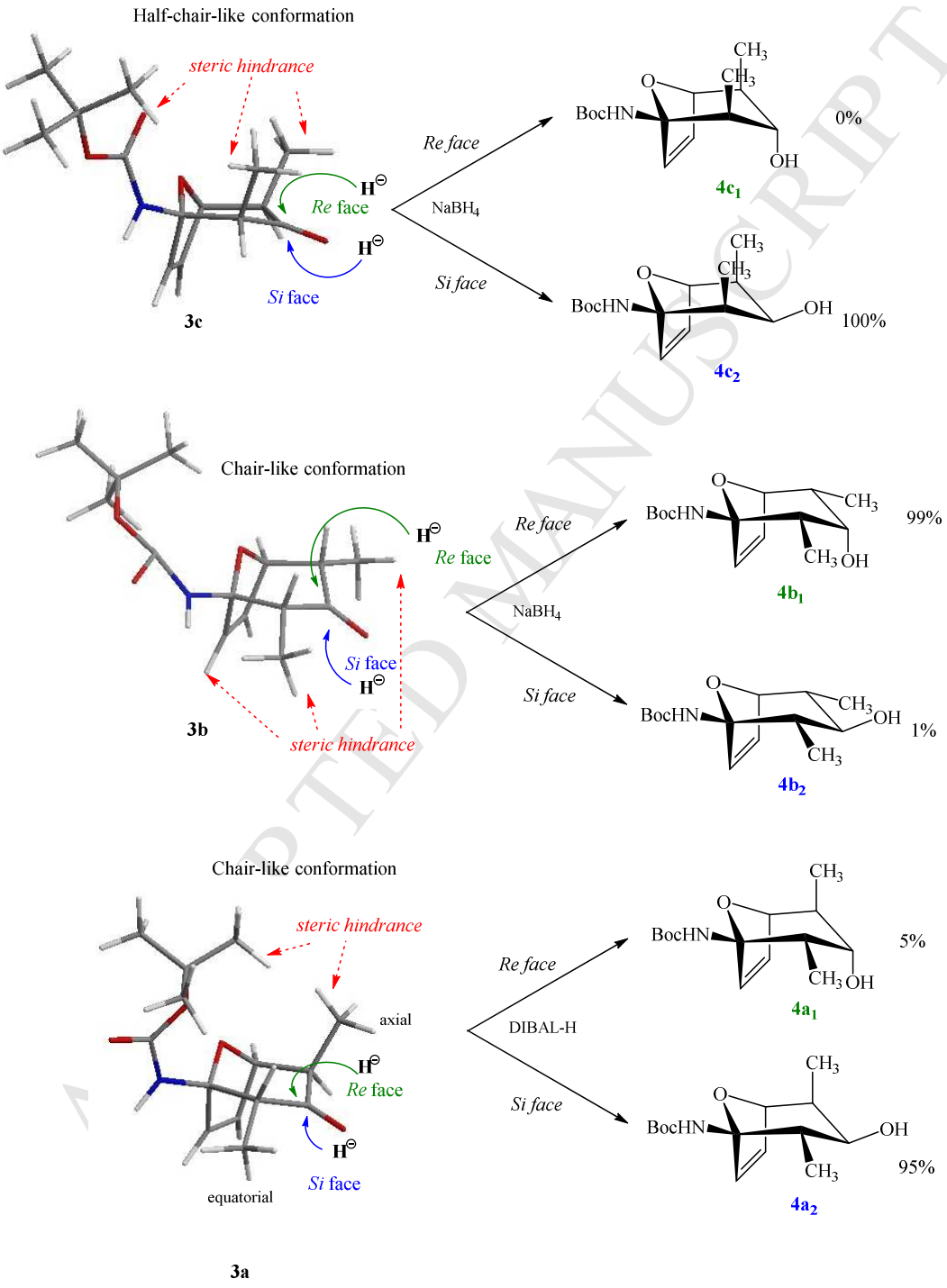
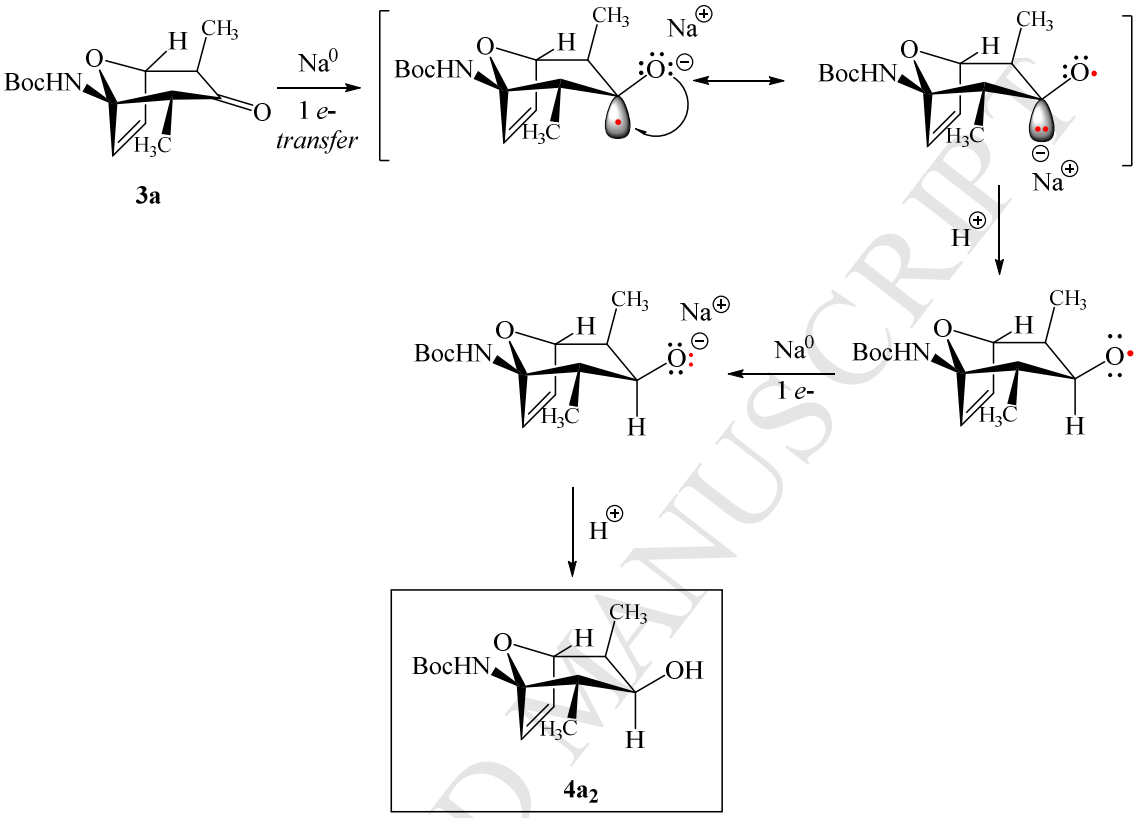


Figure 2. Diastereoselectivity observed in the reduction of carbonyl group in substrates **3a, 3b** and **3c**, at their minimum energy conformation.



Scheme 5. Proposed mechanism for the reduction of ketone **3a** with Na /NH_3.[25]

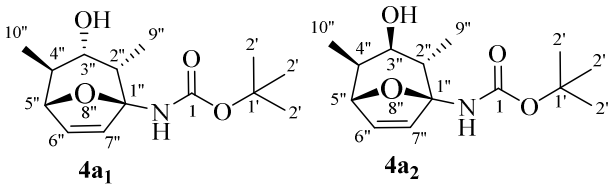
The use of sodium metal in liquid ammonia[17a,b] afforded a rapid and clean reduction of the carbonyl group of **3a**, in a quantitative yield and total diastereoselectivity, obtaining only the *exo* diastereoisomer **4a$_2$**, which is, in addition, the thermodynamically more stable (Scheme 5). [17c-g]

It is worthwhile to mention that a change of *endo / exo* diastereoselectivity was observed when changing the nature of solvent from CH_2Cl_2 (non-chelating) to THF with capability to co-ordinate the Al atom in the case of using DIBAL-H as reducing agent. These co-ordination effects may modify the energy of the transition states leading to products **4a$_1$** and **4a$_2$**.

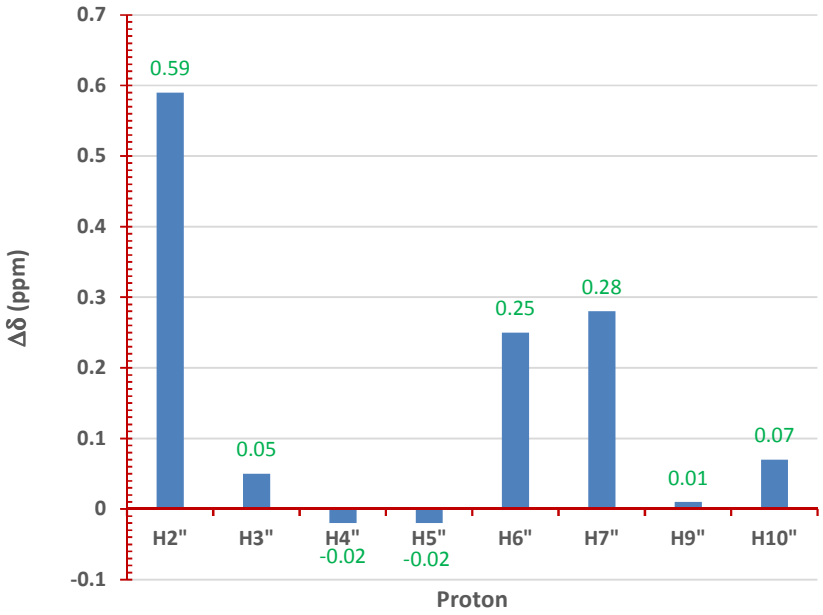
In order to determine the relative configuration of the reduction products, a NMR correlation method was used. This method is based on: a) A complete and unequivocal assignment of signals from ^{1}H and ^{13}C NMR spectra, by performing DEPT, selective irradiation and 2D COSY and HSQC experiments. b) The careful analysis of ^{1}H and ^{13}C NMR data and the use of 2D-NOESY experiments (Figure 3). c) The correlation of the shielding or deshielding effects exerted by the hydroxyl group on C3" depending on the configuration of the substituents on C1", C2" and C4" (see Table 2), and c) By use of the Karplus equation, on the basis of the coupling constants, to find a consistency between the dihedral angles between vicinal hydrogen atoms, at the minimum energy conformation, for a certain relative configuration. Next, we exemplify this methodology of assignment of relative stereochemistry, applied to epimers **4a$_1$** and **4a$_2$**.

