ORGANIC LETTERS

2004
Vol. 6, No. 25
4715−4718

Application of Chiral Lanthanide Shift Reagents for Assignment of Absolute Configuration of Alcohols

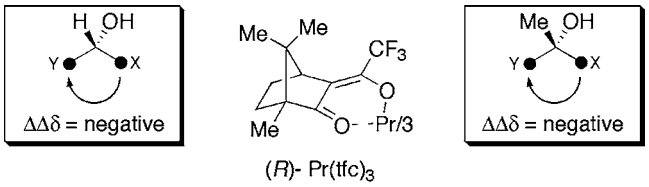
Indranath Ghosh, Hongbo Zeng, and Yoshito Kishi*

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138

kishi@chemistry.harvard.edu

Received September 23, 2004

ABSTRACT



$$\Delta\Delta\delta = \Delta\delta_{R\text{-}4}\,(\delta CX_{R\text{-}4} - \delta CY_{R\text{-}4}) - \Delta\delta_{S\text{-}4}\,(\delta CX_{S\text{-}4} - \delta CY_{S\text{-}4})$$

The absolute configuration of secondary and tertiary alcohols can be predicted from analysis of the chemical shift behaviors of the CX- and CY-carbons in the presence of (*R*)- and (*S*)-Pr(tfc)$_3$ as formulated in the boxes.

We recently reported the assignment of absolute configuration of secondary and tertiary alcohols from simple analysis of their ^{13}C NMR behaviors in chiral bidentate solvents.[1] Despite the operational simplicity and consistent results obtained with the chiral NMR solvent approach, we continued to search for alternative methods of determining the absolute stereochemistry of alcohols. Of particular concern was the technical difficulty that might be encountered while assigning the absolute configuration of 1,5-tetraol systems such as the ones present in glisoprenin A (**1**)[2] (Figure 1). To

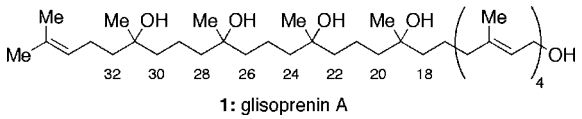


Figure 1. Gross structure of glisoprenin A (**1**).

deduce absolute stereochemistry via the chiral NMR solvent approach, one needs to determine the NMR behaviors of the carbons adjacent to the alcoholic center (referred to as the α-carbons) in question (Figure 2). Thus, to predict the

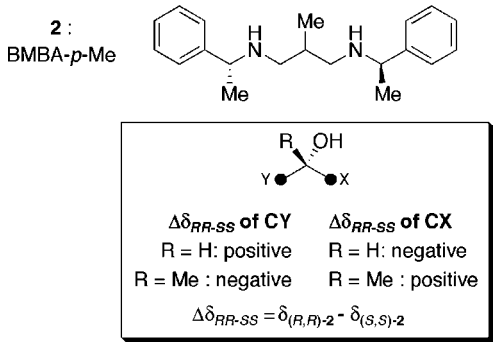


Figure 2. Empirical rules formulated for the determination of absolute stereochemistry of optically active secondary and tertiary alcohols in BMBA-*p*-Me (**2**).

absolute configuration at C-19, C-23, C-27, and C-31 of **1**, it is necessary to establish the chemical shift behaviors in chiral bidentate solvent **2** for at least one carbon, preferably

(1) (a) Kobayashi, Y.; Hayashi, N.; Kishi, Y. *Org. Lett.* **2002**, *4*, 411. (b) Kobayashi, Y.; Hayashi, N.; Kishi, Y. *Tetrahedron Lett.* **2003**, *44*, 7489.

10.1021/ol048061f CCC: $27.50
Published on Web 11/06/2004

both carbons, of the C-18/C-20, C-22/C-24, C-26/C-28, and C-30/C-32 stereoclusters, respectively. However, our concern was that the C-20, C-22, C-24, C-26, C-28, and C-30 carbons of **1** would give overlapping resonances in the chiral medium, thus precluding the assignment of absolute stereochemistry at C-27 and C-23. Experimentally, this was shown to be the case.[3] Such a problem, in principle, can be solved by spreading the chemical shifts of the concerned carbons. This could be achieved either (1) by acquiring the spectrum on a higher magnetic field NMR spectrometer or (2) with the use of lanthanide shift reagents.[4] We found the latter option more appealing and decided to explore the use of chiral lanthanide shift reagents as a possible surrogate to the chiral solvent.

