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Total Synthesis of (−)-Calyciphylline N

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Abstract

The total synthesis of the architecturally complex *Daphniphyllum* alkaloid (−)-calyciphylline N has been achieved. Highlights of the synthesis include a Et_2AlCl promoted, highly stereoselective susbtrate controlled intramolecular Diels-Alder reaction, a transannular enolate alkylation, an effective Stille carbonylation/Nazarov cyclization sequence, and a high risk dia-stereoselective hydrogenation of a fully substituted conjugated diene ester.

The *Daphniphyllum* alkaloids comprise a large family of complex natural products including more than 180 known members,[1] many with diverse biological activities, that have proven challenging as targets for total synthesis.[2] We in particular became interested in the calyciphylline alkaloids, largely due to their unique frameworks and at the time, limited synthetic studies.[3,4] Calyciphylline N [(−)-**1**, Figure 1], isolated in 2008 by Kobayashi and coworkers,[5] was chosen as our initial target.

While the biological activity of (−)-calyciphylline N (**1**) has not been investigated, we reasoned that a synthetic effort towards this alkaloid would not only unveil a wealth of interesting reactivity, but also permit access to other congeners of the family. Notable structural features of **1** include six contiguous stereogenic centers, three of which are quaternary bridgehead, a fused A ring dihydropyrrole, and a DEF decahydrocyclopentazulene ring system surrounding a central bicyclo[2.2.2]octane BC core.

Retrosynthetically (Figure 2), we envisioned that the dihydropyrrole A ring could arise via condensation of a primary amine with the carbonyl group in ring B, while the stereochemistry of the EF ring system could be installed by a challenging/critical, late stage α,β-reduction of an exceptionally hindered diene ester (**2**). The secondary hydroxyl in ring C could in turn be generated via a Tamao-Kumada[7] oxidation of the siloxane ring, while construction of ring F would entail an aldol condensation, simplifying the structure to **3**, the latter accessible from **4** via a cyclopentenone annulation involving a Stille carbonylation[8]/Nazarov cyclization[9] sequence. Continuing with this analysis, tetracycle **4** could be accessed through elaboration of bicyclic ester **5**, anticipated to be the product of an intramolecular Diels-Alder (IMDA) reaction.[10] The requisite IMDA tri-ene**,** in turn, would arise via union of enantiomerically pure homoallylic alcohol **6** and known silyl acrylate **7**.[11]

The synthesis of (−)-calyciphylline N (**1**) began with alcohol (−)-**8** (Scheme 1), prepared in three steps from commercially available *p*-tolylacetic acid.[12] Birch reduction[13] readily furnished the desired cyclohexadiene; olefin isomerization with KO*t*-Bu in DMSO[14] then

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Supporting Information.
Experimental details, spectra, and X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

provided an inseparable mixture (3.5:1) of the 1,3- and 1,4-dienes **6** and (−)-**9**, respectively, in excellent yield. Silylacrylate **7**, obtained via oxidative hydrosilylation of ethyl acrylate with phenyldimethylsilane,[11] was subsequently appended, employing a method introduced by Sieburth.[15] To this end, treatment of **7** with TfOH at 0 °C, followed by sequential addition of pyridine and the mixture of the alcohols **6** and (−)-**9** at −78 °C led to the requisite triene **10** for the IMDA reaction. However, due to the instability of **10** towards silica gel chromatography, the mixture was carried forward without purification. Interestingly, while the thermal Diels-Alder reaction led to a mixture of all possible diastereomers (as determined by ^{1}H NMR), we were pleased to discover that the Et_2AlCl promoted cyclization provided a 9:1 mixture of diastereomers in favor of the desired cycloadduct (−)-**5**.

One carbon homologation of (−)-**5** to alcohol (−)-**13** (Scheme 2) was next achieved by $LiAlH_4$ reduction and conversion to the corresponding iodide (−)-**11**, followed by cyanide displacement and a two step reduction of the resulting nitrile. The overall yield for the five steps was 65%. Epoxidation of the olefin in (−)-**13** with *m*-CPBAthen led to (−)-**14** as a single diastereomer in 70% yield. Installation of the C_1 ketone was next achieved in two steps and 67% yield via an acid promoted epoxide opening and oxidation of the resulting secondary alcohol, employing Dess-Martin periodinane (DMP),[16] to deliver (+)-**15**. Reductive cleavage of the tetrahydropyran ring with SmI_2 in a mixture of THF/MeOH then led to hydroxy ketone (+)-**16** in 82% yield,[17] the primary alcohol of which was protected as the TBS ether (TBSCl/imidazole in DMF) to provide (+)-**17**.

