JOC The Journal of Organic Chemistry

Article

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Strategies toward the Total Synthesis of Calyciphylline B-type Alkaloids: A Computational Perspective Aided by DFT Analysis

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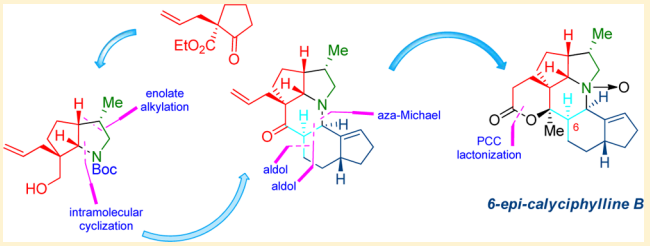
Supporting Information

ABSTRACT: Herein we describe synthetic efforts toward the total synthesis of calyciphylline B-type alkaloids. In the process, we disclose a detailed DFT study of equilibrium geometries and transition states that explains the stereochemical outcome during the formation of critical intermediates. X-ray crystallographic analysis reveals interesting conformational features in the naturally occurring deoxycalyciphylline B and its synthetic congeners.



INTRODUCTION

Since the first isolation of daphnimacrin by Yagi[1] in 1909, more than 320 *Daphniphyllum* alkaloids have been disclosed encompassing over 15 species. These complex azahexacyclic compounds are endowed with unique structural features as well as displaying a wide range of biological activities.[2] *Daphniphyllum* alkaloids were subdivided into 14 different classes that include the calyciphyllines. Calyciphylline B-type alkaloids are one of the subclasses of calyciphylline, which possess a complex hexa- or pentacyclic framework with eight or nine stereogenic centers, including one quaternary carbon center and a tertiary nitrogen atom.

In 2003, the Kobayashi group isolated calyciphylline B (**1**) from the leaves of *Daphniphyllum calycinum*, and its tentative structure was assigned by NMR spectroscopic analysis (Figure 1).[3] Calyciphylline B (**1**) exhibits cytotoxicity against murine lymphoma L1210 cells (IC_{50} 12 μM).[3] Since then, six new calyciphylline B-type alkaloids have been reported by the Yue[4a,b,d,e] and Hao[4c] groups (Figure 1). Deoxycalyciphylline B (**2**) and its C5-epimer deoxyisocalyciphylline B (**3**) were isolated from the stem of *Daphniphyllum subverticillatum*, and the structures were confirmed by X-ray analysis.[4a] Hexacyclic oldhamiphylline A (**4**) and daphnioldhanine J (**5**) were isolated from the stems and leaves of *Daphniphyllum longistylum*.[4b,c] Daphnioldhanine J exhibits strong activity against platelet aggregation induced by PAF.[4c] The pentacyclic methyl ester longistylumphyllline C (**6**) was isolated from the stem and leaves of *Daphniphyllum calycinum*, and its C5-epimer caldaphnidine R (**7**) was isolated from twigs of *D. calycinum*.[4d,e]

Most recently, Hao and co-workers[5] reported the isolation of daphlongamine H (**8**), a new calyciphylline B-type alkaloid, with an *unprecedented* C6/C7-*cis* ring junction, from the leaf extracts of the evergreen tree *Daphniphyllum longeracemosum* Rosenth.

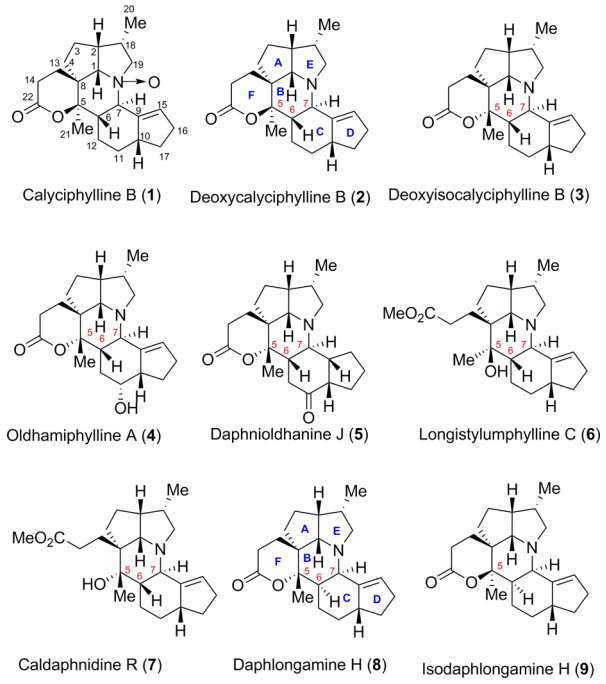


Figure 1. Calyciphylline B-type alkaloids.

A biosynthetic pathway to calyciphylline B-type alkaloids has been proposed by Kobayashi starting with squalene dialdehyde.[3] In an independent study, Yue[4a] has proposed a pathway to deoxycalyciphylline B and deoxyisocalyciphylline B that appears to differ from Kobayashi's in the manner in which the stereogenic centers at C6/C7 at the junction of the B/C rings

Received: March 24, 2016
Published: June 2, 2016

DOI: 10.1021/acs.joc.6b00638
J. Org. Chem. 2016, 81, 5074−5086

are created. Yue proposes a tertiary carbocation intermediate **A** that already has a *cis*-relationship of the C6/C7 hydrogens as found in daphlonganmine H (Figure 2). This is apparently

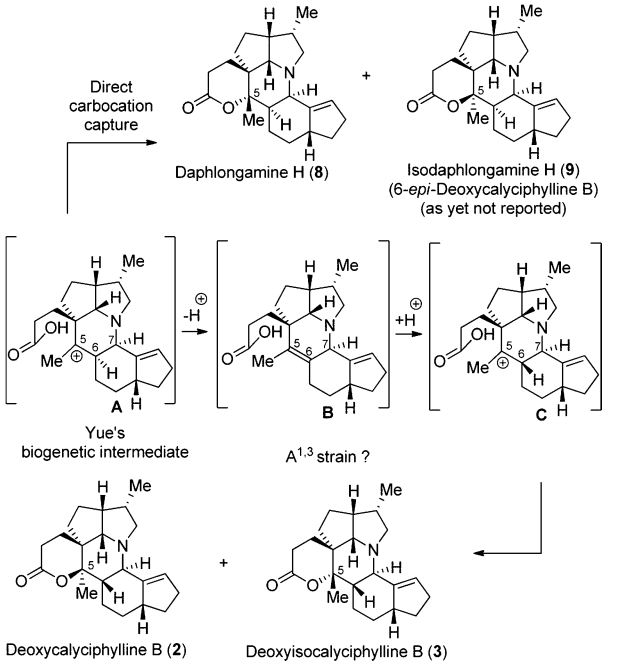


Figure 2. Yue's proposed biosynthetic pathway for deoxycalyciphylline and deoxyisocalyciphylline. The proposed pathway for daphlongamine H.[6]

followed by loss of a proton from C6 to give the tetrasubstituted neutral intermediate **B**, which is now reprotonated to generate the *trans*-6*S*/7*R* stereochemistry observed in all the calyciphylline B alkaloids except for daphlongamine H. We note that the proposed biosynthetic intermediate **B** could experience severe $A^{1,3}$ strain. Considering the Yue proposal,[4a] we suggest that intramolecular lactonization of intermediate **A** could lead *directly* to isodaphlongamine H (**9**) (or 6-*epi*-deoxycalyciphylline B), which can be considered as the "missing link" in the quartet of calyciphylline B alkaloids (Figure 1). Very recently, we reported on the total synthesis of isodaphlongamine H, which is the C5-epimer of daphlongamine H, and alluded to its possible occurrence, though as yet not isolated, in the same plant source.[6]

In the course of our synthetic studies toward the calyciphylline B-type alkaloids, we explored two approaches that led to pentacyclic intermediates albeit with the incorrect 6*R* stereochemistry at the B/C ring junction. In this paper, we delineate the synthesis of advanced intermediates and a detailed DFT analysis that convincingly rationalize the reasons for our failure to chemically alter the course of enolate-trapping experiments toward the expected 6*S*/7*R* stereochemistry at the B/C ring junction of deoxycalyciphylline B and deoxyisocalyciphylline B.

Since the pioneering efforts by Heathcock and co-workers[7] toward the total synthesis of *Daphniphyllum* alkaloids, only three new total syntheses have been disclosed, leading to daphmanidin E, daphenylline, and calyciphylline N by the groups of Carreira,[8] Li,[9] and Smith,[10] respectively. In contrast, a large volume of partial syntheses and syntheses of core subunits of varying structural and stereochemical complexities have been reported.[11] Except for our earlier reports,[6,12] to the best of our knowledge, no synthetic studies have been disclosed toward the calyciphylline B family of alkaloids.

RESULTS AND DISCUSSION

Aldol/Aza-Michael/Aldol Strategy. Our first strategy involved late-stage construction of a lactone ring and *N*-oxide formation to give calyciphylline B (**1**) from **10** (Figure 3). We

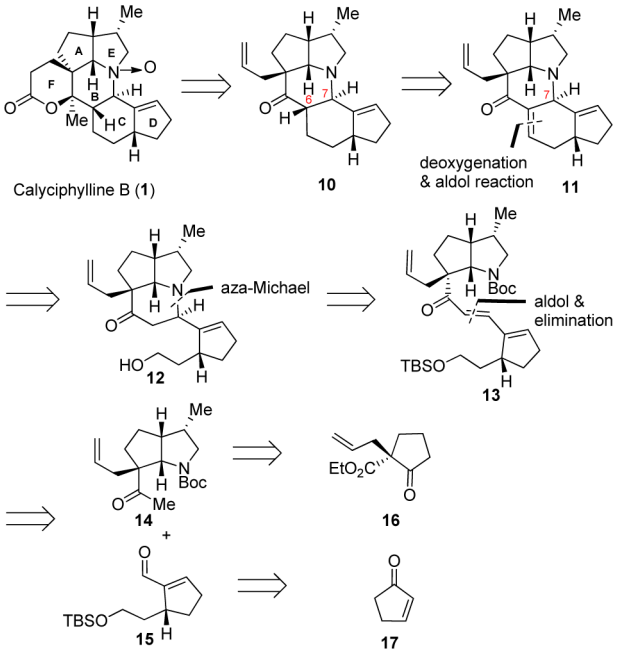
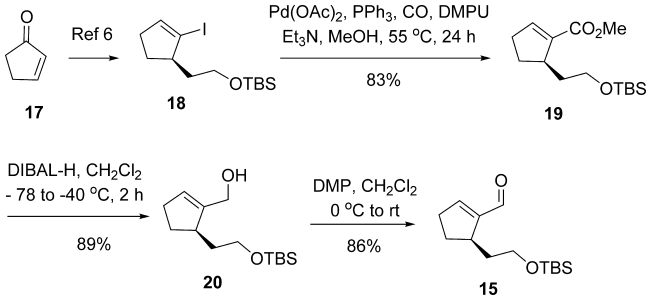


Figure 3. Retrosynthetic analysis of aldol/aza-Michael/aldol strategy.

envisaged that pentacycle **10** could be accessed from enone **11** via 1,4-conjugate hydride addition. Enone **11** could be obtained from **12** via an aldol-elimination reaction sequence. Continuing with the retrosynthetic analysis, intermediate **12** could be obtained via an aza-Michael reaction from dienone **13**, which would arise from an intermolecular aldol-elimination reaction starting from enantiomerically pure ketone **14** and aldehyde **15**. These could be prepared from known β-keto ester **16**[6,13] and cyclopentenone **17**, respectively.

A Pd(II)-mediated carbonylation[14] reaction of **18**[6] with carbon monoxide in methanol afforded methyl ester **19** in 83% yield (Scheme 1). A DIBAL-H reduction of **19**, followed by Dess–Martin periodinane oxidation,[15] afforded α,β-unsaturated aldehyde **15** in 76% yield over two steps.

