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Practical Designed Syntheses of All Stereoisomeric Bis(2,2′)- and Tris(2,2′,2″)-tetrahydrofurans

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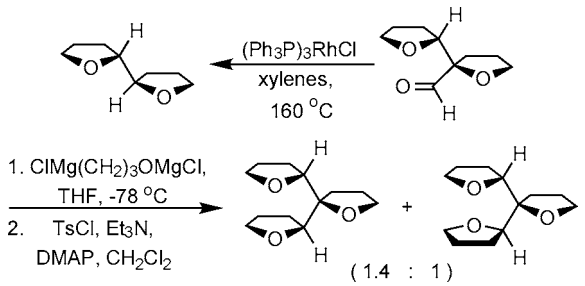
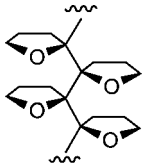
ABSTRACT

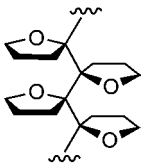


A convenient synthetic entry to the entire group of bis(2,2′)- and tris(2,2′,2″)-tetrahydrofurans has been developed. The method is concise and relies on chromatographic separation, decarbonylation, and annulation to arrive at a specific product of defined relative configuration.

Structurally unusual oligo-tetrahydrofurans exemplified by *threo*-**1** and *erythro*-**2** are of interest for a variety of reasons. Their ladder-like arrays of oxygen atoms hold the prospect of binding to cations provided that appropriate conformations are attainable. The particular three-dimensional features will depend on a number of factors including control by gauche effects[1] and steric interactions. Interestingly, should the stereoalignment depicted for **1** be adopted, the termini of the zigzag chain will continue to be projected in opposite in-plane directions. Comparable alignment of the oxygen centers in **2** results instead in twisting of the chain such that a helical conformation develops (not illustrated). Furthermore, both termini are in this instance properly oriented to propagate the coiling. While this analysis is somewhat conjectural at this time, polyoxymethylene, $(OCH_2CH_2)_n$, is known to adopt a gauche rather than a perfectly staggered spatial arrangement and consequently to assume an overall helical shape.[2]



1



2

Notwithstanding the considerable promise offered by **1** and **2**, minimal progress has been made in accessing this class of molecules. The major challenge has been the development of a synthetic route capable of unambiguously distinguishing the simplest members of the bis(THF) pair **3** and **4**.[3] In 2004, Alexakis and co-workers reported an enantioselective approach to **4**.[4] However, an unequivocal route to **3** has not yet been realized, and the tris(THF) subset **5**−**7** remains entirely unknown. Herein, we define the means for as-

(1) (a) Zefirov, N. S. *Tetrahedron* **1977**, *33*, 3193. (b) Zafirov, N. S.; Samoshin, V. V.; Subbotin, O. A.; Baranenkov, V. I.; Wolfe, S. *Tetrahedron* **1978**, *34*, 2953. (c) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley: New York, 1994; pp 605−615.

(2) (a) Ohsaku, M.; Imamura, A. *Macromolecules* **1978**, *11*, 970. (b) Abe, A.; Mark, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 6468. (c) Eliel, E. L. *Acc. Chem. Res.* **1970**, *3*, 1.

(3) Kelly, D. R.; Nally, J. *Tetrahedron Lett.* **1999**, *40*, 2209 and references therein.

(4) Alexakis, A.; Tomassini, A.; Leconte, S. *Tetrahedron* **2004**, *60*, 9479.

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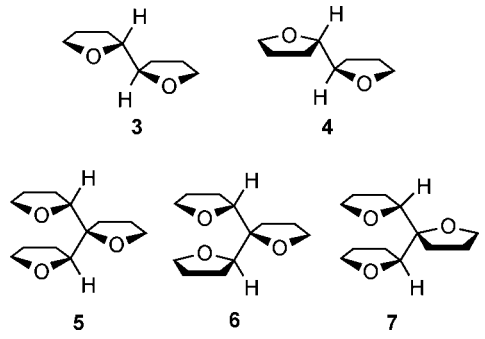
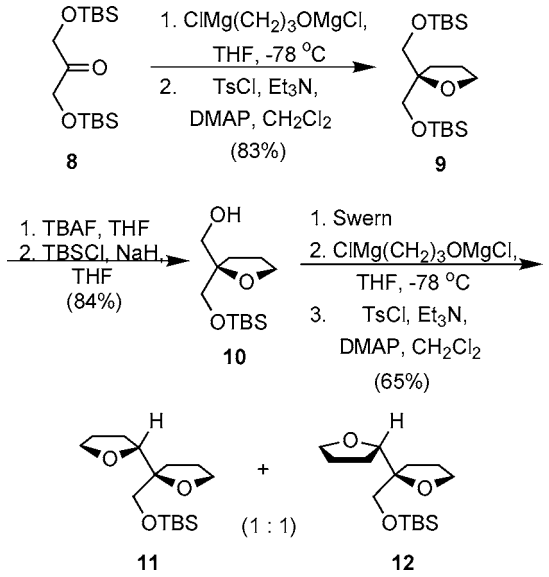
sembling all five key compounds. The pathway makes allowance for the independent selection of two options. The first allows for the chromatographic separation of diastereomers in tandem with crystallographic corroboration of structure. The companion reaction channel allows for use of the same scaffolding to reach **5**−**7** in concise fashion.



