

## Total Synthesis of ( $\pm$ )-Isoprosopinine B and ( $\pm$ )-Desoxoprosopinine

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The synthesis of the title compounds (**10**) and (**16**) in eleven and ten steps respectively from the imine (**1**) and 2-trimethylsilyloxycyclohexa-1,3-diene (**2**) via the azabicyclo-octanone (**3**) and the triol (**5**) illustrates a new general method for the preparation of the prosopis alkaloids.

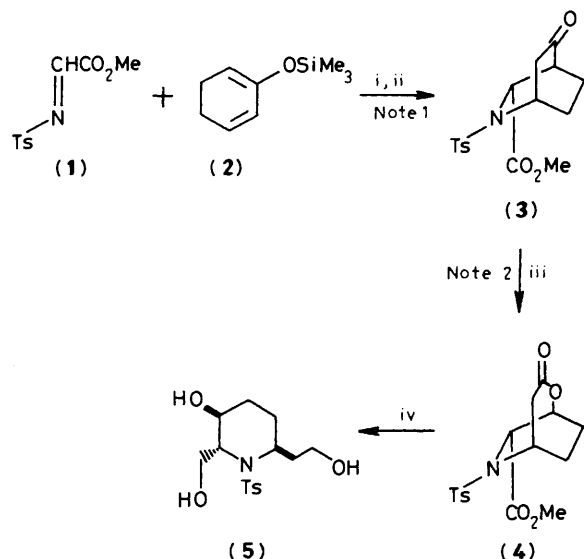
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Whereas numerous reports on the synthesis of all-*cis*-2,3,6-trisubstituted piperidines of the carpaine series have appeared over the past thirteen years,<sup>1</sup> fewer studies have been devoted to the synthesis of the 3,6-*cis*-2-*trans*-trisubstituted piperidines of the prosopis series.<sup>2</sup> We now describe a general synthesis involving the triol (**5**) which should serve as a common precursor to all the known naturally occurring prosopis piperidine alkaloids.

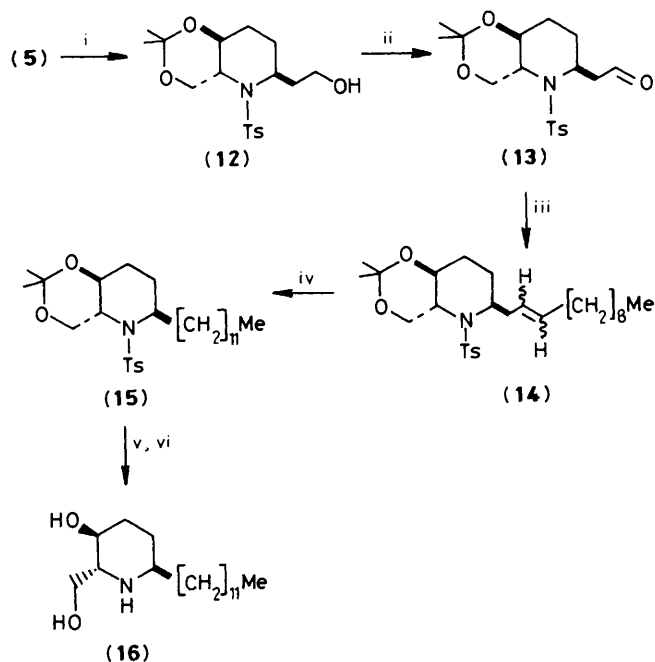
The synthesis of the triol (**5**) is shown in Scheme 1. The azabicyclo-octanone (**3**)<sup>†</sup> is prepared by cycloaddition of the imine (**1**)<sup>3</sup> to 2-trimethylsilyloxycyclohexa-1,3-diene (**2**),<sup>4</sup> followed by mild acid hydrolysis.<sup>5</sup> The cycloaddition is

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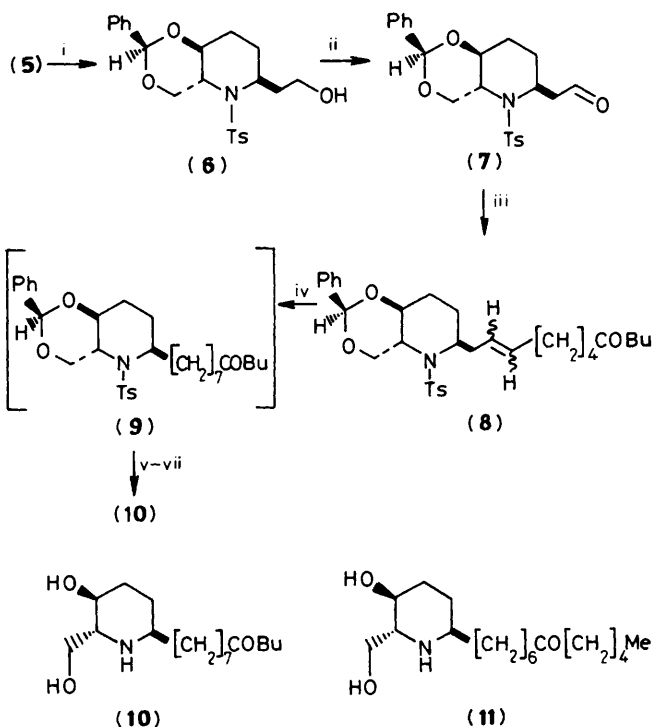
<sup>†</sup> All new compounds exhibited spectroscopic and analytical data consistent with the assigned structure. All compounds are racemic.



