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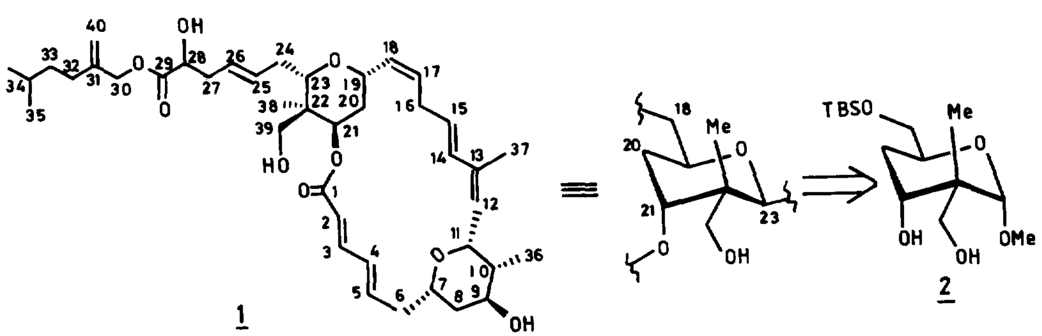
Abstract: A novel route to asymmetric formation of tertiary chiral centres of sugars via 2,2'- spiro-cyclopropane derivatives has been described. This route forms the basis of our proposed synthesis of the C_{18}-C_{23} subunit of lasonolide A. Copyright © 1996 Published by Elsevier Science Ltd

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.

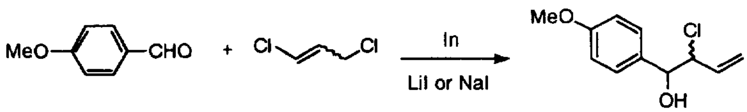


1 **2**

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

Table 1. Reaction of *p*-Anisaldehyde with 1,3-Dichloropropene in Various Solvents[a]

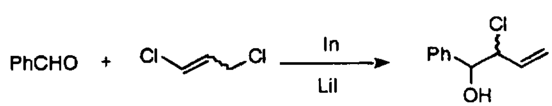


1a

Solvent	Additive	Yield/%	*syn*:*anti*
CH_2Cl_2	LiI	0	---
acetone	NaI	58	69:31
t-BuOH	LiI	56	71:29
THF	LiI	67	73:27
DMF	LiI	75	75:25
THF/H_2O (3:1)	LiI	93	81:19
MeOH	LiI	58	82:18
MeOH/H_2O (1:1)	LiI	45	90:10
H_2O[b]	LiI	26	80:20

[a] All reactions carried out with *p*-anisaldehyde (1 mmol), 1,3-dichloropropene (2 mmol), lithium (or sodium) iodide (2 mmol), and indium (1 mmol) at room temperature for 3 h. [b]Reaction time 15 h.

Table 2. Reaction of Benzaldehyde with 1,3-Dichloropropene[a]



1b

Solvent	Temp./°C	Yield/%	*syn*:*anti*
THF	0	88	79:21
THF	-78	59	81:19
MeOH	0	31	85:15
MeOH	-78	47	86:14
DMF	0	52	84:16
DMF	-60 to -30	83	92: 8

[a] All reactions carried out with benzaldehyde (1 mmol), 1,3-dichloropropene (2 mmol), lithium iodide (2 mmol), and indium (1 mmol) for 2 h.

perature did not affect significantly the diastereoselectivity. It is noted that, in contrast to the above reactions, the reactions of γ-alkyl substituted allylindium reagents, such as cinnamyl- and crotylindium reagents, with carbonyl compounds give *anti*-adducts predominantly.[4] The *syn*-selectivity observed in the present reaction may be explained by the fact that the intermediate γ-chloroallylindium reagent has a *Z*-configuration with an intramolecular chelation of the chlorine atom to the indium. Although the starting 1,3-dichloropropene was an *E*/*Z*-mixture (*E*/*Z*=68/32), *E*/*Z*-isomerization is possible during the oxidative addition of indium.[4] A chair-like cyclic transition state in which the chlorine atom adopts an axial-position furnishes the *syn*-adduct **1** (Scheme 2).

