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Unified Total Syntheses of Benzenoid Cephalotane-Type Norditerpenoids: Cephanolides and Ceforalides

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Abstract

Detailed herein are our synthetic studies toward the preparation of the C_{18}- and C_{19}-benzenoid cephalotane-type norditerpenoids. Guided by chemical network analysis, the core structure of this natural product family was constructed in a concise manner using an iterative cross-coupling, followed by a formal inverse-electron-demand [4 + 2] cycloaddition. Initial efforts to functionalize

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Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c08803.
Experimental procedures; spectroscopic data; NMR spectra; X-ray data for **47** (CCDC 2176920), **53** (CCDC 2176921), and **S8** (CCDC 2201047) (PDF)

Accession Codes
CCDC 2176920–2176921 and 2201047 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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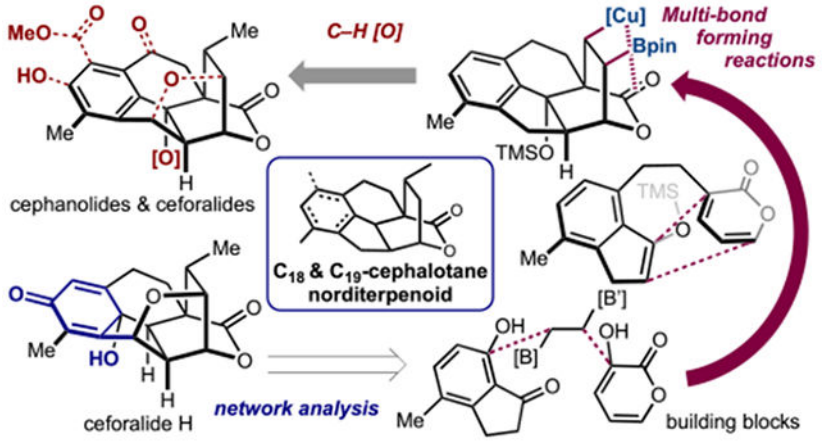
an alkene group in the [4 + 2] cycloadduct using a Mukaiyama hydration and a subsequent olefination led to the complete C_{18}-carbon framework While effective, this approach proved lengthy and prompted the development of a direct alkene difunctionalization that relies on borocupration to advance the cycloadduct to the natural products. Late-stage peripheral C–H functionalization facilitated access to all of the known cephanolides in 6–10 steps as well as five recently isolated ceforalides in 8–13 steps.

Graphical Abstract



INTRODUCTION

The total synthesis of complex natural products continues to provide a proving ground for demonstrating novel strategies and methods for chemical synthesis that achieve rapid generation of target-relevant structural complexity. In addition, strategies that enable divergent preparation of congeners in a natural product family are particularly valuable.[1] As has been established for bioinspired two-phase synthesis of terpenoids,[2] strategies that first identify a way to construct the core carbon framework of a target compound followed by diversifying peripheral functionalization have found much success. We saw the structurally diverse *Cephalotaxus* norditerpenoids (Figure 1) as particularly well-suited to this type of approach whereby chemical network analysis,[3] first advanced by Corey,[4] would unveil a strategy for the construction of the core framework of these compounds, followed by C–H functionalization tactics[5] to tailor the periphery en route to congeners in the family.

Since 1978, over 80 congeners in the cephalotane-type norditerpenoid natural product family have been isolated.[6] Because of their distinctive structural features and range of promising biological activities, the large family of *Cephalotaxus* diterpenoids has held the interest of the chemistry community since that time. The discovery of the benzenoid members of this natural product family has led to even more intense interest in recent years. Representative of the benzenoid class are cephanolides A–D (**1**–**4**),[7] which were isolated in 2017 from *Cephalotaxus sinensis* by Yue and co-workers. These natural products are believed to be biosynthetically related to harringtonolide,[8] which has undergone A-ring contraction. Since their isolation, several total syntheses of the cephanolides have been reported by the groups

of Zhao, Gao, Cai, Zhang, and Zhai,[9] as well as by us in a first-generation route to **1**–**4**.[10] Ongoing research by the Yue group to isolate and identify other biologically relevant cephalotane-type norditerpenoids led to the isolation of ceforalides A–H (**5**–**12**) from the seeds of *Cephalotaxus fortunei* var. *alpina* in early 2022.[11] Due to their recent isolation, the bioactivity of the ceforalides has not been extensively explored and there have been no total syntheses of **5**–**12** reported to date. On the basis of our established approach to **1**–**4**, we saw an opportunity to access **5**–**12** through late-stage peripheral functionalization of a common intermediate. At the same time, to achieve the syntheses of this large group of compounds, we recognized that we would need to develop an even more efficient synthesis of the requisite common intermediate.

Herein, we report the full details of our synthetic studies aimed at the divergent total syntheses of the cephanolides and ceforalides. Previously, on the basis of a retrosynthesis plan guided by chemical network analysis,[12] we disclosed that an iterative cross-coupling, followed by what is formally an intramolecular inverse-electron-demand Diels–Alder cycloaddition effectively constructed the core structure of cephanolides.[10] Our efforts to functionalize a double bond in the resulting cycloadduct using a Mukaiyama hydration and a subsequent olefination, while successful, was lengthy. Ultimately, we have identified an improved alkene difunctionalization approach to access our desired late-stage intermediate in a shorter sequence. In combination with modern late-stage diversification using C–H functionalization reactions, we have now achieved rapid access to nine cephalotane-type norditerpenoids in 6–13 steps from commercial materials. We also describe studies that provide access to enantioenriched intermediates using a silicon-based chiral auxiliary.

RESULTS AND DISCUSSION

Network Analysis of Cephalotane Benzenoid Compounds.

A key to building target-relevant structural complexity in a chemical synthesis campaign is to identify retrosynthetic bond disconnections (strategic disconnections) which lead to rapid structural simplification and yield the most synthetically accessible precursors. In 1975, Corey proposed a general analysis relying on six guidelines to facilitate the identification of strategic bonds in a target structure.[4] For bridged polycyclic compounds, identifying the maximally bridged ring (MBR) and then disconnecting bonds to minimize bridging emerged to be especially useful.[12] In applying this analysis to the core structure of the cephalotane benzenoids, the D and E rings were identified as the MBRs (Figure 2A). The most intuitive bond disconnection to remove bridging in this structure is to disconnect the [2.2.2]bicyclic δ-lactone ring back to alcohol precursors like **13** through a condensation transform. Indeed, the majority of the existing syntheses of the cephalotane natural products have employed this bond disconnection.[9a-c,e,f,13] However, in accordance with Corey's network analysis logic, disconnection of the lactone ("a"; see top left in Figure 2A) is nonstrategic because it yields two functionalized appendages with stereocenters in the precursor. In this way, for example, plausible precursor **13** possesses five stereocenters in ring D. Alternatively, disconnections "b" and "c", regarded as strategic bonds, lead to precursors such as **14** and **15** bearing less appendages and stereocenters. Hypothetically, in the forward sense using these precursors,

the lactone ring might be forged by, for instance, formate radical cyclization[14] of **14** or halolactonization[15] of **15**.

On the basis of Corey's analysis, we envisioned bicyclization reactions as particularly well-suited to forging the MBRs of the cephalotanes. An analysis of all of the bicyclization possibilities to construct the characteristic [2.2.2]bicyclic framework led us to the three plausible bond disconnections illustrated in Figure 2B. Disconnection I would lead to precursor **16**, which, in the forward sense, would generate four stereocenters in a single transformation. Alternatively, bicyclizations II and III, which construct only two stereocenters, would trace back to planar tetracycles **17** and **18** (bearing two stereocenters), which may be more challenging to prepare. Therefore, we selected disconnection I and hypothesized that intramolecular inverse-electron-demand Diels–Alder reactions via endocycloadditions employing indene-pyrone derivatives such as **19** would facilitate formation of the desired core framework of the cephalotanes. Precursor **19** was prepared through cross-coupling reactions using readily available building blocks; commercially available hydroxyindanone **20** (CAS number 67901-82-0, from ChemShuttle) and pyrones related to **22**, which would be tethered by a two-carbon fragment (**21**).