Elaboration of the requisite sidechain for eventual construction of ring D called for introduction of disubstitution α to the carbonyl in ketone (+)-**17** (Scheme 3). Initially, (+)-**17** proved unreactive towards standard acylating agents (EtOAc, Ac_2O, 1-acetylimidazole, etc.), employing the lithium, potassium, or sodium enolates, with the exception of AcCl which led to complex mixtures of C- and O-acylated products. However, an LDA mediated aldol reaction with acetaldehyde, followed without purification by DMP oxidation of the β-hydroxy ketone, provided diketone (+)-**18** in 91% yield for the 2 steps.[18] Introduction of the allyl group via the Tsuji-Trost allylation[19] then furnished (−)-**19** as a single diastereomer (95%), which upon exposure to catalytic *p*-TsOH in MeOH cleanly led to the corresponding alcohol (−)-**20**, the latter converted to primary iodide (−)-**21** in 97% yield. Pleasingly, transannular cyclization utilizing LDA delivered tetracycle (+)-**4** as a crystalline solid (m.p. 123–125 °C), completing the construction of ring D. Interestingly, use of NaHMDS led only to elimination of the iodide. Single crystal X-ray analysis of (+)-**4** confirmed the structure, as well as the relative and absolute configurations.

Before turning to elaboration of the eastern hemisphere, we investigated the proposed Tamao-Kumada[6] oxidation of the siloxane ring in (+)-**4**. Unfortunately, the siloxane was found to be completely inert to the oxidation. Standard conditions (various fluoride sources, H_2O_2, and bicarbonate salts)[7,20] led only to the recovery of starting material, while strongly basic conditions[21] resulted in decomposition. Curiously, the use of TBAF (with or without oxidant) resulted in desilylation rather than oxidation.[22] Attempts to transform the siloxane to a more reactive silane (e.g., silyl halide or hydride)[23] prior to oxidation also proved unrewarding. Earlier studies, however, had demonstrated that a similar siloxane was a substrate for nucleophilic ring opening at the Si-O bond upon treatment with aryllithium reagents. Such reactivity was recently employed for the development of siloxanes as recoverable transfer agents in Pd-catalysed cross coupling reactions.[24] We surmised that an arylsilane could be converted to the corresponding alcohol via the Fleming modification[25] of the Tamao-Kumada oxidation.

With these earlier observations in mind, attempted siloxane opening in (+)-**4** resulted in partial isomerization of the terminal alkene (not shown). We therefore functionalized the

allyl group before moving forward (Scheme 4). Brown hydroboration (9-BBN) and oxidation (NaOH and H_2O_2)[25] delivered the expected primary alcohol in 71% yield. Protection of the alcohol with TBSCl then furnished (+)-**22** in 94% yield. Pleasingly, the siloxane could now be converted to arylsilane (+)-**23** in excellent yield by treatment with 4-methoxyphenyllithium at room temperature. Selection of the methoxyphenyl substituent was in anticipation of greater reactivity towards the protodesilylation step of the Fleming-Tamao oxidation.[26] Notably, both hindered carbonyls in (+)-**23** remained completely inert to nucleophilic addition. Moving forward, rather than protect the newly generated primary alcohol, we introduced the requisite nitrogen with protection via treatment of (+)-**23** with phthalimide under Mitsunobu conditions[27] to provide (+)-**24** in 99% yield.

Turning to construction of ring E via the proposed Stille carbonylation[7]/Nazarov[8] cyclization sequence, exposure of (+)-**24** to KHMDS in the presence of $PhN(Tf)_2$ at −78 °C furnished vinyl triflate (+)-**25**, which underwent a highly efficient Stille carbonylation in DMF at 90 °C, employing only 1 atm. of CO, to provide dienone (+)-**26** in 97% yield. Given that both Nazarov cyclizations and protodesilylations can be achieved with protic acid,[8,24] we reasoned that both transformations could be accomplished in the same flask. Indeed, treatment of (+)-**26** with HBF_4•OEt_2 at ambient temperature directly furnished silyl fluoride (+)-**27** in 82% overall yield (Scheme 5). Under these conditions, the primary TBS group was also removed. We were also pleased to discover that treatment of (+)-**27** with KF and *m*-CPBA in DMF resulted in the successful Fleming-Tamao oxidation to diol (+)-**28** in 74% yield. Differentiation of the alcohols was then realized via chemoselective protection of the primary alcohol as the TES ether, followed by MOM protection of the secondary alcohol to afford protected diol (+)-**30**.

