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Enantioselective Approach to Quinolizidines: Total Synthesis of Cermizine D and Formal Syntheses of Senepodine G and Cermizine C

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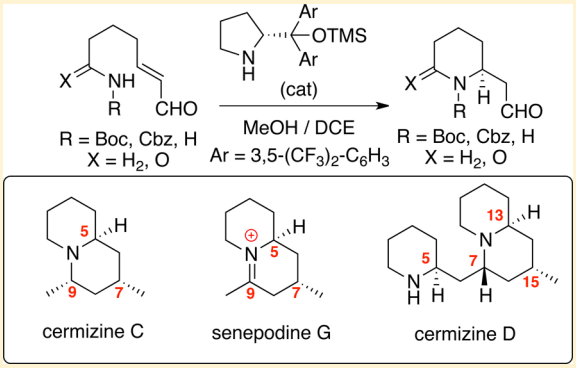
Supporting Information

ABSTRACT: The formal syntheses of C_5-*epi*-senepodine G and C_5-*epi*-cermizine C have been accomplished through a novel diastereoselective, intramolecular amide Michael addition process. The total synthesis of cermizine D has been achieved through use of an organocatalyzed, heteroatom Michael addition to access a common intermediate. Additional key steps of this sequence include a matched, diastereoselective alkylation with an iodomethylphenyl sulfide and sulfone-aldehyde coupling/reductive desulfurization sequence to combine the major subunits. The utility of a Hartwig-style C−N coupling has been explored on functionally dense coupling partners. Diastereoselective conjugate additions to α,β-unsaturated sulfones have been investigated, which provided the key sulfone intermediate in just six steps from commercially available starting materials. The formal syntheses of senepodine G and cermizine C have been accomplished through an intramolecular cyclization process of a *N*-Boc-protected piperidine sulfone.



INTRODUCTION

Since the initial isolation of lycopodine from *Lycopodium complanatum* in Germany by von Karl Bödeker in 1881,[1] a diverse collection of alkaloid natural products has been discovered in the *lycopdium* club mosses. These plants have been used for millennia as treatments for a wide range of ailments, from controlling fever to schizophrenia to memory loss. The first systematic study of the *lycopodium* club mosses was spearheaded by Professor William A. Ayer from the University of Alberta, leading to numerous advances in the field of structural determination, biogenesis, and natural product synthesis.[2] More recently, Professor Jun'ichi Kobayashi's laboratory at the University of Hokkaido has continued to mine these plants for additional alkaloid constituents, providing multiple new compounds and new chemical scaffolds.[3] Several other laboratories have probed these plants for medicinally useful alkaloids.[4]

Pelletierine (**1**) was first isolated from pomegranate by Tanret in 1878 and serves as a common building block in the biosynthesis of many of the *lycopodium* alkaloids (Figure 1).[5] Despite its deceptively simple structure,[6] this compound has been the target of considerable synthetic attention and numerous total syntheses.[7,8] Many of the quinolizidine-natural products identified by Ayer, Kobayashi, and others are derived from pelletierine through the pelletierine condensation.[9] Representative members of these quinolizidine natural products include cermizine C[10] (and its biosynthetic precursor senepodine G), myrtine,[11] and lasbines I−II.[12] More complex versions include the incorporation of a second formal unit of pelletierine such as cermizine D[10] and cernuine.[13] These

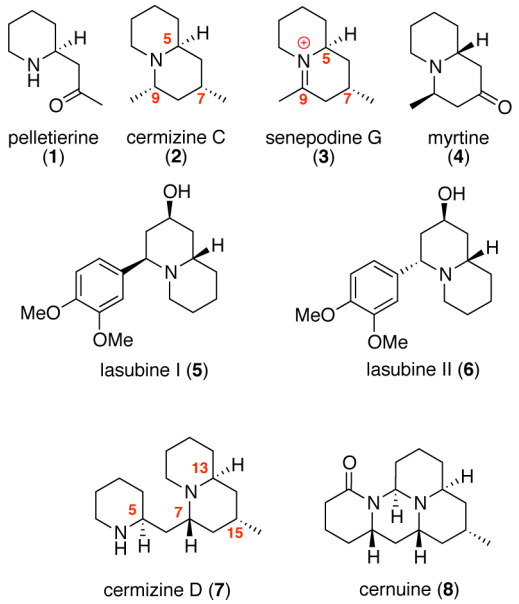


Figure 1. Piperidine- and quinolizidine-based natural products.

quinolizidine natural products **2**−**8** have garnered considerable synthetic attention[14−16] including total syntheses of the more complicated members cernuine (**8**)[14c,17] and cermizine D (**7**).[14c,17,18] This quinolizidine scaffold is also present in other

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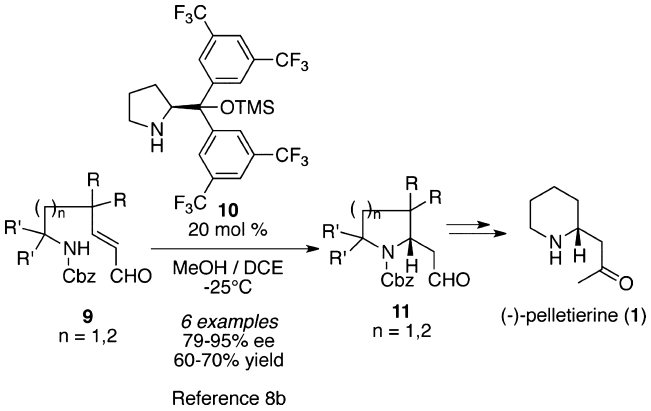
members of the *lycopodium* alkaloids such as himeradine A.[19] Our interest in these compounds was initially stimulated by himeradine A and has expanded into developing general approaches to access significant cross sections of the *lycopodium* alkaloid family.[8b,18,19b,20] Herein, we disclose a full account of our total synthesis of cermizine D (**7**).[18] In addition, we report the formal syntheses of both cermizine C (**2**) and senepodine G (**3**) as well as their C_5 epimers.

RESULTS AND DISCUSSION

Our efforts started with the observation that a core piperidine ring was present in each of these natural products. We envisioned that this piperidine scaffold could be constructed via an organocatalyzed, intramolecular heteroatom Michael addition of a suitably constructed enal precursor **9** (Scheme 1).[8b] To our surprise, this transformation had not been

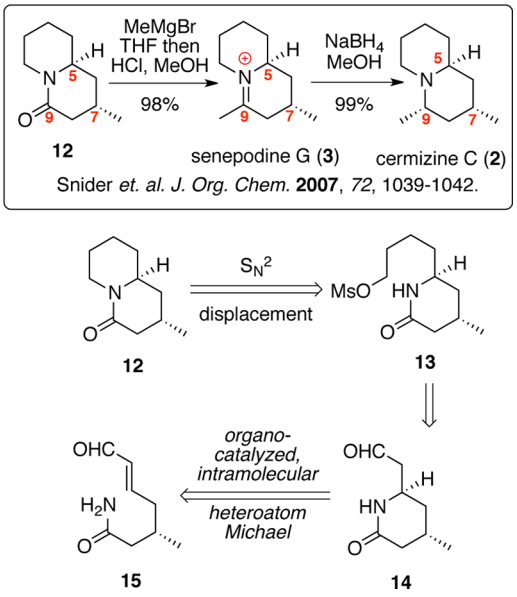
Scheme 1. Organocatalyzed Intramolecular Heteroatom Michael Addition and Total Synthesis of Pelletierine



explored at the time we initiated this project.[15h,21] Prior work in the area had focused on an intermolecular version using highly nucleophilic nitrogen sources;[22] however, it is important to note the pioneering intramolecular contributions from Hsung and co-workers using vinylogous amides.[23] We were pleased to find that a general enantioselective approach could be developed using the Jørgensen catalyst **10**[24] to provide the resultant cyclized product **11** in good yield and high eneantioselectivity.[8b] This approach was used for an efficient enantioselective total synthesis of (−)-pelletierine (**1**).[8b]

Inspired by our initial successes with carbamate nitrogen nucleophiles in the intramolecular heteroatom Michael addition,[8b] we were intrigued by the possibility that alternate nitrogen nucleophiles could be utilized. We were particularly interested in the possibility that amides could serve as a nucleophile for this transformation, specifically on substrates containing additional stereochemistry in the resultant piperidine ring (e.g., **14**) (Scheme 2). Interestingly, only limited examples of simple primary amide nucleophiles[25] have been exploited in γ- or Δ-lactam formation via a heteroatom Michael manifold.[26] Hirama and co-workers explored a silyloxy substituent within the carbon backbone of intramolecular heteroatom Michael addition of an amide in their synthesis of swainsonine.[27] Shultz's laboratory posthumously reported an intramolecular heteroatom Michael addition onto a fused α,β-unsaturated lactone to generate a [4.3.0] bicyclic scaffold.[28] We sought to probe the inherent stereoselectivity of the process and exploit the possibility that catalyst control could be used to

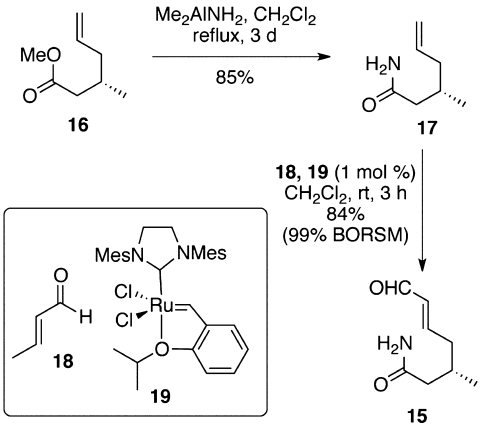
Scheme 2. Retrosynthetic Analysis of Cermizine C and Senepodine G



guide the outcome of the transformation. The resultant product **14** from this cyclization could be readily converted to the [4.4.0] bicyclic lactam **12**, which Snider and co-workers have previously converted onto senepodine G (**3**) and cermizine C (**2**).[14a,29]

The necessary cyclization precursor **15** was constructed in two steps from the previously prepared methyl ester **16**[20] (Scheme 3). Treatment of methyl ester **16** with the

Scheme 3. Synthesis of the Amide Cyclization Precursor



dimethylaluminum-amide complex produced the amide **17**. Cross metathesis with crotonaldehyde (**18**) using the Hoveyda−Grubbs second generation catalyst **19** produced the enal **15** in good yield. This product **15** proved stable for prolonged periods when stored frozen in benzene.

With the cyclization precursor in hand, we set out to explore the possibility of expanding the organocatalyzed intramolecular Michael addition to include amide nucleophiles (Table 1). Using an achiral Lewis acid ($BF_3{\cdot}Et_2O$) we observed slow cyclization with essentially no diastereoselectivity (entry 1). Interestingly, we have exploited a related $BF_3{\cdot}Et_2O$-catalyzed, intramolecular heteroatom Michael addition in our himeradine A work for the construction of a piperidine ring with high

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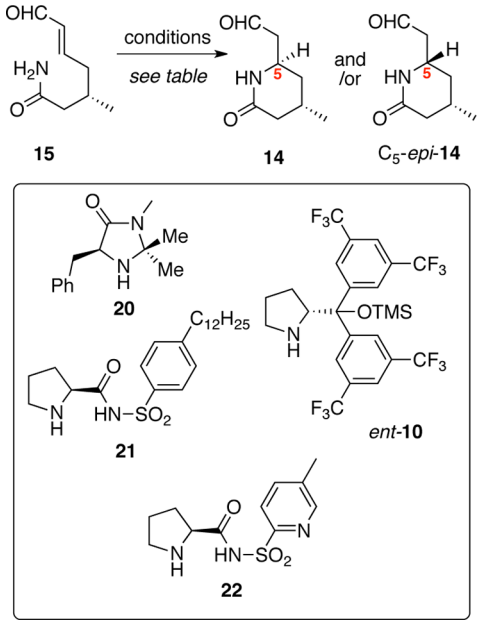
Table 1. Exploration of Intramolecular Heteroatom Michael Addition with Amide

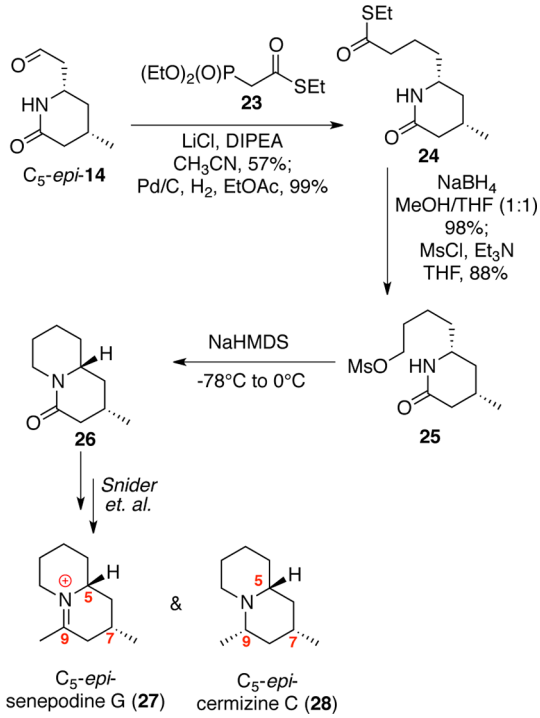


entry	catalyst	conditions	time	yield (**14**:C_5-*epi*-**14**)
1	$BF_3{\cdot}Et_2O$	CH_3CN, rt	1 d	40% (1:1.3)
2	**10**	DCE/MeOH (1:1), rt	5 d	n/d (1:1)
3	*ent*-**10**	DCE/MeOH (1:1), rt	6 d	50% (1:10)
4	**20**	DCE/MeOH (1:1), rt	4 d	45% (1:1)
5	**21**	DCE/MeOH (1:1), rt	3 d	45%(1:2)
6	**22**	DCE/MeOH (1:1), rt	14 h	70% (1:4)
7	**22**	DCE/MeOH (9:1), rt	19 h	69% (1:4)
8	**22**	DCE, rt	1 d	60% (1:4)
9	**22**	DCE, H_2O (1 equiv), rt	19 h	67% (1:4)

diastereocontrol.[19b] Use of our previous Jørgensen catalyst conditions[8b] at low temperatures did not induce any cyclization; however, warming of the reaction mixture to room temperature provided the cyclized product as a 1:1 diastereomeric mixture at C_5 (entry 2). Use of the enantiomeric catalyst *ent*-**10** resulted in clean formation of C_5-*epi*-**14** in reasonable yield [entry 3, 50% yield, 1:10 dr (**14**:C_5-*epi*-**14**)]. We also screened alternative monofunctional catalysts (e.g., MacMillan's catalyst **20**); however, this catalyst proved unselective (entry 4). Our laboratory has extensively exploited the use of proline sulfonamides for a range of transformations.[30] Consequently, we screened catalyst **21** in the transformation, but poor diastereoselectivity was observed (entry 5, 1:2 dr). Use of the alternate sulfonamide **22**[30g] provided a significant rate acceleration but with continued modest levels of selectivity (entry 6, 14 h, 70% yield, 1:4 dr). The reaction did not proceed at any appreciable rate at temperatures below rt. Variation of the solvent mixture had little impact on the transformation (entries 7−9).

The formal synthesis of C_5-*epi*-senepodine G from aldehyde C_5-*epi*-**14** is shown in Scheme 4. Treatment of aldehyde C_5-*epi*-**14** with the known phosphonate **23**[31] under Masamune−Roush conditions followed by hydrogenation yielded the thioester **24**. Reduction using $NaBH_4$ in MeOH/THF followed by treatment with MsCl provided the primary mesylate **25**. The lactam **26** was constructed by treatment of **25** with NaHMDS. This intermediate **26**[32] has been previously converted onto C_5-

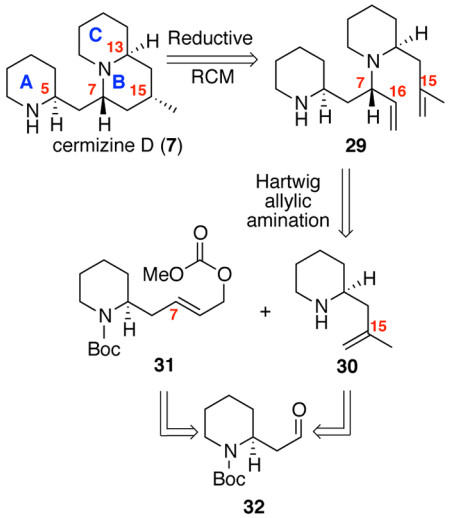
Scheme 4. Formal Synthesis of C_5-*epi*-Senepodine G and C_5-*epi*-Cermizine C



epi-senepodine G (**27**) and C_5-*epi*-cermizine C (**28**) by Snider and co-workers, thereby confirming the stereochemical assignment of the heteroatom Michael addition.[14a]

Next, we turned out attention toward cermizine D (**7**) (Scheme 5). Our initial retrosynthesis toward **7** exploited a

Scheme 5. Retrosynthetic Analysis of Cermizine D



common intermediate strategy to access the A and C rings. The B ring would be incorporated through a reductive ring closing metathesis (RCM) approach.[33] The key C−N bond-forming event between allylic carbonate **31** and amine **30** would be facilitated through allylic amination chemistry developed by Hartwig and co-workers.[34] While we are unaware of an example using α-branched secondary amines for this transformation (e.g., **30**), Helmchen and co-workers demonstrated some promising examples of utilizing this amination chemistry for the

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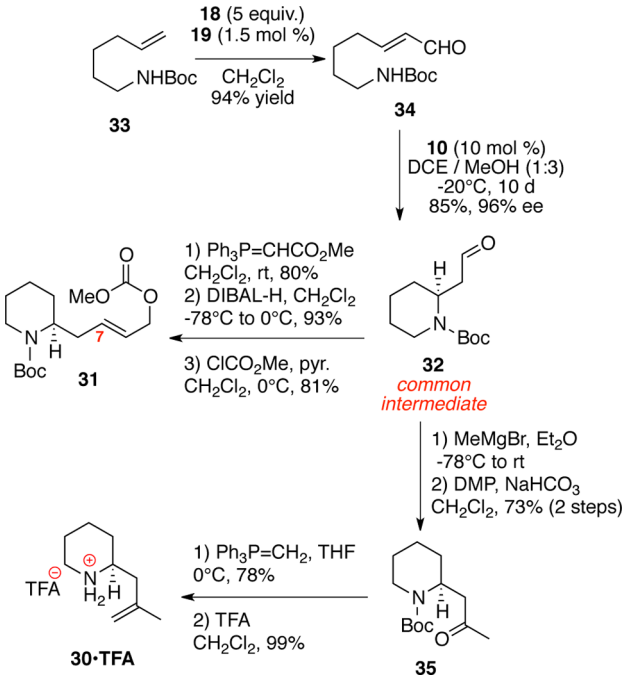
synthesis of a series of piperidine-containing natural products.[35] Both of the proposed coupling partners for this reaction could be derived from a common intermediate **32**. This aldehyde **32** is readily accessible from our intramolecular, heteroatom Michael addition chemistry.[8b]

Synthesis of both of the key subunits from the common intermediate **32** is shown in Scheme 6. Starting from the known

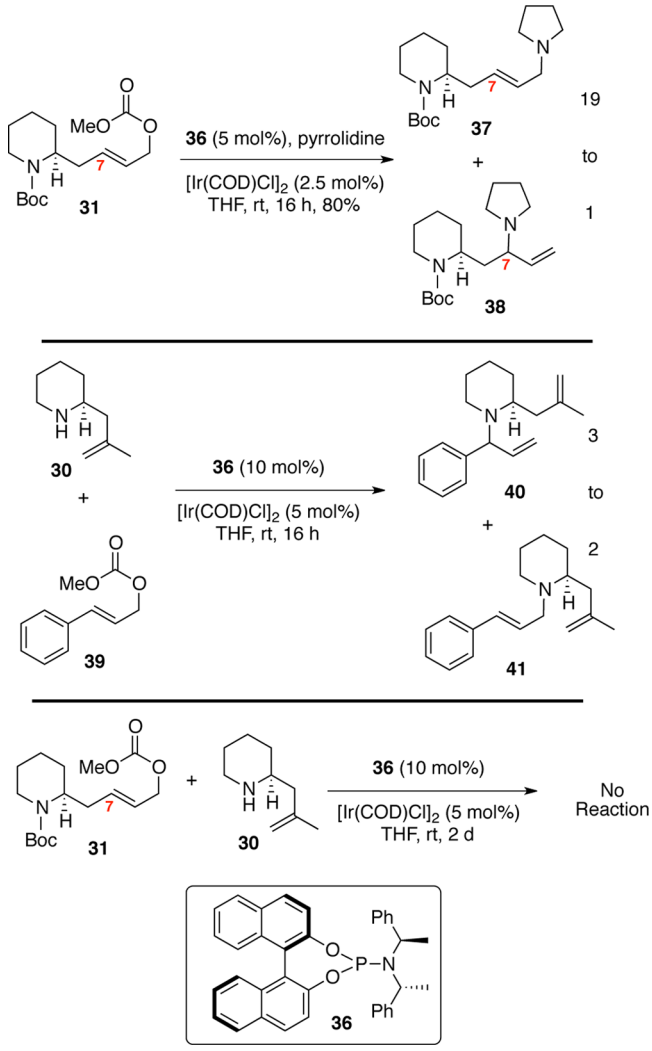
Scheme 6. Synthesis of Major Subunits through a Common Intermediate



Boc-protected amine **33**[15h,21] (accessible in one step from commercially available hex-5-en-1-amine or two steps from 1-bromo-5-hexene), cross metathesis with crotonaldehyde (**18**) provided the Michael addition precursor **34**. Using a modified version of our originally developed conditions,[8b] organocatalyzed, intramolecular heteroatom Michael addition produced the desired common intermediate **32** in excellent yield and enantioselectivity. Conversion of **32** into the allylic carbonate **31** was accomplished through Wittig olefination followed by reduction and carbonate formation. Similarly, addition of MeMgBr to aldehyde **32** followed by DMP oxidation yielded ketone **35**. Wittig olefination and Boc deprotection using TFA gave the target secondary amine as its TFA salt (**30·TFA**).

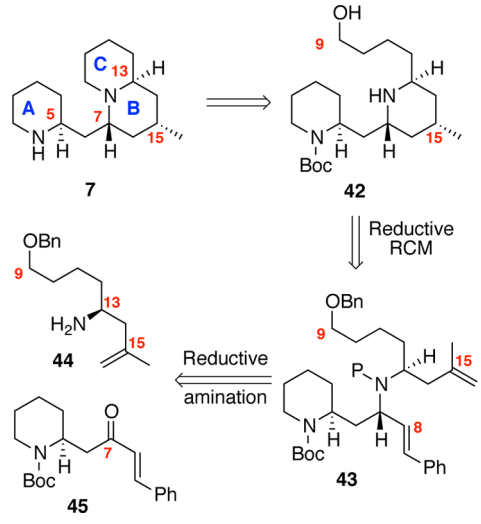
With the two subunits in hand, we turned our attention to the critical C−N bond-forming event (Scheme 7). Given the challenging steric nature of the transformation, we first tested the individual subunits with less demanding coupling partners. While C−N bond formation could be accomplished in both cases, the regioselectivity was disappointing. With the allyl carbonate **31** and pyrrolidine, the undesired linear coupling product **37** was observed in high yield (19:1 rr). The secondary amine **30** proved slightly more compatible with the coupling process, providing a branched to linear product ratio of 3:2 by ^{1}H NMR. Undeterred, we screened the desired combination of **31** and **30**; however, no C−N coupled material was observed. On the basis of these results, it became clear that a revised approach toward cermizine D was necessary.

