Total Synthesis of the Cephalotaxus Norditerpenoids (±)-Cephanolides A–D

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ABSTRACT: Concise syntheses of the cephalotaxus norditerpenoids cephanolides A–D (8–14 steps from commercial material) using a common late-stage synthetic intermediate are described. The success of our approach rested on an early decision to apply chemical network analysis to identify the strategic bonds that needed to be forged, as well as the efficient construction of the carbon framework through iterative Csp^2–Csp^3 cross-coupling, followed by an intramolecular inverse-demand Diels-Alder cycloaddition. Strategic late-stage oxidations facilitated access to all congeners of the benzenoid cephanolides isolated to date.

Among the many considerations in developing a total synthesis of a structurally complex molecule is maximizing the rapid generation of target relevant structural complexity in the forward sense. Therefore, in the retrosynthetic analysis of structurally complex natural products, disconnections that achieve maximum simplification are highly sought after. Bicyclization transforms are broadly recognized to be powerful in this regard.[1] We have found that chemical network analysis,[2-4] which is rooted in seminal reports from Corey,[5] provides an expedient guideline for identifying the strategically most important bonds for this purpose. The benzenoid cephanolide diterpenoids (**1**–**4**, Figure 1) presented an opportunity to test aspects of this type of approach. In addition to identifying strategic disconnections that would ultimately result in the efficient preparation of any of the benzenoid cephanolide congeners isolated to date, we sought to identify a route that could be applied to the synthesis of any of the cephalotaxus diterpenoids. In this Communication, we report our initial studies that have led to the realization of our first goal.

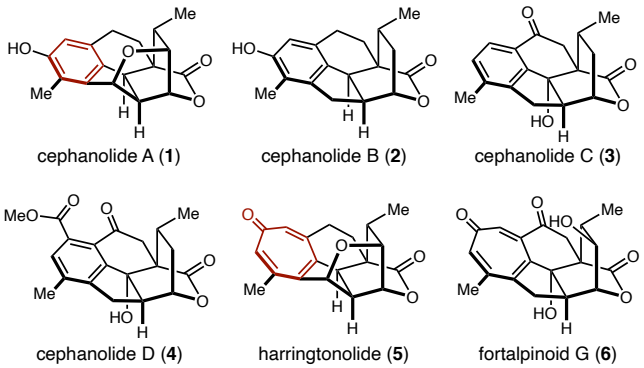


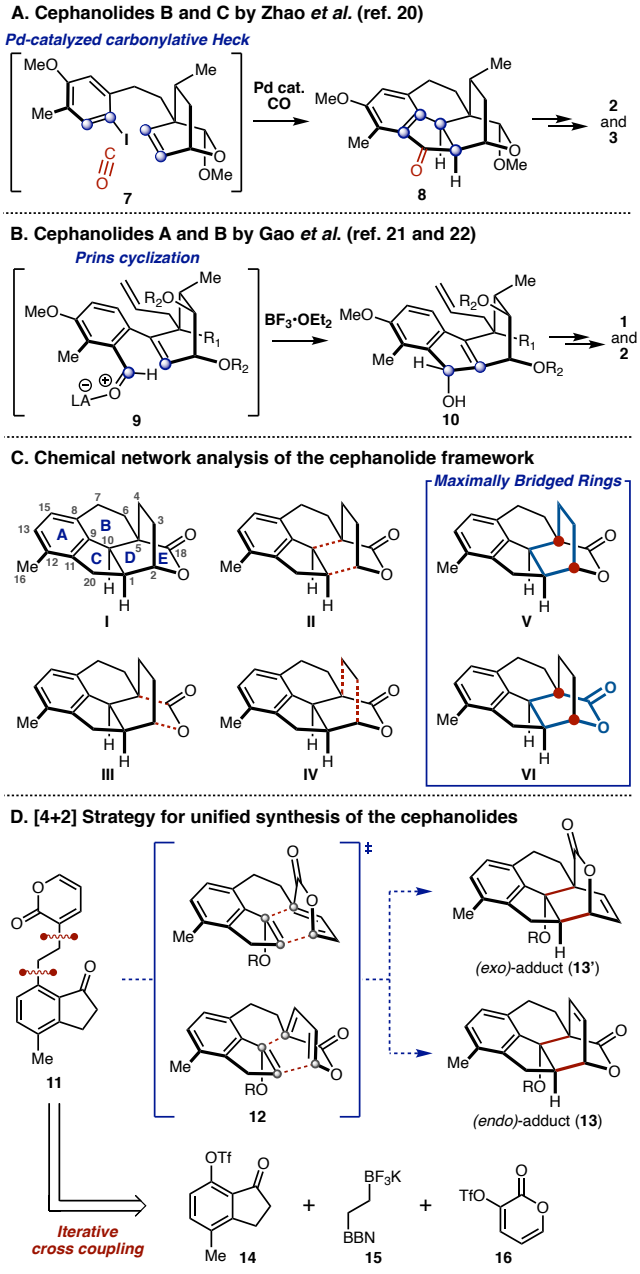
Figure 1. Selected benzenoid and troponoid cephalotaxus diterpenoids.

