Tetrahedron Letters, Vol. 33, No. 5, pp. 671-674, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press plc

Studies Towards the Synthesis of Obtusenyne. Synthesis of the Hexahydrooxonin Nucleus

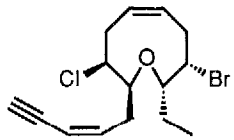
Neil R. Curtis, Andrew B. Holmes,* and Mark G. Looney

University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

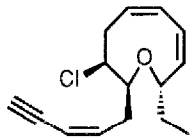
Key Words: Medium ring; Unsaturated lactone; Enolate hydroxylation; Tebbe methylenation; Hydrosilation.

Abstract: The advanced intermediate (the 2,3,4,7,8,9-hexahydrooxonin) **3** for the synthesis of the *Laurencia* oxonane natural product, obtusenyne **1** was prepared in 8 steps from the previously reported lactone **4**. The key transformations were the stereoselective enolate hydroxylation of the lactone **4** and a hydroxyl-directed intramolecular hydrosilation of the enol ether **12**.

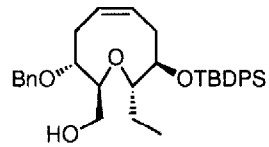
Our interest in the synthesis of medium ring oxygen heterocycles related to *Laurencia* metabolites[1] has led to a rather general approach to the synthesis of saturated (2,n)-disubstituted oxacycles, as well as to the synthesis of unsaturated lactones for elaboration to eight-membered and nine-membered marine natural products.[2] The advanced intermediate **3** (Figure 1) contains all the necessary latent functionality for conversion into both nine-membered targets, obtusenyne **1**[3] and brasilenyne **2**.[4] In this *Letter* we report on the conversion of the lactone **4**[5] into the hexahydrooxonin **3** by enolate hydroxylation, Tebbe methylenation and a hydroxyl-directed intramolecular hydrosilation of the resulting enol ether **12**.