Scheme 7. Attempted Hartwig Coupling of Major Subunits



Our revised approach is shown in Scheme 8. We envisioned a reductive amination strategy to couple the two subunits and our previous reductive RCM approach to form the central B ring. The A ring enone **45** could be derived from previously

Scheme 8. Revised Retrosynthetic Approach



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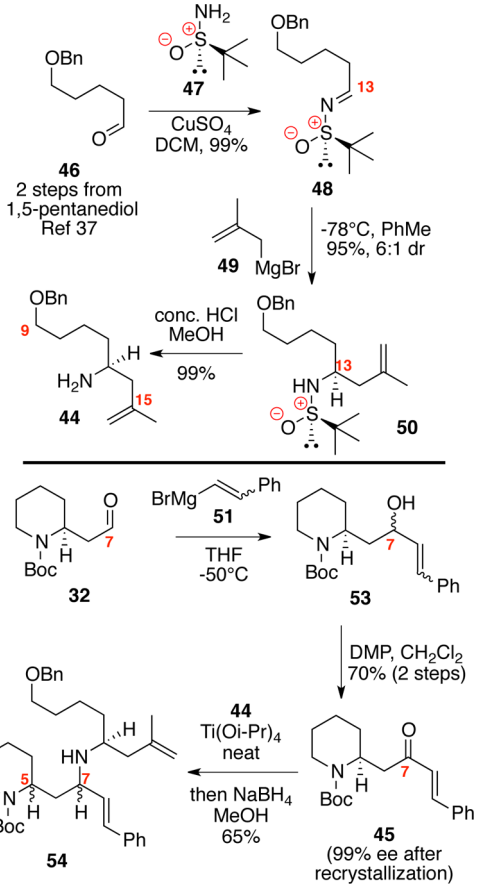
prepared piperidine intermediate **32**. The amine **44** could be accessed through Ellman *tert*-butyl sulfinamide chemistry.[36]

Both the primary amine **44** and the enone **45** could be readily accessed from known intermediates (Scheme 9). The

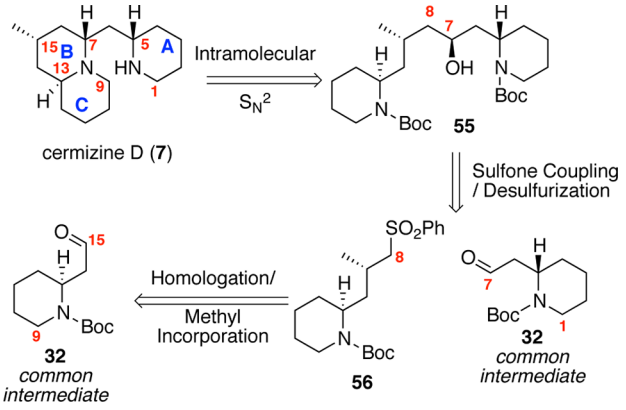
Scheme 9. Synthesis of Primary Amine and Enone Subunits



requisite primary amine **44** was available in three steps from the known aldehyde **46**[37] via imine formation with (*R*)-*tert*-butyl sulfinamide (**47**) followed by addition of methallyl Grignard and treatment with concentrated HCl. The diastereoselectivity in the key C−C bond-forming event was 6:1 based on ^{1}H NMR analysis. The enone **45** was available via Grignard addition to the aldehyde **32** followed by DMP oxidation. Enone **45** provided us with an alternative method to gauge enantioselectivity after nucleophilic addition to the aldehyde **32**. The resultant enantioselectivity was established by chiral HPLC analysis to be 90% ee; however, this enantioselectivity could be increased through a single recrystallization to 99%. Imine formation between enone **45** and amine **44** appeared to be feasible under forcing [Ti(O*i*-Pr)$_4$, neat, overnight] conditions; however, reductive amination of the intermediate imine proved unselective. More troubling was the observation that the C$_5$ stereocenter appeared to have epimerized under the reaction conditions. One possible manifold for this epimerization at C$_5$ could be through *β*-elimination of the intermediate imine followed by reclosure.

Given the roadblocks encountered in both of our approaches involving C−N bond-forming strategies to couple the two subunits of cermizine D, we sought an alternate approach that incorporated the carbon backbone first (Scheme 10). In addition, the *β*-elimination phenomenon observed in the

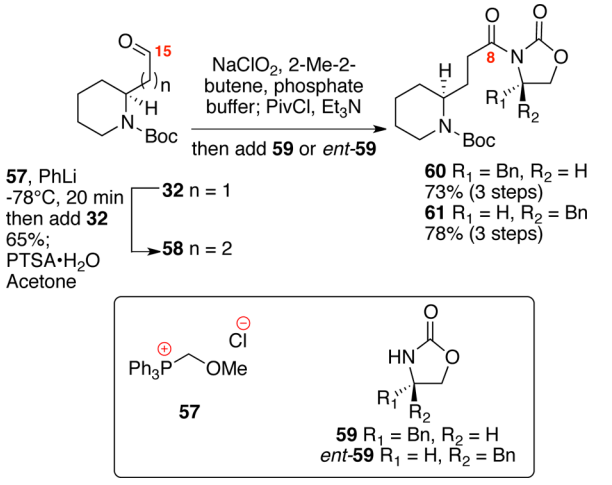
Scheme 10. Successful Retrosynthetic Approach to Cermizine D



reductive amination process would likely need to be circumvented. Finally, we desired to return to the common intermediate approach found in our original strategy toward cermizine D. Based on these requirements, our ultimately successful retrosynthetic approach exploited the key common intermediate **32** to access both the A and C rings of the natural product. The two subunits would be joined through a sulfone-aldehyde coupling/reductive desulfurization sequence. The necessary sulfone **56** would be accessible from the same key aldehyde **32**.

In order to incorporate the C$_{15}$ methyl stereocenter, we envisioned using a diastereoselective Evans alkylation (Scheme 11). This historically reliable method has been routinely

Scheme 11. Synthesis of the Evans Oxazolidinones



employed to circumvent mismatched stereochemical combination in synthesis.[38] Based on the Evans model, we required the (*S*)-benzyl oxazolidinone **60**, which was readily accessed from the aldehyde **32** through homologation followed by Pinnick oxidation and acyl oxazolidinone formation. The analogous (*R*)-oxazolidinone series was also prepared through the same process.

The exploration of the diasteroselectivity in the key alkylation yielded unexpected results (Table 2). In contrast to what is normally seen in Evans alkylations, a pronounced matched/mismatched effect was observed. Treatment of oxazolidinone **60** with LiHMDS led to poor conversion

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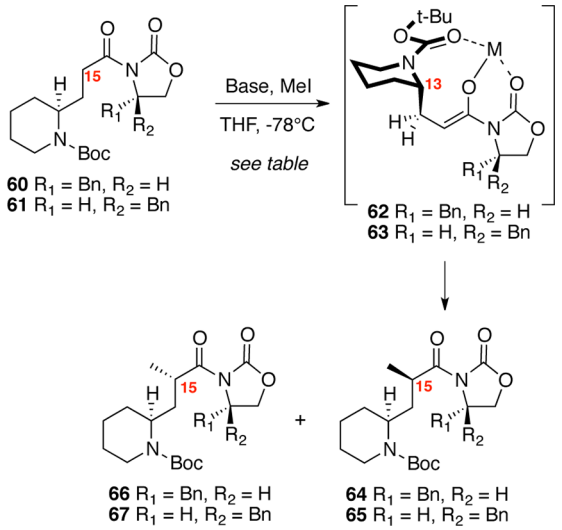
Table 2. Exploration of Evans Alkylation



entry	conditions[a]	yield (%)	dr
1	**60**, LiHMDS (1.1 equiv)	29	1:1 (**66**:**64**)
2	**60**, NaHMDS (1.6 equiv)	92	1.5:1 (**66**:**64**)
3	**60**, KHMDS (2.0 equiv)	87	1:1.4 (**66**:**64**)
4	**61**, NaHMDS (2.0 equiv)	77	1:20 (**67**:**65**)

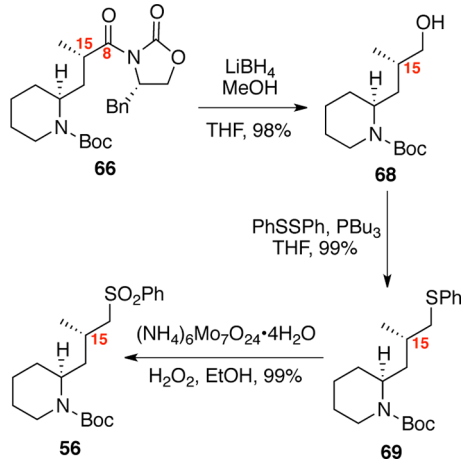
[a]10 equiv of MeI was used in each case.

(entry 1) and essentially no diastereoselectivity. Use of alternate bases (and at slightly higher equivalencies) led to improved levels of reactivity. NaHMDS (entry 2) gave a slight preference for the desired stereochemistry (92% yield, 1.5:1 dr **66**:**64**)]. The major isomer **66** generated crystals suitable for X-ray crystallographic analysis,[39] thereby establishing both the absolute configuration of the newly created stereocenter as well as confirming the stereochemical assignment of the heteroatom Michael reaction. Despite this low selectivity, a 55% isolated yield of the major isomer could be obtained, providing reasonable material throughput. KHMDS (entry 3) gave continued high chemical yields but now with a slight preference for the undesired stereoisomer [87% yield, 1:1.4 dr (**66**:**64**)]. Use of the alternate (*R*)-oxazolidinone **61** led to a highly diastereoselective process, favoring the undesired stereoisomer **65** [77% yield, 20:1 dr (**65**:**67**), entry 4]. Confirmation of the stereochemistry was obtained by reduction of the acyl oxazolidinone and comparison with the products derived from the (*S*)-oxazolidinone series. One possible explanation for this pronounced difference in diastereoselectivity could be a chelation between the enolate derived from oxazolidinone and the Boc moiety (e.g., intermediates **62** and **63**). While this would create a typically unfavorable nine-membered cyclic structure, the presence of multiple sp^2-hybridized atoms would reduce the number of disruptive transannular interactions. Please note that the Boc-protected nitrogen likely forces the C_{13} substituent to adopt an axial conformation.[40]

With the C_{15} alkylated material in hand, we constructed the needed sulfone **56** in three steps (Scheme 12). Borohydride reduction of the C_8 carbonyl provided the alcohol **68**. Conversion to the sulfide was accomplished using diphenyl disulfide and PBu_3 in excellent yield. Subsequent oxidation using ammonium molybdate gave the target sulfone **56** in high yield.

Given the poor diastereoselectivity in the key C_{15} alkylation, we explored alternate approaches to its construction (Scheme 13). Using aldehyde **58**, Eschenmoser methylenation provided the enal **70**, which was reduced to the corresponding alcohol **71**. While compelling precedent existed for diastereoselective hydrogenation of 1,1-disubstituted alkenes similar to **71**,[41] attempted reduction using 10 mol % (*S*)-Ru(OAc)$_2$(T-BINAP) (**74**) gave low yield (40%) and no diastereoselectivity. We also explored a reductive protonation strategy through the *α,β*-unsaturated oxazolidinone **73**. This strategy proved similarly unsuccessful, as L-Selectride reduction showed a slight preference for the undesired C_{15} stereochemistry after protonation with methanol. It should be noted that this reduction strategy is dependent on controlling the *s-cis*/*s-trans* ratio between the 1,1-disubstituted alkene and the C_8 carbonyl moiety.

Scheme 12. Synthesis of the Sulfone Moiety



While our original alkylation sequence did provide an effective way to access the sulfone **56**, we were intrigued by the possibility of exploiting to our advantage the pronounced mismatched/matched relationship of the diastereoselective alkylation (Scheme 14). One possibility would involve using the matched oxazolidinone **61** with an electrophile such as thiophenylmethyl iodide (PhSCH$_2$I) or phenyl iodomethyl sulfone (PhSO$_2$CH$_2$I). We were only aware of a single example for utilizing one of those electrophiles with an oxazolidinone-based nucleophile. Baker and co-workers reported the alkylation of **75** with PhSCH$_2$I in low yield upon extended reaction times (5 d, −20 °C, 30% yield).[42] Alternatively, we considered the possibility of a diastereoselective thio-Michael addition based on some compelling literature precedent;[43] however, our preliminary examples exploring conjugate reduction and hydrogenations as described previously in Scheme 13 made this approach seem less attractive.

Our second generation approach to the synthesis of sulfone **56** is shown in Scheme 15. We were pleased to find that alkylation of oxazolidinone **61** with the PhSCH$_2$I proceeded smoothly to provide the desired product **82** in 70% yield and 10:1 dr. It was key that the electrophile was prepared immediately prior to use as storage for even 3 h resulted in dramatically reduced yields. We attribute the efficiency of this process to the matched relationship of the oxazolidinone and piperidine stereochemistries as shown in intermediate **63**. Reduction of **82** under standard conditions produced the alcohol **83**. Next, oxidation of the sulfide using ammonium molybdate followed by iodide incorporation yielded **84**. Finally,

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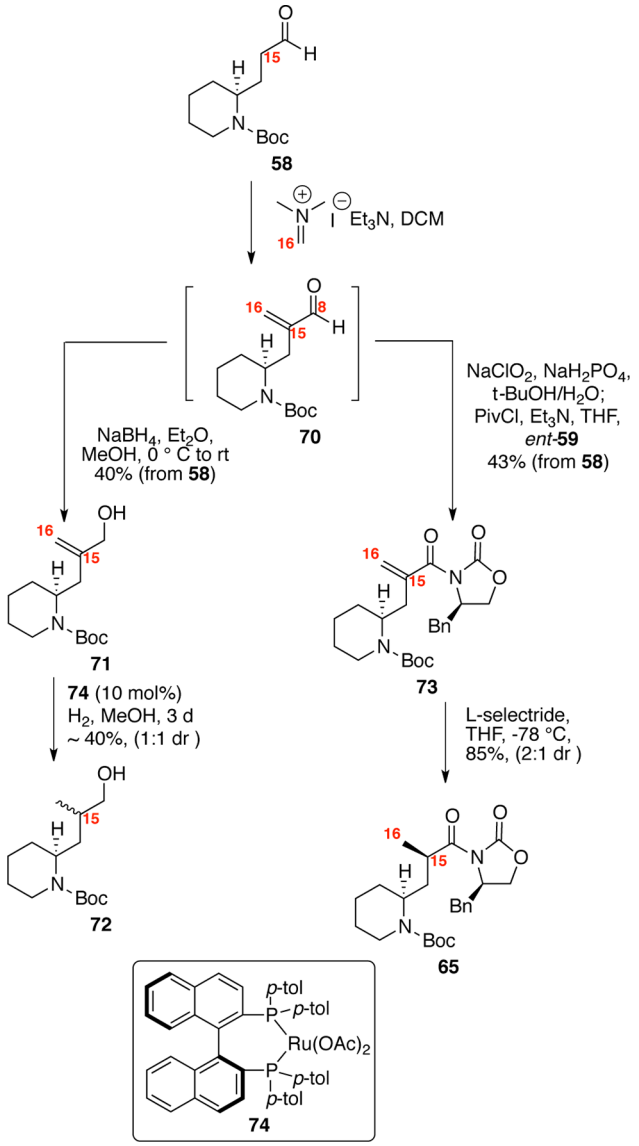
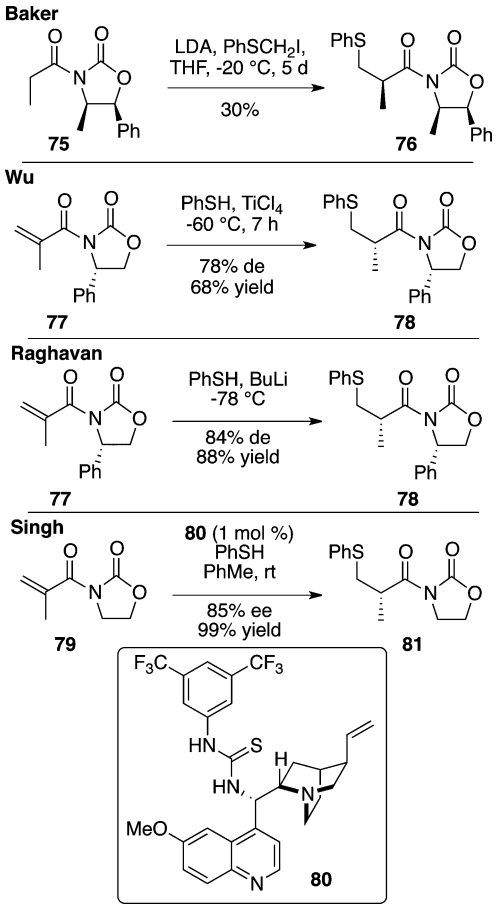
Scheme 13. Attempted Approaches To Improve Stereoselectivity



Scheme 14. Prior Work in Diastereoselective (and Enantioselective) Construction of β-Thio Carbonyl Compounds



dehalogenation using Pd/C and hydrogen gas provided the previously prepared sulfone **56** in 99% yield.

While the second generation route provided noticeable improvements in stereoselectivity and material through-put, the lingering issue of the overall step-count for the process remained. In principle, the conversion of aldehyde **32** into sulfone **56** should be a two-step process: olefination to make the α,β-unsaturated sulfone and diastereoselective conjugate addition of a methyl nucleophile to make the target intermediate **56**. While tempting, serious hurdles remained for implementing such an approach, particularly in the diastereoselective conjugate addition step. We had hoped that substrate control could be exploited to direct the newly formed stereochemistry. While only limited examples of such transformations are known,[44] Isobe's work using 1-TMS, 1-phenylsulfonyl alkenes was compelling.[44b] Regarding reagent-controlled conjugate additions, we were unaware of compelling precedent for conjugate addition of methyl nucleophiles to α,β-unsaturated sulfones. Feringa and co-workers have reported an elegant catalytic process using pyridinyl sulfones and monodentate phosphoramidite ligands; however, they specifically commented in the manuscript that "...with the less reactive dimethyl zinc no conversion was obtained..."[45]

In order to explore a substrate-controlled conjugate addition process, we synthesized the required α,β-unsaturated sulfones and silyl sulfones (Scheme 16). Olefination of aldehyde **32** with the HWE reagent **85** produced the target alkene in modest *E*/*Z* selectivity (4:1, **86**:**87**). No attempt was made to improve this selectivity of this process at this time. In order to study the possible influence of the Boc moiety, we replaced the nitrogen protecting group with a benzyl moiety via TFA deprotection and nitrogen alkylation. The vinyl silyl sulfones **92** and **93** were constructed via Isobe's two-step protocol of Peterson olefination followed by sulfide oxidation in again modest, but unoptimized *E*/*Z* selectivity.

With these Michael acceptors in hand, we first explored the potential of the vinyl silyl sulfones (Table 3). Use of methyl lithium resulted in preferential desilylation followed by olefin isomerization to produce **95** (entry 1). We are unsure of the enantiomeric purity of this product as a viable epimerization mechanism can be envisioned involving a β-elimination process to form a dienyl sulfone intermediate. Using lower order cuprates, we were successful in facilitating the desired conjugate addition (entries 3 and 4); however, these transformations produced primarily the undesired C_{15} epimer after desilylation. Use of the alternate olefin isomer **93** (entry 5) continued to

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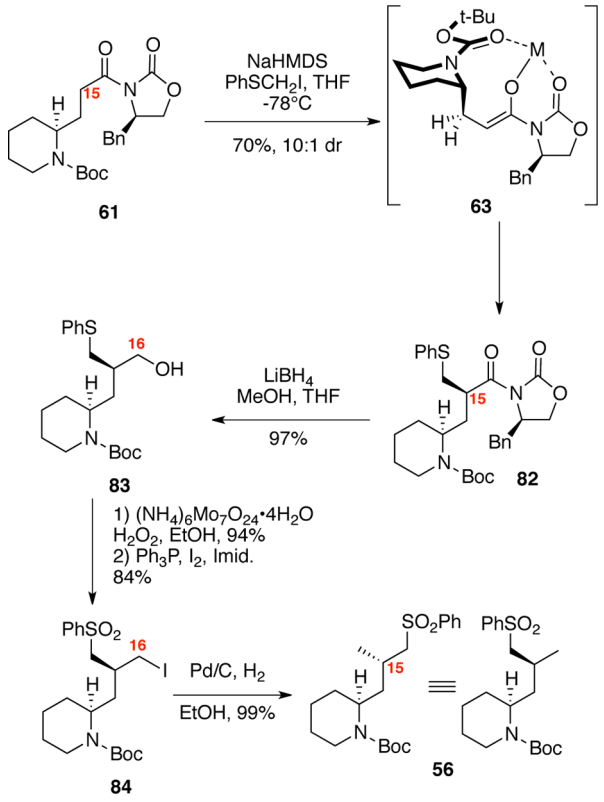
Scheme 15. Second Generation Synthesis of Sulfone Subunit



favor the undesired stereochemistry in the conjugate addition, albiet in reduced selectivity (55% yield, 1.9:1 dr (**94**:**56**).

We also explored the possibility for conjugate addition to the vinyl sulfone **86** with more success (Table 4). Initial attempts with MeLi or high order cuprates resulted in extensive decomposition of the starting material (entries 1 and 2). We attribute this decomposition pathway to a competitive deprotonation process of γ-hydrogens of the vinyl sulfone via a similar pathway to the product **95** seen in the previous table. Fortunately, use of lower order cuprate nucleophiles under carefully controlled conditions did produce the desired conjugate addition product, albeit in modest yield and no diastereoselectivity (entry 3). Despite these shortcomings, this conjugate addition process provides an exceedingly short approach to sulfone **56** – just six steps from commercially available reagents. Attempts to improve the stereoselectivity and chemical yield of this process through use of alternate electrophile **87** resulted in decomposition (entry 4). In addition, use of the benzyl protected series **88** proved similarly ineffective. It is clear from these experiments that a delicate balance exists in controlling the reactivity of these α,β-unsaturated sulfones.

