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# Synthesis and biological evaluation of 6-oxa-nor-tropane glycomimetics as glycosidase inhibitors

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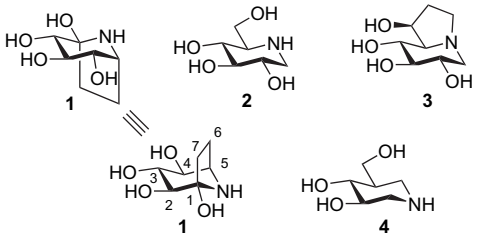
**Abstract**—The preparation of polyhydroxylated 6-oxa-nor-tropane glycomimetics structurally related to the glycosidase inhibitor family of the calystegines is reported. The synthetic strategy involves the furanose → piperidine rearrangement of 5-deoxy-5-ureido-L-idose precursors, followed by intramolecular glycosylation involving the primary hydroxyl group. Inversion of the configuration at C-3 in the resulting 6-oxa-(+)-calystegine $B_2$ analogue allows accessing the elusive 3-*epi*-6-oxa-(+)-calystegine $B_2$ skeleton. Acid-catalyzed opening of the nor-tropane bicycle was observed, however, which could be avoided by careful neutralization of the reaction mixture. The inhibition results suggest that (+)-calystegine $B_2$ derivatives and the corresponding C-3 epimers can be seen as glucomimetics and galactomimetics, respectively, pointing to a 1-azasugar mode of action for this family of alkaloids.


## 1. Introduction

The polyhydroxy-nor-tropane alkaloids of the calystegine family[1–3] are the most recently discovered members of the iminosugar (azasugar[4]) glycosidase inhibitor family. They were first isolated from the root extrudates of *Calystegia sepium* in 1988[5] and further encountered in other plant organs as well as other plant families, including edible vegetables such as potato, egg plant or cabbage.[1,6] Contrary to other well-studied azasugar glycomimetics,[7] the structural basis for glycosidase inhibition by calystegines is poorly understood.[8] (+)-Calystegine $B_2$ (**1**), for instance, is a bicyclic amine that combines a pyrrolydine and a piperidine ring in the structure, with a hydroxylation profile that bears close similarities with that of 1-deoxynojirimycin (**2**) and castanospermine (**3**). Notwithstanding, the biological properties are totally different: while **2** and **3** are potent inhibitors of α-glucosidases, **1** behaves as a potent and specific inhibitor of β-glucosidases.[9] In this respect, calystegine $B_2$ resembles the 1-azasugar glucomimetic isofagomine (**4**).[10] The location of the basic nitrogen atom in **4** at the homologous position of the anomeric carbon is postulated to mimic the situation encountered in the transition state of β-glucosidase hydrolysis, closer to an anomeric carbocation than to the glycosyloxocarbenium cation involved in the case of α-glucosidases.[11]




We have recently reported a new family of highly selective glycosidase inhibitors in which the $sp^3$ amine-type nitrogen typical of azasugars is replaced by a pseudoamide-type (urea, thiourea, carbamate, thiocarbamate, isourea) nitrogen atom, with a substantial $sp^2$-character[12] (*$sp^2$-azasugars*).[13] This subtle structural change has important consequences on the stability of the resulting glycomimetics, favoring dispositions that fulfill the anomeric effect. Interestingly, the neutral $sp^2$-azasugars **5** and **6**, with 1-deoxy-6-oxa-*N*-(thio)-carbamoyl-(+)-calystegine $B_2$ structure, exhibited very selective and strong inhibitory activity against the mammalian cytosolic β-glucosidase/β-galactosidase (bovine liver). Actually, the corresponding inhibition constant ($K_i$) values (2.5 and 30 μM, respectively) were indicative of a more potent inhibition for this particular enzyme than the natural compound **1** ($K_i$=45 μM),[14] suggesting a 1-azasugar inhibition mode. If this hypothesis is correct, the corresponding

