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Synthesis and glycosidase inhibitory activity of enantiopure polyhydroxylated octahydroindoles and decahydroquinolines, analogs to castanospermine

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Abstract—The synthesis of new enantiopure polyhydroxylated octahydroindoles and decahydroquinolines, analogs to castanospermine, via a double reductive amination of enantiopure cyclic ketoaldehyde, and their inhibitory activity against α- or β-D-glucosidases, α-D-mannosidase and α-L-fucosidase are described.

1. Introduction

Polyhydroxylated indolizidine alkaloids are widespread in nature and possess very diverse and important physiological properties.[1] For example, castanospermine **1** (Fig. 1) is a competitive inhibitor of α-D-glucosidase which blocks the processing of N-linked glycoproteins.[2] Consequently, this compound and its derivatives have been extensively studied as potential therapeutic agents to treat various diseases such as diabetes,[3] cancer[4] and HIV.[5] Unfortunately many of these compounds are also toxic to human cells, and the use of castanospermine as a clinical therapeutic has been withdrawn. Nevertheless, there is a need to prepare new polyhydroxylated alkaloid analogs to allow a better understanding of the structural requirements for glycosidase inhibition and to develop more potent, selective and less toxic drugs. In that context, we embarked on the synthesis of new compounds with an octahydroindole skeleton, which is the *N*-atom position isomer of the indolizidine structure encountered in the castanospermine; furthermore, compounds displaying a decahydroquinoline skeleton, homolog to the previous one, were also targeted. In an effort to produce new inhibitors of glycosidases with a good specificity, we wished to explore the *N*-substitution by an aglycon part. The choice of the aglycon moiety was directed by careful examination of known inhibitors, such as miglitol[6] (R=CH_2–CH_2OH), and voglibose[7] (R=$CH(CH_2OH)_2$) which have already been demonstrated as inhibitors of intestinal digestive enzymes and which have been approved to treat diabetes.

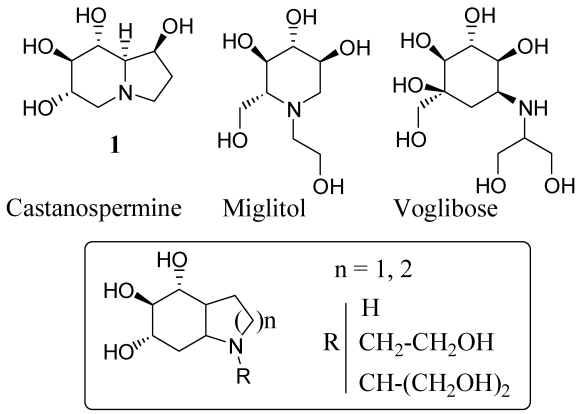

Figure 1.

We report here full results concerning the synthesis of these new compounds and their evaluation as glycosidase inhibitors.[8] Recently, we have delineated a convenient access to a polyhydroxylated cycloalkanone (Fig. 2), protected as its dithioketal, involving a one-pot domino alkylation–cyclization reaction of bis-epoxides derived from D-mannitol.[9] Herein, we further demonstrate the utility of this enantiopure polyhydroxylated cycloalkanone which has the same absolute configuration at the asymmetric carbon atoms as castanospermine **1**. To access to the target molecules, our retrosynthetic analysis involves a formal homologation with one or two carbon moieties of the hydroxymethyl side chain to give the corresponding

Keywords: alkaloid; azasaccharide; bicyclic compounds; castanospermine; glycosidase; octahydroindole; decahydroquinoline; reductive amination.
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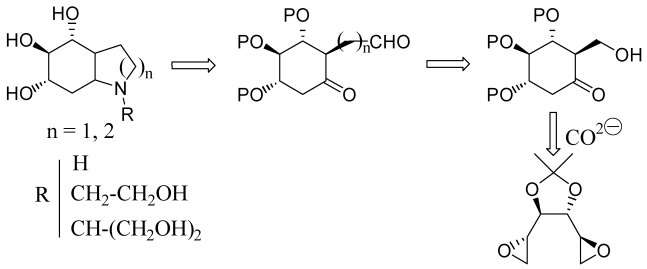
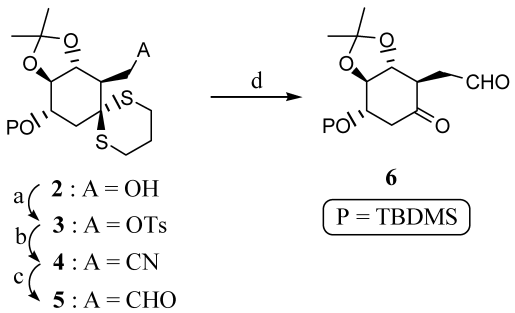


Figure 2. Retrosynthetic analysis.

ketoaldehyde, and a subsequent cyclizing double reductive amination with various primary amines.

2. Results and discussion

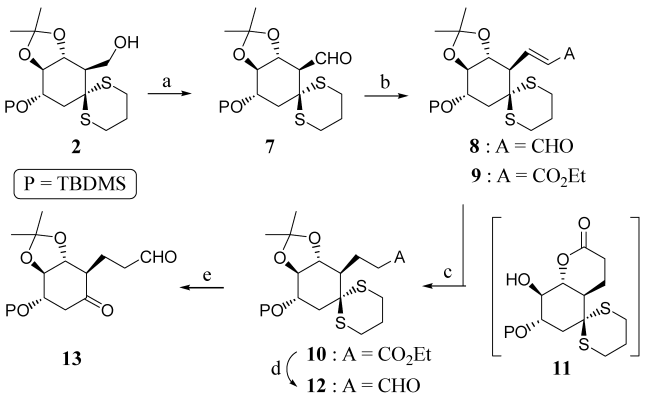
The preparation of the indolizidine analogs of castanospermine requires, at first, elongation of the hydroxymethyl side chain of the dithioketal polyhydroxylated cycloalkanone **2** by one carbon atom to reach the ketoaldehyde **6** (Scheme 1).



Scheme 1. *Reagents and conditions:* (a) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 98%; (b) NaCN, DMSO, 90°C, 92%; (c) DIBAL-H, $PhCH_3$, −78°C, 77%; (d) NBS, acetone, H_2O, −50°C, 75%.

This was easily accomplished by activation of the free primary alcohol function as tosylate (98%) followed by nucleophilic substitution with sodium cyanide in DMSO[10] at 90°C to afford the nitrile **4** (92%). Subsequent reduction by di-*iso*-butylaluminium hydride (DIBAL-H) in toluene at −78°C led to the expected aldehyde **5** (77%). Finally, hydrolysis of the dithioketal function with *N*-bromosuccinimide in aqueous acetone at −50°C[11] gave the ketoaldehyde **6** (75%). No epimerization adjacent to the ketone was observed by ^1H and ^{13}C NMR.

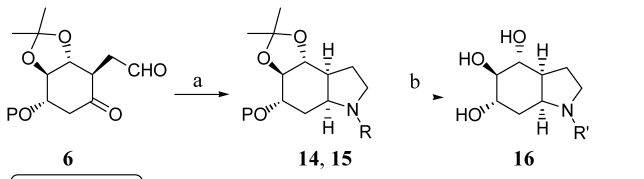
On the other hand, the preparation of the quinolizidine analogs of castanospermine requires elongation of hydroxymethyl side chain of the dithioketal polyhydroxylated cycloalkanone **2** by two carbon atoms to reach the ketoaldehyde **13** (Scheme 2). Oxidation of the primary free alcohol function of **2** was achieved by SO_3-pyridine[12] in the presence of triethylamine at 20°C to afford the corresponding aldehyde **7** (93%). No trace of epimerization could be detected by ^{13}C and ^1H NMR analysis. It should be noted that Swern's oxidation ($(COCl)_2$, DMSO, Et_3N, −78°C) of **2**, only afforded full degradation of the starting material, probably because of the sulphur participation.



Scheme 2. *Reagents and conditions:* (a) SO_3/pyridine, DMSO, Et_3N, CH_2Cl_2, rt, 93%; (b) $Ph_3PCHCHO$, $PhCH_3$, 55°C, 40% or $(EtO)_2POCH_2CO_2Et$, *t*-BuOK, THF, −78°C, 85%; (c) $TsNH\text{-}NH_2$, NaOAc, THF, H_2O, 78°C, 94% from **9**; (d) DIBAL-H, $PhCH_3$, −78°C, 58%; (e) NBS, acetone, H_2O, −50°C, 75%.

Wittig olefination of the aldehyde **7** by treatment with the formylmethylene triphenylphosphorane in toluene at 55°C gave the pure *trans*-α,β-ethylenic aldehyde **8** in 40% yield (J_{trans}=15.8 Hz). Attempts to complete this reaction were unsuccessful. Thus, increasing the reaction time or the temperature did not improve the yield, and increasing the equivalent of the ylide gave the corresponding α,β,γ,δ-diethylenic aldehyde. To overcome this difficulty, we used a Horner–Wadsworth–Emmons reaction with the anion of triethylphosphonoacetate, generated in situ by potassium *tert*-butoxide,[13] to afford the α,β-ethylenic ester **9** in 85% yield. Nevertheless, a second difficulty was encountered during the double bond reduction of the α,β-ethylenic ester **9** which proved troublesome again because of the presence of the dithioketal function. Thus, neither the hetereogeneous hydrogenation in the presence of palladium on charcoal, or palladium black, or rhodium on alumina in ethanol, or in the presence of platinium (IV) oxide in ethyl acetate,[14] nor reduction in the presence of the copper (I) hydride cluster {$((Ph_3P)CuH_6$, $PhCH_3$, 0°C}[15] or K-selectride® (THF, −78°C)[16] or magnesium turnings (MeOH, reflux)[17] gave any expected product. Sodium borohydride reduction in the presence of lithium iodide (MeOH, reflux)[18] only afforded the α,β-ethylenic methyl ester resulting from transesterification. Hydrogenation (P=6 bar) in the presence of Wilkinson's catalyst[19] in benzene or toluene at 80°C gave no expected product, while in benzene–EtOH an unexpected lactone **11**, probably resulting from double bond reduction followed by transketalisation and subsequent lactonization, was isolated in a non-reproducible 63% yield. Fortunately, the double bond reduction performed with tosyl hydrazide[20] in aqueous THF at 78°C followed by slow addition of sodium acetate in H_2O afforded the desired saturated ethyl ester **10** (94%). Then, reduction of the ester[21] **10** was achieved using DIBAL-H in toluene at −78°C giving the corresponding aldehyde **12** in 58% yield. Finally, removal of the dithioketal group, as above, with *N*-bromosuccinimide at −50°C gave the ketoaldehyde **13** (75%). During the chemical modifications of **2** in **13**, no epimerization was observed by ^1H and ^{13}C NMR.

We next turned our attention to the double reductive amination[22] of the ketoaldehyde **6** or **13** with various



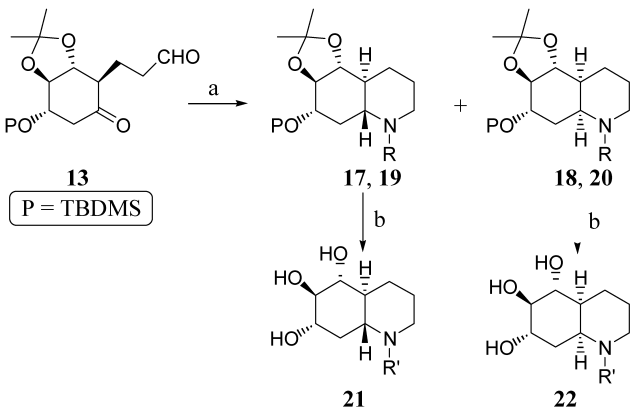
	R = 14	15	R' = 16
a	Bn	H	H
b	CH_2-CH_2OH	–	CH_2-CH_2OH
c	$CH(CH_2OTBDMS)_2$	–	$CH(CH_2OH)_2$

Scheme 3. *Reagents and conditions:* (a) RNH_2, $NaBH_3CN$, MeOH, AcOH, 50–75%; (b) TFA, H_2O, or H_2, $Pd(OH)_2$, EtOH then TFA, H_2O, 50–90%.

primary amines as the origin of the octahydroindole or decahydroquinoline skeleton. Based on diversity, hydrophilicity and expected further reactivity of amino-building blocks, three primary amines were selected: benzylamine, 2-ethanolamine, and bis-*O*-*tert*-butyldimethylsilylserinol, chosen to afford, the *N*-unsubstituted derivative analog of castanospermine, as a reference in the inhibition studies, and the aglycon part of miglitol and voglibose, respectively. For example, treatment of the ketoaldehyde **6** (Scheme 3) with either benzylamine, 2-ethanolamine, or bis-*O*-*tert*-butyldimethylsilylserinol in the presence of acetic acid and sodium borohydride in methanol at 20°C afforded the expected octahydroindole **14a**, **14b**, or **14c**, isolated as a single product in 50, 62 or 75% yield, respectively. ^1H and ^{13}C NMR analysis established without ambiguity firstly, the absence of epimerization during the reaction, and secondly a *cis* relationship at the ring junction (**14a**, for example: $J_{3a,7a}$=ca. 4.4 Hz). Finally, hydrogenolysis of the *N*-benzyl bond of **14a** in the presence of catalytic palladium hydroxide (46%), followed by acidic hydrolysis of both acetonide and silylether and subsequent purification by ion exchange chromatography led to the desired analog of castanospermine **16a** (66%). For compounds **14b** and **14c**, deprotections were achieved in a single step by acidic hydrolysis (TFA-H_2O) to give after purification, as above, the *N*-substituted analogs **16b** and **16c** in 98 and 92% yield, respectively.