With multiple viable routes to the key intermediate **56**, we embarked on our key coupling strategy (Scheme 17). Treatment of sulfone **56** with LDA followed by the addition of aldehyde **32** produced both the expected product **96**/**97** and the unexpected cyclic product **98** as a single diastereomer with undetermined stereochemistry at C_8. Fortunately, the undesired product **98** could be completely suppressed by reducing the reaction time for deprotonation from 15 to 1 min, resulting in a 93% yield of the desired C_7-C_8 coupled material as a stereochemical mixture. This mixture could be interconverted through an oxidation/reduction process. Interestingly, formation of the unexpected product **98** could be optimized to 87% yield through variation in the reaction time and temperature. Subsequent desulfurization produced the known lactam intermediate **12**.[14] This lactam **12** constitutes a formal synthesis of both senepodine G (**3**) and cermizine C (**2**) based on work by Snider and co-workers.[14]

The total synthesis of cermizine D is shown in Scheme 18. Using hydroxyl sulfone **97**, Raney Ni desulfurization yielded the free alcohol, which proved unstable to purification. Consequently, direct Boc deprotection of the crude material revealed the intermediate **99** as its bis HCl salt. While desulfurizations of keto sulfones are well-precedented, proportionally less work has focused on the desulfurization of hydroxy sulfones,[46] likely due to the competitive elimination pathway commonly seen in Julia couplings.[47] Treatment of the salt **99** with triphenyl phosphine and carbon tetrabromide in the presence of triethyl amine generated the natural product **7** in 60% yield over three steps. We were pleased to find that upon comparison of our $^1H/^{13}C$ NMR and optical rotation data for **7**•**TFA** that it was in good agreement with the data reported by Takayama and co-workers.[14c,17] While not directly stated in the original isolation paper, the spectroscopic data reported by Hirasawa and co-workers were collected on the TFA salt of cermizine D.[18]

Scheme 16. Second-Generation Synthesis of Sulfone Subunit

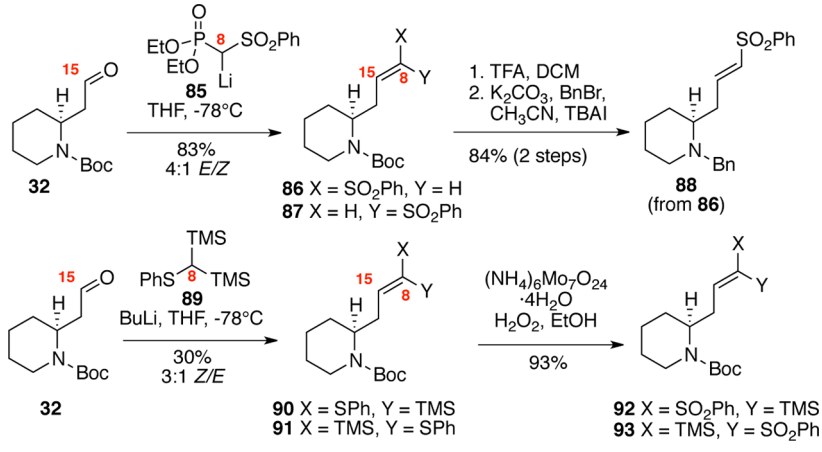


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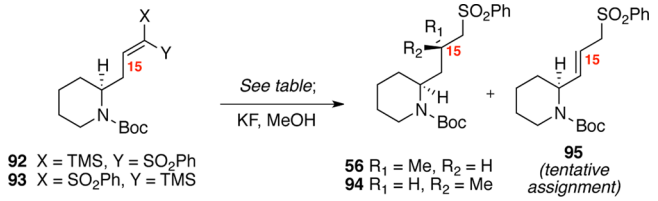
Table 3. Exploration of Conjugate Addition to Vinyl Silyl Sulfones



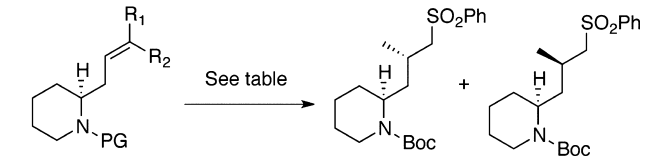
92 X = TMS, Y = SO_2Ph
93 X = SO_2Ph, Y = TMS

56 R_1 = Me, R_2 = H
94 R_1 = H, R_2 = Me

95 *(tentative assignment)*

entry	electrophile	conditions	result (yield, dr)
1	**92**	MeLi (1.5 equiv), Et_2O, −78 to −50 °C	**95** (85%)
2	**92**	CuI (3 equiv), MeLi (5.9 equiv), Et_2O, −78 °C to rt	decomp
3	**92**	CuI (10 equiv), MeLi (19.6 equiv), Et_2O, −78 to 0 °C	**94** (60%, 10:1 dr)
4	**92**	CuI (6 equiv), MeLi (11.8 equiv), Et_2O, 0 °C	**94** (93%, 8:1 dr)
5	**93**	CuI (10 equiv), MeLi (19.7 equiv), Et_2O, −78 °C to rt	**94** (55%, 1.9:1 dr)

Table 4. Exploration of Conjugate Addition to Vinyl Sulfones

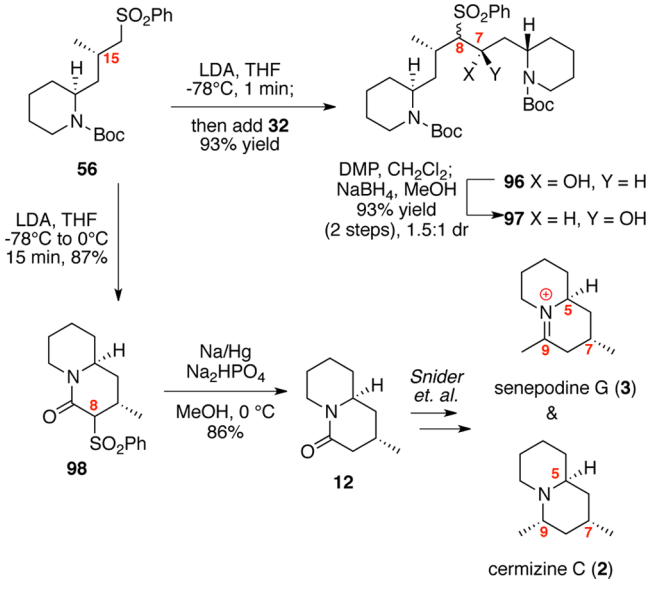


86 PG = Boc
R_1 = SO_2Ph, R_2 = H
87 PG = Boc
R_1 = H, R_2 = SO_2Ph

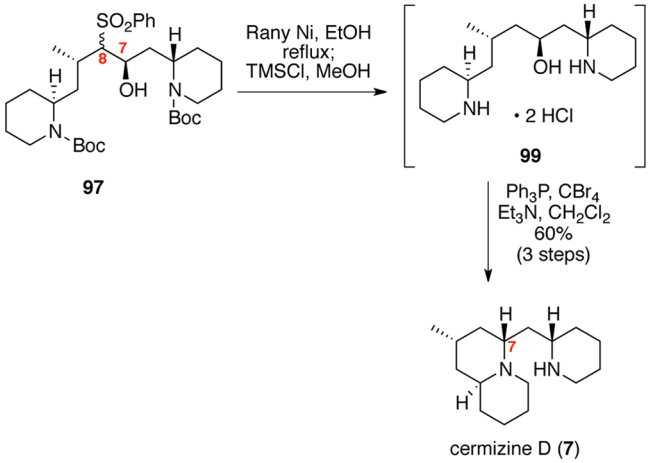
56 **94**

entry	sulfone	conditions	result (yield, dr)
1	**86**	MeLi (1.5 equiv), Et_2O, −78 °C	decomp
2	**86**	CuCN (3 equiv), MeLi (5.9 equiv), Et_2O, −78 °C to rt	decomp
3	**86**	CuI (3 equiv), MeLi (5.9 equiv), Et_2O, −78 °C	**56**:**94** (55%, 1:1.2 dr)
4	**87**	CuI (3 equiv), MeLi (5.9 equiv), Et_2O, −78 °C	decomp

Scheme 17. Coupling of Major Subunits and Formal Synthesis of Senepodine G and Cermizine C



Scheme 18. Total Synthesis of Cermizine D



CONCLUSION

In summary, a novel diastereoselecetive, intramolecular amide Michael addition process has been developed and applied to the formal synthesis of C_5-*epi*-senepodine G and C_5-*epi*-cermizine C. In addition, the total synthesis of cermizine D has been accomplished using a common intermediate **32**, which was accessed via an organocatalyzed, heteroatom Michael addition. This common intermediate **32** is exploited to construct two of the three piperidine rings found in cermizine D as well as the vast majority of the carbon framework. Additional key steps of this sequence include a matched, diastereoselective alkylation with an iodomethylphenyl sulfide and sulfone-aldehyde coupling/reductive desulfurization sequence to combine the major subunits. The longest linear sequence of the synthesis (just nine steps using the cuprate addition strategy in Table 4 or 16 steps via the sulfide alkylation strategy described in Scheme 15) compares favorably to prior work in the field. Through the cermizine D work, the possible

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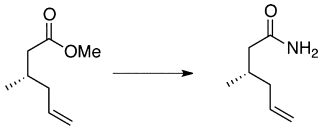
utility of Hartwig-style C−N couplings have been explored on functionally dense coupling partners, providing important limitations to the methodology. Finally, the serendipitous discovery of an intramolecular cyclization process[48] with sulfone **56** provided a rapid route to the formal synthesis of senepodine G and cermizine C. Subsequent application to additional *lycopodium* alkaloids will be reported in due course.

EXPERIMENTAL SECTION

General. Infrared spectra were recorded neat unless otherwise indicated and are reported in cm^{-1}. ^1H NMR spectra were recorded in deuterated solvents and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. ^{13}C NMR spectra were recorded in deuterated solvents and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. HRMS data was collected using a TOF mass spectrometer.

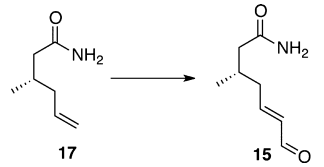
Routine monitoring of reactions was performed using EM Science DC-Alufolien silica gel, aluminum-backed TLC plates. Flash chromatography was performed with the indicated eluents on EM Science Gedurian 230−400 mesh silica gel.

Air- and/or moisture-sensitive reactions were performed under usual inert atmosphere conditions. Reactions requiring anhydrous conditions were performed under a blanket of argon, in glassware dried in an oven at 120 °C or by flame and then cooled under argon. Dry THF and DCM were obtained via a solvent purification system. All other solvents and commercially available reagents were either purified via literature procedures or used without further purification.



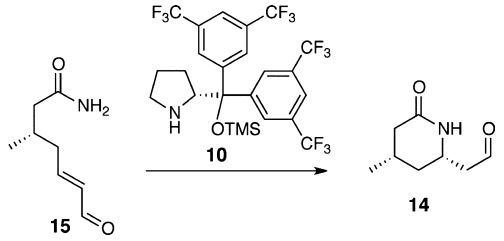
16 17

Amide 17. To a solution of **16** (0.140 g, 0.986 mmol) in CH_2Cl_2 (5 mL) at rt was added dimethylaluminumamide (0.733 mL, 1.13 mmol, 1.5 M in CH_2Cl_2), and the reaction was warmed to 33 °C. After stirring for 16 h, dimethylaluminumamide (0.30 mL, 0.45 mmol, 1.5 M in CH_2Cl_2) was added. After stirring for 24 h, the reaction was cooled to rt, quenched with MeOH (0.5 mL), and allowed to stir for 10 min, and satd aq Rochel's salt (5 mL) was added and stirred 10 min to form two clear layers. The reaction was extracted with CH_2Cl_2 (3 × 15 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10−50% EtOAc/hexanes, to give **17** (0.105 g, 0.83 mmol, 85%) as a white solid. Mp 93.2−91.7 °C; $[\alpha]^{23}_D$ = +5.98° (*c* 1.07, $CHCl_3$); IR (neat) 3352, 3183, 2954, 2911, 1664, 1631, 1413, 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.83−5.48 (m, 3H), 5.05 (d, *J* = 12.4 Hz, 2H), 2.28 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.13−1.97 (m, 4H), 1.00 (d, *J* = 6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 136.5, 116.6, 42.8, 41.0, 30.4, 19.5; HRMS (EI+) calcd for $C_7H_{13}NO$ (M+) 127.0997, found 127.0993.



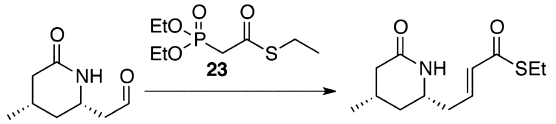
17 15

Enal 15. To a solution of **17** (178 mg, 1.41 mmol) in CH_2Cl_2 (13 mL) at rt were added sequentially crotonaldehyde (0.59 mL, 495 mg, 7.06 mmol) and second generation Hoveyda−Grubbs catalyst (6.7 mg, 0.010 mmol). After 1 h, another portion of the second generation Hoveyda−Grubbs catalyst (2.2, 0.003 mmol) was added. After stirring for 2 h, the reaction was concentrated *in vacuo*, loaded directly onto silica gel, and purified by chromatography, eluting with 10−100% EtOAc/hexanes and 5−10% MeOH/CH_2Cl_2, to give **15** (184 mg, 1.19 mmol, 84%) as a brown oil and recovered alkene **17** (29 mg, 0.22 mmol): $[\alpha]^{23}_D$ = −7.93° (*c* 1.35, $CHCl_3$); IR (neat) 3350, 3198, 2960, 1684, 1405, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.48 (d, *J* = 7.8 Hz, 1H), 6.87−6.77 (m, 1H), 6.14−6.07 (m, 2H), 5.88 (brs, 1H), 2.44−2.39 (m, 1H), 2.30−2.17 (m, 3H), 2.12−2.06 (m, 1H) 1.00 (d, *J* = 6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 173.9, 156.2, 134.6, 42.5, 39.6, 29.9, 19.8; HRMS (EI+) calcd for $C_8H_{13}NO_2$ (M+) 155.0946, found 155.0944.



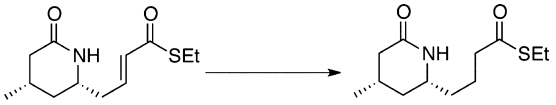
15 14

Aldehyde 14. To a solution of **15** (0.0574 g, 0.401 mmol) in MeOH (2 mL) was added **10** (0.0479 g, 0.080 mmol) in DCE (1.9 mL). After 4 d, the reaction was concentrated *in vacuo* and loaded directly silica gel, purified by chromatography eluting in 100% EtOAc to give a crude mixture of three compounds that were concentrated *in vacuo*. The crude mixture was dissolved in CH_2Cl_2 (2 mL) and stirred with 10% aq HCl (3 mL). After 2 h, the reaction was extracted with CH_2Cl_2 (10 mL × 2). The dried ($MgSO_4$) extract was concentrated *in vacuo* to give **14** (10:1 dr) (0.031 mg, 0.200 mmol, 50%) as a greenish oil: $[\alpha]^{23}_D$ = +10.43° (*c* 1.63, $CHCl_3$); IR (neat) 3213, 2955, 1722, 1660, 1457, 1408, 1338, 1280, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.80 (s, 1H), 6.14 (brs, 1H), 3.97−3.90 (m, 1H), 2.82−2.75 (dd, *J* = 18.6, 3.9 Hz, 1H), 2.65−2.56 (dd, *J* = 18.6, 8.7 Hz, 1H), 2.49−2.44 (dd, *J* = 13.2, 2.4 Hz, 1H), 2.01−1.86 (m, 4H), 1.06 (d, *J* = 12.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 172.4, 50.5, 47.5, 39.6, 37.1, 27.4, 21.3; HRMS (EI+) calcd for $C_8H_{13}NO_2$ (M+) 155.0946, found 155.0921.



14 SI-1

Thioester SI-1. To a solution of **14** (0.280 g, 1.16 mmol) in CH_3CN (5.8 mL) were added sequentially LiCl (0.059 g, 1.39 mmol) and DIPEA (0.150 g, 1.16 mmol). After 10 min, the solution was cooled to 0 °C. After 5 min, a precooled (0 °C) solution of **23** (0.18 g, 1.16 mmol) in CH_3CN (6 mL) was cannulated into the reaction (2 × 0.5 mL MeCN rinse). The reaction was allowed to warm to rt over 10 min. After 30 min, the reaction was quenched with aq HCl (2 mL 1.22 M) and extracted with EtOAc (3 × 20 mL). The dried extract ($MgSO_4$) was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 95% EtOAc/hexanes to give **SI-1** (0.160 g, 0.66 mmol, 57%) as a white solid. Mp 76.5−75.0 °C; $[\alpha]^{23}_D$ = −34.3° (*c* 0.525, $CHCl_3$); IR (neat) 2954, 2927, 2862, 1662 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.76 (m, 1H), 6.20 (d, *J* = 18.8 Hz, 1H), 5.97 (bs, 1H), 3.56 (m, 1H), 2.97 (m, 2H), 2.50−2.25 (m, 3H), 2.00−1.80 (m, 3H) 1.30 (t, 3H), 1.05 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.4, 172.9, 138.8, 131.7, 51.6, 39.5, 39.0, 36.8, 27.4, 23.1, 21.4, 14.7; HRMS (EI+) calcd for $C_{12}H_{20}O_2SN$ (M+) 242.1215, found 242.1214.



SI-1 24

Thioester 24. To a solution of **SI-1** (0.615 g, 2.54 mmol) in EtOAc (60 mL) at rt under an inert argon atmosphere was added Pd/C (10 wt %, 0.490 g), and the reaction flask was purged with a balloon of H_2 gas and allowed to stir under a balloon of H_2 gas. After 2 d, the H_2 atmosphere was purged with argon for 5 min. The reaction was then filtered through Celite (EtOAc 200 mL wash), concentrated *in vacuo*, and purified by chromatography over silica gel, eluting with 10% MeOH/EtOAc, to give **24** (0.615 g, 2.54 mmol, 99%) as a white wax: $[\alpha]^{23}_D$ = −2.46° (*c* 0.65, $CHCl_3$); IR (neat) 3215, 2954, 2927, 1684,

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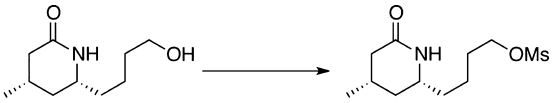
1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.7 (bs, 1H), 3.39 (m, 1H), 2.88 (m, 2H), 2.57 (m, 2H), 2.43 (bd, 1H), 1.50 (m, 2H), 1.27 (t, 3H) 1.05 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0, 172.4, 52.6, 43.5, 39.7, 37.1, 36.1, 27.6, 23.3, 21.5, 21.0, 14.8; HRMS (EI+) calcd for $C_{12}H_{21}NO_2S$ (M+) 243.1293, found 243.1290.

24 SI-2

Alcohol SI-2. To a solution of **24** (0.082 g, 0.34 mmol) in MeOH/THF 1:1 (4 mL) at rt was added $NaBH_4$ (0.100 g, 2.63 mmol) in small portions to maintain continuous hydrogen evolution. After 1 h, the reaction was quenched with satd aq $NaHCO_3$ (6 mL) and extracted with EtOAc (3 × 10 mL). The dried extract ($MgSO_4$) was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 20% MeoH/EtOAc to give **SI-2** (0.061 g, 0.328 mmol, 98%) as a white wax: $[\alpha]^{23}_D$ = −21.6° (*c* 0.37, $CHCl_3$); IR (neat) 3286, 2933, 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.8 (bs, 1H), 3.67 (m, 2H), 3.39 (m, 1H), 2.44 (bd, 2H), 1.95−1.84 (m, 4H), 1.66−1.55 (m, 7H), 1.28 (m, 2H), 1.06 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 61.9, 52.9, 39.5, 37.5, 36.2, 32.2, 27.6, 21.5, 21.2; HRMS (EI+) calcd for $C_{10}H_{19}NO_2$ (M+) 185.14158, found 185.14196.

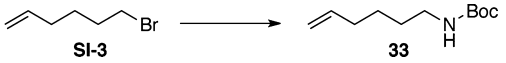


SI-2 25

Mesylate 25. To a solution of **SI-2** (0.120 g, 0.648 mmol) in THF (30 mL) at 0 °C were added sequentially Et_3N (0.131 g, 1.296 mmol) and MsCl (0.118 g, 1.038 mmol). After 15 min, the ice bath was removed, and the reaction was allowed to warm to rt. After 45 min, the reaction was quenched with H_2O (15 mL) and extracted with EtOAc (3 × 15 mL). The dried extract ($MgSO_4$) was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10% MeOH/EtOAc, to give **25** (0.150 g, 0.570 mmol, 88%) as a white solid. Mp 91.5−90.0 °C; $[\alpha]^{23}_D$ = −33.41° (*c* 0.82, $CHCl_3$); IR (neat) 3177, 2943, 2916, 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.45 (bs, 1H), 4.24 (t, 2H), 3.39 (m, 1H), 3.02 (s, 3H), 3.57−3.54 (m, 1H), 2.41 (m, 2H), 1.92−1.84 (m, 3H), 1.83−1.73 (m, 2H), 1.60−1.49 (m, 4H), 1.02 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 69.5, 52.7, 39.7, 37.4, 37.1, 36.3, 29.0, 27.6, 21.5, 21.1; HRMS (EI+) calcd for $C_{11}H_{21}NO_4S$ (M+) 263.1191, found 263.1197.

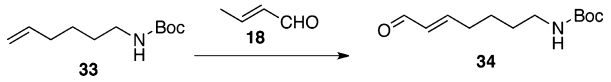
25 26

Lactam 26. To a solution of **25** (11 mg, 0.042 mmol) in THF (2 mL) at 0 °C was added NaHMDS (0.045 mmol, 4.5 μL, 1 M in THF). After 5 min, the ice bath was removed, and the reaction was allowed to warm to rt. After 55 min, the reaction was quenched with H_2O (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The dried extract ($MgSO_4$) was concentrated *in vacuo* to give **26** (6 mg, 0.038 mmol, 90%) as a clear oil. $[\alpha]^{23}_D$ = −29.7° (*c* 0.93, $CHCl_3$); IR (neat) 2928, 2854, 1647 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.78 (bd, 1H), 3.19 (m, 1H), 2.49−2.40 (m, 2H), 1.99−1.69 (m, 6H), 1.44−1.36 (m, 2H), 1.39−1.36 (m, 2H), 0.98 (d, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 56.7, 41.8, 41.2, 39.7, 34.6, 26.5, 25.4, 24.3, 21.3. The spectral data match those previously reported for **26**.[14a]



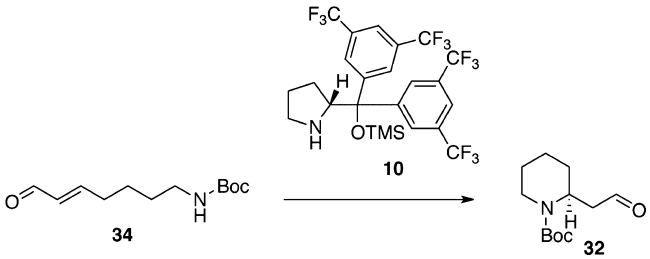
SI-3 33

Boc-Protected Amine 33. To a solution 6-bromo-1-hexene (**SI-3**) (2.08 g, 12.70 mmol) in DMF/H_2O (9:1, 50 mL) was added NaN_3 (2.07 g, 31.83 mmol). After 12 h, brine was added, and the azide was extracted with ether (3 × 40 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* at 0 °C to give crude azide. The crude azide was then redissolved in THF/H_2O (5:1, 50 mL) and PPh_3 (4.00 g, 15.2 mmol) was added. After 15 h, Et_3N (5.14 g, 7.05 mL, 50.83 mmol) and Boc-anhydride (8.33 g, 8.77 mL, 38.13 mmol) were added. After 12 h, THF was removed *in vacuo*, and brine (100 mL) was added and extracted with ether (3 × 100 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 1−20% EtOAc/hexanes to give **33**[21a] (2.43 g, 12.23 mmol, 96% over 3 steps) as a colorless oil. IR (neat) 3364, 3075, 2975, 2931, 1700, 1642, 1365, 1172 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 13.3, 10.1, 6.6 Hz, 1H), 5.02 (dq, *J* = 17.2, 1.7 Hz, 2H), 4.52 (br s, 1 H), 3.12−3.15 (m, 2H), 2.07−2.12 (m, 2H), 1.48−1.55 (m, 3H), 1.47 (s, 9H), 1.43−1.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 138.5, 114.6, 79.0, 40.4, 33.3, 29.5, 28.4, 26.0; HRMS (EI+) calcd for $C_{11}H_{22}NO_2$ (M + H) 200.1651, found 200.1648.

