ORGANIC LETTERS

2002
Vol. 4, No. 13
2265−2267

Synthesis and Use of α-Silyl-Substituted α-Hydroxyacetic Acids†

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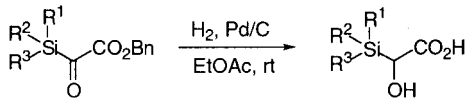
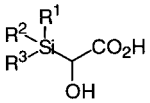
Received May 2, 2002

ABSTRACT

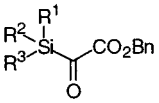


Rhodium-catalyzed oxygen transfer was used to generate benzyl 2-silyl-2-oxoacetates in good yields. The hydrogenation of these compounds led to chiral α-silyl-substituted α-hydroxyacetic acids. Resolution by means of HPLC using a chiral stationary phase afforded an enantiomerically pure representative of this class of compounds, which was successfully applied as a chiral ligand in an asymmetric aldol-type reaction.

Chiral α-hydroxyacids are important components of natural products and may be incorporated as diversely modified building blocks in asymmetric synthesis.[1] In past years, numerous effective methods have been developed in order to obtain enantiomerically pure α-hydroxyacids.[2] In this communication we describe the synthesis and structure of α-silyl-substituted α-hydroxyacetic acids **1**[3] and illustrate the successful implementation of these compounds as ligands in asymmetric catalysis.



1



2

The benzyl 2-silyl-2-oxoacetates **2** play a major role in the synthesis of **1**. In general, various practical routes leading to α-ketoesters are known, including the ozonolysis of alkynes[4a] and diazocompounds[4b] or the oxidation of the latter

† Dedicated to Professor Dr. G. Quinkert on the occasion of his 75th birthday.

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(3) To the best of our knowledge, only one other compound of this class has been reported before. However, in contrast to our work, this derivative had a quartenary α-carbon bearing an additional methyl group at C2, and it was obtained via an entirely different synthetic route (alkyne oxidation). Murray, R. W.; Singh, M.; Rath, N. P. *Acta Crystallogr., Sect. C* **1996**, *52*, 1282.

(4) (a) Schank, K.; Beck, H.; Werner, F. *Helv. Chim. Acta* **2000**, *83*, 1611. (b) Sekiguchi, A.; Ando, W. *J. Chem. Soc., Chem. Commun.* **1979**, 575.

10.1021/ol025911n CCC: $22.00
Published on Web 05/30/2002

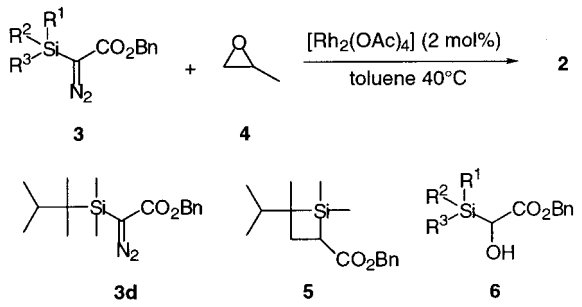
substrates using MCPBA[5] or dioxiranes.[6] Furthermore, photooxidative reactions have also been described.[7] Catalytic variants are particularly attractive and are gaining attention due to their unusual chemoselectivity.[8] On this basis, we chose the rhodium-catalyzed reaction of benzyl 2-silyl-2-diazoacetates **3**[9] with propylene oxide **4**[8a] to prepare **2**. The benzyl 2-silyl-2-oxoacetates **2** were obtained in good yields, and the best results were found for **2b** and **2c** (up to 95%, Table 1). In contrast, **3e** proved inert to these reaction

Table 1. Synthesis of Benzyl 2-Silyl-2-oxoacetates **2**

entry	diazoester	$R^{1/2}$	R^3	product	yield (%)
1	**3a**	Me	Me	**2a**	82
2	**3b**	Et	Et	**2b**	89
3	**3c**	Me	*t*Bu	**2c**	95
4	**3d**	Me	Thex	**5**	91
5	**3e**	*i*Pr	*i*Pr		
6	**3f**	Me	Ph	**3f**	85
7	**3g**	Ph	Me	**2g**	88
8	**3h**	Ph	Ph	**2h**	81

