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Enantioselective Total Syntheses of Various Amphilectane and Serrulatane Diterpenoids via Cope Rearrangements

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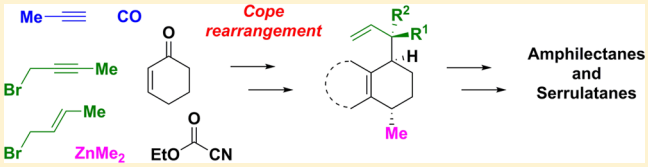
Supporting Information

ABSTRACT: Ampilectane and serrulatane natural products are structurally and stereochemically complex compounds that display various potent pharmacological activities ranging from anti-inflammatory to antituberculosis. A general synthetic route toward this family of natural products has been developed, which accomplished a number of amphilectane and serrulatane natural products. The key step employed a stereoselective Cope rearrangement either promoted by gold catalysis or thermal conditions, while a regioselective gold-catalyzed 6-*endo*-dig cyclization was optimized to afford a precursor. The preparation of the chiral β-ketoester as a starting material was established via an optimized asymmetric 1,4-addition followed by trapping with Mander's reagent, and this initially installed stereogenic center provided good control in the subsequent introduction of all the other stereocenters. A rarely investigated one-pot conversion of α-pyrone into phenol was also examined to enable the syntheses. DFT calculations explain the high stereoselectivity of the Cope rearrangement of the intermediate that eventually led to amphilectolide and caribenol A.



INTRODUCTION

The Cope rearrangement is particularly suited for constructing congested stereocenters in complex molecules.[1,2] However, the reversibility of the Cope rearrangement means that strategies must be designed to shift the equilibrium between the starting material and the product. In one recent noticeable advance of Cope rearrangement, Tantillo and Gagné et al. realized the gold-catalyzed enantioselective Cope rearrangement of 1,5-dienes with a terminal methylenecyclopropane motif.[3] Enabled by the release of ring strain on rearrangement, their work remain the only gold-catalyzed Cope rearrangement reported to date even if gold-catalyzed heteroatom variants of Cope reaction such as aza-Claisen have been well-documented.[4] Another strategy of driving the Cope reaction is the introduction of conjugative stabilization or even aromaticity. This was actually disclosed in the first Cope rearrangement reported[5] but remains rarely explored in total synthesis in comparison to strain-release Cope and oxy-Cope rearrangements.[2,6] Recognizing the structural features of amphilectane and serrulatane diterpenoids isolated from *Pseudopterogorgia elisabethae* (Figure 1)[7] provide a unique opportunity for advancing such strategy, we herein describe a concise and collective synthesis of various bioactive natural products based on the powerful Cope rearrangement, promoted by either the gold catalyst or the thermal conditions.

Among numerous bioactive amphilectane and serrulatane natural products, pseudopterosin diterpene glycosides have attracted most attention because of their promising anti-inflammatory and analgesic properties.[8] Attempts to simplify the lipophilic aglycones have yet to provide analogues superior to their natural counterparts (such as pseudopterosins A and E), revealing the privileged molecular features of the corresponding amphilectane and serrulatane skeletons.[9] Investigation into their molecular mode of action has been inconclusive, even though adenosine receptors have been suggested as potential targets of pseudopterosins to explain their capability of promoting wound healing.[9a,10] Seco-pseudopterosins, such as **2**, also have potent anti-inflammatory activities even though the aglycone has a serrulatane instead of amphilectane skeleton.[11] Interestingly, pseudopterosin A (**1**) has also been reported to possess strong antibacterial activity against several Gram-positive bacteria,[12] while pseudopterosin G (**3**), the aglycone of which is an epimer of pseudopterosin A aglycone, has been recently reported to have similar antibacterial spectrum and potency.[13]

For amphilectane and serrulatane diterpenoids without the sugar moiety, one promising biological activity is their capability to inhibit the growth of $H_{37}R_v$ strain and multidrug resistant *Mycobacterium tuberculosis*.[14] Among these compounds, pseudopteroxazole (**4**) and erogorgiaene (**5**) were isolated from *P. elisabethae*,[14a,b] whereas leubethanol (**6**) was isolated from the root bark of *Leucophyllum frutescens*, an evergreen shrub used in Mexican traditional medicine.[14c] The different origin may explain the variation at the C3 and C6 stereochemistry. Moreover, amphilectolide (**7**) and caribenol A

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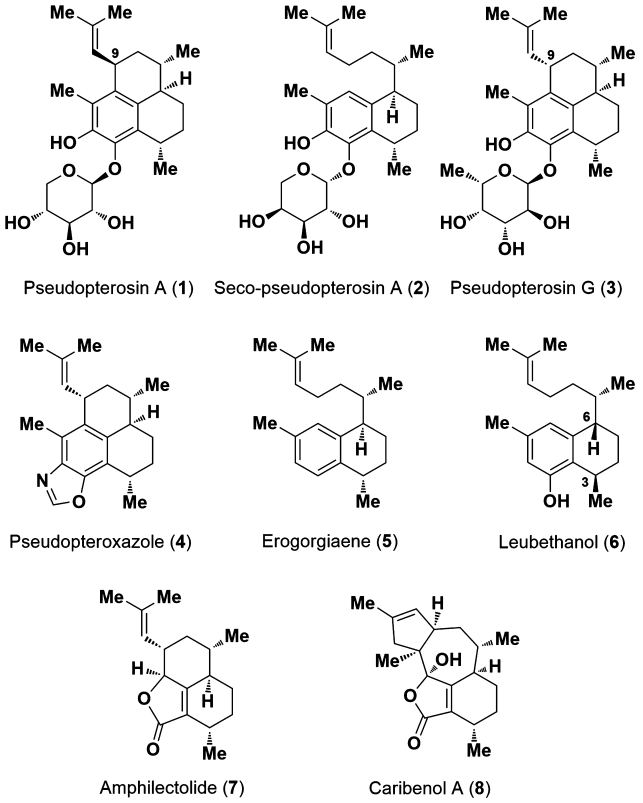

Figure 1. Representative amphilectane and serrulatane diterpenoids.

(**8**), two natural products biosynthetically related to amphilectanes, have also been reported to be active against *M. tuberculosis* $H_{37}R_v$.[15] The structure−activity relationship studies of pseudopteroxazole (**4**) and leubethanol (**6**) have been carried out using analogues obtained through semisynthesis, but the associated mechanism-of-action has yet been identified.[13b,16] Importantly, a number of antibiotic resistant strains do not exhibit cross-resistance to these amphilectane and serrulatane diterpenoids, suggesting the unique mechanism-of-action of this chemotype and the potential for drug development.[13b,14c,16c]

The chemical syntheses of various amphilectane and serrulatane diterpenoids have been intensively investigated, leading to the accomplishment of a variety of natural products within this family.[17−20] As a matter of fact, the total synthesis has significantly helped the structural revision of natural products, such as pseudopterosin G aglycone, pseudopteroxazole (**4**) and helioporins C−E.[18] However, probing the corresponding biological activity using the de novo synthesized natural products or analogues has been limited.

From the starting material point of view, monoterpene natural products and substituted benzenes have been widely used.[19] However, the available chiral monoterpenes limits the potential structural changes that could be made on the natural products, whereas amphilectane and serrulatane diterpenoids without the benzene ring, such as **7** and **8**, would be difficult to access from the aromatic starting materials. For the syntheses commencing from other starting materials, cycloaddition reactions especially Diels−Alder reactions have always been deployed to make the highly substituted six-membered rings within the targeted natural products.[20] A new strategy toward these promising diterpenoids, especially that is amenable to the collective total synthesis,[21] could not only complement to existing synthetic routes but also provide novel analogues and corresponding small-molecule probes for chemical biology studies.

RESULTS AND DISCUSSION

Retrosynthetic Design. Aiming for a modular and efficient synthesis, we postulated that the key intermediate **9**, if realized in a diastereoselective and enantioselective approach, would be converted to a number of the desired natural products (Figure 2). Challenged by the absence of traditional neighboring

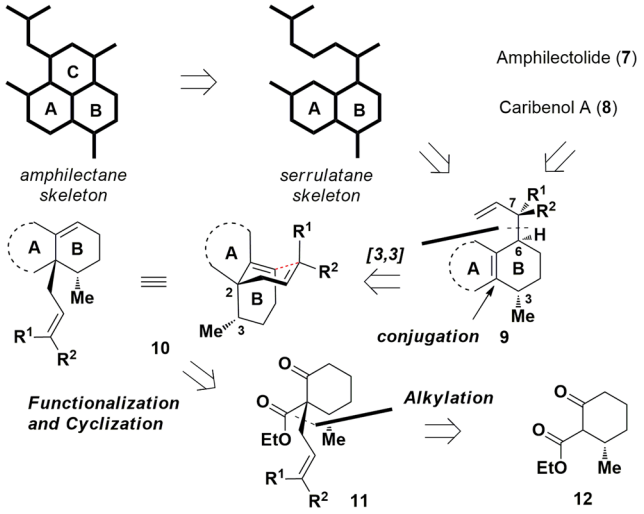

Figure 2. A unified retrosynthetic analysis of amphilectane and serrulatane diterpenoids.

controlling functionalities around C3, C6 and C7 stereogenic centers (pseudopterosin A numbering, throughout), we envisioned a stereocontrolled Cope rearrangement of **10** to transfer the desired chirality via a chairlike transition state. This transformation would introduce not only the vinyl moiety for subsequent manipulations, but also the double bond in the A ring that is tailored to the specific target. We believed the conversion of **10** to **9** could be readily achieved if appropriate thermodynamic driving force was provided. Bicyclic intermediate **10** could in turn be prepared from substituted cyclohexanone **11** by the formation of ring A, while the *trans* relationship of the methyl group and the alkene side chain could be readily established by alkylation of the corresponding *β*-ketoester **12**. Therefore, the preparation of enantiomerically pure **12** would be the starting point for the enantioselective total syntheses of amphilectane and serrulatane diterpenoids.

