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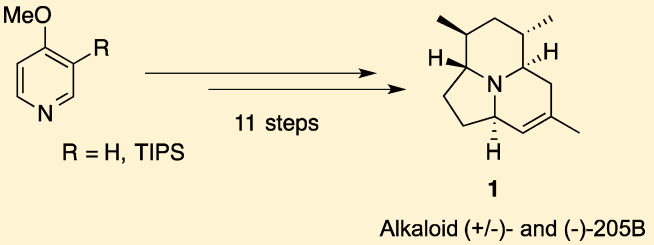
Total Synthesis of Alkaloid 205B

Sergey V. Tsukanov† and Daniel L. Comins*

Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27695-8204, United States

Supporting Information

ABSTRACT: Concise and highly stereocontrolled total syntheses of racemic and enantiopure frog alkaloid 205B (**1**) were accomplished in 11 steps from 4-methoxypyridines **6** and **7** in overall yields of 8 and 8%, respectively. The assembly of the core of the natural product relies on a stereoselective Tsuji–Trost allylic amination reaction and a ring-closing metathesis. The synthesis features the use of an *N*-acylpyridinium salt reaction to introduce the first stereocenter and an unprecedented trifluoroacetic anhydride-mediated addition of an allylstannane to a vinylogous amide with complete facial selectivity. Deoxygenation of the C4 ketone proved difficult but was accomplished via a modified Barton–McCombie reaction in the presence of a catalytic amount of diphenyl diselenide.



INTRODUCTION

Alkaloid 205B (**1**) is a natural product from neotropical poisonous frogs *Dendrobates*. More than 800 different molecules have been isolated from amphibian skins according to the latest reports;[1] the majority of these alkaloids originated from arthropods and accumulated in amphibians as a result of their dietary preferences. *Dendrobates* is the largest family of poisonous frogs, and alkaloids from these amphibians contain structures with a great variety of nitrogen-containing cores, including indolizidines, pyrrolidines, quinolizidines, piperidines, decahydroquinolines. Notably, these alkaloids are especially interesting since they exhibit a range of bioactivities such as noncompetitive inhibition of nicotinic receptors, binding affinity for the human δ-opioid receptor, and blocking of neuromuscular and ganglionic-type channels.[2] Because of their broad structural diversity, unique fused ring systems, and considerable potential for medical applications, these alkaloids became attractive targets for numerous synthetic investigations.[3]

Alkaloid 205B can be classified as an indolizidine; however, it contains unusual architectural elements. Its rare 8b-azaacenonaphthylene ring system has three condensed rings with four out of five stereocenters located on a single piperidine ring. This creates a unique challenge of incorporating four chiral centers diastereoselectively while constructing the tricyclic core (Figure 1).

The first isolation of 205B was reported by Daly and coworkers in 1987.[4a] A year later the same group fully elucidated the structure of the alkaloid.[4b] Synthetic efforts by the Toyooka group led to the first total synthesis of 205B in 2003. Because of the absence of any knowledge about the absolute configuration of the molecule, the enantiomer was prepared.[5] Serendipitously, this lack of information about the absolute stereochemistry of the natural product led to an unexpected discovery. The newly prepared antipode of 205B was shown to possess notable

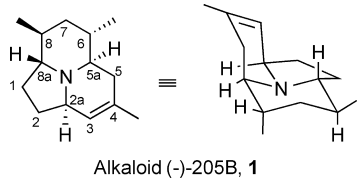


Figure 1. Structure of alkaloid (−)-205B.

bioactivity in selectively inhibiting α7-nicotinic receptors. In contrast, it was demonstrated that the natural enantiomer of the molecule does not possess any significant biological properties.[6] Over the past decade the α7 subtype of neuronal nicotinic acetylcholine receptors has received significant attention. These receptors are abundant in the brain and are expressed in the hippocampus and the cerebral cortex, areas of the brain that are responsible for learning, attention, working, and episodic memory. They are involved in modulation of transmitter pathways in various brain regions and are strongly implicated in many cognitive functions. Arguably, Alzheimer's disease and schizophrenia continue to be on the top of the list of the most challenging neurological conditions that require new medications to stabilize and reduce the symptoms. Considerable knowledge has been collected to support the concept of drugs exploiting α7 receptors as a therapeutic target for treatment of cognitive impairment in patients with Alzheimer's disease and schizophrenia.[7] To date, there are multiple programs pursuing the development of therapeutics that are selective α7 agonists, and several of them have achieved significant progress. Several drug candidates have already reached late stages of clinical trials; however, knowledge about the selective inhibitors of these receptors remains scarce. Consequentially, alkaloid 205B

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and its congeners could serve as effective tools to further investigate this pathway and evaluate the potential of these molecules as therapeutic agents for a variety of applications, including central nervous system pathologies.

The synthetic challenges of this unusual alkaloid, coupled with its potential ability to modulate brain activity, have attracted significant interest over the years, and a few total syntheses have been reported. The first synthesis of 205B came from the Toyooka group.[5] In their approach, the crucial 2,3,5,6-tetrasubstituted piperidine with four stereocenters was constructed stepwise via conjugate additions to unsaturated esters. The Smith group used a consecutive one-pot addition of a dithiane intermediate to a chiral epoxide and aziridine to form an indolizidine upon cyclization, and further elaboration led to the second asymmetric synthesis of the molecule.[8] The most recent total synthesis was reported by Yang and Micalizio.[9] They took advantage of a stereoselective Ti-mediated allylic alcohol−imine reductive cross-coupling and intramolecular [3 + 2] cycloaddition of a glyoxylate-based homoallylic nitrone to set all four stereocenters in the core piperidine ring of the natural product.

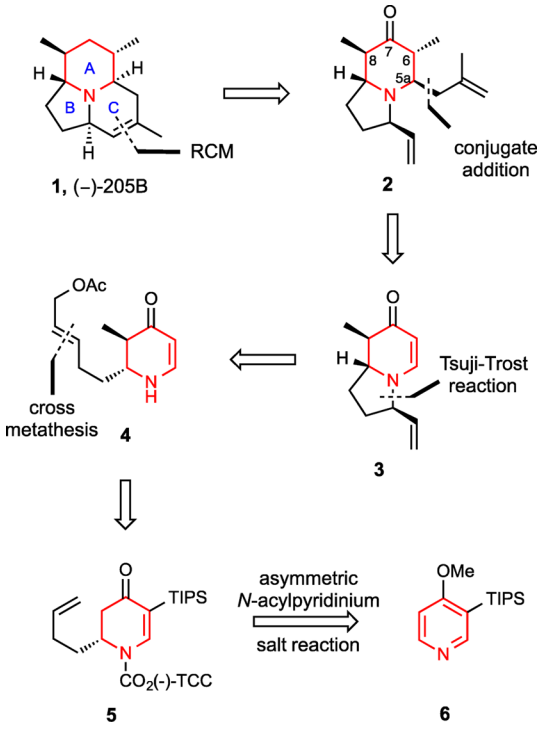
Our interest in the biological properties of 205B and its intricate architectural elements prompted us to initiate a program directed toward the construction of this molecule. Previously, a communication was published describing our total synthesis of the alkaloid.[10] Herein is provided a full report delineating the evolution of our approach with detailed descriptions of all modifications that eventually led to a successful route and the shortest synthesis of 205B to date.

RESULTS AND DISCUSSION

Retrosynthetic Analysis. Our strategy for the total synthesis of **1** was to devise a short route based on our extensive experience with dihydropyridone chemistry, where the stereochemical information on the first stereocenter could effectively guide the stereochemistry of all the following centers in a substrate-controlled manner.[11] On the basis of conventional retrosynthetic logic, the only site of unsaturation in the molecule, the alkene in ring C, was chosen as an evident metathesis disconnection site (Scheme 1). The apparent simplicity of this disconnection was also complemented by well-established functional group compatibility and clear inherent relationships between the resulting indolizidine **2** and our first chiral dihydropyridone intermediate **5**.

The ketone carbonyl group at C7 would be crucial to the successful introduction of the C5a, C6, and C8 substituents and would be reductively cleaved after installations of the required stereocenters. The vinylogous amide **3** was considered as an excellent substrate for the consecutive 1,4-addition followed by enolate alkylation to establish the C5a and C6 stereocenters. Upon judicious consideration of conformations and stereoelectronic factors, a high degree of diastereoselectivity was expected for both of these reactions.[12] It was envisioned that a Tsuji−Trost allylic amination would serve as an excellent transformation to furnish the required indolizidine bicyclic system and introduce the desired vinyl group and C2a stereocenter with minimal functional group manipulations.[13] The Tsuji−Trost precursor **4** could be accessible from dihydropyridone **5** through enolate methylation at C8 and cross-metathesis with (*Z*)-but-2-ene-1,4-diyl diacetate. Efficient access to compound **5** could be achieved via an asymmetric *N*-acylpyridinium salt reaction with 4-butenylmagnesium bromide. This reaction is a well-established and very general method to prepare multigram quantities of chiral dihydropyridones with high enantiomeric excess.[14]

Scheme 1. Retrosynthetic Analysis of Alkaloid (−)-205B (1)



Synthetic Studies toward Racemic 205B. Our initial studies began with the goal of devising a concise sequence to assemble allylic acetate intermediate **4** as a racemic material. The *N*-acylpyridinum salt formed upon mixing of 4-methoxypyridine (**7**) and phenyl chloroformate was treated with 4-butenylmagnesium bromide to furnish upon acidic workup the known dihydropyridone **8**[15a] in excellent yield (Scheme 2). Formation of the kinetic enolate at C3 of **8** with NaHMDS at −78 °C followed by addition of MeI and slow warming of the resulting solution provided the desired dihydropyridone **9** in 90% yield.[15b]

The stereochemical outcome of the methylation reaction was in full accordance with previous results from our group observed in the syntheses of metazocine and dienomycin.[15c,d] The piperidine ring exists mainly in a low-energy half-chair conformation with the butenyl substituent located in a pseudoaxial position to prevent $A^{(1,3)}$ interactions with the carbamate group. The major *trans* product was formed by axial methylation at C3 from the less hindered face opposite to the C2 axial substituent.

