107. Silicon-Directed Regio- and Enantioselective Synthesis of α-Hydroxy-ketones

Preliminary Communication

by **Braj B. Lohray** and **Dieter Enders***

Institut für Organische Chemie, Rheinisch-Westfälische Technische Hochschule Aachen, Professor-Pirlet-Strasse 1, D–5100 Aachen

Dedicated to Dr. *G. Ohloff* on the occasion of his 65th birthday

(10.V.89)

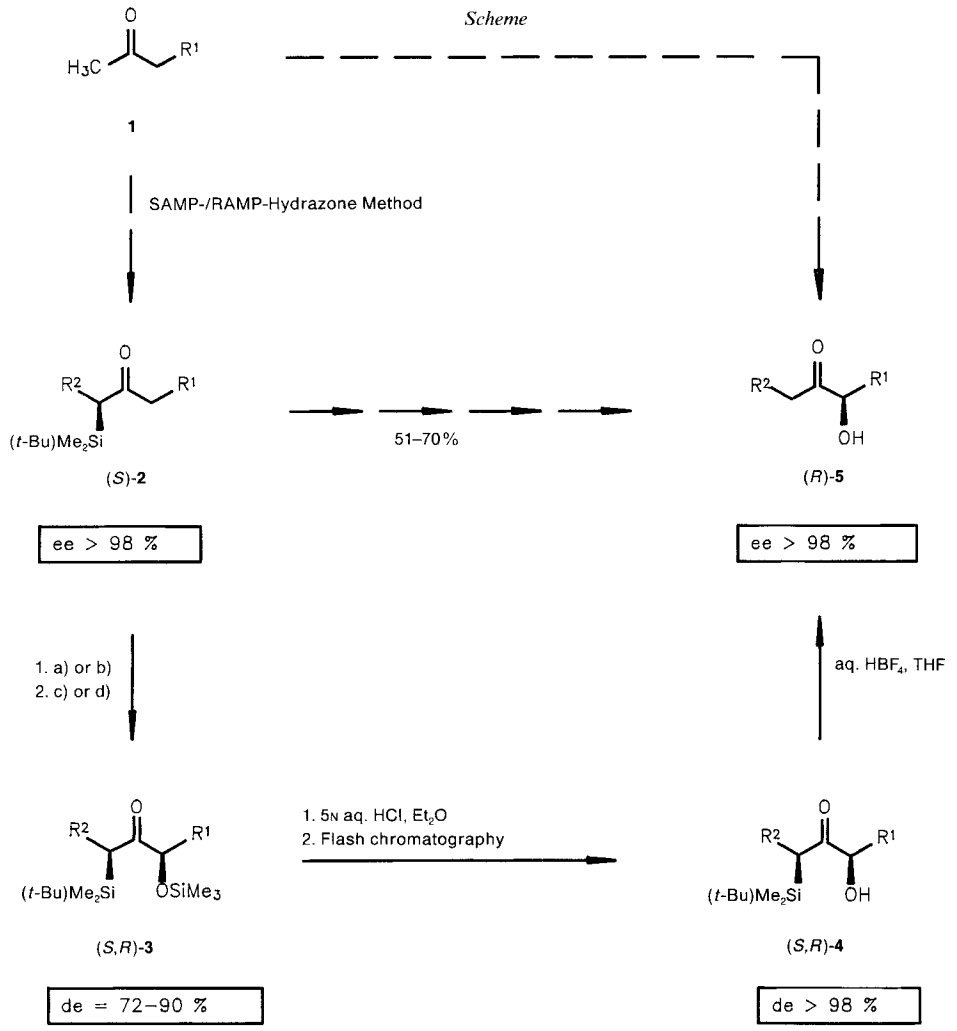
α-Silylated ketones (*S*)-**2** (ee ≥ 98%), easily available through silylation or silylation/alkylation from ketones **1** using the (−)-(*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP)-/(+)-(*R*)-1-amino-2-(methoxymethyl)pyrrolidine (RAMP)-hydrazone method, are oxidized to give α-hydroxy-ketones (*R*)-**5** of high enantiomeric purity (ee ≥ 98%) and in good overall yields (51–70%). The key step of the procedure is the silicon-directed diastereoselective oxidation of the corresponding silyl enol ethers of (*S*)-**2**, with *m*-chloroperbenzoic acid or 3-phenyl-2-(phenylsulfonyl)oxaziridine, followed by flash chromatography and desilylation.

