Pergamon

Tetrahedron Letters, Vol. 38, No. 10, pp. 1853-1856, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00211-6

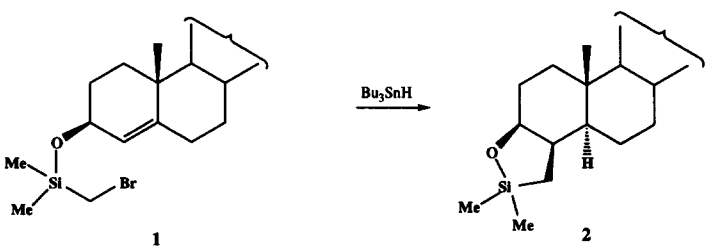
The First Example of a Highly Stereoselective Intramolecular Radical Cyclisation of a Cyclopentenol Derivative.

Paul R. Jenkins* and Andrew J. Wood.

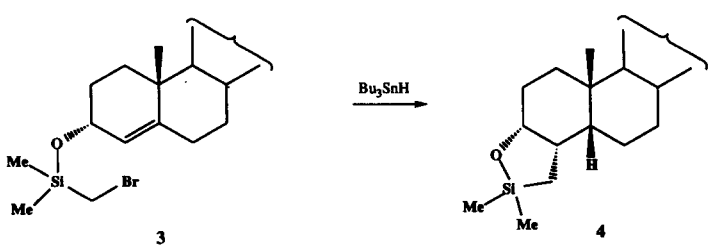
Department of Chemistry, Leicester University, Leicester, UK LE1 7RH.

Abstract: Silyl methylene radical cyclisation of a β-allylic cyclopentaannulated derivative of glucose leads to a single *cis* fused tricyclic ring system whereas the same cyclisation of the corresponding α derivative leads to a mixture of *cis* and *trans* fused products. These results can be explained by the preference for the formation of the *cis* fused 5,6-ring system even when this does not involve reaction from the least hindered side of the molecule. © 1997, Elsevier Science Ltd. All rights reserved.

Radical reactions have become very important in the synthesis of natural products.[1] The main reason for this is the availability of highly stereoselective radical reactions which solve significant synthetic problems.[2] One of the finest examples of this is the radical cyclisation of haloacetals developed by Stork,[3] this work has been extended to the similar cyclisation of silyl methylene radicals also from the Stork group[4] and by related studies by Nishiyama.[5] The silyl ether **1** cyclises in a *trans* addition to produce the *trans* fused steroid system **2** showing a preference for intramolecular *trans* addition across the olefin. Stereoselective *trans* addition is also observed in the the cyclisation of **3** even though this gives the less stable *cis* configuration of the AB ring of the steroid in structure **4**.



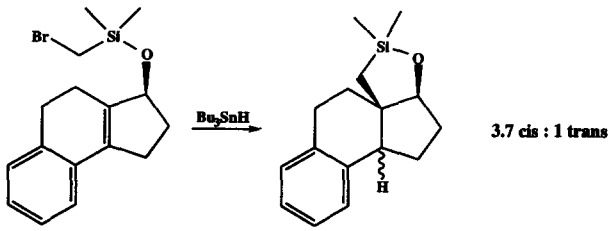
1 **2**



3 **4**

We have previously reported the Robinson annulation of a sugar methyl ketone[6] followed by a study of this radical cyclisation[7] in two epimeric carbohydrate examples. *Trans* addition was observed despite the fact that less stable *cis* fused 6,6 ring fusion was obtained. One of the products in this work was used to produce an enantiomerically pure cyclohexane derivative with a quaternary centre which is a synthon for the C-ring of taxoids.[8] *Trans* addition has been observed in other synthetic applications of this reaction,[9] including other carbohydrate examples.[10]

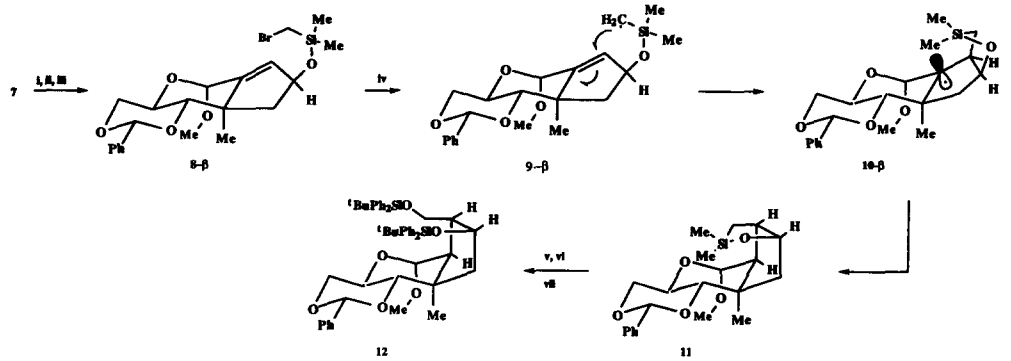
In contrast to these highly selective reactions the cyclisation of related cyclopentenols is far less selective, for example the cyclisation of **5** to **6** leads to a 3.7 : 1 mixture of *cis* and *trans* isomers respectively The reason for this seems likely to be that *trans* addition is leading to the far less stable *trans* fused 5,6 ring system in **6** therefore the less favourable *cis* addition pathway is also observed leading to a mixture of products.



