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Gold(I)-Mediated Cycloisomerization/Cycloaddition Enables Bioinspired Syntheses of Neonectrolides B-E and Analogs

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ABSTRACT: Development of a synthetic route to the oxaphenalenone (OP) natural products neonectrolides B-E is described. The synthesis relies on gold-catalyzed 6-*endo*-dig hydroarylation of an unusual enynol substrate as well as a one-pot Rieche formylation/cyclization/deprotection sequence to efficiently construct the tricyclic oxaphenalenone framework in the form of a masked *ortho*-quinone methide (*o*-QM). A tandem cycloisomerization/[4+2] cycloaddition strategy was employed to quickly construct molecules resembling the neonectrolides. The tricyclic OP natural product SF226 could be converted to corymbiferan lactone E and a related masked *o*-QM. Our study culminates with the application of the tandem reaction sequence to syntheses of neonectrolides B-E as well as previously unreported *exo*-diastereomers.

INTRODUCTION

Oxaphenalenones are a diverse yet largely unstudied class of natural products from fungi and plants bearing a characteristic oxidized, fused tricyclic core.[1] Despite their compelling structures and biological properties, reports on the syntheses of oxaphenalenone (OP) natural products and derivatives remain scarce.[2,3] We first became interested in the spiroketal natural product neonectrolide A (**1**)[4] and the ketal-containing neonectrolides B-E (**2**-**5**)[5] (Figure 1), compounds isolated in 2012 and 2015, respectively, by Che and coworkers. While congeners **1**-**5** show moderate anticancer activity, a patent indicates activity of **1** as a Gram-negative and -positive antibacterial agent.[6] The scarce quantities of the isolated cycloadducts, however, have clearly impeded more detailed systematic evaluation of their biological activities.

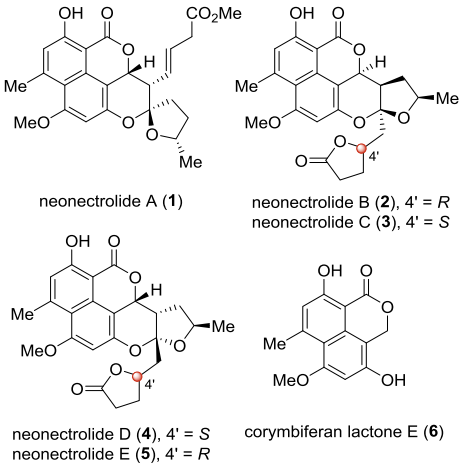
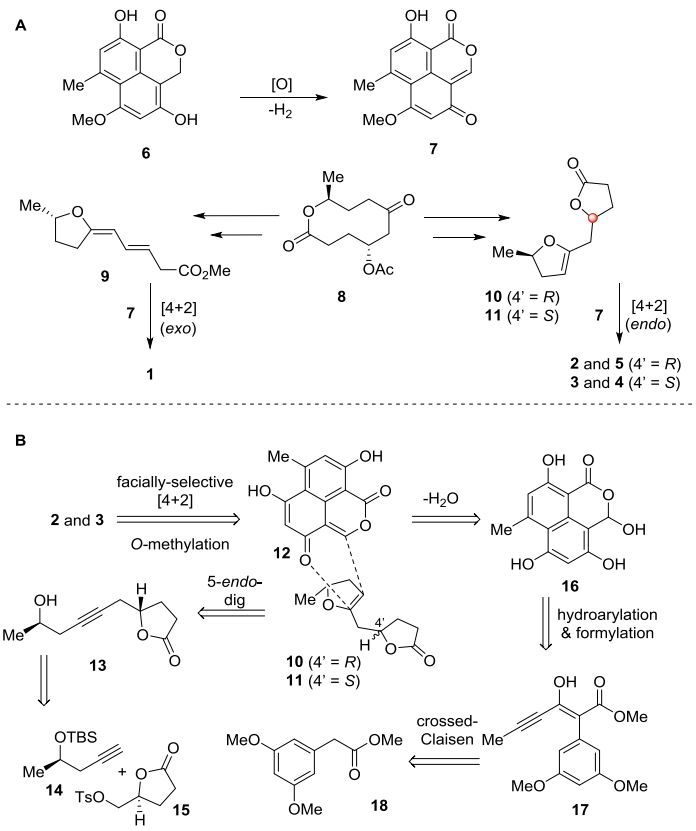
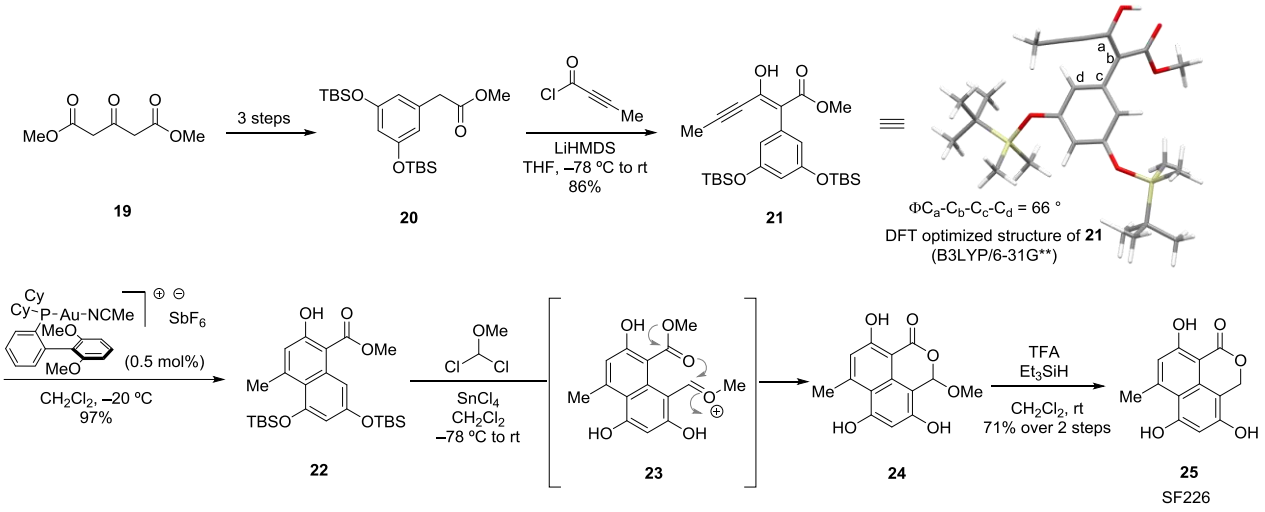


