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Synthetic approaches to quasimarin

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SYNTHETIC APPROACHES TO QUASIMARIN

Iowa State University PH.D. 1984

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Synthetic approaches to quasimarin

by

Michael Edward Krolski

A Dissertation Submitted to the

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1984

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DEDICATION

Dedicated to the memory of my grandparents

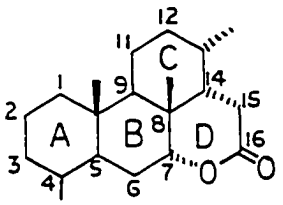
Joseph and Verna Krolski

and

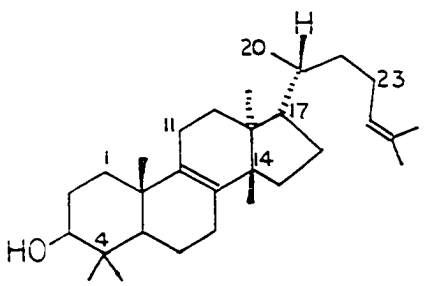
Edward and Vlasta Musil

INTRODUCTION

The quassinoids are a group of highly oxygenated diterpenoids isolated from the bark and leaves of simaroubaceous trees and shrubs (1). Despite their characteristic bitterness, they have long been used in the herbal folk medicine of many cultures (2). Most members of this group of compounds have the basic carbon skeleton shown below.



Quassinoids are formed naturally by the degradation of euphol 1 or apo-tirucallol 2 by loss of the last four carbons of the C-17 side chain with formation and loss of a γ-lactone, and cleavage of the C-13 to C-17 bond, allowing formation of the δ-lactone D ring. Loss of one of the methyl groups at C-4, and migration, in the case of 1, of the C-14 methyl group to C-8, is also postulated (3). Supporting evidence for the acid



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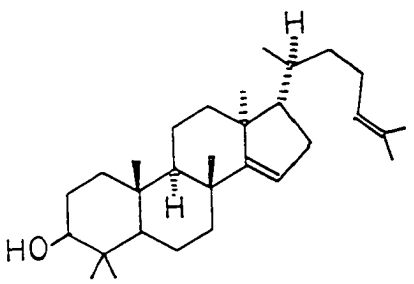
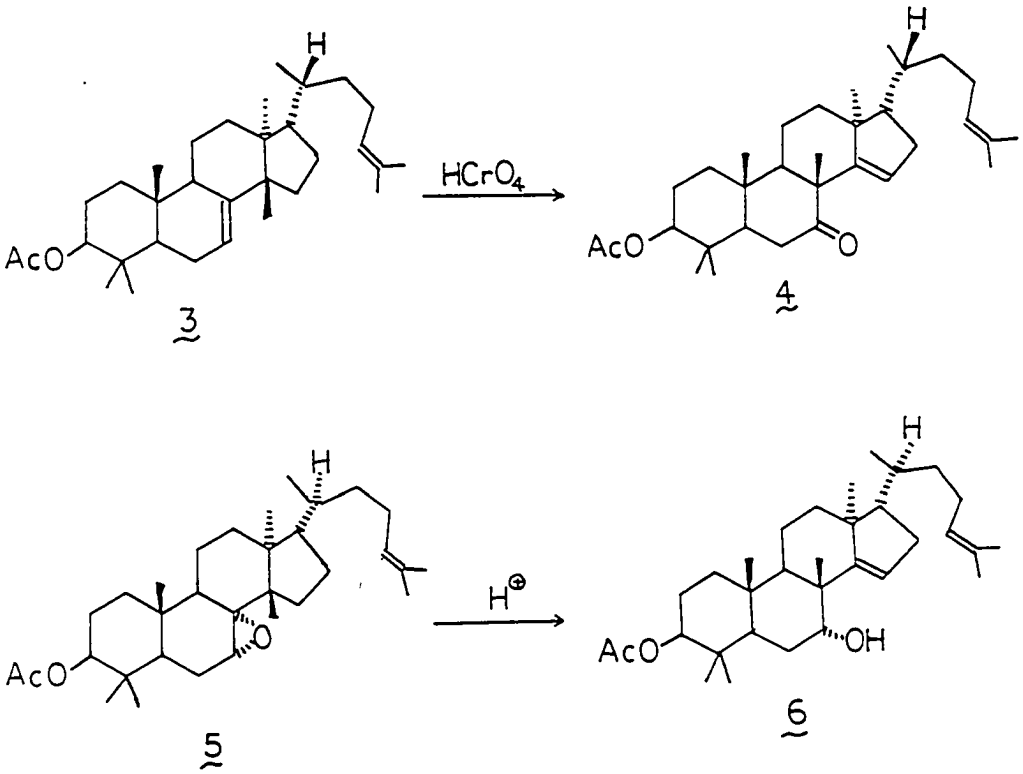


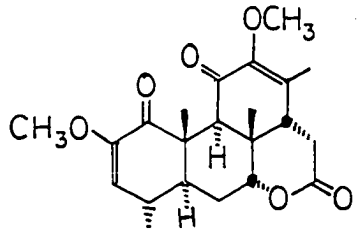
2

catalyzed migration of the C-14 methyl group to C-8 is given by the known rearrangements of 3 to 4 and 5 to 6 by chromic acid and mineral acid, respectively (4).



3 4 5 6

Quassin 7, the parent member of the group, was first isolated from Quassia amara L., also known as surinam quassia, by London and co-workers in 1950 (5). Its structure was determined by Valenta and co-workers over a decade later (6). While quassin has been used as a bitter tonic and a remedy for intestinal parasites, its medicinal value has not been extensively studied.



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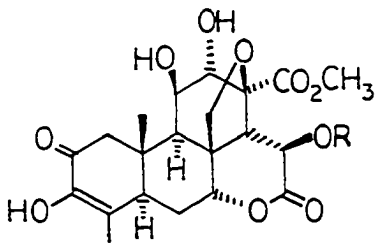
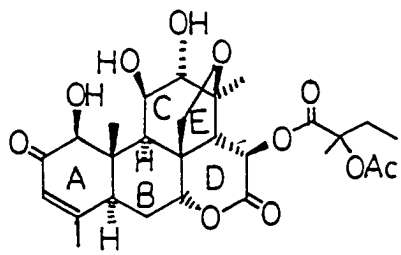
The two most widely studied quassinoids are bruceatin 8a and quasimarin 9. Bruceantin was first isolated, along with bruceantarin 8b





8a R = CO-C(CH3)=CH-CH3

8b R = COC_6H_5

8c R = $COCH_3$

9

by Kupchan et al. in 1973 (7). They were found to have structures very similar to the previously known compound brucine B 8c (8). These compounds were extracted from the bark and leaves of Brucea antidysenterica Mill., a tree used in Ethiopia as a treatment for cancer. While bruceantarin and bruceine B exhibited only moderate biological activity, bruceantin appeared promising. It showed both significant antileukemic activity against P-388 lymphocytic leukemia over a 50-100 fold dosage

range at the microgram per kilogram level, and a cytotoxicity level (ED_{50}) against KB cell culture at a concentration of one nanogram per milliliter (7). Bruceantin was later found to show significant activity against the L-1210 lymphoid leukemia, and against two solid murine tumor systems: the Lewis lung carcinoma and the B-16 melanocarcinoma (9). Kupchan (10) believes the enhanced activity of bruceantin is due to the presence of the α,β-unsaturated ester in the side chain at C-15 in the D ring. His view is supported by recent findings that the C-15 ester functionality is essential for antileukemic activity in the quassinoids (11). The antileukemic activity is believed to be due to deactivation of the DNA synthesizing enzymes (12). Bruceantin has also been studied as both a possible antimalarial (13) and anti-inflammatory (14) agent.

As a result of these findings, bruceantin was chosen for toxicity studies in preparation for clinical trials. Unfortunately, it has not proven to be as effective as hoped, and its future as a chemotherapeutic agent is in doubt (15).

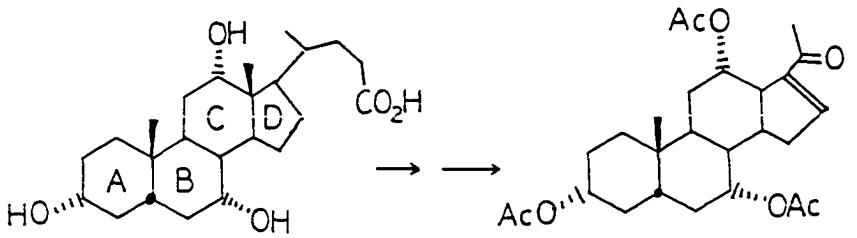
Quasimarin was first isolated in 1976 by Kupchan and Streelman, from the sap of Quassia amara L., a tree native to Costa Rica (16). It has exhibited significant activity against P-388 lymphocytic leukemia in mice at levels as low as fifty micrograms per kilogram body weight, and has shown in vitro activity against cells derived from human carcinoma of the nasopharynx (KB) at levels of one to ten nanograms per milliliter solution.

The potent biological activity exhibited by the quassinoids has prompted many efforts to synthesize them in the short time since their

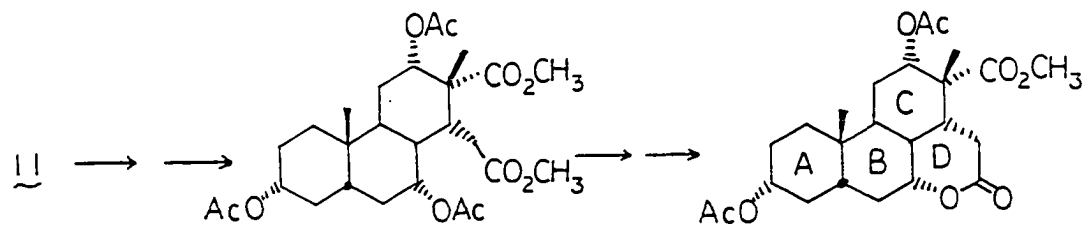
discovery (17-36). While most synthetic work to date has centered on quassin (17-23), other members, most notably bruceantin (27-32) and quasimarin (34-36), have attracted attention.

Synthetic approaches to quassin have included rearrangement and functional group manipulation of readily available biomolecules (17,18) and utilization of the Diels-Alder reaction, either intermolecularly (21-23) or intramolecularly (19,20).

The rearrangement schemes have centered on a biomimetic type of degradation of the steroid nucleus to form the quassin skeleton. Work done by Dias and Ramachandra (17) focused on conversion of the D ring of cholic acid 10 to the δ-lactone of quassin. Cholic acid was converted to the methyl ketone 11 and then carried on to the diester 12. Compound 12 was transformed to the δ-lactone containing 13 in four steps. While



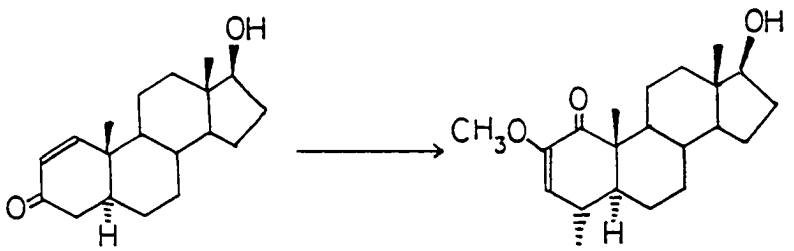
10 11



12 13

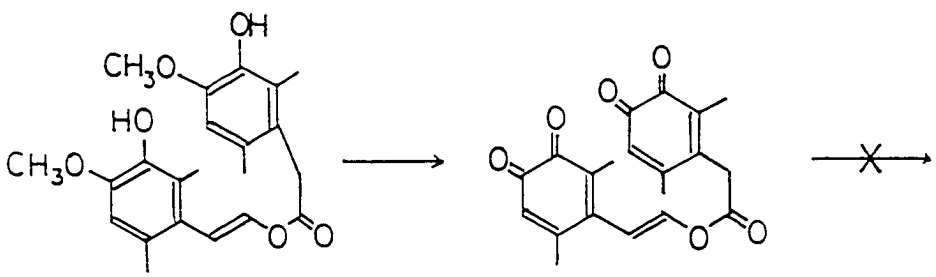
this route forms the necessary δ-lactone, the critical quaternary center at C-8 is not in place. The configuration at C-5 must be inverted, and appropriate functionality must be introduced into the A and C rings.

The steroid nucleus was also the basis of a successful approach to the A ring of quassin (18). Starting from 14, compound 15 was prepared in six steps in 24% yield.



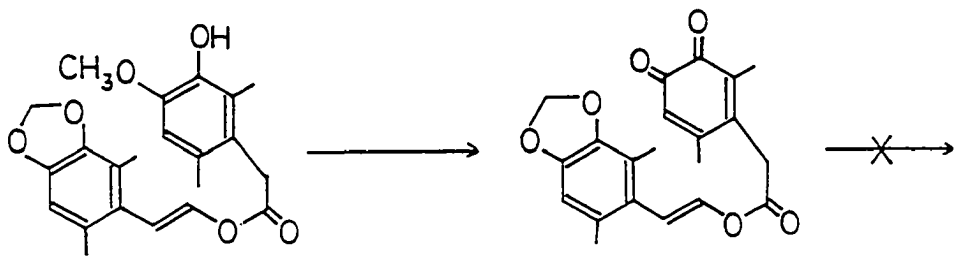
14 15

In two unsuccessful approaches, Mandell et al. (19,20) attempted to utilize an intramolecular Diels-Alder reaction. When the bisorthoquinone 17, formed by treatment of 16 with silver(II) oxide and nitric acid, failed to undergo a Diels-Alder cyclization, it was believed to be due to the presence of an electron withdrawing group on the diene (19). In an attempt to overcome the problem, the monoorthoquinone 19 was generated



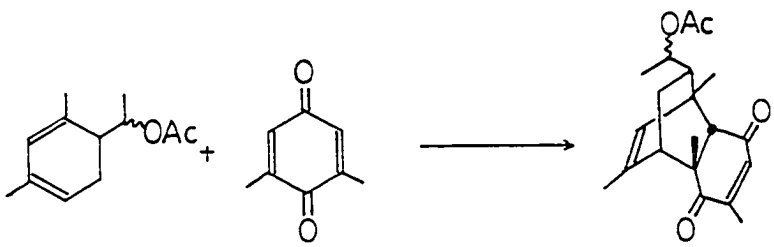
16 17

from compound 18. It also failed to undergo the desired Diels-Alder reaction, probably due to steric factors inhibiting the molecule from attaining the conformation necessary for cyclization (20).

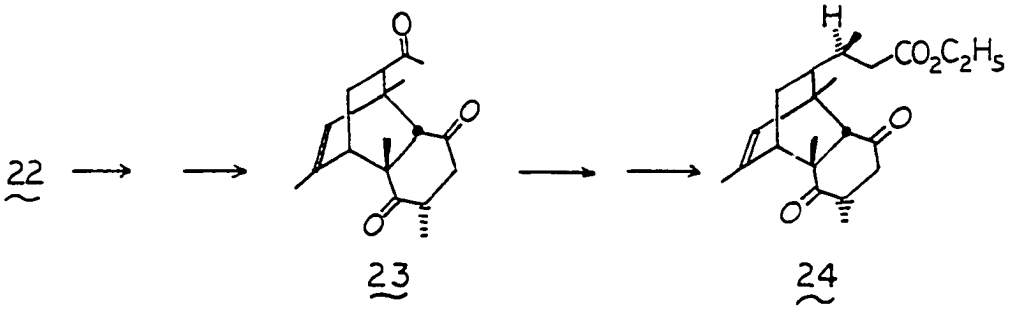


18 19

Stojanac et al. (21) and Stojanac et al. (22), in their synthesis of a secc derivative of quassin, made effective use of a Lewis acid catalyzed Diels-Alder reaction to control regio- and stereochemistry. Reaction of diene 20 and quinone 21 in the presence of boron trifluoride etherate gave compound 22 as a 1:1 mixture of acetates. Compound 22 was reduced, hydrolyzed, oxidized and epimerized to give methyl ketone 23, which was converted to 24 in three steps. Compound 24 contains all of the skeletal carbons of quassin, along with the correct relative configuration at all nonepimerizable centers. Bromination of 24, oxidation,

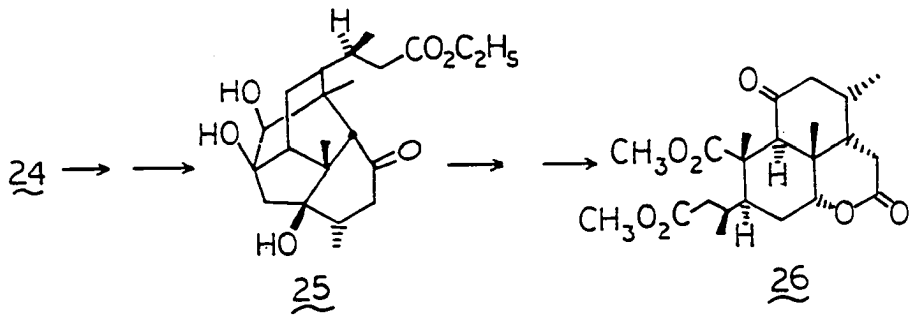


20 21 22



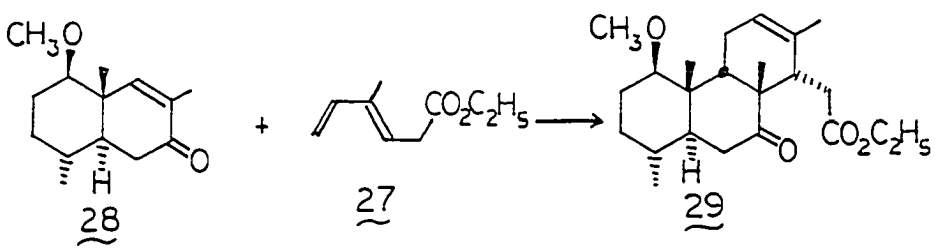
22 23 24

reduction and cyclization gave 25, which was carried on, in 60% overall yield, to give the seco derivative 26. This work is an excellent example of regio- and stereocontrol in the synthesis of a complex molecule.

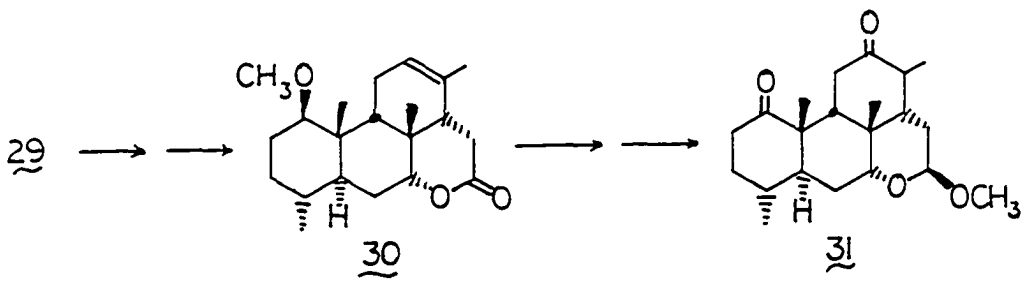


24 25 26

The only total synthesis of quassin to date has been accomplished by Grieco et al. (23). They utilized an intermolecular Diels-Alder reaction between diene 27 and dienophile 28 catalyzed by aluminum trichloride to yield tricyclic compound 29. Reduction of 29 gave lactone 30, which was

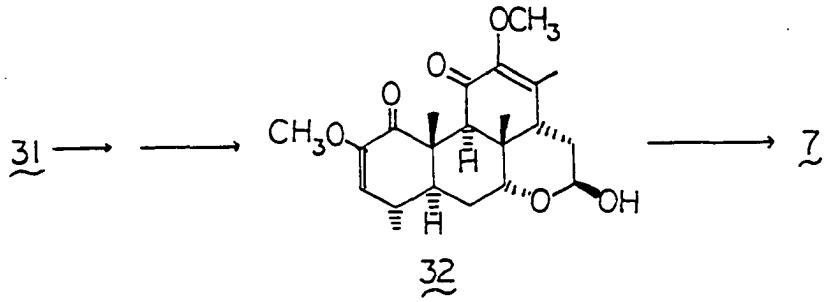


28 + 27 → 29



29 → → 30 → → 31

further reduced to the lactol and protected as the monomethyl acetal. Compound 30 was transformed into 31 in five steps in high overall yield. Oxygenation of both ketones was accomplished using MoOPH (molybdenum pentoxide-hexamethyl phosphoric triamide-pyridine complex) (24). Further transformation gave neoquassin 32, which was oxidized to give quassin 7. While much of the work carried out in efforts to synthesize



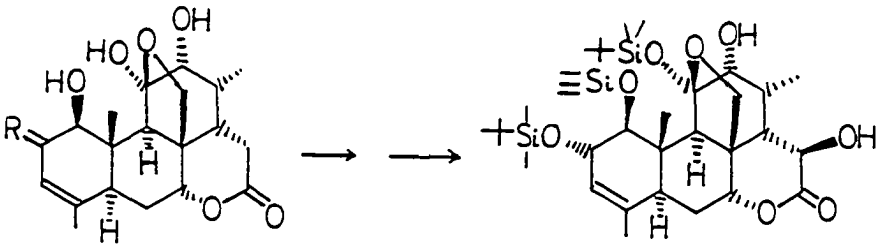
31 → → 32 → 7

quassin is applicable to similar systems, the requirement for oxygenation at the C-8 methyl group in many quassinoids, particularly bruceantin 8a and quasimarin 9, would probably doom a strictly analogous synthetic strategy.