Next, oxidative removal of the TES ether with IBX (Scheme 6) directly provided aldehyde (+)-**31** in excelent yield.[28] The requisite aldol condensation to prepare (+)-**32** was then achieved employing the conditions reported by Carreira and Weiss ($Bn_2NH_2O_2CCF_3$, PhH, 50 °C) in their synthesis of (+)-daphmanidin E.[3]

Turning to the critical 1,4-reduction of the conjugated diene in (+)-**32**, extensive experimentation on a less advanced aldehyde revealed a set of conditions involving the combination of $ZnCl_2$, Ph_2SiH_2, and catalytic $Pd(PPh_3)_4$[29] as uniquely effective (see Supporting Information). Unfortunately, this reduction protocol when applied to (+)-**32** resulted only in decomposition. Undeterred, aldehyde (+)-**32** was oxidized to methyl ester (+)-**2** (AcOH, NaCN, MeOH, then MnO_2) via the method of Corey.[30] A screen of cationic hydrogenation catalysts was next explored with the intent of directing the hydrogenation to the α,β-olefinic bond. Pleasingly, the BArF analog of the Crabtree catalyst,[31] developed by Wuestenberg and Pfaltz,[32] employing 900 psi of H_2 pressure, proved effective in reducing (+)-**2** to furnish a mixture (4:1) of diastereomers in 84% yield (Scheme 7). Detailed 2D NMR analysis revealed the major diastereomer to be (−)-**34**. This transformation, possibly directed by the C_1 carbonyl in (+)-**2**, should prove useful in accessing natural congeners bearing the same mono-unsaturated DEF ring system (Figure 1).

Exposure of (−)-**34** to hydrazine in EtOH led cleanly to removal of the phthalimide. Ring A construction involving imine formation was then readily achieved by heating the resulting amine with aq. NH_4Cl (sat.) in EtOH at 70 °C.[3] Completion of the total synthesis of (−)-calyciphylline N entailed treatment of (−)-**34** with Ph_2BBr[33] to remove the MOM acetal. Totally synthetic (−)-calyciphylline N displayed spectral properties in excellent agreement with those derived from the natural product [i.e., ^1H and ^{13}C NMR (500 and 125 MHz, respectively), HRMS parent ion identification, and chiroptic properties].

