Synthetic Study of Colchicine

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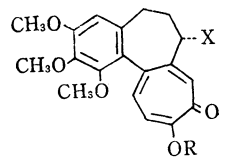
(Received February 16, 1974)

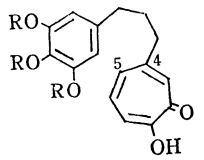
An efficient route based upon solvolytic fragmentation of a cyclopentadiene-dichloroketene adduct **4c** has been investigated for the synthesis of trimethoxyphenylpropyltropolone **2b**, a synthetic intermediate of colchicine **1a**. Attempted synthesis of the corresponding unsaturated tropolones **8a** and **10** is also discussed.

Many synthetic approaches have been reported for colchicine **1a**[1] because of its characteristic biological activity on cell divisions and because of the rarely encountered tricyclic tropolone structure. The synthetic goals in many of these studies were desacetamidocolchiceine **1b** since the conversion of the latter compound into natural colchicine has been accomplished by Corrodi and Hardegger.[2] In some instances 4-substituted tropolones, **2a** and **2b**, were used as precursors for **1b**, and the formers were cyclized by intramolecular oxidative coupling[1d] or by Pschorr cyclization[1g] to tricyclic derivatives. In this paper we describe an efficient route to **2b** and attempted synthesis of the related unsaturated systems, such as **8a** and **10**.



1

a, X=NHCOCH$_3$, R=CH$_3$
b, X=R=H



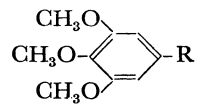
2

a, R=H
b, R=CH$_3$

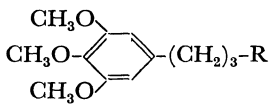
Results and Dicussion

4-*t*-Butyltropolone[3a] and 4-isopropyltropolone (hinokitiol)[3b] were regiospecifically synthesized by the addition of the corresponding 1-alkylcyclopentadienes with dichloroketene followed by solvolytic fragmentation. These results imply that a similar synthetic route *via* 1-(trimethoxyphenylpropyl)cyclopentadiene **4a** and its dichloroketene adduct **4c** would be useful for the regiospecific preparation of 4-(trimethoxyphenylpropyl)tropolone **2b**, although the latter was previously synthesized in devious paths from 4-formyltropolone.[4]

Methyl *trans*-3,4,5-trimethoxycinnamate[5] **3a** was hydrogenated to he cortresponding hydrocinnamate **3b** (91% yield). Reduction of **3b** with lithium aluminum hydride gave hydrocinnamyl alcohol **3c** quantitatively. Tosylation of the alcohol in pyridine at an ice bath temperature afforded tosylate **3d**. By treatment with sodium cyclopentadienide in tetrahydrofuran, the tosylate yielded an oily product. The product showed a single spot on tlc, but it was not so sufficiently stable as to give an analytically pure sample. The NMR spectrum of the product displays an overlapped signal corresponding to three protons at δ 5.92—6.50 ppm, proposing **4a** or **4b** as the possible structure of the product. In view of the selective formation of 4-isopropyltropolone upon isopropylation of cyclopentadienylmagnesium bromide,[3b] the selected reaction conditions seemed favorable to the formation of **4a**. Without further examination of the structure, the crude product was immediately allowed to react with equimolar dichloroketene generated from dichloroacetyl chloride and triethylamine in *n*-hexane, giving an oil (42% yield from **3c**) as homogeneous product (tlc). An intense carbonyl absorption at 1805 cm^{-1} in the IR spectrum and a one-proton multiplet at 5.55 ppm in the NMR spectrum are indicative of an α,α-dichlorocyclobutanone structure and a trisubstituted double bond, respectively. The known regiospecificity in the addition reaction of ketenes with conjugated dienes[6] allows to assign the structures **4c** or **4d** to the adduct. On the basis of the known regiospecific formation of substituted tropolones upon acetolysis,[7] **4c** or **4d** should provide the desired 4-(trimethoxyphenylpropyl)tropolone (**2b**) or the corresponding 5-substituted derivative, respectively. The adduct was refluxed in aqueous acetic acid containing potassium acetate, and the tropolonic product was extracted with alkali to give **2b** (67% yield). No formation of other tropolonic products was observed. The physical data of the tropolone were identical with those reported, and the identity was finally ascertained by direct comparison with an authentic sample.[8] The results demonstrates that the aforementioned substituted cyclopentadiene and its dichloroketene adduct must be **4a** and **4c**, respectively. We thus ensured a brief route of good overall yield (25% from **3a**) for the preparation of the tropolone **2b**.

