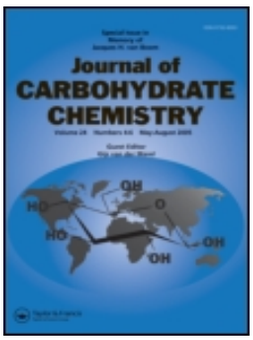

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Concise stereoselective synthesis of 5-hydroxy carba-β-D-rhamnose, carba-β-D-rhamnose, (-)-gabosine O, and carba-α-D-rhamnose

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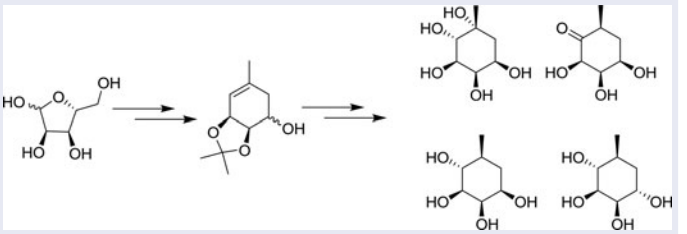
ABSTRACT

A divergent approach was developed for the synthesis of 5-hydroxy carba-β-D-rhamnose **1**, carba-β-D-rhamnose **2**, (-)-gabosine O **3**, and carba-α-D-rhamnose **4** starting from D-ribose using ring closing metathesis (RCM).

GRAPHICAL ABSTRACT



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BH_3-Reduction; Grignard addition; Oxidation; RCM; Silyl protection

Introduction

Carbasugars, a family of carbohydrate mimics, have attracted great interest due to their interesting biological properties. The ability of carbasugars to mimic the natural sugars in size, structure, and polarity and also their stability towards hydrolysis make them potential candidates as inhibitors of glycosidases and glycosyltransferases, etc. The development of synthetic strategies towards carbasugars from carbohydrates as precursors has advantage over other commonly used approaches, as the final product can be obtained with high optical purity and the stereochemistry can be maintained throughout the synthetic sequence.

In 1974, gabosines (Fig. 1), a class of carbasugars, were isolated from *Streptomyces* strains. A total of 14 different gabosines have been identified and the absolute configuration of gabosine A–F, I, L, N, and O has been established.[1,2] The intense interest in these natural products is encouraged by their interesting

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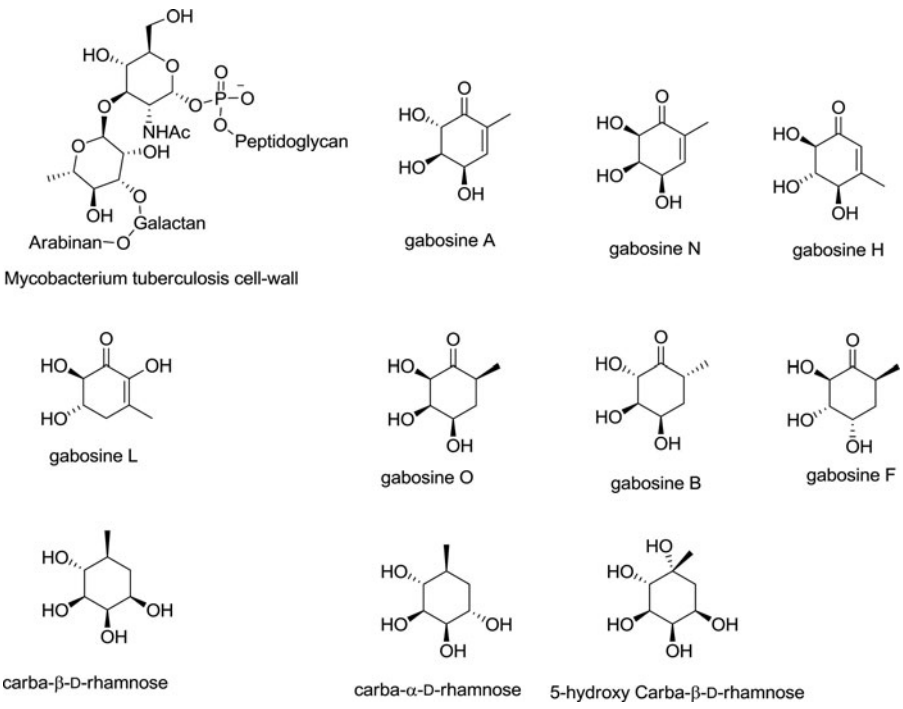


