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Unified Synthesis of 10-Oxygenated *Lycopodium* Alkaloids: Impact of C_{10}-Stereochemistry on Reactivity

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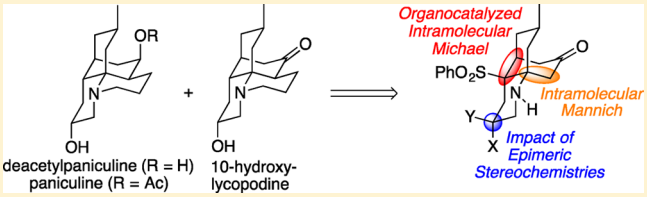
Supporting Information

ABSTRACT: The pronounced impact of the C_{10} stereochemistry on the successful construction of a polycyclic *Lycopodium* alkaloid scaffold has been explored. A wide range of reaction conditions and functionality were investigated to control a keto sulfone Michael addition to construct the C_7–C_{12} linkage. An unexpected, overriding impact of the C_{10} stereochemistry in stereoselectivity and reaction rate in the Michael addition was observed. Furthermore, divergent reactivity of a conformationally accelerated, intramolecular Mannich cyclization based on the C_{10} stereochemistry was discovered. The successful execution of this synthetic route resulted in the total synthesis of all three known 10-oxygenated *Lycopodium* alkaloids: 10-hydroxylycopodine, paniculine, and deacetylpaniculine.



INTRODUCTION

Isolated from multiple different regions throughout the globe, the *Lycopodium* alkaloids have captured the attention of the synthetic community due to their diverse and challenging structural connectivity.[1] Our laboratory has a long-standing interest in the family that was initially inspired by himeradine A (**1**);[2] however, it has led us to develop systematic methods for accessing wide swaths of *Lycopodium* alkaloid architectures (Figure 1). We first developed an organocatalyzed method for accessing piperidine and pyrrolidine ring systems, which was applied to the enantioselective synthesis of pelletierine (**2**), the core building block for the *Lycopodium* alkaloids.[3] Subsequently, we utilized this technology to develop routes for accessing quinolizidine-type scaffolds and for the total synthesis of cermizine D (**5**) as well as the formal synthesis of cermizine C (**3**) and senepodine G (**4**).[4] These cermizine alkaloids have attracted attention from multiple laboratories.[5−7] Building on the knowledge gained in the cermizine D (**5**) campaign, we later reported the synthesis of the eastern half of himeradine A.[8] Subsequent to our original report, Shair and co-workers reported an elegant total synthesis of himeradine A.[9]

In 2008, we reported the first enantioselective total synthesis of the parent member of the *Lycopodium* family, lycopodine (**6**), through a series of intramolecular reactions that zipped up an acyclic backbone (Figure 2).[10] Lycopodine (**6**) has attracted

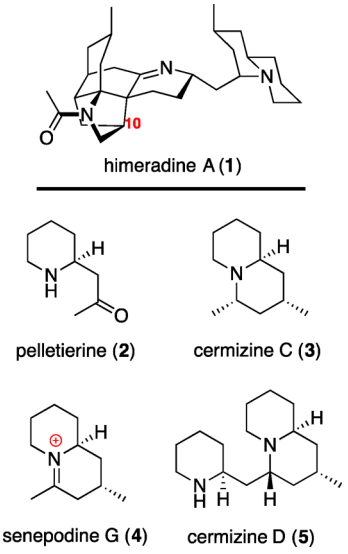


Figure 1. Himeradine A and select piperidine-based and quinolizidine-based *Lycopodium* alkaloids.

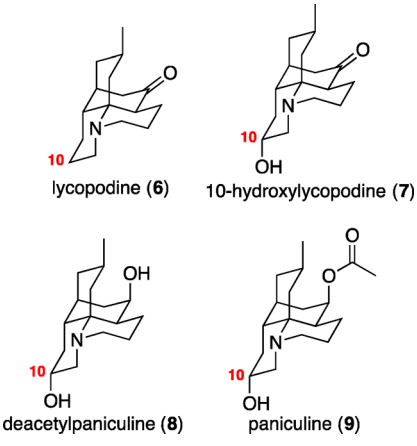


Figure 2. Lycopodine and C_{10}-hydroxylated *Lycopodium* alkaloids.

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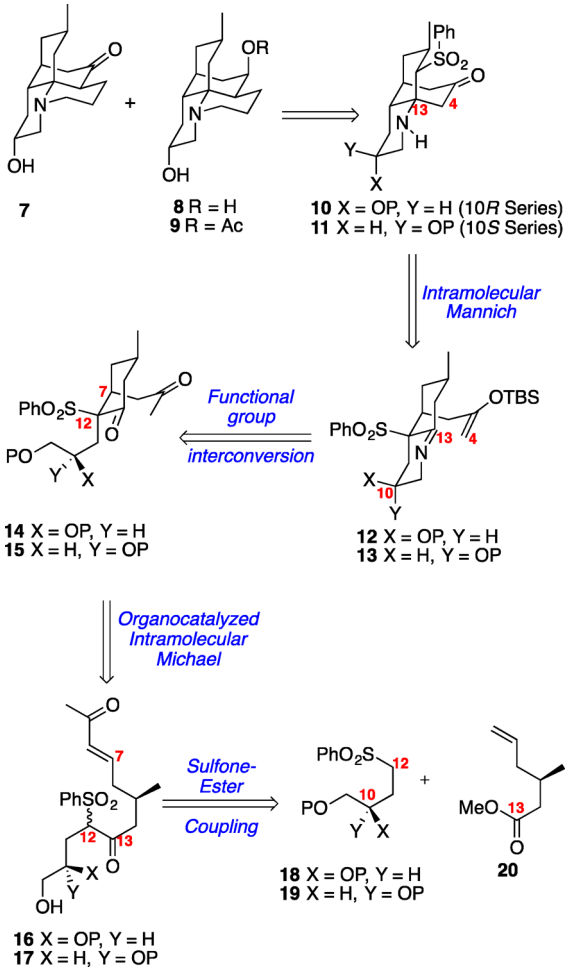
considerable synthetic attention[11−18] since its first syntheses in back-to-back communications by Stork[19] and Ayer[20] in 1968. Other related lycopodine-based natural products such as clavoloine[21−23] and 7-hydroxylycopodine[24] have also garnered interest from the synthetic community. On the basis of our continued focus toward himeradine (**1**), functionalization at the C_{10} position of the lycopodine scaffold was a prerequisite for future campaigns. Isolated from a Chilean club moss *Lycopodium confertum* and *Lycopodium paniculatum*,[25,26] 10-hydroxylycopodine (**7**), deacetylpaniculine (**8**), and paniculine (**9**) are the known members of the *Lycopodium* alkaloids that possess such functionalization. We reported a unified approach to all C_{10} hydroxylated lycopodines in a preliminary communication in 2013.[27] This synthetic effort provided a unique opportunity for the synthetic chemist, as the spectroscopic data obtained from our work filled in the missing pieces in the isolation work that had, in some cases, been published over 40 years ago. In this article, we now disclose a full account of our work toward the C_{10}-oxygenated *Lycopodium* alkaloids 10-hydroxylycopodine (**7**), deacetylpaniculine (**8**), and paniculine (**9**).

RESULTS AND DISCUSSION

Our unified retrosynthetic approach to the 10-hydroxylated *Lycopodium* alkaloids is shown below in Scheme 1. Compounds **7**−**9** could be accessed from a common intermediate which in turn would arise from tandem intramolecular Mannich reaction/1,3-sulfone transposition. This protocol serendipitously arose from our prior work on the total synthesis of lycopodine[10] where we observed an unprecedented 1,3-migration of the sulfone moiety during the intramolecular Mannich process. This transposition likely helped to facilitate the Mannich reaction through locking the aza-decalin type system in the reactive conformation. Through a detailed mechanistic study, we showed that the sulfone migration is likely reversible and location of the sulfone is only locked by the Mannich cyclization.[10] We were unsure at the start of this project if the presence of an additional substituent in the cyclic imine ring would have a positive or detrimental impact on this process (Scheme 1). After functional group manipulation of the enol ether **12**/**13** to the ketone **14**/**15**, we hypothesized that an intramolecular keto sulfone Michael reaction would provide access to the central cyclohexanone **14**/**15**. As with the Mannich process, the influence of the 10-oxygenation on the success of that process was unknown. Finally, the Michael precursor **16**/**17** should be readily accessible from a sulfone ester coupling of **18**/**19** and **20**. While we hoped that the required 10*R* stereochemistry would be compatible with the intramolecular Michael and Mannich reactions, we set out to explore the reactivities of both C_{10} epimers to better understand the inherent behavior in these systems. This systematic approach was intended to ensure that a complete understanding of the stereochemical impact of C_{10} on reactivity and stereoselectivity within this chemical scaffold could be fully explored. Additionally, we were cognizant that the 10*S* series could be useful toward our long-term aspirations of the total synthesis of himeradine (**1**).

Scheme 1. Unified Retrosynthetic Analysis toward the C-10 Oxygenated *Lycopodium* Alkaloids



Exploration of the Intramolecular Michael Addition Using the 10*R* Series. The majority of the synthetic sequence to access the 10*R* keto sulfone **30** has been reported previously (Scheme 2).[27] We have found that the yield for the initial displacement of the homoallylic bromide can be significantly improved by the addition of TBAI. Subsequent epoxidation set up the key Jacobsen's kinetic resolution[28] to provide the desired ring opened diol (*R*)-**25**.[29] Subsequent acetonide incorporation, keto sulfone formation[10,30,31] and the cross metathesis of alkene **27** yielded the Michael cyclization precursor **30**.

With efficient access to the Michael precursor **30**, we set out to explore the stereoselectivity in the key intramolecular, keto sulfone Michael reaction (Scheme 3). We first screened the diisopropylamine conditions which proved highly effective in the lycopodine series (eq 1).[10] We were disappointed to find out that not only was the diastereoselectivity under these conditions low, but also the chemical conversion was unexpectedly sluggish. One possible explanation for this reduced efficiency in the intramolecular Michael addition could be a mismatched relationship between the 10*R* stereochemistry and the C_{15} methyl moiety, which completely controls the diastereoselectivity of this process in the lycopodine series (eq 3).[10] Consequently, we suspected that our prolinesulfonamide-catalyzed conditions developed in parallel with our lycopodine work might improve this transformation (eq 4).[10b] We were gratified to find this prediction to indeed be operable with a modest improvement in diastereoselectivity (3:1 dr) and a dramatic improvement in chemical yield (85% overall yield for the separable mixture of diastereomers) (eq 2). The relative and absolute stereo-

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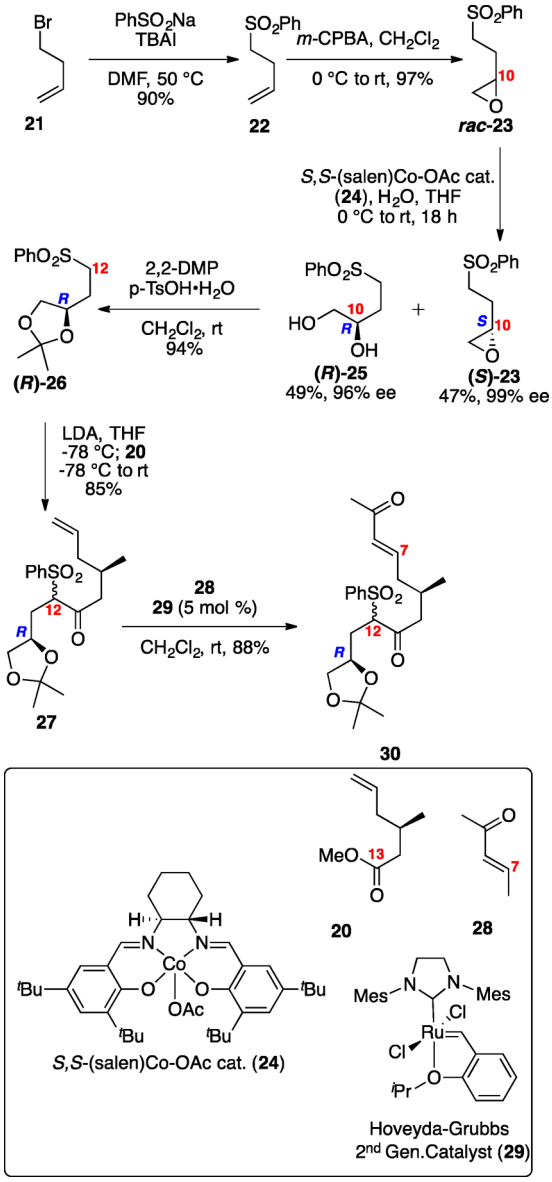
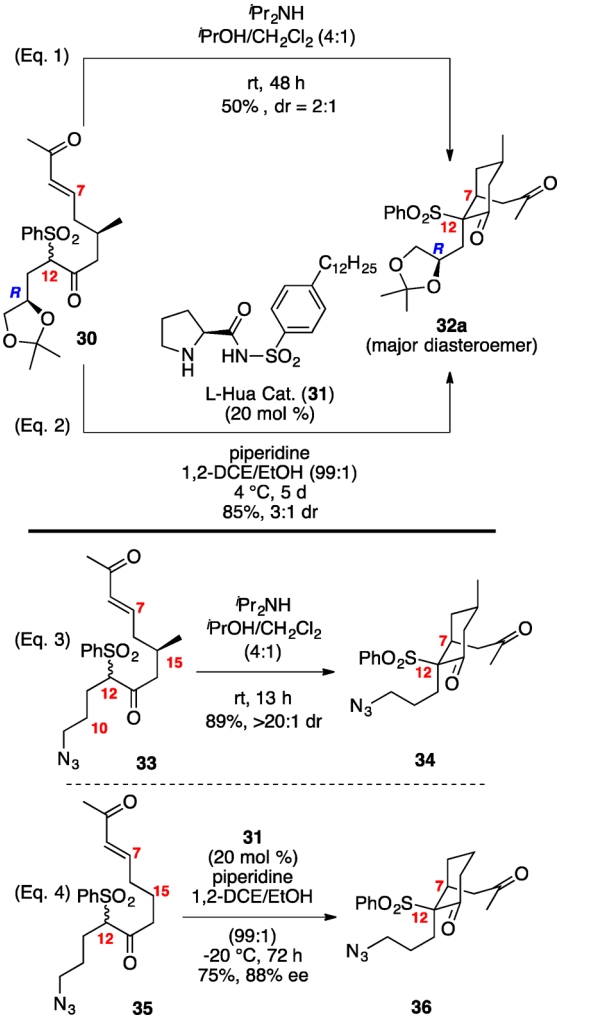
Scheme 2. Synthesis of the Keto Sulfone 30



Scheme 3. Preliminary Exploration of Intramolecular Keto Sulfone Michael Reaction



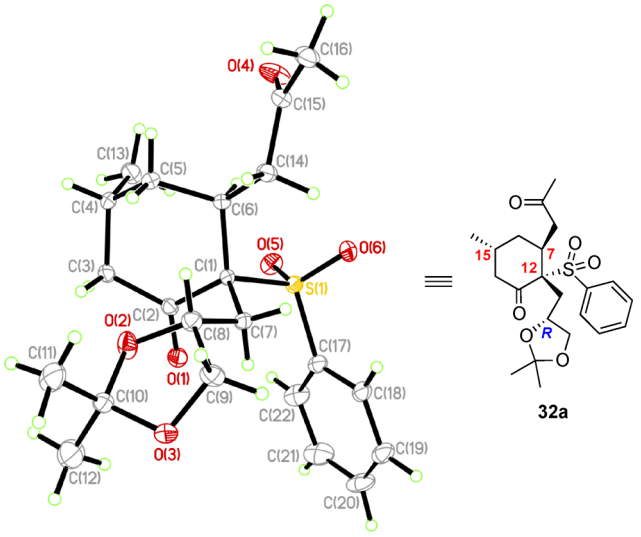


Figure 3. ORTEP representation of X-ray crystallographic data for **32a** (30% probability ellipsoids are plotted for non-hydrogen atoms).[27]

chemistry of this process was confirmed by X-ray crystallographic analysis of the major diastereomer **32a** (Figure 3).

We also explored the impact of variation of the organocatalyst on the stereoselectivity and reaction rate for this process (Table 1). Unfortunately, we were unable to discover alternate chiral organocatalyst-based conditions, which improved the selectivity in this process. Use of HCl or benzoic acid salts of the organocatalyst provided little impact (entries 1 and 2). Interestingly, the enantiomeric catalyst did not switch the stereoselectivity of the process but did lead to dramatic reduction in chemical yield (entry 3). Our Hua Cat II catalyst **37** proved slightly less effective as did the phenyl and triisopropylphenyl versions **38** and **39** (entries 4–6). We even explored the possibility of using proline (**40**) as the organocatalyst (entry 7). While the stereoselectivity and chemical yield were similar, the reaction rate was dramatically reduced, now requiring approximately 1 month to proceed to completion.

Exploration of the Intramolecular Michael Using the 10*S* Series. With a viable route established for accessing the 10*R* series, we built off that chemistry to develop a sequence for the C_{10} epimer (Scheme 4). The enantioenriched diol (*S*)-**25** could be accessed from the previously prepared epoxide (*S*)-**23**

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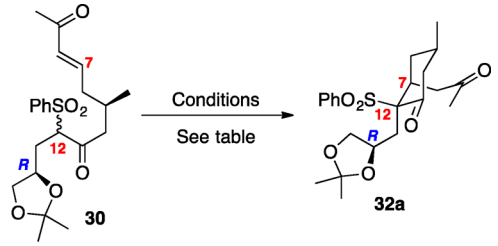
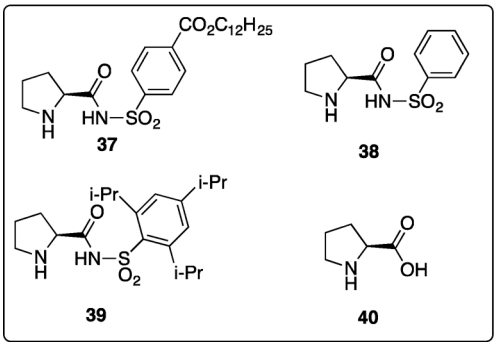
Table 1. Exploration of Organocatalyst Impact on 10*R* Intramolecular Keto Sulfone Michael Reaction





entry	catalyst	conditions	dr	yield (%)
1	**31**·HCl	DCE/EtOH (99:1), piperidine, 4 °C, 5 d	2.7:1	85
2	**31**·$PhCO_2H$	DCE/EtOH (99:1), piperidine, 4 °C, 6 d	2.6:1	81
3	*ent*-**31**	DCE/EtOH (99:1), piperidine, 4 °C, 2 d	1.5:1	<5
4	**37**	DCE/EtOH (99:1), piperidine, 4 °C, 5 d	2.2:1	72
5	**38**	DCE/EtOH (99:1), piperidine, 4 °C, 5 d	2.1:1	61
6	**39**	DCE/EtOH (99:1), piperidine, 4 °C, 7 d	1.8:1	46
7	**40**	DMF, rt, 21−30 d	2.7−3.5:1	81

through a two-step process (benzoate opening followed by hydrolysis) or via use of the enantiomeric Jacobsen catalyst (not shown). Acetonide formation as previously described, followed by sulfone ester coupling, gave the keto sulfone **41**. The cross metathesis proceeded slightly less efficiently than for the 10*R* series. We also prepared the di-TES ether version **43** in the 10*S* series to explore if variation of the protecting group would have an impact on the stereoselectivity.

