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A common strategy for the synthesis of (+)-gabosine N, (+)-gabosine O, and some carbapyranoses using a Nozaki–Hiyama–Kishi reaction and RCM

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ABSTRACT

Stereoselective synthesis of carbasugars (+)-gabosine N **1** and (+)-gabosine O **2**, carba-α-L-rhamnose **17**, and carba-6-deoxy-α-L-talose **18** by using a Nozaki–Hiyama–Kishi (NHK) reaction and ring-closing metathesis.

1. Introduction

Carbasugars[1] are analogues of monosaccharides, in which the ring oxygen is replaced with methylene group[2], and have attracted considerable interest as inhibitors of glycosidases. Glycosidase enzymes are involved in numerous biological processes and their inhibition has enormous potential for the treatment of many diseases.[3] Gabosines isolated from *Streptomyces* strains belong to the sub class of carbasugars known as ketocarbasugars.[4] Gabosines exhibit a variety of biological activities such as antiprotozoal, DNA binding properties, and enzyme inhibition.[5] Fifteen different gabosines have been isolated which possess the trihydroxy methyl (hydroxymethyl) cyclohexenone or cyclohexanone skeleton in common (Fig. 1). Due to their interesting biological activities and fascinating structural features, they have attracted the attention of many synthetic chemists and biologists.[6,7] Furthermore gabosines can be considered as chemical precursors of 6-deoxy-carba pyranose derivatives which are known for the inhibition of oligosaccharide processing enzymes.[8] Recently a new class of compounds called ampelomins A–G (polyoxygenated methyl cyclohexanoids) were isolated from *Ampelomyces* fungus (Fig. 2), which has glycosidase inhibition and antibacterial activities.[9] These compounds can also be considered as reduced forms of gabosines.

Recently our group has been involved in the development of new strategies for the synthesis of carbasugars by using ring-closing metathesis[10] and a Tebbe-mediated cascade reaction.[11] As part of this program we reported the synthesis of (−)-gabosine C using NHK-RCM strategy.[7f] In continuation, we herein report a short, efficient, and common strategy for the synthesis of (+)-gabosine N **1**, (+)-gabosine O **2**, carba-α-L-rhamnose **17**, and carba-6-deoxy-α-L-talose **18**. Earlier few syntheses for gabosine N and gabosine O have been reported.[6] The synthesis of carba-β-D-rhamnose has been reported by Singh et al.[12] while the perbenzoyl derivative of carba-6-deoxy-α-L-talose has been reported by Redlich et al.[13] Retrosynthetic analysis of gabosine N and gabosine O (Scheme 1) revealed that the hydroxyl groups at C_4, C_5, and C_6 can be obtained from D-ribose. For instance, one carbon homologation at C-1 and propenyl group introduction at C-5 on compound **5** will give the RCM precursor **4** which can be elongated to the cyclohexene core **3** of gabosines. The key aspect of the synthesis is to find the stereoselectivity at the newly generated stereogenic center in **4** during the nucleophilic addition of propenyl unit.

2. Results and discussions

Based on the above-described retro synthetic plan, the synthesis of (+)-gabosine N and (+)-gabosine O started from 5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-D-ribofuranose **5** as shown in Scheme 2. One carbon homologation of the lactol **5** afforded the olefin compound **6** using a Wittig reaction.[14] The secondary hydroxy group of **6** was protected as MOM ether using methoxy methyl chloride to give **7**. Deprotection of the silyl group in compound **7** gave **8**, which was followed by oxidation of the resultant alcohol under Swern conditions gave the α-alkoxy aldehyde.

Nucleophilic addition on the α-alkoxy aldehyde with 2-bromo propene under Nozaki–Hiyama–Kishi conditions[15] in DMF gave anti alcohol **10** as the major product along with **9** in a ratio of 3.8:1. When the addition was carried out under Grignard conditions in THF at −78 °C interestingly *syn* alcohol **9** was obtained as a major compound along with **10** in the ratio of 4:1, both isomers could be separated by column chromatography. The reversal of stereoselectivities in the above-mentioned case can be explained as follows (Fig. 3);[16] Generally during the NHK reaction, the nucleophile undergoes addition via non-chelated Felkin–Anh model,[17] whereas in the case of the Grignard addition, chelation of the magnesium ion with the α-alkoxy group allowed nucleophilic addition to give *syn* isomer **9** as the major product.

