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Preparation of 4,5-Cyclopropylsugar Derivatives : Application to the Stereocontrolled Synthesis of Bottom Half (C_7-C_{16}) Segment of Lasonolide A

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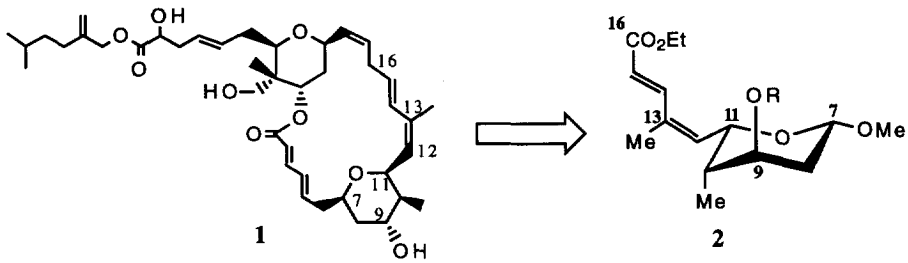
Abstract: Synthesis and application of the cyclopropane incorporated sugar intermediate in the stereoselective synthesis of C_7-C_{16} segment of lasonolide A is described.

Many reports have documented that marine sources contribute significantly towards biologically active natural products with unique structural arrangements[1]. The representative example includes *in vitro* proliferation antagonist of A-549 human carcinoma cells - lasonolide A (**1**)[2]. It was isolated from shallow water caribbean sponge *Forcepia sps*. Compound **1** attracted our attention[3] because of unique structural features coupled with useful biological activity.

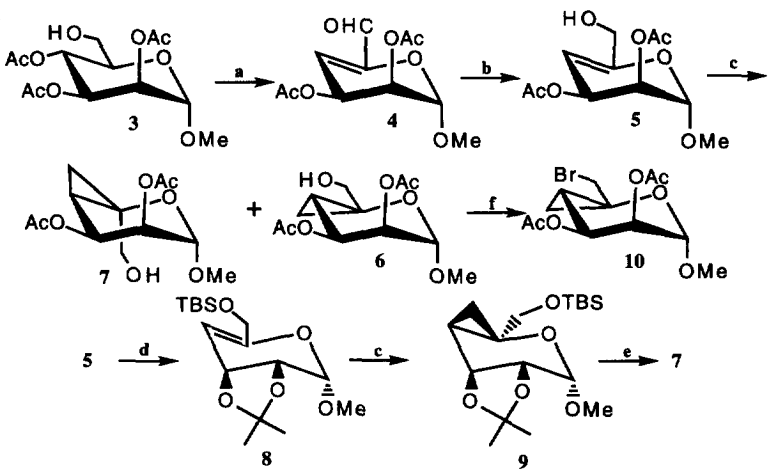
Preparation of cyclopropane containing carbohydrates are relatively rare in literature inspite of the fact that they could be useful synthons for chemical manipulation to obtain stereochemically defined branched chain carbohydrate intermediates. We now describe a novel application of a cyclopropane sugar derivative in the synthesis of bottom half segment (C_7-C_{16}) of lasonolide A. The salient features of our strategy are i) stereoselective synthesis of 4,5-cyclopropane sugars, ii) radical induced reductive opening to obtain branched chain carbohydrate and finally, iii) stereospecific hydroboration-oxidation of 5,6-ene to obtain the advanced sugar intermediate with required L-configuration.



Methyl 2,3,4-tri-*O*-acetyl-α-D-mannopyranoside (**3**) was treated with PCC in refluxing toluene to give the unsaturated aldehyde (**4**) which was reduced with $NaBH_4$ in the presence of Amberlite IR 120 (H+) resin in MeOH to provide the allyl alcohol (**5**) in 60% overall yield[4].