In a similar manner, access to the decahydroquinoline analogs has been carried out from the ketoaldehyde **13** (Scheme 4).

Nevertheless, it should be noted that the reductive amination led to a mixture of the two epimers **17** and **18** at the ring junction which could be easily separated by flash chromatography. The *trans*/*cis* ratio, 75/25, 60/40 and 40/60, respectively for **a**, **b** and **c** has been evaluated by the ^1H NMR spectrum ($J_{4a,8a}$=ca. 12.8 and 3.2 Hz, respectively) of the crude mixture **17/18**. Then, complete deprotection was carried out under similar conditions as in the octahydroindole series to afford after purification by ion exchange chromatography the targeted pure decahydroquinolines **21a**, **21b**, **21c**, **22a**, **22b**, and **22c**.



	17 or 18 R =	19 or 20 R =	21 or 22 R' =
a	Bn	H	H
b	CH_2-CH_2OH	–	CH_2-CH_2OH
c	$CH(CH_2OTBDMS)_2$	–	$CH(CH_2OH)_2$

Scheme 4. *Reagents and conditions:* (a) RNH_2, $NaBH_3CN$, MeOH, AcOH; (b) TFA, H_2O, or H_2, $Pd(OH)_2$, EtOH then TFA, H_2O, 50–92%.

3. Inhibition studies[23]

The new polyhydroxylated alkaloids **16**, **21** and **22** were screened against four common glycosidases (α-D-glucosidase from *Bacillus stearothermophilus*, β-D-glucosidase from almonds, α-D-mannosidase from Jack beans and α-L-fucosidase from bovine kidney). The data are summarized in the Table 1 and compared with the reported activity of the castanospermine **1**. The polyhydroxylated octahydroindoles **16a**, **16b** and **16c** whose structure is closely related to that of indolizidine moiety encountered in the castanospermine are weakly or no-potent on the four commercially available enzymes. The same behavior was observed for the homo-analogs, with a polyhydroxylated decahydroquinoline skeleton **21** and **22**, except for the *N*-substituted derivatives by the aglycon part of the voglibose. In the later case, interestingly both epimers at the ring junction competitively and almost exclusively inhibit the α-L-fucosidase (K_i=70 and 18 μM for **21c** and **22c**, respectively).

Table 1. Comparison of inhibitory activities for castanospermine **1**, polyhydroxylated octahydroindoles **16** and decahydroquinolines **21**, **22**. Percentage of inhibitions at 1 mM and K_i in μM (in bold) when measured

Enzyme	**1**	**16a** (%)	**16b** (%)	**16c** (%)	**21a** (%)	**21b** (%)	**21c** (%)	**22b** (%)	**22c** (%)
α-D-Glu	**8 μM**	12	25	25	29	17	18	12	11
β-D-Glu		9	11	13	8	14	14	5	19
α-D-Man		n.i.[a]	10	29	5	2	4	n.i.[a]	14
α-L-Fuc		24	15	23	26	39	**70 μM**	7	**18 μM**

[a] No inhibition detected.

These K_i values, in the low micromolar range, show that the polyhydroxylated decahydroquinoline skeleton can fit in the active site of the α-L-fucosidase, on one hand and revealed the importance of the aglycon part of voglibose, on the other hand.

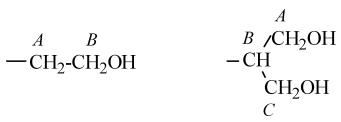
The biological activity of the synthesized compounds was further evaluated towards α-D-galactosidase from green coffee beans, β-D-galactosidase from *Thermus thermophilus* and pancreatic porcine α-amylase. However, none of them exhibited significant activity against these enzymes.

4. Conclusion

The present work outlined an efficient synthetic pathway to build various enantiopure polyhydroxylated octahydroindoles and decahydroquinolines. Biological studies indicate, notably, that the polyhydroxylated decahydroquinoline for which the *N*-atom was substituted by the aglycon part of voglibose is an inhibitor of α-L-fucosidase with K_i in the low micromolar range. This skeleton constitutes a new lead for selective inhibition of this enzyme.

5. Experimental

^{1}H NMR (250 MHz) and ^{13}C NMR (63 MHz) spectra were recorded on a Bruker AM250 in $CDCl_3$ (unless indicated). Chemical shifts (δ) are reported in ppm and coupling constants are given in Hz. IR spectra were recorded on a Perkin–Elmer 783 Infrared Spectrophotometer. Optical rotations were measured on a Perkin–Elmer 241C polarimeter with sodium (589 nm) or mercury (365 nm) lamp. Mass spectra, chemical ionization (CI), and high resolution (HRMS) were recorded by the Service de Spectrométrie de Masse, Ecole Normale Supérieure, Paris. All reactions were carried out under an argon atmosphere, and were monitored by thin-layer chromatography with Merck 60F-254 precoated silica (0.2 mm) on glass. Flash chromatography was performed with Merck Kieselgel 60 (200–500 μm); the solvent systems were given v/v. Spectroscopic (^{1}H and ^{13}C NMR, MS) and/or analytical data were obtained using chromatography homogeneous samples. To simplify the description of NMR-spectroscopic data, *N*-substituents [$(CH_2CH_2OH$ and $CH(CH_2OH)_2$] of octahydroindoles and decahydroquinolines have been named A, B, C:



5.1. To the ketoaldehyde 6

5.1.1. [3*S*,4*S*,5*R*,6*R*]-3-*O*-*tert*-Butyldimethylsilyl-6-tosyloxymethyl-4,5-*O*-methylethylidene-3,4,5-trihydroxycyclohexan-1-one 1,3-propanedithioketal (3). To a solution of the alcohol **2** (700 mg, 1.66 mmol) in dichloromethane (4 mL) at 0°C were successively added 4,4-dimethylaminopyridine (27 mg, 0.225 mmol, 0.1 equiv.), triethylamine (700 μL, 5.02 mmol, 3 equiv.) and tosyl chloride (949 mg, 4.98 mmol, 3 equiv.). After stirring for 14 h, an HCl aqueous solution (1 M, 2 mL) was added and the resulting mixture was extracted with CH_2Cl_2. The combined organic layers were then washed with a saturated aqueous NH_4Cl solution, dried ($MgSO_4$) filtered and concentrated in vacuo. Flash chromatography of the residue (cyclohexane/EtOAc 97:3) afforded the pure tosylate **3** (939.5 mg) as a white solid, in 98% yield. R_f 0.49 (cyclohexane/EtOAc 8:2); mp 112°C; $[\alpha]_D$=+7 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.85 (dd, 2H, $J_{a,b}$=8.2 Hz, Har_a), 7.30 (dd, 2H, $J_{b,a}$=8.2 Hz, Har_b), 4.68 (dd, 1H, $J_{7a,7b}$=10.3 Hz, $J_{7a,6}$=3.9 Hz, H_{7a}), 4.32 (dd, 1H, $J_{7b,7a}$=10.3 Hz, $J_{7b,6}$=5.2 Hz, H_{7b}), 3.92 (ddd, 1H, $J_{3,2b}$=10.2 Hz, $J_{3,4}$=9.1 Hz, $J_{3,2a}$=4.2 Hz, H_3), 3.53 (dd, 1H, $J_{5,6}$=11.5 Hz, $J_{5,4}$=9.1 Hz, H_5), 3.27 (dd, 1H, $J_{4,5}$=$J_{4,3}$=9.1 Hz, H_4), 3.17–3.00 (m, 1H, $H_{1'a}$), 3.06–2.98 (m, 2H, $H_{3'a,2a}$), 2.70–2.53 (m, 2H, $H_{1'b,3'b}$), 2.43 (s, 3H, Me), 2.13–1.98 (m, 1H, $H_{2'a,6}$), 1.85–1.70 (m, 1H, $H_{2'b}$), 1.78 (dd, 1H, $J_{2b,2a}$=14.3 Hz, $J_{2b,3}$=10.2 Hz, H_{2b}), 1.33, 1.29 (2s, 6H, CMe_2), 0.88 (s, 9H, *t*Bu), 0.08 (s, 6H, $SiMe_2$); ^{13}C NMR δ 144.4, 133.2, 129.5, 128.3 (C_{ar}), 110.3 (CMe_2), 84.4 (C_4), 74.9 (C_5), 68.8 (C_3), 68.6 (C_7), 52.0 (C_1), 49.2 (C_6), 46.0 (C_2), 26.8 (CMe_2), 26.6, 25.8, 25.1 ($C_{1',2',3'}$), 25.8, 18.3 (*t*Bu), −4.6, −4.8 ($SiMe_2$).

5.1.2. [3*S*,4*S*,5*R*,6*R*]-3-*O*-*tert*-Butyldimethylsilyl-6-cyanomethyl-4,5-*O*-methylethylidene-3,4,5-trihydroxycyclohexan-1-one 1,3-propanedithioketal (4). To a suspension of the tosylate **3** (707.6 mg, 1.23 mmol) in dimethyl sulfoxide (16 mL) was added sodium cyanide (185.6 mg, 3.79 mmol, 3.1 equiv.). The resulting mixture was heated to 80°C for 4 h and then cooled to 20°C, prior to H_2O (10 mL) addition. After 5 or 6 extractions with ether, the combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography of the residue (cyclohexane/CH_2Cl_2 7:3) gave the nitrile **4** (487.7 mg) as a white solid in 92% yield. R_f 0.1 (cyclohexane/CH_2Cl_2 7:3); mp 129°C; $[\alpha]_D$=+7 (*c* 1.1, CH_2Cl_2); IR (KBr): 2254 cm^{-1}; ^{1}H NMR δ 3.99 (ddd, 1H, $J_{3,2b}$=10.1 Hz, $J_{3,4}$=9.0 Hz, $J_{3,2a}$=4.2 Hz, H_3), 3.64 (dd, 1H, $J_{5,6}$=11.4 Hz, $J_{5,4}$=9.0 Hz, H_5), 3.36 (dd, 1H, $J_{4,3}$=$J_{4,5}$=9.0 Hz, H_4), 3.23–3.06 (m, 1H, $H_{1'a}$), 3.07 (dd, 1H, $J_{7a,b}$=17.3 Hz, $J_{7a,6}$=5.0 Hz, H_{7a}), 3.02–2.86 (m, 1H, $H_{3'a}$), 2.97 (dd, 1H, $J_{2a,b}$=14.3 Hz, $J_{2a,3}$=4.3 Hz, H_{2a}), 2.77 (dd, 1H, $J_{7b,a}$=17.3 Hz, $J_{7b,6}$=5.9 Hz, H_{7b}), 2.78–2.62 (m, 2H, $H_{1'b,3'b}$), 2.19–2.01 (m, 2H, $H_{6,2'a}$), 1.93–1.72 (m, 1H, $H_{2'b}$), 1.84 (dd, 1H, $J_{2b,a}$=14.3 Hz, $J_{2b,3}$=10.1 Hz, H_{2b}), 1.39 (s, 6H, CMe_2), 0.90 (s, 9H, *t*Bu), 0.10 (s, 6H, $SiMe_2$); ^{13}C NMR δ 118.8 (C_8), 110.8 (CMe_2), 82.3 (C_4), 75.8 (C_5), 68.8 (C_3), 53.3 (C_1), 46.6 (C_6), 45.9 (C_2), 26.8 (CMe_2), 26.8, 25.8, 25.1 ($C_{1',2',3'}$), 25.8, 18.3 (*t*Bu), 16.7 (C_7), −4.6, −4.8 ($SiMe_2$).