Chiral shift reagents have been used widely to evaluate enantiomeric excesses.[5] However, only scattered examples are found in the literature that demonstrate their potential to determine the absolute stereochemistry of optically active compounds,[6] and no general rule is postulated in any of these examples that would facilitate stereochemical assignment in a variety of substrates.[7] It is also worthwhile noting that all the reported cases relied on ^{1}H NMR spectroscopy. There are only a few examples that study the effect of shift reagents on the ^{13}C NMR spectrum of an alcohol or any other substrate.[8] To the best of our knowledge, no literature precedent could be found corroborating the correlation of absolute stereochemistry to ^{13}C chemical shifts observed in the presence of a chiral shift reagent. Our particular interest in employing the ^{13}C NMR spectrum rather than the ^{1}H NMR spectrum for stereochemical analysis was twofold. First, we hoped that, in the presence of shift reagent, the carbon resonances would be less susceptible to line broadening. Second, due to the absence of *J* coupling, it should be much simpler to analyze the ^{13}C NMR spectrum of an optically active compound in comparison to its ^{1}H NMR spectrum.

With this in mind, we tested (*R*)-Eu(tfc)$_3$ **3** and (*R*)-Pr(tfc)$_3$ **4** for their capacity to discriminate the enantiotopic C-4/C-6 carbons of *n*-nonan-5-ol (**5**) and tertiary

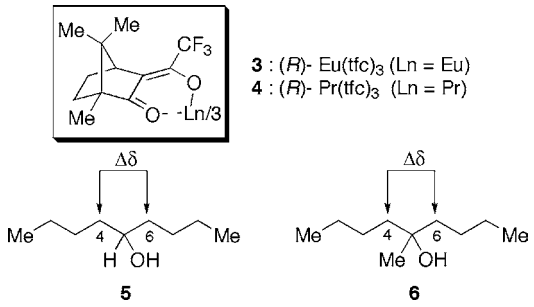


Figure 3. Discrimination of enantiotopic carbons C-4/C-6 in *meso* alcohols **5** and **6** by chiral shift reagents **3** and **4**. For $\Delta\delta$ values, see Table S3 in Supporting Information.

meso alcohol **6** (Figure 3).[9] It was observed that both **3** and **4** clearly discriminated the enantiotopic carbons C-4/C-6 in deuteriobenzene.[10] However, it should be noted that **3** and **4** exhibit marked differences in their behavior.[11] First, as expected, (*R*)-Pr(tfc)$_3$ **4** induces an upfield shift in both the ^{1}H and ^{13}C NMR spectrum, whereas (*R*)-Eu(tfc)$_3$ **3** results in a downfield shift.[12] Second, at the same concentration, the magnitudes of lanthanide-induced shifts[12] and $\Delta\delta$ are always greater with the Pr-based shift reagent than with the corresponding Eu-based shift reagent, thereby suggesting that **4** is superior to **3** in discriminating enantiotopic carbons of **5** and **6**. Third, it is known that lanthanide-induced shifts by a Pr-based shift reagent are primarily due to a pseudocontact mechanism with a negligible contribution from a contact effect.[13] This is in contrast to a Eu-based shift reagent, where an appreciable contribution from contact mechanism has been suggested.[14]

The desymmetrization experiments of *meso* alcohols **5** and **6** indicate the possibility that either **3** or **4** could be used for assigning the absolute configuration of isolated secondary and tertiary alcohols. However, we chose to conduct the subsequent NMR studies with (*R*)- and (*S*)-Pr(tfc)$_3$ **4** in C_6D_6

(2) (a) Tomoda, H.; Huang, X. H.; Nishida, H.; Masuma, R.; Kim, Y. K.; Omura, S. *J. Antibiot*. **1992**, *45*, 1202. (b) Nishida, H.; Huang, X. H.; Tomoda, H.; Omura, S. *J. Antibiot*. **1992**, *45*, 1669.

(3) Ghosh, I.; Kishi, Y.; Tomoda, H.; Omura, S. *Org. Lett*. **2004**, *6*, 4719.

(4) (a) Hinckley, C. C. *J. Am. Chem. Soc*. **1969**, *91*, 5160. (b) Sanders, J. K. M.; Williams, D. H. *J. Chem. Soc., Chem. Commun*. **1970**, 422. Also see ref 5a.

(5) For reviews on determination of enantiomeric excess, see for example: (a) Wenzel, T. J. *NMR Shift Reagents*; CRC Press: Boca Raton, FL, 1987. (b) Frazer, R. R. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Chapter 9, p 173. (c) Sullivan, G. R. In *Topics in Stereochemistry*; Eliel, E. L., Allinger, N. L., Eds.; Wiley & Sons: New York, 1978; p 287.

