Pergamon

Tetrahedron Letters, Vol. 37, No. 26, pp. 4581-4584, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00851-9

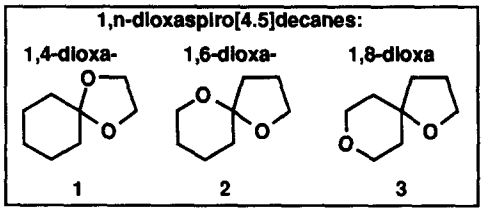
Stereochemically Controlled Synthesis of 1,8-Dioxaspiro[4.5]decanes and 1-Oxa-8-thiaspiro[4.5]decanes by Phenylsulfanyl Migration

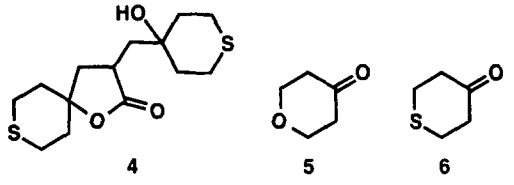
Jason Eames,[a] Maria A. de las Heras,[a] Ray V. H. Jones[b] and Stuart Warren*[a]

[a]University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England
[b]Process Technology Departement, ZENECA Grangemouth Works, Earls Road, Grangemouth FK3 8XG, Scotland

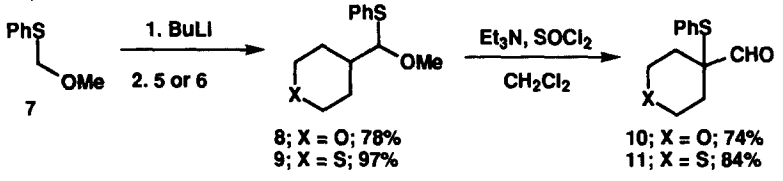
Abstract: Single enantiomers and diastereoisomers of 2- and 3-alkyl-4-phenylsulfanyl-1,8-dioxa- and 1-oxa-8-thiaspiro[4.5]decanes can be prepared in good yield by acid-catalysed phenylsulfanyl migration. Either *syn* or *anti* stereochemistry can be selected by aldol reactions or by reduction of hydroxy-ketones. Copyright © 1996 Elsevier Science Ltd

Dioxaspiro[4.5]decanes where the two oxygen atoms form an acetal, such as **1** and **2**, are well known and easy to prepare. Other isomers, like the 1,8-dioxaspiro compounds **3**, are little known, especially with stereochemistry, though the corresponding lactones have been made,[1-3] and there is a report that some substitued 1,7- and 1,8-dioxaspiro compounds are herbicidal.[4] The 1-oxa-8-thiaspiro[4.5]decane system is even rarer though some lactones are known and the X-ray structure of **4** has been reported.[1] We report syntheses of single diastereoisomers and enantiomers of substituted 1,8-dioxa and 1-oxa-8-thiaspiro[4.5]decanes by PhS migration using the known ketones[5-7] **5** and **6** as starting materials.

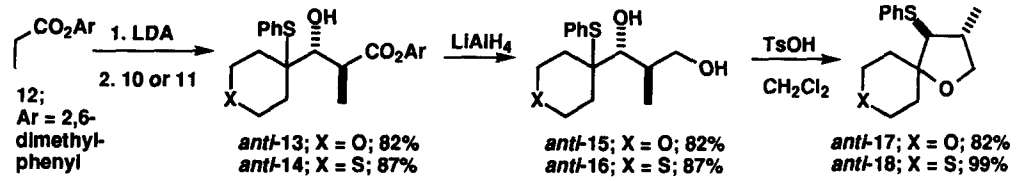


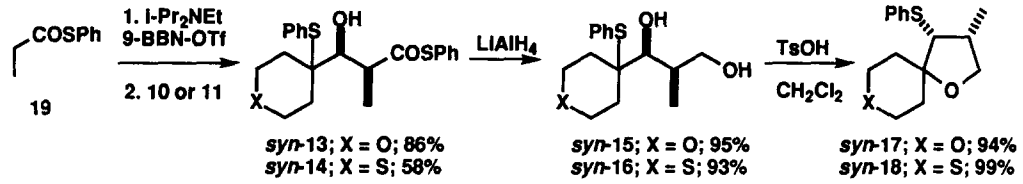


The first steps were to prepare the 2-PhS-aldehydes **10** and **11** by the method of de Groot and Janssen[8-10] These reactions worked well - essentially as well as in the hydrocarbon and amine series (**8-11**; X = CH_2 or NMe).[11]

