[1,4]-SPh Shift Cyclisations or [1,2]-SPh-Cyclisations as Alternative Cascade Sequences for Stereocontrolled Synthesis of Substituted Tetrahydrofurans

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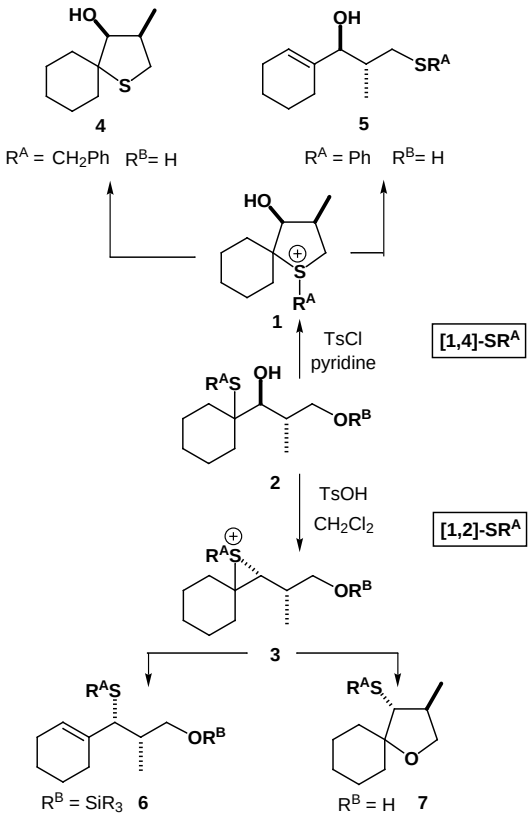
Abstract: Treatment of 4-phenylsulfanyl-1,5,7-triols with TsCl in pyridine gives substituted tetrahydrofurans by [1,4]-SPh participation via a five membered sulfonium salt and then capture by a tethered nucleophile. Acid catalysed rearrangement gives other THFs by [1,2]-SPh migration and cyclisations.

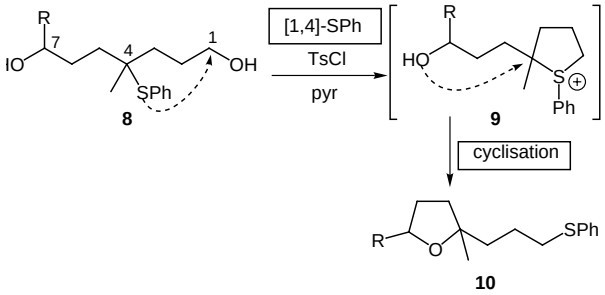
Key words: cyclisations, heterocycles, stereoselective synthesis, sulfur chemistry, rearrangements

In a series of papers we have reported rearrangements on diols such as **2** involving stereospecific [1,2]- or [1,4]-SR^A migrations via three-membered **3** or five-membered **1** cyclic sulfonium salts to give single diastereoisomers or enantiomers of a variety of products.[3-7] The two types of migration can be complementary: heterocycles **4** and **7** as well as allylic derivatives **5** and **6** are related by the exchange of oxygen and sulfur functionality.[8]



