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TOTAL SYNTHESIS OF PROSOPHYLLINE

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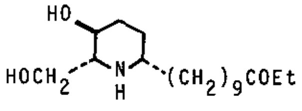
Abstract: The $SnCl_2$-effected reaction of **4** with ethyl vinyl ether and 1-trimethylsilyloxybutadiene afforded **5a**, **17**, and **18**. Prosophylline (**1**), a racemic alkaloid of *Prosopis africana*, was first synthesized by differentiating the double bonds of **17**.

Prosophylline (**1**), prosopinine (**2a**), isoprosopinine A (**2b**), isoprosopinine B (**2c**), and prosopine (**2d**) are 2-hydroxymethyl-6-alkyl-3-piperidinol alkaloids, isolated from *Prosopis africana* (African mimosa)[1] and pharmacological activities including local anesthetic action have been reported for **2a** and **2d**.[2] In continuation of our synthetic study of 2-methyl-6-alkyl-3-piperidinol alkaloids,[3] we devised a stereoselective formation of 2-hydroxymethyl moiety and in this report, we wish to describe a stereo-controlled total synthesis of a racemic alkaloid, prosophylline (**1**).[4]



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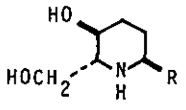

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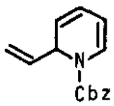
a R= $(CH_2)_9COEt$
b R= $(CH_2)_6CO(CH_2)_4Me$
c R= $(CH_2)_7COBu$
d R= $(CH_2)_{10}CH(OH)Me$

1-Benzyloxycarbonyl-2-vinyl-1,2-dihydropyridine (**3**), prepared from pyridine, vinylmagnesium bromide, and benzyl chloroformate in 83% yield, was photooxidized as reported previously.[5] The resulting endoperoxide **4** was reacted with ethyl vinyl ether in the presence of $SnCl_2$,[3a,6] and work-up of the reaction mixture with addition of EtOH furnished a condensation product **5a** in 58% yield, which was converted to its t-butyldimethylsilyl ether **5b** [t-$BuMe_2SiCl$, Et_3N, 4-dimethylaminopyridine, CH_2Cl_2, r.t., 93%][7] and benzyl ether **5c** [$PhCH_2Cl$, NaH, Et_2O-HMPA, r.t., 91%] in order to discriminate the reactivity of two double bonds in **5a**. Osmium tetroxide oxidation of **5b** and **5c** [OsO_4, hexane-Et_2O-Py (10:10:1), -25°→r.t.]



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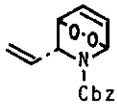

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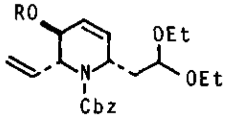
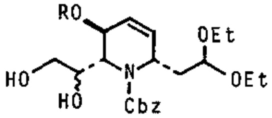
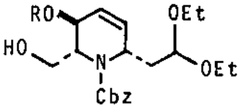


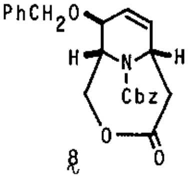
5a R=H
5b R=t-BuMe$_2$Si
5c R=PhCH$_2$



6a R=t-BuMe$_2$Si
6b R=PhCH$_2$



7a R=t-BuMe$_2$Si
7b R=PhCH$_2$



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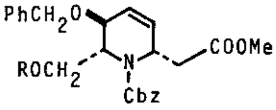
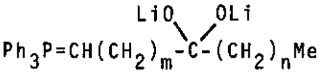
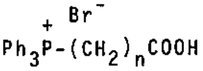


9a R=H
9b R=Ac



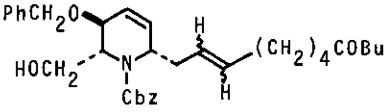
$Ph_3P{=}CH(CH_2)_m\text{-}C(OLi)(OLi)\text{-}(CH_2)_nMe$

10a m=4, n=3
10b m=2, n=3
10c m=4, n=1



$Ph_3\overset{+}{P}\text{-}(CH_2)_nCOOH\ Br^-$

11a n=5
11b n=3



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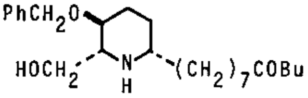

