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Article

Unified Total Synthesis of Benzenoid and Troponoid *Cephalotaxus* Diterpenoids Enabled by Regiocontrolled Phenol-to-Tropone Ring Expansion

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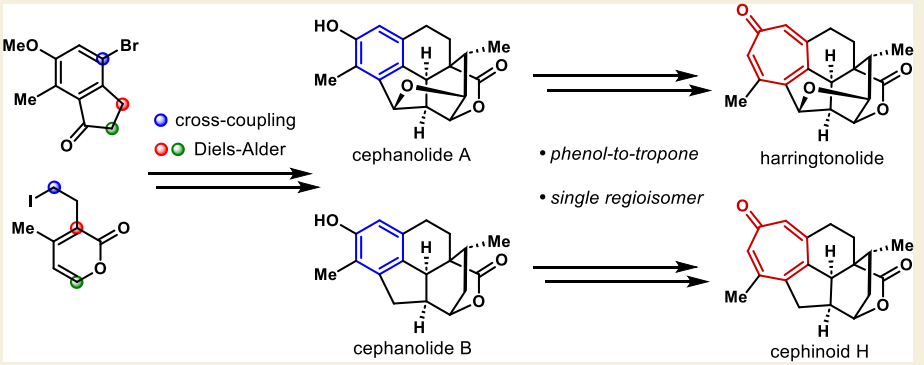

ABSTRACT: Herein, we present a unified strategy for the total synthesis of benzenoid and troponoid *Cephalotaxus* diterpenoids, specifically cephanolides A and B (benzenoids) and harringtonolide and cephinoid H (troponoids), in 13 to 19 longest linear steps. This synthesis relies on a palladium-catalyzed Csp^2-Csp^3 cross−coupling followed by an intramolecular doubly electron-deficient Diels−Alder reaction to establish the core skeleton and complete the synthesis of the *Cephalotaxus* benzenoids. A late-stage regioselective phenol-to-tropone ring expansion was developed to convert the benzenoids to the corresponding troponoid congeners. This work provides a regiocontrolled approach for achieving the synthetic connectivity between benzenoid and troponoid *Cephalotaxus* diterpenoids.

KEYWORDS: *total synthesis, unified strategy, benzenoid Cephalotaxus diterpenoid, troponoid Cephalotaxus diterpenoid, phenol-to-tropone ring expansion*

The *Cephalotaxus* genus is recognized for producing a wide range of structurally diverse diterpenoids (**1**−**6**, Figure 1).[1−3]

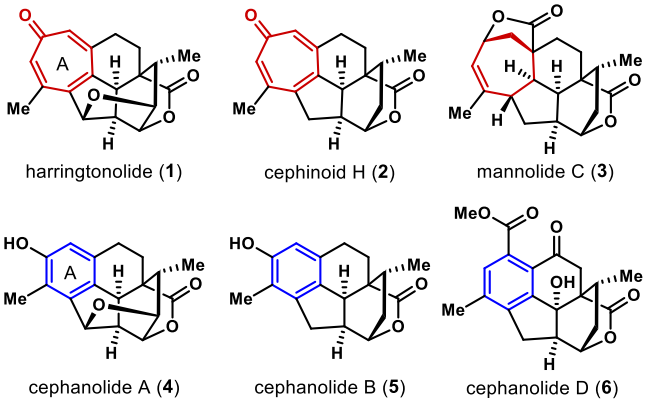

Figure 1. Representative *Cephalotaxus* diterpenoids.

Prior to 2015, only five 19-carbon *nor*-diterpenoids featuring a characteristic tropone ring had been reported.[4−7] As the first member of this family, harringtonolide (**1**) was independently isolated by Buta in 1978[4] and by Sun in 1979,[5] who referred to it as hainanolide. Over the past decade, a substantial number of new diterpenoids has been identified, with more than 100 members now documented.[8−21] Structurally, they are characterized by a rigid tetracyclic 7/6/5/6 or 6/6/5/6 carbon framework with many members featuring an additional bridged δ-lactone ring. Based on the structural variability of the A-ring, *Cephalotaxus* diterpenoids are classified into five subfamilies:

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17-*nor*-diterpenoids, prototype diterpenoids, benzenoid norditerpenoids, A-ring-*seco* norditerpenoids, and dimers.[3] These diterpenoids exhibit a broad spectrum of biological activities, including plant growth inhibition, antiviral effects, and antitumor properties.[3] Interestingly, a stark contrast was observed between different subfamilies. For instance, harringtonolide (**1**) has been reported to exhibit potent inhibitory effects against human tumor cell lines, with high potency on KB cells (IC_{50} = 43 nM).[22] In contrast, cephanolide A (**4**), the benzenoid congener of **1** with one fewer carbon, displayed no significant cytotoxic activity.[12] This highlights the critical role of the tropone motif in the biological activity. The structural diversity and remarkable bioactivity of these natural products have drawn significant interest from the synthetic community, leading to numerous elegant total syntheses over the past 30 years from the groups of Mander,[23−25] Tang,[26] Zhai,[27−29] Zhao,[30,31] Gao,[32−34] Hu,[35−39] Sarpong,[40−42] Cai,[43] Zhang/Yang,[44] and Jia.[45]

