Graphical Abstract

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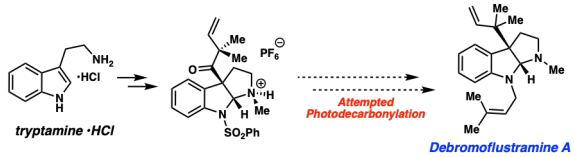

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Evaluation of the Photodecarbonylation of Crystalline Ketones for the Installation of Prenyl Groups

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ABSTRACT

We report synthetic efforts toward the regiocontrolled installation of the prenyl moiety in debromoflustramine A by the regiospecific photodecarbonylation of a prenyl-substitited ketone. Synthetic approaches to access the plausible photodecarbonylation substrates beginning from tryptamine were evaluated. Initial attempts to synthesize a suitable substrate for photodecarbonylation were hampered by a lack of substrate crystallinity (a prerequisite for solid-state photochemistry). Ultimately, a crystalline substrate could be accessed to attempt the key step by judicious selection of *N*-substituents. Although the photodecarbonylation ultimately proved challenging, this study highlights the troubleshooting and optimization required for crystal phase photochemistry and underscores methods that can be used to control substrate crystallinity.

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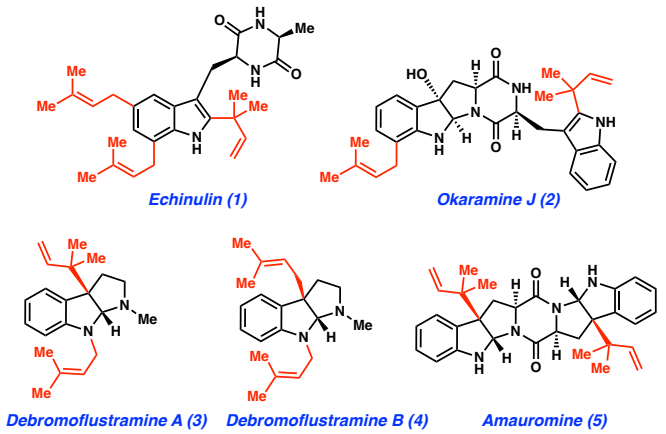
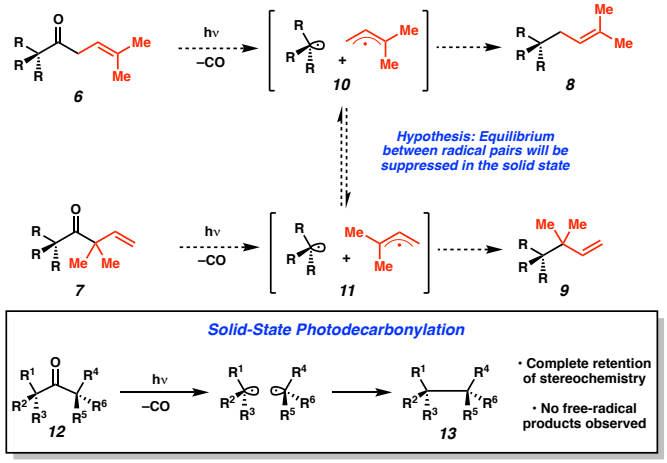
1. Introduction

The regiocontrolled introduction of prenyl or unsymmetrical allyl fragments is a challenging transformation in synthetic organic chemistry.[1] Despite this, prenyl and reverse prenyl decoration is featured widely across diverse classes of biologically active natural products (e.g., **1**–**5**, Scheme 1).[2] As such, regiocontrolled methods for their introduction are highly desirable. Successful methodologies leveraging nucleophilic addition into electrophilic Ir and Pd π-allyl complexes and Pd-catalyzed Suzuki-type prenylations have been developed, however, regiocontrolled prenylation of cationic or radical centers remains challenging.[3]



Scheme 1. Representative prenylated and reverse prenylated indole alkaloids **1**–**5**.