Cephanolides A–D were isolated in 2017 from *Cephalotaxus sinensis* by Yue and coworkers.[6] They are structurally and biosynthetically related to the cephalotaxus diterpenoids harringtonolide (**5**),[7] and fortalpinoid G (**6**).[8] The larger family of cephalotaxus diterpenoids[9] have shown a broad range of bioactivity that includes plant growth inhibition, antineoplastic, antiviral and antitumor properties.[10-14] Preliminary bioactivity studies of the cephanolides by Yue *et al.*[15] suggest that the A-ring (see **I**, Scheme 1C, for lettering and numbering), along with its oxygenation, may be essential to their cytotoxic activity against human cancer cell lines. Their interesting frameworks and bioactivity have spurred many creative and informative total syntheses of the troponoid diterpenoid harringtonolide (**5**) and congeners over the last 20 years.[16-19] Owing to their more recent isolation, it is only over the last three years that syntheses of the benzenoid cephanolides have been reported. In 2018, Zhao *et al.* reported the total syntheses of cephanolides B and C (**2** and **3**; Scheme 1A) using an innovative Pd-catalyzed carbonylative Heck cascade.[20] In 2020, Gao and coworkers reported an effective synthesis of cephanolide A (**1**) that relied on the application of a Prins-type cyclization (Scheme 1B).[21] Recently, they have also synthesized **2**.[22]

In our chemical network analysis of the cephanolide framework, we identified two maximally-bridged rings (see rings highlighted in blue in **V** and **VI**, Scheme 1C). On this basis, three bicyclization disconnections were identified, leading to the hypothetical precursors **II**, **III**, and **IV**. Of these possibilities, **II** would lead to the maximum increase in target-relevant structural complexity given the attendant generation of four stereocenters in this process. As we considered the appropriate substrate for a planned intramolecular Diels-Alder cycloaddition to forge the framework of **1**–**4**, we settled on indanone-pyrone **11** (Scheme 1D), which, *via* silyl enol ether **12** (rendered in a conformation approaching the transition state), should facilitate the anticipated inverse-demand intramolecular [4+2] cycloaddition.[23-29] Desired

endo cycloadduct **13** would therefore bear oxygenation at C10, lending itself directly to the syntheses of **3** and **4**, but necessitating a deoxygenation in order to access **1** and **2**. However**, 13** appeared ideally suited for the myriad late-stage functionalizations of the arene moiety as well as the C7 and C20 benzylic positions that would be required to access all the known cephanolide congeners. Finally, we envisioned indanone-pyrone adduct **11** arising from indanone-triflate **14** and pyrone-triflate **16**, which would be linked with an appropriate two carbon fragment (**15**) *via* an iterative cross coupling sequence.

