STEREOSELECTIVE SYNTHESIS OF dl-PROSAFRININE AND dl-PSEUDOCARPAMIC ACID

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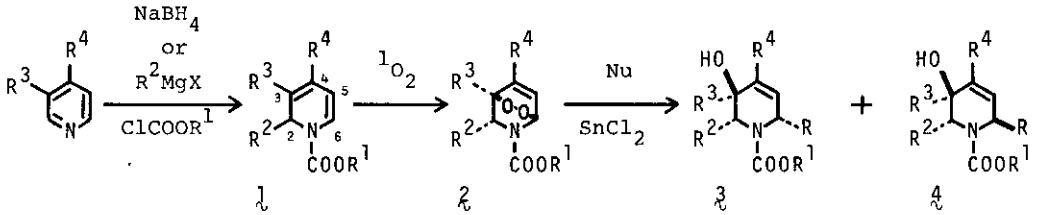
Abstract: The $SnCl_2$-effected carbon-carbon bond formation of endoperoxides was applied to alkyl substituted 1,2-dihydropyridines 1a-h to produce 3a-h and 4a-h, whose stereochemistry was clarified. Starting from 3e and 4e, piperidine alkaloids, prosafrinine and pseudocarpamic acid were synthesized in racemic forms.

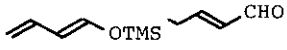
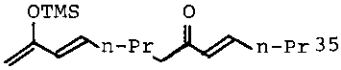
Variously alkylated 1,2-dihydropyridine derivatives 1a-h were synthesized by the reaction of alkylpyridines with either $NaBH_4$[1] or Grignard reagent[2] in the presence of alkyl chloroformates, and submitted to the sensitized photooxygenation reaction, followed by the $SnCl_2$-effected ring opening reaction with trimethylsilylated ketones and an enol ether.[3] Formation of an isomeric pair of condensation products, 3 and 4, was generally observed, one isomer being mostly predominant. In cases of 3a and 4a, where R^2 and R^3 were hydrogen, stereochemical relation between hydroxyl group and the newly introduced substituent R was determined readily by the inspection of coupling pattern of pseudoaxial proton of the 2 position and H-3,[3] and the major product 3a was the trans derivative. In other cases, the above criterion was no longer applicable, because either R^2 or R^3 was an alkyl group and R^2 was always situated in the pseudoaxial configuration.

^{13}C NMR spectra of these compounds were investigated in order to find out a generality, and the chemical shift of olefinic carbons at the 4 position was characteristic as shown in the following Table. When one compared the chemical shift values of each pair of isomers with those of 3a and 4a, it was concluded that major products exhibited the C-4 signals at the higher field and hence seemed to be trans compounds. This rule was tested in two ways. At first, the major product of e series was correlated chemically with the known compound, whose stereochemistry was already determined. 3e was reduced with $NaBH_4$, followed by catalytic

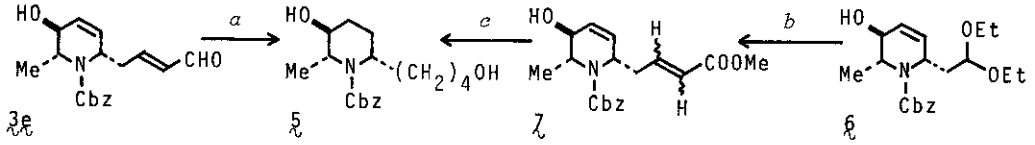
hydrogenation over PtO_2 to obtain 5 in 76% yield. The compound 6,[4] which was the starting material for the synthesis of carpamic and azimic acids was converted into 5 by way of 7, and this experiment confirmed the structure of 3e to be the trans compound. The second evidence came from ^{13}C NMR spectra of 8, 9, and their deriva-



1 2 3 4

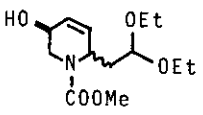
	R1	R2	R3	R4	Yield (%) of 1	Nucleophile	R	Yield (%) 3	Yield (%) 4	13C NMR shift of C-4 (ppm from TMS) 3	13C NMR shift of C-4 (ppm from TMS) 4
a	Me	H	H	Me	91			32†	5†	135.8	138.3
b	Me	H	Et	H	97	"	"	20†	4†	132.0	134.3
c	Me	H	Me	Me	100	"	"	20†	15†	138.5	140.8
d	Me	Me	H	H	96	"	"	22	21	131.5	132.9
e	CH_2Ph	Me	H	H	97			34	9	131.2	133.7
f	CH_2Ph	Me	H	H	"			40	18	131.0	133.3
g	CH_2Ph	H	Me	H	91	"	"	32	6	132.8	135.4
h	Me	n-Pr	H	H	65			35	12	132.0	133.3

† Based on alkylpyridines

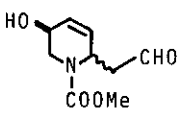


3e 5 7 6

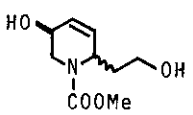
a (i) $NaBH_4$, (ii) H_2, PtO_2. *b* (i) H^+, (ii) Ph_3P=CHCOOMe, 84%. *c* (i) H_2, PtO_2, (ii) $LiAlH_4$, 40%.



