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Fructose-6-phosphate aldolases as versatile biocatalysts for nitrocyclitol syntheses

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ABSTRACT

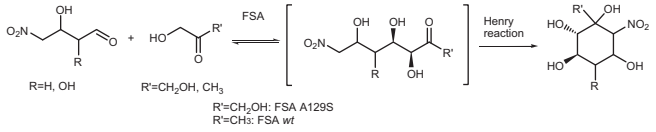
Efficient and stereoselective polyhydroxylated nitrocyclitol syntheses were performed via biocatalysed aldol reactions. The key step was based on a one-pot/one-enzyme cascade reaction process where two reactions occur: aldolase-catalysed aldolisation and spontaneous intramolecular nitroaldolisation. The synthetic methodology was investigated using fructose-6-phosphate aldolase A129S for the synthesis of known nitrocyclitols. Improvements were obtained which involved less steps and increased yields. Several new nitrocyclitols were also prepared using hydroxyacetone (HA) as the donor and FSA *wt*. From nitrocyclitol stereochemical analyses, the intramolecular nitro-Henry reaction stereoselectivity was dependent on the donor substrate used, HA or dihydroxyacetone (DHA). Whereas DHA provided two stereoisomers, four were obtained using HA.

1. Introduction

Cyclitols or carbocyclic polyols are entities that include inositols, conduritols and carbasugars among other variants.[1] These families are involved in the function and regulation of a number of biological processes, such as cellular recognition, signal transduction and selective inhibition of glycosidases.[2] Among them, aminocyclitols, defined as cyclitols bearing one or more amino groups, have emerged as an important, rapidly expanding and diversified family of bioactive compounds with interesting biological properties.[3,4] For instance, certain aminocyclitol derivatives have been shown to act as antibiotics, potent glycosidase inhibitors and have been involved as key components of antiviral agents and artificial receptors.[3a] Thus, there have been continuous efforts over the last decade to prepare natural cyclitols and aminocyclitols as well as their synthetic analogues with enhanced or more selective biological profiles in order to study in depth the influence of this moiety.[1a,5] Nitrocyclitols are essentially found as synthetic precursors of aminocyclitols,[3b,5b,6] to the best of our knowledge, no such naturally occurring cores are described in the literature. However, it should be noted that nitrosugar moieties naturally derived from aminosugars via an oxidation can decorate over 50 bioactive natural products.[7]

Aldol reactions which form C–C bonds have tremendous synthetic utility. In this field, aldolases are one of the most important groups of asymmetric C–C-bond forming enzymes capable of enlarging the carbon skeleton of molecules by stereoselectively catalysing the addition of a ketone donor onto an aldehyde acceptor. The usefulness of aldolases in organic synthesis has recently been reviewed.[8] Among these biocatalysts, fructose 6-phosphate aldolase (FSA) has been well established as an efficient tool for the synthesis of compounds such as rare ketose sugars and iminosugars.[8,9] This enzyme displays excellent activity towards several donor substrates such as dihydroxyacetone (DHA), hydroxyacetone (HA), hydroxybutanone and even more remarkably, glycolaldehyde.[10] In addition, this aldolase accepts a large variety of aldehydes to form optically active ketoses with the highly conserved (3*S*,4*R*) stereochemistry.

Herein we explore the acceptor substrate promiscuous potential of FSA for the synthesis of nitrocyclitols. Based on an original strategy recently developed,[6d–f] various nitrocyclitols are accessible. The key step is a cascade C–C bond formation, which begins with an aldolase-catalysed aldol reaction followed by a spontaneous intramolecular Henry reaction leading to the cyclitol ring (Scheme 1), a process by which four new stereocenters are generated.



Scheme 1. One-pot cascade aldolisation and intramolecular Henry reaction leading to nitrocyclitols.

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Improved syntheses of the nitrobutyraldehyde acceptors are presented. The variant FSA A129S with increased activity for DHA is used with DHA as the donor and FSA *wt* with its best donor HA, the latter affording a new family of C7 deoxy nitrocyclitols.[6c] A discussion on the Henry reaction stereoselectivity is proposed as four stereocenters are created during the cascade reaction process.

2. Results and discussion

2.1. Aldehyde acceptor syntheses

Inspired by our previous work, we first revisited the synthesis of the nitroaldehydes (±)-**1**, (*R*)-**2** and (*S*)-**2**[6d,f] (Fig. 1).

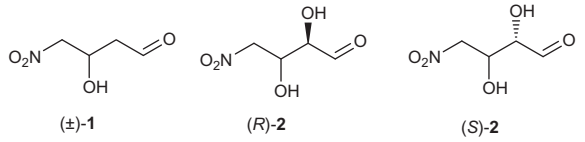
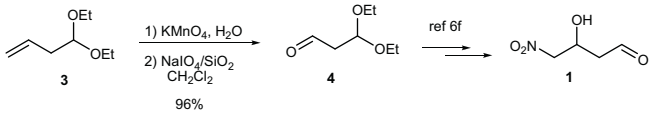


Figure 1. Structure of FSA acceptor substrates.

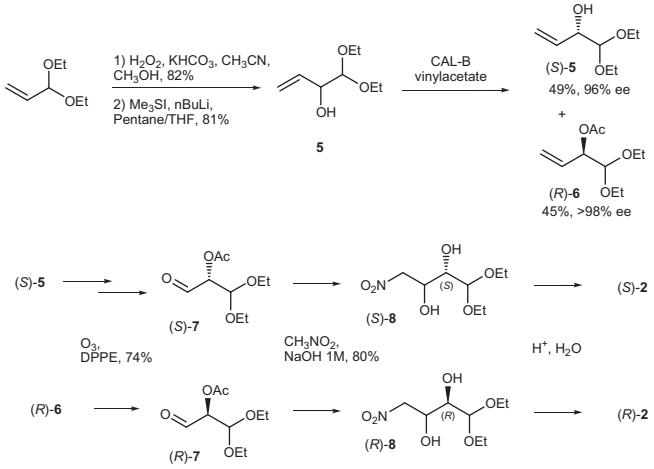
The first nitroaldehyde targeted was the 3-hydroxy-4-nitrobutanal **1** (Scheme 2). Starting from 4,4-diethoxybut-1-ene **3**, which was dihydroxylated with $KMnO_4$ and then oxidised with $NaIO_4$ supported on silica gel, aldehyde **4** was prepared in better overall yield (96%) than the previously reported method using ozonolysis[6f] (78%). Replacement of $KMnO_4$ by catalytic RuO_4 as an oxidising agent was less valuable leading to only 72% yield. Following a previously described protocol,[6f] **4** was reacted with nitromethane to afford an intermediate nitro alcohol. Acetal was then hydrolysed to give the desired nitroaldehyde **1**, which was used directly in the next step.



