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MODEL STUDIES DIRECTED TOWARDS MICROALGAL POLYETHER TOXINS. USE OF 2-PHENYL-SULPHONYL CYCLIC ETHERS IN THE PREPARATION OF TRANS, SYN,TRANS α-ALKYL,β-HYDROXY-SUBSTITUTED TETRAHYDROPYRAN SUBUNITS

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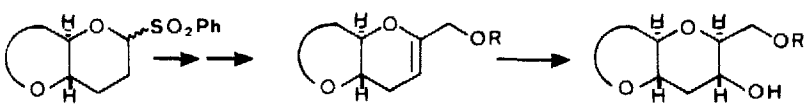
Key Words: 2-Phenylsulphonyl cyclic ethers; trans-fused polyether toxins.

Abstract: A synthesis of optically active C_7- and C_8-tetrahydropyranyl subunits with suitable functionalities for futher elaboration of trans-fused polyether toxins was achieved from glucal acetate via the use of 2-phenylsulphonyl intermediates. The bicyclic trans,syn,trans oxane-oxepanyl substructure **26** was prepared through the application of this methodology.

The generation and use of 2-benzenesulphonyl cyclic ethers is a procedure now widely practised in synthetic organic chemistry.[1] Direct substitution into this anomeric position by carbon nucleophiles represents a specially handy and clean process for preparing biologically active natural products possessing tetrahydropyran subunits with alkyl substituents adjacent to the oxygen atom ring.[2] Our recent need for stereodefined structural units of type III in the course of studies directed towards the synthesis of trans-fused polyether toxins[3] led us to investigate the role of these sulphones to yield cyclic hydroxymethyl enol ethers of type II, which can be easily hydrated to the hydroxypyranyl subunits of type III.[4]