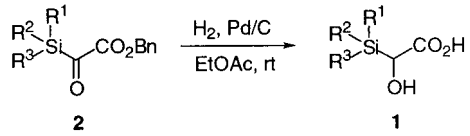
conditions, most probably because of steric hindrance, and the diazocompound **3d** underwent an intramolecular C−H insertion reaction to form silacyclobutane **5**.[10]

Scheme 1



Next, we studied the palladium-catalyzed reduction of the silylketoesters **2** using molecular hydrogen and palladium on charcoal. To our surprise, this reaction led to the formation of the novel α-triorganylsilyl-α-hydroxyacetic acids **1** (Table 2) in up to 89% yield. This result was unexpected, since

Table 2. Synthesis of α-Triorganylsilyl-α-hydroxyacetic Acids **1**



entry	**2**	product	yield (%)
1	**a**	**1a**	78
2	**b**	**1b**	85
3	**c**	**1c**	89
4	**f**	**6f**	67

prior work involving hydrogenation of α-ketobenzyl esters resulted in debenzylation with formation of the corresponding α-ketoacids.[11] In the case of the dimethylphenylsilyl derivative **2f**, the reaction behavior was even completely reversed, such that the benzyl ester **6f** was obtained solely via reduction of the α-keto group.

An X-ray crystal structure analysis confirmed the constitution of the racemic α-silyl-substituted α-hydroxyacetic acid **1c** (Figure 1).[12] The Si−C1 bond 1.927(2) Å in *rac*-**1c** is

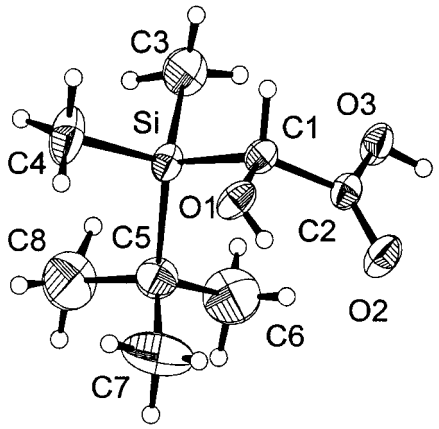


Figure 1. Molecular crystal structure of *rac*-**1c**. Selected distances [Å] and angles [deg]: Si−C1 1.927(2), O1−C1 1.427(3), C2−C1 1.492(3), C2−O2 1.209(3), C2−O3 1.320(3); C2−C1−Si 114.67-(15), O1−C1−Si 109.75(15), O1−C1−C2 111.5(2), C5−Si−C1 112.58(12), C4−Si−C3 110.14(19), C3−Si−C5 111.04(15), C4−Si−C5 110.80(16).

significantly longer than those between the silicon atom and C3 [1.861(3) Å], C4 [1.863(3) Å], and C5 [1.893(3) Å]; the last three lengths fall within the range that is considered average for a bond between a four-coordinate Si atom and

(5) (a) Thorsett, E. D. *Tetrahedron Lett.* **1982**, *23*, 1875. (b) Garcia, F. S.; Cebrián, G. M. P.; López, A. H.; Herrara, F. J. L. *Tetrahedron* **1998**, *54*, 6867.

(6) (a) Darkins, P.; McCarthy, N.; McKervey, M. A.; O'Donnell, K.; Ye, T.; Walker, B. *Tetrahedron: Asymmetry* **1994**, *5*, 195. (b) Saba, A. *Synth. Commun.* **1994**, *24*, 695.

(7) (a) Sekiguchi, A.; Kabe, Y.; Ando, W. *Tetrahedron Lett.* **1979**, 871. (b) Sekiguchi, A.; Kabe, Y.; Ando, W. *J. Org. Chem.* **1982**, *47*, 2900.

(8) (a) Martin, M. G.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 251. (b) McKenna, C. E.; Levy, J. N. *J. Chem. Soc., Chem. Commun.* **1989**, 246. (c) Solbakken, M.; Skramstad, J. *Acta Chem. Scand.* **1993**, *47*, 1214.

(9) (a) For the synthesis of **3** from benzyl 2-diazoacetates with triorganylsilyltriflates, see: Bolm, C.; Kasyan, A.; Drauz, K.; Günther, K.; Raabe, G. *Angew. Chem.* **2000**, *112*, 2374; *Angew. Chem. Int. Ed.* **2000**, *39*, 2288. (b) The synthesis of the required triorganylsilyltriflates was accomplished according to: Uhlig, W. *Chem. Ber.* **1992**, *125*, 43.

