(17) H. Booth, *Tetrahedron Lett.*, 411 (1965), and references cited therein.
(18) The alcohol was reasonably stable when kept under basic or neutral conditions. Slightly acidic solvents such as $CDCl_3$ were sufficient to cause extensive decomposition of the compound.
(19) This reaction is sensitive to the amount of iodine used, giving lower yields of enone when larger amounts were used. The use of iodine for this reaction originated from a seminar given by Professor K. Nakanishi at the University of Rochester.
(20) Several different hydride reagents were examined for the reduction of enone **25.** Most were found to give significant amount of 1,4 reduction together with varying ratios of the alcohols. Vitride, for example, gave the highest ratio of **26**, 85:15, with 20% 1,4 reduction. DIBAL-H, ultimately used in this reduction, gave only trace amounts of 1,4-reduction.
(21) The preparation and use of pyridinium chlorochromate in the oxidation of alcohols is described by E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
(22) Epoxidations of allylic alcohols although generally stereospecific frequently contain some *trans*-epoxide alcohol. It has been reported that the use of $VO(acac)_2$ and $Mo(CO)_6$ with peroxides increases the stereoselectivity of epoxidations. Attempted use of these reagents on alcohol **26** resulted in significant oxidation of the allylic alcohol back into the enone **25.** For examples of the use of $VO(acac)_2$ and $Mo(CO)_6$, see T. Itoch, K. Kaneda, and S. Teranishi, *J. Chem. Soc., Chem. Commun.*, 421 (1976), and S. Tanaka, H. Yamamoto, H. Nozak, K. B. Sharpless, R. C. Michaelson, and J. D. Cutting, *J. Am. Chem. Soc.*, **96**, 5254 (1974), and references cited therein.
(23) Although a rigorous structure proof of the proposed diepoxide was not completed, isolation of a material from epoxidations carried out at 0 °C provided a ^1H NMR spectrum devoid of vinyl protons and a mass spectrum 16 units higher than the desired monoepoxide.
(24) K. Tori, T. Komeno, and T. Nakagawa, *J. Org. Chem.*, **29**, 1136 (1964).
(25) This dianion was generated with 2 equiv of lithium diisopropylamide. The procedure used follows that described by S. N. Huckin and L. Wieler, *J. Am. Chem. Soc.*, **96**, 1082 (1974). The dianion derived from methyl acetoacetate has previously been reported to ring open epoxides by T. A. Bryson, *J. Org. Chem.*, **38**, 3428 (1973).
(26) For a more detailed account of the reaction of these epoxides with *tert*-butyl dilithioacetoacetate, see G. R. Kieczykowski, M. R. Roberts, and R. H. Schlessinger, *J. Org. Chem.*, **43**, 788 (1978); (b) for a description of epoxide opening with dilithioacetate, see S. Danishefsky, M. Tsai, and T. Kitahara, *ibid.*, **42**, 394 (1977).
(27) Oximination α to ketones has ample literature precedence. For an example in which *tert*-butyl acetoacetate was oximinated and degraded to acetic acid, see K. Schank, *Ber.*, **100**, 1245 (1967). Significant quantities of the lactone **31** are formed in this reaction; however, to effectuate complete conversion of the oxime **30** into the lactone **31**, acetic anhydride was used. Interestingly, when only 1 equiv of isoamyl nitrite was used, the major product of the reaction was the oxime.
(28) Oxidation of sulfides to sulfoxides with ceric ammonium nitrate has been reported by T. L. Ho and C. M. Wong, *Synthesis*, 561 (1972). The conversion of **33** into **34** probably occurs by ready sulfoxide rearrangement, facilitated by the adjacent ether oxygen atom, into the corresponding sulfinic ester followed by hydrolysis of this ester into the hemiacetal.
(29) The authors wish to thank Professor S. Danishefsky for a generous sample of bisnorvernolepin which was employed for direct NMR, mass spec, IR, TLC, and melting point comparison with the material made by the route described herein.
(30) Another 25% of bisnorvernolepin was obtained from this reaction with a melting point slightly lower than the pure sample. However,the NMR, IR, and mass spectra along with the TLC showed essentially no differences between this material and completely pure material.
(31) Nuclear magnetic resonance spectra were recorded at 100 Hz on a Jeolco Model JNM-PS-100 high-resolution spectrometer or on a Jeolco Model JNP-PS-100 high-resolution Fourier transform spectrometer. Samples were examined in deuteriochloroform containing 1% by volume of tetramethylsilane unless otherwise noted. Infrared spectra were recorded on a Perkin-Elmer Model 467 grating spectrophotometer. Mass spectra were obtained on a Du Pont Model 21-490 B mass spectrometer. Melting points were determined on a Fisher-Johns melting point block and reported uncorrected.

Gas chromatography was performed on a Hewlett-Packard series 5700 A gas chromatograph with a series 5702 A temperature programmer and 5705 A thermal conductivity detector. Columns were either 6 ft × 0.125 in. or 2 ft × 0.125 in. aluminum tubing packed with 15% S. E. 30 on acid-washed Chromosorb W, 80–100 mesh, and were cured at 270 °C. The carrier gas was dry helium and a flowrate of 20 ± 2 mL/min was maintained. Thin-layer chromatography utilized precoated Analtech medium hard Silica Gel GHLF glass plates of 0.25-mm thickness. Elution of the plate was carried out at approximately a 60° angle and visualization was made by means of an ultraviolet light, and or an iodine chamber, and or by charring with 10% sulfuric acid containing 2% cobaltous chloride. Preparative chromatography was performed as follows: the silica, no. 7731 silica gel G type 60 for TLC, was placed in a sintered glass funnel packed dry. Solvent was flushed through the silica gel under water aspirator vacuum and the silica repressed to avoid channeling between the glass and the silica. The compound to be purified was deposited with a minimal amount of solvent and then eluted with solvent by using a water aspirator as the vacuum source.

Reactions requiring heating were immersed in thermostated silicon oil baths. Reactions requiring −78 °C temperatures were performed in CO_2 acetone baths and those requiring 0 °C utilized ice baths. Temperatures between 0 and −78 °C were maintained by using a Flexi-Cool in conjunction with a heater override system manufactured by FTS Systems Inc. (temperature accuracy ±0.5 °C).

High vacuum distillations utilized a CVC 4 in. oil diffusion pump with a 165-L/min Alcatel rough pump.

All reactions were run in flamed vessels under an atmosphere of nitrogen except those in which water was present. All additions, wherever possible, were made via syringe through a septum, and all reactions were stirred using magnetic stirrers. All solutions were concentrated on a rotary evaporator at 20–30 °C and at pressures of 15–20 mmHg except where otherwise noted. Tetrahydrofuran (THF), diethyl ether, and 1,2-dimethoxyethane (DME) were distilled from lithium aluminum hydride (LAH) immediately before use. When these solvents were used in amide base reactions, nitrogen was bubbled through the solvent for 15 min before use. All lithium amide bases were generated in situ immediately before use. Potassium *tert*-butoxide in *tert*-butyl alcohol was prepared from potassium metal and *tert*-butyl alcohol and stored in the dark under nitrogen at −20 °C.

Methylene chloride was distilled from calcium chloride, *tert*-butyl alcohol from calcium hydride, and methanol from magnesium turnings immediately before use. The following solvents were distilled under nitrogen and stored under an atmosphere of nitrogen over sieves, where appropriate, in bottles fitted with septums: dimethyl sulfoxide (Me_2SO) from calcium hydride; toluene and hexane from lithium aluminum hydride; acetonitrile from phosphorus pentoxide; acetic acid from acetic anhydride.

Diisobutylaluminum hydride (DIBAL-H) in hexane was obtained from Texas Alkyls and used without titration. Sodium hydride (NaH), calcium hydride, and lithium aluminum hydride were purchased from Alfa. Solutions of *n*-butyllithium (BuLi) in hexane were obtained from Alfa and titrated in benzene with *tert*-butyl alcohol/benzene using 1,10-phenanthroline as the indicator.

The Ambient Temperature Ullmann Reaction and Its Application to the Total Synthesis of (±)-Steganacin[1]

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Contribution from the Department of Chemistry, Yale University, New Haven, Connecticut 06520. *Received June 25, 1979*

Abstract: The details of a new method for preparing unsymmetrical biphenyls at room temperature by a modification of the classical Ullmann reaction are discussed. An intramolecularly coordinated organocopper reagent is treated with an aryl iodide bearing a potential coordinating ligand to form the biphenyl. Nitrogen and sulfur have been utilized as ligands and as protecting groups for carbonyls. The application of this methodology to the synthesis of the antileukemic steganacin is detailed.

Introduction

The two antileukemic lactones, steganacin (**31b**) and steganangin (**31c**), which co-occur in nature with steganone (**31a**) and steganol (**31d**) were isolated from *Steganotaenia araliacea* by Kupchan in 1973.[4] These substances[5,6] are representative of a growing class of lignans bearing the dibenzo[*a*,*c*]cyclooctene ring system.[7]

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Table I. Biphenyls Formed Using Nitrogen Ligands

entry	Cu reagent	iodide	biphenyl	yield, %[a]
1	**2d**	**2b**	**5b**	57
2	**1d**	**1b**	**5a**	44
3	**1d**	**2b**	**5c**	54
4	**2d**	**1b**	**5c**	58
5	**1h**	**1f**	**5d**	63
6	**3d**	**3b**	**5f**	49
7	**3d**	**2b**	**5e**	63
8	**4**	**3b**	**6**	54[b]
9	**7**	**3b**	**8**	48[c]

[a] Crystallization yields. NMR integration (benzaldehyde) of the crude hydrolysates indicated optimal yields which are 10–25% higher. [b] Isolated as the imine-oxazoline. [c] Isolated as the imine.

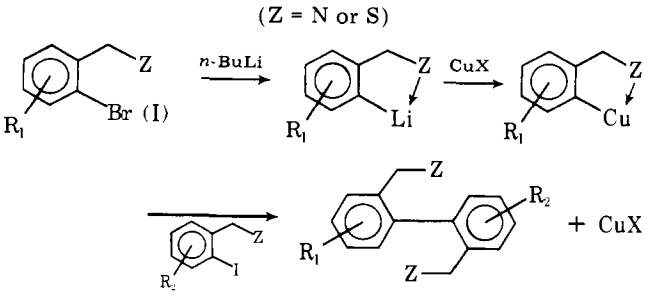
The presence of the biphenyl moiety in these lactones raised the question as to whether or not the classical Ullmann reaction[8,9] might be applicable to the synthesis of the steganes. Although we have answered this question in the negative for the intramolecular reaction,[10] we felt that the intermolecular reaction, as traditionally practiced, was in need of improvement. Among the shortcomings of the reaction are the inconsistencies associated with the copper bronze which can make reproducibility difficult, the inability to obtain selectively cross-coupled biphenyls,[11] and the elevated temperature range (~100–250 °C) which can contribute to the lack of coupling selectivity.

