AN ABSTRACT OF THE THESIS OF

Eugene P. Stirchak for the degree of Doctor of Philosophy

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Title: I. Applicability of the Diels-Alder Reactions of o-Quinones Towards the Synthesis of Quassinoids. II. Preparation of Oxygenated Benzeneacetic Acids.

Redacted for privacy

Abstract Approved: _____
Dr. Dwight D. Weller

The reactions of 3,5-disubstituted o-quinones (59a, 59c) and 4-chloro-3,5-disubstituted o-quinones (59b, 59d) with simple dienes were investigated as a potential route to the quassinoid skeleton. An efficient synthesis of the o-quinones involved bromination of the parent phenol followed by copper catalyzed displacement of the halogen by hydroxide. The chloroquinones showed some preference for Diels-Alder reaction at the 5,6 position, but the additions were characterized generally by low yields, side reactions, and lessened stereoselectivity. Quinones 59a and 59c reacted in high yield at the 3,4-position with only a small excess of diene. Attempted equilibration of the cis-fused cycloadducts to the trans-fused system failed due to the intervention of a stable enol form, as in 86. Compound 59c with ethyl 3,5-hexadienoate gave 90 which upon reduction and lactonization provided BCD-ring tricyclic quassinoid analogs 94 and 95. Again isomerization to the BC trans-fused system

was not possible. Determination of the relative stereochemistry of the adducts of o-quinone 59c by deuteration and NOE experiments is discussed.

II.

An extension of the halogenation-dehalohydroxylation sequence developed for catechol synthesis was used for the preparation of oxygenated benzeneacetic acids 1 and 5b. Selective mono-or dibromination of 4-methoxybenzeneacetic acid 14 was accomplished in high yield. Dehalohydroxylation of monobromo 15 occurred cleanly in excellent yield. Treatment of dibromo 16 with hydroxide in the presence of copper salts afforded a mixture of 1 and 5a, the former acid arising from the reductive elimination of the halogen from the intermediate monobromo, monohydroxyl 24. Esterification of the mixture of acids and chromatography afforded 25 in 40% overall yield from 16.

Applicability of the Diels-Alder Reactions of o-Quinones Towards the Synthesis of Quassinoids and Preparation of Oxygenated Benzeneacetic Acids

by

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Dean of Graduate School

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Typed by WORD PROCESSING SPECIALISTS for Eugene P. Stirchak

For Duffy

Who taught me chasing tennis balls for a living ain't so bad.

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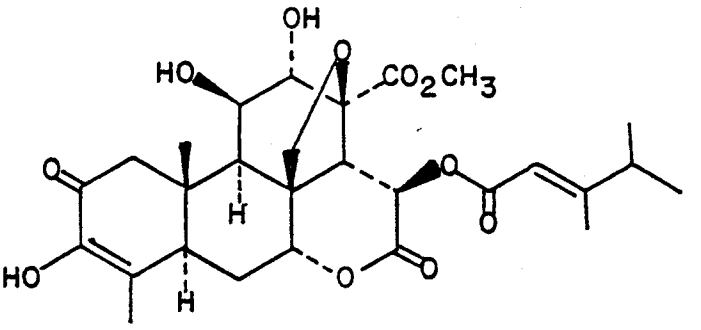
I. APPLICABILITY OF THE DIELS-ALDER REACTIONS OF o-QUINONES TOWARDS THE SYNTHESIS OF QUASSINOIDS

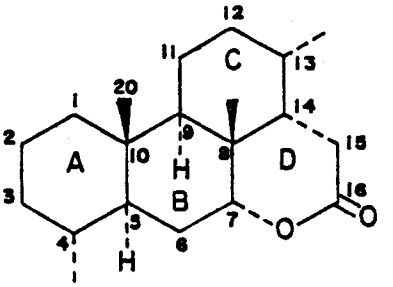
A. INTRODUCTION

The use of folk medicine [1,2] of the extracts of bark, roots and leaves of the plants and trees belonging to the Simaroubaceae family has led in modern times to the isolation and identification of a large number of related compounds known as quassinoids.[3] The of biological activity of this class of compounds includes antiviral[4], antimalarial[5] and antifeedant[6] properties but the greatest attention has been focused on their potent antineoplastic activity[1,4,7,8]. One quassinoid, bruceantin 1, [2], has shown activity against several tumor strains both *in vitro* and *in vivo*, including P 388 lymphocyctic leukemia, L 1210 lymphoid leukemia, an adriamycin resistant P 388 leukemia, a cytoxan resistant P 388 leukemia, the B 16 melanocarcinoma and the Lewis Lung carcinoma.[9] Encouragingly, bruceantin 1 has progressed to clinical trials at the National Cancer Institute[9]. All quassinoids share several common structural features, the most general being the twenty carbon picrasane skeleton 2 with the D ring δ lactone. These compounds are heavily oxygenated, with C_5, C_9 and the methyl substituents at C_4 and C_{10} being the only skeletal atoms at which no oxygen functionality has been found to date.

Certain structural features have been established as necessary for the quassinoid to possess biological activity. An α,β- unsatur-



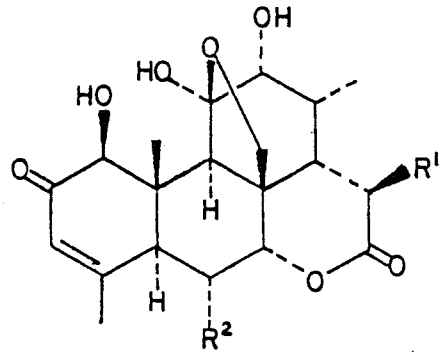
1 bruceantin



2 picrasane skeleton

ated ketone, such as in bruceantin (1) or glaucarubinone (3a), is required for the quassinoid to exhibit activity.[7,9] Reduction of the olefin or alkylation of the free hydroxyl results in greatly diminished activity. It was hypothesized that these cyclohexenone moieties are potent alkylating agents of free sulfhydryl or amino groups in enzymes[9]. A second necessary feature is an epoxymethano bridge, either as a hemiketal from C_8 to C_{11} (as in 3) or as an ether from C_8 to C_{13} (as in 1) . This bridge is thought to function in balancing the hydrophobic/hydrophilic nature of the molecule[8]. The presence of an acyloxy side chain, attached to either C_6 or C_{15} (as in 3b or 1, respectively), greatly increases the biological activity of the quassinoid relative to the nonacylated analog. The finding that the saturated acyloxy side chains are as active as their unsaturated analogs suggests this structural feature assists in transportation of the molecule through cell membranes rather than directly participating in chemical reactions.[7,9]

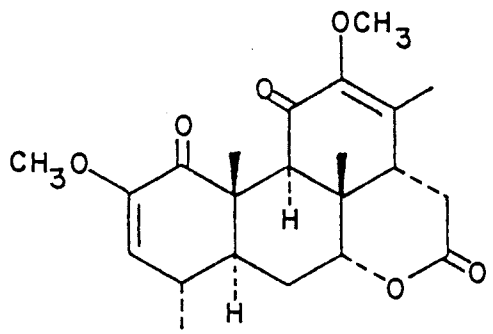
Spurred by the potent biological activity and the intriguingly complex structures, synthetic interest in this class of compounds has grown greatly since the structural elucidiation of quassin (4) in 1961[10,11]. To date, only quassin 4 [12] and castelanolide 5 [13] have been synthesized via total synthesis. Several others, including bruceantin (1) and castelanone (3c) have been prepared from less biologically active quassinoids. In general, the work thus far may be divided into two categories; first efforts toward the construction of



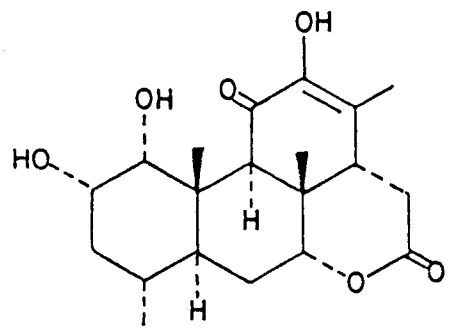
3a glaucarbinone $R^1 = O_2CC(OH)(CH_3)C_2H_5$, $R^2 = H$

3b 6α-senecioylchaparrinone $R^1 = H$, $R^2 = O_2CCH{=}C(CH_3)_2$

3c castelanone $R^1 = O_2CCH_2CH(CH_3)_2$, $R^2 = H$



4 quassin

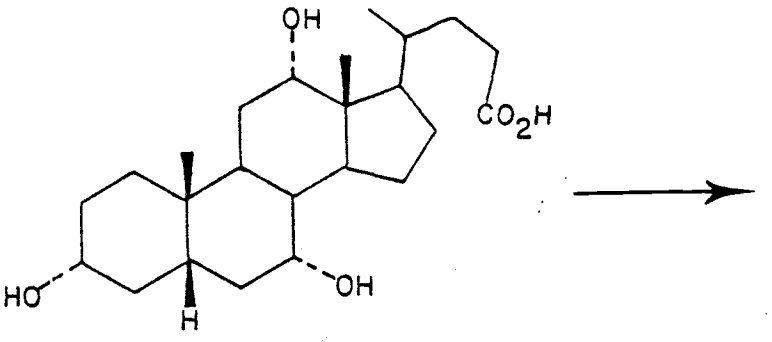


5 castelanolide

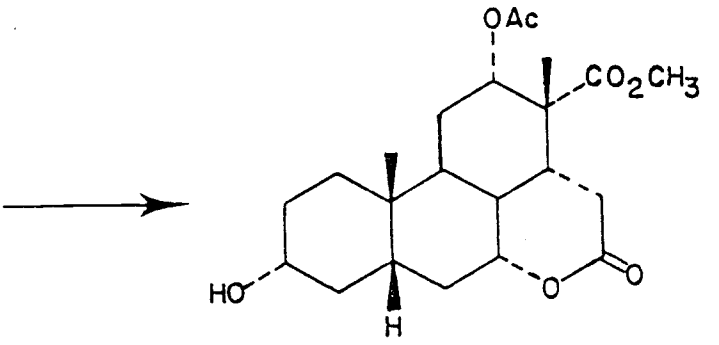
the picrasane carbon skeleton 2 , and second, research aimed at the incorporation of the complex functionality. The latter area has included studies of the functionalization of the A[14], C[16] and D[17-20] rings and the E ring epoxymethano bridge.[16] Although these studies will have contributed greatly towards the ultimate goal of synthesizing the complex quassinoids, the principal concern for most workers in this field has been the construction of the picrasane skeleton 2 , with establishment of the correct stereochemistry. This area is further divisible into the attempted conversion of readily available natural materials into picrasanes, and the attempted preparation by total synthesis.

Several groups have chosen steroids as precursors for the quassinoids. Dias investigated the conversion of cholic acid 6 into 7 by oxidative cleavage of the steroid D ring and lactonization (Scheme I).[17-19] Graf has performed more extensive studies on the transformations of testosterone 8 (Scheme II).[14,21,22] In all these attempts, a key step was the incorporation of the 8β-alkyl substituent of the picrasane (C_{20}). In earlier work, Graf found that alkylation of 9 occurred exclusively from the α face to give the wrong stereochemistry.[21] In a lengthy and tedious synthesis, he was able to convert 10 into 11 via a 2+2 photocycloaddition.[22] Several additional steps converted 11 into the quassin precursor 12.

Elaboration of one quassinoid into another has received a modest amount of attention. Lee has converted the readily available glyco-



6 cholic acid



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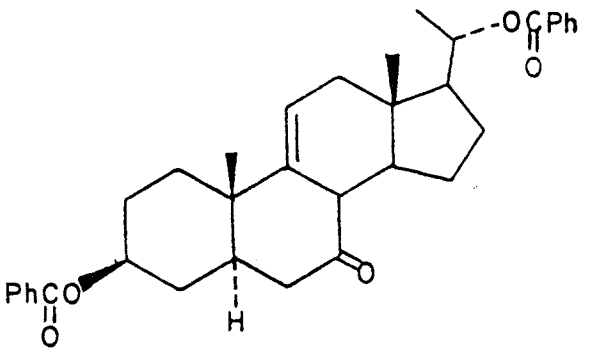
Scheme I



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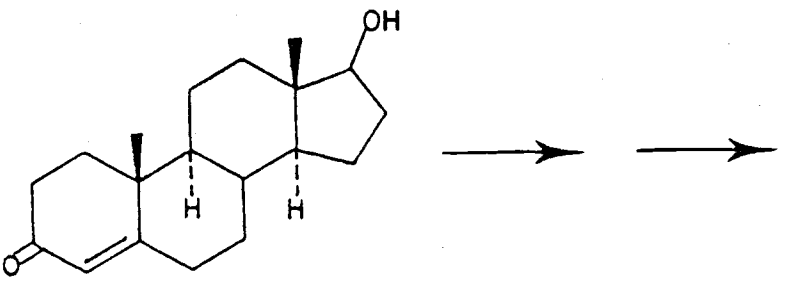
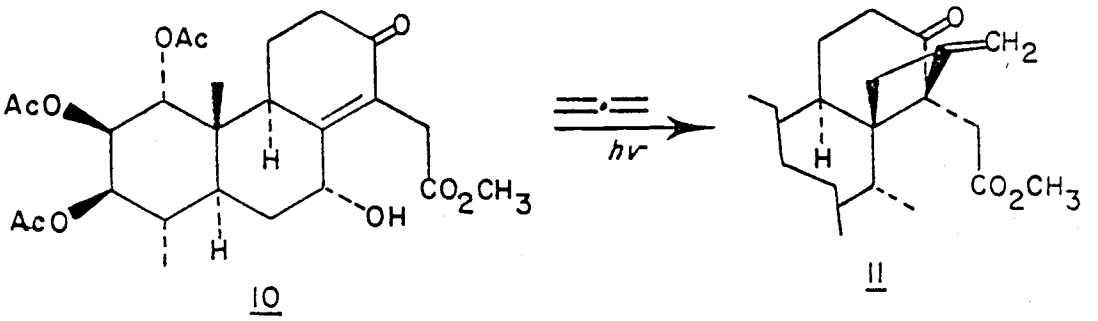
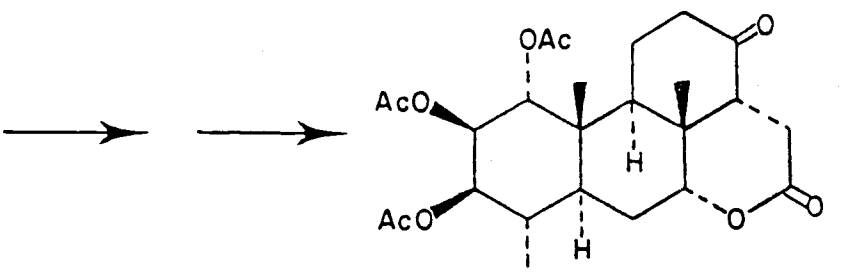


9 testosterone



10 11



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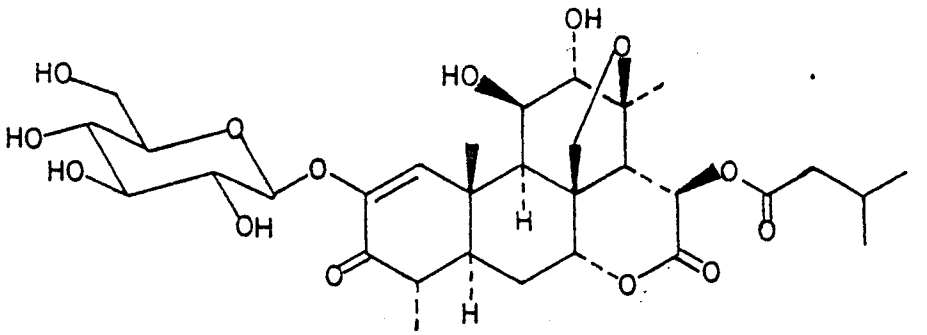
Scheme II

side bruceoside-A (13) into bruceantin 1 by hydrolysis of the glycoside and the C_{15} acyloxy side chain and reesterification at C_{15}.[47] Conversion of quassin 4 into a form possessing the D ring of bruceantin 1 was investigated by Takahashi.[23] Here, anhydroneoquassin 14 was reacted with osmium tetroxide to hydroxylate at C_{15} and C_{16} (Scheme III). Oxidation of the lactol and C_{15} acylation furnished a weakly biologically active compound 15. A successful transformation of the biologically inactive quassinoid chaparrin 16 to the strongly antileukemic castelanone 3c was reported by Polonsky.[24] After silylation of the reactive alcohols, the lactone was hydroxylated and the resulting $C_{15}\beta$ alcohol was acylated in 57% yield. Selective deprotection and oxidation of the C-2 alcohol to the ketone, followed by complete desilylation, yielded 3c.

Several laboratories are currently engaged in the total synthesis of quassinoids. A central issue, which must be addressed early in a synthesis, is the establishment of the proper stereochemistry at the chiral centers. Importantly, the early structural determination work revealed, that, of the seven asymmetric centers of quassin 4, three (C_4, C_9 and C_{14}) are epimerizable, and exist in the more stable configuration. Thus these three configurations can be corrected late in a synthesis, provided that the stereochemistries at C_5, C_7, C_8 and C_{10} have been previously established. Although little is known of the tendencies of partial quassinoid structures to adopt the correct relative stereochemistry, several synthetic schemes,



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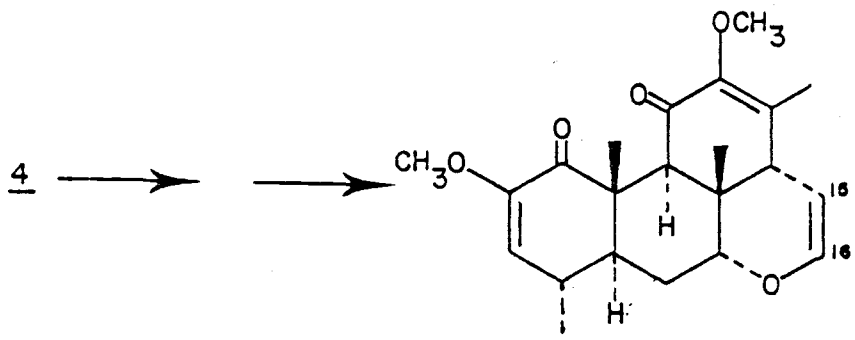

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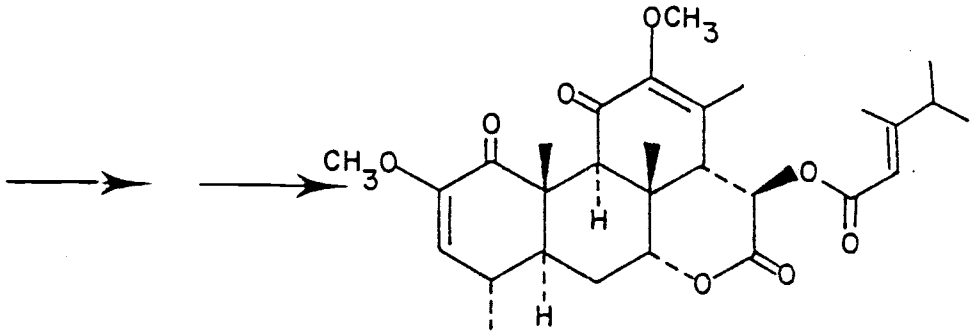

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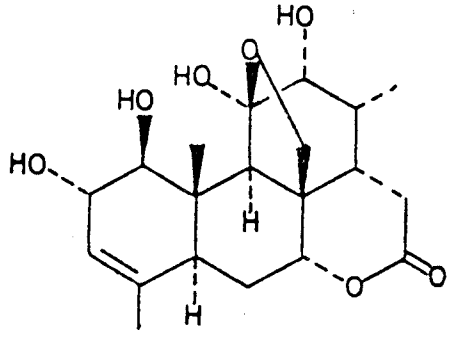
Scheme III



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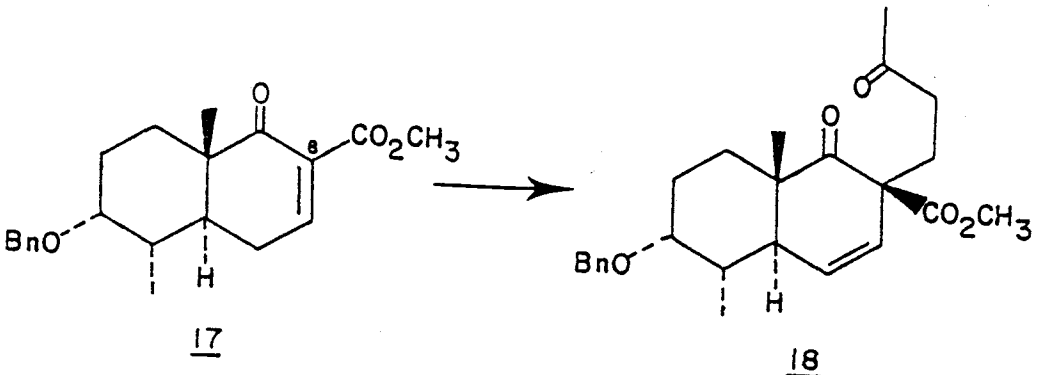
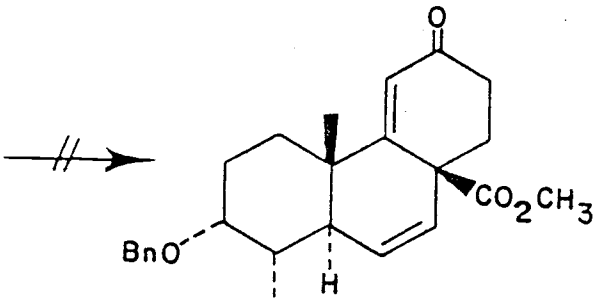
notably those of Grieco[12,13] and Kraus[25,26] have successfully established stereochemistry via equilibration.