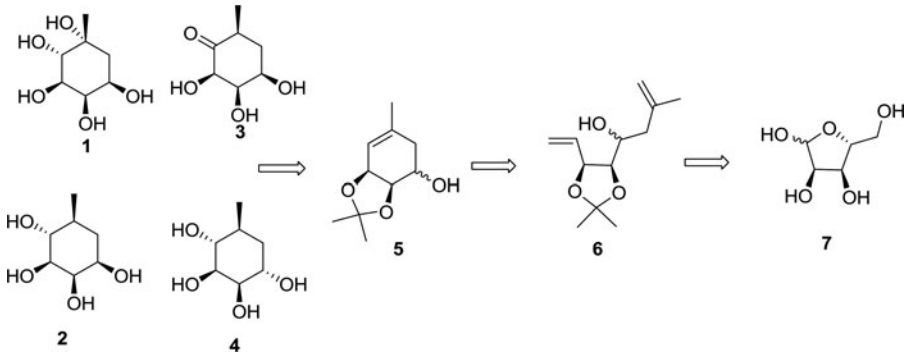
Figure 1. Structures of *Mycobacterium tuberculosis* cell-wall, gabosines, and carbarhamnoses.

biological properties such as antibiotic, anticancer, and DNA binding properties. Furthermore, gabosines can be considered as chemical precursors of 6-deoxy-carba pyranose derivatives which are known for the inhibition of oligosaccharide processing enzymes.[3] Carbarhamnoses are potential inhibitor of rhamnosyl-transferases which are responsible for cell growth of *Mycobacterium tuberculosis*[4] and ultimately become a non-toxic treatment for TB.[5] Furthermore, carbarhamnoses were used in the preparation of stable trisaccharides which were present in synthetic vaccines for *Streptococcus pneumoniae* infections.[6] Because of the interesting structures and biological properties of carbarhamnoses and gabosines, a few syntheses for gabosines and carbarhamnoses have been reported in literature.[7,8]

In the past few years, our group has been involved in developing new strategies for the synthesis of carbasugars from carbohydrates.[9,10] In continuation, herein we are reporting a short, efficient, and common strategy (Sch. 1) for the synthesis of 5-hydroxy carba-β-D-rhamnose **1**, carba-β-D-rhamnose **2**, (-)-gabosine O **3**, and carba-α-D-rhamnose **4** RCM. The key aspect of our synthesis is the efficient preparation of a diene precursor **6** for RCM. Since, we believe that the success of RCM strategy depends on how one can make efficiently the diene precursor.

Results and discussion

Retro synthetic analysis (Sch. 1) indicated that compound **5** can be obtained from RCM of diene **6**, which in turn can be derived from D-ribose 7 by simple transformations. Compound 7 was subjected to acetonide protection followed by one

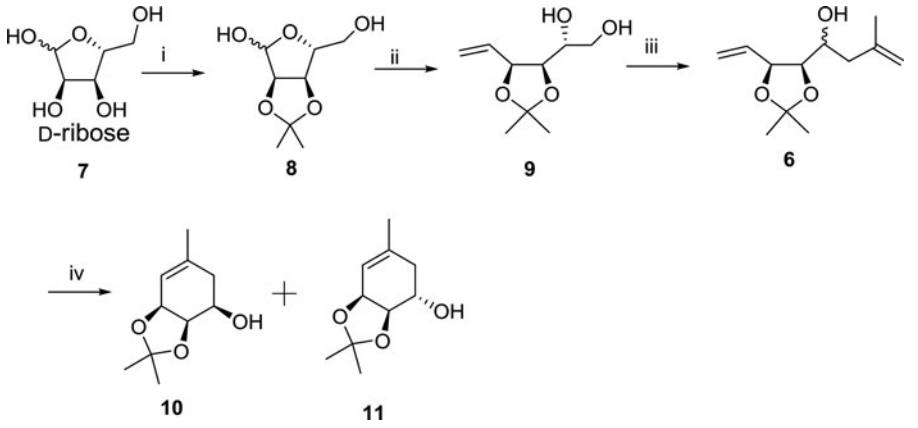


Scheme 1. Retro synthetic analysis of the synthetic targets.

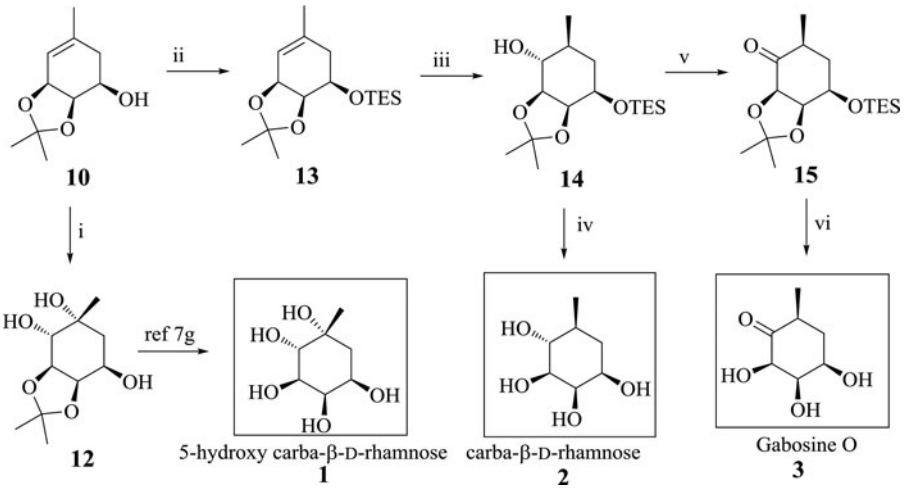
carbon homologation using Wittig reaction to give diol **9** using reported procedure (Sch. 2).[11] Treatment of diol **9** with sodiummetaperiodate in dichloromethane gave aldehyde, which was directly used for Grignard reaction with β-methallyl magnesium chloride[12] in ether at 0°C to yield diene **6** in 3:1 ratio as an inseparable diastereomeric mixture, with *anti*-isomer as the major product. The formation of *anti*-isomer as the major product can be explained by non-chelated *Felkin–Anh* model.