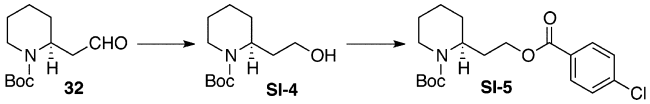


33 34

Enal 34. To a solution of **33** (1.5 g, 7.52 mmol) in dry DCM (85 mL) were added crotonaldehyde **18** (0.266 g, 3.12 mL, 37.5 mmol) and second generation Hoveyda−Grubbs catalyst (71 mg, 0.113 mmol), and the mixture was stirred at room temperature. After 5 h, the solvent was removed *in vacuo*, and the crude was purified by chromatography over silica gel, eluting with 25−40% EtOAc/hexanes to give **34**[21a] (1.59 g, 7.01 mmol, 94%) as a dark colored oil. IR (neat) 3357, 2976, 2934, 2865, 1693, 1521, 1366, 1169 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 9.51 (d, *J* = 7.7 Hz, 1H), 6.85 (dt, *J* = 15.4, 6.3 Hz, 1H), 6.13 (dd, *J* = 15.4, 7.7 Hz, 1H), 4.62 (br s, 1H), 3.15−3.16 (m, 2H), 2.36−2.39 (m, 2H), 1.51−1.57 (m, 4H), 1.45 (s, 9H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 194.1, 158.2, 156.0, 133.2, 79.3, 40.1, 32.3, 29.7, 28.4, 25.0; HRMS (EI+) calcd for $C_{12}H_{22}NO_3$ (M + H) 228.1600, found 228.1608.



Aldehyde 32. To a solution of **34** (970 mg, 4.27 mmol) in MeOH (30.6 mL) was added a solution of the catalyst **10** (254 mg, 0.43 mmol) in DCE (10.2 mL) via syringe, and the mixture was placed in the freezer unstirred (−25 °C). After 10 d, water (50 mL) was added and extracted with DCM (3 × 60 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 0−25% EtOAc/hexanes to give known **32**[21a] (825 mg, 3.63 mmol, 85%) as a colorless oil. $[\alpha]^{20}_D$ = −36.0 (*c* 1.0, $CHCl_3$); IR (neat) 2935, 2864, 2727, 1693, 1521, 1416, 1167, 867 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.60−9.61 (m, 1H), 4.70−4.71 (m, 1H), 3.86 (d, *J* = 12.4 Hz, 1H), 2.58−2.70 (m, 2H), 2.42 (ddd, *J* = 15.2, 6.4, 2.0 Hz, 1H), 1.36−1.60 (m, 5H), 1.32 (s, 9H), 1.25−1.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 154.5, 79.7, 45.8, 44.5, 39.1, 28.8, 28.2, 25.1, 18.8; HRMS (EI+) calcd for $C_{12}H_{21}NO_3$ (M+) 227.1522, found 227.1513.



Benzoate SI-5. To a solution of aldehyde **32** (89.5 mg, 0.394 mmol) in MeOH (3 mL) at 0 °C was added $NaBH_4$ (44.7 mg, 1.183 mmol). After 30 min, the reaction was quenched with aq NH_4Cl (5 mL) solution and extracted with ether (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to give the crude alcohol **32**, which was carried to the next step.

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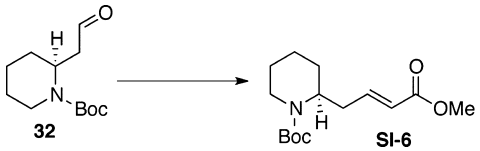
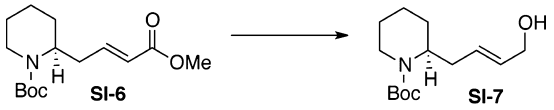
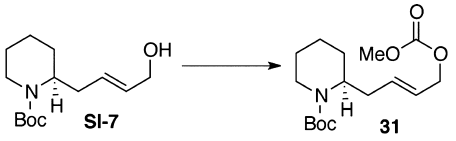
To a solution of crude alcohol **SI-4** (~0.39 mmol) in DCM (1.97 mL) at 0 °C was added DMAP (144.4 mg, 1.18 mmol) followed by *p*-chlorobenzoyl chloride (103.4 mg, 75.5 μL, 0.591 mmol). After 15 min, the reaction mixture was warmed to rt over a period of 30 min. After 12 h, water (5 mL) was added and extracted with ether (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 15−30% EtOAc/hexanes to obtain known **SI-5**[21a] (121.6 mg, 0.33 mmol, 84% over 2 steps) as a colorless oil. The enantiomeric excess was determined with the aid of HPLC analysis Chiralcel IC (25 cm × 0.46 cm column), hexane/isopropanol 90:10, flow = 1.0 mL/min, $t_{R,minor}$ = 11.5 min, $t_{R,major}$ = 10.2 min. $[\alpha]^{20}_D$ = −11.0° (*c* 1.0, $CHCl_3$); IR (neat) 2934, 2861, 1721, 1688, 1595, 1448, 1415, 1365, 1307, 1275, 1169, 1145, 1091, 760 cm^{-1}; ^1H NMR (400 MHz, 40 °C, $CDCl_3$) δ 7.98 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.8 Hz, 2H), 4.47 (br s, 1H), 4.29−4.47 (m, 2H), 4.04 (d, *J* = 13.2 Hz, 1H), 2.82 (t, *J* = 13.2 Hz, 1H), 2.18−2.25 (m, 1H), 1.81−1.90 (m, 1H), 1.55−1.72 (m, 5H), 1.38−1.49 (m, 10H); ^{13}C NMR (100 MHz, 40 °C, $CDCl_3$) δ 165.7, 154.9, 139.3, 131.0, 128.9, 128.6, 79.4, 63.0, 48.0, 38.8, 29.0, 28.8, 28.4, 25.5, 19.0; HRMS (ES+) calcd for $C_{19}H_{27}NO_4Cl$ (M + H) 368.1629, found 368.1618.



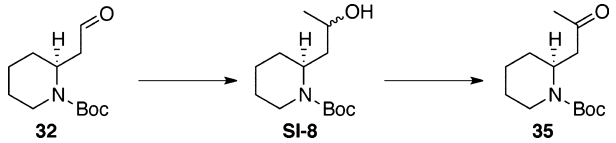
Ester SI-6. To a solution of **32** (450 mg, 1.97 mmol) in CH_2Cl_2 was added $Ph_3P{=}CHCO_2Me$ (522 mg, 2.96 mmol). After 16 h, the resulting solution was concentrated *in vacuo*, suspended in a 3:1 mixture of hexanes/ether (60 mL), filtered over Celite, and then rinsed with a 3:1 mixture of hexanes/ether (30 mL). The resulting solution was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10−30% EtOAc/hexanes to give **SI-6** (445 mg, 1.58 mmol, 80%) as a colorless oil. $[\alpha]^{23}_D$ = −16.5° (*c* 1.0, $CHCl_3$); IR (neat) 2975, 2936, 2858, 1725, 1689, 1412, 1272 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.86 (dt, *J* = 15.6 Hz, *J* = 7.6 Hz, 1H), 5.80 (d, *J* = 15.6, 1H), 4.34 (bs, 1H), 3.96 (d, *J* = 12 Hz, 1H), 3.66 (s, 3H), 2.71 (t, *J* = 12.9 Hz, 1H), 2.52−2.61 (m, 1H), 2.25−2.32 (m, 1H), 1.50−1.70 (m, 5H), 1.30−1.46 (m, 1H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 154.8, 146.0, 122.6, 79.4, 51.3, 49.6, 38.7, 32.9, 28.3, 25.3, 18.8; HRMS (EI+) calcd for $C_{15}H_{26}NO_4$ (M+) 284.1862, found 284.1868.



Alcohol SI-7. To a solution of **SI-6** (356 mg, 1.258 mmol) in CH_2Cl_2 (12 mL) at −78 °C was added DIBAL-H (3.77 mL, 3.77 mmol, 1.0 M in CH_2Cl_2). After 2 h, the mixture was warmed to room temp and quenched with satd aq sodium tartrate (150 mL). After vigorous stirring for 1 h, the mixture was extracted with CH_2Cl_2 (3 × 50 mL) and washed with brine (30 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 20−40% EtOAc/hexanes to give **SI-7** (298 mg, 1.17 mmol, 93%) as a colorless oil. $[\alpha]^{23}_D$ = −33.3° (*c* 2.0, $CHCl_3$); IR (neat) 3446, 2933, 2859, 1685, 1418, 1364, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.54−5.66 (m, 2H), 4.22 (bs, 1H), 3.99−4.02 (m, 2H), 3.91 (d, *J* = 12.4 Hz, 1H), 2.72 (t, *J* = 12.8 Hz, 1H), 2.40 (bs, 1H), 2.33−2.38 (m, 1H), 2.12−2.19 (m, 1H), 1.50−1.70 (m, 5H), 1.40−1.50 (m, 1H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 131.4, 129.0, 79.2, 63.2, 50.2, 38.9, 32.8, 28.4, 27.7, 25.4, 18.8; HRMS (EI+) calcd for $C_{14}H_{26}NO_3$ (M+) 256.1913, found 256.1918.

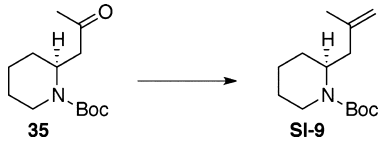


Carbonate 31. To a solution of **SI-7** (158 mg, 0.62 mmol) in CH_2Cl_2 (10.0 mL) at 0 °C were added sequentially pyridine (147 mg, 0.150 mL, 1.86 mmol) and $ClCO_2Me$ (64.4 mg, 0.054 mL, 0.68 mmol). After 1 h, the solution was then diluted with water (15 mL) and sequentially extracted with EtOAc (3 × 20 mL). The combined organic layers were washed sequentially with brine (20 mL) and satd aq NH_4Cl (20 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10−25% EtOAc/hexanes to give **31** (158 mg, 0.502 mmol, 81%) as a colorless oil. $[\alpha]^{23}_D$ = −27.4° (*c* 1.0, $CHCl_3$); IR (neat) 2934, 2857, 1750, 1688, 1266 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.69−5.76 (m, 1H), 5.60−5.68 (m, 1H), 4.56 (d, J = 6 Hz, 2H), 4.28 (bs, 1H), 3.95 (d, J = 12.4 Hz, 1H), 3.78 (s, 3H), 2.75 (t, J = 12.8 Hz, 1H), 2.41−2.49 (m, 1H), 2.20−2.30 (m, 1H), 1.50−1.70 (m, 5H), 1.40−1.50 (m, 1H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 155.0, 133.6, 125.3, 79.2, 68.3, 54.7, 49.9, 38.9, 32.9, 28.4, 27.7, 25.4, 18.8; HRMS (EI+) calcd for $C_{16}H_{28}NO_5$ (M+) 314.1967, found 314.1961.

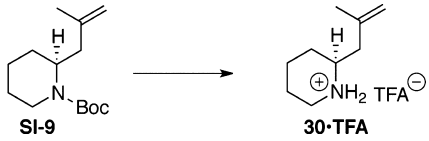


Ketone 35. To a solution of **32** (410 mg, 1.80 mmol) in Et_2O (15 mL) at rt was slowly added a solution of MeMgBr (1.8 mL, 5.4 mmol, 3.0 M in Et_2O). The mixture was allowed to stir at rt for 2 h. The reaction was quenched with satd aqueous NH_4Cl (5 mL). Then the solution was extracted with Et_2O (3 × 30 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give **SI-8**.

To a solution of crude **SI-8** (1.8 mmol) in CH_2Cl_2 (20 mL) was added sodium bicarbonate (756 mg, 9 mmol) followed by Dess Martin's reagent (1.56 g, 3.6 mmol). After 2 h the reaction was quenched with 10% aqueous sodium bicarbonate (10 mL) and extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, concentrated *in vacuo*, and purified by chromatography over silica gel, eluting with 0−25% EtOAc/hexanes to give known **35** (315 mg, 1.3 mmol, 73% over 2 steps) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 4.74 (d, *J* = 4.5 Hz, 1H), 3.98 (d, *J* = 12, 1H), 2.79 (t, *J* = 12.9 Hz, 1H), 2.66 (dd, *J* = 7.8, 1.8 Hz, 2H), 2.20 (s, 3H), 1.50−1.75 (m, 5H), 1.40−1.55 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.1, 154.7, 79.6, 47.3, 44.3, 39.4, 30.1, 29.7, 28.4, 25.3, 18.9.

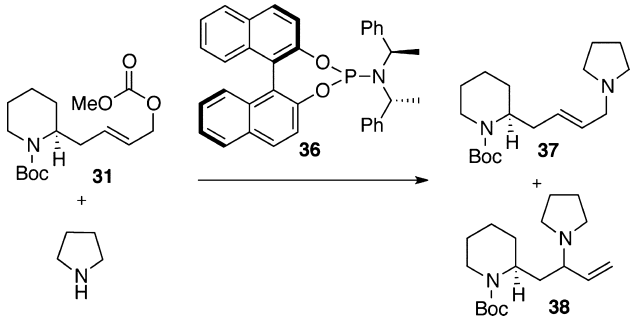


Alkene SI-9. To a solution of **35** (315 mg, 1.3 mmol) in THF (8 mL) was added a premade solution of methyl triphenylphosphonium bromide (932.7 mg, 2.61 mmol) with *n*-BuLi (1.55 mL, 2.48 mmol, 1.6 M in hexanes) in THF (5 mL) at 0 °C. After 2 h, the reaction was quenched with water (5 mL) and extracted with EtOAc (3 × 25 mL), the combined organic layers were dried over $MgSO_4$, concentrated *in vacuo*, and purified by chromatography over silica gel, eluting with 0−25% EtOAc/hexanes to give **SI-9** (242 mg, 1.01 mmol, 78%) as a colorless oil. $[\alpha]^{23}_D$ = −26.1° (*c* 1.0, $CHCl_3$); IR (neat) 3073, 2974, 2934, 2856, 1693, 1647, 1413, 1364, 1266, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.74 (d, *J* = 15.9 Hz, 2H), 4.38 (bs, 1H), 3.98 (d, *J* = 11.1 Hz, 1H), 2.81 (t, *J* = 12.9 Hz, 1H), 2.30−2.37 (m, 1H), 2.18−2.26 (m, 1H), 1.79 (s, 3H), 1.50−1.66 (m, 5H), 1.47 (s, 9H), 1.25−1.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 142.8, 112.6, 79.0, 48.5, 38.8, 38.1, 28.2, 27.3, 25.5, 22.1, 18.8; HRMS (EI+) calcd for $C_{14}H_{26}NO_2$ (M + H) 240.1964, found 240.1960.

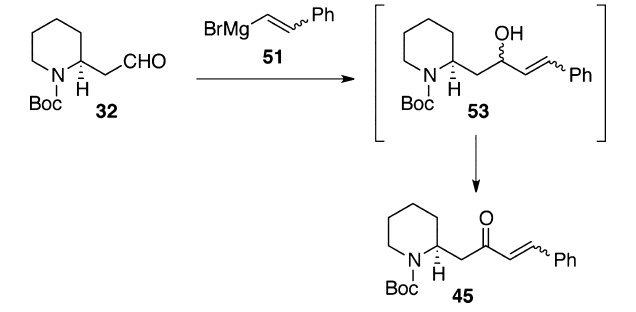


dx.doi.org/10.1021/jo400324t | J. Org. Chem. 2013, 78, 4779−4800

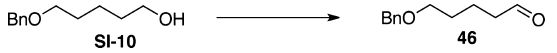
Alkene 30·TFA. To a solution of **SI-9** (120 mg, 0.50 mmol) in CH_2Cl_2 (2.3 mL) was added TFA (2.3 mL). The solution was allowed to stir for 2 h. The solution was concentrated *in vacuo* to give **30·TFA** (127 mg, 0.50 mmol, 99%) as a colorless glassy solid. $[\alpha]^{23}_D = -9.8°$ (*c* 1.0, $CHCl_3$); IR (neat) 2950, 2865, 2545, 1780, 1674, 1437, 1202 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (bs, 1H), 4.84 (d, *J* = 36.8 Hz, 2H), 3.39 (bs, 1H), 3.12 (bs, 1H), 2.90 (bs, 1H), 2.43 (bs, 1H), 2.26 (m, 1H), 1.70−1.90 (m, 3H), 1.60−1.70 (m, 4H), 1.40−1.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 115.5, 55.2, 45.1, 42.0, 28.4, 22.2, 21.7; HRMS (EI+) calcd for $C_{11}H_{18}F_3NO_2$ (M+) 253.1290, found 253.1287.



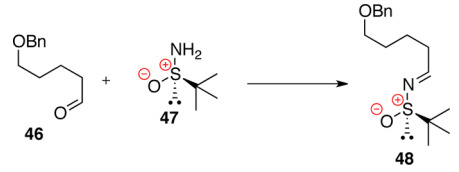
Amines 37/38. To a solution of **31** (25 mg, 0.08 mmol) and pyrrolidine (7.4 mg, 0.10 mmol) in THF (0.5 mL) was added a premade solution of **36** (2.7 mg, 0.004 mmol) and $[Ir(COD)Cl]_2$ (4.3 mg, 0.008 mmol) in THF (0.25 mL) at rt. After 16 h, the solution was concentrated *in vacuo* and purified by chromatography over basic alumina, eluting with 10−30% EtOAc/hexanes to give a 19:1 mixture of **37** (19 mg, 0.062 mmol, 77%) and **38** (1 mg, 0.003 mmol, 4%) as colorless oils. $[\alpha]^{23}_D = -28.5°$, (*c* 0.85, $CHCl_3$); IR (neat) 2930, 2850, 2778, 1694, 1164 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.48−5.68 (m, 2H), 4.25 (bs, 1H), 3.95 (d, *J* = 12.4 Hz, 1H), 3.01 (d, *J* = 6 Hz, 2H), 2.75 (t, *J* = 12.8 Hz, 1H), 2.48 (s, 3H), 2.20−2.45 (m, 2H), 1.77 (s, 4H), 1.50−1.60 (m, 6H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 129.8, 79.0, 58.2, 53.9, 39.0, 33.0, 30.3, 29.7, 28.5, 27.5, 25.5, 23.4, 18.8; HRMS (EI+) calcd for $C_{18}H_{33}N_2O_2$ (M + H) 309.2542, found 309.2543.



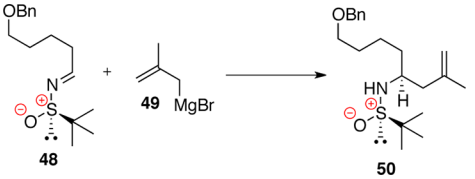
Ketone 45. To a solution of **32** (530 mg, 2.09 mmol) in THF (15 mL) at −78 °C was added a premade solution of **51** (8 mL, 4.0 mmol, 0.2 M in THF) at rt. After 30 min, the temperature was raised to −50 °C and stirred at this temperature for the next 3 h. Then, the reaction was quenched with satd aq NH_4Cl (5 mL), extracted with Et_2O (3 × 30 mL), and washed with brine (15 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to provide crude alcohol **53.** The crude alcohol **53** was then redissolved in DCM (45 mL), and $NaHCO_3$ (877.8 mg, 10.45 mmol) was added followed by Dess Martin's reagent (1.77 g, 4.18 mmol) at rt. After 3 h, the reaction was quenched with satd aq $NaHCO_3$ (15 mL). Then the solution was extracted with Et_2O (3 × 30 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 5−20% EtOAc/hexanes to give **45** (*trans*:*cis* = 1:0.14), (477 mg, 1.46 mmol, 70% over 2 steps) as pale yellow oil. $[\alpha]^{20}_D = +16.5$ (*c* 1.05, $CHCl_3$); IR (neat) 2974, 2934, 2862, 1689, 1609, 1164 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54−7.63 (m, 3.5 H, mixed isomers), 7.34−7.41 (m, 3.7 H, mixed isomers), 6.86 (d, *J* = 12.8 Hz, 0.2 H, cis isomer), 6.79 (d, *J* = 16 Hz, 1H, major isomer), 6.24 (d, *J* = 12.8 Hz, 0.2 H, minor isomer), 4.81 (bs, 1.2 H, mixed isomers), 4.05 (bs, 1.20 H, mixed isomers), 2.68−2.92 (m, 3.7 H, mixed isomers), 1.44−1.68 (m, 8.8 H, mixed isomers), 1.44 (s, 10.8 H, mixed isomers); ^{13}C NMR (400 MHz, $CDCl_3$) δ 200.9, 198.4, 154.8, 154.7, 143.0, 140.3, 135.2, 134.5, 133.1, 130.5, 129.6, 129.3, 128.9, 128.6, 128.4, 128.3, 126.1, 79.6, 47.9, 44.2, 41.7, 39.4, 28.4, 28.2, 25.3, 18.9; HRMS (CI+) calcd for $C_{20}H_{27}NO_3$ (M+) 329.1991, found 329.1978.



Aldehyde 46. To a solution of oxalyl chloride (980.7 mg, 7.726 mmol, 0.663 mL) in DCM (15 mL) at −78 °C was added a solution of DMSO (644 mg, 8.24 mmol, 0.585 mL) in DCM (4 mL). After 10 min, **SI-10** (1.0 g, 5.15 mmol) in DCM (5 mL) was added dropwise at −78 °C. After 1.5 h, Et_3N (2.34 g, 3.23 mL, 23.18 mmol) was added, and the mixture was warmed to 0 °C. Once the mixture reached 0 °C, the reaction was quenched with water (25 mL) and extracted with DCM (3 × 25 mL). The combined organic layers were washed with brine (25 mL), and the dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 8−15% EtOAc/hexanes to obtain **46**[37] (881 mg, 4.60 mmol, 89%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.25−7.40 (m, 5H), 4.52 (s, 2H), 3.51 (t, *J* = 6 Hz, 2H), 2.46−2.50 (m, 2H), 1.73−1.80 (m, 2H), 1.64−1.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 138.5, 128.4, 127.7, 127.6, 73.0, 69.8, 43.6, 29.2, 19.0.



Imine 48. To a solution of **46** (881 mg, 4.58 mmol) and **47** (610 mg, 5.04 mmol) in DCM (8 mL) was added anhydrous $CuSO_4$ (1.827 g, 11.45 mmol), and the mixture was stirred at rt. After 12 h, the mixture was filtered through a pad of Celite, concentrated *in vacuo*, and purified by chromatography over silica gel, eluting with 10−25% EtOAc/hexanes to obtain **48** (1339 mg, 4.53 mmol, 99%) as a pale yellow oil. $[\alpha]^{20}_D = -188.50°$ (*c* 1.00, $CHCl_3$); IR (neat) 3083, 3061, 3027, 2928, 2864, 1621, 1454, 1362, 1083, 737, 698 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 8.08 (t, *J* = 4.9 Hz, 1H), 7.28−7.31 (m, 1H), 7.33−7.36 (m, 4H), 4.51 (s, 2H), 3.51 (t, *J* = 6.3 Hz, 2H), 2.54−2.56 (m, 2H), 1.73−1.78 (m, 2H), 1.68−1.72 (m, 2H), 1.20 (s, 9H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 169.4, 138.5, 128.4, 127.62, 127.58, 72.9, 69.8, 56.5, 35.9, 29.3, 22.4, 22.3; HRMS (EI+) calcd for $C_{16}H_{26}NO_2S$ (M + H) 296.1684, found 296.1690.



