Stereoselective Synthesis of Pyrrolizidine Alkaloids, (+)-Heliotridine and (+)-Retronecine, by means of an Intermolecular Carbenoid Displacement Reaction

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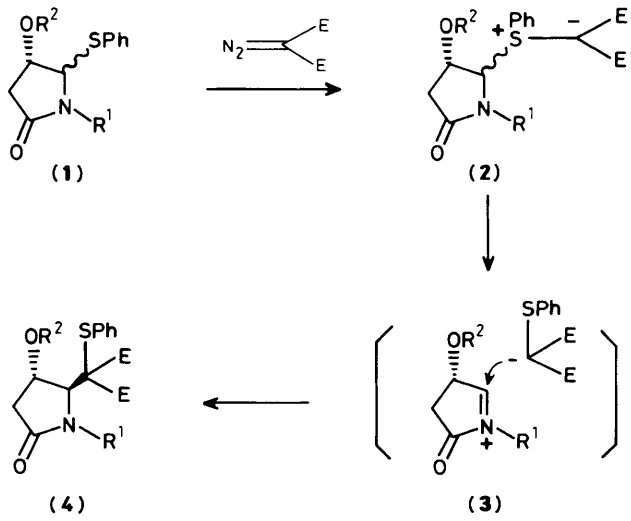
The stereoselective synthesis of the pyrrolizidine alkaloids (+)-heliotridine and (+)-retronecine from (*S*)-malic acid has been achieved by employing an intermolecular carbenoid displacement reaction as a key step.

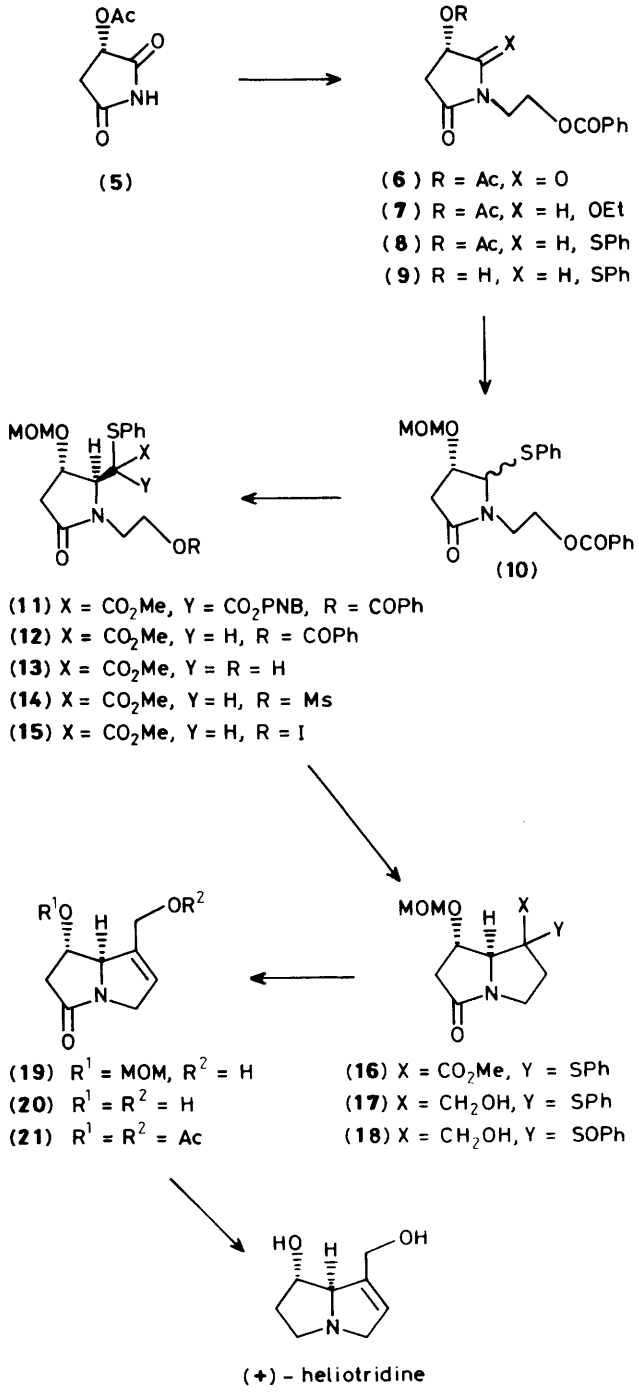
We have recently reported[1] the total synthesis of several pyrrolizidine alkaloids in which an intramolecular carbenoid displacement reaction was exploited for carbon–carbon bond formation at the α-position to a nitrogen to construct a bicyclic ring system. In continuation of our work on the synthesis of necine bases,[2] we have investigated the intermolecular carbenoid displacement of the optically active sulphide (**1**) derived from (*S*)-malic acid with α-diazomalonate in the presence of rhodium acetate to control the stereochemistry at the position previously occupied by the sulphide group, because it would be expected[3] that nucleophilic attack on the acyliminium salt (**3**) generated from the ylide (**2**) would occur from the less hindered side to give a 2,3-*trans*-pyrrolidone derivative (**4**) predominantly as shown in the Scheme 1.

