Pergamon

Tetrahedron Letters, Vol. 37, No. 15, pp. 2651-2654, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00352-8

A General Synthesis of Oligopeptides Containing an Oxirane Ring in the Place of a Peptidic Bond

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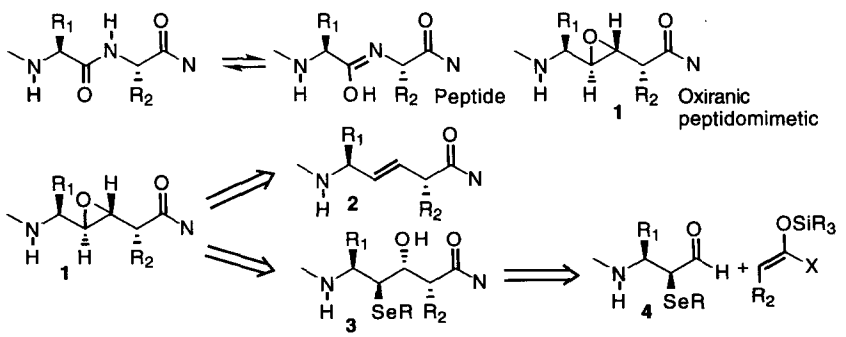
Abstract: *Molecules structurally analogous to dipeptides, containing an oxirane ring in the place of the peptidic bond, can be prepared by oxidative conversion of β-hydroxyselenides obtained by Mukaiyama aldol type reaction of N-protected β-amino α-selenyl aldehydes derived from naturally occurring amino acids.*

Oligopeptides containing an oxirane ring have been recently identified as inhibitors of a variety of proteases, such as HIV-1 protease,[1] cysteine proteases[2] or metalloproteases (for example: carboxypeptidase A).[3] Co-ordination to the metal or protonation of the epoxide in the active site of the enzyme enhance the reactivity of the small heterocycle which can undergo nucleophilic attack from the enzyme. The ring opening product, covalently bonded to the active site, irreversibly blocks the enzyme. For this reason, oxirane containing peptidomimetics are good candidates to become transition states analogues and/or suicide inhibitors with long term efficacy in *vivo*.[4]

Following our experience in the field of peptidomimetic compounds,[5] we designed a "real" oxiranic peptidomimetic structure where the three membered ring mimics the peptidic bond inside the oligopeptidic frame, as for structure **1** in Scheme 1. Accordingly we thought that a *trans* oxirane could be more similar to the *transoid* hydroxy-iminic structure which contributes to the transition state during the peptide cleavage done by a protease.[6]

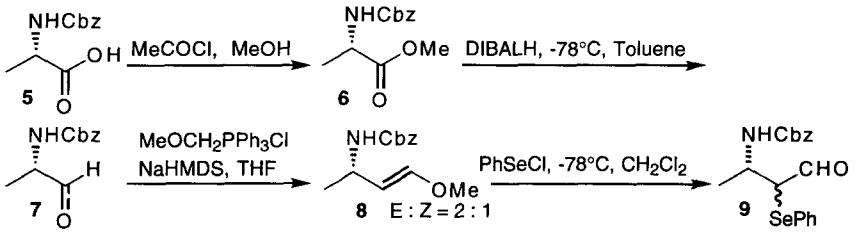


Scheme 1

Two possible retrosynthetic analyses of this epoxide are reported in Scheme 1. A synthesis based on the mCPBA epoxidation of a *trans* alkene isostere (**2**) has been recently reported.[7] The corresponding epoxide has been obtained with good but varying stereoselectivity. We decided to follow the second analysis reported in

Scheme 1, based on a ring closure of the oxirane via oxidative conversion of a β-hydroxyselenide (**3**) which could be obtained from a β-selenyl aldehyde (**4**) using a Mukaiyama aldol type reaction.

The required amino selenyl aldehyde was obtained, following the reaction sequence described in scheme 2, starting from a naturally occurring amino acid.