α-Hydroxy-carbonyl compounds are common structural features of many natural products and are useful chiral building blocks in the synthesis of biologically active compounds. Consequently, numerous studies for their stereoselective synthesis have been reported [1]. Among the most attractive routes to optically active α-hydroxy-carbonyl units are direct oxidations of the parent carbonyl compounds and their enol derivatives [2]. Most of the overall enantioselective procedures lead to α-hydroxy-acid derivatives [3]. It was only very recently, that first asymmetric syntheses of α-hydroxy-ketones have been reported [1] [4]. However, with the exception of the hydroxylation of metalated chiral hydrazones [1], the asymmetric inductions were not high enough. Therefore, novel and efficient entries to optically active α-hydroxy-ketones are desirable.

We now wish to report a new regio- and overall enantioselective α-hydroxylation of dialkyl ketones **1** → (*R*)-**5** *via* α-silylated ketones (*S*)-**2** *(Scheme)*. The latter are easily available from symmetrical dialkyl ketones ($R^1 = R^2$) by asymmetric α-*C*-silylation [5] or from alkyl methyl ketones **1** through silylation/alkylation[1]) using our (−)-(*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP)-/(+)-(*R*)-1-amino-2-(methoxymethyl)pyrrolidine (RAMP)-hydrazone method [6]. We already demonstrated virtually complete asymmetric inductions in diastereo- and enantioselective aldol reactions using the corresponding boron enolates of (*S*)-**2** [7]. This encouraged us to further investigate related silicon-directed asymmetric syntheses.

[1]) The transformation **1** → (*S*)-**2** is achieved as follows: 1. SAMP; 2. LDA, THF, 0°; R_3SiCl, −78°; 3. BuLi, Et_2O, 0°; i-Pr_2NH, −78°; R^2X; 4. O_3, pentane, −78°; flash chromatography; *D. Enders, B.B. Lohray*, manuscript in preparation.

Scheme



a) LDA, THF, – 78°, Me_3SiCl; b) $Me_3SiCH_2CO_2Et$, Bu_4NF, THF;
c) *m*-CPBA, hexane, 0°; d) oxaziridine, $CHCl_3$, reflux.

As shown in the *Scheme*, the α-silylated ketones (*S*)-**2** are first transformed into their corresponding trimethylsilyl enol ethers using LDA or $LiN(SiMe_3)_2$, THF, Me_3SiCl[2]) (**c–g**: $Z/E = 73:27 - 98:2$[3]), or *Kuwajima*'s method [9] (**a,b**: $Z/E = 99:1$[3]), followed by oxidation with either *m*-chloroperbenzoic acid [10] or 3-phenyl-2-(phenylsulfonyl)-oxaziridine [2c]. The diastereoisomeric excess (de 72–90%) of the resulting α-trialkylsilyl-

[2]) The relatively low Z/E ratios obtained with LDA could be significantly improved with lithium hexamethyldisilazide, for example. **d** ($R^1 = CH_3$, $R^2 = C_2H_5$) 60:40 with LDA and 96:4 with $LiN(SiMe_3)_2$; *R. Hett*, diploma work, Technical University Aachen, 1988.

[3]) Determined by capillary GC and assigned by ^{13}C-NMR spectroscopy according to *Heathcock et al.* [8].

Table. *α-Hydroxy-ketones (R)-5 Prepared by Oxidation of α-Trialkylsilyl-ketones (S)-2*

(*R*)-**5**[a]	R^1	R^2	Overall yield [%][b]	$[\alpha]_D^{22}$ (*c*, $CHCl_3$)	ee [%][c]
a	CH_3	CH_3	58	−55 (1.4)	⩾ 98
(*S*)-**a**[d]	CH_3	CH_3	61	+54.8 (1.4)	⩾ 98
b	C_2H_5	CH_3	58	−97.5 (1.0)	⩾ 98
c	C_2H_5	C_2H_5	70	−98 (1.1)	⩾ 98
d	CH_3	C_2H_5	55	−55.5 (0.7)	⩾ 98
e	CH_3	C_3H_7	70	−58.7 (0.75)[e]	⩾ 98
f	CH_3	$PhCH_2$	51	− 8.53 (0.85)[f]	⩾ 98
g	C_2H_5	$PhCH_2$	58	−55.3 (0.6)[g]	⩾ 98

[a] The absolute configurations given are based on the independent synthesis of (*S*)-**5e** from (*S*)-ethyl lactate[5] and assuming a uniform mechanism of the oxidations.
[b] Overall yield of the procedure (*S*)-**2** → (*R*)-**5**.
[c] Determined by ^{13}C- and ^{19}F-NMR spectroscopy of the corresponding MTPA esters.
[d] (*R*)-**2a** [5] was used as starting material.
[e] (*S*)-**5e** synthesized independently from (*S*)-ethyl lactate showed $[\alpha]_D^{22} = +54.4$ (*c* = 0.79, $CHCl_3$) for 93% ee.
[f] Et_2O was used as solvent.
[g] $[\alpha]_D^{22} = 8.4$ (*c* = 1.6, Et_2O).