We next screened a range of reaction conditions with achiral additives on the 10*S* series in order to probe its reactivity (Table 2). As we saw with the 10*R* series, a highly diastereoslective process could not readily be unearthed. The optimized lycopodine conditions (entry 1) gave the highest yield but low diastereoselectivity (1.5:1). Use of just isopropyl alcohol as solvent or reduced temperatures did not positively impact the reaction (entries 2 and 3). The omission of the alcohol additive inhibited the reaction (entry 4). Hexafluoro-2-propanol could be used as an additive to return reactivity but in reduced chemical efficiency (entry 5). DMF and MeCN both proved to be poor substitutes for the alcohol solvent (entries 6 and 7). Finally, the use of a secondary amine proved critical, as replacement of the diisopropylamine with Hunig's base completely inhibited the reaction (entry 8).

Given the success with the proline sulfonamide catalysis on the 10*R* series, we explored its potential with the epimeric keto

Scheme 4. Synthesis of the 10*S* Keto Sulfone Precursors 42 and 43

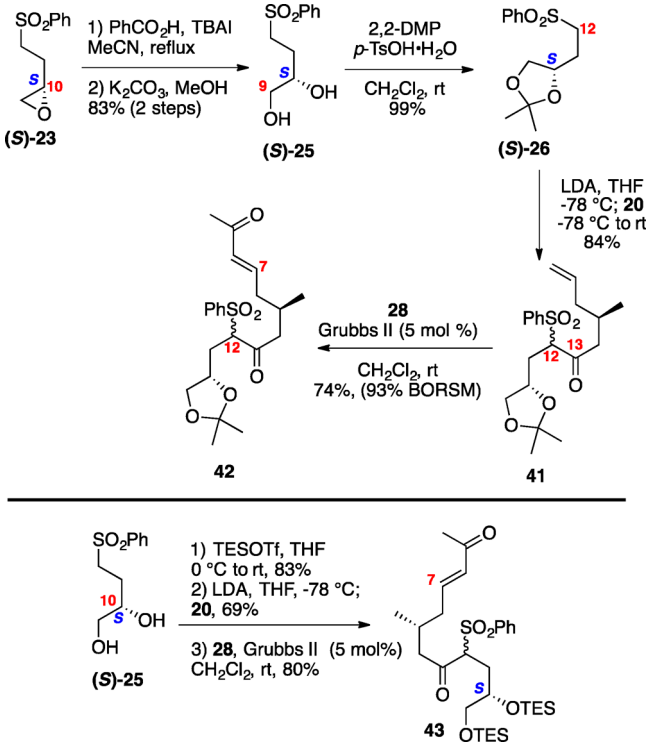
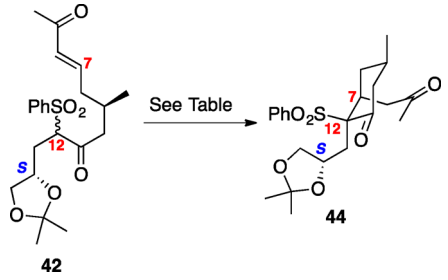


Table 2. Achiral Catalyst Screening for 10*S* Series Michael Reaction



entry	base	conditions	dr	yield (%)
1	*i*-Pr_2NH	*i*-PrOH:CH_2Cl_2 (4:1), rt, 68 h	1.5:1	85
2	*i*-Pr_2NH	*i*-PrOH, rt, 14 h	1.5:1	85
3	*i*-Pr_2NH	*i*-PrOH, 5 °C, 2 d	1.5:1	81
4	*i*-Pr_2NH	CH_2Cl_2, rt, 2 d	nd	<5
5	*i*-Pr_2NH	CH_2Cl_2/$(CF_3)_2CHOH$ (10 equiv), rt, 4 d	1.5:1	68
6	*i*-Pr_2NH	DMF/CH_2Cl_2 (4:1), rt, 3 d	1.3:1	59
7	*i*-Pr_2NH	CH_3CN/CH_2Cl_2 (4:1), rt, 4 d	1.2:1	55
8	*i*Pr_2NEt	*i*-PrOH:CH_2Cl_2 (4:1), rt	nd	NR

sulfone (Scheme 5). We did not observe a noticeable improvement in the reaction performance using our optimized Hua Cat conditions; however, the major diastereomer was readily separable from the minor diastereomer via column chromatography. It appears that use of Hua Cat generates a different collection of minor diastereomer(s) which is more easily removed from the major diastereomer than using amine base additive described in Table 2. Interestingly, the di-TES substrate **43** performed poorly under identical conditions (<20% yield, 1:1 dr). As before, we were able to unequivocally

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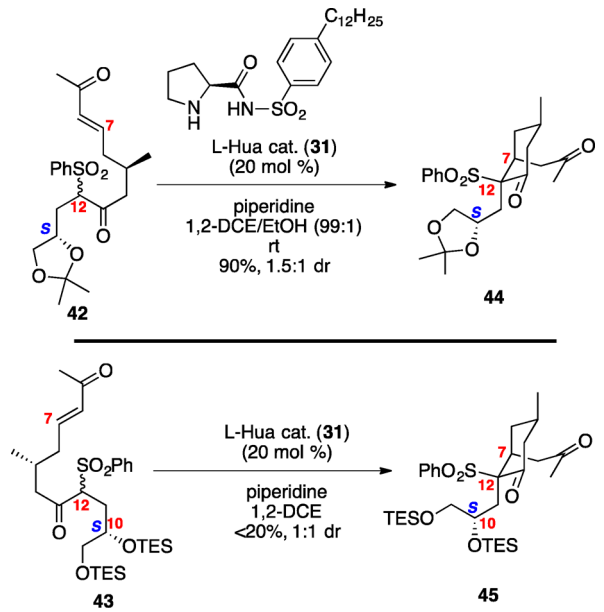
Scheme 5. Proline Sulfonamide-Catalyzed Michael Reaction on the 10*S* Series



establish the absolute stereochemistry of the major diastereomer **44** from the acetonide **42** via X-ray crystallographic analysis (Figure 4).

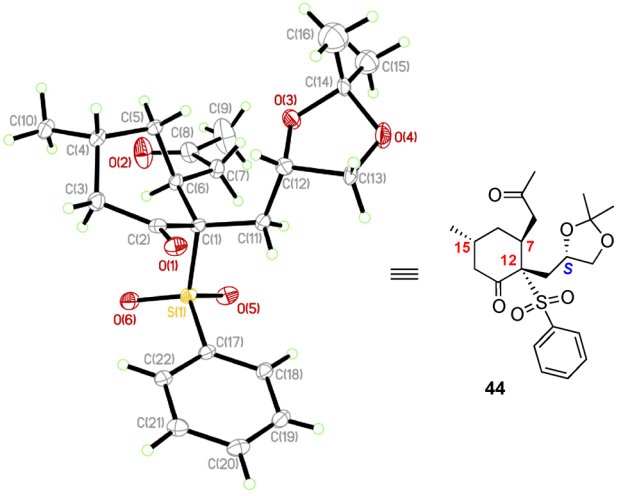
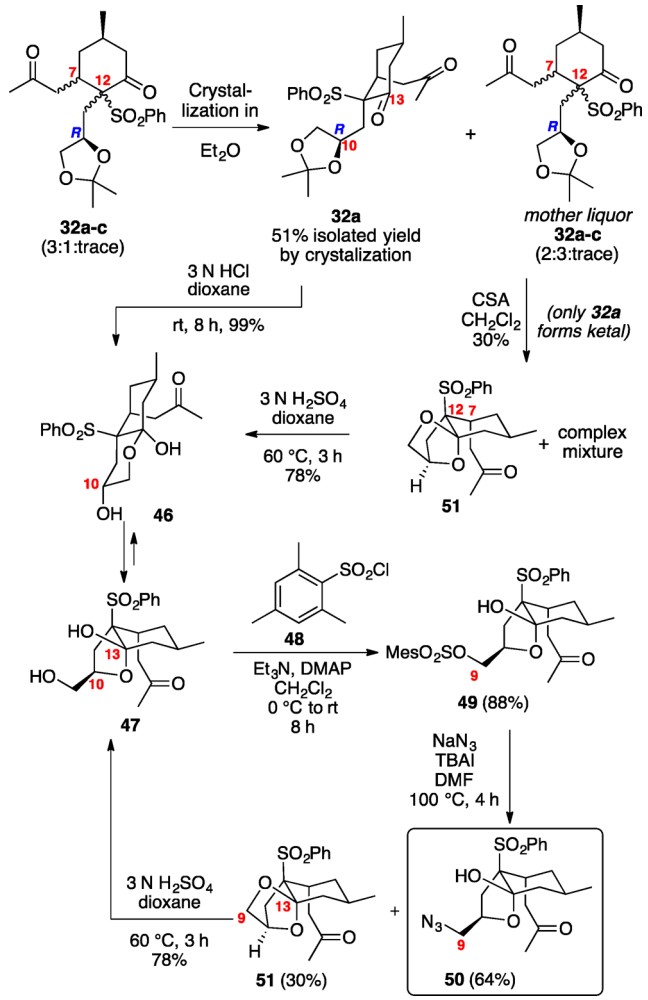


Figure 4. ORTEP representation of X-ray crystallographic analysis of major diasteromer **44** from organocatalyzed michael reaction (30% probability ellipsoids are plotted for non-hydrogen atoms).

Exploration of the Intramolecular Mannich Reaction Using the 10*R* Series. While these intramolecular keto sulfone Michael conditions did provide a reasonable overall yield and acceptable levels of diastereoselectivity, the material throughput in the process required tedious separation of the desired diastereomer **32a** from the minor isomers. We discovered that simple treatment of the mother liquor (Scheme 6) (containing the mixture of diastereomers **32a–c** after crystallization) with anhydrous acid selectively induced construction of ketal **51**. Only the major diastereomer **32a** from the Michael reaction was observed to form an internal ketal under these conditions (likely due to the stereochemistries of the minor diastereomers). The ketal **51** was

Scheme 6. Synthesis of the Methyl Ketone Azide 50



now easily separable from the other isomers **32b,c**, and this modified protocol greatly shortened the purification time. The ketal **51** could be easily hydrolyzed via sulfuric acid in dioxane to yield hemiketal **47**. We had previously reported hydrolysis of the ketal using HCl completed in 3 days;[27] however, our improved conditions using sulfuric acid at elevated temperatures dramatically shortened the reaction time to just 3 h. This same hemiketal **47** can be access directly by treatment of the crystallized Michael product **32a** with aqueous acid. Interestingly, the hemiketal **47** existed in dynamic equilibrium with its six-membered variant **46**; however, the desired five-membered version **47** could be effectively siphoned away through activation at C_9 with a sterically hindered sulfonate in good yield. During this process, a small amount of the unwanted ketal **51** (5–10%) was also formed. This ketal byproduct **51** was also produced in the subsequent azide formation step in greater amounts (30%). Despite considerable attempts to optimize this reaction by varying temperature, additives and concentration, we were unable to suppress this ketal formation. As noted previously, the ketal **51** can be easily reconverted into the hemiketal **47** through treatment with acid.

With the azide **50** in hand, we next focused on formation of the Mannich cyclization precursor (Scheme 7). Treatment of **50** with TBSOTf led to silyl enol ether formation with concomitant ring opening and silylation of the secondary alcohol to yield the bis-silyl ether **53** in high yield. Azide **53** was

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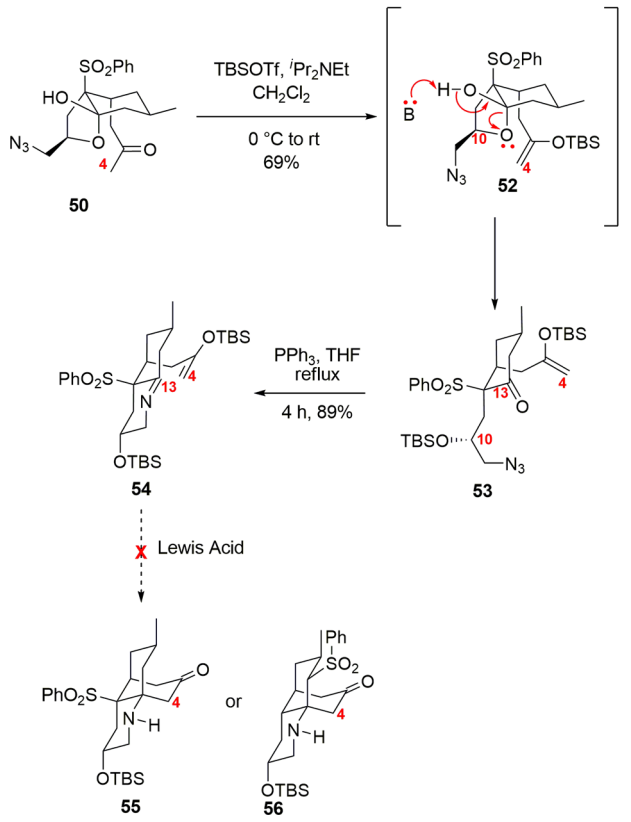
Scheme 7. First-Generation Attempted Mannich Cyclization

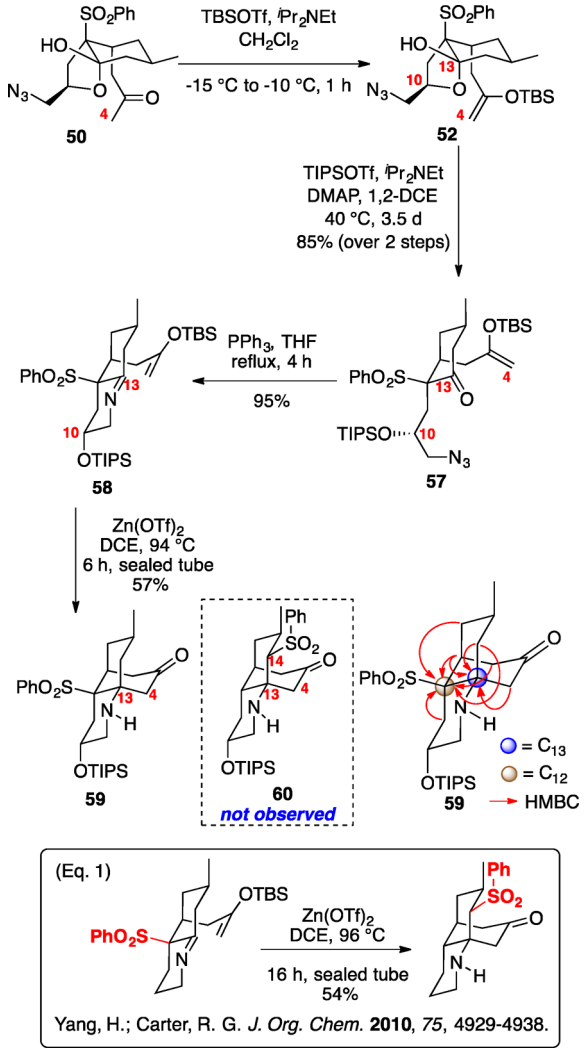


readily converted via an aza-Wittig reaction to the imine **54**. Unfortunately, treatment of **54** under a range of Lewis acids, including our $Zn(OTf)_2$ conditions that worked well for the C_{10}-deoxy series,[10] proved unsuccessful, with decomposition observed under a wide range of conditions. We are unsure of the reason for this divergence in reactivity; however, one possible hypothesis is that the Lewis acid conditions were incompatible with the TBS ether at C_{10}, which led to deprotection and subsequent decomposition.

We ultimately discovered that the C_{10} TIPS-protected alcohol could overcome this hurdle[27] (Scheme 8). After preparation of the necessary cyclization precursor **57**, we were gratified to find that submission of the imine **58** to a slightly modified version of the prior $Zn(OTf)_2$ conditions led to formation of desired tricycle **59** in moderate 57% yield. While this result was pleasing, we were surprised to find that the tandem sulfone migration that occurred in the C_{10}-deoxy series was not observed here (eq 1).[10] This structural assignment was confirmed by careful 2D NMR (Scheme 8). Interestingly, the C_{10}-OTIPS series appeared to be more reactive under comparable reaction conditions than the C_{10}-deoxy series. We hypothesized that the 10*R* substituent led to conformationally accelerated Mannich cyclization, in which this C_{10} substitution likely freezes out the desired aza-decalin conformation shown as **58** required for C−C bond formation, causing the cyclization to proceed at a rate faster than sulfone rearrangement.

Exploration of the Intramolecular Mannich Reaction Using the 10*S* Series. With a viable route to the tricycle established for the 10*R* series, we mapped that approach onto the epimeric 10*S* series (Scheme 9). Cleavage of the acetonide **44** could be readily accomplished with acetic acid to give the

Scheme 8. Synthesis of the 10*R* Tricycle 59



diol in its hemiketal form, and subsequent mesylation of the hemiketal proceeded smoothly to give the primary sulfonate **61**. Displacement of the mesylate moiety with sodium azide cleanly gave the desired azide compound **62** with no ketal formation. One possible explanation is that the epimeric C_{10} stereochemistry is not suitably positioned for intramolecular S_N2 displacement, as was seen in the 10*R* series. Given our knowledge gained with the silyl protecting groups at C_{10}, we chose to place a TIPS ether at that position. While this sterically demanding protecting group would further complicate the likelihood of success in the subsequent Mannich reaction due to further unfavorable interactions with the tertiary sulfone moiety, we were equally cognizant of the fact that variation of alcohol protecting groups has minimal impact on the cyclohexane *A*-values.[32] This desired bis-silylation process proceeded smoothly. After aza-Wittig reaction with polymer-supported PPh_3 to simplify purification, we were disappointed to find that Mannich cyclization of **63** did not proceed under the previously successful reaction conditions to provide either the unmigrated product **64** or the migrated product **65**. The only observable product from this sequence was the methyl ketone **66**. We concluded from this experiment that substitution in any form at the 10*S* position was not tolerated under these Mannich cyclization conditions.

