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FULL PAPER

# Chemoenzymatic synthesis of hygromycin A aminocyclitol moiety and its C2 epimer.

Dr. Gonzalo Carrau,[a] Dra. Ana Inés Bellomo,[b] Dr. Leopoldo Suescun[c] and Dr. David Gonzalez.*[a]

**Abstract:** This manuscript describes the enantioselective synthesis of the aminocyclitol moiety of the antibiotic hygromycin A in eight steps and 39% overall yield from a non-chiral starting material. The sequence made use of an initial enzymatic step to transfer chirality to an aromatic ring and was followed by selective organic chemistry transformations (oxidation, protection, azidation, hydrolysis) of the six-membered ring in order to achieve the target. The approach is also amenable to the synthesis of other related unnatural analogues as exemplified by the synthesis of the C2 epimer of the natural aminocyclitol. All the intermediates were fully characterized, and the absolute stereochemistry assigned by spectrometric methods.

## Introduction

Hygromycin A (Figure 1) is an antibiotic first isolated in 1953 from *Streptomyces hygroscopicus*,[1] that inhibits peptidyl transferase activity.[2] It exerts moderate activity against gram-positive and some gram-negative bacteria,[3] but exhibits potent activity both *in vitro*[4] and *in vivo*[4-5] against the spirochete responsible for swine dysentery. This fact encouraged a research group from Pfizer to synthesize several analogues by a semi-synthetic approach to develop new antibiotics of potential veterinary use (see[6] and references therein). To date, two total syntheses of hygromycin A have been described, the first one by Ogawa group,[7] and the second one by Donohoe et al.[8] One formal synthesis was also accomplished by Yan group,[9] and Trost group has synthesized C-2''-*epi*-hygromycin A.[10]

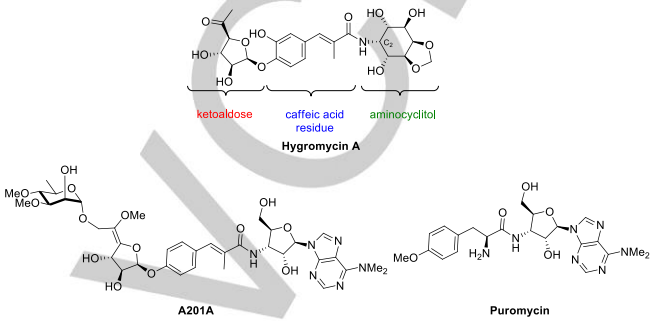
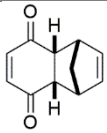



**Figure 1**: Structure of antibiotics: hygromycin A, A201A, and puromycin.

Hygromycin A structure is originated from the assembling of three independent subunits: a ketoaldose, a substituted caffeic acid residue, and an aminocyclitol moiety.[11] Both sugar and caffeic acid residues resemble those of A201A antibiotic (Figure 1), and to a lesser extent, puromycin. However, the aminocyclitol moiety is unique and does not resemble any cyclitol of the aminoglycoside antibiotics family. Hygromycin particular structure encouraged several groups to study its biosynthesis and embrace efficient synthetic approaches. To date, the literature has described five synthetic approaches towards hygromycin A aminocyclitol moiety (Table 1). Yan's group accomplished the shortest sequence to obtain the aminocyclitol core in 2012,[9] although Shashidhar group reported the sequence with best global yield.[12]

**Table 1**: Reported syntheses of the aminocyclitol moiety associated with hygromycin A.

| Year | Research group | Starting material | Steps | Global yield |
|---|---|---|---|---|
| **1989**[7, 13] | Ogawa | Methyl α-D-glucopyranoside | 18 | 2% |
| **2001**[10, 14] | Trost | Benzoquinone | 13 | 10% |
| | | (±)-conduritol B tetraacetate | 10 | 23% |
| **2005**[15] | Donohoe |  | 14 | 12% |
| **2009**[8a] | | | 15 | 20% |
| **2012**[12] | Shashidhar | *myo*-inositol | 11 | 31% |
| **2012**[9] | Yan | L-tartaric acid | 9 | 21% |

Herein we describe a chemoenzymatic approach towards hygromycin A aminocyclitol moiety, as well as its C2 epimer. The development of efficient synthetic routes, with good

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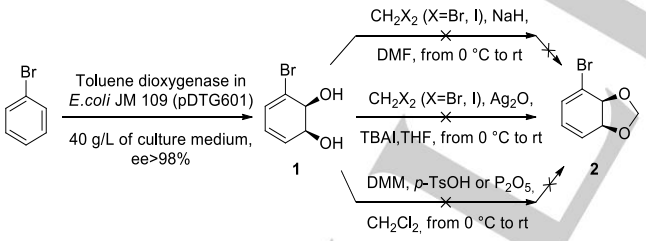
diastereomeric control while introducing new stereogenic centers, could be of great value for synthesizing hygromycin A analogues. This approach would allow exploring new compounds that cannot be synthesized by a semi-synthetic approach.

We have made use of enzymatic transformations, particularly microbial dihydroxylations[16] and, to a minor extent, yeast reductions[17] to prepare a diverse array of optically pure chiral molecules. Aminocyclitols have been preferred targets in chemoenzymatic synthesis. In particular, the dioxygenase catalyzed oxidation of aromatics have resulted in a very efficient approach to optically pure aminoinositols,[18] conduritols,[19] as well as their deoxygenated analogues and conjugates.[20] Initial efforts of Hudlicky et al. since the early nineties of the last century have developed into a full stereodivergent strategy that has been exploited around the world to render a wide diversity of this nitrogen containing polyols.[21] Recently, we have targeted the synthesis of more complicated structures bearing a cyclitol core such as pancratistatin analogues[22] and linear molecules inspired in the hygromycin A skeleton.[23]

## Results and Discussion

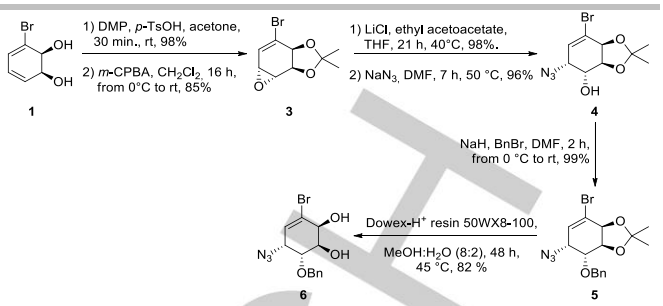
***Synthesis of L-4,5-O-methylene-2-neo-inosamine* (25).**

Bromobenzene was enzymatically dihydroxylated by means of a recombinant strain of *E. coli* (JM109 (pDTG601)), and a final concentration of 40 g/L of culture medium of enantiomerically pure (1*S*,2*S*)-3-bromo-3,5-cyclohexadiene-1,2-diol (**1**) was achieved (Scheme 1).[24] Our initial approach was to introduce the methylenedioxy group directly on compound **1**, not only to avoid aromatization but also to sterically direct the following reactions. Unfortunately, all attempts to protect the diol group led only to aromatization products and we were not able to obtain compound **2**. We, therefore, decided to modify our strategy and protect the diol function as an isopropylidene (Scheme 2).




**Scheme 1**: Attempts to introduce the methylenedioxy group on diol **1.**

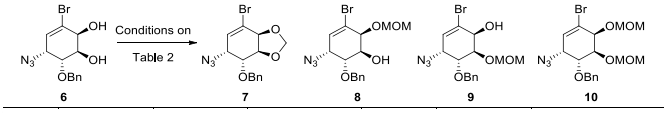
The stereoselective transformation of epoxide **3** into hydroxyazide **4** was achieved by means of a two-step sequence first described by Hudlicky et al. for the corresponding chloro-analogue of compound **3** (Scheme 2).[25] The epoxide ring was initially opened by lithium chloride. In this reaction, the presence of ethyl acetoacetate provided the optimal acidity to catalyze the reaction.[26] In a second stage, the chloride was displaced to render the desired azide **4** with overall retention of configuration. Then the remaining hydroxyl group was protected as the benzyl ether **5** and the acetonide group was deprotected to render diol **6**, which is ready to introduce the methylenedioxy group (Scheme 2).




**Scheme 2**: Functionalization of the electron-richer olefin.

Conduritol **6** was completely resistant to acetalization under basic conditions. The diol was unreactive from 0 °C to room temperature and completely decomposed upon warming up the reaction (Table 2, entries 1-5). On the other hand, the use of silver oxide under neutral conditions to enhance the electrophilicity of the dihalomethane (entries 6-8) led to the isolation of the desired product, but only in 10% yield (entry 6). Much better results were obtained for the acid-catalyzed acetalization with dimethoxymethane (DMM) as electrophile (entries 9-14). Although *p*-TsOH did not promote the reaction at room temperature even using a vast excess of DMM (entry 9), the reaction did take place under reflux in dichloromethane and yielded the desired ketal **7** in 91% yield as the only product (entry 11). Along the study we observed that ketals **8**, **9** and **10** were formed if only moderate excess (1,5 fold excess) of DMM was used, but they were all converted to compound **7** under refluxing temperature (entries 13 and 14).

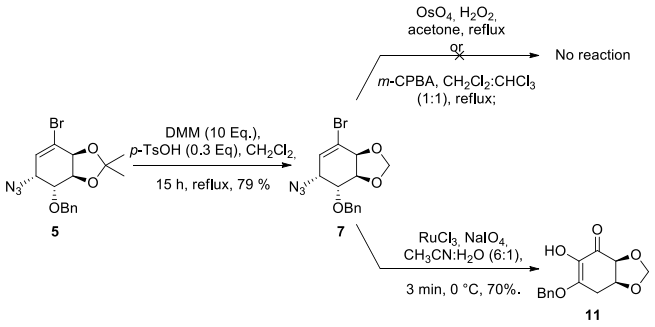
**Table 2.** Protection of azido conduritol derivative **6**.




| Entry | Reagent (eq) | Catalyst (Eq) | Reaction temperature (°C) | Solvent | Reaction time (h) | Product (yield) |
|---|---|---|---|---|---|---|
| 1 | $CH_2I_2$ (5) | NaH | 0 - rt | DMF | 7 | **7** (trace) |
| 2 | $CH_2Br_2$ (3.4) | NaH | 0 - rt | DMF | 19 | Recovered sm |
| 3 | $CH_2Br_2$ (3.4) | NaH | 40 - 85 | DMF | 11 | Decomposition |
| 4 | $CH_2Br_2$ (3.4) | $K_2CO_3$, 18-c-6 | rt | $CH_2Cl_2$ | 96 | Recovered sm (70%) |
| 5 | $CH_2Br_2$ (3.4) | $K_2CO_3$, 18-c-6 | reflux | $CH_2Cl_2$ | 4 | Decomposition |
| 6 | $CH_2I_2$ (15) | $Ag_2O$, TBAI | rt | THF | 24 | **7** (10%) |
| 7 | $CH_2I_2$ (15) | $Ag_2O$, TBAI | reflux | THF | 4 | **7** (trace) |
| 8 | $CH_2I_2$ (100) | $Ag_2O$, TBAI | rt | $CH_2I_2$ | 10 | Decomposition |
| 9 | DMM (100) | *p*-TsOH | rt | $CH_2Cl_2$ | 48 | **7**, **8**, **9, 10** |
| 10 | DMM (10) | *p*-TsOH | reflux | THF | 24 | **7** (trace) |
| 11 | DMM (10) | *p*-TsOH | reflux | $CH_2Cl_2$ | 19 | **7** (91%) |
| 12 | DMM (100) | $P_2O_5$ | rt | $CH_2Cl_2$ | 3 | **10** (quant.) |
| 13 | DMM (1.5) | $P_2O_5$ | rt | $CH_2Cl_2$ | 19 | **8**, **9**, **10** |
| 14 | DMM (1.5) | $P_2O_5$ | reflux | $CH_2Cl_2$ | 2 | **7** (40%) |

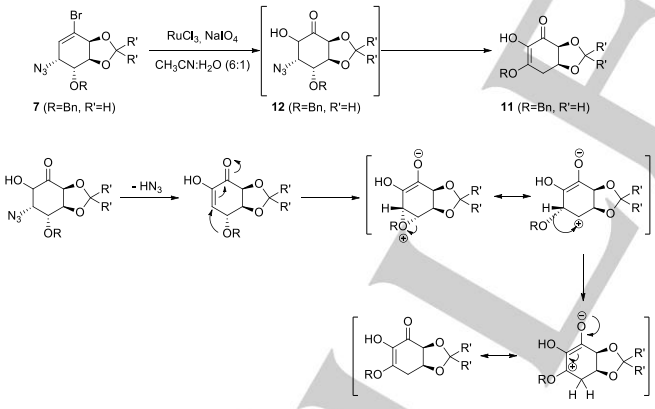
At this point, the introduction of the methylenedioxy group was successfully accomplished, however, it was still necessary to introduce the acetonide first as a transient protective group, then operate on the electron-richer olefin, remove the acetonide and

finally introduce the methylenedioxy group. Since the acidic conditions used to introduce the methylenedioxy group may allow the deprotection of the acetonide, we envisioned that a transacetalization reaction over compound **5** might lead directly to compound **7**, without isolating diol **6**. We gladly observed that after 15 hours the reaction was completed and the desired ketal **7** was obtained in 79% yield (Scheme 3)



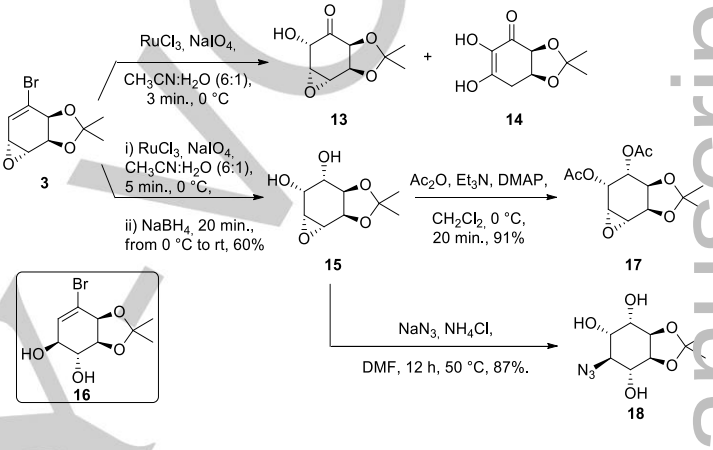

**Scheme 3:** Transacetalization reaction on **5** and functionalization of the electron-poorer olefin on the dioxolane **7**.