Quassinoids containing a tetrahydrofuranyl D ring have also been the objects of considerable interest. Attempts at their synthesis have been carried out using the following strategies: rearrangement and functionalization of biomolecules (24-27), annulation schemes (28,30-31),

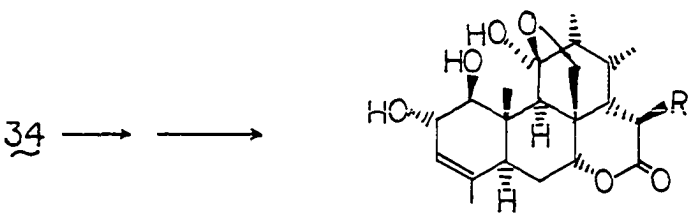
intramolecular Diels-Alder reactions (32,33), and intermolecular Diels-Alder reactions (34-36).

Functionalization approaches using biomolecules have centered on the formation of the δ-lactone D ring of the quassinoids. Starting with relatively abundant chaparrin 33a, Caruso and Polonsky (25) were able to form the oxygenated δ-lactone 34, in three steps, which they carried on to a number of functionalized derivatives 35. Testing of these derivatives for biological activity is now underway.



33a R=α-OH, β H
33b R= O

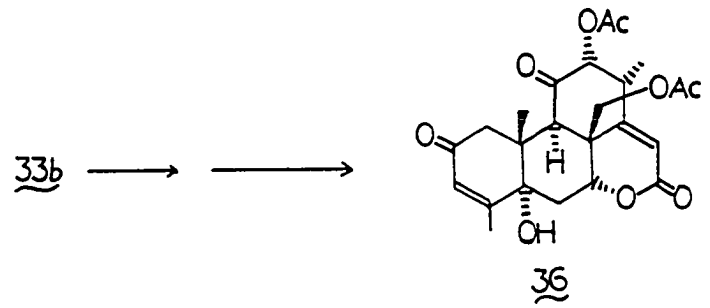
34



35a R=-$O_2CCH_2CH(CH_3)_2$
35b R=-$O_2C(CH_2)_6CH_3$
35c R= -$(CH_2)_3CH_3$
35d R= -$(CH_2)_6CH_3$

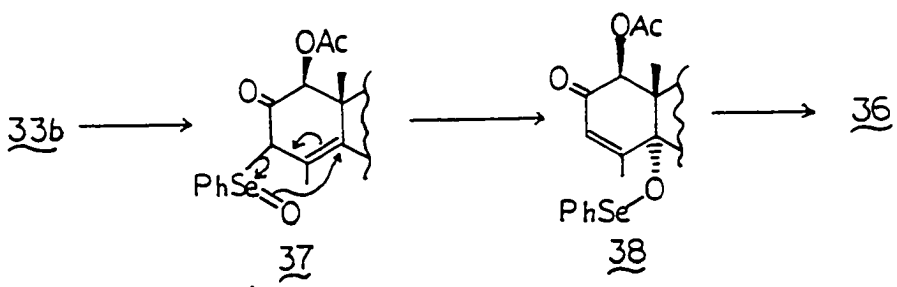
In a similar approach, Khôi and Polonsky (26) transformed chaparrinone 33b into the unsaturated lactonic seco derivative 36, with protection of the alcohols, followed by treatment with phenyl seleninic

anhydride. Their proposed mechanism for incorporation of the axial

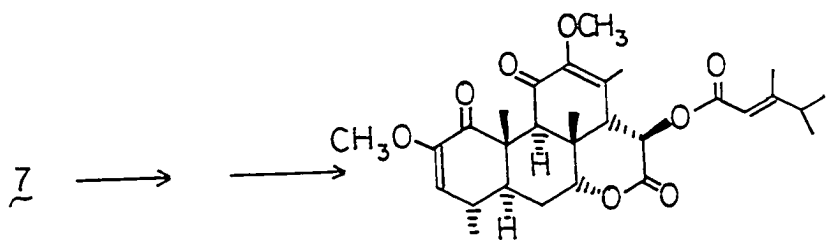


36

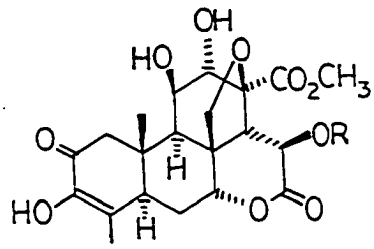
hydroxyl group at C-5 begins with formation of the selenoxide 37 from the enol form of the A ring enone in chaparrinone. The selenoxide then rearranges to the selenenyl ether 38, which can be cleaved to yield the alkoxide, which upon acidification gives the axial alcohol.



Murae and Takahashi (27) were able to convert quassin 7 into a D ring analog of bruceantin 39 via a reduction, elimination and oxidation sequence.

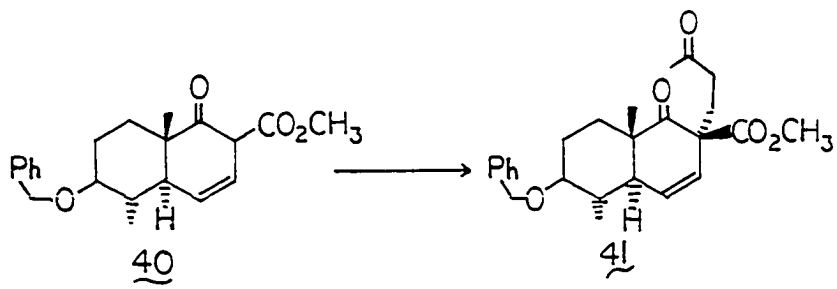


39

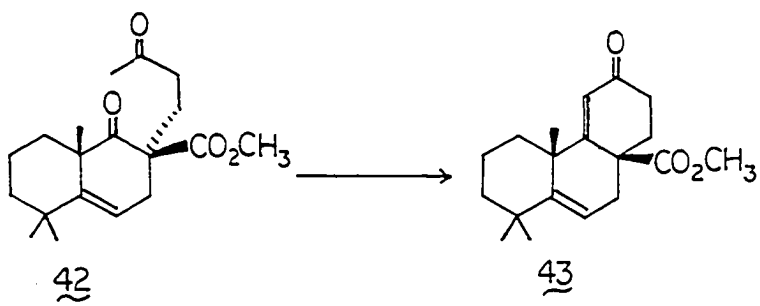


8a R = CO

Work towards bruceantin 8a using a Robinson annulation route was undertaken by Snitman et al. (28). While compound 40 would undergo a Michael addition to methyl vinyl ketone upon treatment with base, the intermediate formed, 41, could not be cyclized in an aldol condensation. The less functionalized compound 42 would only afford small amounts of aldol product 43.

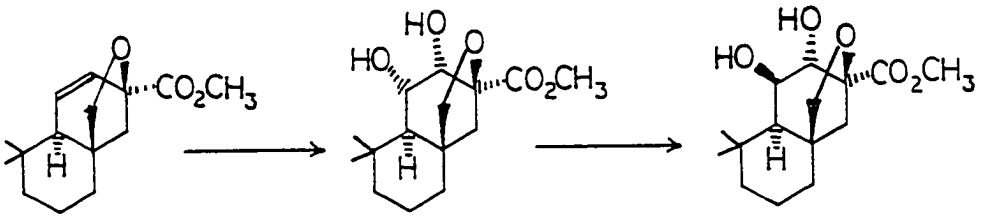


40 41



42 43

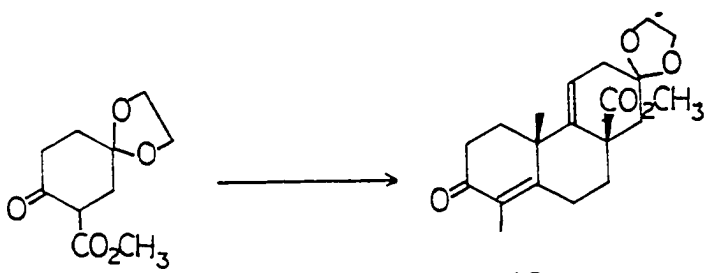
Dailey and Fuchs (29) have carried out model system studies to form the BCE ring system of bruceantin. While epoxidation and epoxide opening of the olefin present in 44 proved unsuccessful, osmium tetroxide afforded good yields of the cis diol 45. Selective oxidation of the equatorial alcohol in 45, followed by reduction, gave trans diol 46.



44 45 46

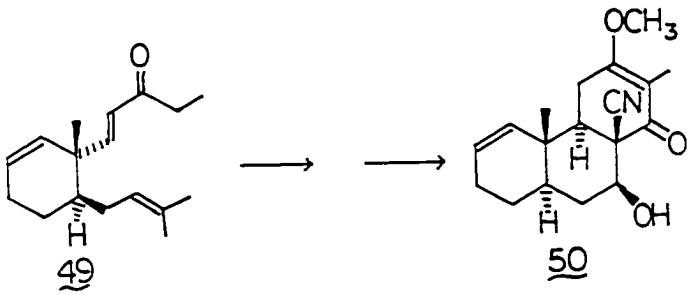
While this system cannot itself be carried on, it proves the feasibility of the approach.

Pariza and Fuchs (30) have been able to effect a double annulation sequence on compound 47, using excess sodium methoxide and ethylvinyl ketone, to give tricyclic intermediate 48. This compound possesses both quaternary centers at C-8 and C-10, as well as oxygenation at the C-10 methyl group. Although useful functionality is available, formation of the δ-lactone ring could prove troublesome.



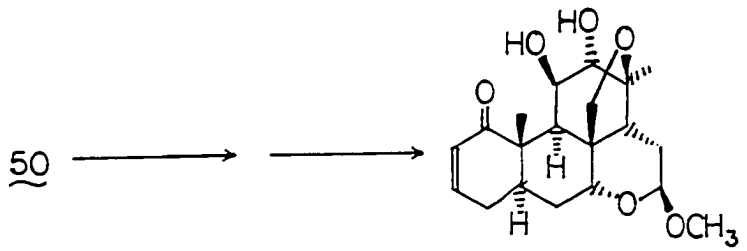
47 48

A novel annulation sequence has recently been published by Batt et al. (31). Addition of ethyl cyanoacetate to 49, followed by ozonolysis and cyclization, gave 50. Intermediate 50 was carried on to a number of



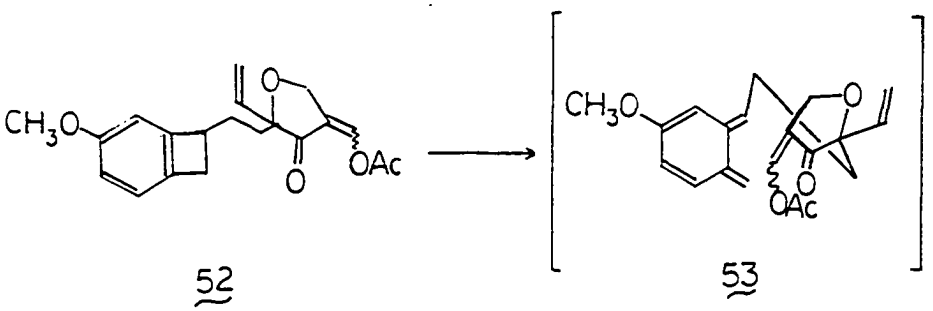
49 50

oxygenated products, including 51, which is undergoing biological testing.

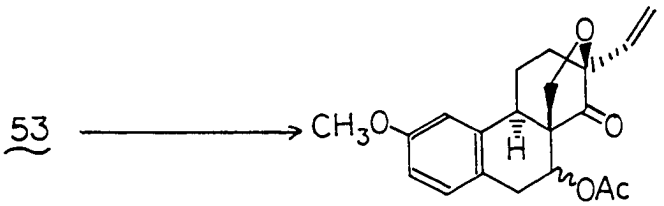


51

An intramolecular Diels-Alder reaction of an orthoquinodimethane was used by Shishido et al. (32) in their approach to bruceantin. Thermolysis of benzocyclobutane 52 generated the orthoquinodimethane 53 *in situ*, which cyclized to give tetracyclic compound 54. While 54 possesses the requisite stereochemistry for bruceantin, there appears to be no easy way, at this point, for the necessary oxygen functionality to be introduced into the C ring. A similar reaction sequence is being used by Weller and Stirchak in their approach to bruceantin (33).

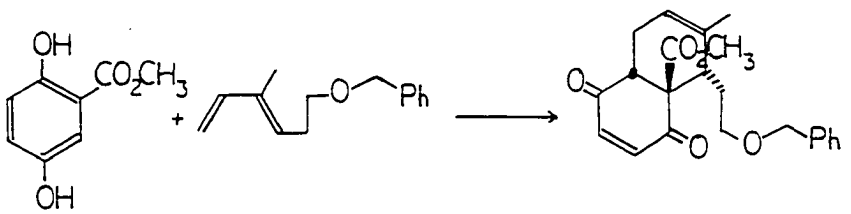


52 53

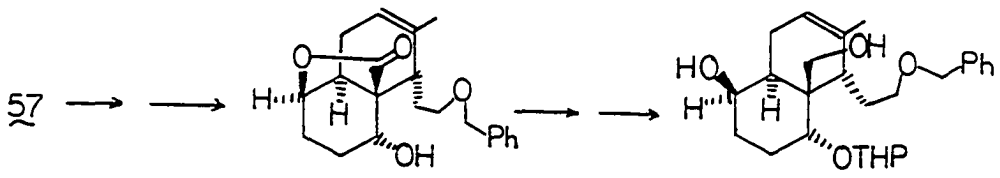


53 54

Kraus and Taschner (34) utilized an intermolecular Diels-Alder reaction of an in situ generated quinone (35), as a starting point for their synthesis of the BCDE ring system of quasimarin. Hydroquinone 55 was oxidized in situ with silver(I) oxide and trapped with diene 56 to give bicyclic compound 57. Compound 57 was then reduced, epimerized and reduced again to give lactone 58. Protection and reduction gave the selectively protected tetraol 59. This intermediate was then carried on,

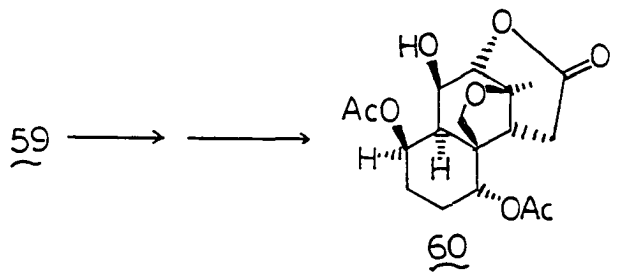


55 56 57



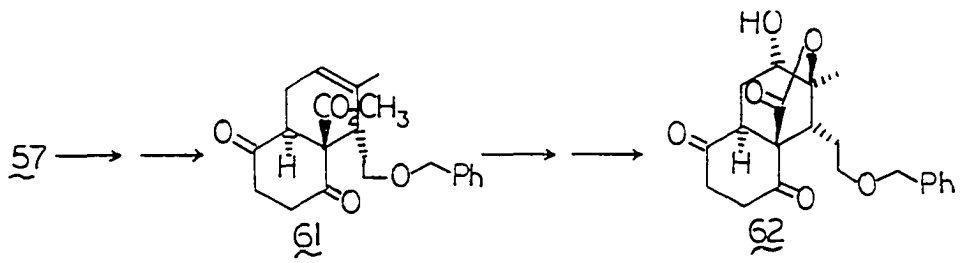
57 → → 58 → → 59

in nine steps, to lactone 60, which possesses the required stereochemistry for the BCDE ring system of quasimarin.

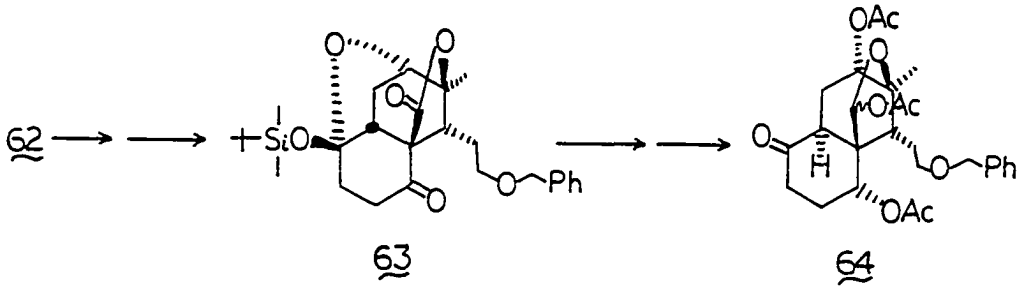


59 → → 60

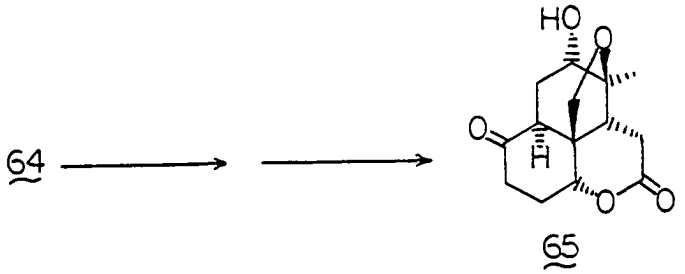
An improvement in this approach has recently been published (36). Reduction and epimerization of Diels-Alder adduct 57 gave 61, which was epoxidized, and opened under acidic conditions to yield lactone 62. Lactone 62 was selectively ketalized with epimerization at the ring junction to give the monoprotected ketone 63, which was reduced, deprotected, and acylated to yield tricyclic ketone 64. Compound 64 was subjected to



57 → → 61 → → 62



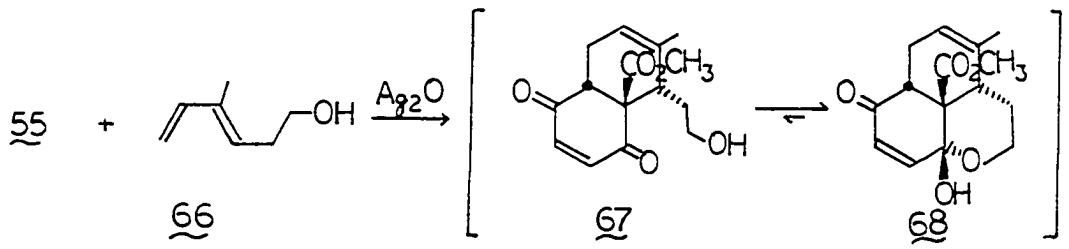
ionic hydrogenation to reduce the protected lactol to the corresponding tetrahydrofuran, and debenzylated, oxidized and saponified to give 65 in 29% overall yield from 61.



While the work to this point has aptly addressed the problems of functionality and stereochemistry in the right hand portion of quasimarin, no attempt has been made to incorporate either the A ring or the methyl group at C-10. The present investigation was done to develop methodology by which these problems could be overcome.

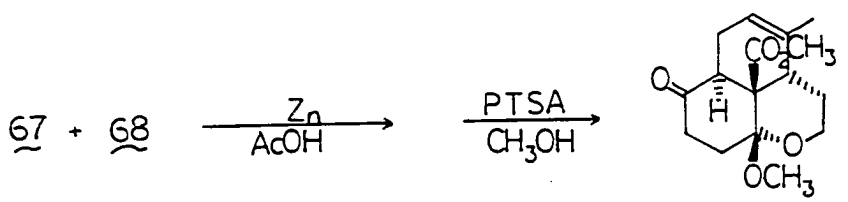
RESULTS AND DISCUSSION

Drawing upon expertise already present within the research group, an intermolecular Diels-Alder approach to the quassinoid skeleton was undertaken. Hydroquinone 55 was oxidized with silver(I) oxide and trapped with diene 66 to give an equilibrium mixture of enedione 67 and hemiacetal 68. Study of the vinyl region of the proton NMR indicated



66 67 68

that the equilibrium favored 68 by a ratio of 4:1. Treatment of the mixture with zinc and acetic acid resulted in the reduction of the electron deficient olefin. Treatment of the crude reduction product with catalytic p-toluenesulfonic acid (PTSA) in methanol resulted in formation of acetal 69, with concomitant epimerization of the ring juncture from cis to trans. While the reduction required 24 hours to go to

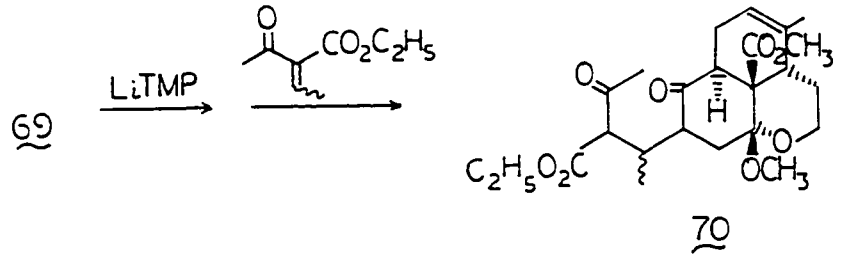


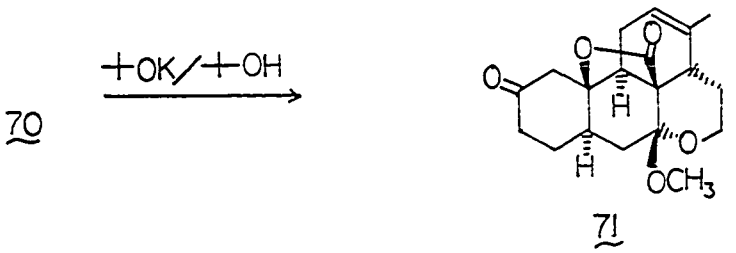
69

completion using mechanical stirring, sonication of the reaction mixture,

with a laboratory cleaning bath, gave total conversion in less than 15 minutes. The dramatic rate enhancement can be attributed to ultrasonic cavitation constantly creating a clean metal surface on which the reaction can take place (37).

While the kinetic anion of 69 could be formed using lithium 2,2,6,6-tetramethyl piperidide (LiTMP), it could only be trapped with the highly reactive Michael acceptor ethylidine ethylacetoacetate (38), to give adduct 70. Attempted cyclization of 70 gave only 71, which could not be further utilized.