Sulfonamide 50. To a solution of **48** (1.40 g, 4.74 mmol) in PhMe (24 mL) at −78 °C was added a premade solution of **49** (7.10 mmol, 14.22 mL, 0.2 M in THF) slowly. After 2 h the reaction mixture was quenched with satd aq NH_4Cl (30 mL) and warmed to rt. The dried ($MgSO_4$) mixture was filtered through Celite, concentrated *in vacuo*, and purified by chromatography over silica gel, eluting with 20−50% EtOAc/hexanes to obtain **50** (1.37 g, 3.87 mmol, 82%) as a colorless oil. $[\alpha]^{20}_D = -74.2°$ (*c* 1.00, $CHCl_3$); IR (neat) 3268, 3225, 3069, 3030, 2937, 2861, 1652, 1455, 1363, 1069 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.34−7.37 (m, 4H), 7.29−7.32 (m, 1H), 4.81 (m, 1H), 4.90 (t, *J* = 2.1 Hz, 1H), 4.53 (s, 2H), 3.49 (t, *J* = 6.3 Hz, 2H), 3.38−3.43 (m, 1H), 3.26 (d, *J* = 4.2 Hz, 1H), 2.32 (dd, *J* = 14.0, 5.6 Hz, 1H), 2.22 (dd, *J* = 14.0, 8.4 Hz, 1H), 1.76 (s, 3H), 1.62−1.66 (m, 2H), 1.51−1.60 (m, 2H), 1.43−1.50 (m, 2H), 1.20 (s, 9H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 142.5, 138.6, 128.4, 127.6, 127.5, 114.2, 72.9, 70.2, 55.6, 51.5, 44.4, 35.1, 29.7, 22.6, 22.0, 21.9; HRMS (EI+) calcd for $C_{20}H_{34}O_2NS$ (M + H) 352.2310, found 352.2310.

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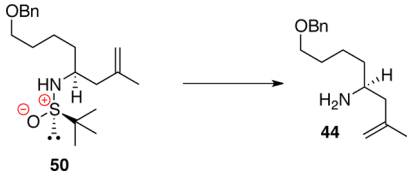
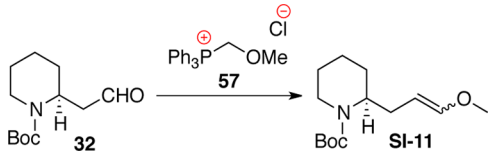
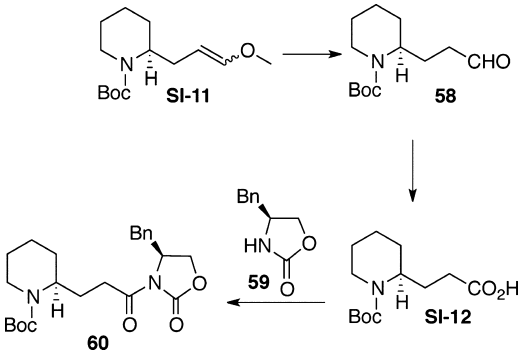


Amine 44. To a solution of **50** (1.140 g, 3.24 mmol) in MeOH (21 mL) was added conc HCl (12.8 M, 6.48 mmol, 0.504 mL). The resulting solution was allowed to stir for 1 h before being concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 50% EtOAc/hexanes to 10% MeOH/DCM to obtain **44** (930 mg, 3.24 mmol, 99%) as the HCl salt, which was then dissolved in satd aq Na_2CO_3 (50 mL) and extracted with DCM (3 × 30 mL) to obtain **44** as the free amine. $[\alpha]^{20}_D$ = +5.6° (*c* 1.00, $CHCl_3$); IR (neat) 3077, 3026, 2933, 2847, 1656, 1454, 1360, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.36 (m, 5H), 4.84 (s, 1H), 4.76 (s, 1H), 4.52 (s, 2H), 3.50 (t, *J* = 6.4 Hz, 2H), 2.91 (br s, 1H), 2.16–2.19 (m, 1H), 1.92 (dd, *J* = 13.6, 9.2 Hz, 1H), 1.73 (s, 3H), 1.62–1.66 (m, 2H), 1.44–1.59 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 138.6, 128.4, 127.7, 127.5, 112.8, 72.9, 70.3, 48.4, 47.0, 37.8, 29.9, 23.0, 22.3; HRMS (EI+) calcd for $C_{16}H_{26}NO$ (M + H) 248.2014, found 248.2015.



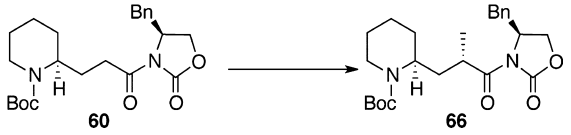
Enol Ether SI-11. To a suspension of methoxymethyl-triphenylphosphonium chloride **57** (15.09 g, 44.01 mmol) in ether (371 mL) was added PhLi (20.7 mL, 41.4 mmol, 2.0 M in Bu_2O) at −78 °C dropwise over 10 min period. The resulting solution was then warmed to rt over a period of 15 min. After 20 min, the reaction mixture was cooled back to 0 °C, and a solution of aldehyde **32** (23.79 mmol) in ether (247 mL) was added. After 2 h, the reaction was quenched with satd aq NH_4Cl (100 mL), and the precipitate was dissolved, extracted with ether (3 × 150 mL), and washed with satd aq $NaHCO_3$. The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by column chromatography over silica gel, eluting with 0–20% EtOAc/hexanes to obtain the enol ether **SI-11**[49] (4.0 g, 15.4 mmol, 65%) as a colorless oil of 1:1.27 (*Z*/*E*) diastereomeric mixture. $[\alpha]^{20}_D$ = −43.5° (*c* 1.0, $CHCl_3$); IR (neat) 2932, 2855, 1693, 1448, 1415, 1270, 1108, 934 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 6.32 (d, *J* = 12.6 Hz, 1H), 5.93 (dt, *J* = 6.3, 1.4 Hz, 1H), 4.67 (dt, *J* = 12.6, 7.7 Hz, 1H), 4.33 (q, *J* = 7.0 Hz, 1H), 4.21 (br s, 2H), 3.97 (br, s, 2H), 3.59 (s, 3H), 3.51 (s, 3H), 2.84 (t, *J* = 12.6 Hz, 1H), 2.76 (td, *J* = 13.3, 2.1 Hz, 1H), 2.42 (m, 1H), 2.27–2.25 (m, 2H), 2.13–2.09 (m, 1H), 1.6–1.51 (m, 9H), 1.47 (s, 18H), 1.43–1.38 (m, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 155.2, 148.1, 147.5, 103.4, 99.6, 79.0, 78.9, 59.5, 55.8, 50.7, 38.9, 28.5, 28.2, 27.8, 27.2, 25.6, 25.5, 24.4, 18.9, 18.8; HRMS (EI+) calcd for $C_{14}H_{25}NO_3$ (M+) 255.1835, found 255.1828.



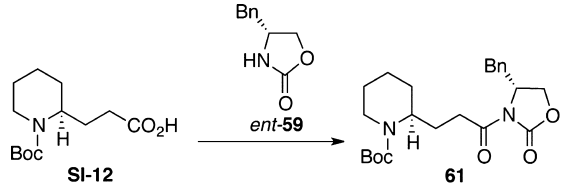
Oxazolidinone 60. To a stirred solution of enol ether **SI-11** (8.1 mmol) in acetone (97 mL) was added PTSA·H_2O (771 mg, 4.05 mmol). After 20 min, the reaction was quenched with water (20 mL) and extracted with DCM (3 × 50 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to obtain crude **58**.[50] The crude aldehyde **58** is taken to the next step.

To a solution of crude aldehyde **58** (~8.1 mmol) in a 1:1 mixture (200 mL) of ^tBuOH and H_2O was added 2-methyl-2-butene (19.94 mL, 186.3 mmol) followed by $NaH_2PO_4·H_2O$ (11.18 g, 81.0 mmol) and $NaOCl_2$ (3.68 g, 40.5 mmol). After 2.5 h, the reaction mixture was quenched with satd aq NaCl (50 mL) and extracted with ether (3 × 100 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to obtain the crude acid **SI-12**. The crude acid **SI-12** was taken to the next step.

To a solution of crude acid **SI-12** (~8.1 mmol) in dry THF (66 mL) was added triethylamine (1.64 g, 2.6 mL, 18.3 mmol) followed by pivaloyl chloride (977 mg, 1.0 mL, 8.1 mmol) at −20 °C. After 3 h, LiCl (364 mg, 8.61 mmol) and (4*S*)-benzyloxazolidin-2-one (**59**) (1.21 g, 6.82 mmol) were added sequentially, and the mixture was warmed to rt over a period of 3 h. After 30 min, the reaction was quenched with water (50 mL) and extracted with ether (3 × 100 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 38–50% ether/pentane to obtain **60**[51] (2.49 g, 5.98 mmol, 73% over 3 steps) as a colorless oil. $[\alpha]^{20}_D$ = +14.87° (*c* 1.58, $CHCl_3$); IR (neat) 2926, 2852, 1783, 1687, 1416, 1389, 1364, 1161, 701 cm^{-1}; ^1H NMR (400 MHz, 40 °C, $CDCl_3$) δ 7.26–7.34 (m, 3H), 7.20–7.22 (m, 2H), 4.67–4.70 (m, 1H), 4.31–4.32 (m, 1H), 4.13–4.22 (m, 2H), 4.00 (d, *J* = 12.0 Hz, 1H), 3.30 (dd, *J* = 13.2, 2.8 Hz, 1H), 2.94–3.00 (m, 1H), 2.74–2.86 (m, 3H), 2.13–2.15 (m, 1H), 1.77–1.80 (m, 1H), 1.59–1.67 (m, 5H), 1.45 (s, 9H), 1.27–1.40 (m, 1H); ^{13}C NMR (100 MHz, 40 °C, $CDCl_3$) δ 173.0, 155.1, 153.4, 135.5, 129.4, 128.9, 127.2, 79.2, 66.2, 55.2, 49.6, 38.7, 38.0, 32.3, 29.0, 28.4, 25.6, 24.3, 19.1; HRMS (EI+) calcd for $C_{23}H_{33}N_2O_5$ (M + H) 417.2390, found 417.2382.



Oxazolidinone 66. To a solution of oxazolidinone **60** (708 mg, 1.70 mmol) in dry THF (9.4 mL) at −78 °C was added NaHMDS (1.36 mL, 2.72 mmol, 2.0 M in THF). After 30 min, MeI (2.4 g, 1.06 mL, 17 mmol) was added. After 2 h, the reaction was quenched with satd aq NH_4Cl (20 mL) and extracted with ether (3 × 50 mL). The dried ($MgSO_4$) extracted was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 25–45% ether/pentane to obtain **66**[52] (396 mg, 0.92 mmol, 54%) as a colorless solid. Mp 135–137 °C; $[\alpha]^{20}_D$ = +23.2° (*c* 1.00, $CHCl_3$); IR (neat) 2933, 2863, 1783, 1681, 1475, 1417, 1392, 1163, 741 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.32–7.34 (m, 2H), 7.26–7.29 (m, 1H), 7.23–7.24 (m, 2H), 4.77 (br s, 1H), 4.24–4.28 (m, 2H), 4.14 (s, 1H), 3.92 (s, 1H), 3.28 (s, 1H), 3.26 (dd, *J* = 13.3, 2.8 Hz, 1H), 2.81 (dd, *J* = 12.6, 9.8 Hz, 1H), 2.75 (t, *J* = 12.6 Hz, 1H), 1.83–1.89 (m, 2H), 1.59 (m, 5H), 1.41 (s, 9H), 1.39–1.42 (m, 1H), 1.26 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 176.9, 155.2, 153.2, 135.7, 129.5, 128.8, 127.2, 79.1, 66.3, 55.4, 47.6, 39.2, 38.3, 34.6, 33.4, 29.5, 28.4, 25.7, 19.2, 18.7; HRMS (EI+) calcd for $C_{24}H_{34}N_2O_5$ (M+) 430.2468, found 430.2460.



Oxazolidinone 61. To a solution of crude acid **SI-12** (~7.17 mmol) in dry THF (58 mL) was added triethylamine (1.45 g, 2.02 mL, 14.34 mmol) followed by pivaloyl chloride (865 mg, 0.883 mL, 7.17 mmol) at −20 °C. After 3 h, LiCl (364 mg, 8.61 mmol) and (4*R*)-benzyloxazolidin-2-one (*ent*-**59**) (1.21 g, 6.82 mmol) were added sequentially, and the mixture was warmed to rt over a period of 3 h. After 30 min, the reaction was quenched with water (50 mL) and extracted with ether (3 × 100 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel,

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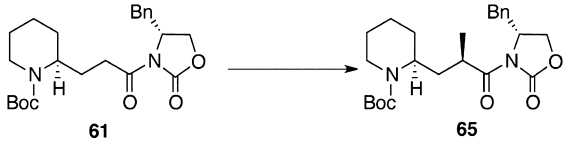
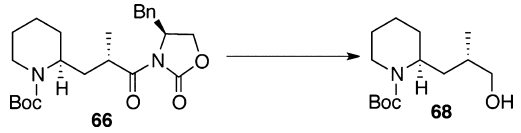
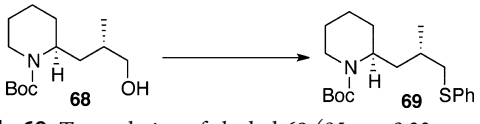
eluting with 38−50% ether/pentane to obtain **61** (2.34 g, 5.62 mmol, 78% over 3 steps) as a colorless oil. $[\alpha]^{20}_{D}$ = −46.4° (*c* 1.12, $CHCl_3$); IR (neat) 2931, 2857, 1783, 1682, 1477, 1416, 1391, 1271, 1162, 762, 702 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.35−7.37 (m, 2H), 7.29−7.31 (m, 1H), 7.24 (d, *J* = 7.0 Hz, 2H), 4.66−4.69 (m, 1H), 4.36 (br s, 1H), 4.17−4.22 (m, 2H), 4.02 (br s, 1H), 3.38 (d, *J* = 10.5, 1H), 3.01−3.06 (m, 1H), 2.75−2.86 (m, 3H), 2.17 (br s, 1H), 1.80 (br s, 1H), 1.60−1.70 (m, 5H), 1.49 (s, 9H), 1.39−1.47 (m, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 175.0, 155.1, 153.4, 135.5, 129.4, 128.9, 127.3, 79.4, 66.2, 55.3, 50.0, 38.9, 38.0, 32.7, 28.9, 28.5, 25.6, 24.4, 19.1; HRMS (CI+) calcd for $C_{23}H_{33}N_2O_5$ (M + H) 417.2390, found 417.2378.



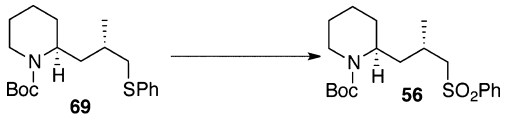
Oxazolidinone 65. To a solution of oxazolidinone **61** (66 mg, 0.158 mmol) in dry THF (0.49 mL) at −78 °C was added NaHMDS (0.127 mL, 0.253 mmol, 2.0 M in THF). After 30 min, MeI (224 mg, 0.1 mL, 1.58 mmol) was added. After 2 h, the reaction was quenched with satd aq NH_4Cl (5 mL) and extracted with ether (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 25−45% ether/pentane to obtain **65** (53 mg, 0.122 mmol, 77%) as a colorless oil. $[\alpha]^{20}_{D}$ = −77.2° (*c* 1.00, $CHCl_3$); IR (neat) 2930, 2855, 1782, 1686, 1454, 1415, 1389, 1168, 730 cm^{-1}; ^1H NMR (400 MHz, 40 °C, $CDCl_3$) δ 7.27−7.36 (m, 4H), 7.22 (d, *J* = 6.8 Hz, 1H), 4.63 (m, 1H), 4.35 (br s, 1H), 4.23 (d, *J* = 8.0 Hz, 1H), 4.15 (dd, *J* = 8.8, 2.0 Hz, 1H) 3.93 (d, *J* = 12.8, 1H), 3.72−3.81 (m, 1H), 3.27 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.78−2.85 (m, 2H), 2.48 (br s, 1H), 1.50−1.62 (m, 5H), 1.48 (s, 9H), 1.34−1.43 (m, 2H), 1.31 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, 40 °C, $CDCl_3$) δ 176.9, 155.2, 152.9, 135.4, 129.4, 128.9, 127.3, 79.5, 66.1, 55.4, 49.6, 38.7, 37.9, 35.6, 33.8, 29.7, 28.4, 25.6, 19.4, 18.2; HRMS (EI+) calcd for $C_{24}H_{34}N_2O_5$ (M+) 430.2468, found 430.2470.



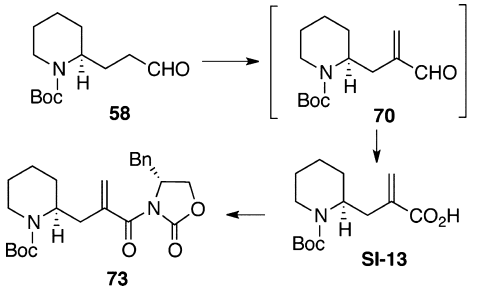
Alcohol 68. To a solution of the oxazolidinone **66** (151 mg, 0.351 mmol) in dry THF (14.6 mL) at 0 °C was added MeOH (56.1 mg, 0.71 mL, 1.75 mmol) followed by $LiBH_4$ (36.7 mg, 1.68 mmol). After 30 min, the reaction mixture was warmed to rt over a period of 10 min. After 2 h, the reaction mixture was quenched with satd aq NH_4Cl (25 mL) and extracted with ether (3 × 30 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 20−30% EtOAc/hexanes to obtain the alcohol **68**[53] (88.5 mg, 0.344 mmol, 98%) as a colorless oil. $[\alpha]^{20}_{D}$ = −44.7° (*c* 1.00, $CHCl_3$); IR (neat) 3438, 2929, 1682, 1417, 1365, 1317, 1270, 1167, 1026, 991, 877, 768 cm^{-1}; ^1H NMR (400 MHz, 40 °C, $CDCl_3$) δ 4.38 (br s, 1H), 3.97 (d, *J* = 12.8 Hz, 1H), 3.51 (d, *J* = 4.8 Hz, 2H), 2.75−2.82 (m, 1H), 1.57−1.60 (m, 8H), 1.47 (s, 9H), 1.32−1.40 (m, 1H), 0.95 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, 40 °C, $CDCl_3$) δ 155.2, 79.3, 68.4, 48.5, 38.9, 33.7, 32.7, 28.5, 25.6, 18.8, 17.4; HRMS (EI+) calcd for $C_{14}H_{27}NO_3$ (M+) 257.1991, found 257.1992.



Sulfide 69. To a solution of alcohol **68** (85 mg, 0.33 mmol) in dry THF (0.78 mL) at 0 °C were added PhSSPh (144 mg, 0.66 mmol) and Bu_3P (153.4 mg, 0.187 mL, 0.76 mmol). After 10 min, the reaction was warmed to rt over a period of 20 min. After 12 h, the solvent was removed *in vacuo* and purified by chromatography over silica gel, eluting with 15−30% ether/pentane to obtain the sulfide **69** (114 mg, 0.327 mmol, 99%) as a colorless oil. $[\alpha]^{20}_{D}$ = −33.1° (*c* 0.96, $CHCl_3$); IR (neat) 2920, 2845, 1733, 1683, 1652, 1635, 1540, 1558, 1506, 1457 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.36 (m, 2H), 7.27 (t, *J* = 7.6 Hz, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 4.29 (br s, 1H), 3.98 (d, *J* = 12.8 Hz, 1H), 2.94 (m, 2H), 2.78 (t, *J* = 12.8 Hz, 1H), 1.69−1.82 (m, 2H), 1.47−1.62 (m, 6H), 1.46 (s, 9H), 1.36−1.45 (m, 1H), 1.08 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 137.4, 129.1, 128.8, 125.6, 79.2, 48.4, 41.2, 38.9, 35.7, 30.4, 28.5, 27.9, 25.6, 19.6, 18.9; HRMS (EI+) calcd for $C_{20}H_{31}NO_2S$ (M+) 349.2076, found 349.2076.



Sulfone 56. To a solution of sulfide **69** (114 mg, 0.327 mmol) in dry EtOH (3.35 mL) was added $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (81.6 mg, 0.066 mmol) followed by H_2O_2 (1.7 mL, 16.5 mmol, 30% aqueous). After 12 h, water (10 mL) was added and extracted with DCM (3 × 20 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 20−30% EtOAc/hexanes to obtain **56** (123.4 mg, 0.32 mmol, 99%) as a colorless oil. $[\alpha]^{20}_{D}$ = −23.48° (*c* 1.15, $CHCl_3$); IR (neat) 2929, 1733, 1683, 1653, 1635, 1418, 1364, 1306, 1148, 1086, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.6 Hz, 2H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.56 (t, *J* = 7.2 Hz, 2H), 4.26 (br s, 1H), 3.94 (d, *J* = 12.8 Hz, 1H), 3.29 (br s, 1H), 2.93−2.98 (m, 1H), 2.72 (t, *J* = 12.8 Hz, 1H), 2.13−2.17 (m, 1H), 1.72−1.76 (m, 1H), 1.44−1.60 (m, 6H), 1.45 (s, 9H), 1.25−1.44 (m, 1H), 1.16 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 140.8, 133.3, 129.1, 127.6, 79.3, 62.0, 47.7, 39.1, 36.3, 28.4, 27.8, 26.1, 25.4, 19.9, 18.8; HRMS (EI+) calcd for $C_{20}H_{31}NO_4S$ (M+) 381.1974, found 381.1962.



Oxazolidinone 73. To a solution of aldehyde **58** (26 mg, 0.107 mmol) in DCM (0.8 mL) were sequentially added *N,N*-dimethylmethyleneiminium iodide (49.8 mg, 0.27 mmol) and Et_3N (21.8 mg, 30.3 μL, 0.215 mmol). After 24 h, satd $NaHCO_3$ (1 mL) was added and extracted with DCM (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to obtain the crude **70**. The crude **70** is taken to the next step.

To a solution of crude enal **70** (~0.107 mmol) in a 1:1 mixture (2.6 mL) of ^{t}BuOH and H_2O was added 2-methyl-2-butene (0.26 mL, 2.4 mmol) followed by $NaH_2PO_4{\cdot}H_2O$ (146.6 mg, 1.06 mmol) and $NaOCl_2$ (48.3 mg, 0.53 mmol). After 2.5 h, the reaction mixture was quenched with satd aq NaCl (5 mL) and extracted with ether (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to obtain the crude acid **SI-13**. The crude acid **SI-13** was taken to the next step.

