Pergamon

Tetrahedron Letters, Vol. 36, No. 41, pp. 7545-7548, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01528-0

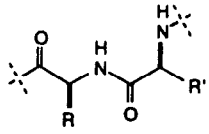
Allylsilanes in Organic Synthesis; Stereoselective Synthesis of *trans*-Alkene Peptide Isosteres

Matthew J. Daly, Richard A. Ward, David F. Thompson, and Garry Procter*

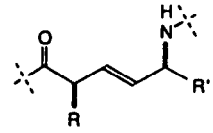
Department of Chemistry and Applied Chemistry, University of Salford, Salford, M5 4WT, Great Britain.

Abstract: Lactones obtained by the diastereoselective dihydroxylation of ester-allylsilanes have been used in the stereocontrolled synthesis of trans-alkene dipeptide isosteres.

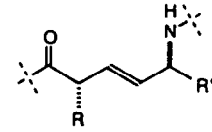
Small peptides can possess a wide range of diverse physiological effects, but despite this, relatively few small peptides find use as drugs.[1] The basis of some of the difficulties in the clinical use of peptides lies in the properties of the amide bond itself. The high polarity of this bond can lead to lower oral activity and make crossing of the blood-brain barrier inefficient. Moreover, endogenous proteases are highly efficient at peptide hydrolysis which can lead to rapid metabolic deactivation of the original biologically active peptide. As a result of these problems, a number of isosteric replacements for the peptide bond have been developed.[2] Of particular interest to us is the replacement of a dipeptide unit **1** by a *trans*-alkene isostere with either the 'natural' or 'unnatural' stereochemistry (**2** and **3** respectively, Scheme 1). There continues to be considerable interest and activity in the development of methods for the synthesis of this type of isostere,[3] and we report here a method based on the chemistry of silanes which provides access to both the 'natural' or 'unnatural' stereochemistry.



(*S,S*)-Dipeptide unit
1



(*S,S*)-*trans*-Alkene isostere
2

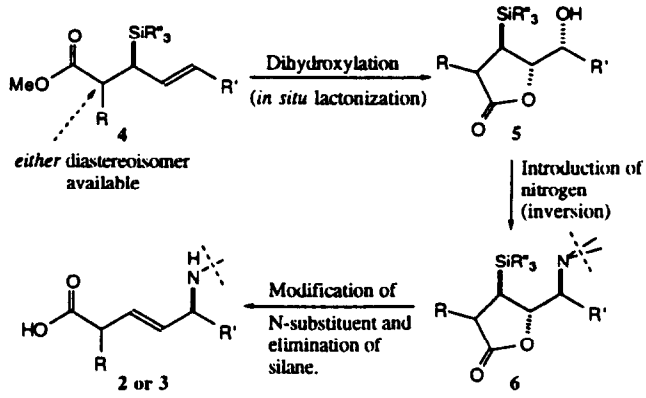


(*R,S*)-*trans*-Alkene isostere
3

Scheme 1

The aim of this work was to develop a strategy which could be used to produce either enantiomer of **2** or **3** predictably, which avoided the use of Wittig and related methods for double bond formation, and which could be adapted to provide either enantiomer without reliance on the 'chiral pool'. The approach which was adopted relies on previous work on the stereoselective dihydroxylation of chiral allylsilanes,[4] and the methods which are available for the control of relative and absolute stereochemistry of allylsilanes such as **4**.[5] The general approach is shown in Scheme 2.[6]

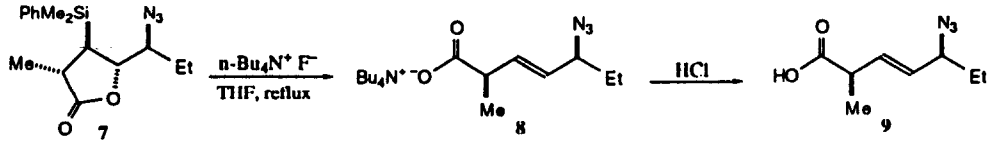
Stereoselective dihydroxylation of **4** gives lactones **5** with good to high diastereoselectivity, and these hydroxy-lactones have previously been converted to the corresponding azido-lactones (equivalent to **6**).[4] In principle elimination of the silane and reduction of the azide (in either order) should give the desired isosteres.