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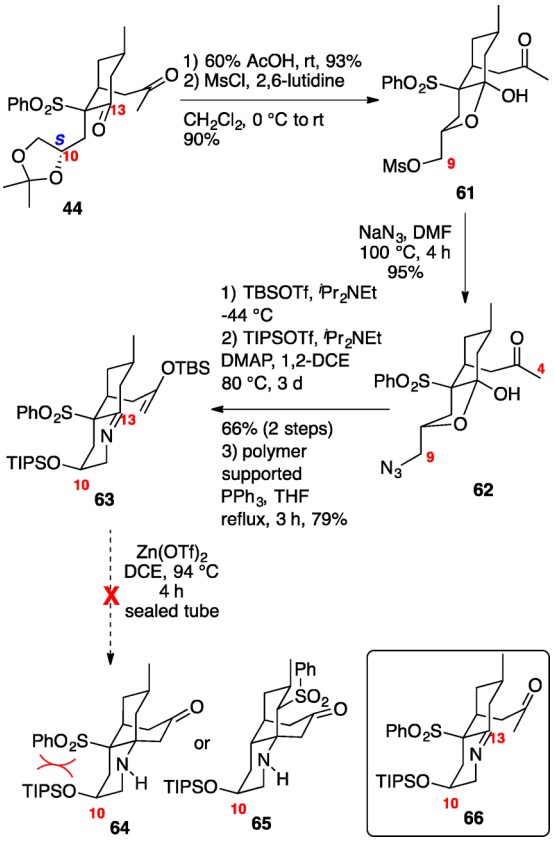
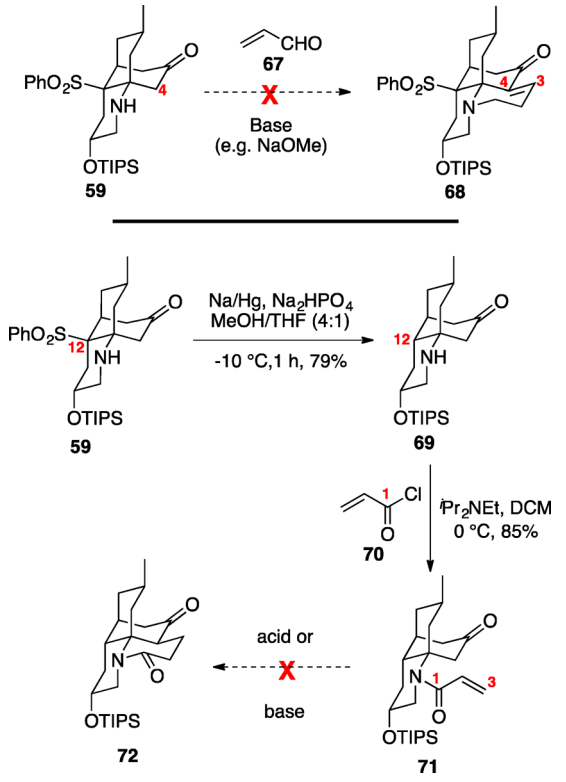
Scheme 9. Attempted Synthesis of the 10*S* Tricycle 64/65



Scheme 10. Attempted One-Pot Synthesis of the Tetracycle



Total Synthesis of 10-Hydroxylated *Lycopodium* Alkaloids. With the successful intramolecular Mannich cyclization on the 10*R* series, we moved forward toward a total synthesis of the 10-oxygenated *Lycopodium* alkaloids. We first set out to identify a common intermediate for constructing all of these natural products. We briefly looked into the possibility of incorporating the fourth ring through a tandem heteroatom Michael addition followed by an in situ aldol condensation (Scheme 10). This process had proven successful in the synthesis of the *Aspidosperma* alkaloids;[33] however, we were unable to facilitate the transformation of amine **59** into tetracycle **68** under a range of conditions. We also explored the possibility of acylation of the lycopodine nitrogen with acryloyl chloride (**70**), which proceeded smoothly after initial desulfonylation. Unfortunately, the subsequent intramolecular Michael addition of **71** proved unsuccessful under a range of conditions. This result was somewhat surprising due to the closely related example by Kim and co-workers.[34]

Given our inability to directly construct the piperidine ring system, we returned to the stepwise approach for accomplishing this transformation used in our lycopodine synthesis (Scheme 11).[10] Treatment of amine **69** with 3-iodopropan-1-ol (**73**) and $NaHCO_3$ in refluxing acetone provided the N-alkylated product **74** in reasonable yield. It should be noted that use of the iodide **73** is key in this experiment because use of the analogous bromo derivative gave low yields. Next, tandem Oppenauer oxidation/intramolecular aldol condensation[12,13,15] with freshly prepared *t*-BuOK generated the desired enone **76** in reproducibly high yields along with a small amount of the tricycle **69** (17%) from a retro-Michael process **77**. After some optimization, we found that hydrogenation of **76** with Adams catalyst proved to be the best protocol for removing the $C_{3,4}$ alkene. Interestingly, use of Stryker's reagent,[35] which proved effective in our lycopodine synthesis, was unproductive in the 10-oxygenated series. Compound **78** served as an ideal common intermediate for accessing all the natural products in this subfamily. As we have described previously,[27] this key tricycle **78** enabled us to complete the total synthesis of the 10-alkoxy *Lycopodium* alkaloids **7**–**9**. TAS-F cleavage of silyl ether **78** provided 10-hydroxylycopodine (**7**). DIBAL-H reduction followed by acetylation gave a common precursor for accessing both deacetylpaniculine (**8**) and paniculine (**9**) by appropriate selection of the pH after TIPS removal.

CONCLUSION

A unified total synthesis of the C_{10}-oxygengated *Lycopodium* alkaloids has been achieved. The stereochemical influence of the C_{10} position on both the intramolecular Michael reaction and the intramolecular Mannich cyclization has been systematically explored. A conformationally accelerated process for the Mannich cyclization has been unearthed that suppressed the sulfone rearrangement observed in the desoxy series.[10] This systematic exploration of the impact of both C_{10} epimers should provide useful mileposts for synthetic chemists in understanding both their stereoselectivity and reactivity within this scaffold and beyond. The unexpected inability to facilitate the Mannich cyclization on the 10*S* series creates additional challenges for accessing the necessary precursors for the biomimetic alkylation of a stereochemically required 10*S* leaving group hypothesized by MacLean[36] and Kobayashi[2] for accessing himeradine (**1**). A common intermediate for constructing natural products **7**–**9** has been identified. Subsequent applications of this technology to the total synthesis of additional members of the *Lycopodium* alkaloids will be reported in due course.

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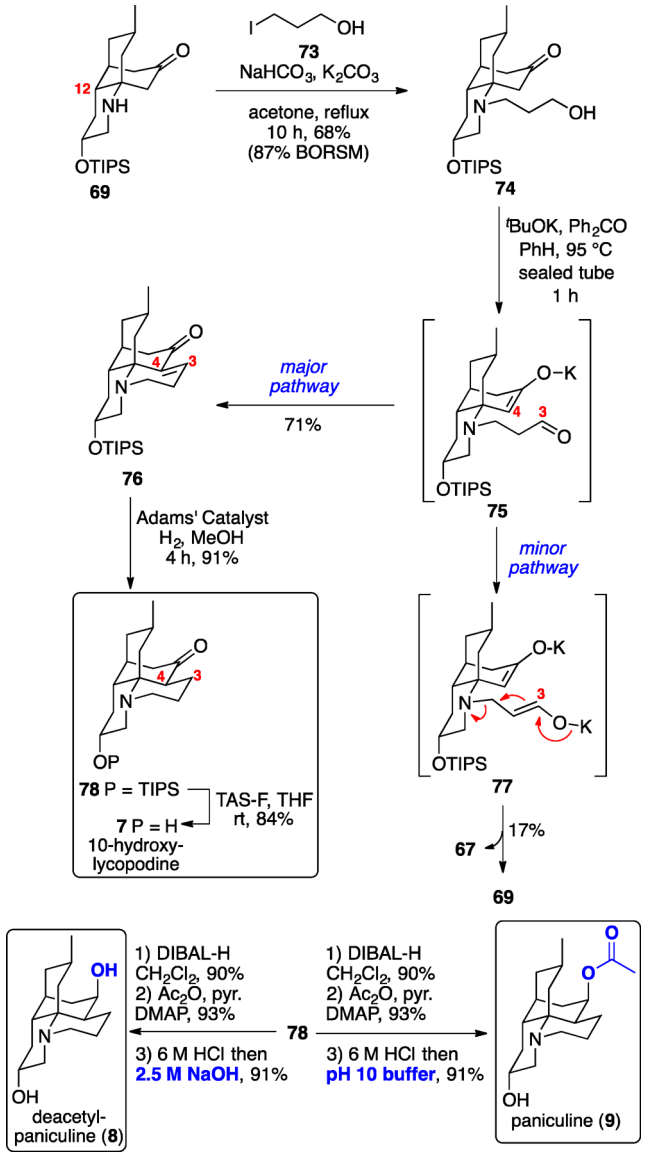
Scheme 11. Successful Stepwise Synthesis of the Tetracycle



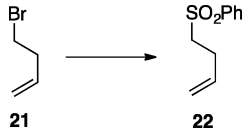
EXPERIMENTAL SECTION

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 acquired on a TOF-MS instrument with an EI or ES source.

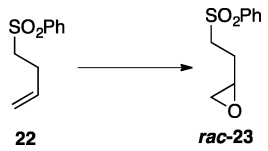
Routine monitoring of reactions was performed using EM Science DC-Alufolien silica gel, aluminum-backed TLC plates. Flash chromatography was performed with the indicated eluents on EM Science Gedurian 230−400 mesh silica gel.

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, ether, toluene, 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.

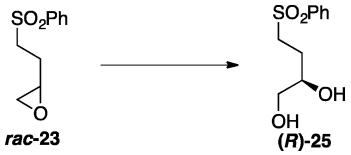
(But-3-en-1-ylsulfonyl)benzene ***22***. To a stirred solution of $NaSO_2Ph$ (7.46 g, 45.7 mmol) in DMF (40 mL) at rt were added



TBAI (1.40 g, 3.80 mmol) and bromide **21** (5.00 g, 37.9 mmol, 3.73 mL), and the reaction mixture was warmed to 60 °C. After 5 h, the reaction was quenched with sat. aq NaCl (80 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with sat. aq NaCl (8 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5−30% EtOAc/hexanes, to give known sulfone **22**[29] (6.67 g, 34.0 mmol, 90%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 7.6 Hz, 2H), 7.67 (t, J = 7.4 Hz, 1H), 7.60 (td, J = 7.8, 1.6 Hz, 2H), 5.74 (m, 1H), 5.07 (m, 2H), 3.19 (m, 2H), 2.47 (m, 2H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$) δ 139.0, 133.80, 133.76, 129.3, 128.1, 117.2, 55.4, 26.8 ppm.



*Epoxide rac-**23***. To a stirred solution of sulfone **22** (18.34 g, 93.44 mmol) in DCM (350 mL) at rt was added *m*-CPBA (46.07 g, 186.9 mmol, 70% weight). After 48 h, the reaction was quenched with sat. aq Na_2SO_3 (80 mL), neutralized with sat. aq $NaHCO_3$ (200 mL), and extracted with DCM (3 × 200 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 15−40% EtOAc/hexanes, to give *rac*-**23**[29] (19.37 g, 91.2 mmol, 98%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 7.5 Hz, 2H), 7.67 (t, J = 7.6 Hz 1H), 7.60 (td, J = 7.7, 1.6 Hz, 2H), 3.23 (m, 2H), 3.01 (m, 1H), 2.77 (dd, J = 4.8, 4.0 Hz 1H), 2.50 (dd, J = 4.8, 2.4 Hz 1H), 2.17 (m, 1H), 1.83 (m, 1H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 138.9, 133.9, 129.4, 128.0, 52.68, 50.01, 47.01, 25.88 ppm.



*(R)-4-(Phenylsulfonyl)butane-1,2-diol (R)-**25***. To a solution of Jacobsen's *S,S*-(salen)Co catalyst (*S,S*)-**24** in toluene (1.1 mL) was added AcOH (12 mL). The solution was stirred at rt open to air for 1 h over which the color changed from orange red to a dark brown. The solution was concentrated in vacuo to leave a crude brown solid. To the resulting catalyst residue was cannulated a solution of epoxide *rac*-**23** (2.23 g, 10.5 mmol) in THF (2.5 mL) at rt. The flask was cooled to 0 °C, and H_2O (0.1 mL) was added over 1 min. The reaction was allowed to warm to rt. After 18 h, the reaction was concentrated in vacuo, loaded over silica gel, and purified by chromatography, eluting with 30−100% EtOAc/hexanes and 10% MeOH/EtOAc to give recovered epoxide **23**[29] (1.11 g, 5.24 mmol, 50%) and known product diol (*R*)-**25**[29] (1.21 g, 5.25 mmol, 49%) as a white solid. $[\alpha]_D^{20}$ = +28.4 (c = 0.13, EtOH); mp 76−78 °C; IR (neat) 3388, 2931, 1447, 1305, 1143, 1086, 1040, 737, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, J = 8.1, 1.1, 2H), 7.70 (t, J = 7.4, 1H), 7.61 (t, J = 7.8, 2H), 3.85 (m, 1H), 3.68 (m, 1H), 3.49 (q, J = 5.8, 1H), 3.19−3.42 (m, 2H), 2.75 (d, J = 4.7, 1H), 2.21 (t, J = 5.5, 2H), 1.81−2.01 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 133.9, 129.4, 128.0, 70.0, 66.3, 52.9, 26.1 ppm.

*Acetonide (R)-**26***. To a solution of diol (*R*)-**25** (1.35 g, 5.86 mmol) in CH_2Cl_2 (54 mL) was added 2,2-dimethoxypropane (3.05 g, 3.6 mL, 29.3 mmol) followed by $TsOH{\cdot}H_2O$ (112 mg, 0.586 mmol) at rt. After 14 h, the reaction mixture was quenched with sat. aq $NaHCO_3$ (80 mL), and the aqueous layer was extracted with Et_2O (3 × 160

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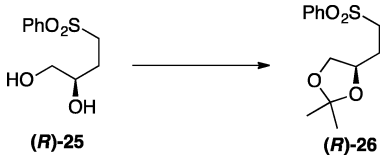
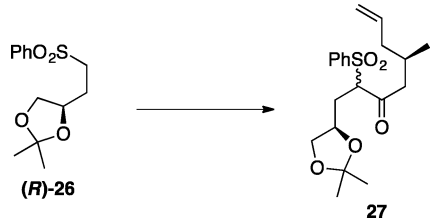
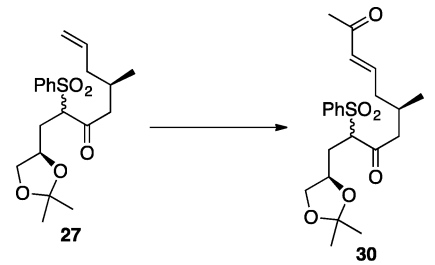


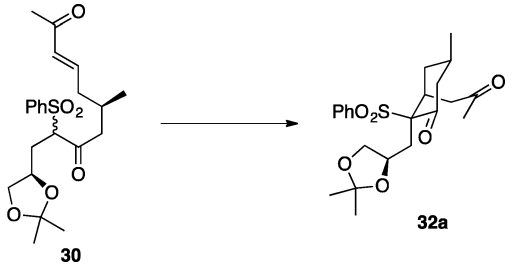
mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel eluting with 20−60% EtOAc/hexanes to give (*R*)-**26** (1.48 g, 5.48 mmol, 94%) as a yellow oil. $[\alpha]_D^{20}$ = +12.9 (*c* = 1.0, $CHCl_3$); IR (neat) 2985, 1652, 1447, 1371, 1306, 1217, 1144, 1063 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.94 (dt, *J* = 7.1, 2.1 Hz, 2H), 7.69 (tt, *J* = 7.5, 2.2 Hz, 1H), 7.60 (tt, *J* = 7.4, 1.5 Hz, 2H), 4.12−4.19 (m, 1H), 4.06 (dd, *J* = 8.3, 4.1 Hz, 1H), 3.57 (dd, *J* = 8.6, 6.5 Hz, 1H), 3.28−3.35 (m, 1H), 3.15−3.22 (m, 1H), 2.00−2.05 (m, 1H), 1.89−1.94 (m, 1H), 1.36 (s, 3H), 1.32 (s, 3H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 139.0, 133.8, 129.4, 128.0, 109.5, 73.7, 68.7, 52.8, 26.9, 26.8, 25.3 ppm; HRMS (ES+) calcd for $C_{13}H_{18}O_4SNa$ (M + Na) 293.0824, found 293.0831.



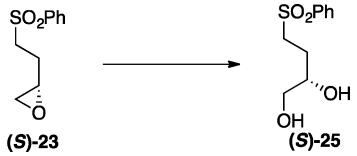
Keto Sulfone ***27***. To a stirred solution of (*R*)-**26** (1.48 g, 5.48 mmol) in THF (8.8 mL) at −78 °C was added LDA[37] (13.7 mL, 13.7 mmol, 1.0 M in THF/hexanes) dropwise. After 20 min, a precooled (−78 °C) solution of ester **20** (934 mg, 6.57 mmol) in THF (12.8 mL) was added via cannula to the previous solution and warmed to rt over 1 h. After being stirred for 20 h, the reaction was quenched with sat. aq NH_4Cl (60 mL) and extracted with Et_2O (3 × 120 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 2−30% EtOAc/hexanes, to give **27** (1.77 g, 4.65 mmol, 85%) as a yellow oil. $[\alpha]_D^{20}$ = +14.9 (*c* = 0.57, $CHCl_3$); IR: (neat) 2958, 2927, 2872, 1720, 1627, 1446, 1370, 1304, 1230, 1152, 1127, 1080, 999, 914 cm^{-1}; ^1H NMR {700 MHz, $CDCl_3$ (2 diastereomers)} δ 7.79 (t, *J* = 7.7 Hz, 2H (2 diastereomers)), 7.71 (td, *J* = 7.3, 2.1 Hz, 1H (2 diastereomers)), 7.59 (t, *J* = 7.7 Hz, 2H (2 diastereomers)), 5.69−5.82 (m, 1H (2 diastereomers)), 5.01−5.08 (m, 2H (2 diastereomers)), 4.23−4.49 (m, 1H (2 diastereomers)), 3.79−4.18 (m, 1H (2 diastereomers)), 3.48−3.54 (m, 1H (2 diastereomers)), 2.71−2.96 (m, 1H (2 diastereomers)), 2.52−2.64 (m, 1H (2 diastereomers)), 1.93−2.21 (m, 5H (2 diastereomers)), 1.26−1.34 (m, 6H (2 diastereomers)), 0.94 (d, *J* = 6.4 Hz, 3H (2 diastereomers)) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 201.9, 201.1, 136.6, 136.3, 136.2, 136.1, 134.4, 129.6, 129.4, 129.1, 116.7, 109.7, 109.6, 74.3, 72.7, 71.9, 71.3, 69.1, 68.9, 52.2, 51.3, 40.7, 40.5, 32.1, 31.5, 28.3, 27.8, 27.0, 26.3, 25.4, 25.4, 19.6, 19.5 ppm; HRMS (ES+) calcd for $C_{20}H_{28}O_5SNa$ (M + Na) 403.1545, found 403.1555.