Figure 1. Structures of neonectrolides A-E (**1**-**5**) and biosynthetic precursor corymbiferan lactone E (**6**)

Scheme 1. A) Proposed biosyntheses of 1-5. B) Retrosynthetic analysis for 2 and 3



Scheme 2. Synthesis of *o*-QM precursor 24 and SF226 (25) *via* Au (I)-catalyzed hydroarylation and interrupted Rieche formylation



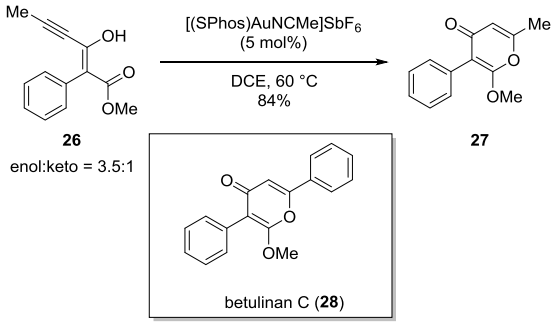
The natural product corymibiferan lactone E (**6**), an apparent biosynthetic precursor,[5] was also coisolated with **1**-**5** (Scheme 1A).[4,5] Along these lines, the neonectrolides likely arise from diastereoselective [4+2] cycloaddition between *ortho*-quinone methide (*o*-QM) **7**, derived from oxidation of **6**, and the chiral dihydrofuran partners (**9**-**11**) that may originate from modification of the putative biosynthetic precursor 3-dehydroxy-4-*O*-acetylcephasporolide C (**8**, Scheme 1A).[5,7] We considered that by first building the tricyclic core of **6**, we could readily access neonectrolide congeners **1**-**5** *via* *o*-QM formation followed by [4+2] cycloaddition. Furthermore, rapid formation of the tricyclic OP ring system would allow for a convergent and modular synthesis, thereby providing a platform for construction of neonectrolide analogs, as well as enabling evaluation of the proposed biosyntheses of **1**-**5**.

Our retrosynthetic analysis for neonectrolide congeners **2** and **3** is shown in Scheme 1B. We sought to emulate the biosynthetically proposed inverse-electron demand Diels-Alder (IEDDA) cycloaddition[8] of **7** to assemble the neonectrolide scaffold which after methylation may provide the desired natural products **2**-**5**. As this key biosynthetic step may be non-enzymatic,[9] we anticipated that use of chiral cycloaddition partners **10** and **11** may provide access to both **2** and **5** or **3** and **4**, respectively, with facial selectivity of the pivotal *endo*-cycloaddition with *o*-QM **12** dictating the formation of either diastereomeric natural product. Cycloaddition partner **10** may be derived from chiral alkynol **13**[10] which may be prepared by union of the known alkynol **14**[11] and butanolide **15**,[12] the latter prepared in three steps from L-glutamic acid. Compound **11,** the 4'-epimer of **10** (neonectrolide numbering), may be prepared in an identical fashion from D-glutamic acid, thereby allowing access to both congeners **3** and **4**. In order to access the tricyclic oxaphenalenone framework of the neonectrolides, we envisioned that dehydration of isochromanone-lactol precursor **16** may provide *o*-QM **12**. We considered that formylation followed by subsequent annulation could form the lactol ring of **16**,[13] while the naphthol moiety may be installed by metal-catalyzed hydroarylation of enynol **17**,[14] readily accessible from phenylacetate derivative **18** through crossed-Claisen condensation.

RESULTS AND DISCUSSION

Our synthesis began with self-condensation of dimethyl 1,3-acetonedicarboxylate (**19**), followed by Fischer esterification of the resulting phenylacetic acid (Scheme 2).[13,15] We elected to first prepare the *bis*-TBS protected phenylacetate derivative **20**.[16] Crossed-Claisen condensation of **20**[17] with freshly prepared 2-butynoyl chloride[18] cleanly afforded the tetrasubstituted enynol **21** in excellent yield[19] as a single stereoisomer[17] and enol tautomer as indicated by ^{1}H chemical shift ($CDCl_3$, 12.6 ppm) of the enynol hydroxyl proton.[15,20] Computational studies (DFT, B3LYP/6-31G**) indicate that the enynol moiety is distorted from the aryl ring plane by approximately 66° (Scheme 2). Enynol **21** was then treated with catalytic [(SPhos)AuNCMe]SbF_6 to induce 6-*endo*-dig hydroarylation,[21] cleanly furnishing the desired naphthoate **22**. As noted by both Barriault[22] and Banwell,[23] we found that bulky phosphino gold(I) salts performed particularly well in the hydroarylation to furnish the desired product **22** in high yield with low catalyst loading. During our efforts to study the scope of this transformation, we noticed that enynol substrates such as **26** (a 3.5:1 mixture of enol:keto tautomers in $CDCl_3$) lacking an activated, electron-rich aromatic ring alternately afforded 4-pyrone products *via* enol isomerization followed by nucleophilic attack of

