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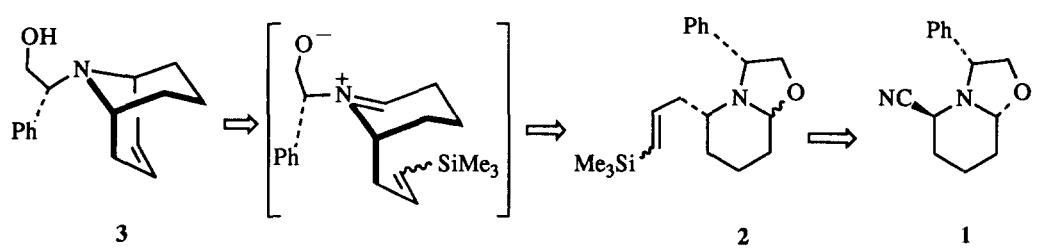
Preparation of Enantiomerically Pure 9-Azabicyclo[3,3,1]nonene Derivatives. Stereochemical Requirements of Vinyl- and Allylsilanes in Iminium Ion Initiated Cyclization.

Laurent Vidal, Jacques Royer* and Henri-Philippe Husson

Institut de Chimie des Substances Naturelles, CNRS, 1 Avenue de la Terrasse, 91198 Gif-sur-Yvette. France

Abstract: Asymmetric synthesis of the 9-azabicyclo[3,3,1]nonene skeleton of granatanine has been achieved through the cyclization of non-racemic (*Z*)-vinylsilane oxazolidine (**Z**)-**2**, an iminium ion precursor. The corresponding (*E*)-isomer (*E*)-**2** did not cyclize in the same conditions.

In the course of our study on the asymmetric synthesis of piperidine derivatives, we have been interested in the preparation of the granatanine skeleton using the CN(*R,S*) strategy.[1] In this series, we recently reported the asymmetric synthesis of (-)-adaline and (-)-euphococcinine, two ladybug alkaloids, through a classical Mannich reaction.[2] We want to report herein our results in the preparation of 9-azabicyclo[3,3,1]nonene derivative **3** *via* an intramolecular π-cationic reaction of a vinylsilane with an iminium ion. Oxazolidine **2**, readily accessible from 2-cyano-6-phenyloxazolopiperidine **1**, appeared as a good precursor for such a cyclization (Scheme 1).



3 **2** **1**

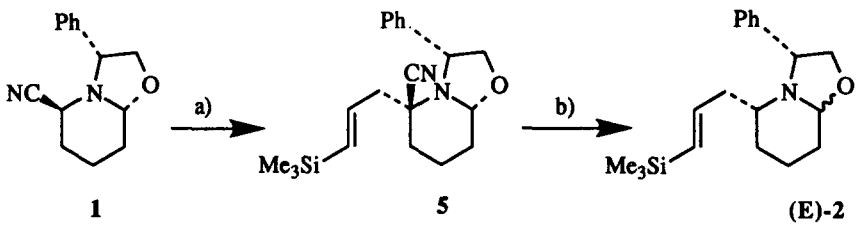
Scheme 1

Vinylsilane-terminated cyclization reactions have been thoroughly studied[3] and it is well established that the geometry of the double bond is important for the overlap of the vacant *p* orbital of the carbocation and the σ orbital of the C-Si bond (β effect). Thus (*Z*)-vinylsilanes react more readily than the (*E*)-isomers. Nevertheless, in the case of iminium-ion-initiated cyclization to form a six-membered ring, it was demonstrated by Overman[4,5] that the stereochemistry of the vinylsilane was not critical for the success of the reaction. The cyclization may occur via a two-step proccess including an aza-Cope rearrangement followed by cyclization of the resulting highly reactive allylsilane intermediate.

Despite these bibliographic data, it appeared to us that in the synthesis of a bridged system as in **3**, there is only one possible route for the cyclization and that, for each isomer, the same carbocationic intermediate would

be formed through the vinyl- or allylsilane cyclization (see scheme 4). We therefore undertook the preparation of both *E* and *Z* isomeric oxazolidines **2** in order to study their cyclizations and to verify our hypothesis.

Alkylation of the anion of 2-cyano-6-phenyloxazolopiperidine **1**[1c], with (*E*)-allylic bromide **4** (obtained by PPh_3/CBr_4 treatment[6] of the corresponding allylic alcohol[7]) gave **5** in 50% yield, which was regio- and stereoselectively reduced to oxazolidine (*E*)-**2**[8] in 77% yield (Scheme 2).

