Pergamon

Tetrahedron Letters 43 (2002) 8963–8966

TETRAHEDRON LETTERS

An interesting dichotomy in the cyclisation of exocyclic enamines with protected dehydroamino acids leading to different β-turn templates

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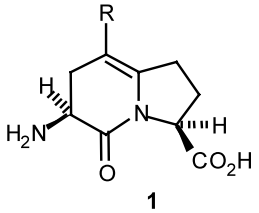
Received 14 August 2002; accepted 26 September 2002

Abstract—Two templates for the preparation of external β-turns have been synthesised. In the course of the synthetic studies an interesting dichotomy was observed in the PCl_3 catalysed reaction of exocyclic enamines such as **6** and **14** with protected dehydroamino acids. When amide protected dehydroamino acids were condensed with **6** and **14** the expected 6/6 and 6/5 fused bicyclic compounds such as **7** and **15** respectively were obtained, whereas when urethane protected dehydroamino acids were used, the 5/6 and 5/5 fused products **9** and **18** were obtained. © 2002 Elsevier Science Ltd. All rights reserved.

We are prompted by the recent publication by Millet et al.[1] to report the results of studies on the synthesis of *beta*-turn mimetics. Millet et al. used methodology developed in our laboratory[2] to prepare bicyclic compounds of type **1** of defined stereochemistry. We now report the synthesis of *beta*-turn templates of this type and also of type **2**, and the discovery of an interesting dichotomy in this synthesis, which appears to depend on the nature of the protecting group used.

Reverse turns connect elements of protein secondary structure such as α-helices and β-sheets and, since they usually occur on the surface of the protein, these turns can be important in molecular recognition processes.[3,4] Since native proteins are large, have poor transport properties and are prone to proteolysis, an interest has developed in synthetic molecules which mimic the turns in these proteins responsible for molecular recognition. These can have the therapeutic effect of the protein they mimic without any of the transport or other associated problems. The external bicyclic turn mimetic BTD **3** prepared by Nagai[5–7] was an early example of such a compound and it was used successfully (a) to replace the Pro-D-Phe dipeptide sequence in gramicidin S,[6] (b) to prepare mimetics of enkephalin and luteinising hormone releasing factor (LRF) with biological activity,[7] and (c) to define a biological conformation in CGRP 8-37.[8]

During work on the synthesis of the bridged β-lactam **4**,[9] we developed[2] a facile one-step synthesis of a series of bicyclic compounds **7** by the method shown in Scheme 1. The products of this synthesis were all esters at C-4 and some (**7a**, **b**, **c** and **d**) were substituted at C-7 with protected amino groups. It was evident, therefore, that suitably protected derivatives of these compounds might act as external β-turn mimetics, since selective deprotection might allow appropriate cyclic peptides to be built on this template. The fact that the compounds **7** were not homochiral was a problem that might be addressed by separation of the diastereoisomers produced when the turn was built up by reaction of the mimetic with L-amino acids.



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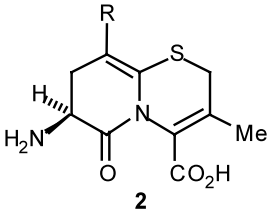

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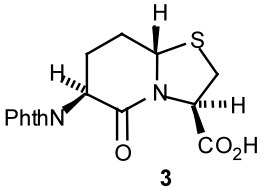

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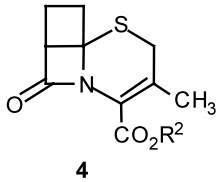

