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SYNTHESIS OF β,γ-UNSATURATED AMINO ACIDS AS POTENTIAL CATALYTIC IRREVERSIBLE ENZYME INHIBITORS

Brian W. METCALF* and Karin JUND

Centre de Recherche Merrell International
16, rue d'Ankara, 67000 Strasbourg - France

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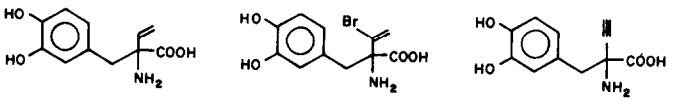
As a continuation of our work on the design and synthesis of catalytic irreversible enzyme inhibitors[1], we wish to present the synthesis of α-vinyl-3,4-dihydroxyphenylalanine (α-vinyl DOPA) (1), α-bromovinyl DOPA (2) and α-acetylenic DOPA (3), potential irreversible inhibitors of the pyridoxal phosphate (PyCHO) - dependent DOPA-decarboxylase.



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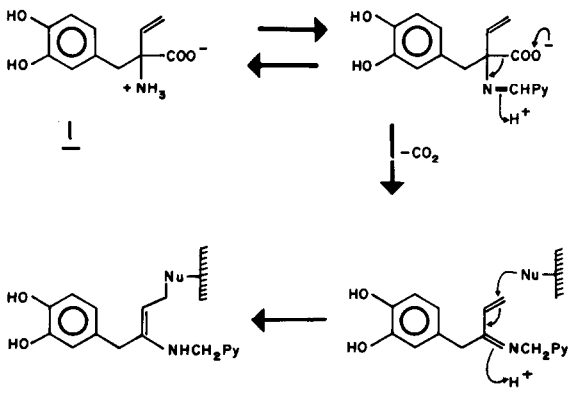
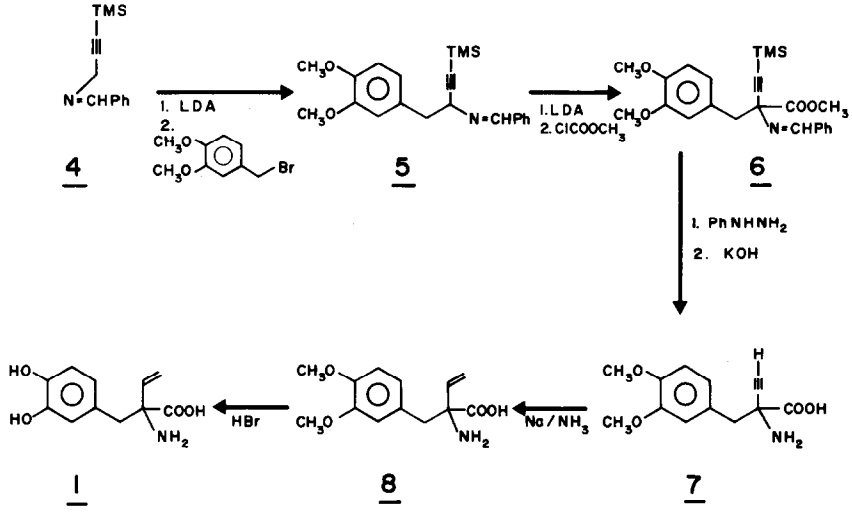
The proposed mechanism of inhibition, illustrated with α-vinyl DOPA (1), is outlined as follows:



Thus loss of CO_2 from the Schiff's base formed between pyridoxal phosphate and the unnatural substrate 1 would lead to formation in the enzyme active site of a vinyl imine. Inactivation could then occur via the Michael addition of a nucleophilic residue (Nu) in the active site to the conjugated imine. In a similar manner α-bromovinyl DOPA (2) and α-acetylenic DOPA (3) may also be expected to produce irreversible inhibition of this enzyme [2].

The synthesis of α-vinyl DOPA (1) is shown below and relies on the consecutive regioselective alkylation and acylation of anions derived from the appropriately activated propargylamine 4 [1a,3]



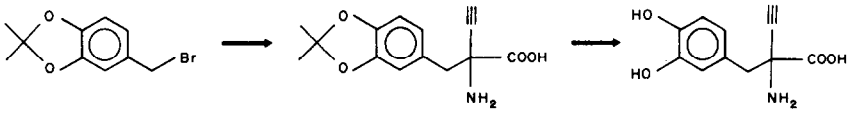
Treatment of the anion derived from the aldimine 4 [1a] (1 eq. lithium diisopropylamide (LDA), THF, -70°C) with 3,4-dimethoxybenzyl bromide (0.9 eq., 30 min. -70°C) led mainly to the monoalkylated imine 5 [4], some dialkylation occurring. The use of LDA to generate the anion from the aldimine 4 was essential in order to avoid the extensive dialkylation observed when n-BuLi was used as base. 5 was treated in situ (1 eq. n-BuLi, -70°C) so as to generate a second propargylic anion. This anion, when trapped with $ClCOOCH_3$ (1 eq., 30 min., -70°C), afforded the protected amino acid 6 [4]. It is to be noted that no allenic products were detected by n.m.r. or i.r. spectroscopy at either stage of the synthesis of 6. The alkylation of 4 and acylation of 5 thus appear to be regioselective processes.

Owing to the instability of intermediates 5 and 6 to chromatography and distillation, crude 6, after isolation by ether extraction, was treated with $PhNHNH_2$ (1 eq., 2 hours, 25°C) to liberate the amine, which when subjected to aqueous KOH (5 eq. in aq. CH_3OH , 1 hour) afforded

the stable amino acid 7 [4,5] (m.p. 225°C). The acetylenic amino acid 7 is thus available in 50 % overall yield from 3,4-dimethoxybenzyl bromide. 7 was reduced ($Na/(NH_4)_2SO_4/NH_3$) [6] to the vinyl amino acid 8 [4,5] (m.p. 250°C) in 85 % yield. Cleavage of the methyl ether protecting groups by treatment of 8 with 47 % HBr (reflux 2 hours) then gave, after neutralisation, α-vinyl DOPA 1 (260° decomp., 62 %) [4,5].

α-Bromovinyl DOPA 2 [4,5] (m.p. 280°C, $J(C=CH_2)$ = 3 Hz) [7] was isolated in 31 % yield when the acetylenic amino acid 7 was treated with 47 % HBr (reflux 4 hours).

Acid hydrolysis (HCl 6N) of the 3,4-isopropylidene analog 9 [4] of 7, prepared in a similar manner from 3,4-isopropylidene benzyl bromide 10 [8] gave α-acetylenic DOPA 3 [4,5] (m.p. 210°C, decomp.) in 24 % overall yield from 10.



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We have observed an irreversible component in the inhibition of DOPA decarboxylase with both α-vinyl DOPA 1 and α-acetylenic DOPA 3, which will be reported elsewhere.

References

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   c) B. Lippert, B.W. Metcalf, M.J. Jung and P. Casara, Eur. J. Biochem., 74, 441 (1977).
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