Stereoselective Syntheses of α-Hydroxy-γ-amino Acids: Possible γ-Turn Mimetics

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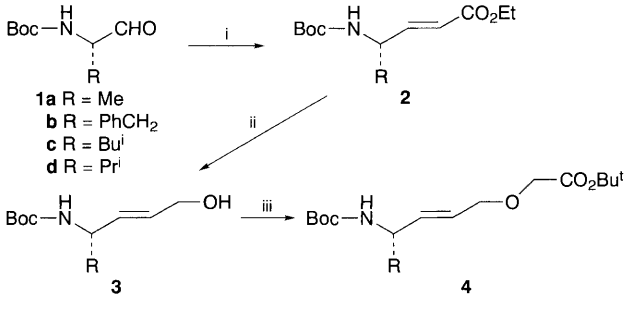
Enantiomerically pure 4-amino-allyloxy-acetates, prepared from L-amino acids, undergo a stereoselective Wittig rearrangements with formation of the corresponding α-hydroxy-γ-amino acid esters having γ-turn conformational features.

There are a variety of reasons for the current interest in the synthesis of unusual amino acids,[1] including the need to prepare β- and γ-turn mimetics for incorporation into biologically active peptides.[2] We report here the synthesis of 4-amino-allyloxy-acetates **4** and their stereoselective Wittig rearrangement[3] to form novel α-hydroxy-γ-amino acids **5** which display γ-turn geometric features.

As shown in Scheme 1, Wittig olefination of the known Boc-protected α-amino aldehydes **1**,[4] derived from the corresponding L-configurated α-amino acids, selectively afforded compounds **2** (90–94%) which were reduced to the corresponding allyl alcohols (**3a** 81%, **3b** 60%, **3c** 83%, **3d** 62%). Williamson ether synthesis then provided the desired starting materials (**4a** 76%, **4b** 96%, **4c** 98%, **4d** 46%). Disappointingly, Li–enolate formation using excess LDA at −40 °C failed to initiate any rearrangement. However, addition of tetramethylethylenediamine (TMEDA) triggered the desired Wittig rearrangement, leading to the preferential formation of one of four possible diastereoisomers [eqn. (1), Table 1].† Control experiments show that the major products **5** are enantiomerically pure (ee > 98%), proving that the reaction occurs without racemization.[5]

This [2,3]sigmatropic rearrangement entails diastereofacial selectivity arising from the stereogenic centre in **4** as well as simple diastereoselectivity involving the prochiral enolate and the alkene group. The latter type of stereoselectivity has been studied theoretically by Houk using *ab initio* calculations.[6]



Scheme 1 *Reagents and conditions*: i, $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 4 h, 22 °C; ii, DIBAL-H, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 2 h, −78 °C; iii, $BrCH_2CO_2Bu^t$, KOH 50% Bu^n_4NBr, toluene, 4 h, 22 °C

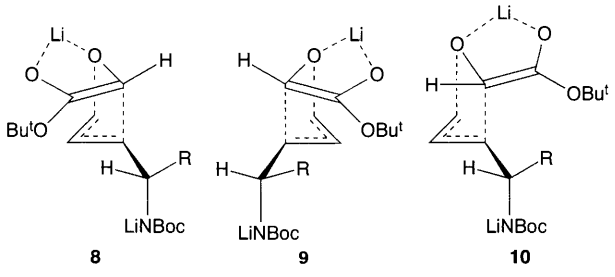
Table 1 Wittig rearrangements of esters **4**

R	Yield of **5** (% isolated)	Ratio[a] **5**: **6**:**7**
Me	78	90: 9:1
$PhCH_2$	76	87:10:3
Me_2CHCH_2	66	91: 6:3
Me_2CH	55	92: 4:4

[a] Determined by HPLC

Accordingly, an early transition state having dyotropic[7] character was postulated.[6] On the basis of the Houk model the *endo*-transition state **8** can be invoked, in which 1,3-allylic strain[8] is minimized and the heteroatom at the stereogenic centre (deprotonated N) is placed in an antiperiplanar manner with respect to the attacking enolate. Transition state **9** is also of the *endo*-type, but entails increased 1,3-allylic strain, leading to the minor diastereoisomer **6**. The second minor diastereoisomer **7** is formed *via* the *exo*-transition state **10** in which the R group and the enolate species undergo unfavourable steric interactions. The geometry of the intermediate enolate is irrelevant to the present discussion, but is probably *cis* due to chelation.