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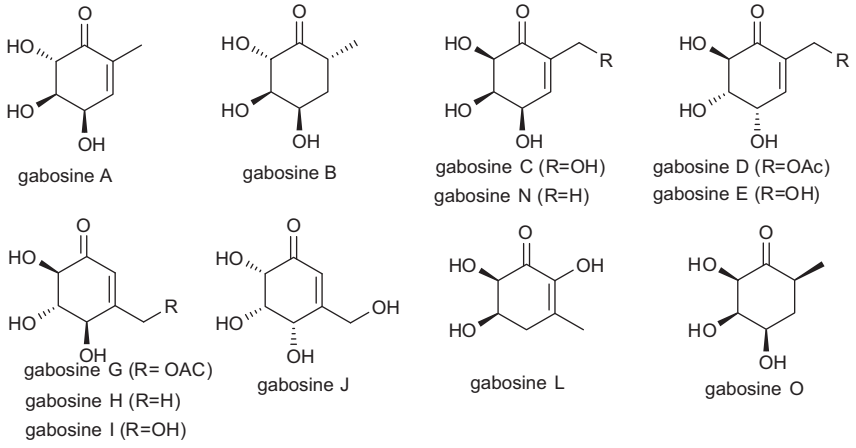


Figure 1. Gabosine family.

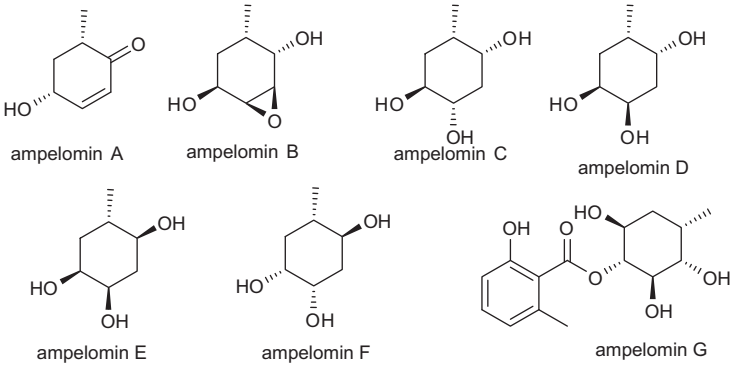
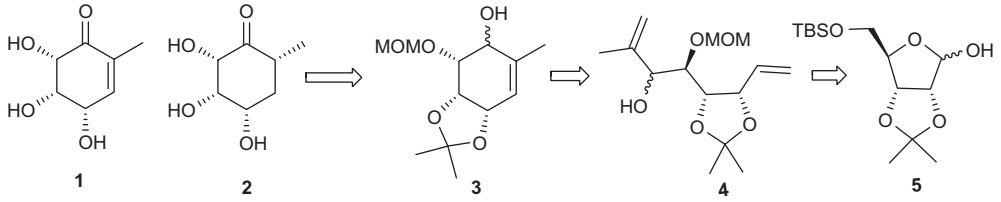


Figure 2. Ampelomins A–G.



Scheme 1. Retrosynthetic analysis.

The diene mixture of **9** and **10** was subjected to ring-closing metathesis using Grubb's 2nd generation catalyst[18] in toluene at reflux to give cyclohexene derivative **3**. The allylic alcohol in compound **3** was oxidized with PDC to yield the enone derivative **11**. Global deprotection of MOM and isopropylidene in compound **11** was achieved with Amberlyst® 15 in THF/H_2O (2:1) to give (+)-gabosine N **1** as a white solid whose physical and spectral data were identical with the reported values.[6d] Hydrogenation of **11** gave **12**. Global deprotection of MOM and isopropylidene group in **12** was achieved with Amberlyst® 15 to give (+)-gabosine O **2** as a white solid whose physical and spectroscopic data were identical with the reported values.[6a,d]

