# Total Synthesis of Cephanolide A and Harringtonolide: A Unified Strategy Connecting Benzenoid and Troponoid Cephalotaxus Diterpenoids

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**Abstract:** The fascinating benzenoid and troponoid *Cephalotaxus* diterpenoids are highly related biosynthetically, both of which are popular targets for total synthesis. Herein, we describe a unified strategy for the concise synthesis of cephanolide A and harringtonolide in 14 and 16 steps respectively. Palladium catalyzed $Csp^2$-$Csp^3$ cross-coupling followed by doubly electron-deficient intramolecular Diels-Alder reaction secure the rapid construction of the *Cephalotaxus* carbon framework. Late-stage benzenoid-to-troponoid ring expansion was accomplished employing Büchner-Curtius-Schlotterbeck (BCS) reaction, furnishing harringtonolide in two steps from cephanolide A. This work shed light on the chemical synthetic connection between benzenoid and troponoid *Cephalotaxus* diterpenoids.

The versatile plants of *Cephalotaxus* genus produce a rich array of secondary metabolites including alkaloids and diterpenoids.[1] While extensive efforts have been focused on anticancer activities of *Cephalotaxus* alkaloids from 1950s, studies on *Cephalotaxus* diterpenoids were rather rare before 2015, with only 5 troponoid *nor*-diterpenoids bearing 19 carbons been isolated.[2] Harringtonolide (**1**) represents the first member isolated from this family by Buta in 1978[2a] and later by Sun in 1979[2b] (under the name of hainanolide) independently. It is only over the past decade that a plethora of new isolations were reported.[3] Of particular note, these work discovered new *Cephalotaxus* diterpenoid skeletons with intact carbon numbers (20), *nor*-diterpenoid (19 carbons) and *di-nor*-diterpenoid (19 carbons) with various oxidation levels, which led to the of a revised biosynthetic pathway by Yue (*vide infra*).[3e]

Structurally, the *Cephalotaxus* diterpenoids are characterized by a rigid 7/6/5/6 or 6/6/5/6 tetracyclic carbon skeleton (A/B/C/D rings, see **I** and **II** in Figure 1A and 1B for lettering and numbering), with most members bearing an additional bridged lactone (E ring). According to the size of A ring, they can be categorized to 'troponoid/A7' type with a tropone or dearomatized 7-membered A ring (Figure 1A) and 'benzenoid/A6' type with a benzene or dearomatized 6-membered A ring (Figure 1B). To date, more than 100 members have been isolated in total, including >80 'troponoid/A7' and >15 'benzenoid/A6' congeners.[4] The family of *Cephalotaxus* diterpenoids have shown a broad range of biological activities including plant growth inhibitory,[2a] antiviral,[5,6] as well as antitumor properties.[3,6] The structural diversity and remarkable bioactivities have spurred considerable interest from the synthetic community, resulting in many creative and elegant total synthesis over the past 25 years.[7,8] To the best of our knowledge, at least 6 strategies have been reported for the total synthesis of 'troponoid/A7' *Cephalotaxus* diterpenoids and 7 for the 'benzenoid/A6' type. Nonetheless, no strategy was reported to aim for the connection of these two highly related categories.[9] Besides, we were fascinated by their different behavior in biological activities. That is to say, 'troponoid/A7' *Cephalotaxus* diterpenoids displayed a variety of bioactivities, while 'benzenoid/A6' *Cephalotaxus* diterpenoids were mostly inactive in biological screening.[4] For example, harringtonolide (**1**) were reported to exert inhibitory effects towards human tumor cell lines, with high potency on KB cells ($IC_{50}$ = 43 nM).[6] Cephanolide A (**4**), the exact one less carbon benzenoid congener of harringtonolide (**1**), was reported to be inactive,[3e] which showed the tropone motif is crucial for such activities. Thus, a total synthesis

of both 'troponoid/A7' and 'benzenoid/A6' *Cephalotaxus* diterpenoids would allow for further understanding of the mode of action.

Biosynthetically, the *Cephalotaxus* diterpenoids were originally proposed to arise from abietane diterpenoids.[1] Yue et al. proposed a revised pathway that the troponoid/A7 skeleton was formed at the early stage, followed by 6π-electrocyclization of the tropone ring to give the corresponding cycloprpanone (**III**, Figure 1C). Subsequent Baeyer-Villiger oxidation and aromatization produced 'benzenoid/A6' type framework (**III**) with 19 carbons. Then, decarboxylation deleted C14 and yielded benzenoids with 18 carbons.[3e] Oxidation of these framework generated a variety of natural products. This revised biosynthetic pathway inspired us to develop a unified strategy for the chemical synthesis of both benzenoid and troponoid *Cephalotaxus* diterpenoids in a 'contra-biosynthetic' way,[10] where the troponoid **1** was transformed to benzenoid **4** through n+1 'single-atom editing'.[11] Functional group interchange proposed compound **7** to be a versatile synthetic intermediate, as the C20 ketone and C3-C4 double bond would assure the generation of *Cephalotaxus* diterpenoids with essentially all the oxidation patterns. **7** was then disconnected to two fragments of α-pyrone **8** and indanone **9** through Diels-Alder and cross coupling reactions, which could be prepared from commercially available starting materials **13**/**14** and **10**/**11** respectively (Figure 1C).

