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Asymmetric total synthesis of benzenoid cephalotane-type diterpenoids through a cascade C(sp^2) & C(sp^3)–H activation

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Cephalotane diterpenoids, featuring unique and complicated carbon skeletons and remarkable antitumor activities from the *Cephalotaxus* genus, have been gaining increasing attention. Herein, we report the asymmetric and divergent total synthesis of benzenoid cephalotane-type diterpenoids containing the identical 6/6/6/5 tetracyclic and the bridged δ-lactone skeleton with different oxidation states. A cascade of C(sp^2) and C(sp^3)–H activation has been developed to efficiently prepare the characteristic and synthetically challenging 6/6/6/5 tetracyclic skeleton through a pivotal palladium/NBE-cocatalyzed process. The feature of this strategy is the construction of three C–C bonds (two C(sp^2)–C(sp^3) bonds and one C(sp^3)–C(sp^3) bond) and the formation of two cycles with two chiral centers in a single step. The application of this method for the rapid assembly of the skeleton of benzenoid cephalotane-type diterpenoids is demonstrated through the concise and asymmetric total synthesis of cephanolides A-D (**1**-**4**) and ceforalide B (**5**) via late-stage modification.

Cephalotane diterpenoids, characterized by unique and intricate carbon skeletons and notable antitumor activities, are distinctive compounds of the *Cephalotaxus* genus, comprising over 110 members[1–6]. Benzenoid cephalotane-type diterpenoids are a relatively novel subtype (Fig. 1a), as the isolation, named cephanolides A-D, was reported in 2017 by Yue and co-workers[7]. Up to now, eight other benzenoid cephalotane-type diterpenoids have been isolated from the seeds of *Cephalotaxus fortunei var. Alpina* by the same group[2,6]. Structurally, these molecules have a unique 6/6/6/5 tetracyclic core embedded with a bridged δ-lactone, containing[5–7] contiguous stereogenic centers (Fig. 1b). In addition, the oxidation states of benzenoid cephalotane-type diterpenoids exhibit diversity at the C3, C7, C10, C13, and C20 positions.

Due to their intricate and diverse structures, as well as their potential biological activities, benzenoid cephalotane-type diterpenoids have garnered significant attention from synthetic chemists (Fig. 1c). Synthetic studies have been comprehensively reviewed by Yue and co-workers[8]. The total synthesis of benzenoid cephalotane-type diterpenoids was reported by Zhao and co-workers[9]. They utilized a palladium-catalyzed cascade cyclization reaction to forge the 6-5-6 *cis*-fused tricyclic core and successfully achieved the synthesis of (±)-cephanolide B and C (**2**-**3**) in 2018. The asymmetric total synthesis of cephanolide A (**1**) was achieved by Gao and co-workers through an intramolecular Prins cyclization, followed by a cation-mediated etherification/Friedel–Crafts cyclization[10]. Later, they also realized the asymmetric total synthesis of cephanolide B (**2**) using the same strategy[11]. Guided by chemical network analysis, Sarpong and co-workers realized the divergent total synthesis of (±)-cephanolides A-D (**1**-**4**) by taking advantage of an intramolecular Diels–Alder cycloaddition to forge the core skeleton[12]. One year later, they optimized the synthesis method to achieve the synthesis of (±)-cephanolides A-D (**1**-**4**), ceforalides C-D, and F-G[13]. The asymmetric total synthesis of cephanolides A-B (**1**-**2**) was completed by Cai and co-workers via an inverse-electron-demand Diels–Alder reaction[14]. Using a tandem