Scheme 3. Rearrangement of enynol 26 to 4-pyrone 27

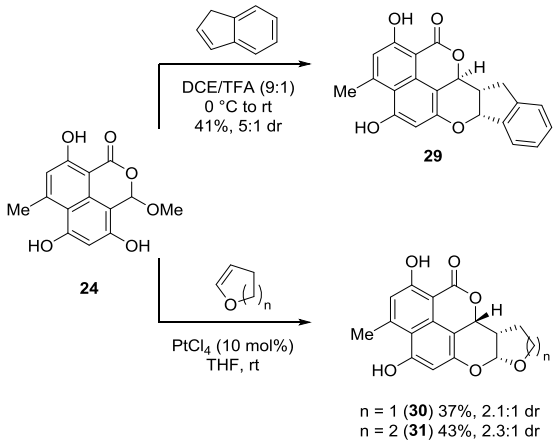


the ester carbonyl onto the enynol triple bond (Scheme 3).[24] Notably, the 4-pyrone **27** bears resemblance to the fungal natural product betulinan C (**28**).[25] While treatment of **26** with TFA afforded **27** in decreased yield (19%), exposure of **21** to Brønsted acid led only to cleavage of the silyl ether protecting groups.

Subjection of **22** to Rieche formylation conditions ($SnCl_4$, dichloromethyl methyl ether)[26] triggered an interrupted formylation/cyclization/deprotection sequence, presumably *via* oxocarbenium intermediate **23**, to provide the isochromanone-acetal **24**, a candidate *o*-QM precursor.[27] Ionic reduction of **24** was cleanly accomplished using trifluoroacetic acid (TFA) and triethylsilane (Et_3SiH) to provide the tricyclic oxaphenalenone natural product SF226 (**25**).[28]

We then studied the ability of **24** to serve as a suitable *o*-QM precursor diene in model inverse demand [4+2] cycloadditions. (Scheme 4). We found that treatment of **24** with TFA in 1,2-dichloroethane followed by addition of indene cleanly afforded the formal *exo*-[4+2] cycloadduct **29** (5:1 dr).[29] We also evaluated the ability of **24** to react with dienophiles in inverse-electron-demand fashion under Lewis acidic conditions, first surveying reactivity with simple enol ethers such as 2,3-dihydrofuran and 2,3-dihydropyran. We observed that $PtCl_4$ successfully catalyzed the formation of cycloadducts **30** and **31**, albeit in moderate yield and diastereoselectivity.[30]

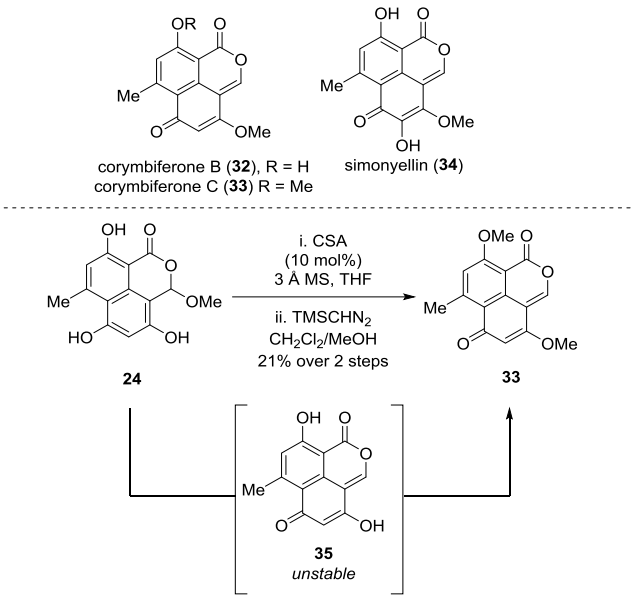
Scheme 4. Initial reactions with *o*-QM precursor 24



As several oxaphenalenone natural products (*cf.* **32**-**34**, Scheme 5) which bear a *para*-quinone methide (*p*-QM) functionality have been isolated,[31] we also considered whether **24** could be converted into a stable and isolable QM derivative (Scheme 5). Gratifyingly, exposure of **24** to catalytic camphorsulfonic acid (CSA) in the presence of 3Å molecular sieves led to precipitation of the insoluble quinone methide **35** which could be isolated by filtration.[32] However, this compound proved to be unstable in solution, likely a consequence of its vinylogous acid functionality. Nonetheless, *O*-methylation of the isolated compound **35** afforded the *p*-QM natural product corymbiferone C (**33**) in 21% yield after preparative HPLC purification (**32**).[31a]

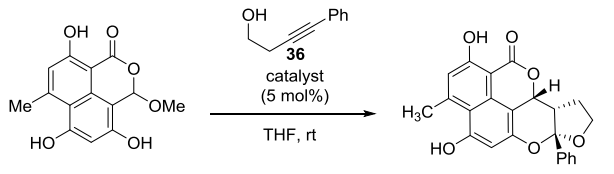
In order to achieve a more efficient and selective cycloaddition, as well as mitigate the isolation and purification of unstable and reactive quinone methide and dihydrofuran reaction partners, we next evaluated a one pot cycloisomerization/cycloaddition process[33] for construction of the neonectrolide core. Tandem processes involving alkynol cycloisomerization and