We first applied the above synthetic strategy to a synthesis of (+)-heliotridine (Scheme 2).

The optically active imide (**5**)[4] prepared from (*S*)-malic acid was treated with ethylene glycol monobenzoate under Mitsunobu reaction conditions[5] to provide the *N*-alkylated product (**6**) in 95.5% yield, which on reduction with sodium borohydride, followed by treatment with ethanolic hydrogen chloride[6] yielded the ethoxy-derivative (**7**). Introduction of the sulphide function was easily achieved by treatment of (**7**) with benzenethiol in the presence of toluene-*p*-sulphonic acid to furnish the sulphides (**8**) and (**9**) in the ratio of 1 : 1.87 in 76.2% yield from (**6**). Deacetylation of (**8**) with sodium carbonate in methanol afforded (**9**). Protection of the alcohol (**9**) as the methoxymethyl ether (MOM) gave the desired sulphide (**10**) as a diastereoisomeric mixture (α : β SPh 1 : 8) in good yield. The major *trans*-sulphide was subjected to an intermolecular carbenoid displacement reaction with methyl

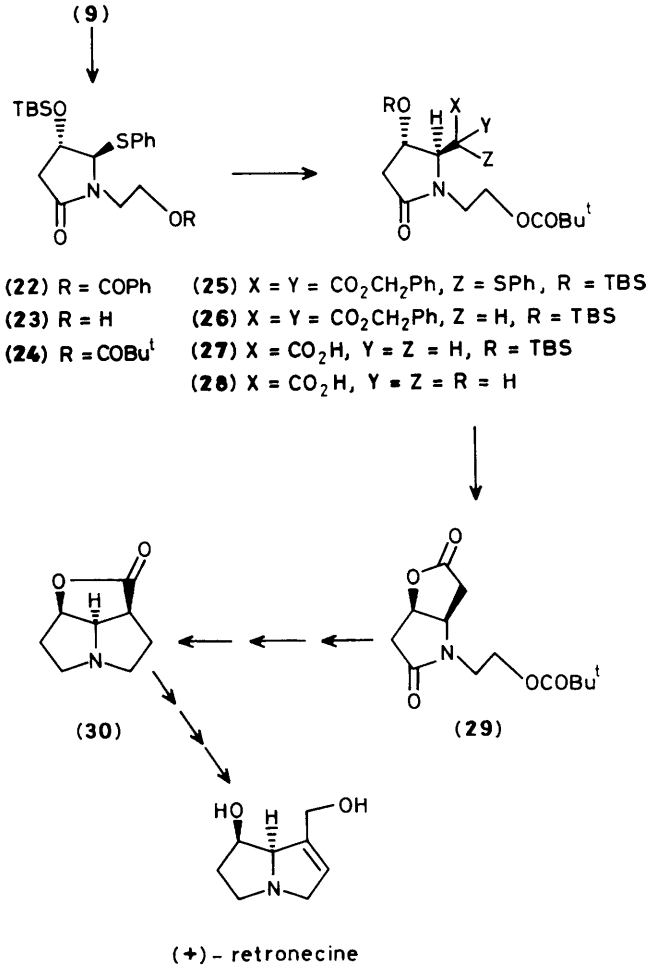


Scheme 1. E = CO_2Et.