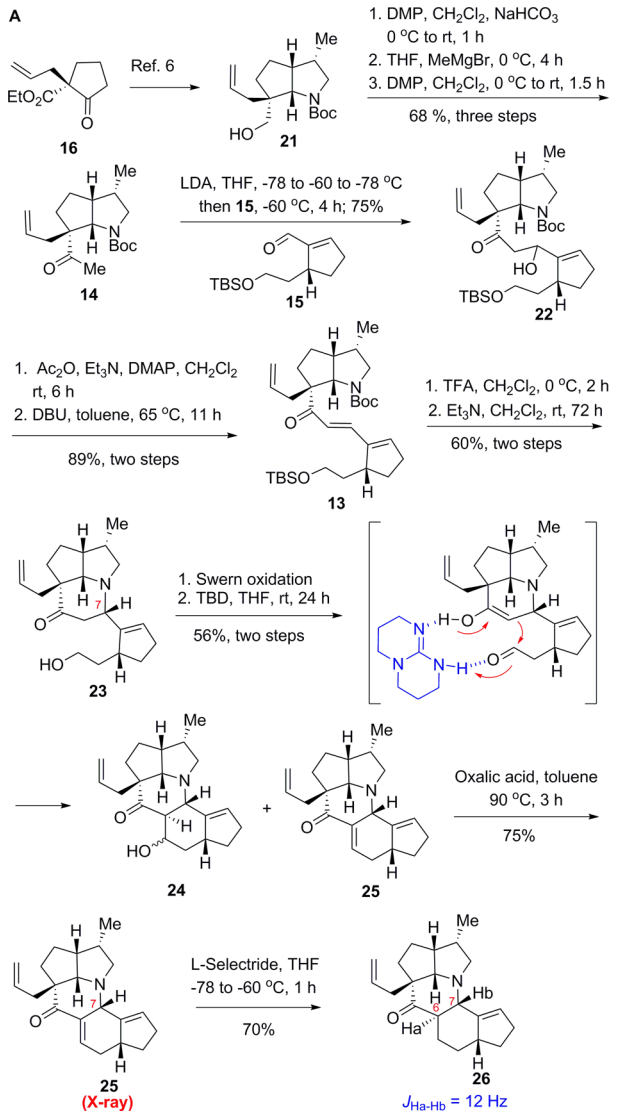
Scheme 1. Aldol/Aza-Michael/Aldol Strategy: Synthesis of the Cyclopentene Intermediate



DOI: 10.1021/acs.joc.6b00638
J. Org. Chem. 2016, 81, 5074–5086

In three consecutive steps, the azaoctahydropentalene intermediate **21**[6] was converted to methyl ketone **14** in 68% overall yield (Scheme 2). Treatment of **14** with LDA at −78 °C

Scheme 2. Aldol/Aza-Michael/Aldol Strategy: Synthesis of the Tricyclic Core



followed by addition of aldehyde **15** afforded the aldol product **22**, which was converted to dienone **13** in 67% yield over three steps. Treatment of **13** with TFA in dichloromethane gave the *N*-Boc-deprotected amine compound, which was further treated with triethylamine in dichloromethane to afford the aza-Michael adduct **23** in 60% yield over two steps. At this stage, the stereochemistry of the newborn chiral center could not be determined using NMR studies. Swern oxidation of **23**, followed by TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene)-mediated aldol reaction,[16] afforded a 1:3 mixture of *β*-hydroxy ketone **24** and *α*,*β*-unsaturated ketone **25** in 56% combined yield over two steps. The TBD-mediated intramolecular aldol reaction to produce **24** is of interest. We suggest that the reaction proceeds via a bifunctional H-bond mediated model, as shown in Scheme 2. The mixture was then further treated with oxalic acid in toluene at 90 °C to give the crystalline enone **25** in 75% yield. The structure and stereochemistry were determined by single crystal X-ray analysis,[17] which revealed that the stereochemistry at C7 was *opposite* to the one found in the natural product.

We attempted to isomerize the enone motif in **25** to an enaminone, to be followed by 1,4-conjugate hydride addition to obtain the desired 7*R* stereochemistry. Unfortunately, all of our efforts ($RuCl_3·H_2O$, EtOH, 100 °C, 24 h; $RhCl_3·H_2O$, EtOH, 100 °C, 24 h; Pd−C, MeOH, 60 °C, 24 h; $KOBu^t$, EtOH, 100 °C, 24 h) failed to isomerize the enone to enaminone, with recovery of starting material or conversion to unknown materials. Alternatively, treatment of **25** with L-Selectride led to the C6/C7 bis-*epi*-pentacycle **26**. The stereochemistry of the newborn chiral center was confirmed by NMR analysis, strongly suggesting that the J_{6-7} of 12 Hz corresponds to a *trans*-orientation. Various attempts to doubly invert the C6/C7 stereochemistry via retro-Mannich/Michael under neutral (imidazole, toluene, 150 °C; pyrrolidine, *p*-TSA, toluene, 150 °C; LDA-DIPEA, THF, rt), basic (NaOAc, AcOH, toluene, 150 °C), or acidic (*p*-TSA, toluene, 150 °C) conditions led to decomposition or recovery of unreacted **26**. Thus, although the aza-Michael step was successful, this approach led to the incorrect bis-*epi* stereochemistry at the B/C ring junction of calyciphylline B-type alkaloids.

Aldol/Aldol/Aza-Michael Strategy. In this approach, we envisaged an aza-Michael reaction as the last step toward constructing the pentacyclic ketone **10**, which would allow access to deoxycalyciphylline B and its C5 isocongener, deoxyisocalyciphylline B, after functional group manipulation. We further expected that the required stereocenters at C6 and C7 could be introduced in one step from a rigid bicyclic dienone **27**. A schematic presentation of our retrosynthetic analysis is shown in Figure 4. The bicyclic conjugated enone **27** could be obtained from **14** via a double aldol reaction strategy.

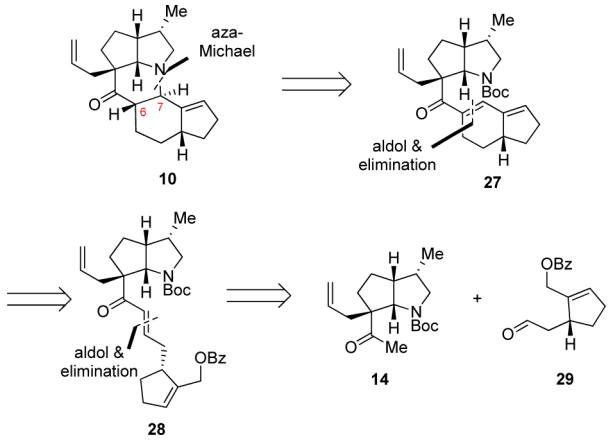


Figure 4. Retrosynthetic analysis of the aldol/aldol/aza-Michael strategy.

With aldehyde **29** readily prepared from **20** in three steps and 80% yield (Scheme 3A), an aldol reaction between the lithium enolate of **14** and **29** afforded **30**, which was further converted to the enone **28** in 51% yield over three steps (Scheme 3B). 1,4-Conjugate hydride addition to **28** with L-Selectride in Et_2O at −60 °C afforded **31** in 60% yield. Deprotection of the benzoate ester with NaOMe in methanol, followed by oxidation with the Dess−Martin periodinane[15] reagent, and an intramolecular aldol reaction mediated by TBD gave bicyclic *β*-hydroxy ketone **33** in 50% yield over three steps.

DOI: 10.1021/acs.joc.6b00638
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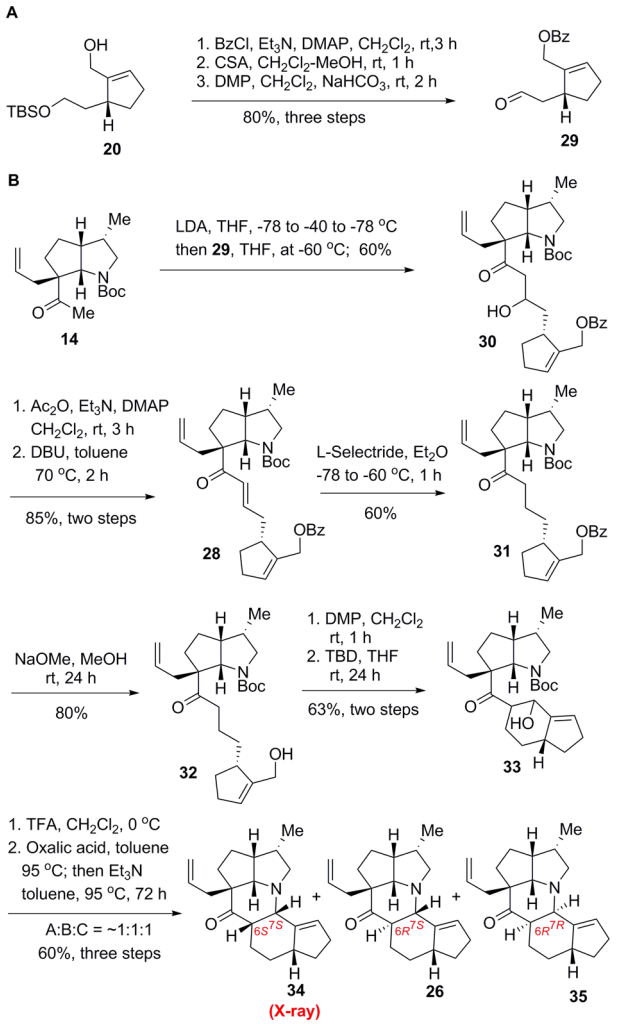
Scheme 3. Aldol/Aldol/Aza-Michael Strategy: (A) Synthesis of the Second Fragment and (B) Synthesis of the Pentacyclic Core

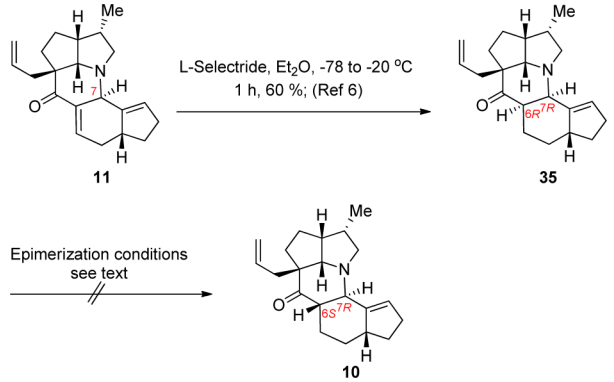


Treatment with TFA in dichloromethane to cleave the N-Boc group, followed by dehydration by heating with oxalic acid in toluene at 95 °C, produced the corresponding enone, which underwent an intramolecular aza-Michael reaction to give a separable mixture of azapentacycles **26**, **34**, and **35** in equal ratios. Interestingly, **34** undergoes a slow conversion to **26** upon silica gel column chromatography. The stereochemistry of **34** was confirmed by single crystal X-ray analysis.[17] In this approach, three of the four possible diastereoisomers at the B/C ring junction were formed, including **35**, which corresponds to the 6*R*/7*R*-*cis* stereochemisty present in daphlongamine H, as evidenced by detailed NMR studies. In spite of this small measure of success, the required 6*S*/7*R*-*trans* stereochemistry found in the other calyciphylline B alkaloids had once again eluded us.

C6 Epimerization, an Unresolved Mystery. An initial foray into the construction of a tetracyclic core structure using an iminium ion/enamine ring closure approach in a model compound led to a tetrasubstituted tetracyclic intermediate with the incorrect strereochemistry at C7 for deoxycalyciphyllin B.[12] It also became clear early on that this strategy would not lead to the desired stereochemistry at C7 when the appropriate bicyclic rings A and E were present.

In the course of our total synthesis of isodaphlongamine H,[6] we had developed a more direct way to access **35**. Thus, conjugate hydride reduction of enone **11**[6] with L-Selectride gave the 6*R*/7*R* diastereomer in 60% yield, confirming that quenching the corresponding enolate showed a high preference for the observed 6*R*/7*R* stereochemistry (Scheme 4).

Scheme 4. Attempts to Epimerize 35



Alternative methods of conjugate reduction with the hope of obtaining the desired 6*S*/7*R* stereochemistry were unsuccessful [Lipshutz (BDP)CuH reagent, toluene, 24 h; Stryker reagent, toluene−H_2O, 24 h; $Pd(PPh_3)_4$, Ph_2SiH_2, $ZnCl_2$, $CHCl_3$, rt; Li, liq NH_3, THF, −78 °C; K-Selectride, THF, −78 to −30 °C].

In order to obtain the required 6*S*/7*R*-*trans* junction in intermediate **10**, we proceeded to explore methods for the epimerization at C6 in intermediate **35** (Scheme 4). Under a variety of thermodynamic conditions (oxalic acid, toluene, 120 °C, 24 h; pivalic acid, 1,1,2-trichloroethane, 120 °C, 8 h; *p*-TSA, 1,1,2-trichloroethane, 120 °C, 8 h; DBU, toluene, 90 °C, 12 h; pyrrolidine, toluene, 120 °C, 12 h; imidazole, toluene, 120 °C, 12 h; azetidine, toluene, 90 °C, 12 h; NH_4Cl, H_2O−THF, 65 °C, 24 h; Et_3N·AcOH, toluene, 120 °C, 24 h; Et_3N·TFA, toluene, 120 °C, 24 h; Et_3N·oxalic acid, toluene, 120 °C, 24 h) and kinetic conditions (LDA, KHMDS, or LHMDS, THF, −78 to −30 °C, 1 h; KH, THF, 0 °C to rt, 20 h) only the 6*R*/7*R* starting product **35** was recovered. A priori, this led us to consider that enolate formation did not take place. Alternatively, we reasoned that the enolate was formed and existed as a stable enol metal-chelated entity that was eventually converted to the ketone upon further treatment or chromatography. Indeed, studies have shown that under certain conditions the enol form of cyclic ketones can exist as transient species.[18]

More curiously, quenching solutions of presumed enolates (generated with L- or K-Selectride from enone **11**/Li-, K-, or Na-HMDS from ketone **35**) with D_2O, MeOD, CD_3OD, or AcOH-D_4 never led to D-incorporation (as determined by MS, where the OD to OH exchange followed by tautomerization is rapid). Again, this result suggested that either the enolate was not formed or quenching led to the D-enol (or a metal-coordinated complex), which was eventually protonated externally during isolation. Formation of a trimethylsilyl enol ether to avoid proton return from the residual base was only partially complete and did not lead to deuteration.[18]

At this juncture, we had no other recourse but to study the equilibrium and transition state geometries of intermediates and their free energies by DFT calculations,[19] using the dispersion-corrected ωB97xD exchange−correlation functional[20] and the def2-TZVP basis set[21,22] (full computational details

DOI: 10.1021/acs.joc.6b00638
J. Org. Chem. 2016, 81, 5074−5086

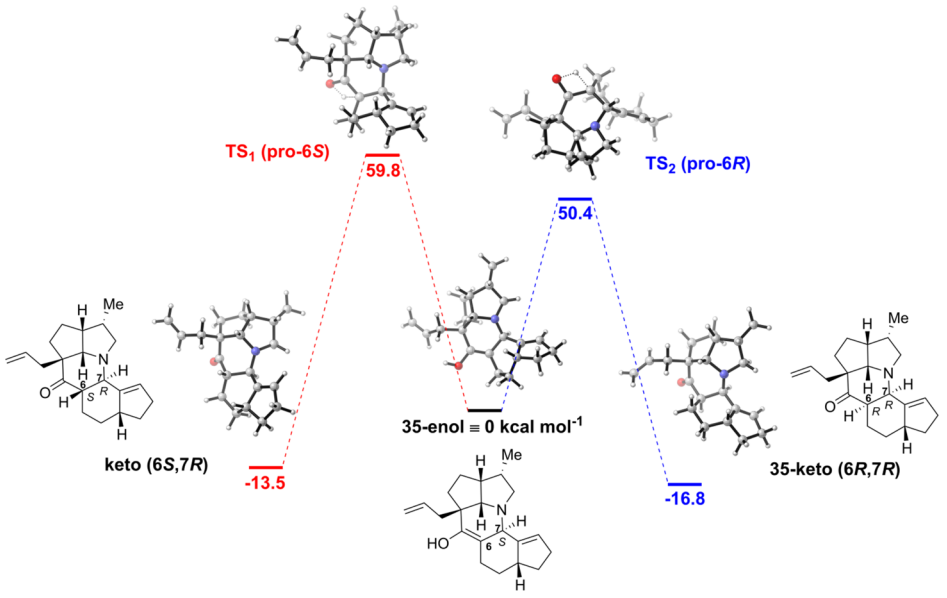


Figure 5. Energy diagram for the keto−enol tautomerism of the 7*R* isomer (gas phase).