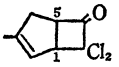
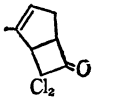


3



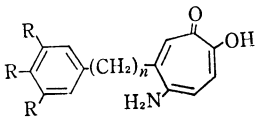
4

a: R=-CH=CH-CO$_2$CH$_3$
b: R=-(CH$_2$)$_2$-CO$_2$CH$_3$
c: R=-(CH$_2$)$_3$-OH
d: R=-(CH$_2$)$_3$-OTs
e: R=-CH=CH-CO$_2$H
f: R=-(CHBr)$_2$-CO$_2$H
g: R=-CH=CHBr
h: R=-C≡CH

a: R= 
b: R= 
c: R= 
d: R= 

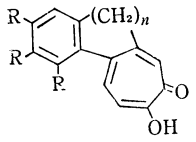
The first successful Pschorr cyclizations of aminotropolones **5a**—**5c** into tricyclic tropolones **6a**—**6c** were achieved by Nozoe *et al.*[9] Kaneko and Matsui[1g] also submitted aminotropolone **7b**, obtained from **2b** *via* azo compound **7a**, to the Pschorr cyclization leading to desacetamidocolchiceine **1b**. We followed the above results and obtained **1b** in a poor yield as reported. The product was reaffirmed by comparison with the au-

thentic compound derived from colchicine according to Eschenmoser *et al.*[1a] In Pschorr cyclization, the fixation of participated aryl groups in *cis* gives better yields of cyclization products than free-rotational systems, *e.g.*, *cis*-2-aminostilbene yielded phenanthrene in 61% yield while 1-phenyl-2-*o*-aminophenylethane gave only a trace of of 9,10-dihydrophenanthrene.[10] In our case *cis*-stilbene type derivative **8b** was presumed to give better yield in the cyclization. We then endeavored to synthesize **8b**.



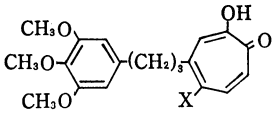
5

a: R=H, n=2
b: R=OCH_3, n=2
c: R=H, n=3



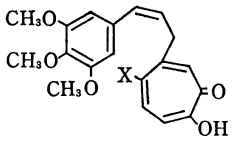
6

a: R=H, n=2
b: R=OCH_3, n=2
c: R=H, n=3



7

a: X=N=N-C_6H_4-CH_3(p)
b: X=NH_2

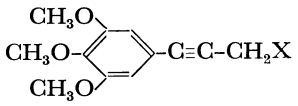


8

a: X=H
b: X=NH_2

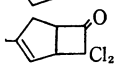
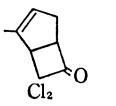
The cinnamic acid **3e** was brominated in chloroform to give crystalline dibromo acid **3f** (95% yield). The dibromo acid was then heated with sodium bicarbonate in dry acetone yielding a mixture of *cis*- and *trans*-bromostyrenes **3g** (91% yield). The mixture showed two peaks in a ratio of 2 : 1 in glc, and the major product was separated by silver nitrate–silica gel tlc. The NMR spectrum of the major product exhibited two olefin proton signals of an AB-pattern, and their coupling constants (8.8 Hz) demonstrate, in accordance with the findings of Grovenstein and Lee,[11a] and Cristol and Norris,[11b] the major decarboxylative dehydrobromination product to be the *cis*-bromostyrene. Upon treatment with sodium amide in liquid ammonia, the mixture of the bromostyrenes **3g** produced phenylacetylene **3h** (85% yield), whose Grignard reagent was then treated with excess formaldehyde in tetrahydrofuran. The reaction afforded two products (68% yield in total), which were separated by silica gel chromatography in a ratio of 3 : 1. The major product ($C_{12}H_{14}O_4$) was identified as the desired compound **9a** by its spectra, while the minor one ($C_{13}H_{14}O_5$) exhibited a strong absorption at 1720 cm^{-1} and a one-proton triplet signal (J=1.5 Hz) at 8.15 ppm in the IR and NMR spectra, respectively. Since these spectra seemed to suggest that the compound is a formate **9b**, the minor product was hydrolyzed with aqueous alkali. The hydrolysis product was found to be identical with the major product **9a**. It was proved by decoupling experiments that the observed splitting of the formate proton signal are due to a spin-spin coupling between this proton and the propargylic methylene protons. The spin-spin coupling through two C-H and two C-O bonds of formate grouping seems to be uncommon. The formation of **9b** may be accounted for oxymethylenation of the initially formed alcoholate **9c** with formaldehyde leading to **9d**, followed by Oppenauer oxidation with excess formaldehyde. The abnormal Grignard reactions of this type have also been reported for some sterically hindered arylmagnesium bromides.[12]