Construction of the Core Skeleton.

Our synthetic studies began with iterative coupling reactions to prepare precursors for our planned Diels–Alder cycloaddition (Scheme 1). To investigate a variety of cross-coupling reactions, we prepared triflate **23** in 97% yield from hydroxyindanone **20** by treatment with Tf_2O and pyridine. We found that treatment of **23** with known borane **21**[16] under the palladium-catalyzed Suzuki coupling conditions, reported by Molander and co-workers, proceeded with good conversion to ethylated indanone **24**. An iterative coupling sequence using **24** with pyrone derivatives (**22**) was then explored. Given our group's interest in the utility of dibromopyrone **22a** for natural product syntheses through site-selective cross-coupling reactions,[17] we initially sought to take advantage of our insights into the reactivity of **22a** in applying it to preparation of indanone-pyrone **25a**. Unfortunately, in this case, when **22a** was subjected to iterative coupling reaction conditions with **24**, we did not observe any productive reactions, presumably because the electron-deficient dibromopyrone **22a** underwent rapid degradation under the basic reaction conditions. We then turned our attention to less electron-deficient pyrone triflates as a coupling partner. To our delight, treatment of **24** with simple pyrone triflate **22b** gave rise to the desired coupled product (**25b**) in 80% yield over two steps. We later found that we could effect a one-pot iterative coupling to afford the product (**25b**) in an acceptable 46% yield. This coupling reaction was also effective using methylpyrone triflate **22c** to provide indanone-methylpyrone **25c** in 64% yield over two steps. With these substrates for the key cycloaddition reaction in hand, we started investigating the proposed intramolecular Diels–Alder step.

Our initial plan was to prepare the silyl enol ether from indanone-pyrone **25b** to investigate the proposed intramolecular Diels–Alder cycloaddition (Scheme 2A). To our delight, we observed that subjecting indanone-pyrone **25b** to soft-enolization conditions with TMSOTf in the presence of *N*,*N*-diisopropylethylamine (DIPEA) effected the desired cycloaddition to produce (*endo*)-adduct **27** along with silyl enol ether **26**. After optimization, we found

that using 2.1 equiv of TMSOTf was crucial for full conversion to the desired cycloadduct. Presumably, 1 equiv of TMSOTf was consumed in the formation of **26** and the additional equivalents served as a Lewis acid to promote the cycloaddition, providing **27** in 80% yield as a single diastereomer. It is possible that the cycloaddition proceeds as a stepwise process akin to a Mukaiyama–Michael addition/aldol process.[18] The structure of **27** was unambiguously confirmed by X-ray crystallographic analysis. This success led us to attempt the cycloaddition with indanone-methylpyrone **25c** to obtain **28**, which would possess all of the carbon atoms of the C_{18}-cephalotane natural products (Scheme 2B). However, this approach was uniformly unsuccessful under a variety of conditions. We only detected eight-membered ring formation under soft-enolization conditions, which likely occurred through generation of undesired silyl ketene acetal **29**, which upon Mukaiyama-type aldol addition yielded **30** in 24% along with nonspecific degradation side products. While direct access to **28** was unsuccessful, we were pleased to find conditions to construct the core structure of the cephalotane benzenoid family (i.e., **27**). Nonetheless, this outcome necessitated a functionalization of the double bond of **27** to install the desired methyl group.

Mukaiyama Hydration Approach and First-Generation Synthesis of Cephanolide C.

We first sought to convert the double bond of **27** to a ketone group which upon either α-alkylation or 1,2-addition, depending on the regioselectivity for ketone installation, would introduce the desired methyl group. To this end, we attempted hydroboration and epoxidation to prepare alcohol **31** or epoxide **32**, respectively (Scheme 3A). Mander and co-workers previously demonstrated that hydroboration proceeds on similar [2.2.2]-bicycles bearing tetracyclic tri-substituted alkenes to install a hydroxy group in moderate yields in their model studies for the synthesis of harringtonolide.[19] Recently, Cai and co-workers adopted an analogous hydroboration in their total syntheses of cephanolides A and B.[9d] However, in our case, these hydroboration conditions as well as other variants[20] did not provide the desired product (**31**). Instead, we observed reaction with the lactone moiety and ensuing decomposition. Epoxidation of **27** was also challenging using a variety of conditions due to low reactivity of the double bond under mild conditions.[21] Competitive benzylic oxidations of the penta-cycle were observed using stronger oxidants.[22] These observations led us to try different reaction types, especially radical-based conditions that are known to be more functional group tolerant. As a result, we turned our attention to the Mukaiyama hydration[23] which could overcome the challenges we observed using two-electron chemistry. To our delight, modified Mukaiyama hydration conditions reported by Inoue[24] gave rise to the desired product, which was later optimized using $Co(thd)_2$ as a catalyst[25] along with careful manipulation of the peroxide intermediate (**33**) to afford **34** in 42% yield as a single constitutional isomer. The selectivity of this alkene functionalization, unambiguously confirmed by X-ray crystallographic analysis, necessitated a 1,2-methylation of the carbonyl group to install the requisite methyl group.

To install the methyl group at C4 of **34**, we attempted enol triflation conditions using a variety of bases and electrophiles as well as 1,2-addition of methyl nucleophiles into the ketone group (Scheme 3B). These approaches were unfortunately unsuccessful because **34** proved extremely labile under basic conditions and underwent E1cb elimination of the lactone via enolization, followed by nonspecific decomposition likely following

decarboxylation. Because of this inherent lability of **34**, we turned our attention to olefination conditions which could convert the ketone group to an *exo*-methylene under mild, neutral conditions. After extensive screening, we found that Nysted[26] and Lombardo[27] olefination conditions gave rise to the desired product (**37**) in low yield. Further optimization based on these conditions[28] led us to modified conditions where $Ti(O\textit{i}\text{-}Pr)_2Cl_2$ used in combination with a variant of the Nysted reagent[29] was effective in accomplishing the desired methylenation to give **37** in an acceptable 53% yield. This sequence facilitated the completion of the C_{18}-cephalotane benzenoid carbon skeleton, forming the basis for late-stage functionalizations en route to the congeners in this subset of the natural product family.

Diastereoselective hydrogenation of exo-methylene **37** was accomplished using Pd/C under a H_2 atmosphere in MeOH in quantitative yield and excellent diastereoselectivity, followed by one-pot benzylic oxidation and deprotection of the tertiary alcohol to give rise to cephanolide C (**3**). The origin of the stereoselectivity in the hydrogenation still remains unclear but may be attributed to a stereoelectronic effect of electron depletion on one face of the alkene group through interaction with the lactone carbonyl π^* by analogy to a previous description by Woodward.[30] Using this route, we prepared **3** in a total of eight steps from hydroxyindanone **20** in a first-generation synthesis; a total of seven steps using the one-pot iterative coupling to access **3**. In addition, allylic C–H oxidation of **37** using SeO_2 and subsequent one-pot Dess–Martin periodinane (DMP) oxidation afforded enone **38** in 76% yield. Subjecting **38** to hydrogenation conditions, followed by epimerization at the α-position gave rise to methyl ketone **39** in 52% yield over two steps. Here, it is notable that the diastereoselectivity for the hydrogenation of **38** is opposite to that observed for **37**, likely reflecting the inherent stereoselectivity of the bicycle. For hydrogenation in the case of **38**, the stereoelectronic effect proposed in **37** is less pronounced due to highest occupied molecular orbital (HOMO) lowering for the alkene group of the enone by virtue of conjugation to the newly installed carbonyl group. Ketone **39** represents our advanced intermediate toward the syntheses of cephanolide A and the ceforalides.

More Direct Alkene Difunctionalization Approach.

