

β -Keto-dioxinones and β,δ -Diketo-dioxinones in Biomimetic Resorcyate Total Synthesis

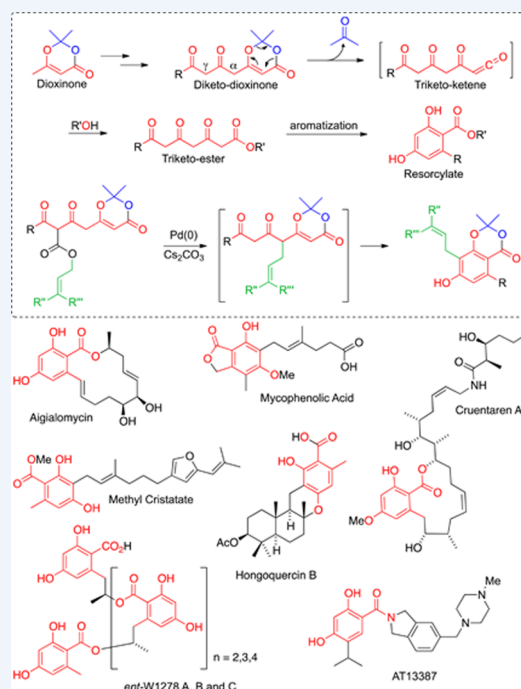
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CONSPECTUS: Resorcyates are a large group of bioactive natural products that are biosynthesized from acetate and malonate units via the intermediacy of polyketides. These polyketides undergo cyclization reactions to introduce the aromatic core. The bioactivities of the resorcyates including resorcyate macrocyclic lactones include anticancer, antimalarial, mycotoxicity, antifungal, and antibiotic properties, and several compounds in the series are already in use in medicine. Examples are prodrugs derived from mycophenolic acid as immunosuppressants and the Hsp-90 inhibitor, AT13387, which is in phase-II clinical trials for the treatment of small cell lung cancer and melanoma. In consequence of these biological activities, methods for the concise synthesis of diverse resorcyates are of considerable importance. In natural product chemistry, biomimetic total synthesis can have significant advantages including functional group tolerance in key steps, the minimization of the use of protection and deprotection reactions and the shortening of the total number of synthetic steps.

This Account provides a description of our adaption of the dioxinone chemistry of Hyatt, Clemens, and Feldman for the synthesis and retro-Diels–Alder reactions of diketo-dioxinones. Such dioxinones, which were synthesized by a range of C-acylation reactions, were found to undergo retro-Diels–Alder reactions on heating to provide the corresponding triketo-ketenes with the loss of acetone. The ketene reactive intermediates were rapidly trapped both inter- and intramolecularly with alcohols to provide the corresponding β,δ,ζ -triketo-esters. These compounds, which



consist of keto–enol mixtures, readily undergo cycloaromatization to produce resorcyate esters and macrocyclic lactones. We have established the use of diketo-dioxinones as key general intermediates for the synthesis of diverse resorcyate natural products and for the synthesis of new classes of compounds for the generation of medicinal chemistry lead structures. Many of the methods used were found to be tolerant of multiple sensitive functional groups. These include enolate C-acylations with acyl chlorides, 1-acyl-benzotriazoles, acyl imidazolides, or Weinreb amides to prepare diketo-dioxinones and their subsequent use to prepare β,δ,ζ -triketo-esters and lactones and hence resorcyates. In addition, in most cases, phenol protection was avoided. As an alternative to the synthesis of β,δ,ζ -triketo-esters, diketo-dioxinones were also found to undergo cycloaromatization with retention of the ketal entity via a nonketene pathway. Finally, diketo-dioxinones with an allyl, prenyl, geranyl, or other 2-alkenyl carboxylate esters at the γ -carbon underwent decarboxylative rearrangement with tetrakis(triphenylphosphine)palladium catalysis to produce α -substituted diketo-dioxinones and resorcyates with 3-allyl, prenyl, geranyl, or other 2-alkenyl groups. Such diketo-dioxinone chemistry was used in the total synthesis of natural products including aigialomycin, cruentaren A, and the oligomeric resorcyate antibiotics ent-W1278 A, B, and C. Additionally, tandem use of the decarboxylative rearrangement process and cycloaromatization was used in the total synthesis of natural products including the methyl ester of cristatic acid, mycophenolic acid, and hongoquercin B. The methodology was also applied to the synthesis of 9,10-anthraquinones, *o*-aminoalkyl resorcyates, dihydroxyisoindolinones, oligomers, and resorcinamides. The development of this methodology is described in this Account, showcasing its applicability and versatility for the synthesis of complex resorcyate products.

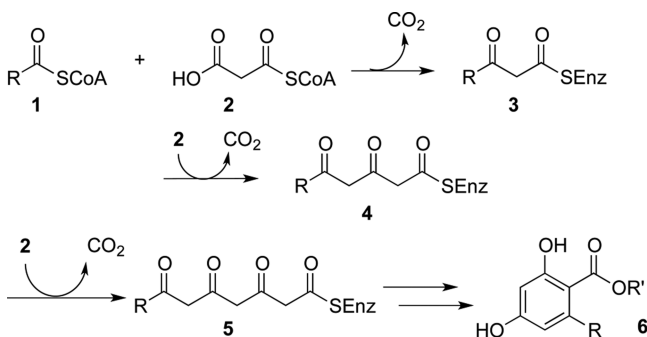
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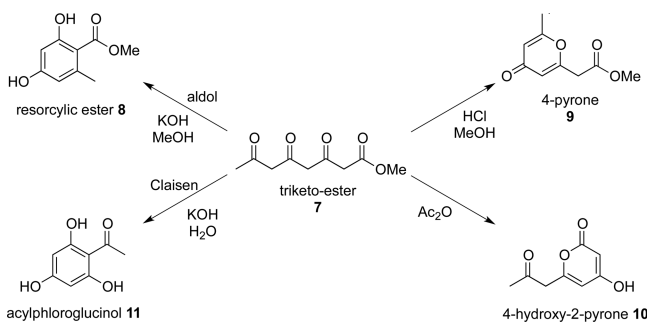
1. INTRODUCTION

Biomimetic syntheses of natural products are important in organic chemistry since they are frequently concise and provide elegant routes to complex targets, for example, the Johnson synthesis of steroids via polyene cyclization.^{1–4} Aromatic acid units containing the 6-alkyl-2,4-dihydroxybenzoic acid unit (β -resorcylic acid) occur widely in nature and are biosynthesized via polyketide cyclizations, the substrates for which are generated *in vivo* via a series of Claisen condensation reactions between acetate and malonate moieties (Scheme 1).^{5,6}

Scheme 1. Biosynthesis of Resorcylics

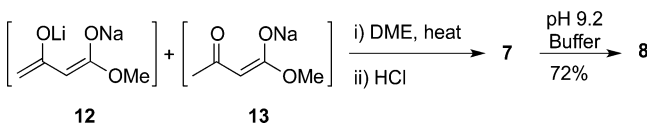


Pioneering work by Weiler⁷ and Harris and Harris⁸ demonstrated that the β,δ,ζ -triketo-ester **7** upon treatment with base underwent a facile aldol cyclization and dehydration, mimicking the biosynthetic pathway, to give β -resorcylic ester **8** (Scheme 2).

Scheme 2. Natural Product Motifs from Triketo-ester **7**

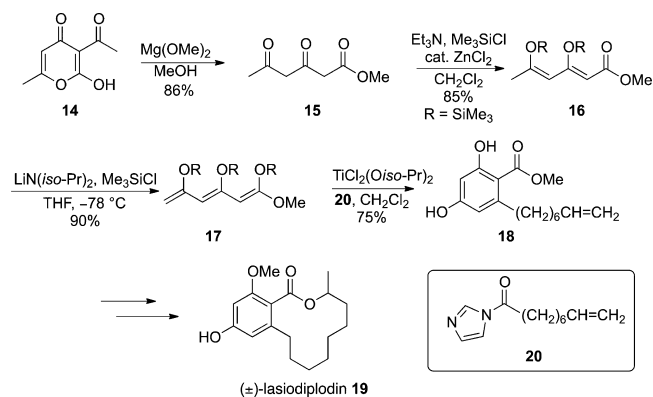
Triketo-ester **7** was also shown to be a precursor to three additional natural product motifs, 4-pyrone **9**, and 4-hydroxy-2-pyrone **10**, and acylphloroglucinol **11**.⁸

In 1980, Barton et al. optimized this synthesis (Scheme 3). Triketo-ester **7** was prepared via a condensation reaction between enolates **12** and **13** and converted into resorcylic ester **8** (72%).⁹

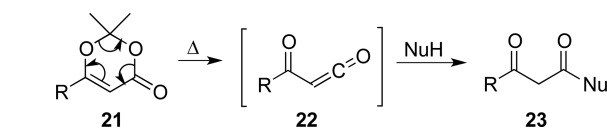
Scheme 3. Barton's Synthesis of Resorcylic Ester **8**

These pioneering studies showed that simple β -resorcylics could be biomimetically synthesized from acetoacetate precursors. However, at that time, the methodology was limited, due to the strongly basic reaction conditions required to generate β,δ,ζ -triketo-esters.

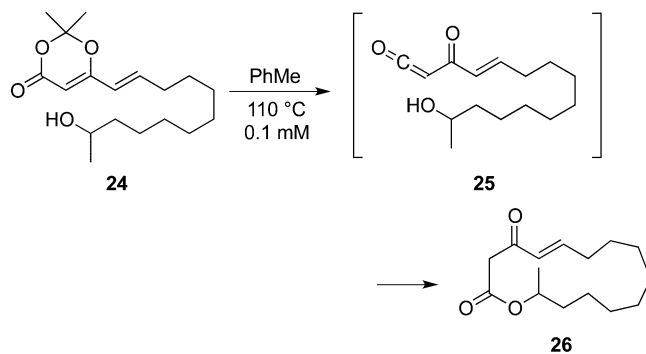
Subsequently, Chan introduced silyl ethers of β -keto-esters and β,δ -diketo-esters for the biomimetic synthesis of resorcylics.^{10,11} Of particular note is his synthesis of (\pm)-lasiodiplodin **19** via ester **18** and acylation of triene **17** with imidazole **20** under Lewis acidic conditions.¹² However, the approach required the use of sensitive silyl enol ethers, limiting its utility (Scheme 4).

Scheme 4. Chan's Synthesis of (\pm)-Lasiodiplodin **19**

In 1984, Hyatt et al. showed that 1,3-dioxin-4-ones **21** are room temperature stable compounds, which upon heating at 100 °C undergo a retro [4 + 2] cycloaddition to generate acyl ketenes **22**.¹³ These intermediates readily reacted with amines and alcohols to give the corresponding β -keto-amides and esters (Scheme 5).

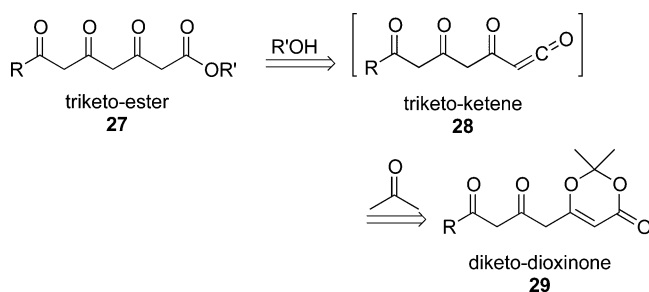
Scheme 5. Thermolysis of **21** To Generate Ketenes **22**

Subsequently, Boeckman utilized intramolecular reactions of acyl ketenes from a 1,3-dioxin-4-one in macrolactamization and macrolactonization reactions and used this elegant strategy in the total syntheses of (+)-ikarugamycin¹⁴ and (-)-kromycin (Scheme 6).¹⁵ Equivalent strategies have been applied in other natural product total syntheses.^{16–20}

Scheme 6. Boeckman's Synthesis of Lactone **26**

Inspired by the work of Harris, Hyatt, and Boeckman, we have focused on the synthesis and retro-Diels–Alder reactions of β,δ -diketo-dioxinones to generate α,γ,ϵ -triketo-ketenes and their inter- and intramolecular trapping with alcohols for the synthesis of resorcylic natural products (Scheme 7).

