# Stereo-controlled Synthesis of (−)-Ajmalicine and (−)-Tetrahydroalstonine

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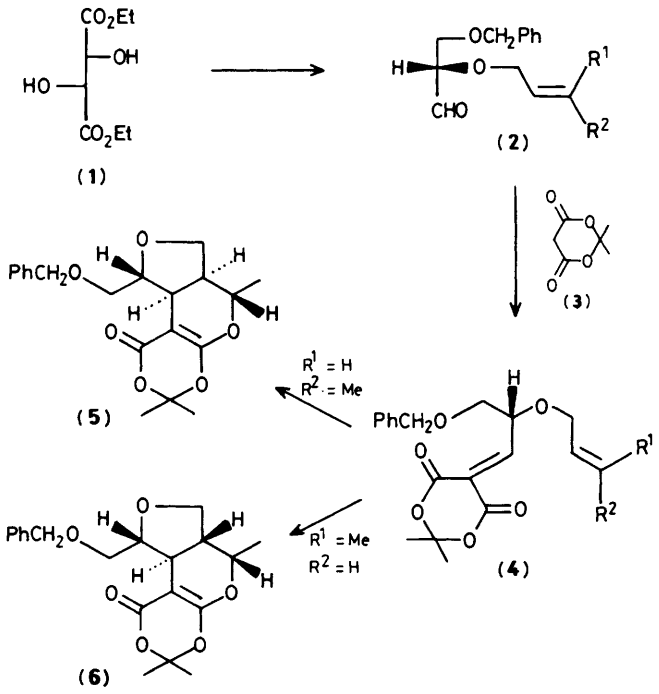
Stereo-controlled synthesis of the heteroyohimbine alkaloids, (−)-ajmalicine and (−)-tetrahydroalstonine, has been developed starting from diethyl L-tartrate by employing the intramolecular hetero-Diels–Alder reaction as the key step.

Recently we discovered a highly diastereoselective intramolecular hetero-Diels–Alder reaction[1] which selectively furnishes either of the *cis*- or *trans*-ring fused adducts [(**5**) or (**6**)] by controlling the configuration of the dienophile alkene: the *E*-alkene (**2a**) yields the *cis*-ring fused adduct (**5**) and the Z-alkene (**2b**) yields the *trans*-ring fused adduct (**6**) on reaction with Meldrum's acid (**3**). These products have retained the chirality of the starting material (**1**) *via* the transient heterodiene intermediates (**4a** and **b**) (Scheme 1). We report here the synthesis of two heteroyohimbine, alkaloids (−)-tetrahydroalstonine and (−)-ajmalicine, which possess *cis*- and *trans*-fused D/E ring systems respectively, from the single adduct (**5**) obtained from diethyl L-tartrate (**1**).

Compound (**5**)[1] obtained from diethyl L-tartrate (**1**) as shown in Scheme 2, was refluxed with methanol[2] to give the methyl ester (**9**)† in 50% overall yield from (**8**). On partial reduction using lithium triethylborohydride, followed by dehydration with toluene-*p*-sulphonic acid, (**9**) yielded the acrylate (**11**) in 80% overall yield *via* the lactol (**10**).‡