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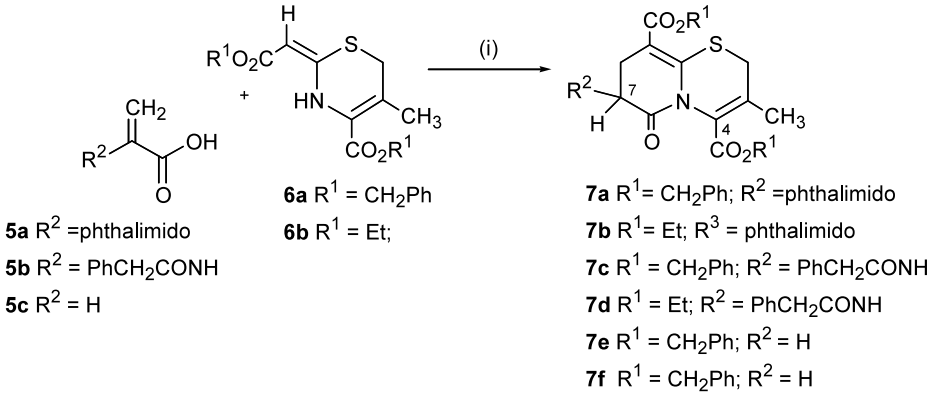
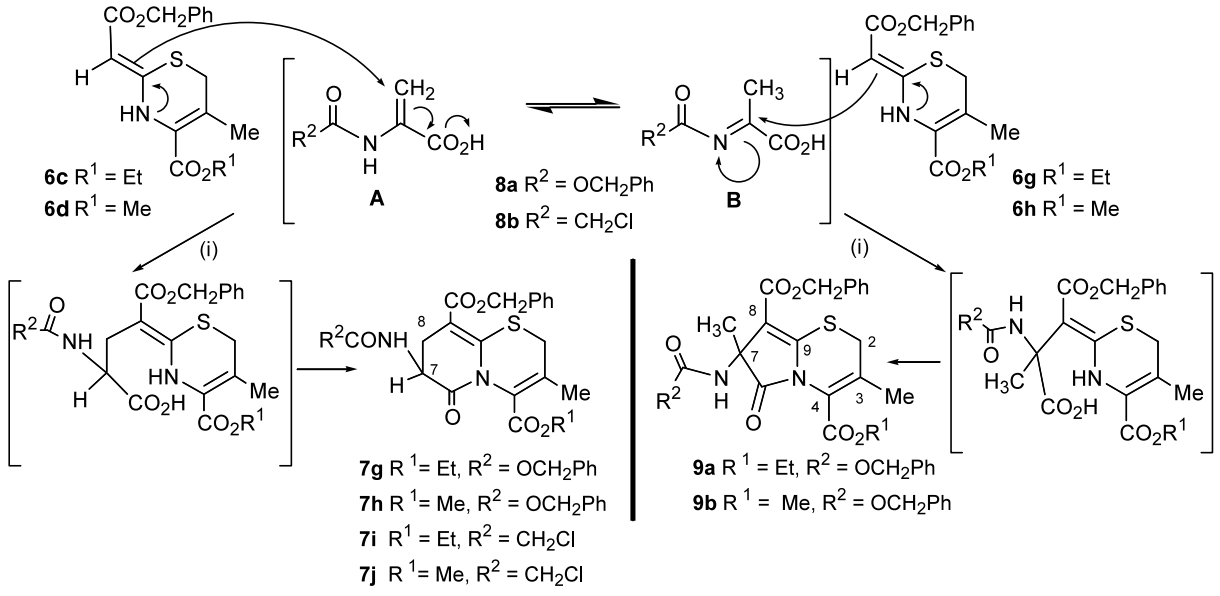
PII: S0040-4039(02)02141-X



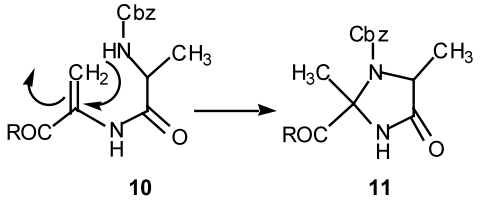
Scheme 1. (i) PCl_3 (**7a** 92%; **7b** 90%; **7c** 80%; **7d** 81%; **7e** 56%; **7f** 39%).



Scheme 2. (i) PCl_3 (**9a** 57%; **9b** 53%).

