Attempted synthesis of ophiocerin A using D-gulonic acid-*δ*-lactone

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Paper dedicated to Professor Richard R. Schmidt, to commemorate his 78th anniversary

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Abstract
The tetrahydropyranyl ring of ophiocerin A has been successfully synthesized from D-gulonic acid-*δ*-lactone with the requisite stereogenic centers. However deoxygenation at C_6 in the precursor was not achieved.

Keywords: Tetrahydropyran, ophiocerins, gulono-lactone, deoxygenation

Introduction

Shearer *et al*., in search of new bioactive metabolites from fresh water fungi, isolated ophiocerins A-C **1**-**3** along with ophiocerin D **4**, an isocrotonyl derivative of tetrahydropyran, from the fresh water aquatic fungus *Ophioceras venezuelense*.[1,2] Besides the promise of biological activities associated with natural product containing tetrahydropyran ring, it was interesting array of substituents on the tetrahydropyran ring in ophiocerins that attracted considerable interest from synthetic organic chemists.[3,4] Ophiocerins A-C have been synthesized earlier using starting material from chiral pool such as carbohydrate and (R)-(-)-4-penten-2-ol,[4] tartaric acid[3c] and enantio-pure epoxides.[3a] Recently Pradeep Kumar reported the synthesis of ophiocerins A-C,[5] wherein the stereogenic centers were generated using Jacobsens hydrolytic kinetic resolution and Sharpless kinetic resolution. Presented herein are our efforts towards synthesis of ophiocerin A. It was the direct semblance of stereochemistry present in ophiocerin A, **1** and D-gulose **5** that prompted this exploration. Hence the synthesis of ophiocerin A, **1** was attempted using the readily available D-gulonic acid-*δ*-lactone **6** (Figure 1).

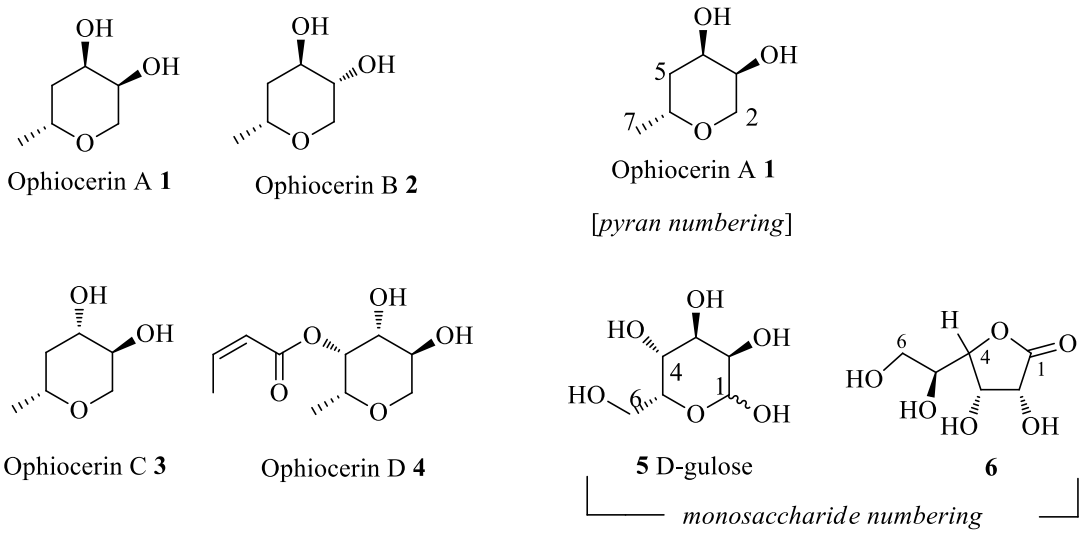


Figure 1. Ophiocerins A-D.

Results and Discussion

The D-gulonic acid-*δ*-lactone **6** has the C4 hydroxyl protected in the form of cyclic ester (lactone). It was envisaged that suitable protection of free hydroxyls and reductive ring opening of the lactone would allow opportunity for deoxygenation at C4 (of **7**), a 1,6-ring closure would effect deoxygenation at C1 (of **8**) and finally deoxygenation at C6 (of **9**) containing the primary hydroxyl would lead to synthesis of ophiocerin A, **1** (Figure 2).

