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Authors: Sarah M. Pound, Steven J. Underwood, and Christopher J. Douglas

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Studies towards the total synthesis of drimentine C. Preparation of the AB and CDEF ring fragments

Sarah M. Pound[a], Steven J. Underwood[a], Christopher J. Douglas[a]*

Abstract: The drimentine family is a class of hybrid isoprenoids derived from *actinomycete* bacteria. Members of this family display weak antitumor and antibacterial activity. Herein we report our efforts toward the total synthesis of drimentine C using three distinct approaches incorporating palladium-catalyzed cyanoamidation, reductive cross-coupling, and photoredox-catalyzed α-alkylation of an aldehyde as key steps. Our synthetic efforts use a convergent synthesis to assemble the terpenoid and alkaloid portions of drimentine C from readily available L-tryptophan, L-proline, and (+)-sclareolide.

Introduction

Drimentines are a family of indolosesquiterpenes isolated as secondary metabolites from several strains of *Streptomyces* bacteria.[1,2] They and the structurally-related indotertines are formed through the same biosynthetic pathway where a diketopiperazine links with farnesylpyrophosphate via the classic mevalonate pathway.[3] Biochemically, drimentines exhibit anticancer, antibacterial, and antifungal properties; in particular, drimentine C (**1**) exhibits modest cytoxicity against human tumor cell lines HCT-8, Bel-7402, BGC-823, A549, and A2780.[2] Being secondary metabolites, isolation of the drimentines from natural sources is difficult, offering a challenge that synthetic efforts can solve.

Drimentines A (**2**), F (**3**), G (**4**), and indotertine A (**5**) were previously synthesized by the Li lab,[4] using a radical conjugate addition to form the crucial C–C bond. This approach had several benefits, notably the construction of a challenging all-carbon quaternary stereocenter as well as late-stage diversification of the diketopiperazine moiety, which allowed several members of the family to be accessed. However, this approach's late-stage installation of the exocyclic alkene ultimately required a low-yielding sequence of organocerium addition followed by dehydration of the resulting tertiary alcohol. This challenging sequence and the desire for material for additional bioactivity screenings motivated our lab to pursue synthesis of members of the drimentine family. Herein we report[5] our attempts to synthesize drimentine C using a set of approaches allowing for early installation of the exocyclic alkene and the potential for diversification of the diketopiperazine ring.

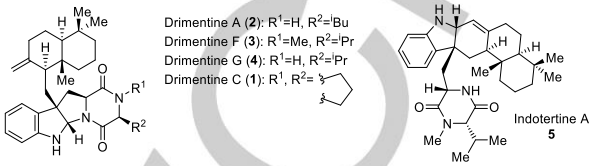
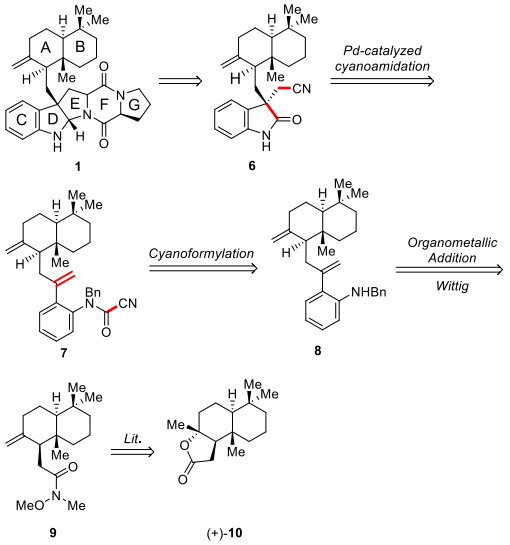


Figure 1. General scaffold of drimentines and structure of indotertine A.

Results and Discussion

We initially envisioned the synthesis of drimentine C as a showcase of the cut-and-sew alkene cyanoamidation methodology studied by our lab and Takemoto.[6–11] Retrosynthetically (Scheme 1), we proposed accessing the natural product through late-stage functionalization of lactam **6** via α-aminonitrile[12] and reductive condensation to form the E ring, hydrolysis of the nitrile to a carboxylic acid,[cit] and condensation with L-proline. Palladium-catalyzed cyanoamidation would form lactam **6** from cyanoformamide **7**, prepared by cyanoformylating benzylaniline **8**. Organometallic insertion into Weinreb amide **9**, followed by Wittig olefination of the resulting ketone would grant access to benzylaniline **8**. Weinreb amide **9** can be prepared from (+)-sclareolide, (+)-**10**, in two steps from a literature procedure.[13]



Scheme 1. Initial retrosynthesis of drimentine C through a cyanoamidation strategy.

