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Asymmetric Total Synthesis of Cephanolide A

Hongyuan Zhang [a], Haibing He[b], Shuanhu Gao*[a,b]

Abstract: The first asymmetric total synthesis of cephanolide A, a complex hexacyclic C_{18} dinorditerpenoid from *cephalotaxus sinensis*, was achieved. The synthesis features a convergent strategy, which provides a flexible approach to prepare the biogenetically *cephalotaxus* diterpenoids and structurally related derivatives for biological studies. A mild intramolecular Prins cyclization was developed to construct the central hexahydrofluorenol skeleton (A−B−C ring) which relies on the originally proposed hydroacylation strategy. A remote hydroxyl group directed hydrogenation was applied to stereospecifically reduce the tetra-substituted enone unit. A sequence of ring forming steps, including lactonization, cation mediated etherification and Friedel−Crafts cyclization, was efficiently utilized to forge the cage-like skeleton.

Polycyclic terpenoids, a big family of structurally diverse natural products, have been used as a fruitful source for the drug discovery. Among them, the subgroups of sesquiterpenoids (C_{15}) and diterpenoids (C_{20}) have been extensively studied for drug discovery. In the past decades, the *cephalotaxus* diterpenoids (Figure 1, **1**−**10**) attracted considerable attention from both the community of chemists and biologists due to their unique structural features and potential biological activities.[1] Harringtonolide (**4**),[2a] (also named hainanolide),[2b] was the first member of this class of natural products that was isolated from the seeds of *cephalotaxus harringtonia* by Buta and coworkers. Structurally, harringtonolide (**4**) belongs to *cephalotaxus* C_{19} norditerpenoids which contain a complex cage-like troponoid skeleton. The same subgroup also includes the members of hainanolidol (**6**),[2a-b] fortunolides A (**7**) and B (**5**) [2c-d] (Figure 1). Notably, Yue and coworkers reinvestigated the plants of the *Cephalotaxaceae* and found out the existence of biogenetically related *cephalotaxus* C_{20} diterpenoids, mannolides A−C (**1**−**3**),[3] and C_{18} dinorditerpenoids, cephanolides A−C (**8**−**10**) etc.,[4] over the past few years. The biosynthetic pathway of this family of molecules was also proposed, which suggested that the biosynthetic precursor should be the tetracyclic C_{20} cephalotane skeleton derived from geranylgeranyl pyrophosphate (GGPP).[3-4] After a sequence of oxidation and cyclization, it would first generate *cephalotaxus* C_{20} diterpenoids (such as **1**−**3**). The *cephalotaxus* C_{19} norditerpenoids (such as **4**−**7**) might be produced through the decarboxylation at C-8 followed by the aromatization of ring A. One-carbon ring contraction of troponoids through the electrocyclization and degradation would yield the C_{18} dinorditerpenoids bearing aromatic benzenoid A−ring (such as **8**−**10**) (see Scheme S1 in the Supporting Information).

The synthetic breakthrough of the *cephalotaxus* diterpenoids came when the Mander group reported the first total synthesis of harringtonolide (**4**) in 1998, which applied an intramolecular arene cyclopropanation followed by ring expansion strategy.[5] Elegant total syntheses of **4** and hainanolidol (**6**) have also been described by the groups of Tang[6] and Zhai[7] using an intramolecular oxidopyrylium-based [5+2] cycloaddition and rhodium-catalyzed intramolecular [3+2] cycloaddition as key steps. More recently, Zhao and coworkers creatively used a palladium-catalyzed cascade cyclization reaction to construct the core skeleton of *cephalotaxus* diterpenoids and achieved the total synthesis of cephanolide B (**9**) and C (**10**).[8] The intriguing architecture and outstanding biological potentials of *cephalotaxus* diterpenoids attracted our research interest, which belongs to a big project of synthesis of fluorenone and fluorene containing natural products.[9] We planned to develop a diverse and efficient synthetic route which could facilitate the preparation of the derivatives for SAR studies. Herein, we report the first asymmetric total synthesis of cephanolide A (**8**), the most complex *cephalotaxus* C_{18} dinorditerpenoids, via a convergent strategy.