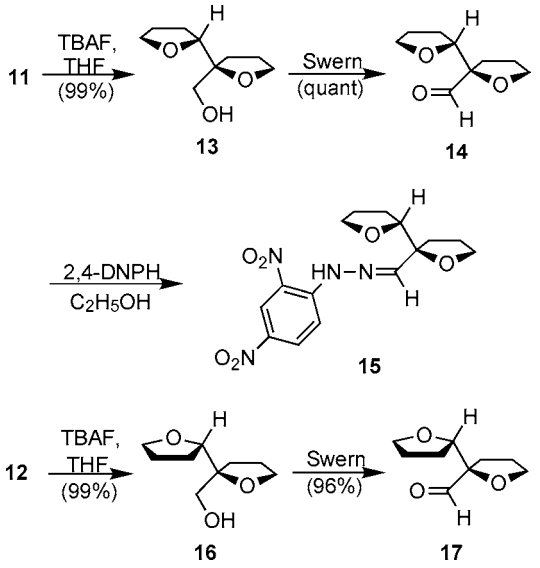
Realization of the proper atom connectivity began by coupling of the Normant reagent[5] with the known ketone **8**[6] (Scheme 1). Without purification, the resulting diol was regioselectively monotosylated at the primary carbinol site. Spontaneous cyclization ensued[7] to generate **9** in 83% overall yield (Scheme 1). The desymmetrization of **9** was preferably achieved by wholesale desilylation and subsequent monoprotection. The aldehyde produced upon the Swern oxidation of **10** proved to be an ideal substrate for second-stage cyclization. It was well appreciated that use had ultimately to be made of both **11** and **12**, and the availability of these two intermediates in a 1:1 ratio was well suited to this objective. Moreover, these bis(THF) derivatives proved to be readily separated by chromatography on silica gel.

Once pure samples of **11** and **12** became available in this way, each was individually transformed via their free alcohols into aldehydes **14** and **17**, respectively (Scheme 2).

Scheme 1. Generation of Pure Siloxymethyl (2,2)-Bis(THF) Diastereomers



Scheme 2. Independent Access to the Bis(THF) Aldehydes



Thereafter, relative stereochemistries were rigorously established on the basis of an X-ray crystallographic determination of 2,4-dinitrophenylhydrazone **15** (see Figure 1). Elucidation of these details allowed advances to be made into projected decarbonylation studies. Early definitive work by Walborsky and Allen[8] involving this reaction constituted important

