Notes

Sila-linalool as a Pheromone Analogue: A Study on C/Si Bioisosterism

Reinhold Tacke,*,† Thomas Schmid,† Matthias Hofmann,† Till Tolasch,‡ and Wittko Francke‡

Institut für Anorganische Chemie, Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany, and Institut für Organische Chemie, Universität Hamburg, Martin-Luther-King-Platz 6, D-20146 Hamburg, Germany

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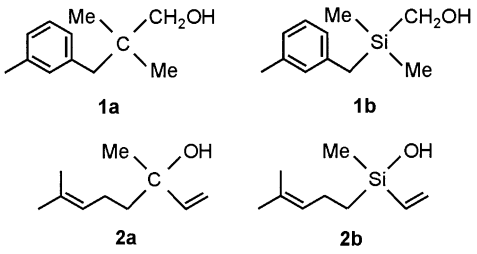
*Summary: rac-Methyl(4-methylpent-3-enyl)vinylsilanol (rac-sila-linalool, rac-**2b**), a sila-analogue of rac-linalool (rac-**2a**), was prepared by a three-step synthesis, starting from dimethoxy(methyl)vinylsilane. Linalool is a widespread natural product with a muguet-type fragrance, and (S)-linalool is an attractant to males of the vernal solitary bee species Colletes cunicularius (Hymenoptera: Colletidae). The enantiomers of the C/Si analogues **2a** and **2b** were separated by gas chromatography using a chiral stationary phase (on-line resolution) and then tested electrophysiologically using antennae of males of C. cunicularius as detectors. In these electroantennographic studies (GC/EAD), both enantiomers of **2a** and **2b** were equally well perceived, indicating distinct bioisosteric relationships between the C/Si analogues linalool and sila-linalool.*

Introduction

In connection with our systematic studies on C/Si bioisosterism,[1] we have been investigating the sensory effects of C/Si exchange (sila-substitution) in organic perfume ingredients.[2] A recent example is the comparison of the olfactory properties of the C/Si pair **1a**/**1b**.[2c] In the same context, the sensory effects of sila-substitution in the terpene linalool (**2a**) (→ sila-linalool (**2b**)), a widespread natural product with a muguet-type fragrance, have been studied by Wrobel and Wannagat in the early 1980s.[3] Recent biological field studies have revealed that (*S*)-linalool ((*S*)-**2a**) is a potent attractant to males of the vernal solitary bee species *Colletes cunicularius* (Hymenoptera: Collitidae).[4] Electrophysiological studies with antennae of males or females of this insect have demonstrated that both enantiomers of linalool were equally well perceived.[4e] These findings prompted us to investigate the biological activity of the enantiomers of sila-linalool (**2b**).[5] We report here on (i) a new synthesis of *rac*-**2b**,[6] (ii) the gas-chromatographic separation of (*R*)-**2b** and (*S*)-**2b**,[7] and (iii) electrophysiological studies with (*R*)-**2b** and (*S*)-**2b** using antennae of males of *C. cunicularius*.



Results and Discussion

Synthesis. *rac*-Sila-linalool (*rac*-**2b**) was prepared by a three-step synthesis, starting from dimethoxy(methyl)vinylsilane (**3**) (Scheme 1). Treatment of **3** with 4-methylpent-3-enylmagnesium iodide in diethyl ether gave *rac*-methoxy(methyl)(4-methylpent-3-enyl)vinylsilane (*rac*-**4**) (yield 50%). Reaction of *rac*-**4** with lithium aluminum hydride in diethyl ether afforded *rac*-methyl-

* To whom correspondence should be addressed. E-mail: r.tacke@mail.uni-wuerzburg.de. Tel: (+49)931-888-5250. Fax: (+49)931-888-4609.
† Universität Würzburg.
‡ Universität Hamburg.

