Pergamon

Tetrahedron Letters 39 (1998) 4959–4962

TETRAHEDRON LETTERS

Unusual Lability of α-Silyloxy β-Amino Carboxylic Acid Derivatives

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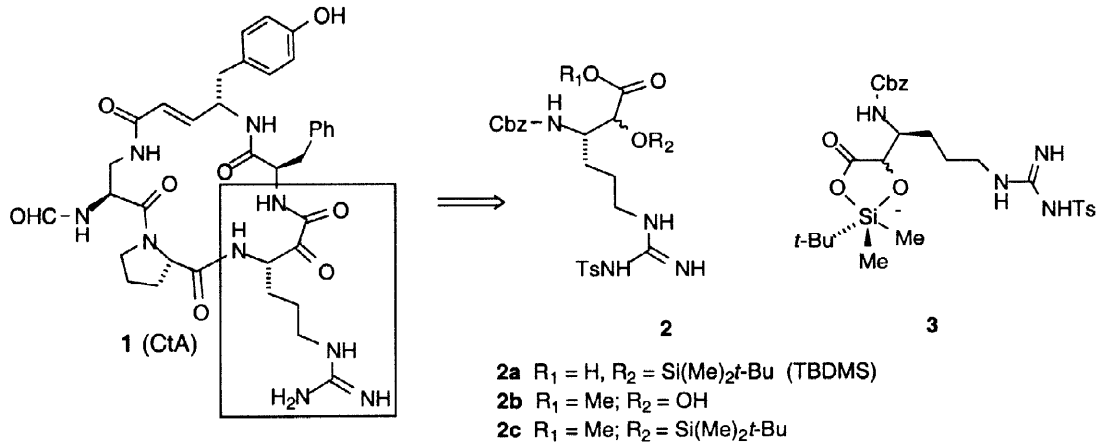
Received 20 April 1998; accepted 5 May 1998

Abstract: Saponification and mild acidification of α-silyloxy homo-arginine derivative **2c** revealed an unusual lability of the silyl protecting group. A systematic study of related substrates indicates that hydrogen bonding between the α-amino hydrogen and the carbonyl oxygen is critical for facile desilylation. A mechanism involving neighboring group participation of NH and carboxyl groups is proposed.

A number of important biologically active compounds contain the α-hydroxy-β-amino acid subunit as an important structural component. For example, there are norstatin and its analogues, which have served as valuable substrate analogue inhibitors of renin[1] and HIV protease.[2] Also, the potent anticancer agent Taxol (paclitaxel),[3] as well as its congeners, contain a C-13 isoserine side chain that is crucial for their antitumor activity. In fact, intense structure-function studies[4] of Taxol have spawned considerable interest in the chemistry of α-hydroxy-β-amino acids.[5]

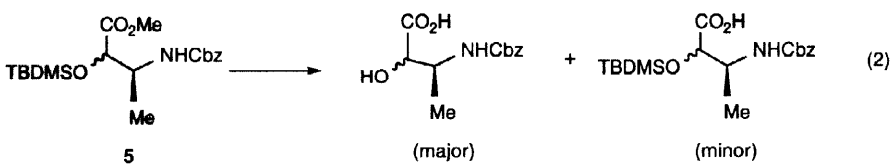
During our studies of cyclotheonamide A (CtA)[6,7] and related macrocycles,[8] we required gram quantities of α-hydroxy homo-arginine derivatives bearing a protected hydroxyl group, as in **2a**. Since saponification of **2b** was accompanied by formation of the corresponding oxazolidinone,[7b] we chose to protect the α-hydroxyl group as a silyl ether. However, saponification of **2c** under standard conditions (3 mol equiv. of LiOH, 9:1 dioxane-water; neutralization with HOAc to pH 4) afforded the desilylated derivative, **2d**, as the major product in low isolated yield (ca. 30%).[7b] Reasoning that a hypervalent silicon complex between the carboxylate oxygen and the silicon atom might be involved, as depicted in **3**, we used the 2-(trimethylsilyl)ethoxymethyl (SEM) group[9] to prevent the loss of protection. Although this strategy successfully addressed our synthetic needs (vide infra), we decided to investigate the nature of this unexpectedly facile desilylation reaction. During our studies, a related desilylation of an oligoribonucleotide derivative appeared.[10]