**Scheme 1.** Ts = *p*-MeC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>. Reagents: i, C<sub>6</sub>H<sub>6</sub>, 5 °C to room temp., 3 h; ii, 0.005 M HCl-tetrahydrofuran(THF), room temp., 1 h (57%); iii, AcOOH, AcOH, NaOAc, 50 °C, 72 h (47%); iv, LiAlH<sub>4</sub>, Et<sub>2</sub>O, 0 °C, 1.5 h (80%). Note 1. The product (3) was accompanied by the *endo*-isomer (24%). Note 2. The product (4) was accompanied by the methylene-migrated lactone (4%).



**Scheme 3.** Ts = *p*-MeC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>. Reagents: i, Me<sub>2</sub>C(OMe)<sub>2</sub>, TsOH, CH<sub>2</sub>Cl<sub>2</sub>, room temp., 16 h (77%); ii, pyridinium dichromate, 4 Å molecular sieve, CH<sub>2</sub>Cl<sub>2</sub>, room temp., 4 h (71%); iii, Ph<sub>3</sub>P=CH[CH<sub>2</sub>]<sub>8</sub>Me, THF, 0 °C, 1 h (50%); iv, H<sub>2</sub>, 5% Pd-C, EtOH (97%); v, Red-Al, C<sub>6</sub>H<sub>6</sub>, reflux, 24 h; vi, 8 M HCl-MeOH (38%).



**Scheme 2.** Ts = *p*-MeC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>. Reagents: i, PhCHO, TsOH, C<sub>6</sub>H<sub>6</sub>, room temp., 12 h (60%); ii, pyridinium dichromate, 4 Å molecular sieve, CH<sub>2</sub>Cl<sub>2</sub>, room temp., 9 h (91%); iii, Ph<sub>3</sub>P=CH[CH<sub>2</sub>]<sub>4</sub>C(OLi)<sub>2</sub>Bu, THF, 0 °C, 1 h (46%); iv, H<sub>2</sub>, 5% Pd-C, EtOH; v, HOCH<sub>2</sub>CH<sub>2</sub>OH, TsOH, C<sub>6</sub>H<sub>6</sub>, reflux, 16 h; vi, Red-Al [sodium bis(2-methoxyethoxy)aluminium hydride], C<sub>6</sub>H<sub>6</sub>, reflux, 24 h; vii, 8 M HCl-MeOH, reflux, 16 h [66% from (8)].

rigorously regioselective and reasonably stereoselective.‡ Baeyer–Villiger oxidation<sup>2b,8–10</sup> of the bicyclic ketone (3) gives largely the bridgehead-migrated lactone (4)† which is reduced to the key triol (5).†

The conversion of the triol (5) into isoprosopine B (10)<sup>11,12</sup> is outlined in Scheme 2. After protection of the triol as its benzylidene derivative (6),† the primary alcohol was oxidised to the aldehyde (7)† which underwent Wittig chain extension with the ylide derived from the reaction of *n*-butyl-lithium (3 equiv.) with 6-(triphenylphosphonio)-hexanoic acid bromide<sup>13</sup> to give (8),† as a mixture of *E* and *Z* isomers. Hydrogenation [to give (9)], detosylation, and deprotection gave (10), which was identical (t.l.c. and n.m.r., i.r., and mass spectra) with one component of an authentic sample of an inseparable mixture of isoprosopine B and its side-chain ketone isomer isoprosopine A (11). The synthesis therefore establishes unambiguously the structure of isoprosopine B. In order to obtain an exact comparison with a single compound derived from natural sources desoxyprosopine (desoxyprosopine) (16)<sup>2c</sup> was prepared as summarised in Scheme 3. The acetonide (12)† proved to be a superior protected form of the triol (5), being generally more stable, easier to handle, and less susceptible to hydrogenolysis than the corresponding benzylidene derivative (6). Elaboration of the aldehyde (13)† through (14)† (*E/Z* mixture) and (15)† proceeded smoothly and yielded, after deprotection, compound (16) which was identical in all respects except optical rotation with an authentic sample.

In summary, a general synthetic route to prosopis alkaloids has been established. The method is the most efficient to have been reported both for any naturally occurring prosopis alkaloid and for desoxyprosopine (16).

‡ The imine (1) adds in high yield to a wide variety of silyloxydienes,<sup>6</sup> and appears in this respect to be superior to iminocarbamates.<sup>7</sup>

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