Synthesis of Necine Bases from Homoproline Derivatives

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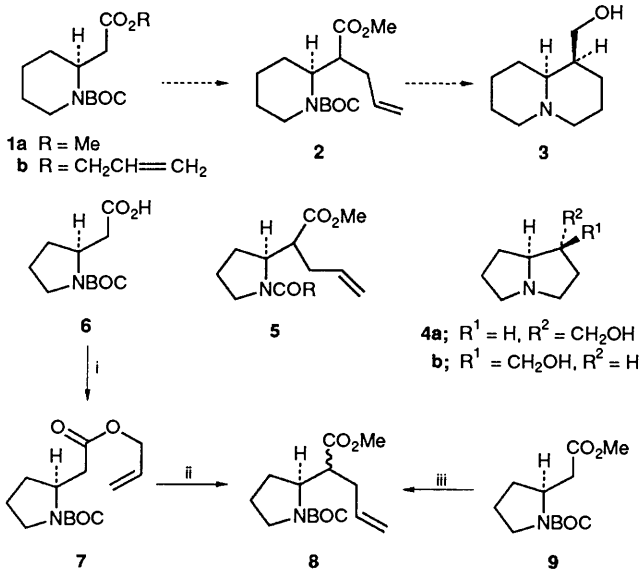
The α-allyl homoproline ester **8**, obtained by Claisen rearrangement of the allyl ester **7** or direct *C*-allylation of the homoproline methyl ester **9** has been converted into (−)-trachelanthamidine **4a** and (−)-isoretronecanol **4b** while allylation of the enolate derived from the lactone **13a** followed by related transformations leads stereospecifically to turneforcidine **12**.

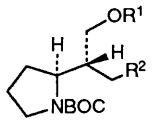
Despite the interest in syntheses of necine bases belonging to the pyrrolizidine group of alkaloids,[1] a minority of approaches provide chiral material.[2] We have found that the related quinolizidine system, *e.g.* (+)-lupinine **3**, can be obtained from the α-allyl piperidinylacetate **2** prepared either by direct *C*-allylation of the piperidinyacetate **1a** or by an enolate Claisen rearrangement of the corresponding allyl ester **1b**.[3] The two approaches are stereochemically complementary; the former route provides largely the *threo* diastereoisomer whereas the Claisen method gives a preponderance of the *erythro* diastereoisomer. In view of this, it appeared that such approaches could be used in the elaboration of related *N*-heterocyclic systems, of which the pyrrolizidines are amongst the most abundant in Nature. Our initial targets were the necine bases (−)-trachelanthamidine **4a** and the epimeric (−)-isoretronecanol **4b**,[1] the key intermediates for which were diastereoisomers of the α-allyl ester **5** which, in turn, should be available either from the allyl ester of an *N*-protected (*S*)-homoproline by an enolate Claisen rearrangement[4] or by direct allylation.[3]

Coupling of (*S*)-*N*-BOC-homoproline **6** with allyl alcohol using DCC–DMAP[5] gave the allyl ester **7** (89%);† enolate Claisen rearrangement of which was effected by sequential

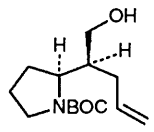


Reagents: i, DCC–DMAP, CH_2Cl_2, 20 °C, 16 h; ii, LHMDS, THF, −78 °C, 20 min, TMSCl, 20 min then +60 °C, 4 h; MeOH, H_2O, 20 °C, 0.5 h then CH_2N_2, Et_2O; iii, LHMDS, THF–5 equiv. HMPA −78 °C, 0.25 h, add allyl bromide −78 °C, 0.5 h then warm to +20 °C, 1 h.

† Satisfactory analytical and spectroscopic data have been obtained for all new compounds reported.