The modified Simmon-Smith cyclopropanation of **5** using Et_2Zn-CH_2I_2 in CH_2Cl_2 at -20° gave a mixture of diastereomeric cyclopropane derivatives **6** (desired) and **7** (undesired) in almost equal amounts (74%), which were separated by chromatography. The stereochemical assignments could not be made by ^1H NMR spectral analysis, but further chemical transformations allowed unequivocal allocation of structures **6** and **7**. In order to improve the diastereoselectivity of cyclopropanation, compound **5** was transformed into sterically more demanding product **8** by a three step sequence. Subsequent Simmon-Smith reaction of **8** gave exclusively one product **9** with the undesired stereochemistry . For the purpose of correlation, compound **9** was converted into **7**. Treatment of **6** with CBr_4-Ph_3P in CH_2Cl_2 at room temperature afforded the corresponding 6- bromo derivative **10** (92%).

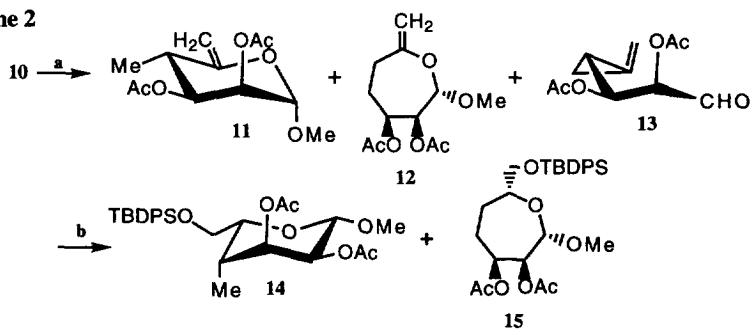
Scheme 1



(a) PCC, $C_6H_5CH_3$, Δ, 1 h, 70%; (b) $NaBH_4$, IR 120(H^+) resin, MeOH, 0°C, 5 min., 85%; (c) CH_2I_2, Et_2Zn, CH_2Cl_2, -20°C, 10 h, 74%; (d)(i) TBS-Cl, Imid, CH_2Cl_2, RT, 2 h, 97%; (ii) NaOMe, MeOH, RT, 15 min., 95%; (iii) $Me_2C(OMe)_2$, PPTS, RT, 3 h, 90%; (e)(i) AcOH-H_2O (1:1), RT, 4 h, 75%; (ii) TBS-Cl, Imid, CH_2Cl_2, RT, 2 h, 90%; (iii) Ac_2O, Et_3N, CH_2Cl_2, RT, 30 min., 97%; (iv) Bu_4NF, THF, AcOH, 0°C, 3 h, 80%, (f) Ph_3P, CBr_4, Imid, CH_2Cl_2, RT, 1 h, 92%.

Interestingly in the proposed radical induced ring opening of **10**, three competing pathways would be envisaged leading to the pyranose derivative **11**, seven membered product **12** or ring opened product **13**. Treatment of **10** with Bu_3SnH-AIBN in refluxing toluene gave a mixture of two products **11** and **12** (3:2) in 93% yield, which were separated with difficulty by preparative tlc. The ^1H NMR spectrum of **11** was amenable to first order analysis in which the characteristic coupling constants ($J_{2,3}$= 3.2 (ax-eq) and $J_{3,4}$= 10.0 (ax-ax) Hz) clearly indicated that the C_4-methyl group was equatorial. This stereochemical

Scheme 2



(a) Bu_3SnH, AIBN, $C_6H_5CH_3$, Δ, 30 min., 93%; (b)(i) 9-BBN, THF 4 h; 1M NaOAc, H_2O_2, 0°C, 3 h, 61%; (ii) TBDPS-Cl, Imid, DMAP, CH_2Cl_2, RT, 4 h, 92%

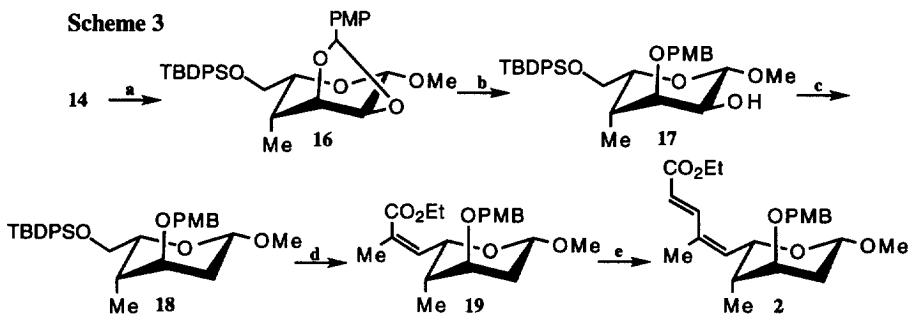
assignment therefore proved the structure of the parent cyclopropane derivative **6**. In the ^1H NMR spectrum of the seven-membered ring product **12**, the characteristic resonances due to methylene protons were located

