

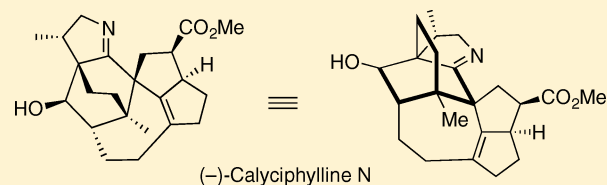
The Daphniphyllum Alkaloids: Total Synthesis of (–)-Calyciphylline N

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S Supporting Information

ABSTRACT: Presented here is a full account on the development of a strategy culminating in the first total synthesis of the architecturally complex daphniphyllum alkaloid, (–)-calyciphylline N. Highlights of the approach include a highly diastereoselective, intramolecular Diels–Alder reaction of a silicon-tethered acrylate; an efficient Stille carbonylation of a sterically encumbered vinyl triflate; a one-pot Nazarov cyclization/proto-desilylation sequence; and the chemoselective hydrogenation of a fully substituted diene ester.



INTRODUCTION

The daphniphyllum alkaloids, a family of natural products numbering more than 200 members,¹ have attracted considerable attention due to both their diverse biological activities and structural complexities.² For example, in the late 1980s, Heathcock and co-workers proposed an innovative biosynthetic pathway for these alkaloids,³ which led to several elegant biomimetic syntheses.⁴ More recently, impressive total syntheses of (+)-daphmanidin E⁵ and daphenylline⁶ have been achieved by Carreira and Li, respectively.

The calyciphyllines, isolated from the leaves and stems of *Daphniphyllum calycinum*, comprise a subclass that likewise have been the subject of multiple, albeit incomplete, synthetic ventures.⁷ Particularly intriguing from the synthetic perspective is (–)-calyciphylline N (**1**, Figure 1), isolated by Kobayashi in 2008,⁸ due not only to the complex architecture, but also to the possibility of developing a unified strategy that would be applicable for the synthesis of related congeners bearing the same DEF ring system.

Notable structural features of the (–)-calyciphylline N (**1**) skeleton include six contiguous stereocenters, three of which are bridgehead quaternary and two are vicinal quaternary; the ring A dihydropyrrole; and a DEF decahydrocyclopentazulene domain surrounding a central bicyclo[2.2.2]octane core. Recently, we reported the total synthesis of (–)-calyciphylline N,⁹ the first synthesis of a member of the calyciphylline family. Herein we disclose a full account of this work, a journey that led us through several initial unsuccessful approaches, but in turn revealed a wealth of interesting reactivity and insight for the construction of the daphniphyllum alkaloids.

An Initial Strategy. From the retrosynthetic perspective (Figure 2), we initially envisioned that the dihydropyrrole ring could be constructed via condensation of a primary amine with the ring B carbonyl, while the stereocenters of the EF ring system would be installed via a critical, late-stage reduction of the α,β -olefin in **2**. Given the high-risk nature associated with this endgame, we also considered the possibility of forming the C14–C15 bond through displacement of a leaving group at

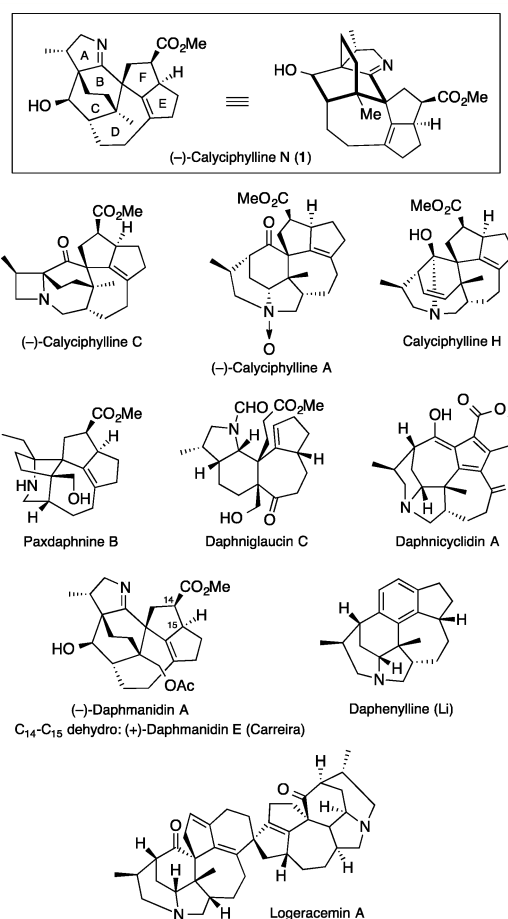


Figure 1. Representative daphniphyllum alkaloids.¹³

Received: April 18, 2014

Published: March 10, 2015

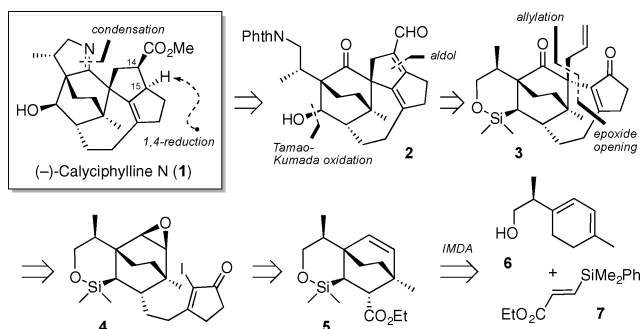


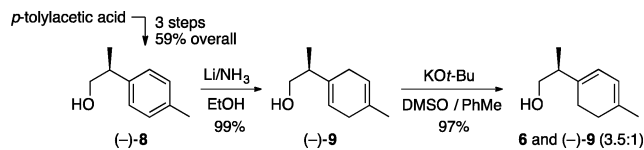
Figure 2. Retrosynthetic analysis.

C15 by an ester enolate generated at C14. In turn, an aldol condensation would serve to construct the diene aldehyde, while installation of the secondary hydroxyl group would entail a Tamao–Kumada oxidation¹⁰ of a cyclic siloxane. A central feature of the initial strategy would involve an intramolecular epoxide opening by a vinyl carbanion derived from iodocyclopentenone **4**, the latter obtained via elaboration of bicyclic ester **5**, envisaged to be the product of an intramolecular Diels–Alder reaction.¹¹ To begin this venture, the requisite triene would be prepared via union of enantiomerically pure homoallylic alcohol **6** with known silyl acrylate **7**.¹²

RESULTS AND DISCUSSION

Bicyclic Ester (–)-5. As outlined, the synthesis of (–)-calyciphylline N (**1**) began with the preparation of alcohol **6** from known homobenzylic alcohol (–)-**8** (Scheme 1),¹⁴

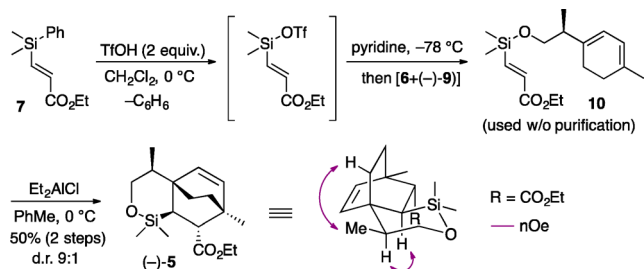
Scheme 1. Synthesis of Diene **6**



available in three steps from commercially available *p*-tolylacetic acid (see Supporting Information). To this end, Birch reduction¹⁵ of (–)-**8** furnished the expected 1,4-cyclohexadiene (–)-**9** in 99% yield, which upon treatment with *KOt*-Bu in DMSO¹⁶ led to an inseparable mixture (3.5:1) of alcohols **6** and (–)-**9**.

