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-deoxycephinoid 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]

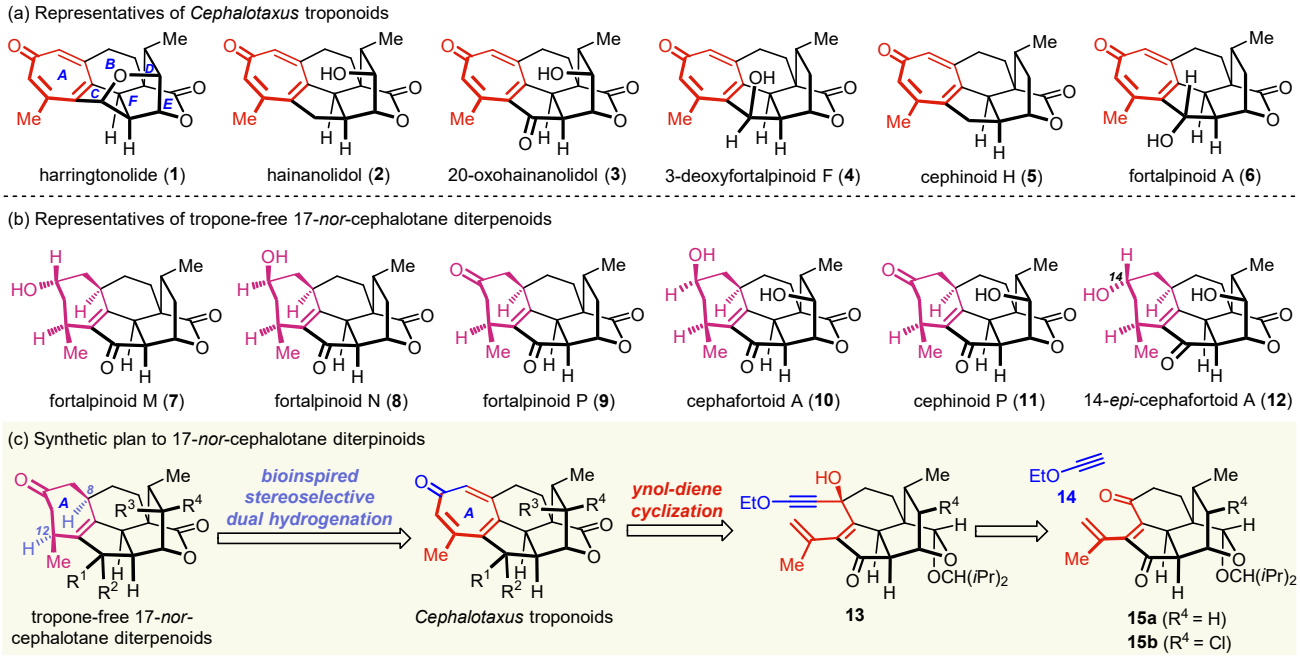


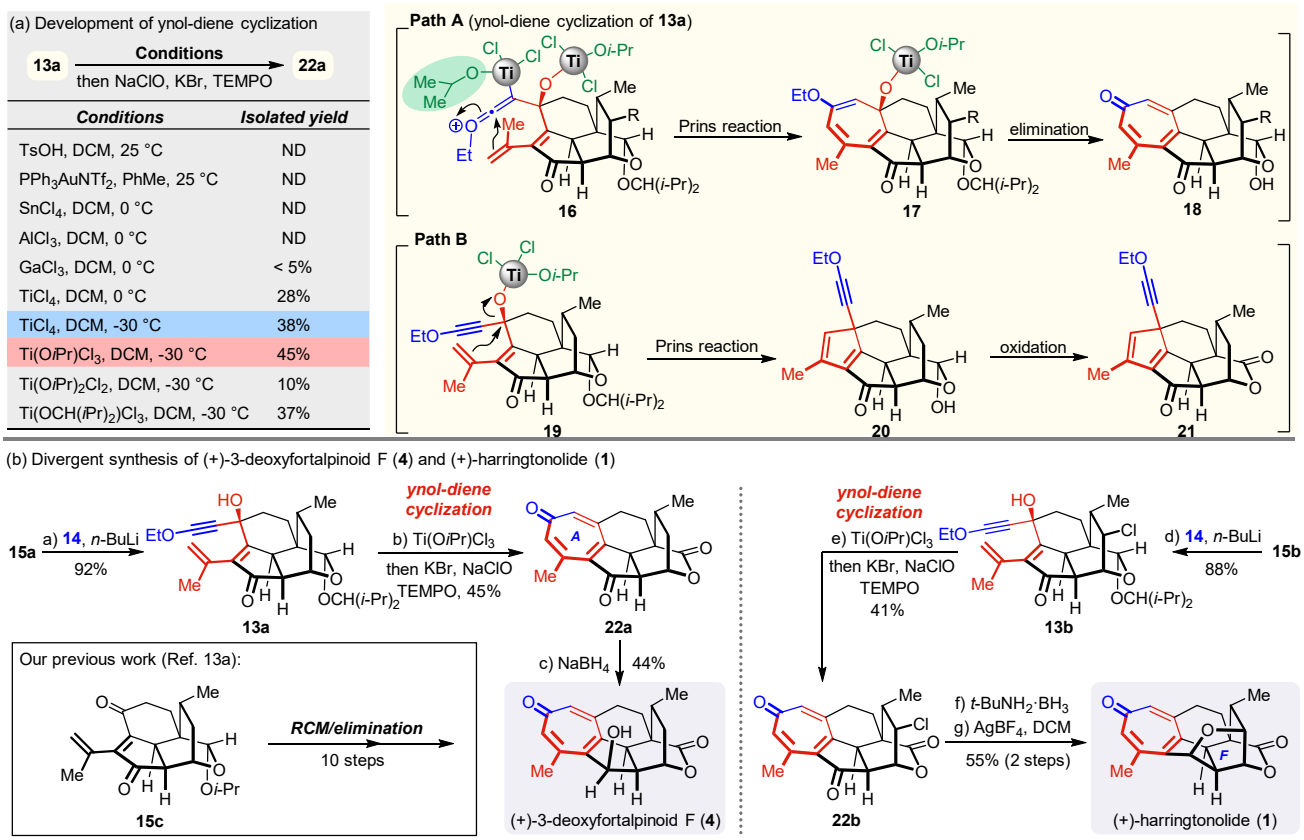
Figure 1. (a) Representatives of *Cephalotaxus* troponoids. (b) Representatives of tropone-free 17-*nor*-cephalotane diterpenoids. (c) Synthetic plan to 17-*nor*-cephalotane diterpenoids.

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.

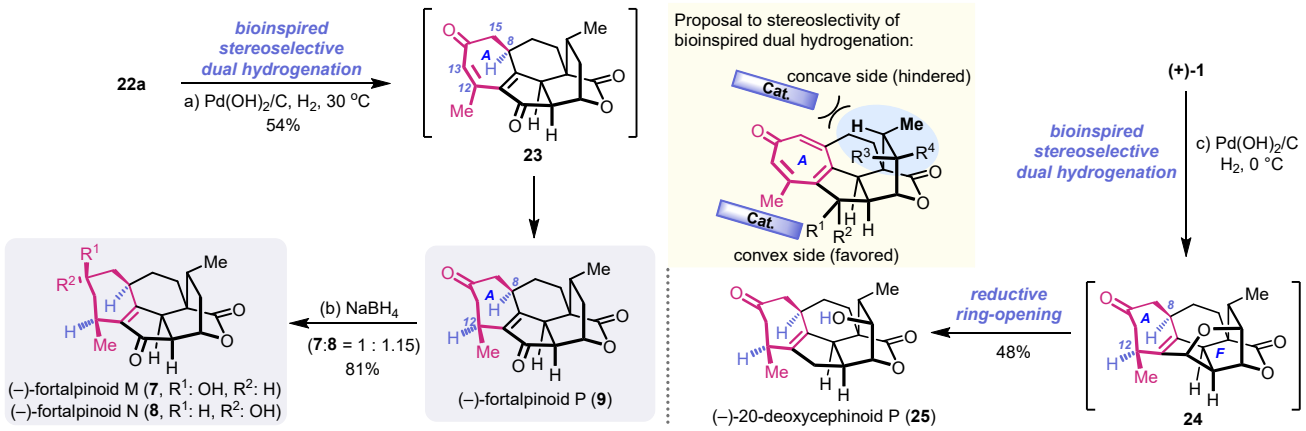


Taking benefits from the stereoselective Pauson−Khand reaction and asymmetric Michael addition tactics developed in our previous works,[13d] the enantioselective preparation of **15a** and **15b** was readily achieved in 11 and 12 steps from commercially available materials, respectively (see SI for 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 to achieve effective regioselectivity for the introduction of the carbonyl, the connection of **14** and **15a** through a nucleophilic addition could be a reliable solution. 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-deoxycephinoid 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-deoxycephinoid 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-deoxycephinoid 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.

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