5 **6**

More recently we have extended our work on carbohydrate annulation to the cyclopentaannulation of a glucose derivative using an intramolecular aldol reaction.[12] We now describe an application of our cyclopentaannulated glucose derivative in a strategy which leads to the first highly stereoselective radical cyclisation of a cyclopentenol.

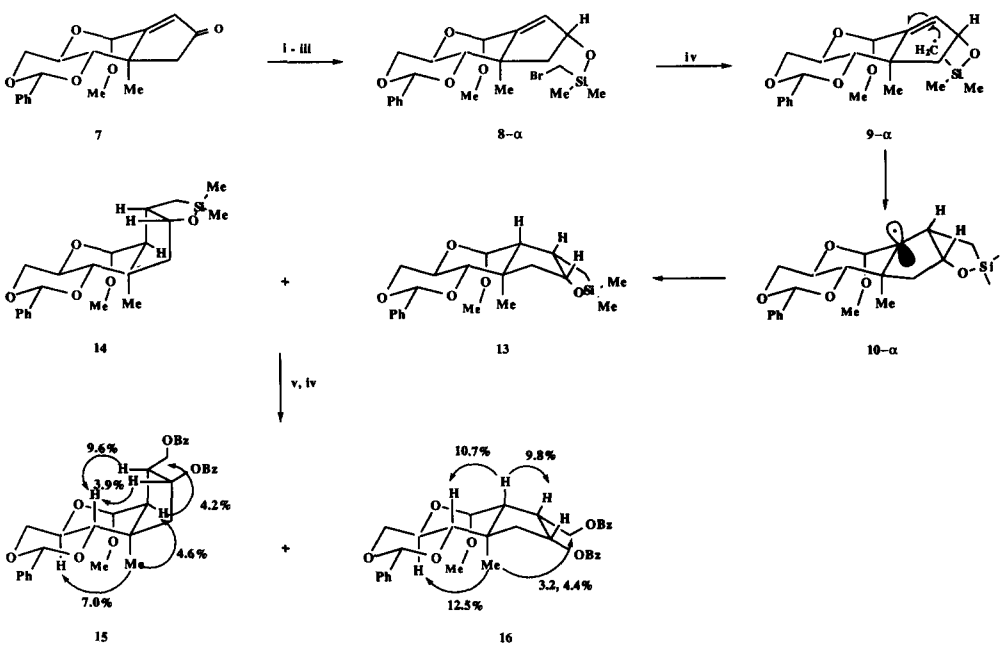
In Scheme 1 reduction of the enone **7** with sodium borohydride and cerium chloride to produces the β-allylic alcohol in a ratio of 8:1 with the α-isomer. We believe that this reduction is noteworthy because it occurs from the most hindered side of the molecule and is comparable to other examples so far recorded.[13] Formation of the silyl ether **8-β** and treatment with Bu_3SnH then produced the radical **9-β** which underwent intramolecular addition to furnish the intermediate radical **10-β**, this time the delivery of the hydride from the α face of the molecule leads to the *cis* fused 5,6 ring system **11** which was then converted to the bis-silylether **12**.



Scheme 1, Reagents: i, $NaBH_4$, $CeCl_3$, 25°C 95%, 8:1; ii, Et_3N, $(PhCO)_2O$, DMAP, CH_2Cl_2, 66%; iii, flash chromatography, K_2CO_3, MeOH, 67% **8-α**; iv, $BrCH_2Si(Me)_2Cl$, Et_3N, CH_2Cl_2, 89%; v, $NaCNBH_3$, AIBN, ^tBuOH,15h, 90°C; vi, H_2O_2, THF, MeOH, reflux, 15h, 83% (two steps), vii, Imidazole, $^tBuPh_2SiCl$, DMAP, CH_2Cl_2, 94%

Reduction of enone **7**, Scheme 2, gave the α-alcohol with an 8:1 selectivity using LS-Selectride® which was separated from the minor isomer by flash chromatography of the corresponding benzoate esters. The pure α-alcohol was then converted into the silyl ether **8-α**. Treatment with tributyltin hydride reduced the bromide to produce the radical **9-α** which underwent cyclisation leading to another radical **10-α** which can take a hydride from tributyl tin hydride on the α or β face of the molecule to produce a mixture of **13** and **14**. *Trans* addition as mentioned above leads to the product **13** in which the 5,6 ring junction is the less stable *trans* configuration, consequently the less favourable *cis* addition pathway also occurs leading to the *cis* product **14**. We believe that the mixture of **13** and **14** is obtained because *trans* addition does not produce the more stable *cis* fused 5,6 ring system **14**. The structure of the products **13** and **14** was determined by n.O.e measurements on the benzoate esters **15** and **16**, as shown in Scheme 1. The n.O.e effect between the angular methyl group and the ring junction hydrogen in **15** and its absence in **16** was the clearest indication of the assignment of the structures.

