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Development of a β-C−H Bromination Approach toward the Synthesis of Jerantinine E

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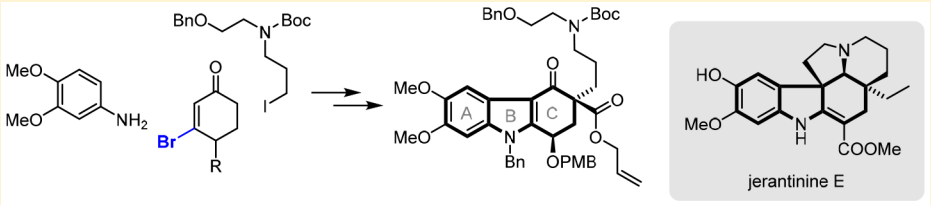
Supporting Information



ABSTRACT: The development of an asymmetric and highly convergent three-component synthesis of the functionalized ABC ring system of the *Aspidosperma* alkaloid jerantinine E is reported. The presented synthetic strategy relies on our recently developed method for the one-pot β-C−H bromination of enones, which allows for rapid construction of the tricyclic tetrahydrocarbazolone core via a palladium-catalyzed amination and oxidative indole formation. Moreover, a secondary amine building block that contains all carbon atoms of the D and E ring of the natural product could be installed in three additional steps.

INTRODUCTION

Monoterpenoid indole alkaloids have been attractive targets for synthetic chemists for several decades, and many of their unique skeletons have been synthesized in the past.[1] In addition to their daunting structural complexity, a variety of biological activities and medicinal applications have been reported, including anticancer (e.g., jerantinine E, vinblastine, brucine)[2] and insecticidal (e.g., aspidophytine)[3] activities (Figure 1A). The *Aspidosperma* alkaloid subfamily consists of more than 250 different members and biosynthetically originates from the condensation of tryptamine with a rearranged secologanin-derived C_9 or C_{10} terpene unit.[4] The secondary metabolites jerantinine A−G (Figure 1B) were isolated in 2008 from leaf extracts of the Malayan plant *Tabernaemontana corymbosa* and exhibit cytotoxic effects against vincristine-sensitive and vincristine-resistant epidermoid carcinoma cell lines (IC_{50} = 0.68−2.55 μM).[2a] In 2013, Waser reported the first synthesis of the *Aspidosperma* alkaloid jerantinine E (**1**) in 17 steps[5] and disclosed its antiproliferative activity against several human-derived breast and lung cancer cell lines (IC_{50} = 1.0−6.0 μM) mediated by inhibition of tubulin polymerization.

In the course of our studies toward novel methods for the site-selective functionalization of α,β-unsaturated compounds,[6] we identified several monoterpenoid indole alkaloids that could be retrosynthetically traced back to a β-halogenated enone. Despite significant advances made in the functionalization of α,β-unsaturated compounds in recent years,[7] only two examples for the direct β-halogenation of enones are known.[8] The syntheses of *Aspidosperma* alkaloids by Desmaële[9] and Qiu[10] both require multistep sequences relying on prefunctionalized vinylogous thioesters for the preparation of the crucial β-enaminone subunit common to several *Aspidosperma* alkaloids (Scheme 1A). We could circumvent these rather inefficient transformations by our two-step sequence starting from simple enones (Scheme 1B). Herein, we describe a convergent synthesis of the ABC ring system of the oxygenated indole alkaloid jerantinine E (**1**) employing our recently developed protocol for the one-pot β-C−H bromination of enones.[6]

RESULTS AND DISCUSSION

Our retrosynthetic analysis of **1** was guided by the proposed use of β-bromo enone **11** (Figure 1B) as a general entry to polycyclic indole alkaloids. Identification of this subunit in jerantinine E (**1**) inspired the strategy illustrated in Scheme 2A. In our analysis, tetracycle **12** would arise from the sequential diastereoselective alkylation of the tetrahydrocarbazolone **13** with iodide **14** and ethyl iodide. For the construction of the D-ring of **1**, we envisioned a sequence that would be initiated by the reduction of the ketone and subsequent acid-mediated elimination of the alcohol followed by in situ addition of the free amine to the resultant vinylogous iminium ion **19** (Scheme 2B).[11] The tetrahydrocarbazolone **13** was traced back to 3,4-dimethoxyaniline (**15**) and β-bromo enone **16** which in turn could be accessed via β-C−H bromination of the parent enone.

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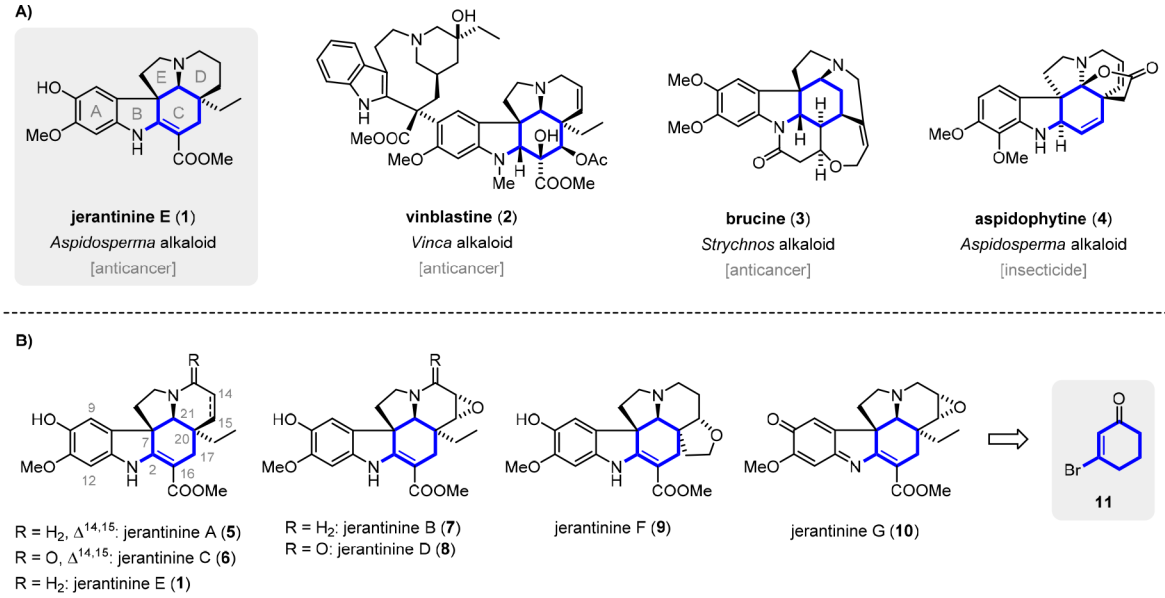
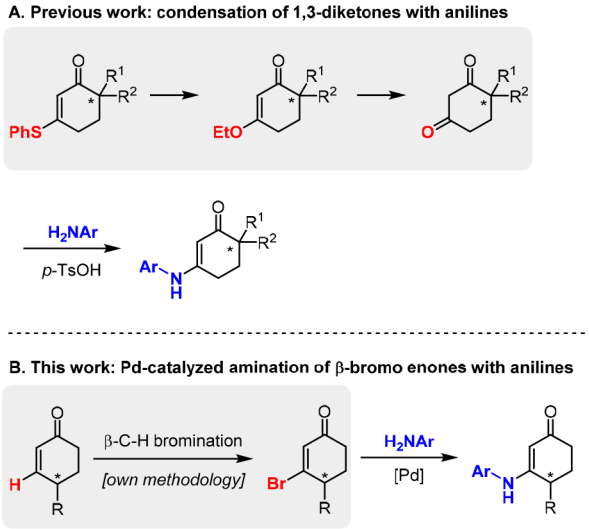


Figure 1. (A) Naturally occurring indole alkaloids and (B) structures of jerantinines A–G.

Scheme 1. Methods for the Preparation of Functionalized *β*-Enaminones for the Synthesis of *Aspidosperma* Alkaloids



In an initial attempt to synthesize jerantinine E (**1**), we targeted racemic intermediate **12**. The synthesis started with our previously reported preparation of tetrahydrocarbazolone *rac*-**13**, prepared in three steps from enone **21** utilizing a *β*-C–H bromination, a palladium-catalyzed amination with 3,4-dimethoxyaniline (**15**), and oxidative indole formation (Scheme 3).[6] Finally, tetrahydrocarbazolone *rac*-**13** was Boc-protected to give **22** in a good yield (88%). To examine the introduction of secondary amine **14**, we performed first alkylation with 1-chloro-3-iodopropane as a model electrophile. Treatment of **22** with lithium bis(trimethylsilyl)amide (LHMDS) and an excess of 1-chloro-3-iodopropane followed by nucleophilic displacement of the chloride provided azide **23**. Unfortunately, alkylation of **23** by treatment with LHMDS and ethyl iodide did not give the desired product. Instead, the elimination of the benzyl ether to give alkene **24** was observed,[12] which was prone to aromatization upon exposure to traces of acid.

Since **23** underwent undesired elimination under basic alkylation conditions, we contemplated exchange of the CH_2OBn moiety for a protected hydroxy group in the *γ*-position of the enone. Our revised retrosynthetic analysis featured the synthesis of a modified, asymmetric tetrahydrocarbazolone core structure which could be constructed from 3,4-dimethoxyaniline (**15**), secondary amine building block **14**, and enantiopure *β*-bromo enone **27** (Scheme 4). The stereocenter of the latter component was planned to direct the sequential introduction of the side chains and enable the asymmetric total synthesis of jerantinine E (**1**).