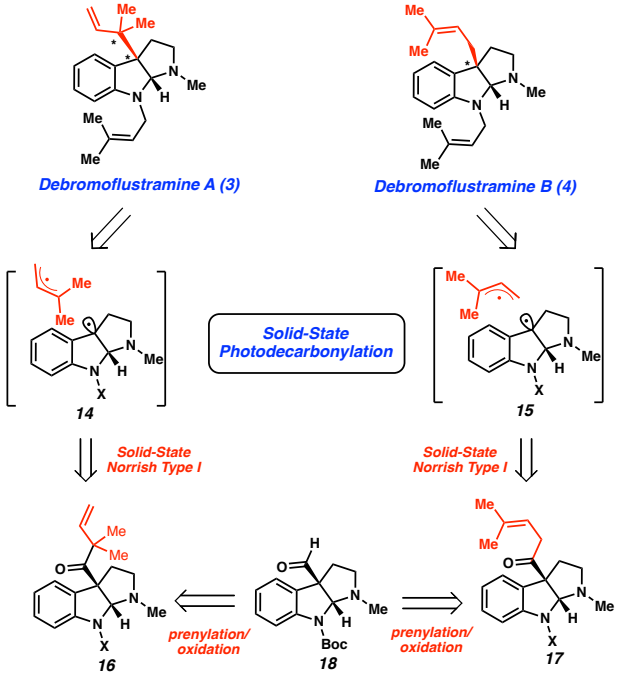
An attractive, albeit underexplored, means of regiocontrolled radical prenylation would involve a Norrish type I photodecarbonylation of isomeric ketones **6** or **7** to furnish prenylated compounds **8** or **9**, respectively (Scheme 2). This type of transformation would be valuable, as it would allow regiochemical information to be encoded into ketones **6** and **7**. In turn, that information could be relayed to products **8** and **9**. The intrinsic difficulty of this approach, however, is the fact that radical pairs **10** and **11** differ only in their orientation with respect to one another. For this reason, rotation of the prenyl radical could allow facile interconversion of **10** and **11** leading to mixtures of regioisomers. Additionally, caged radical pairs **10** and **11** could also dissociate to form free radicals that could undergo deleterious side reactions.



Scheme 2. Radical prenylation using a regioselective Norrish type I photodecarbonylation.

In order to address the aforementioned challenges, we sought to conduct these reactions in the crystalline solid state. It has been shown that Norrish type I photodecarbonylations of β-stereogenic ketones **12** provide recombination products **13** with exquisite stereochemical retention and without dissociation to form free radicals (Scheme 2).[4] This selectivity results from restrictions on translational and rotational degrees of freedom imparted by the crystalline lattice. Efforts to manipulate unsymmetrical allylic radicals using solid-state photodecarbonylation have not been reported.

In order to investigate this approach in the context of complex molecule synthesis, we devised a strategy to access debromoflustramines A (**3**) and B (**4**), which possesses reverse and direct prenylated scaffolds, respectively (Scheme 3).[5,6] Debromoflustramines A (**3**) and B (**4**) possess sterically congested quaternary stereocenters, whereas **3** bears vicinal quaternary carbons.[7] As the construction of vicinal quaternary centers represents a longstanding challenge in organic synthesis, we prioritized the synthesis of debromoflustramine A (**3**). The brominated analogues of these alkaloids, isolated from the marine invertebrate *Flustra foliacea* in the North Atlantic Ocean, are known to act as skeletal and smooth muscle relaxants by blocking voltage-gated calcium channels.[8] Retrosynthetically, we envisioned accessing **3** and **4** from caged radical pairs **14** and **15**, respectively. In turn, these radical pairs would be generated from parent ketones **16** or **17**, with retention of regiochemistry arising from the use of solid-state photodecarbonylation. We hoped to access both ketones from the tricyclic aldehyde **18**, which was previously synthesized by Bisai and coworkers.[9]

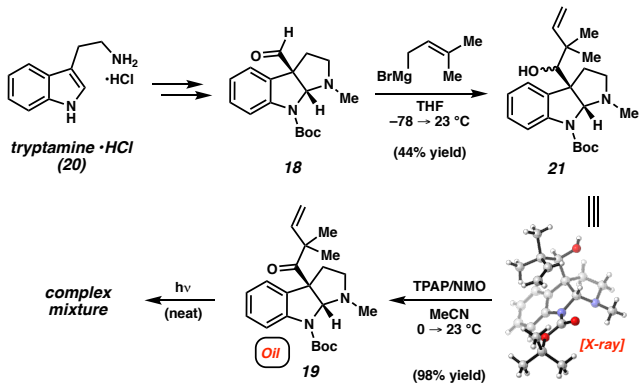


Scheme 3. Retrosynthetic analysis of debromoflustramines A (**3**) & B (**4**) utilizing a key regioretentive solid-state photodecarbonylation.