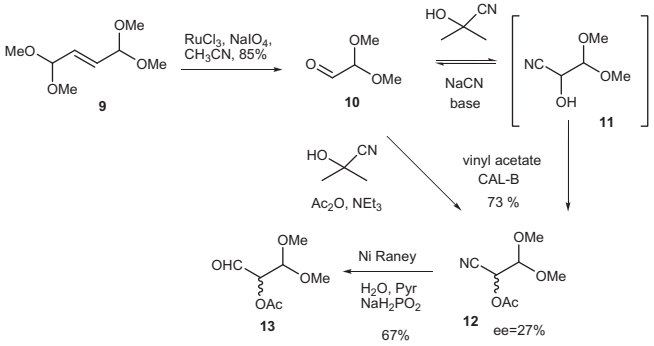
Scheme 2. Improvement of 3-hydroxy-4-nitrobutanal synthesis.

Nitroaldehydes (*R*)-**2** and (*S*)-**2** were synthesised via a new pathway starting from acrolein diethylacetal (Scheme 3). Epoxidation of the alkene with H_2O_2 in the presence of acetonitrile (82% yield) followed by treatment with an excess of dimethylsulfonium methylide afforded the corresponding one-carbon homologated allyl alcohol **5** in 81% yield.[11] Applying a previously described kinetic resolution methodology,[6d] the *Candida antartica* lipase B catalysed transesterification gave enantiomers (*S*)-**5** and (*R*)-**6** (ee >96%) from racemic alcohol **5**. For the next steps, the strategy consisted of the esterification of alcohol (*S*)-**5** while both esters **6** were ozonolysed, followed by a Henry reaction with nitromethane and finally acetal deprotection. During the nitroaldol reaction step, no chiral induction was detected. As for the dimethoxy series,[6d] the compounds were obtained as a 50/50 diastereomeric mixture and were not separable by silica gel chromatography. Nitroaldehydes (*R*)-**2** and (*S*)-**2** were used directly in the next step. The overall yields to reach the protected forms of aldehydes **2** were increased from 10% and 13%[6d] to 15% and 18%, respectively.

We also explored another strategy based on a dynamic kinetic resolution in order to prepare theoretically 100% of one enantiomer of aldehyde **13**, analogous to aldehyde **7** (Scheme 4). Via the reversible formation of a cyanohydrin, an enantioselective



Scheme 3. Synthesis of nitroaldehydes (*R*)-**2** and (*S*)-**2**.



Scheme 4. Dynamic kinetic resolution strategy via reversible formation of a cyanohydrin. Synthesis of racemic aldehyde **13**.

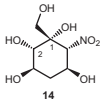
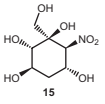
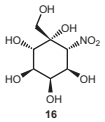
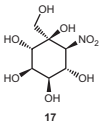
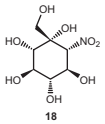
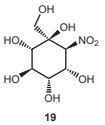
transesterification catalysed by a lipase was investigated on the hydroxyl group. In connection with this, several dynamic kinetic resolutions starting from aromatic and aliphatic aldehydes have been reported in the literature, some of which employ CAL-B as the catalyst.[12]

The methodology depicted in Scheme 4 was first confirmed on the racemic series. Aldehyde **10** was isolated from alkene **9** by classical ruthenium/periodate oxidation. The nitrile ester **12** was then formed chemically using acetone cyanohydrin and acetic anhydride. The desired aldehyde **13** was then directly prepared in 67% yield from **12** by reduction of the nitrile group in the presence of Raney Ni and sodium hypophosphite.[13] Secondly, the dynamic kinetic resolution was studied. Different reaction conditions were varied, for instance the nature of the base (NaCN, KCN, CuCN, etc) and the acylating agent (vinyl acetate, vinyl butyrate, isopropenyl acetate, etc). However, the chemical transesterification was generally much faster than the biocatalysed one and the best conditions (NaCN as a base and vinylacetate) led to 27% ee in 78% yield. Unfortunately, this low ee did not allow further exploitation of this strategy.

2.2. Nitrocyclitol syntheses

With the three aldehydes (±)-**1**, (*R*)-**2** and (*S*)-**2** in hand, the enzymatic reactions were conducted (see Scheme 1) in water at room temperature. The results from the aldolisation catalysed by FSA A129S[6c] in the presence of DHA at pH 7.5 are presented in Table 1. The yields and diastereomeric ratios are compared with the ones previously published using the dihydroxyacetone

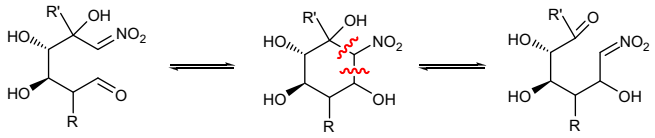
Table 1
FSA A129S biocatalysed preparation of nitrocyclitols

Aldehyde	Nitrocyclitol		Ratio	Yield%
(±)-**1**	 **14**	 **15**	55/45 (50/50)	71 FSA (64) FBA[a]
(*R*)-**2**	 **16**	 **17**	59/41 (65/35)	71 FSA (49) FBA[b]
(*S*)-**2**	 **18**	 **19**	73/27 (61/39)	69 FSA (41) FBA[b]

[a] Ref. 6f.
[b] Ref. 6d.

phosphate (DHAP) dependent fructose-1,6-bisphosphate aldolase (FBA) combined with a phytase for phosphate hydrolysis.[6d,f]