Scheme 1

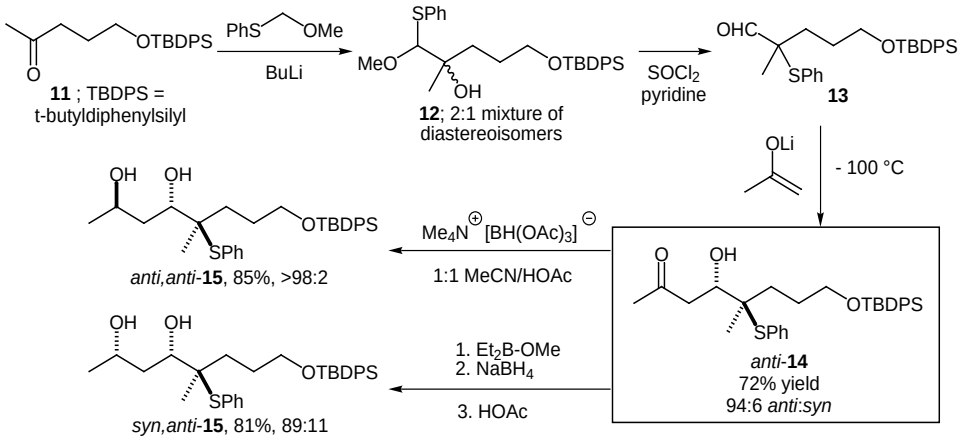
We now report that combining aspects of the two migrations in a cascade reaction sequence leads to a new synthesis of tetrahydrofurans. The idea was to capture the intermediate **9** in the [1,4]-SR^A migration by a nucleophilic OH group in the style of the formation of **7** during [1,2]-SR^A migration. Open chain 1,7-diols **8** were required with a tertiary PhS group at C-4 so that tosylation would be chemoselective at the primary alcohol and formation of the sulfonium salt **9** by [1,4]-SPh participation would be followed by cyclisation of the remaining (secondary) alcohol to give the THF **10**. The arrows show only the direction of cyclisation.



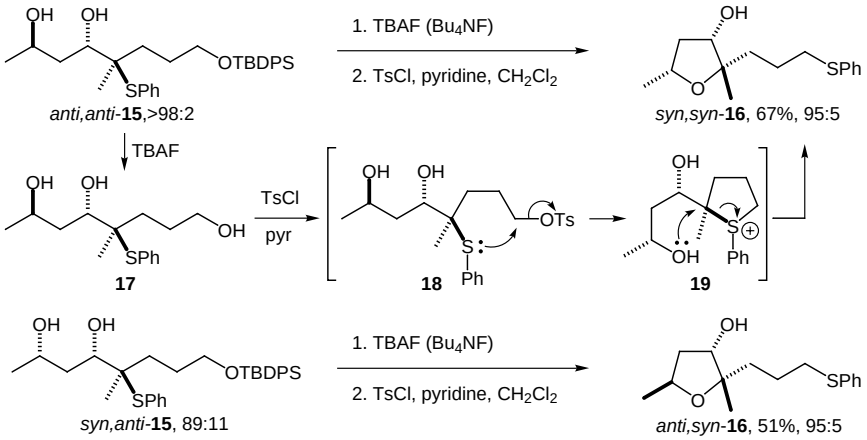
Scheme 2

The synthesis of the required starting materials is outlined below. Starting from TBDPS-protected 4-hydroxy-pentan-2-one[9] **11**, aldehyde **13** was obtained by the Jansen and de Groot methodology[10] using pyridine as the base in the rearrangement step of **12**. The aldehyde **13** has previously been reported.[11] Addition of the lithium enolate of acetone to **13** gave the hydroxy ketone *anti*-**14** as a separable mixture of diastereoisomers (94:6 in favour of the Felkin-Anh product) in moderate yield. Reduction of *anti*-**14** using either Prasad's *syn*-[12] or Evans' *anti*-selective reagents[13] gave the diols *anti,anti*-**15** and *syn,anti*-**15** in good yields and excellent diastereoselectivities. The extra hydroxyl group in **15** compared to **8** at C-5 allows control over the relative stereochemistry at C-4 and C-7 and offers greater versatility in rearrangement.

