Progress Toward the Total Synthesis of Salvadione-A and Related Diterpenoids

Thesis by

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Abstract

Herein, we report our progress toward the total synthesis of salvadione-A, a structurally complex triterpenoid isolated from *Salvia bucharica.* We document a model system of our tandem Claisen/Cope/Diels-Alder strategy. Additionally, we describe the evolution of our strategy toward the synthesis of three structurally related diterpenoids—coulterone, cyclocoulterone, and komaroviquinone—from a cyclopropanation/Friedel-Crafts route to an anionic homo-Fries/intramolecular Barbier cyclization pathway.

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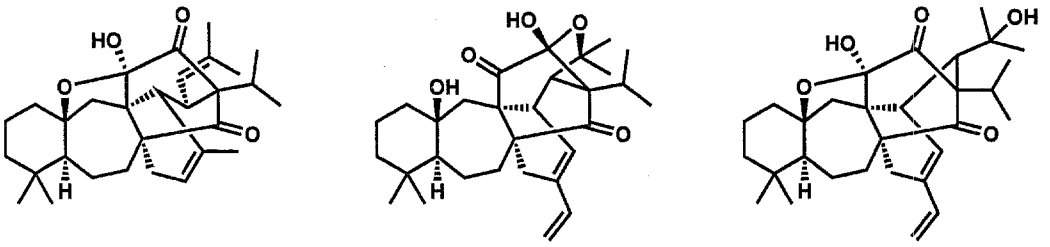
I. Introduction

Isolation and biological activity

In 1999, Ahmad and co-workers isolated the triterpenoid, salvadione-A (**1**), from the *Salvia bucharica* plant in Quetta, Baluchistan, Pakistan[1] (see Figure 1). While the biological activity of salvadione-A has yet to be tested, the *Salvia bucharica* plant has been utilized in traditional practices for the treatment of liver disorders and as a cooling medicine. Additionally, the plant is part of the Lamiaceae family, whose members generally possess compounds with antitumor activity. Despite its unknown biological activity, salvadione-A is attractive synthetically for its structural complexity. The natural product contains a challenging [6-7-6] tricyclic core as well as a propellene-like structural unit.

Figure 1. Salvadione-A and other related triterpenoids from *Salvia bucharica*[1,2]



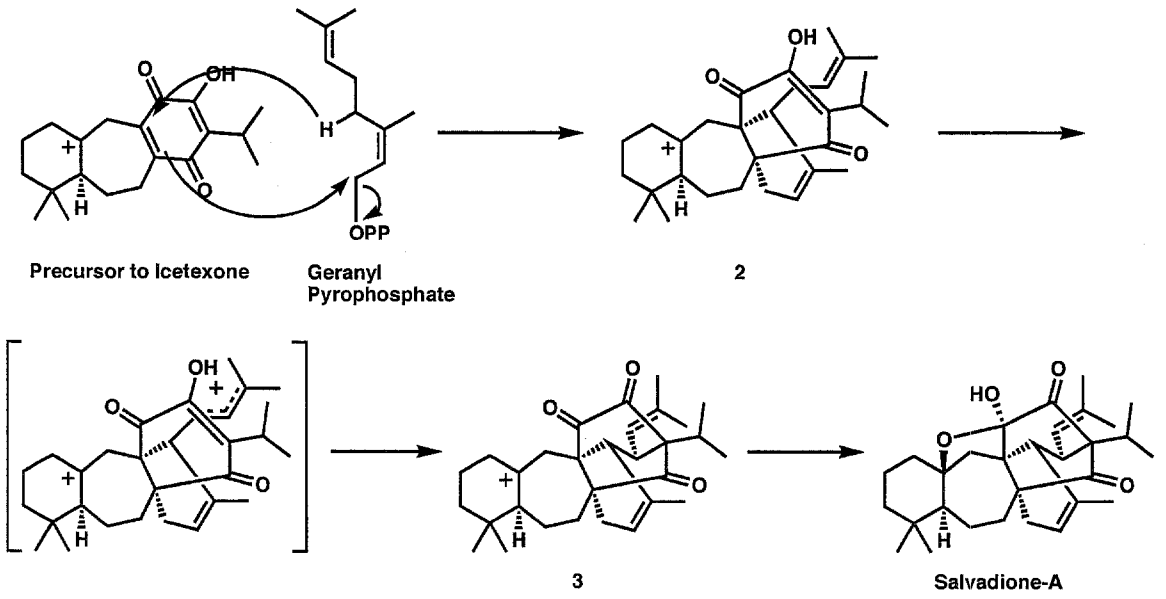
Salvadione-A (1) Salvadione-B Salvadiol

Biogenetic pathway

In the isolation of salvadione-A, Ahmad proposes that the biogenetic pathway of the natural product occurs through the addition of geranylpyrophosphate to an icetexone-type precursor.[1] As shown in Scheme 1, the cycloaddition of these compounds yields tetracycle 2. Oxidation to the allylic cation and subsequent ring closure gives triketone 3. Simple ketone hydrolysis and ring closure then affords salvadione-A. Ahmad has

proposed similar cycloaddition pathways to the biosyntheses of salvadione-B[1] and salvadiol.[2]

Scheme 1. Proposed biogenetic pathway to salvadione-A[3]

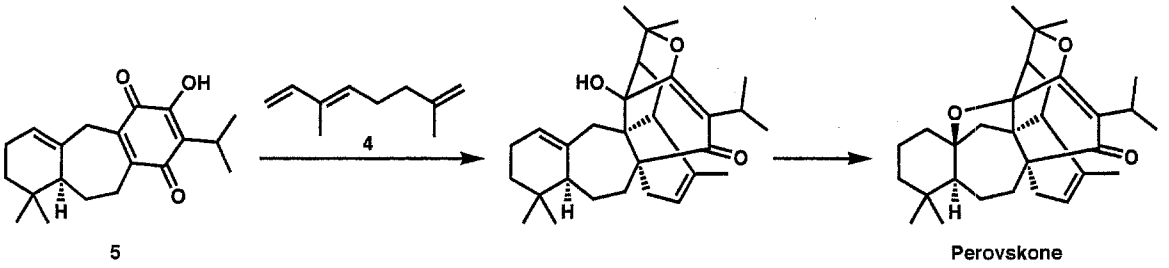


Retrosynthetic analysis

Having started our synthesis of salvadione-A in January of 2003, we assumed that other synthetic groups would be working on biomimetic approaches to the triterpenoid involving similar cycloadditions. In particular, Majetich's total synthesis of (±)-perovskone, a triterpenoid structurally similar to salvadione-A, contained an intermolecular Diels-Alder reaction between *trans*-α-ocimene (4) and hydroxyquinone 5[4] (see Scheme 2). Thus, with hydroxyquinone 5 in hand, Majetich was theoretically on course to complete the biomimetic synthesis of salvadione-A.

In order to avoid an analogous approach to salvadione-A, our retrosynthesis of the triterpenoid involved a tandem Claisen/Cope/Diels-Alder reaction to build the structurally complex carbon framework of the molecule (see Scheme 3). Salvadione-A

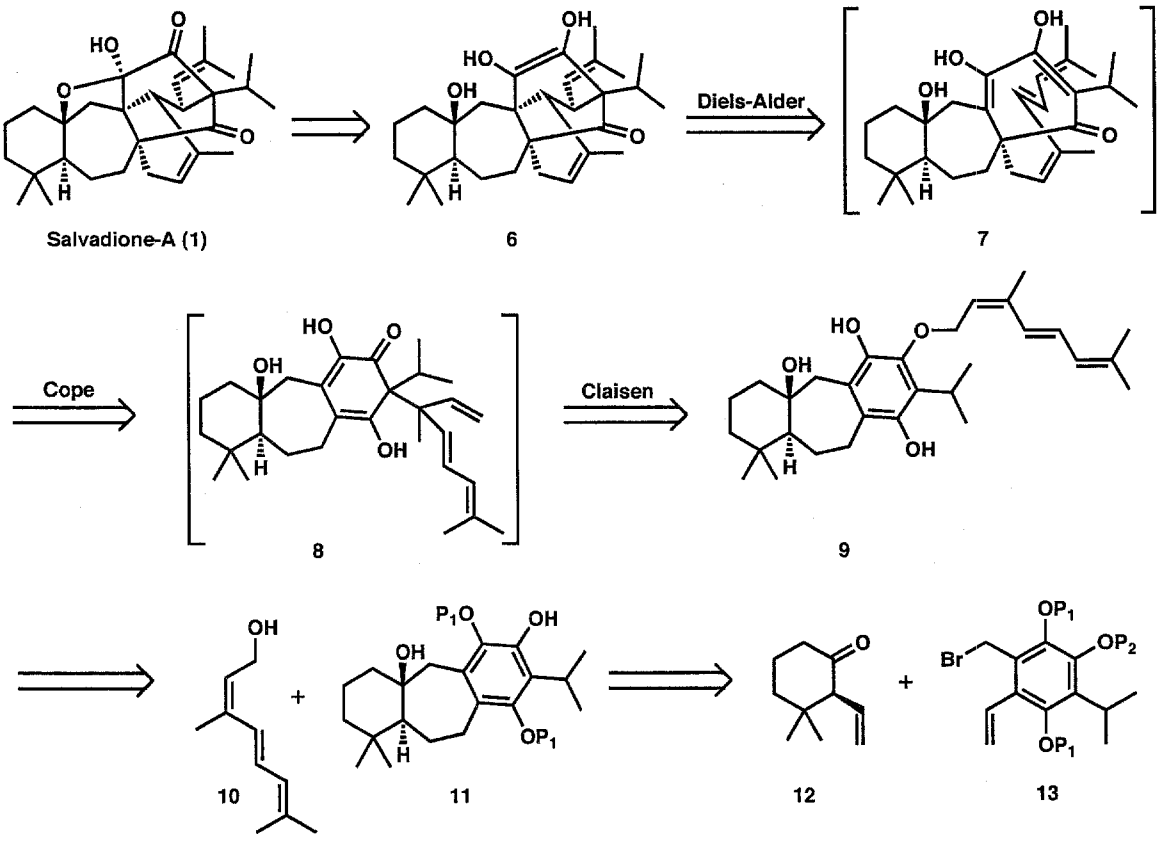
Scheme 2. Majetich's biomimetic approach to perovskone



would be achieved by an oxidation of triol **6**, which we envisioned would be produced by a tandem Claisen/Cope/Diels-Alder reaction of hydroquinone **9**. Experimental evidence for the tandem Claisen/Cope rearrangement, also known as the *para* Claisen rearrangement, was well documented in the literature.[5,6,7,8,9] Certain trends that improve the rate and yield of the *para* Claisen rearrangement included substitution at both *ortho* positions,[5] a hydroxyl substituent in the *ortho* position,[6] and the use of nonpolar solvents.[9] The tandem Claisen/Cope rearrangement had also been reported in total synthesis, such as in Danishefsky's syntheses of Tricycloillicinone and Bicycloillicinone Aldehyde.[10] We also found evidence of a tandem Claisen/Cope/Diels-Alder reaction in Molina's synthesis of fluoreno[2,3,4-i,j]isoquinoline ring derivatives.[11] Given these precedents, the di-*ortho* substitution and the *ortho* hydroxyl group in hydroquinone **9**, the difficulty of enolization for *o*-dienone **8**, and the driving force for the formation of a conjugated triene in tricycle **7**, we were convinced that the tandem Claisen/Cope rearrangement would proceed as outlined. Additionally, after the *para* Claisen rearrangement, tricycle **7** would be perfectly positioned for an intramolecular Diels-Alder reaction, which would construct the carbon framework of salvadione-A. In order to synthesize hydroquinone **9**, triene **10** would be coupled to protected hydroquinone **11**. Olefin reduction and deprotection of the

product formed from a Grignard reaction between cyclohexanone **12** and benzyl bromide **13** and subsequent ring-closing metathesis would then yield protected hydroquinone **11**.

