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Total Synthesis of (–)-Fasicularin and (–)-Lepadiformine A Based on Zn-Mediated Allylation of Chiral *N*-*tert*-Butanesulfinyl Ketimine

San-Lin Mei[a] and Gang Zhao*[a]

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The stereoselective total synthesis of fasicularin (**1**) and lepadiformine A (**2**) is described, which features the utilization of a Zn-mediated allylation of a chiral, aliphatic, *N*-*tert*-butanesulfinyl ketimine to construct the amino-substituted quaternary carbon center in good yield and with excellent diastereoselectivity. The azaspirocyclic scaffold was installed sequentially by a Sharpless dihydroxylation and an internal epoxide-opening reaction, and this scaffold was further converted into common intermediate **5**. Removing the tosyl (Ts) protecting group of **5** and reductively aminating using Luche's reagent completed the synthesis of (–)-fasicularin (**1**), while reducing **5** using L-selectride, deprotecting the Ts group, and finishing with an intramolecular amino alcohol cyclocondensation completed the total synthesis of (–)-lepadiformine A (**2**).

Introduction

Lepadiformines A–C and fasicularin, separately isolated by Biad et al. from *Clavelina lepadiformis* off the coast of Tunisia and later from *Clavelina moluccensis*[1a–1c] and by Patil et al. from *Nephteis fasicularis* collected in Pompeii,[1d] belong to a series of tricyclic, marine alkaloids bearing a common pyrrolo-/pyrido[1,2-*j*]quinoline framework including a *trans*-1-azadecalin, A–B ring system. In addition to their peculiar structures, these compounds also have some biologically interesting activities such as moderate in vitro cytotoxicity against several tumor cell lines, various cardiovascular effects in vitro and in vivo and antiarrythmia properties.[1a,1c,2] Therefore, these complex structures have been the focus of many synthetic efforts.[3,4]

Chiral *N*-*tert*-butanesulfinamide is a versatile reagent in asymmetric synthesis, especially as an excellent chiral auxiliary for asymmetric induction in the preparation of all kinds of synthetically useful chiral amines.[5] However, applications of this useful chiral auxiliary in the total synthesis of complex natural products are rare. With our continued interest in the total synthesis of natural alkaloids bearing an azaspirotricyclic skeleton with a sterically congested, quaternary carbon center,[6] we hypothesized that chiral *N*-*tert*-butanesulfinamides should be highly useful for the synthesis of such alkaloids. Herein, we report the utilization of a Zn-mediated, allylation reaction of a chiral *N*-*tert*-butanesulfinyl ketimine as the key step in the synthesis of (–)-fasicularin and (–)-lepadiformine A (**1** and **2**, respectively, Figure 1).

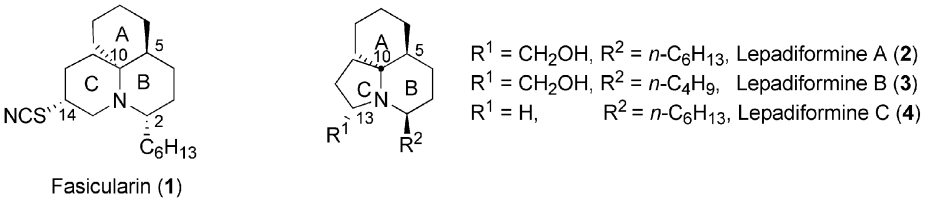

Figure 1. Structures of lepadiformines A–C and fasicularin.

Results and Discussion

Retrosynthetic Analysis

We envisioned that both **1** and **2** could be obtained by different cyclization processes from a common intermediate **5**, which, in turn, could be derived from azaspirobicyclic

[a] Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences,
345 Lingling Road, Shanghai 20032, P. R. of China
Fax: +86-21-64166128
E-mail: Zhaog@mail.sioc.ac.cn

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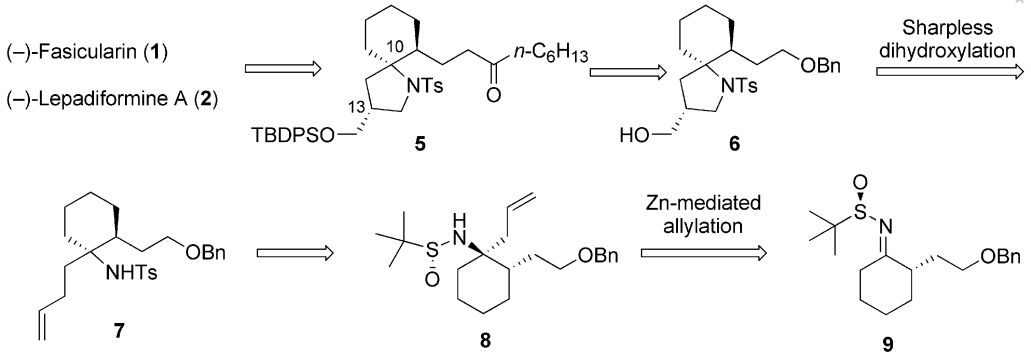
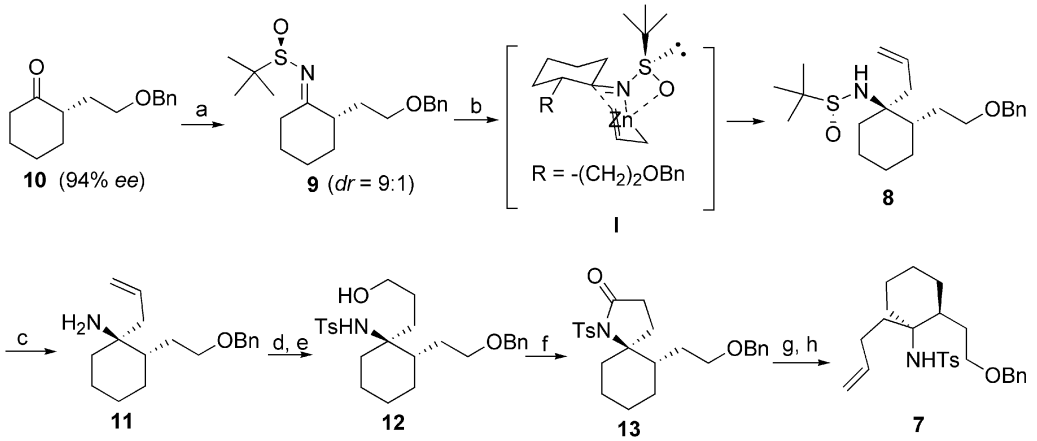


Scheme 1. Retrosynthetic analysis.

alcohol **6** (Scheme 1). The synthesis of **6** could be achieved by an intramolecular Sharpless dihydroxylation sequence from sulfonamide **7** with an amino-substituted, quaternary, carbon center. In view of the recent studies on the synthesis of chiral homoallylic amines by the Zn-mediated allylation of chiral *N*-*tert*-butanesulfinyl imines by Lin and coworkers,[5b,5c] we envisaged that the allylation of the corresponding, chiral, *N*-*tert*-butanesulfinyl ketimine **9** would produce sulfinamide **8** with the desired chiral quaternary carbon center, which could be further converted to **7**.

