ORGANIC LETTERS

2002
Vol. 4, No. 17
2869−2871

Cyclic Chiral Silyl Derivatives for the Determination of the Absolute Configuration of Aliphatic Diols by Gas Chromatography

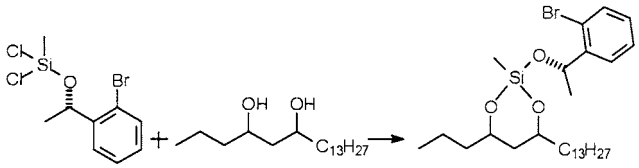
Cristian Arsene and Stefan Schulz*

Institut für Organische Chemie, Technische Universität Braunschweig, Hagenring 30, D-38106 Braunschweig, Germany

stefan.schulz@tu-bs.de

Received May 30, 2002

ABSTRACT



Chiral bidentate silyl reagents have been developed for the GC analysis of aliphatic 1,3- and 1,4-diols. These reagents react with the diols to cyclic siloxanes, which allow the determination of their enantiomeric composition even in complex mixtures. The absolute configuration of 4,6-nonadecanediol 7, occurring in the lipids of sunflower pollen, has been determined to be (4*S*,6*R*) by comparison with derivatized synthetic enantiomers.

Long-chain 1,3-alkanediols, which show interesting antitumor activity[1], have been recently identified in a number of plant species[2−4] and in the silk lipids of a spider.[5] One such compound is 4,6-nonadecanediol (**7**), which occurs together with homologues in the lipids of sunflower pollen and may play a role in host recognition by the sunflower moth, *Homeosoma electellum*.[6] The sunflower pollen lipids are a complex mixture of over 200 components with often similar properties, which makes individual compounds difficult to isolate.[4] We were interested in the determination of the absolute configuration of **7** as a model for other 1,3-diols of the extract. The *syn*- and *anti*-diastereomers of such diols can be readily differentiated by chromatographic methods[3,4] or by NMR experiments when pure samples are available.[7] Nevertheless, no method for the chromatographic separation of the enantiomers of such long-chain diols exists, while short-chain diols have been separated on chiral phases after conversion into different derivatives.[8]

In principle, direct separation of enantiomers without any modification on chiral phases is the most direct and best way. Nevertheless, a lot of chiral GC and LC phases are available, which makes the choice of an appropriate phase more or less a trial and error process, because no good rules for phase selection exist. Therefore, methods that rely on the derivatization of the analyte with a pure enantiomer of a derivatizing reagent (generally called CDA methods) have some advantages. The resulting diastereomers can be separated in

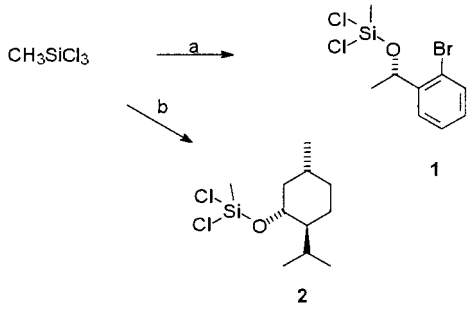
(1) Motohashi, S.; Akihisa, T.; Tamura, T.; Tokutake, N.; Takido, M.; Yasukawa, K. *J. Med. Chem.* **1995**, *38*, 4155−4156.
(2) Akihisa, T.; Oinuma, H.; Tamura, T.; Kasahara, Y.; Kumaki, K.; Yasukawa, K.; Takido, M. *Phytochemistry* **1994**, *36*, 105−108. Jetter, R.; Riederer, M.; Seyer, A.; Mioskowski, C. *Phytochemistry* **1996**, *42*, 1617−1620.
(3) Akihisa, T.; Inoue, Y.; Yasukawa, K.; Kasahara, Y.; Yamanouchi, S.; Kumaki, K.; Tamura, T. *Phytochemistry* **1998**, *49*, 1637−1640.
(4) Schulz, S.; Arsene, C.; Tauber, M.; McNeil, J. N. *Phytochemistry* **2000**, *54*, 325−336.
(5) Schulz, S. *Lipids* **2001**, *36*, 637−647.
(6) McNeil, J. N.; Delisle, J. *Oecologia* **1989**, *80*, 201−205. Delisle, J.; McNeil, J. N.; Underhill, E. W.; Barton, D. *Entomol. Exp. Appl.* **1989**, *50*, 53−60.
(7) Hoffmann, R. W.; Weidmann, U. *Chem. Ber.* **1985**, *118*, 3980−3992.
(8) For example: König, W. A.; Lutz, S.; Colberg, C.; Schmidt, N.; Wenz, G.; von der Bey, E.; Mosandl, A.; Günther, C.; Kustermann, A. *J. High Res. Chrom.* **1988**, *11*, 621−625. König, W. A.; Krebber, R.; Mischnick, P. *J. High Res. Chrom.* **1989**, *12*, 732−738.