The Robinson annulation, widely employed in natural products synthesis, has also found application to the quassinoids. In applying Robinson methodology to quassinoids, Watt[27,28] effected a Micheal addition of the enolate of 17 to methyl vinyl ketone (Scheme IV). The addition occured regioselectively at C_8 of 17 with the attack directed to the α face by the $C_{10\beta}$ angular methyl. Unfortunately, it was not possible to induce aldolization to close the C ring, due to steric hindrance about the C9 carbonyl. Takahashi utilized the Robinson annulation to append the A ring to a BC picrasane fragment 20 (Scheme V)[29] in contrast to Watt's strategy of forming the ABC portion by affixing the C ring last. The Micheal addition (under unspecified conditions) was again regioselective for the site α to the carbonyl of the enone with the presence of the $C_{8\beta}$ methyl directing the attack of the incoming Micheal acceptor to the α face. The low yield of the annulation product 21 (41%) and the difficulty in incorporating the two carbon unit for the D ring diminish the attractiveness of this route. Fuchs devised a third variation of this strategy[30] by employing consecutive Robinson annulations via a C(22)→BC(23)→ABC(24) sequence (Scheme VI).[30] While the mono annulated 23 could be isolated in high yield, the bisannulated 24 was readily available when a stronger base and more forcing conditions were employed. The second annulation, in addition to being directed



17 18



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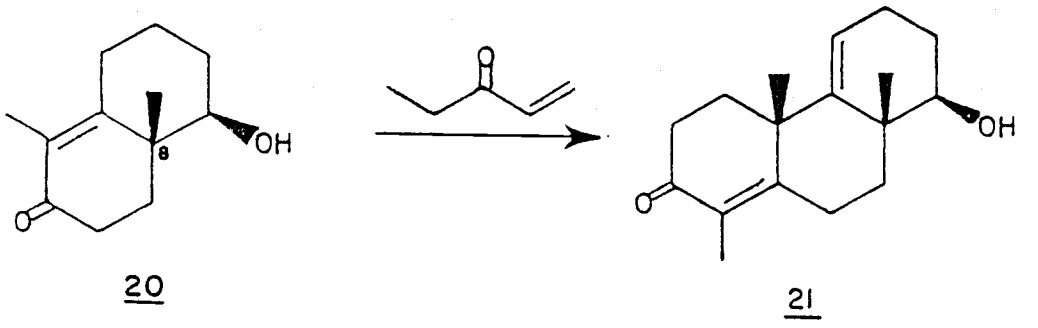
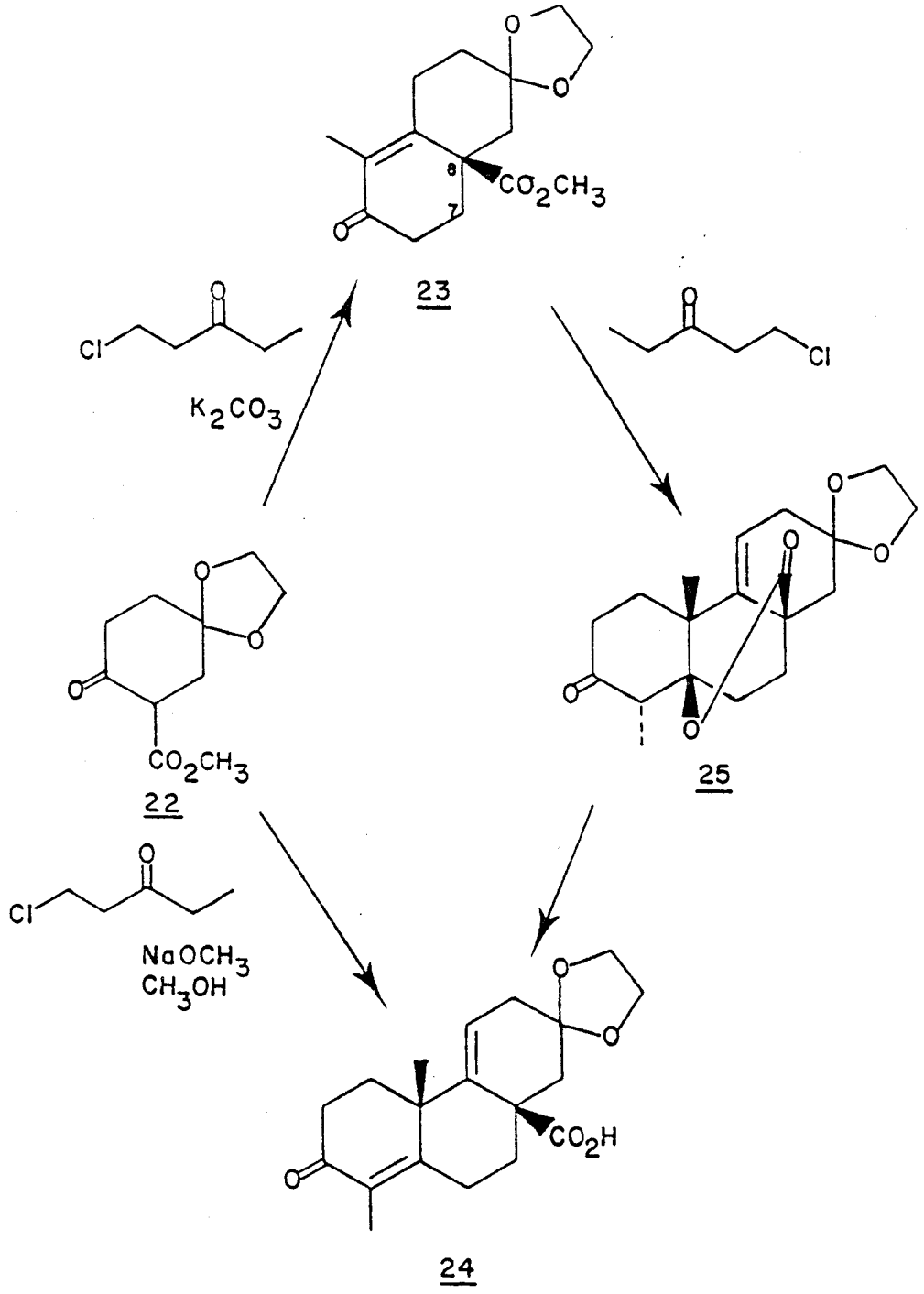
Scheme IV



20 21

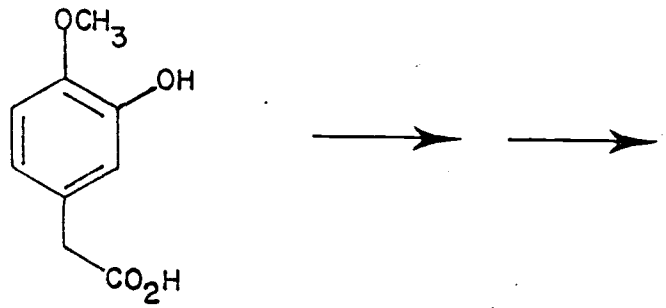
Scheme V



Scheme VI

to the α face by the $C_{8\beta}$ substituent, was also considered to be assisted by lactone (25) formation prior to elimination. This last route again suffers from the lack of an acetic acid side chain for formation of the D ring, but more crucially by the lack of the C_7 hydroxyl substituent.

The ability of the Diels-Alder reaction to simultanously control the stereochemistry at several centers has contributed to its widespread utilization in the construction of the picrasane skeleton. Additionally, the abundance of methodology for the incorporation of functionality into the dienes and dienophiles affords flexibility in introducing the quassinoid functionality. Both inter- and intramolecular versions of the Diels-Alder reaction have been employed. In a very ambitious usage of the intramolecular Diels-Alder, Mandell[31,32] constructed the bis-orthoquinone 27 from a simple aromatic precursor (26) (Scheme VII). In this proposal, an anticipated endo addition of the diene moiety to the dienophile properly sets the stereochemistry at C_7, C_8 and C_{10} in 28. Subsequently C_9 would be inverted and the correct configuration at C_5 achieved via a reduction of the 5,6 olefin. Unfortunatly, the Diels-Alder reaction failed to occur. A second intramolecular Diels-Alder approach to quassinoids, presented by Watt,[33] encompassed the more traditional diene and dienophile 29 and 30, respectively (Scheme VIII). Coupled together by an ester linkage, the stereochemistry at C_7 in 31 should direct the diene to approach only the α face of the dienophile. Again,



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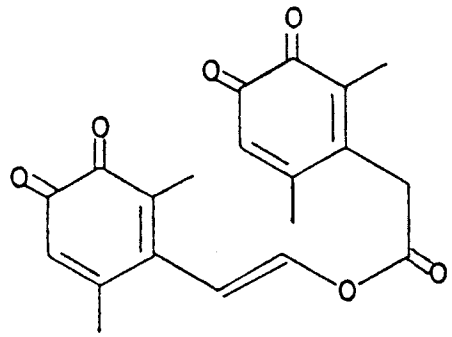

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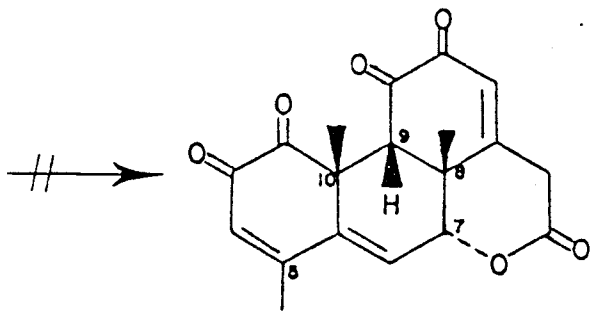

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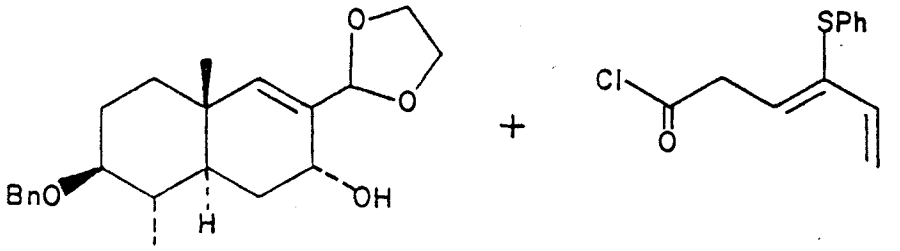
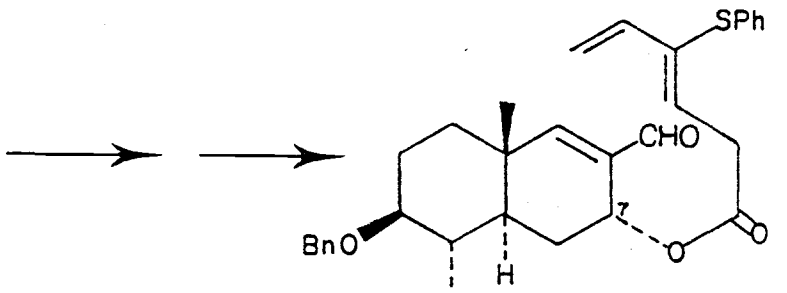
Scheme VII



29 30



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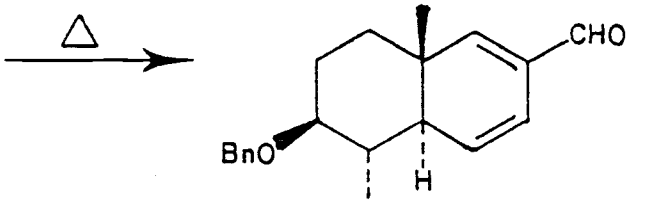

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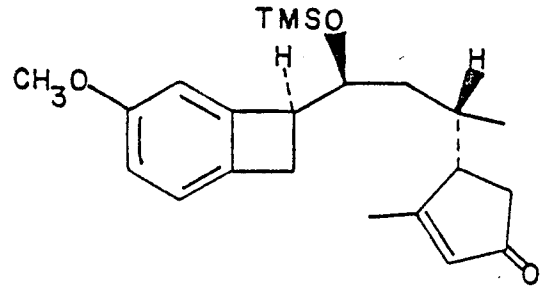
Scheme VIII

however, the desired cycloaddition was not observed; rather, elimination to 32 was predominant. Kametani,[34,35] in his now familiar approach, used an intramolecular Diels-Alder reaction to construct the C_6-C_7 and C_8-C_9 bonds. In this case 33 was thermolyzed to an o-quinodimethane 34 which cyclized in situ to 35. (Scheme IX). The cycloaddition was constrained to proceed thru an exo transition state, with the allylic hydrogen at C_{14} pointing away from the diene. This successfully regulated the stereochemistry at C_7, C_8, C_9 and C_{14}. Methodology for introducing the $C_{10\beta}$ methyl substituent has appeared, as for the conversion of 36 into the hibaol intermediate 37.[36]

The application of the intermolecular Diels-Alder reaction has produced the most success to date of the methodologies utilized to synthesize quassinoids. The earliest report of the application of this reaction was made by Valenta[37,38] in work towards quassin. The stratagem employed in setting the stereochemistry of the chiral centers depended upon the ability to exploit both the endo preference of the Diels-Alder reaction and the rigidity of the [2.2.2] bicyclooctane 40. (Scheme X). From the cycloaddition, the stereochemistry of C_7, C_8 and C_{10} were properly established. By deacylation, oxidation and epimerization to 41, the correct configuration at C_5 was achieved. Elaboration of the acetyl side chain, formation of the C_{15}-C_{14} bond and cleavage of the remaining C_1-C_{16} bond afforded 43, which contains all the required quassin skeletal carbons, with



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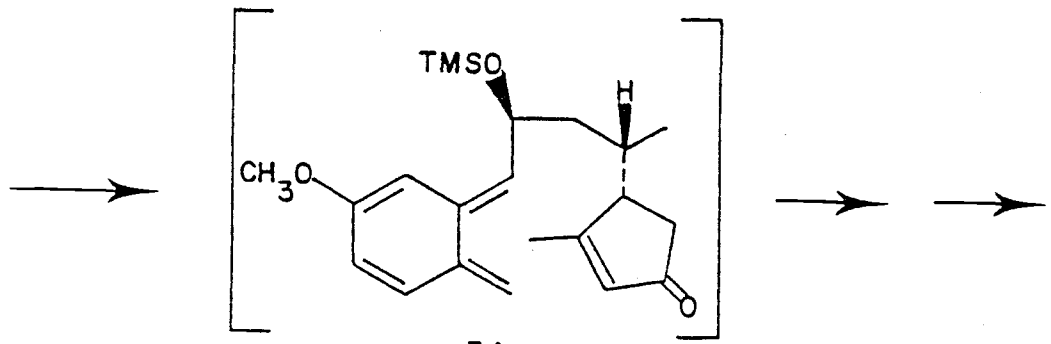

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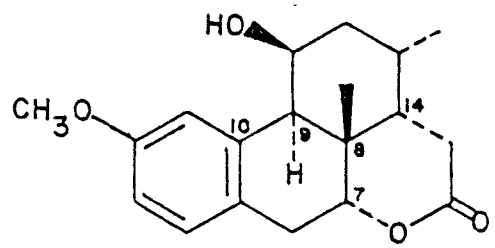

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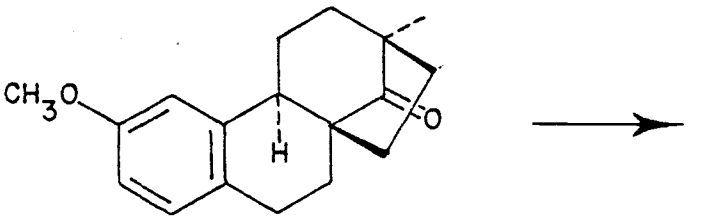
Scheme IX



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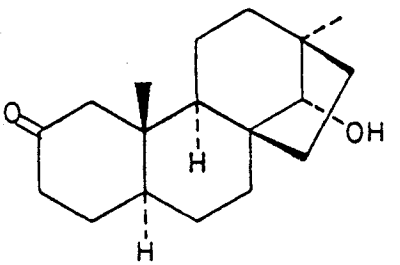

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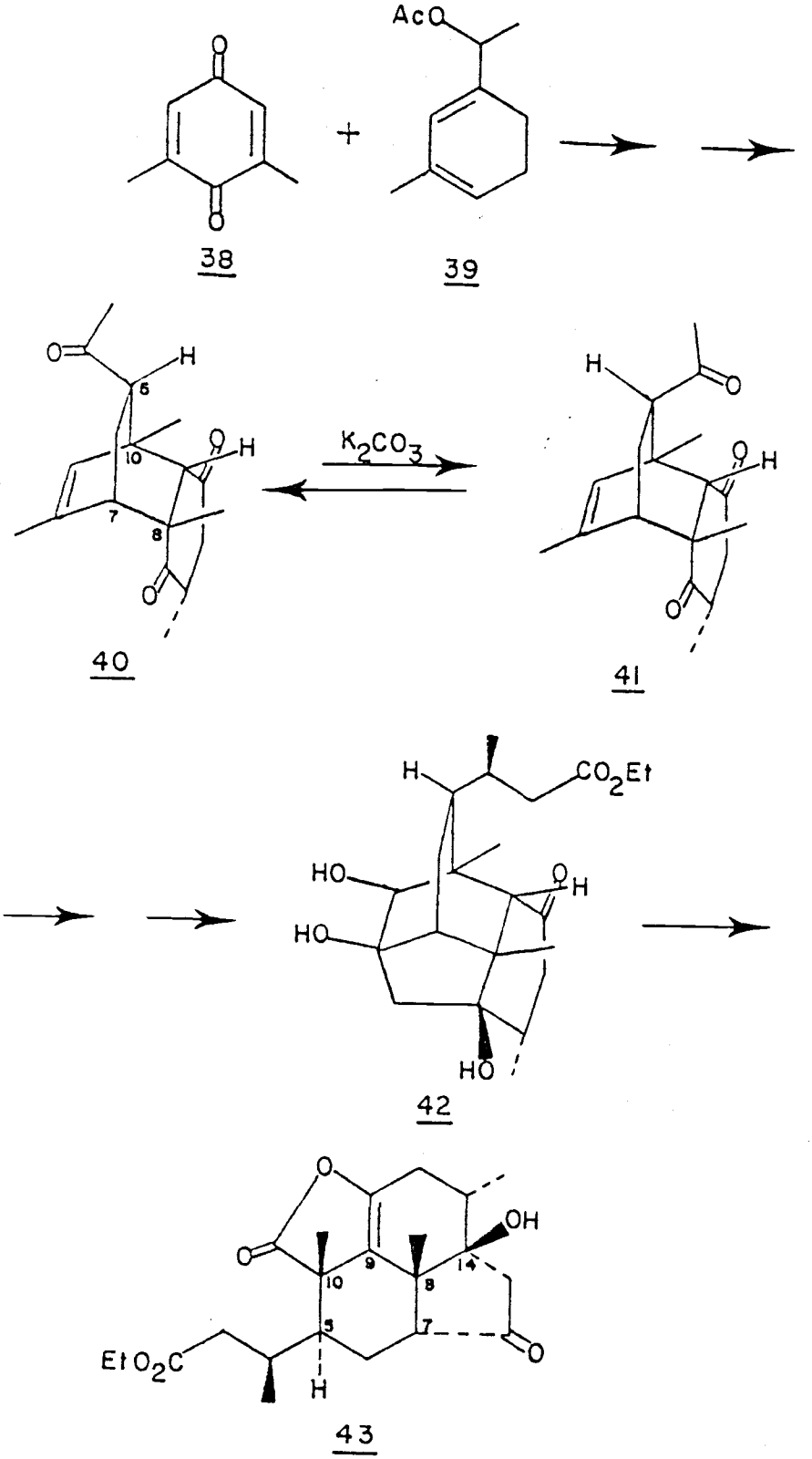
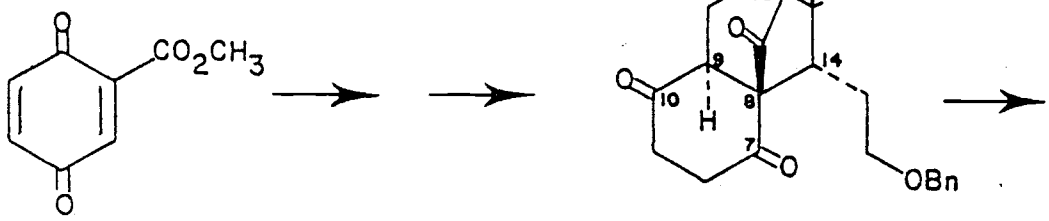


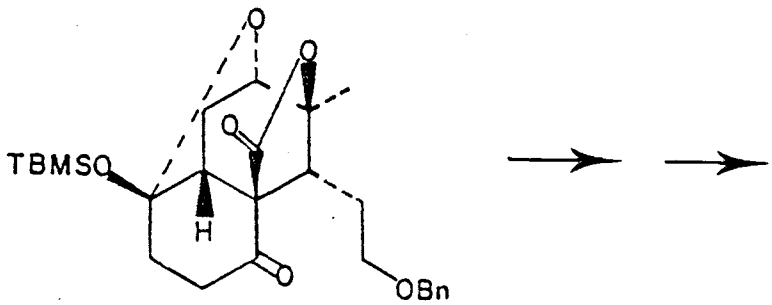
Scheme X

C_5, C_7, C_8 and C_{10} in the proper stereochemical configuration. The correct stereochemistries at centers C_9 and C_{14} may be established later by hydrogenation of olefins. Of the remaining tasks, the C_4 configuration can be adjusted later in the synthesis. The formation of the C_1-C_2 bond may prove very difficult however, due to the juxtaposition of the methyl subsituents at C_4 and C_{10}.

In an efficient synthesis, Kraus[25-26,39] utilized a ring formation scheme wherein a para-quinone (44) serves as the incipient B ring and is sequentially annulated by the scheme B(44) BC(45)→ BCE(46)→BCDE(47) (Scheme XI). The initial Diels-Alder reaction established the correct relative stereochemistry at C_8 and C_{14}. The correct configuration at C_9 was achieved early via epimerization. The formation of the D and E rings was achieved using the carbons already present in 45 *via* functional group manipulation. The key step in these operations was the treatment of 45 with t-butyldimethylsilylchloride under strenous conditions to afford the ketal 46. In this one step, the C_{10} ketone and the $C_{12\alpha}$ alcohol are selectively protected. The reduction of the free ketone now occurs only from the β face due to the cis ring fusion, giving the proper C_7 stereochemistry. In completing the transformations, the ketal is freed after DIBAL reduction, which causes concommitant epimerization of C_9 back to the α configuration. Exhaustive acylation, reduction with triethylsilane/trifluoroacetic acid and oxidation of the free



44 45



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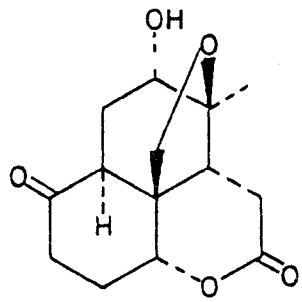


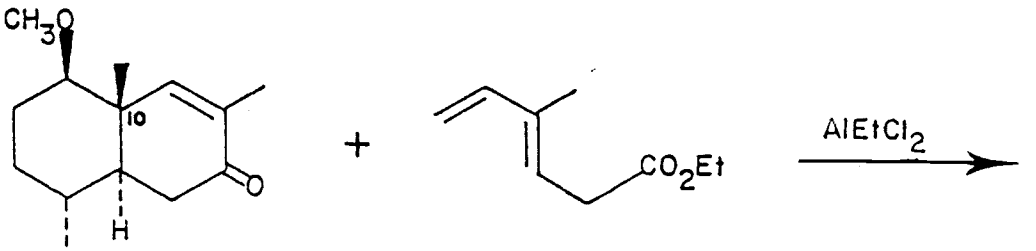
47

Scheme XI

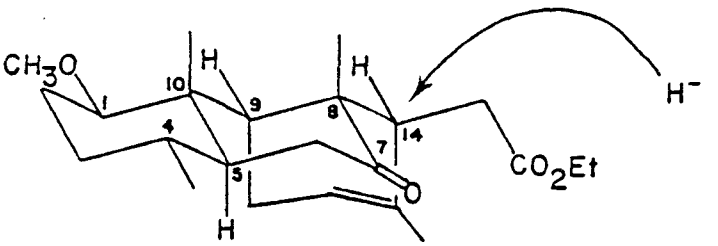
primary alcohol affords 47. Thus at several stages of the synthesis Kraus successfully manipulated the stereochemistry at C_9.

Finally, the total synthesis of quassin 4 and castelanolide 3c has been achieved by Grieco at al.[12,13,44-42] In both syntheses Grieco utilized a common intermediate, 51, which was available from 48 in twelve steps (Scheme XII). The Lewis acid catalyzed Diels-Alder reaction of 48 and 49 afforded a single adduct in excellent yield (64%). The reaction is remarkable in that α substituted α,β- cyclohexenone systems had been regarded as poor dienophiles.[43] The bridgehead methyl at C_{10} directed the addition of the diene to the α face and established the correct stereochemistry at C_8 and C_{14}, relative to C_4, C_5 and C_{10}. The unnatural configuration of C_9 in 50 at this stage serves the purpose of directing the reduction of the C_7 carbonyl. By allowing attack of the reducing agent only from the convex β face the desired $C_{7\alpha}$ alcohol was produced.