Construction of the Quaternary, Amino-Substituted Carbon Center

Our synthetic route to the key sulfonamide intermediate **7** is outlined in Scheme 2. The condensation of chiral ketone **10**[7] (94% *ee*), and (*R*)-*tert*-butanesulfinamide with a known procedure[8] using $Ti(OEt)_4$ as both the Lewis-acid promoter and water scavenger afforded desired ketimine **9** in 72% combined yield and with a *dr* of 9:1; these isomers could be separated by chromatography on a multigram scale. Next, efforts were directed to the construction of the amino-substituted, quaternary, carbon center. To the best of our knowledge, there has been little study on the nucleophilic addition of organometallic reagents with chiral *N*-*tert*-butanesulfinyl imines derived from aliphatic cyclic ketones, notwithstanding the great usefulness of the resulting chiral amine products.[5b,5c] At first, we attempted to synthesize **7** directly by the addition of homoallylic metal reagents. However, both the corresponding organolithium and Grignard reagents provided the desired product in very low yield.[9] We then turned to the known, Zn-mediated, allylation system, because organozinc reagents are generally less basic. To our delight, treating ketimine **9** with preactivated Zn powder and allylic bromide in THF produced the desired sulfinamide **8** in 89% yield and with a *dr* of up to 12:1 in the absence of a Lewis acid. Notably, in the case of the ketimines derived from simple aromatic ketones, stoichiometric $In(OTf)_3$ was required as an additive for the reaction to proceed.[5a] The stereochemical result of this transformation was tentatively explained by a chelated, chair-like, transition state model I (Scheme 2), in which the allyl-Zn could coordinate to the sulfinyl oxygen.[5a] We note that the chiral sulfinyl group prevailed over chiral induction by the substrate in the stereochemical outcome; when the diastereomer of **9** with an (*S*) configuration at the *tert*-



Reagents and conditions: a) $Ti(OEt)_4$/THF, 76%, *dr* = 9:1; b) Zn, allyl bromide/THF, 89%, *dr* = 12:1; c) HCl in dioxirane/MeOH, 92%; d) TsCl, Et_3N, DMAP/CH_2Cl_2; e) 9-BBN, then H_2O_2/$NaHCO_3$, 86% over two steps; f) TPAP, NMO, 4Å sieves/CH_2Cl_2, 80%; g) DIBAL-H/CH_2Cl_2; h) NaHMDS, Ph_3PCH_3Br/THF, 92% over two steps.

Scheme 2. Synthesis of sulfonamide **7** with the quaternary carbon center.

butanesulfinyl group underwent the same reaction, the predominant configuration of the newly created quaternary center was (*R*). The subsequent removal of the *tert*-butanesulfinyl group generated primary amine **11**. After the protection by the tosyl (Ts) group and hydroboration-oxidation of **11**,[10] the resulting primary alcohol **12** was converted into the corresponding lactam **13** by TPAP oxidation.[11,12] Reduction with DIBAL-H followed by a Wittig reaction successfully gave desired sulfonamide **7**. The structure of **13** was confirmed by the X-ray analysis of its ester, which was obtained by replacing the benzyl group with a 4-nitrobenzoyl group (see the Supporting Information for details).

Preparation of Azaspirobicyclic Ketone 5

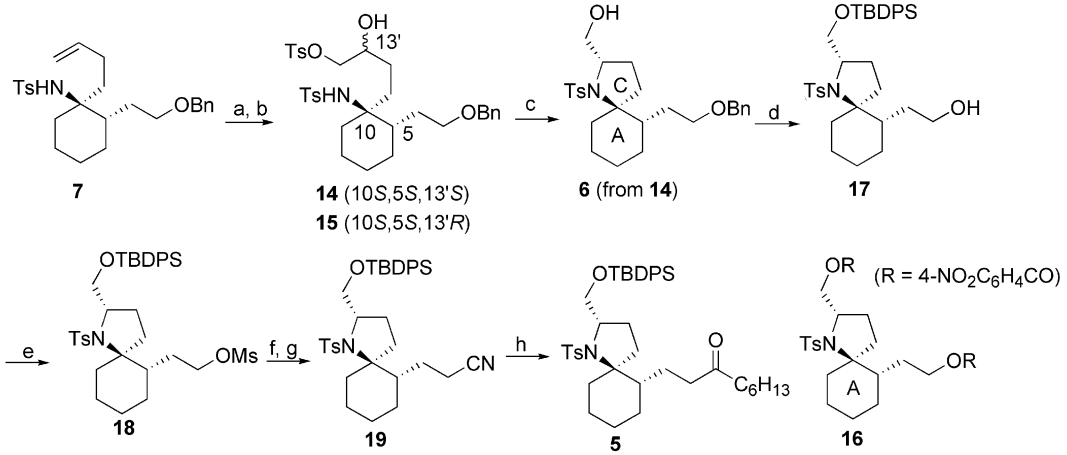
With sulfonamide **7** in hand, our designed strategy subsequently called for the construction of the azaspirobicyclic core. Disappointingly, the direct, intramolecular aminohydroxylation of **7** using *m*-CPBA[13] as the oxygen source unselectively afforded spirocyclic alcohol **6** in 98% yield with a **6**/13-*epi*-**6** diastereoselectivity of 1:1; these isomers could not be separated by flash chromatography (Scheme 3). Attempts to improve the diastereoselectivity by an asymmetric epoxidation and ring-opening sequence using Shi's epoxidation[14a] and Jacobsen's epoxidation[14b] also failed. Finally, Sharpless dihydroxylation[15a,15b] followed by selective protection[15c] gave isomers **14** and **15** (**14/15** = 2.8:1), which could be separated by column chromatography. Treating **14** with NaH gave **6** with the desired configuration, which was confirmed by the X-ray crystallographic analysis of the corresponding diester **16** (see the Supporting Information for details). Having established the azaspirobicyclic structure, the synthesis of ring-closure precursor **5** could be achieved by several routine steps. TBDPS protection of **6** followed by the removal of the benzyl group led to primary alcohol **17**, which was further converted to mesylate **18**. Treating **18** with excess potassium cyanide gave nitrile **19**, which was treated with *n*-hexylmagnesium bromide to generate desired ketone **5** in excellent yield.

Completion of the Total Synthesis of (–)-Fasicularin

Having the ring-closure precursor for the third cycle of the tricyclic alkaloids in hand, we first investigated its transformation to (–)-fasicularin (**1**). The removal of the Ts group of **5** with Na/naphthalene[16] generated a cyclized intermediate enamine in situ, which was directly reduced in the next step without further purification because of its instability (Scheme 4). After performing some experimentation, the Luche reduction[6,17] of the enamine was identified as the optimum method, affording the desired tricyclic tertiary amine **20** as a single isomer. The subsequent removal of the TBDPS group followed by Kibayashi's procedure (see the Experimental Section for details) completed the total synthesis of (–)-fasicularin (**1**), whose spectroscopic data were identical with those of reported values.[4g]

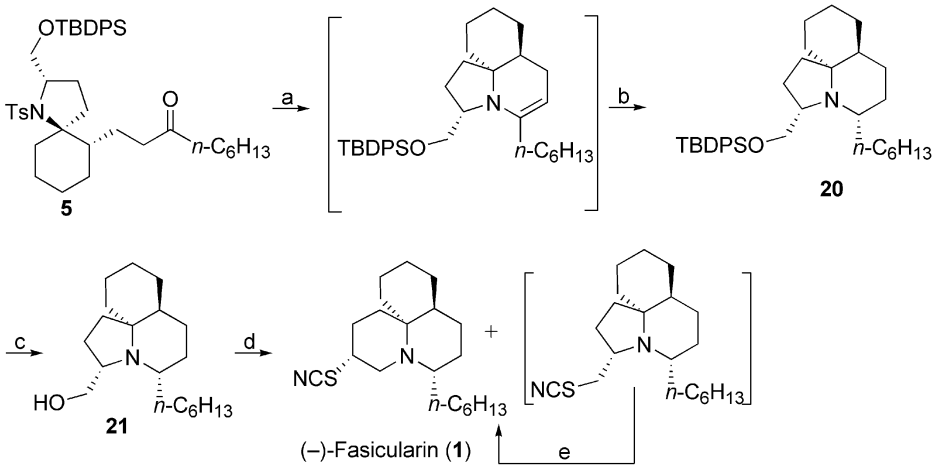
Completion of the Total Synthesis of (–)-Lepadiformin