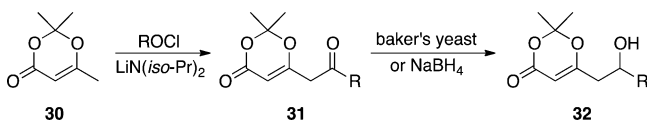
Scheme 7. β,δ -Diketo-dioxinones **29** as Precursors to β,δ,ξ -Triketo-esters **27**



β,δ -Diketo-dioxinones have been found to be versatile precursors of polyfunctional β -resorcyates that allow for aromatization to be carried out at late stages of a synthesis. In this Account, we summarize these contributions to biomimetic synthesis, and the coverage is limited to the reactions of β -keto-dioxinones and β,δ -diketo-dioxinones only. Alternative dioxinone chemistry is reviewed elsewhere.^{20,21} Diketo-dioxinones and triketo-esters exist as mixtures of enolic forms. However, for simplicity, they have been drawn solely as all keto-tautomers.

Kaneko first reported the synthesis of a β -keto-dioxinone, **31**, from the C-acylation of the lithium enolate of dioxinone **30** with acetyl chloride ($R = Me$, Scheme 8). The yield of product **31**

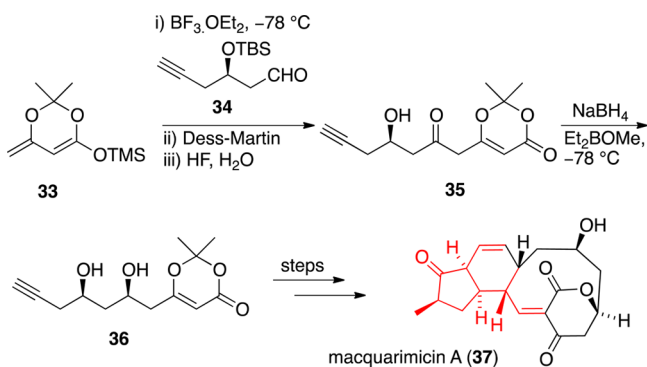
Scheme 8. Kaneko Synthesis of Keto-dioxinones **31**



($R = Ph$) was 48% with reduction of competitive O-acylation observed with the use of excess enolate (2.0 equiv) presumably due to transacylation. Enantioselective reduction of ketone **31** ($R = Me$) with baker's yeast gave the (*S*)-alcohol **32** (44%, ee 90%), whereas reduction of **31** ($R = Ph$) with sodium borohydride gave racemic alcohol **32** (87%).^{22,23} Related syntheses of other dioxinones have been reported.^{24–33} Katritzky reported the use of 1-acylbenzotriazoles as superior electrophiles for the synthesis of β -keto-dioxinones (**31**, $R = aryl$, heteroaryl, alkenyl, etc.), which gave 6-substituted-4-hydroxy-2-pyrones on thermolysis.^{28,34,35}

Tadano utilized a Mukaiyama aldol reaction and oxidation for the synthesis of dioxinone **35** (Scheme 9). Subsequent boron chelate-controlled diastereoselective reduction provided diol **36**, which was converted into macquarimicins A (**37**), B, and C.^{36,37}

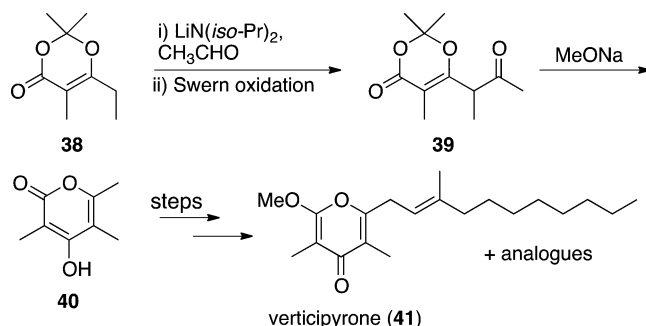
Scheme 9. Tadano Synthesis of Macquarimicin A



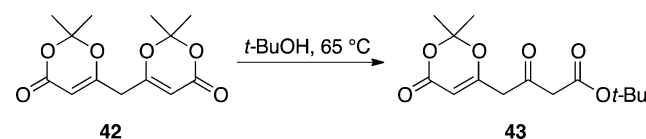
This methodology has been used for the synthesis of other β -keto-dioxinones.^{28,38–40}

Omura prepared β -keto-dioxinone **39** through an aldol reaction and oxidation sequence and keto-dioxinone **39** was converted via pyrone **40** into verticipyron (**41**) and analogues (Scheme 10).^{28,41}

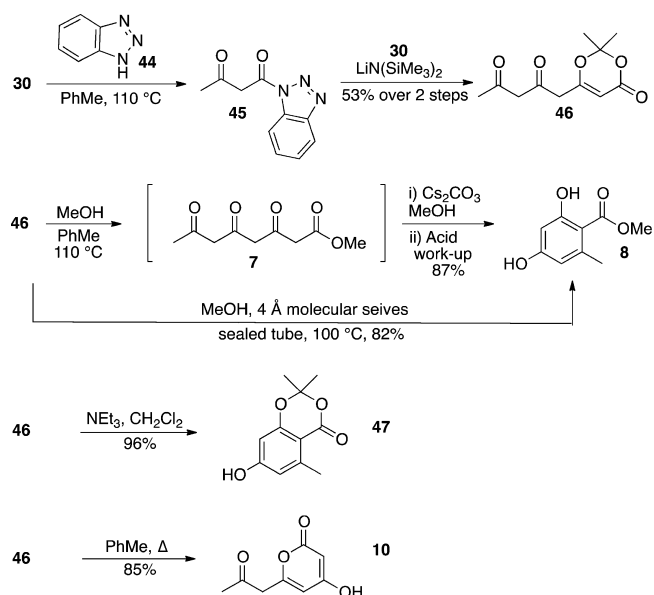
Scheme 10. Omura Synthesis of Verticipyron (**41**)



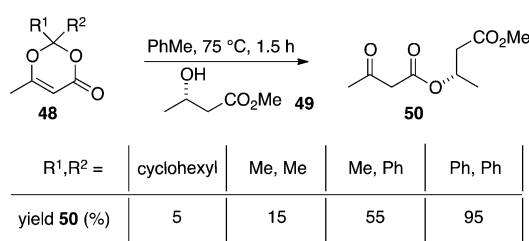
Scheme 11. Kiegel's Synthesis of Keto-ester **43**



Scheme 12. Model Studies on β,δ -Diketo-dioxinone **46**

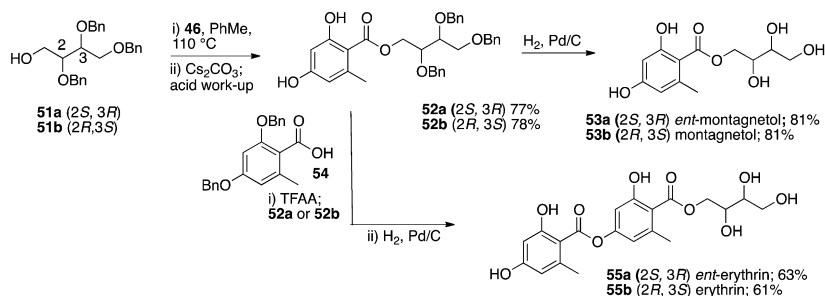


Scheme 13. Studies on the Conversion of Dioxinones into β -Keto-esters

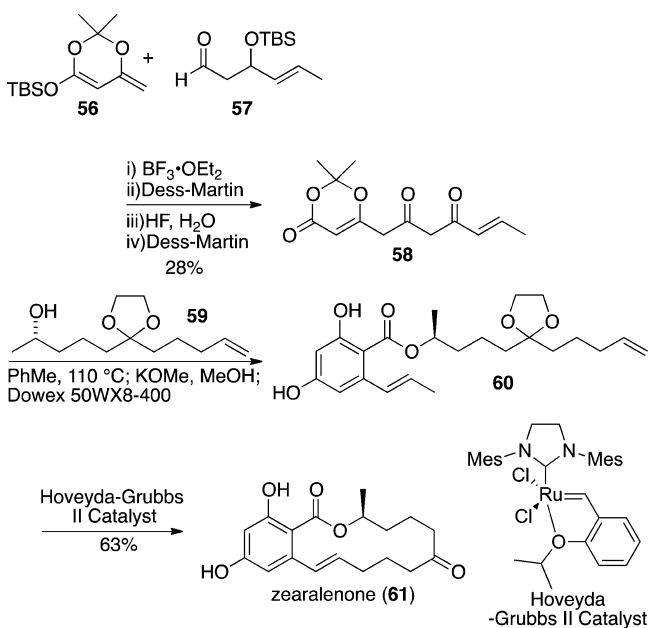


Kiegel reported the generation of the keto-ester derivative **43** from the double dioxinone **42** and *t*-butanol under controlled

Scheme 14. Synthesis of (+)-Montagnetol and (+)-Erythrin



Scheme 15. Synthesis of Zearalenone via Intermolecular Ketene Trapping



conditions. Reaction at 65 °C gave the ester 43, whereas heating to 130 °C gave the di-*t*-butyl ester (Scheme 11).⁴²

Following on from these studies, the Barrett group has sought to expand this chemistry for the general synthesis of diketo-dioxinones and their conversion into diverse arenes including complex resorcyate and terpene-resorcyate natural products. These studies are herein now reviewed.

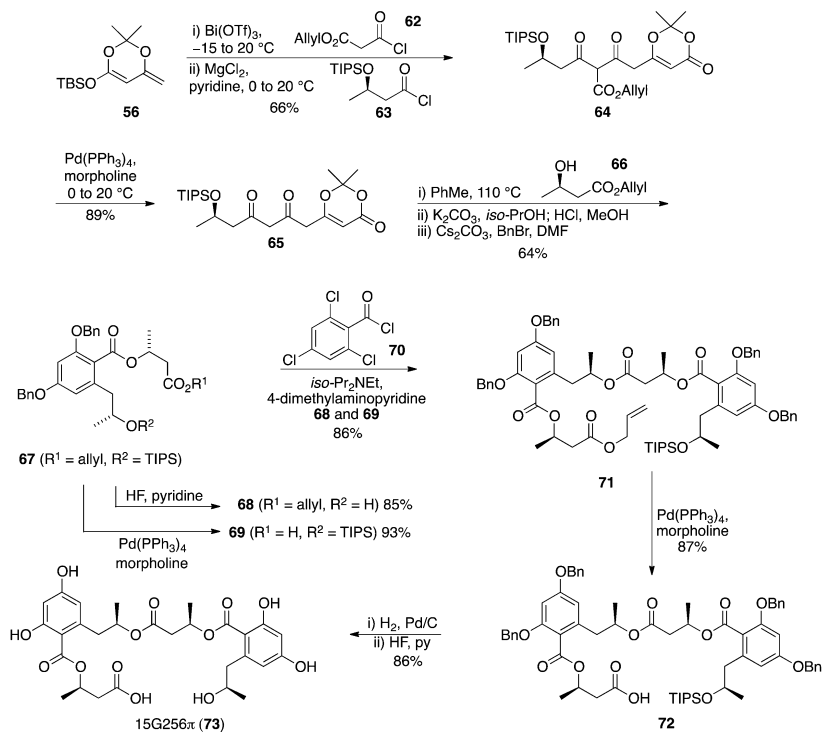
2. NATURAL PRODUCT RESORCYLATES

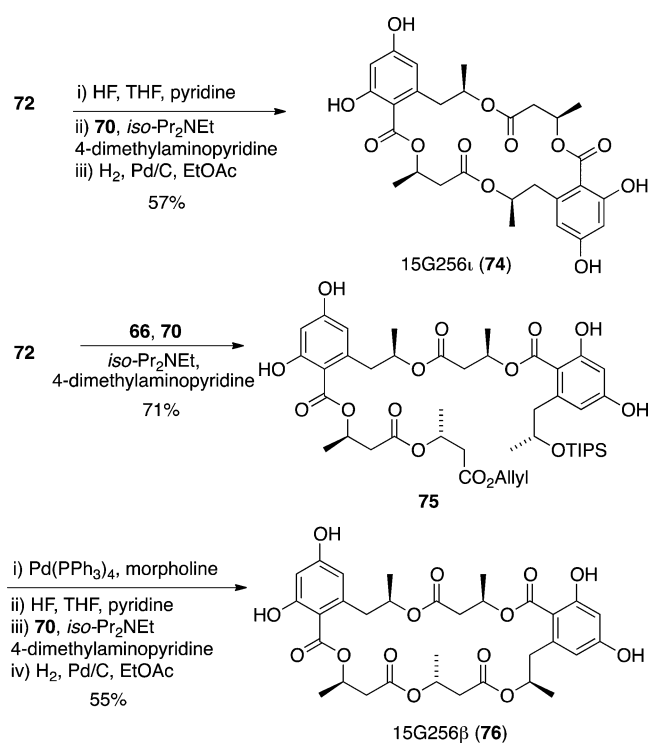
Resorcylic acid derivatives including macrolactones are important bioactive natural products and considerable numbers of total syntheses have been reported. These utilize methods to overcome the low reactivity of resorcyloyl electrophiles and the need for phenol protection.^{43,44} Since α,γ,ϵ -triketo-ketenes were expected to be highly electrophilic, we considered that such reactive intermediates would be especially useful for the total synthesis of resorcyates by rapid inter- or intramolecular trapping with alcohols and aromatization of the derived β,δ,ζ -triketo-esters or lactones.