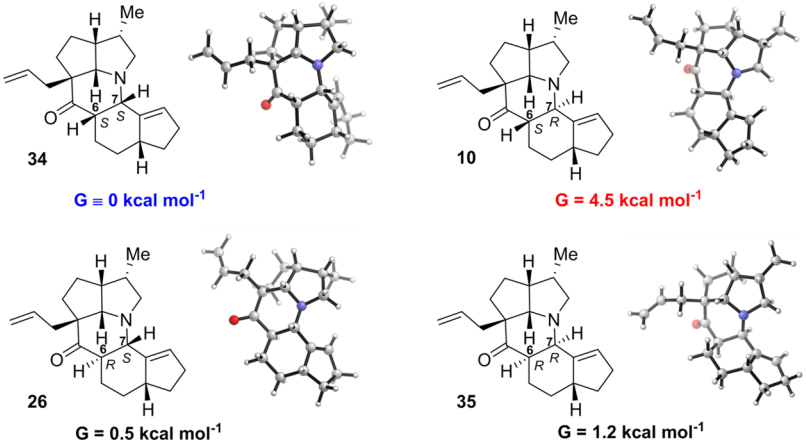


Figure 6. Comparison of the free energies for the three synthetic diastereomeric compounds and the inaccessible 6*S*/7*R* isomer.

can be found in the provided Supporting Information). When necessary, bulk solvent effects were included through the integral equation formalism variant of the polarizable continuum model (IEFPCM).[23]

We first investigated the keto−enol tautomerism of **35**. Taking the enol form of **35** as a starting point (arbitrarily set to 0 kcal mol^{-1}), the pro-6*R* transition state leading to the (6*R*/7*R*)-keto form ($\mathbf{TS_2}$) was found to be 9.4 kcal mol^{-1} lower in free energy than the pro-6*S* transition state ($\mathbf{TS_1}$). Consequently, the 6*R* ketone **35** was 3.3 kcal mol^{-1} more stable than the desired 6*S* epimer **10** (Figure 5), which may explain why the epimerization studies always led to the starting ketone **35**.

We also explored the reaction pathways for both the O- and C-quenching of the Li-enolate in water by DFT calculations. Transition structures for the aqueous C-quenching from both faces were first calculated: usage of the IEFPCM solvation model (water) leads to almost equal energies between both diastereomeric transitions states, showing nonsignificant preference (0.6 kcal mol^{-1}) for the bottom face attack ($\mathbf{TS_3}$, pro-6*R*), whereas this is reverted in the gas phase (2.6 kcal mol^{-1} in favor of the upper face quenching $\mathbf{TS_4}$, pro-6*S*). Aqueous quenching of the Li-enolate was then envisaged as the proton transfer to the enol oxygen (O-quenching). The hypothesis of an enol intermediate can be considered if the O-quenching is indeed of significantly lower activation energy than the C-quenching, which seems to be the case. The latter is found around 13 kcal mol^{-1}, whereas the activation barrier for the O-quenching ($\mathbf{TS_5}$) is much lower, around 2 kcal mol^{-1}.[19]

As mentioned earlier, a relatively stable deuterated-enol form could have been present upon treatment with various sources of ionizable deuterium reagents and the deuterium lost by exchange during the LC−MS analysis.

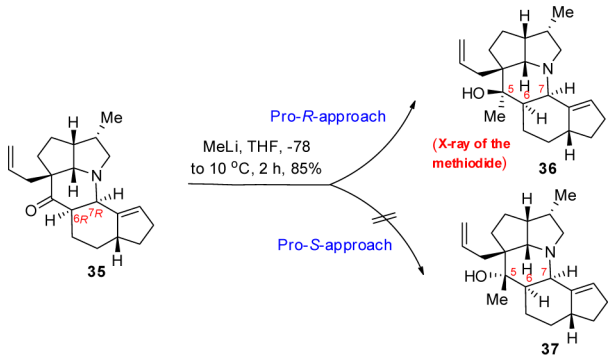
In the aldol/aldol/aza-Michael strategy discussed above, we obtained all three (6*S*/7*S*, 6*R*/7*S*, and 6*R*/7*R*) diastereomers except the desired 6*S*/7*R* isomer, which is found in calyciphylline B (Scheme 3). A geometry optimization starting from the crystal structure of diastereomer **34** (set as the 0 kcal mol^{-1} reference) showed that the "natural" 6*S*/7*R* diastereomer **10** possesses the highest energy compared to the other members of the quartet (Figure 6).

In our recent total synthesis directed toward daphlongamine H,[6] we explored various methods to achieve the 5*S* stereochemistry by addition of methyl Grignard, Me_3Al, and methyl

DOI: 10.1021/acs.joc.6b00638
J. Org. Chem. 2016, 81, 5074−5086

lithium reagents to the C5 carbonyl under a variety of conditions. Of these, only methyl lithium in THF (−78 to 10 °C, 2 h) led to a high yield of the 5*R* adduct (Scheme 5).

Scheme 5. MeLi Addition to Ketone 35



Curiously, methyl Grignard and Me_3Al returned unreacted ketone. In an effort to reverse the stereochemical outcome, we added ligands such as $LaCl_3 \cdot 2LiCl$ or Lewis acids such as $BF_3 \cdot Et_2O$. However, these reactions led to the same 5*R* isomer in lower yields.

DFT calculations indicated that the pro-5*R* and pro-5*S* transition state free energies for the addition of MeLi to **35** differ by 4.4 kcal mol^{-1}, favoring the 5*R* isomer (Figure 7).

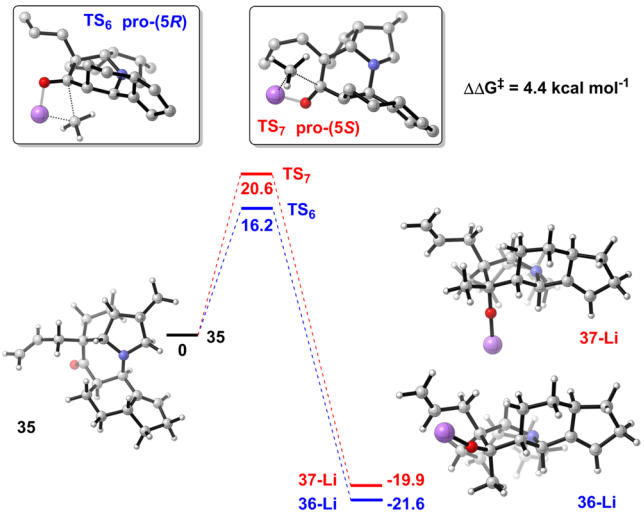


Figure 7. Free energy diagram for the stereoselective addition of MeLi.

The preceding results of DFT analyses of various intermediates favoring a *cis*-6*R*/7*R* ring junction in **35** led us to compare the X-ray crystal structures of natural deoxycalyciphylline B[4a] (**2**) with that of the recently reported isodaphlongamine H (**9** or 6-*epi*-deoxycalyciphylline B)[6] and to correlate energetic profiles by DFT analysis. Interestingly, in the crystal structure of deoxycalyciphylline B (**2**), ring C adopts a boat conformation,[4a] whereas in the crystal structure of synthetic isodaphlongamine H (**9** or 6-*epi*-deoxycalyciphylline B), ring C is in a chair conformation[6] (Figure 8).[17] Not surprisingly, DFT optimization revealed that 6-*epi*-deoxycalyciphylline B (**9**) is 3.4 kcal mol^{-1} more stable compared to its naturally occurring counterpart deoxycalyciphylline B (**2**).

In Figure 2, we show a biosynthetic pathway proposed by Yue leading to calyciphylline B-type alkaloids. Three inter-

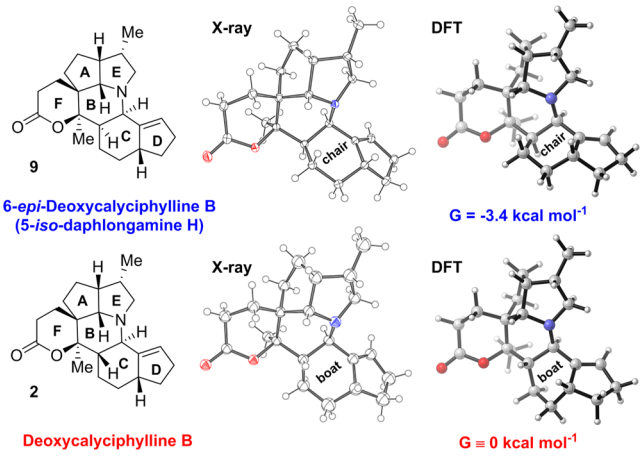


Figure 8. X-ray crystal structures and DFT energy-minimized structures of 6-*epi*-deoxycalyciphyllline B and deoxycalyciphylline B. Thermal ellipsoids drawn at the 50% probability level.

mediates, designated as **A**, **B**, and **C**, were proposed in generating the intended target alkaloids. Cognizant of the nature of the tetrasubstituted neutral intermediate **B**, which could experience severe $A^{1,3}$ strain, we performed DFT calculations to assess energy states of the proposed neutral and carbocationic intermediates (Figure 9). Starting with **B** at G = 0 kcal mol^{-1}, the carbocationic intermediates **A** with (C6/C7-*cis*) and **C** (C6/C7-*trans*) junctions have very similar free energies. In both cases, the B-ring boat conformation is found to be disfavored (around 9 kcal mol^{-1}) in comparison to the twist-boat. The conformational pattern that is observed by DFT calculations in the cyclohexane ring C in the natural lactone products **2**, **3**, and **8** and the synthetic congener **9** is in agreement with the X-ray results for deoxycalyciphylline B (**2**),[4a] and 6-*epi*-deoxycalyciphylline B (**9**) (or isodaphlongamine H).[6] The lowest energy conformation for daphlongamine H (**8**) and deoxyisocalyciphylline B (**3**), for which there are no X-ray structures, was also calculated (Figure 9). The cyclohexane ring C in the C6/C7-*cis*-isomers **8** and **9** adopts a chair form with favorable minimum energy values of −3.3 and −12.2 kcal mol^{-1}, respectively, compared to the tetrasubstituted neutral biosynthetic intermediate **B**. Deoxycalyciphylline B (**2**) and its 5-*epi*-isomer deoxyisocalyciphylline B (**3**) exhibit boat conformations for ring C with energy values that are less favorable than the C6/C7-*cis*-congeners **8** and **9**. Thus, DFT analysis has revealed that the synthetic 6-*epi*-deoxycalyciphylline B (**9**) (or isodaphlongamine H) is more stable compared to the naturally occurring triad of daphlongamine H (**8**), deoxycalyciphylline B (**2**), and deoxyisocalyciphylline B (**3**) (Figure 9).

The natural product calyciphylline B has been reported to have activity against the L1210 cancer cell line.[3] In our previous report,[6] we communicated the in vitro activity of 6-*epi*-deoxycalyciphylline B (**9**, isodaphlongamine H) against a panel of NCI human cancer cell lines and found activity against four cell lines at GI_{50} 35−43 μM. Since the original activity was reported for calyciphylline B, which is an *N*-oxide, we converted our synthetic 6-*epi*-deoxycalyciphylline B (**9**, isodaphlongamine H) to the corresponding *N*-oxide **38** (6-*epi*-calyciphilline B), which was found to be half as active compared to deoxycalyciphylline B in the above cell lines (Scheme 6).