The diastereomeric mixture of diene mixture **6** was subjected to RCM using Grubbs second generation catalyst in dichloromethane under reflux condition [13] to afford the separable cyclohexetols **10** and **11** in 3:1 ratio. We have chosen the major isomer **10** as a common intermediate for the synthesis of 5-hydroxy-carba-β-D-rhamnose **1**, carba-β-D-rhamnose **2**, and (-)-gabosine O **3**.

Dihydroxylation of compound **10** with OsO_4 in THF and H_2O (2:1) gave compound **12** whose spectral data is good in agreement with the reported data.[7g] Deprotection of the acetonide to give 5-hydroxyl carba-β-D-rhamnose **1** was



Scheme 2. (i) acetone, H_2SO_4 (cat), rt, 3 h, 93%. (ii) Ph_3PCH_3Br, KOtBu, THF, 0°C, 10 h, 81%. (iii) (a) $NaIO_4$, CH_2Cl_2, H_2O, 0°C, 1 h; (b) β-methallyl magnesium chloride, ether, 0°C, overnight, 80%. (iv) Grubbs second generation catalyst, CH_2Cl_2, reflux, 8 h, 87%.

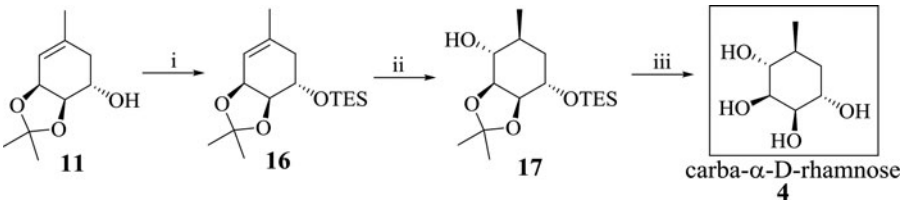


Scheme 3. (i) OsO_4, NMO, THF and H2O (2:1), 0°C to rt, 24 h, 85%. (ii) TESCl, imdizole, CH2Cl2, 0°C to rt, 20 min, 95%. (iii) BH3.DMS, THF, 0°C to rt, 2 h, 70%. (iv) 3 N HCl, MeOH, rt, 12 h, 90%. (v) Dess Martin periodinane, CH2Cl2, 0°C to rt, 1 h, 80%. (vi) Amberlyst®-15, THF, H2O, reflux, 5 h, 92%.

already in the reported literature.[7g] Homo allylic alcohol in compound **10** was converted to silyl ether by treating with TESCl and imidazole in dichloromethane to afford compound **13** in a 95% yield. Then compound **13** was subjected to hydroboration with BH_3.DMS to afford compound **14** as an exclusive product. Global deprotection of compound **14** with 3 N HCl smoothly gave carba-β-D-rhamnose **2** (Sch. 3).

To prepare (-)-gabosine O **3**, the secondary alcohol in compound **14** was subjected to oxidation with Dess Martin periodinane in dichloromethane to produce the keto compound **15**. Then, deprotection of the acetonide and silyl groups in **15** was carried out with Amberlyst®-15 to furnish the gabosine O **3** in a 92% yield (Sch. 3). The spectral and analytical data of 5-hydroxy carba-β-D-rhamnose **12**, carba-β-D-rhamnose **2**, and (-)-gabosine O **3** are in good agreement with reported values.[7f–g]

We also utilized the minor isomer **11** to prepare carba-α-D-rhamnose **4** (Sch. 4). For this purpose, the homo allylic alcohol in compound **11** was converted into silyl ether by reacting with TESCl in dichloromethane to give compound **16**. Compound **16** was subjected to hydroboration followed by deprotection with 3 N HCl to afford



Scheme 4. (i) TESCl, imdizole, CH_2Cl_2, 0°C to rt, 20 min, 95%. (ii) BH_3.DMS, THF, 0°C to rt, 2 h, 70%. (iii) 3 N HCl, MeOH, rt, 12 h, 90%.

Table 1. Glycosidase inhibitory activities of compounds **2** and **3**.

