Stereoselective Synthesis of 2-(1-Alkoxyalkyl)-3-hydroxy-5-substituted-tetrahydrofurans

Gregory W. Bradley and Eric J. Thomas*

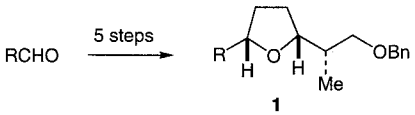
Department of Chemistry, The University of Manchester, Manchester M13 9PL, U.K.

Fax (0)161 275 4939; e.j.thomas@man.ac.uk

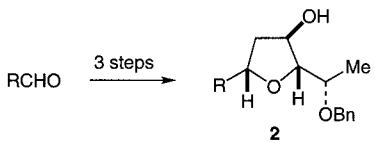
Received 18 February 1997

Abstract: Oxidation of toluene-*p*-sulfonates derived from 1-substituted-1,5-*syn*-5-benzyloxyhex-3-enols using osmium tetraoxide gives stereoselective access to 2-(1-alkoxyalkyl)-3-hydroxy-5-substituted-tetrahydrofurans. This procedure has been applied to synthesize bis-tetrahydrofurans.

The stereoselective synthesis of tetrahydrofurans is of considerable interest at present because of their presence in many natural products.[1] In the preceding communication, we report a short synthesis of 2,5-*cis*-disubstituted tetrahydrofurans **1** in which there is an alkyl-substituted stereogenic centre next to the tetrahydrofuranyl ring.[2] We now report a stereoselective synthesis of 2,5-*cis*-disubstituted tetrahydrofurans **2**, which possess an additional hydroxy substituent in the ring as well as an alkoxy-substituted stereogenic centre next to the ring.



1



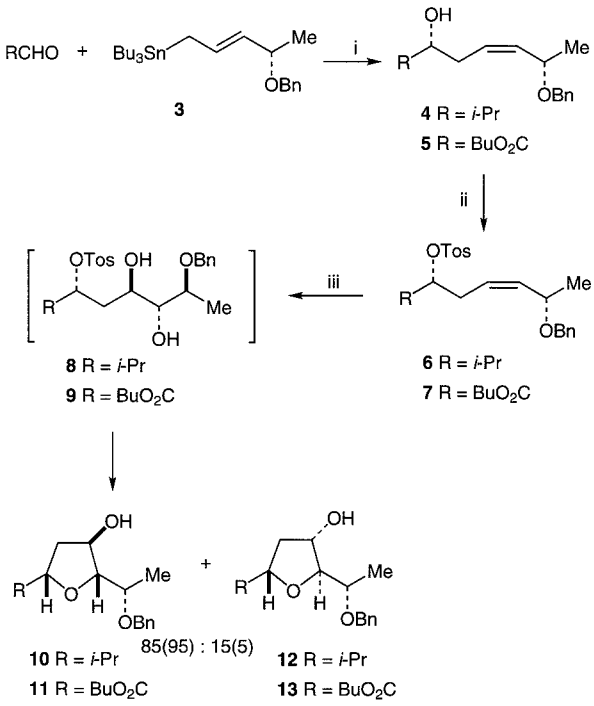
2

2-Methylpropanal is known to react with the allyltin trichloride formed *in situ* from the 4-benzyloxypent-2-enylstannane **3** and tin(IV) chloride, to give the 3,7-*syn*-product **4** with good stereocontrol.[3] Oxidation of the corresponding toluene-*p*-sulfonate **6** using osmium tetraoxide did not give the expected diol **8**. Instead, cyclisation took place under the reaction conditions, and the 2,5-*cis*- and 2,5-*trans*-substituted tetrahydrofurans **10** and **12** were isolated, **10** : **12** = 85 : 15 (87%), see **Scheme 1**.[4] Similar results were obtained for oxidation of the toluene-*p*-sulfonate **7**, which had been prepared in two steps from butyl glyoxalate. The 2,5-*cis*-substituted tetrahydrofuran **11** was the major product of the oxidation, with excellent stereoselectivity, **11** : **13** = 95 : 5.

