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# AN EFFICIENT ROUTE TO 1,3-AMINO HYDROXYL SYSTEM VIA ELECTROPHILIC LACTONIZATION OF 2-AMINO-4-PENTENOIC ACID DERIVATIVES. STEREOSELECTIVE SYNTHESIS OF (-)-BULGECININE

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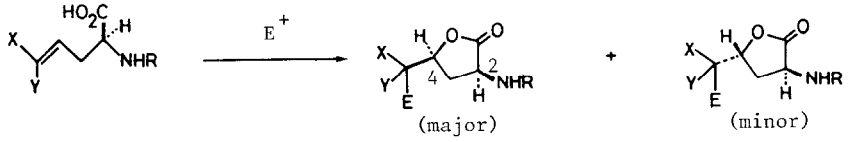
Summary: Several γ-hydroxy-α-amino acid systems were prepared stereoselectively from 2-amino-4-pentenoic acid derivatives using electrophilic lactonization. This strategy was applied to the synthesis of a highly functionalized proline analogue, (-)-bulgecinine (4).

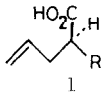
Recently, significant attention has been focused on the stereoselective synthesis of 1,3-amino hydroxyl systems which are found in a variety of nitrogen containing natural products.[1] In view of the syntheses of unusual amino acids with a γ-hydroxy-α-amino acid moiety, the strategy of using an electrophilic lactonization[2] in an acyclic γ,δ-unsaturated-α-amino acid systems is of interest (eq 1). Although a high stereoselectivity was observed in the halolactonization of 3-substituted-4-pentenoic acids[2b,c,3] (stereocontrol directed by the allylic substituent), stereoselectivity in the 2-substituted-4-pentenoic acids was not expected to be high due to the conformational flexibility of the 5-membered ring transition state (stereocontrol by the homoallylic group).[2b,d] On the other hand, significant cis-selective γ-butyrolactonizations[4] in 2-amino-4-pentenoic acid derivatives were reported (1 → 2; vide infra). However, the role of amino group during halolactonization remained unsolved. In this report, we wish to describe the C2 and C5 substituent effect in the electrophilic lactonization, and the synthesis of (-)-bulgecinine (4),[7] which is a constituent amino acid of the novel glycopeptide bulgecin[8] (characterized by its induction of morphological changes in Gram-negative bacteria in cooperation with β-lactam antibiotics such as sulfazecin).

N-Substituent effect in the halolactonization of 2-amino-4-pentenoic acid derivatives were examined first as summarized in Table I.[9] These results indicated that a relatively high cis selectivity was observed in 1b-1f in contrast to those of non-polar substituents (1a). The product ratios were independent of the properties of the N-substituents such as steric bulkiness, electronegativity, the absence of amide hydrogen, etc.[10] It was assumed that the reaction proceeded via cyclic intermediate A in which the bromonium ion is stereoelectronically stabili-



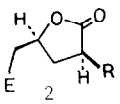

(eq 1)

Table I. Halolactonization of 2-substituted-4-pentenoic acids.[a,b]

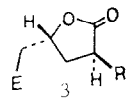


1

Electrophile (solvent) →



2 + (ratio)[c]



3

| | | | | | | | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1a | R=Me or phenyl | $I_2$ | 2a | (3 | : | 2) | 3a[2b,d,4] —— |
| 1b | R=NHZ | NBS(THF) | 2b | (8 | : | 1) | 3b 80 |
| 1c | R=NHBoc | NBS(THF) | 2c | (8 | : | 1) | 3c 82 |
| 1d | R=NHCHO | NBS(THF) | 2d | (8 | : | 1) | 3d 40 |
| 1e | R=NPht | NBS(THF) | 2e | (6 | : | 1) | 3e 81 |
| 1f | R=NHTs | NBS(THF) | 2f | (8.8 | : | 1) | 3f 100 |

[a]All reactions were carried out at 0 °C under nitrogen. [b]Abbriviations of amino protecting groups: Z=benzyloxycarbonyl; Boc=t-butoxycarbonyl; Pht=phthaloyl; Ts=p-toluenesulfonyl. [c]Product ratios were determined by $^1$H NMR and HPLC analysis.