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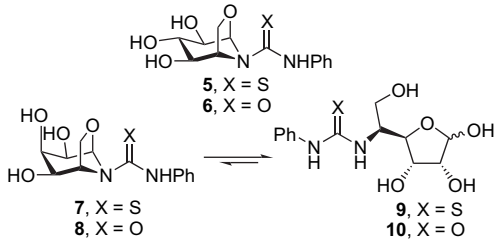
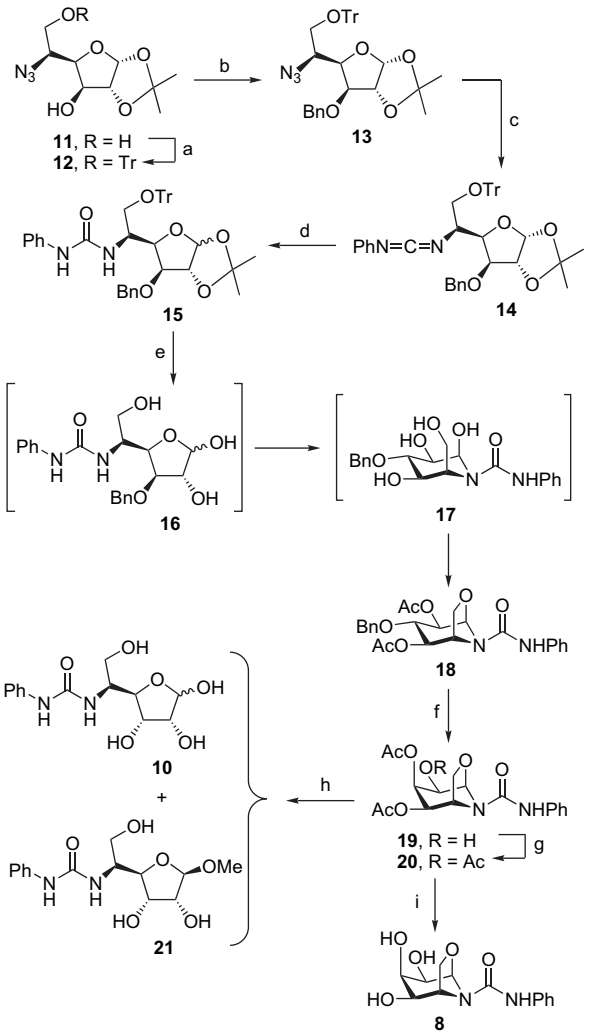
epimers at C-3 should act as galactomimetics and, consequently, inhibit the β-glucosidase/β-galactosidase. Previous attempts to synthesize compounds **7** and **8** by furanose→piperidine rearrangement of hexofuranose precursors failed, however, the L-talofuranose forms **9** and **10**, respectively, being the major species in solution (nor-tropane–furanose ratio 5:95).[15] We reasoned that the nor-tropane structure might be trapped by preforming the bicyclic skeleton prior to C-3 epimerization. This has now been translated into the preparation of **8**, the first example of a 3-*epi*-(+)-calystegine $B_2$ derivative, in pure form. The reactivity of the intermediates and the biological evaluation of the final compound are discussed.




## 2. Results and discussion

Our synthetic approach starts from 5-azido-5-deoxy-1,2-*O*-isopropylidene-β-L-idofuranose (**11**), readily accessible from commercial glucuronolactone.[16] Regioselective tritylation of the primary hydroxyl (→**12**) followed by benzylation of the remaining hydroxyl afforded the key idofuranose precursor **13**. The urea functionality at C-5 was introduced through a two-step sequence that avoids the use of highly toxic isocyanate reagents, involving (i) formation of carbodiimide **14** by tandem Staüdinger–aza-Wittig reaction of azide **13** with triphenylphosphine and phenyl isothiocyanate[17] and (ii) acid-catalyzed addition of water to the heterocumulene group of **14** (→**15**). Simultaneous hydrolysis of the trityl and isopropylidene groups with 90% aqueous trifluoroacetic acid provided the corresponding 5-ureido-L-idofuranose species **16**, which on elimination of the acid by coevaporation with water, underwent spontaneous nucleophilic addition of the urea nitrogen to the masked carbonyl group through the open chain form of the sugar. The resulting transient piperidine **17** experienced in situ intramolecular attack of the primary hydroxyl to the pseudoanomeric hemiaminal center, zipping up the bicyclic nor-tropane core. After conventional acetylation, the corresponding diacetate **18** was isolated in 75% overall yield (Scheme 1).

Compound **18** exhibits a configurational pattern identical to that of (+)-calystegine $B_2$ at the C-2–C-3–C-4 segment, with the hydroxyl group at C-3 purposely differentiated. Inversion of the configuration at this position was effected by sequential catalytic hydrogenolysis of the benzyl group, trifluoromethanesulfonylation of the resulting alcohol and nucleophilic displacement of the triflate ester by nitrite anion. Concomitant migration of the equatorial acetyl group at O-2 to the axial hydroxyl at O-3 occurred under these conditions, affording the diacetate **19** in 69% overall yield. Conventional acetylation provided the corresponding tri-*O*-acetate **20** (Scheme 1).

