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Alpha-amino acids, compositions and process for preparing said compounds.

α -Amino Acids, compositions and process for preparing said compounds α -ethynyl- and α -vinyl- 3,4- disubstituted phenylalanines and esters thereof, have been prepared by reaction of methyl 3,4-dihydroxybenzoate with diphenyldichloromethane, reduction of the so obtained methyl 3,4-diphenylmethylenedioxybenzoate to 3,4-diphenylmethylenedioxybenzyl alcohol, and transforming this to the benzylchloride. This 3,4-diphenylmethylenedioxybenzylchloride reacts with 1-trimethylsilyl-N-benzylidene-3-aminoprop-1-yne to form 3-(3,4-diphenylmethylenedioxybenzyl)-1-trimethylsilyl-N-benzylidene-3-aminoprop-1-yne.

With methyl chloroformate this compound gives 3-carbomethoxy-3-(3,4-diphenylmethylenedioxybenzyl)-1-trimethylsilyl-N-benzylidene-3-aminoprop-1-yne.

The benzylidene-group, the trimethylsilyl-group and the diphenyl-methylene-group are removed, which results in the formation of α -ethynyl- 3,4-dihydroxy- phenylalanine. The α -vinyl- analog is obtained by hydrogenation of an intermediate. The compounds have a pharmaceutical activity.

EP 0 000 035 A1

1 TITLE OF THE INVENTION

Novel α -Amino Acids, Compositions And
Process For Preparing Said Compounds

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BACKGROUND OF THE INVENTION

10 The present invention is concerned with
 α -ethynyl-and α -vinyl-3,4-disubstituted phenyla-
lanines and especially the 3,4-dihydroxyphenyla-
lanine species.

α -Methyl-3,4-dihydroxyphenylalanine,
15 particularly its L-isomer, is a known antihyper-
tensive agent. (U.S. 2,868,818; U.S. 3,344,023).

Novel α -ethynyl-and α -vinyl-3,4-disubsti-
tuted phenylalanines have been discovered. These
novel alanines have pharmaceutical activity in-
20 cluding antihypertensive action.

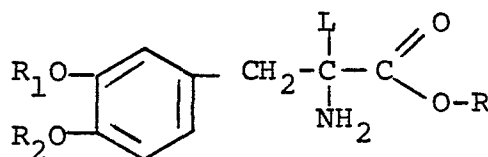
SUMMARY OF THE INVENTION

α -Ethynyl-and α -vinyl-3,4-di-OR-phenyla-
lanines, esters thereof and their pharmaceutical
25 use.

1 DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is embodied in α -ethynyl or α -vinyl phenylalanine compounds having the formula

5



10

I

wherein

L is $-\text{C}\equiv\text{CH}$ or $-\text{CH}=\text{CH}_2$,

R_1 and R_2 are independently selected from H and

15 $\text{C}_2\text{-C}_6$ alkanoyl, and

R is $\text{C}_1\text{-C}_{18}$ alkyl or H.

The pharmaceutically acceptable salts of the formula I compounds are also included. These salts generally are acid addition salts of suitable organic
20 or inorganic acids. Preferred salts are the hydrohalides such as the hydrobromides, the hydrochlorides, the hydrogen iodides. Most preferred salts are the hydrochlorides.

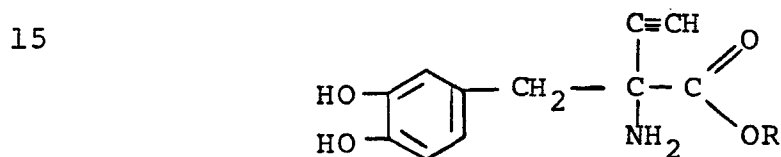
The compounds of formula I have a chiral
25 center and may occur in optically active forms, i.e., as optical isomers. These isomers are conventionally designated as D and L, d and l, + and -, (S) and (R) or by a combination of these symbols. Where the compound name or formula does not specify
30 the isomer form, all forms are included, i.e., the individual isomers, mixtures thereof and racemates.

Of the isomers, the L-form is preferred.

- 1 R may be H or an alkyl group, preferably a C₁-C₁₈ alkyl group. Examples of suitable alkyl groups are octadecyl, 2-ethylhexyl, lauryl, undecyl, methyl, isopropyl, hexyl and the like.
- 5 Preferred R groups are H and C₁-C₆ alkyl. Most preferred R groups are H and ethyl.

R₁ and R₂ include H and C₂-C₆ alkanoyl groups. Examples of suitable alkanoyl groups are acetyl, octanoyl, pivaloyl, 2-methylpropanoyl, heptanoyl, butanoyl and the like. The most preferred R₁/R₂ substituent is hydrogen.