Synthesis of 7-*epi*-Erogorgiaene Based on A Gold-Catalyzed Cascade Reaction. To quickly evaluate our proposed strategy, in particular the feasibility of the Cope rearrangement, our first aim was to synthesize racemic 7-*epi*-erogorgiaene (Scheme 1, **20**). To this end, alkylation of known compound **12**[22] with (*E*)-crotyl bromide provided racemic **13** in 78% yield. Ketone **13** was then converted to corresponding enol triflate that underwent Sonogashira reaction with propyne to afford enyne **14**. A three-step sequence involving DIBAL reduction, Dess−Martin oxidation and Wittig reaction was followed to provide **15** in 75% overall yield. Subsequently, enyne **15** was subjected to the cationic gold catalyst to achieve the closure of ring A through alkyne activation. Gratifyingly, we found that 5 mol % $(PPh_3)AuNTf_2$ enabled a cascade reaction from **15** to give bicycle **19** in 57% yield as the only isolable

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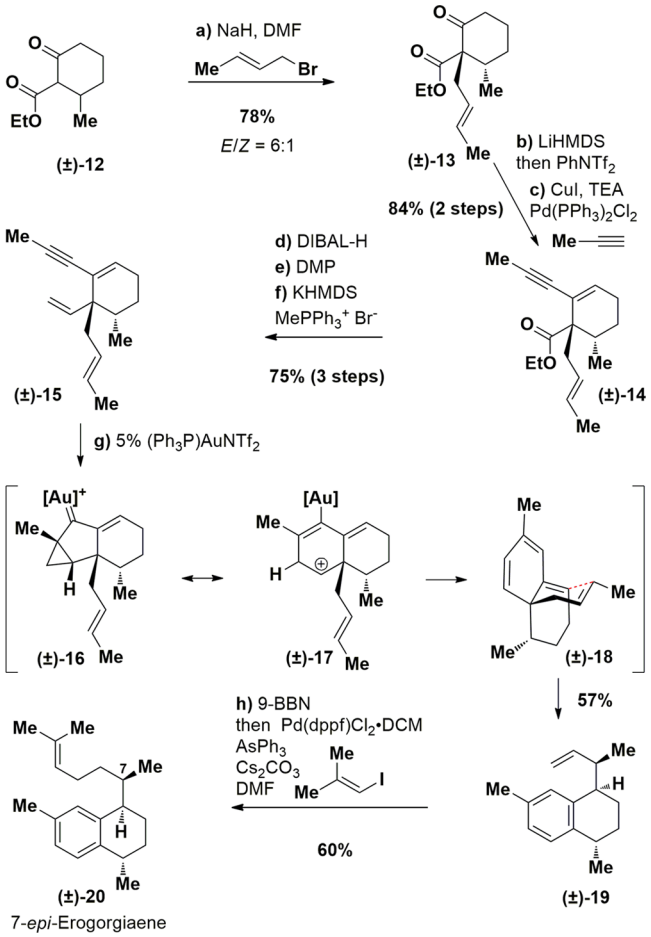
Scheme 1. Synthesis of 7-*epi*-Erogorgiaene (20)[a]

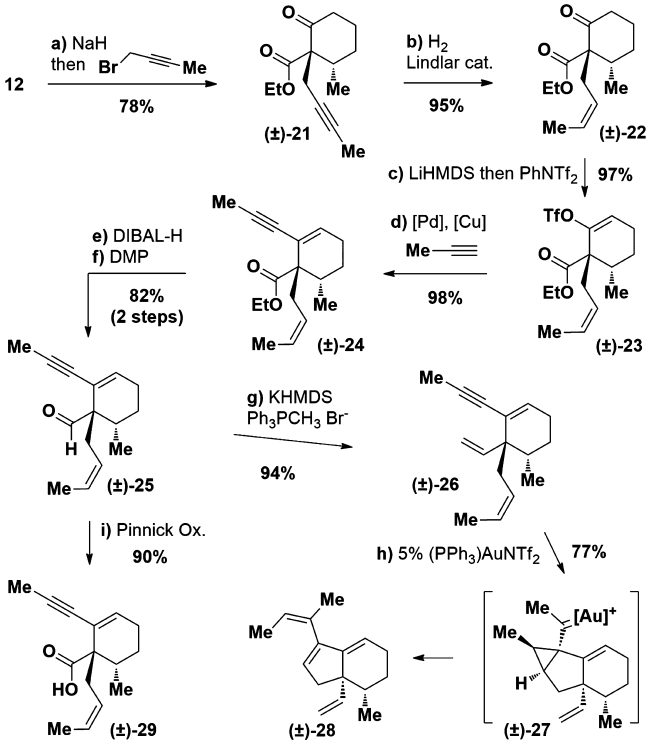


[a]Reagents and conditions: (a) NaH (1.1 equiv), crotyl bromide (1.1 equiv), DMF, 0 °C, 3 h, 78% (*E*/*Z* = 6:1); (b) LiHMDS (1.1 equiv), THF, −78 to 0 °C, 0.5 h; then $PhNTf_2$ (1.1 equiv), −78 to 25 °C, 3 h; (c) $Pd(PPh_3)_2Cl_2$ (0.1 equiv), CuI (0.05 equiv), Et_3N (3.0 equiv), propyne, DMF, 25 °C, 4 h, 84% (2 steps); (d) DIBAL-H (3.0 equiv), THF, −78 to 25 °C, 8 h; (e) DMP (1.04 equiv), pyridine (5.0 equiv), DCM, 0 °C, 4 h; (f) Ph_3PCH_3Br (1.7 equiv), KHDMS (1.7 equiv), THF, −78 to 25 °C, 1 h, 75% (3 steps); (g) $(PPh_3)AuNTf_2$ (0.05 equiv), DCE, 25 °C, 0.5 h, 57%; (h) 9-BBN dimer (2.0 equiv), THF, 25 °C, 3 h; $Pd(dppf)Cl_2$·DCM (0.1 equiv), $AsPh_3$ (0.1 equiv), Cs_2CO_3 (2.0 equiv), 1-iodo-2-methylprop-1-ene (1.5 equiv), H_2O (40.0 equiv), DMF, 40 °C, 12 h, 60%.

product, which furnished the desired skeleton in one step. We propose that the reaction mechanism begins with a 1,5-enyne cycloisomerization en route to **18** via cyclopropyl gold carbene **16** and its resonance structure **17**,[23] and the following reverse aromatic Cope rearrangement produces the final product **19**. Notably, the mild conditions of this Cope rearrangement suggest the involvement of the cationic gold complex as a catalyst. Subsequent hydroboration of **19** with 9-BBN followed by the palladium-catalyzed coupling with 1-iodo-2-methylprop-1-ene furnished 7-*epi*-erogorgiaene (**20**) in 60% yield over two steps. The ^1H NMR and ^{13}C NMR spectra of **20** prepared by us are identical to those reported by Aggarwal and co-workers.[19q]

The Effect of Olefin Geometry on the Gold-Catalyzed Cyclization. Encouraged by the discovery of the cascade reaction that converted **15** to **19**, we were eager to complete the total synthesis of erogorgiaene (**5**) by preparing enyne **26** with a (*Z*)-alkene side chain (Scheme 2). In this scenario, alkylation of **12** with 1-bromo-2-butyne afforded **21** in 78% yield with high diastereoselectivity (dr >19:1). *Cis*-selective alkyne hydrogenation was carried out in the presence of Lindlar catalyst to give **22**, after which installation of the triflate afforded **23** in 92% yield over two steps. Sonogashira reaction afforded **24** in 98% yield. Subsequent redox manipulation and Wittig reaction furnished racemic enyne **26**. However, in the presence of 5 mol % $(PPh_3)AuNTf_2$, enyne **26** intriguingly gave rise to 5,6-bicyclic compound **28** in 77% yield (see the Scheme S1 in Supporting Information for the unequivocal determination of the structure of **28**). A cursory inspection of the reaction mechanism leading to **28** suggests the facile formation of cyclopropyl gold carbene **27** via a 5-*exo*-dig cyclization in this scenario.[24] The observation that enynes **15** and **26**, a pair of configurational isomers, took different reaction pathways under the same reaction conditions could be rationalized by the higher reactivity of *cis*-alkene than *trans*-alkene. Our results not only demonstrate the subtlety and versatility of gold-catalyzed reactions, but also exemplify the conversion of stereochemical diversity to skeletal diversity.[25]

Scheme 2. Gold-Catalyzed Reaction of Enyne 26 Led to 6,5-Bicycle 28[a]



[a]Reagents and conditions: (a) NaH (1.1 equiv), 1-bromo-2-butyne (1.1 equiv), DMF, 0 °C, 3 h, 78%; (b) Lindlar cat. (0.5 equiv), toluene, 25 °C, 20 h, 95%; (c) LiHMDS (1.1 equiv), THF, −78 to 0 °C, 0.5 h; then $PhNTf_2$ (1.1 equiv), −78 to 25 °C, 97%; (d) $Pd(PPh_3)_2Cl_2$ (0.1 equiv), CuI (0.05 equiv), Et_3N (3.0 equiv), propyne, DMF, 25 °C, 4 h, 98%; (e) DIBAL-H (3.5 equiv), THF, −78 to 25 °C, 8 h; (f) DMP (1.06 equiv), pyridine (5.0 equiv), DCM, 0 °C, 4 h, 82% (2 steps); (g) Ph_3PCH_3Br (1.5 equiv), KHDMS (1.4 equiv), 94%; (h) $(PPh_3)AuNTf_2$ (0.05 equiv), DCE, 25 °C, 0.5 h, 77%; (i) $NaClO_2$ (2.0 equiv), $NaH_2PO_4·2H_2O$ (10.0 equiv), 2-Methyl-2-butene (30.0 equiv), H_2O:^{t}BuOH (1:8), 0 °C, 3 h, 90%.