The required allylic acetate intermediate **10** was prepared from **9** in 70% yield using cross-metathesis with 5.0 equiv of (*Z*)-but-2-ene-1,4-diyl diacetate and 5% Grubbs−Hoveyda second-generation catalyst (Scheme 2).[16] Unfortunately, selective hydrolysis of the carbamate group in the presence of the allylic acetate could not be effected, as amino alcohol **11** was obtained in a low yield; the product was characterized by selective reacylation with Ac_2O at room temperature.[17]

Alternatively, initial cleavage of carbamate **9** with K_2CO_3 in MeOH and subsequent cross-metathesis of the resulting N−H dihydropyridone **12** gave allylic acetate **4** in good yield. It is noteworthy that this change in the order of the reaction sequence allowed additional protecting group manipulation to

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Scheme 2. Preparation of Allylic Acetate 10

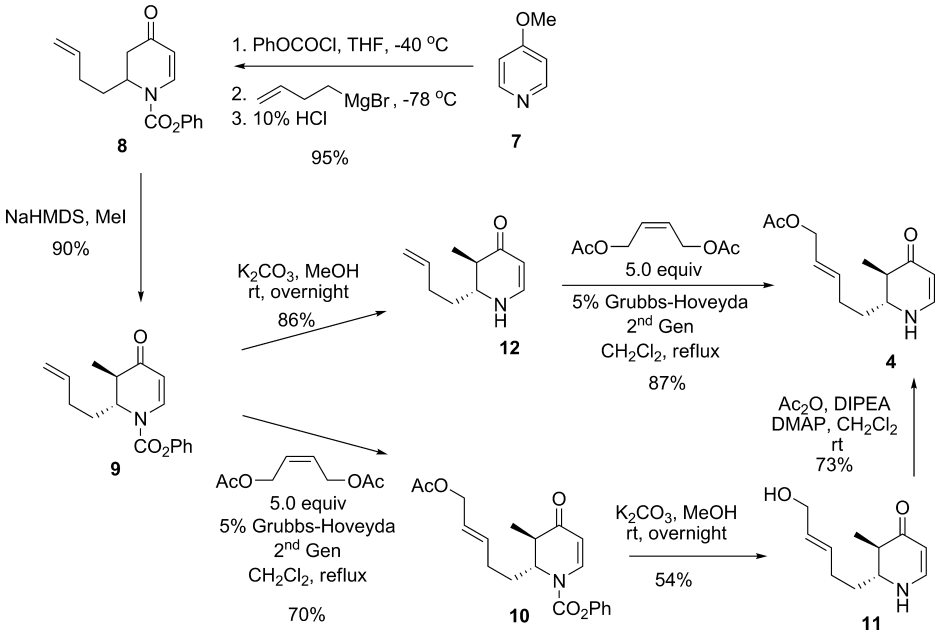
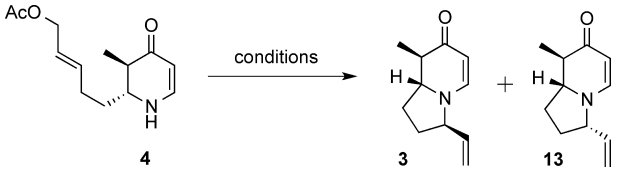


Table 1. Conditions for Tsuji–Trost Pyrrolidine Ring Formation



entry[a]	catalyst	base	T (°C)	ligand	product	dr[b]
1	$Pd_2(dba)_3$	Cs_2CO_3	50	P(*o*-Tol)$_3$	sm	–
2	$Pd_2(dba)_3$·$CHCl_3$	Cs_2CO_3	50	PBu_3	**3** and **13**	1.5:1
3	$Pd_2(dba)_3$·$CHCl_3$	NaOtBu	50	PBu_3	decomp	–
4	Pd(*t*-Bu$_3$P)$_2$	Cs_2CO_3	70	–	**3** and **13**	9:1
5	$Pd_2(dba)_3$·$CHCl_3$	Cs_2CO_3	55	P(*t*-Bu)$_3$	**3**, **13** and sm	9:1
6	$Pd_2(dba)_3$·$CHCl_3$	Cs_2CO_3	75	P(*t*-Bu)$_3$	**3** and **13**	9:1

[a]Conditions: 5 mol % catalyst, 20 mol % ligand, and 2.3 equiv of the base (with respect to substrate) were employed. [b]Diastereoselectivities were determined by ^{1}H NMR analysis of the crude products.

be avoided and accomplished the synthesis of allylic amination precursor **4** in just four steps and 64% overall yield.

With the key fragment **4** in hand, our attention was turned to the construction of the bicyclic indolizidine core. The Tsuji–Trost reaction is a widely utilized transformation that has become an effective tool for the formation of various inter- and intramolecular C–C, C–O, and C–N bonds.[13] Some literature examples highlight the construction of pyrrolidines and piperidines in stereo- and enantioselective fashion and also showcase some prominent applications of the allylic amination reaction in total synthesis.[18] Our initial attempts to effect this transformation using $Pd_2(dba)_3$·$CHCl_3$ as the catalyst provided the desired indolizidinone **3** in good yield but with poor diastereoselectivity (Table 1, entry 2). A variety of ligands were tested with the goal of improving the stereocontrol. Arylphosphines were not effective in this reaction and did not afford any of the desired products (entry 1). Ultimately, it was discovered that the sterically hindered *t*-Bu$_3$P ligand was essential for high selectivity, and under the optimized conditions the reaction delivered the cyclization product as a 9:1 mixture of diastereomers in 70% yield based on a purified single diastereomer (entry 6). The reaction was highly sensitive to the base, and after an examination of different conditions, cesium carbonate was selected since stronger bases generated a significant amount of decomposition (entry 3). The temperature of the reaction was also found to be critical. At lower temperatures (<65 °C), the reaction was sluggish and resulted in significant recovery of unreacted starting material (entry 5), while heating to over 85 °C promoted product formation but with a lower diastereomeric ratio. The oxidation state of Pd appeared to be inconsequential, as Pd(II) catalysts generated the indolizidine in yields similar to those for Pd(0) but with some decrease in reactivity (entry 4). Unfortunately, at this stage the relative stereochemistry of the vinyl group in product **3** could not be confirmed; the structure of the shown isomer was determined in later studies of indolizidine **20** (vide infra).

Preparation of the Tricyclic Core of the Natural Product. Our synthesis plan for the elaboration of indolizidine intermediate **3** involved a conjugate addition/methylation tandem reaction to install the C5a methallyl and C6 methyl group in one pot. Similar reactions of conjugate enone systems have been carried out and are very common in the literature.[19]

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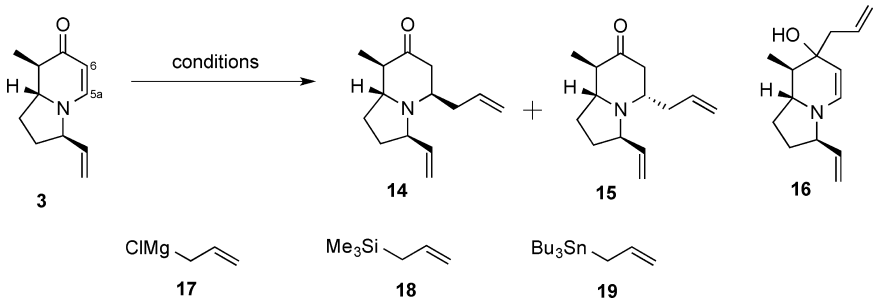
Table 2. Model Studies of Conjugate Addition to 3



