

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

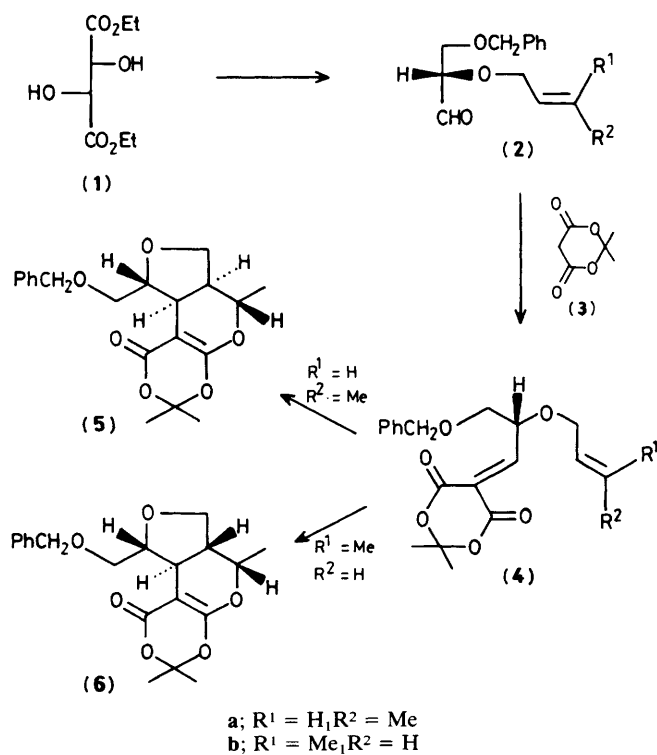
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Stereo-controlled synthesis of the heteroyohimbine alkaloids, (–)-ajmalicine and (–)-tetrahydroalstonine, has been developed starting from diethyl L-tartrate by employing the intramolecular hetero-Diels–Alder reaction as the key step.

Recently we discovered a highly diastereoselective intramolecular hetero-Diels–Alder reaction<sup>1</sup> 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).

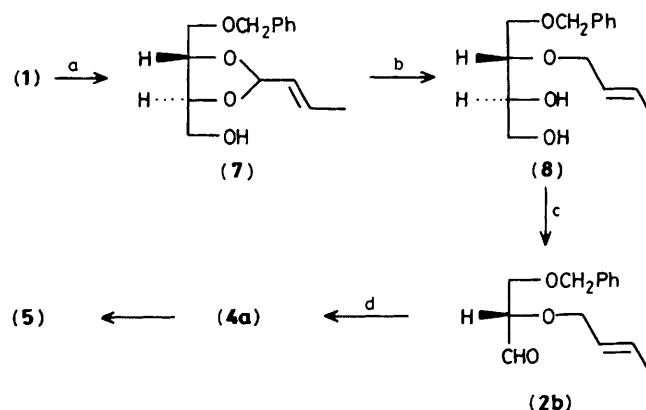
Compound (5)<sup>1</sup> obtained from diethyl L-tartrate (1) as shown in Scheme 2, was refluxed with methanol<sup>2</sup> to give the methyl ester (9)<sup>†</sup> in 50% overall yield from (8). On partial reduction using lithium triethylborohydride, followed by dehydration with toluene-*p*-sulphonic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