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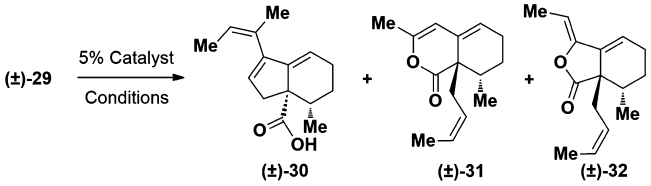
The Optimization of the 6-*endo*-dig Cyclization. The predominant 1,6-enyne cycloisomerization in the reaction pathway prompted us to switch our substrate to **29**, an acid prepared by the Pinnick oxidation of aldehyde **25**. We hypothesized that the aromatic A ring could be obtained from the α-pyrone framework and hence the 6-*endo*-dig cyclization of the acid to the alkyne was envisaged. However, as well as the formation of the 1,6-enyne cycloisomerization product (acid **30**), the potential formation of 5,6-bicyclic lactone **32** via a 5-*exo*-dig cyclization also had to be avoided. We screened various conditions to enable the selective formation of **31** (Table 1 and Table S1). Under the previous reaction conditions, **30** and **31** were obtained in a 1:1 ratio (entry 1), indicating the superior reactivity of the acid compared with the vinyl group. Another set of similar reaction conditions provided a consistent results (entry 2). When the reaction was carried out in the presence of AuCl, **31** and **32** were isolated in a 1:1 ratio, and the formation of **30** was totally inhibited (entry 3). Interestingly, conditions reported to favor 6-*endo*-dig cyclization in the system of *N*-propargyl carboxamides gave more 5-*exo*-dig cyclization product **32** in our scenario (entry 4).[26] Further optimization revealed that employment of triflate anion as the counterion of the cationic gold catalyst was the key for achieving the desired chemo- and regioselectivity (entry 5).[27] Eventually, in the presence of 5% (PPh_3)AuCl/AgOTf in refluxing DCM, the reaction proceeded smoothly to give **31** in 74% isolated yield as the predominant product (entry 6).

Table 1. Optimization of the 6-*endo*-dig Cyclization for the Synthesis of 31 from 29

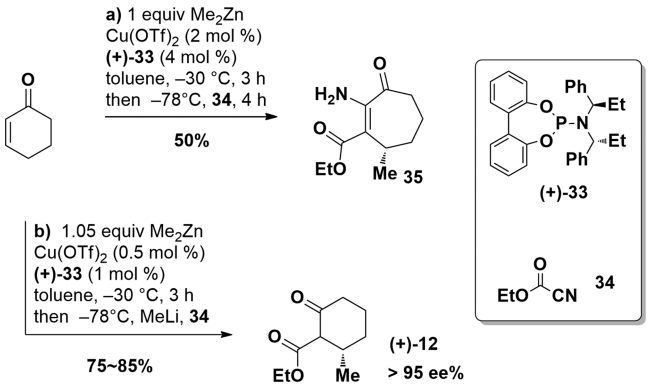


entry	catalyst	conditions[a]	yield[b] (%) 30	31	32
1	$(PPh_3)AuNTf_2$	DCE, RT, 60 min	22	22	–[c]
2	$(PPh_3)AuCl/AgNTf_2$	DCM, RT, 60 min	30	27	–[c]
3	AuCl	DCM, RT, 60 min	–	26	26
4	(IPr)AuCl/AgOTf	THF, RT, 60 min	–	22	55[d]
5	$(PPh_3)AuCl/AgOTf$	DCM, RT, 20 min	9	63	–[c]
6	$(PPh_3)AuCl/AgOTf$	DCM, reflux, 30 min	–[c]	74	–[c]

[a][29] = 0.01 M (0.1 mmol). [b]Isolated yield after flash chromatography. [c]Trace. [d]6 mol % Et_3N was added.

The Catalytic Asymmetric and Scalable Preparation of Chiral 12. With the optimal conditions for the 6-*endo*-dig cyclization in hand, we refocused on the enantioselective syntheses of the target diterpenoids, which necessitated the preparation of enantiopure **12** (Scheme 3). Even though the preparation of enantio-enriched **12** through a chemoenzymatic approach has been reported,[28] we decided to use a catalytic method to install the C3 stereogenic center using asymmetric copper-catalyzed conjugated addition[29] of dimethylzinc to cyclohexenone.[30] Given that trapping zinc enolates at the carbon terminus with alkyl or allyl electrophiles, Michael acceptors or halides has been documented,[31] we were curious about using Mander's reagent **34** in this scenario. Intriguingly, upon the addition of 1.1 equiv **34**, we only isolated the desired product **12** in trace amount and the major product was identified to be cycloheptenone **35**. On the basis of the proposed mechanism (Figure S2), we hypothesized that the zinc(II) species could function as a Lewis acid leading to the formation of **35**. Inspired by a report describing how dimethyl zinc could aid the *C*-acylation of lithium enolates,[32] we envisaged that the addition of 1 equiv methyllithium to the reaction mixture of zinc enolate might generate a similar lithium alkoxydialkylzincate species, which could undergo facile *C*-acylation. Gratifyingly, this modified procedure did afford (+)-**12** as the major product. Further optimization of the reaction revealed that with only 0.5 mol % $Cu(OTf)_2$ and 1 mol % ligand (+)-**33** in the first catalytic 1,4-addition step, (+)-**12** could be obtained in good yield with over 95% *ee* on a multigram scale. This modified procedure could be a useful method for the synthesis of chiral β-ketoesters from enones in one pot.

Scheme 3. Synthesis of Chiral 12[a]



[a]Reagents and conditions: (a) Me_2Zn (1.0 equiv), $Cu(OTf)_2$ (0.01 equiv), (+)-**33** (0.02 equiv), toluene, −30 °C, 3 h; then **34** (1.1 equiv), −78 °C, 3 h, 50%; (b) Me_2Zn (1.05 equiv), $Cu(OTf)_2$ (0.005 equiv), (+)-**33** (0.01 equiv), toluene, −30 °C, 3 h; MeLi (1.1 equiv), −78 °C, 0.5 h; then **34** (1.15 equiv), −78 to 25 °C, 8 h, 75−85%, *ee* ≥ 95%.

Synthesis of (+)-Erogorgiaene (5). With abundant chiral **12** in hand, we continued to complete the total synthesis of erogorgiaene (**5**) (Scheme 4). Chiral aldehyde **25** was obtained from (+)-**12** following the 6 steps described in Scheme 2. The clean Pinnick oxidation of **25** enabled the direct use of the resulting acid in the gold-catalyzed cyclization without flash chromatography, affording **31** in 63% yield on a gram-scale. Fortunately, after screening a number of gold catalysts, we found that 8 mol % $BINAP(AuCl)_2/AgNTf_2$ successfully promoted the stereoselective Cope rearrangement of **31** to produce α-pyrone **36** as a single diastereomer in 70% yield on a gram-scale. The elongation of the side chain was achieved by 9-BBN hydroboration followed by palladium-catalyzed Suzuki coupling to give **37**. By invoking a cascade involving the intermolecular Diels−Alder reaction of the α-pyrone and norbornadiene followed by elimination of CO_2 and cyclopentadiene,[33] (+)-erogorgiaene (**5**) was obtained from **37** in 75% yield under microwave irradiation conditions. The analytic data of **5** corresponded well with those in the literature.[14a]

Synthesis of the Aglycone of Seco-Pseudopterosin A by Optimizing an Annulation Reaction of α-Pyrone with Alkyl Phosphonate. The collective total synthesis of pseudopterosins necessitates the efficient conversion of the α-pyrone motif to a catechol, ideally in one step. We noticed two reported transformations, in which the anion of dimethyl

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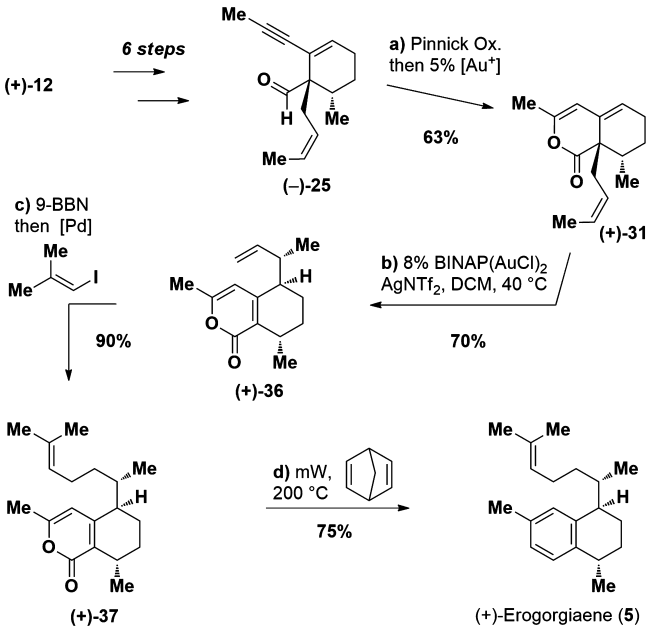
Scheme 4. Total Synthesis of (+)-Erogorgiaene (5)[a]