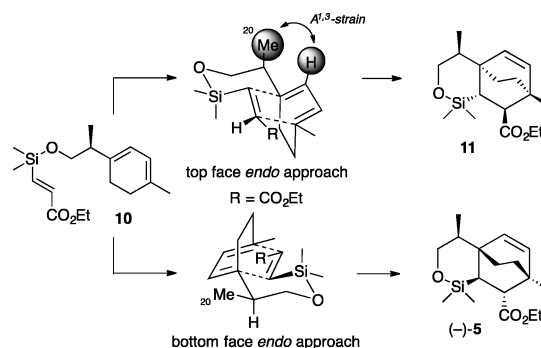
Following the method introduced by Sieburth,¹⁷ exposure of **7** to triflic acid resulted in proto-desilylation to furnish *in situ* the corresponding silyl triflate with concomitant loss of benzene (Scheme 2). Addition of the mixture of alcohols [**6** and (–)-**9**] provided triene **10** for the proposed Diels–Alder cyclization. Thermal cyclization of **10** proved non-stereo-

Scheme 2. Synthesis of Bicyclic Ester (–)-5



selective, furnishing a complex mixture of all possible diastereomers. Pleasingly, however, use of Et_2AlCl smoothly promoted a stereoselective cycloaddition to provide a mixture of only two cycloadducts (9:1) in 50% yield for the two steps. NMR analysis (NOESY) revealed the major product to be the desired diastereomer. The minor diastereomer, unfortunately, could not be isolated as an analytically pure sample for full characterization purposes and was thus tentatively assigned as **11** (Scheme 3).

Scheme 3. Diels–Alder TS Model Leading to (–)-5



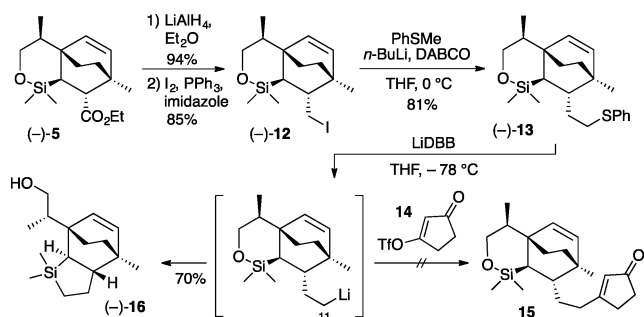
The high diastereoselectivity can be understood by employing a transition-state (TS) model (Scheme 3) very similar to that proposed by Roush for acyclic stereocontrol in intramolecular Diels–Alder reactions.^{11a}

Given the known preference for dienophiles with electron withdrawing substituents to approach the diene pi system in an *endo* fashion,¹⁸ the possible transition states for the two modes of approach are illustrated (*vide supra*). *Endo* approach of the dienophile from the top face of the diene results in an $A^{1,3}$ -interaction between the indicated vinylic hydrogen and the axial C20 methyl group. This interaction is alleviated when the dienophile approaches from the bottom face of the diene pi system, thus favoring formation of (–)-**5**. The increased preference for *endo* addition under Lewis acid catalysis has been attributed to a lowering of the LUMO energy of the dienophile, as well as redistribution of orbital electron densities.¹⁹ This results in increased electron density at the carbonyl carbon, leading to greater secondary orbital interactions, which constitutes the basis for *endo* selectivity in Diels–Alder reactions.

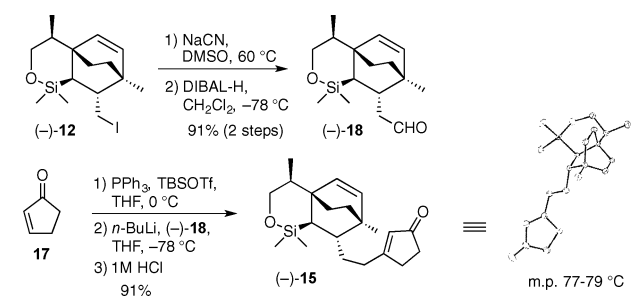
Iodocyclopentenone (+)-4. Having secured access to intermediate (–)-**5**, we next explored elaboration of the side chain en route to iodocyclopentenone **4**. Homologation of (–)-**5** began with LiAlH_4 reduction and conversion of the resulting alcohol to the corresponding iodide, thereby providing (–)-**12** in 80% overall yield (Scheme 4). Utilizing a procedure developed by Corey,²⁰ metalation of thioanisole with *n*-BuLi in the presence of DABCO, followed by addition of (–)-**12** furnished phenyl sulfide (–)-**13**. We had anticipated that reductive lithiation²¹ of (–)-**13**, followed by addition of vinylogous triflate **14**, would serve to install the cyclopentenone motif (**15**). While the reductive lithiation was indeed successful, the resultant alkyllithium underwent an unexpected (and facile) cyclization onto the siloxane, delivering silacyclopentane (–)-**16** in 70% yield.

Unable to avoid this intramolecular siloxane opening, we considered an alternative tactic for side chain elongation (Scheme 5), employing an electrophilic, rather than nucleo-

Scheme 4. Reductive Lithiation Strategy



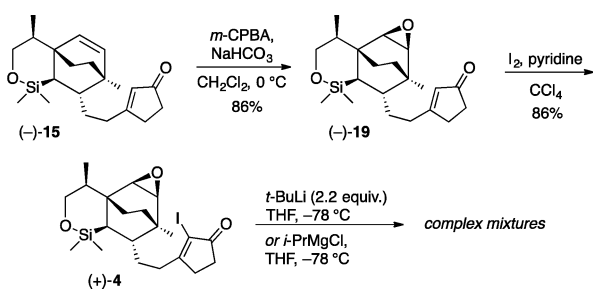
Scheme 5. Synthesis of Cyclopentenone (–)-15



philic carbon at C11. The method introduced by Kozikowski²² that relies upon initial conjugate addition of PPh_3 to cyclopentenone (**17**), trapping of the enolate with TBSOTf, and generation of the phosphorous ylide that reacts with an aldehyde appeared viable. The resulting silyl dienol ether could then be hydrolyzed *in situ* to the corresponding cyclopentenone. Application of this protocol to our system necessitated the synthesis of the appropriate aldehyde, which was readily achieved by NaCN displacement of iodide (–)-**12** (Scheme 5), followed by DIBAL-H reduction of the resulting nitrile and hydrolysis (91% over two steps). We were pleased to find that subjection of (–)-**18** to the Kozikowski scenario cleanly furnished (–)-**15** as a crystalline solid (mp 77–79 °C) in 91% yield. Single-crystal X-ray analysis confirmed the relative and absolute stereochemical configurations.