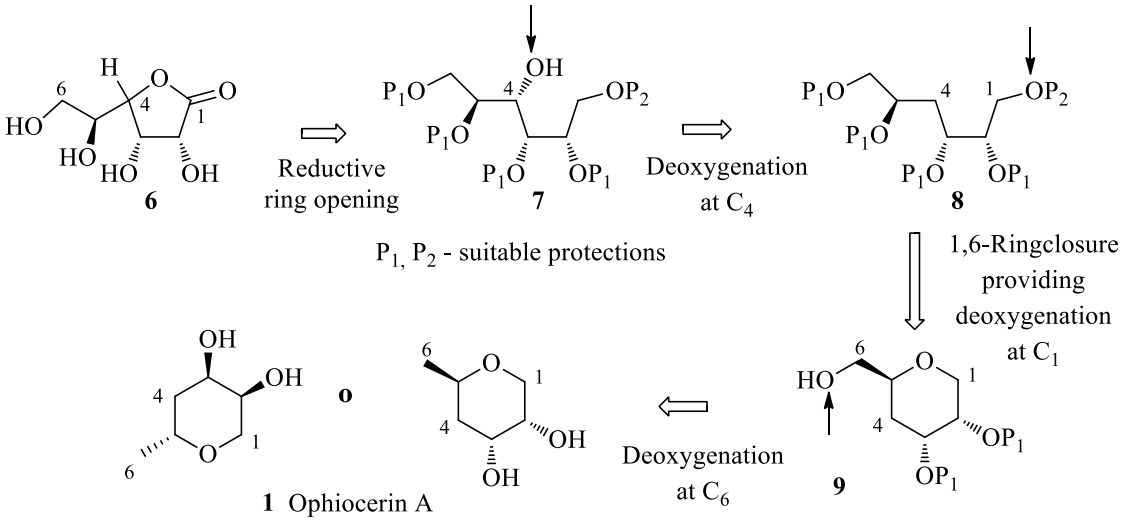
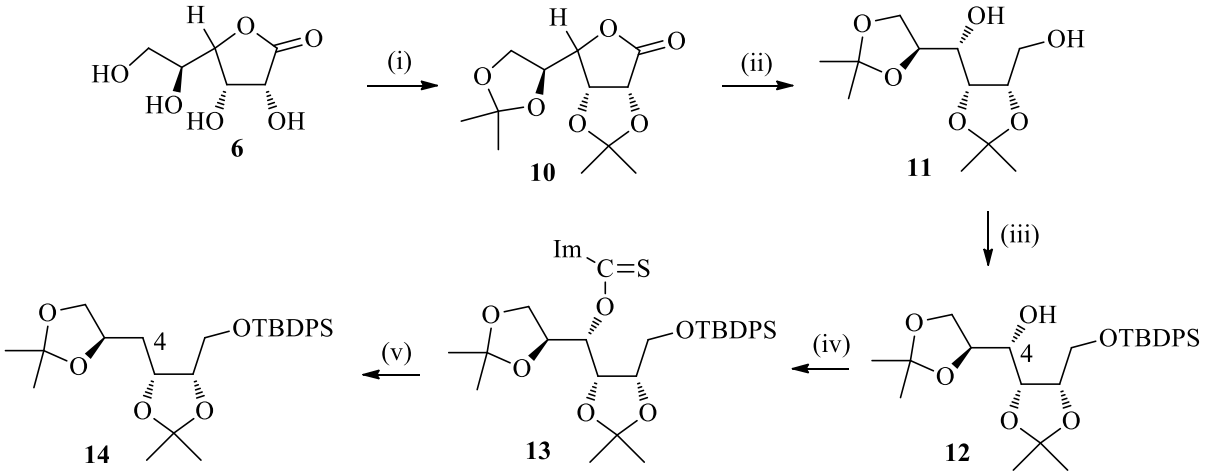


Figure 2. Retrosynthetic analysis.

According to the envisaged strategy our synthetic sequence commenced with D-gulonic acid-*δ*-lactone **6** (Scheme 1). The lactone **6** was subjected to di-*O*-isopropylidenation to obtain compound **10** in 60% yield and the protected lactone was subjected to lithium aluminium hydride reduction to obtain the diol **11** in 90% yield. These two transformations were achieved by using known procedures reported by Son and Fleet.[6] The obtained diol **11** was characterized and all the obtained analytical data matched with those reported in literature. The diol **11** was subjected to regioselective silylation at the primary hydroxyl using *tert*-butyldiphenylsilyl chloride as silylating agent to obtain monosilylated derivative **12** in 63% yield. The compound **12** containing a free secondary hydroxyl was treated with 1,1′-thiocarbonyl diimidazole (TCDI) in refluxing toluene for one hour to obtain the thionocarbonate **13** in 86% yield. The obtained thionocarbonate was treated with tributyltin hydride in presence of a catalytic amount of AIBN in refluxing toluene for 2 h to obtain compound **14**, thus, in effect, achieving deoxygenation of compound **12** at C4.



Reagents and Conditions: (i) Acetone, 2,2-DMP, *p*-TSA, R.T, 2 days, 60% yield. (ii) $LiAlH_4$, THF, RT, 30 min, 80%; (iii) TBDPSCl, Imidazole, DMF, RT, 3h, 63%; (iv) Im_2CS, Toluene, Reflux, 86%; (v) Bu_3SnH, AIBN, Toluene, Reflux, 75%;

Scheme 1. Synthesis of compound **14.**

The compound **14** was subjected to desilylation using tetrabutylammonium fluoride to obtain the corresponding primary alcohol which was isolated and subjected to tosylation to obtain the tosylate **15** in 60% yield over the two steps (Scheme 2). The di-*O*-isopropylidene compound **15** was treated with zinc nitrate hexahydrate in acetonitrile at room temperature to effect selective hydrolysis of terminal ketal protection to obtain the diol **16**. The internal isopropylidene protection of compound **16** was found to be very labile and susceptible to hydrolysis under mild acidic conditions. It was carefully isolated and treated with sodium hydride in THF to affect cyclization leading to construction of pyran ring. Under the given reaction conditions, there are

two possibilities, namely the formation of desired compound **17** or the undesired seven membered ring compound **19**. In order to ascertain the cyclization mode, the obtained cyclized product in 64-71% yield, was subjected to acetylation. On acetylation, if cyclization product is **19**, the conversion **19** → **20**, would significantly affect the chemical shift of methine proton H_B, whereas for the desired product **17**, the conversion **17** → **21** would affect methylene protons $H_{AA'}$ at C6. The ^{1}H-NMR spectrum of obtained acetylated product showed the most significant change in chemical shift of C6 methylene protons, indicating exclusive obtainment of six membered ring compounds **17** / **21** and ruling out the possibility of the seven-membered ring compounds **19** / **20** (Figure 3).