(6) For determination of absolute configuration, see for example: (a) Ajisaka, K.; Kainosho, M.; Kamisaku, M. *Chem. Lett*. **1972**, 857. (b) Cervinka, O.; Malon, P.; Trska, P. *Collect. Czech. Chem. Commun*. **1973**, *38*, 3299. (c) Sullivan, G. R.; Ciavarella, D.; Mosher, H. S. *J. Org. Chem*. **1974**, *39*, 2411 and references therein (d) Tanaka, K.; Ootani, M.; Toda, F. *Tetrahedron: Asymmetry* **1992**, *3*, 709. (e) Buist P. H.; Marecak, D.; Holland, H. L.; Brown, F. M. *Tetrahedron: Asymmetry* **1995**, *6*, 7 and references therein. (f) Inamoto, A.; Ogasawara, K.; Omata, K.; Kabuto, K.; Sasaki, Y. *Org Lett*. **2000**, *2*, 3543 and references therein.

(7) For an empirical rule for determining the absolute configuration of 2- and 3-hydroxycarboxylic acids, esters, and ethers using the chiroptical properties of their Eu(fod)$_3$ complexes, see: Wegrzynski, B.; Toome, V. *Anal. Lett*. **1991**, *24*, 317.

(8) For representative examples, see: (a) Williams, D. H. *Pure Appl. Chem*. **1974**, *40*, 25. (b) Hawkes, G. E.; Liebfritz, D.; Roberts, D. W.; Roberts, J. D. *J. Am. Chem. Soc*. **1973**, *95*, 1659. (c) Hawkes, G. E.; Marzin, C.; Johns, S. R.; Roberts, J. D. *J. Am. Chem. Soc*. **1973**, *95*, 1661.

(9) *R*)-Eu(tfc)$_3$ and (*R*)-Pr(tfc)$_3$ were chosen on the basis of their cost of commercial sample and the ease of large-scale preparation. Chiral shift reagents **3** and **4** were prepared following experimental procedures reported by: McCreary, M. D.; Lewis, D. W.; Wernick, D. L.; Whitesides, G. M. *J. Am. Chem. Soc*. **1974**, *96*, 1038. During the course of this study, we noticed an alternative procedure (Schurig, V. *Tetrahedron Lett*. **1972**, *13*, 3297) especially effective for the preparation of Ln(tfc)$_3$.

(10) To the best of our knowledge, the discrimination of enantiotopic carbons has not been reported. For enantiotopic discrimination of protons or groups within a molecule by chiral shift reagents, see for example: (a) Fraser, R. R.; Petit, M. A.; Miskow, M. *J. Am. Chem. Soc*. **1972**, *94*, 3253. (b) Goering, H. L.; Eikenberry, J. N.; Koermer, G. S.; Lattimer, C. J. *J. Am. Chem. Soc*. **1974**, *96*, 1493.

(11) See Supporting Information.

(12) (a) Horrocks, W. D., Jr.; Sipe, J. P., III. *J. Am. Chem. Soc*. **1971**, *93*, 6800. (b) Bleaney, B.; Dobson, C. M.; Levine, B. A.; Martin, R. B.; Williams, R. J. P.; Xavier, A. V. *J. Chem. Soc., Chem. Commun*. **1972**, 791b. (c) Mayo, B. C. *Chem. Soc. Rev*. **1973**, *2*, 49.

(13) In most cases, the lanthanide-induced shifts (LISs) can be described by the sum of two terms arising from contact (LIS$_C$) and pseudocontact (LIS$_{PC}$).

(14) (a) Reuben, J.; Fiat, D. *J. Chem. Phys*. **1969**, *51*, 4909. (b) Inagaki, F.; Miyazawa, T. *Prog. NMR Spectrosc*. **1981** *14*, 67.

for two reasons: (1) **4** is a sharper discriminator of enantiotopic carbons than **3** and (2) Pr-based shift reagents operate primarily through a pseudocontact mechanism.[15] We next tested the validity of our approach with optically active alcohols **7**−**22** possessing the indicated absolute configuration. Each alcohol was subjected sequentially to 15 mol % (*R*)- and (*S*)-**4** (Figure 4).[16] As expected, the α-carbons