Scheme 5. Conversion of 24 to corymbiferone C (32)



[4+2] cycloaddition have recently been employed for rapid construction of natural products and natural product-like molecules.[34,35] In particular the De Brabander and Rodríguez groups have developed elegant approaches to the structurally-related spiroketal natural product berkelic acid[36,37] utilizing tandem 5-*exo*-dig cycloisomerization/*o*-QM formation/[4+2] cycloadditions *via* isochroman acetal[35a,c] or *ortho*-alkynylbenzaldehyde[35b] intermediates, respectively. To the best of our knowledge, however, these two examples represent the only applications of this powerful methodology in natural product total synthesis. Furthermore, tandem reactions involving *in situ* generation and cycloaddition of a 2,3-dihydrofuran partner have not been applied in such a context.

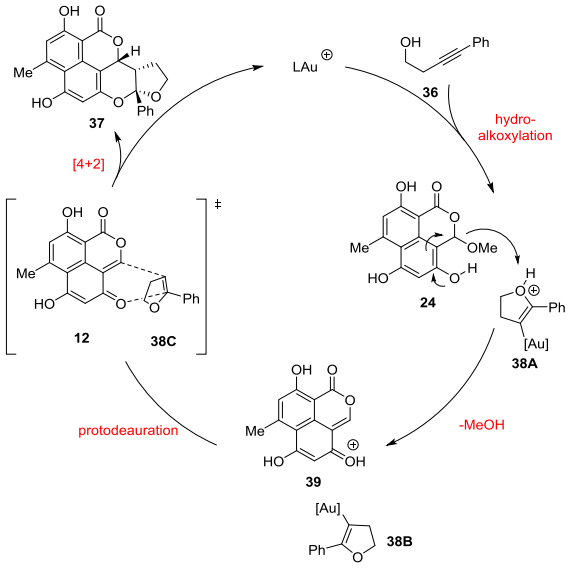
Table 1. Catalyst screen for one-pot cycloisomerization/cycloaddition with 24 and 36



Entry	Catalyst	Yield	dr
1	AgOTf	87%	7.5:1
2	Zeise's dimer	67%	7.5:1
3	$Pd(MeCN)_4(BF_4)_2$	complex mixture	—
4	$AuCl_3$	82%	5:1
5	$[(SPhos)AuNCMe]SbF_6$	92%	5.5:1
6	$PtCl_4$	—	—

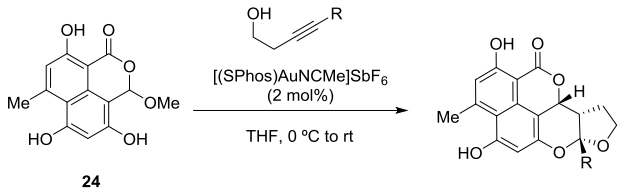
We first studied the proposed cycloisomerization/cycloaddition cascade with 4-phenyl-3-butynol (**36**) as the alkynol reaction partner. We evaluated a range of π-acidic metals to induce alkynol cycloisomerization[38] as well as *o*-QM formation from **24** *via* loss of methanol (Table 1). Gratifyingly, use of Pt(II), Pd(II), Ag(I), Au(III), and Au(I) catalysts all led to formation of the desired cycloadduct as an inseparable mixture of diastereomers (entries 1-5), significantly favoring the *endo*-cycloadduct, the latter defined with respect to the dihydrofuran oxygen.. Notably, despite our previous success employing $PtCl_4$ as catalyst for direct *o*-QM formation and cycloaddition, no reaction was observed when this catalyst was used in the tandem process (entry 6). This observation may be attributed to the "hard" Lewis acidic character of Pt (IV) and inability of this catalyst to serve as a suitable π-acid. Furthermore, treatment of **24** with a cationic gold (I) catalyst and 2,3-dihydrofuran did not afford cycloaddition products. However, addition of CSA (20 mol%) allowed the reaction to proceed, implicating the necessity for a Brønsted acid catalyst in the process. We considered that the alkynol reaction partner may be interacting with the cationic Au(I) catalyst to form a σ complex, thereby generating a Lewis acid-activated Brønsted acid (LBA) which may significantly enhance the acidity of the pendant alcohol. However, addition of benzenebutanol to the mixture of **24**/2,3-dihydrofuran/Au(I) catalyst did not grant reactivity.[15,39,40]

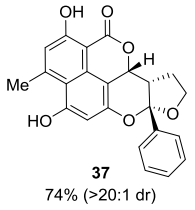
Scheme 6. Proposed mechanism for Au(I)-mediated cycloisomerization/cycloaddition

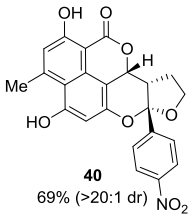


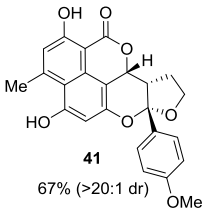
Based on our experimental findings, a proposed mechanism for the tandem cycloisomerization/cycloaddition between phenyl alkynol **36** and isochromanone acetal **24** is shown in Scheme 6. Gold(I)-catalyzed hydroalkoxylation of **36** may generate the aurated dihydrofuran **38A**, an intermediate which may also serve as a Brønsted acid[39,40] to induce formation of the protonated *o*-QM **38** *via* loss of methanol along with the vinyl gold species **38B**. Protonated *o*-QM **39** or **12** bearing a vinylogous acid moiety may also serve as competent Brønsted acids in the process. Protodeauration of **38B** may then generate reaction partners **12** and dihydrofuran **38C** and regenerate the Au(I) catalyst. Final [4+2] cycloaddition of **12** and **38C** may then afford the observed major cycloadduct **37**.[34d, 35a]