zed by the amino group.[11]

The present results seemed to be applicable to the 5-substituted derivatives 5 and 7, where a relatively rigid conformation in the transition state and a high stereoselectivity of product formation were expected. The synthesis of bulgecinine (4) was planned from (2S,4S,5S)-γ-butyrolactone 6a as the key intermediate which would be derived via a halolactonization of the Z-allyl alcohol 5 (Scheme I). Although a large steric repulsion between the amino group and the C5 substituent seems not to favour the hypothetical desired transition state B, we expected that a stereoelectronic stabilization of the amino group to the bromonium ion which is only possible in B should lead to the desired 6a.

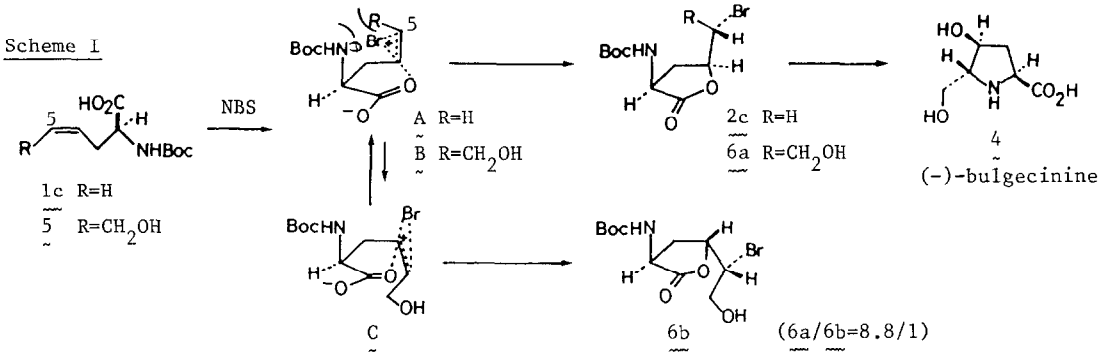
The Z-allyl alcohol 5 prepared from N-t-Boc-L-allylglycine methyl ester 13[12] was thus treated with N-bromosuccinimide (NBS) in tetrahydrofuran (THF), 0 °C, 5 min, to give 8.8 : 1 mixture of the γ-butyrolactones 6a and 6b in 95% yield.[13] The configuration of the major isomer, purified by recrystallization ($CHCl_3$/hexane), mp 139-142 °C, $[\alpha]_D^{28}$ +44.7° (c 0.78, MeOH), to be cis was suggested by its $^1$H NMR data [δ2.24 (3βH, ddd, J=10, 11, and 12 Hz), 2.88 (3αH, ddd, J=6, 9, and 12 Hz)],[9] and finally determined by converting it to 4. Deprotection of 6a with trifluoroacetic acid (TFA), cyclization with 0.1 N $Ba(OH)_2$ (pH 9, room temperature, 3 h), and the subsequent treatment with Dowex 50W x 4 (elution with 1 N $NH_3$) provided bulgecinine (4) in 85% from 5 [amorphous solid, $[\alpha]_D^{27}$ -13.3° (c 1.5, $H_2O$)], of which spectroscopic data were identical with those reported.[7]

On the other hand, treatment of the E-isomer 7 in the same manner as above gave the cis-γ-butyrolactone 8a as the major product [8a/8b=6.3/1: 8a; oil, $[\alpha]_D^{29}$ -3.6° (c 1.25, $CHCl_3$)], which was converted to 9, the C5 epimer of 4, amorphous solid, $[\alpha]_D^{28}$ +5.7° (c 1.47, $H_2O$). In addition, $S_N2'$ lactonization[15] using Z and E allyl chloride, 10 and 11,[12] was examined. Treatment of 10 with silver trifluoromethanesulfonate (AgOTf) (THF, 2,6-lutidine, room temperature, 20 h) gave the cis-4-vinyl-γ-butyrolactone 12a as the major product (73%, 12a/12b=6/1): 12a; mp 124-125 °C, $[\alpha]_D^{28}$ +42.8° (c 1.15, $CHCl_3$). The same ratio of products (92%) was obtained from the reaction of the E-allyl chloride 11. These results suggested that