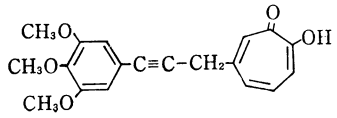
The alcohol **9a** was converted into bromide **9e** with phosphorus tribromide and a catalytic amount of pyridine (83% yield). Upon treatment with sodium cyclopentadienide under conditions similar to those used for the saturated system **4a**. The bromide gave an oil after passing through a short silica gel column (66% yield), which was nearly homogeneous on tlc. The NMR signals of the product at 3.00 (a two-proton multiplet), 3.51 (a two-proton multiplet), and 6.22—6.62 ppm (a three-proton multiplet) are attributable to propargylic methylene, cyclopentadiene methylene, and olefin protons, respectively. Formula **9f** or **9g**, therefore, may be given to the product. Without further investigation on the structure, the product was allowed to react with dichloroketene leading to an oily adduct (32% yield from the substituted cyclopentadiene). The UV spectrum of the adduct (**9h** or **9i**) shows a maximum absorption at 263 nm, and no IR absorption at near 1785 cm^{-1}, a characteristic carbonyl absorption of α,α-dichlorocyclobutenone and its derivatives,[13] was observed. These spectral data demonstrate that the acetylenic bond was unaffected in the course of the addition with dichloroketene. Solvolytic fragmentation of the adduct in acetic acid containing potassium acetate gave a solid product after extraction with aqueous alkali. Despite of some characteristic IR absorptions at 3150, 1610, and 1550 cm^{-1} of the crude product, attempted separation of the desired tropolone **10** was unsuccessful. Catalytic hydrogenation of the crude product over palladium-carbon gave **2b** in only 11% yield.



9

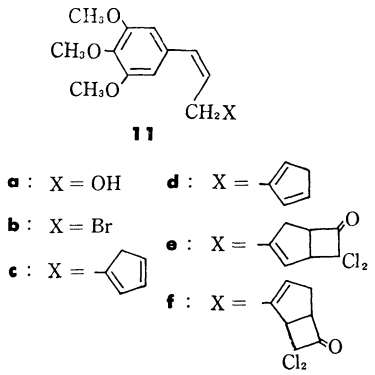
a: X=OH
b: X=OCHO
c: X=OMgBr
d: X=OCH_2OMgBr
e: X=Br

f: X= 
g: X= 
h: X= 
i: X= 



10

Since the pure tropolone **10** was unavailable, we then turned to another approach. The propargyl alcohol **9a** was hydrogenated over Lindlar catalyst to an olefinic alcohol (77% yield), whose NMR spectrum is consistent with the anticipated structure **11a**. Two olefin proton signals of an AB-pattern (J=12 Hz) at 5.80 and 6.50 indicates a cis disubstituted olefin bond. Reaction of **11a** with phosphorus tribromide yielded an unstable bromide **11b**. The crude bromide was submitted to the reaction with sodium cyclopentadienide under conditions similar to those employed for **4a** to give a substituted



cyclopentadiene derivative (36% yield from **11a** after brief purification). The spectra is consistent with the proposed structure **11c** or **11d**. Since the product was also unstable to obtain analytically pure compound, the roughly purified product was immediately submitted to the addition reaction with dichloroketene. A homogeneous oily adduct was obtained on chromatography (5% from **11a**). A UV absorption maximum at 260 nm and an AB-patterned *cis* disubstituted ethylene protons (J=14 Hz) in the NMR spectrum, as disclosed by decoupling (*cf.* Experimental), obviously demonstrate a cis β-substituted styrene moiety. An α,α-dichlorocyclobutanone structure was shown in the IR spectrum (1807 cm^{-1}). These results are in accordance with the structure **11e** or **11f**. The solvolytic fragmentation of the adduct gave an acidic oil, which shows IR absorptions typical of tropolones at 3180, 1615, and 1550 cm^{-1}. The oil, however, was an inseparable mixture. Hydrogenation of the oil, followed by chromatography, gave **2b** in a low yield.

It has still been unclarified why, while the dichloroketene adduct **4c** smoothly yielded the desired tropolone **2a**, the solvolysis of the unsaturated systems resulted in the formation of intractable mixtures.

