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Total Synthesis of (±)-Cephanolides B and C via a Palladium-Catalyzed Cascade Cyclization and Late-stage sp^3 C–H Bond Oxidation

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ABSTRACT: Herein, we report the first total syntheses of complex cephalotaxus diterpenoids cephanolide B and C from commercially available 5-bromo-2-methylanisole. Key to the success of this synthetic route is a palladium-catalyzed cascade cyclization reaction, which allowed us to efficiently forge the 6-5-6 *cis*-fused tricyclic ring systems found in the entire family of cephalotaxus diterpenoids. Additionally, site-selective late-stage sp^3 C–H bond oxidation served as a key strategic element in the chemical synthesis of cephanolide C.

Introduction

Plants of the *Cephalotaxaceae* family produce an extensive array of structurally diverse natural products with a variety of biological properties, particularly potent antitumor activity.[1] Among these secondary metabolites, cephalotaxus diterpenoids represent a relatively rare and structurally fascinating class of natural products. The first member of the cephalotaxus diterpenoids, harringtonolide (**1**) (also named hainanolide[2b]), was isolated from the seeds of cephalotaxus harringtonia in 1978 by Buta *et. al* and was later shown to have potent activity against human KB cells (IC_{50} = 43 nM).[2a,4] To date, over 25 diterpenes with rigid polycyclic frameworks related structurally, and presumably biosynthetically, to **1** have been isolated many of which also possess significant biological activities.[3] Very recently, Yue and co-workers isolated new structurally unique norditerpenoids cephanolides A-D (**2**-**5**) from *cephalotaxus sinensis*, a finding which sheds light on plausible biosynthetic scenarios among this large family (Figure 1a).[3f] Compared with other cephalotaxus diterpenoids, cephanolides A-D represent the first examples which have a rarely encountered aromatic benzenoid ring (A-ring) in this family.

Structurally, cephalotaxus diterpenoids possesses a complex rigid tetracyclic carbon skeleton featuring a *cis*-fused tricarbocycle (BCD-system), a cyclohexane ring bearing five or six contiguous stereogenic centers (D-ring), and a bridging lactone unit (E-ring). These fascinating architectural attributes, as well as the aforementioned biological activities, have made diterpenoids from *Cephalotaxaceae* attractive and challenging targets for total synthesis. From the viewpoint of the synthetic chemist, these molecules also provide an ideal platform for the development of new synthetic strategies and the discovery of novel synthetic methodologies. In this context, great effort has been devoted to the total synthesis of **1** resulting in several model studies and three impressive total syntheses.[5,6] In 1998, Mander and co-workers disclosed the total synthesis of **1**, featuring an elegant intramolecular arene cyclopropanation followed by ring expansion strategy,[5a] work which was a breakthrough in *cephalotaxus* chemistry. Recently, the groups of Tang and Zhai developed efficient total syntheses of **1** through unique intramolecular cycloaddition strategies, respectively.[5b,c] However, the remaining members of this family, including cephanolides A-D (**2**-**5**), have not been synthesized and successful routes to these molecules may shed further light on their biosynthetic relationships. In developing a general synthetic route to this family, we were drawn to a palladium-catalyzed Heck-type/carbonylative C–H activation cascade between aryl halide **7** and a one-carbon unit provided by carbon monoxide (Figure 1b). We viewed this highly efficient construction of the cephalotaxus diterpene pentacyclic core as an ideal platform to explore the entire family from a common synthetic intermediate. Herein, we document the realization of this maneuver which has resulted in the first total syntheses of cephanolide B (**3**), and C (**4**).