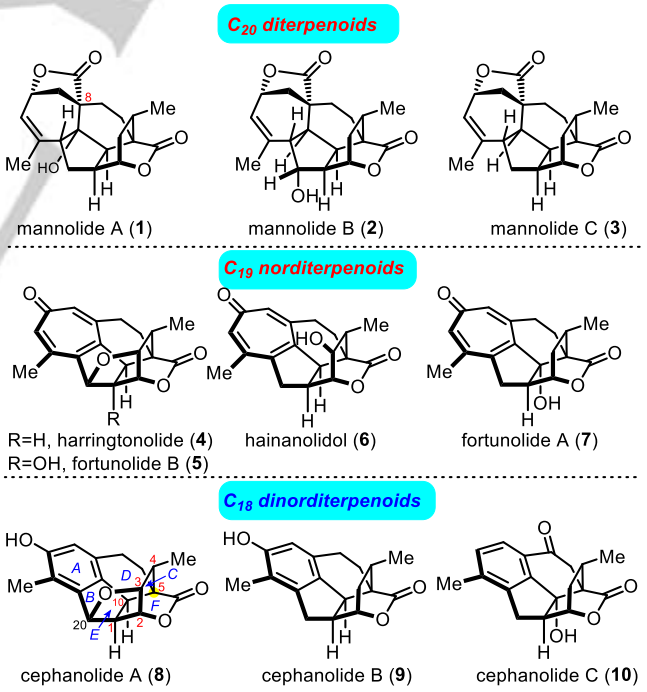

Figure 1. Structure of *cephalotaxus* diterpenoids.

Structural analysis revealed that cephanolide A (**8**) possesses a cage-like hexacyclic rings including a tetracyclic carbon skeleton (A−B−C−D ring), a bridging lactone unit (F ring) and a tetrahydrofuran ring (E ring). Among them, A−B−C tricyclic rings could be regarded as a hexahydrofluorenol.[9] The cyclohexane C