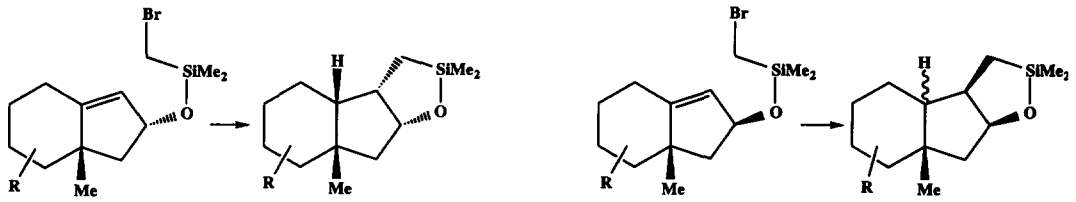
In contrast to the cyclisation of **8-α**, when **8-β** undergoes *trans* addition of the radical the more stable *cis* fused 5,6 ring system is produced and so only a single product **11** is obtained.



Scheme 2, Reagents: i, LS-Selectride, 91%, 8:1; ii, Et_3N, $(PhCO)_2O$, DMAP, CH_2Cl_2, 66%; iii, flash chromatography, K_2CO_3, MeOH, 67% **8-α**; iv, $BrCH_2Si(Me)_2Cl$, Et_3N, CH_2Cl_2, 89%; v, $NaCNBH_3$, AIBN, ^tBuOH,15h, 90°; vi, H_2O_2, THF, MeOH, reflux, 15h, 83% (two steps).

In conclusion we have shown that it is possible to carry out a stereoselective radical cyclisation on a cyclopentenol of general structure**17** if *trans* addition across the olefin leads to the more favoured *cis* fused 5,6-ring system **18**

only one product is obtained. Whereas the epimeric general structure **19** leads to a mixture of products **20** as *trans* addition leads to the less stable *trans* fused 5,6 ring system. We believe that these results will increase the utility of cyclopentenols in radical cyclisation reactions by indicating stereoselective options, further studies to consolidate these notions are in progress.



Acknowledgement: We are grateful to Pharmachemie B.V. Haarlem, Holland and a private bequest for a fellowship to A.J. Wood and to the EPSRC for financial support.

REFERENCES

1. C.P. Jasperese, D. P. Curran and T.L. Fevig. *Chem. Rev.*, **1991**, *91*, 1237.
2. D.P. Curran, N.A. Porter and B. Giese, *Stereochemistry of Radical Reactions*, VCH, Weinheim, 1996.
3. G. Stork, *Bull.Chem.Soc.Chim.Fr.*, **1990**, *127*, 675.
4. (a) G. Stork and M.J. Sofia, *J.Am.Chem.Soc.*, **1986**, *108*, 6826; (b) G. Stork and M. Khan, *ibid.*, **1985**, *107*, 500;
5. H. Nishiyama, T Kitajima, M. Matsumoto and K. Itoh, *J.Org.Chem.*, **1984**, *49*, 2298.
6. R.V. Bonnert , J. Howarth, P.R. Jenkins and N.J. Lawrence, *J. Chem.Soc., Chem.Commun.*, **1987**, 6; *Perkin Trans.1*, **1991**, 1225.
7. R.V. Bonnert , M.J. Davies, J. Howarth and P.R. Jenkins, *J.Chem.Soc., Chem. Commun.*, **1990**, 148; *Perkin 1.*, **1992**, 27.
8. A.N. Boa, J. Clark, P.R. Jenkins and N.J. Lawrence, *J.Chem.Soc., Chem. Commun.*, **1993**, 151.
9. A. Kurek-Tyrlik, J. Wicha and A. Zarecki, *J.Org.Chem.*, **1990**, *55*, 3484; G. Majetich, J.-S. Song, C. Ringold, G.A. Nemeth and M.G. Newton, *J.Org.Chem.*, **1991**, *56*, 3973.
10 V. Pedretti, J.M. Mollett and P. Sinay, *Carbohydr.Res.*, **1993**, *244*, 247.
11. G. Stork and R. Mah, *Tetrahedron Lett.*, **1989**, *30*, 3609.
12. A.J. Wood, P.R. Jenkins, J. Fawcett and D.R. Russell, *J.Chem.Soc., Chem. Commun.*, **1995**, 1567.
13. L.A. Paquette, Ed., *Encyclopedia of Reagents for Organic Synthesis*; J.Wiley and Sons: Chichester, Vol 2, p. 1032.

(*Received in UK* 21 *November* 1996; *revised* 28 *January* 1997; *accepted* 31 *January* 1997)