In conclusion, we have discussed various approaches toward the total synthesis of the calyciphylline B-type and related

DOI: 10.1021/acs.joc.6b00638
J. Org. Chem. 2016, 81, 5074−5086

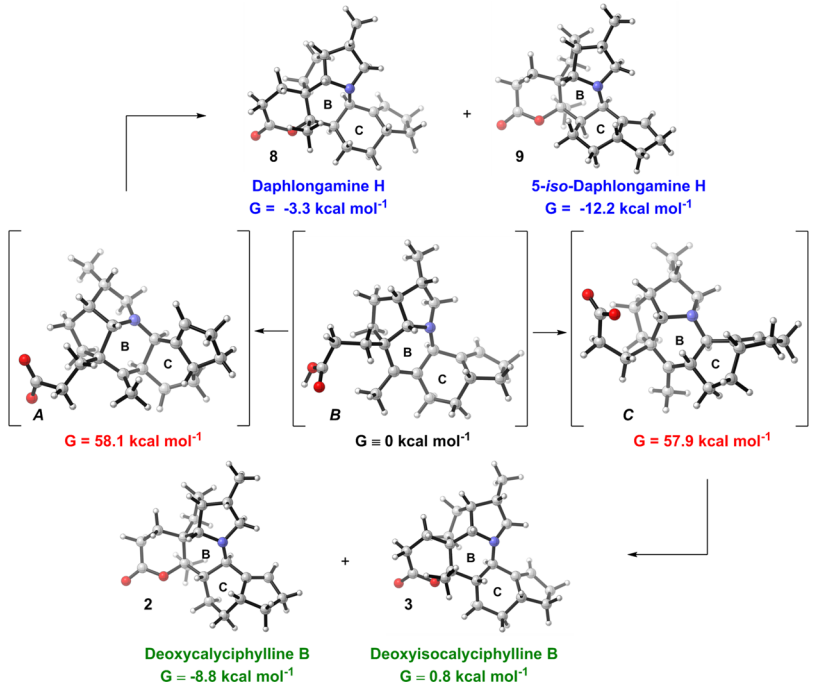
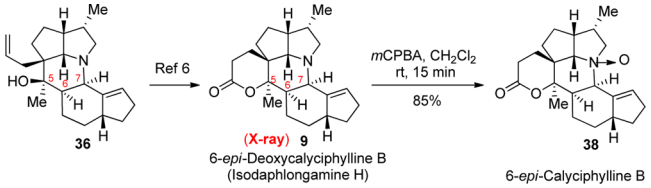


Figure 9. Proposed biosynthetic path from the common intermediate **B** and their DFT free energies in the gas phase.

Scheme 6. Synthesis of 6-*epi*-Calyciphylline B



alkaloids. Although the initial goal of securing the desired 6*S*/7*R* stereochemistry remains to be achieved, we have uncovered interesting aspects about the biosynthesis of this family of *Daphniphyllum* alkaloids and the possible intermediacy of high-energy intermediates. Furthermore, we have come to appreciate the value of performing computational studies using DFT, which provided convincing rationales to explain the recalcitrant enolate chemistry leading to the apparently more stable 6*R*/7*R* diastereomer. In hindsight, had we performed such analyses prior to experimentation, we would have most likely considered alternative bond construction strategies for deoxycalyciphylline B and its congeners. Nevertheless, one of the strategies used herein provided an advanced intermediate to achieve the total synthesis of the antitumor alkaloid 6-*epi*-deoxycalyciphylline B (isodaphlongamine H),[6] which we suggest could exist in the same plant source as daphlongamine H.

EXPERIMENTAL SECTION

All nonaqueous reactions were performed in flame-dried glassware under a positive pressure of argon. Anhydrous solvents were obtained using standard drying techniques. Commercial-grade reagents were used without further purification. Reactions were monitored by analytical thin-layer chromatography (TLC) performed on commercially available precoated, glass-backed silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance or aqueous potassium permanganate. Flash chromatography was performed on 230−400 mesh silica gel with the indicated solvent systems. Infrared spectra were recorded on a FT-IR spectrometer and are reported in reciprocal centimeters (cm^{-1}). Routine nuclear magnetic resonance spectra were recorded on a 400 MHz spectrometer and in some cases a 700 MHz spectrometer. Chemical shifts for ^1H NMR spectra were recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$, δ 7.26 ppm; CD_3OD, δ 3.31 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet and br = broad), and coupling constant in hertz. Chemical shifts for ^{13}C NMR spectra were recorded in parts per million from tetramethylsilane using the central peak of the solvent resonance as the internal standard ($CDCl_3$, δ 77.00 ppm; CD_3OD, δ 49.00). All spectra were obtained with complete proton decoupling. Optical rotations were determined at 589 nm at ambient temperature, and data are reported as follows: $[\alpha]_D$ (concentration *c* in g/100 mL, solvent). High-resolution mass spectra were performed on a LC−MSD-TOF instrument using fast atom bombardment (FAB) or electrospray ionization (ESI) techniques. Protonated molecular ions $(M + H)^+$ and (or) sodium adducts $(M + Na)^+$ were used for empirical formula confirmation.

Experimental procedures and characterization data of compounds **9** and **36** have been reported previously.

(*R*)-Methyl 5-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-cyclopent-1-enecarboxylate (19). To a stirred solution of compound **18** (2 g, 5.68 mmol) in MeOH (14 mL) were added DMPU (11 mL), Et_3N (1.6 mL, 11.66 mmoL), PPh_3 (150 mg, 0.568 mmol), and $Pd(OAc)_2$ (130 mg, 0.568 mmol) sequentially, and the combined mixture was stirred for another 5 min under argon. Then, CO gas was purged over 10 min, and a CO gas balloon was placed over the reaction vessel. The reaction mixture was gradually heat up to 55 °C, and stirring was continued for another 24 h. Then, the reaction mixture was cooled down to room temperature and diluted with dithyl ether. The organic layer was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc−hexanes = 5/95) to give the TBS ether **19** (1.4 g, 83%) as a colorless liquid.

R_f = 0.5 (10% EtOAc−hexanes), [$KMnO_4$], UV visible; $[\alpha]_D^{20}$ = +10.0 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} = 2952, 2927, 2857, 1720, 1436, 1255, 1196, 1095, 834, 774, 631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.79−6.71 (m, 1H), 3.71 (s, 3H), 3.69−3.61 (m, 2H), 2.98 (s, 1H), 2.55−2.43 (m, 1H), 2.43−2.32 (m, 1H), 2.15−2.05 (m, 1H), 2.05−1.95 (m, 1H), 1.80−1.70 (m, 1H), 1.48−1.38 (m, 1H), 0.88 (s, 9H), 0.04 (2s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 143.9, 139.7,

DOI: 10.1021/acs.joc.6b00638
J. Org. Chem. 2016, 81, 5074−5086

62.0, 51.2, 41.2, 36.5, 31.6, 29.5, 25.9, 18.3, −5.3, −5.4; HRMS-ESI (m/z) calcd for $C_{15}H_{28}O_3Si$ $[M + H]^+$ 285.1881, found 285.1876.

(*R*)-(5-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)cyclopent-1-en-1-yl)methanol (20). To a stirred solution of compound **19** (1.3 g, 4.58 mmol) in CH_2Cl_2 (12 mL) at −78 °C was added DIBAL-H (1.5 M in toluene) (9.2 mL, 13.73 mmol) dropwise. The reaction mixture was stirred for 1 h at the same temperature and gradually warmed up to −60 °C over another 1 h. Then, the reaction mixture was quenched with MeOH and gradually warmed up to 0 °C. A 10% aqueous solution of sodium potassium tartarate was added to the reaction mixture and it was vigorously stirred for 1 h. The biphasic layers were extracted with DCM, and combined extracts were dried over anhydrous Na_2SO_4. The organic layer was then concentrated under reduced pressure and flash chromatography with 20% EtOAc−hexanes to give the title compound **20** (1.05 g, 89%) as a colorless liquid.

R_f = 0.35 (20% EtOAc−hexanes), [$KMnO_4$], not seen in UV; $[\alpha]_D^{20}$ = −7.6 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} = 3334, 2953, 2928, 2857, 1472, 1255, 1099, 833, 774, 631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.60 (d, J = 1.3 Hz, 1H), 4.22−4.11 (m, 2H), 3.74−3.58 (m, 2H), 2.75 (s, 1H), 2.36−2.18 (m, 2H), 2.15−2.02 (m, 2H), 1.89−1.78 (m, 1H), 1.60−1.49 (m, 1H), 1.47−1.37 (m, 1H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 125.9, 62.0, 60.9, 41.9, 36.6, 30.8, 30.5, 25.9, 18.3, −5.4, −5.4; HRMS-ESI (m/z) calcd for $C_{14}H_{28}O_2Si$ $[M + H]^+$ 257.1931, found 257.1927.

(*R*)-5-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)cyclopent-1-enecarbaldehyde (15). To a stirred solution of compound **20** (1 g, 3.91 mmol) at 0 °C were added $NaHCO_3$ (948 mg, 11.72 mmol) and DMP (2.5 g, 5.86 mmol) successively. The reaction mixture was then gradually warmed up to room temperature over 45 min. After 30 min the reaction mixture was quenched with aqueous saturated $Na_2S_2O_3$ and $NaHCO_3$ solution and stirred for an additional 20 min. The biphasic layers were extracted with DCM and combined extracts were dried over anhydrous Na_2SO_4. The organic phase was then concentrated under reduced pressure, and flash chromatography with 6% EtOAc−hexanes afforded compound **15** (855 mg, 86%) as a colorless liquid.

R_f = 0.2 (10% EtOAc−hexanes), [$KMnO_4$], UV visible; $[\alpha]_D^{20}$ = +23.4 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} = 2927, 2855, 1681, 1461, 1386, 1360, 1252, 1097, 832, 774, 632 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 6.82 (td, J = 2.6, 1.5 Hz, 1H), 3.72−3.58 (m, 2H), 3.02 (s, 1H), 2.68−2.55 (m, 1H), 2.54−2.41 (m, 1H), 2.22−2.11 (m, 1H), 2.10−2.00 (m, 1H), 1.88−1.75 (m, 1H), 1.49−1.35 (m, 1H), 0.88 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.8, 153.6, 150.6, 61.9, 39.3, 36.0, 32.1, 23.0, 25.9, 18.3, −5.3, −5.4; HRMS-ESI (m/z) calcd for $C_{14}H_{26}O_2Si$ $[M + H]^+$ 255.1775, found 255.1780.

(3*S*,3a*R*,6*S*,6a*S*)-*tert*-Butyl 6-Acetyl-6-allyl-3-methylhexahydrocyclopenta[*b*]pyrrole-1(2*H*)-carboxylate (14). To a stirred solution of compound **21** (950 mg, 3.22 mmol) in dichloromethane (15 mL) at room temperature were added DMP (2 g, 4.83 mmol) and $NaHCO_3$ (812 mg, 9.66 mmol) sequentially. The stirring was continued for 1−3 h, and then the reaction mixture was quenched with saturated aqueous solution of $Na_2S_2O_3$ and $NaHCO_3$. The reaction mixture was stirred for an additional 30 min and then extracted with $CHCl_3$ three times. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and flash column chromatography with 10% EtOAc−hexanes afforded the corresponding aldehyde (858 mg, 91%) as colorless liquid.

R_f = 0.25 (10% EtOAc−hexanes), [$KMnO_4$], not seen in UV; $[\alpha]_D^{20}$ = −14.0 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} = 2966, 1720, 1687, 1395, 1366, 1253, 1164, 1114, 915, 631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.49 (d, J = 15.0 Hz, 1H), 5.81−5.51 (m, 1H), 5.18−4.97 (m, 2H), 4.11 (2d, J = 16.0 Hz, 1H), 3.73 (2dd, J = 11.0, 7.5 Hz, 1H), 3.05−2.55 (m, 3H), 2.37−2.23 (m, 1H), 2.19−1.93 (m, 2H), 1.73−1.52 (m, 2H), 1.45 (2s, 9H), 1.52−1.17 (m, 2H), 0.95 (2d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.1, 203.2, 154.9, 154.1, 133.8, 133.5, 118.2, 118.1, 80.7, 79.7, 71.0, 70.6, 60.9, 59.6, 51.8, 51.5, 49.3, 48.1, 39.6, 38.4, 34.5, 34.2, 32.2, 31.8, 28.4, 28.3, 24.4, 24.2, 12.5.; HRMS-ESI (m/z) calcd for $C_{17}H_{27}NO_3$ $[M + Na]^+$ 316.1883, found 316.1892.

The aldehyde (900 mg, 3.07 mmol) was dissolved in THF (10 mL) at 0 °C and commercial 3 M methyl magnesium bromide (1.6 mL, 4.61 mmol) was added drop-by-drop. The reaction mixture was stirred for another 3 h and then quenched with aqueous saturated NH_4Cl solution. The biphasic layer was extracted with EtOAc three times and concentrated under reduced pressure. The crude residue was redissolved in 30 mL of dichloromethane and passed through a small pad of anhydrous Na_2SO_4, and the clear solution was evaporated to dryness. The alcohol was dried on a vacuum pump over 1 h and used for the next reaction.

To a stirred solution of the crude alcohol in dichloromethane (10 mL) were added DMP (3.9 g, 9.21 mmol) and (516 mg, 6.14 mmol) solid $NaHCO_3$ portionwise at room temperature. After 2 h, the reaction was quenched with aqueous $Na_2S_2O_3$ solution. After 5 min, a saturated aqueous $NaHCO_3$ solution was added drop-by-drop and stirring was continued for another 30 min. The biphasic layers were extracted three times with dichloromethane, and the combined organic layer was washed with a saturated aqueous solution of $NaHCO_3$ and brine sequentially. The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. Flash column chromatography with 7% EtOAc−hexanes afforded ketone **14** (710 mg, 75%) over two steps as a colorless oil.

