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ON THE CONVERSION OF L-GLUTAMATE TO L-DOPA

THE PREPARATION AND CHEMISTRY OF 1-METHOXY-2-ACETOXY-3-TRIMETHYLSILYLOXY-1,3-BUTADIENE

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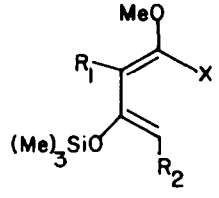
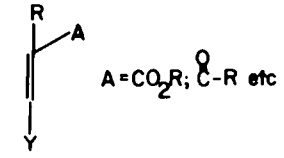
Abstract—The title diene was prepared by the enol silylation of 1-methoxy-2-acetoxybut-1-ene-3-one. It undergoes Diels–Alder cycloaddition with a variety of dienophiles. Through such cycloaddition ther is provided acess to regiospecifically monoderivatized diosphenols and catechols. Cycloaddition of the title compound with dienophile (**28**), derived from L-glutamate, provides a route to optically pure L-Dopa.

In the past several years a major concern of our laboratory has been the development of new kinds of dienes and dienophiles for Diels–Alder reactions. The motivation for these investigations was the expectation that incremental advances in the complexity of the components of such cycloaddition reactions might allow for more orderly transformation of the resulting cycloadducts. This methodology has, in fact, found successful application in the synthesis of a wide variety of natural products.[1]

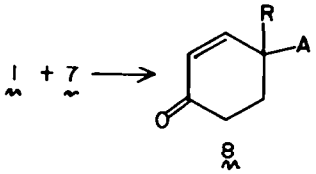
The key methodological developments in the diene area resulted from the use of 1,3-bis-oxygenated compounds such as **1**→**4**. As dienophiles we have made extensive use of novel systems of the type **5** and **6**. The importance of these new dienophiles arises from the fact that in all cases studied, the phenylsulfinyl and phenylsulfonyl functions do not compete with the "A" function (see keto, ester, lactone, and lactam, and lactam type of CO groups) for orientational control. Fortunately, these control groups do not appear to diminish the overall dienophilicity of th system. Finally, upon β-elimination, there is imparted to the resultant products an additional unit of unsaturation relative to that immediately available from the more classical dienophiles, **7**. Among the structural types which have been reached by the new functionalized Diels–Alder dienes and dienophiles which were developed in our laboratory are 4-acylcyclohexenones (**8**)[2,3] cyclohexadienones (**9**),[4,5] 3-methoxycyclohexadienones,[6] (see **10**) and resorcinol derivatives (see **11**[7] and **12**[8]).



1 X = R_1 = R_2 = H
2 X = OMe; R_1 = R_2 = H
3 X = R_1 = H; R_2 = Me
4 X = R_2 = H; R_1 = Me



5 Y = S(O)-φ
6 Y = S(O)2-φ
7 Y = H



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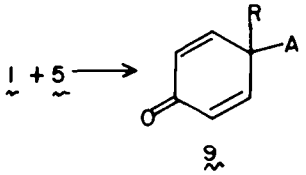

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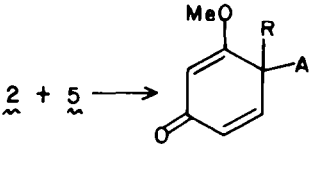

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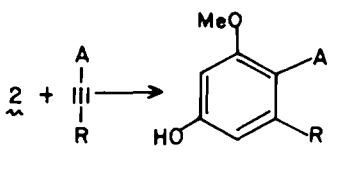

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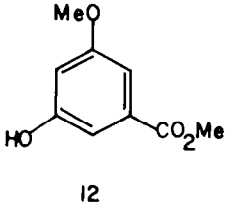

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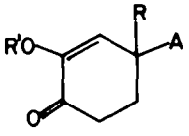
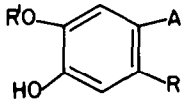
The investigation described below was undertaken with a view toward the attainment of several objectives. First, it was hoped that access could be provided to regiospecifically derivatized diosphenol systems such as **13**. We also sought a Diels–Alder based elaboration of catechol systems (**14**), preferably with provision for regiospecific differentiation of the phenolic groups in the unsymmetrical mode.

