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Complementary Enantioselective Routes To The Quinolizidine Alkaloids Lupinine And Epilupinine

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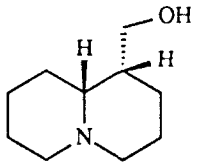
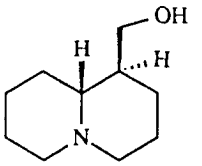
Abstract: Introduction of an α-2-[propenyl] substituent into a chiral 2-piperidineacetate has been effected both by enolate Claisen rearrangement of an allyl ester and by direct allylation of the intermediate lithium enolate [(7) --> (8) + (9)] (Scheme 1). These two approaches give largely the opposite stereochemistry at the newly created centre; subsequent hydroboration and cyclisation of ester (9) leads to (+)-lupinine (12).

The quinolizidine alkaloids (-)-lupinine (1) and (+)-epilupinine (2) occur in many members of the *Lupinus* family[1] and have been the subjects of a number of synthetic studies during recent years[2]. However, despite their relatively straightforward structures, only one very recently reported approach has been used to prepare chiral, non-racemic epilupinine[3]. A possible precursor to this quinolizidine system is the piperidineacetate (3)



(1)



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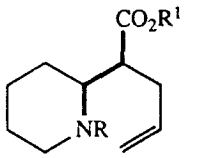
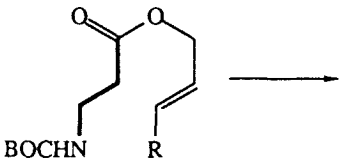


(3)

which can be regarded as an α-allyl-β-amino-acid derivative.We have recently found that this type of structure is accessible using an ester enolate Claisen rearrangement of an allyl ester of a β-amino-acid [(4) --> (5)][4]. Furthermore, our model studies have shown that such rearrangements are usually highly stereoselective.



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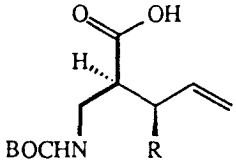

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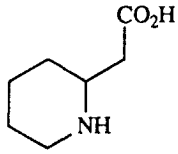
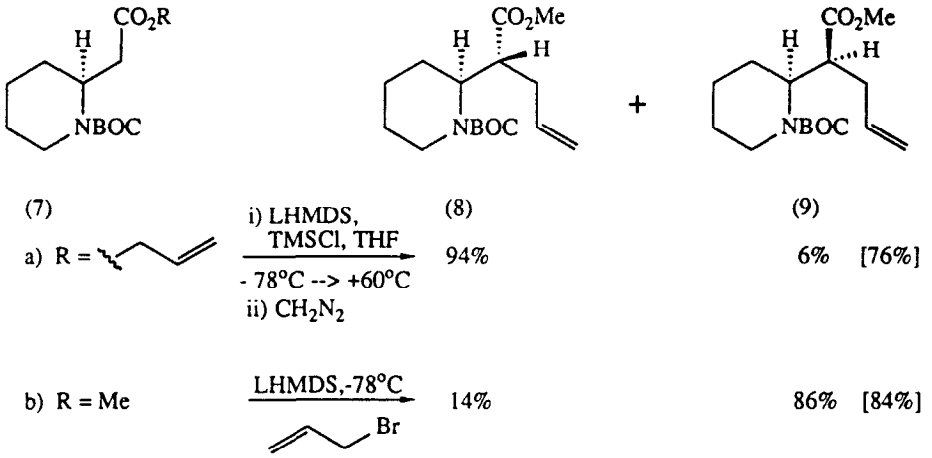


(6)

Therefore, given the availability of pure enantiomers of the piperidineacetic acids (6), it should be possible to

prepare the anticipated precursors (3) in chiral form. In practice, both enantiomers of acid (6) are obtainable by optical resolution of 2-piperidineethanol using *d*-camphorsulphonic acid[5] followed by Jones oxidation[6]. Herein, we report that the Claisen approach can indeed be used to obtain the intermediates (3) stereoselectively and further that direct allylation of the intermediate lithium enolate also leads to good yields of these compounds in a stereochemically complementary way.

