Iminium Ions as Initiators and Allylsilanes as Terminators in Polyolefin Cyclizations: Total Synthesis of (±)-Yohimbone *via* a Vinylogous Aminomethano Desilylation Process

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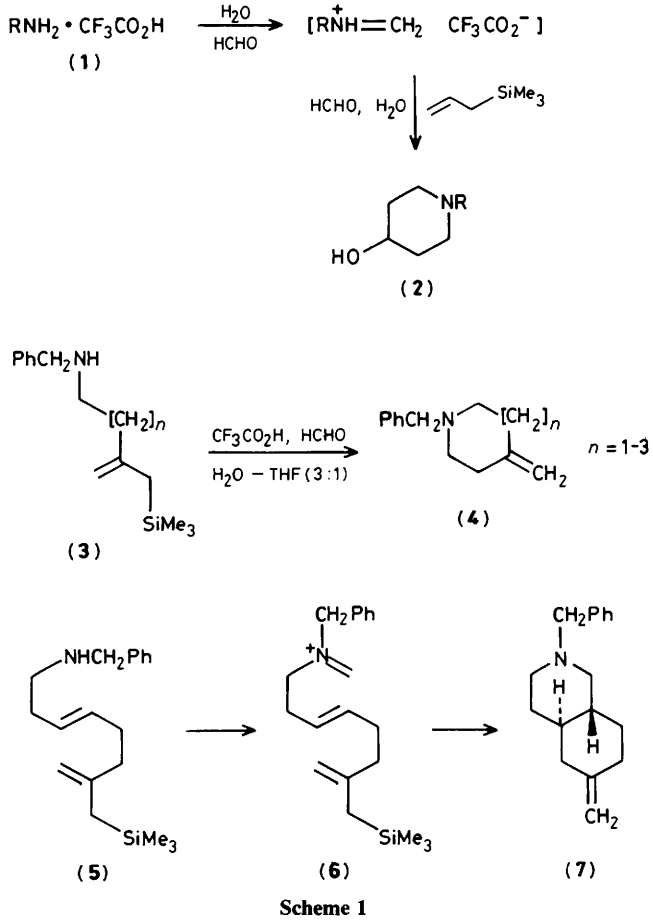
A syntheses of (±)-yohimbone has been realized *via* a concerted iminium ion-induced polyolefin cyclization terminated by an allylsilane.

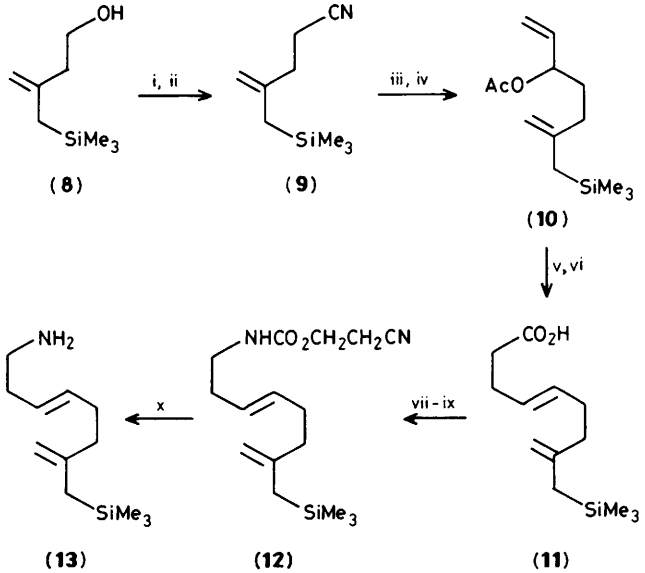
The intermolecular aminomethano desilylation process, (**1**) → (**2**),[1] and its intramolecular counterpart, (**3**) → (**4**),[2] constitute a facile new method for the elaboration of six-, seven-, and eight-membered rings containing nitrogen. In an effort to explore the potential of this novel process for alkaloid synthesis, an intramolecular variant in which a *trans* double bond was suitably situated between an amine and an allylsilane (Scheme 1) was examined. Of critical importance to success was the ability of the *in situ* generated iminium ion (**6**), derived directly from the amine, to initiate a fully concerted olefin cyclization. The use of iminium ions as initiators of olefin cyclization has received scant attention,[3] whereas reports describing allylsilanes as terminators of polyolefin cyclizations have been more numerous.[4] However, the use of an unstabilized iminium ion as an initiator and an allylsilane as a terminator of a polyolefin cyclization within the same carbon framework [*cf.* (**6**) → (**7**)] has not previously been reported.[5] We now describe a successful cyclization of this type (vinylogous aminomethano desilylation) within the context of a total synthesis of racemic yohimbone.



