165. Regio-, Diastereo-, and Enantioselective Synthesis of Vicinal Diols *via* α-Silyl Ketones

by **Dieter Enders*** and **Shiro Nakai**

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

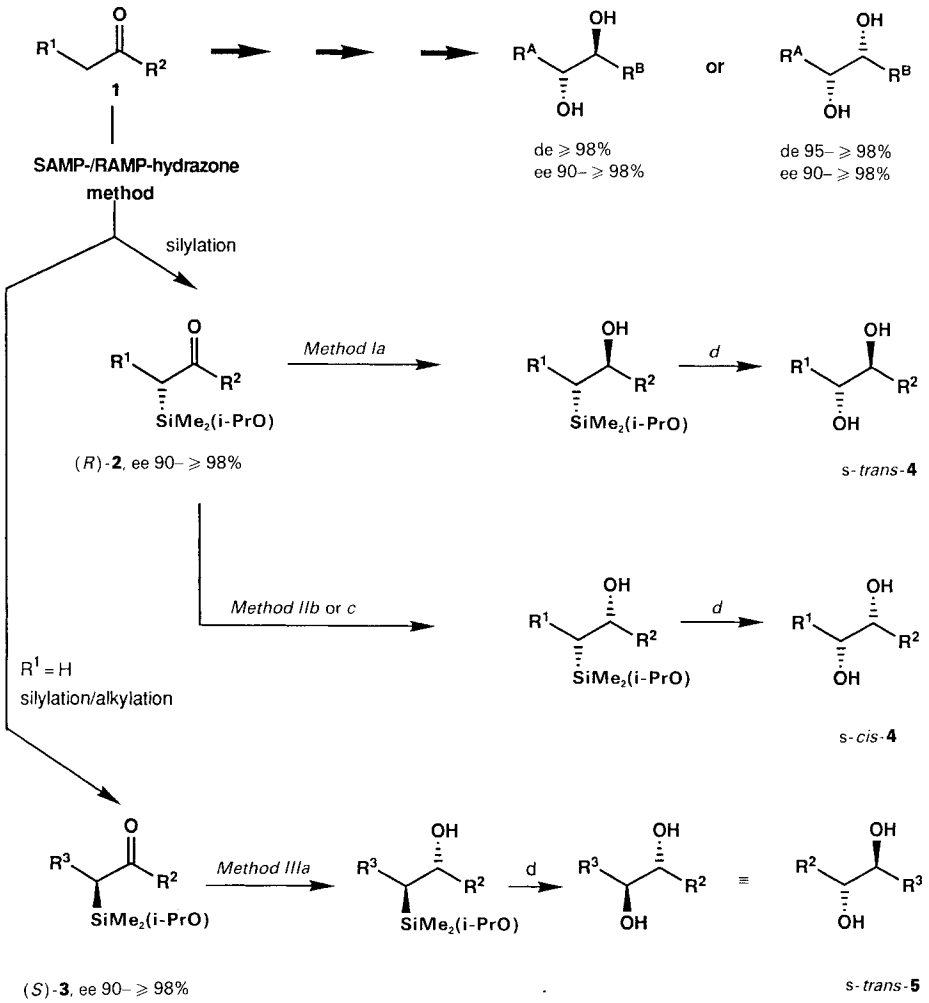
(15.VIII.90)

A new versatile and efficient regio-, diastereo-, and enantioselective synthesis of vicinal diols s-*trans*-**4**, s-*trans*-**5**, and s-*cis*-**4** is described. Symmetrical ketones are converted into their SAMP- or RAMP-hydrazones which are then silylated with (isopropyloxy)dimethylsilyl chloride, followed by ozonolysis to afford the α-silyl ketones (*R*)-**2** of high enantiomeric purity (ee 90– ≥ 98%). On the other hand, methyl ketones, after conversion into the corresponding (–)-(*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) hydrazones, are silylated and then alkylated with RI to afford unsymmetrical α-silyl ketones (*S*)-**3** of high enantiomeric purity (ee 90– ≥ 98%). The reduction of the above obtained α-silyl ketones with L-*Selectride*, followed by oxidative cleavage of the C–Si bond gives rise to s-*trans*-**4**, s-*trans*-**5**, and s-*cis*-**4** with high diastereoselectivity (de 95– ≥ 98%) and without racemization (ee ≥ 90– ≥ 98%).