The earliest total synthesis of *Cephalotaxus* troponoids was accomplished by Mander and co-workers, who completed 3-deoxyfortalpinoid F (isolated as a natural product later in 2019) in 1996[23] and harringtonolide (**1**) in 1998[24] using an elegant intramolecular Büchner ring expansion strategy. Tang and co-workers later developed an intramolecular oxidopyrilium-based [5 + 2] cycloaddition to construct the tropone motif, successfully completing the total synthesis of **1**.[26] In 2016, Zhai's group achieved the first asymmetric total synthesis of **1** featuring a rhodium-catalyzed intramolecular [3 + 2] cycloaddition as the key step.[27] Hu and co-workers synthesized 3-deoxyfortalpinoid F, fortalpinoid A, and cephinoid H (**2**) employing Pauson−Khand reaction and ring-closing metathesis as the key steps in 2021.[35] Recently, the Hu group further developed an impressive ynol−diene cyclization strategy for tropone construction, finishing the asymmetric synthesis of harringtonolide (**1**), 3-deoxyfortalpinoid F, and several other tropone-free 17-*nor*-diterpenoids.[39]

Regarding the synthesis of *Cephalotaxus* benzenoids, there are also notable strategies reported. Zhao's group was the first to complete the total synthesis of cephanolide B (**5**) and C in 2018, by developing an innovative palladium-catalyzed Heck-type/carbonylative C−H activation cascade.[30] In 2020, Gao and co-workers reported the first asymmetric total synthesis of cephanolides A (**4**)[32] and B (**5**),[33] using an intramolecular Prins-type cyclization followed by a Friedel−Crafts cyclization. Sarpong and co-workers achieved the divergent total synthesis of cephanolides A−D in 2021[40] and ceforalides C, D, F, G, and H in 2022,[41] featuring iterative Csp^2−Csp^3 cross-couplings, followed by an intramolecular inverse-demand Diels−Alder cycloaddition to forge the core skeleton. In 2021, Cai's group completed the total syntheses of **4** and **5** by developing a catalytic asymmetric inverse-electron demand Diels−Alder cycloaddition.[43] Zhang/Yang and co-workers developed a tandem reaction sequence comprising an intramolecular Pauson−Khand reaction, a 6π-electrocyclization, and an oxidative aromatization, completing the total synthesis of **5**.[44] Subsequently, Hu and co-workers also reported a similar reaction sequence based on their prior work, finishing the asymmetric synthesis of ceforalide B and cephanolides B−D.[36] While individual molecules from each subfamily have been targeted in synthetic studies, strategies aimed at the unified synthesis of multiple subfamilies remain rare. Herein, we present the development of a divergent synthetic route that bridges the synthesis of *Cephalotaxus* benzenoids and troponoids with exclusive regioselectivity control, culminating in the total synthesis of (±)-cephanolide A/B (**4**/**5**), (±)-harringtonolide (**1**), and (±)-cephinoid H (**2**).

The discovery of new *Cephalotaxus* diterpenoid skeletons led to the revision of the biosynthetic pathway by Yue, where the benzenoids are derived from the corresponding troponoids via a 6π-electrocyclization of the tropone ring, followed by Baeyer−Villiger oxidation and aromatization.[12]

This proposition inspired us to develop a unified synthetic strategy for both benzenoid and troponoid *Cephalotaxus* diterpenoids using a "contra-biosynthetic" approach,[46] where the troponoids (**1**/**2**) were generated from the benzenoids (**4**/**5**) through a late-stage phenol-to-tropone transformation (Figure 2A).[47−50] Functional group interchange proposed