Intramolecular Epoxide Opening of (+)-4** and **20**: A Challenging Proposition.** Exposure of (–)-**15** to *m*-CPBA next furnished the desired epoxide (–)-**19** as a single diastereomer, which upon exposure to Johnson iodination (I_2 , pyridine)²³ completed construction of (+)-**4** (Scheme 6). Curiously, attempts at performing the iodination and epoxidation in reverse order led to very low yields.

Preliminary cyclization studies involving metalation of the vinyl iodide with *t*-BuLi or *i*-PrMgCl, however, led only to

Scheme 6. Completion of Key Intermediate (+)-**4**

complex mixtures. To avoid the possibility of side reactions at the cyclopentenone carbonyl, we explored protection. Ketalization proved difficult; the carbonyl was therefore converted to a protected hydroxyl group via Luche reduction (NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, MeOH),²⁴ followed by treatment of the resulting alcohol with TBSCl to provide **20** as a mixture (1:1) of diastereomers in 76% yield for the two steps. Unfortunately, while metalation of **20** proceeded cleanly, epoxide opening was not observed (Table 1). Increasing the temperature of the THF

Table 1. Selected Conditions for the Cyclization of **20**

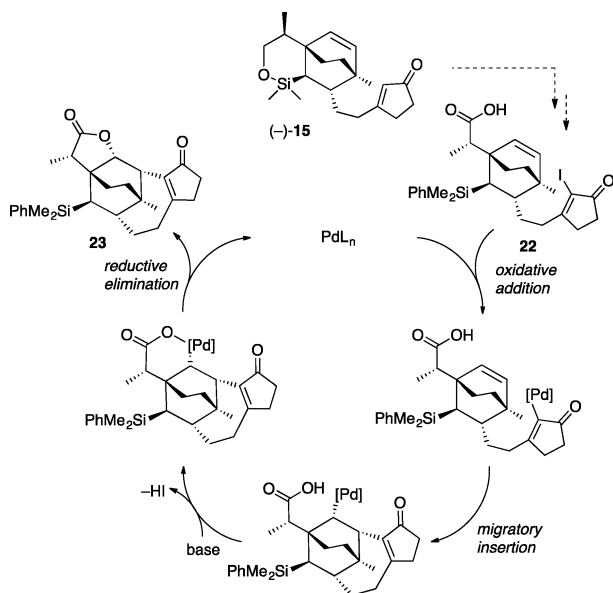
| entry | conditions | result |
|-------|---|------------------------------------|
| 1 | <i>t</i> -BuLi; THF; –78 °C → rt | metal–halogen exchange exclusively |
| 2 | <i>i</i> -PrMgCl; THF; –78 °C → rt | metal–halogen exchange exclusively |
| 3 | <i>t</i> -BuLi, ZnCl ₂ , Ti(O <i>i</i> Pr) ₄ , etc.; THF; –78 °C → rt | metal–halogen exchange exclusively |
| 4 | <i>t</i> -BuLi, BF ₃ ·OEt ₂ , TiCl ₄ , Et ₂ AlCl, etc.; THF; –78 °C | skeletal rearrangement |
| 5 | <i>t</i> -BuLi, CuI or CuBr or CuCN, etc.; THF; –78 °C → rt | metal–halogen exchange exclusively |

to reflux resulted again in complex mixtures. We also attempted to increase the reactivity of the epoxide by addition of various Lewis acids such as Ti(O*i*-Pr)₄, ZnCl₂, etc.; the only product observed was that resulting from metal halogen exchange. Other attempts to forge the requisite bond, namely use of strong Lewis acids (e.g., TiCl₄, BF₃·OEt₂) and conversion of the vinyl lithium or vinylmagnesium species to the corresponding cuprates also proved unsuccessful.

Failure of **20** to undergo the proposed intramolecular epoxide opening required the development of an alternative strategy for ring D construction. Earlier studies had demonstrated that the siloxane ring could be opened by strong nucleophiles such as alkyl- or aryllithiums. We thus became attracted to the possibility of accessing intermediate **22** (Scheme 7), bearing an iodocyclopentenone moiety, as well as a pendant nucleophile at the opposite terminus of the molecule. Such an intermediate might undergo a Pd-mediated cyclization cascade,²⁵ ultimately delivering lactone **23** (*vide infra*).

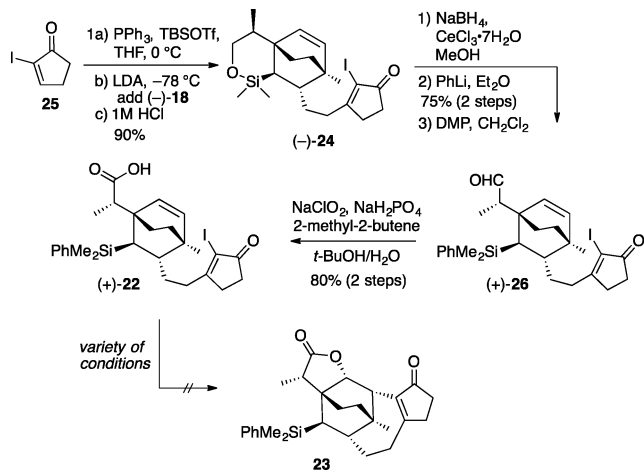
Synthesis of Carboxylic Acid (+)-22**.** Our plan for **22** called initially for iodination of (–)-**15**. The Johnson iodination²³ protocol of (–)-**15**, however, furnished only low yields of (–)-**24** (ca. 30%), along with substantial decomposition, which made workup and purification difficult. Considering that a substantial throughput of material would be required for the cyclization studies, we developed a more efficient approach based on an extension of the Kozikowski

Scheme 7. Proposed Pd-Mediated Cascade Cyclization



chemistry.²² By utilizing 2-iodocyclopentenone (**25**, rather than **17**), we anticipated that (**-**)-**24** could be obtained directly from aldehyde (**-**)-**18**. It would, of course, be necessary to alter the initiating base from *n*-BuLi to LDA in order to avoid metal-halogen exchange. This tactic indeed proved successful, providing (**-**)-**24** in 90% yield (Scheme 8). Luche reduction,²⁴

Scheme 8. Synthesis of Carboxylic Acid (+)-22



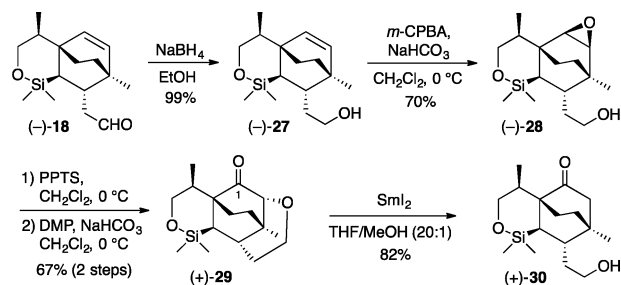
followed by siloxane ring opening with phenyllithium, then furnished a diol (75% over two steps), which was oxidized with Dess–Martin periodinane²⁶ (DMP) to yield aldehyde (**+**)-**26**. Pinnick oxidation²⁷ then provided the requisite intermediate, carboxylic acid (**+**)-**22**, in 80% yield for the two steps.

