Tetrahedron Letters,Vol.28,No.34,pp 3987-3990,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

A NEW MODE OF CYCLIC CARBAMATE FORMATION VIA *tert*-BUTYLDIMETHYLSILYL CARBAMATE. STEREOSELECTIVE SYNTHESES OF STATINE AND ITS ANALOGUE

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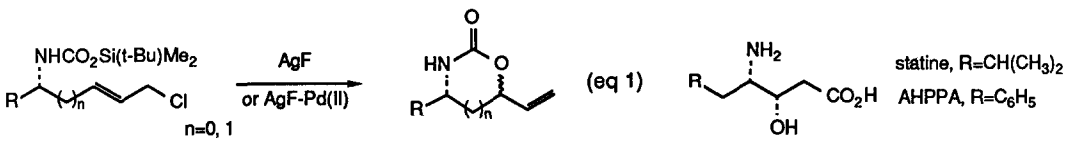
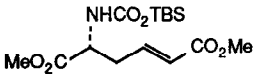
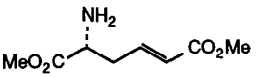
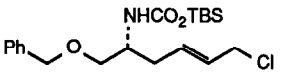
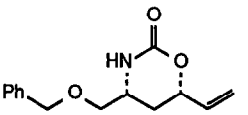
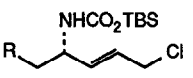
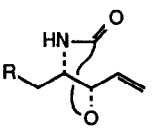
Summary: Stereoselective construction of 1,2- and 1,3-amino hydroxyl systems was carried out using S_N2' (initiated by AgF or AgF-Pd(II)) cyclic carbamate formations from *tert*-butyldimethyl silyl carbamates. This method was applied to the syntheses of statine and AHPPA, efficiently.

1,2- And 1,3-amino hydroxyl systems have attracted significant interests due to their presence in a variety of natural products. Since unusual amino acids possessing the above mentioned moieties are widely distributed in biologically important peptides, development of efficient synthetic methods and application of these methods to the syntheses of such amino acids are currently of importance.[1] Previously, we reported the synthesis of *tert*-butyldimethylsilyl carbamates from the most common amino protecting groups such as N-*tert*-butoxycarbonyl (*t*-Boc) and N-benzyloxycarbonyl (Z) groups.[2] The silylcarbamate can be viewed as an *N-carboxylate ion equivalent* due to its high reactivity, i.e., this group can be converted into many different N-ester groups with an electrophile in the presence of fluoride ion.[2a] Intramolecular trapping of this reactive species provides a stereoselective method for the construction of above mentioned amino hydroxyl systems.[3] Described herein are the S_N2' cyclic carbamate formations (eq 1) from *tert*-butyldimethylsilyl carbamate and the application of this method to the syntheses of unusual amino acids, statine[4] and (3*S*,4*S*)-4-amino-3-hydroxy-5-phenylpentanoic acid (AHPPA)[5] which are the key constituent amino acids of a specific renin inhibitor, pepstatine and its related peptide.



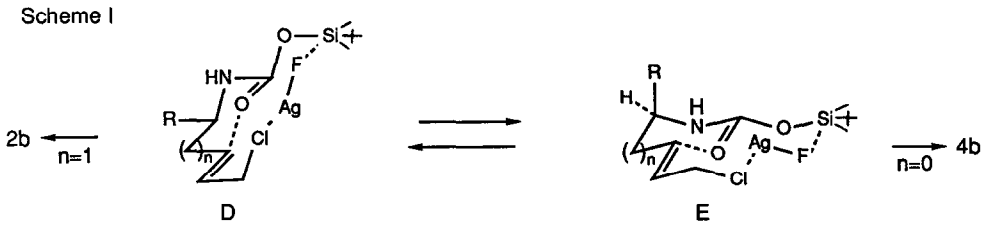
S_N2' type cyclic carbamate formation. Initial attempts to trap the generated reactive species[2a] with an unsaturated ester (Table I,[6,7] entry 1) by intramolecular Michael-addition were not successful but gave the corresponding amine **1b**.[3g] Therefore, we turned our attention to the syntheses of cyclic carbamates from the allyl halides **2a**-**7a**. Silver fluoride was chosen to activate both the silyloxy and the allyl chloride groups. The silyl carbamate **2a** was treated with 1.5 equiv AgF in acetonitrile under nitrogen at room temperature for 24 h to give the desired cyclic carbamate **2b** in 63% yield. As summarized in Table I (entries 2-6), only the *E*-allyl chlorides **2a**, **4a**, and **6a** provided the cyclic carbamates **2b**, **4b**, and **6b**,[8,9] respectively. These results can be explained by assuming that cyclic carbamate formation from the silylcarbamates possessing ***E*** double bonds proceeds via transition state D or E (*syn* S_N2' mechanism)[10a] where the fluoride does not dissociate from the