A preferred class of compounds of the present invention is that having the formula



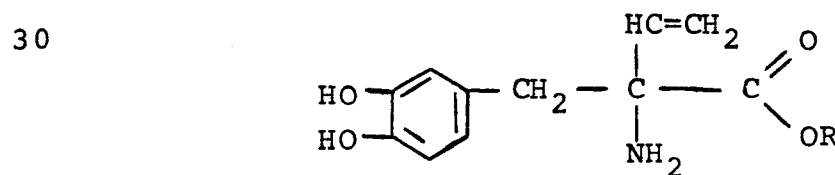
II

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Especially preferred are formula II compounds where R is hydrogen or C₁-C₆ alkyl, preferably ethyl.

The L-isomer form of the formula II compound is also more preferred.

Another preferred class of compounds of the present invention is that having the formula



III

35 Especially preferred are the formula III compounds

1 where R is hydrogen or C₃-C₆ alkyl, preferably ethyl.

The L-isomer form of the formula III compounds are also more preferred.

5 The compounds of the present invention have pharmaceutical activity especially as antihypertensive agents. Thus, the present compounds are useful for treating hypertension in humans.

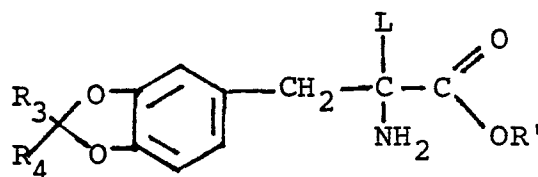
Other biological activities of the present compounds include inhibition of 3,4-dihydroxyphenylalanine (dopa) decarboxylase.

For treating hypertension, the present compounds may be administered to the hypertensive patient orally, parenterally or via any other suitable administration route. Conventional dosage forms are used
15 such as tablets, troches, capsules, liquid formulations, e.g., solutions, dispersions, emulsions, elixirs and the like. Conventional compounding ingredients, i.e., diluents, carriers, etc. and conventional preparation procedures are utilized.

20 The daily dosage of the present compounds may be varied as required. In general, a daily dosage range for the hypertensive patient is about 50 mg. to about 5000 mg. A preferred daily dosage range is about 100 mg. to about 3500 mg. A more preferred
25 daily dosage range is about 250 to about 1500 mg.

Compounds of the present invention may be prepared by any convenient process.

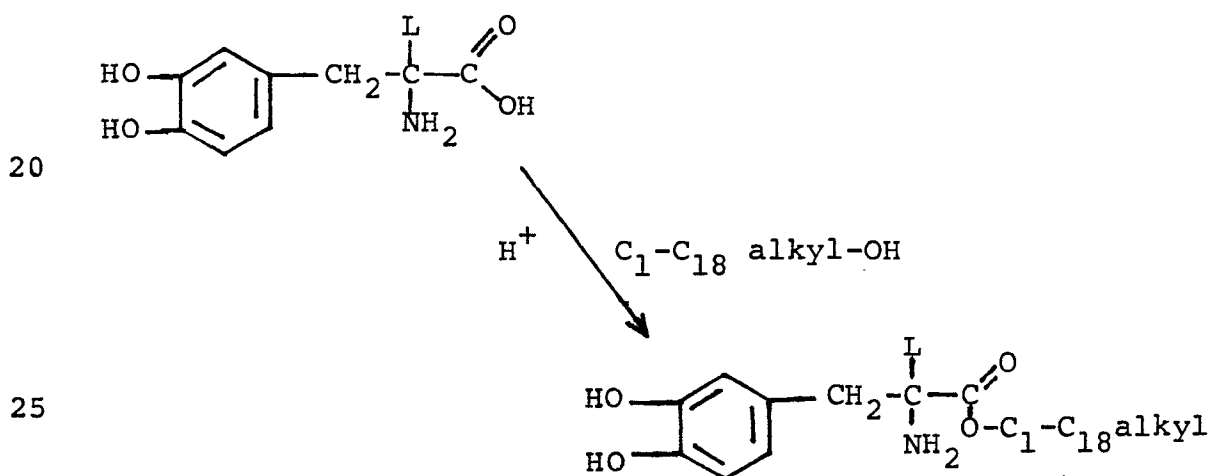
An especially useful process for preparing the compounds of formula I where R is hydrogen
30 is by the hydrolysis of a compound having the formula



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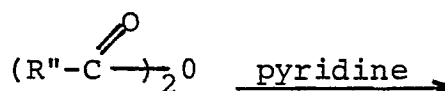
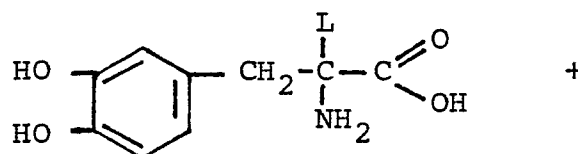
1 where L is $-\text{C}\equiv\text{CH}$ or $-\text{CH}=\text{CH}_2$, R' is alkyl preferably
 C₁-C₆ alkyl, and R₃ and R₄ are groups, e.g., H,
 CH₃ or phenyl, which permit hydrolysis of the
 dioxo moiety. The hydrolysis is carried out using
 5 conventional reagents and conditions, for example
 using an acid such as HCl, HBr, H₃PO₄, in a suitable
 solvent such as water, aqueous alkanols and the
 like. The hydrolysis may be carried out at room
 temperature or at elevated temperatures up to
 10 about 140°C. The reaction time will vary depend-
 ing on other parameters such as temperature, etc.