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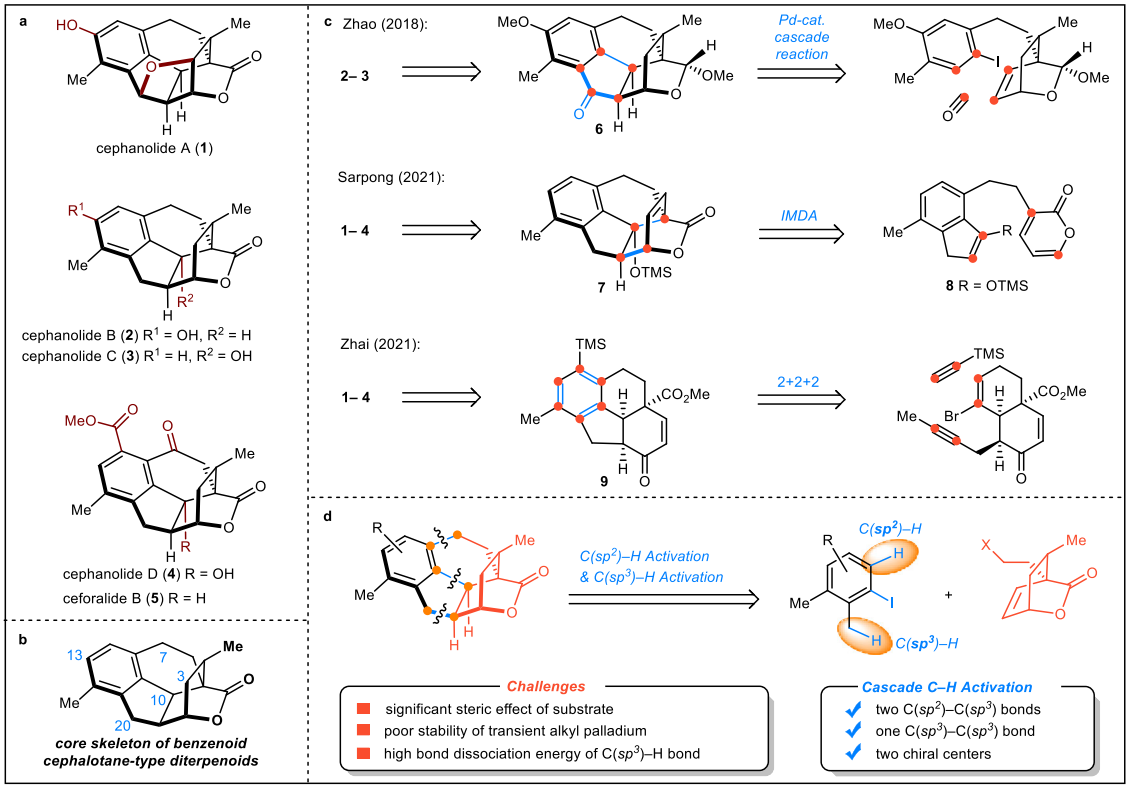


Fig. 1 | Background and reaction design. a Selected examples of benzenoid cephalotane-type diterpenoids. **b** Core skeleton of benzenoid cephalotane-type diterpenoids. **c** Representative cases of total syntheses of benzenoid cephalotane-type diterpenoids. **d** Our convergent synthetic strategy.

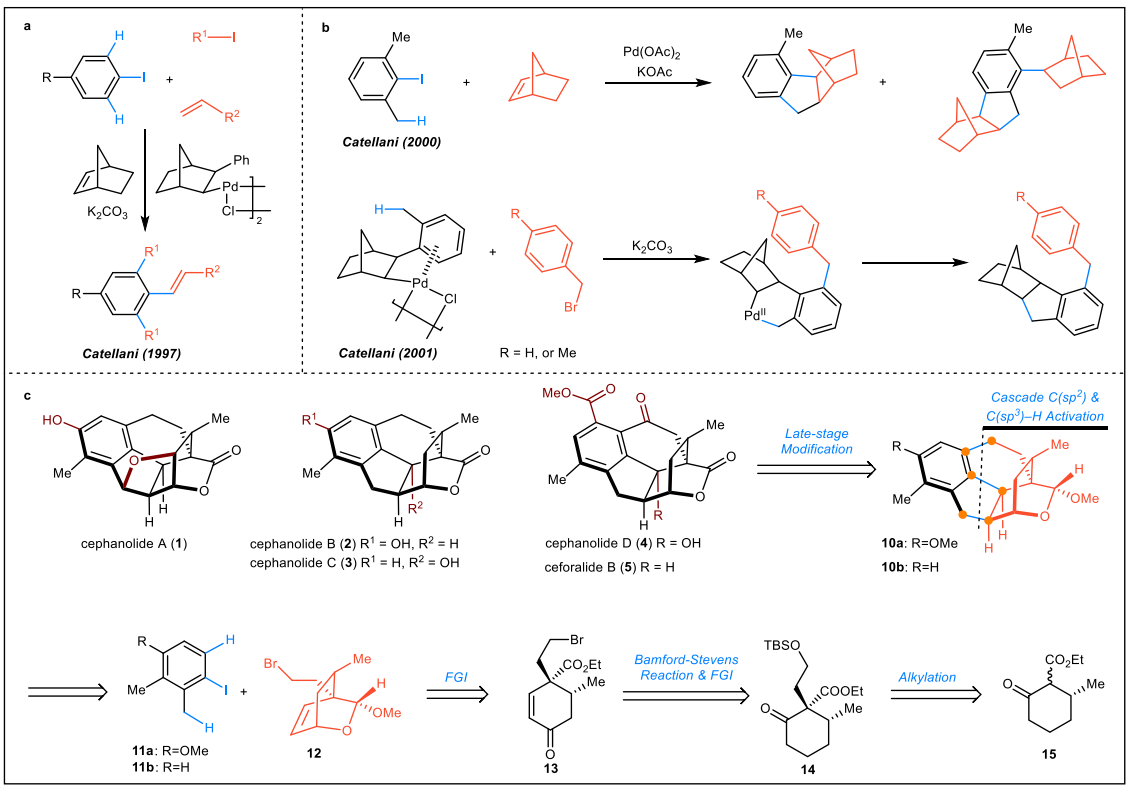


Fig. 2 | C(sp²) & C(sp³)–H activation and retrosynthetic analysis of benzenoid cephalotane-type diterpenoids. a Catellani reported a C(sp²)–H bond activation reaction. **b** Catellani reported C(sp³)–H bond activation reaction. **c** Retrosynthetic analysis of benzenoid cephalotane-type diterpenoids. FGI functional group interconversion.