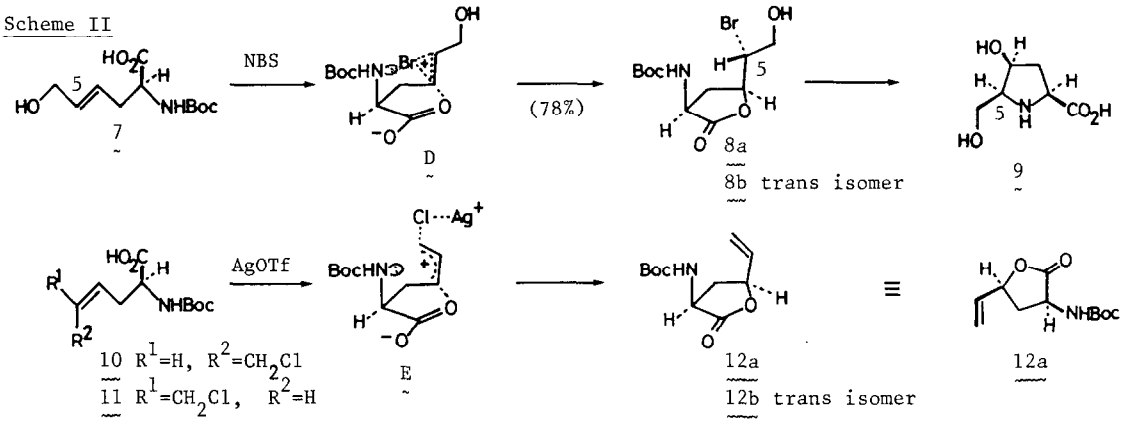
the reaction (10→12) proceeded through the intermediate E in which allyl cation is stabilized by the amino group to give the cis-γ-butyrolactone 12a, predominantly, due to the same reason as in the halolactonization above.

In conclusion, electrophilic lactonization strategy of 2-amino-4-pentenoic acid derivatives provides a method for the synthesis of the useful chiral intermediates (6, 8, 12) as a masked erythro 1,3-amino hydroxyl system.

Scheme I




Scheme II




REFERENCES AND FOOTNOTES


1. For example, see: M. Hirama, T. Shigemoto, Y. Yamazaki, and S. Ito, J. Am. Chem. Soc., 107, 1797 (1985), and references are cited therein.
2. (a) M. D. Dowle, D. I. Davis, Chem. Soc. Rev., 171 (1979). (b) P. A. Bartlett, D. R. Richardson, and J. Myerson, Tetrahedron, 40, 2317 (1984). (c) A. R.Chamberlin, M. Dezube, P. Dussault, and M. C. McMills, J. Am. Chem. Soc., 105, 5819 (1983). (d) P. A. Bartlett and J. Myerson, J. Am. Chem. Soc., 100, 3950 (1978).
3. The synthesis of β,γ-disubstituted-α-amino acids: (a) P. A. Bartlett, D. J. Tanzella, and J. F. Barstow, Tetrahedron Lett., 23, 619 (1982). (b) Y. Ohfune and N. Kurokawa, Tetrahedron Lett., 26, 5307 (1985).
4. Trans-selective γ-butyrolactonization: Y. Tamaru, M. Mizutani, Y. Furukawa, S. Kawamura, Z. Yoshida, K. Yanagi, and M. Minobe, J. Am. Chem. Soc., 106, 1079 (1984).
5. N. Izumiya and B. Witkop, J. Am. Chem. Soc., 85, 1835 (1963).
6. N. Kurokawa and Y. Ohfune, J. Am. Chem. Soc., in press.
7. The synthesis of bulgecinine (4) was reported: (a) from D-glucose; T. Wakamiya, K. Yamanoi,

M. Nishikawa, and T. Shiba, Tetrahedron Lett., 26, 4759 (1985). (b) From D-glucuronolactone; B. P. Bashyal, H.-F. Cho, and G. W. J. Fleet, Tetrahedron Lett., 27, 3205 (1986). We thank Professors Tetsuo Shiba and Tateaki Wakamiya for providing us copies of authentic spectroscopic data of 4.