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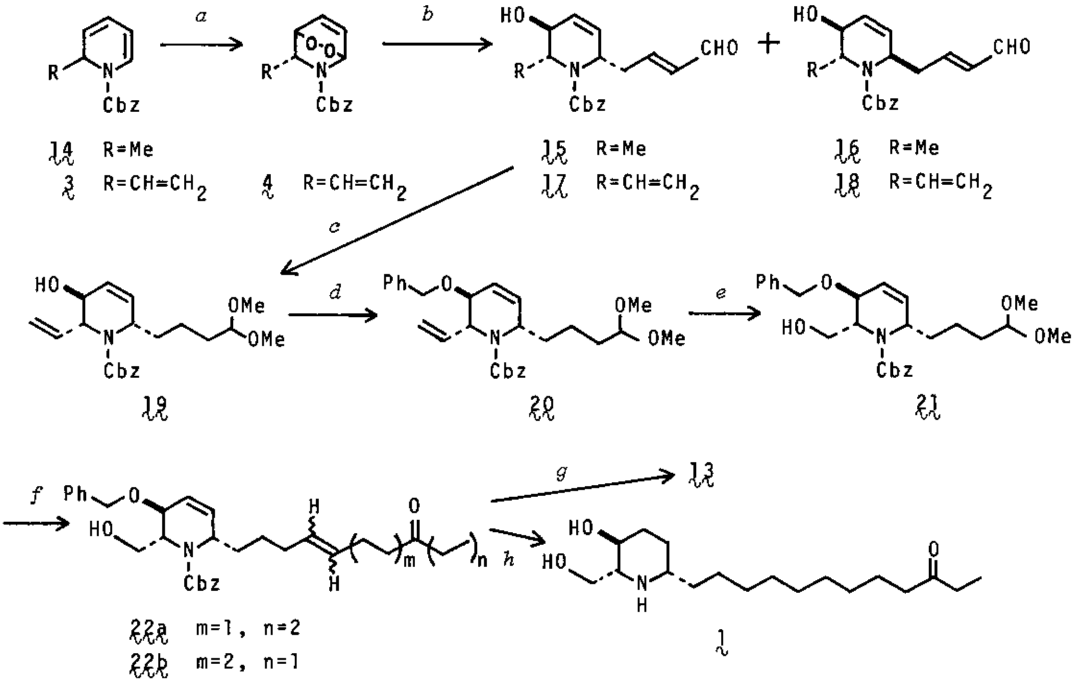
proceeded exclusively at the double bond of vinyl function, affording 6a and 6b in 83% and 78% yields, respectively, and the structure of 6a was verified by its transformation to 7a [(i) $NaIO_4$, $MeOH\text{-}H_2O$ (4:1), 0°→r.t.; (ii) $NaBH_4$, 0°] in 85% yield. Potassium permanganate oxidation of the vinyl double bond was investigated at this stage for the purpose of production in the preparative scale. A satisfactory result was obtained by utilizing a phase transfer catalyst [$KMnO_4$, $n\text{-}Bu_4N\text{-}Br$, $CH_2Cl_2\text{-}H_2O$ (1:1), 0°→r.t.] and formation of 6b was observed from 5c in 70% yield. α-Glycol of 6b was cleaved as above to afford 7b in 62% yield calculated from 5c.

Stereochemical relationship among substituents in 7b was confirmed in the following manner. (i) Hydrolysis of the acetal function in 7b [5% aq. HCl-DME (1:1), r.t.] afforded a compound, whose ^1H nmr spectrum scarcely exhibited an aldehyde signal, and oxidation of this compound [PCC, CH_2Cl_2, r.t.] gave an unstable lactone derivative 8 in 55% yield from 7b. 8 was characteristic of opening

Synthesis of Prosophylline



a. O_2, methylene blue, CH_2Cl_2, 500W halogen lamp, -50—-40°. *b*. TMSO, $SnCl_2$ in EtOAc. *c*. (i) $Fe(CO)_5$-NaOH, EtOH-H_2O (*ca*.40:1), r.t., N_2 and then I_2 in Et_2O. (ii) MeOH, p-TsOH·H_2O, r.t. *d*. $PhCH_2Cl$, NaH, HMPA-Et_2O (1:4), 0°→r.t. *e*. (i) $KMnO_4$, n-Bu_4NBr, CH_2Cl_2-H_2O (1:1), 0°→r.t. (ii) $NaIO_4$, MeOH-H_2O (1:1), 0°→r.t. and then $NaBH_4$, 0°. *f*. (i) 10% aq. HCl-DME (1:1.5), r.t. (ii) 10b, THF, 0°; or 10c [←11a+EtLi, THF, 0°→r.t.], THF, 0°. *g*. H_2, 10% Pd-C, MeOH, r.t. *h*. H_2, 10% Pd-C, 10% aq. HCl, MeOH, r.t.