With ample quantities of (**+**)-**22** in hand, we explored the Pd-mediated cascade. Extensive screening of a variety of conditions (bases, solvents, ligands, and sources of Pd⁰) unfortunately led only to decomposition or proto-dehalogenation. In no cases was the desired lactone **23** detected.

A Fortuitous Result. At this juncture, we became convinced that the Pd-mediated strategy would not prove viable. We therefore revisited the epoxide strategy, speculating that if the epoxide could be opened regioselectively, such an

event would permit access to the C1 carbonyl in ring B, a potentially valuable functional handle for further elaboration. To this end, NaBH₄ reduction of (**-**)-**18** furnished alcohol (**-**)-**27**, which upon treatment with *m*-CPBA led to epoxide (**-**)-**28** as a single diastereomer in 70% yield (Scheme 9).

Scheme 9. Synthesis of Ketone (+)-30



Gratifyingly, (**-**)-**28** underwent rapid transannular cyclization in the presence of pyridinium *p*-toluenesulfonate (PPTS). Oxidation of the derived alcohol facilitated purification to provide ketone (**+**)-**29** in 67% yield over the two steps. Reductive ring opening with SmI₂²⁸ then cleanly furnished hydroxy ketone (**+**)-**30** in 82% yield.

A New Plan Forward. Our ability to install the C1 carbonyl paved the way for the development of a new strategy (Figure 3). While the endgame disconnections would remain identical

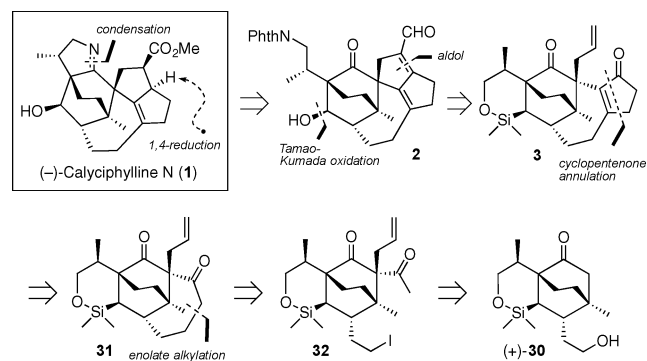
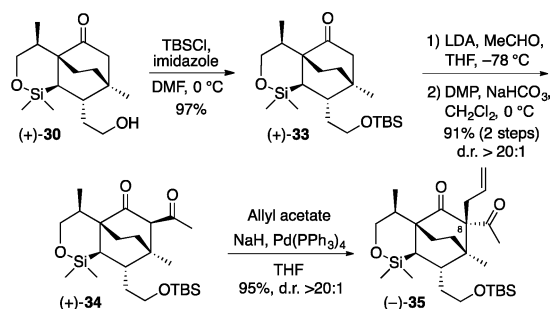


Figure 3. Revised retrosynthetic analysis.

leading to **3**, construction of ring E would now be delayed to a later stage, employing first a cyclopentenone annulation of **31**, the latter accessible via intramolecular enolate alkylation of iodoketone **32**, readily obtained from (**+**)-**30**.

Diketone (+)-31. Protection of (**+**)-**30** (Scheme 10) as the TBS ether was readily achieved with TBSCl/imidazole in DMF.

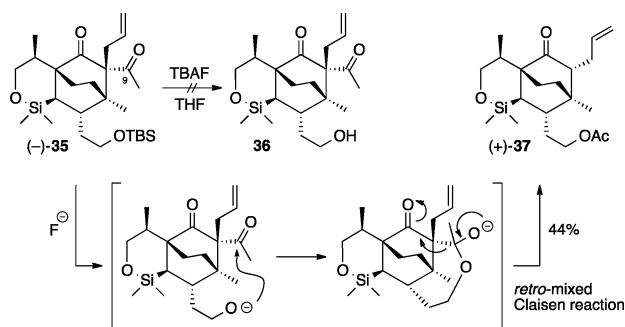
Scheme 10. Synthesis of Diketone (-)-35



Acylation of the hindered carbonyl in (+)-33, however, proved challenging. Consequently, we employed a two step sequence involving an aldol reaction of (+)-33 with acetaldehyde, followed by DMP oxidation of the resulting β -hydroxy ketone, an effective protocol to access 1,3-diketones introduced by our group in 1981.²⁹ This sequence provided diketone (+)-34 in 91% yield with greater than 20:1 selectivity. Not surprisingly, attempted allylation of (+)-34 utilizing a variety of bases and allylating agents led to complex mixtures of C- and O-allylated products. The Tsuji–Trost protocol,³⁰ however, furnished (–)-35 in excellent yield (95%), as a single diastereomer (>20:1), completing installation of the third and final quaternary center at C8 for (–)-calyciphylline N.

Turning to the deprotection of (–)-35, treatment with TBAF furnished none of the desired alcohol 36. Instead, the major product proved to be acetate (+)-37 (Scheme 11).

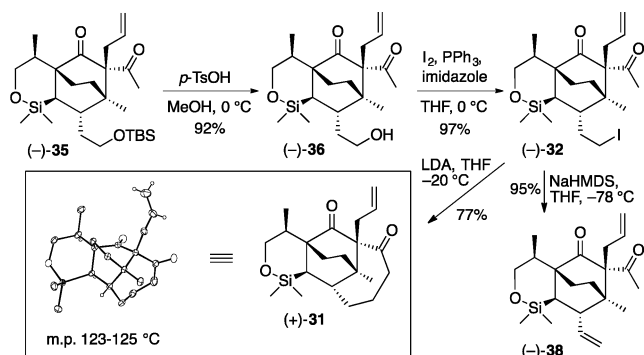
Scheme 11. An Undesired Retro-Mixed Claisen Pathway Leading to (+)-37



Unexpectedly, the intermediate alkoxide formed upon desilylation had undergone intramolecular attack at the C9 carbonyl, resulting in a retro-mixed Claisen reaction. This result, however, demonstrated that the correct stereochemistry at C8 had been established during the allylation (*vide supra*).