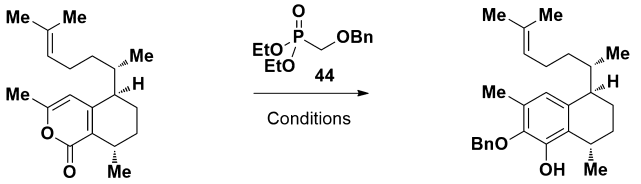


[a]Reagents and conditions: (a) $NaClO_2$ (2.0 equiv), $NaH_2PO_4{\cdot}2H_2O$ (10.0 equiv), 2-methyl-2-butene (30.0 equiv), H_2O: ^{t}BuOH (1:8), 0 °C, 3 h; then $(PPh_3)AuCl/AgOTf$ (0.05 equiv), DCM, 45 °C, 0.5 h, 63%; (b) $BINAP(AuCl)_2/AgNTf_2$ (0.08 equiv), DCM, 40 °C, 12 h, 70%; (c) 9-BBN (2.0 equiv), THF, 25 °C, 3 h; $Pd(dppf)Cl_2{\cdot}DCM$ (0.1 equiv), $AsPh_3$ (0.1 equiv), Cs_2CO_3 (2.0 equiv), 1-iodo-2-methylprop-1-ene (1.5 equiv), H_2O (40.0 equiv), DMF, 40 °C, 90%; (d) 2,5-norbornadiene (30 equiv), toluene, microwave, 200 °C, 75%.

methylphosphonate reacted with α-pyrone **38** and benzopyranone **40** to afford phenol **39** and naphthol **41** respectively (Figure 3, eq 1 and eq 2).[34] By employing the same phosphonate reagent, our substrate **37** was successfully converted to phenol **43** (eq 3), effectively completing the synthesis of 7-*epi*-leubethanol. Over 3 equiv dimethyl methylphosphonate and ^{n}BuLi were required to achieve the complete conversion of α-pyrone **37** and the corresponding phenol **43** was obtained in 79% isolated yield.

However, when we examined phosphonate **44**[35] under the same reaction conditions, only decomposition was observed (Table 2, entry 1). Switching the base to LDA also led to decomposition (entry 2), but the desired product **45** was afforded in 15% yield if the reaction temperature was lowered to −100 °C (entry 3). By changing the solvent from THF to Et_2O, we were able to further lower the reaction temperature, which gave rise to the aglycone of seco-pseudopterosin A **45** in synthetically useful yield (66% based on starting material recovery, entry 4).

Table 2. Optimization of the Annulation Reaction for the Synthesis of Seco-Pseudopterosin A Aglycone 45



entry	conditions[a]	yield[b] (%)
1	3.5 equiv ^{n}BuLi, THF, −78 °C	0
2	3.5 equiv LDA, THF, −78 °C	0
3	3.5 equiv LDA, THF, −100 °C	15
4	3.5 equiv LDA, Et_2O, −116 °C	50[c]

[a][37] = 0.1 M (0.04 mmol), 4 equiv **44**, after reacting under low temperature, the reaction mixture was allowed to warm slowly to room temperature. [b]Isolated yield after column chromatography. [c]Starting material **37** was recovered in 24% yield.

Syntheses of (+)-Pseudopteroxazole (4) and (−)-Pseudopterosin A (1). As the key intermediate in our collective total synthesis, α-pyrone **36** underwent a regioselective intermolecular Heck reaction[36] to afford diene **46** in 88% yield with an *E*/*Z* ratio >19:1 (Scheme 5). Treatment of **46** with methanesulfonic acid provided a separable pair of diastereomers **47** and **48** in 41% and 45% yield, respectively. The annulation reaction of α-pyrone **47** and **44** produced pseudopterosins G–J aglycone **49** in 64% yield (82% based on starting material recovery), while we found the addition of excess 2,5-norbornadiene was beneficial in this scenario. Alternatively, converting **46** to the catechol followed by treatment with methanesulfonic acid also provided **49** but as a 10:1 diastereomeric mixture at C9 in 62% overall yield. The preference for the *S* configuration at C9 in this scenario was consistent with an analogous result reported by the Kerr group.[37] Deprotection of the benzyl ether followed by a published procedure[16a] converted **49** to (+)-pseudopteroxazole (**4**) in 43% yield.

Similarly, the annulation reaction of α-pyrone **48** and **44** produced pseudopterosin A–F aglycone **50** in 56% yield (80% based on starting material recovery, Scheme 6). Eventually, glycosylation of **50** followed by deprotection was achieved by executing the reported procedures to afford the anti-inflammatory natural product, (−)-pseudopterosins A (**1**).[19a] The analytic data of **4** and **1** corresponded well with those in the literature.[14b,19a]

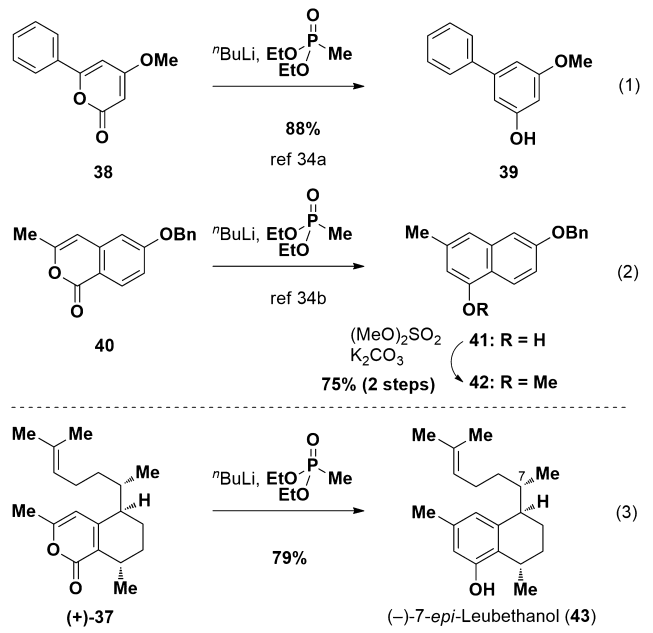


Figure 3. Annulation cascades converting α-pyrones to phenols.

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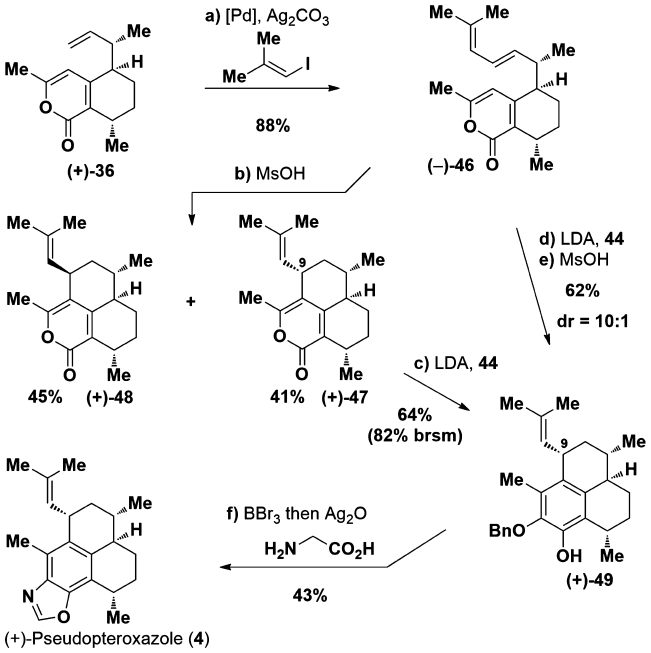
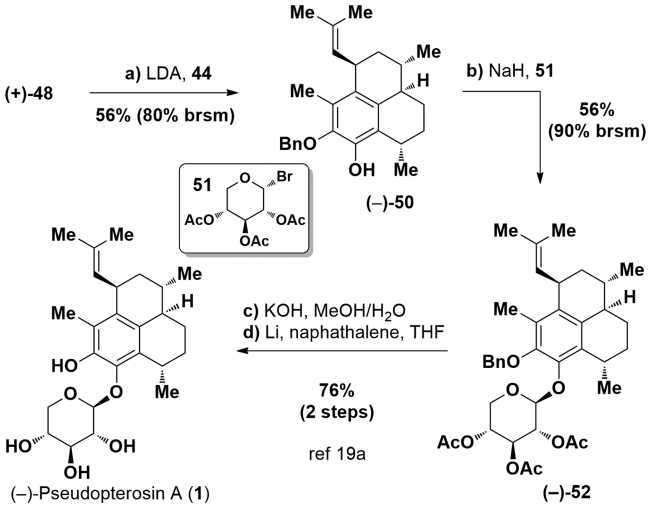
Scheme 5. Total Synthesis of (+)-Pseudopteroxazole (4)[a]



[a]Reagents and conditions: (a) $Pd(OAc)_2$ (0.1 equiv), 1-iodo-2-methylprop-1-ene (1.5 equiv), Ag_2CO_3 (1.1 equiv), DMF, 60 °C, 12 h, 88%; (b) methanesulfonic acid (3.0 equiv), DCM, 0 to 25 °C, 12 h; **47**, 41%; **48**, 45%; (c) **44** (3.5 equiv), LDA (3.0 equiv), 2,5-norbornadiene (25 equiv), Et_2O, −116 °C, 20 min; then **47**, −116 °C, 3 h; −116 to 25 °C, 12 h, 64%, 82% brsm; (d) **44** (3.5 equiv), LDA (3.0 equiv), 2,5-norbornadiene (25 equiv), Et_2O, −116 °C, 20 min; then **46**, −116 °C, 3 h; −116 to 25 °C, 12 h; (e) methanesulfonic acid (3.0 equiv), DCM, −35 °C, 12 h, 62% over two steps (dr = 10:1); (f) BBr_3 (1.5 equiv), DCM, 0 °C, 15 min; Ag_2O (1.4 equiv), glycine (12.0 equiv), MeOH, 65 °C, 18 h, 43%.