Enone ***30***. To a stirred solution of alkene **27** (6.13 g, 16.12 mmol) in CH_2Cl_2 (7. 0 mL) were added 3-penten-2-one (**28**) (2.03 g, 3.37 mL, 24.18 mmol, 70% pure) and second-generation Hoveyda−Grubbs catalyst **29** (505 mg, 0.81 mmol). After being stirred for 36 h, the reaction mixture was concentrated in vacuo and loaded directly onto silica gel. It was purified by chromatography, eluting with 5−50% EtOAc/hexanes, to give **30** (6.01 g, 14.22 mmol, 88%) as brown oil. $[\alpha]_D^{20}$ = −14.6 (*c* = 0.11, $CHCl_3$); IR (neat) 2931, 2877, 1721, 1672, 1626, 1447, 1370, 1310, 1254, 1213, 1151, 1065, 983 cm^{-1}; ^1H NMR {400 MHz, $CDCl_3$ (2 diastereomers)} δ 7.79 (t, *J* = 7.5 Hz, 2H (2 diastereomers)), 7.69−7.74 (m, 1H (2 diastereomers)), 7.59 (t, *J* = 7.6 Hz, 2H (2 diastereomers)), 6.71−6.80 (m, 1H (2 diastereomers)), 6.11 (q, *J* = 8.1 Hz, 1H (2 diastereomers)), 3.78−4.48 (m, 3H (2 diastereomers)), 3.48−3.54 (m, 1H (2 diastereomers)), 2.57−3.02 (m, 2H (2 diastereomers)), 2.07−2.28 (m, 6H (2 diastereomers)), 1.93 (ddd, *J* = 12.5, 9.7, 2.7 Hz, 1H (2 diastereomers)), 1.31 (s, 2H (2 diastereomers)), 1.24−1.27 (m, 5H (2 diastereomers)), 0.98 (d, *J* = 6.5 Hz, 3H (2 diastereomers)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 200.6, 198.4, 198.3, 145.9, 145.6, 136.3, 136.2, 134.4, 133.1, 132.9, 129.6, 129.4, 129.2, 129.1, 109.8, 109.7, 74.3, 72.9, 71.8, 71.3, 68.99, 68.91, 52.2, 51.2, 39.0, 38.9, 32.2, 31.5, 27.9, 27.7, 27.0, 26.9, 26.3, 25.3, 19.7, 19.6 ppm; HRMS (ES+) calcd for $C_{22}H_{30}O_6SNa$ (M + Na) 445.1661, found 445.1654.



Cyclohexanone ***32a***. To a solution of keto sulfone **30** (2.46 g, 5.81 mmol) in 99:1 DCE/EtOH (29.5 mL) was added (*S*)-*N*-(*p*-dodecylphenylsulfonyl)-2-pyrrolidinecarboxamide (L-Hua Cat, **31**) (438 mg 1.04 mmol) at 0 °C, and after 10 min, piperidine (495 mg, 0.57 mL, 5.81 mmol) was added and warmed to 4 °C. After 5 d, the solvent was removed in vacuo. The reaction mixture was loaded directly onto silica gel and was purified by chromatography, eluting with 2:2:96 to 30:30:40 CH_2Cl_2/EtOAc/hexanes, to give **32** as mixture of diastereomers (2.09 g, 4.95 mmol, 85%, dr = 3:1). The mixture of diastereomers was further purified by crystallization from ether to give the major diastereomer **32a** (1.26 g, 2.98 mmol, 51%) and a mixture of diastereomers (0.83 g, 1.96 mmol, 34%). $[\alpha]_D^{23}$ = +26.8 (*c* = 1.4, $CHCl_3$); mp 124−126 °C; IR (neat) 2955, 2927, 2872, 1713, 1447, 1359, 1299, 1140, 1077, 1025, 961 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.64−7.71 (m, 3H), 7.53−7.59 (m, 2H), 4.41−4.47 (m, 1H), 3.99 (dd, *J* = 8.2, 5.9 Hz, 1H), 3.73−3.79 (m, 1H), 3.33 (t, *J* = 7.9 Hz, 2H), 2.68 (dd, *J* = 10.6, 10.3 Hz, 1H), 2.55 (dd, *J* = 6.1, 5.9 Hz, 1H), 2.37 (dd, *J* = 16.4, 10.9 Hz, 1H), 2.18−2.21 (m, 5H), 2.07−2.12 (m, 1H), 1.91 (dd, *J* = 15.9, 2.9 Hz, 1H), 1.73−1.80 (m, 1H), 1.31 (s, 3H), 1.29 (s, 3H), 1.05 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 206.2, 205.3, 136.2, 134.4, 130.0, 129.0, 109.7, 71.3, 70.2, 47.0, 44.5, 33.7, 33.4, 32.2, 29.7, 26.6, 26.4, 25.7, 22.2 ppm; HRMS (ES+) calcd for $C_{22}H_{30}O_6NaS$ (M + Na) 445.1684, found 445.1661.



*(S)-4-(Phenylsulfonyl)butane-1,2-diol (S)-****25***. To a stirred solution of (*S*)-**23** (2.09 g, 9.84 mmol) in MeCN (32.7 mL) were added PhCOOH (1.44 g, 11.8 mmol) and TBAI (109 mg, 0.295 mmol) sequentially, and the reaction mixture was heated to reflux. After 12 h, the reaction was quenched with sat. aq $NaHCO_3$ (30 mL) and extracted with EtOAc (3 × 40 mL). The dried extract ($MgSO_4$) was concentrated in vacuo to give the benzoate.

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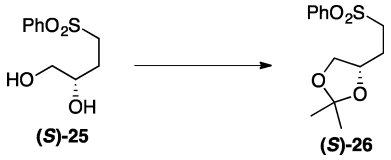
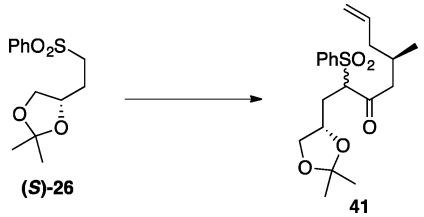
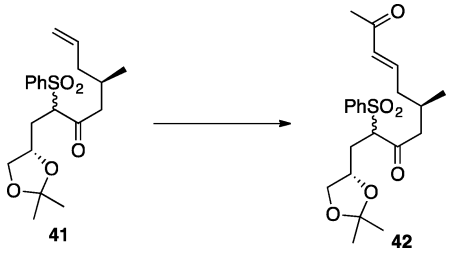
The crude benzoate was dissolved in MeOH (32.7 mL). To the solution was added K_2CO_3 (2.05 g, 14.8 mmol). After 14 h, the reaction mixture was concentrated in vacuo, dissolved in EtOAc (30 mL), and quenched by sat. aq NaCl (20 mL), and the aqueous layer was extracted with EtOAc (3 × 30 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 30−100% EtOAc/hexanes and then 10% MeOH/EtOAc to give product diol (*S*)-**25**[29] (1.87 g, 8.17 mmol, 83%) as a white solid. $[\alpha]_D^{20}$ = −26.4 (*c* = 0.14, EtOH); IR (neat) 3388, 2931, 1447, 1305, 1143, 1086, 1040, 737, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 8.1, 1.1, 2H), 7.70 (t, *J* = 7.4, 1H), 7.61 (t, *J* = 7.8, 2H), 3.85 (m, 1H), 3.68 (m, 1H), 3.49 (q, *J* = 5.8, 1H), 3.19−3.42 (m, 2H), 2.75 (d, *J* = 4.7, 1H), 2.21 (t, *J* = 5.5, 1H), 1.81−2.01 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 133.9, 129.4, 128.0, 70.0, 66.3, 52.9, 26.1 ppm; HRMS (ES+) calcd for $C_{10}H_{15}O_4S$ (M + H) 231.0691, found 231.0691.



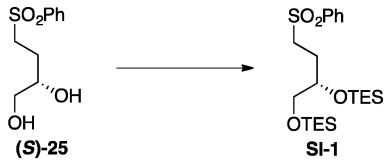
Acetonide (S)-26. To a solution of diol (*S*)-**25** (200 mg, 0.869 mmol) in CH_2Cl_2 (8 mL) was added 2,2-dimethoxypropane (453 mg, 0.5 mL, 4.35 mmol) followed by $TsOH{\cdot}H_2O$ (16.5 mg, 0.087 mmol) at rt. After 11 h, the reaction mixture was quenched with sat. aq $NaHCO_3$ (12 mL) and the aqueous layer was extracted with Et_2O (3 × 25 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20−60% EtOAc/hexanes to give (*S*)-**26** (221 mg, 0.817 mmol, 94%) as a colorless oil. $[\alpha]_D^{20}$ = −13.3 (*c* = 1.0, $CHCl_3$); IR (neat) 2985, 1652, 1447, 1371, 1306, 1217, 1144, 1063 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.0 Hz, 2H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 2H), 4.08−4.14 (m, 1H), 4.01 (t, *J* = 7.1 Hz, 1H), 3.52 (t, *J* = 7.2 Hz, 1H), 3.23−3.31 (m, 1H), 3.11−3.18 (m, 1H), 1.85−2.02 (m, 2H), 1.31 (s, 3H), 1.27 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 133.8, 129.3, 128.0, 109.3, 73.7, 68.7, 52.8, 26.9, 26.8, 25.3 ppm; HRMS (ES+) calcd for $C_{13}H_{18}O_4SNa$ (M + Na) 293.0824, found 293.0831.



Keto Sulfone 41. To a stirred solution of (*S*)-**26** (590 mg, 2.18 mmol) in THF (3.5 mL) at −78 °C was added LDA[39] (5.24 mL, 5.24 mmol, 1.0 M in THF) dropwise. After 20 min, a precooled (−78 °C) solution of **20** (372 mg, 2.62 mmol) in THF (5.1 mL) was added via cannula to the sulfone solution and warmed to rt over 1 h. After being stirred for 20 h, the reaction was quenched with sat. aq NH_4Cl (25 mL) and extracted with Et_2O (3 × 50 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 2−30% EtOAc/hexanes, to give **41** (704 mg, 1.85 mmol, 85%) as a brown oil. $[\alpha]_D^{20}$ = −13.9 (*c* = 0.5, $CHCl_3$); IR: (neat) 2960, 2927, 2872, 1721, 1629, 1446, 1370, 1304, 1232, 1149, 1127, 1070, 999, 916 cm^{-1}; ^1H NMR {400 MHz, $CDCl_3$ (2 diastereomers)} δ 7.69 (dd, *J* = 7.8, 5.5 Hz, 2H (2 diastereomers)), 7.58 (t, *J* = 7.4 Hz, 1H (2 diastereomers)), 7.46 (m, 2H (2 diastereomers)), 5.58−5.66 (m, 1H (2 diastereomers)), 4.91 (d, *J* = 12.1 Hz, 2H (2 diastereomers)), 4.37 (dd, *J* = 11.9, 2.7 Hz, 1H (1 diastereomer)), 4.16 (dd, *J* = 9.5, 2.8 Hz, 1H (1 diastereomer)), 3.69−4.03 (m, 2H (2 diastereomers)), 3.35−3.41 (m, 1H (2 diastereomers)), 2.60−2.69 (m, 2H (2 diastereomers)), 2.36−2.43 (m, 1H (1 diastereomer)), 1.80−2.11 (m, 5H (2 diastereomers)), 1.19 (s, 3H (2 diastereomers)), 1.14 (s, 3H (2 diastereomers)), 0.81 (d, *J* = 6.8, 3H (2 diastereomers)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 200.9, 136.5, 136.4, 136.3, 134.3, 129.4, 129.2, 129.1, 129.0, 116.6, 116.4, 109.5, 109.3, 74.3, 72.7, 71.8, 71.0, 68.9, 68.8, 51.9, 51.3, 40.7, 40.6, 31.9, 31.2, 27.9, 27.7, 26.8, 26.3, 25.4, 25.2, 19.4, 19.3 ppm; HRMS (ES+) calcd for $C_{20}H_{28}O_5SNa$ (M + Na) 403.1545, found 403.1555.



Enone 42. To a solution of alkene **41** (700 mg, 1.84 mmol) in CH_2Cl_2 (0.90 mL) were added 3-penten-2-one **28** (232 mg, 3.8 mL, 2.76 mmol, 70% pure) and second-generation Grubbs catalyst (1.34 mg, 21.5 μmol). After being stirred for 3 d, the reaction mixture was concentrated in vacuo and loaded directly onto silica gel. It was purified by chromatography, eluting with 5−50% EtOAc/hexanes, to give **42** (575 mg, 1.36 mmol, 74%) as brown oil as well as recovered **41** (141 mg, 0.371 mmol, 20%). $[\alpha]_D^{20}$ = +13.6 (*c* = 0.13, $CHCl_3$); IR (neat) 2931, 2877, 1721, 1672, 1626, 1447, 1370, 1310, 1254, 1213, 1151, 1065, 983 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, two diastereomers) δ 7.77 (t, *J* = 8.1 Hz, 2H (2 diastereomers)), 7.69 (t, *J* = 7.5 Hz, 1H (2 diastereomers)), 7.58 (t, *J* = 7.6 Hz, 2H (2 diastereomers)), 6.74 (dt, *J* = 16.0, 6.7 Hz, 1H (2 diastereomers)), 6.09 (dd, *J* = 15.6, 4.7 Hz, 1H (2 diastereomers)), 4.44 (dd, *J* = 11.7, 2.6 Hz, 1H (1 diastereomer)), 3.93−4.22 (m, 2H (2 diastereomers)), 3.75−3.80 (m, 1H (1 diastereomer)), 3.45−3.53 (m, 1H (2 diastereomers)), 2.85 (m, 1H (2 diastereomers)), 2.55−2.69 (m, 1H (2 diastereomers)), 2.25 (d, *J* = 7.8, 5H (2 diastereomers)), 2.03−2.18 (m, 3H (2 diastereomers)), 1.93 (m, 1H (2 diastereomers)), 1.29 (s, 3H (2 diastereomers)), 1.23 (s, 3H (2 diastereomers)), 0.96 (d, *J* = 6.3 Hz, 3H (2 diastereomers)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.0, 200.6, 198.5, 145.9, 145.6, 136.2, 134.4, 129.5, 129.3, 129.2, 129.1, 109.8, 109.6, 74.3, 72.9, 71.8, 71.1, 68.97, 68.90, 52.0, 51.5, 39.2, 39.0, 32.1, 31.4, 27.9, 27.6, 27.0, 26.9, 25.4, 25.3, 19.5 ppm; HRMS (ES+) calcd for $C_{22}H_{30}O_6SNa$ (M + Na) 445.1662, found 445.1655.



DiTES Ether SI-1. To a stirred solution of diol (*S*)-**25** (201 mg, 0.873 mmol) in CH_2Cl_2 (3.5 mL) were added Et_3N (265 mg, 0.37 mL, 2.62 mmol), DMAP (21 mg, 0.175 mmol), and TESCl (394 mg, 2.61 mmol, 0.44 mL) at 0 °C and warmed to rt. After being stirred for 14 h, the reaction mixture was quenched with sat. aq NH_4Cl (15 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5−25% EtOAc/hexanes to give diTES ether **SI-1** (334 mg, 0.728 mmol, 83%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 7.6, 1.6 Hz, 2H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.59 (t, *J* = 7.2 Hz, 2H), 3.78 (m, 1H), 3.53 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.32 (dd, *J* = 10.0, 7.6 Hz, 1H), 3.21−3.30 (m, 2H), 1.97 (m, 1H), 1.83 (m, 1H), 0.93 (t, *J* = 7.8 Hz, 18H), 0.57 (q, *J* = 7.8 Hz, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 133.9, 129.4, 129.3, 128.0, 70.0, 66.3, 52.9, 26.1, 6.8, 6.7, 4.8, 4.2 ppm; HRMS (ES+) calcd for $C_{22}H_{42}O_4NaSi_2S$ (M + Na) 481.2240, found 481.2201.

Ketone SI-2. To a stirred solution of sulfone **SI-1** (144 mg, 0.314 mmol) in THF (0.5 mL) at −78 °C was added LDA (0.72 mL, 0.722 mmol, 1.0 M in THF) dropwise. After 20 min, a solution of ester **20** (53.6 mg, 0.377 mmol) in precooled THF (0.7 mL) was added via

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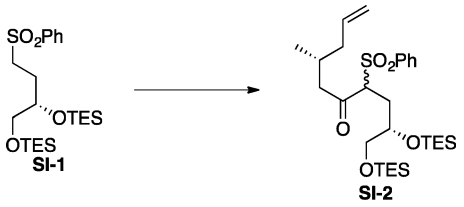
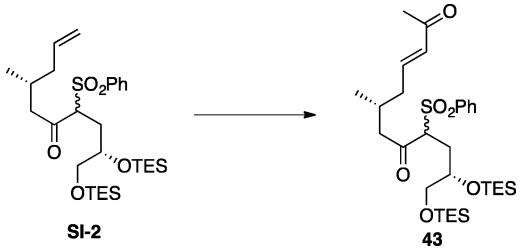
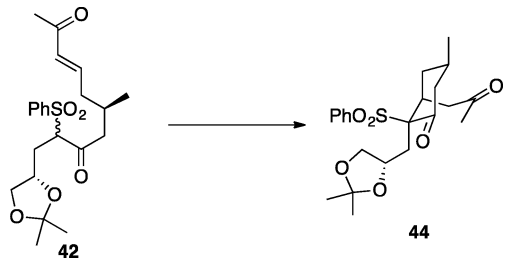


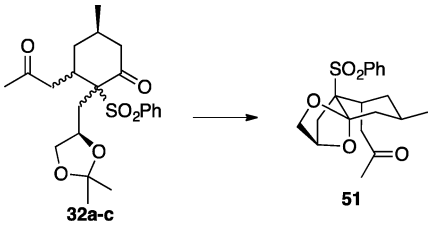
cannula to the sulfone solution and warmed to rt over 1 h. After being stirred for 12 h, the reaction was quenched with sat. aq NH_4Cl (5 mL) and extracted with Et_2O (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 2−25% EtOAc/hexanes, to give keto sulfone **SI-2** (124 mg, 0.218 mmol, 69%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$, two diastereomers) δ 7.76−7.85 (m, 2H (two diastereomers)), 7.63−7.71 (m, 1H (two diastereomers)), 7.50−7.62 (m, 2H (two diastereomers)), 5.67−5.85 (m, 1H (two diastereomers)), 4.98−5.13 (m, 2H (two diastereomers)), 4.34−4.66 (m, 1H (two diastereomers)), 3.24−3.73 (m, 3H (two diastereomers)), 2.47−3.03 (m, 2H (two diastereomers)), 1.90−2.28 (m, 5H (two diastereomers)), 0.89−1.04 (m, 21H (two diastereomers)), 0.49−0.78 (m, 12H (two diastereomers)) ppm.



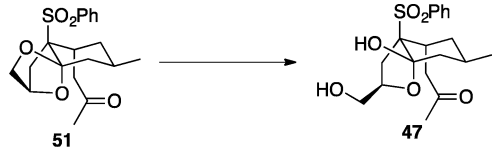
Enone 43. To a solution of alkene **SI-2** (109 mg, 0.192 mmol) in CH_2Cl_2 (0.10 mL) were added 3-penten-2-one[38] (**28**) (24.2 mg, 40 μL, 0.288 mmol, 70% pure) and second-generation Grubbs catalyst (8.2 mg, 9.6 μmol). After being stirred for 3 d, the reaction mixture was concentrated in vacuo and loaded directly onto silica gel. It was purified by chromatography, eluting with 5−25% EtOAc/hexanes, to give enone **43** (94 mg, 0.154 mmol, 80%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, two diastereomers) δ 7.78−7.81 (m, 2H (two diastereomers)), 7.67−7.69 (m,1H (two diastereomers)), 7.56−7.59 (m, 2H (two diastereomers)), 6.70−6.86 (m, 1H (two diastereomers)), 6.11−6.15 (m, 1H (two diastereomers)), 4.35−4.42 (m, 1H (two diastereomers)), 3.56−3.71 (m, 1H (two diastereomers)), 3.43−3.51 (m, 1H (two diastereomers)), 3.31−3.48 (m, 1H (two diastereomers)), 2.84−3.07 (m, 1H (two diastereomers)), 2.56−2.70 (m, 1H (two diastereomers)), 1.93−2.46 (m, 8H (two diastereomers)), 0.83−1.05 (m, 21H (two diastereomers)), 0.48−0.64 (m, 12H (two diastereomers)); ^{13}C NMR (100 MHz, $CDCl_3$, two diastereomers) δ 201.2, 200.6, 198.5, 198.3, 146.0, 145.9, 136.8, 136.5, 134.20, 134.16, 133.04, 132.98, 129.4, 129.3, 129.0, 71.5, 71.2, 70.1, 70.0, 67.4, 65.9, 51.1, 51.0, 39.4, 39.0, 33.0, 31.6, 27.7, 27.6, 26.91, 26.90, 26.8, 25.8, 19.56, 19.53, 6.8, 6.76, 6.72, 4.8, 4.7, 4.2, 4.1 ppm; HRMS (ES+) calcd for $C_{31}H_{54}O_6NaSi_2S$ (M + Na) 633.3077, found 633.3093.