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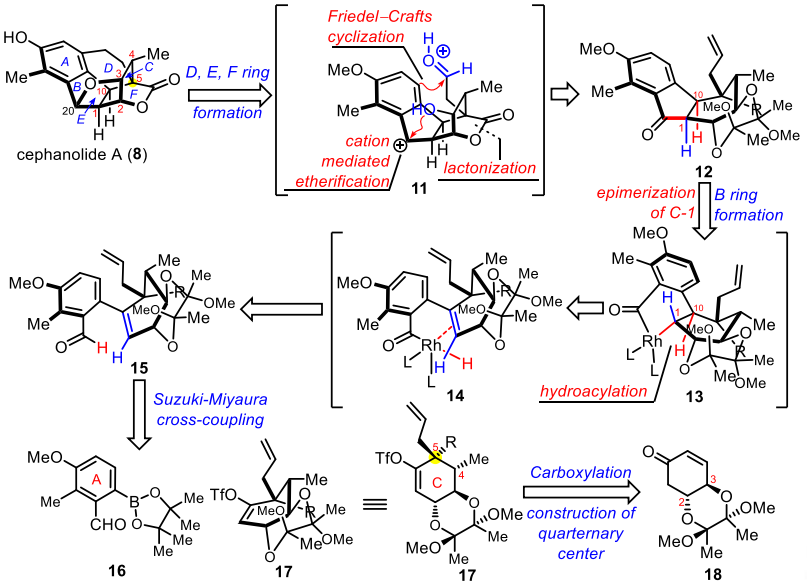
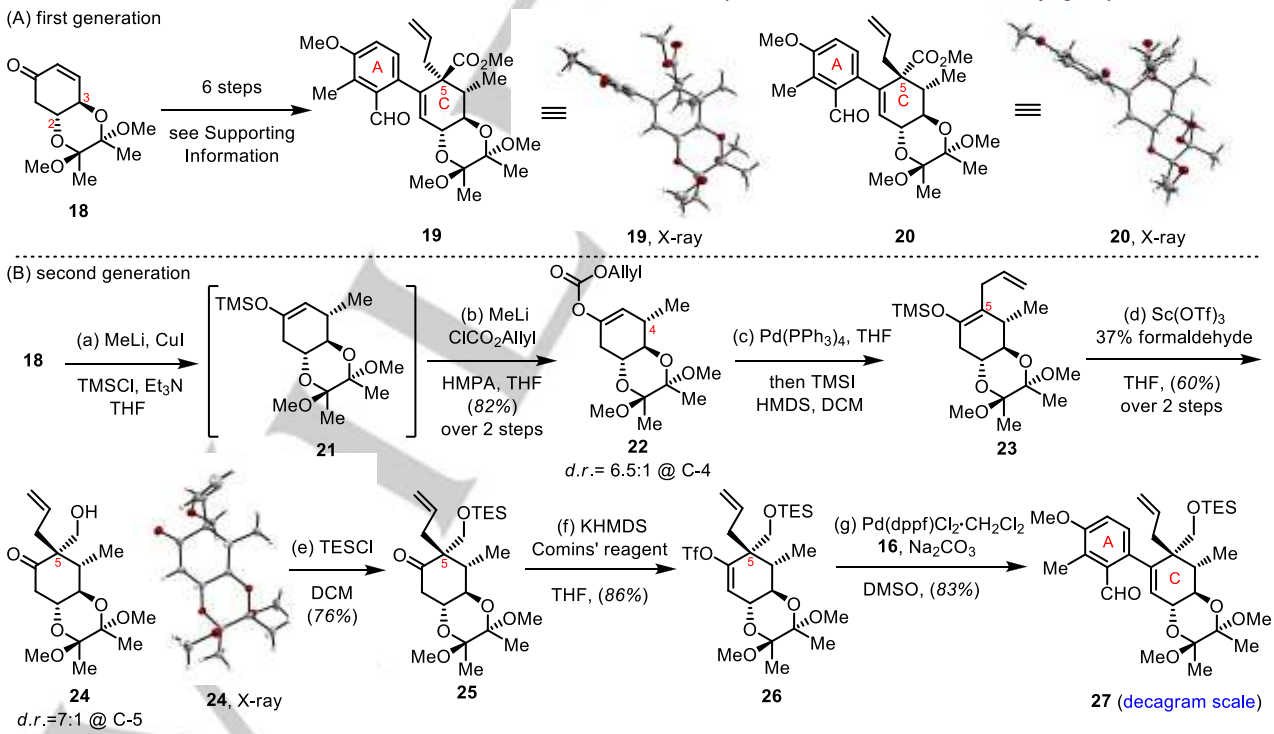


Scheme 1. Retrosynthetic analysis of cephanolide A.

ring contains six contiguous stereogenic centers involving an all-carbon quaternary center at C-5. The only structural difference between harringtonolide (**4**) and **8** relies on the A ring size, which is one-carbon ring contraction from aromatic tropone to benzene ring. Based on this structural analysis, we realized that the key to conquer the challenging *cephalotaxus* diterpenoids was how to precisely construct the heavily-substituted cyclohexane C ring and the rigid architecture.