5.1.3. [3*S*,4*S*,5*R*,6*R*]-3-*O*-*tert*-Butyldimethylsilyl-6-formylmethyl-4,5-*O*-methylethylidene-3,4,5-trihydroxycyclohexan-1-one 1,3-propanedithioketal (5). To a −78°C cooled solution of the nitrile **4** (473.8 mg, 1.10 mmol) in toluene (14 mL) was added dropwise a solution of di-*iso*-butylaluminium hydride in toluene (1.42 M, 1.55 mL, 2.20 mmol, 2 equiv.). After stirring for 1 h while progressively raising the temperature to 20°C, acetone (510 μL), EtOAc (510 μL) and phosphate buffer (pH 7.2, 510 μL) were successively added and the resulting mixture was vigorously stirred for 20 min prior to the further addition of anhydrous sodium sulfate. After stirring

for 20 min, the suspension was filtered through a silica gel pad, the salts were washed with CH_2Cl_2 and the resulting filtrate was concentrated in vacuo. Flash chromatography of the residue (cyclohexane/EtOAc 99:1) led to the aldehyde **5** (372.5 mg) as a white solid in 77% yield. R_f 0.1 (cyclohexane/CH_2Cl_2 7:3); $[\alpha]_D$=+10 (*c* 1.1, CH_2Cl_2); mp 82°C; ^{1}H NMR δ 9.78 (t, 1H, $J_{CHO,7a}$=$J_{CHO,7b}$=1.8 Hz, CHO), 4.00 (ddd, 1H, $J_{3,2b}$=10.3 Hz, $J_{3,4}$=9.1 Hz, $J_{3,2a}$=4.3 Hz, H_3), 3.60 (dd, 1H, $J_{5,6}$=11.3 Hz, $J_{5,4}$=9.1 Hz, H_5), 3.38 (dd, 1H, $J_{4,3}$=$J_{4,5}$=9.1 Hz, H_4), 3.24–3.05 (m, 1H, $H_{1'a}$), 3.15 (ddd, 1H, $J_{7a,b}$=17.6 Hz, $J_{7a,6}$=4.9 Hz, $J_{7a,CHO}$=1.8 Hz, H_{7a}), 3.04–2.86 (m, 1H, $H_{3'a}$), 2.98 (dd, 1H, $J_{2a,b}$=14.2 Hz, $J_{2a,3}$=4.3 Hz, H_{2a}), 2.77–2.57 (m, 3H, $H_{7b,1'b,3'b}$), 2.48 (ddd, 1H, $J_{6,5}$=11.3 Hz, $J_{6,7b}$=6.9 Hz, $J_{6,7a}$=4.9 Hz, H_6), 2.19–1.99 (m, 1H, $H_{2'a}$), 1.94–1.69 (m, 1H, $H_{2'b}$), 1.87 (dd, 1H, $J_{2b,a}$=14.2 Hz, $J_{2b,3}$=10.3 Hz, H_{2b}), 1.34 (s, 6H, CMe_2), 0.90 (s, 9H, *t*Bu), 0.11 (s, 6H, $SiMe_2$); ^{13}C NMR δ 200.8 (C_8), 110.3 (CMe_2), 84.5 (C_4), 76.6 (C_5), 69.0 (C_3), 53.6 (C_1), 46.0 (C_7), 44.4 (C_6), 42.9 (C_2), 26.9, 26.8 (CMe_2), 26.6, 25.3 ($C_{1',2',3'}$), 25.9, 18.3 (*t*Bu), −4.5, −4.8 ($SiMe_2$).

5.1.4. [3*S*,4*S*,5*R*,6*R*]-3-*O*-*tert*-Butyldimethylsilyl-6-formylmethyl-4,5-*O*-methylethylidene-3,4,5-trihydroxycyclohexan-1-one (6). To a −50°C cooled solution of *N*-bromosuccinimide (1.02 g, 5.75 mmol, 8 equiv.) in a 98:2 mixture of acetone/H_2O (33 mL) was added a solution of the dithioketal **5** (311.3 mg, 0.719 mmol) in acetone (11 mL). The mixture was then stirred for 30 min at −50°C prior to the addition of a saturated $Na_2S_2O_3$ aqueous solution (10 mL). After increasing the temperature to 20°C and evaporating the acetone, the resulting residue was extracted with ether and the combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. The crude ketoaldehyde was then purified by flash chromatography (cyclohexane/EtOAc 9:1) to afford **6** (185.4 mg) as a colorless oil in 75% yield. R_f 0.35 (cyclohexane/EtOAc 8:2); $[\alpha]_{Hg}$=+40 (*c* 0.95, CH_2Cl_2); ^{1}H NMR δ 9.79 (s, 1H, CHO), 3.96 (ddd, 1H, $J_{3,2b}$=9.6 Hz, $J_{3,4}$=8.9 Hz, $J_{3,2a}$=5.6 Hz, H_3), 3.82 (dd, 1H, $J_{4,3}$=$J_{4,5}$=8.9 Hz, H_4), 3.36 (dd, 1H, $J_{5,6}$=12.7 Hz, $J_{5,4}$=8.9 Hz, H_5), 3.07 (ddd, 1H, $J_{6,5}$=12.7 Hz, $J_{6,7b}$=7.4 Hz, $J_{6,7a}$=4.0 Hz, H_6), 2.82 (dd, 1H, $J_{7b,a}$=18.0 Hz, $J_{7b,6}$=7.4 Hz, H_{7b}), 2.76 (dd, 1H, $J_{2a,b}$=15.8 Hz, $J_{2a,3}$=5.8 Hz, H_{2a}), 2.64 (dd, 1H, $J_{7a,b}$=18.0 Hz, $J_{7a,6}$=4.0 Hz, H_{7a}), 2.46 (dd, 1H, $J_{2b,a}$=15.8 Hz, $J_{2b,3}$=9.6 Hz, H_{2b}), 1.44, 1.39 (2s, 6H, $(CH_3)_2C$), 0.87 (s, 9H, *t*Bu), 0.09, 0.07 (s, 6H, $SiMe_2$); ^{13}C NMR δ 204.5 (C_1), 199.5 (C_8), 112.2 (CMe_2), 83.9 (C_4), 76.4 (C_5), 67.6 (C_3), 48.7 (C_2), 48.3 (C_6), 40.0 (C_7), 30.2, 29.7 (CMe_2), 26.9, 18.1 (*t*Bu), −4.6, −5.0 ($SiMe_2$).

5.2. To the ketoaldehyde 13

5.2.1. [3*S*,4*S*,5*R*,6*S*]-3-*O*-*tert*-Butyldimethylsilyl-6-formyl-4,5-*O*-methylethylidene-3,4,5-trihydroxycyclohexan-1-one 1,3-propanedithioketal (7). To a solution of the alcohol **2** (1.04 g, 2.47 mmol) in CH_2Cl_2 (4.5 mL) were successively added dimethyl sulfoxide (1.7 mL, 23.9 mmol, 9.7 equiv.), then triethylamine (3.6 mL, 25.6 mmol, 10.4 equiv.) and SO_3/pyridine (1.79 g, 12.9 mmol, 5.2 equiv.) and the resulting mixture was stirred for 2 h at 20°C. After the addition of ether (50 mL) and H_2O (50 mL) followed by decantation, the organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was then purified by flash chromatography (cyclohexane/EtOAc 97:3) to give the pure aldehyde **7** (919.4 mg) as a white solid in 93% yield. R_f 0.57 (cyclohexane/EtOAc 8:2); mp 112°C; $[\alpha]_D$=+33 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 9.99 (d, 1H, $J_{CHO,6}$=2.8 Hz, H_{CHO}), 4.04 (dd, 1H, $J_{5,6}$=11.4 Hz, $J_{5,4}$=9.1 Hz, H_5), 4.03 (ddd, 1H, $J_{3,2b}$=10.1 Hz, $J_{3,4}$=9.1 Hz, $J_{3,2a}$=4.3 Hz, H_3), 3.36 (dd, 1H, $J_{4,3}$=$J_{4,5}$=9.1 Hz, H_4), 3.15 (ddd, 1H, $J_{1'a,b}$=14.7 Hz, $J_{1'a,2'b}$=12.1 Hz, $J_{1'a,2'a}$=2.7 Hz, $H_{1'a}$), 3.07–2.89 (m, 1H, $H_{3'a}$), 2.98 (dd, 1H, $J_{2a,b}$=14.1 Hz, $J_{2a,3}$=4.3 Hz, H_{2a}), 2.78–2.64 (m, 2H, $H_{1'b,3'b}$), 2.62 (dd, 1H, $J_{6,5}$=11.4 Hz, $J_{6,CHO}$=2.8 Hz, H_6), 2.12–2.04 (m, 1H, $H_{2'a}$), 1.95–1.78 (m, 1H, $H_{2'b}$), 1.86 (dd, 1H, $J_{2b,a}$=14.2 Hz, $J_{2b,3}$=10.1 Hz, H_{2b}), 1.39, 1.38 (s, 6H, CMe_2), 0.91 (s, 9H, *t*Bu), 0.11 (s, 6H, $SiMe_2$); ^{13}C δ 198.6 (C_7), 111.1 (CMe_2), 84.4 (C_4), 72.4 (C_5), 68.7 (C_3), 60.7 (C_6), 49.7 (C_1), 46.2 (C_2), 26.9 (CMe_2), 26.6, 26.2, 25.0 ($C_{1',2',3'}$), 25.8, 18.3 (*t*Bu), −4.6, −4.8 ($SiMe_2$); Anal. calcd for $C_{19}H_{34}O_4S_2Si$: C, 54.50; H, 8.19; found: C, 54.44; H, 8.23.

5.2.2. [3*S*,4*S*,5*R*,6*R*]-3-*O*-*tert*-Butyldimethylsilyl-6-formylethylene-4,5-*O*-methylethylidene-3,4,5-trihydroxycyclohexan-1-one 1,3-propanedithioketal (8). To a solution of the aldehyde **7** (83.9 mg, 0.2 mmol) in toluene (1 mL) was added formylmethylene triphenyl-phosphorane (67 mg, 0.22 mmol, 1.1 equiv.) and the mixture was stirred at 55°C for 48 h prior to the addition of H_2O. After ether extractions, the combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography of the residue (toluene/CH_2Cl_2 9:1) led to the unsaturated aldehyde **8** (28.2 mg) as a white solid in 40% yield. R_f 0.1 (toluene/CH_2Cl_2 9:1; $[\alpha]_D$=+39 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 9.60 (d, 1H, $J_{CHO,8}$=7.9 Hz, H_{CHO}), 7.14 (dd, 1H, $J_{7,8}$=15.8 Hz, $J_{7,6}$=6.9 Hz, H_7), 6.38 (ddd, 1H, $J_{8,7}$=15.8 Hz, $J_{8,CHO}$=7.9 Hz, $J_{8,6}$=0.9 Hz, H_8), 4.04 (ddd, 1H, $J_{3,2b}$=10.2 Hz, $J_{3,4}$=9.1 Hz, $J_{3,2a}$=4.3 Hz, H_3), 3.80 (dd, 1H, $J_{5,6}$=11.1 Hz, $J_{5,4}$=9.1 Hz, H_5), 3.36 (dd, 1H, $J_{4,3}$=$J_{4,5}$=9.1 Hz, H_4), 3.14 (ddd, 1H, $J_{1'a,b}$=14.7 Hz, $J_{1'a,2'b}$=12.2 Hz, $J_{1'a,2'a}$=2.8 Hz, $H_{1'a}$), 3.00 (dd, 1H, $J_{2a,b}$=14.2 Hz, $J_{2a,3}$=4.3 Hz, H_{2a}), 3.06–2.88 (m, 1H, $H_{3'a}$), 2.78–2.59 (m, 3H, $H_{1'b,3'b,6}$), 2.18–2.02 (m, 1H, $H_{2'a}$), 1.95–1.73 (m, 1H, $H_{2'b}$), 1.87 (dd, 1H, $J_{2b,a}$=14.2 Hz, $J_{2b,3}$=10.2 Hz, H_{2b}), 1.38 (s, 6H, CMe_2), 0.91 (s, 9H, *t*Bu), 0.11 (s, 6H, $SiMe_2$); ^{13}C NMR δ 193.9 (C_9), 152.4 (C_8), 136.1 (C_7), 110.5 (CMe_2), 84.6 (C_4), 74.9 (C_5), 68.7 (C_3), 52.9 (C_6), 52.8 (C_1), 45.8 (C_2), 26.7 (CMe_2), 26.9, 26.1, 25.1 ($C_{1',2',3'}$), 25.8, 18.3 (*t*Bu), −4.6, −4.8 ($SiMe_2$).