Enzymes	IC_{50} value (in μM)	
	carba-β-D-rhamnose **2**	carba-α-D-rhamnose **4**
α-galactosidase	0.231	NI
β-galactosidaes	NI	NI
α-glucosidase	0.152	NI
β-glucosidase	NI	NI

NI = No Inhibition observed up to 50 μM.

carba-α-D-rhamnose **4**. Spectral data of compound **4** was in good agreement with the reported values.[7c]

Finally, carba-β-D-rhamnose **2** and carba-α-D-rhamnose **4** were biologically evaluated as potential inhibitors of α-galactosidase, β-galactosidase, α-glucosidase, and β-glucosidase. As shown in Table 1, compound **2** was found to have moderate inhibition on α-glucosidase and α-galactosidase with IC_{50} values of 0.152 μM and 0.231 μM, respectively, whereas no inhibition on β-glucosidase and β-galactosidase. On the other hand, compound **4** did not show inhibition of on all four enzymes at up to 50 μM concentration.

Conclusion

In summary, stereoselective and divergent syntheses of 5-hydroxy carba-β-D-rhamnose **1**, carba-β-D-rhamnose **2**, (-)- gabosine O **3**, and carba-α-D-rhamnose **4** were accomplished in good overall yields. This strategy is also useful to prepare some other carbasugar analogues. Studies on the glycosidase inhibitory activity of carba-β-D-rhamnose **2** and carba-α-D-rhamnose **4** revealed that **2** had moderate activities to inhibit α-glucosidase and α-galactosidase with IC_{50} values of 0.152 μM and 0.231 μM, respectively.

Experimental

General methods: Moisture and oxygen sensitive reactions were carried out under N_2 atmosphere in flame or oven dried glassware with magnetic stirring. Solvents were distilled under standard procedures, and THF used was freshly distilled over Na and benzophenone. All reactions were monitored by TLC (silica-coated plates, visualized under UV light or by phosphomolibdidate solution staining). Before concentration of the solvent, the organic layer was dried over Na_2SO_4. Column chromatography (CC) was performed on silica gel (60–120 mesh) using mixtures of AcOEt and hexane as eluents. Melting points (mp) were determined on a Fisher John's melting point apparatus and were uncorrected. IR spectra were recorded on a Perkin–Elmer RX-1 FT-IR system. ^{1}H NMR and ^{13}C NMR spectra were recorded using Varian Gemini-200, Bruker Avance-300, and Inova-500 spectrometers. ^{1}H NMR data are expressed as chemical shifts in ppm followed by multiplicity, number of proton(s), and coupling constant(s) quoted in *J* (Hz). ^{13}C NMR chemical

shifts are expressed in ppm. Optical rotations were measured with a JASCO digital polarimeter. High resolution MS was performed on a Q STAR mass spectrometer. α-Glucosidase from *Saccharomyces cerevisiae* (cat. # G5003), β-glucosidase from almond (cat. # 49290), α-galactosidase from green coffee beans (cat. # G8507), β-galactosidase from *Kluyveromyces lactis* (cat. # G3665), 4-nitrophenyl β-D-glucopyranoside (cat. # N7006), and 4-Nitrophenyl α-D-glucopyranoside (cat # N1377) used in biological assays were purchased from commercial sources.

1-((4*R*,5*S*)-2, 2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-3-methylbut-3-en-1-ol (6). To a stirred solution of diol **9** (6.7 g, 35.6 mmol) in dichloromethane (60 mL) was added drop wise an aqueous solution of $NaIO_4$ (11.4 g, 53.4 mmol, 1.5 M solution) at 0°C and the reaction mixture was stirred at rt for 40 min. After water (50 mL) was added, the mixture was extracted with methylene chloride (600 mL), dried, filtered, and evaporated under reduced pressure. The crude product was directly treated with solution of β-methallyl magnesium chloride prepared from Mg (7.69 g, 320.5 mmol) and β-methyallyl chloride (25.2 mL, 256.4 mmol) in ether (60 mL) at 0°C. After stirring for overnight at rt, the reaction mixture was poured into saturated aqueous NH_4Cl (150 mL) and extracted with ethyl acetate (3 × 150 mL). The combined organic layers were washed with water, brine, and dried over Na_2SO_4, concentrated under reduced pressure and purified through CC (hexane/ethyl acetate 4:1) to afford the corresponding diastereomeric mixture (3:1) diene **6** as a colorless oil (6.6 g, 80%). $[\alpha]^{30}_D = -2.16$ (c = 1.6, $CHCl_3$); IR (neat): 3462, 2923, 2876, 2854, 1792, 1729, 1459, 1380, 1237, 1117, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 6.09–5.96 (*m*, 1H), 5.42, 5.36* (*d, J* = 17.7, *J** = 17.1, 1H), 5.26–5.32 (*dd, J* = 10.2, 9.1, 1H), 4.90, 4.85* (*s, s**, 1H), 4.82, 4.79* (*s, s**, 1H), 4.71–4.65, 4.60–4.55* (*dd, J* = 6.8, *J** = 7.4, 1H), 4.07–4.02*, 4.0–3.94 (*dd, J** = 7.4, 6.2, *J* = 7.4, 6.8, 1H), 3.76 (*m*, 1H), 2.5 (*d, J* = 13.7, 1H), 2.21–2.09 (*m*, 2H), 1.78, 1.75* (*s, s**, 3H), 1.53*, 1.49 (*s**, *s*, 3H), 1.40*, 1.38 (*s**, *s*, 3H,); ^{13}C NMR ($CDCl_3$, 75 MHz,): δ 142.2, 141.9*, 134.3, 134.0*, 119.5*, 117.9, 113.7, 113.2*, 108.6, 108.6, 80.5, 80.1*, 79.1*, 78.8, 67.6*, 67.1*, 42.4, 42.1*, 27.7, 27.3*, 25.3, 25.0*, 22.4; ESIMS: m/z 235 $[M+Na]^+$; HRMS: calcd for $C_{12}H_{20}O_3Na$ $[M+Na]^+ = 235.1304$, found 235.1303. * indicates isomer peaks.