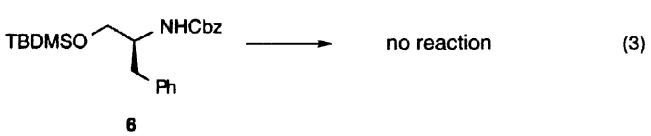


2a R_1 = H, R_2 = Si(Me)$_2$*t*-Bu (TBDMS)
2b R_1 = Me; R_2 = OH
2c R_1 = Me; R_2 = Si(Me)$_2$*t*-Bu
2d R_1, R_2 = H
2e R_1 = OH; R_2 = SEM

0040-4039/98/$19.00
PII: S0040-4039(98)00967-8

Although the intervention of an intramolecular hypervalent silicon species was first considered, this was determined to be unlikely on account of **4** yielding the expected silyl-protected mandelic acid derivative upon saponification (eq 1). We assessed the potential involvement of the various functional groups of **2c** in the desilylation process by exposing modified substrates to the saponification procedure.[11] Since alanine-derived **5**[12] behaves analogously to **2c** under saponification conditions (eq 2), the desilylation process appears to be independent of the amino acid side chain.[13] Furthermore, the unreactivity of **6** rules out direct interaction between the carbobenzoxy and silyloxy functionalites (eq 3). Collectively, these results suggested that the carboxyl and amino functionalities act in concert to facilitate the desilylation. To pinpoint the role of the acetic acid neutralization step in the process, we subjected several modified alanine substrates (**5**, **7-9**) to the saponification conditions, followed by direct purification of the carboxylate salts by flash-column chromatography on silica gel (CH_2Cl_2/MeOH 15:1 to 5:1).[14] Our results are summarized in the Table. Interestingly, although the silyloxy acids were isolated, they rapidly (in ca. one hour) desilylated on standing





in an NMR tube ($CDCl_3$ solution). This combination of results led us to consider a mechanism whereby hydrogen bonding between the NH proton and the carboxylic acid carbonyl enhances charge delocalization throughout the carboxyl group to facilitate protodesilylation (eq 4). Since a substrate unable to experience this hydrogen bond should be stable, we prepared proline derivative **10**[12] and subjected it to the conditions of saponification/acidification (eq 5). In this case, silyloxy acid **11** was isolated in reasonable yield (silica gel; CH_2Cl_2/MeOH, from 30:1 to 15:1) as a stable, colorless oil.[15] Similarly, hydrolysis of the N-Me derivative of **5** yielded the corresponding carboxylic acid,[16] lending further support to the proposed mechanism.

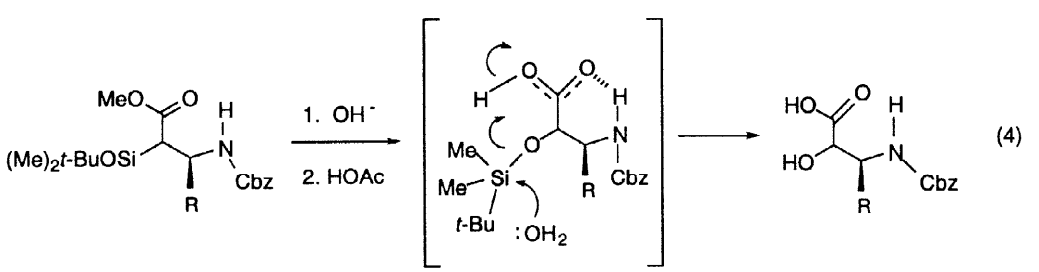
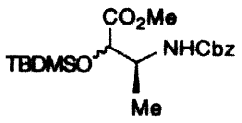
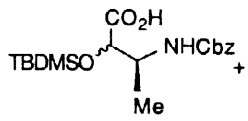
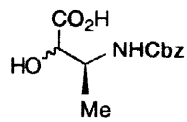
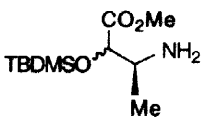
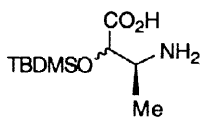
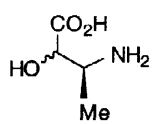
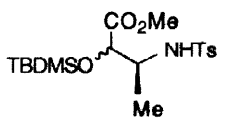
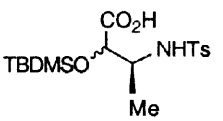
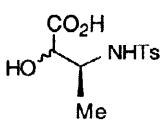
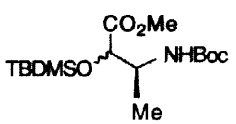
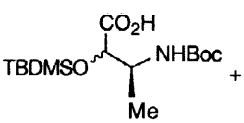
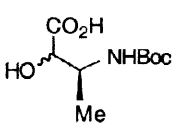
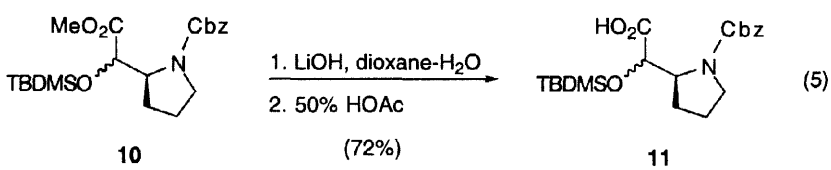