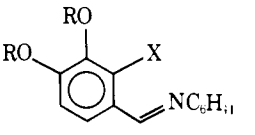
Since it has been demonstrated that the Ullmann reaction proceeds through organocopper intermediates by means of several possible mechanisms, we sought to solve these shortcomings by independently generating an intramolecular, heteroatom-stabilized arylcopper(I) species from the appropriate organolithium reagent. The latter reagents are readily available by metal–hydrogen or metal–halogen exchange with alkyllithiums.[12] The copper reagent could in turn react with an aryl iodide bearing a similar potential heteroatom ligand to produce a biphenyl (Scheme I). By judicious choice of the intramolecular ligands, they could represent chemoselective latent functionality amenable to the realization of our synthetic goal. Although intramolecular ligand stabilized aryl copper,[13] cobalt,[14] platinum,[15] palladium,[15] and silver[16] species have been shown to give biphenyls, they have only been applied in symmetrical couplings.

Results and Discussion

Nitrogen as an Intramolecular Ligand. The feasibility of the ambient-temperature Ullmann reaction was initially explored by conversion of a homogeneous, pale yellow solution (THF, −78 °C) of 6-lithiopiperonal cyclohexylimine (**2c**) (from **2a**)[17] into its organocopper counterpart by treatment with CuI·$(C_2H_5O)_3P$ to produce a homogeneous orange-red solution. The organometallic was treated with aryl iodide **2b** and allowed to warm to 25 °C, at which temperature the reaction was allowed to proceed for 4 h. Hydrolysis of the crude biphenyl dicyclohexylimine provided the symmetrically substituted dialdehyde **5b**. In a similar manner, the more sterically hindered 2-substituted cyclohexylimines (Table I, entries 2 and 6) provided the symmetrical biphenyls **5a** and **5f**, respectively.

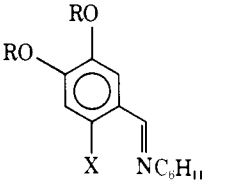
Scheme I



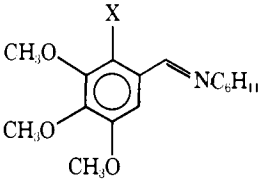


1

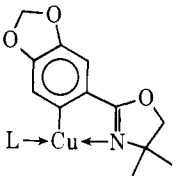
L = $(C_2H_5O)_3P$
a, R = CH_2; X = Br
b, R = CH_2; X = I
c, R = CH_2; X = Li
d, R = CH_2; X = Cu←L
e, R = CH_3; X = Br
f, R = CH_3; X = I
g, R = CH_3; X = Li
h, R = CH_3; X = Cu←L



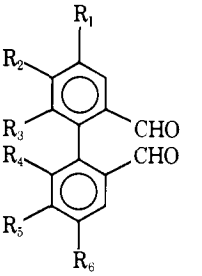
2



3a, X = Br
b, X = I
c, X = Li
d, X = Cu←L



4

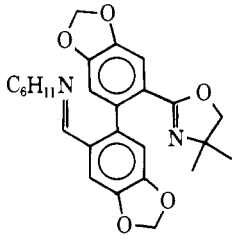


5a, $R_1 = R_6 = H$; $R_2, R_3 = R_4, R_5 = OCH_2O$
b, $R_3 = R_4 = H$; $R_1, R_2 = R_5, R_6 = OCH_2O$
c, $R_1 = R_4 = H$; $R_2, R_3 = R_5, R_6 = OCH_2O$
d, $R_3 = R_4 = H$; $R_1 = R_2 = R_5 = R_6 = OCH_3$
e, $R_3 = H$; $R_1, R_2 = OCH_2O$; $R_4 = R_5 = R_6 = OCH_3$
f, $R_{1-6} = OCH_3$

The crucial question of efficient cross coupling was answered when the two possible modes of reaction (entries 3 and 4) yielded the unsymmetrically substituted biphenyl **5c**. Liquid chromatographic analysis (UV detection) indicated that less than 5% combined yield of other biphenyl products was present. This methodology has proven superior to nickel(0) reagents,[10b,18] since they are primarily suited for symmetrical couplings and are ineffective when two ortho substituents flank the reactive carbon sites.

With the aid of the ambient-temperature Ullmann reaction, Kende and Curran[19] have recently prepared 4,4′-dimethoxy-3,3′-dimethyl-1,1′-biphenyl-2,2′-dialdehyde dicyclohexylimine, a key intermediate in a synthesis of the cytotoxic 9,10-dihydrophenanthrene juncusol, in 93% yield. The application of more traditional Ullmann conditions and nickel(0) reagents gave substantially lower yields.

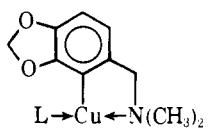
Thus far, the nitrogenous ligands have provided only dialdehydes through the imines. Meyers has utilized oxazolines at latent carboxylic esters[20] which are stable under conditions which hydrolyze imines. Such chemoselectivity would permit stepwise exposure of functionality in a biphenyl bearing both groups. Biphenyl **6** was readily prepared by the reaction of oxazoline stabilized copper reagent **4** and iodo imine **2b**.



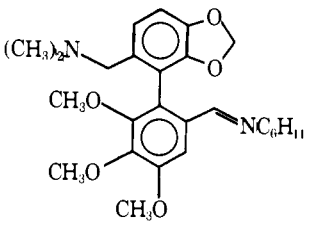
6

The amine complexes copper reagent **7,** prepared by *n*-BuLi metalation of *N,N*-dimethylpiperonylamine[21] and subsequent treatment with $CuI\cdot(C_2H_5O)_3P$, coupled smoothly with the iodo imine **3b** to provide the bifunctional biphenyl **8**.

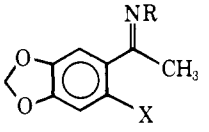
The use of ketimines of acetophenones in the coupling reaction did not prove successful. Attempts to convert 2-iodo-4,5-methylenedioxyacetophenone to the *N*-methylimine with methylamine produced not only the desired product **9a** but also the aromatic substitution product **9b**. This difficulty was overcome by employing $TiCl_4$–CH_3NH_2,[22] which cleanly provided the iodide **9a**. Unfortunately, attempted coupling with **3d** led to protonation of the copper reagent, presumably by the labile methyl protons of **9a**.



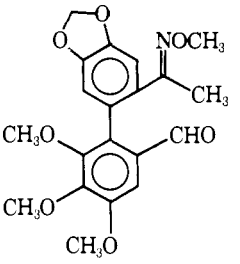
7



8



9a, R = CH_3; X = I
b, R = CH_3; X = $NHCH_3$
c, R = OCH_3; X = I



10

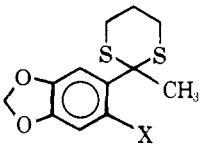
The problem of protonation was avoided by employing the anti *O*-methyloxime **9c** which readily coupled with copper reagent **3d** to provide the selectively protected aldehyde **10**. The *O*-methyloxime of **10** proved difficult to remove without causing extensive decomposition, in spite of the fact that N-alkylation [FSO_3CH_3 or $(CH_3)_3O^+BF_4^-$] of **9a** aided hydrolysis. Moreover, zinc dust/HOAc readily converted **9c** to the corresponding dehalogenated ketone while **10** gave rise to extensive decomposition products.

The difficulties arising from the use of nitrogen ligands were overcome by employing dithioketals.

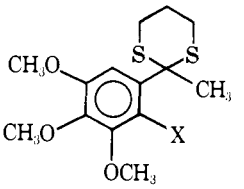
Sulfur as an Intramolecular Ligand. The distinct advantages of dithioketals over nitrogen ligands for masking acetophenones are their stability in the presence of reagents necessary to hydrolyze imines and the absence of labile protons on the methyl group.

Dithiane **11a** underwent facile metal–halogen exchange with *n*-BuLi at −78 °C in THF. The resultant Li reagent **11b** was transformed into its copper reagent **11c** and allowed to react with iodo imine **3b** at 25 °C for 48 h, providing, after acidic hydrolysis, the biphenyl dithiane aldehyde **13** in 65% yield.

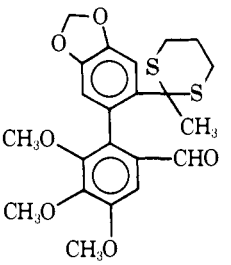
Biphenyl **14,** structurally isomeric with **13,** was at one time desired as a synthon (as was **13**) for steganacin. We sought to determine if organocopper reagent **12c** would successfully couple with iodide **2b,** since the bulky 2-methyldithianyl moiety might hinder the reaction. Attempts to metalate **12a** directly with *n*-BuLi/THF gave a thiobenzylic anion derived from *n*-BuLi attack at sulfur. This cleavage was more facile in THF/HMPA and the resultant anion could be successfully methylated at the benzylic site. Metal–halogen exchange (**12b**) again proved successful, eventually leading to biphenyl **14** (63%) upon reaction with iodo imine **2b**.



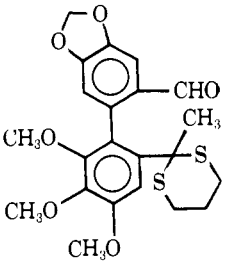
11a, X = Br
b, X = Li
c, X = Cu←L



12a, X = H
b, X = Br
c, X = Cu←L



13

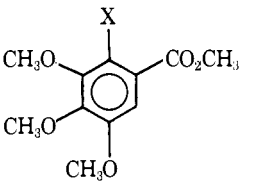


14

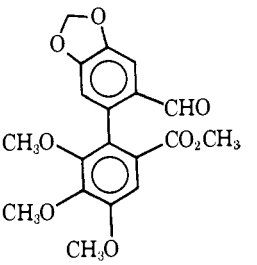
1,3-Oxathiolanes, which have only one sulfur atom available for coordination, are effective alternatives to dithianes in the coupling reactions.

The hydrolytic removal of the sulfur groups was best accomplished by the method of Fetizon[23] (CH_3I, aqueous acetone, reflux). When methods employing mercuric salts to effect dithiane cleavage were utilized, vinyl sulfides were often intermediates in the reactions. Furthermore, the products were frequently contaminated with mercurial residues.