Reasoning that the undesired reaction pathway was initiated by the alkoxide formed upon deprotection, we anticipated that TBS removal under acidic conditions would remedy the problem. Indeed, exposure of (–)-35 to a catalytic amount of *p*-TsOH in MeOH furnished alcohol (–)-36 in 92% yield (Scheme 12). Treatment of the latter with I₂/PPh₃/imidazole then cleanly led to iodoketone (–)-32 in 97% yield, which upon treatment with LDA at –20 °C pleasingly furnished intermediate (+)-31 as a crystalline solid (mp 123–125 °C) in 77% yield. The structure and stereochemical configuration were again confirmed by single-crystal X-ray analysis. Interestingly,

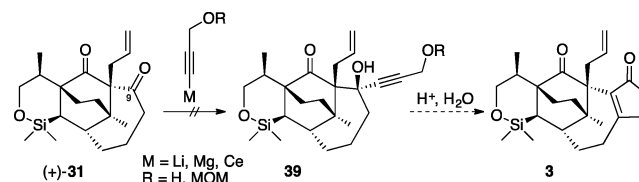
Scheme 12. Synthesis of Diketone (+)-31



use of NaHMDS for ring closure led only to the elimination product (–)-38.

Elaboration of the Eastern Hemisphere. With ring D secure, we turned to construct ring E. Our strategy called for the use of a Nazarov cyclization.³¹ Initially, we attempted addition of an acetylide to (+)-31, followed by a tandem Rupe rearrangement³²/Nazarov cyclization sequence (Scheme 13).

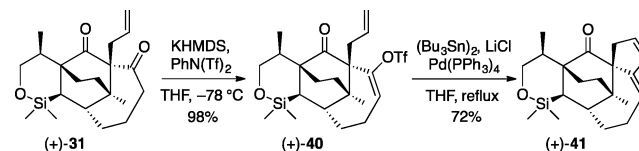
Scheme 13. Failed Acetylide Addition to (+)-31



The C9 carbonyl of (+)-31, however, proved to be completely resistant to nucleophilic attack, even under forcing conditions. Inspection of molecular models suggests that the Bürgi–Dunitz trajectory is blocked from the top face of the carbonyl by the C20 methyl group, and from the bottom face due to the concavity of the substrate.

We turned instead to a Stille carbonylative cross-coupling³³ tactic, followed by Nazarov cyclization. To this end, treatment of (+)-31 with KHMDS in the presence of PhN(Tf)₂ furnished vinyl triflate (+)-40 in 98% yield (Scheme 14). At the outset of

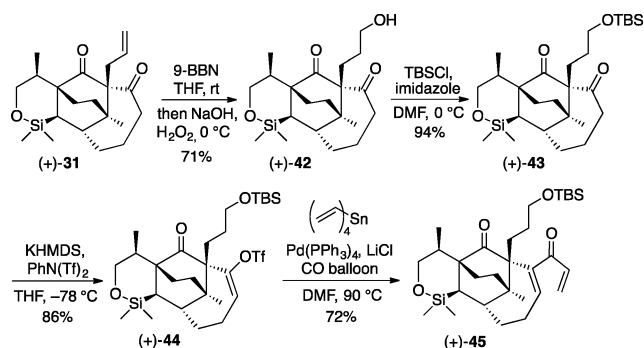
Scheme 14. Undesired Heck Cyclization of (+)-40



this venture, it was unclear whether the allyl group would interfere with the Pd chemistry at the triflate center. Consequently, we decided to test the reactivity of (+)-40, simply by attempting to exchange the vinyl triflate for a vinyl stannane. Treatment of (+)-40 with (Bu₃Sn)₂, Pd(PPh₃)₄, and LiCl in fact led only to the intramolecular Heck product (+)-41.³⁴ This result is unusual, given that 5-*endo-trig* cyclizations are typically disfavored.³⁵ The alternative 4-*exo-trig* cyclization, however, would furnish a cyclobutane, a pathway that is likely much higher in energy. Furthermore, Heck reactions proceeding via a 5-*endo-trig* cyclization have been reported.³⁶

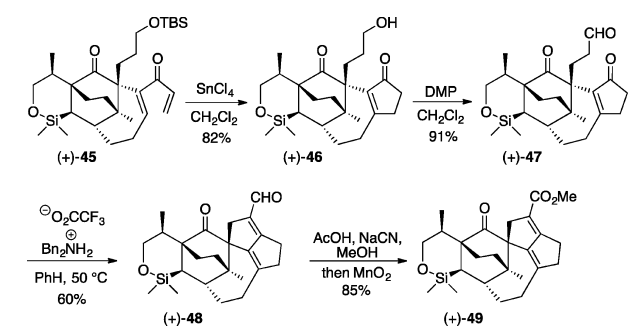
To eliminate the Heck reaction pathway, prior functionalization of the allyl group would be required. Thus, hydroboration of (+)-31 with 9-BBN and oxidation of the resulting organoborane (NaOH, H₂O₂)³⁷ furnished alcohol (+)-42 in 71% yield, which in turn was protected as the TBS ether (Scheme 15). Conversion of (+)-43 to the corresponding vinyl triflate (+)-44 was then achieved under the previously established conditions [KHMDS, PhN(Tf)₂]. Subsequent treatment of (+)-44 to the standard Stille carbonylation protocol [e.g., CO, Pd(PPh₃)₄, (CH₂CH)₄Sn, LiCl] in THF at reflux led only to recovery of starting material. However, upon switching the solvent to DMF and increasing the temperature to 90 °C, divinyl ketone (+)-45 was cleanly obtained in 72% yield.

Scheme 15. Synthesis of Divinyl Ketone (+)-45



The SnCl_4 -promoted Nazarov cyclization³¹ of (+)-45 at ambient temperature then proceeded with concomitant removal of the TBS group to furnish (+)-46 in 82% overall yield, completing the synthesis of ring E (Scheme 16).

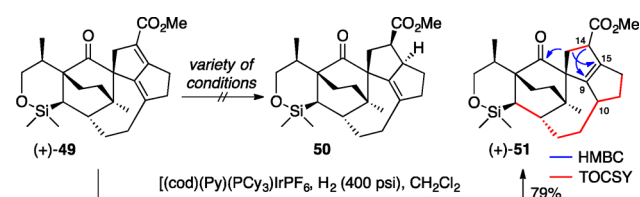
Scheme 16. Synthesis of Diene Ester (+)-49



Construction of ring F next entailed oxidation of (+)-46 to aldehyde (+)-47, followed by an aldol condensation employing the conditions reported by Weiss and Carreira in their synthesis of (+)-daphmanidin E ($\text{Bn}_2\text{O}_2\text{CCF}_3$, PhH, 50 °C)⁵ to furnish (+)-48, which upon oxidation à la Corey³⁸ led to diene ester (+)-49 in 85% yield.