In summary, the first total synthesis of a member of the calyciphylline alkaloids, (−)-calyciphylline N (**1**), has been achieved with a longest linear sequence of 37 steps from known alcohol (−)-**8**. Application of the strategies presented herein for the synthesis of other members of the *Daphniphyllum* alkaloids continues in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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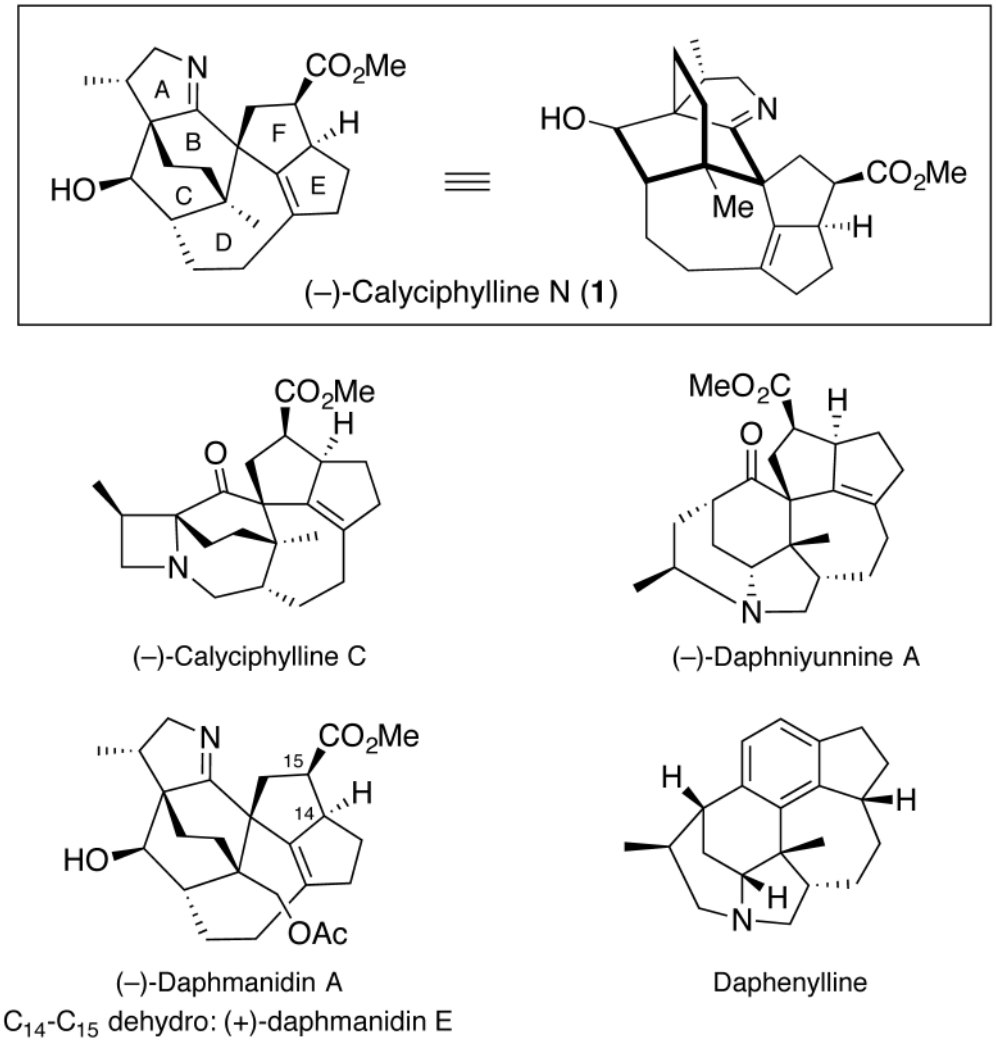


Figure 1.
(–)-Calyciphylline N and related congeners.[6]

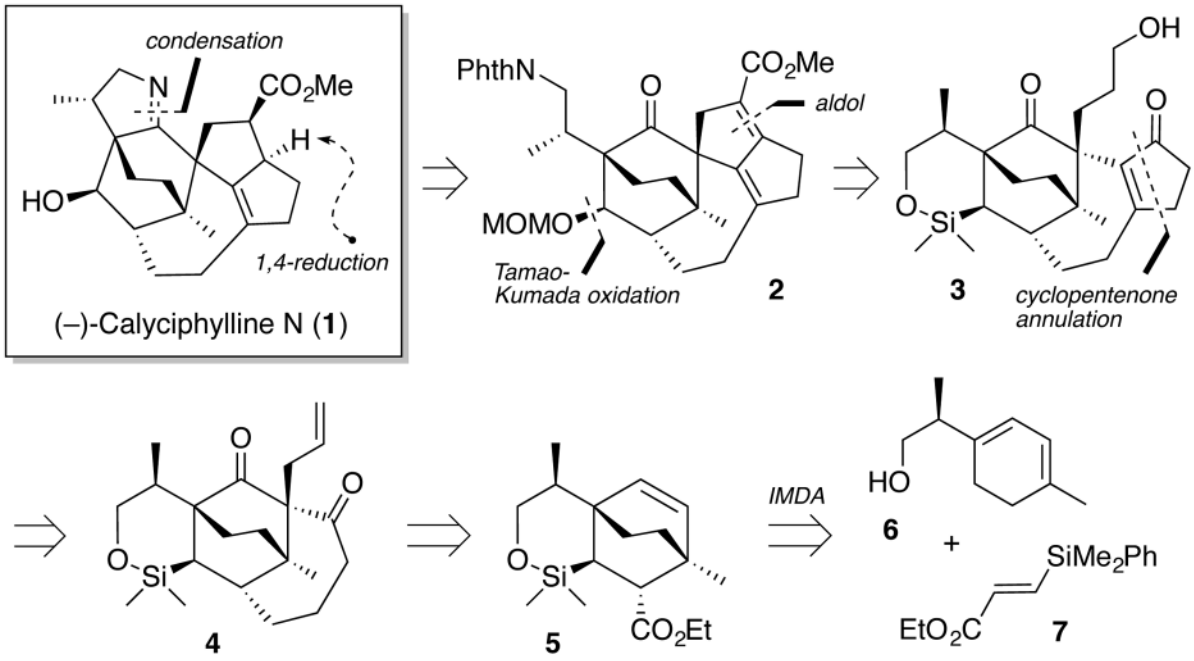
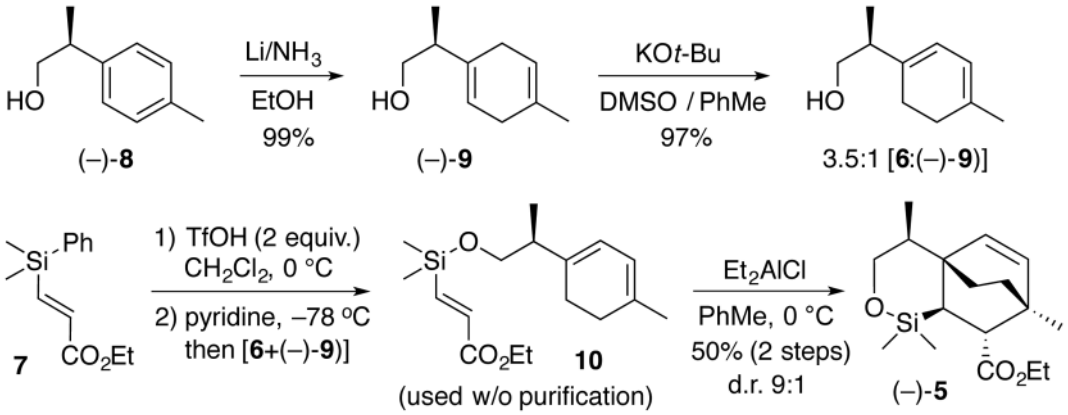