Although a modified Mukaiyama hydration and Lombardo olefination provided access to the cephalotane benzenoid family as described above, we were dissatisfied with this multistep sequence proceeding in moderate yields. Given the success of the metal-hydride hydrogen atom transfer (MHAT)-mediated hydration reaction, we envisioned direct conversion of alkene **27** to the hydromethylation product (**40**) using emerging MHAT conditions.[31] For example, Baran and co-workers reported Fe-mediated hydromethylation using hydrazones as a methyl group surrogate,[32] while Shenvi and co-workers showcased Mn/Ni dual catalytic hydroalkylation using alkylhalides as the electrophile.[33] However, these approaches proved unsuccessful under several conditions, and we only observed partial nonspecific decomposition along with recovered starting material (Figure 3A). We postulated that degradation under these conditions might be attributed to the regioselectivity of the MHAT process (Figure 3B). Although the desired selectivity was observed under Co-catalyzed hydration conditions via intermediate **A**, the resulting product (**34**) was labile, and the yield of the reaction remained unsatisfactory. The undesired intermediate (**B**) was

theorized to undergo rapid degradation through β-elimination of the lactone moiety and attendant decarboxylation. To circumvent these challenges, we turned our attention to alkene difunctionalization[34] in which regioselectivity can be tuned by a choice of ligands and/or reaction conditions.

For our purposes, we were particularly drawn to the work of Fu and co-workers which showcased Cu-catalyzed regiodivergent alkylboration of terminal alkenes using alkylhalides as an electrophile.[35] They proposed that a weak coordination effect of heteroatoms in the substrates to copper was critical in facilitating the desired migratory insertion and thus suppressed problematic side reactions of the copper-borane species with alkylhalides. As described in Scheme 4A, we envisioned that the π-system of the lactone carbonyl group of **27** could serve as the weakly coordinating group via **C** to suppress generation of an unproductive alkyl boronic ester (**42**). Borocupration could therefore lead to organocopper intermediate **D** (which might be engaged in a donor–accepter interaction with the π^* of the lactone carbonyl). Methylation of **D** at that stage would afford desired compound **41**. Notably, while only terminal alkenes were employed in the work of Fu, we anticipated that the strain inherent in the [2.2.2]bicycle of **27** would raise the ground-state reactivity for the internal alkene in this case.

We commenced our investigation using literature conditions to effect the borocupration then methylation sequence by treating **27** with a combination of CuCl and XantPhos in the presence of B_2pin_2, LiO*t*-Bu, and MeOTs or MeOMs as a methylating agent in dimethylacetamide (DMA) at 60 °C (Scheme 4A, entries 1 and 2). However, these established conditions resulted in nonspecific decomposition of the substrate along with only a trace amount of the trimethylsilyl (TMS)-cleaved free alcohol. Changing the solvent to tetrahydrofuran (THF) (entry 3), which is often employed in the alkylboration of alkynes,[36] resulted in productive reactions of **27**; however, the organocopper intermediate underwent competing protonation instead of methylation to afford **43** as a single isomer. Because **43** was unstable during purification using silica gel, NMR yields are provided for this reaction. While the proton source for the formation of **43** was not immediately obvious, we confirmed that addition of H_2O instead of a methyl electrophile afforded **43** in 92% NMR yield (entry 4). It may therefore be the case that **43** was formed from adventitious water likely present in the MeOTs (see the Supporting Information for a more detailed description of this investigation). The structure of **43** was confirmed after its chemical transformation to the corresponding alcohol (**31**) by one-pot oxidation in 90% yield—supporting the anticipated high regio- and diastereoselectivities (Scheme 4B).

Despite the protonation that led to **43** being undesired, the selectivity of the borocupration encouraged us to pursue this transformation further. On the basis of the results in entries 1–4, we hypothesized that nucleophilic addition of the sp^3-organocopper species only occurs in polar solvents, like DMA, and that the generated sulfonate byproducts cleave the TMS group, resulting in decomposition. Therefore, we changed the electrophile to alkyl iodides which were employed as electrophiles in Fu's report, with the exception of their methylation reactions. When we used MeI (entry 5), only a trace amount of **41** was detected along with unreacted **27** (85% yield), probably because of the low boiling point of MeI (42.4 °C). Therefore, $TMSCH_2I$ was used as an electrophile (entry 6). We were pleased to

observe the desired alkylation for the first time, with **44** being obtained in 54% yield as a single isomer. This observation suggested that the desired methylation may also be achieved through operational/technical manipulations. When the reaction was conducted in a sealed tube (entry 7), no improvements were observed and **27** was recovered in 51% yield. Gratifyingly, we found that after treating **27** with 1 equiv of MeI at room temperature and then adding MeI at 60 °C in a dropwise manner gave rise to the desired methyl boronic ester (**41**) in 53% yield as a single isomer (entry 8). Following extensive additional optimization, including increasing equivalents of the reagents and running the reaction in *N*,*N*′-dimethylpropyleneurea (DMPU) at 80 °C, **41** was obtained in 83% yield (entry 9). It is important to add 1 equiv of the electrophile before heating, otherwise decomposition is observed, likely because decarboxylation occurs under thermal heating in the absence of the electrophile. With this selective and direct method to functionalize the double bond of **27** in hand, the stage was set for accessing the natural products by late-stage transformations.

Synthesis of Cephanolide A.

Subjecting **27** to methyl-boration conditions, followed by one-pot oxidation of the corresponding boronic ester to a hydroxy group afforded methyl alcohol **45** in 77% yield as a single isomer (Scheme 5). The resulting alcohol was then converted to ketone **39** by DMP oxidation; a total of two steps from **27**. Previously, **39** was prepared in five steps from **27** (see Scheme 3). Thus, the efficiency of the current approach showcases the power of the alkene difunctionalization approach. Treatment of **39** with $NaBH_4$ reduced the carbonyl group to the corresponding alcohol with the desired stereochemistry for subsequent transformations. Subjection of the alcohol (not shown) to Suárez oxidation conditions[37] and one-pot TMS cleavage furnished hexacyclic tertiary alcohol **46** in excellent yield (99%) over two steps. We initially attempted a direct ionic deoxygenation of **46** under $InCl_3$-catalyzed conditions.[38] However, this unexpectedly led to chloride **47** in 75% yield. The structure of **47** was unambiguously determined by X-ray crystallographic analysis. This unusual transformation might be attributed to the rigid ring system of **46**, which, instead of facilitating an intramolecular hydride delivery from the diphenyl oxysilane intermediate through rehybridization to partial sp^2-like character at the benzylic position, generates a stabilized carbocation through rapid E1 elimination, followed by trapping with the chloride anion. Because a reductive radical dechlorination of **47** was unsuccessful, we instead turned to a Barton–McCombie deoxygenation protocol.

Subjecting **46** to xanthylation conditions and subsequent reductive deoxygenation afforded hexacycle **48** in 82% yield over two steps. We previously reported that **48** could be converted to cephanolide A by treatment with malonoyl peroxide (**49**)[39] and subsequent hydrolysis in 39% yield as a 6:1 mixture of constitutional isomers. Because the yield and selectivity for this oxygenation of arenes were unsatisfactory, we reinvestigated this transformation. While Zhai and co-workers very recently reported a two-step protocol using a Friedel–Crafts acylation/Dakin-type Baeyer–Villiger oxidation sequence from the same intermediate (i.e., **48**),[9f] we found that the C–H thianthrenation chemistry developed by the Ritter group[40] was effective for this purpose. Subjecting **48** to the literature conditions for thianthrenation in the presence of TFTO (**50**) gave rise to thianthrenium salt **51** in quantitative yield and an improved 13:1 selectivity. Ritter and co-workers

separately reported oxygenation of thianthrenium salts using a photoredox catalyst in the presence of copper reagents.[41] Unfortunately, in our case, those conditions only effected protodethianthrenation to give **48** in quantitative yield. However, we were pleased to find that conversion of **51** to boronic ester **52** under photoirradiation conditions[40] and subsequent one-pot oxidation of the resulting Bpin moiety gave rise to **1** in 92% yield. Although the yield was somewhat diminished, this sequence could be conducted effectively in a single pot (50% overall yield). Using these late-stage manipulations, cephanolide A was synthesized in a total of 10 steps from commercially available hydroxyindanone **20**.

