SYNTHESIS AND REACTIVITY OF A 3-VINYLIDENEPIPERIDINE AS A MODEL STUDY OF α-ALLENIC AMINES

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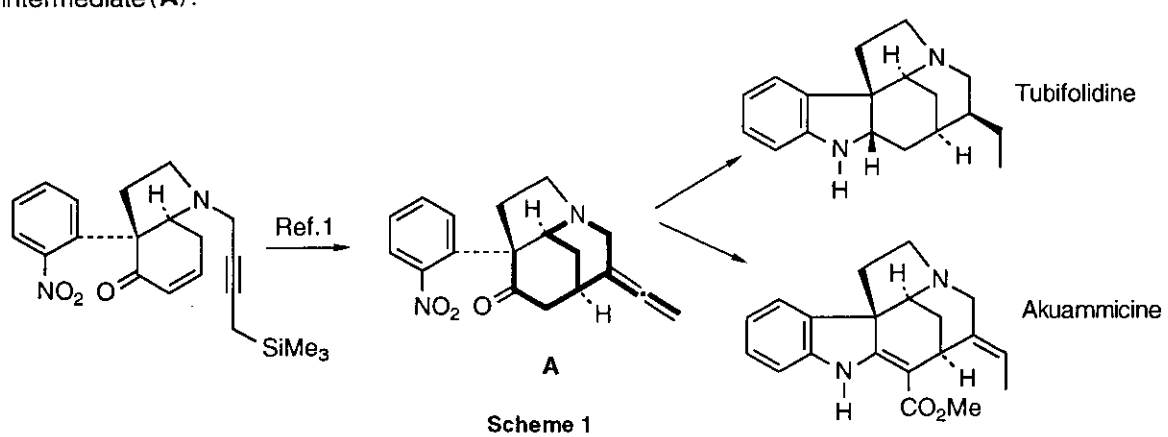
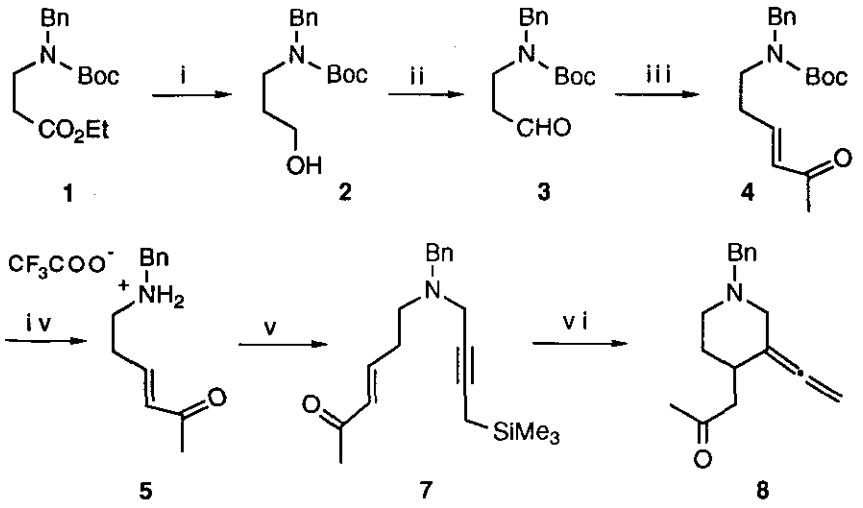
Abstract - 4-Acetonyl-1-benzyl-3-vinylidenepiperidine (**8**), prepared by cyclization of propargylic silane (**7**), was used as a model to study the usefulness of the allene moiety as a precursor of the two-carbon chain present in the piperidine ring of *Strychnos* alkaloids.

We have recently reported[1] a new synthetic entry to pentacyclic *Strychnos* indole alkaloids[2] involving, as the crucial step, the cyclization of a propargylic silane on an α,β-unsaturated ketone to generate a 3-vinylidenepiperidine (Scheme 1). The vinylidene side chain was then converted to the ethylidene and ethyl substituents present in the alkaloids akuammicine and tubifolidine, respectively.[1]

In this context, we are now interested in the transformation of the 3-vinylidenepiperidine moiety into piperidines bearing vinyl, hydroxyethyl, or acetoxyethylidene chains, like those present in the *Strychnos* alkaloids angustimicine,[3] lochneridine,[4] and 18-acetoxy-*N*-deacetylisoretuline,[5] respectively. For this reason, we decided to prepare 4-acetonyl-1-benzyl-3-vinylidenepiperidine (**8**) as a model α-allenic amine to study the reactivity of the allene functionality present in the key intermediate (**A**).



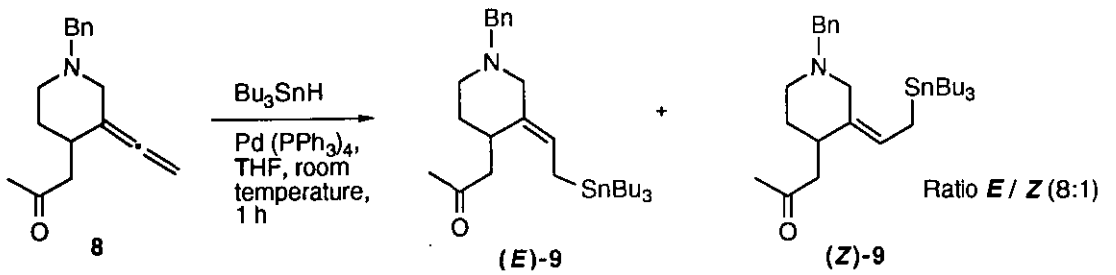
Scheme 1



Scheme 2. *Reagents*: (i) Method A: $NaBH_4$, $CaCl_2$, THF; Method B: $LiBH_4$, THF; (ii) DMSO, $(COCl)_2$, CH_2Cl_2, then Et_3N; (iii) Ph_3P=CHCOMe, THF; (iv) TFA, CH_2Cl_2; (v) $ICH_2C{\equiv}CCH_2SiMe_3$ (**6**), K_2CO_3, DMF; (vi) Method A: $BF_3.Et_2O$, CH_2Cl_2; Method B: $TiCl_4$, CH_2Cl_2.