The diastereo- and enantioselective synthesis of vicinal diols has received considerable interest in recent years, because 1,2-diol structures are not only crucial structural features of many biologically active compounds [1] [2], but also important synthons in synthetic chemistry [1] [3]. Approaches have been carried out by enantioselective ring opening using epoxide hydrase [4], ring opening *via* epoxidation of chiral allylic alcohols [1], selective transformations from natural products [5], coupling of chiral boronic esters with chiral lithio esters [6], homologation of alkyl boronates [7], and enantioselective dihydroxylation of olefins [8]. In addition, diastereoselective reductions of α-hydroxy ketones to form vicinal diols have also been reported [9], but little attention has been paid to enantioselective versions, although previously difficult but now very efficient enantioselective reductions of aliphatic ketones are at hand [10]. Therefore, the development of further flexible techniques for the stereoselective construction of 1,2-diol structures is of considerable interest.

We now report on an efficient, highly regio-, diastereo-, and enantioselective synthesis of vicinal diols based on our (–)-(*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP)-/(+)-(*R*)-1-amino-2-(methoxymethyl)pyrrolidine (RAMP)-hydrazone methodology [11–13]. As is shown in the *Scheme*, dialkyl ketones **1** are transformed into their corresponding SAMP-hydrazones, metalated (LDA, Et_2O), and α-C-silylated with (i-PrO)Me_2SiCl at –78°, followed by ozonolysis (O_3, CH_2Cl_2, –78°) to afford the α-silylated ketones (*R*)-**2** of high enantiomeric purity (ee 90– > 98%) [12]. Alternatively, alkyl methyl ketones (R^1 = H) can be converted into the α-silylated ketones (*S*)-**3** (ee 90– > 98%) through silylation/alkylation (*1.* SAMP, *2.* LDA, Et_2O; (i-PrO)Me_2SiCl, *3.* LDA, Et_2O; R^3I) according to the SAMP-/RAMP-hydrazone method [13]. The sign of the optical rotations of the ketones **2** and **3** are coincident with those of related α-silyl

Scheme 1[a])



[a]) *a*: L-*Selectride*, toluene, −78° (R^1 = Me, R^2 = Me, Et); *b*: L-*Selectride*, Et_2O, $SnCl_4$, −78° (R^1 = Me, R^2 = Me, Et); *c*: L-*Selectride*, toluene, −78° ($R^1 \neq$ Me, $R^2 \neq$ Me, Et); *d*: KF, $KHCO_3$, 30% H_2O_2, MeOH, THF.

ketones [12] [13], and the opposite absolute configurations given are in full agreement with the postulated mechanism for electrophilic substitutions *via* SAMP-/RAMP-hydrazones [11–13]. The ee values were determined by ^{1}H-NMR shift experiments using Eu(hfc)$_3$ or can be deduced from the enantiomeric excesses of the final vicinal diols **4** and **5**, as subsequent transformations are free of racemization (good ee correlation between silyl-ketone educts and 1,2-diol products (*Scheme* and *Table*).