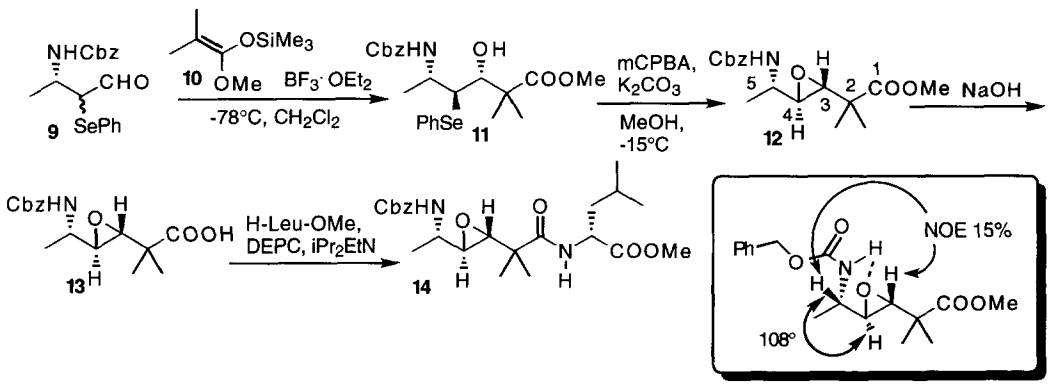


Scheme 2

N-Carbobenzyloxy (Cbz) L-Alanine (**5**) was converted into the methyl ester **6** with acetyl chloride and methanol and reduced to aldehyde **7** with DIBALH in toluene at -78°C in 75% overall yield.[8] Aldehyde **7** was transformed into the methylvinyl ether **8** through a Wittig reaction. The ylide generated from methoxymethyl-triphenylphosphonium chloride with bis-(trimethylsilyl) sodium amide (NaHMDS) gave a 2 : 1 mixture of the *E* and *Z* vinyl ether **8**. Electrophilic addition of phenylselenyl chloride at -78°C gave aldehyde (**9**) in 65% yield as an unseparable mixture of diastereoisomers. The direction of the attack of the selenyl electrophile was not influenced by the stereochemistry of the double bond: a pure sample of *E*-(**8**), obtained after separation by column chromatography, gave the same composition of the mixture of diastereomers. Although disappointed from this result, we carried over the synthesis, putting off to the next step a possible separation of the isomers.

As a model for the Mukaiyama aldol type reaction we chose a nonstereogenic silylketene acetal, (**10,** prepared from 3-methyl butanoic acid methyl ester, LDA and Me_3SiCl in ether) successfully employed by Cozzi et al. in stereo controlled reactions with α-thio-substituted chiral aldehydes.[9]

The reaction performed in the presence of 1 or more equivalents of boron trifluoride etherate gave product **11** in 35-40% yield as *a single diastereoisomer* together with 20% of unreacted starting material (always as a diastereomeric mixture).



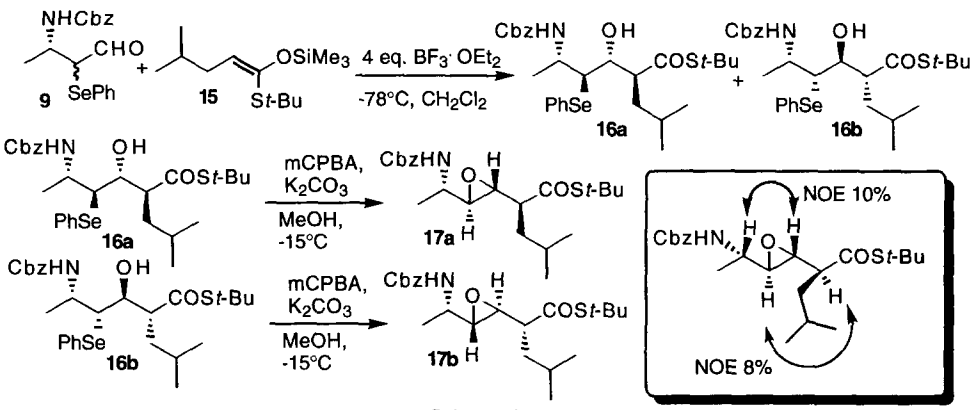
Scheme 3

The identity and the unity of **11** were verified by ^1H NMR (200 and 500 MHz) and ^{13}C NMR (50 MHz) spectra. Although different reaction conditions were tried we never observed increase of the yields or formation