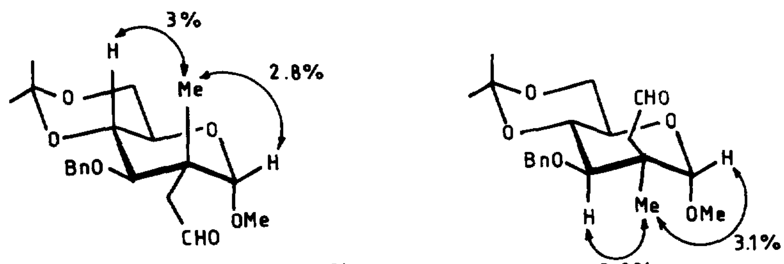
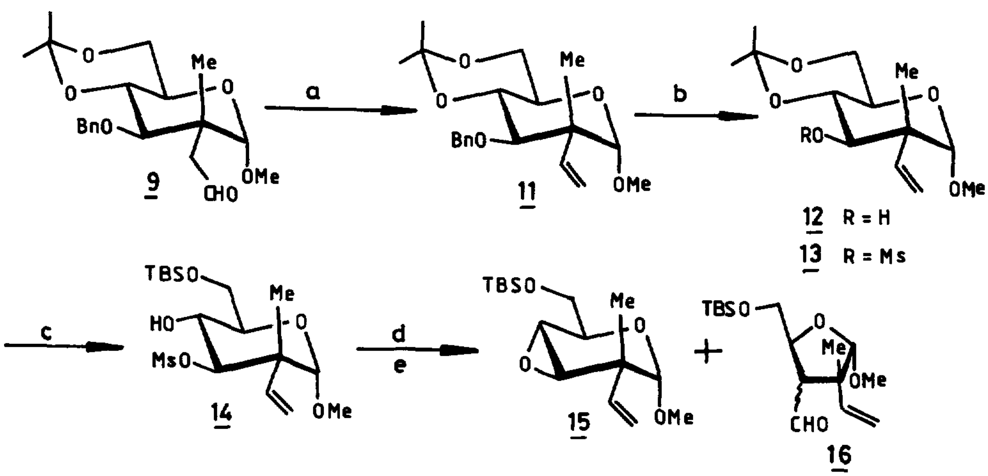


Fig. A

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 - $CHCl_3$

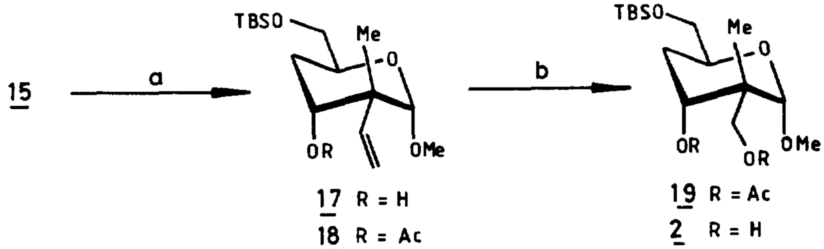
Scheme - 2



(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.

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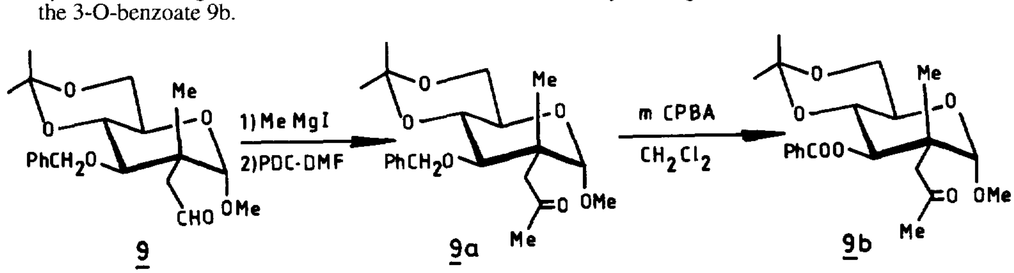
References and Notes

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. ^{1}H 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 ^{1}H-NMR, MS, HRMS and/or elemental analysis.

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