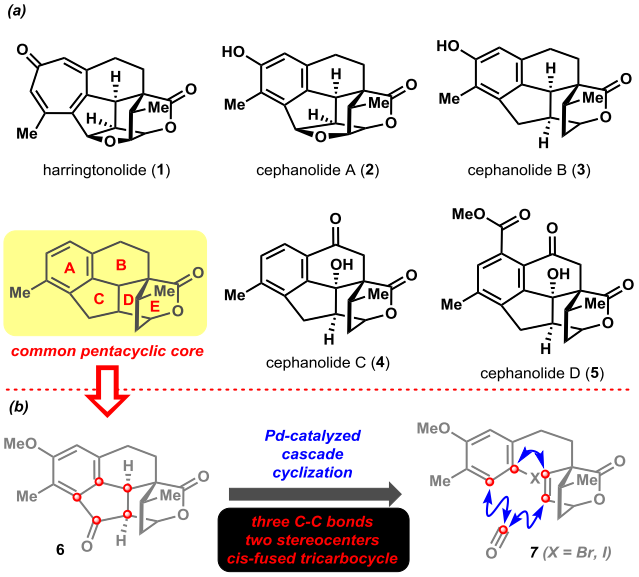


Figure 1. (a) Representative cephalotaxus diterpenoids. (b) A palladium-catalyzed cascade cyclization for rapid polycycle assembly.

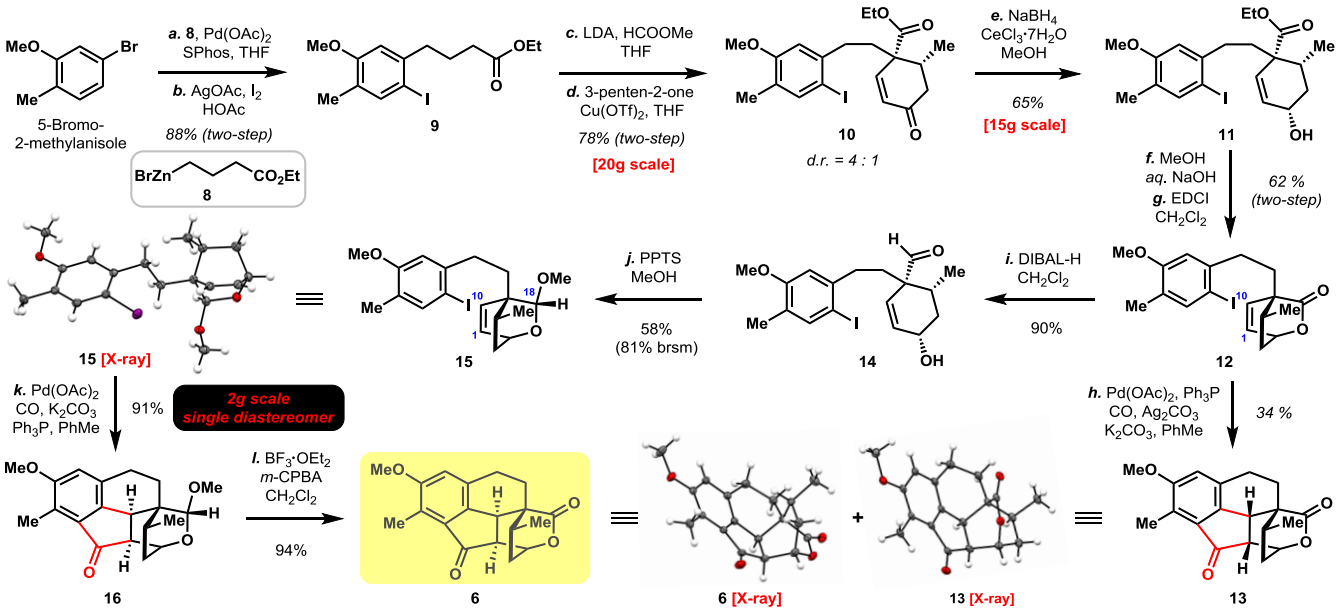
Result and discussion

Our synthetic studies commenced with the preparation of pentacyclic precursor **12** (Scheme 1). Commercially available 5-bromo-2-methylanisole underwent sequential Negishi-coupling with alkyl zinc bromide **8**,[7] and following aromatic

iodination, ester **9** was generated in 88% over two-steps. Formylation of this material [LDA, HCO_2Me] followed by $Cu(OTf)_2$-catalyzed Robinson annulation with 3-penten-2-one afforded an inseparable 4:1 mixture of **10** and its diasteromer in 78% overall yield. Pleasingly, stereoselective Luche reduction of this mixture afforded easily chromatographically separable allylic alcohols thus resulting in the isolation of **11** as a single diasteromer. Hydrolysis of **11** with *aq* NaOH in MeOH at 70 °C followed by an EDCI coupling provided the desired precursor lactone **12** in 62% overall yield. It should be noted that this seven-step sequence, which required only four chromatographic purifications, allowed for the preparation of multigram quantities of **12** in the absence of any substantive optimization.

