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Facile Access to Bridged Ring Systems via Point-to-Planar Chirality Transfer: Unified Synthesis of Ten Cyclocitrinols

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CAS Key Laboratory of Synthetic Chemistry of Natural Substances, Center for Excellence in Molecular Synthesis, Shang-hai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Ling-ling Road, Shanghai 200032, China

ABSTRACT: Bridged ring systems are found in a wide variety of biologically active molecules, including pharmaceuticals and natural products. However, the development of practical methods to access such systems with precise control of the planar chirality presents considerable challenges to synthetic chemists. In the context of our work on the synthesis of cyclocitrinols, a family of steroidal natural products, we herein report the development of a point-to-planar chirality transfer strategy for preparing bridged ring systems from readily accessible fused ring systems. Inspired by the proposed pathway for biosynthesis of cyclocitrinols from ergosterol, our strategy involves a bioinspired cascade rearrangement, which enabled the gram-scale synthesis of a common intermediate in nine steps and subsequent unified synthesis of 10 cyclocitrinols in an additional one to three steps. Our work provides experimental support for the proposed biosynthetic pathway and for the possible interrelationships between members of the cyclocitrinol family. In addition to being a convenient route to 5(10→19)*abeo*-steroids, our strategy also offers a generalized approach to bridged ring systems via point-to-planar chirality transfer. Mechanistic investigations suggest that the key cascade rearrangement involves a regioselective ring scission of a cyclopropylcarbinyl cation, rather than a direct Wagner–Meerwein rearrangement.

■ INTRODUCTION

Natural products have long been invaluable sources of inspiration for drug discovery.[1] An estimated 49% of the cancer drugs approved from the 1940s to the end of 2014 were either natural products or their derivatives.[2] However, the structural diversity and complexity of natural products often limits their therapeutic utility, owing to the lack of efficient syntheses and the resulting difficulty in obtaining sufficient quantities for clinical use.[3] One strategy for addressing this challenge is to develop methods for a unified synthesis of a family of natural products and unnatural congeners in useful quantities. Successful execution of this strategy entails concise, large-scale preparation of a late-stage common intermediate that can then undergo various transformations to generate target molecules.[4]

Bridged ring systems are found in a wide variety of pharmaceuticals and biologically active natural products, including taxol (**1**),[5] ingenol (**2**),[6] berkeleyone A (**3**),[7] CP-263,114 (**4**),[8] and *N*-methylwelwitindolinone C (**5**, **6**)[9] (Fig. 1A). It is noteworthy that although terpene natural products with bridged ring systems are common, steroidal natural products[10] with bridged ring substructure are rare, with one exception being the cyclocitrinols (Fig. 1B, **7**–**16**), which feature an intriguing bicyclo[4.4.1]undecane A/B ring system and a bridgehead double bond.[11] In 2000, Gräfe and co-workers isolated the first member of this family, cyclocitrinol (**7**), from a terrestrial *Penicillium citrinum*, although the structure was incorrectly assigned at that time (not shown).[12] The correct structure was determined by Crews and co-workers in 2003, who isolated isocyclocitrinol A (**10**) from a sponge-derived *P. citrinum*.[13] Later, Zhu and co-workers isolated and elucidated the structure, biosynthetic pathway, and biological activities of a series of C25 steroids with the bicyclo[4.4.1]undecane A/B rings, including 24-*epi*-cyclocitrinol (**8**), 24-oxo-cyclocitrinol (**9**), isocyclocitrinol B (**11**), and neocyclocitrinols A–D (**12**–**15**).[14] In addition, norcyclocitrinol (**16**), the first C25 steroid combining a bicyclo[4.4.1]undecane A/B ring system with a bisnor side chain, was isolated by Zhan and co-workers from the culture broth of *P. chrysogenum* P1X.[15] Importantly, in vitro experiments showed that several cyclocitrinols (**7**, **8**, **13**, and **14**) induce the production of cAMP in GPR12-transfected CHO cells at 10 μM, indicating the therapeutic potential of these compounds for various neurological disorders, including spinal cord injuries and stroke.[14]

Construction of the bridged ring system is clearly the central synthetic challenge posed by cyclocitrinols. Compared with fused ring systems, bridged systems are generally more difficult to access, owing to ring strain. Moreover, control of the planar chirality in bridged systems is a formidable task, especially in the context of the synthesis of complex natural products.[16] Therefore, the development of practical methods for the preparation of bridged systems has been a focus of organic chemists for several decades, and a number of elegant strategies have been reported, including ring closing metathesis,[17] intramolecular Diels–Alder reaction,[18] intramolecular Michael addition,[19] Pauson–Khand reaction,[20] pinacol rearrangement,[6d, 21] C–H bond insertion,[22] and C–C bond activation.[23] Nevertheless, general protocols for building bridged ring systems from readily accessible fused ring systems are scarce,[24] particularly with concomitant installation of the planar chirality. Development of such protocols would simplify installation of the core framework of natural products via skeletal rearrangements of easily prepared precursors and would allow for establishment of the necessary planar chirality via point-to-planar chirality transfer.[25]

For this purpose, we have explored the preparation of bridged bicyclo compound **23** or **24** using fused bicyclo compound **17**

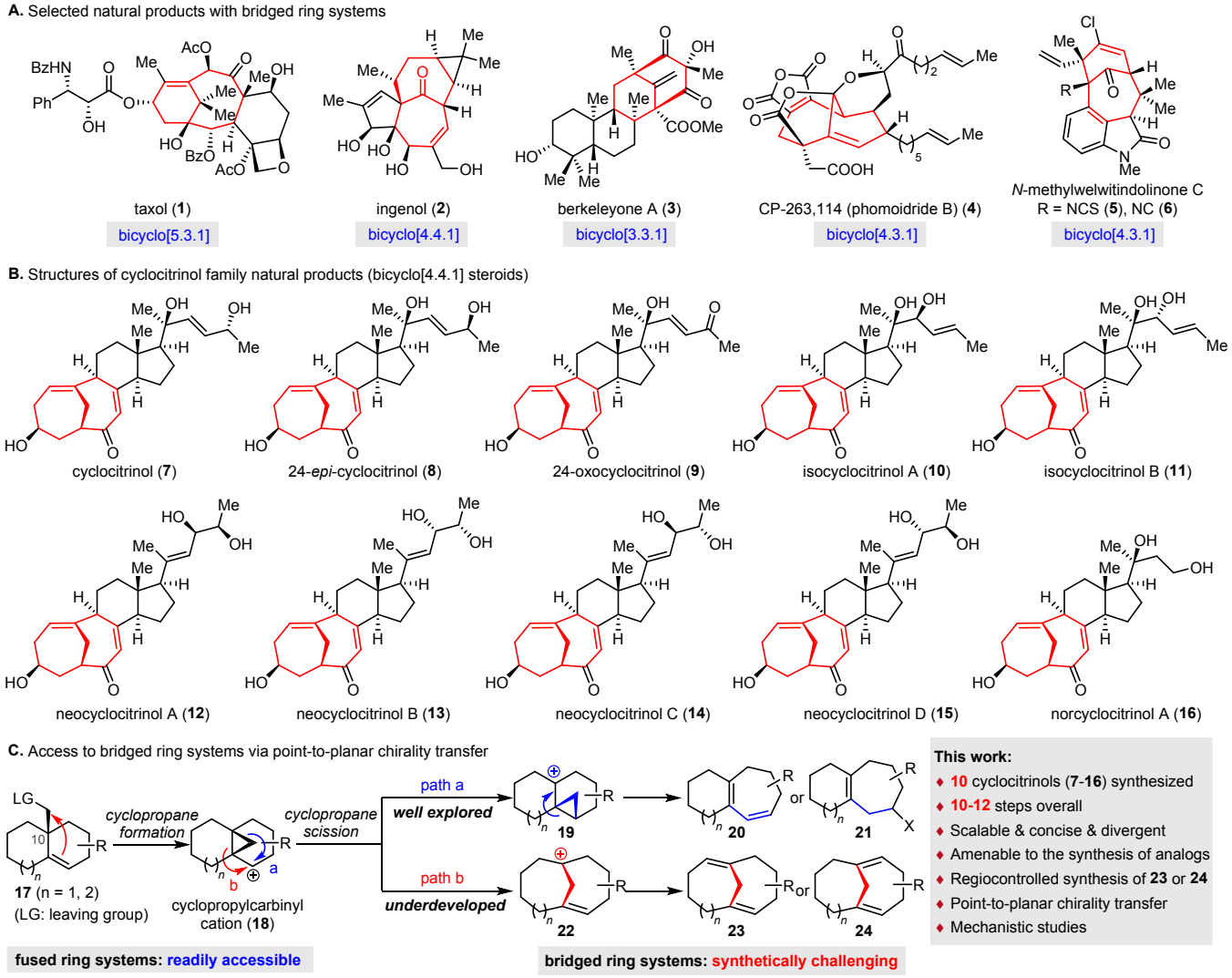


Figure 1. Representative natural products with bridged ring systems, including cyclocitrinols, and modular strategies for their synthesis.