α′-trimethylsiloxy ketones (*S,R*)-**3** was determined by ^1H- and ^{13}C-NMR spectroscopy. Hydrolysis with aqueous HCl and Et_2O, and subsequent separation of the major diastereoisomer by flash chromatography over silica gel (Et_2O/pentane 1:4 R_f((*S,R*)-**4**) 0.3, R_f((*S,S*)-**4**) 0.25) affords the α-silylated α-hydroxy-ketones (*S,R*)-**4** of high diastereo- and enantiomeric purity (de = 33 > 98%). Finally, the (*t*-Bu)Me_2Si group is removed without racemization by treatment with aqueous HBF_4 (60%) in THF to give the practically enantiomerically pure α-hydroxy-ketones (*R*)-**5** in good overall yields (see the *Table*)[4]).

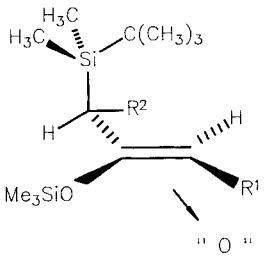
The enantiomeric excess of the hydroxy-ketones (*S,R*)-**4** and (*R*)-**5** was determined spectroscopically *via* their 3,3,3-trifluoro-2-methoxy-2-phenylpropionic-acid (MTPA) esters [11] (^{13}C- and ^{19}F-NMR). The absolute configuration given for the final products, (*R*)-**5**, was established by polarimetry based on the independent synthesis of (*S*)-**5e** from (*S*)-ethyl lactate[5]) (see the *Table*). The diastereoselectivity of the α′-hydroxylation of the α-trialkylsilyl-ketones mainly depends on the *E*/*Z* ratio of the intermediate trimethylsilyl enol ethers used in the oxidation step and the nature of the oxidizing agent. Whereas *m*-chloroperbenzoic acid (*m*-CPBA) gave satisfactory diastereoselectivities in the cases **c**–**g**, low de values (*ca.* 40%) were observed in the *m*-CPBA oxidations of the silyl enol ethers of (*S*)-**2a** and **b** prepared by *Kuwajima*'s method. Here, 3-phenyl-2-(phenylsulfonyl)oxaziridine was the oxidant of choice.

To explain the formation of (*S,R*)-**3** as the predominant diastereoisomer and thus the (*R*)-configuration of the final α-hydroxy-ketones, we propose the open transition states **A** and **B** for the oxidation of the (*Z*) and (*E*) silyl enol ethers, respectively. In this picture, the oxidizing agent approaches *anti* to the (*t*-Bu)Me_2Si group, which compares well with other silicon-directed electrophilic reactions at alkene C=C bonds [13].

---

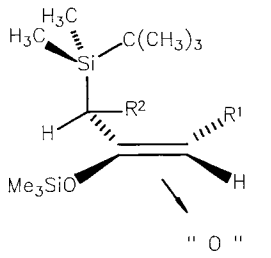
[4]) Cyclohexane was also α-hydroxylated (ee ⩾ 90%; *R*) starting from (*R*)-**2** $R^1 - R^2 = -(CH_2)_3$, but the overall chemical yield was low (30%).

[5]) (*S*)-Ethyl lactate was transformed into the (2-methoxyethoxy)methyl (MEM)-protected lactaldehyde as described by *Kelly* and *Kaul* [12] followed by addition of BuMgBr, *Swern* oxidation, and deprotection ($TiCl_4$) to give (*S*)-**5e** of 93% ee.