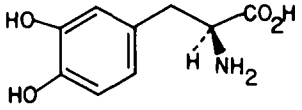
Another of our interests involves the preparation of amino acids *via* Diels–Alder reactions of dienophiles derived from glutamate. This methodology has been used in the optically specific laboratory conversions of glutamate to phenylalanine,[9] arogenate[9] and tyrosine.[10] It was, therefore, of interest to ascertain the applicability of these strategies to the synthesis of the medicinally important L-Dopa (**15**).



13 R' = H; Ac



14 R' = H; Ac



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RESULTS

For purposes of addressing these goals we turned our attentions to the synthesis of the highly functionalized siloxydiene **18**. Fortunately, for our needs, its logical precursor, **17**, was known[11] and readily available by the dehydroacetoxylation (pyridine) of **16** which is, itself, obtained by the action of lead tetraacetate on the commercially available 1-methoxybut-1-ene-3-one. In the event, enol silylation of **17** under our standard conditions[2] afforded **18** in 90% crude yield. The purity of the material thus received was characteristically 90%. The only apparent contaminant was the starting acetoxyenone **17**. This impurity did not interfere with any of our subsequent operations.

The compound which we used gave every indication of being a single stereoisomer. In the absence of both variants it is not possible for us to assign the geometry about the 1,2-double bond of the diene. Given its excellent performance in Diels–Alder reactions, one is tempted to assign the *Z*-stereochemistry (as shown) to this diene though the matter cannot be regarded as settled.

At least qualitatively, it appears that the cycloadditivity of **18** is roughly comparable to that of the parent compound **1**. Diels–Alder reaction of **18** with methyl vinyl ketone occurs in benzene under reflux. Workup in the usual way affords a mixture of enediones from which compound **19** was obtained in 42% yield. A more satisfying result was achieved from the reaction of **18** with methyl methacrylate. Hydrolysis with dilute hydrochloric acid afforded a 77% yield of the acetoxyenedione **20a**. Small amounts of its deacylation product, **20b** were also obtained.

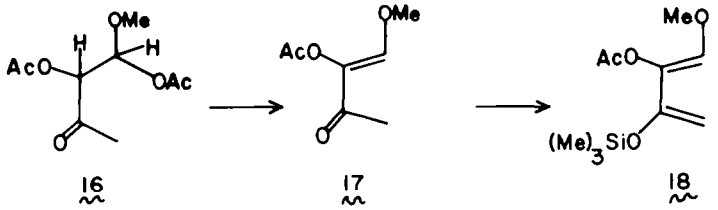
Reaction of **18** with *p*-benzoquinone was conducted in benzene at 50°. After 3 hr, the reaction product was acetylated with pyridine and acetic anhydride. There was thus obtained an 84% yield of tetraacetate **21**.

The *de novo* synthesis of aromatic systems of sophisticated substitution patterns can also be accomplished by recourse to diene **18**. In particular, with acetylenic dienophiles there are obtained, in high yield, monoacetylated catechols. With unsymmetrical acetylenes, an entry is thus available for regiospecifically defined, mono-derivatized catechols. It will be recognized that diene **18** accomplishes, in the catechol series, an objective comparable to that achieved by diene **2** in the resorcinol series.[7]

