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New Silyl Ether Reagents for the Absolute Stereochemical Determination of Secondary Alcohols

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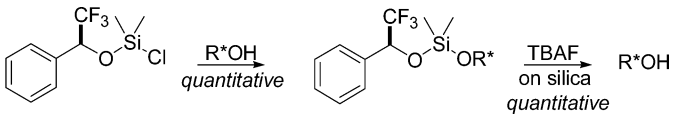
ABSTRACT



Herein we report a new set of silyl ether reagents for determining the enantiomeric purity and absolute stereochemistry of secondary alcohols. These derivatives are easily synthesized, provide straightforward spectroscopic results, and allow for facile recovery of the original chiral alcohol.

The determination of absolute stereochemistry remains a challenging aspect of organic chemistry. Many approaches based on circular dichroism,[1] X-ray crystallography,[2] and the varied use of anisotropic shielding reagents in combination with NMR spectroscopy[3] have been reported in the literature. However, to this date, no one method has proved to be general in its application. As a result, the search for approaches that address the limitations of known methods remains of paramount importance. In this Letter, we present the development of new silyl reagents that can be used in conjunction with NMR spectroscopy to determine the absolute stereochemistry and enantiomeric purity of secondary alcohols.

The advanced Mosher method reported by Ohtani et al. provided a major breakthrough in the field of absolute stereochemical determination.[4] Although these "Mosher esters" provide reliable results and are relatively easy to synthesize, they often prove unsuccessful when working with sterically hindered or elimination-prone alcohols. In addition, harsh hydrolysis conditions are generally required to cleave the ester bond, making recovery of the starting alcohol a difficult task. In our ongoing efforts to develop more efficient methods for stereochemical analysis, we sought to develop a new silicon-based reagent that would address these issues.[5] A silicon-based reagent was chosen because the chemical nature of the silyl ether group allows for simple derivitization[6] and convenient recovery of the original chiral compound of interest.[7]

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(1) For an excellent reference see: *Circular Dichroism: Principles and Applications*, 2nd ed.; Berova, N., Nakanishi, K., Woody, R. W., Eds.; Wiley-VCH: New York, 2000.

(2) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994.

(3) For a practical review see: Seco, J. M.; Quinoa, E.; Riguera, R. *Tetrahedron*: *Asymmetry*, **2001**, *12*, 2915−2925.

(4) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

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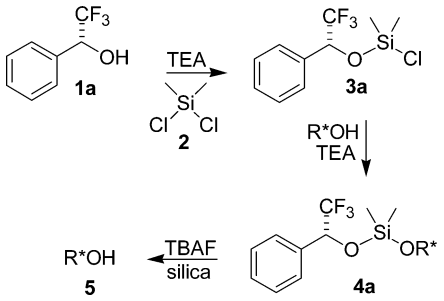
It has recently been shown that chiral silanes can be used to resolve the chemical shifts of enantiotopic stereogenic centers and to determine the absolute configuration of natural products.[5,8,9] However, the absolute stereochemical determination of a molecule with use of these previously described diphenyl alkyl-substituted silyl ethers was only possible when enantiomerically pure standards were available for comparison.[5,9] We suspected that if a derivative could be designed that had a conformationally stabilizing component to its structure, it would be possible to reliably determine absolute stereochemistry by using this type of synthetic tool.

In 1976, Pirkle and co-workers postulated that the interaction of a carbinyl hydrogen and a basic site on a molecule can afford a chelate-like structure that provides a reasonably stable and predictable solution conformation.[10] On the basis of Pirkle's findings, we designed a silyl ether that would allow for conformational control using this principle. For this purpose, dichlorodimethylsilane (**2**) was reacted with *R*- or *S*-α-(trifluoromethyl)benzyl alcohol (**1**) at room temperature in the presence of triethylamine to give α-(trifluoromethyl)benzyl silyl chloride (**3**) (Scheme 1). This silyl chloride can subsequently be used to quickly and smoothly derivatize the chiral alcohol of interest with use of a mild base.

Scheme 1. Synthesis of PhTFE derivatives and recovery of starting alcohol.