The versatility of 51 was demonstrated by its conversion to 4 and 5. The preparation of quassin 4 from 51 required the incorporation of the oxygen functionality of 4 and, critically, the epimerization of configuration of C_9 (Scheme XIII). Under the conditions of the oxidation of the α ketol 52 (sodium methoxide in methanol/dimethylsulfoxide) to 53 , C_9 was epimerized. This same procedure was successfully employed in the synthesis of castelanolide 5a from 51. These two syntheses illustrate the basic strategy of constructing the picrasane skeleton 2 via a Diels-Alder reaction in a manner that



48 49



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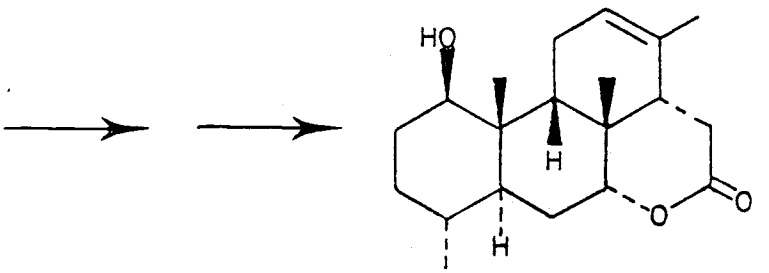
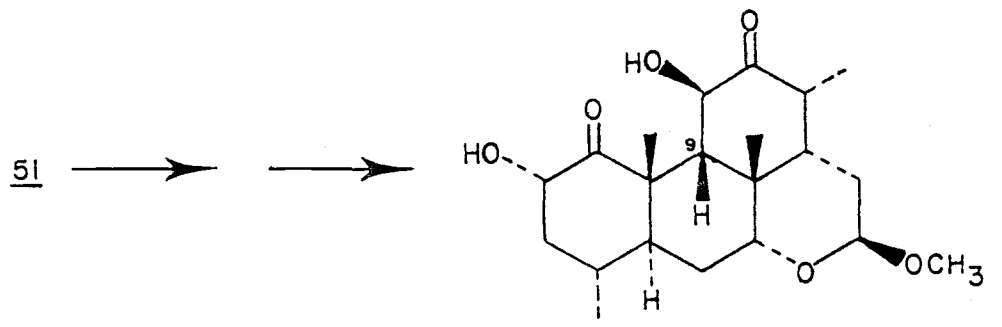


51

Scheme XII



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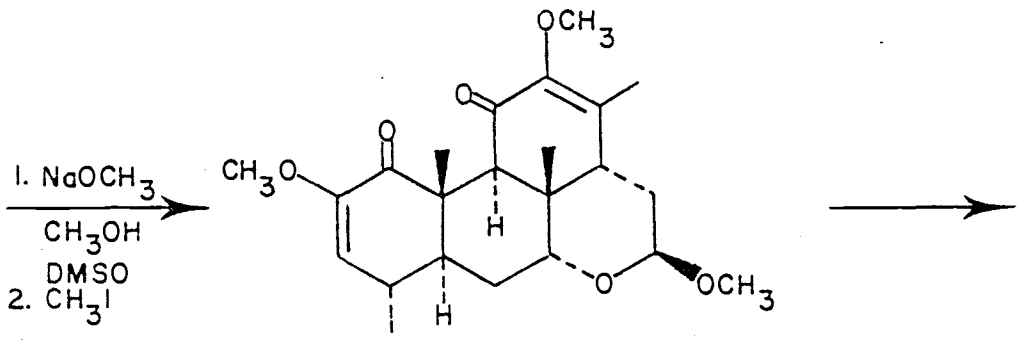

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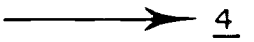
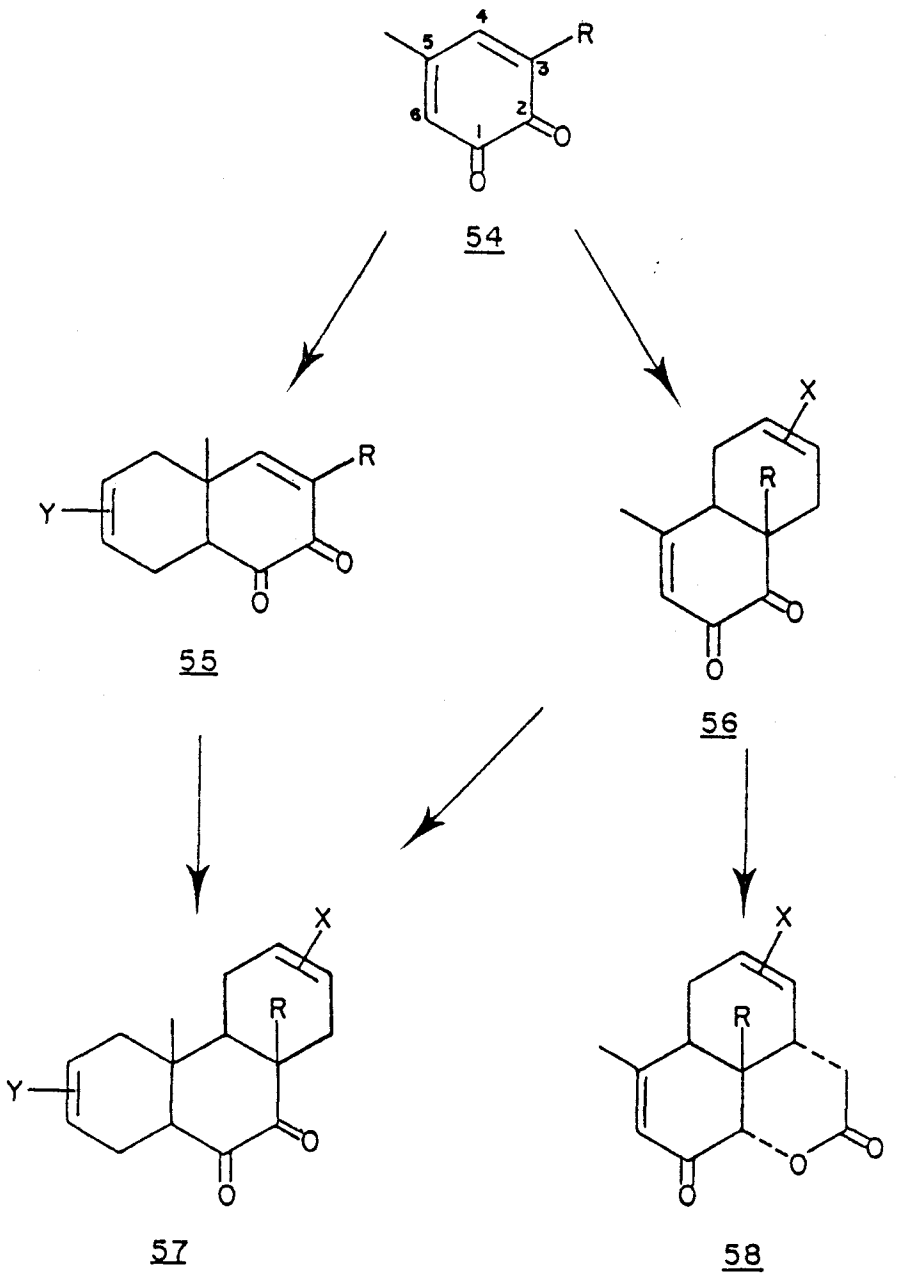


Scheme XIII

assures the proper stereochemistry at the nonepimerizable chiral centers. Following incorporation of the oxygen functionality into that skeleton, the stereochemistry at the remaining chiral centers is set by equilibration to the more stable isomers.

Our approach to the picrasane skeleton 2 also recognized the advantages inherent in the Diels-Alder reaction, and postulated the intermediacy of the ABC carbocyclic unit 57 (Scheme XIV). This fragment was envisioned as arising from an o-quinone which could, in theory at least, be twice annulated via the Diels-Alder reaction. The initial cycloaddition, if effected at the 3,4 olefin of the quinone, would produce a BC ring system 56 while initial attack at the 5,6 olefin provides the AB system 55. The utility of the α-methylcyclohexenone system for the annulation of the C ring was recently confirmed by Grieco in the synthesis of quassin 4[12] and castelanolide 5.[13] Due to the greater Diels-Alder reactivity of the α-methylcyclohexenone system vis-a-vis the β-methylcyclohexenone system, it appeared that the AB system 55 would be a superior substrate for the second Diels-Alder reaction than the BC system 56. In order for o-quinones to represent viable precursors to 2, the initial annulation of the quinone should be regioselective for attack at the 5,6 position.

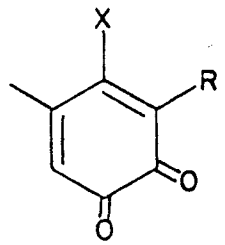
During the pioneering work on the reaction of o-quinones with dienes, Ansell found that 3,5 disubstituted o-quinones undergo reaction primarily at the 3,4 olefin when the C_5 substituent is not an



Scheme XIV

electron withdrawing group.[44a] Further, 3,4,5 trisubstituted o-quinones afforded only 5,6 Diels-Alder adducts, but those quinones often behaved as the diene component in the cycloaddition producing bicyclooctane derivatives. With these studies in mind, we decided to study the Diels-Alder reactions of o-quinones 59a-d. The disubstituted o-quinones 59a and 59c should give predominately 3,4 adducts as products from a Diels-Alder reaction. However the chloro derivatives 59b and 59d would be anticipated to afford mainly 5,6 addition products. We hoped the C_4 chloro substituents of 59b,d would represent an easily introducible group [45] which could later be easily removed via a reductive process.[46] This would allow initial construction of the AB fragment, a more favorable substrate for the second Diels-Alder reaction.

The functionality of the o-quinones is well disposed for quassinoid synthesis. The C_3 and C_5 substituents will ultimately become C_{19} and C_{20} of the quassinoids. While 59a and 59b possess a C_3 methyl and would not be suitable for synthesis of the biologically active quassinoids (which of necessity bear an oxygenated C_{20} carbon), their chemistry should parallel the chemistry of the corresponding o-quinones possessing a C_3 alkoxymethyl substituent. Further, the residual oxo groups of the quinone will become the C_7 oxygen substituent and also, in the case of the 6-oxygenated quassinoids, the C_6 hydroxyl group.

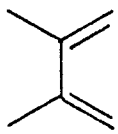


59a R = CH_3, X = H

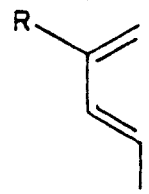
59b R = CH_3, X = Cl

59c R = CO_2CH_3, X = H

59d R = CO_2CH_3, X = Cl



60



61a R = H

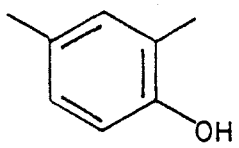
61b R = OAc

The dienes chosen for our study were 60 and 61a,b. The reactions of dimethylbutadiene 60 will serve as a basis for comparison of our results to those of Ansell[44b] in regard to the stability and reactivity of o-quinones 59a-d. Piperylene 61a and 2-acetoxypiperylene 61b,[47] when directed to attack the 5,6 olefin, will provide potentially useful precursors to the AB ring systems. Attack of the latter two dienes at the o-quinone 3,4 position will provide data applicable to analogous dienes for constructing BC ring intermediates.

The second major concern in the utilization of the o-quinone Diels-Alder reaction for quassinoid synthesis was the necessity to epimerize the initially formed cis-fused AB or BC ring systems to the trans isomers. The ring junction stereochemistry is especially critical to our scheme since it will determine in large part the relative stereochemistry of the asymmetric centers at the new ring junctions formed during the second Diels-Alder reaction. When we began our work it was not clear from the literature what the more stable configuration of the o-quinone Diels-Alder adducts would be.[48] Of special interest in this regard was the possibility of incorporating into the BC Diels-Alder product the additional carbons necessary to construct the D ring δ-lactone. Experiments on the epimerization of C-7 and C-9 of the BCD fragments 58 would allow insight into the tendency of partial quassinoid structures to assume the correct quassinoid configurations.

B. THE DIELS-ALDER REACTIONS OF o-QUINONES 59a-d

The recorded route to catechol 64[44a] proceeded by formylation of 2,4-dimethylphenol 62 with hexamethylenetetramine to salicylaldehyde 63, then Dakin-West oxidation to 64. Although the latter reaction was efficient, the formylation was accomplished in only 16% yield. Attempted formylation of 62 by the Vilsmeier reagent (DMF, $POCl_3$) or by triethylorthoformate in the presence of a Lewis acid failed to provide 63. Direct oxygenation of 62 with benzoyl peroxide also was unsuccessful. In a method much superior to the literature synthesis,[44a] 59a was prepared by a process involving bromination of 62 followed by copper catalyzed displacement of the bromide in 65 by hydroxide [49-52] in a hot aqueous solution. This process, which has found little utility outside the patent literature, is an efficient route to catechols and phenols. Catechol 68 was available in 60% yield by a similiar sequence of events from 5-methylsalicylic acid.[33] This acid proved difficult to crystallize and so was routinely esterified, at which point the ester 69 could be easily recrystallized. Although 64 could be readily oxidized to quinone 59a using o-chloranil, [44a] the oxidation of 69 required silver oxide. This reaction proved quite variable, and generally 10-20% of the unreacted catechol was present even when a large excess of the oxidant was used. However, this contaminant could be easily removed following the Diels-Alder reaction (vida infra).



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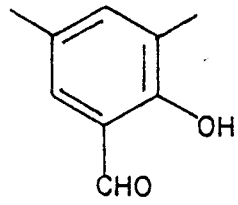

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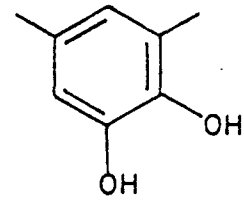
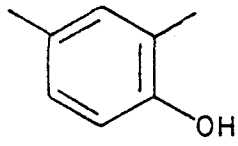
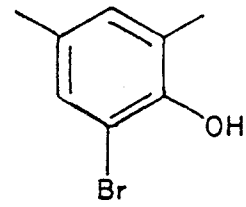


64



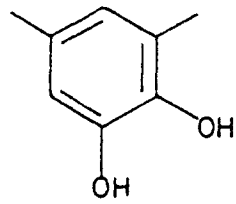
62

NBS, DMF



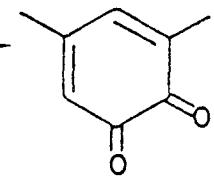
65

NaOH
$CuSO_4$
H_2O, Δ

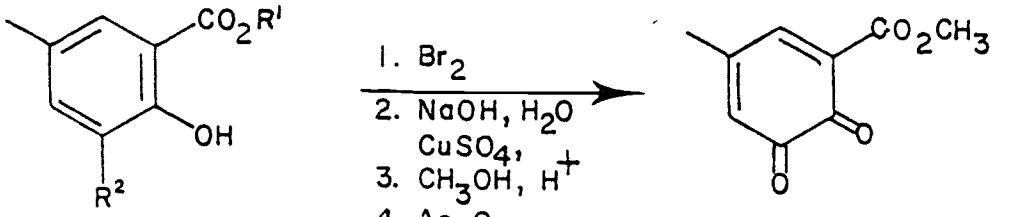


64

o-chloranil



59a



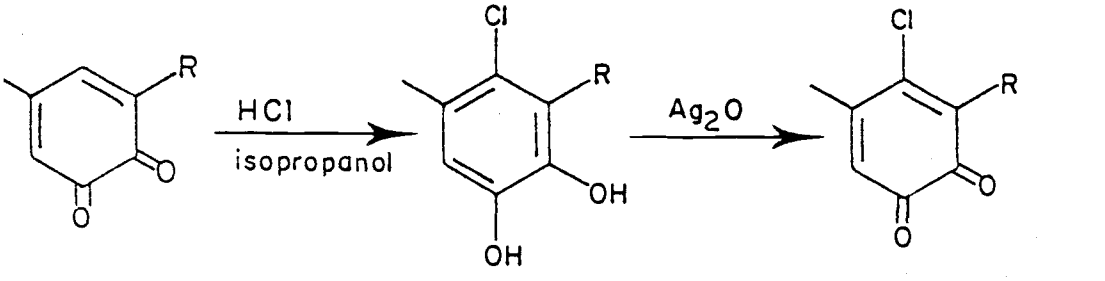
66 $R^1 = H$, $R^2 = H$

67 $R^1 = H$, $R^2 = Br$

68 $R^1 = H$, $R^2 = OH$

69 $R^1 = CH_3$, $R^2 = OH$

59c



59a R = CH_3

59c R = CO_2CH_3

70 R = CH_3

71 R = CO_2CH_3

59b R = CH_3

59d R = CO_2CH_3

Chlorination of the simple o-quinones 59a,c was achieved by treatment with anhydrous hydrogen chloride in isopropanol.[45] Use of methanol or ethanol as solvent led to small amounts of solvent incorporation at C_4. Reoxidation of the intermediate chlorocatechols 70 and 71 with silver oxide provided 59b and 59d in 72% and 70% yields respectively. These silver oxide oxidations proved far less variable than those for the simple catechols, and characteristically afforded greater than 98% conversion. The position of chlorine incorporation was indicated in both cases by the loss, in the ^1H NMR spectrum, of the more downfield (C_4) proton signal that was present in the spectrum of the simple quinones. Although the o-quinones 59a-d were routinely used for Diels-Alder reactions immediately, they are stable to storage at -78°C for several days without decomposition.

The results of the reactions of the o-quinones with the model dienes are shown in Table I. o-Quinone 59a (Scheme XV), when treated with 2,3-dimethylbutadiene 60, afforded both the 3,4 adduct 72 and the 5,6 adduct 73 (in a 9/1 ratio) but after flash chromatography only 72 was isolated, in 77% yield. Integration of the vinylic proton absorptions in the ^1H NMR afforded the ratio of products in these reactions. The major component in this mixture showed signals in the ^1H NMR near δ = 6.36 and 1.94 ppm, indicative of the α-methylcyclohexenone unit of the 5,6 adduct. Treatment of 59a with dienes 61a and 61b afforded inseparable mixtures of 3,4 and 5,6 addition products. The regio- and stereochemistry of adducts 72 - 77 were not

TABLE I. Diels-Alder Addition of Quinones 59a-d With Dienes

Quinone	Diene (mole%,hr)[a]	Products (%,(Cmpd)) 3,4	5,6	Other	Yield (%)[c]
a	60 (300,14)	100[d] (72)	0		77
	61a (320,14)	88 (74)	12 (76)		67
	61b (320,14)	84 (76)	16 (77)		70
b	60 (290,28)	0	100 (81)		27
	61a (300,28)	0	12 (82)	88 (83)[e]	57
	61b (290,120)	0	100 84		13
c	60 (240,124)	100 (78)	0		46
	61a (250,3)	100 (79)	0		87
	61b (310,14)	100 (80)	0		85
	61c (170,14)	100 (90)	0		74
	99 (130,14)	100(100)	0		50
d	60 (300,14)	0	100 (85)		72
	61a (290,14)	0	100 (86)		19
	61b (300,14)	18	18;64		17

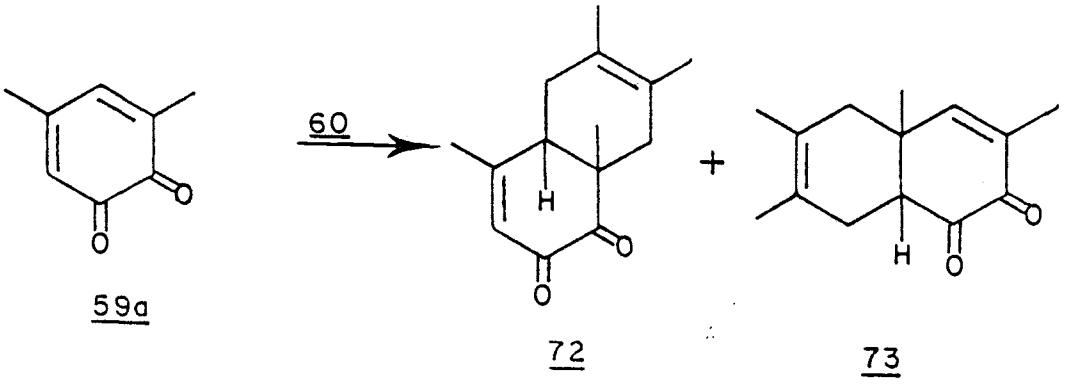
[a] Diene and quinone were mixed in dry chloroform and stirred in the dark for the indicated time. Workup by evaporation and chromatography gave products. See the supplemental experimental section for details.

[b] Relative percent of product arising from Diels-Aldeer reaction of the quinones at the 3,4 or 5,6 positions.

[c] Purified yield.

[d] ^1H NMR of the crude reaction mixture showed the presence of 10% of the 5,6 adduct.

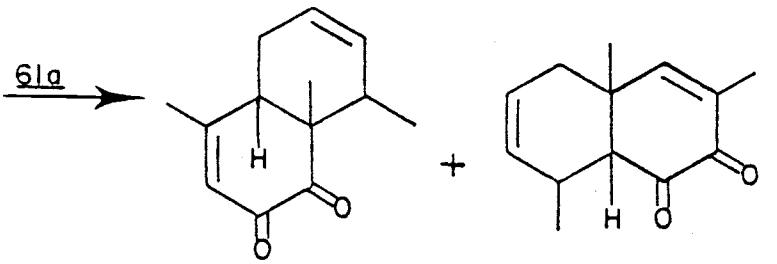
[e] See text for structure.



59a

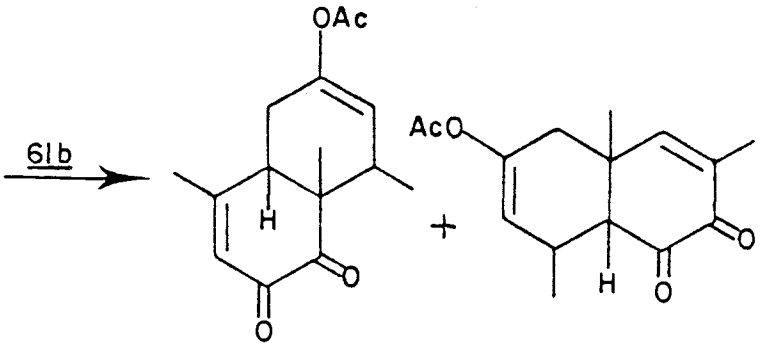
72

73



74

75



76

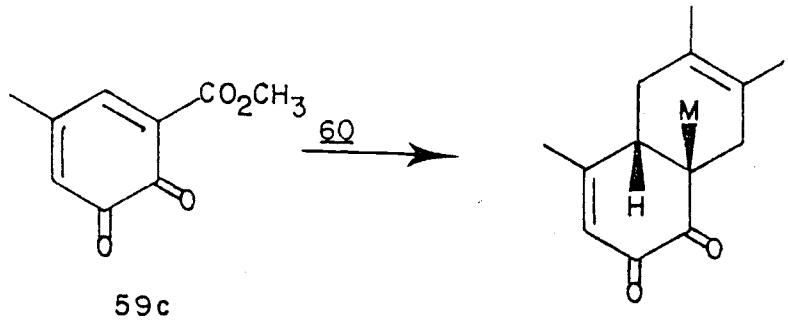
77

Scheme XV

investigated in detail.

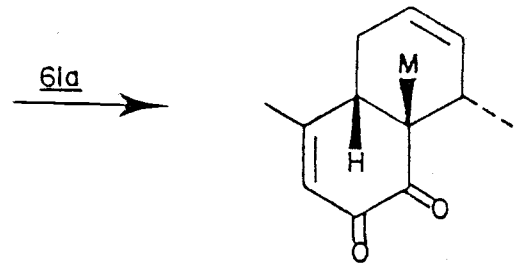
Several experimental features deserve comment. The o-quinones are more stable than previous reports would have predicted. Ansell prescribed the use of a large excess of diene (at least 10 equivalents) in order to promote the Diels-Alder reaction relative to decomposition and dimerization of the o-quinones.[44a,b] In our examples, the cycloadditon reactions were effected using 3.2 equivalents of diene at most and afforded quite reasonable yields. This increases the attractiveness of the method, especially in cases where the diene component is not easily available. Also of note, it was found that flash chromatography [54] of these and later Diels-Alder adducts afforded a significantly better return of material than did gravity chromatography.

o-Quinone 59c reacted with the dienes to produce, in each case, a single adduct (Table I, Scheme XVI). Diels-Alder reactions of 59c may be preformed either in situ with the silver oxide oxidation of catechol 69 or with previously prepared o-quinones. While the in situ oxidation/Diels-Alder procedure afforded a slightly improved yield over the latter method (46 and 38%, respectively) this procedure required a greater excess of diene 60 (3.4 eqts). The adducts 78-80 possessed signals in the ^{1}H NMR at δ=6.2 and 2.15 ppm which are attributable to the β-methylcyclohexenone moiety of a 3,4 adduct. Thus, as Ansell originally found, the inclusion of an electron withdrawing group on the quinone activates that enone moiety sufficiently

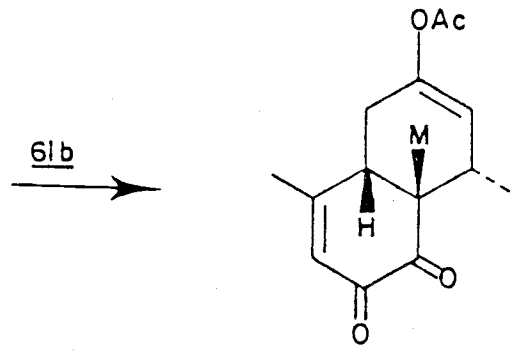


59c

78



79



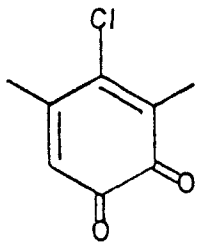
80

Scheme XVI

(M = CO_2CH_3)

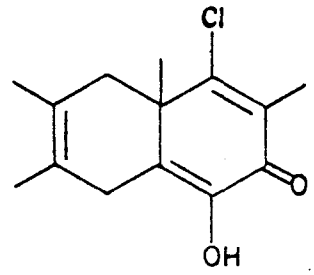
to ensure complete specificity in the site of reaction at the quinone.[44b] The regiochemistry and stereochemistry of 79 and 80 were tentatively assigned by spectral comparisons with the product of quinone 59c and ethyl 3,5-hexadienoate, whose structure was investigated in detail (vida infra).