Cyclohexanone 44. To a solution of keto sulfone **42** (0.378 g, 0.895 mmol) in 2-propanol (4.5 mL) was added diisopropylamine (0.906 g, 1.30 mL, 8.95 mmol) at rt. After 68 h, the solvent was removed in vacuo. The reaction mixture was loaded directly onto silica gel and was purified by chromatography, eluting with EtOAc, to give the mixture of diastereomers (0.319 g, 0.755 mmol, 85%, dr = 1.5:1). The mixture of diastereomers was further purified by chromatography over silica gel, eluting with 5−50% EtOAc/hexanes, to give the major diastereomer **44** (0.181 g, 0.428 mmol, 48%) as a white solid. Mp 108−109 °C (recrystallized from DCM/IPA); $[\alpha]_D^{20}$ = +58.0 (c = 0.5, $CHCl_3$); IR (neat) 2960, 2929, 2870, 1714, 1446, 1360, 1300, 1140, 1082, 757, 718, 690, 600 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.8, 2H), 7.69 (t, J = 7.5, 1H), 7.57 (t, J = 7.8, 2H), 3.97−4.10 (m, 2H), 3.64−3.72 (m, 1H), 3.48 (t, J = 7.5 Hz, 1H), 3.33 (d, J = 17.8 Hz, 1H), 2.82 (q, J = 9.1 Hz, 1H), 2.42−2.57 (m, 3H), 2.03−2.32 (m, 6H), 1.83 (dq, J = 12.5, 7.2 Hz, 1H), 1.44 (s, 3H), 1.29 (s, 3H), 0.97 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 206.4, 206.2, 135.3, 134.3, 130.9, 128.7, 109.6, 78.2, 72.0, 70.4, 46.6, 45.1, 33.5, 32.8, 30.6, 30.4, 27.1, 26.8, 25.5, 21.3 ppm; HRMS (ES+) calcd for $C_{22}H_{30}O_6SNa$ (M + Na) 445.1661, found 445.1645.



Ketal 51. To a stirred solution of diastereomers of cyclohexanone **32a−c** (1.84 g, 3.26 mmol) in CH_2Cl_2 (10.5 mL) at rt was added (+)-CSA (2.17 g, 33.3 mmol). After 14 h, the reaction mixture was quenched with sat. $NaHCO_3$ (20 mL) and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The dried ($MgSO_4$) organic layer was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5−70% EtOAc/hexanes, to give ketal **51** (357 mg, 0.98 mmol, 30%) as a white solid. $[\alpha]_D^{20}$ = +25.2 (c = 1.0, $CHCl_3$); IR (neat) 3439, 1716, 1638, 1443, 1291, 1147, 964.3 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.00 (dt, J = 7.2, 1.3, 2H), 7.69 (tt, J = 7.5, 1.3, 1H), 7.61 (t, J = 7.8, 2H), 4.75 (dd, J = 3.5, 3.5, 1H), 3.76 (d, J = 6.4 Hz, 1H), 3.63 (dt, J = 5.9, 3.2 Hz, 1H), 2.95 (dd, J = 18.7, 5.8 Hz, 1H), 2.85 (dt, J = 9.9, 4.8 Hz, 1H), 2.54 (d, J = 13.5 Hz, 1H), 2.32 (dd, J = 18.7, 5.7 Hz, 1H), 2.07 (s, 3H), 2.05 (dd, J = 12.5, 3.3 Hz, 1H), 1.79−1.89 (m, 4H), 1.34 (ddd, J = 13.6, 4.3, 3.9 Hz, 1H) 0.97 (d, J = 6.4, 3H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 206.8, 138.4, 133.7, 130.3, 128.8, 109.0, 76.5, 76.1, 69.9, 47.3, 35.6, 35.3, 34.2, 32.1, 29.9, 24.4, 21.9 ppm; HRMS (EI+) calcd for $C_{19}H_{24}O_5S$ (M + H) 364.1344, found 364.1339.



Hemiketal 47. To a stirred solution of ketal **51** (590 mg, 1.62 mmol) in dioxane (8 mL) at 70 °C was added H_2SO_4 (16.2 mL, 1.5 M). After 3 h, the reaction was quenched with sat. aq $NaHCO_3$ (40 mL) and extracted with EtOAc (3 × 60 mL). The combined organic layer was washed with brine (20 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20−100% EtOAc/hexanes and 5% MeOH/EtOAc, to give **47** (480 mg, 1.26 mmol, 78%) as a white solid. $[\alpha]_D^{20}$ = +9.8 (c = 0.99, $CHCl_3$); IR (neat) 3493, 2925, 2851, 1708, 1459, 1446, 1376, 1296, 1205, 1170, 1139, 1073, 1015 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.99 (t, J = 8.4 Hz, 2H), 7.71 (t, J = 7.3 Hz, 1H), 7.61 (t, J = 8.4 Hz, 2H), 5.24−5.32 (m, 1H), 4.25−4.53 (m, 1H), 3.85−3.92 (m, 1H), 3.63−3.66 (m, 1H), 3.15−3.24 (m, 1H), 2.99−3.07 (m, 1H), 2.72−2.86 (m, 1H), 2.49−2.59 (m, 1H) 2.26−2.34 (m, 1H), 2.10 (s, 3H), 1.99−2.05 (m, 2H), 1.77−1.84 (m, 1H), 1.59−1.64 (m, 1H), 1.41−1.55 (m, 1H), 1.28−1.34 (m, 1H), 0.86 (d, J = 6.7 Hz, 3H) ppm; ^{13}C

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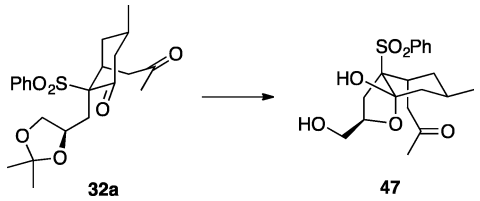
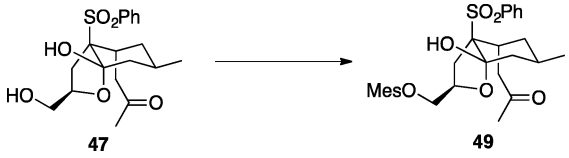
NMR (175 MHz, $CDCl_3$) δ 206.7, 137.5, 134.1, 130.4, 129.0, 104.5, 77.9, 75.4, 63.5, 45.5, 40.2, 34.6, 31.9, 30.4, 30.2, 23.2, 21.4 ppm; HRMS (ES+) calcd for $C_{19}H_{26}O_6SNa$ (M + Na) 405.1355, found 405.1348.



32a **47**

Hemiketal ***47***. To a solution of acetonide **32a** (1.75 g, 4.14 mmol) in dioxane (16 mL) at rt was added aq HCl (6 mL, 3 M). After 8 h, water (10 mL) was added and the reaction mixture was treated with sat. aq $NaHCO_3$ (30 mL). The aqueous mixture was extracted with EtOAc (3 × 80 mL), and the combined organic layer was washed with brine (50 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20−100% EtOAc/hexanes and 5% MeOH/EtOAc, to give hemiketal **47** (1.57 g, 4.11 mmol, 99%) as a white solid. $[\alpha]_D^{20}$ = +9.8 (*c* = 0.99, $CHCl_3$); mp 170−172 °C; IR (neat) 3493, 2925, 2851, 1708, 1459, 1446, 1376, 1296, 1205, 1170, 1139, 1073, 1015 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.99 (t, *J* = 8.4 Hz, 2H), 7.71 (t, *J* = 7.3 Hz, 1H), 7.61 (t, *J* = 8.4 Hz, 2H), 5.24−5.32 (m, 1H), 4.25−4.53 (m, 1H), 3.85−3.92 (m, 1H), 3.63−3.66 (m, 1H), 3.15−3.24 (m, 1H), 2.99−3.07 (m, 1H), 2.72−2.86 (m, 1H), 2.49−2.59 (m, 1H) 2.26−2.34 (m, 1H), 2.10 (s, 3H), 1.99−2.05 (m, 2H), 1.77−1.84 (m, 1H), 1.59−1.64 (m, 1H), 1.41−1.55 (m, 1H), 1.28−1.34 (m, 1H), 0.86 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 206.7, 137.5, 134.1, 130.4, 129.0, 104.5, 77.9, 75.4, 63.5, 45.5, 40.2, 34.6, 31.9, 30.4, 30.2, 23.2, 21.4 ppm; HRMS (ES+) calcd for $C_{19}H_{26}O_6SNa$ (M + Na) 405.1355, found 405.1348.



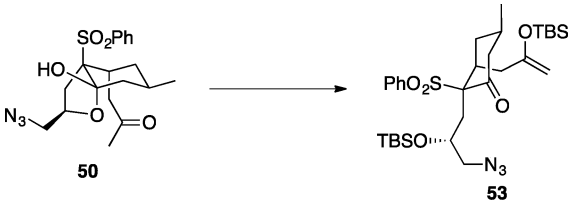
47 **49**

Mesitylate ***49***. To a stirred solution of **47** (1.57 g, 4.11 mmol) in CH_2Cl_2 (11 mL) at 0 °C was added Et_3N (943 mg, 1.3 mL, 9.32 mmol). After 10 min, 2-mesitylenesulfonyl chloride (**48**) (1.09 g, 4.99 mmol) and DMAP (5.4 mg, 0.044 mmol) were added and the mixture was warmed to rt. After 8 h at rt, the reaction mixture was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5−50% EtOAc/hexanes, to give mesitylate **49** (2.04 g, 3.62 mmol, 88%) as a white foam. $[\alpha]_D^{20}$ = −9.7 (*c* = 1.46, $CHCl_3$); IR (neat) 3467, 2954, 1714, 1447, 1356, 1300, 1174, 1143, 974.9 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.96 (dt, *J* = 7.2, 2.0 Hz, 2H), 7.73 (tt, *J* = 7.6, 1.9 Hz, 1H), 7.62 (t, *J* = 7.3 Hz, 2H), 4.25 (dd, *J* = 5.7, 5.7 Hz, 1H), 4.14 (dd, *J* = 6.8, 6.7 Hz, 1H), 4.01 (dd, *J* = 5.4, 5.4 Hz, 1H), 3.87 (s, 1H), 2.90 (ddd, *J* = 4.7, 4.6, 3.6 Hz, 1H), 2.77 (dd, *J* = 7.4, 7.4 Hz, 1H), 2.62−2.65 (m, 6H), 2.53−2.55 (m, 2H), 2.33 (s, 3H), 2.12 (dd, *J* = 7.9, 7.7 Hz, 1H), 2.06 (s, 3H), 1.96 (dd, *J* = 4.8, 4.8 Hz, 1H), 1.71−1.76 (m, 1H), 1.65 (ddd, *J* = 4.4, 4.4, 4.0 Hz, 1H), 1.50 (dd, *J* = 11.7, 11.7 Hz, 1H), 1.24 (ddd, *J* = 13.8, 4.0, 3.8 Hz, 1H) 0.84 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 206.4, 143.6, 140.1, 137.5, 134.2, 131.9, 131.8, 130.3, 130.2, 130.1, 129.1, 105.7, 74.3, 74.1, 72.0, 45.2, 41.1, 34.5, 33.6, 31.9, 30.3, 23.1, 22.7, 22.6, 21.3, 21.0 ppm; HRMS (ES+) calcd for $C_{28}H_{36}O_8S_2Na$ (M + H) 565.1885, found 565.1930.

Azide ***50***. To a stirred solution of mesitylate **49** (1.84 g, 3.26 mmol) in DMF (10.5 mL) at rt were added sodium azide (2.17 g, 33.3 mmol) and TBAI (130 mg, 0.35 mmol), and the reaction was heated to 100 °C. After 4 h, the reaction mixture was cooled to rt, diluted with EtOAc (20 mL), and washed with water (30 mL). The aqueous layer was washed with EtOAc (3 × 25 mL). The dried ($MgSO_4$) organic

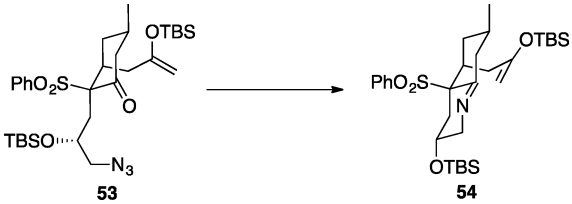
49 **50**

layer was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5−50% EtOAc/hexanes, to give azide **50** (851 mg, 2.09 mmol, 64%) as a colorless oil and ketal **51** (357 mg, 0.98 mmol, 30%) as a white solid. Characterization of azide **50**: $[\alpha]_D^{20}$ = +32.5 (*c* = 0.12, $CHCl_3$); IR (neat) 3450, 2952, 2100, 1714, 1442, 1286, 1142, 1080, 1022 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.99 (dt, *J* = 8.5, 1.3 Hz, 2H), 7.73 (tt, *J* = 7.4, 1.4 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 2H), 4.33 (s, 1H), 4.18−4.22 (m, 1H), 3.68 (dd, *J* = 12.6, 6.4 Hz, 1H), 3.47 (dd, *J* = 12.4, 4.8 Hz, 1H), 2.96−2.99 (m, 1H), 2.92 (dd, *J* = 13.8, 7.7 Hz, 1H), 2.72 (dd, *J* = 17.1, 3.3 Hz, 1H), 2.55 (dd, *J* = 9.3, 9.1 Hz, 1H), 2.17 (dd, *J* = 7.7, 7.6 Hz, 1H), 2.11 (s, 3H), 2.04 (dd, *J* = 5.6, 5.5 Hz, 1H), 1.79−1.84 (m, 1H), 1.54−1.57 (m, 1H), 1.38 (dd, *J* = 14.1, 11.5 Hz, 1H), 1.31 (dd, *J* = 5.7, 5.2 Hz, 1H), 0.82 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 206.3, 137.3, 134.2, 130.4, 129.0, 105.6, 75.9, 74.9, 56.10, 45.58, 40.55, 34.5, 33.1, 31.6, 30.3, 23.1, 21.3 ppm; HRMS (ES+) calcd for $C_{19}H_{25}N_3O_5SNa$ (M + Na) 430.1414, found 430.1413.



50 **53**

TBS Ether ***53***. To a stirred solution of **50** (140 mg, 0.344 mmol) in CH_2Cl_2 (1.7 mL) was added $^iPr_2NEt$ (668 mg, 0.90 mL, 5.168 mmol) at 0 °C. After 10 min, TBSOTf (460 mg, 0.40 mL, 1.742 mmol) was added and the reaction mixture was warmed to rt. After 18 h, the reaction was quenched by sat. aq $NaHCO_3$ (10 mL) and 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 2−20% EtOAc/hexanes, to give **53** (151 mg, 0.237 mmol, 69%) as a colorless liquid. $[\alpha]_D^{20}$ = +16.9 (*c* = 0.36, $CHCl_3$); IR (neat) 2954, 2928, 2856, 2103, 1716, 1629, 1463, 1306, 1257, 1142, 1078, 1024, 837, 780, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.65 (t, *J* = 7.2 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 4.56 (m, 1H), 4.11 (s, 1H), 4.05 (s, 1H), 3.41 (dd, *J* = 13.2, 3.6 Hz, 1H), 3.19 (d, *J* = 14.0 Hz, 1H), 3.07 (dd, *J* = 8.8, 2.8 Hz, 1H), 2.88−2.92 (m, 1H), 2.81 (dd, *J* = 14.0, 6.4 Hz, 1H), 2.39−2.50 (m, 2H), 2.18−2.30 (m, 2H), 1.90−2.03 (m, 2H), 1.68−1.75 (m, 1H), 0.96 (s, 9H), 0.91 (s, 9H), 0.76 (d, *J* = 6.8, 3H), 0.23 (s, 3H), 0.19 (s, 3H), 0.15 (s, 6H), ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 206.4, 156.8, 136.7, 133.8, 130.8, 128.6, 91.4, 79.5, 68.7, 55.9, 47.2, 37.2, 35.1, 33.0, 32.7, 28.1, 26.2, 25.8, 19.9, 18.2, 17.9, −4.4, −4.5 ppm; HRMS (ES+) calcd for $C_{31}H_{54}N_3O_5SSi_2$ (M + H) 636.3323, found 636.3308.



53 **54**

Imine ***54***. To a solution of **53** (34.3 mg, 0.054 mmol) in THF (1.6 mL) was added PPh_3 (23.0 mg, 0.088 mmol) as a solid, and the reaction mixture was heated to reflux. After 4 h, the reaction was cooled to rt and the solvent was removed in vacuo. The concentrated material was purified by chromatography over basic alumina, eluting with 2−15% EtOAc/hexanes, to give **54** (28.3 mg, 0.048 mmol, 89%) as a colorless oil. $[\alpha]_D^{20}$ = +120.2 (*c* = 0.86, $CHCl_3$); IR (neat) 2960,

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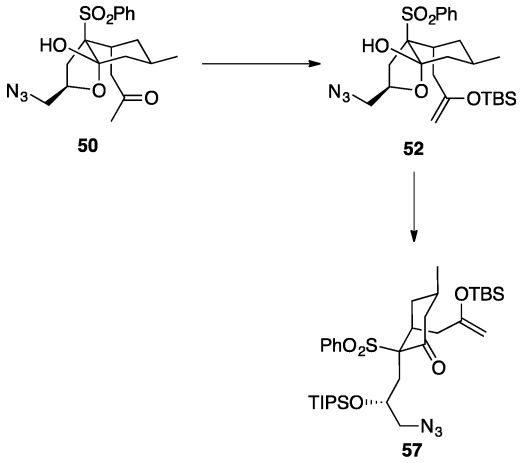
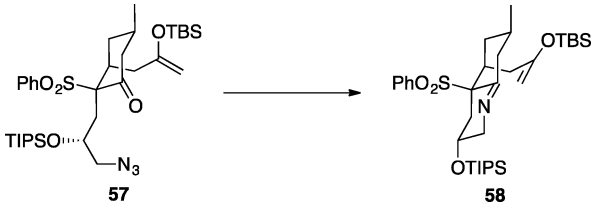
2925, 2855, 1653, 1637, 1466, 1458, 1310, 1252, 1143, 1100, 1026, 870, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J = 8.0, 1.4 Hz, 2H), 7.69 (t, J = 7.6 Hz, 1H), 7.55 (t, J = 8.0 Hz, 2H), 3.96−4.07 (m, 3H), 3.46 (ddd, J = 17.2, 4.8, 2.4 Hz, 1H), 3.30 (ddd, J = 17.2, 6.8, 2.0 Hz, 1H), 2.89 (m, 1H), 2.68−2.75 (m, 1H), 2.46 (td, J = 14.4, 5.6 Hz, 2H), 2.21 (dd, J = 15.2, 4.8 Hz, 1H), 1.97−2.08 (m, 2H), 1.75−1.86 (m, 2H), 1.03 (d, J = 6.0 Hz, 3H), 0.95 (s, 9H), 0.87 (s, 9H), 0.21 (s, 3H), 0.18 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 164.5, 156.6, 137.2, 133.9, 130.0, 129.1, 91.6, 72.3, 62.0, 56.1, 43.7, 37.9, 36.2, 32.7, 31.9, 31.2, 30.3, 28.1, 25.79, 25.74, 22.7, 22.0, 18.0, 17.9, 14.1, 0.01, −4.57, −4.58, −4.7 ppm; HRMS (ES+) calcd for $C_{31}H_{54}NO_4SSi_2$ (M + H) 592.3313, found 592.3316.