Table I. Syntheses of cyclic carbamates from tert-Butyldimethylsilyl (TBS) carbamates

entry	silyl carbamate[a]	major isomer of product	reaction condition[b] (selectivity[c])	yield, %[d]
1	 1a	 1b	A	100
2	 2a	 2b	B (4:1) C (1:1)	63 70
3	3a, Z isomer of 2a	———	B, C	0
4	 4a, R=OCH_2Ph	 4b, R=OCH_2Ph	B (3:1) C (8:1)	55 72
5	5a, Z isomer of 4a	4b	B C (8:1)	0 9
6	6a, R=$CH(CH_3)_2$	6b, R=$CH(CH_3)_2$	B (5:1) C (15:1)	83 78
7	7a, R=Ph	7b, R=Ph	C (10:1)	70

[a] *tert*-Butyldimethylsilyl carbamates **1a-7a** were prepared from the corresponding N-*tert*-butoxycarbonyl (*t*-Boc compounds[6,7] (*t*-$BuMe_2SiOSO_2CF_3$, 2,6-lutidine)[2a] and were used without purification. [b] Reaction conditions for A, B, and C: A; *n*-Bu_4NF, tetrahydrofuran (THF), 0 °C, 1-3 h: B; 1.5 equiv AgF, CH_3CN, room temperature, 24-48 h: C; 2.0 equiv AgF, 0.2 equiv $(C_6H_5)_3P$, 0.05 equiv allylpalladium chloride dimer, CH_3CN, room temperature, 3 h. [c] Determined by 360 MHz ^1H NMR. The major isomers in entries 2 and 4-7 were separated by flash column chromatography and the structures were fully elucidated by spectroscopic data.[8] [d] Isolated overall yield.

Scheme I

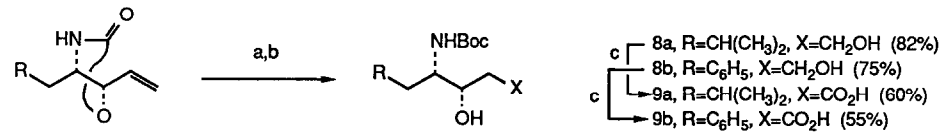


Ag-allyl chloride complex. This transition state is not possible with the *Z*- allyl chlorides **3a** and **5a**.

Of particular note is the addition of a catalytic allylpalladium(II) chloride dimer to the above reaction . This resulted in a rate enhancement as well as an increase in the yields. Increased *threo* selectivity in the five membered cyclic carbamate formations (entries 4 and 6) was observed.[11,12] Thus, we applied this method to the syntheses of statine and AHPPA in which only a limited number of methods have been available for the stereoselective construction of these key vicinal amino hydroxyl systems.[4]

Syntheses of statine and AHPPA. Since the cyclic carbamates **6b** and **7b** were prepared stereoselectively from **6a** and **7a,** respectively (entries 6 and 7) , simple transformations of these intermediates to **9a** and **9b** were examined as follows. The cyclic carbamate **6b** was converted to the diol **8a** (82%) by the following sequence of reactions; (i) 9-borabicyclo[3.3.l]nonane (9-BBN)/30% H_2O_2/6N NaOH, (ii) $Ba(OH)_2$, and (iii) di-*tert*-butyldicarbonate/triethylamine. Conversion to the desired *t*-Boc statine **9a** was carried out selectively by PtO_2/O_2 oxidation in 60% yield: mp118.0-120.0 °C; $[\alpha]_D^{34}$ -38.5°(*c* 1.0, MeOH).[4b] N-*t*-Boc AHPPA **9b** was prepared from **7b** in the same manner as above: **9b**;[5a] mp 151.0-152.0°C; $[\alpha]_D^{30}$ -37.5°(*c* 1.0, MeOH). The synthetic materials showed completely identical spectroscopic data with those reported.[13-15]

Scheme II [a]



6b, R=$CH(CH_3)_2$
7b, R=C_6H_5

[a] (a) (1) 9-BBN,THF, room temperature, 20 h; (2) 6 N NaOH, 30% H_2O_2, ethanol, room temperature, 30 min; (b) (1) $Ba(OH)_2$, ethanol-H_2O, 80 °C, 30 h; (2)Dowex 50Wx4 (elution with 28% NH_3); (3) $(t\text{-BuOCO})_2O$, triethylamine, THF, room temperature, 20 h; (c) PtO_2, O_2, dioxane- H_2O (1:1), 55 °C, 30 h.

References and Notes

1. For reviews, see: (a) Wagner, I.; Musso, H. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 816. (b) Ohfune, Y.; Kurokawa, N. *J. Syn. Org. Chem. Jpn.* **1986**, *44* , 647.
2. (a) Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett.* **1985**, *26*, 5543. (b) Sakaitani, M.; Kurokawa, N.; Ohfune, Y. *Tetrahedron Lett*. **1986**, *27*, 3753.
3. Intramolecular electrophilic 2-oxazolidone formation from N-substituents (benzoyl or benzyloxycarbonyl group) of allyl or homoallyl amines: (a) Pauls, H. W.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1980**, *102*, 3956. (b) Georges, M.; Mackay, D.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1982**, *104*, 1101. (c) Takano, S.; Hatakeyama, S. *Heterocycles* **1982**, *19*, 1243. (d) Overman, L. E.; McCready, R. J. *Tetrahedron Lett.* **1982**, *23*, 4887. (e) Wang, Y.-F.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1982**, *104*, 6465. (f) Parker, K. A.; O'Fee, R. *J. Am. Chem. Soc.* **1983**, *105*, 654. (g) Successful intramoleculer Micheal addition from the O-carbamates, see: Hirama, M.; Shigemoto,T.; Yamazaki,Y.; Ito, S. *J. Am. Chem. Soc.* **1985**, *107*, 1797.

