STEREOCONTROLLED SYNTHESIS OF TETRAHYDROFURANS AND TETRAHYDROPYRANS BY CYCLISATION OF HYDROXYSELENIDES

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Abstract - An efficient stereocontrolled synthesis of 2,3,5-trisubstituted tetrahydrofuran and 2,4,6-trisubstituted tetrahydropyran rings from homoallylic alcohols (**16**) and (**18**) was achieved by: *i*) epoxidation; *ii*) ring opening of the epoxide with sodium phenyl selenide; *iii*) cleavage of the TBDMS group with a stereoconvergent elimination of water followed by intramolecular oxygen nucleophile capture. The presence of a branching near to the selenonium ring made the attack in the *exo* mode faster than the attack in the *endo*/*exo* mode.

The stereoselective synthesis of tetrahydrofurans and tetrahydropyrans is of current interest owing to their occurrence in biologically active natural products such as polyether antibiotics.[1]

The widely employed synthetic approach to them is the formation of properly unsaturated alcohols that undergo an electrophilic attack on double bond followed by intramolecular oxygen nucleophile capture.[2] Suitable starting materials for these cyclizations are 4- and 5-alkenols.[2] The reactions of these two substrates are formally 5- and 6-*exo*-trig, and are favoured according to Baldwin's rules.[3]

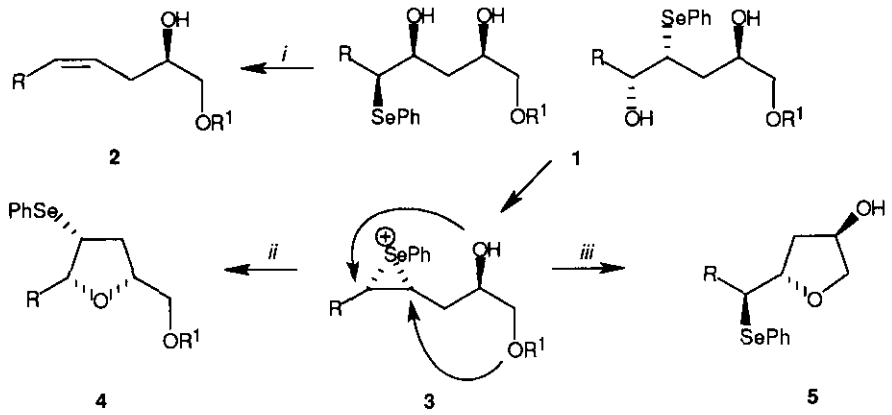
In a previous paper[4] we have described the stereoselective synthesis of 2,5-*cis*-disubstituted tetrahydrofurans based on the epoxidation of homoallylic alcohols, epoxide-ring opening with sodium phenyl selenide and the subsequent cyclisation of the hydroxy selenides.

In the synthesis[4] of the tetrahydrofuran containing fragment of (-)-nonactic acid and the pamamycins, the hydroxy-selenides had two hydroxyl groups protected as benzyl ether to avoid any interference in the reaction conditions adopted.

Now we are interested in the behavior towards acids of the hydroxy selenides as **1** where R^1 is a protecting group labile in the reaction conditions.

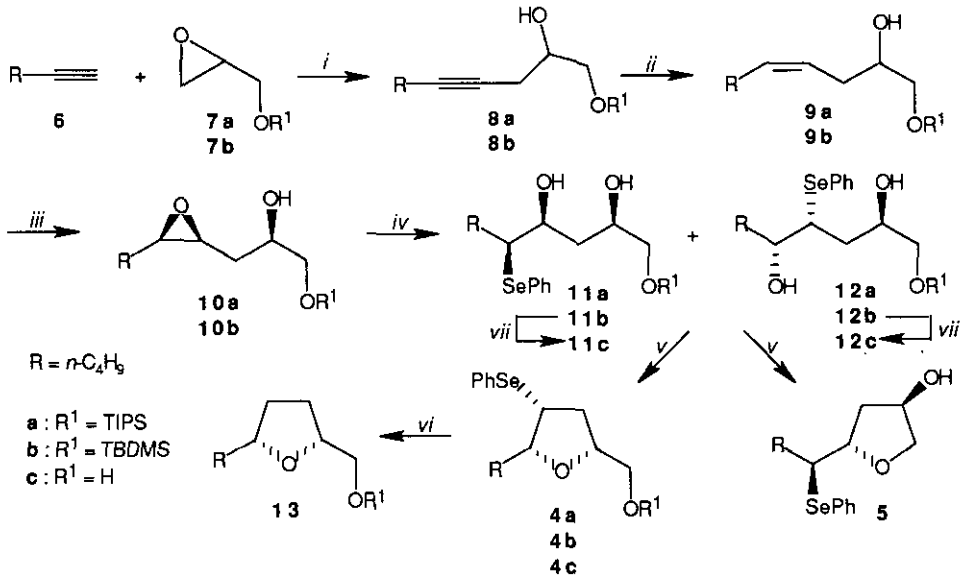
Three different reaction pathways could be followed by the treatment with perchloric acid: *i*) elimination of PhSeSePh to give the corresponding *cis*-alkene[5] (**2**); *ii*) stereoconvergent elimination of water to give **4**