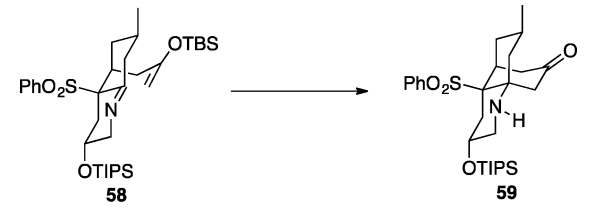


TIPS Ether ***57***. To a stirred solution of **50** (636 mg, 1.56 mmol) in CH_2Cl_2 (7.8 mL) at 0 °C were added $^iPr_2NEt$ (1.2 g, 1.6 mL, 9.3 mmol) and TBSOTf (1.03 g, 0.9 mL, 3.9 mmol) sequentially. After 1 h, the reaction was quenched by sat. aq $NaHCO_3$ (12 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The dried extract ($MgSO_4$) was concentrated in vacuo. An analytical sample of **52** was obtained by purification by chromatography over silica gel, eluting with 0−15% EtOAc/hexanes: $[\alpha]_D^{20}$ = +16.7 (c = 1.21, $CHCl_3$); IR (neat) 3406, 2954, 2928, 2858, 2101, 1631, 1446, 1284, 1258, 1142, 1077, 1023, 910, 840, 781, 689, 601 cm^{-1}; ^1H NMR (700 MHz, $CHCl_3$) δ 7.92 (dd, J = 8.4, 1.4 Hz, 2H), 7.68 (t, J = 7.7 Hz, 1H), 7.57 (t, J = 14.7 Hz, 2H), 4.27 (s, 1H), 4.15−4.19 (m, 1H), 4.04 (s, 1H), 3.98 (s, 1H), 3.69 (dd, J = 12.6, 4.9 Hz, 1H), 2.87 (dd, J = 13.3, 6.3 Hz, 1H), 2.54 (m, 1H), 2.25−2.32 (m, 2H), 2.10−2.14 (m, 2H), 1.78−1.81 (m, 1H), 1.71 (t, J = 13.3 Hz, 1H), 1.55−1.57 (m, 2H), 0.89 (d, J = 6.3 Hz, 3H), 0.84 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H) ppm; ^{13}C NMR (175 MHz, $CHCl_3$) δ 156.2, 138.4, 134.0, 129.7, 129.1, 105.6, 92.3, 75.8, 75.0, 56.4, 42.0, 37.1, 34.2, 34.0, 31.7, 25.7, 22.6, 21.5, 18.0, 0.04, −4.6, −4.8 ppm; HRMS (ES+) calcd for $C_{25}H_{40}N_3O_5SSi$ (M + H) 522.2458, found 522.2482.

The crude TBS-enol ether **52** was dissolved in 1,2-DCE (8.0 mL). To the solution were added $^iPr_2NEt$ (3.1 g, 4.2 mL, 24.1 mmol), DMAP (193 mg, 1.58 mmol), and TIPSOTf (3.2 g, 2.8 mL, 10.4 mmol) sequentially and heated to 40 °C. After 84 h, the reaction was cooled to rt, diluted with CH_2Cl_2 (10 mL), and quenched by sat. aq $NaHCO_3$ (15 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 0−15% EtOAc/hexanes, to give **57** (890 mg, 1.31 mmol, 85%) as a colorless oil. $[\alpha]_D^{20}$ = −34.0 (c = 0.5, $CHCl_3$); IR (neat) 2944, 2892, 2866, 2103, 1713, 1627, 1463, 1447, 1386, 1362, 1297, 1255, 1201, 1170, 1142, 1081, 1015 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 8.05−8.08 (m, 2H), 7.63 (dddd, J = 7.3, 7.4, 1.3, 1.3 Hz, 1H), 7.52 (dd, J = 8.0, 7.4 Hz, 2H), 4.84−4.89 (m, 1H), 4.11 (s, 1H), 3.99 (s, 1H), 3.56 (dd, J = 2.5, 13.3 Hz, 1H), 3.35 (td, J = 1.3, 14.6 Hz, 1H), 3.13 (dd, J = 2.4, 2.4 Hz, 1H), 3.07 (dd, J = 6.0, 5.7, Hz, 1H), 2.48−2.64 (m, 3H), 2.19−2.27 (m, 2H), 2.01 (dd, J = 11.7, 14.5, 1H), 1.73−1.87 (m, 2H), 1.07−1.14 (m, 21H), 0.94 (s, 9H), 0.59 (d, J = 6.7 Hz, 3H), 0.23 (s, 3H), 0.18 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CHCl_3$) δ 206.8, 157.1, 137.0, 133.7, 131.3, 128.6, 91.0, 80.0, 68.8, 55.0, 47.1, 37.2, 36.1, 33.3, 32.4, 28.8, 25.8, 18.7, 18.1, 18.1, 17.7, 12.4, −4.4, −4.6 ppm; HRMS (ES+) calcd for $C_{34}H_{60}N_3O_5SSi_2$ (M + H) 678.3792, found 678.3777.



Imine ***58***. To a stirred solution of **57** (890 mg, 1.31 mmol) in THF (45 mL) was added PPh_3 (516 mg, 1.97 mmol), and the reaction mixture was heated to reflux. After 4 h, the reaction was cooled to rt and the solvent was removed in vacuo. The concentrated compound was purified by chromatography over basic alumina, eluting with 0−20% EtOAc/hexanes, to give imine **58** (790 mg, 1.25 mmol, 95%) as a colorless oil. $[\alpha]_D^{23}$ = +36.0 (c = 1.0, $CHCl_3$); IR (neat) 2946, 2892, 2865, 1650, 1463, 1447, 1388, 1362, 1305, 1256, 1202, 1143, 1105, 1079, 1022 cm^{-1}; ^1H NMR (700 MHz, $CHCl_3$) δ 7.88 (dd, J = 8.8, 2.9 Hz, 2H), 7.68 (dd, J = 7.4, 7.1 Hz, 1H), 7.55 (dd, J = 8.1, 7.4 Hz, 2H), 4.12−4.15 (m, 1H), 4.08 (s, 1H), 4.02 (s, 1H), 3.57 (ddd, J = 17.2, 5.2, 2.7 Hz, 1H), 3.36 (ddd, J = 17.3, 7.0, 2.2 Hz, 1H), 2.90 (qd, J = 14.0, 3.5 Hz, 1H), 2.65 (dddd, J = 12.3, 12.1, 2.3, 2.3 Hz, 1H), 2.50 (dd, J = 3.5, 3.5 Hz, 1H), 2.46 (dd, J = 6.1, 6.1 Hz, 1H), 2.32 (dd, J = 4.8, 14.8 Hz, 1H), 1.98−2.04 (m, 2H), 1.79−1.85 (m, 2H), 1.53 (dddd, J = 5.6, 7.6, 5.6, 7.6 Hz, 1H), 1.03−1.06 (m, 21H), 1.02 (d, J = 6.4 Hz, 3H), 0.94 (s, 3H), 0.20 (s, 3H), 0.18 (s, 9H) ppm; ^{13}C NMR (175 MHz, $CHCl_3$) δ 164.5, 156.8, 137.3, 133.9, 130.1, 129.1, 91.5, 72.4, 62.0, 56.5, 43.5, 37.8, 36.0, 32.7, 31.2, 28.1, 25.7, 22.0, 18.0, 17.9, 12.2, −4.7, −4.8 ppm; HRMS (ES+) calcd for $C_{34}H_{60}NO_4SSi_2$ (M + H) 634.3782, found 634.3773.



Tricycle ***59***. To a sealed tube loaded with imine **58** (251 mg, 0.396 mmol) were added sequentially $Zn(OTf)_2$ (435 mg, 1.19 mmol) and 1,2-dichloroethane (15.8 mL) and heated to 94 °C. After 6 h, the reaction was cooled to rt. After 10 min, the reaction was quenched by sat. aq $NaHCO_3$ (10 mL) and 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 2−30% EtOAc/hexanes, to give **59** (118 mg, 0.227 mmol, 57%) as a white foam. $[\alpha]_D^{20}$ = −23.0 (c = 1.0, $CHCl_3$); IR (neat) 2925, 2864, 1711, 1647, 1462, 1296, 1137, 1077 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.94−7.96 (m, 2H), 7.73 (ddt, J = 7.5, 2.2, 1.1 Hz, 1H), 7.60−7.63 (m, 2H), 4.85−4.90 (m, 1H), 3.36 (dd, J = 14.5, 7.2 Hz, 1H), 3.33 (d, J = 2.5 Hz, 1H), 2.91 (dd, J = 14.5, 9.2 Hz, 1H), 2.71−2.76 (m, 1H), 2.59 (ddd, J = 17.8, 5.7, 1.5 Hz, 1H), 2.49 (dt, J = 15.1, 1.6 Hz, 1H), 2.29 (td, J = 17.9, 1.9 Hz, 1H), 2.23 (dd, J = 18.0, 1.9 Hz, 1H), 2.21 (dd, J = 10.7, 5.3 Hz, 1H), 1.89−1.98 (m, 3H), 1.61 (dd, J = 13.4, 5.4 Hz, 1H), 1.47 (dd, J = 13.9, 5.7 Hz, 1H), 1.06−1.09 (m, 21H), 1.04 (d, J = 6.3 Hz, 3H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 209.5, 137.8, 134.0, 129.6, 129.1, 71.7, 63.4, 57.8, 50.5, 47.5, 45.3, 43.2, 35.6, 35.5, 35.2, 24.9, 21.7, 18.1, 18.0, 12.3 ppm; HRMS (ES+) calcd for $C_{28}H_{46}NO_4SSi$ (M + H) 520.2917, found 520.2891.

Hemiketal ***SI-3***. A solution of acetonide **44** (120 mg, 0.284 mmol) in 60% AcOH (aq) (2.9 mL) was stirred at rt. After 15 h, water (10 mL) was added and the reaction mixture was treated with sat. aq $NaHCO_3$ (30 mL). The aqueous mixture was extracted with EtOAc (3 × 50 mL), washed with brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The concentrated compound was purified by

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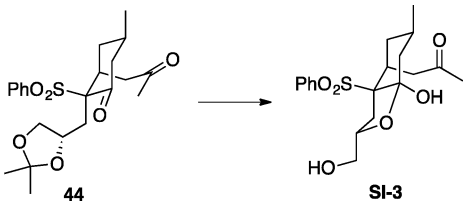
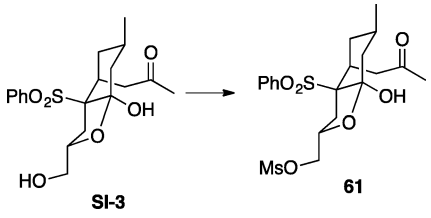


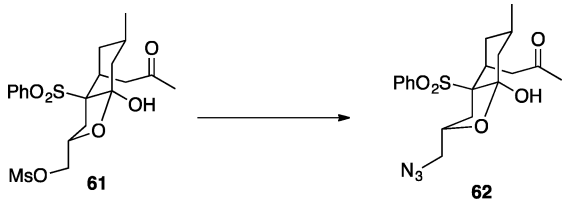
44 SI-3

chromatography over silica gel, eluting with 20−100% EtOAc/hexanes, to give product **SI-3** as a white foam (101 mg, 0.264 mmol, 93%). $[\alpha]_D^{20}$ = +6.2 (*c* = 0.13, $CHCl_3$); IR (neat) 3425, 2953, 2924, 2854, 1712, 1446, 1358, 1298, 1142, 1073, 757, 690, 600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.2 Hz, 2H), 7.74 (t, *J* = 7.6 Hz, 1H), 7.63 (t, *J* = 7.9 Hz, 2H), 5.64 (s, 1H), 4.35−4.41 (m, 1H), 3.99 (dt, *J* = 12.2, 3.5 Hz, 1H), 3.74 (m, 1H), 3.41 (d, *J* = 3.4, 1H), 2.89 (dd, *J* = 14.5, 6.7 Hz, 1H), 2.81 (ddd, *J* = 12.2, 8.3, 3.1 Hz, 1H), 2.32 (dd, *J* = 18.4, 9.2, 1H), 2.04−2.25 (m, 5H), 1.91 (dd, *J* = 14.6, 7.5 Hz, 1H), 1.74−1.87 (m, 2H), 1.61−1.66 (m, 1H), 0.97 (dd, *J* = 13.9, 3.1 Hz, 1H), 0.71 (d, *J* = 6.7, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 135.2, 134.5, 131.0, 128.8, 105.5, 75.5, 75.0, 62.9, 46.0, 38.0, 33.2, 30.7, 30.2, 28.7, 22.1, 21.6 ppm; HRMS (ES+) calcd for $C_{19}H_{26}O_6NaS$ (M + Na) 405.1348, found 405.1351.



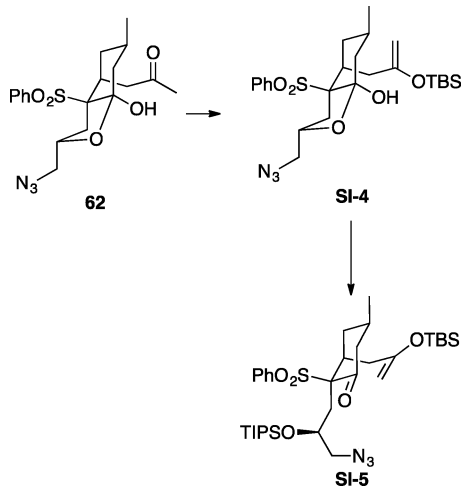
SI-3 61

*Mesylate **61**.* To an ice-bath cooled solution of **SI-3** (60.0 mg, 0.157 mmol) in CH_2Cl_2 (0.5 mL) were added 2,6-lutidine (22 mL, 0.188 mmol) and methanesulfonyl chloride (14.5 mL, 0.188 mmol), and the mixture was warmed to rt. After being stirred for 14 h at rt, the reaction mixture was diluted with CH_2Cl_2 (5.0 mL), washed with sat. aq $NaHCO_3$ (2 × 3.0 mL) and brine (3.0 mL), dried ($MgSO_4$), and concentrated in vacuo. Chromatography of the concentrated compound over silica gel (10−80% EtOAc/hexanes) gave the desired mesylate **61** (65.0 mg, 0.141 mmol, 90%) as a white foam. $[\alpha]_D^{20}$ = −2.0 (*c* = 0.99, $CHCl_3$); IR (neat) 3459, 2926, 2870, 1712, 1447, 1355, 1285, 1175, 1143, 1076, 963, 829, 727, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.7 Hz, 2H), 7.76 (t, *J* = 7.8 Hz, 1H), 7.64 (t, *J* = 7.7 Hz, 2H), 5.61 (s, 1H), 4.41−4.56 (m, 3H), 3.33 (d, *J* = 18.4 Hz, 1H), 3.09 (s, 3H), 3.02 (dd, *J* = 14.6, 6.8, 1H), 2.82 (ddd, *J* = 12.4, 8.7, 2.9 Hz, 1H), 2.32 (q, *J* = 9.2, 1H), 2.07−2.19 (m, 5H), 1.92 (dd, *J* = 14.5, 7.7 Hz, 1H), 1.72−1.86 (m, 1H), 1.59−68 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 1H) 0.98 (dd, *J* = 14.0, 3.1 Hz, 1H) 0.71 (d, *J* = 7.3, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 135.1, 134.6, 131.0, 128.9, 105.4, 76.1, 74.9, 72.6, 68.8, 45.9, 38.0, 37.7, 33.0, 30.7, 29.2, 22.1, 21.5 ppm; HRMS (ES+) calcd for $C_{20}H_{28}O_8S_2Na$ (M + Na) 483.1123, Found 483.1149.



61 62

*Azide **62**.* To a stirred solution of mesylate **61** (135 mg, 0.293 mmol) in DMF (0.8 mL) at rt was added sodium azide (24.8 mg, 0.381 mmol), and the mixture was heated to 100 °C. After 4 h, the reaction mixture was cooled to room temp, diluted with EtOAc (5.0 mL), and then washed with water (4.0 mL). The aqueous layer was extracted with EtOAc (3 × 3.0 mL), and the combined organic layer was dried with $MgSO_4$, concentrated in vacuo, and purified by chromatography over silica gel, eluting with 10−50% EtOAc/hexanes, to give azide **62** as a colorless oil (113 mg, 0.277 mmol, 95%). $[\alpha]_D^{20}$ = +36.9 (*c* = 0.32, $CHCl_3$); IR (neat) 3418, 2954, 2923, 2102, 1713, 1446, 1358, 1286, 1143, 1073, 1036, 729, 690 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.9 Hz, 2H), 7.74 (dt, *J* = 7.6 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 2H), 5.61 (s, 1H), 4.43−4.47 (m, 1H), 3.75 (dd, *J* = 13.3, 3.5 Hz, 1H), 3.38−3.42 (m, 2H), 2.90 (dd, *J* = 14.6, 6.9, 1H), 2.81 (ddd, *J* = 12.1, 8.5, 2.5 Hz, 1H), 2.32 (dd, *J* = 18.8, 9.8, 1H), 2.20 (s, 3H), 2.12−2.16 (m, 1H), 1.85−1.93 (m, 2H), 1.67−1.72 (m, 1H), 0.99 (dd, *J* = 13.8, 2.8 Hz, 1H) 0.72 (d, *J* = 7.0, 3H) 0.64−0.67 (m, 1H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 206.1, 135.1, 134.5, 131.0, 128.8, 105.2, 76.5, 73.9, 52.3, 46.0, 38.0, 33.1, 30.7, 30.1, 29.8, 22.0, 21.6 ppm; HRMS (ES+) calcd for $C_{19}H_{25}N_3O_5NaS$ (M + Na) 430.1413, found 430.1422.