Formal Hydromethylation of 27 and Synthesis of Cephanolide B.

To gain efficient access to other cephanolide congeners, it was necessary to identify conditions for the direct hydromethylation of alkene **27**. We envisioned that instead of the borocupration/methylation sequence that we had employed previously (see Scheme 4), hydrocupration of the double bond in **27**, followed by methyl substitution would provide the desired formal hydromethylation product (i.e., **40**, Scheme 6A). Unfortunately, this approach was unsuccessful even after trying many reaction conditions with a variety of silanes.[42] Mostly, only nonspecific decomposition, likely because of the lability of **27** under strongly reductive conditions, was observed. This outcome first led us to utilize the common intermediate (**45**) from our cephanolide A synthesis by effecting removal of the hydroxy group. For this purpose, methyl alcohol **45** was subjected to xanthylation, followed by Barton–McCombie deoxygenation and deprotection of the tertiary alcohol, which provided, unexpectedly, bicyclo[3.2.1] γ-lactone **53** in 63% yield over three steps (Scheme 6B). The constitution of **53** was confirmed by X-ray crystallographic analysis. We believe that **53** results from translactonization before xanthate formation and it is the resulting secondary alcohol group that is then deoxygenated.

These failures necessitated an alternative approach, leading us to attempt protodeboronation of methyl boronic ester **41** (Scheme 6C). Surprisingly, our perusal of the literature did not reveal many examples of protodeboronation of sp^3 Bpin esters. We initially attempted oxidative conditions developed by the Aggarwal group.[43] However, this resulted in degradation presumably through decarboxylative elimination of the lactone moiety in the corresponding boronate intermediates. Therefore, we turned our attention to reductive conditions reported by Studer and co-workers[44] and found that treatment of **41** with PhLi to form the corresponding borate (**54**), followed by photoinduced reductive protodeboronation in the presence of PhSH and one-pot cleavage of the TMS group, gave rise to pentacyclic alcohol **55** in 76% yield. In Studer's report, they isolated borate intermediates which were then subjected to the photoinduced deborylation conditions. However, in our case, because of the lability of borate **54** (attributed to β-elimination of the strained lactone moiety), it was important that after the formation of borate **54** at −78 °C, the reaction mixture was carefully quenched with MeOH/acetone dropwise at −78 °C, followed by immediate subjection to the irradiation conditions to suppress undesired side reactions. An $InCl_3$-catalyzed ionic deoxygenation[38] of **55** worked well in this case, in comparison to deoxygenation of hexacyclic alcohol **46** (Scheme 4), affording the desired product in 97% yield. Phthaloyl peroxide (PPO)-mediated oxygenation conditions[45] allowed access to cephanolide B (**2**) in 74% yield as a 1.3:1 mixture with its constitutional isomer. We also found that C–H

thianthrenation, followed by the borylation/oxidation sequence was effective for the final step (see the Supporting Information for details), providing **2** (94%, C13/C15 = 1:1) over two steps or 67% yield through a one-pot sequence. In this way, we synthesized **2** in seven total steps from **20**.

First-Generation Synthesis of Cephanolide D.

To synthesize cephanolide D, which is a C_{19}-benzenoid, we sought to employ directed *ortho*-C–H functionalization to install the methyl ester moiety (Scheme 7). The common intermediate (**40**) after hydrogenation of **37** from our first-generation synthesis of cephanolide C (**3**, see Scheme 3B) was subjected to pyridinium chlorochromate (PCC)-mediated benzylic oxidation conditions to provide ketone **56**, which was then condensed with methoxy amine to afford methyloxime **57** in good yield. We found that methyloxime-directed C–H methoxycarbonylation[46] was effective only when a stoichiometric amount of $Pd(OAc)_2$ was used, giving rise to methyl ester **58** in 42% yield. At this point, our extensive investigations to cleave the methyloxime of **58** were uniformly unsuccessful. Therefore, we pivoted to an alternative approach.

In this regard, condensation of **56** with hydroxyamine, followed by one-pot acetylation of the corresponding oxime afforded acetyloxime **59**, which was then subjected to Pd-catalyzed *ortho*-C–H acetoxylation conditions,[47] providing acetate **60**. Global cleavage of the acetyl groups and subsequent oxidative deoximation using a Fe catalyst[48] gave ketophenol **61** in 33% yield over four steps. Triflation of **61** to give the corresponding triflate in 84% yield, followed by Pd-catalyzed methoxycarbonylation and one-pot deprotection of the tertiary alcohol group afforded cephanolide D (**4**) in 93% yield. In this way, albeit indirectly, we were able to achieve the first total synthesis of **4**.

Solving the Previous Challenges toward the Synthesis of Cephanolide D.

While we had already achieved total syntheses of cephanolides A–D, our improved, concise sequence to prepare alcohol **55** enabled us to solve challenges we faced in our original route (Scheme 8A). First, in the previous route, benzylic oxidation of the protected alcohol (**40**) was capricious and scale dependent. In contrast, benzylic oxidation of free alcohol **55** reproducibly provided cephanolide C (**3**) in moderate yield, probably because PCC coordinates with the tertiary alcohol, increasing solubility to promote the desired oxidation. To date, we have prepared several hundred milligrams of **3**; the entire synthesis sequence proceeds in six steps from commercially available **20**. Treatment of **3** with methoxy amine provided the corresponding oxime in quantitative yield, followed by directed *ortho*-C–H methoxycarbonylation using a stoichiometric amount of $Pd(OAc)_2$ to give methyl ester **62** in 52% yield. Finally, we found that cleavage of the methyloxime was possible under ozonolysis conditions[49] to afford cephanolide D (**4**) in 35% yield (RSM: 64%). Using this more direct sequence, we completed the synthesis of **4** in nine steps. In addition, because the C–H methoxycarbonylation did not proceed using a substoichiometric amount of $Pd(OAc)_2$ even after extensive optimization, we sought an alternative catalytic C–H functionalization. To this end, directed C–H cyanation under Rh-catalyzed conditions in the presence of *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS), following the precedent of Fu et al.,[50] successfully afforded nitrile **64** in 73% yield (Scheme 8B). In principle, the nitrile group can

serve as a surrogate for an ester group and provide an opportunity for further derivatization of these natural products at this position.

Synthetic Study of Ceforalides.

During the course of our synthetic studies of the cephanolides, novel natural product congeners of this benzenoid family, namely, the ceforalides, were reported.[11] Our concise synthetic route to the cephanolides set the stage to access some of these newly isolated congeners. For example, treatment of common intermediate **45** with the Jones reagent and additional H_2SO_4 effected oxidation of the secondary alcohol and simultaneous cleavage of the TMS group, affording ketoalcohol **65** in 50% yield (Scheme 9A). Deoxygenation of **65** turned out to be surprisingly difficult. We did not observe the desired precursors for Barton–McCombie deoxygenation[51] under xanthylation, thiocarbonation, and thiocarbamation conditions nor was Zn-mediated hydrodeoxygenation of oxalates[52] successful in our hands. In addition, attempted $InCl_3$-catalyzed ionic deoxygenation[38] gave chloride **66** in 56% yield. Although reductive dechlorination of **66** did not proceed, we were inspired by this approach and converted alcohol **65** to bromide **67** by treatment with DMTU and NBS[53] in 61% yield. Gratifyingly, reductive debromination of **67** proceeded smoothly, followed by reduction of the ketone group to give rise to ceforalide D (**8**) in 68% yield over two steps (overall eight steps). Remarkably, selective benzylic oxidation in the presence of the free secondary alcohol group in **8** was achieved using photoinduced conditions[54] to afford ceforalide C (**7**) in 49% yield, completing the synthesis in nine total steps from commercially available **20**.