To synthesize (–)-lepadiformine A, ketone **5** was first reduced to the corresponding alcohol **22** (Scheme 5). Among the various conditions screened for this transformation, the reduction with L-Selectride[4o] gave the desired product with the best *dr* of 6:1 in 99% yield. After removing the Ts group of **22**, an intramolecular, Mitsunobu-type reaction generated tricyclic **23** in excellent yield. We note that no desired product was found without the addition of a catalytic amount of DMAP to the standard reaction conditions of Ph_3P, CBr_4 and Et_3N.[4g] Finally, the removal of the TBDPS group led to the total synthesis of (–)-lepadiformine A (**2**), whose spectroscopic data were identical with reported values.[4h]

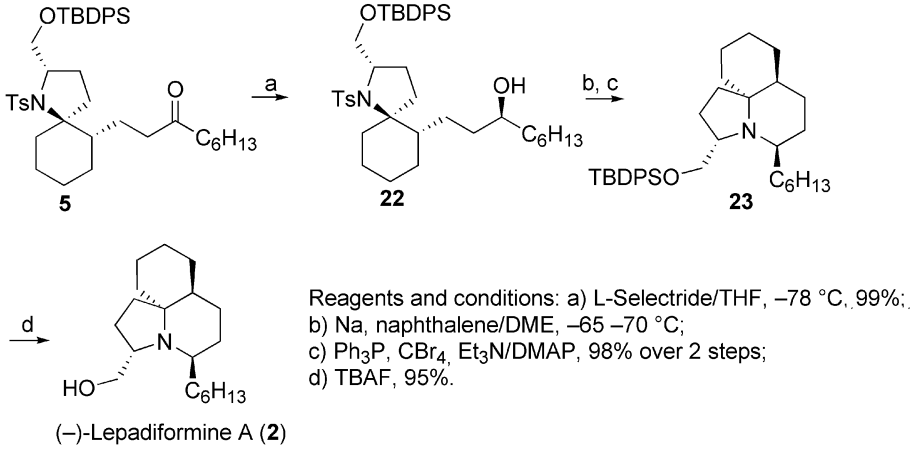


Reagents and conditions: a) AD-mix-α, OsO_4, *t*BuOH/H_2O; b) TsCl, Bu_2SnO, Et_3N;
c) NaH/THF, 0 C, 80% over three steps, dr = 2.8 : 1; d) TBDPSCl, imidazole, DMAP, DMF;
e) $Pd(OH)_2$/C, H_2, 94% over two steps; f) MsCl, Et_3N, DMAP, CH_2Cl_2;
g) KCN, DMSO, 91% over 2 steps; h) $C_6H_{13}MgBr/Et_2O$, reflux, 90%.

Scheme 3. Synthesis of the azaspirobicyclic ketone **5**.



Scheme 4. Completion of the total synthesis of (–)-fasicularin (**1**).



Scheme 5. Completion of the total synthesis of (–)-lepadiformine A (**2**).

Conclusions

In summary, we have successfully developed a Zn-mediated allylation of a chiral, aliphatic, cyclic, *N*-*tert*-butanesulfinyl ketimine for the stereoselective total synthesis of lepadiformine A and fasicularin. This flexible strategy could also provide an amenable approach to the synthesis of other analogues of the azaspirotricyclic alkaloids of this family.

Experimental Section

Explanation of Acronyms: CBS: Corey–Bakshi–Shibata reagent, *m*-CPBA: *m*-chloroperbenzoic acid, $(DHQD)_2PHAL$: 1,4-bis(9-*O*-dihydroquinine)phthalazine, DIBAL-H: diisobutyaluminum hydride, DMP: Dess–Martin periodinane, DMAP: 4-(dimethylamino)pyridine, NaHMDS: sodium hexamethyldisilazane, NMO: *N*-methylmorpholine oxide, PCC: pyridinium chlorochromate, TPAP: tetra-*n*-propylammonium perruthenate, TBDPS: *tert*-butyldiphenylsilyl.

Ketimine 9: To chiral ketone **10** (2.0 g, 8.61 mmol) in distilled THF (20 mL), were added (*R*)-*tert*-butanesulfinamide (1.46 g, 12.07 mmol) and $Ti(OEt)_4$ (3.6 mL, 17.17 mmol) at room temperature, and the reaction mixture was refluxed overnight. After the mixture was cooled to room temperature, the reaction was quenched with anhydrous MeOH (8 mL) and saturated aqueous $NaHCO_3$ (0.2 mL) and stirred for 2 h. After the mixture was filtered and concentrated, the reaction mixture was diluted with ethyl acetate (EA) and dried with anhydrous $MgSO_4$. After the mixture was filtered and concentrated, it was purified by flash chromatography [petroleum ether (PE)/EA, 5:1) to give ketimine **9** as a colorless oil (2.0 g) and 5-*epi*-**9** (200 mg) in a combined yield of 76%. R_f = 0.42 (PE/EA = 3:1). $[a]_D^{22}$ = –42.6 (*c* = 0.96, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1625 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.26 (m, 5 H), 4.45 (s, 2 H), 3.52 (t, *J* = 6.5 Hz, 2 H), 3.45 (d, *J* = 12.9 Hz, 1 H), 2.56–2.44 (m, 1 H), 2.20–1.99 (m, 4 H), 1.73–1.48 (m, 5 H),

1.21 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.0, 138.3, 128.2, 127.5, 127.4, 72.7, 67.8, 56.0, 45.8, 35.2, 34.5, 30.7, 28.6, 25.0, 22.0 ppm. ESI-MS: calcd. for $C_{19}H_{29}NO_2S$ 335.2; found *m*/*z* $[M + Na]^+$ 358.2. HRMS (MALDI): *m*/*z* 358.1811. $[M + Na]^+$; calcd. for $C_{19}H_{29}NO_2SNa$ 358.1817.

5-*epi*-9: R_f = 0.35 (PE/EA = 3:1). $[\alpha]_D^{22}$ = –112.6 (*c* = 0.24, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1618 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 5 H), 4.48 (AB, *J* = 12.6, 15.8 Hz, 2 H), 3.55–3.51 (m, 2 H), 3.33 (d, *J* = 13.5 Hz, 1 H), 2.58–2.49 (m, 1 H), 2.41–2.31 (m, 1 H), 2.27–2.16 (m, 1 H), 2.10–2.05 (m, 1 H), 1.94 (br., 1 H), 1.78 (br., 1 H), 1.65–1.51 (m, 3 H), 1.43–1.29 (m, 1 H), 1.22 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.3, 138.1, 128.0, 127.3, 127.2, 72.6, 67.8, 55.6, 45.6, 34.5, 34.0, 30.6, 27.7, 24.4, 21.9 ppm. ESI-MS: calcd. for $C_{19}H_{29}NO_2S$ 335.2; found *m*/*z* $[M + Na]^+$ 358.1. HRMS (MALDI): *m*/*z* 358.1811, *m*/*z* $[M + Na]^+$; calcd. for $C_{19}H_{29}NO_2SNa$ 358.1817.