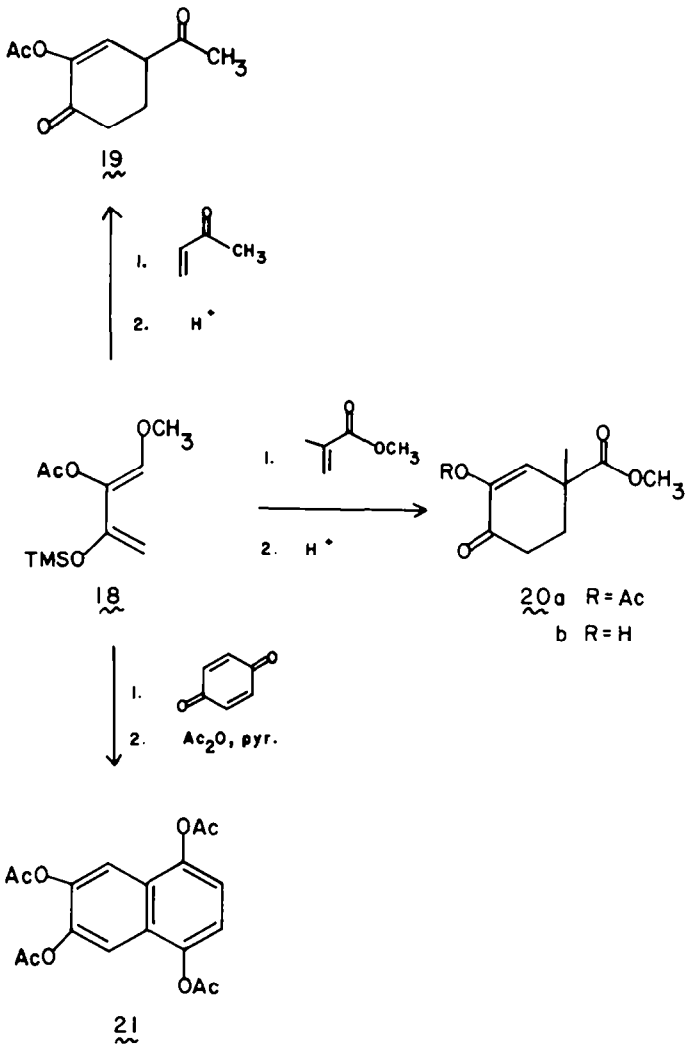
Specifically, reaction of **18** with dimethylacetylene dicarboxylate (benzene reflux, 20 hr) followed by mild hydrolysis affords an 84% yield of **22**. This was accompanied by trace quantities of the known **23**.[12] In a separate step, through the action of potassium carbonate in methanol, **22** could be converted to **23**.

Two unsymmetrical cases were also examined. Cycloaddition of **18** with ethyl propiolate (benzene reflux, 20 hr) followed by hydrolysis afforded **24** in 87% yield. Finally, in this connection, the applicability of a monoactivated disubstituted acetylene was investigated. Such systems are now readily accessible through alkylation of the propiolate anions. For this demonstration we used compound **25** previously prepared in our laboratory[13] for the total synthesis of lasiodiplodin Cycloaddition of **18** with **25** was carried out in xylene at 125° for 80 hr. Hydrolysis in the usual way afforded the differentiated catechol **26** in 74% yield. It is seen that this is a far more satisfactory yield than that obtained in the resorcinol series with the same dienophile, using diene **2**.[13]

The amenability of compound **18** to Diels–Alder cycloadditions with dienophiles of the type **5** was also examined. The hope was that such a reaction would provide access to systems of type **27d**. De-acylation of the vinylogous β-dicarbonyl systems would than be expected to produce the aromatic catechol product, **27**. Of course, catechols can also be produced by reactions of **18** with acetylenic dienophiles (*vide supra*). However, the success of that methodology carries with it a limiting proviso, i.e. that in the first instance the aromatic product



16 **17** **18**



produced must bear benzylic functionality (*cf* esters, ketones, etc) which would have activated the acetylene to Diels–Alder reaction (see compounds **22**, **24**, and **26**). By the strategem suggested below, this potentially serious limitation is avoided.

