Tetrahedron Letters,Vol.23,No.13,pp 1315-1318,1982 0040-4039/82/131315-04$03.00/0
Printed in Great Britain

A SUPERIOR SYNTHESIS OF ASPARTAME

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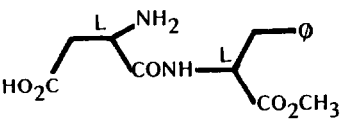
Abstract: The dipeptide sweetener, aspartame, has been prepared in high yield via the coupling of L-phenylalanine methyl ester and L-aspartic acid N-thiocarboxyanhydride.

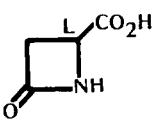
The novel dipeptide sweetener, aspartame,[1] 1, was first synthesized in 1966.[2] Since that time considerable effort has been devoted to discovering a short, highly efficient route to this unique substance.



1

In order to synthesize aspartame effectively one must overcome the inherent difficulty of achieving regiospecific reactivity at the α-carboxyl group of aspartic acid, 2.

Two particularly ingenious solutions to this problem have been reported. Pietsch[3] utilized β-lactam 3 as a means of protecting the aspartyl β-carboxyl group; Isowa and Oyama[4] were able to couple N-carbobenzoxy-L-aspartic acid exclusively at the α-position, employing the enzyme, thermolysin, as a catalyst.



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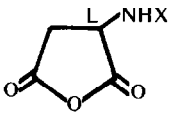
The most commonly used approach to aspartame has, however, involved ring opening of an aspartic anhydride, e.g., 4a-c.[5-8]

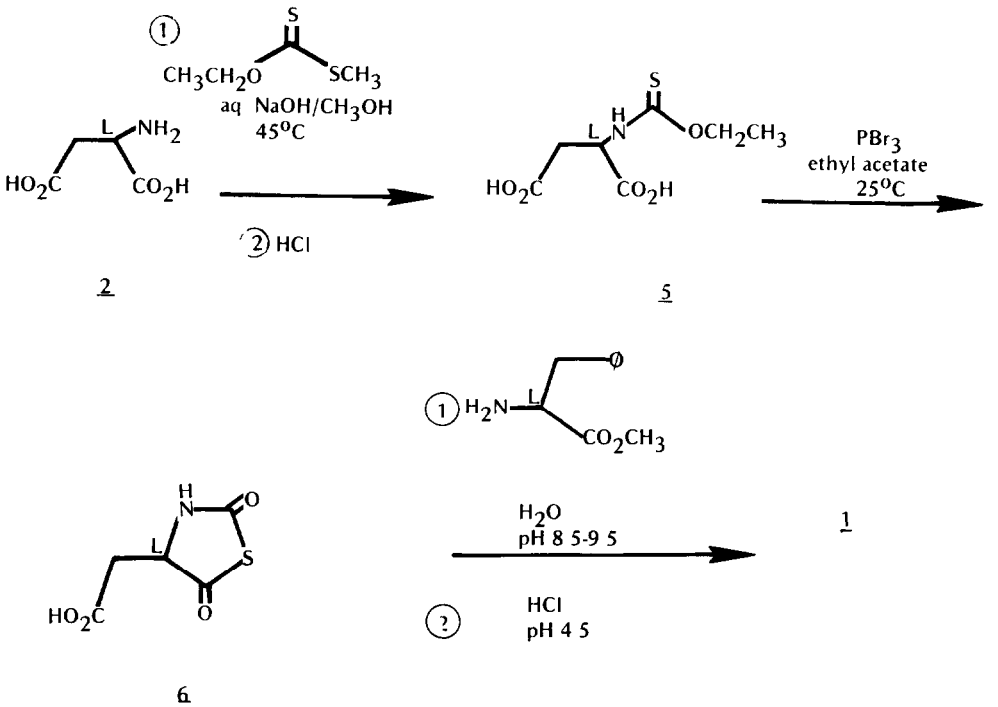


4a X = H•HCl[5a-d]
4b X = CHO[6,7]
4c X = $CO_2CH_2\emptyset$

Due to non-regiospecific ring opening, 4a-c all lead to mixtures of α and β isomers (the α-isomer predominates) which must then be separated.

We wish to report a high yield synthesis of 1 which 1) insures completely regiospecific α coupling, 2) can be carried out in three steps, and 3) utilizes the novel, previously unknown aspartic acid derivative, 6.

The reaction sequence used is outlined in the scheme shown below:



2 5 6 1

Methyl ethyl xanthate (1.1 equivalents) was reacted with 2 (1.0 equivalents) at 45-50°C for 2 hr in a 1:1 mixture of aqueous sodium hydroxide (2.0 equivalents) and methanol to give thionourethane 5 (89%; mp 133°C; $[\alpha]_D^{25°}$ = +57.1° (C=1, THF)). When a solution of 5 (1.0 equivalent) in ethyl acetate was treated with PBr_3 (0.35 equivalents) at 25°C, a mildly exothermic reaction took place, and white crystals of L-aspartic acid N-thiocarboxyanhydride (L-Asp-NTA), 6,[9] precipitated (90%; mp 200-205°C (dec.); $[\alpha]_D^{25°}$ = -109° (C=1, THF)).