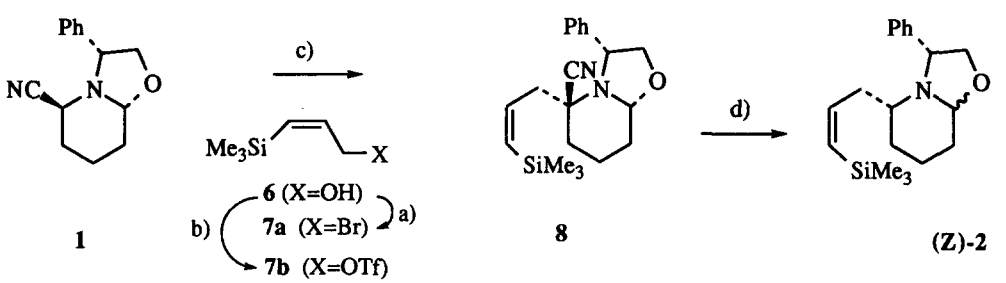


1 **5** (E)-**2**

reagents: a) LDA, THF, -78°C, (E)-Me_3Si-CH=CH-CH_2Br (**4**), 50%;
b) TfOAg, THF, -78°C, $Zn(BH_4)_2$

Scheme 2

The corresponding (*Z*)-isomer (**Z**)-**2** was prepared through the same strategy (Scheme 3). Alkylation of **1** with the (*Z*)-allylic bromide **7a** proceeded in low yield (12%) and it was neccessary to use the triflate **7b** prepared *in situ* from the (*Z*)-allylic alcohol **6** to obtain **8** in a reasonable yield (48% from the alcohol). Selective removal of the cyano group of **8** furnished oxazolidine (**Z**)-**2**[8] in good yield (71%). Isomerically pure (*Z*)-allylic alcohol **6** was obtained by reduction of THP-protected trimethylsilyl propargylic alcohol with DIBAL-H in ether.[4,9]



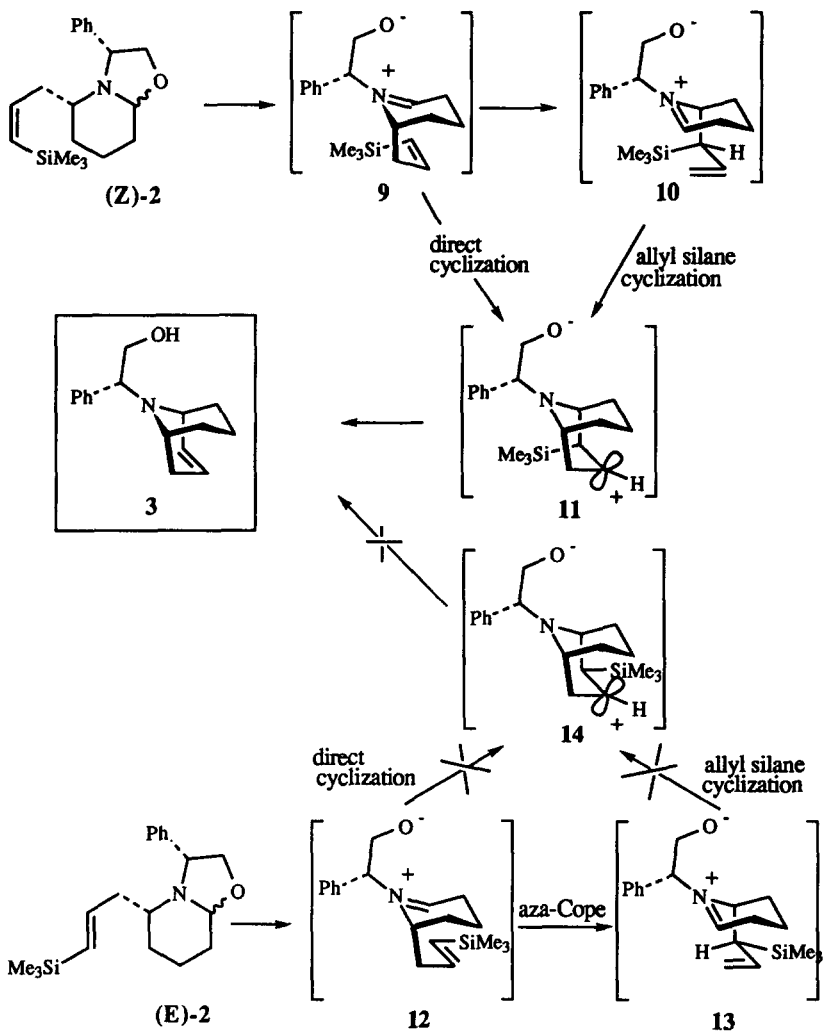
1 **8** (Z)-**2**

reagents: a) PPh_3/CBr_4; b) Tf_2O, Py ; c) LDA, THF, -78°C, **7**;
d) TfOAg, THF, -78°C, $Zn(BH_4)_2$