as a starting material. This compound has a leaving group at the angular methyl position and is thus prone to undergo cyclopropanation to afford cyclopropylcarbinyl cation **18**,[26] which usually gives rise to ring-expanded fused bicyclo compound **20** or **21** via rearranged cyclopropylcarbinyl cation **19** (Fig. 1C, path a).[27] However, cyclopropylcarbinyl-homoallyl cation isomerization[28] of **18** would lead instead to **23** or **24** via homoallylic cation **22** (path b), a path that is much less developed, because of the ring strain in these bridged ring species.[29] Of critical importance in this path is complete transfer of the point chirality of the quaternary carbon (C10) of **17** to the planar chirality of **23** or **24**. Recently, we reported a synthesis of cyclocitrinol (**7**) via a bioinspired cascade rearrangement, a chemical transformation that proceeds by way of path b.[30] Herein, we present our work on the development of a unified synthesis of 10 cyclocitrinols (**7**–**16**) in only 10–12 steps from a commercially available compound (pregnenolone). We describe the evolution of this bioinspired strategy, the synthesis of various 5(10→19)*abeo*-steroids, and our studies of the mechanism of the key cascade rearrangement. Furthermore, we demonstrate that point-to-planar chirality transfer can be utilized as a general strategy for access to bridged ring systems.

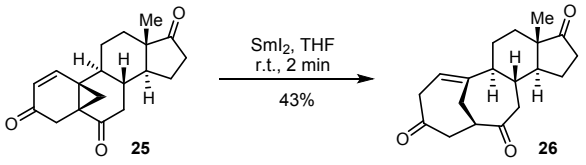
■ RESULTS AND DISCUSSION

Previous Work and Key Considerations. The interesting biological activity profile and structural complexity of the cyclocitrinols have drawn significant attention from synthetic chemists over the past decade. Several elegant approaches to the construction of the cyclocitrinol core framework have been reported, including Schmalz's SmI_2-mediated cyclopropane fragmentation,[31] Leighton's tandem ring-contracting Ireland–Claisen/Cope rearrangement sequence,[32] and Li's type II intramolecular oxidopyrylium-mediated [5+2] cycloaddition (Scheme 1).[33] Li and co-workers recently reported the first total synthesis of cyclocitrinol, starting from a vitamin D_2 degradation product, highlighting the synthetic utility of intramolecular cycloadditions for the synthesis of complex natural products.[34]

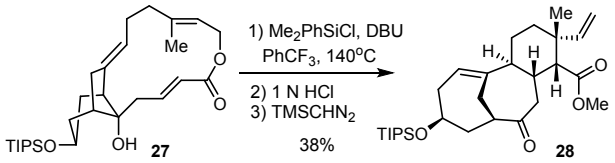
Our synthetic interest in cyclocitrinols derives from their fascinating biosynthesis (see below) and a desire to procure useful quantities of various cyclocitrinols for investigation of their biological activity. To accomplish this goal, we sought (1) to develop a concise, bioinspired, gram-scale route to a late-stage common intermediate bearing the core structure; (2) to transform this intermediate into a variety of cyclocitrinols and unnatural congeners; and (3) to extend the route to the synthesis of other bridged ring systems.

Scheme 1. Previous Synthetic Studies toward Cyclocitrinol[a]

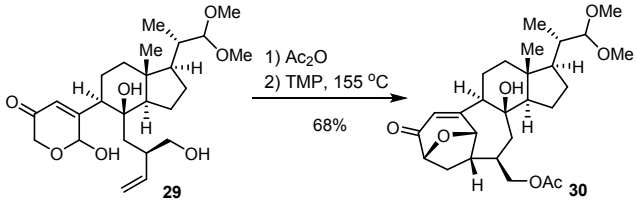
Schmalz (2007): SmI_2-mediated cyclopropane fragmentation



Leighton (2014): tandem Ireland-Claisen/Cope rearrangement



Li (2015): type II intramolecular [5+2] cycloaddition
Li (2018): first completed synthesis



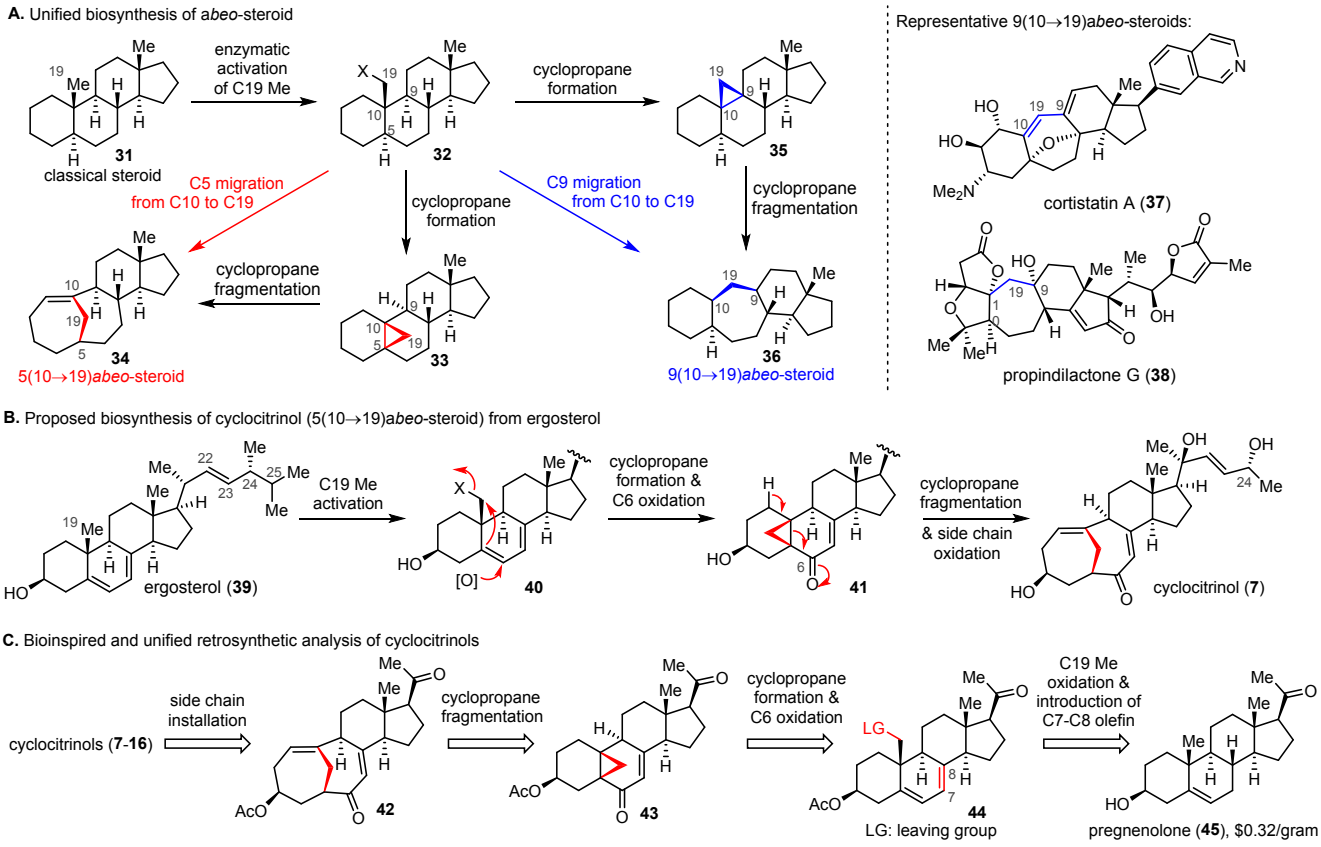
[a]Abbreviations: DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TMP = 2,2,6,6-tetramethylpiperidine.