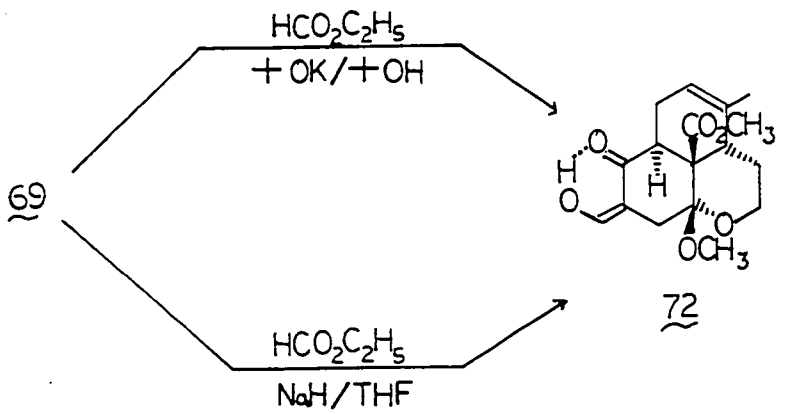




Returning to 69 with the knowledge that anion formation was possible, attempts were made to functionalize the α-position of the ketone. Several variations of the Mannich reaction were tried, including

paraformaldehyde and N-methylanilinium trifluoroacetate (TAMA) (39), bis-(dimethyl amino)-methane and trifluoroacetic acid (40), and N,N-dimethyl methylene ammonium chloride (41), all of which proved unsuccessful.

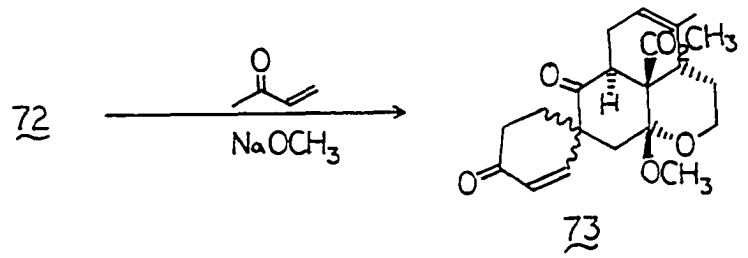
Successful functionalization of ketone intermediate 69 was achieved by α-formylation, either using potassium tert-butoxide and ethyl formate (42), or sodium hydride and ethyl formate (43). Both reagents gave good yields of α-formylation product 72, which was found to exist exclusively in its enol form. The hydroxyl proton of the enol in compound 72 was



found to be so strongly hydrogen bonded to the neighboring ketone carbonyl that it appeared in the proton NMR as a doublet, with a coupling constant of seven Hertz, as did the adjacent vinyl proton. Proton-proton decoupling experiments proved that there was indeed vicinal coupling.

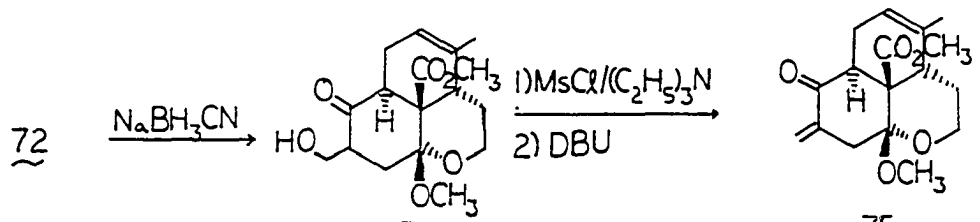
While attempts to further transform the aldehyde of 72 proved fruitless, the anion derived from it proved to be a good nucleophile. Treatment of 72 with methyl vinyl ketone in the presence of sodium methoxide led to the spiroannulated product 73. The generality of this

reaction has recently been shown by Eaton and Jobe (44).



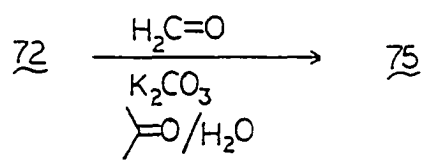
73

Since we were unable to alkylate compound 72, a method was developed to reduce the enol to the corresponding primary alcohol. Treatment with one reducing equivalent of sodium cyanoborohydride (45,46), and titration with acetic acid gave the primary alcohol 74. Alcohol 74 was converted to the corresponding mesylate (47), and eliminated with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) to give exomethylene ketone 75. Alternately,



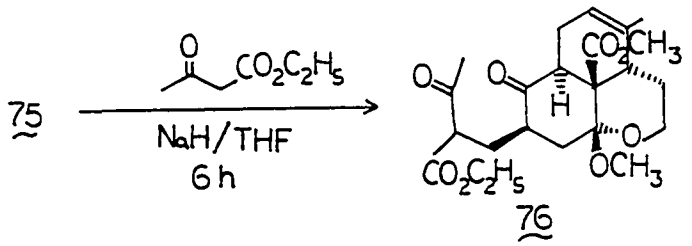
74 75

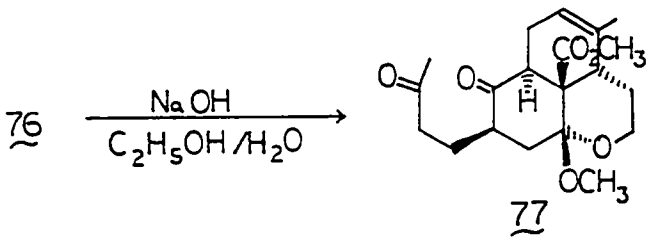
72 could be directly converted to 75 using formaldehyde and potassium carbonate (48). Single crystal x-ray analysis of 75 showed all chiral



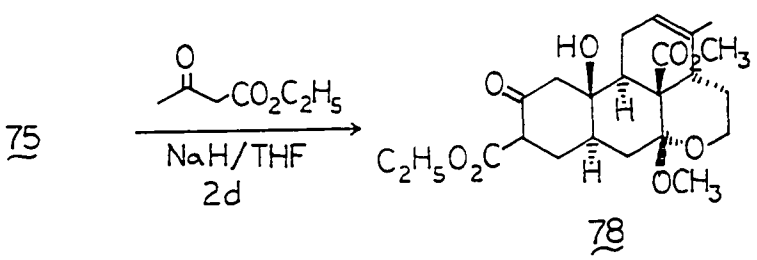
centers to be in the correct relative configuration for both bruceantin and quasimarin (Fig. 1) (49).

Exocyclic enone 75 was found to undergo a smooth Michael addition with ethylacetoacetate to give 76, which was decarboalkoxylated (50) to 77. Unfortunately, 77 could not be induced to undergo either an acid or base catalyzed aldol condensation.





The desired aldol condensation was found to occur, along with the initial Michael addition, under conditions similar to those required for the Michael addition alone. Treatment of 75 with ethylacetoacetate and sodium hydride for extended reaction times gave a high yield of 78.



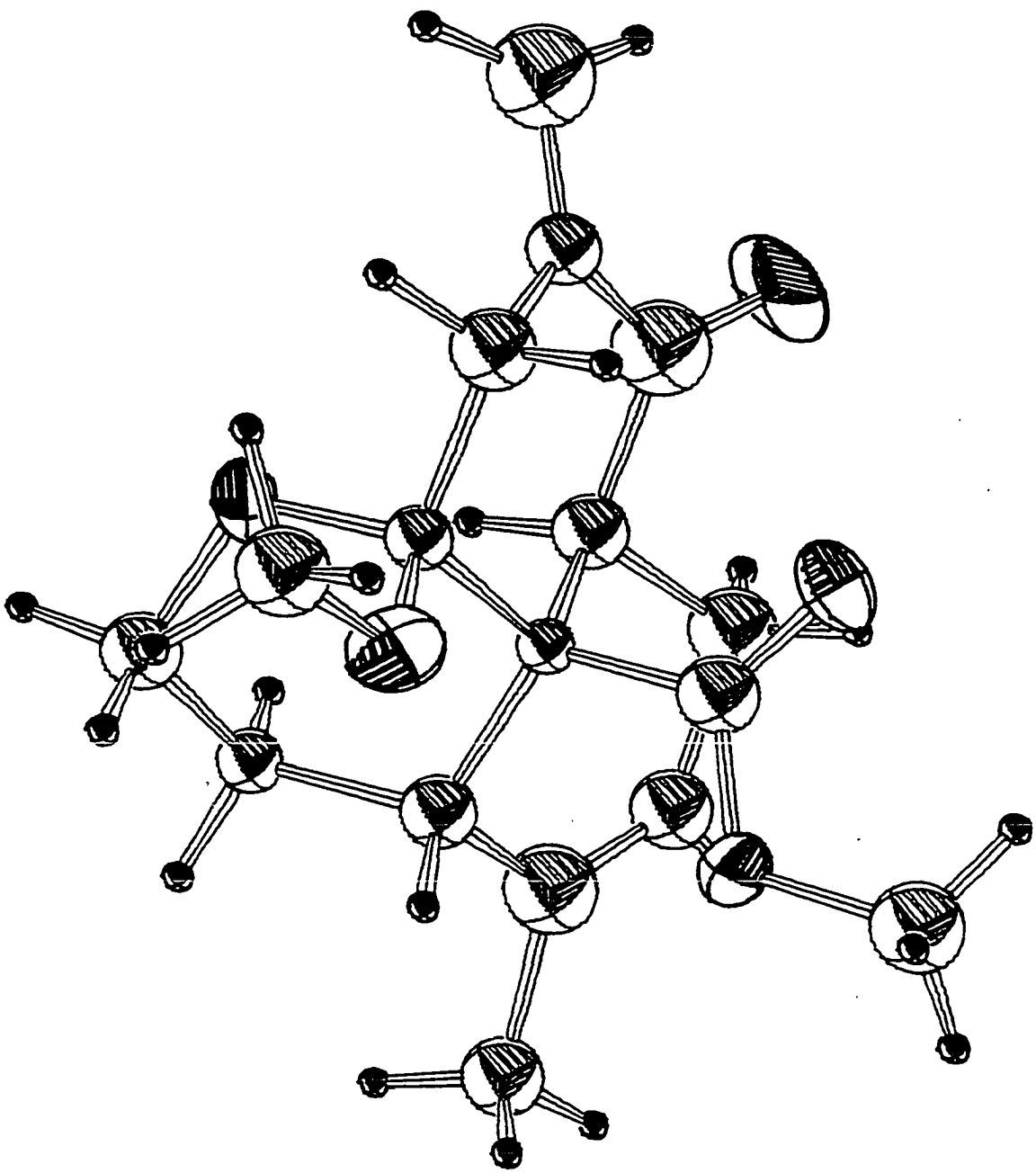
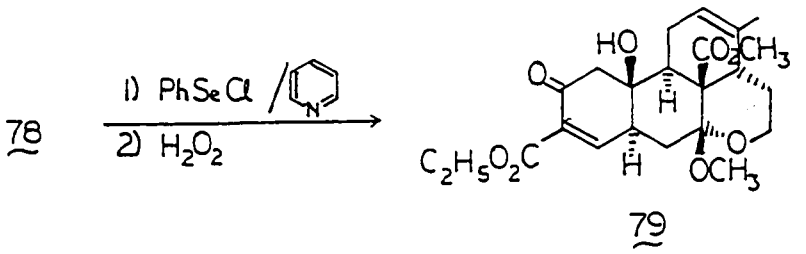


Figure 1. Perspective view of compound 75

Phenylselenenation of 78, followed by oxidative elimination (51), gave a quantitative yield of 79, which was smoothly aromatized to 80 using PTSA.



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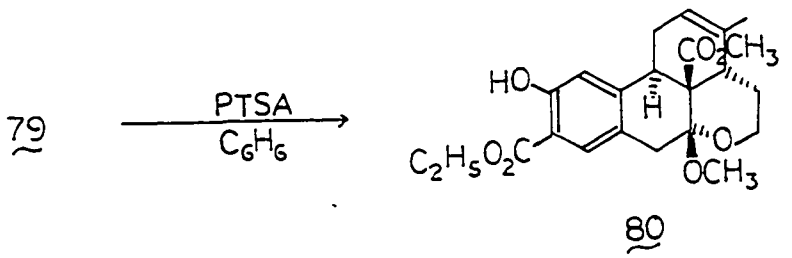
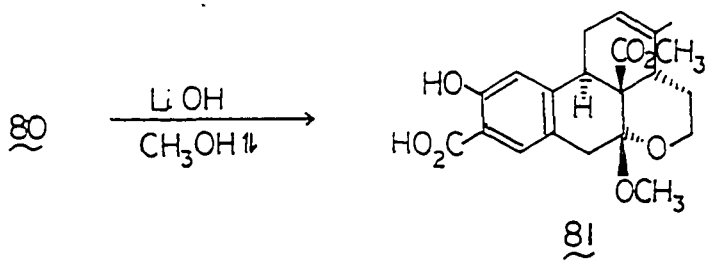


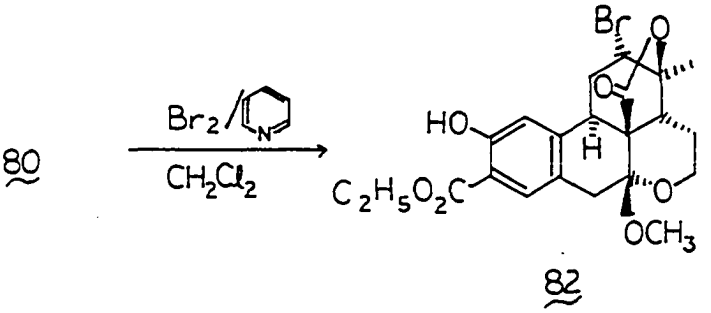
80

Decarboalkoxylation of 80 was attempted by a two step sequence involving hydrolysis and thermolysis in the presence of basic copper carbonate (52). While hydrolysis proceeded smoothly to give acid 81,



81

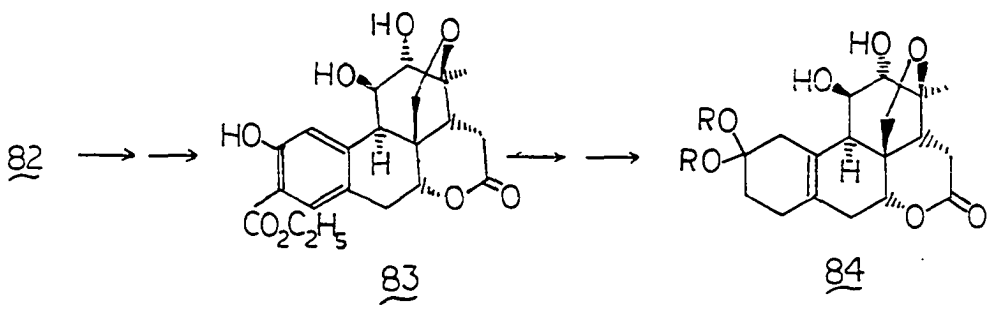
decarboxylation could not be effected. Halolactonization of 80, using bromine and pyridine, resulted in formation of pentacyclic compound 82 (53).



80 → 82

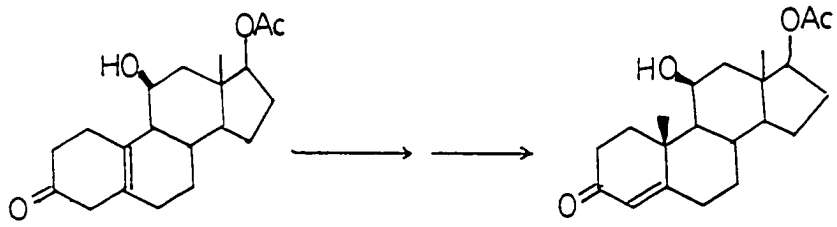
Compound 82 possesses all skeletal carbons required for quasimarin, along with appropriate groups that will allow incorporation of necessary oxygen functionality. Additionally, all chiral centers in 82 have the relative configuration present in quasimarin.

Elaboration of 82 into the quasimarin skeleton will entail C ring oxygenation using the method of Dailey and Fuchs (29) and DE ring formation by the method of Kraus et al. (36) to give 83. Hydrolysis, Birch reduction, ketalization and olefin isomerization would be predicted to



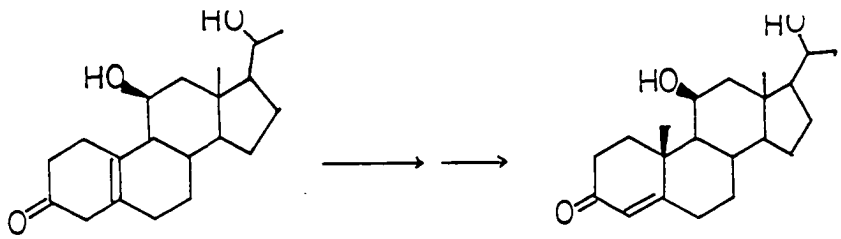
82 → → 83 → → 84

give 84. Incorporation of the angular methyl group at C-10 utilizing a Simmons-Smith reaction should be controlled by the axial hydroxyl group at C-11. Precedent for this selectivity is found in the work of Turnbull et al. (54), who methylated 85 to give 86, and Ziegler and Wang (55), who



85 86

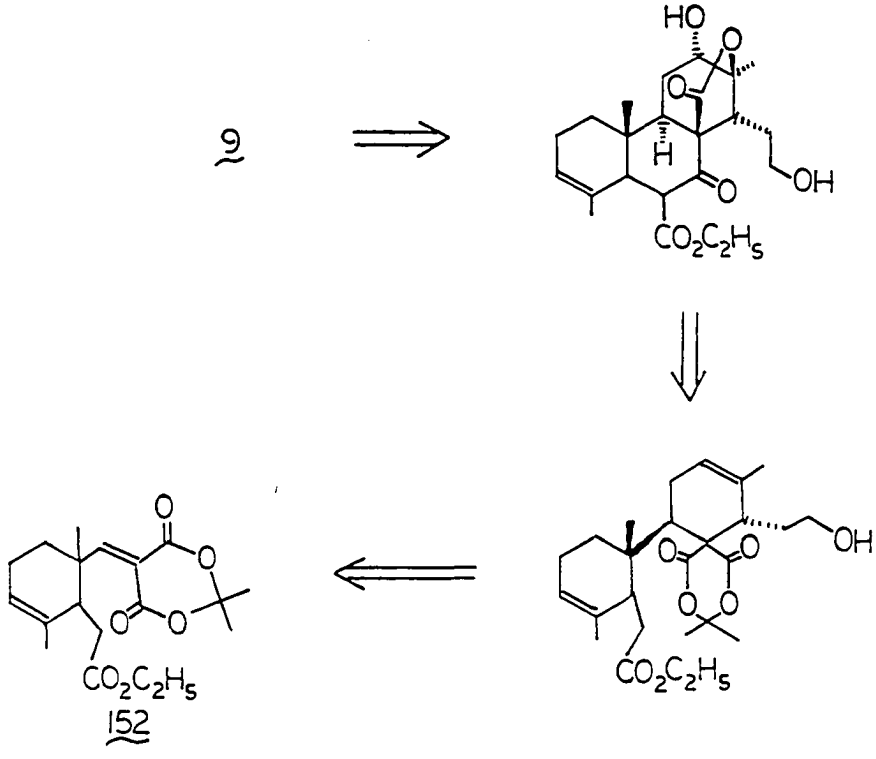
methylated 87 to give 88.



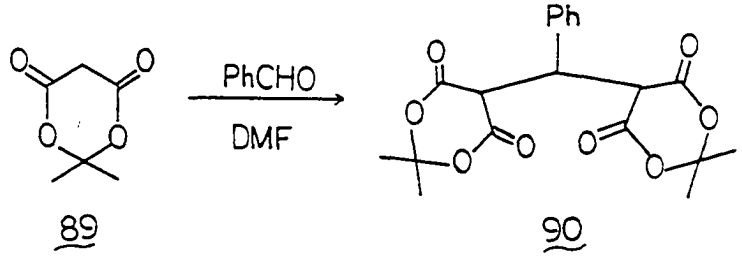
87 88

Although a functionalized pentacyclic intermediate has been made which can be transformed into quasimarin, a parallel, more direct, route was also studied. This alternate approach is dependent upon the successful formation, and Diels-Alder cyclization, of highly functionalized alkylidine isopropylidine malonates, with subsequent differentiation of the carboxyl groups.

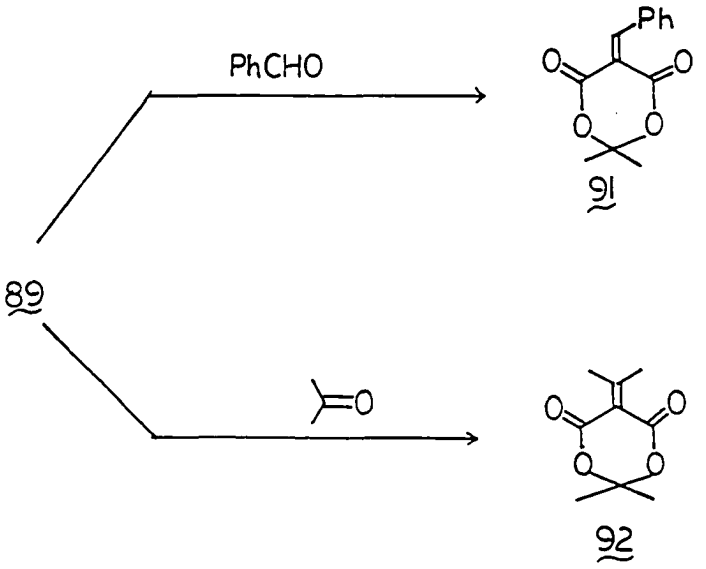
While the alkylidine and benzylidine derivatives of 2,2-dimethyl-1,3-dioxan-4,6-dione, 90, also known as Meldrum's acid (56), have been known for many years, their use in organic synthesis has been limited (57). These derivatives have mainly been used for the generation of substituted allenes (58-64). However, there are some examples of their use as lactone precursors (65,66), and in Diels-Alder reactions, both as a diene (67-69) and as a dienophile (70-73).