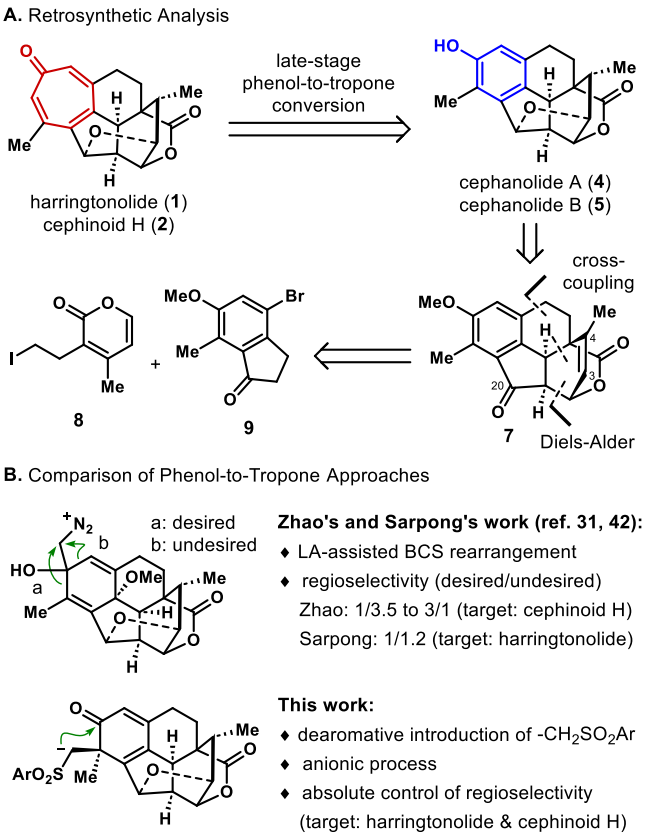

Figure 2. (A) Retrosynthetic analysis. (B) Comparison of phenol-to-tropone approaches in the synthesis of *Cephalotaxus* diterpenoids.

compound **7** to serve as a versatile synthetic intermediate, as the C20 ketone and C3−C4 double bond would enable the generation of *Cephalotaxus* diterpenoids with a wide range of oxidation patterns. Compound **7** was then disconnected to α-pyrone **8** and indanone **9** through Diels−Alder and Csp^2−Csp^3 cross-coupling reactions.[51]

Recently, Zhao,[31] Sarpong,[42] and our group[52] independently reported the synthesis of *Cephalotaxus* troponoids from the corresponding benzenoid congeners, notably employing a similar Büchner−Curtius−Schlotterbeck (BCS) ring expansion strategy.[53] However, all three reports suffered from poor regioselectivity, with the desired to undesired product ratios ranging from 1:1 to 1:3.5. Zhao's work achieved a slight improvement (3:1) by incorporating an α-chloro substitution (Figure 2B). In comparison, this work introduces a methylene sulfone unit in a dearomative fashion, and the ring expansion is

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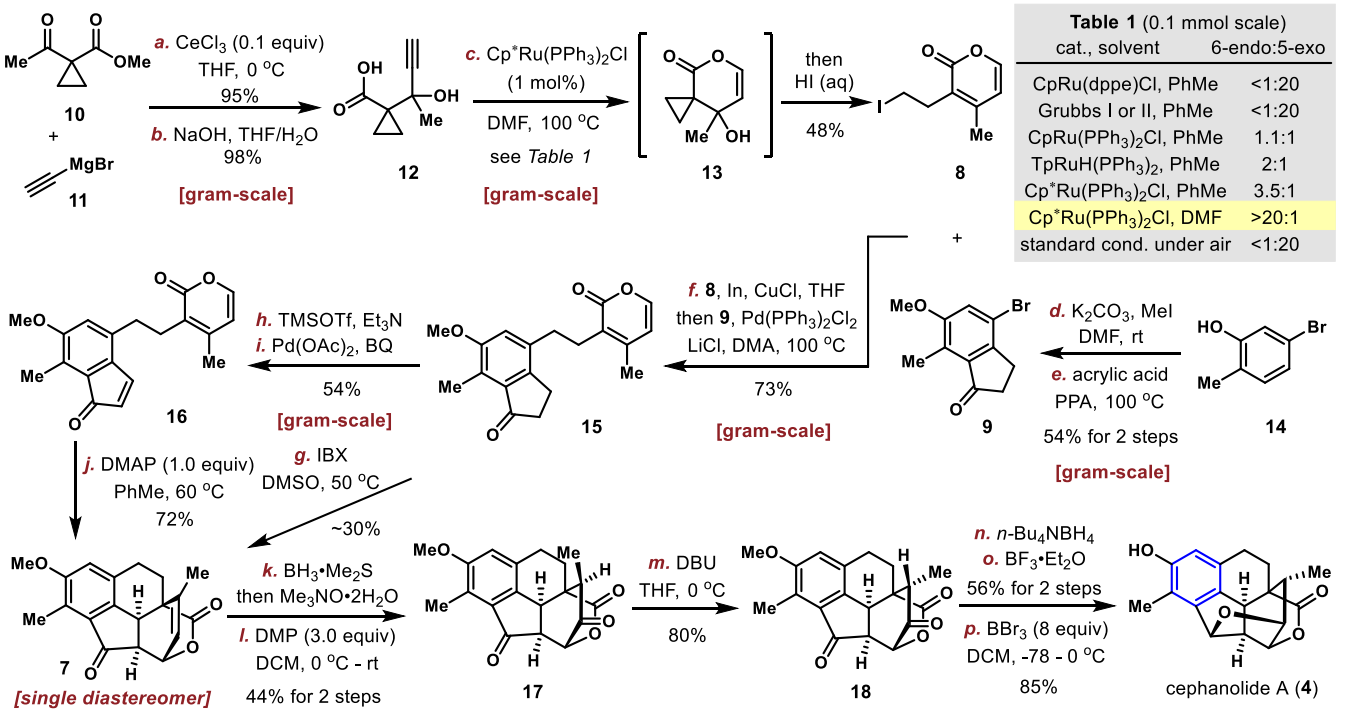
Scheme 1. Total Synthesis of Cephanolide A (4)



