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STEREOSELECTIVE HYDROXYLATION OF N-CARBAMOYL-L-PYROGLUTAMATE. SYNTHESIS OF (-)-BULGECININE

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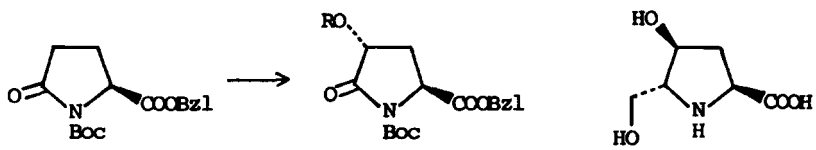
Abstract: Regio- and diastereoselective hydroxylation of the monoenolate derived from N-t-butoxycarbonyl-L-pyroglutamate (1) afforded the optically pure (4R)-hydroxypyroglutamate (2a) from which (-)-bulgecinine (3) was synthesized.

L-Pyroglutamic acid, a simple derivative of L-glutamic acid has been the efficient starting material for the synthesis of nitrogen containing natural products.[1, 2] Because of its bifunctionality, L-pyroglutamic acid has required the prior modification such as reduction[1a] to prevent the racemization at C-2 or thiolactam formation[1b] for the activation at C-5. Recent investigation on the reactivity towards nucleophilic reagents led us to find the direct chain elongation reaction at C-5 of N-carbamoylpyroglutamate.[2]

As the succeeding study on the reactivity of the pyroglutamate, we wish to report that the regio- and diastereoselective hydroxylation of the monoenolate of N-t-butoxycarbonyl-L-pyroglutamate (1) affords the optically pure (4R)-hydroxypyroglutamate (2a) from which we have synthesized (-)-bulgecinine (3).[3]

Our hydroxylation procedure is as follows. The pyroglutamate (1, 3.2 g, 10 mmol) was treated with $LiN(Me_3Si)_2$, prepared from $HN(Me_3Si)_2$ (2.1 ml, 10 mmol) and an equivalent of 15% n-BuLi (6.5 ml, 10 mmol), in THF at -78 °C and the resulting enolate was oxidized with 2-toluenesulfonyl-3-phenyloxazilidine (2.7 g, 15 mmol) to give the 4-hydroxypyroglutamate[4] [2a, mp 108-109 °C, $[\alpha]_D^{25}$ +19.2° (c 2.0, $CHCl_3$), 2.04 g, 61%].[5]



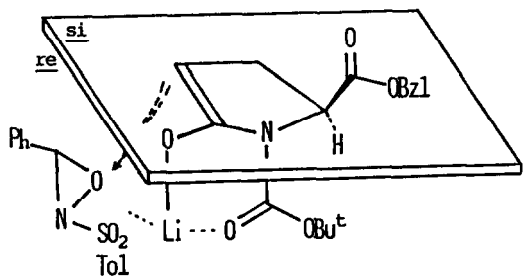
1 2a: R=H b: R=(+)-MTPA 3

No diastereoisomer (4)[6] was detected on HPLC of the alcohol (2a).[7] (4R)-Configuration of the alcohol (2a) was determined by the NMR analysis of alcohols 2a and 4. Namely, desielded signals of 2- and 4-hydrogen (δ 4.61 and 4.41, respectively) of the alcohol (2a) compared to those (δ_{H-2} 4.44 and δ_{H-4} 4.24) of the epimer (4) clearly indicates the 2,4-trans relationship of the alcohol (2a). No racemization during the hydroxylation was detected in the HPLC analysis of (+)-MTPA ester (2b).[8]

Although the effect of N-carbamoyl substituent is not known, it is proposed that re-attack of the oxazilidine may become predominant when the coordination occurs as illustrated in Fig. 1.[9] Steric repulsion of the benzyloxycarbonyl substituent and the lone pair of the enolate nitrogen present on the si-side, to the reagent may also contribute to the stereoselectivity.