Treatment of the chloro-o-quinone 59b with the dienes gave the results shown in (Scheme XVII). With dimethylbutadiene, the o-quinone afforded a single isolable product, 81, in 27% yield. The presence of a hydroxyl group and the absence of vinylic protons led to the assignment of 81 as the enolized 5,6 adduct. The preference for the enol tautomer may be due to the electron withdrawing nature of the chlorine, and had been observed earlier by Ansell[44a]. In contrast, the reaction of o-quinones 59b with piperylene produced two products in 7% and 50% yields. The minor product (7%) was shown to be the enolized 5,6 adduct 82. The major product possessed a radically different structure from that of 82, as evidenced by the UV spectrum (λ_{max} = 314 nm, ε = 85) and the presence, in the ^{1}H NMR, of two vinylic methyls, one of which was a doublet with a coupling constant of 7 Hz. The structure of the major isomer was assigned as the [2.2.2] bicyclooctane derivative 83, and was rigorously proved by interpretation of the 360 MHz ^{1}H NMR spectrum. The bicyclooctane product arises from Diels-Alder reaction in which the o-quinone 59b serves as the diene reactant, and 61a as the dieneophile, and accords with earlier observations by Ansell[44a]. The position of addition of



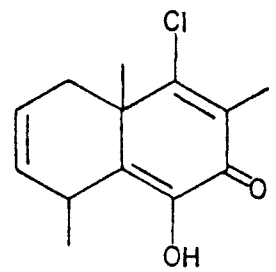
59b

60

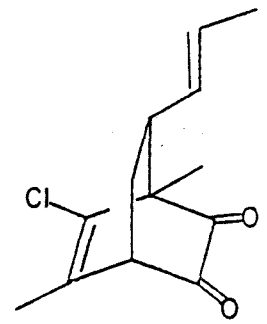


81

61a

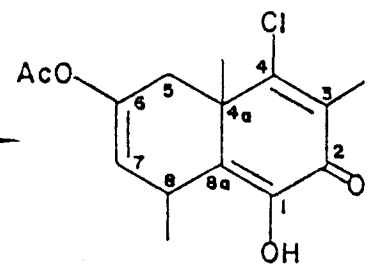


82



83

61b



84

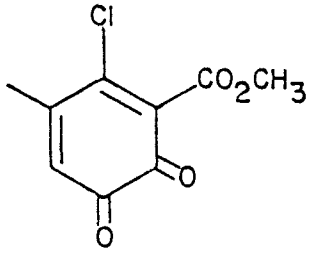
Scheme XVII

59b onto piperylene in 83 was clear from the appearance of the bridgehead proton as a triplet, J = 3 Hz, at δ = 3.36 ppm, indicating that the adjacent carbon of the ethane bridge was a methylene group. The sterochemistry of the adduct was assigned by consideration of the chemical shifts of the protons on the ethane bridge. The two methylene protons show widely different chemical shifts due to the location of one in the deshielding zone of the nearby carbon-carbon double bond[55] and appear at δ = 2.44 ppm (ddd, J = 3, 10, 15 Hz) and at δ = 1.70ppm (multiplet, obscured by the vinyl methyl absorption at δ = 1.70). The methine proton on the bridge must be oriented toward the alkene bridge, due to its relatively downfield chemical shift (δ = 2.53 ppm, dt, J = 5, 10 Hz) and its large coupling (10 Hz) with the adjacent downfield methylene proton, which is consistent with the syn periplanar relationship between these two protons.

The adduct, tentatively assigned structure 84, resulting from treatment of 59b with the diene 61b, isolated in 13% yield, exhibited, in the ^{1}H NMR spectrum a hydroxyl group (δ = 6.84 ppm), one vinylic proton and two aliphatic methyl groups, as would be expected for a 5,6 adduct which has enolized. However, in this molecule, the 8-methyl, a doublet, did not occur near 0.80 ppm as in all the prior 5,6 adducts, but at 1.55 ppm. This anomaly may be explained if the reaction changed transition state orientation i.e., endo to exo, or if the diene approached the 5,6 olefin in a reversed orientation,

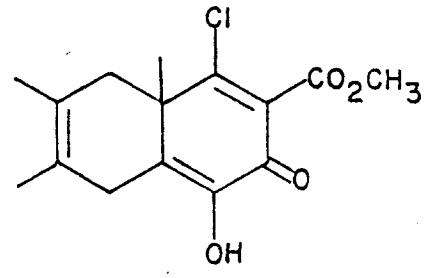
i.e. to provide a 7-acetoxy-5-methyl adduct. Due to the rather low yields the stereochemistry was not investigated. Thus, as expected, the 4-chloro substituent of o-quinones 59b does sterically hinder the approach of a diene to the 3,4 olefin, since no 3,4 adducts were isolated. However this molecule is only poorly dienophilic.

The Diels-Alder reactions of o-quinones 59d at the 5,6 olefin were predicted to occur with greater facility than the corresponding reactions of 59b. In this case, the C-3 carbomethoxy group was expected to increase the dieneophilicity of both the 3,4 and 5,6 enone systems. Although the accelerating effect of the ester group on the cycloaddition will be most strongly felt at the 3,4 position, the presence of the 4-chloro subsituent should hinder attack at this site. Encouragingly, treatment of 59d with dimethylbutadiene afforded a single adduct in 72% after flash chromatography (Table 1, Scheme XVIII). The adduct, 85, was readily identified as the enolized, 5,6 addition product by its ^{1}H NMR spectrum. Unfortunately, reaction of 59d with piperylene was less successful, giving many reaction products, and only 19% of the 5,6 adduct 86. Furthermore, reaction of 59d with 2-acetoxypiperylene was also poor affording three recognizable cycloadducts in low yield. Isolated first from chromatography was an inseparable mixture of a 3,4 adduct and a 5,6 adduct in 7% yield. The former adduct was recognized by the similarity of its ^{1}H NMR spectrum with that of 76. The major cycloadduct in the reaction mixture was another 5,6 adduct, and was isolated in



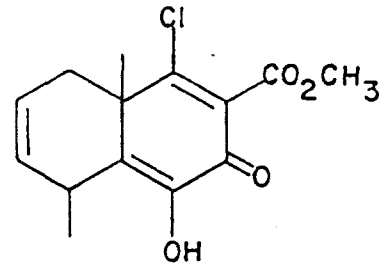
59d

60 →



85

61a →



86

61b → (5,6 + 3,4) + 5,6

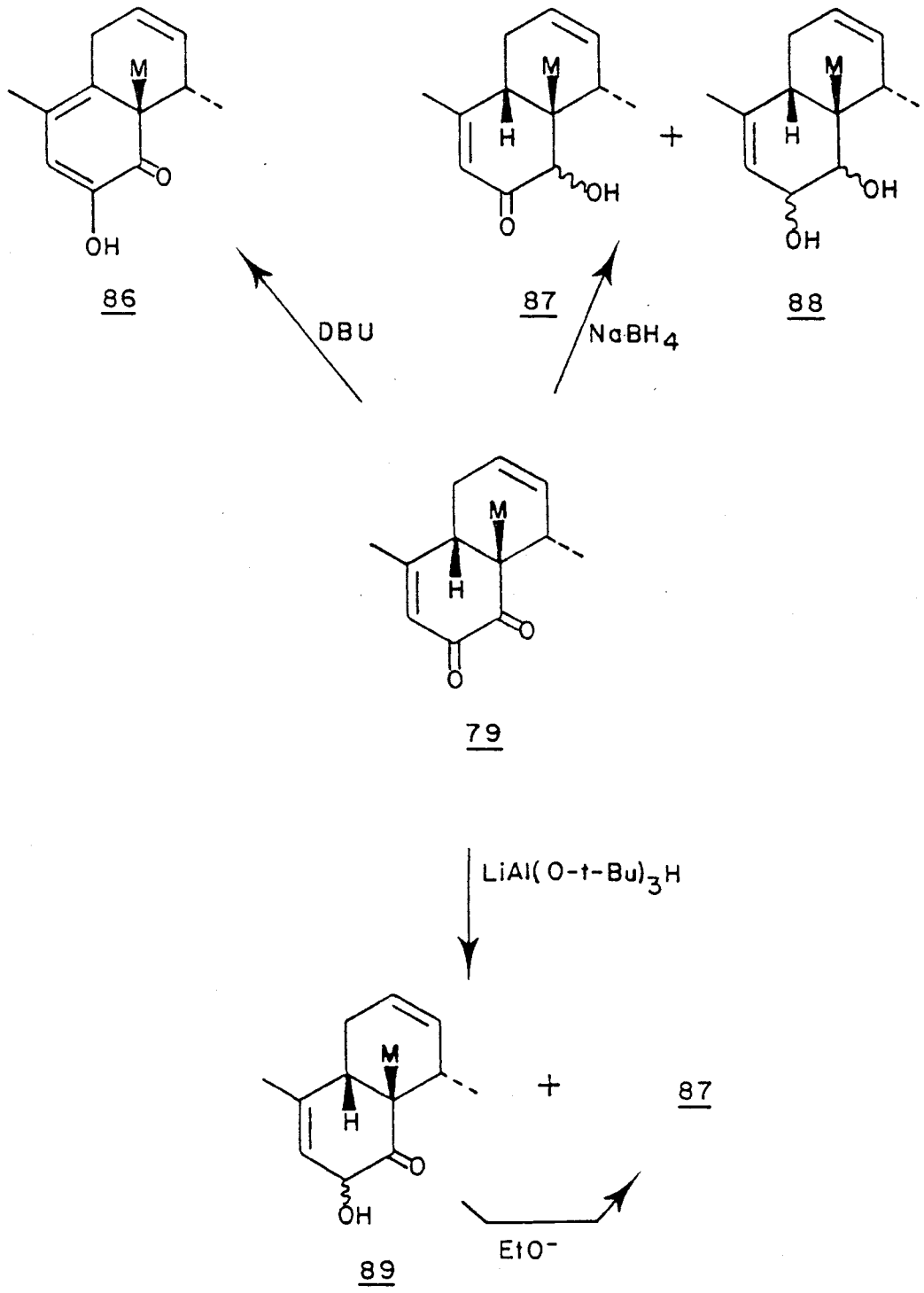
Scheme XVIII

12% yield. Interestingly the 5,6 adducts of this reaction showed the anomalous chemical shift behavior observed for 82 and 84, with one product showing the aliphatic methyl doublet at δ = 1.54 and the other adduct showing the corresponding signal at δ = 0.80 ppm. Because of the mixtures and low yields obtained, these adducts were not further investigated.

A major result of these preliminary studies was that addition of useful dienes to the 5,6 position of the chloro-o-quinones 59b and 59d was characterized by poor yields and poor specificity in mode of reaction. While only in one case was a 3,4 adduct isolated, the dienophilicy of the 5,6 olefin was insufficient for practical Diels-Alder reaction. On the other hand, the addition of diences to the 3,4 site of o-quinones 59a and 59c was facile, and in general quite high yielding. The preference shown by the dienes for the 3,4 olefin of 59a leaves open the possibility of using o-quinones bearing 3-alkoxymethyl substituents as quassinoid precursors. The reactions of 59c were further explored with regard to quassinoid synthesis.

C. APPLICATION OF 3,4 DIELS-ALDER ADDITION ADDUCTS OF o-QUINONE 59c TOWARDS QUASSINOID SYNTHESIS.

At the outset of the exploration of the 3,4 addition approach, we decided to investigate the conversion of these adducts into a form suitable for the second annulation. Specifically, this involves epimerization of the C_9 center. As a simple model we chose the adduct of 59c and piperylene (79). Attempts to epimerize adduct 79 directly by treatment with potassium t-butoxide or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in tetrahydrofuran resulted in formation of an equilibrium between 79 and the enolic tautomer 86 which favored the enol in an 85/15 ratio (as determined by ^{1}H NMR) (Scheme XIX). We postulated that reduction of the free ketone would allow the enol to more readily tautomerize back to the keto form with potential epimerization at the ring junction. However, treatment of enol 86 with sodium borohydride or lithium tri-(t-butoxy)-aluminum hydride returned 86 unchanged. Subsequently, we sought to reverse the order of events in attempting to epimerize the cis ring junction. Reduction of 79 with sodium borohydride afforded two products, the mono-reduced 87 and a bis-alcohol 88 in 50% and 11%, respectively. Lithium tri-(t-butoxy)-aluminum hydride effected only mono-reduction of 79, but it was not chemioselective, producing 87 and 89. Fortuitously, brief treatment of the crude product with ethoxide returned only the conjugated ketone 87 in 68% yield. Longer equilibration of

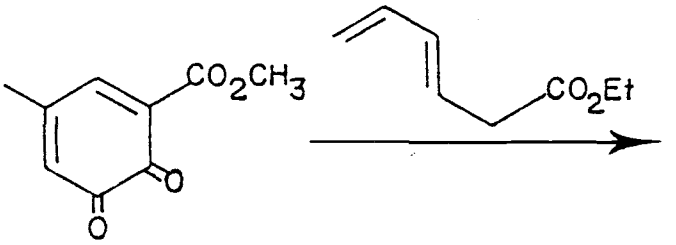


Scheme XIX

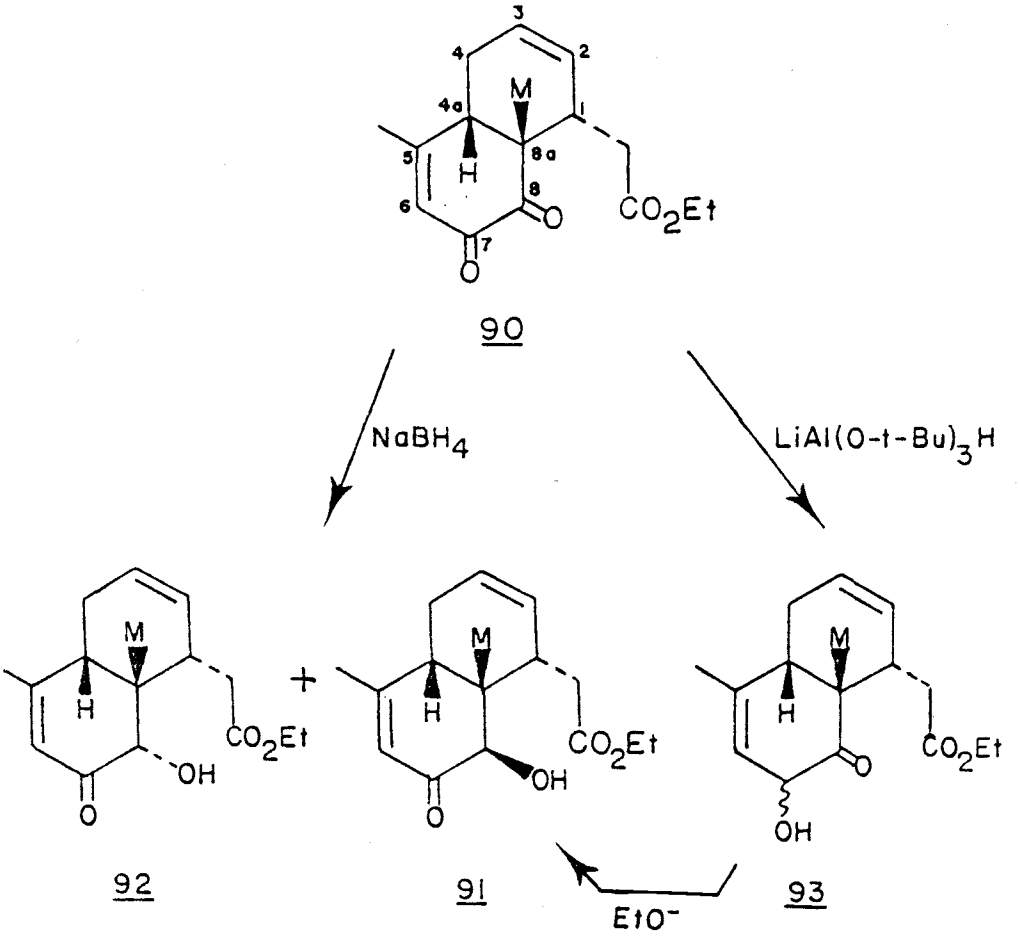
(M = CO_2CH_3)

the alcohol led to decomposition without notable epimerization at the ring junction.

In order to more closely model the natural materials, we decided to synthesize a BCD quassinoid fragment by constructing the δ-lactone moiety. Since treatment of 87 with base under vigorous conditions caused decomposition, potentially through a reverse aldol process, the δ-lactone moiety was postulated as a natural protecting group. Reaction of 59c with ethyl 3,5-hexadienoate[56] produced the adduct 90 in 80% yield. The spectral characteristics of this molecule were virtually indistinguishable from the corresponding data for 79 and 80 indicating the basic structural similarity of these adducts. Reduction of 90 with ethanolic sodium borohydride resulted in a complex mixture containing 90, two conjugated hydroxy ketones, and diols. Preparative chromatography gave 19% and 21% of two hydroxy ketones which were utimately assigned to be the β-hydroxy isomer 91 and the α-hydroxy isomer 92, respectively. A more satisfactory reduction of 90 was again obtained by treatment with lithium tri-(t-butoxy)-aluminum hydride in tetrahydrofuran. The products of this reaction (86%) consisted of 91, 92 and an unconjugated hydroxy ketone 93 of unknown stereochemistry. The assignment of the latter reduction product was made on the basis of the upfield shift of the vinyl methyl group, which now occurred at δ = 1.85 ppm. Significantly however, there was no 90 present and no overreduction to produce diols had occurred. Isomerization of the hydroxy ketone mixture by



59c

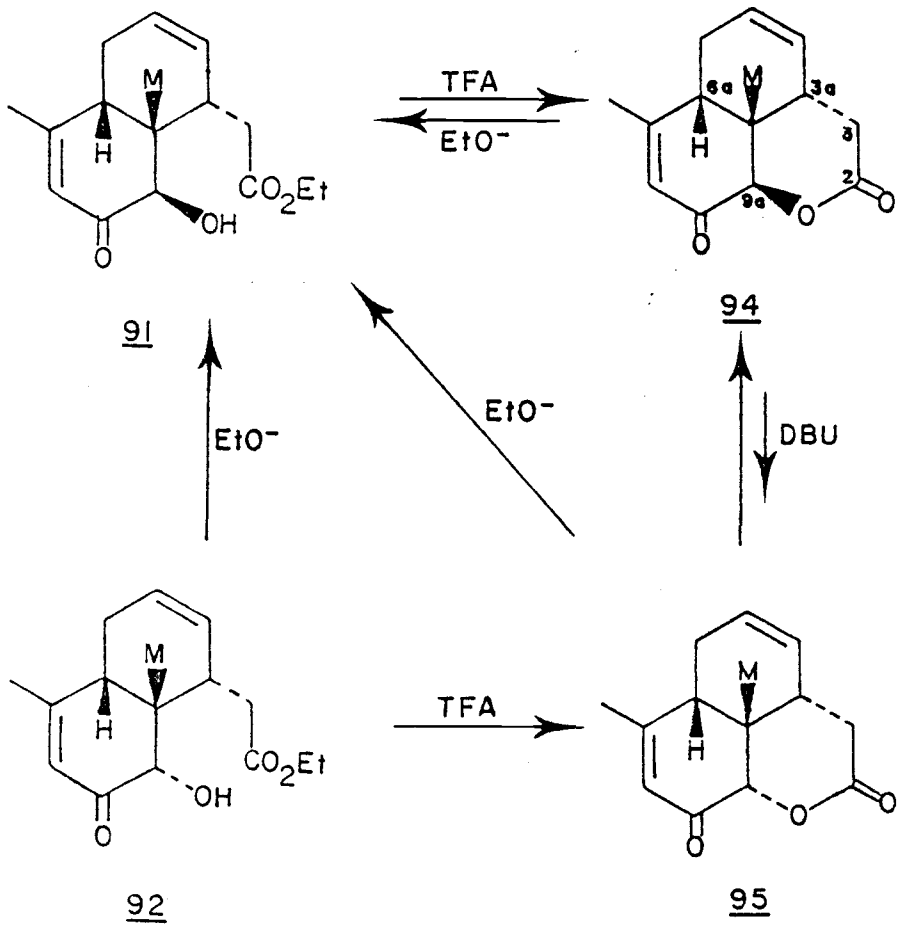


Scheme XX

(M = CO_2CH_3)

brief treatment with sodium ethoxide in ethanol produced a 73% yield of alcohol 91 (63% overall). The regiochemistry of diene addition was now proved by lactonization of 91 and 92 (Scheme XXI). In the case of 92, lactonization to 95 could be achieved with either p-toluenesulfonic acid in refluxing benzene (49%) or using trifluoroacetic acid at 25°C (74%). Cyclization of 91 proceeded only with trifluoroacetic at 25°C giving 95 in 82% yield.

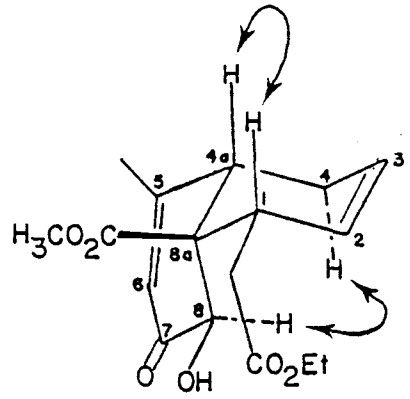
The stereochemistry of these products was established by labeling experiments and ^{1}H NMR. Catechol 69 was treated with 5% sulfuric acid-d_2 in deuterium oxide (at reflux) for five days to yield 69 with greater than 98% deuterium incorporation at C_6 and 93% deuterium at C_4. Esterification using boron trifluoride and methanol-O-d_1 and oxidation as per usual gave labeled 59c. Treatment of 59c-4,6-d_2 with ethyl-3-5-hexadienoate afforded 94-4a,6-d_2. Further treatment of 90-4a,6-d_2 as above produced 91 - 95 with no loss or scrambling of the label at the ring junction or the vinyl position. This indicated that all these materials possess the BC cis ring fusion which was established in the Diels-Alder reaction. That the cycloaddition proceeded with the expected endo stereochemistry was demonstrated by NOE enhancement experiments.[57]. Although the chemical shifts of the H_{6a} and H_{3a} protons of the lactones 94 and 95, and that of the corresponding H_1 and H_{4a} protons of 90 and 92, are too close to observe a meaningful NOE enhancement, the chemical shifts of these protons in 91 are sufficiently separated. Here, a strong enhancement of H_{4a} was



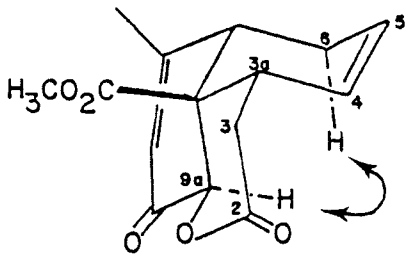
Scheme XXI

observed upon irradiation of H_1 (Figure I). Thus the Diels-Alder reaction of 59c proceeded with the endo orientation to give the correct quassinoid relative configuration at C_1 and C_8 in 90. Due to the similarities in the ^1H NMR spectra of 79 and 80, with that of 90, these adducts are also tentatively assigned the stereochemistry arising from an endo Diels-Alder reaction. The assignment of stereochemistry at C_{8a} of 94 was made on the basis of a strong NOE enhancement between H_{8a} and the pseudoaxial proton at C_4. A similar affect was observed for the lactone to 94. The combined effect of the NOE experiments confirmed the cis nature of the cycloaddition reaction products.