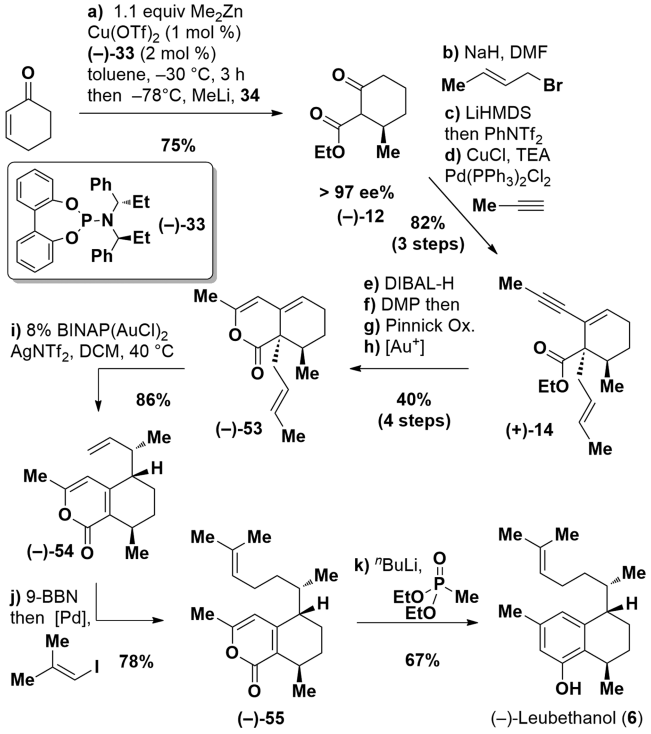
Scheme 6. Total Synthesis of (−)-Pseudopterosin A (1)[a]



[a]Reagents and conditions: (a) **44** (2.5 equiv), LDA (2.0 equiv), 2,5-norbornadiene (25 equiv), Et_2O, −116 °C, 20 min; then **48**, −116 °C, 3 h; −116 to 25 °C, 12 h, 56%, 80% brsm; (b) NaH (1.6 equiv), **51** (2.2 equiv), MeCN, 25 °C, 5 h, 56%, 90% brsm; (c) KOH (6.0 equiv), H_2O:MeOH (1:10), 25 °C, 1 h; (d) Li/naphthalene (1.5 equiv), THF, −78 °C, 0.5 h, 76% (2 steps).

Synthesis of (−)-Leubethanol (6). The synthetic strategy we developed is applicable to not only natural products isolated from *P. elisabethae*, but also diterpenoids with different stereochemical elements, such as leubethanol (**6**).[14c] To illustrate this point, we first used chiral ligand (−)-**33** to prepare (−)-**12** with excellent enantiopurity (Scheme 7). It is

Scheme 7. Total Synthesis of (−)-Leubethanol (6)[a]



[a]Reagents and conditions: (a) Me_2Zn (1.05 equiv), $Cu(OTf)_2$ (0.01 equiv), (−)-**33** (0.02 equiv), toluene, −30 °C, 3 h; MeLi (1.1 equiv), −78 °C, 0.5 h; then **34** (1.15 equiv), −78 to 25 °C, 8 h, 75%, *ee* ≥ 97%; (b) NaH (1.1 equiv), crotyl bromide (1.1 equiv), DMF, 0 °C, 3 h; (c) LiHMDS (1.1 equiv), THF, −78 to 0 °C, 0.5 h; then $PhNTf_2$ (1.1 equiv), −78 to 25 °C, 3 h; (d) $Pd(PPh_3)_2Cl_2$ (0.1 equiv), CuI (0.05 equiv), Et_3N (3.0 equiv), propyne, DMF, 25 °C, 4 h, 82% (3 steps); (e) DIBAL-H (3.0 equiv), THF, −78 to 25 °C, 8 h; (f) DMP (1.04 equiv), pyridine (5.0 equiv), DCM, 0 °C, 4 h; (g) $NaClO_2$ (2.0 equiv), $NaH_2PO_4{\cdot}2H_2O$ (10.0 equiv), 2-methyl-2-butene (30.0 equiv), H_2O: ^{t}BuOH (1:8), 0 °C, 3 h, 57% (3 steps); (h) $(PPh_3)AuCl/AgOTf$ (0.05 equiv), DCM, 45 °C, 0.5 h, 70%; (i) $BINAP(AuCl)_2/AgNTf_2$ (0.08 equiv), DCM, 40 °C, 12 h, 86%; (j) 9-BBN dimer (2.0 equiv), THF, 25 °C, 3 h; $Pd(dppf)Cl_2{\cdot}DCM$ (0.1 equiv), $AsPh_3$ (0.1 equiv), Cs_2CO_3 (2.0 equiv), 1-iodo-2-methylprop-1-ene (1.5 equiv), H_2O (40.0 equiv), DMF, 40 °C, 12 h, 78%; (k) *n*-BuLi (3.0 equiv), dimethyl methylphosphonate (3.5 equiv), THF, −78 °C, 3 h, 67%.

noteworthy that (−)-**12** could be used to synthesize the aglycone of pseudopterosins K−L[38] following our established route (Schemes 4, 5 and 6). The same three-step sequence as shown in Scheme 1, involving crotylation of (−)-**12**, installation of the triflate and Sonogashira reaction afforded (+)-**14** in 82% yield over 3 steps. Subsequent redox manipulation followed by gold-catalyzed cyclization provided **53** successfully. The gold-catalyzed Cope rearrangement proceeded smoothly to give *α*-pyrone **54** in 86% yield. Finally, hydroboration of **54** with 9-BBN followed by the palladium-catalyzed coupling and annulation with dimethyl methylphosphonate furnished (−)-leubethanol (**6**) in 52% yield over two steps. The spectroscopic data of the synthesized samples of **6** were in good agreement with those in the literature.[14c,19t]

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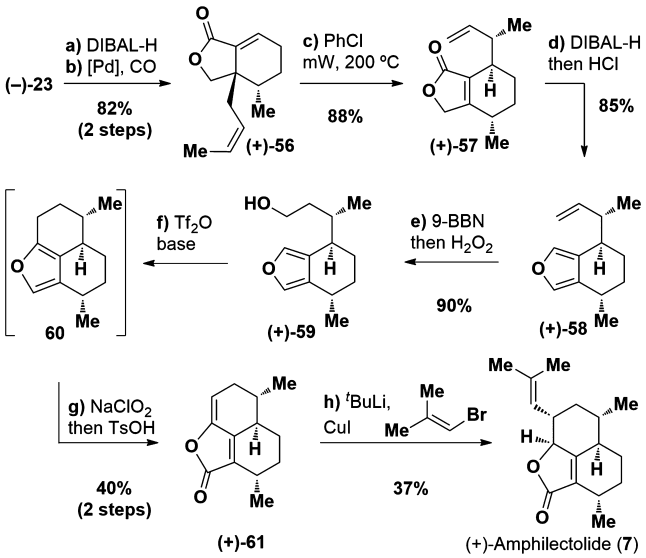
To our knowledge, the Cope rearrangement catalyzed by cationic gold(I) complexes under mild reaction conditions only applies to substrates containing the strained methylenecyclopropane.[3] The gold-catalyzed Cope rearrangement driven by the construction of benzene or α-pyrone ring system in our synthesis is an unique addition to existing methodologies, which suggests the scope of corresponding transformation could be further expanded by deliberated designs.

Syntheses of (+)-Amphilectolide (7) and (+)-Caribenol A (8). Encouraged by the completion of amphilectane and serrulatane diterpenoids with a phenyl A ring, we were intrigued by the possibility to prepare amphilectolide (7) and caribenol A (8) without the substituted aromatic ring. Trauner and co-workers have elegantly used a furan building block in the first total syntheses of amphilectolide (7) and sandresolide B, another diterpenoid also isolated from *Pseudopterogorgia elisabethae*.[19u] We therefore envisaged a similar intermediate, furan **58**, to efficiently construct both our targeting natural products. To this end, the ester of triflate (−)-**23** was first reduced to a hydroxymethyl group, which was followed by Pd-catalyzed intramolecular carbonylative cyclization to afford **56** (Scheme 8).[39] The stage was set for the key Cope rearrangement of **56** to **57**. Various gold catalysts were screened but failed to catalyze the desired transformation in this scenario. We eventually found microwave irradiation conditions successfully provided butenolide **57** as a single diastereomer in 88% yield. In order to realize the subsequent annulations, **57** was first converted to furan **58** via DIBAL-H reduction and aromatization. The following hydroboration of olefin **58** and oxidation afforded alcohol **59** in 90% yield. Compound **59** was subjected to the treatment of triflate anhydride and 2,6-lutidine to effect the cyclization to give tricycle **60**,[40] which was followed by oxidation and elimination under acid conditions to afford **61** in 40% yield over 2 steps. Natural product (+)-amphilectolide (7) was obtained by the 1,6-conjugative addition of the in situ generated isobutenyl cuprate reagent to **61**.

Scheme 8. Total Synthesis of (+)-Amphilectolide (7)[a]



[a]Reagents and conditions: (a) DIBAL-H (2.7 equiv), DCM; (b) $Pd(OAc)_2$ (0.15 equiv), PPh_3 (0.3 equiv), Et_3N (3.0 equiv), MeOH (50.0 equiv), DMF, 82% (2 steps); (c) PhCl, microwave, 200 °C, 88%; (d) DIBAL-H (1.2 equiv), toluene; then HCl, 85%; (e) 9-BBN dimer (2.0 equiv), THF; then H_2O_2 (6.0 equiv), EtOH, NaOH(aq), 90%; (f) Tf_2O (1.1 equiv), DCM, 2,6-lutidine (2.5 equiv); (g) $NaClO_2$ (3.0 equiv), $NaH_2PO_4{\cdot}2H_2O$ (1.5 equiv), *t*-BuOH, H_2O; then $TsOH{\cdot}H_2O$ (2.0 equiv), benzene, 40% (2 steps); (h) 1-bromo-2-methylpropene (4.0 equiv), *t*-BuLi (8.0 equiv), CuI (2.0 equiv), Et_2O, 37%.

