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A Rapid Assembly of Homochiral 2,3,4-Trisubstituted Pyrrolidines

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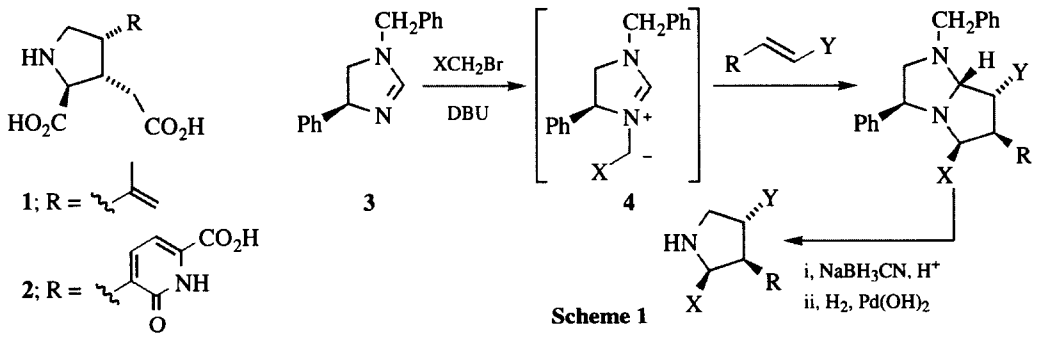
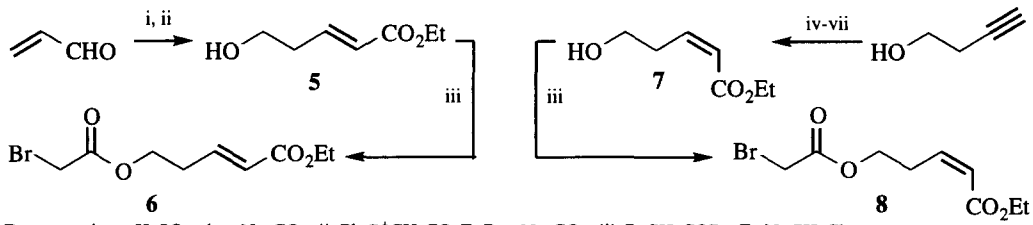
Abstract: The intramolecular 1,3-dipolar cycloaddition of homochiral dihydroimidazolium ylides, generated *in situ*, is the key reaction in a sequence that rapidly affords optically active 2,3,4-trisubstituted pyrrolidines suitably functionalised for further elaboration.

A number of key metabolites with interesting biological profiles, in particular neuroexcitatory properties,[1] feature a 2,3,4-trisubstituted pyrrolidine ring. Synthesis of such systems, exemplified by kainic acid **1** and acromelic acid A **2**, has been the focus of much recent attention.[2] The 1,3-dipolar cycloaddition of azomethine ylides with suitable dipolarophiles is an attractive strategy for the synthesis of highly functionalised pyrrolidines.[3] We have recently developed the 4-phenylimidazolinium ylides **4**, formed *in situ* from the dihydroimidazoles **3**, as new homochiral azomethine ylides in a route to optically active pyrrolidines that generates three of the five bonds of the new pyrrolidine ring in one-pot, illustrated in Scheme 1.[4] We now report the use of these ylides in *intramolecular* cycloadditions that provide a rapid and stereocontrolled approach to 2,3,4-trisubstituted pyrrolidines. The three substituents, each functionalised, are all introduced from a single precursor.



Scheme 1

The proposed dipolarophiles, having an *N*-alkylating agent in the same molecule, were readily assembled. Treatment of acrolein with dilute sulphuric acid afforded 3-hydroxypropanal, unstable but readily handled as its hydrate in aqueous solution. Basification with Na_2CO_3 was followed by addition of carboethoxymethyltriphenylphosphonium bromide and further Na_2CO_3 to effect the Wittig coupling, providing ethyl *E*-5-hydroxypent-2-enoate **5**[5] in an overall 39% yield. *O*-Acylation of **5** with bromoacetyl bromide (Et_3N, CH_2Cl_2; 68%) gave the *E*-dipolarophile **6**, Scheme 2. 3-Butyn-1-ol was first protected by *O*-silylation



