Enantioselective Synthesis of an Ant Venom Alkaloid (−)-[3*S*-(3β, 5β, 8α)]-3-Heptyl-5-methylpyrrolizidine

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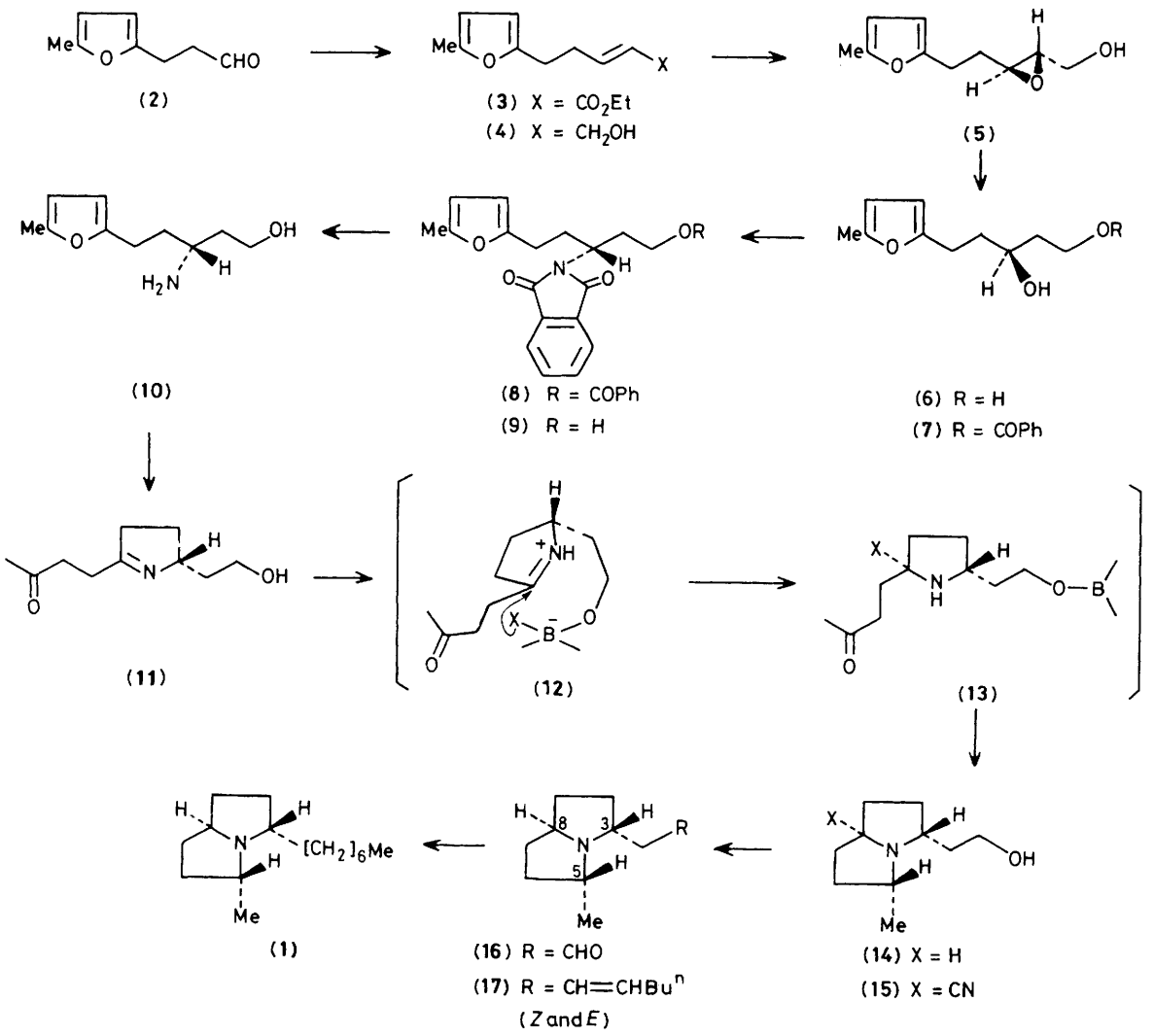
An ant venom alkaloid (−)-[3*S*-(3β, 5β, 8α)]-3-heptyl-5-methylpyrrolizidine (**1**) has been synthesized in an enantioselective fashion from 3-(5-methyl-2-furyl)propionaldehyde (**2**) employing enantioselective epoxidation at the key stage.

