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Synthesis and NMR experiments of (4,5,6-^{13}C)-deoxymannojirimycin. A new entry to ^{13}C-labeled glycosidase inhibitors

Caterina Murruzzu,[a] Mònica Alonso,[a] Angeles Canales,[b] Jesus Jiménez-Barbero[b,*] and Antoni Riera[a,*]

[a]*Unitat de Recerca en Síntesi Asimètrica (URSA-PCB), Institute for Biomedical Research (IRB) and Departament de Química Orgànica, Universitat de Barcelona, Parc Científic de Barcelona c/Josep Samitier, 1-5, 08028 Barcelona, Spain*
[b]*Centro de Investigaciones Biológicas, CSIC, Madrid, Spain*

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Abstract—The synthesis of (4,5,6-^{13}C)-deoxymannojirimycin is described. The route employed is based on Sharpless asymmetric epoxidation of (1,2,3-^{13}C)(*E*)-2,4-pentadien-1-ol and uses ring-closing metathesis as a key step. The labeled compound may be easily used for protein-binding experiments using NMR spectroscopic methods.

Keywords: Glycosidase inhibitors; Azasugars; Labeled compounds; Sharpless epoxidation

1. Introduction

As glycosidases play a crucial role in many significant biological processes, they are promising therapeutic targets for new treatments of diseases such as diabetes, AIDS and cancer.[1] Most glycosidase inhibitors contain polyhydroxylated indolizines, piperidines or pyrrolidines. These motifs have two key structural features in common: a basic nitrogen, which at physiological pH mimics the positive charge formed during the hydrolysis of the glycosidic bond and an array of conformationally restricted hydroxyl groups that fit into the enzyme active site.[2] Nevertheless, the active site interactions between glycosidases and their inhibitors remain poorly understood, thus complicating the design of new, more selective inhibitors.

NMR is the most valuable tool to monitor receptor–ligand interactions. However, NMR studies of inhibitor–enzyme complexes are extremely difficult without the use of ^{13}C-labeled inhibitors to increase the sensitivity of the NMR experiments. Surprisingly, very few examples of ^{13}C-labeled derivatives of glycosidase inhibitors can be found in the literature; to the best of our knowledge, only deuterated or tritiated compounds[3] and 1-^{13}C-1-deoxynojirimycin[4] (with only one labeled atom) have been described.

Although a plethora of syntheses of glycosidase inhibitors have been reported, most of them are not general and are based on natural product transformations. Some years ago, we[5] and others[6–8] envisaged that oxazolidinylpiperidine **1** could be a key intermediate for the synthesis of many glycosidase inhibitors. Ciufolini et al.[6] pioneered the field by transforming **1** (prepared from furyl glycine) into 1-deoxymannojirimycin **2**. Katsumura and co-workers[7] prepared **1** from glycidol and converted it into **2**, 1-deoxyaltrojirimycin **3**, and 1-deoxygalactostatin **4**. Our group synthesized **1** via Sharpless epoxidation and converted it into 1-deoxymannojirimycin **2**, swainsonine **5** and epi-swainsonine **6**.[9] Giannis and co-workers[10] have proved the potential of this class of compounds as inhibitors for other

* Corresponding authors. E-mail: ariera@pcb.ub.es

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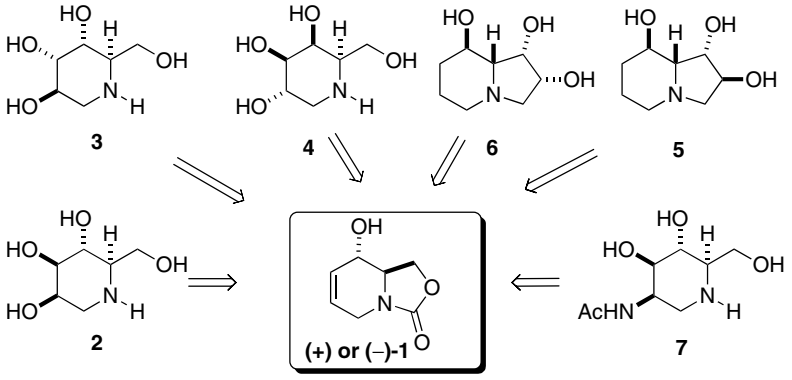


Figure 1. Enzyme inhibitors synthesized from **1**.