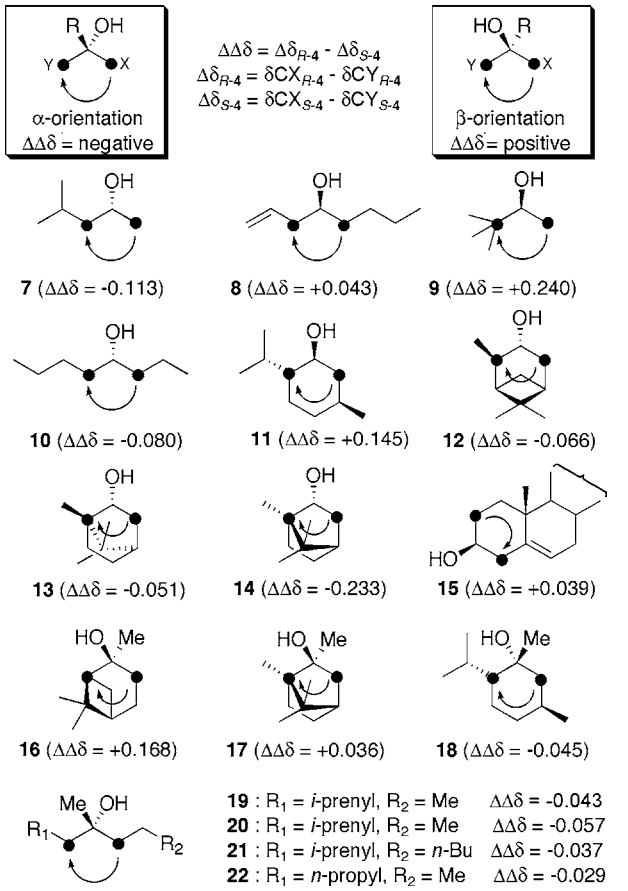


Figure 4. Determination of absolute stereochemistry of optically active secondary and tertiary alcohols **7**−**22** by analysis of the ΔΔδ values for the indicated carbons in the presence of (*R*)- and (*S*)-Pr(tfc)$_3$ (**4**). δCX$_R$ and δCY$_R$ are the chemical shifts of carbons X and Y with (*R*)-Pr(tfc)$_3$, respectively, whereas δCX$_S$ and δCY$_S$ are the chemical shifts of carbons X and Y with (*S*)-Pr(tfc)$_3$, respectively. The ΔΔδ values are calculated by manipulating the chemical shifts of carbons X and Y with (*R*)- and (*S*)-4 in the direction shown.

showed significant chemical shift differences in the presence of (*R*)- and (*S*)-**4**. In the case of the chiral NMR solvent approach, the chemical shifts of the α-carbons in (*R*,*R*)-**2** and (*S*,*S*)-**2** exhibit a consistent relationship between absolute configuration and the signs of $\Delta\delta_{(RR-SS)}$ for C−X and C−Y, where $\Delta\delta_{(RR-SS)}$ = (δ_{C-X} or δ_{C-Y} in (*R*,*R*)-**2**) − (δ_{C-X} or δ_{C-Y} in (*S*,*S*)-**2**) (Figure 2). In principle, we expected a similar empirical rule for the chiral shift reagent approach. In practice, however, because the chemical shifts were found to be highly dependent on several factors, including minute differences in concentration of **4** (relative to the substrate) and moisture, it was technically very challenging to establish the ^{13}C NMR behaviors of α-carbons with an acceptable level of reproducibility and reliability. To overcome this difficulty, we conducted extensive experimentation and data analysis and introduced a new term, ΔΔδ ($\Delta\delta_{R-4} - \Delta\delta_{S-4}$), where $\Delta\delta_{R-4}$ = (δ_{C-X} in the presence of (*R*)-**4**) − (δ_{C-Y} in the presence of (*R*)-**4**) and $\Delta\delta_{S-4}$ = (δ_{C-X} in the presence of (*S*)-**4**) − (δ_{C-Y} in the presence of (*S*)-**4**). Importantly, even with variations in concentration (±5%) of **4**, ΔΔδ was found to remain virtually constant. We then examined the ΔΔδ behaviors for the α-carbons of secondary and tertiary alcohols relative to their absolute configuration.