Scheme 3. Retrosynthetic analysis of salvadione A

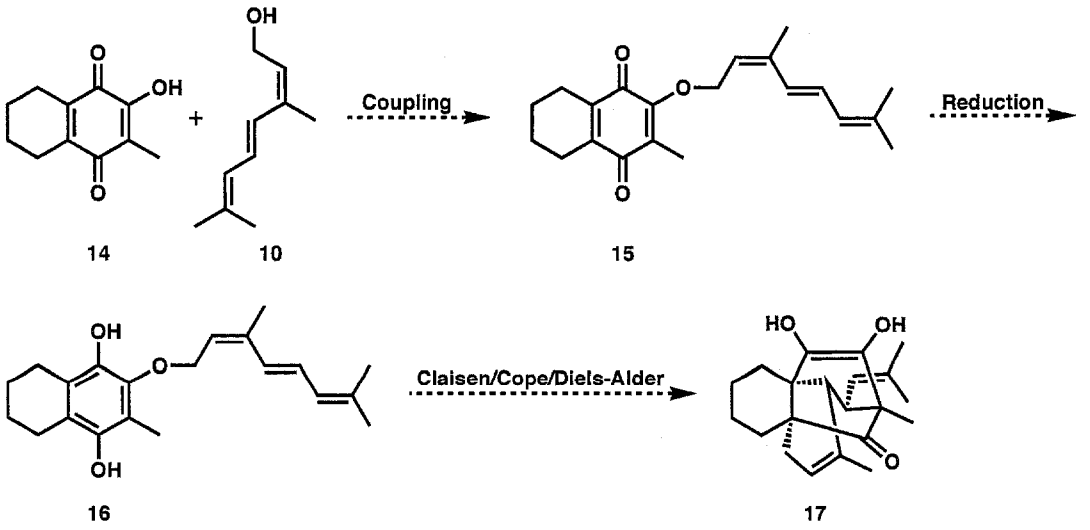


II. Results and Discussion

Model system

In order to test the utility of the tandem Claisen/Cope/Diels-Alder reaction in our synthetic route, we first developed a model system designed to examine the tandem sequence on a less complex, yet structurally similar version of hydroquinone **9**. We therefore chose bicycle **16** as our model compound, which could be achieved from the coupling of hydroxyquinone **14** and triene **10** and subsequent reduction of the product, quinone **15** (see Scheme 4).

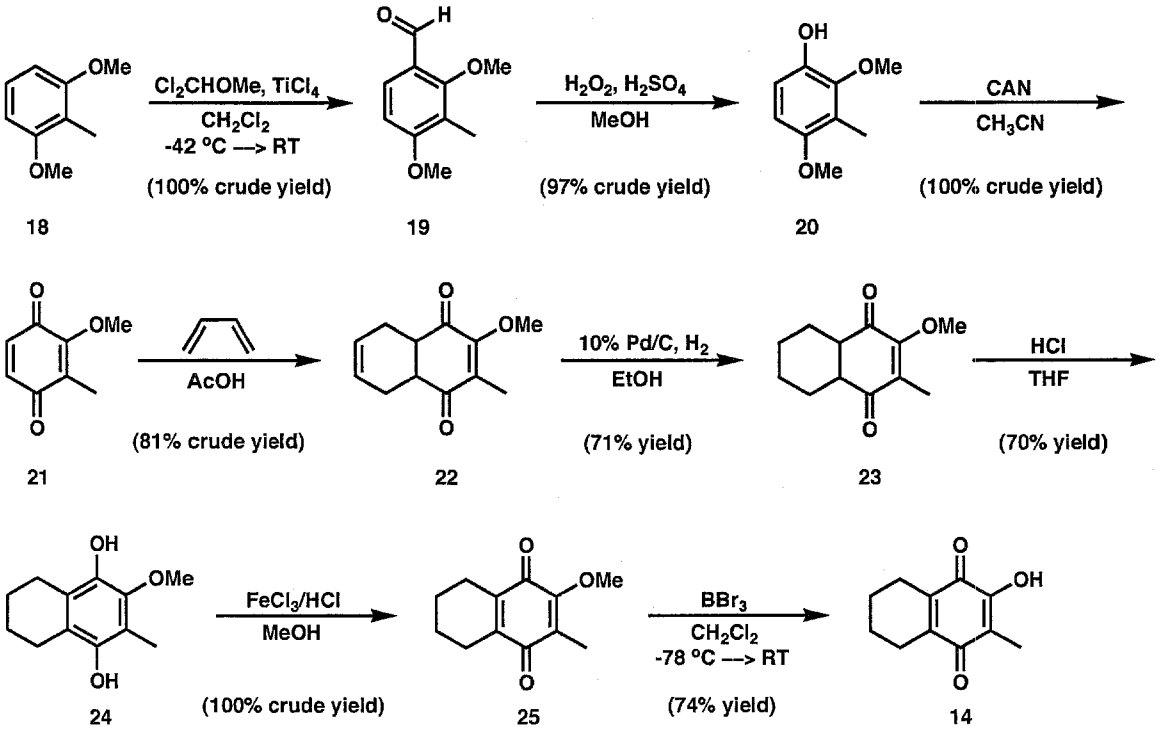
Scheme 4. Model system for the tandem Claisen/Cope/Diels-Alder reaction



Despite the apparent simplicity of hydroxyquinone **14**, there was neither a known route nor a direct method for synthesizing it. In fact, there was not even a literature precedent of the compound. Therefore, after much experimentation and optimization, an eight step synthesis of hydroxyquinone **14** with an overall yield of 29% was completed (see Scheme 5). Commercially available 2,6-dimethoxytoluene (**18**) was formylated with α,α-dichloromethyl methyl ether and $TiCl_4$ to provide benzaldehyde **19** in quantitative yield. An acid catalyzed Baeyer-Villager reaction of **19** also worked in excellent yield to afford phenol **20**, which was oxidized with CAN to quinone **21** exclusively. A Diels-Alder reaction between **21** and 1,3-butadiene in glacial acetic acid provided di-enone **22**.[12] Hydrogenation of **22** proceeded in moderate yield using 1 mol% Pd/C to furnish dihydroquinone **23**. Homogeneous catalysis conditions were not attempted, although their use could have improved the yield of the hydrogenation step. Acid-catalyzed tautomerization to hydroquinone **24** followed by oxidation with $FeCl_3$/HCl provided quinone **25**. Finally, demethylation using BBr_3 afforded hydroxyquinone **14**. It should be noted that only three steps of the synthesis (hydrogenation, tautomerization, and

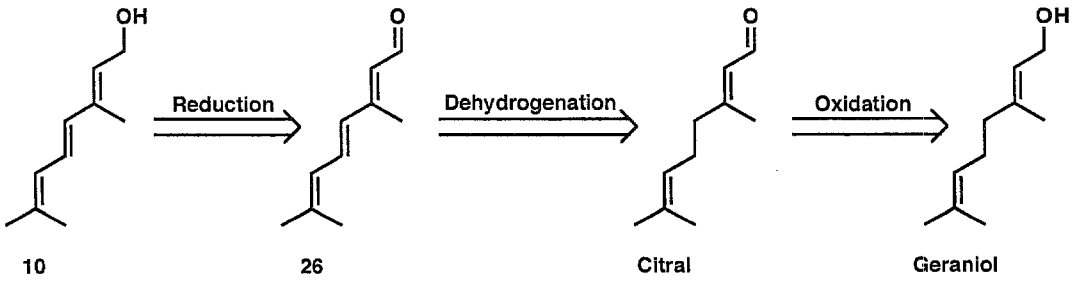
demethylation) required purification.

Scheme 5. Synthesis of hydroxyquinone **14**



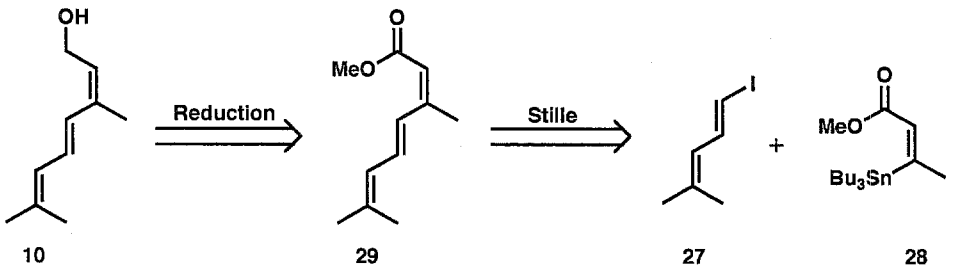
Similar to the synthesis of hydroxyquinone **14**, there was no straightforward route to synthesize triene **10**. Noting that geraniol was simply the γ,δ-dihydro version of triene **10**,[13] we proposed that we could oxidize geraniol to triene **10** in a limited number of steps (see Scheme 6). After successfully oxidizing geraniol to citral under Swern conditions,we employed a number of dehydrogenation methods including Saegusa-Ito oxidation, organoselenium reagents, oxidation/elimination, Nicolaou's hypervalent

Scheme 6. Conversion of geraniol to triene **10**



iodine, and π-allyl palladium chemistry[15] to oxidize citral to aldehyde **26**. Unfortunately, none of these attempts were successful. We therefore modified our strategy to employ a Stille coupling reaction between vinyl iodide **27** and vinyl stannane **28** to afford methyl ester **29** (see Scheme 7). The synthesis of the coupling pieces proved synthetically ineffective, in that low yields and isomer impurities (for vinyl iodide **27**) plagued the route. Nevertheless, with vinyl iodide **27** and vinyl stannane **28** in hand, the Stille reaction was attempted only to afford a low yield of an indeterminate isomer of methyl ester **29**. Despite the futility of the two previous methods, we were fortunate to find

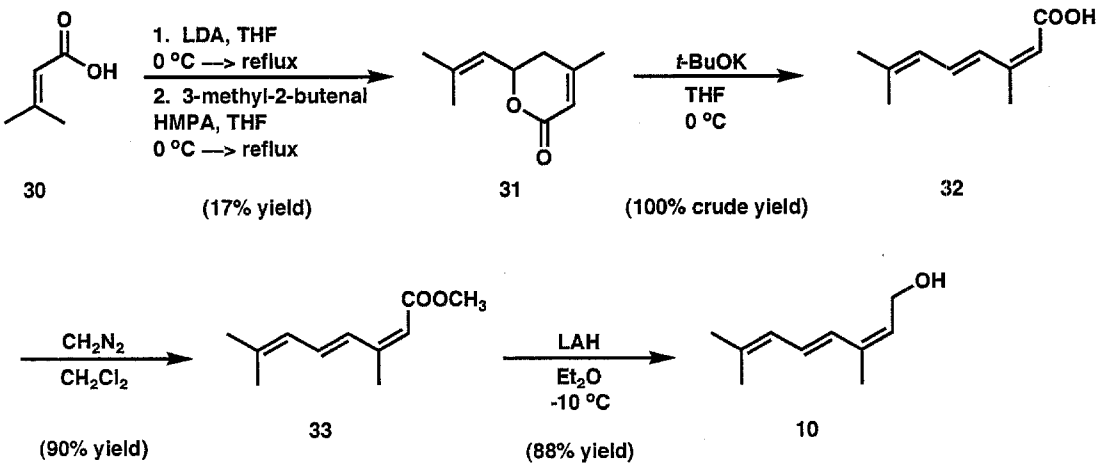
Scheme 7. Stille coupling route to afford triene **10**



Cardillo's four step synthesis of triene **10**.[16] The route started with the formation of the 3,3-dimethylacrylic acid (**30**) dianion by LDA, which, under the right conditions, allowed for a C_4 attack on 3-methyl-2-butenal and subsequent lactonization to form lactone **31** (see Scheme 8). Despite numerous attempts at optimization, we were only able to produce **31** in 17% yield. Lactone **31** was then opened with *t*-BuOK to yield acid **32**. Methylation of crude **32** with diazomethane gave methyl ester **33** in good yield. Finally, LAH reduction of **33** afforded triene **10** in 88% yield. It should be noted that **10** was formed exclusively as the α,β (*Z*)-γ,δ (*E*) isomer.