Preliminary attempts to effect cyclisation were disappointing, firstly since, after deprotection of diols *syn,anti*-**15**, the corresponding triols could not been isolated in pure form due to their poor solubility. Secondly our usual conditions[8] for [1,4] PhS migration (TsCl in neat pyri-



Scheme 3



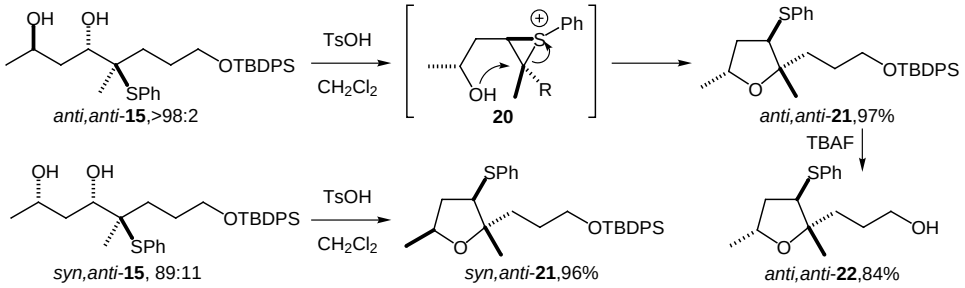
Scheme 4

dine) gave only insoluble oligomeric material. However reaction conditions were found to effect the [1,4] migration–cyclisation cascade, using dilute reaction mixtures (deprotection of the diol **15** with TBAF and *in-situ* cyclisation of the triol **17** with TsCl and pyridine all at 0.01 M in CH_2Cl_2). The THFs *syn,syn*-**16** and *anti,syn*-**16** were obtained in moderate yield as an inseparable 95:5 mixture of diastereoisomers (relative GC-MS area).[14]

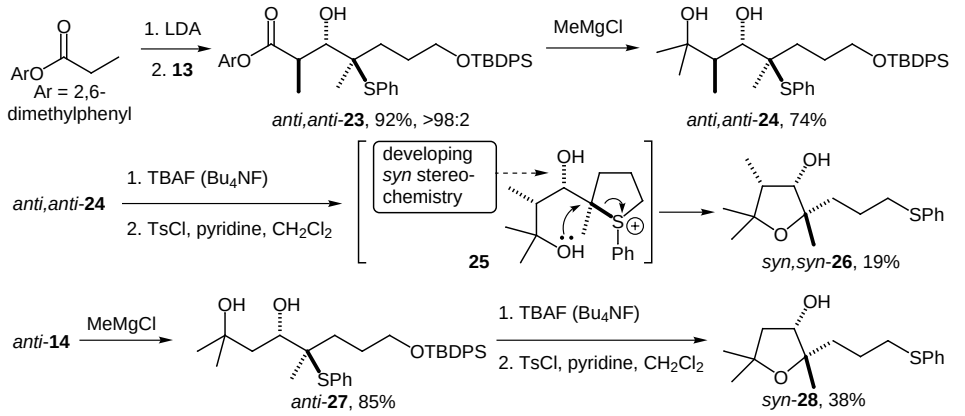
The reaction presumably proceeds via chemoselective tosylation at the primary hydroxyl group, formation of the five membered sulfonium ion **19** and intramolecular cyclisation by the tethered nucleophile. Cyclisation onto the five membered ring sulfonium ion **19** is a favourable 5-*exo-tet* process (by Baldwin's rules[15]). The reaction was shown to be stereospecific with inversion at the migration origin and retention at all other stereogenic centres by 500 MHz NOESY spectroscopy on *syn,syn*-**16** and *anti,syn*-**16**. We believe the minor isomer to be the epimer at the tertiary migration origin C-2; epimerisation presumably occurs by ring opening and reclosing of the sulfonium ion.

In order to exclude the possible isomers resulting from the rearrangement under [1,2]-SPh participation (we have previously observed products resulting from acid catalysed [1,2]-SPh participation, presumably due to the presence of pyH^+ in the reaction mixture)[16] we decided to synthesise these compounds as well. Treatment of diols *anti,anti*-**15** and *syn,anti*-**15** under our usual conditions (TsOH in CH_2Cl_2) gave THFs *anti,anti*-**21** and *syn,anti*-**21** in almost quantitative yield. The reaction presumably proceeds via the episulfonium ion **20** and is stereospecific with inversion at the migration origin and terminus. Deprotection with TBAF gave alcohol *anti,anti*-**22**, which is both a positional isomer (OH and PhS exchanged) of *syn,syn*-**16** and in a different stereochemical series. This compound (*anti,anti*-**22**) was not identical to either minor diastereoisomer found in the [1,4]-SPh migration-cyclisation sequence of reactions.