Next, we sought to prepare ceforalide E (**9**, Figure 1) by benzylic methylene oxidation at C20 directed by the hydroxy group of **8**. Toward this goal, we subjected **8** to Barton reaction conditions[55] and variants of the Suárez oxidation[56] (Scheme 9B). Unfortunately, instead of the desired ketoalcohol, we only observed formation of a THF ring. For example, photoirradiation of **8** with $Pb(OAc)_4$, I_2, and $CaCO_3$ gave **48** in 97% yield. Nevertheless, this reaction could be employed productively since C7 benzylic oxidation of **48** using PCC gave ceforalide F (**10**) in a total of 10 steps.

We then turned our attention to synthesizing ceforalide G (**11**) directly from cephanolide A (**1**), which required installation of the C7 hydroxy group. This transformation proved challenging due to cross reactivity of the phenolic hydroxy group. To circumvent this challenge, thianthrene salt **51** was subjected to borylation conditions to afford boronic ester **52** in 84% yield (Scheme 9C). We found that photoredox oxygenation conditions, which we employed in preparing **7** (Scheme 9A), using a compact fluorescent light (CFL) instead of blue light-emitting diodes (LEDs) (400 nm) afforded alcohol **68** selectively. Finally, the Bpin moiety was converted to the hydroxy group under oxidation conditions to give ceforalide G (**11**) in 42% yield over 2 steps (overall 13 steps).

Lastly, our improved synthesis of cephanolide A (see Scheme 4) also enabled access to the *para*-quinol congener, ceforalide H (**12**, Scheme 10). Oxidative dearomatization of **1** by treatment with phenyliodine(III) diacetate (PIDA) in a $MeCN/H_2O$ mixed solvent system selectively gave rise to **12** in 78% yield as a single constitutional isomer. In this way, the first total synthesis of **12** was accomplished in 11 steps total.

Asymmetric Access by Chiral Silyl Auxiliaries.

As described so far, we have established a unified approach to access the cephanolides and ceforalides. To enable asymmetric access to these benzenoid natural products, we began investigating enantioselective and other asymmetric intramolecular inverse-electron-demand Diels–Alder cycloaddition reaction types (Scheme 11). We initially sought to apply a TMS-enol ether (**26**, see Scheme 2) derived from our total synthesis intermediate **25b** for this purpose. However, only cleavage of the TMS group to return **25b** was observed under a variety of conditions. Therefore, we decided to prepare indene derivatives instead of silyl enol ethers to test enantioselective cycloadditions. Reduction of the ketone group of **25b** gave alcohol **69** in 93% yield, which was then dehydrated under acidic conditions to afford indene **70** in quantitative yield. With indene **70** in hand, we attempted a variety of enantioselective cycloadditions to give cycloadduct **71**. Ultimately, this approach was unsuccessful due to the low reactivity of **70** under the cycloaddition conditions as well as the thermal lability of the cycloadduct (**71**), which was found to undergo decarboxylation/aromatization. We observed background, thermal cycloaddition upon heating **70** at 60 °C; however, a variety of Lewis acids were ineffective at facilitating the desired inverse-electron-demand Diels–Alder reaction to a significant extent at lower temperatures, resulting mostly in low conversions and almost no enantiomeric excess (ee) (in the cases where chiral, enantioenriched Lewis acid complexes were used). Unlike Cai's synthesis which employs an intermolecular asymmetric Diels–Alder reaction,[9d] our substrate does not bear an additional carbonyl group at the α-position of the pyrone moiety that facilitates coordination of the Lewis acid to promote cycloaddition. In addition, heating the attempted cycloaddition to more than 60 °C induced unproductive decarboxylation, suggesting that HOMO raising of the dienophile, which is presumably achieved with the silyl enol ether, is crucial for this type of cycloaddition.

With this insight, we turned our attention to preparing chiral enol derivatives to enable asymmetric diasteroselective synthesis of cycloadducts. In this regard, Gaich and co-workers recently demonstrated the use of chiral silyl ketene acetals in a normal electron-demand Diels–Alder reaction in their synthesis of canataxpropellane.[57] They effected the cycloaddition through in situ generation of silyl ketene acetals by treatment of an ester with sodium hexamethyldisilazide (NaHMDS), followed by trapping with a TADDOL-derived isopropyl silylchloride. However, in our case, because indanone-pyrone **25b** was found to be extremely sensitive toward strongly basic conditions, it was necessary to develop a different approach in preparing the requisite chiral silyl enol ethers (Scheme 11B). To our delight, we found that TADDOL-derived silanol **72** (prepared in one step from commercial materials; see the Supporting Information) upon triflation, followed by addition of **25b** (to promote formation of chiral enol ether **73** through soft enolization), immediately resulted in the formation of **74** in 96% yield. Although this cycloaddition was *endo*-selective, the diastereoselectivity was modest (1.3:1), which is consistent with the observations of Gaich in their synthesis of canataxpropellane. Nevertheless, these diastereomers were separable, and upon cleavage of the silyl auxiliary with TBAF in quantitative yield, we were able to obtain one of the enantiomers of pentacyclic alcohol **75** in >99% ee.

CONCLUSIONS

In this work, we demonstrate a unified approach toward the syntheses of nine C_{18}- and C_{19}-benzenoid cephalotane-type norditerpenoids in the cephanolide and ceforalide families. The key to the highly concise assembly of the core structure of these natural products was the use of chemical network analysis to identify strategic bond disconnections. In the forward sense, these bonds were forged using multibond-forming reactions. An iterative cross-coupling and a formal inverse-electron-demand Diels–Alder cycloaddition of a silyl enol ether enabled construction of the core skeleton in three steps from a commercially available hydroxyindanone. A significant development that distinguishes the current work from our initial report was the design and implementation of an alkene difunctionalization using borocupration which enabled shorter, divergent access to all of the cephanolides. Late-stage selective manipulations using C–H functionalizations including Suarez C–H etherification, arene C–H oxygenation, thianthrenation, PCC-mediated benzylic oxidation, and directed *ortho*-C–H methoxycarbonylation were critical to success.

In addition to our syntheses of the cephanolides, a new way to deoxygenate benzylic tertiary alcohols through an unusual bromination and reductive debromination sequence allowed us to prepare ceforalide D (eight steps). Furthermore, a selective benzylic methylene oxidation facilitated the syntheses of ceforalides C, F, and G (9–13 steps), and oxidative dearomatization of cephanolide A gave rise to ceforalide H (11 steps). Finally, a potential entry to this cephalotane family in enantioenriched form using our route was accomplished by a chiral silyl auxiliary to effect concomitant silyl enol ether formation/cycloaddition.

Overall, our work highlights the importance of retrosynthetic analysis to craft complex natural products in a concise manner and the power of modern C–H functionalization methods to efficiently diversify complex molecules selectively at a late stage.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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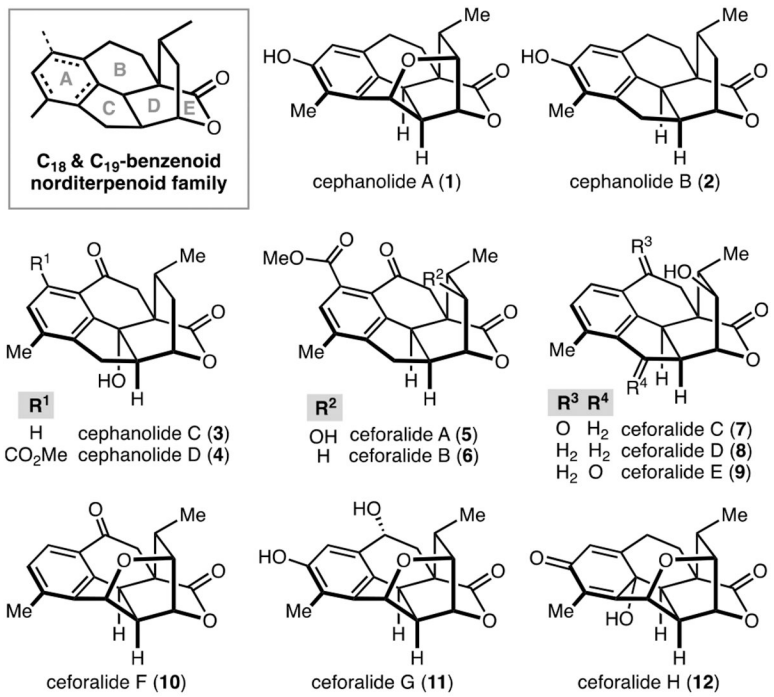


Figure 1.
Benzenoid cephalotane-type norditerpenoids.