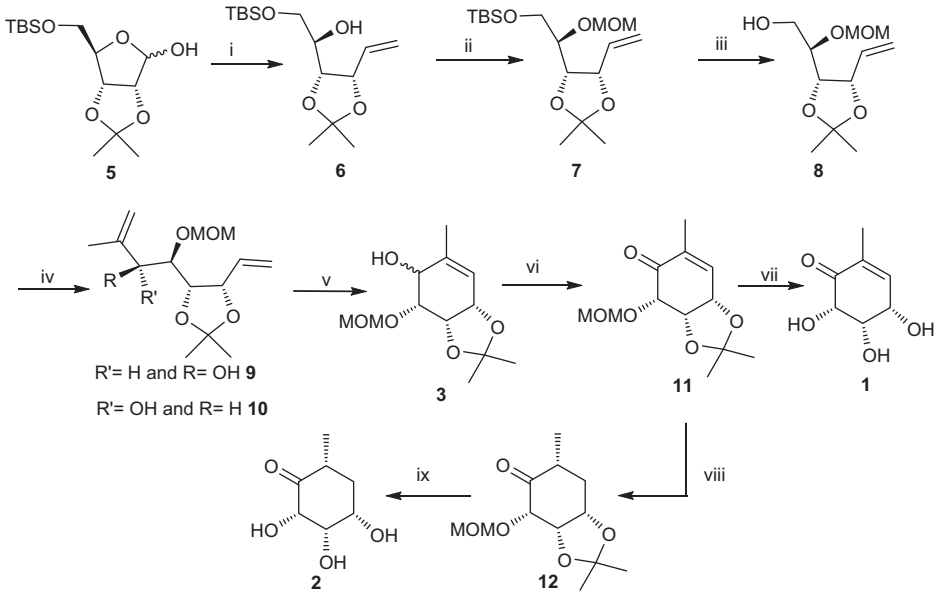
We extended this strategy for the synthesis of 6-deoxy carbasugars, such as carba-α-L-rhamnose **17** and carba-6-deoxy-α-L-talose **18** (Scheme 3); these compounds resemble the structures of ampelomins (Fig. 2). Diene **9** and **10** were independently subjected to ring-closing metathesis using Grubb's 2nd generation catalyst in toluene at reflux to give cyclohexene derivatives **13** and **14**. Stereoselective reduction of the double bond in **13** and **14** was achieved with hydrogenation using PtO_2 as a catalyst to give **15** and **16**. Global deprotection of **15** and **16** with aq 6 M HCl in methanol gave carbapyranoses **17**[12] and **18**.[13] The spectroscopic and physical data of **17** were identical with the reported values, thus confirming the configuration of the newly generated stereogenic centre in **9**. Furthermore, it also confirms the configuration of the hydroxyl group generated by propenyl addition in **10** and **18**.

3. Conclusions

In conclusion, we have developed a diversity-oriented general strategy for the synthesis of (+)-gabosine N, (+)-gabosine O, and carbapyranoses by using nucleophilic addition on α-alkoxy aldehyde under NHK and Grignard conditions followed by ring-closing metathesis.

4. Experimental

TLC was performed on Merck Kiesel gel 60, F254 plates (layer thickness 0.25 mm). Column chromatography was performed on silica gel (60–120 mesh) using ethyl acetate and hexane mixture



Scheme 2. Synthesis of (+)-gabosine N and (+)-gabosine O. Reagents and conditions: (i) $Ph_3P{=}CH_2$, THF, −78 °C to rt, 4 h, 76%; (ii) MOM-Cl, DIPEA, cat. DMAP, CH_2Cl_2, −15 °C to rt, 12 h, 93%; (iii) TBAF, THF, 4 h, 95%; (iv) (a) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C, 2 h; (b) 2-bromo propene, $CrCl_2$, cat. $NiCl_2$, DMF, 12 h, 72% or 2-bromo propene, Mg, THF, −78 °C, 4 h, 85%; (v) 10 mol % Grubbs catalyst 2nd generation, toluene, reflux, 12 h, 85%; (vi) PDC, CH_2Cl_2, 4 Å MS, 12 h, 82%; (vii) Amberlyst® 15, THF/H_2O (2:1), 70 °C, 5 h, 75%; (viii) H_2, Pd/C, MeOH, 1 h, 95%; (ix) Amberlyst® 15, THF/H_2O (2:1), 70 °C, 5 h, 85%.

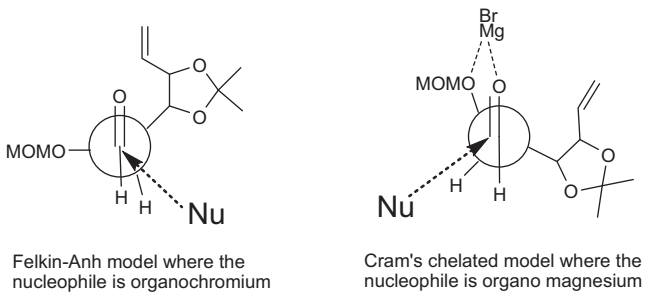
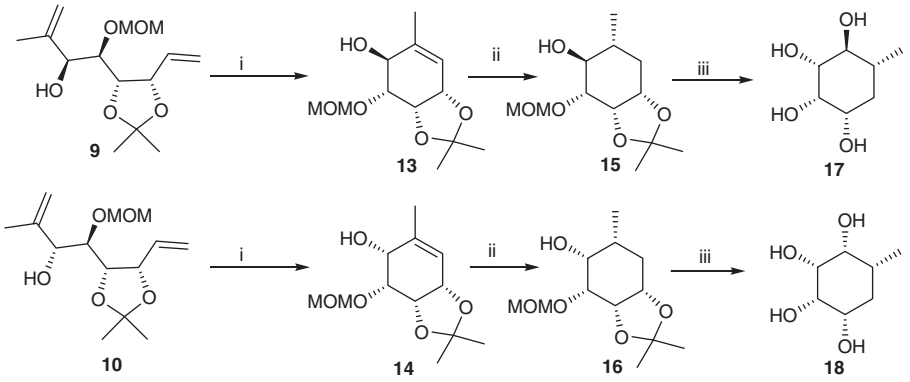