R_f = 0.3 (10% EtOAc in hexanes), [$KMnO_4$], not seen in UV; $[\alpha]_D^{20}$ = −10.0 (*c* = 1.0, $CHCl_3$); IR (neat) ν_{max} = 2965, 1693, 1392, 1365, 1250, 1160, 1112, 916, 773, 630 cm^{-1}; both ^1H and ^{13}C NMR spectra contain Boc rotamer peaks; ^1H NMR (400 MHz, $CDCl_3$) δ 5.63 (td, J = 16.7, 7.1 Hz, 1H), 5.15−5.00 (m, 2H), 4.35−4.05 (2brs, 1H), 3.95−3.55 (2brs, 1H), 3.08−2.80 (2brs, 1H), 2.74−2.60 (m, 1H), 2.54 (t, J = 11.6 Hz, 1H), 2.36−1.96 (m, 6H), 1.83−1.68 (m, 1H), 1.60−1.28 (m, 11H), 0.94 (d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1, 155.1, 134.4, 117.9, 79.6, 71.8, 63.4, 52.2, 47.5, 41.5, 35.0, 34.5, 34.0, 28.3, 28.1, 24.7, 12.2; HRMS-ESI (m/z) calcd for $C_{18}H_{29}NO_3$ $[M + H]^+$ 308.2220, found 308.2236.

(3*S*,3a*R*,6*S*,6a*S*)-*tert*-Butyl 6-Allyl-6-(3-((*R*)-5-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)cyclopent-1-en-1-yl)-3-hydroxypropanoyl)-3-methylhexahydrocyclopenta[*b*]pyrrole-1(2*H*)-carboxylate (22). To a stirred solution of compound **14** (700 mg, 2.28 mmol) in THF at −78 °C was added 0.4 M LDA in THF (8.6 mL, 3.42 mmol). Then the reaction mixture was gradually warmed up to −40 °C over 1 h. The reaction mixture was again cooled down to −78 °C and a 0.1 M solution of aldehyde **15** in THF (637 mg, 2.5 mmol) was cannulated into the mixture. Then the reaction mixture was gradually warmed up to −60 °C over 1 h and the reaction continued for an additional 4 h at the same temperature. After completion, the reaction was quenched with MeOH, diluted with water, and extracted with EtOAc. The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. Flash column chromatography with 6% EtOAc−hexanes afforded ketone **22** (960 mg, 75%), as a colorless oil. The reaction progressed with varying yields of 50−75% with 40−10% recovery of the starting material.

R_f = 0.2 (6% EtOAc in hexanes), [$KMnO_4$], not seen in UV; $[\alpha]_D^{20}$ = −19.7 (*c* = 1.0, $CHCl_3$); IR (neat) ν_{max} = 3430, 2930, 2858, 1690, 1460, 1394, 1366, 1255, 1163, 1104, 912, 835, 775, 709, 631 cm^{-1}; both ^1H and ^{13}C NMR spectra contain Boc rotamer peaks; ^1H NMR (400 MHz, $CDCl_3$) δ 5.70 (s, 1H), 5.68−5.49 (m,1H), 5.19−4.98 (m, 2H), 4.66−4.47 (m, 1H), 4.25−4.10 (m, 1H), 3.79−3.51 (m, 3H), 2.96−2.45 (m, 5H), 2.38−1.93 (m, 7H), 1.87−1.66 (m, 2H), 1.52 (s, 2H), 1.49−1.26 (m, 12H), 0.94 (t, J = 13.8 Hz, 3H), 0.87 (2s, 9H), 0.02 (2s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.8, 155.3, 148.5, 147.8, 134.0, 124.4, 118.4, 80.2, 72.1, 64.9, 63.2, 61.8, 52.6, 47.3, 46.3, 41.8, 41.5, 39.8, 36.7, 36.4, 35.2, 33.1, 30.8, 30.7, 30.3, 30.1, 28.4, 28.3, 28.0, 25.9, 23.5, 18.3, 12.4, −5.3, −5.4; HRMS-ESI (m/z) calcd for $C_{32}H_{55}NO_5Si$ $[M + Na]^+$ 584.3742, found 584.3752.

(3*S*,3a*R*,6*S*,6a*S*)-*tert*-Butyl 6-Allyl-6-((*E*)-3-((*R*)-5-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)cyclopent-1-en-1-yl)acryloyl)-3-methylhexahydrocyclopenta[*b*]pyrrole-1(2*H*)-carboxylate (13). To a stirred solution of compound **22** (900 mg, 1.60 mmol) in CH_2Cl_2 (8 mL) at room temperature were added Et_3N (0.7 mL, 4.8 mmol), Ac_2O (0.25 mL, 2.40 mmol), and DMAP (40 mg, 0.32 mmol) sequentially. After 6 h, the reaction mixture was quenched with

DOI: 10.1021/acs.joc.6b00638
J. Org. Chem. 2016, 81, 5074−5086

NH_4Cl, extracted with $CHCl_3$, washed with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated under reduced pressure. Flash column chromatography of the crude residue with 6−20% EtOAc−hexanes afforded the corresponding acetate (925 mg, 96%), as a colorless oil.

R_f = 0.2 (6% EtOAc in hexanes), [$KMnO_4$], not seen in UV; $[\alpha]_D^{20}$ = −2.5° (*c* = 1.0, $CHCl_3$); IR (neat) ν_{max} = 2931, 2856, 1742, 1690, 1473, 1394, 1366, 1244, 1162, 1104, 913, 835, 775, 743, 631 cm^{-1}; both ^1H and ^{13}C NMR spectra contain Boc rotamer peaks; ^1H NMR (400 MHz, $CDCl_3$) δ 5.87−5.36 (m, 3H), 5.18−5.01 (m, 2H), 4.36−4.12 (m, 1H), 3.89−3.51 (m, 3H), 3.24−2.83 (m, 2H), 2.80−2.48 (m, 3H), 2.47−2.09 (m, 5H), 2.09−1.96 (brs, 5H), 1.91−1.66 (m, 2H), 1.66−1.51 (m, 1H), 1.45 (s, 9H), 1.40 (d, *J* = 12.7 Hz, 3H), 0.92 (m, 3H), 0.90−0.81 (m, 9H), 0.03 (2s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.0, 184.6, 169.9, 169.6, 163.4, 155.6, 147.5, 145.6, 139.6, 134.7, 128.6, 124.6, 122.5, 118.2, 79.7, 77.3, 72.7, 67.4, 61.8, 61.6, 51.6, 48.0, 43.2, 42.7, 42.1, 41.7, 41.5, 36.8, 36.0, 35.8, 34.7, 30.6, 30.2, 29.9, 28.5, 28.4, 28.3, 28.0, 26.0, 21.2, 18.3, 12.2, 11.9, −5.3, −5.4; HRMS-ESI (*m*/*z*) calcd for $C_{34}H_{57}NO_6Si$ $[M + Na]^+$ 626.3847, found 626.3860.

To a stirred solution of acetate (900 mg, 1.5 mmol) in toluene (30 mL) at room temperature was added DBU (1.1 mL, 7.46 mmol). The reaction mixture was gradually heated to 65 °C and the reaction continued for an additional 11 h at the same temperature. The reaction was cooled down to room temperature, concentrated under reduced pressure, and purified by flash column chromatography with 4% EtOAc−hexanes, to give conjugated enone **13** (753 mg, 93%) as a colorless liquid.

R_f = 0.35 (6% EtOAc in hexanes), [$KMnO_4$], UV visible; $[\alpha]_D^{20}$ = −5.0 (*c* = 1.0, $CHCl_3$); IR (neat) ν_{max} = 2931, 2856, 1680, 1606, 1584, 1472, 1393, 1365, 1255, 1164, 1107, 913, 835, 775, 743, 631 cm^{-1}; both ^1H and ^{13}C NMR spectra contain Boc rotamer peaks; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 18.3 Hz, 1H), 6.52 (2d, *J* = 15.3 Hz, 1H), 6.09 (s, 1H), 5.8−5.5 (m, 1H), 5.15−4.90 (m, 2H), 4.39−4.01 (m, 1H), 3.86−3.50 (m, 3H), 3.17 (dd, *J* = 14.0, 6.2 Hz, 1H), 2.97 (brs, 1H), 2.64 (m, 1H), 2.45 (m, 2H), 2.38−2.23 (m, 2H), 2.23−1.71 (m, 6H), 1.70−1.45 (m, 2H), 1.46−1.21 (m, 10H), 0.99−0.78 (m, 12H), 0.03 (2s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 154.8, 145.9, 140.6, 139.7, 137.1, 136.0, 135.1, 134.4, 123.8, 122.8, 117.7, 79.1, 72.7, 72.0, 61.9, 61.8, 52.0, 51.5, 48.9, 47.8, 42.4, 41.5, 40.5, 35.8, 35.3, 34.8, 31.5, 29.6, 28.3, 26.0, 25.7, 18.3, 12.1, −5.3; HRMS-ESI (*m*/*z*) calcd for $C_{32}H_{53}NO_4Si$ $[M + Na]^+$ 566.3636, found 566.3635.

(1*S*,3^1*S*,4*S*,6a*S*,8a*R*)-6a-Allyl-4-((*R*)-5-(2-hydroxyethyl)-cyclopent-1-en-1-yl)-1-methyloctahydrocyclopenta[*hi*]-indolizin-6(3^1*H*)-one (23). To a stirred solution of compound **13** (120 mg, 0.221 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added TFA (0.5 mL); stirring was continued for 1 h at 0 °C and for 1 h at room temperature. Then TFA was removed by azeotroping with anhydrous CH_2Cl_2 and the residue was dried in a vacuum for 1 h. The Boc-deprotected compound was dissolved in anhydrous CH_2Cl_2 (3 mL) at room temperature, and Et_3N (0.2 mL, 1.40 mmol) was added to the reaction mixture. Then stirring was continued for 36−72 h and the mixture was concentrated under reduced pressure. Flash column chromatography of the crude mass with 60% EtOAc−hexanes afforded ketone **23** (44 mg, 60%) over two steps as a yellow liquid. Before loading the crude mass, the silica gel column was flashed with 10% NH_4OH−hexanes.

R_f = 0.35 (60% EtOAc in hexanes), [$KMnO_4$], not visible in UV; $[\alpha]_D^{20}$ = +39.4 (*c* = 1.0, $CHCl_3$); IR (neat) ν_{max} = 3432, 2926, 1698, 1444, 1331, 1219, 1062, 915, 738, 631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.74−5.62 (m, 1H), 5.53−5.49 (m, 1H), 5.08−4.99 (m, 2H), 4.12 (brd, *J* = 9.4 Hz, 1H), 3.76 (d, *J* = 7.8 Hz, 1H), 3.74−3.62 (m, 2H), 2.84 (brs, 1H), 2.76−2.63 (m, 2H), 2.46 (dt, *J* = 14.8, 6.0 Hz, 1H), 2.48 (d, *J* = 5.0 Hz, 1H), 2.34 (d, *J* = 7.5 Hz, 2H), 2.30−2.09 (m, 6H), 2.04 (dd, *J* = 10.6, 9.1 Hz, 1H), 1.81−1.64 (m, 2H), 1.60−1.45 (m, 2H), 1.37−1.27 (m, 2H), 0.91 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.8, 147.4, 134.0, 127.3, 118.2, 73.6, 62.0, 58.7, 52.6, 50.8, 47.4, 42.0, 41.8, 37.7, 37.3, 35.6, 34.7, 32.5, 30.6, 25.0, 12.7; HRMS-ESI (*m*/*z*) calcd for $C_{21}H_{31}NO_2$ $[M + H]^+$ 330.2428, found 330.2441.

(2*S*,2a*R*,2a^1*S*,4a*S*,7a*R*,10b*S*)-4a-Allyl-6-hydroxy-2-methyl-2a,2a^1,3,4,4a,5a,6,7,7a,8,9,10b-dodecahydro-1*H*-cyclopenta-[*hi*]indeno[4,5-*e*]indolizin-5(2*H*)-one (24). To a stirred solution of oxalyl chloride (53 μL, 0.608 mmol) in CH_2Cl_2 (3 mL) at −78 °C was added DMSO (86 μL, 1.22 mmol) and stirring was continued for 15 min. Then, compound **23** (100 mg, 0.304 mmol) was added to the mixture and stirring continued for 1 h at the same temperature. After that, Et_3N (0.25 mL, 1.83 mmol) was added and the reaction mixture was gradually warmed up to 0 °C over 1 h. The stirring was continued for an additional 30 min and the reaction was quenched with NH_4Cl. An excess of saturated aqueous $NaHCO_3$ solution was added and the reaction was extracted with CH_2Cl_2 (three times). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography with 6% EtOAc in hexanes to afford aldehyde (70 mg, 70%) as a colorless liquid.