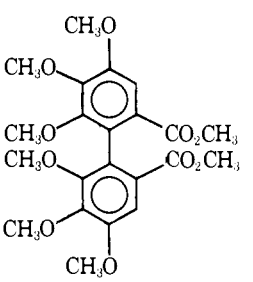
Couplings with Other Aromatic Systems. The reaction between copper reagent **2d** and 6-iodopiperonal was unsuccessful, apparently owing to the reactivity of the aldehyde group toward the organometallic reagent. The coupling between 2-iodo-4,5-methylenedioxyacetophenone and **2d** failed to give biphenyl because of facile proton exchange. When copper reagent **2d** was coupled with iodide **15b,** the reaction was found



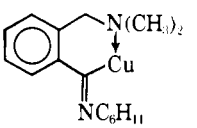
15a, R = H
b, R = I



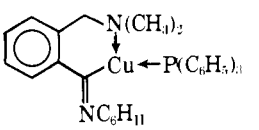
16



17

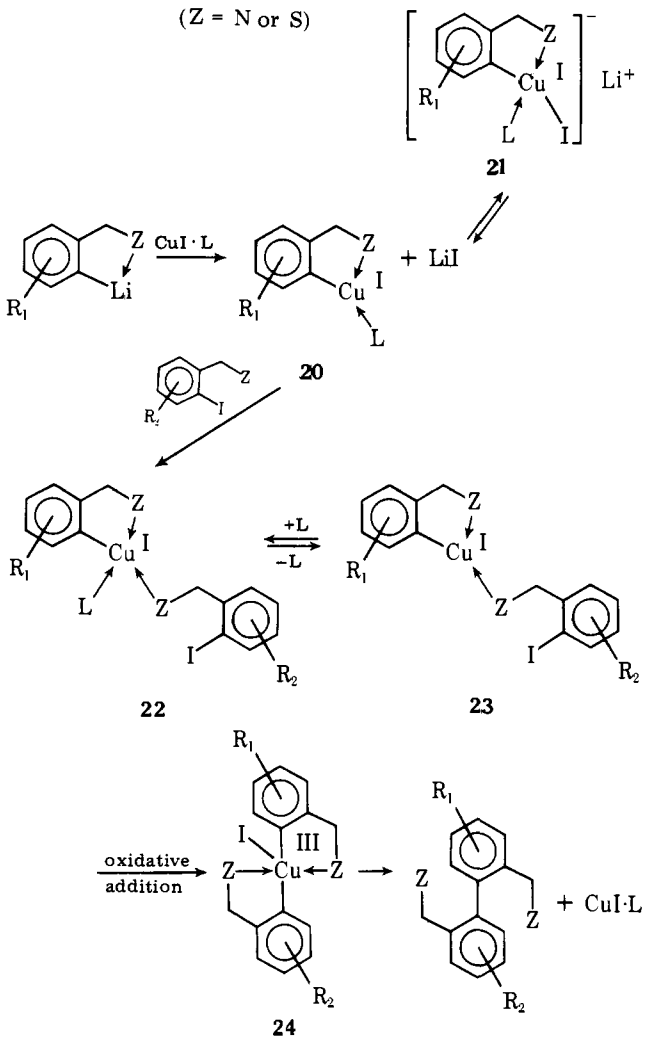


18



19

Scheme II



to be qualitatively slower than coupling reactions using nitrogen and sulfur ligands. In addition to the formation of aldehydo ester **16** (34%), the symmetrical diester **17** (15%), symmetrical dialdehyde **5b** (4%), piperonal (24%), iodo ester **15b** (5%), and ester **15a** (15%) were also formed. The appearance of diester **17** indicated that copper–halogen exchange[24] had occurred. This view is substantiated by the presence of reduced ester **15a**, arising from protonation of an intermediate copper reagent. The presence of piperonal can be justified in the same manner.

Coupling reactions in which only one aromatic partner bears a coordinating ligand were inefficient. Thus, the reaction of phenylcopper–triethyl phosphite complex and **2b** or iodobenzene and **2d** gave low yields of cross-coupled and symmetrical biphenyls in addition to protonated copper reagents and recovered iodides.

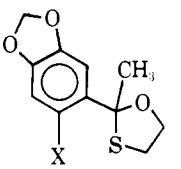
Mechanistic Considerations. Significant contributions to the understanding of the mechanism(s) of the Ullmann reaction have been made. Cohen[25] has demonstrated the intermediacy of arylcopper reagents and the lack of free radicals[26] in the course of the reaction. Arylcopper(I) species can exist as highly aggregated clusters, in particular those reagents bearing stabilizing ligands.[13b,27] Van Koten[13b] has argued that a Cu^{III} state need not be involved in the disproportionation of these aggregates to biphenyls. However, Cohen[28] has observed that *o*-bromonitrobenzene reacts with cuprous triflate in aqueous ammonia to produce 2,2′-dinitrobiphenyl. The kinetics of the reaction are first order in Cu^{I} and second order in aryl halide, indicating that the formal copper(III) intermediate formed by oxidative addition is not reduced to a copper(I) state prior to reacting with a second mol of aryl halide.

The state of aggregation in solution of the copper species studied in this work is unknown. The complex **18** has been shown[29] to be dimeric in benzene solution at 25 °C. Addition of 1 equiv of triphenylphosphine to the reagent produces a yellow solution of a 1:1 adduct (**19**) which is monomeric. The similarity between the complex **19** and the copper reagents used in this study leads us to treat them as monomers as outlined in Scheme II. The d^{10} unsaturated species **20** interacts with the ligand of the aryl iodide generating the d^{10} saturated intermediate **22**. This step is critical in explaining the mild conditions and selectivity observed in these reactions. The fact that the reaction proceeds in spite of a bulky dithiane unit in **12c** argues that the coordination precedes an oxidative addition step. The d^{10} saturated species **22** is able to lose the phosphite ligand to produce the d^{10} unsaturated intermediate **23** which can undergo oxidative addition to the d^{8} saturated Cu^{III} complex **24**. Decomposition of **24** would give rise to the biphenyl with the generation of cuprous iodide.

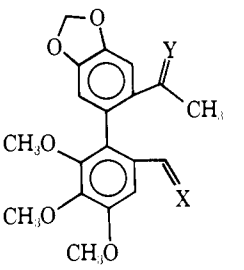
Aryl halides bearing electron-withdrawing groups in the ortho position undergo Ullmann reactions at lower temperatures than aryl halides without such substituents. In the case of iodo ester **15b**, the apparent slower reaction rate indicates that direct oxidative addition might be occurring without the ester oxygen serving as an effective ligand. Under these circumstances copper–halogen exchange in **24** (one intramolecular ligand) and reversal could be competitive with collapse to product.

Synthesis of (±)-Steganacin. With an appreciation for the scope of the ambient-temperature Ullmann reaction, we turned our attention to the synthesis of (±)-steganacin. Our plan was to construct an appropriately substituted biphenyl whose intramolecular ligands could be selectively removed to allow independent elaboration of the 2- and 2′-carbon atoms.

Oxathiolane **25a** was prepared in 50% overall yield from 6-bromopiperonal by reaction with methylmagnesium bromide, oxidation with pyridinium chlorochromate, and thioketalization with β-mercaptoethanol. An orange solution of the copper reagent was prepared in the usual way and was treated with imine **3b** for 20 h. The crude biphenyl **26a** was



25a, X = Br
b, X = Li
c, X = Cu←L



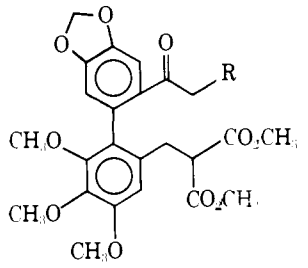
26a, X = NC_6H_{11}; Y = SCH_2CH_2O
b, X = O; Y = SCH_2CH_2O
c, X = $C(CO_2CH_3)_2$; Y = SCH_2CH_2O
d, X = $C(CO_2CH_3)_2$; Y = O

hydrolyzed in aqueous acetic acid to provide the crystalline monoprotected biphenyl aldehyde **26b** in 82% yield. This substance is actually a mixture of diastereomers by virtue of the asymmetry of the oxathiolane ring and the atropisomerism of the biphenyl system. The NMR spectrum displayed two pairs of singlets at δ 9.45 and 9.50 (1/3, 1 H, CHO) and 1.70 and 1.78 (1/3, 1 H, CH_3) in accord with a mixture of diastereomers. The NMR sample showed no change after 4 days in the relative intensities of these signals.

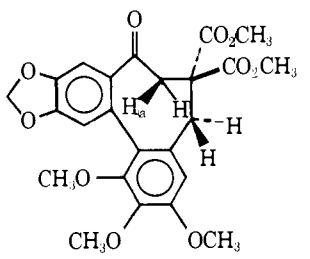
Knoevenagel condensation of the aldehyde with dimethyl malonate under the influence of piperidine catalysis gave rise to the malonylidene derivative **26c**, whose 90-MHz NMR spectrum showed no obvious signs of diastereomerism. The

presence of the sulfur atom dictated that the protecting group be removed prior to catalytic hydrogenation of the double bond, although there was concern about the possibility of acid-catalyzed addition of the methyl ketone to the malonylidene moiety. This concern proved unwarranted, since cleavage of the oxathiolane with methyl iodide in refluxing aqueous acetone readily provided the uncyclized product **26d**. This substance has a unique 90-MHz NMR spectrum in that it consists of 11 uncoupled singlets. The double bond of **26d** was inert to catalytic hydrogenation over Pd/C at atmospheric pressure. Under the same conditions, Ni(R) W-2 served to rapidly produce the dihydro compound **27a**.

In order to effect intramolecular ring closure, it was necessary to convert **27a** to the α-bromo ketone. This conversion was



27a, R = H
b, R = Br



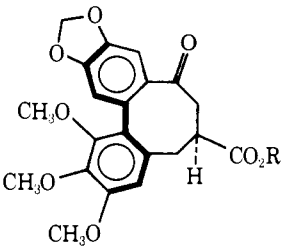
28

slow with pyridinium hydrobromide perbromide in CH_2Cl_2, but was facilitated in the presence of trifluoroacetic acid, which aided in the enolization of the methyl ketone. The bromo ketone contains both methine and methylene protons susceptible to exchange with base. In order to assure exchange should the methylene group be deprotonated, *t*-KO-Bu/*t*-HOBu/THF was chosen as the medium for ring closure. By dropwise addition of the bromo ketone to the basic solution, the dibenzocyclooctanone dicarboxylate **28** was formed in 73% yield. The methylene protons appeared in the NMR spectrum as a pair of doublets of doublets, the highest field doublet (δ 2.76) assigned to H_a which lay in the shielding cone of the trimethoxybenzene ring. The aromatic methoxyl group ortho to the biphenyl ring fusion was likewise shifted to higher field (δ 3.56) owing to the influence of the methylenedioxybenzene ring. These data in conjunction with the presence of a conjugated aromatic ketone (1660 cm^{-1}) indicated that the aromatic rings were orthogonal to each other. Kende and co-workers[5a] have prepared the analogous diethyl ester in their synthesis.

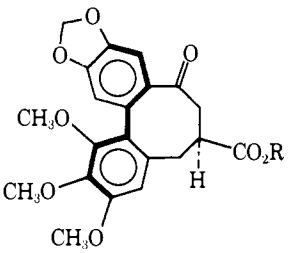
Saponification of the diester followed by thermal monodecarboxylation of the diacid and diazomethane esterification provided esters **29b** and **30b** previously encountered by both Kende[30] and Raphael.[5b] The known thermal interconversion of the esters to a 1:1 mixture of both diastereomers via rotation about the biphenyl bond was confirmed by refluxing either diastereomer in xylene.