Critical to this strategy is the synthesis of cyanoamidation precursor **15**, which contains the cyanoformamide and alkene functionality required for palladium-catalyzed cyanoamidation. Lactone ring opening of (+)-sclareolide by the dimethylaluminum amide derived from *N*-methoxy-*N*-methylamine yields the desired Weinreb amide (Scheme 2).[13] Dehydration of the resulting tertiary alcohol **11** yields exocyclic alkene **9**; performing this reaction at low temperatures prevented the formation of the internal alkene **12**. Anticipating challenges with selectively

[a] S. M. Pound, S. J. Underwood, C. J. Douglas
Department of Chemistry
University of Minnesota – Twin Cities
Smith Hall, 207 Pleasant St SE, Minneapolis, MN 55455
cdouglas@umn.edu
URL: http://www1.chem.umn.edu/groups/douglas/
Twitter: @CJDouglasGroup

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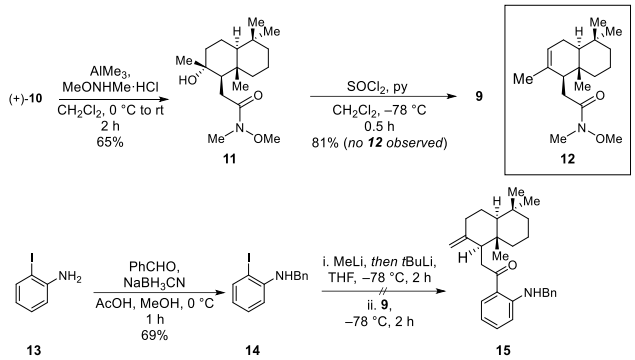
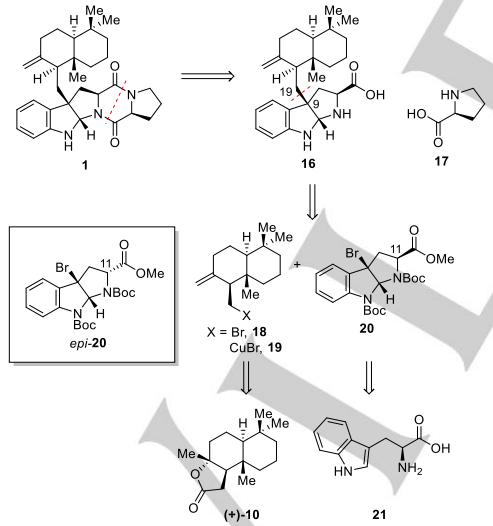
installing the exocyclic alkene at the late stage, we prioritized maintaining it throughout the synthesis; therefore, the exocyclic olefin is retained in all conditions reported herein.

For the aniline coupling partner, the benzyl protecting group was chosen to enhance diastereoselectivity for the later cyanoamidation step,[6] and was easily installed by reductive amination of 2-iodoaniline with benzaldehyde. With **14** in hand, we attempted to form the di-lithiate through deprotonation of the aniline hydrogen and subsequent lithium-halogen exchange. After addition of **9**, only starting **9** and deiodinated **14** was recovered. Attempts to use other protected anilines also proved unsuccessful.



Scheme 2. Synthesis of terpenoid fragment **9** and attempts at organolithium coupling.

At this point, we chose to change strategies, favoring a convergent route with the key disconnection between the alkaloid and terpenoid fragments. We believed that a late-stage condensation could be used to form the diketopiperazine ring, thereby allowing access to other drimentines depending on the amino acid used. Key to this route was determining a method of forming the C_9–C_{19} bond from coupling partners **18** and **20**, derived from **10** and L-tryptophan (**21**), respectively.