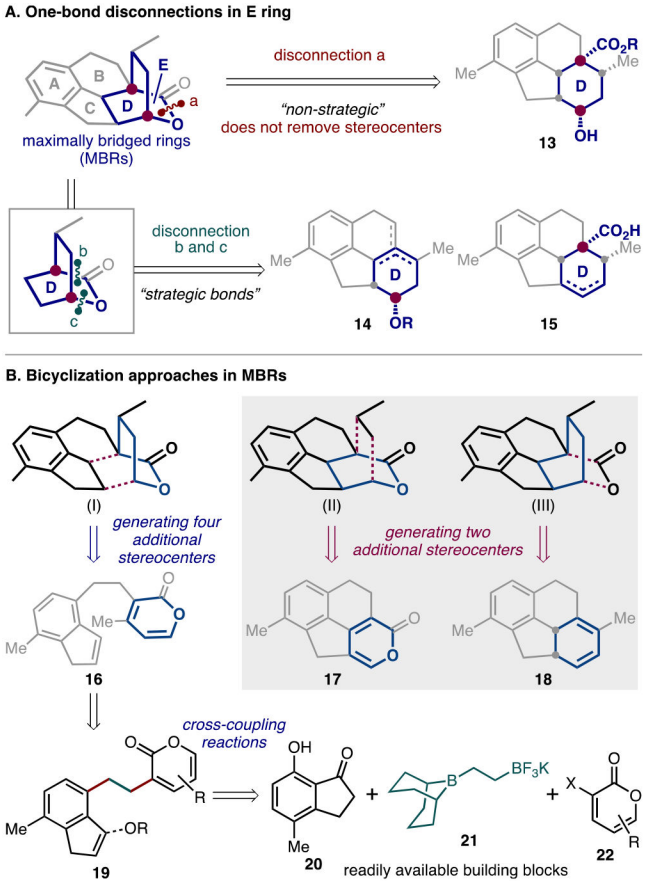


Figure 2.

Network analysis of the cephalotane-type benzenoid core. (A) Classic strategic bond disconnections to reduce structural complexity. (B) Our strategy employing bicyclization to forge MBRs.

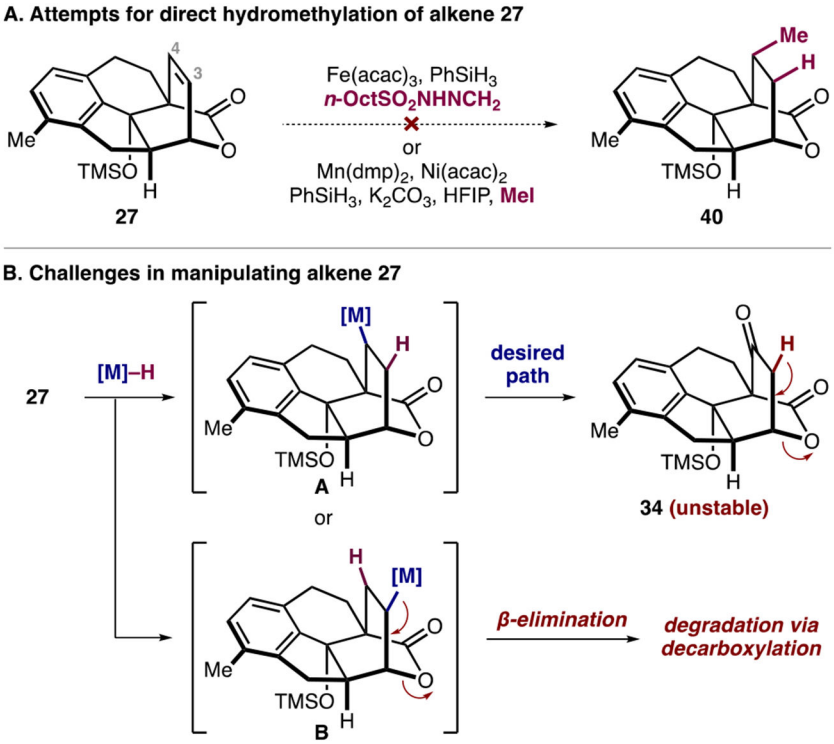
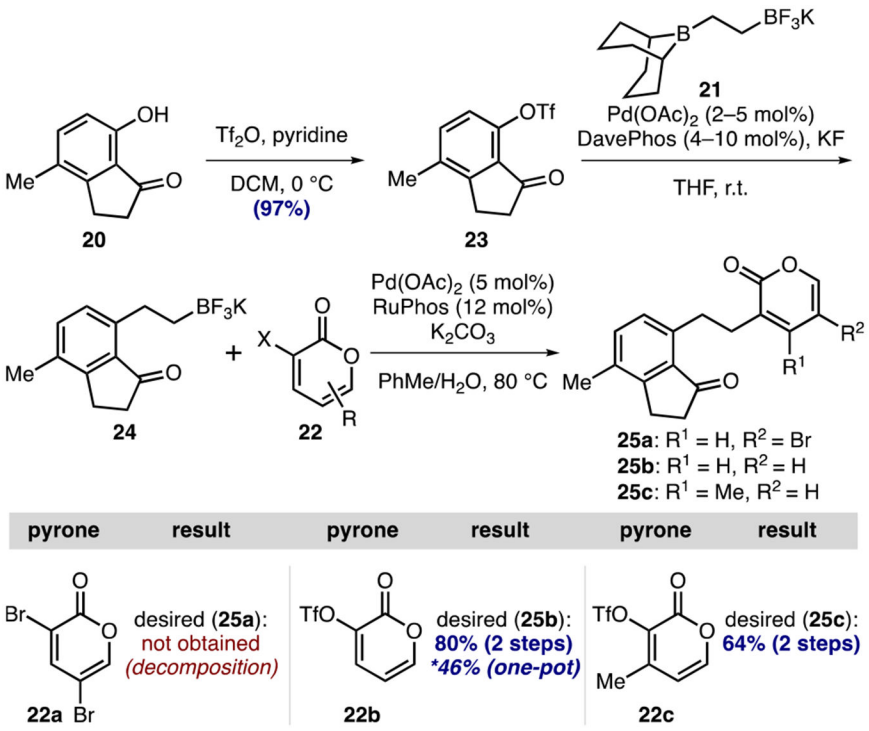
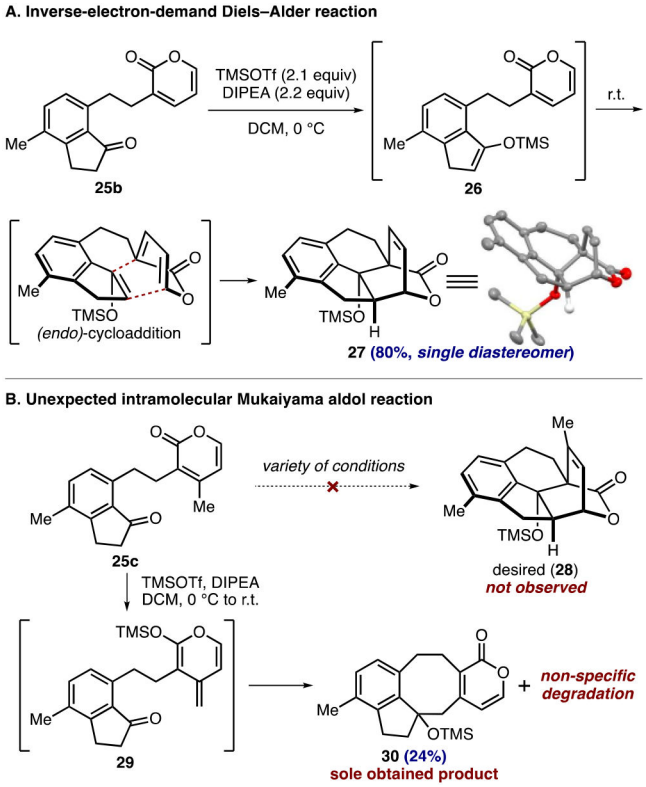


Figure 3.