5.2.3. [3*S*,4*S*,5*R*,6*R*]-3-*O*-*tert*-Butyldimethylsilyl-6-ethylacrylate-4,5-*O*-methylethylidene-3,4,5-trihydroxycyclohexan-1-one 1,3-propanedithioketal (9). To a suspension of potassium *tert*-butoxide (958 mg, 8.54 mmol, 4.01 equiv.) in THF (13 mL), at 0°C, was added triethylphosphonoacetate (1.7 mL, 8.57 mmol, 4.02 equiv.). After stirring for 20 min, the mixture was cooled to −78°C and a solution of the aldehyde **8** (894.3 mg, 2.13 mmol) in THF (1.1 mL) was added dropwise. The resulting mixture was stirred for 3 h at −78°C and a saturated NH_4Cl aqueous solution was added. After ether extraction, the combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography of the residue (cyclohexane/EtOAc 98:2) afforded the unsaturated ester **9**

(919.4 mg) as a white solid in 85% yield. R_f 0.33 (cyclohexane/EtOAc 9:1); $[\alpha]_D$=+27 (*c* 1.0, CH_2Cl_2); ^1H NMR δ 7.19 (dd, 1H, $J_{7,8}$=15.7 Hz, $J_{7,6}$=7.8 Hz, H_7), 6.07 (dd, 1H, $J_{8,7}$=15.7 Hz, $J_{8,6}$=0.8 Hz, H_8), 4.18 (q, 2H, *J*=7.1 Hz, OCH_2CH_3), 4.02 (ddd, 1H, $J_{3,2b}$=10.2 Hz, $J_{3,4}$=9.0 Hz, $J_{3,2a}$=4.2 Hz, H_3), 3.78 (dd, 1H, $J_{5,6}$=11 Hz, $J_{5,4}$=9.0 Hz, H_5), 3.35 (dd, 1H, $J_{4,3}$=$J_{4,5}$=9 Hz, H_4), 3.06 (ddd, 1H, $J_{1'a,b}$=14.4 Hz, $J_{1'a,2'b}$=11.3 Hz, $J_{1'a,2'a}$=3.1 Hz, $H_{1'a}$), 2.99–2.83 (m, 1H, $H_{3'a}$), 2.93 (dd, 1H, $J_{2a,b}$=14.1 Hz, $J_{2a,3}$=4.2 Hz, H_{2a}), 2.77–2.64 (m, 2H, $H_{1'b,3'b}$), 2.56 (dd, 1H, $J_{6,5}$=11.0 Hz, $J_{6,7}$=7.8 Hz, H_6), 2.11–1.97 (m, 1H, $H_{2'a}$), 1.96–1.74 (m, 1H, $H_{2'b}$), 1.82 (dd, 1H, $J_{2b,a}$=14.1 Hz, $J_{2b,3}$=10.2 Hz, H_{2b}), 1.37 (s, 6H, CMe_2), 1.28 (t, 3H, *J*=7.1 Hz, OCH_2CH_3), 0.90 (s, 9H, *t*Bu), 0.10 (s, 6H, $SiMe_2$); ^{13}C NMR δ 166.1 (C_9), 143.7 (C_8), 125.3 (C_7), 110.3 (CMe_2), 84.5 (C_4), 75.2 (C_5), 68.7 (C_3), 60.3 (OCH_2CH_3), 53.3 (C_6), 52.8 (C_1), 46.2 (C_2), 26.8 (CMe_2), 26.2, 25.0 ($C_{1',2',3'}$), 25.8, 18.3 (*t*Bu), 14.3 (OCH_2CH_3), −4.6, −4.8 ($SiMe_2$); Anal. calcd for $C_{23}H_{40}O_5S_2Si$: C, 56.52; H, 8.25; found: C, 56.48; H, 8.42.

5.2.4. [3*S*,4*S*,5*R*,6*R*]-3-*O*-*tert*-Butyldimethylsilyl-6-ethylcarboxyethyl-4,5-*O*-methylethylidene-3,4,5-trihydroxycyclohexan-1-one 1,3-propanedithioketal (10). To a suspension of the unsaturated ester **9** (526.8 mg, 1.08 mmol) and tosyl hydrazide (2.44 g, 13.1 mmol, 12.1 equiv.) in a 1:1 mixture of THF/H_2O (30 mL) heated at 78°C was added dropwise a solution of sodium acetate (1.79 g, 21.8 mmol, 20.2 equiv.) in H_2O (8 mL). After stirring for 8 h at 78°C, the mixture was concentrated to a final volume of 10 mL and a saturated NH_4Cl aqueous solution (30 mL) and pure H_2O (10 mL) were added. After CH_2Cl_2 extractions, the combined organic layers were washed with a NaOH aqueous solution (2N), dried (Na_2SO_4), filtered and concentrated in vacuo. Flash chromatography (cyclohexane/EtOAc 9:1) of the residue gave the saturated ester **10** (494.9 mg) as a white solid in 94% yield. R_f 0.45 (cyclohexane/EtOAc 9:1); mp 115°C; $[\alpha]_{Hg}$=+13 (*c* 1.1, CH_2Cl_2); ^1H NMR δ 4.12 (q, 2H, *J*=7.1 Hz, OCH_2CH_3), 3.26 (ddd, 1H, $J_{3,2b}$=10.3 Hz, $J_{3,4}$=9.1 Hz, $J_{3,2a}$=4.3 Hz, H_3), 3.58 (dd, 1H, $J_{5,6}$=11.0 Hz, $J_{5,4}$=9.1 Hz, H_5), 3.35 (dd, 1H, $J_{4,3}$=$J_{4,5}$=9.1 Hz, H_4), 3.14 (ddd, 1H, $J_{1'a,b}$=14.7 Hz, $J_{1'a,2'b}$=12.5 Hz, $J_{1'a,2'a}$=2.8 Hz, $H_{1'a}$), 3.01–2.85 (m, 1H, $H_{3'a}$), 2.99 (dd, 1H, $J_{2a,b}$=14.1 Hz, $J_{2a,3}$=4.3 Hz, H_{2a}), 2.73–2.58 (m, 3H, $H_{1'b,3'b,8a}$), 2.57–2.35 (m, 2H, $H_{8b,7a}$), 2.14–2.00 (m, 1H, $H_{2'a}$), 1.96–1.60 (m, 3H, $H_{2'b,7b,6}$), 1.81 (dd, 1H, $J_{2b,a}$=14.2 Hz, $J_{2b,3}$=10.3 Hz, H_{2b}), 1.33 (s, 6H, CMe_2), 1.24 (t, 3H, *J*=7.1 Hz, OCH_2CH_3), 0.89 (s, 9H, *t*Bu), 0.10 (s, 6H, $SiMe_2$); ^{13}C NMR δ 173.6 (C_9), 109.8 (CMe_2), 84.6 (C_4), 78.2 (C_5), 69.1 (C_3), 60.1 (OCH_2CH_3), 54.4 (C_1), 49.8 (C_6), 45.7 (C_2), 33.8 (C_8), 26.9 (CMe_2), 26.7, 25.6, 25.0 ($C_{1',2',3',7}$), 25.9, 18.3 (*t*Bu), 14.3 (OCH_2CH_3), −4.5, −4.8 ($SiMe_2$); Anal. calcd for $C_{23}H_{42}O_5S_2Si$: C, 56.29; H, 8.63; found: C, 56.28; H, 8.65.

5.2.5. [3*S*,4*S*,5*R*,6*R*]-3-*O*-*tert*-Butyldimethylsilyl-6-formylethyl-4,5-*O*-methylethylidene-3,4,5-trihydroxycyclohexan-1-one 1,3-propanedithioketal (12). To a −78°C cooled solution of the ester **10** (685.9 mg, 1.40 mmol) in a 8:2 mixture of hexane/CH_2Cl_2 (9 mL) was added dropwise di-*iso*-butylaluminium hydride (1 M in hexane, 1.54 mL, 1.54 mmol). After stirring for 1 h at −78°C, a saturated sodium tartrate aqueous solution (4.2 mL), brine (2.1 mL), H_2O (2.1 mL) and ether (8.4 mL) were successively added and the resulting mixture was stirred at 20°C for 2 h. After decantation, the aqueous layer was extracted with ether and the combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography of the residue (cyclohexane/EtOAc 9:1) afforded the expected aldehyde **12** (359.6 mg) as a white solid in 58% yield. R_f 0.32 (cyclohexane/EtOAc 9:1); mp 87°C; $[\alpha]_D$=+3 (*c* 1.0, CH_2Cl_2); ^1H NMR δ 9.74 (t, 1H, $J_{CHO,8}$=1.1 Hz, H_{CHO}), 3.96 (ddd, 1H, $J_{3,2b}$=10.3 Hz, $J_{3,4}$=9.1 Hz, $J_{3,2a}$=4.2 Hz, H_3), 3.57 (dd, 1H, $J_{5,6}$=11.0 Hz, $J_{5,4}$=9.1 Hz, H_5), 3.29 (dd, 1H, $J_{4,3}$=$J_{4,5}$=9.1 Hz, H_4), 3.14 (ddd, 1H, $J_{1'a,b}$=14.8 Hz, $J_{1'a,2'b}$=12.5 Hz, $J_{1'a,2'a}$=2.7 Hz, $H_{1'a}$), 3.04–2.87 (m, 1H, $H_{3'a}$), 2.95 (dd, 1H, $J_{2a,b}$=14.2 Hz, $J_{2a,3}$=4.2 Hz, H_{2a}), 2.86–2.43 (m, 5H, $H_{1'b,3'b,8a,8b,7a}$), 2.16–2.00 (m, 1H, $H_{2'a}$), 1.99–1.53 (m, 3H, $H_{2'b,7b,6}$), 1.80 (dd, 1H, $J_{2b,a}$=14.2 Hz, $J_{2b,3}$=10.3 Hz, H_{2b}), 1.33 (s, 6H, CMe_2), 0.89 (s, 9H, *t*Bu), 0.09 (s, 6H, $SiMe_2$); ^{13}C NMR δ 202.7 (C_9), 109.9 (CMe_2), 84.6 (C_4), 78.1 (C_5), 69.0 (C_3), 54.5 (C_1), 49.0 (C_6), 45.7 (C_2), 43.1 (C_8), 26.9 (CMe_2), 26.7, 25.9, 25.6 ($C_{1',2',3'}$), 25.9, 18.3 (*t*Bu), 22.2 (C_7), −4.5, −4.8 ($SiMe_2$); Anal. calcd for $C_{21}H_{38}O_4S_2Si$: C, 56.46; H, 8.57; found: C, 56.70; H, 8.99.