2.1. Model Studies on Resorcyate Synthesis

β,δ -Diketo-dioxinone 46 was generated from benzotriazole 45 by enolate C-acylation (53%, Scheme 12). On heating in methanol, diketo-dioxinone 46 was converted into the triketo-ester 7,

Scheme 16. Formation of Double Resorcyate 72



Scheme 17. Synthesis of 15G256 ι and β 

which readily aromatized to produce resorcyate **8** (87%). Alternatively, diketo-dioxinone **46** was aromatized with triethylamine to provide resorcyate **47** via a nonketene pathway (96%), whereas heating of diketo-dioxinone **46** alone gave pyrone **10**.⁴⁵

The rate of the retro-Diels–Alder reaction to generate the α,γ,ϵ -triketo-ketene was investigated. We considered that increasing the steric bulk or replacement of dioxinone ring methyl groups with phenyls would accelerate reaction (Scheme 13).⁴⁶ In competition experiments, comparison of the yield for the conversion of dioxinones **48** on heating (75 °C) for 1.5 h with alcohol **49** to produce keto-ester **50** was consistent with such acceleration. Presumably this

resulted from overlap of the phenyl π -orbitals with the σ^* of the O–CO system thereby increasing the rate of fragmentation.

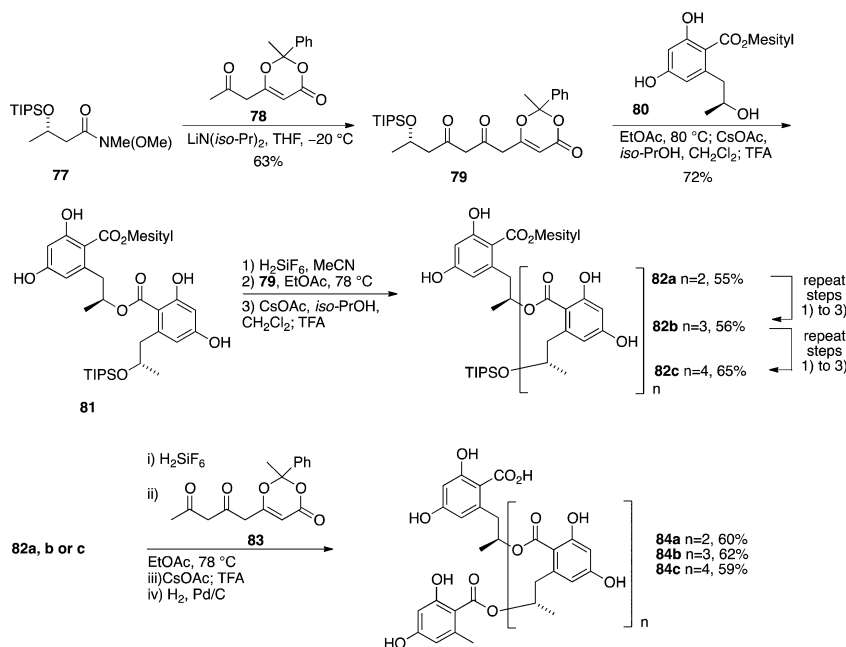
The diketo-dioxinone chemistry was applied to the synthesis of montagnitol (**53**) and erythrin (**55**) from dioxinone **46** (Scheme 14).⁴⁵ The completed synthesis established the natural product absolute stereochemistry to be (2*R*, 3*S*). Although phenols **52a** and **52b** were insufficiently nucleophilic to trap the α,γ,ϵ -triketo-ketene from dioxinone **46**, mixed anhydride esterification and subsequent hydrogenolysis gave *ent*-erythrin **55a** and the natural enantiomer **55b**.

2.2. Synthesis of Zearalenone via Intermolecular Ketene Trapping

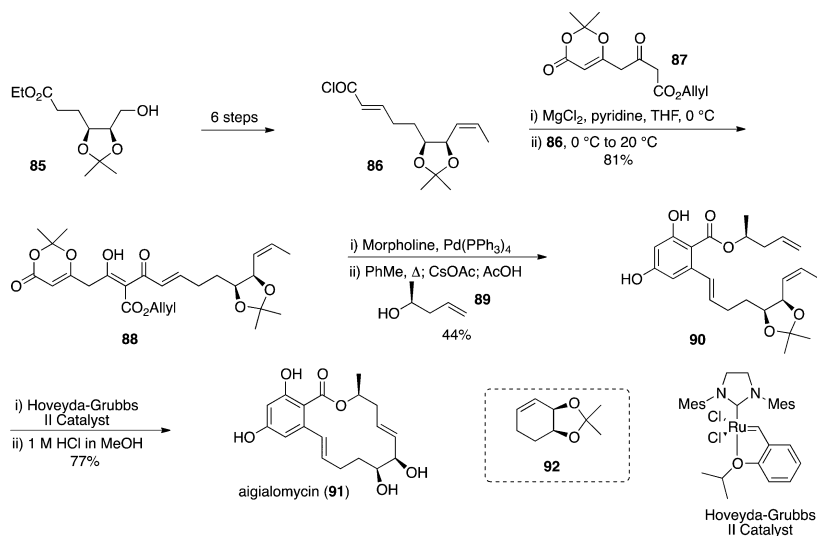
Mukaiyama aldol reaction of aldehyde **57** with enol silane **56**, Dess–Martin oxidation, desilylation, and further oxidation gave diketo-dioxinone **58** (28%, Scheme 15). Following the Fürstner total synthesis, alcohol **59** was synthesized (*ee* > 99%) using a lipase mediated kinetic resolution and allowed to react with diketo-dioxinone **58** in toluene at 110 °C to give the triketo-ester. This was smoothly cycloaromatized with cesium carbonate followed by Dowex to provide resorcyate **60**. Fürstner ring closing metathesis gave zearalenone (**61**) (63%) and the *Z*-isomer (*E/Z*; 86:14).^{47,48} Due to the nature of this synthesis, there is the potential to access many structurally modified analogues of zearalenone (**61**), as is the case for all the syntheses showcased in this Account, allowing for investigations into improved biological activities. By contrast, it can often be seen for previously reported syntheses of these natural products by other groups that this would not be straightforward.

2.3. Syntheses of the 15G256 π , ι , and β and W1278 A, B, and C Antibiotics

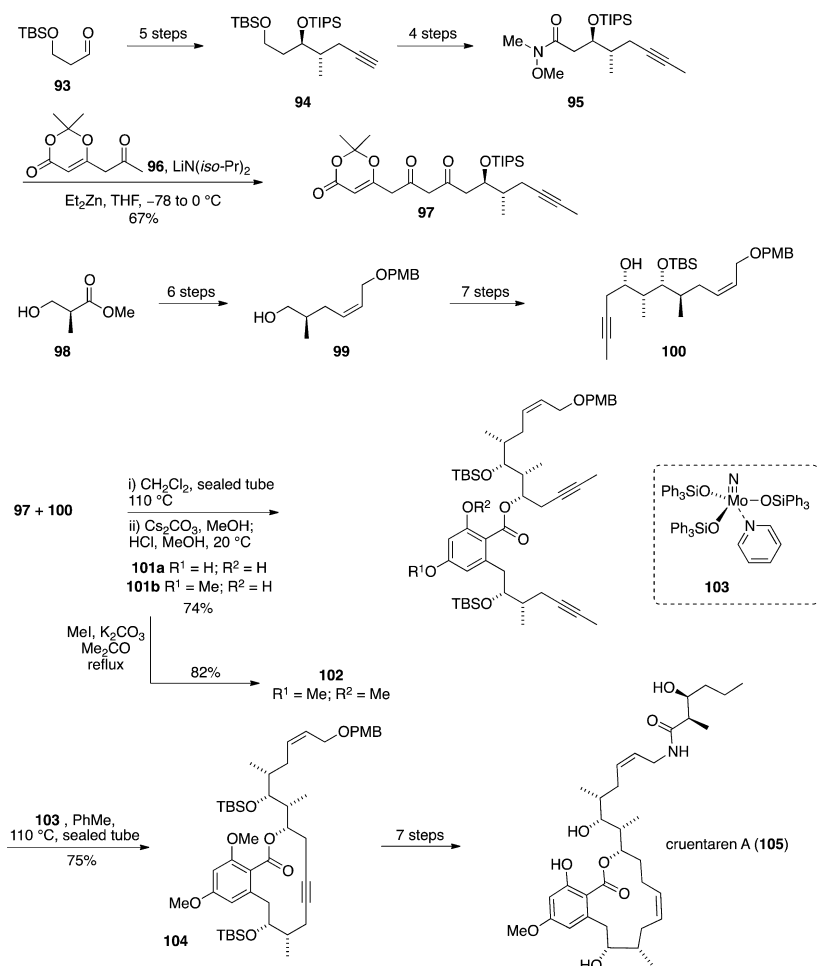
During the synthesis of the antibiotics 15G256 π , ι , and β , highly selective Claisen condensation reactions to produce β,δ -diketo-dioxinones were developed for substrates containing delicate β -hydroxy-butyrates (Scheme 16).⁴⁸ Sequential C-acylations of enol silane **56** with acyl chlorides **62** and **63** using magnesium chloride and pyridine gave ester **64**. Deallylation and decarboxylation with tetrakis(triphenylphosphine)palladium and morpholine

Scheme 18. Synthesis of *ent*-W1278 A, B, and C

Scheme 19. Synthesis of Aigialomycin D (91)



Scheme 20. Synthesis of Cruentaren A (105)



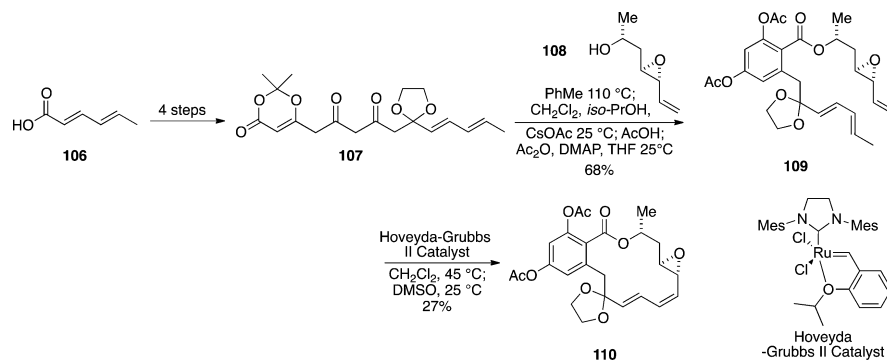
gave diketo-dioxinone **65**. This was converted into resorcyate **67** (64% over three steps) through reaction with alcohol **66**, aromatization, and benzyl protection. Selective deprotection and Yamaguchi esterification of the resultant alcohol **68** with acid **69** gave resorcyate **71** and, following deallylation, resorcyate **72**.