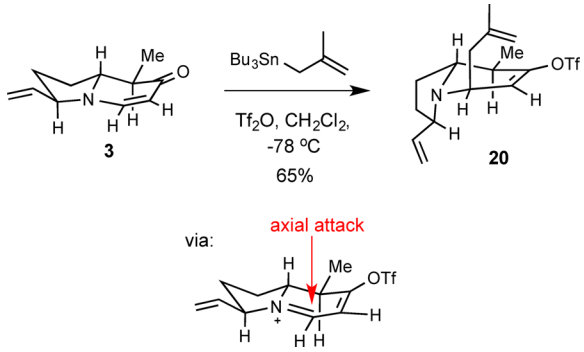
entry[a]	reagent	Lewis acid	conditions	temperature	product	dr[b]
1	**17**	$BF_3{\cdot}OEt_2$	*i*-Pr_2S, CuI, THF	−78 °C	**14** and **15**	1:1
2	**17**	TMSCl	*i*-Pr_2S, CuI, LiCl, THF	−78 °C	**14** and **15**	1:1
3	**17**	–	*i*-Pr_2S, CuI, LiCl, THF	−78 to 10 °C	sm	–
4	**17**	–	benzene	rt	**16**	–
5	**17**	$MnCl_2$	CuI, LiCl, THF	0 °C	sm	–
6	**18**	$BF_3{\cdot}OEt_2$	CH_2Cl_2	−78 to 0 °C	sm	–
7	**19**	$BF_3{\cdot}OEt_2$	CH_2Cl_2	−78 to 0 °C	sm	–
8	**19**	TMSOTf	CH_2Cl_2	−78 to 0 °C	sm	–
9	**19**	TBSOTf	CH_2Cl_2	−78 to 0 °C	sm	–
10	**19**	$InCl_3$, TMSCl[c]	CH_2Cl_2	rt	sm	–

[a]Conditions: 2.0−3.0 equiv of the nucleophile and 2.0 equiv of Lewis acid (with respect to substrate) were employed. [b]Regio- and diastereoselectivities were determined by ^{1}H NMR analysis of the crude reaction mixtures. [c]See ref 24.

Recently, Smith and Dong[20] showed that dihydropyrones could be used as substrates in such tandem sequences; however, there was no precedent for this type of reaction with dihydropyridones or vinylogous amides. Our initial model studies with different allylcuprate reagents were largely unsuccessful, providing mixtures of diastereomeric products **14** and **15** without any stereo preference (Table 2). Formation of the Gilman allylcuprate from the corresponding Grignard reagent and a copper salt (*i*-$Pr_2S{\cdot}CuI{\cdot}LiCl$) followed by slow addition to indolizidinone **3** and $BF_3{\cdot}OEt_2$ resulted in a 1:1 mixture of **14** and **15** and 20% unreacted starting material (entry 1). Lipshutz's conditions with the cuprate and TMSCl led to full consumption of the starting material, but the same 1:1 ratio of the products was observed by ^{1}H NMR analysis of the crude reaction mixture (entry 2).[21] Also, addition of cuprates without a Lewis acid showed no reactivity even when the reaction mixture was warmed to 0 °C (entry 3). Treatment of vinylogous amide **3** with allyl Grignard reagent in benzene provided allylic alcohol **16** as the only product (entry 4).[22] Mild manganese-catalyzed allyllation conditions also failed to generate the required indolizidinone **14** (entry 5).[23] Failure of the copper reagents to deliver product or sufficient stereoselectivity led us to pursue reactions using the softer allylsilane (**18**) and allylstannane (**18** and **19**) as nucleophiles; however, attempts to promote the desired 1,4-addition under a variety of conditions suffered from lack of reactivity and necessitated an alternative approach (entries 6−10).

At this time, studies on activation of the vinylogous amide via formation of a more reactive iminium ion were initiated. To our delight, the Tf_2O-mediated protocol initially developed by Trauner and co-workers was found to be highly effective.[25] Activation of **3** proceeded smoothly at −78 °C upon exposure to triflic anhydride, and in the presence of tributylmethallylstannane, indolizidine **20** was obtained as a single diastereomer in 65% yield (Scheme 3). The stereochemistry of **20** was established unambiguously through multiple NOE studies.

Scheme 3. Stereochemical Outcome of the Methallylation Reaction



Despite this encouraging result, vinyl triflate **20** was not a useful intermediate for the total synthesis of 205B. The pathway to introduce the C6 methyl group utilizing existing functionality was not straightforward. Initially, variants were probed that would allow us to revert back to the originally proposed route. The possibility of direct conversion of the vinyl triflate to a ketone was examined. Although methods to transform vinyl triflates into ketones are not common, some limited literature precedents were found.[26] Unfortunately, these methods usually required harsh reaction conditions with a large excess of hard nucleophiles, resulting in the formation of side products. For example, addition of MeLi to vinyl triflate **20** in the presence of TMEDA and HMPA afforded ketone product **21** only in 30% or lower yield (Scheme 4).[27] After screening of a variety of Brønsted bases (KO*t*Bu, NaOH) and solvents (DME, THF, 2,2,2-trifluoroethanol), no improvement in the yield of the ketone was found, and this strategy was abandoned.[28]

The failure of the nonconventional strategy to cleave the vinyl triflate to a ketone left us with a more traditional set of options for utilizing this intermediate. Vinyl triflates are general

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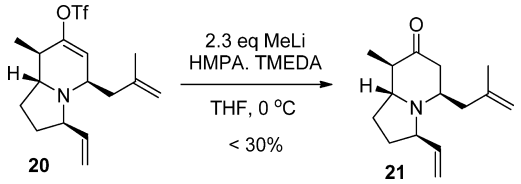
Scheme 4. Vinyl Triflate Cleavage



substrates for a majority of Pd-coupling transformations. Efforts were initiated to study the Pd-mediated reaction of **20** with amines in order to construct an enamine that potentially could be methylated and hydrolyzed to give the desired ketone **2** in a one-pot reaction. Two attempted transformations are shown in Scheme 5. Treatment of triflate **20** with morpholine in the presence of $Pd(OAc)_2$ and Cs_2CO_3 failed to deliver the requisite enamine under a variety of conditions.[29] Reaction with tosylhydrazine, $Pd_2(dba)_3$ and Xantphos as a ligand did not result in any desired product.[30] Since the enamine alkylation route was not successful, our efforts turned toward 1,4-addition strategies that could serve as an alternative where the intended substrates would be accessed using C−S or C−C bond-forming couplings. The C−S strategy was evaluated first since 1,4-addition to the anticipated sulfone **25** and subsequent reduction using Raney Ni is precedented and would open a direct path to an attractive indolizidine intermediate. Electron-poor 2-pyridinethiol was utilized instead of more common phenyl or tolyl thiols to ensure activation of the conjugate system toward 1,4-additions in the corresponding sulfone.[31] After extensive experimentation, the lithium salt of 2-mercaptopyridine was coupled with vinyl triflate **20** using $Pd(PPh_3)_4$ as a catalyst in refluxing THF, albeit in rather low yield.[32] All attempts to effect selective oxidation of sulfide **24** even using mild reagents such as sodium tungstate were hampered by the presence of the electron-rich tertiary amine, which was found to undergo oxidation at a higher rate.[33]

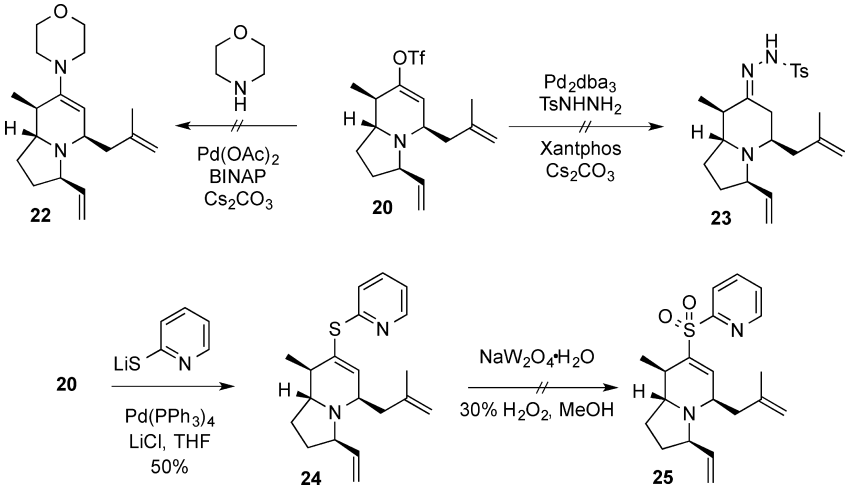
In contrast, carbonylation reactions worked well with triflate **20**, giving the corresponding aldehyde **26** and methyl ester **27** in 70 and 60% yield, respectively (Scheme 6).[34] The price for the simplicity of the substrate formation, however, was the uncertainty of the following decarbonylation strategy, which was precedented but largely unexplored and probed only on certain scaffolds.[35] With the corresponding unsaturated aldehyde **26** in hand in sufficient quantities, attempts at conjugate addition were in order to introduce the last methyl group.

Unfortunately, examination of a variety of different conditions (methylcuprates, methylzinc and aluminum species) afforded only recovered starting material, and no presence of the 1,4-product could be detected. It is noteworthy that with the more reactive methylcopper cyanate and boron trifluoride etherate, 1,2-addition was the predominant outcome, and the secondary alcohol was observed as the major product. To rationalize the results of our studies, we speculate that the low-energy conformation of the molecule prevents an effective overlap between the orbitals of the alkene and the carbonyl, causing deactivation toward 1,4-additions.