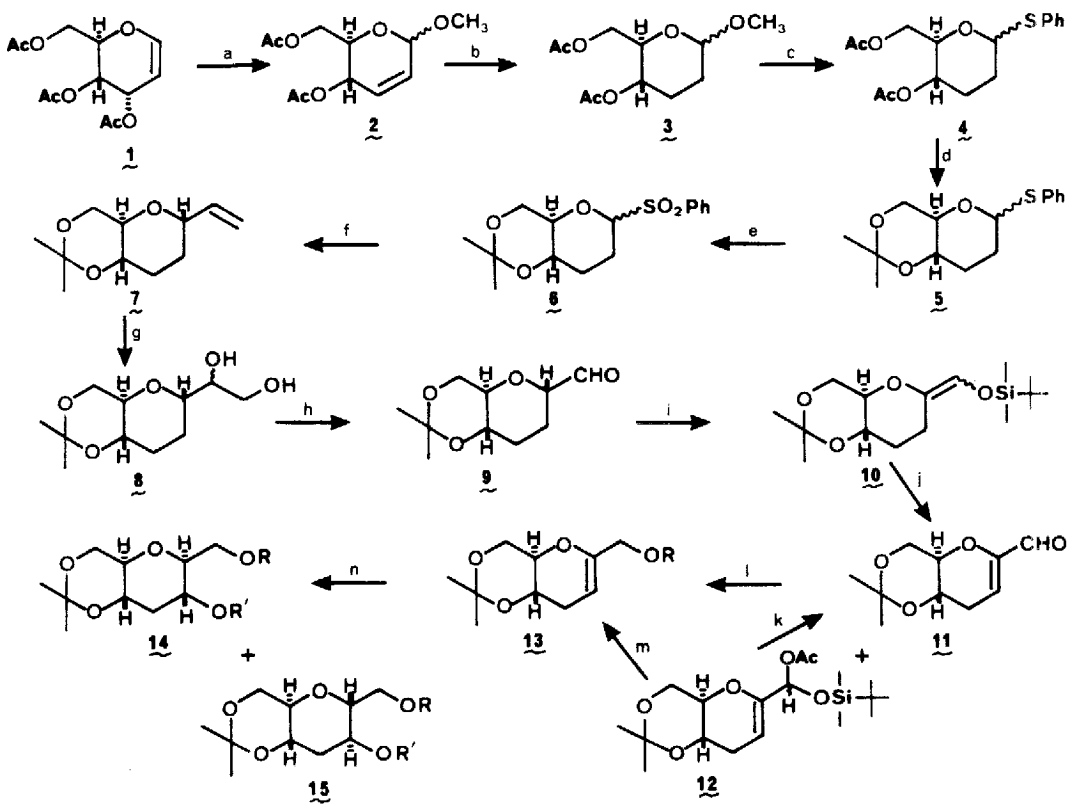


I II III

Scheme 1 outlines the general concepts that led to the development of the present technology to give the trans,syn,trans-substituted C_7-tetrahydropyranyl derivative **14** in 18-22 % overall yield starting from tri-O-acetyl-D-glucal (**1**).

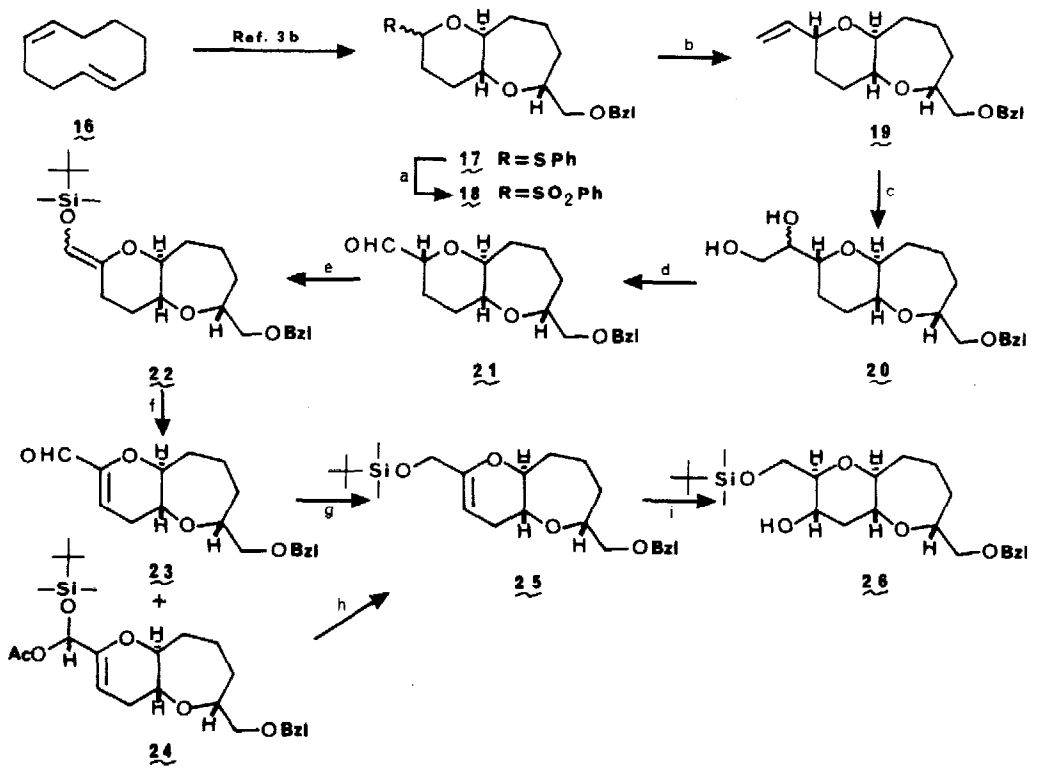
Optimun yields for the direct nucleophilic displacement of the sulphone moiety in **6** to give **7** were obtained by treatment of the filtered solutions of the vinyl zinc reagent in dry THF with the sulphone for several hours at