While modeling the coupling reaction between hydroxyquinone **14** and triene **10**, we were able to successfully couple **14** with geraniol and to produce the hydroquinone by

Scheme 8. Cardillo's synthesis of triene **10**



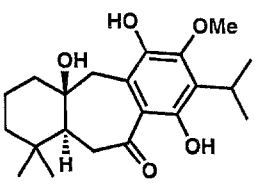
subjecting the coupled product to mild reduction conditions.[17] We even attempted the tandem Claisen/Cope rearrangement[18] but could not verify product formation in the reaction. However, no definitive conclusion about the *para* Claisen rearrangement could be drawn from this experiment, seeing that geraniol lacked the γ,δ olefin and conjugation of triene **10**, which could drastically affect its reactivity. Given the success of our model, we were therefore confident that hydroxyquinone **14** and triene **10** would couple. We initially attempted to combine the pieces under standard Mitsunobu conditions,[19] but these reactions all failed and resulted in a variety of side products. Subsequent coupling reactions employing DCC or EDC conditions and atypical Mitsunobu conditions using PMe_3, PBu_3, or PCy_3 instead of PPh_3 were also unsuccessful and led to numerous side products. It therefore appeared that the triene functionality proved too unstable for the coupling reaction. The conjugation of the system presumably increased the acidity of the allylic hydrogens and thus facilitated the immediate elimination of either the coupled product or the activated electrophile. Because of the reactivity issues of the triene, it seemed that the formation of quinone **15** would require extremely mild coupling

conditions or a different route altogether, such as the piecewise synthesis of the triene moiety onto hydroxyquinone **14**.

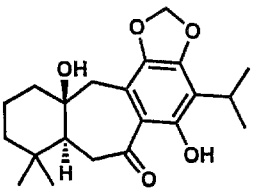
Related diterpenoids

While our model system continued to be problematic, we faced more unfortunate news as Majetich published the total synthesis of (+)-salvadione-A.[20] As we had expected, Majetich employed a Diels-Alder reaction on his previously synthesized hydroxyquinone **5** to construct the triterpenoid. Given these setbacks, we decided to shift our focus to the synthesis of three related diterpenoids, coulterone (**34**)[21], cyclocoulterone (**35**)[22], and komaroviquinone (**36**)[22] (see Figure 2). While coulterone was isolated in 1993 from Mexican *Salvia coulteri*,[21] cyclocoulterone and komaroviquinone were isolated from *Dracocephalum komarovi* in Uzbekistan in 2002.[22] Komaroviquinone was found to have strong *in vitro* trypanocidal activity against epimastigotes of *Trypanosoma cruzi*, which was responsible for Chagas' disease in Central and South America.[22] As of March of 2004, no group has synthesized any one of these compounds. Notwithstanding slight functional group modifications on the aromatic ring, these natural products and the tricyclic core of salvadione-A (see protected hydroquinone **11**) only differed by a benzylic ketone. Based on the biological activity of komaroviquinone and on the straightforward interconversion of these compounds to a salvadione-A intermediate, we

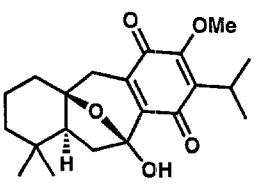
Figure 2. Coulterone, cyclocoulterone, and komaroviquinone



Coulterone (34)



Cyclocoulterone (35)



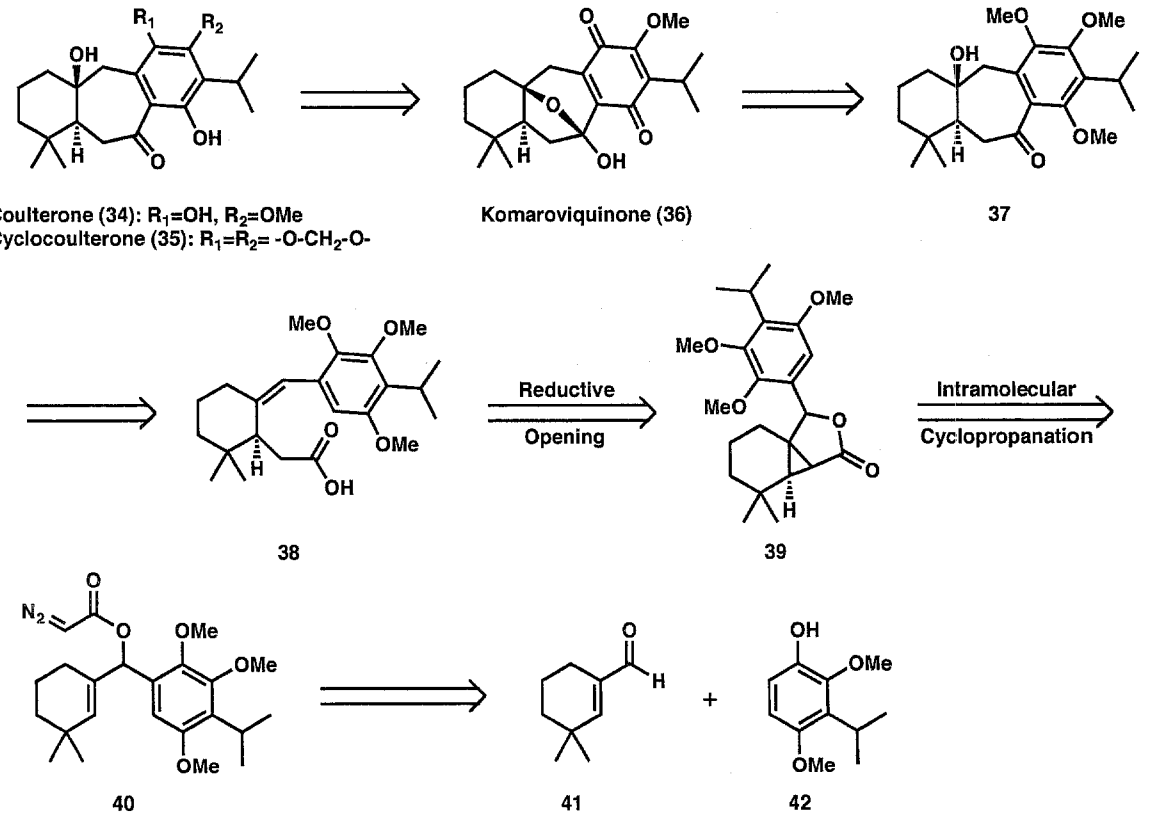
Komaroviquinone (36)

commenced the syntheses of these natural products en route to our total synthesis of salvadione-A.

Retrosynthetic analysis

Given the benzylic ketone functionality, we envisioned a different approach to access the tricyclic core of the diterpenoids. Coulterone could be accessed by the reduction of komaroviquinone (see Scheme 9). Subsequent functional group manipulation of coulterone could then afford cyclocoulterone. Komaroviquinone could be produced by the oxidation of tricycle **37**, which could be synthesized by a Friedel-Crafts reaction and olefin hydrolysis of acid **38**. The reductive opening of lactone **39** could yield **38**. We sought to establish the carbon framework of the seven-membered

Scheme 9. Retrosynthetic analysis of the diterpenoids

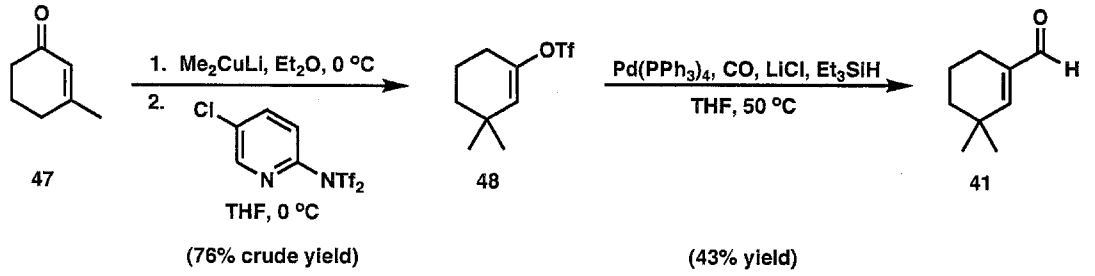


ring via an intramolecular cyclopropanation of diazoacetate **40**. Finally, **40** could be accessed by the coupling of enal **41** and phenol **42** and consequent functional group manipulation of the product.

Cyclopropanation route

Enal **41** was afforded in only two steps from commercially available 3-methyl-2-cyclohexen-1-one (**47**) (see Scheme 10). We employed a cuprate trapping of **47** with Comins' reagent to access vinyl triflate **48** in good yield.[23] Enal **41** was then synthesized by a palladium catalyzed reductive carbonylation of **48** in low yield.[24] As shown in

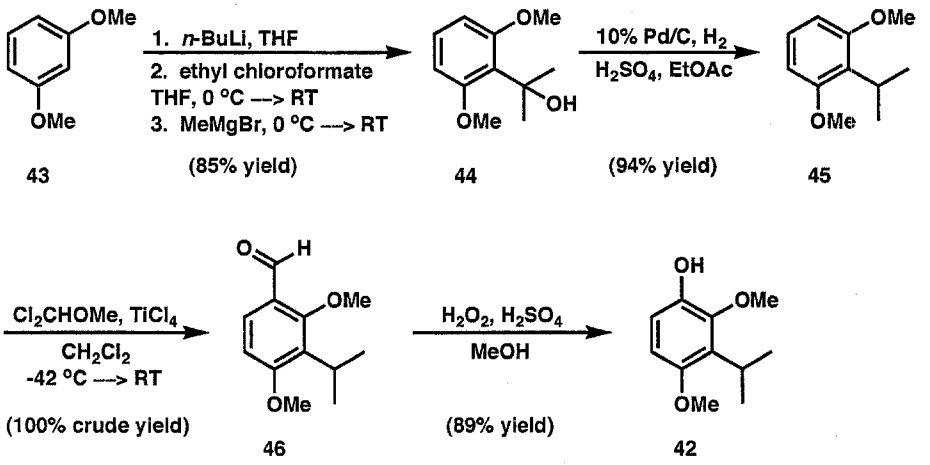
Scheme 10. Synthesis of enal **41**



Scheme 11, the synthesis of phenol **42** was completed in four steps starting from commercially available 1,3-dimethoxybenzene (**43**). Original attempts to synthesize benzyl alcohol **44** resulted in low yields. However, subsequent optimization using Carreno's *ortho*-directed metallation conditions on 1,3-dimethoxybenzene afforded **44** in good yield.[25] Acid-catalyzed hydrogenation of benzyl alcohol **44** yielded isopropylbenzene **45**,[25] which, in turn, was formylated to provide benzaldehyde **46**. Finally, crude **46** was subjected to acid-catalyzed Baeyer-Villager conditions to produce phenol **42** in 89% yield.