Sulfinamide 8: To ketimine **9** (620 mg, 1.85 mmol) in distilled THF (10 mL) were added activated Zn powder (482 mg, 7.41 mmol) and a solution of allyl bromide (0.64 mL, 7.41 mmol) in THF (5 mL), and the mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with brine (15 mL) and saturated aqueous $NaHCO_3$ (2 mL). After the mixture was stirred for 1 h, the mixture was filtered through celite, and the filtrate was separated and extracted with EA. The combined organic phases were washed with brine and dried with anhydrous Na_2SO_4. After the mixture was filtered and concentrated, the mixture was purified by flash chromatography (PE/EA, 5:1) to afford **8** as a colorless oil (622 mg) in 89% yield. R_f = 0.35 (PE/EA, 3:1). $[\alpha]_D^{25}$ = –45.4 (*c* = 0.81, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3290, 1631, 1453, 1261, 1068 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.25 (m, 5 H), 5.94–5.79 (m, 1 H), 5.24–5.14 (m, 2 H), 4.49 (AB, *J* = 12.0, 28.4 Hz, 2 H), 3.55–3.88 (m, 3 H), 2.57 (dd, *J* = 6.9, 14.4 Hz, 1 H), 2.08–1.93 (m, 8 H), 1.39–1.25 (m, 4 H), 1.19 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.5, 133.1, 128.3, 127.6, 127.5, 120.2, 73.0, 69.2, 59.6, 56.2, 40.8, 37.2, 36.6, 29.1, 28.1, 24.8, 22.9 ppm. ESI-MS: calcd. for $C_{22}H_{35}NO_2S$ 377.2; found *m*/*z* $[M + Na]^+$ 400.3. HRMS (MALDI): *m*/*z* 400.2281, *m*/*z* $[M + Na]^+$ calcd. for $C_{22}H_{35}NO_2SNa$ 400.2286.

Primary Amine 11: To **8** (3.45 g, 9.15 mmol) in distilled MeOH (69 mL) was added HCl (4 M in dioxane, 23 mL). After the mixture was stirred for 10 min, saturated aqueous K_2CO_3 (23 mL) was added, and the mixture was stirred for 10 min. After the mixture was concentrated, distilled water (50 mL) was added, and the mixture was extracted with EA (15 mL × 3). The combined organic phases were washed with brine and dried with anhydrous Na_2SO_4. After the mixture was filtered and concentrated, the mixture was purified by flash chromatography (PE/EA, 5:1) to afford primary amine **11** as a colorless oil (2.3 g) in 92% yield. R_f = 0.47 (CH_2Cl_2/EtOH, 9:1). $[\alpha]_D^{27}$ = –32.6 (*c* = 1.77, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1637 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.24 (m, 5 H), 5.91–5.77 (m, 1 H), 5.12–5.05 (m, 2 H), 4.51 (AB, *J* = 11.2, 15.9 Hz, 2 H), 3.58–3.43 (m, 2 H), 2.32 (dd, *J* = 7.5, 13.5 Hz, 1 H), 2.06–1.89 (m, 2 H), 1.74–1.38 (m, 6 H), 1.26–1.03 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.1, 128.3, 127.5, 127.4, 118.0, 72.81, 69.4, 53.3, 45.1, 38.3, 37.4, 29.2, 28.0, 25.3, 22.6 ppm. ESI-MS: calcd. for $C_{18}H_{27}NO$ 273.2; found *m*/*z* $[M + H]^+$ 274.2. HRMS (MALDI): *m*/*z* 274.2165, *m*/*z* $[M + H]^+$ calcd. for $C_{18}H_{28}NO$ 274.2171.

Alcohol 12: To primary amine **11** (2.3 g, 8.42 mmol) in distilled CH_2Cl_2 (50 mL) were added Et_3N (4.65 mL, 33.70 mmol), DMAP (103 mg, 0.84 mmol) and TsCl (3.21 g, 16.84 mmol) at room temperature. After the mixture was stirred overnight, the reaction was quenched by the addition of distilled water (25 mL). The layers were separated, and the aqueous layer was extracted with EA (10 mL × 3). The combined organic phases were washed with brine and dried with anhydrous Na_2SO_4. After the mixture was filtered and concentrated, the mixture was purified by flash chromatography (PE/EA, 25:1 to 3:1) to afford the protected amine product (3.6 g) in quantitative yield.

To the protected amine product (3.6 g, 7.83 mmol) in distilled THF (30 mL) was added 9-BBN (3.8 g, 31.15 mmol). After the mixture was stirred for 24 h, saturated aqueous $NaHCO_3$ (60 mL) and H_2O_2 (30 mL) were added, and the mixture was stirred for 3 h. The mixture was extracted with EA (20 mL × 3). The combined organic phases were washed with brine and dried with anhydrous Na_2SO_4. After the mixture was filtered and concentrated, the mixture was purified by flash chromatography (PE/EA, 3:1) to afford primary alcohol **12** as a colorless oil (3.0 g) in 86% yield.

R_f = 0.46 (PE/EA, 1:1). $[\alpha]_D^{24}$ = –33.0 (*c* = 1.17, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3288, 1599, 1495, 1455 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 7.5 Hz, 2 H), 7.36–7.21 (m, 7 H), 5.70 (s, 1 H), 4.54–4.45 (m, 2 H), 3.62–3.35 (m, 4 H), 2.39 (s, 3 H), 2.05–1.94 (m, 3 H), 1.75–1.11 (m, 11 H), 0.91–0.84 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.5, 141.1, 138.4, 129.4, 128.3, 127.8, 127.5, 126.8, 72.9, 69.5, 62.7, 42.5, 32.1, 29.6, 28.6, 28.1, 25.4, 24.4, 22.1, 21.4 ppm. ESI-MS: calcd. for $C_{25}H_{35}NO_4S$ 445.2; found *m*/*z* $[M + Na]^+$ 468.3. HRMS (ESI): *m*/*z* 446.2360, *m*/*z* $[M + H]^+$ calcd. for $C_{25}H_{36}NO_4S$ 446.2365.

Lactam 13: To alcohol **12** (2.5 g, 5.62 mmol) in CH_2Cl_2 (50 mL) were added 4 Å molecular sieves (2.5 g) and NMO (1.58 g, 13.49 mmol). After the mixture was stirred for 15 min, TPAP (631 mg, 1.80 mmol) was added, and the mixture was stirred for an additional 15 min. After the mixture was filtered and concentrated, the mixture was purified by flash chromatography (PE/EA, 3:1) to afford lactam **13** as a white solid (1.98 g) in 80% yield. R_f = 0.41 (PE/EA, 3:1); m.p. 121–123 °C $[\alpha]_D^{19}$ = +17.8 (*c* = 1.00, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1728 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 8.3 Hz, 2 H), 7.37–7.23 (m, 7 H), 4.54 (AB, *J* = 11.8, 16.2 Hz, 2 H), 3.61 (t, *J* = 6.8 Hz, 2 H), 2.78–2.67 (m, 2 H), 2.40–2.30 (m, 5 H), 2.15–2.06 (m, 1 H), 1.90–1.68 (m, 6 H), 1.40–1.27 (m, 3 H), 1.13–1.04 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.8, 144.5, 138.5, 136.4, 129.2, 129.0, 128.3, 127.7, 127.5, 75.2, 72.9, 68.6, 40.7, 37.8, 30.0, 29.8, 28.9, 25.1, 23.3, 21.6 ppm. ESI-MS: calcd. for $C_{25}H_{31}NO_4S$ 441.2; found *m*/*z* $[M + Na]^+$ 464.3. HRMS (MALDI): *m*/*z* 464.1866, *m*/*z* $[M + Na]^+$ calcd. for $C_{25}H_{31}NO_4SNa$ 464.1871.

Sulfonamide 7: To lactam **13** (1.73 g, 3.92 mmol) in CH_2Cl_2 (40 mL) was added DIBAL-H (9.8 mL, 1.0 M in cyclohexane, 9.8 mmol) at –78 °C, and the mixture was stirred for another 2 h. The reaction was warmed to –40 °C, quenched with MeOH (1.0 mL) and saturated aqueous Rochelle's salt (100 mL) was added. The mixture was stirred for 1 h at room temperature, the layers were separated, and the aqueous layer was extracted with EA. The combined organic phases were washed with brine and dried with anhydrous Na_2SO_4. After the mixture was filtered and concentrated, the mixture was used directly in the next step without further purification.