The (S)-piperidineacetic acid esters (7) were obtained in 70-75% yields from the corresponding resolved amino-acid [*cf.* (6)] by sequential N-protection [$(BOC)_2O$, NaOH] and esterification using the DCC-DMAP method[7]. Enolate Claisen rearrangement (Scheme 1)[4] of the allyl ester (7a) proceeded smoothly to give a

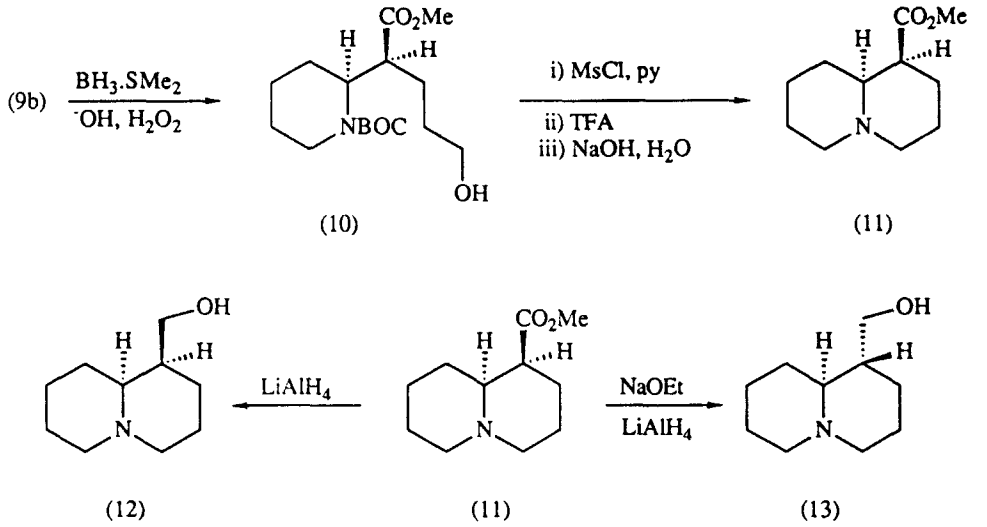


SCHEME 1

mixture of diastereoisomers [(8) and (9)] (76%), following silyl ester hydrolysis [MeOH, H_2O, 20°C, 0.5h] and esterification [CH_2N_2, Et_2O], in a ratio of 94:6, according to integration of the ester proton resonances at 400MHz. The structural assignments were made tentatively on the basis of comparative nmr data [^1H and ^{13}C] but were only confirmed upon completion of the synthetic scheme. In contrast, direct allylation of the lithium enolate derived from ester (7b) by allyl bromide led directly to the same pair of diastereoisomers [(8) and (9)] (84%) but in a ratio of 14:86 (Scheme 1).

The subsequent elaboration of the quinolizidine ring system is outlined in Scheme 2. As the starting material, we chose the direct allylation product from methyl ester (7b) since this should lead to (+)-lupinine (12), the less thermodynamically stable isomer due to the possibility of epimerisation to the more stable epilupinine stereochemistry, once the second ring is established [*ie.* (11) --> (13)]. Hydroboration of ester (9)[+(8)] was effected using borane-dimethyl sulphide complex and led to the alcohol (10) in 95% yield. Of a number of cyclisation methods examined, the best turned out to be sequential mesylation [MsCl, pyridine] and removal of the nitrogen protecting group using trifluoroacetic acid (TFA). Addition of dilute, ice-cold, aqueous sodium hydroxide to the resulting TFA salt followed by immediate solvent extraction gave the desired quinolizidine

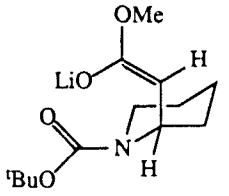
ester (11) in 63% yield from alcohol (10), after chromatography. Finally, reduction using lithium aluminum hydride in ether gave (+)-lupinine (12) in 84% yield after crystallisation. The sample was a single lupinine diastereoisomer (> 98%) according to ^{13}C nmr [8] and showed m.p. 67-68°C (pentane) [lit.[8] m.p. 70-71°C] and $[\alpha]_D$ +19.5° (c 1%, EtOH) [lit.[8] $[\alpha]_D$ for (-)-lupinine -21° (c 1%, EtOH)]. Therefore, the two complementary approaches outlined in Scheme 1 could be used to prepare any one of the four isomers of the quinolizidinemethanols [*ie.*(1) etc.] as both enantiomers of the starting amino-acid (6) are available. (The approach of Nagao and co-workers[3] appears to be limited to syntheses of epilupinines although it can equally well be applied to the elaboration of other ring sizes). Furthermore, as mentioned above, it is known that