Retrosynthetic Analysis. The inspiration for our initial retrosynthetic analysis was largely drawn from the biosynthesis of rearranged *abeo*-steroids. Biosynthetically, the 5(10→19)*abeo*-steroid skeleton (**34**), like that of cyclocitrinol (**7**), is thought to derive from enzymatic activation of the C19 Me group of classical steroidal skeleton **31** to give **32**, followed by migration of C5 from C10 to C19 to afford **34** (Scheme 2A).[35] Alternatively, the migration of C5 could also proceed in two steps, via 5,19-cyclopropane formation to form **33** and subsequent cleavage of the C5–C10 bond. Likewise, activation of the C19 Me group combined with migration of C9 from C10 to C19 or stepwise 9,19-cyclopropane formation followed by fragmentation could lead to 9(10→19)*abeo*-steroid **36**,[36] which is the core structure of compounds such as cortistatin A (**37**)[37] and propindilactone G (**38**).[38] The landmark synthesis of **37** from prednisone by Baran and co-workers has validated the proposed route for biosynthesis of 9(10→19)*abeo*-steroids.[37a] However, experimental support for the biosynthesis of 5(10→19)*abeo*-steroids from classical steroids is lacking.

Consistent with the above-described biosynthesis, the biosynthesis of cyclocitrinol (**7**) from ergosterol (**39**) has been proposed to start with enzymatic activation of the C19 Me group to afford **40** (Scheme 2B).[35] The C5–C6 olefin of **40** can then act as a nucleophile in a C5–C19 bond-forming reaction facilitated by concomitant oxidation at C6 to give **41**. Subsequent cyclopropane fragmentation induced by deprotonation at C1 gives rise to the core structure of **7**. Oxidations at C22, C23, and C25 of **39** and elimination of acetone by C24–C25 bond cleavage generate the carbon skeleton of the cyclocitrinol side chain.

Based on this proposed biosynthesis of **7**, our initial retrosynthetic analysis is outlined in Scheme 2C. Because cyclocitrinols **7**–**16** possess a common parent skeleton (Fig. 1B), we devised a unified synthetic strategy for accessing all these compounds from enone **42**. We envisioned that **42** could be prepared via a regioselective cyclopropane fragmentation reaction of cyclopropyl enone **43**. Furthermore, we postulated that **43** could be

Scheme 2. Proposed Biosynthesis and Unified Retrosynthetic Analysis of Cyclocitrinols



accessed by means of intramolecular cyclopropanation of diene **44**, followed by C6 oxidation. Finally, **44** could be traced back to commercially available pregnenolone (**45**) via oxidation of the C19 methyl group and introduction of the C7–C8 olefin. Pregnenolone is an excellent starting material owing to its low cost ($0.32/gram), ready availability, and remarkable structural similarity to advanced intermediate **42**, missing only the A/B ring system. The challenges posed by this strategy for cyclocitrinol synthesis are the skeletal rearrangement of the pregnenolone A/B ring system, including functionalization of the C19 Me group, oxidation of the B-ring, installation of the 5,19-cyclopropane, and its regioselective fragmentation.

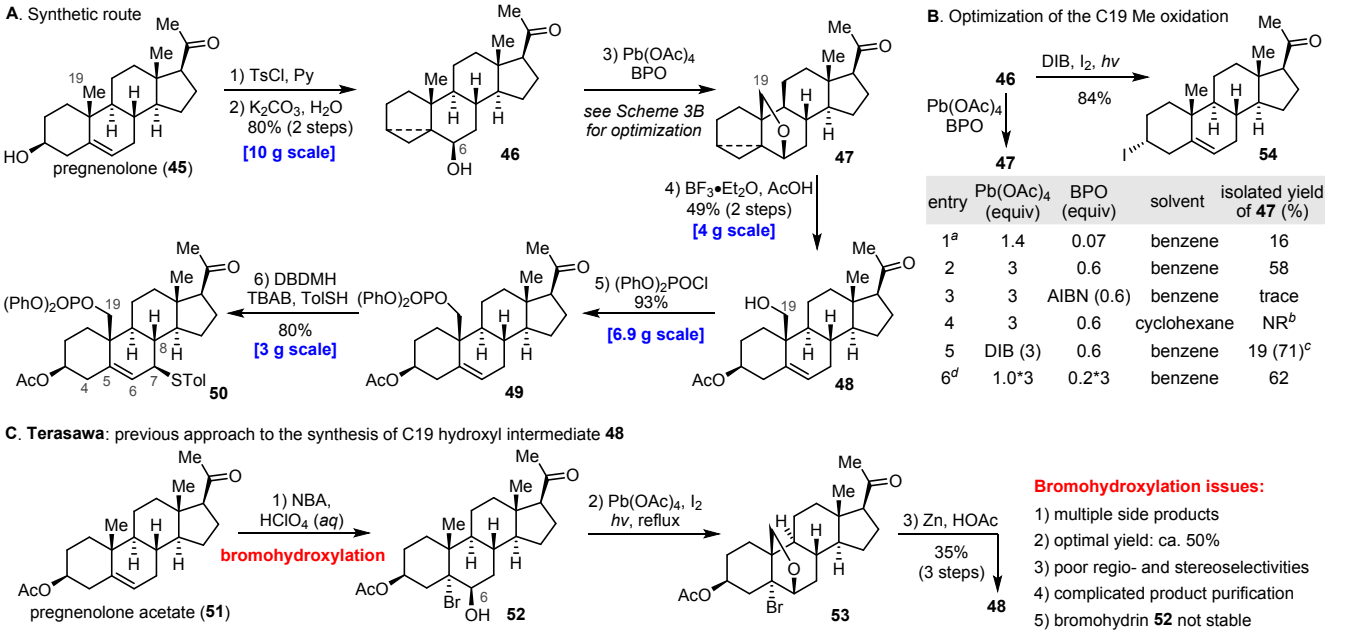
C19 Me Group Functionalization and B-Ring Oxidation. Selective oxidation of the C19 Me group is a classic problem in steroid semisynthesis, and several strategies for this transformation have been developed, including remote radical functionalization directed by the C1β, C6β, or C11β hydroxyl group and Norrish type II photochemistry of the C11 ketone.[39] We posited that the C5–C6 olefin of **45** could be easily elaborated to the C6β hydroxyl group, which could then be used to affect oxidation of the C19 Me group via a 1,5-hydrogen atom transfer reaction of a C6β alkoxy radical. Indeed, Terasawa and Okada used this strategy to prepare desired intermediate **48** in three steps from pregnenolone acetate **51** (Scheme 3C).[40] However, our attempts to repeat this route revealed scalability and purification issues; specifically, the poor regio- and stereoselectivities of the bromohydroxylation of the C5–C6 olefin led to the formation of multiple side products, which complicated purification when the reaction was carried out on a large scale. These issues deterred us from using this approach for the large-scale preparation of bromohydrin **52**, thereby prompting us to develop an alternative route to **48**.

The alternative route involved introduction of the C6β hydroxyl group via a known two-step sequence consisting of tosylation of **45** and solvolysis under basic conditions, which afforded cyclopropylcarbinol **46** in 80% yield (on a 10 g scale) (Scheme 3A).[41] Subsequent remote radical functionalization of **46** to furnish **47** proved to be far from trivial (Scheme 3B). Surprisingly, when **46** was subjected to the standard Suárez conditions,[42] iodide **54** was obtained in 84% yield. In contrast, treatment of **46** with $Pb(OAc)_4$ and benzoyl peroxide (BPO) in refluxing benzene (Tanabe's conditions) furnished **47** in only 16% yield (entry 1).[43] Extensive optimization experiments revealed that **47** could be obtained in 58% yield by increasing the amounts of the two reagents (entry 2). Replacement of BPO with azobisisobutyronitrile or benzene with cyclohexane proved unfeasible (entries 3 and 4), and use of (diacetoxyiodo)benzene as the oxidant led to low conversion (entry 5). Ultimately we found that addition of $Pb(OAc)_4$ (3 equiv total) and BPO (0.6 equiv total) in three portions separated by 1 h reproducibly afforded **47** in 62% yield on a gram scale (entry 6). Acid-catalyzed solvolysis of **47** then generated **48** in 49% yield over two steps. This improved four-step sequence constituted an efficient and scalable route to **48** with simplified purification and set the stage for introduction of the C7–C8 olefin in the B ring.

We envisioned that the C7–C8 olefin could be introduced by allylic bromination of the C5–C6 olefin to give a C7 allylic bromide, followed by HBr elimination. To test the feasibility of this approach, we phosphorylated the C19 hydroxyl group of **48** (affording **49**) to install a leaving group at this position. Although allylic bromination of **49** proceeded smoothly, subsequent HBr elimination under various conditions generated a mixture of the C4–C6 and C5–C7 dienes, with a preference for the former, undesired isomer. To address this issue, we treated the mixture obtained from the allylic bromination of **49** with tetra-*n*-butylammonium bromide and *p*-toluenethiol (Confalone's conditions)[44] to generate allylic sulfide **50** in 80% yield (on a 3 g scale), which was expected to produce the C7–C8 olefin via oxidation of the sulfide and subsequent sulfoxide elimination.

