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SYNTHESES OF α-ETHYNYL-3,4-DIHYDROXYPHENYLALANINE AND α-VINYL-3,4-DIHYDROXYPHENYLALANINE

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Current interest in biologically active β,γ-unsaturated α-amino acids[1] prompts us to report syntheses of α-ethynyl-3,4-dihydroxyphenylalanine 6 and α-vinyl-3,4-dihydroxyphenylalanine 8 - to our knowledge the first examples of α-substituted-α-amino acids bearing unsaturation attached to the quaternary α-carbon. These DOPA analogs are of interest as potential active site directed inhibitors of DOPA decarboxylase.

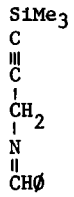
Our synthetic route is based on sequential addition of protected benzylic and carboxy entities to the propargylamine synthon 1.[2] For protection of the base-sensitive catechol system we chose the diphenylmethylene group[3] for its stability to silica gel chromatography and its ready removal by mild acid treatment. Reaction of methyl 3,4-dihydroxybenzoate[4] with diphenyldichloromethane (neat, 150°, 15 min)[3b] yielded methyl 3,4-diphenylmethylenedioxy benzoate, mp 103-105°, which was converted into 3,4-diphenylmethylenedioxybenzyl chloride 2 ($LiAlH_4$, ether, THF, 40°; $SOCl_2$, ether, pyridine, 20°) in 85% overall yield.

Alkylation of 1 with 2 (n-butyl Li, THF, -78°)[2] led quantitatively to crude adduct 3 (ms M^+ 501, 287 ($ArCH_2^+$, base peak), 214 ($Me_3SiC{\equiv}CCHN{=}CH\phi^+$).[5,6] The latter, on acylation with methyl chloroformate (Li diisopropylamide, THF -78°),[7] followed by Schiff base cleavage and purification by dry column chromatography on silica gel H eluting with 2% acetone in $CHCl_3$, gave the trimethylsilyl amino ester 4 in 20-25% yield from 1 [nmr ($CDCl_3$) δ0.17 (s, 9H, $\underline{Me_3}Si$), 1.80 (s, 2H, $\underline{NH_2}$), 3.07 (s, 2H, $Ar\underline{CH_2}$), 3.77 (s, 3H, $COO\underline{Me}$), 6.75 (s, 1H), 6.81 (d, J=7, 2H)-3 ArH, 7.25-7.80 (m, 10 ArH); ms M^+ 471, 412 (M^+-COOMe), 287 ($ArCH_2^+$, base peak), 184 ($Me_3SiC{\equiv}C\text{-}C(NH_2)\text{-}COOMe)^+$].

Desilylation of 4 was easily accomplished by treatment with sodium methoxide (1.2 equiv., 20°, 30 min) in methanol[8] to give the ethynyl amino ester 5 from which minor impurities were removed by silica gel chromatography eluting with 10% acetone in $CHCl_3$ [yield 70%; nmr ($CDCl_3$) δ1.80 (s, 2H, $\underline{NH_2}$), 2.45 (s, 1H, $\underline{HC}\equiv C$), 3.10 (s, 2H $Ar\underline{CH_2}$), 3.75 (s, 3H, COO$\underline{Me}$, 6.75 (s, 1H), 6.79 (d, J=6)-3 ArH, 7.0-7.7 (m, 10 ArH); ms M^+ 399, 340 (M^+-COOMe), 287 ($ArCH_2^+$, base peak)]. The remaining protecting groups were removed by 6N HCl (reflux, 2 hr) and extraction of neutral material with CH_2Cl_2. Concentration of the aqueous acid phase to dryness gave the essentially pure hydrochloride of α-ethynyl DOPA 6 in 90% yield as an amorphous solid [tlc, n-BuOH:H_2O: HOAc:pyr. - 15:3:12:10, single spot R_F ~0.6; nmr (D_2O) δ3.17 (s, 2H, $Ar\underline{CH_2}$), 3.22 (s, 1H, $\underline{HC}\equiv C$), 6.70 (m, 3 ArH); ms M^+ 221, 176 (M^+-COOH), 123 ($ArCH_2^+$, base peak)] which was converted to the free amino acid 6 by treatment with propylene oxide in 1:5 aqueous acetone; mp ~240° dec; M^+, calcd. for $C_{11}H_{11}NO_4$: 221.0687, found: 221.0682.