(3a*R*,4*R*,7a*S*)-2,2,6-Trimethyl-3a,4,5,7a-tetrahydrobenzo[d] [1,3]dioxol-4-ol. (10) & (3a*R*,4*S*,7a*S*)-2,2,6-Trimethyl-3a,4,5,7a-tetrahydrobenzo[d][1,3]dioxol-4-ol (11). To the diene **6** (4.5 g, 21.2 mmol) in dry CH_2Cl_2 (840 mL), Grubbs II generation catalyst (0.89 g, 1.06 mmol) was added and the resulting purple solution was turned to brown after 10 min. The reaction mixture was refluxed for 8 h, concentrated under reduced pressure, and the residue was purified by CC (hexane/ethyl acetate: 7:3) to give compound **10** (2.5 g, 64%) & **11** (0.89 g, 22%) as light brown oils (3.39 g, 87%).

Data for compound **10**: $[\alpha]^{30}_D = +2.5$ (c = 0.5, $CHCl_3$); IR(neat): 3414, 2983, 2922, 1671, 1438, 1377, 1229, 1163, 1104, 1024, 853 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 5.58 (*bs*, 1H), 4.59 (*bs*, 1H), 3.94–3.91 (*dd, J* = 6.4, 8.6, 1H), 3.83 (*m*, 1H), 2.29–2.22 (*dd, J* = 5.2, 16.9, 1H), 2.09–2.02 (*dd, J* = 10.1, 16.9, 1H), 1.78 (*s*, 3H), 1.49 (*s*, 3H), 1.40 (*s*, 3H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 138.6, 118.0, 109,

79.1, 73.1, 69.4, 35.8, 28.4, 25.9, 23.4; ESIMS: m/z 207 $[M+Na]^+$; HRMS: calcd for $C_{10}H_{16}O_3Na = 207.09917$ $[M+Na]^+$, found 207.0994.

Data for compound **11**: $[\alpha]^{30}_D = +1.5$ (c = 0.8, $CHCl_3$); IR(neat): 3437, 2983, 2923, 2854, 1441, 1377, 1214, 1054, 893 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.46 (*bs*, 1H), 4.60 (*bs*, 1H), 4.35–4.27 (*dd, J* = 3.0, 6.0, 1H), 3.89 (*m*, 1H), 2.35–2.22 (*dd, J* = 7.1, 16.9, 1H), 2.18–2.07 (*dd, J* = 4.1, 16.9, 1H), 1.75 (*s*, 3H), 1.42 (*s*, 3H), 1.39 (*s*, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.4, 119.6, 109.1, 75.1, 73.4, 67.18, 33.9, 27.2, 26.0, 23.5; ESIMS: m/z 207 $[M+Na]^+$; HRMS; calcd for $C_{10}H_{16}O_3Na = 207.09917$ $[M+Na]^+$, found 207.0994.

(3a*S*,4*S*,5*R*,7*R*,7a*R*)-2,2,5-Trimethyl hexahydrobenzo [d][1,3]dioxole-4,5,7-triol (12). To a stirred soln. of the compound **10** (0.1 g, 0.5 mmol) in THF/ H_2O (2:1, mL) were added NMO monohydrate (0.12 g, 1 mmol) followed by OsO_4 (0.002 g, 0.01 mmol) at 0°C and stirred at rt for 24 h. After addition of Na_2SO_3 the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure, purified by CC (hexane/AcOEt: 2:8) to give compound **12** as colorless oil (0.1 g, 85%). $[\alpha]^{30}_D = -48.5$ (c = 1.5, $CHCl_3$) {lit.[7g] $[\alpha]$ $^{20}_D = -49.6$ (c = 0.82, $CHCl_3$)}; IR (neat): 3392, 2988, 2884, 1644, 1375, 1215 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz,): δ 4.98 (*d, J* = 6.6, 1H), 4.86 (*d, J* = 6.6, 1H), 4.56 (*s*, 1H), 4.05 (*dd, J* = 6.6, 1H), 3.98 (*dd, J* = 6.0, 1H,), 3.69 (*m*, 1H), 3.26 (*dd, J* = 6.6, 1H,), 1.67–1.61 (*m*, 2H), 1.40 (*s*, 3H), 1.28 (*s*, 3H), 1.14 (*s*, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 107.4, 79.3, 78.2, 74.1, 71.7, 67.3, 40.5, 27.9, 26.3, 25.6; ESIMS: m/z 241 $[M+Na]^+$; HRMS: calcd for $C_{10}H_{18}O_5 = 241.10435$ $[M+Na]^+$, found 241.10464

