

ditionally, they provide valuable insight into the structural range suitable for incorporation into LDL. It is expected that the compounds described here will be useful adjuncts in other areas where highly fluorescent, lipophilic probes are required.

A Stereospecific Synthesis of Highly Substituted Tetrahydrofurans

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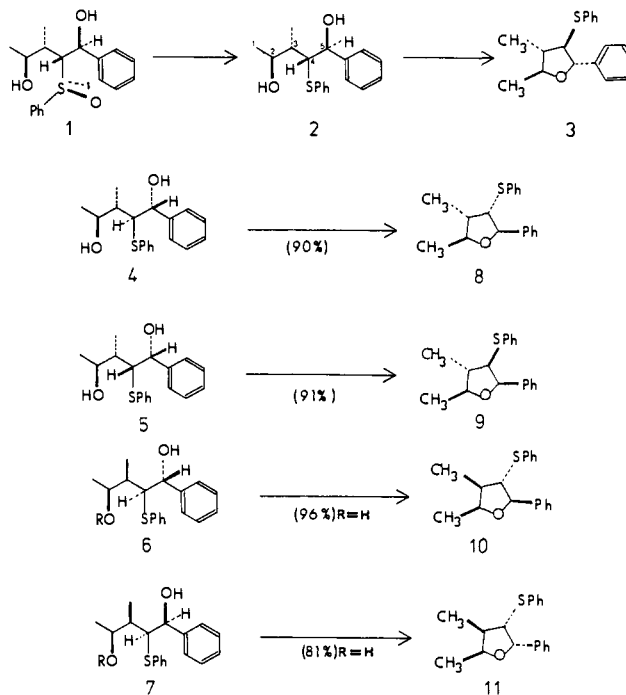
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In recent years, keen interest has developed in the preparation of complex dihydro- and tetrahydrofurans, many of which possess valued biological properties.¹ Numerous representative substances display challenging stereochemical arrangements about the heterocyclic ring demanding stereoselective methodologies for construction.² Several elegant studies have led to the total syntheses of ionophore antibiotics.³ Our investigations toward related natural products have uncovered a remarkably facile transformation of acyclic precursors to tetrasubstituted tetrahydrofurans with complete stereospecificity.

We have recently reported stereoselective condensations of α -lithiosulfinyl carbanions with aldehydes demonstrating useful methodology for construction of 1,3-asymmetric relationships in acyclic systems.⁴ Stereochemical features of a principal sulfoxide adduct **1**, resulting from condensation with benzaldehyde, have been confirmed by X-ray crystallography,⁴ and reduction with borane in tetrahydrofuran at 22 °C (24 h) gave the phenyl sulfide **2** (96%). Treatment of **2** with dimethyl sulfate (CH_2Cl_2 , 0 °C, 10 min, under N_2) cleanly afforded cyclization to the tetrahydrofuran **3** in 85% yield. Other methylating agents such as methyl triflate, methyl fluorosulfonate (added at -78 °C to a methylene chloride solution of sulfide with warming to 0 °C), and methyl iodide (benzene at reflux) also provided ring closure. Likewise, the isomeric sulfides **4**, **5**, **6** (R = H), and **7** (R = H) were individually submitted to the reaction conditions, yielding tetrahydrofurans **8-11**, respectively.⁵

Although spectroscopic data supported the products, it is widely recognized that coupling constants of vicinal protons in these heterocycles often fail to offer a completely reliable basis for stereochemical assignments. Dehydration of the acyclic sulfides could reasonably occur with loss of either hydroxyl group (at C-2 or C-5). One might anticipate preferred loss of the benzylic alcohol owing to a more favorable stabilization of charge in transition state intermediates. However, our experiments also demonstrated the stereospecific cyclization of benzylic ethers **6** (R = $\text{CH}_2\text{C}_6\text{H}_5$) and **7** (R = $\text{CH}_2\text{C}_6\text{H}_5$), under the usual conditions of *S*-methylation, affording tetrahydrofurans **10** (70%) and **11** (72%), respectively, as previously obtained from their corresponding alcohols.⁶ Similar dehydration processes have been



