

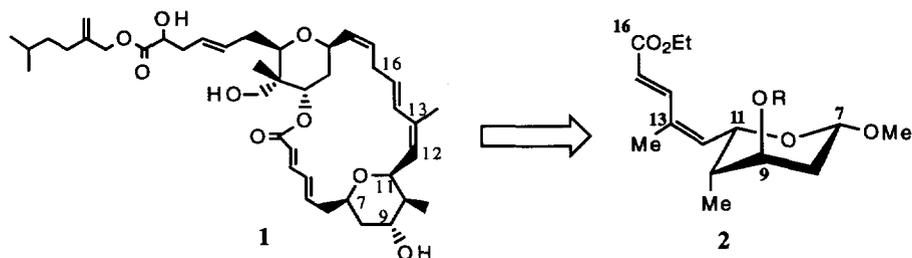
Preparation of 4,5-Cyclopropylsugar Derivatives : Application to the Stereocontrolled Synthesis of Bottom Half (C₇-C₁₆) Segment of Lasonolide A

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Abstract: Synthesis and application of the cyclopropane incorporated sugar intermediate in the stereoselective synthesis of C₇-C₁₆ segment of lasonolide A is described.
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Many reports have documented that marine sources contribute significantly towards biologically active natural products with unique structural arrangements¹. 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 attention³ because of unique structural features coupled with useful biological activity.

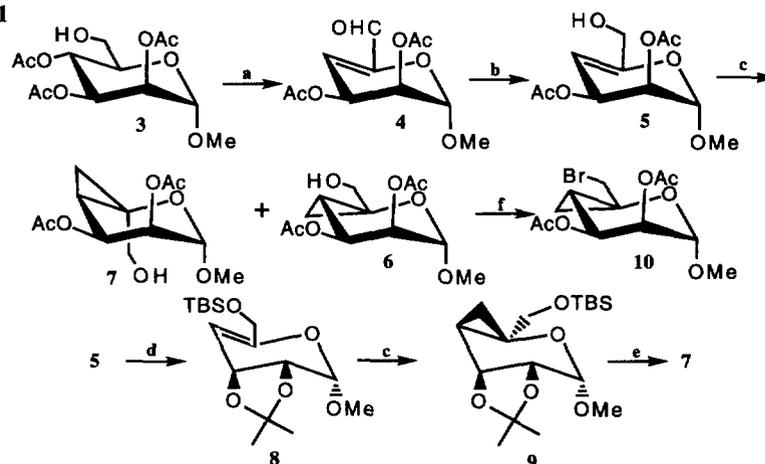
Preparation of cyclopropane containing carbohydrates are relatively rare in literature inspite of the fact that they could be useful synthons for chemical manipulation to obtain stereochemically defined branched chain carbohydrate intermediates. We now describe a novel application of a cyclopropane sugar derivative in the synthesis of bottom half segment (C₇-C₁₆) 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 NaBH₄ in the presence of Amberlite IR 120 (H⁺) resin in MeOH to provide the allyl alcohol (**5**) in 60% overall yield⁴.

The modified Simmon-Smith cyclopropanation of **5** using Et₂Zn-CH₂I₂ in CH₂Cl₂ 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 CBr₄-Ph₃P in CH₂Cl₂ at room temperature afforded the corresponding 6- bromo derivative **10** (92%).

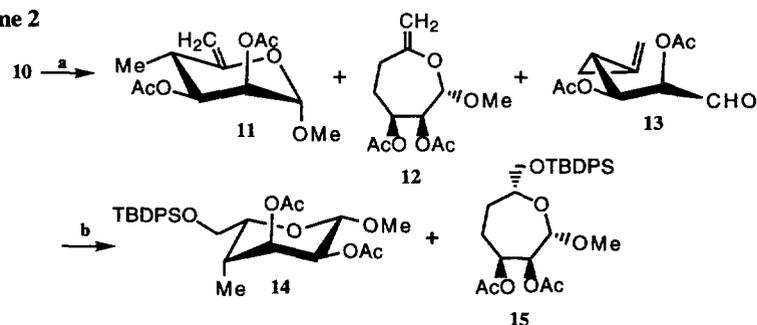
Scheme 1



(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-H₂O (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 C₄-methyl group was equatorial. This stereochemical