5.2.6. [3*S*,4*S*,5*R*,6*R*]-3-*O*-*tert*-Butyldimethylsilyl-6-formylethyl-4,5-*O*-methylethylidene-3,4,5-trihydroxycyclohexan-1-one (13). The dithioketal hydrolysis of the aldehyde **12** (353.1 mg, 0.792 mmol) was carried out under the same conditions as above for the transformation **5→6**, and led to the ketoaldehyde **13** (209.2 mg) as a solid in 75% yield, after flash chromatographic purification (cyclohexane/EtOAc 9:1). R_f 0.46 (cyclohexane/EtOAc 8:2); mp 62°C; $[\alpha]_D$=+9 (*c* 1.0, CH_2Cl_2); ^1H NMR δ 9.79 (t, 1H, $J_{CHO,8a}$=$J_{CHO,8b}$=1.1 Hz, H_{CHO}), 3.91 (ddd, 1H, $J_{3,2b}$=9.9 Hz, $J_{3,4}$=8.9 Hz, $J_{3,2a}$=5.8 Hz, H_3), 3.77 (dd, 1H, $J_{4,3}$=$J_{4,5}$=8.9 Hz, H_4), 3.23 (dd, 1H, $J_{5,6}$=12.5 Hz, $J_{5,4}$=8.9 Hz, H_5), 2.79 (dd, 1H, $J_{2a,b}$=15.5 Hz, $J_{2a,3}$=5.8 Hz, H_{2a}), 2.66–2.45 (m, 3H, $H_{6,8a,8b}$), 2.42 (dd, 1H, $J_{2b,a}$=15.5 Hz, $J_{2b,3}$=9.9 Hz, H_{2b}), 2.17–1.94 (m, 1H, H_{7a}), 1.92–1.72 (m, 1H, H_{7b}), 1.43, 1.38 (2s, 6H, CMe_2), 0.86 (s, 9H, *t*Bu), 0.08, 0.06 (2s, 6H, $SiMe_2$); ^{13}C NMR δ 205.9 (C_1), 201.9 (C_9), 112.0 (CMe_2), 83.8 (C_4), 77.7 (C_5), 67.6 (C_3), 51.9 (C_6), 49.2 (C_2), 41.1 (C_8), 30.2 (C_7), 27.0 (CMe_2), 25.8, 18.2 (*t*Bu), −4.6, −5.0 ($SiMe_2$); Anal. calcd for $C_{18}H_{32}O_4Si$: C, 60.64; H, 9.05; found: C, 60.48; H, 9.19.

5.3. To the octahydroindoles (16)

To a solution of the ketoaldehyde **6** (0.387 mmol) in methanol (1 mL) cooled to 0°C, were successively added sodium cyanoborohydride (0.753 mmol, 1.9 equiv.) and a mixture of a primary amine (387 mmol, 1 equiv.) and acetic acid (0.387 mmol, 1 equiv.) in methanol (0.4 mL). After stirring for 24 h at 20°C, the mixture was concentrated in vacuo, and a 10% aqueous solution of NaOH was added and was followed by CH_2Cl_2 extractions. The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. Flash chromatographic purification (cyclohexane/EtOAc/Et_3N 97:3:0.03) afforded the corresponding pure octahydroindole **14**.

5.3.1. [3a*S*,4*R*,5*S*,6*S*,7a*S*]-*1*-Benzyl-6-*O*-*tert*-butyldimethylsilyl-4,5-*O*-methylethylidene-4,5,6-trihydroxyoctahydroindole (14a). 50% yield from **6** (132.4 mg, 0.387 mmol); R_f 0.3 (cyclohexane/EtOAc 95:5); $[\alpha]_D$=+56 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.35–7.20 (m, 5H, H_{ar}), 4.07–3.94 (m, 1H, H_6), 4.01, 3.08 (AB, 2H, J_{AB}=13.1 Hz, NCH_2Ph), 3.54 (dd, 1H, $J_{4,3a}$=10.3 Hz, $J_{4,5}$=9.2 Hz, H_4), 3.30 (dd, 1H, $J_{5,6}=J_{5,4}$=9.2 Hz, H_5), 2.99 (ddd, 1H, $J_{2,2'}$=13.7 Hz, $J_{2,3'}$=9.0 Hz, $J_{2,3}$=4.4 Hz, H_{2b}), 2.74–2.68 (m, 1H, H_{7a}), 2.30–2.07 (m, 3H, $H_{7,3a,2'}$), 1.94–1.62 (m, 2H, $H_{3,3'}$), 1.54 (ddd, 1H, $J_{7',7}$=14.7 Hz, $J_{7',6}$=10.0 Hz, $J_{7',7a}$=4.5 Hz, $H_{7'}$), 1.40 (s, 6H, CMe_2), 0.89 (s, 9H, *t*Bu), 0.09, 0.08 (s, 6H, $SiMe_2$); ^{13}C NMR δ 140.7, 128.5, 128.2, 126.8 (C_{ar}), 109.1 (CMe_2), 83.7 (C_5), 80.1 (C_4), 69.5 (C_6), 64.4 (C_{7a}), 58.1 (NCH_2Ph), 52.8 (C_2), 42.3 (C_{3a}), 35.0 (C_7), 27.0 (CMe_2), 25.9, 18.2 (*t*Bu), 24.8 (C_3), −4.5 ($SiMe_2$); MS (CI, CH_4) 418 (M^++1); HMRS for $C_{24}H_{40}NO_3Si$ (M^++1): calcd 418.2777; found: 418.2769.

5.3.2. [3a*S*,4*R*,5*S*,6*S*,7a*S*]-*1*-(2′-Hydroxyethyl)-6-*O*-*tert*-butyldimethylsilyl-4,5-*O*-methylethylidene-4,5,6-trihydroxyoctahydroindole (14b). 62% yield from **6** (70.8 mg, 0.207 mmol); R_f 0.33 (cyclohexane/EtOAc 9:1); $[\alpha]_D$=+63 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 3.88 (ddd, 1H, $J_{6,7'}=J_{6,5}$=9.3 Hz, $J_{6,7}$=4.6 Hz, H_6), 3.72–3.49 (m, 2H, $H_{B,B'}$), 3.40 (dd, 1H, $J_{4,3a}$=10.3 Hz, $J_{4,5}$=9.3 Hz, H_4), 3.27 (dd, 1H, $J_{5,6}=J_{5,4}$=9.3 Hz, H_5), 3.33–3.20 (m, 1H, H_A), 2.99 (ddd, 1H, $J_{2,2'}$=12.2 Hz, $J_{2,3'}$=9.8 Hz, $J_{2,3}$=5.7 Hz, H_2), 2.80–2.65 (m, 1H, H_{7a}), 2.34–2.09 (m, 4H, $H_{3a,2',7,A'}$), 2.02–1.74 (m, 2H, $H_{3,3'}$), 1.50 (ddd, 1H, $J_{7',7}$=14.6 Hz, $J_{7',6}$=9.3 Hz, $J_{7',7a}$=4.6 Hz, $H_{7'}$), 1.38, 1.37 (2s, 6H, CMe_2), 0.88 (s, 9H, *t*Bu), 0.08 (s, 6H, $SiMe_2$); ^{13}C NMR δ 109.3 (CMe_2), 85.6 (C_5), 79.5 (C_4), 69.2 (C_6), 64.4 (C_{7a}), 59.6 (C_B), 55.6 (C_A), 52.2 (C_2), 42.2 (C_{3a}), 35.0 (C_7), 27.0 (CMe_2), 25.9, 18.3 (*t*Bu), 25.2 (C_3), −4.6, −4.9 ($SiMe_2$); MS (CI, CH_4) 372 (M^++1); HMRS for $C_{19}H_{38}NO_4Si_2$ (M^++1): calcd 372.2570; found: 372.2570.

5.3.3. [3a*S*,4*R*,5*S*,6*S*,7a*S*]-1-(1′,3′-Di-*tert*-butyldimethylsilyloxy-2′-propyl)-6-*O*-*tert*-butyldimethylsilyl-4,5-*O*-methylethylidene-4,5,6-trihydroxyoctahydroindole (14c). 75% yield from **6** (60.9 mg, 0.178 mmol); $[\alpha]_D$=+24.5 (*c* 1.1, CH_2Cl_2); ^{1}H NMR (500 MHz) δ 3.89 (ddd, 1H, $J_{6,7'}$=9.5 Hz, $J_{6,5}$=9.2 Hz, $J_{6,7}$=5.0 Hz, H_6), 3.75 (dd, 1H, $J_{A,A'}$=10.4 Hz, $J_{A,B}$=6.2 Hz, H_A), 3.72 (dd, 1H, $J_{A',A}$=10.4 Hz, $J_{A',B}$=5.0 Hz, $H_{A'}$), 3.60 (dd, 1H, $J_{C,C'}$=10.0 Hz, $J_{C,B}$=5.9 Hz, H_C), 3.57 (dd, 1H, $J_{C',C}$=10.0 Hz, $J_{C',B}$=6.4 Hz, $H_{C'}$), 3.44 (dd, 1H, $J_{4,3a}$=10.0 Hz, $J_{4,5}$=9.2 Hz, H_4), 3.36 (ddd, 1H, $J_{7a,7'}=J_{7a,3a}$=4.4 Hz, $J_{7a,7}$=2.9 Hz, H_{7a}), 3.26 (dd, 1H, $J_{5,6}=J_{5,4}$=9.2 Hz, H_5), 2.97–2.87 (m, 2H, $H_{B,2'}$), 2.83 (ddd, 1H, $J_{2,2'}$=14.8 Hz, $J_{2,3'}$=9.4 Hz, $J_{2,3}$=5.6 Hz, H_2), 2.15 (ddd, 1H, $J_{7,7'}$=14.2 Hz, $J_{7,6}$=5.0 Hz, $J_{7,7a}$=2.9 Hz, H_7), 2.13–2.06 (m, 1H, H_{3a}), 1.86–1.73 (m, 2H, $H_{3,3'}$), 1.42 (ddd, 1H, $J_{7',7}$=14.2 Hz, $J_{7',6}$=9.5 Hz, $J_{7',7a}$=4.4 Hz, $H_{7'}$), 1.38, 1.36 (2s, 6H, CMe_2), 0.88 (s, 27H, *t*Bu), 0.05 (s, 18H, $SiMe_2$); ^{13}C NMR δ 109.1 (CMe_2), 83.9 (C_5), 79.1 (C_4), 69.4 (C_6), 63.3, 59.3 ($C_{A,C}$), 60.7, 59.4 ($C_{7a,B}$), 44.9 (C_2), 41.9 (C_{3a}), 35.3 (C_7), 29.7 (C_3), 27.0 (CMe_2), 25.9, 18.3, 18.2 (*t*Bu), −4.5, −4.8, −5.4 ($SiMe_2$); MS (CI, CH_4) 630 (M^++1); HMRS for $C_{32}H_{68}NO_5Si_3$ (M^++1): calcd 630.4405; found: 630.4393.

5.3.4. [3a*S*,4*R*,5*S*,6*S*,7a*S*]-6-*O*-*tert*-Butyldimethylsilyl-4,5-*O*-methylethylidene-4,5,6-trihydroxyoctahydro-1*H*-indole (15a). To a suspension of palladium hydroxide (80 mg) in absolute EtOH (0.5 mL), saturated with dihydrogen, was added a solution of the *N*-benzylamine **14a** (90.5 mg, 0.217 mmol) in a mixture of absolute EtOH (0.5 mL) and EtOAc (0.4 mL). After stirring for 4 days at 20°C, the catalyst was removed by filtration through a Celite pad and the filtrate was concentrated in vacuo. Flash chromatography (CH_2Cl_2/MeOH 99:1) gave the pure amine **15** (32.1 mg) as an oil in 45% yield. R_f 0.2 (CH_2Cl_2/MeOH 98:2); $[\alpha]_D$=+49 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 3.94 (ddd, 1H, $J_{6,7'}=J_{6,5}$=9.2 Hz, $J_{6,7}$=5.1 Hz, H_6), 3.46 (dd, 1H, $J_{4,3a}$=10.1 Hz, $J_{4,5}$=9.2 Hz, H_4), 3.25 (dd, 1H, $J_{5,6}=J_{5,4}$=9.2 Hz, H_5), 2.99 (ddd, 1H, $J_{2,2'}$=13.1 Hz, $J_{2,3'}$=8.8 Hz, $J_{2,7a}$=4.0 Hz, H_2), 2.60–2.47 (m, 1H, H_{7a}), 2.25–1.74 (m, 5H, $H_{7,3a,3,3',2'}$), 1.47 (ddd, 1H, $J_{7',7}$=14.6 Hz, $J_{7',6}$=9.2 Hz, $J_{7',7a}$=4.8 Hz, $H_{7'}$), 1.38, 1.37 (2s, 6H, CMe_2), 0.89 (s, 9H, *t*Bu), 0.08 (s, 6H, $SiMe_2$); ^{13}C NMR δ 109.8 (CMe_2), 83.8 (C_5), 79.9 (C_4), 69.0 (C_6), 64.6 (C_{7a}), 51.9 (C_2), 42.1 (C_{3a}), 34.2 (C_7), 27.0 (CMe_2), 25.9, 18.2 (*t*Bu), 25.4 (C_3), −4.5 ($SiMe_2$).