A study of the reduction of (*R*)-2-[(isopropyloxy)methylsilyl]pentan-3-one ((*R*)-**2**; R^1 = Me, R^2 = Et) with various types of metal-hydride reducing agents revealed that L-*Selectride* in toluene at −78° gives the highest diastereoselectivity, affording good yields and s-*trans*-configuration (*Method Ia* or *IIIa*). s-*cis*-Diastereoisomers can also be

Table. *Vicinal Diols Prepared by Reduction/C–Si Oxidation from α-Silyl Ketones (R)-2 or (S)-3*

Entry	R^A	R^B	*Method*	Yield [%][a])	$[\alpha]_D^{22}$ (*c*, $CHCl_3$)	ee [%][b])	de [%][c])
1	R^1 = Me	R^2 = Et	*Ia*	56	−14.0 (0.6)	⩾ 90	⩾ 98
2	R^2 = Me	R^3 = Et	*IIIa*	52	−14.2 (2.1)	⩾ 95	⩾ 98
3	R^1 = Et	R^2 = Me	*Ia*[d])	58	+13.9 (0.7)	⩾ 98	98
4	R^2 = Et	R^3 = Me	*IIIa*	52	+13.2 (1.7)	⩾ 90	⩾ 98
5	R^2 = Et	R^3 = Hexyl	*IIIa*	24	−5.0 (0.3)		⩾ 98[e])
6	R^2 = Hexyl	R^3 = Me	*IIIa*	53	+6.0 (0.5)	⩾ 98	⩾ 98
7	R^1 = Me	R^2 = Et	*IIb*	14	+4.5 (1.0)	⩾ 90	⩾ 98
8	R^1 = Et	R^2 = Pr	*IIc*	47	+19.2 (0.6)		⩾ 95[e])
f	R^1 = Et	R^2 = Et			+22.7 (2.5, H_2O)		

[a]) Yields of pure vicinal diols based on α-silyl ketones **2** and **3**.

[b]) Enantiomeric excesses of *Entries 1, 2, 3,* and *4* were determined by GLC of the bis-*Mosher* esters of vicinal diols on a 25-m *XE-60* (*S*)-Val-S-α-PEA capillary column. Enantiomeric excesses of *Entries 1, 3, 4, 6,* and *7* were also determined by ^{1}H-NMR shift experiments of their α-siliyl-ketone precursors.

[c]) Diastereoisomeric excesses of vicinal diols were determined by ^{13}C-NMR spectroscopy.

[d]) RAMP was used instead of SAMP as the chiral auxiliary.

[e]) After separation of the minor diastereoisomer by column chromatography (twice, silica gel, Et_2O/pentane 1:3–1:1); the first isolated product in *Entry 5* showed de ⩾ 70 and that in *Entry 8* showed de ⩾ 75.

[f]) Data from [5a].

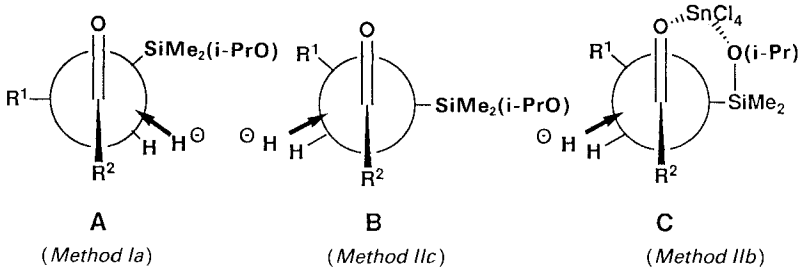
obtained by L-*Selectride* reduction in the presence of $SnCl_4$, although in poor yield (*Method IIb*). The C–Si bond of the intermediate silyl alcohols, thus obtained, was directly oxidized with retention of configuration according to *Tamao* [14]. Non-aqueous workup [15] and purification by column chromatography (silica gel, pentane/Et_2O) gave the vicinal diols in acceptable yields and of excellent stereochemical purity (de 95– ⩾ 98%, ee 90– > 98%, see the *Table*). The de values and s-*trans*/s-*cis*-configurations of the 1,2-diols were determined by ^{13}C-NMR spectroscopy and comparison with authentic samples prepared from (*E*/*Z*)-alkenes by the *cis*-hydroxylation method of *Brutcher* and coworkers [16]. The ee values given are based on GLC measurements (see *Footnote* of the *Table*) or can be deduced from the ee values of the starting silyl ketones. The absolute configurations for the final diols were also established by chemical correlation with authentic samples[1]).