We began our endeavor with the synthesis of known chiral alcohol **29**, itself derived from 1,4-cyclohexanedione monoethylene acetal (**28**) in four steps.[13] Protection of **29** as its *para*-methoxybenzyl ether (PMB) using Dudley's reagent II (2-(4-methoxybenzyloxy)-4-methylquinoline)[14] furnished **30**. Enone **30** was then subjected to our conditions for one-pot *β*-C–H bromination, which includes (1) umpolung of the enone by hydrazone formation with *tert*-butyl carbazate (*tert*-butoxycarbonyl hydrazide), (2) selective *β*-C–H bromination with *N*-bromosuccinimide (NBS) followed by addition of triethylamine to isomerize the allyl bromide, and (3) hydrolysis of the hydrazone moiety, to afford **27** in 57% yield on a 340 mg scale (Scheme 5). Palladium-catalyzed amination with 3,4-dimethoxyaniline (**15**) employing Buchwald's SPhos second generation precatalyst[15] followed by an oxidative indole formation[16] using palladium acetate and copper acetate furnished **32**. It is noteworthy that careful monitoring of the C–H activation reaction proved to be crucial to avoid overoxidation and subsequent hydrolysis of the PMB ether with extended reaction times. Benzyl protection of the tetrahydrocarbazolone **32** provided **33**,[17] whose structure could be validated by single-crystal X-ray diffraction.[18]

Having developed a short and efficient synthesis of key intermediate **33**, the stage was set for the installation of the quaternary stereocenter as the crucial handle to construct the DE ring system of jerantinine E (**1**). However, in sharp contrast to the results obtained for the alkylation of **22**, direct alkylation of **33** with ethyl iodide was not feasible under a variety of conditions. The use of LHMDS, LDA, or LDA/HMPA only led

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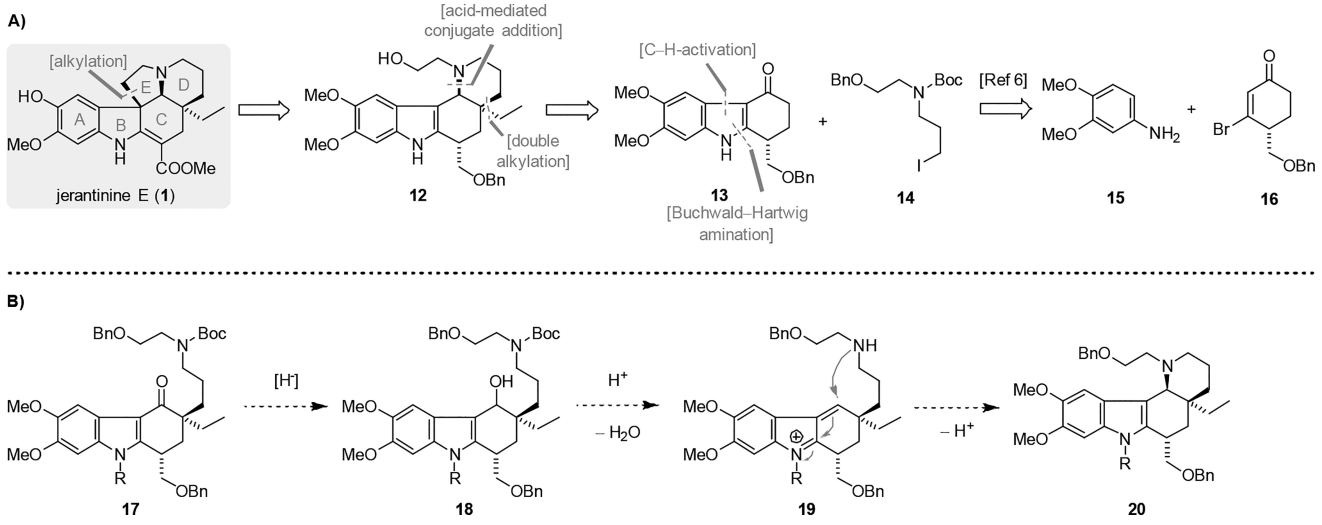
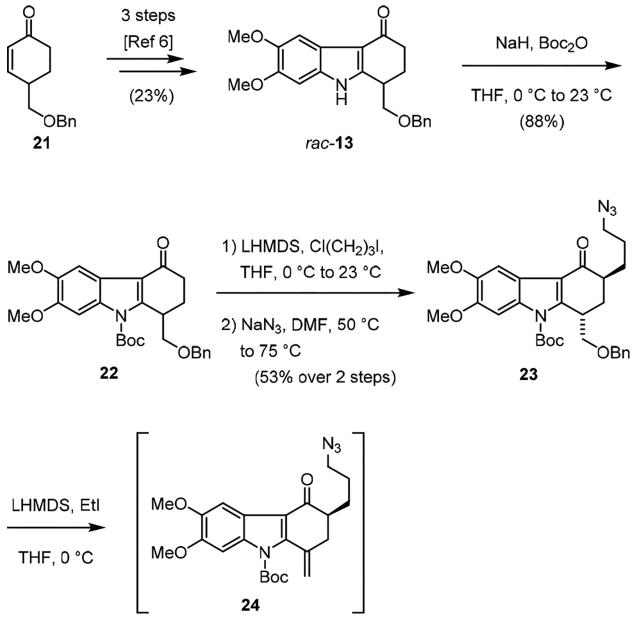
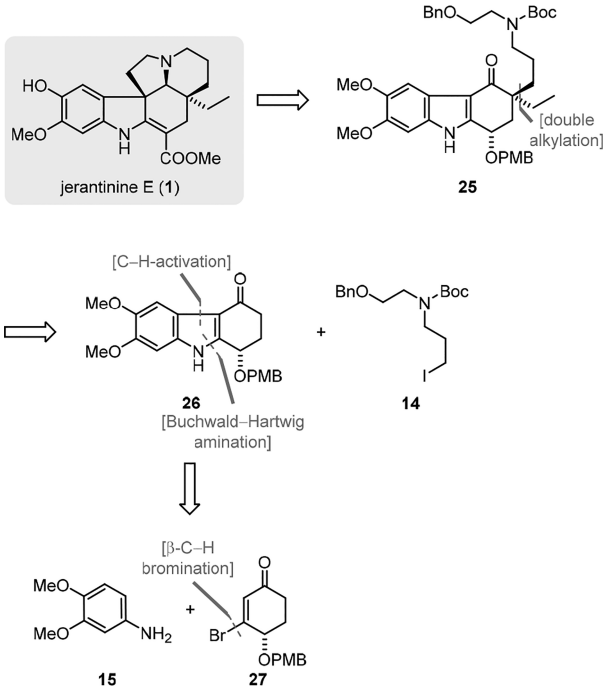
Scheme 2. (A) Initial Retrosynthetic Analysis of Jerantinine E (1) and (B) Envisioned Cascade Reaction for the Construction of the D-Ring



Scheme 3. Synthesis of Tetrahydrocarbazolone 22 and Alkylation with a Model Electrophile



Scheme 4. Revised Retrosynthetic Analysis of Jerantinine E (1)



to recovered starting material. The exact influence of the substituent at the γ-position of the ketone and the protecting groups (Bn and PMB) on the alkylation is unclear.

To overcome this poor reactivity, we investigated the acylation of **33**. Surprisingly, exposure of **33** to LHMDS and Mander's reagent[19] (methyl cyanoformate) at −78 °C followed by alkylation with sodium hydride and ethyl iodide proceeded cleanly and furnished **34** in good yields (Scheme 6). Next, we attempted to convert **34** to **35** by means of a decarboxylation using lithium chloride in aqueous dimethylformamide and subsequent reaction using acrylonitrile as a reactive model electrophile. Although traces of the decarboxylated product were observed, we were unable to detect any of the conjugate addition product.

Based on the successful alkylation of the β-keto ester with ethyl iodide, we decided to investigate the alkylation of **33** using iodide **14**. Thus, the Boc-protected amine building block **14** was synthesized as illustrated in Scheme 7A. Alkylation of commercially available *tert*-butyl *N*-allylcarbamate (**36**) with literature known iodide **37** under standard conditions (NaH, DMF) afforded **38** in good yield (80%).[20] Hydroboration of **38** with 9-borabicyclo[3.3.1]nonane (9-BBN) followed by oxidative workup using aqueous hydrogen peroxide furnished alcohol **39**. The latter was then transformed into iodide **14**, employing Appel's conditions (I_2, PPh_3, imH). With iodide **14** and tricyclic key intermediate **33** in hand, we were poised to examine the challenging fragment coupling. Acylation of **33** followed by reaction of the β-keto ester with sodium hydride and iodide **14** furnished the quaternary stereocenter in **40** in good yield (Scheme 7B). Thus, the introduction of the secondary amine building block could be accomplished in an efficient manner. The methyl ester of **40** could then be