As depicted in Scheme 1, the synthetic plan focused on the formation of the central 6−5−6 architecture **12** (A−B−C ring) bearing all of the stereogenic centers required in the natural molecules.[9b] We envisioned that the D−E−F rings could be realized through a late-stage modification of **12** by a sequence of cascade reactions including lactonization (F ring), cation mediated etherification (E ring) and Friedel−Crafts cyclization (D ring). A crucial Rh-catalyzed hydroacylation of benzyl aldehyde **15** was designed to forge the *cis*-hydrofluorenone skeleton.[10] We speculated that acylrhodium (III) hydride species **14**, generated through oxidative addition of the rhodium (I) catalyst to the aldehyde C−H bond, would undergo a migratory insertion to produce intermediate **13**. After the final reductive elimination, it would give rise to the cyclized product with the *trans*-configuration between C-1 and C-10. A base mediated epimerization could be used to tune the stereochemistry and yielded the thermodynamically favored *cis*-hydrofluorenone. In turn, a Pd-catalyzed Suzuki−Miyaura cross-coupling between borate **16** (A ring) and vinyl triflate **17** (C ring) might be applied to prepare **15**. A substrate controlled introduction of methyl group at C-4 and quaternary center at C-5 could be achieved from enone **18** by means of a sequence of carboxylation and allylation. We planned to introduce the chiral *trans*-diol on C-2 and C-3 at the very beginning of the synthesis from the known enone **18**, which can be readily prepared from (−)-quinic acid in 3 steps.

Our synthesis started from the preparation of the C-ring fragment **17** for the cross-coupling reaction (Scheme 2). The known enone **18**, bearing the require chiral *trans*-diol at C-2 and 3, was easily avaible from (−)-quinic acid on a large scale (>50 g scale).[11] Two generations of synthetic approaches were developed for the introduction of methyl group at C-4 and



Scheme 2. Preparation and cross coupling of rings A and C. TMS=trimethylsilyl, HMPA= hexamethylphosphoramide, HMDS= hexamethyldisilazane, DCM= dichloromethane, THF=tetrahydrofuran, TES= triethylsilyl, KHMDS= potassium bis(trimethylsilyl) amide, Comins' reagent= N-(5-Chloro-2-pyridyl) bis(trifluoromethanesulfonimide), DMSO= dimethyl sulfoxide.

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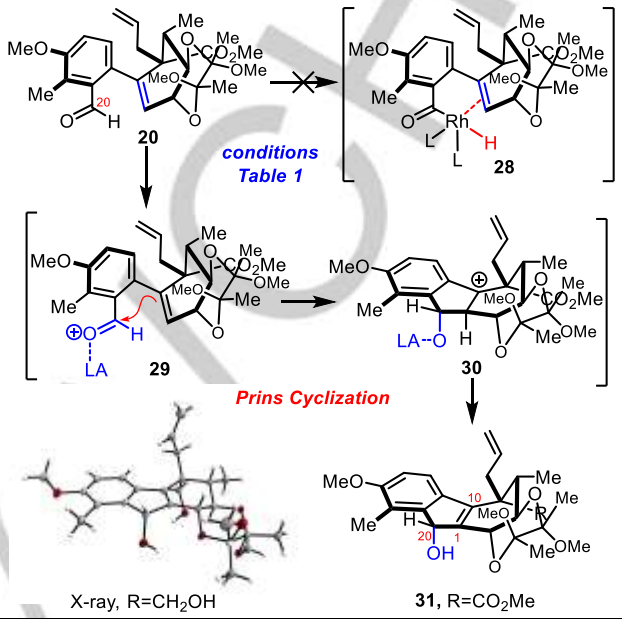
quaternary center at C-5. In the first generation synthesis (Scheme 2A, see details in the Supporting Information), a six-step transformation, including carboxylation, 1,4-addition, allylation and cross coupling reactions was applied, which successfully led the formation of the desired coupling products **20** and its C-5 diastereomer **19**. The relative stereochemistry of both isomers were confirmed by X-ray diffraction analysis. However, this approach suffered with unsatisfied diastereoselectivity and synthetic efficiency. We tried to address this issue by changing the reaction sequence to control the stereoselectivity using the existing chiral center at C-3. Direct treatment of enone **18** with freshly prepared lithium dimethylcuprate [Me_2CuLi] in THF at −78 °C gave the corresponding silyl enolate **21** in the presence of TMSCl. Si/Li exchange generated the lithium enolate, which was trapped by allyl chloroformate to form allyl carbamate **22** in 82% yield over two steps as a mixture of two diastereomers at C-4 (*d.r.* = 6.5:1 at C-4). A one-pot regioselective Pd-catalyzed decarboxylative allylic alkylation [12] followed by enolization were performed to introduce an allyl group at C-5 and transform to the thermodynamic silyl enolate **23**. We then investigated the aldol reaction to construct the quaternary center at C-5, and found that $Sc(OTf)_3$-mediated hydroxymethylation [13] occurred smoothly to give product **24** in 60 % yield over two steps (*d.r.* = 7:1 at C-5). The stereochemistry of **24** was determined by its X-ray crystal diffraction analysis. Silyl protection of the primary alcohol produced TES ether **25**, which was efficiently converted into vinyl triflate **26**. The pinacol boronate **16** was derived from 6-bromo-3-methoxy-2-methylbenzaldehyde [14] via a Pd-catalyzed borylation with bis(pinacolato)diboron[15] (see details in the Supporting Information). The palladium-catalyzed Suzuki–Miyaura cross-coupling reaction was then studied.[16] Treating **16** and **26** with $PdCl_2(dppf)•CH_2Cl_2$ in the presence of Na_2CO_3 in DMSO produced the desired coupling products **27** in 83% yield.