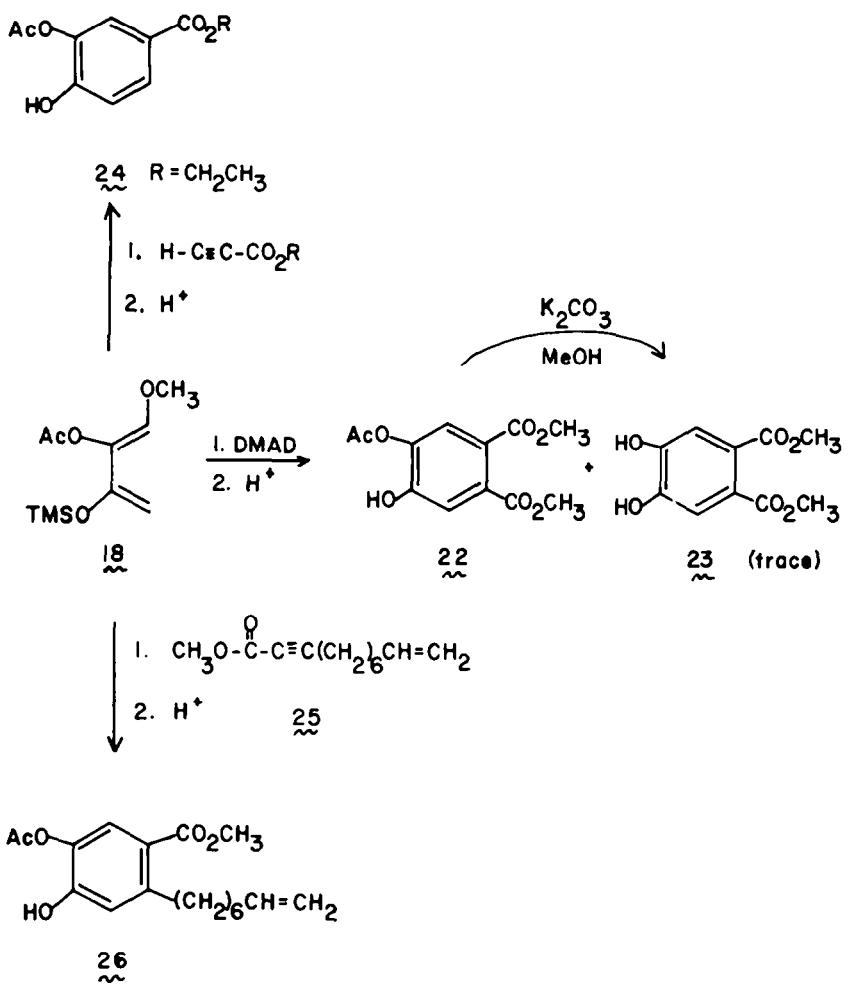
We found it particularly attractive to investigate this possibility in the context of the synthesis of the medicinally important amino acid L-Dopa (**15**).[14] In terms of our synthetic analysis, **15** corresponds to a system of the type **27**. It is further seen that the *R* group (CH_2CHNH_2–CO_2H) which is required is not of the type which would activate an acetylene for cycloaddition. Hence, the strategem **18** + **5** → dienone (**27d**) → catechol (**27**) would provide an important advance.

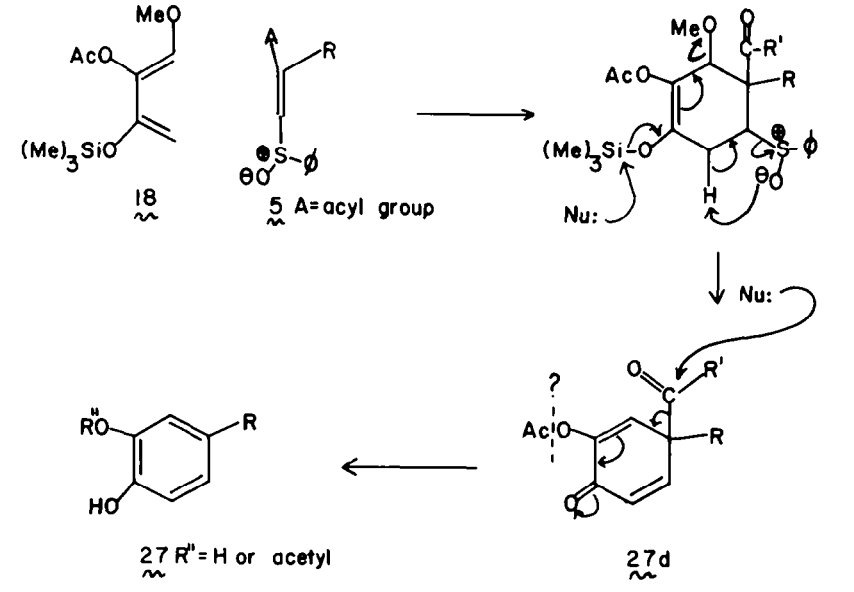
Another feature which added to the attractiveness of the appraoch is that the specific required dienophile **28** had been previously synthesized from L-glutamate in an optically specific way in connection with our recently completed synthesis of L-arogenate.[9] Thus, the possibility of achieving the optically specific conversion of the readily available L-glutamate to the difficulty available L-Dopa presented itself.