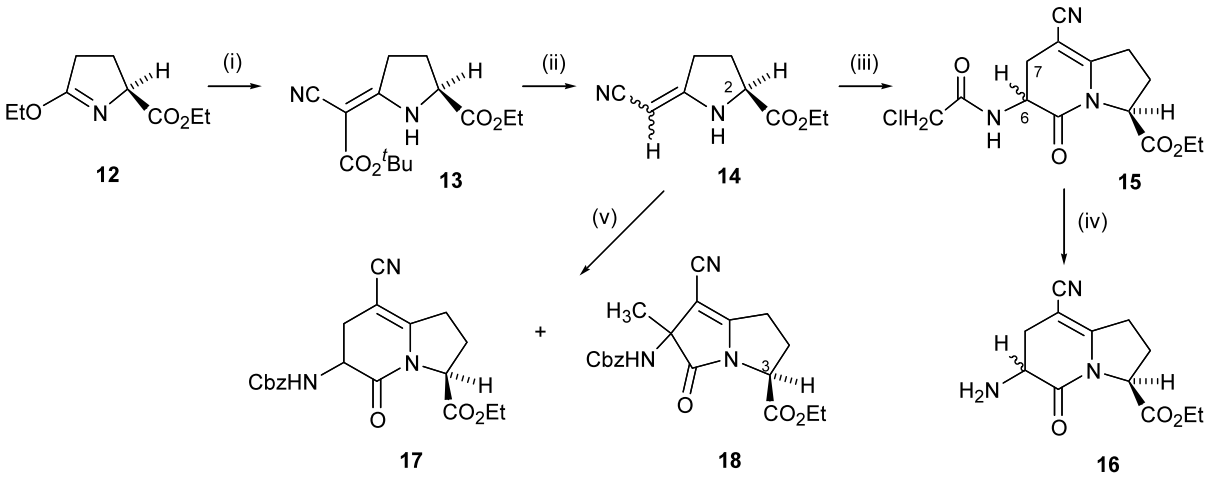
The benzyloxycarbonyl derivatives **7g** and **7h** were chosen as the first targets and so 2-(benzyloxycarbonylamino)-acrylic acid **8a**[10] was reacted with the esters **6c**[2] and **6d**[2] respectively in the presence of PCl_3 as shown in Scheme 2. The products were not the reduced pyridothiazines **7g** or **7h**, expected by analogy to our previous work,[2] since the characteristic signals for H-7 and H-8, seen in the analogous compounds **7a**,**b**,**c** and **d**, were not present in the ^1H NMR spectra of the compounds. An additional methyl singlet was observed in both ^1H NMR spectra. This suggested that the products were in fact the pyrrolinothiazines **9a**[†] and **9b**,[†] an assignment which was confirmed by single crystal X-ray structure analysis of the methyl ester **9b**.[11]

The well-tried synthesis of pyridothiazines[2] had thus proceeded in an anomalous manner when the dehydroamino acid used was protected as a urethane. The structure of the product suggested that the reaction had proceeded by nucleophilic attack on the imine tautomer **B** rather than by nucleophilic attack at C-3 of the enamine tautomer **A**, as shown in Scheme 2. The ^1H NMR spectrum of the urethane **8a** suggested that some of the imine tautomer **B** might accumulate in $(C[^2H_3])_2SO$ with time, as a singlet appeared at 1.89 ppm in the ^1H NMR spectrum on standing in this solvent. It is interesting to note that intramolecular attack by a nitrogen nucleophile occurs in the dehydrodipeptide **10** at the α-carbon atom by the allowed 5-*exo*-*trig* cyclisation mode to give the product **11** (Scheme 3) even though the alternative 6-*endo*-*trig* cyclisation is also allowed.[12] Further, it has been shown that reaction of a 2-(acetylamino)-acrylic ester with HBr first gives the 2-bromo compound as the kinetic



Scheme 3.

[†] These compounds had the expected analytical and spectroscopic properties.



Scheme 4. (i) $NCCH_2CO_2^tBu/NEt_3$ (58%); (ii) CF_3CO_2H (68%); (iii) **8b**+PCl_3/dioxane/benzene (41%); (iv) *ortho*-phenylenediamine (43%); (v) **8a**/PCl_3 (21% **17**+**18**).

product and that this then rearranges to the 3-bromo compound, the product of thermodynamic control.[13] The nitrogen lone pair is certainly more available in the urethane derivative **8a** to allow tautomerism to the form **B** than it is in the compounds **5a** and **5b** which form six membered ring products by preliminary Michael attack on the thiazine **6a**.

Since the pyrrolinothiazines **9** might themselves be useful β-turn mimetics, attempts were made to remove the benzyloxycarbonyl group from **9a** and **9b** under a variety of conditions, but to no avail.

Because of the anomalous reaction observed when urethane protection was used, the reaction was investigated using the chloroacetyl group to protect the amine function of the dehydroamino acid. The esters **6c**[2] and **6d**[2] were therefore reacted with 2-(chloroacetylamino)-acrylic acid **8b**[14] in the presence of PCl_3 as shown in Scheme 2. The products obtained, **7i**† and **7j**,† were those expected from 'normal' cyclisation, having spectral and analytical characteristics of the other pyridothiazines in Scheme 1. An attempt to resolve these racemic products by selective hydrolysis of the L-chloroacetamide using immobilised acylase I from *Aspergillus* proved unsuccessful. The chloroacetylamine **7j** was converted to the corresponding free amine† by reaction with *ortho*-phenylenediamine.