To a solution of crude acid **SI-13** (~0.107 mmol) in dry THF (0.856 mL) was added triethylamine (21.7 mg, 30.1 μL, 0.214 mmol) followed by pivaloyl chloride (12.9 mg, 13.2 μL, 0.107 mmol) at −20 °C. After 3 h, LiCl (5.4 mg, 0.128 mmol) and (4*R*)-benzyloxazolidin-2-one (*ent*-**59**) (18 mg, 0.102 mmol) were added sequentially, and the mixture was warmed to rt over a period of 3 h. After 30 min, the reaction was quenched with water (5 mL) and extracted with ether (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 38−50% ether/pentane to obtain **73** (19.7 mg, 0.046 mmol, 43% over 3 steps) as a colorless oil. $[\alpha]^{20}_{D}$ = −38.8° (*c* 1.43, $CHCl_3$); IR (neat) 2934, 1788, 1684, 1413, 1364, 1160, 1042, 918, 735, 703 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.36 (t, *J* = 7.0 Hz, 2H), 7.29−7.31 (m, 1H), 7.24 (d, *J* = 7.0 Hz, 2H), 5.60 (s, 1H), 5.57 (s, 1H), 4.72−4.76 (m, 1H), 4.40−4.41 (m, 1H), 4.26 (t, *J* = 8.4 Hz, 1H), 4.20 (dd, *J* = 8.4, 4.2

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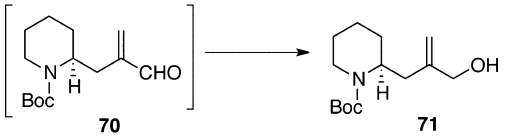
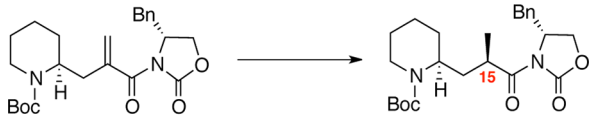
Hz, 1H), 4.00 (br s, 1H), 3.45−3.47 (m, 1H), 2.81−2.86 (m, 2H), 2.77 (dd, J = 14.0, 7.0 Hz, 1H), 2.65−2.67 (m, 1H), 1.74−1.75 (m, 1H), 1.57−1.64 (m, 5H), 1.48 (s, 9H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 170.2, 154.9, 153.1, 141.0, 135.3, 129.4, 129.0, 127.4, 123.3, 79.4, 66.6, 55.6, 49.0, 39.4, 37.6, 33.5, 28.5, 27.1, 25.5, 18.8; HRMS (ES+) calcd for $C_{24}H_{32}N_2O_5Na$ (M + Na) 451.2209, found 451.2190.



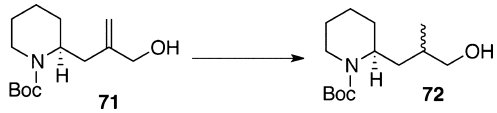
70 71

Alcohol 71. To a solution of crude enal **70** (~0.103 mmol) in MeOH (0.78 mL) and Et_2O (0.22 mL) at 0 °C was added $NaBH_4$ (3.9 mg, 0.103 mmol, 3 portions) portionwise over a period of 20 min. After an additional 30 min, the reaction was quenched with H_2O (2 mL) and extracted with ether (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by column chromatography over silica gel, eluting with 10−30% Et_2O/pentane to obtain a alcohol **71** (17.5 mg, 0.069 mmol, ~40% over 2 steps). $[\alpha]^{20}_D$ = −35.5° (*c* 0.96, $CHCl_3$); IR (neat) 3423, 2934, 2860, 1674, 1418, 1366, 1321, 1265, 1162, 1041, 898, 802, 767 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.03 (br s, 1H), 4.82 (br s, 1H), 4.52 (br s, 1H), 4.14 (d, J = 6.3 Hz, 2H), 3.90−3.95 (m, 2H), 2.85 (t, J = 12.6 Hz, 1H), 2.61 (br s, 1H), 2.12 (br s, 1H), 1.57−1.66 (m, 6H), 1.45 (s, 9H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 156.1, 146.4, 113.8, 79.7, 67.4, 49.1, 39.6, 35.1, 28.4, 25.5, 18.8; HRMS (ES+) calcd for $C_{14}H_{25}NO_3Na$ (M + Na) 278.1732, found 278.1736.



73 65

Oxazolidinone 65. To a solution of **73** (16.5 mg, 0.039 mmol) in THF (0.53 mL) at −78 °C was added L-Selectride (42.4 μL, 42.4 μmol, 1.0 M solution in THF). After 15 min, the reaction was quenched with satd aq NH_4Cl solution (1 mL) and extracted with Et_2O (3 × 5 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to obtain **65** and its C_{15}-epimer (14.1 mg, 0.033 mmol, 85%) as a (2:1) diastereomeric mixture.

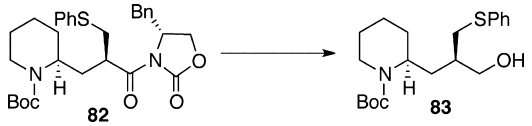


71 72

Alcohol 72. To a solution of allylic alcohol **71** (9.3 mg, 0.036 mmol) in MeOH (0.5 mL) at rt was added (*S*)-Ru(OAc)$_2$(T-BINAP) (5.5 mg, 10 mol %), and the argon was then removed by flushing with H_2 gas. After 5 min, the reaction was sealed under 1 atm of H_2 (balloon). After 3 d, the hydrogen was removed by flushing with argon, and the reaction mixture was filtered through Celite washing with EtOH (5 mL). The filtered extract was concentrated *in vacuo* to give alcohol **72** (3.7 mg, 0.014 mmol, ~40%) as a 1:1 diastereomeric mixture.

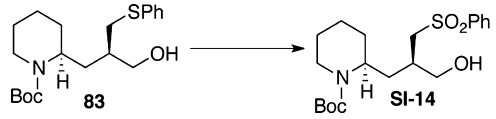
61 82

Oxazolidinone 82. To a solution of **61** (40 mg, 0.14 mmol) in THF (0.58 mL) at −78 °C was added NaHMDS (0.115 mL, 0.23 mmol, 2.0 M in THF). After 30 min, neat $PhSCH_2I$[54] (350 mg, 1.4 mmol) was added. After 1 h, the reaction was quenched with satd aq NH_4Cl (5 mL) and extracted with ether (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 20−40% ether/pentane to obtain **82**[42] (48 mg, 0.088 mmol, 63%) as a colorless oil. $[\alpha]^{20}_D$ = −28.2° (*c* 1.05, $CHCl_3$); IR (neat) 2974, 2929, 1782, 1684, 1482, 1414, 1389, 1364, 1273, 1159, 1107, 739 cm^{-1}; ^{1}H NMR (400 MHz, 40 °C, $CDCl_3$) δ 7.42−7.44 (m, 2H), 7.19−7.34 (m, 8H), 4.64 (br s, 1H), 4.34 (br s, 1H), 4.11−4.27 (m, 3H), 3.92 (d, J = 13.2 Hz, 1H), 3.27−3.41 (m, 3H), 2.72−2.85 (m, 2H), 2.44 (br s, 1H), 1.70−1.77 (m, 1H), 1.48−1.61 (m, 5H), 1.46 (s, 9H), 1.34−1.42 (m, 1H); ^{13}C NMR (100 MHz, 40 °C, $CDCl_3$) δ 174.4, 155.2, 152.9, 136.3, 135.5, 129.8, 129.4, 128.90, 128.86, 127.2, 126.3, 79.7, 66.1, 55.6, 49.2, 40.9, 38.9, 37.8, 36.5, 31.9, 29.4, 28.4, 25.5, 19.3; HRMS (ES+) calcd for $C_{30}H_{39}N_2O_5S$ (M + H) 539.2580, found 539.2593.



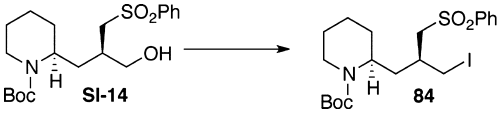
82 83

Alcohol 83. To a solution of **82** (42 mg, 0.078 mmol) in THF (3.3 mL) at 0 °C was added MeOH (12.4 mg, 0.017 mL, 0.39 mmol) followed by $LiBH_4$ (8.2 mg, 0.374 mmol). After 30 min, the reaction mixture was warmed to rt over a period of 10 min. After 2 h, the reaction mixture was quenched with satd aq NH_4Cl (5 mL) and extracted with ether (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 35−45% EtOAc/hexanes to obtain **83** (27.6 mg, 0.076 mmol, 97%) as a colorless oil. $[\alpha]^{20}_D$ = −40.8° (*c* 1.30, $CHCl_3$); IR (neat) 3419, 2927, 2856, 1689, 1665, 1419, 1365, 1272, 1068, 738, 691 cm^{-1}; ^{1}H NMR (400 MHz, 40 °C, $CDCl_3$) δ 7.37−7.39 (m, 2H), 7.27−7.31 (m, 2H), 7.18 (t, J = 7.2 Hz, 1H), 4.29 (br s, 1H), 3.95 (d, J = 10.4 Hz, 1H), 3.72−3.77 (m, 2H), 3.16 (dd, J = 12.8, 6.4 Hz, 1H), 3.03 (dd, J = 12.4, 5.2 Hz, 1H), 2.76−2.83 (m, 1H), 1.75 (br s, 2H), 1.59−1.64 (m, 5H), 1.42−1.50 (m, 11H); ^{13}C NMR (100 MHz, 40 °C, $CDCl_3$) δ 155.5, 137.0, 129.2, 128.9, 125.9, 79.6, 64.3, 48.0, 39.4, 37.8, 36.2, 30.8, 28.5, 28.0, 25.4, 18.8; HRMS (EI+) calcd for $C_{20}H_{32}NO_3S$ (M + H) 366.2103, found 366.2108.



83 SI-14

Sulfone SI-14. To a solution of sulfide **83** (12.5 mg, 0.034 mmol) in EtOH (0.36 mL) was added $(NH_4)_6Mo_7O_{24}\cdot4H_2O$ (8.5 mg, 0.007 mmol) followed by H_2O_2 (0.163 mL, 1.7 mmol, 30% aqueous). After 12 h, water (2 mL) was added and extracted with DCM (3 × 5 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 50−85% EtOAc/hexanes to obtain the sulfone **SI-14** (12.7 mg, 0.032 mmol, 94%) as a colorless oil. $[\alpha]^{20}_D$ = −21.9° (*c* 0.48, $CHCl_3$); IR (neat) 3434, 2926, 2854, 1681, 1447, 1420, 1366, 1305, 1146, 740 cm^{-1}; ^{1}H NMR (400 MHz, 40 °C, $CDCl_3$) δ 7.95−7.97 (m, 2H), 7.64−7.68 (m, 1H), 7.57−7.60 (m, 2H), 4.25 (br s, 1H), 3.93 (d, J = 12.8 Hz, 1H), 3.84 (br s, 2H), 3.31 (br s, 2H), 2.76 (t, J = 13.2 Hz, 1H), 2.17−2.19 (m, 1H), 1.73−1.87 (m, 2H), 1.53−1.63 (m, 5H), 1.47 (s, 10H); ^{13}C NMR (100 MHz, 40 °C, $CDCl_3$) δ 155.0, 140.5, 133.5, 129.3, 127.7, 79.8, 63.8, 57.5, 47.3, 39.5, 33.7, 31.5, 28.5, 27.9, 25.3, 18.8; HRMS (EI+) calcd for $C_{20}H_{31}NO_5SNa$ (M + Na) 420.1821, found 420.1816.



SI-14 84

Iodide 84. To a solution of sulfone **SI-14** (14.0 mg, 0.036 mmol) in THF (1.24 mL) at 0 °C were sequentially added imidazole (7.4 mg, 0.108 mmol), PPh_3 (18.4 mg, 0.07 mmol), and I_2 (17.7 mg, 0.07 mmol). After 20 min, the reaction mixture was warmed to rt over a period of 5 min. After 3 h, the reaction was quenched with satd aq sodium thiosulfate (5 mL) and extracted with ether (3 × 5 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 20−35% EtOAc/hexanes to obtain the iodide **84** (15.3 mg, 0.03 mmol, 84%) as a colorless oil. $[\alpha]^{20}_D$ = −14.6° (*c* 1.0, $CHCl_3$); IR (neat) 2930, 2856, 1681, 1447, 1417, 1365, 1307, 1152, 1086, 738 cm^{-1}; ^{1}H NMR (400 MHz, 40 °C, $CDCl_3$) δ 7.97−7.99 (m, 2H), 7.65−7.69 (m, 1H), 7.57−7.61 (m, 2H), 4.31 (br s, 1H), 3.99 (d, J = 14.0 Hz, 1H), 3.53−3.61 (m, 2H),

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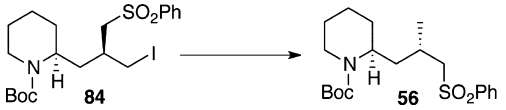
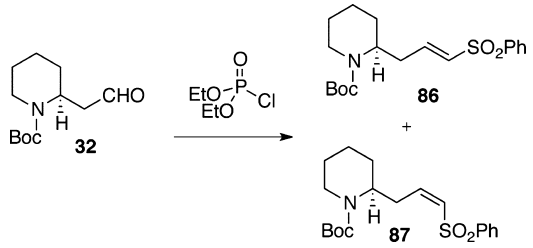
3.21−3.37 (m, 2H), 2.79 (t, J = 13.2 Hz, 1H), 1.96−2.06 (m, 2H), 1.51−1.71 (m, 6H), 1.49 (s, 9H), 1.32−1.46 (m, 1H); ^{13}C NMR (100 MHz, 40 °C, $CDCl_3$) δ 154.9, 140.4, 133.6, 129.3, 127.8, 79.7, 59.4, 47.5, 39.2, 34.8, 32.7, 28.8, 28.5, 25.5, 19.1, 13.7; HRMS (ES+) calcd for $C_{20}H_{30}INO_4SNa$ (M + Na) 530.0838, found 530.0833.



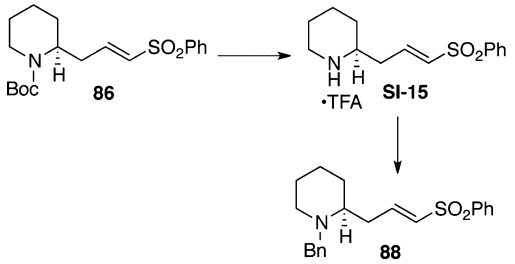
Sulfone 56. To a stirred solution of iodide **84** (10 mg, 0.0197 mmol) in EtOH (0.48 mL) under argon was added Pd/C (20 mg, 20 wt %), and the argon was then removed by flushing with H_2 gas. After 5 min, the reaction was sealed under 1 atm of H_2 (balloon). After 18 h, the hydrogen was removed by flushing with argon, and the reaction mixture was filtered through Celite washing with EtOH (5 mL). The filtered extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 20−30% EtOAc/hexanes to give sulfone **3** (7.4 mg, 0.0195 mmol, 99%) as a colorless oil.



Vinyl Sulfones 86 and 87. To a solution of $PhSO_2Me$ (1.08 g, 6.94 mmol) in THF (61.2 mL) at 0 °C was added ^{n}BuLi (6.1 mL, 15.3 mmol, 2.5 M solution in hexanes). After 20 min, $ClP(O)(OEt)_2$ (1.19 g, 0.99 mL, 6.88 mmol) was added. After 30 min, the reaction mixture was cooled to −78 °C, and a solution of aldehyde **32** (1.16 g, 5.1 mmol) in THF (16.1 mL) was added. After 15 min, the reaction mixture was warmed to 0 °C over a period of 10 min. After 2 h, the reaction was quenched with aq NH_4Cl (100 mL) solution and extracted with ether (3 × 100 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10−30% EtOAc/hexanes to obtain sequentially **86** (1.22 g, 3.4 mmol, 66%) followed by **87** (305 mg, 0.85 mmol, 17%).

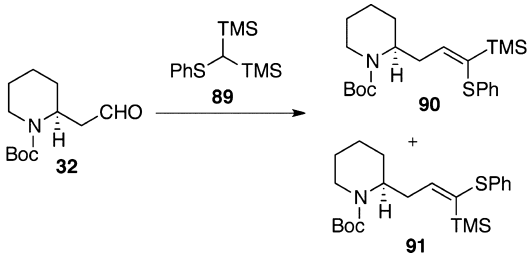
(*E*)-Vinyl Sulfone **86**: $[\alpha]^{20}_D$ = −15.9° (*c* 1.10, $CHCl_3$); IR (neat) 3059, 2975, 2934, 2859, 1693, 1681, 1633, 1476, 1416, 1319, 1147, 1086, 752, 688 cm^{-1}; ^{1}H NMR (700 MHz, 40 °C, $CDCl_3$) δ 7.86−7.88 (m, 2H), 7.60−7.62 (m, 1H), 7.53 (t, J = 7.7 Hz, 2H), 6.90−6.95 (m, 1H), 6.39 (d, J = 15.4 Hz, 1H), 4.41 (br s, 1H), 3.98 (br s, 1H), 2.60−2.69 (m, 2H), 2.37−2.41 (m, 1H), 1.49−1.64 (m, 5H), 1.47 (s, 9H), 1.40−1.43 (m, 1H); ^{13}C NMR (175 MHz, 40 °C, $CDCl_3$) δ 154.7, 143.7, 140.6, 133.2, 132.0, 129.2, 127.6, 79.8, 49.3, 39.0, 32.1, 28.4, 28.1, 25.2, 18.8; HRMS (ES+) calcd for $C_{19}H_{27}NO_4NaS$ (M + Na) 388.1559, found 388.1545.

(*Z*)-Vinyl Sulfone **87**: $[\alpha]^{20}_D$ = −9.0° (*c* 1.0, $CHCl_3$); IR (neat) 3060, 2974, 2934, 2864, 1688, 1681, 1626, 1476, 1447, 1414, 1365, 1317, 1149, 1086, 750, 688 cm^{-1}; ^{1}H NMR (400 MHz, 40 °C, $CDCl_3$) δ 7.92 (d, J = 7.2 Hz, 2H), 7.61−7.65 (m, 1H), 7.54−7.58 (m, 2H), 6.30 (br s, 2H), 4.42 (br s, 1H), 3.97 (d, J = 12.0 Hz, 1H), 3.17−3.22 (m, 1H), 2.83−2.86 (m, 2H), 1.57−1.70 (m, 5H), 1.36−1.47 (m, 10H); ^{13}C NMR (100 MHz, 40 °C, $CDCl_3$) δ 155.0, 143.9, 141.7, 133.3, 131.3, 129.2, 127.2, 79.5, 50.0, 39.1, 28.7, 28.6, 28.4, 25.4, 19.0; HRMS (ES+) calcd for $C_{19}H_{27}NO_4NaS$ (M + Na) 388.1559, found 388.1555.



Vinyl Sulfone 88. To a solution of **86** (105 mg, 0.287 mmol) in DCM (0.66 mL) at 0 °C was added TFA (1.21 g, 0.814 mL, 10.63 mmol). After 30 min, the reaction mixture was warmed to rt. After 10 min, the solvent was removed under reduced pressure, and the crude TFA salt **SI-15** was taken to next step.

To a solution of crude TFA salt **SI-15** (~0.287 mmol) in acetonitrile (0.8 mL) were added K_2CO_3 (79.4 mg, 0.575 mmol) and TBAI (105.3 mg, 0.287 mmol) followed by benzyl bromide (54.1 mg, 37.6 μL, 0.316 mmol). After 1.5 h, the reaction mixture was directly purified by chromatography over silica gel, eluting with 70−100% EtOAc/hexanes to obtain **88** (86 mg, 0.242 mmol, 84% over 2 steps). $[\alpha]^{20}_D$ = −17.1° (*c* 2.20, $CHCl_3$); IR (neat) 3060, 3028, 2932, 2854, 2794, 2756, 1629, 1446, 1318, 1307,1291, 1146, 1086, 1069, 749, 688 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.9 (d, J = 7.0 Hz, 2H), 7.63 (tt, J = 7.0, 1.4 Hz, 1H), 7.54 (t, J = 7.7 Hz, 2H), 7.24−7.31 (m, 5H), 7.10−7.14 (m, 1H) 6.42 (d, J = 15.4 Hz, 1H), 3.93 (d, J = 14.0 Hz, 1H), 3.24 (d, J = 13.3 Hz, 1H), 2.71−2.74 (m, 1H), 2.52−2.63 (m, 3H), 2.08 (t, J = 9.1 Hz, 1H), 1.64−1.67 (m, 2H), 1.52−1.53 (m, 1H), 1.44−1.48 (m, 2H), 1.32−1.38 (m, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 144.9, 140.7, 139.1, 133.3, 131.6, 129.3, 128.7, 128.3, 127.6, 126.9, 59.4, 58.2, 51.3, 33.5, 30.4, 25.1, 23.1; HRMS (ES+) calcd for $C_{21}H_{26}NO_2S$ (M + H) 356.1684, found 356.1667.



Sulfides 90 and 91. To a solution of **89** (0.639 g, 2.38 mmol) in THF (12.9 mL) at −78 °C was added ^{n}BuLi (1.5 mL, 2.38 mmol, 1.6 M solution in hexanes). After 5 min, the reaction mixture was warmed to −45 °C over a period of 3 h. After 10 min, it was warmed to −25 °C over a period of 1 h. After 5 min, it was cooled back to −78 °C, and a solution of aldehyde **32** (250 mg, 1.1 mmol) in THF (1.0 mL) was added. After 5 min, the reaction mixture was warmed to −10 °C over a period of 20 min. After 15 min, the reaction was quenched with aq NH_4Cl (30 mL) solution and extracted with ether (3 × 30 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 5−20% EtOAc/hexanes to obtain a (3:1) diastereomeric mixture of vinyl sulfides **90** and **91** (134 mg, 0.33 mmol, 30%). IR (neat) 2971, 2936, 2860, 1690, 1583, 1476, 1413, 1364, 1248, 1164, 1054, 839, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19−7.28 (m, 5.2 H, mixed isomers), 7.10−7.14 (m, 1.3H, mixed isomers), 6.58 (t, J = 6.8 Hz, 1H, major isomer), 6.46 (t, J = 7.2 Hz, 0.3H, minor isomer), 4.46 (br s, 1H, major isomer), 4.33 (br s, 0.3H, minor isomer), 4.05 (br d, J = 12.4 Hz, 0.3H, minor isomer), 3.96 (br d, J = 10.0 Hz, 1H, major isomer), 2.89 (ddd, J = 15.2, 8.8, 6.8 Hz, 1H, major isomer), 2.74−2.82 (m, 1.3 H, mixed isomers), 2.47−2.64 (m, 1.6 H, mixed isomers), 1.53−1.65 (m, 7H, mixed isomers), 1.49 (s, 9H, major isomer), 1.45 (s, 2.7H, minor isomer), 1.32−1.40 (m, 0.8H, mixed isomers), 0.18 (s, 2.7H, minor isomer), 0.02 (s, 9H, major isomer); ^{13}C NMR (100 MHz, 40 °C, $CDCl_3$) δ 154.9, 149.5, 137.7, 137.6, 135.7, 134.3, 129.7, 128.7, 128.6, 128.2, 125.9, 125.2, 79.4, 79.1, 50.7, 50.0, 39.1, 33.0, 31.7, 28.54, 28.45, 27.8, 25.5, 25.4, 19.1, 0.5, −1.1; HRMS (ES+) calcd for $C_{22}H_{36}NO_2SiS$ (M + H) 406.2236, found 406.2224.