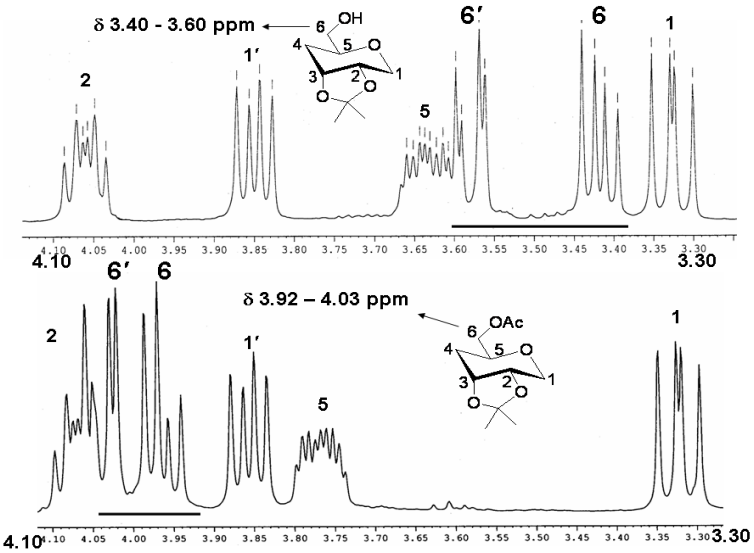
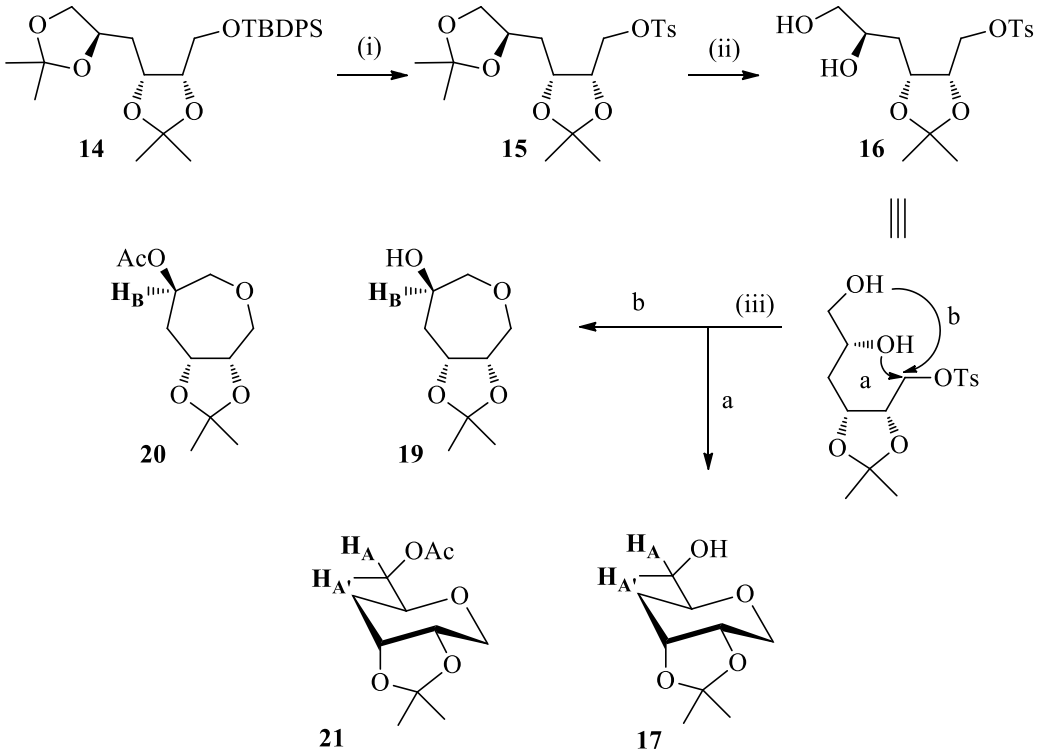


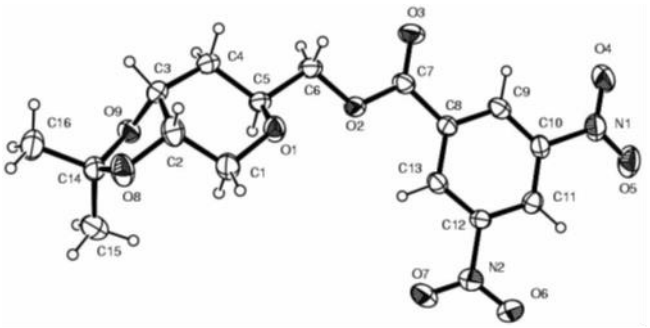
Figure 3. Part ^{1}H NMR Spectrum of **17** and **21.**



Reagents and conditions: (i) (a) TBAF, THF, RT, 1h; (b) TsCl, CH_2Cl_2, Pyridine, RT, 3h, 60%;
(ii) $Zn(NO_3)_2$, CH_3CN, RT, 12h;
(iii) NaH, THF, RT, 2h, 64 - 71% yield over two steps;

Scheme 2. Cyclization of compound **16.**

The compound **17** was further confirmed by ^1H-^1H COSY, ^1H-^{13}C HSQC, HMBC and mass spectra. HRMS data showed base peak at *m/z* 211.0950 ppm representing $[M+Na]^+$, in good agreement with the constitution of compound **17** (Molecular formula: $C_9H_{16}O_4$, Molecular weight 188). Unambiguous confirmation for the obtainment of **17** was obtained through X-ray diffraction studies on the crystal of its dinitrobenzoate derivative **18**.[7]