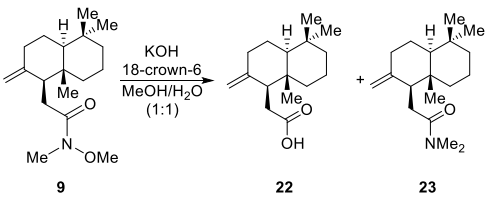
Scheme 3. Revised retrosynthesis via a convergent approach.

The first approach we considered with this convergent route involved primary organocuprate **19**. Using cyclopropanation conditions reported by Rainier and Espejo,[14] we believed that the key carbon-carbon bond formation could be achieved with release of ring strain. However, this ring opening would give the wrong stereochemistry at C_{11}, and work by Reisman et al.[15] suggested that the resulting epimer (*epi*-**20**) would give the undesired diastereomer of the natural product.

To maintain the stereochemistry at C_{11}, we considered radical-based methodologies, which have been successfully applied to pyrroloindoline alkaloid synthesis.[16] We looked specifically at reductive cross-coupling, which is proposed to proceed via radical intermediates without the need for organometallic nucleophiles.[17–19] While the initial work on this sp^2-sp^3 reductive cross-coupling used primary or secondary alkyl halides[19,20], more recent examples have been reported of successful reductive coupling with tertiary halides[16,21,22]

Bromopyrrolidine **20** was synthesized according to a literature procedure[23] through protection of L-tryptophan as the N-Boc-N'-Boc methyl ester and bromocyclization using NBS with PPTS, yielding the desired cyclization product in 74% yield. Primary bromide **18** was synthesized in two steps from intermediate **9**: hydrolysis of the Weinreb amide to carboxylic acid **22** followed by decarboxylation. Initial hydrolysis attempts showed significant amounts of remaining starting material, as well as formation of methyl amide **23** (Table 1). Longer reaction times ensured full conversion of starting material (Entry 2), as did addition of 18-crown-6. Large excess of potassium hydroxide, 18-crown-6 or increased reaction time reduced selectivity for carboxylic acid **22**, suggesting **23** exists as a decomposition byproduct. Reactions sometimes overpressurized at high temperature, leading to solvent loss and decreased selectivity for **22**. Performing the reaction in a sealed pressure vessel (Entries 6–7) mitigated these issues. Alternatively, carboxylic acid **22** could be prepared in two steps by base-catalyzed ring opening of the lactone followed by dehydration, however this sequence was not as selective for the exocyclic alkene compared to the Weinreb amide route. Carboxylic acid **22** was converted to the primary bromide by a thermally-initiated Barton decarboxylative bromination.[24,25]

Table 1. Optimization of the synthesis of carboxylic acid **22**.



Entry	KOH (equiv)	18-crown-6 (equiv)	Temp (°C)	Time (h)	**9** : **22** : **23**	Yield (%)[a]
1[b]	4.0	–	140	0.66	1 : 7 : 5	–
2[c]	4.0	–	130	45	0 : 5 : 1	70[d]
3[e,f]	10.0	–	130	43	1 : 0 : 0	–
4[c]	10.0	1.0	130	25	0 : 3 : 1	37
5[c]	10.0	1.0	130	27	0 : 5 : 1	53[g]
6[h]	10.0	1.0	130	27	0 : 4 : 1	67
7[h]	10.0	1.0	130	55	0 : 7 : 1	50

a. Isolated yield of **22**. b. Reaction run on 0.04 g scale in a microwave reactor. c. Reaction run on 0.1 g scale in a sealed vial with a PTFE-lined cap using an aluminum block. d. Yield given as an average of two trials. e. Reaction run on a 0.3 g scale in a sealed vial with a PTFE-lined cap using an aluminum block. f. 1,4-dioxane used instead of MeOH. g. Yield given as an average of three trials. h. Reaction run in a sealed pressure vessel in an oil bath.

Mixing **22** and Barton salt **24** with triethylamine in bromotrichloromethane at 90 °C for twenty minutes, followed by quench with hydroquinone and acidic workup yielded bromide **18** in a 43% yield after purification (Figure 2). We did not further optimize this reaction.