62 SI-4 SI-5

*TIPS Ether **SI-5**.* To a stirred solution of methyl ketone **62** (19.1 mg, 0.0469 mmol) in CH_2Cl_2 (0.47 mL) at −44 °C were added $^iPr_2NEt$ (36.5 mg, 49.1 μL, 0.282 mmol) and TBSOTf (24.8 mg, 21.6 μL, 0.0939 mmol) sequentially. After 2.2 h, the reaction was quenched with sat. aq $NaHCO_3$ (2 mL) and extracted with CH_2Cl_2 (4 × 5 mL). The dried extract ($MgSO_4$) was concentrated in vacuo.

To a solution of the crude TBS enol ether **SI-4** was dissolved in 1,2-DCE (0.47 mL) were sequentially added Hunig's base (42.4 mg, 57.1 μL, 0.328 mmol), DMAP (5.7 mg, 0.047 mmol), and TIPSOTf (43.3 mg, 38.1 μL, 0.141 mmol), and the solution was heated to 80 °C. After 36 h, to the solution were added Hunig's base (60.6 mg, 81.8 μL, 0.469 mmol) and TIPSOTf (57.7 mg, 50.8 μL, 0.188 mmol) sequentially. After another 24 h, the reaction was cooled to rt, diluted with CH_2Cl_2 (5 mL), and quenched with sat. aq $NaHCO_3$ (4 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 8 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 0−15% EtOAc/hexanes, to give **SI-5** (21.1 mg, 0.0311 mmol, 66%) as a white solid. $[\alpha]_D^{20}$ = +18.5 (*c* = 1.0, $CHCl_3$); IR (neat) 2921, 2851, 2103, 1730, 1658, 1464, 1289, 1142, 1073 cm^{-1}; ^1H NMR (700 MHz, CHCl3) δ 7.84 (d, *J* = 7.6 Hz, 2H), 7.67 (t, *J* = 7.1 Hz, 1H), 7.54 (t, *J* = 7.4 Hz, 2H), 4.26 (m, 1H), 4.12 (s, 1H), 4.08 (s, 1H), 3.37 (t, *J* = 11.8 Hz, 1H), 3.16−3.26 (m, 3H), 2.59−2.69 (m, 2H), 2.41 (dd, *J* = 14.0, 7.2 Hz, 1H), 2.25 (dd, *J* = 14.7, 4.8 Hz, 1H), 2.16 (m, 1H), 2.00 (t, *J* = 12.5 Hz, 1H), 1.92 (dt, *J* = 14.5, 3.7 Hz, 1H), 1.54 (m, 1H), 1.00 (s, 21H), 1.01 (s, 9H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.27 (s, 3H), 0.24 (s, 3H) ppm; ^{13}C NMR (175 MHz, CHCl3) δ 206.6, 156.7, 135.9, 134.0, 131.04, 128.5, 91.2, 78.5, 69.1, 57.6, 46.9, 35.6, 33.6, 32.5, 26.8, 25.7, 21.6, 18.2, 18.1, 13.0, −4.6, −4.7 ppm; HRMS (ES+) calcd for $C_{34}H_{60}N_3O_5Si_2S$ (M + H) 678.3792, found 678.3808.

*Imine **63**.* To a stirred solution of azide **SI-5** (9.8 mg, 0.014 mmol) in THF (0.56 mL) at rt was added polymer supported PPh_3 (21.8 mg, 0.026 mmol, 1.2 mmol/g), and the solution was heated to reflux. After 3 h, the reaction was cooled to rt, the polymer-supported PPh_3 resin was removed by filtration, the polymer was washed with CH_2Cl_2 (8 × 1.5 mL), and the combined solution was concentrated in vacuo. The crude product was purified by chromatography over basic alumina,

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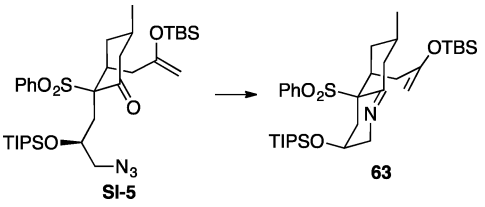
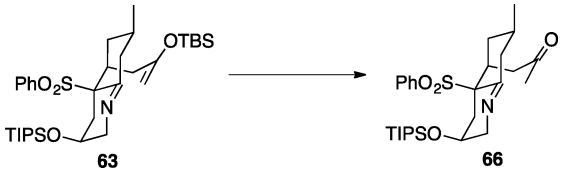
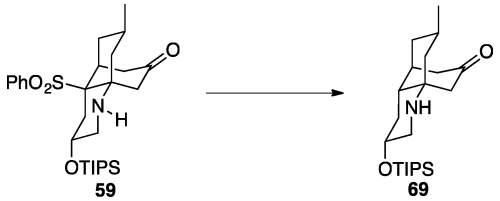


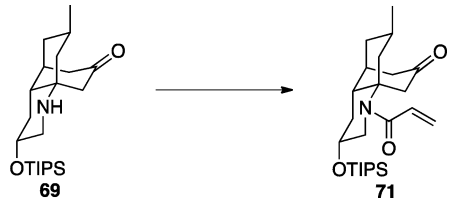
eluting with 0−20% EtOAc/hexanes, to give imine **63** (7 mg, 0.011 mmol, 79%) as a colorless oil. $[\alpha]_D^{20}$ = +58.0 (*c* = 1.0, $CHCl_3$); IR (neat) 2929, 2867, 1642, 1463, 1307, 1147, 1025 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.6 Hz, 2H), 7.69 (t, *J* = 7.4 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 2H), 4.14 (s, 1H), 4.05 (s, 1H), 3.74 (dt, *J* = 15.1, 3.5 Hz, 1H), 3.57 (m, 1H), 3.08 (td, *J* = 13.2, 4.5 Hz, 1H), 2.80 (d, *J* = 11.8 Hz, 1H), 2.52 (dd, *J* = 13.7, 3.6 Hz, 1H), 2.45 (td, *J* = 13.1, 4.2 Hz, 1H), 2.10−2.17 (m, 3H), 1.91−1.96 (m, 2H), 1.87 (dt, *J* = 14.4, 3.7 Hz, 1H), 1.77 (d, *J* = 13.3 Hz, 1H), 1.08 (d, *J* = 6.6 Hz, 3H), 1.00 (s, 21H), 0.92 (s, 9H), 0.21 (s, 3H), 0.17 (s, 3H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 165.8, 155.7, 136.4, 133.9, 130.1, 129.0, 92.3, 72.4, 64.3, 55.4, 45.3, 38.8, 38.7, 37.1, 31.0, 29.7, 27.3, 25.6, 22.0, 17.9, 12.2, −4.6, −4.9 ppm; HRMS (ES+) calcd for $C_{34}H_{60}NO_4Si_2S$ (M + H) 634.3782, found 634.3795.



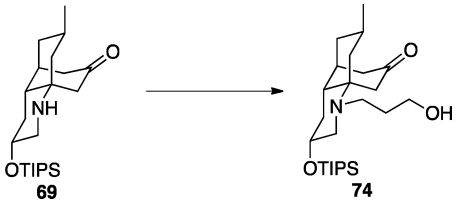
Methyl Ketone ***66***. To a sealed tube loaded with imine **63** (8.9 mg, 14.0 μmol) were added sequentially $Zn(OTf)_2$ (15.3 mg, 42.1 μmol) and 1,2-dichloroethane (0.42 mL) at rt, and the mixture was heated to 94 °C. After 4 h, the reaction was cooled to rt and quenched with sat. aq $NaHCO_3$ solution (1 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 2 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over basic alumina, eluting with 3−30% EtOAc/hexanes, to give methyl ketone **66** (1.1 mg, 2.1 μmol, 15%) as a colorless oil. $[\alpha]_D^{20}$ = +109.0 (*c* = 1.0, $CHCl_3$); IR (neat) 2923, 2853, 1719, 1645, 1464, 1306, 1147, 1106 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.4 Hz, 2H), 7.71 (t, *J* = 7.5 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 2H), 3.72 (dt, *J* = 14.7, 3.6 Hz, 1H), 3.55 (m, 1H), 3.29 (m, 1H), 2.87 (td, *J* = 12.7, 4.0 Hz, 1H), 2.47−2.51 (m, 3H), 2.38 (ddd, *J* = 14.7, 10.4, 3.5 Hz, 1H), 2.18 (s, 3H), 2.10 (ddd, *J* = 14.7, 10.1, 3.8 Hz, 1H), 1.93 (m, 1H), 1.86 (ddd, *J* = 14.4, 4.8, 2.9 Hz, 1H), 1.67 (m, 1H), 1.44 (dt, *J* = 14.4, 3.8 Hz, 1H), 1.08 (d, *J* = 6.4 Hz, 3H), 1.01 (s, 21H), ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 205.5, 165.8, 135.9, 134.3, 130.3, 129.1, 71.8, 64.8, 55.2, 44.5, 44.3, 36.6, 33.5, 30.2, 29.7, 27.6, 21.9, 17.96 17.93, 12.2 ppm; HRMS (ES+) calcd for $C_{28}H_{46}NO_4SiS$ (M + H) 520.2917, found 520.2902.



Amine ***69***. To a stirred solution of sulfone **59** (118 mg, 0.22 mmol) in 4:1 MeOH/THF (9.1 mL) at −10 °C were added sequentially Na_2HPO_4 (224 mg, 1.58 mmol) and 5% Na/Hg (628 mg, 1.37 mmol). After 1 h, the reaction was diluted with hexanes (10 mL), filtered through Celite, concentrated in vacuo, and purified by chromatography over silica gel, eluting with 2−50% EtOAc/hexanes, to give **69** (68 mg, 0.18 mmol, 79%) as a colorless oil. $[\alpha]_D^{20}$ = −16.9 (*c* = 1.0, $CHCl_3$); IR (neat) 2944, 2856, 1711, 1645, 1432, 1355, 1269, 1011, 752.9 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 3.82 (sept, *J* = 5.1 Hz, 1H), 3.04 (ddd, *J* = 12.8, 5.0, 1.9 Hz, 1H), 3.00 (d, *J* = 17.1 Hz, 1H), 2.68 (dd, *J* = 12.5, 10.1 Hz, 1H), 2.45 (dd, *J* = 17.0, 6.3 Hz, 1H), 2.21 (d, *J* = 16.8 Hz, 1H), 2.12−2.09 (m, 1H), 2.01 (d, *J* = 16.8 Hz, 1H), 1.84−1.87 (m, 1H), 1.69−1.72 (m, 1H), 1.55−1.67 (m, 4H), 1.26 (dt, *J* = 12.3, 3.3 Hz, 1H), 1.06−1.09 (m, 21H), 0.96−1.01 (m, 2H), 0.87 (d, *J* = 6.0 Hz, 3H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 212.7, 69.8, 53.7, 50.3, 48.6, 45.7, 42.6, 41.9, 41.7, 35.7, 35.4, 25.5, 22.4, 18.09, 18.03, 12.2 ppm; HRMS (ES+) calcd for $C_{22}H_{42}NO_2Si$ (M + H) 380.2985, found 380.2968.



Amide ***71***. To a stirred solution of amine **69** (17.8 mg, 0.047 mmol) in CH_2Cl_2 (0.47 mL) at 0 °C were added sequentially $^iPr_2NEt$ (18.2 mg, 25.0 μL, 0.141 mmol) and acryloyl chloride (**70**) (6.4 mg, 5.7 μL, 0.057 mmol). After 10 min, the reaction was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5−30% EtOAc/hexanes, to give **71** (17.3 mg, 0.040 mmol, 85%) as a colorless oil. $[\alpha]_D^{23}$ = −27.1 (*c* = 1.0, $CHCl_3$); IR (neat) 2965, 1442, 1298, 1147 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 6.48 (dd, *J* = 16.8, 10.5 Hz, 1H), 6.13 (dd, *J* = 16.8, 1.4 Hz, 1H), 5.60 (dd, *J* = 10.5, 2.1 Hz, 1H), 4.21 (m, 1H), 3.65 (m, 2H), 3.43 (m, 1H), 3.27 (m, 1H), 2.82 (m, 1H), 2.54 (m, 1H), 2.20−2.04 (m, 3H), 1.86 (m, 1H), 1.73 (m, 2H), 1.31−1.27 (m, 4H), 1.11−1.05 (m, 21H), 0.90 (d, *J* = 6.3 Hz, 3H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 210.4, 168.4, 131.7, 126.1, 67.0, 60.6, 49.2, 44.8, 44.4, 42.0, 41.7, 40.1, 35.0, 34.7, 25.9, 22.3, 18.05, 18.00, 12.1 ppm; HRMS (ES+) calcd for $C_{25}H_{44}NO_3Si$ (M + H) 434.3090, found 434.3104.



Alcohol ***74***. To a stirred solution of amine **69** (46 mg, 0.121 mmol) in acetone (1.4 mL) at rt were added sequentially K_2CO_3 (36.8 mg, 0.266 mmol), $NaHCO_3$ (35.6 mg, 0.424 mmol), and 3-iodo-1-propanol (**73**) (29.3 mg, 15 mL, 0.157 mmol) and heated to reflux. After 10 h, the reaction was cooled to rt. The reaction was concentrated in vacuo and purified by chromatography over silica gel, eluting with 2−30% EtOAc/hexanes, to give **74** (36 mg, 0.082 mmol, 68%) as a colorless oil and recovered amine **7** (10 mg, 0.026 mmol, 22%). $[\alpha]_D^{20}$ = −19.8 (*c* = 0.71, $CHCl_3$); IR (neat) 3417, 2936, 2866, 1705, 1461, 1109, 1070, 797.0 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 4.95−5.04 (m, 1H), 3.82−3.86 (m, 1H), 3.78−3.80 (m, 2H), 3.21 (ddd, *J* = 11.9, 4.7, 1.9 Hz, 1H), 3.07 (td, *J* = 12.4, 3.4 Hz, 1H), 2.69 (d, *J* = 16.4 Hz, 1H), 2.53 (dd, *J* = 17.2, 6.4 Hz, 1H), 2.13−2.25 (m, 7H), 1.84−1.93 (m, 2H), 1.71 (d, *J* = 13.2 Hz, 1H), 1.57−1.62 (m, 3H), 1.48 (tt, *J* = 15.0, 3.3 Hz, 1H), 1.30 (td, *J* = 13.0, 3.9 Hz, 1H), 1.07−1.11 (m, 21H), 0.92 (d, *J* = 6.2 Hz, 3H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 211.8, 67.8, 64.2, 58.2, 54.2, 47.9, 46.7, 42.2, 42.1, 41.6, 39.0, 36.3, 35.7, 28.3, 25.7, 22.5, 18.08, 18.06, 12.2 ppm; HRMS (ES+) calcd for $C_{25}H_{48}NO_3Si$ (M + H) 438.3403, found 438.3390.

Enone ***76***. To a sealed tube loaded with ^tBuOK[39] (82 mg, 0.731 mmol) and benzophenone (397 mg, 2.18 mmol) was added a solution of alcohol **74** (53 mg, 0.121 mmol) in benzene[40] (1.7 mL) and heated to 95 °C. After 1 h, the reaction was cooled to rt. The reaction was quenched by sat. aq NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 0−30% EtOAc/hexanes, to give **76** (36 mg, 0.086 mmol, 71%) as a yellow oil

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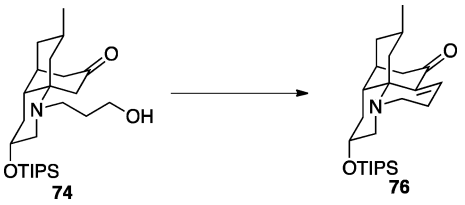
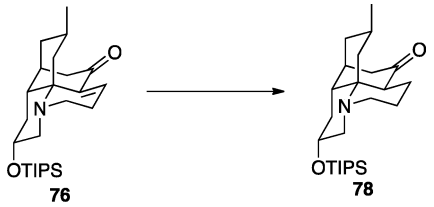
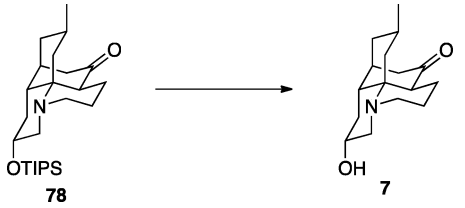


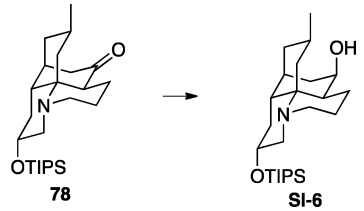
and **69** (8.1 mg, 0.021 mmol, 17%) as a colorless oil. $[\alpha]_D^{20}$ = +36.0 (*c* = 0.5, $CHCl_3$); IR (neat) 2931, 2865, 1685, 1614, 1460, 1244, 1097, 1012, 882.9, 806.6 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.01 (t, *J* = 3.7 Hz, 1H), 3.93 (dddd, *J* = 14.5, 10.3, 8.7, 4.3 Hz, 1H), 3.55 (ddd, *J* = 14.4, 10.9, 6.2 Hz, 1H), 2.80 (ddd, *J* = 10.7, 4.4, 2.0 Hz, 1H), 2.71 (dd, *J* = 14.6, 7.7 Hz, 1H), 2.65 (dd, *J* = 18.9, 7.1 Hz, 1H), 2.57−2.63 (m, 1H), 2.43 (t, *J* = 10.3 Hz, 1H), 2.34 (d, *J* = 18.9 Hz, 1H), 2.13−2.16 (m, 2H), 2.07 (dd, *J* = 6.0, 4.4 Hz, 1H), 1.80 (ddd, *J* = 12.1, 5.5, 3.8 Hz, 1H), 1.74 (ddt, *J* = 13.2, 4.0, 2.0 Hz, 1H), 1.63 (dt, *J* = 13.7, 2.8 Hz, 1H), 1.50−1.55 (m, 1H), 1.34−1.39 (m, 2H), 1.11 (d, *J* = 1.3 Hz, 1H), 1.06−1.10 (m, 21H), 0.92 (d, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 199.1, 137.7, 135.8, 68.4, 57.0, 56.0, 49.3, 42.9, 42.2, 41.6, 41.1, 37.1, 33.9, 25.6, 22.4, 21.1, 18.1, 18.0, 12.3 ppm; HRMS (EI+) calcd for $C_{25}H_{43}NO_2Si$ (M +) 417.3063, found 417.3065.