Attempts to oxidize the bromoalkene either with *m*-CPBA or with $OsO_4$ led only to recovered starting material (Scheme 3). We assayed the use of the more reactive $RuO_4$ (generated *in situ*) and observed complete consumption of the starting material. However, we did not obtain the desired hydroxy ketone, but a compound identified as **11**. We assumed that unsaturated ketone **11** was derived from hydroxy ketone **12** by hydrazoic acid loss followed by a 1,2-hydride shift as proposed in Scheme 4.




**Scheme 4**: Proposed mechanism for the transformation of **7** into **11**.

As we were not able to isolate the desired hydroxy ketone **12**, we decided to change the synthetic steps sequence. Attempts to functionalize the bromoalkene on epoxide **3** with $RuO_4$ (Scheme 5) led to a mixture of the hydroxy ketone **13** and the rearranged product **14**. The stereochemistry of the new stereogenic center in compound **13** was suggested by coupling constant measurement ($J_{2\text{-}3}$ = 1.4 Hz indicates a *cis* stereochemical relationship) and NOE experiments (Figure 2). Crystallization of compound **13** followed by X-ray diffraction analysis confirmed the assigned stereochemistry (Figure 2). Several attempts were made to maximize the formation of epoxide **13**, and it was noticed that **14** was formed during the purification stage by column chromatography. Consequently, we decided to perform a one-pot sequence adding the $NaBH_4$ directly to reaction flask once the consumption of epoxide **3** was verified. This approach rendered diol **15** in 60% yield for both steps. In the same reaction, bromodiol **16** was obtained as a byproduct with 22% yield. The latter probably formed by nucleophilic ring opening of the oxirane by water over the allylic position in a *trans*-diaxial fashion.




**Scheme 5**: Functionalization of the bromo-olefin on the epoxide **3**.

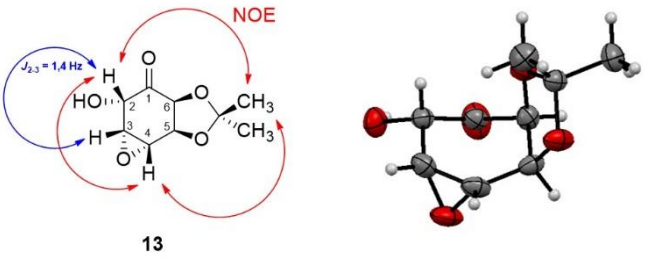



**Figure 2.** NOE correlations of hydroxyl-ketone **13** and ORTEP diagram.

The stereochemistry of **15** could not be derived from the $^1$H-NMR spectra since the coupling constants could not be determined due to second order splitting. Therefore, the hydroxyl groups were protected to render diacetate **17** (Scheme 5). The coupling constant of $H_{3\text{-}4}$ (Figure 3) was determined to be 4.6 Hz, an intermediate value that could arise either from a *cis* or a *trans* relationship between the involved protons. Data from a 1D NOE experiment suggested a *cis* relationship because when irradiating the *endo* methyl group of the isopropylidene an enhancement was observed in all β protons (including $H_4$). In order to confirm the assignment, the epoxide was opened with azide anion. The facial approach of the azide group is governated by the Fürst-Plattner rule, and the regiochemistry of the attack was determined by COSY experiment. The $^1$H-NMR spectrum showed a triplet signal ($J$ = 10.0 Hz) at 3.52 ppm that was assigned to $H_4$ (Figure 4). This

suggested a chair conformation with $H_1$-$H_2$ and $H_2$-$H_3$ in a *trans*-diaxial relationship. If $OH_6$ was on the β face, then $H_5$-$H_6$ should also have a *trans*-diaxial disposition, but this is not what coupling constant suggested. A measured $J_{1\text{-}6}$ value of 3.0 Hz hinted two *pseudo*-equatorial protons, confirming a *cis* relationship between $H_5$ and $H_6$. We were also able to crystallize compound **18**, and its structure was confirmed by single crystal X-ray crystallography (Figure 4).

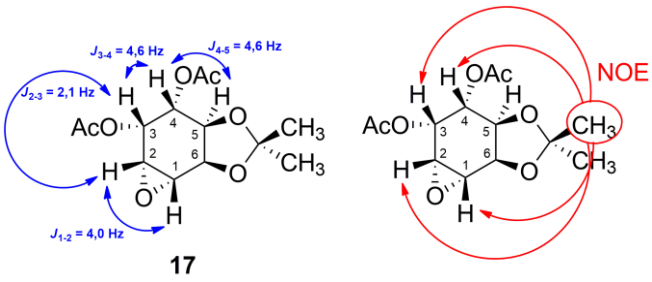



**Figure 3.** Coupling constants and NOE correlations of diacetate **17**.

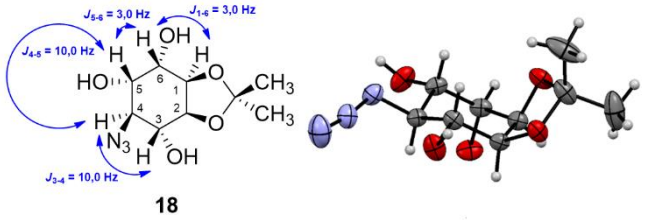
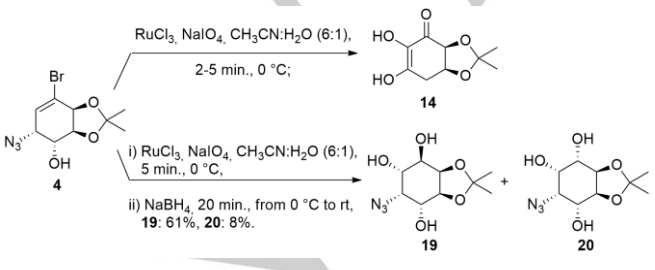



**Figure 4.** Coupling constant of compound **18** and its ORTEP diagram.

As the compound synthesized by the hydroxy-carbonylation/reduction sequence over the epoxide was not a *trans* diol as we expected, we decided to explore the reaction over the less strained substrate **4** (Scheme 6). When we performed only the oxidation stage, the main isolated product was **14** (≈60%). During the reaction, another product was observed by TLC (possibly the hydroxy ketone) but it decomposed during isolation as the amount of **14** increased, so we returned to the one pot dihydroxylation/reduction procedure. In this case, a mixture of *trans*(**19**)/*cis*(**20**) diols was obtained in ratio 7.6/1. The diastereomers could be separated by column chromatography, and the desired product was obtained in 61% yield for both steps.




**Scheme 6**: Functionalization of the bromo-olefin on compound **4**.

Structure confirmation of the *cis* isomer **20** was achieved by single-crystal X-ray diffraction analysis (Figure 5). On the other hand, to verify that **19** had the assigned stereochemistry, the compound was acetylated (**21**, Scheme 7), the acetonide was removed and the product was acetylated again. This rendered *meso* compound **22**, corroborating the assigned stereochemistry.

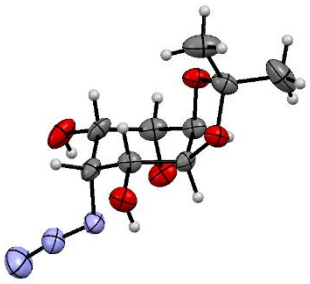
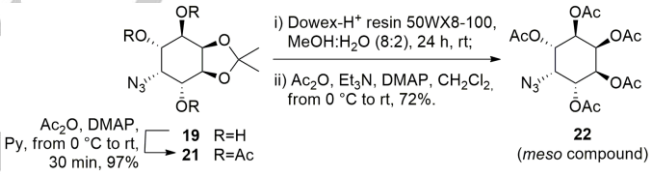
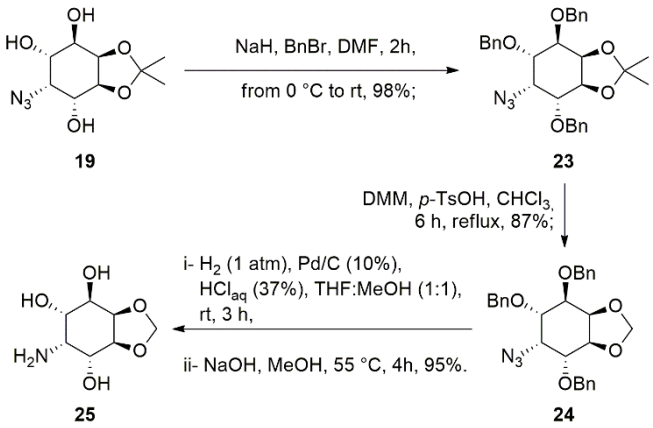


**Figure 5.** Crystal structure of triol **20**.




**Scheme 7**: Confirmation of stereochemistry of compound **19**.

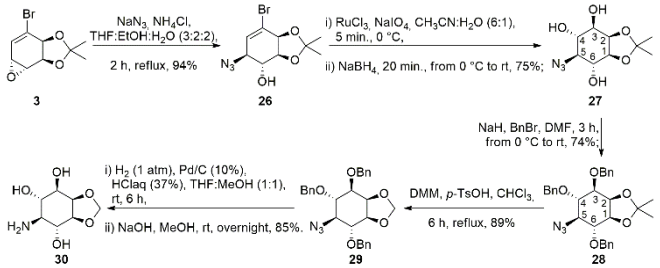
Once the stereochemistry of **19** was confirmed, the three hydroxyl groups were protected as benzyl ethers (**23**, Scheme 8), and the methylenedioxy group was introduced by means of a transacetalization reaction. Finally, simultaneous removal of the benzyl groups and reduction of the azide moiety by hydrogenolysis rendered the natural aminocyclitol **25** in 95% yield (Scheme 8). The recorded NMR data of compound **25** is in full accordance with the reported by Shashidhar.[12]




**Scheme 8**: Synthesis of natural aminocyclitol **25**.

***Synthesis of D-1,2-O-methylene-5-myo-inosamine [2-epi-(L-4,5-O-methylene-2-neo-inosamine)] (30).***

In order to synthesize the C2 epimer, the same strategy was applied but starting from the *trans*-azidoalcohol **26** (obtained from epoxide **3**) instead of compound **4** (Scheme 9). The bromo-olefin was functionalized by the same oxidation/reduction sequence rendering the *trans* diol (**27**). The stereochemistry was confirmed by coupling constant measurement: $J_{3\text{-}4} \approx J_{4\text{-}5} \approx J_{5\text{-}6} \approx 10$ Hz indicating a *trans*-diaxial relationship between those protons. The hydroxyl groups were protected as benzyl ethers (**28**) and then the acetonide was interconverted into the methylenedioxy group to deliver **29**. Finally, a hydrogenolysis reaction rendered aminocyclitol **30** (C2-epimer).




**Scheme 9**: Synthesis of C2 epimer of the natural aminocyclitol.

## Conclusions

The aminocyclitol core present in hygromycin A was prepared in eight steps with an overall yield of 39% from cyclohexadienediol **1**. The latter is commercially available or can be prepared in high yield by whole-cell enzymatic dihydroxylation of bromobenzene. The process has now been optimized in our 5-liter fermenter to render optically pure diol in up to 40 g/L of cell culture. Comparable yields have been described by the Hudlicky group in Canada that has pioneered the technique for over two decades. To the best of our knowledge, this is the shortest synthesis of the hygromycin A core reported to date and provides the highest overall yield.

The preparation of the C2 epimer in an even shorter sequence provided proof of concept that this approach is suitable for the preparation of hygromycin A analogues of unnatural stereochemistry. Our results in the synthesis of a series of analogues are on development and will be reported in due course.

## Experimental Section

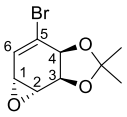
*General methods*

Commercially available reagents were purchased from Sigma–Aldrich and used without further purification. Melting pionts were determined either on a capilar Gallenkamp apparatus or on a capilar Electrothermal IA 9100 MK2 apparatus and are uncorrected. Optical rotation was determined on a Kruss Optronic GmbH P8000 on a 0.5 dm cell (concentration is expressed as W/V percentage). Nuclear Magnetic Resonance spectra were recorded either on a Bruker AVANCE DPX-400 instrument or on a Bruker AVANCE III 500 spectrometer. Chemical shifts ($\delta$) are given in parts per million downfield from tetramethylsilane, and coupling constants ($J$) are reported in Hertz. 1D-NOESY experiments were carried out at 25 °C using the DPFGSE-NOE pulse sequence of Stott et al. and a mixing time of 300 ms.[27] Selective excitation of specific protons was achieved with Gaussian shaped pulses. Infrared spectra (IR) were recorded on a Shimadzu FT-IR model IRprestige-21. Low-resolution mass spectra (MS) were recorded on a Shimadzu GCMS-QP2010 ultra instrument (70 eV electron impact mode), using either Direct Injection (DI) or by means of GC (column DB-WAX: Length 30m, diameter 0.25 mm and Film 0.25 µm). High-resolution mass spectra were performed on a Bruker Daltonics model $ToF_{LC}$ (ESI + mode).

Analytical TLC was performed on silica gel 60F-254 plates and visualized with UV light (254 nm) and/or anisaldehyde–$H_2SO_4$–EtOH or vanillin–$H_2SO_4$–EtOH as detecting agent. Purifications by column chromatography were performed on Merck 60 silica gel (0,040–0,063 mm).