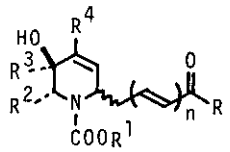
8 α
9 β



10 α
11 β

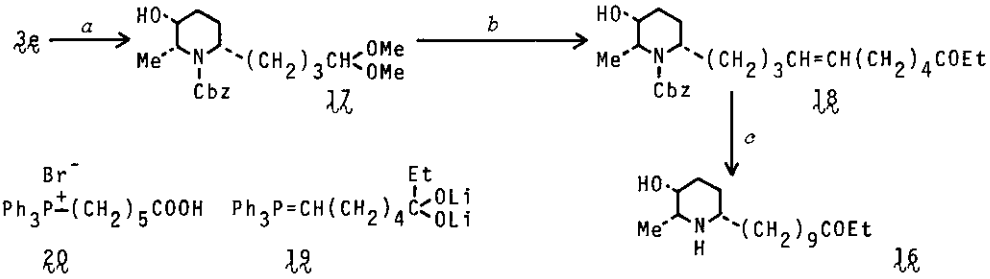


12 α
13 β



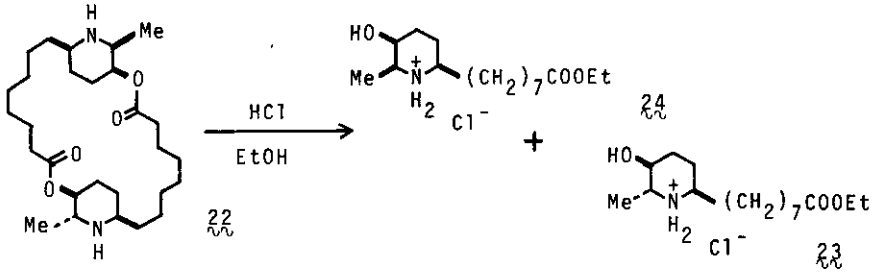
n=0,1
14 α
15 β

tives, whose stereochemical assignment was readily achieved by the ^{1}H NMR spectra. C-4 of 8 and 9 resonated at 133.4 ppm and 132.4 ppm, respectively, which were values out of the rule, but the corresponding aldehydes 10 and 11 demonstrated C-4 signals at 131.4 ppm and 132.9 ppm, which were in good accordance with the rule. The alcohols 12 and 13 exhibited again the values (133.4 ppm and 131.8 ppm), which did not agree with the rule, and therefore, this rule, although the reason is uncertain, is valid to the pair of compounds possessing the structures of 14 and 15.

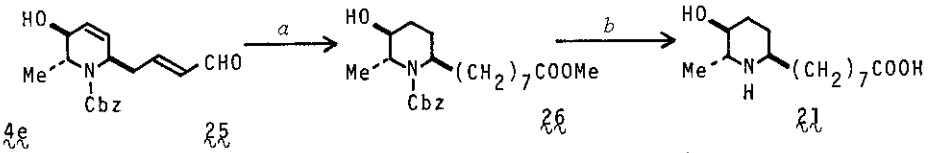


a (i) p-TsOH in MeOH, (ii) $CrO_3 \cdot 2Py$, (iii) $NaBH_4$, (iv) H_2, PtO_2. *b* (i) H^+, (ii) 19. *c* H_2, Pd-C.

Prosafrinine 16 is a piperidine alkaloid, isolated from *Prosopis africana* (Guill. et Perr.)[5] and was synthesized from 3e as follows: Aldehyde function of 3e was once protected as dimethyl acetal by treatment with p-TsOH in MeOH (81% yield) and the stereoselective inversion of the hydroxyl group was carried out according to the method of the previous report.[3] Thus, oxidation with the Collins reagent, reduction with $NaBH_4$ in MeOH, and the catalytic hydrogenation over PtO_2 in dimethoxyethane (DME) gave 17 in 65% yield. Acetal group was hydrolyzed with 2.5% HCl in DME-H_2O (1:1) and elongation of the side chain was achieved in 35% yield with the reagent[6] 19, which was obtained from 20[7] by the reaction with EtLi. Removal of the protecting group on the nitrogen from 18 afforded dl-prosafrinine,[8] 16, mp 78.5-79°, in 71% yield.



Pseudocarpamic acid 21 is a component of pseudocarpaine 22, which is a minor alkaloid of *Carica papaya* and was isolated as its ethyl ester hydrochloride 23,



a (i) $Ph_3P{=}CH(CH_2)_2COOLi$, (ii) CH_2N_2, (iii) H_2, PtO_2. *b* (i) $Ba(OH)_2$, (ii) H_2, Pd-C.

together with ethyl carpamate hydrochloride 24.[9] 4e was reacted with the ylide 25, and the reaction product was isolated as its methyl ester, which was hydrogenated catalytically over PtO_2 to give 26 in 18% yield. Hydrolysis of 26 with $Ba(OH)_2$, followed by the cleavage of the N-protecting group produced in 18% yield a compound 21, mp 182-184°, whose structure was the same as the proposed for pseudocarpamic acid. 21 was converted to an ethyl ester picrate, mp 99-100°, or an ethyl ester hydrochloride 23, mp 69-71°, but direct comparison with the authentic sample was unattainable due to the lack of the natural product.[10]

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