A

(*Z*,*S*) - - - → (*S*,*R*)-**3**



B

(*E*,*S*) - - - → (*S*,*S*)-**3**

A typical procedure for the synthesis of (*R*)-**5c** from (*S*)-**2c** [5][1]) is as follows: a flame-dried, one-necked 100-ml flask with side arm, rubber septum, and magnetic stirring bar is flushed with Ar. After addition of $(i\text{-Pr})_2NH$ (1.5 ml, 10.7 mmol) and dry THF (20 ml), the flask is cooled to −78°, followed by dropwise addition of BuLi (6.56 ml, 10.5 mmol, 1.6N in hexane). Stirring is continued for 20 min, and a soln. of the silyl-ketone (*S*)-**2c** (2.28 g, 10 mmol) in 5 ml of THF and, after 1 h, Me_3SiCl (1.33 ml, 10.5 mmol) are added. The mixture is stirred and allowed to reach *ca.* 15° during 8–10 h. After dilution with pentane (50 ml), the mixture is washed with sat. aq. NH_4Cl and brine. The org. layer is dried ($MgSO_4$) and concentrated *in vacuo* to afford the corresponding crude silyl enol ether in quantitative yield (3.0 g, (*Z*)/(*E*) 9:1, determined by cap. GC). A suspension of *m*-CPBA (90%, 1.92, 10 mmol) in 40 ml of hexane is cooled to 0° and a soln. of the crude silyl enol ether (3.0 g, 10 mmol) in 10 ml of hexane is added. The mixture is stirred for 1 h at 0° after which the oxidation is complete (TLC control). The mixture is filtered through *Celite* and concentrated under reduced pressure. The residue is purified by column chromatography over silica gel (Et_2O/pentane 1:9, R_f 0.75) to give 2.86 g (90%) of (*S*,*R*)-**3c** (de = 90%, ^{13}C-NMR).

The diastereoisomeric mixture (*S*/*R*)/(*S*/*S*)-**3c** is dissolved in 30 ml of Et_2O followed by addition of 15 ml of 5N aq. HCl and stirring for 20 h at r.t. The org. layer is separated, and the aq. phase is extracted with Et_2O (2 × 15 ml). The combined Et_2O layers are washed with aq. $NaHCO_3$ and brine. After drying ($MgSO_4$) and concentration *in vacuo*, 2.07 g (94%) of **4c**, as a mixture of the (*S*,*R*)- and (*S*,*S*)-isomers (95:5), are isolated. The diastereoisomers are separated by flash chromatography (silica gel; Et_2O/pentane 1:4, $R_f(S,R) > R_f(S,S)$) to give 1.93 g (88%) of stereochemically pure (*S*,*R*)-**4c** (de = ee > 98%, ^{13}C- and ^{19}F-NMR of the MTPA ester).

Finally, (*S*,*R*)-**4c** (1.9 g, 7.78 mmol) is dissolved in THF (15 ml) and treated with aq. HBF_4 (60%, 7 ml) at r.t. for 20 h (TLC control for completion of the reaction). The mixture is diluted with Et_2O (30 ml) and the org. phase is washed with H_2O (2 × 10 ml), sat. $NaHCO_3$ soln. and brine. After drying ($MgSO_4$) and concentration *in vacuo*, the crude product (0.93 g, 93%) is purified by chromatography (silica gel, Et_2O/pentane 1:1, R_f 0.5) to give 0.91 g (90%) of optically pure (*R*)-**5c**.

When ethyl trimethylsilyl acetate is employed to generate the intermediate silyl enol ethers, the oxaziridine oxidations are carried out as follows: in a flask as described above, a soln. of silyl enol ether (10 mmol) in dry $CHCl_3$ (20 ml) is treated with 3-phenyl-2-

(phenylsulfonyl)oxaziridine (3.13 g, 12 mmol), and the mixture is refluxed for 1 h at 65°. After evaporation of the solvent under reduced pressure, the residue is extracted with pentane (5 × 20 ml) and the pentane extract is washed with brine, dried ($MgSO_4$), and evaporated to yield (*S,R/S,S*)-**3**.

In conclusion, the regio-controlled and overall enantioselective α-hydroxylation of simple ketones described here offers a new and efficient entry to the important class of α-hydroxy-ketones of high enantiomeric purity[6]).

This research was supported by the *Fonds der Chemischen Industrie*. We thank *Degussa AG, BASF AG,* and *Wacker Chemie GmbH* for providing us with chemicals.

REFERENCES

[1] For a collection of leading references see: D. Enders, V. Bhushan, *Tetrahedron Lett.* **1988**, *29*, 2437.

