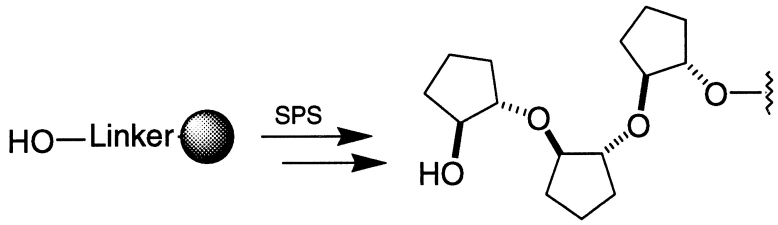
JOURNAL OF combinatorial CHEMISTRY

Report

Polyethers: A Solid-Phase Iterative Approach

Nathalie Bouloc, Nigel Walshe, and Mark Bradley

J. Comb. Chem., **2001**, 3 (1), 6-8• DOI: 10.1021/cc0000545 • Publication Date (Web): 05 December 2000



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 1 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Journal of Combinatorial Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Polyethers: A Solid-Phase Iterative Approach

Nathalie Bouloc,[†] Nigel Walshe,[‡] and Mark Bradley*,[†]

Department of Chemistry, University of Southampton, Southampton, U.K. SO17 1 BJ, and Animal Health, Pfizer Central Research, Sandwich, Kent, U.K.

Received June 29, 2000

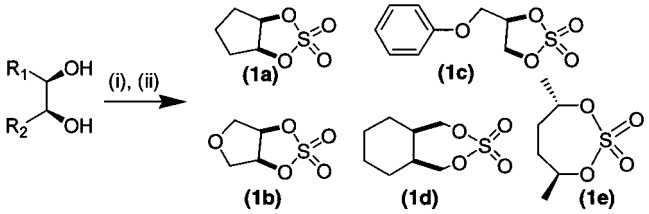
Natural polyether ionophores display a broad range of important biological activities,[1] with the high level of oxygen-containing functionality conferring unique ionophoric properties, which are believed to be involved in their mode of action.[2] Members of this family, such as Monensin,[3] have already found important commercial applications in the veterinary field as anticoccidial feed additives and growth promoters.

The framework of the polyethers is often dominated by the presence of 2,5 disubstituted tetrahydrofurans, substituted tetrahydropyrans, and spiroketals. This complexity makes synthetic access to large numbers of the natural polyethers difficult; thus although a number of very elegant total syntheses[4] have been achieved and an abundant literature deals with stereocontrolled routes to key structural fragments,[5] polyether ionophores are still obtained predominantly from natural sources, by fermentation, and via semi-synthetic approaches.[6]

Given this situation and the current excitement in the solid-phase area with regards to non-peptide oligomers,[7] for example, the recent reports of vinylogous sulfonyl peptides,[8] iterative Diels−Alder cycloadditions,[9] oligoureas,[10] peptide mimics,[11] and peptoids,[12] polyethers appear as ideal targets for solid-phase synthesis. In this communication we report a solid-phase iterative approach to the construction of polyethers. The synthetic strategy adopted was to allow the incorporation of maximum structural diversity in a minimum of chemical steps, utilizing readily available building blocks via a coupling and deprotection strategy akin to peptide synthesis allowing capitalization of the repetitive nature of the polyether structures.

Cyclic sulfates are powerful alkylating agents toward a range of nucleophiles and have often been exploited as epoxide equivalents.[13] They are, however, more reactive and show complementary regioselectivity. Upon nucleophilic reaction, cyclic sulfates open with inversion to give the corresponding sulfate ester which acts as an effective protecting group for the alcohol. Sulfate ester hydrolysis can be readily achieved using catalytic amounts of acid in moist solvents such as ether or dioxane[15] to generate the alcohol functionality which can then undergo further iterations. Thus the use of cyclic sulfates allows activation and protection of the hydroxy function while at the same time avoiding the need to synthesize monoprotected diols. Importantly, a wide range of cyclic sulfates are readily prepared from a broad range of corresponding diols, both cyclic and acyclic in nature. They thus offer a monomer set with a huge potential for library construction/multiple parallel synthesis. A range of cyclic sulfates **(1a−e)** were therefore conveniently prepared in high yield by the Sharpless procedure[15] (Scheme 1).