R_f = 0.5 (20% EtOAc in hexanes), [$KMnO_4$], not visible in UV; $[\alpha]_D^{20}$ = +55.1 (*c* = 1.0, $CHCl_3$); IR (neat) ν_{max} = 2926, 1699, 1392, 1249, 1163, 1103, 917, 834,774, 631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.62 (dd, *J* = 3.6, 1.7 Hz, 1H), 5.75−5.60 (m, 1H), 5.53 (s, 1H), 5.07 4.98 (m, 2H), 3.77−3.69 (m, 1H), 3.50 (d, *J* = 7.6 Hz, 1H), 3.23−3.16 (m, 1H), 2.70−2.51 (m, 3H), 2.45−2.26 (m, 7H), 2.26−2.16 (m, 2H), 2.15−2.05 (m, 2H), 1.55−1.45 (m, 2H), 1.39−1.28 (m, 2H), 0.90 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.4, 201.1, 146.5, 134.2, 127.0, 117.9, 73.6, 59.0, 52.1, 51.9, 48.4, 47.3, 41.5, 39.9, 37.3, 35.3, 34.7, 31.0, 30.7, 24.9, 13.2; HRMS-ESI (*m*/*z*) calcd for $C_{21}H_{29}NO_2$ $[M + Na]^+$ 350.2091, found 350.2099.

To a stirred solution of aldehyde (100 mg, 0.306 mmol) in THF at room temperature was added TBD (85 mg, 0.612 mmol) and the stirring was continued for 2 h. Then, the reaction mixture was quenched with water and extracted with EtOAC (three times). The combined extracts were dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography with 12% EtOAc−hexanes to afford a 3:1 diastereomeric mixture of **24** and the elimination product **25** (85 mg, 85%). Spectroscopic data of major isomer is as follows.

R_f = 0.37 (30% EtOAc in hexanes), [$KMnO_4$], not visible in UV. IR (neat) ν_{max} = 3387, 2920, 2770, 1700, 1445, 1320, 1245, 1150, 1058, 1020, 910, 750, 630 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.79−5.65 (m, 1H), 5.52 (s, 1H), 5.08−4.96 (m, 2H), 4.68 (s, 1H), 4.02 (d, *J* = 11.2 Hz, 1H), 3.93 (d, *J* = 7.1 Hz, 1H), 3.15 (dd, *J* = 8.5, 1.9 Hz, 1H), 2.93 (s, 1H), 2.78 (dq, *J* = 8.5, 4.0 Hz, 1H), 2.55−2.40 (m, 4H), 2.41−2.23 (m, 2H), 2.22−2.07 (m, 4H), 1.80−1.55 (m, 4H), 1.54−1.41 (m, 1H), 1.38−1.20 (m, 1H), 1.10 (dt, *J* = 13.2, 2.4 Hz, 1H), 1.02 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.4, 196.3, 143.3, 140.7, 134.9, 123.7, 118.1, 74.4, 66.8, 59.0, 54.9, 51.8, 48.1, 46.0, 40.1, 39.8, 39.4, 38.4, 35.4, 31.9, 30.9, 25.2, 13.5; HRMS-ESI (*m*/*z*) calcd for $C_{21}H_{29}NO_2$ $[M + H]^+$ 328.2271, found 328.2277.

(2*S*,2a*R*,2a^1*S*,4a*S*,7a*R*,10b*R*)-4a-Allyl-2-methyl-2a,2a1,3,4,4a,7,7a,8,9,10b-decahydro-1*H*-cyclopenta[*hi*]-indeno[4,5-*e*]indolizin-5(2*H*)-one (25). To a stirred solution of aldehyde (100 mg, 0.306 mmol) in THF (3 mL) at room temperature was added TBD (85 mg, 0.612 mmol), and the stirring was continued for 24 h. Then, the reaction mixture was quenched with water and extracted with EtOAC (three times). The combined extracts were dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography with 12% EtOAc−hexanes to afford **24** and **25** (80 mg, 80%) as a 1:3 diastereomeric mixture.

The isomeric mixture was dissolved in toluene (2 mL), oxalic acid (135 mg, 1.50 mmol) was added gradually, and the reaction mixture was warmed up to 90 °C. After 3 h the reaction mixture was cool to rt; water was added and the reaction was extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography with 11% EtOAc in hexanes to give the title compound **25** (60 mg, 75%), as a yellowish solid.

R_f = 0.35 (30% EtOAc in hexanes), [$KMnO_4$], UV visible; $[\alpha]_D^{20}$ = +64.2 (*c* = 1.00, $CHCl_3$); IR (neat) ν_{max} = 2926, 2851, 1684, 1621, 1459, 1441, 1329, 1205, 1172, 1103, 913, 834,770, 650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17−7.08 (m, 1H), 5.72−5.59 (m, 1H), 5.58 (s,

DOI: 10.1021/acs.joc.6b00638
J. Org. Chem. 2016, 81, 5074−5086

1H), 5.06−4.95 (m, 2H), 4.68 (s, 1H), 3.93 (d, J = 8.3 Hz, 1H), 2.90−2.76 (m, 2H), 2.72−2.58 (m, 2H), 2.52−2.18 (m, 7H), 1.97−1.85 (m, 1H), 1.73 (dd, J = 11.0, 9.4 Hz, 1H), 1.56−1.39 (m, 2H), 1.31−1.20 (m, 1H), 1.17−1.04 (m, 1H), 0.86 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8, 140.6, 139.1, 133.8, 132.7, 123.7, 118.0, 73.6, 56.3, 54.6, 49.8, 47.52, 43.5, 42.1, 35.1, 34.7, 34.6, 31.8, 30.2, 25.0, 12.1; HRMS-ESI (m/z) calcd for $C_{21}H_{27}NO$ $[M + H]^+$ 310.2165, found 310.2179.

(2*S*,2a*R*,2a^1*S*,4a*S*,5a*R*,7a*R*,10b*S*)-4a-allyl-2-methyl-2a,2a1,3,4,4a,5a,6,7,7a,8,9,10b-dodecahydro-1*H*-cyclopenta-[*hi*]indeno[4,5-*e*]indolizin-5(2*H*)-one (26). To a stirred solution of compound **25** (60 mg, 0.195 mmol) in THF (4 mL) at −78 °C was added 1 M L-Selectride (0.3 mL, 0.300 mmol) and the mixture gradually warmed up to −60 °C over 2 h. Then, the reaction mixture was quenched with aqueous saturated NH_4Cl solution and gradually brought to room temperature. To the quenched reaction mixture was added excess saturated aqueous $NaHCO_3$ solution, and the mixture was stirred for an additional 30 min and extracted with EtOAc (three times). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography with 9% EtOAc in hexanes to give the title compound **26** (42 mg, 70%), as a yellowish solid.

R_f = 0.4 (30% EtOAc in hexanes), [$KMnO_4$], not visible in UV; $[\alpha]_D^{20}$ = +23.9 (c = 1.0, $CHCl_3$); IR (neat) ν_{max} = 2922, 2852, 1693, 1466, 1441, 1364, 1248, 1211, 1171, 1134, 997, 911, 799, 752, 654 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76−5.61 (m, 1H), 5.50 (s, 1H), 5.06−4.96 (m, 2H), 3.91 (d, J = 7.3 Hz, 1H), 3.52 (d, J = 10.3 Hz, 1H), 3.11 (dd, J = 8.6, 6.5 Hz, 1H), 2.75 (dt, J = 14.5, 7.1 Hz, 1H), 2.49−2.39 (m, 3H), 2.38−2.29 (m, 3H), 2.26−2.18 (m, 2H), 2.18−2.07 (m, 2H), 2.03−1.93 (m, 1H), 1.87−1.76 (m, 1H), 1.60 (dd, J = 14.0, 6.7 Hz, 2H), 1.46 (dt, J = 11.8, 5.7 Hz, 1H), 1.40−1.23 (m, 2H), 1.00 (d, J = 6.9 Hz, 3H), 1.03−0.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.3, 144.0, 134.8, 123.4, 118.0, 74.3, 59.5, 58.7, 51.7, 46.1, 46.0, 44.3, 41.0, 38.0, 35.3, 33.3, 31.9, 30.8, 25.3, 25.1, 13.3; HRMS-ESI (m/z) calcd for $C_{21}H_{29}NO$ $[M + H]^+$ 312.2322, found 312.2333.

(*R*)-(5-(2-Oxoethyl)cyclopent-1-en-1-yl)methyl Benzoate (29). To a stirred solution of alcohol **20** (1 g, 3.90 mmol) in CH_2Cl_2 (11 mL) at room temperature were added Et_3N (1.64 mL, 11.72 mmol), benzoyl chloride (0.9 mL, 7.81 mmol), and DMAP (48 mg, 0.39 mmol) sequentially. The reaction was continued for an additional 2 h and quenched with saturated aqueous NH_4Cl, followed by an excess of aqueous $NaHCO_3$ solution. The biphasic layers were extracted with DCM, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc−hexanes = 6/94) to give the benzoate ester (1.4 g, 99%) as a colorless liquid.

R_f = 0.3 (5% EtOAc−hexanes), [$KMnO_4$], UV visible; $[\alpha]_D^{20}$ = +2.5 (c 1.0, $CHCl_3$); IR (neat) ν_{max} = 2955, 2930, 2858, 1722, 1452, 1271, 1109, 912, 835, 754, 631 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08−8.03 (m, 2H), 7.58−7.52 (m, 1H), 7.43 (dd, J = 10.6, 4.7 Hz, 2H), 5.78 (d, J = 1.6 Hz, 1H), 4.89 (d, J = 0.7 Hz, 2H), 3.75−3.60 (m, 2H), 2.85 (d, J = 4.6 Hz, 1H), 2.41−2.24 (m, 2H), 2.19−2.07 (m, 1H), 2.01−1.91 (m, 1H), 1.67−1.55 (m, 1H), 1.48−1.35 (m, 1H), 0.88 (s, 9H), 0.04 (2s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 141.8, 132.8, 130.3, 129.6, 129.1, 128.3, 62.6, 61.7, 42.1, 36.6, 31.0, 30.1, 25.9, 18.3, −5.3, −5.4; HRMS-ESI (m/z) calcd for $C_{21}H_{32}O_3Si$ $[M + H]^+$ 361.2194, found 361.2204.

To a stirred solution of benzoate ester (1.3 g, 3.61 mmol) in 4:1 DCM−MeOH mixture (10 mL) at room temperature was added (±)-CSA (418 mg, 1.81 mmol) portionwise. After 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (three times). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure, and flash chromatography with 25% EtOAc−hexanes gave the alcohol (800 mg, 90%), as a colorless liquid.

R_f = 0.1 (20% EtOAc−hexanes), [$KMnO_4$], UV visible; $[\alpha]_D^{20}$ = −10.7 (c 1.0, $CHCl_3$); IR (neat) ν_{max} = 3334, 2931, 1716, 1451, 1315, 1274, 1111, 1027, 913, 754, 713, 631 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.7 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 5.80 (s, 1H), 4.95−4.83 (m, 2H), 3.80−3.72 (m, 1H), 3.71−3.63 (m, 1H), 2.84 (s, 1H), 2.43−2.26 (m, 2H), 2.21−2.10 (m, 1H), 2.04−1.93 (m, 1H), 1.68−1.45 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 141.6, 132.94, 130.2, 129.7, 129.6, 128.4, 62.5, 61.5, 42.0, 36.5, 31.0, 30.2; HRMS-ESI (m/z) calcd for $C_{15}H_{18}O_3$ $[M + H]^+$ 247.1329, found 247.1336.

To a stirred solution of the alcohol (700 mg, 2.84 mmol) at 0 °C were added $NaHCO_3$ (720 mg, 8.54 mmol) and DMP (1.81 g, 4.26 mmol) successively. The reaction mixture was then gradually warmed up to room temperature over 45 min. After 30 min, the reaction mixture was quenched with aqueous saturated $Na_2S_2O_3$ and $NaHCO_3$ solution and stirred for an additional 20 min. The biphasic layers were extracted with DCM, and the combined extracts were dried over anhydrous Na_2SO_4. The organic phase was then concentrated under reduced pressure, and flash chromatography with 6% EtOAc−hexanes afforded compound **29** (620 mg, 90%) as a colorless liquid.

R_f = 0.3 (20% EtOAc−hexanes), [$KMnO_4$], UV visible; $[\alpha]_D^{20}$ = −18.5 (c 1.0, $CHCl_3$); IR (neat) ν_{max} = 2931, 1680, 1451, 1314, 1271, 1111, 1070, 913, 742, 713, 631 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (t, J = 1.9 Hz,1H), 8.03 (dd, J = 8, 1.1 Hz, 2H), 7.56 (dd, J = 8, 1.1 Hz, 1H), 7.44 (t, J = 8 Hz, 2H), 5.87 (s, 1H), 4.88 (q, J = 13.1 Hz, 2H), 3.32−3.16 (m, 1H), 2.79 (ddd, J = 16.7, 4.3, 1.4 Hz, 1H), 2.45 (ddd, J = 16.7, 9.3, 2.3 Hz 1H), 2.39−2.35 (m, 2H), 2.34−2.23 (m, 1H), 1.67−1.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 166.3, 140.1, 133.0, 131.5, 130.0, 129.6, 128.4, 62.2, 47.9, 39.7, 30.9, 30.6; HRMS-ESI (m/z) calcd for $C_{15}H_{16}O_3$ $[M+NH_4]^+$ 262.1438, found 262.1444.