(1) Recent publications dealing with C/Si bioisosterism: (a) Tacke, R.; Reichel, D.; Jones, P. G.; Hou, X.; Waelbroeck, M.; Gross, J.; Mutschler, E.; Lambrecht, G. *J. Organomet. Chem.* **1996**, *521*, 305−323. (b) Tacke, R.; Merget, M.; Bertermann, R.; Bernd, M.; Beckers, T.; Reissmann, T. *Organometallics* **2000**, *19*, 3486-3497. (c) Merget, M.; Günther, K.; Bernd, M.; Günther, E.; Tacke, R. *J. Organomet. Chem.* **2001**, *628*, 183−194. (d) Tacke, R.; Kornek, T.; Heinrich, T.; Burschka, C.; Penka, M.; Pülm, M.; Keim, C.; Mutschler, M.; Lambrecht, G. *J. Organomet. Chem.* **2001**, *640*, 140−165. (e) Tacke, R.; Handmann, V. I.; Kreutzmann, K.; Keim, C.; Mutschler, E.; Lambrecht, G. *Organometallics* **2002**, *21*, 3727−3732. (f) Tacke, R.; Handmann, V. I.; Bertermann, R.; Penka, M.; Seyfried, C. *Organometallics*, in press.

(2) (a) Wrobel, D.; Tacke, R.; Wannagat, U.; Harder, U. *Chem. Ber.* **1982**, *115*, 1694−1704. (b) Tacke, R.; Wiesenberger, F. *Z. Naturforsch., B* **1991**, *46*, 275−279. (c) Tacke, R.; Schmid, T.; Burschka, C.; Penka, M.; Surburg, H. *Organometallics* **2002**, *21*, 113−120.

(3) Wrobel, D.; Wannagat, U. *Liebigs Ann. Chem.* **1982**, 734−738.

(4) (a) Bergström, G.; Tengö, J. *J. Chem. Ecol.* **1978**, *4*, 437−449. (b) Hefetz, A.; Batra, S. W. T.; Blum, M. S. *Experientia* **1979**, *35*, 319−320. (c) Cane, J. H.; Tengö, J. O. *J. Chem. Ecol.* **1981**, *7*, 427−436. (d) Borg-Karlson, A.-K.; Unelius, C. R.; Valterová, I.; Nilsson, L. A. *Phytochemistry* **1996**, *41*, 1477−1483. (e) Borg-Karlson, A.-K.; Tengö, J.; Valterová, I.; Unelius, C. R.; Taghizadeh, T.; Tolasch, T.; Francke, W. *J. Chem. Ecol.*, in press.

(5) Review dealing with the topic "chirality in bioorganosilicon chemistry": Tacke, R.; Wagner, S. A. In *The Chemistry of Organosilicon Compounds*; Rappoport, Z., Apeloig, Y., Eds.; Wiley: Chichester, U.K., 1998; Vol. 2, Part 3, pp 2363−2400.

(6) For an alternative synthesis of *rac*-**1b**, see ref 3.

(7) Publications dealing with the chromatographic separation of chiral organosilicon compounds, with the silicon atom as the center of chirality: (a) Tacke, R.; Reichel, D.; Günther, K.; Merget, S. *Z. Naturforsch., B* **1995**, *50*, 568−572. (b) Reference 1c.

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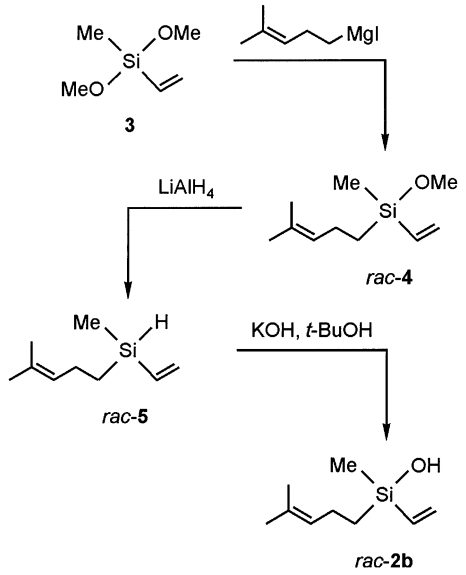
Scheme 1



(4-methylpent-3-enyl)vinylsilane (*rac*-**5**) (yield 63%), which upon treatment with potassium hydroxide in *tert*-butanol finally gave *rac*-methyl(4-methylpent-3-enyl)-vinylsilanol (*rac*-sila-linalool, *rac*-**2b**) (yield 92%). Compounds *rac*-**2b**, *rac*-**4**, and *rac*-**5** were isolated as colorless liquids, and their identities were established by elemental analyses (C, H) and solution NMR studies (^{1}H, ^{13}C, ^{29}Si).