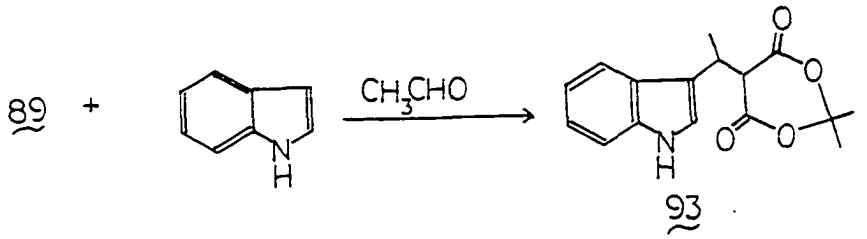
Early attempts to form alkylidine and benzylidine isopropylidine malonates proved troublesome, with the formation of products corresponding to reaction of the carbonyl group of the electrophile with two molecules of Meldrum's acid. Treatment of Meldrum's acid, 89, with benzaldehyde in dimethylformamide (DMF), gave only the adduct 90, and none of the desired benzylidine compound (74).



The first successful synthesis of benzylidine and alkylidine Meldrum's acid derivatives was carried out by Swoboda et al. (75). Using pyridine as the base, they were able to isolate the benzaldehyde 91 and acetone 92 adducts of Meldrum's acid in 58% and 25% yields, respectively, with only minor formation of side products. A novel application of the condensation of Meldrum's acid with aldehydes was carried out by Oikawa

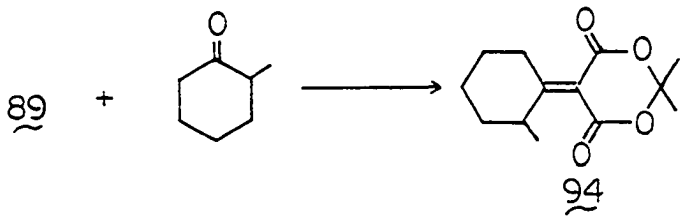


et al. (76). A trimolecular condensation was carried out using acetaldehyde, Meldrum's acid, and indole to give 93, an intermediate in their synthetic route to ellipticine. This reaction was found to be general

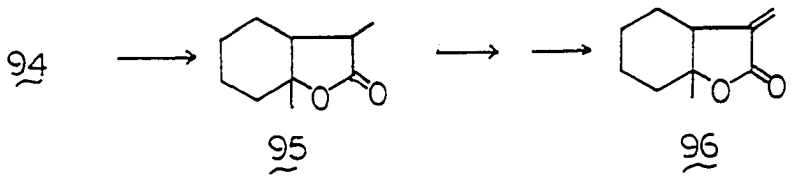


for a wide variety of aliphatic and aromatic aldehydes, with yields ranging from 80% to 98%.

The use of alkylidine isopropylidine malonates as γ-lactone precursors has been developed by Campaigne and Beckman (65). Condensation of 2-methylcyclohexanone with Meldrum's acid gave adduct 94, which formed γ-lactone 95 in high yield upon treatment with concentrated sulfuric acid. Compound 95 was carried on to form the exomethylene lactone 96.

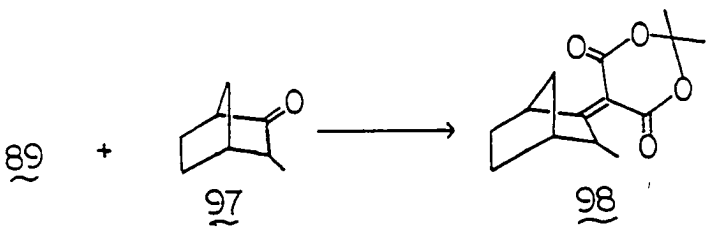


89 + → 94

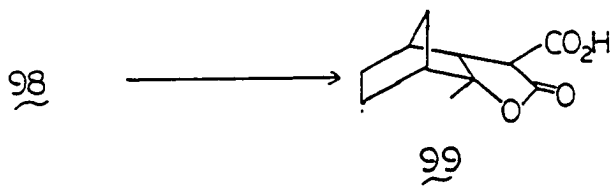


94 → 95 → 96

This reaction proved to be general for a wide variety of cyclic ketones, with lactonization always occurring towards the more substituted side of the adduct. In an extension of this work, Campaigne et al. (66) showed that the Meldrum's acid condensation-hydrolysis sequence can be effected on systems that contain a large amount of steric crowding. Compound 97 was condensed with 89 to give adduct 98 in 56% yield. Hydrolysis of 98 gave lactone 99, in 65% yield, cyclizing to the C-3 position of the



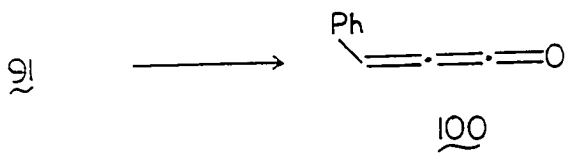
89 + 97 → 98



98 → 99

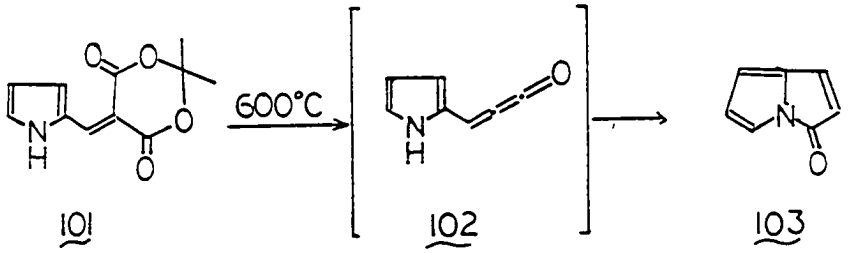
norbornane system, presumably through the more stable tertiary carbonium ion.

The pyrolysis of Meldrum's acid and its derivatives has long been known to give ketenes. This thermal decomposition was first observed by Ott in 1913 (58). The thermal decomposition of alkylidine or benzylidine Meldrum's acid adducts was found to yield methyleneketenes by Brown et al. (59). Pyrolysis of benzylidine isopropylidine malonate, 91, at 430°C gave methylene ketene 100.



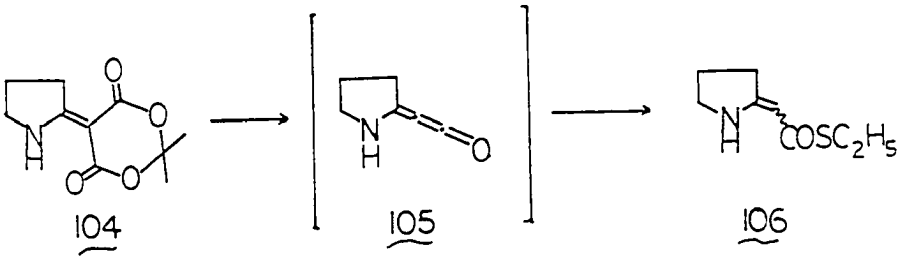
91 → 100

The synthetic utility of this reaction has been shown by McNab (60). Flash vacuum pyrolysis of 101 gave methylene ketene 102, which intramolecularly cyclized to yield bicyclic lactam 103 in 88% yield.



101 102 103

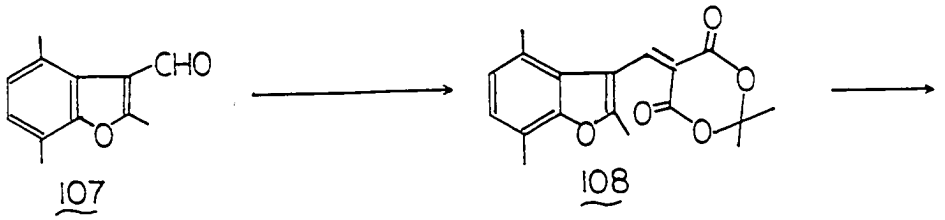
Exceptionally high reaction temperatures are not always necessary for thermal decomposition to occur. Compound 104 was found to decompose at 72°C to give methylene ketene 105, which was trapped with ethane thiol to give thioester 106 (61). These mild conditions suggest that this



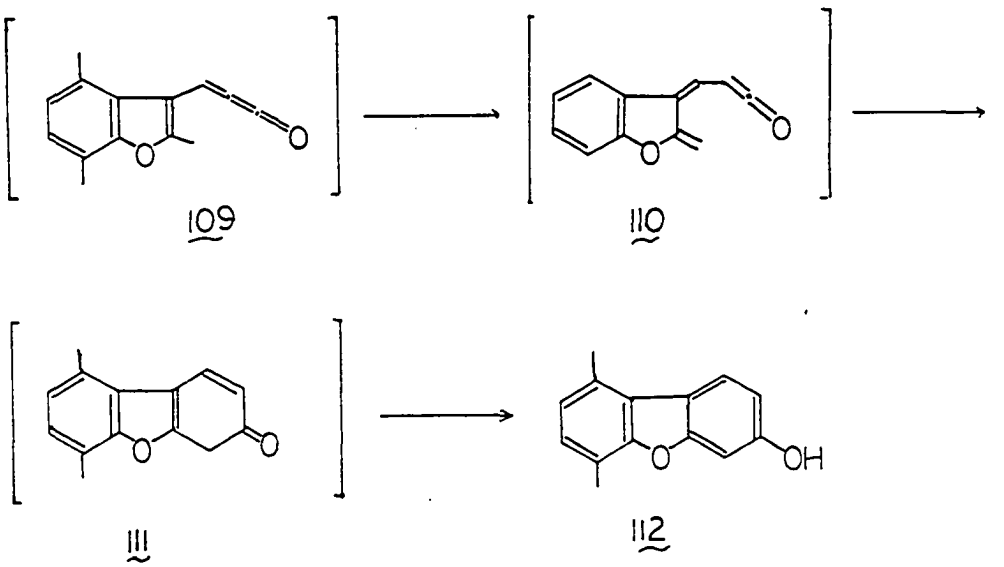
104 105 106

could be a troublesome side reaction in applications of these adducts to synthesis.

An elegant application of this pyrolysis reaction to natural products synthesis has been shown by Brown and Jones (62). Formation of the Meldrum's acid adduct of aldehyde 107, using piperidine and acetic acid

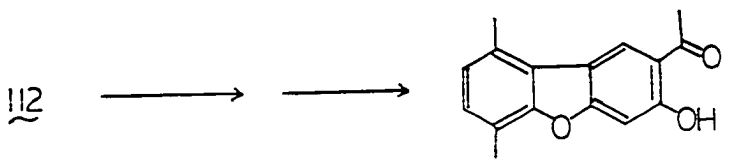


107 108



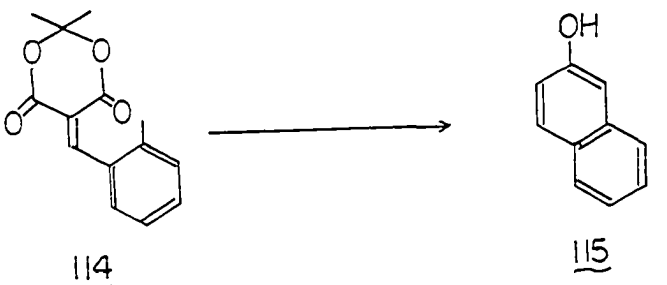
109 110 111 112

gave 108 in 61% yield. Flash vacuum pyrolysis of compound 108 gave phenol 112 in 82% yield. Thermolysis of 108 gave methyleneketene 109, which isomerized through a 1,5-hydride shift to give 110 and cyclized, forming 111. Compound 111 rapidly tautomerized to yield phenol 112. Phenol was transformed into the natural product ruscodibenzofuran 113 (63). The formation of phenol 113 was not surprising, in that the



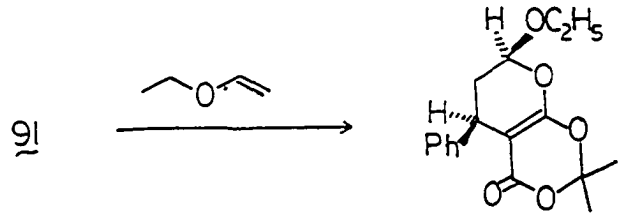
113

transformation of 114 to 115 had been reported previously (64).



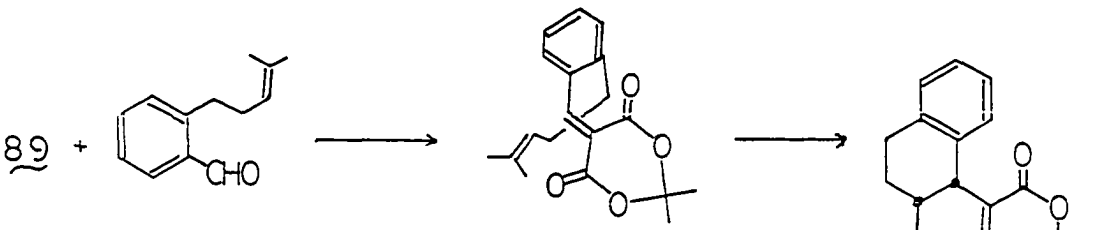
114 115

Alkylidine and benzylidine isopropylidine malonates have been used as dienes in a Diels-Alder reaction to form dihydropyrans. Bitter et al. (67) used 91 as a diene, trapping it with ethyl vinyl ether in an inverse electron demand Diels-Alder reaction to give adduct 116. An intramolecu-



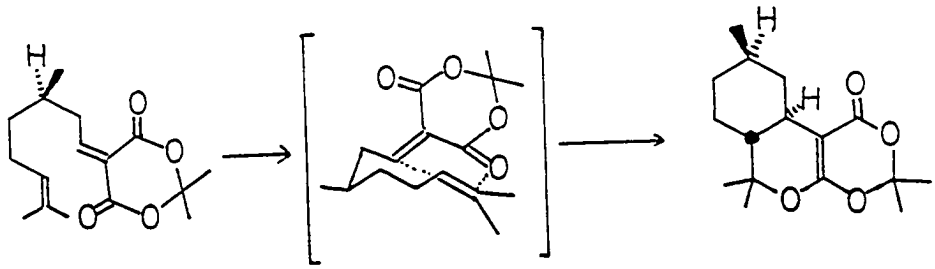
116

lar version of this inverse electron demand Diels-Alder reaction was developed by Tietze et al. (68). Aldehyde 117 was transformed into adduct 118, which underwent Diels-Alder cyclization to give dihydropyran 119. A similar cyclization of R-citronellal adduct 120, gave optically



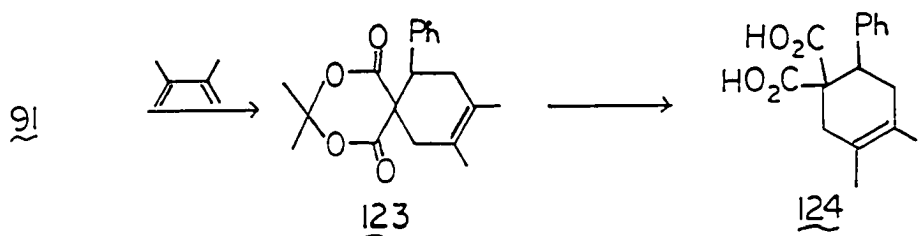
117 118 119

active adduct 122 in 95% yield and 100% enantiomeric excess (69). The reaction appears to proceed through transition state 121. Cyclization of the S-citronellal adduct gave the enantiomer of 122, indicating the reaction is stereospecific.



120 121 122

An early study by Kunz and Polansky (70) indicated that alkylidine and benzylidine isopropylidine malonates can act as effective Diels-Alder dienophiles under mild conditions when used with an electron rich diene. Compound 91 was reacted with 2,3-dimethyl-1,3-butadiene to give adduct 123, which was hydrolyzed to give diacid 124. The reaction

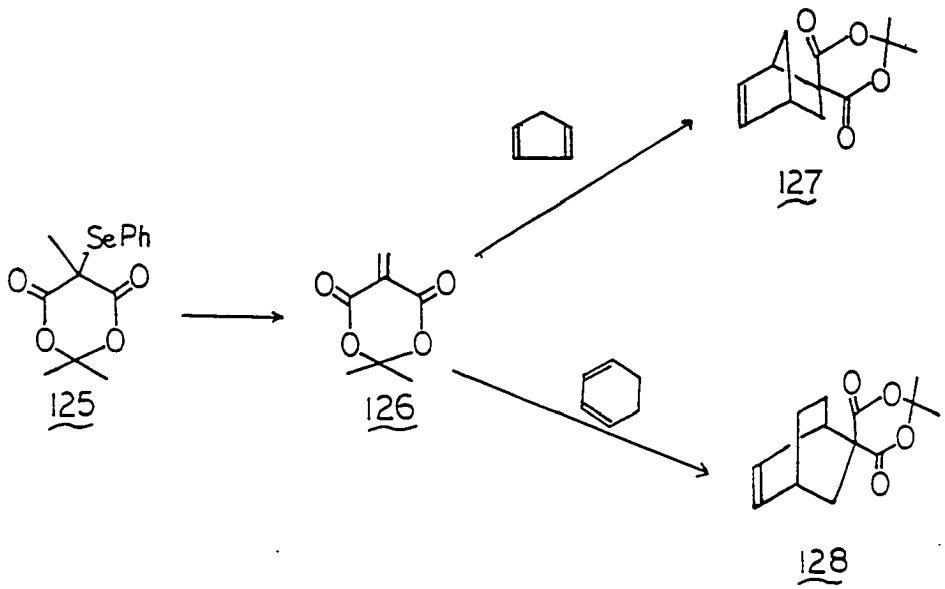


91 123 124

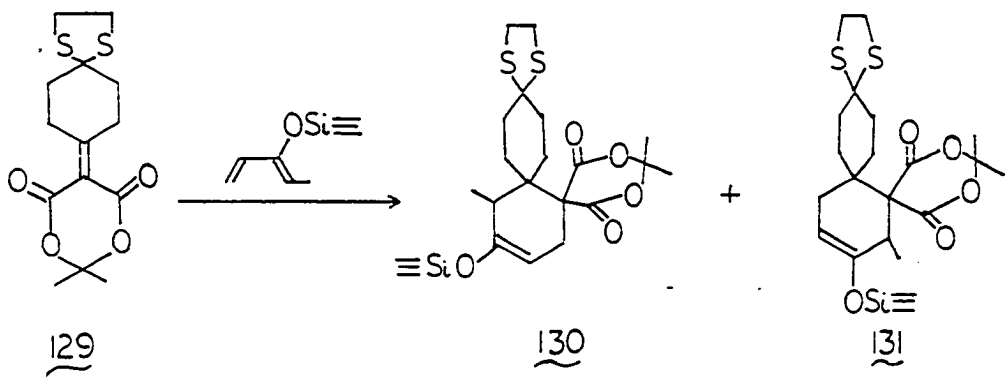
sequence was carried out with a wide variety of alkylidine and benzylidine adducts, with yields ranging from 40% to 90%. The most interesting result of their study, however, was the discovery that the Meldrum's acid adducts gave consistently higher yields, under milder conditions, than the corresponding malonates and malononitriles.

Brown et al. (71) found that Diels-Alder cyclization of the unstable methylene isopropylidine malonate could be used to form functionalized bicyclic systems. Compound 126 was formed by oxidative elimination from 125 and trapped with cyclopentadiene or 1,3-cyclohexadiene to give

adducts 127 and 128 in 53% and 28% yields, respectively. In another

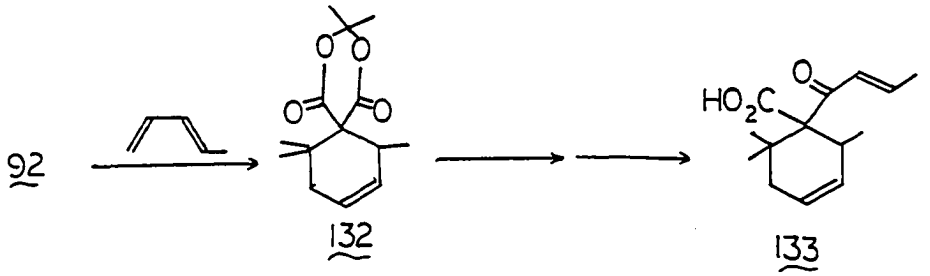


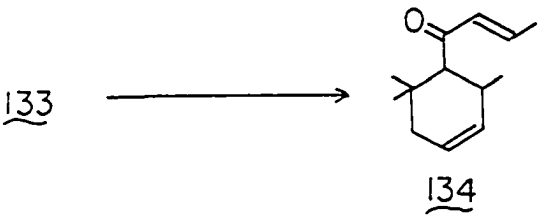
example of a Diels-Alder cyclization (72), compound 129 was treated with 3-trimethylsilyloxy-1,3-pentadiene to give 130 and 131 as a mixture of regioisomers. These compounds are to be used as intermediates in the synthesis of diterpenoids.