Acid **72** was converted into 15G256 π , ι , and β using selective deprotections, incorporation of a β -hydroxy-butyrate unit,

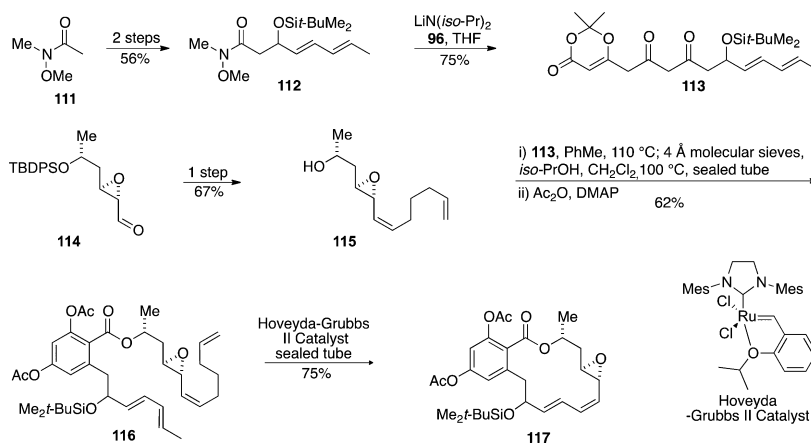
and Yamaguchi macrolactonization as key steps (Schemes 16 and 17).

The antiviral fungal metabolites *ent*-W1278 A, B, and C are oligomers of 6-alkyl-2,4-dihydroxybenzoic acid. Weinreb amide **77** was converted via C-acylation with the enolate dianion from keto-dioxinone **78** to produce diketo-dioxinone **79** (Scheme 18). Triketo-ketene generation and trapping with alcohol **80** took

Scheme 21. Synthetic Studies on Radicol: 1



Scheme 22. Synthetic Studies on Radicol: 2



place at 80 °C giving the dimer **81**. At this lower reaction temperature, competitive δ -lactonization of alcohol **80** was suppressed. Ketene generation, trapping, and aromatization was used iteratively with termination using the keto-dioxinone **83** and deprotection to provide *ent*-W1278 A, B, and C. Comparison of the optical rotation and spectroscopic data of oligomers **84a**, **b**, and **c** with authentic samples of the natural products showed that the original assignments of absolute stereochemistry were incorrect.⁴⁶

2.4. Synthesis of Aigialomycin D

Aigialomycin D (**91**) is an antimalarial agent, an inhibitor of CDK and GSK-3 kinases, and of interest in cancer chemotherapy. We reported a total synthesis of this macrolactone using both biomimetic aromatization and ring closing metathesis (Scheme 19).⁴⁹ Ester **88** was prepared from alcohol **85**⁵⁰ via C-acylation of acyl chloride **86**. Deallylative decarboxylation generated the diketo-dioxinone, which was converted into resorcyate **90** with alcohol **89**. Fürstner ring closing metathesis and deprotection gave aigialomycin D (**91**) (15% overall yield). It is noteworthy that, like zearalenone (**61**) and *ent*-W1278 A, B, and C, there was no need for phenol protection throughout this synthesis. Second, the use of the *Z*-alkene unit in triene **90** directed initiation of the alkene metathesis to the single terminal alkene, suppressing formation of cyclohexene **92** and removing the necessity for *trans*-alkene masking as used in earlier syntheses of the aigialomycins.^{51–54}

2.5. Synthesis of Cruentaren A

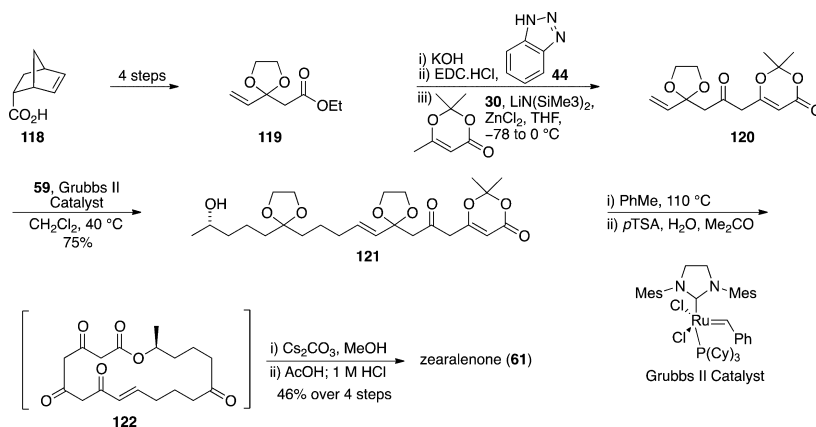
Cruentaren A (**105**), a complex resorcyate, was synthesized in 23 linear steps.⁵⁵ The route utilized Fürstner ring closing alkyne metathesis, which his group invented and applied in syntheses including cruentaren A (**105**) (Scheme 20).⁵⁶ Weinreb amide

95 was generated in nine steps from aldehyde **93** using Brown enantioselective crotonylboration and Seyferth–Gilbert acetylene synthesis as key steps. Subsequent conversion to the β,δ -diketo-dioxinone **97** was carried out by C-acylation using the zinc enolate of keto-dioxinone **96**. Alcohol **100** was synthesized in 13 steps from (*S*)-Roche ester **98** via alcohol **99** using acetylide alkylation, Lindlar semihydrogenation, an Evans aldol reaction, and indium-mediated enantioselective propargylation as key steps. Alcohol **100** and diketo-dioxinone **97** were coupled to provide phenol **101a** accompanied by the corresponding methyl ether **101b**, which were further methylated to provide only ether **102**. Presumably, **101b** was formed via a 1,3-cyclohexanedione methyl ketal intermediate during aromatization. Ring closing alkyne metathesis using precatalyst **103** gave macrolactone **104**, which was transformed into cruentaren A (**105**) using a Mitsunobu azide synthesis, Staudinger reaction, and amide synthesis with HBTU and HOBT as key steps.

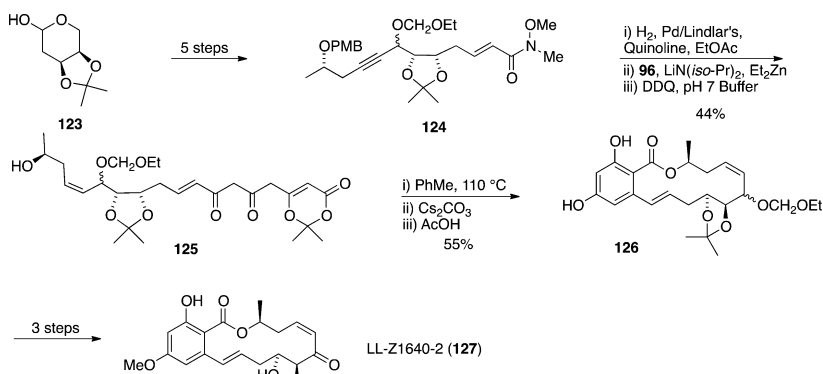
2.6. Studies toward the Synthesis of Radicol

Radicol, a potent, selective Hsp90 inhibitor that contains a sensitive diene-monoepoxide was synthesized by Danishefsky using ring closing metathesis and dithiane deprotection via a Pummerer reaction to reveal the macrocyclic ketone.^{57,58} Our group utilized this triene ring closing metathesis approach toward the synthesis of radicol. Diketo-dioxinone **107** was synthesized from sorbic acid **106**. Reaction of **107** with alcohol **108**, aromatization, and phenol protection gave resorcyate **109** in 68% yield for the one-pot procedure. Ring closing metathesis with the Grubbs–Hoveyda II catalyst gave macrocycle **110** (27%, unoptimized) with DMSO added to remove ruthenium byproducts (Scheme 21).

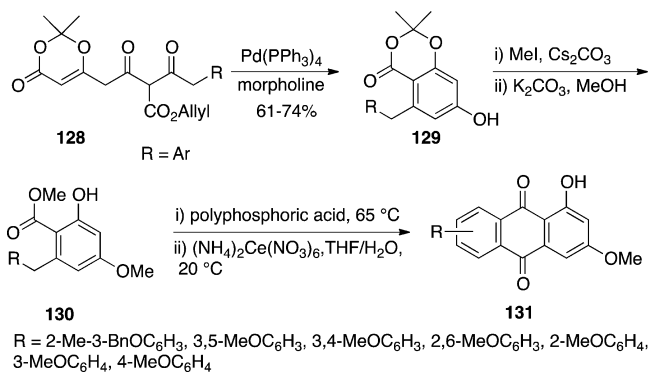
Scheme 23. Synthesis of Zearalenone via Intramolecular Ketene Trapping



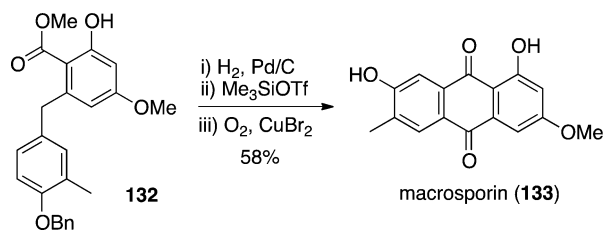
Scheme 24. Synthesis of LL-Z1640-2 (127)



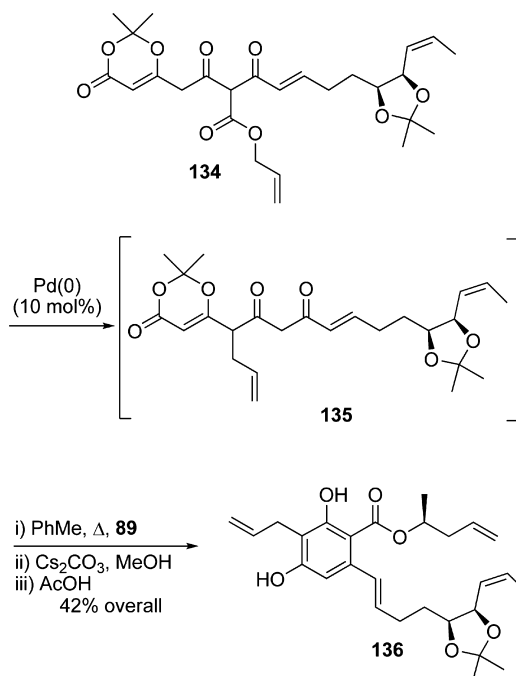
Scheme 25. Formation of the 9,10-Anthraquinones



Scheme 26. Synthesis of Macrosporin 133



Scheme 27. Regiospecific Migration To Form Diketo-dioxinone 135



Alternatively, diketo-dioxinone **113** was synthesized in three steps via Weinreb amide **112** (Scheme 22). Attempted macrocyclization of the triene resorcyolate derived from dioxinone **113** and alcohol **108** was low yielding, and thus a relay alkene metathesis process⁵⁹ was explored. Aromatization of dioxinone

113 and alcohol **115** gave resorcyolate **116**, and relay macrocyclization proceeded in 75% yield. Unfortunately, attempted deprotection of dienes **110** and **117** failed due to more facile ring

opening of the epoxide ring. It is important to note that the epoxide survived the esterification and aromatization conditions although it was not stable on attempted deprotection. This underscores how mild and functional group tolerant diketodioxinone methodology is for the generation of resorcyates.