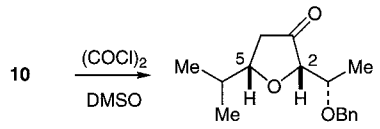
The structures of these tetrahydrofurans were consistent with their spectroscopic data. Stereochemistry was initially assigned to the products on the basis that the osmium tetraoxide had reacted preferentially with the alkenes to give diols **8** and **9**, in line with the well-established rules for hydroxylation of (*Z*)-allylic ethers.[5] Cyclisation with inversion would then give the 2,5-*cis*-disubstituted tetrahydrofurans **10** and **11** as the major products. This assignment was confirmed for the tetrahydrofuran **10** by oxidation to the ketone **14** (65%). In the ^{1}H NMR spectrum of this ketone, n.O.e. enhancements were observed between the 2- and 5-hydrogens.

To test the suitability of this approach for the synthesis of more complex tetrahydrofurans, the ester **11** was converted into the protected hydroxyaldehyde **15** which was taken through to the bis-tetrahydrofuran **17**, see **Scheme 2**.

The reaction of the aldehyde **15** with the allyltin trichloride prepared *in situ* from the pentenylstannane **3** proceeded with excellent stereocontrol (≥ 95:5) to give the 1,5-*syn*-product **16**. In this case, the *syn*-preference of the stannane is matched with the Felkin-Anh preference of the aldehyde.[3] The alkenol **16** was converted into its toluene-*p*-sulfonate



Scheme 1 ***Reagents:*** i, $SnCl_4$ (**4**, 84%, 1,5-*syn* : 1,5-*anti* = 93 : 7; **5**, 70%, 1,5-*syn* : 1,5-*anti* = 98 : 2); ii, toluene-*p*-sulfonyl chloride, pyridine (**6**, 95%; **7**, 86%); iii, osmium tetraoxide (cat.), N-methylmorpholine N-oxide (**10** and **12**, 87%, **10** : **12** = 85 : 15; **11** and **13**, 90%; **11** : **13** > 95 : 5).

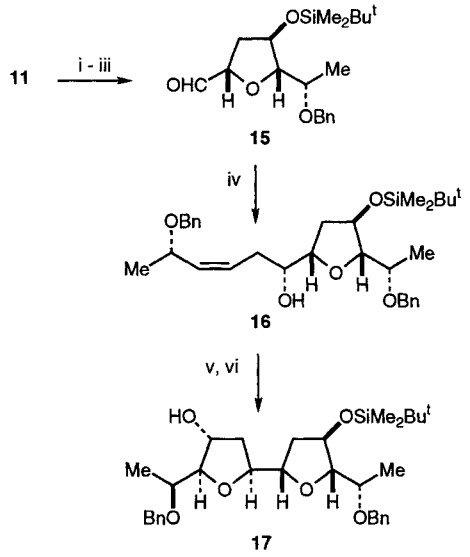


14

ester which was oxidised with osmium tetraoxide in the presence of *N*-methylmorpholine *N*-oxide to give a mixture of two diols, ratio *ca.* 8 : 1. The major diol was treated with sodium hydride which induced cyclisation to give the bis-tetrahydrofuran **17** (25%).[6]

For a second synthesis of bis-tetrahydrofurans, the aldehyde **15** was converted into the 5-[(tributylstannyl)propenyl]tetrahydrofuran **20**, see **Scheme 3**. Olefination using a Wittig procedure and reduction gave the allylic alcohol **18**. This was converted into its xanthate which was rearranged to the dithiocarbonate **19** by heating under reflux in toluene. Treatment with tributyltin hydride, under free radical conditions, gave the allylstannane **20**.

The allylstannane **20** was transmetallated with tin(IV) chloride, and the allyltin trichloride formed reacted with benzaldehyde. Two products were isolated and were identified as the alkenol **21** (50%) together with the dienol **24**, which accounted for the rest of the starting material. Similar results were obtained using tin(IV) bromide and 2-methylpropanal and butyl glyoxalate, which gave the alkenols **22** (70%) and **23** (50%) together with the dienol **24** (25-45%).