intramolecular Pauson-Khand reaction, 6π-electrocyclization reaction, and oxidative aromatization strategy, (±)-cephanolide B (**2**) and cephanolides B-D (**2**-**4**) were synthesized by Yang's group[15] and Hu's group[16], respectively. The asymmetric total synthesis of cephanolides A-D (**1**-**4**) was reported by Zhai and co-workers via a palladium-catalyzed formal bimolecular [2 + 2 + 2] cycloaddition reaction[17]. In addition, other subgroups of *cephalotaxus* diterpenoids have also been extensively studied[8,18–21].

A challenging synthetic strategy was envisioned wherein the core skeleton of benzenoid cephalotane-type diterpenoids was disconnected into two intermediates, such as aryl iodide and bridged δ-lactone, by breaking three C-C bonds (Fig. 1d). The strategy has its own unique challenges, which involves a cascade C(sp^2) & C(sp^3)–H activation and the precise construction of three C–C bonds and two chiral centers. The cascade C(sp^2) & C(sp^3)–H activation strategy, if effective, might also prove valuable for total syntheses of a variety of natural products featuring the 6/6/6/5 tetracyclic skeleton.

As widely acknowledged, C–H bond activation has been regarded as the Holy Grail of organic chemistry and the ideal strategy of organic synthesis[22–25]. The selective cleavage of C–H bonds enables the efficient formation of other functional groups or novel chemical bonds, thereby significantly enhancing the synthesis efficiency and atom economy for natural product syntheses[26–31]. The Catellani reaction, renowned as a classical C(sp^2)–H bond activation reaction, was discovered by Catellani[32] in 1997 (Fig. 2a). The reaction has been expanded by Catellani[33], Lautens[34–36], Dong[37–39], and others[40,41] as a very powerful tool used in the synthesis of complex molecules featuring polysubstituted arenes. To date, numerous synthetic chemists have employed the Catellani reaction to accomplish the sophisticated synthesis of natural products[42–54].

Compared the C(sp^2)–H bond activation in the Catellani reaction, the activation of C(sp^3)–H bonds has been less explored, particularly in the formation of C(sp^3)–C(sp^3) bonds through the activation of a C(sp^3)–H by transient alkylpalladium[55,56]. (Fig. 2b) The main challenges lie in the C(sp^3)–H bond possessing high bond dissociation energy and a lack of stabilizing orbital interactions with the metal center[57,58]. Herein, we present the realization of the rare cascade C(sp^2)–H and C(sp^3)–H activation via Pd(0)/NBE-cocatalysis, resulting in the concise and convergent synthesis of cephanolides A-D (**1**-**4**) and ceforalide B (**5**).

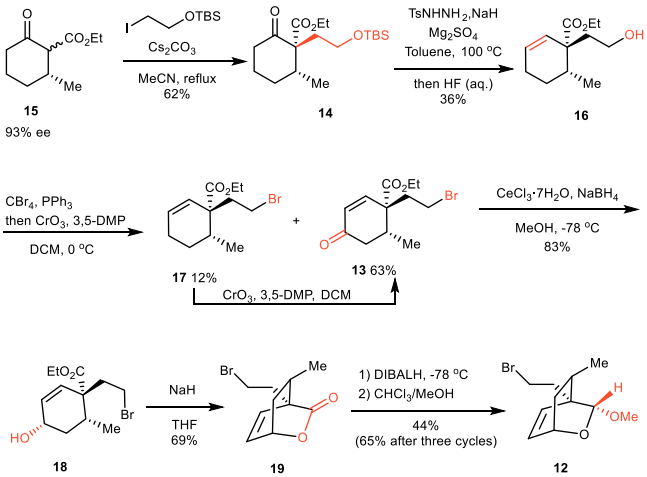


Fig. 3 | Synthesis of key intermediate 12. 3, 5-DMP: 3,5-dimethylpyrazole.