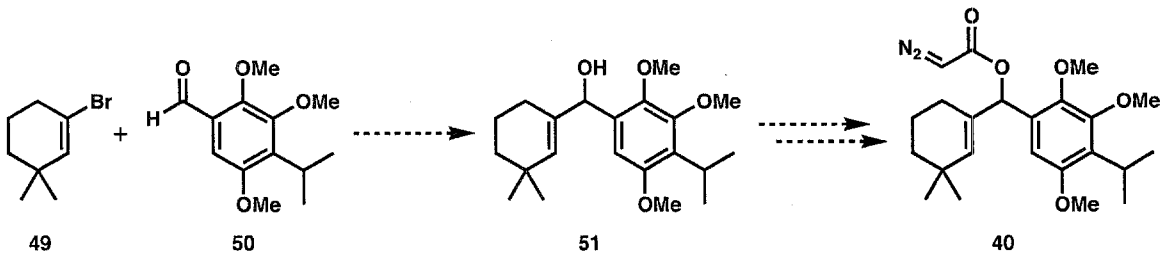
With both enal **41** and phenol **42** in hand, we sought to couple the two pieces.

Scheme 11. Synthesis of phenol **42**



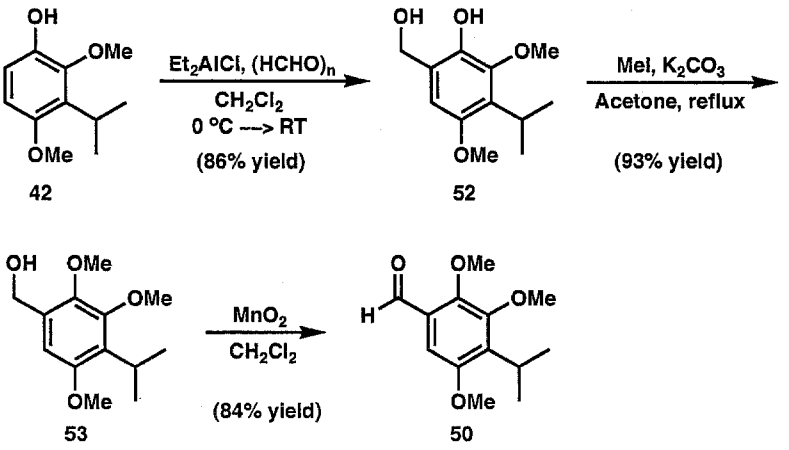
Nevertheless, despite numerous attempts including a Et_2AlCl promoted aldol and a Nagata coupling reaction,[26] we were unable to synthesize the coupled product. Because of this and the inefficient preparation of enal **41**, we decided to slightly alter our approach to diazoacetate **40** (see Scheme 12). In our modified synthesis, vinyl bromide **49** would be reacted with benzaldehyde **50** to yield benzyl alcohol **51**, which would then be elaborated to **40**.

Scheme 12. Modified synthesis of diazoacetate **40**



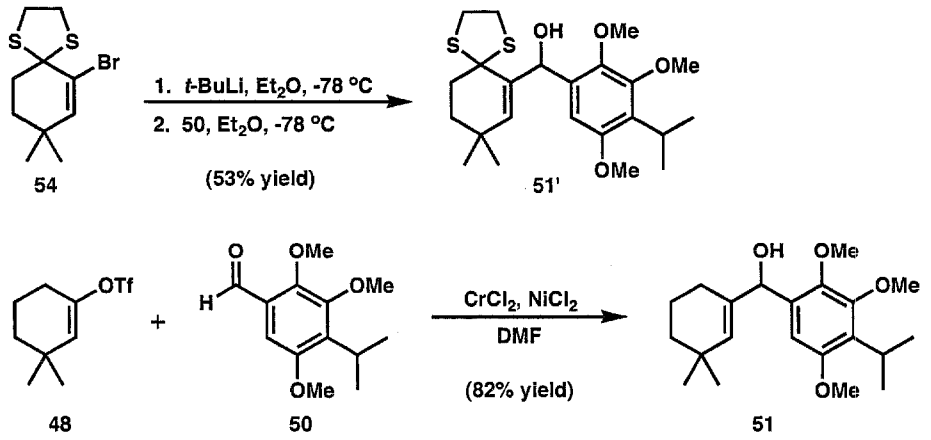
After Et_2AlCl promoted *o*-alkylation of phenol **42** afforded diol **52**, methylation with MeI yielded trimethoxybenzene **53** (see Scheme 13). Subsequent benzylic oxidation of trimethoxybenzene **53** with MnO_2 provided benzaldehyde **50** in good yield. While we were unable to synthesize vinyl bromide **49** despite numerous attempts, we were able to couple dithiane **54** with benzaldehyde **50** in moderate yield using metal-

Scheme 13. Synthesis of benzaldehyde **50**



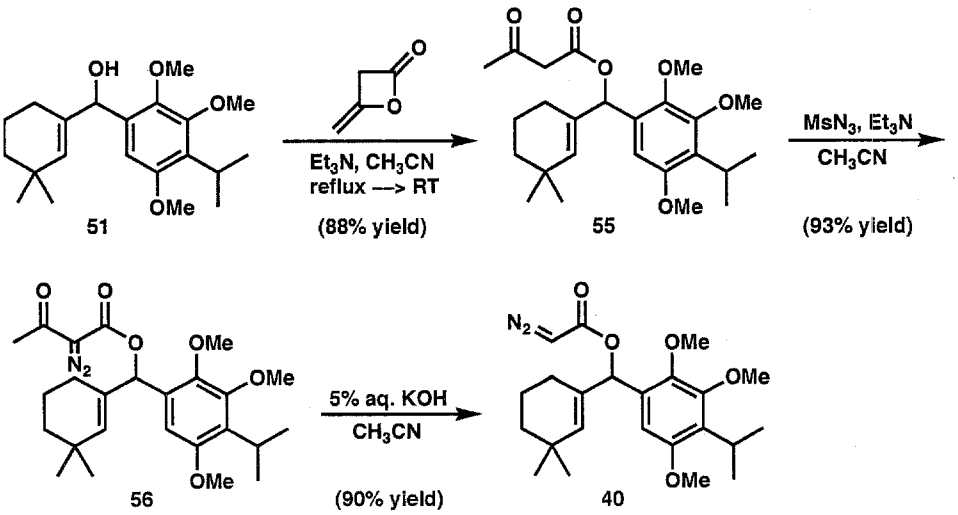
halogen exchange conditions (see Scheme 14). While further manipulations appeared promising, we discovered a much more effective and efficient route to benzyl alcohol **51**. Using Takai's alkenylchromium conditions, we were able to couple vinyl triflate **48** with benzaldehyde **50** to afford **51** in good yield.[27]

Scheme 14. Synthesis of benzyl alcohol **51**



With the synthesis of benzyl alcohol **51** complete, we continued our synthesis of lactone **39**. As shown in Scheme 15, esterification of **51** with diketene yielded ester **55** in 88% yield. Diazotization of **55** with mesyl azide followed by acetyl cleavage accessed diazoacetate **40** in high yield.[28] With **40** in hand, we attempted the intramolecular cyclopropanation reaction using a variety of catalysts, including $Rh_2(OAc)_4$, $Cu(TBS)_2$,

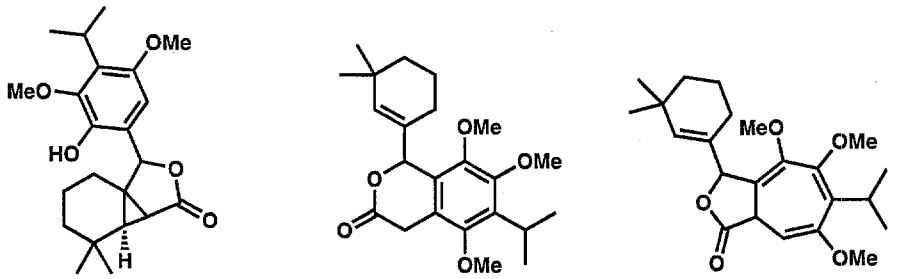
Scheme 15. Synthesis of diazoacetate **40**



$Cu(acac)_2$, Cu Bronze, $CuI{\bullet}P(OEt)_3$,[29] and $Rh_2(cap)_4$.[30] With the notable exception of $Rh_2(OAc)_4$, the reactions yielded a similar variety of products, based on TLC analysis. While most of these products were unidentifiable, there appeared to be formation of lactone **39** in the reactions, albeit in low yield (less than 20%). It was possible that the unknown products of these reactions were a combination of aromatic C-H insertion and Buchner reaction products, although a number of different insertion reactions also could have occurred. It was well documented that reacting diazo compounds such as diazoacetate **40** with these transition metal catalysts could potentially yield three main products: lactone **39** (intramolecular cyclopropanation), bicycle **57** (aromatic C-H insertion),[30] and cycloheptatriene **58** (Buchner reaction)[31] (see Figure 3). Because none of the catalysts seemed to favor intramolecular cyclopropanation over the other reactions, we sought a different synthetic route.