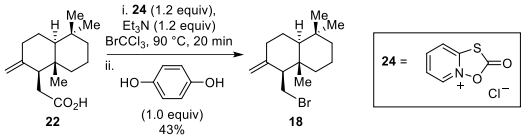
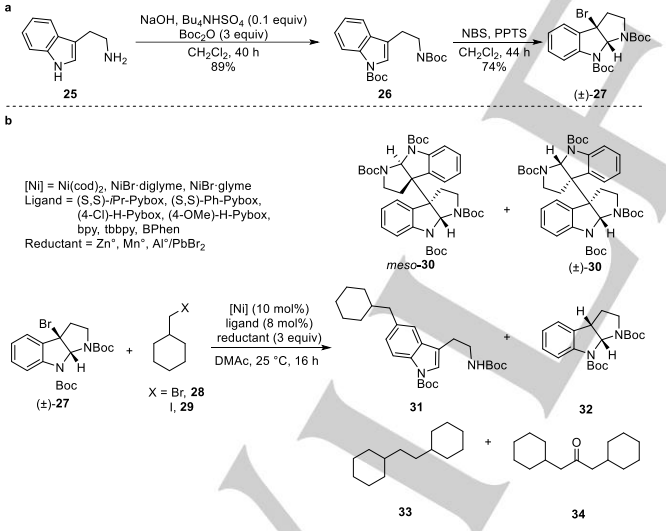


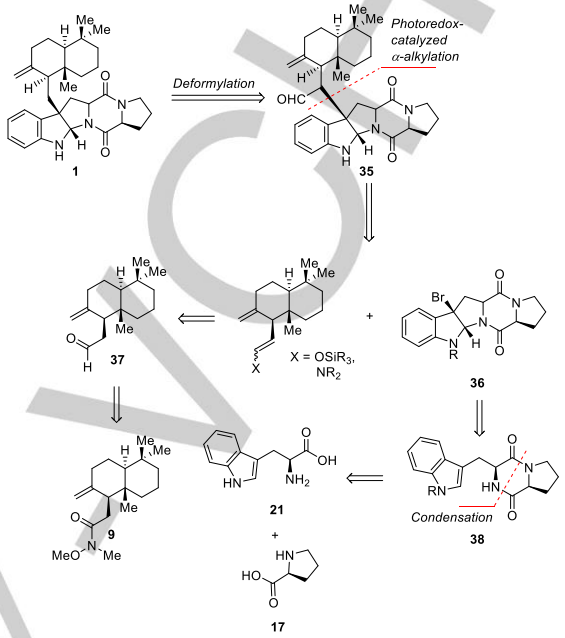
Figure 2. Synthesis of primary bromide **18**.

To test the viability of reductive cross-coupling in the synthesis of drimentine C, we studied the reaction on a model system. Beginning with tryptamine **25**, double Boc protection with subsequent bromocyclization[23] yielded bromopyrrolidine (±)-**27** (Scheme 4a). We reacted (±)-**27** with 2-cyclohexylbromide and iodide using a variety of nickel catalysts, ligands, and terminal reductants (Scheme 4b). These reactions consistently formed four major alkaloid products, confirmed by spectroscopic analysis and independent synthesis (see supplementary information for individual trials and details of independent synthesis). Dimerization of the pyrroloindoline occurred, with both *meso* and chiral dimers formed. Reduction of the C–Br bond occurred to yield **33**. Mass spectrometry of the fourth alkaloid product suggested coupling of (±)-**27** and the (cyclohexyl)methyl moiety, but spectroscopic analysis after purification revealed the structure of **31**, where coupling occured at the 5 position with opening of the pyrrolidine ring. Other cyclohexyl-containing products observed were dicyclohexylethane **33** and ketone **34**.



Scheme 4. Reductive cross-coupling a) substrate synthesis and b) model study

Because no desired coupling was observed in our model study, we considered other strategies involving single-electron transfer. In this context, photoredox catalysis was enticing, as the stereocenter at C_{11} should not be affected, and photoredox catalysis has previously been used for related alkaloid synthesis.[4,29] Retrosynthetically (**Scheme 5.** Revised retrosynthesis using a photoredox-catalyzed α-alkylation approach.Scheme 5), we envisioned drimentine C stemming from a late-stage deformylation of a fused isoprenoid alkaloid like intermediate **35**. Formation of the key C–C bond could occur from α-alkylation under photoredox conditions of two intermediates: the fully formed diketopiperazine core from **17** and **21** and a masked aldehyde of (+)-**10**, such as an enamine[30–32] or silyl enol ether.[33]



Scheme 5. Revised retrosynthesis using a photoredox-catalyzed α-alkylation approach.