With the key benzyl aldehydes **20** and **27** in hand, the crucial intramolecular hydroacylation to close the *cis*-hydrofluorenone skeleton (B ring) was then investigated (Table 1). We first tested the methodology reported by Stanley and co-workers.[17] Treatment of **20** with Rh-catalyst, generated from $[Rh(COD)Cl]_2$ and PPh_3, in the presence of NaBARF [sodium tetrakis(3,5-bis-(trifluoromethyl) phenyl)borate] in 1,4-dioxane at 100 °C gave rise to the cyclized product **31** (20%, single diastereomer) with a cyclopentenol B ring instead of the desired hydrofluorenone fragment (entry 1, Table 1). The structure and stereochemistry of **31** was determined by X-ray crystal diffraction analysis of its reduced primary alcohol. When the solvent was exchanged to DCE, the reaction underwent at lower temperature (40 °C) and gave a mixture of two diastereomer at C-20 (**31** and **31'**, *d.r.*=1:6) in 58 % total yield (entry 2, Table 1). To understand the mechanism of this reaction, we explored the control experiments by changing the ligands, additives and metal catalysts (entries 3−8, Table 1). Based on these results, we concluded that the cyclized product **31** was formed through a Prins cyclization [18] and NaBARF acts as a key Lewis acid during this process.[19] It is reasonable to assume that the acylrhodium(III) hydride species **28** was not formed due to the congested functional groups and strong coordination effects of the heteroatoms on the substrate **20**. Instead, the benzyl aldehyde group was activated by Lewis acid to generate an oxonium cation species **29**, which was intramolecularly trapped by the olefin unit and yielded **31** after the E_1 elimination of cation **30**. To confirm and optimize this reaction, we used $BF_3•Et_2O$ as the Lewis acid and found the Prins cyclization occurred smoothly to give the desired product **31** as a single diastereomer in 84 % yield (entry 9, Table 1).