To explain the observed stereochemical results, we use the following models. The s-*trans*-selectivity obtained through *Methods Ia* and *IIIa* may be due to considerable steric repulsion between R^2 and the sterically very demanding (i-PrO)Me_2Si group leading to a favourite conformation depicted in transition state **A**. However, when longer C chains are present, repulsion between R^1 and R^2 is increased and the addition of hydride can be explained using the *Felkin-Anh* model [17] (transition state **B**). In the *Lewis*-acid-mediated reduction a six-membered chelate including Sn directs the attack by hydride towards the side away from the (i-PrO)Me_2Si group (transition state **C**).

It is well known that the reduction of α-substituted ketones with L-*Selectride* affords s-*cis*-alcohols, whilst reduction with $Zn(BH_4)_2$ gives rise to s-*trans*-products [18]. The improvement of the s-*trans*-selectivity by the modification of the substrate is an alternative [19], which, when combined with the SAMP-/RAMP-hydrazone methodology, should allow the enantioselective synthesis of a wide variety of vicinal diols with relative and absolute configurations of choice.

[1]) From propan-2-one and MeI, *meso*-butane-2,3-diol (s-*trans*: ⩾ 98%) was isolated along with a small amount of the s-*cis*-diastereoisomer (2*S*,3*S*), whose optical rotation was coincident with that of an authentic sample (*Method IIIa*).

Scheme 2. *Transition States*



Shiro Nakai thanks the *Alexander-von-Humboldt-Stiftung* for a fellowship. This work was supported by the *Fonds der Chemischen Industrie*. We thank *Degussa AG, Wacker Chemie GmbH, BASF AG, Bayer AG*, and *Hoechst AG* for generously providing us with chemicals.