With the relative stereochemistry of the adduct 90, the alcohols 91 and 92 and the lactones 94 and 95 secured, the epimerization of the BC cis ring junction was studied. Epimerization (DBU in tetrahydrofuran or methanol) of 90 yielded only a 9/1 mixture of enolic 96 and 90. Interestingly, in an attempted saponification of the ethyl ester, enolization occurred towards the methyl group rather than the ring junction and gave 97, with undetermined stereochemistry at the ring junction. Alcohol 92 was rapidly converted to 91 by brief treatment with base. Prolonged exposure of either alcohol to base or vigorous conditions caused decomposition as was expected. When 94 or 95 was treated with DBU in tetrahydrofuran-d_6 at 25°C for five minutes, a 2/1 ratio of 94/95 was produced in high yield. Prolonged treatment, or mild heating, did not change this distribution of prod-



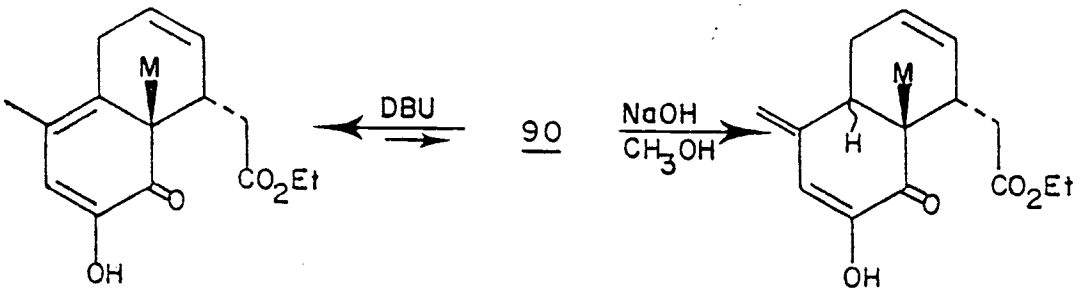
91



94

Figure 1

NOE Relationships in 91 and 94

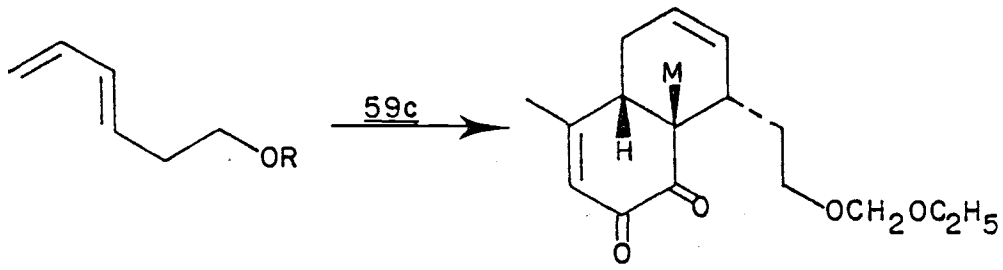


98 97

(M = CO_2CH_3)

ucts and no new isomers appeared. Isomerization of 94 under more vigorous conditions, potassium t-butoxide in t-butanol at 25°C, also produced no new lactones, but the return of material was poor. Attempted heating with this reagent resulted in decomposition of the lactones. The instability of 94 and 95 may arise from a sequence involving lactone ring cleavage by alkoxide or adventitious water, and a retro-aldol reaction of the resulting β-hydroxy ester. The susceptibility of 94 and 95 toward nucleophilic attack was demonstrated by the rapid conversion of both lactones into alcohol 91 by treatment with a catalytic amount of sodium ethoxide in ethanol. In order to establish whether equilibration at C_{6a} had occurred the lactones were subjected to potassium t-butoxide in t-butanol-o-d_1. While greater than 95% of H_{9a} was exchanged for deuterium, no incorporation of deuterium into C_{6a} or the vinylic methyl was noted. Additionally, treatment of 94-6a,8-d_2 (*vida supra*) with DBU in tetrahydrofuran at 65°C caused no scrambling of the label. Further, no exchange at C_{6a} was observed with potassium t-butoxide in t-butanol/tetrahydrofuran.

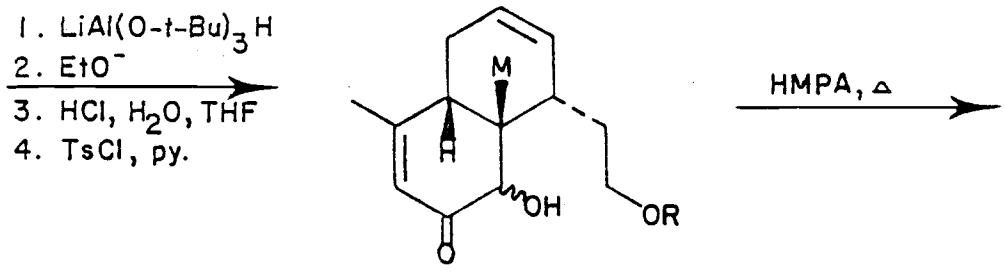
Although no equilibration of C_{6a} was observed for 94 and 95, the instability of the lactone had prohibited the use of vigorous isomerization conditions. In order to remove this constraint, the ethers 104 and 105 were prepared (Scheme XXII). Ethyl 3,5-hexadienoate was reduced with lithium aluminum hydride and the resulting alcohol 98 was protected as its ethoxymethyl ether, to give 99[58]. When reacted



98 R = H

99 R = $CH_2OC_2H_5$

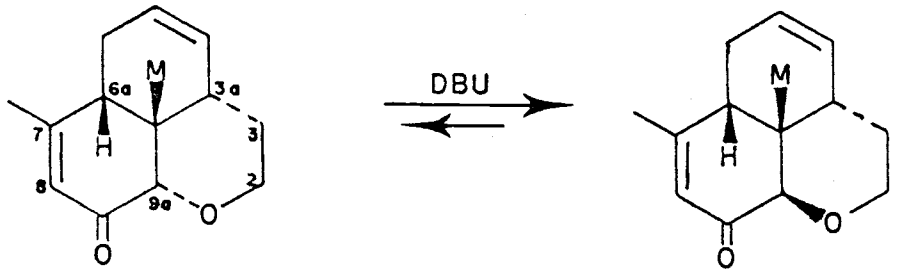
100



101 R = $CH_2OC_2H_5$, a =  , b = 

102 R = H

103 R = Ts



104

105

Scheme XXII

(M = CO_2CH_3)

with o-quinone 59c, this diene afforded a single adduct 100 in 50% yield. Reduction of 100 with lithium tri-(t-butoxy)-aluminum hydride and isomerization by brief treatment with sodium ethoxide in ethanol gave a 58% yield of alcohols 101. Treatment of 101 with 0.5 N hydrochloric acid in tetrahydrofuran produced the diols 102. These diols were immediately tosylated to 103, and heated in hexamethylphosphoramide at 80°C[16] to produce the tricyclic ethers 104 and 105, which were readily separable by chromatogrohy. Assignment of conformation of the molecules was made on the basis of decoupling and NOE difference experiments in the 360 MHz ^1H NMR, wherein the ethers 104 and 105 showed close analogy to the lactones 94 and 95.

Treatment of either ether with sodium methoxide in methanol rapidly produced a mixture of 105 and 104 (6/1). The use of methanol-O-d_1 for this isomerization led to rapid incorporation of deuterium into C_{9a} and the vinyl methyl at C_7. After 72 hours at 25°C approximately 50% exchange was observed at C_8, however no exchange at C_{6a} was found. Again, heating in base led to decomposition of the system. Similar results were observed for potassium t-butoxide in t-butanol-O-d_1. The failure to achieve equilibration at C_6 is apparently due to the reluctance of the molecule to incorporate an additional sp^2 carbon at this position. Models show that the resulting enolate can only adopt the required planar conformation at the expense of severe angle strain in the remaining carbons of the C-ring. The facile equilibration at C_{9a} is possible since, in that

enolate intermediate, the coplanarity of the enolate and the α,β - unsaturation is not required.

In conclusion, the 3,5-disubstituted o-quinones 59a and 59c undergo high yield addition of useful dienes preferentially or exclusively at the 3,4-position. The reaction requires only small excesses of diene. The 4-chloro-3,5-disubstituted o-quinones 59b and 59d are much less dienophilic. While preferential addition to the 5,6-position does occur, the Diels-Alder reactions of these quinones are accompanied by numerous side reactions, and decomposition. It was not possible to isomerize the 3,4-addition products of 59c (90, 94, 95, 104 and 105) into the desired trans-fused ring systems. In order to achieve this isomerization, it will be necessary to alter the conformational preferences of the system. Formation of the E ring ether bridge would force the BC ring fusion into the trans configuration. Early incorporation of this structural feature at a stage where ring junction equilibration is facile appears then as the most useful strategy for the future.

D. EXPERIMENTAL

Low resolution mass spectrometry was performed on a Varian MAT CH-7 or a Finnigan 4320. Infrared spectra were recorded on Perkin-Elmer spectrophotometers, Model 727B and Model 137. Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. ^{1}H NMR analyses were performed on Varian spectrometers, Model FT-80, Model HA-100, or Model EM-360. High resolution ^{1}H NMR spectra were obtained on a Nicolet 360 MHz instrument at the University of Oregon. Chemical shifts (δ) are reported as parts per million downfield from tetramethylsilane as internal standard. High resolution mass spectra were obtained on a CEC-103B mass spectrometer by Richard Wielesek at the University of Oregon Micro-Analytical Lab. Combustion analyses were performed by Richard Wielesek at the University of Oregon Micro-Analytical Lab and by MicAnal, Tucson, AZ.

6-Bromo-2,4-dimethylphenol (65).

To a solution of 30.0 g (0.25 mol) of phenol 62 in 125 mL of DMF, a solution of 43.8 g (0.25 mol) of N-bromosuccinimide in 125 mL of DMF was added dropwise. The mixture was stirred for 1 d then poured into 1500 mL of H_2O. The aqueous solution was extracted with 5% benzene/hexane, the extracts combined, washed with H_2O and brine and dried ($MgSO_4$). The solvent was removed and the residue distilled (5.5 torr, 85-90°C, lit[59] 24 torr, 135-7°C) to afford 43.0 g (87%) of

the bromophenol 65 as an oil: MS m/z 200 (M+), 202 (M+2), 121 (100); IR (thin film) 3550, 1485, cm^{-1}; ^1H NMR ($CDCl_3$) δ = 7.25 (1H, s), 7.01 (1H,s), 5.53 (1H, OH), 2.41 (3H, s), 2.38 (3H, s).

3,5-Dimethyl-1,2-benzenediol (64).

A solution of 300 g (7.5 mol) of NaOH in 3000 mL of H_2O was stirred under reduced pressure (aspirator) for 1.5 h. Then, 2 g of $CuSO_4$ was added to the solution and stirring under reduced pressure was continued for an additional 15 min. The aqueous solution was transferred by cannula to a 5 L flask containing 55.6 g (0.28 mol) of the bromophenol 65. The resulting solution was refluxed for 6 h, cooled and acidified with HCl. The aqueous mixture was extracted with ether, the ethereal extracts were combined and washed with brine, dried (Na_2SO_4), and evaporated to provide 28.09 g (73.5%) of a crude solid. Short path distillation (1 torr, 110°C, lit[44a] 12 torr, 134-135°C) and recrystallization (hexane/toluene) afforded pure 64: mp 69.5-71°C (lit[44a] mp 71°C); MS m/z 138 (M+, 100), 123; IR (KBr) 3470, 3300, 1610, 1520, cm^{-1}; ^1H NMR ($CDCl_3$) δ = 6.67 (2H, s), 2.37 (6H, s).

3,5-Dimethyl-3,5-cyclohexadiene-1,2-dione (59a).

As previously described by Ansel[44a], 1.02 g (7.39 mmol) of catechol 64 was treated with 1.95 g (7.96 mmol) of o-chloranil in 70 mL

of ether and produced 0.97 g (96%) of the desired o-quinone 59a: ^1H NMR ($CDCl_3$) δ = 6.66 (1H, br s), 6.15 (1H, br s), 2.14 (3H, d, J = 1 Hz), 1.99 (3H, s).

2,3-Dihydroxy-5-methylbenzoic acid (68).

By the procedure described above for the preparation of 64, 30.2 g (0.13 mol) of 67[60], 252 g (6.3 mol) of NaOH and 2 g of $CuSO_4$ in 3000 mL of H_2O gave 20.1 g (92%) of the crude dihydroxybenzoic acid, which was not purified but further reacted directly. Purification could be accomplished by sublimation (100°C at 0.25 torr): mp 204-205°C (lit[61] mp, 204°C); MS m/z 168 (M+), 150 (100); IR (KBr) 3520, 3300-2400, 1670, 1620 cm^{-1}; ^1H NMR ($CDCl_3$ with trace d_6-DMSO) δ = 7.34 (1H, br s), 7.05 (1H, d,J = 2 Hz), 2.40 (3H, s).

2,3-Dihydroxy-5-methylbenzoic acid, methyl ester (69).

To a solution of 20.1 g (0.12 mol) of 68 in 360 mL of MeOH was added 28.6 mL (0.238 mol) of $BF_3 \cdot Et_2O$ and the resulting mixture heated at reflux for 4 h. Aqueous $NaHCO_3$ was added to the reaction mixture until the pH of the aqueous layer was 6, then the mixture was further diluted with H_2O and extracted with ether. The combined ethereal extracts were washed with saturated brine, dried ($MgSO_4$) and evaporated to give 18.0 g (80%) of a crude solid which was recrystallized from 20% MeOH/H_2O to yield 17.0 g (75%) of the catechol ester

69: mp 99-100°C; MS m/z 182 (M+), 150 (100); IR (KBr) 3360, 1665, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 7.19 (1H, s), 6.96 (1H, s), 5.64 (2H, s, OH), 3.96 (3H, s), 2.28 (3H, s).

Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.35; H, 5.41.

3-Methyl-5,6-dioxo-1,3-cyclohexadienecarboxylic acid, methyl ester (59c).

To a solution of 1.03 g (5.66 mmol) of catechol 69 in ether (75 mL) was added 6.06 g (26.1 mmol) of Ag_2O and 5.01 g of Na_2SO_4. The heterogeneous solution was vigorously stirred for 20 min, filtered and the solid Ag_2O washed extensively with ether. The combined ether solutions returned 0.87 g (85%) of the desired quinone 59c as a red-green solid which was used immediately: MS m/z (M^+), 121 (100), 65, 39, IR (KBr) 1690, 1630; ^1H NMR ($CDCl_3$) δ = 7.64 (1H, d, J = 2 Hz), 6.44 (1H, s), 3.90 (3H, s), 2.29 (3H, d, J = 2 Hz).

Anal. Calcd for $C_9H_8O_4$: Mol wt, 180.042. Found: mol wt, 180.043.

4-Chloro-3,5-dimethyl-1,2-benzenediol (70) and 4-Chloro-3,5-dimethyl-3,5-cyclohexadiene-1,2-dione (59b).

A solution of 1.64 g (1.21 mmol) of 59a in 15 mL dry benzene was added to 150 mL of 0.3M HCl in anhydrous isopropanol. The resulting solution was vigorously stirred for 5 min during which time the color

of the solution changed from red to light yellow. The volume of the solution was reduced to 15 mL by evaporation and diluted with 100 mL of ether. The ethereal solution was washed with water and brine, then dried ($MgSO_4$). Removal of the solvent afforded 2.08 g (100%) of the crude chlorocatechol 70. The crude product was purified by column chromatography with silica gel (4% acetone/$CHCl_3$) which yielded 1.72 g (83%) of pure chlorocatechol70: mp 83.5-84.5°C; MS m/z, 172 (174) (M+), 137 (100); IR (KBr) 3300 (br), 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 6.43 (1H, s), 2.33 (3H, s), 2.29 (3H, s).

Anal. Calcd for $C_8H_9ClO_2$: Mol wt, 172.029. Found: Mol wt, 172.028.

As was previously descirbed for the preparation of carbomethoxy-o-quinine 59c, 0.92 g (5.23 mmol) of the chlorocatechol 70 was treated with 6.27 g (27.0 mmol) of Ag_2O and 6.00 g of Na_2SO_4 to produce 0.73 g (80%) of chloroquinone 59b as red solid. The product was not purified and was used immediately: MS m/z 170 (M^+), 172 (M+2, 100), 174 (M+4); IR (KBr) 1740, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 6.27 (1H, broad m), 2.29 (3H, d, J = 1.5 Hz), 2.14 (3H, s).

Anal. Calcd for $C_8H_7ClO_2$: Mol wt, 170.013. Found: Mol wt, 170.013.

6-Chloro-2,3-dihydroxy-5-methylbenzoic acid, methyl ester, (71) and 2-Chloro-3-methyl-5,6-dioxo-1,3-cyclohexadienecarboxylic acid, methyl ester (59d).

As previously desribed for the preparation of the chlorodimethylcatechol 70, 1.75 g (9.7 mmol) of quinone 59c in 15 mL of benzene was added to 80 mL of 0.25M HCl in isopropanol and produced 2.10 g (100%) of a crude solid. Chromatography of silica gel with 5% acetone/$CHCl_3$ afforded 1.27 g (60%) of pure chlorocatechol 71: mp 75-77°C; MS m/z 216 (M^+) 218 (M+2), 182 (100); IR (KBr) 3440, 1710, 785 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 6.99 (1H, s), 4.03 (3H, s), 2.31 (3H, s).

Anal. Calcd for $C_9H_9ClO_4$: Mol wt, 216.019. Found: Mol wt, 216.019.

As was previously described for the oxidation of 70, 0.88 g (4.62 mmol) of the chlorocatechol 71 was reacted with 5.27 g (22.7 mmol) of Ag_2O in the presence of 4.30 g of Na_2SO_4 and gave 0.76 (87%) of the desired chloroquinone 59d which was not purified but used immediately: MS m/z 214 (M^+), 216 (M+2), 184, 134; IR (neat) 1770, 1940, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 6.44 (1H, d, J = 2 Hz), 3.93 (3H, s), 2.31 (3H, d, J = 2 Hz).

Anal. Calcd for $C_9H_7ClO_4$: Mol wt, 214.003. Found: Mol wt, 214.004.

Diels-Alder Reactions of Quinones 59a-d with Dienes.

To a solution of the quinone in chloroform (35% w/v) was added 200-350 mole % of the diene. The reaction was stirred in the dark for the indicated number of hours, then worked up by evaporation and chromatography.

4a,5,8,8a-Tetrahydro-4,6,7,8a-tetramethylnaphthalene-1,2-dione, (72).

From 59a and dimethylbutadiene 60 (300 mol %, 14 h, 77%). Purified on silica using 5% acetone/$CHCl_3$ to give an oil which by ^1H NMR appeared to be only the 3,4 addition product 72[62]: ^1H NMR ($CDCl_3$) δ = 6.26 (1H, d, J = 1 Hz), 2.18 (3H, d, J = 1 Hz), 1.67 (3H, s), 1.60 (3H, s), 1.30 (3H, s); IR (neat) 1730, 1675 cm^{-1}; MS m/z 218 (M^+), 190, 175 (100).

Anal. Calcd for $C_{14}H_{18}O_2$: Mol wt, 218.131. Found: Mol wt, 218.130.

4a,5,8a-Tetrahydro-4,8,8a-trimethylnaphthalene-1,2-dione (74) and 4a,5,8,8a-Tetrahydro-3,4a,8-trimethylnaphthalene-1,2-dione, (75).

From 59a and 61a (300 mol %, 14 h, 67%). Purified by chromatography (SiO_2, $CHCl_3$) to give an oil containing both the 3,4 and 5,6 adducts which could not be sepearted: MS m/z 204 (M^+, 100); IR (neat) 1730, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) major isomer (3,4) δ = 6.19 (1H, s), 5.62 (2H, s), 2.18 (3H, d, J = 1 Hz), 1.44 (3H, s), 1.33

(3H, d, J = 7 Hz); minor isomer (5,6) δ = 6.36 (1H, s), 1.94 (3H, br s), 0.63 (3H,d). The ratio of the isomers is 88/12.

Anal. Calcd for $C_{13}H_{16}O_2$: Mol wt, 204.115. Found: Mol wt, 204.115.

6-Acetoxy-4a,5,8,8a-tetrahydro-4,8,8a-trimethylnaphthalene-1,2-dione (76) and 6-Acetoxy-4a,5,8,8a-tetrahydro-3,4a,8-trimethylnaphthalene-1,2-dione, (77.)

From 59a and 61b[47] (320 mol %, 14 h, 76%). Purified by chromatography (5% acetone/$CHCl_3$) as a mixture. MS m/z (M^+), 151 (100); IR (neat) 1750, 1670, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) major isomer (3,4) δ = 6.22 (1H, d, J = 1 Hz), 5.39 (1H, br s), 2.17 (3H, d, J = 1 Hz), 2.10 (3H, s), 1.44 (3H, s), 1.33 (3H, d, J = 8 Hz); minor isomer (5,6) δ = 6.36 (1H, s), 5.48 (1H, m), 1.93 (3H, s), 1.36 (3H, s), 0.65 (3H, d, J = 7 Hz). The ratio is 84/16.

Anal. Calcd for $C_{15}H_{18}O_4$: Mol wt, 262.121. Found: Mol wt, 262.121.

1,8a-Dihydro-5,6-dioxo-2,3,8-trimethylnaphthalene-4a(4H)-carboxylic acid, methyl ester, (78).

1) Using prepared quinone. From 59c and 60 (240 mol %, 14 h, 38%). The crude product was chromatographed on silica, eluting with 3% $CH_3OH/CHCl_3$, then recrystallized using 20% toluene/hexane: mp 85-86°C; MS m/z 262 (M^+), 69 (100); IR (neat) 1730, 1680, 1620 cm^{-1}; ^1H

NMR ($CDCl_3$) δ = 6.22 (1H, br s), 3.78 (3H, s), 2.21 (3H, d, J = 1 Hz), 1.71 (3H, s), 1.59 (3H,s).

Anal. Calcd for $C_{15}H_{18}O_4$: Mol wt, 262.121. Found: Mol wt, 262.120.

2) Diels-Alder with in situ oxidation of catechol. At room temperature, 3.10 g (13.4 mmol) of Ag_2O and 3.07 g of Na_2SO_4 were added to an ether (50 mL) solution of 0.57 g of 70 (3.13 mmol). To this resulting mixture, 0.70 mL (0.51 g, 6.2 mmol) of 2,3-dimethyl-1,3-butadiene 60 was added. The reaction solution was stirred in darkness for 2.75 h. The solid was removed by filtration and washed with 15 mL of $CHCl_3$. The organic solutions were combined and to this resulting solution, an additional 0.50 mL (0.36 g, 4.4 mmol) of diene 60 was added. The solution was stirred in darkness overnight, then the solvent and diene were removed in vacuo and the residue column chromatographed as above to produce 0.38 g (46%) of adduct 78.

1,8a-Dihydro-4,8-dimethyl-5,6-dioxonaphthalene-4a(4H)-carboxylic acid, methyl ester, (79).

From 59c and 61a (250 mol %, 3 h, 87%). Chromatography on silica, using 5% acetone/$CHCl_3$, and recrystallization (30% toluene/hexane) furnished a yellow green crystalline solid mp 104-105°C; MS m/z 248 (M^+), 161 (100); IR (neat) 1775, 1755, 1705, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 6.19 (1H, s), 5.70 (2H, br s), 3.80 (3H, s), 2.25 (3H, d, J = 1 Hz), 1.35 (3H, d J = 7 Hz).

Anal. Calcd for $C_{14}H_{16}O_4$: Mol wt, 248.105. Found: Mol wt, 248.104.

2-Acetoxy-1,8a-dihydro-4,8-dimethyl-5,6-dioxonaphthalene-4a(4H)-carboxylic-acid, methyl ester, (80).

From 59c and 61b[47] (310 mol %, 14 h, 85%). The product was purified by chromatography (SiO_2, 4% acetone/$CHCl_3$) and recrystallization from 40% toluene/hexane: mp 116-118°C; MS m/z 306 (M^+), 43 (100); IR ($CHCl_3$) 1770, 1710, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 6.16 (1H, br s), 5.48 (1H, br s), 3.73 (3H, s), 2.14 (3H, d, J = 1.5 Hz), 2.09 (3H, s), 1.32 (3H, d, J = 9 Hz).

Anal. Calcd for $C_{16}H_{18}O_6$: Mol wt, 306.110. Found: Mol wt, 306.111.