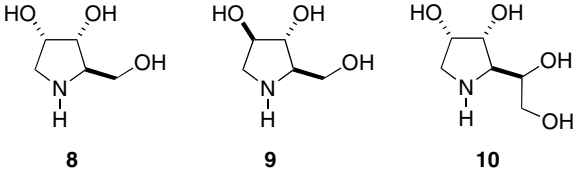


Figure 2. Polyhydroxylated pyrrolidines prepared from 2,4-pentadien-1-ol.

enzymes of carbohydrate biosynthesis by synthesizing reversible inhibitors of UDP-*N*-acetylglucosamine 2-epimerase such as **7** from **1** (Fig. 1).

Our synthesis[5,9] of **1** was based on the Sharpless asymmetric epoxidation[11] of (*E*)-2,4-pentadien-1-ol, and used ring-closing-metathesis[12] as a key step.[13] It is the shortest synthesis of **1** reported to date; it is very high yielding and can selectively afford either enantiomer of the product if the tartrate used in the epoxidation is simply changed. Moreover, the same starting material was used in the preparation of polyhydroxylated pyrrolidines **8**–**10** (Fig. 2).[14]

Therefore, by preparing ^{13}C-labeled 2,4-pentadien-1-ol **11**, we could gain synthetic access to ^{13}C-labeled derivatives of **2**–**10** in any absolute configuration. We describe herein the preparation of (1,2,3-^{13}C)-**11**, the key intermediate (1,8,8a-^{13}C)-**1** and its transformation into (4,5,6-^{13}C)-1-deoxymannojirimycin **2** (Fig. 3).

2. Results and discussion

2.1. Synthesis

To design the synthesis of ^{13}C-labeled glycosidase inhibitors, we first looked at all commercially available labeled starting materials. We determined that ^{13}C-propargyl alcohol would be the most useful compound, as a Sonogashira coupling[15] with allyl bromide followed by reduction could provide the desired unsaturated allylic alcohol **11** (Fig. 3).

As expected, Sonogashira coupling of propargyl alcohol with vinyl bromide afforded enyne **12** in good yield. The optimized reaction conditions comprised diethyl ether as the solvent, diethylamine as the base, and $Pd(CH_3CN)_2Cl_2$ as the palladium source. The enyne was difficult to isolate on small scale owing to its volatility. Therefore, the crude product was directly used in the next step. Reduction of enyne **12** with $LiAlH_4$ or DIBAL gave a mixture of compounds due to substantial conjugate addition. Fortunately, these side products could be minimized by using a solution of Red-Al.[16] Allyl alcohol **11** was thus obtained in 55% overall yield. With

