Enantioselective Construction of a Quaternary Stereogenic Centre *via* Tandem Acid Anhydride Formation–Intramolecular Michael Reaction

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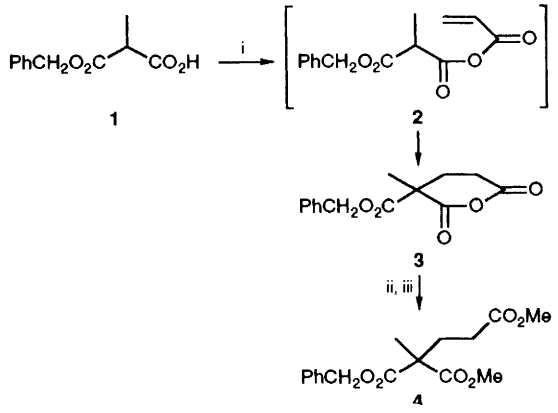
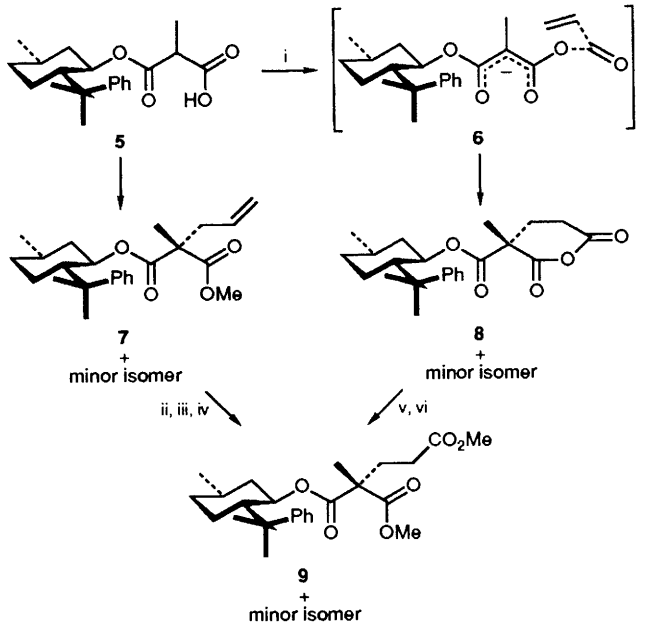
A novel method for the enantioselective construction of a quaternary stereogenic centre by tandem acid anhydride formation–intramolecular Michael reaction has been developed; a synthetic intermediate **16** for *Hunteria* and *Aspidosperma* indole alkaloids has been prepared by the application of this procedure.

Recently we developed a general method for the assembly of the quaternary stereogenic centre *via* the diastereoselective alkylation of chiral half esters of monosubstituted malonic acid.[1] Michael addition of dianions, derived from chiral half esters, to α,β-unsaturated esters was studied, but the diastereoselectivity as well as the yields were rather poor.† In an effort to improve the enantioselectivity of the Michael reaction we devised an approach based on initial formation of a mixed anhydride, followed by an intramolecular cyclisation.



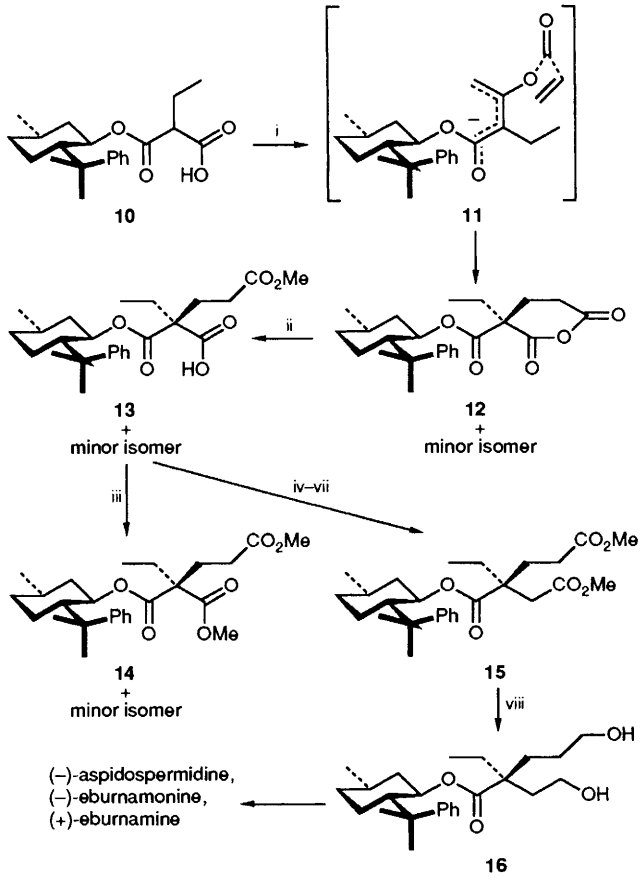
Scheme 1 *Reagents*: i, CH_2=CHCOCl, DMAP, Pr^i_2NEt; ii, HCl, MeOH; iii, CH_2N_2



