Highly Stereoselective Route toward the Synthesis of β- and γ-Amino Alcohols from Homochiral α- and β-Amino Acylsilanes as Synthetic Equivalents of α- and β-Amino Aldehydes

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In recent years there has been a growing interest in the synthesis of homochiral 1,2- and 1,3-amino alcohols with two stereogenic centers bearing the amino and the hydroxyl groups, which are structural units found in a number of important bioactive compounds. The 1,2-amino alcohol unit is, in fact, present in compounds such as antibiotics,[1] among which Taxol[2] is certainly the most famous, and hydroxyethylene dipeptide isosteres acting as HIV-1 protease inhibitors.[1,3] The 1,3-amino alcohol unit is present in a number of widely prescribed antidepressants.[4]

A variety of different methods have been reported for the diastereoselective synthesis of 1,2-[1,5−7] and 1,3-amino hydroxyl sistems.[4,5,8,9] A general synthetic strategy toward 1,2-amino hydroxyl compounds consists of the diastereoselective addition of organometallic reagents to protected α-amino aldehydes that, in turn, are accessible from the corresponding amino acids.[1,3,10−12] However, several basic problems are connected with the use of α-amino aldehydes, such as their chemical and configurational instability, as well as the stereocontrol in the addition step. Due to their instability, special precautions are necessary for their synthesis, handling, and storage.[1,13] The degree of stereoselectivity in the addition step, not high enough in many cases,[1] has been recently increased by specific variations of protecting groups and reagents.[10,11]

To the best of our knowledge an analogous protocol toward the diastereoselective synthesis of 1,3-amino alcohols has never been used. This is probably due to the difficulty in obtaining the β-amino aldehydes in a pure state owing to their high instability.[14,15]

To overcome the problems connected with the use of α- and β-amino aldehydes, we propose an approach to 1,2- and 1,3-amino alcohols focusing on the use of homochiral α- and β-amino acylsilanes, obtained from natural α-amino acids, as synthetic equivalents of α- and β-amino aldehydes, based on the well-known facility to replace the silyl group with a proton by means of fluoride ion. In this way we take advantage of the stability of amino acylsilanes (*vide infra*) and of the bulkiness of the silyl group in increasing the degree of diastereoselectivity.[16]

The synthetic equivalence between acylsilanes and aldehydes has already been exploited by Ohno et al. in the addition reactions of organometallic reagents to acylsilanes bearing an α-[17] and a β-chiral carbon.[18]

Our strategy involves the addition of an organometallic reagent to homochiral, nitrogen-protected α- and β-amino acylsilanes to give α-hydroxysilanes, followed by stereospecific protiodesilylation and deprotection of the amino group.

The aminoacylsilanes of choice were the [3-phenyl-2(*S*)-phthalimidopropionyl]dimethylphenylsilane (**5**)[19] and the [4-phenyl-3(*S*)-phthalimidobutanoyl]dimethylphenylsilane (**4**), both obtained from *N*-Pht-L-phenylalanine (**1**).

For the synthesis of **4**, *N*-Pht-L-phenylalanine was homologated with the Arndt−Eistert reaction which is known[20−22] to give enantiopure β-amino acids from their α-analogues with retention of configuration at the chiral carbon. The 4-phenyl-3(*S*)-phthalimidobutanoic acid (**2**) obtained was transformed into the acyl chloride **3**, which in turn was allowed to react with bis(dimethylphenylsilyl)zinc cyanocuprate under the same conditions[19] used for compound **5**, giving **4** in 45% yield (Scheme 1).

The (aminoacyl)silanes **5** and **4** were purified on silica gel and stored in the refrigerator (4−10 °C) for long periods, without experiencing any chemical degradation or racemization, thus proving their chemical and optical stability.

The first step of our synthetic protocol toward 1,2- and 1,3-amino hydroxyl systems was accomplished through a titanium tetrachloride-mediated addition of allyltrimethylsilane to both α-**5** and (β-aminoacyl)silane **4**, resulting in the formation of the α-hydroxysilanes **6** and **8** in 75% and 80% yield, respectively. The NMR spectra (H-1 and C-13) of **6** and **8** indicate the presence of a single diastereoisomer for each α-hydroxysilane, thus suggesting de values equal to or higher than 98%.[24] Subsequent protiodesilylation of **6** and **8** with tetrabutylammonium fluoride (TBAF) in THF afforded 60% of 6-phenyl-5(*S*)-phthalimido-1-hexen-4-ol (**7**) and 80% of (4*R*,6*R*)-7-phen-