previously reported. For example, 1,4-butanediol is smoothly converted into tetrahydrofuran upon reaction with a diaryldialkoxysulfurane, $\text{Ph}_2\text{S}(\text{OC}(\text{CF}_3)_2\text{Ph})_2$ (10-20 min at room temperature).⁷ Stereospecific epoxide formation is observed from 1,2-diols under these conditions. More recently, the acid-catalyzed ring closure of *rac*- and *meso*-2,5-hexanediol has been shown to proceed with inversion of configuration, affording *cis*- and *trans*-2,5-dimethyltetrahydrofuran, respectively.⁸ The stereochemical features of our products were unambiguously assigned by X-ray crystallography of the sulfone of cyclic ether **11**, thus demonstrating net retention of configuration at each of the four asymmetric carbon centers.⁹

In addition, the phenyl ring (originally derived from benzaldehyde) may be replaced by an alkyl substituent without affecting the course or ease of the reaction. Condensation of the α -lithiosulfinyl carbanion of 1-[2(*S*)-methyl-3(*S*)-hydroxy]butyl phenyl (*R*)-sulfoxide with 3-methylbutanal gave two major adducts which were chromatographically separated (silica gel) and reduced with borane in tetrahydrofuran. Treatment of each of these

(5) All compounds are racemic, and purified samples were characterized by infrared, nuclear magnetic resonance, and mass spectral analysis. Infrared and mass spectral data are unexceptional and not useful for isomer identification of these substances. The ^1H NMR spectra were recorded on a 220-MHz instrument in CDCl_3 (0.1% Me_4Si) solutions. Partial characterization is as follows. Ether **3**: ^1H NMR δ 7.23 (10 H), 4.82 (d, $J = 9$ Hz, 1 H), 3.92 (m, 1 H), 3.03 (dd, $J = 11$ Hz, $J = 9$ Hz, 1 H), 1.84 (m, 1 H), 1.30 (d, $J = 7$ Hz, 3 H), 1.11 (d, $J = 7$ Hz, 3 H); mass spectrum, m/e 284.8 (18.3%) M^+ , 283.8 (85.8%), 177.8 (100%), 109.9 (63.1%), 68.9 (51.9%). Ether **8**: ^1H NMR δ 7.25 (10 H), 4.85 (d, $J = 5$ Hz, 1 H), 3.91 (m, 1 H), 3.70 (dd, $J = 8$ Hz, $J = 5$ Hz, 1 H), 2.19 (m, 1 H), 1.41 (d, $J = 6$ Hz, 3 H), 1.11 (d, $J = 7$ Hz, 3 H). Ether **9**: ^1H NMR δ 7.23 (10 H), 5.22 (d, $J = 7.5$ Hz, 1 H), 3.66 (m, 2 H), 1.87 (m, 1 H), 1.43 (d, $J = 7$ Hz, 3 H), 1.09 (d, $J = 6$ Hz, 3 H). Ether **10**: ^1H NMR δ 7.25 (10 H), 4.67 (d, $J = 7.5$ Hz, 1 H), 4.32 (m, 1 H), 3.09 (t, $J = 7$ Hz, 1 H), 2.30 (m, 1 H), 1.27 (d, $J = 6$ Hz, 3 H), 1.05 (d, $J = 7$ Hz, 3 H). Ether **11**: ^1H NMR δ 7.13 (10 H), 5.18 (d, $J = 8$ Hz, 1 H), 4.23 (m, 1 H), 4.06 (t, $J = 8$ Hz, 1 H), 2.69 (m, 1 H), 1.34 (d, $J = 6$ Hz, 3 H), 1.11 (d, $J = 7$ Hz, 3 H).

(6) Benzyl ethers **6** and **7** were obtained by condensation of the α -lithiosulfinyl carbanion available from 1-[2(*R*)-methyl-3(*S*)-benzyloxy]butyl-phenyl(*R*)-sulfoxide (LDA, THF, -78 °C) with benzaldehyde.

(7) Martin, J. C.; Franz, J. A.; Arhart, R. J. *J. Am. Chem. Soc.* **1974**, *96*, 4604.

(8) Molnár, Á.; Felföldi, K.; Bartók, M. *Tetrahedron* **1981**, *37*, 2149.