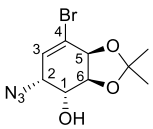
Single crystal X-ray diffraction data was collected on a Bruker D8 Venture diffractometer using Siemens Sealed-tube Mo$K_\alpha$ radiation monochromatized with a graphite single crystal (Compounds **13** and **18**) and Incoatec I microfocus source 1.0 Cu$K_\alpha$ radiation focused and monochromatized with a Quazar multilayer mirror (Compound **20**). A single crystal of each compounds was mounted on the four-circle *kappa* goniometer and data was collected in all cases in shutterless mode using a PHOTON100 CMOS detector. The diffractometer was operated using APEX2 control software providing cell determination, data collection and processing and structure report routines. Data scaling and absorption correction was performed with SADABS.[28] Structure determination was performed by modern direct methods with SHELXT program[29] and least-squares structure refinement with SHELXL[30] in shelXle environment.[31] CIF preparation and molecular graphics were prepared with enCIFer (v 1.6.2) and Mercury CSD 3.10.1 respectively. Figures S1, S2 and S3 show ORTEP representations of compounds **13**, **18** and **20** and Tables S1, S2 and S3 the crystallographic data, processing and refinement details respectively. CCDC 1535525 **13**, 1535526 **18**, and 1535562 **20**, contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

***(1R,2R,3S,4S)-5-bromo-1,2-epoxy-3,4-isopropylidenedioxy-5-cyclohexene*** (**3**).[32]



The $^1$H- and $^{13}$C-NMR spectra data of the compound were found to be in agreement with previous reports.[32] $\alpha_D^{21,0}$ = +101 (c = 1.55, MeOH). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.48 (dd, $J_{1\text{-}6}$ = 4.5 Hz, $J_{4\text{-}6}$ = 1.3 Hz, 1H, $H_6$), 4.87 (ddd, $J_{3\text{-}4}$ = 6.7 Hz, $J_{2\text{-}3}$ = 1.9 Hz, $J_{1\text{-}3}$ = 1.1 Hz, 1H, $H_3$), 4.42 (dd, $J_{3\text{-}4}$ = 6.7 Hz, $J_{4\text{-}6}$ = 1.3 Hz, 1H, $H_4$), 3.60 (dd, $J_{1\text{-}2}$ = 3.7 Hz, $J_{2\text{-}3}$ = 1.9 Hz, 1H, $H_2$), 3.34 (ddd, $J_{1\text{-}6}$ = 4.6 Hz, $J_{1\text{-}2}$ = 3.7 Hz, $J_{1\text{-}3}$ = 1.1 Hz, 1H, $H_1$), 1.46 (s, 3H, $CH_3$), 1.44 (s, 3H, $CH_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ (ppm): 130.0 ($C_5$), 126.6 ($C_6$), 111.5 ($C_{isopropylidene}$), 74.2 ($C_4$), 72.7 ($C_3$), 49.6 ($C_2$), 48.4 ($C_1$), 27.6 ($CH_3$), 26.1 ($CH_3$).

***(1R,2R,5S,6S)-2-azido-4-bromo-5,6-isopropylidenedioxycyclohexa-3-ene-1-ol*** (**4**).[33]

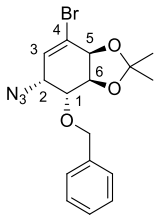


The $^1$H- and $^{13}$C-NMR spectra data of the compound were found to be in agreement with previous reports.[33] $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.15 (d, $J_{3\text{-}2}$ = 3.1 Hz, 1H, $H_3$), 4.66 (d, $J_{5\text{-}6}$ = 5.3 Hz, 1H, $H_5$), 4.40 (t, $J_{1\text{-}6}$ = $J_{5\text{-}6}$ =5.3 Hz, 1H, $H_6$), 4.25-4.17 (m, 2H, $H_1$ and $H_2$), 2.49 (bs, 1H, $OH_1$), 1.44 (s, 3H, $CH_3$), 1.40 (s, 3H, $CH_3$). $^{13}$C NMR (100 MHz, $CDCl_3$) δ ppm: 126.3 ($C_3$), 126.4 ($C_4$), 110.4 ($C_{isopropylidene}$), 76.1 ($C_6$), 76.0 ($C_5$), 69.2 ($C_1$), 59.5 ($C_2$), 27.6 ($CH_3$), 26.0 ($CH_3$).

10.1002/ejoc.201801424

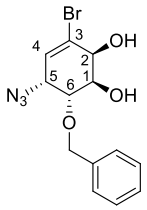


***(1R,2R,5S,6S)-2-Azido-1-benzyloxy-4-bromo-5,6-isopropylidenedioxy-3-cyclohexene*** (**5**).



122 mg of NaH 55% dispersion in mineral oil (2.8 mmol, 1.6 eq.) were added to a solution of 511 mg of compound **4** (1.7 mmol, 1 eq.) in 8 mL of dry DMF at 0 °C under $N_2$ atmosphere. The reaction mixture was left to stir during 15 minutes, and then 0.67 mL of BnBr (5.6 mmol, 3.2 eq.) were added. The reaction was kept at 0°C for 10 minutes, and then it was warmed up to room temperature. The reaction was monitored by TLC, and after completion of the reaction, a saturated aqueous solution of $NH_4Cl$ was added and the system was extracted with three portions of AcOEt. The combined organic phases were washed with three portions of saturated aqueous solution of $CuSO_4$, then washed with brine, dried over $Na_2SO_4$, filtered and the solvent was evaporated under reduced pressure to render an oily crude. Purification was accomplished by flash chromatography, using $SiO_2$ as stationary phase, and performing the following gradient elution: 0%, then 5% and finally 10 % (v/v of AcOEt in Hexane). 663 mg of **5** were obtained as a colorless oil (99 % yield). $\alpha_D^{22}$ = - 36 (c = 3.4, AcOEt). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.41-7.28 (m, 5H, H arom), 6.17 (d, $J_{2\text{-}3}$ = 3.6 Hz, 1H, $H_3$), 4.80 (d, $J_{gem}$ = 12.0 Hz, 1H, -O$\underline{C}H_2$Ph), 4.71 (d, $J_{gem}$ = 12.0 Hz, 1H, -O$\underline{C}H_2$Ph), 4.64 (dd, $J_{5\text{-}6}$ = 5.5 Hz, $J_{1\text{-}5}$ = 1.4 Hz, 1H, $H_5$), 4.39 (t, $J_{1\text{-}6}$ = $J_{5\text{-}6}$ = 5.5 Hz, 1H, $H_6$), 4.03-3.98 (m, 1H, $H_1$), 3.97 (dt, $J_{1\text{-}2}$ = $J_{2\text{-}3}$ = 3.6 Hz, $J_{2\text{-}6}$ = 1.5 Hz, 1H, $H_2$), 1.40 (s, 3H, $CH_3$), 1.37 (s, 3H, $CH_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ (ppm): 137.4 ($C_{Ph\text{-}quaternary}$), 128.7 ($C_{Ph\text{-}m}$), 128.3 ($C_{Ph\text{-}p}$), 128.1 ($C_{Ph\text{-}o}$), 127.3 ($C_3$), 125.5 ($C_4$), 110.5 ($C_{isopropylidene}$), 76.5 ($C_{1or5}$), 76.5 ($C_{5or1}$), 75.0 ($C_6$), 73.6 (-O$\underline{C}H_2$Ph), 57.9 ($C_2$), 27.7 ($\underline{C}H_3$), 26.2 ($\underline{C}H_3$). FT-IR ($\nu_{max}$/cm): 3032 (=C-H arom), 2988 ($CH_2$), 2934 ($CH_3$), 2899 ($CH_3$), 2102 ($N_3$), 1645 (C=C), 1227 (C-O-C), 1074 (O-C-O), 739 (=C-H arom), 698 (=C-H arom). DI-MS m/z (Rel. Int): 352 (1), 350 (1), 324 (0.6), 322 (0.7), 191 (22), 91 (100). HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $[C_{16}H_{18}BrN_3O_3Na]^+$ 402.0424; found: 402.0443.

***(1R,2S,5R,6R)-5-Azido-3-bromo-6-benzyloxy-cyclohex-3-ene-1,2-diol*** (**6**).



7.06 g of DOWEX-$H^+$ 50WX8-100 resin were added to a stirring solution of 706 mg of compound **5** in 18 mL of a mixture MeOH:$H_2O$ (8:2, V/V) at room temperature, and the mixture was warmed up to 45 °C by means of an oil bath. The reaction was monitored by TLC, and once the starting material was consumed (approximately 48 h), the resin was filtered off and washed several times with methanol. The solvent was removed under reduced pressure, and a brownish solid was obtained. The product was purified by column chromatography, using $SiO_2$ as stationary phase, and eluting with a solution 20% (v/v) of AcOEt in Hexane. 516 mg of **6** were obtained as a white solid (82% yield). M.P. = 103-104 °C. $\alpha_D^{22}$ = - 182 (c = 1.05, MeOH). $^1$H NMR ($(CD_3)_2CO$, 400 MHz) $\delta$ (ppm): 7.47-7.39 (m, 2H, $H_{Ph}$), 7.39-7.25 (m, 3H, $H_{Ph}$), 6.18 (d, $J_{4\text{-}5}$ = 4.1 Hz, 1H, $H_4$), 4.79 (s, 2H, -O$\underline{C}H_2$Ph), 4.48 (bs, 1H, $OH_1$), 4.45 (bs, 1H, $OH_2$), 4.31 (bd, $J_{5\text{-}6}$ = 4.1 Hz, 1H, $H_6$), 4.27 (dt, $J_{4\text{-}5}$ = $J_{5\text{-}6}$ = 4.1 Hz, $J$ = 1.6 Hz, 1H, $H_5$), 4.16 (dd, $J_{1\text{-}2}$ = 7.4 Hz, $J_{1\text{-}OH}$ = 4.0 Hz, 1H, $H_1$), 4.03 (dd, $J_{1\text{-}2}$ = 7.7 Hz, $J_{2\text{-}OH}$ = 4.0 Hz, 1H, $H_2$). $^{13}$C NMR ($(CD_3)_2CO$, 101 MHz) $\delta$ (ppm): 139.3 ($C_{Ph\text{-}quaternary}$), 129.8 ($C_3$), 129.1 ($C_{Ph\text{-}m}$), 128.7 ($C_{Ph\text{-}o}$), 128.5 ($C_{Ph\text{-}p}$), 128.0 ($C_4$), 78.1 ($C_2$), 73.7 (O$\underline{C}H_2$Ph), 71.8 ($C_6$), 69.9 ($C_1$), 59.5 ($C_5$). FT-IR ($\nu_{max}$/cm): 3296 (OH), 2124 ($N_3$), 1651 (C=C), 731 (=C-H arom), 696 (=C-H arom). DI-MS m/z (Rel. Int): 312 (4), 310 (4), 254 (1), 252 (1), 150 (13), 91 (100). HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $[C_{13}H_{14}BrN_3O_3Na]^+$ 362.01108; found: 362.01195.

**General procedure for the synthesis of dioxolane under basic media.**

14 mg of NaH 55 % dispersion in mineral oil (0.32 mmol, 2.1 eq.) were added to a solution of 50 mg of diol **6** (0.15 mmol, 1 eq.) in 1 mL of dry DMF at 0 °C under $N_2$ atmosphere. The reaction mixture was left to stir during 45 minutes, and then 35 µL of $CH_2Br_2$ (0.50 mmol, 3,4 eq.) were added in the absence of light. The reaction was taken up to the temperature listed on Table 2. After completion of the reaction, a saturated aqueous solution of $NH_4Cl$ was added and the system was extracted with three portions of AcOEt. The combined organic phases were treated with four portions of a saturated aqueous solution of $CuSO_4$, then washed with one portion of brine, dried over $Na_2SO_4$, filtered and the solvent was evaporated under reduced pressure to render an oily crude. Purification was accomplished by flash chromatography using $SiO_2$ as stationary phase.

**General procedure for the synthesis of dioxolane under neutral conditions.**

41 mg of diol **6** (0.12 mmol, 1 eq.) were dissolved in 1 mL of dry THF at room temperature under nitrogen atmosphere, and 145 µL of $CH_2I_2$ (1.81 mmol, 15 eq.) and 9.0 mg of TBAI (tetrabutilamonium iodide, 0.024 mmol, 0,2 eq.) were added in the absence of light. After stirring for 15 minutes, 224 mg of $Ag_2O$ (0.97 mmol, 8eq.) were added and the reaction was stirred until consumption of the starting material (conditions listed in Table 2). $Et_2O$ was added and $Ag_2O$ was filtered off through a pad of celite. The solvent was evaporated to render an oily crude product that was subjected to flash chromatography on silica gel.

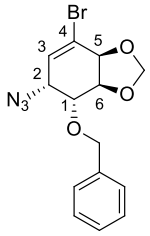
**General procedure for the synthesis of dioxolane under acidic conditions using *p*-toluenesulfonic acid as catalyst.**

A solution of 516 mg of diol **6** (1.52 mmol, 1 eq.) in 80 mL of dry $CH_2Cl_2$ was treated with the corresponding amount of DMM (Table 2) under $N_2$ atmosphere and 72 mg of *p*-TsOH (0.46 mmol, 0.3 eq.) were added. The reaction mixture was refluxed until consumption of the starting material, then solid $NaHCO_3$ was added and the resulting system was left to stand at room temperature for 5 minutes. Saturated aqueous solution of $NaHCO_3$ was added, and the system was extracted with three portions of $CH_2Cl_2$. The combined organic layers were washed with one portion of brine, dried over $Na_2SO_4$, filtered and the solvent was removed under reduced pressure rendering an oily crude that was purified over silica flash.

**General procedure for the synthesis of dioxolane under acidic conditions using $P_2O_5$ as catalyst.**

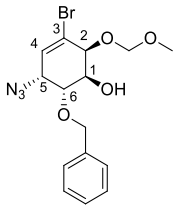
A solution of 25 mg of diol **6** (0.074 mmol, 1 eq.) in 1 mL of dry $CH_2Cl_2$, under $N_2$ atmosphere, was treated with the corresponding amount of DMM (Table 2) and 17 equiv. of $P_2O_5$ were added. The reaction mixture was stirred at room temperature until consumption of the starting material, and then the reaction was cooled by means of an ice bath. Cooled $CH_2Cl_2$ was added, and $P_2O_5$ excess was destroyed with cooled saturated aqueous solution of $NaHCO_3$. Then, the mixture was extracted with sat. $NaHCO_3$, washed with sat. NaCl and dried over $Na_2SO_4$. The solvent was evaporated under reduced pressure after the desiccant agent was filtered off, and the product was then purified by flash chromatography.