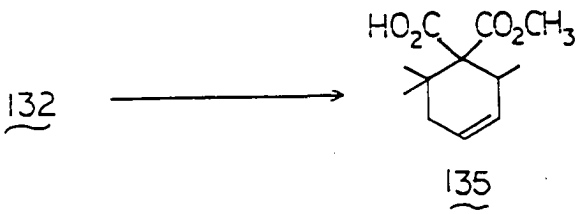
The only natural product synthesis to date utilizing the Diels-Alder cyclization of an alkylidine isopropylidine malonate is the synthesis of δ-damascone 135 by Dauben et al. (73). Cyclization of 92 with

1,3-pentadiene gave compound 132 in 60% yield. This reaction shows the





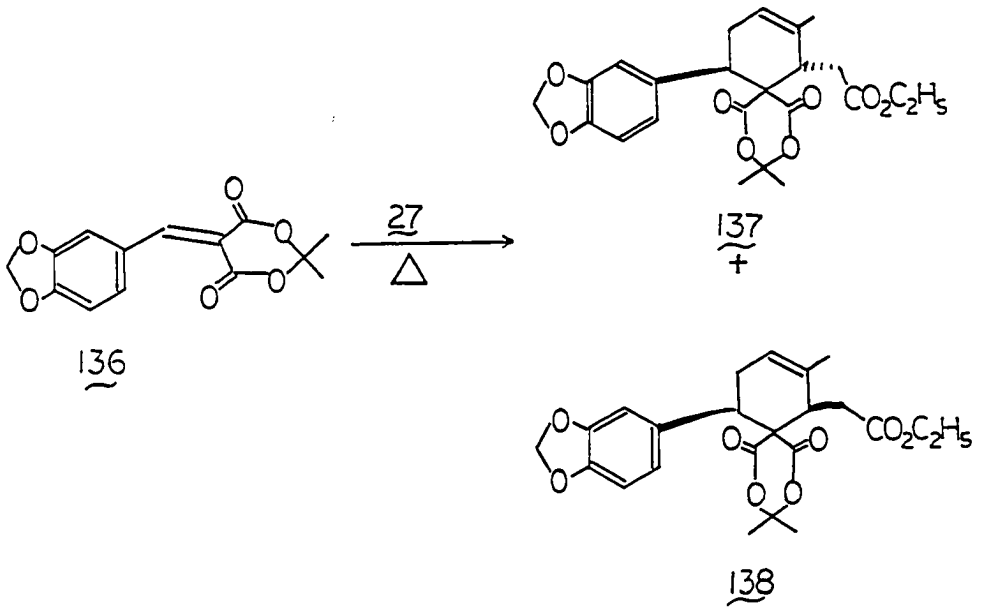
superiority of these adducts as dienophiles, since an earlier report indicated that the corresponding alkylidine malonate failed to react (77). Treatment of compound 132 with allyllithium, followed by hydrolysis, gave compound 133, which was thermally decarboxylated to give δ-damascone in 66% yield from 132. Treatment of 132 with methanolic sodium hydroxide gave a quantitative yield of 135, indicating that Meldrum's acid can act as a masked half ester of a dicarboxylic acid.



With literature precedent for both the condensation and cyclization steps, preliminary studies were undertaken to test this new approach to quasimarin. To minimize possible side reactions and to simplify

product characterization, initial reactions were carried out on benzylidine derivative 136, prepared from Meldrum's acid and piperonal by the method of Brown et al. (59).

Thermal cyclization in hot toluene of compound 136 with diene 27 gave two products, 137 and 138, in a 3:2 ratio, which were readily



separable by flash chromatography (78). The relative stereochemistry of Diels-Alder adduct 138 was confirmed by single crystal x-ray analysis (Fig. 2) (49).

Study of the structure in Fig. 2 reveals that one of the methyl groups on the dioxane ring is centered directly over the aromatic ring, at a distance comparable to one carbon-carbon bond length. Assuming that the crystal structure corresponds to the most stable conformation in solution, a significant ring current effect should be observed (79). The high field NMR of compound 138 does reveal a methyl resonance at δ

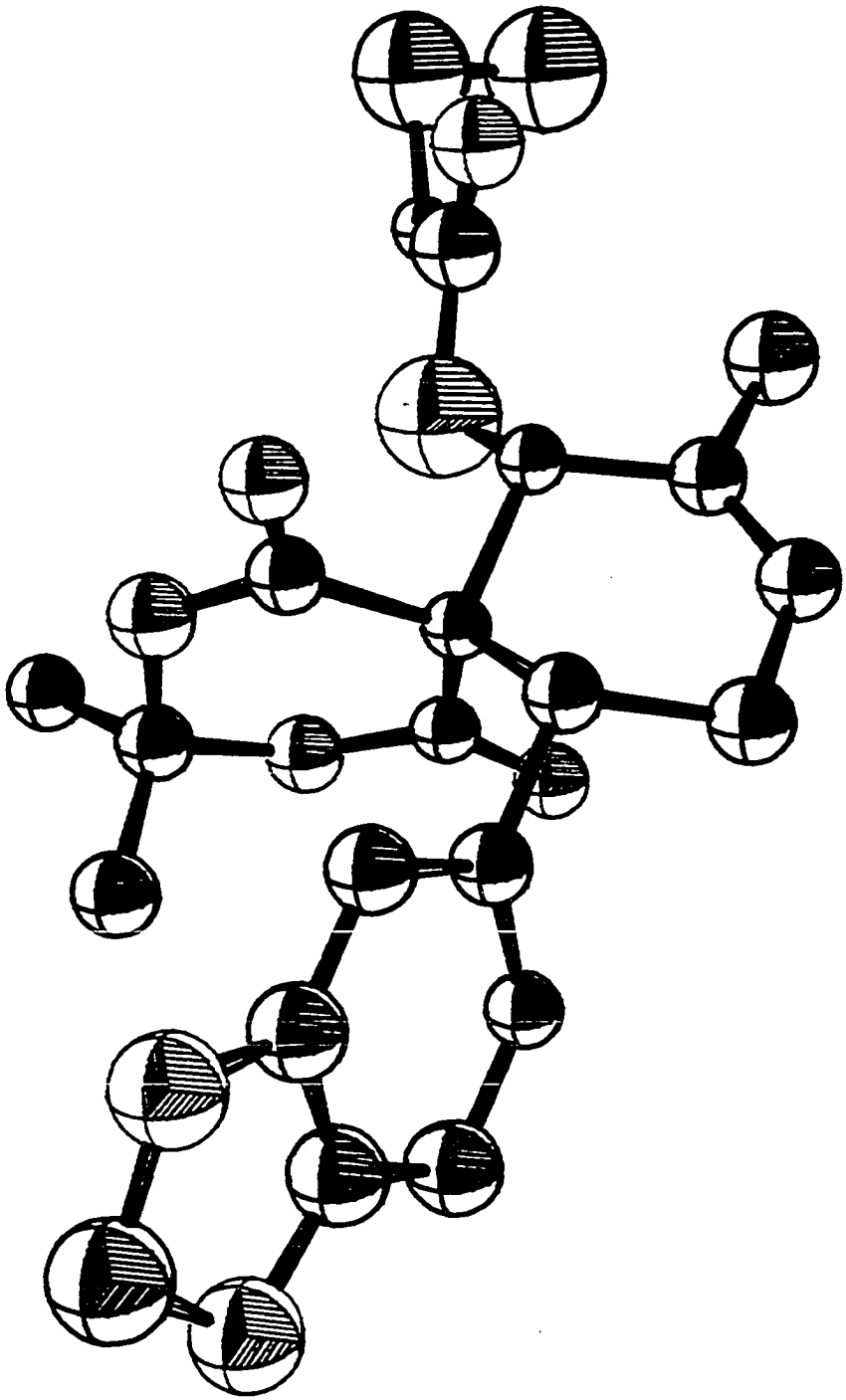
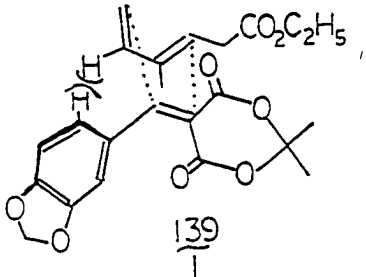


Figure 2. Perspective view of 138

0.72. This upfield shift of 1.07 ppm from the corresponding resonance in 136 corresponds to the methyl group being about 3.6 Å directly above the plane of the benzene ring (80). The methyl group anti to the aromatic ring also exhibits a small ring current shielding, but it is only a 0.20 ppm shift. Similarly, the corresponding methyl groups in adduct 137 show a smaller ring current shielding of 0.52 ppm and no shielding effect for syn and anti, respectively, possibly due to the greater conformational mobility of the compound.

The fact that 137 and 138 are not formed in a 1:1 ratio must be explained on steric grounds, since both carbonyl groups of the dienophile are equally capable of electronically controlling the cyclization. If the conformation of the dienophile is not strictly planar, that is, if the aryl ring is skewed, then the vinyl proton on C-5 of the diene will interfere with the aryl ring, destabilizing 139 as a possible transition state. The fact that 140 is apparently favored slightly over 139 implies that the dienophile is indeed skewed.



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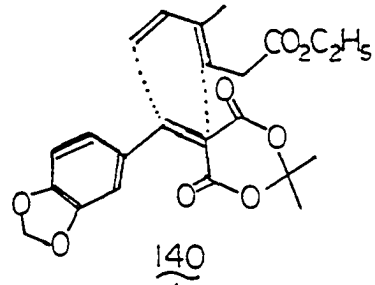
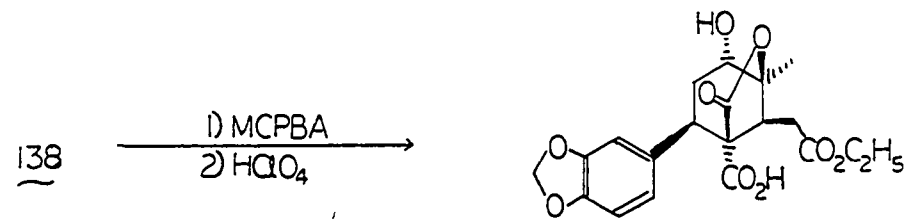


140

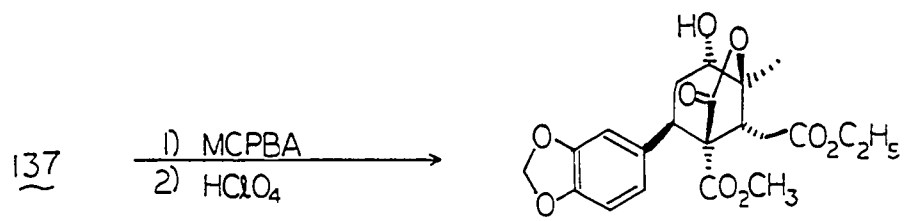
138

137

Diels-Alder adduct 138 was epoxidized from the α-face using MCPBA and hydrolyzed with perchloric acid to give lactone 141 in 82% yield (81). Similarly, adduct 137 was converted to 142 in 98% yield. By utilizing this intramolecular lactonization, the two seemingly identical carboxyl



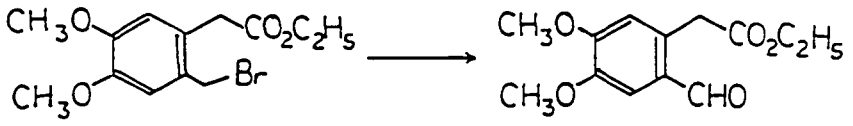
141



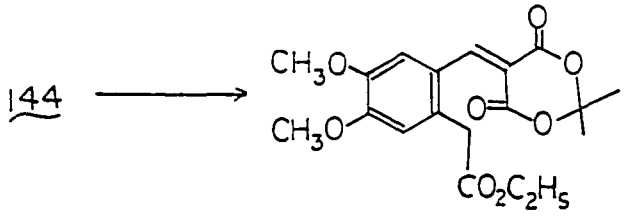
142

groups were chemodifferentiated. Only the axial carboxyl group was in a proper orientation to trap the tertiary carbonium ion formed by hydrolysis of the epoxide.

Encouraged by these results, the synthesis of dienophile 145 was undertaken. Treatment of readily available benzyl bromide 143 (82) with tetrabutylammonium dichromate (83) gave aldehyde 144. Compound 144 was condensed with Meldrum's acid to give dienophile 145 in 92% yield.

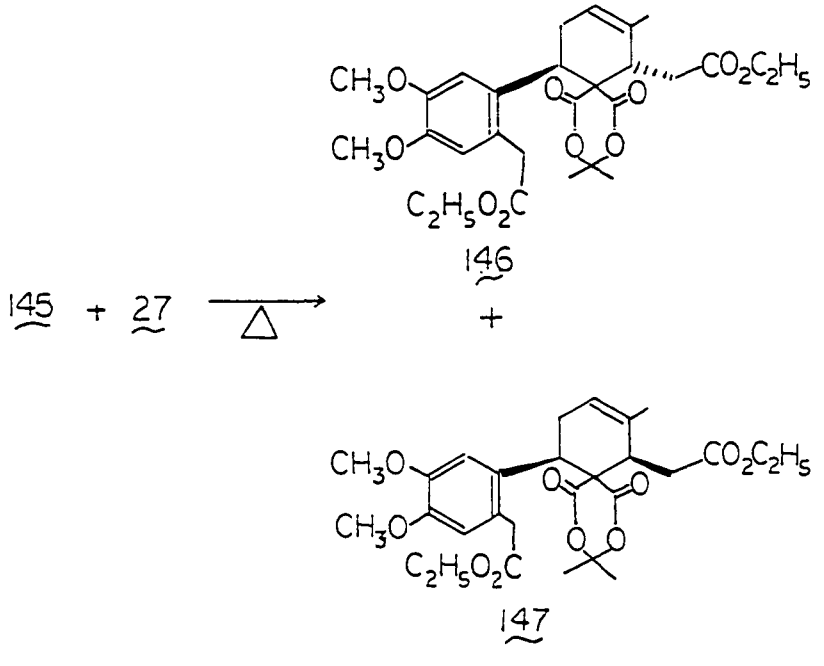


143 144



144 145

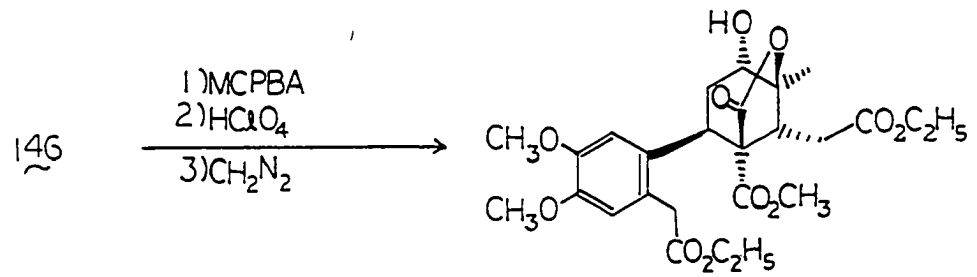
Diels-Alder cyclization of 145 with diene 27 gave compounds 146 and 147 in a 5:2 ratio in 84% yield. The increased selectivity favoring the product where the substituents on the newly formed ring are trans



145 + 27 → 146 + 147

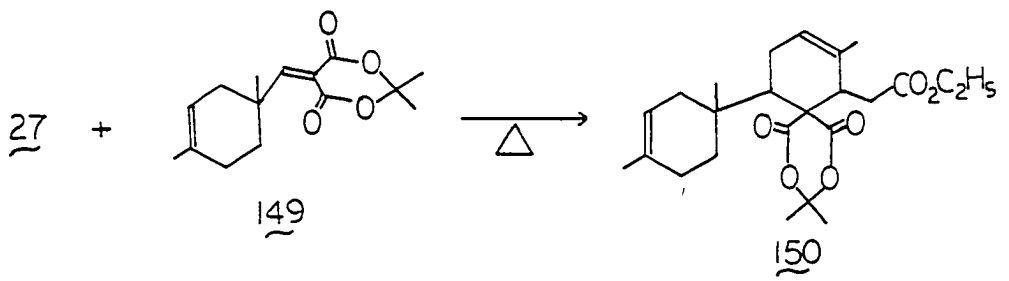
supports my postulate of steric control, since the only difference between dienophiles 136 and 145 is in the steric bulk of their aryl substituents.

Adduct 146 was epoxidized and lactonized. Due to the insolubility of the crude acid formed, purification and characterization required formation of the methyl ester 148.



148

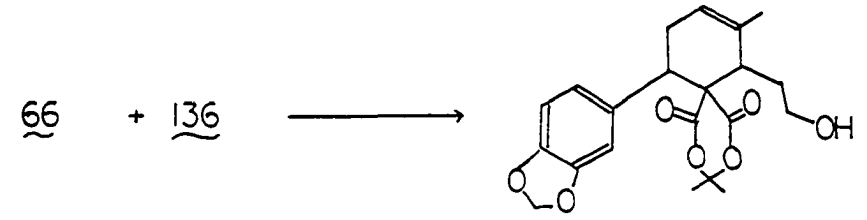
Direct incorporation of the C-10 methyl group using this approach requires formation of a hindered alkylidine isopropylidine malonate. To test the approach, dienophile 149 was prepared. Diels-Alder cyclization of 149 with 27 gave 150 as a mixture of diastereomers, showing that incorporation of the C-10 methyl group into the dienophile is feasible.



149 150

While a variety of dienophiles were studied, the work to this point has utilized only one diene. A model reaction between dienophile 136

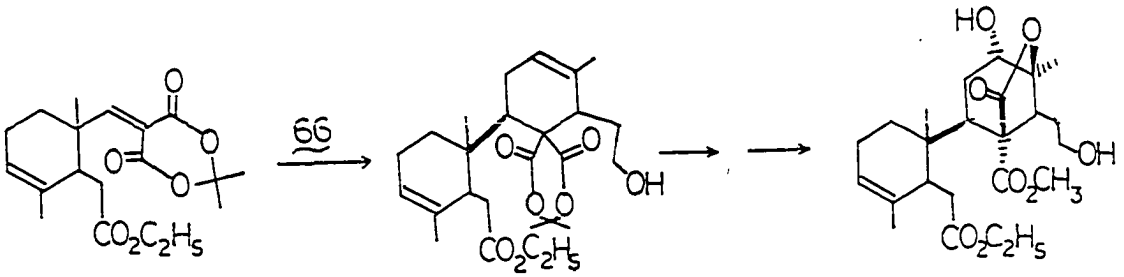
and diene 66 gave the predicted adduct 151, showing both the scope of this reaction and the applicability of this route to the total synthesis of quassinoids.



151

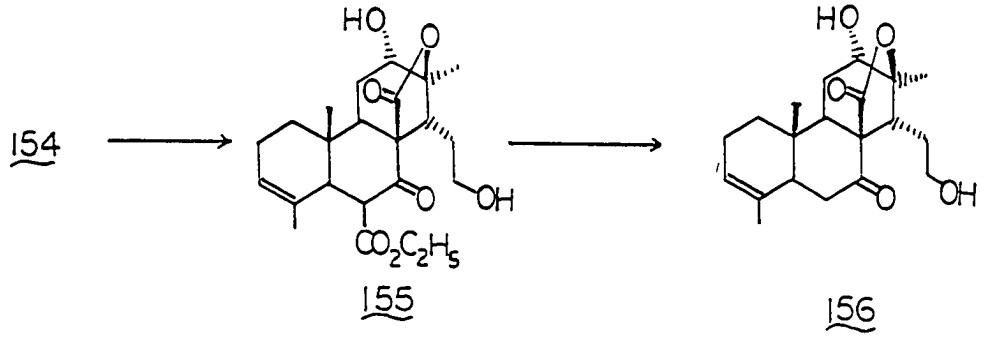
Future Work

The application of this new Diels-Alder strategy promises to afford a rapid entry to the quasimarin skeleton. Thermal cyclization of diene 66 with dienophile 152 would give compound 153, which should readily be transformed into 154 using already developed chemistry. Dieckmann

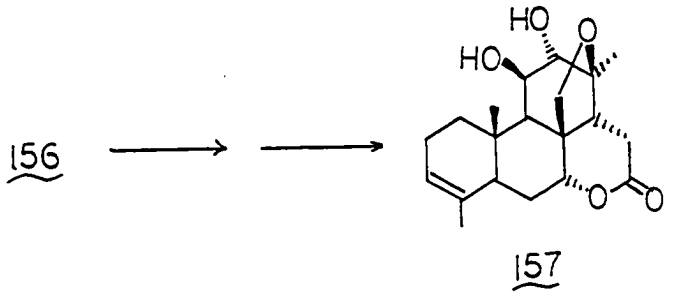


152 153 154

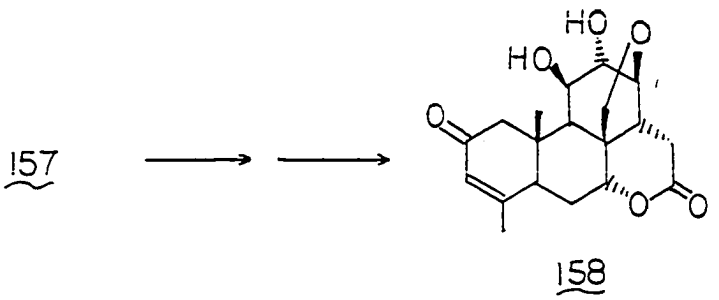
condensation of 154 would give tetracyclic ester 155, which should readily decarboalkoxylate to give 156. DE ring formation (36) and C ring



oxygenation (29) would lead to compound 157. Incorporation of oxygenation



into the A ring can be accomplished using an allylic hydroxylation-oxidation sequence (84) to give the quassinoid skeleton 158.



EXPERIMENTAL

General

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran (THF) was distilled from $LiAlH_4$ prior to use. All reactions were conducted under a nitrogen atmosphere, and all organic extracts were dried over Na_2SO_4, unless otherwise stated. Melting points were determined using a Fischer-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Beckman Acculab 2 spectrometer. Nuclear magnetic resonance spectra were obtained on either a Varian EM-360 or HA-100 spectrometer. High field (300 MHz) proton spectra were obtained using a Nicolet NT-300 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. All C-13 spectra were recorded using either a Joel FX-90Q or Nicolet NT-300 instrument, and are reported in ppm downfield from internal tetramethylsilane, relative to the central peak of $CDCl_3$ (77.06 ppm). Mass spectral data were obtained using either an AEI-MS902 or a Finnegan GC-MS instrument. Elemental analyses were determined by Galbraith Laboratories, Inc.