2. Results and Discussion

Our efforts commenced by synthesizing Boc-protected pyrrolidinoindoline ketone **19** using the sequence shown in Scheme 4. Beginning from commercially available tryptamine hydrochloride (**20**), aldehyde **18** was synthesized in 9 steps following the route reported by Bisai and coworkers.[9] With this aldehyde in hand, addition of prenylmagnesium bromide

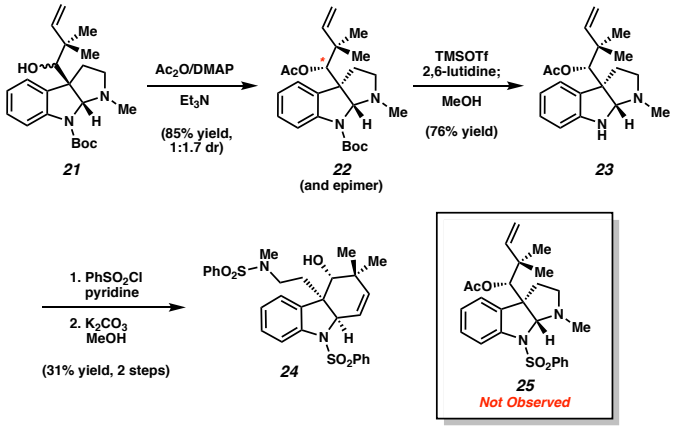
provided secondary alcohol **21** as an inconsequential mixture of diastereomers. The structure of the major diastereomer was verified by X-ray crystallography. Oxidation of **21** under Ley-Griffith conditions furnished the target substrate for photodecarbonylation, ketone **19**.[10] Unfortunately, despite extensive attempts to nucleate crystallization, **19** remained a viscous oil at room temperature. While the physical state of the substrate would typically be inconsequential for a solution-phase photochemical reaction, substrate crystallinity is imperative for the solid-state photochemical reaction we desired. Nonetheless, irradiation of **19** as a neat oil was attempted, but provided a complex mixture of products.



Scheme 4. Synthesis of ketone **19** and attempted photodecarbonylation of neat oil.

Several strategies were investigated to derivatize **19** to arrive at a crystalline substrate. Formation of ammonium salts by protonation of the pyrrolidine were unsuccessful and often accompanied by Boc cleavage with subsequent decomposition. To circumvent this issue, we envisioned exchanging the acid labile Boc protecting group with a benzenesulfonamide. In addition to displaying greater stability to acid, the presence of a benzenesulfonyl protecting group is known to furnish crystalline solids when appended to pyrrolidinoindoline motifs.[11]

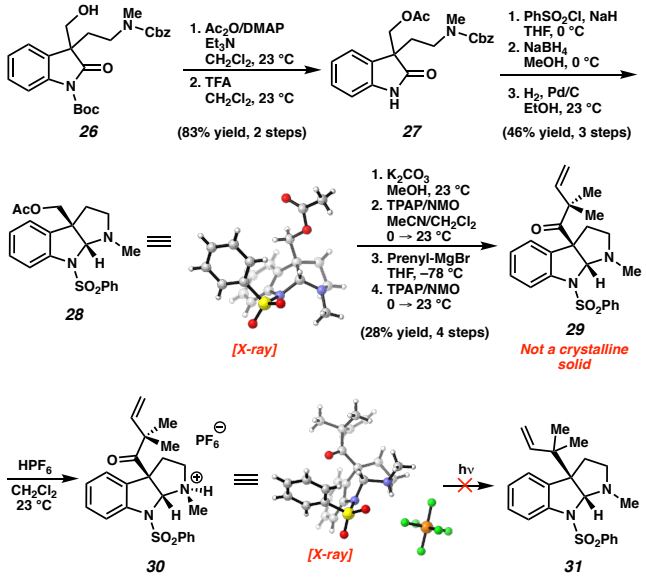
In order to synthesize a benzenesulfonyl protected ketone, protecting group exchange was attempted on alcohol **21** (Scheme 5). Acetylation of the secondary alcohol to provide ester **22** followed by Lewis acid-mediated cleavage of the carbamate furnished **23** in good yield. With free *N*-H compounds in hand, we were optimistic that phenylsulfonamide formation could be accomplished as Rainier and coworkers reported successful sulfonylation on a closely related pyrrolidinoindoline scaffold.[12] To our surprise, upon subjecting **23** to phenylsulfonyl chloride, we observed structural rearrangement rather than the desired product **25**. The rearranged compound was isolated following acetate cleavage and was determined to be **24**. This product likely arises from a cationic aza-Prins-type cascade to give the 6,5,6-Strychnos scaffold. This type of aza-Prins cyclization to give hydrocarbazole ring systems has been reported on similar substrates by Reisman and coworkers.[13,14]



Scheme 5. Attempted protecting group exchange leads to undesired aza-Prins rearrangement to give **24** bearing the Strychnos core.