The lactone ring was formed as previously described using 40% formalin/KOH followed by Jones oxidation to provide of mixture of steganone (**31a**) and isosteganone (**32**). The latter ketone was converted to the former by refluxing a xylene solution of the mixture. The 270-MHz NMR spectrum of synthetic racemic steganone was identical with that of a sample of authentic natural (−)-steganone.[31] Sodium borohydride reduction of steganone gave the expected 1:1 mixture of steganol (**31d**) and episteganol (**31e**).[4] Steganol upon acetylation provided (±)-steganacin whose 270-MHz NMR spectrum was identical with that of natural (−)-steganacin.[31]

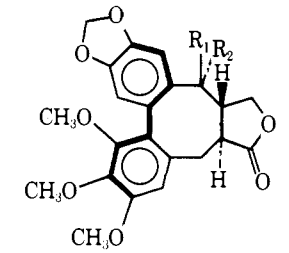
The successful synthesis of these antileukemic natural products exemplifies the synthetic potential of the ambient-temperature Ullmann reaction. We anticipate that this new variation of a classical reaction will find extensive use in the synthesis of biphenyl systems.



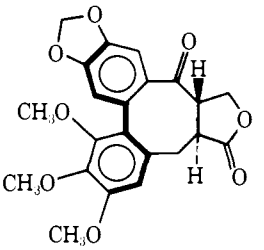
29a, R = H
b, R = CH_3



30a, R = H
b, R = CH_3



31a, R_1, R_2, = O
b, R_1 = OAc, R_2 = H
c, R_1 = O_2C ; R_2 = H
d, R_1 = OH; R_2 = H
e, R_1 = H; R_2 = OH



32

Experimental Section

Melting points are corrected and were determined on a Fisher-Johns apparatus. Elemental analyses were performed by Atlantic Microlabs, Inc., Atlanta, Ga. NMR chemical shifts were determined on a Perkin-Elmer R-32 90-MHz spectrometer in Fourier transform mode or on a Jeolco Minimar 100-MHz instrument or Bruker HX-270 on internal lock with tetramethylsilane as internal reference. IR spectra were recorded on a Beckman 4250 spectrophotometer. Analytical LC chromatograms were obtained with a 50 × 2 mm Porasil T column equipped with an ISCO UV Type 6 detector and integrator at a pumping rate of 0.5 mL/min. Thin layer chromatography was performed on Baker-Flex 1B-F plates and visualized by UV quenching and/or spraying with concentrated sulfuric acid. Preparative TLC purifications were carried out on Analtech silica gel GF 2000-μ plates dried for 1 h at 100 °C before use. Column chromatography, except where indicated, was performed with Grace 100/200 mesh silica gel. Tetrahydrofuran and ether were distilled from sodium benzophenone ketyl solution under nitrogen. *n*-Butyllithium in hexane was purchased from Alfa-Ventron and titrated by the method of Kofron.[32] Reactions requiring anhydrous conditions were conducted in flame-dried glassware under nitrogen or argon. Solutions were transferred by oven-dried syringes through rubber septa. Organic solutions were dried over anhydrous magnesium sulfate.

2-Iodo-3,4,5-trimethoxybenzaldehyde. Oxidation of 2-iodo-3,4,5-trimethoxybenzyl alcohol[10a] with MnO_2[33] in benzene solution as described by Harfenist[34] provided the aldehyde: mp 66–66.5 °C (ether–hexane); NMR ($CDCl_3$) δ 10.04 (1 H, s), 7.34 (1 H, s), 3.97 (3 H, s), and 3.91 (6 H, s). Anal. Calcd for $C_{10}H_{11}IO_4$: C, 37.29; H, 3.44; I, 39.40. Found: C, 37.42; H, 3.46; I, 39.42.

2-Bromo-3,4,5-trimethoxybenzyl Alcohol.[35] A mixture of 9.9 g (50.0 mmol) of 3,4,5-trimethoxybenzyl alcohol and 9.0 g (51.0 mmol) of freshly recrystallized *N*-bromosuccinimide dissolved in 100 mL of $CHCl_3$ was refluxed for 3 h. The cooled solution was washed with four portions of water and dried. Filtration and removal of solvent left an oil which was crystallized from hexane to give 11.1 g (80%) of a white powder. Recrystallization from hexane afforded an analytical sample: mp 54.5–55.5 °C; IR ($CHCl_3$) 3450 and 2950 cm^{-1}; NMR ($CDCl_3$) δ 6.92 (1 H, s), 4.69 (2 H, s), 3.90 (3 H, s), 3.88 (3 H, s), and 3.84 (3 H, s). Anal. Calcd for $C_{10}H_{13}BrO_4$: C, 43.34; H, 4.73; Br, 28.83. Found: C, 43.30; H, 4.76; Br, 28.74.

2-Bromo-3,4,5-trimethoxylbenzaldehyde was prepared in 85% yield

as described (vide supra) for the iodo analogue, mp 69–71 °C (lit.[36] 70.5–71.5 °C).

Preparation of Cyclohexylimines. The halo imines were prepared from the aldehydes as previously described.[17]

6-Bromoveratraldehyde cyclohexylimine (2e) was prepared from 6-bromoveratraldehyde[37] in 79% yield: mp 170–170.5 °C (hexane); NMR ($CDCl_3$) δ 8.54 (1 H, s), 7.55 (1 H, s), 6.97 (1 H, s), 3.92 (3 H, s), 3.89 (3 H, s), 3.30 (1 H, m), and 1.82–1.07 (10 H, m). Anal. Calcd for $C_{15}H_{20}BrNO_2$: C, 55.22; H, 6.18; Br, 24.50; N, 4.29. Found: C, 55.04; H, 6.24; Br, 24.37; N, 4.26.

6-Iodoveratraldehyde cyclohexylimine (2f) was prepared from **2e** in 54% yield:[17] mp 178.5–179 °C; NMR ($CDCl_3$) δ 8.32 (1 H, s), 7.53 (1 H, s), 7.22 (1 H, s), 3.92 (3 H, s), 3.88 (3 H, s), 3.31 (1 H, m), and 1.82–1.07 (10 H, m). Anal. Calcd for $C_{15}H_{20}INO_2$: C, 48.27; H, 5.40; I, 34.00; N, 3.75. Found: C, 48.10; H, 5.49; I, 33.84; N, 3.71.

2-Bromo-3,4,5-trimethoxybenzaldehyde Cyclohexylimine (3a): 88% yield; mp 82.5–83.5 °C (hexane); NMR ($CDCl_3$) δ 8.63 (1 H, s), 7.41 (1 H, s), 3.90 (9 H, s), 3.30 (1 H, m), and 1.90–1.10 (10 H, m). Anal. Calcd for $C_{16}H_{22}BrNO_3$: C, 53.93; H, 6.22; N, 3.93; Br, 22.43. Found: C, 53.76; H, 6.27; N, 3.96; Br, 22.54.

2-Iodo-3,4,5-trimethoxybenzaldehyde Cyclohexylimine (3b): 68% yield; mp 72–73 °C (ether–hexane); NMR ($CDCl_3$) δ 8.48 (1 H, s), 7.42 (1 H, s), 3.92 (3 H, s), 3.87 (6 H, s), 3.31 (1 H, m), and 1.95–1.30 (10 H, m). Anal. Calcd for $C_{16}H_{22}INO_3$: C, 47.65; H, 5.50; I, 31.47; N, 3.47. Found: C, 47.74; H, 5.52; I, 31.33; N, 3.42.

2-[1′-(2′-Bromo-4′,5′-methylenedioxyphenyl)]-5,5-dimethyloxazoline was prepared by the method of Meyers[20] from 6-bromopiperonylic acid[38] in 45% yield: mp 58–60 °C (ether–hexane); IR ($CHCl_3$) 1655 cm^{-1}; NMR ($CDCl_3$) δ 7.12 (1 H, s), 7.04 (1 H, s), 5.99 (2 H, s), 4.09 (2 H, s), and 1.38 (6 H, s). Anal. Calcd for $C_{12}H_{12}BrNO_3$: C, 48.34; H, 4.06; Br, 26.80; N, 4.70. Found: C, 48.57; H, 4.10; Br, 26.65; N, 4.64.

2-Iodo-4,5-methylenedioxyacetophenone *O*-Methyl Oxime (9c). A solution of 11.4 g (39.2 mmol) of 2-iodo-4,5-methylenedioxyacetophenone[10a] and 4.9 g (58.8 mmol) of methoxylamine hydrochloride in 50 mL of pyridine was stirred at 25 °C for 18 h. The solvent was removed in vacuo and the residue dissolved in ether, washed with water, dried, and concentrated to give 12.66 g of oil. NMR analysis indicated two methyl oximes in a ratio of 3.5/1. Crystallization from ether–hexane provided 4.11 g (33%) of a 9:1 mixture (anti/syn). A second crop, 4.93 g (39%), was fractional crystallized from ether–hexane to separate the two isomers. Anti *O*-methyl oxime: mp 96–97 °C; NMR ($CDCl_3$) δ 7.25 (1 H, s), 6.54 (1 H, s), 5.97 (2 H, s), 3.83 (3 H, s, OCH_3), and 2.12 (3 H, s). Anal. Calcd for $C_{10}H_{10}INO_3$: C, 37.64; H, 3.16; I, 39.77; N, 4.39. Found: C, 37.78; H, 3.19; I, 39.58; N, 4.39. Syn *O*-methyl oxime: mp 58–61 °C; NMR ($CDCl_3$) δ 7.25 (1 H, s), 6.75 (1 H, s), 5.97 (2 H, s), 3.97 (3 H, s), and 2.14 (3 H, s).

3,4-Methylenedioxy-6-bromoacetophenone.[35] To a solution of 12.25 g (50.0 mmol) of α-methyl-6-bromopiperonyl alcohol[10a] in 100 mL of reagent grade acetone at 5 °C was added 12.5 mL of Jones reagent.[39] After the mixture was stirred for 0.5 h, 14 mL of 2-propanol was added and the reaction mixture was warmed to 25 °C. Water was added and the acetone removed in vacuo. The aqueous residue was extracted thoroughly with ether, and the combined ether extracts were washed with saturated aqueous $NaHCO_3$ and water, dried, and concentrated. Two crystallizations of the residue from ether–petroleum ether afforded 64% of the ketone as white needles: mp 64.5–65 °C; NMR ($CDCl_3$) δ 7.02 (2 H, s), 6.03 (2 H, s), and 2.60 (3 H, s); IR ($CHCl_3$) 1690 cm^{-1}. Anal. Calcd for $C_9H_7O_3Br$: C, 44.48; H, 2.90; Br, 32.87. Found: C, 44.26; H, 2.91; Br, 33.00.

2-[1′-(2′-Bromo-4′,5′-methylenedioxyphenyl)]-2-methyl-1,3-dithiane (11a). A solution of 60.3 g (0.25 mol) of 2-bromo-4,5-methylenedioxyacetophenone and 32 mL (0.32 mol) of 1,3-propanedithiol in 200 mL of $CHCl_3$ was cooled in an ice bath and treated with a slow stream of HCl gas for 40 min. After standing for 48 h at 25 °C, the solution was washed with 1 N NaOH and twice with water, dried, and concentrated to afford 89.2 g of crude, yellow liquid. Crystallization from ether–hexane gave 57.6 g (70%) of **11a** as white prisms: mp 102–102.5 °C; NMR ($CDCl_3$) δ 7.82 (1 H, s), 7.11 (1 H, s), 6.00 (2 H, s), 2.85–2,70 (4 H, m), 2.03 (3 H, s), and 2.03 (2 H, m). Anal. Calcd for $C_{12}H_{13}BrO_2S_2$: C, 43.24; H, 3.93; Br, 23.98; S, 19.24. Found: C, 43.19; H, 3.95; Br, 24.10; S, 19.22.

