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Applications of ring closing metathesis. Total synthesis of (±)-pseudotabersonine

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This paper is dedicated to the memory of Professor Alan R. Katritzky, a long-time colleague and friend

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ABSTRACT

A novel approach to the *Aspidosperma* family of alkaloids was developed and applied to a concise total synthesis of (±)-pseudotabersonine that was accomplished in 11 steps. Key transformations include a stepwise variant of a Mannich-like multicomponent assembly process, a double ring-closing metathesis sequence, and a one-pot deprotection/cyclization reaction.

1. Introduction

The design and development of new strategies and tactics that may be generally applied to the efficient synthesis of biologically important natural products has long been a cornerstone of research in our laboratories and is vital to advancing the science of organic chemistry. Reactions that form new carbon–carbon bonds assume particular importance. It is in that context that we were drawn in the early 1990s to the potential power of ring-closing metathesis (RCM),[1,2] which has since emerged as one of the most powerful tools in organic synthesis. Beginning with developing methods in which RCM was used to construct nitrogen heterocycles,[3] we have since applied RCM as a key step in the syntheses of a number of alkaloids of varying complexity, including FR900482, manzamine A, (+)-anatoxin-a, dihydrocorynantheol, isolysergol, and a number of other natural products.[4] In connection with our continued interest in expanding the scope and utility of RCM as a strategic construct for the synthesis of complex molecules, we queried whether we might be able to apply a double RCM sequence as a key step in forming the pentacyclic core of the *Aspidosperma* alkaloids.

The *Aspidosperma* family of alkaloids is one of the largest families of indole alkaloids known, and over 250 unique alkaloids have been isolated from numerous plant sources.[5] Compounds of this family have long captured the attention of the synthetic community because of the biological activities of many of its members. Most *Aspidosperma* alkaloids feature a pentacyclic core with an ethyl group or a functionalized ethyl group at C20, as illustrated by the structure of aspidospermidine (**1**) (Fig. 1). However, there is a small family of *Aspidosperma* alkaloids that are related to pandoline (**2**), which bears a proton at the C14 bridge-head position (Fig. 1). Pseudotabersonine (**4**), which was isolated from *Pandaca caducifolia* in 1975,[6] is a representative member of this family of alkaloids. Prior to our work, only two total syntheses of pseudotabersonine (**4**) had been reported, and one other synthesis has been

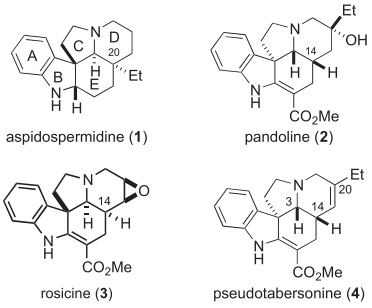

Fig. 1. Representative *Aspidosperma* alkaloids.

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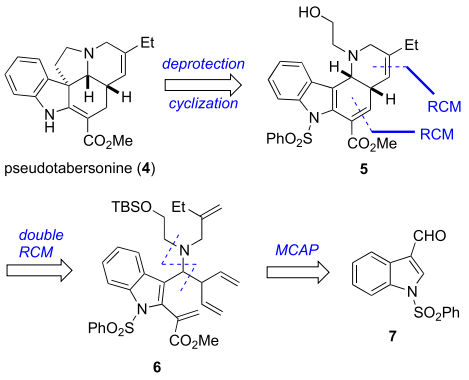
published subsequently.[7] Herein we report the details of our total synthesis of (±)-pseudotabersonine.[8]

2. Results and discussion

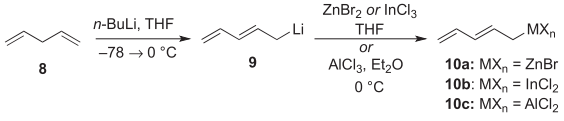
The endgame in our approach to pseudotabersonine (**4**), which is outlined in retrosynthetic format in Scheme 1, involves transforming the tetracyclic alcohol **5** into **4** using a one-pot deprotection and cyclization sequence that was inspired by Bosch.[9] Access to **5** would then feature the key double ring-closing metathesis reaction of the tetraene **6**. The preparation of **6** would then be achieved by a stepwise variant of a Mannich-type multicomponent assembly process (MCAP), which has been extensively developed in our laboratory for the rapid construction of functionalized heterocyclic scaffolds,[10] from the readily available 1-(phenylsulfonyl)-3-indolecarboxaldehyde (**7**).



Scheme 1. Retrosynthetic analysis of (±) pseudotabersonine (**4**).

Formation of the adduct **6** entailed the regioselective addition of a pentadienyl organometallic reagent to an imine to generate the branched pentadienyl adduct. Although there was a body of prior art relevant to the regiochemistry of additions of pentadienyl anions to carbonyl compounds,[11] there were only a few reports of such additions to imines.[4h,12] These reports suggest that the branched adduct likely arises from a Zimmerman-Traxler transition state, whereas the linear product is formed via either an eight-membered or open transition state. The challenge was to identify conditions that favored a six-membered transition state, and from what was known in the literature coupled with our contemporaneous work directed toward the synthesis of lysergol,[4h] it was apparent that some experimentation would be required.

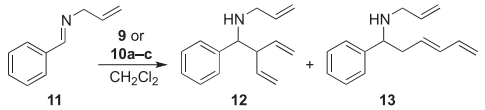
Toward identifying optimal conditions for inducing the addition of pentadienyl anions to imines to furnish the branched adducts, a brief exploratory study was undertaken. In the event, 1,4-pentadiene (**8**) was deprotonated by treatment with *n*-BuLi at −78 °C, and transmetalation of the lithio anion **9** thus produced with other metal halide salts gave the anions **10a**–**c** (Scheme 2).



Scheme 2. Synthesis of pentadienyl metal reagents.

With a selection of metalated pentadienyl anions in hand, we examined the regioselectivities in their additions to the model imine **11**. Reactions of **11** with **9** and **10a**–**c** at −78 °C gave a mixture of branched and linear products **12** and **13**, respectively (Table 1). The additions of the pentadienyl lithium reagent **9** and the indium reagent **10b** to **11** proceeded with similar selectivities to afford the linear adduct **13** as the major product (**12**:**13**=1:3 and 1:4, respectively). Although previous work in our lab[4h] and the labs of others[12] suggested that the pentadienyl zinc reagent **10a** should add with a high preference for forming the branched product, the addition of **10a** to imine **11** led mainly to the linear product **13** (**12**:**13**≈1:10). Miginiac had observed increased selectivities for branched products when pentadienyl aluminum reagent **10c** was allowed to react with aldehydes and ketones.[13] Gratifyingly, **10c** added to **11** to afford the branched product **12** as the major adduct (**12**:**13**≈7.5:1). It was essential to allow this reaction to warm to room temperature, because increased amounts of the linear adduct **13** were isolated if the reaction was quenched at −78 °C.

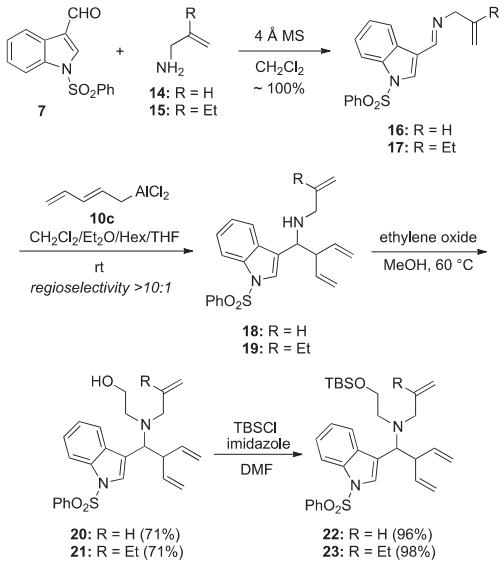
Table 1
Regioselectivity in additions of pentadienyl anions to **11**



Entry	MX_n	Branched (**12**): linear (**13**)[a]	% Conv.[a]
1	Li	1:3	30
2	ZnBr	1:10	100
3	$InCl_2$	1:4	50
4	$AlCl_2$	7.5:1	100

[a] Determined by ^1H NMR spectrum of crude reaction mixture.