1



2

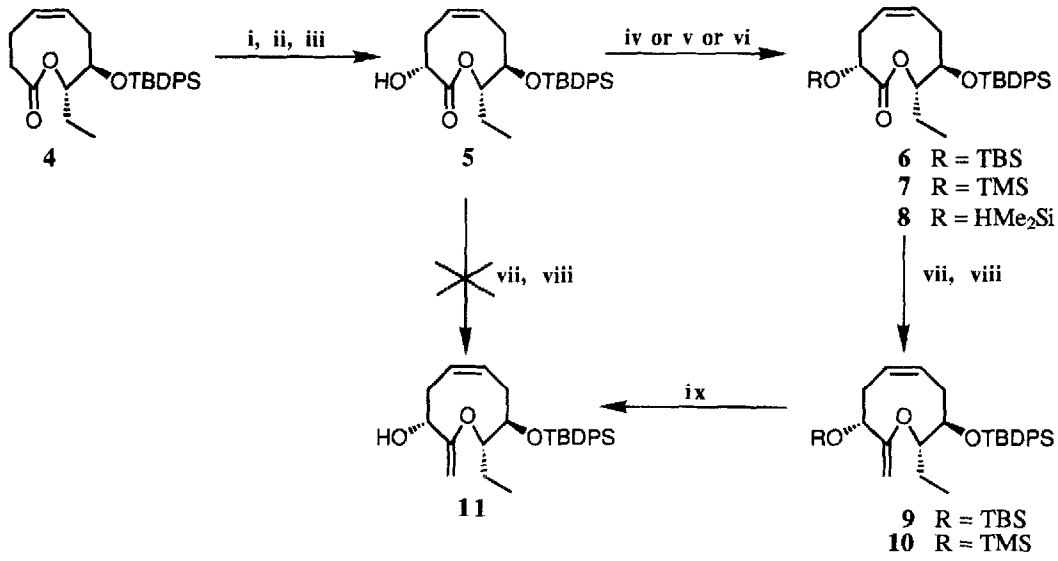


3

Figure 1

It was envisaged that introduction of the hydroxyl group at C-3 would be possible by selective hydroxylation of lactone **4**. Treatment of the potassium enolate of **4** with 2-(phenylsulphonyl)-3-phenyloxaziridine,[6] followed by a low temperature quench of the resulting intermediate afforded the α-hydroxy lactone **5** as a single diastereomer. The stereochemistry of the hydroxyl group relative to the other ring substituents was determined by *X*-ray crystallographic analysis of a rearrangement product derived from the methylene enol ether **9**.[7] Protection of the newly introduced hydroxyl group as the *tert*-butyldimethylsilyl (TBS) ether **6** prior to methylenation was necessary as direct conversion of **5** to the α-hydroxy enol ether **11** was unsuccessful. Treatment of **6** with the Tebbe reagent,[8] under standard conditions in the presence of 4-dimethylaminopyridine (DMAP),[9] afforded the protected enol ether **9**. However, removal of the *tert*-butyldimethylsilyl group with tetrabutylammonium fluoride (TBAF) was relatively unselective, and gave the required α-hydroxy enol ether **11** in moderate yield. The poor selectivity in the deprotection step was

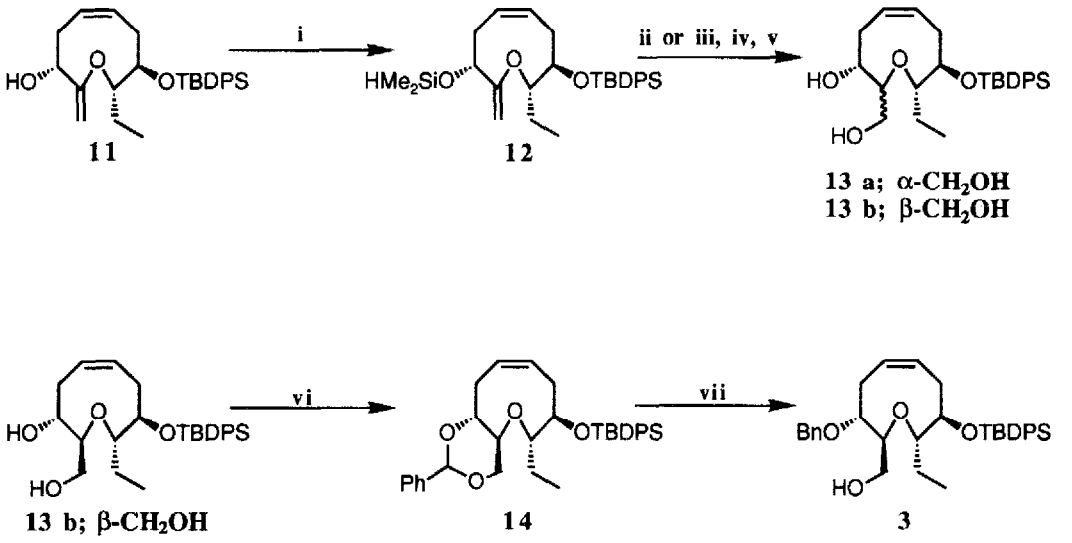
overcome by use of the more labile trimethylsilyl (TMS) protecting group. Protection and Tebbe methylenation of **7** gave in good yield the trimethylsilyl enol ether **10**, which upon treatment with TBAF afforded the α-hydroxy enol ether **11** in excellent yield.



Scheme 1

Scheme 1. *Reagents and conditions:* i, KHMDS (1.5 eq.), THF, toluene, -78 °C; ii, 2-(phenylsulphonyl)-3-phenyloxaziridine (1.5 eq.), -78 °C; iii, CSA (5 eq.), -78 °C to RT (79 % from **4**); iv, TBSCl, imidazole, DMF, 60 °C (98 %); v, TMSCl, Et_3N, THF (98 %); vi, $(HMe_2Si)_2NH$, cat. NH_4Cl, 60 °C (98 %); vii, Tebbe reagent (1.1 eq.), DMAP, THF, toluene, -40 °C to RT, 2.5 h; viii, NaOH, -15 °C to RT (R = TBS 94 %, R = TMS 90 %); ix, TBAF, THF (R = TBS 29-38 %, R = TMS 99 %).