In general, the aldolisations afforded the same nitrocyclitols but in higher yields when FSA was employed rather than FBA/phytase. Contrary to what has been reported on biocatalysed nitro-Henry reactions and more precisely on rabbit muscle FBA aldolase,[14] the intramolecular nitro-Henry cyclisation was not catalysed by an aldolase as this reaction occurs spontaneously due to classical reactivity of nitro derivatives in slightly basic medium.[15] As expected, the FSA A129S variant and FBA have shown a similar acceptor substrate tolerance. These results confirm once more FSA as an efficient tool for aldolisation avoiding laborious DHAP production and the use of a phosphatase. As previously observed, the Henry reaction stereoselectivity was determined by the C-3 hydroxyl configuration of the nitroaldehyde, affording two series of diastereoisomers: (1*S*,6*R*) when C-3 is (*R*) [**14** (1*S*,2*S*,3*R*,5*S*,6*R*), **16** (1*S*,2*S*,3*R*,4*R*,5*R*,6*R*) and **18** (1*S*,2*S*,3*R*,4*S*,5*R*,6*R*)) and (1*R*,6*S*) when C-3 was (*S*) [**15** (1*R*,2*S*,3*R*,5*R*,6*S*), **17** (1*R*,2*S*,3*R*,4*R*,5*S*,6*S*) and **19** (1*R*,2*S*,3*R*,4*S*,5*S*,6*S*)].



Scheme 5. Retro-Henry reaction possible in two directions.

Overall, comparable stereoisomer ratios were obtained when using FSA A129S instead of FBA/phytase. The slight differences can probably be explained by the reaction and work-up conditions. As discussed in previous publications,[6d,f] under smooth heating during the water removal or at a slightly alkaline pH, whatever the C3 configuration of the acceptor aldehyde, compounds **15**, **17** and **19** can be partially isomerised into the corresponding compounds **14**, **16** and **18**, respectively. This has suggested a twofold retroaldolisation process as illustrated in Scheme 5.[15] In all of the series, the (1*S*,6*R*)-stereoisomer was the thermodynamic one.

We next studied FSA *wt*, which is known to have a better activity towards HA than DHA.[6c] We focused some of our work on the synthesis of a new class of nitrocyclitols based on the aldolisation between HA and the nitroaldehydes (±)-**1** and (*R*)-**2** and (*S*)-**2** (Table 2). The same procedure discussed above was applied for the synthesis of nitrocyclitols from DHA.

The reactions with HA and the three different aldehydes (±)-**1**, (*R*)-**2** and (*S*)-**2** catalysed by FSA *wt* afforded the nitrocyclitols in higher overall yields than with DHA and FSA A129S. All the isomers were separated by flash chromatography after two rounds of purification. Based on the (3*S*)-stereoselectivity afforded by the aldolase and on NMR studies (e.g., coupling constants and NOESY experiments) the nitrocyclitol conformations and stereochemistries (Fig. 2) were determined.

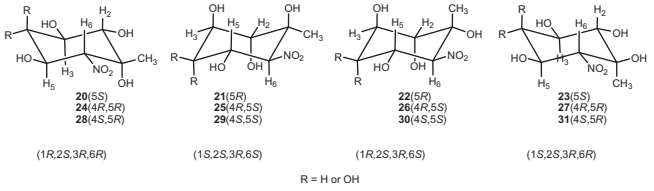
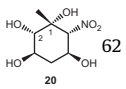
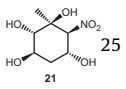
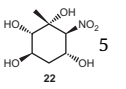
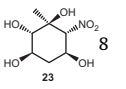
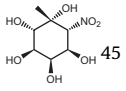
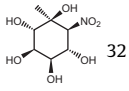
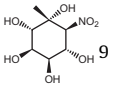
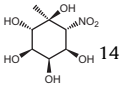
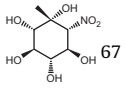
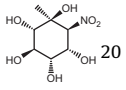
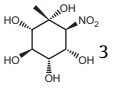
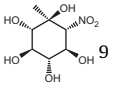


Figure 2. Conformation of deoxy C7 nitrocyclitols, prepared using aldehydes **1** or **2** and HA.

The stereoselectivity of the nitroaldol reaction was lower in the presence of the methyl group than in the presence of the hydroxymethyl group at the C1 position. In fact the two major isomers bearing a methyl at the equatorial position were formed together with two minor isomers bearing the methyl group at the axial position. The nitro group was always found at the equatorial position. A difference of 1.5 kJ mol^{-1} for the free energy calculated at the ab initio level in the gas phase[6d] was found as expected, to disfavour **21** and by 11 kJ mol^{-1} disfavour **23**, compared to **20**. The lower stereoselectivity could be explained by a decrease of the electronic effects or a lack of hydrogen bonds stabilising the transition state while a C1–C6 bond forms due to the missing hydroxyl. It could

Table 2
FSA *wt* biocatalysed preparation of deoxy C7 nitrocyclitols

Aldehyde	Nitrocyclitol ratio				Yield[a] %
(±)-**1**	 **20** 62	 **21** 25	 **22** 5	 **23** 8	84
(*R*)-**2**	 **24** 45	 **25** 32	 **26** 9	 **27** 14	85
(*S*)-**2**	 **28** 67	 **29** 20	 **30** 3	 **31** 9	86

[a] Overall yields (see Section 4 for individual yields).

also be explained by steric effects, with methyl and hydroxyl groups being closer in size than hydroxymethyl and hydroxyl groups.

3. Conclusion

Herein, we have demonstrated the high efficiency of FSA A129S in the nitrocyclitol syntheses, which is applicable on a larger scale and can be carried out in fewer steps than when the FBA/phytase couple was used. These improvements, concerning the preparation of the acceptor aldehydes, also led to better overall yields. Remarkably, twelve new nitrocyclitols were prepared from the aldolisation between HA and the nitroaldehydes catalysed by FSA *wt*. The Henry reaction in the presence of the methyl group (i.e., using HA as donor substrate) was less stereoselective as four isomers were isolated whereas only two isomers were formed with the hydroxymethyl group (i.e., using DHA as a donor substrate).