Failure to utilize the triflate **20** as a useful intermediate for the synthesis of alkaloid 205B led us to consider an alternative strategy to install the methallyl substituent. Since the only reactive intermediate found that allowed stereoselective addition of the methallyl group was an iminum ion, our attention was focused on finding a proper activating reagent that would promote iminium ion formation, tolerate nucleophilic addition at C5a, and allow easy conversion to ketone intermediate **21**. Reactions were carried out using trifluoroacetic anhydride as the activating agent instead of triflic anhydride. After extensive optimization, treatment of vinylogous amide **3** in the presence of methallyltributyltin at −40 °C with 1.5 equiv of trifluoroacetic anhydride, subsequent warming to 0 °C, and addition of aqueous $NaHCO_3$ to hydrolyze the intermediate vinyl acetate **28** provided the desired ketone **21** (Scheme 7). The diastereoselectivity of the process was similar to that of the Tf_2O reaction, and ketone **21** was isolated in good yield as a single stereoisomer with the desired relative configuration. Furthermore, the NMR data for newly prepared **21** were identical in all respects to those for the products previously obtained from cleavage of vinyl triflate **20** or conjugate addition to **3**.

With a route to effectively introduce the methallyl group finally secured, the stage was set for the installation of the last stereocenter. A standard alkylation of **21** with NaHMDS and MeI at −78 °C generated the desired product **29** in an unsatisfactory 10−15% yield. Treatment of the ketone with NaHMDS in the presence of 5−20% HMPA led to an improved yield of 85%, but the material was obtained as a

Scheme 5. Vinyl Triflate Modification Strategy



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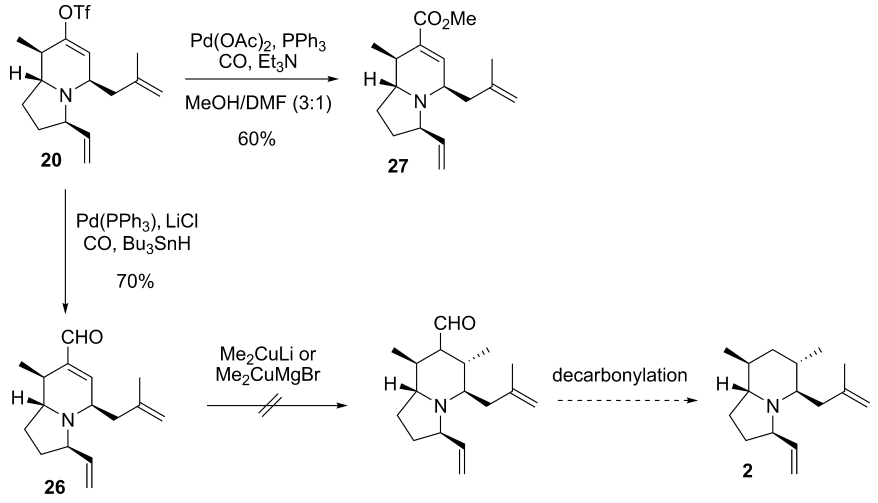
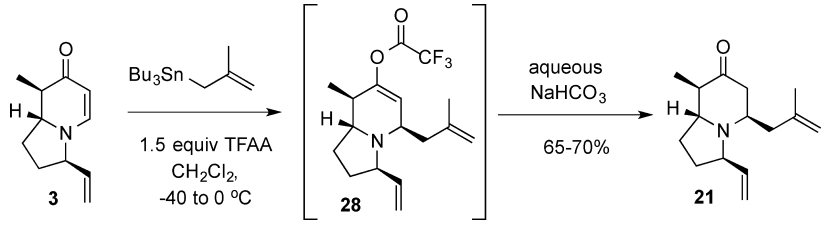
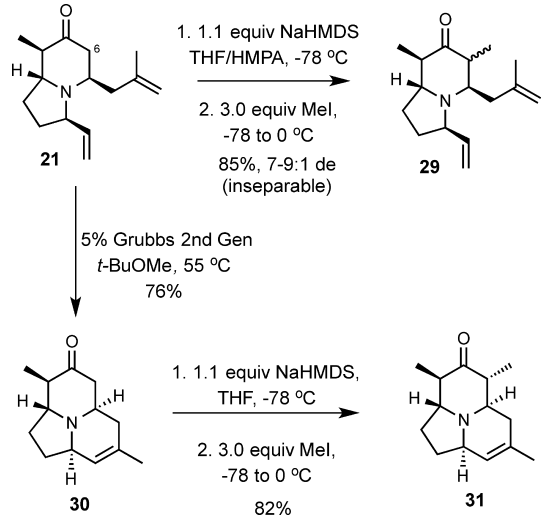
Scheme 6. Conjugate Addition Attempts



Scheme 7. Conjugate Addition Promoted by TFAA



Scheme 8. Introduction of the Second Methyl Group



mixture of diastereomers (7−9:1) that were not separable by column chromatography (Scheme 8).[36] Since efforts to stereospecifically incorporate the last methyl group were unsuccessful, an alternative approach was needed. It was reasoned that a higher level of selectivity could be achieved by initially forming the more rigid tricyclic system prior to the methylation. In this case, the piperidine ring would be locked in the conformation where the electrophile could easily distinguish between two faces of the enolate and deliver the methyl group via axial attack. Cyclization was accomplished by addition of 5% Grubbs second-generation catalyst to **21** through a syringe pump over a period of 5 h to furnish tricyclic product **30** in 76% yield.[37] Application of more traditional conditions with CH_2Cl_2 and catalyst addition in a single portion led to substantial decomposition and provided only a very moderate yield of the product. As expected, the rigid tricyclic ring system allowed the desired alkylation product **31** to be conveniently accessed with complete stereocontrol as a single diastereomer by treatment of **30** with NaHMDS at −78 °C followed by addition of MeI and warming of the reaction mixture to 0 °C.

Reductive Cleavage of the Ketone. With all of the atoms of the alkaloid's core properly installed, the completion of the total synthesis of 205B required only reductive cleavage of the carbonyl group at C7. Luche reduction of ketone **31** delivered **32** as a 3:1 diastereomeric mixture with the equatorial alcohol **32a** as the major isomer (Scheme 9). Subsequent heating of the alcohol mixture in toluene with 3.0 equiv of 1,1′-thiocarbonyldiimidazole (**33**) in the presence of DMAP furnished thiocarbonylimidazolides **34**.[38] To our surprise, no natural product was obtained upon reduction of **34** using the classical Barton−McCombie procedure[39] with Bu_3SnH and AIBN in refluxing toluene. Switching to a milder protocol developed by Nicolaou and co-workers using benzene and UV light as an initiator also failed to deliver any of the natural product.[40] Phenyl thionoformate **35** was also subjected to the standard reduction conditions but without any change in the overall outcome, as 205B remained elusive.[41]

Our difficulties in reductively cleaving the excessive ketone carbonyl through radical reduction in a straightforward manner led us to consider different options, and our attention was focused on the preparation of axial alcohol **32b**.[42] It was envisioned that studies with a single stereoisomer would simplify the analysis and separations of the reaction mixtures, and furthermore, axial alcohol **32b** should be more reactive since it is more sterically accessible. With sufficient amounts of

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Scheme 9. Barton–McCombie Deoxygenation Approach

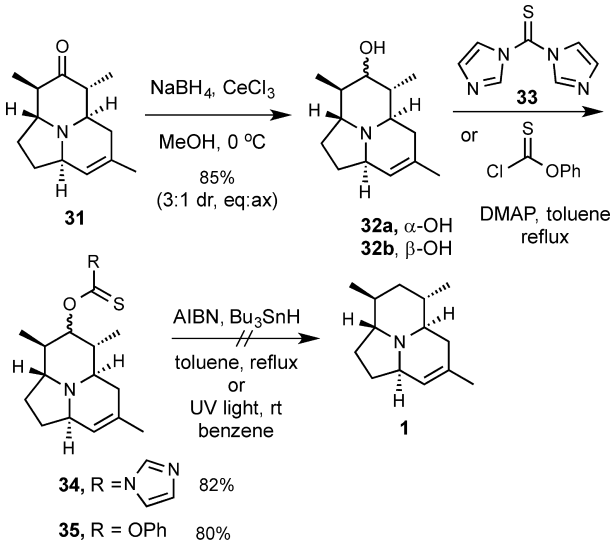
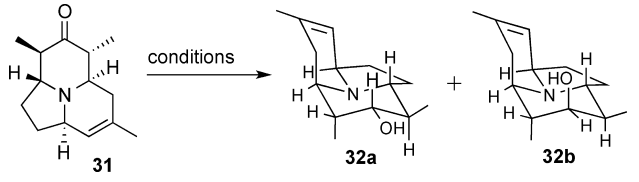