30-40°C. Direct dehydrogenation of the aldehyde **9** to **11** was achieved in high yield by the reaction of the E,Z-silyl enol ether mixture **10** with $Pd^{II}(OAc)_2$ in acetonitrile.[5] An interesting feature of this reaction is the formation of **12** which can be converted into **11** by base treatment or to the silyl derivative **13**, R=$SiMe_2Bu^t$, by reduction with DIBAH in quantitative yields. Compound **13**, R=$SiMe_2Bu^t$, was hydroborated and oxidized to give a 5:2 mixture of **14** and **15** (R=$SiMe_2Bu^t$, R'=H). The ratio was improved up to 9:1 by hydroboration of the benzyl ether derivative of **13**, R=Bzl.[6]



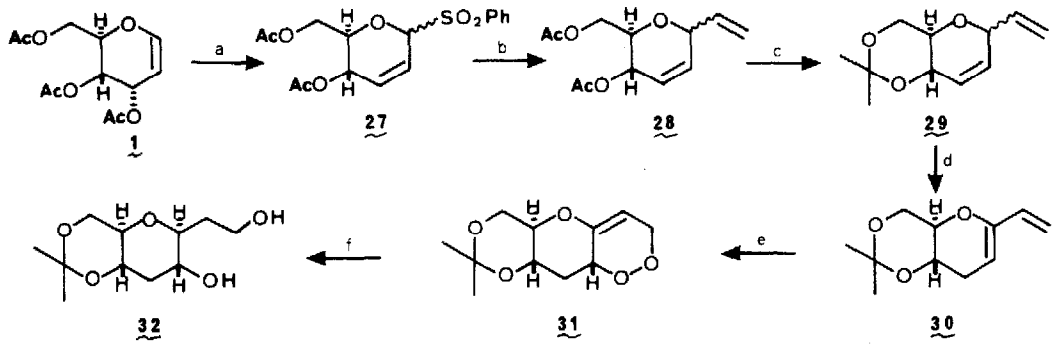
Scheme 1. Reagents and conditions: (a), MeOH (1.1 equiv.), $SnCl_4$ (1.1 equiv.), CH_2Cl_2 -78°C, 10 min, 83%,[ca. α:β (6:1) stereoselectivity]; (b), H_2/PtO_2, THF, 25°C, 4 h, 95%; (c), $PhSSiMe_3$ (1.5 equiv.), $Me_3SiOSO_2CF_3$ (1.2 equiv.), CH_2Cl_2, 0 - 25°C, 10 h, 86% [ca. α:β (4:1) stereoselectivity] ; (d), i, K_2CO_3 (0.1 equiv.), MeOH, 25°C, 1 h, 100%; ii, $Me_2C(OMe)_2$ (2.0 equiv.), $POCl_3$ cat., CH_2Cl_2, 25°C, 12 h, 92%; (e), m-CPBA (3.0 equiv.), $NaHCO_3$ (3.0 equiv.), EtOAc, 0 - 25°C, 5 h, 94%; (f), CH_2=CHMgBr (2.5 equiv.), $ZnBr_2$ (1.5 equiv.), THF, 25 - 40°C, 24 h (84%, ca. 17:1 stereoselectivity); (g), NMO (2.0 equiv.), OsO_4 (0.01 equiv.), THF:H_2O (1:1), 25°C, 12h, 100%; (h), $NaIO_4$ (3.0 equiv.), MeOH:H_2O (4:1), 25°C, 30 min., 84%; (i), t-$BuMe_2SiOTf$ (2.0 equiv.), Et_3N (2.0 equiv.), CH_2Cl_2, 0 - 25°C, 12 h , 72%,[E:Z (3:1) stereoselectivity] ; (j), $Pd(OAc)_2$ (1.1 equiv.), CH_3CN, 25°C, 12 h, 60% (**11**), 20% (**12**); (k), K_2CO_3 (0.1 equiv.), MeOH, 25°C, 100%; (l), i, DIBAH (2.0 equiv.), Et_2O, 0°C, 3 h, 95%, **13**,R=H; ii, t-$BuMe_2SiCl$ (1.1 equiv.), imidazole (2.2 equiv.), DMF, 0°C, 6 h,100%, **13**,R =$SiMe_2Bu^t$; (m), DIBAH (2.0 equiv.), Et_2O, 0°C, 4 h, 100%, **13**, R = $SiMe_2Bu^t$; (n), $BH_3.Me_2S$ (1.5 equiv.), THF, 25°C, 12 h, then excess NaOH, excess H_2O_2, 0°C, 1 h, 72%,**14**(R=$SiMe_2Bu^t$, R'=H), 18%, **15**(R=$SiMe_2Bu^t$, R'=H).