We intended to functionalise the enol ether **11** by a directed hydrometallation reaction. In earlier studies of saturated eight- and nine-membered ethers we had made good use of hydroboration.[2] However, hydroboration of the unsaturated ethers **9** or **10**, under a variety of conditions, only gave products which were derived from elimination of the intermediate organoborane or competitive reaction at the endocyclic double bond. Functionalisation of the enol ether was finally achieved by an intramolecular hydrosilation reaction.[10] Preparation of the enol ether **12** directly from the protected lactone **8** by Tebbe methylenation resulted in cleavage of the dimethylsilyl group. However the silane **12** was eventually prepared by treatment of the α-hydroxy enol ether **11** with 1,1,3,3-tetramethyldisilazane. Intramolecular hydrosilation with platinum(0)/divinylsiloxane catalyst[10] in the presence of 1,1,3,3-tetramethyldisilazane gave the intermediate silacycle, which upon oxidative cleavage afforded, in 84 % yield, the triol derivatives **13a** and **13b** as a mixture of isomers (1 : 4.8 respectively). Greater selectivity (≤5:95) was achieved using (acetylacetonato)(norbornadiene)rhodium(I)[11] as the hydrosilation catalyst, thus avoiding the need to separate isomers, although the yield (61 %) was lower owing to partial cleavage of the dimethylsilyl group. Thus by appropriate choice of catalyst either the diol **13a** or **13b** could be prepared diastereoselectively. Chemoselective differentiation of the hydroxyl groups in the diol **13b** by acylation could not be achieved. However, formation of the benzylidene acetal **15** and selective reduction with DIBAL,[12] resulted in highly selective formation of the secondary benzyl ether **3**.



Scheme 2

Scheme 2. *Reagents and conditions:* i, $(HMe_2Si)_2NH$, cat. NH_4Cl, 60 °C (quantitative); ii, Rh(acac)(C_7H_8) 2 mol % catalyst, THF, reflux, 16 h; iii, bis(1,3-divinyl-1,1,3,3-tetramethyldisiloxane)/platinum(0) 2 mol % (0.1 M in toluene), $(HMe_2Si)_2NH$ 10 mol %, RT, 3 h; iv, EDTA.2Na.2H_2O; v, KOH, H_2O_2; vi, $C_6H_5CH(OMe)_2$, *p*-TsOH cat., C_6H_6, reflux, 19 h (92 %); vii, DIBAL, CH_2Cl_2, RT, 96 h (75 %).

In summary, preparation of the 2,3,4,7,8,9-hexahydrooxonin **3**, an advanced intermediate in the synthesis of obtusenyne **1** and brasilenyne **2**, was achieved in 8 steps and 29 % overall yield from the 5,6-unsaturated-2-oxonanone **4**.[5] The key transformations were the stereoselective enolate hydroxylation and the functionalisation of the enol ether using a novel hydroxyl-directed intramolecular hydrosilation reaction.[13] Aspects of the control of this last mentioned process are discussed in greater detail in the following *Letter*.

Acknowledgements

We thank the S.E.R.C. for supporting this research and Pfizer Central Research and I.C.I. Pharmaceuticals for financial support. We thank Dr. D.T. Thompson (Johnson Matthey) for a generous loan of (acetylacetonato)(norbornadiene)rhodium(I).