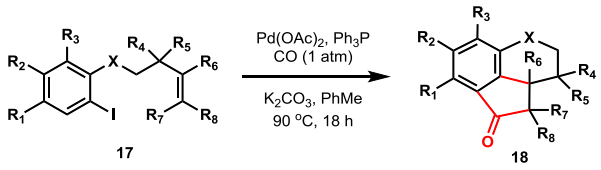
With substantial amounts of **12** in hand, we were in a position to test the crucial C–C bond-forming reaction, a palladium-catalyzed cascade annulation of **12** in the presence of carbon monoxide. Though palladium-catalyzed Mizoroki–Heck reactions between aryl halides and alkenes are well-exploited,[8,9] as are carbonylative processes,[10] to the best of our knowledge, there is only one literature precedence wherein the transformation terminated with an annulative formal C–H activation.[10a,e] Moreover, this reaction only worked with thiophenes and furans. A palladium-catalyzed this type of carbonylative annulation reactions which terminate with a phenyl ring have not been developed (Scheme 1, **12**→**6**). Initially, standard palladium-catalyzed Heck conditions [cat. $Pd(OAc)_2$, PPh_3, K_2CO_3, PhMe, 90 °C] were examined under carbon monoxide atmosphere; To our surprise, the desired cascade reaction proceeded smoothly and only one cyclized product was obtained. Unfortunately, further structural analysis revealed that the product of the annulation was undesired diastereomer **13**, not **6**. The structure of **13** was unambiguously confirmed by single crystal X-ray diffraction. Interestingly, incorporation of one equivalent of Ag_2CO_3 as additive could generate the desired **6** as a minor product along with majority of **13** in 34% combined yield (**6**:**13** = 1:1.6). Extensive optimization through varying silver salts, ligand, bases, and solvent, all failed to improve this outcome. Molecular modeling suggests that the face of alkene (C1=C10 double bond) which is closer to the lactone unit in **12**, is sterically less hindered, thus resulting in the above-mentioned diastereoselectivity. Taking this analysis in account, we sought to alter the steric constraints surrounding the alkene diastereofaces. It was found that simple reduction of lactone **12** into **14** followed by PPTS-catalyzed acetal formation gave **15** as a single diastereomer. An X-ray crystal structure of **15** shows the orientation of methoxy group at C-18, which increases the steric hindrance of one face of the alkene. Much to our delight, subjecting **15** to the palladium-catalyzed cascade cyclization conditions afforded **16** as a single diastereomer in 91% yield. Oxidation of this material [$BF_3{\cdot}OEt_2$, *m*-CPBA] then afforded **6**.[11] Notably, multigram quantities of **6** are readily prepared in our laboratory through this sequence, which is envisioned to serve as the foundation for syntheses of multiple cephalotaxus diterpenes.

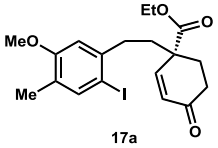
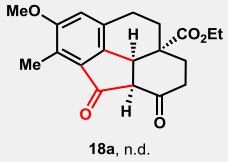
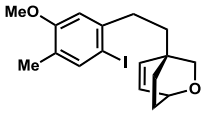
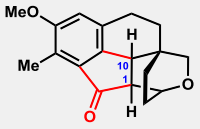
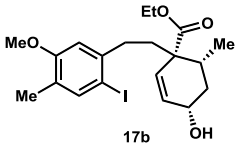
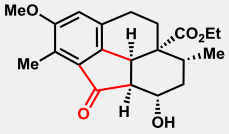
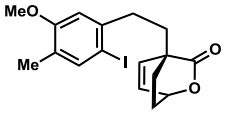
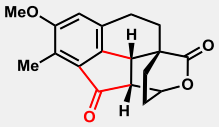
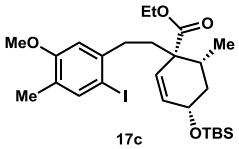
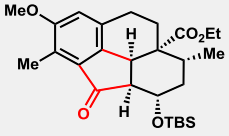
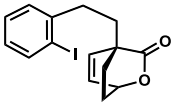
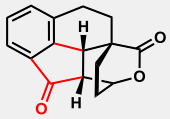
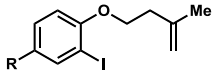
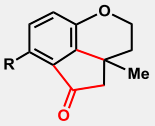
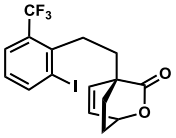
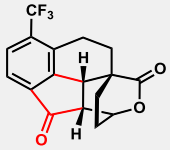
Scheme 1. Synthesis of common pentacyclic core intermediate 6.[a]

