Tetrahedron Letters, Vol. 33, No. 23, pp. 3375-3376, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

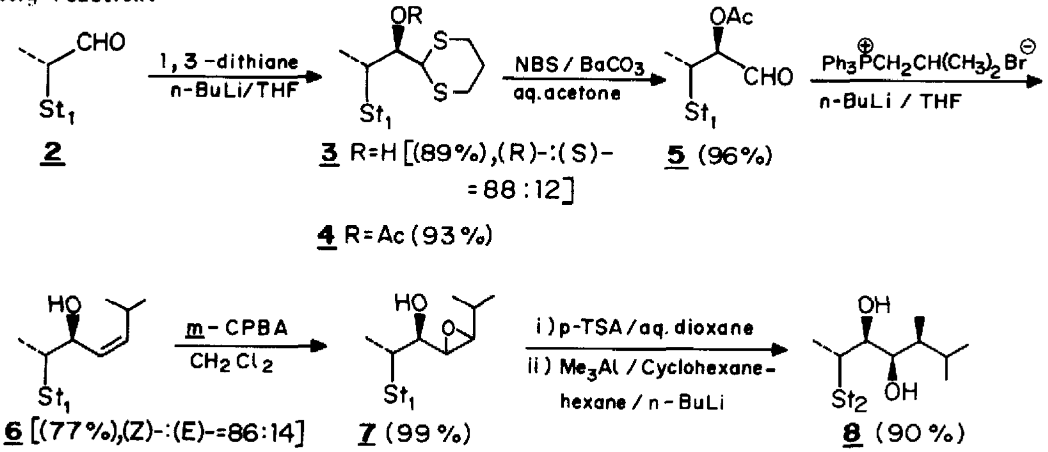
A Stereoselective Approach to the Brassinolide Side Chain via Wittig Reaction

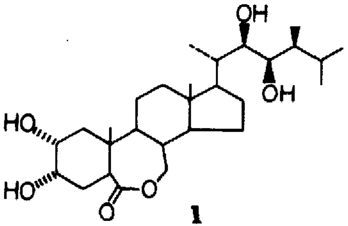
Braja G. Hazra*, Narshinha P. Argade and Padmakar L. Joshi

Division of Organic Chemistry(Synthesis)
National Chemical Laboratory, Pune 411 008, India.

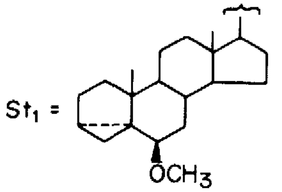
Abstract: Wittig reaction of the (22R)-acetoxy-23-aldehyde 5 furnished mainly the (22R)-hydroxy-(23Z)-olefin 6, which was further elaborated to the brassinolide side chain.

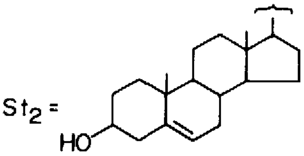
A number of useful methods for the stereoselective synthesis of the side chain[1] of plant growth promoter brassinolide 1[2] have been published. We herein report a simple, efficient and stereoselective conversion of C-22-aldehyde 2 to (22R)-acetoxy-C-23-aldehyde 5 and its further elaboration to construct the desired side chain in 1 via Wittig reaction.





1





Aldehyde 2 (1.0 mmol) readily available[3] from 3β-hydroxyandrost-5-ene-17-one was treated with 2-lithio-1,3-dithiane [prepared from 1,3-dithiane (2.0 mmol) and n-BuLi in hexane (3.0 mmol) at -5°C to 0°C, 1h] in THF under inert atmosphere at -20°C for 2h, followed by aqueous workup furnished the hydroxydithiane 3 in 89% yield [(22R) : (22S) = 88 : 12]. The desired (22R)-isomer on treatment with Ac_2O/py yielded