4. Experimental

4.1. General

FSA *wt* and FSA A129S biocatalysts were produced and their activities were measured as described in the literature.[6c,16] All of the reactions were monitored by TLC with Merck 60F-254 precoated silica (0.2 mm) on aluminium. Flash chromatography was performed using Merck Kieselgel 60 (40–63 μm); the solvent systems are given in v/v. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance 400 in $CDCl_3$, CD_3OD or D_2O (see indication). Chemical shifts (δ) are reported in ppm and coupling constants are given in Hz. IR spectra were recorded on a Perkin–Elmer FT-IR Paragon 500. Optical rotations were measured on a JASCO DIP-370 polarimeter with a sodium (589 nm) lamp at 25 °C. High resolution mass spectra (HRMS) were recorded by the Centre Régional de Mesures Physiques, Aubière, France.

4.2. Aldehyde syntheses

4.2.1. 3,3-Diethoxypropanal 4

To a suspension of alkene **3** (1 g, 7.1 mmol) in water (10 mL) was added 1.1 equiv of $KMnO_4$ (1.2 g) diluted in water (30 mL) at 0 °C. The mixture was then stirred overnight at rt. Sodium bisulphite (1.6 g, 1.2 equiv) was then added and the reaction medium was stirred continuously until discoloration. The reaction medium was then filtered and continuously extracted with ethyl acetate to afford the crude diol. It was then dissolved in dichloromethane (DCM) (32 mL) and $NaIO_4$ supported on silica gel[17] (13 g, 2.4 equiv, 17 mmol) was added. The suspension was stirred for 30 min, then filtered and the solid was rinsed with DCM (3 × 20 mL). The organic phase was dried over $MgSO_4$ filtered and concentrated under vacuum. Aldehyde **4** was isolated in 96% yield (0.99 g). It was used as crude in the next step.

The protocol applied for aldehyde **1** preparation is described in the literature.[6f]

4.2.2. 1,1-Diethoxybut-3-en-2-ol 5

2-(Diethoxymethyl)oxirane: To a suspension of $KHCO_3$ (3.1 g, 30 mmol) in methanol (80 mL) was added acrolein diethyl acetal (23.4 mL, 150 mmol) followed by acetonitrile (9,7 mL, 180 mmol) and 30% hydrogen peroxide (18.9 mL, 180 mmol). The reaction mixture was heated at 40 °C for several hours. After 10, 20 and 30 h of reaction, 1 equiv of hydrogen peroxide (16 mL) and acetonitrile (8 mL) were added. After stirring for 40 h, the reaction was quenched with water (20 mL) and extracted with DCM. The residue was a clear oil (18.3 g, 82% crude), which was used in the next step without further purification. R_f = 0.4 (Cyclohexane/EtOAc 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.32 (d, J = 4.4 Hz, 1H, 3-H), 3.72–3.58 (m, 4H, 4-H, 4′-H), 3.08 (m, 1H, 2-H), 2.76 (m, 2H, 1-H), 1.23 (pt, J = 7.0 Hz, 3H, 5-H), 1.20 (t, J = 7.0 Hz, 3H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 101.4 (3-C), 62.8 (4-C), 62.3 (4′-C), 51.8 (2-C), 43.8 (1-C), 15.2 (5-C, 5′-C).

To a suspension of trimethylsulfonium iodide (21 g, 100 mmol) in a mixture of anhydrous THF/pentane 50:50 (350 mL) was added dropwise an *n*-BuLi solution (2.5 M in hexane, 40 mL, 100 mmol) at −10 °C under argon. The reaction mixture was stirred for 90 min at −10 °C. The epoxide (5 g, 34 mmol) diluted in anhydrous THF (100 mL) was then added. The resulting mixture was stirred for 30 min at −10 °C and then 1 h at room temperature. The reaction was neutralised with saturated aqueous NH_4Cl (50 mL). Volatile compounds were removed (20 °C, 300 mmHg) before extraction of the alkene with DCM. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude product was purified by flash chromatography (DCM/acetone 98:2 then 96:4) to afford **5** as a yellow oil (4.4 g, 81%). R_f = 0.3 (Cyclohexane/EtOAc 8:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.92 (ddd, J = 5.3, 10.8, 17.4 Hz, 1H, 3-H), 5.39 (dd, J = 1.6, 17.4 Hz, 1H, 4-H), 5.22 (dd, J = 1.6, 10.6 Hz, 1H, 4′-H), 4.28 (d, J = 6.0 Hz, 1H, 1-H), 4.07 (dd, J = 5.3, 6.0 Hz, 1H, 2-H), 3.75–3.57 (m, 4H, H_5, H'_5), 2.28 (s, 1H, O-H), 1.23 (pt, J = 7.0 Hz, 3H, 6-H), 1.20 (pt, J = 7.0 Hz, 3H, 6′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.6 (3-C), 116.6 (4-C), 104.6 (1-C), 72.7 (2-C), 63.5 (5-C, 5′-C), 15.2 (6-C, 6′-C) ppm.

4.2.3. Kinetic resolution of alcohol 5

To a solution of alcohol **5** (4.4 g, 28 mmol) in vinyl acetate (80 mL) was added Novozym435® lipase (*C. antartica*, 2.2 g) and the mixture was stirred at room temperature. The reaction course was monitored by GC and when the conversion reached 50% (28 h), the reaction was quenched by filtration. The solvent was evaporated and the mixture was purified by flash chromatography (DCM/acetone 99:01 then 96:04). Ester (*R*)-**6** was isolated (2.5 g, 45%, ee >98%, $[\alpha]_D^{25} = +27$ (*c* 1.0, $CHCl_3$)) and alcohol (*S*)-**5** was isolated (2.0 g, 49%, ee = 96%, $[\alpha]_D^{25} = -29$ (*c* 1.0, $CHCl_3$)).