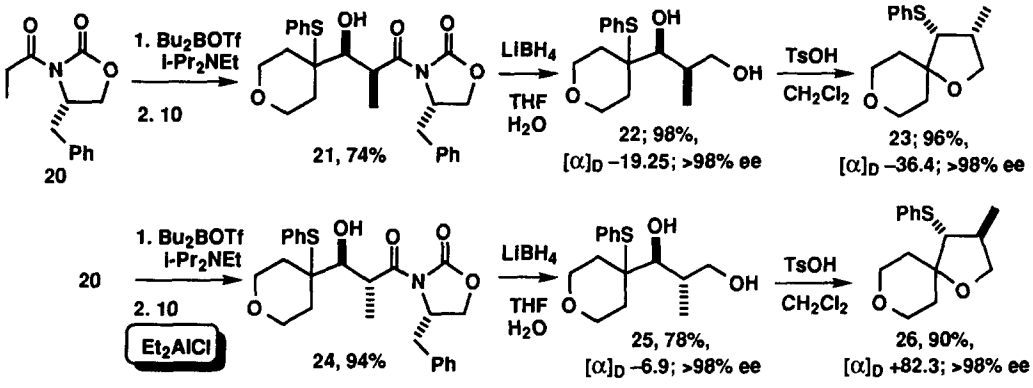


We next applied the reliable *anti*- and *syn*-selective aldol reactions of Heathcock[12,13] and Masamune[14] to these aldehydes to make, after reduction, the *syn* and *anti*-diols **15** and **16**. The rearrangement of these diols in acid solution was stereospecific and gave in good yield spirocyclic ethers **17** and **18** of the two systems in the title. It is noteworthy that the oxygen and sulfur atoms in the six-membered rings of these compounds did not compete in the rearrangement steps to form the 2-PhS aldehydes **10** and **11** nor in the cyclisations to form spirocyclic compounds **17** and **18**.

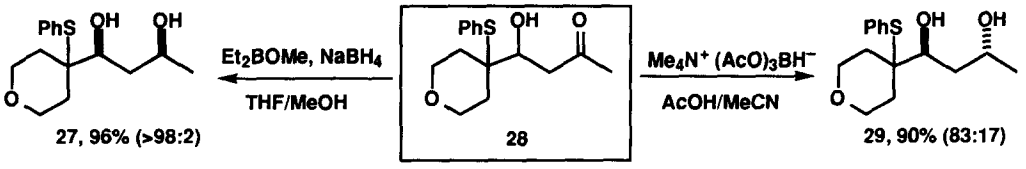


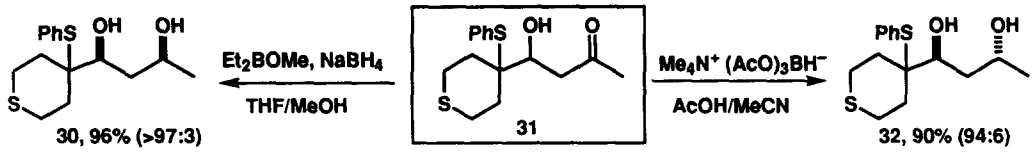


The optically active spirocyclic compounds were prepared[15] using boron enolates from the Evans phenylalanine-derived oxazolinone chiral auxiliary[16] **20**. Aldol reactions gave single diastereoisomers of *syn* aldols[17,18] **21** or, in the presence of the Lewis acid Et_2AlCl according to Heathcock,[19,20] single diastereoisomers of *anti* aldols **24**. Removal of the chiral auxilary with $LiBH_4$ was very efficient, giving the diols **22** and **25** in high yield and near perfect e.e.[15] Cyclisation gave both diastereoisomers of the spirocyclic ethers **23** and **26** in high yield and occurred without loss of diastereomeric or enantiomeric purity.