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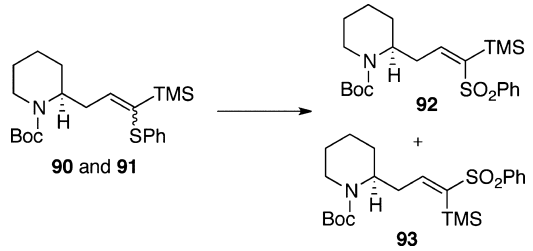
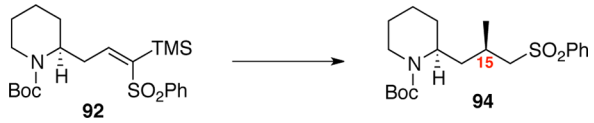


Sulfones 92 and 93. To a solution of mixture of sulfides **90** and **91** (64 mg, 0.158 mmol) in EtOH (1.6 mL) was added $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (39 mg, 0.032 mmol) followed by H_2O_2 (0.82 mL, 7.9 mmol, 30% aqueous). After 4 h, water (10 mL) was added and extracted with DCM (3 × 15 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 30−50% ether/pentane to obtain **92** (48.2 mg, 0.11 mmol, 70%) and **93** (16.1 mg, 0.037 mmol, 23%).

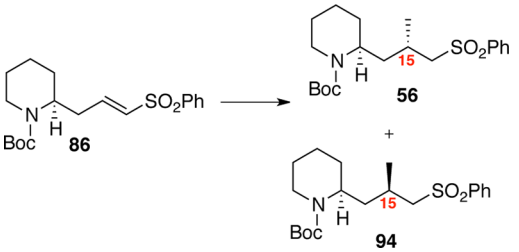
(*Z*)-Vinyl Sulfone **92**: IR (neat) 2974, 2937, 2863, 1685, 1593, 1476, 1446, 1414, 1299, 1249, 1165, 1141, 1085, 884, 843, 760, 590 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 7.2 Hz, 2H), 7.52−7.61 (m, 3H), 6.59 (br s, 1H), 4.35 (br s, 1H), 3.86 (br d, J = 12.4 Hz, 1H), 2.91 (br s, 1H), 2.51−2.55 (m, 2H), 1.52−1.66 (m, 3H), 1.45 (s, 9H), 1.27−1.40 (m, 3H), 0.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 154.8, 147.9, 143.4, 132.7, 129.0, 127.0, 79.5, 49.8, 38.9, 31.4, 28.7, 28.5, 25.3, 18.9, −0.4; HRMS (ES+) calcd for $C_{22}H_{36}NO_4SiS$ (M + H) 438.2134, found 438.2136.

(*E*)-Vinyl Sulfone **93**: IR (neat) 2974, 2933, 2857, 1686, 1588, 1475, 1446, 1414, 1365, 1295, 1164, 1143, 1086, 847, 761, 721, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.2 Hz, 2H), 7.45−7.57 (m, 4H), 4.48−4.51 (m, 1H), 4.08 (br d, J = 13.6 Hz, 1H), 2.72−2.81 (m, 2H), 2.58 (ddd, J = 14.8, 8.0, 6.8 Hz, 1H), 1.52−1.72 (m, 5H), 1.50 (s, 9H), 1.45−1.47 (m, 1H), 0.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 154.8, 143.9, 141.8, 132.6, 128.8, 127.3, 80.0, 50.1, 39.2, 31.7, 28.5, 28.3, 25.3, 19.1, 0.5; HRMS (ES+) calcd for $C_{22}H_{36}NO_4SiS$ (M + H) 438.2134, found 438.2137.

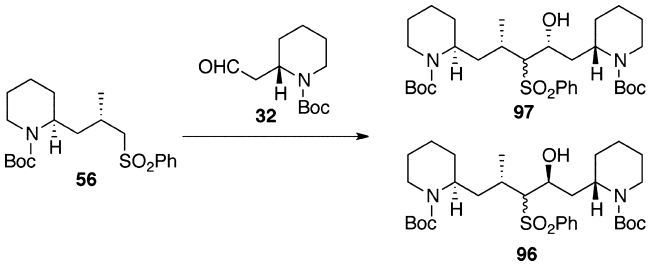


Sulfone 94. To a stirred suspension of CuI (24.0 mg, 0.126 mmol) in ether (0.32 mL) at 0 °C was added MeLi (0.155 mL, 0.248 mmol, 1.6 M solution in ether). After 25 min, a solution of vinyl sulfone **92** (9.2 mg) in ether (0.05 mL) was added. After 35 min, the reaction mixture was quenched with aq NH_4Cl (5 mL) and extracted with ether (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo*, and the crude was taken to the next step.

To a solution of crude sulfone (~21 μmol) in MeOH (0.26 mL) was added KF (6.3 mg, 0.109 mmol) at rt. Aft 1 h, the reaction mixture was quenched with aq $NaHSO_3$ solution (5 mL) and extracted with DCM (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by column chromatography over silica gel, eluting with 10−30% EtOAc/hexanes to obtain a 1:8 diastereomeric mixture of sulfones (**3** and *epi*-C_{15} **3**, respectively) (7.5 mg, 20 μmol, 93%, 2 steps). $[\alpha]^{20}_D$ = −21.67° (*c* 0.48, $CHCl_3$); IR (neat) 2926, 2852, 1682, 1447, 1416, 1365, 1305, 1271, 1149, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 7.6 Hz, 2H), 7.67 (t, J = 7.2 Hz, 1H), 7.59 (t, J = 7.2 Hz, 2H), 4.29 (br s, 1H), 3.97 (br s, 1H), 3.16 (dd, J = 14.0, 5.6 Hz, 1H), 3.01 (dd, J = 14.4, 6.0 Hz, 1H), 2.81 (t, J = 12.8 Hz, 1H), 2.15−2.22 (m, 1H), 2.01 (br s, 1H), 1.58 (m, 5H), 1.45 (s, 9H), 1.18−1.30 (m, 2H) 1.13 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 140.2, 133.4, 129.3, 127.9, 79.2, 62.6, 47.7, 38.8, 36.8, 29.2, 28.5, 25.9, 25.6, 20.3, 19.1; HRMS (EI+) calcd for $C_{20}H_{31}NO_4S$ (M+) 381.1974, found 381.1964.



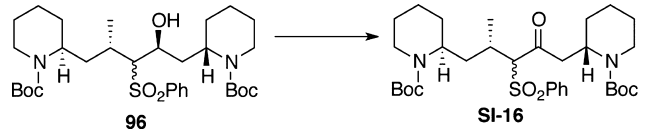
Sulfone 56. To a stirred suspension of CuI (28.8 mg, 0.151 mmol) in ether (0.88 mL) at 0 °C was added MeLi (0.185 mL, 0.296 mmol, 1.6 M solution in ether). After 5 min, the reaction was cooled to −78 °C. After 5 min, a solution of vinyl sulfone **86** (18 mg, 50 μmol) in ether (0.13 mL) was added. After 5 min, the reaction mixture was slowly warmed to −20 °C over a period of 45 min. After 5 h, the reaction was quenched with aq NH_4Cl (5 mL) and extracted with ether (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by column chromatography over silica gel, eluting with 10−30% EtOAc/hexanes to obtain a 1.0:1.2 mixture of sulfones (**56** and **94**, respectively) (10.8 mg, 28.3 μmol, 55%).



Hydroxy Sulfones 96 and 97. To a solution of sulfone **56** (60 mg, 0.157 mmol) in dry THF (0.253 mL) at −78 °C was added LDA[55] (0.236 mL, 0.236 mmol, 1.0 M in THF/hexanes). After 1 min, a solution of aldehyde **32** (89.1 mg, 0.392 mmol) in THF (0.147 mL) was added. After 20 min, the reaction was quenched with satd aq NH_4Cl (5 mL) and extracted with ether (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 20−80% ether/pentane to obtain a 1.0:1.5 mixture of **97** and **96**, respectively (84.9 mg, 0.146 mmol, 93%), as a colorless oil.

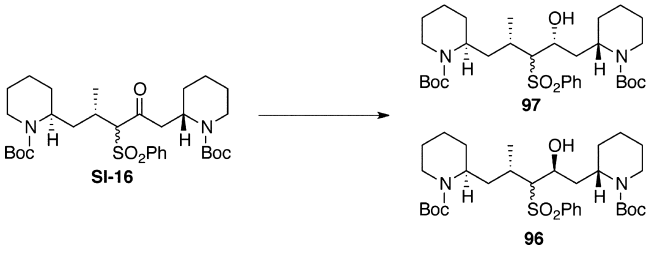
Hydroxy Sulfone **97**: $[\alpha]^{20}_D$ = −45.0° (*c* 1.00, $CHCl_3$); IR (neat) 3391, 2929, 2851, 1683, 1652, 1418, 1366, 1273, 1166, 1145, 868, 723, 613 cm^{-1}; ^1H NMR (400 MHz, 40 °C, $CDCl_3$) δ 7.88 (d, J = 7.6 Hz, 4H), 7.50−7.56 (m, 6H), 4.30−4.38 (m, 4H), 3.94−3.96 (m, 4H), 3.82 (br s, 2H), 3.38 (br s, 2H), 2.74−2.80 (m, 4H), 2.26 (br s, 4H), 1.67−1.73 (m, 4H), 1.47−1.59 (m, 24H), 1.41−1.42 (m, 40 H), 1.26−1.28 (6H); ^{13}C NMR (100 MHz, 40 °C, $CDCl_3$) δ 156.5, 155.0, 142.7, 133.5, 132.8, 129.2, 129.0, 128.7, 128.3, 128.2, 128.1, 128.0, 80.2, 79.4, 79.3, 72.8, 66.1, 49.0, 46.4, 39.2, 34.7, 34.4, 29.6, 29.5, 29.2, 28.6, 28.5, 28.4, 28.3, 28.1, 28.0, 25.6, 25.4, 19.3, 19.0, 18.9, 18.0; HRMS (ES+) calcd for $C_{32}H_{53}N_2O_7S$ (M + H) 609.3573, found 609.3569.

Hydroxy Sulfone **96**: $[\alpha]^{20}_D$ = −37.7° (*c* 0.98, $CHCl_3$); IR (neat) 3420, 2929, 2854, 1683, 1652, 1473, 1456, 1418, 1365, 1271, 1165, 1145, 1083 cm^{-1}; ^1H NMR (400 MHz, 40 °C, $CDCl_3$) δ 7.88−7.96 (m, 4H), 7.50−7.60 (m, 6H), 4.18−4.25 (m, 4H), 4.04 (br s, 2H), 3.80−3.90 (m, 4H), 3.45−3.52 (m, 2H), 3.28 (br s, 2H), 2.69−2.78 (m, 4H), 2.13−2.29 (m, 4H), 1.71−1.80 (m, 8H), 1.32−1.54 (m, 58 H), 1.23−1.25 (6H); ^{13}C NMR (100 MHz, 40 °C, $CDCl_3$) δ 155.3, 155.2, 155.1, 154.9, 141.9, 141.6, 140.5, 133.5, 133.3, 129.14, 129.07, 129.0, 128.1, 128.0, 128.0, 79.5, 79.3, 79.2, 71.1, 68.0, 48.4, 39.5, 39.3, 39.1, 37.0, 35.4, 35.1, 34.9, 29.6, 29.1, 28.53, 28.47, 28.46, 28.43, 28.33, 28.30, 28.0, 27.8, 25.5, 25.4, 25.3, 25.2, 19.1, 19.0, 18.9, 18.5, 17.4; HRMS (ES+) calcd for $C_{32}H_{53}N_2O_7S$ (M + H) 609.3573, found 609.3562.

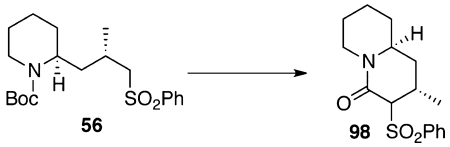


dx.doi.org/10.1021/jo400324t | J. Org. Chem. 2013, 78, 4779−4800

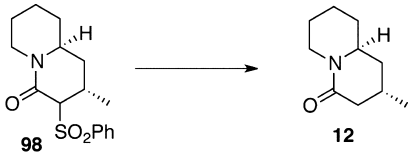
Keto Sulfone SI-16. To a solution of alcohol **96** (15 mg, 24.6 μmol) in DCM (0.71 mL) at 0 °C was added solid $NaHCO_3$ (10.35 mg, 0.123 mmol) followed by DMP (20.87 mg, 0.049 mmol). After 30 min, the reaction mixture was warmed to rt over a period of 15 min. After 1.5 h, the reaction was quenched with satd aq $Na_2S_2O_3$ (5 mL) solution and extracted with DCM (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 20−30% EtOAc/hexanes to obtain the keto sulfone **SI-16** (13.9 mg, 23.0 μmol, 93%) as a colorless oil. $[\alpha]^{20}_D$ = −13.3° (*c* 0.70, $CHCl_3$); IR (neat) 2929, 2855, 1717, 1684, 1447, 1417, 1365, 1271, 1165, 1083, 1083, 872 cm^{-1}; ^1H NMR (400 MHz, 40 °C, $CDCl_3$) δ 7.79−7.84 (m, 4H), 7.56−7.61 (m, 2H), 7.47−7.51 (m, 4H), 4.56 (m, 2H), 4.21−4.37 (m, 4H), 3.84−3.86 (m, 4H), 2.84−2.91 (m, 2H), 2.40−2.65 (m, 6H), 2.24 (br s, 1H), 2.09 (br s, 1H), 1.76−1.80 (m, 2H), 1.49 (m, 10 H), 1.35−1.40 (m, 44H), 1.20−1.31 (m, 8H), 1.16 (d, *J* = 6.8 Hz, 3H), 1.03−1.04 (m, 3H); ^{13}C NMR (100 MHz, 40 °C, $CDCl_3$) δ 200.8, 200.7, 200.5, 200.4, 154.8, 154.7, 154.5, 139.0, 133.94, 133.90, 129.1, 129.0, 128.9, 128.8, 79.42, 79.38, 79.2, 78.4, 48.0, 47.1, 46.8, 46.0, 45.9, 45.7, 40.0, 39.7, 39.2, 34.5, 33.7, 31.1, 30.5, 28.5, 28.42, 28.35, 27.7, 27.3, 25.3, 25.14, 25.11, 18.9, 18.84, 18.76, 18.67, 17.5, 17.0, 16.8; HRMS (ES+) calcd for $C_{32}H_{50}N_2O_7NaS$ (M + Na) 629.3236, found 629.3194.



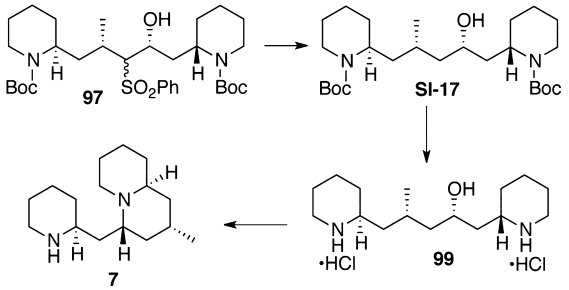
Hydroxy Sulfones 97 and 96. To a solution of keto sulfone **SI-16** (4.0 mg, 6.6 μmol) in MeOH (0.12 mL) at rt was added $NaBH_4$ (2.5 mg, 6.6 μmol). After 1 h, the reaction was quenched with aq NH_4Cl (5 mL) and extracted with DCM (3 × 5 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 30−80% ether/pentane to obtain a 1.0:1.5 mixture (4.0 mg, 6.5 μmol, 99%) of **97** and **96** respectively as colorless oil.



Cyclic Sulfone 98. To a solution of sulfone **56** (20 mg, 52.4 μmol) in THF (0.39 mL) at −78 °C was added LDA[9] (0.131 mL, 0.131 mmol, 1.0 M in THF/hexanes). After 20 min, the reaction mixture was warmed to 0 °C. After 15 min, the reaction was quenched with satd aq NH_4Cl (5 mL) and extracted with ether (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 70−80% EtOAc/hexane to obtain **98** (14 mg, 45.5 μmol, 87%) as a colorless oil. $[\alpha]^{20}_D$ = +55.0° (*c* 0.2, $CHCl_3$); IR (neat) 3064, 2926, 2854, 1645, 1447, 1308, 1148, 1083, 688.6, 525.7, 458.0 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.4, 0.7 Hz, 2H), 7.67 (tt, *J* = 7.0, 1.4 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 2H), 4.72−4.74 (m, 1H), 3.75 (t, *J* = 1.4 Hz, 1H), 3.32−3.35 (m, 1H), 3.06−3.07 (m, 1H), 2.44 (td, *J* = 13.3, 2.8 Hz, 1H), 2.32 (ddd, *J* = 14.7, 11.2, 4.2 Hz, 1H), 1.86−1.88 (m, 1H), 1.74−1.80 (m, 3H), 1.42−1.50 (m, 3H), 1.13 (d, *J* = 7.7 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 160.3, 139.9, 133.7, 128.93, 128.85, 72.3, 53.3, 42.8, 33.8, 32.2, 25.5, 25.3, 24.2, 18.9; HRMS (ES+) calcd for $C_{16}H_{22}NO_3S$ (M + H) 308.1320, found 308.1309.



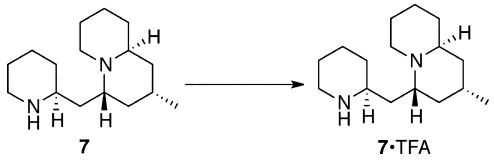
Amide 12. To a solution of sulfone **98** (8.5 mg, 28 μmol) in dry MeOH (0.55 mL) at 0 °C was added Na_2HPO_4 (199 mg, 1.4 mmol) followed by 5% Na/Hg (318 mg, 0.69 mmol). After 20 min, the reaction was quenched with satd aq NH_4Cl (2 mL), diluted with EtOAc (5 mL) and filtered through Celite and extracted with EtOAc (3 × 5 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 40−60% EtOAc/hexanes to obtain the known amide **12**[14a] (4.0 mg, 23.9 μmol, 86%) as a colorless oil. $[\alpha]^{20}_D$ = −24.4° (*c* 0.32, $CHCl_3$); IR (neat) 2929, 2855, 1636, 1463, 1447, 1279, 1258, 1103 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 4.79 (dq, *J* = 12.6, 2.1 Hz, 1H), 3.34−3.38 (m, 1H), 2.47 (ddd, *J* = 16.8, 4.2, 2.1 Hz, 1H), 2.43 (td, *J* = 12.6, 2.8 Hz, 1H), 2.06−2.10 (m, 1H), 2.02 (dd, *J* = 16.8, 9.1 Hz, 1H), 1.89−1.92 (m, 1H), 1.61−1.69 (m, 4H), 1.51−1.58 (m, 1H), 1.45−1.49 (m, 1H), 1.37−1.45 (m, 1H), 1.00 (t, *J* = 6.3 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 168.5, 55.6, 43.0, 40.6, 36.9, 33.6, 25.4, 25.1, 24.5, 20.5; HRMS (ES+) calcd for $C_{10}H_{18}NO$ (M + H) 168.1388, found 168.1394.



Cermizine D (7). To a solution of sulfone **97** (44.2 mg, 73.0 μmol) in EtOH (1.46 mL) at 80 °C was added skeletal Raney Ni (1.77 g, 3 portions) portionwise over a period of 7 h. After an additional 8 h, the reaction mixture was cooled down to rt and filtered through Celite. The solvent was removed *in vacuo* to obtain the crude alcohol **SI-17**, which was unstable to purification and carried on as crude.

To a solution of the crude alcohol **SI-17** (~73 μmol) in MeOH (1.53 mL) was added TMSCl (133.3 mg, 0.156 mL, 1.23 mmol). After 4 h, the solvent was removed *in vacuo* to obtain the crude **99**. The crude **99** is taken to the next step.

To a solution of crude alcohol **99** (~73 μmol) in DCM (2.1 mL) at 0 °C were added sequentially PPh_3 (28.8 mg, 0.11 mmol), CBr_4 (36.3 mg, 0.11 mmol), and Et_3N (44.3 mg, 0.06 mL, 0.438 mmol). The solution was slowly warmed to rt over a period of 15 min. After 3 h, the solvent was removed *in vacuo* and purified by chromatography over silica gel, by eluting with (2:4:94) to (2:10:88) ratio of NH_4OH/MeOH/$CHCl_3$ to afford cermizine D (7)[10] (11.0 mg, 0.044 mmol, 60% over 3 steps) as a pale yellow oil. $[\alpha]^{20}_D$ = +40.8° (*c* 0.90, MeOH); IR (neat) 3360, 3294, 2926, 2853, 1639, 1455, 1442, 1373, 1121 cm^{-1}; ^1H NMR (700 MHz, MeOH-d_4) δ 3.39 (br d, *J* = 15.4 Hz, 1H), 3.15−3.19 (m, 1H), 3.03−3.07 (m, 2H), 2.59−2.68 (m, 3H), 2.01 (qd, *J* = 12.6, 4.2, 1H), 1.78−1.90 (m, 5H), 1.62−1.74 (m, 3H), 1.53−1.60 (m, 2H), 1.43−1.49 (m, 2H), 1.40 (td, *J* = 12.6, 5.6 Hz, 1H), 1.19−1.24 (m, 3H), 1.12 (ddd, *J* = 14.0, 9.8, 4.2 Hz, 1H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.83 (q, *J* = 11.9 Hz, 1H); ^{13}C NMR (175 MHz, MeOH-d_4) δ 57.7, 53.5, 48.6, 46.2, 39.9, 39.8, 39.0, 33.2, 25.3, 25.1, 24.3, 24.0, 21.3, 18.2; HRMS (EI+) calcd for $C_{16}H_{30}N_2$ (M+) 250.2409, found 250.2414.



TFA Salt of Cermizine-D (7·TFA). To a solution of cermizine D (7) (2.0 mg, 8.0 μmol) in dry DCM (0.1 mL) was added TFA (3 drops) at 0 °C. After 10 min, the solvent was removed *in vacuo* to afford the cermizine D bis-TFA salt (**7·TFA**)[14c] (3.8 mg, 8.0 μmol, 99%) as pale yellow oil. $[\alpha]^{20}_D$ = +16.8° (*c* 0.41, MeOH) {lit.[11] $[\alpha]^{20}_D$ = +24.2° (*c* 0.50, MeOH)}; IR (neat) 3390, 2960, 2925, 2853, 1674,

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1455, 1430, 1202, 1139, 799, 721 cm^{-1}; ^1H NMR (700 MHz, MeOH-d_4) δ 3.96 (br t, J = 11.2 Hz, 1H), 3.71−3.74 (m, 2H), 3.45 (br d, J = 6.3 Hz, 1H), 3.35−3.37 (m, 1H), 3.18 (td, J = 13.3, 3.5 Hz, 1H), 3.08 (td, J = 14.2, 2.8 Hz, 1H), 2.33 (ddd, J = 11.2, 9.1, 3.5 Hz, 1H), 2.16−2.25 (m, 2H), 1.93−2.06 (m, 5H), 1.55−1.85 (m, 10H), 1.02 (m, 1H), 1.02 (d, J = 6.3 Hz, 3H); ^{13}C NMR (175 MHz, MeOH-d_4) δ 62.5, 54.2, 51.5, 50.0, 46.0, 39.1, 38.1, 36.4, 31.0, 25.0, 24.7, 23.7, 23.2, 23.1, 21.6, 18.6; HRMS (EI+) calcd for $C_{16}H_{31}N_2$ (M + H) 251.2487, found 251.2478.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C spectra for all new compounds; X-ray crystallographic data (in CIF format) for compound **66**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Bödeker, K. *Justus Liebigs Ann. Chem.* **1881**, *208*, 363−367.