Forays into the Bridged Ring System. Oxidation of **50** with *m*-chloroperoxybenzoic acid (*m*-CPBA) gave a pair of diastereomers, which were subjected to thermal elimination to afford diene **55** in 47% yield (Scheme 4). Treatment of **55** with

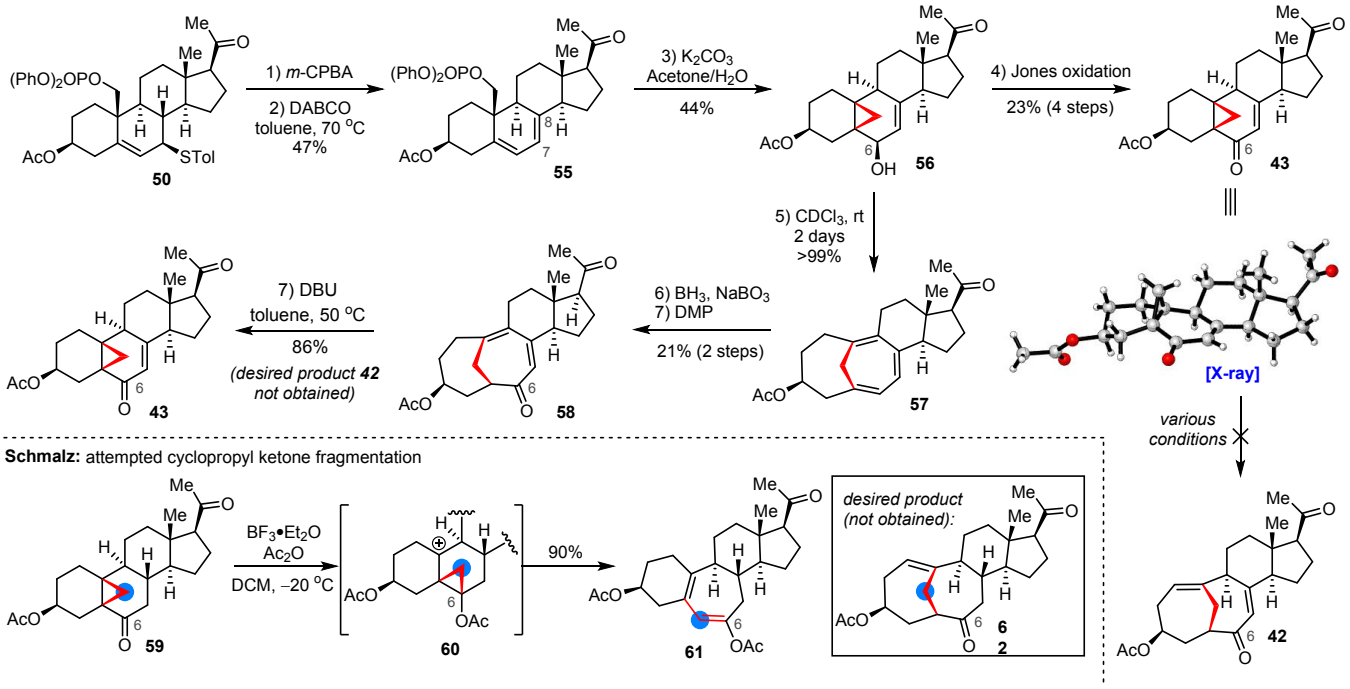
Scheme 3. Synthesis of C19 Functionalized Allylic Sulfide 50



entry	$Pb(OAc)_4$ (equiv)	BPO (equiv)	solvent	isolated yield of **47** (%)
1[a]	1.4	0.07	benzene	16
2	3	0.6	benzene	58
3	3	AIBN (0.6)	benzene	trace
4	3	0.6	cyclohexane	NR[b]
5	DIB (3)	0.6	benzene	19 (71)[c]
6[d]	1.0*3	0.2*3	benzene	62

[a]Reported condition in ref. 43. [b]No reaction. [c]Isolated yield of recovered **46** shown in parenthesis. [d]Reaction performed on gram scale. Abbreviations: Ts = tosyl, BPO = benzoyl peroxide, DIB = (diacetoxyiodo)benzene, AIBN = 2,2'-azo-bis-isobutyronitrile, DBDMH = 1,3-dibromo-5,5-dimethylhydantoin, TBAB = tetra-*n*-butylammonium bromide, TolSH = *p*-toluenethiol, NBA = *N*-bromoacetamide.

Scheme 4. Initial Forays into Bridged Ring Systems



Abbreviations: *m*-CPBA = *meta*-chloroperbenzoic acid, DABCO = 1,4-diazabicyclo[2.2.2]octane, DMP = Dess-Martin periodinane.

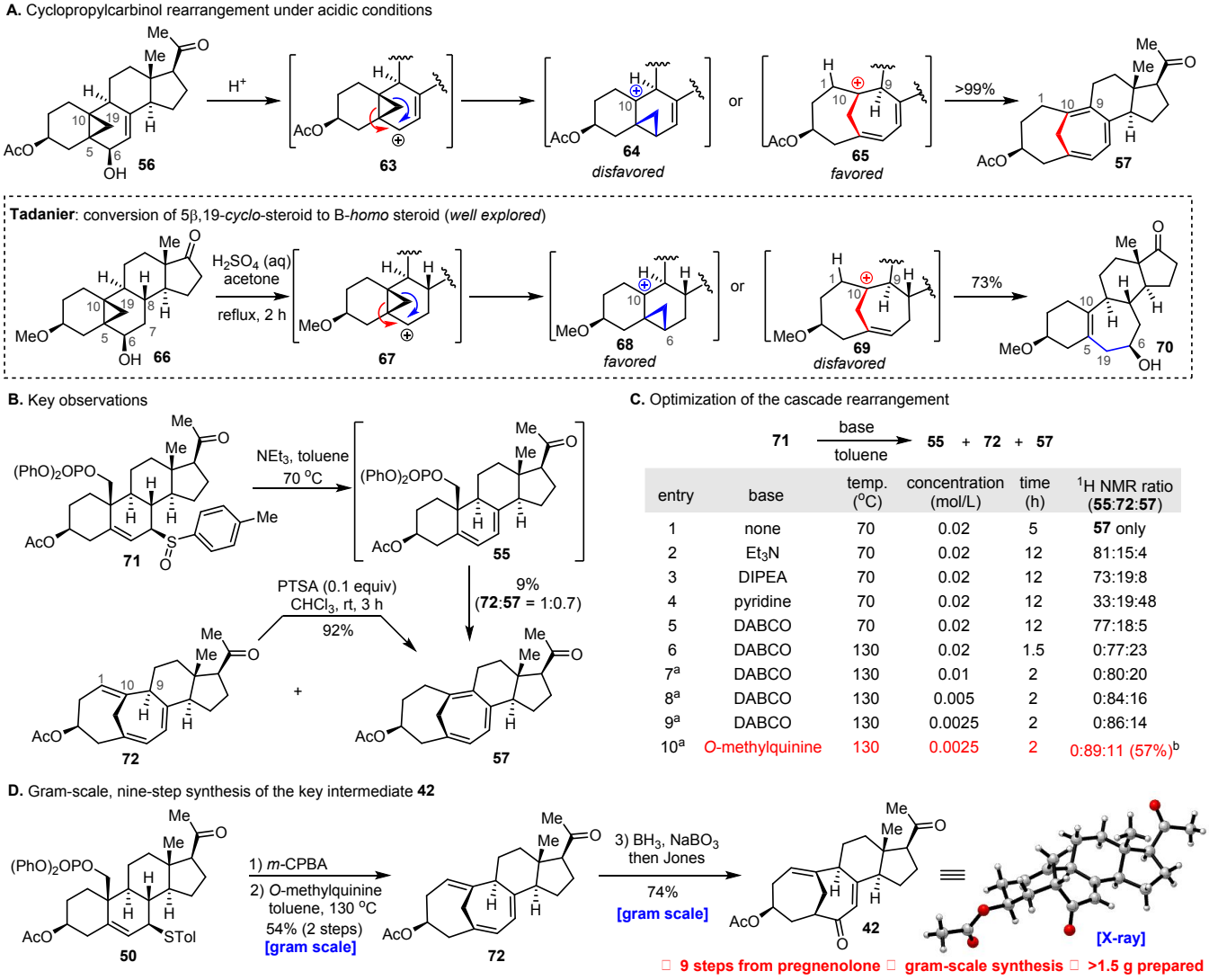
base in aqueous acetone delivered cyclopropylcarbinol **56**, which was oxidized with Jones reagent to generate desired enone **43** in 23% yield over four steps. After confirming the structure of **43** by X-ray crystallographic analysis, we investigated the key cyclopropane fragmentation to access the core bridged ring system. Disappointingly, desired product **42** was not observed under any of the various conditions we tried (including acidic or basic conditions and microwave heating conditions), with the only products being those resulting from epimerization at the allylic position. Schmalz and co-workers investigated a similar cyclopropyl ketone fragmentation, on compound **59**:[27d] under acidic conditions, they obtained only B-ring-expanded diene **61** (90% yield), possibly via **60**.