Figure 3. Felkin–Anh and Cram model.

as eluant. Melting points were determined on a Fisher John's melting point apparatus and are 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 a Varian Gemini-200 MHz and 400 MHz or a Bruker Avance-300 MHz spectrometer. ^{1}H NMR data are expressed as chemical shifts in parts per million (ppm) followed by multiplicity (s-singlet; d-doublet; t-triplet; q-quartet; m-multiplet), number of proton(s), and coupling constant(s) J (Hz). ^{13}C NMR chemical shifts are expressed in ppm. Optical rotations were measured with a Horiba-SEPA-300 digital polarimeter. Accurate mass measurement was performed on a Q STAR mass spectrometer (Applied Biosystems, USA).

4.1. (*R*)-5-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-8,8,9,9-tetramethyl-2,4,7-trioxa-8-siladecane 7

To an ice-cooled stirred solution of alcohol **6** (2.08 g, 6.88 mmol) in CH_2Cl_2 (20 mL) were added DIPEA (4.5 mL, 34.44 mmol), MOM-Cl (1.1 mL, 13.77 mmol), and DMAP (5 mg). The reaction mixture was allowed to warm to room temperature and then stirred for 12 h. The reaction mixture was extracted with CH_2Cl_2 (3 × 30 mL) and water (30 mL). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4, and the solvent was concentrated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate/petroleum ether (1:19) to afford compound **7** (2.2 g, 93%) as a liquid. $[\alpha]_D^{28} = -5.6$ (c 0.92, $CHCl_3$); IR (neat) ν_{max} 2930, 1464, 1373, 1215, 836 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): 0.06 (s, 3H),



Scheme 3. Synthesis of carbapyranoses. Reagents and conditions: (i) 10 mol % Grubbs catalyst 2nd generation, toluene, reflux, 12 h, 85%; (ii) (a) H_2, PtO_2, MeOH, 4 h, 90%; (b) aq 6 M HCl, MeOH, rt, 80%.

0.91 (s, 9H), 1.34 (s, 3H), 1.45 (s, 3H), 3.36 (s, 3H), 3.45–3.57 (m, 1H), 3.73 (dd, 1H, J = 3.9, 10.9 Hz), 3.91 (dd, 1H, J = 2.7, 10.9 Hz), 4.26 (dd, 1H, J = 6.2, 8.2 Hz), 4.57–4.66 (m, 1H), 4.62 (d, 1H, J = 7.0 Hz), 4.70 (d, 1H, J = 7.0 Hz), 5.21 (d, 1H, J = 10.1 Hz), 5.34 (d, 1H, J = 17.2 Hz), 5.83–6.03 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.1, 18.7, 25.6, 26.2, 28.0, 56.1, 63.7, 76.6, 77.9, 78.9, 97.2, 108.7, 117.9, 134.7; ESI/MS (m/z) 369 (M^++Na); HRMS calcd for $C_{17}H_{34}O_5NaSi$ 369.2073, found 369.2063.

4.2. (*R*)-2-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-(methoxymethoxy)ethanol 8

To an ice-cooled stirred solution of silyl compound **7** (2.0 g, 5.78 mmol) in THF (10 mL) was added TBAF (8.7 mL, 1 M solution in THF, 8.67 mmol). The reaction mixture was allowed to warm to room temperature, and then stirred for 4 h. The reaction was quenched with saturated $NaHCO_3$ solution (20 mL) and the reaction mixture was extracted with ethyl acetate (3 × 75 mL). The combined organic fractions were collected and washed with water and brine, then dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate/petroleum ether (1:4) to afford compound **8** (1.27 g, 95%) as a viscous liquid. $[\alpha]_D^{28} = +76.1$ (c 0.86, $CHCl_3$); IR (neat) ν_{max} 3454, 2935, 1645, 1375, 1035 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.46 (s, 3H), 3.11 (br s, 1H), 3.41 (s, 3H), 3.45–3.49 (m, 1H), 3.57 (dd, 1H, J = 5.8, 11.2 Hz), 3.79 (d, 1H, J = 11.7 Hz), 4.08 (dd, 1H, J = 6.8, 8.8 Hz), 4.59 (dd, 2H, J = 6.8, 10.7 Hz), 4.62 (dd, 1H, J = 5.8, 6.8 Hz), 5.19 (dt, 1H, J = 2.0, 10.7 Hz), 5.33 (dt, 1H, J = 2.0, 17.5 Hz), 5.81–5.89 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 27.3, 55.6, 63.1, 76.6, 78.3, 80.4, 97.2, 108.4, 117.1, 133.5; ESI/MS (m/z) 255 (M^++Na); HRMS calcd for $C_{11}H_{20}O_5Na$ 255.1208, found 255.1197.