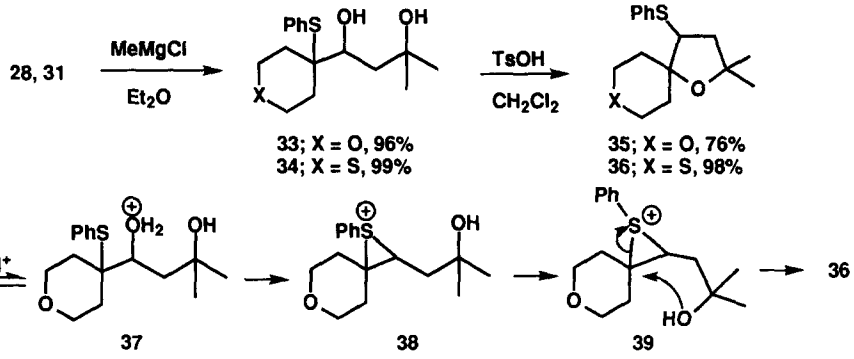


Cyclisation with secondary and tertiary alcohols as nucleophiles was also successful. The starting point for these compounds was an aldol reaction with the lithium enolate of acetone onto the two aldehydes **10** and **11** to give the hydroxyketones **28** (90%) and **31** (89%) in high yield. These 1,3-hydroxyketones could be reduced with high stereoselectivity to the *syn* 1,3-diols **27** and **30** by Prasad's method[21] using $NaBH_4$ as external reducing agent in the presence of Et_2BOMe as chelating agent and to the *anti*-1,3-diols **29** and **32** by intramolecular delivery of hydride with Me_4N^+ $(AcO)_3BH^-$, another reliable Evans procedure.[22] Addition of MeMgCl gave the tertiary alcohols **33** and **34** in good yield.

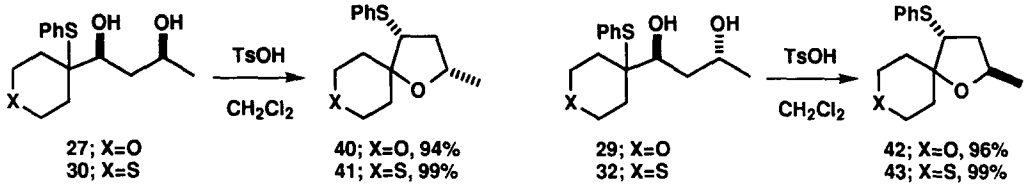




Rearrangement of all these diols gave the spirocyclic ethers, e.g. **36** by nucleophilic attack of the secondary or tertiary alcohols on the episulfonium ion intermediate, e.g. **38**. It is remarkable that the secondary alcohol in **33** is sufficiently protonated to give the episulfonium ion **38** and hence the rearrangement **39** because both competing protonation and decomposition of the tertiary alcohol in **33** and steric hindrance to the cyclisation disfavour this route. Under prolonged reflux, the dioxa compound **35** decomposes whereas **36** is stable. This is presumably the cause of the lower yield of **35**.



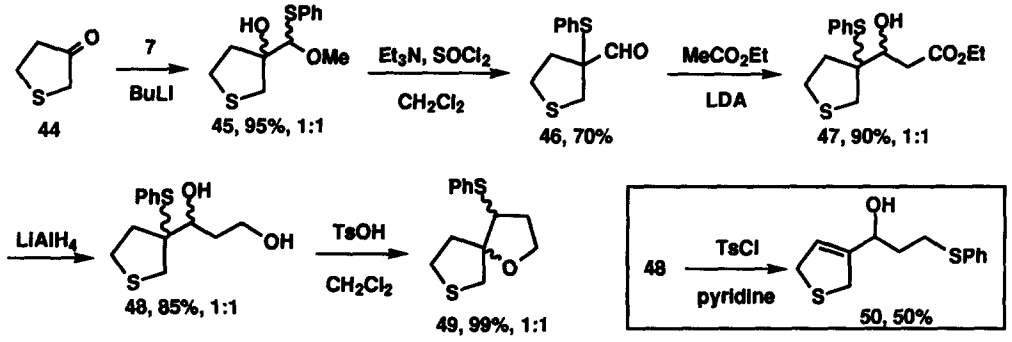
The cyclisation of the secondary alcohols **27**, **29**, **30**, and **32** is fully stereospecific and goes in excellent yield. This is perhaps less remarkable though we have shown that an alternative pathway involving [1,4]-PhS shift occurs easily when the corresponding primary alcohols are treated with TsCl in pyridine.[23] The efficiency of the [1,2]-PhS shift must be very high - indeed it must compensate for the equal protonation of the two secondary alcohols in **27**, **29**, **30**, and **32**, and more than compensate for the greater tendency of the tertiary alcohols to be protonated and lost in **33** and **34**. In simple open chain systems, kinetic measurements suggest[24] that [1,2]- and [1,4]-RS participation are about equally efficient. Fortunately that is not the case here.