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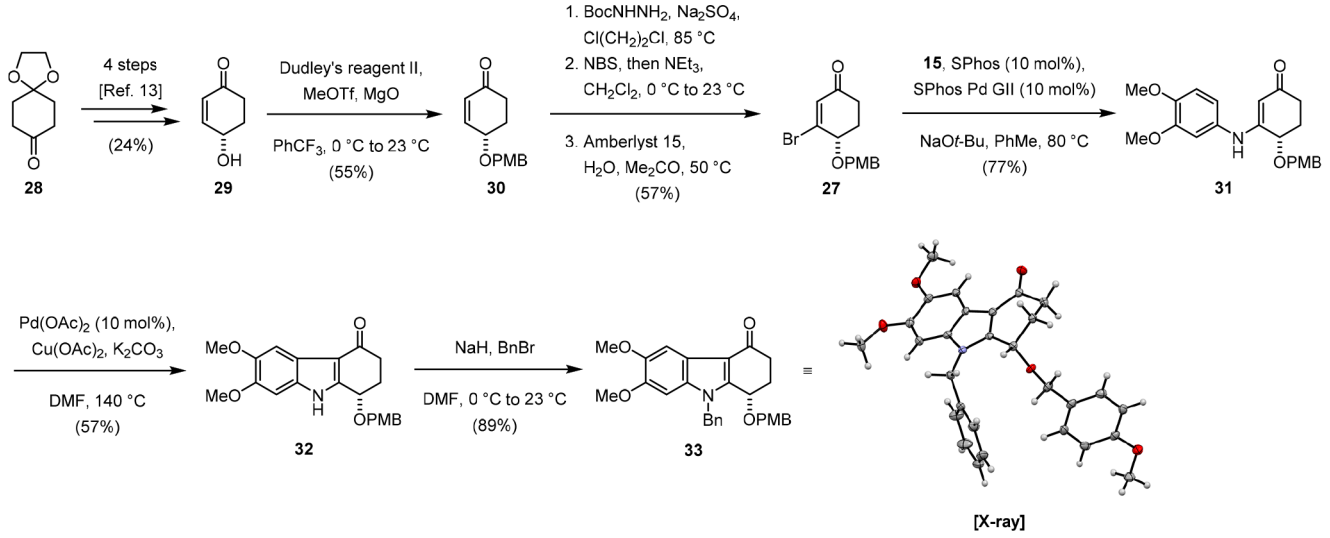
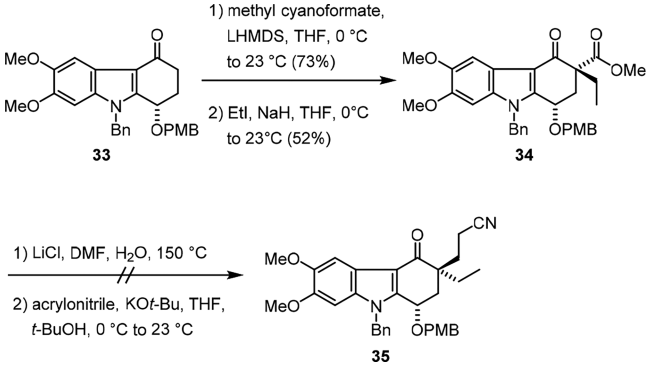
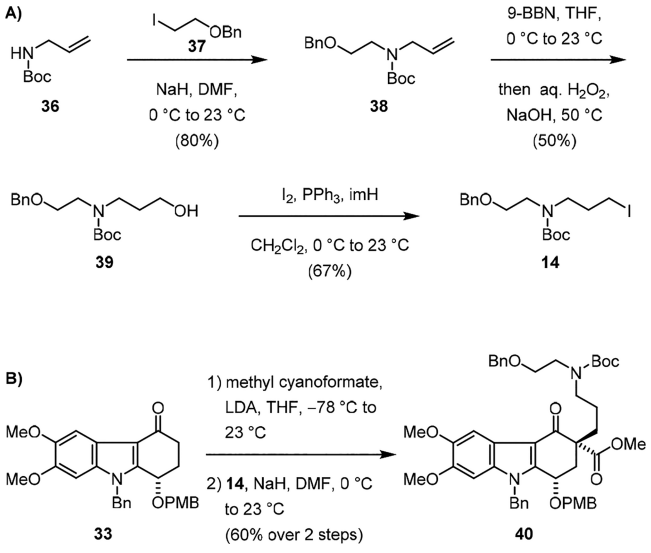
Scheme 5. Synthesis of Tetrahydrocarbazolone 33



Scheme 6. Attempted Formation of the Quaternary Stereocenter



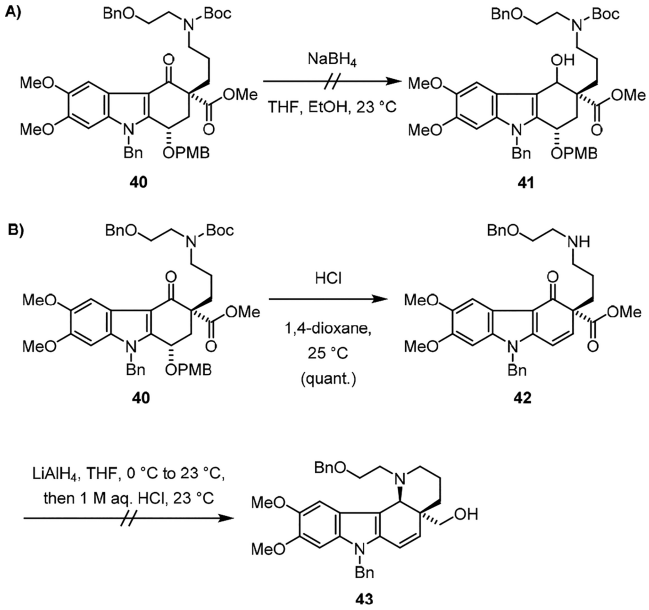
Scheme 7. (A) Preparation of the Boc-Protected Amine Building Block 14 and (B) Introduction of the Quaternary Stereocenter



transformed to the ethyl group of the natural product at a later stage of the synthesis.

For the construction of the D-ring of **1** (see Scheme 1B), we first tried to selectively reduce **40** using sodium borohydride (Scheme 8A). Since these conditions turned out to be

Scheme 8. Attempted Closure of the D-Ring of Jerantinine E



ineffective and no conversion was observed, we opted for more forcing conditions. As direct reduction of **40** with lithium aluminum hydride could not be considered due to concomitant reduction of the Boc protecting group, **40** was treated with 4 M hydrochloric acid in 1,4-dioxane to remove the Boc protecting group (Scheme 8B). Unfortunately under these conditions, deprotection of the Boc group and elimination of the PMB ether occurred, giving compound **42** as the major product. Exposure of the crude reaction mixture to lithium aluminum hydride followed by treatment with either 1 M aqueous hydrochloric acid or Rochelle's salt did not afford any detectable amounts of tetracycle **43**. Attempts to remove the Boc group under basic conditions (K_2CO_3, DMSO/H_2O, 65 °C; DIBAL-H, CH_2Cl_2, 23 °C) without affecting the PMB

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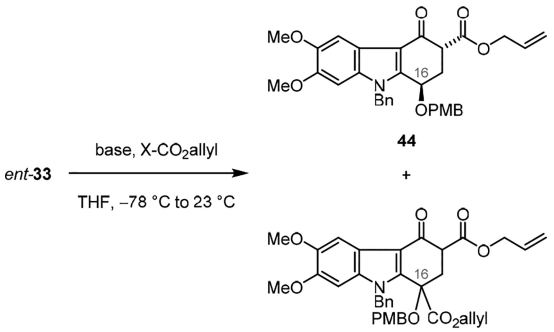
group were unsuccessful, and only complex product mixtures were obtained.

In order to avoid these undesired pathways in the functionalization of **40**, we decided to replace the methyl with an allyl ester and set the quaternary stereocenter in a subsequent diastereoselective palladium-catalyzed decarboxylative allylation reaction.[21] The obtained allyl group could then be converted to the ethyl group in three additional steps.[22] We anticipated that the stereochemical outcome of the allylation step could be controlled by the stereocenter at C16. To obtain the desired stereochemistry in the decarboxylative allylation reaction, we prepared *ent*-**33** according to the route described above.[23]

For the incorporation of the allyl ester, we examined the conditions shown in Table 1. Initially, the acylation reaction of

Table 1. Screen of Conditions for the Acylation of *ent*-33[a]



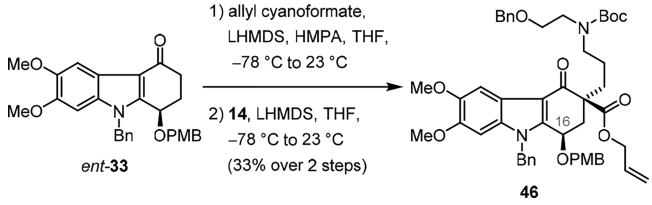
entry	base	X	product: yield[b]
1[c]	NaH	Cl	–
2	LDA	Cl	**45**: 24%
3	LHMDS	Cl	**45**[d]
4	LiTMP	Cl	**45**[d]
5	LTBTA	Cl	**45**[d]
6	LDA	im	**45**[d]
7	LHMDS	im	**45**[d]
8	LDA	CN	**44**: 42%
9	LHMDS	CN	**44**: 62%
10[e]	**LHMDS, HMPA**	**CN**	**44: 70%**

[a]All reactions were performed on a 0.02 mmol scale in THF (c = 0.02 M) with 1.1−1.2 equiv of base and 1.2 equiv of electrophile. [b]Yields of isolated products. [c]The reaction was performed at 0 °C. [d]The reactions were monitored by ^{1}H NMR spectroscopy. The yields were not determined. [e]2 equiv of HMPA were used as additive. LiTMP = lithium 2,2,6,6-tetramethylpiperidide, LTBTA = lithium *tert*-butyltrityl-amide, im = 1-imidazoyl.

ent-**33** with sodium hydride (1.1 equiv) and commercially available allyl chloroformate (1.2 equiv) at −78 °C resulted in no product formation. Surprisingly, treatment of *ent*-**33** with lithium diisopropylamide (LDA, 1.2 equiv) and allyl chloroformate (1.2 equiv) resulted in the formation of the diacylated product **45** (entry 2). Extensive screening using a variety of lithium amide bases and allyl chloroformate or allyl 1*H*-imidazole-1-carboxylate failed to provide β-keto ester **44**, and only formation of the diacylated product was observed (entries 3−7). Based on our previous findings that acylation of **44** works best with methyl cyanoformate, we investigated the use of allyl cyanoformate. This modification resulted in the formation of β-keto ester **44** for the first time (entry 8, 42%). Further optimization of the reaction conditions by variation of lithium amide bases and solvents revealed that the use of LHMDS (1.5 equiv) in the presence of hexamethylphosphoramide (HMPA, 2 equiv) is crucial to reproducibly obtain **44** in good yield (70%).

