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Chiral Silylation Reagents for the Determination of Absolute Configuration by NMR Spectroscopy

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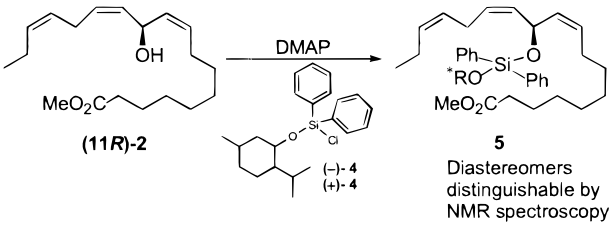
ABSTRACT



We have investigated the use of chiral silylating reagents as analytical probes for determining the absolute stereochemistry of natural products by NMR spectroscopy. These reagents are prepared in high chemical yield in one step and can be used to derivatize chiral allylic alcohols which are incompatible with ester-based methodologies. Microscale (~400 nmol) derivatization conditions have been defined. The resulting siloxane diastereomers are readily distinguished by their ^{1}H NMR spectra.

A common method of defining absolute stereochemistry in small molecules involves derivatizing samples with a chiral reagent and comparing the product with authentic samples of derivatized stereoisomers by either chromatography or NMR spectroscopy. A variety of optically pure reagents have been used to determine absolute stereochemistry in this manner, and the introduction of optically pure (*R*)- and (*S*)-α-(trifluoromethyl)phenylacetic acid[1] (MTPA) and the corresponding acid chlorides for this purpose has made a particularly important contribution to determining the absolute configuration of natural products.

Recently we found ourselves faced with determining the absolute configuration of a heat- and acid-sensitive macrolide (**1**) containing a bis-allylic ester moiety.[2] To establish the absolute configuration of **1**, we converted the macrolide into the corresponding hydroxy methyl ester **2** (Figure 1), with the intention of using the MTPA methodology to compare natural **2** with synthetic, optically pure (*R*)- and (*S*)-**2**.[2]

Unfortunately, due to facile elimination of the free or esterified hydroxyl group in **2** to form a mixture of conjugated tetraenes, we were unable to use MTPA to determine this sensitive alcohol's absolute stereochemistry. Similar difficulties in preparing useful esters with MTPA have been encountered in the determination of the absolute

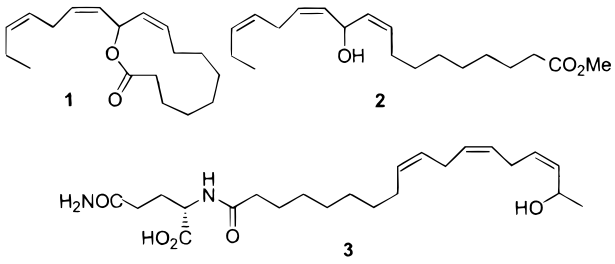


Figure 1. Structures of macrolide **1**, open-chain derivative **2**, and volicitin **3**.

(1) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
(2) Manuscript in preparation.

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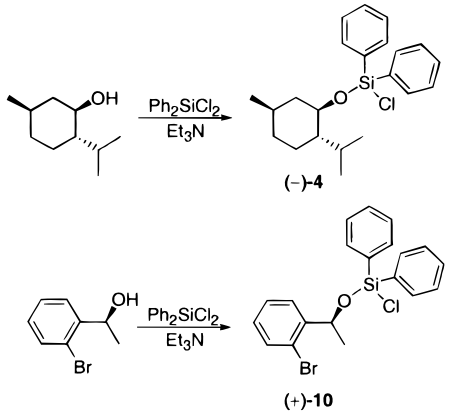
configuration of *N*-(17-hydroxylinolenoyl)-L-glutamine (volicitin, **3**), an important elicitor of "plant volatile" biosynthesis recently identified from the saliva of beet armyworms (Figure 1).[3] Consequently, the absolute configuration of volicitin remains undetermined.[4]

Since MTPA and similar chiral ester-forming reagents are likely to prove unsuitable for the characterization of optically active alcohols which are prone to undergo elimination, we considered the use of chiral silylating reagents for this purpose. Silylations can be carried out under very mild conditions, and the resulting silyl ethers would be expected to be much more resistant to elimination than the corresponding *O*-acyl derivatives. Furthermore, silyl ethers are easily cleaved, allowing recovery of the original alcohol. A survey of the literature revealed two investigations of chiral silylating reagents for examining the optical purity of alcohols. Clausen and Bols[5] have shown that trimenthoxychlorosilane can distinguish between enantiomers of a racemic homoallylic alcohol by ^{13}C NMR spectroscopy, and Chan et al.[6] showed that chiral silyl derivatives could be used to determine ee's for simple secondary alcohols by ^{1}H and ^{13}C NMR analysis. Surprisingly, no application of this methodology has been reported in elucidating the absolute stereochemistry of natural products. We now report the preparation of two chiral silylation reagents, **4** and **10**, which should prove generally useful for the stereochemical characterization of labile alcohols.