Intrigued by the excellent diastereoselectivity of the Cope rearrangement of **56**, we performed preliminary density functional theory (DFT) calculations using the M06-2X functional (Figure 4).[41] Both the chair- and boat-like Cope rearrangement transition states TS1 and TS2, leading to **57** and its epimer **57′** respectively, were located. DFT calculations indicated that TS1 is favored over TS2 by 10.8 kcal/mol, suggesting that **57** should be formed exclusively, which is in good agreement of the experimentally observed diastereoselectivity.[42] Moreover, the activation Gibbs free energy of the Cope rearrangement via the chairlike transition state TS1 is 36.1 kcal/mol, which is also in good accordance with the high reaction temperature (200 °C) employed. The significantly exothermic nature of this Cope rearrangement (5.9 kcal/mol) is also revealed by the calculation, resulting in **57** that is thermodynamically more stable than **56**.

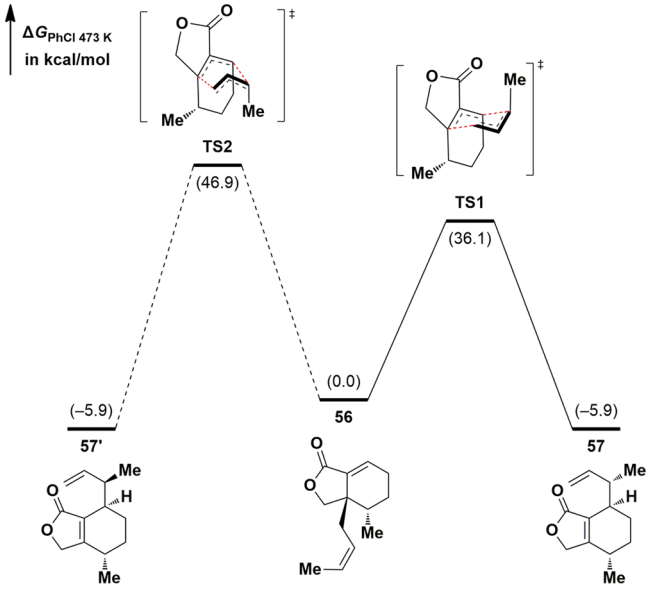


Figure 4. Free-energy profile of the Cope rearrangement.

Finally, we turned our attention to the total synthesis of caribenol A (8) (Scheme 9). Furan **58** underwent 9-BBN hydroboration followed by Pd-catalyzed Suzuki coupling with iodide **62** to furnish enone **63** in 82% yield. We were delighted to find an intramolecular Michael addition catalyzed by $AuCl_3$[43] delivered tricyclic compound **65** in 85% yield with 10:1 diastereoselectivity at C15 favoring the desired diastereomer.[44] The high diastereoselectivity could be rationalized by invoking the chairlike transition state **64**, whereas it invites further investigation to determine whether the C−H activation was involved. By exposing **65** to lithio-TMS-diazomethane, an alkylidene carbene-mediated 1,5-CH insertion[45] was achieved presumably via intermediate **66**, and tetracycle **67** was isolated in 37% yield as a pair of inseparable diastereomer (C9, α-H:β-H = 3:1) from the reaction mixture. Selective oxidation of the furan ring in **67** by $NaClO_2$ ultimately resulted in (+)-caribenol A (8). The analytic data of the synthesized samples of natural

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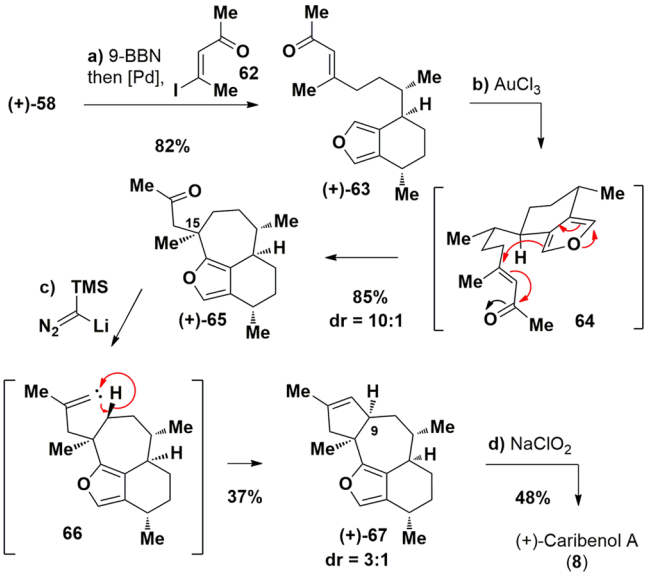
Scheme 9. Total Synthesis of (+)-Caribenol A (8)[a]



[a]Reagents and conditions: (a) 9-BBN dimer (2.0 equiv), THF, 40 °C, 3 h; $Pd(dppf)Cl_2$·DCM (0.1 equiv), $AsPh_3$ (0.1 equiv), Cs_2CO_3 (5.0 equiv), **62** (1.2 equiv), H_2O (40.0 equiv), DMF, 45 °C, 5 h, 82%; (b) $AuCl_3$ (0.1 equiv), DCM, −20 °C, 10 h, 85% (dr = 10:1); (c) $TMSCHN_2$ (4.0 equiv), *n*-BuLi (3.0 equiv), DME, −56 to 25 °C over 5 h, 37% (dr = 3:1); (d) $NaClO_2$ (3.2 equiv), $NaH_2PO_4·2H_2O$ (2.0 equiv), 2-methyl-2-butene (10.0 equiv), H_2O:*t*-BuOH (1:5), 25 °C, 10 h, 48%.

products **7** and **8** corresponded well with those in the literature.[15,19u,20a]

CONCLUSION

In summary, we have developed an efficient and modular synthesis to accomplish, in an enantioselective manner, pseudopterosin A (**1**), pseudopteroxazole (**4**), erogorgiaene (**5**), seco-pseudopterosin A aglycone (**45**), pseudopterosin G–J aglycone (**49**), amphilectolide (**7**) and caribenol A (**8**) within 32 transformations starting from cyclohexenone (Figure 5). In addition, (−)-leubethanol (**6**) was separately synthesized in 11 steps based on the same strategy. Even if the step count of our synthesis toward a particular target might not be the shortest—for instance, Sherburn and co-workers reported an impressive 11-step synthesis of the aglycone of *ent*-pseudopterosin G-J[20c]—we took full advantage of the power of collective total synthesis to maximize the number of bioactive natural products that could be provided by our approaches.

Besides the gold-catalyzed chemo- and regioselective cyclization and Cope rearrangement, the salient features of our synthesis include a modified procedure to prepare chiral *β*-ketoesters from enones and the use of *α*-pyrone as a masked benzene ring. More importantly, our route offers great flexibility to allow deep-seated structural changes of the interested natural products and enables the design and preparation of small-molecule probes for identifying corresponding biochemical targets, which is underway and will be reported in due course.