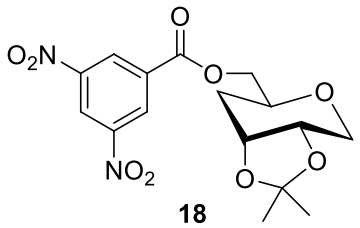
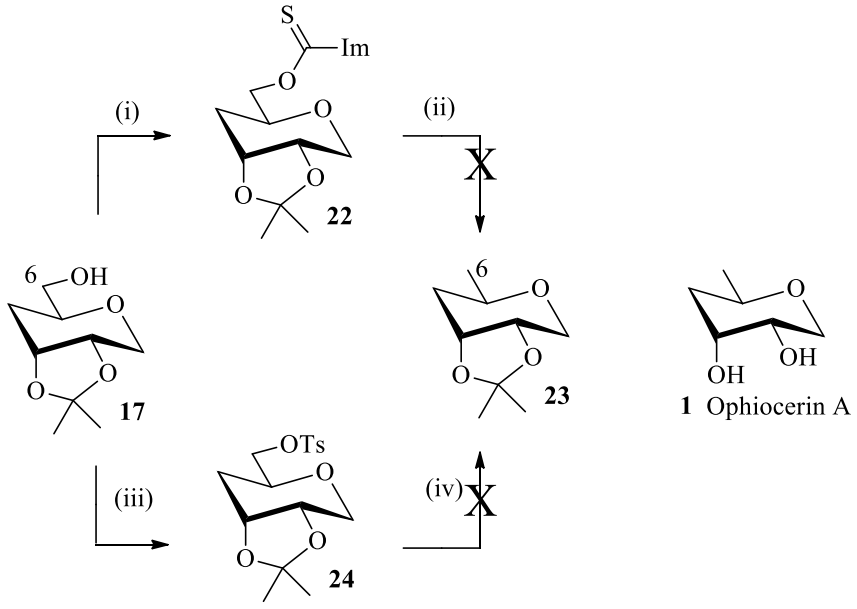


Figure 4. ORTEP plot of compound **18.**

Having ascertained that compound **17** was indeed obtained, the stage was set for the final deoxygenation to arrive at the targeted ophiocerin A. With this aim, compound **17** was treated with 1,1′-thiocarbonyl diimidazole (TCDI) in refluxing toluene for one hour to obtain the thionocarbonate derivative **22** in 50% yield. Unfortunately the anticipated radical deoxygenation through this thionocarbonate derivative **22** with tributyltin hydride in presence of a catalytic amount of AIBN in refluxing toluene did not furnish the desired product **23** as only a complex mixture was seen on TLC. To our surprise, even the tosylate derivative **24** did not furnish the anticipated deoxygenated compound **23** on reaction with lithium aluminium hydride. (Scheme 3) Although these initial efforts were intriguing and disappointing,[8] we are hopeful ultimately to deoxygenate the penultimate precursor **17** and obtain ophiocerin A. Efforts are currently under way towards this objective.



Reagents and Conditions:
(i) Im_2CS, Toluene, Reflux, 50%. (ii) Bu_3SnH, AIBN, Toluene, Reflux, 1h
(iii) TsCl, Et_3N, CH_2Cl_2, R.T, 5h, 50% (iv) $LiAlH_4$, THF, reflux, 12 h.

Scheme 3. Deoxygenation attempts on compound **17.**

Conclusions

D-gulonic acid-*δ*-lactone envisaged for the synthesis of ophiocerin A, has successfully furnished the tetrahydropyranyl ring of ophiocerin A, with requisite stereogenic centers. The final deoxygenation at C_6 in the penultimate precursor **17** is currently underway.

Experimental Section

General. All reactions were carried out in oven dried glassware. Dry DMF was prepared by stirring with calcium hydride, downward distilled and stored on 4 Å molecular sieves. Dry THF was prepared by distilling over Na wire. Solvents used for column chromatography were LR grade. Thin-layer chromatography was performed on aluminum plates coated with silica gel 60. Visualization was observed by UV light or by dipping into a solution of cerium (IV) sulfate (2.5 g) and ammonium molybdate (6.25 g) in 10% sulfuric acid (250 mL) followed by charring on a hot plate. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in chloroform-*d* ($CDCl_3$) and tetramethylsilane (TMS) as reference. HRMS were recorded on a MICRO-Q TOF mass spectrometer by using the ESI technique at 10 eV. IR spectra were recorded on JASCO-FT/IR-4100 spectrometer. Optical rotations were recorded on Autopol IV polarimeter. X-ray data collection was performed with Bruker AXS (kappa Apex 2) CCD Diffractometer equipped with graphite monochromated Mo (Kα) (λ. 0.7107 Å) radiation. The structure was solved using SHELXL-97 and refined by full-matrix least square technique using SHELXL-97. Molecular graphics were drawn using ORTEP32.

Preparation of 1-*O*-(*tert*-butyldiphenyl)silyl-2,3:5,6-di-*O*-isopropylidene-D-gulitol (12). To a solution of anhydrous DMF (15 mL) containing the diol **11** (1.00 g, 3.82 mmol) and imidazole (0.468 g, 6.87 mmol), was added *tert*-butyldiphenylsilyl chloride (1 mL, 3.82 mmol) under inert atmosphere and at -15 °C. The reaction mixture was allowed to slowly warm up to room temperature and was stirred for 4h. After completion of the reaction as monitored by thin layer chromatography, the reaction mixture was extracted with ethyl acetate (60 mL) and the DMF was removed by washing with water (60 mL × 2). The organic layer was separated and concentrated under reduced pressure and the residue obtained as a syrupy liquid was subjected to silica gel column chromatography using ethyl acetate-hexane (1:20). The pure product was obtained as a colorless syrupy liquid.