4.3. (*S*)-2-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-(methoxymethoxy)acetaldehyde

To a stirred solution of oxalyl chloride (0.9 mL, 10.3 mmol) in dry CH_2Cl_2 (10 mL) under nitrogen atmosphere was added DMSO (1.5 mL, 20.7 mmol) slowly at −78 °C and stirred for 30 min at the same temperature. Then alcohol **8** (1.2 g, 5.17 mmol) in dry CH_2Cl_2 (10 mL) was added slowly over 10 min and stirred for a further 2 h after which Et_3N (4.3 mL, 31.03 mmol) was added. The temperature was slowly raised to room temperature over 20 min and the reaction mixture was diluted with CH_2Cl_2 (100 mL). The organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator to give an aldehyde, which was used as such for the next reaction without any purification.

Procedure for Grignard reaction: To the solution of isopropenyl magnesium bromide prepared from Mg (0.26 g, 10.86 mmol) and 2-bromopropene (0.76 mL, 8.7 mmol) in THF (10 mL) was added the solution of aldehyde (0.5 g, 2.17 mmol) in THF over 10 min at −78 °C under nitrogen. After stirring for 4 h at room temperature, the mixture was poured into saturated NH_4Cl (50 mL) and extracted with ethyl acetate (3 × 50 mL). The collected organic layers were combined, washed with water, brine, and then dried over Na_2SO_4, concentrated under reduced pressure and purified through column chromatography (hexane/ethyl acetate, 12:1) to afford the corresponding alcohol **9** (68%)and **10** (17%) as yellow oils in a ratio of 4:1 (0.51 g, 85% for two steps).

Procedure for Nozaki–Hiyama–Kishi reaction: A mixture of $CrCl_2$ (1.33 g, 8.69 mmol) and a catalytic amount of $NiCl_2$ (0.028 g, 0.217 mmol) in dry DMF (7 mL) was stirred at 25 °C for 10 min under a nitrogen atmosphere. A solution of aldehyde (0.5 g, 2.17 mmol) in DMF (5 mL) followed by 2-bromo propene (0.76 mL, 8.69 mmol) was added at 25 °C successively. After stirring at room temperature for 12 h, the reaction mixture was diluted with ether (30 mL) poured into water (20 mL), and extracted with ether repeatedly. The combined extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel column chromatography using ethyl acetate/hexane (12:1) as the eluant provided alcohol **9** (15%) and **10** (57%) as yellow color oils in the ratio of 1:3.8 (0.42 g, 72%).

4.3.1. (1*R*,2*S*)-1-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-1-(methoxymethoxy)-3-methylbut-3-en-2-ol 9

$[\alpha]_D^{28} = -19.1$ (c 1.52, $CHCl_3$); IR (neat) ν_{max} 3332, 2924, 1649, 1455, 1215, 1076 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 1.34 (s, 3H), 1.47 (s, 3H), 1.78 (s, 3H), 2.88 (d, 1H, J = 6.2 Hz, *OH*), 3.37 (s, 3H), 3.74 (dd, 1H, J = 4.2, 6.2 Hz), 4.16–4.22 (m, 2H), 4.58 (t, 1H, J = 6.8 Hz), 4.62 (q, 2H, J = 6.2 Hz), 4.92 (s, 1H), 5.03 (s, 1H), 5.24 (d, 1H, J = 10.4 Hz), 5.33 (d, 1H, J = 17.1 Hz), 5.97–6.06 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0, 25.1, 27.7, 56.3, 74.3, 77.6, 78.6, 79.0, 97.9, 108.4, 112.7, 118.4, 134.7, 144.3; ESI/MS (m/z) 295 (M^++Na); HRMS calcd for $C_{14}H_{24}O_5Na$ 295.1521, found 295.1510.