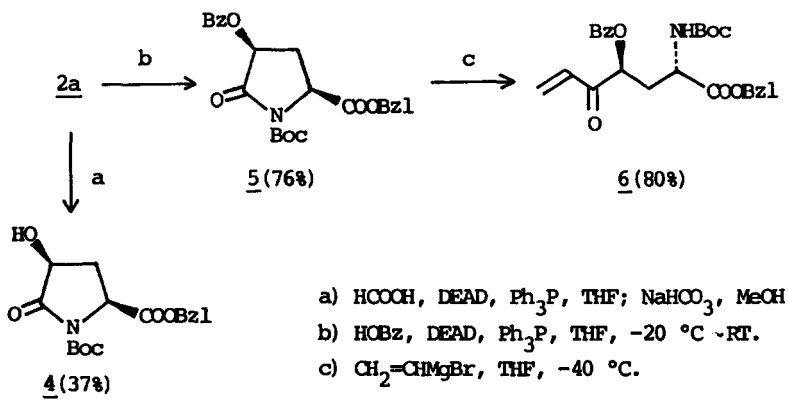
4-Hydroxypyroglutamate (2a) thus synthesized was found to be the effective synthon for hydroxypyrrolidine derivatives such as (-)-bulgecinine (3) which is the main component of bulgecines, the unique glycopeptides isolated from Pseudomonas acidophila and P. mesoacidophila.[3] According to the procedure we developed,[2] (4S)-benzoxypyroglutamate (5) was treated with vinylmagnesium bromide at -40 °C in THF to afford the enone (6). Reduction of the enone (6) with $NaBH_4$-$CeCl_3$[10] at -20 °C gave the alcohol (7) as an oil whose configuration at C-5 was not assigned.[11]

Fig. 1



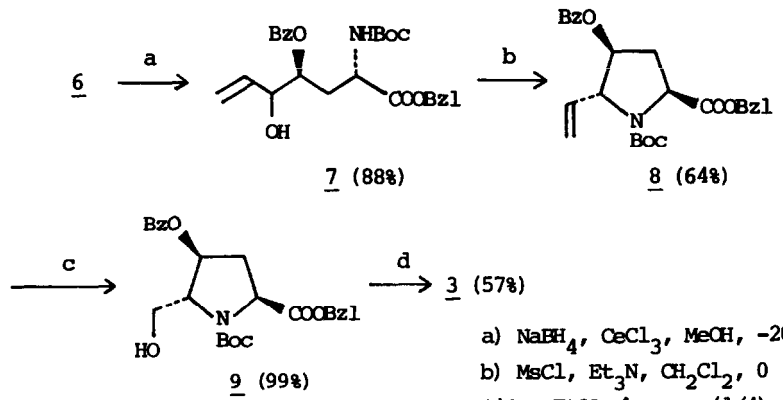
(Hypothetical Transition State Model)

Scheme 1



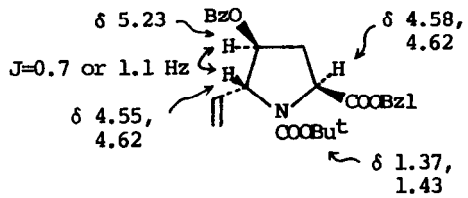
a) HCOOH, DEAD, Ph_3P, THF; $NaHCO_3$, MeOH.
b) HOBz, DEAD, Ph_3P, THF, -20 °C ~RT.
c) CH_2=$CHMgBr$, THF, -40 °C.

Scheme 2



a) $NaBH_4$, $CeCl_3$, MeOH, -20 °C.
b) MsCl, Et_3N, CH_2Cl_2, 0 °C; SiO_2, EtOAc/hexane (1/4).
c) O_3, MeOH, -78 °C; $NaBH_4$, -78~0 °C.
d) 1N NaOH, MeOH, RT; TFA, PhOMe, 0 °C; Dowex 50W, 1N Py.

Fig. 2



Crude mesylate derived from the alcohol 7 on the treatment with $MsCl/Et_3N$ in CH_2Cl_2 at 0 °C, did not change with Et_3N treatment, but rearranged to the 5-vinylprolinate (8) when the crude mesylate was adsorbed on silica gel.[12] The cyclized product (8) was slowly eluted with 20% EtOAc in n-hexane. The fact that 2- and 5-hydrogens of the vinylprolinate (8) showed two sets of NMR signals, δ 4.58 and 4.62 for H-2, and δ 4.55 and 4.62 for H-5, is characteristic for the 2,5-trans substituted N-carbamoylpyrrolidine derivatives.[13] Moreover, the observed small coupling constant between 4- and 5-hydrogens, 0.7 or 1.1 Hz, clearly indicates the trans relationship of those hydrogens (Fig. 2).[14]

Vinylprolinate 8 was then transformed to the alcohol (9) by ozonolysis at -78 °C and reduction with $NaBH_4$. Hydrolysis of the ester (9) followed by deprotection with trifluoroacetic acid gave the amino acid 3 [mp 195-196 °C, $[\alpha]_D^{29}$ -14.1° (c 0.80, H_2O)] which showed identical spectroscopic data and physical constants with the natural bulgecinine[3] in all respect.