We now turned our attention to the synthesis of the 6/5-bicyclic system **1**. The imino ether **12**† was first prepared from ethyl (2*S*)-pyroglutamate[15] in 92% yield using Meerwein's reagent (Scheme 4). This was then reacted with *tert*-butyl cyanoacetate and triethylamine to yield the vinylogous urethane **13**† as a single geometrical isomer in 58% yield. This compound was assumed to be the *Z*-isomer shown, as it would be expected to be stabilised by hydrogen bonding. Treatment with trifluoroacetic acid gave a 1:1 mixture of the *E* and *Z* isomers **14**,† the identity of the isomers in the mixture being determined with the aid of a 2D-COSY spectrum and nOe studies.

The mixed geometric isomers **14** were now reacted with chloroacetylaminoacrylic acid **8b** and PCl_3 to afford the protected hexahydroindolizine **15**† in 41% yield, and treatment of this with *ortho*-phenylenediamine gave the template amino acid **16**.†

The 6/6- and 6/5-bicyclic β-turn free amine templates had now been prepared and it was interesting to see if an 'anomalous' cyclisation reaction might be observed in the reaction of 2-(benzyloxycarbonylamino)-acrylic acid **8a** with the enamine **14**. When these compounds were reacted in the presence of PCl_3, a product was obtained in 21% yield which appeared to be a mixture of pairs of diastereoisomers of **17** and **18**. The only pure product to be obtained by repeated column chromatography was one of the diastereoisomers of the 'anomalous' product **18**. It is interesting that when Millet et al.[1] conducted the condensation of the dehydroamino acid **8a** with a very similar compound to our enamine **14** using 1-ethyl-3-(3′-dimethylaminopropyl)-carbodiimide, only the 'normal' condensation product analogous to **17** was obtained. The PCl_3 cyclisation conditions are therefore important if the anomalous condensation products are to be obtained.

Acknowledgements

One of us (J.M.B.) thanks the EPSRC and GlaxoWellcome for a CASE award.

References

1. Millet, R.; Domarkas, J.; Rombaux, P.; Rigo, B.; Houssin, R.; Hénichart, J.-P. *Tetrahedron Lett*. **2002**, *43*, 5087–5088.
2. Capps, N. K.; Davies, G. M.; Loakes, D.; McCabe, R. W.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3077–3086.
3. Rose, G. D.; Gierasch, L. M.; Smith, J. A. *Adv. Protein Chem*. **1985**, *37*, 1–109.

4. Smith, J. A.; Pease, L. G. *CRC Crit. Rev. Biochem.* **1980**, *8*, 315–399.
5. Nagai, U.; Sato, K. *Tetrahedron Lett.* **1985**, *26*, 647–650.
6. Sato, K.; Nagai, U. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1231–1234.
7. Nagai, U.; Sato, K.; Nakamura, R.; Kato, R. *Tetrahedron* **1993**, *49*, 3577–3592.
8. Wisskirchen, F. M.; Doyle, P. M.; Gough, S. L.; Harris, C. J.; Marshall, I. *Br. J. Pharm.* **1999**, *126*, 1163–1170.
9. Capps, N. K.; Davies, G. M.; Loakes, D.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4373–4381.
10. Frankel, M.; Reichmann, M. E. *J. Chem. Soc.* **1952**, 289–291.
11. **Crystal data** and structure determination were by Molecular Structure Corporation—compound **9b**: $C_{27}H_{26}N_2O_7S$, $M=522.57$, monoclinic, space group $P2_1/a$ (No14), $a=9.799(2)$, $b=19.412(2)$, $c=14.241(1)$ Å, $\beta=98.653(10)$, $V=2678.2(6)$ Å^3, $Z=4$, $D_{calc}=1.296$ mg m^{-3}, μ(Cu-Kα, λ 1.54178 Å)$=14.78$ cm^{-1}, T 296 K. Rigaku AFC5R, 8767 total reflections measured; 4107 unique ($R_{int}=0.085$). Refined by full-matrix least squares minimising $\Sigma\omega(|Fo|-|Fc|)^2$. Final $R=0.060$ for 1584 reflections with $I>3.00\sigma(I)$, $R_w=0.067$ for all reflections and 275 variables. The atomic coordinates are available on request from The Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW (deposition number CCDC 190455).
12. Öhler, E; Schmidt, U. *Chem. Ber.* **1977**, *110*, 921–941.
13. Love, A. L.; Olsen, R. K. *J. Org. Chem.* **1972**, *37*, 3431–3433.
14. Bergmann, M.; Grafe, K. *Z. Physiol. Chem.* **1930**, *187*, 187–195.
15. Fischer, E.; Boehner, R. *Ber.* **1911**, *44*, 1332–1337.