1-*O*-(*tert*-Butyldiphenyl)silyl-2,3:5,6-di-*O*-isopropylidene-D-gulitol (12). Colorless syrupy liquid; Yield: 60%; R_f 0.15 (ethyl acetate / hexane, 1: 20); $[\alpha]^{25}_D$= +8.989 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3497, 2932, 1066, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$ / TMS, 400 MHz): δ 1.06 (s, 9H, $C(CH_3)_3$); 1.37, 1.39, 1.48 (3s, 12H, $C(CH_3)_2$ × 2); 3.78-3.87 (m, 2H, H_{1a}, H_{6a}); 3.90-3.95 (m, 1H, H_2); 3.96-4.05 (m, 2H, H_{1b}, H_{6b}); 4.12-4.16 (m, 1H, C*H*OH); 4.25-4.33 (m, 2H, H_3, H_5); 7.35-7.45 (m, 6H, Aromatic); 7.63-7.70 (m, 4H, Aromatic); ^{13}C NMR ($CDCl_3$/TMS, 100 MHz) δ

19.6 ((CH$_3$)$_3$*C*-Si); 25.1, 25.4, 26.5, 27.0 (C(*C*H$_3$)$_2$ × 2); 26.9 ((*C*H$_3$)$_3$C-Si); 62.7 (CH$_2$OTBDPS); 65.9(C$_6$); 69.5 (C$_2$); 76.8 (CHOH); 76.9, 77.1 (C$_3$, C$_5$); 108.7, 109.5 (*C*(CH$_3$)$_2$ × 2); (127.8, 129.9, 132.92, 132.96, 135.5 (Aromatic); HRMS (ESI) *m/z* [M+Na]$^+$ Calcd for $C_{28}H_{40}O_6$ NaSi 523.2492 found 523.2490.

Preparation of 1-*O*-(*tert*-butyldiphenyl)silyl-4-*O*-(1*H*-imidazol-1yl-methanethionyl) 2,3:5,6-di-*O*-isopropylidene-D-gulitol (13). A solution of the secondary alcohol **12** (0.400 g, 0.92 mmol) and thiocarbonyl diimidazole (0.180g, 1.1 mmol) in anhydrous toluene (5 mL) was refluxed for one hour. After completion of the reaction as monitored by thin layer chromatography, the solvent was evaporated under reduced pressure and the resulting residue was subjected to silica gel column chromatography using ethyl acetate-hexanes (1:10). The pure product was obtained as colorless syrup (0.480 g, 86%).

1-*O*-(*tert*-Butyldiphenyl)silyl-4-*O*-(1*H*-imidazol-1ylmethanethionyl) 2,3:5,6-di-*O*-isopropylidene-D-gulitol (13). Colorless syrupy liquid; R_f 0.15 (ethyl acetate / hexane, 1: 20); $[\alpha]^{25}_D$= +8.989 (*c* 1.0, CHCl$_3$); IR (neat) ν_{max} 1765, 1388, 1285, 1218, 1112, 977, 702, 505 cm^{-1}; ^{1}H NMR (CDCl$_3$ / TMS, 400MHz): δ 1.06 (s, 9H, C(CH$_3$)$_3$); 1.30, 1.311, 1.314, 1.44 (4s, 12H, C(CH$_3$)$_2$ × 2); 3.67-3.71 (dd, *J*. 10.4, 4.0 Hz, 1H, H$_{1a}$); 3.85-3.95 (m, 3H, H$_{1b}$, H$_{6a}$, H$_{6b}$); 4.32-4.39 (m, 1H, H$_2$); 4.63-4.70 (m, 2H, H$_3$, H$_5$); 6.16-6.20 (dd, J. 7.6, 2.8 Hz, 1H, H$_4$); 7.08 (s, 1H, Imidazolyl); 7.36-7.48 (m, 6H, phenyl); 7.62-7.70 (m, 5H, phenyl, imidazolyl); 8.43 (s, 1H, Imidazolyl); ^{13}C NMR (CDCl$_3$/TMS, 100 MHz) *δ* 19.2 ((CH$_3$)$_3$*C*-Si); 24.9, 25.3, 26.2, 27.7 (C(*C*H$_3$)$_2$ × 2); 26.9 ((*C*H$_3$)$_3$C-Si); 62.7 (CH$_2$OTBDPS); 65.2(C$_6$); 74.3 (C$_2$); 75.7, 76.8 (C$_3$, C$_5$); 80.2 (C$_4$); 108.8, 109.9 (*C*(CH$_3$)$_2$ × 2); 118.5 (Imidazolyl); 127.9, 129.7, 130.00, 130.04, 132.7 (Phenyl); 135.50, 135.55 (phenyl); 136.7 (Imidazolyl); 184.1 (C=S); HRMS (ESI) *m/z* [M+Na]$^+$ Calcd for $C_{32}H_{43}N_2O_6SSi$ 611.2611 found 611.2614.

Preparation of 4-deoxy-1-*O*-(*tert*-butyldiphenylsilyl)-2,3:5,6-di-*O*-isopropylidene-D-gulitol (**14**). A solution of imidazolate **13** (0.400g, 0.63 mmol) and catalytic amount of AIBN in anhydrous toluene (6 mL) was set to reflux under inert atmosphere and to the refluxing solution tributyltin hydride (0.6 mL, 1.2 mmol) was added and the reaction mixture was stirred for two hour. After completion of reaction as indicated by TLC the reaction mixture was concentrated under reduced pressure to obtain a residue which was subjected to silica gel column chromatography (solvent system: ethyl acetate / hexanes, 2: 8) to obtain the pure product (0.268 g, 75%).