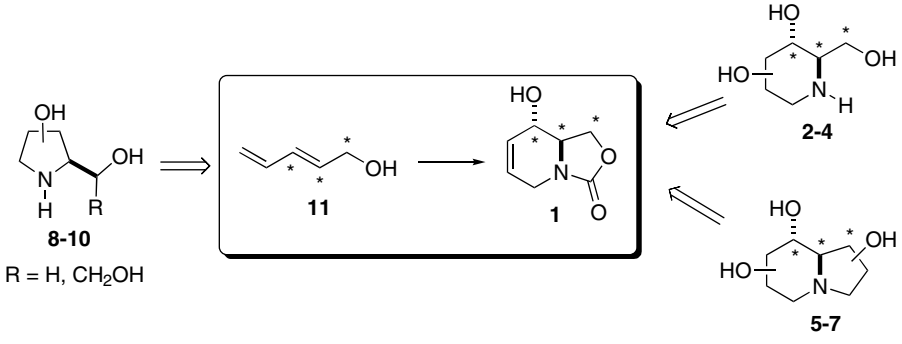
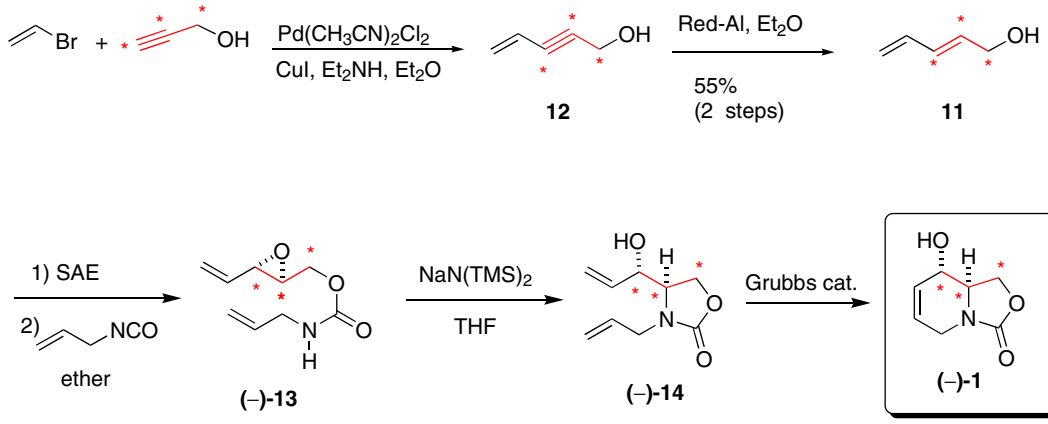
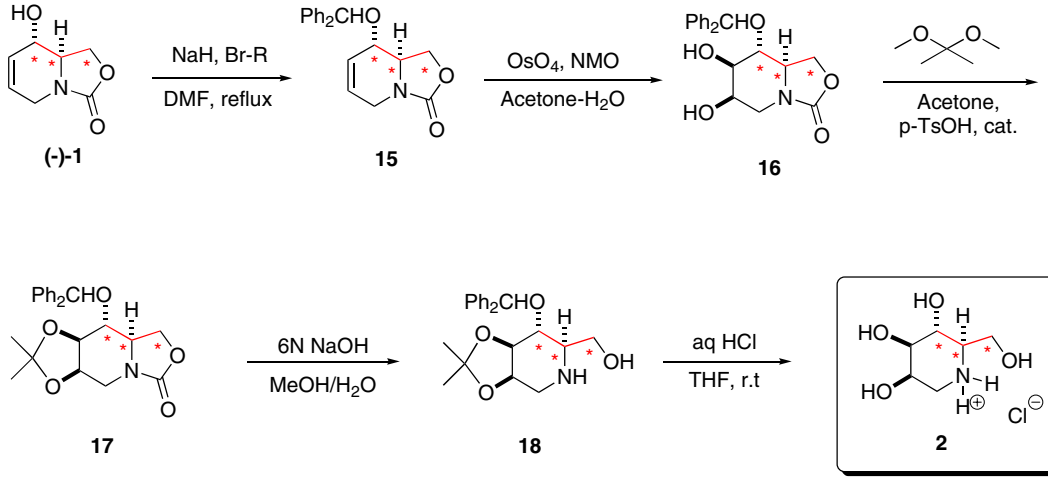


Figure 3. General retrosynthetic analysis.



Scheme 1.



Scheme 2.

(1,2,3-^{13}C)-2,4-pentadien-1-ol (**11**) in hand, we followed our reported procedure to the desired carbamate. The crude product from the Sharpless epoxidation was reacted with allyl isocyanate/triethylamine in diethyl ether at reflux, providing allyl carbamate **13** in 50% yield for the two steps. The product was then subjected to intramolecular ring-opening by sodium bis(trimethylsilyl)amide in ether, providing the desired oxazolidinone **14** in 90% yield. As expected, ring-closing metathesis of **14** ran smoothly using 5 mol % of Grubbs's catalyst[17] in dichloromethane at room temperature, affording the target ^{13}C-oxazolidinylpiperidine **1** in excellent yield (Scheme 1).

The ^{13}C-labeled key intermediate (−)-**1** was then used as the starting material in the synthesis of (4,5,6-^{13}C)-deoxymannojirimycin **2** by following our previously reported procedure. The synthesis proceeded smoothly through intermediates **15**–**18** as shown in Scheme 2.

2.2. NMR experiments

Once compound **2** was available, standard NMR methods were used to assess its binding to protein receptors. As a test model, jack bean α-mannosidase was employed, because DMJ has been shown to act as a moderate inhibitor of this enzyme.[18]

The mixture in the NMR tube of unlabeled DMJ and the enzyme (1:20 molar ratio) gives rise to a complex NMR spectrum in which the protein signals strongly overlap with the inhibitor resonances (Fig. 4). Line broadening of the inhibitor signals is evident, thus indicating its binding to the enzyme. However, under these experimental conditions, regular experiments (STD,[19] trNOESY[20]) to assess binding are rather difficult to perform and, indeed, did not allow us to extract definitive conclusions on interactions, due to the low quality (overlapping) of the obtained spectra (data not shown).

In contrast, the use of (4,5,6-^{13}C)-deoxymannojirimycin allowed us to monitor binding easily, making use of the ^{13}C-labels. The HSQC experiment of **2** only shows the cross peaks for the C4, C5, and C6 proton–carbon pairs (Fig. 5A). Obviously, the proton-decoupled 1D ^{13}C NMR (Fig. 5B) only shows the three signals, with splittings due to the ^{13}C–^{13}C couplings.