10.1021/ol026265v CCC: $22.00
Published on Web 08/02/2002

favorable cases on standard achiral phases and allow the determination of the enantiomeric composition of the analyte. This procedure has been used for alcohols using different derivatizing reagents, e.g., acetyllactic acid,[9] Mosher's acid (3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid),[10] or chlorofluoroacetic acid.[11] Due to the inherent flexibility of open-chain compounds, long-chain aliphatic 1,3-diols are difficult to separate, resulting in failure of the mentioned methods. Furthermore, some of the used reagents do not easily form esters with sterically demanding alcohols, e.g., Mosher's acid.

We therefore designed enantiomerically pure bidentate derivatizing agents, which form a ring with the 1,3-diol moiety, thus reducing the flexibility of the molecule. The inclusion of a dichlorosilyl moiety seemed to be promising, because silyl ethers are readily formed with alcohols. Such compounds can be synthesized starting from trichloromethylsilane (Scheme 1). Reaction with 1 equiv of (*S*)-1-(2-bromophenyl)ethanol furnished (*S*)-[1-(2-bromophenyl)-ethoxy]dichloromethylsilane (**1**) in 83% yield, while the corresponding menthyl derivative **2** was obtained in 56% yield from (−)-menthol. These dichlorosilanes react smoothly with 1,3-diols in the presence of toluene and NEt_3, forming 1,3-dioxa-2-silacyclohexanes.[12]

Scheme 1[a]



[a] Key: (a) (*S*)-(−)-1-(2-bromophenyl)ethanol, NEt_3, CH_2Cl_2; (b) (−)-menthol, NEt_3, CH_2Cl_2.

The reaction of a mixture of the four stereoisomers of **7** with enantiomerically pure **1** resulted in the formation of eight diastereomers (see Figure 1). These isomers can be separated into seven peaks on a usual apolar BPX-5 GC phase (SGE). This phase was chosen because of its widespread use and high thermal stability, which allowed separation of even larger diols (see below). The derivatives of the menthyl reagent **2** were resolved into only five peaks. For peak assignment, the four stereoisomers of **7** were synthesized according to Scheme 2. Ethyl 3-oxohexanoate (**3**) was enantioselectively hydrogenated with the commercially available [Ru(*p*-cymene)-(*R*)-BINAP)]Cl catalyst, yielding ethyl (*R*)-3-hydroxyhexanoate (**4**). After protection and transformation into the Weinreb amide **5**, chain elongation was achieved with tridecylmagnesium bromide. Deprotection

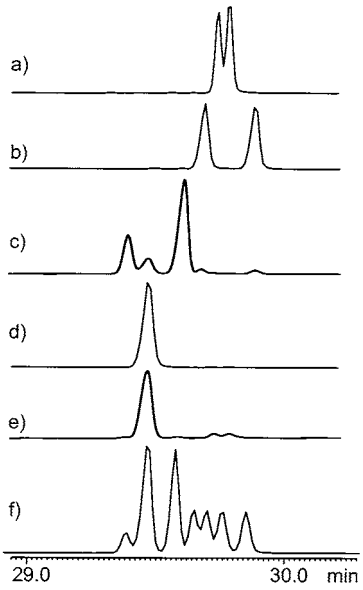
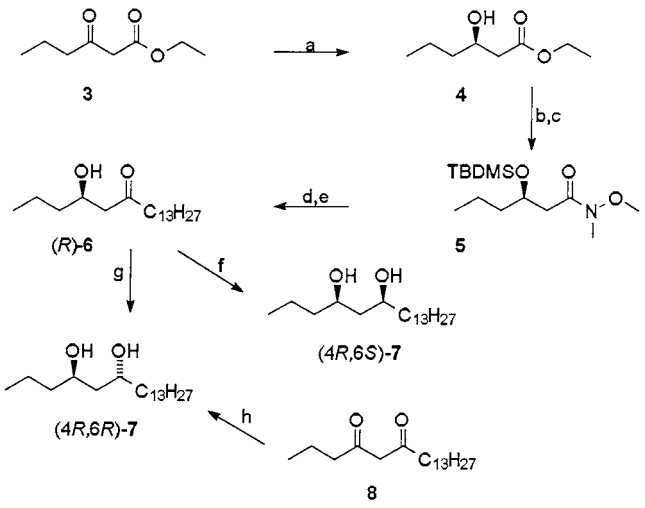