The configurational assignments were confirmed by X-ray structural analyses.‡ Thus, products **5** have the relative and absolute configurations as shown. Interestingly, the compounds display intramolecular hydrogen bonding in the solid state arising from the amide group and the alcohol function (Fig. 1). The solution conformation is the same, as shown by extensive NMR studies in $CDCl_3$.[5]



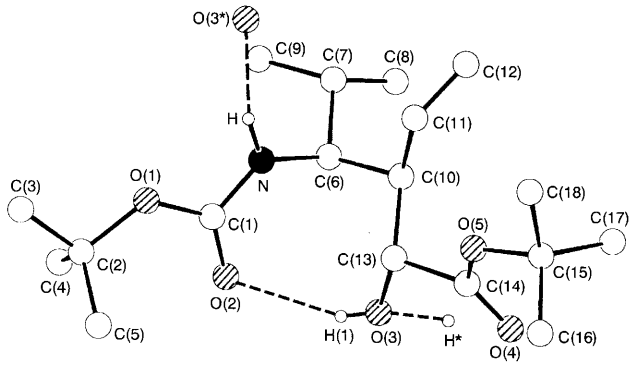
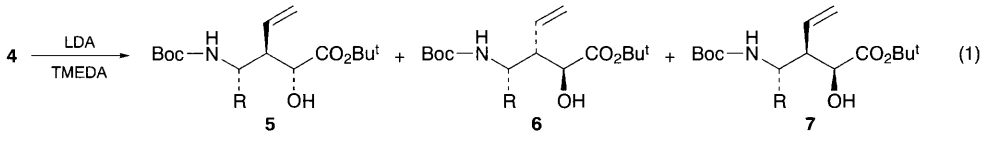
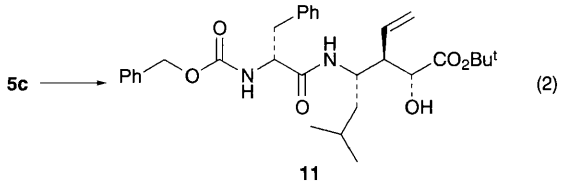


Fig. 1 Structure of **5d** in the crystal, showing the major inter- and intramolecular interactions (symmetry related atoms denoted by *). H atoms except H and H(1) omitted for clarity. Selected interatomic distances (Å), angles and torsion angles (°): N···O(3*) 3.082(4), O(2)···O(3) 2.795(4), C(1)–N–C(6) 120.5(3), O(2)–C(1)–N–C(6) 16.6(6), C(1)–N–C(6)–C(7) 124.5(5), C(1)–N–C(6)–C(10) −107.8(5), N–C(6)–C(10)–C(13) −173.9(4), C(6)–C(10)–C(13)–C(14) 173.9(4), C(6)–C(10)–C(13)–O(3) 54.4(4).



X-Ray structural and NMR analyses of several other derivatives **5** show that this particular conformation is general.[5] It incorporates the features of a γ-turn, which means that α-hydroxy-γ-amino acids can be considered to be γ-turn mimetics.[2,9] Indeed, deprotection of the amine function followed by peptide formation affords compounds which have the same hydrogen bonding-induced conformational property [*e.g.* **11**, eqn. (2)].[5]



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In summary, we have shown that the Wittig rearrangement is a useful tool in the stereoselective transformation of 4-amino-allyloxy-acetates into α-hydroxy-γ-amino acid derivatives. Such compounds display the conformational features of γ-turn mimetics and also contain an alkene functional group useful for possible further transformations.

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Footnotes

† *General Procedure*: To a stirred solution of Bu^nLi (7.6 mmol) and Et_3N (7.6 mmol) in dry THF (15 ml) was added dropwise an ester (2.53 mmol) at −78 °C under an Ar atmosphere. Following the addition of TMEDA (1.47 g, 12.7 mmol) the mixture was stirred for 2 d at −35 °C and then quenched with sat. NH_4Cl solution (10 ml). The aqueous phase was extracted three times with diethyl ether and the combined organic phases were washed with 1 mol dm^{-3} HCl, sat. $NaCO_3H$ and NaCl solutions. After drying over $MgSO_4$, the solvent was removed *in vacuo* and the residue was recrystallized or chromatographed over SiO_2 (pentane–diethyl ether 2 : 1).

‡ *Crystal data* for **5d**: $C_{18}H_{33}NO_5$, M = 343.5 g mol^{-1}, colourless, crystal size 0.28 × 0.49 × 0.63 mm, a = 10.180(1), b = 12.289(1), c = 16.386(1) Å, V = 2050.0(2) Å^3, T = 293 K, D_c = 1.11 g cm^{-3}, μ = 6.18 cm^{-1}, $F(000)$ = 752 e, Z = 4, orthorhombic, space group $P2_12_12_1$ (No. 19), Enraf-Nonius CAD4 diffractometer, λ = 1.54178 Å, measuring method ω–2θ, 2419 measured reflections (+h, +k, +l), $[(\sin\theta)/\lambda]_{max}$ 0.63 $Å^{-1}$, 2395 independent reflections, 2248 observed reflections [$I \geqslant 2\sigma(I)$] for 225 refined parameters, structure solved by direct methods, non H atoms refined anisotropically, H and H(1) atom positions found and refined isotropically, the remainder calculated and fixed (U_H = 0.10 Å^2) in the final refinement stages, $\Sigma w(F_o - F_c)^2$ minimized, R = 0.066, Rw = 0.086 [$w = 1/\sigma^2(F_o)$], max. shift/error 0.10, final difference Fourier maximum residual electron density 0.30 e $Å^{-3}$. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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