Experimental

All melting points and boiling points were uncorrected. The spectra were taken with the following instruments: UV, Cary Model 14 spectrophotometer; IR, Hitachi EPI-S2 spectrophotometer; NMR, JEOL Model C-60-HL (60 MHz) and JEOL Model PS-100 (100 MHz). Unless otherwise stated, NMR spectra were recorded in deuterochloroform solutions containing tetramethylsilane (δ=0 ppm) as internal standard. Coupling constants were given in Hz.

*Methyl 3-(3,4,5-Trimethoxyphenyl)-propionate (**3b**).* A solution of methyl *trans*-3,4,5-trimethoxycinnamate[5] **3a** (10 g) in methanol (250 ml) was hydrogenated over 10% palladium-carbon (0.7 g) under atmospheric pressure at room temperature. After hydrogen uptake ceased, the solution was filtered and concentrated to leave an oily **3b** (9.1 g, 91%), which was homogeneous in tlc. IR (Liquid film): 1735 cm^{-1}. NMR: 2.77 (2H, octet), 3.70 (3H, s), 3.81 (3H, s), 3.83 (6H, s), and 6.43 (2H, s).

An analytical sample was obtained by distillation *in vacuo* [bp 110 °C (bath temperature)/0.2 mmHg].

Found: C, 61.24; H, 6.72%. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14%.

*3-(3,4,5-Trimethoxyphenyl)-propyl Alcohol (**3c**).* A solution of the hydrocinnamate **3b** (20 g) in dry ether (150 ml) was added dropwise into a suspension of lithium aluminum hydride (2.3 g) in the same solvent (350 ml) over 4 hr with stirring in an ice bath. After the reaction mixture was allowed to stand overnight at room temperature, the excess reagent was destroyed by adding moist ether and then water. The organic layer was dried and evaporated to give an oily **3c** (17 g), which was homogeneous in tlc. IR (liquid film): 3300 cm^{-1}. NMR: 1.96 (2H, q, J=6), 2.70 (2H, t, J=6), 3.73 (2H, t, J=6), 3.88 (9H, s), and 6.49 (2H, s).

An analytical sample was obtained by distillation *in vacuo* [bp 120—130 °C (bath temperature)/1 mmHg (lit.[14] bp 136—139 °C/0.3 mmHg) as colorless oil.

Found: C, 63.47; H, 7.92%. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02%.

*1-[3-(3,4,5-Trimethoxyphenyl)-propyl]-cyclopentadiene (**4a**).* A solution of tosyl chloride (17.2 g) in dry pyridine (50 ml) was added dropwise to a solution of **3c** (18.5 g) in the same solvent (200 ml) over 2 hr with stirring in an ice bath. The mixture was kept in a refrigerator overnight and then filtered. The filtrate was diluted with cold ether (500 ml) and then washed with cold 10% hydrochloric acid to remove the pyridine. The organic layer was washed with water and brine, and dried. Evaporation of the solvent gave oily tosylate **3d** (27.1 g), which was homogeneous in tlc. The tosylate was used, without further purification, in the next step. IR (liquid film): 1360 and 1180 cm^{-1}.

A solution of freshly distilled cyclopentadiene (380 mg) in dry tetrahydrofuran (3 ml) was added dropwise to a stirred suspension of sodium hydride (126 mg) in the same solvent (4 ml) under nitrogen in an ice bath. After hydrogen evolution ceased, a solution of the crude tosylate (985 mg) in dry tetrahydrofuran (7 ml) was added dropwise to the above cyclopentadienide solution with stirring. Stirring was continued for an additional 3 hr, and the reaction mixture was poured into cold water. The mixture was extracted with ether, and the extracts were washed with water and brine, and dried. Removal of the solvent left a yellow oil (715 mg). The oil was chromatographed on silica gel. Petroleum ether–ether (1 : 1) eluted a small amount of an olefin fraction and then **4a** (576 mg) as a yellow oil. NMR: 1.55—3.05 (8H, m), 3.82 (3H, s), 3.86 (6H, s), 6.43 (2H, s), and 5.92—6.50 (3H, m). Further purification was attempted to obtain an analytically pure sample, but removal of a small amount of impurity from the main fraction was unsuccessful. Thus the roughly purified product was used in the next step.

