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

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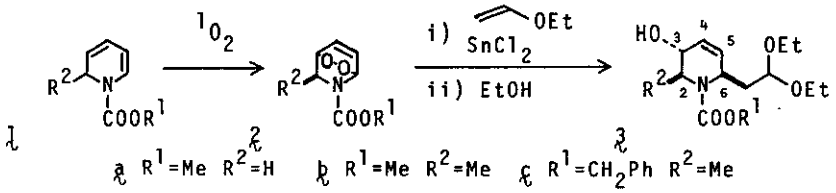
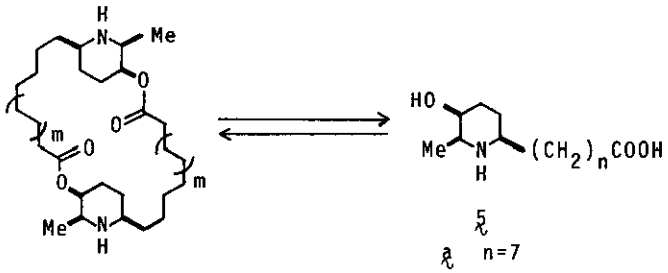
Abstract — Carpamic acid and azimic acid, which are constructing units of dimeric lactone alkaloids, carpaine and azimine, were synthesized stereoselectively from endoperoxide of 2-methyl-1,2-dihydropyridine derivative.

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 $SnCl_2$, 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*



1 a R^1=Me R^2=H b R^1=Me R^2=Me c R^1=CH_2Ph R^2=Me

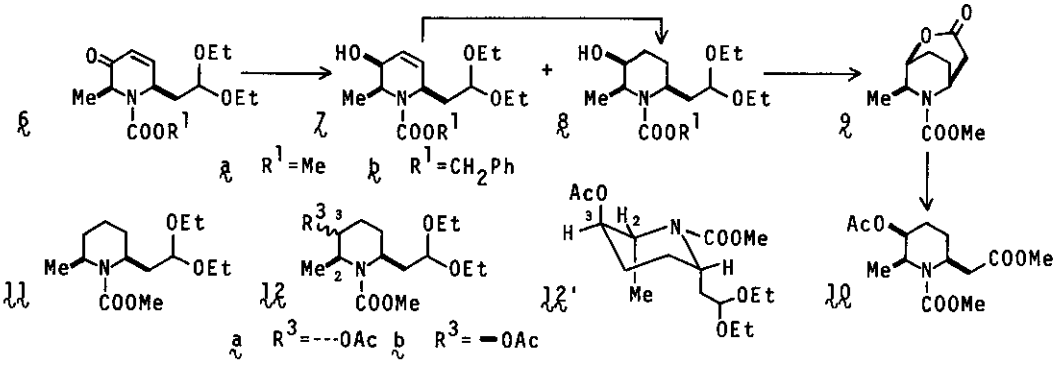


4 a m=1 b m=0

5 a n=7 b n=5

tetracantha, respectively, and conversion[7] of 5a to 4a as well as the syntheses of 5a[8] and 5b[9,8b] were already recorded.

We started the synthetic work by assuming the relative stereochemistry of three substituents of 3b as shown above, on the basis of the previous experiment.[10,11] Oxidation of 3b with the Collins reagent[12] afforded in 61% yield an unsaturated ketone (6a), which was reduced with sodium borohydride to obtain 7a and 8a in 74% and 20% yield, respectively, and 7a was hydrogenated to 8a over Raney Ni in 93% yield. The saturated acetal (8a) was hydrolyzed with acid, oxidized with Ag_2O, and the product was allowed to stand in CH_2Cl_2 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 3b acetate or 7a 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 12a (81%) or 12b (31%), implying that the configuration of the methyl group remained unchanged during the process by way of the enone (6a), and the stereoselective inversion of the hydroxyl group was achieved in good yield from the compound (3b) obtained by our new procedure to the intermediate (7 or 8), which was suitable for further synthesis.