These failures led us to search for an alternative pathway. Fortuitously, during the NMR characterization of **56**, we found that cycloheptatriene **57** was generated in quantitative yield when a solution of **56** in $CDCl_3$ was allowed to stand at room temperature for 2 days. We attributed this unexpected result to the presence of trace acid in $CDCl_3$. Although the mechanism for this ring expansion reaction deserved further investigation (see below), we proceeded to elaborate **57** into enone **42**. Hydroboration-oxidation of **57**, followed by Dess–Martin oxidation, yielded **58** in 21% yield over two steps. From here, the only remaining step was deconjugation of **58**, but unfortunately we were unable to accomplish this transformation, despite extensive experimentation. Interestingly, when **58** was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene, cyclopropyl enone **43** was isolated in 86% yield, possibly via enolization of the C6 ketone and subsequent 6π electrocyclization.

Although cycloheptatriene **57** could not be transformed into a compound with the cyclocitrinol skeleton, the formation of **57** from **56** under acidic conditions deserves further comment (Scheme 5A). We speculate that in the presence of an acid, **56** was first converted to cyclopropylcarbinyl cation **63**, which then rearranged to produce homoallylic cation **65** (rather than **64**); cation **65** would in turn give rise to **57** after losing the proton at C9. Tadanier and co-workers reported a related reaction: specifically, upon treatment with acid, compound **66**, which does not have the C7–C8 olefin of **56**,[27a] affords ring-expanded fused product **70**, possibly via **68**. The reason for the difference between the rearrangement pathways of **56** and **66** is not clear. However, the likely formation of homoallylic cation **65** suggested that we could obtain our desired C1–C10 olefin if deprotonation of **65** could be made to occur at C1 rather than at C9.

We were pleased to discover that careful purification of the mixture produced by the thermal elimination reaction of sulfoxide **71** (which was generated by *m*-CPBA oxidation of allylic sulfide **50**) led to the isolation of a 1:0.7 mixture of desired triene **72** and cycloheptatriene **57** in 9% combined yield (Scheme 5B). We were particularly encouraged by the formation of the requisite C1–C10 olefin, which might have arisen from cation **65,** and we focused our efforts on optimizing the yield of triene **72** (Scheme 5C). We found that in the absence of base, **57** was produced exclusively (entry 1), perhaps by release of diphenyl phosphate, as suggested by the fact that **72** could be converted to **57** in 92% yield by treatment with a catalytic amount of *p*-toluenesulfonic acid (PTSA) in $CHCl_3$. Screening of various bases revealed 1,4-diazabicyclo[2.2.2]octane (DABCO) to be the optimal choice (entries 2–5). Increasing the reaction temperature to 130 °C resulted in complete conversion of diene **55** (entry 6), and decreasing the concentration of **71** dramatically affected the regioselectivity of the reaction: the **72**:**57** ratio improved to 86:14 when the concentration was decreased to 0.0025 mol/L. Finally, replacing DABCO with a derivative of a cinchona alkaloid (such as quinine or quinidine) resulted in slightly higher regioselectivity. *O*-Methylquinine was chosen as the optimal base owing to the low cost of the parent alkaloid (quinine), and **72** was obtained in 57% yield (54% on a gram scale) starting from sulfide **50**.

Scheme 5. Gram-Scale Synthesis of Enone 42 in Nine Steps



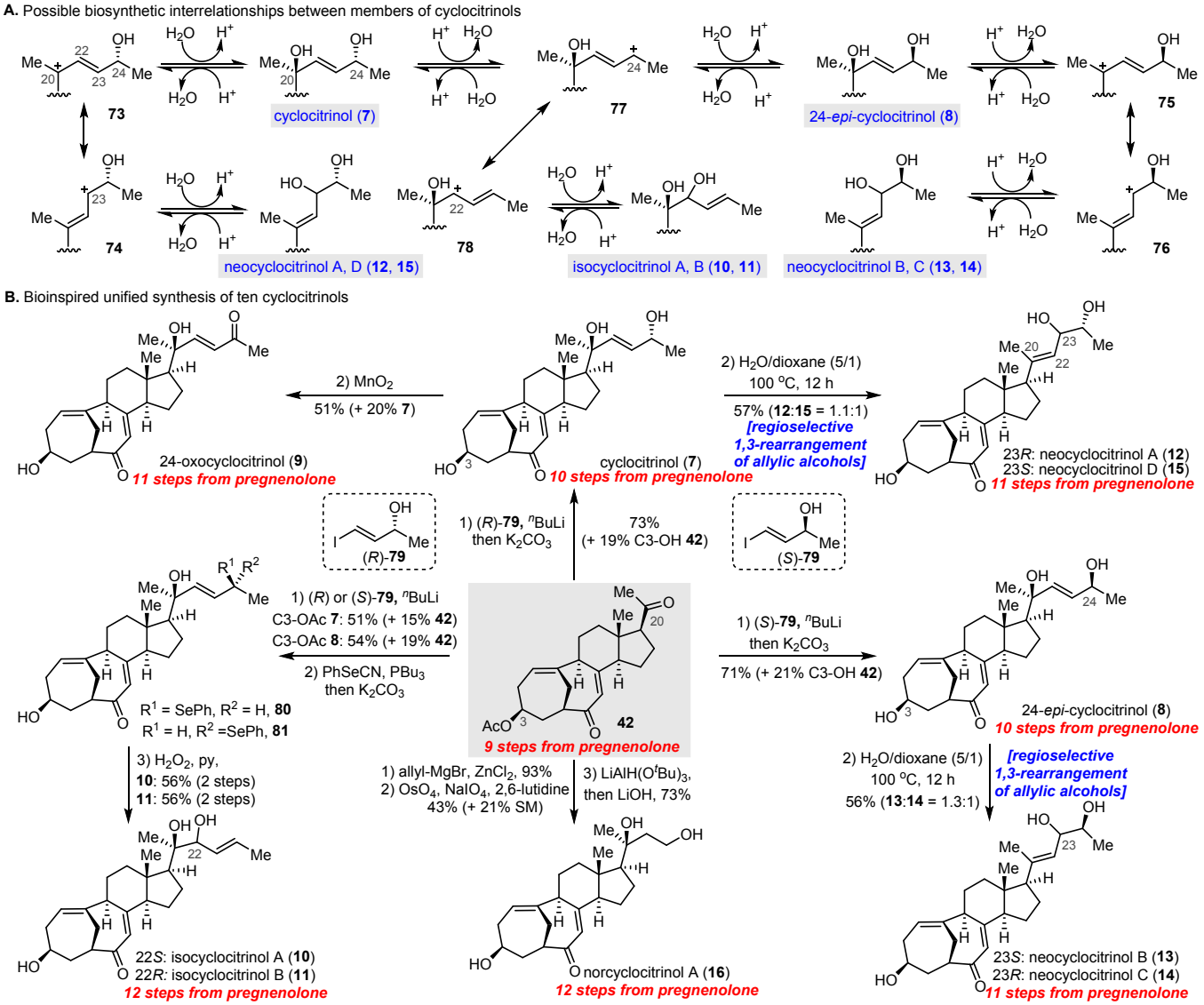
entry	base	temp. (°C)	concentration (mol/L)	time (h)	^{1}H NMR ratio (**55**:**72**:**57**)
1	none	70	0.02	5	**57** only
2	Et_3N	70	0.02	12	81:15:4
3	DIPEA	70	0.02	12	73:19:8
4	pyridine	70	0.02	12	33:19:48
5	DABCO	70	0.02	12	77:18:5
6	DABCO	130	0.02	1.5	0:77:23
7[a]	DABCO	130	0.01	2	0:80:20
8[a]	DABCO	130	0.005	2	0:84:16
9[a]	DABCO	130	0.0025	2	0:86:14
10[a]	*O*-methylquinine	130	0.0025	2	0:89:11 (57%)[b]

[a]**71** was used as a crude mixture from the *m*-CPBA oxidation of **50**. [b]Isolated yield of **72** shown in parenthesis. Abbreviations: PTSA = *p*-toluenesulfonic acid, DIPEA = diisopropylethylamine.