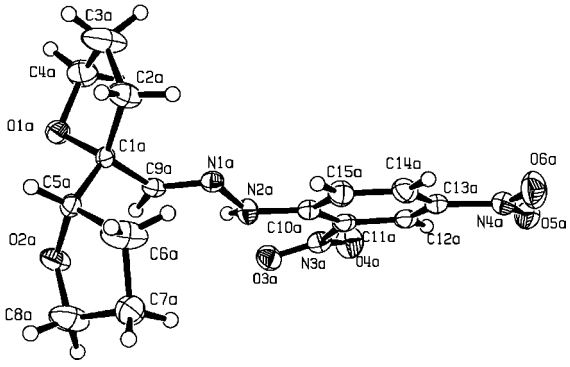


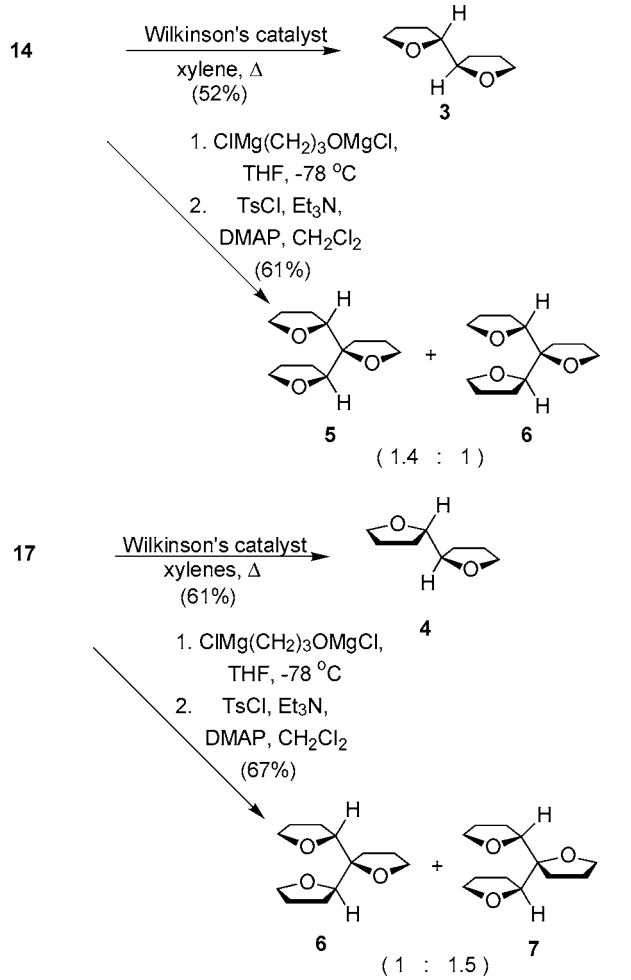
Figure 1. ORTEP diagram of **15**.

(5) (a) Cahiez, G.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1978**, 3013. (b) Conley, R. T.; Annis, M. C. *J. Org. Chem.* **1962**, *27*, 1961. (c) Ibuka, T.; Mitsui, Y.; Kayashi, K.; Minakata, H.; Inubushi, Y. *Tetrahedron Lett.* **1981**, *22*, 4425. (d) Ibuka, T.; Minakata, H.; Mitsui, Y.; Hayashi, K.; Taga, T.; Inubushi, Y. *Chem. Pharm. Bull.* **1982**, *30*, 2840.

(6) Calter, M. A.; Zhu, C.; Lachicotte, R. J. *Org. Lett.* **2002**, *4*, 209.

(7) (a) Negri, J. T.; Rogers, R. D.; Paquette, L. A. *J. Am. Chem. Soc.* **1991**, *113*, 5073. (b) Paquette, L. A.; Negri, J. T.; Rogers, R. D. *J. Org. Chem.* **1992**, *57*, 3947. (c) Paquette, L. A.: Stepanian, M.; Mallavadhani, U. V.; Cutarelli, T. D.; Lowinger, T. B.; Klemeyer, H. J. *J. Org. Chem.* **1996**, *61*, 7492.

Scheme 3. Branching of the Reaction Pathways



precedent. These workers determined that optically active aldehydes bearing an adjacent stereocenter experience loss of CO with retention of configuration irrespective of the particular hybridization at the seat of reaction. Indeed, heating **14** as well as **17** with Wilkinson's catalyst in xylene solution prompted clean conversion to **3** and **4**, respectively, without any evidence for the admixture of diastereomers (Scheme 3).

We were now in a position to introduce the third THF subunit. In the case of **14**, reaction with the Normant reagent followed by ring closure afforded a pair of readily separable tris(THF) diastereomers. The stereochemical assignments to these products awaited the comparable processing of **17**. Once again, low diastereoselectivity was observed, thereby indicating that chelate control was not operating effectively in either series. This behavior parallels the response customarily seen for the 1,2-addition of Grignard reagents to highly substituted aldehydes[9] and was not unexpected. Relevantly, the minor product formed in these experiments proved to be identical and must therefore be **6**. On this basis, the relative configurational assignments to **5** and **7** can be confidently assigned.

In summary, direct routes to **3**−**7** have been developed that allow each target to be generated in stereochemically pure condition. Issues surrounding the assignment of configuration have been resolved in their entirety. While the two non-*meso* structures **4** and **6** have been made available in racemic condition, opportunities for accessing them enantioselectively are available at several stages. We continue to examine the ligating properties and preferred conformational features of these polytetrahydrofuranyl networks.

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Supporting Information Available: Experimental procedures and spectroscopic (^{1}H/^{13}C NMR) characterization for all new compounds, as well as crystallographic details for **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Walborsky, H. M.; Allen, L. E. *J. Am. Chem. Soc.* **1971**, *93*, 5465.
(9) For example: Paquette, L. A.; Wiedeman, P. E.; Bulman-Page, P. C. *J. Org. Chem.* **1988**, *53*, 1441.