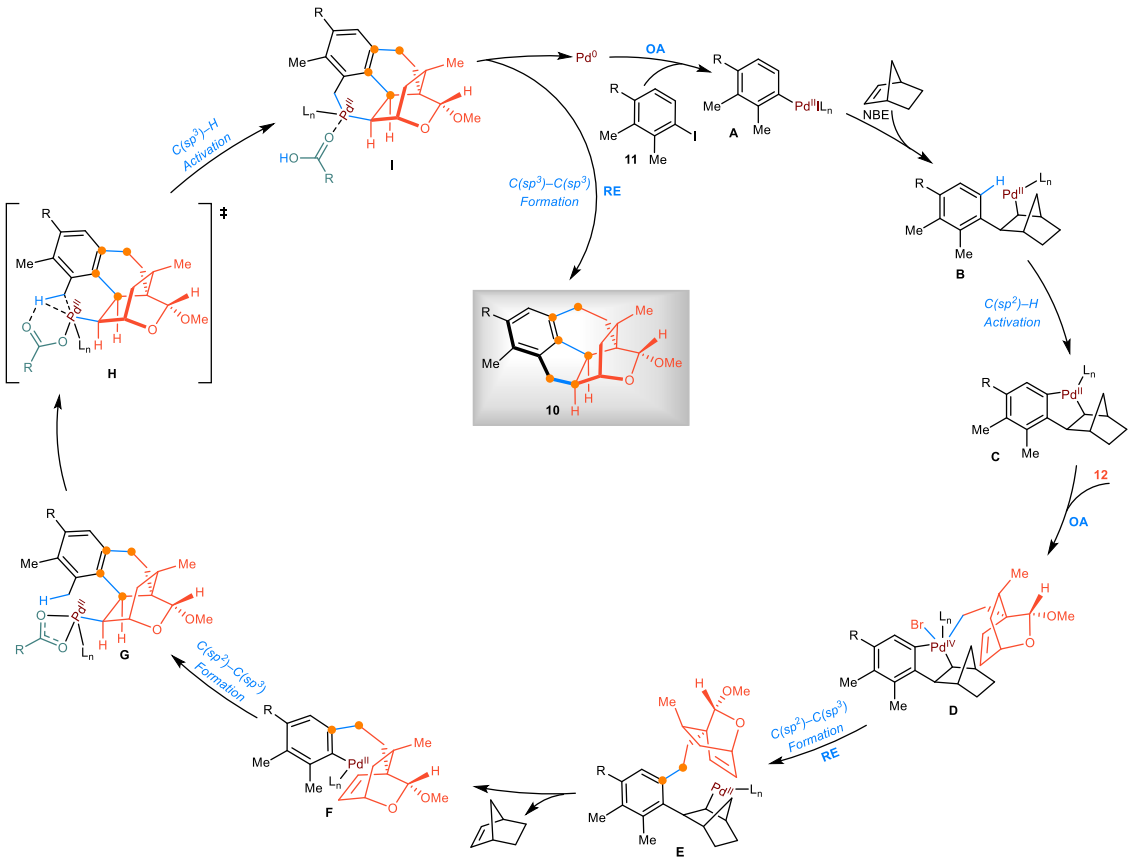


Fig. 4 | Proposed mechanism of cascade C(sp^2) & C(sp^3)–H activation. Arylpalladium (**A**), intermediate (**B**), aryl-norbornyl-palladacycle (ANP) (**C**), Pd(IV) intermediate (**D**), ortho-alkylated intermediate (**E**), intermediate (**F**), transient secondary alkylpalladium (**G**), transient secondary alkylpalladium (**H**), six-membered palladacycle (**I**). OA oxidative addition, RE reductive elimination.

The key cascade C(sp^2)–H and C(sp^3)–H activation reaction, featuring the construction of three C–C bonds and two chiral centers accurately, allows access to the core skeleton of benzenoid cephalotane-type diterpenoids, such as **10a** and **10b**, from iodobenzene derivatives (**11a** and **11b**) and alkyl bromide **12** in one step, respectively (Fig. 2c). Thus, the asymmetric total synthesis of benzenoid cephalotane-type diterpenoids could be easily achieved from **10a** and **10b** via a late-stage modification strategy. The alkyl bromide **12** could be constructed from cyclohexenone **13** via reduction and acetalization. Ketone **13** could be prepared by Bamford-Stevens reaction and subsequent functional group interconversion (FGI) from compound **14**, which could be derived from a known compound **15**[59].

Results

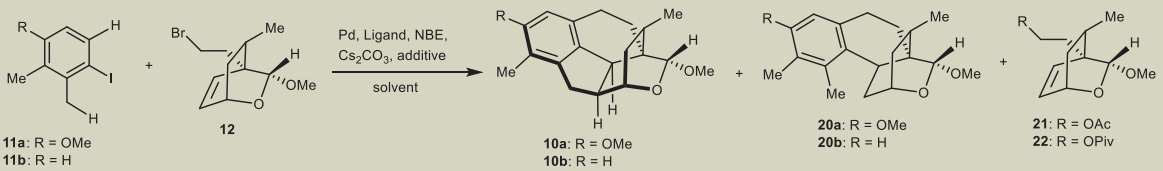
Our synthesis work commenced with the preparation of C10 unit acetal **12** from the known chiral compound **15**, which was prepared from cyclohexenone in one step with 75% yield and 93% ee[59] (Fig. 3).