(1) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149 and references therein.
(2) Nicolaou, K. C.; Dai, W.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15.
(3) D'Aniello, F.; Mann, A.; Mattii, D.; Taddei, M. *J. Org. Chem.* **1994**, *59*, 3762 and references therein.
(4) Carlier, P. R.; Lo, K. M.; Lo, M. M. C.; Williams, I. D. *J. Org. Chem.* **1995**, *60*, 7511.
(5) Ohfune,Y. *Acc. Chem. Res.* **1992**, *25*, 360.
(6) Sakaitani, M.; Ohfune, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1150.
(7) Barrett, A. G. M.; Seefeld, M. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1996**, *61*, 2677.
(8) Gmeiner, P.; Junge, D.; Kärtner, A. *J. Org. Chem.* **1994**, *59*, 6766.
(9) Chesney, A.; Markò, I. E. *Synth. Commun.* **1990**, *20*, 3167.
(10) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531. Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141.
(11) Dondoni, A.; Perrone, D.; Merino, P. *J. Org. Chem.* **1995**, *60*, 8074. Dondoni, A.; Perrone, D.; Semola, T. *Synthesis* **1995**, 181.
(12) Prasad, J. V. N. V.; Rich, D. H. *Tetrahedron Lett.* **1990**, *31*, 1803. Prasad, J. V. N. V.; Rich, D. H. *Tetrahedron Lett.* **1991**, *32*, 5857.
(13) Rein, T.; Kreuder, R.; von Zezschwitz, P.; Wulff, G.; Reiser, O. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1023.
(14) Markò, I. E.; Chesney, A. *Synlett* **1992**, 275.
(15) Davis, S. G.; McCarthy, T. D. *Synlett* **1995**, 700.
(16) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199.
(17) Nakada, M.; Urano, Y.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1988**, *110*, 4826.
(18) Nakada, M.; Urano, Y.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1994**, *35*, 741.
(19) Bonini, B. F.; Comes-Franchini, M.; Mazzanti, G.; Passamonti, U.; Ricci, A.; Zani, P. *Synthesis* **1995**, 92.
(20) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517.
(21) Plucinska, K.; Liberek, B. *Tetrahedron* **1987**, *43*, 3509.
(22) Cassal, J. M.; Fürst, A.; Meier, W. *Helv. Chim. Acta* **1976**, *59*, 1917.
(23) Sheehan, J. C.; Chapman, D. W.; Roth, R. W. *J. Am. Chem. Soc.* **1952**, *74*, 3822.
(24) The estimate of the de values assigned to compounds **6**−**9** derives from a measure of the signal to noise ratio of their NMR spectra. In addition, in the case of compound **9**, the value has been confirmed by the observation that in the ^{1}H NMR spectrum no signal, which might be attributed to a possible minor diastereoisomer, was higher than the pair of C-13 satellites (0.55% each) of the major diastereoisomer.

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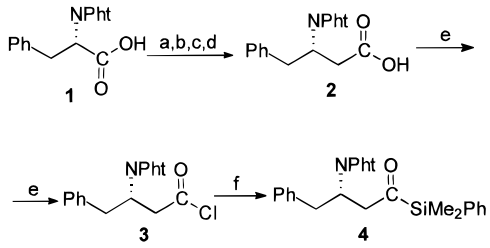
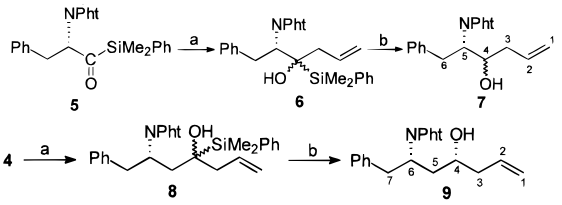
Scheme 1[a]



[a] Reaction conditions: (a) ref 23, 90%; (b) CH_2N_2, Et_2O/THF, rt, 1 h, 93%; (c) Ag_2O, MeOH, 50 °C, 40 min, 85%; (d) HCl, H_2O, aceton, reflux, 150 min, 80%; (e) $SOCl_2$, 55 °C, 4 h, 93%; (f) $(PhMe_2Si)_2CuCN(ZnCl)_2$ (see ref 19), 45%.

Scheme 2[a]



[a] Reaction conditions: (a) allyltrimethylsilane (1 equiv), CH_2Cl_2, $TiCl_4$ 1 M in CH_2Cl_2 (1 equiv), −78 °C, 24 h, 75% for **6**, 80% for **8**; (b) TBAF 1 M in THF (1 equiv) diluted with THF to obtain a 0.1 M solution, rt, 72 h, 60% for **7**, 72% for **9**.

yl-6-phthalimido-1-epten-4-ol (**9**), respectively, as single diastereoisomers, suggesting, also in this case, de values ≥98%[24] (Scheme 2).

The absolute stereochemistry of the newly formed stereogenic center in **9** was established by ^{1}H NMR analysis of the corresponding esters of Mosher's acids (*R*)-MTPA and (*S*)-MTPA. From the differences in the chemical shifts, the *R* configuration was attributed[25,26] to the carbon bearing the hydroxylic group (C-4) (Table 1). Unfortunately, Mosher's method could not be used

Table 1. Determination of the Absolute Configuration of 9

	δ_H C(2)	δ_H C(3)	δ_H C(5)	δ_H C(6)
(*R*)-MTPA ester of **9**	5.464	2.275	1.982	4.521
(*S*)-MTPA ester of **9**	5.617	2.398	1.965	4.444
$\Delta\delta_H = \delta_{(R)} - \delta_{(S)}$	−0.153	−0.123	+0.017	+0.077

to predict the absolute configuration at C-4 of the *β*-amino alcohol **7**, since the differences of chemical shifts in the ^{1}H NMR spectra of the corresponding (*R*)-MTPA and (*S*)-MTPA esters were not significant.[27]

In conclusion, these results describe the possibility of obtaining 1,2- and 1,3-amino alcohol units by overcoming the problems associated with the use of α- and *β*-amino aldehydes. In fact, we found that α- and *β*-amino acylsilanes **4** and **5** are stable and react in a highly stereoselective fashion (de ≥98%) with allyltrimethylsilane in the presence of $TiCl_4$. Moreover, the protiodesilylation step is stereospecific, thus proving the synthetic equivalence of these species with α- and *β*-amino aldehydes.

Further investigations regarding the use of other (α-aminoacyl)- and (*β*-aminoacyl)silanes and the improvement of their yields, as well as the use of different protecting groups and of other organometallic reagents are currently underway in our laboratory.

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Supporting Information Available: Experimental procedures and compound characterization data (6 pages).

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(25) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(26) Ohtani, I.; Kusumi, I.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092 and references therein.

(27) The spectra, recorded at 300 MHz in $CDCl_3$ and C_6D_6, displayed chemical shift differences smaller than 1 Hz. Other examples are known in which Mosher's method is inapplicable (see ref 26).