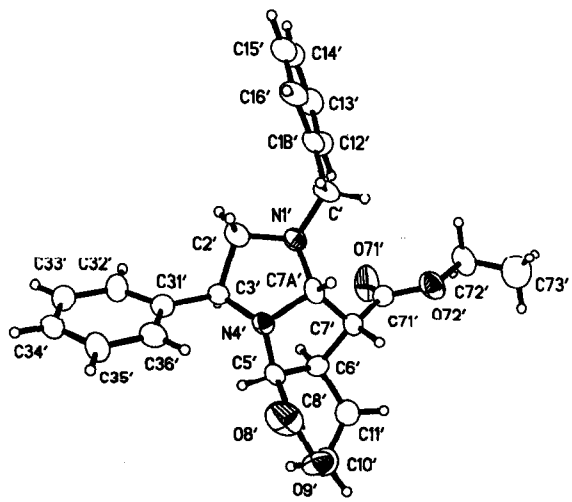
Reagents: i, aq. H_2SO_4, then Na_2CO_3; ii, $Ph_3P^+CH_2CO_2Et\ Br^-$, Na_2CO_3; iii, $BrCH_2COBr$, Et_3N, CH_2Cl_2; iv, TBDMSCl, DMAP, Et_3N; v, EtMgBr, THF, then $ClCO_2Et$; vi, PPTS, EtOH; vii, H_2, Pd-$BaSO_4$, quinoline, MeOH

Scheme 2

[Bu^{t}Me$_2$SiCl (TBDMSCl), Et_3N, DMAP; 91%], then treated successively with ethylmagnesium bromide and ethyl chloroformate (THF; 81%) before desilylation to yield ethyl 5-hydroxypent-2-ynoate (PPTS, EtOH; 79%). Partial hydrogenation (H_2, 1 atm., Pd–$BaSO_4$, quinoline, MeOH; quantitative) to the *Z*-alkene **7** and final *O*-acylation (bromoacetyl bromide, Et_3N, CH_2Cl_2; 66%) led to the *Z*-dipolarophile **8**.

As a point of reference, we examined various of the intermediates above as dipolarophiles in intermolecular reactions with heterocycles **3** using our one-pot protocol [**3**, bromoacetate ester as *N*-alkylating agent, and dipolarophile in THF at reflux; 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) added dropwise over 4 h].[4] Thus *E*-hydroxy ester **5**, its TBDMS ether,[6] and the TBDMS ethers of ethyl 5-hydroxypent-2-ynoate and of *Z*-hydroxy ester **7** failed to yield any identifiable cycloadduct; similar observations were made with diethyl glutaconate, 2(5*H*)-furanone and 5,6-dihydro-2*H*-pyran-2-one.[7] We were also disappointed to find that the *Z*-bromo-acetate **8** appeared to undergo polymerization under the reaction conditions.

On the other hand, treatment of the *E*-bromoacetate **6** with either enantiomer of **3** (THF at reflux, DBU added over 4 h) led in one-pot to the crystalline tricyclic adducts **9a** (from *R*-**3a**; 31%) and **9b** (from *S*-**3b**; 40%), Scheme 3.[8] The structures of these tricyclic adducts were secured by nOe and COSY NMR studies, and by an *X*-ray crystal structure analysis of **9b**, Figure 1.[9] The stereochemistry of the adducts is fully consistent with our transition state model,[4a] i.e. *anti* dipole and *endo* approach of dipolarophile, with facial selectivity controlled by the 4-phenyl substituent.[10]



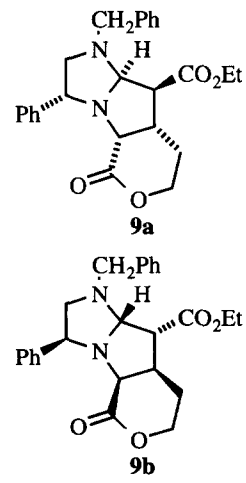
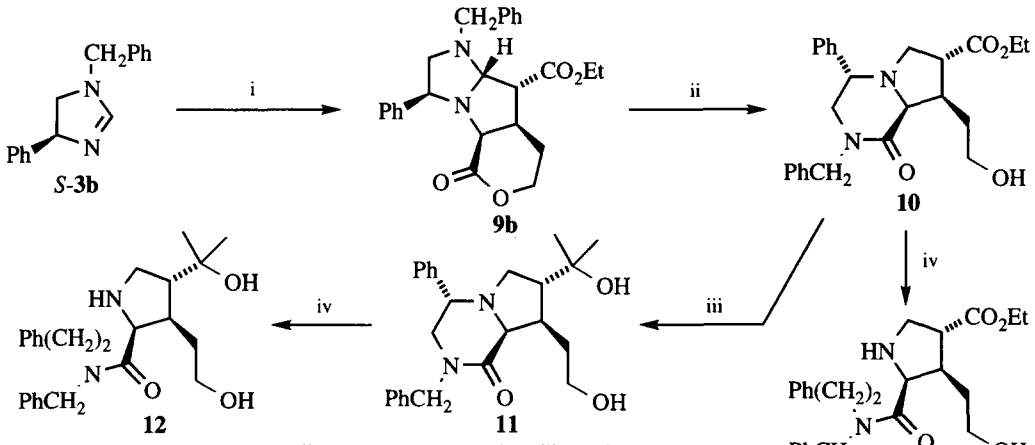