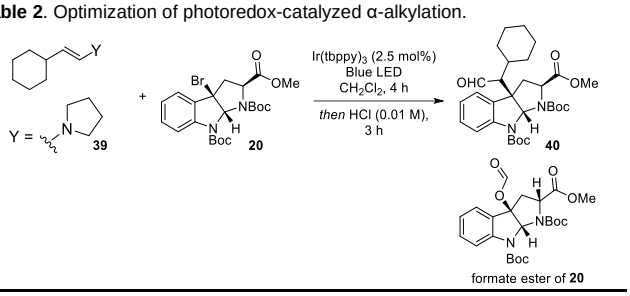
As with the reductive cross-coupling strategy, we studied α-alkylation on a model system using simplified bromopyrroloindole **20** and the enamine **39** formed from cyclohexylacetaldehyde and pyrrolidine (

Table 2). Initially, the reaction was irradiated with a 15 W fluorescent lamp in the presence of $Ru(bpy)_3Cl_2$ and common additives (triethylamine, 2,6-lutidine, and Hantzsch ester) using dimethylformamide as a solvent, but only reduced product **33** was observed (entries 1-3). Cyclic voltammetry of **20** gave a first reduction potential of –0.800 eV, suggesting that the pyrroloindoline radical forms through a reductive quench of the excited photocatalyst. Since many of the additives screened can act as both electron and hydrogen donors, their presence likely led to formation of **33**. To remove the need for said additives, we moved to the Ir^{3+} family of photocatalysts. With *fac*-$Ir(ppy)_3$ used as photocatalyst (entry 4) a new product was observed; the formate ester of **20**, indicating that the solvent acted in a non-innocent manner (see supplementary information for additional details).[34] In addition, the formate ester of **20** experienced epimerization at the stereogenic center bearing the methyl ester.

To minimize these background reactions, we optimized the solvent. *Fac*-$Ir(ppy)_3$ was insoluble in ethereal solvents like THF and 1,4-dioxane, as well as aromatic solvents like toluene. While only sparingly soluble in acetonitrile (entry 5), new products were observed: coupling product **40** and *epi*-**40**. Changing the solvent to dichloromethane increased the solubility of the photocatalyst, and changing the photocatalyst to the more strongly reducing *fac*-$Ir(tbppy)_3$ and light source to a blue LED increased conversion of **20**, forming **40** in 74% yield after acidic workup. Alternate radical acceptors were tested, specifically the morpholine-derived enamine and the TMS, TIPS, and TBS silyl

ethers, but under the reaction conditions only **33** was observed as a product.

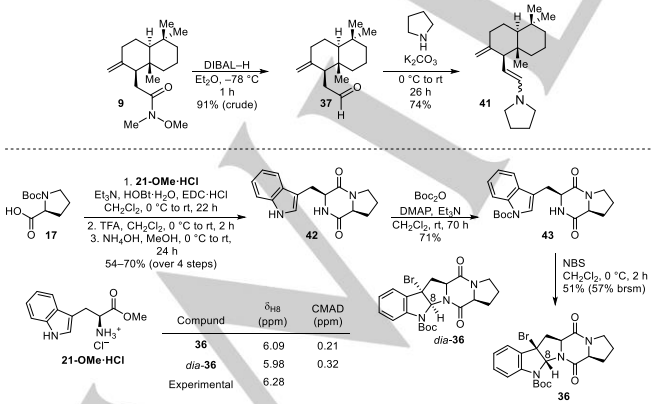
Table 2. Optimization of photoredox-catalyzed α-alkylation.