4. Synthesis of statine: (a) Morishima, H.; Takita, T.; Umezawa, H.; *J. Antibiot.* **1973**, *26*, 115. (b) Rittle, K. E.; Homnick, C. F.; Ponticello, G. S.; Evans, B. E. *J. Org. Chem.* **1982**,*47*, 3016. (c) Woo, P. W. K. *Tetrahedron Lett.* **1985**, *26*, 2973. Other references are cited therein.

5. Isolation of AHPPA: Omura, S.; Imamura, N.; Kawakita, K.; Mori, Y.; Yamazaki, Y.; Masuma, R.; Takahashi, Y.; Tanaka, H.; Huang, L.-Y.; Woodruff, H. B. *J. Antibiot.* **1986**, *39*, 1079. Synthesis of AHPPA: (a) Rich, D. H.; Sun, E. T. *J. Med. Chem.* **1980**, *23*, 27. (b) see, ref 4b

6. The N-*t*-Boc Compounds **1a**-**5a** listed in Table I were prepared from allylglycine or 2-amino- 3-butenol derivatives.[1b] Details will be described in a full paper, to be published.

7. The allyl chloride **6a** and **7a** were prepared from the known N-*t*-Boc-leucinol and N-*t*-Boc-phenylalaninol, respectively, in 4 steps (each 72% yield); (i) SO_3-Py, (ii) $Ph_3P{=}CHCO_2Et$, (iii) *i*-Bu_2AlH/BF_3-OEt_2,[a] and (iv) N-chlorosuccinimide/Ph_3P. No racemization during these process was confirmed by converting the allyl alcohols (*i*-Bu_2AlH reduction products for **6a** and **7a**) to their N,O-bis-(+)-MTPA amide esters. ^1H NMR indicated their homogeneity.[b] (a) Moriwake, T.; Hamano, S.; Miki, D.; Saito, S.; Torii, S. *Chem. Lett.* **1986**, 815. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

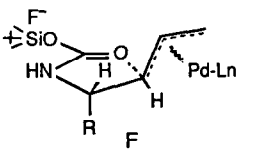
8. Stereochemistry of 2-oxazolidones were fully assigned by their 360MHz ^1H NMR as well as NOE experiments. NMR studies of *threo* and *erythro* 2-oxazolidones, see: Fujikawa, S.; Inui, T.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3308.

9. All new compounds exhibited satisfactory ^1H NMR, IR, MS, and elementary analytical or high resolution mass spectral data.

10. (a) Review for S_N2' reactions, see: Magid, R. M. *Tetrahedron* **1980**, *36*, 1901. (b) Pd(II) catalyzed *syn* S_N2' reactions, see: Takahashi, T.; Miyazawa, M.; Ueno, H.; Tsuji, J. *Tetrahedron Lett.* **1986**, *27*, 3881.

11. Formation of **4b** from the *Z*-isomer **5a** (9%) would be due to isomerization of double bond (*Z* to *E*) during the reaction.

12. In this reaction, a palladium catalyzed S_N2' mechanism was assumed: in entries 4-7, a strong 1,2-steric interaction between the R and the π-allyl-palladium groups in the hypothetical transition state F resulted in the selective formation of the threo carbamates **4b**-**7b**. However, It is not clear whether the reaction proceeds via *syn* or *anti* S_N2' mechanism.[10b] Efforts to explain these reaction mechanisms are currently in progress.



13. Conversions to statine and AHPPA by removal of the *t*-Boc group have been reported.[4b,5a]

14. Melting points (mp) and $[\alpha]_D$ values of the selected intermediates for the syntheses of statine and AHPPA [$[\alpha]_D$ values were measured using methanol as the solvent (*c* 1.0)]. **6a**: oil; $[\alpha]_D^{28}$ -27.7°. **7a**: mp 68.0-69.0 °C; $[\alpha]_D^{33}$ -6.0°. **6b**: oil; $[\alpha]_D^{34}$ -76.4°. **7b**: mp 71.0-72.0 °C; $[\alpha]_D^{34}$ -53.1°. **8a**: oil; $[\alpha]_D^{29}$ -40.2°. **8b**: mp 106.0-108.0 °C; $[\alpha]_D^{29}$ -38.2°.

15. We thank Professor Koji Nakanishi, Director of Suntory Institute for Bioorganic Research, for continuous encouragement.

(Received in Japan 6 April 1987)