When the three carbon framework is *drawn* as depicted in the boxed structures of Figure 4, we were able to formulate an empirical rule that states that *a hydroxyl in the* α*-orientation corresponds to a negative value of* ΔΔδ. *Alternatively, a hydroxyl in the* β*-orientation corresponds to a positive value of* ΔΔδ.[11,17] The ΔΔδ values are calculated by manipulating the chemical shifts of carbons C−X and C−Y with both (*R*)- and (*S*)-Pr(tfc)$_3$ (**4**) in the direction shown in Figure 4. This relationship is found to be independent of the steric bulk of substituents and, unlike the chiral NMR solvent approach, is maintained for both secondary and tertiary alcohols.[18]

Previous work in our laboratory has shown steric and/or stereoelectronic interactions between structural clusters separated by two or more carbons to be negligibly small. This characteristic, referred to as a self-contained box, constitutes one of the key foundations for our NMR database approach.[19] Naturally, we were curious to examine whether the concept of a self-contained box could be extended to the chiral shift reagent approach. Thus, lanthanide-induced chemical shifts observed in the presence of 15, 30, and 45 mol % **4** were plotted for each carbon of **5** and **6** (Figure 5). The slope of each curve should estimate the effect of Pr-based shift reagent on that particular carbon. Upon inspection, it is evident that the effectiveness of **4** sharply diminishes along the carbon chain and becomes almost negligible three or more carbons away from its complexation site, thereby demonstrating that the concept of a self-contained box can, at least at the first order of approximation, be extended to the current approach.

(15) ^{13}C-Nuclei give rise to lanthanide-induced shifts containing substantial contributions from contact shifts (LIS$_C$). This is true especially for ^{13}C-nuclei close to the point of lanthanide coordination. It was our belief that higher contribution from contact shifts would interfere in the development of a universal empirical rule. Thus, to minimize LIS$_C$, we decided to employ a Pr-based shift reagent rather than a Eu-shift reagent. Also see ref 22.

(16) Samples were prepared using 0.035 mmol of alcohol in 0.7 mL (0.05 M) of C_6D_6 with 15 mol %/OH of chiral shift reagent (CSR). To minimize line broadening, the concentration of the shift reagent was fixed at the absolute minimum of 15 mol %/OH. See Supporting Information for additional experimental details.

(17) For substrates having ΔΔδ values lower than 0.03 ppm, it is recommended that ΔΔδ be determined using three separate sets of data to check for consistency and account for any systematic error.

(18) Currently, optically active allylic and benzylic alcohols are being investigated for a similar empirical rule.

(19) (a) Boyle, C. D.; Harmange, J.-C.; Kishi, Y. *J. Am. Chem. Soc.* **1994**, *116*, 4995. (b) Zheng, W.; DeMattei, J. A.; Wu, J.-P.; Duan, J. J.-W.; Cook, L. R.; Oinuma, H.; Kishi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 7946. (c) Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *Helv. Chim. Acta* **2000**, *83*, 2562. (d) Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *J. Am. Chem. Soc.* **2001**, 123, 2076. (e) Higashibayashi, S.; Czechtizky, W.; Kobayashi, Y.; Kishi, Y. *J. Am. Chem. Soc.* **2003**, *125*, 14379 and references therein.

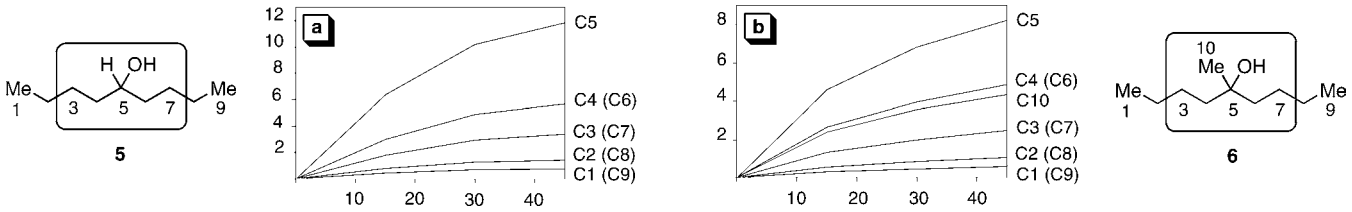


Figure 5. (a) Lanthanide-induced-shift (LIS) plot for *meso* alcohol **5** with 15, 30, and 45 mol % (*R*)-Pr(tfc)$_3$ (**4**). (b) LIS plot for *meso* tertiary alcohol **6** with 15, 30, and 45 mol % (*R*)-Pr(tfc)$_3$ (**4**). The *x*- and *y*-axes represent the concentration of (*R*)-Pr(tfc)$_3$ (**4**) in mol % and LIS in ppm, respectively. The self-contained box is highlighted in structures **5** and **6**.