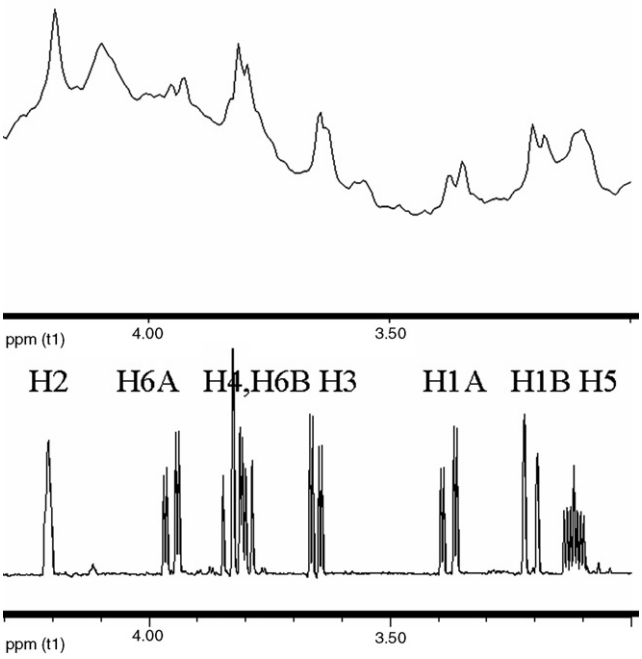


Figure 4. Bottom: 1D ^{1}H NMR spectrum (500 MHz) of unlabeled DMJ in D_2O and 298 K. Top: Unlabeled DMJ in D_2O in the presence of α-mannosidase in a 20:1 inhibitor:enzyme molar ratio.

The intrinsic high sensitivity of the HSQC experiment allows us to monitor binding easily. Addition of a 5% molar ratio of α-mannosidase to the NMR tube containing **2** leads to broadening of the HSQC cross peaks (Fig. 5C). Although this fact indicated binding (due to the exchange process conducting to faster T2 relaxation), STD experiments are the most robust method to monitor binding. The presence of binding permitted the use of STD-HSQC experiments as described by Vogtherr and Peters.[21] Indeed, the signals corresponding to the labelled ^{1}H–^{13}C pairs appear in the STD-HSQC with different intensities, indicating their different proximities to the protein protons. Quantitative analyses of this experiment are beyond the scope of this article, but the experiment with the labelled molecule unequivocally permits us to detect the interaction of the inhibitor with the enzyme. Moreover, a HMQC-trNOESY experiment (Fig. 6) also permitted to extract conformational information in the bound state.[22] Negative cross peaks (same sign as diagonal peaks) were obtained for DMJ **2** in the presence of α-mannosidase, in contrast to those obtained for free DMJ (small molecule, positive NOEs[23]). Again, the quantitative analysis of the conformational information contained in the cross peaks of this experiment is beyond the scope of this article, but Figure 6 shows that information on binding features may be used when labeled compounds are used.

In summary, we have described the first synthesis of (4,5,6-^{13}C)-deoxymannojirimycin (**2**). Because the present approach relies on a key intermediate (**1**) that has been used in the preparation of several glycosidase inhibitors, an efficient synthesis of many ^{13}C labeled biologically active compounds is now accessible. Moreover, we have shown that the obtained compounds may be easily used to monitor ligand binding to receptors by simple NMR methods. The application of this methodology to other systems is currently underway.

3. Experimental section

3.1. General methods

Because the NMR spectra of all compounds in their unlabeled form are known, only the signals for ^{13}C-labeled atoms are given. ^{13}C NMR spectra for characterization purposes were recorded on a Varian Mercury 400 spectrometer, obtained at 100.6 MHz in $CDCl_3$ and referenced to the solvent signal. The remaining physical and spectroscopic properties of the labeled analogs are consistent with literature reports. Chromatographic separations were carried out using SiO_2 (70–230 mesh) pre-treated with NEt_3 (2.5% v/v). ^{13}C-enriched (99%) propargyl alcohol with a chemical purity of 98% was obtained from Cambridge Isotope Laboratories.

