Divergent Synthesis of 17-*nor*-Cephalotane Diterpenoids through Developed Ynol-diene Cyclization

Zezhong Sun,[†] Xin Shu,[†] Fuli Ma, Ao Li, Yali Li, Shuang Jin, Yunxia Wang, and Xiangdong Hu*

ABSTRACT: The diversity of complex molecular structures of *Cephalotaxus* diterpenoids poses great challenges in uncovering the pharmaceutical potential of these natural products. As a subfamily of *Cephalotaxus* diterpenoids, 17-*nor*-cephalotane diterpenoids possess polycyclic frameworks with seven-membered A ring bearing different oxidation states. On the basis of a novel ynol-diene cyclization developed as a rapid access to tropone unit, a concise and divergent strategy to 17-*nor*-cephalotane diterpenoids has been successfully established. Combining with a bioinspired stereoselective dual hydrogenation, the enantioselective total synthesis of (+)-3-deoxyfortalpinoid F, (+)-harringtonolide, (−)-fortalpinoids M/N/P, and analog (−)-20-deoxocephinoid P have been achieved in 14-17 linear longest steps starting from commercially available materials.

Diversity is an intrinsic property of *Nature*, enriching the world with countless beauties and surprises. As a case in molecular architecture of natural products, the complex polycyclic structures of *Cephalotaxus* diterpenoids exhibit a prominent structural diversity, which poses significant obstacles to the synthesis of these natural species and the achievement of their pharmaceutical values.

Since the discovery of harringtonolide (**1**) as the first member of *Cephalotaxus* diterpenoids in 1978,[1] great efforts have been contributed to discover new congeners,[2] which effectively promoted the expansion of *Cephalotaxus* diterpenoids into a compelling natural product family comprising over 100 members, some of which exhibit intriguing biological activities. For instance, harringtonolide (**1**) demonstrates selective anticancer activity on KB tumor cells.[3] 3-Deoxyfortalpinoid F (**4**) exhibits distinct antitumor activity.[2l] Cephinoid H (**5**) shows significant inhibition of the NF-κB signaling pathway and cytotoxicity against human tumor cell lines.[2k] The structural diversity of *Cephalotaxus* diterpenoids is categorized into five subfamilies:[2t] 17-*nor*-cephalotane diterpenoids, prototype diterpenoids, benzenoid norditerpenoids, A-ring-*seco* norditerpenoids, and dimers. Their complex polycyclic skeletons, combing with valuable biological properties, have attracted great attention from the organic synthesis community. Impressive progresses had been made toward total synthesis of *Cephalotaxus* diterpenoids by groups of Mander,[4] Tang,[5] Zhai,[6] Zhao,[7] Gao,[8] Sarpong,[9] Cai,[10] Yang[11] and Wang,[12] and our group.[13]

It is noteworthy that 17-*nor*-cephalotane diterpenoids are subdivided into two categories,[2t] *Cephalotaxus* troponoids and tropone-free 17-*nor*-cephalotane diterpenoids, which share the same skeleton with different oxidation states on ring A (Figure 1). And it was proposed by Zhang, Shen, and co-workers that tropone-free 17-*nor*-cephalotane diterpenoids could be biosynthetically derived from partial reduction of the tropone unit of *Cephalotaxus* troponoids.[14] Up to date, there are elegant strategies leading to the formation of the peculiar tropone motif reported in total synthesis of *Cephalotaxus* troponoids. Application of the Buchner reaction strategy came from Mander and co-workers in the earliest total synthesis of 3-deoxyfortalpinoid F (**4**)[4a] and harringtonolide (**1**).[4b] Tang and co-workers employed an

oxidopyrylium mediated intramolecular [5+2] cycloaddition protocol in their total synthesis of **1**.[5] In the first asymmetric total synthesis of (+)-**1**, Zhai and co-workers developed a Rh-enabled intramolecular [3+2] cycloaddition strategy.[6a] Our group reported a ring-closing metathesis (RCM)/elimination protocol in the asymmetric total synthesis of (+)-**4**, (+)-**5** and (+)-fortalpinoid A (**6**).[13a] A divergent carbon introduction/ring-expansion strategy had been validated by Zhao and co-workers in their total synthesis of **5**, fortalpinoid C, cephanolide E and their analogs.[7b] In the total synthesis of **1**, an oxidative dearomatization/ring-expansion protocol had been developed by groups of Sarpong[9c] and Wang,[12] respectively. Regarding the synthesis of cycloheptene unit in tropone-free 17-*nor*-cephalotane diterpenoids, there is only one effective strategy reported, which is the elegant Nicholas/Hosomi−Sakurai reaction tactic developed by Gao and co-workers in their asymmetric total synthesis of (−)-cephafortoid A (**10**), (−)-cephinoid P (**11**), (−)-14-*epi*-cephafortoid A (**12**) and (−)-fortalpinoids M/N/P (**7**/**8**/**9**).[8c] Notably, in the asymmetric total synthesis of (+)-mannolide C achieved by Zhai, Chen and co-workers, an ingenious double RCM strategy was established for the construction of a similar cycloheptene A ring.[6b]

