The First Liquid-Chromatographic Separation of the (*R*)- and (*S*)-Enantiomers of a Chiral Silanol, Silane and Germane

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Dedicated to Prof. Dr. H. Schmidbaur on the occasion of his 60th birthday.

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The racemic mixtures of the muscarinic antagonists cyclohexyl(phenyl)(2-pyrrolidinoethyl)silanol (sila-procyclidine, *rac*-**1**), cyclohexyl(hydroxymethyl)phenyl(2-piperidinoethyl)silane (*rac*-**2**) and cyclohexyl(hydroxymethyl)phenyl(2-piperidinoethyl)germane (*rac*-**3**) were resolved by analytical liquid chromatography (HPLC) using chemically modified cellulose (**1**) or amylose (**2**, **3**) as the chiral stationary phase. This chromatographic method was used for the quantitative determination of enantiomeric purity of the (*R*)- and (*S*)-enantiomers of **1–3**, which were obtained by preparative resolution with chiral auxiliary agents. Furthermore, the enantiomeric purity of these samples was established by ¹³C NMR studies using chiral shift reagents. According to these studies, the resolved antipodes of **1–3** (obtained by preparative resolution) were almost enantiomerically pure [HPLC: $\geq 98.2\%$ ee ((*R*)-**3**) to 99.4% ee ((*R*)-**1**, (*S*)-**1**); NMR: $\geq 97\%$ ee].

1. Introduction

In recent years, there has been an increasing interest in optically active silicon and germanium compounds of the formula type **A** [1–3]. The methods used for the preparation of the (*R*)- and (*S*)-enantiomers of this particular type of chiral compounds (center of chirality: Si, Ge) are based on (i) classical resolutions of the respective racemic mixtures *via* fractional crystallization of appropriate diastereomeric derivatives, (ii) stereoselective chemical transformations of the optically active compounds obtained by the aforementioned method and, more recently, (iii) stereoselective biotransformations of suitable racemic or prochiral organosilicon and organogermanium substrates. To the best of our knowledge, prepara-

tive chromatographic resolutions of racemic silicon and germanium compounds of type **A** have not yet been reported in the literature. However, an analytical gas-chromatographic resolution of a series of racemic silanes and silanols has recently been described [4]. Here we report on the first liquid-chromatographic resolution of a racemic silanol, silane and germane.

2. Results and Discussion

The muscarinic antagonists *rac*-cyclohexyl(phenyl)(2-pyrrolidinoethyl)silanol (*rac*-sila-procyclidine, *rac*-**1**), *rac*-cyclohexyl(hydroxymethyl)phenyl(2-piperidinoethyl)silane (*rac*-**2**) and *rac*-cyclohexyl(hydroxymethyl)phenyl(2-piperidinoethyl)germane (*rac*-**3**) were resolved by analytical liquid chromatography (HPLC). As shown by pharmacological studies on various muscarinic receptor subtypes, the (*R*)-enantiomers of **1–3** are significantly more potent than the corresponding (*S*)-antipodes, and the pharmacological receptor selectivity of these drugs is dependent on their absolute configuration [2d, m].

For the liquid-chromatographic separation of the (*R*)- and (*S*)-enantiomers of **1–3**, chemically

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modified cellulose (**1**) or amylose (**2**, **3**) was used as the chiral stationary phase [5], and the antipodes of **1–3** were eluted with a mixture consisting of *n*-hexane, 2-propanol and diethylamine (980:20:0.2, v/v/v). Detection of the respective enantiomers was performed with a UV-VIS detector at 215 nm. Further details of the experimental conditions used for these chromatographic separations are given in the experimental section. Representative chromatograms obtained in these studies are shown in Fig. 1; the retention times of the (*R*)- and (*S*)-enantiomers of **1–3** are listed in Table I.

The separation achieved for the racemic samples of *rac*-**1**, *rac*-**2** and *rac*-**3** was sufficient for quantification of the resolved enantiomers. We took advantage of this for the quantitative determination of enantiomeric purity of the respective (*R*)- and (*S*)-enantiomers obtained by preparative resolution with the antipodes of tartaric acid (**1**

Fig. 1. Chromatograms obtained for the liquid-chromatographic (HPLC) separation of the (*R*)- and (*S*)-enantiomers of **1** (left), **2** (middle) and **3** (right) [(a): racemic mixture; (b): (*R*)-enantiomer obtained by preparative resolution using a chiral auxiliary agent (see experimental section); (c): (*S*)-enantiomer obtained by preparative resolution using a chiral auxiliary agent (see experimental section)].

Table I. Data for the analytical liquid-chromatographic separation (HPLC) of the (*R*)- and (*S*)-enantiomers of **1–3**^a.

Compound	Retention time [min]	Enantiomeric purity [% ee]
(<i>R</i>)- 1	6.74 (6.71) ^b	≥ 99.4 ^c
(<i>S</i>)- 1	8.84 (8.77) ^b	≥ 99.4 ^c
(<i>R</i>)- 2	6.27 (6.25) ^b	≥ 98.8 ^c
(<i>S</i>)- 2	8.97 (8.95) ^b	≥ 99.0 ^c
(<i>R</i>)- 3	5.99 (5.99) ^b	≥ 98.2 ^c
(<i>S</i>)- 3	8.53 (8.48) ^b	≥ 99.0 ^c

^a For details, see experimental section; ^b the first value was measured when starting from the racemic mixture; the second value (in brackets) was measured when starting from the pure enantiomer obtained by preparative resolution using a chiral auxiliary agent (see experimental section); ^c sample obtained by preparative resolution using a chiral auxiliary agent (see experimental section).