Thus, on Table 2 and attached bars chart it is possible to appreciate the differences observed between the ^{1}H NMR spectral data of diastereoisomers **4a$_1$** and **4a$_2$**. The most significant differences between the two compounds are observed for hydrogen atoms H2'', H6'' and H7'', which appear more shielded in compound **4a$_2$** due to the particular spatial orientation of the hydroxyl group. The olefinic protons H6'' and H7''are deshielded by electric field effect[26] due the proximity of the axial hydroxyl group in compound **4a$_1$**, effect that is not possible for compound **4a$_2$** (Figure 3). The presence of H2" at lower field in **4a$_1$** is consistent with the axial disposition of the OH group, which deshields vicinal axial *trans* hydrogens between 0.25 and 0.30 ppm.[27] In both **4a$_1$** and **4a$_2$** H9" appears at higher field than H10" because of two concomitant effects: axial H10" is deshielded by an electric field effect exerted by the oxygen bridge (1,3-dipolar interaction) and, simultaneously, H9" is shielded by the anisotropy cone of the C6"-C7" double bond.

Table 2. Correlation of ^{1}H NMR spectral data of epimers **4a$_1$** and **4a$_2$**.



Product	δ (ppm)							
	H2"	**H3"**	**H4"**	**H5"**	**H6"**	**H7"**	**H9"**	**H10"**
4a$_1$	2.34	3.55	1.85	4.65	6.40	6.50	1.04	1.21
4a$_2$	1.75	3.50	1.87	4.67	6.15	6.22	1.03	1.14
Δδ (**4a$_1$**–**4a$_2$**)	0.59	0.05	-0.02	-0.02	0.25	0.28	0.01	0.07



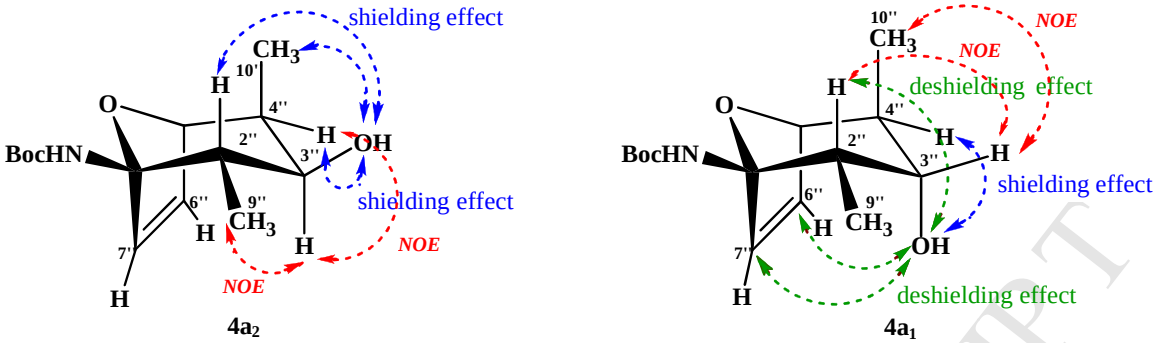
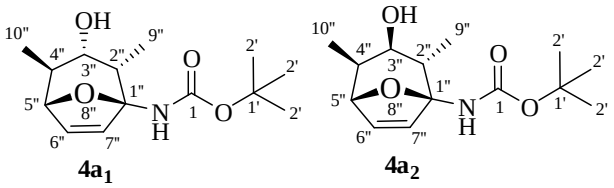


Figure 3. Shielding, deshielding and NOE effects depending on the configuration of the hydroxyl group for reduction alcohols **4a$_1$** and **4a$_2$**.

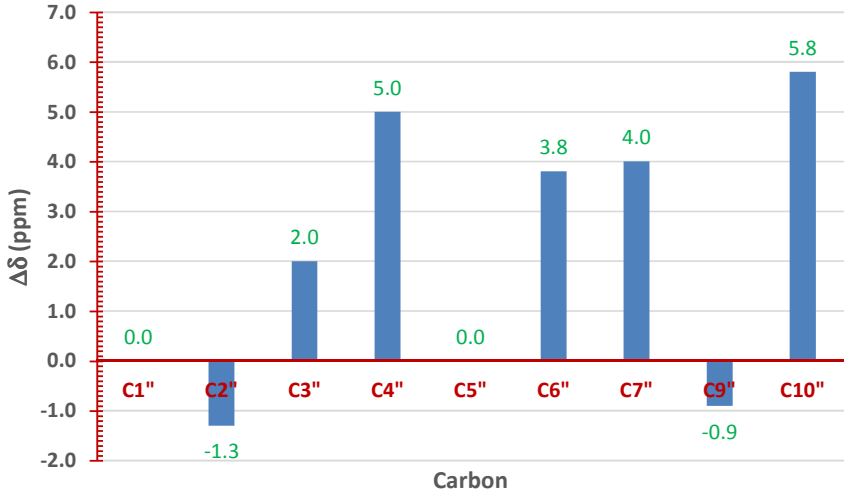
The NOE effects observed in alcohol **4a$_2$** , from NOESY experiments, are due to the proximity in space of H3" and H_3C9" and also of H3" and H4". On the other hand, clear NOE effects were also observed in alcohol **4a$_1$** between H3" and H_3C10" and also between H3" and H2". Both NOE effects are consistent with the assigned configuration to C3".

If we compare the chemical shifts of ^{13}C NMR spectra of alcohol **4a$_1$** and **4a$_2$**, it is possible to appreciate important differences (see Table 3 and bars chart attached). Looking at Figure 4 it is possible to observe that in **4a$_1$** the olefinic carbons C6" and C7" are shifted to a lower field by the axial hydroxyl group, due to a δ-effect, interaction that is not possible in **4a$_2$**. In addition, the OH group exerts a γ-*gauche* effect on both methyl groups in **4a$_2$**, but only on C9" in **4a$_1$**, producing an upfield shift due to sterically induced polarization of C-H bonds. Contrary to α and β effects, which are transmitted through the bonds, γ-*gauche* interaction works through the space. Previous studies on this type of effects[28] showed that non-bonding interactions between CH-CH or CH-OC perturbed the charge density on the atoms. In this sense, that conformation in which the distance between groups is lower or of the same order than the addition of the Van der Waals radius, presents an induced polarization effect due to steric hindrance and it results in a deshielding of protons and a simultaneous shielding of carbon atoms. On the other hand, the higher difference Δδ for C10" is due to the concomitant γ-*trans* effect exerted by the axial OH group on C10" in **4a$_1$**, due to hyperconjugative effects.[13,29]

Table 3. Correlation of ^{13}C NMR spectral data of **4a$_1$** and **4a$_2$**.



Product	δ(ppm)								
	C1"	C2"	C3"	C4"	C5"	C6"	C7"	C9"	C10"
4a$_1$	94.9	39.9	75.5	39.6	82.9	135.1	135.0	12.4	17.6
4a$_2$	94.9	41.2	73.5	34.6	82.9	131.3	131.0	13.5	11.8
Δδ (**4a$_1$**–**4a$_2$**)	0	-1.3	2.0	5.0	0	3.8	4.0	-0.9	5.8



