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Stereocontrolled Synthesis of Spirocyclopropane Sugars and Their Application to Asymmetric Formation of Tertiary Chiral Centres: A Route to 2,2'-Dialkylated Pyranose Subunit (C_{18}-C_{23}) of Lasonolide A

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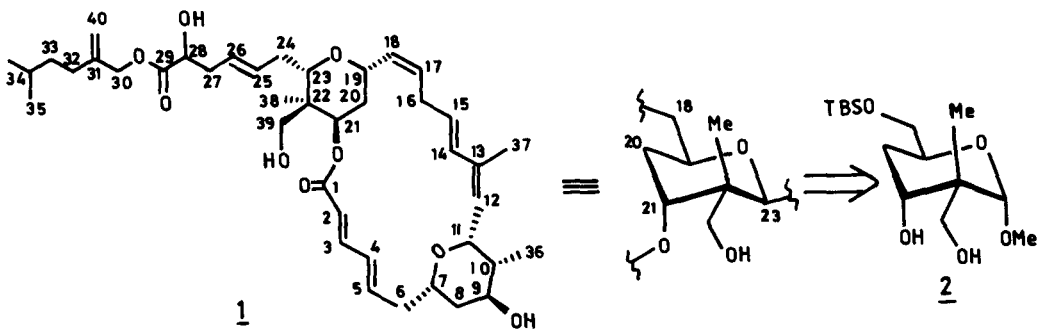
Abstract: A novel route to asymmetric formation of tertiary chiral centres of sugars via 2,2'- spirocyclopropane derivatives has been described. This route forms the basis of our proposed synthesis of the C_{18}-C_{23} subunit of lasonolide A. Copyright © 1996 Published by Elsevier Science Ltd

During the search for new antitumor agents from marine organisms, McConnell *et al*[1] reported the isolation of a cytotoxic macrolide lasonolide A (**1**) from the shallow water caribbean marine sponge, *Forcepia sps*. Lasonolide A antagonises *in vitro* proliferation of A-549 human lung carcinoma cells as well as inhibits cell adhesion in whole cell assay, that detects signal transduction agents[2]. The structure of lasonolide A was elucidated by NMR studies. The unique structural features and the important biological activity of lasonolide-A prompted us to undertake its total synthesis. Herein, we present a stereoselective synthesis of tetrahydropyran moiety (**2**) of the top half (C_{18}-C_{23} carbon). The general plan, in obtaining the pyranose derivative, examines (i) the stereocontrolled formation of 2,2'-spirocyclopropane sugars, (ii) regioselective-reductive cleavage of spirocyclopropyl-aldehyde, and (iii) functional group manipulations involving a non-protic Bamford-Stevens reaction.