Where R in formula I is an alkyl group,
 the compound is prepared by conventional esterifi-
 cation of the corresponding compound where R is H
 15 as illustrated by the following equation

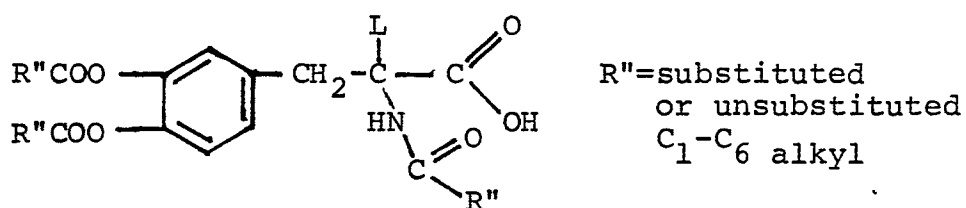


The pharmaceutically acceptable salts of
 the present compounds may be obtained directly
 30 from the hydrolysis reaction described above.
 Such salts may also be obtained by treatment of
 the formula I free base with an appropriate acid
 under suitable conditions.

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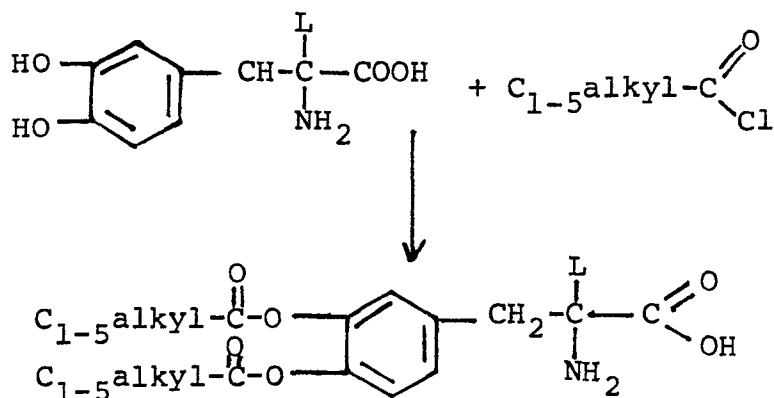


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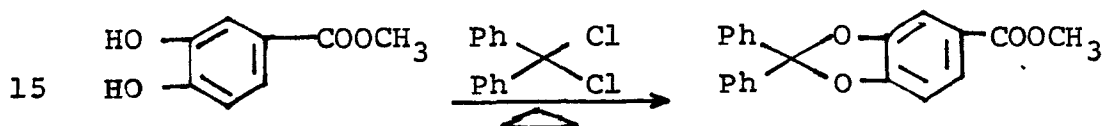
1 To prevent acylation of the α -NH₂ group, the reaction may be carried out in an acid medium, e.g., glacial acetic acid. An example illustrating such an acylation system is in U.S. 3,983,138.

5 The following examples illustrate preparation of compounds of the present invention via a series of intermediate steps. All temperatures are °C. The symbol Ph represents the phenyl group in the formulae below:

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EXAMPLE 1

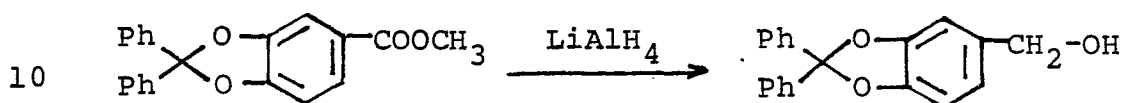
A.)



A mixture of methyl 3,4-dihydroxybenzoate (8.40 g.; 50 mmol) and diphenyldichloromethane
 20 was stirred at $150 \pm 5^\circ$ for 15 minutes. The mixture was cooled, taken up in benzene and the benzene solution washed with 5% aqueous KHCO₃, saturated

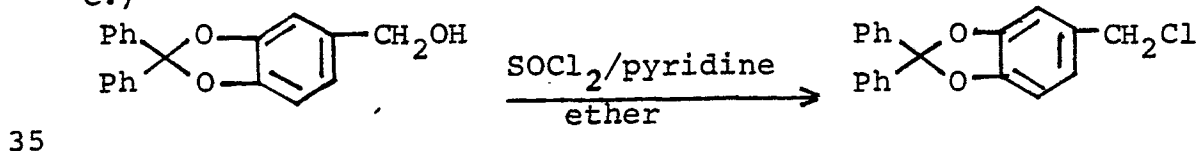
- 1 aqueous NaCl, dried over MgSO_4 and concentrated
to dryness. The crystalline residue (m.p. 98-
100°) was recrystallized from hexane containing
a little benzene to give pure methyl 3,4-diphenyl-
5 methylenedioxybenzoate (15.3 g., 96%) m.p. 103-
105°.