Scheme 2

In order to the explore the feasibility of the conversion of systems such as **6** into **2/3** and to examine the scope of this approach, the initial work in this area has been carried out using racemic materials.[7]

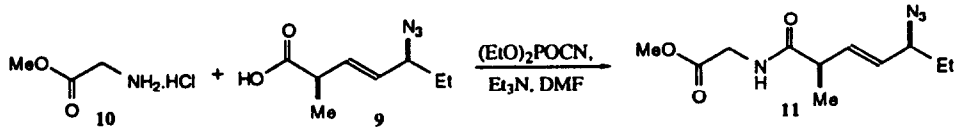
Given the versatility of azides as masked amino groups and that in previous work we have prepared azido-lactones equivalent to **6**,[4] the elimination (**6** → **2/3**) was studied initially. The product of such an elimination would be an allylic azide, which are known to equilibrate readily *via* 3,3-sigmatropic rearrangement.[8] We hoped that in these systems the desired regioisomer, in which the two secondary centres are remote, would be more stable than the alternative regioisomer in which the secondary centres would be adjacent. To probe this we studied the elimination of the azide-lactone **7**, available from our earlier work.[4]



Scheme 3

Elimination of the azide-lactone **7** was achieved simply by reflux with tetrabutylammonium fluoride (Scheme 3) to give the salt **8** in essentially quantitative yield, and acidification gave a similar yield of the corresponding acid **9**.[9]

The coupling of acids such as **9** with suitably protected amino acids would be an important step in the synthesis of tripeptide (and higher) analogues. However, this could in principle be complicated by movement of the double bond into conjugation with the carboxyl group, or by elimination of azide to produce the corresponding conjugated diene, under the conditions required for coupling. In order to examine this the coupling of acid **9** and methyl glycinate hydrochloride **10** was studied, and efficient coupling was achieved



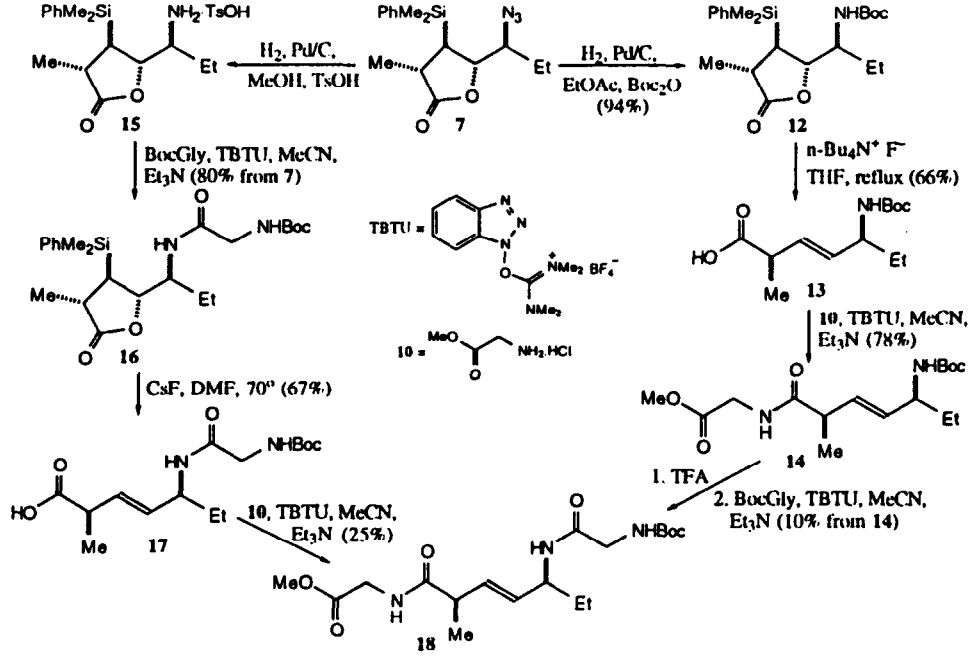
Scheme 4

with diethyl phosphorocyanidate (DEPC, $(EtO)_2P(O)CN$)[10] in the presence of triethylamine (Scheme 4).[11]

So far, we have been unable to reduce the allyl azides **9** and **11** cleanly to the corresponding amines, or derivatives thereof, thereby limiting their usefulness in the synthesis of peptide isosteres, although in principle such stereodefined allyl azides do have potential in other areas of organic synthesis. The solution to this problem proved to be simple, and is outlined below.

Azido-lactones such as **7** can be reduced in the presence of di-*tert*-butyl dicarbonate to produce the protected amino-lactone **12** (Scheme 5).[4,12] Treatment of this lactone with tetrabutylammonium fluoride followed by acidification resulted in formation of the *N*-protected isostere **13** (Scheme 5). Isostere **13** could be coupled with methyl glycinate to provide the tripeptide analogue **14**. An alternative strategy for the construction of tripeptide analogues was also explored (Scheme 5). This involved reduction of the azide in **7** to provide salt **15**, which could be coupled under standard conditions to Boc-glycine to give **16**. This coupling proceeded smoothly and in high yield despite the intermediacy of the corresponding free amine, presumably lactam formation is slower than the coupling step. Elimination of lactone **16** was more difficult than for **12** and required CsF in DMF at 70°. The two tripeptide analogues **14** and **17** were be converted into the same tetrapeptide analogue for comparison purposes, as shown in Scheme 5. Although the yields are low for these latter conversions, no attempt has been made as yet to identify the cause and the yields are not optimized.