8. A. Imada, K. Kintaka, M. Nakao, and S. Shinagawa, J. Antibiot., 35, 1400 (1982).

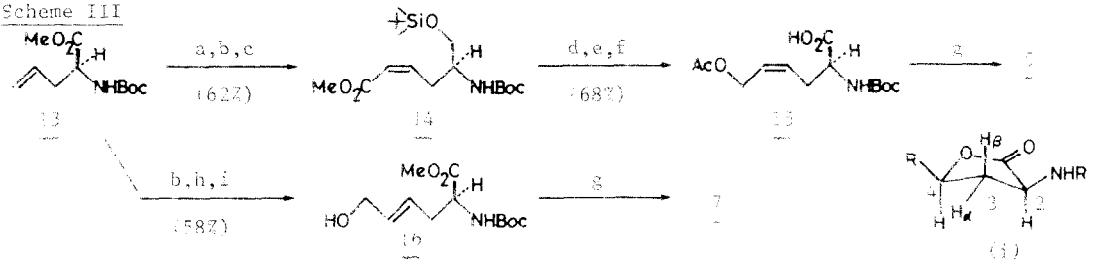
9. The stereochemistry of the cis and trans-γ-butyrolactones was assigned by $^1$H NMR studies: In the case of the cis isomers (2b-2f, 6a, 8a, and 12a), the signals for 3α and 3βH were split into two sets of add pattern, usually separated (0.5-1.0 ppm). The 3βH with the large J values ($J_{2-3\beta}$ and $J_{3\beta-4}$ ≃ 10 Hz) appeared at higher field (δ2.0) than those of the 3αH(δ2.8), which suggests the conformation of the cis isomer to be (i). On the other hand, the chemical shift of the C3 methylene signals of the trans isomers (3b-3f, 6b, 8b, and 12b) appeared (overlapped) between the 3αH and 3βH of the cis isomer. Finally, 2b and 2c were converted to cis-4-hydroxyproline, and 6a to 4. In addition, we are grateful to Professor Paul Williard of Brown University for confirming the structure of 2f by X-ray cryatallographic analysis (details will be described eleswhere).

10. Y. Ohfune and N. Kurokawa, Tetrahedron Lett., 25, 1587 (1984).

11. We thank Professor Kichisuke Nishimoto for valuable discussions. In addition to Table II, halolactonization of the 2-hydroxy and benzyloxy-4-pentenoic acids with NBS was examined to give a mixture of γ-butyrolactones in poor yield (cis/trans=2/1, 20% yield).

12. Syntheses of 5, 7, 10, and 11 from 13 (Scheme III).

Scheme III




(a) 1. $LiAlH_4$, THF; 2. t-butyldimethylsilyl chloride (TBDMSCl), DMF, imidazol; (b) $O_3$, MeOH, -78 °C/dimethylsulfide (DMS); (c) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, NaH, 18-crown-6, THF, -78 °C, Z/E= 7/1; (d) DIBAL, $CH_2Cl_2$, -78 °C; (e) 1. $Ac_2O$, pyridine; 2. p-TsOH, MeOH; (f) pyridinium dichromate (PDC), DMF; (g) 0.5 N NaOH; (h) $Ph_3PCHCHO$, benzene; (i) $LiAlH(O\text{-}t\text{-}Bu)_3$, THF, -40 °C. Preparation of the Z-allyl chloride 10 from 5: (i) $CH_2N_2$, (ii) NCS, $Ph_3P$, and (iii) (g). Preparation of the E-allyl chloride 11 from 16: (i) NCS, $Ph_3P$, and (ii) (g).

13. Although hydrogen bonding between the amide and the hydroxyl groups is not negligible in the transition state B, the product ratio was still 3.4/1(cis/trans) when the hydroxyl group was protected with t-butyldimethylsilyl (TBDMS) group.

14. Protection of the hydroxyl group of 7 with TBDMS group resulted in an increased cis/trans ratio (17/1).

15. For a review, see: R. M. Magid, Tetrahedron, 36, 1901 (1980).

16. The configuration of 12a was confirmed by converting this to 2c in three steps: (i) $O_3$, MeOH, -78 °C/DMS, (ii) $NaBH_4$, EtOH, and (iii) NBS, $Ph_3P$.

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