Finally, treatment of **44** with LHMDS, HMPA, and iodide **14** resulted in the smooth formation of β-keto ester **46** (Scheme 9). Other alkylation conditions explored (Cs_2CO_3, MeCN; NaH, DMF; KHMDS, THF) were inferior. Unfortunately, initial attempts to induce the palladium-catalyzed decarboxylative allylation reaction ($Pd(PPh_3)_4$ or $Pd_2(dba)_3$, (*S*)-*t*-Bu-PHOX)[24] only resulted in decarboxylation without incorporation of the allyl group. A more exhaustive screen of ligands is currently underway in our laboratories and should ultimately allow us to complete the total synthesis of jerantinine E.

Scheme 9. Successful Alkylation with Building Block 14



CONCLUSION

We have reported a synthetic route toward the total synthesis of the *Aspidosperma* alkaloid jerantinine E (**1**). The presented strategies rely on an efficient one-pot β-C−H bromination protocol to provide the C-ring subunit of the target structure. A palladium-catalyzed amination reaction was used to further functionalize the β-bromo enones and oxidative indole formation enabled formation of the tricyclic ABC tetrahydrocarbazolone fragment of jerantinine E (**1**). Our initial strategy to construct the functionalized tricyclic key intermediate of the natural product was hampered by the base-mediated elimination of the benzyl ether at C16 of the C-ring. Starting from a γ-hydroxylated enone instead, we were able to prepare highly functionalized precursor **46**. The overall sequence to the functionalized tetrahydrocarbazolone core of **1** proceeds in 11 linear steps from commercially available ketone **28** and the secondary amine component **14**. The latter contains all carbon atoms of the D and E rings of the natural product. The presented strategy is amenable to rapid modification to give a variety of tetrahydrocarbazolone structural motifs.

EXPERIMENTAL SECTION

General Methods. All reactions were performed in oven-dried or flame-dried glassware fitted with rubber septa under a positive pressure of argon unless otherwise stated. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from benzophenone and sodium prior to use. Dichloromethane (CH_2Cl_2), triethylamine (NEt_3), and *N*,*N*-diisopropylamine (DIPA) were distilled from CaH_2 prior to use. Commercially available *N*-bromosuccinimide (NBS) was purified by recrystallization from water.[25] All other reagents and solvents were purchased from commercial suppliers and were used without further purification. The reactions were magnetically stirred and monitored by NMR spectroscopy or analytical thin-layer chromatography (TLC). The TLC plates were visualized by exposure to ultraviolet light (UV, 254 nm) and exposure to either an aqueous solution of ceric ammoniummolybdate (CAM) or an aqueous solution of potassium permanganate ($KMnO_4$) followed by heating with a heat gun. ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ or CD_2Cl_2. Proton chemical shifts are expressed in parts per million (δ scale) and

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are calibrated using residual undeuterated solvent as an internal reference. Additionally to ^{1}H and ^{13}C NMR measurements, 2D NMR techniques such as homonuclear correlation spectroscopy (COSY), heteronuclear single quantum coherence (HSQC), and heteronuclear multiple bond coherence (HMBC) were used to assist signal assignment. Infrared (IR) spectra were recorded on an FT-IR spectrometer. IR data are reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained by electrospray ionization (ESI) or electron ionization (EI) using a sector field mass spectrometer. Melting points (Mp's) were determined on a B-450 melting point apparatus from BÜCHI Labortechnik AG. Optical rotations were recorded on a PerkinElmer 241 or Anton Paar MCP 200 polarimeter with a sodium lamp and are reported as follows: $[\alpha]_D^{T[^\circ C]}$ (c [g/100 mL], solvent). X-ray structural analyses were performed on a diffractometer using Mo Kα radiation (λ = 0.71073 Å, graphite monochromator).

Preparation of Azide 19. *N-Boc-tetrahydrocarbazolone 22.* To a solution of tetrahydrocarbazolone *rac*-**13**[6] (80 mg, 0.22 mmol, 1 equiv) in tetrahydrofuran (2.74 mL) was added sodium hydride (13 mg, 0.3 mmol, 1.5 equiv, 60% dispersion in mineral oil) at 0 °C. After 30 min, di-*tert*-butyl dicarbonate (72 mg, 0.3 mmol, 1.5 equiv) was added and the solution was allowed to warm to 23 °C. After 1.5 h, the solution was diluted with saturated aqueous ammonium chloride solution (10 mL) and diethyl ether (10 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (40% ethyl acetate in hexanes) to afford **22** as a white solid (90 mg, 88%). TLC (25% ethyl acetate in hexane): R_f = 0.38 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.71 (s, 1H), 7.34−7.24 (m, 5H), 4.60 (d, J = 12.1 Hz, 1H), 4.50 (d, J = 12.1 Hz, 1H), 4.09−4.02 (m, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.78 (dd, J = 9.2, 3.8 Hz, 1H), 3.62 (app t, J = 9.1 Hz, 1H), 2.72 (ddd, J = 17.4, 14.4, 5.2 Hz, 1H), 2.52−2.42 (m, 2H), 2.33−2.22 (m, 1H), 1.67 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 149.7, 149.4, 147.9, 147.6, 138.1, 130.3, 128.5, 127.9, 127.9, 118.6, 117.9, 102.9, 99.3, 85.5, 73.2, 69.4, 56.3, 56.2, 34.8, 33.9, 28.2, 25.4. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2937, 1736, 1660, 1550, 1493, 1475, 1453, 1369, 1307, 1251, 1209, 1134 cm^{-1}. HR-MS (EI): calcd for $(C_{27}H_{31}O_6N)^+$: 465.2146; found, 465.2150.

Azide 23. *N*-Boc-tetrahydrocarbazolone **22** (12 mg, 0.026 mmol, 1 equiv) was dissolved in tetrahydrofuran (0.3 mL) and 1-chloro-3-iodopropane (21.1 mg, 0.10 mmol, 4.00 equiv) was added. The solution was cooled to 0 °C, and a solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 36 μL, 0.036 mmol, 1.40 equiv) was added dropwise over 6 min. After 2 h, the reaction mixture was allowed to warm to 23 °C. After 1 h, the reaction mixture was diluted with diethyl ether (5 mL), one drop of acetic acid was added, and the resulting suspension was filtered through a fritted glass funnel (Por. 4). The filter cake was rinsed with diethyl ether (10 mL). The filtrate was concentrated, and the crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford the chloride as a colorless oil (8.8 mg, dr = 5:1). No separation of the two diastereomers could be achieved, and the diastereomeric mixture was used for the next step.

The chloride was dissolved in *N*,*N*-dimethylformamide (0.16 mL), and sodium azide (5.3 mg, 0.08 mmol, 5.00 equiv) was added. The reaction mixture was stirred at 50 °C for 2 h, and then the temperature was increased to 75 °C. After 5 h, heating was ceased and the reaction mixture was diluted with water (5 mL) and ethyl acetate (5 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (25% ethyl acetate in hexanes) to afford **23** as a yellow oil (7.5 mg, 53% over 2 steps, dr = 5:1). The major diastereomer could be separated by flash column chromatography. TLC (25% ethyl acetate in hexanes): R_f = 0.48 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.70 (s, 1H), 7.37−7.25 (m, 5H), 4.63 (d, J = 12.2 Hz, 1H), 4.48 (d, J = 12.2 Hz, 1H), 4.09−4.04 (m, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 3.80 (dd, J = 9.1, 3.9 Hz, 1H), 3.63 (t, J = 9.1 Hz, 1H), 3.33 (t, J = 7.0 Hz, 2H), 2.67 (ddd, J = 17.9, 8.3, 4.7 Hz, 1H), 2.52 (ddd, J = 13.4, 4.7, 2.1 Hz, 1H), 2.11−1.99 (m, 2H), 1.76−1.70 (m, 2H), 1.67 (s, 9H), 1.48−1.43 (1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 149.7, 148.8, 147.9, 147.6, 138.0, 130.5, 128.6, 128.0, 128.0, 118.7, 117.8, 102.8, 99.4, 85.6, 73.3, 69.5, 56.3, 56.2, 51.9, 41.5, 35.2, 31.1, 28.2, 26.9, 26.7. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2930, 2096, 1737, 1654, 1476, 1371, 1309, 1206, 1141, 1105 cm^{-1}. HR-MS (ESI): calcd for $(C_{30}H_{37}O_6N_4)^+$ (M + H)$^+$: 549.2713; found, 549.2706.