We were still determined that we could access the seven-membered ring via a cyclopropanation pathway. Thus, with benzyl alcohol **51** in hand, we attempted both intramolecular and intermolecular cyclopropanation routes (see Scheme 16). Starting

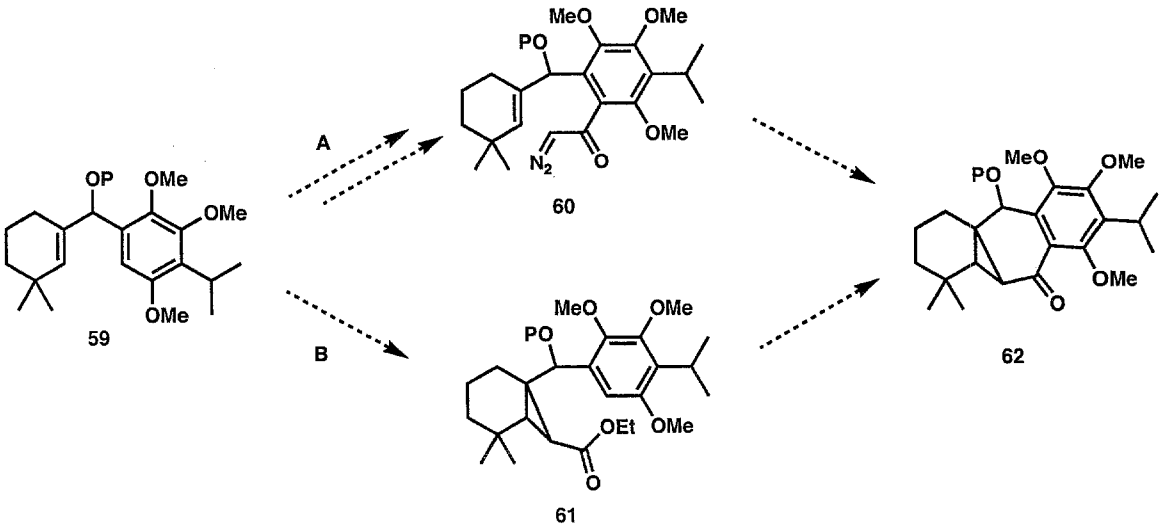
Figure 3. Possible products of the attempted intramolecular cyclopropanation reaction



39 57 58

from protected benzyl alcohol **59**, path A involved the installment of a diazoketone functionality onto the unsubstituted carbon of the aromatic ring, followed by intramolecular cyclopropanation to yield cyclopropane **62**. The substitution of the diazoketone directly onto the aromatic ring would obviously limit the possibility of competitive aromatic C-H insertion or Buchner reactions. In path B, **59** could be intermolecularly cyclopropanated by ethyl diazoacetate with subsequent ring closure to afford cyclopropane **62**. In either route, **62** could be manipulated to produce tricycle **37**.

Scheme 16. Two cyclopropanation routes



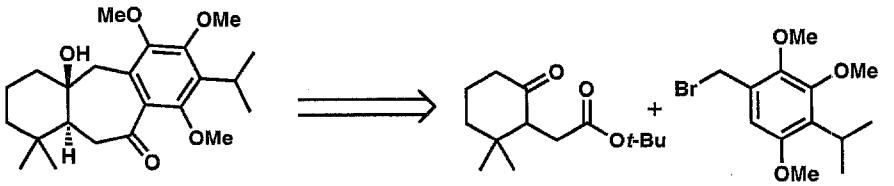
With P = TBS, SEM, or Ac in protected benzyl alcohol **59**, we unfortunately were unable to functionalize the aromatic ring, despite numerous halogenation, formylation,

and carboxylation attempts. With the failure of these reactions, we proceeded with path B and encountered just as much difficulty. Using P = TBS or Ac, protected benzyl alcohol **59** was unreactive towards conditions using ethyl diazoacetate and either $Rh_2(OAc)_4$ or $Cu(TBS)_2$ as a catalyst. Based on the persistent failure of the cyclopropanation route, we decided again to amend our synthetic plan.

Modified approach to the tricyclic core

Ironically, we returned to one of our original ideas to afford the [6-7-6] tricyclic core. As shown in Scheme 17, we envisioned that tricycle **37** could be quickly constructed from a Grignard and subsequent Friedel-Crafts reaction between *t*-butyl ester **63** and benzyl bromide **64**, both of which could be efficiently prepared from commercially available starting materials. Based on steric arguments, the Grignard reaction would yield the correct relative stereochemistry of the *trans*-fused ring system.

Scheme 17. Retrosynthetic analysis of tricycle **37**

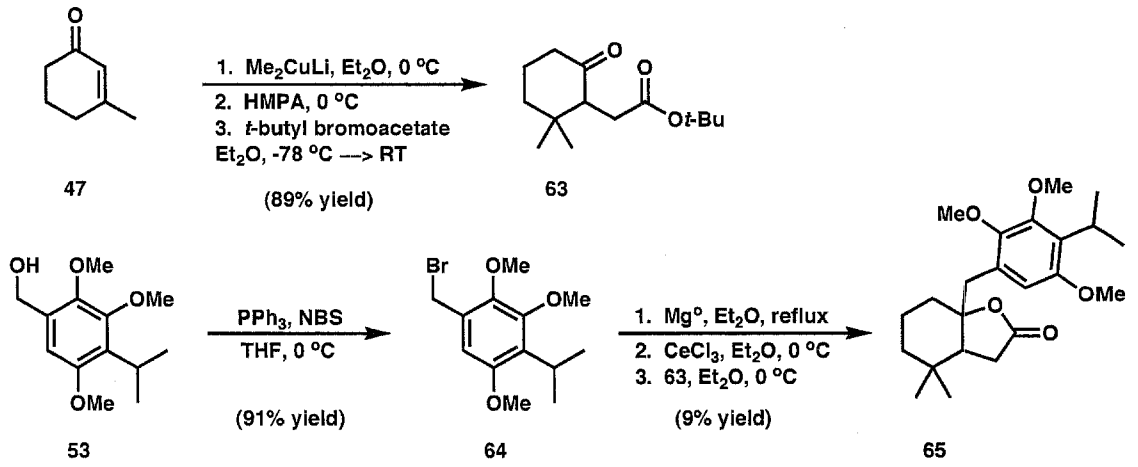


37 **63** **64**

A three component coupling reaction using 3-methyl-2-cyclohexen-1-one (**47**), Me_2CuLi, and *tert*-butyl bromoacetate yielded *t*-butyl ester **63** in excellent yield (see Scheme 18). Benzyl bromide **64** was also afforded in one step in 91% yield via the bromination of previously synthesized trimethoxybenzene **53**. Our initial attempts of the Grignard reaction were unsuccessful and resulted mostly in the quenched Grignard reagent. This seemed reasonable given the number of acidic protons in *t*-butyl ester **63**.

Thus, in order to limit competitive enolization, we employed Imamoto's Grignard/$CeCl_3$ conditions and achieved addition to produce lactone **65**, albeit in very low yield.[32] We anticipated the lactonization of the Grignard product, given the precedent of a related system,[32] and also expected subsequent ring closure to proceed without difficulty. Nevertheless, the lactone formation actually became detrimental to our synthetic route. Performing a Friedel-Crafts reaction directly on lactone **65** was unsuccessful using either $AlCl_3$ or $TiCl_4$. Additionally, attempts at opening the lactone under saponification conditions worked, but the product was prone to lactonize back to starting material. To avoid lactonization issues, we even tried the Grignard/$CeCl_3$ conditions using an allyl group in place of the *tert*-butyl acetate in **63**, but the reaction failed to yield any reasonable amount of product.

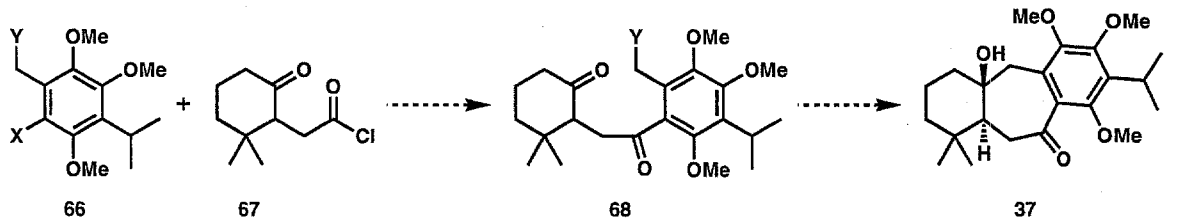
Scheme 18. Grignard reaction



Given the low yields of the Grignard reaction and the problems associated with lactonization, we reversed the order of our synthetic plan, such that we would first react arene **66** with acid chloride **67**, and then close the seven membered ring using a Grignard or Barbier reaction to yield tricycle **37** (see Scheme 19). This approach would directly

address our difficulties with substituting the aromatic ring before attempting the addition reaction, which we had previously shown to work.

Scheme 19. Modified approach to tricycle **37**

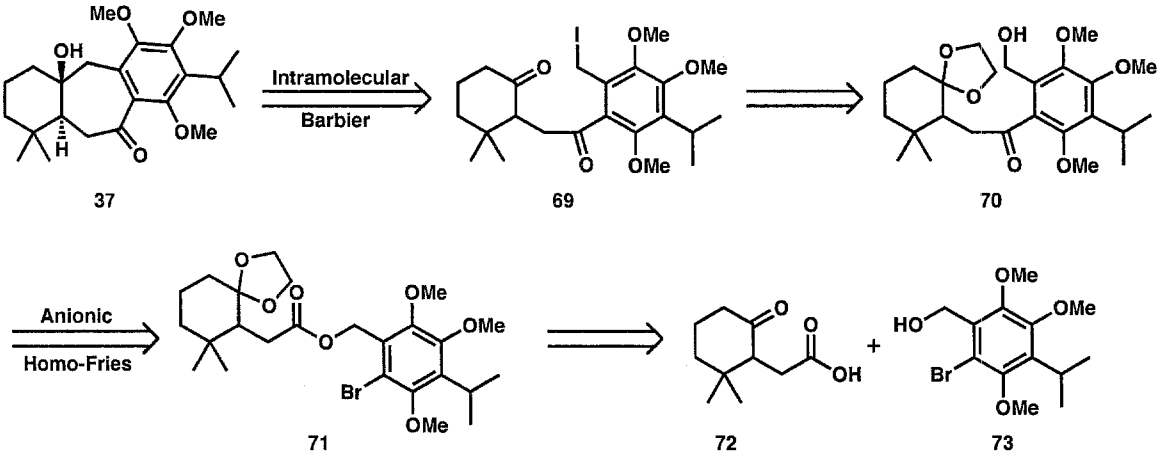


We first attempted the simplest approach to accessing diketone **68**, which was a Friedel-Crafts reaction between benzyl bromide **64** or acetylated arene **66** (X = H, Y = OAc) and acid chloride **67**, synthesized by the hydrolysis and subsequent chlorination of *t*-butyl ester **63**. Unfortunately, both of these reactions failed to afford **68** and instead yielded unidentifiable compounds that were presumably arene polymerization products. We therefore focused on a Stille reaction between aryl stannane **66** (X = $SnBu_3$, Y = OAc) and acid chloride **67**. We were able to easily access acetylated iodobenzene **66** (X = I, Y = OAc) by the iodination and acetylation of trimethoxybenzene **53**. Nevertheless, despite numerous attempts, we could not perform the coupling reaction to make the aryl stannane. We believed that the steric encumbrance of the aromatic ring resulted in the lack of reactivity. Finally, we attempted a lithium-halogen exchange reaction between TBS-protected bromobenzene **66** (X = Br, Y = OTBS) and acid chloride **67**, which succeeded in forming TBS-protected diketone **68** (Y = OTBS) in 7% yield. To achieve better reactivity, we attempted coupling TBS-protected bromobenzene **66** (X = Br, Y = OTBS) with the Weinreb amide version of acid chloride **67**. Nevertheless, this reaction did not yield any product.