It was envisioned that the final silyl diether product (**4**) would adopt a predominant conformation similar to the one shown in Figure 1. We also hypothesized that this conformation would be encouraged by a key interaction between the carbinyl proton of the α-(trifluoromethyl)benzyl ether and the oxygen of the derivatized alcohol (Figure 1). Once the corresponding *R*- and *S*-α-(trifluoromethyl)benzyl silyl derivatives (*R*- and *S*-PhTFE) are synthesized, the absolute stereochemistry can be determined through analysis of the chemical shift differences ($\delta R - \delta S$) observed for the two

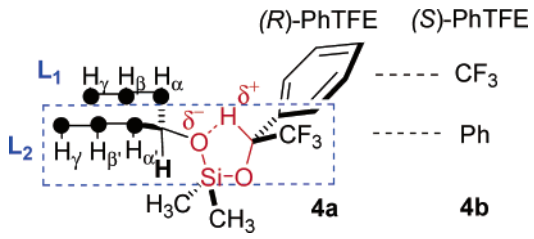


Figure 1. General conformational model for the PhTFE derivatives discussed in the text.

derivatives in much the same way as has been described previously for the advanced Mosher method.[4]

According to our conformational model, the protons on L_1 (Figure 1) will be shielded upfield by the aromatic ring of the PhTFE functionality when using the *R*-PhTFE (**4a**) derivative. Similarly, the protons on L_2 will be shielded upfield when using the *S*-PhTFE derivative (**4b**). It follows that in **4a** protons with a ($\delta R - \delta S$) value <0 would be placed on the L_1 face and those protons with a value >0 would be positioned on the L_2 face. If the chemical shift trends (<0 or >0) are consistent on each of the L_1 and L_2 faces of the model, the absolute stereochemistry can be assigned by using this method. In analogy to the advanced Mosher method, if the ($\delta R - \delta S$) value signs are not consistent on L_1 and L_2, it can be assumed that the derivatizing agent must be forced into a nonideal conformation and the stereochemistry cannot be confidently assigned with use of this method.

As an initial test of this theory, the *R*- and *S*-PhTFE derivatives of (*S*)-butanol (**6a** and **6b**, respectively) were synthesized and analyzed by NMR spectroscopy. As can be seen in Figure 2, the observed chemical shift changes agree very well with our predictions.

Encouraged by these results, we synthesized the (*R*)-PhTFE derivative of (*R*)-pantolactone (**7a**) and acquired a

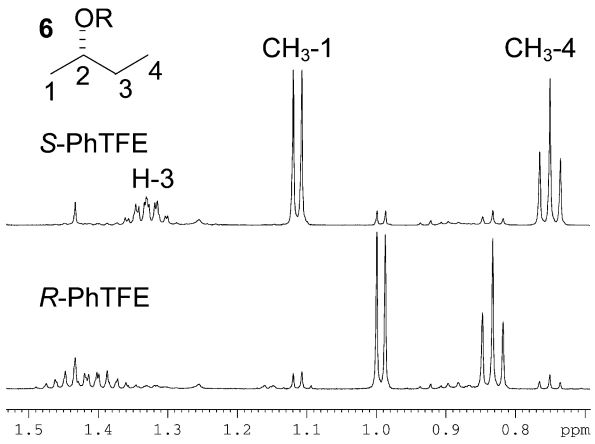


Figure 2. ^{1}H NMR spectra of the *R*- (**6a**) and *S*-PhTFE (**6b**) derivatives of *S*-butanol in $CDCl_3$. Note the 9% (*R*)-enantiomer present in the commercially available chiral alcohol.

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(7) Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549−2550.

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set of DPFGSE 1D-NOE experiments to obtain NMR spectroscopic evidence for the proposed conformation. The geminal methyl groups in alcohol **7** allowed us to glean information on the functional entities surrounding both the "bottom" and "top" faces of this molecule. As depicted in Figure 3, strong NOE enhancements supporting the proposed

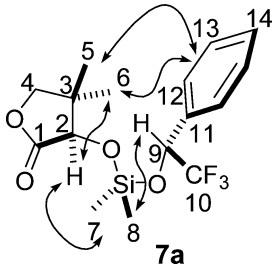

Figure 3. Results from the NOE study on the *R*-α-(trifluoromethyl)benzyl silyl ether of *R*-pantolactone (**7**).

conformation were observed from CH_3-5 and CH_3-6 to the aromatic protons H-12 and H-13. This result shows the proximity of CH_3-5 and CH_3-6 to the phenyl group, which is the origin of the shielding effect. In addition, strong interactions were observed between H-2 and the silyl methyl groups (CH_3-7 and CH_3-8), as well as between the H-9 proton of the benzyl alcohol and CH_3-7 and CH_3-8.