5.3.5. [3a*S*,4*R*,5*R*,6*S*,7a*S*]-Octahydro-1*H*-indole-4,5,6-triol (16a). The protected derivative **15a** (31.6 mg, 97 μmol) in a 9:1 solution of trifluoroacetic acid/H_2O (2 mL) was stirred at 20°C for 14 h. After concentration in vacuo, the resulting oil was triturated in dry ether and the supernatant was discarded to afford a brownish solid which was purified by ion-exchange chromatography (Dowex® 50X8-100, 3% aqueous ammonium hydroxide) to give the octahydroindole **16a** (11.1 mg) as a solid in 66% yield. $[\alpha]_D$=+49 (*c* 1.0, H_2O); ^{1}H NMR (D_2O) δ 3.95–3.77 (m, 1H, H_6), 3.42–3.26 (m, 2H, $H_{4,5}$), 3.23 (ddd, 1H, $J_{2,2'}$=13.2 Hz, $J_{2,3'}$=9.4 Hz, $J_{2,3}$=3.4 Hz, H_2), 2.72–2.54 (m, 1H, H_{7a}), 2.40–1.94 (m, 4H, $H_{3a,7,2',3}$), 1.88–1.58 (m, 2H, $H_{7',3'}$); ^{13}C NMR (D_2O) δ 81.1 (C_5), 77.9 (C_4), 71.5 (C_6), 65.5 (C_{7a}), 53.8 (C_2), 46.5 (C_{3a}), 33.4 (C_7), 28.0 (C_3).

5.3.6. [3a*S*,4*R*,5*R*,6*S*,7a*S*]-*1*-(2′-Hydroxyethyl)-octahydroindole-4,5,6-triol (16b). The octahydroindole **16b** was obtained from the protected derivative **14b** (47.1 mg, 0.128 mmol) under the same conditions as above for **16a** and was isolated (27.6 mg) as a solid in 98% yield. $[\alpha]_D$=+37 (*c* 1.0, H_2O); ^{1}H NMR (D_2O) δ 3.99 (t, 2H, $J_{B,A}$=5.3 Hz, H_B), 3.95–3.77 (m, 3H, $H_{6,\ 7a,2}$), 3.61 (dt, 1H, $J_{A,A'}$=13.4 Hz, $J_{A,B}$=5.3 Hz, H_A), 3.51–3.36 (m, 3H, $H_{4,5,2'}$), 3.30 (dt, 1H, $J_{A',A}$=13.4 Hz, $J_{A',B}$=5.3 Hz, $H_{A'}$), 2.63–2.32 (m, 3H, $H_{3a,7,3}$), 2.27–2.15 (m, 1H, $H_{3'}$), 2.07 (ddd, 1H, $J_{7',7}$=16.0 Hz, $J_{7',6}$=10.9 Hz, $J_{7',7a}$=5.6 Hz, $H_{7'}$); ^{13}C NMR (D_2O) δ 80.5 (C_5), 75.8 (C_4), 71.1 (C_6), 68.4 (C_{7a}), 60.0 (C_B), 59.1 (C_A), 56.0 (C_2), 45.9 (C_{3a}), 32.3 (C_7), 28.4 (C_3); MS (FAB+) 218 (M^++1); HMRS for $C_{10}H_{20}NO_4$ (M^++1): calcd 218.1392; found: 218.1395.

5.3.7. [3a*S*,4*R*,5*R*,6*S*,7a*S*]-*1*-(1′,3′-Dihydroxy-2′-*N*-propyl)octahydroindole-4,5,6-triol (16c). The octahydroindole **16c** was obtained from the protected derivative **14c** (80.2 mg, 0.128 mmol) under the same conditions as above for **16a** and was isolated (29 mg) as a solid in 92% yield. $[\alpha]_D$=+65 (*c* 1.0, H_2O); ^{1}H NMR (500 MHz, D_2O) δ 3.86 (dd, 1H, $J_{A,A'}$=11.7 Hz, $J_{A,B}$=5.0 Hz, H_A), 3.80–3.64 (m, 4H, $H_{A',C,C',6}$), 3.67 (dd, 1H, $J_{4,3a}$=10.6 Hz, $J_{5,4}$=9.3 Hz,

H_4), 3.48–3.42 (m, 1H, H_{7a}), 3.33 (dd, 1H, $J_{5,6}$=$J_{5,4}$=9.3 Hz, H_5), 3.11–3.00 (m, 2H, $H_{2,2'}$), 2.90–2.79 (m, 1H, H_B), 2.23 (ddd, 1H, $J_{7,7'}$=14.4 Hz, $J_{7,6}$=$J_{7,7a}$=3.4 Hz, H_7), 2.16–2.06 (m, 1H, H_{3a}), 2.03–1.92 (m, 1H, H_3), 1.90–1.80 (m, 1H, $H_{3'}$), 1.42 (ddd, 1H, $J_{7',7}$=14.4 Hz, $J_{7',6}$=11.0 Hz, $J_{7',7a}$=3.9 Hz, $H_{7'}$); ^{13}C NMR (D_2O) δ 81.5 (C_5), 76.8 (C_4), 71.7 (C_6), 63.3, 60.3 ($C_{A,C}$), 62.5, 61.4 ($C_{7a,B}$), 47.3 (C_2), 47.2 (C_{3a}), 34.2 (C_7), 28.8 (C_3); MS (FAB+) 248 (M^++1); HMRS for $C_{11}H_{22}NO_5$ (M^++1): calcd 248.1498; found: 248.1493.

5.4. To the decahydroquinolines 21 and 22

The reductive amination of the ketoaldehyde **13** was accomplished under the same experimental conditions as for **6**.

5.4.1. [4a*S*,5*R*,6*S*,7*S*,8a*R*]-*1*-Benzyl-7-*O*-*tert*-butyldimethylsilyl-5,6-*O*-methylethylidene-5,6,7-trihydroxydecahydroquinoline (17a), and its 8a epimer (18a). 17a/18a=75:25 determined by the ^{1}H NMR spectrum of the crude.

17a (31%) from **13** (120.4 mg, 0.34 mmol) after separation by chromatography (cyclohexane/EtOAc 95:5); R_f 0.39 (cyclohexane/EtOAc 8:2); $[\alpha]_D$=−22.5 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.33–7.16 (m, 5H, H_{ar}), 4.04, 3.20 (AB, 2H, $J_{A,B}$=13.4 Hz, NCH_2Ph), 3.79 (ddd, 1H, $J_{7,8'}$=10.3 Hz, $J_{7,6}$=9.1 Hz, $J_{7,8}$=4.8 Hz, H_7), 3.38 (dd, 1H, $J_{6,7}$=$J_{6,5}$=9.1 Hz, H_6), 3.04 (dd, 1H, $J_{5,4a}$=10.8 Hz, $J_{5,6}$=9.1 Hz, H_5), 2.91–2.74 (m, 1H, H_2), 2.33 (ddd, 1H, $J_{8,8'}$=12.8 Hz, $J_{8,7}$=$J_{8,8a}$=4.8 Hz, H_8), 2.25–2.04 (m, 3H, $H_{2',4,8a}$), 1.70–1.45 (m, 4H, $H_{3,3',8',4a}$), 1.40, 1.38 (2s, 6H, CMe_2), 1.16–0.92 (m, 1H, $H_{4'}$), 0.88 (s, 9H, *t*Bu), 0.09, 0.08 (s, 6H, $SiMe_2$); ^{13}C NMR δ 139.3, 128.9, 128.2, 126.8 (C_{ar}), 110.4 (CMe_2), 84.2 (C_6), 80.0 (C_5), 70.1 (C_7), 62.7 (C_{8a}), 57.8 (NCH_2Ph), 53.7 (C_2), 42.8 (C_{4a}), 39.0 (C_8), 28.0 (C_3), 27.0 (CMe_2), 25.9, 18.3 (*t*Bu), 24.1 (C_4), −4.5, −4.8 ($SiMe_2$); MS (CI, CH_4) 432 (M^++1); HRMS for $C_{25}H_{42}NO_3Si$ (M^++1): calcd 432.2934; found: 432.2934.

18a (16%); R_f 0.70 (cyclohexane/EtOAc 8:2); $[\alpha]_D$=+40 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 7.35–7.20 (m, 5H, H_{ar}), 4.17 (dd, 1H, $J_{5,4a}$=11.3 Hz, $J_{5,6}$=9.0 Hz, H_5), 4.10–4.00 (m, 1H, H_7), 4.09, 2.97 (AB, 2H, J_{AB}=13.5 Hz, NCH_2Ph), 3.31 (dd, 1H, $J_{6,7}$=$J_{6,5}$=9.0 Hz, H_6), 2.84–2.69 (m, 1H, H_2), 2.58–2.47 (m, 1H, H_{8a}), 2.38 (ddd, 1H, $J_{8,8'}$=14.8 Hz, $J_{8,7}$=$J_{8,8a}$=3.4 Hz, H_8), 2.03–1.80 (m, 3H, $H_{4,2',4a}$), 1.79–1.56 (m, 2H, $H_{3,3'}$), 1.53–1.29 (m, 2H, $H_{4',8'}$), 1.43, 1.41 (2s, 6H, CMe_2), 0.86 (s, 9H, *t*Bu), 0.06, 0.03 (s, 6H, $SiMe_2$); ^{13}C NMR δ 139.4, 128.6, 128.3, 126.8 (C_{ar}), 109.0 (CMe_2), 85.3 (C_6), 74.6 (C_5), 68.7 (C_7), 61.5 (C_{8a}), 57.9 (NCH_2Ph), 54.1 (C_2), 39.6 (C_{4a}), 37.5 (C_8), 27.0 (CMe_2), 25.9, 18.2 (*t*Bu), 25.4 (C_3), 21.2 (C_4), −4.5, −4.8 ($SiMe_2$); MS (CI, CH_4) 432 (M^++1); HRMS for $C_{25}H_{42}NO_3Si$ (M^++1): calcd 432.2934; found: 432.2929.

5.4.2. [4a*S*,5*R*,6*S*,7*S*,8a*R*]-*1*-(2′-Hydroxyethyl)-7-*O*-*tert*-butyldimethylsilyl-5,6-*O*-methylethylidene-5,6,7-trihydroxydecahydroquinoline (17b) and its 8a epimer (18b). 17b/18b=60:40 determined on the ^{1}H NMR spectrum of the crude.

17b (41%) from **13** (82.2 mg, 0.232 mmol) after separation by chromatography (cyclohexane/EtOAc 8:2); R_f 0.1 (cyclohexane/EtOAc 8:2); $[\alpha]_{Hg}$=−18 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 3.74 (ddd, 1H, $J_{7,8'}$=10.0 Hz, $J_{7,6}$=9.1 Hz, $J_{7,8}$=4.2 Hz, H_7), 3.67–3.44 (m, 2H, H_B), 3.31 (dd, 1H, $J_{6,7}$=$J_{6,5}$=9.1 Hz, H_6), 3.11–2.87 (m, 3H, $H_{5,A',2}$), 2.96 (ddd, 1H, $J_{A,A'}$=13.0 Hz, $J_{A,B}$=$J_{A,B'}$=4.3 Hz, H_A), 2.24–1.92 (m, 4H, $H_{2',8,8a,4}$), 1.69–1.45 (m, 3H, $H_{3,4a,3'}$), 1.43–1.28 (m, 1H, $H_{8'}$), 1.40, 1.38 (2s, 6H, CMe_2), 1.17–0.97 (m, 1H, $H_{4'}$), 0.87 (s, 9H, *t*Bu), 0.07, 0.06 (2s, 6H, $SiMe_2$); ^{13}C NMR δ 110.5 (CMe_2), 84.1 (C_6), 79.8 (C_5), 69.8 (C_7), 62.4 (C_{8a}), 58.7 (C_B), 53.6 (C_A), 53.2 (C_2), 42.4 (C_{4a}), 38.9 (C_8), 27.9 (C_3), 26.9 (CMe_2), 25.8, 18.3 (*t*Bu), 23.7 (C_4), −4.5, −4.9 ($SiMe_2$); MS (CI, CH_4) 386 (M^++1); HRMS for $C_{20}H_{40}NO_4Si$ (M^++1): calcd 386.2727; found: 386.2726.