Preparation of Tetrahydrocarbazolone 33. *(S)-4-[(4-Methoxyphenyl)oxy]cyclohex-2-en-1-one (30).* To a suspension of (*S*)-4-hydroxycyclohex-2-en-1-one (**29**)[26] (2.30 mg, 20.5 mmol, 1 equiv), magnesium oxide (1.66 g, 41.0 mmol, 2.00 equiv, vacuum-dried), and Dudley reagent II[14] (11.5 g, 41.0 mmol, 2.00 equiv) in α,α,α-trifluorotoluene (200 mL) was added dropwise methyl triflate (4.64 mL, 41.0 mmol, 2.00 equiv) at 0 °C. Upon completion of the addition, the reaction mixture was allowed to warm to 23 °C. After 75 min, ethyl acetate (40 mL) was added and the suspension was filtered through a fritted glass funnel. The filter cake was rinsed with ethyl acetate (2 × 20 mL). The filtrate was washed with water (50 mL), and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residual yellow oil was purified by flash column chromatography on silica gel (9% to 14% ethyl acetate in hexanes) to afford **30** as a colorless oil (2.60 mg, 55%). The obtained characterization data were in full agreement with those values reported in the literature.[27]

(S)-3-Bromo-4-[(4-methoxyphenyl)oxy]cyclohex-2-en-1-one (27). (*S*)-4-[(4-Methoxyphenyl)oxy]cyclohex-2-en-1-one (**30**) (340 mg, 1.46 mmol, 1 equiv) was added to a mixture of sodium sulfate (643 mg, 4.53 mmol, 3.10 equiv) and *tert*-butyl carbazate (203 mg, 1.54 mmol, 1.05 equiv) in degassed 1,2-dichloroethane (1.2 mL) in a pressure flask. The resulting suspension was heated to 85 °C. After 4.5 h, the orange mixture was allowed to cool to 23 °C. Dichloromethane (4.4 mL) was added, the solution was cooled to 0 °C, and recrystallized *N*-bromosuccinimide (274 mg, 1.54 mmol, 1.05 equiv) was added. After 1 h at 0 °C, triethylamine (427 μL, 3.07 mmol, 2.10 equiv) was added in one portion. The resulting orange solution was stirred for 24 h at 23 °C. Acetone−water (v/v = 9:2, 6.1 mL) and Amberlyst 15 (1.76 g) were added, and the yellow suspension was heated to 50 °C. After 12 h, the reaction mixture was allowed to cool to 23 °C and then was diluted with dichloromethane (3 mL). The crude mixture was dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated. The residual yellow oil was purified by flash column chromatography on silica gel (14% ethyl acetate in hexanes) to afford **27** as a yellow oil (261 mg, 57%). TLC (20% ethyl acetate in hexane): R_f = 0.32 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.31 (m, 2H), 6.94−6.87 (m, 2H), 6.48 (s, 1H), 4.68 (s, 2H), 4.26 (t, J = 4.7 Hz, 1H), 3.81 (s, 3H), 2.72−2.61 (m, 1H), 2.36 (dt, J = 16.9, 5.6 Hz, 1H), 2.23−2.14 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.9, 159.7, 149.4, 133.8, 129.8, 129.4, 114.0, 76.0, 72.6, 55.4, 33.2, 28.0. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2934, 2836, 1682, 1611, 1513, 1464, 1331, 1302, 1278, 1247, 1174, 1084 cm^{-1}. HR-MS (EI): calcd for $(C_{14}H_{15}{}^{79}BrO_3)^+$, 310.0199; found, 310.0200. $[\alpha]_{589}^{20}$ = −46.4 (c = 1.0 × 10 g·mL^{-1}, CH_2Cl_2).

Enaminone 31. To an oven-dried pressure tube were added chloro(2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl)(2′-amino-1,1′-biphenyl-2-yl) palladium(II) (126 mg, 0.18 mmol, 0.10 equiv), 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (72 mg, 0.18 mmol, 0.10 equiv), sodium *tert*-butoxide (252 mg, 2.63 mmol, 1.50 equiv), 3,4-dimethoxyaniline (**15**) (402 mg, 2.63 mmol, 1.50 equiv), and toluene (12 mL). (*S*)-3-Bromo-4-[(4-methoxyphenyl)-oxy]cyclohex-2-en-1-one (**27**) (545 mg, 1.75 mmol, 1 equiv) was added, and the dark red suspension was heated to 80 °C for 18 h. The reaction mixture was allowed to cool to 23 °C and was filtered through a short plug of Celite. The filter cake was rinsed with dichloromethane (30 mL). The filtrate was concentrated and the residual red oil was

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purified by flash column chromatography on silica gel (1% methanol in dichloromethane) to afford **31** as a brown foam (474 mg, 77%). TLC (2% methanol in dichloromethane): R_f = 0.22 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.3 Hz, 2H), 6.98 (s, 1H), 6.94 (d, J = 8.3 Hz, 2H), 6.80 (d, J = 8.5 Hz, 1H), 6.69 (dd, J = 8.5, 2.4 Hz, 1H), 6.63 (d, J = 2.4 Hz, 1H), 5.39 (s, 1H), 4.80 (d, J = 11.2 Hz, 1H), 4.56 (d, J = 11.2 Hz, 1H), 4.41 (dd, J = 11.4, 4.4 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 2.60−2.40 (m, 2H), 2.34 (ddd, J = 17.2, 13.4, 4.6 Hz, 1H), 1.99 (qd, J = 11.9, 4.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 162.0, 159.9, 149.5, 147.3, 130.7, 129.9, 129.1, 116.8, 114.3, 111.5, 108.5, 97.9, 74.1, 71.4, 56.2, 56.1, 55.5, 35.1, 27.7. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3250, 2393, 1611, 1581, 1500, 1463, 1235, 1196, 1172, 1026 cm^{-1}. HR-MS (EI): calcd for $(C_{22}H_{25}NO_5)^+$, 383.1727; found, 383.1727. $[\alpha]_{589}^{20}$ = +12.8 (c = 0.31 × 10 g·mL^{-1}, CH_2Cl_2).

Tetrahydrocarbazolone ***32***. A solution of enaminone **31** (485 mg, 1.26 mmol, 1 equiv) in *N*,*N*-dimethylformamide (16 mL) was added to an oven-dried pressure tube containing palladium(II) acetate (28.4 mg, 0.13 mmol, 0.10 equiv), copper(II) acetate (689 mg, 3.79 mmol, 3.00 equiv), and potassium carbonate (524 mg, 3.79 mmol, 3.00 equiv). The resulting green-brown mixture was placed in a preheated oil bath at 140 °C. After 1 h, the reaction mixture was allowed to cool to 23 °C, and the dark solution was filtered through a short plug of Celite. The filter cake was rinsed with dichloromethane (40 mL). The filtrate was concentrated. The residual black oil was purified by flash column chromatography on silica gel (50% to 66% ethyl acetate in hexanes) to afford **32** as a gray solid (275 mg, 57%). TLC (1% methanol in dichloromethane): R_f = 0.12 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 7.66 (s, 1H), 7.32 (d, J = 8.3 Hz, 2H), 6.89 (d, J = 8.3 Hz, 2H), 6.83 (s, 1H), 4.88 (dt, J = 8.8, 3.2 Hz, 1H), 4.75 (d, J = 11.2 Hz, 1H), 4.56 (d, J = 11.2 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 2.75 (dt, J = 15.5, 4.0 Hz, 1H), 2.60−2.46 (m, 2H), 2.29−2.10 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 159.6, 148.7, 147.8, 146.9, 130.1, 129.8, 129.7, 117.5, 114.2, 112.8, 103.1, 94.8, 71.0, 70.8, 56.3, 56.2, 55.4, 36.3, 30.5. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3294, 2949, 1626, 1585, 1540, 1513, 1466, 1340, 1295, 1247, 1135 cm^{-1}. HR-MS (EI): calcd for $(C_{22}H_{23}NO_5)^+$, 381.1571; found, 381.1570. Mp 196−199 °C. $[\alpha]_{589}^{20}$ = −1.4 (c = 1.0 × 10 g·mL^{-1}, CH_2Cl_2).

N-Benzyltetrahydrocarbazolone ***33***. Tetrahydrocarbazolone **32** (203 mg, 0.532 mmol, 1 equiv) was dissolved in *N*,*N*-dimethylformamide (2.7 mL), and the solution was cooled to 0 °C. Sodium hydride (25.5 mg, 0.639 mmol, 1.20 equiv, 60% dispersion in mineral oil) was added, and the suspension was stirred for 1 h at 0 °C. Benzyl bromide (76 μL, 0.639 mmol, 1.20 equiv) was added, and the reaction mixture was allowed to warm to 23 °C. After 2 h, saturated aqueous ammonium chloride solution (5 mL) and ethyl acetate (5 mL) were added, the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), the washed solution was dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (60% ethyl acetate in hexanes) to afford **33** as a slightly beige solid (224 mg, 89%). Crystals that were suitable for X-ray diffraction analysis were obtained by crystallization from dichloromethane. TLC (50% ethyl acetate in hexanes): R_f = 0.22 (UV, $KMnO_4$). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.67 (s, 1H), 7.27−7.22 (m, 3H), 7.14 (d, J = 8.4 Hz, 2H), 6.95 (dd, J = 6.7, 2.8 Hz, 2H), 6.84−6.76 (m, 2H), 6.64 (s, 1H), 5.22 (q, J = 16.7 Hz, 2H), 4.76 (t, J = 3.6 Hz, 1H), 4.66 (d, J = 11.2 Hz, 1H), 4.43 (d, J = 11.1 Hz, 1H), 3.88 (s, 3H), 3.77 (s, 3H), 3.72 (s, 3H), 2.88 (ddd, J = 16.4, 11.8, 4.4 Hz, 1H), 2.57−2.49 (m, 1H), 2.41 (dt, J = 16.6, 4.2 Hz, 1H), 2.26 (ddt, J = 15.0, 11.7, 4.0 Hz, 1H). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 194.2, 160.0, 148.7, 147.8, 146.7, 137.1, 132.1, 130.3, 130.2, 129.3, 128.1, 126.7, 117.6, 114.3, 113.7, 103.8, 94.4, 71.1, 67.5, 56.6, 56.5, 55.8, 47.9, 34.3, 27.9. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2943, 1700, 1647, 1558, 1540, 1513, 1483, 1444, 1303, 1270, 1248, 1173, 1106 cm^{-1}. HR-MS (ESI): calcd for $(C_{29}H_{29}NO_5)^+$, 471.2046; found, 471.2054. Mp 139−144 °C. $[\alpha]_{589}^{20}$ = −6.4 (c = 1.0 × 10 g·mL^{-1}, CH_2Cl_2).