REFERENCES

[1] T. Matsumoto, Y. Kitano, F. Sato, *Tetrahedron Lett.* **1988**, *29*, 5685, and ref. cit. therein.
[2] T. Nakata, M. Fukui, T. Oishi, *Tetrahedron Lett.* **1988**, *29*, 2219.
[3] a) B. M. Kim, K. B. Sharpless, *Tetrahedron Lett.* **1989**, *30*, 655; b) Y. Gao, K. B. Sharpless, *J. Am. Chem. Soc.* **1988**, *110*, 7538.
[4] G. D. Prestwich, S. McG. Graham, W. A. König, *J. Chem. Soc., Chem. Commun.* **1989**, 575.
[5] a) A. C. Cope, T. Y. Shen, *J. Am. Chem. Soc.* **1956**, *78*, 5916; b) V. Schurig, B. Koppenhoefer, W. Buerkle, *J. Org. Chem.* **1980**, *45*, 538.
[6] D. S. Matteson, P. B. Tripathy, A. Sarkar, K. M. Sadhu, *J. Am. Chem. Soc.* **1989**, *111*, 4399.
[7] D. S. Matteson, K. M. Sadhu, M. L. Peterson, *J. Am. Chem. Soc.* **1986**, *108*, 810.
[8] a) S. G. Hentges, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 4263; b) T. Yamada, K. Narasaka, *Chem. Lett.* **1986**, 131; c) M. Tokles, J. K. Snyder, *Tetrahedron Lett.* **1986**, *27*, 3951; d) K. Tomioka, M. Nakajima, K. Koga, *J. Am. Chem. Soc.* **1987**, *109*, 6213; e) K. Tomioka, M. Nakajima, Y. Iitaka, K. Koga, *Tetrahedron Lett.* **1988**, *29*, 573; f) R. Annuntiata, M. Cinquini, F. Cozzi, L. Raimondi, S. Stefanelli, *ibid.* **1987**, *28*, 3139; g) E. N. Jacobsen, I. Markó, W. S. Mungall, G. Schröder, K. B. Sharpless, *J. Am. Chem. Soc.* **1988**, *110*, 1968; h) J. S. M. Wai, I. Markó, J. S. Svendsen, M. G. Finn, E. N. Jacobsen, K. B. Sharpless, *ibid.* **1989**, *111*, 1123; i) B. B. Lohray, T. H. Kalantar, B. M. Kim, C. Y. Park, T. Shibata, J. S. M. Wai, K. B. Sharpless, *Tetrahedron Lett.* **1989**, *30*, 2041; j) J. S. Svendsen, I. Markó, E. N. Jacobsen, C. Pulla Rao, S. Bott, K. B. Sharpless, *J. Org. Chem.* **1989**, *54*, 2264; k) G. D. H. Dijkstra, R. M. Kellogg, H. Wynberg, J. S. Svendsen, I. Markó, K. B. Sharpless, *J. Am. Chem. Soc.* **1989**, *111*, 8069; l) E. J. Corey, P. D. Jardine, S. Virgil, P.-W. Yuen, R. D. Connell, *ibid.* **1989**, *111*, 9243; m) E. J. Corey, G. I. Lotto, *Tetrahedron Lett.* **1990**, *31*, 2665.
[9] a) J. A. Katzenellenbogen, S. B. Bowlus, *J. Org. Chem.* **1973**, *38*, 627; b) S. B. Bowlus, J. A. Katzenellenbogen, *ibid.* **1974**, *39*, 3309; c) T. Nakata, T. Tanaka, T. Oishi, *Tetrahedron Lett.* **1983**, *24*, 2653; d) M. Fujita, T. Hiyama, *J. Am. Chem. Soc.* **1984**, *106*, 4629; e) M. Fujita, T. Hiyama, *J. Org. Chem.* **1988**, *53*, 5405.
[10] a) H. C. Brown, J. Chandrasekharan, P. V. Ramachandran, *J. Org. Chem.* **1986**, *51*, 3394; b) H. C. Brown, J. Chandrasekharan, P. V. Ramachandran, *J. Am. Chem. Soc.* **1988**, *110*, 1539.
[11] Review: D. Enders, in 'Asymmetric Synthesis', Ed. J. D. Morrison, Academic Press, Orlando, 1984, Vol 3, p. 275; D. Enders, P. Fey, H. Kipphardt, *Org. Synth.* **1987**, *65*, 173, 183.
[12] D. Enders, B. B. Lohray, *Angew. Chem.* **1987**, *99*, 359; *ibid. Int. Ed.* **1987**, *26*, 351.
[13] a) D. Enders, B. B. Lohray, *Angew. Chem.* **1988**, *100*, 594; *ibid. Int. Ed.* **1988**, *27*, 581; b) B. B. Lohray, D. Enders, *Helv. Chim. Acta* **1989**, *72*, 980; c) D. Enders, B. B. Lohray, unpublished results.
[14] K. Tamao, *J. Synth. Org. Chem. (Japan)* **1988**, *46*, 861, and ref. cit. therein.
[15] K. Tamao, N. Ishida, *Tetrahedron Lett.* **1984**, *25*, 4245.
[16] a) R. B. Woodward, F. V. Brutcher, *J. Am. Chem. Soc.* **1958**, *80*, 209; b). F. V. Brutcher, G. Evans III, *J. Org. Chem.* **1958**, *23*, 618; c) L. Rebrovic, G. F. Koser, *ibid.* **1984**, *49*, 2462.
[17] M. Chérest, H. Felkin, N. Prudent, *Tetrahedron Lett.* **1968**, *18*, 2199.
[18] M. Shimagaki, T. Maeda, Y. Matsuzaki, I. Hori, T. Nakata, T. Oishi, *Tetrahedron Lett.* **1984**, *25*, 4775.
[19] M. Shimagaki, Y. Matsuzaki, I. Hori, T. Nakata, T. Oishi, *Tetrahedron Lett.* **1984**, *25*, 4779.