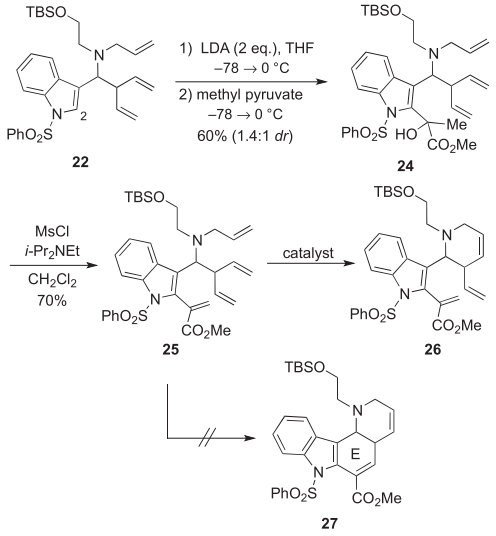
Having thus established the necessary conditions to effect the preferential formation of branched adducts in the additions of pentadienyl anions to imines, we could initiate our synthesis of members of the *Aspidosperma* alkaloids. Although our primary interest was in pseudotabersonine (**4**), we also wanted to explore the option of using a double RCM strategy to prepare *Aspidosperma* alkaloids such as rosicine (**3**), which lack the ethyl group at C20. Accordingly, the commercially-available aldehyde **7** was condensed with the allylamines **14** and **15** to give the corresponding intermediate imines **16** and **17** with nearly 100% conversion (Scheme 3). When the crude imines **16** and **17** were treated with **10c** under conditions previously developed for the pentadienylation of **11**, the branched adducts **18** and **19** were formed with high (>10:1) regioselectivity. These adducts were not purified, but rather they were treated directly with ethylene oxide at 60 °C in MeOH in



Scheme 3. Synthesis of branched trienes **22** and **23**.

a sealed tube to deliver the corresponding alcohols **20** and **21**. After a single recrystallization, **20** and **21** were isolated in 71% overall yields from **16** and **17**, respectively. Protection of the primary alcohol groups in **20** and **21** as their TBS ethers then afforded **22** and **23**.

It was now necessary to introduce an acrylate ester moiety at C2 of **22** and **23** in order to set the stage for the anticipated double RCM. This objective was readily achieved in a straightforward two-step sequence starting with **22** (Scheme 4). Deprotonation of **22** with LDA followed by trapping the anion thus formed with methyl pyruvate provided the alcohol **24** as an inconsequential mixture of diastereoisomers ($dr \approx 1.4{:}1$) in 60% yield (74% conversion based upon 26% recovery of starting **22**). Dehydration of **24** with MsCl and Hünig's base furnished the desired tetraene **25** in 70% crude yield. Unfortunately, tetraene **25** proved to be somewhat unstable and could not be purified to homogeneity by column chromatography.



Scheme 4. Double RCM approach to **27**.

Notwithstanding the instability of the tetraene **25**, we attempted to induce the planned double RCM. However, to our dismay, when impure **25** was subjected to a number of RCM conditions using a variety of standard precatalysts (Fig. 2), none of the desired product **27**, which would arise from the anticipated double RCM process, was observed. Under all of the conditions tried, the major isolable product was the mono-cyclized product **26**, which was formed in at best 50% yield. Attempts to drive the reaction to **27** at higher temperatures and using microwave heating were uniformly unsuccessful. Even the Grubbs-Stewart catalyst, which is known to show increased reactivity towards sterically hindered olefins,[14] failed to provide **27**. In retrospect the inability to close the E ring in **27** via RCM is not completely surprising because electron deficient olefins are known to react more slowly in such cyclizations.[15] Moreover, the acrylate is also a 2,2-disubstituted olefin, and such alkenes are also known to be less reactive toward RCM.

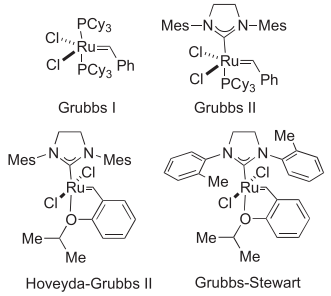
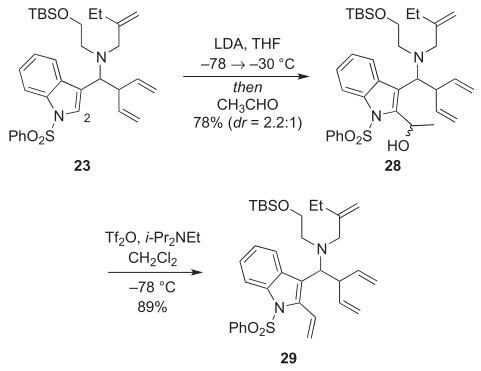


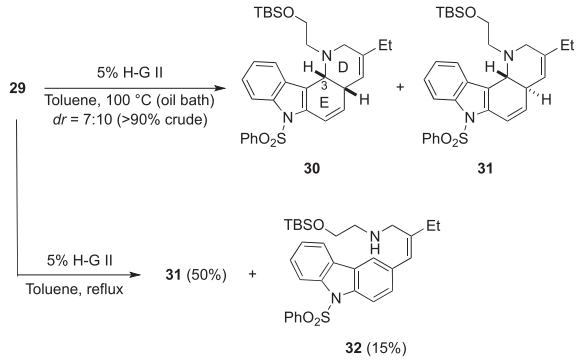
Fig. 2. Selected precatalysts for RCM reactions.

At this juncture, it was clear that our initial plan to generate a fully substituted E ring by RCM was going to be problematic. We also decided to focus our attention on the synthesis of pseudotabersonine (**4**) because there are more *Aspidosperma* alkaloids that contain an ethyl group at C20 than those lacking such an ethyl group. Accordingly, we turned our attention toward introducing a vinyl group at the C2 position of **23**. This was easily achieved by treating **23** with LDA followed by the addition of acetaldehyde to give the alcohol **28**, which was smoothly converted to tetraene **29** upon reaction with Tf_2O and Hünig's base in about 70% overall yield (Scheme 5).



Scheme 5. Synthesis of tetraene **29**.

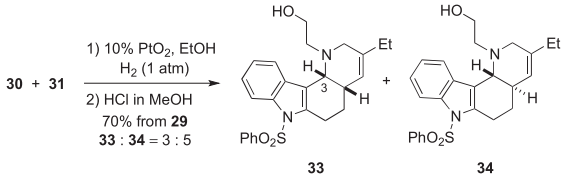
The opportunity for a double RCM was again at hand. However, considerable experimentation was required in order to optimize this transformation because the course of the reaction was highly dependent upon the conditions, especially the reaction temperature. For example, when a solution of **29** containing 5% of Hoveyda-Grubbs catalyst was heated at 100 °C (oil bath), the double RCM proceeded smoothly to afford a mixture (7:10) of the D/E *cis*-fused and D/E *trans*-fused tetracycles **30** and **31**, respectively, in >90% combined overall crude yield (Scheme 6).[16] It should be noted that pseudotabersonine has a *cis*-fused D/E ring junction, and **30** was unfortunately the minor diastereoisomer produced by the RCM. Interestingly, if the RCM reaction was performed at lower temperatures, the ratio of **30** to **31** improved to approximately 1:1, but the overall conversions were low. On the other hand, when the RCM was conducted in refluxing toluene, none of the desired D/E *cis*-fused product **30** was observed. Instead, the D/E *trans*-fused tetracycle **31** was isolated in 50% yield together with about 15% of the ring-opening product **32**. Collectively, these findings suggest that the desired D/E *cis*-fused product **30** was unstable at higher



Scheme 6. Double RCM of tetraene **29**.

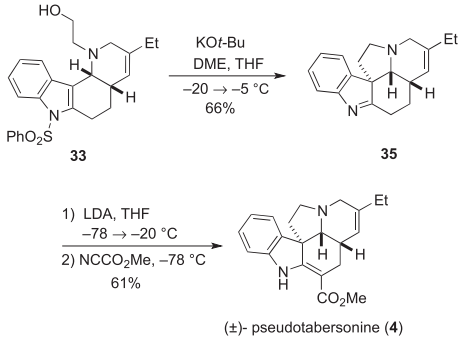
temperatures, undergoing sequential 1,4-elimination and aromatization reactions that led to the formation of **32**.[17] Owing to the apparent thermal instability of **30**, it was necessary to carefully monitor the temperature and time for the double RCM of **29** to give optimal quantities of **30**.