2.7. Syntheses of Zearalenone (61) and LL-Z1640-2 (127) via Intramolecular Ketene Trapping

We adapted Boeckman's method (section 1) for the total syntheses of zearalenone (61) and LL-Z1640-2 (127) using the generation and intramolecular trapping of $\alpha,\gamma,\varepsilon$ -triketo-ketenes. β -Keto-dioxinone 120 was synthesized from norbornenecarboxylic acid 118 using a Claisen condensation, ketal formation, and retro-Diels–Alder reaction as key steps. Ketal protection was necessary to prevent undesired Michael addition reactions of terminal enones. Ester 119 was converted into keto-dioxinone 120 via the acyl benzotriazole and C-acylation. Cross metathesis with alkene 59 gave dioxinone 121, which was macrocyclized via ketene generation and intramolecular ring closure. Subsequent deprotection and transannular aromatization gave zearalenone (61) (Scheme 23).⁶⁰

The methodology was also applied to the more complex LL-Z1640-2 in a 15-step total synthesis (Scheme 24).⁶¹ Diketodioxinone 125 was prepared from 123 via Weinreb amide 124,

with the second ketone unprotected. Macrolactonization and transannular aromatization occurred smoothly to generate resorcyate 126, which was converted into LL-Z1640-2 (127) in a further three steps.

Both these syntheses show there is no need for phenol protecting groups in the synthesis of resorcyate macrolactones. Equivalent methods were also applied toward the total synthesis of radicicol.⁵⁷

2.8. Synthesis of 9,10-Anthraquinones

Although bioactive 9,10-anthraquinones are not resorcyates, they are of polyketide biosynthetic origin and are available using Claisen chemistry.⁶² Esters 128 (R = aryl), prepared by C-acylation, were allowed to react with morpholine and tetrakis(triphenylphosphine)palladium and aromatized giving resorcyates 129. Methylation, transesterification, Friedel–Crafts acylation, and oxidation with ceric ammonium nitrate gave 9,10-anthraquinones 131 (Scheme 25).

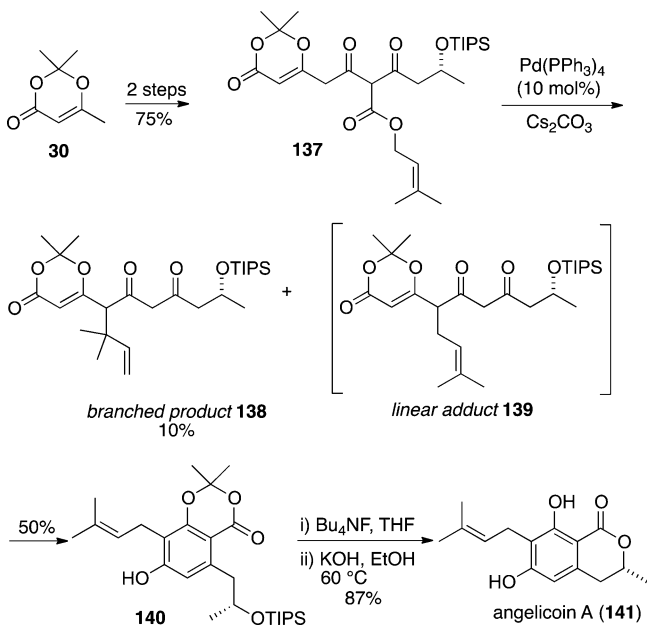
The method was extended to the synthesis of macrosporin (133) via hydrogenolysis of ether 132, Friedel–Crafts acylation, and oxidation (Scheme 26).

3. DECARBOXYLATIVE ALLYL MIGRATION

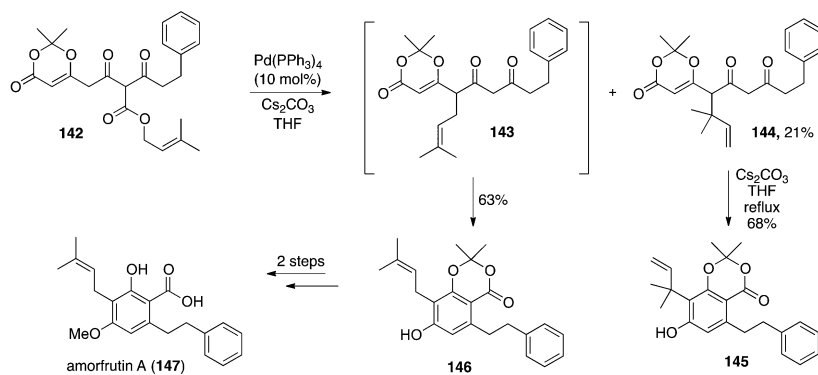
During our synthesis of aigialomycin D (91), we observed that reaction of allyl ester 134 with tetrakis(triphenylphosphine)palladium without morpholine as a palladium π -allyl cation scavenger gave diketodioxinone 135 regiospecifically, presumably due to intermolecular C-allylation of 134 occurring prior to Pd(0) insertion and decarboxylation (Scheme 27; see also Scheme 32).^{63,64} Subsequent ketene trapping with alcohol 89 and aromatization gave resorcyate 136 (42% overall).

Application of this rearrangement reaction to prenyl esters was used in the total synthesis of angelicoin A (141) (Scheme 28).⁶³

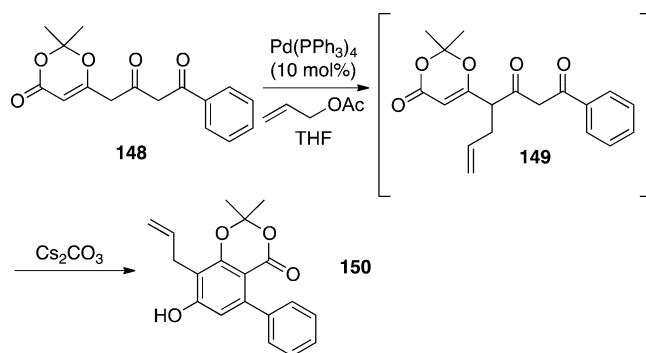
Scheme 28. Synthesis of Angelicoin A



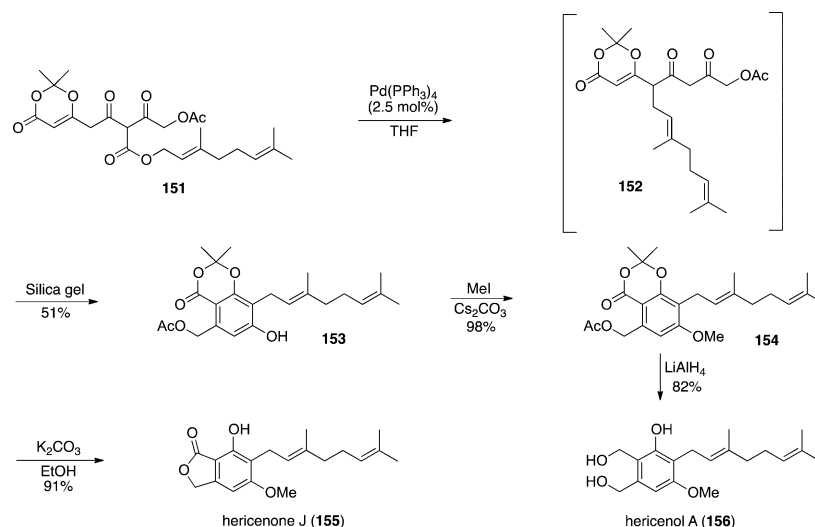
Scheme 29. Synthesis of Amorfrutin A



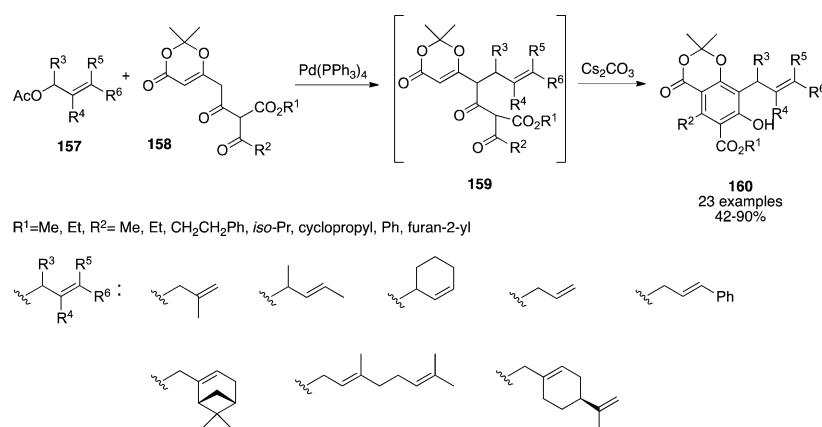
Scheme 30. Formation of Resorcyate 150



Scheme 31. Synthesis of Hericenone J and Hericenol A



Scheme 32. Hexasubstituted Arenes 160



Decarboxylation of ester 137 in the presence of tetrakis-(triphenylphosphine)palladium and reaction with cesium carbonate gave resorcyate 140 and diketo-dioxinone 138 (5:1). Under these conditions, the linear isomer 139 rapidly underwent aromatization whereas the branched isomer did not cyclize. Deprotection and lactonization gave angelicoin A (141) (33% overall).

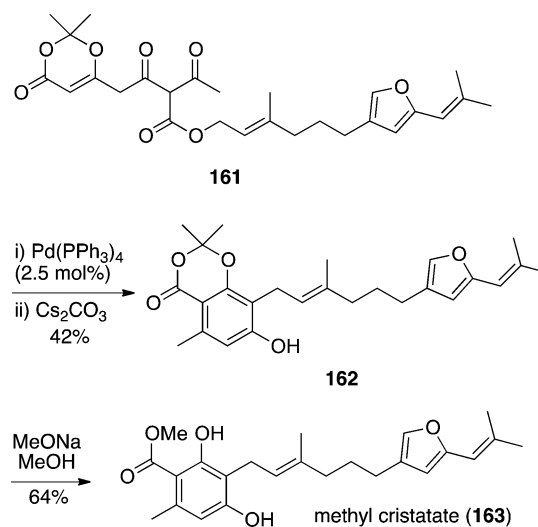
A related strategy was used for the total synthesis of amorfrutin A from dioxinone 142 via resorcyate 146 (63%).⁶⁵ In these studies, it was also observed that the branched isomer 144 underwent aromatization to resorcyate 145 at higher temperatures (Scheme 29).

We consider that the mechanism of the allyl migrations could be via an intermolecular modified Tsuji–Carroll rearrangement. This suggestion was in accord with variation of yields with concentration, deuterium-labeled competition experiments, and the conversion of dioxinone 148 into resorcyate 150 (Scheme 30).⁶⁴

A geranyl migration–aromatization sequence was applied in the total syntheses of the antibiotics hericenone J and hericenol A (Scheme 31).⁶⁶ Reaction of ester 151 with palladium(0) resulted in decarboxylative geranyl migration and intermediate 152 was directly cyclized to resorcyate 153 over silica gel. Interestingly, resorcyate 153 was obtained as the linear *E*-isomer exclusively. Phenol methylation and lactonization gave hericenone J (155) (24%), whereas reduction gave hericenol A (156) (21%).

