

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

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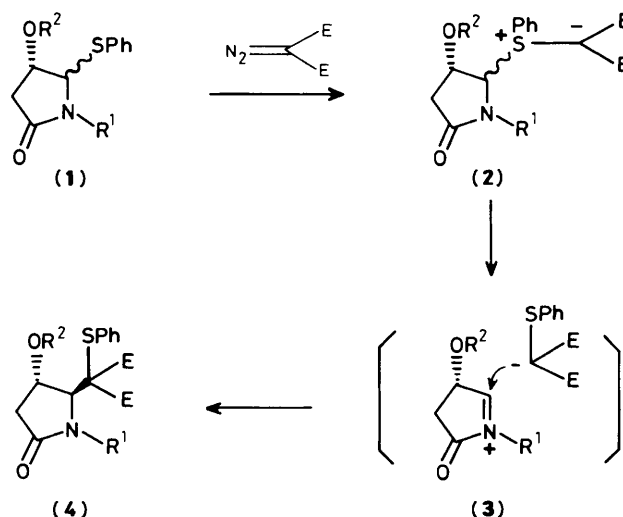
The stereoselective synthesis of the pyrrolizidine alkaloids (+)-heliotridine and (+)-retronecine from (*S*)-malic acid has been achieved by employing an intermolecular carbenoid displacement reaction as a key step.

We have recently reported¹ 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 expected³ 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.

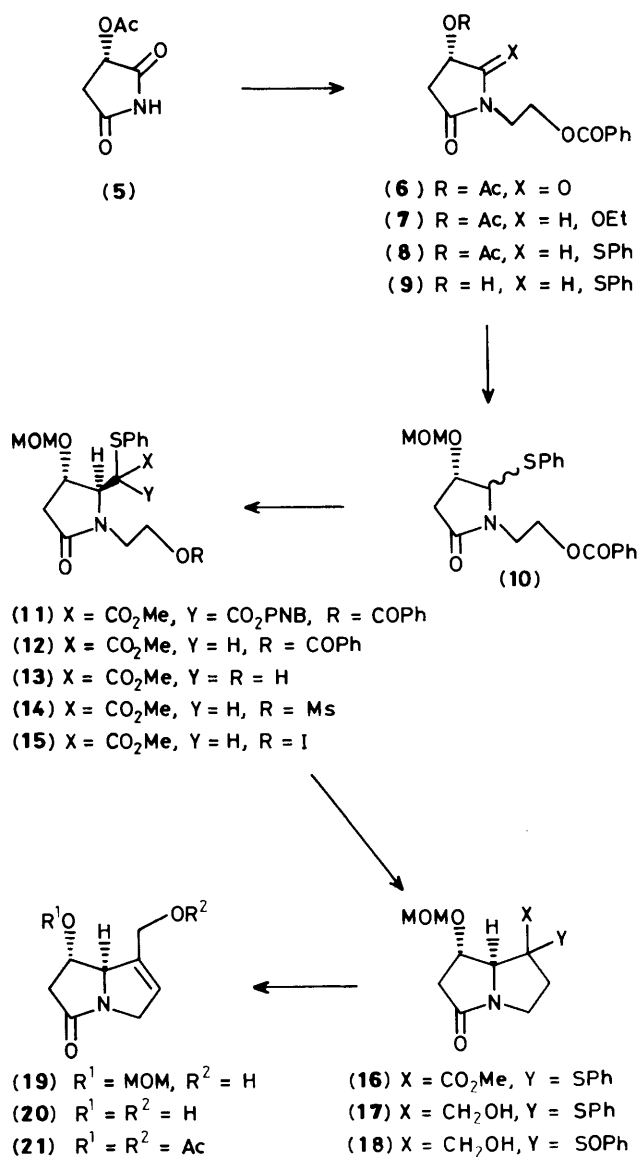
We first applied the above synthetic strategy to a synthesis of (+)-heliotridine (Scheme 2).

The optically active imide (**5**)⁴ prepared from (*S*)-malic acid was treated with ethylene glycol monobenzoate under Mitsunobu reaction conditions⁵ to provide the *N*-alkylated product (**6**) in 95.5% yield, which on reduction with sodium borohydride, followed by treatment with ethanolic hydrogen chloride⁶ 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

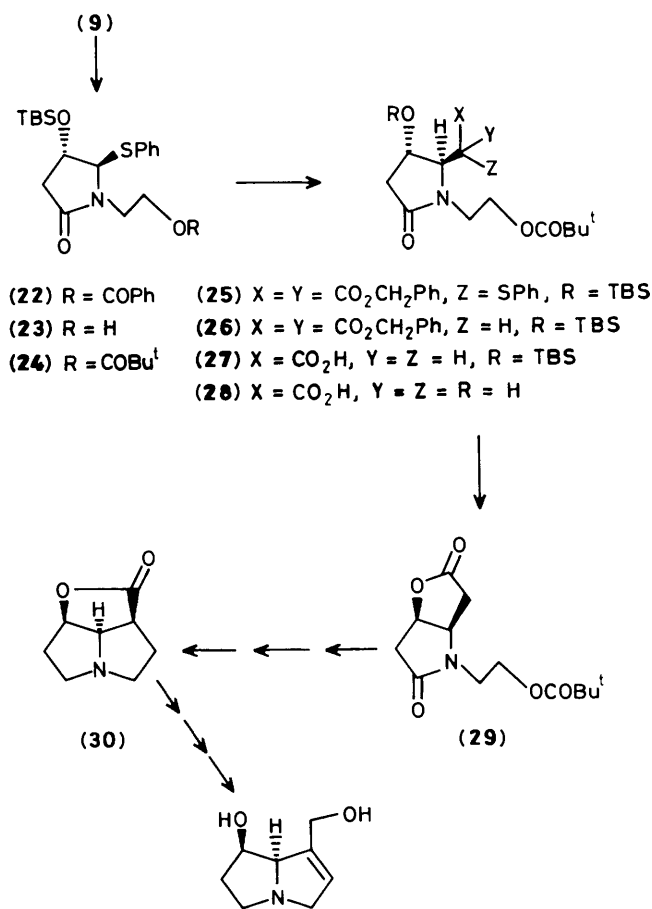


Scheme 1. E = CO₂Et.



Scheme 2. PNB = *p*-O₂NC₆H₄CH₂; Ms = MeSO₂; MOM = MeOCH₂.

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^tMe₂Si.

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 data⁷ and specific optical rotation⁸ of the amide (21), [α]_D²⁵ +34.4° (*c* 2.2, CHCl₃) {lit.,⁷ [α]_D²⁵ +36.2° (*c* 1.1, CHCl₃)} were identical with those reported. Since the conversion of the diacetate (21) into (+)-heliotridine had already been achieved⁷ 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 synthesised⁹ 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: $[\alpha]_{\text{D}}^{26} + 55.2^{\circ}$ (*c* 0.69, CHCl_3) {lit., $[\alpha]_{\text{D}}^{17} + 48.8^{\circ}$ (*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 converted⁹ 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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