Table 3. Stereoselective Reduction of Ketone 31

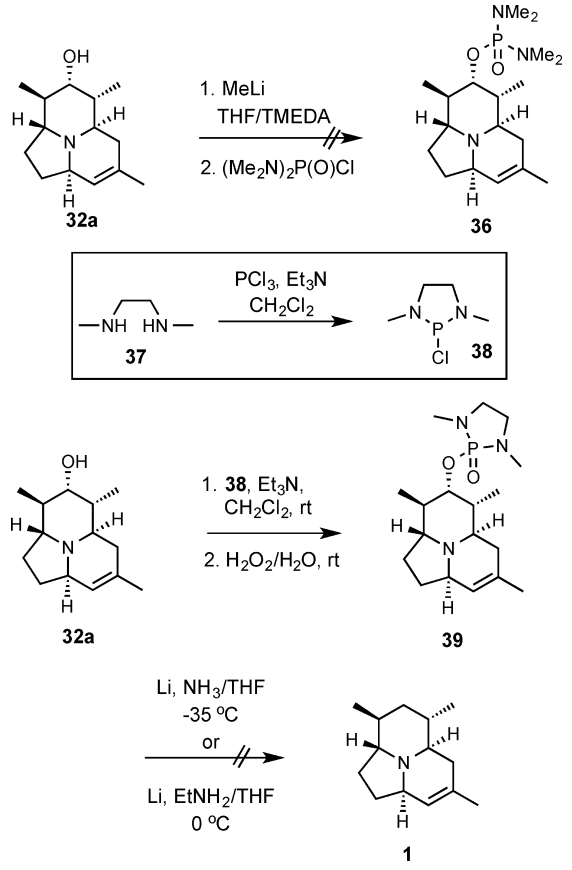


entry	reagent	temperature	dr (32a:32b)
1	$NaBH_4$, $CeCl_3 \cdot 7H_2O$	rt	3:1
2	DIBAL	−78 °C to rt	1:3
3	Red-Al	−78 °C	1:1
4	L-Selectride	−78 °C	–
5	Super Hydride	−78 °C	–
6	*i*-Bu_3Al	60 °C	–
7	Li, NH_3	−78 °C	1:0

the ketone in hand, the effect of different reducing agents on the stereoselectivity of alcohol formation was investigated (Table 3). Reactions with bulky L-Selectride and Super Hydride did not result in any of the alcohol products. It was hypothesized that the electron-rich tertiary nitrogen might coordinate with boron species, opening decomposition pathways (entries 4 and 5). In contrast, aluminum-based reagents were effective in reducing the ketone but furnished the alcohol as mixtures of diastereomers (entries 2 and 3). Fortunately, Li/NH_3 dissolving metal reduction delivered the equatorial product **32a** stereoselectively in 83% yield (entry 7).[12a] Alcohol **32a** was found to be hindered and unreactive. Numerous attempts to promote Appel or Mitsunobu reactions failed to provide any of the desired axial halide/alcohol via inversion of configuration.[43] In addition, alcohol **32a** completely decomposed upon exposure to MsCl and Et_3N. Potential elimination or fragmentation pathways are possible explanations of the observed outcome.

At this stage our attention shifted to the transformation of equatorial alcohol **32a** into phosphoramidate **36**. It is known that the C–O bond in corresponding phosphoramidate compounds can be selectively cleaved under dissolving metal conditions (Scheme 10).[44] Exposure of alcohol **32a** to MeLi in the presence of TMEDA and commercially available bis(dimethylamino)phosphoryl chloride resulted in recovery of

Scheme 10. Phosphoramidate Reduction Strategy



unreacted starting material, probably because of steric hindrance. As an alternative, a two-step procedure was implemented in which the required P–O bond was installed first using a more reactive phosphorus(III) electrophile, after which an oxidation step was performed to give the desired phosphoramidate. With these considerations in mind, 2-chloro-1,3-dimethyl-1,3,2-diazaphospholidine (**38**) was prepared from *N*,*N*′-dimethylethylenediamine (**37**) and phosphorus trichloride utilizing a known literature procedure.[45] Alcohol **32a** was treated with **38** in the presence of triethylamine at rt, and subsequent oxidation with aqueous H_2O_2 provided the corresponding phosphoramidate **39**; the crude product was used directly in the next step. In accordance with Corey's protocol, phosphoramidate **39** was subjected to Li in refluxing NH_3 at −35 °C, but no reaction occurred.[46] It was considered possible that the sterically constrained C–O bond in the phosphoramidate might require more forceful conditions to accomplish the desired cleavage. A modified version of this reduction in dry ethylamine at 0 °C has been developed and used in the synthesis of natural products.[47] Unfortunately, under these conditions, even after 2 h with 10.0 equiv of Li, the phosphoramidate failed to provide the desired product. Because of the lack of reactivity of this phosphoramidate, a search for an alternative approach commenced.

In effort to obviate the aforementioned problems with the alcohol reduction, we turned next to the earlier intermediate **31**. In accessing the options for a more direct cleavage of the ketone, the preparation of dithiolane **40** from ketone **31** was investigated. It was anticipated that **40** might be reduced with Raney Ni to give the desired alkaloid 205B (Scheme 11). Unfortunately, multiple approaches under a variety of

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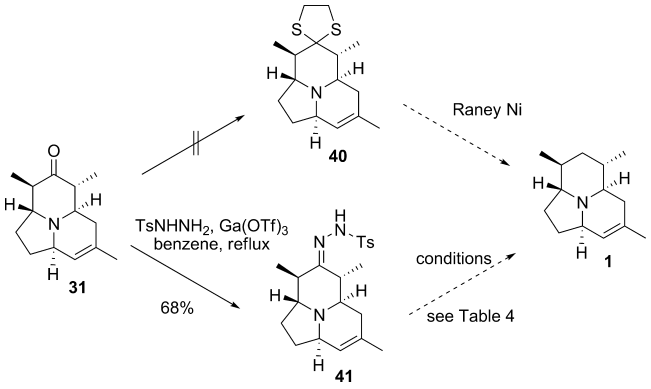
Scheme 11. Thioketal and Tosylhydrazone Formation

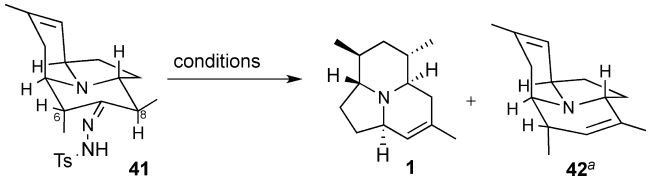


conditions with **31**, ethanedithiol, and various Brønsted and Lewis acids as catalysts all met with failure.[48] In all cases, the reactions provided either recovered starting material or products of decomposition, and no evidence of thioketal formation was found. It is important to mention that the application of similar conditions to simple piperidones in many cases resulted in quantitative yields of the thioketals.[49]

Concurrent to the thioketal study, tosylhydrazone formation was also investigated using a range of conventional protocols[50] without success. In contrast, we were pleased to find that **31**, tosylhydrazine, and 20% gallium triflate in refluxing benzene afforded the desired tosylhydrazone **41** in 68% yield (Scheme 11).

With a successful route for the formation of **41** established, our efforts were focused on conditions for the reductive cleavage of the tosylhydrazone group. All attempts to effect this reduction under an array of conditions found in the literature were unsuccessful (Table 4).[51] Reduction with mild reducing agents was not able to promote this transformation, while acidic or Lewis acid-catalyzed conditions resulted in significant decomposition of the starting material. Exposure of **41** to $NaBH_4$ in *t*-BuOH delivered some of the tentatively assigned alkene **42** on the basis of ^1H NMR analysis of the crude product (entry 5). Two factors could potentially shed some light on the unexpected results of this experiment. First, the C8 proton is in an axial position and thereby could be readily available for deprotonation. Second, release of strain in the system and elimination of 1,3-diaxial interactions could facilitate this transformation.

Table 4. Attempts at Tosylhydrazone Reduction



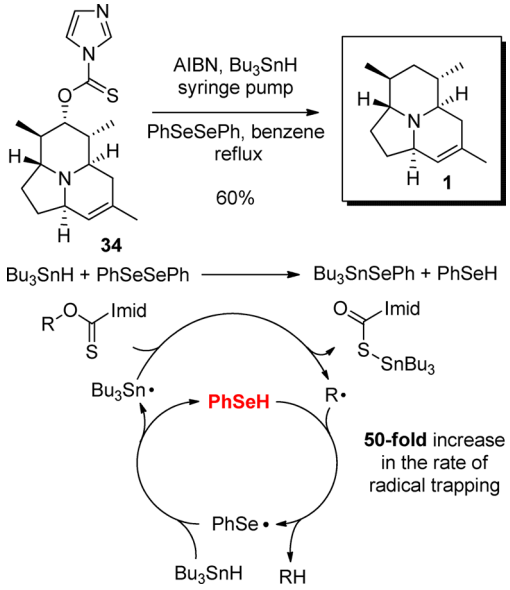
entry	reagent	solvent	temperature	product
1	$NaBH_4$	MeOH	reflux	sm
2	$NaBH_4$	*i*-PrOH	reflux	decomp
3	$NaBH_4$	*t*-BuOH	reflux	traces of **42**
4	$NaBH_4$	CF_3CH_2OH	reflux	sm
5	$NaBH_4$/NaOAc	*t*-BuOH	reflux	traces of **42**
6	$NaBH(OAc)_3$	AcOH	70 °C	decomp
7	Bu_4NBH_4	benzene	reflux	decomp
8	$NaBH_3CN$	*t*-BuOH	reflux	sm
9	$NaBH_3CN$	MeOH/AcOH	rt	sm

[a]Structure tentatively assigned by NMR analysis.