Finally, we explored a strategy involving earlier swapping of the Boc group with a benzenesulfonyl moiety (Scheme 6). From intermediate **26**, acetylation of neopentylic alcohol **26** and Boc cleavage provided oxidindole **27**. Subsequent treatment with sodium hydride and benzenesulfonyl chloride allowed for the desired *N*-sulfonylation. Next, a two-step reduction sequence involving carbonyl reduction and Cbz removal furnished pyrrolidinoindoline **28**. Treatment of acetate **28** with K_2CO_3/methanol, followed by a three-step oxidation-prenylation-oxidation sequence, furnished **29**.

With **29** in hand, we explored methods to achieve crystallinity and attempt the desired solid-state photodecarbonylation (Scheme 6). Although ketone **29** was not a crystalline solid, the benzenesulfonamide group proved stable to acid, which allowed us to attempt the synthesis of crystalline ammonium salts. Indeed, an extensive survey of Brønsted acids gave rise to ammonium hexafluorophosphate salt **30** which was a crystalline solid. The structure of **30** was verified using single-crystal X-ray diffraction. Eager to test the solid-state photodecarbonylation reaction, salt **30** was exposed to UV irradiation. Unfortunately, all various UV light irradiation conditions gave a complex mixture of products, rather than the expected photodecarbonylation product **31**. We suspect that the reaction fails due to competitive photochemical decomposition of the phenylsulfonyl group.[15] Future studies will allow us to test introduction of the prenyl group present in debromoflustramine B using an analogous approach.



Scheme 6. Synthesis of crystalline ketone **30** and attempted photodecarbonylation.

3. Conclusion

In summary, we have devised a strategy for the introduction of reverse prenyl and prenyl groups using solid-state photodecarbonylation. Our synthetic efforts focused on the former en route to the natural product debromoflustramine A (**3**). Although our initial synthetic efforts were thwarted by difficulties in accessing a crystalline substrate and undesired structural rearrangements, we were ultimately able to access a crystalline substrate using multistep synthesis. The attempted photodecarbonylation, however, was unfortunately unsuccessful. Although disappointing, it is plausible that an alternative substrate may prove more successful in solid-state reverse prenylation. We hope future studies will determine the viability of using regiocontrolled reverse prenylation and prenylation reactions in the solid-state to access complex indole alkaloids. Furthermore, this endeavor highlights a workflow and troubleshooting strategy that can be used to surmount one of the key challenges intrinsic to solid-state chemistry: achieving substrate crystallinity.

4. Experimental Section

4.1 Materials and Methods. Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of argon using anhydrous solvents (either freshly distilled or passed through activated alumina columns). All commercially available reagents were used as received unless otherwise specified. Tetrapropylammonium perruthenate (TPAP), trifluoroacetic acid, *N*-methylmorpholine-*N*-oxide (NMO), acetic anhydride, 4-dimethylaminopyridine (DMAP), trimethylsilyl trifluoromethanesulfonate (TMSOTf), 2,6-lutidine, phenylsulfonyl chloride, sodium hydride (60% dispersion in mineral oil), sodium borohydride, and palladium on activated carbon (Pd/C) were obtained from Sigma-Aldrich. Hexafluorophosphoric acid (60 wt% in water) was purchased from Fischer Scientific. Prenylmagnesium bromide was prepared from a known literature procedure.[16] Unless stated otherwise, reactions were performed at room temperature (approximately 23 °C). Thin-layer chromatography (TLC) was conducted with EMD gel 60 F254 pre-coated plates (0.25 mm) and visualized using a combination of UV, ceric ammonium molybdate, and potassium permanganate staining. Silicycle silica gel 60 (particle size 0.040–0.063 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on Bruker spectrometers (at 300, 400, or 500 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra are reported in terms of chemical shift (125 MHz). High-resolution mass spectra were obtained on Thermo ScientificTM Exactive Mass Spectrometers with DART ID-CUBE. X-ray crystallographic images in Schemes 4 and 6 were rendered using CYLview.[17]