3.2. NMR spectroscopy

The other NMR experiments were performed at 500 MHz on Bruker AVANCE spectrometers, using temperatures between 298 and 318 K with a 1 mM concentration of **2**. For the experiments with the free inhibitor, the corresponding compound was dissolved in D_2O. The ge-HSQC experiments were performed using the standard sequence provided by the manufacturer (hsqcetgp). α-Mannosidase was purchased from SIGMA. STD and TRNOE experiments were performed at 500 MHz by simply adding a HSQC module to detect the proton signals coupled to the ^{13}C labels. The HSQC-trNOESY experiment was performed with a mixing time of 250 ms, for a 20:1 molar ratio of **2**:enzyme. Key NOEs were shown to exhibit the same sign as diagonal peaks. The STD–HSQC-experiments were carried out by using the method proposed by Vogtherr and Peters,[21] on the same sample described above. A time of 1.5 s was employed for the on- (−0.5 ppm) and off-resonance (50 ppm) saturation periods.

3.3. (1,2,3-^{13}C)-4-Penten-2-yn-1-ol (12)

To a suspension of $Pd[(CH_3CN)_2Cl_2]$ (0.22 g, 0.84 mmol) and CuI (0.3 g, 1.69 mmol) in 5 mL of Et_2O was added Et_2NH (3.5 mL, 33.9 mmol). After 10 min vinyl bromide (16.95 mL, 16.95 mmol) and ^{13}C-propargyl alcohol (1 g, 16.95 mmol) were added. The

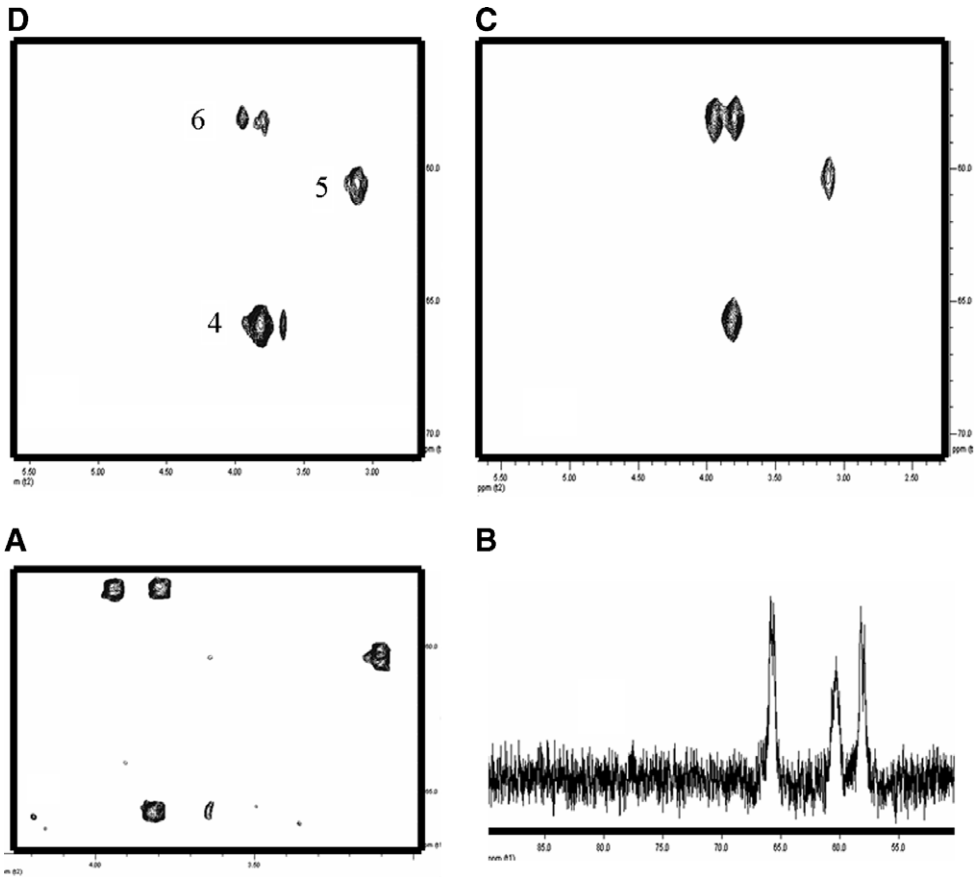


Figure 5. (A) ^{1}H–^{13}C HSQC spectrum (500 MHz) of labelled DMJ (**2**) in D_2O and 298 K. (B) 1D ^{13}C NMR spectrum (125 MHz) of labeled DMJ (**2**) in D_2O and 298 K. (C) ^{1}H–^{13}C HSQC spectrum (500 MHz) of labelled DMJ (**2**) in D_2O in the presence of α-mannosidase in a 20:1 inhibitor:enzyme molar ratio. (D) STD-HSQC spectrum (500 MHz) of labelled DMJ (**2**) in D_2O in the presence of α-mannosidase in a 20:1 inhibitor:enzyme molar ratio. A time of 1.5 s was employed for the on- (−0.5 ppm) and off-resonance (50 ppm) saturation periods.