Figure 1: *X*-Ray crystal structure of cycloadduct **9b**

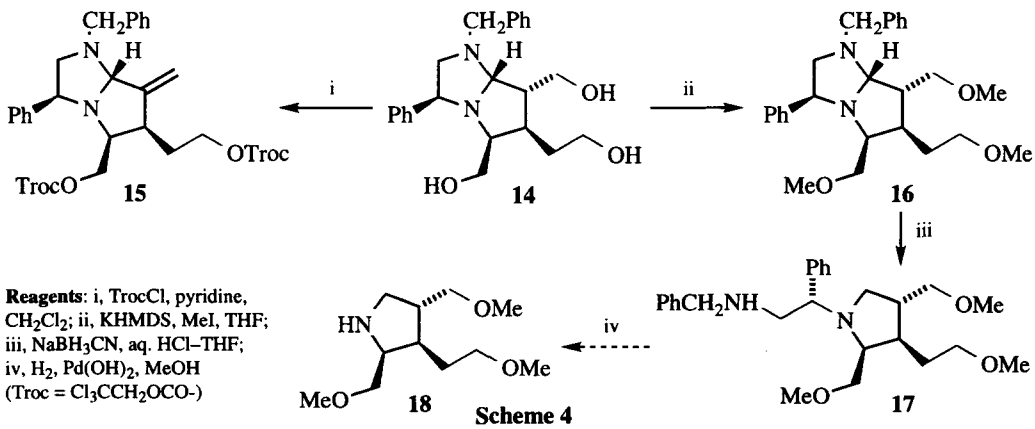
Removal of the chiral template to reveal the new trisubstituted pyrrolidine began with aminal reduction of adduct **9b**, accompanied by spontaneous lactamisation of the liberated secondary amino-group to afford the bicyclic lactam **10** ($NaBH_3CN$, aq. HCl–THF; 70%),[4b] $[\alpha]_D^{24}$ +1.9 (*c* 3.8, CH_2Cl_2) whilst severing the ester that had served as the dipole-dipolarophile tether. Reaction with excess methyl-lithium (cumene–THF) gave the tertiary alcohol **11** (50%), $[\alpha]_D^{24}$ –29.6 (*c* 0.62, CH_2Cl_2), and subsequent hydrogenolysis [H_2, $Pd(OH)_2$, MeOH; 54%] finally removed the template from *N*-1 to leave amide **12**.[11] Alternatively, subjecting **10** directly to hydrogenolysis again cleaved the template from *N*-1 to yield amide **13** (45%).



Reagents: i, **6**, DBU, THF at reflux; ii, $NaBH_3CN$, aq. HCl–THF; iii, MeLi, cumene–THF; iv, H_2, $Pd(OH)_2$, MeOH

Scheme 3

To avoid lactamisation, tricycle **9b** was reduced ($LiAlH_4$, THF; quantitative) to the bicyclic triol **14**. Attempted protection of this polar triol as the *tris*-(2,2,2-trichloroethylcarbonate) (Cl_3CCH_2OCOCl, pyridine, CH_2Cl_2) unexpectedly yielded **15** (67%), presumably by formation and subsequent elimination of the *C*-7 carbonate function, Scheme 4. In order to circumvent this, triol **14** was trimethylated (KHMDS, MeI, THF; quantitative) to afford **16**, and the aminal function smoothly reduced as before to give **17** in quantitative yield. Hydrogenolysis, however, proved surprisingly difficult; trimethoxy pyrrolidine **18** was tentatively identified in the product mixture although it could not be separated from other polar materials, even by reverse phase HPLC.



Reagents: i, TrocCl, pyridine, CH_2Cl_2; ii, KHMDS, MeI, THF; iii, $NaBH_3CN$, aq. HCl–THF; iv, H_2, $Pd(OH)_2$, MeOH (Troc = Cl_3CCH_2OCO-)

Scheme 4

We have thus demonstrated a rapid synthesis of 2,3,4-trisubstituted pyrrolidines, related to a number of natural products, and shown how the three substituents may be separately manipulated. Further exploitation of this intramolecular cycloaddition strategy is underway.