4.2 Alcohol 21 (Scheme 4). To a solution of aldehyde **18**[9] (110 mg, 0.36 mmol, 1.0 equiv) at –78 °C, prenylmagnesium bromide (10.1 mL, 0.18 M in THF, 1.82 mmol, 5.0 equiv) was added dropwise over 1 min. The reaction was then allowed to warm to 23 °C over 10 min before being quenched by the dropwise addition of sat. aq. NH_4Cl (0.5 mL) over 1 min. 1.0 M aq. NaOH (50 mL) was added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified via column chromatography (7:3 Hexanes:EtOAc → 1:1 Hexanes:EtOAc) to afford alcohol **21** (99 mg, 44% yield) as a white solid in a 2:1 mixture of diastereomers. Crystals of the major diastereomer suitable for X-ray diffraction studies (CCDC **xxxxxxx**) were obtained using slow evaporation of the diastereomeric mixture from $CDCl_3$. R_f 0.19 (1:1 Hexanes:EtOAc); ^{1}H NMR (500 MHz, C_6D_6): 8.02 (m, 3H), 7.37–7.35 (m, 1H), 7.15–7.08 (m, 3H), 6.89–6.80 (m, 5H), 5.68–5.56 (m, 6H), 4.84–4.72 (m, 6H), 3.50 (s, 2H), 3.44 (s, 1H), 2.61–2.50 (m, 14H), 2.45–2.40 (m, 2H), 2.32–2.23 (m, 2H), 2.14–2.08 (m, 1H), 1.83–1.76 (m, 2H), 1.48 (m, 27H), 0.82–0.81 (m, 12H), 0.76 (s, 6H); ^{13}C NMR (125 MHz, C_6D_6): 153.1, 145.6, 145.3, 143.2, 135.5, 128.3, 125.1, 122.7, 116.4, 115.7, 113.1, 84.0, 83.2, 82.7, 81.2, 80.1, 61.3, 52.4, 51.8, 43.5, 43.3, 40.5, 39.4, 38.0, 36.8, 28.5, 28.5, 26.2 23.3; HRMS-APCI (*m/z*) $[M + H]^+$ calcd for $C_{22}H_{33}N_2O_3^+$, 373.2485; found 373.2467. Note: **21** was obtained as a mixture of rotamers of two diastereomers. The ^{1}H and ^{13}C spectra reported were collected at 70 °C to sharpen the observed peaks; however, broad resonances in the ^{13}C NMR spectrum due to rotation on the NMR timescale resulted in overlapping carbon signals. The empirical spectra are reported.

Ketone 19 (Scheme 4). Finely ground 4 Å molecular sieves (160 mg), NMO (93 mg, 0.79 mmol, 4.0 equiv) and alcohol **21** (74 mg, 0.20 mmol, 1.0 equiv) were suspended in a mixture of CH_2Cl_2 (30 mL) and MeCN (4 mL). The mixture was cooled to 0 °C and a solution of TPAP (12.7 mg, 0.036 mmol, 18 mol%) in MeCN (2 mL), also cooled to 0 °C, was then added to the reaction dropwise over 1 min. The reaction was warmed to 23 °C. After stirring for 2 hours, the reaction mixture was filtered over silica gel (~2 x 5 cm) using EtOAc as the eluent (100 mL). The crude reaction mixture was concentrated under reduced pressure and purified via column chromatography (9:1 Hexanes:EtOAc → 4:1 Hexanes:EtOAc) to afford ketone **19** (72 mg, 98% yield) as a yellow oil. R_f 0.32 (4:1 Hexanes:EtOAc); ^{1}H NMR (500 MHz, C_6D_6): δ 7.90 (s, 1H), 7.08–7.00 (m, 2H), 6.76 (t, J = 7.5 Hz, 1H), 5.98 (s, 1H), 5.62 (dd, J = 17.5, 10.6 Hz, 1H), 4.90–4.85 (m, 2H), 4.82 (d, J = 10.7 Hz, 1H), 2.76 (ddd, J = 12.2, 10.5, 6.5 Hz, 1H), 2.48 (s, 3H), 2.42 (ddd, J = 8.8, 6.5, 2.0 Hz, 1H), 2.26 (td, J = 9.9, 5.0 Hz, 1H), 1.91 (ddd, J = 12.2, 5.0, 2.0 Hz, 1H), 1.43 (s, 9H), 1.15 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 207.7, 153.0, 144.3, 141.8, 133.2, 128.5, 123.8, 122.8, 115.8, 114.2, 84.2, 80.4, 68.5, 51.5, 50.9, 38.6, 36.9, 27.9, 25.4, 25.3. HRMS-APCI (*m/z*) $[M + H]^+$ calcd for $C_{22}H_{31}N_2O_3^+$,

371.2329; found 371.2317. Note: NMR spectra of ketone **19** were obtained at 70 °C.