Reaction between **18** and **28** was conducted in benzene under reflux for 48 hr in the presence of traces of hydroquinone. Hydrolysis with dilute hydrochloric acid followed by silica gel chromatography afforded two principal products. One (27%) was clearly the desired acetoxydienone **29**.[15] The other (25%) was formulated to be the methoxyacetoxyenone **30**.[16] While **29** is eminently usable in the synthesis (*vide infra*), several attempts to achieve concurrent β-elimination of methanol and deacylation of the imide like function of **30** were unsuccessful. Accordingly, conditions were sought to imporve the yield of the formation of **29**.

Based on previous observations,[3] it appeared that our opportunities in this connection would be improved if the elimination of the phenysulfenic acid could be achieved prior to the hydrolytic cleavage of the silyl enol ether.

To promote this possibility, cycloaddition was carried out in xylene at 120°. After 7 hr there was isolated a 48% yield of homogeneous cyclohexadienone **29**,[15] m.p. 202–205°. In addition, sulfoxide **28** was recovered to the extent of 22%. Alkaline treatment of **29** afforded a 58% yield of optically homogeneous N-Cbz L-Dopa (**31**), identical in its infrared and NMR spectra as well as in its optical rotation with an authentic sample.[17] Finally, hydrogenolysis of **31**[18] afforded **15** itself ($[\alpha]_D^{20} = -11.3$, Lit.[14] $[\alpha]_D^{20} = -11.7$). The conversion of L-glutamate to L-Dopa was thus complete.


AcO
CO2R
HO
24 R = CH2CH3
1. H-C≡C-CO2R
2. H+
K2CO3
MeOH
OCH3
AcO
TMSO
1. DMAD
2. H+
AcO
CO2CH3
HO
CO2CH3
HO
CO2CH3
HO
CO2CH3
18
22
23 (trace)
1. CH3O-C(=O)-C≡C(CH2)6CH=CH2
2. H+
25
AcO
CO2CH3
HO
(CH2)6CH=CH2
26


MeO
AcO
(Me)3SiO
18
A
R
S-ϕ
5 A=acyl group
MeO
C-R'
AcO
R
(Me)3Si-O
S-ϕ
Nu:
H
Nu:
Nu:
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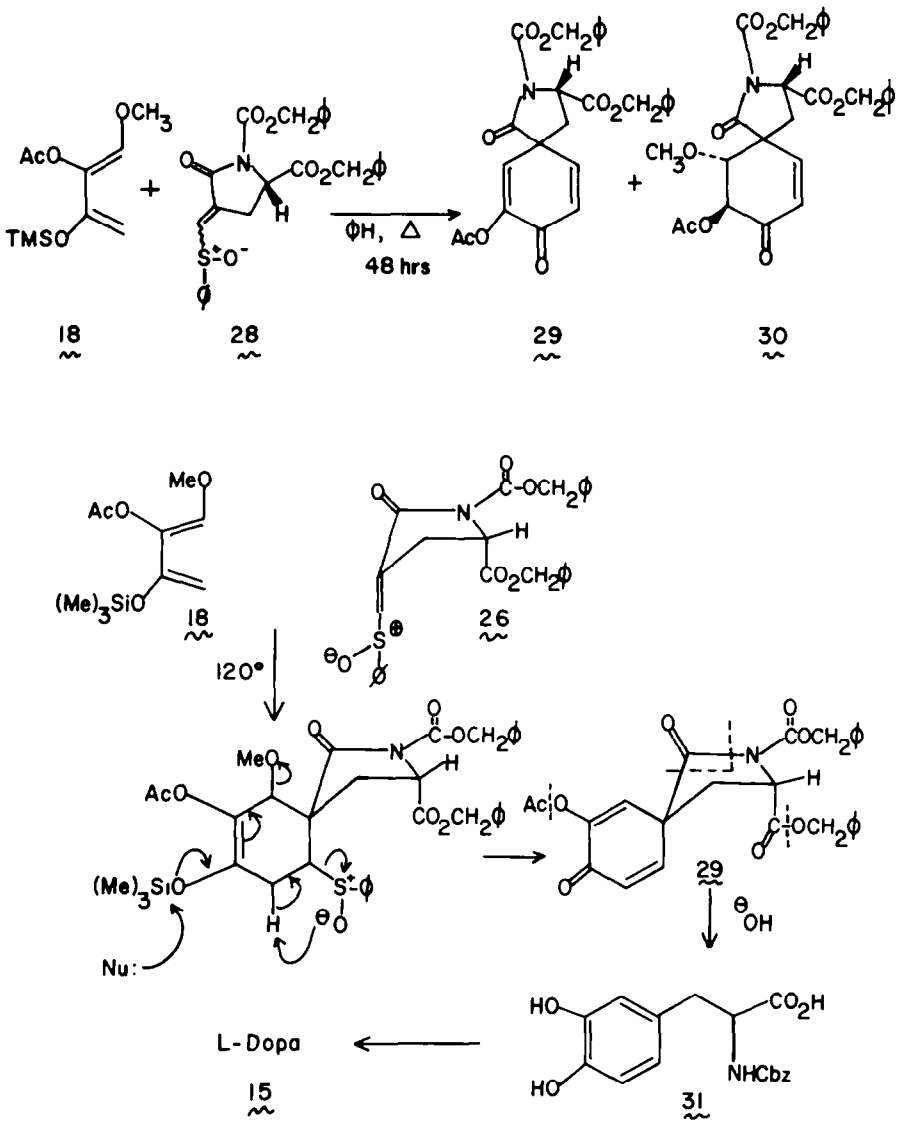
R'
C
?
AcO
R
RO"
R
HO
27 R" = H or acetyl
27d