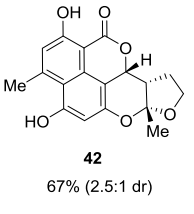
Scheme 7. Evaluation of alkynol scope in the tandem reaction with masked *o*-QM 24

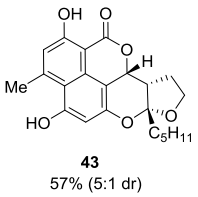


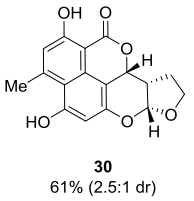












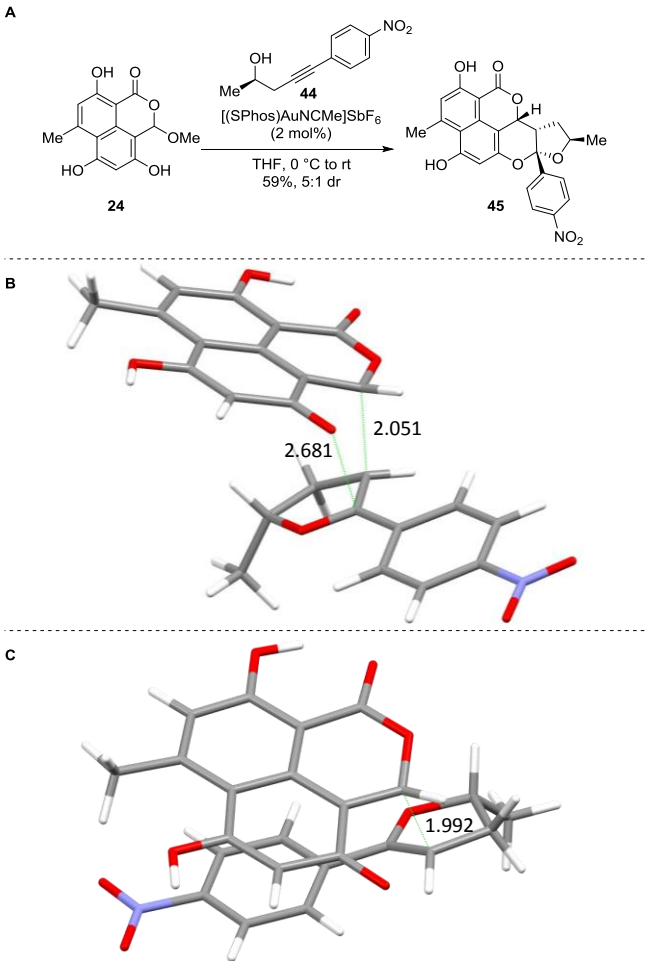
We next explored a small set of electronically and sterically distinct substrates to evaluate the scope of the tandem process for the synthesis of neonectrolide analogs (Scheme 7). Reaction of **24** with alkynol **36** at 0 °C with 2 mol% of catalyst enabled formation of **37** in high diastereoselectivity (>20:1 dr), thereby generating two rings and three stereocenters in a single reaction. While both electron-rich and electron-poor aryl alkynols provided the corresponding cycloadducts in good yield as nearly single diastereomers (**40**, **41**), diastereoselectivity was found to drop dramatically when alkyl alkynol substrates were employed (*cf.* **42** and **43**). It is worth noting that the majority of tandem alkynol cycloisomerization/cycloadditions have been conducted with aryl-substituted reaction partners which typically afford products as single diastereomers.[34] As expected, conducting the reaction with the parent alkynol (R = H) afforded cycloadduct **29**.

As the chiral methyl group of partners **9**-**11** may be responsible for directing the approach of the dihydrofuran reaction partner in the biosynthesis of the neonectrolides,[4,5] we sought to probe the effect of this component's introduction on the diastereofacial selectivity in the [4+2] cycloaddition. As anticipated, conducting the tandem reaction with chiral alkynol **44** provided the *endo-anti* cycloadduct **45** as the major product (Scheme 8A). Notably, the minor cycloadduct generated in this reaction was derived from *endo* cycloaddition from the opposite face of the *o*-QM (*endo-syn* approach).[15] The observed facial

selectivity in the reaction likely arises from a simple steric bias for the *in situ*-generated dihydrofuran to approach the *o*-QM *anti* to the methyl substituent.

Transition state calculations (PBEh-3C/SMD(THF),DLPNO-CCSD(T)/CBS/CPCM(THF))[15] were performed to compare both stepwise and concerted asynchronous reaction pathways to form the four possible stereoisomers of cycloadduct **45**.[41, 42] These calculations (*cf.* Table SQ1-SQ2) are consistent with the experimentally observed product distribution. Schemes 8B and 8C show a comparison of concerted *vs.* stepwise transition states leading to *anti-endo* adduct **45**. The computations indicate that concerted and stepwise pathways are highly competitive for each stereoisomer; however, the *endo* isomers prefer to form *via* a stepwise mechanism, whereas the *exo* isomers appear to prefer a concerted, asynchronous transition state. Interestingly, we also noticed that the most energetically favorable transition states are stabilized by π-stacking and electrostatic/hydrogen bonding interactions between the aryl moiety of the dihydrofuran partner with the oxaphenalenone ring system (*cf.* Scheme 8C, Figure SZ1).