Pyrrolidinoindoline 23 (Scheme 5). To a solution of alcohol **21** (131 mg, 0.35 mmol, 1.0 equiv) in CH_2Cl_2 (12 mL) were added sequentially Et_3N (0.49 mL, 3.5 mmol, 10 equiv), Ac_2O (0.32 mL, 3.5 mmol, 10 equiv), followed by DMAP (43 mg, 0.25 mmol, 0.7 equiv). The resulting reaction mixture was allowed to stir for 1 h at 23 °C, before being poured into a solution of sat. aq. $NaHCO_3$ (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over $MgSO_4$, and then concentrated under reduced pressure. The resulting residue was purified by column chromatography (9:1 Hexanes:EtOAc) to give ester **22** and its epimer (125 mg, 85% yield, 1.7:1 dr).

A solution of 2,6-lutidine (51 μL, 47 mg, 0.44 mmol, 13 equiv) in CH_2Cl_2 (0.36 mL) and **22** (14.3 mg, 0.035 mmol, 1.0 equiv) was cooled to 0 °C and then TMSOTf (80 μL, 98 mg, 0.44 mmol, 13 equiv) was added. After 105 min 1 drop of sat. aq. $NaHCO_3$ followed by MeOH (1 mL) were added, the reaction mixture was flushed through a plug of Na_2SO_4, and then concentrated under reduced pressure. The resulting residue was purified by flash chromatography (9:1 Hexanes:EtOAc with 5% v/v Et_3N) to provide pyrrolidinoindoline **23** (8.2 mg, 76% yield, 2 steps) as a colorless oil. R_f 0.39 (1:1 Hexanes:EtOAc with 5% v/v Et_3N); ^{1}H NMR (500 MHz, C_6D_6): δ 6.97 (t, *J* = 7.7 Hz, 1H), 6.75 (d, *J* = 7.4 Hz, 1H), 6.60 (t, *J* = 7.4 Hz, 1H), 6.33 (d, *J* = 7.7 Hz, 1H), 5.82 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.54 (s, 1H), 4.80–4.64 (m, 3H), 3.53 (s, 1H), 2.43–2.32 (m, 1H), 2.32–2.19 (m, 2H), 2.16 (s, 3H), 1.93–1.82 (m, 4H), 0.92 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 170.4, 151.2, 145.6, 132.4, 128.5, 125.9, 118.4, 110.5, 109.0, 82.3, 81.2, 62.5, 51.5, 43.3, 39.9, 37.0, 25.7, 25.4, 20.8. HRMS-APCI (*m/z*) $[M + H]^+$ calcd for $C_{19}H_{27}N_2O_2^+$, 315.2067; found 315.2056.

Strychnos tricycle 25 (Scheme 5). Pyrrolidinoindoline **23** (4.2 mg, 0.013 mmol, 1.0 equiv) was dissolved in pyridine (0.18 mL) and cooled to 0 °C. Phenylsulfonyl chloride (17 μL, 24 mg, 0.13 mmol, 10 equiv) was added and reaction was warmed to 23 °C and allowed to stir for 16 hours before being diluted with CH_2Cl_2 (4 mL) and washed with 1 M HCl (4 mL). The layers were separated and the organic layer was concentrated under reduced pressure. The resulting residue was purified by column chromatography (7:3 Hexanes:EtOAc) and the tricycle was carried on to the subsequent step.

The tricycle from the previous step (2.3 mg, 0.0051 mmol, 1.0 equiv) was dissolved in MeOH (2.0 mL) and K_2CO_3 (38 mg, 0.28 mmol, 55 equiv) was added. The reaction mixture was submerged in a preheated 57 °C oil bath and stirred for 5 min. The reaction was cooled to 23 °C and then diluted with EtOAc (15 mL) and washed sequentially with DI H_2O (10 mL) and sat. aq. NaCl (10 mL). The layers were separated and the organic layer was dried over $MgSO_4$ and then concentrated under reduced pressure. The resulting residue was purified by flash chromatography (7:3 Hexanes:EtOAc) to afford Strychnos tricycle **25** (2.3 mg, 33% yield, 2 steps) as an off-white foam. R_f 0.15 (7:3 Hexanes:EtOAc); ^{1}H NMR (500 MHz, C_6D_6): δ 8.00 (d, *J* = 8.1 Hz, 1H), 7.71–7.58 (m, 2H), 7.58–7.46 (m, 2H), 6.93–6.81 (m, 5H), 6.77–6.63 (m, 4H), 6.20 (dd, *J* = 10.3, 4.0 Hz, 1H), 5.34 (d, *J* = 10.3 Hz, 1H), 4.19 (t, *J* = 4.1, 1.0 Hz, 1H), 3.31 (d, *J* = 6.6 Hz, 1H), 2.87–2.77 (m, 1H), 2.14–1.98 (m, 6H), 0.91–0.81 (m, 4H), 0.50 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 141.1, 138.8, 138.0, 137.6, 135.3, 132.6, 131.7, 128.7, 128.6, 128.3, 127.2, 125.4, 123.3, 122.7, 116.1, 115.0, 76.0, 65.9, 49.9, 45.9, 36.8, 34.2, 32.8, 30.0, 24.6; HRMS-APCI (*m/z*) $[M + H]^+$ calcd for $C_{29}H_{33}N_2O_5S_2^+$, 553.1825; found 553.1829.