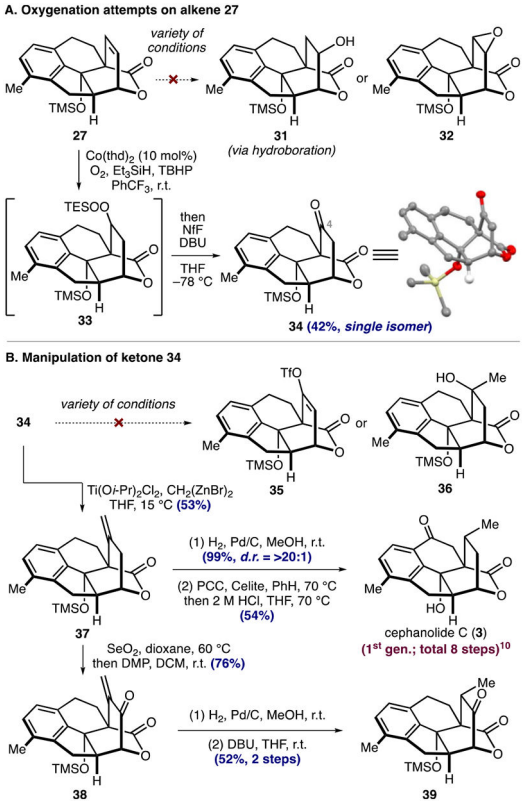
Issues in the MHAT-based reaction approach. (A) Unsuccessful attempts to directly access **40**. (B) Undesired reactivity and lability challenges.



Scheme 1. Iterative Cross-Coupling of Indanone (23) with Borane (21) and Different Pyrone Electrophiles (22)

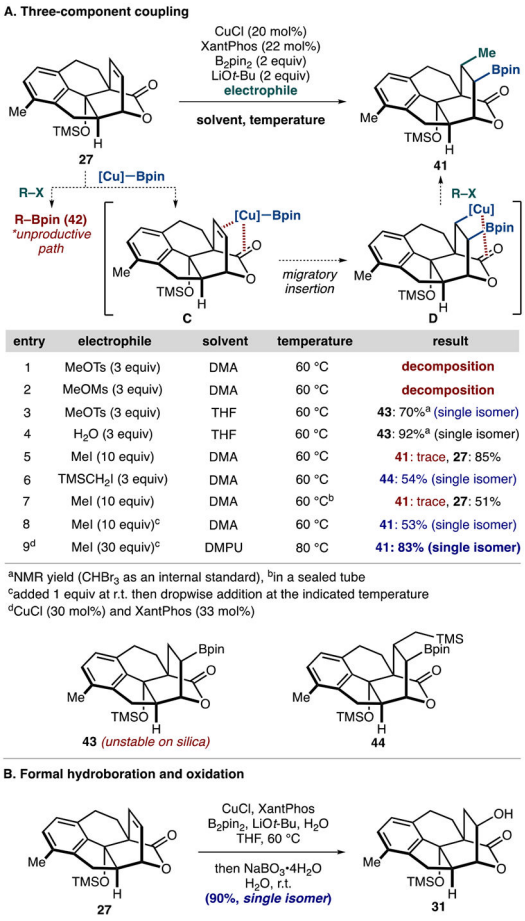


Scheme 2. Bicyclization Attempts Using Indanone-Pyrones



Scheme 3. Manipulation of the Cephalotane Benzenoid Core[a]

[a](A) Mukaiyama hydration and its regioselectivity. (B) Synthesis of cephanolide C and a precursor en route to cephanolide A.



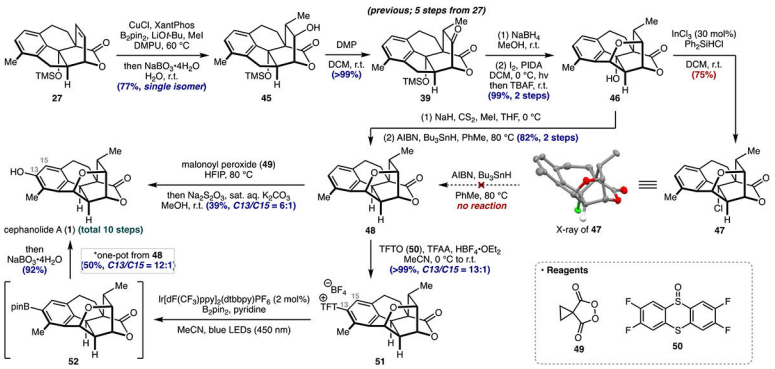
entry	electrophile	solvent	temperature	result
1	MeOTs (3 equiv)	DMA	60 °C	**decomposition**
2	MeOMs (3 equiv)	DMA	60 °C	**decomposition**
3	MeOTs (3 equiv)	THF	60 °C	**43**: 70%[a] (single isomer)
4	H_2O (3 equiv)	THF	60 °C	**43**: 92%[a] (single isomer)
5	MeI (10 equiv)	DMA	60 °C	**41**: trace, **27**: 85%
6	$TMSCH_2I$ (3 equiv)	DMA	60 °C	**44**: 54% (single isomer)
7	MeI (10 equiv)	DMA	60 °C[b]	**41**: trace, **27**: 51%
8	MeI (10 equiv)[c]	DMA	60 °C	**41**: 53% (single isomer)
9[d]	MeI (30 equiv)[c]	DMPU	80 °C	**41: 83% (single isomer)**

[a]NMR yield ($CHBr_3$ as an internal standard), [b]in a sealed tube
[c]added 1 equiv at r.t. then dropwise addition at the indicated temperature
[d]CuCl (30 mol%) and XantPhos (33 mol%)

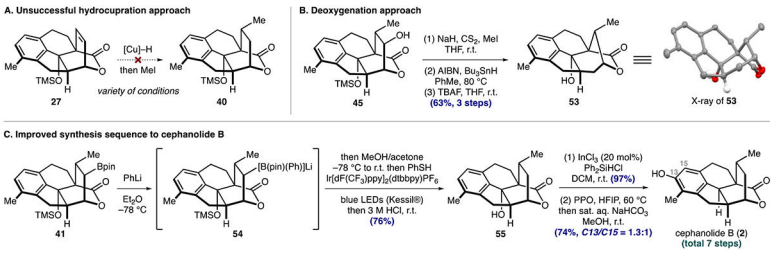
43 *(unstable on silica)* **44**

Scheme 4. Investigation of Alkene Difunctionalization[a]

[a](A) Optimization of carboboration. (B) Structure determination of the unstable formal hydroboration products.