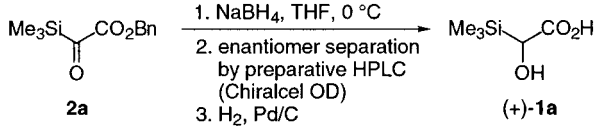
(10) (a) For an analogous reactivity, see: Maas, G.; Bender, S. *Chem. Commun.* **2000**, 437. (b) An excellent overview of silyl-substituted carbenes may be found in: Maas, G. In *The Chemistry of Organic Silicon Compounds*; Rappoport, Z., Apeloig, Y., Eds.; Wiley: Chichester, 1998; Vol. 2, Part 1, Chapter 13, p 703.

(11) Hilbert, J. M.; Fedor, L. *J. Org. Chem.* **1978**, *43*, 452.

an sp^3-hybridized carbon atom [1.863(24) Å].[13] Analogous observations were made in the case of the crystal structure of a comparably protected α-amino acid.[9]

The study was further extended in order to resolve racemic **1a** into its enantiomers. However, this was initially unsuccessful, and the first enantiomerically pure α-triorganylsilyl-α-hydroxyacetic acid was finally obtained via a three-step strategy (Scheme 2). First, α-ketoester **2a** was reduced to

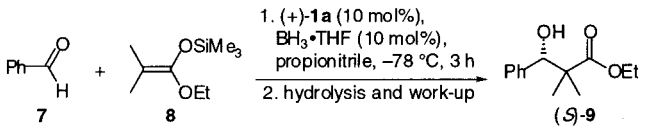
Scheme 2



α-hydroxybenzyl ester *rac*-**6a** using sodium borohydride in THF at 0 °C, and second, the enantiomers of the latter compound were separated using preparative HPLC.[14] Thereafter, a palladium-catalyzed hydrogenolytic debenzylation of the (+)-enantiomer of **6a** afforded (+)-**1a** in 76% yield.[15]

Next, we were interested in determining whether the α-silylated α-hydroxyacetic acids could be used as chiral ligands in asymmetric catalysis. The aldol-type reaction between benzaldehyde **7** and silylketeneketal **8** in the presence of 10 mol % (+)-**1a** and a borane−THF complex was chosen to test this hypothesis (Scheme 3).[16] Running

Scheme 3



the reaction with an in situ generated CAB-type[17] catalyst showed a considerably high asymmetric induction, producing (*S*)-**9** in 86% ee.[18]

This result opens up the possibility of using chiral α-triorganosilyl-α-hydroxyacids in other catalytic reactions, and extending their scope as a new class of ligands.[19]

In conclusion, we have synthesized the novel α-silyl-substituted α-hydroxyacetic acids and proved their structure by means of X-ray crystallography. Moreover, the synthetic utility of these compounds as ligands in asymmetric catalysis has been illustrated. Further applications are currently underway and will be reported in due course.

Acknowledgment. We are grateful to the Deutsche Forschungsgemeinschaft (SPP 1118, Graduiertenkolleg 440) and the Fonds der Chemischen Industrie for financial support. A.K. thanks Degussa for a postdoctoral fellowship.

Supporting Information Available: Experimental procedures and full characterization (^{1}H and ^{13}C NMR data, MS, IR, and CHN analyses) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The crystallographic data for the compound (*rac*-**1c**) was deposited as Supporting Information at the Cambridge Crystallographic Data Centre under the publication no. CCDC-174123. Copies may be obtained free of charge from the following location in Great Britain: CCDC, 12 Union Road, Cambridge CB2 1EZ (FAX: (+44) 1223-336-033. E-mail: deposit@ccdc.cam.ac.uk).

(13) F. H. Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, S1.

(14) HPLC separation. Analytic: Chiralpak AS (Daicel); 4.6 mm × 250 mm; isohexane/2-propanol 95:5; 215 nm; 0.5 mL/min; 25 °C, t_R (−)-**6a** 11.6 min, t_R (+)-**6a**: 25.3 min. Preparative: as for analytic separation but using 40 mm × 250 mm, 225 nm, and 40 mL/min