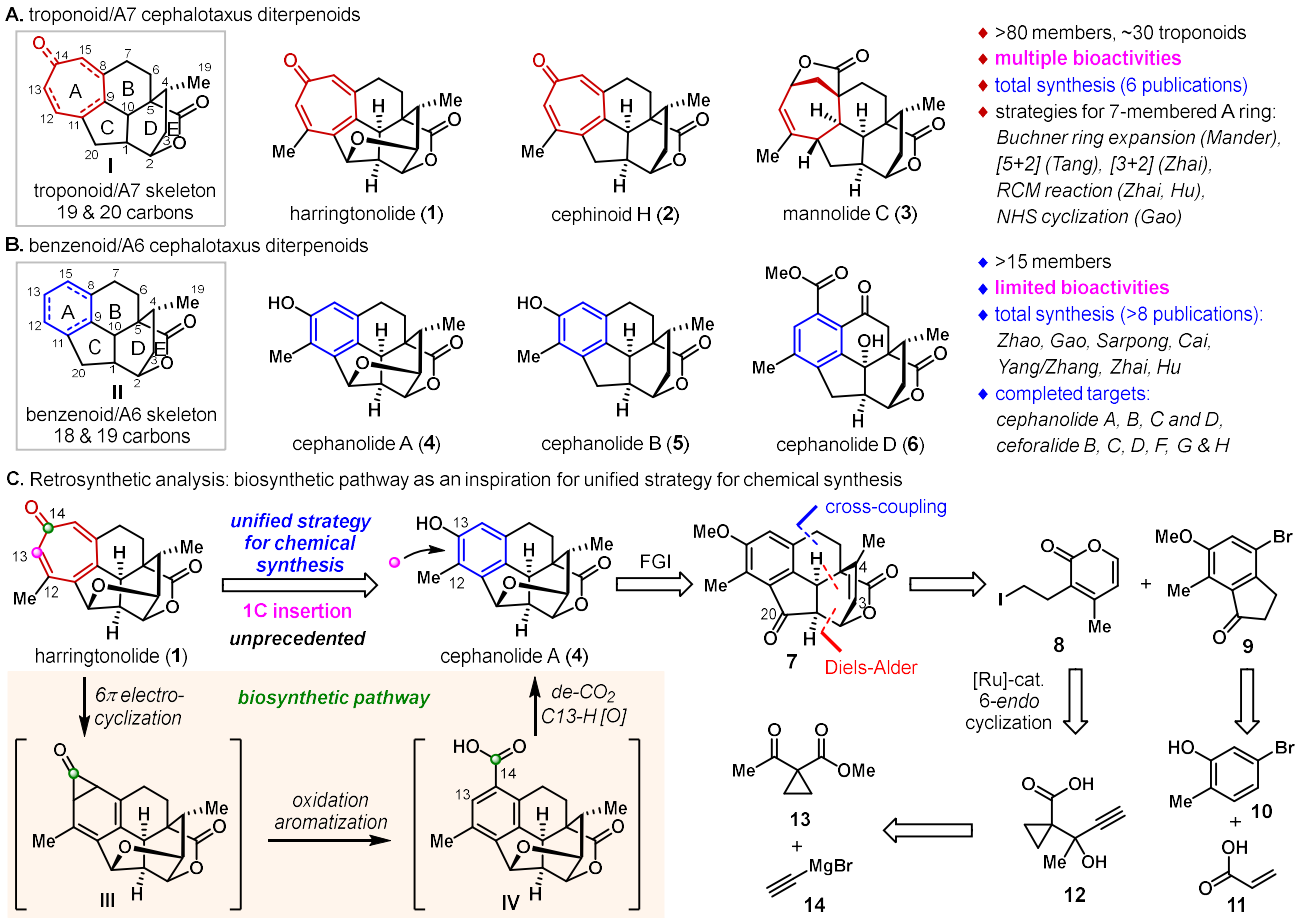


**Figure 1**. A) Representative troponoid/A7 *Cephalotaxus* diterpenoids. B) Representative benzenoid/A6 *Cephalotaxus* diterpenoids. C) Biosynthetic pathway as an inspiration for unified strategy for chemical synthesis.

Our forward synthesis commenced with the preparation of α-pyrone **8** and indanone **9** fragments (Figure 2). Grignard addition of acetylene magnesium bromide **14** to methyl acetoacetate **13** 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,[12] which is possible to control *endo* selectivity over *exo* provided the reaction proceeds *via* ruthenium-vinylidene pathway.[13] As listed in Table 1, CpRu(dppe)Cl, Grubbs I or II catalysts afforded undesired 5-*exo* cyclization product exclusively. The desired 6-*endo* product **15** could be obtained with $CpRu(PPh_3)_2Cl$, $TpRuH(PPh_3)_2$ and $Cp^*Ru(PPh_3)_2Cl$ as catalysts, albeit in low *endo*/*exo* selectivities (1/1, 2/1 and 3.5/1, respectively). After extensive screening, the selectivity could be improved to >20/1 using 1 mol% of $Cp^*Ru(PPh_3)_2Cl$