Scheme 2.*Reagents:* i,Bu^tMe_2SiCl, imidazole (73%); ii, DIBAL-H (93%); iii, $(COCl)_2$, dimethylsulfoxide; iv, **3**. $SnCl_4$ (74%); v, toluene-*p*-sulfonyl chloride, pyridine (65%); vi, osmium tetraoxide (cat.), N-methylmorpholine N-oxide, then sodium hydride (25%)

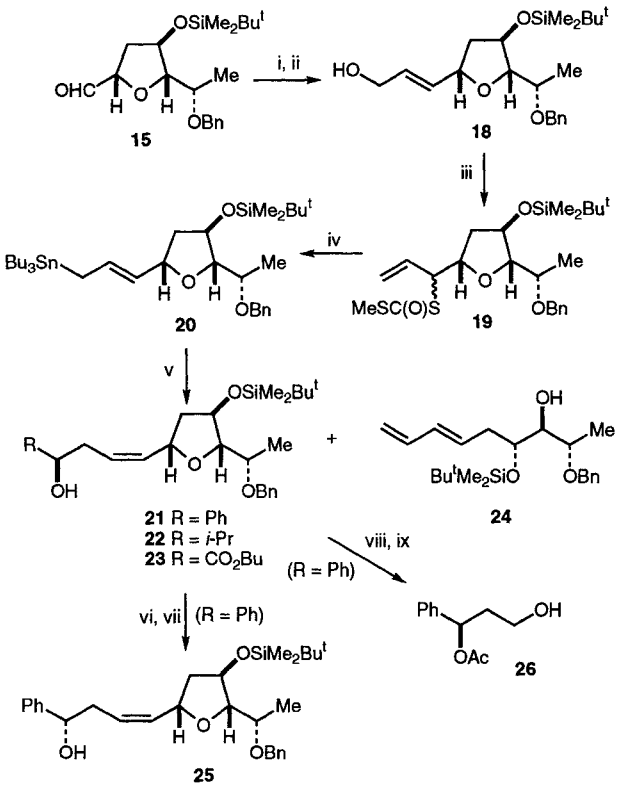
The stereoselectivity of formation of the alcohol **21** from benzaldehyde was estimated to be *ca.* 94 : 6 by HPLC. A sample of the epimer **25** was prepared by Mitsunobu inversion of **21** using *p*-nitrobenzoic acid followed by hydrolysis. The isomers **21** and **25** were clearly distinguishable by ^1H NMR, with **25** corresponding to the minor product detected by HPLC. The absolute configuration of the hydroxy-bearing carbon of alcohol **21** was established by acetylation and ozonolysis followed by a reductive work-up. This gave the dextrorotatory 3-acetoxy-3-phenylpropanol which is known to be the (*R*)-enantiomer **26**.[3,7] The structures of the other alkenols **22** and **23** were assigned by analogy. Interestingly, the stereoselectivity of the reactions of the stannane **20** with aldehydes would appear to be controlled by the 4-alkoxy substituent in just the same manner as observed for simpler stannanes, e.g. **3**.[3] The formation of the diene **24** involves a 1,4-elimination from the stannane. Similar eliminations have been observed before on treatment of heavily substituted 4-alkoxyalk-2-enyl-stannanes with Lewis acids,[8] and can compete with transmetallation of the stannane and reaction of the allyltin trichloride so formed with aldehydes. In the present case, improved conditions for the reaction with the aldehyde, e.g. the use of different Lewis acids, lower reaction temperatures, etc. were not examined.

Preliminary studies into the synthesis of bis-tetrahydrofurans were carried out using the 2-methylpropanal derived alkenol **22**. It was found that, after conversion of the alcohol into its toluene-*p*-sulfonate ester, oxidation using osmium tetraoxide was accompanied by direct cyclisation and gave the bis-tetrahydrofuran **27** albeit in only modest yield (29%).

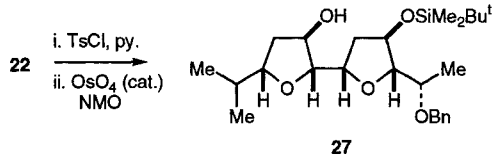
This work shows how stereoselective hydroxylation of the products obtained from reactions of allylstannanes with aldehydes with remote induction, can be used to prepare 2,5-*cis*-substituted tetrahydrofurans. This chemistry is to be applied to the synthesis of complex natural products.

Acknowledgements

We thank the E.P.S.R.C. for support (to G. W. B.)