The alkylation of compound **15** with a 2-iodoethanol derivative, conditions previously reported by Zhu[60], furnished compound **14** as a single diastereomer in up to 62% yield on decagram scale. Exposure of **14** to a one-pot olefin formation[61]/deprotection protocol yielded alcohol **16**, which was then subsequently treated with CBr_4 and PPh_3, followed by CrO_3 and 3,5-DMP to obtain cyclohexanone **13**, along with a small amount of compound **17**. Noteworthy, olefin **17** can convert to cyclohexanone **13** through the same oxidation. Cyclohexanone **13** was reduced by $CeCl_3{\cdot}7H_2O$ and $NaBH_4$ to produce allyl alcohol **18**, which was transformed to lactone **19** in the presence of NaH. Finally, to avoid potential stereoselectivity issues during the cascade reaction, lactone **19** was further converted to acetal **12**, which has been proven effective in precisely constructing stereochemistry at the C1 and C10 positions by Zhao[8], Yang[14], and Hu[15]. Thus, lactone **19** was reduced by DIBALH to produce the corresponding aldehyde, which was then directly transformed into acetal **12** in the presence of chloroform and methanol to prevent the formation of the dimethyl acetal byproduct.

Cascade C(sp^2) & C(sp^3)–H activation

With acetal **12** in hand, our focus turned toward the pivotal palladium/NBE-cocatalyzed cascade C(sp^2) & C(sp^3)–H activation for the assembly of the tetracyclic skeleton. First, the reaction mechanism was proposed[62–64] (Fig. 4). Iodobenzene derivative **11** and Pd(0) undergo oxidative addition to generate arylpalladium **A**, which is followed by insertion into NBE to produce intermediate **B**. Subsequently, C(sp^2)–H activation generates aryl-norbornyl-palladacycle (ANP) **C**. Next, the ANP **C** undergoes oxidative addition with compound **12** to produce

Table 1 | Investigation of the palladium-mediated cascade C(sp^2) & C(sp^3)–H activation[a]



Entry	[Pd]	Solvent	Additive (Delay before addition & Addition time)	Result[b]
1[c]	20 mol% $Pd(OAc)_2$	DMF	-	**20a** (43%), **21** (24%)
2	20 mol% $Pd(OAc)_2$	DMF	-	**10a**/**20a** (46%, 1/4.9), **21** (24%)
3[d]	20 mol% $Pd(OAc)_2$	DMF	-	**10a**/**20a** (45%, 1/5), **21** (23%)
4	20 mol% $Pd(OAc)_2$	DMF	0.4 equiv. KOPiv	**10a**/**20a** (34%, 1/4.6), **21** (23%), **22** (21%)
5	20 mol% $PdCl_2$	DMF	0.4 equiv. KOPiv	**10a**/**20a** (46%, 1/5), **22** (21%)
6	20 mol% $PdCl_2$	DMF	1.5 equiv. KOPiv (60 s & 30 s)	**10a**/**20a** (29%, 4.1/1), **22** (68%)
7	20 mol% $PdCl_2$	DMF	1.8 equiv. KOPiv (60 s & 30 s)	**10a**/**20a** (27%, 4.4/1), **22** (73%)
8	20 mol% $PdCl_2$	DMF	2.0 equiv. KOPiv (60 s & 30 s)	**10a**/**20a** (23%, 4.4/1), **22** (75%)
9	20 mol% $PdCl_2$	DMF	1.8 equiv. KOPiv (50 s & 30 s)	**10a**/**20a** (24%, 4.5/1), **22** (72%)
10	20 mol% $PdCl_2$	DMF	1.8 equiv. KOPiv (70 s & 30 s)	**10a**/**20a** (26%, 3.8/1), **22** (72%)
11[e]	20 mol% $PdCl_2$	DMF	1.8 equiv. KOPiv (60 s & 30 s)	**10a**/**20a** (17%, 2.4/1), **22** (79%)
12[f]	20 mol% $PdCl_2$	DMF	1.8 equiv. KOPiv (60 s & 30 s)	**10a**/**20a** (12%, 2.2/1), **22** (85%)
13[g]	20 mol% $PdCl_2$	DMF	1.8 equiv. KOPiv (60 s & 30 s)	**10a**/**20a** (10%, 2.2/1), **22** (86%)
14[h]	20 mol% $PdCl_2$	DMF	1.8 equiv. KOPiv (60 s & 30 s)	**22** (95%)
15	20 mol% $PdCl_2$	PhMe	1.8 equiv. KOPiv (60 s & 30 s)	not detected
16	20 mol% $PdCl_2$	PhCN	1.8 equiv. KOPiv (60 s & 30 s)	**10a**/**20a** (<10%, 1/5.6), **22** (33%)
17	20 mol% $PdCl_2$	*t*-BuCN	1.8 equiv. KOPiv (60 s & 30 s)	**10a**/**20a** (<10%, 1.5/1), **22** (56%)
18	20 mol% $PdCl_2$	DMF/PhMe = 1/1	1.8 equiv. KOPiv (60 s & 30 s)	**10a**/**20a** (49%, 10/1), **22** (61%)
19	20 mol% $PdCl_2$	DMF/PhMe = 1/2	1.8 equiv. KOPiv (60 s & 30 s)	**10a**/**20a** (28%, 16/1), **22** (73%)
20[i]	20 mol% $PdCl_2$	DMF/PhMe = 1/1	1.8 equiv. KOPiv (120 s & 50 s)	**10a** (42%), **22** (64%)
21	20 mol% $PdCl_2$	DMF/PhMe = 1/1	1.8 equiv. KOPiv (80 s & 30 s)	**10b**/**20b** (38%, 10/1), **22** (67%)