18b (29%); R_f 0.1 (cyclohexane/EtOAc 6:4); $[\alpha]_D$=+29 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 4.03–3.88 (m, 1H, H_7), 3.96 (dd, 1H, $J_{5,4a}$=11.5 Hz, $J_{5,6}$=9.0 Hz, H_5), 3.69 (ddd, 1H, $J_{B,B'}$=10.7 Hz, $J_{B,A}$=6.5 Hz, $J_{B,A'}$=4.1 Hz, H_B), 3.54 (ddd, 1H, $J_{B',B}$=10.7 Hz, $J_{B',A'}$=5.2 Hz, $J_{B',A}$=3.8 Hz, $H_{B'}$), 3.38 (dd, 1H, $J_{6,5}$=$J_{6,7}$=9.0 Hz, H_6), 3.14–2.93 (m, 2H, $H_{2,A}$), 2.60–2.52 (m, 1H, H_{8a}), 2.24 (ddd, 1H, $J_{8,8'}$=14.2 Hz, $J_{8,7}$=$J_{8,8a}$=3.3 Hz, H_8), 2.18–1.81 (m, 3H, $H_{A',2',4a}$), 1.79–1.56 (m, 3H, $H_{4,3,3'}$), 1.53–1.44 (m, 1H, $H_{4'}$), 1.39 (s, 6H, CMe_2), 1.29–1.17 (m, 1H, $H_{8'}$), 0.89 (s, 9H, *t*Bu), 0.09, 0.08 (s, 6H, $SiMe_2$); ^{13}C NMR δ 109.1 (CMe_2), 85.1 (C_6), 74.5 (C_5), 68.4 (C_7), 61.5 (C_{8a}), 58.3 (C_B), 54.4 (C_A), 54.0 (C_2), 39.5 (C_{4a}), 37.3 (C_8), 30.2 (C_3), 27.0 (CMe_2), 25.8, 18.2 (*t*Bu), 25.0 (C_4), −4.6, −4.9 ($SiMe_2$), MS (CI, CH_4) 386 (M^++1); HRMS for $C_{20}H_{40}NO_4Si$ (M^++1): calcd 386.2727; found: 386.2719.

5.4.3. [4a*S*,5*R*,6*S*,7*S*,8a*R*]-*1*-(1′,3′-Di-*tert*-butyldimethylsilyloxy-2′-propyl)-7-*O*-*tert*-butyldimethylsilyl-5,6-*O*-methylethylidene-5,6,7-trihydroxydecahydroquinoline (17c) and its 8a epimer (18c). 17c/18c=40:60 determined on the ^{1}H NMR spectrum of the crude.

17c (20%) from **13** (42.3 mg, 0.119 mmol) after separation by chromatography (cyclohexane/EtOAc 8:2); R_f 0.42 (cyclohexane/EtOAc 9:1); $[\alpha]_{Hg}$=+5 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 3.75 (dd, 1H, $J_{A',A}$=10.4 Hz, $J_{A',B}$=8.2 Hz, $H_{A'}$), 3.71 (dd, 1H, $J_{A,A'}$=10.4 Hz, $J_{A,B}$=4.6 Hz, H_A), 3.81–3.66 (m, 1H, H_7), 3.59 (dd, 1H, $J_{C,C'}$=10.0 Hz, $J_{C,B}$=5.3 Hz, H_C), 3.53 (dd, 1H, $J_{C',C}$=10.0 Hz, $J_{C',B}$=7.4 Hz, $H_{C'}$), 3.32 (dd, 1H, $J_{6,7}$=$J_{6,5}$=9.1 Hz, H_6), 3.27–3.14 (m, 1H, H_B), 2.97 (dd, 1H, $J_{5,6}$=10.8 Hz, $J_{5,4a}$=9.1 Hz, H_5), 2.91–2.80 (m, 1H, H_2), 2.48 (dd, 1H, $J_{8a,4a}$=12.8 Hz, $J_{8a,8'}$=9.0 Hz, $J_{8a,8}$=4.0 Hz, H_{8a}), 2.45–2.31 (m, 2H, $H_{2',8}$), 2.04–1.90 (m, 1H, H_4), 1.69–1.54 (m, 1H, H_3), 1.50–1.39 (m, 2H, $H_{4a,3'}$), 1.37, 1.36 (2s, 6H, CMe_2), 1.31–1.20 (m, 1H, $H_{8'}$), 1.07–0.93 (m, 1H, $H_{4'}$), 0.88, 0.87 (2s, 27H, *t*Bu), 0.08, 0.07, 0.03, 0.02 (s, 18H, $SiMe_2$); ^{13}C NMR δ 111.3 (CMe_2), 84.2 (C_6), 79.9 (C_5), 70.3 (C_7), 64.2 (C_A), 61.4 (C_B), 60.6 (C_C), 59.2 (C_{8a}), 48.1 (C_2), 44.5 (C_{4a}), 38.6 (C_8), 28.5 (C_3), 27.0 (CMe_2), 25.9, 18.2 (*t*Bu), 25.6 (C_4), −4.4, −4.9, −5.3, −5.4, −5.6 ($SiMe_2$); MS (CI, CH_4) 644 (M^++1); HRMS for $C_{33}H_{70}NO_5Si_3$ (M^++1): calcd 644.4562; found: 644.4570.

18c (35%); R_f 0.78 (cyclohexane/EtOAc 9:1); $[\alpha]_D$=+14 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 4.12 (dd, 1H, $J_{5,4a}$=11.1 Hz,

$J_{5,6}$=9.1 Hz, H_5), 3.95 (ddd, 1H, $J_{7,8'}$=11.0 Hz, $J_{7,6}$=9.0 Hz, $J_{7,8}$=3.2 Hz, H_7), 3.72 (dd, 1H, $J_{A',A}$=10.3 Hz, $J_{A',B}$=6.9 Hz, $H_{A'}$), 3.56 (dd, 1H, $J_{A,A'}$=10.3 Hz, $J_{A,B}$=4.6 Hz, H_A), 3.60–3.49 (m, 2H, $H_{C,C'}$), 3.24 (dd, 1H, $J_{6,7}$=$J_{6,5}$=9.0 Hz, H_6), 3.20–3.10 (m, 1H, H_B), 3.06 (ddd, 1H, $J_{8a,4a}$=$J_{8a,8}$=$J_{8a,8'}$≈3.2 Hz, H_{8a}), 2.93–2.77 (m, 1H, H_2), 2.39 (ddd, 1H, $J_{8,8'}$=14.7 Hz, $J_{8,7}$=$J_{8,8a}$=3.2 Hz, H_8), 2.26 (ddd, 1H, $J_{2',2}$=$J_{2',3'}$=11.5 Hz, $J_{2',3}$=1.9 Hz, $H_{2'}$), 2.04–1.85 (m, 1H, H_4), 1.81–1.53 (m, 3H, $H_{4a,3,3'}$), 1.52–1.40 (m, 1H, $H_{4'}$), 1.40–1.34 (m, 1H, $H_{8'}$), 1.38 (s, 6H, CMe_2), 0.88, 0.87 (2s, 27H, *t*Bu), 0.09, 0.08, 0.06, 0.04, 0.02 (s, 18H, $SiMe_2$); ^{13}C NMR δ 108.7 (CMe_2), 85.4 (C_6), 74.9 (C_5), 68.6 (C_7), 62.9 (C_A), 59.8 (C_B), 59.4 (C_C), 58.8 (C_{8a}), 47.8 (C_2), 40.0 (C_{4a}), 37.5 (C_8), 30.2 (C_3), 27.1, 26.9 (CMe_2), 25.9, 18.2 (*t*Bu), 22.0 (C_4), −4.4, −4.7, −5.4, −5.6 ($SiMe_2$); MS (CI, CH_4) 644 (M^++1); HRMS for $C_{33}H_{70}NO_5Si_3$ (M^++1): calcd 644.4562; found: 644.4556.

5.4.4. [4a*S*,5*R*,6*S*,7*S*,8a*R*]-7-*O*-*tert*-Butyldimethylsilyl-5,6-*O*-methylethylidene-5,6,7-trihydroxydecahydro-1-*H*-quinoline (19a). To a suspension of palladium hydroxide (44.6 mg) in absolute EtOH (1 mL), saturated with dihydrogen, was added a solution of the *N*-benzylamine **17a** (44.6 mg, 0.103 mmol) in absolute EtOH (0.5 mL). After stirring for 14 h at 20°C, the catalyst was removed by filtration through a Celite pad and the filtrate was concentrated in vacuo. Flash chromatography (CH_2Cl_2/MeOH 98:2) gave the pure amine **19a** (29.6 mg) as an oil in 84% yield. R_f 0.1 (CH_2Cl_2/MeOH 98:2); $[\alpha]_D$=+19 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 3.86–3.69 (m, 1H, H_7), 3.35 (dd, 1H, $J_{6,7}$=$J_{6,5}$=9.0 Hz, H_6), 3.14–3.04 (m, 1H, H_2), 3.01 (dd, 1H, $J_{5,4a}$=10.0 Hz, $J_{5,6}$=9.0 Hz, H_5), 2.70–2.53 (m, 1H, $H_{2'}$), 2.27 (ddd, 1H, $J_{8a,4a}$=12.4 Hz, $J_{8a,8'}$=9.1 Hz, $J_{8a,8}$=4.0 Hz, H_{8a}), 2.13–2.01 (m, 1H, H_4), 1.95 (ddd, 1H, $J_{8,8'}$=13.2 Hz, $J_{8,7}$=4.7 Hz, $J_{8,8a}$=4.0 Hz, H_8), 1.72–1.59 (m, 2H, $H_{3,3'}$), 1.51–1.29 (m, 2H, $H_{4a,8'}$), 1.39, 1.37 (2s, 6H, CMe_2), 1.18–1.07 (m, 1H, $H_{4'}$), 0.88 (s, 9H, *t*Bu), 0.07 (s, 6H, $SiMe_2$); ^{13}C NMR δ 110.4 (CMe_2), 84.6 (C_6), 79.6 (C_5), 69.6 (C_7), 57.5 (C_{8a}), 47.1 (C_2), 43.9 (C_{4a}), 41.3 (C_8), 27.9 (C_3), 26.9 (CMe_2), 25.8, 18.3 (*t*Bu), 25.6 (C_4), −4.5, −4.9 ($SiMe_2$); MS (CI, CH_4) 342 (M^++1); HRMS for $C_{18}H_{36}NO_3Si$ (M^++1): calcd 342.2464; found: 342.2462.

5.4.5. [4a*S*,5*R*,6*S*,7*S*,8a*S*]-7-*O*-*tert*-Butyldimethylsilyl-5,6-*O*-methylethylidene-5,6,7-trihydroxydecahydro-1-*H*-quinoline (20a). The decahydroquinoline **20a** was obtained from the protected derivative **18a** (144 mg, 0.269 mmol) under the same conditions as above for the compound **19a** except that the reaction was carried out in EtOAc and that the crude product **20a** (71.9 mg) was submitted to further reaction without purification. R_f 0.3 (CH_2Cl_2/MeOH 98:2); $[\alpha]_D$=+24 (*c* 1.0, CH_2Cl_2); ^{1}H NMR δ 4.10 (ddd, 1H, $J_{7,8'}$=$J_{7,6}$=9.1 Hz, $J_{7,8}$=5.2 Hz, H_7), 4.01 (dd, 1H, $J_{5,4a}$=11.1 Hz, $J_{5,6}$=9.1 Hz, H_5), 3.01 (dd, 1H, $J_{6,7}$=$J_{6,5}$=9.1 Hz, H_6), 3.12–2.95 (m, 2H, $H_{2,8a}$), 2.69–2.51 (m, 1H, $H_{2'}$), 2.08–1.90 (m, 1H, H_4), 1.83–1.34 (m, 6H, $H_{4a,8,8',3,4',3'}$), 1.39 (s, 6H, CMe_2), 0.88 (s, 9H, *t*Bu), 0.08 (s, 6H, $SiMe_2$); ^{13}C NMR δ 108.9 (CMe_2), 85.2 (C_6), 74.8 (C_5), 68.8 (C_7), 58.8 (C_{8a}), 56.1 (C_2), 52.9 (C_{4a}), 47.0 (C_8), 39.2 (C_3), 27.0 (CMe_2), 25.9, 18.3 (*t*Bu), 25.4 (C_4), −4.5, −4.8 ($SiMe_2$).