With (+)-49 in hand, the central challenge of the (–)-calyciphylline N synthesis entailed selective reduction of the α,β -olefin of the diene ester. Not surprisingly, this high risk transformation proved difficult. Typical conjugate reduction conditions including Stryker's reagent,³⁹ the DIBAL-H/CuI/HMPA protocol,⁴⁰ rhodium-catalyzed hydrosilylations, and heterogeneous hydrogenation (Pd/C or PtO_2/C) at pressures up to 1000 psi were completely ineffective. Strongly basic conditions (Li/NH_3), on the other hand, led to complex mixtures of products. We finally discovered that the Crabtree catalyst⁴¹ employing 400 psi of H_2 in CH_2Cl_2 cleanly furnished a single new product with the correct mass [$(\text{M}+\text{H})^+$ = 429] in 79% yield. Analysis of the HMBC and TOCSY NMR, however, revealed the product to be ester (+)-51 (Scheme 17), in which

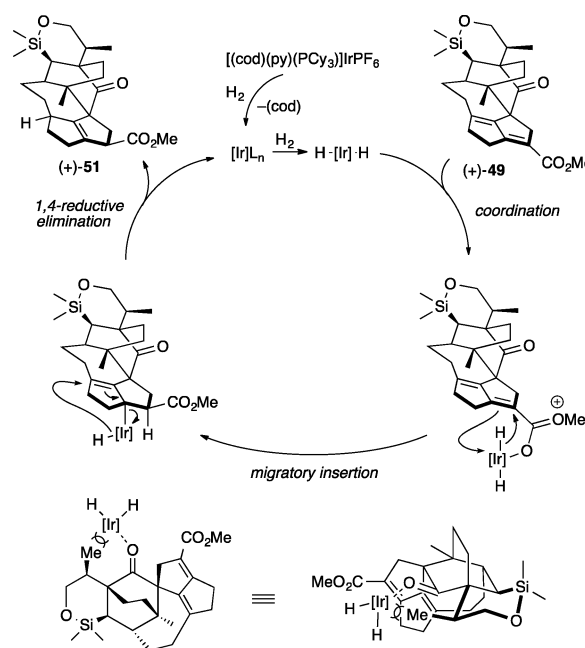
Scheme 17. Crabtree Hydrogenation of (+)-49



the reduction was accompanied by olefin isomerization to the C9–C15 position (e.g., HMBC and TOCSY NMR experiments). The stereochemical outcome at C10 and C14, however, was not determined.

This result was quite surprising in that isomerization was observed, but hydrogenation to the fully saturated system was not. A plausible mechanism leading to the formation of (+)-51 is outlined below (Scheme 18). This involves initial

Scheme 18. Proposed Mechanism for the Formation of (+)-51



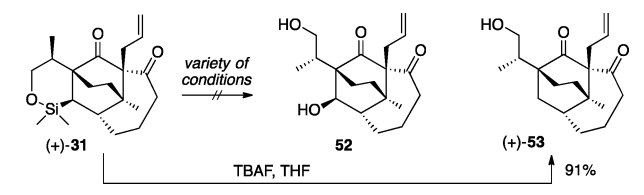
coordination of the iridium dihydride complex to the ester moiety of (+)-49. Migratory insertion then delivers a hydride to the α -carbon of the diene ester, thereby leading to the indicated allylic iridium species. Delivery of hydride to the α , rather than β -position, may be a consequence of increased steric congestion at the β -carbon. A typical reductive elimination mechanism would furnish 50. In this case, however, we propose a 1,4-reductive elimination pathway that appears to be favored, leading exclusively to (+)-51. Such 1,4-hydrogenations have previously been reported with chromium and ruthenium catalysis,⁴² but not for iridium. Clearly, there is a preference for the olefin to reside at the C9–C15 position over C9–C10. While we attempted to rationalize this outcome by determining the relative thermodynamic stability of (+)-51 versus 50 via computational studies, the results proved to be inconclusive.

On the basis of molecular models, we had anticipated that the C1 carbonyl is ideally situated to direct the hydrogenation, both in terms of stereo and chemoselectivity. In fact, it is known that ketones are stronger directing groups than esters in directed hydrogenation.⁴³ However, coordination of the iridium catalyst in this fashion may not be feasible due to a steric interaction with the C20 methyl group (*vide supra*). We speculated that hydrogenation of a system with an elaborated western hemisphere might prove more rewarding, as opening of the siloxane ring should alleviate this interaction.

Elaboration of the Western Hemisphere. Guided by this hypothesis, we turned to the Tamao–Kumada oxidation of (+)-31. Siloxane (+)-31, however, was found to be extremely

resistant to oxidation (Scheme 19). Typical conditions (various fluoride sources, bases, H₂O₂ or *m*-CPBA)^{10,44} led to the

Scheme 19. Attempted Tamao–Kumada Oxidation of (+)-31⁴⁷

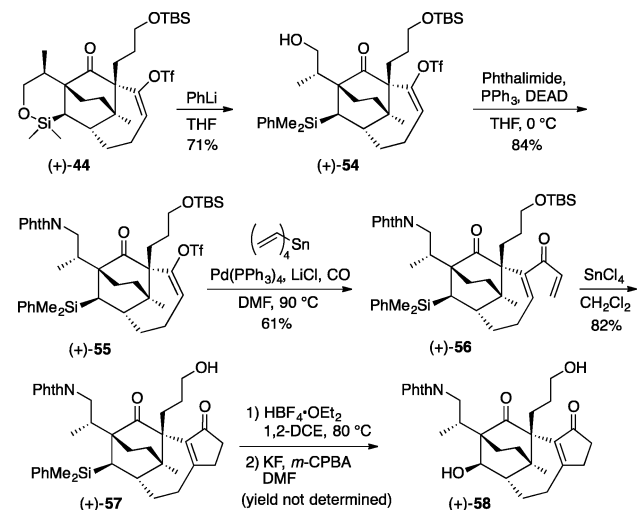


recovery of starting material. The strongly basic oxidations of Woerpel for hindered silyl groups (CsOH·H₂O or KH, *t*-BuOOH),⁴⁵ on the other hand, only resulted in decomposition, while TBAF treatment furnished desilylated compound (+)-53.⁴⁶

Undaunted, we turned to opening the siloxane ring with a strong carbon nucleophile (i.e., phenyllithium), recognizing that phenylsilanes of this type can be converted to highly reactive silyl species under a wide range of electrophilic conditions (Hg²⁺, Br₂, BF₃·OEt₂, etc.), which in turn could be oxidized to the corresponding alcohol, employing the Fleming modification of the Tamao–Kumada oxidation.⁴⁸ Triflate (+)-44 was chosen as the initial substrate, given the lack of functional groups incompatible with phenyllithium.

