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SYNTHESIS AND STEREOCHEMISTRY OF CARNOSADINE, A NEW CYCLOPROPYL AMINO ACID FROM RED ALGA *GRATELOUPIA CARNOSA*

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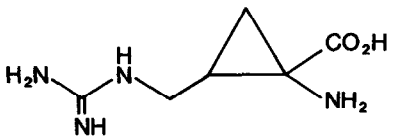
Summary: Optically active carnosadine, a new cyclopropyl amino acid from red alga *Grateloupia carnosa*, was synthesized and its absolute structure was determined.

In a previous paper, we reported an isolation of a new amino acid carnosadine (**1**), 1-amino-2-guanidinomethylcyclopropane-1-carboxylic acid, from marine red alga *Grateloupia carnosa*.[1] By comparison of the ^{1}H-NMR spectrum of carnosadine[2] with those of 1-amino-2-methylcyclopropane-1-carboxylic acid and its derivatives studied by Baldwin *et al.*[3], the relative configuration of carnosadine was assumed to be *Z*.[4]



Carnosadine (1)

In order to confirm the absolute structure of carnosadine, synthetic study of this amino acid was then carried out as shown in Scheme 1.[5] *N*-Benzoyl-α, β-dehydroglutamic acid (**2**) prepared according to the Erlenmeyer's method[6] was used as a starting material. (*Z*)-Configuration of **2** was confirmed by the comparison of its dimethyl ester with an authentic sample prepared from *threo*-β-hydroxyglutamic acid.[7] The cyclopropane ring was constructed by thermal or photochemical degradation of pyrazoline intermediate **3**. ω-Methoxycarbonyl group of the product **4** was then effectively converted into amino group by the Hofmann reaction. The diamino acid derivative **7** thus obtained was benzyloxycarbonylated and then coupled with (*R*)-(+)-α-methylbenzylamine. Two diastereoisomers of the amide, **8a** and **8b**, were successfully separated by silica-gel column chromatography. Each diastereoisomer was converted into optically active carnosadine, respectively.

Of the synthetic intermediates after chemical resolution, the debenzyloxycarbonylated compound **9a** was obtained as fine crystals applicable for X-ray crystallographic analysis and its absolute configuration was determined to be 1*S*,2*S*.[8] Guanidination of the (1*S*,2*S*)-derivative **9a** gave carnosadine of natural form and the synthetic product **1a** was completely identical with natural product as dihydrochloride in all respects.[9] Thus, we achieved not only the total synthesis but also the determination of the absolute structure of carnosadine, a naturally occurring unique cyclopropyl amino acid.

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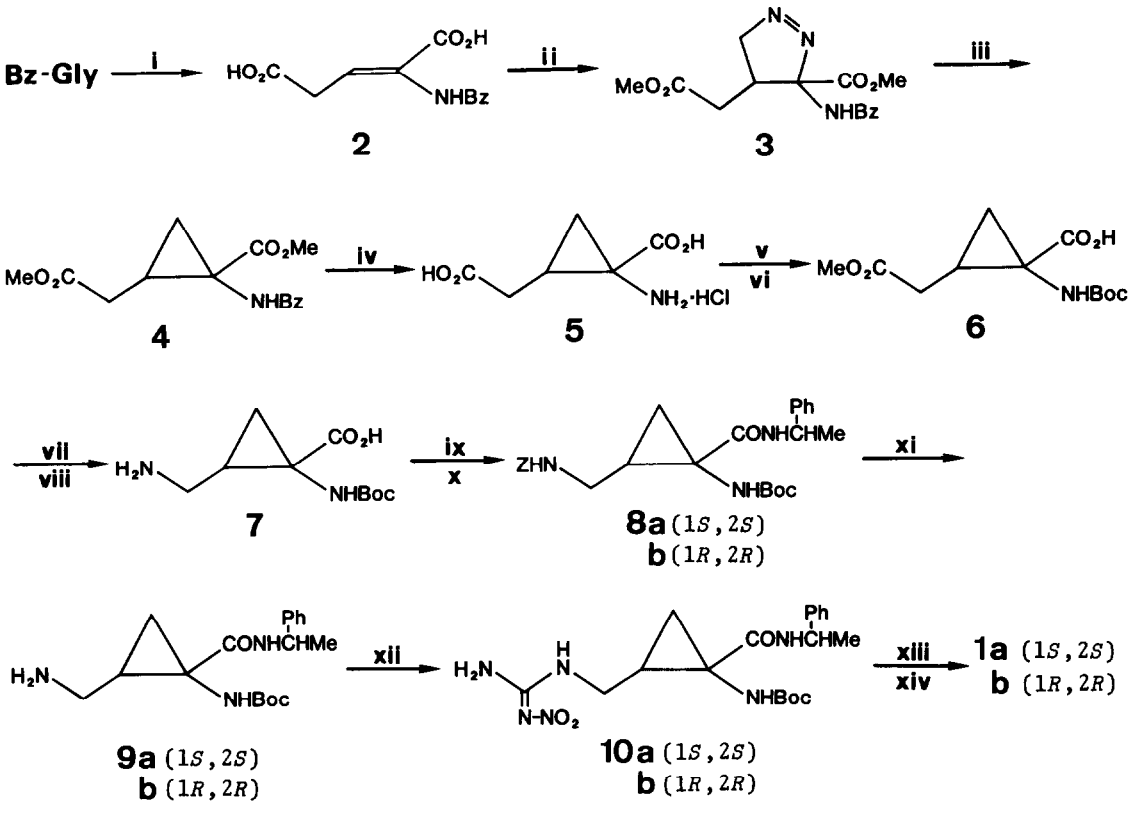
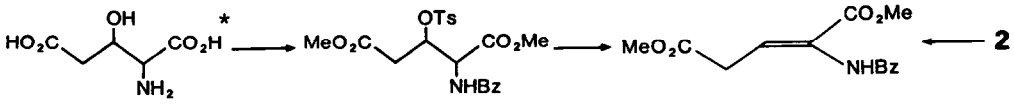
References