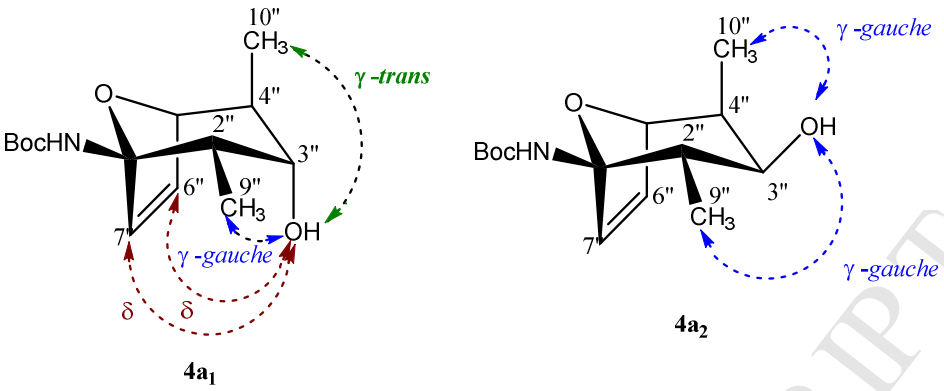
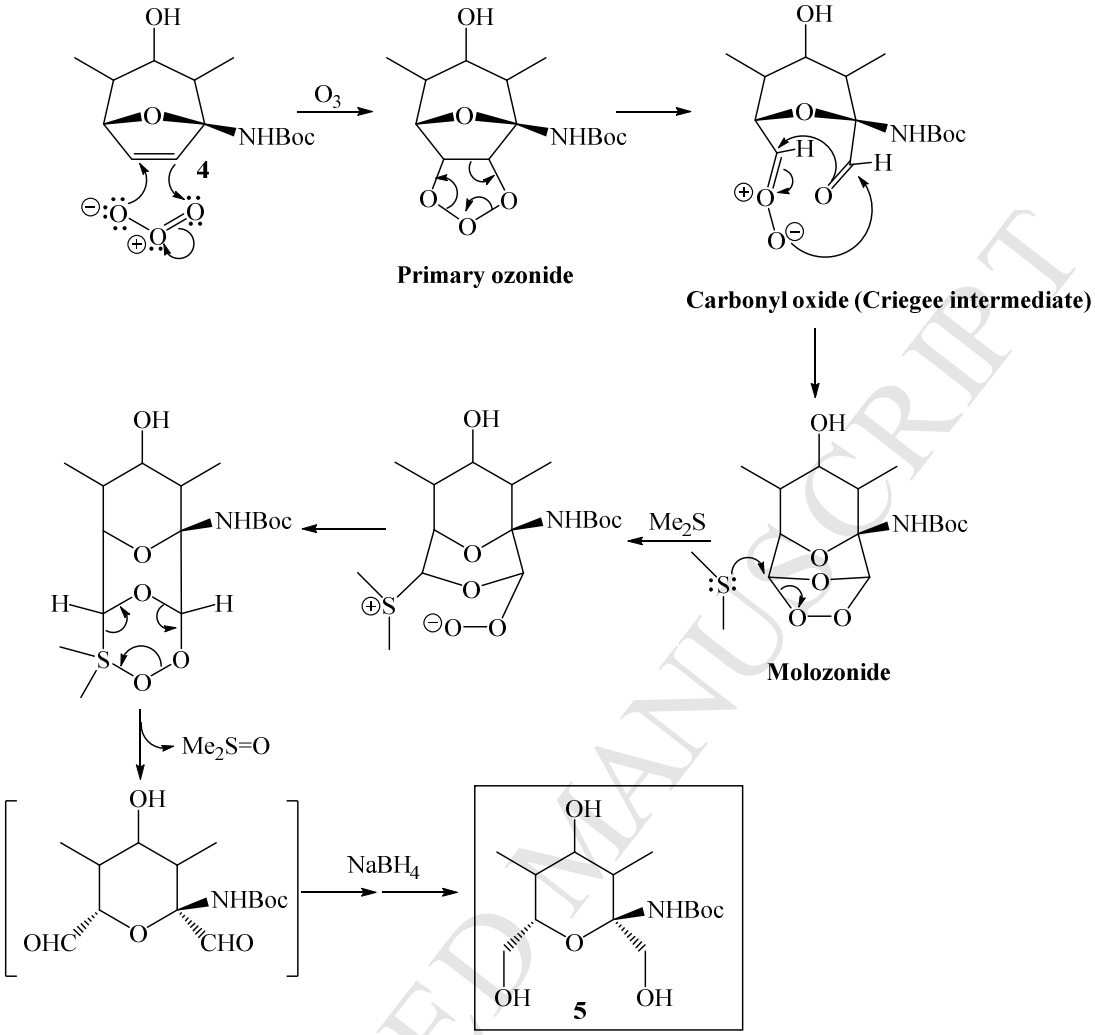


Figure 4. δ, γ-gauche and γ-*trans* effects in **4a**$_1$ and **4a**$_2$.

2.3. Reductive ozonolysis[30]

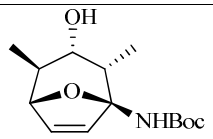
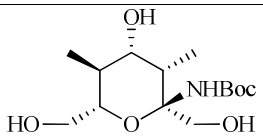
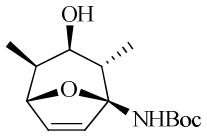
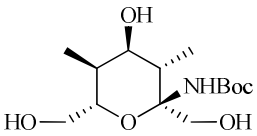
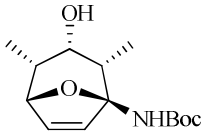
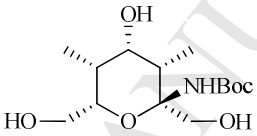
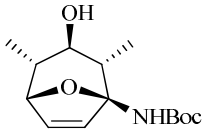
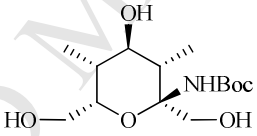
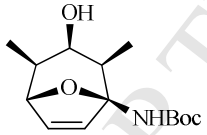
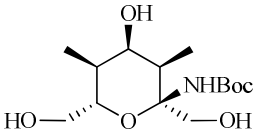
The other key step in the approach to the synthesis of the final 2-aminopyran synthons was the reductive ozonolysis of the reduction alcohols **4** (Scheme 6).[31] The same reaction conditions and solvent type were used in all cases.[32] The successive addition of SMe_2 and $NaBH_4$ as reducing agents, in a solvent system DCM / Methanol (4:1), gave very good results, affording always the desired final products with good to excellent yields. (Table 4). The use of two consecutive reducing agents lead the reaction to the complete reduction of the ozonide intermediate and the obtention of two hydroxymethyl side chains on the original positions C6" and C7" (Scheme 6).



Scheme 6. Mechanism of ozonolysis of **4** to obtain 2-aminopyrans **5**.[33]

It is worth nothing that very high yields were obtained with the use of SMe_2 and $NaBH_4$ and also a great functional group compatibility was observed. Thus, both functional groups present on the substrates (OH and NHBoc) resulted unchanged.

Table 4. Results from the reductive ozonolysis reaction of substrates **4** for the obtention of THP final products, **5**.

Entry	Substrate	Products	Yield[a, b, c] (%)
1	 **4a$_1$**	 **5a$_1$**	88
2	 **4a$_2$**	 **5a$_2$**	75
3	 **4b$_1$**	 **5b$_1$**	70
4	 **4b$_2$**	 **5b$_2$**	73
5	 **4c$_2$**	 **5c$_2$**	94

[a] Reaction conditions used: 1) O_3, –78 ºC, 0.5 h. 2) SMe_2, (2.3 eq.), –78 ºC, 1 h. 3) $NaBH_4$, (2.3 eq.), r.t., 3 h. [b] Solvent system: CH_2Cl_2 / MeOH (4:1). [c] Yield on isolated product. In all cases, the conversion of the starting material was complete.

3. Conclusions

By the herein describe synthetic methodology it is possible to obtain 2-aminopyrans with high stereochemical diversity and in good yield. Selecting the type of substitution pattern and electrophilicity of the oxyallyl cation, in the [4+3]-cycloaddition reaction,

we may design the type of substituents in the final 2-aminopyran and also their relative stereochemistry. The configuration of the alcohol on C4 of pyrans may be also selected by using the adequate reduction methodology and reaction conditions. All stereoisomers of precursors, intermediates and final products are easily separable by chromatography, and pure samples of them were obtained and physically and spectroscopically characterized. Finally the objective of synthesizing the C32-C38 subunit of immunosuppressant sanglifehrin A has been fulfilled by the obtention of 2-aminopyran **5c$_2$**. Derivatives having formyl, hydroperoxy-hemiacetals or epoxides at C2 and C6 of pyran, instead of hydroxymethyl groups, may be obtained by oxidative epoxidation; results from these studies will be published at due course. These derivatives may facilitate the connection of the 2-aminopyran synthons to other molecular subunits for the total synthesis of complex natural products.

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Notes

The authors declare neither competing financial interest nor any other conflict of interest.

5. Acknowledgements

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6. Experimental section

6.1. General procedures

NMR spectra were recorded on a Varian Inova 200 or 300 MHz, on a Varian Mercury 400 MHz and/or in a Bruker DMX 500 MHz apparatus. Chemical shifts (δ) are

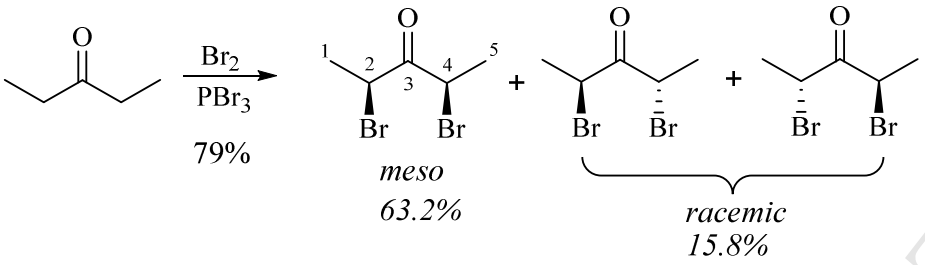
expressed in ppm *versus* tetramethylsilane as an internal standard. IR spectra were recorded on a NICOLET 6700 FT-IR by film, KBr pellet or ATR (Attenuated Total Reflectance) methods. Mass spectrometry was performed on a Hewlett-Packard 5890 apparatus, generally under a CI (Chemical Ionization) method by using NH_3 or CH_4 or by direct insertion under Electron Impact at 70 eV and 150 ºC. The elemental analyses were obtained in a FISONS Elemental Analyzer, Model Na-1500. The samples were previously pyrolized al 1000 ºC in the presence of a catalyst, under oxygen atmosphere, and the content of carbon, hydrogen and nitrogen were determined by evaluation of the combustion gases by gas chromatography using a FID detector. Solvents were dried, according to standard procedures, and distilled prior to use. All other major chemicals were obtained from commercial sources and used without further purification. Gas chromatography was performed by using a Shimatzu AOC-20i apparatus with a capillary column (HP-5 Crosslinked 5% Phe-Me-Siloxane, 0.25 μm film thickness, 30 m length and 0.32 mm diameter). Used carrier gas brands and pressures were: He = 5.5 bar (Linde, Helium 5.0), Air = 3 bar (Linde, synthetic air), H_2 = 3 bar (Linde, Hydrogen 5.0). The experimental conditions are specified in each case. Ozonolysis reaction was carried out using an ozone-generator Fischer Ozone-500 apparatus, under the following conditions: Intensity = 0.25-0.40 A, P_{O2} = 0.25 bar, O_3 flow = 50-100 mL/min.

