# TOTAL SYNTHESIS OF PROSOPHYLLINE

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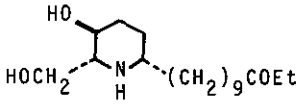
*Abstract*: The $SnCl_2$-effected reaction of 4 with ethyl vinyl ether and 1-trimethylsilyloxybutadiene afforded 5a, 17, and 18. Prosophylline (1), a racemic alkaloid of *Prosopis africana*, was first synthesized by differentiating the double bonds of 17.

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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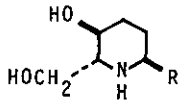


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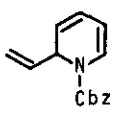
a R= $(CH_2)_9COEt$
b R= $(CH_2)_6CO(CH_2)_4Me$
c R= $(CH_2)_7COBu$
d R= $(CH_2)_{10}CH(OH)Me$

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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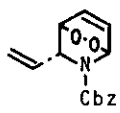

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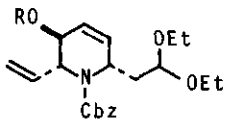
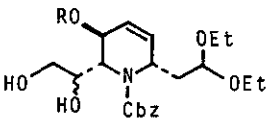
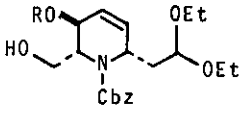


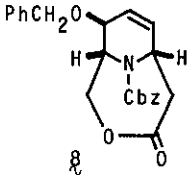
5a R=H
5b R=t-BuMe$_2$Si
5c R=PhCH$_2$



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



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



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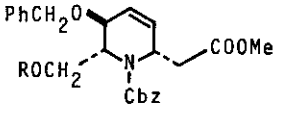
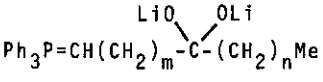
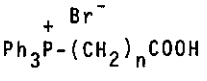


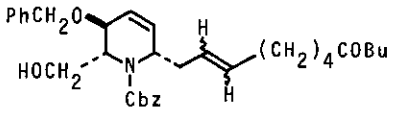
9a R=H
9b R=Ac



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



11a n=5
11b n=3



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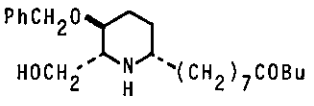
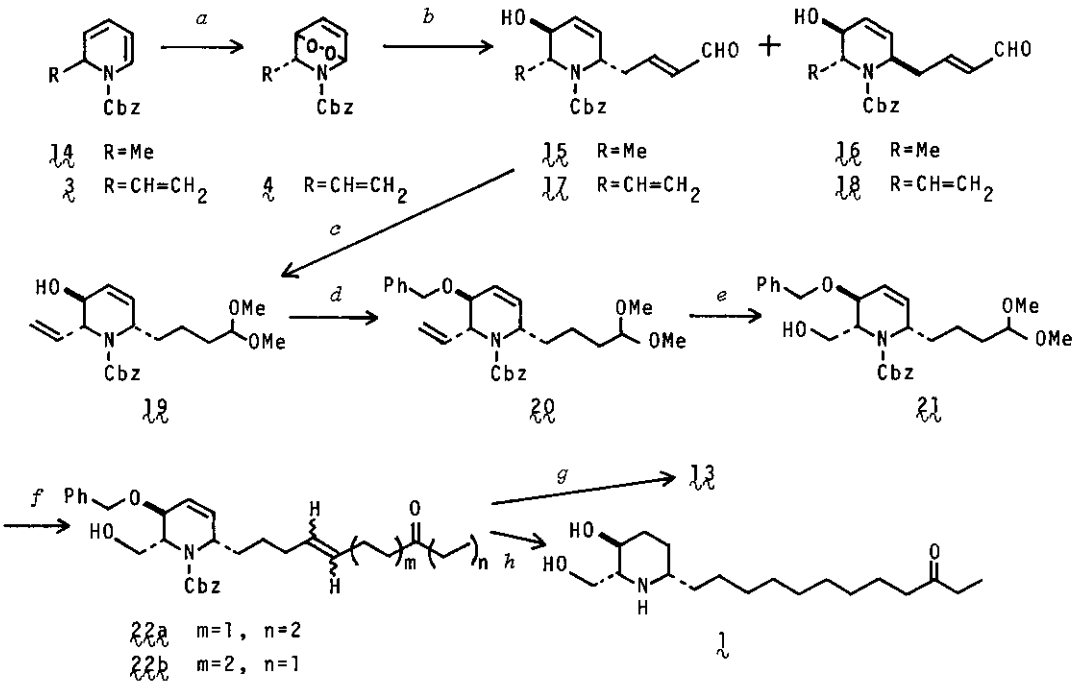


13

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-$H_2O$ (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-$Bu_4N$-Br, $CH_2Cl_2$-$H_2O$ (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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