B.)



- To a stirred suspension of 1.48 g.
 LiAlH_4 in 80 ml. of ether was added dropwise a
15 solution of methyl 3,4-diphenylmethylenedioxy-
benzoate (13.09 g.; 39.4 mmol) in 80 ml. ether
and 10 ml. tetrahydrofuran. The rate of addition
was controlled to maintain the reaction mixture
at a gentle reflux. The mixture was then refluxed
20 45 minutes. It was then cooled and 5 ml of ethyl
acetate was added dropwise followed by 15 ml. of
saturated aqueous Na_2SO_4 and about 5 g. anhydrous
 MgSO_4 . The mixture was filtered, the inorganic
precipitate washed with 1:1 ether-benzene, and
25 the combined filtrate and washings concentrated
to dryness to give 11.65 g. of 3,4-diphenyl-
methylenedioxybenzyl alcohol as a colorless vis-
cous oil which partially solidified on cooling.
On recrystallization from hexane-benzene an ali-
30 quot had m.p. 63-64°.

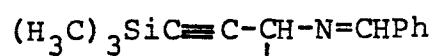
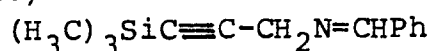
C.)



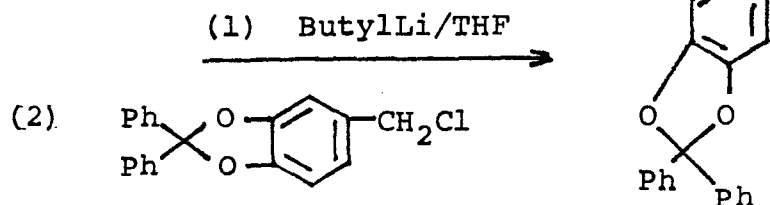
1 To a stirred solution of 11.6 g. (38
mmol) of 3,4-diphenylmethylenedioxybenzyl alcohol
in ether (80 ml.) and pyridine (0.6 ml.) at 20°C.
was added dropwise a solution of SOCl_2 in ether
5 (40 ml.). The mixture was cooled to 0-5°C.,
and CH_2Cl_2 and water were added. The layers were
separated, and the organic layer was washed with
water and saturated aqueous NaCl, dried over
 MgSO_4 and concentrated to dryness to yield 3,4-
10 diphenylmethylenedioxybenzyl chloride (11.43 g.)
as a colorless viscous oil: tlc (silica gel
 CH_2Cl_2 : R_f 0.8; ir (CCl_4) no -OH-, nmr (CCl_4) δ
4.34 (s, 2H), 6.74 (d, $j=8$) 2H, 6.67 (s, 1H),
7.1-7.6 (m, 10H).

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D.)



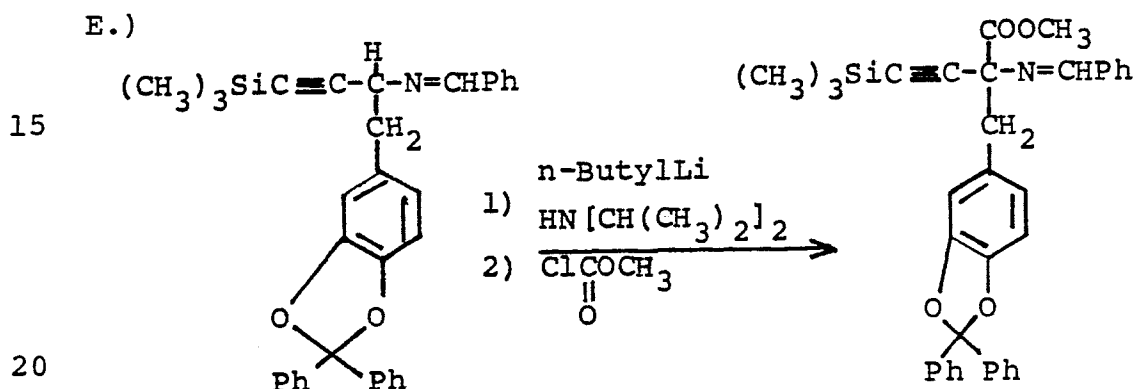
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To a stirred solution of 1-trimethyl-
silyl-N-benzylidene-3-aminoprop-1-yne (7.609 g.;
34.4 mmol) in 106 ml. of tetrahydrofuran maintained
at -78° under N_2 was added dropwise 19.5 ml. of
1.63 N n-butyl lithium. To the stirred deep red
30 solution was then added dropwise 11.43 g. (35.4
mmol) of 3,4-diphenylmethylenedioxybenzyl chloride
in 35 ml. of tetrahydrofuran. After an additional
30 minutes at -78° water (25 ml.) was added drop-
wise, the mixture was warmed to 20°, 10% aqueous