Preliminary approaches to the 1-oxa-7-thiaspiro[4.4]nonane system were equally successful except in the important area of stereochemistry. The spiro carbon atom is now a stereogenic centre and we were unable to separate the diastereoisomers of **47** to **49**. This is not important if the PhS group is to be removed subsequently[25] but it did detract from the route as a synthetic method. Even the one reaction to give a single product **50**, the [1,4]-PhS shift referred to above, goes in only 50% yield.

In conclusion, the assembly of spirodecanes with two oxygen atoms not having an acetal relationship, i.e. being 1,5-related rather than joined to the same carbon atom, or their thia-analogues, can be achieved in

high yield by phenylsulfanyl migration with full control over relative or absolute stereochemistry. Neither heteroatom, oxygen or sulfur, interferes with any of the rearrangements.



Acknowledgements. We thank EPSRC for a grant (J.E.) and the Spanish Ministerio de Educación y Ciencia and Comisión Interministerial de Ciencia y Technología (CICYT) for support (of M. A. H.).

References.

1. Satyamurthy, N.; Berlin, K. D.; Powell, D. R.; Helm, D. V. d. *Phosphorus Sulfur*, **1984**, *19*, 137-153.
2. Kuroyan, R. A.; Pogosyan, S. A.; Grigoryan, N. P.; Aleksanyan, M.; Karapetyan, A. A.; Lindeman, S. V.; Struchkov, Y. T. *Arm. Khim. Zh.*, **1991**, *44*, 152-158.
3. Sargsyan, M. S.; Petrosyan, K. A.; Gevorkyan, A. A. *Arm. Khim. Zh.*, **1990**, *43*, 132-135.
4. Sundelin, K. G. R.; Powell, J. E.; Kollmeyer, W. D. *U.S. Pat.* 4,410,354, (1983), *Chem. Abstr.*, **1984**, *100*, 103178;
5. Kondo, K.; Negishi, A.; Matsui, K.; Tunemoto, D.; Masamune, S. *J. Chem. Soc., Chem. Commun.*, **1972**, 1311-1312.
6. Owen, G. R.; Reese, C. B. *J. Chem. Soc. (C)*, **1970**, 2401-2403.
7. Arentzen, R.; Kui, Y. T. Y.; Reese, C. B. *Synthesis*, **1975**, 509-510.
8. Otera, J. *Synthesis*, **1988**, 95-102.
9. de Groot, A.; Jansen, B. J. M. *Synthesis*, **1985**, 434-436.
10. de Groot, A.; Jansen, B. J. M. *Tetrahedron Lett.*, **1981**, *22*, 887-888.
11. Aggarwal, V. K.; Coldham, I.; McIntyre, S.; Warren, S. *J. Chem. Soc., Perkin Trans. 1*, **1991**, 451-460.
12. Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.*, **1980**, *45*, 1066-1081.
13. Heathcock, C. H.; Pirrung, M. C.; Montgomery, S. H.; Lampe, J. *Tetrahedron*, **1981**, *37*, 4087-4095.
14. Hirama, M.; Garvey, D. S.; Lu, L. D. L.; Masamune, S. *Tetrahedron Lett.*, **1979**, 3937.
15. Chibale, K.; Warren, S. *J. Chem. Soc., Perkin Trans. 1*, **1995**, 2411-2418.
16. Gage, J. R.; Evans, D. A. *Org. Synth.*, **1990**, *68*, 77-82.
17. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.*, **1981**, *103*, 2127-2129.
18. Gage, J. R.; Evans, D. A. *Org Synth.*, **1990**, *68*, 83-91.
19. Walker, M. A.; Heathcock, C. H. *J. Org. Chem.*, **1991**, *56*, 5747-5750.
20. Danda, H.; Hansen, M. M.; Heathcock, C. H. *J. Org. Chem.*, **1990**, *55*, 173-181.
21. Chen, K.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.*, **1987**, *28*, 155-158.
22. Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.*, **1988**, *110*, 3560-3578.
23. Eames, J.; de las Heras, M. A.; Jones, R. V. H.; Warren, S. *Tetrahedron Lett.*, **1996**, *37*, 1117-1120.
24. Eliel, E. L.; Pearson, W. H.; Jewell, L. M.; Abatjoglou, A. G.; Kenan, W. R. *Tetrahedron Lett.*, **1980**, *21*, 331-334.
25. Coldham, I.; Warren, S. *J. Chem. Soc., Perkin Trans. 1*, **1993**, 1637-1656.

(*Received in UK* 11 *April* 1996; *accepted* 3 *May* 1996)