Partial Synthesis and the Absolute Configuration of Two New *Gelsemium* Alkaloids, Koumidine and (19*Z*)-Taberpsychine

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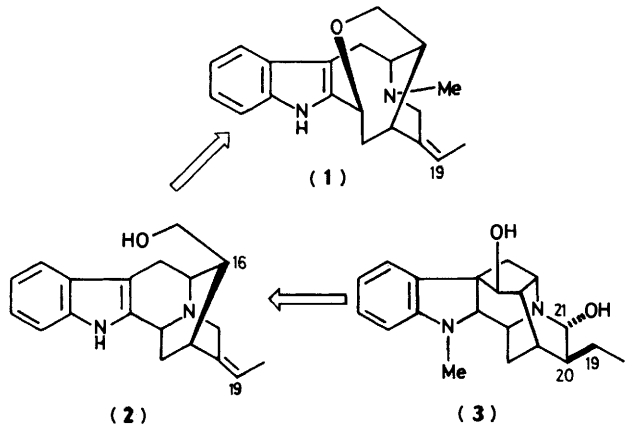
The stereoselective transformation of ajmaline (**3**) into a new *Gelsemium* alkaloid, (19*Z*)-taberpsychine (**1**), *via* koumidine (**2**) is described.

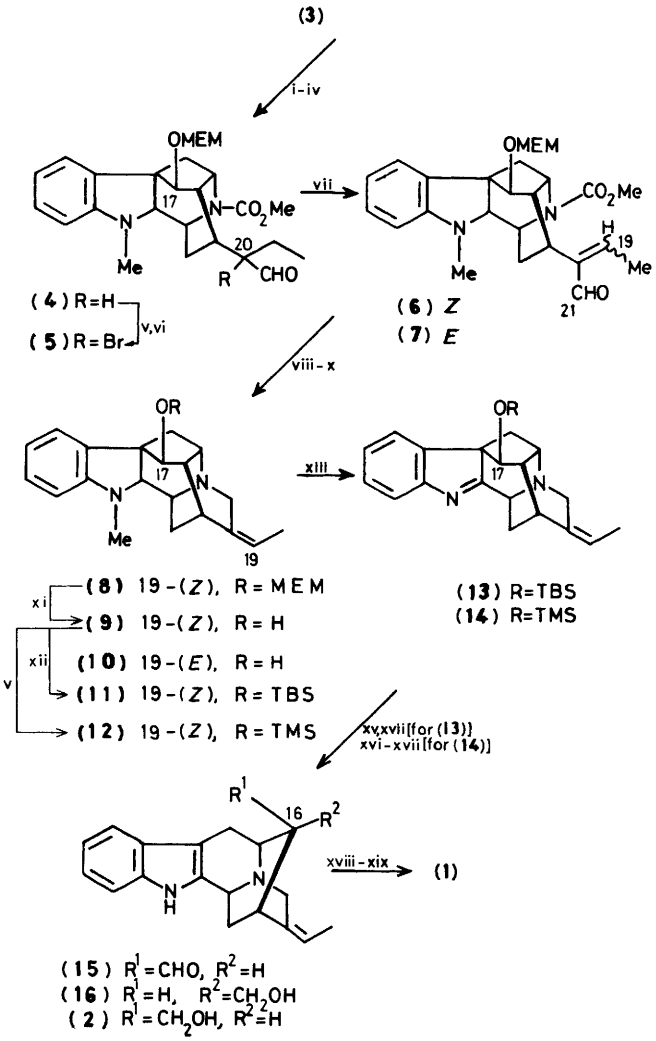
Recently we elucidated the structure of a minor *Gelsemium* alkaloid, (19*Z*)-taberpsychine (**1**) and revised the structure of koumidine (**2**) by spectroscopic analysis.[1] These alkaloids possess an unusual (19*Z*) ethylidene side chain compared with that of the conventional sarpagine class of indole alkaloids.[2] In order both to provide support for the spectroscopic assignments and to determine the absolute configurations of these compounds we have synthesized them from ajmaline (**3**)[3] (Scheme 1). The transformation involves mainly two



Scheme 1.

structural changes of the starting material (**3**): (i) stereoselective introduction of a 19,20 double bond and (ii) an indoline to indole transformation without epimerization at C-16.

In order to liberate the masked aldehyde (C-21) from the amino acetal function and to protect the N_b group as carbamate, ajmaline (**3**) was successively treated with *N,N*-dimethylhydrazine and a catalytic amount of H_2SO_4, methyl chloroformate in 1M NaOH–CH_2Cl_2, and then $CuCl_2$ in aqueous THF (pH 7)[4] to afford the aldehyde (**4**) in 60% overall yield (Scheme 2). Attempts at the direct conversion of (**3**) into (**4**) by the reaction with chloroformates gave the carbonate (21-OCO_2R) derivatives. After the protection of the 17-hydroxy group as a methoxyethoxymethyl (MEM) ether, bromine was introduced at the 20 position *via* the t-butyldimethylsilyl (TBS) enol ether. Treatment of (**5**) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMF gave the desired (19*Z*) olefin (**6**) in 60% yield, selectively [(**6**):(**7**) = 5:1]. The geometry of the olefins (**6**) and (**7**) was unambiguously determined by n.O.e. experiments.† The major α,β-unsaturated aldehyde (**6**) was reduced with $NaBH_4$ and then ring closure between C-21 and N_b was