Scheme 8. (A) Tandem reaction with chiral alkynol 44 (B) Optimized concerted, asynchronous *endo-anti* transition state leading to cycloadduct 45 (C) Rate-limiting, stepwise transition state leading to 45



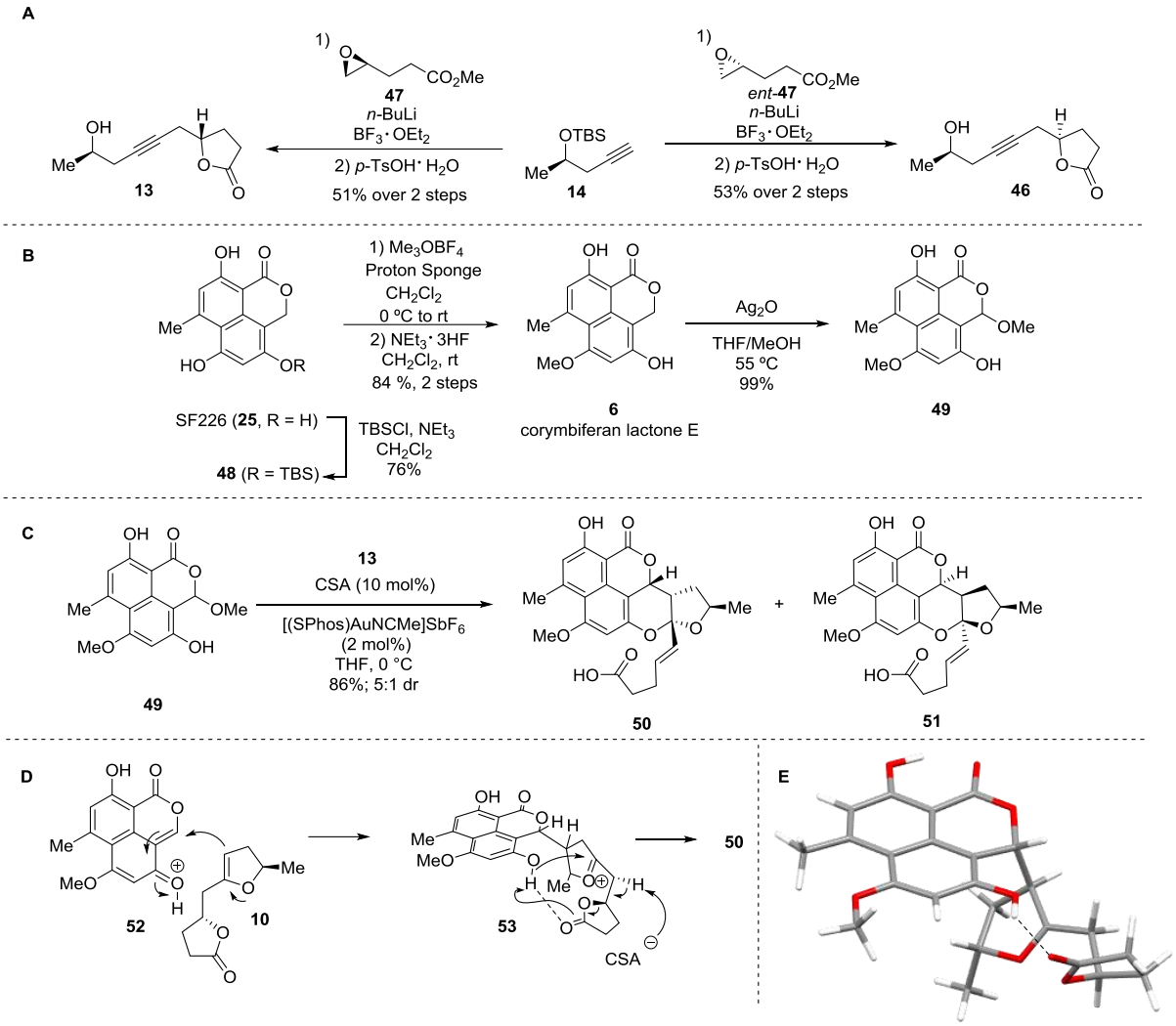
Encouraged by our experimental results, we next focused on the construction of the natural products neonectrolides **2**-**5** by synthesizing the chiral, γ-butyrolactone-containing alkynol epimers **13** and **46**. Alkylation of **14** was readily achieved by use of epoxide **47** or *ent*-**47** on a multigram scale, which was followed by one-pot silyl deprotection and lactonization under acidic conditions to yield the desired alkynols **13** and **46** (Scheme 9A).[10]

We also developed a three-step sequence to access corymbiferan lactone E (**6**), the likely biosynthetic precursor of **1**-**5**, from SF226 (**25**) (Scheme 9B). While direct methylation of **24** or **25** proved to be unselective, **25** could be converted regioselectively to the silyl ether **48**. Methylation was achieved with Meerwein's salt, which was followed by desilylation to afford **6** in excellent yield. Exposure of **6** to silver (I) oxide in a 1:1 mixture of THF and methanol cleanly oxidized **6** to install the isochromanone-acetal functionality of the masked *o*-QM **49**.[43]