Preparation of Tetrahydrocarbazolone 34. *Tetrahydrocarbazolone* ***34***. *N*-Benzyltetrahydrocarbazolone **33** (49 mg, 0.10 mmol, 1 equiv) in tetrahydrofuran (0.5 mL) was added dropwise to a solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 0.12 mL, 0.12 mmol, 1.2 equiv) and hexamethylphosphoramide (36 μL, 0.20 mmol, 2.0 equiv) in tetrahydrofuran (0.5 mL) at −78 °C. After 1 h, methyl cyanoformate (12 μL, 0.15 mmol, 1.5 equiv) was added in one portion and the solution was slowly allowed to warm to 23 °C. After 20 h, the solution was diluted with saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes) to afford the β-keto ester as a red oil (40 mg, 73%) containing minor impurities. The β-keto ester was used without additional purification for the next step.

Sodium hydride (2.5 mg, 62 μmol, 1.5 equiv, 60% suspension in mineral oil) was added a solution of the β-keto ester (22 mg, 41 μmol, 1 equiv) in *N*,*N*-dimethylformamide (0.4 mL) at 0 °C. After 1 h, ethyl iodide (13 μL, 0.16 mmol, 4.0 equiv) was added, the reaction flask was covered with aluminum foil, and the reaction mixture was allowed to warm to 23 °C. After 20 h, the reaction mixture was diluted with saturated aqueous ammonium chloride solution (10 mL) and ethyl acetate (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were washed with saturated aqueous sodium chloride solution (10 mL), and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (40% ethyl acetate in hexanes) to afford **34** as a brown oil (12 mg, 52%, dr = 4:1). All characterization data refer to the major diastereomer shown in the scheme. TLC (50% ethyl acetate in hexanes): R_f = 0.40 (UV, CAM). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.26−7.24 (m, 3H), 7.16−7.11 (m, 2H), 6.98−6.92 (m, 2H), 6.81−6.78 (m, 2H), 6.59 (s, 1H), 5.42−5.29 (m, 2H), 5.21 (dd, J = 7.7, 5.4 Hz, 1H), 4.71 (d, J = 11.1 Hz, 1H), 4.47 (d, J = 11.0 Hz, 1H), 3.95 (s, 3H), 3.79 (s, 3H), 3.76 (s, 3H), 3.66 (s, 3H), 3.05 (dd, J = 13.3, 5.3 Hz, 1H), 2.29 (dd, J = 13.9, 7.5 Hz, 1H), 2.24 (dd, J = 13.2, 7.8 Hz, 1H), 2.09 (dd, J = 14.1, 7.3 Hz, 1H), 1.00 (t, J = 7.5 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.7, 172.5, 159.6, 148.1, 147.3, 146.2, 136.5, 132.4, 129.8, 128.9, 127.7, 126.3, 117.8, 114.0, 112.7, 103.4, 93.8, 70.5, 68.9, 58.9, 56.3, 55.4, 52.7, 48.3, 36.0, 28.2, 9.4. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2936, 2252, 1726, 1648, 1483, 1441, 1246, 1162, 1029 cm^{-1}, HR-MS (EI): calcd for $(C_{33}H_{35}NO_7)^+$, 557.2408; found, 557.2403.

Synthesis of the Tertiary Amine Building Block 14. *((2-Iodoethoxy)methyl)benzene (****37****).* 2-Benzyloxyethanol (5.00 g, 32.9 mmol, 1 equiv) was dissolved in dichloromethane (95 mL), and triphenylphosphine (12.9 g, 49.3 mmol, 1.50 equiv) and imidazole (3.36 g, 49.3 mmol, 1.50 equiv) were added. Iodine (12.5 g, 49.3 mmol, 1.5 equiv) was carefully added in three portions, and the yellow suspension was stirred at 23 °C. After 18 h, aqueous sodium thiosulfate solution (1 M, 100 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 100 mL), and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (5% ethyl acetate in hexanes) to afford **37** (8.00 g, 93%) as a colorless oil. The obtained characterization data were in full agreement with those values reported in the literature.[20]

*tert-Butyl N-Allyl-N-(2-benzyloxyethyl) Carbamate (****38****).* *tert*-Butyl allylcarbamate (**36**) (3.14 g, 20.0 mmol, 1 equiv) was dissolved in *N*,*N*-dimethylformamide (66 mL) and was added dropwise to a suspension of sodium hydride (1.20 g, 30.0 mmol, 1.50 equiv, 60% dispersion in mineral oil) in *N*,*N*-dimethylformamide (100 mL) at 0 °C. After 45 min, ((2-iodoethoxy)methyl)benzene (**37**) (6.81 g, 26.0 mmol, 1.30

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equiv) was added dropwise. The reaction mixture then was allowed to warm to 23 °C. After 16 h, the reaction mixture was carefully diluted with ammonium chloride solution (200 mL) and ethyl acetate (100 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL), and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **38** as a colorless oil (4.65 g, 80%). TLC (33% ethyl acetate in hexanes): R_f = 0.83 (UV, CAM). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.38−7.25 (m, 5H), 5.79 (dddd, J = 17.7, 9.8, 6.0, 5.2 Hz, 1H), 5.15−5.06 (m, 2H), 4.51 (s, 2H), 3.88 (br s, 2H), 3.58 (t, J = 5.9 Hz, 2H), 3.39 (br s, 2H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 155.8, 139.3, 135.2, 128.8, 128.0, 128.0, 116.3, 116.0, 79.8, 73.4, 69.4, 51.3, 50.7, 46.9, 28.7. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2976, 2930, 2861, 1690, 1477, 1454, 1405, 1365, 1244, 1173, 1150, 1103, 1029 cm^{-1}. HR-MS (ESI): calcd for $(C_{17}H_{26}NO_3)^+$ (M + H)$^+$, 292.1913; found, 292.1909.

*tert-Butyl N-(3-Hydroxypropyl)-N-(2-benzyloxyethyl) Carbamate (**39**).* *tert*-Butyl *N*-allyl-*N*-(2-benzyloxyethyl) carbamate (**38**) (3.1 g, 10.6 mmol, 1 equiv) was dissolved in tetrahydrofuran (5.6 mL), and a solution of 9-borabicyclo[3.3.1]nonane (0.5 M solution in tetrahydrofuran, 29.8 mL, 14.9 mmol, 1.40 equiv) was added at 0 °C. After 3 h at 0 °C, the reaction mixture was allowed to warm to 23 °C. After 16 h, aqueous sodium hydroxide solution (10 wt %, 4.9 mL) and aqueous hydrogen peroxide solution (30 wt %, 4.9 mL) were added dropwise and the reaction was heated to 50 °C. After 2 h, heating was ceased and the solution was allowed to cool to 23 °C. The reaction mixture was saturated with sodium carbonate, and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution, and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (33% ethyl acetate in hexanes) to afford **39** as a colorless oil (1.64 g, 50%). TLC (9% ethyl acetate in hexanes): R_f = 0.10 (UV, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.27 (m, 5H), 4.51 (s, 2H), 3.80 (t, J = 7.1 Hz, 1H), 3.67−3.31 (m, 8H), 1.87−1.59 (m, 2H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 138.1, 128.6, 127.9, 127.7, 80.4, 73.3, 68.8, 58.4, 47.3, 43.9, 30.7, 28.5. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 3444, 2974, 2866, 1688, 1667, 1479, 1454, 1413, 1366, 1246, 1166, 1139, 1103 cm^{-1}. HR-MS (ESI): calcd for $(C_{17}H_{28}NO_4)^+$ (M + H)$^+$, 310.2018; found, 310.2015.

*tert-Butyl N-(3-Iodopropyl)-N-(2-benzyloxyethyl) Carbamate (**14**).* Iodine (541 mg, 2.13 mmol, 1.20 equiv) was added to a solution of triphenylphosphine (559 mg, 2.13 mmol, 1.20 equiv) and imidazole (145 mg, 2.13 mmol, 1.20 equiv) in dichloromethane (17.5 mL) at 0 °C. After 15 min, a solution of *tert*-butyl *N*-(3-hydroxypropyl)-*N*-(2-phenoxyethyl) carbamate (**39**) (550 mg, 1.78 mmol, 1 equiv) in dichloromethane (3.5 mL) was added dropwise. Upon completion of the addition, the yellow suspension was allowed to warm to 23 °C. After 3 h, the reaction mixture was diluted with water (15 mL) and ethyl acetate (15 mL). The layers were separated, and the organic layer was washed with aqueous sodium thiosulfate solution (1 M, 40 mL) and saturated aqueous sodium chloride solution (40 mL). The washed solution was dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (10% ethyl acetate in hexanes) to afford **14** as a yellow oil (592 mg, 79%). TLC (20% ethyl acetate in hexanes): R_f = 0.68 (UV, $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.25 (m, 5H), 4.52 (s, 2H), 3.68−3.51 (m, 2H), 3.49−3.37 (m, 2H), 3.34 (t, J = 7.0 Hz, 2H), 3.18−3.08 (m, 2H), 2.18−1.98 (m, 2H), 1.47 (s, 5H), 1.41 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, ∼1:1 rotamer ratio, asterisk denotes signals of the second rotamer) δ 155.6, 138.3, *138.3, 132.5, *132.4, *128.6, 128.6, *127.8, 127.7, 80.0, *79.8, 73.2, 69.1, *69.0, 49.2, *47.9, 47.6, 40.6, 32.7, *32.5, 28.6, *28.6. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2974, 1671, 1477, 1465, 1454, 1409, 1366, 1241, 1156, 1114 cm^{-1}. HR-MS (ESI): calcd for $(C_{17}H_{27}NO_3I)^+$ (M + H)$^+$, 420.1036; found, 420.1034.