The tetracycles **30** and **31** were inseparable by column chromatography, so they were simply subjected as a crude mixture to the regioselective catalytic hydrogenation of the less substituted carbon–carbon double bond, followed by acid-induced deprotection of the TBS ether to afford a readily separable mixture (3:5) of **33** and **34** in 70% overall yield from **29** (Scheme 7).[18]



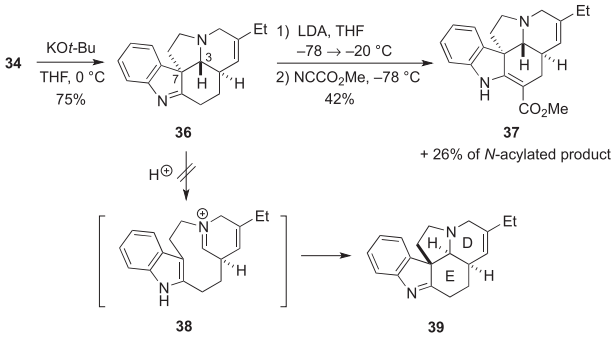
Scheme 7. Synthesis of tetracycles **33** and **34**.

Conversion of **33** to pentacycle **35** was achieved via a one-pot *N*-deprotection/*O*-sulfonylation sequence followed by a cyclization that was inspired by a report by Bosch and co-workers who performed a similar transformation.[9] Namely, addition of a solution of KO*t*-Bu in THF to a solution of **33** in DME delivered **35** in 66% yield (Scheme 8). The choice of solvent was critical for the success of this process. Solvents other than DME (e.g., THF, hexane, dichloromethane, toluene and Et_2O) gave only trace amounts of **35**. Finally, following a procedure developed by Rawal,[19] pentacycle **35** was deprotonated with LDA, and the intermediate imine anion was allowed to react with Mander's reagent to furnish (±)-pseudotabersonine (**4**) in 61% yield; only a trace of the corresponding *N*-acylated product was observed. The synthetic pseudotabersonine thus obtained gave ^1H and ^{13}C NMR spectra that are consistent with the assigned structure of **4** and with those reported and provided by Kuehne.[7a,20]



Scheme 8. Completion of the synthesis of (±)-pseudotabersonine (**4**).

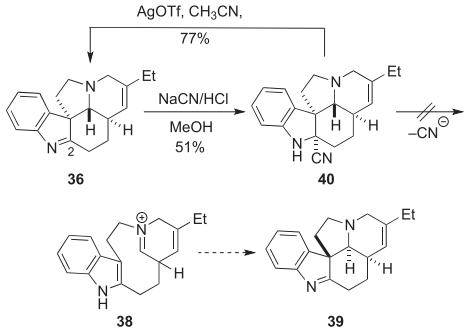
This sequence of reactions was then readily applied to the synthesis of (±)-14-*epi*-pseudotabersonine (**37**). Although the conversion of **34** into **36** proceeded without event, the *C*-carbomethoxylation of **36** to give **37** following the Rawal protocol was accompanied by extensive *N*-acylation, and the carbamate analog of **37** was formed in about 26% yield (Scheme 9). The significant difference in the regioselectivity in the acylations of the anions derived from **34** and **36** using Mander's reagent is noteworthy and unexpected, but we tentatively speculate that differences in ring strain in the two systems might be at play.



Scheme 9. Synthesis of (±)-14-*epi*-pseudotabersonine (**37**) and attempt to prepare **39**.

We also explored the possibility of inverting the two stereocenters at C3 and C7 of **36** via a reversible retro-Mannich/Mannich sequence involving the intermediacy of **38** to furnish the pentacycle **39** in which the D/E fusion is *cis*. This process is well precedented for related compounds having a *cis*-fused D/E ring system.[21] However, to our chagrin, all of our efforts to epimerize **36** under a variety of acidic conditions (TsOH, TFA, AcOH, $BF_3{\cdot}Et_2O$, $Cu(OTf)_2$ and HCl) led only to recovery of starting material or decomposition. In retrospect, this finding was not entirely unexpected because Kuehne had also failed to isomerize a *trans*-fused D/E ring in a similar system.[22]

Undaunted we examined another strategy to transform **36** into **39** (Scheme 10). Imine **36** underwent an acid promoted cyanide addition to afford **40** in an unoptimized 51% yield. We had envisioned that treating **40** with AgOTf might result in a Grob-like fragmentation to generate the tetracyclic iminium ion intermediate **38** that would cyclize via a Mannich-like reaction to give **39**. However, heating of **40** with AgOTf in CH_3CN at 120 °C led only to the regeneration of **36** in 77% yield. Presumably, loss of cyanide ion from **40** occurred without scission of the C3 and C7 carbon–carbon bond, so none of the isomerized product **39** was formed.



Scheme 10. Other attempts to isomerize **36** to give **39**.

3. Summary

In conclusion, we developed a concise route to access the pentacyclic core of *Aspidosperma* alkaloids via a double RCM strategy. The total synthesis of (±)-pseudotabersonine was accomplished in 11 steps from commercially available 1-(phenylsulfonyl)-3-indolecarboxaldehyde (**7**). Key transformations include a stepwise variant of a Mannich-like, multicomponent assembly process, a double RCM, and a one-pot deprotection/cyclization reaction.

4. Experimental procedures

4.1. General

Unless otherwise noted, all other reagents and solvents were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) and ether (Et_2O) were dried by passage through two columns of activated neutral alumina. Methanol (MeOH) and *N*,*N*-dimethylformamide (DMF) were dried by passage through two columns of activated molecular sieves. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), and *N*,*N*-diisopropylamine (*i*-Pr_2NH) were distilled from calcium hydride. *N*,*N*-Diisopropylethylamine (*i*-Pr_2NEt) was distilled from KOH. Dimethoxyethane (DME) was dried by 4 Å molecular sieves. $AlCl_3$ and KO*t*-Bu were sublimed under reduced pressure. Reactions involving air- or moisture-sensitive reagents were performed using oven-dried glassware under an atmosphere of dry nitrogen or argon. Removal of solvent or concentration under reduced pressure was performed using a rotary evaporator. Unless otherwise indicated, all ^1H and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$, C_6D_6 or DMSO-d_6. Chemical shifts were reported in parts per million (ppm, δ) downfield from TMS (δ=0.00 ppm) and referenced relative to $CDCl_3$ (7.26 ppm for ^1H and 77.0 ppm for ^{13}C), C_6D_6 (7.15 ppm for ^1H and 128.0 ppm for ^{13}C) and DMSO-d_6 (2.50 ppm for ^1H and 39.4 ppm for ^{13}C). Coupling constants were reported in hertz (Hz). Splitting patterns were designated as: s=singlet; d=doublet; dd=doublet of doublet; ddd=doublet of doublet of doublets; t=triplet; q=quartet; p=pentuplet; hep=heptet; m=multiplet; comp=overlapping multiplets of non-magnetically equivalent protons; br=broad; app=apparent. Melting points were determined on a melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained as thin films on sodium chloride plates and reported in wave numbers (cm^{-1}). Analytical thin-layer chromatography (TLC) was performed on Merck-60 TLC plates with the indicated solvents. Visualization was accomplished by UV light or stained with $KMnO_4$ solution. Flash chromatography was performed with Merck 250–400 mesh silica gel with the indicated solvents according to the procedure of Still.[23]

4.2. Preparation and characterization of selected new compounds

*4.2.1. Amine **12**.* *n*-BuLi (0.4 mL, 2.3 M in hexane, 0.94 mmol) was added to a solution of 1,4-pentadiene (0.1 mL, 66 mg, 0.97 mmol) in THF (0.5 mL) at −78 °C. The reaction was stirred at −78 °C for 15 min, whereupon the bath was replaced with a 0 °C bath. The reaction was stirred for an additional 30 min at 0 °C. A solution of $AlCl_3$ (140 mg, 1.05 mmol) in Et_2O (1 mL) was added, and the reaction was stirred for 1 h at 0 °C. The pentadienyl Al reagent **10c** thus prepared was added to a solution of imine **11** (112 mg, 0.77 mmol) in CH_2Cl_2 (2 mL), and the reaction was stirred for 18 h at room temperature. H_2O (3 mL) and 6 M NaOH (4 mL) were added, and the mixture was filtered through a pad of Celite, washing with CH_2Cl_2 (3×5 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2×5 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexane (1:9 to 1:3) to give 116 mg (70%) of amine **12** and 4 mg (2%) of amine **13** as colorless oils. Amine **12**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.21 (comp, 5H), 5.87–5.72 (comp, 2H), 5.59 (ddd, *J*=17.8, 10.8, 7.2 Hz, 1H), 5.19–5.03 (comp, 4H), 4.95–4.89 (comp, 2H), 3.58 (d, *J*=7.9 Hz, 1H), 3.08 (ddt, *J*=14.3, 5.2, 1.7 Hz, 1H), 3.02 (dt, *J*=7.8, 7.8 Hz, 1H), 2.94 (ddt, *J*=14.3, 6.8, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 138.1, 137.7, 136.8, 128.3, 127.9, 127.0, 117.4, 116.0, 115.6, 65.1, 55.1, 49.7; IR (neat) 3078, 2977, 2817, 1642, 1453, 1111, 994, 917, 700 cm^{-1}; Mass spectrum (CI) *m*/*z* 214.1601 [$C_{15}H_{20}N$ (M+1) requires 214.1596].