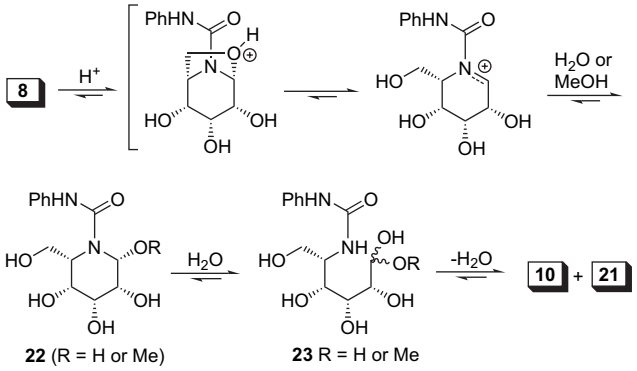



**Scheme 1**. Reagents: (a) TrCl, pyridine, rt, 24 h (70%); (b) NaH, BnBr, DMF, rt, 40 min (80%); (c) PhNCS, $Ph_3P$, toluene, 80 °C, 2 h (70%); (d) 1% aq TFA, 2:1 acetone–water, rt, 18 h (70%); (e) (1) 90% TFA-water, 0 °C, 30 min; (2) $Ac_2O$–pyridine (1:1), rt, 6 h (75%); (f) (1) $H_2$, $Pd(OH)_2$, EtOH, rt, 1 h; (2) $Tf_2O$, pyridine, $CH_2Cl_2$, −25 °C, 30 min; (3) $NaNO_2$, DMF, rt, 18 h (69% overall); (g) $Ac_2O$–pyridine (1:1), rt, 6 h (90%); (h) (1) NaMeO, MeOH, rt, 30 min; (2) Amberlite® IR-120 ($H^+$) (**10**, 55%; **21**, 25%); (i) (1) NaMeO, MeOH, rt, 30 min; (2) solid $CO_2$ (86%).

Attempts to prepare the target fully unprotected 3-*epi*-(+)-calystegine $B_2$ derivative **8** by catalytic transesterification of **20** with methanolic sodium methoxide followed by neutralization with Amberlite® IR-120 ($H^+$) ion-exchange resin failed, however, resulting in reversion to the L-talofuranose ureidosugar **10**. Formation of the corresponding methyl α-L-talofuranoside **21** as a minor compound was also observed under these conditions (Scheme 1). It seems that the presence of the three axially-oriented substituents at the six-membered ring is hardly compatible with the existence of an aminoacetal center, which probably accounts for the fact that 3-*epi*-(+)-calystegine $B_2$ is the only diastereomer missing in the calystegine B natural compound series.

Our previous results in the synthesis of $sp^2$-azasugar glycomimetics point to the anomeric effect as the driving force for the furanose→piperidine rearrangement. The π symmetry of the orbital hosting the lone pair in the endocyclic

pseudoamide nitrogen atom results in a very efficient overlapping with the σ* antibonding orbital of the axially-oriented vicinal C–O bond. Orbitalic interactions additionally stabilize transient azacarbenium cations, thereby facilitating acid-promoted intra- as well as intermolecular glycosylation processes. In the case of **8**, the unfavorable steric interactions probably overcome the anomeric effect stabilization. Formation of a reducing piperidine or the corresponding methyl glycoside (**22**) occurs then at the surface of the acid resin. Both compounds can undergo conversion into furanose derivatives through open chain intermediates (**23**), the driving force being in this case the release of the steric constrain. The fact that the 5-ureido talofuranose derivative **10** did not form the methyl glycoside **21** under identical conditions supported this reaction pathway (Scheme 2).




**Scheme 2**. Probable acid-catalyzed mechanism for the reversion reaction of the 3-*epi*-6-oxacalystegine derivative **8** into the L-talofuranose derivatives **10** and **21**.

According to the above mechanistic proposal, reversion of the preformed 3-*epi*-(+)-calystegine $B_2$ bicyclic system must imply prior protonation at the endocyclic oxygen. In order to carefully control the neutralization step after deacetylation, we replaced the sulfonic acid resin by solid carbon dioxide. We were delighted to see that using these conditions the elusive trihydroxylated nor-tropane structure **8** could be isolated in 86% yield (Scheme 1).

The structures of the new compounds were confirmed by NMR spectroscopy, mass spectrometry, and microanalytical data. The $^{13}C$ resonance for the aminoketal carbon atom C-5 in nor-tropane derivatives was found at 88–85 ppm, while the anomeric carbon in furanose compounds resonated at 108–104 ppm, allowing unequivocal structural assignment. The lowfield shift of the C-5 resonance in the latter (54–52 ppm) accounts for the presence of the nitrogen functionality at this position. The anomeric configuration was attributed by comparison of the $^{13}C$ NMR spectra with data for D-talofuranose derivatives.[18,19] For example, C-2 resonates at ~76–74 ppm in α-talofuranose derivatives and is about 5 ppm highfield shifted for β-anomers. The $^3J_{H,H}$ values around the six-membered ring in calystegine $B_2$ and 3-*epi*-calystegine $B_2$ derivatives were in agreement with the all-equatorial and equatorial–axial–equatorial arrangement of the oxygen substituents, respectively.

Compound **8** was stable for several days in $D_2O$ solution at 4 °C at neutral pH. Slow conversion into the talofuranose tautomer **10** was observed, however, at room temperature. Even though the reversion process precludes the direct measurement of the inhibition constant values for **8**, comparison of the results obtained for mixtures of **8** and **10** with pure **10** and **21** allowed an indirect determination. Neither of the furanose derivatives inhibited the bovine β-glucosidase/β-galactosidase. Any inhibitory activity observed for samples containing **8** and **10** must be related, therefore, to the existing concentration of the nor-tropane derivative **8**. In control experiments, a 1:10 (**8/10**) relative proportion was determined after the standard incubation periods for determination of the glycosidase inhibitory properties (phosphate buffer, pH 7.3). From the observed $K_i$ value for this mixture (750±60 μM) a $K_i$ value of 68±6 μM can be estimated for **8**, in the same order of magnitude as compared with the value previously found for the glucomimetic epimer **6**.[14] No inhibition was observed against β-glucosidase from almonds, α-glucosidase from yeast or α-galactosidase from green coffee beans, which is in agreement with the high enzyme selectivity already encountered in the calystegine-type $sp^2$-azasugar series.[14,15] This result confirms that compound **8** behaves as a galactomimetic and strongly supports a 1-azasugar mode of action for calystegine glycosidase inhibitors, in line with recent crystallographic evidence for the natural compound **1**.[20] In this orientation, the nitrogen substituent probably projects into the aglyconic binding site of the enzyme, providing additional interactions, which offers a possibility for further improvement of the molecular design. Research in that direction is currently sought in our laboratories.