Triethyl((3a*S*,4*R*,7a*S*)-2,2,6-Trimethyl-3a,4,5,7a-tetrahydro benzo[d][1,3]dioxol-4-yloxy)silane (13). To an ice cooled stirred soln. of alcohol **10** (2 g, 10.8 mmol) in dry CH_2Cl_2 (20 mL) was added imidazole (1.47 g, 21.7mmol) and TESCl (2.49 mL, 16.3 mmol) and stirred for 20 min. The reaction mixture was extracted in CH_2Cl_2 (50 mL) and washed with brine. The organic layer was separated, dried over anhydrous Na_2SO_4, concentrated, and purified by CC using hexane/ethyl acetate (19:1) to give **13** (2.8 g, 95%) as a colors oil $[\alpha]^{30}_D = +6.2$ (c = 1.8, $CHCl_3$); IR (neat): 2954, 2912, 2876, 1457, 1378, 1212, 1103, 1058, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 5.53 (bs, 1H), 4.59 (bs, 1H), 3.93 (m, 1H), 3.83 (m, 1H), 2.17–2.11 (dd, *J* = 5.0, 17.0, 1H), 2.05–1.98 (dd, *J* = 8.6, 17.0, 1H), 1.74 (s, 3H), 1.46 (s, 3H), 1.38 (s, 3H), 0.97 (9H, *J* = 7.9 1t), 0.7–0.53 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.5, 118.3, 108.5, 78.4, 73.2, 69.8, 37.2, 28.2, 25.9, 23.5, 6.7, 4.8; ESIMS: m/z 321 $[M+Na]^+$; HRMS: calcd for $C_{16}H_{30}O_3NaSi = 321.1856$ $[M+Na]^+$, found 321.1850.

(3a*S*,4*R*,5*S*,7*R*,7a*S*)-2,2,5-Trimethyl-7-(triethylsilyloxy)hexahydrobenzo [d][1,3]dioxol-4-ol (14). To a solution of **13** (2 g, 7.4 mmol) in THF (20 mL), $BH_3.Me_2S$ (1.2 mL, 14.8 mmol) was added drop wise at –10°C. Stirring was continued for 30 min at rt. The reaction mixture was quenched by the addition of 10% NaOH (3mL) followed by 30% H_2O_2 (3 mL) at 0°C. The reaction was allowed to warm to rt and stirred for another 2 h. The reaction mixture was extracted with

AcOEt (2 × 50 mL) and the combined organic extracts were washed with brine, separated, and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator and the residue was purified by CC on silica gel using hexane/AcOEt (7:3) as the eluant to give pure compound **14** (1.5 g, 70%) as a colorless liquid. $[\alpha]^{30}{}_D = +135$ (c = 0.18, $CHCl_3$); IR (neat): 3395, 2953, 2910, 2876,1457, 1414, 1219, 1044, 723 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 4.21 (*t, J* = 4.1, 1H), 3.90 (*m*, 1H), 3.83–3.77 (*dd, J* = 4.9, 7.5, 1H), 3.34–3.24 (*dd, J* = 7.5, 10.5, 1H), 2.50 (*bs*, 1H), 1.65–1.57 (*m*, 2H), 1.53 (*s*, 3H), 1.35 (*s*, 3H), 1.03 (*d, J* = 6.4, 3H), 0.95 (*t, J* = 7.9, 9H), 0.7–0.58 (*m*, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 109.6, 81.8, 77.9, 77.7, 68.8, 36.2, 32.8, 28.4, 26.1, 17.7, 6.7, 4.6; ESIMS: m/z 317 $[M+H]^+$; HRMS: calcd for $C_{16}H_{33}O_4Si$ = 317.2142 $[M+H]^+$, found 317.2138.