[a]Reaction conditions: **11a** or **11b** (0.05 mmol), **12** (0.075 mmol), [Pd]: tri(2-furyl)phospine (ligand) = 1: 2, NBE (0.2 mmol), and Cs_2CO_3 (0.15 mmol) in solvent (1.2 mL) under an argon atmosphere, 120 °C.
[b]The ratio of **10a** and **20a** was determined by ^{1}H NMR spectroscopy. The yields of **10a-b** and **20a-b** were calculated against **11a-b**. The yields of **21-22** were calculated against **12**. Isolated yield.
[c]The reaction was conducted in 110 °C.
[d]The reaction was conducted in 130 °C.
[e]Triphenylphosphine as ligand.
[f]Tris(4-methoxyphenyl)phosphine as ligand.
[g]Tris[4-(trifluoromethyl)phenyl]phosphine as ligand.
[h]1,3-Bis(diphenylphosphino)propane as ligand.
[i]0.9 mmol**11a**.

Pd(IV) intermediate **D**, followed by reductive elimination to obtain ortho-alkylated intermediate **E**. Then, the β-carbon elimination of intermediate **E** leads to the formation of intermediate **F**, which subsequently proceeds through an intramolecular migratory insertion to generate the crucial transient secondary alkylpalladium **G**. In the last stage, transient secondary alkylpalladium **H** undergoes a concerted metalation deprotonation (CMD) process to yield six-membered palladacycle **I**, and subsequent reductive elimination to provide the desired **10**.

As shown in Table 1, an initial attempt with tri(2-furyl)phospine as the ligand and Cs_2CO_3 as the base was conducted at 110 °C. The C(sp^2)–H activation product **20a** was obtained in 43% yield along with the nucleophilic substitution byproduct **21**, but the cascade C(sp^2) & C(sp^3)–H activation product was not observed (entry 1). When the reaction temperature was raised to 120 °C, the desired compound **10a** was obtained, albeit accompanied by a significant amount of compounds **20a** and **21** (entry 2). Further increasing the reaction temperature did not achieve a better result (entry 3). The yield of byproduct **21** indicates that nucleophilic substitution by acetate anions is fast, rendering them unable to participate in the CMD process of crucial C(sp^3)–H activation. Therefore, to inhibit nucleophilic substitution and promote the CMD process, KOPiv, which has a larger steric effect, was added. However, the yield of **10a**/**20a** (1/4.6) decreased to 34%, while the yield of **21**/**22** increased to 44% (entry 4). This result may indicate that the nucleophilic substitution of acetal **12** with carboxylate is much faster than the oxidative addition of acetal **12** with aryl-norbornyl-palladacycle (ANP) **C** (Fig. 4). To mitigate the tendency of nucleophilic substitution of acetal **12**, $PdCl_2$ was used instead of $Pd(OAc)_2$ as a catalyst (entry 5). Although the nucleophilic substitution of acetal **12** is inevitable, the yield of nucleophilic substitution product **22** is slightly reduced. Subsequently, the dosage of KOPiv and delayed addition time were screened to promote the oxidative addition of **12** with ANP **C** (entries 6-10). It was found that the reaction proceeded more efficiently with 1.8 equivalents KOPiv when a 60 s delay was implemented for the addition (entry 7). Next, a few other ligands were tested; however, no improved results were obtained (entries 11-14). In the screening of solvents (entries 15-19), the optimal result was achieved using a mixed solvent of DMF and PhMe in a 1:1 ratio (entry 18). Notably, on a hundred-milligram scale, compound **10a** was obtained in 42% yield, and the by-product **20a**