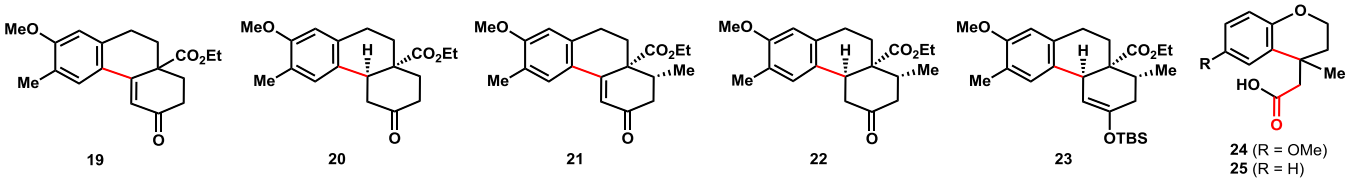


[a]Reagents and conditions: (a) **8** (1.5 equiv), $Pd(OAc)_2$ (2.0 mol %), SPhos (4.0 mol %), THF, 50 °C, 8 h, 90%; (b) AgOAc (1.0 equiv), I_2 (1.0 equiv), HOAc, 12 h, rt, 98%; (c) LDA (1.5 equiv, 1.0 M in THF), HCOOMe (3.0 equiv), –78 °C→rt, 5 h; (d) 3-penten-2-one (1.5 equiv), $Cu(OTf)_2$ (0.2 equiv), THF, 50 °C, 7 days, *78% over two steps*; (e) $NaBH_4$ (0.8 equiv), $CeCl_3{\cdot}7H_2O$ (1.2 equiv), MeOH, 0 °C, 2 h, 65%; (f) NaOH (10 equiv), MeOH/H_2O (v/v = 1:1), 70 °C, 12 h; (g) EDCI (1.2 equiv), DMAP (0.2 equiv), CH_2Cl_2, 0 °C→rt, 12 h, *62% over two steps*; (h) $Pd(OAc)_2$ (5.0 mol %), Ph_3P (10 mol %), Ag_2CO_3 (1.05 equiv), K_2CO_3 (2.0 equiv), CO (1 atm), PhMe, 90 °C, 18 h, 13% **6**, 21% **13**; (i) DIBAL-H (2.0 equiv), CH_2Cl_2, –78 °C, 12 h, 90%; (j) PPTS (0.1 equiv), MeOH, 50 °C, 7 h, 58%, 81% (brsm); (k) $Pd(OAc)_2$ (2.0 mol %), Ph_3P (4.0 mol %), CO (1 atm), K_2CO_3 (2.0 equiv), PhMe, 90 °C, 18 h, 91%; (l) $BF_3{\cdot}OEt_2$ (1.2 equiv), *m*-CPBA (1.5 equiv), CH_2Cl_2, 0 °C, 1 h, then Et_3N (3.0 equiv), 0 °C→rt, 5 min, 94%. SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, LDA = lithium diisopropylamide, EDCI = N-ethyl-N′-(3-dimethylaminopropyl)carbodiimide, DMAP = 4-(dimethylamino)pyridine, DIBAL-H = diisobutylaluminum hydride, PPTS = pyridinium *p*-toluenesulfonate, *m*-CPBA = 3-chloroperbenzoic acid.