The required piperidine (**8**) was prepared as outlined in Scheme 2, the key step of this sequence being the closure of the piperidine ring with simultaneous elaboration of the vinylidene substituent by conjugate addition of a propargylic silane to an enone.[6] The synthetic sequence starts from the *N*-protected amino ester (**1**), which was easily accessible by conjugate addition of benzylamine to ethyl acrylate[7] followed by reaction with di-*tert*-butyl dicarbonate. Conversion of ethyl ester (**1**) to the aldehyde (**3**) was carried out in two steps (reduction to alcohol (**2**) and then Swern oxidation) in 80% overall yield.[8] Wittig olefination of aldehyde (**3**) afforded α,β-unsaturated ketone (**4**) in a satisfactory way.[9] However, the introduction of the propargylic chain proved to be troublesome, probably due to the instability under basic conditions of the secondary amine (**5**), which could never be isolated as the free base. The best results (45% overall yield for the deprotection and alkylation steps) were obtained when, after deprotection of **4** with trifluoroacetic acid, the resulting trifluoroacetate (**5**) was treated with 1-iodo-4-trimethylsilyl-2-butyne (**6**)[10] in DMF solution using K_2CO_3 as a base. Finally, cyclization of propargylic silane (**7**) to 3-vinylidenepiperidine (**8**) was satisfactorily accomplished with either boron trifluoride etherate or titanium tetrachloride.

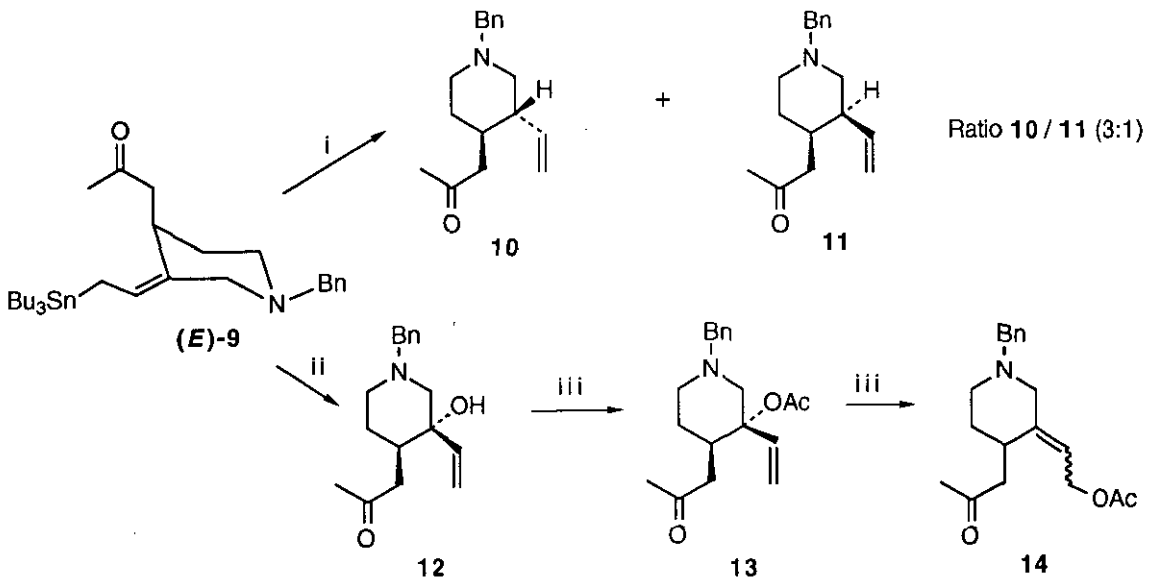
The studies for the elaboration of the allene moiety began with the palladium-catalysed hydrostannation of **8**, a process that involves the regioselective attachment of the trialkyltin group to the less highly substituted terminal carbon of the allene[13] (Scheme 3). The reaction was stereoselective, the *E* and *Z* isomers being formed in a 8:1 ratio. Comparison of the ^{13}C nmr spectra of both isomers allowed the assignment of the ethylidene configuration.[14] Thus, in the minor



Scheme 3

isomer (*Z*-**9**) a γ-gauche interaction between the tributylstannyl group and C_2-H , resulting in an upfield shift (6 ppm) of *C*-2 as compared with *E*-**9**, was observed. A similar interaction between the tributylstannyl group and C_4-H in *E*-**9** results in an upfield shift (8.5 ppm) of *C*-4 when compared with *Z*-**9**. Both isomers could also be differentiated by ^{1}H nmr, by considering the deshielding effect exerted by the tributylstannyl group on the equatorial H-2 proton in the *Z* isomer (δ ~ 3.25; compare with δ 2.99 in *E* isomer).[15] Interestingly, in the *E* isomer the piperidine ring adopts a conformation with the acetonyl substituent in an axial disposition in order to minimize the steric crowding with the adjacent tributylstannylethylidene substituent.[16] The upfield shift of *C*-6 in the ^{13}C nmr spectrum of *E*-**9**, as compared with *Z*-**9**, corroborates this conformation.

The protonolysis[17] of allyltin derivatives (**9**) gave the 3-vinylpiperidines (**10**) and (**11**) (Scheme 4). Thus, after treatment with hydrogen chloride, the isomer (*E*-**9**) yielded piperidines *trans* (**10**) and *cis*



Scheme 4. *Reagents*: (i) HCl-Et_2O ; (ii) $BF_3.Et_2O$, -70 °C, then *m*-CPBA, CH_2Cl_2 (iii) Ac_2O, AcOH, TsOH, 55 °C, 30 h.

(**11**) in a 3:1 ratio, whereas under the same conditions, the minor (*Z*-**9**) isomer led to the *cis* piperidine (**11**) as the major product. The relative configuration of both epimers (**10**) and (**11**) was clearly established from their ^{13}C nmr data, in particular from the upfield shift for all piperidine carbons in the *cis* derivative (**11**) as a consequence of the axial disposition of the vinyl substituent. The chemical shift of the methine vinylic proton in the ^{1}H nmr spectrum was of diagnostic value in assigning the disposition of the vinyl group: this proton appears more deshielded when the vinyl group is axial [δ 6.17 in (**11**) (vinyl axial); δ 5.48 in (**10**) (vinyl equatorial)].[18]

Attempts to oxidize the stannyl derivatives (**9**) with CAN[19] or $Pb(OAc)_4$[20] failed. In contrast, using *m*-CPBA[21] the oxidation was succesfully achieved. In order to avoid the oxidation of the nitrogen atom, we formed an adduct with $BF_3.Et_2O$[22] prior to the treatment with *m*-CPBA. In these conditions, piperidine (**9**) stereoselectively gave allylic alcohol (**12**) in 61% yield.[23] The same result was observed operating with either isomer of **9** (*Z* or *E*). The stereoselectivity in the oxidation step of stannyl derivatives (**9**) can be accounted for by considering steric factors. Thus, it seems reasonable to assume that, in the *E* isomer, the electrophilic attack of the oxidizing agent occurs *anti* to the axially located acetonyl side chain. In contrast, in the *Z* isomer the approach takes place from the least hindered equatorial side to give the same *trans* isomer (**12**). The stereochemistry of allylic alcohol (**12**) was deduced from its nmr data, in particular from the chemical shift of the methine vinylic proton (δ 6.33) and the chemical shifts of carbons *C*-2, *C*-3, and *C*-4, which appear deshielded with respect to compound (**11**).