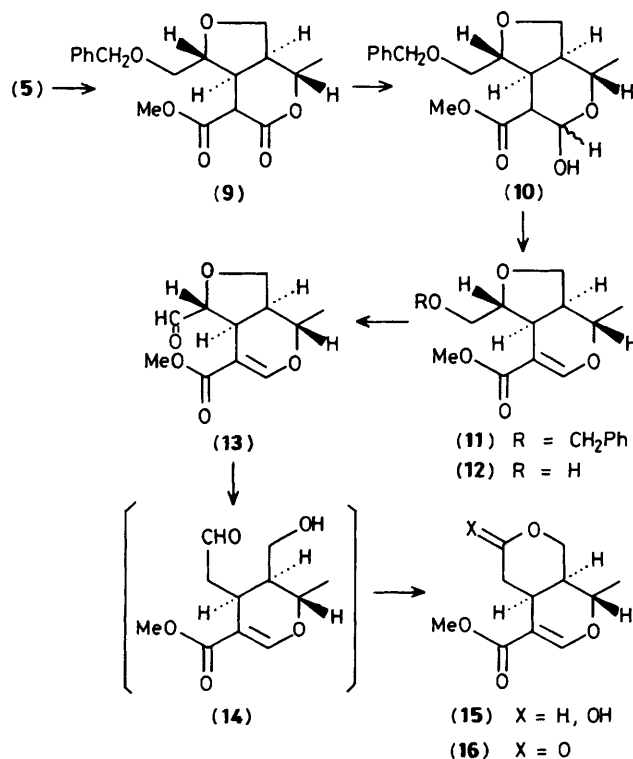
Scheme 1

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

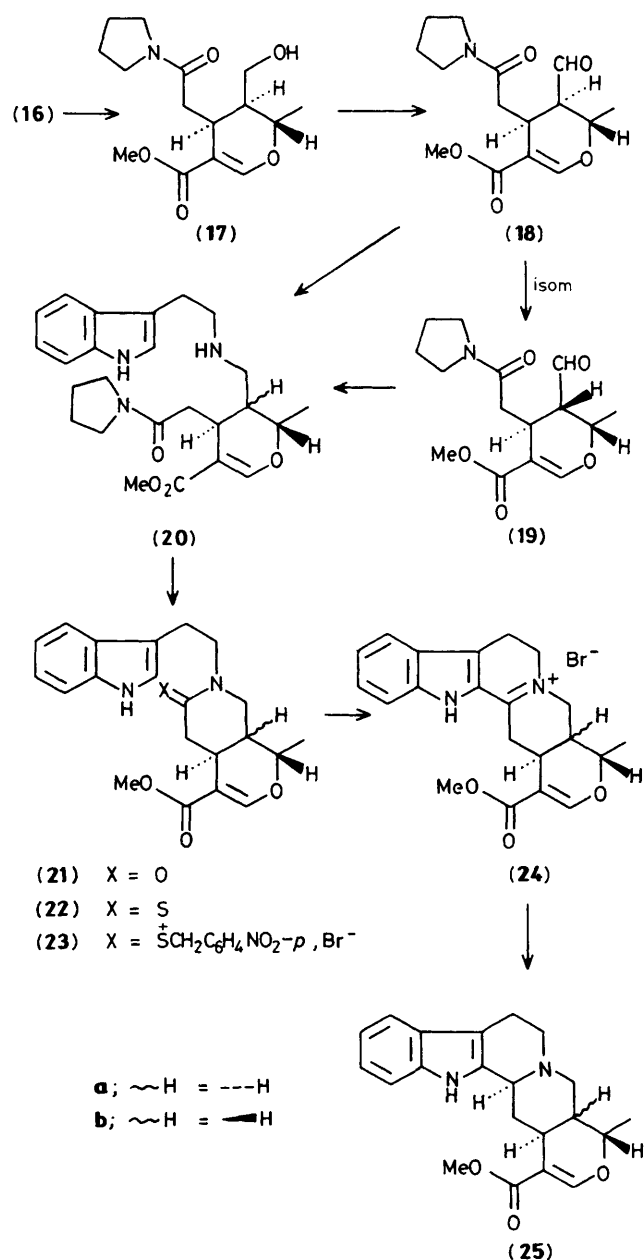
<sup>‡</sup> Conversion of (9) to (10) was accompanied by recovery of (9) (ca. 65%) which was easily separable and recycled.



**Scheme 2. Reagents and conditions:** (a) i, *E*-MeCH=CHCH(OEt)<sub>2</sub>, PPTS, benzene, reflux; ii, NaBH<sub>4</sub>, MeOH, 0°C; iii, PhCH<sub>2</sub>Br, NaH, THF–DMF, –20 to 0°C; (b) DIBAL, toluene, 0°C; (c) NaIO<sub>4</sub>, aq. MeOH, 0°C to r.t.; (d) Meldrum's acid (3), (CH<sub>2</sub>NH<sub>3</sub>)<sub>2</sub>(AcO<sup>–</sup>)<sub>2</sub> (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<sup>3</sup> 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  $\delta$ -lactone (16) by oxidation with silver carbonate on Celite<sup>4</sup> (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<sup>5</sup> 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*- $\delta$ -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*- $\delta$ -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.<sup>6</sup> Reaction of the lactams (21a and b) with Lawesson's reagent<sup>7</sup> 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<sub>4</sub> in methanol (−50°C) afforded the amines (25a and b); the *cis*-lactam (21a) afforded (−)-tetrahydroalstonine<sup>8–10</sup> (25a), m.p. 229–231°C, [ $\alpha$ ]<sub>D</sub><sup>27</sup> −122.0° (*c* 0.28, CHCl<sub>3</sub>), {lit.<sup>9</sup> m.p. 221–223°C; [ $\alpha$ ]<sub>D</sub><sup>27</sup> −110° (*c* 0.5, CHCl<sub>3</sub>)}. The *trans*-lactam (21b) afforded (−)-ajmalicine (25b), m.p. 257.5–258.5°C, [ $\alpha$ ]<sub>D</sub><sup>27</sup> −44.0° (*c* 0.2, MeOH) {lit.<sup>11b</sup> m.p. 257–258°C, [ $\alpha$ ]<sub>D</sub><sup>27</sup> −40.2° (MeOH)} in overall yields of *ca.* 100 and 68%, respectively.

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