Figure 1. Separation of (*S*)-[1-(2-bromophenyl)ethoxy]methylsilyl derivatives of 4,6-nonadecanediol (**7**) on a BPX-5 GC phase. (a) (4*S*,6*S*)-**7**; (b) (4*R*,6*R*)-**7**; (c) (4*R*,6*S*)-**7**; (d) sunflower pollen extract; (e) (4*S*,6*R*)-**7**; (f) mixture of all eight diastereomers.

Scheme 2[a]



[a] Key: (a) H_2, [Ru(*p*-cymene)-(*R*)-BINAP)]Cl; (b) TBDMSOTf, NEt_3; (c) CH_3NHOCH_3·HCl, $AlMe_3$; (d) $BrMgC_{13}H_{27}$; (e) TBAF; (f) BEt_3, $NaBH_4$; (g) $NaBH(OAc)_3$; (h) H_2, [Ru(*p*-cymene)-(*R*)-BINAP)]Cl.

(9) Slessor, K. N.; King, G. G. S.; Miller, D. R.; Winston, M. L.; Cutforth, T. L. *J. Chem. Ecol.* **1985**, *11*, 1659−1667.

(10) Michelsen, P.; Odham, G. *J. Chromatogr.* **1985**, *331*, 295−302.

(11) Ruzicka, J.; Streinz, L.; Saman, D.; Havlas, Z.; Wimmer, Z.; Zarevucka, M.; Koutek, B.; Leseticky, L. *Coll. Czech. Chem. Commun.* **2000**, *65*, 695−707.

(12) Derivatizations were performed as follows: about 1 mg of extract or other sample was dissolved in 500 μL of toluene and 25 μL of triethylamine, and 25 μL of dichlorosilane reagent was added; the mixture was kept for 1 h at 60 °C. After the mixture was cooled to room temperature, 25 μL of methanol was added to destroy excess reagent and the mixture filtered over a short plug of silica. The filtrate was directly used for GC analysis.

furnished the labile (*R*)-ketol **6**, which was transformed with sodium borohydride reduction in the presence of triethylborane into the *syn*-diol (4*R*,6*S*)-**7** with 5:1 *syn*/*anti* selectivity. Its enantiomer was prepared in a similar manner, using the (*S*)-BINAP-Ru catalyst. The two *anti*-isomers (4*R*,6*R*)- and (4*S*,6*S*)-**7** were easily accessible by enantioselective hydrogenation of 4,6-nonadecandione **8** with the mentioned BINAP catalysts according to our published procedure.[13] The sense of induction of the BINAP catalysts in the diketone reduction was proved by conversion of the ketol (*R*)-**6** into the *anti*-diol (4*R*,6*R*)-**7** and comparison of specific rotations, as well as GC investigations, and is in accord with previous observations on the enantioselective reduction of 2,4-hexandione using another Ru-BINAP catalyst.[14]

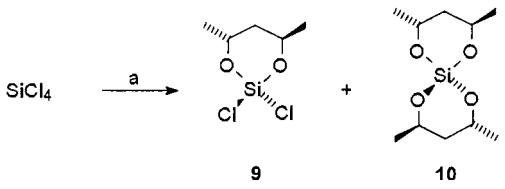
Figure 1 shows the chromatograms obtained from the four stereoisomers of **7** after derivatization with **1** and a derivatized natural sunflower pollen extract. Each enantiomer of **7** gives rise to two unique peaks with the exception of the (4*S*,6*R*)-enantiomer; no peak overlapping of different enantiomer derivatives occurs. Thus, for each enantiomer, the ee and the dr can be deduced from the peak areas. Both *anti*-enantiomers are enantiomerically pure, and their dr is better than 98:2. In contrast, the (4*R*,6*S*)-enantiomer shows an ee of 80% and a dr of 95:5 after purification by column chromatography, while in the (4*S*,6*R*) case, the ee is 92% and the dr 95:5. Under the reported conditions, the employed catalysts [Ru(*p*-cymene)-BINAP]Cl are highly stereoselective in the hydrogenation of diketones, while in β-ketoester hydrogenations, other catalysts reported in the literature give superior results.[15] The natural sunflower pollen extract was directly derivatized[12] and analyzed without any further separation. The naturally occurring enantiomer has a (4*S*,6*R*)-configuration and is enantiomerically pure (see Figure 1d). The characteristic mass spectrum of the derivative allows positive identification even in complex mixtures.