Preparation of Tetrahydrocarbazolone 40. *Tetrahydrocarbazolone **40**.* *N*-Benzyltetrahydrocarbazolone **33** (50 mg, 0.11 mmol, 1 equiv) was dissolved in tetrahydrofuran (1.1 mL) and was added dropwise to a solution of lithium diisopropylamide (0.5 M in tetrahydrofuran, 320 μL, 0.16 mmol, 1.50 equiv; freshly prepared) at −78 °C. After 1 h, methyl cyanoformate (17 μL, 0.21 mmol, 2.00 equiv) was added in one portion and the solution was slowly allowed to warm to 23 °C. After 14 h, the red solution was diluted with saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL), and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes) to afford β-keto ester as an orange oil (43 mg, dr = 2.5:1) which contained minor impurities. The β-keto ester was used without additional purification for the next step. To a suspension of sodium hydride (4.9 mg, 0.12 mmol, 1.5 equiv, 60% suspension in mineral oil) in *N*,*N*-dimethylformamide (0.4 mL) was added a solution of β-keto ester (43 mg, 0.08 mmol, 1 equiv) in *N*,*N*-dimethylformamide (0.8 mL) at 0 °C. After 30 min, *tert*-butyl *N*-(3-iodopropyl)-*N*-(2-phenoxyethyl) carbamate (**14**) (136 mg, 0.33 mmol, 4.00 equiv) was added, the reaction flask was covered with aluminum foil, and the reaction mixture was allowed to warm to 23 °C. After 20 h, the reaction mixture was diluted with saturated aqueous ammonium chloride solution (10 mL) and ethyl acetate (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were washed with saturated aqueous sodium chloride solution (10 mL), and the washed solution was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (25% to 50% ethyl acetate in hexanes) to afford **40** as a yellow solid (54 mg, 60% over 2 steps). Partial separation of the diastereomeric mixture could be achieved by flash column chromatography on silica gel (25% ethyl acetate in hexanes). All characterization data refer to the major diastereomer shown in the scheme. TLC (50% ethyl acetate in hexanes): R_f = 0.28 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.79 (s, 1H), 7.34−7.27 (m, 5H), 7.27−7.21 (m, 3H), 7.15−7.11 (m, 2H), 6.96−6.92 (m, 2H), 6.81−6.78 (m, 2H), 6.60 (s, 1H), 5.34 (q, J = 16.5 Hz, 2H), 5.19 (dd, J = 7.9, 5.4 Hz, 1H), 4.68 (d, J = 11.2 Hz, 1H), 4.51 (s, 2H), 4.44 (d, J = 11.2 Hz, 1H), 3.94 (s, 3H), 3.78 (s, 3H), 3.75 (s, 3H), 3.63 (s, 3H), 3.64−3.55 (m, 2H), 3.42 (t, J = 5.9 Hz, 2H), 3.36−3.25 (m, 3H), 3.02 (dd, J = 13.2, 5.5 Hz, 1H), 2.28−2.11 (m, 2H), 2.02 (td, J = 13.3, 12.6, 4.7 Hz, 1H), 1.63 (ddt, J = 31.4, 13.1, 6.2 Hz, 2H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 189.3, 172.5, 159.8, 155.7, 148.4, 147.7, 146.3, 138.7, 136.6, 132.6, 129.9, 128.9, 128.5, 127.7, 126.4, 118.2, 114.2, 112.8, 103.9, 94.4, 79.5, 73.3, 70.5, 69.1, 69.0, 58.4, 56.5, 56.4, 55.5, 52.6, 48.5, 47.4, 36.8, 32.5, 28.7, 28.6. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2935, 1727, 1689, 1658, 1650, 1513, 1494, 1483, 1452, 1365 cm^{-1}. HR-MS (ESI): calcd for $(C_{48}H_{57}N_2O_{10})^+$, 821.4013; found, 821.4008. $[\alpha]_{589}^{20}$ = −3.6 (c = 0.5 × 10 g·mL^{-1}, CH_2Cl_2).

Preparation of Amine 42. *Amine **42**.* Tetrahydrocarbazolone **40** (13.5 mg, 16.4 μmol, 1 equiv) was added to a solution of hydrogen chloride in 1,4-dioxane (4 M, 0.1 mL) at 23 °C. After 2 h, the reaction mixture was diluted with saturated aqueous potassium carbonate solution (5 mL) and ethyl acetate (5 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over sodium sulfate, the dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (4% to 8% methanol in dichloromethane) to afford **41** (9.6 mg, quant.) which contained minor impurities. The product was used without additional purification for the next step. HR-MS (ESI): calcd for $(C_{35}H_{39}N_2O_6)^+$ (M + H)$^+$: 583.2808; found, 583.2805.

Preparation of Allyl Cyanoformate. *Allyl Cyanoformate.* Trimethylsilyl cyanide (1.98 g, 20.0 mmol, 1 equiv) was added to a suspension of allyl chloroformate (2.41 g, 20.0 mmol, 1 equiv) and 1,4-diazabicyclo[2.2.2]octane (12.30 mg, 0.110 mmol, 0.005 equiv) at 0

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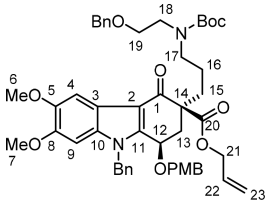
°C. The solution was allowed to warm to 23 °C. After 12 h, 1,4-diazabicyclo[2.2.2]octane was removed by filtration to afford allyl cyanoformate as a yellow oil (1.80 g, 81%). The product was used without further purification for the next step. The obtained characterization data were in full agreement with those values reported in the literature.[28]

Preparation of Diacylated Tetrahydrocarbazolone 45. *Diacylated Tetrahydrocarbazolone* ***45***. *N*-Benzyltetrahydrocarbazolone **33** (92 mg, 0.19 mmol, 1 equiv) was dissolved in tetrahydrofuran (2 mL) and was added dropwise to a solution of lithium diisopropylamide (freshly prepared from diisopropylamine (0.036 mL, 0.25 mmol, 1.3 equiv) and *n*-butyl lithium (2.3 M in hexanes, 0.10 mL, 0.23 mmol, 1.2 equiv)) in tetrahydrofuran (3 mL) at −78 °C. After 1 h, allyl chloroformate (0.041 mL, 0.39 mmol, 2.0 equiv) was added in one portion. The solution was allowed to warm to 23 °C. After 18 h, the reaction was diluted with saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude material was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes) to afford **45** as a yellow oil (30 mg, 24%). TLC (50% ethyl acetate in hexanes): R_f = 0.60 (UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.27−7.20 (m, 3H), 7.19−7.10 (m, 2H), 6.87−6.78 (m, 4H), 6.59 (s, 1H), 5.94 (ddt, J = 17.2, 10.5, 5.6 Hz, 1H), 5.80 (ddt, J = 17.2, 10.5, 5.6 Hz, 1H), 5.36 (dq, J = 17.2, 1.6 Hz, 1H), 5.27−5.02 (m, 5H), 4.79−4.71 (m, 3H), 4.66 (d, J = 11.2 Hz, 1H), 4.64−4.50 (m, 2H), 4.37 (d, J = 11.2 Hz, 1H), 3.94 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H), 3.28 (dd, J = 14.5, 3.7 Hz, 1H), 2.99 (dd, J = 14.4, 3.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.1, 168.4, 168.1, 159.7, 148.4, 147.5, 144.9, 136.0, 132.0, 131.5, 130.5, 128.9, 127.9, 126.1, 118.7, 118.4, 117.6, 113.9, 112.1, 103.4, 93.6, 70.5, 66.8, 66.8, 65.1, 64.8, 56.3, 56.2, 55.4, 47.5, 34.0. IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2936, 1731, 1658, 1611, 1542, 1514, 1485, 1443, 1272, 1247, 1164, 1075, 1029 cm^{-1}. HR-MS (ESI): calcd for $(C_{37}H_{38}NO_9)^+$ $(M + H)^+$, 640,2547; found, 640.2542.

Preparation of Tetrahydrocarbazolone 46.