Finally, acetylation of allylic alcohol (**12**) under drastic conditions (Ac_2O, AcOH, TsOH, 55 °C, overnight)[24] brought about not only the acetylation of hydroxyl group but also the rearrangement of the resulting allylic acetate to render the desired acetoxyethylidene derivative (**14**) as a mixture of *Z/E* isomers.[25] When the process was carried out for a shorter time the non-rearranged acetate (**13**) was isolated.[26]

The extension of these results to azatricyclic derivative(**A**)(Figure 1) in order to synthesize *Strychnos* indole alkaloids is in course.

EXPERIMENTAL

Unless otherwise noted, ^{1}H and ^{13}C nmr spectra were recorded in $CDCl_3$ solution at 300 and 75 MHz respectively, using Me_4Si as internal standard. Chemical shifts are reported in ppm downfield (δ) from Me_4Si. Ir spectra were recorded on a Nicolet 205 FT infrared spectrophotometer, and only noteworthy absorptions are listed (cm^{-1}). Tlc was carried out on SiO_2 (silica gel 60 F_{254}, Merck), and the spots were located with iodoplatinate reagent. Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230-400 mesh ASTM). Solvents were dried and purified prior to use when deemed necessary. Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvents was accomplished with a rotatory evaporator. Microanalyses and HRms were performed by Centro de Investigación y Desarrollo (CSIC), Barcelona.

Ethyl 3-[*N*-Benzyl-*N*-(*tert*-butoxycarbonyl)amino]propanoate (1). A solution of benzylamine (20.4 ml, 186 mmol) and ethyl acrylate (22.7 ml, 209.4 mmol) in absolute EtOH (53 ml) was stirred at room temperature for 16 h. The reaction mixture was evaporated to dryness to give **ethyl 3-(benzylamino)-propanoate** as an oil (38.6 g, quantitative), which was used in the next reaction without further purification: ^{1}H Nmr (200 MHz) 1.24 (t, J = 7.2 Hz, 3H, CH_3), 1.75 (br s, 1H, NH), 2.51 (t, J = 6.3 Hz, 2H, CH_2CO), 2.88 (t, J = 6.3 Hz, 2H, CH_2N), 3.79 (s, 2H, CH_2Ar), 4.12 (q, J = 7.2 Hz, 2H, CH_2O), 7.20-7.35 (m, 5H, ArH). To a solution of the above amino ester (23.85 g, 115.1 mmol) in 9:1 MeOH-TEA (173 ml) was added di-*tert*-butyl dicarbonate (50.2 g, 230 mmol). The mixture was heated at 50 °C for 2 h. The solvent was removed in vacuo, and the residue, was cooled (0 °C) and acidified with 1N HCl. The resulting mixture was immediately extracted with EtOAc. The organic extracts were dried and concentrated to give carbamate (**1**) as an oil (33.9 g, 96%), which was used without further purification. An analytical sample was obtained by column chromatography (CH_2Cl_2): Ir (film) 1736, 1697; ^{1}H nmr 1.25 (t, J = 7.1 Hz, 3H, CH_3), 1.45 and 1.51 (2 br s, 9H, CH_3), 2.54 (m, 2H, CH_2CO), 3.43 and 3.52 (2 br t, J = 5.6 Hz, 2H, CH_2N), 4.11 (q, J = 7.1 Hz, 2H, CH_2O), 4.47 (br s, 2H, CH_2Ar), 7.20-7.40 (m, 5H, ArH); ^{13}C nmr 14.1 (CH_3), 27.3 and 28.3 (CH_3), 33.3 and 33.6 (CH_2), 42.6 and 42.9 (CH_2N), 50.4 and 51.2 (CH_2Ar), 60.4 (CH_2O), 79.9 (C), 127.1 and 128.4 (*o*-, *m*-C), 127.6 (*p*-C), 138.5 (*ipso*-C), 155.2 (OCON), 171.7 (COO). Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.50; H, 8.38; N, 4.54.

3-[*N*-Benzyl-*N*-(*tert*-butoxycarbonyl)amino]propanol (2). Method A: To a solution of $NaBH_4$ (0.295 g, 7.80 mmol) in THF (13 ml) was added anhydrous $CaCl_2$ (0.432 g, 3.89 mmol). After 1 h at room temperature, a solution of **1** (1 g, 3.25 mmol) in THF (13 ml) was added. The resulting mixture was stirred at room temperature for 10 h. The solvent was removed in vacuo, and the resulting residue was basified with 10% aqueous NaOH and extracted with $CHCl_3$. The organic extracts were washed with water, dried, and concentrated to afford crude alcohol (**2**) (0.8 g, 95%).

Method B: To a solution of $LiBH_4$ (1.95 g, 89.46 mmol) in THF (179 ml) was added **1** (11 g, 35.79 mmol) under nitrogen. The solution was stirred at room temperature for 24 h. After cooling with an ice-bath, the excess of $LiBH_4$ was quenched by addition of 5% AcOH. The mixture was extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give alcohol (**2**) (7.86 g, 84%) as an oil, which was used directly in the next step without purification: Ir (film) 3400, 1675-1700; ^{1}H nmr (200 MHz) 1.47 (s, 9H, *t*-bu), 1.63 (m, 2H, CH_2), 2.90 (br s, 1H, OH), 3.38 (m, 2H, CH_2N), 3.56 (t, J = 5.6 Hz, 2H, CH_2O), 4.39 (br s, 2H, CH_2Ar), 7.20-7.40 (m, 5H, ArH); ^{13}C nmr 27.8 (CH_3), 29.9 and 30.7 (CH_2), 42.4 and 43.0 (CH_2N), 49.5 and 50.1 (CH_2Ar), 58.2 and 59.1 (CH_2OH), 79.7 (C), 126.7 and 128.0 (*o*-, *m*-C), 127.1 (*p*-C), 137.8 (*ipso*-C), 156.1 (NCOO).