Table 1. A preliminary substrate scope of palladium-catalyzed cascade annulation.[a,b]



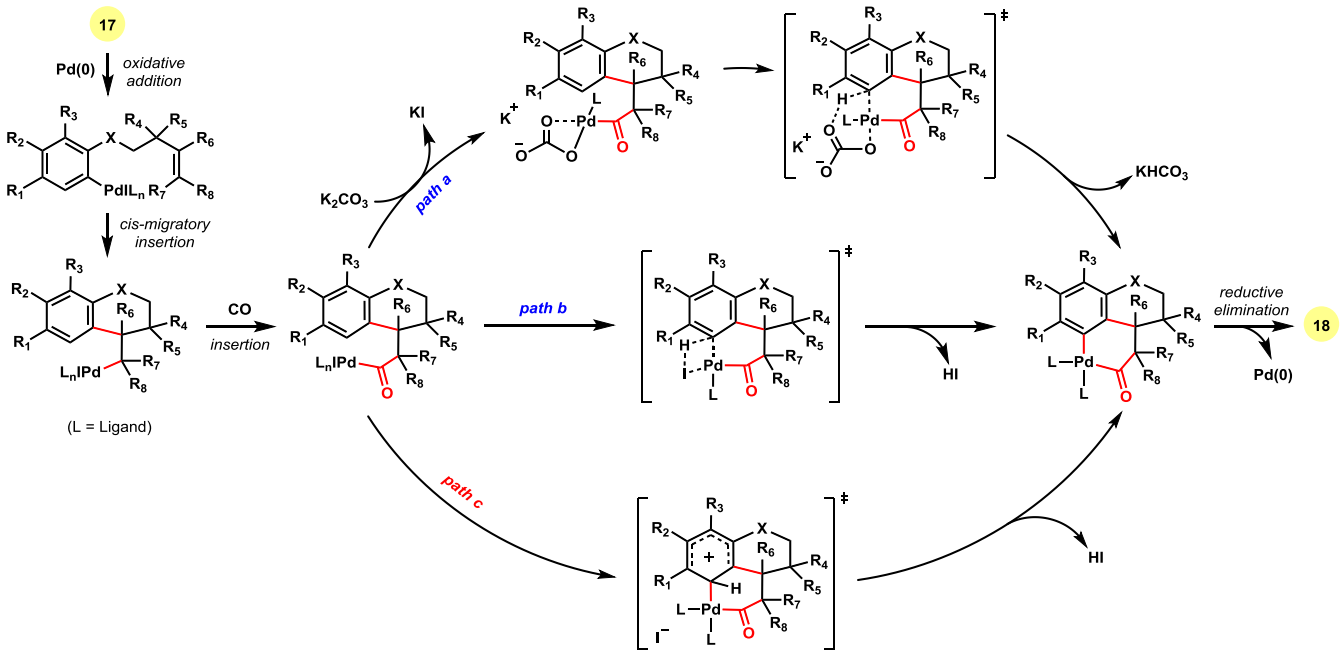
Entry	Substrates	Products		Entry	Substrates	Products
1	 17a	 18a, n.d.	19, 58% 20, 20%	5	 17f	 18f: 1-Hβ,10-Hβ 18f':1-Hα,10-Hα 84% (18f : 18f' = 2 : 1[c])
2	 17b	 18b, n.d.	21, 22% 22, 60%	6	 17g	 18g, 62%
3	 17c	 18c, n.d.	23, 56%	7	 17h	 18h, 50%
4	 17d (R = OMe) 17e (R = H)	 18d (R = OMe), < 5% 18e (R = H), n.d.	24 (R = OMe), 72% 25 (R = H), 78%	8	 17i	 18i, 31%



[a]Reactions were performed on a 0.1 mmol scale, $Pd(OAc)_2$ (10 mol %), Ph_3P (20 mol %), K_2CO_3 (2.0 equiv), CO (1 atm), PhMe (0.07 M), 90 °C, 18 h. [b]Isolated yield. [c]Determined by ^1H NMR analysis. n.d = not detected.