To explore the generality and scope of this method, the previously synthesized[3b] oxane-oxepanyl system **17** was subjected to the described sequence leading to the trans-fused oxabicyclic subunit **26** in excellent overall yield (40%) (Scheme 2).



Scheme 2. Reagents and conditions: (a), m-CPBA (3.0 equiv.), $NaHCO_3$ (3.0 equiv.), EtOAc, 25°C, 12 h, 96%; (b), CH_2=CHMgBr (5.0 equiv.), $ZnBr_2$ (2.5 equiv.), THF, 30 - 40°C, 5 h, 92%; (c), NMO (2.0 equiv.), OsO_4 (0.02 equiv.), THF:H_2O (1:1), 25°C, 10 h 100%; (d), $NaIO_4$ (3.0 equiv.), MeOH:H_2O (5:1), 25°C, 15 min., 81%; (e), t-$BuMe_2SiO^-f$ (2.0 equiv.), CH_2Cl_2, 0-25°C, 10 h [81%, E:Z (4:1) stereoselectivity]; (f), $Pd(OAc)_2$ (1.2 equiv.), CH_3CN, 25°C, 10 h, 58% (23), 28% (24); (g), i, DIBAH (2.0 equiv.), Et_2O 0°C, 4 h, 97%; ii, t-$BuMe_2SiCl$ (1.2 equiv.), imidazole (2.4 equiv.), DMF, 0°C, 5 h, 100%; (h), DIBAH (2.0 equiv.), $NaHCO_3$ (3.0 equiv.), Et_2O, 0°C, 3 h, 100%; (i), BH_3.Me_2S (1.5 equiv.), THF, 25°C, 8 h, then excess NaOH, excess H_2O_2, 0°C, 30 min., 82%.

Finally, an application of the described technology to yield the trans, syn,trans-substituted C_8-tetrahydropyranyl subunit **32** is outlined in Scheme 3. A sample of **32** was independently prepared from **14**, (R=H, R'=$SiMe_2Bu^t$), by treatment first with Tf_2O in CH_2Cl_2 in the presence of pyridine at -30°C to provide the unstable triflate which was subjected to single-carbon homologation by reaction with powdered sodium cyanide and HMPA followed by LAH reduction and further desilylation.



Scheme 3. Reagents and conditions: (a), $BF_3.Et_2O$ (1.1 equiv.), $PhSO_2H$ (2.0 equiv.), CH_2Cl_2, -78 - 0°C, 6 h, [97%, $\alpha:\beta$ (9:1) diastereoselectivity] ; (b), CH_2=CHMgBr (3.0 equiv.), $ZnBr_2$ (1.5 equiv.), THF, 25°C, 24 h, 85%; (c), i, K_2CO_3 (0.1 equiv.), MeOH, 25°C, 30 min., 100%; ii, $Me_2C(OMe)_2$ (2.5 equiv.), CSA cat., CH_2Cl_2, 25°C, 12 h, 86%; (d), KOBu^t (1.0 equiv.), DMSO, THF, 25°C, 0.5 h, 67%; (e), O_2 , hν , TPP cat., CH_2Cl_2, 25°C, 3 h, 53%; (f), H_2, PtO_2 cat., MeOH, 25°C, 62%.

The potential of the present technology in the synthesis of trans-fused polyether toxins is obvious and is currently under exploration in these laboratories.

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6. All new compounds exhibited satisfactory spectral and analytical and/or exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.

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