## 3. Experimental

### 3.1. General methods

Optical rotations were measured at room temperature in 1 cm or 1 dm tubes. IR spectra were recorded on a FTIR instrument. $^1H$ (and $^{13}C$) NMR spectra were recorded at 500 (125.7) and 300 (75.5) MHz. 2D COSY and HMQC experiments were carried out to assist in signal assignment. In the FABMS spectra, the primary beam consisted Xe atoms with a maximum energy of 8 keV. The samples were dissolved in *m*-nitrobenzyl alcohol or thioglycerol as the matrixes and the positive ions were separated and accelerated over a potential of 7 keV. NaI was added as cationizing agent. TLC was performed with E. Merck precoated TLC plates, silica gel 30F-245, with visualization by UV light, and by charring with 10% $H_2SO_4$ or 0.2% w/v cerium (IV) sulfate–5% ammonium molybdate in 2 M $H_2SO_4$. Column chromatography was carried out with Silica Gel 60 (E. Merk, 230–400 mesh). Microanalyses were performed by Instituto de Investigaciones Químicas (Sevilla, Spain).

The glycosidases α-glucosidase (from yeast), β-glucosidase (from almonds), β-glucosidase/β-galactosidase (from bovine liver, cytosolic), and α-galactosidase (from green coffee beans), used in the inhibition studies, as well as the corresponding *o*- and *p*-nitrophenyl glycoside substrates were purchased from Sigma Chemical Co. Inhibitory potencies were determined by spectrophotometrically measuring the residual hydrolytic activities of the glycosidases against the respective *o*- (for β-glucosidase/β-galactosidase from bovine liver) or *p*-nitrophenyl α- or β-D-glycopyranoside, in the presence of the corresponding calystegine or

L-talofuranose derivative. Each assay was performed in phosphate buffer at the optimal pH for each enzyme. The $K_m$ values for the different glycosidases used in the tests and the corresponding working pHs are listed herein: α-glucosidase (yeast), $K_m$=0.35 mM (pH 6.8); β-glucosidase (almonds), $K_m$=3.5 mM (pH 7.0); β-glucosidase/β-galactosidase (bovine liver), $K_m$=1.8 mM (pH 7.3); α-galactosidase (coffee beans), $K_m$=2.02 mM (pH 6.8). The reactions were initiated by addition of enzyme to a solution of the substrate in the absence or presence of various concentrations of inhibitor. After the mixture was incubated for 10–30 min at 37 °C the reaction was quenched by addition of 1 M $Na_2CO_3$. The absorbance of the resulting mixture was determined at 405 nm. The $K_i$ value and enzyme inhibition mode were determined from the slope of Lineweaver–Burk plots and double reciprocal analysis.

**3.1.1. 5-Azido-5-deoxy-1,2-*O*-isopropylidene-6-*O*-trityl-β-L-idofuranose (12).** Trityl chloride (1.2 g, 4.3 mmol, 1.3 equiv) was added to a solution of 5-azido-5-deoxy-1,2-*O*-isopropylidene-β-L-idofuranose[16] (**11**, 781 mg, 3.2 mmol) in pyridine (7 mL) and the solution was stirred at room temperature for 24 h. The reaction mixture was poured into ice-water (30 mL) and the resulting solid was dissolved in toluene (15 mL) and washed with iced 10% aq AcOH (6 mL), saturated aq $NaHCO_3$ (6 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography (1:3 EtOAc–petroleum ether) to furnish **12** (1.1 g, 70%). $R_f$=0.57 (1:1 EtOAc–petroleum ether); $[\alpha]_D$=−10.8 (*c* 1.02, $CH_2Cl_2$); IR (KBr) $\nu_{max}$ 3449, 3059, 2988, 1489, 1379, 1262, 1097 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.45–7.26 (m, 15H, 3Ph), 5.93 (d, 1H, $J_{1,2}$=3.7 Hz, H-1), 4.47 (d, 1H, H-2), 4.15–4.03 (m, 2H, H-3, H-4), 3.69 (dt, 1H, $J_{5,6a}$=$J_{5,6b}$=5.6 Hz, $J_{4,5}$=7.7 Hz, H-5), 3.39 (d, 2H, H-6a, H-6b), 1.48, 1.29 (2s, 6H, $CMe_2$); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) δ 142.9–127.3 (Ph), 111.7 (*C*$Me_2$), 104.4 (C-1), 87.0 (*C*$Ph_3$), 84.9 (C-2), 80.8 (C-4), 75.0 (C-3), 63.6 (C-6), 60.7 (C-5), 26.6, 26.1 (C*Me*$_2$); FABMS: *m/z* 510 (100, $[M+Na]^+$). Anal. Calcd for $C_{28}H_{29}N_3O_5$: C, 68.98; H, 6.00; N, 8.62. Found: C, 68.95; H, 5.78; N, 8.52.