6.2. Molecular computer calculations

Geometry and energy minimization of molecules were preoptimized by molecular mechanics MM2 followed by semiempirical quantum mechanical PM7 algorithm,[34] implemented in the MOPAC-2012 software.[35] This software was also used to calculate the formation enthalpy. Density functional theory (DFT) based methods at the B3LYP functional level[36,37] were used for subsequent full refinements, within the Gaussian-03W (Revision E.01, version 6.1) software package[38] and using the 6–31++G(d, p) basis set.[39] All calculations were performed on isolated molecules (gas phase).

6.4. Synthetic procedures

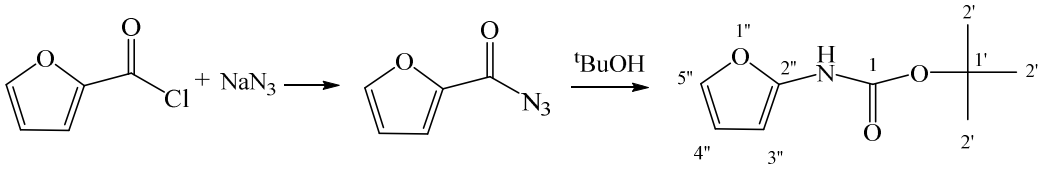
6.4.1. Synthesis of 2,4-dibromo-3-pentanone, (1)



In an oven-dried 250 mL three neck round-bottom flask, equipped with a stirring bar, a Dimroth condenser, a calcium chloride trap, a thermometer and a pressure equalized addition funnel, 3-pentanone (54 mL, 0.52 mmol) and phosphorous tribromide (1 mL, 0.01 mmol) were added. The mixture was cooled to 0 ºC and bromine (54 mL, 0.53 mmol) was slowly added along 5 hours, maintaining the reaction mixture between 5 ºC and 10 ºC. During the addition of bromine, the release of hydrogen bromide was observed. One hour after the complete addition of bromine, the conversion of 3-pentanone was complete as observed by GC. Then, the mixture was submitted to vacuum (20 torr) for 30 min at rt to eliminate the dissolved hydrogen bromide. The reaction crude was purified by fractional distillation under vacuum (10 mmHg), collecting the fraction between 65 ºC and 70 ºC. This fraction was redistilled to obtain chemically pure 2,4-dibromopentan-3-one (71.96 g, 79% yield) as a colourless oily diastereoisomeric mixture: *meso* / *dl* pair 4/1.

IR (film) $\bar{\upsilon}$ (cm^{-1}): 3445 (C=O), 2980, 2920, 2875 (H─Csp^3), 1730 (C=O), 1440, 1380, 1350 (C─C), 1200, 1120, 1070, 1050, 1020 (C─O). **^{1}H NMR** (200 MHz, $CDCl_3$) δ (ppm): ***pair dl*** 1.88 (2H, d, *J* = 6.9 Hz, H2, H4), 4.77 (6H, q, *J* = 6.9 Hz, H1, H5); ***meso*:** 1.81 (2H, d, *J* = 6.7 Hz, H2, H4), 4.99 (6H, q, *J* = 6.7 Hz, H1, H5). **^{13}C NMR** (50 MHz, $CDCl_3$) δ (ppm): ***pair dl*** 21.61 (C1, C5), 43.95 (C2, C4), 195.77 (C3); ***meso*:** 19.42 (C1, C5), 43.75 (C2, C4), 195.77 (C3). **MS** (GC-MS, CI, NH_3, 70 eV, 150 ºC, t_R = 6.16-7.03 min) m/z (%): 279 (12, M+N_2H_7), 262 (100, M+NH_4), 246 (1, M+2H), 244 (1, M), 182 (6, $C_5H_{10}O_2Br$). **GC** (T_i = 100 ºC, t_i = 2 min., r = 10 ºC/min., T_f = 200 ºC, t_f = 30 min.) ***meso*:** t_R = 5.7 min.; ***pair dl***: t_R = 6.4 min.

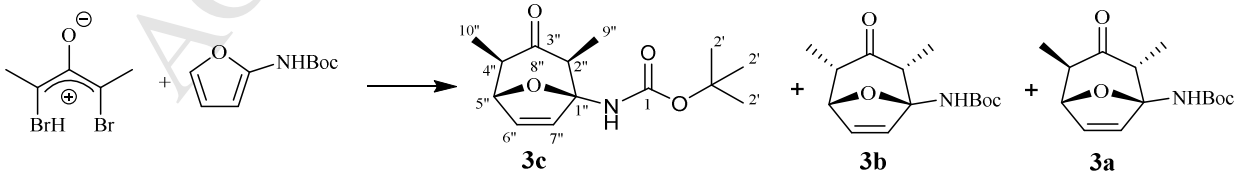
6.4.2. Synthesis of *tert*-butyl furan-2-yl-carbamate, (2)



In a round-bottom flask equipped with a stirring bar and a Dimroth condenser, 2-furyl chloride (10 g, 0.07 mol), *tert*-butyl alcohol (80 mL, 0.85 mol) and sodium azide (5.1g, 0.08 mol) were placed, under argon atmosphere. The mixture was stirred for 20 h at room temperature and the formation of the intermediate 2-furylazide as a white solid was observed. The mixture was heated to reflux (100 ºC) and maintained under these conditions for additional 15 h. Once 2-furylazide was completely converted (control by TLC eluted with hexane/ethyl acetate 4:6), the solvent was removed *in vacuo*, obtaining a white solid, which was submitted to a flash column chromatography on silica gel, eluting with a mixture of hexane and ethyl acetate of increasing polarity. The elution with a mixture of hexane and EtOAc (9:1), afforded the desired product as a white solid (10.8 g, 82% yield). The product has to be stored in a cold place and away from light, in order to avoid its photochemical decomposition.

MP = 98-99 ºC (ethyl acetate). **TLC:** R_f = 0.66 (SiO_2, hexane/ethyl acetate 4:6, developed by ninhydrin). **IR** (film) $\tilde{\upsilon}$ (cm^{-1}): 3267 (N─H, st), 2980, 1700 (C=O, st), 1546 (N─H, def), 1250 (^{t}Bu). **^{1}H NMR** (300 MHz, $CDCl_3$) δ (ppm): 1.50 (9H, s, H2'), 6.04 (1H, brs, H4"), 6.63 (1H, brs, H3"), 7.00-7.12 (1H, m, H5"). **^{13}C NMR** (50 MHz, $CDCl_3$) δ (ppm): 28.2 (C2'), 81.3 (C1'), 95.1 (C4"), 111.2 (C3'), 136.0 (C5'), 145.4 (C2'), 151.9 (C1). **MS** (CI, NH_3, 70 eV, 150 ºC) m/z (%): 285 (13, M+NH_4), 268 (100, M+1H), 212 (22, M+2H–^{t}Bu), 167 (36, M+1H–COO^{t}Bu).

6.4.3. Synthesis of *tert*-butyl *N*-{2,4-dimethyl-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-1-yl}carbamate, (3)



[4+3] Cycloaddition procedure using Fe_2CO_9

In a round bottomed flask fitted with a magnetic stirrer, under argon atmosphere, compound **2** was placed. Afterwards, inside an Atmosbag® filled with argon, the pyrophoric diironnonacarbonyl was added to the reactor, (in a molar ratio Fe_2CO_9 : furan = 1.75 : 1), as a bright yellow solid. Then, anhydrous acetonitrile (in a ratio of 0.82 mL of ACN : 1 mol Fe_2CO_9) was added and the mixture was stirred for 5 min. Dibromoketone **1**, freshly filtered through neutral alumina, was added dropwise at –10 ºC, (in a molar ratio of 1.2 : 1; dibromoketone : furan). The reaction mixture was stirred at room temperature for 6.5 h. The crude was concentrated to dryness and the residue was dissolved in acetone. Cerium ammonium nitrate (in a molar ratio CAN : Fe_2CO_9 = 1 : 1) was added and the reaction mixture was stirred for 5 min. Afterwards, the solvent was evaporated under vacuum and the residue was filtered through a short path of silica gel, and then it was submitted to a flash column chromatography on silica gel, using mixtures of hexane and diethyl ether of increasing polarity to isolate cycloadduct **3** in a 76% yield and diastereoselectivity: **3a**/**3b**/**3c** = 55/40/5.

***tert-Butyl N-{(1S*, 2R*, 4R*, 5R*)-2,4-dimethyl-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-1-yl}carbamate,* (3a)**

Colourless oil. **TLC:** R_f = 0.60 (SiO_2, eluted with hexane /EtOAc 3:7, developed with $KMnO_4$). **IR** (film) $\bar{\upsilon}$ (cm^{-1}): 3341 (N–H, st), 2977, 2936, 1709 (C=O, st), 1503 (N–H, def), 1460, 1369, 1331, 1246 (^{t}Bu), 1167 (C–O–C, st), 1055 (C–O–C, st as). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 1.08 (3H, d, $J_{9,2}$ = 7 Hz, H9''), 1.35 (3H, d, $J_{10,4}$ = 7.6 Hz, H10''), 1.46 (9H, s, H2'), 2.31 (1H, q, $J_{4,10}$ = 7.6 Hz, H4''), 3.01 (1H, q, $J_{2,9}$ = 7 Hz, H2''), 4.74 (1H, s, H5''), 5.19 (1H, s, NH), 6.28 (2H, s, H6'' and H7''). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 9.8 (C9''), 16.4 (C10''), 28.4 (C2'), 48.2 (C4''), 52.9 (C2''), 80.9 (C1'), 81.3 (C5''), 95.3 (C1''), 132.8 (C6''), 134.1 (C7''), 153.9 (C1), 210.7 (C3''). **MS** (CI, NH_3, 70 eV, 150ºC) m/z (%)**:** 285 (13, M+NH_4), 268 (100, M+H), 212 (22, M+2–^{t}Bu), 167 (36, M+H–COO^{t}Bu). **GC** (T_i = 100 ºC, t_i = 1 min, r = 10 ºC/min, T_f = 250 ºC, t_f = 20 min)**:** t_R = 9.57 min. **Anal.** Calcd for $C_{14}H_{21}NO_4$ (267.32 g·mol^{-1}): C, 62.90; H, 7.92; N, 5.24. Found: C, 62.95; H, 7.96; N, 5.22.