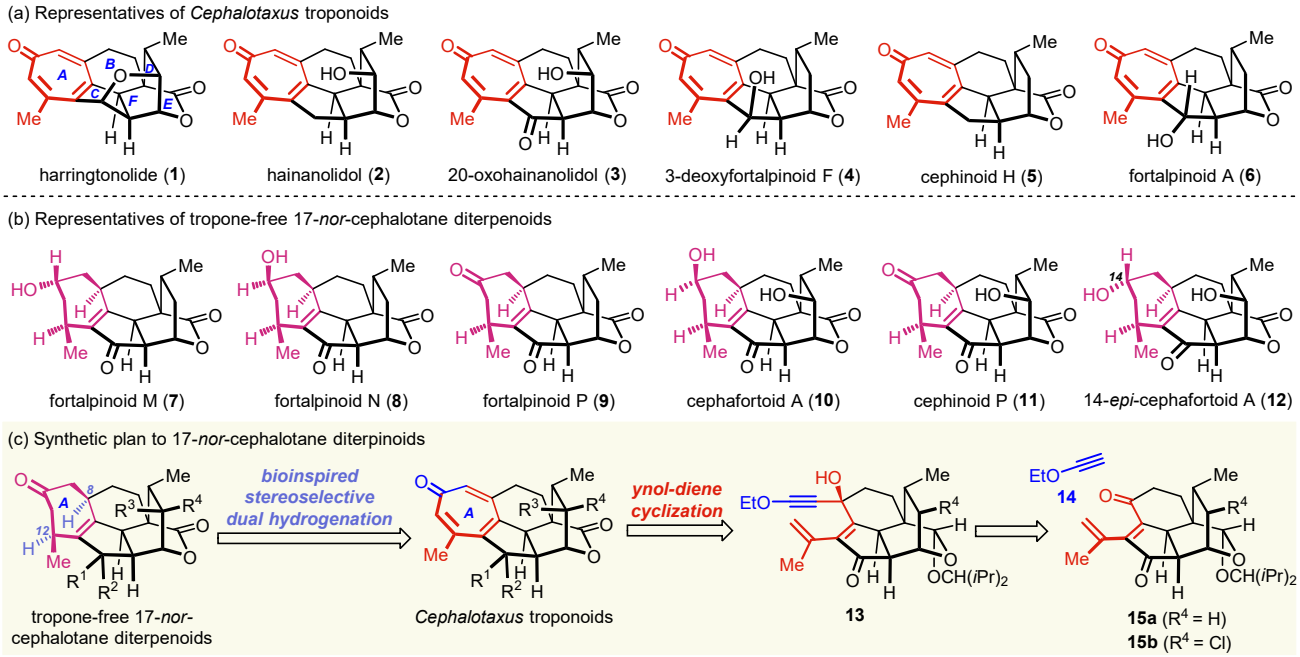


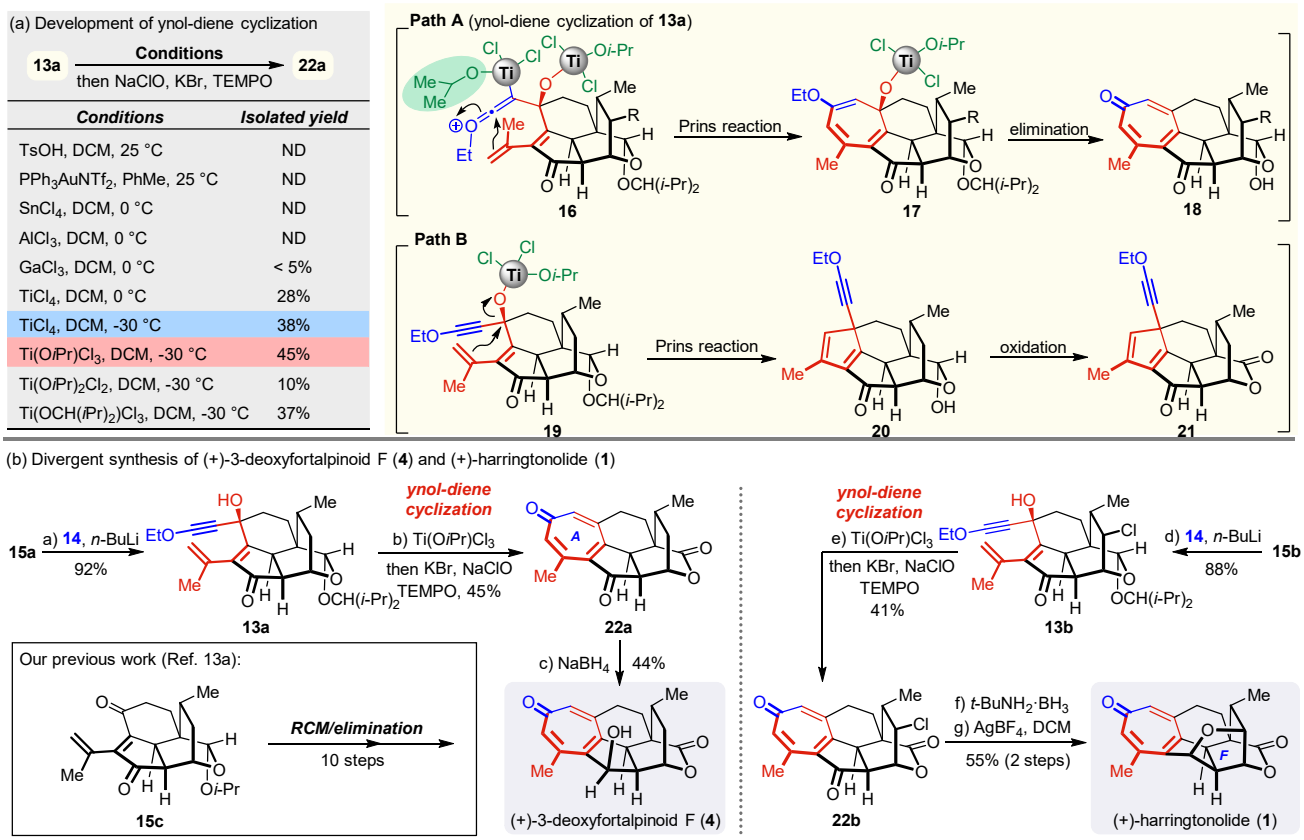
Figure 1. (a) Representatives of *Cephalotaxus* troponoids. (b) Representatives of tropone-free 17-*nor*-cephalotane diterpenoids. (c) Synthetic plan to 17-*nor*-cephalotane diterpenoids.

Although some synthetic strategies had been successfully developed for *Cephalotaxus* troponoids and tropone-free 17-*nor*-cephalotane diterpenoids, a divergent strategy to synthesize two categories of 17-*nor*-cephalotane diterpenoids is still not available. And it is noticeable that the introduction of carbonyl group into the tropone unit encountered regioselectivity issues sometimes.[7b, 9c, 12] Therefore, it is a challenging task to develop a divergent and efficient synthetic route to both categories of 17-*nor*-cephalotane diterpenoids.

In recent years, our group had developed a stereoselective Pauson−Khand reaction tactic as a general access to the B-C-D-E ring skeleton of *Cephalotaxus* diterpenoids.