**3.1.2. 5-Azido-3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-6-*O*-trityl-β-L-idofuranose (13).** To a solution of **12** (1.1 g, 2.3 mmol) in DMF (10 mL) under Ar at 0 °C, NaH (60% in mineral oil, 230 mg, 5.75 mmol, 2.5 equiv) was slowly added and the mixture was stirred for 10 min. Benzyl bromide (0.6 mL, 4.6 mmol, 2 equiv) was added dropwise and the reaction mixture was further stirred at room temperature for 40 min, then quenched by addition of MeOH (1 mL) and concentrated under reduced pressure. The residue was purified by column chromatography (1:3 EtOAc–petroleum ether) to give **13** (1.1 g, 80%). $R_f$=0.52 (1:2 EtOAc–petroleum ether); $[\alpha]_D$=−20.7 (*c* 1.06, $CH_2Cl_2$); IR (KBr) $\nu_{max}$ 3061, 2988, 1603, 1487, 1381, 1262, 1097 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.50–7.02 (m, 20H, 4Ph), 5.94 (d, 1H, $J_{1,2}$=3.8 Hz, H-1), 4.50 (d, 1H, H-2), 4.48 (dd, 1H, $J_{4,5}$=9.1 Hz, $J_{3,4}$=3.2 Hz, H-4), 4.27 (d, 1H, $^2J_{H,H}$=11.2 Hz, C*H*Ph), 3.85 (ddd, 1H, $J_{5,6b}$=5.0 Hz, $J_{5,6a}$=2.5 Hz, H-5), 3.75 (d, 1H, C*H*Ph), 3.53 (d, 1H, H-3), 3.44 (dd, 1H, $J_{6a,6b}$=9.7 Hz, H-6a), 3.07 (dd, 1H, H-6b), 1.54, 1.31 (2s, 6H, $CMe_2$); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) δ 143.3–127.0 (Ph), 111.7 (*C*$Me_2$), 104.7 (C-1), 86.6 (*C*$Ph_3$), 82.1 (C-3), 81.7 (C-2), 79.6 (C-4), 71.6 (*C*$H_2$Ph), 62.9 (C-6), 61.2 (C-5), 26.6, 26.3 (C*Me*$_2$); FABMS: *m/z* 578 (20, $[M+H]^+$). Anal. Calcd for $C_{35}H_{35}N_3O_5$: C, 72.77; H, 6.11; N, 7.27. Found: C, 72.73; H, 5.97; N, 7.20.

**3.1.3. 3-*O*-Benzyl-5-deoxy-1,2-*O*-isopropylidene-5-(*N*′-phenylcarbodiimido)-6-*O*-trityl-α-D-glucofuranose (14).** To a solution of **13** (1 g, 1.73 mmol) in toluene (18 mL) under $N_2$ at room temperature, phenyl isothiocyanate (0.23 mL, 2.08 mmol, 1.2 equiv) and a solution of $PPh_3$ (499 mg, 1.90 mmol, 1.1 equiv) in toluene (5 mL) were successively added. The resulting solution was stirred at 80 °C for 2 h then concentrated and the resulting residue purified by column chromatography (1:5 EtOAc–petroleum ether) to afford **14** (790 mg, 70%). $R_f$=0.44 (1:3 EtOAc–petroleum ether); $[\alpha]_D$=−10.8 (*c* 1.02, $CH_2Cl_2$); IR (KBr) $\nu_{max}$ 2988, 2128, 1593, 1501, 1483, 1380, 1262, 1094 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.50–7.03 (m, 20H, Ph), 5.93 (d, 1H, $J_{1,2}$=3.8 Hz, H-1), 4.56 (dd, 1H, $J_{4,5}$=8.5 Hz, $J_{3,4}$=3.3 Hz, H-4), 4.51 (d, 1H, H-2), 4.27 (d, 1H, $^2J_{H,H}$=11.3 Hz, C*H*Ph), 4.03 (ddd, 1H, $J_{5,6b}$=4.6 Hz, $J_{5,6a}$=2.6 Hz, H-5), 3.76 (d, 1H, $^2J_{H,H}$=11.3 Hz, C*H*Ph), 3.54 (d, 1H, H-3), 3.51 (dd, 1H, $J_{6a,6b}$=9.5 Hz, H-6a), 3.09 (dd, 1H, H-6b), 1.46, 1.30 (2s, 6H, $CMe_2$); $^{13}C$ NMR (125.7 MHz, $CDCl_3$) δ 140.3 (NCN), 143.5–127.0 (Ph), 111.7 (*C*$Me_2$), 104.8 (C-1), 86.7 (*C*$Ph_3$), 82.1 (C-2, C-3), 80.5 (C-4), 71.7 (*C*$H_2$Ph), 63.5 (C-6), 57.6 (C-5), 26.7, 26.2 (C*Me*$_2$); FABMS: *m/z* 675 (100, $[M+Na]^+$), 653 (30, $[M+H]^+$). Anal. Calcd for $C_{42}H_{40}N_2O_5$: C, 77.27; H, 6.17; N, 12.25. Found: C, 77.34; H, 6.15; N, 4.29.