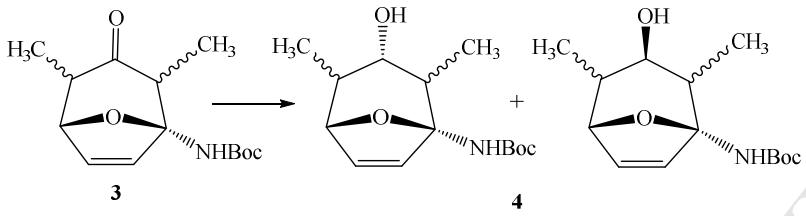
***tert-Butyl N-{(1S*, 2R*, 4S*, 5R*)-2,4-dimethyl-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-1-yl}carbamate,* (3b)**

Colourless oil. **TLC:** R_f = 0.60 (SiO_2, eluted with hexane /EtOAc 3:7, developed with $KMnO_4$). **IR** (film) $\bar{\upsilon}$ (cm^{-1}): 3347 (N–H, st), 2979, 2936, 1715 (C=O, st), 1522 (N–H, def), 1456, 1368, 1348, 1250 (^{t}Bu), 1157 (C–O–C, st), 1038 (C–O–C, st as). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 0.97 (3H, d, $J_{10,4}$ = 7 Hz, H10''), 1.08 (3H, d, $J_{9,2}$ = 7 Hz, H9''), 1.46 (9H, s, H2'), 2.79 (1H, dq, $J_{4,10}$ = 7 Hz, $J_{4,5}$ = 4.6 Hz, H4''), 3.02 (1H, q, $J_{2,9}$ = 7 Hz, H2''), 4.91 (1H, dd, $J_{5,4}$ = 4.6 Hz, $J_{5,6}$ = 1.2 Hz, H5''), 5.27(1H, s, NH), 6.29 (2H, s, H6'' and H7''). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 10.0 (C9''), 10.6 (C10''), 28.5 (C2'), 48.9 (C4''), 54.2 (C2''), 80.9 (C5''), 80.9 (C1'), 95.7 (C1''), 132.8 (C6''), 134.1 (C7''), 154.0 (C1), 208.0 (C3''). **MS** (CI, NH_3, 70 eV, 150ºC) m/z (%)**:** 285 (13, M+NH_4), 268 (100, M+H), 212 (22, M+2–^{t}Bu), 167 (36, M+H–COO^{t}Bu). **GC** (T_i=100 ºC, t_i = 1 min, r = 10 ºC/min, T_f = 250 ºC, t_f = 20 min)**:** t_R = 9.87 min. **Anal.** Calcd for $C_{14}H_{21}NO_4$ (267.32 g·mol^{-1}): C, 62.90; H, 7.92; N, 5.24. Found: C, 62.88; H, 7.90; N, 5.25.

***tert-Butyl N-{(1S*, 2S*, 4R*, 5R*)-2,4-dimethyl-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-1-yl}carbamate,* (3c)**

Colourless oil. **TLC:** R_f = 0.60 (SiO_2, eluted with hexane /EtOAc 3:7, developed with $KMnO_4$). **IR** (film) $\bar{\upsilon}$ (cm^{-1}): 3341 (N–H, st), 2977, 2936, 1709 (C=O, st), 1503 (N–H, def), 1460, 1369, 1331, 1246 (^{t}Bu), 1167 (C–O–C, st), 1055 (C–O–C, st as). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 1.29 (3H, d, $J_{9,2}$ = 7.6 Hz, H9''), 1.33 (3H, d, $J_{10,4}$ = 7.6 Hz, H10''), 1.46 (9H, s, H2'), 2.28 (1H, q, $J_{4,10}$ = 7.6 Hz, H4''), 2.65 (1H, q, $J_{2,9}$ = 7.6 Hz, H2''), 4.73 (1H, d, $J_{5,6}$ = 2 Hz, H5''), 5.17 (1H, s, NH), 6.21 (1H, ddd, $J_{6,7}$ = 6.1 Hz, $J_{6,5}$ = 2 Hz, $J_{6,4}$ = 0.5 Hz, H6''), 6.38 (1H, d, $J_{7,6}$ = 6.1 Hz, H7''). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 13.8 (C9''), 17.8 (C10''), 28.5 (C2'), 48.6 (C4''), 53.0 (C2''), 80.9 (C1'), 81.1 (C5''), 95.3 (C1''), 132.2 (C6''), 135.4 (C7''), 153.9 (C1), 213.0 (C3''). **MS** (CI, NH_3, 70 eV, 150ºC) m/z (%)**:** 285 (13, M+NH_4), 268 (100, M+H), 212 (22, M+2–^{t}Bu), 167 (36, M+H–COO^{t}Bu). **GC** (T_i = 100 ºC, t_i = 1 min, r = 10 ºC/min, T_f = 250 ºC, t_f = 20 min)**:** t_R = 9.20 min. **Anal.** Calcd for $C_{14}H_{21}NO_4$ (267.32 g·mol^{-1}): C, 62.90; H, 7.92; N, 5.24. Found: C, 62.93; H, 7.89; N. 5,27.

6.4.4. General methods for the reduction of the carbonyl group in (3). Synthesis of epimeric alcohols (4)



a) Use of $NaBH_4$ (applied to* 3b *and* 3c*)

In a 50 mL oven-dried round-bottomed flask, equipped with a stirring bar and fitted with septa, $NaBH_4$ (567.4 mg, 15 mmol) and anhydrous MeOH (8 mL) were placed, under argon atmosphere. The system was cooled by an ice-water bath and the cycloadduct **3** (1 g, 3.74 mmol), dissolved in anhydrous MeOH (8 mL), was slowly added to the reaction flask *via* syringe. Once the reaction was complete after 6 h (control by TLC: SiO_2, chloroform/methanol 95:5, two elutions, developed with ninhydrin), the excess of $NaBH_4$ was quenched with distilled water (2 mL) and the resulting mixture was stirred at room temperature for 15 min at 0 ºC. Then, the reaction mixture was concentrated to dryness *in vacuo*. The resulting crude product was dissolved in anhydrous $CHCl_3$ (20 mL) and the organic solution was filtered out *via* cannula, washing the solid residue (3 x 5 mL of $CHCl_3$). The organic solution was concentrated to dryness and the resulting crude oil was submitted to a flash column chromatography on silica gel, eluting with mixtures of hexane and ethyl acetate of increasing polarity. The elution with hexane / EtOAc (7:3), allowed the separation of both diastereoisomeric alcohols **4**, as white solids, in excellent yields (99% for **3b** and 82% for **3c**). Diastereoselectivity: **$4b_1$**(*endo*)/**$4b_2$** (*exo*) = 99/1 and **$4c_1$**(*endo*)/**$4c_2$** (*exo*) = 0/100.

b) Use of DIBAL-H (applied to* 3a*)

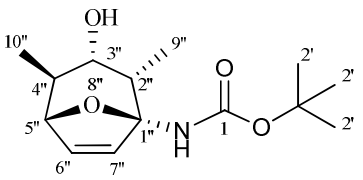
To a solution of ketone **3a** (300 mg, 1.12 mmol) in anhydrous THF (3 mL), a solution 1 M in hexane of DIBAL-H (3.36 mmol) was added at –78 ºC and stirred along 75 min under argon atmosphere (control by TLC). At the end of the reaction a saturated aqueous solution of NH_4Cl (12 mL) was added , at –78 ºC, to quench the excess of reducing agent and the mixture was stirred for 10 min. The organic solvent (THF) was evaporated *in vacuo* at room temperature, water was added (10 mL) and the system

extracted with diethyl ether (4 x 10 mL). The organic layers were combined together, dried over anhydrous $MgSO_4$, filtered and concentrated to dryness. The resulting residue was submitted to a flash column chromatography on silica gel, eluting with mixtures of chloroform and ethyl acetate of increasing polarity, isolating pure diastereoisomeric compounds **4a$_2$** (0.258 g) and **4a$_1$** (0.014 g). Yield = 90%. Diastereoselectivity: **4a$_1$** (*endo*) /**4a$_2$** (*exo*) = 5/95.

c) Use of Na / NH_3 (applied to* 3a*)

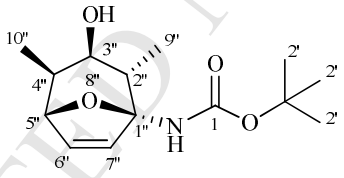
Dry ammonia was liquefied (Pe = –33 ºC) by using a gas condenser (cooled by dry ice and acetone) fitted to an oven-dried heart-shaped three-necked flask, equipped with magnetic stirring and a cooling bath of dry ice /acetone. 40 mL of liquid ammonia were generated and the bicyclic ketone **3a** (0.135 g, 0.505 mmol) was added dissolved in diethyl ether (10 mL) by a syringe. Afterwards, Na (46 mg, 2.010 mmol) was added in small pieces, observing the formation of a blue colour that disappears in a few seconds. The reaction mixture was stirred under these conditions for 30 min (control by TLC: SiO_2, chloroform / methanol 95:5, two elutions, developed with ninhydrin). The cooling bath was removed and the ammonia was evaporated by an argon stream, obtaining a yellowish solid, which was lixiviated with diethyl ether (5 x 5 mL). The organic extracts were combined together and concentrated to dryness, obtaining a colourless oil that was submitted to a flash column chromatography on silica gel, eluting with mixtures of chloroform and ethyl acetate of increasing polarity, isolating pure diastereoisomer compounds **4a$_2$** (134.6 mg). Yield = 99%. Diastereoselectivity: **4a$_1$** (*endo*) /**4a$_2$** (*exo*) = 0/100. Control by GC of the reaction crude prior to the column chromatography showed no presence of diastereoisomer **4a$_1$**.