as catalyst in DMF at 100 °C under argon. Running the reaction under air completely reversed the selectivity (<1/20 *endo*/*exo*), which pointed inert atmosphere to be crucial for generating the ruthenium-vinylidene intermediate. The labile **15** was then quickly treated with aqueous HI to induce ring opening of the cyclopropane to arrive at the aromatized α-pyrone **8** in 48% yield from **12**. The indanone fragment **9** was prepared from commercially available phenol **10** by methyl protection ($K_2CO_3$, MeI in DMF) following a one-step Friedel-Craft alkylation/acylation reaction (acrylic acid, PPA 100 °C) in 53% yield over two steps.[14] Subsequently, the union between fragment **8** and **9** was achieved by palladium-catalyzed $Csp^2$-$Csp^3$ cross coupling through the intermediacy of alkyl indium reagent developed by Loh,[15] providing pyrone **16** in 73% yield. Oxidation of **16** by IBX in DMSO[16] directly afforded the desired Diels-Alder product **7** in ~30% yield as a single diastereomer, with fully established *Cephalotaxus* diterpenoid carbon skeleton. However, the reaction yield was not steady over batches and scale up proved to be problematic. Compared to previous Diels-Alder strategy in the synthesis of *Cephalotaxus* diterpenoids,[17,8d-e] the current work represents an intramolecular doubly electron-deficient one, the challenge of which mainly stemmed from the contradiction between the low reactivity of substrate and the ease of decarboxylation of the product under elevated temperature or any slight acidic conditions. Thus, two separate steps were employed and optimized. First, Saegusa-Ito oxidation delivered indanone **17** in 54% yield. After condition screening, the combination of PhMe as solvent and 1 equivalent of DMAP as a basic additive was identified to guarantee the Diels-Alder reaction with good yield (65%), robustness and reproducibility. The 6-step sequence could be implemented on gram-scale to produce **7** in quantities, setting the stage for functional group manipulations to access cephanolide A (**4**) and harringtonolide (**1**).

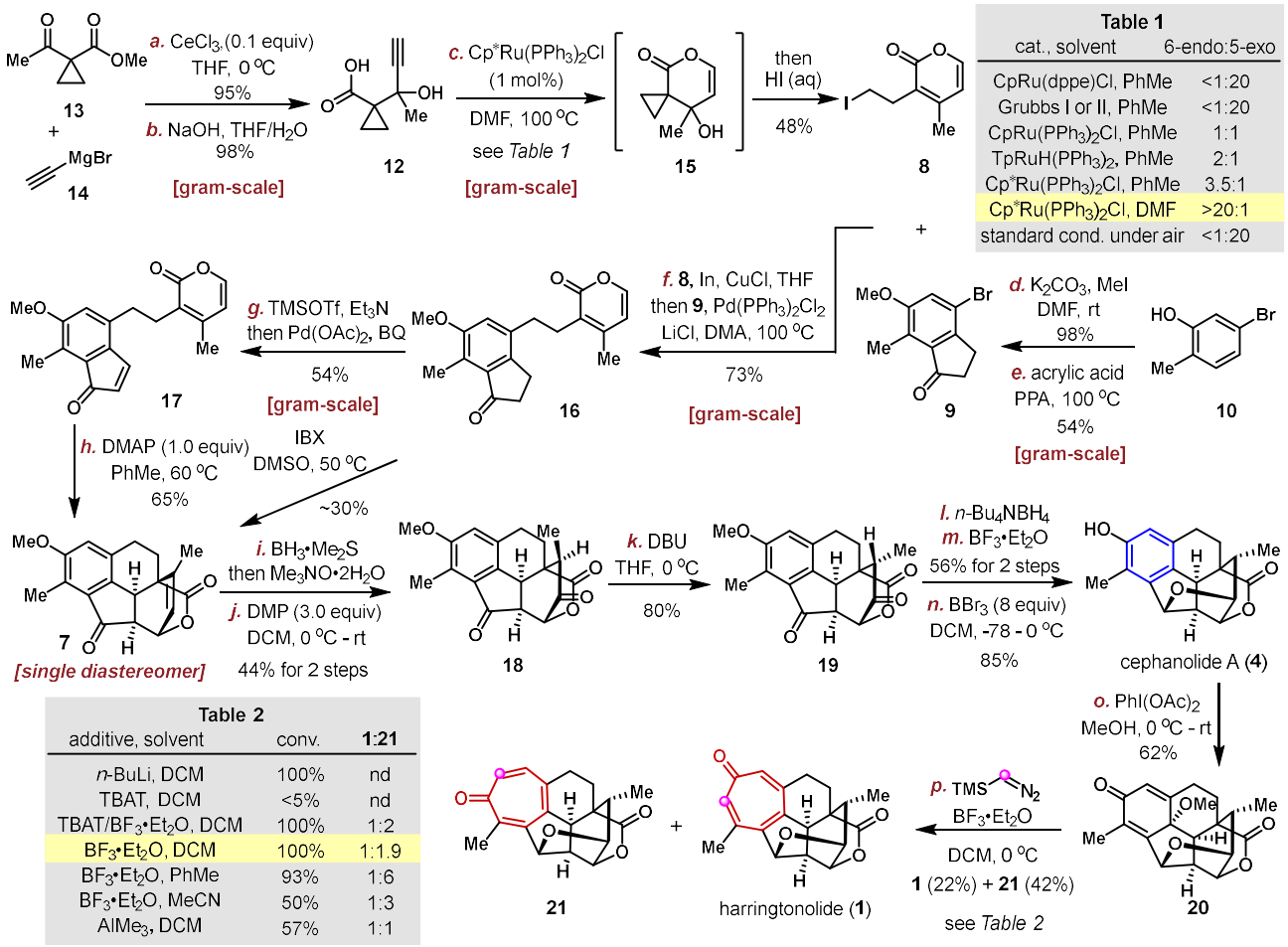


**Figure 2**. Unified total synthesis of cephanolide A (**4**) and harringtonolide (**1**).

Diastereoselective hydroboration-oxidation ($BH_3$•$Me_2S$, then $Me_3NO$•$2H_2O$) of C3-C4 alkene in **7** generated C3-hydroxyl and also reduced the C20 ketone to give a diol intermediate, which was oxidized with DMP to diketone **18** 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 **19** in 80% yield. Both ketone groups in **19** were reduced at once with *n*-$Bu_4NBH_4$ to arrive at a diol, with single stereochemical control at C3 and 1:1 *dr* at C20. The mixture of