EXPERIMENTAL[19]

Preparation of 1-*methoxy*-2-*acetoxy*-3-*trimethylsilyloxy butadiene* (**18**). Anhyd powdered $ZnCl_2$ (0.20 g, 0.0015 mol) was added to Et_3N (8.0 mLs, 0.057 mol). The mixture was stirred for 30 min until the salt was suspended in the amine. To this was added a soln of **17**[11] (4.00 g, 0.025 mol) in 30 mLs benzene followed by addition of chlorotrimethylsilane (6.4 mLs, 0.050 mol). After 30 min the reaction was taken to reflux for 16 hr. After cooling, the mixture was added to 200 mLs of pentane an filtered. The filtrate and combined pentane washings were concentrated *in vacuo*, filtered, and then reconcentrated to give a dark brown oil. Short path distillation (62–64°, 2 mm) gave 5.12 g of diene **18** as a clear distillate. The NMR indicated the presence of *ca.* 5–10% of **17**. NMR (90 MHz, $CDCl_3$) δ 1.28(s, 9H), 2.20(s, 3H), 3.70(s, 3H), 4.12(d, 1H, J = 1.5 Hz), 4.30(d, 1H, J = 1.5 Hz), 6.44(s, 1H); IR ($CHCl_3$) 3.38, 3.41, 5.68, 5.96, 6.04, 7.28, 7.62, 7.92, 8.80, 9.92, 11.80 μ.

Preparation of 2-*acetoxy*-4-*methyl*-4-*carbomethoxy-cyclohex*-2-*en*-3-*one* (**20**). A soln of methyl methacrylate (0.100 g, 0.0010 mol) and **18**(0.300 g, 0.0013 mol) in 0.5 mLs benzene was refluxed under argon for 20 hr. After cooling, the volatiles were removed *in vacuo* and the remaining residue was treated with 2.5 mLs of a 0.5 N HCl/THF solution at room temp for 30 min. Extraction with 4 × 20 mLs CH_2Cl_2 followed by drying over $MgSO_4$, filtration, and evaporation *in vacuo* afforded a crude residue which was flash chromatographed on 80 g of silica gel. Elution with 40% EtOAc/hexane gave 198 mg of a mixture. Hplc purification and separation afforded 175 mg (77%) of **20a** and 20 mg (11%) of a product which has tentatively been assigned structure **20b**. For **20a**: NMR (90 MHz, $CDCl_3$) δ 1.51(s, 3H), 2.24(s, 3H), 2.01–2.73(m, 4H), 3.76(s, 3H), 6.55(s, 1H); IR($CHCl_3$) 3.32, 5.68, 5.78, 5.89, 8.13 μ; *m/e* 226 (*P*).