Figure 2.
Retrosynthetic Analysis.



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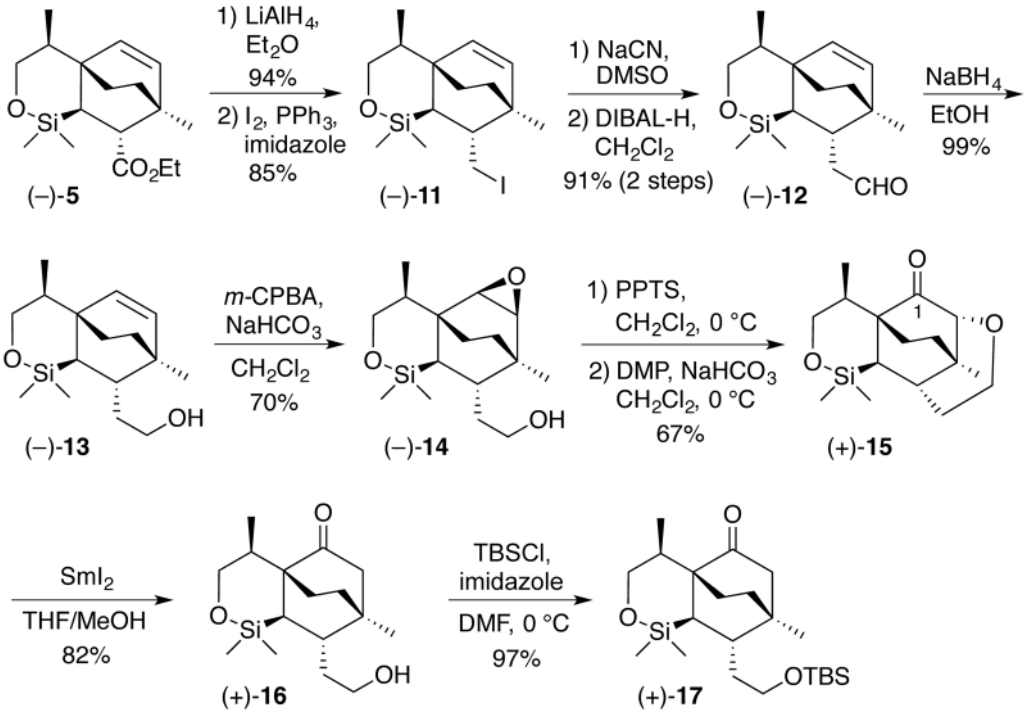

