Synthesis of 4*RS*,6*S*,7*S*-Serricornine and the Corresponding Pair of Racemates

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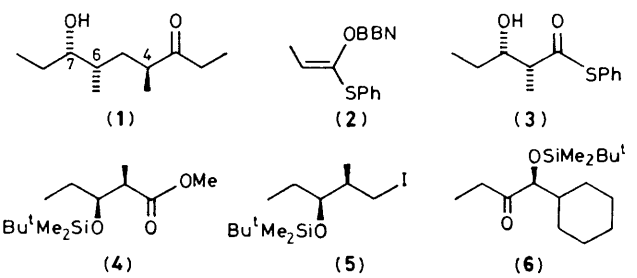
Directed aldol condensations utilising boron enolates (**2**) and (**7**) allowed the stereospecific synthesis of the racemic thioester (**3**) and the chiral ester (**4**) in high yield; these were converted by standard methodology into the title compounds.

Serricornine (**1**) is a sex pheromone produced by the female cigarette beetle, *Lasioderma serricorne* F, which is a major pest of cured tobacco leaves.[1] The structure of this molecule has been assigned as 4*S*,6*S*,7*S* by a lengthy synthesis of the natural pheromone and several of its diastereomers.[2,3] An enantioselective synthesis of 4*RS*,6*S*,7*S* serricornine with an optical purity of >85%, based on reduction of a β-ketoester derivative by a yeast has recently been reported.[4] Since it has been demonstrated that natural serricornine is readily epimerised at C-4 our objective was a synthesis of 4*RS*,6*S*,7*S* serricornine.[2] Here we report a diastereospecific synthesis which affords the title compound with an optical purity of >100:1. The same method was initially used to prepare the racemate of this material.†

The *erythro* disposition of the methyl and hydroxy-groups at C-6 and C-7 of the pheromone suggested that this unit



(**1**) (**2**) (**3**)

(**4**) (**5**) (**6**)

BBN = 9-Borabicyclo[3.3.1]nonan-9-yl.

could be obtained by a kinetically controlled aldol condensation. It has been shown that the 9-borabicyclo[3.3.1]nonane enolate (**2**) derived from *S*-phenyl propanethioate reacts with aldehydes to yield the *erythro* aldol product with a diastereoselectivity of >97:3.[5] Reaction of this enolate with propionaldehyde followed by oxidative work-up and silica column chromatography gave the *erythro* isomer (**3**) in 70% yield. The stereochemical purity of this material was evident from

† Diastereomeric purity was determined by ^{1}H and ^{13}C n.m.r. spectroscopy. Enantiomeric excess was estimated by optical rotation measurement and n.m.r. spectroscopy in the presence of a chiral shift reagent.

its ^{13}C n.m.r. and ^{1}H n.m.r. spectra. Transesterification ($MeOH$–$HgCl_2$) and protection (t-butyldimethylsilyl chloride–*N*,*N*-dimethylformamide–imidazole) yielded the racemic protected ester (**4**). The ester was converted into the required iodide (**5**) by reduction (di-isobutylaluminium hydride–Et_2O), tosylation ($TsCl$–NEt_3) and displacement by iodide (NaI–acetone). Treatment of the iodide with the lithium enolate of pentan-3-one in tetrahydrofuran (THF)–hexamethylphosphoramide by the method of Mori,[2] followed by deprotection (Bu_4NF–THF) and acetylation (Ac_2O–pyridine) afforded the mixture of acetates (**10**) in 30% yield. This material gave identical spectra (^{1}H n.m.r., ^{13}C n.m.r.) to those reported for the acetate of natural sericornine which had been epimerised at C-4 by standing in $CDCl_3$ at room temperature.

Following the success of this approach to the racemic material the route was adapted to allow the synthesis of 4*RS*,6*S*,7*S*-sericornine (**9**). Chiral enolate (**7**) was prepared from ketone (**6**) by treatment with dicyclopentyl boron trifluoromethanesulphonate in the presence of *N*,*N*-di-isopropylethylamine;[6] ketone (**6**) was derived from (*S*)-mandelic acid in three steps in 70% overall yield by hydrogenation (Ru–Al_2O_3), treatment with ethyl-lithium, and protection (t-butyldimethylsilane).[7] Reaction of (**7**) with propionaldehyde in ether at −80 °C afforded, after desilyation and oxidative cleavage ($NaIO_4$), the carboxylic acid (**8**) $[\alpha]_D^{25}$ −4.11° (c 1.72, $CHCl_3$).[7,8] This reaction afforded only the *erythro* product and furthermore, the enantiomeric excess of (**8**) (2*R*,3*S*:3*S*,2*R*) was greater than 100:1. This was converted into the protected ester (**4**) and then into the iodide (**5**), $[\alpha]_D^{25}$ +11.84° (*c* 3.5, $CHCl_3$) under the same conditions as before in 50% yield based on enolate (**7**). Treatment with the lithium enolate of pentan-3-one followed by deprotection gave 4*RS*,6*S*,7*S*-sericornine (**9**) in 30% yield (Scheme 1).[2] Conversion into the acetate, $[\alpha]_D^{25}$ −15.50° (*c* 1.5, MeOH), allowed spectral comparison with the data published for (**10**), confirming the structure of our synthetic material.[2,9] Utilising specific boron enolates it is, therefore, possible to synthesise several stereoisomers of sericornine on an appreciable scale (*ca.* 15% overall yield) which would allow investigation of the specificity of insect antennal receptor sites to stereoisomers other than the endogeneous pheromone.

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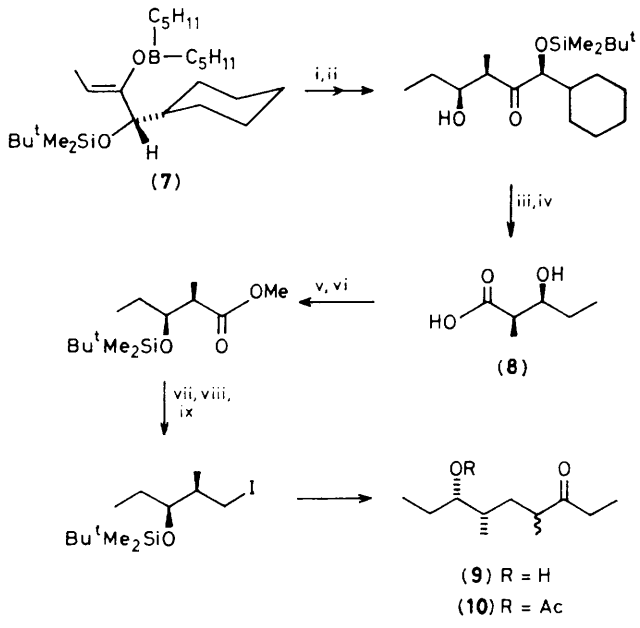

Scheme 1. i, EtCHO; ii, H_2O_2–MeOH, pH 7; iii, Bu_4NF, iv, IO_4^-; v, CH_2N_2; vi, Bu^tMe_2SiCl–imidazole–Me_2NCHO; vii, Bu_2AlH; viii, $TsCl$–Et_3N; ix, NaI–Me_2CO.

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