***tert-Butyl N-{(1S*,2S*,3S*,4S*,5R*)-3-hydroxy-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-1-yl}carbamate,* (4a$_1$)**



Colourless oil. **TLC:** R_f = 0.47 (SiO_2, chloroform/methanol 95:5, two elutions, developed by ninhydrin). **IR** (film) $\bar{\upsilon}$ (cm^{-1}): 3330 (O–H, st), 2973, 2932, 1717 (C=O, st), 1526 (N–H, def), 1366, 1250 (^{t}Bu), 1161 (C–O–C, st), 995. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm):1.04 (3H, d, $J_{9,2}$ = 7.4 Hz, H9''), 1.21 (3H, d, $J_{10,4}$ = 7.6 Hz, H10''), 1.44 (9H, s, H2'), 1.85 (1H, q, $J_{4,10}$ = 7.6 Hz, H4''), 2.03 (1H, d, J = 10.6 Hz, OH), 2.34 (1H, dq, $J_{2,9}$ = 7.4 Hz, $J_{2,3}$ = 5.6 Hz, H2''), 3.55 (1H, brs, H3''), 4.65 (1H, d, $J_{5,6}$ = 1.6 Hz, H5''), 5.10 (1H, s, NH), 6.40 (1H, dd, $J_{6,5}$ = 1.6 Hz, $J_{6,7}$ = 5.6 Hz, H6''), 6.50 (1H, d, $J_{7,6}$ = 5.6 Hz, H7''). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 12.4 (C10''), 17.6 (C9''), 28.5 (C2'), 39.6 (C4''), 39.9 (C2''), 75.7 (C3''), 82.9 (C5''), 94.9 (C1''), 135.0 (C7''), 135.1 (C6''), 154.2 (C1). **MS** (CI, NH_3, 70 eV, 150ºC) m/z (%)**:** 270 (43, M+H), 214 (89, M+2–^{t}Bu), 196 (96, M–O^{t}Bu), 170 (100, M+2–COO^{t}Bu), 152 (83, M–NH_2Boc). **Anal.** Calcd for $C_{14}H_{23}NO_4$ (269.34 g·mol^{-1}): C, 62.43; H, 8.61; N, 5.20. Found: C, 62.40; H, 8.59; N, 5.23.

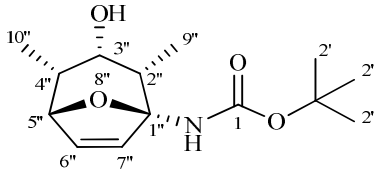
***tert-Butyl N-{(1S*,2S*,3R*,4S*,5R*)-3-hydroxy-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-1-yl}carbamate,* (4a$_2$)**



Colourless oil. **TLC:** R_f = 0.32 (SiO_2, chloroform/methanol 95:5, two elutions, developed by ninhydrin). **IR** (film) $\bar{\upsilon}$ (cm^{-1}): 3342 (N–H, st), 3336 (O–H, st), 2975, 2932, 1717 (C=O, st), 1526 (N–H, def), 1324, 1248 (^{t}Bu), 1161 (C–O–C, st), 1094, 1053 (C–O–C, st as), 1014, 982. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 1.03 (3H, d, $J_{9,2}$ = 6.7 Hz, H9''), 1.14 (3H, d, $J_{10,4}$ = 6.9 Hz, H10''), 1.44 (9H, s, H2'), 1.48 (1H, d, J = 7.0 Hz, OH), 1.75 (1H, dq, $J_{2,9}$ = 6.7 Hz, $J_{2,3}$ = 8.0 Hz, H2''), 1.87 (1H, ddq, $J_{4,5}$ = 1.5 Hz, $J_{4,3}$ = 6.9 Hz, $J_{4,10}$ = 6.9 Hz, H4''), 3.50 (1H, dd, $J_{3,4}$ = 6.9 Hz, $J_{3,2}$ = 8.0 Hz, H3''), 4.67 (1H, brs, H5''), 5.08 (1H, s, NH), 6.15 (1H, dd, $J_{6,5}$ = 1.7 Hz, $J_{6,7}$ = 5.9 Hz, H6''), 6.22 (1H, d, $J_{7,6}$ = 5.9 Hz, H7''). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 11.8 (C10''), 13.5 (C9''), 28.5 (C2'), 34.6 (C4''), 41.2 (C2''), 73.5 (C3''), 82.9 (C5''), 94.9 (C1''), 131.0 (C7''), 131.3 (C6''), 153.9 (C1). **MS** (CI, NH_3, 70 eV, 150ºC) m/z (%): 270 (28, M+H), 214 (51, M+2–^{t}Bu), 170 (100, M+2–COO^{t}Bu), 152 (63, M–NH_2Boc). **Anal.** Calcd for

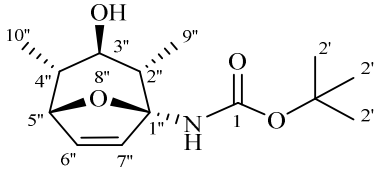
$C_{14}H_{23}NO_4$ (269.34 g·mol^{-1}): C, 62.43; H, 8.61; N, 5.20. Found: C, 62.46; H, 8.63; N, 5.19.

***tert-Butyl N-{(1S*,2S*,3S*,4R*,5R*)-3-hydroxy-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-1-yl}carbamate,* (4b$_1$)**



White solid. **MP =** 137-138 ºC (CCl_4). **TLC:** R_f = 0.47 (SiO_2, chloroform/methanol 95:5, two elutions, developed by ninhydrin). **IR** (film) $\bar{\upsilon}$ (cm^{-1}): 3334 (O–H, st), 2973, 2930, 1723 (C=O, st), 1624, 1520 (N–H, def), 1456, 1364, 1250 (^{t}Bu), 1165 (C–O–C, st), 1084, 1016. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 0.98 (3H, d, $J_{10,4}$ = 7.6 Hz, H10"), 1.08 (3H, d, $J_{9,2}$ = 7.6 Hz, H9"), 1.44 (9H, s, H2'), 1.62 (1H, brs, OH), 2.25-2.35 (2H, m, H2" y H4"), 3.73-3.79 (1H, m, H3"), 4.62 (1H, ddd, $J_{5,6}$ = 1.6 Hz, $J_{5,3}$ = 1.6 Hz, $J_{5,4}$ = 3.2 Hz, H5"), 5.18 (1H, s, NH), 6.47 (1H, dd, $J_{6,5}$ = 1.6 Hz, $J_{6,7}$ = 6.2 Hz, H6"), 6.50 (1H, d, $J_{7,6}$ = 6.2 Hz, H7"). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 12.8 (C10"), 12.9 (C9"), 28.5 (C2'), 38.7 (C2"), 41.9 (C4"), 73.1 (C3"), 82.8 (C5"), 94.7 (C1"), 134.7 (C6"), 136.5 (C7"), 154.2 (C1). **MS** (CI, NH_3, 70 eV, 150ºC) m/z (%)**:** 214 (40, M+2–^{t}Bu), 196 (53, M–O^{t}Bu), 170 (100, M+2–COO^{t}Bu), 152 (63, M–NH_2Boc), 110 (93). **Anal.** Calcd for $C_{14}H_{23}NO_4$ (269.34 g·mol^{-1}): C, 62.43; H, 8.61; N, 5.20. Found: C, 62.45; H, 8.62; N, 5.23.

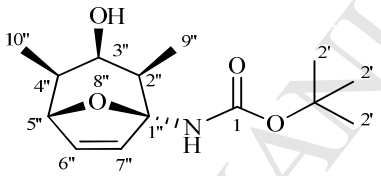
***tert-Butyl N-{(1S*,2S*,3S*,4R*,5R*)-3-hydroxy-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-1-yl}carbamate,* (4b$_2$)**



White solid. **MP =** 58-59 ºC (CCl_4). **TLC:** R_f = 0.27 (SiO_2, chloroform/methanol 95:5, two elutions, developed by ninhydrin). **IR** (film) $\bar{\upsilon}$ (cm^{-1}): 3334 (O–H, st), 2973, 2930, 1713 (C=O, st), 1526 (N–H, def), 1456, 1393, 1366, 1250 (^{t}Bu), 1163 (C–O–C, st), 1024, 993, 955. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 0.95 (3H, d, $J_{10,4}$ = 7.0 Hz,

H10''), 1.04 (3H, d, $J_{9,2}$ = 7.0 Hz, H9''), 1.44 (9H, s, H2'), 1.71-1.79 (3H, m, H2'',H4'' and OH), 2.85 (1H, dd, $J_{3,2}$ = 8.6 Hz, $J_{3,4}$ = 8.6 Hz, H3''), 4.63 (1H, d, $J_{5,6}$ = 1.8 Hz, $J_{5,4}$ = 3.6, H5''), 5.14 (1H, s, NH), 6.19 (1H, dd, $J_{6,5}$ = 1.8 Hz, $J_{6,7}$ = 6.4 Hz, H6''), 6.24 (1H, d, $J_{7,6}$ = 6.4 Hz, H7''). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 13.8 (C9''), 14.3 (C10''), 28.5 (C2'), 40.8 (C4''), 44.4 (C2''), 78.5 (C3''), 81.9 (C5''), 95.3 (C1''), 130.0 (C7''), 132.0 (C6''), 154.0 (C1). **MS** (CI, NH_3, 70 eV, 150ºC) m/z (%)**:** 214 (34, M+2–^{t}Bu), 196 (90, M–O^{t}Bu), 170 (100, M+2–COO^{t}Bu), 152 (55, M–NH_2Boc). **Anal.** Calcd for $C_{14}H_{23}NO_4$ (269.34 g·mol^{-1}): C, 62.43; H, 8.61; N, 5.20. Found: C, 62.39; H, 8.64; N, 5.23.