(1*R*,2*R*,3*S*,4*R*,5*S*)-5-Methylcyclohexane-1,2,3,4-tetraol (2). Compound **14** (0.5 g, 1.7 mmol) was taken in MeOH (5 mL), to this soln. at rt aq. 3 N HCl (2 mL) was added. Then the reaction was stirred for 12 h at r.t. After completion of the reaction, volatiles were removed under vacuum. Purification by silica flash chromatography using MeOH/$CHCl_3$ (1:20) as the eluant provided alcohol **2** (0.25 g, 90%) as white solid. Mp: 160–161°; $[\alpha]^{30}{}_D = +6.2$ (c = 1.0, CH_3OH) {lit.[7f] for enantiomer $[\alpha]^{28}{}_D = -5.4.0$. (c = 0.7, CH_3OH)}; IR (neat): 3315, 2923, 1645, 1552, 1412, 1220, 1056, 966, 771 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz,): δ 3.98 (*bs*, 1H), 3.65 (*m*, 1H), 3.26–3.31 (*m*, 2H), 1.49–1.61 (*m*, 2H), 1.36 (*m*, 1H), 1.07 (*d, J* = 6.8, 3H); ^{13}C NMR (CD_3OD, 300 MHz): δ 76.2, 76.1, 75.0, 70.6, 36.2, 35.2, 18.5; ESIMS: m/z 185 $[M+Na]^+$; HRMS: calcd for $C_7H_{14}O_4Na$ = 185.07805 $[M+Na]^+$, found 185.07843.

(3a*R*,5*S*,7*R*,7a*S*)-2,2,5-Trimethyl-7-triethylsilyloxy)tetrahydrobenzo[d][1,3] dioxol-4(3aH)-one (15). To an ice cold soln. of compound **14** (1 g, 3.4 mmol) in CH_2Cl_2 (10 mL), Dess Martin periodane (2.9 g, 6.9 mmol) was added. After being stirred at 0°C for 1 h, the reaction mixture was diluted with ether (20 mL) followed by 1:1 sat. $NaHCO_3$ and Na_2SO_3 solution (5 mL) was added. The reaction mixture was extracted with ether (3 × 20 mL) and the organic layer was washed with H_2O and brine, dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude was purified through CC (hexane/AcOEt: 7:3) to afford corresponding alcohol **15** (0.8 g, 80%) as a colorless oil. $[\alpha]^{30}{}_D = -220$ (c = 0.7, $CHCl_3$); IR (neat): 2923, 2854, 1791, 1729, 1459, 1380, 1220, 1117, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 4.48 (*m*, 1H), 4.31–4.26 (*m*, 2H), 2.36 (*m*, 1H), 1.99–1.93 (*m*, 2H), 1.44 (*s*, 3H), 1.38 (*s*, 3H), 1.11 (*d, J* = 6.5, 3H), 0.98 (*t, J* = 8.0, 9H), 0.66 (*q, J* = 7.7, 15.7, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.1, 110.4, 80.0, 78.3, 67.6, 39.3, 36.2, 26.9, 25.7, 14.2, 6.7, 4.7; ESIMS: m/z 316 $[M+H]^+$; HRMS: calcd for $C_{16}H_{31}O_4Si$ = 315.1986 $[M+H]^+$, found 315. 1990.

Gabosine O (3). To the solution of compound **15** (0.5 g, 1.7 mmol), in THF (5 mL) and H_2O (1 mL), Amberlyst®−15 resin (20 mg) was added and refluxed at 70°C for 5 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give syrup which was purified through CC to give gabosine O **3** (0.25 g, 92%) yield as a white solid, mp: 108–109°; $[\alpha]^{30}{}_D = -20$ (c = 1.0,

CH_3OH) {lit.[8a] $[\alpha]^{20}_D = -21.0$ (c 0.07, MeOH}; IR (neat): 3434, 3278, 2926, 1718, 1435, 1409, 1219, 1034, 990, 772 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz): δ 4.25–4.28 (*m*, 1H), 4.18–4.22 (*m*, 1H), 4.14–4.18 (*m*, 1H), 2.46–2.60 (*m*, 1H), 1.96–2.07 (*m*, 1H), 1.82 (*q, J* = 12.3, 1H,), 1.03 (*d, J* = 6.5, 3H); ^{13}C NMR (CD_3OD, 300 MHz): δ 212.1, 78.1, 76.9, 69.4, 39.7, 37.8, 14.0; ESIMS: m/z 183 $[M+Na]^+$, HRMS: calcd for $C_7H_{13}O_4 = 161.0808$ $[M + H]^+$, found 161.0809.

Triethyl (3a*S*,4*S*,7a*S*)-2,2,6-trimethyl-3a,4,5,7a-tetrahydro benzo[d][1,3]dioxol-4-yloxy)silane (16). To an ice cooled stirred solution of alcohol **11** (0.8 g, 4.3 mmol) in dry CH_2Cl_2 (5 mL) was added imidazole (0.59 g, 8.7 mmol) and TESCl (1.1 mL, 6.5 mmol) and stirred for 20 min. The reaction mixture was extracted in CH_2Cl_2 (20 mL) and washed with brine. The organic layer was separated, dried over anh. Na_2SO_4, concentrated, and purified by CC using hexane/AcOEt (19:1) to give **16** (1.1 g, 95%) as a colors oil $[\alpha]^{30}_D = +11$ (c = 1.0, $CHCl_3$); IR (neat): 2954, 2912, 2876, 1457, 1378, 1212, 1103, 1058, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 5.26 (*bs*, 1H), 4.56 (*bs*, 1H), 4.26 (*m*, 1H), 3.90–3.85 (*dd, J* = 2.2, 5.3, 10.3, 1H), 2.40 (*m*, 1H), 1.96–1.90 (*dd, J* = 5.4, 16.1 1H), 1.70 (*s*, 3H), 1.37 (*s*, 6H), 0.97 (*t, J* = 8, 9H), 0.64 (*m*, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.5, 118.3, 108.5, 78.4, 73.2, 69.8, 37.2, 28.2, 25.9, 23.5, 6.7, 4.8; ESIMS: m/z 321 $[M+Na]^+$; HRMS: calcd for $C_{16}H_{30}O_3NaSi = 321.1856$ $[M+Na]^+$, found 321.1850.