*7,7-Dichloro-3-[3-(3,4,5-trimethoxyphenyl)-propyl]-bicyclo[3.2.0]-hept-2-en-6-one (**4c**).* Dichloroacetyl chloride (73 mg) was added to a stirred solution of **4a** (137 mg) in *n*-hexane (4 ml), and then the solution was cooled in an ice bath. A solution of triethylamine (60 mg) in the same solvent was added to the above solution over 2 min with stirring. The mixture was stirred for an additional 5 hr. Cold water was added, and the mixture was extracted with ether. The extracts were washed with water and brine, and dried. An oil obtained by evaporation of the solvent was chromato-

graphed on silica gel. Petroleum ether–ether eluted the unreacted **4a** (30 mg) and then the oily adduct **4c** (114 mg, 42% from **3c**). IR: 1805 and 1640 cm^{-1}. NMR: 1.5—2.8 (8H, m), 3.82 (3H, s), 3.85 (6H, s), 4.25 (1H, d.t., J= 7.5 and 2.5, assigned to the proton adjacent to carbonyl[3b]), 5.55 (1H, m), and 6.38 (2H, d, J=2.2).

Found: C, 58.94; H, 5.46%. Calcd for $C_{19}H_{22}O_4Cl_2$: C, 59.21; H, 5.75%.

*4-[3-(3,4,5-Trimethoxyphenyl)-propyl]-tropolone (**2b**).* A mixture of **4c** (4.16 g), potassium acetate (10.6 g), acetic acid (60 ml), and water (0.5 ml) was refluxed for 2 days. The reaction mixture was concentrated *in vacuo*, and the residue was diluted with water. The product was extracted with ether. The organic layer was extracted with dilute sodium hydroxide, and the aqueous layer was acidified with dilute hydrochloric acid. The precipitate was filtered and recrystallized from ethanol to give **2b** (2.40 g, 66%), mp 111—112.5 °C (lit.[1d] 113—115 °C). UV (methanol): 238 nm (log ε, 4.81) and 338 (3.93). IR (KBr): 3180, 1606, 1590, and 1540 cm^{-1}. NMR:[15] 2.00 (2H, m), 2.64 (2H, t, J=8), 2.70 (2H, t, J=8), 3.86 (3H, s), 3.88 (6H, s), 6.44 (2H, s), and 6.8—7.4 (6H, m).

The spectra were identical with those of the authentic compound[1d] provided by Professor Scott.

*4-[3-(3,4,5-Trimethoxyphenyl)-propyl]-5-p-tolylazotropolone (**7a**) and 4-[3-(3,4,5-Trimethoxyphenyl)-propyl]-5-aminotropolone (**7b**).* These compounds were prepared according to the known procedure,[1g] and similar results were obtained. The unreported NMR data of **7a** are given below. NMR of **7a**: 2.00 (2H, m), 2.45 (3H, s), 2.75 (3H, t, J=7), 3.32 (3H, t, J=7), 3.37 (3H, s), 6.43 (2H, s, assigned to the aromatic protons of trimethoxyphenyl), 7.37 and 8.20 (1H, d, J=12 each, assigned to the C-6 and C-7 tropolone protons), 7.40 nad 7.80 (1H, d, J=6 each, assigned to the aromatic protons of tolylazo group), and 7.51 (1H, s, assigned to the C-3 tropolone proton).

*Desacetamidocolchiceine (**1b**).* The cyclization reaction was performed under reaction conditions essentially identical with those described by Kaneko and Matsui,[1g] except that no copper catalyst was used in decomposition of the diazonium salt of **7b**.

Thus a solution of isoamyl nitrite (0.1 ml) in dioxane (1 ml) was added dropwise to a stirred solution of **7b** (69 mg) and sulfuric acid (0.1 ml) in dioxane (1.5 ml) at room temperature. After stirring for an additional 2 hr, the mixture was heated at 55—57 °C for 1 hr. The mixture was diluted with water and extracted with methylene chloride. After usual work-up, the crude product was chromatographed on phosphoric acid impregnated Celite. After an unidentified product was eluted with a mixture of *n*-hexane and benzene, **1b** was eluted with benzene as crystals, which was recrystallized from ethanol giving 2 mg (3%) of the pure product melting at 167—169 °C (lit. 168—169 °C,[1a] 165—167 °C[1b]). The IR and NMR spectra of the product were identical with those of an authentic sample of desacetamidocolchiceine.

*3-(3,4,5-Trimethoxyphenyl)-2,3-dibromopropionic Acid (**3f**).* A solution of bromine (176 mg) in chloroform (1 ml) was added dropwise to an ice-cooled solution of **3a** (238 mg) in the same solvent (2 ml) over 2 min with stirring. The reaction mixture was filtered to separate the precipitate after 30 min, and the filtrate was concentrated to give an additional solid. The combined solids were recrystallized from benzene–ligroin to afford colorless crystals (377 mg, 95%), mp 153—155 °C. IR(KBr): 1745 cm^{-1}. NMR (acetone-d_6): 3.80 (3H, s), 3.91 (6H, s), 5.22 and 5.52 (1H, d, J=12 each), and 7.04 (2H, s).