(15) (a) **Synthesis of *rac*-2-*tert*-Butyldimethylsilyl-2-hydroxyacetic Acid (1c).** To a stirring and degassed solution of **3c** (580 mg, 2 mmol[9]) and propylene oxide (2 mL) in dry toluene (10 mL) at rt was added [Rh_2(OAc)$_4$] (18 mg, 0.04 mmol, 2 mol %). The reaction mixture was heated to 40 °C and was left stirring at this temperature for 48 h. After the mixture cooled to room temperature, the solvent was removed in vacuo, and the crude silylketoester was purified by flash chromatography on silica gel (25:1 petroleum ether/ethyl acetate) to give 524 mg (95%) of **2c** as yellow oil. To a solution of **2c** (276 mg, 1 mmol) in ethyl acetate (5 mL) was added 10% Pd/C (10 mg), and the reaction mixture was stirred at room temperature for 5 h in the presence of a blanket of hydrogen. After filtration, the solvent was removed in vacuo, and purification via flash chromatography on silica gel (3:1 petroleum ether/ethyl acetate) afforded 169 mg (89%) *rac*-**1c** as a white solid, mp 101−102 (petroleum ether/ethyl acetate). The molecular structure of *rac*-**1c** in the solid state was confirmed by X-ray crystal structural analysis.[12] (b) **Synthesis of (+)-2-Trimethylsilyl-2-hydroxyacetic Acid [(+)-1a].** To a stirring and degassed solution of **2a** (472 mg, 2 mmol) under argon in dry THF (5 mL) was added $NaBH_4$ at 0 °C (40 mg, 1.1 mmol). The reaction mixture was stirred for another 3 h at room temperature after the addition was complete. After the solvent was removed in vacuo, dichloromethane (10 mL) was added to the residue, and the solution was washed with 3% HCl (20 mL). The organic layer was separated and dried over anhydrous $MgSO_4$, before the solvent was removed in vacuo. The pure product was isolated via flash chromatography on silica gel (10:1 petroleum ether/ethyl acetate) to provide 228 mg (48%) of the hydroxyacetic benzyl ester **6a** as a colorless oil. The enantiomers of **6a** were separated via preparative HPLC.[14] The (+)-enantiomer of **6a** was hydrogenolytically debenzylated to the hydroxyacetic acid (+)-**1a** (76% yield) by means of Pd/C catalysis.

(16) For current overviews of this field, see: (a) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357. (b) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., A. Pfaltz, A., H. Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, p 998.

(17) CAB stands for "chiral acyloxyborane" and describes catalysts that are synthesized from boranes with chiral carboxylic acids (i.e., α-hydroxy- and α-amino acids). For examples, see: (a) Takasu, M.; Yamamoto, H. *Synlett* **1990**, 194. (b) Sartor, D.; Saffrich, J.; Helmchen, G. *Synlett* **1990**, 197. (c) Ishihara, K.; Kondo, S.; Yamamoto, H. *J. Org. Chem.* **2000**, *65*, 9125 and references therein.

(18) **Standard protocol for Aldol-Type Reaction.** To the hydroxyacetic acid (+)-**1a** (0.1 mmol, 14.8 mg, 0.1 equiv) in propionitrile (1.5 mL) was added BH_3·THF (100 μL of 1 M solution in THF, 0.1 mmol, 0.1 equiv). The solution was heated for 1 h at 45 °C and then cooled to −78 °C. Silylketeneketal **8** (126 μL, 125 mg, 1.2 mmol, 1.2 equiv) was added, followed by benzaldehyde (106 mg, 1.0 mmol, 1.0 equiv) in propionitrile (1 mL) using a syringe pump over 3 h. The reaction mixture was stirred for another 1 h at −78 °C after the addition was complete and then added to Sörensen buffer (pH 7) at 0 °C. After the standard purification procedure, the silyl ether was hydrolyzed to the corresponding β-hydroxyester by using 1 N HCl in THF (5 mL). Flash chromatography on silica gel (3:7 ether/pentane) afforded 204 mg (92%) of (*S*)-**9**. The enantiomer ratio of **9** was determined by HPLC using a chiral column (Chiralcel-OD; 0.5 mL/min; 95:5 hexane/2-propanol; t_R (*R*)-**9** 30 min (minor), t_R (*S*)-**9** 35 min (major).

(19) Recently, it has been shown that α-hydroxyacids with bulky substituents may be successfully used as chiral ligands in the enantioselective addition of diethylzinc to benzaldehyde, achieving good ee's. Bauer, T.; Tarasiuk, J. *Tetrahedron Lett.* **2002**, *43*, 687.