(3a*S*,4*R*,5*S*,7*S*,7a*S*)-2,2,5-Trimethyl-7-(triethylsilyloxy)hexahydrobenzo [d][1,3]dioxol-4-ol (17). To a solution of **16** (1 g, 3.7 mmol) in THF (10 mL), $BH_3.Me_2S$ (0.57 mL, 7.4 mmol) was added drop wise at –10 °C. Stirring was continued for 30 min at rt. The reaction mixture was quenched by the addition of 10% NaOH (2 mL) followed by 30% H_2O_2 (2 mL) at 0°C. The reaction was allowed to warm to rt and stirred for another 2 h. The reaction mixture was extracted with AcOEt (2 × 20 mL) and the combined organic extracts were washed with brine, separated, and dried over anh. Na_2SO_4. The solvent was removed on a rotary evaporator and the residue was purified by CC on silica gel using hexane/AcOEt (7:3) as the eluant to give pure compound **17** (0.74 g, 70%) as a colorless liquid. $[\alpha]^{30}_D = -2.8$ (c = 1.4, $CHCl_3$); IR (neat): 3395, 2953, 2911, 2877, 1457, 1414, 1219 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 4.10–4.02 (*m*, 3H), 3.35–3.25 (*dd, J* = 6.2, 9.4, 1H), 1.92 (*m*, 1H), 1.80–1.56 (*m*, 2H), 1.49 (*s*, 3H), 1.35 (*s*, 3H), 1.09–0.88 (*m*, 2H), 0.65–0.54 (*m*, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 108.8, 80.2, 78.8, 77.4, 67.5, 35.8, 29.5, 28.0, 25.9, 18.1, 6.7, 4.6; ESIMS: m/z 317 $[M+Na]^+$; HRMS: calcd for $C_{16}H_{33}O_4Si = 317.2142$ $[M+Na]^+$, found 317.2138.

(1*S*,2*R*,3*S*,4*R*,5*S*)-5-Methylcyclohexane-1,2,3,4-tetraol (4). Compound **17** (0.5 g, 1.7 mmol) was taken in MeOH (5 mL) to this soln. at rt aq. 3 N HCl (2 mL) was added. The mixture was stirred for 12 h at rt. After completion of the reaction mixture solvent was removed under vacuum. Purification by silica flash chromatography using MeOH&$CHCl_3$ (1:20) as the eluant provided alcohol **4** (0.25 g, 90%) as a colorless oil. $[\alpha]^{30}_D = -18.3$ (c = 1.5, CH_3OH); {lit[7c] $[\alpha]^{20}_D = -17.24$ (c 0.58, CH_3OH} IR (neat): 3315, 2923, 1412, 1220, 1056, 966 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz): δ 3.87 (*dd, J* = 3.5, 3.0, 1H,), 3.83 (*dd, J* = 3.5, 3.0, 3.0, 1H), 3.61

(*dd, J* = 9.6, 3.0, 1H) 3.26 (*dd, J* = 9.6, 9.6, 1H), 1.78 (*m*, 1H), 1.64–1.56 (*m*, 2H), 1.01 (*d, J* = 6.6, 3H); ^{13}C NMR(75 MHz, CD_3OD): δ 76.8, 75.0, 74.3, 71.1, 35.9, 33.1, 18.6. ESIMS: m/z 185 $[M + Na]^+$; HRMS: calcd for $C_7H_{14}O_4Na$ = 185.07805, $[M + Na]^+$, found 185.07843.

Glycosidase inhibitory study. These assays were performed with fixed concentration of substrate (1.6 mM) in sodium phosphate buffer (0.05 M, pH 6.8) and enzyme (100 uL, 1mg/mL). The substrate solution (2 mL) was pre-incubated with compound for 1 min, and the reaction was started by the addition of the enzyme and the activity was followed for 5 min at 405 nm. Increasing amount of the inhibitors at fixed enzyme and substrate concentrations, typical dose-response curves were observed for both inhibitors. The data was analyzed by the following equation:

$$Y = \text{Bottom} + (\text{Top-Bottom})/(1 + 10\hat{}((\text{LogIC50-X})^*\text{HillSlope}))$$

Where *Y* is inhibition% and *X* is log [inhibitor].

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