reaction mixture was stirred at room temperature for 3 h and then quenched by the addition of 10 mL aqueous saturated NH_4Cl, filtered, and extracted with Et_2O (3×10 mL). The combined organic phases were dried and directly used in the next step. ^{13}C NMR (100 MHz, $CDCl_3$): δ 88.4 (dd, $J = 70.9$, 175.7 Hz, C), 83.6 (dd, $J = 14.4$, 175.7 Hz, C), 51.1 (dd, $J = 14.4$, 70.9 Hz, CH_2) ppm.

3.4. (1,2,3-^{13}C)-2,4-Pentadien-1-ol (11)

To a solution of 4-penten-2-yn-1-ol (1.47 g, 16.95 mmol) in Et_2O at −20 °C was carefully added a solution of Red-Al (8.32 mL, 25.42 mmol) in toluene. The reaction mixture was stirred at room temperature for 3 h, cooled to −20 °C, and quenched by the addition of a 1 M solution of HCl (10 mL). After 30 min, the salts were filtered, and the aqueous phase was extracted with Et_2O (3×15 mL). The combined organic phases were dried, and the solvent was removed at atmospheric pressure. The product was purified by column chromatography (pentane–Et_2O) to afford **11** (0.77 g, 55%). ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.7 (dd, $J = 39.3$, 70.7 Hz, CH), 131.7 (dd, $J = 8.7$, 70.7 Hz, CH), 63.2 (dd, $J = 8.7$, 39.2 Hz, CH_2).

3.5. (1,2,3-^{13}C)-(2*S*,3*S*)-*N*-Allyl-2,3-epoxypentylcarbamate (13)

To a round-bottomed flask equipped with a magnetic stir-bar was added 0.32 g of 4 Å powdered, activated molecular sieves and 20 mL of dry CH_2Cl_2. The flask was cooled to −20 °C, and L-(+)-diisopropyl tartrate (0.28 g, 1.19 mmol) and $Ti(O\text{-}^{i}Pr)_4$ (0.27 mL, 0.92 mmol) were then added sequentially. The reaction mixture was stirred at −20 °C, TBHP (6.13 mL, 18.4 mmol) was added, and after 1 h, the 2,4-pentadien-1-ol (0.77 g, 9.2 mmol) was added. The mixture was stirred for an additional 3 h at −20 °C and then quenched by the addition of PPh_3 (3.0 g, 11.4 mmol), citric acid (0.1 g, 0.52 mmol), 10 mL of acetone and 10 mL of Et_2O. After 30 min the solution was filtered.

To a solution of (2*S*,3*S*)-2,3-epoxypent-4-en-1-ol (9.2 mmol) in Et_2O (15 mL) was added NEt_3 (1.89 mL, 25.77 mmol). The resulting solution was stirred at room temperature. After 30 min, allyl isocyanate (1.5 mL,