Without a doubt, the efficient preparation of pentacyclic intermediate **6** can be attributed to the novel palladium-catalyzed cascade reaction. To the best of our knowledge, this is the first example of a palladium-catalyzed cascade reaction of this kind wherein the process terminates with aryl ring attachment.[10a,e] To further understand the nature of this cascade reaction, a preliminary study of substrate scope was conducted under similar conditions [cat. $Pd(OAc)_2$, PPh_3, K_2CO_3, PhMe, 90 °C] and these results are summarized in Table 1. As predicted, substrates containing monocyclic alkenes, whether activated enones or relatively neutral allylic alcohols and their TBS derivatives (entry 1-3) all failed to afford any desired products (**18a-18c**). Analysis of side-products formed in these reactions resulted in the observation of tricyclic products (**19-23**). These experimental results supported the proposal that a palladium-catalyzed Heck-type cyclization was involved in the initial step of cascade reaction (*vide infra*). Subsequently, disubstituent terminal alkene substrates **17d** and **17e** were synthesized and examined under standard conditions (entry 4). To our disappointment, only **17d** afforded the desired cascade product **18d** and in very low yield (< 5%). Interestingly, acid **24** or **25** was isolated from the reaction in both cases, which is likely generated by the hydrolysis of acylpalladium intermediate. Ether bridged bicyclic alkene substrate **17f** could also give an inseparable 2:1 mixture of diastereoisomers in 84% combined yield favoring **18f** (entry 5). The selectivity shown here was consistent with our previous analysis for the face-selectivity of alkene **12** (see Scheme 1). Finally, three lactone bridged bicyclic alkene substrates (**17g-17i**), which have differing aromatic electronic character, were prepared and investigated (entry 6-8). Much to our delight, all of these bicyclic substrates afforded the desired products (**18g-18i**) under standard condition. However, it was easy to find that the reaction efficiency was highly dependent on the electronegativity of aromatic ring.

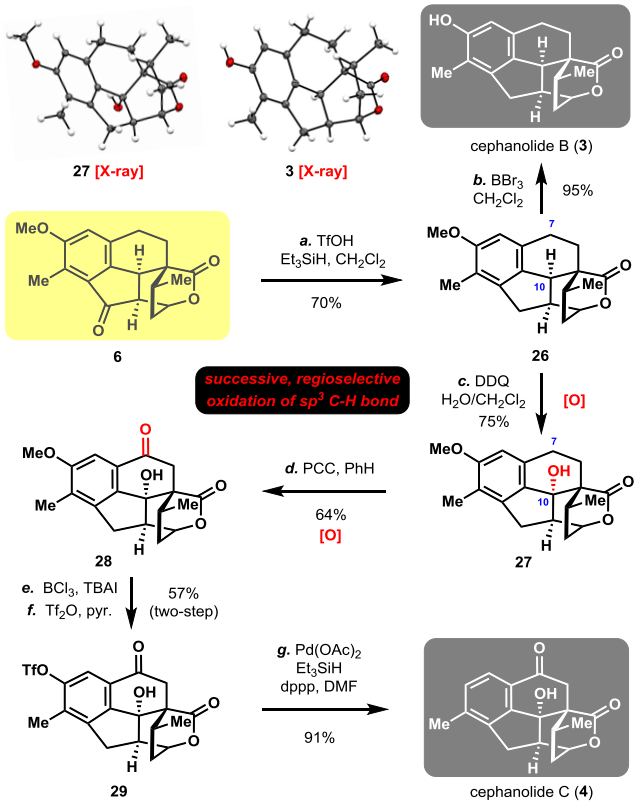
Scheme 2. Potential mechanism for palladium-catalyzed cascade annulation.