2-Bromo-3,4,5-trimethoxyacetophenone. A solution of 4.23 g (15.4 mmol) of 2-bromo-3,4,5-trimethoxybenzaldehyde in ether was added dropwise to 100 mL of 0.23 M ethereal methylmagnesium bromide. After 1 h of stirring, the reaction mixture was poured onto ice and aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted with ether. The combined organic extracts were washed with water and brine, dried, and concentrated to afford 4.46 g of crude alcohol: NMR ($CDCl_3$) δ 6.99 (1 H, s, aryl), 5.18 (1 H, q, J = 6 Hz), 3.85 (9 H, s), 2.75 (1 H, br, s), and 1.41 (3 H, d, J = 6 Hz).

The crude alcohol dissolved in a minimum amount of CH_2Cl_2 was added rapidly to a suspension of pyridinium chlorochromate (1.5 equiv) in 15 mL of CH_2Cl_2 and allowed to stir for 18 h. The reaction mixture was diluted with 150 mL of ether and filtered through Celite. The residual gum was digested with three portions of boiling ether and the combined organic extracts were washed with 15% aqueous KOH, aqueous NH_4Cl, and brine. The extracts were dried, concentrated, and crystallized from ether–hexane to yield 3.42 g (77%) of the ketone: mp 34.5–35 °C; NMR ($CDCl_3$) δ 6.82 (1 H, s), 3.92, 3.90, 3.86 (3 × 3 H, s), and 2.64 (3 H, s). Anal. Calcd for $C_{11}H_{13}BrO_4$: C, 45.69; H, 4.53; Br, 27.64. Found: C, 45.61; H, 4.54; Br, 27.67.

2-[1′-(2′-Bromo-3′,4′,5′-trimethoxyphenyl)]-2-methyl-1,3-dithiane (12b). A solution of 10.0 g (34.6 mmol) of 2-bromo-3,4,5-trimethoxyacetophenone and 7 mL (69.7 mmol) of 1,3-propanedithiol in 60 mL of $CHCl_3$ was cooled in an ice bath as a stream of dry HCl gas was passed through the solution for 10 min. After 1 h the solution was washed with 1 N NaOH, aqueous NH_4Cl, and brine. The organic solution was dried and concentrated to 15.0 g of oil which was chromatographed on 75 g of silica gel. Elution with 25% benzene–hexane removed polymeric material and excess dithiol. Elution with 5% ether–benzene provided 12.5 g (96%) of liquid dithiane which was unstable toward distillation: NMR ($CDCl_3$) δ 7.78 (1 H, s), 3.91 (6 H, s), 3.87 (3 H, s), 2.80 (4 H, m), 2.00 (2 H, m), and 2.06 (3 H, s). Anal. Calcd for $C_{14}H_{19}BrO_3S_2$: C, 44.32; H, 5.05; Br, 21.07; S, 16.91. Found: C, 44.50; H, 5.08; Br, 21.19; S, 16.69.

General Coupling Procedure. To a solution of 1 mmol of aromatic halide dissolved in 5 mL of dry THF maintained under a nitrogen atmosphere at −78 °C was added via syringe (through a serum cap) 1.1 mmol (0.53 mL, 2.1 M in hexane) of *n*-BuLi, forming a pale yellow to orange organolithium reagent. After the mixture was stirred for 15 min, 536 mg (1.5 mmol) of $CuI{\cdot}(EtO)_3P$[40] was added in one portion and stirred for 15 min. The resulting clear orange to red solution[41] was treated with 1 mmol of iodide in one portion and allowed to warm to 25 °C. After 4–5 h in the case of imine couplings (18 h for all others), the reaction was complete. The reaction mixture was diluted with CH_2Cl_2 and washed with 10% aqueous NaCN solution to remove cuprous salts (or less efficiently with aqueous ammonia until the washings were no longer blue). The organic solution was dried and concentrated to provide the crude coupled products. Imines were hydrolyzed by stirring for 2 days with 10% aqueous HCl/CH_2Cl_2.[42] The organic layer was washed with aqueous $NaHCO_3$ solution, dried, and filtered to provide the crude aldehydes.

5,6:5′,6′-Bis(methylenedioxy)-1,1′-biphenyl-2,2′-dicarboxaldehyde (5a): 44%; mp 186–187 °C (CH_3OH); NMR ($CDCl_3$) δ 9.75 (1 H, s), 7.64 (1 H, d, J = 8 Hz), 7.00 (1 H, d, J = 8 Hz), and 6.05 (2 H, s). Anal. Calcd for $C_{16}H_{10}O_6$: C, 64.43; H, 3.38. Found: C, 64.17; H, 3.44.

4,5:4′,5′-Bis(methylenedioxy)-1,1′-biphenyl-2,2′-dicarboxaldehyde (5b): 57%; mp 244–247 °C (CH_3OH, uncorrected) (lit.[43] 238–240 °C (benzene–acetone)); NMR ($CDCl_3$) δ 9.61 (1 H, s), 7.48 (1 H, s), 6.77 (1 H, s), and 6.15 (2 H, s). Anal. Calcd for $C_{16}H_{10}O_6$: C, 64.43; H, 3.38. Found: C, 64.38; H, 3.39.

4,5:5′,6′-Bis(methylenedioxy)-1,1′-biphenyl-2,2′-dicarboxaldehyde (5c): Table I, entry 4, 58%; mp 144–147 °C (CH_3OH); NMR ($CDCl_3$) δ 9.67 (1 H, s), 9.73 (1 H, s), 7.50 (1 H, s), 6.78 (1 H, s), 7.65 (1 H, d, J = 8 Hz), 7.00 (1 H, d, J = 8 Hz), 6.05 (2 H, s), and 6.12 (2 H, s). Anal. Calcd for $C_{16}H_{10}O_6$: C, 64.43; H, 3.38. Found: C, 64.27; H, 3.47.

4,5,4′,5′-Tetramethoxy-1,1′-biphenyl-2,2′-dicarboxaldehyde (5d): 62%; mp 213–215 °C (CH_3OH, lit.[44] 215 °C); NMR ($CDCl_3$) δ 9.67 (1 H, s), 7.56 (1 H, s), 6.80 (1 H, s), 4.01 (6 H, s), and 3.96 (6 H, s).

4,5-Methylenedioxy-4′,5′,6′-trimethoxy-1,1′-biphenyl-2,2′-dicarboxaldehyde (4e): 63%; mp 138–140 °C (CH_3OH); NMR ($CDCl_3$) δ 9.64 (1 H, s), 9.58 (1 H, s), 7.50, 7.38, 6.73 (3 × 1 H, s), 6.14 (2 H, s), 3.99, 3.98, and 3.63 (3 × 3 H, s). Anal. Calcd for $C_{18}H_{16}O_7$: C, 62.79; H, 4.68. Found: C, 62.92; H, 4.73.

4,4′,5,5′,6,6′-Hexamethoxy-1,1′-biphenyl-2,2′-carboxaldehyde (5f). The crude hydrolysate was chromatographed on silica gel. Elution with ether–hexane provided a tan solid which was recrystallized from

CH_3OH to afford **5f** in 49% yield: mp 126–127.5 °C (lit.[45] 128 °C); NMR ($CDCl_3$) δ 9.61 (1 H, s), 7.52 (1 H, s), 4.00 (4 × 3 H, s), and 3.63 (2 × 3 H, s).

2-[2″-(5″,5″-Dimethyloxazolinyl)]-4,5:4′,5′-bis(methylenedioxy)-1,1′-biphenyl-2′-carboxaldehyde Cyclohexylimine (6). The crude imine was recrystallized from ether–hexane in 54% yield: mp 157.5–160.5 °C; NMR ($CDCl_3$) δ 7.91 (1 H, s), 7.55, 7.26, 6.68, 6.66 (4 × 1 H, s), 6.05, 5.98 (2 × 2 H, br s), 3.70 (2 H, br s), 1.84–1.07 (10 H, m), 1.19 and 1.16 (2 × 3 H, s). Anal. Calcd for $C_{26}H_{28}N_2O_5$: C, 69.62; H, 6.29; N, 6.25. Found: C, 69.50; H, 6.38; N, 6.20.

2-Dimethylaminomethylene-5,6-methylenedioxy-3′,4′,5′-trimethoxy-1,1′-biphenyl-2′-carboxaldehyde Cyclohexylimine (8). The crude residue prior to hydrolysis was crystallized from benzene–hexane to give white prisms of **8** in 48%: mp 137–138.5 °C; NMR ($CDCl_3$) δ 7.86 (1 H, s), 7.49 (1 H, s), 6.99 (1 H, d, J = 8 Hz), 6.80 (1 H, s, J = 8 Hz), 5.89 (2 H, s), 3.98, 3.91, 3.65 (3 × 3 H, s), 3.04 (2 H, s), 2.04 (6 H, s), 3.30 (1 H, m), and 1.70–1.10 (10 H, m). Anal. Calcd for $C_{26}H_{34}N_2O_5$: C, 68.70; H, 7.54; N, 6.16. Found: C, 68.64; H, 7.59; N, 6.17.

2-Acetyl-4,5-methylenedioxy-4′,5′,6′-trimethoxy-1,1′-biphenyl-2-carboxaldehyde *anti*-*O*-Methyl Oxime (10). The hydrolysate was purified by preparative TLC (60% ether–hexane) and the eluant recrystallized from ether–hexane: 90%, mp 100–101 °C; NMR ($CDCl_3$) δ 9.56 (1 H, s), 7.30, 6.92, 6.75 (3 × 1 H, s), 6.04 (2 H, s), 3.95 (6 H, s), 3.72 (3 H, s), 3.67 (3 H, s), and 1.73 (3 H, s). Anal. Calcd for $C_{20}H_{21}NO_7$: C, 62.01; H, 5.46; N, 3.63. Found: C, 61.95; H, 5.48; N, 3.61.

2-[2″-(2″-Methyl-1″,3″-dithianyl)]-4,5-methylenedioxy-4′,5′,6′-trimethoxy-1,1′-biphenyl-2′-carboxaldehyde (13). The reaction time was 48 h. The crude hydrolysate was chromatographed on acid-washed alumina with benzene. The concentrated, crystalline fractions were combined and recrystallized from $CHCl_3$–ether in 65% yield: mp 178–180 °C; NMR ($CDCl_3$) δ 9.56 (1 H, s), 7.93, 7.28, 6.53 (3 × 1 H, s), 6.05 (2 H, s), 3.96, 3.94, 3.73 (3 × 3 H, s), 2.89–2.50 (4 H, m), 2.00–1.80 (2 H, m), and 1.69 (3 H, s). Anal. Calcd for $C_{22}H_{24}O_6S_2$: C, 58.91; H, 5.39; S, 14.30. Found: C, 59.03; H, 5.37; S, 14.23.