*4.2.2. 2-Methylenebutan-1-amine hydrochloride (**15**).* $NaBH_4$ (7.1 g, 0.19 mol) was added portionwise to a solution of 2-ethylacrolein (18.5 mL, 15.89 g, 0.19 mol) in Et_2O (125 mL) and MeOH (35 mL) at 0 °C. The reaction was stirred for 1 h at 0 °C and then for 1 h at room temperature. The reaction was partitioned between H_2O (200 mL) and Et_2O (100 mL). The aqueous layer was backwashed with Et_2O (3×100 mL), and the combined organics were dried ($MgSO_4$), filtered, and concentrated by simple distillation to give 15.6 g of 2-methylidenebutan-1-ol as a ~78% solution in Et_2O (by NMR). An additional volume of Et_2O (200 mL) was added, and the solution was cooled to 0 °C. PBr_3 (13.5 mL, 38.88 g, 0.14 mol) was added dropwise, and the reaction was warmed to room temperature and stirred for 15 h. The reaction was then cooled to 0 °C, and ice water (100 mL) was slowly added. Additional H_2O (100 mL) and Et_2O (100 mL) were then added, and the phases were separated. The organic phase was washed sequentially with H_2O (50 mL), saturated aqueous $NaHCO_3$ (50 mL) and brine (2×50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated by simple distillation to give 23.1 g of 2-(bromomethyl)but-1-ene as a ~70% solution in Et_2O (by NMR). This solution of crude 2-(bromomethyl)but-1-ene was added to LiHMDS (1.44 M in hexane, 90 mL) at −40 °C. The reaction was warmed to room temperature and then heated under reflux for 24 h. The reaction was cooled to room temperature and filtered through a pad of Celite that was washed with pentane (3×20 mL). The filtrates and washings were concentrated under reduced pressure, and the residue was diluted with pentane (100 mL). The suspension was filtered through a pad of Celite that was washed with pentane (3×20 mL). The filtrates and washings were concentrated under reduced pressure, and the crude bis(silyl)amine was added dropwise to a solution of HCl in MeOH/Et_2O [prepared from AcCl (35 mL) and MeOH (100 mL) in Et_2O (100 mL) at 0 °C]. The reaction was warmed to room temperature and stirred for 15 h, whereupon the reaction was concentrated under reduced pressure. The residue was crystallized from EtOH (~15 mL) to give 5.27 g (22%) of **15** as a white waxy solid, mp=158–159 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 3H), 5.22 (s, 1H), 5.11 (s, 1H), 3.58 (s, 2H), 2.17 (q, *J*=7.4 Hz, 2H), 1.08 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 113.6, 43.8, 27.0, 11.7; IR (film) 3409, 2971, 1603, 1515, 1458, 1378, 909, 736 cm^{-1}; Mass spectrum (CI) *m*/*z* 86.0973 [$C_5H_{12}N(M+H)^+$ requires 86.0970].

*4.2.3. Imine **17**.* A mixture of indole-3-carboxaldehyde (**7**) (4.28 g, 15.0 mmol), 2-ethylallylamine hydrochloride (**15**) (3.65 g, 30.0 mmol), Et_3N (4.32 mL, 3.13 g, 31.0 mmol) and activated 4 Å molecular sieves (~2 g) in CH_2Cl_2 (50 mL) was stirred for 20 h at room temperature, and then Et_2O (250 mL) was added. The mixture was stirred for 10 min at room temperature and filtered through a pad of Celite that was washed with Et_2O (3×50 mL). The combined filtrates and washings were concentrated under reduced pressure to give ~5.4 g (100%) crude imine **17** as an orangish brown oil that was used without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.37 (d, *J*=7.6 Hz, 1H), 7.98 (d, *J*=8.2 Hz, 1H), 7.92 (d, *J*=8.0 Hz, 2H), 7.85 (s, 1H), 7.55 (t, *J*=7.6 Hz, 1H), 7.45 (t, *J*=8.0 Hz, 2H), 7.38 (td, *J*=8.2, 1.0 Hz, 1H), 7.31 (t, *J*=7.6 Hz, 1H), 4.96 (s, 1H), 4.87 (s, 1H), 4.19 (s, 2H), 2.19 (q, *J*=7.4 Hz, 2H), 1.21 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 149.5, 137.8, 135.5, 134.1, 129.5, 129.4, 128.0, 126.8, 125.6, 124.2, 123.2, 120.8, 113.2, 109.0, 66.8, 27.5, 12.1; IR (film) 1642, 1446, 1378, 1177, 1126, 1100, 979 cm^{-1}; Mass spectrum (CI) *m*/*z* 353.1316 [$C_{20}H_{21}N_2O_2S$ $(M+H)^+$ requires 353.1310].

*4.2.4. Amine **19**.* *n*-BuLi (7.97 mL, 2.5 M in hexane, 20.0 mmol) was added to a solution of 1,4-pentadiene (2.1 mL, 1.36 g, 20.0 mmol) in THF (10 mL) at −78 °C. The reaction was stirred at −78 °C for

15 min, whereupon the bath was replaced with a 0 °C bath, and the reaction was stirred for 30 min at 0 °C. A solution of $AlCl_3$ (2.86 g, 21.4 mmol) in Et_2O (10 mL) was added, and the reaction was stirred for 1 h at 0 °C. The pentadienyl Al reagent **10c** thus prepared was added to a solution of imine **17** (~5.4 g, 15.0 mmol) in CH_2Cl_2 (50 mL), and the reaction was stirred for 24 h at room temperature, whereupon the reaction was opened to air, and 1 N NaOH (200 mL) was added. The mixture was stirred vigorously for 5 min and then filtered through a pad of Celite, and the pad was washed with CH_2Cl_2 (3×50 mL). The filtrates were combined, and the aqueous layer was separated and extracted with CH_2Cl_2 (2×100 mL). The combined organic layers were concentrated under reduced pressure to give ~6.5 g crude **19** as an orangish brown oil that was used without further purification. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (d, J=8.3 Hz, 1H), 7.82–7.80 (m, 2H), 7.70 (d, J=7.8 Hz, 1H), 7.49 (t, J=7.5 Hz, 1H), 7.42 (s, 1H), 7.38 (t, J=7.5 Hz, 2H), 7.29 (t, J=7.8 Hz, 1H), 7.20 (t, J=7.8 Hz, 1H), 5.75 (ddd, J=17.1, 10.2, 8.7 Hz, 1H), 5.65–5.59 (m, 1H), 5.14 (dd, J=10.2, 1.7 Hz, 1H), 5.09 (d, J=17.1 Hz, 1H), 4.83 (d, J=1.1 Hz, 1H), 4.82–4.80 (m, 1H), 4.77 (s, 1H), 4.74 (s, 1H), 3.82 (d, J=7.7 Hz, 1H), 3.14 (app q, J=7.7 Hz, 1H), 3.02 (d, J=14.3 Hz, 1H), 2.91 (d, J=14.3 Hz, 1H), 1.97 (dq, J=23.1, 7.4 Hz, 1H), 1.92 (dq, J=23.1, 7.4 Hz, 1H), 1.61 (s, 1H), 0.93 (t, J=7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.4, 138.2, 137.8, 137.7, 135.8, 133.6, 130.3, 129.0, 126.6, 124.8, 124.6, 123.8, 123.1, 120.9, 117.7, 116.1, 113.9, 108.9, 57.7, 53.7, 52.0, 27.0, 12.2. IR (film) 3073, 2964, 1446, 1368, 1176, 1120, 918, 747 cm^{-1}; Mass spectrum (CI) m/z 421.1949 [$C_{25}H_{29}N_2O_2S$ $(M+H)^+$ requires 421.1950].