Synthesis of a diol with a tertiary alcohol as potential nucleophile was accomplished using Heathcock's *anti*-aldol methodology[17] to give the hydroxy ester *anti,anti*-**23** and, after further addition of two equivalents of MeMgCl, the diol *anti,anti*-**24**. Cyclisation of diol *anti,anti*-**24** with a tertiary alcohol as an internal nucleophile gave the THF *syn,syn*-**26** in only poor yield. Moreover overlapping of the Me-NMR signals (500 MHz) prevented an unambigious assigment of stereochemistry. That this poor result is partly because of the developing *syn* stereochemistry in the migration **25** was shown by the more successful rearrangement of *anti*-**27**. Yields are still not as good as when a secondary alcohol is the nucleophile.



Scheme 5



Scheme 6

In conclusion we have shown that chemoselective tosylation of 4-PhS-1,5,7-triols takes place at the primary hydroxy group and gives, via a five membered cyclic sulfonium ion and subsequent nucleophilic attack by the tethered nucleophile, highly substituted tetrahydrofurans in which three stereogenic centres are built up.

The reaction proceeds with inversion at the migration origin and retention at all other stereogenic centres. Furthermore it was shown that in this reaction, unlike the cyclisations following [1,2]-SPh participation, secondary alcohols are better nucleophiles than tertiary alcohols. The same 4-Ph*S*-1,5,7-triols undergo cyclisation following [1,2]-SPh shift in acidic conditions to give positional and diasteroisomeric THFs. All new compounds gave satisfactory ^1H and ^{13}C NMR spectra and MS data.[18]

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References and Notes

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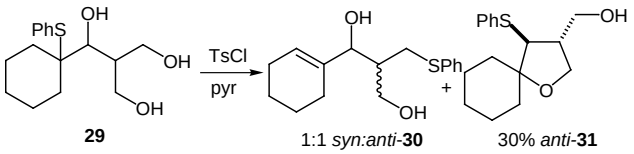
(3) Aggarwal, V. K.; Coldham, I.; McIntyre, S.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1991**, 451.
(4) Villa, M.-J.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2953.
(5) Eames, J.; Heras, M. A. d. l.; Jones, R. V. H.; Warren, S. *Tetrahedron Lett.* **1996,** *37*, 1117.
(6) Chibale, K.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2411.
(7) Coldham, I.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1637.
(8) (a) Djakovitch, L.; Eames, J.; Jones, R. V. H.; McIntyre, S.; Warren, S. *Tetrahedron Lett.* **1995**, *36*, 1723. (b) Eames, J.; Jones, R. V. H.; Kuhnert, N.; Warren, S. *Tetrahedron Lett.* **1998**, *39*, 1247.
(9) Protection of 4-hydroxy-pentan-2-one turned out in our hands to be very capricious, since formation of a silylated cyclic five-membered acetal, resulting from a highly favourable 5-*exo-tet* process, was a competing reaction. Protection was achieved by extremely slow addition of TBDPSCl to a stirred solution of the alcohol in DMF/imidazole and stirring for 14 days.
(10) (a) Groot, A. d.; Jansen, B. J. M. *Synthesis* **1985**, 434. (b) Groot, A. d.; Jansen, B. J. M. *Tetrahedron Lett.* **1981,** *22*, 887.
(11) McIntyre, S.; Sansbury, F. H.; Warren, S. *Tetrahedron Lett.* **1991**, *32*, 5409.
(12) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.
(13) Chapman, K. T.; Evans, D. A.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
(14) As an alternative product, an eight membered ring resulting from a 8-*exo-tet* cyclisation, would be feasible but could be excluded by MS data.
(15) Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, 734. Attempted stereoselective [1,4]-PhS migration on the triol **29** gave a 1:1 mixture of the two products of a [1,4]-SPh shift,

syn- and *anti*-**30**, and about 30% of the product of a [1,2]-SPh shift, the THF *anti*-**31**



Scheme 7

(17) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.