3-[*N*-Benzyl-*N*-(*tert*-butoxycarbonyl)amino]propanal (3). To a solution of oxalyl chloride (4.8 ml, 56 mmol) in CH_2Cl_2 (350 ml) at -78 °C was added DMSO (19.9 ml, 280 mmol) under argon. After stirring at -78 °C for 30 min, alcohol (**2**) (7.43 g, 28 mmol) was added. The mixture was maintained at -78 °C for 1 h, and TEA (58.5 ml, 420 mmol) was dropwise added. The solution was stirred at -78 °C for 10 min, and then allowed to warm to room temperature. The reaction mixture was partitioned between Et_2O and saturated aqueous $NaHCO_3$. The organic extracts were washed with saturated aqueous $NaHCO_3$, dried, and concentrated to afford crude aldehyde (**3**) as an oil (7 g, 95%), which was used without further purification: Ir (film) 1692; ^{1}H nmr (200 MHz) 1.47 (s, 9H, *t*-bu), 2.64 (br, 2H, CH_2CO), 3.50 (br, 2H, CH_2N), 4.45 (s,

2H, CH_2Ar), 7.15-7.40 (m, 5H, ArH), 9.74 (s, 1H, CHO); ^{13}C nmr 27.5 (CH_3), 39.6 and 40.1 (CH_2), 42.3 and 43.2 (CH_2N), 49.7 and 50.4 (CH_2Ar), 78.8 and 79.3 (C), 126.2 and 127.7 (*o*-, *m*-C), 126.7 (*p*-C), 137.6 (*ipso*-C), 154.0 and 155.1 (NCOO), 199.9 and 200.0 (CO).

(*E*)-6-[*N*-Benzyl-*N*-(*tert*-butoxycarbonyl)amino]-3-hexen-2-one (4). A solution of **3** (10.92 g, 41.45 mmol) in THF (300 ml) was dropwise added at room temperature under argon to 1-triphenylphosphoranylidene-2-propanone (26.39 g, 82.9 mmol). The mixture was refluxed under argon for 3 days, quenched by addition of saturated aqueous NH_4Cl, and extracted with Et_2O. The organic extracts were dried, evaporated, and then taken up with hexanes. Triphenylphosphine oxide was removed by filtration, and the filtrate was evaporated to give a residue. Chromatography (Al_2O_3, CH_2Cl_2) yielded ketone (**4**) as an oil (8.65 g, 69%): Ir (film) 1694, 1679, 1414, 1366, 1251, 1164; ^1H nmr (200 MHz) 1.47 (br s, 9H, *t*-bu), 2.22 (s, 3H, CH_3), 2.40 (br, 2H, CH_2), 3.35 (br, 2H, CH_2N), 4.42 (br s, 2H, CH_2Ar), 6.02 (d, J = 15.8 Hz, =CHCO), 6.60-6.80 (m, 1H, =CH), 7.20-7.40 (m, 5H, ArH); ^{13}C nmr 27.2 (CH_3), 28.1 (CH_3), 31.2 (CH_2), 45.1 (CH_2N), 49.9 and 50.5 (CH_2Ar), 79.7 (C), 127.1 and 128.3 (*o*-, *m*-C), 127.5 (*p*-C), 132.3 (=CH), 137.9 (*ipso*-C), 144.3 and 145.3 (=CH), 155.3 (NCOO), 199.0 (CO). Anal. Calcd for $C_{18}H_{26}NO_3$: C, 71.01; H, 8.61; N, 4.60. Found: C, 70.88; H, 8.74; N, 4.55.

4-Iodo-1-(trimethylsilyl)-2-butyne (6). To a cooled solution (0 °C) of 4-trimethylsilyl-2-butyn-1-ol[13] (5 g, 35.2 mmol) in DMF (100 ml) was added triphenoxymethylphosphonium iodide (31.8 g, 70.3 mmol). The mixture was allowed to reach room temperature and stirring was continued for 6 h. Methanol (1 ml) was added to the reaction mixture and, after dilution with Et_2O, the mixture was sequentially washed with saturated aqueous sodium thiosulfate and brine. The organic layer was dried and evaporated to afford an oil, which was chromatographed (hexane) to yield 7.75 g (87%) of iodide (**6**) as an oil: ^1H Nmr 0.12 (s, 9H), 1.48 (t, J = 2.5, 2H), 3.75 (t, J = 2.5, 2H); ^{13}C nmr -15.0 (CH_2I), -1.9 (CH_3), 7.7 (CH_2), 77.7 and 87.2 (C≡≡C).

(*E*)-6-[*N*-Benzyl-*N*-[4-(trimethylsilyl)-2-butynyl]amino]-3-hexen-2-one (7). To a solution of **4** (1 g, 3.3 mmol) in CH_2Cl_2 (10 ml) cooled at 0 °C was dropwise added TFA (15.2 ml, 1.98 mmol). The mixture was stirred at 0 °C for 5 min and at room temperature for 30 min. The solvent and the excess of acid were removed in vacuo to give the trifluoroacetic salt of **5**: ^1H nmr (200 MHz) 2.29 (s, 3H, CH_3), 2.69 (m, 2H, CH_2), 3.25 (br, 2H, CH_2N), 4.23 (m, 2H, CH_2Ar), 6.25 (d, J = 12 Hz, 1H, =CHCO), 6.72 (dt, J = 16, 6 Hz, 1H, =CH), 7.30-7.50 (m, 5H, ArH), 8.20 (br, 2H, NH_2). The crude salt (**5**) was dissolved in dry DMF (10 ml), and anhydrous K_2CO_3 (1.82 g, 13.20 mmol) was added. To the resulting mixture were added 4-trimethylsilyl-2-butynyl iodide (**6**) (0.83 g, 3.3 mmol) and *t*-butylammonium chloride (0.195 g, 0.66 mmol). After stirring at room temperature for 3 h, the mixture was partitioned between Et_2O and brine. The organic extracts were washed with brine, dried, and concentrated to give a residue. Chromatography (CH_2Cl_2-MeOH 0.5%) yielded amine (**7**) (485 mg, 45%) as an oil: Ir (film) 1677, 1250, 851; ^1H nmr (200 MHz) 0.15 (s, 9H, TMS), 1.53 (t, J = 2.4 Hz, 2H, CH_2Si), 2.24 (s, 3H, CH_3), 2.42 (td, J = 7.0, 6.8 Hz, CH_2), 2.69 (t, J = 7.0 Hz, 2H, CH_2N), 3.33 (t, J = 2.4 Hz, 2H, CH_2N), 3.63 (s, 2H, CH_2Ar), 6.09 (dt, J = 15.5, 1.4 Hz, =CHCO), 6.80 (dt, J = 16, 6.8 Hz, =CH), 7.25-7.35 (m, 5H, ArH); ^{13}C nmr -1.9 ($SiMe_3$), 7.0 (CH_2Si), 26.7 (CH_3), 30.6 (CH_2), 41.9 (CH_2N), 51.3 (CH_2N), 58.0 (CH_2Ar), 72.5 (C), 83.2 (C), 127.1 (*p*-C), 128.2 and 129.4 (*o*-, *m*-C), 133.0 (=CH), 138.7 (*ipso*-C), 146.0 (=CH), 198.6 (CO); Anal. Calcd for