via the selenonium ion (**3**)[6] (cyclisation in the *endo*/*exo*[7] mode); *iii*) cleavage of a very labile protecting group and a stereoconvergent elimination of water to give **5** *via* **3** (R^1 = H) (cyclisation in the *exo* mode).



In order to investigate this reaction we prepared the homoallylic alcohol (**9a**) as outlined in Scheme 1. Epoxidation using *tert*-butyl hydroperoxide and $VO(acac)_2$ gave the *syn*-hydroxy epoxide (**10a**) with useful stereoselectivity (95 : 5) with the configuration of the major epoxide being assigned by analogy with the literature.[8] Ring opening with sodium phenyl selenide gave a mixture (6 : 4) of the hydroxy selenides (**11a**) and (**12a**) which were separated. Both the hydroxy selenides were treated with a catalytic amount of perchloric acid in dichloromethane at room temperature. They gave the same mixture of products perhaps *via* the intermediate selenonium ion (**3**). Two principal products were isolated besides a small amount of the *cis*-alkene (**2**) (R^1 = H).

scheme 1



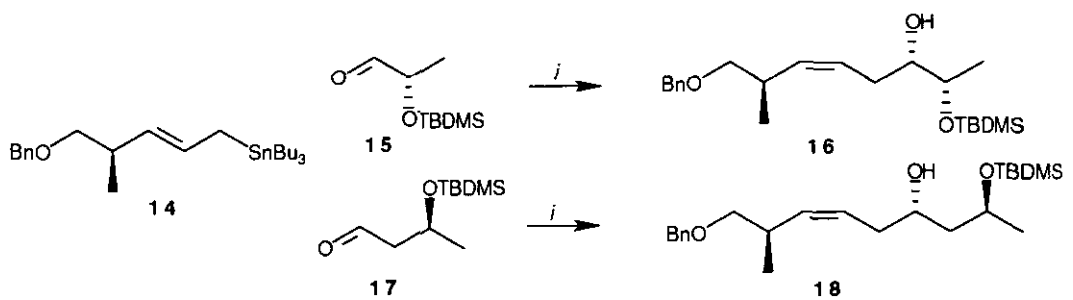
Reagents: *i*, BuLi, $BF_3.OEt_2$, THF, -78 °C, 80-85%; *ii*, H_2, Lindlar, EtOH, rt, 96-98%; *iii*, *t*-BuOOH, $VO(acac)_2$, CH_2Cl_2, rt, 85-88%; *iv*, $(PhSe)_2$, $NaBH_4$, EtOH, rt, 80-84%; *v*, $HClO_4$, CH_2Cl_2, rt; *vi*, *n*-Bu_3SnH, AIBN, toluene, reflux, 80%; *vii*, TBAF, THF, 92%.

These two products were identified as the 2,5-*cis*-disubstituted tetrahydrofurans (**4a**) (58%) and (**4c**) (17%); tetrahydrofuran (**5**) was detected only in traces. The structure of these products was proven by the usual spectroscopic and analytical techniques.[9] Compound (**4c**) is simply formed by deprotection of **4a** in the reaction conditions. The *cis*-geometry was confirmed by NOESY spectrum of compound (**13**) obtained by the reduction of compound (**4c**) with tributyltin hydride and AIBN.

We next examined the cyclisation of the hydroxy-selenides (**11b**) and (**12b**) with the primary hydroxyl group protected with the TBDMS group to see if, in the reaction conditions adopted, the removal of the more labile protecting group allows the *exo* attack faster than the *endo*/*exo* attack. However, we again obtained the 2,5-*cis*-disubstituted tetrahydrofurans (**4b**) and (**4c**) with a bigger amount of compound (**4c**) (70%) respect to **4b** (15%). In these reactions, the *endo*/*exo* attack takes place faster than the cleavage of the protecting group and the subsequent *exo* attack. The comparison of these results with our previous investigation[4] and with the literature data[6] showed that when R is a linear chain the yields of cyclisation in the *endo*/*exo* mode are high, but when there is a branching in the α position to the selenonium ring the yields are lower.