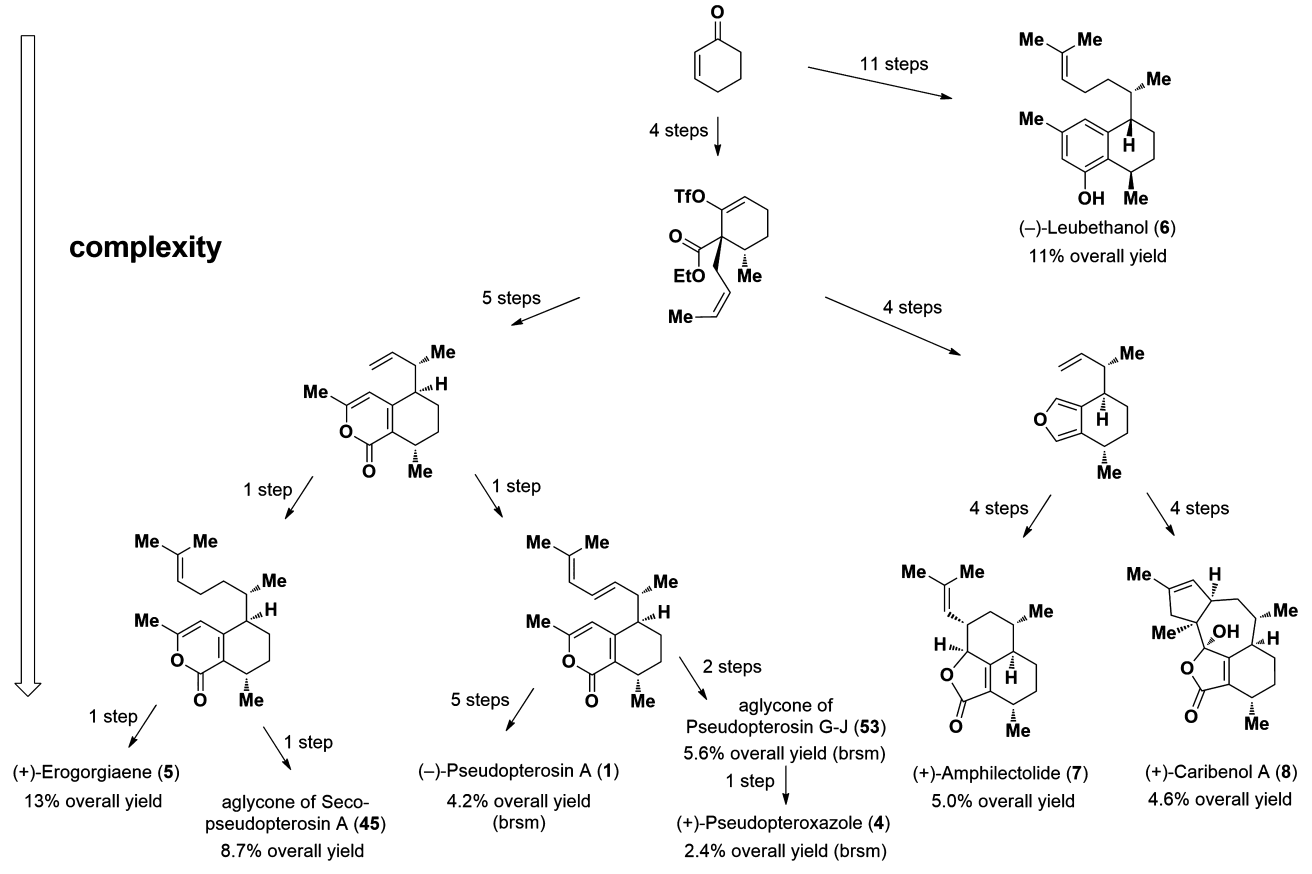


Figure 5. Summary of the natural products prepared.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b02624.

Detailed experimental procedures and compound characterization data. (PDF)

Crystal data for **S7**. (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews of the Cope rearrangement, see: (a) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205−247. (b) Paquette, L. A. *Angew. Chem.* **1990**, *102*, 642−660; *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 609−626. (c) Ilardi, E. A.; Stivala, C. E.; Zakarian, A. *Chem. Soc. Rev.* **2009**, *38*, 3133−3148. (d) Jones, A. C.; May, J. A.; Sarpong, R.; Stoltz, B. M. *Angew. Chem.* **2014**, *126*, 2590−2628; *Angew. Chem., Int. Ed.* **2014**, *53*, 2556−2591.

(2) For recent application of the Cope rearrangement in the organic synthesis of natural products, see: (a) Malachowski, W. P.; Paul, T.; Phounsavath, S. *J. Org. Chem.* **2007**, *72*, 6792−6796. (b) Arns, S.; Lebrun, M.-E.; Grisé, C. M.; Denissova, I.; Barriault, L. *J. Org. Chem.* **2007**, *72*, 9314−9322. (c) Li, F.; Tartakoff, S. S.; Castle, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 6674−6675. (d) Lian, Y.; Miller, L. C.; Born, S.; Sarpong, R.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 12422−12425. (e) Hu, D. X.; Clift, M. D.; Lazarski, K. E.; Thomson, R. J. *J. Am. Chem. Soc.* **2011**, *133*, 1799−1804. (f) Jeker, O. F.; Carreira, E. M. *Angew. Chem.* **2012**, *124*, 3531−3534; *Angew. Chem., Int. Ed.* **2012**, *51*, 3474−3477. (g) Chou, Y.-Y.; Liao, C.-C. *Org. Lett.* **2013**, *15*, 1584−1587. (h) Thandavamurthy, K.; Sharma, D.; Porwal, S. K.; Ray, D.; Viswanathan, R. *J. Org. Chem.* **2014**, *79*, 10049−10067. (i) Plummer, C. W.; Wei, C. S.; Yozwiak, C. E.; Soheili, A.; Smithback, S. O.; Leighton, J. L. *J. Am. Chem. Soc.* **2014**, *136*, 9878−9881. (j) Anagnostaki, E. E.; Demertzidou, V. P.; Zografos, A. L. *Chem. Commun.* **2015**, *51*, 2364−2367.

(3) (a) Felix, R. J.; Weber, D.; Gutierrez, O.; Tantillo, D. J.; Gagné, M. R. *Nat. Chem.* **2012**, *4*, 405−409. (b) Felix, R. J.; Gutierrez, O.; Tantillo, D. J.; Gagné, M. R. *J. Org. Chem.* **2013**, *78*, 5685−5690.

(4) (a) Morion, N.; Gealageas, R.; Nolan, S. P. *Org. Lett.* **2007**, *9*, 2653−2656. (b) Gourlaouen, C.; Marion, N.; Nolan, S. P.; Maseras, F. *Org. Lett.* **2009**, *11*, 81−84. (c) Xing, D.; Yang, D. *Org. Lett.* **2010**, *12*, 1068−1071. (d) Phillips, N.; Tirfoin, R.; Aldridge, S. *Chem. - Eur. J.* **2014**, *20*, 3825−3830.

(5) Cope, A. C.; Hardy, E. M. *J. Am. Chem. Soc.* **1940**, *62*, 441−444.

(6) (a) Miller, B. *J. Am. Chem. Soc.* **1965**, *87*, 5115−5120. (b) Bramley, R. K.; Grigg, R. *J. Chem. Soc. D* **1969**, 99b−100. (c) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1997**, *62*, 7950−7960. (d) Kawasaki, T.; Nonaka, Y.; Watanabe, K.; Ogawa, A.; Higuchi, K.; Terashima, R.; Masuda, K.; Sakamoto, M. *J. Org. Chem.* **2001**, *66*, 1200−1204. (e) Babinski, D. J.; Bao, X.; El Arba, M.; Chen, B.; Hrovat, D. A.; Borden, W. T.; Frantz, D. E. *J. Am. Chem. Soc.* **2012**, *134*, 16139−16142.

(7) (a) Look, S. A.; Fenical, W.; Jacobs, R. S.; Clardy, J. *Proc. Natl. Acad. Sci. U. S. A.* **1986**, *83*, 6238−6240. (b) Look, S. A.; Fenical, W.; Matsumoto, G. K.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 5140−5145. (c) Heckrodt, T. J.; Mulzer, J. *Top. Curr. Chem.* **2005**, *244*, 1−41.

(8) (a) Kijjoa, A.; Sawangwong, P. *Mar. Drugs* **2004**, *2*, 73−82. (b) Haimes, H.; Glasson, S.; Harlan, P.; Jacobs, R.; Fenical, W.; Jiménez, P. A. *Inflamm. Res.* **1995**, *44* (Suppl. 3), W13/17. (c) Day, D.; Jabaiah, S.; Jacobs, R.; Little, R. D. *Mar. Drugs* **2013**, *11*, 3258−3271.

(9) (a) Tanis, V. M.; Moya, C.; Jacobs, R. S.; Little, R. D. *Tetrahedron* **2008**, *64*, 10649−10663. (b) Flachsmann, F.; Schellhaas, K.; Moya, C. E.; Jacobs, R. S.; Fenical, W. *Bioorg. Med. Chem.* **2010**, *18*, 8324−8333.

(10) For pharmacological studies of pseudopterosins, see: (a) Zhong, W.; Moya, C.; Jacobs, R. S.; Little, R. D. *J. Org. Chem.* **2008**, *73*, 7011−7016. (b) Mayer, A. M. S.; Jacobson, P. B.; Fenical, W.; Jacobs, R. S.; Glaser, K. B. *Life Sci.* **1998**, *62*, PL401−PL407. (c) Zhong, W.; Little, R. D. *Tetrahedron* **2009**, *65*, 10784−10790. (d) Moya, C. E.; Jacobs, R. S. *Comp. Biochem. Physiol., Part C: Toxicol. Pharmacol.* **2006**, *143*, 436−443.

(11) Look, S. A.; Fenical, W. *Tetrahedron* **1987**, *43*, 3363−3370.

(12) Ata, A.; Win, H. Y.; Holt, D.; Holloway, P.; Segstro, E. P.; Jayatilake, G. S. *Helv. Chim. Acta* **2004**, *87*, 1090−1098.

(13) (a) Correa, H.; Aristizabal, F.; Duque, C.; Kerr, R. *Mar. Drugs* **2011**, *9*, 334−344. (b) McCulloch, M. W. B.; Haltli, B.; Marchbank, D. H.; Kerr, R. G. *Mar. Drugs* **2012**, *10*, 1711−1728.

(14) (a) Rodríguez, A. D.; Ramírez, C. *J. Nat. Prod.* **2001**, *64*, 100−102. (b) Rodríguez, A. D.; Ramírez, C.; Rodríguez, I. I.; González, E. *Org. Lett.* **1999**, *1*, 527−530. (c) Molina-Salinas, G. M.; Rivas-Galindo, V. M.; Said-Fernandez, S.; Lankin, D. C.; Munoz, M. A.; Joseph-Nathan, P.; Pauli, G. F. *J. Nat. Prod.* **2011**, *74*, 1842−1850.

(15) (a) Rodriguez, A. D.; Ramirez, C.; Medina, V.; Shi, Y. P. *Tetrahedron Lett.* **2000**, *41*, 5177−5180. (b) Wei, X.; Rodriguez, I. I.; Rodriguez, A. D.; Barnes, C. L. *J. Org. Chem.* **2007**, *72*, 7386−7389.

(16) (a) McCulloch, M. W. B.; Berrue, F.; Haltli, B.; Kerr, R. G. *J. Nat. Prod.* **2011**, *74*, 2250−2256. (b) Perez-Meseguer, J.; del Olmo, E.; Alanis-Garza, B.; Escarcena, R.; Garza-González, E.; Salazar-Aranda, R.; San Feliciano, A.; Waksman de Torres, N. *Bioorg. Med. Chem.* **2010**, *20*, 4155−4163. (c) Escarcena, R.; Perez-Meseguer, J.; del Olmo, E.; Alanis-Garza, B.; Garza-González, E.; Salazar-Aranda, R.; Waksman de Torres, N. *Molecules* **2015**, *20*, 7245−7262.