To PPh_3CH_3Br (5.6 g, 15.68 mmol) in THF (20 mL) was slowly added NaHMDS (7.65 mL, 2.0 M in THF, 15.3 mmol) at 0 °C, and stirring was continued for 0.5 h. After the mixture was cooled to –78 °C, a solution of the reduced lactam, prepared above, in THF (20 mL) was added, and stirring was continued at this temperature for 20 min. The reaction mixture was allowed to stir at 0 °C and then slowly warmed to room temperature and stirred for 2 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with EA. The combined organic phases were washed with

brine and dried with anhydrous Na_2SO_4. After the mixture was filtered and concentrated, the mixture was purified by flash chromatography (PE/EA, 9:1) to afford **7** as a colorless oil (1.6 g) in 92% yield over two steps. R_f = 0.45 (PE/EA, 5:1). $[\alpha]_D^{24}$ = –22.7 (c = 1.29, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3284, 1094 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, J = 8.2 Hz, 2 H), 7.36–7.26 (m, 5 H), 7.23 (d, J = 7.9 Hz, 2 H), 5.75–5.62 (m, 1 H), 5.22 (s, 1 H), 4.96–4.90 (m, 2 H), 4.52 (AB, J = 11.8, 19.4 Hz, 2 H), 3.56–3.42 (m, 2 H), 2.39 (s, 3 H), 2.07–1.07 (m, 15 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.6, 141.0, 138.30, 138.26, 129.4, 128.3, 127.7, 127.5, 126.9, 114.8, 72.9, 69.4, 62.7, 42.8, 31.7, 31.4, 29.8, 28.7, 26.8, 24.4, 22.0, 21.4 ppm. ESI-MS: calcd. for $C_{26}H_{35}NO_3S$ 441.2; found m/z [M + Na]$^+$ 464.1. HRMS (MALDI): m/z 464.2220, m/z [M + Na]$^+$ calcd. for $C_{26}H_{35}NO_3SNa$ 464.2235.

14 and 15: To $K_3Fe(CN)_6$ (3.22 g, 9.8 mmol), $NaHCO_3$ (821 mg, 9.7 mmol), K_2CO_3 (1.35 g, 9.8 mmol), $(DHQD)_2PHAL$ (102 mg, 0.13 mmol), OsO_4 (9 mg, 0.035 mmol) and $MeSO_2NH_2$ (310 mg, 3.3 mmol) in tBuOH/H_2O (15:18, 33 mL), which was stirred at room temperature for 20 min, was added **7** (1.44 g, 3.26 mmol) in tBuOH (5 mL) at 0 °C, and stirring was continued overnight. The reaction was then quenched with Na_2SO_3 (6.0 g), and distilled water (10 mL) was added to dissolve the solid. The mixture was extracted with EA (3 × 10 mL), and the combined organic phases were washed with brine and dried with anhydrous $MgSO_4$. After the mixture was filtered and concentrated, the mixture was purified by flash chromatography (CH_2Cl_2/EtOH, 20:1) to afford the diol (1.54 g) in 99% yield, and the crude product was directly used in the next step.

To the diol (1.7 g, 3.57 mmol) in CH_2Cl_2 (40 mL) were added Bu_2SnO (889 mg, 3.57 mmol), Et_3N (0.59 mL, 4.28 mmol) and TsCl (715 mg, 3.75 mmol), and the mixture was stirred overnight. EA (40 mL) was added to dilute the mixture. After the mixture was filtered and concentrated, the mixture was purified by flash chromatography (PE/EA, 3:2) to afford **14** (1.49 g) and **15** (532 mg) in a combined yield of 89%.

14: R_f = 0.42 (PE/EA, 1:1). $[\alpha]_D^{19}$ = –15.2 (c = 0.91, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3524, 3305 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, J = 8.2 Hz, 2 H), 7.73 (d, J = 7.9 Hz, 2 H), 7.37–7.27 (m, 7 H), 7.22 (d, J = 8.2 Hz, 2 H), 5.63 (s, 1 H), 4.52–4.44 (m, 2 H), 3.91 (dd, J = 9.9, 3.2 Hz, 1 H), 3.80 (dd, J = 6.5, 10.0 Hz, 1 H), 3.62 (s, 1 H), 3.49–3.42 (m, 1 H), 3.40–3.35 (m, 1 H), 2.64 (d, J = 4.1 Hz, 1 H), 2.45 (s, 3 H), 2.39 (s, 3 H), 1.89–1.10 (m, 15 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.1, 142.6, 140.9, 138.2, 132.5, 130.0, 129.4, 128.4, 127.9, 127.8, 127.6, 126.8, 73.7, 72.9, 69.5, 69.3, 62.4, 42.4, 32.0, 29.5, 28.3, 27.5, 25.5, 24.1, 22.0, 21.6, 21.5 ppm. ESI-MS: calcd. for $C_{33}H_{43}NO_7S_2$ 629.2; found m/z [M + Na]$^+$ 652.1. HRMS (MALDI): m/z 652.2373, m/z [M + Na]$^+$ calcd. for $C_{33}H_{43}NO_7S_2Na$ 652.2379.

15: R_f = 0.5 (PE/EA, 1:1). $[\alpha]_D^{19}$ = –13.7 (c = 1.30, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3524, 3299 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.81 (d, J = 7.9 Hz, 2 H), 7.71 (d, J = 8.0 Hz, 2 H), 7.38–7.27 (m, 7 H), 7.22 (d, J = 8.2 Hz, 2 H), 5.58 (s, 1 H), 4.55 (AB, J = 11.7, 14.7 Hz, 2 H), 3.91 (dd, J = 9.6, 3.2 Hz, 1 H), 3.82 (dd, J = 6.7, 10.0 Hz, 1 H), 3.69 (s, 1 H), 3.52–3.42 (m, 1 H), 3.40–3.35 (m, 1 H), 2.45 (s, 4 H), 2.39 (s, 3 H), 1.82–1.11 (m, 15 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.1, 142.7, 140.8, 138.2, 132.5, 130.0, 128.58, 128.4, 127.9, 127.8, 127.6, 126.8, 73.6, 72.9, 69.4, 69.3, 62.4, 42.8, 31.9, 29.8, 28.69, 27.4, 25.6, 24.3, 21.9, 21.6, 21.4 ppm. ESI-MS: calcd. for $C_{33}H_{43}NO_7S_2$ 629.2; found m/z [M + Na]$^+$ 652.1. HRMS (MALDI): m/z 652.2373, m/z [M + Na]$^+$ calcd. for $C_{33}H_{43}NO_7S_2Na$ 652.2379.