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diastereomers was then treated with $BF_3$•$Et_2O$ in DCM to build the oxo-bridge affording methyl protected cephanolide A in 56% yield over two steps. After deprotection using $BBr_3$, cephanolide A (**4**) was successfully synthesized in 85% yield uneventfully.

The stage is now setting for the benzenoid-to-troponoid ring expansionto access harringtonolide (**1**), which required '1C insertion' between C12 and C13.[18] After extensive exploration (refer to Figure 3), this process was realized with the Büchner-Curtius-Schlotterbeck (BCS) reaction.[19] Thus, cephanolide A (**4**) first underwent oxidative dearomatization using $PhI(OAc)_2$ in MeOH to give the corresponding 4-quinol methyl ether **20** in 62% yield.[20] With $TMSCHCN_2$ as one-carbon synthon and $BF_3$•$Et_2O$ as Lewis acid additive in DCM at 0 °C, harringtonolide (**1**) can be successfully obtained together with the other regio isomer **21** in 22% and 42% yield respectively. The spectroscopic data for **4** and **1** are all in good agreement with those reported from the previous literature. A brief condition screening of the BCS reaction was listed in Table 2. While *n*-BuLi led to decomposition of the starting material, TBAT on its own gave almost no conversion. The combination of TBAT with $BF_3$•$Et_2O$ successfully delivered **1** and **21** in 1:2 ratio. Control reactions revealed that omitting TBAT led to unaltered efficiency, however, other solvents (PhMe, MeCN) were deleterious to both reaction conversion and regioselectivity (1:6 and 1:3, respectively). The Lewis acid $AlMe_3$ was found to give improved regioselectivity (1:1), however, conversion of this reaction was relatively low (57%). This transformation was proposed to proceed by 1,2-addition of trimethylsilyldiazomethane to the 4-quinol methyl ether **20**, followed by ring expansion of the alkyldiazonium intermediate and elimination of methanol to form the desired troponoids.[21] Likely, both the 1,2-addition and ring expansion steps were promoted by Lewis acid ($BF_3$•$Et_2O$). The interesting structural feature of **21** is also worth noting. Such a troponoid bearing the ketone group at C13 has not yet been reported for this class of natural products. Notwithstanding, it was proposed in a recent study by Zhao and Yue to be a biosynthetic intermediate accounting for the formation of a newly discovered 12-acyl benzenoid *Cephalotaxus* diterpenoid skeleton.[22]

To explore the benzenoid-to-troponoid ring expansion, our initial studies selected 2,4-dimethyl phenol **22** as a model substrate, in mimicking cephanolide A (**4**) where one of the ortho position of phenol been occupied by Me and the other by H. As illustrated in Figure 3A, **22** was first converted to the corresponding 4-quinol methyl ether **23** in 58% yield. In general, the BCS reaction has been well explored for ring expansion of saturated ketones.[23] In light of Herzon's disclosure using phenol derived enone as substrate,[24] we explored the BCS reaction on **23** with $TMSCHN_2$ under various conditions according to Lee's studies.[25] However, [3+2] cycloaddition of $TMSCHN_2$ to the dienone was predominant, with ring expansion product not observed even in the slightest amount.[26] The successful total synthesis of troponoid natural products Phaeocaulisin D[27] and Malettinins C/E[28] inspired us to investigate dearomative installation of $NO_2CH_2$- or $ArSO_2CH_2$-group at C2, which has only been testified intramolecularly. This

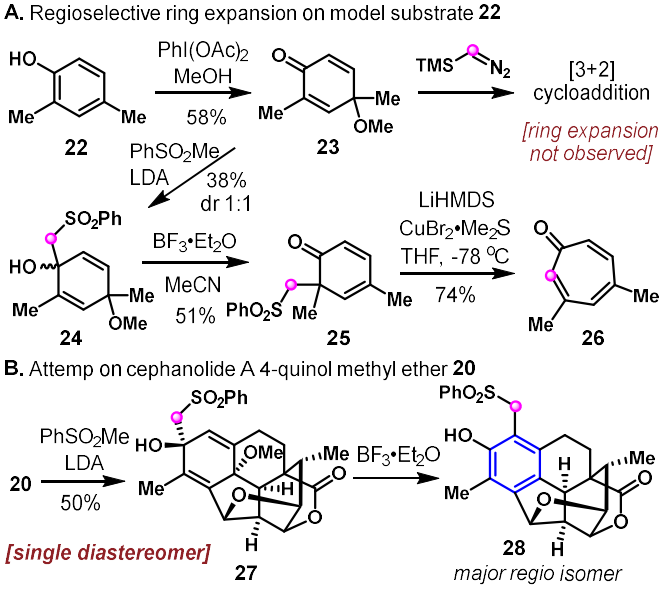


**Figure 3.** Study of strategies for benzenoid-to-troponoid ring expansion.

goal was realized through 1,2-addition of $PhSO_2CH_2$ anion to the dienone moiety giving **24** in 38% yield and 1:1 dr. Subsequent regioselective vinylogous semi-pinacol rearrangement induced by $BF_3•Et_2O$ in MeCN afforded **25** in 51% yield,[29] which was subjected to LiHMDS/$CuBr_2•Me_2S$ conditions under -78 °C delivering the desired regioselective ring expansion tropone **26** in 74% yield. When applying this protocol to cephanolide A 4-quinol **20**, sulfone **27** was obtained in 50% as a single diastereomer. Unfortunately, the $PhSO_2CH_2$- migration took place in low efficiency under the $BF_3•Et_2O$/MeCN conditions with the undesired regioisomer **28** observed as the major product. Nonetheless, this protocol provided a new opportunity for the benzenoid-to-troponoid ring expansion.