Found: C, 35.77; H, 3.78%. Calcd for $C_{12}H_{14}O_5Br_2$: C, 36.11; H, 3.51%.

*3,4,5-Trimethoxy-β-styrene (**3g**).* A suspension of **3f** (100 mg) and sodium bicarbonate (252 mg) in dry acetone (10 ml) was refluxed with stirring for 2 hr. The acetone was removed *in vacuo*, and water (3 ml) was added to the residue. The mixture was extracted with ether. The combined extracts were washed with water and brine, and dried. Removal of the solvent left an oil, which was distilled *in vacuo* [120—130 °C (bath temperature)/1 mmHg] giving a colorless oil (62 mg, 91%).

Found: C, 48.81; H, 4.73%. Calcd for $C_{11}H_{13}O_3Br$: C, 48.47; H, 4.79%.

The mixture of the isomers showed two peaks in glc (SE-30 column) in an approximate ratio of 1 : 2. The major isomer was separated by silver nitrate-silica gel preparative tlc. IR (liquid film): 3050 and 1615 cm^{-1}. NMR (carbon tetrachloride):[15] 3.70 (3H, s), 3.75 (6H, s), 6.35 (2H, s), and 6.55 and 6.85 (1H, d, J=8.8 each).

*3,4,5-Trimethoxyphenylacetylene (**3h**).* A solution of the isomeric mixture of **3g** (27.3 g) in dry ether (100 ml) was added dropwise to a stirred sodium amide solution, prepared from sodium (2.7 g) and liquid ammonia (500 ml), over 20 min. A vigorous reaction took place and appeared to complete when the addition finished. Stirring was continued for an additinal 30 min, and ammonium chloride was added. After removal of the liquid ammonia, water was added, and the mixture was extracted with ether. The combined extracts were washed with dilute hydrochloric acid and water, and then brine. Evaporation of the solvent left crystals, which was recrystallized from ether–petroleum ether to give colorless crystals melting at 68—68.5 °C (16.3 g, 85%). IR (KBr): 3250 cm^{-1}. NMR (carbon tetrachloride): 2.93 (1H, s), 3.81 (3H, s), 3.89 (6H, s), and 6.74 (2H, s).

Found: C, 68.79; H, 6.03%. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29%.

*3-(3,4,5-Trimethoxyphenyl)-propargyl Alcohol (**9a**) and Its Formate (**9b**).* A solution of **3h** (192 mg) in dry tetrahydrofuran (0.5 ml) was added dropwise to a Grignard reagent solution prepared from ethyl bromide (131 mg) and magnesium (29 mg) in the same solvent (0.5 ml). Excess formaldehyde vapor was passed through the above acetylenic Grignard reagent solution with stirring at room temperature, and then water was added to quench. The organic layer was separated and washed with water and brine, and dried. Evaporation of the solvent left an oil, which showed three spots in tlc. The oil was chromatographed on silica gel. Petroleum ether–ether (3 : 2) eluted the unreacted **3h** (33 mg) and then the formate **9b** (40 mg, 16%). Petroleum ether–ether (2 : 3—1 : 4) eluted **9a** (115 mg, 52%).

An analytical sample of **9a** was obtained by recrystallization from ether–petroleum ether as colorless crystals melting at 89—91 °C. IR (KBr): 3300, 2210, and 1127 cm^{-1}. NMR:[15] 3.85 (9H, s), 4.51 (2H, s), and 6.71 (2H, s).

Found: C, 64.55; H, 6.45%. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35%.

An analytical sample of **9b** was obtained by recrystallization from *n*-hexane–benzene as colorless crystals melting at 89—90 °C. IR (KBr): 2200, 1720, and 1210 cm^{-1}. NMR: 3.86 (9H, s), 5.00 (2H, d, J=1.5), 6.71 (2H, s), and 8.15 (1H, t, J=1.5). The doublet at 5.00 or the triplet at 8.15 ppm collapsed to a singlet on decoupling of the other signal.

Found: C, 62.59; H, 5.87%. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64%.

A solution of the formate **9b** (50 mg) and sodium hydroxide (16 mg) in ethanol (10 ml) was allowed to stand overnight. After evaporation of the solvent, the residue was diluted with water and extracted with chloroform. A usual work-up

gave **9a** (41 mg, 93%).