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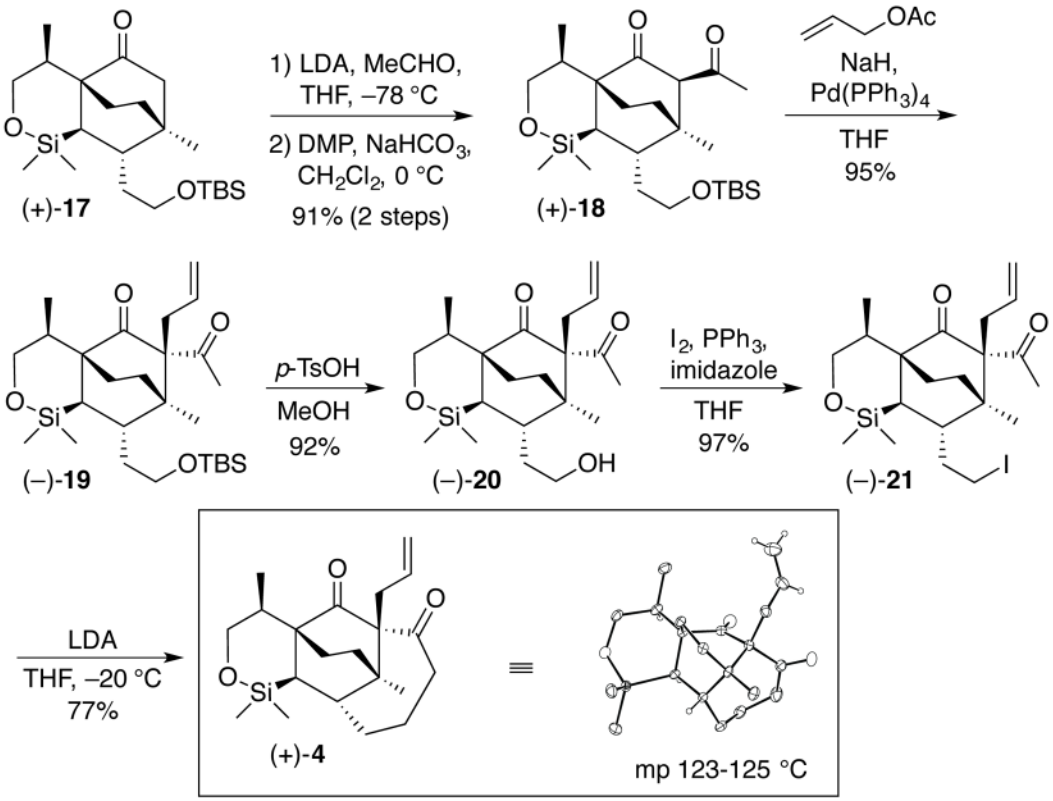