Table 1. Attempts to close the *cis*-hexahydrofluorenone B ring.



entry	*conditions*	*results*
1	$[Rh(COD)Cl]_2$, PPh_3, NaBARF, 1,4-dioxane, 100 °C, 12 h	**31**, *20%*
2	$[Rh(COD)Cl]_2$, PPh_3, NaBARF, DCE, 40 °C 2.5 h	**31** and **31'**, *58%* *d.r.*=1:6 @ C-20
3	$[Rh(COD)Cl]_2$, dppp, $AgBF_4$, DCE, 40 °C 2.5 h	messy
4	$AgBF_4$, DCE, 40 °C, 24 h	NR
5	$Rh(PPh_3)_2Cl$, benzene, 100 °C, 12 h	NR
6	$[Rh(COD)Cl]_2$, PPh_3, DCE, 40 °C, 12 h	NR
7	NaBARF, DCE, 80 °C, 7 h	**31**, *30%*
8	NaBARF, dioxane, 100 °C, 20 h	**31**, **31'**, *27%*, *d.r.*=1:1 @ C-20
9	$BF_3·Et_2O$, Et_2O, 0 °C, 30 min	**31**, *84%*

This Prins cyclization also works for the coupling product **27** and afforded the enone **32** in 73% yield after the oxidation of the benzylic alcohol with Dess–Martin periodinane in one-pot operation (Scheme 3). Comparing the structure of **31** and **32** with the required **12**, the fused C1=C10 olefin needed to be reduced. Inspired by Hsung's work,[20] we explored the remote hydroxyl-directed reduction strategy. The TES group of **32** was revoved by *p*-TSA in DMSO giving the required primary hydroxyl group, followed by addition of $NaBH(OAc)_3$ to afford **33** with the desried stereochemistry at C-1 and C-10 in good yield. The structure of **33** was confirmed by the X-ray diffraction analysis, which contains the required six contiguous stereogenic centers in C ring of *cephalotaxus* diterpenoids.

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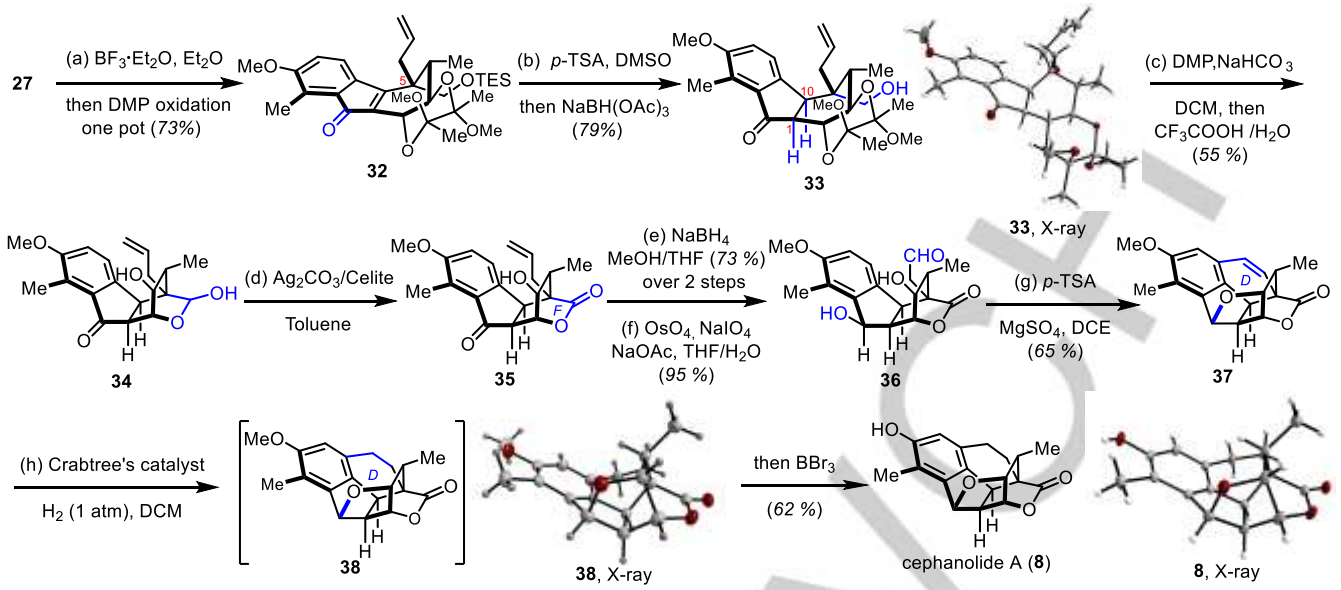

Scheme 3. Total synthesis of cephanolide A. DMP=Dess–Martin periodinane, *p*-TSA=*p*-Toluenesulfonic acid, *p*-TSA=*p*-toluenesulfonic acid, DCE=1,2-dichloroethane.

