

STEREOSELECTIVE SYNTHESIS OF dl-CARPAMIC ACID AND dl-AZIMIC ACID

Mitsutaka Natsume* and Masashi Ogawa

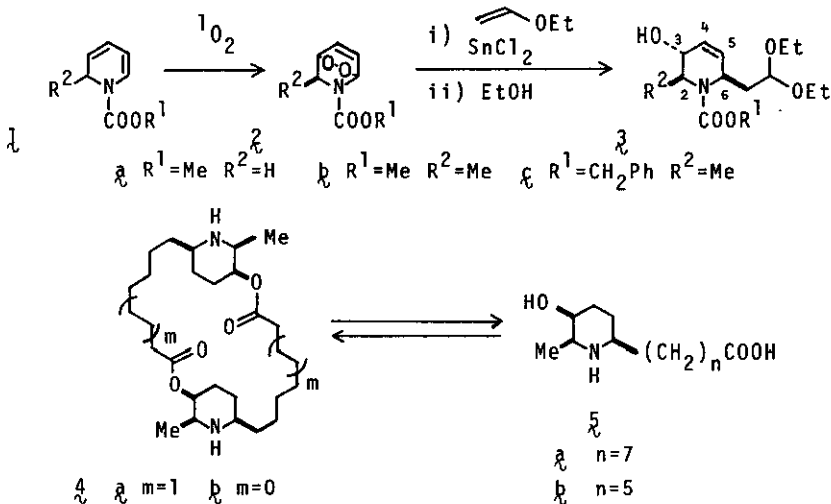
Research Foundation Itsuu Laboratory

Tamagawa 2-28-10, Setagaya, Tokyo 158, Japan

Abstract — Carpamic acid and azimic acid, which are constructing units of dimeric lactone alkaloids, carpaine and azimine, were synthesized stereoselectively from endoperoxide of 2-methyl-1,2-dihydropyridine derivative.

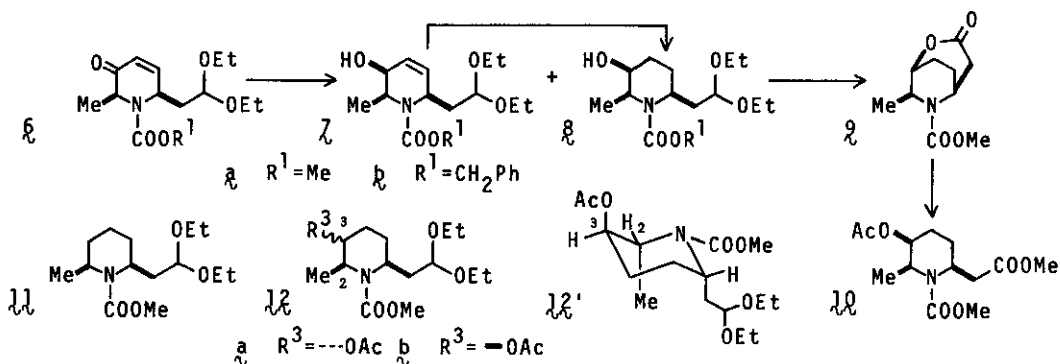
In the recent communication,¹ we reported that the endoperoxide of methoxycarbonyl-1,2-dihydropyridine (1a) afforded a condensation product (3a) with ethyl vinyl ether in the presence of SnCl₂, followed by the addition of EtOH. The same treatment starting from the corresponding 2-methyl derivative (1b)² produced a single product (3b) in 74% yield, whose regio-structure of carbon and oxygen arrangement reminded us of some piperidine alkaloids of 2,6-dialkyl-3-piperidinol structure.³ We describe herein a stereoselective synthesis of dl-carpamic acid (5a) and dl-azimic acid (5b).

Carpamic acid (5a)⁴ and azimic acid (5b) are monomeric constituents of carpaine (4a)^{3,5} and azimine (4b),⁶ the alkaloids isolated from *Carica papaya* and *Azima*



tetracantha, respectively, and conversion⁷ of 5_R to 4_R as well as the syntheses of 5_R⁸ and 5_R^{9,8b} were already recorded.