Electroantennographic Studies. Electrophysiological studies (GC/EAD)[8] with (*R*)-**2a**, (*S*)-**2a**, (*R*)-**2b**, and (*S*)-**2b** were performed using on-line gas-chromatographic separation of *rac*-**2a** and *rac*-**2b**, respectively, on an optically active stationary phase and using antennae of males of the bee species *C. cunicularius* as detectors. The gas chromatogram and the corresponding electroantennogram obtained with a mixture of the C/Si analogues *rac*-**2a** and *rac*-**2b** are shown in Figure 1 (for details, see Experimental Section). As can be seen from this graphic, both enantiomers of the monoterpene alcohol **2a** and both enantiomers of its sila-analogue **2b** were equally well perceived, and there is no big difference between the activity of the natural pheromone and its sila-analogue (eight separate runs). These results again demonstrate that there are distinct bioisosteric relationships between analogous carbon and silicon compounds. Comparing the electrophysiological activity of (*Z*)-13-hexadecen-11-ynyl acetate, the main component of the female-produced sex pheromone of the processionary moth *Thaumetopoea pityocampa* with its *Si*,*Si*-dimethyl-15-sila-analogue revealed that the latter is 10 times less active than the natural product.[9]

Provided that the identically configurated enantiomers of the C/Si analogues **2a** and **2b** undergo the same kind of interaction with the chiral stationary phase (→ analogous diastereomeric discrimination), the absolute configurations of the separated enantiomers of sila-linalool can be assigned by comparison with the relative retention times of the enantiomers of linalool whose absolute configurations are known: (*R*)-**2a** and (*R*)-**2b**, lower retention time; (*S*)-**2a** and (*S*)-**2b**, higher retention time. As chiral silanols are not configurationally stable in aqueous solution,[10] we have not attempted to prepare the enantiomers of sila-linalool on a preparative scale to study them in field tests.

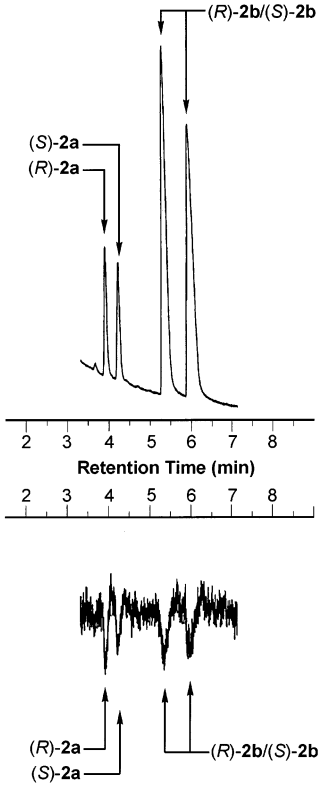


Figure 1. Gas chromatogram (above) and electroantennogram (below) obtained with a mixture of the C/Si analogues *rac*-**2a** and *rac*-**2b** (for details, see Experimental Section; for unambiguous assignment of the linalool signals, (*R*)-**2a** and *rac*-**2b** were also measured separately).

Experimental Section

General Procedures. All syntheses were carried out under dry nitrogen. Methanol, *tert*-butanol, diethyl ether, and *n*-pentane were dried and purified according to standard procedures and stored under nitrogen. ^{1}H, ^{13}C, and ^{29}Si NMR spectra were recorded at 22 °C on a Bruker DRX-300 NMR spectrometer (^{1}H, 300.1 MHz; ^{13}C, 75.5 MHz; ^{29}Si, 59.6 MHz) using $CDCl_3$ as the solvent. Chemical shifts (ppm) were determined relative to internal $CHCl_3$ (^{1}H, δ 7.24), internal $CDCl_3$ (^{13}C, δ 77.0), and external TMS (^{29}Si, δ 0). Assignment of the ^{13}C NMR data was supported by DEPT 135 and ^{13}C HMQC experiments.