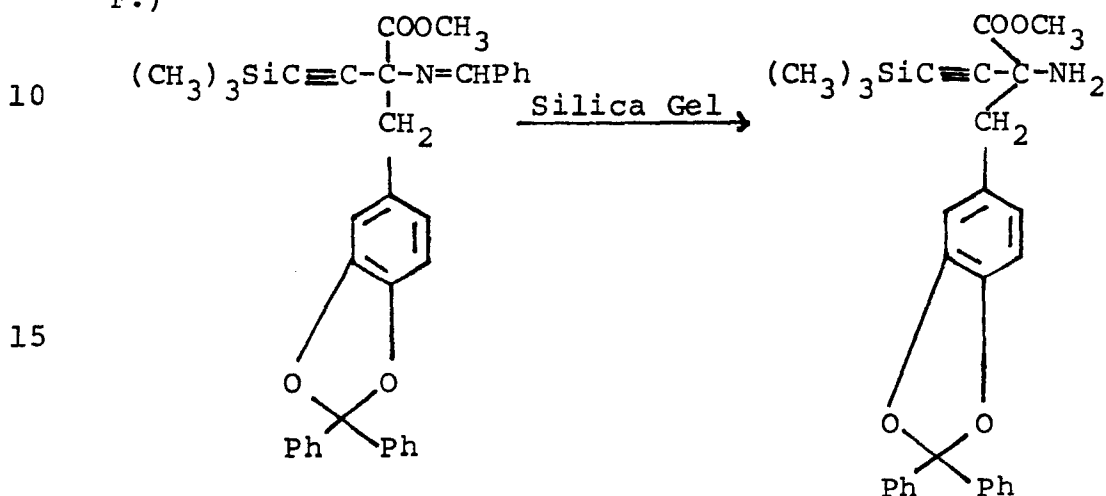
- 1 NH_4Cl , solution was added and the layers were separated. The aqueous layer was washed twice with benzene, the combined organic phases were washed twice with cold 10% aqueous NH_4Cl , once
 5 with saturated NaCl solution, dried over Na_2SO_4 and concentrated to dryness to give 3-(3,4-diphenylmethylenedioxybenzyl)-1-trimethylsilyl-NN-benzylidene-3-aminoprop-1-yne as a viscous orange oil (18,86 g).
 10 The mass spectrum showed a large molecular ion peak at 501.



- To diisopropylamine (700 mg.) in 15 ml. tetrahydrofuran at -78° under N_2 was added 3.8 ml. of 1.64 M n-butyllithium dropwise. After 5 minutes,
 25 3-(3,4-diphenylmethylenedioxybenzyl)-1-trimethylsilyl-N-benzylidene-3-aminoprop-1-yne (3.378 g.; 6.74 mmol) in 15 ml. tetrahydrofuran was added dropwise (10 minutes). After an additional 5
 30 minutes, methyl chloroformate (680 mg.) in tetrahydrofuran (10 ml.) was added dropwise (5 minutes). After 40 minutes at -78° the solution was warmed to 0° and the color lightened from deep red to orange. After 10 minutes at 0° , water (5 ml.)
 35 was added dropwise followed by 10% aqueous NH_4Cl (30 ml.). The layers were separated and the mixture extracted as in the previous example, dried

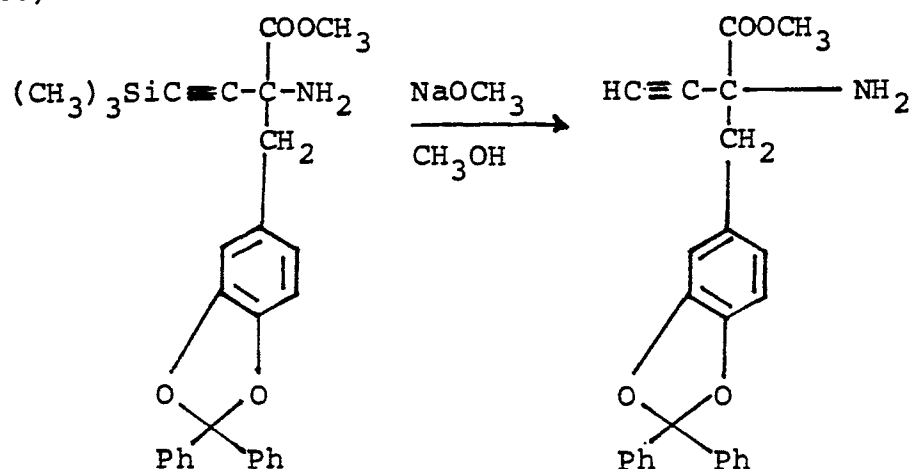
1 over Na_2SO_4 and concentrated to dryness to give
 3-carbomethoxy-3-(3,4-diphenylmethylenedioxy-
 benzyl)-1-trimethylsilyl-N-benzylidene-3-aminoprop-
 1-yne (3.645 g.) as an orange foam; mass spectrum
 5 M/e 559, large fragmentation peaks at 287 (base
 peak) and 272.