We prepared (+)- and (−)-chloromenthoxydiphenylsilanes **4** (Scheme 1) from commercially available dichlorodiphenylsilane and optically pure (+)- and (−)-menthol.[7]

Scheme 1



The derivatization of synthetic (11*R*)-hydroxyoctadeca-9(*Z*),12(*Z*),15(*Z*)-trienoic acid methyl ester **2** with (−)-silane and (+)-silane **4** proceeded rapidly at 0 °C in the presence of DMAP to afford the diastereomeric siloxanes **5** and **6** in good yield.[8] As anticipated, the ^{1}H NMR spectra of these products showed significant differences in their chemical shift patterns (Figure 2).

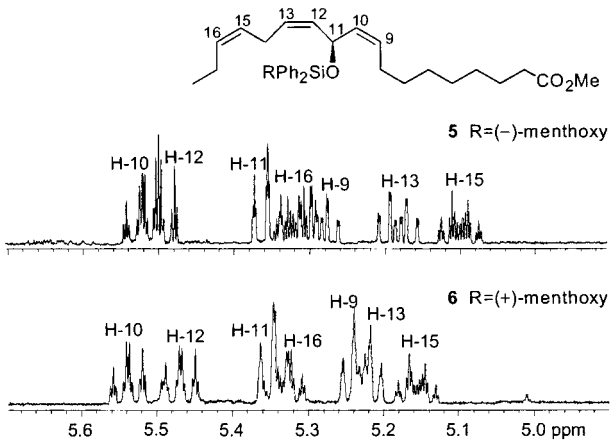


Figure 2. ^{1}H NMR spectra of siloxane diastereomers **5** and **6** (500 MHz, $CDCl_3$).

Turning our attention to the volicitin example, we derivatized the closely related (17*R*)-hydroxyoctadeca-9(*Z*),12(*Z*),-15(*Z*)-trienoic acid methyl ester[4] **7** with (+)- and (−)-silane

(3) Alborn, H. T.; Turlings, T. C. J.; Jones, T. H.; Stenhagen, G.; Loughrin, J. H.; Tumlinson, J. H. *Science* **1997**, *276*, 945.

(4) Pohnert, G.; Koch, T.; Boland, W. *Chem. Commun.* **1999**, 1087.

(5) Clausen, R. P.; Bols, M. *J. Org. Chem.* **1997**, *62*, 4457.

(6) Chan, T. H.; Peng, Q. J.; Wang, D.; Guo, J. A. *J. Chem. Soc., Chem. Commun.* **1987**, 325.

(7) Triethylamine (4.90 mL, 35.2 mmol) was added dropwise to a stirred solution of dichlorodiphenylsilane (6.58 mL, 32.0 mmol) in CH_2Cl_2 (100 mL) at 0 °C. Subsequently, a solution of (−)-menthol (5.00 g, 31.99 mmol) in CH_2Cl_2 (10 mL) was added dropwise via cannula. The reaction mixture was slowly warmed to rt and then heated to 42 °C for 72 h. After removing the solvent, 100 mL of 50% hexane in ether was added to the viscous oil, and the resulting mixture was stirred for 5 min under argon. Filtration was carried out under argon and the filter cake washed with 50 mL of 50% hexane in ether. The resulting clear solution was concentrated in vacuo and vacuum distilled to provide 7.82 g (66%) of (−)-**4** as a clear oil: bp 192−194 °C at 0.5 mm; $[\alpha]^{22}_D$ −47° (*c* 1.68, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66−7.74 (m, 4 H), 7.36−7.49 (m, 6 H), 3.78 (dt, 1 H, J = 4.3 and 10.4 Hz), 2.24 (dquin, 1 H, J = 2.3 and 6.9 Hz), 1.94−2.01 (m, 1 H), 1.56−1.64 (m, 2 H), 1.24−1.36 (m, 2 H), 0.82−0.92 (m, 9 H), 0.58 (d, 3 H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.8, 134.7, 131.0, 128.1, 74.9, 50.0, 44.8, 34.5, 31.8, 25.5, 22.8, 22.3, 21.4, 15.7; MS (EI^+) *m*/*z* (rel intensity) 336 (3), 295 (24), 294 (98), 217 (100), 181 (33), 138 (49), 123 (52), 95 (86), 81 (89).