Upon analysis of all the results, it is fair to emphasize that the reductive cleavage of the carbonyl of **31** was an unexpected serious challenge. Several considerations that led to our successful approach deserve comment. First, we recognized that the two neighboring tertiary stereocenters create significant steric hindrance, thereby strongly attenuating the reactivity of the carbonyl group and its derivatives. Second, it was empirically demonstrated that under numerous reaction conditions, anionic and radical intermediates resulting from ketone **31** and its derivatives are quite unstable and have very low energy barriers for rearrangements and eliminations. Finally, we envisioned that the natural product could be accessed via a reduction pathway that is kinetically favorable and outcompetes potential rearrangements. In this regard, an alternative source of the hydrogen donor proved crucial for the success of the Barton–McCombie route. We speculated that the hydrogen source should ensure fast delivery of a hydrogen in order to quench the secondary radical faster than it would undergo the undesired rearrangements.

To this end, we proceeded to identify a suitable set of conditions that would allow us to test the possibility of the proposed approach. Indeed, Crich and co-workers, who have extensively studied radical cyclizations, developed an excellent protocol using catalytic amounts of diphenyl diselenide.[52] Upon mixing with Bu_3SnH, diphenyl diselenide generates PhSeH, which provides a 50-fold increase in the rate of hydrogen transfer in comparison with Bu_3SnH and thereby can suppress some undesired rearrangement byproducts (Scheme 12). To our delight, treatment of thiocarbamate **34** with a mixture of AIBN and Bu_3SnH in the presence of 20% PhSeSePh in refluxing benzene finally furnished the natural product **1** in 60% yield.

Scheme 12. Modified Barton–McCombie Protocol



Enantioselective Synthesis of 205B. With a concise route to the racemic natural product completed, our efforts focused on accomplishing an enantioselective synthesis of the alkaloid. For this purpose, our powerful asymmetric *N*-

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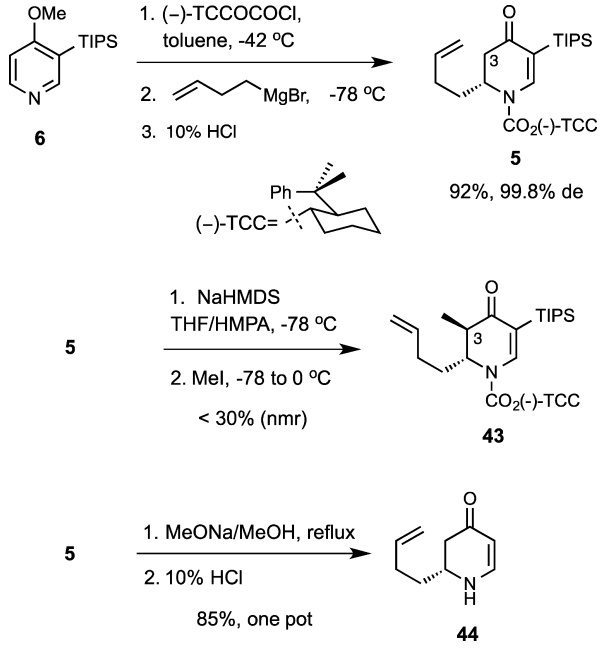
acylpyridinium salt chemistry was used to introduce the first stereocenter in the starting material **5**. Relying on a previously published protocol applied toward the total synthesis of (−)-tylophorine, we treated 3-TIPS-4-methoxypyridine (**6**) with chiral (−)-TCC chloroformate at −78 °C (Scheme 13).[14]

Scheme 13. Conversions of Dihydropyridone 5



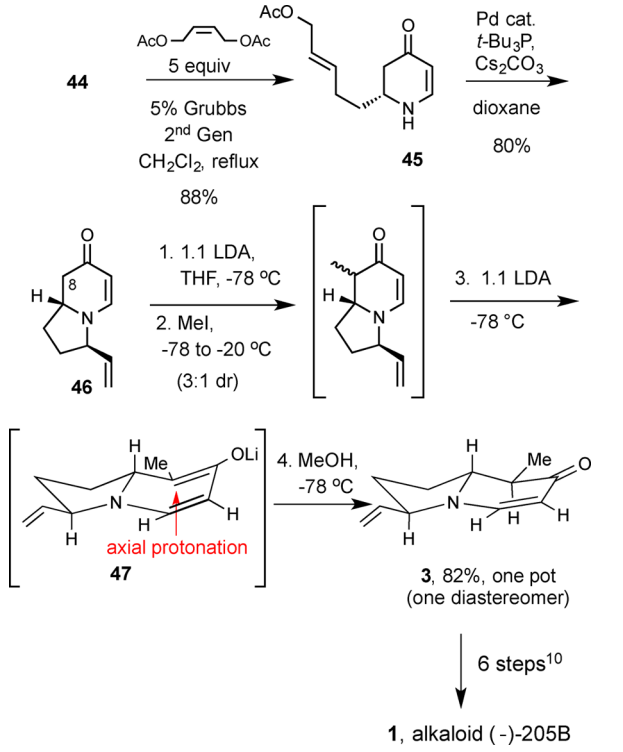
The resulting *N*-acylpyridinium salt was treated with 4-butenyl Grignard reagent followed by workup with 10% HCl to provide diastereomerically pure dihydropyridone **5** in 92% yield after recrystallization.

In contrast to the racemic route, no conditions, even including HMPA as an additive, proved to be efficient to deliver the desired alkylation product **43** in yields higher than 30%. Our analysis attributed this outcome to the steric effect of the bulky C5-TIPS group. To circumvent this difficulty, it was decided to install the C3 methyl group at a later stage in the synthesis. Removal of the carbamate and TIPS groups was carried out in one pot by initially subjecting dihydropyridone **5** to sodium methoxide in methanol to cleave the chiral auxiliary and then treating the resulting mixture with 10% HCl at rt to effect protodesilylation of the TIPS group.

Following procedures established during the racemic synthesis, dihydropyridine **44** was transformed into the allylic acetate with (*Z*)-but-2-ene-1,4-diyl diacetate and Grubbs–Hoveyda second-generation catalyst (Scheme 14). Dihydropyridone **45** was then subjected to the standard allylic amination conditions with cesium carbonate, tri-*tert*-butylphosphine, and $Pd_2(dba)_3{\cdot}CHCl_3$ at 75 °C. To our delight, the absence of the C3 methyl group in the dihydropyridone did not have any effect on the diastereoselectivity, and indolizidinone **46** was isolated in 75% yield with a similar 9:1 ratio of stereoisomers favoring the desired one.

With an established strategy for the preparation of indolizidinone **46**, the problem of installing the C8 methyl group was addressed. Unfortunately, in comparison with carbamate-protected dihydropyridone **8**, where the conformation was restricted by allylic strain, the enolate derived from indolizidinone **46** proved to be quite flexible. In the absence of

Scheme 14. Successful Introduction of the C8 Methyl Group



any significant conformational bias, facial differentiation was significantly diminished, and consequently, alkylation with LDA and MeI generated the product with a rather frustrating 3:1 (eq/ax) diastereoselectivity. Since a direct methylation failed to provide the desired stereochemical outcome, a revised strategy was devised to control the stereochemistry of the C8 center. Fortunately, in situ treatment of the alkylated product mixture with 1 equiv of LDA and careful kinetic protonation of the newly formed intermediate **47** with MeOH at −78 °C afforded dihydropyridone **3** as a single stereoisomer in 82% yield.

With enantiopure intermediate **3** in hand, the rest of the enantioselective synthesis was accomplished by closely following the previously described procedures without any substantial modifications.[10] Comparison of the spectral data of synthetic (−)-205B with those reported by the Smith group did not reveal any discrepancies. Additionally, the synthetic alkaloid exhibited optical properties in agreement with those reported for the natural sample.