in the high field region δ 1.9 and 2.5 ppm, the remaining protons had expected chemical shifts. The seven-membered ring product **12** which was obtained in 37% yield, could form a useful synthon[5] for many biologically important polyhydroxy-cycloheptane compound subject to the Ferrier reaction or subsequent Sinay's modification[6].

Since the mixture of **11** and **12** were difficult to separate in multigram-quantities, it was directly subjected to hydroboration-oxidation with 9-BBN-H_2O_2 followed by TBDPS-protection to give a chromatographically separable mixture of **14** and **15.** The structures were assigned based on extensive ^1H NMR spectral analysis. The L-configuration of **14** was established by the chemical shift and coupling constant data of its ^1H NMR spectrum: δ_{H-1} 4.58 (d, J= 8.3 Hz), δ_{H-2} 4.82 (dd, J= 3.3, 8.3 Hz), δ_{H-3} 5.20 (t, J= 3.3 Hz).

Our next concern was the deoxygenation of **14** at C-2 for which **14** was first deacetylated and then treated with p-anisaldehyde dimethylacetal-PPTS to afford the 4-methoxybenzylidene derivative **16.** Subsequent treatment with DIBAL at -78° in CH_2Cl_2 afforded 3-O-PMB derivative **17** as a sole product[7]. The Barton deoxygenation[8] of **17** *via* the phenylxanthate derivative afforded the 2-deoxy product **18** in 74% yield.

Scheme 3



(a)(i) NaOMe, MeOH, RT, 10 min., 93%; (ii) MeO-$C_6H_4CH(OMe)_2$, PPTS, CH_2Cl_2, RT, 30 min., 97%; (b) DIBAL-H, CH_2Cl_2, -78°, 15 min., 81%); (c) (i) PhOC(S)COCl, Py.-DMAP, CH_2Cl_2, RT, 6 h; (ii) Bu_3SnH-AIBN, $C_6H_5CH_3$, Δ, 2 h, 74%; (d)(i) Bu_4NF, THF, RT, 1 h, 89%; (ii) $(COCl)_2$, DMSO, Et_3N, -78°C, 30 min., 91%; (iii) $(MeO)_2P(O)CH(Me)CO_2Et$, NaH, -78°C, 3 h, 80%; (e)(i) DIBAL-H, CH_2Cl_2,- 78°C, 15 min., 81%; (ii) $(COCl)_2$, DMSO, Et_3N, -78°C, 30 min., 91%; (iii) $Ph_3P=CHCO_2Et$, C_6H_6, RT, 5 h, 77%.

Removal of TBDPS group and Swern oxidation of **18** gave the corresponding aldehyde which was subjected to Wittig-Horner reaction with $(MeO)_2P(O)CH(Me)CO_2Et$-NaH at -78° in THF to give the Z-olefin **19** in 80% yield[9]. The corresponding E-isomer was also isolated in 10% yield[10]. The stereochemical assignments for **19** were based on ^1H NMR and NOE studies. Compound **19** was converted into the final product **2** (R = PMB) in three high yielding steps which involved 1) reduction of CO_2Et group with DIBAL at -78° 2) oxidation of CH_2OH group under Swern condition and 3) Wittig reaction with stabilised ylide $Ph_3P=CHCOOEt$[11].