(8) A solution of (−)-silane **4** (14.6 mg, 0.039 mmol) in CH_2Cl_2 (100 μL) was added dropwise to a solution of (11*R*)-**2** (11 mg, 0.035 mmol) in CH_2Cl_2 (300 μL) at 0 °C. DMAP (6.0 mg, 0.046 mmol) was added and the reaction stirred for 2 h at 0 °C. The reaction was then warmed to rt, concentrated in vacuo, and chromatographed on SiO_2 (2.5% ethyl acetate in hexane) to afford siloxane **5** as a clear oil in 75% yield (17.3 mg): R_f = 0.15 (2.5% ethyl acetate in hexane); $[\alpha]^{22}_D$ −39° (*c* 1.60, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60−7.67 (m, 4 H), 7.36−7.41 (m, 2 H), 7.30−7.35 (m, 4 H), 5.52 (m, $J_{10,9}$ = 10.8, $J_{10,11}$ = 8.7, $J_{10,8}$ = 1.6 Hz, 1 H, 10-H), 5.49 (m, $J_{12,13}$ = 10.8, $J_{12,11}$ = 8.7, $J_{12,14}$ = 1.6 Hz, 1 H, 12-H), 5.35 (m, $J_{11,10} = J_{11,12}$ = 8.7, $J_{11,9} = J_{11,13}$ = 1.2 Hz, 1 H, 11-H), 5.31 (m, $J_{16,15}$ = 10.8, $J_{16,17}$ = 7.2, $J_{16,14}$ = 1.6 Hz, 1 H, 16-H), 5.28 (m, $J_{9,10}$ = 10.8, $J_{9,8}$ = 7.3, $J_{9,11}$ = 1.2 Hz, 1 H, 9-H), 5.18 (m, $J_{13,12}$ = 10.8, $J_{13,14}$ = 7.3, $J_{13,11}$ = 1.2 Hz, 1 H, 13-H), 5.10 (m, $J_{15,16}$ = 10.8, $J_{15,14}$ = 7.2, $J_{15,17}$ = 1.6 Hz, 1 H, 15-H), 3.67 (s, 3 H), 3.58 (dt, 1 H, J = 4.2 and 10.2 Hz), 2.50−2.58 (m, 1 H, 14-H), 2.39−2.47 (m, 1 H, 14-H), 2.25−2.38 (m, 3 H), 1.99−2.06 (m, 1 H), 1.92 (quintet, 2 H, J = 7.3 Hz), 1.75−1.84 (m, 2 H), 1.52−1.64 (m, 5 H), 1.15−1.32 (m, 10 H), 1.06−1.14 (m, 1 H), 0.92 (t, 3 H, J = 7.4 Hz), 0.88 (d, 3 H, J = 7.1 Hz), 0.83 (t, 3 H, J = 6.5 Hz), 0.75−0.87 (m, 1 H), 0.54 (d, 3 H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 135.4, 135.3, 134.4, 134.2, 132.2, 131.8, 131.6, 130.0, 128.1, 127.7, 127.6, 126.9, 73.6, 65.6, 51.6, 50.2, 45.4, 34.7, 34.3, 31.7, 29.7, 29.4, 29.36, 29.32, 28.0, 25.9, 25.4, 25.1, 22.8, 22.4, 21.5, 20.6, 15.8, 14.3; HRMS calcd for $C_{41}H_{60}O_4Si$ 644.4260, found 644.4252.

4. The resulting siloxanes **8** and **9** were obtained in 80% yield after chromatography on SiO_2. Investigation of **8** and **9** by ^1H NMR spectroscopy again revealed clearly different chemical shifts and splitting patterns which could be applied toward determining the absolute configuration of natural volicitin (Figure 3).

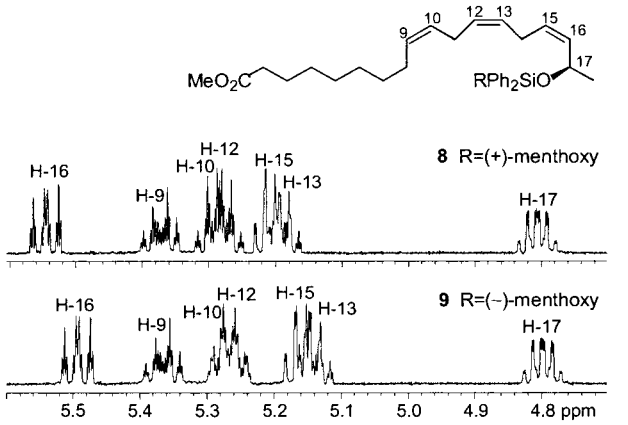


Figure 3. ^1H NMR spectra of siloxane diastereomers **8** and **9** (500 MHz, $CDCl_3$).