Pleasingly, treatment of (+)-44 with PhLi led to phenylsilane (+)-54 in 71% yield (Scheme 20). Rather than protect the

Scheme 20. Synthesis of Diol (+)-58



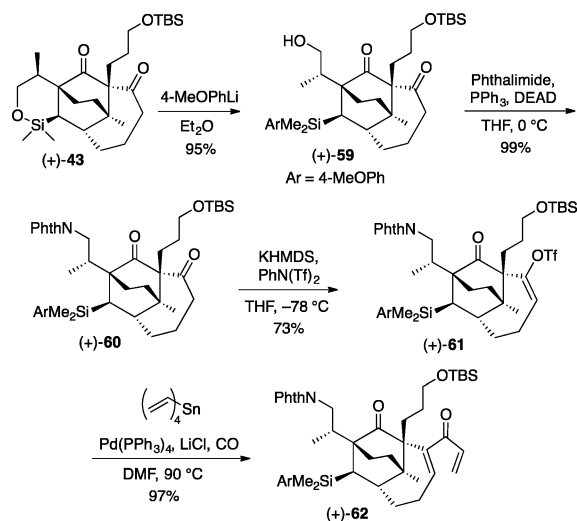
newly generated hydroxyl, we elected to introduce the requisite nitrogen for (–)-calyciphylline N (1) in the form of a robust phthalimide, via a Mitsunobu reaction.⁴⁹ Recognizing that the vinyl triflate and TBS group of (+)-55 would not survive the strong oxidative conditions of the Fleming–Tamao protocol, we chose to elaborate further this substrate. To this end, Stille carbonylation furnished divinyl ketone (+)-56 in 61% yield, which upon employing the Nazarov conditions established for (+)-45 (SnCl₄, 25 °C) proceeded with equal efficiency (82%).

The Fleming one-pot oxidation conditions for conversion of phenylsilanes to alcohols⁵⁰ initially proved problematic, resulting in complex mixtures when applied to (+)-57. However, after considerable screening, we identified HBF₄·

OEt₂ in 1,2-dichloroethane (1,2-DCE) at 80 °C as an effective protocol to convert the phenylsilane to the corresponding silyl fluoride. Gratifyingly, this highly activated silyl species was readily oxidized to diol (+)-58 under the standard Fleming conditions (KF, *m*-CPBA, DMF). We surmised, however, that the proto-desilylation step would be substantially more facile if an electron-donating substituent were present on the phenyl ring. We therefore set out to prepare the 4-methoxyphenyl analogue of (+)-57.

Total Synthesis of (–)-Calyciphylline N. Treatment of (+)-43 with 4-MeOPhLi furnished arylsilane (+)-59 in 95% yield (Scheme 21). Importantly, the hindered carbonyls at C1

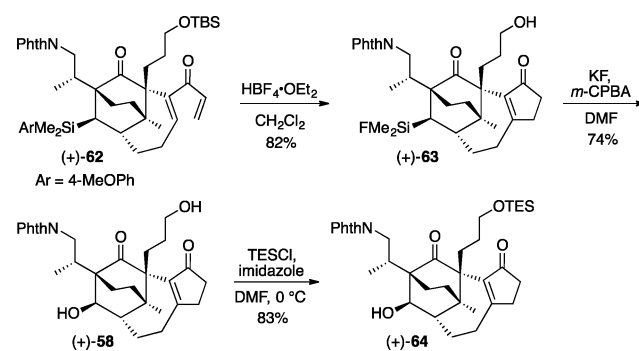
Scheme 21. Synthesis of Arylsilane (+)-62



and C9 were completely inert to nucleophilic addition by the aryllithium. Mitsunobu reaction⁴⁹ then led to phthalimide (+)-60 in 99% yield, which was converted to the corresponding vinyl triflate (+)-61 in 73% yield by enolization with KHMDS in the presence of PhN(Tf)₂. Stille carbonylation next proved highly effective to provide the Nazarov precursor (+)-62 in excellent yield.

Given that Nazarov cyclizations and proto-desilylations can both be carried out with protic acid,^{31,48} we reasoned that both reactions should be feasible in the same flask. Since earlier studies had demonstrated that HBF₄·OEt₂ would remove the phenyl group [cf. (–)-57], we selected this reagent as the acid promoter. Pleasingly, exposure of (+)-62 to HBF₄·OEt₂ at ambient temperature led directly to silyl fluoride (+)-63 in 82% yield (Scheme 22), wherein the primary TBS group was also

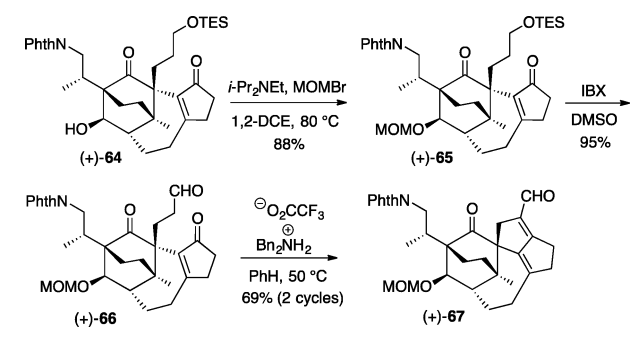
Scheme 22. Improved Route to Diol (+)-58



removed. Following the Fleming–Tamao oxidation, diol (+)-58 was cleanly isolated in 74% yield. Chemoselective protection of the primary hydroxyl was then achieved with TESCl/imidazole to complete construction of alcohol (+)-64 in 83% yield.

Turning to the required protection of the hindered secondary hydroxyl of (+)-64, difficulties were encountered. Several conditions including BzCl/pyridine and NaH/BnBr resulted in decomposition, while treatment with both silyl chlorides and silyl triflates proved ineffective. Formation of the MOM ether at room temperature also proved sluggish. However, heating (+)-64 with MOMBr and *i*-Pr₂NEt in 1,2-DCE to 80 °C furnished the protected diol (+)-65 in 88% yield (Scheme 23). One-pot removal of the TES group and oxidation

Scheme 23. Synthesis of Diene Aldehyde (+)-67



of the resulting alcohol was next achieved with 2-iodoxybenzoic acid (IBX) in DMSO,⁵¹ thereby providing aldehyde (+)-66 in excellent yield. Aldol condensation to furnish (+)-67 utilizing the same conditions as described for aldehyde (+)-47 then proceeded without incident.

Diene aldehyde (+)-67 was next advanced to methyl ester (+)-68 in 82% yield by employing conditions identical to those described for the preparation of (+)-48 (Scheme 16). Surprisingly, contrary to diene ester (+)-49, hydrogenation of (+)-68 with Crabtree's catalyst at 400 psi of H₂ led only to the recovery of starting material. A careful review of the literature, however, revealed an important report by Wuestenberg and Pfaltz,⁵² demonstrating that the reactivity of the Crabtree catalyst can be enhanced by replacing the hexafluorophosphate (PF₆⁻) anion with tetrakis[bis(trifluoromethyl)phenyl]borate (BARF⁻). The more weakly coordinating BARF⁻ anion is suggested to permit directing groups such as hydroxyl or carbonyl groups to coordinate more easily with the cationic iridium center.^{43,53} Subjection of (+)-68 to the Pfaltz-modified Crabtree catalyst [(cod)(Py)(PCy₃)IrBARF under 900 psi of H₂ furnished a 4:1 mixture of two products with the correct mass [(M+H)⁺ = 562] in 84% yield (Scheme 24).

After separation of the diastereomers by medium-pressure liquid chromatography, a series of 2D NMR spectra (HMBC, TOCSY, NOESY) were collected for the major diastereomer (Figure 4 and Supporting Information). Analysis of the NMR data revealed the major product to be the desired diastereomer (–)-69. Looking forward to future synthetic studies, we anticipate that this critical chemo- and stereoselective hydrogenation, possibly directed by the C1 carbonyl, will prove useful in accessing related congeners bearing the same mono-unsaturated DEF ring system.