SCHEME 2

esters [*eg.* (11)] can be epimerised at the centre α to the ester function[9]. However, attempts to effect such an epimerisation of chiral ester (11) led to samples with lower than expected optical rotations. This could be due to the epimerisation occurring to some extent via a retro-Michael-Michael ring opening- closure mechanism. Possible explanations for the high levels of diastereoselection in the key C-C bond forming steps are based on considerations of the likely enolate geometries and conformations. Extrapolating from our previous studies[4], it is probable that the initial lithium enolate has the (E)-geometry (14) because of a favourable association between the anionic centre and the N-BOC group. In addition, the acetic acid side chain would be expected to adopt an axial position in order to avoid steric interaction with the N-BOC function, an established feature in carbamates of 2-substituted piperidines[10]. Approach by the incoming electrophile (allyl bromide) would then occur from the more exposed *si* face to give predominantly the (S,S) enantiomer (15) [=(9)]. In contrast, O-silylation of the lithium enolate (14) would give the (Z)-silyl enolate (16) in which free rotation to the more stable conformer (17) is likely to take place prior to rearrangement. During this latter process, the allyl side

chain will be delivered from the *re* face, again to avoid unfavourable interactions with the piperidine ring, and thus lead to a preponderance of the (S,R) epimer (18) [*cf.*(8)].



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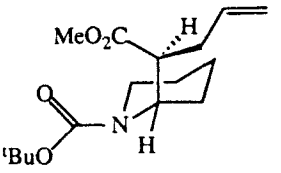

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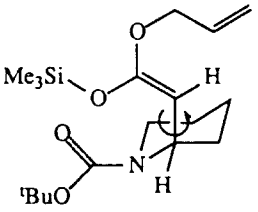

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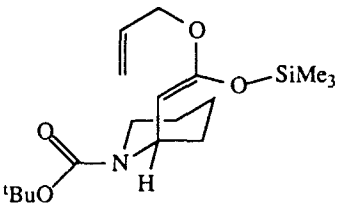

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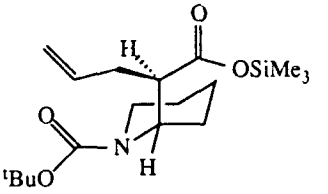

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Acknowledgements

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References

1) R. Willstater and E. Forneau, Chem. Ber., 1902, *35*, 1910; E.P. White, New Zealand J. Sci. Technol., 1955, *33B*, 50; J.F. Crouch, J. Am. Chem. Soc., 1934, *56*, 2434; A.F. Thomas, H.J. Vipond and L. Marion, Can. J. Chem., 1955, *33*, 1290.

2) For some recent synthetic studies, see H. Hiemstra, M.H.A.M. Sno, R.J. Vign and W.N. Speckamp, J. Org. Chem., 1985, *50*, 4014; M. Ihara, T. Kirihara and K. Fukumoto, Heterocycles, 1985, *23*, 1097; H. Takahara, K. Yamabe, T. Suzuki and T. Yamazaki, ibid., 1986, *24*, 37; D.L. Comins and J.D. Brown, Tetrahedron Lett., 1986, *27*, 2219; M. Ihara, T. Kirihara, A. Kawaguchi, M. Tsurata, K. Fukumoto and T. Kametani, J. Chem. Soc., Perkin Trans. 1, 1987, 1719.

3) Y. Nagao, W.-M. Dai, M. Ochiai, S. Tsukagoshi and E. Fujita, J. Am. Chem. Soc., 1988, *110*, 289.

4) C.P. Dell, K.M. Khan and D.W. Knight, J. Chem. Soc., Chem. Commun., 1989, 1812.

5) M.S. Toy and C.C. Price, J. Am. Chem. Soc., 1960, *82*, 2613.

6) W.D. Marshall, T.T. Nguyen, D.B. McLean and I.D. Spenser, Can. J. Chem., 1975, *53* 41.

7) B. Neiss and W. Steglich, Angew. Chem. Int. Ed. Engl., 1978, *17*, 522.

8) H. Podkowinska and J. Skolik, Org. Magn. Reson., 1984, *22*, 379, and references therein.

9) S.F. Goldberg and A.H. Lipkin, J. Org. Chem., 1970, *35*, 242.

10) Y.L. Chow, C.J. Colon and J.N.S. Tam, Can. J. Chem., 1968, *46*, 2821.