Azaspirocyclic 6: To **14** (866 mg, 1.38 mmol) in THF (17 mL) was added NaH (133 mg, 3.33 mmol) at 0 °C, and the mixture was stirred for 12 h. The reaction was quenched with saturated aqueous NH_4Cl (5.0 mL) and extracted with EA (3 × 10 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. After the mixture was filtered and concentrated, the mixture was purified by flash chromatography (PE/EA, 5:3) to afford **6** (560 mg) in 89% yield. R_f = 0.56 (PE/EA, 5:4); m.p. 120–122 °C. $[\alpha]_D^{24}$ = +41.1 (c = 0.98, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3480, 1153, 1095 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.79 (d, J = 7.9 Hz, 2 H), 7.37–7.31 (m, 5 H), 7.22 (d, J = 8.2 Hz, 2 H), 4.43 (s, 2 H), 3.80–3.62 (m, 3 H), 3.47–3.39 (m, 1 H), 3.22–3.14 (m, 1 H), 2.87 (s, 1 H), 2.59 (td, J = 3.2, 12.9 Hz, 1 H), 2.42–2.37 (m, 1 H), 2.10 (s, 1 H), 2.07–1.60 (m, 9 H), 1.25–0.96 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.1, 138.5, 138.4, 129.5, 128.4, 127.65, 127.56, 127.3, 75.7, 73.1, 69.2, 65.9, 63.2, 42.4, 39.7, 32.2, 31.1, 30.4, 28.0, 25.2, 24.6, 21.5 ppm. ESI-MS: calcd. for $C_{26}H_{35}NO_4S$ 457.2; found m/z [M + Na]$^+$ 480.1. HRMS (MALDI): m/z 480.2179, m/z [M + Na]$^+$ calcd. for $C_{26}H_{35}NO_4SNa$ 480.2184.

Primary Alcohol 17: To **6** (400 mg, 1.38 mmol) in DMF (1.0 mL) was added imidazole (239 mg, 3.51 mmol) and DMAP (11 mg, 0.09 mmol) at 0 °C, and the mixture was stirred overnight at room temperature. The reaction was quenched with distilled water (5.0 mL) and extracted with EA (3 × 5 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. After the mixture was filtered and concentrated, the mixture was directly used in the next step without further purification. To the crude material, dissolved in MeOH (12 mL), was added $Pd(OH)_2$/C under an atmosphere of H_2, and the mixture was stirred overnight. After the mixture was filtered and concentrated, the mixture was purified by flash chromatography (PE/EA, 10:1 to 2:1 to 1:4) to afford **17** (500 mg) in 94% yield over two steps. R_f = 0.69 (PE/EA, 2:1); m.p. 140–142 °C. $[\alpha]_D^{24}$ = –24.6 (c = 1.10, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3523 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.62–7.58 (m, 6 H), 7.44–7.38 (m, 6 H), 7.14 (d, J = 7.6 Hz, 2 H), 4.03–3.96 (m, 1 H), 3.71 (d, J = 9.6 Hz, 1 H), 3.63 (br., 1 H), 3.45–3.36 (m, 2 H), 2.47–2.29 (m, 5 H), 2.08–1.04 (m, 11 H), 1.00 (s, 9 H), 0.96–0.82 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.7, 140.0, 135.63, 135.61, 133.44, 133.40, 129.73, 129.69, 129.3, 127.67, 127.65, 127.2, 75.0, 64.4, 62.5, 61.2, 42.2, 39.8, 34.1, 31.8, 30.3, 26.9, 26.1, 25.3, 24.5, 21.4, 19.2 ppm. ESI-MS: calcd. for $C_{35}H_{47}NO_4SSi$ 605.3; found m/z [M + Na]$^+$ 628.2. HRMS (MALDI): m/z 628.2887, m/z [M + Na]$^+$ calcd. for $C_{35}H_{47}NO_4SSiNa$ 628.2894.

Mesylate 18: To **17** (467 mg, 0.77 mmol) in CH_2Cl_2 (12 mL) were added Et_3N (0.32 mL, 2.32 mmol), DMAP (11 mg, 0.09 mmol) and MsCl (0.12 mL, 1.55 mmol) at 0 °C, and the mixture was stirred for 1 h. The reaction was quenched with distilled water (5 mL) and extracted with EA (3 × 5.0 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. After the mixture was filtered and concentrated, the mixture was directly used in the next step without further purification. R_f = 0.44 (PE/EA, 3:1). $[\alpha]_D^{24}$ = –18.7 (c = 0.70, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1094 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.38 (12 H), 7.15 (d, J = 8.2 Hz, 2 H), 4.24–4.13 (m, 1 H), 4.04–3.92 (m, 2 H), 3.68 (dd, J = 3.7, 10.1 Hz, 1 H), 3.35 (t, J = 9.6 Hz, 1 H), 3.00 (s, 3 H), 2.51–2.42 (m, 2 H), 2.37 (s, 3 H), 2.05–1.83 (m, 2 H), 1.69–1.60 (m, 8 H), 1.25–1.02 (m, 2 H), 0.90 (s, 9 H), 0.88–0.81 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.0, 135.6, 133.4, 129.8, 129.7, 129.5, 127.69, 127.66, 127.03, 74.6, 68.5, 64.1, 62.2, 42.1, 39.9, 37.4, 31.8, 30.4, 30.2, 29.7, 26.9, 26.3, 25.1, 24.4, 21.5, 19.2 ppm. ESI-MS: calcd. for $C_{36}H_{49}NO_6S_2Si$ 683.3; found m/z [M + Na]$^+$ 706.1.

HRMS (MALDI): *m/z* 706.2663, *m/z* [M + Na]$^+$ calcd. for $C_{36}H_{49}NO_6S_2SiNa$ 706.2668.

Nitrile 19: To **18** (the mixture described above) in DMSO (15 mL) was added KCN (301 mg, 4.63 mmol), and the mixture was heated at 60–70 °C for 5 h. After the mixture was cooled to room temperature, the reaction was quenched with distilled water (15 mL) and extracted with EA (3 × 10 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. After the mixture was filtered and concentrated, the mixture was purified by flash chromatography (PE/EA, 4:1) to afford **19** (430 mg) in 91% yield over two steps. R_f = 0.5 (PE/EA = 4:1); m.p. 137–139 °C. $[\alpha]_D^{24}$ = –40.4 (*c* = 0.84, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2235 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65–7.56 (m, 6 H), 7.47–7.41 (m, 6 H), 7.20 (d, *J* = 7.6 Hz, 2 H), 4.03–3.95 (br., 1 H), 3.87 (dd, *J* = 3.0, 10.0 Hz, 1 H), 3.45 (dd, *J* = 9.3, 10.2 Hz, 1 H), 2.45–2.37 (m, 4 H), 2.22–2.12 (m, 2 H), 2.02–1.88 (m, 2 H), 1.78–1.71 (m, 6 H), 1.61–1.11 (m, 3 H), 1.05 (s, 9 H), 1.00–0.88 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.3, 139.8, 135.7, 135.6, 133.4, 129.8, 129.7, 129.6, 127.71, 127.67, 126.7, 119.7, 74.2, 64.7, 62.6, 42.4, 42.3, 31.8, 29.2, 27.3, 26.9, 26.1, 25.0, 24.3, 21.5, 19.2, 15.0 ppm. ESI-MS: calcd. for $C_{36}H_{46}NO_3SSi$ 614.3; found *m/z* [M + H]$^+$ 615.3. HRMS (ESI): *m/z* 615.3071, *m/z* [M + Na]$^+$ calcd. for $C_{36}H_{47}NO_3SSi$ 615.3077.