4.2.4. (*R*)-1-(1,1-Diethoxy)prop-2-enyl acetate (*R*)-6

$[\alpha]_D^{25} = +27$ (*c* 1.0, $CHCl_3$). R_f = 0.8 (Cyclohexane/EtOAc 6:4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.90 (ddd, J = 5.9 Hz, 10.6 Hz, 17.2 Hz, 1H, 3-H), 5.31 (m, 2H, 4-H, 4′-H), 5.25 (ddd, $^3J_{4-2}$ = 1.5, 5.9, 5.7 Hz, 1H, 2-H), 4.44 (d, J = 5.7 Hz, 1H, 1-H), 3.70–3.56 (m, 4H, 5-H, 5′-H), 2.10 (s, 3H, CO CH_3), 1.20 (t, J = 7.1 Hz, 3H, 6-H), 1.19 (t, J = 7.1 Hz, 3H, 6′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9 (C═O), 132.3 (3-C), 118.1 (4-C), 102.3 (1-C), 73.7 (2-C), 63.5 (5-C), 62.8 (5′-C), 21.0 ($CO\mathit{CH_3}$), 15.2 (6-C), 15.1 (6′-C) ppm. IR: ν = 3092, 2976–2888, 1744, 1645, 1236, 1067, 1445–1373, 737 cm^{-1}. HRMS (ES$^+$): *m*/*z* calcd for $C_{10}H_{18}O_4$+Na$^+$: 225.1103 [M+Na$^+$], found: 225.1105. Elemental analysis calcd (%) for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97; O, 31.64. Found: C, 59.62; H, 9.19; O, 31.19.

4.2.5. (*S*)-1-(1,1-Diethoxy)prop-2-enyl acetate (*S*)-6

Following the procedure for the protection of the hydroxyl group previously described,[6d] compound (*S*)-**6** was purified by flash chromatography (DCM/acetone 99:01) and isolated as slightly yellow oil {1.7 g, 83%, $[\alpha]_D^{25} = -27$ (*c* 1.0, $CHCl_3$)}.

4.2.6. 2-Acetoxy-3,3-diethoxypropanal 7

Compound **7** was isolated after flash chromatography (DCM/acetone 98:02) (1.5 g, 74%) following the general procedure for ozonolysis previously described using 1,2-bis(diphenylphosphino)ethane (DPPE) instead of PPh_3 to simplify the purification.[6d] (*S*)-**7**: $[\alpha]_D^{25} = -28$ (*c* 1.0, $CHCl_3$). (*R*)-**7**: $[\alpha]_D^{25} = +29$ (*c* 1, $CHCl_3$).

R_f = 0.6 (Cyclohexane/EtOAc 6:4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.62 (s, 1H, 3-H), 5.17 (d, J = 4.8 Hz, 1H, 2-H), 4.72 (d, J = 4.9 Hz, 1H, 1-H), 3.75–3.59 (m, 4H, 4-H, 4′-H), 2.18 (s, 3H, $COCH_3$), 1.23 (m, 3H, 5-H), 1.21 (m, 3H, 5′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.9 (3-C), 169.9 (6-C), 101.0 (1-C), 77.7 (2-C), 64.3 (4-C), 63.5 (4′-C), 20.4 ($COCH_3$), 15.1 (5-C), 15.0 (5′-C) ppm. IR: ν = 2980–2899, 2733, 1740, 1233, 1067, 1445–1375 cm^{-1}. HRMS (ES+): m/z calcd for $C_9H_{16}O_5 + CH_3OH\ Na^+$: 259.1158 [M+$CH_3$OH+Na$^+$], found: 259.1158.

4.2.7. 4,4-Diethoxy-1-nitrobutan-2,3-diol 8 (protected form of aldehyde 2)

Compound **8** was isolated in the form of 2 diastereoisomers after flash chromatography (Cyclohexane/EtOAc 2:8) (1.79 g, 80%) following the general procedure for the Henry reaction previously described.[6d] (*S*)-**8**: $[\alpha]_D^{25} = -21$ (*c* 1.6, $CHCl_3$). (*R*)-**8**: $[\alpha]_D^{25} = 20$ (*c* 1, $CHCl_3$). R_f = 0.4–0.35 (Cyclohexane/EtOAc 2:8). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.71–4.51 (m, 2H, 1-H), 4.61–4.51 (m, 1H, 2-H), 4.61–4.60 (2 d, $^3J_{4-3}$ = 5.4–7.0 Hz, 1H, 4-H), 3.82–3.63 (m, 4H, 5-H, 5′-H), 3.63–3.51 (2 dd, J = 5.4–7.0 Hz, 1.1–1.5 Hz, 1H, 3-H), 3.35–2.99 (s, 2H, 2 OH), 1.25 (pt, J = 7.0 Hz, 3H, 6-H),1.24 (pt, J = 7.0 Hz, 3H, 6′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 102.6 (4-C), 78.1–77.8 (1-C), 71.2–70.8 (2-C), 69.0–67.5 (3-C), 64.8–64.1 (5-C), 64.0–63.8 (5′-C), 15.0 (6-C), 14.9–14.8 (6′-C) ppm. IR: ν = 3430, 2978–2901, 1557, 1381, 1117, 1061, 1423–1348 cm^{-1}. HRMS (ES+): m/z calcd for $C_8H_{17}NO_6$+Na$^+$: 246.0962 [M+Na$^+$], found: 246.0954. Elemental analysis calcd (%) for $C_8H_{17}NO_6$: C, 43.04; H, 7.68; N, 6.27; O, 43.01. Found: C, 42.88; H, 7.65; N, 6.08; O, 43.39.

4.2.8. Dimethoxyacetaldehyde 10

To a suspension of $NaIO_4$ (3 g, 14 mmol) supported on silica (10 g) in DCM (30 mL) was added alkene **9** (355 mg, 2 mmol) previously diluted in DCM (20 mL). The mixture was stirred for 30 min at room temperature before being filtered. The solid residue was washed twice with DCM (20 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under vacuum very carefully (20 °C, 300 mmHg) due to the high volatility of aldehyde **10**. The residue was a clear liquid (350 mg, 85% crude) used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.47 (d, J = 1.5 Hz, 1H, 1-H), 4.50 (d, J = 1.5 Hz, 1H, 2-H), 3.46 (s, 6H, 3-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.2 (1-C), 122.3 (2-C), 54.6 (3-C) ppm.