4-Deoxy-1-*O*-(*tert*-butyldiphenyl)silyl-2,3:5,6-di-*O*-isopropylidene-D-gulitol (14). R_f 0.34 (ethyl acetate / hexanes, 2: 8); $[\alpha]^{25}_D$= + 12.98 (*c* 1.0, CHCl$_3$); ^{1}H NMR (CDCl$_3$ / TMS, 400MHz): *δ* 1.06 (s, 9H, C(CH$_3$)$_3$); 1.32, 1.36, 1.38, 1.42 (4s, 12H, C(CH$_3$)$_2$ × 2); 1.80-2.06 (m, 2H, H$_{4a}$, H$_{4b}$); 3.61-3.70 (m, 2H, H$_{1a}$, H$_{6a}$); 3.72-3.77 (dd, *J*. 10.8, 7.6 Hz, 1H, H$_{1b}$); 4.04-4.08 (dd, J. 8.0, 6.0 Hz, 1H, H$_{6b}$); 4.19-4.26 (m, 2H, H$_2$, H$_5$); 4.28-4.36 (m, 1H, H$_3$); 7.37-7.44 (m, 6H, Aromatic); 7.64-7.70 (m, 4H, Aromatic); ^{13}C NMR (CDCl$_3$/TMS, 100 MHz) δ 19.2 ((CH$_3$)$_3$*C*-Si); 25.6, 25.8, 26.9, 28.1 (C(*C*H$_3$)$_2$ × 2); 26.87 ((*C*H$_3$)$_3$C-Si); 33.06 (C$_4$), 62.6 (CH$_2$OTBDPS); 69.0 (C$_6$); 73.5 (C$_2$); 74.2, 77.6 (C$_3$, C$_5$); 108.1, 108.7 (*C*(CH$_3$)$_2$ × 2); 127.8, 129.8, 133.1, 133.2,

135.54, 135.58 (Aromatic); HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{28}H_{40}O_5SiNa$ 507.2543, found 507.2543.

Preparation of 4-deoxy-2,3:5,6-di-*O*-isopropylidene-1-*O*-tosyl-D-gulitol (15). A solution of compound **14** (0.200 g, 0.429 mmol) and tetra-*n*-butylammonium fluoride (0.4 mL, 0.429 mmol) in anhydrous THF (3 mL) was stirred at room temperature for one hour. After completion of reaction as indicated by TLC the reaction mixture was concentrated under reduced pressure to obtain a residue. The residue was diluted with ethyl acetate (20 mL) and the solution was given a wash with water (10 mL). The organic layer was separated and the aqueous layer was saturated with sodium chloride and extracted with ethyl acetate (20 mL × 2). The combined organic extract was concentrated under reduced pressure till the resulting residue was free of any solvent. The residue was dissolved in anhydrous dichloromethane (5 mL) and to the solution pyridine (0.2 mL, 3.36 mmol) was added under inert atmosphere. This was followed by addition of tosyl chloride (0.100 g, 0.51 mmol) and the reaction mixture was stirred at room temperature for 3 h. After completion of reaction as indicated by TLC the reaction mixture was diluted with dichloromethane (20 mL) and then given a wash with saturated sodium bicarbonate solution (20 mL). The organic layer was separated and concentrated under reduced pressure to obtain a residue which was subjected to silica gel column chromatography to obtain the pure product **15** as a colorless syrupy liquid (0.196 g, 60%).

4-Deoxy-2,3:5,6-di-*O*-isopropylidene-1-*O*-tosyl-D-gulitol (15). R_f 0.34 (ethyl acetate / hexane, 2: 8); $[\alpha]^{25}_D$. + 12.98 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$ / TMS, 400MHz): δ 1.24, 1.27, 1.30, 1.36 (4s, 12H, $C(CH_3)_2$ × 2); 1.68-1.78, 1.81-1.90 (2m, 2H, $H_{4a,}H_{4b}$); 2.43 (s, 3H, Ar-CH_3); 3.57-3.63 (t, *J*. 7.6 Hz, 1H, H_{6a}); 3.85-3.91 (dd, *J*. 10.0, 5.6 Hz, 1H, H_{1a}); 3.99-4.05 (m, 2H, H_{1b}, H_{6b}); 4.14-4.26 (m, 3H, H_2, H_3, H_5); 7.33 (d, *J*. 8.0 Hz, 2H, Ar); 7.76 (d, *J*. 8.0 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$/TMS, 100 MHz) δ 21.6 (Ar-CH_3); 25.3, 25.6, 26.8, 27.9 ($C(CH_3)_2$ × 2); 32.0 (C_4), 67.7 (CH_2OTs); 68.6 (C_6); 72.9 (C_2); 73.4, 74.6 (C_3, C_5); 108.7, 108.9 ($C(CH_3)_2$ × 2); 127.9, 129.9, 132.5, 145.1 (Aromatic); HRMS (ESI) *m/z* $[M+H]^+$ Calcd. for $C_{19}H_{29}O_7S$ 401.1634, found 401.1639.