Scheme 2



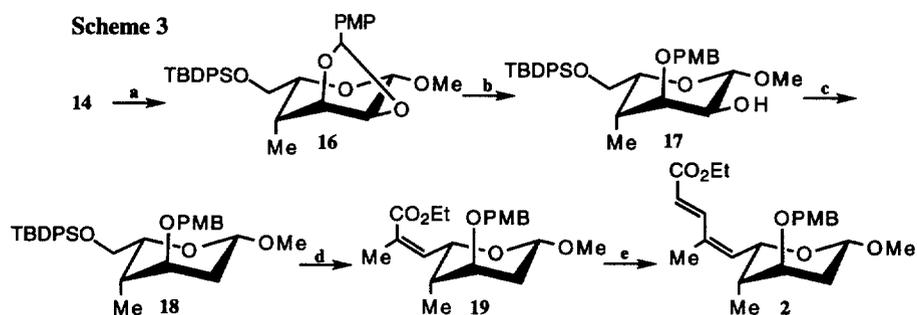
(a) Bu_3SnH , AIBN, $C_6H_5CH_3$, Δ , 30 min., 93%; (b)(i) 9-BBN, THF 4 h; 1M NaOAc, H_2O_2 , 0°C, 3 h, 61%; (ii) TBDPS-Cl, Imid, DMAP, CH_2Cl_2 , RT, 4 h, 92%

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 synthon⁵ for many biologically important polyhydroxy-cycloheptane compound subject to the Ferrier reaction or subsequent Sinay's modification⁶.

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 product⁷. The Barton deoxygenation⁸ of **17** via the phenylxanthate derivative afforded the 2-deoxy product **18** in 74% yield.



(a)(i) NaOMe, MeOH, RT, 10 min., 93%; (ii) MeO-C₆H₄CH(OMe)₂, PPTS, CH₂Cl₂, RT, 30 min., 97%; (b) DIBAL-H, CH₂Cl₂, -78° , 15 min., 81%; (c) (i) PhOC(S)COCl, Py.-DMAP, CH₂Cl₂, RT, 6 h; (ii) Bu₃SnH-AIBN, C₆H₅CH₃, Δ , 2 h, 74%; (d)(i) Bu₄NF, THF, RT, 1 h, 89%; (ii) (COCl)₂, DMSO, Et₃N, $-78^\circ C$, 30 min., 91%; (iii) (MeO)₂P(O)CH(Me)CO₂Et, NaH, $-78^\circ C$, 3 h, 80%; (e)(i) DIBAL-H, CH₂Cl₂, $-78^\circ C$, 15 min., 81%; (ii) (COCl)₂, DMSO, Et₃N, $-78^\circ C$, 30 min., 91%; (iii) Ph₃P=CHCO₂Et, C₆H₆, 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)CO₂Et-NaH at -78° in THF to give the *Z*-olefin **19** in 80% yield⁹. The corresponding *E*-isomer was also isolated in 10% yield¹⁰. 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 CO₂Et group with DIBAL at -78° 2) oxidation of CH₂OH group under Swern condition and 3) Wittig reaction with stabilised ylide Ph₃P=CHCOOEt¹¹.

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 ^1H NMR spectrum of compound **19** in which the coupling constant $J_{4,5} = 2.5$ Hz was observed for H-5 ($\delta_{\text{H-5}} 5.15$ ppm) characteristic for vicinal protons with ax-eq. relationship.
11. All the new compounds were characterised by ^1H NMR, Mass and HRFABMS: spectral data of some selected compounds: **6** ^1H 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: $\text{C}_{11}\text{H}_{15}\text{O}_6$ (M-OMe) Calcd. m/z 243.0868, found 243.0872 (error 1.6 ppm). Compound: **11** ^1H 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** ^1H 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: $\text{C}_{27}\text{H}_{35}\text{O}_6\text{Si}$ (M-OMe) Calcd. m/z 483.2202, found 483.2222 (error 4.1 ppm). Compound: **19** ^1H 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: $\text{C}_{20}\text{H}_{27}\text{O}_5$ (M-OMe) Calcd. m/z 347.1858, found 347.1865 (error 1.9 ppm). Compound: **2** ^1H 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: $\text{C}_{15}\text{H}_{23}\text{O}_4$ (M-OPMB) Calcd. m/z 267.1596, found 267.1599 (error 1.1 ppm).

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