***(1R,2R,5S,6S)- 2-Azido-1-benzyloxy-4-bromo-5,6-methylendioxy-3-cyclohexene*** (**7**).



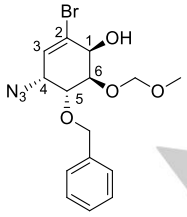
Compound **7** was synthesized from **5**, following the general procedure for the synthesis of dioxolane under acidic conditions using *p*-toluenesulfonic acid as catalyst. 10 eq. of DMM were used, and the reaction was kept at reflux temperature for 19h. The crude was purified by flash chromatography, performing a gradient elution: first hexane, and then a 5% v/v solution of AcOEt in hexane. Colorless oil. $\alpha_D^{22}$ = - 93 (c = 1.24, AcOEt). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ (ppm): 7.39-7.30 (m, 5H, $H_{Ph}$), 6.26 (dd, $J_{2\text{-}3}$ = 3.9 Hz, $J_{3\text{-}5}$ = 0.7 Hz,1H, $H_3$), 5.00 (s, 1H, -OC$H_2$O-), 4.98 (s, 1H, -OC$H_2$O-), 4.80 (d, $J_{gem}$ = 11.9 Hz, 1H, -OC$H_2$Ph), 4.72 (d, $J_{gem}$ = 11.9 Hz, 1H, -OC$H_2$Ph), 4.65 (bd, $J_{5\text{-}6}$ = 5.7 Hz, 1H, $H_5$), 4.31 (t, $J_{1\text{-}6}$ = $J_{5\text{-}6}$ = 5.7 Hz, 1H, $H_6$), 4.01-3.94 (m, 2H, $H_1$ and $H_2$). $^{13}$C NMR ($CDCl_3$, 101 MHz) $\delta$ (ppm): 137.2 ($C_{Ph\text{-}quaternary}$), 128.7 ($C_{Ph\text{-}p}$), 128.6 ($C_{Ph\text{-}m}$), 128.2 ($C_3$), 128.0 ($C_{Ph\text{-}o}$), 123.6 ($C_4$), 94.4 (-OC$H_2$O-), 76.4 ($C_5$), 75.9 ($C_1$), 74.9 ($C_6$), 73.5 (-OC$H_2$Ph), 57.7 ($C_2$). FT-IR ($\nu_{max}$/cm): 2870 ($CH_2$), 2104 ($N_3$), 1645 (C=C), 1088 (O-C-O), 926 (O-C-O), 739 (=C-H arom), 698 (=C-H arom). DI-MS m/z (Rel. Int): 324 (3), 322 (3), 296 (1), 294 (1), 91 (100). HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $[C_{14}H_{14}BrN_3O_3Na]^+$: 374.01108; found: 374.01139.

***(1S,2S,5R,6R)-5-Azido-6-benzyloxy-3-bromo-2-(methoxymethoxyl)-cyclohex-3-ene-1-ol*** (**8**).



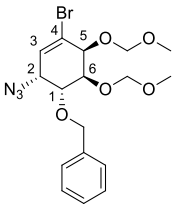
Colorless oil. $\alpha_D^{21}$ = - 98 (c = 1.35, AcOEt). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.41 – 7.30 (m, 5H, $H_{Ph}$), 6.16 (dt, $J_{4\text{-}5}$ = 3.9 Hz, $J_{2\text{-}4}$ = $J_{4\text{-}6}$ = 1.0 Hz, 1H, $H_4$), 4.84 (d, $J_{gem}$ = 6.8 Hz, 1H, -OC$H_2$OMe), 4.80 (d, $J_{gem}$ = 6.8 Hz, 1H, -OC$H_2$OMe), 4.79 (d, $J_{gem}$ = 11.8 Hz, 1H, -OC$H_2$Ph), 4.68 (d, $J_{gem}$ = 11.8 Hz, 1H, -OC$H_2$Ph), 4.36 (bd, $J_{1\text{-}2}$ = 3.9 Hz, 1H, $H_2$), 4.13 (dt, $J_{1\text{-}6}$ = 7.6 Hz, $J_{1\text{-}2}$ = $J_{1\text{-}OH}$ = 3.9 Hz, 1H, $H_1$), 4.09 (td, $J_{4\text{-}5}$ = $J_{5\text{-}6}$ = 4.0 Hz, $J_{4\text{-}6}$ = 1.0 Hz, 1H, $H_5$), 3.99 (dd, $J_{1\text{-}6}$ = 7.6 Hz, $J_{5\text{-}6}$ = 4.0 Hz, 1H, $H_6$), 3.45 (s, 3H, -OC$H_3$), 2.87 (d, $J_{1\text{-}OH1}$ = 3.9 Hz, 1H, $OH_1$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ (ppm): 137.5 ($C_{Ph\text{-}quaternary}$), 128.8 ($C_{Ph\text{-}m}$), 128.6 ($C_4$), 128.4 ($C_{Ph\text{-}p}$), 128.3 ($C_{Ph\text{-}o}$), 125.5 ($C_3$), 98.0 (-OC$H_2$OMe), 77.5 ($C_2$), 76.8 ($C_6$), 73.8 (-OC$H_2$Ph), 69.1 ($C_1$), 58.3 ($C_5$), 56.6 (-OC$H_3$). FT-IR ($\nu_{max}$/cm): 3458 (OH), 2897 ($CH_2$), 2851 ($CH_3$), 2102 ($N_3$), 1641 (C=C), 1105 (C-O-C), 1030 (C-O-C), 741 (=C-H arom), 700 (=C-H arom). DI -MS m/z (Rel. Int): 356 (0.9) 354 (0.9), 340 (0.4), 338 (0.4), 235 (4), 233 (4), 91 (100), 45 (62). HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $[C_{15}H_{18}BrN_3O_4Na]^+$: 406.0373; found: 406.0378.

***(1S,4R,5R,6R)-4-Azido-5-benzyloxy-2-bromo-6-(methoxymethoxyl)-cyclohex-2-ene-1-ol*** (**9**)



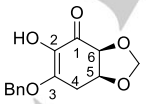
Colourless oil. $\alpha_D^{21}$ = - 54 (c = 0.85, AcOEt). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.38 – 7.29 (m, 5H, $H_{Ph}$), 6.15 (dt, $J_{3\text{-}4}$ = 3.8 Hz, $J_{1\text{-}3}$ = $J_{3\text{-}5}$ = 0.7 Hz, 1H, $H_3$), 4.78 (d, $J_{gem}$ = 6.7 Hz, 1H, -OC$H_2$OMe), 4.75 (d, $J_{gem}$ = 11.8 Hz, 1H, -OC$H_2$Oh), 7.71 (d, $J_{gem}$ = 6.7 Hz, 1H, -OC$H_2$OMe), 4,71 (d, $J_{gem}$ = 11.8 Hz, 1H, -OC$H_2$Ph), 4.45-4.41 (m, 1H, $H_1$), 4.08-4.03 (m, 2H, $H_5$ + $H_6$), 4.00 (td, $J_{3\text{-}4}$ = $J_{4\text{-}5}$ = 3.8 Hz, $J$ = 1.5 Hz, 1H, $H_4$), 3.39 (s, 3H, -OC$H_3$), 2.99 (d, $J_{1\text{-}OH1}$ = 6.6 Hz, 1H, OH). $^{13}$C NMR (101 MHz, $CDCl_3$) δ (ppm): 137.5 ($C_{Ph\text{-}quaternary}$), 128.7 ($C_{Ph\text{-}m}$), 128.3 ($C_{Ph\text{-}p}$), 128.1 ($C_{Ph\text{-}o}$), 128.0 ($C_3$), 127.4 ($C_2$), 98.0 (-OC$H_2$OMe), 76.5 ($C_5$ or $C_6$), 76.1 ($C_6$ or $C_5$), 73.9 (-OC$H_2$Ph), 70.6 ($C_1$), 58.9 ($C_4$), 56.2 (-OC$H_3$). FT-IR ($\nu_{max}$/cm): 3447 (OH), 2928 ($CH_2$), 2897 ($CH_2$), 2102 ($N_3$), 1643 (C=C), 1115 (C-O-C), 1034 (C-O-C), 749 (=C-H arom), 698 (=C-H arom). DI -MS m/z (Rel. Int): 356 (0.4), 354 (0.6), 312 (1.0), 310 (1), 194 (11), 91 (100), 45 (54). HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $[C_{15}H_{18}BrN_3O_4Na]^+$ 406.0373; found: 406.0371.

***(1R,4R,5S,6R)-2-Azido-1-benzyloxy-4-bromo-5,6-bis(methoxymethoxyl)-3-cyclohexene*** (**10**)



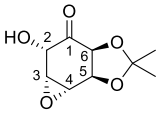
Compound **10** was synthesized from **6**, following the general procedure for the synthesis of dioxolane under acidic conditions using $P_2O_5$ acid as catalyst. 100 eq. of DMM were used, and the reaction was stirred at 0°C for 3h. The crude was purified by flash chromatography, performing a gradient elution: first hexane, and then a 5% v/v solution of AcOEt in hexane. Colorless oil (quantitative yield). $\alpha_D^{22}$ = - 74 (c = 0.50, AcOEt). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.41-7.29 (m, 5H, $H_{arom}$), 6.13 (d, $J_{2\text{-}3}$ = 3.8 Hz, 1H, $H_3$), 4.86 (d, $J_{gem}$ = 6.8 Hz, 1H, -OC$H_2$OMe), 4.82 (d, $J_{gem}$ = 6.8 Hz, 1H, -OC$H_2$OMe), 4.76 (d, $J_{gem}$ = 6.7 Hz, 1H, -OC$H_2$OMe), 4.74 (d, $J$ = 0.9 Hz, 2H, -OC$H_2$Ph), 4.71 (d, $J_{gem}$ = 6.7 Hz, 1H, -OC$H_2$OMe), 4.43 (d, $J_{5\text{-}6}$ = 3.1 Hz, 1H, $H_5$), 4.12-4.08 (m, 1H, $H_6$), 4.08-4.03 (m, 2H, $H_1$ y $H_2$), 3.47 (s, 3H, -OC$H_3$), 3.37 (s, 3H, -OC$H_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ (ppm): 137.5 ($C_{Ph\text{-}quaternary}$), 128.5 ($C_{Ph\text{-}m}$), 128.1 ($C_{Ph\text{-}p}$), 128.0 ($C_3$), 127.9 ($C_{Ph\text{-}o}$), 126.0 ($C_4$), 97.5 (-OC$H_2$OMe), 97.0 (-OC$H_2$OMe), 76.0 ($C_1$), 75.9 ($C_5$), 74.4 ($C_6$), 73.7 (-OC$H_2$Ph), 59.0 (C2), 56.4 (-OC$H_3$), 55.9 (-OC$H_3$). FT-IR ($\nu_{max}$/cm): 2930 ($CH_2$), 2893 ($CH_2$), 2824 (-$OCH_3$), 2102 ($N_3$), 1641 (C=C), 1030 (O-C-O), 920 (O-C-O), 739 (=C-H arom), 698 (=C-H arom). DI-MS m/z (Rel. Int): 296 (1), 294 (1), 250 (1), 248 (2), 194.1 (11), 91 (100). HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $[C_{17}H_{22}BrN_3O_5Na]^+$ 450.06350; found 450.06519.

***(5S,6S)-3-benzyloxy-2-hydroxy-5,6-methylendioxycyclohexa-2-ene-1-one*** (**11**).



59 mg of compound **7** (0.17 mmol, 1 eq.) were dissolved in 3 mL of $CH_3CN$, and the system was cooled to 0 °C. 43 mg of $NaIO_4$ (0.20 mmol, 1.2 eq.) and 2.4 mg of $RuCl_3{\cdot}2H_2O$ (0.010 mmol, 0.06 eq) were dissolved in 0.5 mL of water on a separated vial, and were also cooled to 0 °C. Once both solutions were at 0°C, the aqueous solution was added all at once over de organic solution, and the reaction was kept at 0°C under vigorous stirring during 5 minutes, and then it was quenched by the addition of 0.5 mL of an aqueous solution of $Na_2S_2O_3$ (20% W/V). The reaction was filtered through a $SiO_2$ pad, washed with abundant AcOEt and the eluted was evaporated rendering 50 mg of a brownish oily crude. Purification was accomplished by flash chromatography, using $SiO_2$ as stationary phase, and performing the following gradient elution: 10% followed by 20%, 30% and finally 40 % (v/v of AcOEt in Hexane). 33 mg of **11** were obtained as white solid (67 % yield). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.41 – 7.29 (m, 5H, $H_{Ph}$), 5.73 (s, 1H, -OC$H_2$O-), 5.49 (bs, 1H, $OH_2$), 5.43 (s, 1H, -OC$H_2$O-), 4.84 (d, $J_{gem}$ = 11.7 Hz, 1H, -OC$H_2$Ph), 4.80 (d, $J_{5\text{-}6}$ = 8.2 Hz, 1H, $H_6$), 4.69 (d, $J_{gem}$ = 11.7 Hz, 1H, -OC$H_2$Ph), 3.99 (ddd, $J_{4'\text{-}5}$ = 11.7 Hz, $J_{5\text{-}6}$ = 8.2 Hz, $J_{4\text{-}5}$ = 5.4 Hz, 1H, $H_5$), 2.92 (dd, $J_{gem}$ = 16.9 Hz, $J_{4\text{-}5}$ = 5.4 Hz, 1H, $H_4$), 2.52 (dd, $J_{gem}$ = 16.9 Hz, $J_{4'\text{-}5}$ = 11.7 Hz, 1H, $H_{4'}$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ (ppm): 190.0 ($C_1$), 146.7 ($C_3$), 137.3 ($C_2$), 128.6 ($C_{Ph\text{-}m}$), 128.1 ($C_{Ph\text{-}p}$), 127.8 ($C_{Ph\text{-}o}$), 126.9 ($C_{Ph\text{-}quaternary}$), 99.9 (OC$H_2$O), 81.5 (OC$H_2$Ph), 75.5 ($C_6$), 72.2 ($C_5$), 39.2 ($C_4$). HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $[C_{14}H_{14}O_5Na]^+$ 285.0733; found 285.0735.