Scheme 1. Cyclic Sulfates Used in Oligomer Synthesis[a]



[a] Reagents and conditions: (i) $SOCl_2$ (1.2 equiv), DCM, △; (ii) $NaIO_4$ (1.5 equiv), cat. $RuCl_3 \cdot 3H_2O$, CH_3CN/H_2O.

Since the polyethers we intended to synthesize would contain no chromophores, reaction monitoring by HPLC analysis would be problematic, and therefore we utilized 1,4-benzenedimethanol (**2**) as a starter residue to aid reaction analysis. Initially, the 2-chloro-trityl linker[16] was used based on solution studies which showed that the sulfate protecting group could be rapidly and selectively removed in the presence of a trityl ether. However, on the solid phase this proved not to be the case, and the more acid stable Wang linker[17] had to be used in its place. Thus the Wang linker-resin (**3**) was activated to the trichloracetimidate[18] and loaded with diol (**2**) (Scheme 2) to give (**4**) with a loading of 85% as determined by cleavage and HPLC analysis.

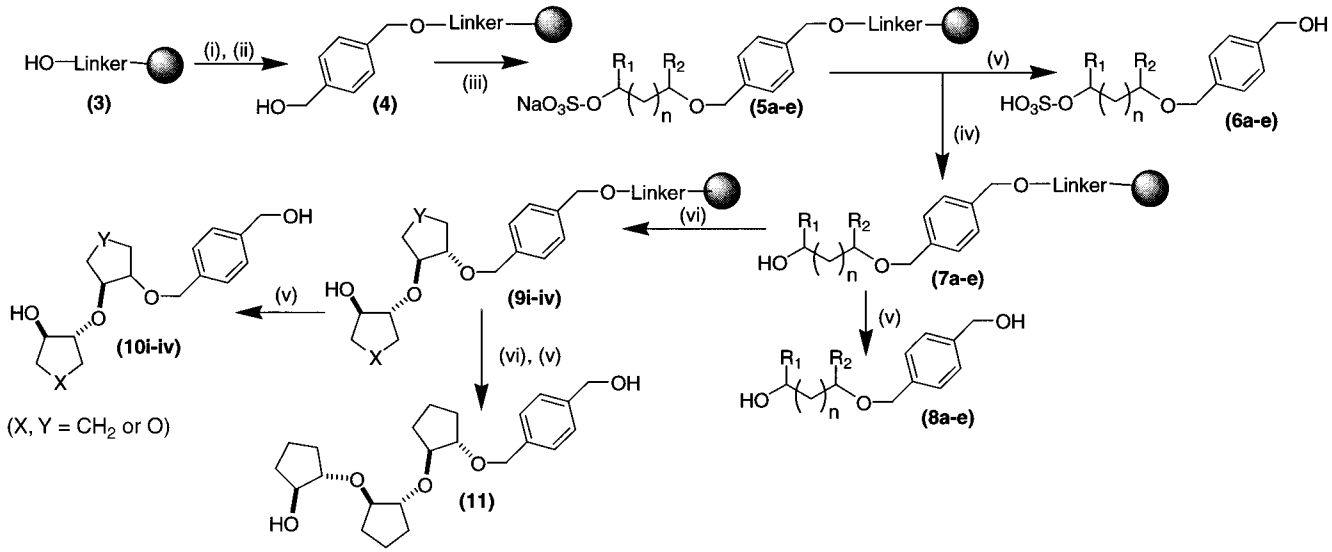
To optimize solid-phase ether formation, a number of different parameters were investigated, including solvent, base, reaction time, resin type, etc. Although a wide range of bases was utilized, NaH in DMF or DMSO was surprisingly the most successful, even when competing against soluble bases such as LHDMS or ^{t}BuOK which would certainly appear to be more compatible with solid-phase synthesis. The addition of 15-crown-5 led to improved yields. A 2% cross-linked polystyrene resin was used with very limited success. Changing to a 1% cross-linked polystyrene resin significantly improved yields, which we believe is due to the removal of possibile charge−charge interactions, due to the nature of the sulfate esters. The best results, however, were obtained with TentaGel resin.