4.2.9. 1-Cyano-2,2-dimethoxyethyl acetate 12

To a solution of aldehyde **10** freshly prepared, (2.85 mmol, 300 mg) diluted in anhydrous DCM (5 mL) were added acetone cyanohydrin (2.85 mmol, 260 μL), triethylamine (5.7 mmol, 800 μL) and acetic anhydride (4.28 mmol, 400 μL). The mixture was stirred at room temperature overnight. The reaction was neutralised with saturated aqueous NH_4Cl (5 mL) and extracted with DCM. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash chromatography (Cyclohexane/EtOAc 7:3) to afford **12** (360 mg, 73%). R_f = 0.3 (Cyclohexane/EtOAc 7:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.40 (d, J = 5.9 Hz 1H, 2-H), 4.60 (d, J = 5.9 Hz, 1H, 3-H), 3.53 (s, 3H, 4-H), 3.43 (s, 3H, 4′-H), 2.17 (s, 3H, $COCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2 (C=O), 120.6 (1-C), 102.9 (3-C), 70.3 (2-C), 54.7–54.5 (4-C, 4′-C), 20.3 ($COCH_3$) ppm.

4.2.10. Racemic 2-acetoxy-3,3-dimethoxypropanal 13

To a solution of **12** (0.55 mmol, 95 mg) diluted in a mixture of 1:1:2 water–acetic acid–pyridine (6 mL) was added at 0 °C Raney nickel (6.6 mmol, 0.4 g) followed by sodium hypophosphite (3.3 mmol, 0.4 g). The reaction mixture was stirred at 0 °C for 30 min before being filtered. The filtrate was extracted with DCM. The combined organic phases were washed with 5% aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated under vacuum to give aldehyde **13** as a clear liquid (65 mg, 67% crude). R_f = 0.6 (Cyclohexane/EtOAc 6:4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.6 (d, J = 2.2 Hz, 1H, 1-H), 5.2 (dd, J = 4.9, 2.2 Hz, 1H, 2-H), 4.6 (d, J = 4.9 Hz, 1H, 3-H), 3.47–3,46 (s, 6H, 4-H, 4′-H), 2.2 (s, 3H, $COCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.6 (HC=O), 169.8 (OC=O), 102.7 (3-C), 77 (2-C), 56–54.9 (4-C, 4′-C), 20.5 ($COCH_3$) ppm.

4.3. Nitrocyclitol syntheses

General procedure for the preparation of nitrocyclitols with FSA A129S: To a solution of acetal **1a**, (*R*)-**8**, (*S*)-**8** (4.3 mmol) in H_2O (5 mL) was added a cation exchange resin (Dowex 50x8, H^+ form, 1 g). The suspension was stirred at 45 °C overnight to afford aldehyde **1**, (*R*)-**2** and (*S*)-**2**, respectively (quantitative by TLC). The resin was filtered off and rinsed with H_2O (3.5 mL). Next, pH was adjusted to 7.5 with 1 M NaOH affording a 0.5 M solution of aqueous aldehyde. To this solution were added DHA (350 mg, 3.9 mmol) followed by FSA A129S (100 mg lyophilised powder, 300 U).[15] The reaction mixture was placed on a reciprocal shaker for 17 h at 25 °C (175 rpm). MeOH (50 mL) was added and the mixture was centrifuged (20,000 rpm, 40 min, 5 °C). The supernatant was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM/MeOH gradient 9:1 to 8:2), to afford the desired nitrocyclitols **14** (39%), **15** (32%), **16** (42%), **17** (29%), **18** (50%) and **19** (19%). The NMR data were identical to those previously reported.[6d,f]

General procedure for the preparation of nitrocyclitols with FSA *wt*: To a solution of 0.5 M aqueous aldehyde **1**, (*R*)-**2** and (*S*)-**2** (6.5 mL, 3.25 mmol) adjusted at pH 7.5 with NaOH 0.1 M were added HA (200 mg, 2.7 mmol) followed by FSA *wt* (680 mg lyophilised powder, 210 U).[15] The reaction mixture was placed on a reciprocal shaker for 18 h at 25 °C (175 rpm). MeOH (40 mL) was added and the mixture was centrifuged (20000 rpm, 40 min, 5 °C). The supernatant was concentrated under reduced pressure. The residue was purified by flash chromatography (DCM/MeOH gradient 9:1 to 8:2, two rounds of purification), affording the desired nitrocyclitols **20** (52%), **21** (21%), **22** (4%), **23** (7%), **24** (38%), **25** (27%), **26** (8%), **27** (12%), **28** (58%), **29** (17%), **30** (3%), **31** (8%).

For all isomers **20**–**23**: IR: ν = 3368, 1551, 1372, 1067–1034 cm^{-1}. HRMS (ES+): m/z calcd for $C_7H_{13}NO_6$+Na$^+$: 230.0640 [M+Na$^+$], found 230.0636.

4.3.1. (1*R*,2*S*,3*R*,5*S*,6*R*)-1-Methyl-6-nitrocyclohexane-1,2,3,5-tetrol 20

R_f = 0.26 (DCM/MeOH 8:2). $[\alpha]_D^{25} = +13$ (*c* 1, CH_3OH). ^{1}H NMR (400 MHz, MeOD): δ = 4.43 (ddd, J = 10.2, 10.6, 4.9 Hz, 1H, 5ax-H), 4.35 (d, J = 10.2 Hz, 1H, 6ax-H), 3.76 (ddd, J = 12.2, 9.1, 4.9 Hz, 1H, 3ax-H), 3.07 (d, J = 9.1 Hz, 1H, 2ax-H), 2.25 (m, 1H, 4eq-H), 1.42 (ddd, J = 12.2, 10.6, 11.9 Hz, 1H, 4ax-H), 1.32 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 98.2 (6-C), 79.6 (2-C), 74.3 (1-C), 69.2 (3-C), 66.7 (5-C), 39.3 (4-C), 23.1 (7-C) ppm.