F.)

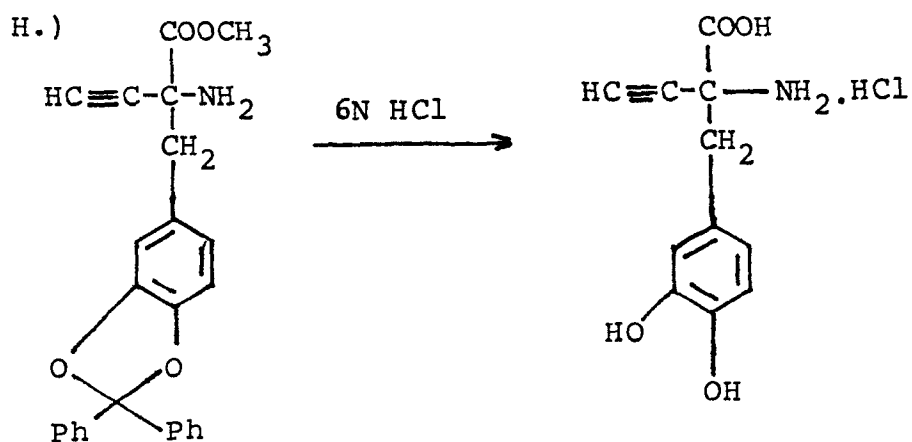


Chromatography of crude 3-carbomethoxy-
 3-(3,4-diphenylmethylenedioxybenzyl) 1-trimethyl-
 silyl-N-benzylidene-3-aminoprop-1-yne (3.55 g.)
 25 over 180 g. of silica gel H eluting with 2%
 acetone in chloroform led to hydrolysis of the
 Schiff base protecting group to give the free
 amine, 3-carbomethoxy-3-(3,4-diphenylmethylenedioxybenzyl)-3-aminoprop-1-yne (tlc silica gel
 30 3% acetone in CHCl_3 $R_F \sim .2$) Mass spec. M/e 471.

G.)



- 1 To a solution of 3-carbomethoxy-3-
 (3,4-diphenylmethylenedioxybenzyl)-1-trimethyl-
 silyl-N-benzylidene-3-aminoprop-1-yne (610 mg.)
 in 6 ml. of methanol under nitrogen at 20°C was
 5 added. 1.1 ml. of 1.6 M NaOCH₃ in CH₃OH. The
 solution was stirred 30 minutes, CH₂Cl₂ and cold
 water were added and the layers separated. The
 aqueous layer was washed with CH₂Cl₂ and the com-
 bined CH₂Cl₂ phase washed with cold water and
 10 saturated NaCl solution, dried over Na₂SO₄ and
 concentrated to dryness to give 3-carbomethoxy-3-
 (3,4-diphenylmethylenedioxybenzyl)-3-aminoprop-1-
 yne (505 mg.) as a viscous orange foam; nmr (CDCl₃)
 1.80 (broad s, 2H) 2.45 (s, 1H) 3.10 (s, 2H), 3.75
 15 (s, 3H) 6.79(d, j=5, 2H), 6.75 (s, 1H), 7.0-7.7
 (m, 10H).