[13] However, our asymmetric total synthesis of *Cephalotaxus* troponoids (+)-**4**/**5**/**6** was quite cumbersome with the requirement of 23-25 linear longest steps starting from a known chiral building block obtained from chiral resolution process,[15] which made the further biological evaluation of these compounds difficult. Herein, we present the development of a divergent synthetic route to 17-*nor*-cephalotane

diterpenoids and enantioselective total synthesis of (+)-**4**, (+)-**1** and (−)-**7**/**8**/**9** with decent efficiency. Our synthetic plan is outlined in Figure 1c. Inspired by the biosynthetic proposal from Zhang, Shen, and co-workers,[14] we anticipated that a dual hydrogenation of *Cephalotaxus* troponoids could be a feasible pathway to achieve the lower oxidation state of A ring in tropone-free 17-*nor*-cephalotane diterpenoids, and more importantly a stereoselective access to stereocenters on C8 and C12. For synthesis of *Cephalotaxus* troponoids, our expectation is that, through a novel ynol-diene cyclization, commercially available ynol compound **14** could be applied to fill up the loophole of tropone A ring of **15a** and **15b**.

Scheme 1. Development of ynol-diene cyclization and divergent synthesis of (+)-3-deoxyfortalpinoid F and (+)-harringtonolide.