2-[2″-(2″-Methyl-1″,3″-dithianyl)]-4′,5′-methylenedioxy-4,5,6-trimethoxy-1,1′-biphenyl-2′-carboxaldehyde (14). The hydrolysate was chromatographed (medium-pressure chromatography, 15% THF–hexane, 2 mL/min) to provide the biphenyl in 63% yield: mp 132.5–133.5 °C; NMR δ 9.57 (1 H, s), 7.84, 7.42, 6.72 (3 × 1 H, s), 6.09 (2 H, s), 3.96, 3.89, 3.55 (3 × 3 H, s), 2.90–2.50 (4 H, m), 2.00–1.80 (2 H, m), and 1.72 (3 H, s). Anal. Calcd for $C_{22}H_{24}O_6S_2$: C, 58.91; H, 5.39; S, 14.30. Found: 58.83; H, 5.40; S, 14.23.

Methyl 2-Formyl-4,5-methylenedioxy-4′,5′,6′-trimethoxy-1,1′-biphenyl-2′-carboxylate (16). The coupling was run for 4 days at 25 °C. Hydrolysis was accomplished in CH_2Cl_2–10% aqueous HCl at 25 °C for 14 h. Chromatography on silica gel removed monomers followed by dimer **5b** (4%, 2–30% ether–hexane), dimer **16** (34%, 35% ether–hexane) [mp 134.5–135.5 °C (CH_3OH); NMR ($CDCl_3$) δ 9.55 (1 H, s), 7.45, 7.35, and 6.62 (3 × 1 H, s), 6.08 (2 H, s), 3.95 (6 H, s), 3.62 (3 H, s), and 3.59 (3 H, s). Anal. Calcd for $C_{19}H_{18}O_8$: C, 60.96; H, 4.85. Found: C, 61.18; H, 4.88], and dimer **17** (15% ether–hexane) [NMR ($CDCl_3$) δ 7.37 (2 H, s), 3.94 (12 H, s), and 3.61 (12 H, s) (lit.[46] ($CDCl_3$) 7.33 (2 H, s), 3.92 (12 H, s), and 3.59 (12 H, s)].

2-[1′-(2′-Bromo-4′,5′-methylenedioxyphenyl)]-2-methyl-1,3-oxathiolane (25a). To an ethereal solution of methylmagnesium bromide (prepared from 18.1 mL (0.33 mol) of methyl bromide and 5.28 g (0.22 mol) of magnesium turnings in 700 mL of ether) was added dropwise a warm solution of 40.0 g (0.17 mol) of 6-bromopiperonal in 200 mL of THF at such a rate that vigorous refluxing occurred. After stirring at 25 °C for 18 h, the reaction mixture was decomposed with saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted thoroughly with ether. The combined organic fractions were washed with saturated brine and dried. After filtration and evaporation, 41.0 g of crude alcohol was obtained as an oil: NMR ($CDCl_3$) δ 7.01 (1 H, s), 6.90 (1 H, s), 5.95 (2 H, s), 5.18 (1 H, q, J = 7 Hz), 2.8 (1 H, br s), and 1.4 (3 H, d, J = 7 Hz).

A solution of the crude alcohol in 90 mL of CH_2Cl_2 was added over 15 min to a stirred suspension of 73.3 g (0.34 mol) of pyridinium chlorochromate[47] and 14.0 g (0.34 mol) of sodium acetate in 90 mL of CH_2Cl_2. After the addition was complete, the mixture was stirred at 25 °C for 24 h. The reaction mixture was diluted with 500 mL of ether, and the ether layer decanted. The residual solids were triturated with ether (2 × 250 mL). The combined organic fractions were washed with 5% NaOH solution, water, 5% HCl solution, and finally saturated brine. The ether solution was dried, filtered, and concentrated to give 32.2 g of crude 6-bromo-3,4-methylenedioxyacetophenone: NMR ($CDCl_3$) δ 7.01 (2 H, s), 6.01 (2 H, s), and 2.59 (3 H, s).

The crude ketone was dissolved in 200 mL of benzene containing 32.0 g (0.43 mol) of β-mercaptoethanol and 2.5 g (0.013 mol) of *p*-$TsOH \cdot H_2O$ and refluxed for 3 h (Dean-Stark trap to remove water). The cooled solution was washed with 5% NaOH solution and brine, dried, filtered, and concentrated to give an oil which crystallized from ether to provide 25.7 g (50% yield) of **25a:** mp 105–106 °C; NMR ($CDCl_3$) δ 7.15 (1 H, s), 7.00 (1 H, s), 5.93 (2 H, s), 2.85 (4 H, m), and 1.98 (3 H, s). Anal. Calcd for $C_{11}H_{11}BrOS$: C, 43.57; H, 3.66; Br, 26.35; S, 10.57. Found: C, 43.57; H, 3.68; Br, 26.38; S, 10.56.

2-[2″-Methyl-1″,3″-oxathiolane)]-4,5-methylenedioxy-4′,5′,6′-trimethoxy-1,1′-biphenyl-2′-carboxaldehyde (26b). To a solution of 3.0 g (0.01 mol) of bromooxathiolane **25a** in 20 mL of dry THF maintained under N_2 at −78 °C was added (via syringe-septum technique) 4.48 mL (0.011 mol) of 2.45 M *n*-BuLi over a period of 10 min followed by stirring for an additional 20 min. To the solution of **25b** was added 5.16 g (0.014 mol) of cuprous iodide–triethyl phosphate complex[40] in one portion and stirring was continued for an additional 20 min. To the organocopper reagent **25c** was added 3.9 g (0.01 mol) of solid imine **3b** followed by gradual warming (removal of CO_2–acetone bath) to 25 °C and continued stirring for an additional 20 h. The reaction mixture was diluted with 100 mL of CH_2Cl_2 and washed with 10% NH_4OH solution, 10% NaCN solution, and brine. The organic solution of crude imine **26a** was stirred with 75 mL of 15% aqueous acetic acid for 12 h. The layers were separated and the organic layer was extracted with 100 mL of CH_2Cl_2. The combined organic fractions were washed with saturated $NaHCO_3$ solution and saturated brine, dried, filtered, and concentrated to give a yellow solid which was recrystallized (ether–CH_2Cl_2) to yield 3.38 g (82%) of biphenyl **26b:** mp 126–127 °C; NMR ($CDCl_3$) δ 9.50, 9.45 (1 H, s, 3/1 ratio), 7.31, 7.22 (1 H, s, 1/3 ratio), 7.25, 7.15 (1 H, s, 1/3 ratio), 6.52 (1 H, s), 5.98 (2 H, s), 3.93 (6 H, s), 3.68 (3 H, s), 2.85 (4 H, m), and 1.78, 1.70 (3 H, s, 3/1 ratio); IR ($CHCl_3$) 1680 cm^{-1}. Anal. Calcd for $C_{21}H_{22}O_7S$: C, 60.27; H, 5.30; S, 7.66. Found: C, 60.19; H, 5.35; S, 7.61.

Dimethyl 2-[2″-Methyl-1″,3″-oxathiolane)]-4,5-methylenedioxy-4′,5′,6′-trimethoxy-1,1′-biphenyl-2′-β-methylenemalonate (26c). A solution of 6.30 g (0.015 mol) of aldehyde **26b,** 10 mL (0.087 mol) of dimethyl malonate, and piperidine (0.4 mL) in 75 mL of benzene was refluxed with a Dean-Stark trap at 125–130 °C (bath temp) for 10 h. Excess benzene, piperidine, and dimethyl malonate were removed in vacuo to leave an oil which crystallized upon trituration with ether. The solid was recrystallized (ether–CH_2Cl_2) to afford 6.23 g (78%) of Knoevenagel product: mp 123–124 °C; NMR ($CDCl_3$) δ 7.42, 7.18, 6.82, 6.40 (4 × 1 H, s), 5.97 (2 H, s), 3.90, 3.70, 3.62 (3 × 3 H, s), 3.82 (6 H, s), 2.70, 3.10 (4 H, m), and 1.76 (3 H, s); IR ($CHCl_3$) 1716 cm^{-1}. Anal. Calcd for $C_{26}H_{28}O_{10}S$: C, 58.63; H, 5.29; S, 6.02. Found: C, 58.47; H, 5.34; S, 6.01.

Dimethyl (2-Acetyl-4,5-methylenedioxy-4′,5′,6′-trimethoxy-1,1′-biphenyl-2′-β-methylenemalonate (26d). A solution of 5.80 g (0.011 mol) of oxathiolane **26c** and 66.5 g (0.47 mol) of methyl iodide in 95 mL of 90% aqueous acetone was refluxed for 12 h. The solvent was removed in vacuo, and the residue was dissolved in 100 mL of CH_2Cl_2, washed with saturated Na_2SO_3 solution and brine, dried, filtered, and evaporated to give an oil which solidified upon cooling. Recrystallization (ether–CH_2Cl_2) gave 4.69 g (91%) of **26d** as white crystals: mp 120–122 °C; NMR ($CDCl_3$) δ 7.32, 7.25, 6.72, 6.58 (4 × 1 H, s), 6.04 (2 H, s), 3.88, 3.82, 3.76, 3.72, 3.57, and 2.12 (6 × 3 H, s); IR ($CHCl_3$) 1730 and 1682 cm^{-1}. Anal. Calcd for $C_{24}H_{24}O_{10}$: C, 61.01; H, 5.12. Found: C, 60.98; H, 5.12.

Dimethyl 2-[1′-(2′-Acetyl-4′,5′-methylenedioxyphenyl)]-3,4,5-trimethoxybenzylmalonate (27a). A solution of 4.48 g (9.4 mmol) of malonylidene ester **26d** in 200 mL of ethanol was hydrogenated at atmospheric pressure in the presence of 3 mL of Ni(R) W-2 (ethanol slurry). Filtration over Celite and evaporation of the solvent gave a solid which was recrystallized from ethanol–ether to give 4.28 g (95%) of **27a:** mp 97–98 °C; NMR ($CDCl_3$) δ 7.30, 6.00, 6.57 (3 × 1 H, s), 6.03 (2 H, s), 3.86 (6 H, s), 3.66 (3 H, s), 3.64 (6, H, s), 3.36 (1 H, t, J = 8 Hz), 2.92 (2 H, d, J = 8 Hz), and 2.12 (3 H, s); IR ($CHCl_3$) 1732 and 1680 cm^{-1}. Anal. Calcd for $C_{24}H_{26}O_{10}$: C, 60.75; H, 5.52. Found: C, 60.70; H, 5.59.