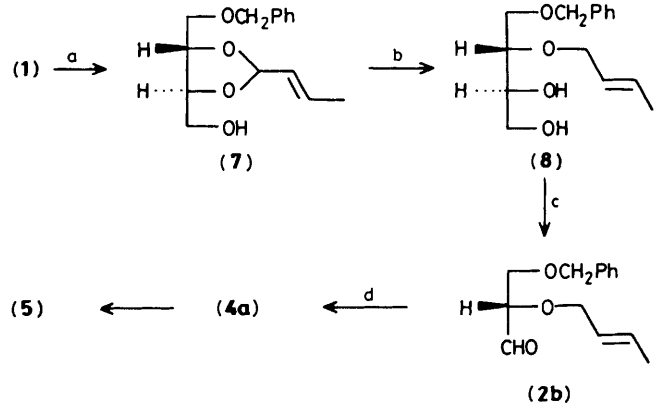



**a**; $R^1 = H, R^2 = Me$
**b**; $R^1 = Me, R^2 = H$

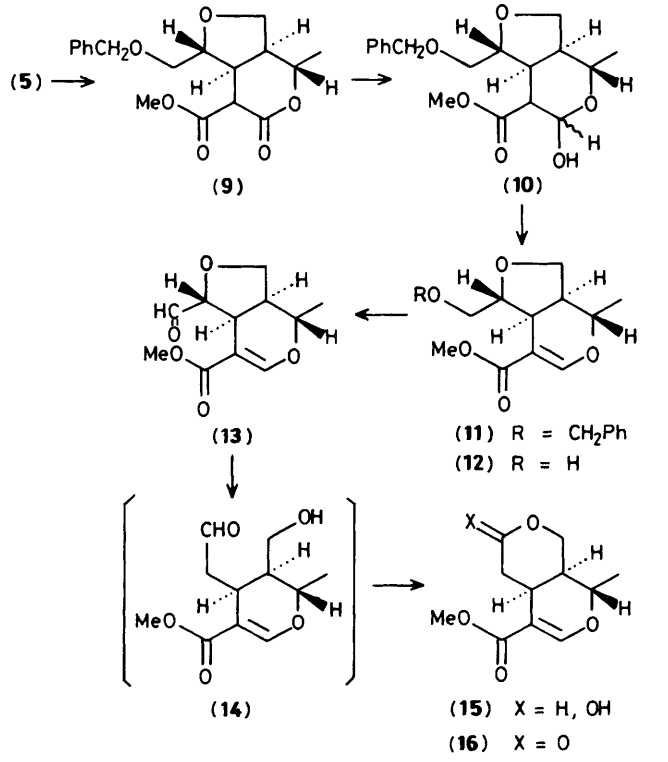
**Scheme 1**

† Satisfactory spectral (i.r., $^1H$ n.m.r., m.s.) and analytical (combustion and/or high resolution mass spectral) data were obtained for all new isolable compounds.

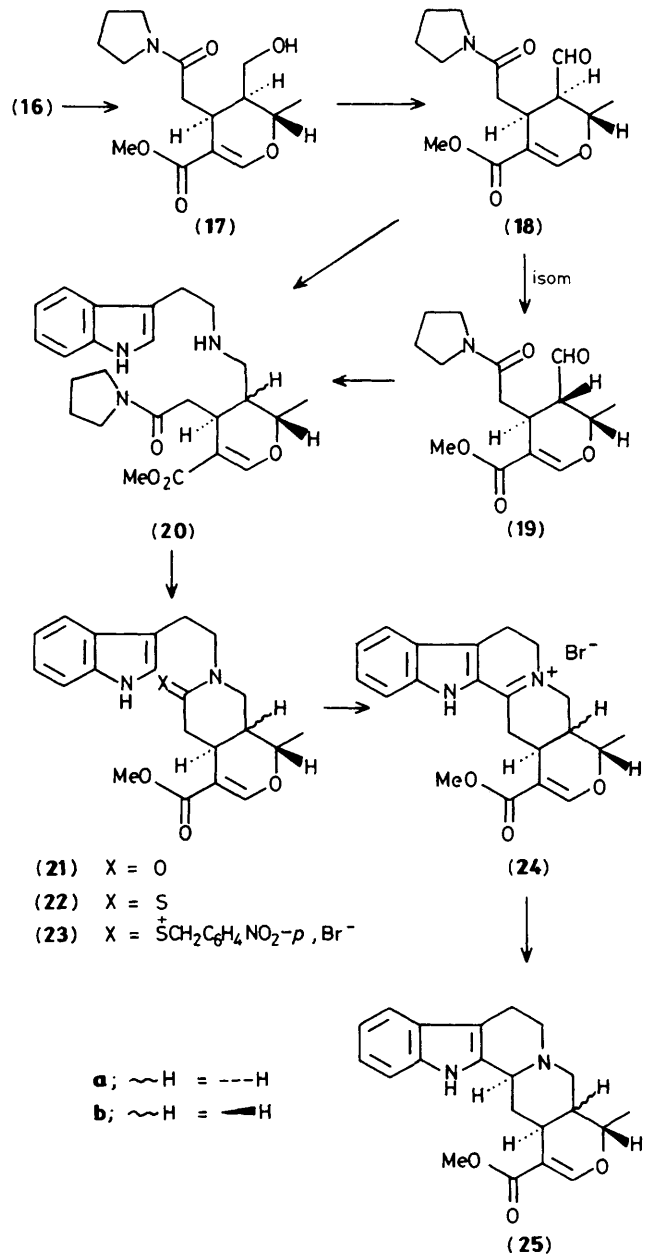
‡ Conversion of (**9**) to (**10**) was accompanied by recovery of (**9**) (*ca.* 65%) which was easily separable and recycled.