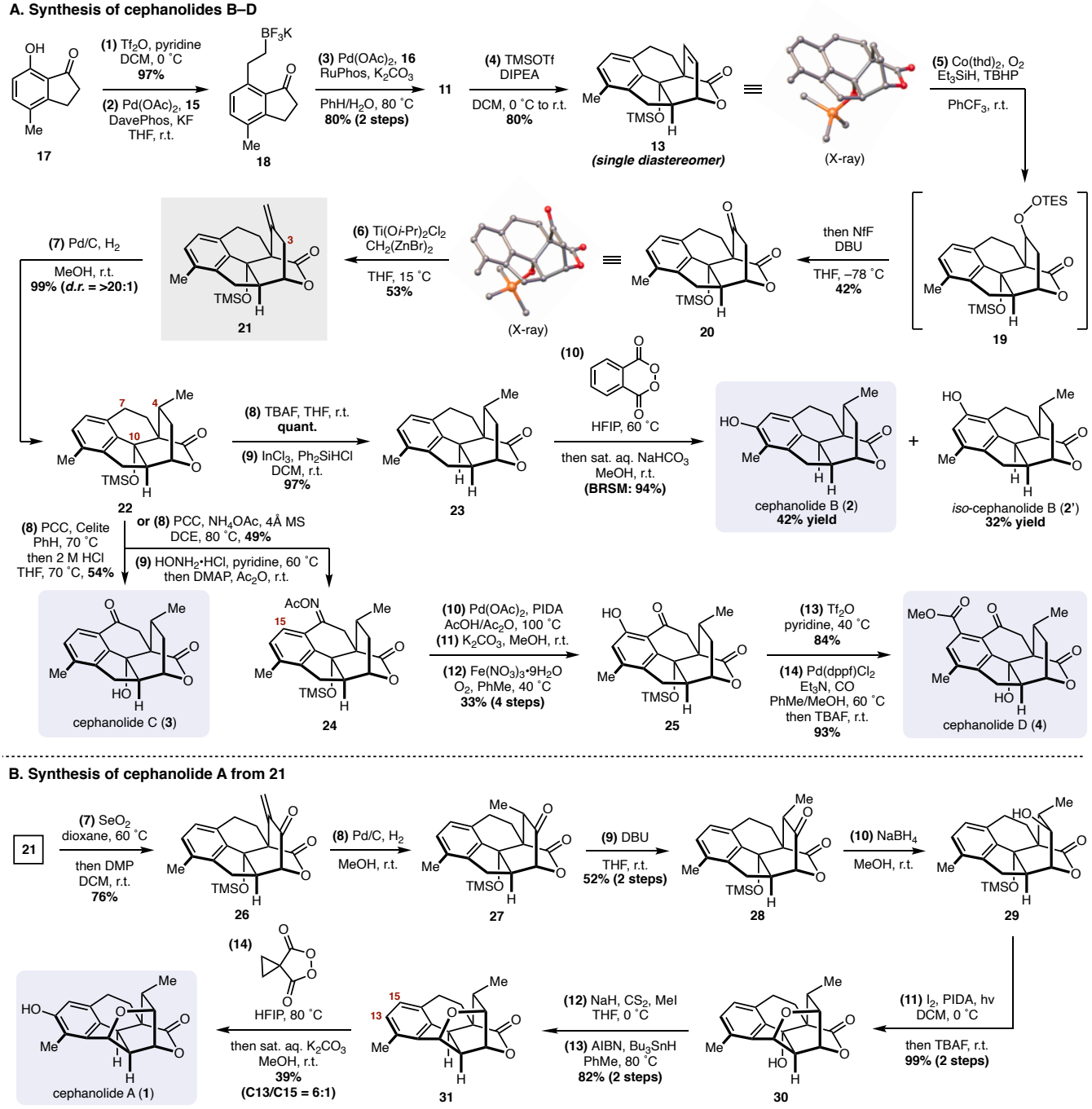
Scheme 1. (A) Key transformations in Zhao's total synthesis of cephanolides B and C (B) Key transformations in Gao's asymmetric total synthesis of cephanolides A and B (C) Chemical network analysis of the cephanolide framework (D) [4+2] cycloaddition strategy identified through network analysis.