of other isomers of **11**. This β-hydroxyphenylselenyl derivative was transformed into the desired epoxide (**12**) by treatment with mCPBA and K_2CO_3 in methanol at -15°C in 85% yield.[10] Hydrolysis of the methyl ester with a solution of NaOH (0.1 M in MeOH) gave the acid **13** in 96% yield. Compound **13** behaves as a "normal" Cbz protected amino acid and can be coupled, using standard liquid phase techniques, with other amino acids or peptides as described in Scheme 3 for compound **14**.

The stereochemistry of **12** was assigned by ^1H NMR analysis. The *trans* arrangement of the epoxide was established from the value of the epoxide coupling constant (J = 2.2 Hz). The relative stereochemistry between C-5 and C-4 was determined by NOE experiments. Irradiation of the doublet at δ 3.0 (CH-3) gave a significative enhancement (15 %) at CH-5 and no effect at CH-4. Analogously irradiation at CH-4 did not show any enhancement at CH-5. These results, together with the value of the coupling constant between CH-5 and CH-4 (J = 3.0 Hz), corresponding to a dihedral angle of about 108°, suggest that the (3*R*,4*R*,5*S*) epoxide was formed and that one of the possible low energy conformers in solution was the intramolecularly hydrogen bonded product described in Scheme 3. This structure was correlated with the (3*R*,4*S*,5*S*) hydroxyselenyl derivative **11** having an *anti* relationship between C-3 and C-4.[10] This result points out that only the (2S,3S) selenyl aldehyde **9** reacts with the hindered silyl ketene acetal **10** to give selectively the non-chelation-controlled anti product (of course in less than 50% yield). Unfortunately it was not possible to recover the pure unreacted (2*R*,3*S*) selenyl aldehyde **9** due to the epimerisation at C-2 which occurs during chromatographic separation.[11]

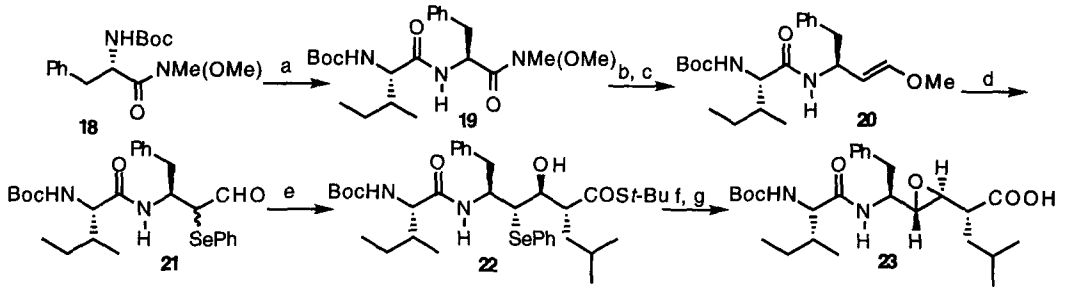
The condensation between stereogenic silyl thio-ketene acetal **15**[12] and aldehyde **9** gave the aldol product in 75% yield as a 1 : 1 mixture of only two diastereoisomers (**16a** and **16b**).



Scheme 4

These isomers were separated by column chromatography on silica gel and independently transformed into the corresponding epoxides **17a** and **17b** with excellent yields (85-90%). Simple ^1H NMR and NOE analysis of epoxide **17a** and **17b** confirmed that the structures of the products are those reported in Scheme 4. That means that the only stereodifferentiation occurring in the reaction is due to the different configuration of the C-2 of aldehyde **9.** This result points out also that the high diastereofacial preference observed for the reaction of nonstereogenic nucleophiles is maintained and that the selenyl substituent in α- position on the chiral aldehyde can be exploited to promote good levels of stereocontrol in Mukaiyama aldol type addition of silylated nucleophiles.