With an efficient route to triene **72** in hand, what remained for the construction of the cyclocitrinol skeleton was the selective oxidation of the C5–C6 olefin to obtain the C6 ketone (Scheme 5D). Gratifyingly, the C5–C6 olefin of **72** was innately more reactive toward oxidants than the C7–C8 and C1–C10 olefins. Thus, hydroboration-oxidation of **72** with concomitant reduction of the C20 ketone, followed by in situ oxidation with Jones reagent, delivered enone **42** in 74% yield on a gram scale. The structure of **42** was established by X-ray crystallographic analysis. Notably, this gram-scale route to **42** involved only nine steps from pregnenolone **45** and provided more than 1.5 g of **42**, an amount that was sufficient for late-stage diversification studies to prepare various cyclocitrinols and unnatural congeners.

Unified Synthesis of 10 Cyclocitrinols. As alluded to earlier, cyclocitrinols **7**–**16** differ only in their side chains (Fig. 1B). With the shared tetracyclic ring system in hand, we posited that cyclocitrinols **7**–**9** and norcyclocitrinol (**16**) could be synthesized via chemo- and diastereoselective addition of the necessary side chains to the C20 ketone of **42**. Furthermore, we surmised that isocyclocitrinols **10** and **11** and neocyclocitrinols **12**–**15** could be prepared from **7** and **8** by regiocontrolled 1,3-rearrangement of the allylic alcohols. On the basis of the proposed biosynthetic interrelationships between the cyclocitrinols (Scheme 6A),[14] we expected that protonation of the C20 hydroxyl group of **7** under acidic conditions would afford C20 allylic cation **73**. Trapping its resonance form **74** with H_2O would produce neocyclocitrinols A (**12**) and D (**15**) after loss of a proton. Likewise, neocyclocitrinols B (**13**) and C (**14**) could be obtained from **8** in the same manner. Alternatively, protonation of the C24 hydroxyl group of **7** under acidic conditions would generate C24 allylic cation **77** or its resonance form **78**, which could be trapped by H_2O to give 24-*epi*-cyclocitrinol (**8**) or isocyclocitrinols A (**10**) and B (**11**), respectively.. It is worth mentioning that Zhu and co-workers explored the acid-catalyzed equilibrium and isomerization reactions of cyclocitrinols by means of HPLC and LC-MS analysis.[14] However, regiocontrolled synthesis of isocyclocitrinols **10** and **11** and neocyclocitrinols **12**–**15** from **7** and **8** in synthetically useful yields would obviously be highly appealing (albeit challenging) in that it would facilitate evaluation of their biological activities and elucidation of their

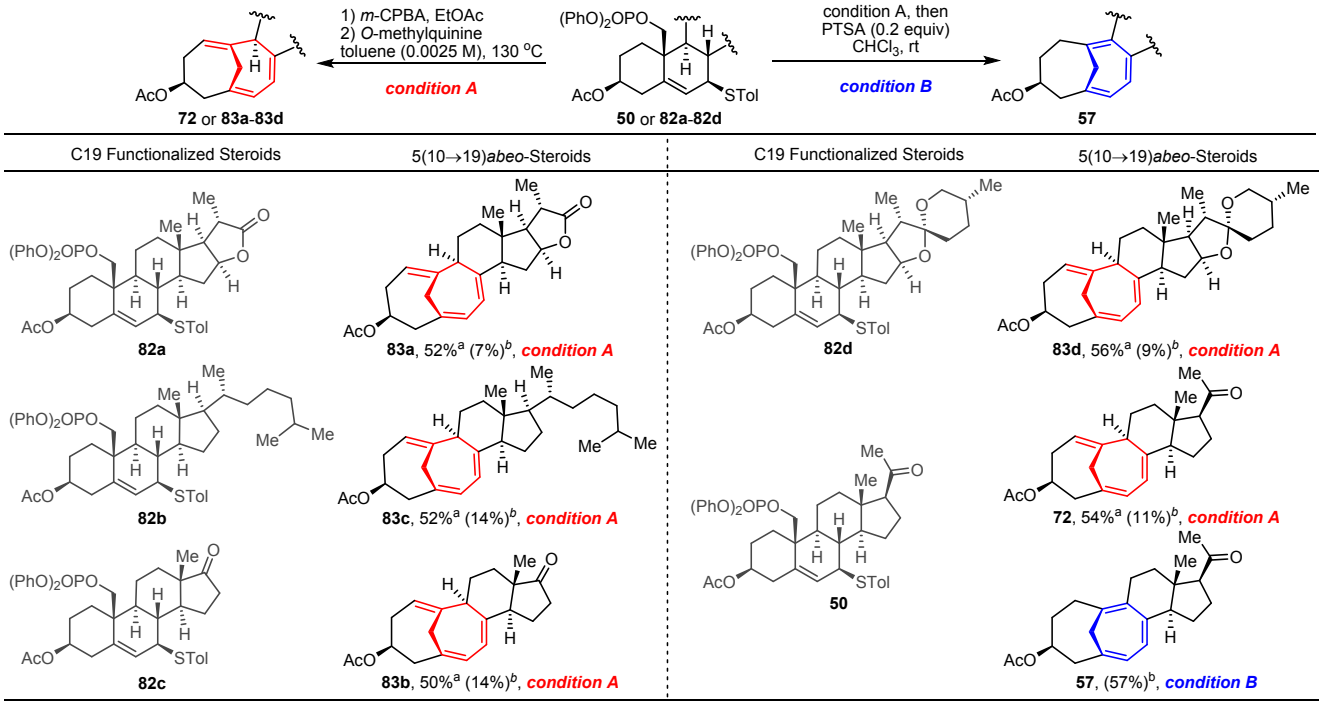
Scheme 6. Bioinspired Unified Synthesis of 10 Cyclocitrinols



biosynthetic interrelationships. Our unified synthesis of cyclocitrinols commenced with the preparation of **7** (Scheme 6B). Treatment of **42** with a lithium reagent derived from allylic alcohol (*R*)-**79**[45] provided **7** in 73% yield after in situ removal of the C3 acetyl group. Selective oxidation of **7** with MnO_2 gave 24-oxocyclocitrinol (**9**) in 51% yield. Likewise, 24-*epi*-cyclocitrinol (**8**) was synthesized in 71% yield from **42** by reaction with (*S*)-**79** and *n*-BuLi. A three-step sequence involving nucleophilic addition of an allylic zinc reagent to **42** followed by oxidative cleavage[46] of the terminal olefin and selective reduction of the resulting aldehyde led to norcyclocitrinol (**16**), which has a hydroxyethyl side chain.

With these four cyclocitrinols prepared, the next challenge was to accomplish the bioinspired synthesis of **10**–**15** from **7** and **8** via regiocontrolled 1,3-rearrangements of allylic alcohols. Although Zhu and co-workers reported the isomerization of cyclocitrinols under acidic conditions,[14] we found that subjecting **7** to various acidic conditions led to complex mixtures, with the major products arising from uncontrolled dehydration. Eventually, we discovered that heating an aqueous mixture of **7** in the absence of acid[47] successfully effected the desired 1,3-rearrangement of the C20 tertiary allylic alcohol, delivering a 1.1:1 mixture of neocyclocitrinols A (**12**) and D (**15**) in 57% combined yield (Scheme 6B). Notably, the C20–C22 olefins of **12** and **15** were exclusively in the *E* configuration. Under the same conditions, neocyclocitrinols B (**13**) and C (**14**) were obtained from **8** in 56% combined yield. These results provide important insights into the biosynthetic origin of the neocyclocitrinols. Attempts to synthesize isocyclocitrinols **10** and **11** using the same strategy (that is, direct 1,3-rearrangement of C24 secondary allylic alcohols) were unsuccessful under a variety of conditions. Ultimately, we found that **10** and **11** could be obtained in three steps from **42** by means of a seleno-Mislow–Evans rearrangement.[48] Thus, cyclocitrinol protected with an acetyl group at C3 was converted to allylic selenide **80** by means of the Grieco protocol.[49] Oxidation of **80** by H_2O_2 triggered a [2,3]-sigmatropic rearrangement of the resulting selenoxide, giving rise to isocyclocitrinol A (**10**) in 56% yield over two steps. Isocyclocitrinol B (**11**) was prepared by subjecting C3-acetyl-protected 24-*epi*-cyclocitrinol to the same sequence. Thus, unified synthesis of 10 cyclocitrinols (**7**–**16**) was accomplished in one to three steps

Table 1. Regiodivergent Synthesis of Functionalized 5(10→19)*abeo*-Steroids



[a]Isolated yields of non-conjugated triene products (in red color). [b]Isolated yields of heptatriene products (in blue color) shown in parenthesis.

from enone **42** (that is, 10–12 steps from pregnenolone).