(9) Full details of the X-ray crystallographic study of the sulfone derived from tetrahydrofuran **11** will be published elsewhere and are also available from the Indiana University Chemistry Library. Request Molecular Structure Center Report 81053.

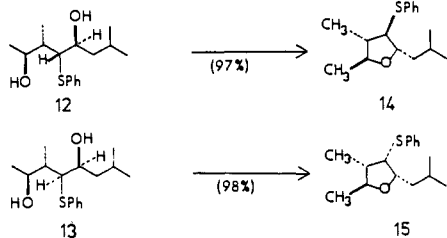
(1) For a review: Semple, J. E.; Joullié, M. M. *Heterocycles* **1980**, *14*, 1825.

(2) Some recent developments not included in ref 1: Amouroux, R.; Folefoc, G.; Chastrette, F.; Chastrette, M. *Tetrahedron Lett.* **1981**, *22*, 2259. Suzuki, H.; Yashima, H.; Hirose, T.; Takahashi, M.; Moro-oka, Y.; Ikawa, T. *Ibid.* **1980**, *21*, 4927. Ireland, R. E.; Vevert, J.-P. *J. Org. Chem.* **1980**, *45*, 4260. Bartlett, P. A.; Jernstedt, K. K. *Tetrahedron Lett.* **1980**, *21*, 1607.

(3) Ireland, R. E.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1980**, *102*, 1155. Fukuyama, T.; Akasaka, K.; Karanewsky, D. S.; Wang, C. L. J.; Schmid, G.; Kishi, Y. *Ibid.* **1979**, *101*, 260-262. Collum, D. B.; McDonald, J. H., III; Still, W. C. *Ibid.* **1980**, *102*, 2119, 2120.

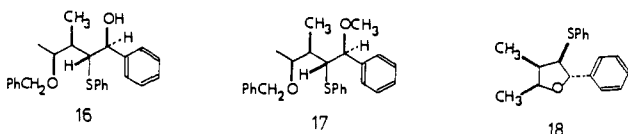
(4) Williams, D. R.; Phillips, J. G.; Huffman, J. C. *J. Org. Chem.* **1981**, *46*, 4101. Stereochemical arrangements, as represented by phenyl sulfides **1** and **6**, are readily available.

diastereomeric sulfides **12** and **13** with dimethyl sulfate (CH_2Cl_2 , 22 °C, 10 min, under N_2) provided a single tetrasubstituted tetrahydrofuran **14** (98%) and **15** (97%), respectively.¹⁰



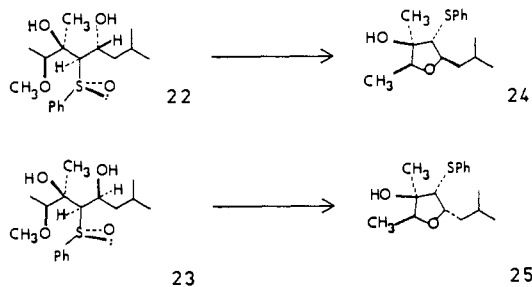
Raney nickel desulfurization (ethanol, 22 °C, 30 min) of these cyclic ethers afforded identical products (90%), illustrating the accessibility of 2,3,5-trisubstituted tetrahydrofurans.¹¹

Further evidence was provided by reaction of dimethyl sulfate (1 equiv) with the phenyl sulfide **16** in methylene chloride (0 °C) containing 1 equiv of pyridine, affording predominantly the methyl ether **17**, which failed to undergo subsequent ring closure under these conditions. On the other hand, treatment of **17** with *p*-toluenesulfonic acid (1 equiv) in methylene chloride (0 °C) led to the expected tetrahydrofuran **18** (65%). Omission of pyridine resulted in the direct formation of **18** (72%).¹²



These investigations suggest an initial alkylation and solvolysis of methanol assisted by backside participation of the neighboring sulfur yielding a sulfonium salt. Interaction of the hydroxy (alkoxy) substituent at C-2 through a five-membered transition state provides a developing oxonium ion, which suffers deprotonation or dealkylation, affording the observed tetrahydrofurans with net retention of configuration at C-5.¹³