*3-(3,4,5-Trimethoxyphenyl)-propargyl Bromide (**9e**).* A solution of phosphorus tribromide (300 mg) in dry tetrahydrofuran was added dropwise to a stirred solution of **9a** (889 mg) and a catalytic amount of pyridine in the same solvent (8 ml) over a period of 10 min in an ice bath. After stirring for an additional 2 hr, the mixture was poured into cold water and extracted with ether. The combined extracts were washed with water and brine, and dried. Removal of the solvent left an oil, which was chromatographed on silica gel. Petroleum ether–ether eluted **9e** (1.14 g, 83%) as crystals, which was recrystallized from petroleum ether–ether to afford colorless crystals, mp 48—50 °C. IR (KBr): 2200 cm^{-1}. NMR (carbon tetrachloride): 3.75 (3H, s), 3.81 (6H, s), 4.11 (2H, s), and 6.60 (2H, s).

Found: C, 50.27; H, 4.58%. Calcd for $C_{12}H_{13}O_3Br$: C, 50.53; H, 4.58%.

*1-[3-(3,4,5-Trimethoxyphenyl)-2-propynyl]cyclopentadiene (**9f** or **9g**).* A solution of **9e** (550 mg) in dry tetrahydrofuran (5 ml) was added dropwise to a stirred cyclopentadienide solution, prepared from cyclopentadiene (152 mg) and sodium hydride (53 mg) in the same solvent (5 ml), over 10 min in an ice bath. Stirring was continued for an additional 3 hr, and the reaction mixture was extracted with ether. The extracts were washed with water and brine, and dried. Removal of the solvent *in vacuo* gave a yellow oil, which was chromatographed on a short silica gel column. A mixture of petroleum ether–ether eluted an oil (344 mg, *ca.* 66%), whose tlc showed it to be nearly homogeneous. Further purification, however, was unsuccessful owing to its instability. IR (liquid film): 2300 cm^{-1}. NMR:[15] 3.00 (2H, m), 3.51 (2H, m), 3.85 (9H, s), 6.22—6.62 (3H, m), and 6.65 (2H, s).

*Dichloroketene Adduct of the Propargylcyclopentadiene (**9h** or **9i**).* Dichloroacetyl chloride (888 mg) was added to a stirred solution of the above propargylcyclopentadiene (1.48 g) in *n*-hexane (40 ml), and the mixture was cooled in an ice bath. A solution of triethylamine (638 mg) in the same solvent was added to the above mixture over 5 min with stirring at the same temperature. The mixture was stirred for an additional 5 hr, and then water was added. The organic layer was washed with water and brine, and dried. Removal of the solvent gave an oil. Petroleum ether containing ether eluted an oily adduct (668 mg, 32%). UV (methanol): 218 nm (log ε, 4.60) and 263 (4.23). IR (liquid film): 1807 cm^{-1}. NMR: 2.77 (2H, m), 3.10—3.80 (2H, m), 3.85 (9H, s), 3.95—4.50 (2H, m), 5.95 (1H, m), 6.70 (1H, s), and 6.75 (1H, s).

Found: C, 59.34; H, 4.90%. Calcd for $C_{19}H_{18}O_4Cl_2$: C, 59.69; H, 4.75%.

*Solvolysis of the Adduct (**9h** or **9i**) and Hydrogenation of the Product.* A solution of the adduct (**9h** or **9i**) (215 mg), potassium acetate (320 mg), and water (2 drops) in acetic acid (5 ml) was refluxed for 2 days. The solvent was removed *in vacuo*, and the residue was diluted with water and extracted with chloroform. The combined extracts were washed with dilute sodium hydroxide solution. The aqueous layer was acidified with dilute hydrochloric acid and extracted with chloroform. The extracts were washed with water and brine. Evaporation of the solvent left a solid (72 mg), which could not be purified by recrystallization or chromatography.

The crude product (70 mg) dissolved in ethyl acetate (5 ml) was hydrogenated over 10% palladium-carbon (5 mg). After hydrogen uptake ceased, the catalyst was filtered off. The filtrate was evaporated to give a solid (61 mg), which was then dissolved in hot methanol (10 ml). The solution was filtered, and the filtrate was concentrated and cooled to give **2b** (8 mg).