---

NCL Communication No.5357

acetoxydithiane **4** in 93% yield. Dethioacetalisation of **4** with NBS/BaCO$_3$ in aq. acetone at 25°C for 1h afforded (22R)-acetoxyaldehyde 5 in 96% yield. The synthesis of aldehyde 5 is of particular importance as a key intermediate for the construction of side chain in brassinosteroids using variety of strategies[4]. The Wittig olefination of 5 with isobutyltriphenylphosphonium bromide in presence of n-BuLi at 0°C to 25°C for 18h gave a mixture of (22R)-hydroxy-(23Z)-olefin **6** and the corresponding (23E)-isomer in 77% yield (23Z : 23E = 86 : 14). The olefin **6** has been synthesised earlier[5], the observed melting point and spectral data were found to be identical. The (23Z)-isomer **6** gave exclusively hydroxyepoxide **7** with m-CPBA in CH$_2$Cl$_2$ at 25°C, 1h in 99% yield. Considering the susceptibility of 3α,5-cycloether moiety to Lewis acids, the cycloether was first converted to corresponding 3β-hydroxyderivative (p-TSA, aq. dioxane, 60°C, 1h) followed by stereospecific epoxide opening at -75°C with excess of trimethylaluminium(10 equiv) in hexane-cyclohexane mixture (1:1) and n-BuLi(2 equiv) furnished the triol **8** as a single isomer in 90% yield. The triol **8** has been synthesised earlier[6,7] by different routes and its conversion to brassinolide is known[7].

This approach, therefore, provides an elegant, stereoselective and practical route to the brassinolide side chain starting from 3β-hydroxyandrost-5-ene-17-one taking the advantage of Wittig reaction.

Melting points and spectral data of desired isomers:

C.No.	M.P. °C	I.R.cm^{-1}	M$^+$	PMR (side chain)
3	163	3460	464	3.71(d,1H,J=8Hz), 3.87(d,1H,J=8Hz)
4	145	1750	506	2.07(s,3H), 3.71(d,1H,J=10Hz), 5.36(d,1H,J=10Hz)
5	56	1740,1750	416	2.16(s,3H), 5.08(d,1H,J=2Hz), 9.43(s,1H)
6	44	3450	414	1.00(d,6H,J=6Hz), 4.51(d,1H,J=6Hz), 5.27(m,2H)
7	70	3530	430	1.11(d,6H,J=7Hz), 2.70(dd,1H,J=4&4Hz), 3.08(dd,1H,J=4&5Hz), 3.62(d,1H,J=6Hz)
8	217	3530	432	0.90(d,6H,J=6Hz), 0.94(d,3H,J=6Hz), 3.60(m,3H)

Elemental analyses observed were within the limits of accuracy (± 0.3%).

Acknowledgement:- We are grateful to Dr.S.Rajappa, Head, Organic Chemistry(Synthesis) for constant encouragement and NPA thanks CSIR, New Delhi, for the award of R.A.

References:

1.(a) Adam,G.; Marquardt,V. Phytochemistry, **1986**, 25, 1787-1799. (b) Khripach,V.A.; Zhabinskiy,V.N.; Olkhovic,V.K. Tetrahedron Lett. **1990**, 31, 4937-4940. (c) Back,T.G.; Blazecka,P.G.; Krishna,M.V. Tetrahedron Lett. **1991**, 32, 4817-4818. (d) Zhou,W.S.; Huang,L.F.; Sun,L.Q.; Pan,X.F. Tetrahedron Lett. **1991**, 32, 6745-6748.

2.Grove,M.D.; Spencer,G.F.; Rohwedder,W.K.; Mandava,N.; Worley,J.F.; Warthen,J.D. Jr.; Steffens,G.L.; Flippen-Anderson,J.L.; Cook,J.C.Jr. Nature, **1979**, 281, 216-217.

3.Hazra,B.G.; Joshi,P.L.; Pore,V.S. Tetrahedron Lett. **1990**, 31, 6227-6230.

4.Mikami,K.; Loh,T.P.; Nakai,T. Tetrahedron Asymm. **1990**, 1, 13-16 and references cited therein.

5.Preus,M.W.; McMorris,T.C. J.Am.Chem.Soc. **1979**, 101, 3066-3071.

6,Takahashi,T.; Ootake,A.; Yamada,H.; Tsuji,J. Tetrahedron Lett. **1985**, 26, 69-72.

7.Fung,S.; Siddall,J.B. J.Am.Chem.Soc. **1980**, 102, 6580-6581.

(Received in UK 31 March 1992)