Therefore, we decided to remove the protecting group to carry out the reaction of the hydroxy selenides (**11c**) and (**12c**) with a catalytic amount of perchloric acid in order to study which cyclisation takes place faster. The reaction was very fast giving two major products that were identified as the tetrahydrofurans (**4c**) (attack in the *endo*/*exo* mode) and (**5**) (attack in the *exo* mode) in almost the same yield (40%). No regiocontrol was then observed because the carbon atoms of the selenonium ring are both secondary. Furthermore, we believe that high degree in the regiocontrol could be obtained if a branching in the α position is present considering that the yields of the cyclisations in the *endo*/*exo* mode are not high.[4] In order to check this idea, we prepared (2S, 3S, 7R)-8-benzyloxy-2-*tert*-butyldimethylsilyloxy-7-methyloct-5-en-3-ol (**16**) and (2S, 4S, 8R)-9-benzyloxy-2-*tert*-butyldimethylsilyloxy-8-methylnon-6-en-4-ol (**18**) in enantiomeric pure form using the tin chemistry.

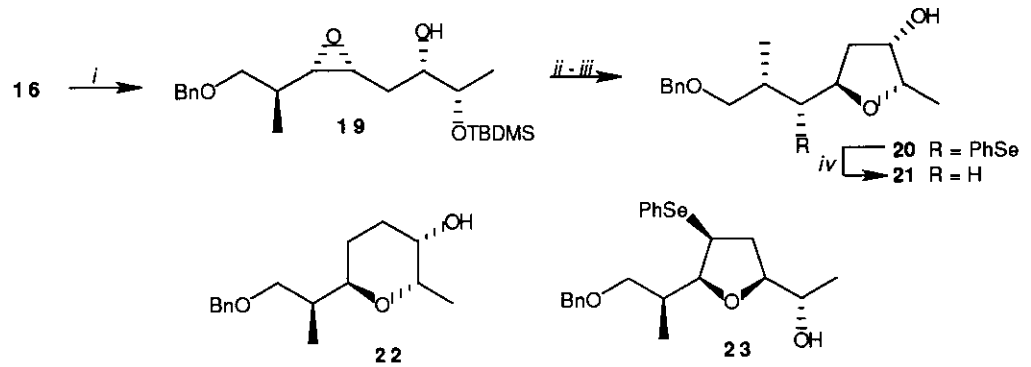
Thus, we were able to realise an efficient stereocontrolled synthesis of a 2,3,5-trisubstituted tetrahydrofuran and a 2,4,6-trisubstituted tetrahydropyran rings using this methodology. First we carried out the reaction between (4R)-4-methyl-5-benzyloxy-2-pentenyl(tributyl)stannane[10] (**14**) and the aldehydes (**15**) and (**17**). Excellent stereoselectivity in favor of the 3,7-*anti*-products was observed (77%, 3,7-*anti* : 3,7-*syn* 95/5 for **16**; 83%, 3,7-*anti* : 3,7-*syn* 95/5 for **18**). In the reaction with aldehyde (**15**), the observed product is consistent with *si*-face attack which is *anti* to Felkin-Anh's model.



Reagents: *i*, **14**, $SnCl_4$, CH_2Cl_2, -78 °C.

Epoxidation of **16** with *t*-BuOOH and $VO(acac)_2$ gave the expected *syn*-hydroxy epoxide (**19**) (55%, 87/13 diasteromeric ratio). The epoxide (**19**) was treated with sodium phenyl selenide. The reaction proceeded smoothly, affording the intermediates hydroxy selenides. The unseparable mixture[11] of the two hydroxy-selenides was treated with perchloric acid in dichloromethane.

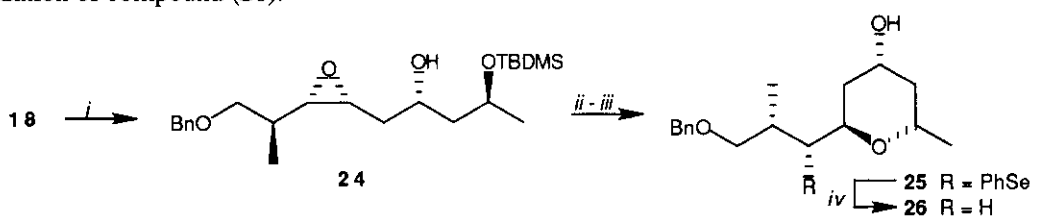
The treatment with perchloric acid gave a clean reaction: cleavage of the TBDMS group and a stereoconvergent elimination of water to give **20** *via* the corresponding selenonium ion.



Reagents: *i*, *t*-BuOOH, $VO(acac)_2$, CH_2Cl_2, rt, 55%; *ii*, $(PhSe)_2$, $NaBH_4$, EtOH, rt, 81%; *iii*, $HClO_4$, CH_2Cl_2, rt, 62%; *iv*, *n*-Bu_3SnH, AIBN, toluene, reflux, 85%.