*3-(3,4,5-Trimethoxyphenyl)-allyl Alcohol (**11a**).* A mixture of **9a** (66 mg), 5% palladium-barium sulfate (20 mg), quinoline (0.4 ml), and methanol (2 ml) was treated with hydrogen under atmospheric pressure at room temperature. After hydrogen uptake ceased (1 molar equivalent), the catalyst was filtetered off, and then the filtrate was passed through a 5% silver nitrate-silica gel column to remove the quinoline. The solvent was removed, and the residue was submitted to preparative tlc using petorleum ether–ether (1 : 1) as eluent. The allylic alcohol (**11a**) was obtained (51 mg, 77%) as an oil. IR (liquid film): 3400 and 1640 cm^{-1}. NMR: 3.83 (9H, s), 4.42 (2H, q, J=6 and 1.5), 5.80 (1H, d.t, J=12 and 6), 6.50 (1H, br. d, J=12), and 6.45 (2H, s).

Found: C, 64.12; H, 7.25%. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19%.

*Dichloroketene Adduct(**11e** or **11f**).* Phosphorus tribromide (1.39 g) was added dropwise to a stirred solution of **11a** (3.12 g) and pyridine (0.2 ml) in dry tetrahydrofuran (70 ml) over 5 min in an ice bath, and stirring was continued for an additional 1 hr. The mixture was poured into water and extracted with ether. The combined extracts were washed with water and brine, and dried. Removal of the solvent gave an unstable oil (4.09 g), whose IR spectrum showed no hydroxyl absorptions. The freshly prepared bromide was used, without further purification, in the next step.

A solution of the crude bromide (4.09 g) in dry tetrahydrofuran (70 ml) was added dropwise to a stirred cyclopentadienide solution, prepared from cyclopentadiene (1.06 g) and sodium hydride (370 mg) in the same solvent (70 ml), over 10 min at an ice-bath temperature. After stirring for an additional 2 hr, the mixture was poured into water and extracted with ether. A usual work-up gave a yellow oil, which was chromatographed on a short silica gel column. Petroleum ether–ether (2 : 1) eluted an oily product (1.37 g, 36% from **11a**), which was homogeneous in tlc. NMR: 3.02 (2H, m), 3.36 (2H, m), 3.87 (3H, s), 3.91 (6H, s), 6.12—6.60 (5H, m), and 6.67 (2H, s).

Owing to its instability, no analytical sample of the product was obtained.

Dichloroacetyl chloride (54 mg) was added to a stirred solution of the roughly purified product (100 mg) in *n*-hexane (5 ml) in an ice bath. A solution of triethylamine (38 mg) in the same solvent (3 ml) was added dropwise to the above mixture. After stirring for an additional 2 hr, the mixture was poured into water and extracted with ether. A usual work-up gave an oil, which was purified twice by preparative silica gel tlc using petroleum ether–ether (1 : 1) as eluent. A homogeneous product **11e** (or **11f**) (20 mg, 5% from **11a**) was obtained. UV (methanol): 260 nm (log ε, 4.22). IR (liquid film): 1807 cm^{-1}. NMR:[15] 2.67 (2H, m), 3.00 (2H, br. d, J=6), 3.81 (3H, s), 3.84 (6H, s), 3.95 (1H, m, assigned to the C-1 proton[16]), 4.25 (1H, d. t, assigned to the C-5 proton[16]), 5.48 (1H, br. s), 6.04 (1H, q, J=14 and 6), 6.32 (1H, d, J=14), and 6.45 (2H, s). On irradiation at 3.00 ppm, the quartet signal at 6.04 ppm changed into a doublet (J=14).

Found: C, 59.66; H, 4.61%. Calcd for $C_{19}H_{20}O_4Cl_2$: C, 59.31; H, 4.82%.

*Solvolysis of the Adduct (**11e** or **11f**) and Hydrogenation of the Product.* A mixture of the adduct (**11e** or **11f**) (95 mg), potassium acetate (200 mg), water (2 drops), and acetic acid (2 ml) was refluxed for 2 days. The solvent was evaporated *in vacuo*, and the residue was poured into water and extracted with ether. The extracts were washed with aqueous sodium hydroxide, and the aqueous layer was acidified with dilute hydrochloric acid. The acidic product was extracted with chloroform. The organic layer was extracted

with 85% phosphoric acid, and the phosphoric acid extracts were diluted with water. The liberated product was collected with ether. An oil (27 mg) was obtained by evaporation of the solvent. The oil was a mixture and gave no homogeneous product upon attempted purification.

A mixture of the crude solvolysis products (20 mg), 10% palladium-carbon (3 mg) and ethyl acetate (2 ml) was hydrogenated under atmospheric pressure at room temperature. After usual work-up, an oil obtained was passed through a phosphoric acid-Celite column. Benzene eluted crystals, which were recrystallized from methanol to give **2b** (4 mg), as identified by IR.

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