Most importantly, the coupling step could be repeated due to the presence of the "protecting" sulfate ester, akin to peptide synthesis, leading to improved coupling yields. Two cleavage strategies were investigated. TFA based cleavages were initially problematic due to extensive trifluoroacetyl ester formation. However, short reaction times and careful control of temperatures solved these problems and allowed isolation of the sulfate esters. 4 M HCl in dioxane was also successful; this latter method proved slower than the TFA proceedure and also resulted in the hydrolysis of the sulfate esters.

* To whom correspondence should be addressed.
[†] University of Southampton.
[‡] Pfizer Central Research.

10.1021/cc0000545 CCC: $20.00
Published on Web 12/05/2000

Scheme 2[a]



[a] Reagents and conditions: (i) Cl_3CCN (20 equiv), DBU (1 equiv), DCM, 0 °C, 2 h; (ii) 1,4-benzenedimethanol (**2**) (5 equiv), BF_3OEt_2 (0.5 equiv), THF/DCM (1:1), 4 h; (iii) NaH (5 equiv), 15-crown-5, DMF, 2 h; then cyclic sulfate (**1a**−**e**) (5 equiv), DMF; (iv) 0.01 M HCl in 1% H_2O/dioxane, 12 h; (v) 50% TFA/DCM, (30 min); (vi) repeat iii → iv.

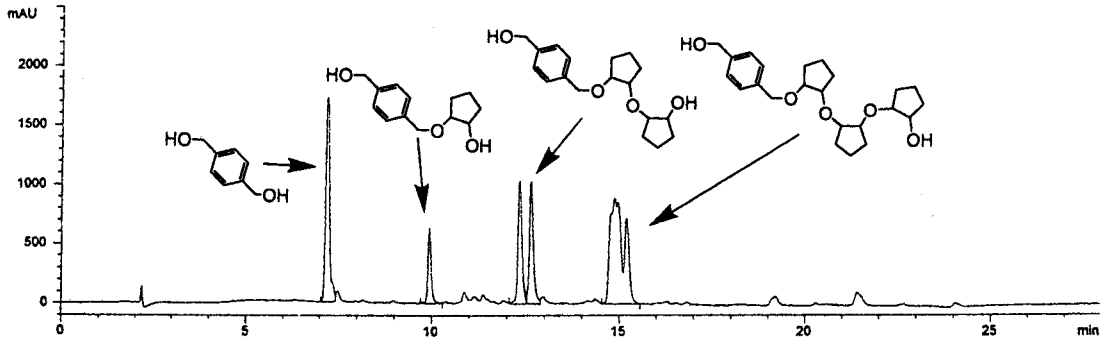


Figure 1. HPLC trace for the synthesis of tetramer **11**.

Table 1. Polyether Synthesis: Cyclic Sulfate Synthesis and Coupling Efficiency

cyclic sulfate (yield, %)	**8** conversion, % (HPLC)	**8** isolated yield, %
1a (81)	74	66
1b (73)	63	56
1c (70)	62	57
1d (83)	70	44
1e (82)	53	41

Having optimized the chemistry, **4** was treated with the cyclic sulfates **1a**−**e** to give **5a**−**e** which were cleaved from the resin with TFA to give **6a**−**e**. The sulfate esters **5a**−**e** were quantitatively cleaved (0.01 M HCl/water/dioxane) to furnish resin bound ethers **7a**−**e** which were cleaved from the resin to give **8a**−**e** (Table 1).

The methodology was extended to the synthesis of trimers. Thus **7a** and **7b** were alkylated with **1a** or **1b** to give resin bound ethers **9i**−**iv** which upon cleavage provided a series of trimers **10i**−**iv** (in isolated, purified yields of 28%, 29%, 28%, and 19%, respectively). The sequence was finally extended to yield tetramer **11** in 13% purified yield starting from the initial resin. Analytical complications arose in the synthesis of the trimers **10** and the tetramer **11** due to the *meso*-cyclic sulfates used, thus giving rise to two pairs of diastereoisomers for the trimers and four pairs of diastereoisomers for the tetramer. However HPLC analysis clearly showed the distinction between the various dimers, trimers, and tetramers (Figure 1).

The characterization and monitoring of the polyethers being synthesized by ES-MS was initially only possible in the negative ion mode when the compounds were at the sulfate ester stage. However, the longer polyethers (trimers and tetramers) chelated Na^+, thereby enabling their ES-MS (positive ion mode) analysis and showing that, like their counterparts in nature, they too coordinate metal ions.