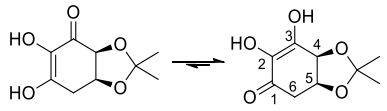
***(2S,3R,4R,5S,6S)-3,4-epoxy-2-hydroxy-5,6-isopropylidenedioxy-1-cyclohexanone*** (**13**).[34]



The same procedure described for compound **11** was applied to synthetize **13**, but the system was left to react during 2 minutes. Purification was accomplished by flash chromatography, using deactivated $SiO_2$ as stationary phase (deactivation was achived by adding 10 mL of distilled water to 100 g of $SiO_2$ and stirring

several hours until it is homogeneous), and performing the following gradient elution: 20% followed by 25%, 30%, 35% and finally 40 % (v/v of AcOEt in Hexane) (*NOTE*: The column should be done as quickly as possible to avoid decomposition of the product, and avoid absorbing the crude in $SiO_2$; load it in the less possible amount of DCM). White solid. The spectroscopic data of the compound were found to be in agreement with previous reports.[34] M.P = 125 – 126 °C. $\alpha_D^{21.5}$ = + 77 (c = 0.60, MeOH). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.11 (d, $J_{2\text{-}OH2}$ = 5.0 Hz, 1H, $H_2$), 4.85 (dt, $J_{5\text{-}6}$ = 6.0 Hz, $J_{4\text{-}6}$ = $J_{3\text{-}6}$ = 1.4 Hz, 1H, $H_6$), 4.41 (dd, $J_{5\text{-}6}$ = 5.9 Hz, $J_{4\text{-}5}$ = 1.5 Hz, 1H, $H_5$), 3.66 (dt, $J_{3\text{-}4}$ = 3.8 Hz, $J_{2\text{-}3}$ = $J_{3\text{-}6}$ = 1.4 Hz, 1H, $H_3$), 3.38 (dt, $J_{3\text{-}4}$ = 3.8 Hz, $J_{4\text{-}5}$ = $J_{4\text{-}6}$ = 1.4 Hz, 1H, $H_4$), 3.34 (d, $J$ = 5.0 Hz, 1H, $OH_2$), 1.59 (s, 3H, C$\underline{H_3}$), 1.38 (s, 3H, C$\underline{H_3}$).$^{13}$C NMR (101 MHz, $CDCl_3$) δ (ppm): 202.6 ($C_1$), 113.5 ($C_{isopropylidene}$), 78.3 ($C_5$), 77.5 ($C_6$), 70.2 ($C_2$), 59.7 ($C_3$), 54.2 ($C_4$), 27.5 ($\underline{C}H_3$), 25.5 ($\underline{C}H_3$). FT-IR ($\nu_{max}$/cm): 3507 (OH), 2947 ($CH_3$), 2820 ($CH_3$), 1744 (C=O), 1383 (gem dimethyl), 1244 (epox), 1219 (C-O), 1188 (C-O-C-O-C), 1159 (C-O-C-O-C), 1101 (C-O-C-O-C), 1069 (C-O-C-O-C). DI-MS m/z (Rel. Int): 185 (18, $[M\text{-}Me]^+$), 142 (2), 100 (61), 85 (100), 71 (81). HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $[C_9H_{12}O_5Na]^+$ 223.0577; found 223.0569.

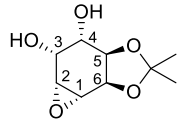
***(5S,6S)-2,3-dihydroxy-5,6-isopropylidenedioxycyclohexa-2-ene-1-one*** (**14**).[34]



**I** **II**

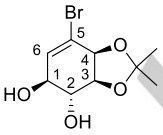
Structure **I** could be in equilibrium with structure **II**. As HMBC experiments shows a long distance coupling of $C_1$-$H_6$ and $C_1$-$H_{6'}$, as well as $C_3$-$H_4$, we propose that the main structure in a methanolic solution is **II**. White solid. The spectroscopic data of the compound were found to be in agreement with previous reports.[34] $^1$H NMR (400 MHz, $CD_3OD$) δ (ppm): 4.90-4.85 (m-signal partially overlapped with water signal, 1H, $H_4$), 3.97 (ddd, $J_{5\text{-}6'}$ = 11.6 Hz, $J_{4\text{-}5}$ = 8.5 Hz, $J_{5\text{-}6}$ = 5.3 Hz, 1H, $H_5$), 2.66 (dd, $J_{gem}$ = 16.5 Hz, $J_{5\text{-}6}$ = 5.3 Hz, 1H, $H_6$), 2.44 (dd, $J_{gem}$ = 16.5 Hz, $J_{5\text{-}6'}$ = 11.6 Hz, 1H, $H_{6'}$), 1.64 (s, 3H, C$\underline{H_3}$), 1.59 (s, 3H, C$\underline{H_3}$). $^{13}$C NMR (101 MHz, $CD_3OD$) δ (ppm): 192.5 ($C_1$), 152.0 ($C_3$), 128.1 ($C_2$), 118.5 ($C_{isopropylidene}$), 82.1 ($C_4$), 71.1 ($C_5$), 43.4 ($C_6$), 26.9 ($\underline{C}H_3$), 24.3 ($\underline{C}H_3$). FT-IR ($\nu_{max}$/cm): 3441 (OH), 2992 ($CH_3$), 2936 ($CH_2$), 1771 (enodiol-enone), 1385 (gem dimethyl), 1221 (C-C(O)-C), 1152 (C-O-C-O-C), 1130 (C-O-C-O-C), 1192 (C-O-C-O-C), 1066 (C-O-C-O-C). DI-MS m/z (Rel. Int): 200 (63, $[M]^{\cdot+}$), 142 (99), 114 (58), 71 (100), 68 (99). HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $[C_9H_{12}O_5Na]^+$ 223.0577; found 223.0575.

***D-1,2-anhydro-5,6-O-isopropylidene-allo-inositol*** (**15**).[35]



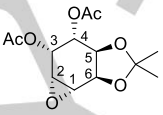
3.000 g of epoxide **3** (12.15 mmol, 1 eq.) were dissolved in 97.5 mL of $CH_3CN$, and the system was cooled to 0 °C. 3.117 g of $NaIO_4$ (14.57 mmol, 1.2 eq.) and 88 mg of $RuCl_3{\cdot}2H_2O$ (0.36 mmol, 0.03 eq.) were dissolved in 16.3 mL of water on a separated vial, and were also cooled to 0 °C. Once both solutions were at 0°C, the aqueous solution was added all at once over de organic solution, and the reaction was kept at 0°C under vigorous stirring during 5 minutes, and then 923 mg of $NaBH_4$ (24.29 mmol, 2 eq.) were added <u>in small portions</u>. The reaction was kept at 0°C during 10 minutes, and then it was left to stir at room temperature for another 10 minutes. The reaction was filtered through a $SiO_2$ pad, washed with abundant AcOEt and the eluted was evaporated rendering 2.830 mg of a brownish solid. Purification was accomplished by flash chromatography, using $SiO_2$ as stationary phase, and performing the following gradient elution: 10% followed by 20%, 30%, 35% and finally 40 % (v/v of AcOEt in Hexane). 1.470 g of **15** were obtained as white solid (60 % yield). $\alpha_D^{21.5}$ = + 22 (c = 1.41, MeOH). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.58 (dt, $J_{5\text{-}6}$ = 5.8 Hz, $J_{1\text{-}6}$ = $J_{2\text{-}6}$ = 1.3 Hz, 1H, $H_6$), 4.51 (ddd, $J_{5\text{-}6}$ = 5.8 Hz, $J_{4\text{-}5}$ = 3.6 Hz, $J_{1\text{-}5}$ = 1.3 Hz, 1H, $H_5$), 4.25 – 4.19 (m, 1H, $H_3$), 4.04 (dtd, $J_{4\text{-}OH4}$ = 11.7 Hz, $J_{4\text{-}5}$ = 3.6 Hz, $J$ = 3.6 Hz, $J$ = 1.6 Hz, 1H, $H_4$), 3.53 (dq, $J_{1\text{-}2}$ = 4.0 Hz, $J_{1\text{-}6}$ = 1.3 Hz, $J$ = $J$ = 1.3 Hz, 1H, $H_1$), 3.38 (dt, $J_{1\text{-}2}$ = 4.0 Hz, $J$ = $J$ = 1.4 Hz, 1H, $H_2$), 3.10 (d, $J_{3\text{-}OH3}$ = 9.4 Hz, 1H, $OH_3$), 2.87 (d, $J_{4\text{-}OH4}$ = 11.8 Hz, 1H, $OH_4$), 1.41 (s, 3H, C$\underline{H_3}$), 1.34 (s, 3H, C$\underline{H_3}$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ (ppm): 110.1 ($C_{isopropylidene}$), 77.0 ($C_5$), 69.8 ($C_6$), 68.6 ($C_4$), 64.3 ($C_3$), 57.9 ($C_1$), 56.1 ($C_2$), 27.4 ($\underline{C}H_3$), 25.1 ($\underline{C}H_3$). FT-IR ($\nu_{max}$/cm): 3318 (OH), 3244 (OH), 2988 (C-H), 2945 (C-H), 2909 (C-H), 1385 (gem dimethyl), 1370 (gem dimethyl), 1225 (epox), 1169 (C-O-C-O-C), 1144 (C-O-C-O-C), 1088 (C-O-C-O-C), 1061 (C-O-C-O-C). DI-MS m/z (Rel. Int): 187 (100, $[M\text{-}Me]^+$), 109 (72), 81 (52), 73 (53). HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $[C_9H_{14}O_5Na]^+$: 225.0733; found: 225.0774.

***(1S,2R,3S,4S)-5-bromo-3,4-isopropylidenedioxycyclohexa-5-en-1,2-diol*** (**16**).[36]



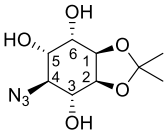
White solid. The $^1$H- and $^{13}$C-NMR spectra data of the compound were in agreement with previous reports.[36] $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.26 (d, $J_{1\text{-}6}$ = 2.5 Hz, 1H, $H_6$), 4.69 (d, $J_{3\text{-}4}$ = 6.1 Hz, 1H, $H_4$), 4.21 (dd, $J_{2\text{-}3}$ = 7.8 Hz, $J_{3\text{-}4}$ = 6.1 Hz, 1H, $H_3$), 4.13 – 4.05 (m, 1H, $H_1$), 3.75 (t, $J_{1\text{-}2}$ = $J_{2\text{-}3}$ = 7.8 Hz, 1H, $H_2$), 1.55 (s, 3H, C$\underline{H_3}$), 1.43 (s, 3H, C$\underline{H_3}$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ (ppm): 134.3 ($C_6$), 119.8 ($C_5$), 111.3 ($C_{isopropylidene}$), 77.7 ($C_4$), 77.2 ($C_3$), 73.3 ($C_1$), 71.0 ($C_2$), 28.2 ($\underline{C}H_3$), 26.2 ($\underline{C}H_3$).

***D-1,2-anhydro-3,4-di-O-acetyl-5,6-O-isopropyliden-allo-inositol*** (**17**).



24 mg of compound **15** (0.12 mmol, 1 eq) were dissolved in 1.0 mL of $CH_2Cl_2$ under nitrogen atmosphere, and the system was cooled to 0 °C. Then 132 µL of $Et_3N$ (0.95 mmol, 8 eq), 45 µL of $Ac_2O$ (0.48 mmol, 4 eq) and a catalytic amount of 4-dimethylaminopyridine were added at 0°C. The reaction was kept at 0 °C during 10 minutes, then it was warmed up to room temperature and continued to stir during another 10 minutes. A saturated solution of $NaHCO_3$ was added, and the aqueous solution was extracted with three portions of AcOEt. The combined organic layers were washed with three portions of saturated solution of $CuSO_4$ and one portion of brine, dried over $Na_2SO_4$, filtered and the solvent was removed under reduced pressure. Purification was accomplished by flash chromatography, using $SiO_2$ as stationary phase, and eluting with a solution 20 % (v/v) of AcOEt in Hexane. 31 mg of **17** were obtained as a colorless oil (91 % yield). $\alpha_D^{21.5}$ = + 57 (c = 0.93, MeOH). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.51 (dd, $J_{3\text{-}4}$ = 4.6 Hz, $J_{2\text{-}3}$ = 2.1 Hz, 1H, $H_3$), 5.41 (td, $J_{3\text{-}4}$ = $J_{4\text{-}5}$ = 4.6 Hz, $J_{2\text{-}4}$ = 1.0 Hz, 1H, $H_4$), 4.53 (d, $J_{5\text{-}6}$ = 5.7 Hz, 1H, $H_6$), 4.25 (ddd, $J_{5\text{-}6}$ = 5.7 Hz, $J_{4\text{-}5}$ = 4.6 Hz, $J_{1\text{-}5}$ = 1.4 Hz, 1H, $H_5$), 3.37 (ddt, $J_{1\text{-}2}$ = 4.0 Hz, $J_{2\text{-}3}$ = 2.1 Hz, $J_{2\text{-}4}$ = $J_{¿2\text{-}6?}$ = 1.0 Hz, 1H, $H_2$), 3.28 (ddd, $J_{1\text{-}2}$ = 4.0 Hz, $J_{1\text{-}5}$ = 1.4 Hz, $J_{1\text{-}6}$ = 0.8 Hz, 1H), 2.09 (s, 3H, C(O)C$\underline{H_3}$), 2.09 (s, 3H, C(O)C$\underline{H_3}$), 1.45 (s, 3H, C$\underline{H_3}$), 1.34 (s, 3H, C$\underline{H_3}$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ (ppm): 170.3 (O$\underline{C}$(O)$CH_3$), 170.2 (O$\underline{C}$(O)$CH_3$), 110.2 ($C_{isopropylidene}$), 74.3 ($C_5$), 70.4 ($C_6$), 66.6 ($C_3$), 65.5 ($C_4$), 53.6 ($C_1$), 52.1 ($C_2$), 27.7 ($\underline{C}H_3$), 25.5 ($\underline{C}H_3$), 21.0 (OC(O)$\underline{C}H_3$), 20.9 (OC(O)$\underline{C}H_3$). FT-IR ($\nu_{max}$/cm): 2990 ($CH_3$), 2940 ($CH_3$), 1748 (C=O), 1433 (gem dimethyl), 1373 (gem dimethyl), 1240 (epox), 1221 (epox), 1171 (C-O-C-O-C), 1155 (C-O-C-O-C), 1090 (C-O-C-O-C), 1065 (C-O-C-O-C). DI-MS m/z (Rel. Int): 271 (90, $[M\text{-}Me]^+$), 229 (5), 184 (28), 127 (43), 109 (100), 81 (29). HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $[C_{13}H_{18}O_7Na]^+$: 309.0945; found: 309.0946.

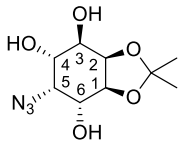
***L-4-azido-4-deoxy-1,2-O-isopropyliden-chiro-inositol*** (**18**).