(18) Selected experimental and spectroscopic details;
Typical experimental procedure for [1,2] cascade sequence: e.g. THF *syn-anti*-**21**: TsOH (3.4 mg, 0.02 mmol) was added to a stirred solution of diol *syn-anti*-**15** (52 mg, 0.1 mmol) in CH_2Cl_2 (5 mL). The solution was refluxed for 5 min, cooled to room temperature and filtered through a silica plug. The solvent was removed under reduced pressure to give the THF *syn-anti*-**21** (48 mg, 96%) as an oil; ν_{max} (film, $CDCl_3$)/cm^{-1} 1550 (SPh); δ_H(400MHz, $CDCl_3$) 7.67-7.20 (15 H, m, Ar), 4.07 (1 H, dq *J* 9.8 and 5.9, C*H*CH_3), 3.65 (2H, t, J 6.2, CH_2OSi), 3.44 (1 H, dd, *J* 11.0 and 6.8, C*H*SPh), 2.45 (1 H, q, *J* 5.64, C$H_A$$H_B$), 1.70-1.85 (2H, m, CH_2), 1.52-1.59 (2H, m, CH_2), 1. 25 (3 H, s, CH_3), 1.26 (3 H, d, *J* 6.13, CH_3CH) and 1.03 (9H, s, *t*-Bu); δ_C(100MHz, $CDCl_3$) 137.4, 137.2, 135.8, 131.3, 129.6, 129.0, 127.6, 126.8 (Ar), 82.2 (CO), 72.0 (CHO), 64.0 (COSi), 56.3 (*C*HSPh), 42.2 (CH_2), 33.1 (CH_2), 30.4 and 28.2 (CH_3) 27.4 (CH_2), 27.1 (t-Bu) and 22.1 (*C*H_3CH); m/z 489 (15%, M - CH_3), 447 (25, M - *t*-Bu), 337 (M - *t*-Bu - PhS) and 110.0 (20, PhSH).
Typical Procedure for [1,4] Cascade: e.g. preparation of *syn*-**28**: TBAF (0.3 mL, 1 M solution in THF, 0.3 mmol) was added to a solution of diol *anti*-**27** (0.16 g, 0.3mmol) in THF (3 mL) and stirred for 20 h at r.t. The solvent was removed under reduced pressure and the residue was redissolved in CH_2Cl_2 (30 mL). Pyridine (0.5 mL) and TsCl (54 mg, 0.3 mmol) was added, and the solution was stirred overnight. The organic phase was washed with HCl (5 mL, 3 M), $NaHCO_3$ (5 mL), brine (5 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was further purified by column chromatography (light petroleum (40-60 °C)/ether 9:1) to give the THF *syn*-**28** (31 mg, 38%) as an oil; ν_{max} (film, $CDCl_3$)/cm^{-1} 3500-3300 (OH) and 1551 (PhS); δ_H(200MHz, $CDCl_3$) 7.44-7.20 (5H, m, SPh), 3.79 (1H, m, C*H*OH), 2.92-2.95 (2H, m, CH_2SPh), 2.21-2.28 (2H, m, CH_2CHOH), 1.95-2.01 (1H, m, C$H_A$$H_B$), 1.63-1.79 (3H, m, $CH_A$$H_B$ and CH_2), 1.21 (6H, s, 2 x, CH_3) and 1.19 (3H, s, CH_3); δ_C(50MHz, $CDCl_3$) 136.5, 128.8, 128.6, 125.7 (SPh), 87.1 (C-O), 82.6 (CO), 82.0 (*C*HOH), 44.2 (*C*SPh), 34.7, 32.2, 28.1 and 25.6; m/z 280 (2%, M) and 110 (30, PhS).

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