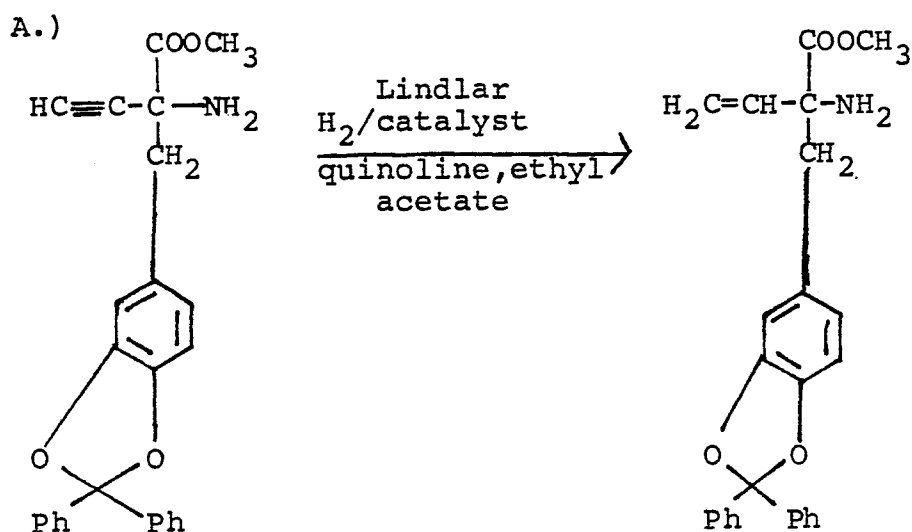


- 1 A solution of 3-carbomethoxy-3-(3,4-diphenylmethylenedioxybenzyl)-3-aminoprop-1-yne (230 mg.) in 6N HCl (15 ml.) was refluxed for 2 hours, cooled and extracted with CH_2Cl_2 . The aqueous acid phase was taken to dryness to give
- 5 α -ethynyl-3,4-dihydroxyphenylalanine hydrochloride (135 mg, 90%) tlc-n butanol :acetic acid: water 25:4:10 single spot R_F 0.4; n-butanol:acetic acid:water:pyridine 15:3:12:10 single spot R_F
- 10 0.6; mass spec. M^+ 221; (D_2O) δ 3.17 (s,2H), 3.22 (s,1H) 6.70 m,3H).

The HCl salt obtained in Example 1 H.) may be conventionally neutralized or treated with an HCl scavenger such as propylene oxide

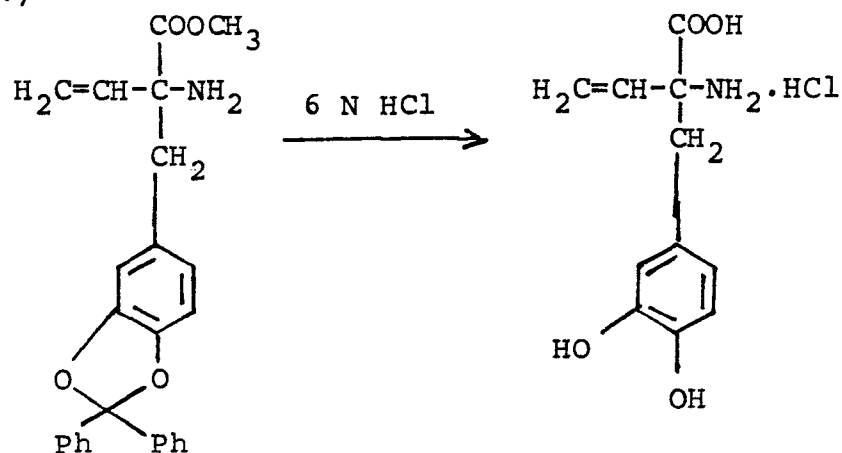
15 to obtain the corresponding free amino acid.

EXAMPLE 2



- 1 A solution of 3-carbomethoxy-3-(3,4-diphenylmethylenedioxybenzyl)-3-aminoprop-1-yne (90 mg.) in 10 ml. of ethyl acetate and 0.02 ml. quinoline was stirred in 1 atm of hydrogen
- 5 over 20 mg. of Lindlar's catalyst [5%Pd-CaCO₃ + Pb(OAc)₂] at 25° until hydrogen uptake ceased. The catalyst was removed by filtration and the filtrate taken to dryness. The nearly pure product, was purified by dry column chromatography
- 10 on 10 g. of silica gel eluting with 15% acetone in chloroform to give pure 3-carbomethoxy-3-(3,4-diphenylmethylenedioxybenzyl)-3-aminoprop-1-ene, .
- mass spec. M⁺ 401; nmr (CDCl₃) 1.72 (s, 2H), 2.75 (d, J=14, 1H), 3.18 (d, J=14.1H)-AB quartet
- 15 3.70 (s, 3H), 5.17 (d, d, J=10, 2, 1H), 5.35 (d, d, J=18, 2, 1H) 6.17 (d, d, J=18, 10, 1H) 6.72-6.77 (m, 3H); 7.25-7.8 (mk 10 H).

B.)



- 1 Utilizing the procedure of Example 1 H.), 3-carbomethoxy-3(3,4-diphenylmethylenedioxybenzyl)-3-aminoprop-1-ene was hydrolyzed to produce α -vinyl-3,4-dihydroxyphenylalanine hydrochloride.
- 5 tlc-n-butanol, acetic acid:water: pyridine-15:3:12:10 single spot $R_F \sim 0.65$; mass spec M^+ 223:nmr(D_2O) δ 3.03 (d, J=15, 1H), 3.33 (d, J=15, 1H) AB quartet, 5.35 (d, J=18, 1H); 5.50 (d, J=12, 1H), 6.18 (d, d, J=18, 12 1H), 6.6-7.1 (m 3H).

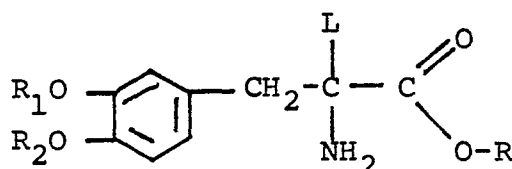
- 10 The HCl salt obtained in Example 2 B may be conventionally neutralized or treated with an HCl scavenger such as propylene oxide to obtain the corresponding free amino acid.