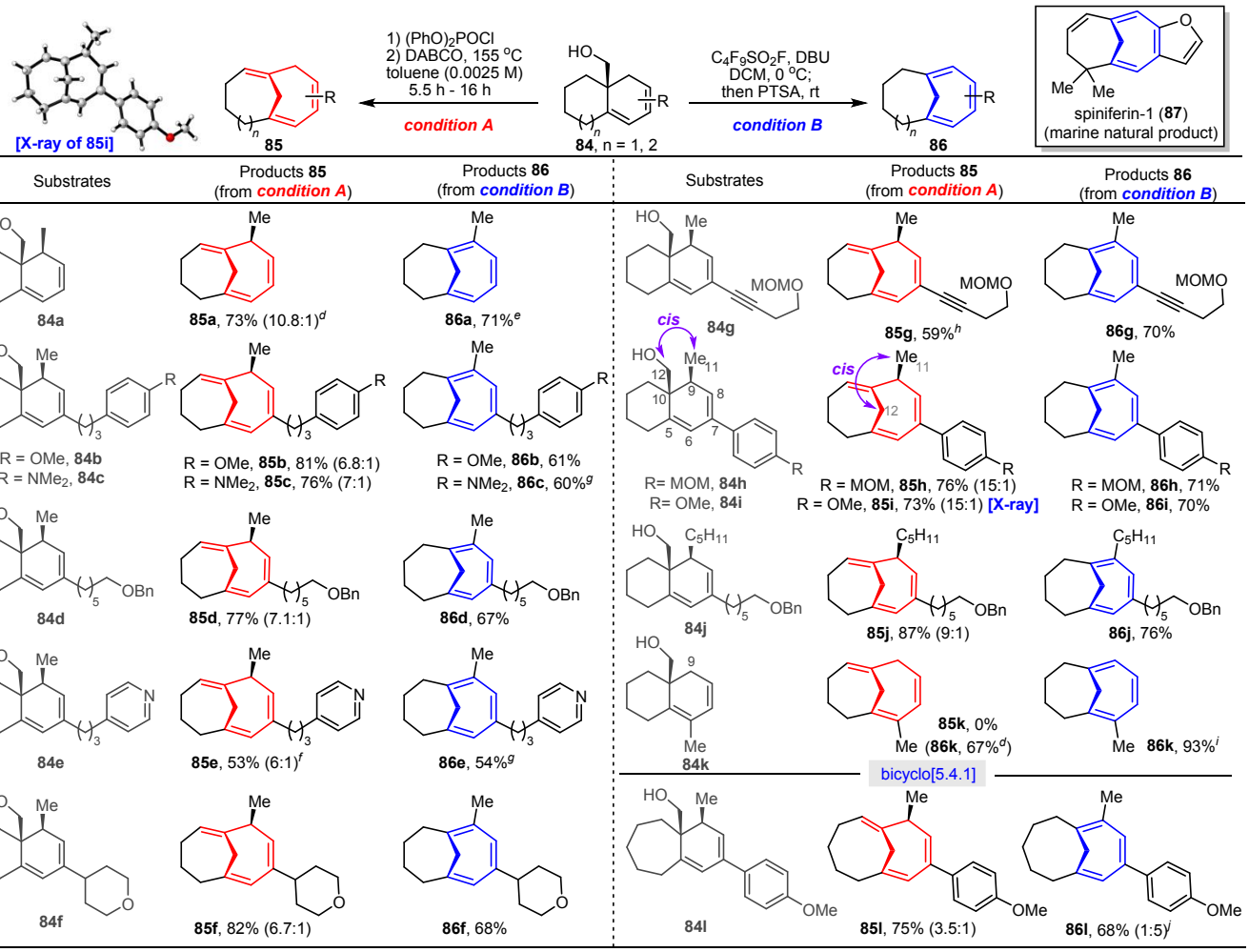
Modular Approach to Bridged Ring Systems. Our concise, unified synthesis of cyclocitrinols hinged on a regioselective cascade rearrangement, which transformed classical steroids into 5(10→19)*abeo*-steroids. To facilitate investigation of the biological activities of this class of compounds, we used this strategy to synthesize various cyclocitrinol congeners (Table 1). Four allylic sulfides (**82a**–**82d**) with a variety of structural motifs were smoothly transformed into the corresponding bicyclo[4.4.1]undeca-5,7,10-triene products (**83a**–**83d**) under standard conditions (condition A) in 50–56% yields, attesting to the viability of our strategy for accessing 5(10→19)*abeo*-steroids from C19-functionalized steroids. In addition, when the crude product mixture obtained by subjecting sulfide **50** to condition A was treated with catalytic PTSA in $CHCl_3$ (condition B), **53** was formed exclusively in 57% yield starting from **50**. This finding demonstrates that regioisomer **72** or **57** could be selectively prepared, each of which provides ready access to cyclocitrinol congeners with a nonconjuated triene or cycloheptatriene substructure.

It should be noted that all the products shown in Table 1 were obtained as single atropisomers, and their planar chirality arose from the point chirality of the C10 quaternary carbon of **50** or **82**. Therefore, our cascade rearrangement constitutes a facile method for installation of bridged ring systems with full control of the planar chirality via point-to-planar chirality transfer. Inspired by these results, we were interested in generalizing this strategy to prepare other bridged ring systems (Table 2). Specifically, we surmised that regioisomers **85** and **86** (the core structure of marine natural product spiniferin-1 (**87**)[50]) could be regiodivergently synthesized from bicyclic alcohol **84**, which could in turn be easily synthesized via Robinson annulation (see Supporting Information for details). Under the previously described optimal conditions, **84** was converted to the corresponding phosphate, which was then treated with DABCO in toluene at 155 °C (condition A, Table 2) to yield nonconjugated triene **85** as the major product. In addition, we were pleased to find that the desired cascade rearrangement also proceeded at 0 °C when a strong activating reagent, such as perfluoroalkylsulfonyl fluoride (condition B, Table 2), was used; this protocol resulted in the formation of a mixture of regioisomers **85** and **86**. However, subsequent addition of PTSA to the reaction mixture delivered cycloheptatriene **86** exclusively in good yield.

Using these two distinct sets of reaction conditions, we next examined the scope of the point-to-planar chirality transfer strategy to produce **85**, starting with condition A. Gratifyingly, bicyclo[4.4.0] dienes **84a**–**84f**, which have a variety of functional groups (e.g., anisole, aniline, ether, and pyridine), were found to be compatible substrates, delivering desired products **85a**–**85f** in 53–82% yields with good regioselectivity. The presence of the pyridine ring in **84e** reduced the conversion of the second step, but treatment of the recovered phosphate intermediate with DABCO in boiling toluene for 12 h gave **85e** in 53% overall yield. Moreover, dienes **84g**–**84i**, which have alkynyl and aryl substituents, afforded corresponding products **85g**–**85i** with excellent regioselectivities; **85g** was formed as a single regioisomer. The structure and relative configuration of **85i** were unambiguously determined by X-ray crystallographic analysis, which confirmed that the point chirality of the C10 quaternary carbon of **84i** were transferred with complete fidelity to the planar chirality of **85i**.