In addition to the two examples presented, several chiral aliphatic alcohols were derivatized. Again, the ^1H NMR spectra of the resulting diastereomeric siloxanes showed significant differences, indicating the general applicability of our method. It should be noted that even in cases where proton NMR signals partially overlap, commonly available software packages for the analysis of NMR data can be used to deconvolute the signals of interest, making determination of ee's and absolute configuration feasible.

While silane **4** clearly distinguishes between the enantiomers of the allylic alcohols we have studied thus far, the proton signals of the menthoxy group might in some cases cause undesirable overlap with important proton signals of the substrate in the aliphatic region. As an alternative derivatization reagent, we therefore prepared chiral chlorodiphenylsilanes **10** from optically pure (*R*)-(+)- and (*S*)-(−)-2-bromo-α-methylbenzyl alcohol (Scheme 1). Both (+)- and (−)-silane **10** were used to derivatize (11*R*)-**2**; the resulting siloxane diastereomers **11** and **12** again showed significant differences in their ^1H NMR spectra (Figure 4).

We next adapted the silylation procedures to microscale reactions. After investigating a variety of conditions, we found that as little as 100 μg (~400 nmol) of trienol **2** could be derivatized in a nearly quantitative manner using 100 equiv of DMAP and of (−)-silane **4**.[9] Reactions were immediately complete and were quenched with excess methanol to reveal two products on SiO_2 TLC: one spot corresponding to menthoxymethoxydiphenylsilane and one

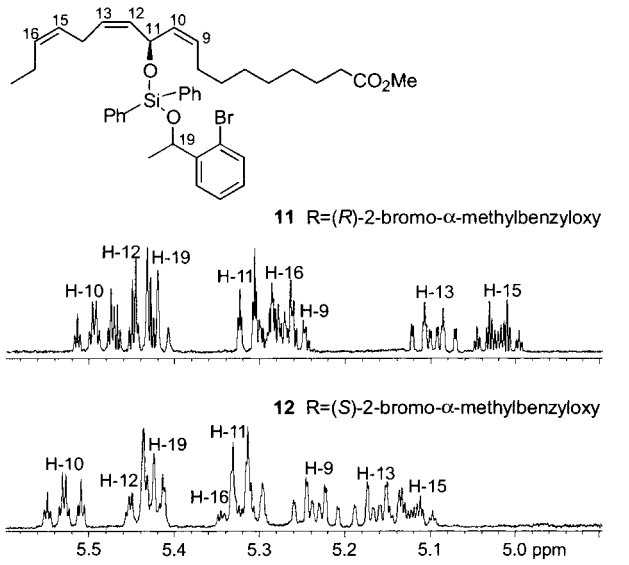


Figure 4. ^1H NMR spectra of siloxane diastereomers **11** and **12** (500 MHz, $CDCl_3$).

to the desired product. Column chromatography or HPLC yielded the pure siloxanes. We anticipate that this method can be extended to even smaller amounts of chiral alcohols that approach the limits of ^1H NMR sensitivity.

In conclusion, we have prepared chiral silylation reagents that can be used for the determination of absolute configuration and enantiomeric excess of labile chiral alcohols. In the two examples we have described, stable diastereomeric siloxane derivatives are obtained; their ^1H NMR spectra clearly allow us to distinguish between the enantiomers of alcohols from which they are derived. Derivatization conditions are mild and have been optimized for microscale reactions. Alcohols can be conveniently recovered by briefly treating their siloxane derivatives with TBAF. While in this Letter we have illustrated the utility of this procedure for the determination of the absolute configuration of allylic alcohols, we anticipate that this method can be extended easily to a variety of other structures.

Acknowledgment. We are indebted to Dr. Georg Pohnert for providing us with a sample of synthetic TBDMS-protected (17*R*)-hydroxylinolenic acid methyl ester. The partial support of this research by the National Institutes of Health (GM53830) is gratefully acknowledged.

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(9) (11*R*)-**2** (136 μg, 440 nmol) was placed in a microvial, dissolved in CH_2Cl_2 (75 μL), and cooled to 0 °C. (−)-Silane **4** (16.4 mg, 0.044 mmol) was added to the vial dropwise as a solution in CH_2Cl_2 (75 μL) followed by addition of DMAP (5.4 mg, 0.044 mmol). The reaction was shown to be immediately complete by TLC and was quenched by dropwise addition of methanol (250 μL). Concentration in vacuo followed by chromatography on a SiO_2 pipet column provided siloxane **5** in nearly quantitative yield.