Preparation of 1,4,6,7-*tetraacetoxynaphthalene* (**21**). A soln of benzoquinone (0.090 g, 0.00083 mol) and **18** (0.250 g, 0.0011 mol) in 1 mL benzene was heated at 50° under argon for 3 hr. After cooling, the volatiles were removed *in vacuo* to give a crude residue which was refluxed overnight with 1.5 mLs Ac_2O and 3 drops pyridine. The volatiles were evaporated *in vacuo* and the remaining residue was flash chromatographed on 80 g of silica gel. Elution with 50% EtOAc/hexane afforded 239 mg (81%) of **21**, m.p. 162–163.5. NMR(90 MHz, $CDCl_3$) δ 2.46(s, 6H), 2.55(s, 6H), 7.40(s, 2H), 7.83(s, 2H); IR($CHCl_3$) 5.68, 7.32, 8.42, 8.80 μ; MS Calc. for $C_{18}H_{16}O_8$: 360.0845; Found: 360.0809.

Preparation of dimethyl-4-*acetoxy*-5-*hydroxyphthalate* (**22**). A soln of dimethyl acetylene dicarboxylate (0.200 g, 0.0014 mol), **18** (0.400 g, 0.0017 mol), hydroquinone (0.001 g, 0.00001 mol), and 1.5 mLs benzene was refluxed under argon for 20 hr. After cooling, 3 mLs of a 0.5 N HCl/THF soln was added and the reaction stirred for 1 hr, after which 4 mLs H_2O was added and the aqueous system extracted with 3 × 20 mLs of $CHCl_3$. The residue obtained upon evaporation of the combined organic extracts was flash chromatographed on 80 g of silica gel. Elution with 40%

EtOAc/hexane afforded 317 mg (84%) of **22** and 48 mg (15%) of known **23**. Data for **22**: NMR(90 MHz, $CDCl_3$) δ 2.16(s, 3H), 3.70(s, 3H), 3.73(s, 3H), 7.34(s, 1H), 7.44(s,1H); IR($CHCl_3$) 2.85–3.50(br), 5.68, 5.80 μ; *m/e* 268 (*P*).

Preparation of ethyl-3-acetoxy-4-hydroxybenzoate (**24**). A soln of ethyl propiolate (0.200 g, 0.0020 mol) and **18** (0.600 g, 0.0026 mol) in 1 mL benzene was refluxed under argon for 20 hr. After cooling, the volatiles were removed *in vacuo* and the remaining residue was treated with 4 mLs of a 0.5 N HCl/THF soln at room temp for 30 min. Extraction with 4 × 20 mLs CH_2Cl_2 followed by drying over $MgSO_4$, filtration, and evaporation *in vacuo* afforded a crude residue which was flash chromatographed on 80 g of silica gel. Elution with 50% EtOAc/hexane gave 391 mg (87%) of **24**, m.p. 81°C–83°. NMR(90 MHz, $CDCl_3$) δ 1.30(t, 3H, J = 7.5 Hz), 2.30(s, 3H), 4.26(q, 2H, J = 7.5 Hz), 6.28–6.43(br, 1H), 6.90(d, 1H, J = 7 Hz) 7.70(s, 1H), 7.76(d, 1H, J = 7 Hz); IR($CHCl_3$) 2.85–3.20(br), 5.68, 5.85, 6.20 μ; (Found: 224.0685. MS Calc. for $C_{11}H_{12}O_5$: 224.0691).

Preparation of methyl-2-oct-7-en-4-hydroxy-5-acetoxybenzoate (**26**). A soln of **25**[13] (0.200 g, 0.0010 mol) and **18** (0.300 g, 0.0013 mol) in 0.1 mL xylene was heated at 125° for 80 hr in a sealed tube under N_2. After cooling, the mixture was treated directly with 2.5 mLs of a 0.5 N HCl/THF soln for 1 hr. Extraction with 4 × 20 mLs CH_2Cl_2 followed by drying over $MgSO_4$, filtration, and evaporation *in vacuo* afforded a crude residue which was flash chromatographed on 80 g of silica gel. Elution with 40% EtOAc/hexane gave 38 mg (19%) of starting material **25**. Further elution afforded 244 mg (74%) of **26**. NMR(90 MHz, $CDCl_3$) δ 1.15–1.62(m, 8H), 1.78–2.14(m, 2H), 2.25(s, 3H), 2.68(m, 2H), 3.78(s, 3H), 4.82–5.02(m, 2H), 5.46–6.00(m, 1H), 6.35–6.80(br, 1H), 6.83(s, 1H), 7.62(s, 1H); IR($CHCl_3$) 3.40, 5.68, 5.82 μ; (Found: 320.1606. MS Calc. for $C_{18}H_{24}O_5$: 320.1627).