(2) (a) Ayer, W. A.; Trifonov, S. Lycopodium alkaloids. In *Alkaloids*; Academic Press: New York, 1994; Vol. *45*, pp 233−266. (b) Ayer, W. A.; Ma, Y.-T.; Liu, J.-S.; Huang, M.-F.; Shultz, L. W.; Clardy, J. *Can. J. Chem.* **1994**, *72*, 128−130. (c) Tori, M.; Shimoji, T.; Takaoka, S.; Nakashima, K.; Sono, M.; Ayer, W. A. *Tetrahedron Lett.* **1999**, *40*, 323−324. (d) Tori, M.; Shimoji, T.; Shimura, E.; Takaoka, S.; Nakashima, K.; Sono, M.; Ayer, W. A. *Phytochemistry* **2000**, *53*, 503−509.

(3) (a) Hirasawa, Y.; Kobayashi, J. *Heterocycles* **2009**, *77*, 679−729. (b) Kubota, T.; Yahata, H.; Yamamoto, S.; Hayashi, S.; Shibata, T.; Kobayashi, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3577−3580. (c) Ishiuchi, J.; Kubota, T.; Hayashi, S.; Shibata, T.; Kobayashi, J. *Tetrahedron Lett.* **2009**, *50*, 4221−4224. (d) Ishiuchi, K.; Kodama, S.; Kubota, T.; Hayashi, S.; Shibata, T.; Kobayashi, J. *Chem. Pharm. Bull.* **2009**, *57*, 877−881. (e) Ishiuchi, K.; Kubota, T.; Hayashi, S.; Shibata, T.; Kobayashi, J. *Tetrahedron Lett.* **2009**, *50*, 6534−6536. (f) Ishiuchi, K.-I.; Kubota, T.; Ishiyama, H.; Hayashi, S.; Shibata, T.; Kobayashi, J. *Tetrahedron Lett.* **2011**, *52*, 289−292. (g) Ishiuchi, K.; Kubota, T.; Ishiyama, H.; Hayashi, S.; Shibata, T.; Mori, K.; Obara, Y.; Nakahata, N.; Kobayashi, J. *Bioorg. Med. Chem.* **2011**, *19*, 749−753.

(4) For comprehensive reviews of the *lycopodium* alkaloid family, see: (a) Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752−772. (b) Kitajima, M.; Takayama, H. *Top. Curr. Chem.* **2012**, *309*, 1−32.

(5) (a) Tanret, C. *Compt. Rend.* **1878**, *86*, 1270−71. (b) Tanret, C. *Compt. Rend.* **1880**, *90*, 695−98. (c) Hess, K. *Ber. Dtsch. Chem. Ges.* **1917**, *50*, 368−379. (d) Hess, K.; Eichel, A. *J. Chem. Soc., Abs.* **1918**, *114(I)*, 33. (e) Beets, M. G. J. *Recl. Trav. Chim. Pays-Bas.* **1943**, *62*, 553−556. (f) Galinovsky, F.; Vogl, O.; Weiser, R. *Monatsh. Chem.* **1952**, *83*, 114−122.

(6) King, J. A.; Hofmann, V.; McMillan, F. H. *J. Org. Chem.* **1951**, *16*, 1100−1110. Bowman, R. E.; Evans, D. D. *J. Chem. Soc.* **1956**, 2553−2555.

(7) Early total syntheses: (a) Beyerman, H. C.; Maat, L. *Recl. Trav. Chim. Pays-Bas* **1963**, *82*, 1033−39. (b) Beyerman, H. C.; Maat, L. *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 385−88. (c) Beyerman, H. C.; Maat, L.; van Veen, A.; Zweistra, A. *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 1367−79.

(8) Total syntheses since 2005: (a) Turcaud, S.; Martens, T.; Sierecki, E.; Perard-Viret, J.; Royer, J. *Tetrahedron Lett.* **2005**, *46*, 5131−5134. (b) Carlson, E. C.; Rathbone, L. K.; Yang, H.; Collett, N. D.; Carter, R. G. *J. Org. Chem.* **2008**, *73*, 5155−5158. (c) Cheng, G.; Wang, X.; Su, D.; Liu, H.; Liu, F.; Hu, Y. *J. Org. Chem.* **2010**, *75*, 1911−1916. (d) Beng, T. K.; Gawley, R. E. *J. Am. Chem. Soc.* **2010**, *132*, 12216−12217. (e) Liu, J. D.; Chen, Y. C.; Zhang, G. B.; Li, Z. Q.; Chen, P.; Du, J. Y.; Tu, Y. Q.; Fana, C. A. *Adv. Synth. Catal.* **2011**, *353*, 2721−2730. (f) Monaco, M. R.; Renzi, P.; Schietroma, D. M. S.; Bella, M. *Org. Lett.* **2011**, *13*, 4546−4549. (g) Bosque, I.; González-Goḿez, J. C.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2012**, *77*, 780−784. (h) Chiou, W. H.; Chen, G. T.; Kao, C. L.; Gao, Y. K. *Org. Biomol. Chem.* **2012**, *10*, 2518−2520.

(9) (a) Matsunaga, T.; Kawasaki, I.; Kaneko, T. *Tetrahedron Lett.* **1967**, *8*, 2471−2473. (b) Quick, J.; Meltz, C. *J. Org. Chem.* **1979**, *44*, 573−578.

(10) Morita, H.; Hirasawa, Y.; Shinzato, T.; Kobayashi, J. *Tetrahedron* **2004**, *60*, 7015−7023.

(11) (a) Slosse, P.; Hootele, C. *Tetrahedron Lett.* **1978**, 397−398. (b) Slosse, P.; Hootele, C. *Tetrahedron Lett.* **1979**, 4587−4588. (c) Slosse, P.; Hootele, C. *Tetrahedron* **1981**, *37*, 4287−4292.

(12) Fuji, K.; Yamada, T.; Fujita, E.; Murata, H. *Chem. Pharm. Bull.* **1978**, *26*, 2515−2521.

(13) Marion, L.; Manske, R. H. F. *Can. J. Res.* **1948**, *26*, 1−2.

(14) Cermizine C and Senepodine G: (a) Snider, B.; Grabowski, J. F. *J. Org. Chem.* **2007**, *72*, 1039−1042. (b) Amat, M.; Griera, R.; Fabregat, R.; Bosch, J. *Tetrahedron: Asymm.* **2008**, *19*, 1233−1236. (c) Nishikawa, Y.; Kitajima, M.; Kogure, N.; Takayama, H. *Tetrahedron* **2009**, *65*, 1608−1617. (d) Cui, L.; Peng, Y.; Zhang, L. *J. Am. Chem. Soc.* **2009**, *131*, 8394−8395. (e) Cheng, G.; Wang, X.; Su, D.; Liu, H.; Liu, F.; Hu, Y. *J. Org. Chem.* **2010**, *75*, 1911−1916. (f) Taber, D. F.; Guo, P.; Pirnot, M. T. *J. Org. Chem.* **2010**, *75*, 5737−5739. (g) Bosque, I.; González-Goḿez, J. C.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2012**, *77*, 780−784.

(15) Myrtine: (a) Comins, D. L.; LaMunyon, D. H. *J. Org. Chem.* **1992**, *57*, 5807−5809. (b) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *J. Org. Chem.* **1995**, *60*, 717−722. (c) Gardette, D.; Mialhe, Y. G.; Gramain, J. C.; Perrin, B.; Remuson, R. *Tetrahedron: Asymmetry* **1998**, *9*, 1823−1828. (d) Back, T. G.; Hamilton, M. D.; Lim, V. J. J.; Parvez, M. *J. Org. Chem.* **2005**, *70*, 967−972. (e) Davis, F. A.; Xu, H.; Zhang, J. *J. Org. Chem.* **2007**, *72*, 2046−2052. (f) Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Org. Biomol. Chem.* **2008**, *6*, 3464−3466. (g) Amorde, S. A.; Jewett, I. T.; Martin, S. F. *Tetrahedron* **2009**, *65*, 3222−3231. (h) Fustero, S.; Moscardo, J.; Rosello, M. S.; Flores, S.; Guerola, M.; Pozo, C. *Tetrahedron* **2011**, *67*, 7412−7417.

(16) Lasubines I and II: (a) Comins, D. L.; LaMunyon, D. H. *J. Org. Chem.* **1992**, *57*, 5807−5809. (b) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *J. Org. Chem.* **1995**, *60*, 717−722. (c) Ma, D.; Zhu, W. *Org. Lett.* **2001**, *3*, 3927. (d) Back, T. G.; Hamilton, M. D. *Org. Lett.* **2002**, *4*, 1779−1781. (e) Back, T. G.; Hamilton, M. D.; Lim, V. J. J.; Parvez, M. *J. Org. Chem.* **2005**, *70*, 967−972. (f) Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 12370−12371. (g) Mancheno, O. G.; Arrayas, R. G.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2007**, *72*, 10294−10297.

(17) Nishikawa, Y.; Kitajima, M.; Takayama, H. *Org. Lett.* **2008**, *10*, 1987−1990.

(18) Veerasamy, N.; Carlson, E. C.; Carter, R. G. *Org. Lett.* **2012**, *14*, 1596−1599.

(19) (a) Morita, H.; Hirasawa, Y.; Kobayashi, J. *J. Org. Chem.* **2003**, *68*, 4563−4566. (b) Collett, N. D.; Carter, R. G. *Org. Lett.* **2011**, *13*, 4144−4147.

(20) (a) Yang, H.; Carter, R. G.; Zakharov, L. N. *J. Am. Chem. Soc.* **2008**, *130*, 9238−9239. (b) Yang, H.; Carter, R. G. *J. Org. Chem.* **2010**, *75*, 4929−4938. (c) Saha, M.; Carter, R. G. *Org. Lett.* **2013**, *15*, 736−739.

(21) (a) Fustero, S.; Jiménez, D.; Moscardó, J.; Catalán, S.; del Pozo, C. *Org. Lett.* **2007**, *9*, 5283−5286. (c) Fustero, S.; Moscardo, J.; Jimenez, D.; Peerez-Carrion, M. D.; Sanchez-Rosesllo, M.; del Pozo, C. *Chem.—Eur. J.* **2008**, *14*, 9868−9872.

(22) Metal-catalyzed: (a) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959−8960. (b) Taylor, M. S.; Zalatan, D.; Lerchner, A. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 1313−1317. (c) Gandelman, M.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 2393−2397. (d) Wagner, A. M.; Knezevic, C. E.; Wall, J. L.; Sun, V. L.; Buss, J. A.; Allen, L. T.; Wenzel, A. G. *Tetrahedron Lett.* **2012**, *53*, 833−836. (e) Hashimoto, T.; Maeda, Y.; Omote, M.; Nakatsu, H.; Maruoka, K. *J. Am. Chem. Soc.* **2010**, *132*, 4076−4077. (f) Zhong, C.; Wang, Y.-K.; Hung, Alvin, W.; Schreiber, S. L.; Young, D. W. *Org. Lett.* **2011**, *13*, 5556−5559. (g) Murru, S.; Gallo, A. A.; Srivastava, R. S. *J. Org. Chem.* **2012**, *77*, 7119−7123. Organocatalyzed: (h) Horstmann, T. E.; Guerin, D. J; Miller, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3635−3638. (i) Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328−9329. (j) Ibrahem, I.; Rios, R.; Vesely, J.; Zhao, G.-L.; Córdova, A. *Chem. Commun.* **2007**, 849−851. (k) Vesely, J.; Ibrahem, I.; Rios, R.; Zhao, G.-L.; Xu, Y.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 2193−2198. (l) Dinér, P.; Nielsen, M.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1983−1987. (m) Li, H.; Wang, J.; Xie, H.; Zu, L.; Jiang, W.; Duesler, E. N.; Wang, W. *Org. Lett.* **2007**, *9*, 965−968. (n) Wang, J.; Zu, L.; Xie, H.; Wang, W. *Synthesis* **2007**, 2576−2580. (o) Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2007**, 2065−2092. (p) Yoshitomi, Y.; Arai, H.; Makino, K.; Hamada, Y. *Tetrahedron* **2008**, *64*, 11568−11579. (q) Zhao, G.-L.; Rios, R.; Vesely, J.; Eriksson, L.; Cordova, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8468−8472. (r) Li, H.; Zu, L.; Xie, H.; Wang, J.; Wang, W. *Chem. Commun* **2008**, *43*, 5636−5638. (s) Arai, H.; Sugaya, N.; Sasaki, N.; Makino, K.; Lectard, S.; Hamada, Y. *Tetrahedron Lett.* **2009**, *50*, 3329−3332. (t) Lin, Q.; Meloni, D.; Pan, Y.; Xia, M.; Rodgers, J.; Shepard, S.; Li, M.; Galya, L.; Metcalf, B.; Yue, T.-Y.; Liu, P.; Zhou, J. *Org. Lett.* **2009**, *11*, 1999−2002. (u) Hong, L.; Sun, W.; Liu, C.; Wang, L.; Wang, R. *Chem.—Eur. J.* **2010**, *16*, 440−444. (v) Deiana, L.; Zhao, G.-L.; Lin, S.; Dziedzic, P.; Zhang, Q.; Leijonmarck, H.; Cordova, A. *Adv. Synth. Catal.* **2010**, *352*, 3201−3207. (w) Albrecht, L.; Jiang, H.; Dickmeiss, G.; Gschwend, B.; Hansen, S. G.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 9188−9196. (x) Yu, X.; Du, B.; Wang, K.; Zhang, J. *Org. Lett.* **2010**, *12*, 1876−1879. (y) Appayee, C.; Brenner-Moyer, S. E. *Org. Lett.* **2010**, *12*, 3356−3359. (z) Bae, J.-Y.; Lee, H.-J.; Youn, S.-H.; Kwon, S.-H.; Cho, C.-W. *Org. Lett.* **2010**, *12*, 4352−4355. (aa) Kriis, K.; Ausmees, K.; Pehk, T.; Lopp, M.; Kanger, T. *Org. Lett.* **2010**, *12*, 2230−2233. (bb) Volkova, Y. A.; Averina, E. B.; Grishin, Y. K.; Rybakov, V. B.; Kuznetsova, T. S.; Zefirov, N. S. *Tetrahedron Lett.* **2011**, *52*, 2910−2913. (cc) Deiana, L.; Dziedzic, P.; Zhao, G.-L.; Vesely, J.; Ibrahem, I.; Rios, R.; Sun, J.-L.; Cordova, A. *Chem.—Eur. J.* **2011**, *17*, 7904−7917. (dd) Sun, W.; Zhu, G.; Hong, L.; Wang, R. *Chem.—Eur. J.* **2011**, *17*, 13958−13962. (ee) Li, H.; Zhao, J.; Zeng, L.; Hu, W. *J. Org. Chem.* **2011**, *76*, 8064−8069. (ff) Yokosaka, T.; Hamajima, A.; Nemoto, T.; Hamada, Y. *Tetrahedron Lett.* **2012**, *53*, 1245−1248. (gg) Murru, S.; Gallo, A. A.; Srivastava, R. S. *J. Org. Chem.* **2012**, *77*, 7119−7123. (hh) Lin, H.; Tan, Y.; Sun, X.-W.; Lin, G.-Q. *Org. Lett.* **2012**, *14*, 3818−3821.

(23) Gerasyuto, A. I.; Hsung, R. P.; Sydorenko, N.; Slafer, B. *J. Org. Chem.* **2005**, *70*, 4248−4256.

(24) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794−797.

(25) Secondary amides have been somewhat explored: (a) Nagao, Y.; Dai, W.; Ochiai, M.; Shiro, M. *J. Org. Chem.* **1989**, *54*, 5211−5217. (b) Baxendale, I. R.; Ley, S. V.; Piutti, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2194−2197. (c) Baxendale, I. R.; Ley, S. V.; Nessi, M.; Piutti, C. *Tetrahedron* **2002**, *58*, 6285−6304. (d) Marino, J. P.; Rubio, M. B.; Cao, G.; de Dios, A. *J. Am. Chem. Soc.* **2002**, *124*, 13398−13399. (e) Nagata, T.; Nakagawa, M.; Nishida, A. *J. Am. Chem. Soc.* **2003**, *125*, 7484−7485. (f) Marino, J. P.; Cao, G. *Tetrahedron Lett.* **2006**, *47*, 7711−7713.

(26) Fonseca de Godoy, L. A.; Pilli, R. A. *Quim. Nova* **2010**, *33*, 2042−2045.

(27) Oishi, T.; Iwakuma, T.; Hirama, M.; Ito, S. *Synlett* **1995**, 404−406.

(28) Dai, M.; Zhang, X.; Khim, S.-K.; Schultz, A. G. *J. Org. Chem.* **2005**, *70*, 384−387.

(29) Ban, Y.; Kimura, M.; Oishi, T. *Chem. Pharm. Bull.* **1976**, *24*, 1490−1496.

(30) (a) Yang, H.; Carter, R. G. *Org. Lett.* **2008**, *10*, 4649−4652. (b) Yang, H.; Carter, R. G. *J. Org. Chem.* **2009**, *74*, 2246−2249. (c) Yang, H.; Carter, R. G. *J. Org. Chem.* **2009**, *74*, 5151−5156. (d) Yang, H.; Carter, R. G. *Tetrahedron* **2010**, *66*, 4854−4859. (e) Yang, H.; Carter, R. G. *Org. Lett.* **2010**, *12*, 3108−3111. (f) Yang, H.; Carter, R. G. *J. Org. Chem.* **2010**, *75*, 4929−4938. (g) Yang, H.; Mahapatra, S.; Cheong, P. Y.-H.; Carter, R. G. *J. Org. Chem.* **2010**, *75*, 7279−7290. (h) Yang, H.; Carter, R. G. *Synlett* **2010**, 2827−2838. (i) Yang, H.; Banerjee, S.; Carter, R. G. *Org. Biomol. Chem.* **2012**, *10*, 4851−4863. (j) Pierce, M.; Johnston, R. C.; Mahapatra, S.; Yang, H.; Carter, R. G.; Cheong, P. H.-Y. *J. Am. Chem. Soc.* **2012**, *134*, 13624−13631.

(31) Schaumann, E.; Mergardt, B.; Fittkau, S. *Synthesis* **1990**, 47−51.

(32) Please note that Snider and co-workers do not report a purification procedure for compound **26**; however, our spectral data ($^{1}H/^{13}C$ NMR) matched with their reported values. In our hands, the compound did prove to be somewhat unstable to column chromatography.

(33) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312−11313.

(34) (a) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164−15165. (b) Leitner, A.; Shekhar, S.; Pouy, M. J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15506−15514. (c) Tosatti, P.; Nelson, A.; Marsden, S. P. *Org. Biomol. Chem.* **2012**, *10*, 3147−3163.

(35) (a) Gnamm, C.; Krauter, C. M.; Brödner, K.; Helmchen, G. *Chem.—Eur. J.* **2009**, *15*, 2050−2054. (b) Gnamm, C.; Brödner, K.; Krauter, C. M.; Helmchen, G. *Chem.—Eur. J.* **2009**, *15*, 10514−10532.

(36) For earlier reports on the methodology, see: (a) Liu, G.; Cogan, D.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913−9914. (b) Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268−269. (c) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278−1284. For the application of this method to a closely related system, see: (d) Nielsen, L.; Lindsay, K. B.; Faber, J.; Nielsen, N. C.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 10035−10044.

(37) Yungui, P.; Heunging, P.; Zhengshung, X.; Tao, Y. *Lett. Org. Chem.* **2005**, *2*, 703−706.

(38) Evans, D. A.; Kim, A. S. *Handbook of Reagents for Organic Synthesis: Chiral Reagents for Asymmetric Synthesis*; Paquette, L. A., Ed.; John Wiley and Sons: New York, 2003; pp 57−68.

(39) See Supporting Information.

(40) (a) Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679−3681. (b) Martin, R.; Murruzzu, C.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **2005**, *70*, 2325−2328. (c) Coombs, T. C.; Lushington, G. H.; Douglas, J.; Aubé, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 2734−3737.

(41) Kitamura, M.; Nagai, K.; Hsiao, Y.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 549−552.

(42) (a) Baker, R.; O'Mahony, M. J.; Swain, C. *J. Chem. Soc., Chem. Commun.* **1985**, 1326−1328. (b) Baker, R.; O'Mahony, M. J.; Swain, C. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1623−1633.

(43) (a) Tseng, T.-C.; Wu, M.-J. *Tetrahedron: Asymmetry* **1995**, *6*, 1633−1640. (b) Raghavan, S.; Tony, K. A. *J. Org. Chem.* **2003**, *68*, 5002−5005. (c) Rana, N. K.; Singh, V. K. *Org. Lett.* **2011**, *13*, 6520−6523.

(44) (a) De Chirico, G.; Fiandanese, V.; Marchese, G.; Naso, F.; Sciacovelli, O. *J. Chem. Soc., Chem. Commun.* **1981**, 523−524. (b) Ichikawa, Y.; Isobe, M.; Masaki, H.; Kawai, T.; Goto, T. *Tetrahedron* **1987**, *43*, 4759−4766. (c) Dominguez, E.; Carretero, J. C. *Tetrahedron Lett.* **1993**, *34*, 5803−5806.

(45) Bos, P. H.; Macía, B.; Fernández, Ibáñez; Minnard, A. J.; Feringa, B. L. *Org. Biomol. Chem.* **2010**, *8*, 47−49.

(46) Truchot, C.; Wang, Q.; Sasaki, A. *Eur. J. Org. Chem.* **2005**, 1765−1776.

(47) Alonso, D. A.; Nájera, C. *Org. React.* **2008**, *72*, 367−656.

(48) Liu, Y.; Jacobs, H. K.; Gopalan, A. S. *Tetrahedron* **2011**, *67*, 2206−2214.
(49) Zhang, J.; Zhang, Y.; Zhang, Y.; Herndon, J. W. *Tetrahedron* **2003**, *59*, 5609−5616.
(50) Michel, P.; Rassat, A. *J. Org. Chem.* **2000**, *65*, 8908−8918.
(51) Kulkarni, S. J.; Pedduri, Y.; Chittiboyina, A. G.; Avery, M. A. *J. Org. Chem.* **2010**, *75*, 3113−3116.
(52) Jin, Y.; Liu, Y.; Wang, Z.; Kwong, S.; Xu, Z.; Ye, T. *Org. Lett.* **2010**, *12*, 1100−1103.
(53) Rosser, E. M.; Morton, S.; Ashton, K. S.; Cohen, P.; Hulme, A. N. *Org. Biomol. Chem.* **2004**, *2*, 142−149.
(54) Procedure to make $PhSCH_2I$: To a solution of $PhSCH_2Cl$ (500 mg, 0.42 mL, 3.2 mmol) in acetone (2.7 mL) was added NaI (465 mg, 3.1 mmol), and the reaction was covered with aluminum foil. After 12 h, the reaction mixture was poured into ether (10 mL) and washed with satd aq sodium thiosulfate solution (15 mL), satd aq $NaHCO_3$ solution (15 mL), and brine (15 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and used immediately as the compound was highly unstable. Trost, B. M.; King, S. A. *J. Am. Chem. Soc.* **1990**, *112*, 408−422.
(55) Procedure to make LDA: To a solution of diisopropylamine (607 mg, 0.848 mL, 6.0 mmol) in THF (2.75 mL) at −78 °C was added ^{n}BuLi (2.4 mL, 6.0 mmol, 2.5 M solution in hexanes). After 5 min, the white slurry was warmed to −10 °C. After 15 min, the LDA solution (1.0 M in THF/hexanes) was used for the reaction.