The next step in our study was to implement ab initio molecular modeling calculations at the B3LYP6-31G* level using 403 basis functions to examine the proposed structure.[11] As can be seen in Figure 4, these results agree quite well

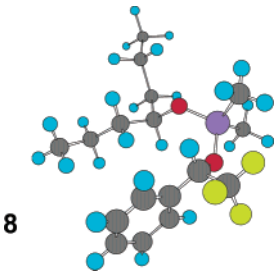

Figure 4. Results from ab initio calculations on the (*S*)-PhTFE derivative of the meso compound 4-heptanol (**8**).

with our predicted conformation. In addition, these calculations confirm the presence of a partial positive charge on the α-proton of the α-(trifluoromethyl)benzyl silyl ether (0.239 NPA) and a partial negative charge on the silylated oxygen of *R*-pantolactone (−0.947 NPA). These findings are consistent with the hypothesis that charge−charge interactions may exist to help stabilize the structure.

(11) (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (b) Ab initio calculations were done with the Titan software package.

Following these results, we synthesized a small library of silyl derivatives using commercially available chiral alcohols with increasing structural complexity. These examples include the natural products podophyllotoxin **13**, cholesterol **14**, and cytochalasin B **15** (Figure 5). All of the results

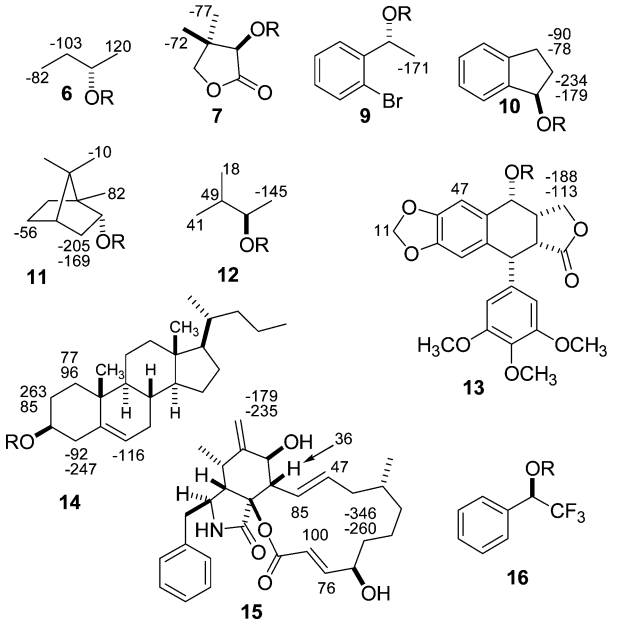

Figure 5. Structures of *R*- and *S*-PhTFE derivatives synthesized from commercially available alcohols. Selected ($\delta R - \delta S$) are shown in ppb.

obtained (Figure 5) agree with our predictions based on the general model shown in Figure 1. Free alcohols were easily recovered with use of TBAF bound to silica.[7]

As part of our library, we chose to derivatize one enantiomer of the starting α-(trifluoromethyl)benzyl alcohol (**1**) with both the *R*- and *S*-PhTFE reagents (**3a,b**). This sterically hindered alcohol has been shown to be resistant to standard Mosher-type esterification conditions.[12] However, as in the case of all other alcohols tested, we observed essentially quantitative conversion to the desired *R* and *S* silyl ethers (**16**).