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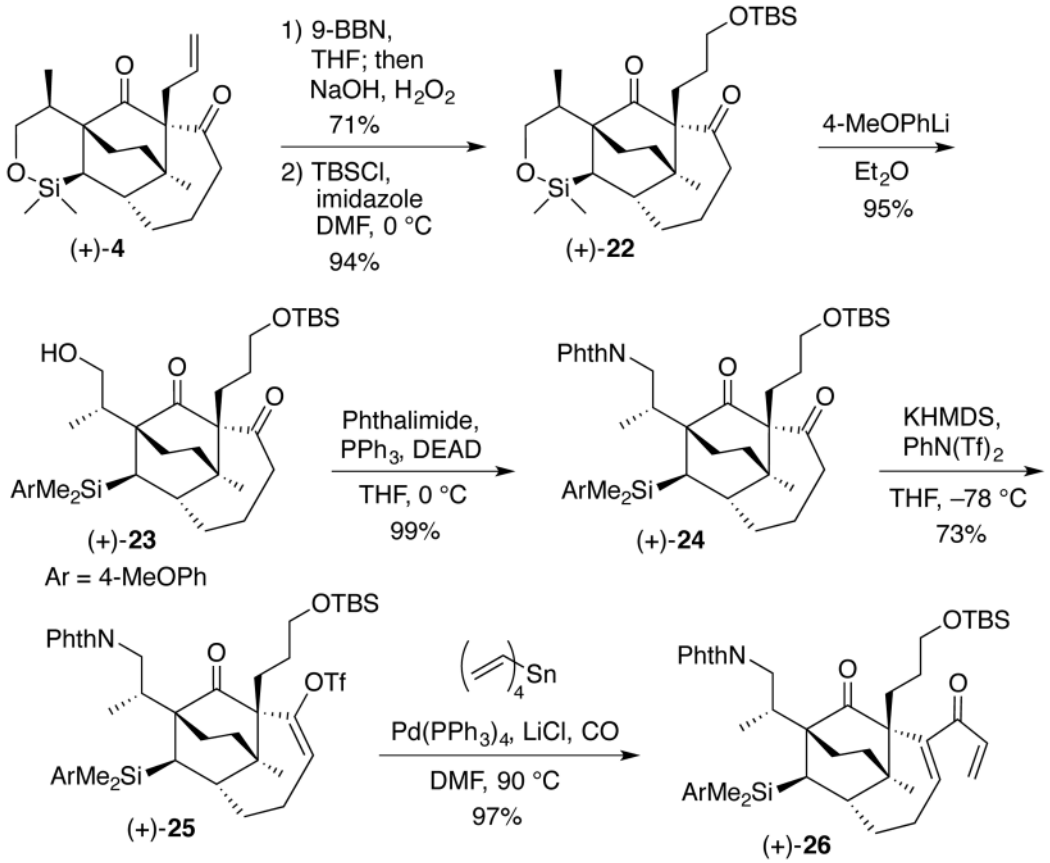

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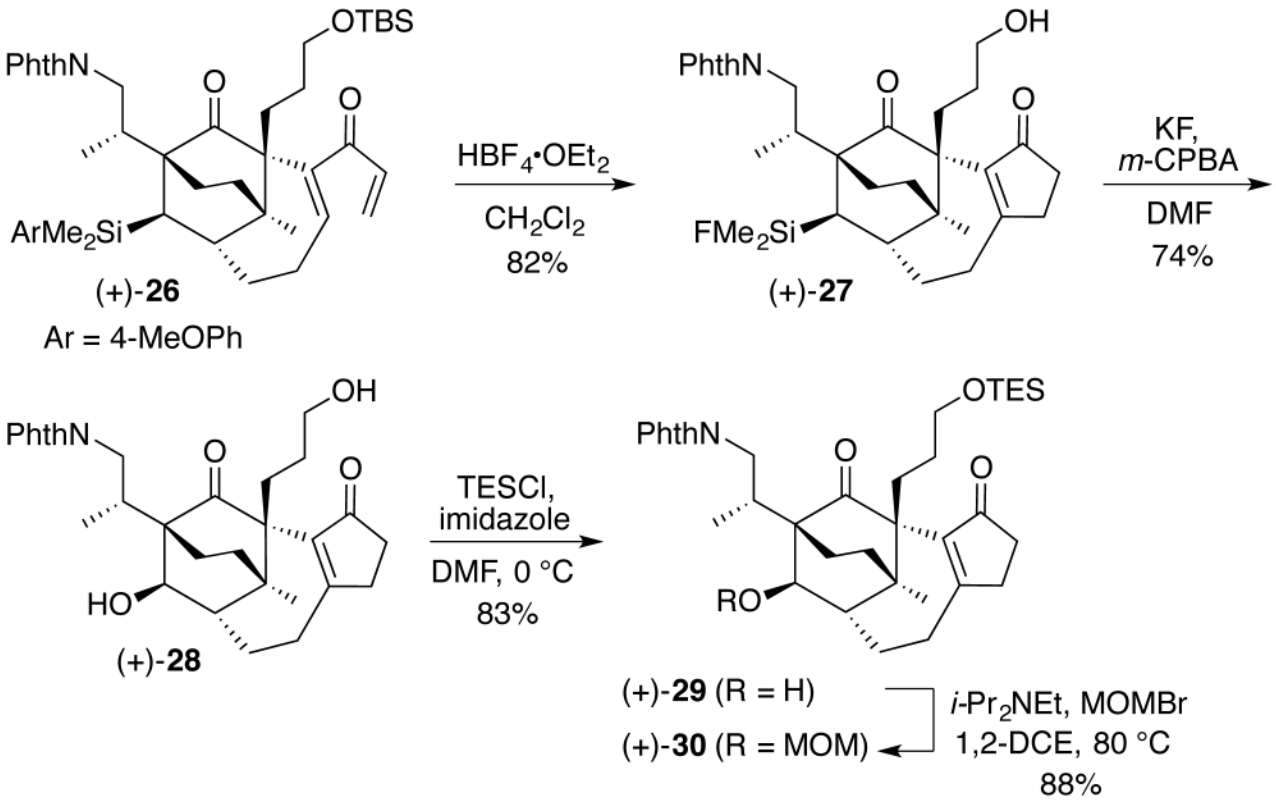