700 mg of epoxide **15** (3.47 mmol, 1 eq) were dissolved in 7 mL of DMF under nitrogen atmosphere. 450 mg of $NaN_3$ (6.93 mmol, 2 eq) and 371 mg of $NH_4Cl$ (6.93 mmol, 2 eq) were added, and the system was warmed up to 50 °C. The reaction was monitored by TLC, and once the starting material was consumed (approximately 12h) the solid (inorganic salts) was filtered through filter

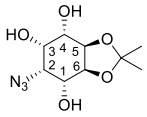
paper, and washed with methanol. The organic solution was evaporated at reduced pressure rendering 1.192 g of a white solid. Purification was accomplished by flash chromatography, using $SiO_2$ as stationary phase, and performing the following gradient elution: 30% followed by 40%, 50%, 60% and finally 70% (v/v of AcOEt in Hexane). 739 mg of **18** were obtained as white solid (87 % yield). M.P = 153.2 – 154.1 °C. $\alpha_D^{21.5}$ = - 122 (c = 1.27, MeOH). $^1$H NMR (400 MHz, $CD_3OD$) δ (ppm): 4.22 (dd, $J_{1\text{-}2}$ = 5.4 Hz, $J_{1\text{-}6}$ = 3.0 Hz, 1H, $H_1$), 4.10 (t, $J_{1\text{-}6}$ = $J_{5\text{-}6}$ = 3.0 Hz, 1H, H6), 4.04 (dd, $J_{2\text{-}3}$ = 7.4 Hz, $J_{1\text{-}2}$ = 5.4 Hz, 1H, $H_2$), 3.58 (dd, $J_{4\text{-}5}$ = 10.0 Hz, $J_{5\text{-}6}$ = 3.0 Hz, 1H, $H_5$), 3.52 (t, $J_{3\text{-}4}$ = $J_{4\text{-}5}$ = 10.0 Hz, 1H, $H_4$), 3.42 (dd, $J_{3\text{-}4}$ = 10.0 Hz, $J_{2\text{-}3}$ = 7.4 Hz, 1H, $H_3$), 1.44 (s, 3H, C$\underline{H}_3$), 1.33 (s, 3H, C$\underline{H}_3$). $^{13}$C NMR (101 MHz, $CD_3OD$) δ (ppm): 110.5 ($C_{isopropylidene}$), 80.5 ($C_2$), 78.7 ($C_1$), 76.2 ($C_3$), 71.7 ($C_5$), 70.4 ($C_6$), 66.5 ($C_4$), 28.4 (C$\underline{H}_3$), 26.3 (C$\underline{H}_3$). FT-IR ($\nu_{max}$/cm): 3350 (OH), 2999 (C-H), 2986 (C-H), 2969 (C-H), 2914 (C-H), 2124 ($N_3$), 1387 (gem dimethyl), 1223 (C-O-C-O-C), 1063 (C-O-C-O-C). DI-MS m/z (Rel. Int): 230 (100, [M-Me]$^+$), 187 (2), 100 (17), 85 (24), 73 (75), 60 (25). HRMS (ESI/Q-TOF) m/z: [M+Na]$^+$ Calcd for $[C_9H_{15}N_3O_5Na]^+$: 268.0904; found: 268.0907.

***D-5-azido-5-deoxy-1,2-O-isopropyliden-neo-inositol*** (**19**).



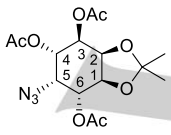
The same procedure described for compound **15** was applied to synthesize **19**. Purification was accomplished by flash chromatography, using $SiO_2$ as stationary phase and performing the following gradient elution: 30% followed by 40%, 50%, 60%, 70% and finally 80 % (v/v of AcOEt in Hexane). White solid (61 % yield). M.P = 139.7 - 140.5 °C. $\alpha_D^{21.5}$ = - 14 (c = 1.23, MeOH). $^1$H NMR (400 MHz, $CD_3OD$) δ (ppm): 4.35 (t, $J_{1\text{-}2}$ = $J_{2\text{-}3}$ = 4.6 Hz, 1H, $H_2$), 4.04 (dd, $J_{1\text{-}6}$ = 7.9 Hz, $J_{1\text{-}2}$ = 4.6 Hz, 1H, $H_1$), 3.94 (ddd, $J_{3\text{-}4}$ = 10.6 Hz, $J_{2\text{-}3}$ = 4.6 Hz, $J_{3\text{-}5?}$ = 0.9 Hz, 1H, $H_3$), 3.89 – 3.84 (m, 2H, $H_4$ + $H_5$), 3.77 (dd, $J_{1\text{-}6}$ = 7.9 Hz, $J_{5\text{-}6}$ = 3.0 Hz, 1H, $H_6$), 1.48 (s, 3H, C$\underline{H}$3), 1.34 (s, 3H, C$\underline{H}$3). $^{13}$C NMR (101 MHz, $CD_3OD$) δ (ppm): 110.5 ($C_{isopropylidene}$), 80.3 ($C_1$), 77.5 ($C_2$), 72.8 ($C_6$), 71.1 ($C_4$), 70.0 ($C_3$), 69.7 ($C_5$), 28.7 (C$\underline{H}_3$), 26.3 (C$\underline{H}_3$). FT-IR ($\nu_{max}$/cm): 3399 (OH), 2988 (C-H), 2936 (C-H), 2911 (C-H), 2108 ($N_3$), 1375 (gem dimethyl), 1219 (C-O), 1163 (C-O-C-O-C), 1076 (C-O-C-O-C), 1053 (C-O-C-O-C). DI-MS m/z (Rel. Int): 230 (80, [M-Me]$^+$), 185 (2), 100 (18), 85 (26), 73 (100), 60 (31). HRMS (ESI/Q-TOF) m/z: [M+Na]$^+$ Calcd for $[C_9H_{15}N_3O_5Na]^+$: 268.0904; found: 268.0903.

***D-2-azido-2-deoxy-5,6-O-isopropyliden-allo-inositol*** (**20**).



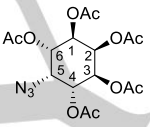
White solid (8 % yield). M.P = 140.2 - 141.1 °C. $\alpha_D^{21.5}$ = + 23 (c = 1.55, MeOH). $^1$H NMR (400 MHz, $CD_3OD$) δ (ppm): 4.29 – 4.22 (m, 2H, $H_5$ + $H_6$), 4.08 – 4.00 (m, 2H, $H_1$ + $H_3$), 3.79 (dd, $J$ = 5.0, 3.4 Hz, 1H, $H_4$), 3.64 (dd, $J$ = 3.5, 2.5 Hz, 1H, $H_2$), 1.45 (s, 3H, $CH_3$), 1.35 (s, 3H, $CH_3$). $^{13}$C NMR (101 MHz, $CD_3OD$) δ (ppm): 110.2 ($C_{isopropylidene}$), 79.1 ($C_{5or6}$), 79.0 ($C_{5or6}$), 72.9 ($C_{1or3or4}$), 72.8 ($C_{1or3or4}$), 72.1 ($C_{1or3}$), 63.0 ($C_2$), 28.6 ($CH_3$), 26.4 ($CH_3$). FT-IR ($\nu_{max}$/cm): 3412 (OH), 2990 (C-H), 2938 (C-H), 2110 ($N_3$), 1383 (gem dimethyl), 1219 (C-O), 1163 (C-O-C-O-C), 1101 (C-O-C-O-C), 1067 (C-O-C-O-C), 1055 (C-O-C-O-C). DI-MS m/z (Rel. Int): 230 (24, [M-Me]$^+$), 160 (15), 142 (9), 100 (61), 85 (33.9), 73 (100), 60 (44). HRMS (ESI/Q-TOF) m/z: [M+Na]$^+$ Calcd for $[C_9H_{15}N_3O_5Na]^+$: 268.0904; found: 268.0904.

***D-3,4,6-tri-O-acetyl-5-azido-5-deoxy-1,2-O-isopropyliden-neo-inositol*** (**21**).



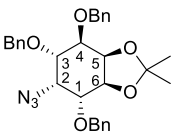
70 mg of triol **19** (0.29 mmol, 1 eq) were dissolved in 0.5 mL of pyridine under nitrogen atmosphere, and the system was cooled to 0 °C. 162 µL of $Ac_2O$ (1.71 mmol, 6 eq) and a catalytic amount of 4-dimethylaminopyridine were added. The system was left to react during 15 minutes at 0 °C, and was then warmed up to rt and left to stir for another 15 minutes. The reaction was quenched by addition of saturated aqueous solution of $NH_4Cl$, and extracted with three portions of AcOEt. The combined organic layers were washed with four portions of saturated aqueous solution of $CuSO_4$, one portion of brine, dried over $Na_2SO_4$, filtered and evaporated under reduced pressure. 107 mg of a colorless oil were obtained. Purification was accomplished by flash chromatography, using $SiO_2$ as stationary phase and performing the following gradient elution: 10% and then 20 % (v/v of AcOEt in Hexane). 103 mg of **21** were obtained as a colourless oil (97 % yield). $\alpha_D^{21.5}$ = - 8 (c = 0.91, MeOH). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.44 (dd, $J_{3\text{-}4}$ = 10.4 Hz, $J_{2\text{-}3}$ = 4.1 Hz, 1H, $H_3$), 5.36 (dd, $J_{3\text{-}4}$ = 10.4 Hz, $J_{4\text{-}5}$ = 3.0 Hz, 1H, $H_4$), 5.07 (dd, $J_{1\text{-}6}$ = 8.0 Hz, $J_{5\text{-}6}$ = 3.0 Hz, 1H, $H_6$), 4.49 (t, $J_{1\text{-}2}$ = $J_{2\text{-}3}$ = 4.5 Hz, 1H, $H_2$), 4.29 (dd, $J_{1\text{-}6}$ = 8.0 Hz, $J_{1\text{-}2}$ = 4.5 Hz, 1H, $H_1$), 4.16 (t, $J_{4\text{-}5}$ = $J_{5\text{-}6}$ = 3.0 Hz, 1H, $H_5$), 2.14 (s, 3H, OC(O)C$\underline{H}_3$), 2.11 (s, 3H, OC(O)C$\underline{H}_3$), 2.09 (s, 3H, OC(O)C$\underline{H}_3$), 1.53 (s, 3H, C$\underline{H}_3$), 1.31 (s, 3H, C$\underline{H}_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ (ppm): 170.3 (O$\underline{C}$(O)$CH_3$), 170.0 (O$\underline{C}$(O)$CH_3$), 169.7 (O$\underline{C}$(O)$CH_3$), 110.9 ($C_{isopropylidene}$), 75.6 ($C_1$), 73.0 ($C_2$), 71.9 ($C_6$), 69.0 ($C_4$), 68.0 ($C_3$), 61.8 ($C_5$), 28.0 (C$\underline{H}_3$), 26.2 (C$\underline{H}_3$), 20.9 (OC(O)C$\underline{H}_3$), 20.9 (OC(O)C$\underline{H}_3$), 20.7 (OC(O)C$\underline{H}_3$). FT-IR ($\nu_{max}$/cm): 2990 (C-H), 2938 (C-H), 2920 (C-H), 2110 ($N_3$), 1748 (C=O), 1433 (gem dimethyl), 1373 (gem dimethyl), 1225 (C-O-C-O-C), 1159 (C-O-C-O-C), 1007 (C-O-C-O-C), 1069 (=C-O-C), 1047 (=C-O-C). DI-MS m/z (Rel. Int): 356 (57, [M-Me]$^+$), 328 (0.6), 184 (19), 166 (100), 142 (23), 124 (99), 109 (28), 73 (19). HRMS (ESI/Q-TOF) m/z: [M+Na]$^+$ Calcd for $[C_{15}H_{21}N_3O_8Na]^+$: 394.1221; found: 394.1215.

***meso-1,2,3,4,6-penta-O-acetyl-5-azido-5-deoxy-neo-inositol*** (**22**).



Compound **22** was synthesized from **21** following the same procedure described for the synthesis of compound **6** (but at room temperature). The crude was subjected to esterification following the same procedure described for the synthesis of compound **17**. Purification was accomplished by flash chromatography, using $SiO_2$ as stationary phase and performing the following gradient elution: 20% and then 30 % (v/v of AcOEt in Hexane). White solid (72 % yield). $\alpha_D^{21.5}$ = 0 (c = 0.67, MeOH). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.57 (s, 1H, $H_2$), 5.30 (bs, 4H, $H_1$ + $H_3$ + $H_4$ + $H_6$), 4.35 (s, 1H, $H_5$), 2.14 (s, 3H, $CH_3$), 2.10 (s, 6H, 2x$CH_3$), 1.98 (s, 6H, 2x$CH_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ (ppm): 169.9 (2xAc), 169.9 (Ac), 169.5 (2xAc), 68.7 ($C_1$ + $C_3$ or $C_4$ + $C_6$), 68.1 ($C_2$), 67.3 ($C_4$ + $C_6$ or $C_1$ + $C_3$), 60.7 ($C_5$), 20.8 (Ac), 20.7 (2xAc), 20.6 (2xAc). FT-IR ($\nu_{max}$/cm): 2990 (C-H), 2941 (C-H), 2106 ($N_3$), 1748 (C=O), 1372 (C-N), 1225 (C-O), 1076 (=C-O-C), 1045 (=C-O-C). DI-MS m/z (Rel. Int): 356 (3, [M-OAc]$^+$), 225 (35), 183 (54), 157 (46), 115 (100), 103 (35), 73 (26). HRMS (ESI/Q-TOF) m/z: [M+Na]$^+$ Calcd for $[C_{16}H_{21}N_3O_{10}Na]^+$: 438.1119; found: 438.1138.

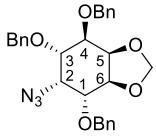
***D-2-azido-1,3,4-tri-O-benzyl-2-deoxy-5,6-O-isopropyliden-neo-inositol*** (**23**).