The preparation of this NTA, a unique substance with interesting physical and chemical properties, merits further discussion.

Amino acid NTA's have rarely been used in peptide synthesis.[10a] Compound 6 has been alluded to in the patent literature,[10b] but its preparation, characterization, and utilization have never been reported. In light of the instability of the Leuch's anhydride (NCA) of L-aspartic acid,[10c] we were not sure that 6 could, in fact, be synthesized. Consequently, we were surprised to find that 6 could be made in high yield as a stable, crystalline material. Attempts to prepare 6 using reagents other than PBr_3 (e.g., PCl_3, PCl_5, acetyl bromide) led to significant decreases in yield and/or optical purity.[11]

The critical peptide coupling reaction was then carried out under conditions of pH and temperature control[10a] as described below:

L-Phenylalanine methyl ester hydrochloride (108 g, 0.50 mol) was dissolved in 900 ml of water at 0-5°C and the pH of the solution adjusted to 9.1 with 50% aqueous sodium hydroxide. Compound 6 (105 g, 0.60 mol) was then added portionwise with vigorous stirring; the pH was maintained at 8.5-9.5 by the addition of more base as needed. After the completion of the NTA addition, stirring was continued at 0-5°C until the pH stabilized at 9.1 (1 hr). The reaction mixture was diluted with an equivalent volume of methanol and adjusted to pH 4.5-5.0 at 0°C with 12N HCl (COS gas evolution). The precipitated aspartame was collected by filtration and washed with 350 ml of ice water.[12] The crude product was redissolved in fresh water (1% solution) and purified by ion exchange chromatography[5c] (Bio•Rad AG 1-X4 resin; acetate form). The eluate was concentrated to a 6% slurry of 1 and chilled. The aspartame was collected by filtration, washed with 100 ml of ice water, and thoroughly dried. The yield of analytically pure 1 was 96.0 g (63%; mp 243°C (dec.); lit mp 246-247°C[2] and 235-236°C (dec.)[5c]; $[\alpha]_D^{25°}$ = +31.2° (C=1, acetic acid; $[\alpha]_D^{25°}$ = +32.0° (C=1, acetic acid)[5a]). This material had spectral and physical properties which were identical to those of an authentic sample.

Our synthesis of aspartame thus demonstrates that this novel sweetener can be prepared in high yield with complete regiochemical control via a short, simple series of chemical steps.

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2. J. M. Davey, A. H. Laird, and J. S. Morley, J. Chem. Soc., 555 (1966). This classical approach to the synthesis of aspartyl peptides utilizes N-carbobenzoxy-L-aspartic acid-β-benzyl ester. As pointed out by Isowa and Oyama,[4] selective esterification at the β-carboxyl group of aspartic acid is difficult and does not proceed in high yield. Furthermore, side chain aspartyl ester groups are prone to undergo unwanted ring closure reactions.
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5. a) Y. Ariyoshi and N. Sato, Bull. Chem. Soc. Jap., 45, 942 (1972); b) Y. Ariyoshi, T. Yamatani, N. Uchiyama, and N. Sato, ibid., 45, 2208 (1972); c) Y. Ariyoshi, T. Yamatani, N. Uchiyama, Y. Adachi, and N. Sato, ibid., 46, 1893 (1973); d) Y. Ariyoshi, T. Yamatani, and Y. Adachi, ibid., 46, 2611 (1973).

6. U.S. patent, 3,933,781 (1976).
7. U.S. patent, 3,879,372 (1975).
8. Br. patent, 1,243,169 (1971).
9. ir (KBr 3225, 1739, 1724, 1653, 1399 cm^{-1}; nmr (DMSO-d_6) δ 2.83 (d, 2H, J=5.0 Hz), 4.70 (t, 1H, J=5.0 Hz), 9.23 (bs, 2H, ex.); MS m/e 175 (M^+), 87, 60.
10. a) R. S. Dewey, E. F. Schoenewaldt, H. Joshua, W. J. Paleveda, Jr., H. Schwam, H. Barkemeyer, B. H. Arison, D. F. Veber, R. G. Strachan, J. Milkowski, R. G. Denkewalter, and R. Hirschmann, J. Org. Chem., 36, 49 (1971); b) U.S. patent, 3,846,398 (1974); c) R. Hirschmann, H. Schwam, R. G. Strachan, E. F. Schoenewaldt, H. Barkemeyer, S. M. Miller, J. B. Conn, V. Garsky, D. F. Veber, and R. G. Denkewalter, J. Am. Chem. Soc., 93, 2746 (1971). Aspartic acid NCA is moisture-sensitive, difficult to isolate in crystalline form, and available in only 20-25% yield.
11. A more detailed discussion of the synthesis of optically pure L-Asp-NTA will be presented in a separate paper.
12. The water wash removes both occluded sodium chloride and D-Asp-L-PheOMe. This impurity results from racemization of 6 during the coupling reaction; it is formed to the extent of ca. 8%. Unlike aspartame, D-Asp-L-PheOMe is extremely water soluble and thus readily purged.

(Received in USA 24 November 1981)