Table. Substrates and Products from Direct Chromatographic Purification of Carboxylate Salts

Substrates	Products [a]	
 **5**	 63%	 19%
 **7**	 55%	 31%
 **8**	 53%	 22%
 **9**	 55%	 38%

(a) Isolated yields.



10 **11** (5)

The results of our study help rationalize the stability of SEM-protected arginine derivative **2e** to the extent that a siloxy group is unavailable for interaction, as in eq 4. Our results complement the findings of Kawahara et al.,[10] which suggested that neighboring group participation between TBDMS and a phosphate functionality is involved in the exceptionally mild desilylation of TBDMS-protected oligoribonucleotide intermediates. Taken together, these two studies suggest a generality for the enhanced hydrolytic cleavage of a siloxy functionality by neighboring group participation.

Acknowledgments. We thank Prof. Dennis Liotta for helpful discussions.

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11. Saponification procedure: To a solution of α-silyloxy homo-amino acid methyl ester in dioxane/water (5:1) was added LiOH (5 mol equiv) in one portion and the resulting mixture was stirred at 23°C for 24 h. The reaction was quenched with 50% aqeous AcOH to achieve pH = 4 and extracted twice with EtOAc. The combined EtOAc extracts were washed with brine and dried over Na_2SO_4. After removal of solvent in vacuo, the crude product was purified by flash-column chromatography (silica gel; CH_2Cl_2-MeOH).
12. Prepared analogously to **2c** according to procedure described in ref 2b.
13. Other α-N-substituted derivatives of **5** were subjected to the saponification procedure; *p*-toluenesulfonyl, BOC, *N,N*-dimethyl, and NH_2 all underwent rapid desilylation.
14. In this case, the reaction was lyophilized and the crude products were chromatographed directly. Although the acetic acid neutralization step was omitted, we assume that protonation occurred at least partially during chromatography and to a further extent in $CDCl_3$. All compounds in the Table were homogeneous by silica gel TLC (CH_2Cl_2-MeOH; 9:1 for substrates, 5:1 for products) and were characterized by ^1H NMR ($CDCl_3$, 300 MHz) and electrospray mass spectrometry. Compounds **7-9** were prepared from **5** by conventional methods and were purified by flash-column chromatography (silica gel, gradient from 20:1 to 9:1 CH_2Cl_2-MeOH).
15. Isolated as a mixture of diastereomers: R_f = 0.60 (CH_2Cl_2-MeOH, 9:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 5H), 5.06 (m, 2H), 4.60 (m, 1H), 4.15 (m, 1H), 3.35 (m, 2H), 1.90 (m, 2H), 1.71 (m, 2H), 0.88 (m, 9H), 0.00 (m, 6H); MS (ESI) m/e 394 (MH^+).
16. Isolated as a mixture of diastereomers: R_f = 0.33 (CH_2Cl_2-MeOH, 9:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H), 5.08 (m, 2H), 4.40 (br m, 2H), 2.88 (m, 3H), 1.19 (m, 3H), 0.89 (m, 9H), 0.03 (m, 6H); MS (ESI) m/e 388 $(M + Li)^+$.