4.3.2. (1*S*,2*S*,3*R*,5*R*,6*S*)-1-Methyl-6-nitrocyclohexane-1,2,3,5-tetrol 21

R_f = 0.49 (DCM/MeOH 8:2). $[\alpha]_D^{25} = -15$ (*c* 1, CH_3OH). ^{1}H NMR (400 MHz, MeOD): δ = 4.62 (ddd, J = 11.3, 11.3, 4.8 Hz, 1H, 5ax-H), 4.52 (d, J = 10.4 Hz, 1H, 6ax-H), 3.97 (m, 1H, 3eq-H), 3.57 (d, J = 2.0 Hz, 1H, 2eq-H), 2.12 (ddd, J = 4.8, 2.1, 13.5 Hz, 1H, 4eq-H), 1.93 (ddd, J = 11.3, 11.3, 2.4 Hz, 1H, 4ax-H), 1.28 (s, 3H, CH_3) ppm.^{13}C NMR (100 MHz, MeOD): δ = 96.3 (6-C), 77.1 (1-C), 74.8 (2-C), 72.6 (3-C), 65.0 (5-C), 36.4 (4-C), 24.2 (7-C) ppm. IR: ν = 3374 (OH), 1549 (NO), 1377 (CN), 1047 (CO) cm^{-1}. HRMS

(ES+): m/z calcd for $C_7H_{13}NO_6$+Na^+: 230.0640 [M+Na^+], found 230.0634.

4.3.3. (1*R*,2*S*,3*R*,5*R*,6*S*)-1-Methyl-6-nitrocyclohexane-1,2,3,5-tetrol 22

R_f = 0.41 (DCM/MeOH 8:2). $[\alpha]_D^{25} = +32$ (c 1.0, CH_3OH). ^1H NMR (400 MHz, MeOD): δ = 4.63 (d, J = 10.6 Hz, 1H, 6ax-H), 4.35 (m, 1H, 5ax-H), 3.97 (m, 1H, 3eq-H), 3.54 (d, J = 2.4 Hz, 1H, 2eq-H), 1.98 (m, 1H, 4eq-H), 1.91 (ddd, J = 11.3, 11.3, 3.3 Hz, 1H, 4ax-H), 1.34 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 97.9 (6-C), 78.1 (2-C), 74.8 (1-C), 70.4 (3-C), 66.6 (5-C), 36.5 (4-C), 21.7 (7-C) ppm. IR: ν = 3362 (OH), 1549 (NO), 1377 (CN), 1046 (CO) cm^{-1}. HRMS (ES+): m/z calcd for $C_7H_{13}NO_6$+Na^+: 230.0640 [M+Na^+], found 230.0632.

4.3.4. (1*S*,2*S*,3*R*,5*S*,6*R*)-1-Methyl-6-nitrocyclohexane-1,2,3,5-tetrol 23

R_f = 0.30 (DCM/MeOH 8:2). $[\alpha]_D^{25} = -35$ (c 1, CH_3OH). ^1H NMR (400 MHz, MeOD): δ = 4.41 (d, J = 10.8 Hz, 1H, 6ax-H), 4.16 (ddd, J = 10, 11.2, 4.9 Hz, 1H, 5ax-H), 3.46 (ddd, J = 11.2, 9.5, 4.9 Hz, 1H, 3ax-H), 3.26 (d, J = 9.5 Hz, 1H, 2ax-H), 2.25 (m, 1H, 4eq-H), 1.46 (q, J = 11.7 Hz, 1H, 4ax-H), 1.17 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 99.6 (6-C), 81.3 (2-C), 74.7 (1-C), 68.8 (3-C), 66.9 (5-C), 39.7 (4-C), 16.4 (7-C) ppm.

For all isomers **24**–**27**: IR: ν = 3357, 1554, 1375, 1053 cm^{-1}. HRMS (ES+): m/z calcd for $C_7H_{13}NO_7$+Na^+: 246.0590 [M+Na^+], found 246.0578.

4.3.5. (1*R*,2*S*,3*R*,4*R*,5*R*,6*R*)-1-Methyl-6-nitrocyclohexane-1,2,3,4,5-pentol 24

R_f = 0.22 (DCM/MeOH 8:2). $[\alpha]_D^{25} = +28$ (c 1.0, CH_3OH). ^1H NMR (400 MHz, MeOD): δ = 4.64 (d, J = 10.8 Hz, 1H, 6ax-H), 4.39 (dd, J = 10.8, 3.1 Hz, 1H, 5ax-H), 4.03 (t, J = 3.1 Hz, 1H, 4eq-H), 3.70 (dd, J = 3.1, 9.7 Hz, 1H, 3ax-H), 3.46 (d, J = 9.7 Hz, 1H, 2ax-H), 1.33 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 94.0 (6-C), 77.0 (1-C), 74.7 (2-C), 73.3 (4-C), 71.8 (3-C), 69.3 (5-C), 23.2 (7-C) ppm.

4.3.6. (1*S*,2*S*,3*R*,4*R*,5*S*,6*S*)-1-Methyl-6-nitrocyclohexane-1,2,3,5-pentol 25

R_f = 0.42 (DCM/MeOH 8:2). $[\alpha]_D^{25} = -16$ (c 1.0, CH_3OH). ^1H NMR (400 MHz, MeOD): δ = 4.56 (d, J = 10.6 Hz, 1H, 6ax-H), 4.43 (pt, 9.9, 9.9 Hz, 1H, 5ax-H), 3.99 (m, 1H, 3eq-H), 3.75 (dd, J = 9.7, 3.5 Hz, 1H, 4ax-H), 3.69 (d, J = 3.5 Hz, 1H, 2eq-H), 1.28 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 94.9 (6-C), 75.8 (3-C), 75.4 (2-C), 73.7 (1-C), 72.6 (4-C), 69.6 (5-C), 24.0 (7-C) ppm.