■ SUMMARY

Highly stereocontrolled, protecting-group-free syntheses of racemic and enantiopure (−)-205B were accomplished in 11 steps from 4-methoxypyridines **6** and **7** in overall yields of 8 and 8%, respectively. Dihydropyridone-based functionalization was key to our strategy for developing a concise synthesis. After the first chiral center was introduced through the preparation of dihydropyridone **5** or **8**, the remaining four stereocenters were efficiently incorporated by substrate-controlled installation. This work demonstrates once again the versatile utility of chiral dihydropyridones as building blocks for the stereoselective and concise construction of piperidine-containing natural products.[11]

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EXPERIMENTAL SECTION

(2*R,3*R**)-Phenyl 2-(But-3-enyl)-3-methyl-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (9).** To a solution of **8**[15a] (460 mg, 1.70 mmol) in anhydrous THF (15 mL) at −78 °C was added a THF solution of NaHMDS (1 M in THF, 1.87 mL, 1.87 mmol). The mixture was stirred for 30 min at −78 °C. Methyl iodide (0.320 mL, 5.10 mmol) was added dropwise, and then the solution was warmed to 0 °C over 1 h. The reaction mixture was quenched with a solution of saturated aqueous $NaHCO_3$ (20 mL). The resulting solution was diluted with Et_2O (20 mL) and transferred to a separatory funnel, and the phases were allowed to separate. The aqueous layer was extracted with Et_2O (2 × 20 mL). The organic layers were combined, washed with saturated $NaHCO_3$ (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. The crude product was purified by PLC (SiO_2, 10% EtOAc/hexanes), affording 436 mg (90% yield) of **9** as a clear oil. IR (neat) 3076, 2974, 2931, 2873, 1739, 1672, 1604, 1495, 1456, 1419, 1335, 1265, 1196, 1045, 914, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, 1H, J = 8.3 Hz), 7.43 (m, 2H), 7.29 (m, 1H), 7.18 (m, 2H), 5.78 (m, 1H), 5.35 (m, 1H), 5.03 (m, 2H), 4.44 (m, 1H), 2.50 (q, 1H, J = 7.2 Hz), 2.21 (m, 1H), 2.11 (m, 1H), 1.89 (m, 1H), 1.76 (m, 1H), 1.28 (d, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 151.3, 150.4, 139.8, 136.7, 129.6, 126.3, 121.2, 115.7, 105.9, 59.3, 43.6, 29.8, 17.0; HRMS calcd for $C_{17}H_{20}NO_3$ [$(M + H)^+$] 286.1438, found 286.1444.

(2*R,3*R**)-Phenyl 2-((*E*)-5-Acetoxypent-3-enyl)-3-methyl-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (10).** To a degassed solution of alkene **9** (150 mg, 0.526 mmol) in 20 mL of anhydrous methylene chloride was added (*Z*)-but-2-ene-1,4-diyl diacetate (271 mg, 1.580 mmol) followed by Grubbs−Hoveyda second-generation catalyst (16.5 mg, 0.0263 mmol). The mixture was heated to reflux for 2 h, cooled, and filtered through a Celite pad with a methylene chloride wash. After concentration under reduced pressure, purification by radial PLC (SiO_2, 30−50% EtOAc/1% methanol/1% Et_3N/hexanes) gave 131 mg (70% yield) of **10** as a clear oil. IR (neat) 3075, 2969, 2933, 1733, 1669, 1605, 1492, 1420, 1334, 1262, 1228, 1198, 1026, 967 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, 1H, J = 8.0 Hz), 7.34 (m, 2H), 7.30 (m, 1H), 7.18 (m, 2H), 5.74 (m, 1H), 5.61 (m, 1H), 5.35 (bs, 1H), 4.49 (d, 2H, J = 6.1 Hz), 4.44 (m, 1H), 2.48 (q, 1H, J = 7.2 Hz), 2.21 (m, 1H), 2.12 (m, 1H), 2.03 (s, 3H), 1.90 (m, 1H), 1.76 (m, 1H), 1.28 (d, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 197.2, 170.7, 151.0, 150.4, 139.7, 133.9, 129.6, 126.4, 125.1, 121.1, 105.9, 64.7, 59.3, 43.7, 29.9, 28.3, 20.9, 16.9; HRMS calcd for $C_{20}H_{23}NO_5Na$ [$(M + Na)^+$] 380.1468, found 380.1462.

(2*R,3*R**)-2-((*E*)-5-Hydroxypent-3-enyl)-3-methyl-2,3-dihydropyridin-4(1*H*)-one (11).** To a solution of **10** (147 mg, 0.411 mmol) in 5 mL of methanol was added K_2CO_3 (113 mg, 0.822 mmol). After 12 h of stirring at rt, the solvent was removed in vacuo. To the resulting solid was added EtOAc, and the mixture was filtered through a Celite pad with an EtOAc wash. After concentration under reduced pressure, purification by radial PLC (SiO_2, 25−30% EtOAc/1% Et_3N/hexanes) gave 43 mg (54% yield) of vinylogous amide **11** as a clear oil. This product was characterized as its acetate (**4**).

(2*R,3*R**)-2-(But-3-enyl)-3-methyl-2,3-dihydropyridin-4(1*H*)-one (12).** To a solution of **9** (170 mg, 0.596 mmol) in 5 mL of methanol was added K_2CO_3 (164 mg, 1.192 mmol). After 12 h of stirring at rt, the solvent was removed in vacuo. To the resulting solid was added EtOAc, and the mixture was filtered through a Celite pad with an EtOAc wash. After concentration under reduced pressure, purification by radial PLC (SiO_2, 20−30% EtOAc/1% methanol/1% Et_3N/hexanes) gave 85 mg (86% yield) of vinylogous amide **12** as a clear oil. IR (neat) 3257, 3041, 2972, 2929, 1576, 1452, 1408, 1346, 1246, 1205, 914, 791 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.10 (t, 1H, J = 6.9 Hz), 6.23 (bs, 1H), 5.75 (m, 1H), 4.99 (m, 2H) 4.85 (d, 1H, J = 6.9 Hz), 3.27 (m, 1H), 2.19 (m, 1H), 2.11 (m, 2H), 1.78 (m, 1H), 1.61 (m, 1H), 1.13 (d, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0, 150.0, 137.3, 115.5, 95.8, 57.5, 43.8, 30.8, 29.5, 14.8; HRMS calcd for $C_{10}H_{16}NO$ [$(M + H)^+$] 166.1226, found 166.1226.

5-((2*R,3*R**)-3-Methyl-4-oxo-1,2,3,4-tetrahydropyridin-2-yl)-pent-2-enyl Acetate (4).** To a degassed solution of **12** (105 mg, 0.635 mmol) in 20 mL of anhydrous methylene chloride was added (*Z*)-but-2-ene-1,4-diyl diacetate (437 mg, 2.542 mmol) followed by Grubbs−Hoveyda second-generation catalyst (20 mg, 0.0318 mmol). The mixture was heated to reflux for 2 h, cooled, and filtered through a Celite pad with a methylene chloride wash. After concentration under reduced pressure, purification by radial PLC (SiO_2, 30−40% EtOAc/1% methanol/1% Et_3N/hexanes) gave 130 mg (87% yield) of **4** as a clear oil. IR (neat) 3261, 3041, 2929, 1738, 1579, 1450, 1365, 1242, 1026, 970 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.11 (t, 1H, J = 7.0 Hz), 5.76 (m, 1H), 5.61 (m, 1H), 5.55 (bs, 1H), 4.94 (d, 1H, J = 7.0 Hz), 4.52, (d, 2H, J = 6.3 Hz), 3.29 (m, 1H), 2.29−2.14 (m, 3H), 2.07 (s, 3H), 1.84 (m, 1H), 1.66 (m, 1H), 1.18 (d, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.8, 171.0, 149.2, 134.6, 125.1, 97.1, 64.9, 58.1, 44.1, 31.0, 28.4, 21.0, 14.6; HRMS calcd for $C_{13}H_{20}NO_3$ [$(M + H)^+$] 238.1438, found 238.1437.

(3*R,5*R**,8*R**,8a*R**)-8-Methyl-5-(2-methylallyl)-3-vinyl-1,2,3,5,8,8a-hexahydroindolizin-7-yl Trifluoromethanesulfonate (20).** To a stirred solution of **3** (250 mg, 1.41 mmol) in 8 mL of anhydrous methylene chloride at −78 °C was added methallyltributylstannane (973 mg, 2.82 mmol) followed by dropwise addition of trifluoromethanesulfonic anhydride (0.33 mL, 1.97 mmol). The mixture was stirred for 1 h at −78 °C, and then reaction mixture was quenched with a solution of saturated aqueous $NaHCO_3$ (5 mL). The resulting solution was diluted with methylene chloride (5 mL) and transferred to a separatory funnel, and the phases were allowed to separate. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. The crude product was purified by radial PLC (SiO_2, 10% EtOAc/hexanes) to give 334 mg (65% yield) of triflate **20** as a clear oil. IR (neat) 3078, 2935, 1682, 1645, 1417, 1246, 1211, 1144, 993, 918, 862 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.79 (dd, 1H, J = 1.9, 4.1 Hz), 5.61 (ddd, 1H, J = 8.3, 9.9, 17.3 Hz), 5.10 (dd, 1H, J = 1.7, 17.3 Hz), 5.07 (dd, 1H, J = 1.7, 9.9 Hz), 4.78 (s, 1H), 4.69 (s, 1H), 3.53 (m, 1H), 3.14 (dd, 1H, J = 7.8, 15.2 Hz), 3.04 (dd, 1H, J = 6.1, 8.8 Hz), 2.26−1.97 (m, 5H), 1.72 (s, 3H), 1.67−1.56 (m, 2H), 1.10 (d, 3H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 142.3, 141.3, 119.6, 118.5 (q, J_{C-F} = 319 Hz), 116.6, 112.7, 65.6, 60.7, 51.6, 44.7, 32.1, 29.2, 28.1, 22.4, 14.6; HRMS calcd for $C_{16}H_{23}F_3NO_3S$ [$(M + H)^+$] 366.1345, found 366.1341.