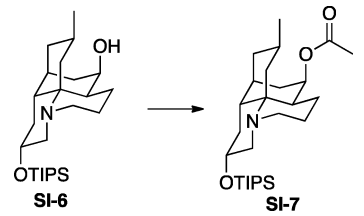
Tetracycle ***78***. To a stirred solution of enone **76** (36 mg, 0.086 mmol) in methanol (4 mL) at rt was added PtO_2 (8 mg).[24a] An atmosphere of H_2 was introduced. After 4 h under 1 atm H_2 (balloon), the reaction mixture was filtered through a pad of Celite. The reaction mixture was concentrated in vacuo and purified by chromatography over silica gel, eluting with 2−30% EtOAc/hexanes, to give **78** (33 mg, 0.079 mmol, 91%) as a colorless oil. $[\alpha]_D^{20}$ = −3.7 (*c* = 1.0, $CHCl_3$); IR (neat) 2938, 2865, 1703, 1460, 1382, 1108, 1067, 882.2, 804.9 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 3.97 (sept, *J* = 5.0 Hz, 1H), 3.37 (dt, *J* = 13.9, 3.6 Hz, 1H), 2.98 (t, *J* = 10.3 Hz, 1H), 2.91 (dd, *J* = 11.8, 2.9 Hz, 1H), 2.82 (ddd, *J* = 11.5, 4.7, 1.6 Hz, 1H), 2.64 (dd, *J* = 13.3, 4.0 Hz, 1H), 2.59 (dd, *J* = 15.9, 6.1 Hz, 1H), 2.52 (dd, *J* = 14.5, 4.9 Hz, 1H), 2.23 (d, *J* = 15.9 Hz, 1H), 2.12−2.15 (m, 1H), 2.07 (d, *J* = 13.5 Hz, 1H), 1.83−1.92 (m, 2H), 1.73−1.80 (m, 2H), 1.59−1.63 (m, 1H), 1.48−1.55 (m, 1H), 1.40 (d, *J* = 13.7 Hz, 1H), 1.31 (dt, *J* = 12.3, 3.3 Hz, 1H), 1.11−1.09 (m, 21H), 0.88 (d, *J* = 6.3 Hz, 3H), 0.82 (t, *J* = 13.0 Hz, 1H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 213.1, 68.9, 58.7, 55.4, 46.5, 43.1, 43.0, 42.77, 42.75, 42.4, 36.6, 35.6, 25.3, 22.7, 19.4, 18.8, 18.12, 18.10, 12.3 ppm; HRMS (ES+) calcd for $C_{25}H_{46}NO_2Si$ (M + H) 420.3298, found 420.3278.



*10-Hydroxylycopodine (****7****).* To a stirred solution of TIPS ether **78** (4.0 mg, 3.5 μL, 9.5 μmol) in THF (0.48 mL) at rt was added TASF (7.9 mg, 28.6 μmol). After 4 h, the reaction was concentrated in vacuo and purified by chromatography over silica gel, eluting with 1−10% methanol/CH_2Cl_2, to give the natural product **7** (2.1 mg, 8.0 μmol, 84%), which was matched with the literature values,[25] as a white solid. $[\alpha]_D^{20}$ = −19.5 (*c* = 0.92, $CHCl_3$);[41] IR (neat) 3365, 2924, 2866, 1698, 1454, 1356, 1230, 1176, 1118, 1097, 1052, 1024 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 3.93 (sept, *J* = 4.9 Hz, 1H), 3.36 (dt, *J* = 14.2, 3.6 Hz, 1H), 2.96 (t, *J* = 10.9 Hz, 1H), 2.90−2.85 (m, 2H), 2.64 (dd, *J* = 13.4, 3.8 Hz, 1H), 2.57 (dd, *J* = 6.2, 6.1 Hz, 1H), 2.54 (dd, *J* = 5.1, 4.9 Hz, 1H), 2.26 (dt, *J* = 15.9, 1.3 Hz, 1H), 2.15−2.17 (m, 1H), 2.07−2.11 (m, 1H), 1.89−1.92 (m, 1H), 1.87 (qt, *J* = 13.8, 4.9 Hz, 1H), 1.67−1.76 (m, 4H), 1.58−1.65 (m, 1H), 1.48−1.56 (m, 1H), 1.43 (d, *J* = 13.8 Hz, 1H), 1.32 (dt, *J* = 12.8, 3.9 Hz, 1H), 0.86 (d, *J* = 6.3 Hz, 3H), 0.82 (t, *J* = 13.1 Hz, 1H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 212.8, 68.1, 58.8, 54.8, 46.4, 43.0, 42.73, 42.70, 42.3, 36.6, 34.7, 25.3, 22.8, 19.3, 18.7 ppm; HRMS (EI+) calcd for $C_{16}H_{25}NO_2$ (M^+) 263.1885, found 263.1875.



Alcohol ***SI-6***. To a stirred solution of ketone **78** (5 mg, 11.9 μmol) in THF (0.6 mL) at −78 °C was added DIBAL-H (35.7 μL, 35.7 μmol, 1 M in hexanes). After 4 h, the reaction was warmed to −30 °C and quenched by sat. aq Rochelle's salt (3 mL). After being stirred for 6 h, the reaction mixture was extracted with EtOAc (3 × 5 mL). The dried (Na_2SO_4) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 0−10% methanol/CH_2Cl_2, to give **SI-6** (4.5 mg, 10.7 μmol, 90%) as a colorless oil. $[\alpha]_D^{20}$ = −16.9 (*c* = 0.16, $CHCl_3$); IR (neat) 3374, 2928, 2864, 1460, 1193, 1111, 1081, 882 cm^{-1}; ^1H NMR (700 MHz, MeOH-d_4) δ 4.09 (sept, *J* = 4.9 Hz, 1H), 3.99 (t, *J* = 5.8 Hz, 1H), 3.69 (td, *J* = 13.6, 3.8 Hz, 1H), 3.45 (t, *J* = 10.9 Hz, 1H), 3.16−3.27 (m, 1H), 2.99 (dd, *J* = 11.8, 4.3 Hz, 1H), 2.91 (dd, *J* = 13.6, 3.7 Hz, 1H), 2.69 (dd, *J* = 12.8, 5.8 Hz, 1H), 2.50 (dd, *J* = 9.2, 5.2 Hz, 1H), 2.13−2.20 (m, 2H), 2.05−2.15 (m, 1H), 1.88−1.94 (m, 2H), 1.82−1.85 (m, 1H), 1.76−1.77 (m, 1H), 1.55−1.61 (m, 3H), 1.22−1.28 (m, 1H), 1.07−1.17 (m, 21H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.91 (dd, *J* = 7.0, 2.9 Hz, 1H) ppm; ^{13}C NMR (175 MHz, MeOH-d_4) δ 66.8, 65.7, 52.3, 42.8, 40.5, 40.0, 35.4, 33.5, 32.9, 32.6, 29.3, 23.2, 22.3, 21.3, 19.0, 17.09, 17.06, 13.0, 12.0 ppm; HRMS (ES+) calcd for $C_{25}H_{48}NO_2Si$ (M + H) 422.3454, found 422.3459.



Acetate ***SI-7***. To a stirred solution of alcohol **SI-6** (4.5 mg, 10.7 μmol) in pyridine (0.25 mL) at rt were added DMAP (2.2 mg, 18.0 μmol) and Ac_2O (42 mg, 39 mL, 41.3 μmol). After 4 h, the reaction was quenched by pH 7.0 buffer solution (2 mL) and extracted with EtOAc (3 × 4 mL). The dried (Na_2SO_4) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 0−5% methanol/CH_2Cl_2, to give **SI-7** (4.6 mg, 99 μmol, 93%) as a yellow oil. $[\alpha]_D^{20}$ = −7.5 (*c* = 0.2, $CHCl_3$); IR (neat) 2924, 2854, 1738, 1555, 1460, 1232, 1114 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 5.06 (dd, *J* = 6.5, 6.3 Hz, 1H), 3.85 (sept, *J* = 5.3 Hz, 1H), 3.40 (ddd, *J* = 13.7, 13.7, 3.7 Hz, 1H), 2.97 (dd, *J* = 10.7, 10.7 Hz, 1H), 2.45−2.76 (m, 5H), 2.07−2.12 (m, 1H), 2.02 (s, 3H), 1.95 (ddddd, *J* = 13.8, 13.7, 13.4, 5.0, 5.0 Hz, 1H), 1.50−1.78 (m, 7H), 1.33−1.42 (m, 3H), 1.04−1.06 (m, 21H), 0.91 (d, *J* = 5.7 Hz, 3H), 0.73 (dd, *J* = 12.8, 12.9 Hz, 1H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 170.6, 70.2, 69.2, 55.1, 54.1, 47.0, 43.4, 42.6, 41.7, 35.2, 35.0, 31.2, 31.0, 24.3, 23.6, 23.1, 21.6, 20.4, 18.31, 18.30, 12.4 ppm; HRMS (ES+) calcd for $C_{27}H_{50}NO_3Si$ (M + H) 464.3560, found 464.3560.

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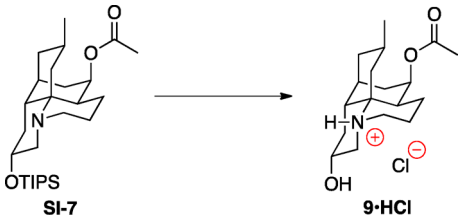
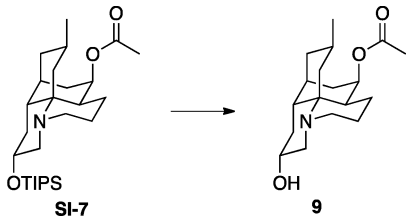
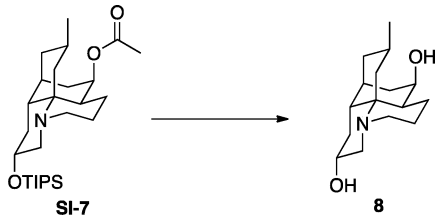


*HCl Salt of Paniculine (**9**·HCl).* To a stirred solution of TIPS ether **SI-7** (4.5 mg, 9.7 μmol) in MeOH (0.8 mL) at rt was added aq HCl (0.4 mL, 6 M). After 4 h, the reaction was concentrated in vacuo at 50 °C for 1 h and dried in vacuo for 12 h to give **9**·HCl (3.2 mg, 9.3 μmol, 96%) as a white solid.[42] $[\alpha]_D^{20}$ = −29.3 (*c* = 0.15, EtOH); IR (neat) 3302, 2923, 2868, 1734, 1455, 1366, 1252, 1235, 1192, 1117, 1065, 1023 cm^{-1}; ^1H NMR (700 MHz, MeOH-d_4) δ 5.23 (dd, *J* = 6.4, 6.4 Hz, 1H), 3.94 (dddd, *J* = 10.4, 10.4, 5.2, 5.2 Hz, 1H), 3.80 (dt, *J* = 13.8, 3.8 Hz, 1H), 3.53 (dd, *J* = 11.9, 11.7 Hz, 1H), 3.12 (ddd, *J* = 12.5, 5.1, 1.4 Hz, 1H), 3.05 (dd, *J* = 13.5, 4.9 Hz, 1H), 2.91 (dddd, *J* = 6.3, 6.1, 6.1, 6.1 Hz, 1H), 2.83 (dd, *J* = 6.1, 6.1 Hz, 1H), 2.80 (dd, *J* = 6.6, 6.4 Hz, 1H), 2.26 (ddd, *J* = 16.4, 6.3, 6.7 Hz, 1H), 2.08−2.13 (m, 1H), 2.07 (s, 3H), 1.99−2.02 (m, 1H), 1.78−1.88 (m, 5H) 1.74 (dd, *J* = 12.7 Hz, 1H), 1.62 (d, *J* = 16.4 Hz, 1H), 1.51−1.54 (m, 1H), 1.34 (ddd, *J* = 4.5, 13.0, 12.8 Hz, 1H), 1.06 (dd, *J* = 11.9, 11.9 Hz, 1H), 1.04 (d, *J* = 6.3 Hz, 3H), ppm; ^{13}C NMR (175 MHz, MeOH-d_4) δ 170.2, 67.8, 64.2, 62.5, 51.2, 47.1, 42.1, 39.9, 39.1, 34.6, 31.5, 31.4, 29.6, 23.7, 22.4, 20.2, 19.7, 18.4 ppm; HRMS (ES+) calcd for $C_{18}H_{30}NO_3$ (M^+) 308.2226, found 308.2234.



*Paniculine (**9**).* To a stirred solution of acetate **SI-7** (4.6 mg, 10 μmol) in MeOH (1 mL) at rt was added aq HCl (0.5 mL, 6 M). After 4 h, the reaction was concentrated in vacuo and treated with pH 10 buffer solution (1 mL). After 1 h, the reaction mixture was extracted with CH_2Cl_2 (3 × 3 mL). The dried (Na_2SO_4) extract was concentrated in vacuo and purified by chromatography over basic alumina, eluting with 0−8% methanol/CH_2Cl_2, to give paniculine (**9**) (2.8 mg, 9.1 μmol, 91%), which was matched with the literature values,[26e] as a colorless oil. $[\alpha]_D^{20}$ = −14.0 (*c* = 0.2, $CHCl_3$);[41] IR (neat) 3360, 2923, 2863, 1735, 1455, 1365, 1251, 1233, 1188, 1112, 1019, 972, 931 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 5.07 (dd, *J* = 6.4, 6.5 Hz, 1H), 3.82 (dddd, *J* = 10.6, 10.2, 5.2, 5.1 Hz, 1H), 3.42 (ddd, *J* = 13.9, 13.8, 3.8 Hz, 1H), 2.95 (dd, *J* = 10.9, 10.6 Hz, 1H), 2.76 (ddd, *J* = 10.8, 5.5, 1.8 Hz, 1H), 2.66 (dd, *J* = 12.7, 6.0 Hz, 1H), 2.63 (qdddd, *J* = 14.1, 14.4, 6.0, 6.0, 6.1 Hz, 1H), 2.50 (dd, *J* = 14.1, 4.9 Hz, 1H), 2.42 (ddd, *J* = 12.8, 6.1, 2.8 Hz, 1H), 2.09 (ddd, *J* = 16.2, 6.5, 6.7 Hz, 1H), 2.03 (s, 3H), 2.42 (ddd, *J* = 12.8, 6.1, 2.8 Hz, 1H), 1.93 (ddddd, *J* = 13.6, 13.5, 13.6, 5.0, 4.9 Hz, 1H), 1.78 (brs, 1H) 1.69 (dddd, *J* = 13.5, 13.2, 13.0, 4.4 Hz, 1H), 1.66 (ddd, *J* = 13.2, 6.7, 3.5 Hz, 1H), 1.63 (m, 1H), 1.51 (d, *J* = 16.5 Hz, 1H), 1.47 (m, 1H), 1.42 (m, 1H), 1.38 (m, 1H), 1.34 (brd, *J* = 13.7 Hz, 1H), 1.24 (ddd, *J* = 13.1, 13.1, 5.2 Hz, 1H), 0.91 (d, *J* = 6.3 Hz, 3H), 0.75 (t, *J* = 12.8, 12.3 Hz, 1H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 170.8, 70.1, 68.6, 54.7, 54.0, 47.1, 43.5, 42.8, 41.8, 34.9, 34.4, 31.1, 31.2, 24.3, 23.6, 23.1, 21.8, 20.4 ppm; HRMS (ES+) calcd for $C_{18}H_{30}NO_3$ (M + H) 308.2226, found 308.2228.

*Deacetylpaniculine (**8**).* To a stirred solution of acetate **SI-7** (4.1 mg, 8.7 μmol) in MeOH (1 mL) at rt was added aq HCl (0.5 mL, 6 M). After 4 h, the reaction was concentrated in vacuo and treated with 2.5 M aq NaOH solution (1 mL) in MeOH (0.5 mL). After 20 h, the reaction mixture treated with pH 7.0 buffer solution (2 mL) and extracted with EtOAc (3 × 3 mL). The dried (Na_2SO_4) extract was concentrated in vacuo and purified by chromatography over basic alumina, eluting with 2−10% methanol/CH_2Cl_2, to give deacetylpaniculine (**8**) (2.1 mg, 7.9 μmol, 91%), which was matched with the literature values, as a white solid. $[\alpha]_D^{20}$ = −13.3 (*c* = 0.12, $CHCl_3$);[41] IR (neat) 3344, 2920, 2863, 1455, 1372, 1257, 1190, 1115, 1041, 972 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 3.96 (dd, *J* = 6.1, 6.1 Hz, 1H), 3.82 (dddd, *J* = 10.6, 10.6, 5.5, 4.8 Hz, 1H), 3.44 (ddd, *J* = 13.9, 13.9, 3.7 Hz, 1H), 2.97 (dd, *J* = 10.6, 10.6 Hz, 1H), 2.89 (qdddd, *J* = 6.4, 12.7, 6.3, 12.7, 6.4 Hz, 1H), 2.76 (ddd, *J* = 11.0, 4.7, 1.4 Hz, 1H), 2.60 (dd, *J* = 13.1, 5.8 Hz, 1H), 2.52 (dd, *J* = 14.3, 4.7 Hz, 1H), 2.30 (ddd, *J* = 12.6, 5.7, 3.1 Hz, 1H), 2.08 (ddd, *J* = 15.5, 6.0, 6.2 Hz, 1H), 1.98 (ddddd, *J* = 13.4, 13.4, 13.4, 4.8, 4.8 Hz, 1H), 1.83 (dddd, *J* = 13.6, 13.6, 11.9, 4.7 Hz, 1H), 1.77 (m, 1H), 1.71 (dd, *J* = 5.9, 1.8 Hz, 1H), 1.62 (m, 1H), 1.52 (dd, *J* = 8.5, 7.2 Hz, 1H), 1.50 (m, 1H), 1.48 (m, 1H), 1.45 (m, 1H), 1.41 (brs, 1H), 1.20 (ddd, *J* = 12.7, 12.7, 5.0 Hz, 1H), 0.87 (d, *J* = 6.4 Hz, 3H), 0.71 (dd, *J* = 12.9, 12.8 Hz, 1H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 68.8, 68.3, 54.6, 54.3, 47.1, 43.7, 42.8, 41.7, 35.3, 34.5, 33.8, 32.4, 24.0, 23.5, 23.3, 20.6 ppm; HRMS (ES+) calcd for $C_{16}H_{28}NO_2$ (M + H) 266.2120, found 266.2111.



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H and ^{13}C NMR spectra for all synthesized compounds as well as crystallographic data for compounds **32a**, **44**, **47**, and **51**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00900.

Copies of ^1H and ^{13}C NMR spectra for all synthesized compounds (PDF)

Crystallographic data for compounds **32a**, **44**, **47**, and **51** (PDF)

X-ray data (CIF)

X-ray data (CIF)

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Notes

The authors declare no competing financial interest.

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(37) Preparation of LDA: To a solution of diisopropylamine (2.024 g, 2.8 mL, 20 mmol) in THF (9.2 mL) at −78 °C was added *n*-BuLi (8.0 mL, 20 mmol, 2.5 M in hexanes). After 5 min, the white slurry was warmed to −10 °C and stirred for 15 min prior to use.
(38) We purchased 3-penten-2-one (70% pure) from Aldrich's Flavors and Fragrances Division (Aldrich catalog no. W341703, 25 g, $126). The impurity (mesityl oxide) does not affect the performance of the cross metathesis. Alternate sources of 3-penten-2-one were significantly higher in cost and less pure.
(39) Preparation of ^{t}BuOK: To a flame-dried flask loaded with K metal (0.300 g, 7.67 mmol) was added ^{t}BuOH (6.0 mL, 62.7 mmol) (freshly distilled over Na metal) at rt and heated to 90 °C. After 15 min, the white slurry was cooled to rt and concented in vacuo to remove the excess solvents. Then the flask containing ^{t}BuOK was transferred to a glovebox prior to use.
(40) Benzene was always freshly distilled over CaH_2 before the reaction was performed.
(41) Please note that the optical rotation data for the natural product has not been previously reported.
(42) Please note that compound **9**·HCl was also fully characterized. Both paniculine (**9**) and deacetylpaniculine (**8**) were prone to protonation in $CDCl_3$ during prolonged data collection (e.g., ^{13}C NMR), which complicated the resultant spectra.

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