To our surprise, however, treatment of **49** and **13** with [(SPhos)AuNCMe]SbF_6 did not lead to the formation of any detectable cycloaddition products. We suspected that exogenous Brønsted acid may be needed to promote *o*-QM formation from **49**. Indeed, conducting the transformation in the presence of 10 mol% of CSA enabled the reaction to proceed (Scheme 9C). However, in the process the γ-butyrolactone moiety unexpectedly underwent elimination to afford the alkenoic acids **50** and **51** as major products. Notably, the same products were obtained in comparable yield and diastereoselectivity when epimeric alkynol **46** was used in the process. The outcome of these reactions reinforced that a stepwise mechanism was operative (*cf.* Scheme 8C).[42b]As detailed in Scheme 9D, dihydrofuran **10** may undergo conjugate addition to the reactive, protonated *o*-QM **52** generating oxonium intermediate **53**. Computational studies indicate that the lactone carbonyl of this intermediate may participate in a hydrogen bond with the phenolic proton of the OP ring system, while also placing the requisite oxocarbenium moiety within suitable proximity for ring closure.[15] We believe that subsequent cyclization to afford the benzyopyran functionality may be accompanied by intramolecular proton transfer and deprotonation by the camphorsulfonate anion leading to *anti* elimination affording the observed *endo-anti* alkenoic acid cycloadduct **50** as the major product. In further support of a stepwise process, cycloisomerization of **46** was conducted in the presence of tetracyanoethylene (TCNE) to afford dihydrofuran **54** (Scheme 10). This result is consistent with the ability of dihydrofurans to undergo formal [2+2] cycloaddition with suitable electrophiles such as TCNE[44] and dimethyl acetylenedicarboxylate (DMAD)[45] through proposed zwitterionic intermediates similar to **55**.

Based on recent work reported by Xu and coworkers, we also attempted the cycloisomerization/[4+2] cycloaddition between **49** and **13** in the presence of [(SPhos)AuNCMe]SbF_6 and $Sc(OTf)_3$.[46] We were pleased to find that the use of $Sc(OTf)_3$ as Lewis acid led to the formation of neonectrolides C and D (**3** and **4**) as well as the *exo*-diasteromer **56**, with the *endo-anti* and *exo-anti* cycloadducts comprising the majority of the product mixture as determined by analysis of the crude reaction mixture (**3**:**56**:**4** = 5:3:1). Comparable results were observed with alkynol **46** as reaction partner to afford neonectrolides B and E (**2** and **5**) as well as the *exo-anti* diastereomer **57**, again in a 5:3:1 ratio, favoring the *anti*-cycloadducts (Scheme 11A). While they remain unisolated, we believe that neonectrolide stereoisomers

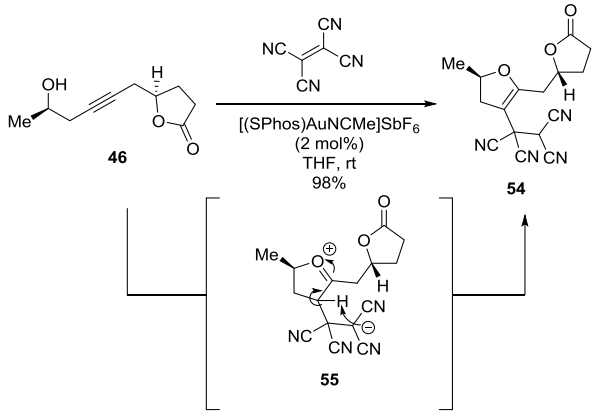
Scheme 9. (A) Syntheses of chiral butyrolactone-containing cycloaddition partners 13 and 46 (B) Synthesis of corymbiferan lactone E (6) and the derived isochromanone-acetal 49 (C) Synthesis of alkenoic acids 50 and 51 (D) Mechanistic rationale for formation of elimination product 50 (E) Relevant conformer of adduct 53 leading to 50.



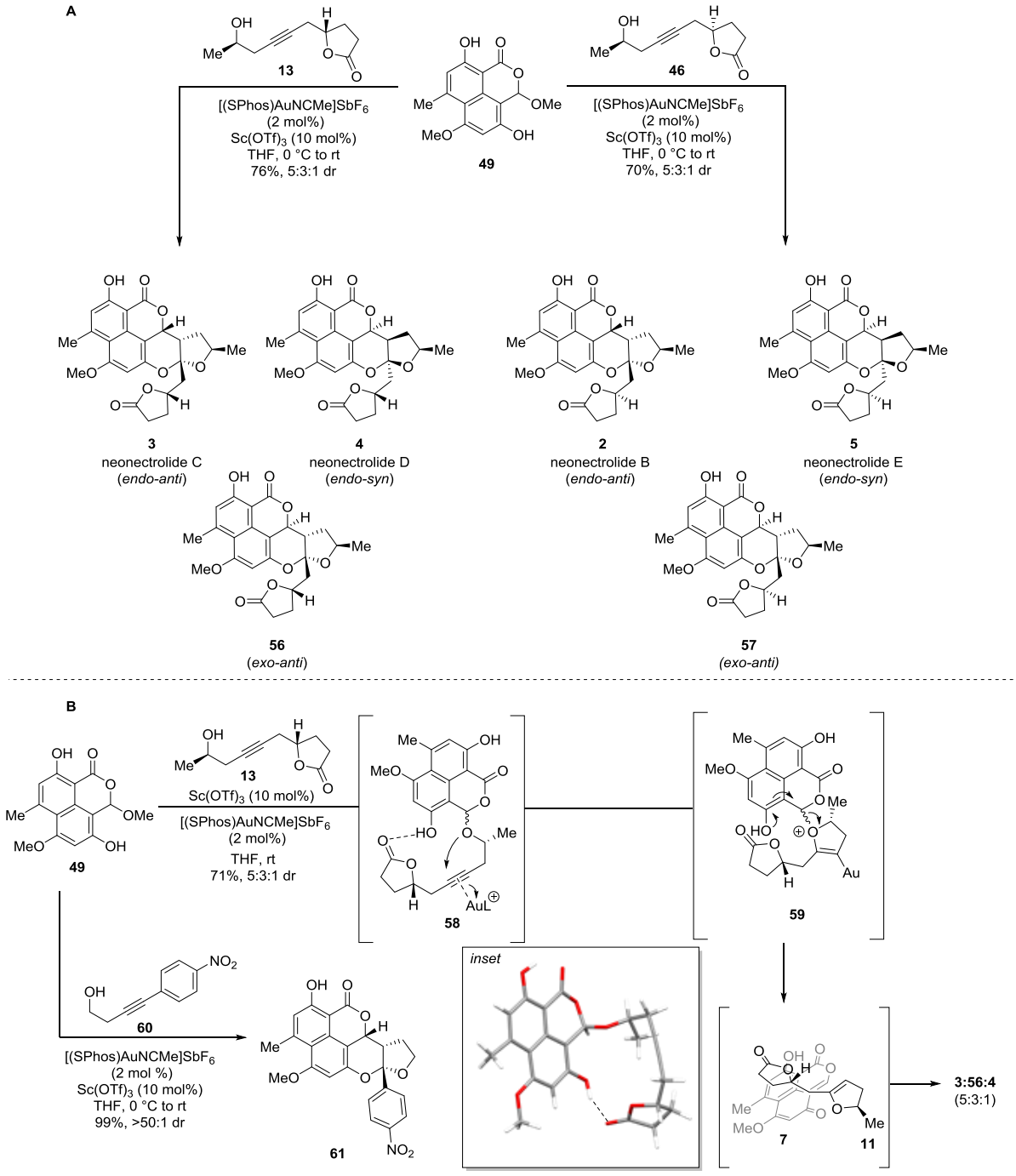
56 and **57** represent "anticipated" natural products that likely exist in Nature.[47,48]