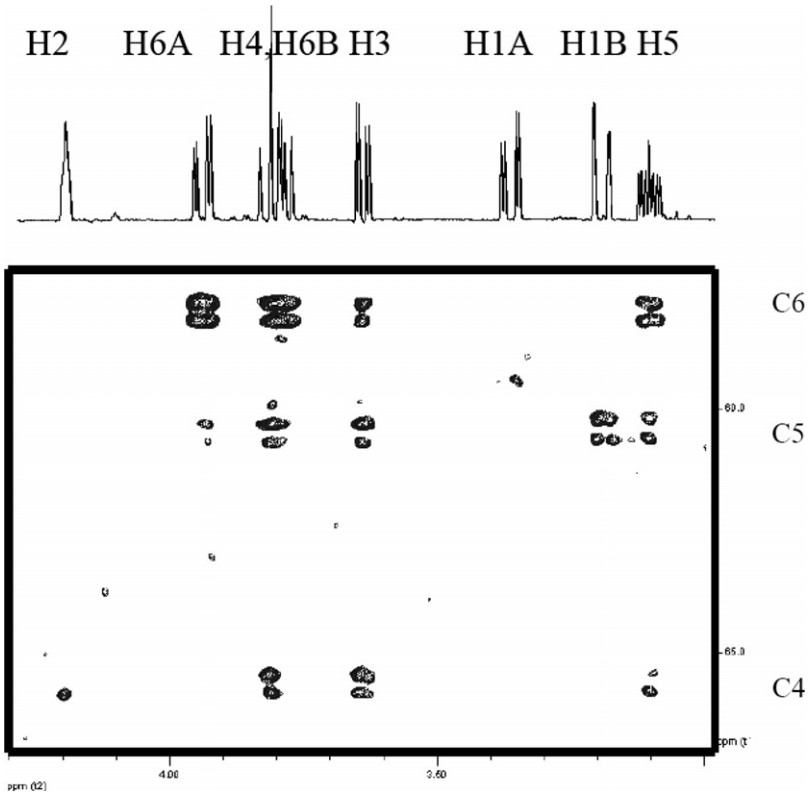


Figure 6. HSQC-trNOESY spectrum (500 MHz, mixing time, 250 ms) of labeled DMJ (**2**) in D_2O in the presence of α-mannosidase in a 20:1 inhibitor:enzyme molar ratio.

19.2 mmol) was added, and the solution was stirred at 65 °C until TLC showed complete conversion of the starting material (4 h). The reaction mixture was diluted with Et_2O and quenched by the addition of a saturated aqueous solution of NH_4Cl (15 mL). A standard extractive work-up followed by column chromatography (hexane/EtOAc) gave **13** as a colorless oil (0.7 g, 50%). ^{13}C NMR (100 MHz, $CDCl_3$): δ 64.6 (d, $J = 48.4$ Hz, CH), 57.3 (dd, $J = 28.2$, 48.4 Hz, CH), 56.3 (d, $J = 28.2$ Hz, CH_2) ppm.

3.6. (4,5,1′-^{13}C) (4*R*)-4-[(1′*S*)-1′-Hydroxy-2′-propenyl]-3-allyl-1,3-oxazolidin-2-one (14)

A solution of sodium bis(trimethylsilyl)amide (0.76 g, 4.17 mmol) in anhydrous THF (5 mL) was added to a solution of (2*S*,3*S*)-2,3-epoxypentyl-*N*-allylcarbamate (0.7 g, 3.80 mmol) in anhydrous THF (5 mL). The resulting mixture was stirred at room temperature until TLC showed reaction completion (30 min). The solution was quenched by the addition of a saturated aqueous solution of NH_4Cl (10 mL) and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried and evaporated, and the crude product was purified by column chromatography (hexane–EtOAc) to yield **14** as a white solid (0.63 g, 90%). ^{13}C NMR (100 MHz, $CDCl_3$): δ 68.4 (d, $J = 39.6$ Hz, CH), 61.5 (d, $J = 33.5$ Hz, CH_2), 57.5 (dd, $J = 33.5$, 39.6 Hz, CH) ppm.

3.7. (1,8,8a-^{13}C)-(8*S*,8a*R*)-8-Hydroxy-1,5,8,8a-tetrahydro-oxazolidin[3,4-*a*]-piridin-3-one (1)

A solution of Grubbs's catalyst (0.13 g, 5 mol %, 0.16 mmol) in anhydrous CH_2Cl_2 (20 mL) was added to a solution of **14** (0.6 g, 3.28 mmol) in CH_2Cl_2 (20 mL). The resulting mixture was stirred for 1 h, at which point the reaction was complete. The black solution was then concentrated and the resulting residue purified by chromatography (hexane–EtOAc) to afford **1** as a black solid (0.45 g, 90%). ^{13}C NMR (100 MHz, $CDCl_3$): δ 67.72 (d, $J = 40.4$ Hz, CH), 67.67 (d, $J = 33.5$ Hz, CH_2), 56.6 (dd, $J = 33.5$, 40.4 Hz, CH) ppm.