The same procedure described for the synthesis of compound **5** was followed for synthetizing compound **23**, with the following modifications: 300 mg of compound **19** (1.22 mmol, 1 eq) were dissolved in 2 mL of DMF, 4.5 eq of NaH (55% mineral oil dispersion) and 5 eq of BnBr were used. Purification was accomplished by flash chromatography, using $SiO_2$ as stationary phase, and performing the following gradient elution: 0%, then 2% and finally 5 % (v/v of AcOEt in Hexane). 619 mg of **23** were obtained as a coloruless oil (98 % yield). $\alpha_D^{25.5}$ = + 18 (c = 1.16, MeOH:AcOEt 3:1). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.43 – 7.27 (m, 15H, 3xPh), 4.86 (d, $J_{gem}$ = 12.2 Hz ,1H, $OCH_2Ph$), 4.85 (d, $J_{gem}$ = 11.9 Hz, 1H, $OCH_2Ph$), 4.76 – 4.63 (m, 4H, 2x$OCH_2Ph$), 4.22 (t, $J_{4\text{-}5}$ = $J_{5\text{-}6}$ = 4.7 Hz, 1H, $H_5$), 4.17 (dd, $J_{1\text{-}6}$ = 7.6 Hz, $J_{5\text{-}6}$ = 4.7 Hz, 1H, $H_6$), 4.01 (dd, $J_{3\text{-}4}$ = 9.6 Hz, $J_{4\text{-}5}$ = 4.7 Hz, 1H, $H_4$), 3.94 (t, $J_{1\text{-}2}$ = $J_{2\text{-}3}$ = 3.0 Hz, 1H, $H_2$), 3.82 (dd, $J_{3\text{-}4}$ = 9.6 Hz, $J_{2\text{-}3}$ = 3.0 Hz, 1H, $H_3$), 3.45 (dd, $J_{1\text{-}6}$ = 7.6 Hz, $J_{1\text{-}2}$ = 3.0 Hz, 1H, $H_1$), 1.37 (s, 3H, $CH_3$), 1.32 (s, 3H, $CH_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ (ppm):

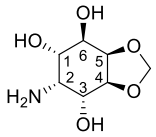
138.3 ($Ph_{quaternary}$), 138.2 ($Ph_{quaternary}$), 137.8 ($Ph_{quaternary}$), 128.6 (2x$C_{Ph}$), 128.6 (2x$C_{Ph}$), 128.5 (2x$C_{Ph}$), 128.2 (2x$C_{Ph}$), 128.0 (1x$C_{Ph}$), 128.0 (2x$C_{Ph}$), 127.9 (2x$C_{Ph}$), 127.8 (2x$C_{Ph}$), 109.6 ($C_{isopropylidene}$), 78.0 ($C_6$), 77.6 ($C_1$), 77.5 ($C_3$), 75.9 ($C_4$), 74.4 ($C_5$), 73.8 (O<u>C</u>$H_2$Ph), 73.7 (O<u>C</u>$H_2$Ph), 72.0 (O<u>C</u>$H_2$Ph), 62.5 ($C_2$), 28.3 ($CH_3$), 26.1 ($CH_3$). FT-IR ($\nu_{max}$/cm): 3032 (=C-H arom), 2987 (C-H), 2916 (C-H), 2872 (C-H), 2106 ($N_3$), 1954 (Ph), 1877 (Ph), 1811 (Ph), 1748 (Ph), 1497 (Ph), 1454 (Ph), 1381 (gem dimethyl), 1371 (gem dimethyl), 1219 (C-O-C-O-C), 1155 (C-O-C-O-C), 1094 (C-O-C-O-C), 1076 (C-O-C-O-C), 1051 (C-O-C-O-C), 737 (Ph), 698 (Ph). DI-MS m/z (Rel. Int): 500 (0.1, $[M\text{-}Me]^+$), 424 (0.6), 396 (2), 106 (6), 91 (100), 65 (4). HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $[C_{30}H_{33}N_3O_5Na]^+$: 538.2312; found: 538.2305.

***D-2-azido-1,3,4-tri-O-benzyl-2-deoxy-5,6-O-methylen-neo-inositol*** (**24**).



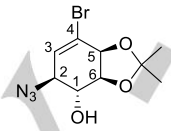
The general procedure for the synthesis of dioxolane under acidic conditions using p-TsOH as catalyst was used, but changing DCM for $CHCl_3$ as solvent, in order to increase de boiling point temperature. Purification was accomplished by flash chromatography, using $SiO_2$ as stationary phase, and performing the following gradient elution: 5%, then 10% and finally 20 % (v/v of AcOEt in Hexane). Coloruless oil (87 % yield). $\alpha_D^{25.5}$ = - 18 (c = 1.21, MeOH). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.34 – 7.27 (m, 15H, Phx3), 5.07 (s, 1H, O<u>C</u>$H_2$O), 4.97 (s, 1H, O<u>C</u>$H_2$O), 4.83 (d, $J_{gem}$ = 11.8 Hz, 1H, O<u>C</u>$H_2$Ph), 4.81 (d, $J_{gem}$ = 11.8 Hz, 1H, O<u>C</u>$H_2$Ph), 4.77 (d, $J_{gem}$ = 11.8 Hz, 1H, O<u>C</u>$H_2$Ph), 4.73 (d, $J_{gem}$ = 12.2 Hz, 1H, O<u>C</u>$H_2$Ph), 4.68 (d, $J_{gem}$ = 11.8 Hz, 1H, O<u>C</u>$H_2$Ph), 4.65 (d, $J_{gem}$ = 12.2 Hz, 1H, O<u>C</u>$H_2$Ph), 4.30 (dd, $J_{1\text{-}6}$ = 7.8 Hz, $J_{6\text{-}5}$ = 4.6 Hz, 1H, $H_6$), 4.12 – 4.04 (m, 2H, $H_4$ + $H_5$), 3.94 (t, $J_{1\text{-}2}$ = $J_{2\text{-}3}$ = 2.9 Hz, 1H, $H_2$), 3.80 (dd, $J_{3\text{-}4}$ = 9.0 Hz, $J_{2\text{-}3}$ = 2.9 Hz, 1H, $H_3$), 3.39 (dd, $J_{1\text{-}6}$ = 7.8 Hz, $J_{1\text{-}2}$ = 2.9 Hz, 1H, $H_1$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ (ppm): 138.1 ($Ph_{quaternary}$), 138.0 ($Ph_{quaternary}$), 137.7 ($Ph_{quaternary}$), 128.7 (2x$C_{Ph}$), 128.6 (2x$C_{Ph}$), 128.5 (2x$C_{Ph}$), 128.1 (2x$C_{Ph}$), 128.0 (1x$C_{Ph}$), 128.0 (1x$C_{Ph}$), 127.9 (3x$C_{Ph}$), 127.8 (2x$C_{Ph}$), 95.0 (O<u>C</u>$H_2$O), 77.5 ($C_3$), 77.4 ($C_6$), 75.9 ($C_{1\text{ or }4\text{ or }5}$), 75.8 ($C_{1\text{ or }4\text{ or }5}$), 75.6 ($C_{1\text{ or }4\text{ or }5}$), 73.6 (O<u>C</u>$H_2$Ph), 73.6 (O<u>C</u>$H_2$Ph), 72.2 (O<u>C</u>$H_2$Ph), 62.5 ($C_2$). FT-IR ($\nu_{max}$/cm): 3030 (=C-H arom), 2974 (C-H), 2102 ($N_3$), 1956 (Ph), 1879 (Ph), 1813 (Ph), 1797 (Ph), 1454 (Ph), 1206 (C-O-C-O-C), 1098 (C-O-C-O-C), 945 (-O$CH_2$O), 737 (Ph), 696 (Ph). DI-MS m/z (Rel. Int): 458 (0.2), 396 (1, $[M\text{-}Bn]^+$), 368 (2), 106 (6), 91 (100), 65 (5). HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $[C_{28}H_{29}N_3O_5Na]^+$: 510.1999; found: 510.1968.

***L-2-amino-2-deoxy-4,5-O-methylen-neo-inositol*** (**25**).[12]



213 mg of **24** (0.44 mmol, 1 eq) were dissolved in 8 mL of a solution THF:MeOH (1:1). 21 mg of Pd-C 10% and 40 µL of $HCl_{cc}$ (0.48 mmol, 1.1 eq) were added, and hydrogen was bubbled into the system (P=1 atm). Once the reaction was completed (approximately 3 h), nitrogen was bubbled during 10 minutes to remove dissolved $H_2$, then the catalyst was removed by filtration and washed with a solution MeOH:$H_2O$ (8:2, v/v). The solvent was evaporated under reduced pressure (absolute EtOH was used to remove $H_2O$ by azeotropic destillation) rendering 100 mg of a very hygroscopic white solid (gum). Pure product was obtained as the hydrochloride, then no purification was needed. <u>Hydrochloride</u>: $^1$H NMR (400 MHz, $D_2O$, with MeOH as internal reference at δ = 3.34 ppm[37]) δ (ppm): 5.23 (s, 1H, O<u>C</u>$H_2$O), 4.81 (s, 1H, O<u>C</u>$H_2$O), 4.36-4.30 (m, 2H, $H_4$ + $H_5$), 4.21 (dd, $J_{1\text{-}6}$ = 7.9 Hz, $J_{5\text{-}6}$ = 2.3 Hz, 1H, $H_6$), 4.11 (dd, $J_{1\text{-}6}$ = 7.9 Hz, $J_{1\text{-}2}$ = 6.5 Hz, 1H, $H_1$), 4.01 (t, $J_{2\text{-}3}$ = $J_{3\text{-}4}$ = 3.3 Hz, 1H, $H_3$), 3.78 (dd, $J_{1\text{-}2}$ = 6.5 Hz, $J_{2\text{-}3}$ = 3.3 Hz, 1H, $H_2$). $^{13}$C NMR (101 MHz, $D_2O$, with MeOH as internal reference at δ = 49.50 ppm[37]) δ (ppm): 95.5 (O$CH_2$O), 76.8 ($C_{4\text{ o }5}$), 76.2 ($C_{5\text{ o }4}$), 70.5 ($C_6$), 67.7 ($C_{1\text{ o }3}$), 67.7 ($C_{3\text{ o }1}$), 50.9 ($C_2$). FT-IR ($\nu_{max}$/cm): 3402 (OH), 2930 (NH), 1630 ($NH_3^+$), 1508 ($NH_3^+$), 1080 (C-O), 957 (methylenedioxy). ID-MS m/z (Int. Rel.): 192 (1, $M^+$), 191 (3), 173 (6), 126 (9), 101 (26), 88 (100), 73 (65). <u>Free base</u>: an ion exchange chromatography was employed for obtaining the free base. DOWEX 50WX8-100 resin was used as stationary phase, and a gradient elution was applied: first a solution 9:1 (MeOH:$NH_4OH_{cc}$), followed by a 8:2 solution (MeOH:$NH_4OH_{cc}$), then a 7:3 solution (MeOH:$NH_4OH_{cc}$), followed by a 6:4 solution (MeOH:$NH_4OH_{cc}$), and finally a 5:5 solution (MeOH:$NH_4OH_{cc}$). Methanol was removed under reduced pressure, and the remaining water was lyophilized rendering the free base aminocyclitol as a hygroscopic white solid. Spectroscopic data was in concordance with previously described values.[12] $^1$H NMR (400 MHz, $D_2O$, HDO signal was used as internal reference at δ = 4.79 ppm) δ (ppm): 5.19 (s, 1H, O$CH_2$O), 4.93 (s, 1H, O$CH_2$O), 4.28 (dd, $J_{3\text{-}4}$ = 7.5 Hz, $J_{4\text{-}5}$ = 5.1 Hz, 1H, $H_4$), 4.18 (t, $J_{4\text{-}5}$ = $J_{5\text{-}6}$ = 4.7 Hz, 1H, $H_5$), 4.13 (dd, $J_{1\text{-}6}$ = 9.6 Hz, $J_{5\text{-}6}$ = 4.3 Hz, 1H, $H_6$), 3.87 (dd, $J_{1\text{-}6}$ = 9.6 Hz, $J_{1\text{-}2}$ = 3.9 Hz, 1H, $H_1$), 3.74 (dd, $J_{3\text{-}4}$ = 7.5 Hz, $J_{2\text{-}3}$ = 3.5 Hz, 1H, $H_3$), 3.40 (t, $J_{1\text{-}2}$ = $J_{2\text{-}3}$ = 3.7 Hz, 1H, $H_2$). $^{13}$C NMR (101 MHz, $D_2O$, <u>C</u>$H_2$O signal of EtOH was used as internal reference at δ = 58.05 ppm[37]) δ (ppm): 94.9 (O$CH_2$O), 77.7 ($C_4$), 77.5 ($C_5$), 70.3 ($C_{1o3}$), 70.2 ($C_{3o1}$), 68.8 ($C_6$), 55.1 ($C_2$). FT-IR ($\nu_{max}$/cm): 3370 (OH), 2982 (C-H), 2929 (C-H), 1634 (N-H), 1389 (O-H), 1138 (C-O-C-O-C), 1088 (C-O-C-O-C), 1045 (C-O-C-O-C), 972 (N-H). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $[C_7H_{14}NO_5]^+$: 192.0866; found: 192.0866.

***(1R,2S,5S,6S)-2-azido-4-bromo-5,6-isopropylidenedioxycyclohexa-3-ene-1-ol*** (**26**).[38]



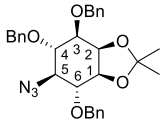
6.008 g of epoxide **3** (24.32 mmol, 1 eq) were dissolved in 175 mL of a solution THF:EtOH:$H_2O$ (3:2:2). 4.743 g of $NaN_3$ (72.97 mmol, 3 eq) and 2.863 g of $NH_4Cl$ (53.51 mmol, 2.2 eq) were added. The system was heated to reflux temperature and kept stirring at that temperature until consumption of the starting material (approximately 2 h). Water was added, and the system was extracted with three portions of AcOEt. The combined organic layers were washed with brine, dried with $Na_2SO_4$, filtered and concentrated under reduced pressure, rendering 7 g of a white solid. Purification was accomplished by flash chromatography, using $SiO_2$ as stationary phase, and performing the following gradient elution: 10%, then 15% and finally 20 % (v/v of AcOEt in Hexane). 6.597 g of a white solid were obtained (94 % yield). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.12 (d, $J_{2\text{-}3}$ = 1.6 Hz, 1H, $H_3$), 4.69 (dd, $J_{5\text{-}6}$ = 6.2 Hz, $J_{2\text{-}5}$ = 1.6 Hz, 1H, $H_5$), 4.17 (dd, $J_{1\text{-}6}$ = 8.6 Hz, $J_{5\text{-}6}$ = 6.2 Hz, 1H, $H_6$), 3.92 (dt, $J_{1\text{-}2}$ = 8.6 Hz, $J_{2\text{-}3}$ = $J_{2\text{-}5}$ = 1.6 Hz, 1H, $H_2$), 3.71 (t, $J_{1\text{-}2}$ = $J_{1\text{-}6}$ = 8.6 Hz, 1H, $H_1$), 2.84 (bs, 1H, $OH_1$), 1.56 (s, 3H, $CH_3$), 1.44 (s, 3H, $CH_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ (ppm): 131.0 ($C_3$), 120.6 ($C_4$), 111.4 ($C_{isopropylidene}$), 77.9 ($C_5$), 77.2 ($C_5$, signal overlapped with the central peak of $CDCl_3$), 73.0 ($C_4$), 62.3 ($C_2$), 28.3 ($CH_3$), 26.0 ($CH_3$). FT-IR ($\nu_{max}$/cm): 3447 (OH), 2986 (C-H), 2943 (C-H), 2880 (C-H), 2112 ($N_3$), 1377 (gem dimethyl), 1331 (gem dimethyl), 1252 (O-H), 1157 (C-O-C-O-C), 1084 (C-O-C-O-C), 1072 (C-O-C-O-C). DI-MS m/z (Rel. Int): 276 (52, $[M\text{-}Me]^+$), 274 (53, $[M\text{-}Me]^+$), 188 (2), 101 (48), 59 (35), 43 (100). HRMS (ESI/Q-TOF) m/z: $[M+Na]^+$ Calcd for $[C_9H_{12}BrN_3O_3Na]^+$: 311.9954; found: 311.9954.