Final strategy: anionic homo-Fries/intramolecular Barbier

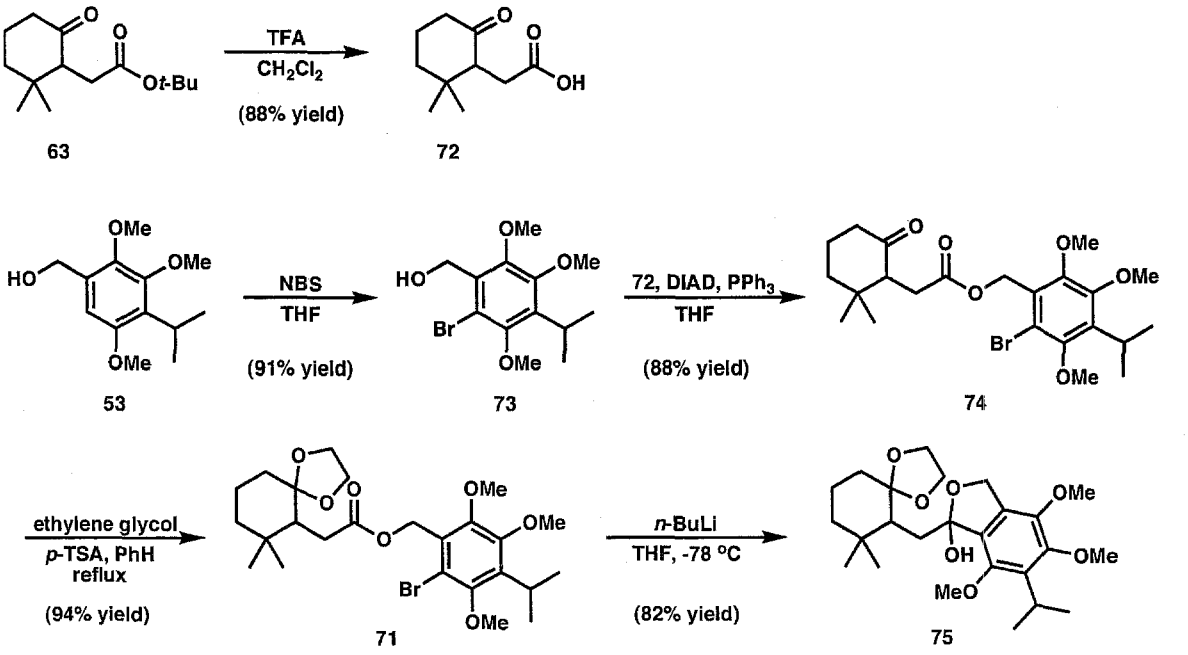
Despite the poor yield of the initial lithium-halogen exchange reaction, we were satisfied with finally being able to substitute the aromatic ring. We concluded that the low product yield was a result of both competitive enolization and the poor reactivity of the acid chloride functionality with an organolithium species. Therefore, we designed a new synthesis of tricycle **37,** which reduced the number of acidic protons and involved a more reactive electrophile (see Scheme 20). We envisioned synthesizing tricycle **37** through Molander's SmI_2 promoted intramolecular Barbier cyclization on benzyl iodide **69**.[33] Iodination and deprotection of keto-alcohol **70** could lead to **69**. Keto-alcohol **70** could be accessed by an anionic homo-Fries rearrangement of ketal **71**,[34] which, in turn, could be formed by the coupling of acid **72** and bromobenzene **73** and subsequent protection of the product.

Scheme 20. Final approach to tricycle **37**



Hydrolysis of *t*-butyl ester **63** with TFA yielded acid **72** in good yield (see Scheme 21). Bromination of trimethoxybenzene **53** with *N*-bromosuccinimide then afforded bromobenzene **73** in 91% yield. Mitsunobu coupling of **72** with **73** proceeded smoothly to yield ester **74**, which was protected with ethylene glycol to afford ketal **71**.

Scheme 21. Anionic homo-Fries rearrangement

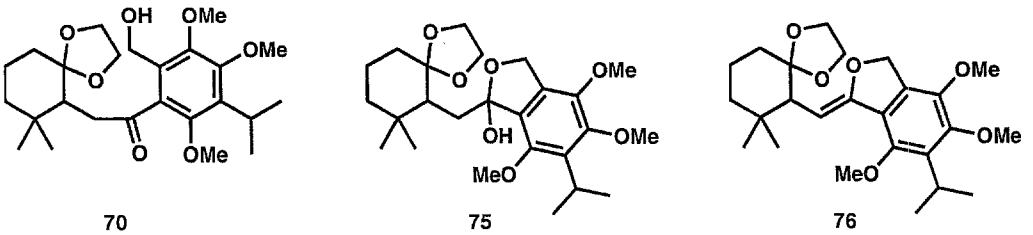


With **71** in hand, we successfully performed the anionic homo-Fries rearrangement in 82% yield.[35] Based on ^{1}H NMR analysis, we assigned the structure of the product to be lactol **75** instead of keto-alcohol **70**. Our next step to iodinate **75** proved to be quite difficult despite numerous attempts. We predicted that the stability of the lactol resulted in the poor reactivity of **75**. Therefore, in an attempt to reduce lactol **75**, we noted that a white solid precipitated when it was stirred in methanol. While TLC analysis confirmed a different R_f value for the precipitate, ^{1}H NMR showed the same spectrum as lactol **75**. We assumed that the solid was actually keto-alcohol **70** and that it cyclized into lactol **75** in certain solvents. An IR spectrum of the solid showed both hydroxyl (3448 cm^{-1}) and carbonyl (1674 cm^{-1}) bands and therefore validated our hypothesis. With **70** in hand, we again attempted numerous iodination conditions, but these reactions failed to yield any product and resulted mostly in unreacted starting material. We then tried numerous functionalization reactions including mesylation, bromination, acetylation, and protection

with ethylene glycol, but these all afforded mostly unreacted keto-alcohol **70**. When oxidation reactions using DMP, PDC, or MnO_2 and reduction attempts with LAH failed to react with **70**, we reasoned that the product of the anionic homo-Fries rearrangement must be neither lactol **75** nor keto-alcohol **70**.

After further spectroscopic analysis, it was discovered that the product was actually enol ether **76** (see Figure 4).[36] The mistaken identification of the product resulted from ambiguous ^1H NMR peaks and IR bands. What was believed to be diastereomeric benzylic hydrogen peaks (lactol **75**) was actually a complex multiplet of benzylic and vinyl hydrogen peaks (enol ether **76**). Additionally, the olefin band (enol ether **76**) in the IR was mistaken for a carbonyl band (keto-alcohol **70**). It was possible that the hydroxyl band (keto-alcohol **70**) in the IR was a result of water contamination as it was fairly weak. High Resolution Mass Spectrometry confirmed the identification of the product as enol ether **76**. While it is possible that the initial product of the rearrangement was keto-alcohol **70**, lactol **75**, or an equilibrium mixture of both, the reaction work-up and subsequent drying under methanol appeared to result in the exclusive formation of enol ether **76**.

Figure 4. Possible structures of the anionic homo-Fries rearrangement product

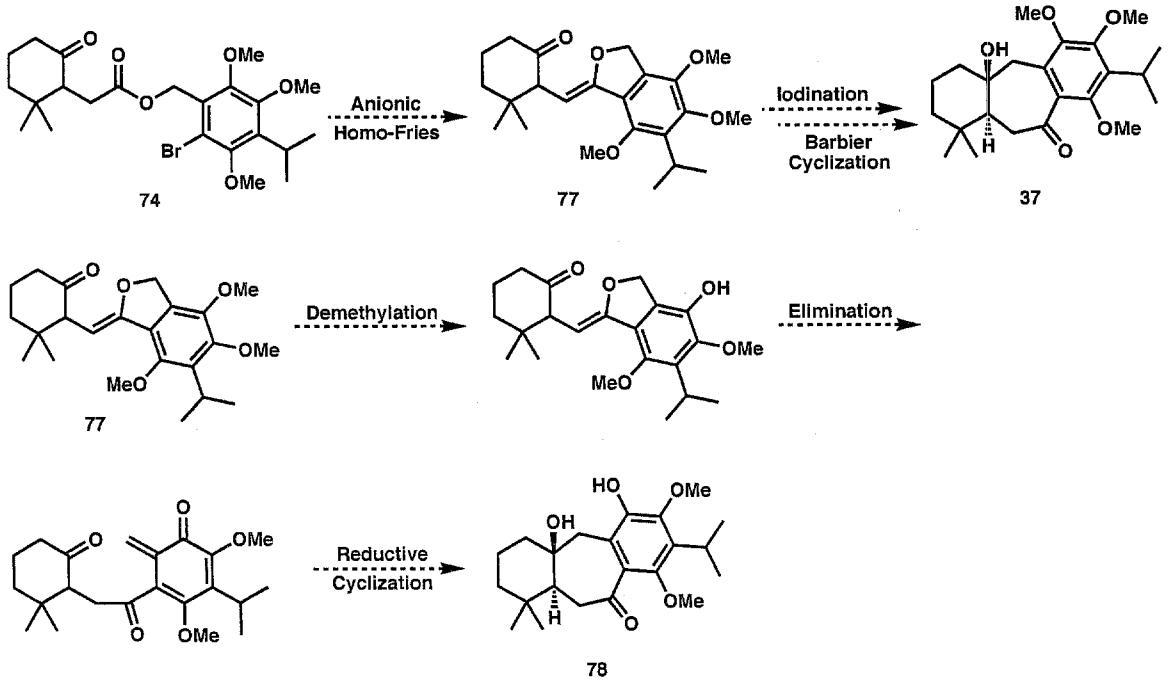


70 75 76

With the identity of the product finally resolved, we sought to iodinate, deprotect, and then cyclize enol ether **76** as shown in Scheme 20. Nevertheless, using a number of nucleophilic iodine sources such as NaI, KI, HI, TMSI, or $Bu_4N^+I^-$ and TsOH, enol ether

76 either was unreactive or resulted in a large number of compounds, none of which was confirmed to be the iodinated product. Presuming that steric hindrance and/or competitive reaction participation of the ketal functionality resulted in the varied reactivity, we attempted to remove the protecting group. However, the deprotection step resulted in a number of products, which could not be isolated. We therefore concluded that we would need to study the anionic homo-Fries of the unprotected cyclohexanone, ester **74** (see Scheme 22). An initial reaction did appear to afford enol ether **77**, albeit in low yield and contaminated with trimethoxybenzene **53**.[37] Further optimization therefore needed to be performed before making any definitive conclusions about the utility of this reaction. Assuming the success of the unprotected anionic homo-Fries rearrangement, we could access the tricyclic core either through our previous iodination/intramolecular Barbier cyclization route or through an elimination/reductive cyclization pathway.

Scheme 22. Anionic homo-Fries rearrangement and endgame strategy



Although we have only started our study of the reactivity of ester **74**, we are optimistic that our new strategy will afford tricycle **37**.

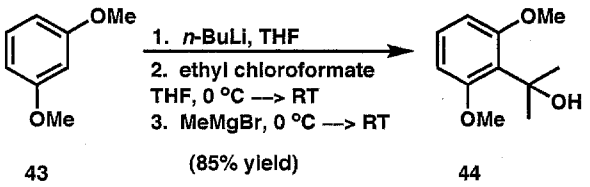
III. Conclusion

In summary, we have reported our progress toward the total synthesis of salvadione-A. While we were not able to fully assess the utility of the tandem Claisen/Cope/Diels-Alder reaction in our model system, we learned valuable information about the reactivity of our triene moiety and future coupling strategies. Shifting our focus toward the total synthesis of the related diterpenoids en route to salvadione-A, we attempted a cyclopropanation/Friedel-Crafts approach to afford the [6-7-6] core of the compounds. Low yielding reactions and aromatic substitution issues caused us to modify our synthetic approach to an anionic homo-Fries rearrangement/intramolecular Barbier cyclization strategy. In this route, we successfully completed the synthesis of advanced intermediate **76** in ten linear steps from 1,3-dimethoxybenzene in 27% overall yield. Future research on this project should focus on the anionic homo-Fries rearrangement with ester **74** and subsequent aforementioned pathways to yield tricycle **37**, the diterpenoids, and salvadione-A.