We also synthesized hexasubstituted arenes 160 from dioxinones 158 by cross-coupling with alkenyl acetates 157 and aromatization (Scheme 32).⁶⁷

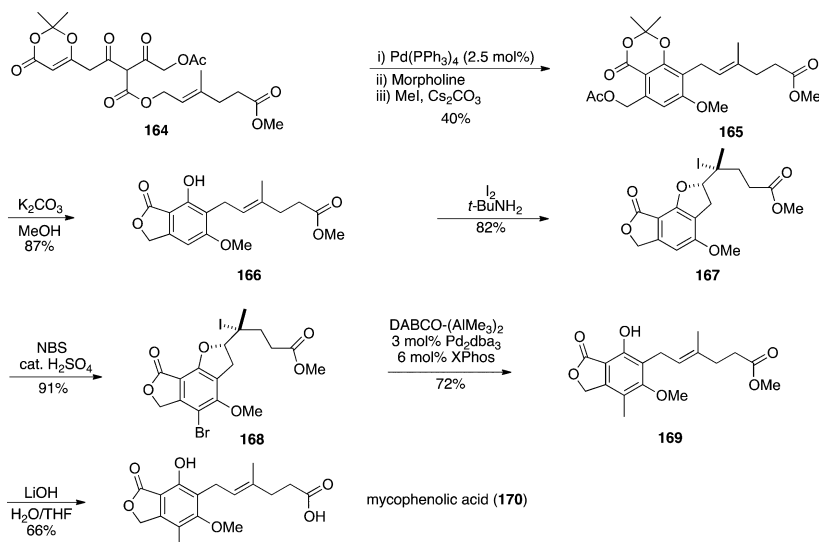
Scheme 33. Synthesis of Methyl Cristatate



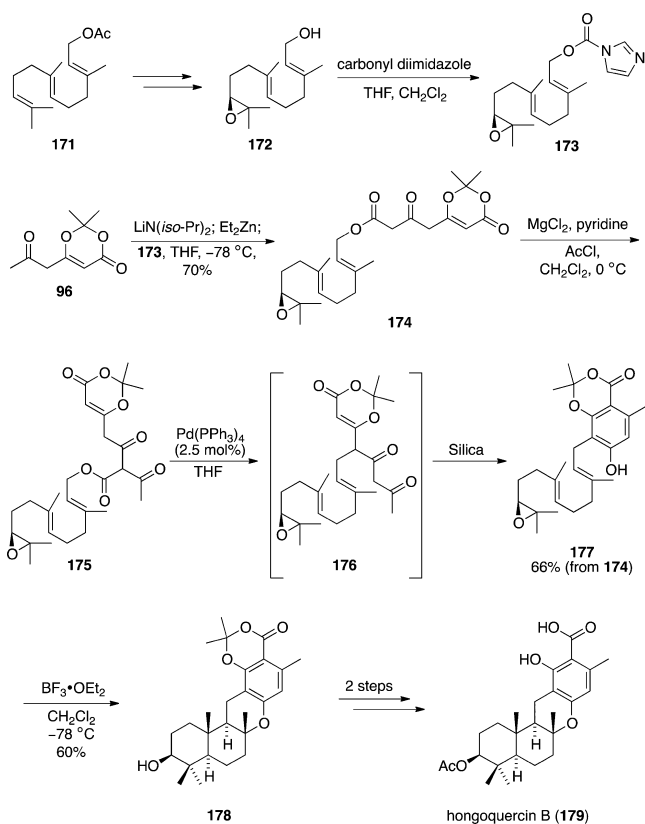
Terpenoid groups containing furanyl and ester moieties also proved compatible with the regioselective allyl migration aromatization sequence as exemplified by the total syntheses of methyl cristatate (163, Scheme 33)⁶⁸ and immunosuppressant mycophenolic acid (170, Scheme 34)⁶⁹ respectively.

In the total synthesis of mycophenolic acid (170), the aryl methyl group was installed after aromatization from

Scheme 34. Synthesis of Mycophenolic Acid (170)

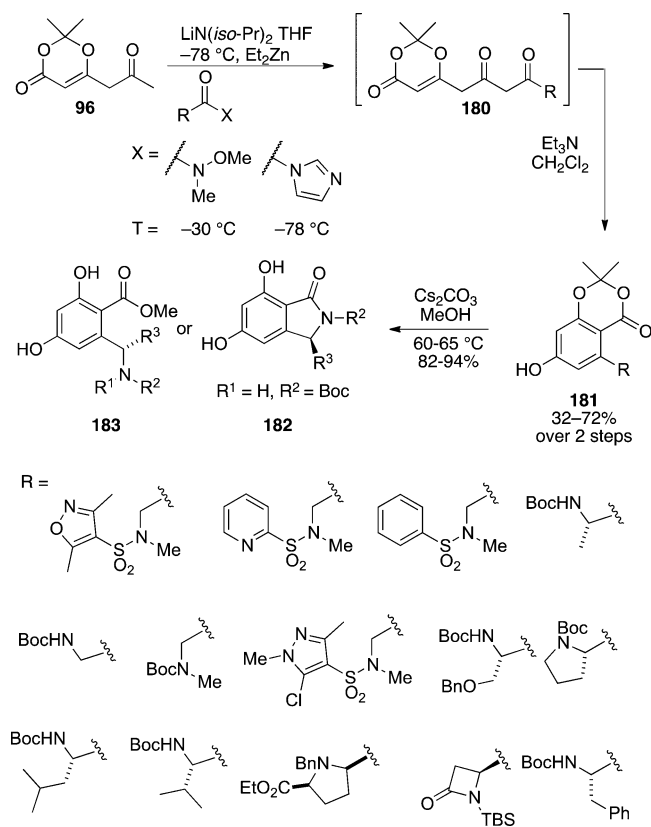


Scheme 35. Synthesis of Hongoquercin B (179)



dioxinone **164** (Scheme 34). Iodoetherification of alkene **166** and ring bromination gave bromide **168**, which on treatment with DABCO-(AlMe₃)₂ and palladium catalysis resulted in bromine–methyl exchange and reductive iodolactone ring opening to give methyl mycophenolate (**169**) (72%) and thence mycophenolic acid (**170**).⁶⁹

Recently, a palladium catalyzed, decarboxylative π -farnesyl rearrangement of diketo-dioxinone ester **175** was used to synthesize the meroterpenoid hongoquercin B (**179**). Intermediate **176** underwent double biomimetic aromatization and Lewis acid mediated, stereocontrolled, diene epoxide cyclization to generate the tetracyclic product **178**. Scheme 35 represents a nine step synthesis

Scheme 36. Preparation of *O*-Aminoalkyl Resorcylicates and Dihydroxyisoindolinones

with control of five stereocenters in the natural product from a single epoxide (**172**) stereocenter generated from acetate (**171**) via enantioselective Sharpless dihydroxylation (Scheme 35).^{70–73}

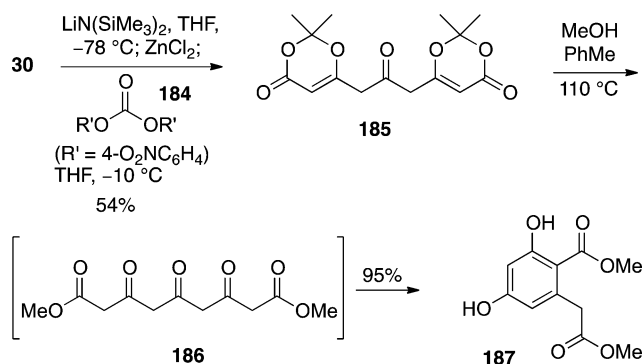
4. APPLICATION OF BIOMIMETIC AROMATIZATION TO NOVEL PHARMACOPHORES

The resorcylic biomimetic methodology was employed in the synthesis of additional classes of resorcylicates from readily available building blocks, as potential novel pharmacophores. Intermediates **180** were prepared utilizing a Claisen-condensation of the zinc dianion from keto-dioxinone **96** with imidazoles or

Weinreb amides. Subsequent aromatization gave resorcyates **181**, which on transacylation gave the corresponding aminoalkyl resorcyates **183** or dihydroxyisoindolinones **182** (82–94%) (Scheme 36).⁷⁴ These resorcyates have shown activities against several receptors and kinases including CDK2 and CDK7 as well as in the MCF7 breast cancer cell line.⁷⁴

The homophthalate ester **187**, a building block for the synthesis of DNA-binding ligands⁷⁵ and an intermediate in other total syntheses,⁷⁶ was prepared via methanolysis and aromatization of di-dioxinone **185** (Scheme 37).⁷⁷ Di-dioxinone

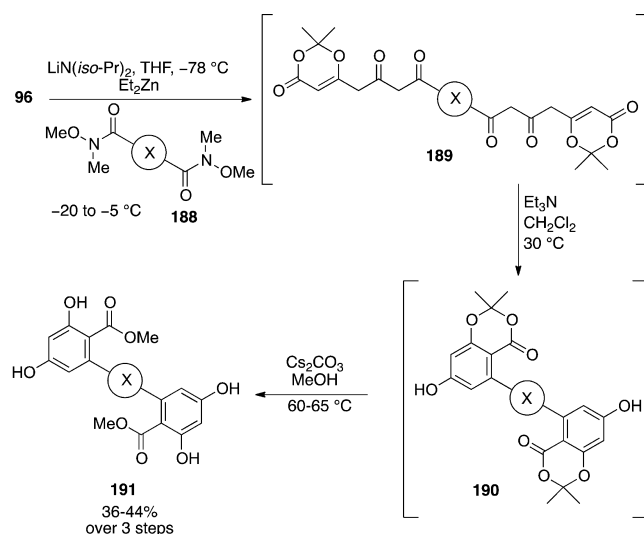
Scheme 37. Preparation of Homophthalate Ester 187



185 was prepared using a double Claisen condensation of the zinc enolate of dioxinone **30** with bis(4-nitrophenyl) carbonate **184**. This convenient two-step synthesis is notable in that the use of desiccants or elevated pressure were not required.

The di-dioxinone strategy was extended to the synthesis of resorcyate oligomers **191** with two resorcylic ester entities linked by spacers (Scheme 38).⁷⁷ Reaction of the zinc enolate

Scheme 38. Synthesis of Resorcyate Oligomers



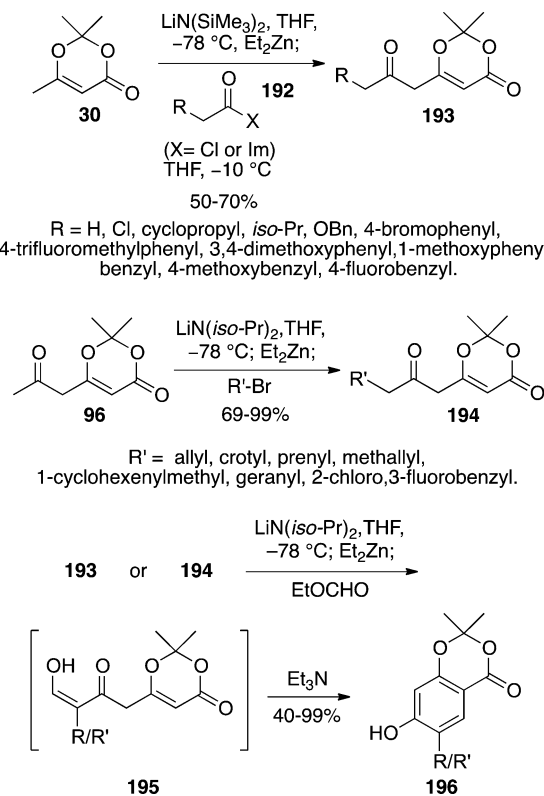
X = *trans*-1,4-cyclohexadiyl, CH₂CH₂, 1,4-phenylene, 2,6-pyridiyl, 1,4'-biphenylene

from keto-dioxinone **96** with the Weinreb diamides **188** gave diketodioxinones **189**. Base mediated aromatization and transesterification gave the double resorcylic esters **191** in 36–44% over three steps.

Diketodioxinone chemistry has also been applied for the synthesis of C5-substituted resorcyates and resorcinamides including the Hsp90 inhibitor AT13387 (**199**).^{78,79} Functionalized

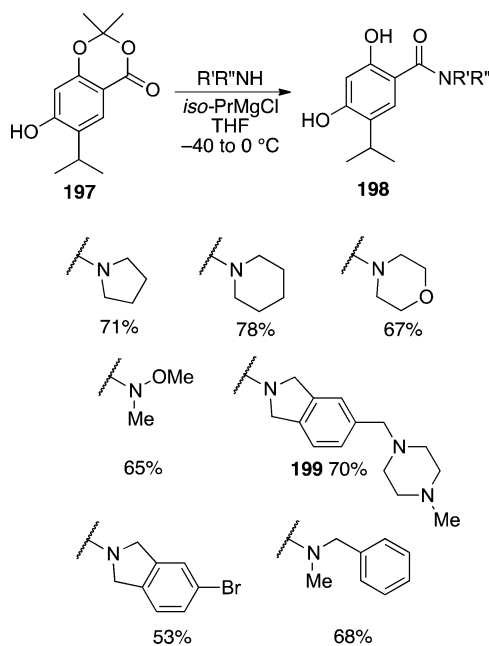
keto-dioxinones **193** and **194** were synthesized via C-acylation of the zinc enolate of dioxinone **30** or alkylation of the dianion of keto-dioxinone **96**. C-Formylation of keto-dioxinones **193** and **194** gave enols **195**, which were subsequently cyclized to arenes **196** (Scheme 39).