performed under complementary anionic conditions, resulting in complete control over the regioselectivity. This strategy proved effective for the synthesis of both harringtonolide (**1**) and cephinoid H (**2**).

Our forward synthesis commenced with the preparation of α-pyrone **8** and indanone **9** (Figure 2). The Grignard addition of acetylene magnesium bromide **11** to acetoacetate **10** followed by hydrolysis of the methyl ester provided alkynoic acid **12** in 93% yield over two steps. Next, regioselective cyclization of **12** was attempted using ruthenium catalysis, which can control *endo* selectivity over *exo* provided the reaction proceeds via a ruthenium-vinylidene pathway.[54] As listed in the inset Table 1 in Scheme 1, catalysts, such as CpRu(dppe)Cl, Grubbs I, or II, produced the undesired 5-*exo* cyclization product exclusively. The desired 6-*endo* product **13** could be obtained with $CpRu(PPh_3)_2Cl$, $TpRuH(PPh_3)_2$, and $Cp^*Ru(PPh_3)_2Cl$ as catalysts, albeit with low *endo*/*exo* selectivities (1.1/1, 2/1, and 3.5/1, respectively). After extensive screening, the selectivity was improved to >20/1 using 1 mol % of $Cp^*Ru(PPh_3)_2Cl$ as a catalyst in DMF at 100 °C under argon. Performing the reaction under air completely reversed the selectivity (<1/20 *endo*/*exo*), indicating that the formation of the ruthenium-vinylidene intermediate was inhibited. Instead, the ruthenium catalyst functioned as a Lewis acid, leading exclusively to 5-*exo* cyclization.[54] The labile intermediate **13** was then quickly treated with aqueous HI to induce ring opening of the cyclopropane, yielding the aromatized α-pyrone **8** in 48% yield from **12**.

Indanone fragment **9** was prepared from commercially available phenol **14** through methyl protection (K_2CO_3, MeI in DMF) followed by a one-step Friedel–Craft alkylation/acylation reaction (acrylic acid, PPA, 100 °C), resulting in 54% yield over two steps.[55] Subsequently, the union of fragments **8** and **9** was achieved using palladium-catalyzed Csp^2–Csp^3 cross-coupling via the intermediacy of alkyl indium reagent developed by Loh,[56] providing pyrone **15** in 73% yield. Other cross-coupling variants, such as nickel-catalyzed reductive coupling and preactivation of one of the coupling partners to zincate or boronate, failed to yield any desired product. Oxidation of **15** with IBX in DMSO[57] directly afforded the desired Diels–Alder adduct **7** in ~30% yield as a single diastereomer, fully establishing the *Cephalotaxus* benzenoid carbon skeleton. However, compound **7** was prone to decarboxylation under an elevated temperature or slightly acidic conditions, leading to inconsistent yields over batches and complicating scale-up. Compared to previous Diels–Alder strategies employed in the synthesis of *Cephalotaxus* diterpenoids, the current work utilized a doubly electron-deficient diene and dienophile in an intramolecular manner, which posed challenges due to the contradiction between the low reactivity of substrates and the susceptibility of the product to decarboxylation under forced reaction conditions.[25,40,43] To address this, two separate steps were optimized. First, Saegusa–Ito oxidation delivered indenone **16** in 54% yield.[58] Condition screening identified the combination of toluene as a solvent and 1 equiv of DMAP as a basic additive to ensure the Diels–Alder reaction with good yield (72%), robustness, and reproducibility. The role of DMAP was proposed to maintain slightly basic conditions, minimizing further decarboxylation of **7**.