IV. Experimental Section

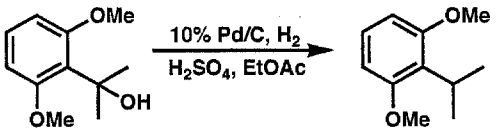
Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received. HMPA was distilled over calcium hydride before use. *N*-bromosuccinimide

was recrystallized by hot gravity filtration in water. The following reagents were prepared according to literature procedure: Comins' reagent,[23] $Cu(TBS)_2$,[38] and $Rh_2(cap)_4$.[39] Reaction temperatures were controlled using an IKAmag temperature modulator. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized using a combination of UV and anisaldehyde staining. ICN silica gel (particle size 0.032-0.063 mm) was used for flash column chromatography. ^1H NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 75 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility.



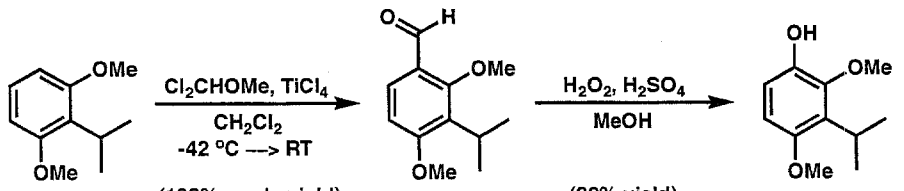
43 44

Benzyl Alcohol 44. A solution of 1,3-dimethoxybenzene (1.0 mL, 7.6 mmol) in THF (6.0 mL) was added dropwise to *n*-BuLi (2.5 M in hexanes, 3.3 mL, 8.3 mmol) in THF (3.7 mL) under Ar. After stirring at room temperature for 1 h, the reaction mixture was cooled to 0 °C and charged with the dropwise addition of ethyl chloroformate (0.77 mL, 7.9 mmol) in THF (2.6 mL). After stirring at room temperature for 1 h, the reaction mixture was again cooled to 0 °C and charged with the dropwise addition of methylmagnesium bromide (3.0M in diethyl ether, 15 mL, 45 mmol). The mixture was stirred at room temperature for 3 h and then slowly poured into cold saturated aq NH_4Cl. After acidifying with 1 N HCl (aq), the reaction mixture was extracted with EtOAc (3x). The combined organic layers were washed with brine (1x), dried with $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (5:1 hexanes:EtOAc) to yield benzyl alcohol **44** (1.3 g, 85% yield). R_f 0.37 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (t, J = 8.3 Hz, 1H), 6.62 (d, J = 8.3 Hz, 2H), 5.75 (s, 1H), 3.85 (s, 6H), 1.66 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 127.8, 124.6, 106.2, 74.3, 56.3, 31.2; IR (film): 3529, 2970, 2942, 1593, 1582, 1474, 1451, 1434, 1387, 1367, 1273, 1247, 1215, 1160, 1098, 1071, 1032 cm^{-1}; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_{11}H_{16}O_3$, 196.1100; found, 196.1090.



44 (94% yield) 45

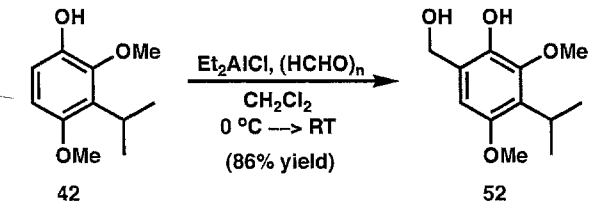
Isopropylbenzene 45. Benzyl alcohol **44** (5.77 g, 29.4 mmol), 10% Pd/C (0.626 g, 0.588 mmol), conc. H_2SO_4 (39 drops), and EtOAc (84 mL) were combined, and the reaction vessel was evacuated and back-filled three times with hydrogen gas (1 atm). The reaction mixture was stirred under a hydrogen atmosphere overnight and then filtered through a plug of silica gel (EtOAc eluent). After concentrating the solution *in vacuo*, the crude product was diluted with Et_2O and extracted with saturated aq $NaHCO_3$ (3x). The organic layer was washed with brine (1x), dried with $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (20:1 hexanes:EtOAc) to yield isopropylbenzene **45** (4.96 g, 94% yield). R_f 0.65 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (t, J = 8.3 Hz, 1H) 6.56 (d, J = 8.3 Hz, 2H), 3.82 (s, 6H), 3.70-3.55 (m, 1H), 1.30 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 126.7, 124.7, 104.8, 55.9, 24.3, 20.9; IR (film): 2989, 2957, 2872, 2836, 1593, 1474, 1437, 1361, 1274, 1249, 1207, 1142, 1113, 1088, 1054, 1042 cm^{-1}; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_{11}H_{16}O_2$, 180.1150; found, 180.1153.



45 (100% crude yield) 46 (89% yield) 42

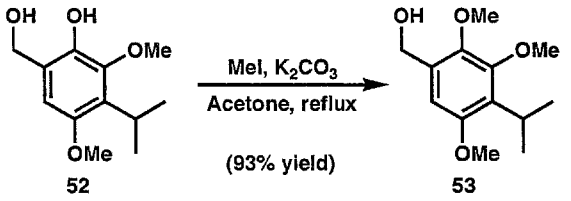
Phenol 42. To a solution of isopropyl benzene **45** (4.95 g, 27.5 mmol) in CH_2Cl_2 (39 mL) was added α,α-dichloromethyl methyl ether (3.3 mL, 35.8 mmol). The reaction

mixture was cooled to -42 °C and charged with the dropwise addition of $TiCl_4$ (5.7 mL, 51.9 mmol). After stirring at -42 °C for 30 min and at room temperature for 40 min, the mixture was poured into cold H_2O and extracted with EtOAc (3x). The combined organic layers were then dried with $MgSO_4$ and evaporated under reduced pressure to yield benzaldehyde **46**. To a solution of crude **46** (5.72 g, 27.5 mmol) in MeOH (39 mL) was added conc. H_2SO_4 (0.40 mL, 7.2 mmol) and H_2O_2 (30% $^{w}/_{w}$ H_2O, 4.4 mL, 39 mmol). After stirring for 2.5 h, the reaction mixture was quenched with saturated aq $NaHSO_3$ and extracted with EtOAc (3x). The combined organic layers were washed with H_2O (1x) and brine (1x), dried with $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (5:1 hexanes:EtOAc) to yield phenol **42** (4.79 g, 89% yield over two steps). R_f 0.44 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (d, J = 8.8 Hz, 1H), 6.57 (d, J = 8.8 Hz, 1H), 5.24 (s, 1H), 3.77 (s, 3H), 3.77 (s, 3H), 3.47-3.32 (m, 1H), 1.35 (d, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 145.4, 143.2, 130.0, 112.2, 108.3, 62.1, 56.0, 26.1, 21.2; IR (film): 3421 (br), 2990, 2958, 2907, 2836, 1485, 1458, 1431, 1361, 1258, 1218, 1190, 1150, 1105, 1052, 1013 cm^{-1}; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_{11}H_{16}O_3$, 196.1100; found, 196.1095.



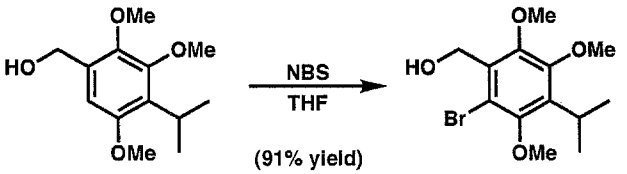
Diol 52. To a solution of Et_2AlCl (1.0 M in hexanes, 28 mL, 28 mmol) in CH_2Cl_2 (28 mL) was added phenol **42** (4.78 g, 24.4 mmol) in CH_2Cl_2 (41 mL) at 0 °C. After stirring at room temperature for 2 h, the reaction mixture was charged with

paraformaldehyde (1.08 g, 34.1 mmol). The mixture was stirred at room temperature for 21.5 h, quenched with saturated aq NH_4Cl, and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with H_2O (1x), dried with $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (2:1 hexanes:EtOAc, then 1:1 hexanes:EtOAc) to yield diol **52** (4.73 g, 86% yield). R_f 0.15 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (s, 1H), 5.95 (s, 1H), 4.72 (s, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.46-3.31 (m, 1H), 2.39 (s, 1H), 1.33 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 145.6, 141.5, 129.6, 124.0, 107.6, 62.5, 62.0, 56.1, 26.0, 21.2; IR (film): 3537, 3407 (br), 3019, 2959, 1483, 1454, 1423, 1216, 1188, 1131, 1063 cm^{-1}; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_{12}H_{18}O_4$, 226.1205; found, 226.1211.



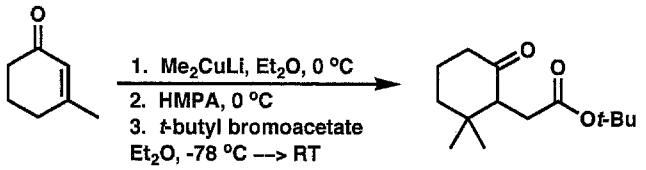
Trimethoxybenzene 53. A mixture of diol **52** (4.72 g, 20.9 mmol), K_2CO_3 (7.29 g, 52.8 mmol), acetone (64 mL), and iodomethane (4.0 mL, 64.3 mmol) was refluxed for 26.5 h at 60 °C. The reaction mixture was cooled to 0 °C, quenched with saturated aq NH_4Cl, and extracted with EtOAc (3x). The combined organic layers were washed with brine (1x), dried with $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (3:1 hexanes:EtOAc, then 2:1 hexanes:EtOAc, then 1:1 hexanes:EtOAc) to yield trimethoxybenzene **53** (4.66 g, 93% yield). R_f 0.26 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.61(s, 1H), 4.67 (d, J = 0.6 Hz, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 3.58-3.43 (m, 1H), 2.14 (s, 1H), 1.32 (s, 3H),

1.30 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 151.8, 145.3, 131.8, 130.4, 106.6, 61.8, 61.0, 56.0, 25.4, 21.4; IR (film): 3385 (br), 2987, 2957, 2937, 2873, 1481, 1454, 1411, 1357, 1342, 1232, 1131, 1075, 1056, 1028 cm^{-1}; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_{13}H_{20}O_4$, 240.1362; found, 240.1363.