$C_{20}H_{29}NOSi$: C, 73.34; H, 8.92; N, 4.28. Found: C, 73.19; H, 8.87; N, 4.35. In some runs ***N*-Benzyl-*N*,*N*-bis[4-(trimethylsilyl)-2-butynyl]amine** was isolated: Ir (film) 1250, 845; ^{1}H nmr 0.13 (s, 18H, CH_3), 1.51 (t, J = 2.5 Hz, 4H, CH_2Si), 3.36 (t, J = 2.5 Hz, 4H, CH_2N), 3.67 (s, 2H, CH_2Ar), 7.20-7.45 (m, 5H, ArH); ^{13}C nmr -1.9 (TMS), 7.1 (CH_2Si), 42.5 (CH_2N), 56.9 (CH_2Ar), 73.6 (C), 82.8 (C), 127.6 (*p*-C), 128.2 and 129.3 (*o*-, *m*-C), 138.5 (*ipso*-C).

4-Acetonyl-1-benzyl-3-vinylidenepiperidine (8). Method A: To a solution of **7** (1.04 g, 3.21 mmol) in CH_2Cl_2 (80 ml) was added dropwise at 0 °C under nitrogen BF_3·Et_2O (2 ml, 16 mmol). The mixture was allowed to warm to room temperature (4 h), poured into water, basified with 10% aqueous Na_2CO_3, and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to afford a residue. Chromatography (Florisil®, CH_2Cl_2-MeOH 2%) yielded allene (**8**) as a foam (490 mg, 60%).
Method B: To a solution of **7** (300 mg, 0.92 mmol) in CH_2Cl_2 (60 ml) was added dropwise at 0 °C under nitrogen $TiCl_4$ (0.3 ml, 2.75 mmol). The mixture was stirred at -50 °C for 2 h, and then allowed to warm to room temperature (3 h). $TiCl_4$ (0.15 ml, 1.37 mmol) was added dropwise, and stirring was maintained for 2 h. The reaction mixture was poured into water, basified with 10% aqueous Na_2CO_3 solution, and extracted with CH_2Cl_2 (severe emulsions were formed). The organic extracts were washed with brine, dried, and evaporated to give a residue. Chromatography yielded **8** (130 mg, 57%): Ir (film) 1950, 1716; ^{1}H nmr (200 MHz) 1.38 (qd, J = 12.2, 3.6 Hz, 1H, *H*-5_{ax}), 1.72 (ddt, J = 12.2, 4.4, 3.0 Hz, 1H, *H*-5_{eq}), 2.14 (s, 3H, CH_3), 2.17 (td, J = 11.9, 2.6 Hz, 1H, *H*-6_{ax}), 2.32 (dd, J = 16.8, 5.6 Hz, 1H, CH_2CO), 2.54 (m, 1H, *H*-4), 2.72 (dt, J = 16.8, 6.7 Hz, 1H, CH_2CO), 2.75 (dt, J = 11.6, 3.5 Hz, 1H, *H*-2_{ax}), 2.92 (ddd, J = 11.9, 5.1, 3.7 Hz, 1H, *H*-6_{eq}), 3.37 (dd, J = 11.6, 1.8 Hz, 1H, *H*-2_{eq}), 3.51 (d, J = 13.2, CH_2N), 3.58 (d, J = 13.2 Hz, 1H, CH_2N), 4.67 (dt, J = 9.4, 3.5 Hz, 1H, $=CH_2$), 4.80 (dt, J = 9.4, 3.5 Hz, 1H, $=CH_2$), 7.30-7.40 (m, 5H, ArH); ^{13}C nmr 30.5 (CH_3), 31.3 (*C*-5), 32.8 (*C*-4), 47.1 (CH_2), 52.9 (*C*-6), 56.7 (*C*-2), 62.3 (CH_2Ar), 77.1 ($=CH_2$), 101.3 (C), 127.0 (*p*-C), 128.1 and 129.2 (*o*-, *m*-C), 137.6 (*ipso*-C), 203.0 (=C=), 207.5 (CO). Anal. Calcd for $C_{17}H_{21}NO.2/3H_2O$: C, 76.37; H, 8.42; N, 5.24. Found: C, 76.40; H, 8.35; N, 5.12.