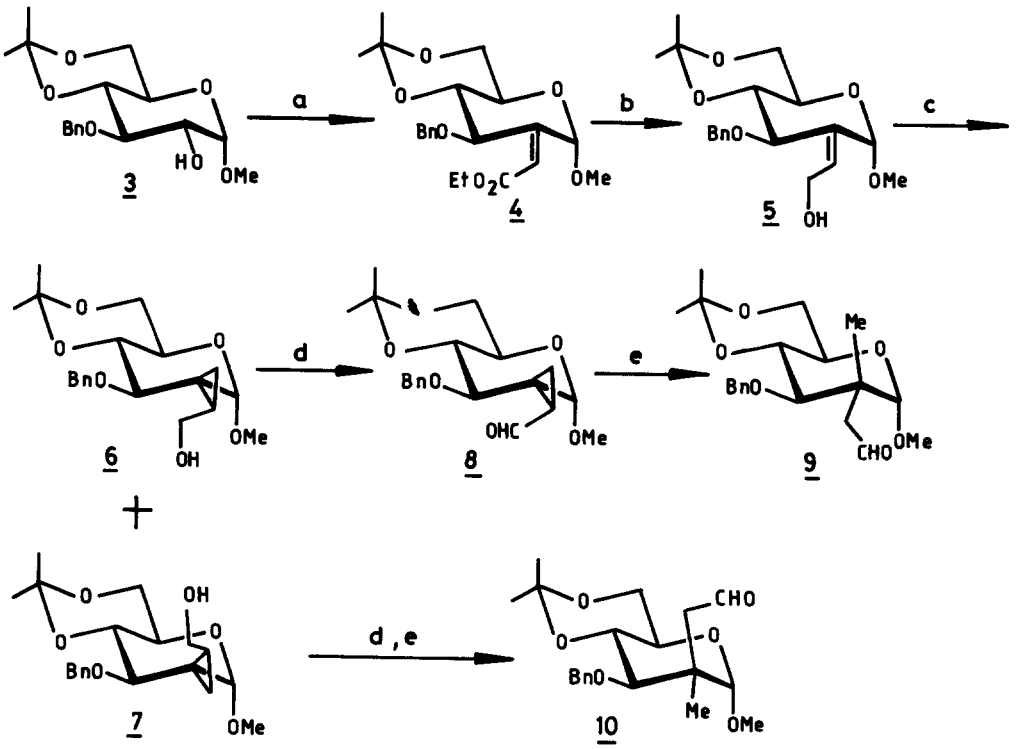


1 ≡ **2**

Our first concern was the preparation of 2,2'-spirocyclopropane pyranose derivative. Methyl 3-O-benzyl-4,6-O-isopropylidene-α-D-glucopyranoside (**3**) was prepared by a literature procedure[3]. Subsequent oxidation using $(CF_3CO)_2O$/DMSO gave the 2-ulose derivative which was subjected to two-carbon homologation using Ph_3P=CHCOOEt in refluxing acetonitrile to afford **4**. Reduction of **4** with LAH in ether at 0°C provided the allylic alcohol **5**.

Cyclopropanation of **5** using modified Simmon-Smith reaction[4] was performed with Et_2Zn/CH_2I_2. This step furnished a chromatographically separable mixture of two stereomeric cyclopropane derivatives 2R-(**6**) and 2S-(**7**) in 6.5:3.5 ratio. The absolute stereostructures of **6** and **7** could not be assigned by the ^{1}H-NMR studies. However, later reaction coupled with NOE studies of products formed herewith confirmed

Scheme - 1



(a) (i) TFAA, DMSO, Et_3N, DCM, -78°C (ii) Ph_3P=CHCOOEt, CH_3CN, reflux (overall yield 67%) (b) LAH, 0°C, ether, 0.5 hr (86%) (c) Et_2Zn, CH_2I_2, 0°C, ether, 3 hrs (90%) (d) PDC, DMF, r.t. (62%) (e) Pd/C, MeOH, 50 psi, Et_3N (Cat) (65%).

the assigned structures of parent products (**6** and **7**) unambiguously . We believe that the steric factors caused by α-anomeric methoxy group perhaps directed predominant formation of 2R-isomer (**6**).

In order to effect regiocontrolled ring cleavage under mild conditions[5], **6** was oxidised with PDC/DMF to provide the aldehyde **8** , which was then hydrogenated over 10% Pd/C at 50 psi in the presence of catalytic amount of Et_3N to give **9**. In the presence of Et_3N, the debenzylation was minimised[6]. Similarly 2S isomer (**7**) was converted into **10.** The NOE studies on both these compounds revealed the NOE effects as shown in figure A which conclusively confirmed these structures.

Treatment[7] of **9** with $TsNHNH_2$ in ether gave the corresponding hydrazone which was immediately heated under modified Bamford-Stevens reaction conditions with KH, 18-crown-6 in diglyme to give **11**[8]. The next plan of action involved deoxygenation at C-4 and concomitant epimerisation at C-3.

Hydrogenolysis of **11** with Li/liq NH_3 cleaved the 3-O-benzyl group cleanly to furnish **12**. Subsequent protection of the free OH group with MsCl/Et_3N gave the 3-O-mesylate **13** whose structure was substantiated by its ^1H NMR spectrum. To cleave the isopropylidene group, compound **13** was treated with