Partial hydrogenation of the protected amino ester 5 (Lindlar catalyst, EtOAc, 1 Atm H_2, 25°) and chromatographic removal of a minor amount of α-ethyl over reduction product yielded vinyl ester 7 [75%; nmr ($CDCl_3$) δ1.72 (s, 2H, $\underline{NH_2}$), 2.75, 3.18 (AB quartet J=14, 2H, $Ar\underline{CH_2}$),[9] 3.70 (s, 3H, COO$\underline{Me}$), 5.17 (d,d, J=10, 2, 1H), 5.35 (d,d, J=18, 2, 1H), 6.17 (d,d, J=18, 10, 1H)-3 vinyl H, 6.6-6.9 (m, 3 ArH), 7.25-7.80 (m, 10 ArH); ms M^+ 401, 342 (M^+-COOMe), 287 ($ArCH_2^+$)]. Hydrolysis of 7[10] as in the case of 5 → 6 led to the hydrochloride of α-vinyl DOPA 8 [tlc n-BuOH:H_2O:HOAc:pyr - 15:3:12:10 single spot R_F ~0.65; nmr (D_2O) δ3.03, 3.33 (AB quartet, J=15, 2H, $Ar\underline{CH_2}$), 5.35 (d, J=18, 1H), 5.50 (d, J=12, 1H), 6.18 (d,d, J=18, 12, 1H), 6.60-6.95 (m, 3 ArH); ms M^+ 223, 178 (M^+-COOH), 123 ($ArCH_2^+$, base peak). Propylene oxide-aqueous acetone treatment as above led to free amino acid 8, mp ~285° dec; M^+, calcd. for $C_{11}H_{13}NO_4$: 223.0843, found: 223.0837.

Compounds 6 and 8 are potent DOPA decarboxylase inhibitors. Details of the biological studies will be reported elsewhere.[11]



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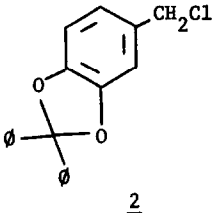

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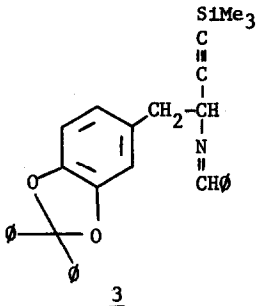

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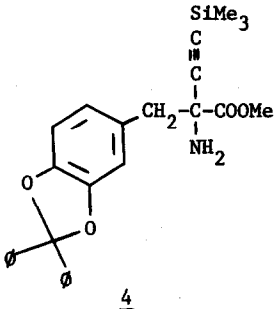

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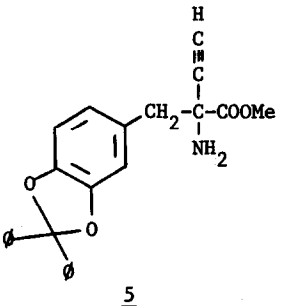

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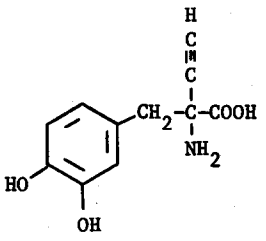

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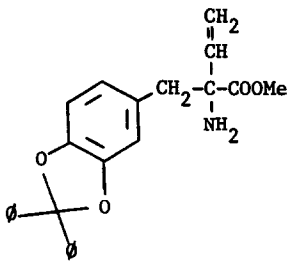

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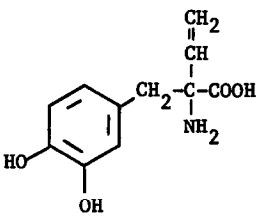

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References

1. See for example, J. E. Baldwin, S. B. Haber, C. Haskins and L. I. Kruse, J. Org. Chem., 42, 1229 (1977) and references therein.

2. B. W. Metcalf and P. Casara, Tetrahedron Lett., 3337 (1975).

3. (a) W. Bradley, R. Robinson and G. Schwarzenbach, J. Chem. Soc., 793 (1930); (b) L. Jurd, J. Am. Chem. Soc., 81, 4606 (1959).

4. K. U. Matsmoto, Ber., 11, 122 (1878).

5. The mass spectra in this series show characteristic strong molecular ion peaks and intense benzyl fragmentation peaks.

6. In the alkylation step a significant amount of the 2:1 adduct is formed. In model studies leading to α-ethynylphenylalanine (hydrochloride, mp 212-215°) distillation of the benzyl chloride - 1 alkylation product gave ~50% of the 1:1 adduct and ~15% of the 2:1 adduct. Presumably equilibration involving proton transfer leads in part to the 1:1 adduct carbanion which is alkylated.

7. Alkylation prior to acylation is important. Attempted monoacylation of synthon 1 led largely to 2:1 adduct and recovered 1.

8. Cf. C. Eaborn and D. R. M. Walton, J. Organometallic Chem., 4, 217 (1965).

9. The non-equivalence of the benzylic hydrogens in 7 and 8 (nmr, 2H AB quartet) is in striking contrast to their equivalence in the analogous ethynyl compounds 5 and 6 (nmr, 2H singlet).

10. The a priori possibilities of decarboxylation or γ-lactone formation were not observed.

11. Personal communication from Dr. Alan Maycock of these laboratories.