We have demonstrated a successful iterative synthesis toward a class of polyethers, using cyclic sulfates as the monomer units for both activation and protection of the hydroxyl functionalities. The synthesis of trimer and tetramer polyethers was clearly practical, and due to the accessibility of cyclic sulfates, a wide range of polyethers are now synthetically accessible via solid-phase synthesis.

Acknowledgment. We thank the Royal Society for a University Research Fellowship (M.B.) and Pfizer Central Research for generous financial support (N.B.).

Supporting Information Available. Experimental data. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Dutton, C. J.; Banks, B. J.; Cooper, C. B. *Nat. Prod. Rep.* **1995**, *12*, 165. *Polyether Antibiotics*; Westley, J. W., Ed.; Marcel Dekker: New York, 1982; Vol I. Omura, S. *Macrolide Antibiotics*; Academic Press: Orlando, 1984. Westley, J. W. *Adv. Appl. Microbiol*. **1977**, *22*, 177. Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, 275.

(2) Pressman, B. C. *Annu. Rev. Biochem*. **1976**, *45*, 501.

(3) Agtarap, A.; Chamberlin, J. W.; Pinkerton, M.; Steinrauf, L. *J. Am. Chem. Soc.* **1967**, *89*, 3737. Agtarap, A.; Chamberlin, J. W. *Antimicrob. Agents Chemother.* **1968**, 359.

(4) Vaillancourt, V.; Pratt, N. E.; Albbizati, K. F. *Total synthesis of Natural products*; John Wiley and Sons: New York, 1992; Vol. 8, 533.

(5) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. Harmange, J. C.; Figadere, B. *Tetrahedron Asymmetry*, **1993**, *4*, 1711.

(6) Westley, J. M.; Liu, C. M.; Evans, R. H.; Sello, L. H.; Troupe, N.; Hermann, T. *J. Antibiot.* **1983**, *36*, 1195.

(7) Kessler, H. *Angew. Chem., Int. Ed. Engl*. **1993**, *32*, 543.

(8) Gennari, C.; Nestler, H. P.; Salom, B.; Still, W. C. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 1763. Gennari, C.; Nestler, H. P.; Samom, B.; Still, W. C. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 1765.

(9) Winkler, J. D.; Kwak, Y−S. *J. Org. Chem*. **1998**, *63*, 8634.

(10) Burgess, K.; Ibarzo, J.; Linthicum, D. S.; Russell, D. H.; Shin, H.; Shitangkoon, A.; Totani, R.; Zhang, A. J. *J. Am. Chem. Soc*. **1997**, *119*, 1556.

(11) Wipf, P.; Henninger, T. C. *J. Org. Chem*. **1997**, *62*, 1586.

(12) Simon, R. J.; Kania, R. S.; Zuckermann, R. N.; Huebner, V.D; Jewell, D. A.; Banville, S.; Ng, S.; Wang, L.; Rosenberg, S.; Marlowe, C. K.; Spellmeyer, D. C.; Tan, R.; Frankel, A. D.; Santi, D. V.; Cohen, F. E.; Bartlett, P. A. *Proc. Natl. Acad. Sci.* **1992**, *89*, 9367.

(13) Lohray, B. B. *Synthesis* **1992**, 1035. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483.

(14) Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett*. **1989**, *30*, 655. Goren, M. B.; Kochansky, M. E. *J. Org. Chem*. **1973**, *38*, 3510.

(15) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538.

(16) Frechet, J. M. J.; Nuyens, L. J. *Can. J. Chem*. **1976**, *54*, 926. Barlos, K.; Gatos, D.; Kallitsis, J.; Papaphotiu, G.; Sotiriu, P.; Wenqing, Y.; Schäfer, W. *Tetrahedron Lett.* **1989**, *30*, 3943. Barlos, K.; Gatos, D.; Kapolos, S.; Papaphotiu, G.; Schäfer, W.; Yao, W. *Tetrahedron Lett.* **1989**, *30*, 3947.

(17) Wang, S−W. *J. Am. Chem. Soc.* **1973**, *95*, 1328.

(18) Hannessian, S.; Xie, F. *Tetrahedron Lett*. **1998**, *39*, 737.

CC0000545