9bβ-Carbomethoxy-6aα-methoxy-3-methyl-6-oxa-3aβ,4,5,6a,7,8,9,9aα,9b-decahydro-1H-phenalene-9-one (69)

To a stirred solution of 4.50 g (16 mmol) of the crude reduction product of 67 and 68 (85) in 25 ml of methanol was added four crystals of PTSA. The stirred mixture was heated at reflux for 36 hours, cooled,

and filtered to yield 3.34 g (71%) of product. NMR ($CDCl_3$) δ 1.72 (br s, 3 H), 1.75-3.10 (envelope, 10 H), 3.25 (s, 3 H), 3.65 (s, 3 H), 3.73 (d, 1 H, J = 4 Hz), 5.25 (br s, 1 H). C-13 NMR ($CDCl_3$) δ 21.718, 23.345, 27.637, 30.954, 36.482, 36.667, 42.009, 47.991, 51.958, 56.966, 60.217, 97.154, 118.484, 137.213, 172.785, 208.943. IR (CH_2Cl_2) cm^{-1} 3070, 2980, 2960, 1740, 1715, 1630, 1440, 1280, 1260, 1100, 1075, 1045, 1020.

3-Carboethoxy-7β-methoxy-21-oic acid methyl ester-seco-1,10-nor-10-picrasa-12-en-2,10-dione (70)

A 0.5 M solution of 69 in THF (0.294 g, 1.00 mmol) was added dropwise to a preformed solution of 1.10 mmol LiTMP in 2 ml THF cooled to -78°C. The mixture was stirred 3 hours at -78°C, and 0.172 g (1.10 mmol) ethylidine ethylacetoacetate was added dropwise in 1.5 ml THF. The mixture was warmed to 0°C and stirred 2.5 hours. Acetic acid (0.07 ml, 1.21 mmol) was added neat. The mixture was diluted with ether, washed with saturated sodium bicarbonate solution and brine, and dried and concentrated to give a yellow oil. NMR ($CDCl_3$) δ 1.20 (br s, 3 H), 1.30 (t, 3 H, J = 7 Hz), 1.73 (br s, 3 H), 1.85-2.50 (envelope, 10 H), 2.17 (s, 3 H), 2.70-3.15 (envelope, 3 H), 3.26 (s, 3 H), 3.63 (s, 3 H), 4.22 (m, 2 H), 5.21 (br s, 1 H). IR ($CDCl_3$) cm^{-1} 3010, 2970, 1740, 1720, 1660, 1370, 1275, 1215, 1095.

7β-Methoxy-21-oic acid-(10-hydroxyester)-nor-10-picras-12-en-2-one (71)

Crude 70 (0.450 g, 1.00 mmol) was added as a solution in 1.5 ml tert-butanol to 0.223 g (1.20 mmol) of potassium tert-butoxide-tert-

butanol complex, in 4.5 ml tert-butanol at room temperature, and stirred for four hours. The reaction was quenched with 0.07 ml glacial acetic acid and concentrated in vacuo. The residue was dissolved in 20 ml ether, and washed with 10 ml water and 10 ml brine. The solution was dried and chromatographed in 20:1 hexane:ethyl acetate to yield a colorless oil. NMR ($CDCl_3$) δ 0.85-1.45 (envelope 7 H), 1.72 (br s, 3 H), 1.82-3.00 (envelope, 8 H), 3.25 (s, 3 H), 3.53 (br s, 2 H), 4.12 (m, 2 H), 5.21 (r s, 1 H). IR ($CDCl_3$) cm^{-1} 3560-3200, 2970, 1770, 1740 (sh), 1720 (sh), 1715, 1660, 1450, 1380, 1300, 1270, 1240, 1095.

9bβ-Carbomethoxy-8-formyl-6aα-methoxy-3-methyl-6-oxa-3aβ,4,5,6,6a,7,8-9,9aα,9b-decahydro-1H-phenalene-9-one (72)

Method A Potassium tert-butoxide-tert-butanol complex (0.770 g, 4.14 mmol), and compound 69 (0.609 g, 2.07 mmol) were dissolved in 10 ml dry benzene at room temperature. Ethyl formate (0.414 g, 5.59 mmol) was added neat. The mixture was stirred at room temperature for 18 hours, after which it was poured into 30 ml ice water, and extracted with 25 ml of ether. The aqueous layer was acidified to pH 3 with 1 N HCl, and allowed to stand in a refrigerator for 36 hours. The crystalline product was filtered and dried in vacuo to yield 0.453 g (68%).

Method B Sodium hydride dispersion (0.192 g, 4.00 mmol) was washed with two 2 ml portions of hexane. Ethyl formate (3.27 g, 44.0 mmol) was added neat at room temperature. After 20 minutes, 69 (0.294 g, 1.00 mmol) was added as a solution in 5 ml THF, followed by 0.02 ml absolute ethanol. The reaction was stirred at room temperature 6 hours, poured into 20 ml half saturated ammonium chloride, and extracted with

three 20 ml portions of ether. The extracts were combined, concentrated, and chromatographed using 1:2 hexane:ether as eluent, to give 0.197 g (61%) of product. NMR ($CDCl_3$) δ 1.34 (m, 1 H), 1.72 (br s, 3 H), 2.11 (br s, 1 H), 2.27 (br s, 1 H), 2.63 (s, 2 H), 2.96 (m, 2 H), 3.29 (s, 3 H), 3.64 (s, 3 H), 3.81 (m, 3 H), 5.22 (br s, 1 H), 7.47 (d, 1 H, J = 8 Hz), 14.11 (d, 1 H, J = 8 Hz). C-13 NMR δ 21.783, 24.126, 27.572, 32.255, 36.222, 40.058, 47.860, 52.153, 53.129, 60.412, 96.829, 105.868, 118.874, 137.994, 169.664, 172.655, 198.017. IR ($CDCl_3$) cm^{-1} 3600-3250, 3020, 2980, 1740 (sh), 1725 (sh), 1715, 1655, 1645, 1585, 1435, 1300, 1120, 1080, 1050, 1030. High resolution mass spectrum for $C_{16}H_{18}O_5$ (M^+-CH_3OH) requires 290.11542, measured 290.11534. The melting point is 158-160°C.

9bβ-Carbomethoxy-6aα-methoxy-3-methyl-6-oxa-8-(spiro-cyclohex-2-ene-4-one)-3aβ,4,5,6,6a,7,8,9,9aα,9b-decahydro-1H-phenalene-9-one (73)

Compound 72 (0.102 g, 0.317 mmol) and methyl vinyl ketone (0.027 g, 0.380 mmol) were dissolved in 5 ml methanol at room temperature. Sodium methoxide (0.05 ml of 1 N solution in methanol) was added, and the reaction was stirred 36 hours at room temperature. The reaction mixture was diluted with brine, acidified with 1 ml of 1 N HCl, and extracted with two 10 ml portions of ether. The extracts were concentrated and chromatographed using 1:3 hexane:ether as eluent to yield 0.065 g (52%) of 73 as a colorless oil. NMR ($CDCl_3$) δ 1.71 (br s, 3 H), 1.85-2.55 (envelope, 9 H), 2.60-3.10 (m, 2 H), 3.27 (s, 2 H), 3.65 (s, 3 H), 3.55-3.95 (m, 3 H), 5.23 (br s, 1 H), 6.02 (d, 1 H, J = 10 Hz), 6.83 (d, 1 H, J = 10 Hz). IR ($CDCl_3$) cm^{-1} 3060, 2970, 1740, 1725, 1710,

1690, 1685, 1640, 1440, 1430, 1300, 1265, 1100, 1050. High resolution mass spectrum for $C_{21}H_{26}O_6$ requires 374.17295, measured 374.17147.

9bβ-Carbomethoxy-8-hydroxymethyl-6aα-methoxy-3-methyl-6-oxa-3aβ,4,5,6,6a,-7,8,9,9aα,10-decahydro-1H-phenalene-9-one (74)

Hydroxyenone 72 (0.121 g, 0.30 mmol) was dissolved in 2.0 ml methanol at room temperature. Sodium borohydride (0.0095 g, 0.15 mmol) was added in one portion. Acetic acid (0.50 N in methanol) was added in 0.10 ml increments, at ten minute intervals, until 0.40 mmol total had been added. The reaction was allowed to stir an additional 60 minutes, then was concentrated in vacuo. The residue was dissolved in 20 ml brine, and extracted with three 20 ml portions of ether. The extracts were concentrated and chromatographed using 2:1 hexane:ether as eluent to yield 0.0975 g (79%) of 74 as a pale yellow oil. NMR ($CDCl_3$) δ 1.70 (br s, 3 H), 1.81 (m, 2 H), 1.90-2.40 (envelope, 3 H), 2.60-3.40 (envelope, 4 H), 3.25 (s, 3 H), 3.63 (s, 3 H), 3.45-3.90 (envelope, 5 H), 5.20 (br s, 2 H). IR ($CDCl_3$) cm^{-1} 3650-3150, 2970, 2950, 1740 (sh), 1715, 1580, 1450, 1385, 1300, 1275, 1240, 1110, 1080, 1050, 1020. High resolution mass spectrum for $C_{16}H_{20}O_5$ (M^+-CH_3OH) requires 292.13108, found 292.13161.

9bβ-Carbomethoxy-6aα-methoxy-3-methyl-8-methylene-6-oxa-3aβ,4,5,6,6aα,-7,8,9,9aα,9b-decahydro-1H-phenalene-9-one (75)

Method A Hydroxyketone 74 (0.0972 g, 0.30 mmol) was dissolved in 2 ml methylene chloride and cooled to 0°C. Methanesulfonyl chloride (0.0343 g, 0.30 mmol) was added neat. After 10 minutes, triethylamine

(0.121 g, 1.20 mmol) was added dropwise, and the mixture was stirred an additional 30 minutes at 0°C. The solution was diluted with 5 ml methylene chloride, washed with 5 ml each of water, 1 N HCl, and brine, dried and concentrated. The crude sulfonyl ester was dissolved in 4 ml benzene and treated with one drop of DBU. After stirring at room temperature 24 hours, the mixture was concentrated. The residue was dissolved in 25 ml ether, and washed with water to yield 0.0881 g (96%) of 75.

Method B Compound 72 (0.0975 g, 0.30 mmol) was dissolved in 10 ml acetone at room temperature. Potassium carbonate (0.250 g, 1.81 mmol) and 37% formalin solution (2.5 µl, 2.5 mmol) were added with rapid stirring. Stirring was continued for 18 hours. The reaction mixture was then diluted with 40 ml methylene chloride, washed with 20 ml of 1 N of HCl, and chromatographed using 2:1 hexane:ethyl acetate as eluent to give 0.044 g (48%) of 75. 300 MHz NMR ($CDCl_3$) δ 1.54 (m, 1 H), 1.71 (d, 3 H, J = 0.5 Hz), 1.70 (d of m, 1 H, J = 7 Hz), 2.12 (d of d of m, 1 H, J = 7 Hz, 6 Hz), 2.41 (d of m, 1 H, J = 8 Hz), 2.88 (d of t, 1 H, J = 7 Hz, 1 Hz), 2.99 (m, 3 H), 3.28 (s, 3 H), 3.63 (s, 3 H), 3.79 (m, 2 H), 5.18 (br s, 1 H), 5.24 (br s, 1 H), 5.52 (br s, 1 H). C-13 NMR ($CDCl_3$) δ 21.718, 24.061, 27.572, 36.547, 39.343, 42.334, 47.991, 52.153, 55.730, 60.607, 97.349, 118.679, 120.695, 137.213, 141.050, 172.720, 200.423. IR ($CDCl_3$) cm^{-1} 3010, 2960, 1740, 1710, 1695 (sh), 1620, 1465, 1440, 1380, 1300, 1270, 1230, 1110, 1080, 1050, 1020. Melting point 169-172°C. High resolution mass spectrum for $C_{17}H_{22}O_5$ requires 306.14673,

measured 306.14610. Elemental analysis calculated for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24; found: C, 66.57; H, 7.16.

3-Carboethoxy-7β-methoxy-21-oic acid methyl ester-seco-1,10-bisnor-4,10-picras-12,en-2,10-dione (76)

Sodium hydride dispersion (0.442 g, 9.20 mmol) was suspended in 20 ml THF and cooled to 0°C. Ethyl acetoacetate (1.20 g, 9.20 mmol) was added neat dropwise, and the reaction mixture was stirred 60 minutes at 0°C. Enone 75 (0.563 g, 1.84 mmol) was added dropwise in 20 ml THF, and the reaction was slowly warmed to room temperature, and stirred 6 hours. The mixture was diluted with ether, washed with 25 ml each of saturated sodium bicarbonate and brine, and dried. Concentration and chromatography afforded 76 as a colorless oil (0.610 g, 76%). NMR ($CDCl_3$) δ 1.28 (t, 3 H, J = 8 Hz), 1.70 (br s, 3 H), 2.17 (d, 3 H, J = 2 Hz), 1.35-3.05 (envelope, 12 H), 3.23 (s, 3 H), 3.60 (s, 3 H), 3.76 (envelope, 4 H), 4.22 (q, 2 H, J = 8 Hz), 5.21 (br s, 1 H). IR ($CDCl_3$) cm^{-1} 3020, 2960, 1745, 1725, 1715, 1650, 1635, 1465, 1450, 1380, 1370, 1300, 1270, 1240, 1100, 1080, 1050, 1020.

7β-Methoxy-21-oic acid methyl ester-seco-1,10-bisnor-4,10-picras-12-en-2,10-dione (77)

Ketoester 76 (0.120 g, 0.275 mmol) was dissolved in 1.5 ml absolute ethanol. Aqueous sodium hydroxide (1 N, 0.50 ml) was added, and the mixture was stirred at room temperature for 48 hours. The mixture was concentrated in vacuo, and the residue was taken up in 20 ml water, acidified to pH 2 with 1 N HCl, and extracted with two 20 ml portions of

ether. Chromatography using 2:1 hexane:ethyl acetate as eluent yielded 0.075 g (75%) of 77 as a colorless oil. NMR ($CDCl_3$) δ 1.68 (d, 3 H, J = 2 Hz), 2.13 (s, 3 H), 3.23 (s, 3 H), 1.20-3.15 (envelope, 13 H), 3.62 (s, 3 H), 3.70 (d, 1 H, J = 3 Hz), 3.83 (br s, 1 H), 5.20 (br s, 1 H). C-13 NMR ($CDCl_3$) δ 21.458, 23.150, 27.572, 29.523, 36.677, 37.197, 40.839, 41.814, 43.505, 47.860, 51.698, 57.291, 60.152, 97.219, 118.354, 137.018, 172.598, 208.292, 209.138. IR ($CDCl_3$) cm^{-1} 2980, 2960, 1740 (sh), 1720 (sh), 1715, 1445, 1435, 1380, 1360, 1295, 1265, 1235, 1100, 1080, 1050, 1005. High resolution mass spectrum for $C_{20}H_{20}O_6$ requires 364.18860, measured 364.18962.

3-Carboethoxy-10β-hydroxy-7β-methoxy-21-oic acid methyl ester-bisnor-4,-10-picras-12-en-2-one (78)

Sodium hydride dispersion (0.957 g, 19.90 mmol) was suspended in 20 ml THF and cooled to 0°C. Ethyl acetoacetate (2.59 g, 19.90 mmol) was added dropwise in 10 ml THF, and the reaction mixture was stirred 30 minutes at 0°C. Enone 75 (1.22 g, 3.99 mmol) was added dropwise in 20 ml THF, the solution was allowed to slowly warm to room temperature, and was stirred for 48 hours at room temperature. The mixture was diluted with 100 ml ether, washed with 25 ml each of saturated sodium bicarbonate and brine, and dried. Concentration and chromatography using 2:1 hexane:ethyl acetate as eluent afforded 0.839 g (48%) of 78 as colorless needles. 300 MHz NMR ($CDCl_3$) δ 1.28 (t, 3 H, J = 8 Hz), 1.68 (br s, 3 H), 2.14 (br s, 2 H), 1.46-2.18 (envelope, 7 H), 2.19 (br s, 1 H), 2.23 (br s, 1 H), 2.51 (d, 1 H, J = 13 Hz), 2.97 (d of d, 1 H, J = 10 Hz, 4 Hz), 3.19 (s, 3 H), 3.52-3.67 (envelope, 2 H), 3.67 (s, 3 H), 4.21 (q,

2 H, J = 8 Hz), 5.30 (br s, 1 H), 5.97 (d, 1 H, J = 1 Hz), 12.2 (s, 1 H). C-13 NMR ($CDCl_3$) δ 14.243, 21.458, 23.020, 25.686, 26.922, 31.474, 36.937, 38.107, 39.213, 39.668, 42.465, 47.535, 52.674, 54.299, 60.022, 68.606, 96.959, 98.390, 119.850, 137.018, 169.664, 172.200, 177.077. IR (CCl_4) cm^{-1} 3450-3360, 3010, 2960, 1740, 1700, 1665, 1620, 1450, 1440, 1420, 1405, 1385, 1375, 1355, 1340, 1300, 1270, 1245, 1215, 1130, 1090, 1055, 1040, 1025, 975. High resolution mass spectrum for $C_{23}H_{32}O_8$ requires 436.20973, measured 436.21170. High resolution mass spectrum for $C_{22}H_{28}O_7$ (M^+-CH_3OH) requires 404.18351, measured 404.18234. Elemental analysis calculated for $C_{23}H_{32}O_8$: C, 63.29; H, 7.39; found: C, 63.13; H, 7.42. The melting point is 165.5-166.5°C.

3-Carboethoxy-10β-hydroxy-7β-methoxy-21-oic acid methyl ester-bisnor-4,-10-picras-3,12-dien-2-one (79)

Phenylselenenyl chloride (0.096 g, 0.50 mmol) was dissolved in 4 ml methylene chloride at room temperature. Pyridine (0.0395 g, 0.50 mmol) was added neat, and the mixture was stirred 10 minutes, after which the reaction mixture was cooled to 0°C. Ketoester 78 (0.207 g, 0.47 mmol) was added dropwise in 4 ml methylene chloride, and the mixture was stirred 30 minutes at -78°C. The reaction mixture was transferred to a separatory funnel and washed with two 5 ml portions of 1 N HCl. The organic layer was once again cooled to 0°C, and treated with three ten drop portions of 30% hydrogen peroxide at ten minute intervals. The reaction mixture was stirred an additional ten minutes at 0°C, diluted with 25 ml methylene chloride, and washed with 10 ml portions of water and saturated sodium bicarbonate. The organic layer was concentrated

to yield 0.196 g (96%) of 79 as a pale yellow oil. 300 MHz NMR ($CDCl_3$) δ 1.33 (t, 3 H, J = 8 Hz), 1.69 (br s, 3 H), 1.84 (m, 2 H), 2.09 (m, 3 H), 2.28 (m, 2 H), 2.92 (d, 1 H, J = 13 Hz), 3.02 (d of d, 1 H, J = 13 Hz, 3 Hz), 3.09 (br t, 1 H, J = 5 Hz), 3.21 (m, 1 H), 3.25 (s, 3 H), 3.67 (s, 3 H), 3.74 (m, 2 H), 4.27 (m, 2 H, J = 8 Hz), 5.29 (br s, 1 H), 6.39 (d, 1 H, J = 2 Hz), 7.36 (d, 1 H, J = 1 Hz). C-13 NMR ($CDCl_3$) δ 14.178, 21.523, 22.825, 26.857, 30.369, 38.368, 39.213, 42.790, 47.860, 51.308, 52.999, 54.429, 60.412, 60.933, 72.442, 98.520, 119.655, 132.231, 137.018, 156.853, 164.331, 176.882, 192.880. IR ($CDCl_3$) cm^{-1} 3450-3240, 2970, 2950, 1750, 1705 (sh), 1695, 1455, 1440, 1380, 1330, 1275, 1240, 1095, 1050, 1035, 1020. MS 434, 402, 384, 325, 311, 279, 252, 237, 223, 211, 197, 185, 165.

3-Carboethoxy-2-hydroxy-7β-methoxy-21-oic acid methyl ester-bisnor-4,10-picras-1,2,5(10),12-tetraene (80)

Compound 79 (0.633 g, 1.46 mmol) was dissolved in 20 ml dry benzene at room temperature. Three crystals of PTSA were added, and the mixture was stirred for 6 hours. The benzene solution was washed with 10 ml each of saturated sodium bicarbonate and brine, concentrated, and chromatographed using 2:1 hexane:ether as eluent, to give 0.137 g (94%) of 80 as white crystals. 300 MHz NMR ($CDCl_3$) δ 1.38 (t, 3 H, J = 8 Hz), 1.63 (m, 2 H), 1.72 (br s, 3 H), 1.89 (d of t, 1 H, J = 11 Hz, 2 Hz), 2.13 (br t, 1 H, J = 11 Hz), 2.77 (br d, 1 H, J = 9 Hz), 2.95-3.20 (envelope, 3 H), 3.31 (s, 3 H), 3.51 (s, 3 H), 3.67 (m, 1 H), 3.78 (m, 1 H), 4.37 (q, 2 H, J = 8 Hz), 5.32 (br s, 1 H), 6.83 (s, 1 H), 7.51 (s, 1 H), 10.58 (s, 1 H). C-13 NMR ($CDCl_3$) δ 14.308, 21.783, 27.572, 28.288, 34.141,

36.612, 47.665, 51.698, 52.218, 60.282, 61.128, 78.945, 97.479, 110.225, 113.607, 119.070, 124.142, 129.084, 138.709, 146.968, 160.039, 170.054, 172.850. IR (CCl_4) cm^{-1} 3240-3140, 3005, 2960, 1740, 1730, 1675, 1630, 1580, 1550, 1500, 1450, 1405, 1380, 1320, 1310, 1279, 1255, 1165, 1120, 1090, 1050, 1030, 910. MS 416, 384, 338, 325, 279, 252, 223, 211, 197, 185, 165. The melting point is 137-140°C.