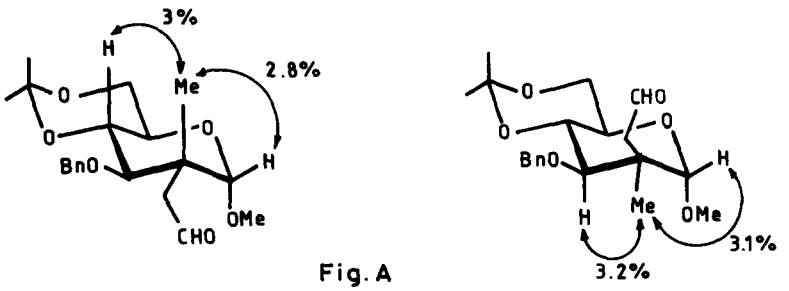
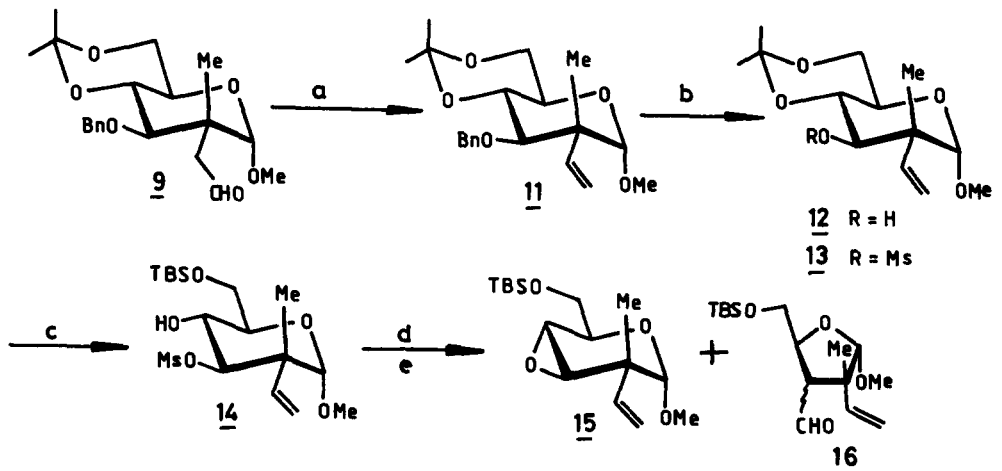


Fig. A

PTSA/MeOH at room temperature and the corresponding diol was selectively protected with TBSCl / imidazole in DMF to produce 6-O-silyl derivative **14**. Treatment of **14** with NaOMe in MeOH - $CHCl_3$

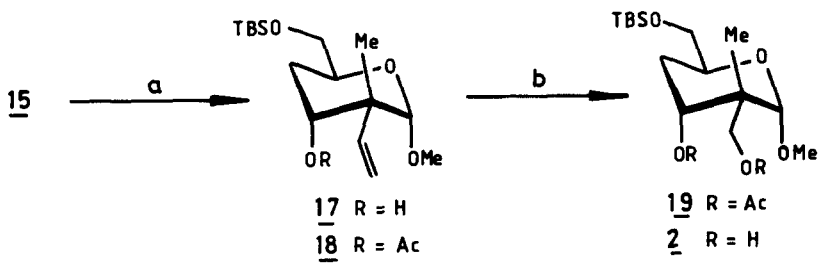
Scheme-2



(a) (i) NH_2NHTS, ether, 2 h, r.t. (ii) KH, 18-crown-6, diglyme 100°C (73%), (b) (i)NH_3, THF, Li (6 eq.), -79°C (78%) (ii) MsCl, TEA, DCM (80%) (c) (i) MeOH, PTSA, 0.5 hr r.t. (ii) TBS-Cl, imidazole, DMF, r.t. (68%) (d) NaOMe, $CHCl_3$, MeOH (8:1), r.t., 6 hrs (e) KH, HMPA, THF, 15 min. (90%).

(1:8) gave **15** as a minor compound, whose ^1H NMR spectrum was consistent with the epoxide structure. However, the major compound isolated from the reaction was the product generated due to ring contraction rearrangement. The structure of the product was tentatively assigned as **16**. Further studies on this compound are in progress. When compound **14** was subjected to the treatment of KH in THF/HMPA, the required epoxide **15** was obtained in 90% yield. The smooth formation of **15** under non-protic conditions was rather interesting. We believe that the non protic reaction conditions provides required conformational mobility[9] to the ring system of **14** and helps the formation of epoxide **15** over the rearranged product **16**. Reductive opening of the epoxide with LAH in THF at 50°C provided the 4-deoxy product **17** whose structure was substantiated by comparison of its ^1H NMR spectrum and that of its 3-O-acetyl derivative **18**. The degradation of vinyl group in **18** by OsO_4-$NaIO_4$ in THF followed by reduction and acetylation gave

Scheme - 3



(a) (i) LAH, THF, 50°C, 0.5 hr (85%) (ii) Et_3N, DMAP (Cat), Ac_2O (quantitave) (b) (i) OsO_4, $NaIO_4$, THF, $NaHCO_3$, (ii) MeOH, $NaBH_4$ (70%) (iii) Ac_2O, DMAP (Cat), Et_3N (iv) Na, MeOH (quantitative).