Scheme 39. Synthesis of 5-Substituted Resorcyates



Grignard-mediated amidation of resorcyate **197** gave the corresponding resorcinamides **198** (53–78%) without the need for phenolic protection (Scheme 40).^{78,79}

Scheme 40. Grignard-Mediated Amidation of Resorcyates 197



5. CONCLUSION

In summary, we have described versatile biomimetic methods for the synthesis of polyfunctional resorcyates. The types of functionality that are compatible with diketo-dioxinone synthesis, triketo-ketene generation, and aromatization are large and varied. The route usually eliminates the need for phenol protection, decreases the number of synthetic steps, and avoids poor yielding transformations. The methods are applicable for the synthesis of natural products but also to access novel templates for medicinal chemistry. Decarboxylative allyl migration and aromatization provide convenient and concise routes to terpenoid resorcyates. In the future, the diketo-dioxinone methodology should allow for the facile optimization of structure–activity relationships in diverse classes of aromatic compounds including, but not limited to, resorcyates and meroterpenoids. We hope the versatility of the methodology will inspire others to use this approach in drug discovery and natural product total synthesis.

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Notes

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REFERENCES

- (1) Johnson, W. S. Biomimetic Polyene Cyclizations. *Bioorg. Chem.* **1976**, *5*, 51–98.
- (2) Johnson, W. S.; Wiedhaup, K.; Brady, S. F.; Olson, G. L. The Nonenzymic, Biogenetic-like Cyclization of a Tetraenic Acetal. *J. Am. Chem. Soc.* **1968**, *90*, 5277–5279.
- (3) Johnson, W. S.; Crandall, J. K. Olefinic Cyclizations. VII. Formolysis of *cis*- and *trans*-5,9-Decadienyl *p*-Nitrobenzenesulfonate and of Some Isomeric Monocyclic Esters. *J. Org. Chem.* **1965**, *30*, 1785–1790.
- (4) Johnson, W. S.; Kinnel, R. B. Stereospecific Tricyclization of a Polyolefinic Acetal. *J. Am. Chem. Soc.* **1966**, *88*, 3861–3862.
- (5) Birch, A.; Donovan, F. Studies in Relation to Biosynthesis. IV. The Structures of Some Natural Quinones. *Aust. J. Chem.* **1955**, *8*, 529.
- (6) Staunton, J.; Weissman, K. J. Polyketide Biosynthesis: A Millennium Review. *Nat. Prod. Rep.* **2001**, *18*, 380–416.
- (7) Huckin, S. N.; Weiler, L. The Acylation of β -Keto Ester Dianions. *Can. J. Chem.* **1974**, *52*, 1343–1351.

(8) Harris, T. M.; Harris, C. M. Synthesis of Polyketide-Type Aromatic Natural Products by Biogenetically Modeled Routes. *Tetrahedron* **1977**, *33*, 2159–2185.

(9) Barrett, A. G. M.; Morris, T. M.; Barton, D. H. R. Convenient Syntheses of Alkyl β -Resorcyate Derivatives. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2272.

(10) Brownbridge, P.; Chan, T. H.; Brook, M. A.; Kang, G. J. Chemistry of Enol Silyl Ethers. A General Synthesis of 3-Hydroxyhomophthalates and a Biomimetic Synthesis of Sclerin. *Can. J. Chem.* **1983**, *61*, 688–693.

(11) Chan, T. H.; Chaly, T. A Biomimetic Synthesis of Δ^1 -Tetrahydrocannabinol. *Tetrahedron Lett.* **1982**, *23*, 2935–2938.

(12) Chan, T. H.; Stossel, D. Chemistry of 1,3,5-Tris(trimethylsilyloxy)-1-methoxyhexa-1,3,5-triene, a β -Tricarbonyl Trianion Equivalent. *J. Org. Chem.* **1986**, *51*, 2423–2428.

(13) Hyatt, J. A.; Feldman, P. L.; Clemens, R. J. Ketenes. 20. Thermal Decomposition of 2,2,6-Trimethyl-4H-1,3-dioxin-4-one and 1-Ethoxybutyn-3-one. Acetylketene. *J. Org. Chem.* **1984**, *49*, 5105–5108.

(14) Boeckman, R. K.; Weidner, C. H.; Perni, R. B.; Napier, J. J. An Enantioselective and Highly Convergent Synthesis of (+)-Ikurugamycin. *J. Am. Chem. Soc.* **1989**, *111*, 8036–8037.

(15) Boeckman, R. K.; Pruitt, J. R. A New, Highly Efficient, Selective Methodology for Formation of Medium-Ring and Macrocyclic Lactones via Intramolecular Ketene Trapping: An Application to a Convergent Synthesis of (–)-Kromycin. *J. Am. Chem. Soc.* **1989**, *111*, 8286–8288.

(16) Petasis, N. A.; Patane, M. A. Synthesis of 8-Membered Ring Lactones from Dioxolenones. *J. Chem. Soc., Chem. Commun.* **1990**, 836.

(17) Hoyer, T. R.; Danielson, M. E.; May, A. E.; Zhao, H. Total Synthesis of (–)-Callipeltoside A. *J. Org. Chem.* **2010**, *75*, 7052–7060.

(18) Trost, B. M.; Gunzner, J. L.; Dirat, O.; Rhee, Y. H. Callipeltoside A: Total Synthesis, Assignment of the Absolute and Relative Configuration, and Evaluation of Synthetic Analogues. *J. Am. Chem. Soc.* **2002**, *124*, 10396–10415.

(19) Cramer, N.; Laschat, S.; Baro, A.; Schwalbe, H.; Richter, C. Enantioselective Total Synthesis of Cylindramide. *Angew. Chem., Int. Ed.* **2005**, *44*, 820–822.

(20) Reber, K. P.; Tilley, S. D.; Sorensen, E. J. Bond Formations by Intermolecular and Intramolecular Trappings of Acylketenes and Their Applications in Natural Product Synthesis. *Chem. Soc. Rev.* **2009**, *38*, 3022–3034.

(21) Parenty, A.; Moreau, X.; Niel, G.; Campagne, J.-M. Update 1 of: Macrolactonizations in the Total Synthesis of Natural Products. *Chem. Rev.* **2013**, *113*, PR1–40.

(22) Sakaki, J.; Suzuki, M.; Kobayashi, S.; Sato, M.; Kaneko, C. Synthesis of 1,3-Dioxin-4-Ones and Their Use in Synthesis. Part 25. Baker's Yeast Mediated Bioreduction of Prochiral Ketones Having 6-(4-Oxo-1,3-Dioxinyl) Group. *Chem. Lett.* **1990**, 901–904.

(23) Sato, M.; Sakaki, J.; Sugita, Y.; Yasuda, S.; Sakoda, H.; Kaneko, C. Two Lactone Formation Reactions from 1,3-Dioxin-4-Ones Having Hydroxyalkyl Group at the 6-Position: Difference in Ring Opening and Closure. *Tetrahedron* **1991**, *47*, 5689–5708.

(24) Sakaki, J.; Sugita, Y.; Sato, M.; Kaneko, C. Synthesis of 1,3-Dioxin-4-Ones Having Chiral Hydroxyalkyl Groups at the 6-Position by Means of Baker's Yeast Reduction and Their Uses for Epc Synthesis. *Tetrahedron* **1991**, *47*, 6197–6214.

(25) Sugita, Y.; Sakaki, J.; Sato, M.; Kaneko, C. Use of 1,3-Dioxin-4-ones and Related Compounds in Synthesis. Part 39. Enantioselective Synthesis of 1,3-Dioxin-4-ones Having 2,3-Dihydroxy- or 2,3,4-Trihydroxyalkyl Groups at the 6-Position: Versatile Building Blocks of Polyhydroxylated 4–7 Carbon Backbones. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2855.

(26) Sakaki, J.; Sugita, Y.; Sato, M.; Kaneko, C. Enantioselective Synthesis of (S)- and (R)-6-(2,3-Dihydroxypropyl)-1,3-dioxin-4-ones: The Versatile Building Blocks of Four- and Six-Carbon Backbones. *J. Chem. Soc., Chem. Commun.* **1991**, 434.

(27) Selness, S. R.; Devraj, R. V.; Devadas, B.; Walker, J. K.; Boehm, T. L.; Durlay, R. C.; Shieh, H.; Xing, L.; Rucker, P. V.; Jerome, K. D.; Benson, A. G.; Marruffo, L. D.; Madsen, H. M.; Hitchcock, J.; Owen, T. J.; Christie, L.; Promo, M. A.; Hickory, B. S.; Alvira, E.; Naing, W.;

Blevis-Bal, R.; Messing, D.; Yang, J.; Mao, M. K.; Yalamanchili, G.; Vonder Embse, R.; Hirsch, J.; Saabye, M.; Bonar, S.; Webb, E.; Anderson, G.; Monahan, J. B. Discovery of PH-797804, a Highly Selective and Potent Inhibitor of p38 MAP Kinase. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4066–4071.

(28) Fang, Z. (A.); Clarkson, G. J.; Wills, M. Asymmetric Reduction of 2,2-Dimethyl-6-(2-Oxoalkyl/oxoaryl)-1,3-Dioxin-4-Ones and Application to the Synthesis of (+)-Yashabushitriol. *Tetrahedron Lett.* **2013**, *54*, 6834–6837.

(29) Shreder, K.; Hu, Y.; Fraser, A.; Kohno, Y.; Kojima, A.; Ishiyama, J. Preparation of (heteroaryl)benzoxazinone Derivatives for Use as Serine Hydrolase Inhibitors. International Patent WO 2008036379 A2, 2008.

(30) Scarborough, R.; Kalaritis, P.; Steenrod, J. G.; Yiannikouros, G. Methods for Producing Amino Substituted Chromanes and Intermediates Therfor as Platelet Aggregation Inhibitors. International Patent WO 2001087872 A1, 2001.

(31) Devadas, B.; Walker, J.; Selness, S. R.; Boehm, T. L.; Durley, R. C.; Devraj, R.; Hickory, B. S.; Rucker, P. V.; Jerome, K. D.; Madsen, H. M. Preparation of Substituted Pyridinones as Modulators of p38 MAP Kinase. PCT Int. Appl. WO 2005018557 A2, 2005.

(32) Devadas, B.; Walker, J.; Selness, S. R.; Boehm, T. L.; Durley, R. C.; Devraj, R.; Hickory, B. S.; Rucker, P. V.; Jerome, K. D.; Madsen, H. M. Preparation of Substituted Pyridinones as Modulators of p38 MAP Kinase. PCT Int. Appl. WO 2003068230 A1, 2003.

(33) Kaneko, C.; Sato, M. Optically Active 2,2-Dimethyl-1,3-Dioxin-4-Ones and Method for Preparing Same. U.S. Patent US 5256800 A, 1993.

(34) Katritzky, A. R.; Wang, Z.; Wang, M.; Hall, C. D.; Suzuki, K. Facile Syntheses of 2,2-Dimethyl-6-(2-Oxoalkyl)-1,3-Dioxin-4-Ones and the Corresponding 6-Substituted 4-Hydroxy-2-Pyrones. *J. Org. Chem.* **2005**, *70*, 4854–4856.

(35) Wagner, B.; Mongiat, S.; Herzog, B.; Baschong, W.; Buthe, A.; Oehrlein, R. Preparation and Formulation of Pyranobenzofuranone Coumestan-like Glycoside Antioxidants and UV Absorbants. International Patent WO 2008110465 A1, 2008.

(36) Munakata, R.; Katakai, H.; Ueki, T.; Kurosaka, J.; Takao, K.-I.; Tadano, K.-I. Total Synthesis of Macquarimicins Using an Intramolecular Diels-Alder Approach Inspired by a Biosynthetic Pathway. *J. Am. Chem. Soc.* **2004**, *126*, 11254–11267.

(37) Munakata, R.; Katakai, H.; Ueki, T.; Kurosaka, J.; Takao, K.; Tadano, K. Total Synthesis of (+)-Macquarimicin A. *J. Am. Chem. Soc.* **2003**, *125*, 14722–14723.