4.3.2. (1*R*,2*R*)-1-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-1-(methoxymethoxy)-3-methylbut-3-en-2-ol 10

$[\alpha]_D^{28} = +5.1$ (c 1.4, $CHCl_3$); IR (neat) ν_{max} 2923, 1647, 1457, 1076 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 1.32 (s, 3H), 1.47 (s, 3H), 1.81 (s, 3H), 3.41 (s, 3H), 3.60 (d, 1H, J = 8.4 Hz, *OH*), 3.66 (dd, 1H, J = 3.1, 8.9 Hz), 4.09 (dd, 1H, J = 5.7, 8.9 Hz), 4.21 (dd, 1H, J = 3.1, 8.3 Hz), 4.52–4.58 (m, 3H), 4.93 (s, 1H), 4.99 (s, 1H), 5.20 (d, 1H, J = 10.4 Hz), 5.31 (d, 1H, J = 17.2 Hz), 5.85–5.95 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 25.3, 27.9, 56.5, 74.5, 77.1, 79.1, 83.3, 99.0, 108.5, 113.7, 117.6, 134.6, 143.9; ESI/MS (m/z) 295 (M^++Na).

4.4. General procedure for Ring-Closing Metathesis

To the solution of diene **10** (0.3 g, 1.10 mmol) in toluene (44 mL), Grubbs' 2nd generation catalyst (0.093 g, 0.110 mmol) was added at room temperature and the reaction mixture was refluxed for 12 h. Toluene was removed under vacuum, and applied for column chromatography using ethyl acetate/hexane (1:4) as eluant provided cyclohexenol **3** as an oily compound (0.23 g, 85%).

4.4.1. (3a*S*,4*R*,5*S*,7a*S*)-4-(Methoxymethoxy)-2,2,6-trimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-5-ol 13

$[\alpha]_D^{28} = +27.6$ (c 1.23, $CHCl_3$); IR (neat) ν_{max} 3620, 2923, 1647, 1461, 1035 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 1.33 (s, 3H), 1.34 (s, 3H), 1.82 (d, 3H, J = 1.1 Hz), 3.3 (br s, 1H, *OH*), 3.5 (s, 3H), 3.48–3.53 (m, 1H), 4.27–4.31 (m, 1H), 4.45–4.50 (m, 1H), 4.53 (m, 1H), 4.81 (d, 1H, J = 7.2 Hz), 4.84 (d, 1H, J = 7.2 Hz), 5.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.7, 26.7, 27.7, 56.0, 69.0, 73.9, 75.5, 82.8, 97.8, 109.6, 121.8, 136.7; ESI/MS (m/z) 267 (M^++Na); HRMS calcd for $C_{12}H_{20}O_5Na$ 267.1208, found 267.1207.

4.4.2. (3a*S*,4*R*,5*R*,7a*S*)-4-(Methoxymethoxy)-2,2,6-trimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-5-ol 14

$[\alpha]_D^{28} = -82.4$ (c 1.2, $CHCl_3$); IR (neat) ν_{max} 3620, 2923, 1641, 1461, 1036 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 1.35 (s, 3H), 1.43 (s, 3H), 1.89 (dd, 3H, J = 1.1, 1.5 Hz), 3.05 (d, 1H, J = 10.9 Hz, *OH*), 3.46 (s, 3H), 3.73 (dd, 1H, J = 2.3, 4.1 Hz), 3.96 (dd, 1H, J = 4.1, 10.6 Hz), 4.49–4.52 (m, 1H), 4.53–4.58 (m, 1H), 4.76 (d, 1H, J = 7.2 Hz), 4.9 (d, 1H, J = 7.2 Hz), 5.36–5.40 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 26.5, 28.0, 55.8, 68.4, 72.0, 73.9, 75.5, 95.1, 110.6, 121.4, 137.3; ESI/MS (m/z) 267 (M^++Na).

4.5. (3a*S*,4*S*,7a*S*)-4-(Methoxymethoxy)-2,2,6-trimethyl-3a,4-dihydrobenzo[*d*][1,3]dioxol-5(7a*H*)-one 11

To a solution of alcohol **3** (0.1 g, 0.41 mmol) in CH_2Cl_2 (5 mL), PDC (0.385 g, 1.02 mmol) was added at 0 °C. After stirring at rt for 12 h., the reaction mixture was filtered through a Celite pad,

washed with CH_2Cl_2. Filtrate and washings were combined and concentrated to a syrup and applied for column chromatography using ethyl acetate/hexane (1:5) as the eluant to give cyclohexenone **11** as syrup (0.081 g, 82%). $[\alpha]_D^{28} = -61.0$ (*c* 0.8, $CHCl_3$); IR (neat) ν_{max} 2927, 1706, 1516, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.34 (s, 1H), 1.41 (s, 1H), 1.85 (s, 3H), 3.47 (s, 3H), 4.44–4.47 (m, 1H), 4.79–4.83 (m, 2H), 4.86 (d, 1H, *J* = 7.2 Hz), 4.99 (d, 1H, *J* = 7.2 Hz), 6.32–6.35 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.5, 26.9, 27.8, 56.0, 72.7, 74.8, 77.6, 96.5, 111.2, 125.9, 139.0, 195.1; ESI/MS (*m*/*z*) 265 (M^++Na); HRMS calcd for $C_{12}H_{18}O_5Na$ 265.1051, found 265.1044.