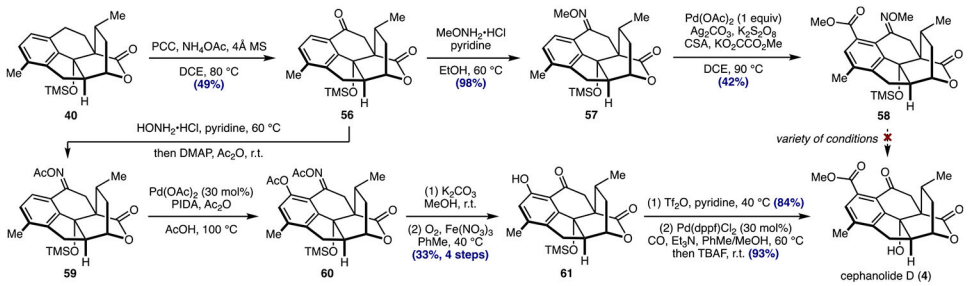


Scheme 5. Improved Synthesis Sequence to Cephanolide A

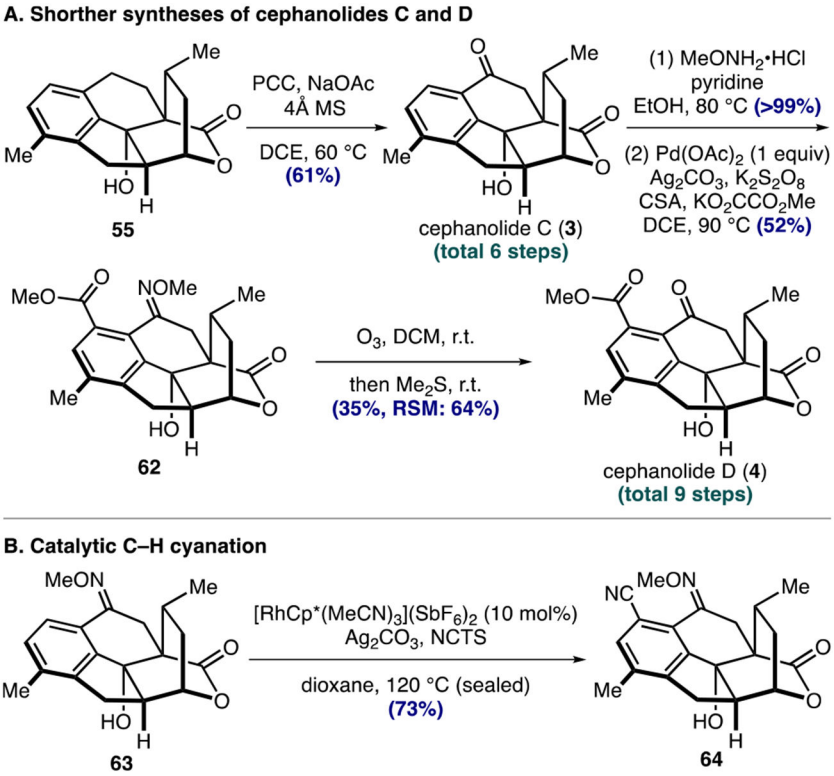


Scheme 6. Total Synthesis of Cephanolide B[a]

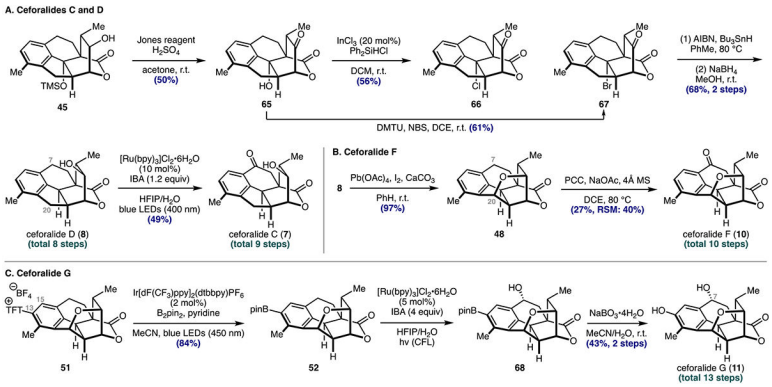
[a](A) Hydrocupration attempts using alkene **27**. (B) Unexpected translactonization/ deoxygenation of alcohol **45**. (C) Successful protodeboronation approach to access cephanolide B.



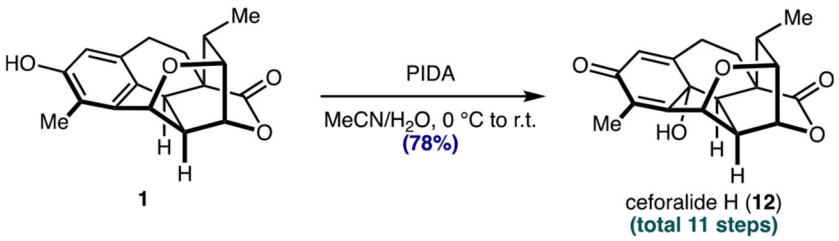
Scheme 7. Oxime-Directed *ortho*-C–H Functionalization and the First Synthesis of Cephanolide D



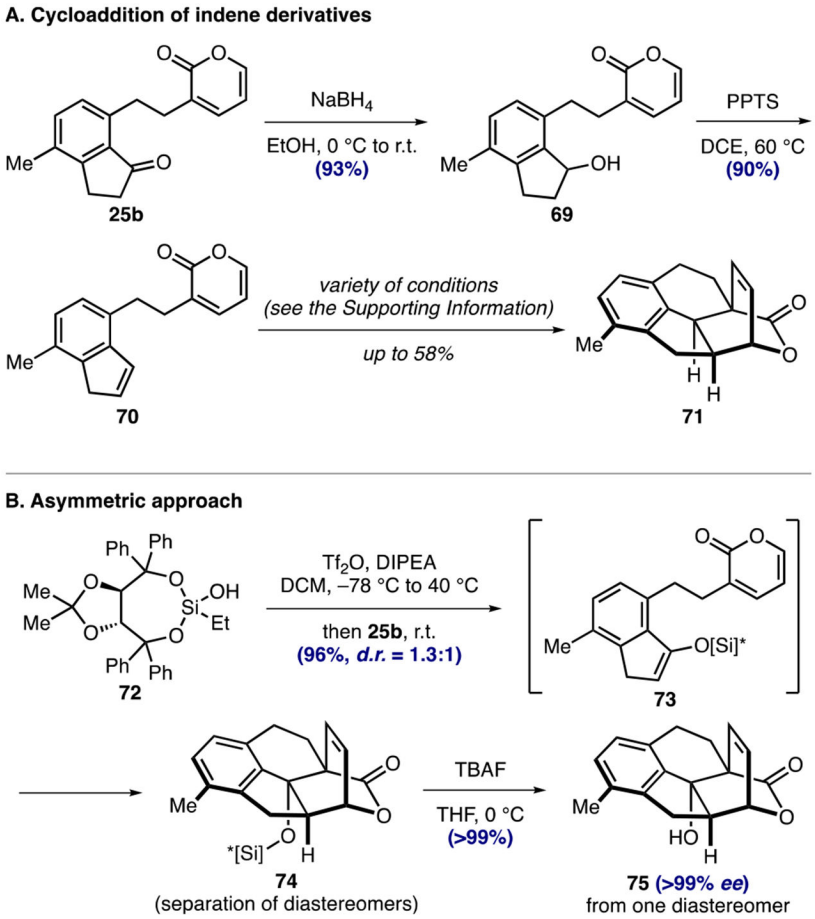
Scheme 8. (A) Ozonolysis-Enabled Shorter Synthesis of Cephanolide D; (B) Discovery of a Catalytic-in-Metal Oxime-Directed *ortho*-C–H Functionalization



Scheme 9. Syntheses of Ceforalides



Scheme 10. Synthesis of Ceforalide H



Scheme 11. Asymmetric Entry into Cephalotane-Type Benzenoids[a]

[a](A) Cycloaddition attempts using indene **70**. (B) Cycloaddition of chiral silyl enol ethers.