This seven-step sequence can be performed on a gram scale, allowing for the production of **7** in significant quantities. Next, diastereoselective hydroboration/oxidation ($BH_3{\cdot}Me_2S$, then $Me_3NO{\cdot}2H_2O$) of the C3–C4 alkene generated a C3-hydroxyl and reduced the C20 ketone to give a diol intermediate. After oxidation with Dess–Martin periodinane, diketone **17** was obtained in 44% yield from **7**, with the methyl group sitting at an incorrect stereochemistry. Epimerization of the C4 stereocenter by DBU in THF at 0 °C furnished diketone **18** in 80% yield. Both ketone groups were then simultaneously reduced with n-Bu_4NBH_4, resulting in a diol with a single stereochemical control at C3 and 1:1 *dr* at C20. The mixture of

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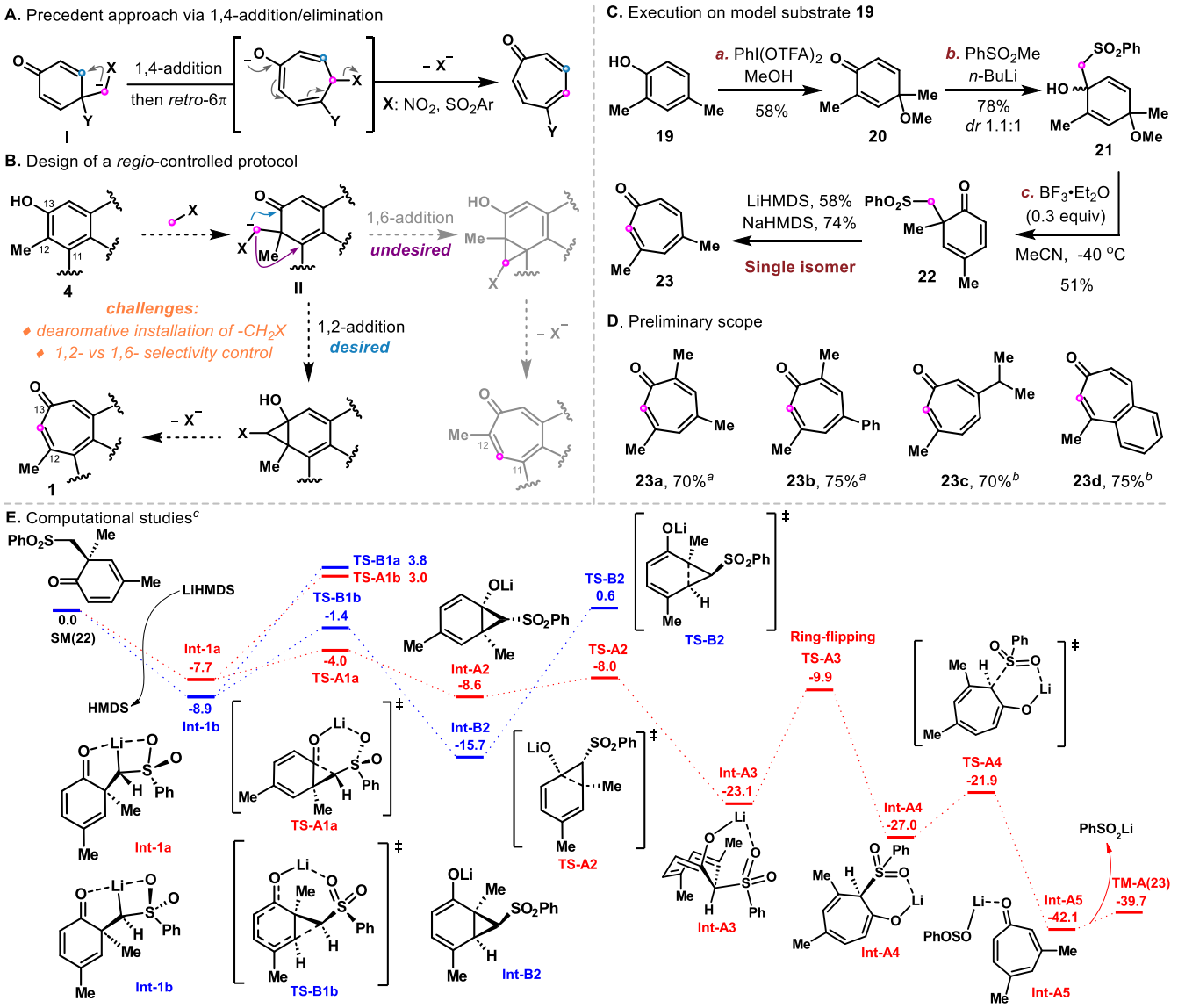
Scheme 2. Regiocontrolled Phenol-to-Tropone Conversion: Design, Execution, and Computational Studies



[a]NaHMDS, THF, −78 °C. [b]NaH, THF, room temperature. [c]Free energy profile of two reaction pathways (A in red and B in blue), calculated at the level of M06-2X/6-311+G(d,p)(SMD)//M06-2X/6-31G(d)(IEFPCM) at 195.15 K.

diastereomers was then treated with $BF_3{\cdot}Et_2O$ in DCM to construct the oxo-bridge, yielding methyl-protected cephanolide A in 56% yield over two steps. After deprotection using BBr_3, cephanolide A (**4**) was successfully synthesized in 85% yield.