(3*S*,3a*R*,6*S*,6a*S*)-*tert*-Butyl 6-Allyl-6-(4-((*R*)-2-((benzoyloxy)-methyl)cyclopent-2-en-1-yl)-3-hydroxybutanoyl)-3-methylhexahydrocyclopenta[*b*]pyrrole-1(2*H*)-carboxylate (30). To a stirred solution of compound **14** (300 mg, 0.98 mmol) in THF (3 mL) at −78 °C was added 0.4 M LDA in THF (3.7 mL, 1.47 mmol). Then, the reaction mixture was gradually warmed up to −40 °C over 1 h. The reaction mixture was again cooled down to −78 °C, and a 0.1 M solution of aldehyde **29** (244 mg, 1.00 mmol) in THF (1 mL) was cannulated into the reaction. Then, the reaction mixture was gradually warmed up to −60 °C over 1 h, and stirring continued for an additional 4 h at the same temperature. After completion, the reaction mixture was quenched with MeOH, diluted with water, and extracted with EtOAc. The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. Flash column chromatography with 4% EtOAc gave starting material (120 mg, 40%) and that with 7% EtOAc−hexanes afforded ketone **30** (263 mg, 50%, BSRM 85% after three cycle), as a colorless oil. The reaction progressed with varying yields of 50−60% with 40−20% recovery of the starting material.

R_f = 0.15 (10% EtOAc in hexanes), [$KMnO_4$], UV visible; $[\alpha]_D^{20}$ = −3.9 (c 1.0, $CHCl_3$); IR (neat) ν_{max} = 3431, 2968, 1719, 1688, 1452, 1395, 1366, 1271, 1162, 1109, 913, 835, 772, 709, 631 cm^{-1}; both ^{1}H and ^{13}C NMR spectra contain Boc rotamer peaks; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 7.2 Hz, 2H), 7.54 (ddd, J = 7.5, 2.5, 1.2 Hz, 1H), 7.43 (td, J = 7.6, 3.2 Hz, 2H), 5.76 (d, J = 9.2 Hz, 1H), 5.69−5.53 (m, 1H), 5.16−5.00 (m, 2H), 4.93−4.79 (m, 2H), 4.18 (d, J = 7.1 Hz, 1H), 4.07 (d, J = 7.4 Hz, 1H), 3.67 (s, 1H), 3.56 (s, 1H), 3.22−2.99 (m, 1H), 2.97−2.78 (m, 2H), 2.77−2.48 (m, 3H), 2.46−1.96 (m, 7H), 1.84−1.68 (m, 2H), 1.63−1.48 (m, 2H), 1.41 (s, 9H), 0.96 (t, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.6, 166.4, 166.3, 142.1, 134.0, 132.9, 132.8, 130.4, 130.3, 129.6, 129.6, 128.7, 128.3, 128.3, 118.6, 118.3, 72.1, 66.1, 63.2, 62.6, 62.6, 47.4, 42.6, 41. 5, 40.4, 40.1, 30.9, 30.7, 29.9, 28.5, 28.4, 23.6, 12.4; HRMS-ESI (m/z) calcd for $C_{33}H_{45}NO_6$ $[M + Na]^+$ 574.3139, found 574.3149.

(3*S*,3a*R*,6*S*,6a*S*)-*tert*-Butyl 6-Allyl-6-((*E*)-4-((*R*)-2-((benzoyloxy)methyl)cyclopent-2-en-1-yl)but-2-enoyl)-3-methylhexahydrocyclopenta[*b*]pyrrole-1(2*H*)-carboxylate (28). To a stirred solution of compound **30** (260 mg, 0.485 mmol) in CH_2Cl_2 (5 mL) at room temperature were added Et_3N (0.11 mL, 1.46 mmol), Ac_2O (92 μL, 0.97 mmol), and DMAP (6 mg, 0.05 mmol) sequentially. After 4 h, the reaction was quenched with NH_4Cl, extracted with $CHCl_3$, washed with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated under reduced pressure. Flash column chromatography of the crude residue with

DOI: 10.1021/acs.joc.6b00638
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10−20% EtOAc−hexanes afforded acetate (282 mg, 98%), as a colorless oil.

R_f = 0.2 (15% EtOAc in hexanes), [$KMnO_4$], UV visible; $[\alpha]_D^{20}$ = −0.8 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} = 2964, 1725, 1699, 1452, 1394, 1366, 1270, 1247, 1161, 1110, 1070, 1027, 913, 736, 715, 631 cm^{-1}; both ^1H and ^{13}C NMR spectra contain Boc rotamer peaks; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.1 Hz, 2H), 7.54 (dd, *J* = 10.5, 4.2 Hz, 1H), 7.43 (dd, *J* = 12.5, 7.4 Hz, 2H), 5.76 (s, 1H), 5.61 (td, *J* = 16.9, 8.4 Hz, 1H), 5.42−5.29 (m, 1H), 5.14−4.99 (m, 2H), 4.94−4.79 (m, 2H), 4.37−4.09 (m, 1H), 3.90−3.55 (m, 1H), 3.28−2.77 (m, 3H), 2.77−2.46 (m, 3H), 2.46−2.16 (m, 4H), 2.16−1.99 (m, 3H), 1.96 (d, *J* = 8.7 Hz, 3H), 1.90−1.68 (m, 3H), 1.61−1.47 (m, 2H), 1.42 (s, 9H), 0.93 (dd, *J* = 6.4, 4.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3, 209.0, 170.3, 166.1, 166.1, 155.4, 141.2, 141.0, 134.5, 133.8, 132.8, 130.1, 129.5, 129.5, 129.0, 128.3, 128.2, 118.3, 118.0, 79.6, 72.5, 71.9, 68.8, 62.2, 62.2, 61.9, 52.3, 51.7, 47.8, 47.41, 44.7, 43.6, 42.4, 41.6, 40.3, 38.0, 37.6, 35.2, 34.7, 33.5, 30.9, 30.6, 30.1, 29.9, 28.3, 28.3, 25.5, 24.1, 21.2, 21.0, 11.9; HRMS-ESI (*m*/*z*) calcd for $C_{35}H_{47}NO_7$ $[M + Na]^+$ 616.3245, found 616.3251.

To a stirred solution of acetate (280 mg, 0.47 mmol) in toluene (6 mL) at room temperature was added DBU (0.35 mL, 2.35 mmol). The reaction mixture was gradually heated to 65 °C, and stirring continued for 2 h. Then, the reaction mixture was cooled down to room temperature, concentrated under reduced pressure, and purified by flash column chromatography with 10% EtOAc−hexanes to give conjugated enone **28** (218 mg, 87%) as a colorless liquid.

R_f = 0.40 (20% EtOAc in hexanes), [$KMnO_4$], UV visible; $[\alpha]_D^{20}$ = +3.0 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} = 2957, 1720, 1688, 1621, 1452, 1396, 1365, 1270, 1163, 1110, 1070, 1027, 913, 742, 714, 631 cm^{-1}; both ^1H and ^{13}C NMR spectra contain Boc rotamer peaks; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05−8.00 (m, 2H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.4 Hz, 2H), 6.75 (s, 1H), 6.84−6.37 (m, 1H), 5.78 (s, 1H), 5.70−5.46 (m, 1H), 5.01 (d, *J* = 17.0 Hz, 1H), 4.94 (d, *J* = 10.2 Hz, 1H), 4.85 (s, 2H), 4.37−4.10 (2d, *J* = 7.8 Hz, 1H), 3.84−3.52 (2dd, *J* = 10.2, 7.4 Hz, 1H), 3.18−2.81 (m, 2H), 2.65 (pent, *J* = 8.1 Hz, 1H), 2.55−2.40 (m, 2H), 2.27 (brs, 3H), 2.22−1.95 (m, 5H), 1.80−1.66 (m, 1H), 1.65−1.48 (m, 2H), 1.45−1.30 (2s, 9H), 0.91 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8, 199.8, 166.2, 155.0, 143.6, 142.6, 140.6, 134.7, 134.1, 132.8, 130.4, 130.2, 129.5, 128.9, 128.3, 128.0, 117.6, 80.0, 79.3, 72.1, 71.7, 62.3, 61.7, 60.8, 51.9, 51.1, 49.0, 47.8, 44.5, 42.0, 36.3, 36.1, 34.8, 34.2, 30.8, 29.5, 28.3, 25.6, 25.2, 12.0; HRMS-ESI (*m*/*z*) calcd for $C_{33}H_{43}NO_5$ $[M + Na]^+$ 556.3033, found 556.3040.

(3*S*,3a*R*,6*S*,6a*S*)-*tert*-Butyl 6-Allyl-6-(4-((*S*)-2-((benzoyloxy)-methyl)cyclopent-2-en-1-yl)butanoyl)-3-methylhexahydro-cyclopenta[*b*]pyrrole-1(2*H*)-carboxylate (31). To a stirred solution of compound **28** (210 mg, 0.39 mmol) in diethyl ether (10 mL) at −78 °C was added 1 M L-Selectride (0.51 mL, 0.51 mmol), and the reaction gradually warmed up to −60 °C over 2 h. Then, the reaction mixture was quenched with aqueous saturated NH_4Cl solution and gradually brought to room temperature. Then, excess saturated aqueous $NaHCO_3$ solution was added, and the reaction was stirred for an additional 30 min and extracted with EtOAc (three times). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography with 6−10% EtOAc in hexanes to give the title compound **31** (125 mg, 60%), as a yellowish liquid.

R_f = 0.30 (15% EtOAc in hexanes), [$KMnO_4$], UV visible; $[\alpha]_D^{20}$ = −8.3 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} = 2933, 1720, 1695, 1478, 1453, 1393, 1365, 1272, 1162, 1110, 913, 743, 714, 631 cm^{-1}; both ^1H and ^{13}C NMR spectra contain Boc rotamer peaks; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.2 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 5.74 (s, 1H), 5.61 (td, *J* = 17.1, 7.0 Hz, 1H), 5.12−4.99 (m, 2H), 4.91−4.78 (m, 2H), 4.29−4.09 (2brs, 1H), 3.90−3.56 (2brs, 1H), 3.03−2.77 (m, 2H), 2.77−2.60 (m, 2H), 2.59−2.45 (m, 1H), 2.45−2.16 (m, 4H), 2.15−1.95 (m, 3H), 1.85−1.70 (m, 1H), 1.67−1.46 (m, 6H), 1.39 (s, 10H), 0.93 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.3, 166.3, 155.0, 141.8, 134.5, 132.8, 130.4, 129.6, 128.8, 128.3, 117.9, 79.4, 71.9, 62.7, 62.6, 52.4, 47.4, 45.4, 40.6, 40.1, 35.1, 33.9, 33.1, 31.3, 31.1, 30.9, 29.9, 28.4, 24.5, 21.6, 12.2; HRMS-ESI (*m*/*z*) calcd for $C_{33}H_{45}NO_5$ $[M + Na]^+$ 558.3190, found 558.3200.

(3*S*,3a*R*,6*S*,6a*S*)-*tert*-Butyl 6-Allyl-6-(4-((*S*)-2-(hydroxymethyl)cyclopent-2-en-1-yl)butanoyl)-3-methylhexa-hydrocyclopenta[*b*]pyrrole-1(2*H*)-carboxylate (32). To a stirred solution of benzoate ester **31** (120 mg, 0.23 mmol) in MeOH (4 mL) at room temperature was added 0.5 M NaOMe in MeOH (1.8 mL, 0.90 mmol), and the reaction mixture was stirred overnight. Then, the reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (three times). The combined extracts were dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography with 20−30% EtOAc−hexanes to give the title compound **32** (79 mg, 80%) as a colorless liquid.

R_f = 0.15 (20% EtOAc in hexanes), [$KMnO_4$], not seen in UV; $[\alpha]_D^{20}$ = −12.6 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} = 3458, 2933, 1715, 1478, 1453, 1393, 1366, 1255, 1224, 1160, 1111, 913, 743, 631 cm^{-1}; both ^1H and ^{13}C NMR spectra contain Boc rotamer peaks; ^1H NMR (400 MHz, $CDCl_3$) δ 5.67−5.53 (m, 2H), 5.14−5.00 (m, 2H), 4.28−4.06 (m, 3H), 3.71 (2s, 1H), 2.97 (dd, *J* = 14.4, 6.6 Hz, 1H), 2.90−2.45 (m, 4H), 2.43−2.14 (m, 4H), 2.12−1.91 (m, 4H), 1.77 (s, 1H), 1.64−1.28 (m, 15H), 1.17−1.03 (m, 1H), 0.93 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.5, 155.1, 147.1, 134.4, 126.4, 125.7, 117.9, 79.5, 72.4, 71.9, 62.8, 62.2, 60.9, 52.4, 51.4, 48.9, 47.4, 45.1, 41.9, 40.5, 40.1, 35.1, 34.4, 33.8, 33.1, 30.7, 30.1, 29.6, 28.4, 28.3, 25.8, 24.4, 21.4, 12.2; HRMS-ESI (*m*/*z*) calcd for $C_{26}H_{41}NO_4$ $[M + Na]^+$ 454.2928, found 454.2935.

(3*S*,3a*R*,6*S*,6a*S*)-*tert*-Butyl 6-Allyl-6-((7a*R*)-4-hydroxy-2,4,5,6,7,7a-hexahydro-1*H*-indene-5-carbonyl)-3-methylhexa-hydrocyclopenta[*b*]pyrrole-1(2*H*)-carboxylate (33). To a stirred solution of alcohol **32** (70 mg, 0.16 mmol) in dichloromethane (2 mL) at room temperature were added DMP (138 mg, 0.33 mmol) and $NaHCO_3$ (54 mg, 0.64 mmol) sequentially. The stirring was continued for 1 h, and then the reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$ and $NaHCO_3$. The reaction mixture was stirred for an additional 30 min and then extracted with $CHCl_3$ three times. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and flash column chromatography with 15% EtOAc−hexanes afforded aldehyde (55 mg, 81%) as a colorless liquid.