Preparation of spirodienone (**29**). A soln of **28** (0.300 g, 0.00061 mol), 0.001 g HQ, and **18** (0.184 g, 0.00080 mol) in 0.4 mLs xylene was heated at 120° in a sealed tube under N_2 for 7 hr. After cooling, the reaction contents were purified by flash column chromatography on 100 g of silica gel. Elution with 40% EtOAc/hexane afforded 145 gm (48%) of **29** (R_f = 0.35). Further elution gave 66 mg (22%) of unreacted **28** (R_f = 0.3). The hydrolyzed diene, which yields **17**, was the major contaminant (R_f = 0.2). For dienone **29**: m.p. 202–205; NMR (90 MHz, $CDCl_3$) δ 2.07–2.91(m, 2H), 2.27(s, 3H), 4.87(dd, 1H, J_1 = 9.4, J_2 = 3.3), 5.21(s, 2H), 5.28(s, 2H), 6.30(d, 1H, J = 9.9), 6.37(d, 1H, J = 2.8), 6.72(dd, 1H, J_1 = 9.9, J_2 = 2.8), 7.37(s, 10H; IR($CHCl_3$) 5.56, 5.70, 5.95, 6.03 μ; (Found: 489.1464; $[\alpha]_D^{20} = -21°$ (*c* = 0.1, MeOH). MS Calc. for $C_{27}H_{23}NO_8$: 489.1456).

Preparation of N-(*benzyloxycarbonyl*) - 3 - (3,4-*dihydroxyphenyl*)-L-*alanine* (**31**). A soln of **29** (0.050 g, 0.00012 mol) in 4 mLs THF was cooled to 0° *via* an icewater bath. To this was added 2 N NaOH (0.19 mLs; 0.00038 mol). The reaction was stirred for 15 min at 0° before quenchine with 1 N H_2SO_4. Adjust to pH 1 and extract with 5 × 20 mLs ether. Wash the combined ether extracts 2 × 20 mLs H_2O, dry over Na_2SO_4, filter, and evaporate to obtain a crude residue which was flash chromatorgaphed on 20 g of silica gel. Elution with 10% MeOH/$CHCl_3$ afforded **31** (19.5 mg; 58%), which was identical in all respects with data previously reported for N-CBZ-L-Dopa.[17] NMR (90 MHz, $CDCl_3$) δ 2.78–3.02(m, 2H), 4.36–4.68(m, 1H), 5.05(s, 2H), 5.31–5.51(m, 1H), 6.37–7.19(m, 5H), 7.26(s, 5H); IR($CHCl_3$) 2.70–3.20(br), 5.83(br) μ. $[\alpha]_D^{20}$ = 1.2 (*c* = 0.1, MeOH).[20]

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[15]The stereochemistry at the "spiro" carbon is unassigned. Compound **29** gives every indication of being a single substance. The possibility that small amounts of the stereoisomer of **29** may have been produced from the reaction, but lost on workup and crystallization, can not be excluded.
[16]Compound **30**: IR($CHCl_3$) 5.56, 5.70, 5.86 μ; NMR(90 MHz, $CDCl_3$) δ 1.79–2.35(m, 1H), 2.23(s, 3H), 3.07–3.42(m, 1H), 3.47(s, 3H), 4.16(d, 1H, J = 11.6 Hz), 4.92(dd, 1H, J_1 = 10.8 Hz, J_2 = 3.5 Hz), 5.15(s, 2H), 5.29(s, 2H), 5.31(d, 1H, J = 11.6 Hz), 5.95(d, 1H, J = 10.1 Hz), 6.72(d, 1H, J = 10.1 Hz), 7.34(s, 10 H). This compound gives every indication of being a single substance. The relative stereochemistry is unassigned.
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[20]The literature value for the optical rotation of N-CBZ-L-Dopa is reported as $[\alpha]_D$ = 1.5,[17] but the value of *c* is given as a percent. If one assumes this refers to a weight percent, then their value (1.5) is in good agreement with ours. It should be noted that we subsequently prepared N-CBZ-L-Dopa by the previous route and obtained material whose optical rotation was $[\alpha]_D^{20}$ = 1.19 (*c* = 1, MeOH).