4.6. (3a*S*,4*S*,6*R*,7a*S*)-4-(Methoxymethoxy)-2,2,6-trimethyltetrahydrobenzo[*d*][1,3]dioxol-5(6*H*)-one 12

Compound **11** (0.05 g, 0.206 mmol) was taken in to methanol (2 mL) and to it was added Pd/C (10 mg). The flask was then purged with H_2 and hydrogenated at room temperature for 1 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a syrup, which was purified by column chromatography ethyl acetate/hexane (1:5) as the eluant to give cyclohexane derivative **12** (0.048 g, 95%). $[\alpha]_D^{28} = -36.6$ (*c* 0.7, $CHCl_3$); IR (neat) ν_{max} 2979, 1728, 1377, 1213, 1023 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.26 (d, 3H, *J* = 6.8 Hz), 1.30 (s, 3H), 1.40 (s, 3H), 1.97–2.08 (m, 1H), 2.28–2.49 (m, 2H), 3.39 (s, 3H), 4.34 (d, 1H, *J* = 4.5), 4.54–4.61 (m, 1H), 4.68–4.74 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.9, 24.0, 26.3, 31.3, 39.8, 55.9, 73.3, 76.9, 78.2, 95.6, 109.5, 207.5; ESI/MS (*m*/*z*) 267 (M^++Na); HRMS calcd for $C_{12}H_{20}O_5Na$ 267.1208, found 267.1210.

4.7. (+)-Gabosine N 1

To the solution of protected gabosine **11** (0.05 g, 0.206 mmol) in THF (2 mL) and H_2O (1 mL), Amberlyst®-15 resin (40 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 a syrup, which was purified by column chromatography to give (+)-gabosine N **1** in 75% yield as a white solid. Mp: 180–181 °C; $[\alpha]_D^{28} = +172$ (*c* 0.2, CH_3OH) {lit.[6d], $[\alpha]_D^{28} = +180$ (*c* 0.15, CH_3OH)}; IR (neat) ν_{max} 3422, 2923, 1684, 1363, 1055 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): 1.80 (dd, 3H, *J* = 1.5, 2.2 Hz), 4.22 (d, 1H, *J* = 1.9 Hz), 4.32–4.37 (m, 1H), 4.52–4.59 (m, 1H), 6.46–6.50 (m, 1H); ^{13}C NMR (75 MHz,) δ 15.3, 69.2, 76.7, 77.7, 134.6, 145.9, 200.3; ESI/MS (*m*/*z*) 181 (M^++Na); HRMS calcd for $C_7H_{10}O_4Na$ 181.0476, found 181.0468.

4.8. (+)-Gabosine O 2

Gabosine O was obtained from compound **12** (0.05 g, 0.205 mmol) in 85% yield as a white solid according to the procedure described for (+) gabosine N. Mp: 105–107 °C; $[\alpha]_D^{28} = +17.5$ (*c* 0.1, CH_3OH) {lit.[6d] $[\alpha]_D = +20.0$ (*c* 0.3, CH_3OH)}; IR (neat) ν_{max} 3422, 1715, 1349, 1033 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): 1.03 (d, 3H, *J* = 6.6 Hz), 1.82 (q, 1H, *J* = 12.5 Hz), 1.96–2.07 (m, 1H), 2.46–2.60 (m, 1H), 4.14–4.18 (m, 1H), 4.18–4.22 (m, 1H), 4.25–4.28 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 14.0, 37.9, 39.7, 69.5, 76.9, 78.2, 212.6; ESI/MS (*m*/*z*) 183 (M^++Na); HRMS calcd for $C_7H_{12}O_4Na$ 183.0633, found 183.0630.