Next, we aimed to address the regioselectivity challenges encountered in previous phenol-to-tropone conversions. An elegant approach developed by Kende in 1986, and later explored by other groups, involves the oxidative dearomatization of phenol to yield dienone **I**, where X represents an electron-withdrawing group with leaving group capability, such as a nitro or sulfonyl group.[59−62] Intramolecular 1,4-addition under basic conditions, followed by retro-6π electrocyclization and elimination of the X anion, leads to the efficient construction of the tropone moiety (Scheme 2A). In the ring expansion of cephanolide A (**4**) to harringtonolide (**1**), one carbon atom must be inserted between C12 and C13 (Scheme 2B). To achieve this, we propose introducing a CH_2X unit at the *ortho* position of **4** to generate dienone **II**. Subsequent intramolecular 1,2- or 1,6-addition followed by elimination of the X anion would lead to the tropone moiety with two different regioisomeric outcomes. A key challenge of this design lies in the intermolecular introduction of the CH_2X unit, as prior reports have only achieved this type of dearomatization at the *para* position in an intramolecular fashion.[59−62] Additionally, controlling the 1,2- versus 1,6-addition is pivotal for determining the regioselectivity. The methyl group at C11 of **4** is expected to enhance the desired outcome by diminishing the preference for the undesired 1,6-addition.

With these considerations in mind, 2,4-dimethyl phenol **19** was selected as a model substrate to implement this plan, which mimicked **4** where one of the *ortho* positions of phenol was occupied by a methyl group and the other by hydrogen. As illustrated in Scheme 2C, **19** was first converted to the corresponding 4-quinol methyl ether **20** in 58% yield. The introduction of a $PhSO_2CH_2$ group was achieved through 1,2-addition of $PhSO_2CH_2$ anion to the dienone moiety, followed

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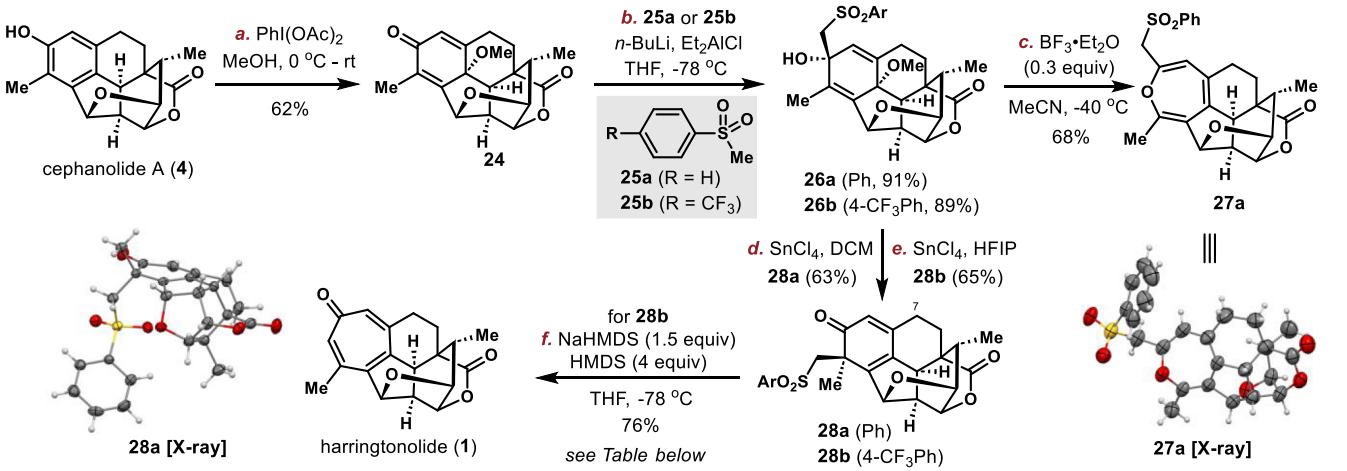
Scheme 3. Synthesis of Harringtonolide (1) from Cephanolide A (4)



Entry	Substrate	Conditions	Yield[a]
1	**28a**	LiHMDS (1.0 equiv), THF, -78 °C	trace
2	**28a**	LiHMDS (1.0 equiv), THF, 0 - 40 °C	N.D.
3	**28a**	DBU (1.0 equiv), DMSO, 120 °C	N.D.
4	**28b**	LiHMDS (1.0 equiv), THF, -78 °C	<10%
5	**28b**	LDA (1.0 equiv), THF, -78 °C	11%
6	**28b**	KHMDS (1.0 equiv), THF, -78 °C	14%
7	**28b**	NaHMDS (1.0 equiv), THF, -78 °C	18%
8	**28b**	*t*-BuOK (3.0 equiv), *t*-BuOH, rt	N.D.
9	**28b**	NaHMDS (1.0 equiv), HMDS (10.0 equiv), THF, -78 °C	51%
10	**28b**	NaHMDS (1.5 equiv), HMDS (4.0 equiv), THF, -78 °C	90%[b] (76%)[c]