Scheme 3.*Reagents:* i, $Ph_3P{=}CHCO_2Me$ (93%); ii, DIBAL-H (80%); iii, BuLi, carbon disulfide, MeI, then heat in toluene under reflux (84% from **18**); iv, Bu_3SnH, AIBN (78%); v, $SnCl_4$, RCHO (**21**, 55%) or $SnBr_4$, RCHO (**22**, 77%; **23**, 52%); vi, Ph_3P, $EtO_2CN{=}NCO_2Et$, *p*-$NO_2C_6H_4CO_2H$ (89%); vii, NaOH, MeOH (80%); viii, Ac_2O, triethylamine, DMAP (98%); ix, ozone, then dimethyl sulfide followed by $NaBH_4$.



References and Notes

(1) Harmange, J.-C.; Figadere, B. *Tetrahedron Asymmetry*, **1993**, *4*, 1711; Boivin, T. L. B. *Tetrahedron*, **1987**, *43*, 3309.

(2) Arista, L.; Gruttadauria, M.; Thomas, E. J. *Synlett*, **1997**, 627.

(3) McNeill, A. H.; Thomas, E. J. *Synthesis*, **1994**, 322; Thomas, E. J. *ChemTracts: Org. Chem.*, **1994**, 207.

(4) All new compounds were characterised by spectroscopic data and microanalysis and/or accurate mass measurement: data for **10**, $[\alpha]_D$ +25.6 (*c* 1.1, $CHCl_3$) (Found: C, 72.4; H, 9.0. $C_{16}H_{24}O_3$ requires C, 72.7; H, 9.15%. Found: M^+ + H, 265.1801. $C_{16}H_{25}O_3$ requires *M*, 265.1804); υ_{max} /cm^{-1} 3422, 1496, 1454, 1373, 1330, 1081, 1027, 736; δ_H 0.89 and 0.99 (each 3 H, d, *J* 7, CH_3), 1.32 (3 H, d, *J* 6, 2'-H_3), 1.6 - 2.00 (3 H, overlapping m, 4-H_2 and 1"-H), 2.15 (1 H, s, OH), 3.5 (1 H, m, 1'-H), 3.59 (1 H, dd, *J* 6.5, 3.5, 2-H), 3.84 (1 H, m, 5-H), 4.3 (1 H, m, 3-H), 4.51 and 4.69 (each 1 H, d, *J* 11.5, HC*H*Ph), and 7.36 (5 H, m, aromatic H); δ_C 16.6, 18.3, 19.2, 33.1, 37.9, 71.1, 74.3, 76.5, 83.7, 89.3, 127.7, 127.8, 128.5, and 138.5; *m/z* (CI) 282 (M^+ + 18, 100%) and 265 (M^+ + 1, 30).

(5) Evans, D. A.; Kaldor, S. W. *J. Org. Chem.*, **1990**, *55*, 1698; Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron*, **1984**, *40*, 2247; Brimacombe, J. S.; Hanna, R.; Kabir, A. K. M. S.; Bennett, F.; Taylor, I. D. *J. Chem. Soc., Perkin Trans. I*, **1986**, 815.

(6) Data for **17**: (Found: $M^+ + NH_4$, 574.3561. $C_{32}H_{52}NO_6Si$ requires *M*, 574.3564); υ_{max} /cm^{-1} 3432, 1454, 1373, 1257, 1094, 1073, 1030, 834; δ_H 0.05 [6 H, s, $Si(CH_3)_2$], 0.84 [9 H, s, $SiC(CH_3)_3$], 1.16 and 1.25 (each 3 H, d, *J* 6, CH_3), 1.61, 1.67, 1.78, and 1.86 (each 1 H, m), 1.91 (1 H, br s, OH), 3.43 and 3.49 (each 1 H, m), 3.56 (1 H, dd, *J* 6.5, 3.5, 5'-H), 3.72 (1 H, dd, *J* 5, 1.5, 5-H), 4.04 (2 H, m, 2-H and 2'-H), 4.3 (1 H, m, 4'-H), 4.33 (1 H, d, *J* 5, 4-H), 4.44, 4.46, 4.58 and 4.61 (each 1 H, d, *J* 11.5, HC*H*Ph), and 7.28 (10 H, m, aromatic H); *m/z* (CI) 574 ($M^+ + 18$, 90%).

(7) Mukaiyama, T.; Tomimori, K.; Oriyama, T. *Chem. Lett.*, **1985**, 1359.

(8) Menager, E.; Thomas, E. J. unpublished observations.