Preparation of *rac*-Methyl(4-methylpent-3-enyl)vinylsilanol (*rac*-Sila-linalool, *rac*-2b). Potassium hydroxide powder (1.60 g, 28.5 mmol) was added in portions over a period of 10 min at room temperature to a stirred solution of *rac*-**5** (2.00 g, 13.0 mmol) in *tert*-butanol (20 mL), and stirring was continued until no further gas evolution was observed (ca. 1.5 h). The solid was removed by decantation and the resulting solution poured into a stirred mixture of diethyl ether (60 mL) and hydrochloric acid (3%, 4 mL) at 0 °C. The organic layer was separated, washed with water (2 × 10 mL), and then dried over anhydrous sodium sulfate. The solvent was removed

(8) For a detailed description of this method, see: Bjostad, L. B. In *Methods in Chemical Ecology*; Millar, J. G., Haynes, K. F., Eds.; Kluwer Acad. Publ.: Boston, MA, 1998; Vol. 1, pp 339−375.

(9) Arsequell, G.; Camps, F.; Fabriàs, G.; Guerrero, A. *Tetrahedron Lett.* **1990**, *31*, 2739−2742.

(10) Tacke, R.; Linoh, H.; Ernst, L.; Moser, U.; Mutschler, E.; Sarge, S.; Cammenga, G.; Lambrecht, G. *Chem. Ber.* **1987**, *120*, 1229−1237.

under reduced pressure and the residue purified in a Kugelrohr apparatus (oven temperature 60 °C, 0.01 mbar) to give *rac*-**2b** in 92% yield as a colorless liquid (2.03 g, 11.9 mmol). ^{1}H NMR ($CDCl_3$): δ 0.19 (s, 3 H, $SiCH_3$), 0.70−0.73 (m, 2 H, $SiCH_2C$), 1.57−1.59 (m, 3 H, CCH_3), 1.65−1.67 (m, 3 H, CCH_3), 2.04−2.10 (m, 3 H, $CHCH_2C$ and SiOH), 5.10−5.15 (m, 1 H, C=CH), 5.79 (δ_A), 6.00 (δ_M), and 6.11 (δ_X) ($CH_X{=}CH_AH_M$, $^3J_{AX}$ = 20.6 Hz, $^2J_{AM}$ = 3.6 Hz, $^3J_{MX}$ = 14.9 Hz). ^{13}C NMR ($CDCl_3$): δ −1.9 ($SiCH_3$), 16.6 ($SiCH_2C$), 17.6 (CCH_3), 21.3 ($CHCH_2C$), 25.6 (CCH_3), 127.3 ($SiCH{=}CH_2$), 130.5 ($SiCH{=}CH_2$), 132.9 (C=CH), 137.7 (C=CH). ^{29}Si NMR ($CDCl_3$): δ 6.3. Anal. Calcd for $C_9H_{18}OSi$: C, 63.47; H, 10.65. Found: C, 63.2; H, 10.5.

Dimethoxy(methyl)vinylsilane (3). This compound was commercially available (ABCR).

Preparation of *rac*-Methoxy(methyl)(4-methylpent-3-enyl)vinylsilane (*rac*-4). A solution of 4-methylpent-3-enylmagnesium iodide (prepared from magnesium (1.84 g, 75.7 mmol) and 5-iodo-2-methylpent-2-ene[11] (15.9 g, 75.7 mmol) in diethyl ether (90 mL)) was added dropwise over a period of 1.5 h at room temperature to a solution of **3** (10.0 g, 75.6 mmol) in diethyl ether (60 mL), and the mixture was then stirred for another 16 h. *n*-Pentane (40 mL) was added, and the precipitate was filtered off and washed with *n*-pentane (2 × 20 mL). The filtrate and the washing solutions were combined, the solvent was removed under reduced pressure, and the residue was distilled in vacuo to give *rac*-**4** in 50% yield as a colorless liquid (6.93 g, 37.6 mmol); bp 78−81 °C/12 mbar. ^{1}H NMR ($CDCl_3$): δ 0.15 (s, 3 H, $SiCH_3$), 0.70−0.73 (m, 2 H, $SiCH_2C$), 1.57−1.59 (m, 3 H, CCH_3), 1.65−1.67 (m, 3 H, CCH_3), 2.01−2.07 (m, 2 H, $CHCH_2C$), 3.41 (s, 3 H, OCH_3), 5.08−5.14 (m, 1 H, C=CH), 5.76 (δ_A), 5.99 (δ_M), and 6.12 (δ_X) ($CH_X{=}CH_AH_M$, $^3J_{AX}$ = 20.4 Hz, $^2J_{AM}$ = 3.7 Hz, $^3J_{MX}$ = 14.6 Hz). ^{13}C NMR ($CDCl_3$): δ −4.8 ($SiCH_3$), 14.9 ($SiCH_2C$), 17.5 (CCH_3), 21.2 ($CHCH_2C$), 25.6 (CCH_3), 50.5 (OCH_3), 127.2 ($SiCH{=}CH_2$), 130.2 ($SiCH{=}CH_2$), 133.7 (C=CH), 136.0 (C=CH). ^{29}Si NMR ($CDCl_3$): δ 7.9. Anal. Calcd for $C_{10}H_{20}OSi$: C, 65.15; H, 10.93. Found: C, 65.1; H, 10.7.