4.3.7. (1*R*,2*S*,3*R*,4*R*,5*S*,6*S*)-1-Methyl-6-nitrocyclohexane-1,2,3,4,5-pentol 26

R_f = 0.37 (DCM/MeOH 8:2). $[\alpha]_D^{25} = +33$ (c 1.0, CH_3OH). ^1H NMR (400 MHz, MeOD): δ = 4.67 (d, J = 11.0 Hz, 1H, 6ax-H), 4.16 (dd, J =11.0, 9.9 Hz, 1H, 5ax-H), 3.99 (m, 1H, 3eq-H), 3.75 (m, 1H, 4ax-H), 3.65 (d, J = 3.5 Hz, 1H, 2eq-H), 1.36 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 96.1 (6-C), 78.4 (2-C), 76.9 (1-C), 76.0 (4-C), 73.4 (3-C), 70.4 (5-C), 21.9 (7-C) ppm.

4.3.8. (1*S*,2*S*,3*R*,4*R*,5*R*,6*R*)-1-Methyl-6-nitrocyclohexane-1,2,3,4,5-pentol 27

R_f = 0.28 (DCM/MeOH 8:2). $[\alpha]_D^{25} = -35$ (c 1.0, CH_3OH). ^1H NMR (400 MHz, MeOD): δ = 4.79 (d, J = 11.2 Hz,1H, 6ax-H), 4.10 (dd, J = 11.0, 3.3 Hz, 1H, 5ax-H), 4.00 (pt, J = 3.3, 3.3 Hz, 1H, 4eq-H), 3.72 (d, J = 9.9 Hz, 1H, 2ax-H), 3.40 (dd, J = 3.1, 10.2 Hz, 1H, 3ax-H), 1.19 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 95.3 (6-C), 76.4 (1-C), 75.3 (4-C), 73.2 (2-C), 72.6 (3-C), 69.8 (5-C), 23.9 (7-C) ppm.

For all isomers **28**–**31**: IR: ν = 3368, 1552, 1376, 1042 cm^{-1}. HRMS (ES+): m/z calcd for $C_7H_{13}NO_7$+Na^+: 246.0590 [M+Na^+], found 246.0582.

4.3.9. (1*R*,2*S*,3*R*,4*S*,5*R*,6*R*)-1-Methyl-6-nitrocyclohexane-1,2,3,4,5-pentol 28

R_f = 0.2 (DCM/MeOH 8:2). $[\alpha]_D^{25} = +27$ (c 1, CH_3OH). ^1H NMR (400 MHz, MeOD): δ = 4.60 (d, J = 10.6 Hz, 1H, 6ax-H), 4.41 (dd, J = 10.6, 11.0 Hz, 1H, 5ax-H), 4.01 (pt, J = 11.1, 11.1 Hz, 1H, 4ax-H), 3.71 (dd, J = 11.1, 9.7 Hz, 1H, 3ax-H), 3.43 (d, J = 9.7 Hz, 1H, 2ax-H), 1.33 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 94.1 (6-C), 77.1 (1-C), 74.8 (2-C), 73.5 (4-C), 71.9 (3-C), 69.5 (5-C), 24.1 (7-C) ppm.

4.3.10. (1*S*,2*S*,3*R*,4*S*,5*S*,6*S*)-1-Methyl-6-nitrocyclohexane-1,2,3,4,5-pentol 29

R_f = 0.43 (DCM/MeOH 8:2). $[\alpha]_D^{25} = -15$ (c 1.0, CH_3OH). ^1H NMR (400 MHz, MeOD): δ = 4.60 (d, J = 10.6 Hz, 1H, 6ax-H), 4.39 (dd, J = 11.0, 3.3 Hz, 1H, 5ax-H), 3.99 (dd, J = 3.5, 3.1 Hz, 1H, 3eq-H), 3.75 (pt, J = 3.1, 3.1 Hz, 1H, 4eq-H), 3.61 (d, J = 3.5 Hz, 1H, 2eq-H), 1.28 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 94.9 (6-C), 76.6 (4-C), 75.0 (2-C), 71.7 (3-C), 71.2 (1-C), 69.5 (5-C), 20.0 (7-C) ppm.

4.3.11. (1*R*,2*S*,3*R*,4*S*,5*S*,6*S*)-1-Methyl-6-nitrocyclohexane-1,2,3,4,5-pentol 30

R_f = 0.37 (DCM/MeOH 8:2). $[\alpha]_D^{25} = +25$ (c 1.0, CH_3OH). ^1H NMR (400 MHz, MeOD): δ = 4.79 (d, J = 11.2 Hz, 1H, 6ax-H), 4.12 (dd, J = 11.0, 3.2 Hz, 1H, 5ax-H), 4.00 (dd, J = 3.1, 2.5 Hz, 1H, 3eq-H), 3.69 (pt, J = 3.1, 3.1 Hz, 1H, 4eq-H), 3.45 (d, J = 2.5 Hz, 1H, 2eq-H), 1.18 (s, 3H, CH_3) ppm.^{13}C NMR (100 MHz, MeOD): δ = 95.1 (6-C), 76.7 (4-C), 73.1 (2-C), 72.6 (1-C), 71.7 (3-C), 68.7 (5-C), 21.1 (7-C) ppm.

4.3.12. (1*S*,2*S*,3*R*,4*S*,5*R*,6*R*)-1-Methyl-6-nitrocyclohexane-1,2,3,4,5-pentol 31

R_f = 0.27 (DCM/MeOH 8:2). $[\alpha]_D^{25} = -25$ (c 1.0, CH_3OH). ^1H NMR (400 MHz, MeOD): δ = 4.69 (d, J = 11.0 Hz,1H, 6ax-H), 4.09 (dd, J = 10.6, 9.9 Hz, 1H, H-5ax), 3.99 (pt, J = 9.9, 9.9 Hz, 1H, 4ax-H), 3.72 (dd, J = 10.0, 10.0 Hz, 1H, 3ax-H), 3.40 (d, J = 10.0 Hz, 1H, 2ax-H), 1.19 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 95.0 (6-C), 75.6 (2-C), 73.8 (1-C), 73.3 (4-C), 70.5 (3-C), 69.7 (C-5), 22.0 (7-C) ppm.

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