3-Carboxy-2-hydroxy-7β-methoxy-21-oic acid methyl ester-bisnor-4,10-picras-1,2,5(10),12-tetraene (81)

Compound 80 (0.195 g, 0.47 mmol) was dissolved in 7 ml methanol. Lithium hydroxide (0.059 g, 1.41 mmol) was added, and the reaction mixture was heated at reflux for 18 hours. The crude mixture was concentrated in vacuo; the residue was taken up in 10 ml H_2O, acidified to pH 2 with 1 N HCl, and extracted with two 20 ml portions of ether to give 0.182 g (94%) of 81. NMR ($CDCl_3$) δ 1.35 (br s, 1 H), 1.78 (br s, 3 H), 1.70-2.05 (envelope, 2 H), 3.15 (br s, 2 H), 3.40 (s, 3 H), 3.59 (s, 3 H), 2.90-3.95 (envelope, 5 H), 5.43 (br s, 1 H), 6.95 (s, 1 H), 7.64 (s, 1 H), 10.30 (s, 2 H). IR ($CDCl_3$) cm^{-1} 3700-2450, 2960, 2930, 1725, 1675, 1665 (sh), 1630, 1585, 1500, 1450 (sh), 1440, 1310, 1270, 1255, 1245, 1175, 1160, 1115, 1085, 1040, 1020, 905.

12α-Bromo-3-carboethoxy-2-hydroxy-7β-methoxy-21-oic acid-(13β-hydroxy ester)-bisnor-4,10-picras-1,3,5(10)-triene (82)

Compound 80 (0.257 g, 0.61 mmol) was dissolved in 5 ml methylene chloride and cooled to 0°C. Pyridine (0.072 g, 0.92 mmol) was added, followed by 1 N bromine solution in methylene chloride (0.61 ml, 0.61

mmol). The mixture was stirred 45 minutes at 0°C, diluted with 25 ml methylene chloride, and washed with 20 ml each of 10% $Na_2S_2O_3$ and brine. Chromatography using 3:1 hexane:ethyl acetate as eluent gave 0.235 g (80%) of 82 as a pale yellow solid. 300 MHz NMR ($CDCl_3$) δ 1.38 (t, 3 H, J = 8 Hz), 1.68 (s, 3 H), 1.15-180 (envelope, 2 H), 2.04 (m, 1 H), 2.41 (m, 1 H), 2.92 (br s, 2 H), 3.33 (s, 3 H), 2.65-4.20 (envelope, 5 H), 4.32 (m, 2 H), 6.76 (s, 1 H), 7.60 (s, 1 H), 10.52 (s, 1 H). IR ($CDCl_3$) cm^{-1} 3550-3100, 3150, 2980, 2960, 1775, 1720, 1670, 1620, 1580, 1495, 1450, 1400, 1375, 1320, 1260, 1230, 1130, 1045, 1010, 990, 905. MS 482, 280, 450, 448, 399, 357, 295, 279, 197.

5-(3,4-Methylenedioxy)-benzylidene-2,2-dimethyl-1,3-dioxan-4,6-dione (136)

Piperonal (9.00 g, 67 mmol) and 2,2-dimethyl-1,3-dioxane-4,6-dione (5.62 g, 39 mmol) were dissolved in 150 ml benzene at room temperature. Piperidine (0.634 g, 7.5 mmol) and glacial acetic acid (2.5 ml, 43.5 mmol) were added, and the mixture was heated at reflux, utilizing a Dean-Stark trap to remove generated water. After three hours, when 0.80 ml water had been collected, the Dean-Stark trap was replaced with a distillation head, and 100 ml of benzene was distilled off. The concentrate was allowed to cool, and 10.01 g (93%) of 84 crystallized as bright yellow needles. NMR ($CDCl_3$) δ 1.79 (s, 6 H), 6.08 (s, 2 H), 6.85 (d, 1 H, J = 8 Hz), 7.53 (d of d, 1 H, J = 8 Hz, 2 Hz), 8.04 (d, 1 H, J = 2 Hz), 8.30 (s, 1 H). C-13 ($CDCl_3$) δ 27.572, 102.292, 104.112, 108.470, 111.981, 112.631, 126.678, 133.702, 148.399, 153.081, 157.503, 160.104. IR (CH_2Cl_2) cm^{-1} 3050, 2990, 1720, 1570, 1560 (sh), 1500, 1485, 1450,

1400, 1390, 1240, 1235, 1080, 995, 935. The melting point is 178.5-179.5°C.

Spiro[5.5]-11-carboethoxymethyl-7β-(3,4-methylenedioxy)phenyl-3,3-10-trimethyl-2,4-diox-undec-9-en-1,5-dione

Compound 136 (1.22 g, 4.42 mmol) and diene 27 (0.693 g, 4.50 mmol) were dissolved in 25 ml toluene, and heated for 48 hours at reflux. The reaction mixture was cooled and filtered to remove unreacted dienophile. The filtrate was concentrated in vacuo, and flash chromatographed using 6:1 hexane:ethyl acetate as eluent to yield 0.696 g (37%) of 137 as the first eluting adduct, followed by 0.429 g (23%) of 138, both as colorless crystalline solids.

137: 300 MHz NMR ($CDCl_3$) δ 1.27 (s, 3 H), 1.27 (t, 3 H, J = 7 Hz), 1.79 (br s, 3 H), 1.83 (br s, 3 H), 2.36 (d of m, 1 H, J = 16 Hz), 2.56 (d, 1 H, J = 16 Hz), 2.61 (m, 1 H), 3.07 (m, 2 H), 3.45 (d of d, 1 H, J = 6 Hz, 4 Hz), 4.14 (m, 2 H), 5.72 (br s, 1 H), 5.89 (d, 2 H, J = 2 Hz), 6.69 (s, 1 H), 6.72 (s, 1 H). C-13 NMR ($CDCl_3$) δ 14.175, 22.503, 28.881, 29.111, 31.042, 35.232, 42.290, 42.540, 55.243, 60.853, 100.976, 105.167, 108.152, 109.834, 122.710, 123.616, 130.257, 133.040, 146.911, 147.526, 166.388, 167.650, 172.438. IR (film) cm^{-1} 3005 (sh), 2995, 2940, 2900, 1770, 1730, 1620, 1505, 1480, 1445, 1405, 1395, 1380, 1330, 1280, 1260, 1230, 1180, 1110, 1065, 1035, 930, 910, 770, 750, 730. MS 430, 372, 344, 328, 310, 300, 256, 241, 212, 183, 174, 162, 149, 135. Elemental analysis calculated for $C_{23}H_{26}O_8$: C, 64.18; H, 6.09; found: C, 64.19; H, 6.45. The melting point is 146.5-148°C.

138: 300 MHz NMR ($CDCl_3$) δ 0.72 (s, 3 H), 1.25 (t, 3 H, J = 7 Hz), 1.59 (s, 3H), 1.71 (br s, 3 H), 2.06 (m, 2 H), 2.56 (d of d, 1 H, J = 9 Hz, 4 Hz), 2.82 (br t, 1 H, J = 11 Hz), 3.61 (d of d, 1 H, J = 7 Hz, 3 Hz), 3.78 (br s, 1 H), 4.14 (m, 2 H), 5.70 (br s, 1 H), 5.90 (s, 2 H), 6.71 (s, 3 H). C-13 (NMR ($CDCl_3$) δ 14.091, 21.351, 28.691, 29.355, 29.804, 35.200, 44.500, 46.853, 59.427, 61.173, 101.163, 106.211, 108.664, 109.831, 122.743, 123.390, 131.090, 133.031, 147.429, 148.036, 169.526, 171.500. IR ($CDCl_3$) cm^{-1} 2990, 2960, 2920, 1770, 1740 (sh), 1730, 1620, 1580, 1570, 1505, 1490, 1450, 1395, 1380, 1325, 1280, 1265, 1250, 1185, 1095, 1045, 905, 790, 760. MS 372 ($M^+-C_3H_6O$) 344, 328, 300, 282, 256, 241, 212, 183, 174, 162, 149, 135. Elemental analysis calculated for $C_{23}H_{26}O_8$: C, 64.18; H, 6.09; found: C, 64.20; H, 6.05. The melting point is 149-151°C.

6-Oxabicyclo[3.2.1]-8-carboethoxymethyl-1-carboxy-4α-hydroxy-5-methyl-2β-(3,4-methylenedioxy)phenyl-octan-7-one

Diels-Alder adduct 138 (2.00 g, 4.65 mmol) was dissolved in 20 ml methylene chloride and cooled to 0°C. MCPBA (0.970 g, 4.75 mmol) was added as a solid in one portion. The reaction mixture was slowly warmed to room temperature, and stirred for two hours. The mixture was diluted with 50 ml of ether, and washed with 20 ml each of saturated sodium bicarbonate and brine. The organic layer was concentrated in vacuo, dissolved in 25 ml THF, and treated with 5 ml of 3 N perchloric acid. After stirring at room temperature for 12 hours, the mixture was diluted with 20 ml of water, and extracted with two 20 ml portions of ether. The extracts were combined, washed with 20 ml brine, dried and

concentrated. The crude product was chromatographed using 1:2 hexane: ether as eluent to give 1.54 g (82%) of 141 as white plates. 300 MHz NMR ($CDCl_3$) δ 1.21 (t, 3 H, J = 7 Hz), 1.53 (s, 3 H), 2.08 (d of d, 1 H, J = 9 Hz, 2 Hz), 2.27 (t of d, 1 H, J = 7 Hz, 2 Hz), 2.49 (d of d, 1 H, J = 8 Hz, 1.5 Hz), 2.69 (d of d, 1 H, J = 8 Hz, 5 Hz), 3.56 (d of d, 1 H, J = 5 Hz, 1.5 Hz), 3.68 (d of d, 1 H, J = 7 Hz, 3 Hz), 4.08 (m, 3 H), 5.95 (s, 2 H), 6.71 (m, 3 H). C-13 NMR ($CDCl_3$) δ 14.036, 18.789, 31.018, 35.524, 45.053, 46.388, 61.368, 71.139, 87.569, 101.259, 108.342, 108.544, 122.104, 128.319, 129.860, 130.275, 130.831, 133.860, 168.001, 171.270. IR ($CDCl_3$) cm^{-1} 3680-2400, 3060, 2940, 2640, 1770, 1725, 1705, 1600, 1575, 1505, 1485, 1440, 1290, 1250, 1190, 1100, 1030. The melting point is 163-167°C.

Compound 142 was prepared from 137 under the same conditions in 98% yield on a 0.71 mmol scale. 300 MHz NMR δ 1.28 (t, 3 H, J = 7 Hz), 1.57 (s, 3 H), 1.98-2.15 (m, 2 H), 2.36 (d, 1 H, J = 3 Hz), 3.04 (d, 2 H, J = 4 Hz), 3.22 (t, 1 H, J = 4 Hz), 3.99 (br s, 1 H), 4.14 (q, 2 H, J = 7 Hz), 5.90 (s, 2 H), 6.68 (d, 1 H, J = 6 Hz), 6.83 (d, 1 H, J = 6 Hz), 6.89 (s, 1 H). IR ($CDCl_3$) cm^{-1} 3650-2400, 3520, 2990, 2950, 2910, 2600, 1775, 1740 (sh), 1725, 1620, 1500, 1485, 1440, 1380, 1320, 1290, 1250, 1230, 1195, 1125, 1090, 1050, 1030, 905. MS 406, 360, 314, 286, 273, 270, 256, 239, 232, 204, 177, 156, 148. Elemental analysis calculated for $C_{20}H_{22}O_9$: C, 59.11; H, 5.46; found: C, 58.88; H, 5.43. The melting point is 166-170°C.

2-Carboethoxymethyl-4,5-dimethoxybenzaldehyde (144)

Compound 143 (1.67 g, 5.30 mmol) was dissolved in 15 ml chloroform at room temperature. Tetrabutylammonium dichromate (7.58 g, 10.60 mmol) was added, and the mixture was heated at reflux for two hours. The crude mixture was allowed to cool to room temperature, and was filtered through 30 g of silica gel with 400 ml of ether to yield 1.24 g (93%) of 90 as a colorless oil. NMR ($CDCl_3$) δ 1.21 (t, 3 H, J = 7 Hz), 3.93 (s, 6 H), 3.96 (s, 1 H), 4.14 (q, 2 H, J = 7 Hz), 6.75 (s, 1 H), 7.35 (s, 1 H), 10.08 (s, 1 H). IR (CCl_4) cm^{-1} 3030, 2990, 2960, 2920, 2840, 1740, 1730, 1695, 1680, 1605, 1575, 1520, 1470, 1360, 1330, 1280, 1170, 1115, 1030.

5-(2-Carboethoxymethyl-4,5-dimethoxy)-benzylidine-2,2-dimethyl-1,3-dioxan-4,6-dione (145)

Compound 145 was prepared on a 7.67 mmol scale in 92% yield utilizing the procedure developed for 136. 300 MHz NMR ($CDCl_3$) δ 1.23 (t, 3 H, J = 7 Hz), 1.80 (s, 6 H), 3.78 (s, 2 H), 3.91 (s, 3 H), 3.95 (s, 3 H), 4.13 (q, 2 H, J = 7 Hz), 6.83 (s, 1 H), 8.03 (s, 1 H), 8.65 (s, 1 H). IR ($CDCl_3$) cm^{-1} 3060, 2990, 1740, 1720, 1570, 1555, 1500, 1485, 1450, 1405, 1390, 1240, 1080, 995, 930.

Sprio[5.5]-11-carboethoxymethyl-7β-(2-carboethoxymethyl-4,5-dimethoxy) phenyl-3,3,10-trimethyl-2,4-diox-undec-9-en-1,5-dione

Compound 145 (2.68 g, 7.1 mmol) and diene 27 (1.09 g, 7.1 mmol) were dissolved in 25 ml toluene, and heated at reflux for 72 hours The reaction mixture was cooled, concentrated in vacuo, and flash

chromatographed using 6:1 hexane:ethyl acetate as eluent to give 2.26 g (60%) of 146 as the first eluting adduct, followed by 0.91 g (24%) of 147.

146: 300 MHz NMR ($CDCl_3$) δ 1.22 (t, 3 H, J = 7 Hz), 1.26 (t, 3 H, J = 7 Hz), 1.35 (s, 3 H), 1.77 (s, 3 H), 1.83 (s, 3 H), 2.39 (br d, 1 H, J = 8 Hz), 2.62 (m, 2 H), 3.03 (m, 2 H), 3.35 (br d, 1 H, J = 6 Hz), 3.68-3.87 (envelope, 2 H), 3.76 (s, 3 H), 3.83 (s, 3 H), 4.11 (m, 4 H), 5.71 (br s, 1 H), 6.64 (s, 1 H), 6.74 (s, 1 H). C-13 NMR ($CDCl_3$) δ 14.075, 14.121, 22.415, 28.834, 29.124, 31.695, 35.056, 38.132, 38.781, 42.986, 53.365, 54.315, 55.585, 55.641, 60.689, 60.776, 105.045, 110.242, 114.094, 124.214, 126.394, 130.024, 130.890, 147.618, 167.003, 167.941, 171.856, 172.309. IR ($CDCl_3$) cm^{-1} 3030, 2995, 2950, 2920, 1770, 1740 (sh), 1730, 1615, 1520, 1465, 1445, 1395, 1380, 1300, 1280, 1260, 1090, 1030.

147: 300 MHz NMR ($CDCl_3$) δ 0.86 (s, 3 H), 1.24 (t, 3 H, J = 7 H), 1.28 (t, 3 H, J = 7 Hz), 1.62 (s, 3 H), 1.71 (br s, 3 H), 2.18 (d of d, 1 H, J = 14 Hz, 4 Hz), 2.37 (br d, 1 H, J = 14 Hz), 2.59 (d of d, 1 H, J = 12 Hz, 7 Hz), 2.74 (br t, 1 H, J = 12 Hz), 3.42 (d, 1 H, J = 15 Hz), 3.85 (br s, 6 H), 3.94 (m, 2 H), 4.08-4.23 (envelope, 5 H), 5.62 (br s, 1 H), 6.67 (s, 1 H), 6.77 (s, 1 H). C-13 NMR ($CDCl_3$) δ 14.040, 14.172, 21.216, 28.913, 29.967, 31.020, 35.125, 38.263, 42.296, 44.965, 55.782, 55.868, 56.094, 58.414, 60.850, 61.142, 106.213, 111.244, 114.134, 123.838, 126.158, 130.656, 130.831, 148.128, 165.078, 169.753, 171.403, 171.688. IR ($CDCl_3$) cm^{-1} 3020, 2990, 2950, 2920, 2850, 1770, 1735, 1695, 1610, 1575, 1520, 1465, 1450, 1390, 1375, 1370, 1300, 1270, 1200, 1175, 1090, 1025, 910. High resolution mass spectrum for $C_{28}H_{36}O_{10}$ requires 532.23086, measured 532.23245.

6-Oxabicyclo[3.2.1]-8α-carboethoxymethyl-1-carbomethoxy-4α-hydroxy-5-methyl-2β-(2-carboethoxymethyl-4,5-dimethoxy)phenyl-oct-7-one (148)

Compound 146 (0.710 g, 1.33 mmol) was dissolved in 10 ml methylene chloride and cooled to 0°C. MCPBA (0.285 g, 1.40 mmol) was added as a solid in one portion. The reaction mixture was slowly warmed to room temperature, and stirred for two hours. The mixture was diluted with 25 ml of ether, and washed with 10 ml each of saturated sodium bicarbonate and brine. The organic layer was concentrated *in vacuo*, dissolved in 10 ml of THF, and treated with 5 ml of 3 N perchloric acid. After stirring 12 hours at room temperature, the mixture was diluted with 10 ml of water, and extracted with two 10 ml portions of ether. The extracts were combined, washed with 10 ml of brine, dried and concentrated. The residue was dissolved in 10 ml methylene chloride, and treated with ethereal diazomethane until gas evolution ceased. Concentration *in vacuo*, and chromatography using 1:1 hexane:ether as eluent, gave 0.522 g (76%) of 148 as a colorless oil. 300 MHz NMR ($CDCl_3$) δ 1.28 (t, 6 H, J = 7 Hz), 1.58 (s, 3 H), 2.10 (m, 2 H), 2.79 (br s, 1 H), 3.08 (m, 1 H), 3.24 (br t, 1 H, J = 8 Hz), 3.52 (2, 3 H), 3.70 (m, 1 H), 3.83 (s, 3 H), 3.84 (s, 3 H), 3.82-4.08 (envelope, 4 H), 4.14 (m, 4 H), 6.67 (s, 1 H), 7.13 (s, 1 H). C-13 NMR ($CDCl_3$) δ 14.132, 20.648, 29.308, 31.017, 37.718, 39.333, 50.764, 52.378, 55.712, 55.842, 59.615, 60.907, 61.023, 67.900, 71.133, 84.117, 110.222, 113.877, 125.105, 128.150, 128.948, 132.123, 147.174, 168.491, 172.309, 172.626. IR ($CDCl_3$) cm^{-1} 3030, 2990, 2970, 2950, 2920, 2870, 1780, 1740 (sh), 1730, 1615, 1525, 1465, 1450, 1405, 1385, 1370, 1325, 1280, 1210, 1185, 1120, 1095, 1060, 1040,

1025, 1010. High resolution mass spectrum for $C_{26}H_{34}O_{11}$ requires 522.21012, measured 522.21083.

5-(1,4-dimethyl-Δ^3)-tetrahydrobenzylidine-2,2-dimethyl-1,3-dioxan-4,6-dione (149)

Compound 149 was prepared on a 7.7 mmol scale in 72% yield from 1,4-dimethyl-3-cyclohexene-1-carboxaldehyde (86) using the procedure developed for compound 136. Excess aldehyde was removed by Kugelrohr distillation to give pure 149. NMR ($CDCl_3$) δ 1.33 (s, 3 H), 1.62 (br s, 3 H), 1.72 (s, 6 H), 1.35-2.58 (envelope, 6 H), 5.22 (br s, 1 H), 7.71 (s, 1 H). C-13 NMR ($CDCl_3$) δ 23.000, 23.432, 27.008, 27.139, 27.895, 33.100, 37.200, 38.561, 104.107, 119.268, 119.341, 133.970, 158.816, 162.635, 173.917. IR ($CDCl_3$) cm^{-1} 2990, 2960, 2940, 1760 (sh), 1740, 1610, 1440, 1385, 1375, 1275, 1200, 1020, 1000, 905.

Sprio[5.5]-11-carboethoxymethyl-7-(1,4-dimethyl-3-cyclohexene)-3,3,10-trimethyl-2,4-diox-undec-9-ene-1,5-dione (150)

Compound 149 (0.48 g, 1.82 mmol) and diene 27 (0.308 g, 2.00 mmol) were dissolved in 5 ml toluene and heated at reflux for 4 days. Concentration of the reaction mixture, and chromatography using 1:1 hexane: ether as eluent gave 0.101 g (13%) of 150 as a pale yellow oil, along with 0.092 g (30%) unreacted diene. 300 MHz NMR ($CDCl_3$) δ 0.82 (br s, 3 H), 1.26 (t, 3 H, J = 7 Hz), 1.38 (m, 3 H), 1.62 (br s, 3 H), 1.68 (br s, 3 H), 1.62-2.04 (envelope, 9 H), 2.42 (m, 3 H), 3.04 (d, 2 H, J = 6 Hz), 4.06 (q, 2 H, J = 7 Hz), 4.65 (m, 1 H), 5.12 (br s, 1 H), 5.70 (m, 1 H). IR ($CDCl_3$) cm^{-1} 2975, 2920, 2890, 1750 (sh), 1735, 1635, 1460, 1435, 1375, 1360, 1250, 1160, 1050, 1020, 905.