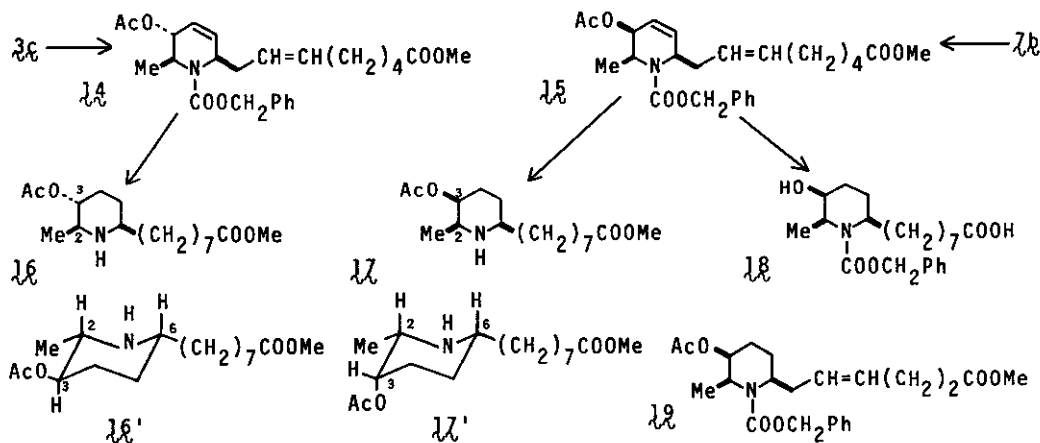
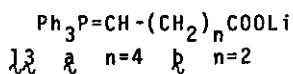
We started the synthetic work by assuming the relative stereochemistry of three substituents of 3_b as shown above, on the basis of the previous experiment.^{10,11} Oxidation of 3_b with the Collins reagent¹² afforded in 61% yield an unsaturated ketone (6_R), which was reduced with sodium borohydride to obtain 7_R and 8_R in 74% and 20% yield, respectively, and 7_R was hydrogenated to 8_R over Raney Ni in 93% yield. The saturated acetal (8_R) was hydrolyzed with acid, oxidized with Ag₂O, and the product was allowed to stand in CH₂Cl₂ saturated with HCl to obtain a lactone (9) in 27% overall yield. The structure of 9 was confirmed by its transformation into an ester acetate (10), establishing the stereochemistry between the hydroxyl group and the acetal side-chain in 8 to be in the *cis* relationship. Either 3_b acetate or 7_R acetate was subjected to catalytic hydrogenation over Raney Ni or platinum oxide and the formation of a common product (11) was observed in 17% or 36% yield, accompanied by 12_a (81%) or 12_b (31%), implying that the configuration of the methyl group remained unchanged during the process by way of the enone (6_R), and the stereoselective inversion of the hydroxyl group was achieved in good yield from the compound (3_b) obtained by our new procedure to the intermediate (7 or 8), which was suitable for further synthesis.



1-Benzoyloxycarbonyl-2-methyl-1,2-dihydropyridine (12_c) prepared from pyridine, benzyl chloroformate, and methylmagnesium iodide in 97% yield, was submitted to the sensitized photooxygenation, followed by application of the SnCl₂ effected reaction with ethyl vinyl ether. Treatment with EtOH afforded the corresponding condensation product (3_c) in 50% yield, and the Collins reagent oxidized 3_c in 58% yield to the enone (6_b), whose NaBH₄ reduction proceeded analogously to yield 7_b (63%) and 8_b (27%).

Elongation of the side chain was carried out by the Wittig reaction, and aldehydes

derived from \mathfrak{A} and \mathfrak{B} were reacted with ylide (\mathfrak{A}),¹³ and the reaction products were isolated as ester acetates (\mathfrak{A} and \mathfrak{A}) in 35% and 34% yield. Judging from the appearance of PMR signals of methyl protons as two sets of doublet, these products were considered to be E+Z mixtures at the side chain double bond and, therefore, both products (\mathfrak{A} and \mathfrak{A}) were hydrogenated over Raney Ni to obtain free amines (\mathfrak{A}^{14} and \mathfrak{A}^{15}) in 38% and 22% yield, respectively. Compared with a small coupling constant value (~ 0 Hz) of $J_{2,3}$ in the PMR spectrum of \mathfrak{A} , the free amine (\mathfrak{A}) showed a large value (10 Hz) for trans diaxial relationship between H-2 and H-3, suggesting that all substituents in the former compound were located in the axial configuration as depicted by \mathfrak{A}' in order to avoid the planar proximity of the alkoxycarbonyl group against two alkyl substituents at C-2 and C-6.¹⁶ In the latter compound, such interaction no longer existed and the structure (\mathfrak{A}') represented a stable conformation resulting in a large $J_{2,3}$ value, and this fact conclusively provided an evidence for the trans nature of the methyl and hydroxyl groups in \mathfrak{A} and \mathfrak{A} . PMR spectrum of \mathfrak{A} coincided with the structure (\mathfrak{A}').



Now that all stereochemical problems were settled, syntheses for carpamic and azimic acids were carried out without difficulty. \mathfrak{A}^{15} was treated with $\text{Ba}(\text{OH})_2$ and then hydrogenated over platinum oxide. Benzyloxycarbonyl-dl-carpamic acid (\mathfrak{A}^{18}) was once isolated, and further, removal of the protecting group by catalytic hydrogenation over Pd-C produced dl-carpamic acid (\mathfrak{A}^{19}), mp 213-215°, in 58% yield from \mathfrak{A}^{15} .

The aldehyde prepared from **8b** was condensed with the Wittig reagent (**13b**) and the reaction product was isolated as ester acetate (**19**) in 57% yield. **19** was hydrolyzed with Ba(OH)₂ and the subsequent hydrogenation over Pd-C afforded dl-azimic acid (**5b**), mp 228-229° (decomp.), in 58% yield. Our synthetic materials of dl-carpamic and dl-azimic acids were identical with samples of Prof. Brown.

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 15. PMR (CDCl₃) δ : 1.06 (d, J=7 Hz, Me), 1.40 (s, NH), 2.12 (s, Ac), 2.32 (t, J=7 Hz, CH₂COOMe), 2.90 (dq, J=1.5, 7 Hz, H-2), 3.72 (s, COOMe), 4.88 (ddd, J=1.5, 1.5, 1.5 Hz, H-3).
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