The reagent can also be used for 1,4-diols. Thus, derivatization of 2,5-hexanediol resulted in formation of four different stereoisomers (two diastereomers and two meso-forms), which are all separated by GC on standard phases. In contrast, 1,2-diols could not be derivatized under the reported conditions. The respective derivatives were formed only in low yields, even after 24 h of reaction time.

A drawback of the reagent **1** is the need for separation of eight peaks, because during derivatization of unsymmetrical diols a new stereogenic center at the Si-atom is formed. We therefore designed a chiral dichlorosilane containing a C_2-axis. Reaction of equimolar amounts of (2*R*,4*R*)-2,4-pentanediol and $SiCl_4$ furnished the dichlorosilane reagent **9**, which is accompanied by the spirosiloxane **10**. With this reagent, 1,3- and 1,4-diols readily form derivatives under the conditions reported above.[12] The three stereoisomers formed after reaction with 2,5-hexanediol were readily separated. After reaction with the diol **7**, only three of the expected four stereoisomers were separated. In this case, the reagent **1** gave superior results. On the other hand, the small size of the reagent **9** makes it suitable for the analysis of larger diols. The derivative of 14,17-pentatriacontanediol was separated into three peaks. In this case, two long alkyl chains are present in the molecule, thus making the (14*R*,17*S*)- and (14*S*,17*R*)-enantiomers in quasimeso-compounds. They cannot be separated under the reported conditions. Further work is in progress to develop small chiral dichlorosilanes with C_2-symmetry with improved selectivities.

So far, chiral silyl reagents have only been used for NMR investigations.[16,17] We have shown that such reagents can be successfully used as CDA for GC. The promising results will allow development of even better silyl reagents in the future. Furthermore, these bidentate reagents could also be useful for NMR CDA methods.

Scheme 3[a]



[a] Key: (a) (2*R*,4*R*)-pentanediol, NEt_3, CH_2Cl_2.

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft and the Fonds der chemischen Industrie for financial support.

Supporting Information Available: GC separation of derivatives of 2,5-hexanediol and synthetic procedures for **1**, **2**, **9**, and (4*R*,6*S*)- and (4*R*,6*R*)-**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026265V

(13) Schulz, S. *Chem. Commun.* **1999**, 1239−1240.
(14) Kawano, H.; Ishii, Y.; Saburi, M.; Uchida, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 87−88.
(15) Ager, D. J.; Laneman, S. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3327−3355. Ratovelomanana-Vidal, V.; Genêt, J.-P. *J. Organomet. Chem.* **1998**, *567*, 163−171. Ohkuma, T.; Kitamura, M.; Noyori, R. in *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 1−110. Rossen, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 4611−4523. Genêt, J. P. *Pure Appl. Chem.* **2002**, *74*, 77−83.
(16) Terunuma, D.; Kato, M.; Kamie, M.; Uchida, H.; H., N. *Chem. Lett.* **1985**, 13−14. Chan, T. H.; Peng, Q.-J.; Wang, D.; Guo, J. A. *J. Chem. Soc., Chem. Commun.* **1987**, 325−326. Clausen, R. P.; Bols, M. *J. Org. Chem.* **1997**, *62*, 4457−4464.
(17) Weibel, D. B.; Walker, T. R.; Schröder, F. C.; Meinwald, J. *Org. Lett.* **2000**, *2*, 2381−2383. Smedley, S. R.; Schröder, F. C.; Weibel, D. B.; Meinwald, J.; Lafleur, K. A.; Renwick, J. A.; Rutowski, R.; Eisner, T. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 6822−6827