In summary, a unified strategy was developed for the concise synthesis of cephanolide A (**4**) and harringtonolide (**1**) in 14 and 16 steps respectively from commercially available starting materials. This synthesis features: (i) ruthenium catalyzed 6-*endo* cyclization of alkynoic acid to prepare 3,4-disubstituted α-pyrone fragment **8**, (ii) palladium catalyzed $Csp^2$-$Csp^3$ cross-coupling followed by doubly electron-deficient intramolecular Diels-Alder reaction to construct the carbon framework (**7**) of *Cephalotaxus* diterpenoid rapidly, and (iii) late-stage benzenoid-to-troponoid ring expansion to synthesize harringtonolide (**1**) from cephanolide A (**4**) in two steps. In addition, a protocol using $PhSO_2Me$ as 1C synthon was also described for the benzenoid-to-troponoid conversion. These studies shed light on the chemical synthetic connection between benzenoid and troponoid *Cephalotaxus* diterpenoids. Efforts to apply these ring expansion techniques to the synthesis of other structurally related nature products are ongoing.

**Acknowledgements**

Financial support for this work was provided by the National Natural Science Foundation of China (Grant No. 22101290), Chinese Academy of Sciences and the State Key Laboratory of Chemical Biology, Shanghai Institute of Materia Medica.

**References**

1. Abdelkafi, H.; Nay, B. Natural Products from Cephalotaxus sp.: Chemical Diversity and Synthetic Aspects. *Nat. Prod. Rep.* **2012**, *29*, 845–869.
2. (a) Buta, J. G.; Flippen, J. L.; Lusby, W. R. Harringtonolide, a Plant Growth Inhibitory Tropone from Cephalotaxus Harringtonia (Forbes) K. Koch. *J. Org. Chem.* **1978**, *43*, 1002–1003. (b) Sun, N.-J.; Xue, Z.; Liang, X.-T.; Huang, L. Studies on the Structure of a New Antitumor Agent−Hainanolide. *Acta Pharm. Sin.* **1979**, *14*, 39–44. (c) Du, J.; Chiu, M.-H.; Nie, R.-L. Two New Lactones from Cephalotaxus fortune var. alpnia. *J. Nat. Prod.* **1999**, *62*, 1664–1665. d) Yoon, K. D.; Jeong, D. G.; Hwang, Y. H.; Ryu, J. M.; Jim, J. Inhibitors of Osteoclast Differentiation from Cephalotaxus koreana. *J. Nat. Prod.* **2007**, *70*, 2029–2032.
3. (a) He, Y.-R.; Shen, Y.-H.; Shan, L.; Yang, X.; Wen, B.; Ye, J.; Yuan, X.; Li, H.-L.; Xu, X.-K.; Zhang, W.-D. Diterpenoid lanceolatins A–G from *Cephalotaxus lanceolata* and Their Anti-inflammatory and Antitumor Activities. *RSC Adv.* **2015**, *5*, 4126–4134. (b) Ni, G.; Zhang, H.; Fan, Y.-Y.; Liu, H.-C.; Ding, J.; Yue, J.-M. Mannolides A–C with an Intact Diterpenoid Skeleton Providing Insights on the Biosynthesis of Antitumor Cephalotaxus Troponoids. *Org. Lett.* **2016**, *18*, 1880–1883. (c) Xu, J.-B.; Fan, Y.-Y.; Gan, L.-S.; Zhou, Y.-B.; Li, J.; Yue, J.-M. Cephalotanins A–D, Four Norditerpenoids Represent Three Highly Rigid Carbon Skeletons from *Cephalotaxus sinensis*. *Chem. Eur. J.* **2016**, *22*, 14648–14654. (d) Zhao, J.-X.; Fan, Y.-Y.; Xu, J.-B.; Gan, L.-S.; Xu, C.-H.; Ding, J.; Yue, J.-M. Diterpenoids and Lignans from Cephalotaxus fortunei. *J. Nat. Prod.* **2017**, *80*, 356–362. (e) Fan, Y.-Y.; Xu, J.-B.; Liu, H.-C.; Gan, L.-S.; Ding, J.; Yue, J.-M. Cephanolides A–J, Cephalotane-Type Diterpenoids from *Cephalotaxus sinensis*. *J. Nat. Prod.* **2017**, *80*, 3159–3166. (f) Ni, L.; Zhong, X. H.; Chen, X. J.; Zhang, B. J.; Bao, M. F.; Cai, X. H., Bioactive Norditerpenoids from Cephalotaxus fortunei var. alpina and C. lanceolata. *Phytochemistry* **2018**, *151*, 50–60. (g) Ge, Z.-P.; Liu, H.-C.; Wang, G.-C.; Liu, Q.-F.; Xu, C.-H.; Ding, J.; Fan, Y.-Y.; Yue, J.-M. 17-*nor*-Cephalotane-Type Diterpenoids from *Cephalotaxus fortune*. *J. Nat. Prod.* **2019**, *82*, 1565–1575. (h) Zhao, C.-X.; Li, B.-Q.; Shao, Z.-X.; Li, D.-H.; Jing, Y.-K.; Li, Z.-L.; Hua, H.-M., Cephasinenoside A, a New Cephalotane Diterpenoid Glucoside from Cephalotaxus sinensis. *Tetrahedron Lett.* **2019,** *60*, 151154. (i) Li, Y.; Wang, Y.; Shao, Z.; Zhao, C.; Jing, Q.; Li, D.; Lin, B.; Jing, Y.; Li, Z.; Hua, H. Diterpenoids from *Cephalotaxus fortunei var. alpina* and Their Cytotoxic Activity. *Bioorg. Chem.* **2020**, *103*, 104226. (j) Ge, Z. P.; Fan, Y. Y.; Deng, W. D.; Zheng, C. Y.; Li, T.; Yue, J. M., Cephalodiones A-D: Compound Characterization and Semisynthesis by [6+6] Cycloaddition. *Angew. Chem. Int. Ed.* **2021,** *60*, 9374–9378. (k) Ge, Z.-P.; Zhou, B.; Zimbres, F. M.; Cassera, M. B.; Zhao, J.-X.; Yue, J.-M. Cephalotane-Type Norditerpenoids from *Cephalotaxus fortunei var. alpina*. *Chin. J. Chem.* **2022**, *40*, 1177–1184. (l) Ge, Z. P.; Zhou, B.; Zimbres, F. M.; Haney, R. S.; Liu, Q. F.; Wu, Y.; Cassera, M. B.; Zhao, J. X.; Yue, J. M., Cephalotane-type C(20) diterpenoids from Cephalotaxus fortunei var. alpina. *Org. Biomol. Chem.* **2022,** *20*,