Because the major product of this reaction bears an olefin at the C9–C10 rather than the C9–C15 position, the implication

Scheme 24. Hydrogenation of Diene Ester (+)-68

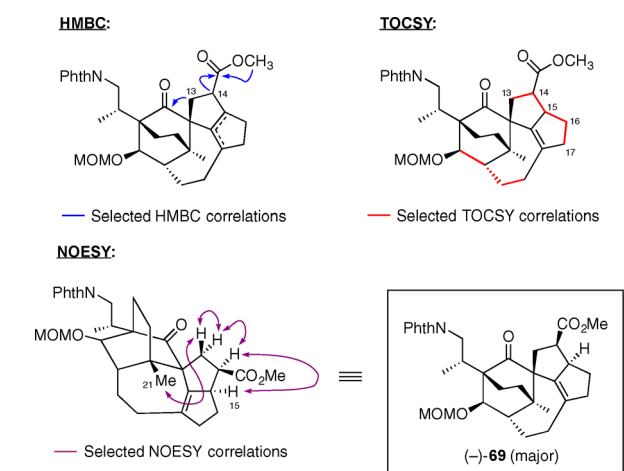
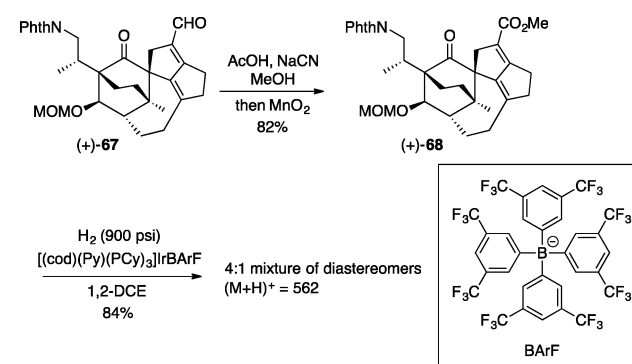
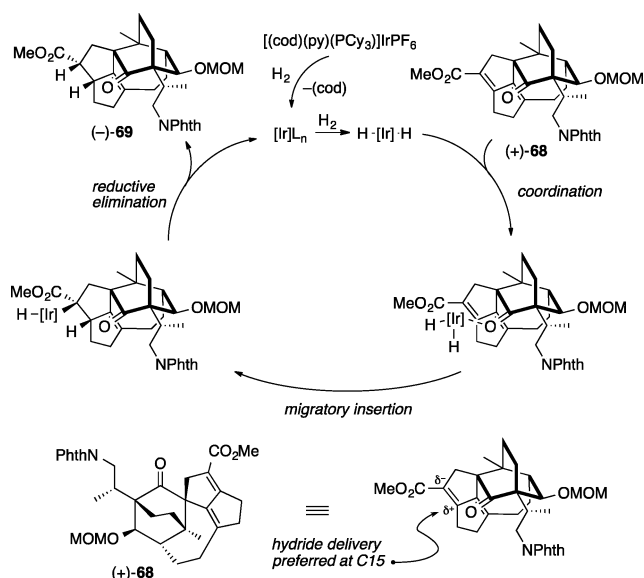


Figure 4. 2D NMR analysis of (–)-69.

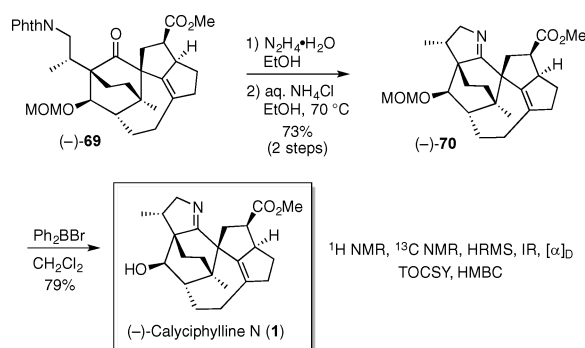
is that hydrogenation of (+)-68 is proceeding via a pathway that is mechanistically distinct from that of (+)-49. We propose that coordination of the iridium catalyst to the C1 carbonyl is now possible due to decreased steric congestion; migratory insertion then leads to the indicated homoallylic iridium species, which is incapable of the 1,4-reductive elimination pathway outlined earlier (Scheme 18). Consequently, standard reductive elimination then furnishes (–)-69 (Scheme 25). Given that iridium insertion to both C14 and C15 would proceed via 6-membered transition states, the observed outcome can be rationalized by considering the electronics of the migratory insertion step. The presence of the electron-withdrawing ester moiety results in greater positive charge at C15, thereby favoring hydride delivery to this center. The C9–C10 olefin resides far within the concavity of the molecule and is thus too sterically hindered to be reduced.

Removal of the phthalimide was then readily achieved by treatment of (–)-69 with hydrazine at room temperature (Scheme 26). The resulting amine pleasingly underwent intramolecular condensation to the imine by heating the ammonium salt (sat. NH₄Cl) in EtOH at 70 °C,⁵ thus providing penultimate intermediate (–)-70 in 73% yield over two steps. Removal of the MOM acetal with Ph₂BBr⁵⁴ completed construction of (–)-calyciphylline N (1), which displayed spectral and chiroptic properties in excellent agreement to the natural product [i.e., ¹H and ¹³C NMR (500 and 125 MHz, respectively), HRMS parent ion identification, and chiroptic properties].

Scheme 25. Proposed Mechanism for the Formation of (–)-69



Scheme 26. Total Synthesis of (–)-Calyciphylline N



SUMMARY

The first total synthesis of a calyciphylline alkaloid, (–)-calyciphylline N (1), has been achieved with a longest linear sequence of 37 steps from known alcohol (–)-8. Highlights of the successful synthesis include a substrate-controlled, intramolecular Diels–Alder reaction to construct the bicyclic core and set four contiguous stereocenters; a highly efficient one-pot Nazarov cyclization/proto-desilylation sequence, which in one flask completes ring E and activates the silicon moiety toward Fleming–Tamao oxidation, demonstrating the use of the 4-methoxyphenyl substituent as a readily introduced and easily replaced aryl group for the activation of otherwise unreactive hindered siloxanes; and finally, exploitation of a subtle structural change permitting chemo- and diastereoselective hydrogenation of an extremely hindered diene ester that installed the C14 and C15 stereogenic centers. In all, the strategies delineated herein should prove useful for the future synthesis of related members of this alkaloid class.

ASSOCIATED CONTENT

Supporting Information

Experimental details, spectra, and X-ray crystallography. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support was provided by the National Institutes of Health (National Cancer Institute) through CA-19033. We also thank Drs. George Furst, Rakesh Kohli, and Patrick Carroll for help obtaining high-resolution NMR, mass spectral, and X-ray data, respectively.

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