**3.1.4. 3-*O*-Benzyl-5-deoxy-1,2-*O*-isopropylidene-5-(*N*′-phenylureido)-6-*O*-trityl-α-D-glucofuranose (15).** To a solution of carbodiimide **14** (423 mg, 1.2 mmol) in acetone–water (2:1, 18 mL), TFA (0.2 mL) was added. The reaction mixture was stirred at room temperature for 18 h, then the solvents were evaporated under vacuum and the resulting residue was purified by column chromatography (1:6 EtOAc–petroleum ether→EtOAc) to give **15** (296 mg, 70%). $R_f$=0.14 (1:4 EtOAc–petroleum ether); $[\alpha]_D$=−5.8 (*c* 1.04, $CH_2Cl_2$); IR (KBr) $\nu_{max}$ 3393, 3059, 2963, 1657, 1545, 1445, 1379, 1213, 1092 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.40–7.00 (m, 20H, Ph), 6.65 (bs, 1H, N′H), 5.92 (d, 1H, $J_{1,2}$=3.8 Hz, H-1), 5.29 (d, 1H, $J_{5,\ NH}$=7.8 Hz, NH), 4.59 (dd, 1H, $J_{4,5}$=7.4 Hz, $J_{3,4}$=3.1 Hz, H-4), 4.54 (d, 1H, H-2), 4.38 (d, 1H, $^2J_{H,H}$=11.3 Hz, C*H*Ph), 4.33 (m, 1H, H-5), 4.02 (d, 1H, C*H*Ph), 3.64 (d, 1H, H-3), 3.43 (dd, 1H, $J_{6a,6b}$=9.5 Hz, $J_{5,6a}$=4.5 Hz, H-6a), 3.09 (dd, 1H, $J_{5,6b}$=3.6 Hz, H-6b), 1.52, 1.27 (2s, 6H, $CMe_2$); $^{13}C$ NMR (125.7 MHz, $CDCl_3$) δ 156.4 (CO), 146.9–120.4 (Ph), 111.7 (*C*$Me_2$), 104.6 (C-1), 86.6 (*C*$Ph_3$), 82.3 (C-2), 82.0 (C-3), 79.0 (C-4), 71.9 (*C*$H_2$Ph), 63.4 (C-6), 52.1 (C-5), 26.7, 26.2 (C*Me*$_2$); FABMS: *m/z* 693 (40, $[M+Na]^+$). Anal. Calcd for $C_{42}H_{42}N_2O_6$: C, 75.20; H, 6.31; N, 4.17. Found: C, 75.12; H, 6.28, N, 4.13.

**3.1.5. (1*S*,2*R*,3*S*,4*R*,5*R*)-2,4-Diacetoxy-3-benzyloxy-*N*-(*N*′-phenylcarbamoyl)-6-oxa-nor-tropane (18).** A solution of urea **15** (354 mg, 0.78 mmol) in a mixture of TFA–$H_2O$ (9:1, 4 mL) was stirred at 0 °C for 30 min. The solvent was then removed under vacuum and the residue was coevaporated several times with water. Conventional acetylation of the resulting residue by treatment with 1:1 $Ac_2O$–pyridine

(3 mL) at room temperature for 6 h and purification of the crude reaction mixture by column chromatography (1:3 EtOAc–petroleum ether) gave **18** (266 mg, 75%). $R_f$=0.54 (1:1 EtOAc–petroleum ether); $[\alpha]_D$=+46.3 (*c* 1.08, $CH_2Cl_2$); IR (KBr) $\nu_{max}$ 3030, 2963, 1746, 1661, 1601, 1537, 1373, 1225, 1094 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.42–7.08 (m, 10H, Ph), 5.67 (d, 1H, $J_{4,5}$=1.6 Hz, H-5), 5.08 (ddd, 1 H, $J_{2,3}$=8.3 Hz, $J_{1,2}$=4.1 Hz, $J_{2,7b}$=1.1 Hz, H-2), 4.89 (dd, 1H, $J_{3,4}$=8.3 Hz, H-4), 4.71 (t, 1H, $J_{1,7b}$= 4.1 Hz, H-1), 4.67 (s, 2H, C$H_2$Ph), 4.00 (d, 1H, $J_{7a,7b}$= 8.2 Hz, H-7a), 3.92 (t, 1H, H-3), 3.74 (ddd, 1H, H-7b), 2.09, 2.04 (2s, 6H, *Me*CO); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ 170.6, 169.7 (CO ester), 153.7 (CO urea), 137.8–123.8 (Ph), 85.6 (C-5), 77.9 (C-3), 77.0 (C-4), 74.5 (*C*$H_2$Ph), 73.1 (C-2), 65.6 (C-7), 54.6 (C-1), 20.8, 20.7 (*Me*CO); FABMS: *m/z* 477 (100, $[M+Na]^+$). Anal. Calcd for $C_{24}H_{26}N_2O_7$: C, 63.43; H, 5.77; N, 6.16. Found: C, 63.33; H, 5.63; N, 6.14.