Preparation of (3*S*,4*R*,6*S*)-6-hydroxymethyl-3,4-*O*-isopropylidenetetrahydro-2*H*-pyran-3,4-diol (17). The tosylate **15** (0.100 g, 0.250 mmol) and zinc nitrate hexahydrate (0.323 g, 1.25 mmol) were dissolved in acetonitrile (10 mL) and the solution was stirred at room temperature for twelve hour. After completion of reaction as indicated by TLC the reaction mixture was stirred with saturated solution of potassium carbonate. The precipitate formed was filtered off and washed with acetonitrile (15 mL). The filtrate and washings were combined and concentrated under reduced pressure and at room temperature to obtain a residue free of any solvent. The residue was dissolved in anhydrous THF (3 mL) and the solution was added to suspension of sodium hydride (0.21 g, 0.903 mmol) in anhydrous THF (1 mL) and the mixture was stirred at room temperature for two hour. After completion of reaction as indicated by TLC, saturated ammonium chloride solution (10 mL) was added to the reaction mixture with stirring and then the reaction mixture was extracted with ethyl acetate (20 mL). The aqueous layer was saturated with sodium chloride and extracted with ethyl acetate (20 mL × 2). The combined

organic extract was concentrated under reduced pressure to obtain a residue. The residue was subjected to silica gel column chromatography. Prior to loading the crude sample over the column, the silica gel column was treated with 1% solution of triethylamine in hexane. The column chromatography was carried out using ethyl acetate-hexane-triethylamine (40:59:1) solvent system. The pure product was obtained as colorless syrupy liquid (0.080g, 64%). A fresh trial of the above procedure provided the product (0.092 g, 71%).

(3*S*,4*R*,6*S*)-6-Hydroxymethyl-3,4-*O*-isopropylidenetetrahydro-2*H*-pyran-3,4-diol (17). Colorless syrupy liquid; R_f 0.34 (ethyl acetate / hexane, 2: 8); $[\alpha]^{25}_D$= + 12.98 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3436, 2933, 1370, 1215, 1057 cm^{-1}; ^1H NMR ($CDCl_3$ / TMS, 400MHz): δ 1.34, 1.48 (2s, 6H, $C(CH_3)_2$); 1.73-1.82, 1.91-1.97 (2m, 2H, $H_{4a,}H_{4b}$); 3.32-3.40 (dd, *J*. 11.6, 9.2 Hz, 1H, H_{1a}); 3.43-3.49 (dd, *J*. 11.6, 2.8 Hz, 1H, H_{6a}); 3.60-3.64 (dd, *J*. 11.6, 6.8 Hz, 1H, H_{6b}); 3.64-3.72 (m, 1H, H_5); 3.86-3.92 (dd, *J*. 11.6, 6.0 Hz, 1H, H_{1b}); 4.07-4.13 (dt, *J*. 8.8, 6.0 Hz, H_2); 4.36-4.50 (m, 1H, H_3); ^{13}C NMR ($CDCl_3$/TMS, 100 MHz): δ 26.1, 28.1 ($C(CH_3)_2$); 28.2 (C_4), 65.4 (CH_2OH); 67.2 (C_1); 70.2 (C_2); 71.2 (C_3), 72.6 (C_5); 109.0 ($C(CH_3)_2$); HRMS (ESI) *m/z* $[M+Na]^+$ Calcd. for $C_9H_{16}O_4Na$ 211.0946, found 211.0950.

Preparation of (3*S*,4*R*,6*S*)-3,4-*O*-isopropylidene-6-(3,5-dinitrobenzoyloxymethyl)tetrahydro-2*H*-pyran-3,4-diol (18). To a solution of alcohol **17** (0.100 g, 0.5319 mmol) and triethylamine (0.2 mL, 1.170 mmol) in anhydrous dichloromethane (3 mL), 3,5-dinitrobenzoyl chloride (0.135 g, 0.585 mmol) was added under inert atmosphere and the reaction mixture was stirred for six hour at room temperature. After completion of reaction as indicated by TLC, the reaction mixture was diluted with dichloromethane and the solution was given a wash with saturated sodium bicarbonate solution. The organic layer was separated and concentrated under reduced pressure to obtain a residue. The residue was subjected to silica gel column chromatography. Prior to loading the crude sample over the column, the silica gel column was treated with 1% solution of triethylamine in hexane. The column chromatography was carried out using ethyl acetate-hexane-triethylamine (40:59:1) solvent system. The pure product was obtained as a colorless syrupy liquid in 50% yield.

(3*S*,4*R*,6*S*)-3,4-*O*-Isopropylidene-6-(3,5-dinitrobenzoyloxymethyl)tetrahydro-2*H*-pyran-3,4-diol (18). Colorless syrupy liquid; R_f 0.19 (ethyl acetate / hexane, 2: 8); ^1H NMR ($CDCl_3$ / TMS, 400MHz): δ 1.38, 1.53 (2s, 6H, $C(CH_3)_2$); 1.81-1.90, 2.07-2.17 (2m, 2H, $H_{4a,}H_{4b}$); 3.40-3.47 (dd, *J*. 11.6, 8.8 Hz, 1H, H_{1a}); 3.90-3.97 (dd, *J*. 11.6, 6.4 Hz, 1H, H_{1b}); 4.00-4.07 (m, 1H, H_5); 4.14-4.21 (m, 1H, H_2); 4.42-4.49 (m, 3H, H_3, $H_{6a,}$ H_{6b}); 9.16 (s, 2H, Aromatic); 9.22 (s, 1H, Aromatic).^{13}C NMR ($CDCl_3$ / TMS, 100 MHz): δ 26.0, 28.1 ($C(CH_3)_2$); 28.8 (C_4), 67.2 (C_1); 68.5 (C_6); 69.6, 70.0, 70.9 (C_2, C_3, C_5); 109.2 ($C(CH_3)_2$); 122.4, 122.5, 129.5, 129.6, 133.6, 148.7 (Aromatic); 162.4 (C=O).