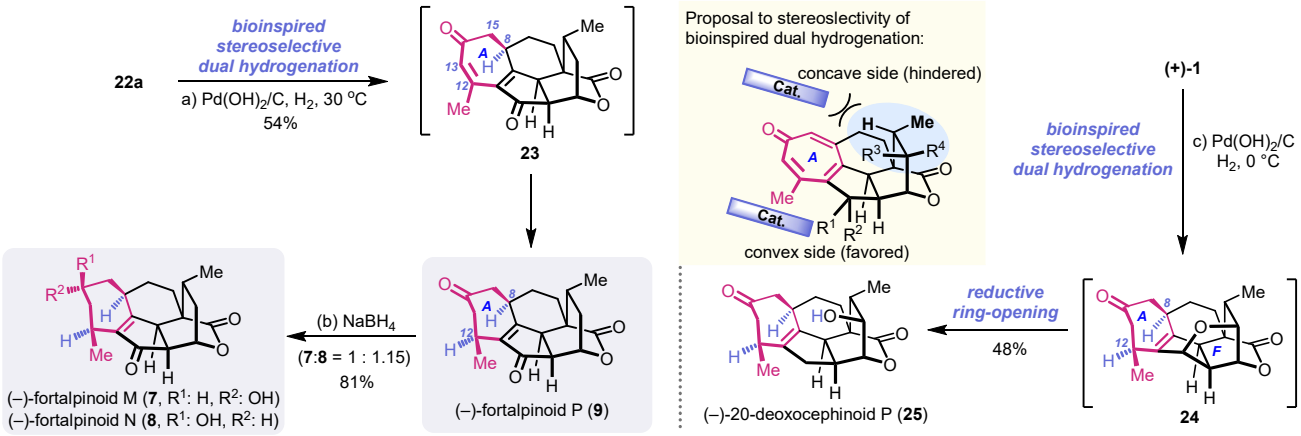


Taking benefits from the stereoselective Pauson−Khand reaction and asymmetric Michael addition tactics developed in our previous works,[13d] the enantioselective preparation of **15a** and **15b** was readily achieved in 11 and 12 steps from commercially available materials, respectively (see SI for details). Then, we carried out the exploration on the proposed ynol-diene cyclization and synthesis of *Cephalotaxus* troponoids (Scheme 1). Comparing with the skeleton of *Cephalotaxus* troponoids, the structural analysis revealed that there is only an ynol unit missing in **15a**. And the nucleophilic connection of **14** and **15a** could be a regioselective solution to the subsequent introduction of carbonyl into the tropone unit. Our expectation is that, under acidic conditions, the adduct **13a** could generate the ketenium cation intermediate **16** (Scheme 1, Path A). The subsequent Prins reaction will result in the formation of the seven-membered ring in **17**, which could deliver the tropone unit in **18** through an elimination process. To the best of our knowledge, the proposed ynol-diene cyclization is an unexplored process. There is a similar ynol-ene cyclization reported by Takikawa and co-workers, which led to the construction of a cyclohexadienone skeleton.[16] However, **13a** may go through another cyclization pathway (Path B), which could release the acid activated tertiary hydroxy directly and afford cyclopentadiene-type product **20**. Therefore, it will be challenging to achieve the construction of tropone

unit through the proposed ynol-diene cyclization.

The cyclization of **13a** was then examined under various acidic conditions (Scheme 1a). Of note, the hydrolysis of the acetal motif could take place readily under acidic conditions, which will pose a problem for characterization of the unstable intermediates **18** and **20**. Therefore, the *one-pot* oxidation with NaClO/TEMPO/KBr was applied at the end of the treatment to form the stable lactone products **22a** and **21**. Preliminary results demonstrated that $TiCl_4$ exhibited obvious superiority to facilitate the proposed ynol-diene cyclization, which led to the formation of expected **22a** in 38% yield without the observation of **21**. We speculated that, due to the ring strain existing in the seven-membered transition state, the intramolecular Prins reaction of the ketenium cation **19** could be a difficult process. With the purpose to improve the cyclization's efficiency, we anticipated that a bulky substituent on titanium could increase the stability of the active ketenium cation by preventing the nucleophilic attack outside. Therefore, the *in-situ* prepared $Ti(OiPr)Cl_3$[17] was checked. To our delight, the generation of **22a** was improved to 45% yield. Further examinations with $Ti(OiPr)_2Cl_2$ and $Ti(OCH(iPr)_2)Cl_3$ didn't give better results. To this point, we have succeeded in the development of a novel ynol-diene cyclization as a new access to tropone unit.[18] The reduction of **22a** readily accomplished the enantioselective total synthesis of (+)-3-deoxyfortalpinoid F (**4**). It is noteworthy that the RCM/elimination protocol applied in our previous synthesis of (+)-**4** required 10 steps from a similar precursor **15c**. As the result, this novel ynol-diene cyclization significantly improved the synthetic efficiency of (+)-**4**. Then, we turned our attention to total synthesis of (+)-harringtonolide (**1**), one of the most bio-active members of *Cephalotaxus* diterpenoids. The ynol-diene cyclization of **13b** was executed under the treatment of $Ti(OiPr)Cl_3$. Pleasingly, the expected tropone product **22b** was obtained in 41% yield after the *one-pot* oxidation treatment. Besides, the treatment of **13b** with $TiCl_4$ delivered **22b** in 35% yield, which demonstrated concordance with the enhancement of the ynol-diene cyclization by bulky substituent on titanium. Subsequently, **22b** was submitted to the reduction with *t*-$BuNH_2{\cdot}BH_3$ and $AgBF_4$ promoted formation of F ring, which readily accomplished the total synthesis of (+)-harringtonolide (**1**).

