Total Synthesis of (±)-Isoprosopinine B and (±)-Desoxoprosopinine

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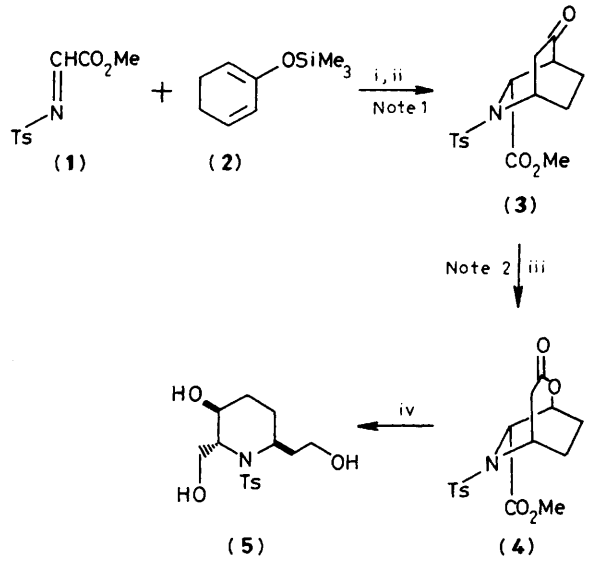
The synthesis of the title compounds (**10**) and (**16**) in eleven and ten steps respectively from the imine (**1**) and 2-trimethylsilyloxycyclohexa-1,3-diene (**2**) *via* the azabicyclo-octanone (**3**) and the triol (**5**) illustrates a new general method for the preparation of the prosopis alkaloids.

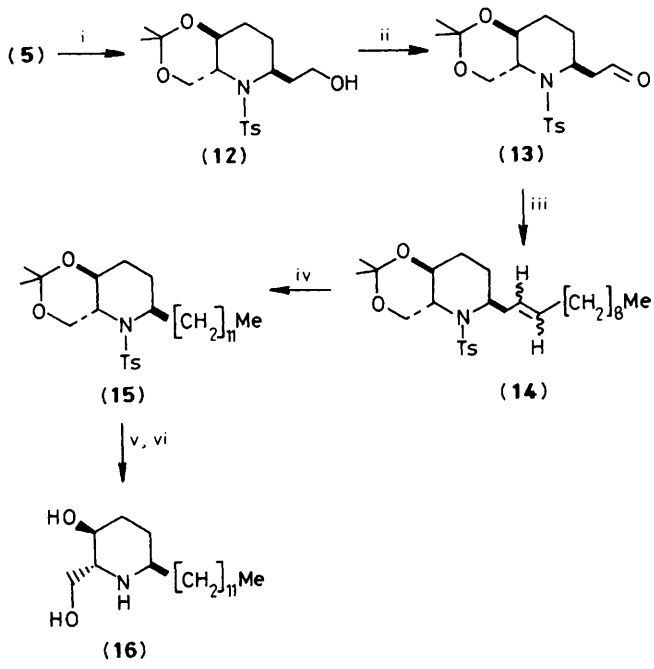
Whereas numerous reports on the synthesis of all-*cis*-2,3,6-trisubstituted piperidines of the carpaine series have appeared over the past thirteen years,[1] fewer studies have been devoted to the synthesis of the 3,6-*cis*-2-*trans*-trisubstituted piperidines of the prosopis series.[2] We now describe 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**)† is prepared by cycloaddition of the imine (**1**)[3] to 2-trimethylsilyloxycyclohexa-1,3-diene (**2**),[4] followed by mild acid hydrolysis.[5] The cycloaddition is

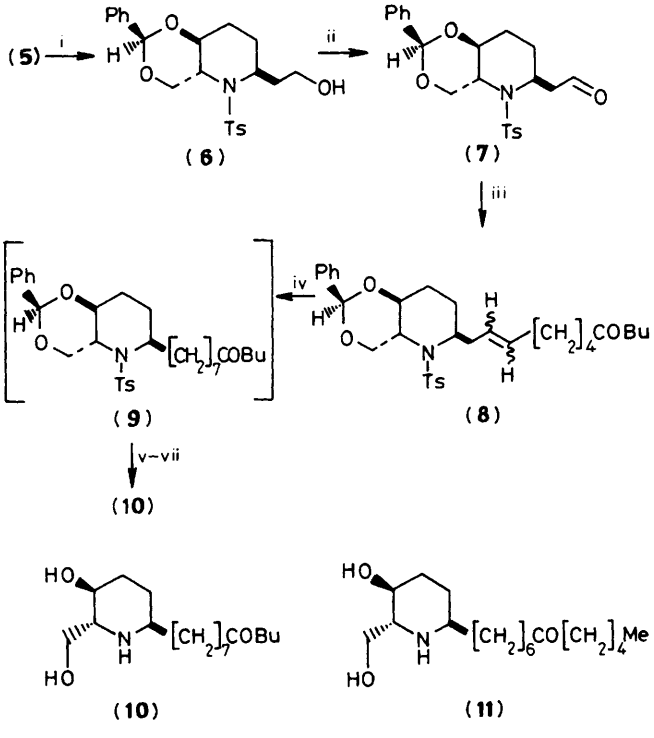
† All new compounds exhibited spectroscopic and analytical data consistent with the assigned structure. All compounds are racemic.



Scheme 1. Ts = *p*-$MeC_6H_4SO_2$. *Reagents:* i, C_6H_6, 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, $LiAlH_4$, Et_2O, 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*-$MeC_6H_4SO_2$. *Reagents:* i, $Me_2C(OMe)_2$, TsOH, CH_2Cl_2, room temp., 16 h (77%); ii, pyridinium dichromate, 4 Å molecular sieve, CH_2Cl_2, room temp., 4 h (71%); iii, $Ph_3P{=}CH[CH_2]_8Me$, THF, 0 °C, 1 h (50%); iv, H_2, 5% Pd–C, EtOH (97%); v, Red-Al, C_6H_6, reflux, 24 h; vi, 8 M HCl–MeOH (38%).



Scheme 2. Ts = *p*-$MeC_6H_4SO_2$. *Reagents:* i, PhCHO, TsOH, C_6H_6, room temp., 12 h (60%); ii, pyridinium dichromate, 4 Å molecular sieve, CH_2Cl_2, room temp., 9 h (91%); iii, $Ph_3P{=}CH[CH_2]_4C(OLi)_2Bu$,[13] THF, 0 °C, 1 h (46%); iv, H_2, 5% Pd–C, EtOH; v, $HOCH_2CH_2OH$, TsOH, C_6H_6, reflux, 16 h; vi, Red-Al [sodium bis(2-methoxyethoxy)aluminium hydride], C_6H_6, reflux, 24 h; vii, 8 M HCl–MeOH, reflux, 16 h [66% from (**8**)].

rigorously regioselective and reasonably stereoselective.‡ Baeyer–Villiger oxidation[2b,8–10] 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 isoprosopinine B (**10**)[11,12] 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[13] 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 isoprosopinine B and its side-chain ketone isomer isoprosopinine A (**11**). The synthesis therefore establishes unambiguously the structure of isoprosopinine B. In order to obtain an exact comparison with a single compound derived from natural sources desoxoprosopinine (desoxyprosopine) (**16**)[2c] 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,[6] and appears in this respect to be superior to iminocarbamates.[7]

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