***tert-Butyl N-{(1S*,2R*,3R*,4S*,5R*)-3-hydroxy-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-1-yl}carbamate,* (4c$_2$)**

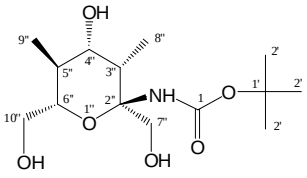


White solid. **MP =** 109-110 ºC (CCl_4). **TLC:** R_f = 0.50 (SiO_2, hexane/diethyl ether (3:7), three elutions, developed by ninhydrin). **IR** (film) ῡ (cm^{-1}): 3332 (O–H, st), 2977, 2934, 1699 (C=O, st), 1651, 1559 (N–H, def), 1505, 1458, 1368, 1323, 1246 (^{t}Bu), 1167 (C–O–C, st), 1051 (C–O–C, st as), 995. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 1.10 (3H, d, $J_{9,2}$ = 6.8 Hz, H9''), 1.12 (3H, d, $J_{10,4}$ = 6.8 Hz, H10''), 1.44 (9H, s, H2'), 1.70-1.74 (1H, m, OH), 1.77 (1H, dq, $J_{4,3}$ = 6.4 Hz, $J_{4,10}$ = 6.8 Hz, H4''), 2.17 (1H, dq, $J_{2,9}$ = $J_{2,3}$ = 6.8 Hz, H2''), 4.13 (1H, dd, $J_{3,2}$ = $J_{3,4}$ = 6.8 Hz, H3''), 4.64 (1H, brs, H5''), 5.25 (1H, s, NH), 6.09 (1H, dd, $J_{6,5}$ = 1.6 Hz, $J_{6,7}$ = 6.0 Hz, H6''), 6.24 (1H, d, $J_{7,6}$=6.0 Hz, H7''). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 8.9 (C9''), 13.7 (C10''), 28.5 (C2'), 34.4 (C4''), 38.7 (C2''), 67.5 (C3''), 82.9 (C5''), 94.2 (C1''), 129.8 (C6''), 132.9 (C7''), 153.8 (C1). **MS** (CI, NH_3, 70 eV, 150ºC) m/z (%)**:** 214 (29, M+2–^{t}Bu), 196 (100, M–O^{t}Bu), 170 (49, M+2–COO^{t}Bu), 152 (69, M–NH_2Boc). **Anal.** Calcd for $C_{14}H_{23}NO_4$ (269.34 g·mol^{-1}): C, 62.43; H, 8.61; N, 5.20. Found: C, 62.41; H, 8.65; N, 5.24.

6.4.5. General method for the reductive ozonolysis reaction: use of SMe_2 and $NaBH_4$ as reducing agents. Synthesis of (5)

In a 25 mL two-neck heart-shaped oven-dried flask, equipped with a Dimroth condenser connected to a $CaCl_2$ trap tube, the corresponding alcohol (**4**) (269 mg, 1 mmol), $NaHCO_3$ (136 mg, 1.62 mmol), anhydrous CH_2Cl_2 (10 mL) and anhydrous MeOH (2.5 mL) were placed. The mixture was cooled with a solid CO_2/acetone bath at –78 ºC. Then, O_3 was bubbled inside the solution for 0.5 h, by a diffusor, until the reaction mixture was saturated of ozone (adopting a blue colour). After reaction completion (control by TLC), the system was purged with N_2, in order to remove the excess of ozone. Then, a stirring bar was placed in the flask; the Dimroth condenser removed and two septa were adapted to the necks of the flask. Afterwards, SMe_2 (0.17 mL, 2.3 mmol) was added at –78 ºC and the mixture was stirred for 20 minutes. Then, the mixture was warmed to room temperature, $NaBH_4$ (91 mg, 2.3 mmol) was added and the reaction system was stirred for 3 h. After reaction completion (control by TLC), the reaction mixture was cooled to 0 ºC and the $NaBH_4$ excess was quenched with water (0.5 mL) and the mixture was stirred for 15 minutes. Then, MeOH (5 mL) was added to dissolve and quench the formed boron byproducts and the mixture was concentrated to dryness under vacuum at room temperature. The obtained crude was lixiviated with ethyl acetate (8 x 10 mL), and filtered by cannula. The organic phases were combined together and the solvent was evaporated *in vacuo*. The resulting residue was submitted to a flash column chromatography on silica gel eluting with mixtures of hexane and ethyl acetate of increasing polarity to isolate pure 2-aminopyran **5**.

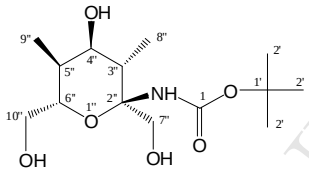
***tert-Butyl N-[(2R*,3S*,4S*,5S*,6S*)-4-hydroxy-2,6-bis(hydroxymethyl)-3,5-dimethyltetrahydropyran-2-yl]carbamate,* (5a$_1$)**



White solid, 269 mg, 88% yield. **MP =** 181-182 ºC (CCl_4). **TLC:** R_f = 0.26 (SiO_2, EtOAc, developed by ninhydrin). **IR** (film) $\bar{\upsilon}$ (cm^{-1}): 3345 (O–H, st), 2975, 2930, 2456, 1699 (C=O, st), 1514 (N–H), 1460, 1396, 1371, 1250 (^{t}Bu), 1167 (C–O–C, st), 1099, 1065 (C–O–C, st as), 1011. **^{1}H NMR** (400 MHz, CD_3OD) δ (ppm): 0.94 (3H, d, $J_{9,5}$ = 6.8 Hz, H9"), 0.97 (3H, d, $J_{8,3}$ = 7.0 Hz, H8"), 1.44 (9H, s, H2'), 1.66 (1H, ddq, $J_{5,9}$ = 6.8 Hz, $J_{5,6}$ = $J_{5,4}$ = 10.3 Hz, H5"), 2.20 (1H, dq, $J_{3,4}$ = 5.0 Hz, $J_{3,8}$ = 7.0 Hz, H3"), 3.30-331 (1H, m, H6"), 3.53 (1H, d, $J_{10a,10b}$ = 11.2 Hz, H10a"), 3.57 (1H, dd, $J_{7a,OH}$ = 6.0 Hz, $J_{7a,7b}$

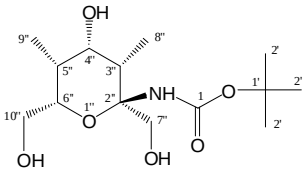
= 11.0 Hz, H7a''), 3.67 (1H, dd, $J_{4,3}$ = 5.0 Hz, $J_{4,5}$ = 10.3 Hz, H4''), 3.69 (1H, dd, $J_{7b,OH}$ = 2 Hz, $J_{7b,OH}$ = 11.0 Hz, H7b''), 3.96 (1H, d, $J_{10b,10a}$ = 11.2 Hz, H10b''). **^{13}C NMR** (100 MHz, CD_3OD) δ (ppm): 6.4 (C8''), 12.3 (C9''), 27.6 (C2'), 32.4 (C5''), 37.8 (C3''), 62.0 (C10''), 62.6 (C7''), 71.2 (C4''), 76.5 (C6''), 79.2 (C1'), 88.3 (C2''), 155.1 (C1). **MS** (CI, NH_3, 70 eV, 150ºC) m/z (%)**:** 206 (56, M+2–COO^{t}Bu), 189 (68, M–NHBoc), 171 (100, M–NHBoc–H_2O). **Anal.** Calcd for $C_{14}H_{27}NO_6$ (305.37 g·mol^{-1}): C, 55.07; H, 8.91; N, 4.59. Found: C, 55.05; H, 8.93; N, 4.57.

***tert-Butyl N-[(2R*,3S*,4R*,5S*,6S*)-4-hydroxy-2,6-bis(hydroxymethyl)-3,5-dimethyltetrahydropyran-2-yl]carbamate,* (5a$_2$)**



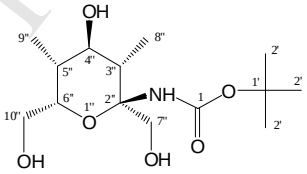
Colourless oil, 229 mg, 75% yield. **TLC:** R_f = 0.36 (SiO_2, EtOAc, developed by ninhydrin). **IR** (film) ῡ (cm^{-1}): 3341 (O–H, st), 2971, 2923, 1705 (C=O, st), 1510 (N–H, def), 1460, 1368, 1283, 1234 (^{t}Bu), 1167 (C–O–C, st), 1065 (C–O–C, st as), 989, 920. **^{1}H NMR** (400 MHz, CD_3OD) δ (ppm): 0.95 (3H, d, $J_{9,5}$ = 7.2 Hz, H9''), 1.04 (3H, d, $J_{8,3}$ = 7.2 Hz, H8''), 1.44 (9H, s, H2'), 1.90 (1H, ddq, $J_{5,9}$ = 7.2 Hz, $J_{5,4}$ = 2.4 Hz, $J_{5,6}$ = 10.4 Hz , H5''), 2.09 (1H, dq, $J_{3,4}$ = 2.4 Hz, $J_{3,8}$ = 7.2 Hz, H3''), 3.51 (1H, dd, $J_{7a,OH}$ = 8.8 Hz, $J_{7a,7b}$ = 11.2 Hz, H7a''), 3.57 (1H, dd, $J_{10a,10b}$ = 8.8 Hz, $J_{10a,OH}$ = 11.2 Hz, H10a''), 3.68 (1H, dd, $J_{10a,10b}$ = 8.8 Hz, $J_{10a,6}$ = 2.0 Hz, H10b''), 3.69-371 (1H, m, H6''), 3.76 (1H, m, H4''), 4.34 (1H, d $J_{7b,OH}$ = 3.4 Hz, $J_{7b,7a}$ = 11.2 Hz, H7b''). **^{13}C NMR** (100 MHz, CD_3OD) δ (ppm): 13.1 (C9''), 13.8 (C8''), 28.5 (C2'), 30.4 (C5''), 38.6 (C3''), 63.3 (C7''), 63.5 (C10''), 71.1 (C6''), 76.4 (C4''), 80.2 (C1'), 87.0 (C2''), 154.9 (C1). **MS** (CI, NH_3, 70 eV, 150ºC) m/z (%)**:** 189 (49, M–NHBoc), 171 (100, M–NHBoc–H_20), 153 (68, M–NHBoc–$2H_2O$). **Anal.** Calcd for $C_{14}H_{27}NO_6$ (305.37 g·mol^{-1}): C, 55.07; H, 8.91; N, 4.59. Found: C, 55.10; H, 8.89; N, 4.61.