*4.2.5. Triene **21**.* A solution of **19** (~6.5 g, ~15 mmol) and ethylene oxide (7.7 mL, 6.8 g, 154 mmol) in MeOH (15 mL) was heated at 65 °C in a sealed tube for 64 h. After cooling to room temperature, the reaction was concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexane (1:3) to give 6.39 g (89%) of a mixture (>10:1) of branched and linear adducts as a slightly brown gum that was crystallized from MeOH (~2 mL) to give 5.1 g (71% overall yield from **7**) **21** as a pale yellow solid, mp=90–92 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (d, J=7.8 Hz, 1H), 7.83–7.81 (m, 2H), 7.54–7.51 (m, 1H), 7.43–7.40 (comp, 3H), 7.32 (ddd, J=8.4, 7.2, 0.9 Hz, 1H), 7.24 (ddd, J=8.4, 7.2, 0.9 Hz, 1H), 5.91–5.85 (m, 1H), 5.40–5.35 (m, 1H), 5.24–5.20 (comp, 2H), 4.95 (m, 1H), 4.91 (m, 1H), 4.84 (dt, J=16.8, 1.2 Hz, 1H), 4.66 (ddd, J=16.2, 1.5, 0.9 Hz, 1H), 4.00 (d, J=12.0 Hz, 1H), 3.67 (td, J=10.8, 3.0 Hz, 1H), 3.53 (app d, J=10.8 Hz, 1H), 3.47–3.43 (m, 1H), 3.12 (d, J=13.8 Hz, 1H), 2.97 (ddd, J=13.2, 10.8, 4.8 Hz, 1H), 2.64 (app d, J=13.8 Hz, 2H), 2.18 (dt, J=13.2, 2.4 Hz, 1H), 2.16–2.10 (m, 1H), 2.06–2.00 (m, 1H), 1.05 (t, J=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.5, 139.7, 138.0, 137.9, 134.9, 133.8, 132.1, 129.1, 126.6, 125.1, 124.8, 123.3, 120.2, 118.7, 116.6, 116.1, 113.8, 112.2, 58.8, 58.2, 56.2, 51.5, 51.2, 26.6, 12.1; IR (film) 3468, 3077, 2965, 2921, 2833, 1447, 1369, 1177, 1121, 914 cm^{-1}; Mass spectrum (CI) m/z 465.2215 [$C_{27}H_{33}N_2O_3S$ $(M+H)^+$ requires 465.2212].

*4.2.6. TBS ether **23**.* A solution of amino alcohol **21** (5.1 g, 11.0 mmol), TBSCl (1.99 g, 13.2 mmol) and imidazole (1.12 g, 16.5 mmol) in DMF (12 mL) was stirred for 6 h at room temperature. The reaction was partitioned between H_2O (100 mL) and Et_2O (100 mL). The organic phase was separated, and the aqueous phase was extracted with Et_2O (2×100 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexane (1:4) to give 6.23 g (98%) **23** as a white solid, mp=58–59.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 (d, J=8.3 Hz, 1H), 7.82–7.80 (m, 2H), 7.59 (app d, J=7.7 Hz, 1H), 7.50 (t, J=7.5 Hz, 1H), 7.40 (s, 1H), 7.38 (t, J=7.5 Hz, 2H), 7.29 (t, J=7.7 Hz, 1H), 7.21 (t, J=7.7 Hz, 1H), 6.06 (ddd, J=17.5, 10.4, 7.4 Hz, 1H), 5.43 (ddd, J=17.5, 10.3, 7.4, Hz, 1H), 5.12–5.07 (comp, 2H), 4.84–4.82 (comp, 3H), 4.70 (d, J=10.3 Hz, 1H), 4.07 (d, J=10.9 Hz, 1H), 3.71–3.62 (comp, 2H), 3.40 (dt, J=10.3, 7.4 Hz, 1H), 3.12 (d, J=13.9 Hz, 1H), 2.76 (dt, J=13.2, 6.7 Hz, 1H), 2.62 (d, J=13.9 Hz, 1H), 2.30 (dt, J=13.2, 6.5 Hz, 1H), 2.03 (dq, J=23.2, 7.4 Hz, 1H), 2.00 (dq, J=23.2, 7.4 Hz, 1H), 0.98 (t, J=7.4 Hz, 3H), 0.90 (s, 9H), 0.059 (s, 3H), 0.056 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.6, 139.9, 138.4, 138.1, 134.9, 133.7, 132.5, 129.1, 126.7, 124.7, 124.6, 123.2, 120.7, 120.1, 116.0, 115.1, 113.7, 110.8, 62.9, 59.6, 57.3, 52.3, 50.9, 26.5, 26.0, 18.4, 12.2, −5.30, −5.31; IR (film) 2928, 1446, 1370, 1255, 1176, 1095, 835 cm^{-1}; Mass spectrum (CI) m/z 579.3087 [$C_{33}H_{47}N_2O_3SSi$ $(M+H)^+$ requires 579.3077].

*4.2.7. TBS ether **22**.* The TBS ether **22** was prepared as an off-white solid in 68% overall yield from **7** without purifying any intermediates using the same procedures outlined for the synthesis of **23** from **7**, mp=85.5–87.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (d, J=8.2 Hz, 1H), 7.78 (d, J=8.5 Hz, 1H), 7.59 (d, J=8.2 Hz, 1H), 7.49 (t, J=7.6 Hz, 1H), 7.40 (s, 1H), 7.38 (t, J=7.6 Hz, 1H), 7.27 (t, J=8.2 Hz, 1H), 7.20 (t, J=8.2 Hz, 1H), 5.97 (ddd, J=17.5, 10.3, 7.5 Hz, 1H), 5.74 (dddd, J=17.7, 10.2, 7.7, 4.5 Hz, 1H), 5.47 (ddd, J=17.3, 10.3, 7.5 Hz, 1H), 5.08–5.03 (comp, 4H), 4.84 (dt, J=17.3, 1.3 Hz, 1H), 4.73 (d, J=10.3 Hz, 1H), 4.03 (d, J=10.4 Hz, 1H), 3.67–3.60 (comp, 2H), 3.38 (app q, J=7.4 Hz, 1H), 3.27–3.23 (m, 1H), 2.73 (dd, J=14.5, 7.7 Hz, 1H), 2.70 (ddd, J=13.2, 7.2, 6.1 Hz, 1H), 2.35 (dt, J=6.6, 13.2 Hz, 1H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.8, 138.3, 138.1, 137.4, 134.9, 133.7, 132.3, 129.1, 126.7, 124.7, 124.6, 123.2, 120.6, 120.4, 116.6, 116.1, 115.0, 113.6, 63.0, 59.9, 54.7, 52.3, 50.9, 26.0, 18.3, −5.3; IR (neat) 2928, 1447, 1370, 1176, 1119, 1094, 914, 834 cm^{-1}; Mass spectrum (CI) m/z 551.2765 [$C_{31}H_{42}N_2O_3SSi$ (M+1) requires 551.2764].