Dimethyl 2-[1′-(2′-Bromoacetyl-4′,5′-methylenedioxyphenyl)]-3,4,5-trimethoxybenzylmalonate (27b). To a 25 °C solution of 4.0 g

(8.4 mmol) of ketone **27a** in 50 mL of CH_2Cl_2 containing 0.3 mL of trifluoroacetic acid was added 3.0 g (9.2 mmol) of pyridinium hydrobromide perbromide in small portions over 2 h. After stirring for an additional 1.5 h, the solution was washed with aqueous $NaHCO_3$ solution, 10% aqueous HCl, and brine, dried, filtered, and concentrated. The residual oil was crystallized from ether-CH_2Cl_2 to give 3.9 g (85%) of bromo ketone **27b**: mp 123–124 °C; NMR ($CDCl_3$) δ 7.29, 6.63, 6.57 (3 × 1 H, s), 6.08 (2 H, s), 3.98 (1 H, d, J = 14 Hz), 4.15 (1 H, d, J = 14 Hz), 3.86 (6 H, s), 3.65, 3.63, 3.61 (3 × 3 H, s), 3.42 (1 H, m), and 2.95 (2 H, m). Anal. Calcd for $C_{24}H_{25}O_{10}Br$: C, 52.09; H, 4.45; Br, 14.44. Found: C, 51.96; H, 4.60; Br, 14.40.

Dimethyl 5,6,7,8-Tetrahydro-1,2,3-trimethoxy-10,11-methylenedioxy-8-oxodibenzo[a,c]cyclooctene-6,6-dicarboxylate (28). To a stirred solution of K-*t*-OBu (from 55 mg (1.4 mmol) of potassium) in 25 mL of dry *tert*-butyl alcohol at 25 °C was added dropwise a solution of 700 mg (1.26 mmol) of bromo ketone **27b** in 7 mL of dry THF over a period of 45 min. After the addition was complete, the mixture was stirred for an additional 45 min, acidified with HOAc, and concentrated in vacuo. The residue was dissolved in CH_2Cl_2, washed with aqueous $NaHCO_3$ solution and brine, and dried. Filtration and evaporation of the solution gave an oil which was chromatographed on neutral alumina using ether-hexane (15 → 85%). The crystalline fractions were combined and recrystallized from ether, providing 390 mg (73%) of diester **28**: mp 143–144 °C; NMR ($CDCl_3$, 270 MHz) δ 7.56, 6.64, 6.44 (3 × 1 H, s), 6.08, 6.05 (2 H, d, d, J = 2 Hz), 3.91, 2.85, 3.79, 3.74, 3.56 (5 × 3 H, s), 3.32, 3.20 (2 H, d, d, J = 14 Hz), 3.06 and 2.76 (2 H, d, d, J = 14 Hz); IR ($CHCl_3$) 1732 and 1660 cm^{-1}. Anal. Calcd for $C_{24}H_{24}O_{10}$: C, 61.01 H, 5.12. Found: C, 61.07; H, 5.18.

Methyl 5,6,7,8-Tetrahydro-1,2,3-trimethoxy-10,11-methylenedioxy-8-oxodibenzo[a,c]cyclooctene-6-carboxylate (29 and 30). To a solution of 5 mL of 2.7 M KOH and 5 mL of ethanol was added 300 mg (0.64 mmol) of diester **28** and the mixture was refluxed under N_2 for 10 h. The cooled solution was washed with ether and the aqueous layer acifidied with concentrated HCl. The aqueous suspension was extracted with ethyl acetate, and the organic extracts were washed with saturated brine, dried, and evaporated. The residual oil was crystallized from ethanol to afford 220 mg of diacid: mp 165–168 °C dec; NMR (Me_2SO) δ 7.36, 6.68, 6.60 (3 × 1 H, s), 6.16 (2 H, br, s), 3.83 (6 H, s), 3.5 (3 H, s), and 2.46–3.16 (4 H, m).

The neat diacid was heated under N_2 at 200 °C for 10 min. The residue was taken up in $CHCl_3$, washed with brine, dried, filtered, and evaporated. The residue was esterified with excess diazomethane in ether-CH_2Cl_2 to yield a mixture (~1:1, LC) of diastereomeric esters. Preparative layer chromatography (3:1 ethyl acetate-hexane) separated the two diastereomers. The less polar component was crystallized from methanol to provide 80 mg of **30b**: mp 133–134 °C (lit. 133–134,[5b] 131–133 °C[30]); NMR ($CDCl_3$, 270 MHz) δ 7.68, 6.67, 6.46 (3 × 1 H, s), 6.08 (1 H, s), 6.05 (1 H, s), 3.92, 3.85, 3.71, 3.57 (4 × 3 H, s), 3.17–2.56 (5 H, m). The more polar fraction was crystallized from $CHCl_3$-methanol to afford 80 mg of **29b**: mp 128–130 °C (lit.[5b] mp 127–129, 132–133.5 °C[30]); NMR ($CDCl_3$, 270 MHz) δ 7.54, 6.63, 6.54 (3 × 1 H, s), 6.07 (1 H, br s), 6.05 (1 H, br s), 3.91 (6 H, s), 3.70, 3.56 (2 × 3 H, s), and 2.86–2.44 (5 H, m).

Refluxing a xylene solution of either isomer for 1.5 h provided a 1:1 mixture of both isomers (LC).

(±)-Steganone (31a), (±)-Steganol (31d), (±)-Episteganol (31e), and (±)-Steganacin (31b). These substances were prepared as previously described from a mixture of the acids **29a** and **30a**. The mixture of steganone (**31a**) and episteganone (**32**) was converted to the former substance by refluxing the mixture in xylene solution.

(±)-Steganone: mp 224–225 °C (lit.[5b] mp 227–229, 229–230 °C[30]); NMR ($CDCl_3$, 270 MHz) δ 7.53, 6.63, 6.53 (3 × 1 H, s), 6.11 (1 H, d, J = 1.5 Hz), 6.10 (1 H, d, J = 1.5 Hz), 4.48 (1 H, t, J_{AX} = 10 Hz), 4.37 (1 H, d, d, J_{AB} = 10, J_{BX} = 6 Hz), 3.89, 3.88, 3.61 (3 × 3 H, s), and 3.29–3.07 (4 H, m); IR ($CHCl_3$) 1765 and 1665 cm^{-1}.

The 270-MHz NMR spectra of naturally occurring (−)-steganone and (±)-steganone were identical.

(±)-Steganol: mp 114–115 °C (as a methanol solvate) (lit.[5b] mp 112–114 °C); NMR ($CDCl_3$) δ 6.76, 6.56 6.44 (3 × 1 H, s), 6.00 (2 H, br s), 4.38–4.58 (2 H, m), 3.90 (1 H, m), 3.88, 3.85, 3.72 (3 × 3 H, s), 3.63 (3 H, s, CH_3OH), 2.90–3.20 (1 H, m), 1.90–2.70 (3 H, m), and 1.25 (2 H, br s, OH).

(±)-Episteganol: mp 215–216 °C (lit.[5b] mp 215–217 °C); NMR ($CDCl_3$) δ 7.08, 6.70, 6.50 (3 × 1 H, s), 6.04 (2, H, br s), 4.98 (1 H, m), 4.32, 4.07 (2 H, m), 3.88 (6 H, s), 3.62 (3 H, s), 2.18–3.34 (4 H, m), and 1.85 (1 H, s, OH).

(±)-Steganacin: mp 215–217 °C (lit.[5b] 214–217 °C); NMR ($CDCl_3$, 270 MHz) δ 6.90, 6.60, 6.44 (3 × 1 H, s), 6.03 (2 H, s), 5.82 (1 H, d, J = 9 Hz), 4.29 (1 H, d, d, J_{AX} = 7, J_{AB} = 10 Hz), 4.00 (1 H, t, J_{BX} = J_{AB} = 10 Hz), 3.91, 3.86, 3.72 (3 × 3 H, s), 3.90 (1 H, m), 3.11–2.96 (1 H, m), 2.81–2.37 (2 H, m), and 1.90 (3 H, s).

The 270-MHz NMR spectra of naturally occurring (−)-steganacin and (±)-steganacin were identical.