Preparation of (3*S*,4*R*,6*S*)-3,4-*O*-isopropylidene-6-[(1*H*-imidazol-1-yl)thiocarbonyloxymethyl]tetrahydro-2*H*-pyran-3,4-diol (22). A solution of the alcohol **17** (0.100 g, 0.53 mmol) and thiocarbonyl diimidazole (0.104 g, 0.585 mmol) in anhydrous toluene (4 mL) was refluxed for one hour. After completion of the reaction as monitored by thin layer chromatography, the solvent was evaporated under reduced pressure and the resulting residue was subjected to silica

gel column chromatography using ethyl acetate-hexane (1:10). The pure product (0.060 g) was obtained as a colorless syrup in 50 % yield.

(3*S*,4*R*,6*S*)-3,4-*O*-Isopropylidene-6-[(1*H*-imidazol-1-yl)thiocarbonyloxymethyl]tetrahydro-2*H*-pyran-3,4-diol (22). Colorless syrupy liquid; R_f 0.15 (ethyl acetate / hexane, 1: 20); $[\alpha]^{25}_D$= +8.989 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 1765, 1388, 1285, 1218, 1112, 977, 702, 505 cm^{-1}; ^1H NMR ($CDCl_3$ / TMS, 400MHz): δ 1.37, 1.52 (2s, 6H, $C(CH_3)_2$); 1.80-1.88, 2.04-2.15 (2m, 2H, $H_{4a,}H_{4b}$); 3.40-3.46 (dd, *J*. 11.6, 8.8 Hz, 1H, H_{1a}); 3.88-3.96 (dd, *J*. 11.6, 6.0 Hz, 1H, H_{1b}); 4.04-4.12 (m, 1H, H_5); 4.13-4.19 (dt, *J*. 11.2, 5.6 Hz, H_2); 4.42-4.46 (m, 1H, H_3); 4.56-4.61 (dd, *J*. 11.6, 6.4 Hz, 1H, H_{6a}); 4.64-4.68 (dd, *J*. 11.6, 8.0 Hz, 1H, H_{6b}); 7.04, 7.64, 8.38 (3s, 3H, Imidazolyl); ^{13}C NMR ($CDCl_3$/TMS, 100 MHz): δ 26.0, 28.02 ($C(CH_3)_2$); 28.72 (C_4), 67.1 (C_1); 69.1, 70.0, 70.8 (C_2, C_3, C_5); 74.9 (CH_2OC=O); 109.2 ($C(CH_3)_2$); 130.5, 183.9 (Imidazolyl).

Preparation of (3*S*,4*R*,6*S*)-3,4-*O*-isopropylidene-6-(tosyloxymethyl)tetrahydro-2*H*-pyran-3,4-diol (24). To a solution of alcohol **17** (0.100 g, 0.53 mmol) and triethylamine (0.2 mL, 1.17 mmol) in anhydrous dichloromethane (5 mL), *p*-toluenesulfonyl chloride (0.304 g, 1.6 mmol) was added under inert atmosphere and the reaction mixture was stirred for 5 h at room temperature. After completion of reaction as indicated by TLC, the reaction mixture was diluted with dichloromethane and the solution was given a wash with saturated sodium bicarbonate solution. The organic layer was separated and concentrated under reduced pressure to obtain a residue. The residue was subjected to silica gel column chromatography. Prior to loading the crude sample over the column, the silica gel column was treated with 1% solution of triethylamine in hexane. The column chromatography was carried out using ethylacetate-hexane-triethylamine (40:59:1) solvent system. The pure product was obtained as colourless syrupy liquid (0.53 g, 50%).

(3*S*,4*R*,6*S*)-3,4-*O*-Isopropylidene-6-(tosyloxymethyl)tetrahydro-2*H*-pyran-3,4-diol (24). Colorless syrupy liquid; R_f 0.25 (ethyl acetate / hexane, 2: 8); IR (neat) ν_{max} 2932, 1176, 1066, 700 cm^{-1}; ^1H NMR ($CDCl_3$ / TMS, 400 MHz): δ 1.32, 1.44 (2s, 6H, $C(CH_3)_2$); 1.70-1.77, 1.91-1.97 (2m, 2H, $H_{4a,}H_{4b}$); 3.25-3.32 (dd, *J*. 12.0, 8.4 Hz, 1H, H_{1a}); 3.76-3.82 (dd, *J*. 12.0, 6.0 Hz, 1H, H_{1b}); 3.92-3.97 (dd, *J*. 11.4, 5.2 Hz, 1H, H_{6a}); 3.98-4.02 (dd, *J*. 11.4, 3.6 Hz, 1H, H_{6b}); 4.03-4.22 (m, 2H, $H_{2,}$ H_5); 4.33-4.38 (m, 1H, H_3); 7.32 (d, *J*. 8.0 Hz, 2H, Aromatic); 7.76 (d, *J*. 8.0 Hz, 2H, Aromatic).^{13}C NMR ($CDCl_3$/TMS, 100 MHz) δ 21.6 (Ar-CH_3); 25.9, 27.9 ($C(CH_3)_2$); 28.2 (C_4), 66.9 (C_1); 69.2, 70.0, 70.8 (C_2, C_3, C_5); 71.7 (CH_2OTs); 109.0 ($C(CH_3)_2$); 127.9, 129.8, 132.8, 144.9 (Aromatic).

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