*4.2.8. Alcohols **24**.* TBS ether **22** (318 mg, 0.58 mmol) was dried by azeotroping with benzene (3×~10 mL) and dissolved in THF (4 mL). The solution was cooled to −78 °C. LDA (1 M in THF/hexane, 1.1 mL, 1.1 mmol) was added, and the reaction was stirred for 10 min at −78 °C. The −78 °C bath was exchanged for a 0 °C bath, and the reaction was stirred for 2 h at 0 °C. The reaction was recooled to −78 °C, and methyl pyruvate (226 mg, 2.21 mmol) was added. The reaction was stirred for 2 h over, which time the mixture warmed to 5 °C. The mixture was partitioned between Et_2O (5 mL) and saturated aqueous NH_4Cl (5 mL). The organic phase was removed, and the aqueous layer was extracted with CH_2Cl_2 (2×5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexane (gradient elution, 1:19 to 1:9) to give 84 mg (26%) of **22** together with two diastereomers of **24**: 135 mg (35%) (major diastereomer) and 95 mg (25%) (minor diastereomer). **Major diastereomer**: ^{1}H NMR (500 MHz, C_6D_6) δ 10.14 (s, 1H), 7.99–7.96 (comp, 3H), 7.30–7.28 (m, 1H), 6.94–6.91 (comp, 2H), 6.71 (t, J=7.4 Hz, 1H), 6.63 (t, J=7.4, 1H), 6.06–5.98 (m, 1H), 5.89 (ddd, J=17.7, 10.4, 7.6 Hz, 1H), 5.30 (ddd, J=16.9, 10.0, 8.7 Hz, 1H), 5.07 (d, J=17.7 Hz, 1H), 5.03–5.00 (comp, 2H), 4.91 (d, J=16.9 Hz, 1H), 4.80 (d, J=17.1 Hz, 1H), 4.51 (d, J=7.6 Hz, 1H), 4.40 (dd, J=10.0, 1.8 Hz, 1H), 3.96–3.87 (comp, 2H), 3.81–3.77 (comp, 3H), 3.62 (s, 1H), 3.37 (dt, J=6.5, 13.0 Hz, 1H), 2.92–2.87 (m, 1H), 2.40 (s, 3H), 0.97 (s, 9H), 0.69 (s, 3H), 0.65 (s, 3H); ^{13}C NMR (125 MHz, C_6C_6) δ 174.6, 142.8, 142.6, 139.0, 138.1, 136.9, 133.1, 131.6, 128.6, 127.7, 125.1, 124.4, 123.7, 119.6, 115.9, 115.3, 115.2, 77.7, 61.6, 61.3, 54.5, 51.8, 51.6, 27.4, 26.2, 18.5, −5.3, −5.4; IR (neat) 3070, 2950, 1755, 1728, 1448, 1376, 1176, 1116, 916, 836 cm^{-1}; Mass spectrum (CI) m/z 653.3081 [$C_{35}H_{48}N_2O_6SSi$ (M+1) requires 653.3081]. **Minor Diastereomer**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.77 (br, 1H), 7.72 (d, J=7.6 Hz, 2H), 7.68–7.66 (m, 1H), 7.46–7.42 (comp, 2H), 7.33–7.30 (m, 2H), 7.17–7.11 (comp, 2H), 6.05 (app dt, J=10.0, 17.6 Hz, 1H), 5.93 (ddt, J=17.2, 10.3, 7.0 Hz, 1H), 5.83 (ddd, J=17.4, 10.3, 7.9 Hz, 1H), 5.22 (d, J=10.3 Hz, 1H), 5.18 (d, J=17.4 Hz, 1H), 5.07

(d, J=17.2 Hz, 1H), 5.05 (d, J=17.6 Hz, 1H), 5.01 (d, J=10.3 Hz, 1H), 4.84 (dd, J=10.0 Hz, 1H), 4.07 (d, J=7.4 Hz, 1H), 3.87 (ap q, J=7.9 Hz, 1H), 3.79–3.73 (comp, 2H), 3.47 (dd, J=14.9, 5.6 Hz, 1H), 3.67 (s, 3H), 3.35–3.28 (m, 1H), 2.98–2.86 (comp, 2H), 2.01 (s, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.2, 142.1, 140.9, 139.2, 138.4, 136.2, 133.3, 132.3, 130.8, 128.7, 127.0, 125.0, 123.3, 122.3, 119.9, 115.5, 115.3, 115.0, 77.4, 60.9, 60.1, 52.9, 51.9, 51.1, 50.2, 30.3, 26.0, 18.3, −5.38, −5.41; IR (neat) 3072, 2950, 1738, 1637, 1448, 1361, 1255, 1117, 1098, 914, 836 cm^{-1}; Mass spectrum (CI) m/z 653.3083 [$C_{35}H_{48}N_2O_6SSi$ (M+1) requires 653.3081].

*4.2.9. Alcohols **28**.* TBS ether **23** (1.16 g, 2.0 mmol) was azeotroped from benzene (3× ~10 mL), dissolved in THF (8 mL) and cooled to −78 °C. LDA (1.0 M in THF/hexane, 4.0 mL, 4.0 mmol) was added, and the reaction was stirred for 10 min at −78 °C. The −78 °C bath was exchanged for a 0 °C bath, and the reaction was stirred for 2 h at 0 °C. The reaction was then cooled to −78 °C, and freshly distilled acetaldehyde (0.45 mL, 353 mg, 8.0 mmol) was added. The reaction was allowed to slowly warm to −30 °C over 2 h. The reaction was cooled to −78 °C, and saturated NH_4Cl (3 mL) was added. The reaction was partitioned between Et_2O (20 mL) and brine (15 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexane (gradient elution, 1:49 to 1:19 to 1:9) to give 0.71 g (56%) of **28a** (major diastereomer, less polar) as a colorless oil, and 0.27 g (22%) of **28b** (minor diastereomer, more polar) as a colorless oil. For **28a** (major diastereomer). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.99 (d, J=8.2 Hz, 1H), 7.90–7.88 (m, 1H), 7.69 (d, J=7.5 Hz, 2H), 7.59 (t, J=7.5 Hz, 1H), 7.45 (d, J=7.5 Hz, 1H), 7.22 (t, J=7.7 Hz, 1H), 7.16 (t, J=7.7 Hz, 1H), 6.04–6.00 (m, 1H), 5.56–5.53 (m, 1H), 5.46–5.40 (m, 1H), 5.27 (d, J=4.7 Hz, 1H), 5.05 (d, J=17.5 Hz, 1H), 5.00 (d, J=10.3 Hz, 1H), 4.84 (s, 1H), 4.71 (s, 1H), 4.65 (d, J=9.3 Hz, 1H), 4.56 (d, J=16.7 Hz, 1H), 4.43 (d, J=9.4 Hz, 1H), 3.70 (app q, J=8.3 Hz, 1H), 3.52 (t, J=6.8 Hz, 1H), 3.14 (d, J=13.8 Hz, 1H), 2.75 (d, J=13.8 Hz, 1H), 2.61 (dt, J=13.4, 6.8 Hz, 1H), 2.44 (dt, J=13.4, 6.8 Hz, 1H), 2.01 (dq, J=14.9, 7.4 Hz, 1H), 1.91 (dq, J=14.9, 7.4 Hz, 1H), 1.57 (d, J=6.6 Hz, 3H), 0.86 (t, J=7.4 Hz, 3H), 0.81 (s, 9H), −0.06 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 150.0, 142.4, 140.9, 138.4, 137.0, 136.5, 134.1, 130.2, 129.1, 126.1, 124.3, 123.4, 123.3, 122.2, 114.8, 114.6, 114.3, 109.9, 62.5, 61.2, 60.9, 57.6, 52.2, 49.1, 25.72, 25.71, 24.7, 17.8, 11.9, −5.5; IR (film) 3551, 2930, 1447, 1362, 1254, 1174, 1092, 835 cm^{-1}; Mass spectrum (CI) m/z 623.3331 [$C_{35}H_{51}N_2O_4SSi$ $(M+H)^+$ requires 623.3339]. For **28b** (minor diastereomer). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.02 (d, J=8.3 Hz, 1H), 7.86–7.84 (m, 1H), 7.63 (d, J=7.5 Hz, 2H), 7.58 (t, J=7.5 Hz, 1H), 7.43 (t, J=7.5 Hz, 1H), 7.24 (t, J=7.3 Hz, 1H), 7.17 (t, J=7.3 Hz, 1H), 6.01 (ddd, J=17.2, 10.3, 6.9 Hz, 1H), 5.69 (br, 1H), 5.45–5.39 (comp, 2H), 5.08 (d, J=17.2 Hz, 1H), 5.03 (d, J=10.3 Hz, 1H), 4.75 (m, 1H), 4.71 (s, 1H), 4.68 (d, J=17.4 Hz, 1H), 4.65 (s, 1H), 4.57 (d, J=10.3 Hz, 1H), 3.74–3.72 (m, 1H), 3.50–3.42 (comp, 2H), 3.08 (d, J=13.8 Hz, 1H), 2.61 (d, J=13.8 Hz, 1H), 2.52–2.47 (m, 1H), 2.35 (dt, J=12.6, 5.8 Hz, 1H), 1.99 (dq, J=15.1, 7.2 Hz, 1H), 1.88 (dq, J=15.1, 7.2 Hz, 1H), 1.48 (d, J=5.4 Hz, 1H), 0.83 (t, J=7.2 Hz, 3H), 0.82 (s, 9H), −0.05 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 150.4, 142.8, 140.7, 138.1, 136.9, 136.5, 134.0, 131.0, 129.1, 126.1, 124.2, 123.5, 122.2, 115.4, 115.1, 114.7, 109.4, 63.1, 61.3, 60.0, 57.5, 51.9, 48.4, 26.1, 25.8, 25.6, 17.9, 11.8, −5.41, −5.42; IR (film) 3555, 2929, 1448, 1362, 1173, 1091, 914, 836 cm^{-1}; Mass spectrum (CI) m/z 623.3333 [$C_{35}H_{51}N_2O_4SSi$ $(M+H)^+$ requires 623.3339].