(*Z*)- and (*E*)-4-Acetonyl-1-benzyl-3-[2-(tributylstannyl)ethylidene]piperidine (9). To a solution of **8** (75 mg, 0.294 mmol) and a catalytic amount of $Pd(PPh_3)_4$ (5% molar) in THF (2 ml) was added dropwise under argon Bu_3SnH (93 µl, 0.353 mmol). The mixture was stirred at room temperature for 1 h and concentrated to dryness to give a residue. Chromatography (from hexane to hexane-EtOAc 20%) yielded allylic stannanes (**9**) (103 mg, 71%) as a 8:1 mixture of *Z* and *E* isomers. After a further column chromatography, the isomers could be separated, both as oils. (**9**, *E* isomer): Ir (film) 1716; ^{1}H nmr 0.75-1.01 (m, 13H), 1.20-1.90 (m, 18H), 2.14 (s, 3H, CH_3), 2.26 (br t, J = 13 Hz, 1H), 2.41 (dd, J = 16, 5.3 Hz, 1H, CH_2CO), 2.70 (dd, J = 16, 9.1 Hz, 1H, CH_2CO), 2.65-2.85 (m, 2H), 2.99 (d, J = 11.9 Hz, 1H, *H*-2_{eq}), 3.24 (m, 1H), 3.51 (broad s, 2H, CH_2Ar), 5.36 (t, J = 9 Hz, 1H, =CH), 7.20- 7.35 (m, 5H, ArH); ^{13}C nmr 9.4 (CH_2Sn), 9.9 (CH_2Sn), 13.7 (CH_3), 27.4 (CH_2), 27.8 (*C*-5), 28.9 (*C*-4), 29.1 (CH_2), 30.6 (CH_3), 44.9 (CH_2), 48.9 (*C*-6), 58.4 (*C*-2), 62.3 (CH_2Ar), 124.8 (CH), 127.0 (*p*-C), 128.1 and 129.0 (*o*-, *m*-C), 130.1 (C), 138.3 (*ipso*-C), 208.0 (CO). HRms Calcd for $C_{29}H_{49}NOSn$ 547.2851, found 547.2836. (**9**, *Z* isomer): Ir (film) 1716; ^{1}H nmr 0.75-1.00 (m, 12H), 1.20-1.80 (m, 18H), 2.15 (s, 3H, CH_3), 2.23-2.53 (m, 3H), 2.57-2.75 (m, 3H), 3.20-3.35 (m, 2H), 3.55 (br s, 2H, CH_2Ar), 5.26 (t, J = 9 Hz, 1H, =CH), 7.20-7.40 (m, 5H, ArH); ^{13}C nmr 9.3 (CH_2Sn), 10.1 (CH_2Sn), 13.7 (CH_3), 27.4 (CH_2), 29.2 (CH_2), 30.5

(CH_3), 32.3 (*C*-5), 37.4 (*C*-4), 46.5 (CH_2), 52.4 (*C*-2), 52.7 (*C*-6), 63.2 (CH_2Ar), 121.5 (CH), 126.9 (*p*-C), 128.1 and 129.2 (*o*-, *m*-C), 130.1 (C), 138.0 (*ipso*-C), 208.3 (CO).

4-Acetonyl-*N*-benzyl-3-vinylpiperidine (10 and 11). To a solution of allylic stannane (*E*-**9**) (89 mg, 0.16 mmol) in MeOH (3 ml) was added dropwise a saturated Et_2O solution of anhydrous HCl (1 ml). After 10 min at room temperature the solvent and the excess of acid were removed in vacuo. The residue was dissolved in CH_2Cl_2 and sequentially washed with saturated Na_2CO_3 and 10% KF aqueous solutions. The organic extracts were dried and evaporated to give a residue. Chromatography (hexane to hexane-EtOAc 40%) gave **10** and **11** (15 and 5 mg, respectively, 48% combined yield) as oils. When the isomer (*Z*-**9**) (21 mg) was treated in a similar manner, the vinyl derivatives (**11**) (3.5 mg) and (**10**) (1.5 mg) were isolated in 50% overall yield.

***trans*-4-Acetonyl-*N*-benzyl-3-vinylpiperidine (10)**: Ir (film) 1716, 1356, 1340; ^{1}H nmr 1.24-1.44 (m, 2H), 1.60-1.72 (m, 1H), 1.76 (br d, *J* = 11 Hz, 1H, *H*-5_{eq}), 1.90 (t, *J* = 11 Hz, 1H, *H*-2_{ax}), 2.04 (br t, *J* = 11.2 Hz, 1H, *H*-6_{ax}), 2.09 (s, 3H, CH_3), 2.14 (dd, *J* = 17, 8.5 Hz, 1H, CH_2CO), 2.62 (dd, *J* = 17, 3.5 Hz, 1H, CH_2CO), 2.87 (ddd, *J* = 11, 3.6, 2 Hz, 1H, *H*-2_{eq}), 2.92 (br d, *J* = 11.2 Hz, 1H, *H*-6_{eq}), 3.56 (s, 2H, CH_2Ar), 5.02 (dd, *J* = 10, 2.0 Hz, 1H, H-*trans*), 5.06 (dd, *J* = 17.2, 2 Hz, 1H, H-*cis*), 5.48 (ddd, *J* = 17.2, 10, 9 Hz, 1H, =CH), 7.20-7.40 (m, 5H, ArH); ^{13}C nmr 30.7 (CH_3), 31.1 (*C*-5), 35.4 (*C*-4), 46.9 (*C*-3), 47.9 (CH_2), 53.1 (*C*-6), 58.2 (*C*-2), 62.9 (CH_2Ar), 117.1 (=CH_2), 127.2 (*p*-C), 128.1 and 129.4 (*o*-, *m*-C), 137.1 (*ipso*-C), 139.3 (=CH), 208.6 (CO). HRms Calcd for $C_{17}H_{23}NO$ 257.1778, found 257.1779.

***cis*-4-Acetonyl-*N*-benzyl-3-vinylpiperidine (11)**: Ir (film) 1714, 1643, 1365, 1335; ^{1}H nmr 1.20-1.75 (m, 5H), 2.10 (s, 3H, CH_3), 2.30 (m, 1H), 2.35-2.50 (m, 2H), 2.75 (m, 1H), 2.90 (m, 1H), 3.56 (d, *J* = 13.3 Hz, 1H, CH_2Ar), 3.67 (d, *J* = 13.3 Hz, 2H, CH_2Ar), 4.96 (dd, *J* = 17.2, 2 Hz, H-*cis*), 5.09 (dd, *J* = 10.3, 2 Hz, 1H, H-*trans*), 6.17 (ddd, *J* = 17.2, 10.3, 9.5 Hz, 1H, =CH), 7.20-7.40 (m, 5H, Ar); ^{13}C nmr 29.7 (*C*-5), 30.6 (CH_3), 33.3 (*C*-4), 42.5 (*C*-3), 46.2 (CH_2), 52.6 (*C*-6), 57.2 (*C*-2), 62.6 (CH_2Ar), 116.6 (=CH_2), 127.2 (*p*-C), 128.2 and 129.4 (*o*-, *m*-C), 136.5 (*ipso*-C), 137.7 (=CH), 208.1 (CO).