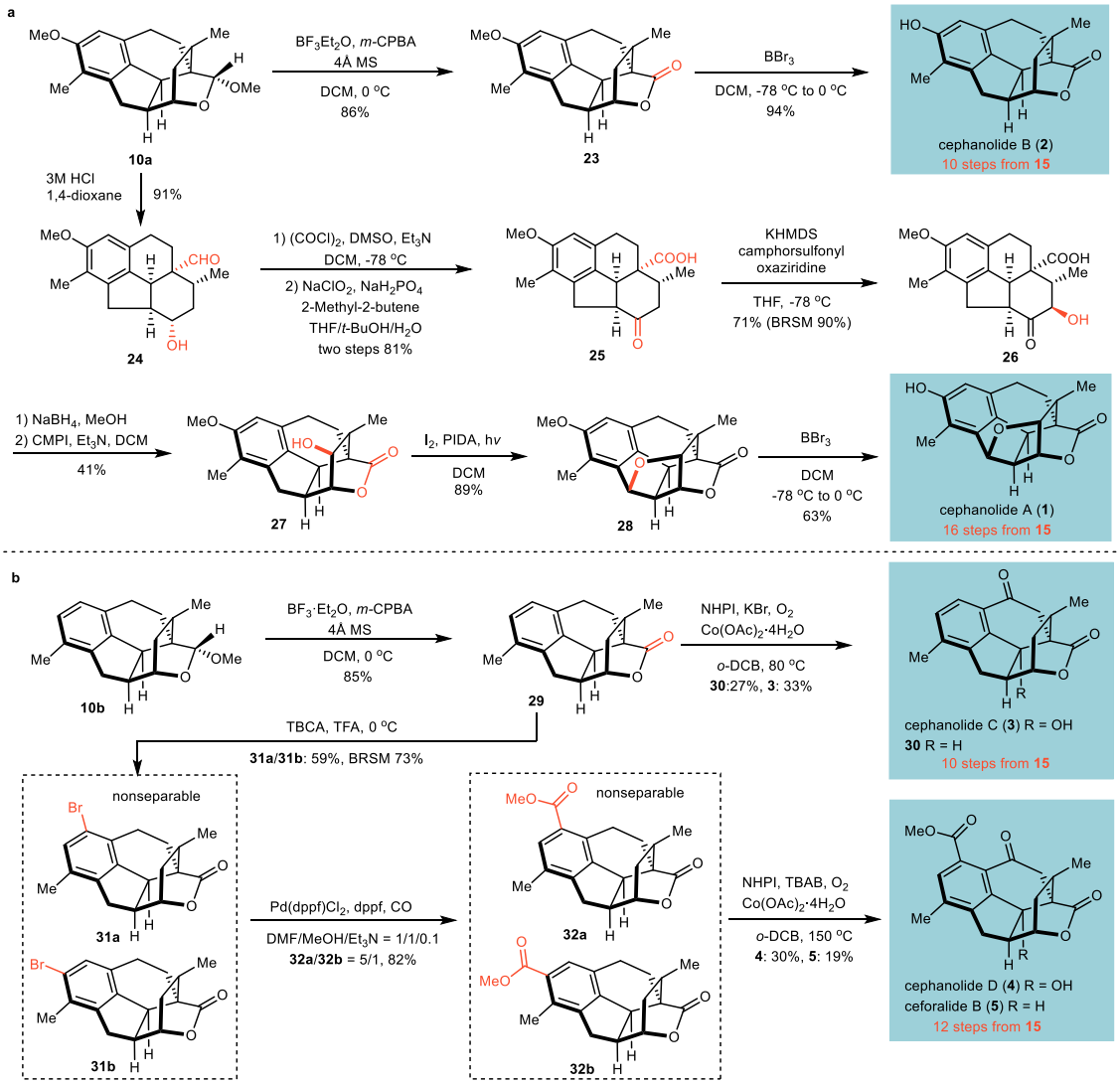


Fig. 5 | Total Synthesis of Benzenoid Cephalotane-type Diterpenoids. a Total Synthesis of Cephanolides A-B (**1**-**2**). **b** Total Synthesis of Cephanolides C-D (**3**-**4**) and Ceforalide B (**5**). *m*-CPBA = *m*-chloroperbenzoic acid, 4 Å MS = 4 Å molecular sieves, DCM = dichloromethane, DMSO = dimethyl sulfoxide, THF = tetrahydrofuran, KHMDS = potassium bis(trimethylsilyl)amide, BRSM = based on recovered starting material, CMPI = 2-chloro-1-methylpyridinium iodide, PIDA = phenyliodine(III) diacetate, NHPI = N-hydroxyphthalimide, *o*-DCB = o-dichlorobenzene, TBCA = tetrabromocinnamic acid, dppf = 1,1′-bis(diphenylphosphino)ferrocene, DMF = N,N-dimethylformamide, TBAB = tetrabutylammonium bromide.

was not observed under these conditions (entry 20). Compound **10b** was obtained when **11b** reacted with acetal **12**, with a delay in the time of adding KOPiv (entry 21). It is worth mentioning that the nucleophilic substitution compounds **21** and **22** could be reconverted to compound **12** by reduction and bromination (see Supplementary Information).