4-Chloro-5,8-dihydro-1-hydroxy-3,4a,6,7-tetramethylnaphthalene-2(4aH)-one (81).

From 59b and 60 (290 mol %, 28 h, 27%) and purified on silica using 25% hexane/$CHCl_3$: MS m/z 252 (M^+), 254 (M+2) 31 (100); IR (neat) 3405, 1740, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 6.45 (OH, s), 2.10 (3H, s), 1.75 (3H, s), 1.68 (3H, s), 1.37 (3H, s).

Anal. Calcd for $C_{14}H_{17}O_2Cl$: Mol wt, 252.092. Found: Mol wt, 252.091.

4-Chloro-5,8-dihydro-1-hydroxy-3,4a,8-trimethylnaphthalene-2(4aH)-one (82) and 6-Chloro-1,5-dimethyl-7-(1-E-propenyl)-bicyclo[2.2.2]octa-2,3-dione (83).

From 59b and 61a (300 mol %, 28 h, 93% crude yield). Separation of the components was effected by chromatography on silica ($CHCl_3$) and afforded 0.06 g (7%) of the desired 5,6 adduct 82 and 0.42 g (50%) of the reverse role adduct 83. (5,6 adduct 82): R_f ($CHCl_3$) = 0.40; UV (MeOH) λ_{max} = 286 nm (ε = 1300); MS m/z 238 (M^+), 240 (M+2), 209 (100); IR (thin film) 3460, 1740, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 6.53 (OH, s), 5.74 (2H, br s), 2.13 (3H,s), 1.32 (3H,s), 0.71 (3H, d, J = 7 Hz).

Anal. Calcd for $C_{13}H_{15}ClO_2$: Mol wt, 238.076. Found: Mol wt, 238.076.

83: Recrystallization from hexane gave mp 97-8°; R_f ($CHCl_3$) = 0.25; UV (MeOH) λ_{max} = 314 nm (ε = 85); MS m/z 238 (M^+), 240 (M+2), 184, 182, 169, 167, 147, (100), 119, 105, 91; IR (KBr) 2980, 1725, 1630, 1450, 995, cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ = 5.51 (1H, dq, J = 15, 6.5 Hz), 5.13 (1H, ddq, J = 15, 9.7, 1.8 Hz), 3.37 (1H, t, J = 2.9 Hz), 2.54 (1H, dt, J = 4.7, 9.7 Hz), 2.34 (1H, ddd, J = 15, 9.7, 2.9 Hz), 2.04 (3H, s), 1.79 (3H, dd, J = 6.5, 1.8 Hz), 1.65 (1H, m), 1.28 (3H, s); ^{13}C NMR ($CDCl_3$) δ = 190, 189, 135, 130, 129, 128, 57, 54, 44, 31, 18, 17, 14.

Anal. Calcd for $C_{13}H_{15}O_2Cl$: Mol wt, 238.076. Found: Mol wt, 238.076.

6-Acetoxy-4-chloro-5,8-dihydro-1-hydroxy-3,4a,8-trimethylnaphthalene-2(4aH)-one, (84).

From 59b and 61b[47] (290 mol%, 120 h, 13%). The residue was chromatographed on silica with $CHCl_3$ and afforded an oil: UV (MeOH) λ_{max} = 256 nm (δ = 10,000), 305 nm (δ = 3,800); MS m/z 296 (M^+), 43 (100); IR (neat) 3540, 1760, 1700, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 6.84 (OH, s), 5.40 (1H, m), 2.15 (3H, s), 2.10 (3H, s), 1.55 (3H, d, J = 6 Hz), 1.52 (3H, s).

Anal. Calcd for $C_{15}H_{17}ClO_4$: Mol wt, 296.082. Found: Mol wt, 296.082.

1-Chloro-8,8a-dihydro-4-hydroxy-3(5H)-oxo-6,7,8a-trimethylnaphthalene-2-carboxylic acid, methyl ester, (85).

From 59d and 60 (300 mol%, 14 h, 72%). The residue was chromatographed on silica with 5% acetone/$CHCl_3$: MS m/z 296 (M^+), 298 (M+2), 249 (100); IR (neat) 3450, 1750, 640, cm^{-1}; ^1H NMR ($CDCl_3$) δ = 6.33 (OH, s), 3.91 (3H, s), 1.84 (3H, s), 1.68 (3H, s), 1.43 (3H, s).

Anal. Calcd for $C_{15}H_{17}ClO_4$: Mol wt, 296.082. Found: Mol wt, 296.081.

1-Chloro-8,8a-dihydro-5,8a-dimethyl-4-hydroxy-3(5H)-oxonaphthalene-2-carboxylic acid, methyl ester, (86).

From 51d to 61a (290 mol%, 14h, 19%). Flash chromatography on silica ($CHCl_3$) afforded the adduct 86: MS m/z 282 (M^+), 284 (M+2),

250 (100); IR (thin film) 3450, 1745, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 6.36 (OH, br s), 5.73 (2H, br s), 3.93 (3H, s), 1.52 (3H, s), 0.75 (3H, d, J = 7 Hz).

Anal. Calcd for $C_{14}H_{15}ClO_4$: Mol wt, 282.066. Found: Mol wt, 282.067.

Reaction of 59d with 61b.

From 59d and 61b[47] (300 mol%, 14 h). The product was chromatographed on silica ($CHCl_3$) to give two fractions with yields of 0.07 g (7%) and 0.12 g (12%). The former was a two component mixture of a 5,6 adduct and a 3,4 adduct while the latter contained only a 5,6 adduct. (First fraction): R_f ($CHCl_3$) = 0.44; MS m/z 340 (M^+), 342 (M+2), 43 (100); IR (neat) 3430, 1750, 1690, 1620 cm^{-1}; (5,6 adduct): ^1H NMR ($CDCl_3$) δ = 6.71 (OH, br s), 3.93 (3H, s), 2.17 (3H, s), 1.61 (3H, s), 1.54 (3H, d, J = 7 Hz); (3,4 adduct) δ = 6.16 (1H, d, J = 1.5 Hz), 5.48 (1H, br s), 3.86 (3H, s), 2.18 (3H, d, J = 1.5 Hz), 1.34 (3H, d, J = 6.5 Hz).

Anal. Calcd for $C_{16}H_{17}ClO_6$: Mol wt, 340.071. Found: Mol wt, 340.069.

Second Fraction: (5,6 adduct): R_f ($CHCl_3$) = 0.36; MS m/z 340 (M^+), 342 (M+2), 69 (100), 43; IR (neat) 3430, 1750, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 6.53 (OH, s), 5.53 (1H, d), 3.92 (3H, s), 2.17 (3H, s), 1.63 (3H, s), 0.80 (3H, d, J = 6 Hz).

Anal. Calcd for $C_{16}H_{17}ClO_6$: Mol wt, 340.071. Found: Mol wt, 340.069.

4,8-Dimethyl-6-hydroxy-5(1H)-oxonaphthalene-4a(4H)-carboxylic acid, methyl ester, (86).

Bu^tOK (0.2 mL, 0.83 M, 0.16 mmoles) was slowly added to a stirred solution of 0.20 g (0.18 mmoles) of adduct 79 in 3 mL of THF. After 3.5 hr at room temperature, the reaction was diluted with ether, washed with aq. $NaHCO_3$, then with brine and finally dried (Na_2SO_4). Removal of solvent produced 0.18 g (90%) of a crude red-brown solid which had an approximate composition of 85/15 86/79 (determined by 60 MHz ^1H NMR). Chromatography on silica eluting with 5% acetone/$CHCl_3$ afforded a small amount of enol 86 as a light brown solid which was futher purified by recrystalization using toluene/hexane: mp 163-164°C; MS m/z 248 (M^+), 189, 171 (100), 143; ^1H NMR ($CDCl_3$) δ = 6.41 (1H, s), 6.18-5.47 (3H, m, loss of 1H with D_2O), 3.66 (3H, s), 2.02 (3H, d, J = 2 Hz), 0.71 (3H, d, J = 7 Hz); IR ($CHCl_3$) 3490, 1750, 1660, 1590, 1430, 1230 cm^{-1}.

Anal. Calcd for $C_{14}H_{16}O_4$: Mol wt; 248.105. Found: Mol wt, 248.104.

4,8-dimethyl-5-hydroxy-6(5H)-oxonaphthalene-4a(4H)-carboxcylic acid, methyl ester, (87).

To a solution of 0.20 g (0.18 mmoles) of adduct 79 in 3 mL of ethanol was added 10.7 mg (0.40 mmoles) of sodium borohydride. After

being stirred for 0.5h, the solution was poured into H_2O and the aqueous solution extracted with ether. The combined ethereal extracts were washed with aq. $NaHCO_3$, water and brine, then dried (Na_2SO_4). Evaporation of the solvent afforded a greasy solid which was a two component mixture as shown by TLC (5% acetone/$CHCl_3$). Preparative TLC, eluting with 5% acetone/$CHCl_3$, afforded 43.5 mg (48%) of enone 87 and 11.8 mg (13%) of diol 88. Enone 87 could be isolated directly from the crude reaction mixture by recrystallization using 20% hexane/toluene. 87: mp 156.5-157.5°C; MS m/z 250 (M^+), 110 (100), ^1H NMR ($CDCl_3$) δ = 5.92 (1H, s), 5.69 (2H, s), 4.66 (1H, s), 3.72 (3H, s), 2.04 (3H, s), 1.09 (3H, d, J = 7.5 Hz); IR ($CHCl_3$) 3530, 2960, 1720, 1680, 1630, cm^{-1}.

Anal. Calcd for $C_{14}H_{18}O_4$: Mol wt, 250.121. Found: Mol wt, 250.121.

Compound 88: mp 87-90.5°C; MS m/z 252 (M^+), 175 (100); ^1H NMR ($CDCl_3$) δ = 5.9-5.3 (3H, m), 4.6 (1H, s), 3.7 (3H, s), 1.7 (3H, d, J = 7Hz); IR ($CHCl_3$) 3400 (br), 2950, 1710 1670 cm^{-1}.

Anal. Calcd for $C_{14}H_{20}O_4$: Mol wt, 252.136. Found: Mol wt, 252.136.

8a-Carbomethoxy-4,8-dioxo-5-methyl-1,4,4a,8a-tetrahydronaphthalene-1-acetic acid, ethyl ester (90).

To a solution of 1.89 g (10.5 mmol) of 59c in 4 mL of $CHCl_3$ was added 2.53 g (18.1 mmol) of ethyl 3,5-hexadienoate[56]. The solution

was stirred overnight in darkness. The solvent was removed and 0.92 g of excess diene was recovered by short path distillation (80-100°C/5 torr). The residue was flash chromatographed on silica (4% acetone/$CHCl_3$) and afforded 2.41 g (74%) of the adduct 90 as a yellow solid. Recrystallization with toluene/hexane (1/2) gave: mp 101-102.5°C; UV (MeOH) λ_{max} = 264 nm (ε = 4600); MS m/z 320 (M^+), 215 (100); IR ($CHCl_3$) 1735, 1685, 1620 cm^{-1}; ^1H NMR ($CHCl_3$, 360 MHz) δ = 6.14 (1H, d, J = 1.8 Hz), 5.65 (2H, m), 4.12 (2H, dq, J = 6.8, 4.0 Hz), 3.70 (3H, s), 3.27 (1H, dd, J = 12.6, 6.5 Hz), 3.16 (1H, m), 3.03 (1H, dd, J = 17.0, 10.2 Hz), 2.70 (1H, m), 2.56 (1H, dd, J = 17.0, 4.3 Hz), 2.16 (3H, d, J = 1.8 Hz), 1.75 (1H, m), 1.24 (3H, t, J = 6.8 Hz).

Anal. Calcd for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29. Found: C, 63.32; H, 6.00.

8a-Carbomethoxy-7-hydroxy-5-methyl-8(8aH)-oxo-1,4-dihydronaphthalene-1-acetic acid, ethyl ester (96).

To a solution of 196 mg (0.61 mmol) of 90 in 3 mL of THF was added 0.19 mL (1.57M, 0.30 mmol) of potassium t-butoxide in t-butanol. After 19 h, the solution was diluted with ether and poured into 2% aq $NaHCO_3$. The layers were separated and the aqueous solution was further extracted with ether. The combined ethereal solutions were washed with brine, dried (Na_2SO_4) and evaporated to give 150 mg (76%) of a 9/1 mixture of 96/90. Chromatography on silica gel

(5% acetone/$CHCl_3$) and recrystallization (25% toluene/hexane) gave 96: mp 129-131°C; UV (MeOH) λ_{max} = 365 nm (ε = 3200), (MeOH, with 2 drops 4N aq NaOH) λ_{max} = 410 (ε = 3200); MS m/z: 320 (M^+), 187 (100): IR (neat) 3420, 1735, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 6.42 (1H, s), 6.14-5.57 (2H, m), 4.10 (2H, q, J = 7 Hz), 3.66 (3H, s), 1.98 (3H, d, J = 1 Hz), 1.23 (3H, t, J = 7 Hz).

Anal. Calcd for $C_{17}H_{20}O_6$: Mol wt, 320.126. Found: Mol wt, 320.127.

8a-Carbomethoxy-7-hydroxy-5(4aH)-methylene-8(8aH)-oxo-1,4-dihydronaphthalene-1-acetic acid, (97).

To a solution of 0.23 g (0.72 mmoles) of 90 in 10 mL of MeOH was added 4 mL of 2N aq. NaOH. After stirring for 2 h at room temperature, an additional 6 mL of 2N aq. NaOH was added to the reaction solution. The stirring was continued for another 2h. The reaction solution was acidified, then extracted with ether. The combined extracts were washed with brine, then dried (Na_2SO_4). Evaporation of solvent afforded 0.14 g (67%) of 97 as a crude solid. Further purification was effected by recrystallization of 97 from toluene/hexane: mp 163-165°C, MS m/z 292 (M^+), 91 (100); IR (KBr) 3520, 3400-2500, 1740, 1720, 1680, 880 cm^{-1}; ^1H NMR ($CDCl_3$ and d_6-DMSO) δ = 6.13 (1H, br s), 5.57 (2H, m), 5.02 (2H, m), 3.67 (3H, s), 3.55 - 2.13 (6H, m).

Anal. Calcd for $C_{15}H_{16}O_6$: Mol wt, 292.095. Found: Mol wt, 292.096.

8a-Carbomethoxy-8α-hydroxy-5-methyl-7(4H)-oxo-1,4,8,8a-tetrahydronaphthalene-1-acetic acid, ethyl ester (91); 8a-carbomethoxy-8β-hydroxy-5-methyl-1,4,8,8a-tetrahydronaphthalene-1-acetic acid, ethyl ester (92).

At room temperature, 0.22 g (5.87 mmol) of $NaBH_4$ was added in six batches over 10-15 min to a solution of 5.09 g (15.9 mmol) of 90 in 50 mL of THF and 25 mL of EtOH. The solution was stirred an additional 5 min and poured into dilute aq HOAc and extracted with ether. After washing with aq $NaHCO_3$, H_2O, brine and drying (Na_2SO_4), the solvent was removed to furnish 4.87 g (95%) of a semi-solid which was flash chromatographed on silica gel (5% acetone/$CHCl_3$). The first fraction, 2.19 g (43%) contained unreacted 90 and considerable amounts of reduced materials. The second fraction, 1.55 g (30%), contained both hydroxy ketones and a mixture of diols. The third fraction, 0.58 (11%) contained only a mixture of diols as an oil (total recovery, 4.32 g, 84%). The first two fractions were further chromatographed (SiO_2, 2% acetone/$CHCl_3$) using an LC 500 HPLC system. From an initial 3.91 g, 0.41 g of 90, 1.11 g of alcohol 92 and 1.30 g of alcohol 91 were recovered (total recovery from HPLC, 82%). Recrystallization from toluene/hexane afforded 0.97 g (19%) of the alcohol 91: R_f (5% acetone/$CHCl_3$) = 0.36; mp 144-145°C; MS m/z 322 (M^+), 217 (100); IR($CHCl_3$) 3530, 1725, 1680, 1620 cm^{-1}; ^1H NMR

($CDCl_3$, 360 MHz) δ = 5.85 (2H, m) 5.68 (1H, dt, J = 10, 2 Hz), 4.42 (1H, d, J = 5.7 Hz), 4.14 (2H, q, J = 7.1 Hz), 3.66 (3H, s), 3.49 OH, d, J = 5.7 Hz, 3.37 (1H, m), 3.06 (1H, dd, J = 11.5, 7 Hz), 2.82 (1H, dd, J = 17, 11 Hz), 2.68 (1H, m), 2.54 (1H, dd, J = 17, 4 Hz), 1.99 (3H, d, J = 1.2 Hz), underlying 1.99 (1H, m), 1.26 (3H, t, J = 7.1 Hz).

Anal. Calcd for $C_{17}H_{22}O_6$: Mol wt, 322.142. Found: Mol wt, 322.142.

92: R_f (5% acetone/$CHCl_3$) = 0.26; mp 143-144.5°C (toluene/hexane); MS m/z 322 (M^+), 171 (100); IR ($CHCl_3$) 3500, 1730, 1675, 1625 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ = 5.94 (1H, s), 5.74 (2H, m), 4.58 (1H, s), 4.14 (2H, q, J = 7.1 Hz), 3.72 (3H, s), 3.43 (1H, m), 3.23 (1H, t, J = 7.2 Hz), 3.04 (OH, s) 2.63 (1H, dd, J = 16, 4.6 Hz), 2.40 (1H, dd, J = 16, 11 Hz), 2.36 (2H, m), 2.04 (3H, s), 1.26 (3H, t, J = 7.1 Hz).

Anal. Calcd for $C_{17}H_{22}O_6$: Mol wt, 322.143. Found: Mol wt, 322.141.

Alternatively, a solution of $LiAl(OBu^t)_3H$ (80 mg, 0.314 mmol) in THF (1 mL) was added slowly to a solution of 90 (78.5 mg, 0.245 mmol) in THF (1 mL). The reaction was stirred for 30 min, diluted with ether, poured into 0.5 N HCl, and extracted thoroughly with ether. The extracts were washed with H_2O and brine, dried, and then evaporated to afford 67.8 mg (86%) of a mixture of hydroxy ketones. The mixture was dissolved in ethanol (3 mL) and toluene (1 mL) and

treated with NaOEt/ethanol (0.02 mL, 1.69 M). The solution was stirred for 2 h and worked up as usual to provide 49.7 mg (73%, 63% overall) of 91.

MnO_2 oxidation of 92

A solution of 92 (32.2 mg, 0.1 mmol) in ether (3 mL) was treated with γ-MnO_2[63] (1 g). The solution was stirred at 25° for 72 h, filtered through Celite, and evaporated to give 92 and 90. Chromatography (SiO_2; 5% acetone/$CHCl_3$) provided 19 mg (59%) of 90.

6,6aα-Dihydro-2,9(3H,9aβH)-dioxo-7-methylnaphthalene[1,8-bc]pyran-9bα(3aαH)-carboxylic acid, methyl ester (95).

A solution of 68.4 mg (0.21 mmoles) of 92 in 1 mL of TFA was stirred 3 minutes and solvent was removed in vacuo. Chromatography of the residue by MPLC on silica (3% acetone/$CHCl_3$) furnished 43.2 mg (74%) of the desired lactone 95: R_f (5% acetone/$CHCl_3$) = 0.29; mp 142-143°C (toluene/hexane); MS m/z 276 (M^+, 100); IR (KBr) 1750, 1730, 1680, 1625 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ = 6.01 (2H, br s), 5.63 (1H, br d, J = 10 Hz), 5.17 (1H, s), 3.78 (3H, s), 3.23 (1H, br s), 3.07 (1H, dd, J = 10, 4 Hz), 2.99 (1H, dd, J = 15, 6 Hz), 2.45 (1H, dd, J = 15, 4 Hz), 2.36 (1H, dt, J = 16, 5 Hz), 2.11 (3H, s), underlying 2.11 (1H, m).

Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.21; H, 5.82.

6,6aα-Dihydro-2,9(3H,9aαH)-dioxo-7-methylnaphthalene[1,8-bc]pyran-9bα(3aαH)-carboxylic acid, methyl ester (94).

A solution of 66.7 mg (0.21 mmol) of alcohol 91 in 1 mL of TFA was stirred 5 min and the solvent was removed in vacuo. Recrystallization of the residue using 40% toluene/hexane afforded 46.8 mg (82%) of lactone 94: R_f (5% acetone/$CHCl_3$) = 0.15; mp 171-171.5°C; MS m/z 276 (M^+), 121 (100); IR (KBr) 1735, 1700, 1630 cm^{-1}; ^1H NMR ($CHCl_3$, 360M Hz), δ= 5.98 (1H,m), 5.84 (1H, s), 5.68 (1H, dd, J = 11, 2.5 Hz) 4.98 (1H, s), 3.72 (3H, s), 3.18 (1H, dd, j = 11, 7 Hz), 3.10 (1H, m), 2.74 (1H, dd, J = 17, 8 Hz), underlying 2.74 (1H, m), 2.57 (1H, dd, J=18, 3 Hz), 2.04 (3H, s), underlying 2.04 (1H, m).

Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.05; H, 5.74.

Isomerization of Lactones 94 and 95

To a solution of lactone 95 (29 mg) in THF (0.5 mL) in an NMR tube was added DBU (30.2 μL). The temperature was maintained at 23°C between acquisitions of ^1H NMR spectra. After 10 min elapsed time, an equilibrium mixture of 94 to 95 (2/1) was achieved and maintained for 24 h. The ratio of products was determined by integration of the

^{1}H NMR signals at δ 5.16 ppm for 95 and 4.98 ppm for 94. Identical results were obtained with lactone 94.

Ethoxide catalyzed ring opening of lactones 94 and 95.

To a solution of lactone 95 (15.0 mg, 0.054 mmol) in ethanol (1 mL) and toluene (0.5 mL) was added 20 μL of NaOEt/EtOH (0.17 M). After 20 min, the reaction solution was poured into benzene and the resulting solution was washed with aq $NaHCO_3$, brine and dried (Na_2SO_4). Removal of solvent gave 15 mg of 91, which was identified on the basis of ^{1}H NMR and TLC. Similar results were obtained using lactone 94, which also yielded alcohol 91.

6-(Ethoxymethoxy)-1,3-hexadiene (99).

To a solution of alcohol 98[58] (1.06 g, 10.8 mmol) in CH_2Cl_2 (25 mL) was added N,N-diisopropylethylamine (3.48 g, 27.0 mmol), and then chloromethyl ethyl ether (2.55 g, 27.0 mmol). The resulting solution, after stirring 13 h, was diluted with ethanol and conc NH_4OH (15mL) and stirred an additional 0.5 h. After the addition of H_2O, and extraction with ether, the combined extracts were washed with 0.5 N HCl, H_2O, brine and dried (Na_2SO_4). Evaporation and distillation (5 torr, 70-80°C) afforded 1.47 g (87%) of the diene 99: MS m/z 59 (100); IR (thin film) 955, 895 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 6.50-4.75 (5H, m), 4.66 (2H, s), 3.75-3.35 (4H, m), 2.31 (2H, q, J = 7 Hz), 1.22 (3H, t, J = 7 Hz).

1,8-Dihydro-5,6-dioxo-4-[2-(ethoxymethoxy)ethyl]-8-methylnaphthalene-4a[4H]-carboxylic acid, methyl ester (100).

From 59c and 99 (130 mol %, 14 h, 50%). The product was purified first by removing excess diene by Kugelrohr distillation (0.2 torr, 80-80°C), then dissolving the residue in ether and washing the solution with aq NaOH to remove the residual catechol 70. After removal of solvent, the product was chromatographed on silica (5% acetone/$CHCl_3$). 100: mp 73-75°C; MS m/z 336 (M^+), 201, 59 (100); IR (KBr) 1730, 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 6.09 (1H, m), 5.90-5.45 (2H, m), 4.59 (2H, s), 3.70 (3H, s), 3.53 (2H, q, J = 7 Hz), 2.13 93H, d, J = 2 Hz), 1.19 (3H, t, J = 7 Hz).

Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.27, H, 7.19. Found: C, 64.33; H, 7.30.

4-[2-(Ethoxymethoxy)ethyl]-5α-hydroxy-8-methyl-6[5H]-oxo-1,4,4a,8a-tetrahydronaphthalene-4a-carboxylic acid, methyl ester (101a) and 4-[2-(ethoxymethoxy)-ethyl]-5β-hydroxy-8-methyl-6[5H]-oxo-1,4,4a,8a-tetrahydronaphthalene-4a-carboxylic acid, methyl ester (101b).

