

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

Paul A. Grieco* and William F. Fobare

Department of Chemistry, Indiana University, Bloomington, Indiana 47405, U.S.A.

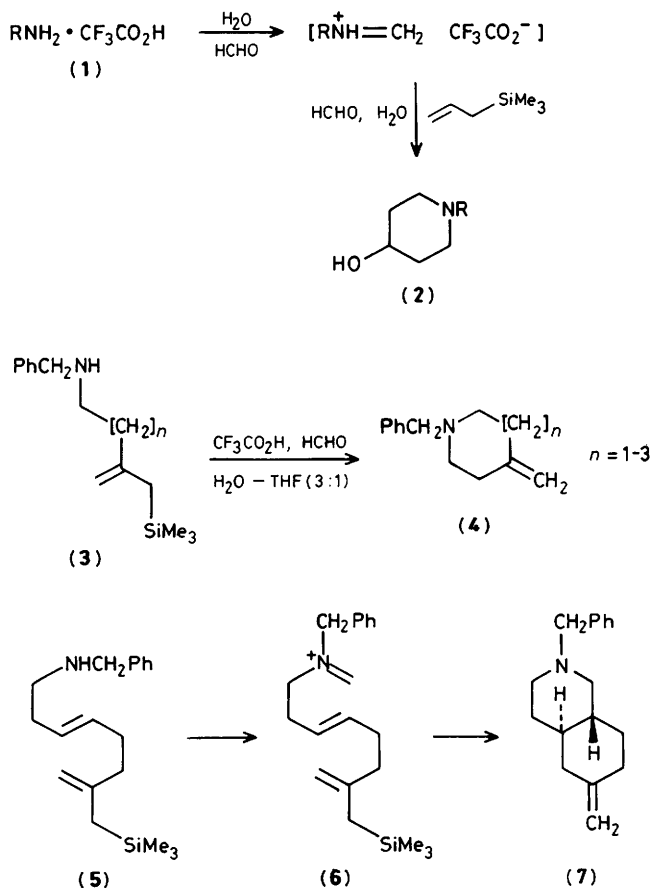
A syntheses of (±)-yohimbone has been realized via a concerted iminium ion-induced polyolefin cyclization terminated by an allylsilane.

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 (vinyl-

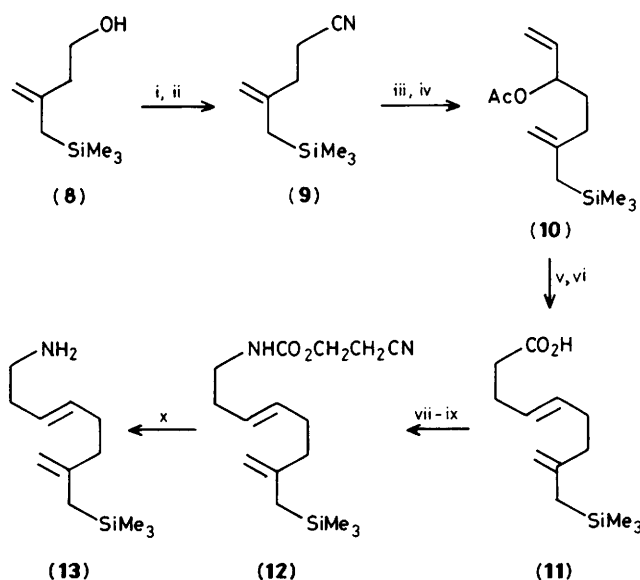
ogous aminomethano desilylation) within the context of a total synthesis of racemic yohimbone.

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-isobutylaluminum 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 rearrangement⁷ 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 reaction⁸ 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. Benzoylation [PhCH₂Br, Et₃N, tetrahydrofuran (THF), 50 °C, 3 h] of (13) afforded the secondary amine (5).

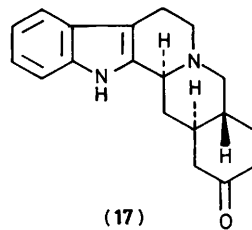
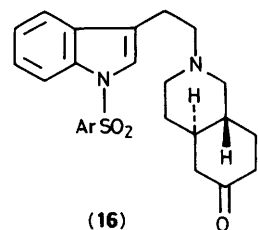
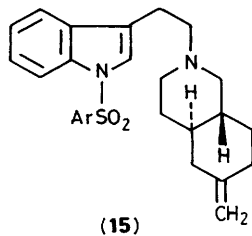
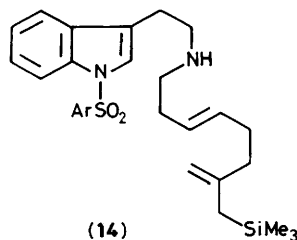
Having secured amine (5), efforts were focused on examining the iminium ion-induced polyolefin cyclization. In the event a 0.25 M solution of the trifluoroacetate of the amine (5) in water-THF (1:1) was treated with 1.5 equiv. of 37% aqueous formaldehyde. After 72 h at 48 °C, an 80% yield of



Scheme 1



Scheme 2. Reagents: i, *p*-MeC₆H₄SO₂Cl, Et₃N, CH₂Cl₂; ii, NaCN, Me₂SO; iii, Bu₂AlH, C₆H₆; iv, CH₂=CHMgBr, THF, -78 °C; AcCl, 0 °C; v, Pr₂NLi, THF, hexamethylphosphoric triamide; Bu^tMe₂SiCl, -78 to 0 °C; vi, H₂O, MeOH, K₂CO₃; vii, Et₃N, ClCO₂Et, Me₂CO, 0 °C, 30 min; NaN₃, H₂O, 0 °C, 1 h; viii, C₆H₆, reflux, 45 min; ix, HOCH₂CH₂CN, 55 °C, 12 h; x, Et₂NH, H₂O, THF, 3 h.



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 (\pm)-yohimbone was probed next employing substrate (14; Ar = *p*-MeOC₆H₄) which was made in *ca.* 50% yield by alkylation (Me₂SO, Et₃N, Bu₄NI) 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*-MeOC₆H₄). The spectral data of (15) were in accord with the assigned structure. Unequivocal proof of structure was obtained by transformation of (15) into (\pm)-yohimbone (17). Cleavage (OsO₄, CH₂Cl₂, 0°C; NaIO₄, Et₃N, MeOH, H₂O) 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 sulphon-

amide moiety followed by reduction (NaBH₄, 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, Me₂SO, CF₃CO₂H) provided in 10% overall yield (\pm)-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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