Oxindole 27 (Scheme 6). A solution of alcohol **26**[9] (1.10 g, 2.4 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (60 mL) and cooled to 0 °C. Et_3N (3.0 mL, 22 mmol, 9.0 equiv), Ac_2O (2.0 mL, 21 mmol, 9.0 equiv), and DMAP (263 mg, 2.1 mmol, 0.9 equiv) were added sequentially and the reaction mixture was allowed to stir at 0 °C for 15 min before being poured into sat. aq. $NaHCO_3$ (40 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried over Na_2SO_4 and then concentrated under reduced pressure. The resulting residue was purified by column chromatography (4:1 Hexanes:EtOAc) and the acetate protected oxindole was carried on to the subsequent step.

The acetate protected oxindole from the previous step (557 mg, 1.1 mmol, 1.0 equiv) and anisole (0.12 mL, 120 mg, 1.1 mmol, 1.0 equiv) were dissolved in CH_2Cl_2 (18 mL) and cooled to 0 °C. TFA (2 mL) was added. The mixture was warmed to 23 °C and stirred for 30 min before being quenched with a solution of sat. aq. $NaHCO_3$ (100 mL) and diluted with CH_2Cl_2 (50 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by column chromatography (7:3 Hexanes:EtOAc → 1:1 Hexanes:EtOAc) to furnish **27** as a white foam (550 mg, 83% yield, 2 steps). R_f 0.26 (1:1 Hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37–8.06 (m, 1H), 7.48–7.27 (m, 5H), 7.24–7.17 (m, 1H), 7.09–6.91 (m, 2H), 6.89–6.80 (m, 1H), 5.12–4.85 (m, 2H), 4.60–4.37 (m, 1H), 4.30–4.08 (m, 1H), 3.30–2.89 (m, 2H), 2.83–2.69 (m, 3H), 2.30–1.98 (m, 2H), 1.95–1.82 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.9, 178.8, 170.5, 170.5, 156.0, 141.1, 137.0, 136.7, 129.1, 129.0, 128.8, 128.6, 128.5, 128.1, 128.0, 123.9, 123.8, 122.9, 122.9, 110.0, 67.6, 67.5, 67.3, 67.1, 51.5, 51.4, 44.9, 44.4, 34.8, 34.2, 31.2, 30.6, 20.7; HRMS-APCI (*m/z*) $[M + H]^+$ calcd for $C_{22}H_{25}N_2O_5^+$, 397.1758; found 397.1744. Note: **27** was obtained as a mixture of rotamers. These data represent empirically observed chemical shifts from the ^{1}H and ^{13}C-NMR spectra.

Pyrrolidinoindoline 28 (Scheme 6). NaH (240 mg, 60 wt% dispersion in mineral oil, 6.1 mmol, 6.0 equiv) was suspended in THF (6 mL) and cooled to 0 °C. Oxindole **27** (400 mg, 1.0 mmol, 1.0 equiv) was dissolved in THF (12 mL) and added to the stirring suspension of NaH. After stirring for 15 min, phenylsulfonyl chloride (0.25 mL, 2.0 mmol, 2.0 equiv) was added and the solution was warmed to 23 °C. After stirring at 23 °C for 10 min, the reaction mixture was quenched with a solution of sat. aq. NH_4Cl (1 mL) and diluted with CH_2Cl_2 (10 mL) and DI H_2O (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with sat. aq. NaCl (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (7:3 Hexanes:EtOAc → 1:1 Hexanes:EtOAc) and the resultant phenylsulfonyl oxindole was carried forward to the subsequent step.