Total synthesis of cephanolides A-D and ceforalide B

After obtaining the key compounds **10a** and **10b**, benzenoid cephalotane-type diterpenoids were synthesized through late-stage modification. Consequently, **10a** was oxidized using $BF_3{\cdot}Et_2O$ and *m*-CPBA to produce lactone **23**, which was subsequently deprotected with BBr_3 to yield cephanolide B (**2**)[9,15,16] (Fig. 5a). For the synthesis of cephanolide A (**1**), compound **10a** was hydrolyzed in the presence of 3 M HCl (aq.)[65] resulting in compound **24**. The structure of **24** was confirmed by X-ray crystallographic analysis (see Supplementary Information). Compound **24** underwent Swern oxidation and Pinnick oxidation to yield compound **25**. The Davis oxaziridine has been demonstrated to be efficacious in introducing a hydroxyl group at the C3 position[17], resulting in compound **26** with 71% yield. The carbonyl of compound **26** was reduced by sodium borohydride and then underwent lactonization to give lactone **27** in the presence of Mukaiyama reagent. Lactone **27** was subjected to Suárez oxidation[12,14,17,66] to form the tetrahydrofuran ring of compound **28**, followed by the removal of the protective group with BBr_3 to yield cephanolide A (**1**). From compound **10b**, three additional benzenoid cephalotane-type diterpenoids were synthesized (Fig. 5b). Compound **10b** was oxidized to produce lactone **29**, which was then converted to cephanolide C (**3**) using the NHPI /$Co(OAc)_2$-catalyzed oxidation as reported by Hu[16]. To efficiently introduce a methyl ester group in the late stage, the selective bromination at the C15 position was attempted. The expected compound **31a** was obtained in a modest yield using TBCA/TFA[67], along with a small amount of non-separable C13 brominated by-product **31b**. Finally, the Pd-catalyzed methoxycarbonylation[12,17] resulted in compounds **32a** and **32b**, which were further oxidized to cephanolide D (**4**) and ceforalide B (**5**) via NHPI/$Co(OAc)_2$-catalyzed oxidation.

Discussion

In summary, we have developed a cascade $C(sp^2)$–H and $C(sp^3)$–H activation strategy to efficiently access the characteristic and synthetically challenging 6/6/6/5 tetracyclic skeleton of the benzenoid cephalotane-type diterpenoids, which was used to complete a short total synthesis of cephanolide B (**2**). A late-stage modification and divergent strategy were employed to complete the syntheses of four additional benzenoid cephalotane-type diterpenoids. The key feature of the cascade $C(sp^2)$ & $C(sp^3)$–H activation reaction is the construction of three C–C bonds (two $C(sp^2)$–$C(sp^3)$ bonds and a $C(sp^3)$–$C(sp^3)$ bond) and two chiral centers accurately in one step via palladium/NBE-cocatalysis. Analogous strategies may prove effective in the preparation of various natural products. This encourages us to further investigate the synthesis of natural products through cascade $C(sp^2)$ & $C(sp^3)$–H activation.

Methods

Cascade $C(sp^2)$ & $C(sp^3)$–H activation

In a 50 mL round-bottom flask, **11a** (182.0 mg, 0.9 mmol), $PdCl_2$ (32.0 mg, 20 mol%), tri(2-furyl)phospine (83.6 mg, 40 mol%), Cs_2CO_3 (880.0 mg, 2.7 mmol) were added and charged with argon more than three times (The flask was plugged with rubber plugs and sealed with a parafilm). Then, 5.5 mL DMF was injected into the flask via plastic syringes. The resulting light-yellow suspension was stirred vigorously at room temperature for 15 min. Norbornene (339.0 mg, 3.6 mmol) and compound **12** (353.0 mg, 1.35 mmol) were dissolved in 5.5 mL DMF, and the mixture was injected into the tube via plastic syringes. Subsequently, the reaction tube was placed in an oil bath at 120 °C, stirred for 2 min, and then a suspension of potassium pivalate (11.0 mL in toluene) was added over 50 s. After the reaction was completed (4 h), the flask was cooled to room temperature and filtered to remove the solid residue. The filtrate is concentrated under reduced pressure, and the residue is purified by silica gel column chromatography (petroleum ether/ethyl acetate = 50/1 to 10/1) to afford compound **10a** (119.1 mg, 42%, white solid) and compound **22** (244.5 mg, 64%, colorless oil).

Data availability

The data generated during this study are included in this article and the Supplementary Information. The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Center (CCDC), under deposition numbers 2353280 (24). These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif. Details about materials and methods, experimental procedures, characterization data, and NMR spectra are available in the Supplementary Information. All data are available from the corresponding author upon request.

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Z.X. Xie conceived the projects. X.X. Li, Z.X. Lu, S.C. Liu, M.Y. Sun, and S.F. Duan performed the experiments under the supervision of Z.X. Xie. Z.X. Xie and X.X. Li wrote the manuscript with the feedback of all other authors.

Competing interests

The authors declare no competing interests.

Additional information

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