Our syntheses commenced with the triflation of commercially available 7-hydroxy-4-methylindanone (**17**, Scheme 2A).[30] Pyrone triflate **16** was prepared from mucic acid following a known sequence reported by the group of Maulide.[31] Iterative sp^2-sp^3 Suzuki cross-couplings of BF_3K-ethylene-9BBN (**15**), generated *in situ* from hydroboration of vinylBF_3K, with **14** and then **16** was accomplished following the precedent established by Molander and coworkers.[32-34] This sequence proceeded on multigram scale with only one chromatographic purification to provide indanone derivative **11** in 80% yield (over two steps). In preparation for the crucial intramolecular Diels-Alder cycloaddition, we sought to prepare various enol ethers of indanone **11**. We were pleased to observe that the cycloaddition proceeded smoothly under conditions to form the silyl enol ether to provide the somewhat unstable endo cycloadduct (**13**). Analysis of the X-ray crystallographic data of a single crystal of **13** unambiguously confirmed its structure. Optimization of this cascade silyl enol formation/[4+2] cycloaddition revealed that two equivalents of TMSOTf were required. Presumably, the first equivalent leads to the formation of the enol ether, while the second equivalent likely serves as a Lewis acid for the cycloaddition.[35-37] We next sought to functionalize the bridging olefin group of **13**. Various attempted hydroborations as well as epoxidation of the olefin group failed, in line with observations made by Mander *et al.* on a similar bridged [2.2.2] bicycle that also bears a lactone.[25] The recalcitrance of the olefin group to react under these conditions was attributed by Mander to its electron deficiency by virtue of the attached electron-withdrawing lactone. Therefore, instead of electrophilic reagents for olefin functionalization, we chose to focus on hydrogen atom transfer (HAT) processes.[38] We were pleased to find that a variant of the Mukaiyama-hydration protocol developed by Inoue *et al.* for their ryanodol synthesis[39-40] proved particularly effective for our purposes. Thus, ketone **20** (confirmed by X-ray crystallographic analysis) was obtained from **13** through a one-pot protocol in moderate yield. The regioselectivity of the initial hydrocobaltation likely results from a directing effect by the proximal oxygen lone-pair of the lactone. For optimal results, the Inoue protocol had to be modified to avoid the use of excess DBU, which was needed for converting a nonaflate-peroxide, generated from TES peroxide **19**, to **20**. Excess DBU caused enolization of the resulting ketone group in **20**, followed by decarboxylation from the strained lactone at temperatures higher than –78 °C. This inherent lability of the bridged bicyclic [2.2.2] lactone also manifested itself in the subsequent olefination of ketone **20** to *exo*-methylene **21**. Initial Wittig olefination attempts failed, as phosphorous-ylides proved to be too basic, even at cryogenic temperatures and resulted in opening of the lactone. Cognizant of the base-lability of **20**, we focused our efforts on olefination reagents that are known to be less basic. From our investigations of the Tebbe,[41] Petasis,[42] Johnson-Peterson,[43] Kauffmann,[44] Nystedt,[45-46] and Lombardo[47] olefinations, only the latter two delivered trace amounts of **21**. While we were unable to improve the yield and/or scalability using the initially published Lombardo protocol, the observed reactivity of the combination of CH_2Br_2/Zn/$TiCl_4$ led us to investigate similar reagent combinations.[48-54] Gratifyingly, a slight modification of an olefination protocol published by Barnych and Vatéle,[55] employing a combination of

$Ti(Oi\text{-}Pr)_2Cl_2$ and the Nystedt-reagent, gave *exo*-methylene **21** in 53% yield. The reaction could be routinely performed on 500 mg scale. The synthesis of **21** set the stage for late-stage manipulations to access cephanolides A–D.

Scheme 2. Total Syntheses of Cephanolides A, B, C and D



We were pleased to find that heterogenous hydrogenation of **21** with Pd/C in MeOH delivered the desired stereochemistry at C4 (*d.r.* = >20:1) of **22** in almost quantitative yield. While the reason for this selectivity is not immediately obvious, it may be that the nucleophilicity of the two π-faces of the *exo*-methylene differ by virtue of stereo-electronic interactions on one face with the π*-orbital of the lactone carbonyl group as proposed by Woodward.[56-58] Thus, hydrogenation occurs from the less electron-depleted face. Deprotection of the C10 tertiary hydroxy group of **22** (TBAF in THF) and subsequent ionic deoxygenation ($InCl_3/Ph_2SiHCl$)[59-60] furnished **23** in 97% yield. Phthaloylperoxide in HFIP, following the precedent of Siegel *et al.*,[61] effected direct oxygenation of the arene moiety to give the desired phenol in 42% yield, along with 32% of the constitutional phenol isomer. This direct, albeit modestly selective, oxidation yielded cephanolide B (**2**) in 10 steps from 7-hydroxy-4-methyl-1-indanone (**17**).

To access cephanolide C from **22**, all that was required was a selective oxidation of the C7 benzylic position and deprotection of the tertiary alcohol. Selective C7 benzylic oxidation had already been demonstrated by Zhao and

coworkers in their synthesis of cephanolides B and C.[20] Using these conditions, along with a strong acid work-up, we realized the C7 oxygenation along with TMS-cleavage in one pot to access cephanolide C (**3**) in 54% yield from **22** (8 steps from **17**).

To access cephanolide D, we effected the same benzylic oxidation of **22** using PCC, but left the tertiary hydroxy group protected using slightly modified conditions. We explored, without success, many ketone[62] and other carbonyl-based auxiliaries in attempts to achieve directed C–C bond-forming ortho C–H functionalization[63-65] of **3** and its derivatives. Our failure to install the methyl ester directly necessitated the following effective, albeit indirect, approach. The ketone installed at C7 of **22** was converted to the acetyl oxime by condensation with hydroxylamine and subsequent acetylation in the same pot to afford **24**. Oxime-directed ortho C–H acetoxylation following the precedent of Sanford *et al.*[66] successfully functionalized the arene at C15. Global cleavage of the acetyl groups, followed by oxidative removal of the oxime[67] gave hydroxyketone **25** in 33% yield over the 4 steps. Of note, while Sanford successfully employed free oximes in ortho acetoxylations through *in situ* acetylation of the oxime, in our case, the free oxime was not easily acetylated under the acetoxylation conditions (AcOH/Ac_2O, heating), resulting in its oxidative cleavage to give the precursor ketone. Finally, phenol **25** was treated with Tf_2O in pyridine to give the corresponding triflate (84% yield), which was then subjected to Pd-catalyzed methoxy carbonylation and a subsequent one-pot deprotection of the tertiary alcohol to afford cephanolide D in 93% yield (14 steps from **17**).