Spiro[5.5]-11-(2-hydroxyethyl)-7-(3,4-methylenedioxy)phenyl-3,3,10-trimethyl-2,3-diox-undec-9-en-2,5-dione (153)

Compound 152 (0.276 g, 1.00 mmol) and diene 66 (0.112 g, 1.00 mmol) were dissolved in 6 ml toluene and heated at reflux for 36 hours. Concentration of the reaction mixture and chromatography using 1:1 hexane: ether as eluent afforded 0.350 g (90%) of 153 as a yellow oil. 300 MHz NMR ($CDCl_3$) δ 1.75 (s, 3 H), 1.79 (s, 6 H), 2.05-2.40 (envelope, 3 H), 2.50-2.78 (envelope, 3 H), 3.86 (m, 1 H), 4.07 (m, 1 H), 4.39 (m, 1 H), 5.68 (br s, 1 H), 5.89 (br s, 2 H), 6.69 (m, 1 H), 6.88 (m, 2 H). IR ($CDCl_3$) cm^{-1} 3650-3450, 3010, 2980, 2940, 1730, 1690, 1610, 1570, 1500, 1485, 1450, 1400, 1265, 1255, 1230, 1100, 1040.

CONCLUSION

Two routes to the quassinoid skeleton have been developed. The first synthetic scheme utilized the Diels-Alder reaction of an *in situ* generated benzoquinone, followed by a 3+3 annulation. This system was elaborated to give a pentacyclic intermediate containing all of the skeletal carbons of quasimarin.

A second, more efficient, approach involved the Diels-Alder cyclization of benzylidine and alkylidine isopropylidine malonates. This reaction effectively set the proper relative stereochemistry for the quassinoids, while rapidly assembling their carbon framework.

Another aspect of this research was the development of several synthetic methods. The selective reduction of β-formyl ketones was found to proceed smoothly with sodium cyanoborohydride. The generality of formation, and Diels-Alder cyclization, of benzylidine and alkylidine malonates was shown. Finally, an apparently general method for spiroannulation was serendipitously discovered.

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APPENDIX A: CRYSTALLOGRAPHIC DATA FOR COMPOUND 75

CELL 11.857 15.24 0.414 [illegible] 90.0 [illegible] 0

A, B, C, ALPHA, BETA, GAMMA =	11.857	15.240	
AS, BS, CS, COSAS, COSBS, COSGS =	0.084	0.066	

ATOM	X	Y	Z	U11	U22
O1	2203(9)	4648(10	-1934(20	101(13)	100(
O2	6035(13)	3558(8)	-3779(15	59(10)	52(
O3	5078(14)	4600(7)	-2773(18	109(14)	41(
O4	4381(13)	2403(7)	310(13	55(10)	42(
O5	6077(12)	3006(8)	-509(14	46(9)	59(
C1	2674(22)	4474(16	1847(29	74(8)	0(
C2	3401(16)	4202(11	332(22	44(6)	0(
C3	4576(19)	3908(12	403(23	47(6)	0(
C4	4914(14)	3113(11	-404(20	31(5)	0(
C5	6639(19)	3009(13	1027(25	58(7)	0(
C6	4584(18)	1556(11	-240(22	46(6)	0(
C7	4244(15)	1489(10	-2075(20	38(5)	0(
C8	4791(17)	2217(10	-3048(21	43(6)	0(
C9	4265(19)	2226(12	-4670(24	65(7)	0(
C10	4747(19)	1528(11	-5819(23	54(6)	0(
C11	3478(18)	2801(11	-5182(23	53(6)	0(
C12	3016(19)	3528(13	-4209(26	69(7)	0(
C13	3324(17)	3353(11	-2371(24	47(6)	0(
C14	2904(22)	4152(14	-1309(27	59(8)	0(
C15	459(16)	3149(10	-2203(18	22(4)	0(
C16	5244(17)	3869(12	-3073(23	45(6)	0(
C17	6616(18)	4222(13	-4726(26	58(7)	0(

240	8.416	90.000	90.000	90.000	
066	0.119	0.000	0.000	0.000	

	U22	U33	U23	U13	U12
3)	100(10)	102(13)	21(12)	-6(13)	62(11)
0)	52(7)	51(8)	4(8)	21(9)	-1(8)
4)	41(7)	80(11)	-1(8)	17(11)	-7(9)
0)	42(7)	39(8)	15(8)	-3(10)	1(9)
)	59(8)	43(8)	-9(8)	-2(9)	-7(9)
)	0(0)	0(0)	0(0)	0(0)	0(0)
)	0(0)	0(0)	0(0)	0(0)	0(0)
)	0(0)	0(0)	0(0)	0(0)	0(0)
)	0(0)	0(0)	0(0)	0(0)	0(0)
)	0(0)	0(0)	0(0)	0(0)	0(0)
)	0(0)	0(0)	0(0)	0(0)	0(0)
)	0(0)	0(0)	0(0)	0(0)	0(0)
)	0(0)	0(0)	0(0)	0(0)	0(0)
)	0(0)	0(0)	0(0)	0(0)	0(0)
)	0(0)	0(0)	0(0)	0(0)	0(0)
)	0(0)	0(0)	0(0)	0(0)	0(0)
)	0(0)	0(0)	0(0)	0(0)	0(0)
)	0(0)	0(0)	0(0)	0(0)	0(0)
)	0(0)	0(0)	0(0)	0(0)	0(0)
)	0(0)	0(0)	0(0)	0(0)	0(0)
)	0(0)	0(0)	0(0)	0(0)	0(0)
)	0(0)	0(0)	0(0)	0(0)	0(0)

BOND ANGLE CALCULATION

I	J	K	DIJ	DJK	ANGLE	SANG	I	
O1	-C14	-O2	1.214	1.491	123.96	2.02	O1	-C
O2	-C16	-O7	1.351	1.151	124.95	1.83	O2	-C
O3	-C16	-O2	1.151	1.351	124.95	1.83	O3	-C
O4	-O8	-O7	1.420	1.388	111.09	1.35	O4	-C
O4	-O8	-C10	1.420	1.539	111.55	1.35	O4	-C
O5	-O8	-O4	1.388	1.420	111.09	1.35	O5	-C
O5	-O4	-C10	1.388	1.539	103.66	1.32	C1	-C
O1	-O2	-C14	1.346	1.481	113.90	1.86	C2	-C
O2	-C14	-O1	1.481	1.214	125.96	2.02	C2	-C
O3	-O2	-O1	1.480	1.346	126.29	1.86	C3	-C
O3	-O4	-O4	1.514	1.420	103.80	1.39	C3	-C
O3	-O4	-C10	1.514	1.539	115.23	1.45	C4	-C
O4	-O5	-O5	1.388	1.455	116.19	1.38	C4	-C
O4	-C15	-O9	1.539	1.587	109.80	1.34	C4	-C
O4	-C15	-C16	1.539	1.491	108.54	1.40	C5	-C
O6	-O4	-O4	1.425	1.420	115.63	1.32	C6	-C
O7	-O8	-O8	1.520	1.425	112.51	1.47	C7	-C
O7	-O8	-C10	1.524	1.587	111.19	1.39	C8	-C
O8	-O9	-C10	1.517	1.532	113.61	1.64	C8	-C
O8	-C15	-O4	1.587	1.539	109.80	1.34	C8	-C
O8	-C15	-C16	1.587	1.491	113.46	1.42	C9	-C
O9	-O8	-C15	1.517	1.587	108.33	1.45	C9	-C
C10	-O9	-O8	1.532	1.517	113.61	1.64	C10	-C
C11	-O9	-O5	1.346	1.517	124.85	1.81	C11	-C
C11	-C12	-C13	1.482	1.611	108.86	1.66	C12	-C
C12	-C10	-C14	1.611	1.554	107.99	1.62	C12	-C
C13	-C12	-C11	1.611	1.482	108.86	1.66	C13	-C
C13	-C14	-C10	1.554	1.481	113.57	1.78	C13	-C
C13	-C19	-O8	1.538	1.587	107.47	1.37	C13	-C
C14	-O2	-O1	1.481	1.346	113.90	1.86	C14	-C
C14	-C10	-C11	1.554	1.611	107.99	1.62	C14	-C
C15	-O4	-O4	1.539	1.420	111.85	1.35	C15	-C
C15	-O4	-C10	1.539	1.514	115.23	1.45	C15	-C
C15	-O8	-O4	1.587	1.517	108.33	1.45	C15	-C
C15	-C10	-C14	1.538	1.554	113.94	1.61	C15	-C
C15	-C16	-O1	1.491	1.151	122.99	1.78	C16	-C
C16	-C15	-O4	1.491	1.539	108.54	1.40	C16	-C
C16	-C15	-C10	1.491	1.538	109.24	1.45	C17	-C

J	K	DIJ	DJK	ANGLE	SANG
-C14	-C13	1.214	1.554	120.36	1.95
-C16	-C15	1.351	1.491	112.05	1.55
-C16	-C15	1.151	1.491	122.99	1.78
-C4	-C3	1.420	1.514	103.80	1.39
-C6	-C7	1.425	1.520	112.51	1.47
-C4	-C3	1.388	1.514	111.40	1.45
-C2	-C3	1.346	1.480	126.28	1.86
-C3	-C4	1.480	1.514	114.29	1.60
-C14	-C13	1.481	1.554	113.57	1.78
-C2	-C14	1.480	1.481	119.65	1.70
-C4	-C5	1.514	1.388	111.40	1.45
-C4	-C6	1.420	1.425	115.63	1.32
-C3	-C2	1.514	1.480	114.29	1.60
-C15	-C13	1.539	1.538	108.20	1.38
-C5	-C4	1.455	1.388	116.19	1.38
-C7	-C8	1.520	1.524	110.65	1.44
-C8	-C9	1.524	1.517	108.67	1.49
-C7	-C6	1.524	1.520	110.65	1.44
-C9	-C11	1.517	1.346	124.65	1.81
-C15	-C13	1.587	1.538	107.47	1.37
-C9	-C7	1.517	1.524	108.67	1.49
-C11	-C12	1.346	1.482	124.95	1.85
-C9	-C11	1.532	1.346	121.46	1.81
-C9	-C10	1.346	1.532	121.46	1.81
-C11	-C9	1.482	1.346	124.95	1.85
-C13	-C15	1.611	1.538	108.47	1.51
-C14	-O1	1.554	1.214	120.36	1.95
-C15	-C4	1.538	1.539	108.20	1.38
-C15	-C16	1.538	1.491	109.24	1.45
-O2	-C3	1.481	1.480	119.65	1.70
-C13	-C15	1.554	1.538	115.94	1.61
-C4	-O5	1.539	1.388	103.66	1.32
-C8	-C7	1.587	1.524	111.19	1.39
-C13	-C12	1.538	1.611	108.47	1.51
-C16	-O2	1.491	1.351	112.05	1.55
-O2	-C17	1.351	1.440	114.32	1.49
-C15	-O2	1.491	1.587	113.46	1.42
-O2	-C16	1.440	1.351	114.32	1.49

APPENDIX B: CRYSTALLOGRAPHIC DATA FOR COMPOUND 138

A, B, C, ALPHA, BETA, GAMMA = 10.294
AS, BS, CS, COSAS, COSBS, COSCS = 0.098

NO.	ATOM	X	Y	Z	R
1,	O1	0.81696	1.06309	0.57336	7.
2,	O2	0.78022	1.06830	0.34506	7.
3,	O3	0.55063	0.58764	0.16764	5.
4,	O4	0.62282	0.47467	0.34860	5.
5,	O5	0.82273	0.41772	0.39024	7.
6,	O6	0.67788	0.63519	0.02417	6.
7,	O7	0.68506	0.29508	0.07288	6.
8,	O8	0.70393	0.23807	-0.16629	7.
9,	C1	0.75968	1.13898	0.47423	6.
10,	C2	0.83939	0.94061	0.50183	7.
11,	C3	0.88582	0.83531	0.55777	8.
12,	C4	0.90589	0.72906	0.46098	8.
13,	C5	0.88270	0.73075	0.32079	8.
14,	C6	0.83751	0.84647	0.27046	7.
15,	C7	0.81798	0.94475	0.36529	7.
16,	C8	0.90073	0.61188	0.21495	8.
17,	C9	1.03331	0.54846	0.26236	10.
18,	C10	1.03383	0.41175	0.18471	10.
19,	C11	0.93778	0.34603	0.11194	9.
20,	C12	0.80199	0.39599	0.08158	8.
21,	C13	0.78085	0.51967	0.19485	7.
22,	C14	0.66957	0.58851	0.12627	6.
23,	C15	0.53111	0.56560	0.30295	4.
24,	C16	0.74975	0.47058	0.31930	7
25,	C17	0.39582	0.49638	0.28924	3
26,	C18	0.54840	0.69079	0.39681	4
27,	C19	0.95142	0.20042	0.04412	9
28,	C20	0.67012	0.20517	-0.06343	6
29,	C21	0.60196	0.09975	-0.05700	6
30,	C22	0.55774	0.00772	-0.19183	5
31,	C23	0.65005	-0.09312	-0.17353	6

TOTAL 31 ATOMS SET UP

4	10.430	9.996	98.160	96.500	92.230
3	0.097	0.102	0.147	0.120	0.056

RX	RY	RZ	SD	RAD
7.3295	10.2403	5.6323	.0000	0.68
7.2076	10.6288	3.3896	.0000	0.68
5.2400	5.8790	1.6468	.0000	0.68
5.8242	4.4367	3.4244	.0000	0.68
7.8581	3.7822	3.8335	.0000	0.68
6.6930	6.5846	0.2374	.0000	0.68
6.8497	2.9687	0.7159	.0000	0.68
7.3378	2.7247	-1.6335	.0000	0.68
6.8234	11.1763	4.6585	.0000	0.68
7.6911	9.0685	4.9296	.0000	0.68
8.1484	7.8891	5.4791	.0000	0.68
8.5077	6.9234	4.5283	.0000	0.68
8.4270	7.1463	3.1512	.0000	0.68
7.9717	8.4261	2.6568	.0000	0.68
7.6235	9.3116	3.5883	.0000	0.68
8.7805	6.0624	2.1115	.0000	0.68
10.1174	5.3320	2.5773	.0000	0.68
10.2661	4.0209	1.8145	.0000	0.68
9.3864	3.4425	1.0996	.0000	0.68
8.0027	4.0076	0.8013	.0000	0.68
7.6067	5.1308	1.9141	.0000	0.68
6.5109	5.9486	1.2404	.0000	0.68
4.8949	5.4512	2.9760	.0000	0.68
7.1656	4.4370	3.1366	.0000	0.68
3.5458	4.7499	2.8413	.0000	0.68
4.9159	6.6186	3.8980	.0000	0.68
9.6626	2.0242	0.4334	.0000	0.68
6.8867	2.2311	-0.6231	.0000	0.68
6.2206	1.1230	-0.5599	.0000	0.68
5.9553	0.3613	-1.8844	.0000	0.68
6.9258	-0.7165	-1.7046	.0000	0.68

BOND ANGLE CALCULATION OF SERVICE # 45 ORGANIC

I	J	K	DIJ	DJK	ANGLE	I	J	K	DI
O1	-C1	-O2	1.442	1.434	104.81	O1	-C2	-C3	1.4
O2	-C1	-O1	1.434	1.442	104.81	O2	-C7	-C2	1.3
O3	-C14	-O6	1.336	1.202	115.18	O3	-C14	-C13	1.3
O3	-C15	-C17	1.438	1.526	105.51	O3	-C15	-C18	1.4
O4	-C15	-C17	1.447	1.526	105.83	O4	-C15	-C18	1.4
O4	-C16	-C13	1.372	1.473	117.84	O5	-C16	-O4	1.1
O6	-C14	-O3	1.202	1.336	115.18	O6	-C14	-C13	1.2
O7	-C12	-C13	1.554	1.630	108.54	O7	-C20	-O8	1.5
O8	-C20	-O7	1.212	1.529	122.87	O8	-C20	-C21	1.2
C1	-O2	-C7	1.434	1.396	108.31	C2	-O1	-C1	1.4
C2	-C7	-O2	1.365	1.396	108.82	C2	-C7	-C6	1.3
C3	-C2	-C7	1.379	1.365	124.08	C3	-C4	-C5	1.4
C4	-C5	-C6	1.397	1.446	119.77	C4	-C5	-C8	1.3
C5	-C6	-C7	1.446	1.332	115.56	C5	-C8	-C9	1.5
C6	-C5	-C4	1.446	1.397	119.77	C6	-C5	-C8	1.4
C6	-C7	-C2	1.332	1.365	123.77	C7	-O2	-C1	1.3
C7	-C2	-C3	1.365	1.379	124.08	C7	-C6	-C5	1.3
C8	-C5	-C6	1.543	1.446	117.61	C8	-C9	-C10	1.5
C8	-C13	-C14	1.512	1.524	106.58	C8	-C13	-C16	1.5
C9	-C8	-C13	1.593	1.512	114.03	C9	-C10	-C11	1.5
C10	-C11	-C12	1.273	1.524	124.67	C10	-C11	-C19	1.2
C11	-C12	-O7	1.524	1.554	115.88	C11	-C12	-C13	1.5
C12	-C11	-C10	1.524	1.273	124.67	C12	-C11	-C19	1.5
C12	-C13	-C14	1.630	1.524	104.05	C12	-C13	-C16	1.6
C13	-C8	-C9	1.512	1.593	114.03	C13	-C12	-O7	1.6
C13	-C14	-O3	1.524	1.336	121.44	C13	-C14	-O6	1.5
C13	-C16	-O5	1.473	1.181	125.12	C14	-O3	-C15	1.3
C14	-C13	-C12	1.524	1.630	104.05	C14	-C13	-C16	1.5
C15	-O4	-C16	1.447	1.372	124.25	C16	-O4	-C15	1.3
C16	-C13	-C12	1.473	1.630	108.35	C16	-C13	-C14	1.4
C17	-C15	-O4	1.526	1.447	105.83	C17	-C15	-C18	1.5
C18	-C15	-O4	1.488	1.447	110.42	C18	-C15	-C17	1.4
C19	-C11	-C12	1.591	1.524	113.97	C20	-O7	-C12	1.5
C21	-C20	-O7	1.294	1.529	110.97	C21	-C20	-O8	1.2
C22	-C21	-C20	1.551	1.294	117.84	C23	-C22	-C21	1.4

DIJ	DJK	ANGLE	I	J	K	DIJ	DJK	ANGLE
.413	1.379	126.58	O1	-C2	-C7	1.413	1.365	109.17
.396	1.365	108.82	O2	-C7	-C6	1.396	1.332	127.27
.336	1.524	121.44	O3	-C15	-O4	1.438	1.447	109.93
.438	1.488	109.63	O4	-C15	-O3	1.447	1.438	109.93
.447	1.488	110.42	O4	-C16	-O5	1.372	1.181	116.70
.181	1.372	116.70	O5	-C16	-C13	1.181	1.473	125.12
.202	1.524	122.95	O7	-C12	-C11	1.554	1.524	115.88
.529	1.212	122.87	O7	-C20	-C21	1.529	1.294	110.97
.212	1.294	125.52	C1	-O1	-C2	1.442	1.413	107.00
.413	1.442	107.00	C2	-C3	-C4	1.379	1.402	113.82
.365	1.332	123.77	C3	-C2	-O1	1.379	1.413	126.58
.402	1.397	122.94	C4	-C3	-C2	1.402	1.379	113.82
.397	1.543	122.61	C5	-C4	-C3	1.397	1.402	122.94
.543	1.593	108.50	C5	-C8	-C13	1.543	1.512	110.06
.446	1.543	117.61	C6	-C7	-O2	1.332	1.396	127.27
.396	1.434	108.31	C7	-C2	-O1	1.365	1.413	109.17
.332	1.446	115.56	C8	-C5	-C4	1.543	1.397	122.61
.593	1.524	109.27	C8	-C13	-C12	1.512	1.630	108.97
.512	1.473	114.48	C9	-C8	-C5	1.593	1.543	108.50
.524	1.273	127.19	C10	-C9	-C8	1.524	1.593	109.27
.273	1.591	121.34	C11	-C10	-C9	1.273	1.524	127.19
.524	1.630	110.03	C12	-O7	-C20	1.554	1.529	110.65
.524	1.591	113.97	C12	-C13	-C8	1.630	1.512	108.97
.630	1.473	108.35	C13	-C8	-C5	1.512	1.543	110.06
.630	1.554	108.54	C13	-C12	-C11	1.630	1.524	110.03
.524	1.202	122.95	C13	-C16	-O4	1.473	1.372	117.84
.336	1.438	121.67	C14	-C13	-C8	1.524	1.512	106.58
.524	1.473	113.85	C15	-O3	-C14	1.438	1.336	121.67
.372	1.447	124.25	C16	-C13	-C8	1.473	1.512	114.48
.473	1.524	113.85	C17	-C15	-O3	1.526	1.438	105.51
.526	1.488	115.32	C18	-C15	-O3	1.488	1.438	109.63
.488	1.526	115.32	C19	-C11	-C10	1.591	1.273	121.34
.529	1.554	110.65	C20	-C21	-C22	1.294	1.551	117.84
.294	1.212	125.52	C21	-C22	-C23	1.551	1.461	98.26
.461	1.551	98.26						