Despite this observation, the behavior of **4** with polyfunctional substrates still needed to be tested, particularly in the case of diols where chelate formation with the shift reagent might be a plausible mode of interaction.[20] To test such a notion, optically active diols **23**−**25** were prepared and treated sequentially with 15 mol %/OH of (*R*)- and (*S*)-**4** (Figure 6). This experiment demonstrated that both the

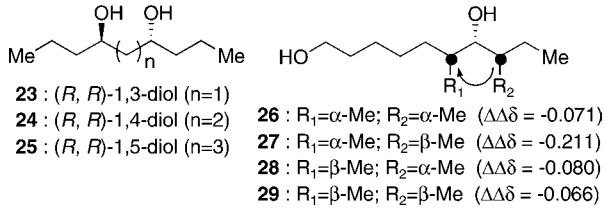


Figure 6. Behavior of optically active 1,*n*-diols **23**−**25** and α,α′-substituted alcohols **26**−**29** with Pr(tfc)$_3$ (**4**).

alcoholic centers of **24** and **25** can be treated as an isolated secondary alcohol and their behaviors can be predicted from the empirical rule summarized in Figure 3.[21] This result indicates that, as long as the hydroxyl groups are separated by two or more carbons, the shift reagent **4** interacts with each hydroxyl in an *independent* fashion. Therefore, the absolute configuration at each stereocenter can be deduced not only simultaneously but also independently from the rest of the molecule via simple analysis of the $\Delta\Delta\delta$ values of the α-carbons belonging to that particular stereogenic center. Finally, the chiral shift reagent approach can also be used to assign the absolute configuration of α,α′-substituted alcohols such as **26**−**29**, which represent the dipropionate structural motif often found in the polyketide class of natural products (Figure 6).

In conclusion, we have demonstrated for the first time that a chiral shift reagent such as **4** can be used to assign the absolute configuration of a variety of secondary and tertiary alcohols with the aid of a *single* empirical rule formulated in Figure 3.[22] In addition, the current approach has the added benefit of easy accessibility to both enantiomers of the shift reagent, thus making it a *user-friendly* procedure.[23] Last, the most unique value of this approach lies in the fact that the chiral shift reagent can resolve closely placed or overlapped carbon resonances into distinct peaks, thereby providing crucial stereochemical information. In the following Letter,[3] we will demonstrate this distinct value by assigning the absolute stereochemistry of glisoprenin A (**1**).

Acknowledgment. Financial support from the National Institutes of Health (NS 12108) and Eisai Research Institute is gratefully acknowledged.

Supporting Information Available: Experimental details for the synthesis of **3** and **4**, 2° alcohols **7**−**10** and **13**, 3° alcohols **16**−**22**, and diols **23**−**25** and **26**−**29**; ^{13}C shifts of 2° alcohols **7**−**10** and 3° alcohols **16**−**22** in the presence of 15 mol % per OH of (*R*)- and (*S*)-Pr(tfc)$_3$ (**4**); and LIS profiles for diols **23**−**25** and secondary mono-ol **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048061F

(20) For representative examples of interaction of bifunctional substrates with a shift reagent, see: (a) Brederode, van H.; Huysmans, W. G. B. *Tetrahedron Lett*. **1971**, *12*, 1695. (b) Sanders, J. K. M.; Hanson, S. W.; Williams, D. H. *J. Am. Chem. Soc*. **1972**, *94*, 5325. (c) ApSimon, J. W.; Beierbeck, H.; Saunders: J. K. *Can. J. Chem*. **1973**, *51*, 3874. (d) Reuben, J. *J. Am. Chem. Soc*. **1977**, *99*, 1765. (e) Hofer, O.; Griengl, H.; Nowak, P. *Monatsh. Chem.* **1978**, *109*, 21.

(21) LIS profiles of diols **24** and **25** closely matched that of the isolated secondary alcohol **10**. See Supporting Information for actual LIS profiles.

(22) For the Eu(tfc)$_3$ case, we have also formulated an empirical rule for predicting the absolute configuration of an unknown compound. However, some exceptions have been found for the Eu-based empirical rule. These include (+)-menthol (**11**) and tertiary alcohol **18**. Thus, we recommend the use of the Pr-based chiral shift reagent over the Eu-based reagent for predicting absolute stereochemistry of alcohols.

(23) *R*)-**4** is commercially available, whereas (*S*)-**4** is readily prepared in multigram quantities in two steps from (*S*)-camphor and $PrCl_3 \cdot 6H_2O$.