Mechanistically, this pivotal cascade reaction probably takes place by an intramolecular Heck-type cyclization, followed by CO insertion and Friedel–Crafts acylation sequence. However, a potential palladacycle involved aryl sp^2 C–H bond activation pathway in the final stage of sequence couldn't be ruled out in this case (Scheme 2). Generally, there are two potential mechanisms which have received the most support in the reaction of palladium-catalyzed aryl sp^2 C–H bond functionalization: (*i*) concerted metalation-deprotonation (CMD) with simple, electron-deficient benzenes (path a or path b)[12] and (*ii*) electrophilic aromatic substitution (S_EAr) with electron-rich, nucleophilic aromatic ring (path c). Moreover, the CMD involved mechanism normally favors reaction with electron-deficient, C–H acidic benzenes, which constitutes a complete inversion of reactivity compared to the S_EAr pathway.[12b] In the contrast, the electron-withdrawing group on the aromatic ring dramatically reduces the reactivity of the ring to further attack in S_EAr, thus resulting in a much lower reaction efficiency. Based on the above experimental observation and general reactivity displayed in palladium chemistry, it seems that the processes, involving initial Heck-type cyclization to generate σ-alkylpalladium (II) species, sequential CO insertion, and a final Friedel–Crafts acylation of acylpalladium (II) intermediate, may be operative in this palladium-catalyzed cascade reaction.

After the preliminary substrate evaluation of the palladium-catalyzed cascade process, we turned our attention to the total synthesis of cephanolides B (**3**) and C (**4**) (Scheme 3). Toward this end, ionic reduction of ketone **6** [TfOH, Et_3SiH, CH_2Cl_2] generated lactone **26** in 70% yield. Demethylation of **26** with BBr_3 smoothly afforded cephanolide B (**3**) in nearly quantitative yield (95%). Gratifyingly, single crystals of **3**, suitable for X-ray diffraction, could be grown thus allowing for unambiguous structure determination.

Scheme 3. Completion of the syntheses of Cephanolides B and C from common pentacycle 6.[a]

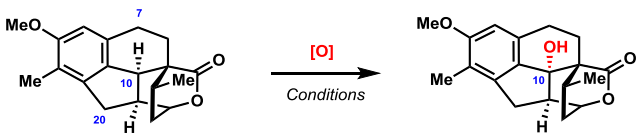


[a]Reagents and conditions: (a) TfOH (10.0 equiv), Et_3SiH (10.0 equiv), CH_2Cl_2, rt, 40 h, 70%; (b) BBr_3 (8.0 equiv), CH_2Cl_2, –78 °C→rt, 6 h, 95%; (c) DDQ (2.0 equiv), 1:1 CH_2Cl_2/H_2O (v/v), rt, 8 h, 75%; (d) PCC (4.0 equiv), NaOAc (5.0 equiv), PhH, 70 °C, 12 h, 64%; (e) BCl_3 (5.0 equiv), TBAI (4.0 equiv), CH_2Cl_2, –78 → –40 °C, 4 h; (f) Tf_2O (1.2 equiv), pyr. (1.5 equiv), CH_2Cl_2, 0 °C, 1 h, *57% over two steps*; (g) $Pd(OAc)_2$ (10 mol%), dppp (10 mol%), Et_3SiH (2.5 equiv), DMF, 60 °C, 8 h, 91%. DDQ = 2,3-dichloro-

5,6-dicyano-1,4-benzoquinone, PCC = pyridinium chlorochromate, TBAI = tetrabutylammonium iodide, pyr. = pyridine, dppp = 1,3-bis(diphenylphosphino)propane, DMF = N,N-dimethylformamide.