9000–9009. (m) Jiang, C.; Han, Z.; Sun, W.; Tan, J.; Gao, G.; Wang, X.; Hua, H.; Zhao, R.; Han, T., Diterpenolignans and cephalotane diterpenoids from Cephalotaxus oliveri mast. with antitumor activity. *Phytochemistry* **2024,** *217*, 113924.

4. Jiang, C.; Xue, J.; Yuan, Y.; Li, Y.; Zhao, C.; Jing, Q.; Zhang, X.; Yang, M.; Han, T.; Bai, J.; Li, Z.; Li, D.; Hua, H. Progress in Structure, Synthesis and Biological Activity of Natural Cephalotane Diterpenoids. *Phytochemistry* **2021**, *192*, 112939.
5. Kang, S.-Q.; Cai, S.-Y.; Teng, L. *Acta Pharm. Sin.* **1981**, *16*, 867−868.
6. Evanno, L.; Jossang, A.; Nguyen-Pouplin, J.; Delaroche, D.; Herson, P.; Seuleiman, M.; Bodo, B.; Nay, B. Further Studies of the Norditerpene (+)-Harringtonolide Isolated from *Cephalotaxus harringtonia var. drupacea*: Absolute Configuration, Cytotoxic and Antifungal Activities. *Planta Med.* **2008**, *74*, 870–872.
7. For the total synthesis of troponoid Cephalotaxus diterpenoids, see: (a) Frey, B.; Wells, A. P.; Rogers, D. H.; Mander, L. N. Synthesis of the Unusual Diterpenoid Tropones Hainanolidol and Harringtonolide. *J. Am. Chem. Soc.* **1998**, *120*, 1914–1915. (b) Zhang, M.; Liu, N.; Tang, W. Stereoselective Total Synthesis of Hainanolidol and Harringtonolide via Oxidopyrylium-Based [5+2] Cycloaddition. *J. Am. Chem. Soc.* **2013**, *135*, 12434–12438. (c) Zhang, H.-J.; Hu, L.; Ma, Z.; Li, R.; Zhang, Z.; Tao, C.; Cheng, B.; Li, Y.; Wang, H.; Zhai, H. Total Synthesis of the Diterpenoid (+)-Harringtonolide. *Angew. Chem. Int. Ed.* ***2016***, *55*, 11638–11641. (d) Ao, Q.; Zhang, H.-J.; Zheng, J.; Chen, X.; Zhai, H. Asymmetric Total Synthesis of (+)-Mannolide C. *Angew. Chem. Int. Ed.* **2021**, *60*, 21267–21271. (e) Ren, Z.; Sun, Z.; Li, Y.; Fan, X.; Dai, M.; Wang, Y.; Hu, X. Total Synthesis of (+)-3-Deoxyfortalpinoid F (+)-Fortalpinoid, A., and (+)-Cephinoid H. *Angew. Chem. Int. Ed.* **2021**, *60*, 18572–18576. (f) Wang, H.; Liu, Y.; Zhang, H.; Yang, B.; He, H.; Gao, S. Asymmetric Total Synthesis of Cephalotaxus Diterpenoids: Cephinoid P, Cephafortoid A, 14-*epi*-Cephafortoid A and Fortalpinoids M–N, P. *J. Am. Chem. Soc.* **2023**, *145*, 16988–16994.
8. For the total synthesis of benzenoid Cephalotaxus diterpenoids, see: (a) Xu, L.; Wang, C.; Gao, Z.; Zhao, Y.-M. Total Synthesis of (±)-Cephanolides B and C via a Palladium-Catalyzed Cascade Cyclization and Late-Stage $sp^3$ C–H Bond Oxidation. *J. Am. Chem. Soc.* **2018,** *140*, 5653–5658. (b) Zhang, H.; He, H.; Gao, S. Asymmetric Total Synthesis of Cephanolide A. *Angew. Chem. Int. Ed.* **2020**, *59*, 20417–20422. (c) Zhang, H.; He, H.; Gao, S. Asymmetric Total Synthesis of Cephanolide B. *Org. Chem. Front.* **2021**, *8*, 555–559. (d) Haider, M.; Sennari, G.; Eggert, A.; Sarpong, R. Total Synthesis of the Cephalotaxus Norditerpenoids (±)-Cephanolides A–D. *J. Am. Chem. Soc.* **2021**, *143*, 2710–2715. (e) Lu, Y.; Xu, M.-M.; Zhang, Z.-M.; Zhang, J.; Cai, Q. Catalytic Asymmetric Inverse-Electron-Demand Diels-Alder Reactions of 2-Pyrones with Indenes: Total Syntheses of Cephanolides A and B. *Angew. Chem. Int. Ed.* **2021**, *60*, 26610–26615. (f) Li, A.; He, Z.; Liu, B.; Yang, Z.; Zhang, Z. Stereoselective Synthesis of (±)-Cephanolide B. *Org. Lett.