***t*-4-Acetonyl-*N*-benzyl-*r*-3-hydroxy-3-vinylpiperidine (12).** To a solution of **9** (8:1 mixture of *Z* and *E* isomers, 70 mg, 0.126 mmol) in THF (3 ml) cooled to -78 °C was dropwise added under argon BF_3·Et_2O (16 µl, 0.126 mmol). After 5 min at this temperature, the solvent was removed in vacuo without heating, and the residue was dissolved in CH_2Cl_2 (5 ml). *m*-CPBA (28 mg, 0.16 mmol) was added, and the mixture was stirred at room temperature for 2 h, poured into water, and extracted with CH_2Cl_2. The organic extracts were sequentially washed with saturated $NaHCO_3$ and 10% KF aqueous solutions, dried, and concentrated to give a residue. Chromatography (hexane to hexane-EtOAc 40%) afforded **12** as an oil (21 mg, 61%): Ir (film) 3400, 1707, 1358, 1340; ^{1}H nmr 1.35 (m, 1H, *H*-5_{eq}), 1.40 (qd, *J* = 12.8, 4.2 Hz, 1H, *H*-5_{ax}), 1.67 (m, 1H, *H*-4), 2.03 (m, 1H, *H*-6_{ax}), 2.12 (d, *J* = 9.2 Hz, *H*-2_{ax}), 2.15 (s, 3H, CH_3), 2.23 (dd, *J* = 17.6, 6 Hz, 1H, CH_2CO), 2.68 (dd, *J* = 17.6, 6 Hz, 1H, CH_2CO), 2.75 (d, *J* = 9.4 Hz, 1H, *H*-2_{eq}), 2.85 (m, 1H, *H*-6_{eq}), 3.48 (d, *J* = 13.2, 1H, CH_2Ar), 3.57 (d, *J* = 13.2, 1H, CH_2Ar), 5.21 (dd, *J* = 11, 2 Hz, 1H, H-*trans*), 5.34 (dd, *J* = 17.6, 2 Hz, 1H, H-*cis*), 6.33 (dd, *J* = 17.6, 11 Hz, 1H, =CH), 7.20-7.40 (m, 5H, ArH); ^{13}C nmr 29.2 (*C*-5), 30.3 (CH_3), 40.8 (*C*-4), 44.9 (CH_2), 52.6 (*C*-6), 62.4 (CH_2Ar), 64.6 (*C*-2), 72.7 (*C*-3), 114.4 (=CH_2), 127.1 (*p*-C), 128.2 and 128.9 (*o*-, *m*-C), 137.8 (*ipso*-C), 139.4 (=CH), 209.9 (CO); HRms Calcd for $C_{17}H_{23}NO_2$ 273.1737, found 273.1729.

4-Acetonyl-3-(2-acetoxyethylidene)-1-benzylpiperidine (14). To a solution of alcohol (**12**) (20 mg, 0.073 mmol) in glacial AcOH (0.18 ml) were added a solution of Ac_2O (0.07 ml, 0.73 mmol) in glacial AcOH (0.18 ml) and a catalytic amount of *p*-TsOH·H_2O. The solution was heated at 50-60 °C for 30 h. The mixture was cooled in an ice-bath, and a saturated $NaHCO_3$ solution was added. After 30 min at room temperature the mixture was extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give a residue. Chromatography (hexane-EtOAc 0% to hexane-EtOAc 100%) yielded **14** (6 mg, 28%) as a 2:1 mixture of *Z* and *E* isomers: Ir (film, mixture of *Z* and *E* isomers) 1713, 1454, 1365, 1231; ^{1}H nmr (Mixture of *Z* and *E* isomers) 1.40-2.20 (m), 2.04 (s, 3H, CH_3CO), 2.14 (s, 1H, CH_3COO), 2.17 (s, 2H, CH_3COO), 2.35-2.55 (m), 2.60-2.90 (m), 3.10 (d, *J* = 8.5 Hz, 0.33H), 3.30-3.50 (m, 1H), 3.50-3.65 (m, 2H, CH_2Ar), 4.53 (d, *J* = 6.9 Hz, 1.33H, CH_2OAc), 4.67 (d, *J* = 6.9 Hz, 0.66H, CH_2OAc), 5.27 (br t, *J* = 7 Hz, 0.66H, =CH), 5.40 (br t, *J* = 7 Hz, 0.33H, =CH), 7.20-7.45 (m, 5H, ArH); ^{13}C nmr (Major isomer:*Z*) 21.0 (CH_3), 30.6 (CH_3), 31.9 (*C*-5), 37.4 (*C*-4), 45.8 (CH_2), 52.2 (*C*-2), 53.2 (*C*-6), 60.2 (CH_2OAc), 62.7 (CH_2Ar), 116.4 (=CH), 127.2 (*p*-C), 128.3 and 129.1 (*o*-, *m*-C), 142.0 (*C*-3), 170.5 (COO). HRms Calcd for $C_{19}H_{25}NO_3$ 315.1834, found 315.1834. When the reaction was carried out for 5-6 h, ***t*-4-acetonyl-*r*-3-acetoxy-*N*-benzyl-3-vinylpiperidine (13)** was obtained as an oil in 63 % yield: Ir (film) 1742, 1717, 1368, 1238; ^{1}H nmr 1.25-1.40 (m, 2H, *H*-4 and *H*-5_{ax}), 1.66 (dm, *J* = 13.2, 1H, *H*-5_{eq}), 2.04 (s, 3H, CH_3COO), 2.19 (s, 3H, CH_3), 2.19 (dd, *J* = 16.5, 9 Hz, 1H, CH_2CO), 2.36 (dm, *J* = 12 Hz, 1H, *H*-6_{ax}), 2.39 (d, *J* = 10.2, 1H, *H*-2_{ax}), 2.72 (dd, *J* = 16.5, 3.6 Hz, 1H, CH_2CO), 2.77 (dm, *J* = 12 Hz, 1H, *H*-6_{eq}), 3.45 (d, *J* = 13.5 Hz, 1H, CH_2N), 3.67 (d, *J* = 13.5 Hz, 1H, CH_2N), 3.81 (d, *J* = 10.2 Hz, 1H, *H*-2_{eq}), 5.37 (dd, *J* = 11.4, 1.5 Hz, 1H, H-*trans*), 5.39 (dd, *J* = 17.7, 1.5 Hz, 1H, H-*cis*), 6.26 (dd, *J* = 17.7, 11.4 Hz, 1H, =CH), 7.20-7.40 (m, 5H, ArH); ^{13}C nmr 22.0 (CH_3), 28.4 (*C*-5), 30.5 (CH_3), 40.4 (*C*-4), 43.8 (CH_2), 52.0 (*C*-6), 60.4 (*C*-2), 62.7 (CH_2Ar), 82.4 (*C*-3), 116.0 ($=CH_2$), 127.0 (*p*-C), 128.2 and 128.8 (*o*-, *m*-C), 135.5 (=CH), 138.3 (*ipso*-C), 169.3 (COO), 207.9 (CO).