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References and Notes

(1) For preliminary accounts of this work see F. E. Ziegler, K. W. Fowler, and S. J. Kanfer, *J. Am. Chem. Soc.*, **98**, 8282 (1976); F. E. Ziegler, K. W. Fowler, and N. D. Sinha, *Tetrahedron Lett.*, 2767 (1978).
(2) National Institutes of Health Career Development Awardee, 1973–1978.
(3) Taken in part from the Ph.D. Thesis of K.W.F., Yale University, 1978.
(4) S. M. Kupchan, R. W. Britton, M. F. Ziegler, C. J. Gilmore, R. J. Restivo, and R. F. Bryan, *J. Am. Chem. Soc.*, **95**, 1335 (1973).
(5) Syntheses: (a) A. S. Kende and L. S. Liebeskind, *J. Am. Chem. Soc.*, **98**, 267 (1976); (b) D. Becker, L. R. Hughes, and R. A. Raphael, *J. Chem. Soc., Perkin Trans. 1*, 1674 (1977). Preliminary communication: L. R. Hughes and R. A. Raphael, *Tetrahedron Lett.* 1543 (1976). G. R. Krow, K. M. Damodaran, E. Michner, R. Wolf, and J. Guare, *J. Org. Chem.*, **43**, 3950 (1978); E. Brown, R. Dahl, and J. P. Robin, *Tetrahedron Lett.*, 733 (1979).
(6) Syntheses of steganes: R. E. Damon, R. H. Schlessinger, and J. F. Blout, *J. Org. Chem.*, **41**, 3776 (1976); E. Brown and J. P. Robin, *Tetrahedron Lett.*, 3613 (1978); K. Tomioka, H. Mizuguchi, and K. Koga, *ibid.*, 1409 (1979).
(7) Schizandrin: N. K. Kochetkov, A. Khorlin, O. S. Chizhov, and V. I. Scheichenko, *Tetrahedron Lett.*, 730 (1961); N. K. Kochetkov, A. Khorlin, and O. S. Chizhov, *J. Gen. Chem. USSR. (Engl. Transl.)*, **31**, 3218 (1961); E. Ghera and Y. Ben-David, *J. Chem. Soc., Chem. Commun.*, 480 (1978). Deoxyshizandrin: N. K. Kochetkov, A. Khorlin, and O. S. Chizhov, *Tetrahedron Lett.*, 361 (1962); *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, **963** (1964); E. Ghera, Y. Ben-David, and D. Becker, *Tetrahedron Lett.*, 463 (1977); T. Biftu, B. H. Hazra, and R. Stevenson, *J. Chem. Soc., Chem. Commun.*, 491 (1978). Kadsurin and kadsurarin: Y.-P. Chen, R. Liu, H.-Y. Hsu, and S. Yamamura, Y. Shizuri, and Y. Hirata, *Tetrahedron Lett.*, 4257 (1973); M. Mervic and E. Ghera, *J. Am. Chem. Soc.*, **99**, 7673 (1977). Gomisins: H. Taguchi and Y. Ikeda, *Chem. Pharm. Bull.*, **23**, 3296 (1975); *Tetrahedron Lett.*, 1359 (1976); *Chem. Pharm. Bull.*, **25**, 364 (1977); Y. Ikeya, H. Taguchi, and I. Yosioka, *ibid.*, **26**, 328 (1978); Y. Ikeya, H. Taguchi, I. Yosioka, and H. Kobayashi, *ibid.*, **26**, 3257 (1978).
(8) Fritz Ullmann, 1875–1939, first reported the formation of biphenyls from aryl halides in the presence of copper metal before the Chemical Society (Geneva), Nov 8, 1900. F. Ullmann and J. Bielecki, *Chem. Ber.*, **34**, 2174 (1901).
(9) Recent reviews: J. F. Normant, *Synthesis*, 63 (1972); M. Goshaev, O. S. Ostroshchenko, and A. S. Sadykok, *Russ. Chem. Rev. (Engl. Transl.)*, **41**, 1046 (1972); P. E. Fanta, *Synthesis*, 9 (1974); A. E. Jukes, *Adv. Organomet. Chem.*, **12**, 215 (1974).
(10) (a) F. E. Ziegler and J. A. Schwartz, *J. Org. Chem.*, **43**, 985 (1978); see also (b) M. F. Semmelhack and L. S. Ryono, *J. Am. Chem. Soc.*, **97**, 3873 (1975).
(11) At elevated temperatures cross coupling is usually more efficient when one of the aryl halides bears an electron-withdrawing group, because the copper reagent is formed more rapidly than from unactivated aryl halides. For an improved classical Ullmann coupling see E. Brown and J.-P. Robin, *Tetrahedron Lett.* 2015 (1978).
(12) F. N. Jones, M. F. Zinn, and C. R. Hauser, *J. Org. Chem.*, **28**, 663 (1963).
(13) (a) G. van Koten and J. G. Noltes, *J. Organomet. Chem.*, **104**, 127 (1976); (b) G. van Koten, J. T. B. H. Jastrzebski, and J. G. Noltes, *J. Chem. Soc., Chem. Commun.*, 203 (1977); *J. Org. Chem.*, **42**, 2047 (1977).
(14) A. C. Cope and R. N. Gourley, *J. Organomet. Chem.*, **8**, 527 (1967).
(15) A. C. Cope and E. C. Friedrich, *J. Am. Chem. Soc.*, **90**, 909 (1968).
(16) A. J. Leusink, G. van Koten, and J. G. Noltes, *J. Organomet. Chem.*, **56**, 379 (1973).
(17) All of the organolithium reagents in this study were prepared by metal–halogen exchange except for **1c**. F. E. Ziegler and K. W. Fowler, *J. Org. Chem.*, **41**, 1564 (1976).
(18) M. F. Semmelhack, P. M. Helquist, and L. D. Jones, *J. Am. Chem. Soc.*, **93**, 5908 (1971); A. S. Kende, L. S. Liebeskind, and D. M. Braitsch, *Tetrahedron Lett.*, 3375 (1975); M. Zembayashi, K. Tamao, J. Yoshida, and M. Kumada, *ibid.*, 4089 (1977).
(19) A. S. Kende and D. P. Curran, *J. Am. Chem. Soc.*, **101**, 1857 (1979).
(20) A. I. Meyers and D. L. Temple, Jr., *J. Am. Chem. Soc.*, **92**, 6646 (1970).
(21) A. C. Ranade, R. S. Mali, S. R. Bhide, and S. R. Mehta, *Synthesis*, 123 (1976).
(22) D. A. Evans and L. A. Domeier, *Org. Synth.*, **54**, 93 (1974).
(23) M. Fetizon and M. Jurion, *J. Chem. Soc., Chem. Commun.*, 382 (1972).
(24) M. Nilsson and O. Wennerström, *Tetrahedron Lett.*, 3307 (1968).
(25) A. H. Lewin and T. Cohen, *Tetrahedron Lett.*, 4531 (1965).
(26) T. Cohen and T. Poeth, *J. Am. Chem. Soc.*, **94**, 4363 (1972); A. H. Lewin, A. H. Dinwoodie, and T. Cohen, *Tetrahedron*, **22**, 1527 (1966).
(27) A. Cairncross and W. Sheppard, *J. Am. Chem. Soc.*, **93**, 247 (1971); J. van

Koten and J. G. Noltes, *J. Chem. Soc., Chem. Commun.*, 575 (1974); *J. Organomet. Chem.*, **84**, 419 (1975); G. van Koten, A. J. Leusink, and J. G. Noltes, *ibid.*, **84**, 117 (1975); G. van Koten and J. G. Noltes, *ibid.*, **84**, 129 (1975).
(28) T. Cohen and I. Cristea, *J. Am. Chem. Soc.*, **98**, 748 (1976); *J. Org. Chem.*, **40**, 3649 (1975).
(29) G. van Koten and J. G. Noltes, *J. Chem. Soc., Chem. Commun.*, 59 (1972).
(30) A. S. Kende, L. S. Liebeskind, C. Kubiak, and R. Eisenberg, *J. Am. Chem. Soc.*, **98**, 6389 (1976).
(31) We are indebted to Professor A. T. Sneden, Virginia Commonwealth University, for this sample.
(32) W. C. Kofron and L. M. Baclawski, *J. Org. Chem.*, **41**, 1879 (1976).
(33) J. Attenburrow, A. F. B. Cameron, J. G. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).
(34) M. Harfenist, A. Bavley, and W. A. Lazier, *J. Org. Chem.*, **19**, 1608 (1954).
(35) John Anthony Schwartz, Ph.D. Thesis, Yale University, 1977.
(36) C. D. Gutsche, E. F. Jason, R. S. Coffey, and H. E. Johnson, *J. Am. Chem. Soc.*, **80**, 5756 (1958).
(37) R. Pschorr, *Justus Liebigs Ann. Chem.*, **391**, 23 (1912).
(38) H. M. Fales, E. W. Warnhoff, and W. L. Wildman, *J. Am. Chem. Soc.*, **77**, 5885 (1955).
(39) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(40) Y. Nishizawa, *Bull. Chem. Soc. Jpn.*, **34**, 1170 (1961).
(41) Some of the copper reagents precipitate at this point. Homogeneity is achieved during warming of the reaction mixture.
(42) Hydrolysis with aqueous HOAc/CH_2Cl_2 has been found to be superior to mineral acid hydrolysis. See the Experimental Section, compound **26b**.
(43) T. Ikeda, W. I. Taylor, Y. Tsuda, S. Uyeo, and H. Yahima, *J. Chem. Soc.*, 4749 (1956).
(44) I. R. C. Bick, J. Harley-Mason, N. Sheppard, and M. J. Verengo, *J. Chem. Soc.*, 1896 (1961).
(45) M. Hanaoka, H. Sussa, C. Shimezawa, and Y. Arata, *Chem. Pharm. Bull.*, 1216 (1974).
(46) Y. Naya and M. Kotake, *Nippon Kagaku Zasshi*, **86**, 313 (1965).
(47) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).

Synthesis of Chartreusin Aglycone

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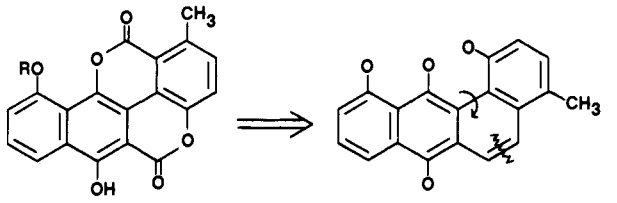
Abstract: A short regiospecific synthesis of chartreusin aglycone (**2**) is described. Diels–Alder addition of **4** and **5** under oxidizing conditions affords benzanthracenedione **6**. Reductive methylation of **6** gives **7** (90%), which is oxidatively cleaved to diacid **8** (54%). Treatment of **8** with HBr/HOAc provides **2** (64%).

The antibiotic chartreusin (**1**)[2] was first fully characterized by Schmid et al. in 1960.[3,4] Although the antibacterial properties of **1** failed to attract lasting attention, recent findings that chartreusin exhibits pronounced activity in a number of anticancer screens[5] led to a resurgence of interest in the pharmaceutical applications of this structurally unique molecule. To date no synthesis of either **1** or its aglycone **2** has appeared. We now report a short, regiospecific preparation of **2**.

The general strategy was based on the perception that **2** might be available by oxidative cleavage of an appropriately



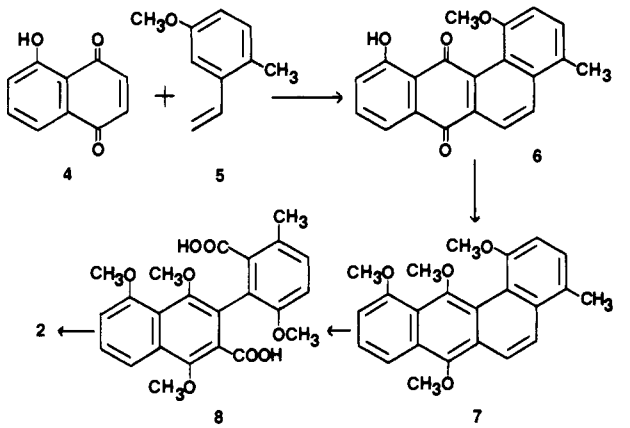
1, R= fucose–digitalose
2, R= H

3

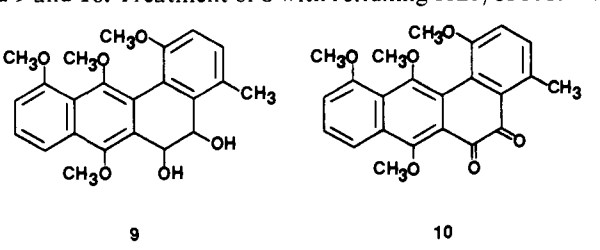
substituted benzanthracene as shown in **3**. The synthesis is outlined in Scheme I. Thus Diels–Alder reaction between 21 g of juglone (**4**) and 33 g of **5**[6] in refluxing toluene for 1 week under oxidizing conditions (chloranil plus O_2 atmosphere) following the procedure of Manning et al.[7,8] affords 14.5 g of **6** regiospecifically. There is no evidence to indicate that any of the alternative regioisomer is produced. The assignment of regiochemistry to **6** was initially based on the known regiochemical propensities of juglone[9] and styrenes[10] in their Diels–Alder reactions with unsymmetrical partners;[11] the eventual obtention of **2** affirms this assignment.

Reductive methylation of **6** ($Na_2S_2O_4$, K_2CO_3, and $(CH_3)_2SO_4$ in refluxing acetone) provides **7** (90%). Attempts to effect conversion of **7** to **8** in a single step (O_3, purple benzene, $IO_4^-/KMnO_4$) failed, but the more circumspect approach employing successive oxidations with OsO_4/$NaClO_3$,[12,13] CrO_3, and H_2O_2[14] gives **8** in 54% overall yield via **9** and **10**. Treatment of **8** with refluxing HBr/HOAc[3] for 16 h followed by workup in hot aqueous acid[3] affords **2** (64%), identical with an authentic sample.

Scheme I



4 5 6 7 8



9 10

Experimental Section

Melting points were determined in Pyrex capillaries and are uncorrected. NMR spectra were recorded on a Hitachi Perkin-Elmer Model R-24 spectrometer in $CDCl_3$; chemical shifts are reported in

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