(11) Biernacki, W.; Gdula, A. *Synthesis* **1979**, 37−38.

Preparation of *rac*-Methyl(4-methylpent-3-enyl)vinylsilane (*rac*-5). A solution of *rac*-**4** (6.88 g, 37.3 mmol) in diethyl ether (65 mL) was added dropwise over a period of 1 h at −78 °C to a stirred suspension of lithium aluminum hydride (720 mg, 19.0 mmol) in diethyl ether (30 mL). The mixture was warmed to room temperature, the solid was filtered off, and the solvent of the filtrate was removed under reduced pressure. The residue was distilled in vacuo to give *rac*-**5** in 63% yield as a colorless liquid (3.62 g, 23.5 mmol); bp 60−61 °C/12 mbar. ^{1}H NMR ($CDCl_3$): δ 0.13 (s, 3 H, $SiCH_3$), 0.66−0.74 (m, 2 H, $SiCH_2C$), 1.58−1.60 (m, 3 H, CCH_3), 1.66−1.68 (m, 3 H, CCH_3), 2.00−2.08 (m, 2 H, $CHCH_2C$), 3.94−4.05 (m, 1 H, SiH), 5.08−5.14 (m, 1 H, C=CH), 5.78 (δ_A), 6.03 (δ_M), and 6.08 (δ_X) ($CH_X{=}CH_AH_M$, $^3J_{AX}$ = 20.6 Hz, $^2J_{AM}$ = 3.7 Hz, $^3J_{MX}$ = 15.0 Hz). ^{13}C NMR ($CDCl_3$): δ −6.8 ($SiCH_3$), 13.4 ($SiCH_2C$), 17.6 (CCH_3), 22.6 ($CHCH_2C$), 25.6 (CCH_3), 127.0 ($SiCH{=}CH_2$), 130.3 ($SiCH{=}CH_2$), 133.3 (C=CH), 135.9 (C=CH). Anal. Calcd for $C_9H_{18}Si$: C, 70.05; H, 11.76. Found: C, 70.3; H, 11.8.

Electroantennographic Studies. Electrophysiological investigations were performed with a commercially available instrument (Syntec, Hilversum, The Netherlands) using a conventional experimental setup.[8] Electroantennographic studies (GC/EAD) of linalool (**2a**) and sila-linalool (**2b**) were carried out with the respective racemates, which were on-line resolved by chiral gas chromatography using a fused silica capillary column coated with 2,3-diethyl-6-*tert*-butyldimethylsilyl-β-cyclodextrine (PS-086 capillary column (25 m, i.d. 0.25 mm), MEGA, Legnano, Italy; injector, 180 °C; split injection, 1:20; carrier gas, hydrogen; flow rate, 3 mL/min; temperature program, 100 °C isothermal). To assign the signals of (*R*)-**2a**, (*S*)-**2a**, and (*R*)-**2b**/(*S*)-**2b** in the antennogram, *rac*-**2b** and commercially available (*R*)-**2a** were also analyzed under the same experimental conditions.

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