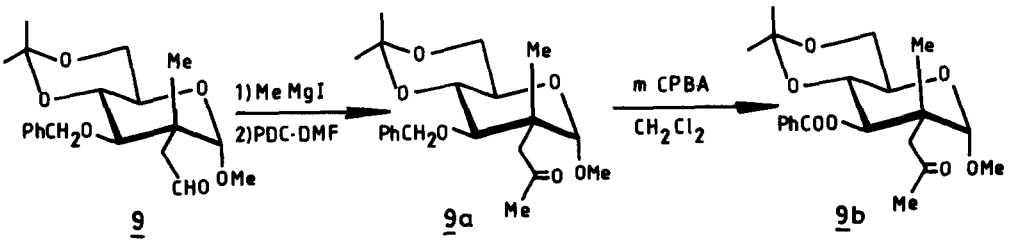
the diacetate **19** whose structure was confirmed by spectral analysis[10]. Removal of acetyl groups in **19** with NaOMe/MeOH gave **2**[11].

In conclusion, we have demonstrated for the first time the stereocontrolled synthesis of 2,2'-spirocyclopropane and its conversion into *gem*-dialkylated tertiary chiral centre, in order to achieve the stereospecific synthesis of C_{18}-C_{23} fragment of lasonolide A.

One of us (PK) is thankful to CSIR Delhi for awarding a SRF.

References and Notes

1. Horton, P.A.; Koehn, F.E.; Longley, R.E. and McConnell, O.J. *J. Amer. Chem. Soc.* **1994**, 116, 6015-16.
2. Drug Data Report, **1996**, 18, 90.
3. Koto, S.; Takabe, Y. and Zen, S. *Bull. Chem. Soc. Jpn.*, **1972**, 45, 291-3.
4. a) Furukawa, J.; Kawabata, N and Nishimura, J. *Tetrahedron Lett.*, **1966**, 3353-54.
   b) Furukawa, J.; Kawabata, N and Nishimura, J. *Tetrahedron* , **1968**, 24, 53-58.
   c) Furukawa, J.; Kawabata, N and Nishimura, J. *Tetrahedron Lett.*, **1968**, 3495-98.
   d) Furukawa, J.; Kawabata, N and Nishimura, J. *Tetrahedron* , **1969**, 25, 2647-59.
   e) Friedrich, E.C. and Biresaw, G. *J. Org. Chem.* **1982**, 47, 1615-18.
5. Wong, H.N.C.; Hon, Moon-Yuen.; Tse, Chun-wah and Yip, Yu-chi. *Chem. Rev.*, **1989**, 89, 165-198.
6. Enders, D.; Noyori, R and Trost, B.M. *Protecting Groups* ; Thieme: Stuttgart, **1994**, pp.46.
7. Alternatively we attempted one carbon degradation of 9 by converting it into the ketone derivative (9a) by succesive Grignard reaction and PDC oxidation. The Baeyer-villiger oxidation of 9a only provided the 3-O-benzoate 9b.



8. Freeman, P.K. and Swenson, K.E. *J. Org. Chem.*, **1982**, 47, 2033-39.
9. Tsuchiya, T., Ajito, K., Umezawa, S and Ikeda, A. *Carbohydrate Research.*, **1984**, 126, 45-60.
10. ^1H NMR (200 MHz, $CDCl_3$) compound **19** : δ 0.06 (s, 6 H), 0.9 (s, 9H), 1.14 (s, 3 H), 1.5 - 2.0 (m, 2 H), 2.06, 2.10 (2s, 6 H), 3.36 (s, 3 H), 3.64 (m, 2 H), 3.80, 4.30 (2d, 2 H, J= 12 Hz), 3.95 (m, 1 H), 4.36 (s, 1 H), 4.96 (bs, 1 H).
11. All the new compounds were characterised by ^1H-NMR, MS, HRMS and/or elemental analysis.

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