1. Reduction. Adduct 100 (738.8 mg, 2.20 mmol) was dissolved in dry THF (10 mL). A solution of $LiAlH(t\text{-}BuO)_3$ (842 mg, 3.31 mmol) in THF (7 mL) was prepared and added slowly to the ice bath cooled substrate solution. Upon completion of addition the reaction vessel was allowed to warm to room temperature over 30 min. The reaction was quenched with 0.1 N aq HCl and the resulting solution extracted with ether. The combined extracts were washed with water, brine and

dried (Na_2SO_4). Removal of the solvent afforded 684 mg (92%) of a mixture of mono-reduced products.

2. Isomerization. The reduction product (684 mg, 202 mmol) was dissolved in EtOH (7.0 mL), then treated wtih NaOEt in EtOH (1.7 M, 0.3 mL). After 30 min at 25°C, the reaction solution was diluted with ether, washed with water and brine, and dried (Na_2SO_4). Removal of solvent afforded 603 mg of material which was fractionated by flash chromatography (35 g silica, 5% acetone/95% $CHCl_3$) to give 80.2 mg of adduct 100, 94.3 mg of 101b, 104.2 mg of 101b and 101a as a mixture, and 232.6 mg of 101a (58% yield of 101a and 101b combined). 101a: mp 93-94°C (benzene/hexane); MS m/z, 59 (100); IR (KBr) 3520, 1740, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 5.89 (1H, m), 5.77 (2H, m), 4.61 (2H, s), 4.57 (1H, d, J = 3 Hz), 3.68 (3H, s), 3.54 (2H, q, J = 7 Hz), 2.81 (OH, d, J = 3 Hz 2.01 (3H, s), 1.20 (3H, t, J = 7 Hz).

Anal. For $C_{18}H_{26}O_6$: C, 63.89; H, 7.74. Found: C, 64.08; H 7.73.

101b: MS m/z 59(100); IR (thin film) 3540, 1735, 1685, cm^{-1}, ^1H NMR ($CDCl_3$) δ = 5.78 (3H, m), 4.61 (2H, s), 4.41 (1H, d, J = 6Hz), 3.64 (3H, s), 3.70-3.30 (2H, m), 1.96 (3H, d, J = 2 Hz), 1.19 (3H, t, J = 7 Hz).

4-(2-Hydroxyethyl)-5-hydroxy-8-methyl-6[5H]-oxo-1,4,4a,8a-tetrahydronaphthalene-4a-carboxylic acid, methyl ester (102).

Compound 101a (107.2 mg, 0.32 mmol) was dissolved in THF (3.3 mL) and 0.5 N aq HCl (2.2 mL), and heated at 50°C for 36 h. The resulting solution was diluted with brine and extracted with ethyl acetate. The organic solutions were combined, dried over Na_2SO_4 and evaporated to afford 87.7 mg (100%) of a mixture of 102. The product was not further purified but used directly. Purification of a small amount was accomplished by recrystallization from benzene/hexane to give one isomer of 102: mp 165-167°C; MS m/z 280 (M^+), 237, 157 (100); IR (KBr) 3510, 3270, 1715, 1650; ^1H NMR ($CDCl_3$) δ = 5.90 (1H, br s), 5.74 (2H, br s), 4.5 (1H, d, J = 3 Hz), 3.71 (3H, s), 2.75 (OH, d, J = 3 Hz) 2.01 (3H, br s).

Anal. Calcd for $C_{15}H_{20}O$: Mol wt, 280.131. Found: Mol wt, 280.131.

7-Methyl-9(9a$_\alpha$H)-oxo-2,3,6,6a$_\alpha$-tetrahydronaphthalene[1,8-bc]pyran-9b$_\alpha$(3a$_\alpha$H)-carboxylic acid, methyl ester (105) and 7-methyl-9(9a$_\beta$H)-oxo-2,3,6,6a$_\alpha$-tetrahydronaphthalene[1,8-b,c]pyran-9b$_\alpha$(3a$_\alpha$H)-carboxylic acid (104).

1. Tosylation. To a solution of the mixture of alcohols 102 (447 mg, 1.60 mmol) in pyridine (14 mL) was added tosyl chloride (606 mg, 2.18 mmol). All solids were dissolved and the pot was placed in a 0°C refrigerator for 14 h. Aqueous 0.1 N HCl was added and the resulting solution was extracted with ethyl acetate. The combined

organics were washed with 1/1 brine/0.1 N HCl, 10% aq $NaHCO_3$, brine and dried (Na_2SO_4). Removal of solvent afforded 683 mg (99%) of tosylates 103, which were carried on directly without purificiation.

2. Etherification. Tosylates 103 (681 mg, 1.57 mmol) were dissolved in HMPA (8.2 mL), and heated at 70°C for 6.5 h. After cooling, H_2O was added, the solution was extracted with ether, and the combined extracts were washed with 10% aq $NaHCO_3$, brine, dried (Na_2SO_4) and evaporated to afford 308 mg (73%) of a crude mixture of ethers 104 and 105. Flash chromatography (acetone/$CHCl_3$) on SiO_2 of the crude ethers afforded 100 mg of a solid. Recrystallization using benzene/hexane afforded a solid ditosylate while evaporation of the mother liquors afforded 65 mg of 104 as a glass. Ditosylate: mp 163-164°C (decomposes); MS m/z 588 (M^+), 91 (100); IR (KBr) 3510, 1740, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 7.80-7.65 (4H, m), 7.35-7.10 (4H, m), 6.00-5.45 (3H, m), 5.37 (1H, s), 3.97 (2H, dd, J = 7, 5 Hz), 3.60 (3H, s), 2.41 (6H, s), 1.92 (3H, d, J = 1 Hz).

104: MS m/z 262 (M^+), 203 (100); IR (thin film) 1720, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ = 5.94 (1H, m), 5.89 (1H, s), 5.59 (1H, d, (br), J = 10 Hz), 4.52 (1H, s), 4.06 (1H, dt, J = 8.8, 2.4 Hz), 3.89 (1H, td, J = 10, 6.8 Hz), 3.72 (3H, s), 2.96 (1H, dd, J = 10, 4.9 Hz), 2.90 (1H, m), 2.35 (1H, dt, J = 17, 5.3 Hz), 2.25 (1H, m), 2.15 (1H, m), 2.04 (3H, s), 1.60 (1H, m).

Anal. Calcd for $C_{15}H_{18}O_4$: Mol wt, 262.121. Found: Mol wt 262.120.

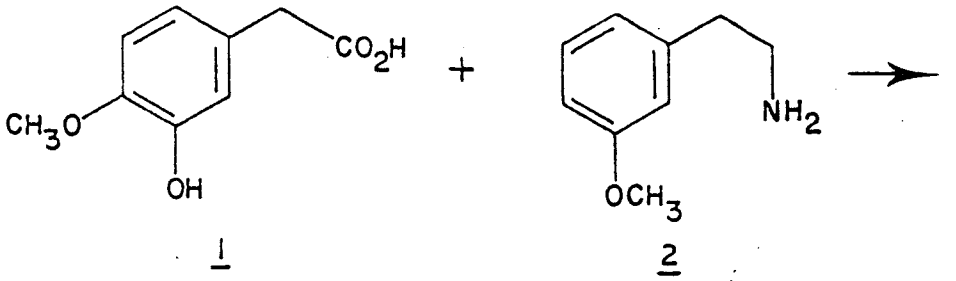
3. Isomerization of 104. To a solution of 104 (6.1 mg, 0.23 mmol) in THF (150 μL) was added $NaOCH_3/HOCH_3$ (6 μL, 1.04 M). TLC showed rapid conversion of 104 to 105. After 24 h, water was added and the mixture extracted with ether. The combined extracts were washed with brine, dried (Na_2SO_4) and evaporated to afford 6 mg (100%) of a mixture of 105/104 in a 6/1 ratio. Preparative TLC of the mixture (5% acetone/$CHCl_3$) afforded pure 105: mp. 89-91°C (benzene/hexane); MS m/z 262 (M^+), 203 (100); IR (thin film) 1725, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz NMR) δ = 6.01 (1H, m), 5.78 (1H, d, J = 1.1 Hz), 5.62 (1H, dq, J = 10, 2.9 Hz), 4.17 (1H, s), 4.00 (1H, dd (br), J = 13, 4.0 Hz), 3.70 (3H, s), 3.56 (1H, td, J = 13, 2.2 Hz), 3.02 (1H, m), 2.91 (1H, dd, J = 12, 7.2 Hz), 2.64 (1H, m), 1.96 (3H, d, J = 1.1 Hz), 1.91 (2H, m), 1.51 (1H, dq, J = 14, 2.2 Hz).

Anal. Calcd for $C_{15}H_{18}O_4$: Mol wt, 262.121. Found: Mol wt, 262.120.

II. PREPARATION OF OXYGENATED BENZENACETIC ACIDS

A. INTRODUCTION

Oxygen substituted benzenacetic acids have been employed in the synthesis of many natural products. Examples embrace such diverse species as flavonoids and alkaloids[64,65]. One especially important area is their use in the synthesis of the opiate alkaloids[66,67]. Rice has employed 3-hydroxy-4-methoxybenzeneacetic acid 1 (homoisovanillic acid) in a concise synthesis of the opiate percursor dihyrothebainone 4c (Scheme I). In this scheme, 1 was reacted with m-methoxyphenethylamine 2, and the amide converted by well known procedures into the 1-benzyltetrahydroisoquinoline 3a[66a,d]. Grewe type cyclization of 3a gave predominately the isomeric 4a. However, bromination of 3a to 3b then cyclization provided the 1-bromodihydrothebainone derivative 4b. In a related approach to the synthesis of the opiate skeleton, Beyerman[67a-c] employed 3,5-bis-(benzyloxy)-4-methoxybenzeneacetic acid 5b as the acid precursor (Scheme II). A similar construction of the isoquinoline nucleus provided 6, in which the phenyl ring is now symmetrically substituted. Cyclization to either free position provided 7. Schwartz[67d] obtained similar results when employing phenolic oxidative coupling conditions (8 → 9) (Scheme III). In each of these approaches, the now superfluous heteroatom



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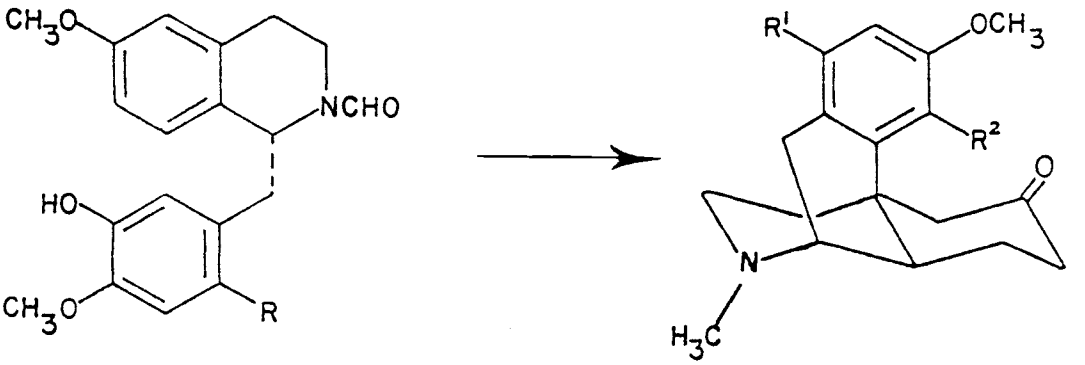


3a R = H

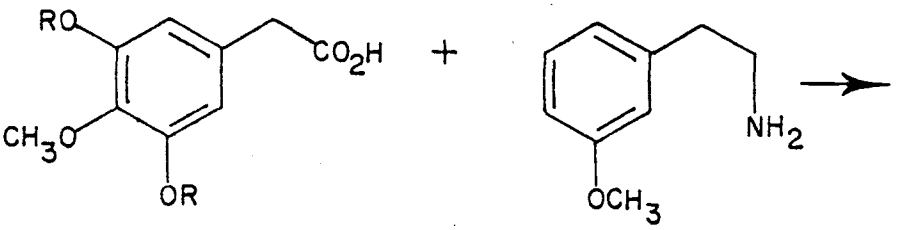
3b R = Br

4a R^1 = OH, R^2 = H

4b R^1 = Br, R^2 = OH

4c R^1 = H, R^2 = OH

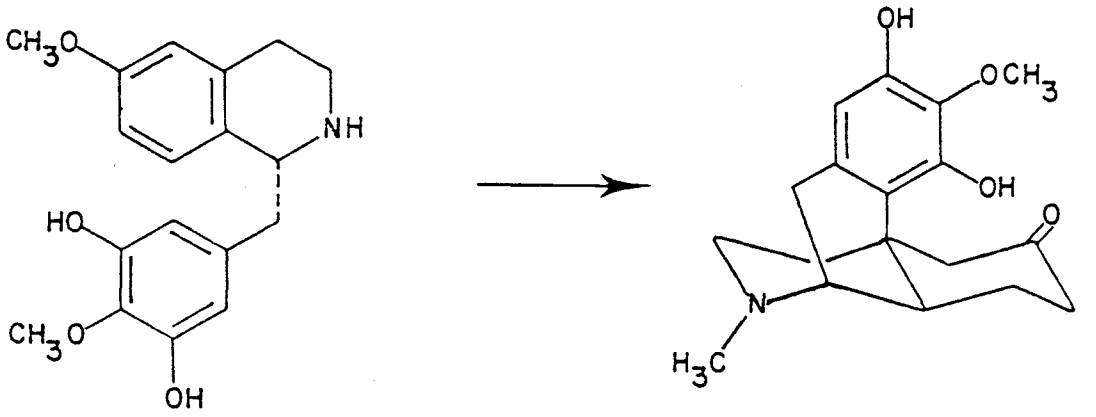
Scheme I



5a R = H

5b R = Benzyl (Bn)

2



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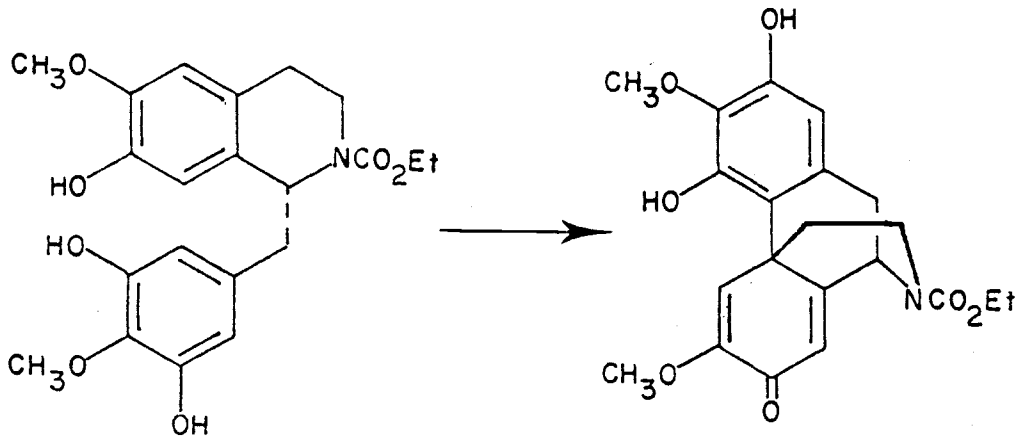
Scheme II



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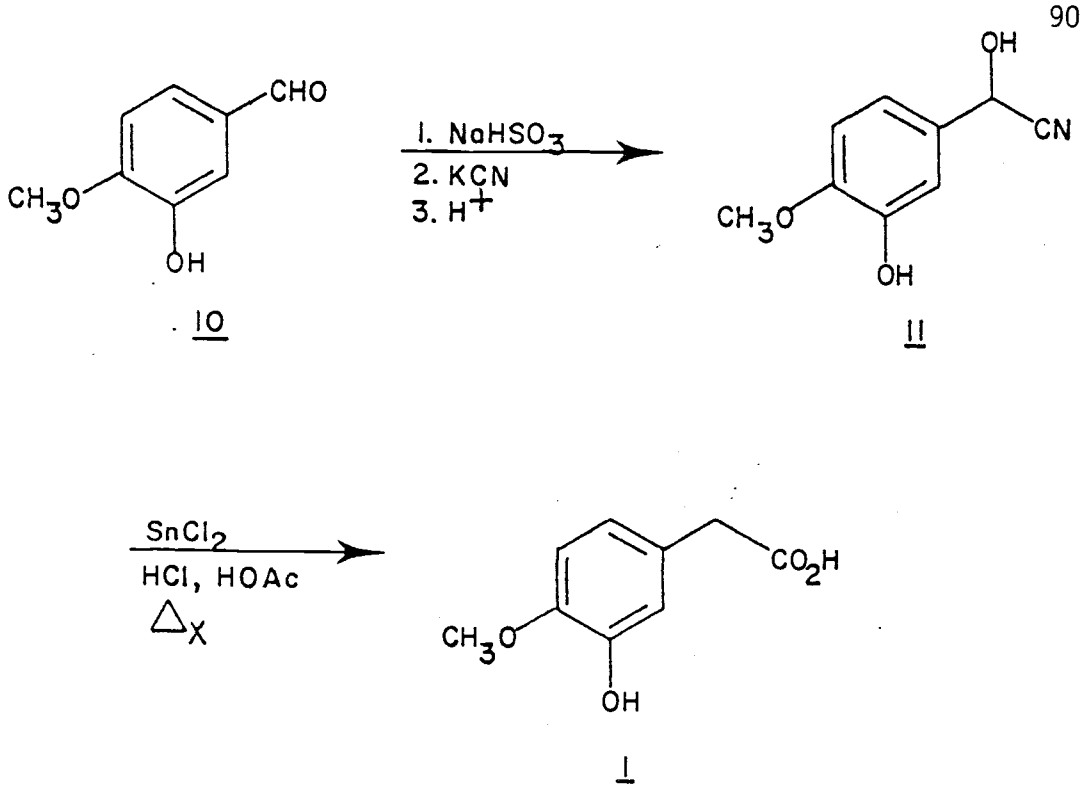
Scheme III

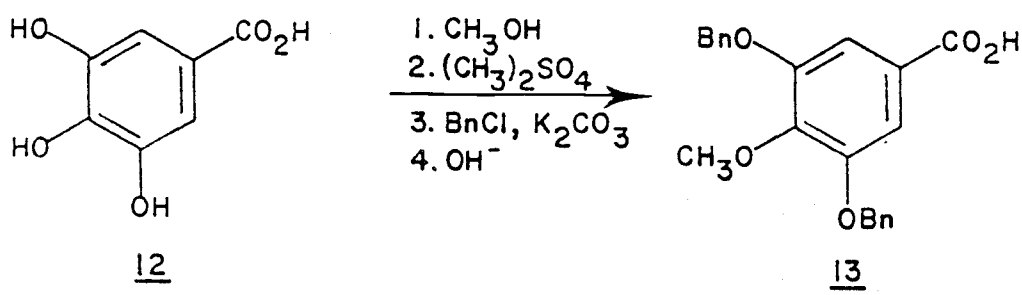
substituent of the cyclized product was reductively removed to obtain dihydrothebainone 4c.

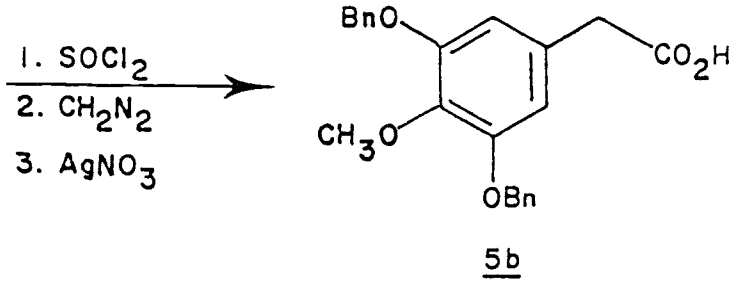
Due to the importance of 1 and 5a as codeine precursors much attention has been given to their preparation[68]. In general, the systheses of these compounds involves the one carbon homologation of a benzyl derivative, then manipulation of the aromatic functionality. The most convenient preparations of 1 use isovanillin 10 as the starting material. This strategy was demonstrated by Grewe and Fischer[68f] (Scheme IV) wherein isovanillin was converted to the cyanohydrin 11 which was then successively hydrolyzed and reductively dehydroxylated to give 1 in greater than 80% yield. To date, only one synthesis of an analog of 5a has been reported.[70] (Scheme V). Gallic acid 12 was esterified, then selectively methylated in poor yield at the 4-hydroxyl group. After benzylation of the remaining free phenols to give 13, the acid was homologated to 5b using the Arndt-Eistert procedure[71]. The Grewe-Fischer preparation of 1, while affording a good yield of material, suffers in that it is experimentally tedious and involves procedures during which hydrogen cyanide is evolved. The synthesis of 5b given above is low yielding and quite long.

The disadvantages noted above prompted us to devise a general method for the preparation of 1 and 5a from a common starting material. An excellent candidate for the initiation of this strategy is the relatively inexpensive and readily available 4-methoxybenzene-



Scheme IV

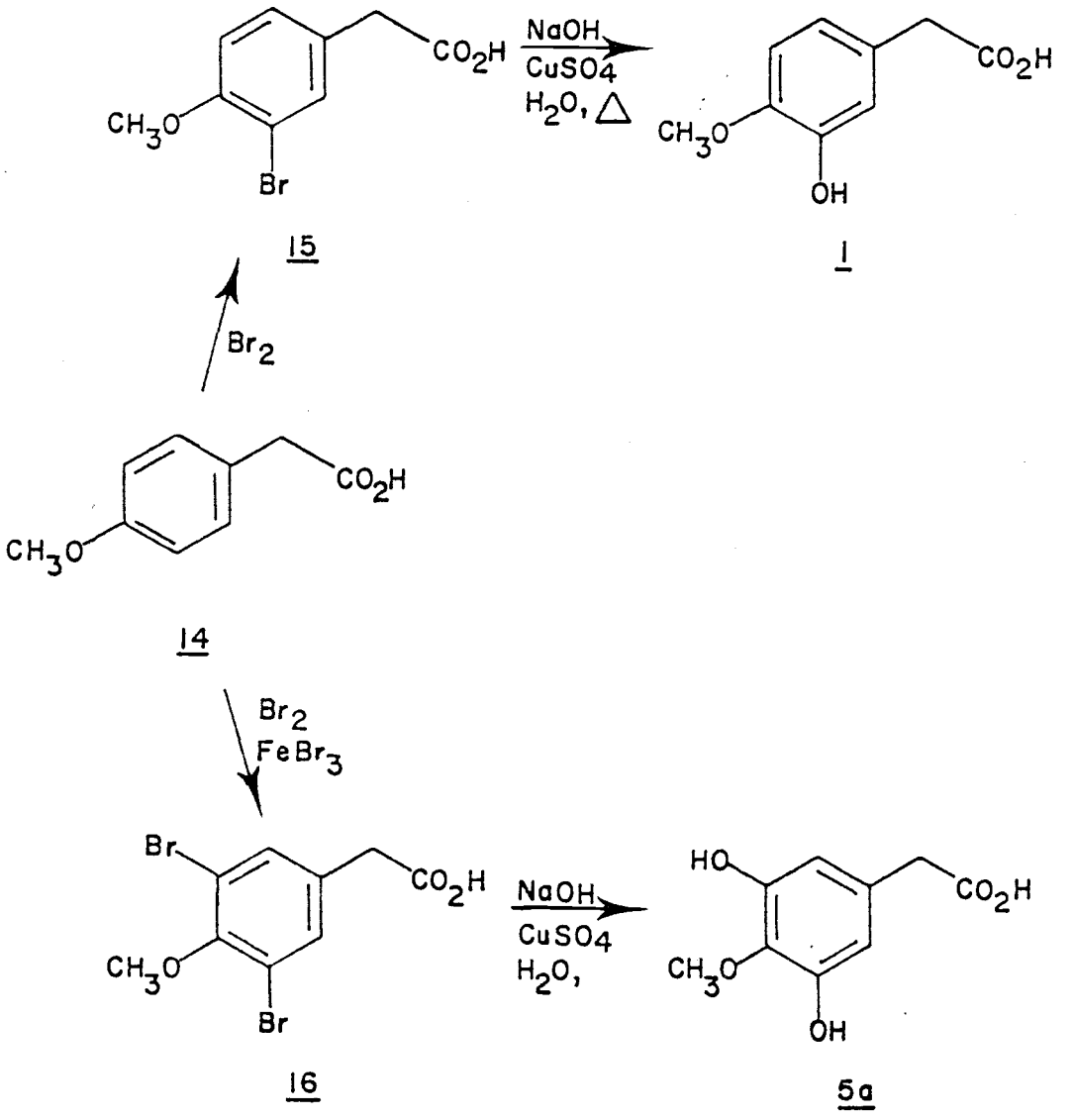




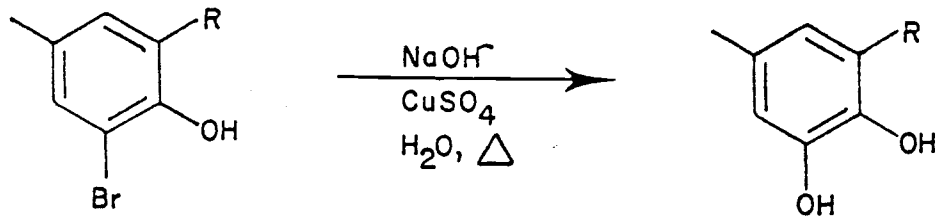
Scheme V

acetic acid 14[72]. Our proposed synthesis of 1 and 5a (Scheme VI) required bromination of 14 to 15 and 16 followed by displacement of the halides by hydroxide in a copper catalyzed reaction. The rationale for this scheme derives from our work on the synthesis of catechols wherein orthobromophenols 17a and 17b were readily dehalohydroxylated. In that case, the conversion was effected by refluxing 17 for 12 hours in 10% aqueous sodium hydroxide with a catalytic amount of cupric sulfate. The yields of 18 ranged from 60-90%.

