Tetrahedron Letters,Vol.28,No.23, pp 2595-2596,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

# A FORMAL SYNTHESIS OF ASPARTAME VIA THE OXAZIRIDINE - AMIDE REARRANGEMENT

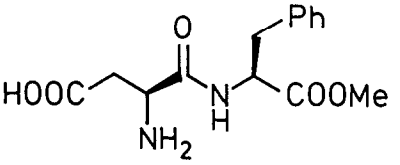
Pierre DUHAMEL *, Bertrand GOUMENT and Jean - Christophe PLAQUEVENT

Laboratoire de Chimie Organique de l'UFR Sciences et Techniques de ROUEN
UA CNRS 464 et IRCOF, BP 67, F 76130 MONT SAINT AIGNAN

Summary : A formal synthesis of the dipeptide sweetener aspartame via the oxaziridine - amide rearrangement is reported. Thus, the peptidic oxaziridine 4 was prepared and was photochemically isomerized into the aspartame precursor 5.

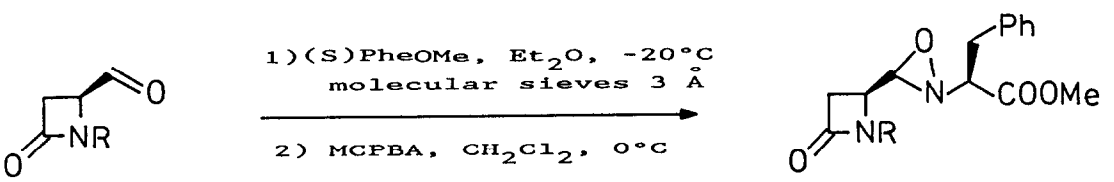
As part of our programme for the non classical creation of peptide bonds, we recently described a non isohypsic method (1) essentially based on oxaziridine - amide isomerization (2). Here we wish to report a formal synthesis of the dipeptide sweetener aspartame by this method.

ASPARTAME :




Since the discovery of aspartame (3), much work has been devoted to various syntheses (4) in the search for selective formation of the peptide bond in the α position of the aspartic acid moiety. A recently described α - aminoaldehyde in the β - lactam series (5) appeared to be a valuable starting material for synthesis of aspartame via our oxaziridine approach to peptide bonds.

Thus, (S) N-tertiobutyldimethylsilyl 4-formyl azetidinone 1 (5) was allowed to react with (S) methylphenylalaninate. The intermediate imine 2 was oxidized in situ to give the oxaziridine 3 ( Scheme 1 ) :



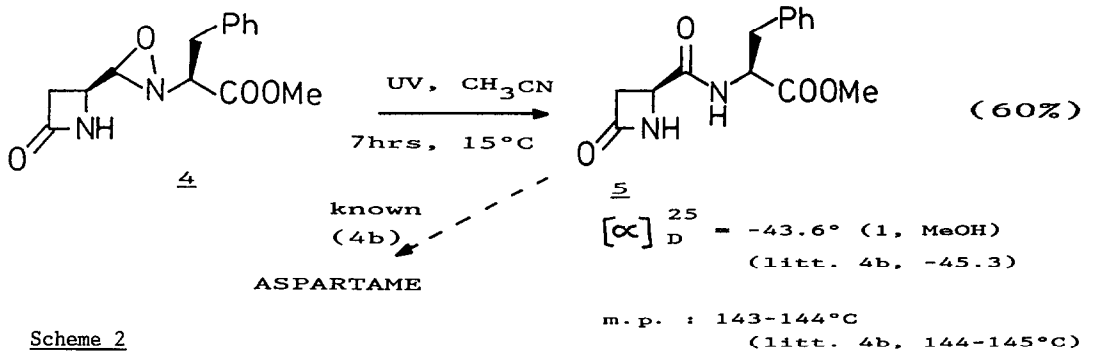

1

R = SitBuMe$_2$

3 ( 65% )

Scheme 1

The corresponding desilylated oxaziridine 4 ( HF/ pyridine, 85% ) was then irradiated with UV light ( Hanovia TQ 150 ) up to complete conversion (6). The material recovered was identified after purification as the dipeptide 5 ( Scheme 2 ) :




Scheme 2

The compound S,S 5 has previously been described by Pietsch (4b) as the direct precursor of aspartame.

The aim of this study was to demonstrate the validity of unusual procedures for the creation of peptide bonds in particular examples. The increasing interest in α - aminoaldehydes (7) and derivatives will offer numerous possibilities of creating peptide bonds with this method.

REFERENCES AND NOTES :

(1)a- P.DUHAMEL, D.BENARD, J.C.PLAQUEVENT, Tet. Lett., 26, 6065 (1985) ; b- D.BENARD, Thèse de Doctorat, ROUEN (1986).

(2)a- W.D.EMMONS, J. Am. Chem. Soc., 79, 5739 (1957) ; b- for a review, see for example E. SCHMITZ, "Advances in Heterocyclic Chemistry", Academic Press, 24, 63 (1979).

(3)a- J.M.DAVEY, A.H.LAIRD, J.S.MORLEY, J. Chem. Soc. (C), 555 (1966) ; b- R.H.MAZUR, J.M. SCHLATTER, A.H.GOLDKAMP, J. Am. Chem. Soc., 91, 2684 (1969).

(4)a- Y.ARIYOSHI, T.YAMATANI, N.UCHIYAMA, Y.ADACHI, N.SATO, Bull. Chem. Soc. Jap., 46, 1893 (1973) ; b- H.PIETSCH, Tet. Lett., 4053 (1976) ; c- Y.ISOWA, M.OHMORI, T.ICHIKAWA, K.MORI, Y. NONAKA, K.KIHARA, K.OYAMA, ibid., 28, 2611 (1979) ; d- F.J.VINICK, S.JUNG, ibid., 23, 1315 (1982) ; e- J.S.TOU, B.D.VINEYARD, J. Org. Chem., 50, 4982 (1985) ; f- C.FUGANTI, P.GRASSELLI, L.MALPEZZI, ibid., 51, 1126 (1986).

(5) R.LABIA, C.MORIN, Chem. Lett., 1007, 2009 (1984). We thank Dr C.MORIN for helpful discussion about the synthesis of (S) 1 and for the generous gift of a precursor of 1.

(6)a- E.OLIVEROS, M.RIVIERE, A.LATTES, Nouv. J. Chim., 3, 739 (1979) ; b- A.LATTES, E.OLIVEROS, M.RIVIERE, C.BELZECKI, D.MOSTOWICZ, W.ABRAMSKJ, C.PICCINNI-LEOPARDI, G.GERMAIN, M.VAN MEERSCHE, J. Am. Chem. Soc., 104, 3929 (1982).

(7) See ref. 5 and a- J.A.FEHRENTZ, B.CASTRO, Synthesis, 676 (1983) ; b- Y.HAMADA, T.SHIOIRI, Chem. Pharm. Bull., 30, 1921 (1982) ; c- C.FREEMAN STANFIELD, J.E.PARKER, P.KANELLIS, J. Org. Chem., 46, 4797 (1981) ; d- K.E.RITTLE, C.F.HOMNICK, G.S.PONTICELLO, B.E.EVANS, ibid., 47, 3016 (1982) ; e- B.GARRIGUES, M.LAZRAQ, Tet. Lett., 27, 1685 (1986) ; f- T.SHONO, Y.MATSUMURA, S.KATOH, K.INOUE, Y.MATSUMOTO, ibid., 27, 6083 (1986) ; g- W.D.LUBELL, H.RAPOPORT, J. Am. Chem. Soc., 109, 236 (1987).

(Received in France 12 April 1987)