***D-5-azido-5-deoxy-1,2-O-isopropyliden-myo-inositol*** (**27**).

The same procedure described for compound **15** was applied for synthetizing **27**. Purification was accomplished by flash chromatography, using $SiO_2$ as stationary phase and performing the following gradient elution: 30% followed by 40%, 50%, 60%, 70%, 80% and finally 90% (v/v of AcOEt in Hexane). Colourless syrup (75 % yield). $\alpha_D^{25.5}$ = - 52 (c = 1.54, MeOH). $^1$H NMR (400 MHz, $(CD_3)_2CO$) δ (ppm): 4.74 (d, $J_{6\text{-}OH6}$ = 5.0 Hz, 1H, $OH_6$), 4.58 (d, $J_{4\text{-}OH4}$ = 4.2 Hz, 1H, $OH_4$), 4.38 (dd, $J_{1\text{-}2}$ = 5.2 Hz, $J_{2\text{-}3}$ = 3.9 Hz, 1H, $H_2$), 4.07 – 3.99 (m, 2H, $H_1$ + $OH_3$), 3.79 (ddd, $J_{3\text{-}4}$ = 9.3 Hz, $J_{3\text{-}OH3}$ = 5.8 Hz, $J_{2\text{-}3}$ = 3.9 Hz, 1H, $H_3$), 3.63 (td, $J_{3\text{-}4}$ = $J_{4\text{-}5}$ = 9.3 Hz, $J_{4\text{-}OH4}$ = 4.2 Hz, 1H, $H_4$), 3.58 (ddd, $J_{5\text{-}6}$ = 10.3 Hz, $J_{1\text{-}6}$ = 7.3 Hz, $J_{6\text{-}OH6}$ = 5.0 Hz, 1H, $H_6$), 3.18 (dd, $J_{5\text{-}6}$ = 10.3 Hz, $J_{4\text{-}5}$ = 9.3 Hz, 1H, $H_5$), 1.41 (s, 3H, $CH_3$), 1.29 (s, 3H, $CH_3$). $^{13}$C NMR (101 MHz, $(CD_3)_2CO$) δ (ppm): 109.8 ($C_{isopropylidene}$), 80.6 ($C_1$), 77.1 ($C_2$), 74.8 ($C_6$), 72.6 ($C_4$), 71.8 ($C_3$), 68.9 ($C_5$), 28.4 ($CH_3$), 26.1 ($CH_3$). FT-IR ($\nu_{max}$/cm): 3383 (OH), 2990 (C-H), 2938 (C-H), 2922 (C-H), 2110 ($N_3$), 1377 (O-H), 1221 (C-O), 1146 (C-O-C-O-C), 1099 (C-O-C-O-C), 1042 (C-O-C-O-C). DI-MS m/z (Rel. Int): 230 (100, [M-

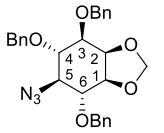
Me]$^+$), 109 (13), 96 (12), 85 (22), 73 (88), 60 (35). HRMS (ESI/Q-TOF) m/z: [M+Na]$^+$ Calcd for [$C_9H_{15}N_3O_5Na$]$^+$: 268.0904; found: 268.0912.

***D-5-azido-3,4,6-tri-O-benzyl-5-deoxy-1,2-O-isopropyliden-myo-inositol*** (**28**).



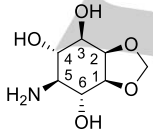
The same procedure described for the synthesis of compound **23** was followed for synthetizing compound **28**. Purification was accomplished by flash chromatography, using $SiO_2$ as stationary phase, and performing the following gradient elution: 0%, then 2%, 5% and finally 10 % (v/v of AcOEt in Hexane). Coloruless oil (74 % yield). $\alpha_D^{25.5}$ = + 19 (c = 1.37, MeOH). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.44 – 7.27 (m, 15H, 3xPh), 4.91 – 4.70 (m, 6H, 3xOC$\underline{H}_2$Ph), 4.26 (dd, $J_{1\text{-}2}$ = 5.5 Hz, $J_{2\text{-}3}$ = 3.6 Hz, 1H, $H_2$), 4.10 (dd, $J_{1\text{-}6}$ = 6.9 Hz, $J_{1\text{-}2}$ = 5.5 Hz, 1H, $H_1$), 3.74 (t, $J_{3\text{-}4}$ = $J_{4\text{-}5}$ = 8.9 Hz, 1H, $H_4$), 3.68 (dd, $J_{3\text{-}4}$ = 8.9 Hz, $J_{2\text{-}3}$ = 3.6 Hz, 1H, $H_3$), 3.56 (dd, $J_{5\text{-}6}$ = 10.3 Hz, $J_{1\text{-}6}$ = 6.9 Hz, 1H, $H_6$), 3.34 (dd, $J_{5\text{-}6}$ = 10.3 Hz, $J_{4\text{-}5}$ = 8.9 Hz, 1H, $H_5$), 1.51 (s, 3H, $CH_3$), 1.36 (s, 3H, $CH_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ (ppm): 138.0 ($Ph_{quaternary}$), 138.0 (2x$Ph_{quaternary}$), 128.6 (2xPh), 128.6 (2xPh), 128.5 (2xPh), 128.4 (2xPh), 128.2 (2xPh), 128.2 (2xPh), 128.1 (Ph), 128.0 (Ph), 127.9 (Ph), 110.2 ($C_{isopropylidene}$), 80.9 ($C_6$), 79.4 ($C_{1\text{ or }4}$), 79.3 ($C_{4\text{ or }1}$), 77.4 ($C_3$), 75.6 (O$\underline{C}$H$_2$Ph), 74.6 ($C_1$), 73.7 (O$\underline{C}$H$_2$Ph), 73.4 (O$\underline{C}$H$_2$Ph), 65.9 ($C_5$), 28.0 ($CH_3$), 25.9 ($CH_3$). FT-IR ($\nu_{max}$/cm): 3063 (=C-H arom), 3032 (=C-H arom), 2988 (C-H), 2911 (C-H), 2874 (C-H), 2106 ($N_3$), 1952 (Ph), 1877 (Ph), 1811 (Ph), 1497 (Ph), 1454 (Ph), 1371 (gem dimethyl), 1265 (C-O), 1242 (C-O-C-O-C), 1219 (C-O-C-O-C), 1153 (C-O-C-O-C), 1072 (C-O-C-O-C), 1047 (C-O-C-O-C), 737 (Ph), 696 (Ph). DI-MS m/z (Rel. Int): 500 (0.3, [M-Me]$^+$), 424 (0.4), 290 (1), 181 (2), 106 (6), 91 (100), 65 (4). HRMS (ESI/Q-TOF) m/z: [M+Na]$^+$ Calcd for [$C_{30}H_{33}N_3O_5Na$]$^+$: 538.2312; found: 538.2278.

***D-5-azido-3,4,6-tri-O-benzyl-5-deoxy-1,2-O-methylen-myo-inositol*** (**29**).



The general procedure for the synthesis of dioxolane under acidic conditions using *p*-TsOH as catalyst was used, but changing DCM for $CHCl_3$ as solvent, in order to increase de boiling point temperature. Purification was accomplished by flash chromatography, using $SiO_2$ as stationary phase, and performing the following gradient elution: 5%, then 10% (v/v of AcOEt in Hexane). Coloruless oil (89 % yield). $\alpha_D^{25.5}$ = + 10 (c = 0.73, MeOH). $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.42 – 7.26 (m, 15H, 3xPh), 5.18 (s, 1H, $OCH_2O$), 4.99 (s, 1H, $OCH_2O$), 4.86 (d, $J_{gem}$ = 11.3 Hz, 1H, OC$\underline{H}_2$Ph), 4.82 – 4.69 (m, 5H, $OCH_2$Ph), 4.20 – 4.12 (m, 2H, $H_1$ +$H_2$), 3.75 (dd, $J_{3\text{-}4}$ = 8.3 Hz, $J_{2\text{-}3}$ = 3.2 Hz, 1H, $H_3$), 3.69 (t, $J_{3\text{-}4}$ = $J_{4\text{-}5}$ = 8.3 Hz, 1H, $H_4$), 3.61 – 3.50 (m, 1H, $H_6$), 3.39 (dd, $J_{5\text{-}6}$ = 10.3 Hz, $J_{4\text{-}5}$ = 8.3 Hz, 1H, $H_5$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ (ppm): 137.9 (2x$Ph_{quaternary}$), 137.8 ($Ph_{quaternary}$), 128.6 (2xPh), 128.6 (2xPh), 128.5 (2xPh), 128.4 (2xPh), 128.3 (2xPh), 128.1 (Ph), 128.1 (Ph), 128.0 (2xPh), 128.0 (Ph), 95.5 (O$\underline{C}$H$_2$O), 79.3 ($C_4$), 79.0 ($C_6$), 78.9 ($C_{1\text{ or }2}$), 77.3 ($C_3$), 75.3 ($C_{2\text{ or }1}$), 75.2 (O$\underline{C}$H$_2$Ph), 73.9 (O$\underline{C}$H$_2$Ph), 73.2 (O$\underline{C}$H$_2$Ph), 65.8 ($C_5$). FT-IR ($\nu_{max}$/cm): 3030 (=C-H arom), 2876 (C-H), 2106 ($N_3$), 1954 (Ph), 1877 (Ph), 1811 (Ph), 1497 (Ph), 1454 (Ph), 1207 (C-O-C-O-C), 1094 (C-O-C-O-C), 920 (-$OCH_2O$-), 737 (Ph), 698 (Ph). DI-MS m/z (Rel. Int): 458 (0.2), 396 (0.6, [M-Bη]$^+$), 262 (2), 106 (7), 91 (100), 65 (5). HRMS (ESI/Q-TOF) m/z: [M+Na]$^+$ Calcd for [$C_{28}H_{29}N_3O_5Na$]$^+$: 510.1999; found: 510.1966.

***D-5-amino-5-deoxy-1,2-O-methylen-myo-inositol*** (**30**).



The same procedure described for compound **25** was applied for synthetizing **30**. Colourless syrup (85 % yield). Hydrochloride: $\alpha_D^{25.5}$ = - 42 (c = 1.41, MeOH). $^1$H NMR (400 MHz, $D_2O$, HDO signal was used as internal reference at δ = 4.79 ppm) δ (ppm): 5.22 (s, 1H, $OCH_2O$), 4.98 (s, 1H, $OCH_2O$), 4.26 – 4.13 (m, 2H, $H_1$ and $H_2$), 3.95 – 3.86 (m, 1H, $H_3$), 3.71 (t, $J_{3\text{-}4}$ = $J_{4\text{-}5}$ = 9.9 Hz, 1H, $H_4$), 3.65 – 3.55 (m, 1H, $H_6$), 2.96 (t, $J_{4\text{-}5}$ = $J_{5\text{-}6}$ = 9.9 Hz, 1H, $H_5$). $^{13}$C NMR (101 MHz, $D_2O$, $CH_3$ signal of EtOH was used as internal reference at δ = 17.47 ppm) δ (ppm): 95.4 ($OCH_2O$), 78.7 ($C_1$), 77.9 ($C_2$), 70.9 ($C_3$), 70.4 ($C_6$), 70.1 ($C_4$), 55.3 ($C_5$). FT-IR ($\nu_{max}$/cm): 3404 (OH), 2922 ($CH_2$), 2851 (C-H), 1636 (N-H), 1240 (C-N), 1165 (C-O-C-O-C), 1069 (C-O-C-O-C), 924 (-$OCH_2O$-). DI-MS m/z (Rel. Int): 191 (2, [M]$^{\cdot+}$), 173 (4), 126 (3), 113 (6), 101 (20), 88 (100) 72 (38), 60 (31). HRMS (ESI/Q-TOF) m/z: [M+H]$^+$ Calcd for [$C_7H_{14}NO_5$]$^+$: 192.0866; found: 192.0866.

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**Keywords:** Cyclitol • Biocatalysis • Amino alcohols • Dihydroxylation • Asymmetric synthesis.

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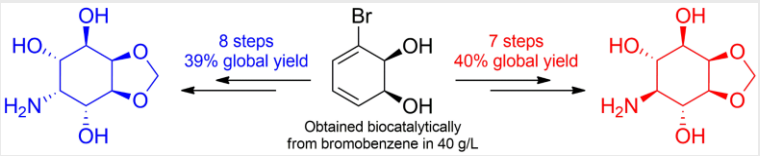


This article describes the synthesis of hygomycin A aminocyclitol moiety and its C2 epimer from bromobezene by a chemoenzymatic strategy. The sequence involved epoxidation, stereocontrolled oxirane ring opening, dihydroxylation of an electron-poor olefin, and introduction of a methylenedioxy group. The aminocyclitols were obtained in high chemical and optical purity.

**Key Topic: Aminocyclitol synthesis**

*Gonzalo Carrau, Ana Inés Bellomo, Leopoldo Suescun and David Gonzalez**

***Page No. – Page No.***

**Title "Chemoenzymatic synthesis of hygromycin A aminocyclitol moiety and its C2 epimer"**