The product distribution in the latter process may be explained by the ability of $Sc(OTf)_3$ to promote acetal exchange as suggested by Xu and coworkers.[46] We observed that the mixed acetal **58** could be isolated as roughly a 1:1 mixture of inseparable diastereomers when the experiment was conducted in a stepwise fashion (Scheme 11B). Exposure of isolated **58** to Au(I) catalysis afforded a 2:1:1 mixture of products (**3**:**56**:**4**) similar to that obtained in the one-pot transformation. In terms of reaction mechanism, treatment of **58** with cationic Au(I) may form the tethered dihydrofuran intermediate **59** after alkyne activation by the Au(I) catalyst. Formation of the requisite *o*-QM may proceed by elimination of the dihydrofuran, generating the two reaction partners, *o*-QM **7** and dihydrofuran **11**. Subsequent [4+2] cycloaddition provides the observed products **3**, **4**, and **56**.[46] It is worth noting that the butyrolactone carbonyl of **58** and **59** may interact with the phenolic proton of the tethered oxaphenalenone scaffold, as previously described in the formation of cycloadducts **50** and **51** (Scheme 9D/9E). We believe that this hydrogen-bonding interaction may orient the dihydrofuran partner in an *exo*-cycloaddition geometry, thereby leading to the significant formation of *exo-anti* isomer **56**. A representative conformer from a conformational search[15] for one diastereomer

Scheme 10. Au(I)-catalyzed cycloisomerization of 49 in the presence of TCNE



Scheme 11. Syntheses of neonectrolides 2-5 and *exo*-diastereomers 56 and 57 *via* Au(I)/Sc(III) catalysis



of **58** is shown in Scheme 11B (*inset*). Similar results were also achieved when employing alkynol **46**.[15] Furthermore, reaction between **49** and **60** under synergistic Au(I)/Sc(III) conditions led to the isolation of *endo*-cycloadduct **61** as nearly a single diastereomer, underscoring the significance of the hydrogen-bonding lactone moiety present in **13** and **46** to access *exo*-cycloadducts **56** and **57**.

CONCLUSION

In conclusion, we have described the first total syntheses of neonectrolides B-E (**2**-**5**), the first oxaphenalenone natural products to be synthesized in over three decades. We have utilized gold-catalyzed hydroarylation of an enynol substrate and an interrupted Rieche formylation sequence to efficiently construct the oxaphenalenone framework in the form of a masked *o*-quinone methide. Access to this core structure has enabled synthesis of the isolatable *p*-quinone methide natural product corymbiferone C[31a] as well as the natural product SF226 (**25**).[28] Our convergent and bioinspired approach to the neonectrolides has also provided access to natural product analogs *via* gold(I)-mediated alkynol cycloisomerization/*o*-QM cycloaddition and

has led to further understanding of substrate-controlled induction of diastereoselectivity in such processes. Additionally, we have demonstrated the power of *5-endo*-dig cycloisomerization/[4+2] cycloaddition pathways for the efficient and concise construction of natural products **2-5**. Our synthetic route is highly flexible and scalable, allowing for preparation of multigram amounts of oxaphenalenone core structure **24** in a single campaign. Finally, syntheses of **2-5** support their postulated biosynthetic origins while highlighting the power of biomimetic synthetic design not only in the efficient execution of total syntheses, but in the production of "anticipated" natural products.[47,48] Efforts in our laboratory to develop catalytic, enantioselective cycloisomerization/cycloaddition processes[49] towards oxaphenalenone natural products including neonectrolide A (**1**)[50] as well as biological studies of this underexplored class of natural products are currently in progress and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest.

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