(17) For a recent review on the total synthesis of the pseudopterosin aglycones see: Newton, C. G.; Sherburn, M. S. *Nat. Prod. Rep.* **2015**, *32*, 865−876.

(18) (a) Geller, T.; Jakupovic, J.; Schmalz, H.-G. *Tetrahedron Lett.* **1998**, *39*, 1541−1544. (b) Hörstermann, D.; Kociok-Köhn, G.; Schmalz, H.-G. *Tetrahedron* **1999**, *55*, 6905−6916. (c) Johnson, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2001**, *123*, 4475−4479. (d) Davidson, J. P.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 13486−13489.

(19) (a) Broka, C. A.; Chan, S.; Peterson, B. *J. Org. Chem.* **1988**, *53*, 1584−1586. (b) Corey, E. J.; Carpino, P. *J. Am. Chem. Soc.* **1989**, *111*, 5472−5474. (c) McCombie, S. W.; Cox, B.; Lin, S.-I.; Ganguly, A. K.; McPhail, A. T. *Tetrahedron Lett.* **1991**, *32*, 2083−2086. (d) Buszek, K. R.; Bixby, D. L. *Tetrahedron Lett.* **1995**, *36*, 9129−9132. (e) Majdalani, A.; Schmalz, H.-G. *Synlett* **1997**, *1997*, 1303−1305. (f) Corey, E. J.; Lazerwith, S. E. *J. Am. Chem. Soc.* **1998**, *120*, 12777−12782. (g) Kocienski, P. J.; Pontiroli, A.; Qun, L. *J. Chem. Soc. Perkin, Trans. 1* **2001**, 2356−2366. (h) Horrowven, D. C.; Tyte, M. J. *Tetrahedron Lett.* **2004**, *45*, 2089−2091. (i) Cesati, R. R., III; de Armas, J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 96−101. (j) Harmata, M.; Hong, X. *Org. Lett.* **2005**, *7*, 3581−3583. (k) Davies, H. M. L.; Walji, A. M. *Angew. Chem.* **2005**, *117*, 1761−1763; *Angew. Chem., Int. Ed.* **2005**, *44*, 1733−1735. (l) Yadav, J. S.; Basak, A. K.; Srihari, P.

DOI: 10.1021/jacs.6b02624
J. Am. Chem. Soc. 2016, 138, 6261−6270

Tetrahedron Lett. **2007**, *48*, 2841−2843. (m) Dai, X.; Wan, Z.; Kerr, R. G.; Davies, H. M. L. *J. Org. Chem.* **2007**, *72*, 1895−1900. (n) Harmata, M.; Hong, X.; Schreiner, P. R. *J. Org. Chem.* **2008**, *73*, 1290−1296. (o) Harmata, M.; Cai, Z.; Chen, Y. *J. Org. Chem.* **2009**, *74*, 5559−5561. (p) Mans, D. J.; Cox, G. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2011**, *133*, 5776−5779. (q) Elford, T. G.; Nave, S.; Sonawane, R. P.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2011**, *133*, 16798−16801. (r) Lölsberg, W.; Werle, S.; Neudörfl, J.-M.; Schmalz, H.-G. *Org. Lett.* **2012**, *14*, 5996−5999. (s) Cooksey, J. P.; Kocieński, P. J.; Schmidt, A. W.; Snaddon, T. N.; Kilner, C. A. *Synthesis* **2012**, *44*, 2779−2785. (t) Lu, J. M.H.; Perkins, M. V.; Griesser, H. J. *Tetrahedron* **2013**, *69*, 6468−6473. (u) Chen, I. T.; Baitinger, I.; Schreyer, L.; Trauner, D. *Org. Lett.* **2014**, *16*, 166−169. (v) O'Hora, P. S.; Incerti-Pradillos, C. A.; Kabeshov, M. A.; Shipilovskikh, S. A.; Rubtsov, A. E.; Elsegood, M. R. J.; Malkov, A. V. *Chem. - Eur. J.* **2015**, *21*, 4551−4555. (w) Yang, M.; Yang, X.; Sun, H.; Li, A. *Angew. Chem.* **2016**, *128*, 2901−2905; *Angew. Chem., Int. Ed.* **2016**, *55*, 2851−2855.

(20) (a) Liu, L.-Z.; Han, J.-C.; Yue, G.-Z.; Li, C.-C.; Yang, Z. *J. Am. Chem. Soc.* **2010**, *132*, 13608−13609. (b) Williams, D. R.; Shah, A. A. *J. Am. Chem. Soc.* **2014**, *136*, 8829−8836. (c) Newton, C. G.; Drew, S. L.; Lawrence, A. L.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. *Nat. Chem.* **2015**, *7*, 82−86.

(21) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183−188.

(22) Bunce, R. A.; Harris, C. R. *J. Org. Chem.* **1992**, *57*, 6981−6985.

(23) (a) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858−10859. (b) Grisé, C. M.; Barriault, L. *Org. Lett.* **2006**, *8*, 5905−5908. (c) López-Carrillo, V.; Huguet, N.; Mosquera, Á.; Echavarren, A. M. *Chem. - Eur. J.* **2011**, *17*, 10972−10978.

(24) A mechanism of the transformation of **26** to **28** is proposed in Figure S1. For precedent gold-catalyzed skeletal rearrangement of 1,6-enynes involving *Z*-alkenes, see: (a) Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M. *Chem. - Eur. J.* **2006**, *12*, 1677−1693. (b) Jiménez-Núñez, E.; Claverie, C. K.; Bour, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem.* **2008**, *120*, 8010−8013; *Angew. Chem., Int. Ed.* **2008**, *47*, 7892−7895.

(25) Burke, M. D.; Schreiber, S. L. *Angew. Chem.* **2004**, *116*, 48−60; *Angew. Chem., Int. Ed.* **2004**, *43*, 46−58.

(26) Hashmi, A. S. K.; Schuster, A. M.; Gaillard, S.; Cavallo, L.; Poater, A.; Nolan, S. P. *Organometallics* **2011**, *30*, 6328−6337.

(27) For a selection of recent reports on the role of counterions in homogeneous gold catalysis, see: (a) Zhdanko, A.; Maier, M. E. *ACS Catal.* **2014**, *4*, 2770−2775. (b) Jia, M.; Cera, G.; Perrotta, D.; Monari, M.; Bandini, M. *Chem. - Eur. J.* **2014**, *20*, 9875−9878.

(28) Fráter, G.; Günther, W.; Müller, U. *Helv. Chim. Acta* **1989**, *72*, 1846−1851.

(29) (a) Jerphagnon, T.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2009**, *38*, 1039−1075. (b) Alexakis, A.; Krause, N.; Woodward, S. Copper-Catalyzed Asymmetric Conjugate Addition. In *Copper-Catalyzed Asymmetric Synthesis*; Alexakis, A.; Krause, N.; Woodward, S., Eds.; Wiley-VCH: Weinheim, 2014; Chapter 2, pp 33−68.

(30) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262−5263.

(31) (a) Li, K.; Alexakis, A. *Tetrahedron Lett.* **2005**, *46*, 5823−5826. (b) Li, K.; Alexakis, A. *Chem. - Eur. J.* **2007**, *13*, 3765−3771. (c) Jarugumilli, G. K.; Zhu, C.; Cook, S. P. *Eur. J. Org. Chem.* **2012**, *2012*, 1712−1715.

(32) Morita, Y.; Suzuki, M.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 1785−1787.

(33) Martin, P.; Steiner, E.; Streith, J.; Winkler, T.; Bellus, D. *Tetrahedron* **1985**, *41*, 4057−4078.

(34) (a) Tanyeli, C.; Tarhan, O. *Synth. Commun.* **1989**, *19*, 2749−2753. (b) Hauser, F. M.; Dorsch, W. A.; Mal, D. *Org. Lett.* **2002**, *4*, 2237−2239.

(35) Kluge, A. F.; Cloudsdale, I. S. *J. Org. Chem.* **1979**, *44*, 4847−4852.

(36) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1991**, 324−325.

(37) Ferns, T. A.; Kerr, R. G. *J. Org. Chem.* **2005**, *70*, 6152−6157.

(38) Roussis, V.; Wu, Z.; Fenical, W.; Strobel, S. A.; VanDuyne, G. D.; Clardy, J. *J. Org. Chem.* **1990**, *55*, 4916−4922.

(39) Levin, S.; Nani, R. R.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 774−776.

(40) Miles, W. H.; Connell, K. B.; Ulas, G.; Tuson, H. H.; Dethoff, E. A.; Mehta, V.; Thrall, A. J. *J. Org. Chem.* **2010**, *75*, 6820−6829.

(41) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215−241.

(42) Considering that **57** and **57′** are isoenergetic, the Cope rearrangement of **56** should be under typical kinetic control under the reaction conditions employed.

(43) Dyker, G.; Muth, E.; Hashmi, A. S. K.; Ding, L. *Adv. Synth. Catal.* **2003**, *345*, 1247−1252.

(44) An alternative mechanism suggested by a reviewer is that the $AuCl_3$ could serve as a source of protons that catalyzed the intramolecular Michael addition. For a perspective on catalysis by gold versus catalysis by proton, see: Hashmi, A. S. K. *Catal. Today* **2007**, *122*, 211−214.

(45) Zheng, J.-C.; Yun, S. Y.; Sun, C.; Lee, N.-K.; Lee, D. *J. Org. Chem.* **2011**, *76*, 1086−1099.

DOI: 10.1021/jacs.6b02624
J. Am. Chem. Soc. 2016, 138, 6261−6270