(38) Dong, Y.; Nakagawa-Goto, K.; Lai, C.-Y.; Morris-Natschke, S. L.; Bastow, K. F.; Lee, K.-H. Antitumor Agents 287. Substituted 4-Amino-2H-pyran-2-one (APO) Analogs Reveal a New Scaffold from Neo-Tanshinlactone with in Vitro Anticancer Activity. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2341–2344.

(39) Bach, T.; Kirsch, S. Synthesis of 6-Substituted 4-Hydroxy-2-pyrones from Aldehydes by Addition of an Acetoacetate Equivalent, Dess-Martin Oxidation and Subsequent Cyclization. *Synlett* **2001**, *2001*, 1974–1976.

(40) Lee, K.-H.; Dong, Y.; Bastow, K. F.; Lee, Y.-H. P.; Nakagawa-Goto, K. 4-Amino-2H-pyran-2-one Analogs as Anticancer Agents and Their Preparation. PCT Int. Appl. WO 2012061012 A2, 2012.

(41) Shimamura, H.; Sunazuka, T.; Izuhara, T.; Hirose, T.; Shiomi, K.; Omura, S. Total Synthesis and Biological Evaluation of Verticypyrone and Analogues. *Org. Lett.* **2007**, *9*, 65–67.

(42) Kiegiel, J.; Józwiak, J.; Woźniak, K.; Jurczak, J. Synthesis and Asymmetric Hydrogenation of 3,5-Dioxoheptanedioates. Preparation of Enantiomerically Pure Substituted Δ -Valerolactones. *Tetrahedron Lett.* **2000**, *41*, 4959–4963.

(43) Winssinger, N.; Barluenga, S. Chemistry and Biology of Resorcylic Acid Lactones. *Chem. Commun.* **2007**, 22–36.

(44) Xu, J.; Jiang, C.; Zhang, Z.; Ma, W.; Guo, Y. Recent Progress Regarding the Bioactivities, Biosynthesis and Synthesis of Naturally Occurring Resorcinolic Macrolides. *Acta Pharmacol. Sin.* **2014**, *35*, 316–330.

(45) Basset, J.-F.; Leslie, C.; Hamprecht, D.; White, A. J. P.; Barrett, A. G. M. Studies on the Resorcylics: Biomimetic Total Syntheses of

(+)-Montagnetonol and (+)-Erythrin. *Tetrahedron Lett.* **2010**, *51*, 783–785.

(46) Navarro, I.; Pöverlein, C.; Schlingmann, G.; Barrett, A. G. M. Tuning Diketodioxinone Reactivity: Biomimetic Synthesis of the Resorcylic Antibiotic Fungal Metabolites Ent-W1278A, -B, and -C, Using Iterative Aromatization Reactions. *J. Org. Chem.* **2009**, *74*, 8139–8142.

(47) Fürstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. Total Syntheses of (S)-(-)-Zearalenone and Lasiodiplodin Reveal Superior Metathesis Activity of Ruthenium Carbene Complexes with Imidazol-2-Ylidene Ligands. *J. Org. Chem.* **2000**, *65*, 7990–7995.

(48) Navarro, I.; Basset, J.-F.; Hebbe, S.; Major, S. M.; Werner, T.; Howsham, C.; Bräckow, J.; Barrett, A. G. M. Biomimetic Synthesis of Resorcylic Natural Products Utilizing Late Stage Aromatization: Concise Total Syntheses of the Marine Antifungal Agents 15G256i and 15G256j. *J. Am. Chem. Soc.* **2008**, *130*, 10293–10298.

(49) Calo, F.; Richardson, J.; Barrett, A. G. M. Total Synthesis of Aigialomycin D Using a One-Pot Ketene Generation-Trapping-Aromatization Sequence. *Org. Lett.* **2009**, *11*, 4910–4913.

(50) Gypser, A.; Peterek, M.; Scharf, H.-D. D-Erythronolactone as a C4 Building Unit. Part 2.1 A Short and Efficient Synthesis of Both Enantiomers of Epi-Muricatacin, a Diastereoisomer of the Native Acetogenin from *Annona muricata*. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1013–1016.

(51) Geng, X.; Danishefsky, S. J. Total Synthesis of Aigialomycin D. *Org. Lett.* **2004**, *6*, 413–416.

(52) Baird, L. J.; Timmer, M. S. M.; Teesdale-Spittle, P. H.; Harvey, J. E. Total Synthesis of Aigialomycin D Using a Ramberg-Bäcklund/RCM Strategy. *J. Org. Chem.* **2009**, *74*, 2271–2277.

(53) Vu, N. Q.; Chai, C. L. L.; Lim, K. P.; Chia, S. C.; Chen, A. An Efficient and Practical Total Synthesis of Aigialomycin D. *Tetrahedron* **2007**, *63*, 7053–7058.

(54) Barluenga, S.; Dakas, P.-Y.; Ferandin, Y.; Meijer, L.; Winssinger, N. Modular Asymmetric Synthesis of Aigialomycin D, a Kinase-Inhibitory Scaffold. *Angew. Chem., Int. Ed.* **2006**, *45*, 3951–3954.

(55) Fouché, M.; Rooney, L.; Barrett, A. G. M. Biomimetic Total Synthesis of Cruentaren A via Aromatization of Diketodioxinones. *J. Org. Chem.* **2012**, *77*, 3060–3070.

(56) Fürstner, A.; Bindl, M.; Jean, L. Concise Total Synthesis of Cruentaren A. *Angew. Chem., Int. Ed.* **2007**, *46*, 9275–9278.

(57) Cookson, R.; Pöverlein, C.; Lachs, J.; Barrett, A. G. M. Synthetic Studies towards Radicol through Biomimetic Macrolactonization and Transannular Aromatization Reactions. *Eur. J. Org. Chem.* **2014**, *2014*, 4523–4535.

(58) Garbaccio, R. M.; Stachel, S. J.; Baeschlin, D. K.; Danishefsky, S. J. Concise Asymmetric Syntheses of Radicol and Monocillin I. *J. Am. Chem. Soc.* **2001**, *123*, 10903–10908.

(59) Wang, X.; Bowman, E. J.; Bowman, B. J.; Porco, J. A. Total Synthesis of the Salicylate Enamide Macrolide Oximidine III: Application of Relay Ring-Closing Metathesis. *Angew. Chem., Int. Ed.* **2004**, *43*, 3601–3605.

(60) Miyatake-Ondozabal, H.; Barrett, A. G. M. A Novel Biomimetic Synthesis of (S)-(-)-Zearalenone: Via Macrocyclization and Transannular Aromatization. *Tetrahedron* **2010**, *66*, 6331–6334.

(61) Miyatake-Ondozabal, H.; Barrett, A. G. M. Total Synthesis of TAK-Kinase Inhibitor LL-Z1640-2 via Consecutive Macrocyclization and Transannular Aromatization. *Org. Lett.* **2010**, *12*, 5573–5575.

(62) Cordes, J.; Barrett, A. G. M. Synthesis of Macrosporin and Related 9,10-Anthraquinones by Biomimetic Polyketide Aromatization and Cyclization of 6-Benzylresorcylics. *Eur. J. Org. Chem.* **2013**, *2013*, 1318–1326.

(63) Anderson, K.; Calo, F.; Pfaffeneder, T.; White, A. J. P.; Barrett, A. G. M. Biomimetic Total Synthesis of Angelicoin A and B via a Palladium-Catalyzed Decarboxylative Prenylation-Aromatization Sequence. *Org. Lett.* **2011**, *13*, 5748–5750.

(64) Anderson, K.; Laclef, S.; Barrett, A. G. M. Mechanistic Studies of Highly Regioselective Decarboxylative-Prenyl Migration Reactions of Prenyloxycarbonyl-Diketo-Dioxinones. *Tetrahedron* **2014**, *70*, 5569–5579.

(65) Laclef, S.; Anderson, K.; White, A. J. P.; Barrett, A. G. M. Total Synthesis of Amorfrutin A via a Palladium-Catalyzed Migratory Prenylation–aromatization Sequence. *Tetrahedron Lett.* **2012**, *53*, 225–227.

(66) Cordes, J.; Calo, F.; Anderson, K.; Pfaffeneder, T.; Laclef, S.; White, A. J. P.; Barrett, A. G. M. Total Syntheses of Angelicoin A, Hericenone J, and Hericenol A via Migratory Prenyl- and Geranylation-Aromatization Sequences. *J. Org. Chem.* **2012**, *77*, 652–657.

(67) Cordes, J.; Laclef, S.; White, A. J. P.; Barrett, A. G. M. Palladium(0)-Catalyzed Allylic Alkylation of Diketoester-Dioxinones with Allyl Acetates under Neutral Conditions: Synthesis of Hexasubstituted Benzene Derivatives. *J. Org. Chem.* **2012**, *77*, 3524–3530.

(68) George, N. S.; Anderson, K. E.; Barrett, A. G. M. Total Synthesis of Cristatic Acid Based on Late-Stage Decarboxylative Allylic Migration and Biomimetic Aromatization of a Diketo Dioxinone. *Eur. J. Org. Chem.* **2013**, *2013*, 7604–7610.

(69) Brookes, P. A.; Cordes, J.; White, A. J. P.; Barrett, A. G. M. Total Synthesis of Mycophenolic Acid by a Palladium-Catalyzed Decarboxylative Allylation and Biomimetic Aromatization Sequence. *Eur. J. Org. Chem.* **2013**, *2013*, 7313–7319.

(70) Barrett, T. N.; Barrett, A. G. M. Cascade Polyketide and Polyene Cyclizations: Biomimetic Total Synthesis of Hongoquercin B. *J. Am. Chem. Soc.* **2014**, *136*, 17013–17015.

(71) Tsujimori, H.; Mori, K. Synthesis and Absolute Configuration of Hongoquercin B, a Sesquiterpene-Substituted Orsellinic Acid Isolated as a Fungal Metabolite. *Biosci., Biotechnol., Biochem.* **2014**, *64*, 1410–1415.

(72) Domingo, V.; Silva, L.; Diéguez, H. R.; Arteaga, J. F.; Quílez del Moral, J. F.; Barrero, A. F. Enantioselective Total Synthesis of the Potent Anti-Inflammatory (+)-Myrrhanol A. *J. Org. Chem.* **2009**, *74*, 6151–6156.

(73) Corey, E. J.; Noe, M. C.; Lin, S. A Mechanistically Designed Bis-Cinchona Alkaloid Ligand Allows Position- and Enantioselective Dihydroxylation of Farnesol and Other Oligoprenyl Derivatives at the Terminal Isopropylidene Unit. *Tetrahedron Lett.* **1995**, *36*, 8741–8744.

(74) Patel, B. H.; Mason, A. M.; Patel, H.; Coombes, R. C.; Ali, S.; Barrett, A. G. M. Conversion of α -Amino Acids into Bioactive *o*-Aminoalkyl Resorcylicates and Related Dihydroxyisoindolinones. *J. Org. Chem.* **2011**, *76*, 6209–6217.

(75) Imoto, S.; Haruta, Y.; Watanabe, K.; Sasaki, S. New DNA Binding Ligands as a Model of Chromomycin A3. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4855–4859.

(76) Kim, S.; Fan, G.; Lee, J.; Lee, J. J.; Kim, D. Synthesis of 4-Acetylisocoumarin: First Total Syntheses of AGI-7 and Sescandelin. *J. Org. Chem.* **2002**, *67*, 3127–3130.

(77) Patel, B. H.; Heath, S. F. A.; Mason, A. M.; Barrett, A. G. M. Efficient Two Directional Syntheses of a Homophthalate Ester and Novel Resorcylic Oligomers. *Tetrahedron Lett.* **2011**, *52*, 2258–2261.

(78) Barrett, T. N.; Patel, B. H.; Barrett, A. G. M. Synthesis of C-5-Substituted Resorcylicates and Resorcinamides via Formylation–aromatization of Functionalized Keto-dioxinones. *Tetrahedron* **2014**, *70*, 6894–6901.

(79) Patel, B. H.; Barrett, A. G. M. Total Synthesis of Resorcinol Amide Hsp90 Inhibitor AT13387. *J. Org. Chem.* **2012**, *77*, 11296–11301.