*4.2.10. Tetraene **29**.* Freshly distilled Tf_2O (0.92 mL, 1.53 g, 5.4 mmol) and Hünig's base (2.3 mL, 1.74 g, 13.4 mmol) were added in rapid succession to a solution of alcohol **28** (2.8 g, 4.5 mmol) in CH_2Cl_2 (15 mL) at −78 °C. The reaction was stirred for 30 min at −78 °C and then partitioned between 1 M NaOH (6 mL) and CH_2Cl_2 (10 mL). The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexane (1:10) to give 2.5 g (92%) of **29** as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.24 (d, J=7.7 Hz, 1H), 7.77 (d, J=7.7 Hz, 1H), 7.60–7.58 (m, 2H), 7.45 (t, J=7.5 Hz, 1H), 7.32–7.25 (comp, 3H), 7.21 (t, J=7.7 Hz, 1H), 6.96 (dd, J=17.7, 11.4 Hz, 1H), 5.92 (ddd, J=16.8, 10.8, 7.4 Hz, 1H), 5.59 (dd, J=11.4, 1.8 Hz, 1H), 5.35 (ddd, J=17.3, 10.3, 7.4 Hz, 1H), 5.31 (dd, J=17.7, 1.8 Hz, 1H), 5.10–5.06 (comp, 2H), 4.84 (s, 1H), 4.73 (s, 1H), 4.71 (d, J=17.3 Hz, 1H), 4.54 (d, J=10.3 Hz, 1H), 4.14 (d, J=10.7 Hz, 1H), 3.70 (dt, J=10.7, 7.4 Hz, 1H), 3.56–3.51 (m, 1H), 3.48–3.44 (m, 1H), 3.15 (d, J=14.0 Hz, 1H), 2.74 (ddd, J=13.1, 8.4, 6.5 Hz, 1H), 2.65 (d, J=14.0 Hz, 1H), 2.23 (ddd, J=13.1, 7.8, 5.0 Hz, 1H), 2.00 (dq, J=15.1, 7.5 Hz, 1H), 1.91 (dq, J=15.1, 7.5 Hz, 1H), 0.94 (t, J=7.4 Hz, 3H), 0.86 (s, 9H), −0.011 (s, 3H), −0.014 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.7, 139.8, 138.2, 138.1, 137.8, 136.9, 133.5, 128.7, 128.1, 126.6, 124.7, 123.5, 122.9, 122.1, 120.7, 115.5, 115.34, 115.33, 110.0, 61.6, 60.7, 57.3, 52.2, 48.7, 26.5, 26.0, 18.3, 12.1, −5.30, −5.31; IR (film) 2928, 1448, 1374, 1253, 1175, 1091, 987, 916, 836, 751 cm^{-1}; Mass spectrum (CI) m/z 605.3246 [$C_{35}H_{49}N_2O_3SSi$ $(M+H)^+$ requires 605.3233].

*4.2.11. D/E cis Tetracycle 33 and D/E trans tetracycle **34**.* A solution of tetraene **29** (326 mg, 0.57 mmol) and Hoveyda-Grubbs II catalyst (18 mg, 0.029 mmol) in toluene (56 mL) was placed in a pre-heated oil bath (100 °C) and heated for 3.5 h. The mixture was cooled to room temperature, and the toluene was removed under reduced pressure. The residue was dissolved in degassed EtOH (3 mL) containing PtO_2 (13 mg, 0.057 mmol), and the mixture was stirred under H_2 (1 atm) for 21 h at room temperature. The reaction was filtered through a pad of Celite, and the pad was washed with MeOH (10 mL). The combined filtrates and washings were concentrated under reduced pressure. The residue was dissolved in MeOH (5 mL), and 1.25 M HCl in MeOH (5 mL) was added. The reaction was stirred for 1 h at room temperature and then partitioned between 1 N NaOH (10 mL) and CH_2Cl_2 (20 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with EtOAc/hexane (1:6) and EtOAc/hexane (1:4) to give 45 mg (26%) **33** as a white foam and 76 mg (44%) **34** as a white foam. **D/E *cis* tetracycle 33**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (d, J=7.8 Hz, 1H), 7.68 (dd, J=8.7, 0.9 Hz, 2H), 7.63 (d, J=7.2 Hz, 1H), 7.49 (tt, J=7.5, 1.2 Hz, 1H), 7.37 (app t, J=8.1 Hz, 2H), 7.26 (app td, J=7.8, 1.2 Hz, 1H), 7.21 (td, J=7.4, 1.2 Hz, 1H), 5.36 (s, 1H), 4.03 (d, J=4.8 Hz, 1H), 3.63–3.50 (m, 2H), 3.00–2.97 (m, 2H), 2.90–2.83 (comp, 2H), 2.76–2.69 (comp, 2H), 2.60 (app br s, 1H), 2.02 (m, 1H), 1.86–1.77 (comp, 3H), 0.92 (t, J=7.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.9, 138.1, 137.9, 136.7, 133.5, 130.2, 129.1, 126.1, 124.1, 123.6, 120.3, 119.6, 118.4, 114.6, 58.9, 55.8, 53.7, 49.0 (br), 30.3 (br), 27.6, 26.7, 22.3, 12.0; IR (film) 3419, 2960, 2923, 2875, 1449, 1369, 1187, 1170, 1146, 1092, 1051 cm^{-1}; Mass spectrum (ESI) m/z 437.1895 [$C_{25}H_{29}N_2O_3S$ $(M+H)^+$ requires 437.1893]. **D/E *trans* tetracycle 34**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (dt, J=7.8, 0.90 Hz, 1H), 7.90 (d, J=7.8 Hz, 1H), 7.77–7.75 (comp, 2H), 7.52 (tt, J=7.5, 1.2 Hz, 1H), 7.43–7.40 (comp, 2H), 7.26 (app td, J=7.8, 1.2 Hz, 1H), 7.21 (td, J=7.5, 1.2 Hz, 1H), 5.49 (s, 1H), 3.93 (d, J=9.6 Hz, 1H), 3.69 (ddd, J=10.8, 9.6, 4.8 Hz, 1H), 3.60 (d, J=18.0 Hz, 1H), 3.48 (ddd, J=10.8, 9.6, 3.0 Hz, 1H), 3.22 (d, J=17.4 Hz, 1H), 3.16 (ddt, J=18.0, 5.4, 1.8 Hz, 1H), 3.02–2.96 (m, 1H), 2.45 (dt, J=12.6, 3.9 Hz, 1H), 2.42–2.37 (m, 1H), 2.29 (ddd, J=15.0, 9.0, 6.0 Hz, 1H), 2.07 (app ddt, J=13.2, 6.0, 2.1 Hz, 1H), 2.01–1.90 (comp, 2H), 1.53 (qd, J=13.2, 5.4 Hz, 2H), 1.04 (t,

J=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.0, 138.2, 137.4, 136.8, 133.6, 129.2, 128.8, 126.3, 124.2, 123.4, 122.2, 120.5, 119.5, 114.4, 61.6, 59.9, 53.1, 48.2, 31.4, 28.5, 27.4, 25.6, 12.2; IR (film) 3416 (br), 2960, 2926, 2855, 1449, 1370, 1173, cm^{-1}; Mass spectrum (CI) m/z 437.1906 [$C_{25}H_{29}N_2O_3S$ $(M+H)^+$ requires 437.1889].