[2] For some recent examples see: a) E. Vedejs, D.A. Engler, J.E. Telschow, *J. Org. Chem.* **1978**, *43*, 188; E. Vedejs, S. Larsen, *Org. Synth.* **1985**, *64*, 127; b) T. Cuvigny, G. Valette, M. Larcheveque, H. Normant, *J. Organomet. Chem.* **1978**, *155*, 147; c) F.A. Davis, L.C. Vishwakarma, J.M. Billmers, J. Finn, *J. Org. Chem.* **1984**, *49*, 3241; d) R.M. Moriarty, K.-C. Hou, *Tetrahedron Lett.* **1984**, *25*, 691; e) N.K. Dunlap, M.R. Sabol, D.S. Watt, *ibid.* **1984**, *25*, 5839; f) G.M. Rubottom, J.M. Gruber, H.D. Juve, Jr., D.A. Charleson, *Org. Synth.* **1985**, *64*, 118; g) C. Iwata, Y. Takemoto, A. Nakamura, T. Imanishi, *Tetrahedron Lett.* **1985**, *26*, 3227; h) R.V. Hoffmann, C.S. Carr, B.C. Jankowski, *J. Org. Chem.* **1985**, *50*, 5148; i) R.M. Moriarty, O. Prakash, M.P. Duncan, K. Vaid, *ibid.* **1987**, *52*, 150; j) F.A. Davis, A.C. Sheppard, *ibid.* **1987**, *52*, 955.

[3] a) R. Gamboni, P. Mohr, N. Waespe-Sarcevic, Ch. Tamm, *Tetrahedron Lett.* **1985**, 26, 203; R. Gamboni, Ch. Tamm, *Helv. Chim. Acta* **1986**, *69*, 615; b) W. Oppolzer, P. Dudfield, *ibid.* **1985**, *68*, 216; c) D.A. Evans, M.M. Morrissey, R.L. Dorow, *J. Am. Chem. Soc.* **1985**, *107*, 4346; d) F.A. Davis, L.C. Vishwakarma, *Tetrahedron Lett.* **1985**, *26*, 3539; e) F.A. Davis, M.S. Haque, T.G. Ulatowski, J.C. Towson, *J. Org. Chem.* **1986**, *51*, 2402; f) M.P. Gore, J.C. Vederas, *ibid.* **1986**, *51*, 3700; g) F.A. Davis, T.G. Ulatowski, M.S. Haque, *ibid.* **1987**, *52*, 5288.

[4] a) C.M. Cain, N.S. Simpkins, *Tetrahedron Lett.* **1987**, *28*, 3723; b) M. Masui, A. Ando, T. Shioiri, *ibid.* **1988**, *29*, 2835; c) F.A. Davis, A.C. Sheppard, *ibid.* **1988**, *29*, 4365; d) F.A. Davis, A.C. Sheppard, G.S. Lai, *ibid.* **1989**, *30*, 779.

[5] D. Enders, B.B. Lohray, *Angew. Chem.* **1987**, *99*, 359; *ibid. Int. Ed.* **1987**, *26*, 351.

[6] a) D. Enders, in 'Asymmetric Synthesis', Ed. J.D. Morrison, Academic Press, Orlando, 1984, Vol. 3, pp. 275–339; b) D. Enders, P. Fey, H. Kipphardt, *Org. Synth.* **1987**, *65*, 173, 183.

[7] D. Enders, B.B. Lohray, *Angew. Chem.* **1988**, *100*, 594; *ibid. Int. Ed.* **1988**, *27*, 581.

[8] C.H. Heathcock, C.T. Buse, W.A. Kleschick, M.C. Pirrung, J.E. Sohn, J. Lampe, *J. Org. Chem.* **1980**, *45*, 1066.

[9] E. Nakamura, K. Hashimoto, I. Kuwajima, *Tetrahedron Lett.* **1978**, 2079.

[10] a) A.G. Brook, D.M. MacRae, *J. Organomet. Chem.* **1974**, *77*, C19; b) G.M. Rubottom, M.A. Vazquez, D.R. Pelegrina, *Tetrahedron Lett.* **1974**, 4319; c) A. Hassner, R.H. Reuss, H.W. Pinnick, *J. Org. Chem.* **1975**, *40*, 3427.

[11] J.A. Dale, H.S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512.

[12] T.R. Kelly, P.N. Kaul, *J. Org. Chem.* **1983**, *48*, 2775.

[13] a) I. Fleming, *Pure Appl. Chem.* **1988**, *60*, 71; b) T. Hayashi, *Chem. Scr.* **1985**, *25*, 61.

[6]) The spectroscopic data (IR, NMR, MS) and elemental analyses of all new compounds are in agreement with the structures given.