In conclusion this communication elaborated the new synthesis of 4,5-cyclopropane sugar derivatives and novel applications to branched chain carbohydrate intermediates such as **2.**

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10. The possibility of epimerisation at C-5 was ruled out by the ^{1}H NMR spectrum of compound **19** in which the coupling constant $J_{4,5}$= 2.5 Hz was observed for H-5 ($\delta_{H\text{-}5}$ 5.15ppm) characteristic for vicinal protons with ax-eq. relationship.
11. All the new compounds were characterised by ^{1}H NMR, Mass and HRFABMS: spectral data of some selected compounds: **6** ^{1}H NMR ($CDCl_3$) : δ 0.8-1.15 (m, 3 H), 2.10, 2.12 (2s, 6 H), 3.30 (d, 1 H, J= 12.0 Hz), 3.42 (s, 3 H), 3.90 (d, 1 H, J= 12.0 Hz), 4.78 (d, 1 H, J= 4.4 Hz), 4.90 (t, 1 H, J= 4.4 Hz), 5.36 (brs, 1 H), HRFABMS: $C_{11}H_{15}O_6$ (M-OMe) Calcd. m/z 243.0868, found 243.0872 (error 1.6 ppm). Compound: **11** ^{1}H NMR ($CDCl_3$) : δ 1.10 (d, 3 H, J= 6.0 Hz), 2.00, 2.10 (2s, 6 H), 3.40 (s, 3 H), 4.45 (s, 1 H), 4.62 (s, 1 H), 4.70 (s, 1 H), 4.95 (dd, 1 H, J= 3.2, 10.0 Hz), 5.23 (brs, 1 H). Compound: **14** ^{1}H NMR ($CDCl_3$) : δ 1.03 (d, 3 H, J= 7.3 Hz), 1.07 (s, 9 H), 2.03 (s, 3 H), 2.04 (m, 1 H), 2.14 (s, 3 H), 3.47 (s, 3 H), 3.60 (dd, 1 H, J= 6.4, 10.5 Hz), 3.80 (dd, 1 H, J= 6.8, 10.5 Hz), 4.03 (m, 1 H), 4.58 (d, 1 H, J= 8.3 Hz), 4.82 (dd, 1 H, J= 3.3, 8.3 Hz), 5.20 (t, 1 H, J= 3.3 Hz), 7.4 (m, 6 H), 7.66 (m, 4 H), HRFABMS: $C_{27}H_{35}O_6Si$ (M-OMe) Calcd. m/z 483.2202, found 483.2222 (error 4.1 ppm). Compound: **19** ^{1}H NMR ($CDCl_3$) : δ 0.96 (d, 3 H, J= 7.25 Hz), 1.26 (t, 3 H, J= 7.2 Hz), 1.55-1.83 (m, 2 H), 1.94 (s, 3 H), 2.24 (m, 1 H), 3.42 (s, 3 H), 3.54 (m, 1 H), 3.78 (s, 3 H), 4.16 (q, 2 H, J= 7.2 Hz), 4.37 (d, 1 H, J= 11.0 Hz), 4.63 (brd, 2 H), 5.15 (dd, 1 H, J= 2.5, 6.6 Hz), 5.97 (d, 1 H, J= 6.6 Hz), 6.80 (d, 2 H, J= 8.2 Hz), 7.26 (d, 2 H, J= 8.2 Hz), HRFABMS: $C_{20}H_{27}O_5$ (M-OMe) Calcd. m/z 347.1858, found 347.1865 (error 1.9 ppm). Compound: **2** ^{1}H NMR ($CDCl_3$) : δ 0.97 (d, 3 H, J= 7.1 Hz), 1.30 (t, 3 H, J= 3.5 Hz), 1.65-1.9 (m, 3 H), 1.93 (s, 3 H), 3.50 (s, 3 H), 3.64 (m, 1 H), 3.83 (s, 3 H), 4.24 (q, 2 H, J= 7.1 Hz), 4.54 (ABq, 2 H, J= 11.5 Hz), 4.78 (dd, 1 H, J= 2.5, 9.0 Hz),5.01 (dd, 1 H, J= 2.5, 7.4 Hz), 5.83 (d, 1 H, J= 7.4 Hz), 5.95 (d, 1 H, J= 15.7 Hz), 6.9 (d, 2 H, J= 8.6 Hz), 7.35 (d, 2 H, J= 8.6 Hz), 7.85 (d, 1 H, J= 15.7 Hz), HRFABMS: $C_{15}H_{23}O_4$ (M-OPMB) Calcd. m/z 267.1596, found 267.1599 (error 1.1 ppm).

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