3.8. (1,8,8a-^{13}C)-(8*S*,8a*R*)-8-Diphenylmethoxy-1,5,8,8a-tetrahydro-oxazolidin[3,4-*a*]-pyridin-3-one (15)

To a suspension of NaH (0.08 g, 3.19 mmol) in anhydrous DMF (5 mL) at 0 °C was slowly added a solution of **1** (0.45 g, 2.9 mmol) in DMF (5 mL). After 30 min a solution of diphenylmethyl bromide (1.15 g, 4.64 mmol) in DMF (10 mL) was added, and the reaction mixture was stirred for 24 h. The solution was diluted with

Et_2O (15 mL) and quenched by the addition of H_2O (10 mL). The combined organic phases were dried and evaporated. The crude was purified by column chromatography (hexane–EtOAc) to yield **15** as a yellow oil (0.74 g, 80%). ^{13}C NMR (100 MHz, $CDCl_3$): δ 73.2 (d, $J = 41.4$ Hz, CH), 67.6 (d, $J = 33.6$ Hz, CH_2), 54.8 (dd, $J = 33.6$, 41.4 Hz, CH) ppm.

3.9. (1,8,8a-^{13}C)-(6*R*,7*R*,8*S*,8a*R*)-6,7-Dihydroxy-8-diphenylmethoxy-1,5,8,8a-tetrahydro-oxazolidin[3,4-*a*]-pyridin-3-one (16)

To a solution of **15** (0.7 g, 2.18 mmol) and NMO (1.21 g, 4.80 mmol) in acetone (20 mL) and water (2 mL) was added a solution of OsO_4 in ^{t}BuOH (3.4 mL, 0.17 mmol, 8%). The mixture was stirred for 24 h at room temperature. Na_2SO_3 (0.7 g, 5.55 mmol) was then added, and the mixture was stirred for 2 h. A standard extractive work-up followed by column chromatography (CH_2Cl_2–MeOH) gave diol **16** as a colorless syrup (0.7 g, 90%, diastereomeric ratio 12:1). ^{13}C NMR (100 MHz, $CDCl_3$): δ 77.5 (d, $J = 39.6$ Hz, CH), 66.1 (d, $J = 33.7$ Hz, CH_2), 57.2 (dd, $J = 33.7$, 39.6 Hz, CH) ppm.

3.10. (6*R*,7*R*,8*S*,8a*R*)-6,7-Diisopropylidene acetal of 8-diphenylmethoxy-hexahydro-oxazolidin[3,4-*a*]-pyridin-3-one (17)

To a solution of **16** (0.7 g, 1.97 mmol) in acetone (10 mL) was added 2,2-dimethoxypropane (0.6 mL, 4.92 mmol) and a catalytic amount of *p*-toluenesulfonic acid. After 3 h the reaction was complete as determined by TLC. The mixture was concentrated, and then purified by column chromatography (hexanes–EtOAc) to afford **17** as a white solid (0.62 g, 80%, single diastereomer). ^{13}C NMR (100 MHz, $CDCl_3$): δ 75.8 (d, $J = 41.2$ Hz, CH), 66.2 (d, $J = 33.5$ Hz, CH_2), 54.9 (dd, $J = 33.5$, 41.2 Hz, CH) ppm.

3.11. (2,3,1′-^{13}C)-(2*R*,3*S*,4*R*,5*R*)-4,5-Diisopropylidene acetal of 3-diphenylmethoxy-2-hydroxymethylpiperidine (18)

To a solution of **17** (0.6 g, 1.51 mmol) in 20 mL MeOH–H_2O (18:2) was added 6 N NaOH (5 mL, 30.2 mmol). The mixture was stirred for 15 h at 100 °C, diluted with EtOAc (10 mL) and quenched by the addition of a saturated aqueous solution of NaCl (3 × 10 mL). The combined organic phases were dried and evaporated, and the product was purified by column chromatography (CH_2Cl_2–MeOH) to yield **18** as a yellow oil (0.5 g, 88%). ^{13}C NMR (100 MHz, $CDCl_3$): δ 75.6 (d, $J = 38.9$ Hz, CH), 63.4 (d, $J = 40.4$ Hz, CH_2), 59.2 (dd, $J = 38.9$, 40.4 Hz, CH) ppm.

3.12. (4,5,6-^{13}C)-1-Deoxymannojirimycin, hydrochloride (2)

A solution of **18** (0.5 g, 1.35 mmol) in THF (8 mL) and aqueous 1 M HCl (8 mL) was stirred at room temperature for 8 h. Water and THF were then removed under vacuum, and the residue was triturated with Et_2O (3 × 5 mL) yielding hydrochloride **2** as a yellow solid (0.2 g, 74%). ^{13}C NMR (100 MHz, $CDCl_3$): δ 65.8 (d, $J = 38.9$ Hz, CH), 60.5 (t, $J = 38.9$ Hz, CH), 58.2 (d, $J = 38.9.6$ Hz, CH_2) ppm.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2007.04.018.

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