5.4.6. [4a*S*,5*R*,6*R*,7*S*,8a*R*]-Decahydro-1*H*-quinoline-5,6,7-triol (21a). The decahydroquinoline **21a** was obtained from the protected derivative **19a** (28.8 mg, 84 μmol) under the same conditions as above for **16a** and was isolated (14.9 mg) as a solid in 94% yield. $[\alpha]_D$=+65 (*c* 1.0, H_2O); ^{1}H NMR (D_2O) δ 3.68–3.50 (m, 1H, H_7), 3.32 (dd, 1H, $J_{6,7}$=$J_{6,5}$=9.1 Hz, H_6), 3.25–3.10 (m, 1H, H_2), 3.17 (dd, 1H, $J_{5,4a}$=10.2 Hz, $J_{5,6}$=9.1 Hz, H_5), 2.82–2.67 (m, 1H, $H_{2'}$), 2.56 (ddd, 1H, $J_{8a,4a}$=$J_{8a,8'}$=11.8 Hz, $J_{8a,8}$=3.0 Hz, H_{8a}), 2.25–2.04 (m, 2H, $H_{8,4}$), 1.95–1.77 (m, 1H, H_3), 1.75–1.15 (m, 4H, $H_{8',4a,4',3'}$); ^{13}C NMR (D_2O) δ 81.2 (C_6), 76.9 (C_5), 72.1 (C_7), 56.3 (C_{8a}), 47.5 (C_2), 46.9 (C_{4a}), 39.6 (C_8), 28.5 (C_3), 25.9 (C_4).

5.4.7. [4a*S*,5*R*,6*R*,7*S*,8a*R*]-*1*-(2′-Hydroxyethyl) decahydroquinoline-5,6,7-triol (21b). The decahydroquinoline **21b** was obtained from the protected derivative **17b** (35.1 mg, 91 μmol) under the same conditions as above for **16a** and was isolated (16.9 mg) as a solid in 80% yield. $[\alpha]_D$=−17 (*c* 1.0, H_2O); ^{1}H NMR (D_2O) δ 3.81 (t, 2H, $J_{B,A}$=6.5 Hz, H_B), 3.65–3.47 (m, 1H, H_7), 3.31 (dd, 1H, $J_{6,7}$=$J_{6,5}$=9.2 Hz, H_6), 3.14 (dd, 1H, $J_{5,4a}$=10.0 Hz, $J_{5,6}$=9.2 Hz, H_5), 3.07–2.94 (m, 1H, H_2), 2.96 (td, 1H, $J_{A,A'}$=13.8 Hz, $J_{A,B}$=$J_{A,B'}$=6.5 Hz, H_A), 2.69 (td, 1H, $J_{A',A}$=13.8 Hz, $J_{A',B}$=$J_{A',B'}$=6.5 Hz, $H_{A'}$), 2.50–2.32 (m, 2H, $H_{2',8}$), 2.21 (ddd, 1H, $J_{8a,4a}$=$J_{8a,8'}$=11.7 Hz, $J_{8a,8}$=2.6 Hz, H_{8a}), 1.87–1.69 (m, 1H, H_4), 1.87–1.69 (m, 1H, H_3), 1.66–1.45 (m, 1H, $H_{3'}$), 1.44–1.21 (m, 2H, $H_{4a,8'}$), 1.08 (dddd, 1H, $J_{4',4}$=$J_{4',4a}$=$J_{4',3'}$=12.6 Hz, $J_{4',3}$=3.6 Hz, $H_{4'}$); ^{13}C NMR (D_2O) δ 81.1 (C_6), 77.4 (C_5), 72.6 (C_7), 61.3 (C_{8a}), 60.3 (C_B), 56.1 (C_A), 55.6 (C_2), 47.4 (C_{4a}), 38.2 (C_8), 29.2 (C_3), 26.2 (C_4); MS (CI, NH_3) 232 (M^++1); HRMS for $C_{11}H_{22}NO_4$ (M^++1): calcd 232.1549; found: 232.1446.

5.4.8. [4a*S*,5*R*,6*R*,7*S*,8a*R*]-*1*-(1′,3′-Dihydroxy-2′-*N*-propyl)-decahydroquinoline-5,6,7-triol (21c). The decahydroquinoline **21c** was obtained from the protected derivative **17c** (33 mg, 51 μmol) under the same conditions as above for **16a** and was isolated (11.4 mg) as a solid in 86% yield. $[\alpha]_D$=−17 (*c* 1.0, H_2O); ^{1}H NMR (D_2O) δ 3.95 (dd, 1H, $J_{A,A'}$=12.0 Hz, $J_{A,B}$=5.2 Hz, H_A), 3.84–3.67 (m, 3H, $H_{A',C,C'}$), 3.65–3.50 (m, 1H, H_7), 3.42–3.23 (m, 1H, H_B), 3.33 (dd, 1H, $J_{6,7}$=$J_{6,5}$=9.7 Hz, H_6), 3.15 (dd, 1H, $J_{5,6}$=$J_{5,4a}$=9.7 Hz, H_5), 3.11–3.00 (m, 1H, H_2), 2.67–2.33 (m, 3H, $H_{2',8,8a}$), 2.20–2.01 (m, 1H, H_4), 1.89–1.70 (m, 1H, H_3), 1.62–1.20 (m, 3H, $H_{3',4a,8'}$), 1.08 (dddd, 1H, $J_{4,4'}$=$J_{4',4a}$=$J_{4',3'}$=12.2 Hz, $J_{4',3}$=3.2 Hz, $H_{4'}$); ^{13}C NMR (D_2O) δ 81.4 (C_6), 77.8 (C_5), 73.0 (C_7), 63.5 (C_A), 62.1 (C_B), 60.2 (C_{8a}), 60.1 (C_C), 49.6 (C_2), 48.4 (C_{4a}), 38.1 (C_8), 29.7 (C_3), 27.2 (C_4); MS (CI, NH_3) 262 (M^++1); HRMS for $C_{12}H_{24}NO_5$ (M^++1): calcd 262.1654; found: 262.1653.

5.4.9. [4a*S*,5*R*,6*R*,7*S*,8a*S*]-Decahydro-1*H*-quinoline-5,6,7-triol (22a). The decahydroquinoline **22a** was obtained from the protected derivative **20a** (20 mg, 56 μmol) under the same conditions as above for **16a** and was isolated (9 mg) as a solid in 92% yield. $[\alpha]_D$=+65 (*c* 1.0, H_2O); ^{1}H NMR (D_2O) δ 3.87–3.68 (m, 1H, $H_{7,5}$), 3.40–3.21 (m, 1H, H_2), 3.16–2.97 (m, 2H, $H_{6,8a}$), 2.77–2.58 (m, 1H, $H_{2'}$), 2.16–1.87 (m, 2H, $H_{8,4}$), 1.80–1.42 (m, 5H, $H_{4A,8',4',3,3'}$); ^{13}C NMR (D_2O) δ 79.8 (C_4), 74.7 (C_5), 70.5 (C_3), 67.8 (C_1), 54.1 (C_8), 45.7 (C_6), 31.3 (C_2), 27.3 (C_7); MS (CI, NH_3) 188

(M^++1); HRMS for $C_9H_{18}NO_3$ (M^++1): calcd 188.1287; found: 188.1286.

5.4.10. [4a*S*,5*R*,6*R*,7*S*,8a*S*]-*1*-(2′-Hydroxyethyl)-decahydroquinoline-5,6,7-triol (22b). The decahydroquinoline **22b** was obtained from the protected derivative **18b** (24.7 mg, 64 μmol) under the same conditions as above for **16a** and was isolated (10.2 mg) as a solid in 92% yield. $[\alpha]_D$=+27 (*c* 0.93, H_2O); ^1H NMR (D_2O) δ 3.93–3.74 (m, 3H, $H_{5,B,B'}$), 3.71 (ddd, 1H, $J_{7,8'}$=12.2 Hz, $J_{7,6}$=9.0 Hz, $J_{7,8}$=2.6 Hz, H_7), 3.35 (dd, 1H, $J_{6,5}$=$J_{6,7}$=9.0 Hz, H_6), 3.15–3.02 (m, 1H, H_2), 3.01–2.73 (m, 3H, $H_{8a,A,A'}$), 2.67–2.49 (m, 1H, H_2), 2.46–2.30 (m, 1H, H_8), 2.13–1.97 (m, 1H, H_4), 1.92–1.78 (m, 1H, H_{4a}), 1.77–1.43 (m, 4H, $H_{8',4',3,3'}$); ^{13}C NMR (D_2O) δ 82.3 (C_6), 72.3 (C_5), 70.8 (C_7), 61.4 (C_{8a}), 58.8 (C_B), 56.8 (C_A), 56.5 (C_2), 43.6 (C_{4a}), 35.9 (C_8), 25.9 (C_3), 22.5 (C_4); MS (CI, NH_3) 232 (M^++1); HRMS for $C_{11}H_{22}NO_4$ (M^++1): calcd 232.1549; found: 232.1546.

5.4.11. [4a*S*,5*R*,6*R*,7*S*,8a*S*]-*1*-(1′,3′-Dihydroxy-2′-*N*-propyl)-decahydroquinoline-5,6,7-triol (22c). The decahydroquinoline **22c** was obtained from the protected derivative **18c** (59 mg, 92 μmol) under the same conditions as above for **16a** and was isolated (16.5 mg) as a solid in 69% yield. $[\alpha]_D$=+35 (*c* 1.0, H_2O); ^1H NMR (D_2O) δ 4.04 (dd, 1H, $J_{5,4a}$=10.6 Hz, $J_{5,6}$=9.0 Hz, H_5), 3.89 (dd, 1H, $J_{A,A'}$=11.7 Hz, $J_{A,B}$=5.3 Hz, H_A), 3.83–3.62 (m, 3H, $H_{C,C',7}$), 3.56 (dd, 1H, $J_{A',A}$=11.7 Hz, $J_{A',B}$=6.9 Hz, $H_{A'}$), 3.35 (dd, 1H, $J_{6,7}$=$J_{6,5}$=9.0 Hz, H_6), 3.29–3.17 (m, 1H, H_B), 3.16–3.08 (m, 1H, H_{8a}), 3.06–2.94 (m, 1H, H_2), 2.51–2.36 (m, 1H, H_8), 2.35–2.18 (m, 1H, $H_{2'}$), 2.10–1.94 (m, 1H, H_4), 1.84–1.69 (m, 1H, H_{4a}), 1.62–1.20 (m, 4H, $H_{8',3,3',4'}$); ^{13}C NMR (D_2O) δ 83.1 (C_6), 73.0 (C_5), 71.3 (C_7), 62.0 (C_A), 60.1 (C_B), 60.0 ($C_{8a,C}$), 49.0 (C_2), 45.0 (C_{4a}), 36.8 (C_8), 27.2 (C_3), 23.7 (C_4); MS (CI, NH_3) 262 (M^++1); HRMS for $C_{12}H_{24}NO_5$ (M^++1): calcd 262.1654; found: 262.1656.

5.5. Inhibition studies

The inhibition studies against α-D-glucosidase from *Bacillus stearothermophilus* (EC 3.2.1.20), β-D-glucosidase from almonds (EC 3.2.1.21), α-D-mannosidase from Jack beans (EC 3.2.1.24), α-L-fucosidase from bovine kidney (EC 3.2.1.51), α-D-galactosidase from green coffee bean (EC 3.2.1.22), β-D-galactosidase from *Thermus thermophilus* and pancreatic porcine α-amylase (EC 3.2.1.1) were performed according to the procedure previously described.[23]

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