References and Footnotes

1. Moore, R. E. In *Marine Natural Products*; Scheuer, P.J.; Ed.; Academic Press: New York; **1978**, Vol. 1, Ch.2, p. 43;
   Erickson, K.L. In *Marine Natural Products*, Scheuer, P.J.; Ed.; Academic Press: New York; **1983**, Vol. 5, Ch. 4, p. 131;
   Faulkner, D. J. *Nat. Prod. Rep.*, **1984**, *1*, 251; *ibid* **1986**, *3*, 1; *ibid* **1987**, *4*, 539; *ibid* **1988**, *5*, 613; *ibid*, **1990**, *7*, 269; *ibid*, **1991**, *8*, 97;
   Garson, M.J. *Nat. Prod. Rep.*, **1989**, *6*, 143;
   For a review of the synthesis of medium ring ethers, see Moody, C.J.; Davies, M.J. In *Studies in Natural Product Chemistry*; Atta-Ur-Rahman; Ed.; **1991**, *in press*.

2. Carling, R.W.; Holmes, A.B. *J. Chem. Soc., Chem. Commun.*, **1986**, 565;
Carling, R.W.; Holmes, A.B. *Tetrahedron Lett.*, **1986**, *27*, 6133;
Clark, J.S.; Holmes, A.B. *Tetrahedron Lett.*, **1988**, *29*, 4333;
Carling, R.W.; Curtis, N.R.; Holmes, A.B. *Tetrahedron Lett.*, **1989**, *30*, 6081;
Carling, R.W.; Holmes, A.B. *J. Chem. Soc., Chem. Commun.*, **1986**, 325;
3 King, T.J.; Imre, S.; Öztunc, A.; Thomson, R.H. *Tetrahedron Lett.* **1979**, 1453;
Howard, B.M.; Schulte, G.R.; Fenical, W.; Solheim, B.; Clardy, J. *Tetrahedron* **1980**, *36*, 1747.
4. Kinnel, R.B.; Dieter, R.K.; Meinwald, J.; van Engen, D.; Clardy, J.; Eisner, T.; Stallard, M.O.; Fenical, W. *Proc. Natl. Acad. Sci. USA* **1979**, *76*, 3576.
5. Curtis, N.R.; Holmes, A.B.; Looney, M.G. *Tetrahedron*, **1991**, *47*, 7171.
6. Davis, F.A.; Sheppard, A.C. *Tetrahedron*, **1989**, *45*, 5703, and references cited therein;
Davis, F.A.; Vishwakarma, L.C.; Billmers, J.M.; Finn, J. *J. Org. Chem.*, **1984**, *49*, 3241;
Vishwakarma, L.C.; Stringer, O.D.; Davis, F.A. *Org. Synth.*, **1988**, *66*, 203;
Davis, F.A.; Chattopadhyay, S.; Towson, J.C.; Lal, S.; Reddy, T. *J. Org. Chem.*, **1988**, *53*, 2087.
7. Curtis, N.R.; Holmes, A.B.; Collins, I.; Tse Debenham, F.K.; Raithby, P.R. manuscript in preparation.
8. Tebbe, F.N.; Parshall, G.W.; Reddy, G.S. *J. Am. Chem. Soc.*, **1978**, *100*, 3611.
9. Pine, S.H.; Zahler, R.; Evans, D.A.; Grubbs, R.H. *ibid.*, **1980**, *102*, 3270;
Brown-Wensley, K.A.; Buchwald, S.L.; Cannizzo, L.; Clawson, L.; Ho, S.; Meinhardt, D.; Stille, J.R.; Straus, D.; Grubbs, R.H. *Pure Appl. Chem.*, **1983**, *55*, 1733, and references cited therein.
10. Tamao, K.; Nakagawa, Y.; Arai, H.; Higuchi, H.; Ito,Y. *J. Am. Chem. Soc.*, **1988**, *110*, 3712.
Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics*, **1983**, *2*, 1694.
11. For an intramolecular hydrosilation using a rhodium(1) catalyst in refluxing THF see: Anwar, S.; Davis, A.P. *Proc. R. Ir. Acad.*, **1989**, *89B*, 71.
12. Schreiber, S.L.; Wang, Z.; Schulte, G. *Tetrahedron Lett.*, **1988**, *29*, 4085.
13. All new compounds exhibited spectroscopic (IR and NMR) and analytical (combustion analysis and/or high resolution MS) data in accord with the assigned structure.

(Received in UK 31 October 1991)