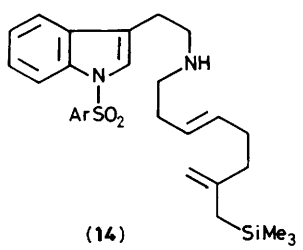
Scheme 1

In a preliminary study we set out to prepare the secondary amine (**5**), starting from the homoallyl alcohol (**8**)[6] (Scheme 2) which was smoothly transformed (84% overall) into the nitrile (**9**) *via* displacement of the corresponding toluene-*p*-sulphonate by cyanide. Reduction of the nitrile (**9**) with di-isobutylaluminium hydride and sequential treatment of the resultant aldehyde with vinylmagnesium bromide and acetyl chloride provided the allylic acetate (**10**) in *ca.* 60% overall yield. Application of an Ireland ester–enolate Claisen rearrangement[7] to the allylic acetate (**10**) provided the carboxylic acid (**11**) in 90% yield. The carboxylic acid (**11**) was subjected to a modification of the Weinstock–Curtius reaction[8] wherein the resultant isocyanate was trapped with 3-hydroxypropionitrile giving rise (75% overall) to the urethane (**12**).[9] Use of 20% aqueous hydrochloric acid to decompose the isocyanate resulted in considerable protodesilylation. Exposure of (**12**) to diethylamine in aqueous tetrahydrofuran at 45 °C provided the amine (**13**) in near quantitative yield. Benzylation [$PhCH_2Br$, Et_3N, tetrahydrofuran (THF), 50 °C, 3 h] of (**13**) afforded the secondary amine (**5**).

Having secured amine (**5**), efforts were focused on examining the iminium ion-induced polyolefin cyclization. In the event a 0.25 M solution of the trifluoroacetate of the amine (**5**) in water–THF (1:1) was treated with 1.5 equiv. of 37% aqueous formaldehyde. After 72 h at 48 °C, an 80% yield of



Scheme 2. *Reagents:* i, *p*-$MeC_6H_4SO_2Cl$, Et_3N, CH_2Cl_2; ii, NaCN, Me_2SO; iii, Bu^i_2AlH, C_6H_6; iv, CH_2=CHMgBr, THF, −78 °C; AcCl, 0 °C; v, Pr^i_2NLi, THF, hexamethylphosphoric triamide; Bu^tMe_2SiCl, −78 to 0 °C; vi, H_2O, MeOH, K_2CO_3; vii, Et_3N, $ClCO_2Et$, Me_2CO, 0 °C, 30 min; NaN_3, H_2O, 0 °C, 1 h; viii, C_6H_6, reflux, 45 min; ix, $HOCH_2CH_2CN$, 55 °C, 12 h; x, Et_2NH, H_2O, THF, 3 h.



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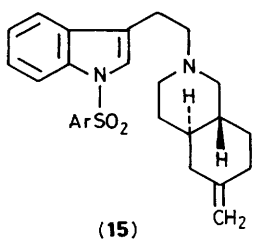

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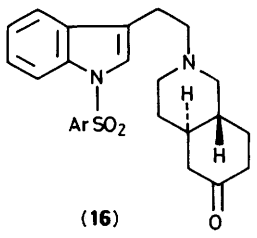

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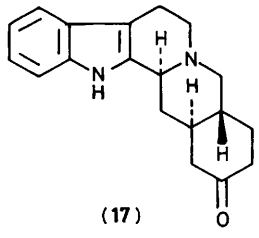

(17)

the *trans*-isoquinoline derivative (**7**) was obtained. None of the corresponding *cis*-isoquinoline could be detected. The exclusive formation of (**7**) establishes the concerted nature of the iminium ion-induced olefin cyclization in Scheme 1.

Application of this cyclization to a total synthesis of (±)-yohimbone was probed next employing substrate (**14**; Ar = *p*-$MeOC_6H_4$) which was made in *ca.* 50% yield by alkylation (Me_2SO, Et_3N, Bu_4NI) of the amine (**13**) with N-*p*-methoxyphenylsulphonyl tryptophyl toluene-*p*-sulphonate. A 0.2 M solution of the trifluoroacetate of (**14**) in water–THF (1 : 1) containing 10 equiv. of formaldehyde (37% aqueous) was treated at 40 °C for 82 h. Work-up provided a 63% yield of cyclized product (**15**; Ar = *p*-$MeOC_6H_4$). The spectral data of (**15**) were in accord with the assigned structure. Unequivocal proof of structure was obtained by transformation of (**15**) into (±)-yohimbone (**17**). Cleavage (OsO_4, CH_2Cl_2, 0 °C; $NaIO_4$, Et_3N, MeOH, H_2O) of the exocyclic double bond in (**15**) gave rise (61%) to the ketone (**16**) which was converted into yohimbone (**17**) *via* a five-step sequence. Hydrolysis (KOH, MeOH, reflux) of the sulphonamide moiety followed by reduction ($NaBH_4$, MeOH) of the ketone provided in *ca.* 90% overall yield the corresponding *seco*-alcohol which was cyclized employing excess of mercury(II) acetate–ethylenediaminetetra-acetic acid disodium salt (1 : 1) in refluxing 5% aqueous acetic acid (6 h).[10] Reduction of the crude iminium ion with 1.0 equiv. of sodium borohydride in methanol (0 °C, 30 min) followed by oxidation (dicyclohexylcarbodiimide, Me_2SO, CF_3CO_2H) provided in 10% overall yield (±)-yohimbone (**17**) whose spectral properties were identical with those of an authentic sample.

The intramolecular vinylogous aminomethano desilylation process in Scheme 1 should provide a new avenue for the elaboration of a number of yohimbine alkaloids.

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