the lactone ring in very mild condition [0.5% KOH in MeOH, 0°], producing in 92% yield an ester 9a, which was converted to an ester acetate 9b [Ac_2O, Py, r.t.] in 97% yield. These facts clearly demonstrated the cis relationship between 2-hydroxymethyl group and 6-alkyl side chain. (ii) The diethyl acetal group in 7b was hydrolyzed as above, and the resulting hemiacetal derivative was directly reacted with a ylide 10a [THF, 0°], derived from a phosphonium salt 11a and n-butyllithium [THF, 0°→r.t.].[3b] The condensation product 12, obtained in 34% yield, was catalytically hydrogenated [H_2, 10% Pd-C, MeOH, 58%] to a compound 13, which corresponded to the benzyl ether of a 6-epimer of isoprosopinine B (2c). Inspection of ^1H nmr spectrum of 13 revealed that the H-3 signal appeared at 3.24 ppm as a doublet of double doublet having J=10, 10, and 4 Hz. This coupling pattern represented the trans nature of 2-hydroxymethyl and 3-benzyloxyl substituents.

In the previous work,[3b] we have shown that **15** and **16** were the reaction products between the endoperoxide of 1-benzyloxycarbonyl-2-methyl-1,2-dihydropyridine (**14**) and 1-trimethylsilyloxybutadiene. This knowledge was coupled with the above finding and we planned to establish a general synthetic route not only leading to prosophylline (**1**) but also to the alkaloids of type **2**, starting from products of the sole key reaction.[8] The $SnCl_2$-effected reaction of **4** with 1-trimethylsilyloxybutadiene took place as expected to afford **17** and **18** in 38% and 20% yields, respectively, from **3**. The ^{13}C nmr spectral criterion[3b] of both products (131.1 ppm and 132.8 ppm for C-4 signals of **17** and **18**) suggested the stereochemistry as depicted.

The double bond of an α,β-unsaturated aldehyde portion in **17** had to be reduced at first. This was achieved by application of Noyori's reagent[9] [$Fe(CO)_5$-NaOH in $EtOH-H_2O$],[10] and the reduction product was isolated as its dimethyl acetal **19** in 61% yield. A benzyl ether **20** was prepared from **19** in 83% yield in order to carry out the transformation of the vinyl function to the hydroxymethyl group. A series of reactions, *i.e.* glycol formation, $NaIO_4$ cleavage, and $NaBH_4$ reduction proceeded nicely, and **21** was obtained in 57% yield. An aldehyde derived from **21** was reacted with a ylide **10b**, which was prepared from **11b** and n-butyllithium, and the reaction product **22a** (38% yield) was hydrogenated catalytically to give the afore-mentioned compound **13** in 63% yield. This correlation between **21** and **7b** supplied us a rigorous proof with respect to the structure of **17** and **18**.

For the total synthesis, the aldehyde from **21** was condensed with **10c**, that was the reagent formed from **11a** and ethyllithium, and **22b**, thus obtained in 38% yield, was submitted to the catalytic hydrogenation in the presence of an acid. Final product **1** was obtained as colorless prisms, mp 82-83° (lit.[1] mp 79°), in 79% yield. Identification was performed by comparison of ms, ir, and ^1H nmr spectra with those described in the dissertation of Dr. G. Ratle. The present synthesis also provided the unambiguous support for the chemical structure of prosophylline (**1**).

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8. Syntheses of 2 are subjects of papers in the near future.
9. R. Noyori, I. Umeda, and T. Ishigami, *J. Org. Chem.*, 37, 1542 (1972).
10. Selection of solvents was critical in our case. Usage of MeOH resulted in the formation of Michael addition product of MeOH into α,β-unsaturated aldehyde in a considerable amount. No reaction took place in i-PrOH-H_2O, Et_2O-H_2O, DME-H_2O, DMF-H_2O, and HMPA-H_2O.

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