Scheme 2. PNB = p-$O_2NC_6H_4CH_2$; Ms = $MeSO_2$; MOM = $MeOCH_2$.

p-nitrobenzyl α-diazomalonate in refluxing benzene in the presence of a catalytic amount of rhodium acetate to afford the carbon-introduced product (**11**), in 82.6% yield. Catalytic reduction of (**11**) over palladium–carbon in methanol gave the decarboxylated product (**12**), whose hydrolysis with potassium carbonate in methanol yielded the alcohol (**13**) in 58.4% yield from (**11**). In order to construct a bicyclic ring system, the alcohol (**13**) was converted into the iodide (**15**) *via* the methanesulphonate (**14**) in two steps. Treatment of the iodide (**15**) with lithium hexamethyldisilazide in tetrahydrofuran at −78 to 0 °C brought about an intramolecular alkylation to give



Scheme 3. TBS = Bu^tMe_2Si.

rise to the bicyclic compound (**16**) in 46.6% yield from (**14**). Since the basic skeleton of (+)-heliotridine was constructed stereoselectively, our attention was focused on the conversion of (**16**) into the natural product by manipulation of the sulphide group. Lithium aluminium hydride reduction of the ester group of (**16**) at 0 °C in ether furnished the alcohol (**17**), which on oxidation with *m*-chloroperbenzoic acid afforded the sulphoxide (**18**) in 67.0% yield from (**16**). The 1,2 unsaturation system was introduced by thermolysis of the sulphoxide (**18**) in refluxing toluene to give the elimination product (**19**), which was further converted to the diacetate (**21**), *via* the diol (**20**) by treatment with hydrochloric acid in methanol and then with acetic anhydride–triethylamine in dichloromethane.

The spectroscopic data[7] and specific optical rotation[8] of the amide (**21**), $[\alpha]_D^{25}$ +34.4° (*c* 2.2, $CHCl_3$) {lit.,[7] $[\alpha]_D^{25}$ +36.2° (*c* 1.1, $CHCl_3$)} were identical with those reported. Since the conversion of the diacetate (**21**) into (+)-heliotridine had already been achieved[7] by lithium aluminium hydride reduction by Hart and co-workers, this synthesis constitutes its total synthesis.

(+)-Retronecine, an epimeric isomer of the secondary alcohol of (+)-heliotridine, was recently synthesised[9] from (*R*)-malic acid *via* the lactone (**29**) as a key intermediate. Therefore we next attempted a synthesis of (**29**) from the sulphide (**9**) by employing a similar strategy to that described above (Scheme 3). Protection of the alcohol (**9**) with t-butyldimethylsilyl chloride (TBSCl) afforded the silyl ether

(**22**), which was then converted to the pivaloyl ester (**24**) by hydrolysis with potassium carbonate in methanol, followed by esterification of the alcohol (**23**) with pivaloyl chloride and pyridine in ether in 54.5% yield from (**22**). An intermolecular carbenoid displacement reaction of the sulphide (**24**) with dibenzyl α-diazomalonate in the presence of a catalytic amount of rhodium acetate in refluxing benzene afforded (**25**). Reductive desulphurisation of (**25**) with Raney Ni in ethanol gave (**26**) in 67.2% yield from (**24**), whose hydrogenolysis over palladium–carbon in methanol, followed by decarboxylation in refluxing toluene, provided the acid (**27**) in 83.2% yield from (**25**). In order to synthesise the lactone (**29**), an inversion of the stereochemistry of the secondary alcohol function of (**27**) was required, and we decided to adopt the Mitsunobu reaction for this purpose.[10] After deprotection of the silyl group of the acid (**27**) on exposure to tetra-n-butylammonium fluoride in tetrahydrofuran at ambient temperature, the resulting alcohol–acid (**28**) was treated with diethyl azodicarboxylate in tetrahydrofuran in the presence of triphenylphosphine to furnish the lactone (**29**) with the inversion of the alcohol function as expected, in 49.3% yield from (**27**). The specific optical rotation of the lactone (**29**) obtained: $[\alpha]_D^{26}$ + 55.2° (*c* 0.69, $CHCl_3$) {lit., $[\alpha]_D^{17}$ + 48.8° (*c* 0.53, $CHCl_3$)} and its melting point [112—113 °C (from benzene–n-hexane); lit., m.p. 109—110 °C] were identical with those reported.[9] The lactone (**29**) had already been converted[9] into (+)-retronecine *via* compound (**30**).

A stereoselective synthesis of (+)-heliotridine and (+)-retronecine has thus been achieved. The methodology opens up many fascinating possibilities in the chiral synthesis of biologically important pyrrolizidine alkaloids.

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