* **2021**, *23*, 9237–9240. (g) Sennari, G.; Gardner, K. E.; Wiesler, S.; Haider, M.; Eggert, A.; Sarpong, R. Unified Total Syntheses of Benzenoid Cephalotane-Type Norditerpenoids: Cephanolides and Ceforalides. *J. Am. Chem. Soc.* **2022**, *144*, 19173–19185. (h) Qing, Z.; Mao, P.; Wang, T.; Zhai, H. Asymmetric Total Syntheses of Cephalotane-Type Diterpenoids Cephanolides A–D. *J. Am. Chem. Soc.* **2022**, *144*, 10640–10646. (i) Sun, Z.; Fan, X.; Sun, Z.; Li, Z.; Niu, L.; Guo, H.; Ren, Z.; Wang, Y.; Hu, X. Total Synthesis of (−)-Ceforalide B and (−)-Cephanolides B–D. *Org. Lett*. **2022**, *24*, 7507–7511.
9. During our manuscript preparation, a preprint was disclosed by the Sarpong group: Wiesler, S.; Sennari, G.; Popescu, M.V.; Gardner, K. E.; Aida K.; Paton R. S.; Sarpong, R. Late-Stage "Benzenoid-to-Troponoid" Skeletal Modification of the Cephalotanes: Total Synthesis of Harringtonolide and Computational Analysis. *ChemRxiv.* **2024**, doi:10.26434/chemrxiv-2024-v0670.
10. Hardy, M. A.; Hayward Cooke, J.; Feng, Z.; Noda, K.; Kerschgens, I.; Massey, L. A.; Tantillo, D. J.; Sarpong, R. Unified Synthesis of 2-Isocyanoallopupukeanane and 9-Isocyanopupukeanane through a "Contra-biosynthetic" Rearrangement. *Angew. Chem. Int. Ed.* **2024,** *63*, e202317348.
11. (a) Jurczyk, J.; Woo, J.; Kim, S. F.; Dherange, B. D.; Sarpong, R.; Levin, M. D. Single-atom Logic for Heterocycle Editing. *Nat. Syn.* **2022**, *1*, 352–364. (b) Dherange, B. D.; Kelly, P. Q.; Liles, J. P.; Sigman, M. S.; Levin, M. D., Carbon Atom Insertion into Pyrroles and Indoles Promoted by Chlorodiazirines. *J. Am. Chem. Soc.* **2021**, *143*, 11337–11344. (c) Kelly, P. Q.; Filatov, A. S.; Levin, M. D. A Synthetic Cycle for Heteroarene Synthesis by Nitride Insertion. *Angew. Chem. Int. Ed.* **2022**, *61*, e202213041. (d) Hyland, E. E.; Kelly, P. Q.; McKillop, A. M.; Dherange, B. D.; Levin, M. D., Unified Access to Pyrimidines and Quinazolines Enabled by N–N Cleaving Carbon Atom Insertion. *J. Am. Chem. Soc.* **2022**, *144*, 19258–19264. (e) Schmitt, H. L.; Martymianov, D.; Green, O.; Delcaillau, T.; Park Kim, Y. S.; Morandi, B., Regiodivergent Ring-Expansion of Oxindoles to Quinolinones. *J. Am. Chem. Soc.* **2024**, doi: 10.1021/jacs.3c12119.
12. (a) Jiménez-Tenorio, M.; Carmen Puerta, M.; Valerga, P.; Javier Moreno-Dorado, F.; Guerra, F. M.; Massanet, G. M. Regioselective Cyclization of α,ω-Alkynoic Acids Catalysed by TpRu Complexes: Synthesis of Endocyclic Enol Lactones [Tp = hydrotris(pyrazolyl)borate]. *Chem. Commun.* **2001**, 2324–2325. (b) Melis, K.; Opstal, T.; Verpoort, F. Selective Dimerisation and Addition of Carboxylic Acids to Terminal Alkynes, Catalysed by Thermolysed Grubbs' Catalyst: A Novel Synthesis of Enynes and Vinyl Esters, *Eur. J. Org. Chem*. **2002**, 3779–3784.
13. Bruneau, C. *Top. Organomet. Chem.* **2004**, *11*, 125–153.
14. Leeuwen, T.; Neubauer, T. M.; Feringa, B. L. Regioselective Synthesis of Indanones. *Synlett* **2014**, *25*, 1717–1720.
15. Shen, Z.-L.; Goh, K. K. K.; Yang, Y.-S.; Lai, Y.-C.; Wong, C. H. A.; Cheong, H.-L; Loh, T.-P. Direct Synthesis of Water-Tolerant Alkyl Indium

Reagents and Their Application in Palladium-Catalyzed Couplings with Aryl Halides. *Angew. Chem. Int. Ed*. **2011**, *2*, 511–514.

16. Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y. L. Iodine(V) Reagents in Organic Synthesis. Part 4. o-Iodoxybenzoic Acid as a Chemospecific Tool for Single Electron Transfer-Based Oxidation Processes. *J. Am. Chem. Soc.* **2002,** *124*, 2245–2258.
17. O'Sullivan, T. P.; Zhang, H.; Mander, L. N. Model Studies toward the Synthesis of the Bioactive Diterpenoid, Harringtonolide. *Org. Biomol. Chem*. **2007**, *5*, 2627–2635.
18. (a) Kats-Kagan, R.; Herzon, S. B., The Discovery of a Novel Route to Highly Substituted α-Tropolones Enables Expedient Entry to the Core of the Gukulenins. *Org. Lett.* **2015**, *17*, 2030–2033. (b) Liang, X.; Li, L.; Wei, K.; Yang, Y.-R., Gram-Scale, Seven-Step Total Synthesis of (−)-Colchicine. *Org. Lett.* **2021**, *23*, 2731–2735. (c) Liu, N.; Song, W.; Schienebeck, C. M.; Zhang, M.; Tang, W. Synthesis of Naturally Occurring Tropones and Tropolones. *Tetrahedron* **2014**, *70*, 9281–9305. (b) Murelli, R. P.; Berkowitz, A. J.; Zuschlag, D. W. Carbocycloaddition Strategies for Troponoid Synthesis. *Tetrahedron* **2023**, *130*, 133175.
19. (a) Büchner, E.; Curtius, T. Synthese von Ketonsaureanthern aus Aldehyden und Diazoessigäther. *Chem. Ber.* **1885**, *18*, 2371–2377. (b) Schlotterbeck, F. Transformation of Aldehydes into Ketones by Means of Diazomethane. *Chem. Ber.* **1907**, *40*, 1826–1827. (c) Büchner–Curtius–Schlotterbeck Reaction. In Comprehensive Organic Name Reactions and Reagents. John Wiley & Sons, Inc. **2010**, 567–569.
20. Roche, S. P.; Porco, J. A. Dearomatization Strategies in the Synthesis of Complex Natural Products. *Angew. Chem. Int. Ed.* **2011**, *50*, 4068–4093.
21. Sakai, T.; Ito, S.; Furuta, H.; Kawahara, Y.; Mori, Y. Mechanism of the Regio- and Diastereoselective Ring Expansion Reaction Using Trimetheylsilyldiazomethane. *Org. Lett.* **2012**, *14*, 4564–4567.
22. Ge, Z.-P.; Xu, J.-B.; Zhao, P.; Xiang, M.; Zhou, Y.; Lin, Z.-M.; Zuo, J.-P.; Zhao, J.-X.; Yue, J.-M. Highly Modified Cephalotane-type Diterpenoids from Cephalotaxus fortunei var. alpina and C. sinensis. *ChemRxiv.* **2023**, doi: 10.26434/chemrxiv-2023-8v6dr-v2.
23. Candeias, N. R.; Paterna, R.; Gois, P. M. P. Homologation Reaction of Ketones with Diazo Compounds. *Chem. Rev.* **2016**, *116*, 2937–2981.
24. Combs, J.; Wright, T.; Chen, L.; Holmes, R.;Qin, B.; Oh, J.; Crawford, J.; Herzon, S. Enantioselective synthesis of anhydrogukulenin A C2-acetate. *ChemRxiv*. **2023**, DOI: 10.26434/chemrxiv-2023-8dj1k.
25. Liu, H.; Sun, C.; Lee, N. K.; Henry, R. F.; Lee, D. New methylene homologation method for cyclic ketones. C *Chem. Eur. J.*, **2012**, *18*, 11889-11893.
26. Liu, H.; O'Connor, M. J.; Sun, C.; Wink, D. J.; Lee, D. Sequential Reactions of Trimethylsilyldiazomethane with 4-Alkenyl Ketones and Aldehydes Catalyzed by Lewis Bases. *Org. Lett.* **2013**, *15*, 2974–2977.
27. Ezzat, N.; Bobek, K.; Yuan, Y. Total Synthesis of (±)-Phaeocaulisin D. *Synlett* **2021**, *32*, 689–692.
28. Umekubo, N.; Yokoshima, S. Total Synthesis of Malettinins C and E. *Org. Lett.* **2023**, *25*, 4530–4533.
29. Qiu, D.; Shi, J.; Guo, Q.; Xu, Q.; Li, B.; Li, Y. Cyclohexenynone Precursors: Preparation via Oxidative Dearomatization Strategy and Reactivity. *J. Am. Chem. Soc.* **2018,** *140*, 13214–13218.