Scheme 2. *Reagents and conditions:* i, *N,N*-Dimethylhydrazine, cat. H_2SO_4, 3A molecular sieves, dry EtOH, reflux, 5 h; ii, methyl chloroformate, 1M NaOH, CH_2Cl_2, 0 °C, 40 min., 79% from (**3**); iii, $CuCl_2$, THF–H_2O, phosphate buffer, r.t., overnight, 75%; iv, MEM chloride, di-isopropyl(ethyl)amine, dry CH_2Cl_2, reflux, 4.5 h, 81%; v, TBS–trifluoromethanesulphonate, Et_3N, dry CH_2Cl_2, 0 °C, 2.5 h, 71%; vi, *N*-bromosuccinimide, dry THF, −15 °C, 30 min, 76%; vii, DBU, dry DMF, r.t. overnight, (**6**) 60%, (**7**) 12%; viii, $NaBH_4$, MeOH, r.t., 88%; ix, NaOH, ethylene glycol, H_2O, reflux, 1 h, 87%; x, methanesulphonylchloride, pyridine, r.t., 30 min, 62%; xi, conc. HCl, MeOH, reflux, 5 h, 95%; xii, TBS–trifluoromethanesulphonate, Et_3N, dry CH_2Cl_2, 0 °C, 1 h, 80%; xiii, $Pb(OAc)_4$, dry CH_2Cl_2, −70 °C to minus 10 °C, (**13**) 59%, (**14**) 48% from (**9**) *via* (**12**); xiv, TMS–trifluoromethanesulphonate, Et_3N, dry CH_2Cl_2, 0 °C; xv, Bu_4NF, THF, r.t. 15 min; xvi, AcOH–THF–H_2O (3:1:1), r.t., 30 min; xvii, $NaBH_4$, MeOH, r.t. 30 min, (**16**) 60% from (**13**), (**2**) 70% from (**14**); xviii, methyl chloroformate, MgO, THF–H_2O, r.t., 1.5 h; xix, $LiAlH_4$, THF, r.t., 1.5 h, 30% from (**2**)

† Irradiation of the 18-methyl protons (δ 2.14) in (**6**) led to enhancement (17%) of the C-21 aldehyde proton (δ 10.2), while 25% enhancement was observed between the C-19 olefinic proton (δ 6.50) and C-21 aldehyde proton (δ 9.33) in (**7**).

performed by successive treatment of the resulting alcohol with NaOH in aqueous ethylene glycol and methanesulphonyl chloride in pyridine to afford the deoxyajmaline derivative (**8**). A similar sequential reduction (removal of the protective group in N_b, ring closure, and deprotection of the 17-hydroxy group), of the minor *E* olefin (**7**) gave tetraphyllicine (**10**).[5,*]

The indoline to indole transformation for (**13**) was accomplished by deprotection of the 17-hydroxy group. In order to prevent epimerization at C-16 during this process, mild removal of the protective group was required. Since the MEM ether utilized in earlier stages in this transformation could not be cleanly removed by the reported procedure,[6] we substituted the MEM group with TBS ether. We then prepared the indolenine (**13**) by lead tetra-acetate oxidation[7] of (**11**). After deprotection of the TBS ether in (**13**) by the use of tetrabutylammonium fluoride in THF at room temperature, the resulting aldehyde (**15**) was immediately reduced with $NaBH_4$ in MeOH to afford, however, surprisingly 16-*epi*-koumidine (**16**) [(19*Z*)-normacusine B, m.p. 169—173 °C] as the sole product. The same result was obtained by use of AcOH–THF–H_2O (at 70 °C) for the deprotection of TBS group instead of F^-. The epimerization at C-16 could be prevented by use of the trimethylsilyl (TMS) group in place of the TBS ether. Thus, the indolenine (**14**), which was unstable both to work-up in the customary manner and column chromatography, was treated with AcOH–THF–H_2O (at room temp.) and then reduced with $NaBH_4$ in MeOH to yield koumidine (**2**), $[\alpha]_D^{23}$ −23.8° (*c* 0.6, MeOH), in 70% overall yield form (**14**). The ^1H n.m.r., i.r., and mass spectra and m.p. (202—204 °C) were identical with those of natural koumidine (**2**), $[\alpha]_D^{20}$ −20.8° (*c* 1.8, MeOH).

Koumidine (**2**) was treated with methyl chloroformate in THF–H_2O in the presence of MgO and the resulting carbamate was reduced with lithium aluminium hydride to furnish (19*Z*)-taberpsychine (**1**), $[\alpha]_D^{23}$ −151° (*c* 0.3, $CHCl_3$), in 30% overall yield from (**2**). The synthetic compound exhibited spectral properties (^1H n.m.r., i.r., u.v., and mass) in accord with those of an authentic sample, $[\alpha]_D^{23}$ −180° (*c* 0.4, $CHCl_3$).

* Direct comparison of synthetic (**10**), m.p. 294—296 °C, $[\alpha]_D^{16}$ + 16° (*c* 0.4, pyridine), with the authentic sample sent by Prof. P. J. Scheuer, established the identity in all respects (t.l.c., mixed m.p., and i.r., ^1H n.m.r., and mass spectra).

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