Ketone 5: To **19** (420 mg, 0.684 mmol) in Et_2O (15 mL) was added *n*-$C_6H_{13}MgBr$ (5.5 mL, 1.0 M in Et_2O, 5.5 mmol), and the mixture was refluxed for 5 h. After the mixture was cooled to room temperature, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with EA (3 × 5.0 mL). The combined organic phases were washed with brine and dried with $MgSO_4$. After the mixture was filtered and concentrated, the mixture was purified by flash chromatography (PE/EA, 20:1) to afford **5** (432 mg) in 90% yield. R_f = 0.5 (PE/EA, 9:1). $[\alpha]_D^{24}$ = –40.4 (*c* = 0.84, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2235 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62–7.61 (m, 4 H), 7.55 (d, *J* = 8.2 Hz, 2 H), 7.42–7.36 (m, 6 H), 7.12 (d, *J* = 8.2 Hz, 2 H), 3.96–3.91 (m, 1 H), 3.86 (dd, *J* = 3.3, 9.5 Hz, 1 H), 3.44 (t, *J* = 9.3 Hz, 1 H), 2.48–2.38 (m, 1 H), 2.34 (s, 1 H), 2.28–2.22 (m, 3 H), 2.13–1.67 (m, 24 H), 1.04 (s, 9 H), 0.95–0.86 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.9, 142.4, 140.1, 135.64, 135.62, 133.5, 129.7, 129.6, 129.3, 127.64, 127.61, 127.0, 75.0, 64.7, 62.6, 42.6, 42.5, 42.2, 40.7, 31.8, 31.6, 29.8, 28.9, 26.9, 26.2, 25.3, 24.8, 24.5, 23.7, 22.5, 21.4, 19.2, 14.0 ppm. ESI-MS: calcd. for $C_{42}H_{59}NO_4SSi$ 701.4; found *m/z* [M + Na]$^+$ 724.2. HRMS (ESI): *m/z* 724.3826, *m/z* [M + Na]$^+$ calcd. for $C_{42}H_{59}NO_4SSiNa$ 724.3832.

Tertiary Amine 20: To **5** (12 mg, 17.1 μmol) in DME (1.0 mL) was added Na/naphthalene [which was prepared by stirring fresh sodium and naphthalene (13.2 mg, 103.1 μmol) in DME (1.0 mL) for 30 min at room temperature] at –68 °C, and the mixture was stirred for 10 min at this temperature. The reaction was quenched with saturated aqueous NH_4Cl (2.0 mL) and stirred at room temperature for awhile. The layers were separated, and the aqueous layer was extracted with EA (3 × 3.0 mL). The combined organic phases were washed with brine and dried with anhydrous K_2CO_3. After the mixture was filtered and concentrated, the mixture was purified by flash chromatography (PE/EA, 9:1) to afford the desired enamine (7 mg) in 77% yield.

To the enamine (7 mg, 12.66 μmol) in THF/MeOH (1:2.5, 1.4 mL) was added $CeCl_3{\cdot}7H_2O$ (29 mg, 76.6 μmol), and the mixture was stirred until the $CeCl_3{\cdot}7H_2O$ dissolved. To the mixture was added $NaBH_4$ (3 mg, 78.9 μmol) at –78 °C, and the mixture was stirred at this temperature for 15 min. The reaction was quenched with distilled water (1.0 mL) and extracted with EA (3 × 2.0 mL). The combined organic phases were washed with brine and dried with anhydrous $MgSO_4$. After the mixture was filtered and concentrated, the mixture was purified by flash chromatography (PE/EA, 5:1) to afford the desired tertiary amine **20** (6 mg) in 89% yield. R_f = 0.46 (PE/EA, 2:1). $[\alpha]_D^{28}$ = –3.7 (*c* = 0.80, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3070, 2928, 2857, 1462, 1428 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 6.9 Hz, 2 H), 7.42–7.33 (m, 6 H), 3.82 (dd, *J* = 5.9, 10.0 Hz, 1 H), 3.53 (dd, *J* = 9.6, 10.1 Hz, 1 H), 3.03–2.98 (m, 1 H), 2.38–2.23 (m, 1 H), 2.11–2.04 (m, 3 H), 1.80–1.06 (m, 26 H), 1.05 (s, 9 H), 0.88 (t, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.6, 129.5, 127.55, 127.52, 70.1, 67.6, 67.2, 62.6, 43.6, 38.6, 37.1, 32.0, 31.4, 30.8, 29.7, 27.0, 26.62, 26.55, 26.5, 26.3, 26.0, 24.7, 23.6, 22.6, 19.3, 14.1 ppm. ESI-MS: calcd. for $C_{35}H_{53}NOSi$ 531.4; found *m/z* [M + H]$^+$ 532.4. HRMS (MALDI): *m/z* 532.3969, *m/z* [M + H]$^+$ calcd. for $C_{35}H_{54}NOSi$ 532.3975.

Amino Alcohol 21: To **20** (19 mg, 0.036 mmol) in THF (1.0 mL) was added TBAF (0.18 mg, 0.18 mmol) at 0 °C, and the mixture was stirred for 48 h at room temperature. The reaction was quenched with iced water (1 mL) and extracted with EA (3 × 2.0 mL). The combined organic phases were washed with brine and dried with anhydrous K_2CO_3. After the mixture was filtered and concentrated, the mixture was purified by flash chromatography (Et_2O/MeOH, 20:1) to afford **21** (9 mg) in 85% yield. R_f = 0.44 (EA/MeOH, 5:1). $[\alpha]_D^{25}$ = +11.2 (*c* = 0.50, MeOH). IR (neat): $\tilde{\nu}$ = 3346 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.53 (dd, *J* = 6.0, 10.5 Hz, 1 H), 3.38–3.32 (m, 1 H), 3.16–3.10 (m, 1 H), 2.84 (br., 1 H), 2.24 (br., 1 H), 1.97–1.88 (m, 2 H), 1.78–1.52 (m, 7 H), 1.44–1.08 (m, 18 H), 0.87 (t, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 67.2, 66.6, 64.9, 60.6, 41.8, 39.0, 37.6, 31.9, 31.2, 29.5, 27.8, 27.0, 26.3, 25.8, 25.7, 24.5, 23.8, 22.6, 14.1 ppm. ESI-MS: calcd. for $C_{19}H_{35}NO$ 293.2; found *m/z* [M + H]$^+$ 294.2. HRMS (MALDI): *m/z* 294.2791, *m/z* [M + H]$^+$ calcd. for $C_{19}H_{36}NO$ 294.2797.

Fasicularin (1):[4g] To PPh_3 (49 mg, 0.187 mmol), NH_4SCN (17 mg, 0.223 mmol) and DEAD (30 μL, 0.190 mmol) was added dropwise **21** (9 mg, 0.031 mmol) in CH_2Cl_2 (1.0 mL) at room temperature, and the mixture was stirred overnight at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with EA (3 × 2.0 mL). The combined organic phases were washed with brine and dried with anhydrous K_2CO_3. After the mixture was filtered and concentrated, the mixture was purified by flash chromatography (PE/EA, 100:1 to 10:1 to 3:1) to afford fasicularin (**1**, 4 mg) and a more polar isomer (4 mg) which was stirred in CH_3CN (1 mL) for 24 h to obtain fasicularin (**1**, 3.5 mg). R_f = 0.55. $[\alpha]_D^{26}$ = –4.4 (*c* = 0.34, MeOH). IR (neat): $\tilde{\nu}$ = 2152 cm^{-1}. ^{1}H NMR (400 MHz, [D$_5$]-Py): δ = 3.63–3.54 (m, 1 H), 3.42 (dd, *J* = 14.2, 11.9 Hz, 1 H), 3.31 (dd, *J* = 4.1, 13.2 Hz, 1 H), 2.98–2.90 (m, 1 H), 2.57 (d, *J* = 13.3 Hz, 1 H), 1.98–1.96 (m, 1 H), 1.91–1.74 (m, 1 H), 1.61–1.06 (m, 24 H), 0.86 (t, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 111.6, 56.3, 52.3, 46.5, 46.1, 40.2, 34.3, 34.1, 32.3, 32.1, 30.3, 29.5, 27.7, 27.2, 26.3, 24.0, 22.9, 22.7, 19.3, 14.3 ppm. ESI-MS: calcd. for $C_{20}H_{34}N_2S$ 334.2; found *m/z* [M + H]$^+$ 335.1. HRMS (MALDI): *m/z* 335.2516, *m/z* [M + H]$^+$ calcd. for $C_{20}H_{35}N_2S$ 335.2521.