Interestingly, although the magnitude of the observed chemical shift changes is reduced in polar NMR solvents such as methanol, the observed *trend* of the chemical shift changes remains the same. This observation suggested that the weak interaction between the carbinyl proton and the oxygen of the starting chiral alcohol was not the only driving force behind this lowest energy conformation. To further explore this hypothesis, we performed an exhaustive Monte Carlo conformational search using the Maestro/MacroModel molecular modeling software (Ver 5.0.19).[13]

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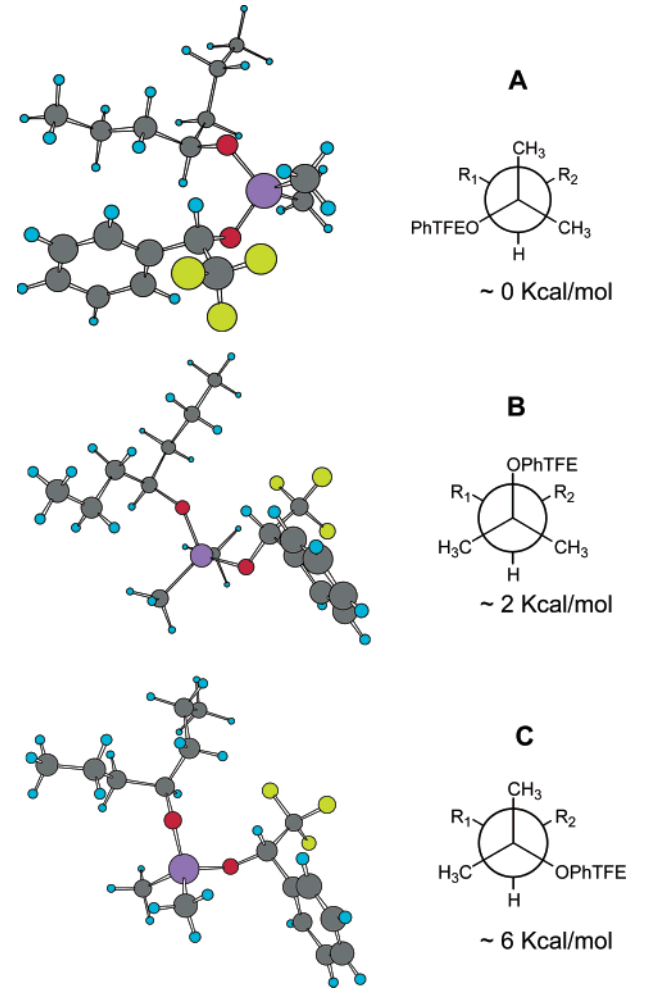

Figure 6. Representative structures from the three families of lowest energy conformers obtained from a Monte Carlo conformational search. The approximate energy differences between structures B and C relative to structure A are also indicated.

These results showed that, based on steric interactions alone, there are three discrete families of possible low-energy conformations. Each of these conformations reflects a 120° rotation about an imaginary line through the stereogenic center of the starting material (4-heptanol) and the silicon atom of the derivatizing reagent (Figure 6). Rotamer A, which is almost identical with the conformation obtained from the ab initio calculations, possessed the lowest energy of the three families.

As can be seen in rotamer A, Figure 6, the phenyl ring would be expected to provide a significant shielding effect to the *pro-R* hydrogens of 4-heptanol. In the next lowest energy rotamer, rotamer B, the *pro-R* protons would experience a weaker shielding effect than that expected in rotamer A. Finally, rotamer C, which would not be expected to provide shielding to either the *pro-R* or *pro-S* protons of the derivatized 4-heptanol, was found to be the next lowest energy conformation. All other conformations were calculated to be more than 10 kcal/mol higher in total energy to rotamer A. For this reason, they would not be expected to contribute significantly to the overall conformational population of the derivatized alcohol.

In summary, we have developed an alternative approach to the Advanced Mosher method for the determination of absolute stereochemistry. These new silicon-based reagents provide efficient derivitization of even sterically hindered chiral secondary alcohols that are resistant to standard esterification conditions. For these reasons, we believe that the PhTFE reagents described here should find wide application in the fields of multistep asymmetric synthesis and natural products chemistry. In addition, we are currently exploring the use of these compounds as derivatizing agents for chiral separations. The results of these studies and others will be reported in due course.

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Supporting Information Available: General experimental procedures for derivitization and desilylation and NMR data for **7**, **13**, **14**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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