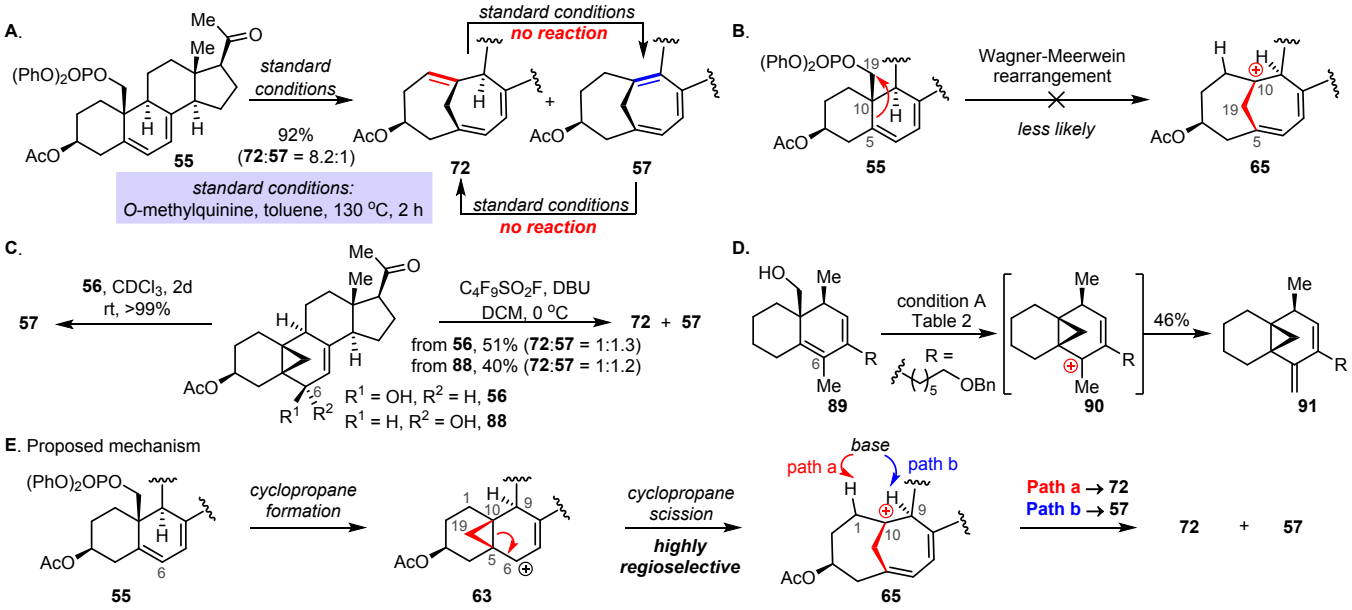
Diene **84j**, which has an *n*-pentyl group at C9, also smoothly underwent the desired reaction to give rise to **85j** in 87% yield with 9:1 regioselectivity. Surprisingly, **84k**, which has no substituent at C9, afforded cycloheptatriene **86k** as the only product, which indicates the importance of steric hindrance at C9 for the preferential formation of **85** over **86**. Importantly, bicyclo[5.4.0] diene **84l** was also amenable to this reaction,

Table 2. Regiodivergent Synthesis of Bridged Ring Systems via Point-to-Planar Chirality Transfer[a–c]



[a]Condition A: 1) $(PhO)_2POCl$ (4 equiv), Et_3N (5 equiv), DMAP (0.3 equiv), DCM, 0 °C, 50 min; 2) DABCO (2 equiv), toluene (0.0025 M), 155 °C. Condition B: $C_4F_9SO_2F$ (2 equiv), DBU (3 equiv), DCM, 0 °C, 50 min; then PTSA (1.5 equiv), rt, 1.5 h. [b]Isolated yields of purified products unless otherwise stated. [c]Ratio of nonconjugated triene **85** and cycloheptatriene **86** shown in parentheses. [d]Due to low polarity of the product, ^1H NMR yields using 1,3,5-trimethoxybenzene as the internal standard were used instead. [e]MsCl (4 equiv), Et_3N (3 equiv), DCM, 0 °C to rt, 22 h. [f]Some unreacted phosphate was recovered and resubjected to the same condition for 12 h to get a combined yield of 53%. [g]PTSA (3 equiv). [h]Second step: 165 °C. [i]MsCl (2 equiv), Et_3N (4 equiv), DCM, 0 °C to rt, 1.5 h. [j]Condition A, then PTSA (0.7 equiv), $CHCl_3$, rt, 12 h.

Scheme 7. Investigation of the Cascade Rearrangement Mechanism



giving corresponding bicyclo[5.4.1] triene **85l** in 75% yield, albeit with only moderate regioselectivity.

Encouraged by the above-described results, we next examined the regioselective preparation of compounds **86** under condition B. To our delight, exclusive formation of **86** was observed for all of the tested bicyclo[4.4.0] substrates. Interestingly, **84a** was very reactive, and MsCl was sufficient to initiate the reaction, leading to **86a** in 71% yield. It should be noted that in this case, an excess of MsCl relative to NEt_3 was used to maintain the acidity of the reaction system. Additionally, dienes **84b**–**84i**, which bear a diverse array of primary and secondary alkyl, alkynyl, and aryl groups, proved to be viable substrates, furnishing desired products **86b**–**86i** in 54–71% yields. Owing to the basicity of the pyridine and amine groups in **86c** and **86e**, 3 equiv of PTSA was required to drive the reactions of these substrates to completion. A longer-chain substituent at C9 was also compatible with condition B; **84j** afforded corresponding product **86j** in 76% yield. As expected, treatment of **84k** with MsCl and NEt_3 provided **86k** in excellent yield. Owing to the formation of nonconjugated triene **85k** even under condition A, an excess of NEt_3 relative to MsCl could be employed in this case, in sharp contrast to the situation with the preparation of **86a**. Finally, addition of PTSA in $CHCl_3$ to the crude mixture obtained by subjecting **84l** to condition A gave the desired bicyclo[5.4.1] cycloheptatriene **86l** in 68% yield with moderate regioselectivity.

Mechanistic Investigations. The mechanism of this cascade rearrangement was investigated by means of a series of control experiments (Scheme 7A). In results similar to those depicted in Table 2, steroidal diene **55** was shown to be the precursor of the cascade rearrangement, affording **72** and **57** in 92% combined yield with 8.2:1 regioselectivity under the standard conditions (Scheme 7A). In addition, we observed no interconversion between **72** and **57** under the standard conditions. In light of these results, we speculated that this pair of regioisomers might arise from homoallylic cation **65** (Scheme 7B) via two possible pathways: (1) direct migration of C5 of diene **55** from C10 to C19 via a Wagner–Meerwein rearrangement (Scheme 7B) or (2) a cyclopropane formation and scission cascade via cyclopropylcarbinyl cation **63** (Scheme 7E).

The following experiments showed that the second pathway was more likely (Scheme 7C and 7D). First, cyclopropylcarbinol **56** was quantitatively transformed to **57** under acidic conditions. Additionally, treatment of **56** or **88** with perfluoroalkylsulfonyl fluoride and DBU afforded similar results, suggesting that the configuration of the C6 leaving group had little effect on the reaction outcome. Furthermore, subjecting diene **89**, which bears a C6 methyl group, to condition A (Table 2) gave cyclopropyl diene **91** (46% yield), possibly via cyclopropylcarbinyl cation **90** (Scheme 7D). In light of the above-described observations, we propose a cascade mechanism involving cyclopropane formation and regioselective scission to generate **65**, as shown in Scheme 7E. Subsequent regiodivergent deprotonation at C1 or C9 of **65** leads to **72** or **57**, respectively.

■ CONCLUSION

We have shown that consideration of the proposed pathway for biosynthesis of a family of complex natural products can facilitate the development of a concise, scalable method for preparation of a common intermediate bearing the core framework, which can then be divergently elaborated into a collection of structurally diverse family members as well as unnatural congeners. In this study, we used this strategy to accomplish a concise, unified synthesis of 10 cyclocitrinols in only 10–12 steps from an inexpensive commercially available starting material (pregnenolone). The strategy was also useful for the preparation of various 5(10→19)*abeo*-steroids. The salient features of our synthesis are as follows: (1) a bioinspired cascade rearrangement was used to establish the core bicyclo[4.4.1]undecane skeleton, (2) late-stage common intermediate **42** was obtained on a gram scale in only nine steps, and (3) 10 cyclocitrinols were divergently synthesized via chemo- and diastereoselective nucleophilic addition to the C20 ketone of **42** and regiocontrolled 1,3-rearrangement of the resulting allylic alcohols. Our work provides experimental evidence for the proposed biosynthesis of cyclocitrinols from ergosterol and the possible interrelationships between members of the cyclocitrinol family. More importantly, our point-to-planar chirality transfer strategy could be used to synthesize challenging bridged ring systems from readily accessible fused ring systems and can be expected to find additional applications for natural product synthesis. This work should facilitate investigation of the biological activities of this fascinating class of 5(10→19)*abeo*-steroids and may lead to the development of therapies for various neurological disorders. Work toward this end is currently being pursued in our laboratory and will be reported in due course.

ASSOCIATED CONTENT

Experimental procedures, and NMR spectra for all new compounds (PDF)
X-ray crystallographic data for **42**, **43** and **85i** (CIF)

AUTHOR INFORMATION

Corresponding Author

*guijh@sioc.ac.cn

Notes

The authors declare no competing financial interest.

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