4.9. (3a*S*,4*R*,5*S*,6*R*,7a*S*)-4-(Methoxymethoxy)-2,2,6-trimethylhexahydrobenzo[*d*][1,3]dioxol-5-ol 15

Compound **13** (0.1 g, 0.41 mmol) was taken into methanol (5 mL) and to it was added PtO_2 (10 mg). The flask was then purged with H_2 and hydrogenated at room temperature for 4 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a syrup, which was purified by column chromatography using ethyl acetate/hexane (1:5) as the eluant to give **15** in 90% yield as a syrup. $[\alpha]_D^{28} = +3.0$ (*c* 0.23, $CHCl_3$); IR (neat) ν_{max} 3620, 2919, 1464, 1177 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.06 (d, 3H, *J* = 6.04 Hz), 1.25–1.37 (m, 2H), 1.32 (s, 3H), 1.51 (s, 3H), 1.79 (dd, 1H, *J* = 6.8, 10.6 Hz), 2.93 (br s, 1H), 3.43–3.48 (m, 2H), 3.46 (s, 3H), 4.07–4.15 (m, 1H), 4.42 (dd, *J* = 4.1, 3.7 Hz), 4.81 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 26.1, 28.5, 32.8, 36.2, 55.8, 73.4, 74.1, 76.2, 82.1, 97.6, 109.2; ESI/MS (*m*/*z*) 269 (M^++Na); HRMS calcd for $C_{12}H_{22}O_5Na$ 269.1364, found 269.1369.

4.10. (3a*S*,4*R*,5*R*,6*R*,7a*S*)-4-(Methoxymethoxy)-2,2,6-trimethylhexahydrobenzo[*d*][1,3]dioxol-5-ol 16

Compound **16** was obtained from compound **14** (0.07, 0.28 mmol) according to the procedure described for the aforementioned compound **15** in 90% yield. $[\alpha]_D^{28} = -39.8$ (*c* 0.2, $CHCl_3$); IR (neat) ν_{max} 3620, 2921, 1647, 1037 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.06 (d, 3H, *J* = 7.06 Hz), 1.25–1.28 (m, 1H), 1.34 (s, 3H), 1.38–1.43 (m, 1H), 1.55 (s, 3H), 1.57–1.64 (m, 1H), 2.63 (d, 1H, *J* = 7.1 Hz), 3.45 (s, 3H), 3.66 (dd, 1H, *J* = 3.7, 4.7 Hz), 3.80–3.84 (m, 1H), 4.12–4.15 (m, 1H), 4.34 (dd, 1H, *J* = 3.7, 4.7 Hz), 4.77 (d, 1H, *J* = 7.1 Hz), 4.87 (d, 1H, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.7, 26.2, 28.9, 30.5, 31.7, 55.8, 71.0, 74.0, 74.5, 75.6, 94.8, 109.6; ESI/MS (*m*/*z*) 269 (M^++Na).

4.11. 5a-Carba-α-L-rhamnopyranose 17

Compound **15** was taken in methanol (2 mL), to this solution at room temperature was added aq 6 M HCl (1.5 mL). This mixture was stirred for 12 h at room temperature. After completion of the reaction, the solvent was removed under vacuum. Purification by silica gel flash chromatography using MeOH/chloroform (1:20) as the eluant provided alcohol **17** as a white solid in 80% yield. Mp: 159–162 °C; $[\alpha]_D^{28} = -5.4$ (*c* 0.7, CH_3OH) {lit.[12] for enantiomer $[\alpha]_D^{28} = +7.0$ (*c* 1.1, CH_3OH)}; IR (neat) ν_{max} 3356, 2295, 1456, 1054 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): 1.07 (d, 3H, *J* = 6.4 Hz), 1.3–1.41 (m, 1H), 1.49–1.61 (m, 2H), 3.26–3.31 (m, 2H), 3.60–3.70 (m, 1H), 3.98 (br s, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 18.5, 35.3, 36.3, 70.7, 75.1, 76.2, 76.3; ESI/MS (*m*/*z*) 185 (M^++Na); HRMS calcd for $C_7H_{14}O_4Na$ 185.0789, found 185.0791.

4.12. Carba-6-deoxy-α-L-talose 18

Compound **18** was obtained from compound **16** (0.03, 0.12 mmol) according to the procedure described for the aforementioned compound **17** as a yellow color oil in 80% yield. $[\alpha]_D^{28} = -2.58$ (*c* 1.1, CH_3OH), IR (neat) ν_{max} 3356, 2295, 1456, 1054 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): 1.03 (d, 3H, *J* = 6.0 Hz), 1.39–1.68 (m, 3H), 3.41 (dd, 1H, *J* = 2.6, 3.0 Hz), 3.48–3.58 (m, 1H), 3.65 (br s, 1H), 3.92 (br s, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 17.8, 31.4, 33.6, 71.2, 71.7, 76.1, 76.2; ESI/MS (*m*/*z*) 185 (M^++Na); HRMS calcd for $C_7H_{14}O_4Na$ 185.0789, found 185.0792.

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