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Tetrahydrocarbazolone ***46***. *N*-Benzyltetrahydrocarbazolone *ent*-**33** (10 mg, 0.020 mmol, 1 equiv) was dissolved in tetrahydrofuran (0.5 mL), and hexamethylphosphoramide (0.040 mL, 0.040 mmol, 2.00 equiv) was added. A solution of lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 0.30 mL, 0.30 mmol, 1.5 equiv) was added dropwise at −78 °C. After 1 h, allyl cyanoformate (4.71 mg, 0.04 mmol, 2.00 equiv) was added in one portion. The solution was allowed to warm to 23 °C. After 13 h, the reaction was diluted with saturated aqueous sodium bicarbonate solution (2 mL) and ethyl acetate (2 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (2 mL) and dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude material was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes) to afford β-keto ester **44** as a beige foam, which contained minor impurities. **44** was used without additional purification for the next step. To a solution of β-keto ester **44** (12 mg, 0.020 mmol, 1 equiv) and carbamate **7** (36.2 mg, 0.080 mmol, 4.0 equiv) in tetrahydrofuran (0.5 mL) was added lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 0.04 mL, 0.040 mmol, 2.0 equiv) dropwise over 15 min at −78 °C. The solution was allowed to warm to 23 °C. After 12 h, the reaction mixture was diluted with ethyl acetate (2 mL) and saturated aqueous sodium bicarbonate solution (2 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The crude product was purified by flash column chromatography on silica gel (25% to 50% ethyl acetate in hexanes) to afford **46** as a yellow oil (4.0 mg, 33% over 2 steps). TLC (50% ethyl acetate in hexanes): R_f = 0.21 (UV, CAM). *Protons of diastereotopic methylene groups are reported as HA and HB, where HA is the more downfield shifted proton. In cases where resonances overlap or cannot be unambiguously assigned to a single proton or carbon atom, multiple assignments are listed (e.g., the* ^{13}*C assignment "130.0 (PMB, Bn)" indicates that the resonance at 130.0 is either PMB or Bn).* ^{1}H NMR (400 MHz, $CDCl_3$,) δ 7.80 (s, 1H, H-4), 7.35−7.27 (m, 4H, Bn), 7.26−7.22 (m, 4H, Bn), 7.16−7.10 (m, 2H, PMB), 6.91−6.89 (m, 2H, Bn), 6.81−6.76 (m, 2H, PMB), 6.59 (s, 1H, H-9), 5.78 (ddt, $^3J_{22/23}$ = 17.2, $^3J_{22/23}$ = 10.4, $^3J_{22/21}$ = 5.5 Hz, 1H, H-22), 5.40 (d, $^2J_{HA/HB}$ = 16.6 Hz, 1H, Bn), 5.28 (d, $^2J_{HA/HB}$ = 16.6 Hz, 1H, Bn), 5.20−5.06 (m, 3H, H-12, H-23), 4.68 (app t, $^2J_{HA/HB}$ = 11.0 Hz, 1H, PMB), 4.54 (d, $^3J_{21/22}$ = 5.5 Hz, 2H, H-21), 4.51 (s, 2H, Bn), 4.42 (d, $^2J_{HA/HB}$ = 11.0 Hz, 1H, PMB), 3.94 (s, 3H, H-6), 3.78 (s, 3H, PMB), 3.76 (s, 3H, H-7), 3.63−3.52 (m, 2H, H-19), 3.41 (br s, 2H, H-18), 3.31 (br s, 2H, H-17), 3.03 (t, $^3J_{13/12}$ = 12.7 Hz, 1H, H_A-13), 2.31−2.09 (m, 3H, H_B-13, H-15), 1.66−1.56 (m, 2H, H-16), 1.43 (app d, J = 10.0 Hz, 9H, Boc). ^{13}C NMR (100 MHz, $CDCl_3$, asterisks denotes rotamer peaks) δ 189.3 (C-1), 171.5 (C-20), 159.6 (PMB), 155.7 (Boc), 155.5* (Boc), 148.1 (C-8), 147.3 (C-5), 146.1 (C-11), 145.9* (C-11), 138.5 (Bn), 136.4 (Bn), 132.4 (C-10), 131.7 (C-22), 130.0 (PMB, Bn), 129.8 (PMB, Bn), 129.2 (PMB), 128.9 (Bn), 128.5 (Bn), 127.6 (Bn), 126.2 (Bn), 118.5 (C-3, C-23), 117.7 (C-3, C-23), 114.0 (PMB), 112.7 (C-2), 103.3 (C-4), 93.7 (C-9), 79.5 (Boc), 73.1 (Bn), 70.3 (PMB), 69.0 (C-12), 68.7 (C-19), 65.9 (C-21), 58.3 (C-14), 56.3 (C-6), 56.2 (C-7), 55.4 (PMB), 48.2 (Bn), 47.2 (C-17), 47.0 (C-18), 36.5 (C-13), 32.3 (C-15), 32.1* (C-15), 28.6 (Boc), 24.2 (C-16), 23.7* (C-16). IR (Diamond-ATR, neat) $\tilde{\nu}_{max}$: 2932, 1728, 1689, 1513, 1453, 1411, 1365, 1248, 1163, 1103, 1067, 1029 cm^{-1}. HR-MS (ESI): calcd for $(C_{50}H_{59}N_2O_{10})^+$ $(M + H)^+$, 847.4170; found, 847.4155.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01095.

Experimental procedures, X-ray crystallographic data for **33**, NMR spectra of products (PDF)

Crystallographic data for **33** (CIF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Gribble, G. W.; Joule, J. A. *Progress in Heterocyclic Chemistry*; Elsevier Ltd.: 2011; Vol. *23*, pp 1−25.
(2) (a) Lim, K.-H.; Hiraku, O.; Komiyama, K.; Kam, T.-S. *J. Nat. Prod.* **2008**, *71*, 1591−1594. (b) Gigant, B.; Wang, C.; Ravelli, R. B. G.; Roussi, F.; Steinmetz, M. O.; Curmi, P. A.; Sobel, A.; Knossow, M. *Nature* **2005**, *435*, 519−522. (c) Serasanambati, M.; Chilakapati, S. R.; Vangavaragu, J. R.; Chilakapati, D. R. *International Journal of Drug Delivery* **2014**, *6*, 133−139 and references therein.
(3) He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771−6772.
(4) Saxton, J. E. *Chemistry of Heterocyclic Compounds*, Vol. *25*; WILEY VCH Verlag: 1983; pp 331−437.
(5) Frei, R.; Staedler, D.; Raja, A.; Franke, R.; Sasse, F.; Gerber-Lemaire, S.; Waser, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 13373−13376.
(6) Huber, T.; Rickmeier, J.; Kaiser, D.; Magauer, T. *J. Org. Chem.* **2015**, *80*, 2281−2294.
(7) (a) Jung, S. H.; Kim, J. H. *Bull. Korean Chem. Soc.* **2002**, *23*, 365−366 and references cited therein. (b) Lee, S. I.; Kang, B. C.; Hwang, G.-S.; Ryu, D. H. *Org. Lett.* **2013**, *15*, 1428−1431. (c) Matsuo, J.; Aizawa, Y. *Chem. Commun.* **2005**, 2399−2401.
(8) (a) Eckelbarger, J.; Wilmot, J. T.; Gin, D. Y. *J. Am. Chem. Soc.* **2006**, *128*, 10370−10371. (b) Araki, K.; Saito, K.; Arimoto, H.; Uemura, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 81−84.
(9) (a) Desmaële, D.; d'Angelo, J. *J. Org. Chem.* **1994**, *59*, 2292−2303. (b) d'Angelo, J.; Desmaële, D. *Tetrahedron Lett.* **1990**, *31*, 879−882.
(10) Yang, R.; Qiu, F. G. *Angew. Chem., Int. Ed.* **2013**, *52*, 6015−6018.
(11) Jing, P.; Yang, Z.; Zhao, C.; Zheng, H.; Fang, B.; Xie, X.; She, X. *Chem. - Eur. J.* **2012**, *18*, 6729−6732.
(12) The elimination product **24** could not be characterized due to its instability. However, the decomposition pathway was confirmed by high resolution mass spectroscopy of a model system. See Supporting Information for further details.
(13) Matsuzawa, M.; Kakeya, H.; Yamaguchi, J.; Shoji, M.; Onose, R.; Osada, H.; Hayashi, Y. *Chem. - Asian J.* **2006**, *1*, 845−851.
(14) Nwoye, E. O.; Dudley, G. B. *Chem. Commun.* **2007**, 1436−1437.
(15) Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073−14075.
(16) Neumann, J. J.; Rakshit, S.; Dröge, T.; Würtz, S.; Glorius, F. *Chem. - Eur. J.* **2011**, *17*, 7298−7303.
(17) Other indole protecting groups (Boc, Ts) were unstable under the alkylation conditions.
(18) CCDC 1547827 contains the supplementary crystallographic data for compound **33**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures/.
(19) Crabtree, S. R.; Chu, W. L. A.; Mander, L. N. *Synlett* **1990**, *1990*, 169−170.
(20) Borbas, K. E.; Chandrashaker, V.; Muthiah, C.; Kee, H. L.; Holten, D.; Lindsey, J. S. *J. Org. Chem.* **2008**, *73*, 3145−3158.
(21) Reviews on decarboxylative allylation: (a) Weaver, J. D.; Recio, A., III; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846−1913. (b) Mohr, J. T.; Stoltz, B. M. *Chem. - Asian J.* **2007**, *2*, 1476−1491.
(22) Shen, X.-L.; Zhao, R.-R.; Mo, M.-J.; Peng, F.-Z.; Zhang, H.-B.; Shao, Z.-H. *J. Org. Chem.* **2014**, *79*, 2473−2480.
(23) Analytical data were in full agreement with those reported for **33**.
(24) Gartshore, C. J.; Lupton, D. W. *Angew. Chem., Int. Ed.* **2013**, *52*, 4113−4116.
(25) Wilcox, C. F.; Blain, D. A.; Clardy, J.; Van Duyne, G.; Gleiter, R.; Eckert-Masic, M. *J. Am. Chem. Soc.* **1986**, *108*, 7693−7702.
(26) (*S*)-4-Hydroxycyclohex-2-en-1-one was prepared according to a known literature procedure using L-proline.[13]
(27) Audia, J. E.; Boisvert, L.; Patten, A. D.; Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 3738−3740.
(28) Donnelly, D. M. X.; Finet, J.-P.; Rattigan, B. A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1729−1735.

DOI: 10.1021/acs.joc.7b01095
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