**3.1.6. (1*S*,2*R*,3*R*,4*R*,5*R*)-3,4-Diacetoxy-2-hydroxy-*N*-(*N*′-phenylcarbamoyl)-6-oxa-nor-tropane (19).** A solution of **18** (238 mg, 0.52 mmol) in EtOH (7 mL) was hydrogenated at atmospheric pressure for 1 h using 10% $Pd(OH)_2$ (253 mg) as heterogeneous catalyst. The suspension was filtered through Celite, concentrated and the resulting residue was dissolved in $CH_2Cl_2$ (2 mL) and cooled at −25 °C. Trifluoromethanesulfonic anhydride (0.66 mmol, 0.12 mL) and pyridine (0.1 mL) were added under $N_2$. The reaction mixture was stirred for 30 min at the same temperature, diluted with $CH_2Cl_2$ (5 mL), washed with saturated aq $NaHCO_3$ (4 mL), dried ($MgSO_4$), and concentrated. The resulting crude triflate ester was dissolved in DMF (1.4 mL), $NaNO_2$ (168 mg, 2.52 mmol, 5 equiv) was added and the reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the resulting residue was dissolved in $CH_2Cl_2$ and washed with water. The organic extract was dried ($MgSO_4$) and concentrated to give a solid, which was purified by column chromatography (1:1 EtOAc–petroleum ether) to furnish **19** (130.7 mg, 69%). $R_f$=0.29 (2:1 EtOAc–petroleum ether); $[\alpha]_D$=+26.7 (*c* 1.05, $CH_2Cl_2$). IR (KBr) $\nu_{max}$ 3370, 3061, 2963, 1748, 1627, 1603, 1537, 1445, 1380, 1260, 1094 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.53–7.03 (m, 5H, Ph), 5.66 (s, 1H, H-5), 5.48 (t, 1H, $J_{2,3}$=$J_{3,4}$=2.5 Hz, H-3), 5.10 (t, 1H, $J_{1,2}$=2.5 Hz, H-2), 4.59 (t, 1H, $J_{1,7b}$= 2.5 Hz, H-1), 4.22 (d, 1H, $J_{7a,7b}$=4.7 Hz, H-7a), 3.89 (d, 1H, H-4), 3.64 (dd, 1H, H-7b), 2.13, 1.99 (2s, 6H, *Me*CO); $^{13}C$ NMR (125.7 MHz, $CDCl_3$) $\delta$ 170.6, 169.4 (CO ester), 154.5 (CO urea), 138.6–123.4 (Ph), 88.1 (C-5), 69.4 (C-4), 68.5 (C-3), 67.8 (C-2), 65.3 (C-7), 54.0 (C-1), 20.7, 20.5 (*Me*CO); FABMS: *m/z* 387 (100%, $[M+Na]^+$). HRFABMS: calculated for $C_{17}H_{21}N_2O_7$ (365.1348). Found: 365.1339. Anal. Calcd for $C_{17}H_{20}N_2O_7$: C, 56.04; H, 5.53; N, 7.69. Found: C, 55.83; H, 5.47; N, 7.57.

**3.1.7. (1*S*,2*R*,3*R*,4*R*,5*R*)-2,3,4-Triacetoxy-*N*-(*N*′-phenylcarbamoyl)-6-oxa-nor-tropane (20).** Conventional acetylation of **19** (200 mg, 0.547 mmol) with 1:1 $Ac_2O$–pyridine at room temperature for 6 h and purification of the crude reaction mixture by column chromatography gave **20** (199 mg, 90%). $R_f$=0.33 (1:1 EtOAc–petroleum ether); $[\alpha]_D$=+41.0 (*c* 1.0, $CH_2Cl_2$); IR (KBr) $\nu_{max}$ 3310, 3090, 2905, 1751, 1653, 1541, 1445, 1377, 1231, 1092 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.40–7.03 (m, 5H, Ph), 5.67 (t, 1H, $J_{2,3}$=$J_{3,4}$=4.9 Hz, H-3), 5.65 (d, 1H, $J_{4,5}$=1.6 Hz, H-5), 5.15 (t, 1H, $J_{1,2}$=4.9 Hz, H-2), 5.00 (dd, 1H, H-4), 4.59 (t, 1H, $J_{1,7b}$=4.9 Hz, H-1), 4.40 (d, 1H, $J_{7a,7b}$=7.8 Hz, H-7a), 3.79 (dd, 1H, H-7b), 2.15, 2.05, 2.02 (3s, 9H, *Me*CO); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ 170.2, 170.1, 169.3 (CO ester), 153.4 (CO urea), 137.8–119.9 (Ph), 85.8 (C-5), 70.3 (C-4), 67.5 (C-2), 66.5 (C-3), 66.0 (C-7), 54.3 (C-1), 20.6, 20.5, 20.4 (*Me*CO); FABMS: *m/z* 429 (100%, $[M+Na]^+$). Anal. Calcd for $C_{19}H_{22}N_2O_8$: C, 56.15; H, 5.46; N, 6.89. Found: C, 56.12; H, 5.45; N, 6.89.