10 a; R^1 = H, R^2 = CH=CH_2
b; R^1 = TBDMS, R^2 = CH=CH_2
c; R^1 = TBDMS, R^2 = CH_2OH
d; R^1 = TBDMS, R^2 = CH_2OMs



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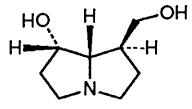
4b



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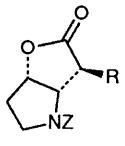
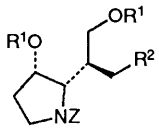
treatment with LHMDS in THF at −78 °C, *O*-silylation (TMSCl) and reflux for 4 h. After hydrolysis (MeOH) and esterification (CH_2N_2), the α-allyl ester **8** was isolated in 78% yield. Alternatively, enolisation of the methyl ester **9** using LHMDS in THF containing HMPA at −78 °C followed by addition of allyl bromide also gave the homologated ester **8** (84%). The good yields of the ester **8** from both approaches were offset by an almost total lack of stereoselectivity in either, at best 1.3:1 of difficult to separate diastereoisomers.

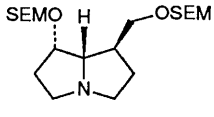
However, reduction of the epimeric esters **8** using DIBAL and BF_3·OEt_2[2d] led to the alcohols (**10a** and **11**) which were readily separable by column chromatography.* The stereochemistries of the two isomers were inferred from comparative spectra data but were only confirmed upon completion of the syntheses. The less polar *erythro* isomer **10a** {$[\alpha]_D$ −25 (CH_2Cl_2)} was protected as the TBDMS ether **10b** (87%) and the alkene function then reductively cleaved by sequential treatment with OsO_4–$NaIO_4$[6] and $NaBH_4$ to give the alcohol **10c** (77%). Subsequent mesylation [MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h] gave the mesylate **10d** (98%). Removal of the BOC function



13 a; R = H
b; R = CH_2CH=CH_2



14 a; R^1 = H, R^2 = CH=CH_2
b; R^1 = SEM, R^2 = CH=CH_2
c; R^1 = SEM, R^2 = CH_2OH
d; R^1 = SEM, R^2 = CH_2OMs



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(20% trifluoroacetic acid in CH_2Cl_2, 0.5 h, 20 °C) and basification of the resulting TFA salt (2 mol dm^{-3} NaOH) resulted in cyclisation and deprotection of the primary alcohol group to give, after chromatography [SiO_2; $CHCl_3$–MeOH–NH_4OH, 5:4:1], (−)-trachelanthamidine **4a** (65%) spectral data for which were identical with those previously recorded as well as $[\alpha]_D$ −14 (*c*, 0.5; EtOH) {lit.,[7] $[\alpha]_D$ −13.8 (*c*, 1.28; EtOH)}. In exactly the same manner, the more polar *threo* alcohol **11** was converted into (−)-isoretronecanol **4b** which also displayed spectral data identical with those previously reported in addition to $[\alpha]_D$ −77 (*c*, 0.3; EtOH) {lit.,[8] $[\alpha]_D$ −78.2 (*c*, 2.8; EtOH)}. Both samples were single diastereoisomers according to ^{13}C spectral data.

This led us to consider better methods for stereochemical control in approaches to more highly oxygenated pyrrolizidines such as turneforcidine **12**.[9] In this respect, a likely candidate was the lactone **13a**,[1,10] both enantiomers of which are available.[11] Sequential treatment of the racemic *N*-(*Z*)-lactone **13a** with LHMDS in THF at −78 °C and allyl bromide gave the α-allyl derivative **13b** (60%) as a single diastereoisomer according to ^{13}C NMR data. Subsequent reduction [$NaBH_4$, EtOH, 20 °C, 16 h] gave the diol **14a** (81%) which was protected as its bis-SEM ether **14b** [SEMCl, Pr^iNEt_2, CH_2Cl_2, (78%)]. Reductive cleavage as outlined above then provided the alcohol **14c** (85%). Conversion into the corresponding mesylate **14d** [MsCl, Et_3N; 89%] followed by hydrogenolysis using 10% Pd–C in EtOAc containing Li_2CO_3 [16 h; 20 °C] gave the pyrrolizidine **15** (94%). Finally, removal of the two protecting groups (1 mol dm^{-3} TBAF in THF) gave (±)-turneforcidine **12**, a viscous oil [lit.,[12] (±)-oil], which exhibited spectroscopic and chromatographic properties identical with those reported.[11,14] The availability of both enantiomers of the starting lactone **13a** suggests that either enantiomer of turneforcidine should be available using this approach.

* Silica gel eluted with CH_2Cl_2–EtOAc, 9:1. R_f **10a** = 0.53: R_f **11** = 0.25.

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