After completing the synthesis of cephanolide B, we then turned our attention to the more heavily oxidized member cephanolide C (**4**) which poses additional challenges (Scheme 3). Strategically, an ideal synthetic approach to this target would be the direct late-stage sp^3 C–H oxidation of an intermediate similar to **3**, a tactic which nature may employ in the construction of this molecule.[3f] Considering the steric and electronic nature of the sp^3 C–H bonds in **26**,[13] we expected that a benzylic oxidation would take place regioselectively to install the challenging C-10 oxygenation. Initially, a Cu-catalyzed Kharasch–Sosnovsky reaction was investigated but proved to be fruitless, leading only to highly complex reaction mixtures (Table 2, entry 1). Taking inspiration from the general observations of Ishii and others,[14] NHPI-catalyzed aerobic oxidation of **26** was examined. Gratefully, the desired **27** could be obtained after the *in-situ* reduction of the terminal peroxide with Ph_3P, but in only 18% yield (entry 2). Optimization of various initiators to improve the yield of **27** was unsuccessful (entry 3-5). Fortunately, it was found that oxidation of **26** with DDQ in a mixture of CH_3CN/H_2O at room temperature afforded the desired **27** in moderated yield, along with recovery of **26** (entry 6). Encouraged by this result, extensive studies were carried out and revealed that solvent had a crucial effect on the reaction efficiency (entry 7 and 8). Ultimately it was discovered that stirring **26** with DDQ in a mixture of CH_2Cl_2/H_2O (v/v = 1:1) at room temperature afforded **27** in synthetically useful yield (75%). Moreover, the structure and stereochemistry of **27** were unambiguously confirmed by X-ray crystallographic analysis confirming the stereochemistry at C-10. Next, the C-7 benzylic position could be oxidized using a chromium-based protocol [PCC, NaOAc, PhH] successfully, affording ketone **28** in 64% yield.[15] With the proper oxygenation in place, all that remained to complete the synthesis of cephanolide C (**4**) was the removal of the methoxy group from the benzene ring. This was accomplished with cleavage of methyl ether with BCl_3,[16] followed by triflation with Tf_2O to give triflate **29** in 57% yield over two-steps. Finally, palladium-catalyzed reduction of **29** with Et_3SiH afforded cephanolide C (**4**) in 91% yield.[17] The spectral properties of synthetic **4** were in good agreement with those of the natural isolate.

Table 2. Optimization of late-stage site-selective oxidation of 26 at C-10.[a]



26 27

Entry	Conditions	Yield[b]
1[c]	CuX (X = Cl, Br), PhCOOO^{t}Bu, PhH, 50 °C, 5 h	--
2	NHPI, AIBN, O_2, CH_3CN, 75 °C, 5 h; then Ph_3P, CH_2Cl_2, rt, 2 h	18%
3	NHPI, CH_3CHO, O_2, CH_3CN, 50 °C, 5 h; then Ph_3P, CH_2Cl_2, rt, 5 h	26%
4	NHPI, 2-ethylbutyraldehyde, O_2, CH_3CN, 50 °C, 5 h; then Ph_3P, CH_2Cl_2, rt, 5 h	24%
5	NHPI, trimethylacetaldehyde, O_2, CH_3CN, 50 °C, 5 h; then Ph_3P, CH_2Cl_2, rt, 5 h	20%
6[d]	DDQ, CH_3CN/H_2O (1:1), rt, 10 h	30%
7[e]	DDQ, THF/H_2O (1:1), rt, 10 h	--
8[d]	DDQ, dioxane/H_2O (1:1), rt, 10 h	28%
9	DDQ, CH_2Cl_2/H_2O (1:1), rt, 10 h	75%

[a]Reactions were performed on a 0.06 mmol scale. [b]Isolated yield. [c]Decomposed. [d]>85% (brsm). [e]No reaction. NHPI = N-hydroxyphthalimide, AIBN = 2,2'-azobis(2-methylpropionitrile), DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

In summary, we have achieved the first chemical syntheses of the complex cephalotaxus diterpenoids natural products cephanolide B (**3**) and cephanolide C (**4**) in a longest linear sequence of 13 and 17 steps, respectively. The synthesis featured a novel palladium-catalyzed cascade annulation reaction, which enabled rapid construction of common pentacyclic skeleton **6** of cephalotane-type diterpenoids. In addition, a regioselective and successive late-stage sp^3 C–H bond oxidation served as key element to install the challenging C-10 and C-7 oxygenation. We anticipate that the palladium-catalyzed annulation described herein may find use in the synthesis of other complex, polycyclic natural products. Moreover, Further application of this chemistry to the synthesis of other cephalotaxus diterpenoids is underway and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

X-ray crystallographic data for **3** (CIF)
X-ray crystallographic data for **6** (CIF)
X-ray crystallographic data for **13** (CIF)
X-ray crystallographic data for **15** (CIF)
X-ray crystallographic data for **27** (CIF)
Experimental procedures and spectroscopic data (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interests.

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