***tert-Butyl N-[(2R*,3S*,4S*,5R*,6S*)-4-hydroxy-2,6-bis(hydroxymethyl)-3,5-dimethyltetrahydropyran-2-yl]carbamate,* (5b$_1$)**



Colourless oil, 214 mg, 70% yield. **TLC:** R_f = 0.26 (SiO_2, EtOAc, developed by ninhydrin). **IR** (film) ῡ (cm^{-1}): 3336 (O–H, st), 2925, 2855, 1838, 1701 (C=O, st), 1653, 1514 (N–H, def), 1458, 1393, 1368, 1292, 1244 (^{t}Bu), 1167 (C–O–C, st), 1095, 1057 (C–O–C, st as), 1014. **^{1}H NMR** (400 MHz, CD_3OD) δ (ppm): 0.89 (3H, d, $J_{9,5}$ = 7.6 Hz, H9''), 1.01 (3H, d, $J_{8,3}$ = 7.2 Hz, H8''), 1.44 (9H, s, H2'), 1.99 (1H, ddq, $J_{5,9}$ = 7.6 Hz, $J_{5,6}$ = 3.0 Hz, $J_{5,4}$ = 5.2 Hz, H5''), 2.15 (1H, dq, $J_{3,4}$ = 5.2 Hz, $J_{3,8}$ = 7.2 Hz, H3''), 3.48 (1H, dd, $J_{7a,OH}$ = 4.8 Hz, $J_{7a,7b}$ = 11.3 Hz, H7a''), 3.56 (1H, d, $J_{10a,10b}$ = 11.1 Hz, H10a''), 3.64 (1H, dd, $J_{7b,OH}$ = 7.6 Hz, $J_{7b,7a}$ = 11.3 Hz, H7b''), 3.86 (1H, ddd, $J_{6,5}$ = 3.0 Hz, $J_{6,10a}$ = 4.8 Hz, $J_{6,10b}$ = 8.0 Hz ,H6''), 4.02 (1H, d, $J_{10b,10a}$ = 11.1 Hz, H10b''), 4.07 (1H, dd, $J_{4,3}$ = $J_{4,5}$ = 5.2 Hz, H4''). **^{13}C NMR** (100 MHz, CD_3OD) δ (ppm): 7.5 (C9''), 8.1 (C8''), 27.6 (C2'), 38.3 (C3''), 36.0 (C5''), 61.5 (C10''), 62.5 (C7''), 68.9 (C6''), 72.6 (C4''), 79.2 (C1'), 88.6 (C2''), 155.1 (C1). **MS** (CI, NH_3, 70 eV, 150ºC) m/z (%)**:** 206 (38, M+2–COO^{t}Bu), 189 (64, M–NHBoc), 171 (100, M–NHBoc–H_2O), 153 (40, M–NHBoc–$2H_2O$), 101 (44).

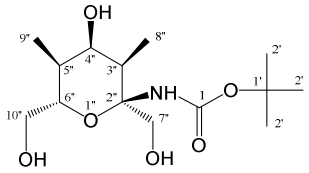
***tert-Butyl N-[(2R*,3S*,4R*,5R*,6S*)-4-hydroxy-2,6-bis(hydroxymethyl)-3,5-dimethyltetrahydropyran-2-yl]carbamate,* (5b$_2$)**



Colourless oil, 223 mg, 73% yield. **TLC:** R_f = 0.30 (SiO_2, EtOAc, developed by ninhydrin). **IR** (film) ῡ (cm^{-1}): 3351 (O–H, st), 2975, 2927, 1838, 1701 (C=O, st), 1653, 1514 (N–H, def), 1456, 1393, 1368, 1288, 1246 (^{t}Bu), 1167 (C–O–C, st), 1061 (C–O–C, st as), 864. **^{1}H NMR** (400 MHz, CD_3OD) δ (ppm): 0.97 (3H, d, $J_{9,5}$ = 7.8 Hz, H9''), 1.08 (3H, d, $J_{8,3}$ = 7.4 Hz, H8''), 1.44 (9H, s, H2'), 1.77 (1H, ddq, $J_{5,9}$ = 7.8 Hz, $J_{5,6}$ = 3.5 Hz, $J_{5,4}$ = 3.2 Hz, H5''), 1.91 (1H, dq, $J_{3,4}$ = 4.4 Hz, $J_{3,8}$ = 7.4 Hz, H3''), 3.46 (1H, dd, $J_{7a,OH}$ = 5 Hz, $J_{7a,7b}$ = 11.2 Hz, H7a''), 3.51 (1H, d, $J_{10a,10b}$ = 11.2 Hz, H10a''), 3.61 (1H, dd, $J_{7b,OH}$ = 7.8 Hz, $J_{7b,7a}$ = 11.2 Hz, H7b''), 3.63-3.65 (1H, m, H4''), 4.16 (1H, ddd, $J_{6,5}$ =

3.5 Hz, $J_{6,10a}$ = 4.6 Hz, $J_{6,10b}$ = 8.0 Hz ,H6''),4.26 (1H, d, $J_{10b,10a}$ = 11.2 Hz, H10b''). **^{13}C NMR** (100 MHz, CD_3OD) δ (ppm): 12.0 (C9''), 13.0 (C8''), 27.5 (C2'), 37.1 (C5'), 38.8 (C3''), 61.2 (C10''), 62.5 (C7''), 69.2 (C6''), 76.2 (C4''), 79.3 (C1'), 87.6 (C2''), 155.3 (C1). **MS** (CI, NH_3, 70 eV, 150ºC) m/z (%)**:** 206 (100, M+2–COO^{t}Bu), 189 (61, M–NHBoc), 171 (30, M–NHBoc–H_2O). **Anal.** Calcd for $C_{14}H_{27}NO_6$ (305.37 g·mol^{-1}): C, 55.07; H, 8.91; N, 4.59. Found: C, 55.09; H, 8.94; N, 4.55.

***tert-Butyl N-[(2R,3R,4R,5S,6S)-4-hydroxy-2,6-bis(hydroxymethyl)-3,5-dimethyltetrahydropyran-2-yl]carbamate,* (5c$_2$)**



Colourless oil, 287 mg, 94% yield. **TLC:** R_f = 0.10 (SiO_2, EtOAc, developed by ninhydrin). **IR** (film) ῡ (cm^{-1}): 3390 (O–H, st), 2925, 1838, 1701 (C=O, st), 1647, 1514 (N–H, def), 1459, 1369, 1254 (^{t}Bu), 1161 (C–O–C, st). **^{1}H NMR** (400 MHz, CD_3OD) δ (ppm): 0.93 (3H, d, $J_{9,5}$ = 6.8 Hz, H9''), 1.04 (3H, d, $J_{8,3}$ = 7.2 Hz, H8''), 1.44 (9H, s, H2'), 1.79 (1H, ddq, $J_{5,9}$ = 6.8 Hz, $J_{5,6}$ = 10.4 Hz, $J_{5,4}$ = 2.8 Hz, H5''), 2.09 (1H, dq, $J_{3,4}$ = 2.8 Hz, $J_{3,8}$ = 7.2 Hz, H3''), 3.52 (1H, d, $J_{10a,10b}$ = 12 Hz, H10a''), 3.51-3.71 (4H, m, H6'', H7a'', H4'' and H7b''), 4.41 (1H, d, $J_{10b,10a}$ = 12 Hz, H10b''). **^{13}C NMR** (100 MHz, CD_3OD) δ (ppm): 12.3 (C8''), 12.7 (C9''), 27.4 (C2'), 35.6 (C5'), 36.7 (C3''), 62.3 (C7''), 63.7 (C10''), 71.6 (C6''), 73.5 (C4''), 88.6 (C2''), 155.2 (C1). **MS** (CI, NH_3, 70 eV, 150ºC) m/z (%)**:** 206 (100, M+2–COO^{t}Bu), 189 (88, M–NHBoc), 171 (40, M–NHBoc–H_2O), 116 (33, NHBoc), 101 (25, Boc). **Anal.** Calcd for $C_{14}H_{27}NO_6$ (305.37 g·mol^{-1}): C, 55.07; H, 8.91; N, 4.59. Found: C, 55.11; H, 8.92; N, 4.55.

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HIGHLIGHTS

- 2-Amino-pyrans are readily available in three steps, in high yield.
- [4+3]-Cycloaddition, stereoselective reduction and ozonolysis are the key steps.
- With this methodology, up to five stereocenters are generated, in a stereoselective manner.
- High molecular diversity may be obtained by designing the structure of starting materials.
- This synthetic methodology contributes to the preparation of 2-aminopyrans, present in natural products with important bioactivity.