[a]Unless otherwise noted, all reactions were performed under argon with 0.01 mmol of substrate. Yield determined by crude ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard. [b]One mg scale. [c]Isolated yield on 0.023 mmol scale. N.D. = not detected.

by a regioselective vinylogous semipinacol rearrangement induced by BF_3·Et_2O in MeCN, delivering **22** in 40% yield over two steps.[63] After treatment with LiHMDS or NaHMDS at −78 °C, the desired tropone **23** was obtained in 58% or 74% yield as a single regioisomer. A preliminary study revealed that this tropone synthesis can also be extended to other substrates (**23a**-**e**) in 70%−75% isolated yield (Scheme 2D).

To understand the regioselectivity outcome, density functional theory calculations were performed using the Gaussian 09 software package with substrate **22** and LiHMDS as the base. As illustrated in Scheme 2E, pathway A (in red) represents the carbanion of **Int-1** attacking the carbonyl (1,2-addition), while pathway B (in blue) corresponds to its 1,6-Michael addition (see the Supporting Information for the computational details). The methylene adjacent to the $PhSO_2$ group in substrate **22** is first deprotonated by LiHMDS. The resulting carbanion can coordinate with the Li ion by using either of its prochiral faces, leading to the formation of **Int-1a** and **Int-1b**. For **Int-1a**, the energy barrier of the 1,2-addition (**TS-A1a**) is 3.7 kcal/mol, while the corresponding barrier of 1,6-addition (**TS-A1b**) is 10.7 kcal/mol, suggesting that the formation of the 1,2-adduct **Int-A2** is favored. Conversely, **Int-1b** is more likely to undergo 1,6-addition (**TS-B1b**) to form **Int-B2**. The energy barrier for **Int-1a** to **TS-A1a** is 3.8 kcal/mol lower than that for **Int-1b** to **TS-B1b**, indicating that the reaction proceeds mainly via the former to yield **Int-A2**.

For **Int-B2**, the only possible further conversion is a retro-6π electrocyclic ring opening (**TS-B2**). However, under −78 °C conditions, the energy barrier of **TS-B2** is too high for **Int-B2** to overcome. In contrast, **Int-A2** can easily undergo an electrocyclic ring opening to yield **Int-A3**, which features a seven-membered ring. The $PhSO_2$ group in **Int-A3** occupies a pseudoequatorial position, with no π molecular orbital parallel to it. As a result, **Int-A3** must undergo a ring flip to form **Int-A4**, ultimately eliminating $PhSO_2Li$ to produce the final product (**23**). The total free energy barrier for pathway A is the ring-flipping step (13.2 kcal/mol), which is obviously lower than that of pathway B (16.3 kcal/mol for **TS-B2**), indicating that the reaction predominantly proceeds via the former.

The stage is now set for the phenol-to-tropone ring expansion to access harringtonolide (**1**). Cephanolide A (**4**) first underwent oxidative dearomatization using $PhI(OAc)_2$ in MeOH to produce the corresponding 4-quinol methyl ether **24** in 62% yield (Scheme 3). Nucleophilic addition with sulfone **25a** delivered **26a** in 91% yield as a single diastereomer. Unfortunately, $PhSO_2CH_2$ migration did not occur under the same BF_3·Et_2O/MeCN conditions. Instead, oxepin **27a** was isolated in 68% yield, proceeding via the in situ generation of benzene oxide followed by *retro*-6π-electrocyclization.[64] We then screened the reaction conditions and found that $SnCl_4$ in DCM successfully yielded migrated product **28a** in 63% yield. This outcome may be attributed to the strong coordination of $SnCl_4$ with the free hydroxyl group, which attenuates its nucleophilicity and thereby promotes the desired alkyl migration pathway. The structures of **27a** and **28a** were confirmed unambiguously by X-ray crystallographic analysis.

Next, the ring expansion was attempted under basic conditions. With sulfone **28a**, only trace product was obtained using LiHMDS as the base under −78 °C (entry 1, inset Table in Scheme 3). Raising the reaction temperature or changing