Acknowledgements: We thank EPSRC for a postdoctoral fellowship (J.S.S.).

References and Notes

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8. *Alkylation-Cycloaddition of* (S)-*4-phenyl-4,5-dihydroimidazole* **3b** *with ethyl* E-*5-(bromoacetoxy)-pent-2-enoate* **6**: To the imidazoline **3b** (1.69 g, 7.17 mmol) in dry THF (30 cm^3) heated at reflux under nitrogen, was added the bromoester **6** (1.9 g, 7.17 mmol) in one portion. DBU (1.09 g, 1.07 cm^3, 7.17 mmol) was then added to the mixture dropwise over 5 h. After a further 1 h at reflux, the mixture was cooled, diluted with water (50 cm^3) and extracted with chloroform (3 x 50 cm^3), and the organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (Merck Kieselgel 60, Art. 7729), eluting with petroleum ether (b.p. 40-60°C):ethyl acetate (1:3 v/v) to yield the *cycloadduct* **9b** as a colourless solid (1.06 g, 35%). Crystallisation gave colourless plates from diethyl ether, m.p. 109-111°C, $[\alpha]_D^{24}$ +34.7 (*c* 1.23, $CHCl_3$); (Found: C, 71.75; H, 7.0; N, 6.9%. $C_{25}H_{28}N_2O_4$ requires C, 71.41; H, 6.71; N, 6.66%); ν_{max} (KBr)/cm^{-1} 3000-2800 (m, CH), 1754 and 1724 (s, C=O); δ_H (400 MHz; $CDCl_3$) 1.21 (3H, t, *J* 7Hz, CH_3), 1.72 and 2.24 (each 1H, m, $CHCH_2CH_2$), 2.39 (1H, t, *J* 9Hz, $CHCHHN$), 2.98 (1H, t, *J* 7Hz, $CHCO_2Et$), 3.24 (1H, d, *J* 13Hz, $NCHHPh$), 3.29 (1H, dd, *J* 6, 9Hz, $CHCHHN$), 3.44 (1H, m, $CHCH_2CH_2$), 3.86 (1H, d, *J* 8Hz, NCHCO), 4.06 (1H, d, *J* 13Hz, $NCHHPh$), 4.05-4.3 (4H, m, $CHCH_2CHH$, $CHCH_2N$, CH_2CH_3), 4.46 (1H, m, $CHCH_2CHH$), 4.65 (1H, d, *J* 7Hz, NCHN), 7.2-7.3 (8H, m, Ar-H) and 7.40 (2H, d, *J* 8Hz, Ar-H); δ_C (100 MHz; $CDCl_3$) 13.9 (CH_3), 27.6 ($CHCH_2CH_2$), 38.2 ($CHCH_2CH_2$), 56.7 ($CHCO_2Et$), 58.2 (NCH_2Ph), 60.8 (CH_2CH_3), 62.8 ($CHCH_2N$), 64.9 (NCHCO), 66.5 ($CHCH_2CH_2$), 68.3 ($CHCH_2N$), 86.8 (NCHN), 126.4, 126.9, 127.1, 128.1, 128.15 and 128.2 (Ar-CH), 138.1 and 140.5 (Ar-C), 170.8 and 171.3 (C=O); *m/z* 420 (M^+, 28%), 374 (37), 245 (30), 235 (59), 120 (44), 104 (71), 91 (100) and 77 (60).
9. We thank Dr A.J. Blake, University of Nottingham, for this determination.
10. Interestingly, semi-empirical quantum mechanics calculations using the AM1 method (Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.*, **1985**, *107*, 3902-3909) *via* the SPARTAN 4.0.4 interface indicate that the heat of formation value ΔH_f for cycloadduct **9b** is 25 kJ mol^{-1} more exothermic than that for the C-6 epimer that would be predicted from our transition state model with *Z*-dipolarophile **8**. This stability difference, if reflected in the transition states, may explain the reluctance of **8** to undergo the cycloaddition before alternative degradation intervenes.
11. Selected data: **11** had: ν_{max} ($CDCl_3$)/cm^{-1} 1636 (s, tert. lactam C=O); *m/z* 408 (M^+, 75%). **12** had: ν_{max} ($CDCl_3$)/cm^{-1} 1646 (s, tert. amide C=O); *m/z* (FAB) 411 (MH^+, 7%). *Cf.* Bellamy, L. J. *The Infrared Spectra of Complex Molecules*, 2nd ed.; Methuen: London, 1958; p. 213.

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