Scheme 2 *Reagents*: i, CH_2=CHCOCl, DMAP, Pr^i_2NEt, $LiClO_4$; ii, $(C_6H_{11})_2BH$, H_2O_2, NaOH; iii, Jones oxidation; iv, CH_2N_2; v, HCl, MeOH; vi, CH_2N_2

The feasibility of this approach was demonstrated with the racemate as indicated in Scheme 1. Treatment of **1** for 1 h at 0 °C with acryloyl chloride in the presence of a catalytic amount of *N*,*N*-dimethylaminopyridine (DMAP) and an excess of Pr^i_2NEt in tetrahydrofuran (THF) gave **3** [IR: ν_{max}/cm^{-1} (neat) 1812, 1769 and 1740] as a labile compound. Subsequent treatment of **3** with 20% HCl in MeOH afforded the monoacid accompanied with diester **4**. Reaction of the crude products with CH_2N_2 provided the triester **4** in 83% overall yield from **1**. It is thought that the cyclic anhydride **3** is formed by the intramolecular conjugate addition of **2**.

Applying the above procedure, the reaction of the chiral half ester **5**[2] with acryloyl chloride was carried out in the presence of several bases and additives in different solvents. As shown in Table 1, the diastereoselectivity and yields of the tandem reaction were improved by use of lithium salts[3] (Runs 1–3) and by the use of dimethylformamide (DMF) as solvent (Run 5). The best result was obtained using DMAP, Pr^i_2NEt and $LiClO_4$ in THF (Run 1). The (*R*)-configuration of the newly produced stereogenic centre of the major product **9** was determined by correlation with **7**, prepared by allylation of **5**[1]



Scheme 3 *Reagents and conditions*: i, CH_2=CHCOCl, DMAP, Pr^i_2NEt, $LiClO_4$; ii, HCl, MeOH; iii, CH_2N_2; iv, $(COCl)_2$; v, CH_2N_2; vi, *hν*, MeOH; vii, HPLC; viii, DIBALH

† Reaction of **5**[2] with methyl acrylate in the presence of lithium hexamethyldisilazide produced a 66 : 34 ratio of the adducts **9** in 51% yield, while **10**[2] gave a 60 : 40 ratio of **14** and its epimer in only 28% yield.

Table 1 Conversion of the chiral half ester **5** into the triester **9** and its diastereoisomer

Run	Conditions for tandem reaction	Yield (%)	Ratio of two diastereoisomers
1	Pr^i_2NEt, DMAP, $LiClO_4$, THF, −10–0 °C, 16 h	63	87 : 13
2	Pr^i_2NEt, DMAP, $LiBr·H_2O$, THF, −10–0 °C, 16 h	58	81 : 19
3	Pr^i_2NEt, DMAP, LiI, THF, −10–0 °C, 16 h	51	81 : 19
4	Pr^i_2NEt, DMAP, THF, −10–0 °C, 16 h	35	75 : 25
5	Pr^i_2NEt, DMAP, DMF, −45 °C, 16 h	52	80 : 20

(Scheme 2). Thus the preferred formation of **8** could be ascribed to the conjugate addition of the anion *via* the conformation **6**.

The reaction of **10**[2] with acryloyl chloride for 16 h at −10 to 0 °C in the presence of Pr^i_2NEt, DMAP and $LiClO_4$ in THF, followed by treatment of **12** and its epimer with 5% HCl in MeOH at room temperature for 5 h, gave mainly **13** and its epimer. Methylation of the initial products using CH_2N_2 produced a 77 : 23 ratio of **14** and its epimer in 65% overall yield from **10** (Scheme 3). Homologation of the above products containing **13** afforded **15** and its epimer in 41% overall yield from **10** in the same ratio as above. The major component **15**, obtained by purification using HPLC, was reduced with diisobutylaluminium hydride (DIBALH) at −30 °C to give, in 80% yield, the diol **16**. The 500 MHz NMR spectrum was identical with that of the authentic sample,[1] which had been correlated with (−)-eburnamonine, (+)-eburnamine and (−)-aspidospermidine.[4] From the above result, the (*S*)-configuration of the major product **14** was established, which indicates that the Michael addition occurs *via* the conformation **11**. It is noteworthy that different conformations **6** and **11** operate depending on the bulkiness of substituent on the malonate and the stereochemical outcomes are consistent with those observed on diastereoselective alkylation.[1] Therefore the argument, previously proposed,[1b,c] would be valid for the intramolecular Michael reaction.

In summary, the tandem acid anhydride formation–intramolecular Michael reaction is useful for the diastereoselective construction of the quaternary stereogenic centres.

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