A previous attempt to employ this general strategy for the synthesis of 1 was performed by Hrothama (Scheme VII)[73]. In that report, the necessary ipso substitution of the halogen atom in 19 was not observed. This compound was found to be relatively unreactive to reagents such as aqueous barium hydroxide at 170°C and reacted via aryne mechanisms (19→20) at higher temperatures. Recently it has been shown that the order of reactivity of aromatic halogens to displacement by hydroxide is I > Br > Cl[53,74,75]. Bacon, exploring the related case of ipso substitution of arylhalides by alkoxides[75], found the p-bromoanisole was converted in 95% yield to 1,4-dimethoxybenzene by refluxing sodium methoxide in collidine containing 0.5 equivalents cuprous iodide. From this and other examples, Bacon drew several general conclusions: 1) while iodides are slighly more reactive towards substitution than bromides, the latter are much less prone to reduction, and 2) the presence, in the halide, of a phenol (except at the ortho position[49]) lowers the yields.



Scheme VI

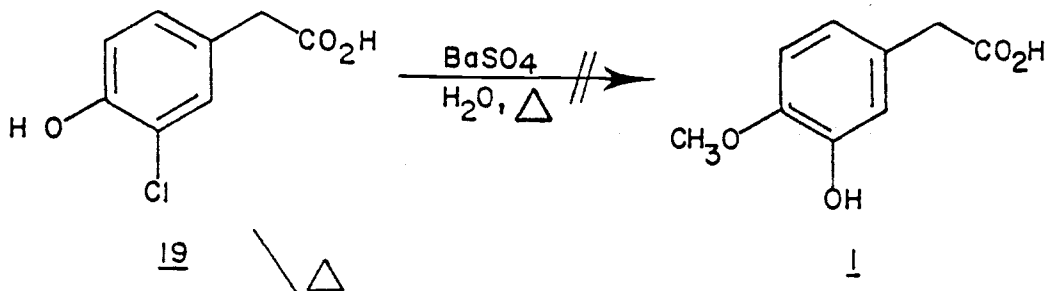


17a R = CH_3

17b R = CO_2H

18a R = CH_3

18b R = CO_2H



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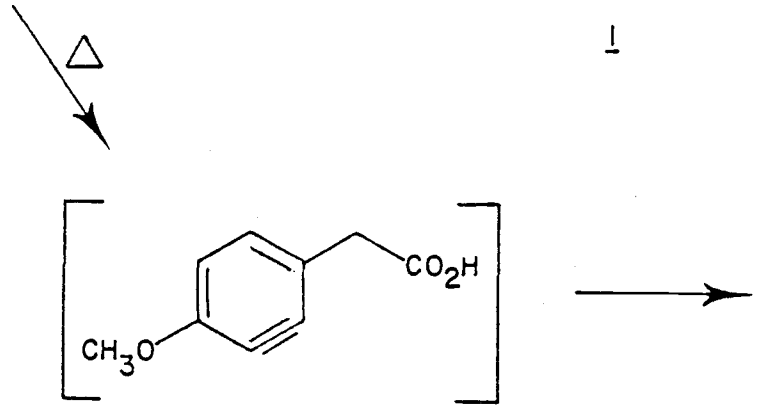

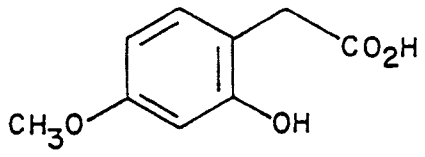

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Scheme VII

B. SYNTHESIS OF HYDROXYLATED BENZENEACETIC ACIDS

The preparation of 12 was easily accomplished in greater than 95% yield by monobromination of 14 using bromine in either chloroform or glacial acetic acid.[69] Dibromination of 14 in chloroform or 1,2-dichloroethane to give 16 required a large excess of bromine and the presence of ferric bromide catalyst. While in the former reaction there was no trace of dibrominated products even when a large excess of bromine was used, the latter preparation required careful monitering to insure that no trace of monohalogenated product remained. This reaction was conveniently analyzed by gas chromatography of the methyl esters following esterification of the crude reaction mixture with diazomethane.

The dehalohydroxylations were performed in a stainless steel Paar reaction vessel. Before each run the bomb was cleaned by filling the vessel with 6M nitric acid, rinsing, then filling again with conc. ammonia. Without this cleansing, the reaction results were extremely variable, especially for the reaction of 16. The reactions were performed at 1% - 5% concentrations of the halide in 10% aqueous sodium hydroxide containing a catalytic amount of cupric sulfate. The basic cupric sulfate mixture was deaerated prior to addition of the acid by stirring under reduced pressure. The workup consisted of acidification with conc. hydrochloric acid followed by separatory funnel and continuous extractions. The hand extractions, in the

preparation of 1, generally recovered greater than 90% of the hydroxylated product, while in the case of 5a these were much less efficient.

Monobromoacid 15 did not react under the conditions used for the conversion of 17 to 18. Heating to 125°C in the sealed bomb also afforded no conversion of 15 but after 36 hours at 150°C very good yields of 1 could be obtained (Table II). Small scale reactions (3g) usually provided material having a narrow melting point range. A large scale reaction of 15 (25g), in which the substrate concentrations was increased from 1% to 5% for convenience, afforded a 97% conversion to 1, but with a slightly lower purity. The reaction product showed essentially one spot which moved by silica gel TLC, with the presence of some very polar material which remained at the origin. In contrast, Rice reported that the homoisovanillic acid prepared via the cyanohydrin contained several impurities which were removed with difficulty. In order to determine the viability of using 1 directly without further purification, the crude product was allowed to react with m-methoxyphenethylamine to afford amide 21[66a]. The yield of amide 21 was comparable to that obtained by Rice using rigorously purified materials.

Dehalohydroxylation of the dibromo compound 16 gave variable results (Table III). Initial reaction conditions were 1% substrate concentrations, temperatures of 150-160°C and reaction times of two days. The desired product 5a was the major component of the reaction

Table II

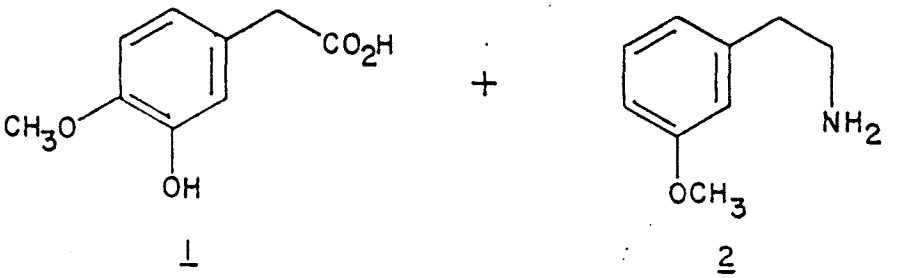
Preparation of Benzeneacetic Acid 1

% substrate	Scale (g)	Temperature (°C)	Yield	MP of Product (°C)
1%	5.0	150-160	90%	125
1%	5.0	150	99%	127-129
5%	25.0	150	97%	123-127

Table III

Dehalohydroxylation of 16

% substrate	scale(g)	Temp(°C)	Run Time(d)	Yield	Product %1	Comp %5a
1	1.47	150	2.5	80%	<10	90
3	3.0	160	2	81%	20	80
5	5.0	160	2	114%	38	62
4	3.0	110	7	86.5%	25	75
4	2.6	110	5	78%	15	85
5	20.0	110	9	90%	35	65



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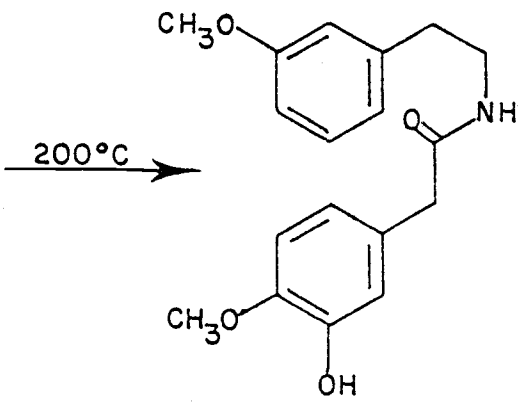
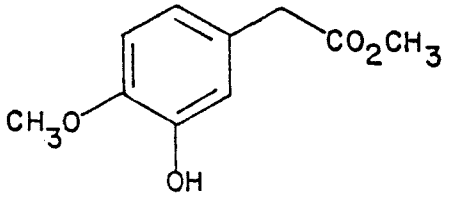


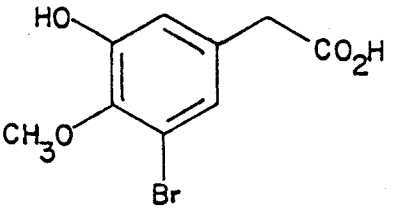
21

mixture, but an additional component (10-40%) was also found. After esterification of the reaction product with methanol and conc. sulfuric acid, the resulting esters were separated by chromatography. The minor product was identified as the monohydroxylmethyl ester of 23 which resulted from a reductive removal of one of the bromides. In order to determine at what step the reduction had occurred, a dehalohydroxylation reaction was interrupted prior to completion. ^{1}H NMR analysis showed the presence of 16, 1 and 5a in varying amounts while the additional component was identified as 3-bromo-5-hydroxy-4-methoxybenzeneacetic acid 24. No monobromo derivative 15 was detected. Esterification, separation by chromatography, and saponification of the reaction mixture afforded pure 24. When 24 was resubjected to the reaction conditions for the conversion of 16 to 5a, similar product compositions were obtained as from the complete reaction of 16. The presence of a meta or para hydroxy substituent in the aryl bromide has been previously noted to lower the yields of substitution of products.[75] The mechanism of reduction as proposed by Bacon[76] involves hydrogen atom donation from a phenol to an aryl radical (formed from the halide and the copper catalyst (see Scheme VIII)). Bacon, while stating that phenols were generally converted into resins (as in our case), isolated several oxidatively coupled phenolic products to support his claim.[76]

Several attempts at modification of reaction conditions to limit the amount of reduction failed to afford any consistent improvement



23



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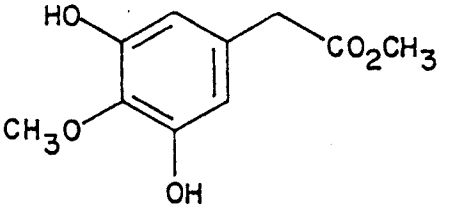
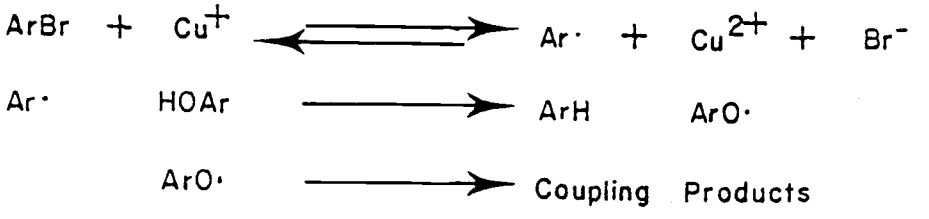


25



Scheme VIII

in results over our initial conditions. The modifications included lowering the reaction temperature (and concommitment extension of the reaction time) and increasing the amount of cupric sulfate present in the reaction mixture. Increasing the substrate concentration up to 5% had no consistent effect on the yield or composition of the product. With our inability to obtain exclusive bis-dehalohydroxylation from this reaction, we sought means of separating 5a from 1. All attempts at fractionally recrystallizing 5a failed, as did trituration to remove 1. Due to their carboxyl moieties 1 and 5a exhibited poor chromatographic behavior. However, the very polar resinous byproducts could be removed by filtration of the reaction product through florosil, eluting with acetone. Ten grams of florosil were employed to each gram of product and the return of material was generally 90%. Esterification of the acid gave more readily chromatographable materials. The combined extracts from the hydroxylation reaction were esterified using methanol and conc. sulfuric acid[77] in 85% yield. Chromatography of the mixture on silica gel with 20% acetone in chloroform smoothly effected separation, affording 23 in 18% and 25 in 40% yields. While column chromatography provides pure 25 on a small to medium size scale, we also sought for means to isolate 25 in methods amenable to large scale preparations. Trituration using 50/50 benzene/hexane as solvent afforded an 80% return of material but analysis of purity by ^{1}H NMR indicated to 15% of the product to be 23. Recrystallization using toluene afforded a 40% return of

material, but the purity (as determined by melting point determination) was not adequate (Table IV). In an attempt to remove the polar resinous material, the esterified product was passed through silica (ten grams silica per one gram product), however subsequent recrystallization afforded results similar to those above.

After isolation and characterization of the ester 25, it was saponified to the free acid 5a. After two recrystallizations from chloroform, 5a possessed a melting point of 181-182°C. The literature value for the melting point of 3,5-dihydroxy-4-methoxybenzeneacetic acid however, was 130°C.[78] The ^{1}H NMR spectrum and the ^{13}C NMR spectrum of our 5a were found to be consistent for the symmetrical structure of 3,5-dihydroxy-4-methoxybenzeneacetic acid. The cause of this discrepancy is unknown.

In conclusion, the preparation of 1 from 15 using a bromination, dehalohydroxylation sequence, is rapid, gives a product of high purity and is amenable to large scale preparations. While less attractive for the preparation of 5a (or 25), this method does rival the known method for synthesis of 5b in yield and is a much less lengthy preparation.

Table IV

Attempted Recrystallization of Ester 25

Yield for Recrystallization	yeild from 13	mp[a] (°C)
40%	29%	110-112
56%	40%	105-108
55%	39%	111-113

[a] Pure 25 had a mp of 115-116° C.

C. EXPERIMENTAL[79]

3-Bromo-4-methoxybenzeneacetic acid (15).

A. In chloroform.

To a solution of 5.23 g (31.5 mmole) of 4-methoxybenzeneacetic acid 14 in 50 mL of $CHCl_3$ a solution of 7.5g (47 mmoles) of Br_2 in 5 mL of $CHCl_3$ was added slowly. The solution was stirred at room temperature for 3 h, then poured into an aqueous $NaHSO_3$ solution. This solution was diluted with ether, the layers were separated and the aqueous portion was further extracted with ether. The combined etheral solutions were washed with water and brine, then dried ($MgSO_4$). Removal of solvent by rotovap afforded 7.54 g (98%) of 15. The crude product was routinely used without further purification but could be recrystallized from toluene/hexane; mp 113 - 115°C (Lit[69] 112-115°C) ^1H NMR ($CDCl_3$) δ = 7.47 (1H, d, J = 2 Hz), 7.20 (1H, dd, J = 2, 9 Hz), 6.85 (1H, d, J = 9 Hz), 3.87 (3H, s), 3.57 (3H, s).

B. In acetic acid.

A solution of 5.4 g (34 mmoles) of Br_2 in 5 mL of acetic acid was slowly added to a solution of 5.12 g (30.8 mmoles) of 4-methoxybenzeneacetic acid 50 in 14 mL of acetic acid. The resulting solution was heated to 70°C for 4 h, cooled, poured into an aqueous $NaHSO_3$ solution and the aqueous solution was extracted with ether.

The combined extracts were washed with water and brine and dried (Na_2SO_4). The solvent was removed in vacuo to yield 6.90 g (91.3%) of 15.

3-Hydroxy-4-methoxybenzeneacetic acid (1).

In a stainless steel bomb was place 5.05 g (20.6 mmoles) of 12. A degassed solution of 45 g (1.1 moles) of NaOH in 450 mL of H_2O containing a catalytic amount of $CuSO_4$ (1 g) was added to the bomb. The bomb was sealed, heated to 150°C for 1.5 d and cooled. The solution was rapidly acidified and extracted with ether. The aqueous solution was continuously extracted overnight with ether. The combined etheral solutions were evaporated to dryness and afforded 3.72 g (99%) of 1 (mp: 127-129°C, lit mp:[66d] 128.5-130.5°C). Further purification was effected by recrystallization of the crude product with 20% isopropanol/$CHCl_3$; mp 128-130°C; ^1H NMR ($CDCl_3$) δ = 6.87 (2H, br s), 6.79 (1H, br s), 3.87 (3H, s), 3.55 (2H, s).

3,5-Dibromo-4-methoxybenzeneacetic acid, (16).

To a solution of 20.09 g (0.120 moles) of benzeneacetic acid 14 in 220 mL of freshly distilled $CHCl_3$ (from P_2O_5) was added 4.28 g (20 mmoles) of $FeBr_2$. A solution of 18.5 mL (0.36 moles) of Br_2 in 30 mL of $CHCl_3$ was added dropwise to the reaction vessel. After stirring 42 h at room temperature, an additional 10 mL of Br_2 (0.19 moles) and

1.04 g (4.8 mmoles) of $FeBr_2$ were added to the reaction pot. The reaction solution was stirred for a further 18 h, then poured carefully into a 5% aq. $NaHSO_3$ solution. After the color of the resulting solution had changed from red to yellow, the solution was extracted with ether. The combined etheral extracts were washed with H_2O and brine, then dried (Na_2SO_4). Removal of the solvent afforded 37.76 g (96%) of dibromo 13, in greater than 98% purity, as determined by ^1H NMR. The crude solid was routinely used directly, but further purification could be achieved via recrystallization using toluene/hexane: mp 132-134°C; MS m/z 324 (M^+, 91), 326 (M + 2, 44) 322 (48), 281 (48), 279 (100), 277 (53); IR (KBr) 3200-2600, 1710 cm^{-1}; ^1H NMR (d_6-acetone) δ = 8.85 (COOH, br s), 7.47 (2H, s), 3.77 (3H, s), 3.58 (2H, s); ^{13}C NMR (d_6-acetone) δ=171, 152, 133, 116, 59, 38.

Anal. Calcd for $C_9H_8Br_2O_3$: C, 33.37; H, 2.49. Found: C, 33.24; H, 2.47.

3-Hydroxy-4-methoxybenzeneacetic acid, 1 and 3,5-Dihydroxy-4-methoxybenzeneacetic acid, (5a).

In a stainless bomb was placed 20.00 g (61.6 mmoles) of 16. A degassed solution of 47.0 g (1.18 moles) of NaOH in 470 mL of H_2O containing a catalytic amount of $CuSO_4$ (1.0g) was added to the bomb. The bomb was sealed, heated to 110°C for 9 d and cooled. The solution was rapidly acidifed, then extracted 4X with ETOAc. The aqueous solution was continuously extracted overnight with ether.

The organic solution was washed with brine, then dried over Na_2SO_4. Removal of solvent afforded 9.55 g (78%, based on conversion of 16 to 5a) of a 1.7/1 mixture of 5a and 1. Removal of solvent from the continous extraction afforded 1.50 g (12%, 90% yield combined) of a 3/1 mixture of 5a and 1. These mixtures were combined and submitted to esterification.

3-Hydroxy-4-methoxybenzeneacetic acid, methyl ester, (23) and 3,5-Dihydroxy-4-methoxybenzeneacetic acid, methyl ester, (25).

Following the method of Durham, McLeod and Cason,[77] the mixture of 1 and 5a from the dehalohydroxylation reaction (10.89 g) was treated with 95 mL of methanol and 10 mL of conc H_2SO_4 at reflux for 3 h. A soxhlet extractor charged with 3A molecular sieves was employed to remove water. After cooling, the solution was diluted with water and the resulting aqueous solution extracted with ETOAC. The combined extracts were washed with 10% aq. $NaHCO_3$, H_2O and brine, then dried over Na_2SO_4. Removal of solvent *in vacuo* gave 9.31 g (80%, based on the conversion of 5a to 25) of a 1.6/1 mixture of 25 and 23 (ratio determined by ^1H NMR). A portion of this product (1.58 g) was column chromatographed on silica gel eluting with 20% acetone in $CHCl_3$. This returned 0.39 g (18.7% from dibromo 16) of 23 as an oil and 0.90 g (40.0% from dibromo 16) of 25 as a solid (mp 116-117° C). Further purification of 25 was accomplished by recrystallization from toluene. An analytical sample of 25 was prepared by sublima-

tion (0.1 torr, 100°C). 23: ^{1}H NMR ($CDCl_3$) δ = 6.83 (m, 3H), 5.24 (OH, s) 3.92 (3H, s) 3.73 (3H, s), 3.55 (2H, s).

25: mp 115-116°C; MS m/z 212 (M+), 153 (100); IR (KBr) 3300, 1720, 1200, 1160, 1040, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 7.45 (2 OH, s), 6.32 (2H, s) 3.84 (3H, s) 3.56 (3H, s), 3.40 (2H, s).

Anal. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.61; H, 5.66.

3, 5-Dihydroxy-4-methoxybenzeneacetic acid, (5a).

To 0.106 g (0.50 mmoles) of the methyl ester 25 was added 1.1 mL of 10% aq. NaOH. The solution was stirred for 30 min at room temperature, then acidified with 4N HCl. The resulting aqueous solution was extracted with ETOAC. The combined organic extracts were washed with brine then dried over Na_2SO_4. Removal of solvent by evaporation afforded 0.10 g (100%) of 2 as a solid. The acid was recrystallized from $CHCl_3$: mp 181-182° C; MS m/z 198 (M^+), 197 (100), 153 (89.7); IR (KBr) 3490, 3300-2700, 1705, 1600, 1505 CM^{-1}; ^{1}H NMR (d_6-acetone) δ = 8.40 (CO_2H, 2 OH, br s), 6.36 (2H, s), 3.76 (3H, s) 3.42 (2H, s); ^{13}C NMR (d_6-acetone) δ = 174, 157, 135, 131, 109, 60, 41.

Anal. Calcd for $C_9H_{10}O_5$: C, 54.55; H, 5.09. Found: C, 54.11; H 4.94.

3-Bromo-5-hydroxy-4-methoxybenzeneacetic acid, (24).

Via the above methods, 24 was prepared from 16 by interruption of the dehalohydroxylation before the reaction had gone to completion. Subsequent esterification, chromatography and saponification afforded 24 which was recrystallized from toluene: mp 159.5-160.5° C; MS m/z 260 (M+, 100), 262 (M+2, 99), 247 (13.1) 245 (13.9), 217 (80), 215 (93); IR (KBr) 3500-2800, 1715, 1570, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 7.58 (1H, d, J=2Hz), 7.21 (1H, d, J=2Hz), 3.75 (3H, s), 3.34 (2H, s).

Anal. Calcd for $C_9H_9BrO_4$: C, 41.41; H, 3.48. Found: C, 41.43; H, 3.34.

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79. See Experimental, Chapter I, for general features of analytical data acquisition.