ACKNOWLEDGMENT

Support for this research was provided by DGICYT (Spain) through Grants PB94-0214 and PB94-0858.

REFERENCES AND NOTES

1. D. Solé, J. Bonjoch, S. García-Rubio, R. Suriol, and J. Bosch, *Tetrahedron Lett.*, 1996, **37**, 5213.
2. J. Bosch, J. Bonjoch, and M. Amat, 'The Alkaloids: *Strychnos* Alkaloids,' Vol. 48, ed. by G. A. Cordell, Academic Press, New York, 1996, pp. 75-189.
3. K. Bojthe-Horvath, A. Kocsis, I. Mathe, J. Tamas, and O. Clauder, *Acta Pharm. Hung.*, 1974, **44**, Suppl., 66 (*Chem. Abstr.*, 1974, **81**, 136347y).
4. C. Djerassi, Y. Nakagawa, J. M. Wilson, H. Budzikiewicz, B. Gilbert, and L. D. Antonaccio, *Experientia*, 1963, **19**, 467.
5. G. Massiot, P. Thépenier, M.-J. Jacquier, J. Lounkokobi, C. Mirand, M. Zèches, L. L. Men-Olivier, and C. Delaude, *Tetrahedron*, 1983, **39**, 3645.
6. For the intramolecular addition of propargylic silanes to enones in the carbocyclic series, see D. Schinzer, *Synthesis*, 1988, 263. For more recent applications, see: D. Schinzer and K. Ringe, *Synlett*, 1994, 463; D. Schinzer, K. Ringe, P. G. Jones, and D. Döring, *Tetrahedron Lett.*, 1995, **36**, 4051.

7. G. Stork and S. M. McElvain, *J. Am. Chem. Soc.*, 1947, **69**, 971.
8. This procedure improves the previously reported preparation of **3** by DIBAH reduction of the methyl ester analogue of **1** : A. Barco, S. Benetti, C. De Risi, G. P. Pollini, R. Romagnoli, G. Spalluto, and V. Zanirato, *Tetrahedron*, 1994, **50**, 2583. See also: A. Barco, S. Benetti, A. Casolari, G. P. Pollini, and G. Spalluto, *Tetrahedron Lett.*, 1990, **31**, 3039.
9. After we had concluded the experimental work, Overman reported an alternative method for the preparation of alcohol (**2**), its oxidation to aldehyde (**3**), and the conversion of the latter to the enone (**4**): M. Lögers, L. E. Overman, and G. S. Welmaker, *J. Am. Chem. Soc.*, 1995, **117**, 9139.
10. The alkylating agent (**6**) was prepared by a modification of a previously reported method,[11] by treatment of 4-trimethylsilyl-2-butyn-1-ol[12] with methyltriphenoxyphosphonium iodide in DMF.
11. W. J. Klaver, M. J. Moolenaar, H. Hiemstra, and W. N. Speckamp, *Tetrahedron*, 1988, **44**, 3805.
12. H. Mastalerz, *J. Org. Chem.*, 1984, **49**, 4092.
13. T. N. Mitchell and U. Schneider, *J. Organomet. Chem.*, 1991, **405**, 195.
14. For a ^{13}C nmr analysis of the stereochemistry of 3-alkylidenepiperidines or analogues, see: G. Van Binst and D. Tourwé, *Org. Magn. Reson.*, 1972, **4**, 625; M. R. Uskokovic, R. L. Lewis, J. J. Partridge, C. W. Despreaux, and D. L. Pruess, *J. Am. Chem. Soc.*, 1979, **101**, 6742; M.-L. Bennasar and J. Bosch, *Tetrahedron*, 1986, **42**, 637.
15. For a ^{1}H nmr analysis of the stereochemistry of 3-alkylidenepiperidines or analogues, see: W. R. Ashcroft and J. A. Joule, *Tetrahedron Lett.*, 1980, **21**, 2341; J. C. Nouls, G. Van Binst, and R. H. Martin, *Tetrahedron Lett.*, 1967, 4065.
16. For a similar conformational effect, see: I. Ninomiya, T. Naito, O. Miyata, T. Shinada, E. Winterfeldt, R. Freund, and T. Ishida, *Heterocycles*, 1990, **30**, 1031.
17. J. A. Verdone, J. A. Mangravite, N. M. Scarpa, and H. G. Kuivila, *J. Am. Chem. Soc.*, 1975, **97**, 843
18. The downfield shift of this proton in piperidines with an axial 3-vinyl substituent has previously been observed in the meroquinene series: S. Hanessian, A.-M. Faucher, and S. Léger, *Tetrahedron*, 1990, **46**, 231; B. Danieli, G. Lesma, M. Mauro, G. Palmisano, and D. Passarella, *Tetrahedron: Asymmetry*, 1990, **1**, 793.
19. S. Hanessian and R. Léger, *Synlett*, 1992, 402.
20. M. Yamamoto, S. Irie, M. Miyashita, S. Kohmoto, and K. Yamada, *Chem. Lett.*, 1989, 221; S. Kim and P. L. Fuchs, *J. Am. Chem. Soc.*, 1993, **115**, 5934.
21. Y. Ueno, H. Sano, and M. Okawara, *Synthesis*, 1980, 1011.
22. M. Ferrer, F. Sánchez-Baeza, A. Messeguer, A. Diez, and M. Rubiralta, *J. Chem. Soc., Chem. Commun.*, 1995, 293.
23. Initial attempts to obtain allylic alcohol (**12**) by hydroboration of allene (**8**) with 9-BBN were abandoned because of the reduction of the carbonyl group.
24. J. H. Babler and D. O. Olsen, *Tetrahedron Lett.*, 1974, 351.
25. For the isomerization of Z/E isomers in the *Strychnos* field, see: M. E. Kuehne and F. Xu, *J. Org. Chem.*, 1993, **58**, 7490.
26. This acetate (**13**) was the sole compound isolated together with the starting alcohol, when the acetylation was carried out under basic conditions (AcCl, pyridine).

Received, 24th June, 1996