Scheme 2. Divergent synthesis of (−)-fortalpinoids M/N/P and analog (−)-20-deoxocephinoid P through bioinspired stereoselective dual hydrogenation.



As a category of 17-*nor*-cephalotane diterpenoids, tropone-free 17-*nor*-cephalotane diterpenoids are featured with lower oxidation state on the seven-membered A ring. To date, there is only one successful synthesis report on these *Cephalotaxus* diterpenoids. Inspired by the biosynthetic proposal on partial reduction of the tropone unit, we commenced exploration of the reduction of **22a**, which could establish a new pathway to (−)-fortalpinoid P (**9**). Notably, the stereocenters on C8 and C12 require precise site-selectivity and stereoselectivity of the reduction of the

tropone unit. In this regard, we anticipated that heterogeneous catalytic dual hydrogenation could be a favorable pathway to reduce the tropone A ring in **22a** from the convex side, which could lead to the construction of the expected stereocenters on C8 and C12. Although the heterogeneous catalytic hydrogenation of tropone unit is known,[19] the site-selectivity and stereoselectivity in this case is still challenging. To our surprise, the employment of $Pd(OH)_2/C$ facilitated the dual hydrogenation of **22a** smoothly. Our anticipation is that, due to the electron-withdrawing effect from two conjugated carbonyl groups, the C8-C15 double bond in **22a** could be hydrogenated preferentially, giving **23** as the intermediate. Subsequently, the stereoselective hydrogenation of C12-C13 double bond in **23** completed the total synthesis of (−)-**9** with expected C8-C15/C12-C13 site-selectivity and C8/C12 stereoselectivity. The reduction of (−)-**9** then completed synthesis of (−)-fortalpinoid M (**7**) and (−)-fortalpinoid N (**8**), as reported in Gao's approach to tropone-free 17-*nor*-cephalotane diterpenoids.[8c] Stimulated by the curiosity, we carried out the bioinspired stereoselective dual hydrogenation of (+)-**1**. To our surprise, with the completion in few minutes at 0 ℃, the hydrogenation of (+)-**1** proceeded much faster than that of **22a**, affording (−)-20-deoxocephinoid P (**25**) as an analog of (−)-cephinoid P (**11**). Our speculation is that the tropone ring in (+)-**1** could be significantly activated by the ring strain delivered from the adjacent THF ring. In the beginning, the intermediate **24** could be generated through the stereoselective dual hydrogenation. Then, the ring strain will promote the subsequent reductive THF ring-opening to generate (−)-**25** in the end.

In summary, a divergent synthetic approach to both categories of 17-*nor*-cephalotane diterpenoids has been successfully developed for the first time. And the concise and enantioselective total synthesis of (+)-3-deoxyfortalpinoid F, (+)-harringtonolide, (−)-fortalpinoids M/N/P and analog (−)-20-deoxocephinoid P have been accomplished in 14-17 linear longest steps starting from commercially available materials, which could facilitate further assessment of their pharmaceutical potentials. The salient features of the synthetic route include (1) an unprecedented ynol-diene cyclization to construct the tropone unit in decent efficiency, and (2) the bioinspired stereoselective dual hydrogenation to achieve expected site-selectivity and stereoselectivity. Further application of the developed ynol-diene cyclization is currently underway in our laboratory.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We are grateful for financial support from the National Natural Science Foundation of China (22071192, 21772153) and Science and Technology Department of Shaanxi Province (2019JM-151).

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