The synthesis described here is quite general allowing the preparation of any kind of oligopeptides containing a *trans* oxirane ring in the place of a peptidic bond, as described in Scheme 5 for the preparation of a N-Boc tripeptide (**23**) that can be further coupled at the acidic function with other aminoacids.



a) TFA, Et_3SiH, CH_2Cl_2 followed by Boc-Ile-OH, DEPC, i-Pr_2EtN, CH_2Cl_2, rt, 12 h. (**19**, 67%). b) $LiAlH_4$, THF 0°C c) $MeOCH_2PPh_3Br$, NaHMDS, toluene, rt (**20**, 59%, E/Z = 7/2). d) PhSeCl, K_2CO_3, CH_2Cl_2, -78°C (**21**, 71%) e) **15**, 4 eq $BF_3{\cdot}OEt_2$, -15°C, 12 h, chromatographic separation. f) mCPBA, (3 eq) MeOH, Na_2CO_3, -15°C. g) NaOH 0.1 M, MeOH, rt, 12 h. (**23** 39%).

Scheme 5

Acknowledgements. *This work has been partially financed by C.N.R (Rome) as a " Contributo di Ricerca n. 93.03239.03.*

References and Notes.

1. Park, C.; Koh, J. S.; Son, Y. C.; Choi, H.; Lee, C. S.; Choy, N.; Moon, K. Y.; Jung, W. H.; Kim, S. C. Yoon, H. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1843.
2. Albeck, A.; Persky, R.; Kliper, S. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1767. Giordano, C.; Gallina, C.; Consalvi, V.; Scandurra, R. *Eur. J. Med. Chem.* **1990**, *25*, 479.
3. Kim, D.H.; Kim, K.B.J. *J. Am. Chem. Soc.* **1991**, *13*, 3200.
4. Cane, D.E.; Sohng, J-K. *Biochemistry*, **1994**, *33*, 6524 and references therein.
5. D'Aniello, F.; Mann, A.; Mattii, D.; Taddei, M. *J. Org. Chem.* **1994**, *59*, 3762. Ciapetti, P.; Taddei, M.; Ulivi, P. *Tetrahedron Lett.* **1994**, *35*, 3183.
6. Gante, J. *Angew. Chem. Int. Ed. Eng.* **1994**, *33*, 1699.
7. Jenmalm, A.; Berts, W.; Li, Y-L.; Luthman, K.; Csöregh, I.; Hacksell, U. *J. Org. Chem.* **1994**, *59*, 1139. For recent efficent syntheses of *trans* alkene isosteres see: Daly, M.J.; Ward, R.; Thompson, D.F.; Procter, G. *Tetrahedron Lett.* **1995**, *36*, 7545. Baresis, R.T.; Masse, C.E.; Panek, J.S. *J. Org. Chem.* **1995**, *60*, 7714. Wai, J.S.; Fisher, T.E.; Embrey, M.W. *Tetrahedron Lett.* **1995**, *36*, 3461.
8. This protocol was the only one that (in our hands) guaranteed high yields of N-Cbz-α-amino aldehydes.
9. Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P. G.; Consolandi, E. *J. Org. Chem.* **1992**, *57*, 456.
10. Uemura, S.; Ohe, K; Sugita, N. *J. Chem. Soc. Chem. Commun.* **1988**, 111. Ceccherelli, P.; Curini, M.; Epifanio, F.; Marcotullio, M.C. Rosati, O. *Tetrahedron Lett.* **1995**, *36*, 5079.
11. Poli, G.; Belvisi, L.; Mantoni, L.; Scolastico, C. *J. Org. Chem.* **1993**, *58*,3165
12. Gennari, C.; Beretta, M.G.; Bernardi, A.; Moro, G.; Scolastico, C.; Todeschini, R. *Tetrahedron* **1986**, *42*, 893.

(*Received in UK* 23 *January* 1996; *revised* 16 *February* 1996; *accepted* 23 *February* 1996)