Synthesis of (−)-Ajmalicine from (−)-Tryptophan

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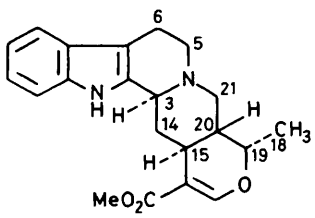
(−)-Tryptophan has been converted into (−)-ajmalicine in 15 steps; the key step is an intramolecular Michael reaction in which the C(15)–C(20) bond is formed with full stereocontrol.

Ajmalicine (**1**) (raubasine) is the only member of the heteroyohimbine family used in therapeutics and is mainly prescribed in the treatment of cardiovascular diseases. Although (±)-(**1**) was synthesised as early as 1961,[1] to the best of our knowledge, only partial synthetic routes to (−)-(**1**) from elenolic acid,[2] from tetrahydroalstonine,[3] and from corynantheine[4] *inter alia*, have been reported. Other relevant work in the asymmetric synthesis of heteroyohimbines has been done by Uskokovic *et al.*[5] and Khuong-Huu *et al.*[6] Based on our synthetic approach to optically active tetrahydro-β-carbolines from (−)-tryptophan,[7] we herein describe a stereocontrolled synthesis of (−)-(**1**).

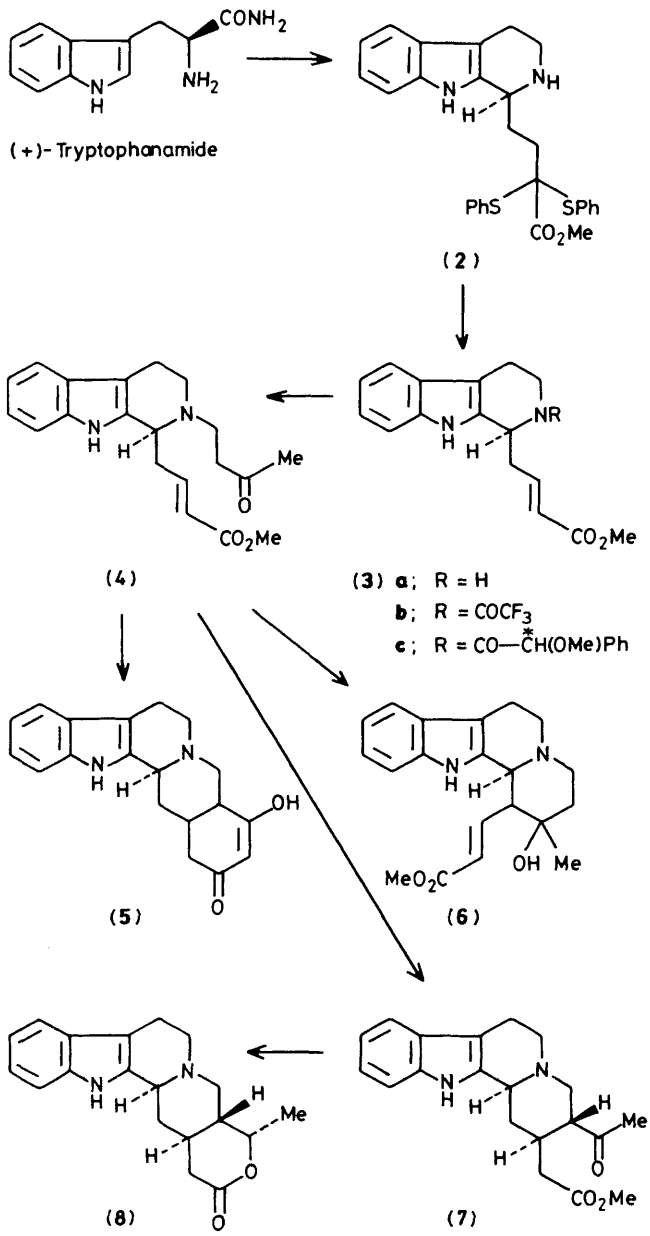
The α,α′-bis(phenylthio)ester (**2**), which is available in optically pure form from (+)-tryptophanamide,[7] is converted into the unsaturated ester (**3a**) {$[\alpha]_D$ −27° (*c* 1, $CHCl_3$)} by means of a reductive desulphenylation[8] followed by a sulphoxide elimination. Transient protection of the basic nitrogen atom as the trifluoroacetamide (**3b**) proved necessary to avoid lactamisation; deprotection was achieved by $NaBH_4$ reduction. Preparation of a single methoxymandelamide (**3c**) from



(**1**) Ajmalicine

(**3a**) and (+)-methoxymandelic acid showed that no racemisation had occurred during the process [(**3c**), ^1H n.m.r. δ 5.12 (s, 1H) and 3.51 (s, 3H)]. Addition of methyl vinyl ketone to (**3a**) yielded (**4**) {98%, $[\alpha]_D^{21}$ −11° (*c* 0.5, $CHCl_3$)} which contained all but one of the carbon atoms in the skeleton of (**1**).

Whereas compounds (**5**) and (**6**) of undetermined configurations were obtained under strongly basic conditions [for (**5**): NaH, tetrahydrofuran (THF); MeONa, MeOH; (**6**):



Triton B, dimethoxyethane], addition of pyrrolidine to a THF solution of (**4**) led to a smooth cyclisation to (**7**) {85%, $[\alpha]_D$ −16° (*c* 0.5, $CHCl_3$)}. The purity of (**7**) was checked by ^{13}C n.m.r. spectroscopy and the configuration of its three asymmetric centres was shown by 400 MHz ^1H n.m.r. spectroscopy[9] to be 3*S*, 15*S*, 20*S* and confirmed by its conversion into (−)-(**1**). The first step in producing the fourth asymmetric centre in (**1**) was $NaBH_4$ reduction of (**7**) to lactone (**8**), in accordance with the method of Winterfeldt *et al.*[10] Lactone (**8**) was, in all respects, identical to an authentic sample obtained by the Siphar process[3] {$[\alpha]_D^{21}$ −120° (*c* 0.5, pyridine), m.p. 262 °C (decomp.), no depression of m.p. in test mixed m.p.}. Conversion of (**8**) into (**1**)† was uneventfully accomplished by a previously published route.[1] The synthetic material could not be distinguished from a sample of natural (−)-(**1**) {identical R_f in t.l.c., m.p., $[\alpha]_D$, and i.r. and high field ^1H n.m.r. spectra}. The overall yield of lactone (**8**) from tryptophan was 7.5%; conversion of lactone (**8**) into (−)-ajmalicine was accomplished in *ca.* 50% yield.

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† Synthetic (**1**) had m.p. 252—253 °C (MeOH) and $[\alpha]_D$ −44° (*c* 0.3, $CHCl_3$).