The 4-hydroxypyroglutamate (2a) we synthesized may be regarded as an effective chiron for the synthesis of other useful nitrogen containing natural products.

Acknowledgment: The authors are grateful to Dr. Susumu Shinagawa, Takeda chemical Industries, Ltd., for his kind donation of natural bulgecinine and its spectral data.

References and Notes

1. a) Y. Ohfune and M. Tomita, J. Am. Chem. Soc., 104, 3511 (1982); b) J. S. Petersen, G. Fels, and H. Rapoport, J. Am. Chem. Soc., 106, 4539 (1984); K. Shiosaki and H. Rapoport, J. Org. Chem., 50, 1229 (1985).
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3. Structure: S. Shinagawa, F. Kasahara, Y. Wada, S. Harada, and M. Asai, Tetrahedron, 40, 3465 (1984). Synthesis: T. Wakamiya, K. Yamanoi, M. Nishikawa, and T. Shiba, Tetrahedron Lett., 26, 4759 (1985); B. P. Bashyal, H.-F. Cho, and G. W. J. Fleet, Tetrahedron Lett., 27, 3205 (1986); Y. Ohfune, K. Hori, and M. Sakaitani, Tetrahedron Lett., 27, 6079 (1986).
4. δ_H ($CDCl_3$, 100 MHz): 1.40 (9H, s), 4.41 (1H, dd, J=8, 10 Hz), 4.61 (1H, dd, J=2, 9 Hz), 5.19 (2H, s), 7.30 (5H, s).
5. D. A. Evans, M. M. Morrissey, and R. L. Dorow, J. Am. Chem. Soc., 107, 4346 (1985).
6. δ_H ($CDCl_3$, 100 MHz): 1.42 (9H, s), 4.24 (1H, dd, J=4, 6 Hz), 4.44 (1H, dd, J=8, 8 Hz), 5.18 (2H, s), 7.32 (5H, s).
7. Column: 5 nm Lichrosorb SI-60, 4 mm id x 250 mm. Eluent: EtOAc-hexane (1:1), 2 ml/min. Detection at 254 nm. t_R: 2a, 4.0 min; 4, 5.9 min.
8. Column: 5 nm Lichrosorb SI-60, 4 mm id x 250 mm. Eluent: EtOAc-hexane (3:17), 1ml/min. Detection at 254 nm. t_R: 2b, 8.2 min; (±)-2a (+)-MTPA ester, 8.2, 9.8 min.
9. Stereodifferential reduction of N-benzyloxycarbonyl-4-oxoprolin has been reported: A. A. Patchett and B. Witkop, J. Am. Chem. Soc., 79, 185 (1957).
10. J.-L. Luche, L. Rodriguez-Hahn, and P. Crabbe, J. Chem. Soc., Chem. Commun., 601, (1978).
11. Although complex signals of carbinyl hydrogens (δ around 4.3 due to H-2 and H-5, and 5.2 due to H-4) made it difficult to assign the configuration of 5-hydroxyl, the simple splitting of 6-hydrogen signal (ddd at δ 5.86) implied that the alcohol (7) was given with a high diastereomeric excess. 7, δ_H ($CDCl_3$, 100 MHz): 1.35 (9H, s), 4.3 (2H, m), 5.11 (2H, s), 5.0-5.5 (4H, m), 5.86 (1H, ddd, J=5, 10, 17 Hz), 7.30 (5H, s), 7.3-7.6 (3H, m), 7.99 (2H, dd, J=2, 8 Hz).
12. Wakogel C-200, 100-200 mesh.
13. Unpublished results. Cf. reference 2.
14. Signal assignments were aided by H-H 2DJ, H-H and C-H COSY spectra at 500 or 125 MHz.

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