Lastly, we addressed the synthesis of cephanolide A from common intermediate **21** (Scheme 2B). While the syntheses of cephanolides B–D arose directly from reduction of the *exo*-methylene group of **21**, the synthesis of **1** required the installation of a hydroxy group at C3. For this purpose, we employed an allylic oxidation. Analyses of the crystal structures of **13** or **20** indicated that the oxygenation was likely to occur from the undesired convex face. Therefore, the allylic alcohol resulting from SeO_2 oxidation of **21** was oxidized to give an enone (**26**) in one-pot using DMP in 76% yield. Hydrogenation of **26** (Pd/C in MeOH), followed by epimerization of the methyl-bearing stereocenter of **27** gave the desired ketone (**28**) in 52% yield over 2 steps. Reduction of the ketone group with $NaBH_4$ delivered alcohol **29**, which was subjected to Suarez oxidation conditions[68-69] employing I_2 and PIDA to forge the desired THF-ring without event. The free tertiary alcohol was obtained after TMS-cleavage in the same pot (98% yield over 2 steps), underlining the power of the Suarez variant of the 1,5-HAT process for late-stage oxygenation. Surprisingly, the resulting tertiary alcohol did not undergo ionic deoxygenation under the same conditions[59-60] that had worked in the cephanolide B synthesis. As a consequence, we had to concede to a two-step procedure of xanthate preparation followed by classical Barton-McCombie deoxygenation to give **31** in 82% yield over 2 steps. Oxygenation of the arene moiety of **31** using phthaloyl peroxide[61] as employed in the final step en route to **2** did not afford the desired phenol in this case. Ultimately, we found that **31** was oxygenated using the cyclopropane malonyl peroxide,[70] which was identified after an extensive survey of reagents, to provide cephanolide A (**1**) in 39% yield (6:1 ratio with the C15 hydroxylated constitutional isomer), in 14 steps from **17**.

In summary, on the basis of a retrosynthesis guided by chemical network analysis, we have developed highly concise syntheses of cephanolide A (**1**, 14 steps), cephanolide B (**2**, 10 steps), cephanolide C (**3**, 8 steps) and cephanolide D (**4**, 14 steps) from a commercially available indanone (**17**). A key design element of our synthesis plan was to identify a common, versatile intermediate that could be applied to preparation of all the cephanolide congeners. Our approach features rapid construction of the core-framework of the cephanolides by employing an iterative Csp^2–Csp^3 cross-coupling, followed by an enolether/intramolecular inverse-demand Diels-Alder reaction. We also showcased late-stage oxygenation tactics as a powerful tool for achieving efficient peripheral structural diversification. Our synthesis plan sets the stage for the preparation of other structurally complex cephalotaxus norditerpenoids that involve scaffold modifications. These efforts, as well as the development of an enantioselective variant of the intramolecular Diels-Alder reaction applied here, are the subject of ongoing studies in our laboratory.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge on the ACS Publications Website. Experimental details and spectroscopic data are provided including:
X-ray data (CIF) for **13**
X-ray data (CIF) for **20**.

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Funding Sources

Any funds used to support the research of the manuscript should be placed here (per journal style).
Notes
Any additional relevant notes should be placed here.

ACKNOWLEDGMENT

R.S. thanks the NSF under the CCI Center for Selective C–H functionalization (CHE-1700982) and the National Science Foundation (CHE-18566228) for support. G. S. thanks the Uehara Memorial Foundation for a postdoctoral fellowship. A. E. thanks Leibniz PROMOS for support of a visiting student stay at UC Berkeley. We thank Dr. Hasan Celik and UC Berkeley's NMR facility in the College of Chemistry (CoC-NMR) for spectroscopic assistance. Instruments in CoC-NMR are supported in part by

NIH S10OD024998. We are grateful to Dr. Nicholas Settineri (UC Berkeley) for X-ray crystallographic studies of **13** and **20** and Dr. Rita Nichiporuk (UC Berkeley) for mass spectrometric analysis.

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TOC Graphic.