4.2.12. D/E cis Pentacycle ***35***. A solution of KO*t*-Bu (40 mg, 0.36 mmol) in THF (2 mL) was added to a solution of **33** (62 mg, 0.14 mmol) in DME (4 mL) at −20 °C, and the reaction was slowly warmed to −5 °C over 10 min. After being stirred for 15 min at −5 °C, the reaction was quenched with brine (1.5 mL). The reaction was partitioned between brine (5 mL) and Et_2O (10 mL). The organic phase was separated, and the aqueous phase was extracted with Et_2O (3×10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with EtOAc/hexane (2:1), DCM/MeOH (50:1) and DCM/MeOH (25:1) to give 26 mg (66%) of **35** as a yellow oil. ^{1}H NMR (600 MHz, C_6D_6) δ 7.76 (d, J=7.8 Hz, 1H), 7.21 (app dq, J=7.2, 0.6 Hz, 1H), 7.17 (td, J=7.8, 1.2 Hz, 1H), 7.05 (td, J=7.2, 1.2 Hz, 1H), 5.19–5.17 (m, 1H), 3.13 (d, J=15.0 Hz, 1H), 2.93 (t, J=7.2 Hz, 1H), 2.89–2.82 (comp, 2H), 2.74–2.70 (comp, 2H), 2.57 (ddd, J=10.8, 8.4, 4.8 Hz, 1H), 2.28–2.20 (m, 1H), 2.03 (ddd, J=12.6, 10.8, 6.6 Hz, 1H), 1.78 (q, J=7.6 Hz, 2H), 1.60–1.54 (comp, 2H), 1.52–1.46 (m, 1H), 0.88 (t, J=7.6 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 188.5, 156.2, 147.9, 138.7, 128.0, 125.2, 123.1, 121.7, 120.6, 70.7, 61.5, 54.5, 53.6, 35.1, 34.2, 27.9, 26.9, 25.9, 12.8. IR (film) 2962, 2931, 2872, 2783, 1576, 1455, 1535, 1239, 1148; Mass spectrum (CI) m/z 279.1861 [$C_{19}H_{23}N_2$ $(M+H)^+$ requires 279.1861].

*4.2.13. Pseudotabersonine (****4****).* Pentacycle **35** (26 mg, 0.09 mmol) was azeotroped from benzene (3×~10 mL), dissolved in THF (2 mL) and cooled to −78 °C. LDA (1.0 M in THF/hexane, 0.28 mL, 0.28 mmol) was added. The reaction was allowed to warm slowly to −20 °C over 1 h and then stirred at −20 °C for 30 min. The solution was cooled to −78 °C, freshly distilled methyl cyanoformate (37 μL, 40 mg, 0.46 mmol) was added, and the reaction was stirred for 30 min at −78 °C. Brine (2 mL) was added, and the reaction was partitioned between Et_2O (10 mL) and brine (5 mL). The organic phase was separated, and the aqueous phase was extracted with Et_2O (3×5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexane (1:5) to give 19 mg (61%) of **4** as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.30 (d, J=7.2 Hz, 1H), 7.15 (td, J=7.8, 1.2 Hz, 1H), 6.88 (td, J=7.2, 0.6 Hz, 1H), 6.81 (d, J=7.8 Hz, 1H), 5.51 (app d, J=6.0 Hz, 1H), 3.77 (s, 3H), 3.36 (d, J=15.6 Hz, 1H), 3.27 (d, J=15.6 Hz, 1H), 3.05–3.01 (comp, 2H), 2.83–2.77 (m, 1H), 2.68 (dd, J=15.0, 3.0 Hz, 1H), 2.15 (dd, J=15.0, 11.4 Hz, 1H), 2.09–2.03 (comp, 3H), 1.90 (ddd, J=11.6, 4.8, 2.0 Hz, 1H), 1.77 (app br s, 1H), 1.06 (t, J=7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.7, 165.9, 143.6, 139.3, 138.0, 127.7, 121.9, 121.4, 120.6, 109.1, 95.4, 65.2, 55.5, 53.2, 51.0, 50.95, 44.4, 36.8, 27.8, 26.4, 12.5; IR (film) 3367, 2965, 2916, 1675, 1609, 1465, 1436, 1240, 1203, 1118 cm^{-1}; Mass spectrum (CI) m/z 336.1833 [$C_{21}H_{24}N_2O_2$ $(M)^+$ requires 336.1838].

4.2.14. D/E trans Pentacycle ***36***. A solution of KO*t*-Bu (191 mg, 1.7 mmol) in THF (5 mL) was added to a solution of **34** (313 mg, 0.71 mmol) in THF (10 mL) at 0 °C, and the reaction was stirred for 30 min at 0 °C. Brine (5 mL) was added, and the reaction was partitioned between brine (5 mL) and Et_2O (10 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (basic Al_2O_3) eluting with EtOAc/hexane (1:10) to give 151 mg (75%) of **36** as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J=7.0 Hz, 1H), 7.54 (d, J=7.5 Hz, 1H), 7.30 (td, J=7.5, 1.0 Hz, 1H), 7.19 (td, J=7.5, 1.0 Hz, 1H), 5.49 (app dd, J=3.0, 1.5 Hz, 1H), 3.65–3.59 (comp, 2H), 3.24 (dt, J=18.5, 2.5 Hz, 1H), 3.08 (ddd, J=11.0, 9.0, 5.0 Hz, 1H), 2.98 (ddd, J=13.5, 3.7, 2.5 Hz, 1H), 2.67 (td, J=13.0, 5.5 Hz, 1H), 2.46 (ddd, J=13.3, 10.8, 5.0 Hz, 1H), 2.40–2.33 (m, 1H), 2.32 (d, J=9.5 Hz, 1H), 2.11 (dp, J=13.0, 2.5 Hz, 1H), 1.96–1.89 (comp, 3H), 1.25 (qd, J=12.5, 3.5 Hz, 1H), 1.00 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.4, 153.8, 146.2, 104.1, 127.4, 125.3, 123.2, 121.0, 119.6, 72.0, 63.1, 51.4, 51.3, 31.5, 31.0, 30.9, 30.7, 27.3, 12.4; IR (film) 3248, 3047, 2963, 2928, 2877, 1574, 1454, 1338, 1145; Mass spectrum (ESI) m/z 279.1858 [$C_{19}H_{23}N_2$ $(M+H)^+$ requires 279.1856].

*4.2.15. 14-epi Pseudotabersonine (****37****).* Pentacycle **36** (70 mg, 0.25 mmol) was azeotroped from benzene (3×~10 mL), dissolved in THF (3 mL) and cooled to −78 °C. LDA (1.0 M in THF/hexane, 0.75 mL, 0.75 mmol) was added, and the reaction was stirred for 1 h while warming to −20 °C. Stirring was continued at −20 °C for 1 h, whereupon the reaction was cooled to −78 °C, and methyl cyanoformate (0.09 mL, 96 mg, 1.13 mmol) was added. The reaction was stirred for 1 h at −78 °C. The reaction was then partitioned between CH_2Cl_2 (5 mL) and saturated aqueous NH_4Cl (5 mL). The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexane (3:97) to give 39 mg (46%) of **37** as a viscous oil and 22 mg (26%) of the *N*-acylated analog of **37**. **14-*epi* pseudotabersonine (37)**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.07 (s, 1H), 7.52 (d, J=7.5 Hz, 1H), 7.08 (td, J=7.5, 1.3 Hz, 1H), 6.83 (td, J=7.5, 1.0 Hz, 1H), 6.75 (d, J=7.5 Hz, 1H), 5.51 (d, J=1.5 Hz, 1H), 3.75 (s, 3H), 3.70 (d, J=18.5 Hz, 1H), 3.39 (ddd, J=9.0, 9.0, 5.5 Hz, 1H), 3.20 (d, J=18.5 Hz, 1H), 2.92 (ddd, J=10.8, 9.0, 4.7 Hz, 1H), 2.81 (d, J=9.8 Hz, 1H), 2.71 (dd, J=15.6, 5.5 Hz, 1H), 2.56–2.50 (comp, 2H), 2.06 (dd, J=15.6, 12.8 Hz, 1H), 1.99–1.96 (comp, 2H), 1.91 (ddd, J=13.3, 9.0, 4.7 Hz, 1H), 1.05 (t, J=7.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.1, 165.3, 144.2, 138.9, 138.2, 127.3, 123.1, 121.2, 120.8, 109.2, 95.0, 63.4, 55.0, 51.5, 51.0, 49.8, 40.7, 29.3, 28.1, 27.3, 12.3; IR (film) 3354, 2963, 1677, 1606, 1463, 1283, 1233, 1215, 1163 cm^{-1}; Mass spectrum (CI) m/z 337.1910 [$C_{21}H_{25}N_2O_2$ $(M+H)^+$ requires 337.1916].

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