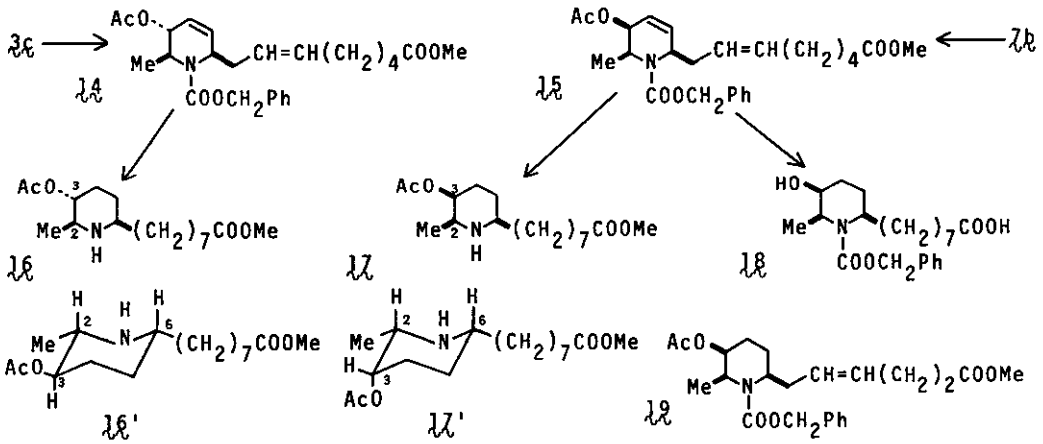
1-Benzyloxycarbonyl-2-methyl-1,2-dihydropyridine (1c) prepared from pyridine, benzyl chloroformate, and methylmagnesium iodide in 97% yield, was submitted to the sensitized photooxygenation, followed by application of the $SnCl_2$ effected reaction with ethyl vinyl ether. Treatment with EtOH afforded the corresponding condensation product (3c) in 50% yield, and the Collins reagent oxidized 3c in 58% yield to the enone (6b), whose $NaBH_4$ reduction proceeded analogously to yield 7b (63%) and 8b (27%).

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

derived from 3c and 7b were reacted with ylide (13a),[13] and the reaction products were isolated as ester acetates (14 and 15) 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 (14 and 15) were hydrogenated over Raney Ni to obtain free amines (16[14] and 17[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 12a, the free amine (16) 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 12' 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 (16') 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 3b and 3c. PMR spectrum of 17 coincided with the structure (17').

$Ph_3P{=}CH\text{-}(CH_2)_nCOOLi$

13 a n=4 b n=2



Now that all stereochemical problems were settled, syntheses for carpamic and azimic acids were carried out without difficulty. 15 was treated with $Ba(OH)_2$ and then hydrogenated over platinum oxide. Benzyloxycarbonyl-dl-carpamic acid (18) was once isolated, and further, removal of the protecting group by catalytic hydrogenation over Pd-C produced dl-carpamic acid (5a), mp 213-215°, in 58% yield from 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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10. In the case of 1-benzoyl-2-benzoyloxymethyl-5-cyano-1,2-dihydropyridine, singlet oxygen approached from the back of the C-2 alkyl group and the subsequent reaction afforded a product having 2,3-trans substituents. M. Natsume,

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11. The criterion for determining the stereochemistry between C-3 and C-6 substituents was the coupling constant value between H-2(pseudo-axial) and H-3,[1] but the methyl group in 3b was situated in pseudo-axial configuration.
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14. PMR ($CDCl_3$) δ: 1.09 (d, J=6.5 Hz, Me), 1.48 (s, NH), 2.06 (s, Ac), 2.33 (t, J=7 Hz, CH_2COOMe), 2.71 (dq, J=10, 6.5 Hz, H-2), 3.73 (s, COOMe), 4.41 (ddd, J=10, 10, 5 Hz, H-3).
15. PMR ($CDCl_3$) δ: 1.06 (d, J=7 Hz, Me), 1.40 (s, NH), 2.12 (s, Ac), 2.32 (t, J=7 Hz, CH_2COOMe), 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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