

STEREOSELECTIVE SYNTHESIS OF dl-PROSAFRININE AND dl-PSEUDOCARPAMIC ACID

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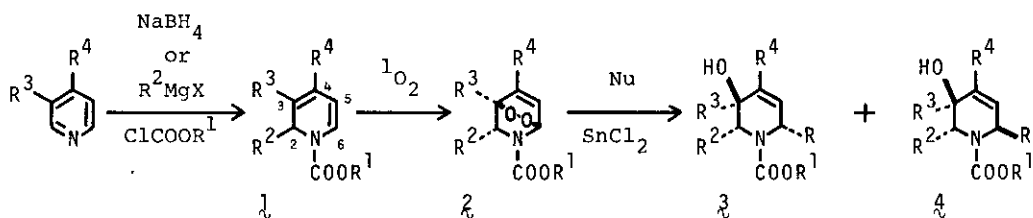
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Abstract: The SnCl_2 -effected carbon-carbon bond formation of endoperoxides was applied to alkyl substituted 1,2-dihydropyridines $1a-h$ to produce $3a-h$ and $4a-h$, whose stereochemistry was clarified. Starting from $3e$ and $4e$, piperidine alkaloids, 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 reagent² 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 In other cases, the above criterion was no longer applicable, because either R^2 or R^3 was an alkyl group and R^2 was always situated in the pseudoaxial configuration.

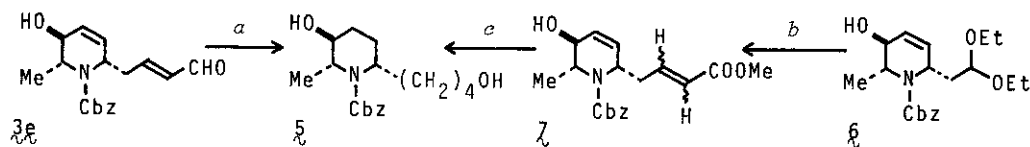
¹³C NMR spectra of these compounds were investigated in order to find out a generality, and the chemical shift of olefinic carbons at the 4 position was characteristic as shown in the following Table. When one compared the chemical shift values of each pair of isomers with those of $3a$ and $4a$, it 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-

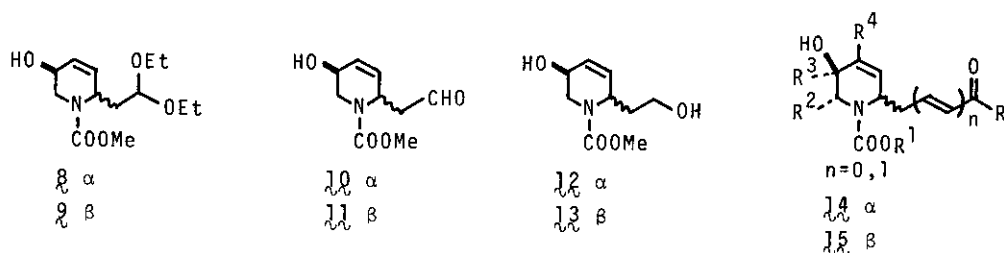


R ¹	R ²	R ³	R ⁴	Yield (%) of 1	Nucleophile	R	¹³ C NMR shift of			
							Yield (%)	C-4 (ppm from TMS)	3	4
a	Me	H	Me	91			32 [†]	5 [†]	135.8	138.3
b	Me	H	Et	97	"	"	20 [†]	4 [†]	132.0	134.3
c	Me	H	Me	100	"	"	20 [†]	15 [†]	138.5	140.8
d	Me	Me	H	96	"	"	22	21	131.5	132.9
e	CH ₂ Ph	Me	H	97			34	9	131.2	133.7
f	CH ₂ Ph	Me	H	"			40	18	131.0	133.3
g	CH ₂ Ph	H	Me	91	"	"	32	6	132.8	135.4
h	Me	n-Pr	H	65			35	12	132.0	133.3

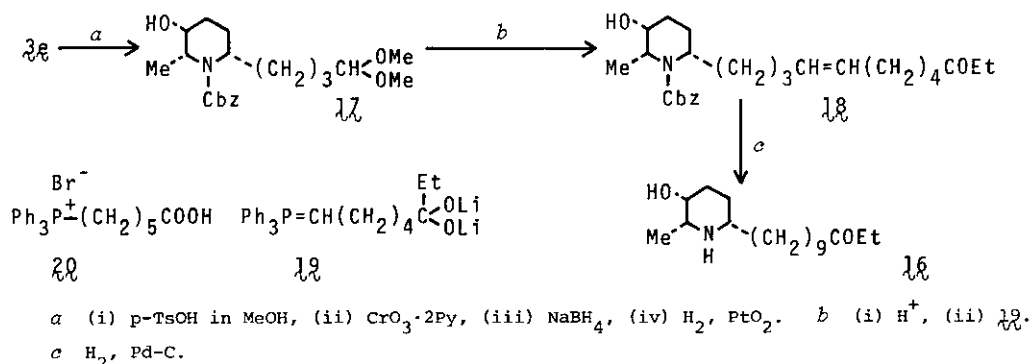
[†] Based on alkylpyridines



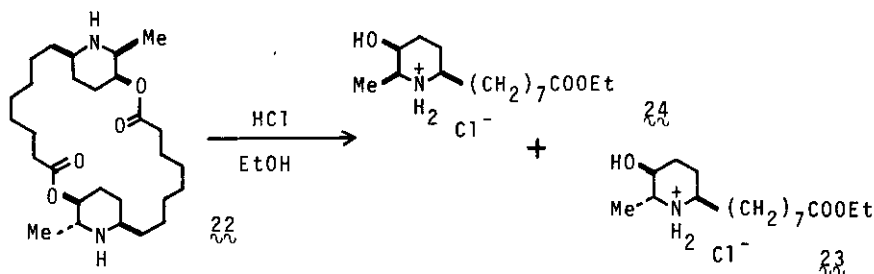
a (i) NaBH_4 , (ii) H_2 , PtO_2 . **b** (i) H^+ , (ii) $\text{Ph}_3\text{P}=\text{CHCOOMe}$, 84%. **c** (i) H_2 , PtO_2 , (ii) LiAlH_4 , 40%.



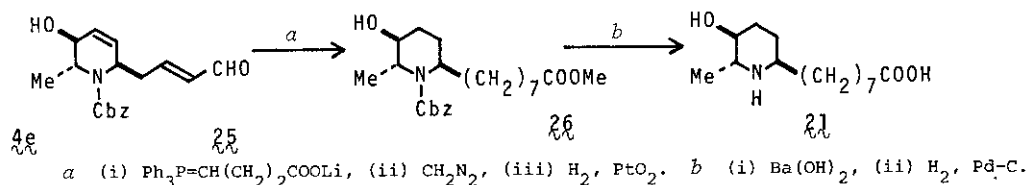
tives, whose stereochemical assignment was readily achieved by the ^1H NMR spectra. C-4 of **8** and **9** resonated at 133.4 ppm and 132.4 ppm, respectively, which were values out of the rule, but the corresponding aldehydes **10** and **11** demonstrated C-4 signals at 131.4 ppm and 132.9 ppm, which 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**.



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 reagent⁶ **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**,



together with ethyl carbamate hydrochloride **24**.⁹ **24** 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 $182-184^\circ$, whose structure was the same as the proposed for pseudocarpamic acid. **21** was converted to an ethyl ester picrate, mp $99-100^\circ$, or an ethyl ester hydrochloride **23**, mp $69-71^\circ$, but direct comparison with the authentic sample was unattainable due to the lack of the natural product.¹⁰

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