This procedure has permitted the stereoselective synthesis of a trisubstituted 2,5-*anti*-tetrahydrofuran ring; this reaction shows stronger stereochemical control than approach based on direct selenocyclisation.[12] Moreover, the opening of the epoxide ring by the sodium phenyl selenide followed by the closure *via* the corresponding selenonium ion have inverted the configuration of the tetrahydrofuran ring that can be obtained by treatment with *t*-BuOOH and $VO(acac)_2$.[13]

Tetrahydrofuran (**20**) was finally reduced (Bu_3SnH, AIBN, toluene, 85%) to give **21**. Structure (**22**) that could be obtained from a cyclization on C-6, due to an attack of the oxygen atom on C-2, was rejected by analysis of ^1H NMR and COSY spectra of compound (**21**) and structure (**23**) that could be obtained from an attack on C-6 of the oxygen atom on C-3 was rejected by analysis of ^1H NMR of ketone obtained by Swern oxidation of compound (**20**).



Reagents: *i*, *t*-BuOOH, $VO(acac)_2$, CH_2Cl_2, rt, 80%; *ii*, $(PhSe)_2$, $NaBH_4$, EtOH, rt, 89%; *iii*, $HClO_4$, CH_2Cl_2, rt, 70%; *iv*, *n*-Bu_3SnH, AIBN, toluene, reflux, 88%.

In the same manner, compound (**18**) gave the *syn*-hydroxy-epoxide (**24**) (80%, 88/12 diasteromeric ratio). Ring opening of the epoxide (**24**) gave the intermediate hydroxy-selenides[11] that were treated with perchloric acid to give the trisubstituted 2,6-*trans*-tetrahydropyran ring (**25**). Compound (**25**) was then

reduced (Bu_3SnH, AIBN, toluene, 88%) to give **26**. The tetrahydropyran structure was confirmed by ^1H NMR and COSY spectra of compound (**26**) and by ^1H NMR spectrum of ketone obtained by Swern oxidation.

These two synthesis confirmed our idea that the branching in the α position of the chain plays an important role. It made the *endo/exo* attack slower than the deprotection of the hydroxyl group and the subsequent *exo* attack. This methodology can be applied to the synthesis of substituted tetrahydrofurans as well as tetrahydropyrans and efforts to broaden the scope and develop synthetic application are in progress.

AKNOWLEDGMENTS

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9. Selected spectroscopic data: compound (**21**) ^1H NMR (250 MHz) δ 0.99 (3H, d, J = 6.8 Hz, 2'-CH_3), 1.27 (3H, d, J = 6.4 Hz, 2-CH_3), 1.39 (1H, ddd, J = 13.7, 8.2 and 5.3 Hz, 1'-H), 1.52 (1H, ddd, J = 9.1, 6.9 and 2.1 Hz, 4-H overlapped with 1H, OH), 1.80 (1H, ddd, J = 13.7, 8.2 and 5.3 Hz, 1'-H'), 2.01 (1H, m, 2'-H), 2.42 (1H, ddd, J = 14.1, 7.8 and 6.9 Hz, 4-H') 3.28 (1H, dd, J = 9.0 and 6.3 Hz, 3'-H), 3.37 (1H, dd, J = 9.0 and 5.8 Hz, 3'-H'), 3.70 (1H, dq, J = 6.4 and 2.7 Hz, 2-H), 3.89 (1H, m, 5-H), 4.11 (1H, m, 3-H), 4.50 (2H, s, $PhCH_2$), 7.33 (5H, m, aromatic H); ^{13}C NMR (62 MHz) δ 14.58, 17.79, 31.60, 41.62, 43.25, 73.52, 74.45, 76.03, 76.64, 79.11, 128.10, 128.20, 128.98, 139.40. Compound (**26**) ^1H NMR (300 MHz) δ 1.00 (3H, d, J = 6.7 Hz, 2'-CH_3), 1.16 (2H, m, 3-H and 5-H overlapped with 2-CH_3), 1.23 (3H, d, J = 6.2 Hz, 2-CH_3 overlapped with 1H, 1'-H), 1.70 (1H, ddd, J = 14.9, 8.2 and 5 Hz, 1'-H'), 1.82 (1H, s, OH), 1.94 (2H, m, 3-H' and 5-H'), 2.09 (1H, m, 2'-H), 3.28 (1H, dd, J = 9.0 and 6.8 Hz, 3'-H), 3.42 (3H, m, 2-H, 6-H and 3'-H'), 3.79 (1H, m, 4-H), 4.53 (2H, s, $PhCH_2$), 7.35 (5H, m, aromatic H); ^{13}C NMR (75 MHz) δ 17.21, 21.77, 29.97, 40.18, 41.59, 42.96, 68.26, 71.57, 72.93, 73.18, 76.12, 127.45, 127.59, 128.33, 138.78.

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