We then turned our attention to build D–E–F rings. Selective oxidation of the primary alcohol followed by the acid-mediated deprotection of the cyclic acetal group led the formation of the cyclic hemiacetal **34** in 55% yield. An Ag_2CO_3-promoted selective oxidation was applied to effectively convert **34** to the lactone **35**.[21] Subsequently, the crude **35** was reduced to benzylic alcohol which was followed by the oxidative cleavage of the terminal olefin to give the corresponding aldehyde **36** in excellent yield. Treatment of **36** with *p*-TSA and anhydrous magnesium sulfate in refluxing DCE directly furnished the cyclized product **37** bearing the tetrahydrofuran E ring and D ring in one-pot reaction. This process involves a C–O and a C–C bond formation through a cation-mediated etherification and an intramolecular Friedel–Crafts reaction. After the homogeneous hydrogenation catalyzed by Crabtree's catalyst, product **38** was achieved, whosed struture was determined by its X-ray crystal diffraction analysis. Finally, the total synthesis of cephanolide A (**8**) was accomplised in the same pot by removol of methy group of the precursor **38**. The structure of cephanolide A (**8**) was also confirmed by its X-ray crystallographic analysis. The spectroscopic data (^{1}H and ^{13}C NMR spectra, as well as HRMS, and CD spectra), crystal structure, and melting point of synthetic sample were fully consistent with the corresponding data for the natural product reported by Yue.[4a]

In summary, the first asymmetric total synthesis of cephanolide A, the most complex *cephalotaxus* C_{18} dinorditerpenoid, was achieved through a convergent approach in 15 steps from the known enone **18**. Commercially available chiral pool was selected as the starting material, which not only ensured the precise construction of the contiguous stereogenic centers in C ring, but also improved the overall synthetic efficiency. To build the central A–B–C ring, a mild intramolecular Prins cyclization followed by a remote hydroxyl group directed hydrogenation was developed to forge the hexahydrofluorenol skeleton. For the formation of D–E–F ring, a sequence of ring forming reactions, including lactonization, cation mediated etherification and Friedel–Crafts cyclization, was efficiently applied. This strategy provides a flexible approach to prepare the biogenetically *cephalotaxus* diterpenoids and structurally related derivatives. We are currently exploring the total synthesis of *cephalotaxus* C_{20} diterpenoids and C_{19} norditerpenoids, which will be reported in due course.

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Keywords: diterpenoids • cephanolide A • Prins cyclization • total synthesis

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Natural Product Synthesis

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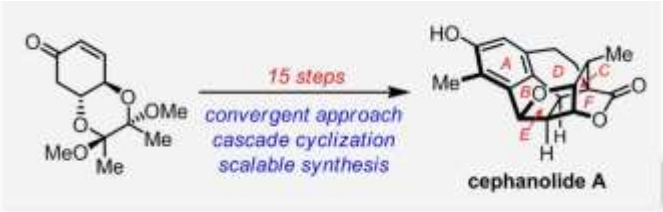
Asymmetric Total Synthesis of Cephanolide A



The first asymmetric total synthesis of cephanolide A, a complex hexacyclic C_{18} dinorditerpenoid from *cephalotaxus sinensis,* is described herein. The key features include the stereo-controlled formation of the contiguous stereogenic centers on C ring, a Prins cyclization (B ring), a cation-mediated etherification (E ring) and an intramolecular Friedel–Crafts reaction (D ring).