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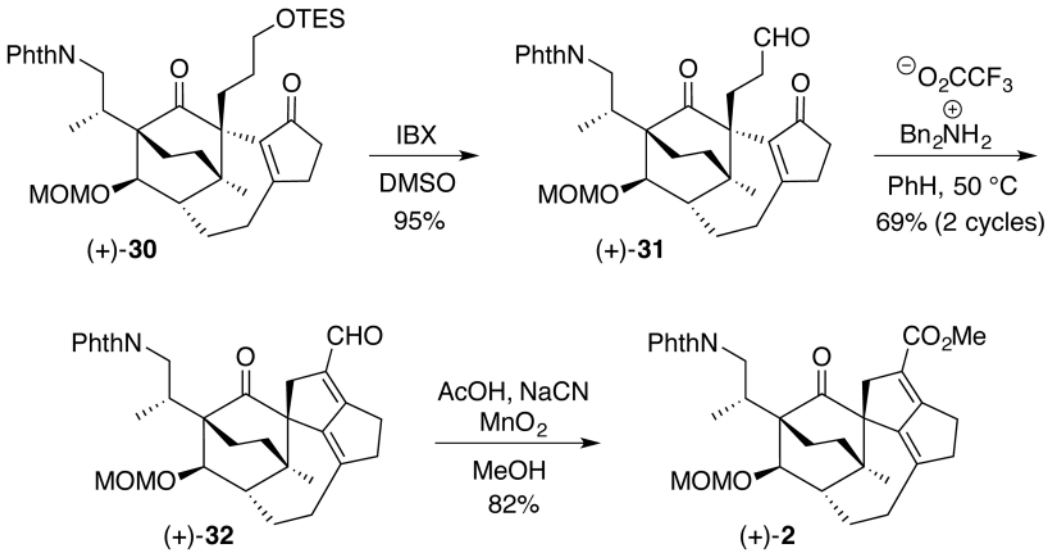
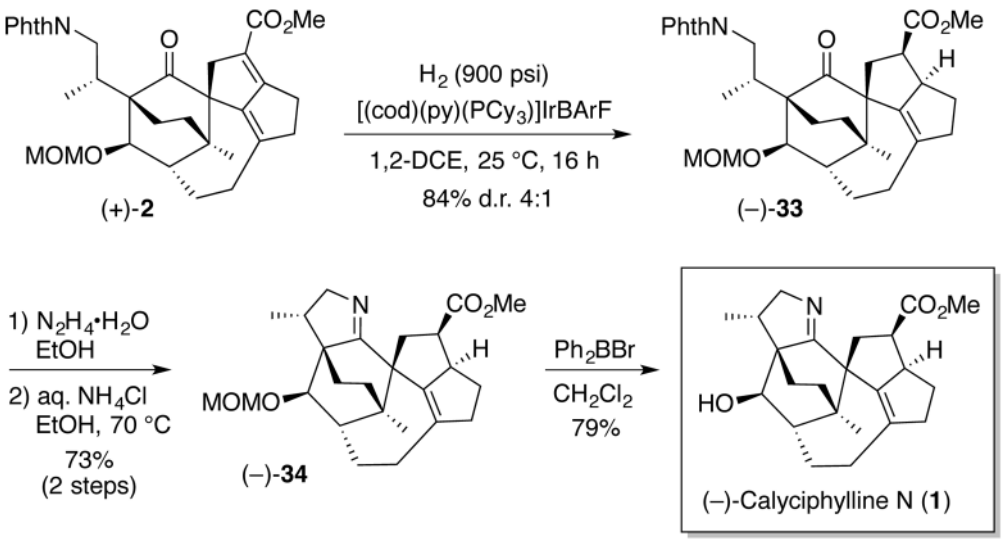


Scheme 6.



Scheme 7.