In conclusion, we have demonstrated that silyl-lactones such as **5**, which are readily available using stereocontrolled syntheses, are convenient precursors for units which represent *trans*-alkene peptide isosteres. Moreover, two coupling/elimination strategies are possible, making this a flexible approach to such isosteres.

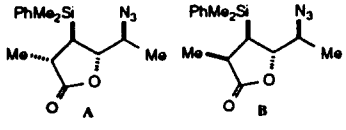


Scheme 5

Acknowledgement: We thank Wellcome and the SERC for CASE studentships (to R.A.W. and M.J.D.).

References

1. For example, see *Peptide Pharmaceuticals*, (ed. D. Ward), Open University Press, Buckingham, 1991.
2. Spatola, A.F. in *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*, Vol 7, (ed. B. Weinstein), Marcel Dekker, New York, 1983.
3. For recent work, and comprehensive references to the literature, see Fujii, N.; Nakai, K.; Tamamura, H.; Otaka, A.; Mimura, N.; Miwa, Y.; Taga, T.; Yamamoto, Y.; Ibuka, T. *J. Chem. Soc., Perkin Trans. 1*, **1995**, 1359–1371; Wipf, P.; Fritch, P.C. *J. Org. Chem.*, **1994**, *59*, 4875–4886; McKinney, J.A.; Eppley, D.F.; Keenan, R.M. *Tetrahedron Lett.*, **1994**, *35*, 5985–5988.
4. Ward, R.A.; Procter, G. *Tetrahedron Lett.*, **1992**, *33*, 3363–3366. For a discussion of the stereoselectivity of the reaction of allylsilanes with osmium tetroxide, see Fleming, I.; Lawrence, N.J.; Sarker, A.K.; Thomas, A.P. *J. Chem. Soc., Perkin Trans. 1*, **1992**, 3303–3308.
5. For example:- a) Crump, R.A.N.C.; Fleming, I.; Hill, J.H.M.; Parker, D.; Reddy, N.L.; Waterson, D. *J. Chem. Soc., Perkin Trans. 1*, **1992**, 3277–3294; b) Fleming, I.; Kilburn,J. *J. Chem. Soc., Perkin Trans. 1*, **1992**, 3295–3302; c) Sparks, M.A.; Panek, J.S. *J. Org. Chem.*, **1991**, *56*, 3431–3438; d) Clark, T.D.; Panek, J.S. *J. Org. Chem.*, **1992**, *57*, 4323–4326; e) Panek, J.S.; Beresis, R.; Xu, F.; Yang, M. *J. Org. Chem.*, **1991**, *56*, 7341–7344; f) Procter, G.; Russell, A.T.; Murphy, P.J.; Tan, T.S.; Mather, A.M. *Tetrahedron*, **1988**, *44*, 3953–3973; g) Murphy, P.J.; Procter, G. *Tetrahedron Lett.*, **1990**, *31*, 1059–1062.
6. For approaches related to this strategy, see a) Clayden, J.; Collington, E.W.; Lamont, R.B.; Warren, S. *Tetrahedron Lett.*, **1993**, *34*, 2203–2206; b) Rehders, F.; Hoppe, D. *Synthesis*, **1992**, 859–870. In this latter paper, *N,N*-dibenzyl protected lactones such as **6** (N= = NBn_2, R=H, R'=Bu^i, SiR"$_3$=$SiMe_2Ph$) were prepared in a 1:1 ratio, separated, and alkylated *anti* to the silicon group. The corresponding *syn*-isomer was obtained by epimerization (up to 1.79:1 in favour of the *syn*-isomer). Both of these diastereoisomers iwere converted to the*N,N*-dibenzyl protected *trans* alkene peptide isosteres.
7. Ref. 5d and references cited therein.
8. For example, Panek, J.S.; Yang, M.; Muler, I. *J. Org. Chem.*, **1992**, *57*, 4063–4064; Beresis, R.; Panek, J.S. *Bioorg. Med. Chem. Lett.*, **1993**, *3*, 1609–1614.
9. To check that the relative stereochemistry was not affected in the elimination, **A**, **B**, and a 1:1 mixture of **A** and **B** were subjected to elimination. A comparison of the ^{1}H n.m.r. spectra of crude products from these reactions indicated little loss of stereochemistry.



10. Takuma, S.; Hamada, Y.; Shioiri, T. *Chem. Pharm. Bull.*, **1982**, *30*, 3147–3153.
11. We have also shown that the tetrabutylammonium salt of the *trans*-alkene isostere can be used in this coupling. Conversion of the lactone-azide into the potential tripeptide analogue becomes a single pot reaction.
12. Gosh, A.K.; McKee, S.P.; Thompson, W.J. *J. Org. Chem.*, **1991**, *56*, 6500–6503.

(*Received in UK* 24 *July* 1995; *accepted* 11 *August* 1995)