Claims to the invention.

1 WHAT IS CLAIMED IS:

1. Compounds having the formula

5



10 wherein

L is $-\text{C}\equiv\text{CH}$ or $-\text{CH}=\text{CH}_2$,

R_1 and R_2 are independently selected from
H and C_1-C_6 alkanoyl, and

R is C_1-C_{18} alkyl or H.

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2. The pharmaceutically acceptable
salts of the Claim 1 compounds.

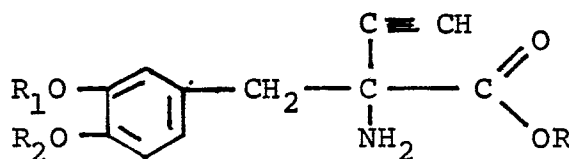
3. Compounds of Claim 1 having the L-
20 isomer configuration.

4. Compounds of Claim 1 wherein R_1
and R_2 are both hydrogen.

25 5. Compounds of Claim 4 wherein R
is hydrogen.

6. Compounds of Claim 1 having the
formula

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1 7. Compounds of Claim 6 having the
L-isomer configuration.

5 8. Compounds of Claim 6 wherein R_1
and R_2 are both hydrogen.

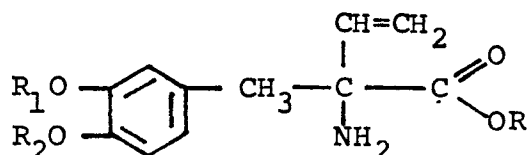
9. Compounds of Claim 6 wherein R is
H or C_1-C_6 alkyl.

10 10. Compounds of Claim 8 wherein R is
ethyl.

11. Compounds of Claim 8 wherein R is
hydrogen.

15 12. Compounds of Claim 11 having the
L-isomer configuration.

13. Compounds of Claim 1 having the
20 formula



25 14. Compounds of Claim 13 having the
L-isomer configuration.

15. Compounds of Claim 13 wherein R_1
30 and R_2 are both hydrogen.

16. Compounds of Claim 15 wherein R is
H or C_1-C_6 alkyl.

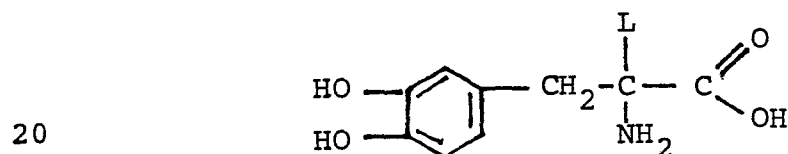
1 17. Compounds of Claim 14 wherein R
is ethyl.

 18. Compounds of Claim 16 wherein R
5 is H.

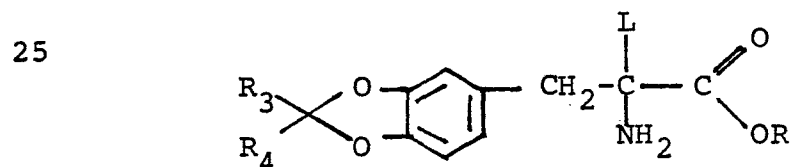
 19. Compounds of Claim 18 having the
L-isomer configuration.

10 20. Pharmaceutical composition contain-
ing a therapeutical effective amount of a com-
pound of Claim 1 or a pharmaceutically acceptable
salt thereof.

15 21. A process for preparing a com-
pound having the formula



which comprises hydrolysing a compound having the
formula



wherein

30 L is $-\text{C}\equiv\text{CH}$ or $-\text{CH}=\text{CH}_2$,
 R is $\text{C}_1\text{-C}_{18}$ alkyl and
 R_3 and R_4 are independently selected from
 the group consisting of H, CH_3 or a
 phenyl group.

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- 1 22. The process of Claim 21 wherein
R is $-\text{CH}_3$.
- 5 23. The process of Claim 22 wherein
L is $-\text{C}\equiv\text{CH}$.
24. The process of Claim 22 wherein
L is $-\text{CH}=\text{CH}_2$.



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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. ²)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
	<u>FR - M - 1 850</u> (MERCK) * Page 4, abstract * --- <u>US - A - 3 132 176</u> (F.W.BOLLINGER e.a.) * Column 1, lines 12 to 39 * -----	1,2,20 1,2,20	C 07 C 101/77 A 61 K 31/195 A 61 K 31/215
			TECHNICAL FIELDS SEARCHED (Int.Cl. ²)
			C 07 C 101/77
			CATEGORY OF CITED DOCUMENTS
			X: particularly relevant A: technological background O: non-written disclosure P: intermediate document I: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons
			&: member of the same patent family, corresponding document
X The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
The Hague	18-08-1978	MOREAU	