Further efforts have shown that the starting acyclic sulfoxides



may be directly used for cyclization. For example, the sulfoxides **22** and **23** have been individually characterized,¹⁴ and treatment with freshly distilled oxalyl chloride (2.1 equiv) and sodium iodide (2.1 equiv) in dry acetonitrile (22 °C, 30 min, nitrogen atmosphere) provided a remarkably facile conversion to the tetrahydrofurans **24** (82%) and **25** (70%), respectively. Evidence that these reactions initially achieve reduction to the corresponding phenyl sulfides with subsequent ring closure was demonstrated by using only 1 equiv of the reagents and led to isolation of acyclic phenyl sulfide and smaller quantities of cyclic ether and starting sulfoxide.¹⁵

In summary, we have described a novel reaction process which provides, under exceptionally mild conditions, an efficient and totally stereospecific preparation of complex tetrahydrofurans bearing four consecutive asymmetric centers. Further studies and the application of these results to natural product synthesis are under way.

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Supplementary Material Available: Tables of fractional coordinates, thermal parameters, bond distances, and bond angles of the sulfone of **11** and sulfoxide **22** (9 pages). Ordering information is given on any current masthead page.

(10) Ether **14**: $^1\text{H NMR}$ δ 7.34 (5 H), 3.89 (m, 1 H), 3.59 (m, 1 H), 2.68 (dd, $J = 10$ Hz, 1 H), 1.75 (m, 1 H), 1.64 (m, 1 H), 1.34 (m, 2 H), 1.18 (d, $J = 6$ Hz, 3 H), 1.06 (d, $J = 6$ Hz, 3 H), 0.87 (d, $J = 7$ Hz, 3 H), 0.85 (d, $J = 7$ Hz, 3 H). Ether **15**: $^1\text{H NMR}$ δ 7.32 (5 H), 4.21 (m, 1 H), 3.50 (m, 1 H), 3.43 (dd, $J = 8$ Hz, $J = 8$ Hz, 1 H), 1.77 (m, 2 H), 1.59 (m, 1 H), 1.45 (m, 1 H), 1.27 (d, $J = 7$ Hz, 3 H), 1.07 (d, $J = 6$ Hz, 3 H), 0.91 (d, $J = 7$ Hz, 3 H), 0.86 (d, $J = 7$ Hz, 3 H).

(11) Raney nickel was prepared according to: Dominquez, O. A.; Lopez, I. C.; Franco, R. *J. Org. Chem.* **1961**, *26*, 1625.

(12) Ether **18**: $^1\text{H NMR}$ δ 7.25 (10 H), 4.84 (d, $J = 9$ Hz, 1 H), 4.51 (m, 1 H), 3.75 (dd, $J = 9$ Hz, $J = 6$ Hz, 1 H), 2.50 (m, 1 H), 1.28 (d, $J = 7$ Hz, 3 H), 1.11 (d, $J = 7$ Hz, 3 H).

(13) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963.

(14) Structural assignments of **22** and **23** are known based on X-ray crystallographic analysis of sulfoxide **22**. Details of this study will be published elsewhere. Complete crystallographic data are also available from the Indiana University Chemistry Library. Request Molecular Structure Center Report 81030.

(15) Oxalyl chloride-sodium iodide has previously been used for reduction of sulfoxides to sulfides: Olah, G. A.; Malhotra, R.; Narang, S. C. *Synthesis* **1979**, 58. Cyclic ether **24**: $^1\text{H NMR}$ δ 7.35 (m, 5 H), 3.59 (m, 2 H), 3.28 (d, $J = 7$ Hz, 1 H), 1.92 (s, OH), 1.84 (m, 1 H), 1.54 (m, 2 H), 1.28 (s, 3 H), 1.22 (d, $J = 6$ Hz, 3 H), 0.89 (t, $J = 6$ Hz, 6 H). Cyclic ether **25**: $^1\text{H NMR}$ δ 7.34 (m, 5 H), 4.30 (dt, $J = 9$ Hz, $J = 4$ Hz, 1 H), 3.69 (d, $J = 9$ Hz, 1 H), 3.63 (q, $J = 6$ Hz), 2.31 (s, OH), 1.87 (m, 1 H), 1.60 (m, 2 H), 1.23 (d, $J = 6$ Hz, 3 H), 1.20 (s, 3 H), 0.92 (t, $J = 6$ Hz, 6 H).