R_f = 0.45 (20% EtOAc in hexanes), [$KMnO_4$], UV visible; $[\alpha]_D^{20}$ = +7.0 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} = 2957, 1698, 1457, 1394, 1366, 1163, 1110, 913, 742, 631 cm^{-1}; both ^1H and ^{13}C NMR spectra contain Boc rotamer peaks; ^1H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 6.79 (s, 1H), 5.67−5.54 (m, 1H), 5.12−4.99 (m, 2H), 4.30−4.10 (2s, 1H), 3.88−3.53 (2s, 1H), 2.93 (s, 2H), 2.86−2.21 (m, 7H), 2.17−1.95 (m, 3H), 1.84−1.64 (m, 3H), 1.60−1.30 (2s, 13H), 1.25−1.10 (m, 1H), 0.93 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.3, 189.8, 155.0, 153.6, 150.5, 134.5, 118.0, 79.4, 71.9, 62.7, 52.4, 47.4, 42.1, 40.5, 40.1, 35.1, 33.9, 32.6, 32.1, 29.4, 28.4, 24.4, 21.4, 12.2; HRMS-ESI (*m*/*z*) calcd for $C_{26}H_{39}NO_4$ $[M + Na]^+$ 452.2771, found 452.2781.

To a stirred solution of aldehyde (50 mg, 0.12 mmol) in THF (3 mL) at room temperature was added TBD (34 mg, 0.24 mmol), and the stirring was continued for 24 h. Then, the reaction mixture was quenched with water and extracted with EtOAC (three times). The combined extracts were dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography with 15−20% EtOAc−hexanes to afford compound **33** (39 mg, 78%) as a colorless liquid.

R_f = 0.45 (20% EtOAc in hexanes), [$KMnO_4$], not seen in UV; $[\alpha]_D^{20}$ = −61.8 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} = 3445, 2927, 1691, 1393, 1161, 1110, 913, 742, 631 cm^{-1}; both ^1H and ^{13}C NMR spectra contain Boc rotamer peaks; ^1H NMR (400 MHz, $CDCl_3$) δ 5.64−5.47 (m, 2H), 5.14−5.01 (m, 2H), 4.55 (s, 1H), 4.36−4.22 (m, 1H), 3.78 (s, 1H), 2.98−2.73 (m, 3H), 2.71−2.63 (m, 1H), 2.54 (s, 1H), 2.36−2.26 (m, 2H), 2.20−2.02 (m, 3H), 2.01−1.83 (m, 3H), 1.82−1.67 (m, 1H), 1.67−1.55 (m, 2H), 1.44 (s, 9H), 1.51−1.30 (m, 3H), 1.07−0.90 (m, 1H), 0.97 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.0, 155.1, 147.6, 145.0, 134.7, 134.1, 125.1, 120.4, 118.4, 79.7, 72.7, 71.8, 71.4, 66.8, 63.7, 55.5, 52.7, 51.0, 47.8, 45.3, 40.4, 39.9, 35.1, 34.5,

DOI: 10.1021/acs.joc.6b00638
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34.0, 33.8, 33.2, 31.6, 31.2, 30.4, 29.8, 29.7, 29.4, 28.5, 28.5, 28.4, 24.8, 23.5, 12.4; HRMS-ESI (m/z) calcd for $C_{26}H_{39}NO_4$ $[M + Na]^+$ 452.2771, found 452.2791.

(2*S*,2a*R*,2a^1*S*,4a*S*,5a*S*,7a*R*,10b*S*)-4a-Allyl-2-methyl-2a,2a1,3,4,4a,5a,6,7,7a,8,9,10b-dodecahydro-1*H*-cyclopenta[*hi*]indeno[4,5-*e*]indolizin-5(2*H*)-one (34), (2*S*,2a*R*,2a^1*S*,4a*S*,5a*S*,7a*R*,10b*R*)-4a-Allyl-2-methyl-2a,2a1,3,4,4a,5a,6,7,7a,8,9,10b-dodecahydro-1*H*-cyclopenta[*hi*]indeno[4,5-*e*]indolizin-5(2*H*)-one (35), and (2*S*,2a*R*,2a^1*S*,4a*S*,5a*R*,7a*R*,10b*S*)-4a-Allyl-2-methyl-2a,2a1,3,4,4a,5a,6,7,7a,8,9,10b-dodecahydro-1*H*-cyclopenta[*hi*]indeno[4,5-*e*]indolizin-5(2*H*)-one (26). To a stirred solution of compound **33** (20 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added TFA (0.3 mL); stirring was continued for 1 h at 0 °C and for 1 h at room temperature. Then, TFA was removed by azeotroping with anhydrous CH_2Cl_2, and the residue was dried in a vacuum for 1 h. The Boc-deprotected compound was dissolved in toluene (1.5 mL), and oxalic acid (23 mg, 0.25 mmol) was added to the reaction mixture. The heterogeneous mixture was heated to 95 °C for 4 h and then gradually cooled down to room temperature. To this heterogeneous mixture was added Et_3N (0.14 mL, 1 mmol) and the mixture was heated up to 95 °C over 60−72 h. The reaction mixture was cooled down to room temperature; an aqueous $NaHCO_3$ solution was added, and the mixture was stirred for 30 min at rt. The biphasic layer was extracted with EtOAc, dried over Na_2SO_4, and concentrated under reduced pressure. Flash column chromatography of the crude mass with 1−6% EtOAc−hexanes (impregnated with 2% NH_4OH) afforded ketones **34**, **26**, and **35** (9 mg, 60% over two steps) as a ∼1:1:1 separable mixture of diastereomers. Before loading the crude mass, the silica gel column was flashed with 10% NH_4OH−hexanes. The reaction was performed in several 20−30 mg batches.

For **34**: R_f = 0.6 (7% EtOAc in hexanes), [$KMnO_4$], not seen in UV; $[\alpha]_D^{20}$ = −20.0 (c 1.0, $CHCl_3$); IR (neat) ν_{max} = 2929, 2860, 1726, 1459, 1369, 1240, 1161, 1096, 916, 801, 753, 666); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77−5.65 (m, 1H), 5.34 (s, 1H), 5.06−4.96 (m, 2H), 3.60 (d, J = 8.4 Hz, 1H), 3.35 (d, J = 5.7 Hz, 1H), 3.03−2.96 (m, 1H), 2.87 (dd, J = 8.3, 2.4 Hz, 1H), 2.61−2.52 (m, 1H), 2.47 (t, J = 8.3 Hz, 1H), 2.44−2.34 (m, 2H), 2.29−2.21 (m, 2H), 2.20−2.11 (m, 2H), 2.09−1.94 (m, 3H), 1.82−1.72 (m, 1H), 1.69−1.57 (m, 3H), 1.53−1.43 (m, 1H), 1.42−1.30 (m, 2H), 1.03 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.0, 146.7, 134.1, 121.7, 117.7, 73.9, 61.5, 60.1, 59.2, 47.6, 45.0, 44.3, 39.7, 34.4, 32.3, 30.9, 30.8, 29.6, 24.3, 22.7, 17.4; HRMS-ESI (m/z) calcd for $C_{21}H_{29}NO$ $[M + H]^+$ 312.2322, found 312.2330.

For **35**: R_f = 0.5 (7% EtOAc in hexanes), [$KMnO_4$], not seen in UV; $[\alpha]_D^{20}$ = −53.0 (c 1.0, $CHCl_3$); IR (neat) ν_{max} = 2923, 1702, 1480, 1321, 1244, 1148, 915, 633 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66−5.50 (m, 1H), 5.37 (d, J = 1.9 Hz, 1H), 5.02−4.93 (m, 2H), 3.80 (d, J = 4.7 Hz, 1H), 3.49 (t, J = 2.9 Hz, 1H), 3.00 (dd, J = 8.5, 6.4 Hz, 1H), 2.85−2.75 (m, 1H), 2.73−2.63 (m, 2H), 2.38 (sept, J = 6.4 Hz, 1H), 2.32−2.20 (m, 3H), 2.16−1.95 (m, 3H), 1.91 (dd, J = 13.7, 8.8 Hz, 1H), 1.84 (dq, J = 13.0, 3.5 Hz, 1H), 1.74−1.58 (m, 2H), 1.56−1.46 (m, 3H), 1.42−1.28 (m, 1H), 1.07 (ddd, J = 16.3, 7.1, 3.7 Hz, 1H), 1.00 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.6, 145.6, 134.9, 123.0, 117.5, 67.5, 60.1, 59.2, 57.9, 52.0, 49.6, 40.3, 39.3, 37.5, 35.3, 34.6, 31.0, 29.9, 25.4, 21.9, 13.5; HRMS-ESI (m/z) calcd for $C_{21}H_{29}NO$ $[M + H]^+$ 312.2322, found 312.2327.

(2*S*,2a*R*,2a^1*S*,4a*S*,5*R*,5a*R*,7a*R*,10b*R*)-4a-Allyl-2,5-dimethyl-2,2a,2a1,3,4,4a,5,5a,6,7,7a,8,9,10b-tetradecahydro-1*H*-cyclopenta[*hi*]indeno[4,5-*e*]indolizin-5-ol (36). Ketone **35** (30 mg, 0.096 mmol) was dissolved in THF at −78 °C and a commercial solution of 1.6 M MeLi solution in diethyl ether (0.2 mL, 0.32 mmol) was added to it. The reaction mixture was gradually warmed up to 10 °C over 2 h and stirred for another 30 min at the same temperature. Then the reaction mixture was quenched with H_2O and extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (EtOAc−hexanes = 25/75) to afford the title compound **36** (27 mg, 85%) as a colorless liquid.

R_f = 0.15 (20% EtOAc−hexanes), [$KMnO_4$], not seen in UV; $[\alpha]_D^{20}$ = −150.0° (c 0.25, $CHCl_3$); IR (neat) ν_{max} = 3468, 2926, 2774, 1631, 1458, 1375, 1289, 1155, 910, 794 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17−6.02 (m, 1H), 5.32 (s, 1H), 5.15−5.02 (m, 2H), 3.37 (d, J = 4.2 Hz, 1H), 3.28 (s, 1H), 2.86 (t, J = 7.4 Hz, 1H), 2.74 (s, 1H), 2.53 (dd, J = 10.2, 5.0 Hz, 1H), 2.34−2.23 (m, 4H), 2.14−2.00 (m, 2H), 1.99−1.72 (m, 5H), 1.71−1.46 (m, 5H), 1.42−1.06 (m, 4H), 1.25 (s, 3H), 1.02−0.83 (m, 1H), 0.97 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 138.1, 121.3, 116.7, 73.4, 68.5, 59.5, 56.5, 56.2, 53.6, 48.3, 40.8, 38.6, 35.5, 35.2, 34.7, 31.4, 30.1, 29.8, 23.8, 20.8, 13.3; HRMS-ESI (m/z) calcd for $C_{22}H_{33}NO$ $[M + H]^+$ 328.26349, found 328.26503.

6-*epi*-Calyciphylline B (38). To a stirred solution of amine **9** (3 mg, 0.009 mmol) in CH_2Cl_2 (1.5 mL) at room temperature was added *m*-CPBA (3 mg, 0.012 mmol) in one portion, and after 15 min the reaction mixture was quenched with aqueous saturated $NaHCO_3$ solution. The biphasic layers were extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography with 16% MeOH−$CHCl_3$, to afford the title compound **38** (2.6 mg, 85%) as colorless liquid.

R_f = 0.4 (10% MeOH−$CHCl_3$), [$KMnO_4$], not seen in UV; mp 115−120 °C; $[\alpha]_D^{20}$ = −43.0 (c 0.1, $CHCl_3$); IR (neat) ν_{max} = 2919, 2849, 1725, 1454, 1377, 1264, 1156, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (s, 1H), 4.92 (s, 1H), 4.03 (s, 1H), 3.92 (d, J = 6.3 Hz, 1H), 3.77 (dd, J = 10.7, 1.8 Hz, 1H), 3.36 (s, 2H), 2.99 (pent, J = 7.7 Hz, 2H), 2.66−2.34 (m, 4H), 2.23−1.96 (m, 6H), 1.91−1.70 (m, 4H), 1.55−1.39 (m, 2H), 1.5 (s, 3H), 1.11−0.93 (m, 14H), 1.05 (d, J = 6.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 138.6, 136.2, 88.8, 82.0, 76.0, 68.3, 47.5, 46.8, 46.0, 43.7, 36.3, 34.5, 31.9, 31.4, 30.5, 29.6, 26.6, 26.2, 23.8, 21.7, 13.7; HRMS-ESI (m/z) calcd for $C_{22}H_{31}NO_3$ $[M + H]^+$ 358.2377, found 358.2393.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00638.

NMR spectra for all the new compounds, X-ray crystallographic data, and DFT data (PDF)
Crystallographic data for **2** (CIF)
Crystallographic data for **9** (CIF)
Crystallographic data for **25** (CIF)
Crystallographic data for **34** (CIF)
Crystallographic data for **36** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are thankful to Dr. Michel Simard for X-ray crystallographic determinations and to Dr. Cédric Malveau for high-resolution NMR studies. We are also grateful to Prof. J.-M. Yue for an X-ray-quality sample of deoxycalyciphylline B as a reference compound. We acknowledge NSERCC for financial support and the National Cancer Institute, Washington, D.C., for biological testing. We also thank Vu Linh Ly and Shashidhar Jakkepally for technical support.

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