1) T. Wakamiya, H. Nakamoto, and T. Shiba, Tetrahedron Lett., 25, 4411 (1984). Recently, we also isolated (*E*)-isomer of carnosadine and 2-aminomethyl-1-guanidino isomer named isocarnosadine from the same alga. The results will be reported soon elsewhere.



Scheme 1. i)Ref. 6; ii)CH_2N_2, MeOH, quant.; iii)(a)hν(high pressure mercury arc), toluene, 78%, (b)reflux, toluene, 71%; iv)reflux, 6M HCl, 95%; v)2M HCl/MeOH, 84%; vi)di-*t*-butyl dicarbonate (Boc_2O), $NaHCO_3$, 83%; vii)liq. NH_3/MeOH, 94%; viii)3M NaOH, Br_2, 73%; ix)benzyloxycarbonyl chloride (Z-Cl), 1M NaOH, quant.; x)(*R*)-(+)-α-methylbenzylamine, *N*,*N*'-dicyclohexylcarbodiimide—1-hydroxybenzotriazole(DCC-HOBt), THF, 82%; xi)H_2, Pd black, MeOH, 92%(**9a**), 94%(**9b**); xii)3,5-dimethyl-1-nitroguanylpyrazole, MeOH, 72%(**10a**), 59%(**10b**); xiii)H_2, Pd black, MeOH; xiv)reflux, 6M HCl, 63%(**1a**), 59%(**1b**) as 2HCl salt from **10a** and **10b**, respectively.

2) Chemical shift of 1.51 ppm corresponding to one of C_3-methylene protons in the ref. 1 should be read as 1.21 ppm. [Erratum: Tetrahedron Lett., 26, 2138 (1985).]
3) a) J. E. Baldwin, R. M. Adlington, and B. J. Rawlings, Tetrahedron Lett., 26, 481 (1985); b) J. E. Baldwin, R. M. Adlington, B. J. Rawlings, and R. H. Jones, *ibid.*, 26, 485 (1985).
4) As far as we know, two C_3-methylene protons of (*Z*)-isomers of 2-alkylated-1-aminocyclopropane-1-carboxylic acid show clearly different chemical shifts, while those of (*E*)-isomers appear overlapping each other.
5) A part of this work was presented at 51st National Meeting of the Chemical Society of Japan, Kanazawa, October 1985, Abstr. No. 1R07.
6) T. Kaneko and Y. Nakayama, Nippon Kagaku Zasshi, 77, 1054 (1956).
7)



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* T. Kaneko, R. Yoshida, and H. Katsura, Nippon Kagaku Zasshi, 80, 316 (1959).
8) Details will be reported soon elsewhere.
9) For example: $[\alpha]_D^{19}$-21.0°(*c* 1.00, 1M HCl) [natural product: -20.0°(*c* 1.00, 1M HCl)].

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