Scheme 3

Attempts to cyclize (*E*)-**2** proved unsuccessful under several experimental conditions,[10] while (**Z**)-**2** readily gave the granatanine derivative **3** in 82% yield after 2.5 h in refluxing CH_3CN in the presence of camphorsulfonic acid (1 equivalent). Thus in such a bridged system, cyclization of *E*-vinylsilane (or of rearranged allylsilane) has remained unfavoured, and a plausible explanation is as follows (Scheme 4).

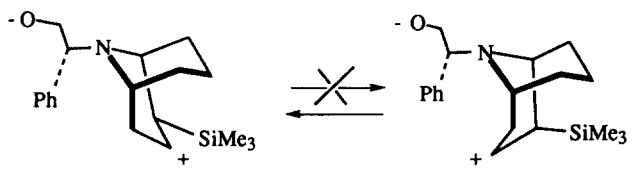
Vinylsilane iminium **9** generated from (*Z*)-**2** could undergo a direct cyclization since in the carbocationic intermediate **11** the TMS group occupies an axial position which allows a stabilization by a maximum orbital overlap. It is also possible to imagine a two-step proccess: aza-Cope rearrangement to the allylsilane **10** which could cyclize through the same cationic intermediate **11**.



Scheme 4

In the case of (*E*)-vinylsilane (*E*)-**2**, the cyclization of iminium ion **12** could not operate through the carbocation **14** in which stabilization by equatorial silyl group was inefficient, as has been widely reported in the literature. According to Overman's results,[4,5] an aza-Cope rearrangement could also have occurred from **12** to give the more reactive allylsilane **13**, it can be seen that this rearrangment generates stereospecifically a chiral carbon bearing the TMS group. This chiral carbon together with the bridged structure do not allow cyclization

since the same unstabilized cationic intermediate **14** must be involved. The conformationnal equilibrium which would lead to a stabilized carbocation through a boat form appears disfavored by a severe interaction between the axial $SiMe_3$ group with the piperidine ring (scheme 5). Stereoselective cyclizations of chiral allylsilanes on carbonyl compounds have been already reported and constitute supplementary support for the above mechanism.[11]



Scheme 5

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1) a) Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754-7755.
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8) (*E*)-**2** and (*Z*)-**2** were isolated as a mixture of epimers at the oxazolidine centre in a 60:40 ratio.
(*E*)-**2**: ^{1}H NMR (200MHz, $CDCl_3$) δ: 0.2(s), 4.35(t, J=7.7Hz), 4.5(m), 5.6(d, J=17.5Hz), 5.75(d, J=17.5Hz), 5.85(ddd, J=17.5, 6.0, 7.0Hz, 0.4 X 1H), 6.2(dt, J=17.5, 6.6Hz, 0.6 X 1H), 7.4(m).
(*Z*)-**2**: ^{1}H NMR (200MHz, $CDCl_3$) δ: 0.1(s, 0.6 X 9H), 0.2(s, 0.4 X 9H), 4.35(t, J=8.5Hz), 5.62(d, J= 14.5Hz, 0.6 X 1H), 5.75(d, J=14.5Hz, 0.4 X 1H), 6.25(ddd, J=14.5, 8.0, 5.0Hz, 0.6 X 1H), 6.52(ddd,J=14.5, 8.0, 5.0Hz, 0.4 X 1H).
3: $[\alpha]_D$ -20 ($CHCl_3$, c 1.7); ^{1}H NMR (250MHz, $CDCl_3$) δ: 1.00-1.75(m, 6H), 2.45(m, 1H), 3.00(m, 1H), 3.35(m, 1H), 3.60(dd, J=10.5, 3.2Hz, 1H), 3.70(dd, J=4.5, 3.2Hz, 1H), 3.9(dd, J=10.5, 4.5Hz, 1H), 5.40(m, 1H), 6.00(dt, J=10.5, 3.2Hz, 1H), 7.35(m, 5H);^{13}C NMR (50MHz, $CDCl_3$) δ:15.3, 26.4, 28.3, 33.5, 49.0, 50.6, 63.6, 65.0, 127.2, 127.7, 128.3, 128.6, 128.7.

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10)AcOH, PTSA, CSA in CH_2Cl_2 or CH_3CN at ambiant or reflux temperatures were checked; the starting material or the protodesylilation product was obtained.

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