**Scheme 2.** *Reagents and conditions*: (a) i, *E*-MeCH=CHCH(OEt)$_2$, PPTS, benzene, reflux; ii, $NaBH_4$, MeOH, 0 °C; iii, $PhCH_2Br$, NaH, THF–DMF, −20 to 0 °C; (b) DIBAL, toluene, 0 °C; (c) $NaIO_4$, aq. MeOH, 0 °C to r.t.; (d) Meldrum's acid (**3**), $(CH_2NH_3)_2(AcO^-)_2$ (cat.), MeOH, 0 °C to r.t. PPTS = Pyridinium toluene-*p*-sulphonate, THF = tetrahydrofuran, DMF = dimethylformamide, DIBAL = di-isobutylaluminium hydride.




**Scheme 3**




Scheme 4

Debenzylation of (**11**) followed by Swern oxidation[3] of the resulting alcohol (**12**) yielded the aldehyde (**13**). Treatment of (**13**) with zinc in tetrahydrofuran (THF), containing a catalytic amount of hydrochloric acid, allowed smooth cleavage of the ether bond to give the seco-aldehyde (**14**), isolated as the lactol (**15**). Compound (**15**) was then converted into the δ-lactone (**16**) by oxidation with silver carbonate on Celite[4] (Fetizon reagent). Overall yield of (**16**) from (**11**) was 82%.

In order to introduce the tryptamine moiety into the required site (**16**) was treated with dimethylaluminium pyrrolidinide[5] in benzene (0 °C to room temperature) to give the tertiary amide (**17**) in 98% yield. The primary hydroxy group of (**17**) was then oxidized under Swern conditions to give the aldehyde (**18**) which was immediately condensed with tryptamine perchlorate in the presence of sodium cyanoborohydride to give the secondary amine (**20a**). Refluxing (**20a**) in toluene in the presence of di-isopropylethylamine and pyridine afforded the *cis*-δ-lactam (**21a**) in 54% overall yield from (**17**). Also, the same aldehyde (**18**) was stirred with silica gel in methylene chloride at room temperature (*ca.* 12 h) to give rise to the epimer (**19**) by facile isomerization. Compound (**19**), on reductive condensation with tryptamine perchlorate, followed by lactamization as above, gave the *trans*-δ-lactam (**21b**) in 30% overall yield from (**17**).

Cyclization of the lactams (**21a** and **b**) could be efficiently achieved *via* thioamide intermediates using the method of Ishida and co-workers.[6] Reaction of the lactams (**21a** and **b**) with Lawesson's reagent[7] in benzene yielded the corresponding thio-lactams (**22a** and **b**). Treatment of (**22a** and **b**) with *p*-nitrobenzyl bromide in acetonitrile (*ca.* 60 °C) yielded the crude salts (**24a** and **b**) *via* the intermediates (**23**). Addition of $NaBH_4$ in methanol (−50 °C) afforded the amines (**25a** and **b**); the *cis*-lactam (**21a**) afforded (−)-tetrahydroalstonine[8–10] (**25a**), m.p. 229—231 °C, $[\alpha]_D^{27}$ −122.0° (*c* 0.28, $CHCl_3$), {lit.[9] m.p. 221—223 °C; $[\alpha]_D^{27}$ −110° (*c* 0.5, $CHCl_3$)} and the *trans*-lactam (**21b**) afforded (−)-ajmalicine (**25b**), m.p. 257.5—258.5 °C, $[\alpha]_D^{27}$ −44.0° (*c* 0.2, MeOH) {lit.[11b] m.p. 257—258 °C, $[\alpha]_D^{27}$ −40.2° (MeOH)} in overall yields of *ca.* 100 and 68%, respectively.

We thank Professors S. Sakai and N. Aimi, Faculty of Pharmaceutical Sciences, Chiba University, for providing us with an authentic sample of (−)-tetrahydroalstonine.

*Received, 14th September 1987; Com. 1324*

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