(3*R*,5*R*,8*R*,8a*R*)-8-Methyl-5-(2-methylallyl)-3-vinylhexahydroindolizin-7(1*H*)-one (21). To a stirred solution of enantiopure **3** (56 mg, 0.316 mmol) in 4 mL of anhydrous methylene chloride at −50 °C was added methallyltributylstannane (218 mg, 0.632 mmol) followed by dropwise addition of trifluoroacetic anhydride (0.07 mL, 0.474 mmol). The mixture was warmed to 0 °C over 1 h and then quenched with a solution of saturated aqueous $NaHCO_3$ (5 mL). The resulting mixture was diluted with methylene chloride (5 mL) and transferred to a separatory funnel, and the phases were allowed to separate. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. The crude product was purified by radial PLC (SiO_2, 5% EtOAc/hexanes) to afford 51 mg (69% yield) of ketone **21** as a clear oil. $[\alpha]_D^{22}$ +55.2 (*c* 0.92, MeOH); IR (neat) 3074, 2970, 2933, 1706, 1649, 1423, 1377, 1323, 1194, 993, 920, 887 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.68 (ddd, 1H, J = 8.3, 9.9, 17.5 Hz), 5.18 (dd, 1H, J = 1.7, 17.5 Hz), 5.11 (dd, 1H, J = 1.7, 9.9 Hz), 4.76 (bs, 1H), 4.67 (bs, 1H), 3.62−3.51 (m, 2H), 3.19 (dd, 1H, J = 9.9, 6.1 Hz), 2.66 (dd, 1H, J = 12.7, 6.1 Hz), 2.24−2.10 (m, 6H), 1.78−1.64 (m, 2H), 1.68 (s, 3H), 0.97 (d, 3H, J = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.3, 142.6, 141.7, 116.2, 112.5, 64.6, 63.2, 54.2, 46.6, 42.6, 40.0, 30.0, 28.5, 22.1, 10.5; HRMS calcd for $C_{15}H_{24}NO$ [$(M + H)^+$] 234.1852, found 234.1855.

(3*R,5*R**,8*S**,8a*R**)-8-Methyl-5-(2-methylallyl)-3-vinyl-1,2,3,5,8,8a-hexahydroindolizine-7-carbaldehyde (26).** A degassed solution of flame-dried LiCl (74 mg, 1.75 mmol), $Pd(PPh_3)_4$ (51 mg, 0.0438 mmol), and triflate **20** (160 mg, 0.438 mmol) in anhydrous THF (5 mL) was put under a carbon monoxide atmosphere. The mixture was heated to 50 °C and treated with a solution of tributyltin hydride (159 mg, 0.548 mmol) in THF (1 mL)

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via syringe pump over 5 h. After the addition was complete, the mixture was cooled to rt, diluted with Et_2O, washed with brine (3 × 25 mL), dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. The crude product was purified by radial PLC (SiO_2, 5% EtOAc/0.5% methanol/0.5% Et_3N/hexanes) to give 80 mg (70% yield) of aldehyde **26** as a clear oil. IR (neat) 3076, 2933, 2812, 2710, 1691, 1637, 1452, 1373, 1171, 1124, 918 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.40 (s, 1H), 6.82 (dd, 1H, J = 1.7, 4.4 Hz), 5.63 (ddd, 1H, J = 8.5, 10.7, 19.0 Hz), 5.04 (m, 2H), 4.81 (bs, 1H), 4.73 (bs, 1H), 3.58 (m, 1H), 2.97 (m, 2H), 2.35−1.95 (m, 5H), 1.77 (s, 3H), 1.66−154 (m, 2H), 1.2 (d, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.0, 152.4, 142.7, 142.4, 141.6, 116.2, 112.6, 63.6, 59.4, 52.2, 43.7, 29.3, 28.2, 27.7, 22.5, 16.7; HRMS calcd for $C_{16}H_{24}NO$ $[(M + H)^+]$ 246.1852, found 246.1847.

(3*R,5*R**,8*S**,8a*R**)-Methyl 8-Methyl-5-(2-methylallyl)-3-vinyl-1,2,3,5,8,8a-hexahydroindolizine-7-carboxylate (27).** After a stirred solution of PPh_3 (11 mg, 0.0436 mmol), $Pd(OAc)_2$ (5 mg, 0.0218 mmol), and triflate **20** (40 mg, 0.109 mmol) in anhydrous MeOH (3 mL) and DMF (1 mL) was degassed, triethylamine (0.2 mL) was added, and carbon monoxide was introduced into the flask. The resulting mixture was heated to 50 °C for 4 h under a carbon monoxide atmosphere. The mixture was cooled to rt, diluted with Et_2O, washed with brine (3 × 15 mL), dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. The crude product was purified by radial PLC (SiO_2, 4% EtOAc/0.5% methanol/0.5% Et_3N/hexanes) to give 18 mg (60% yield) of ester **27** as a clear oil. IR (neat) 3074, 2951, 1718, 1645, 1435, 1255, 1217, 1124, 1063, 920, 887 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.87 (dd, 1H, J = 1.9, 4.7 Hz), 5.62 (m, 1H), 5.06−5.00 (m, 2H), 4.78 (bs, 1H), 4.71 (bs, 1H), 3.74 (s, 3H), 3.43 (m, 1H), 3.02 (q, 1H, J = 6.9 Hz), 2.96 (dd, 1H, J = 6.1, 8.8 Hz), 2.23−2.15 (m, 3H), 2.06−1.96 (m, 2H), 1.75 (s, 3H), 1.64−1.57 (m, 2H), 1.06 (d, 3H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 142.8, 141.8, 139.7, 132.7, 116.1, 112.3, 63.5, 59.6, 51.7, 51.4, 43.8, 29.3, 28.7, 28.5, 22.5, 17.8; HRMS calcd for $C_{17}H_{26}NO_2$ $[(M + H)^+]$ 276.1958, found 276.1956.

1,3-Dimethyl-2-(((2a*R,3*R**,4*S**,5*R**,5a*R**,8a*R**)-3,5,7-trimethyl-2,2a,3,4,5,5a,6,8a-octahydro-1*H*-pyrrolo[2,1,5-*de*]quinolizin-4-yl)oxy)-1,3,2-diazaphospholidine 2-Oxide (39).** To a solution of alcohol **32a** (26 mg, 0.117 mmol) in CH_2Cl_2 (1 mL) at rt was added Et_3N (0.1 mL, 0.712 mmol) followed by chlorodiazaphospholidine **38** (53 mg, 0.351 mmol). After 1 h at rt, 5 drops of H_2O_2 were added, and the resulting mixture was stirred for additional 10 min. The reaction mixture was quenched with a saturated solution of $NaHCO_3$ (5 mL) and extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with $NaHCO_3$ (10 mL) and brine (10 mL), dried with $MgSO_4$, filtered, and concentrated to give 10 mg (24% yield) of crude **39** as an oil that was used in the reduction step without additional purification.

(*Z*)-4-Methyl-*N*′-((2a*R,4*R**,6*R**,6a*R**,9a*R**)-4,6,8-trimethyl-2a,4,6a,7-tetrahydro-1*H*-pyrrolo[2,1,5-*de*]quinolizin-5-(2*H*,6*H*,9a*H*)-ylidene)benzenesulfonohydrazide (41).** To a solution of **31** (10 mg, 0.046 mmol) in anhydrous benzene (10 mL) was added tosyl hydrazide (12 mg, 0.068 mmol) followed by gallium triflate (8 mg, 0.014 mmol). The mixture was heated at reflux for 5 h. The solution was cooled to rt, diluted with Et_2O (10 mL), washed with saturated $NaHCO_3$ (15 mL) and brine (15 mL), dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. The crude product was purified by radial PLC (SiO_2, 15% EtOAc/1% methanol/1% Et_3N/hexanes) to yield 12 mg (68% yield) of tosylhydrazone **41** as a white solid. IR (neat) 3219, 2964, 2929, 2873, 1450, 1377, 1335, 1167 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, 2H, J = 8.1 Hz), 7.31 (d, 2H, J = 8.1 Hz), 5.1 (bs, 1H), 3.77 (bs, 1H), 3.06 (dd, 1H, J = 6.2, 9.8 Hz), 2.61, 2.43 (q, 1H, J = 7.0 Hz), (s, 3H), 2.30−2.08 (m, 3H), 1.91 (m, 1H), 1.53−1.48 (m, 2H), 1.42−1.31 (m, 2H), 1.17 (d, 3H. J = 6.9 Hz), 0.98 (d, 3H, J = 5.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 143.9, 129.3, 128.9,148, 128.1, 125.4, 60.1, 57.6, 56.6, 41.0, 34.7, 29.7, 28.7, 28.6, 23.2, 21.6, 17.1, 12.3; HRMS calcd for $C_{21}H_{30}N_3O_2S$ $[(M + H)^+]$ 388.2053, found 388.2055.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR spectra for **1**, **4**, **9**, **10**, **12**, **20**, **26**, **27**, and **41**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Daniel_comins@ncsu.edu.

Present Address

†S.V.T.: Department of Chemistry, Vanderbilt University, 7330 Stevenson Center, Nashville, TN 37235-1822, United States. E-mail: sergey.v.tsukanov@vanderbilt.edu.

Notes

The authors declare no competing financial interest.

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