[2d]) or *O,O'*-di-*p*-toluoyltartaric acid (**2** [2m], **3** [4]). The enantiomeric purities (% ee) and retention times of the resolved antipodes of **1–3** determined in these experiments are listed in Table I.

Interestingly, even the enantiomers of the silanol **1** could be separated by this particular chromatographic technique without any problems; there were no indications of a significant degree of racemization of (*R*)-**1** and (*S*)-**1** under the experimental conditions used (for the racemization

Fig. 2. Characteristic ^{13}C NMR partial spectra of the (*R*)- and (*S*)-enantiomers of **1** (left), **2** (middle) and **3** (right) obtained in the presence of the chiral shift reagents (+)- $\text{Eu}(\text{hfc})_3$ (for **1**) or (–)-TFAE (for **2** and **3**) (for details, see experimental section) [(a) racemic mixture; (b): (*R*)-enantiomer obtained by preparative resolution using a chiral auxiliary agent (see experimental section); (c) (*S*)-enantiomer obtained by preparative resolution using a chiral auxiliary agent (see experimental section)].

of chiral silanols, see ref. 2d and literature cited therein).

The chromatographically determined ee values of the resolved (*R*)- and (*S*)-enantiomers of **1–3** are in good agreement with the results obtained by NMR-spectroscopic studies. As shown in Fig. 2, the respective enantiomers of **1–3** can be clearly discriminated by ^{13}C NMR spectroscopy in the presence of the chiral shift reagents (+)-tris-[3-(2,2,3,3,4,4,4-heptafluoro-1-hydroxybutylidene)-*d*-camphorato]europium(III) (for **1**) or (–)-2,2,2-trifluoro-1-(9-anthryl)ethanol (for **2** and **3**) (for details, see experimental section). For the silanol **1** the characteristic partial spectrum of the SiC_6H_5 group was recorded, and for the silane **2** and the

germane **3** the characteristic partial spectra of the ElCH_2O ($\text{El} = \text{Si}, \text{Ge}$) and NCH_2C moieties were measured. As only one particular enantiomer could be detected in the respective NMR spectra of the resolved antipodes of **1–3** (see Fig. 2), the ee values of these samples were estimated to be $\geq 97\%$ ee.

In conclusion, liquid chromatography on chiral stationary phases has been demonstrated to be a useful method for the separation of the enantiomers of chiral organosilicon and organogermanium compounds. This technique can be used for analytical purposes (determination of enantiomeric purities). In principle, application of this method for preparative chromatographic resolu-

tions should also be possible. Further studies in this respect will be conducted.

3. Experimental Section

3.1. Preparation of *rac*-**1**, (*R*)-**1** and (*S*)-**1**

The racemate and the (*R*)- and (*S*)-enantiomers of cyclohexyl(phenyl)(2-pyrrolidinoethyl)silanol (sila-procycloidine, **1**) were prepared according to ref. 2d.

3.2. Preparation of *rac*-**2**, (*R*)-**2** and (*S*)-**2**

The racemate and the (*R*)- and (*S*)-enantiomers of cyclohexyl(hydroxymethyl)phenyl(2-piperidinoethyl)silane (**2**) were prepared according to ref. 2m.

3.3. Preparation of *rac*-**3**, (*R*)-**3** and (*S*)-**3**

The racemate and the (*R*)- and (*S*)-enantiomers of cyclohexyl(hydroxymethyl)phenyl(2-piperidinoethyl)germane (**3**) were prepared by analogy to *rac*-**2**, (*R*)-**2** and (*S*)-**2** (synthesis of *rac*-**3** from $\text{Cl}_3\text{GeCH}_2\text{Cl}$; resolution of *rac*-**3** with the antipodes of *O,O'*-di-*p*-toluoyltartaric acid) [6].

3.4. Chromatographic studies

HPLC pump: Shimadzu LC6-A. Detector: Soma S-3702 UV-VIS. Integrator: Shimadzu

C-R3 A. Eluent: *n*-hexane/2-propanol/diethylamine (980:20:0.2, v/v/v); the HPLC-grade solvents were purchased from Merck. Column: CHIRALCEL OD (**1**) or CHIRALPAK AS (**2**, **3**) (Daicel Chemical Industries); 4.6 mm i. d. × 250 mm. Flow rate: 0.8 ml/min. Detection: 215 nm. Temperature: 25 °C (**1**) or 30 °C (**2**, **3**). Injection volume: 20 µl (3 mg of the sample material dissolved in 10 ml of the eluent).

3.5. NMR-spectroscopic studies

The ^{13}C NMR spectra were recorded at room temperature on a Bruker AC-250 (**1**) and AM-400 (**2**, **3**) NMR spectrometer operating at 62.9 MHz and 100.6 MHz, respectively. (+)-Tris-[3-(2,2,3,3,4,4,4-heptafluoro-1-hydroxybutylidene)-*d*-camphorato]europium(III) [(+)-Eu(hfc)₃] and (−)-2,2,2-trifluoro-1-(9-anthryl)ethanol[(−)-TFAE] were purchased from Aldrich and Sigma, respectively. Composition of the samples used for the NMR experiments: 165 µmol **1**, 67.0 µmol (+)-Eu(hfc)₃, 0.6 ml CDCl_3 ; 30.2 µmol **2**, 152 µmol (−)-TFAE, 0.5 ml CDCl_3 ; 31.9 µmol **3**, 192 µmol (−)-TFAE, 0.5 ml CDCl_3 .

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