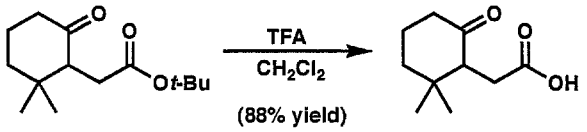
53 73

Bromobenzene 73. A reaction vessel covered in foil was charged with trimethoxybenzene **53** (933 mg, 3.88 mmol) in THF (3.9 mL). *N*-bromosuccinimide (725 mg, 4.07 mmol) was added portionwise every 5 min for 1 h. The reaction mixture was stirred for an additional hour and then concentrated *in vacuo*. The crude product was purified by flash chromatography (4:1 hexanes:EtOAc) to yield bromobenzene **73** (1.13 g, 91% yield). R_f 0.37 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.84 (s, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.78 (s, 3H), 3.53-3.38 (m, 1H), 2.35 (s, 1H), 1.34 (d, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.6, 149.5, 137.0, 132.6, 114.1, 100.2, 61.8, 61.4, 60.6, 60.6, 27.1, 22.1; IR (film): 3475 (br), 3017, 2962, 2939, 1454, 1405, 1342, 1320, 1216, 1121, 1081, 1052, 1026 cm^{-1}; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_{13}H_{19}O_4Br$, 318.0467; found, 318.0464.



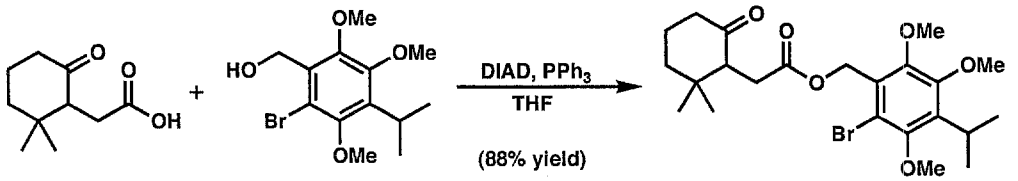
47 (89% yield) 63

***t*-Butyl Ester 63.** To a solution of copper iodide (3.08 g, 15.9 mmol) in Et_2O (52 mL) was added methyllithium (1.6 M in Et_2O, 19.8 mL, 31.7 mmol) dropwise at 0 °C under Ar. After stirring at 0 °C for 30 min, the mixture was charged with the dropwise addition of 3-methyl-2-cyclohexen-1-one (1.5 mL, 13 mmol) in Et_2O (13 mL) and stirred at 0 °C for an additional 65 min. HMPA (9.2 mL, 53 mmol) was then added dropwise at 0 °C, and the mixture was slowly cooled to –78 °C. The reaction mixture was charged with the dropwise addition of *tert*-butyl bromoacetate (5.9mL, 40 mmol) in Et_2O (10 mL) at –78 °C and was then warmed to room temperature. After stirring at room temperature for 2 h, the mixture was diluted with Et_2O and extracted with 5% aq NH_4OH (3x) The organic layer was washed with brine (1x), dried with $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (20:1 hexanes:EtOAc, then 10:1 hexanes:EtOAc) to yield *t*-butyl ester **63** (2.8 g, 89% yield). R_f 0.50 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.80 (dd, J = 9.9, 3.3 Hz, 1H), 2.62 (dd, J = 16.4, 10.0 Hz, 1H), 2.40-2.33 (m, 2H), 2.17 (dd, J = 16.4, 3.4 Hz, 1H), 2.02-1.54 (comp. m, 4H), 1.44 (s, 9H), 1.07 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.5, 172.8, 80.5, 56.6, 41.4, 40.6, 39.2, 30.2, 29.9, 28.3, 23.0, 21.2; IR (film): 2966, 1731, 1714, 1368, 1156 cm^{-1}; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_{14}H_{24}O_3$, 240.1726; found, 240.1715.



63 72

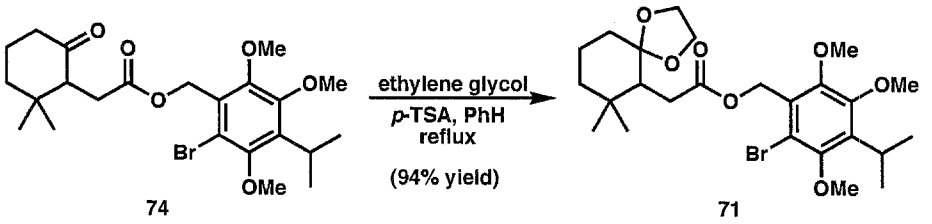
Acid 72. A solution of *t*-butyl ester **63** (2.83 g, 11.8 mmol), TFA (29 mL), and CH_2Cl_2 (29 mL) was stirred for 45 min and then concentrated *in vacuo*. The crude product was purified by flash chromatography (2:1 hexanes:EtOAc, then 1:1 hexanes:EtOAc, then EtOAc) to yield acid **72** (1.91 g, 88% yield). R_f 0.23 (1:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.98 (s, 1H), 2.84–1.52 (comp. m, 9H), 1.09 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.3, 179.2, 56.4, 41.3, 40.5, 39.3, 30.0, 28.9, 22.9, 21.0; IR (film): 3413 (br), 2956, 1703, 1426, 1397, 1372, 1323, 1267, 1227, 1182, 1168, 1080 cm^{-1}; HRMS-EI (*m/z*): $[M]^+$ calc'd for $C_{10}H_{16}O_3$, 184.1100; found, 184.1096.



72 73 74

Ester 74. To a mixture of acid **72** (246 mg, 1.34 mmol), bromobenzene **73** (425 mg, 1.33 mmol), and PPh_3 (384 mg, 1.46 mmol) in THF (16.5 mL) was added DIAD (310 μL, 1.48 mmol) at 0 °C. After stirring overnight at room temperature, the mixture was concentrated *in vacuo*. The crude product was purified by flash chromatography (6:1 hexanes:EtOAc) to yield ester **74** (569 mg, 88% yield). R_f 0.52 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.26 (dd, J = 19.9, 11.1 Hz, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 3.79 (s, 3H), 3.56-3.40 (m, 1H), 2.90 (dd, J = 9.8, 3.2 Hz, 1H), 2.77 (dd, J = 16.5, 9.9 Hz,

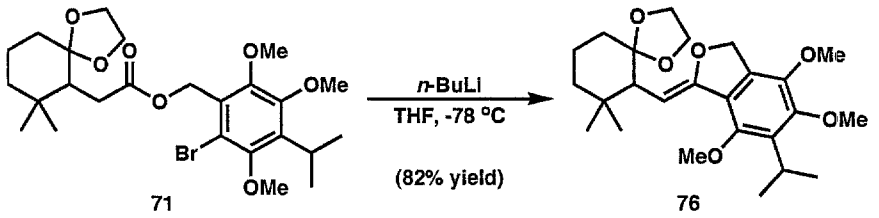
1H), 2.43-2.34 (m, 2H), 2.28 (dd, J = 16.5, 3.0 Hz, 1H), 2.06-1.53 (comp. m, 4H), 1.34 (d, J = 7.2 Hz, 6H), 1.08 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.2, 173.3, 152.5, 151.8, 150.4, 137.9, 127.9, 115.6, 61.7, 61.5, 60.6, 56.5, 41.4, 40.5, 39.3, 30.0, 29.0, 27.1, 23.0, 22.0, 22.0, 21.1; IR (film): 2961, 1737, 1713, 1455, 1405, 1342, 1323, 1242, 1163, 1122, 1083, 1028 cm^{-1}; HRMS-FAB (*m/z*): $[M]^+$ calc'd for $C_{23}H_{33}O_6Br$, 484.1460; found, 484.1468.



74 71

Ketal 71. Ester **74** (552 mg, 1.14 mmol), ethylene glycol (0.19 mL, 3.4 mmol), *p*-toluenesulfonic acid monohydrate (5.0 mg, 0.026 mmol), and benzene (12 mL) were combined and refluxed with a Dean-Stark apparatus at 110 °C for 21.5 h. The reaction mixture was then cooled to room temperature, diluted with Et_2O, and extracted with H_2O (3x). The organic layer was washed with brine (1x), dried with $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (9:1 hexanes:EtOAc) to yield ketal **71** (569 mg, 94% yield). R_f 0.47 (2:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.26 (dd, J = 22.0, 11.0 Hz, 2H), 4.02-3.78 (comp. m, 13H), 3.56-3.40 (m, 1H), 2.41 (dd, J = 14.7, 7.8 Hz, 1H), 2.31-2.15 (comp. m, 2H), 1.83-1.24 (comp. m, 12H), 0.98 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 152.5, 151.7, 150.4, 137.8, 128.3, 115.7, 110.7, 65.3, 63.6, 61.7, 61.4, 61.4, 60.6, 50.0, 40.9, 35.3, 34.6, 31.6, 29.9, 27.1, 22.1, 21.7, 19.8; IR (film): 2939, 1736, 1455, 1405, 1341,

1323, 1272, 1242, 1170, 1138, 1087, 1056, 1030 cm^{-1}; HRMS-FAB (*m/z*): $[M]^+$ calc'd for $C_{23}H_{33}O_6Br$, 528.1723; found, 528.1749.



71 76

Enol Ether 76. To a solution of ketal **71** (569 mg, 1.07 mmol) in THF (4.3 mL) was added *n*-BuLi (1.6M in hexanes, 740 μL, 1.18 mmol) dropwise at –78 °C. After stirring for 2.5 h at –78 °C, the reaction mixture was quenched with saturated aq NH_4Cl, warmed to room temperature, and extracted with EtOAc (3x). The combined organic layers were washed with brine (1x), dried with $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash chromatography (5:1 hexanes:EtOAc) and dried under MeOH to yield enol ether **76** (378 mg, 82% yield). R_f 0.51 (2:1 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 5.36–5.18 (comp. m, 3H), 4.07-3.78 (comp. m, 10H), 3.74 (s, 3H), 3.56-3.40 (m, 1H), 2.80 (d, J = 10.7 Hz, 1H), 1.85-1.25 (comp. m, 12H), 1.01 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 152.4, 148.6, 144.0, 135.8, 131.6, 122.6, 111.1, 96.7, 71.2, 65.6, 64.5, 61.0, 60.8, 59.8, 50.7, 40.5, 36.5, 35.7, 31.7, 25.7, 22.3, 22.2, 22.2, 20.1; IR (KBr pellet): 3448 (br), 2954, 2870, 1674, 1468, 1422, 1413, 1382, 1365, 1343, 1322, 1288, 1249, 1192, 1167, 1153, 1131, 1116, 1094, 1066, 1034, 1014 cm^{-1}; HRMS-FAB (*m/z*): $[M + H]^+$ calc'd for $C_{25}H_{37}O_6$, 433.2590; found, 433.2575.

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13. It is important to note that we are unsure of which olefin geometry (*E* or *Z*) of the α,β olefin in triene **10** will lead to the correct framework of salvadione-A in the tandem Claisen/Cope/Diels-Alder reaction due to uncertainties in transition state configurations (no theoretical calculations were performed to determine the most stable configuration). Because of this, I refer to both the *E* and *Z* isomers as triene **10**. If the wrong isomer were to be synthesized, olefin isomerization could potentially be utilized to form the other isomer.

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19. Standard Mitsunobu conditions: DIAD or DEAD with PPh_3 in THF or Toluene.

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36. I am grateful to Uttam Tambar for suggesting the possibility that the product was an enol ether.

37. I believe that trimethoxybenzene **53** was yielded in the reaction, because too much *n*-BuLi was used. This caused the excess to act as a nucleophile and open the desbromo-starting material to yield **53**.

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