Various alkyl-substituted piperidines and pyrrolidines have been reported as venomous constituents from ant species in the related genera *Monomorium* and *Solenopsis*.[1] Although the relative configurations of these compounds have been determined by racemic syntheses, their absolute configurations have not yet been established to date probably owing



to the limited amounts of natural materials available. We report here the first enantioselective synthesis of [3*S*-(3β, 5β, 8α)]-3-heptyl-5-methylpyrrolizidine (**1**) which is the only known bicyclic alkaloid from *Solenopsis* species as well as the first 3,5-dialkylpyrrolizidine derivative from a natural source.[2]

Horner–Emmons reaction of 3-(5-methyl-2-furyl)propionaldehyde (**2**)[3] with triethyl phosphonoacetate[4] (NaH, tetrahydrofuran–dimethylformamide, THF–DMF) gave the unsaturated ester (**3**)† in 96% yield which was then reduced with di-isobutylaluminium hydride to give the allylic alcohol (**4**) in 90% yield. Oxidation of (**4**) with t-butyl hydroperoxide in the presence of titanium isopropoxide and (+)-diethyl L-tartrate[5] gave the chiral epoxide (**5**), $[\alpha]_D$ −35.23° (*c* 1.02, $CHCl_3$) in 92% yield. Regioselective cleavage of the epoxide (**5**) was effected by bis-(2-methoxyethoxy)aluminium hydride[6] (THF, 0 °C) to give the 1,3-diol (**6**), $[\alpha]_D$ −16.76° (*c* 1.04, $CHCl_3$), in 93% yield. Treatment of (**6**) with 1 mol. equiv. of benzoyl chloride (Et_3N, 0 °C) produced the primary benzoate (**7**), $[\alpha]_D$ −5.15° (*c* 1.05, $CHCl_3$) in 65% yield, the secondary hydroxy group of which was then substituted by phthalimide with inversion of the configuration to give (**8**), $[\alpha]_D$ −57.39° (*c* 0.93, $CHCl_3$) in 82% yield, by employing Mitsunobu's conditions.[7] Following debenzoylation (K_2CO_3, MeOH, room temp.) and then treatment with hydrazine hydrate (EtOH, reflux), (**9**) afforded the amino-alcohol (**10**), $[\alpha]_D$ +1.14° (*c* 0.874, $CHCl_3$), in 72% overall yield from (**8**), $[\alpha]_D$ −16.6° (*c* 1.06, $CHCl_3$). Under normal conditions[8] (**10**) could not be hydrolysed cleanly, but it gave the pyrroline derivative (**11**) on treatment with a small molar excess of perchloric acid in water (pH *ca.* 1) at 90 °C. Reduction of the crude pyrrolinium perchlorate of (**11**) with sodium cyanoborohydride[9] in THF–methanol (15:1) at pH 4 adjusted by addition of 20% acetic acid, afforded a mixture (*ca.* 1:1) of pyrrolizidines (**14**), $[\alpha]_D$ −34.09° (*c* 0.26, $CHCl_3$), and (**15**) in 57% overall yield from (**10**), which could be separated by column chromatography (Al_2O_3). Since no detectable amount of isomers of either product could be isolated, we conclude that the reaction proceeded in a highly stereoselective fashion. Upon treatment with sodium borohydride in ethanol[10] (36 °C) or sodium in liquid ammonia in the presence of ethanol, the nitrile (**15**) could be converted into (**14**) in virtually quantitative yield. Compounds (**14**) and (**15**) show no Bohlmann bands in their i.r. spectra and their ^1H n.m.r. spectra exhibit single-proton multiplets at δ 2.67, 3.15, and 3.67 and at δ 2.83 and 3.13 for (**14**) and (**15**), respectively, which are characteristic of *cis*-fused pyrrolizidines with the 3- and 5-H *trans* to the nitrogen lone pair.[11,12] Interestingly, the observed stereochemical out-

† All new compounds exhibited satisfactory analytical (combustion and/or high resolution mass spectrum) and spectral (i.r., ^1H n.m.r., and mass) data.

come was in disagreement with a reported observation on a related compound which lacked a hydroxy group.[13] This difference may be attributed to the participation of the hydroxy group which directs delivery of hydride ion or cyanide ion from the *si*-face of the imino group by forming a boronate complex (**12**) to give the *trans*-2,5-dialkyl pyrrolidine (**13**) selectively at the first stage of the reaction.

Oxidation of the amino-alcohol (**14**) under Moffatt–Swern conditions[14] yielded the unstable amino-aldehyde (**16**) which was converted into the desired pyrrolizidine (**1**), $[\alpha]_D$ −6.25° (*c* 0.16, $CHCl_3$), in 28% overall yield, *via* a *Z*/*E* mixture of the olefin (**17**), by Wittig condensation with n-pentylidenetriphenylphosphorane, followed by catalytic hydrogenation on platinum. The i.r., ^1H n.m.r., and mass spectra of the synthetic material (**1**) were identical with those reported for the natural product.[2]

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