Entry	Deviation from above	Yield **40** (%)
1	**none**	**74%**
2	$Ru(bpy)_3Cl_2$ (2.5 mol%), NEt_3 (2 equiv), 15W fluorescent lamp, DMF	0
3	$Ru(bpy)_3Cl_2$ (2.5 mol%), Hünig's base (2 equiv), 15W fluorescent lamp, DMF	0
4	$Ru(bpy)_3Cl_2$ (2.5 mol%), Hantzsch ester (2 equiv), 15W fluorescent lamp, DMF	0
5	*Fac*-Ir(ppy)$_3$ (5 mol%), 15W fluorescent lamp, DMF	0[a]
6	*Fac*-Ir(ppy)$_3$ (2.5 mol%), 15W fluorescent lamp, MeCN	8%
7	Y = morpholinyl, -OTMS, -OTIPS, -OTBS	0

Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene, isolated yields represented in parentheses. *a*. Formate ester of **20** isolated as major product.

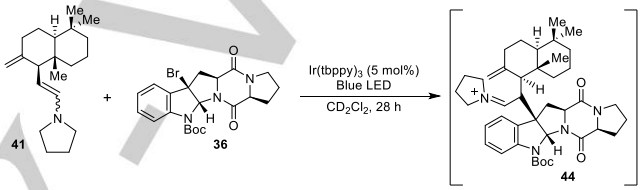
With this promising result in hand, the coupling partners for α-alkylation were synthesized. From Weinreb amide **9**, a simple DIBAL-H reduction yields aldehyde **37** in a 91% yield with high enough purity to be carried forward without further purification. From protected amino acids **17** and **21-OMe·HCl**, the diketopiperazine moiety can be formed by peptide coupling, Boc cleavage, and condensation-cyclization in 54–70% yield over three steps after recrystallization from methanol.[35] Selective Boc protection of the indole nitrogen occurs in good yield, with bromocyclization forming **36** in a modest 51% yield as a single diastereomer.



Scheme 6. Synthesis of coupling partners for α-alkylation.

Two diastereomers are possible in the bromocyclization step, assuming no epimerization in the diketopiperazine ring; **36** and *dia*-**36**. Because the relative stereochemistry of **36** could not be conclusively determined by NOESY, **36** and *dia*-**36** were examined computationally. Single point NMR calculations (B3LYP/6-311+G(2d,p)/M06-2X/6-31+G(d,p))[36] of **36** and *dia*-**36** showed closer agreement for the synthesized sample being compound **36**.

Initial reactions between bromopyrollidine **20** and enamine **41** were promising—a new product was observed by high resolution mass spectrometry with the chemical formula $C_{38}H_{54}N_2O_7$, consistent with productive coupling between **20** and **41.** This product could not be isolated by column chromatography, decomposing after several attempts at purification. Attempts to perform the photoredox-catalyzed coupling with **36** and **41** were also attempted (Scheme 7). After 28 h, **36** was fully consumed, an ion consistent with iminium ion **44** was observed by high resolution mass spectrometry (see supplementary information). Attempts to hydrolyze the product to an aldehyde were unsuccessful, and this product could not be isolated.



Scheme 7. Proposed intermediate formed after reaction of **36** and **42** under optimized photoredox-catalyzed conditions

Conclusions

In summary, we have developed three distinct approaches toward the total synthesis of drimentine C. With each of these approaches, we identified the quaternary stereocenter at C_9 as a key disconnection and prioritized early installation of the exocyclic alkene. Of these approaches, the photoredox-catalyzed coupling of enamine **41** and bromopyrrolidine **36** seems the most promising, but is hampered by challenging isolation of the potential iminium ion product. Further studies are underway in our lab, focusing on the key coupling reaction, as well as completing the synthesis of the natural product.

Acknowledgements

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Keywords: natural products • alkaloids • photoredox • cross coupling

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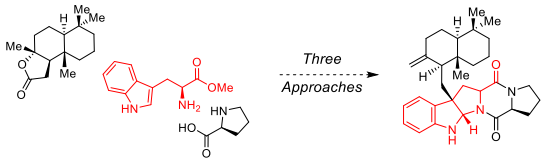

Total Synthesis*

*Sarah M. Pound, Steven J. Underwood, Christopher J. Douglas**

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Studies towards the total synthesis of drimentine C. Preparation of the AB and CDEF ring fragments

Synthetic efforts towards the total synthesis of the natural product drimentine C are described. Three distinct approaches are discussed incorporating palladium-catalyzed cyanoamidation, reductive cross-coupling and photoredox-catalyzed α-alkylation of an aldehyde as key steps to join the alkaloid and terpenoid fragments.

*alkaloid synthesis