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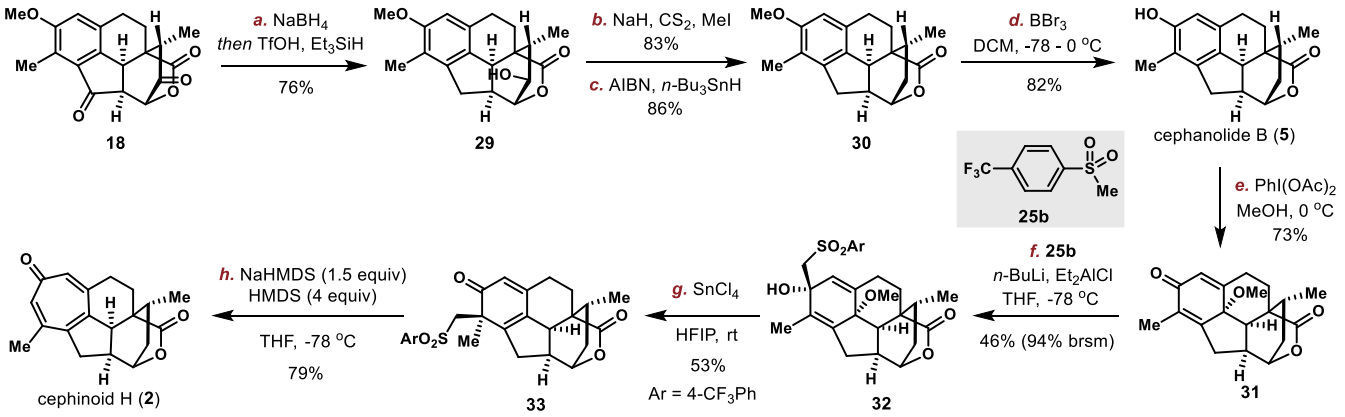
Scheme 4. Total Synthesis of Cephanolide B (5) and Cephinoid H (2)



bases led to complete decomposition of the starting material (entries 2−3). We reasoned that competing deprotonation at C7 of **28a** prevented 1,2-addition to the ketone, leading to slow decomposition of the starting material. To solve this issue, a CF_3 group was introduced para to the sulfone in order to lower the pK_a of its α position.[62] The 4-CF_3-substituted sulfone (**25b**) was then used to synthesize **28b** in the same two-step sequence, with the necessary change of the solvent to HFIP to achieve a good yield (65% yield) in the vinylogous semipinacol rearrangement step. Encouragingly, with **28b** as the substrate, improved yields could be obtained (>10%). However, we could not obtain yields higher than 18%, despite various bases screened (entries 4−7). Considering that the unproductive deprotonation at C7 remained non-negligible, we attempted to add proton sources to maintain enolate−ketone equilibrium, thereby driving the reaction toward the desired pathway. While *t*-BuOK/*t*-BuOH proved inefficient (entry 8), the addition of 10 equiv of HMDS to NaHMDS (1.0 equiv) successfully increased the yield to 51% (entry 9). The optimal result was achieved with 1.5 equiv of NaHMDS and 4 equiv of HMDS, ultimately delivering harringtonolide (**1**) in 90% yield by ^{1}H NMR and 76% isolated yield (entry 10). The spectroscopic data of **1** are in good agreement with those reported in the previous literature.

Next, we sought to apply this four-step regioselective phenol-to-tropone approach to synthesize cephinoid H (**2**) from cephanolide B (**5**). As shown in Scheme 4, reduction of the diketone intermediate **18** using $NaBH_4$ followed by treatment with TfOH/Et_3SiH provided Gao's intermediate **29** in 76% yield.[32] Barton−McCombie deoxygenation following deprotection afforded cephanolide B (**5**) in 59% overall yield from **29**. Oxidative dearomatization generated dienone **31**, which underwent a similar nucleophilic addition/vinylogous semipinacol rearrangement sequence with sulfone **25b**, delivering dienone **33** in 53% yield. Under the same ring expansion conditions as described above, cephinoid H (**2**) was accomplished in 79% yield without complications.

In summary, we have developed a unified strategy for the total synthesis of benzenoid and troponoid *Cephalotaxus* diterpenoids. A ruthenium-catalyzed 6-*endo* cyclization was utilized to prepare 3,4-disubstituted α-pyrone fragment **8**. Following a palladium-catalyzed Csp^2−Csp^3 cross-coupling to unite fragments **8** and **9**, an intramolecular doubly electron-deficient Diels−Alder reaction rapidly established the core skeleton, thus completing the total synthesis of the benzenoid natural products cephanolide A (**4**) and B (**5**) in 13 and 15 longest linear steps. A four-step sequence was then developed for a regioselective phenol-to-tropone ring expansion, finishing the troponoid congeners harringtonolide (**1**) and cephinoid H (**2**) from **4** and **5**, respectively. This work provides a regiocontrolled approach to establishing the synthetic connection between benzenoid and troponoid *Cephalotaxus* diterpenoids under complementary basic conditions. Efforts to extend this ring expansion strategy to other structurally related natural products are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.4c01067.

Experimental procedures, spectroscopic data, NMR spectra of all new compounds, and X-ray crystallographic data for compounds **27a** and **28a** (PDF)

Accession Codes

Accession Codes: CCDC 2338981 (**27a**) and CCDC 2394170 (**28a**) 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 1223336033.

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