**3.1.8. 5-Deoxy-5-(*N*′-phenylureido)-L-talofuranose and methyl 5-deoxy-5-(*N*′-phenylureido)-α-L-talofuranoside (10 and 21).** To a solution of **20** (100 mg, 0.246 mmol) in dry MeOH (5 mL) methanolic NaOMe (1 M, 0.1 equiv per mole of acetate) was added and the reaction mixture was stirred at room temperature for 30 min. Neutralization with Amberlite IR-120 ($H^+$) ion-exchange resin and column chromatography (EtOAc–EtOH–$H_2O$ 45:5:3) of the resulting mixture afforded, sequentially, the L-talofuranoside **21** (19.2 mg, 25%) and the L-talofuranose derivative **10** (40.4 mg, 55%). Compound **10** showed spectroscopic and physicochemical data identical to those previously reported.[14] Compound **21** had $R_f$=0.38 (EtOAc–EtOH–$H_2O$ 45:5:3); $[\alpha]_D$=−22.5 (*c* 1.0, $H_2O$); $^1H$ NMR (500 MHz, $D_2O$) $\delta$ 7.22–7.06 (m, 5H, Ph), 4.74 (s, 1H, H-1), 4.08 (dd, 1H, $J_{3,4}$=7.5 Hz, $J_{2,3}$=4.6 Hz, H-3), 3.99 (d, 1H, $J_{4,5}$= 3.3 Hz, H-4), 3.95 (m, 1H, H-5), 3.89 (d, 1H, H-2), 3.63 (dd, 1H, $J_{6a,6b}$=11.6 Hz, $J_{5,6a}$=5.7 Hz, H-6a), 3.56 (dd, 1H, $J_{5,6b}$=7.2 Hz, H-6b), 3.24 (s, 3H, OMe); $^{13}C$ NMR (75.5 MHz, $D_2O$) $\delta$ 158.2 (CO), 137.9–122.1 (Ph), 108.3 (C-1), 81.3 (C-4), 74.2 (C-2), 71.2 (C-3), 62.2 (C-6), 55.7 (OMe), 52.3 (C-5); FABMS: *m/z* 335 (100, $[M+Na]^+$). Anal. Calcd for $C_{14}H_{20}N_2O_6$: C, 53.84; H, 6.45; N, 8.97. Found: C, 53.71; H, 6.11; N, 8.87.

**3.1.9. (1*S*,2*R*,3*R*,4*R*,5*R*)-*N*-(*N*′-Phenylcarbamoyl)-2,3,4-trihydroxy-6-oxa-nor-tropane (8).** To a solution of **20** (77 mg, 0.211 mmol) in dry MeOH (5 mL), methanolic NaOMe (1 M, 0.1 equiv per mole of acetate) was added. The reaction mixture was stirred at room temperature for 30 min, then neutralized with solid $CO_2$, and concentrated. The resulting residue was purified by column chromatography (45:5:3 EtOAc–EtOH–$H_2O$) to give **8** (51 mg, 86%). $R_f$=0.53 (45:5:3 EtOAc–EtOH–$H_2O$); $[\alpha]_D$=+51.7 (*c* 1.0, $H_2O$); $^1H$ NMR (500 MHz, $D_2O$) $\delta$ 7.36–7.15 (m, 5H, Ph), 5.59 (d, 1H, $J_{4,5}$=1.8 Hz, H-5), 4.46 (dd, 1H, $J_{1,7b}$=5.2 Hz, $J_{1,2}$=4.1 Hz, H-1), 4.32 (d, 1H, $J_{1a,1b}$=7.9 Hz, H-7a), 4.11 (dd, 1H, $J_{3,4}$=5.0 Hz, $J_{2,3}$=4.2 Hz, H-3), 3.98 (t, 1H, H-2), 3.78 (dd, 1H, H-4), 3.63 (dd, 1H, H-7b); $^{13}C$ NMR (125.7 MHz, $D_2O$) $\delta$ 158.2 (CO), 138.0–123.9 (Ph), 87.8 (C-5), 70.7 (C-4), 70.1 (C-3), 68.8 (C-3), 66.4 (C-7), 57.4 (C-1); FABMS: *m/z* 303 (100%, $[M+Na]^+$). Anal. Calcd for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99. Found: C, 55.149; H, 5.58; N, 9.77.

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