Amino Alcohol 22: To **5** (108 mg, 0.154 mmol) in THF (5.0 mL) was added L-Selectride (1.6 mL, 1 M in THF, 1.6 mmol) at –78 °C, and the mixture was stirred at this temperature for 5 h. The reaction was quenched with MeOH (1.0 mL) and stirred at room temperature for 0.5 h. After the mixture was concentrated, the mixture was purified by flash chromatography (PE/EA, 10:1 to 3:1) to afford **22** (91 mg) and the epimer of **22** (16 mg) in a combined yield of 99%. R_f = 0.56 (PE/EA, 6:1). $[\alpha]_D^{25}$ = –42.2 (*c* = 1.00, $CHCl_3$).

IR (neat): $\tilde{\nu}$ = 3548 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.60 (d, J = 7.9 Hz, 6 H), 7.45–7.35 (m, 6 H), 7.15 (d, J = 7.9 Hz, 2 H), 3.97–3.90 (m, 1 H), 3.78 (dd, J = 4.1, 9.9 Hz, 1 H), 3.38 (dd, J = 9.7, 9.4 Hz, 1 H), 3.27–3.19 (br., 1 H), 2.48–2.40 (m, 1 H), 2.36 (s, 3 H), 2.23–2.15 (m, 1 H), 2.04–1.76 (m, 3 H), 1.59–1.26 (m, 10 H), 1.03–0.96 (13 H), 0.96 (s, 9 H), 0.89 (t, J = 5.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.5, 140.2, 135.64, 135.62, 133.53, 133.49, 129.68, 129.66, 129.3, 127.7, 127.6, 127.3, 75.6, 72.4, 64.5, 62.4, 42.9, 42.5, 37.4, 35.2, 31.84, 31.76, 30.1, 29.7, 29.3, 27.3, 26.9, 26.3, 25.4, 24.6, 22.6, 21.4, 19.2, 14.1 ppm. ESI-MS: calcd. for $C_{42}H_{61}NO_4SSi$ 703.4; found m/z $[M + Na]^+$ 726.3. HRMS (ESI): m/z 726.3983, m/z $[M + Na]^+$ calcd. for $C_{42}H_{61}NO_4SSiNa$ 726.3988.

Minor Epimer of 22: R_f = 0.36 (PE/EA, 6:1). $[\alpha]_D^{22}$ = –42.2 (c = 2.18, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3545 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.59–7.56 (m, 6 H), 7.45–7.26 (m, 6 H), 7.09 (d, J = 8.2 Hz, 2 H), 3.99–3.92 (m, 1 H), 3.61 (dd, J = 3.7, 9.6 Hz, 1 H), 3.34–3.27 (m, 2 H), 2.48–2.40 (m, 1 H), 2.34 (s, 3 H), 2.28–2.25 (m, 1 H), 2.05–1.17 (m, 24 H), 1.02 (s, 9 H), 1.02–0.95 (m, 1 H), 0.89 (t, J = 6.9 Hz, 3 H), 0.87–0.81 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.4, 140.1, 135.6, 135.57, 133.5, 133.4, 129.7, 129.6, 129.3, 127.63, 127.60, 127.1, 75.9, 70.9, 64.3, 62.3, 42.3, 42.2, 37.9, 34.6, 31.9, 31.8, 29.8, 29.4, 26.9, 26.8, 26.4, 25.9, 25.4, 24.7, 22.6, 21.4, 19.1, 14.1 ppm. ESI-MS: calcd. for $C_{42}H_{61}NO_4SSi$ 703.4; found m/z $[M + Na]^+$ 726.2. HRMS (ESI): m/z 726.3983, m/z $[M + Na]^+$ calcd. for $C_{42}H_{61}NO_4SSiNa$ 726.3988.

Amine 23: To **22** (58 mg, 0.082 mmol) in DME (4.0 mL) was added Na/naphthalene [which was prepared by stirring fresh sodium and naphthalene (64 mg, 0.5 mmol) in DME (1.0 mL) for 30 min at room temperature] at –68 °C, and the mixture was stirred for 5 min at this temperature. The reaction was quenched with saturated aqueous NH_4Cl (4.0 mL) and stirred at room temperature for awhile. The layers were separated, and the aqueous layer was extracted with EA (3 × 3.0 mL). The combined organic phases were washed with brine and dried with anhydrous K_2CO_3. After the mixture was filtered and concentrated, the mixture was purified by flash chromatography (CH_2Cl_2/MeOH, 20:1) to afford the desired amino alcohol (45 mg) in quantitative yield.

To the above amino alcohol (40 mg, 0.073 mmol) in CH_2Cl_2 (12 mL) was added PPh_3 (115 mg, 0.439 mmol), CBr_4 (144 mg, 0.439 mmol) and DMAP (1.3 mg, 0.01 mmol) at 0 °C, and the mixture was stirred at room temperature for 24 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5.0 mL) and extracted with EA (3 × 2.0 mL). The combined organic phases were washed with brine and dried with anhydrous K_2CO_3. After the mixture was filtered and concentrated, the mixture was purified by flash chromatography (PE/EA, 3:1) to afford light yellow oil **23** (38 mg) in 98% over two steps. R_f = 0.29 (PE/EA, 3:1). $[\alpha]_D^{28}$ = –21.8 (c = 0.3, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3072, 1466, 1427 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.71–7.64 (m, 4 H), 7.41–7.34 (m, 6 H), 3.75 (dd, J = 3.7, 8.2 Hz, 1 H), 3.26 (dd, J = 9.6, 8.7 Hz, 1 H), 3.21–3.14 (m, 1 H), 3.01–2.93 (m, 1 H), 2.12–2.03 (m, 2 H), 1.72–1.61 (m, 6 H), 1.51–1.40 (m, 4 H), 1.31–1.07 (m, 14 H), 1.05 (s, 9 H), 1.01–0.90 (m, 1 H), 0.85 (t, J = 6.8 Hz, 3 H) ppm.

(–)-Lepadiformine A (2): To **23** (38 mg, 0.072 mmol) in THF (1.0 mL) was added TBAF (0.36 mL, 0.36 mmol) at 0 °C, and the mixture was stirred for 24 h at room temperature. The reaction was quenched with iced water (1.0 mL) and extracted with EA (3 × 2.0 mL). The combined organic phases were washed with brine and dried with anhydrous K_2CO_3. After the mixture was filtered and concentrated, the mixture was purified by flash chromatography (Et_2O/MeOH, 20:1) to afford **2** as a colorless oil **2** (20 mg) in 95% yield. R_f = 0.35 (EA/MeOH, 4:1). $[\alpha]_D^{28}$ = –14.7 (c = 0.25, MeOH). IR (neat): $\tilde{\nu}$ = 3331 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.42–3.30 (m, 2 H), 3.23 (d, J = 8.7 Hz, 1 H), 3.16–3.10 (m, 1 H), 1.78–1.07 (m, 27 H), 1.02–0.94 (m, 1 H), 0.87 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 67.6, 62.2, 58.5, 53.4, 39.8, 38.1, 33.9, 31.8, 30.5, 29.5, 28.0, 27.6, 27.5, 26.2, 24.2, 23.2, 22.5, 22.4, 14.0 ppm. ESI-MS: calcd. for $C_{19}H_{35}NO$ 293.2; found m/z $[M + H]^+$ 294.1. HRMS (MALDI): m/z 294.2791, m/z $[M + H]^+$ calcd. for $C_{19}H_{36}NO$ 294.2797.

Supporting Information (see also the footnote on the first page of this article): Procedures for the synthesis of **6**, **16** and **24**, HPLC analysis of **10**, X-ray crystal structure of **16** and **24** and copies of the ^1H and ^{13}C NMR spectra of the prepared compounds.

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