The phenylsulfonyl oxindole from the previous step (230 mg, 0.43 mmol, 1.0 equiv) was dissolved in MeOH (6 mL) and cooled to 0 °C. $NaBH_4$ (32 mg, 0.85 mmol, 2.0 equiv) was added and the solution was allowed to stir at 15 min before more $NaBH_4$ (32 mg, 0.85 mmol, 2.0 equiv) was added. The reaction was allowed to stir for 10 min before being quenched with a solution of sat. aq. $NaHCO_3$ (25 mL) and diluted with CH_2Cl_2 (25 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was carried on to the subsequent step.

The residue from the previous step was dissolved in EtOH (10 mL). Pd/C (75 mg) was added and the suspension was stirred for 10 min before being sparged with H_2 for 10 min. After stirring under H_2 (1 atm) for 16 h, the reaction was filtered over a short silica plug (~2 x 5 cm) and then rinsed with EtOAc (100 mL). The reaction mixture was then concentrated under reduced pressure and the resultant residue was purified by flash chromatography (4:1 Hexanes:EtOAc → 7:3 Hexanes:EtOAc) to afford pyrrolidinoindoline **28** (87 mg, 53% yield, 3 steps) as a white crystalline solid. Crystals suitable for X-ray diffraction studies (CCDC xxxxxxx) were obtained using slow evaporation from 1:2 Benzene/CH_2Cl_2. R_f 0.25 (4:1 Hexanes:EtOAc); ^{1}H NMR (500 MHz, C_6D_6): δ 7.92 (d, *J* = 8.1 Hz, 1H), 7.61–7.58 (m, 2H), 6.94 (ddd, *J* = 8.2, 7.5, 1.3 Hz, 2H), 6.79–6.75 (m, 1H), 6.72 (td, *J* = 7.5, 1.0 Hz, 1H), 6.68 (t, *J* = 7.7 Hz, 2H), 6.63–6.58 (m, 1H), 5.18 (s, 1H), 3.48 (d, *J* = 11.2 Hz, 1H), 3.19 (d, *J* = 11.3 Hz, 1H), 2.76 (s, 3H), 2.38 (ddd, *J* = 9.7, 6.8, 3.1 Hz, 1H), 2.28 (td, *J* = 8.9, 5.4 Hz, 1H), 1.89 (ddd, *J* = 11.8, 8.7, 6.5 Hz, 1H), 1.52–1.48 (m, 1H), 1.45 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 169.3, 142.7, 138.5, 135.7, 132.6, 128.6, 128.5, 127.0, 124.8, 124.0, 117.3, 88.6, 66.6, 56.5, 51.8, 36.2, 34.9, 19.8. HRMS-APCI (*m/z*) $[M + H]^+$ calcd for $C_{20}H_{23}N_2O_4S^+$, 387.1373; found 387.1357.

Alcohol 32 (Scheme 6). Pyrrolidinoindoline **28** (74 mg, 0.19 mmol, 1.0 equiv) was dissolved in MeOH (3.5 mL) and K_2CO_3 (270 mg, 2.0 mmol, 11 equiv) was added. After stirring for 5 min, the reaction was diluted with CH_2Cl_2 (10 mL), filtered over a short silica plug (~1 x 1 cm), and then rinsed with EtOAc (20 mL). The reaction mixture was then concentrated under reduced pressure and the resultant residue was carried forward without further purification.

The alcohol from the previous step (65 mg, 0.19 mmol, 1.0 equiv) was dissolved in a mixture of CH_2Cl_2 (16 mL) and MeCN (4 mL). NMO (44 mg, 0.38 mmol, 2.0 equiv) and finely ground 4 Å molecular sieves (72 mg) were added and the reaction mixture was cooled to 0 °C. TPAP (15 mg, 0.038 mmol, 10 mol%) was then added as a solution in MeCN (1 mL). The reaction was warmed to 23 °C, stirred for 15 min. The mixture was then diluted with EtOAc (30 mL), flushed through a short silica plug (~2 x 5 cm), and rinsed with EtOAc (30 mL). The mixture was concentrated under reduced pressure and the resultant residue was purified by flash chromatography (1:1 Hexanes:EtOAc) to furnish the corresponding pyrrolidinoindoline aldehyde.

A solution of the pyrrolidinoindoline aldehyde from the last step (15 mg, 0.044 mmol, 1.0 equiv) was dissolved in THF (2 mL) and cooled to 0 °C. Prenylmagnesium bromide (0.5 mL, 0.34 M in THF, 0.17 mmol, 3.9 equiv) was added and the reaction was stirred 5 min before being quenched by the addition of solid NH_4Cl (~15 mg), followed by acetone (10 mL). The suspension was then concentrated directly onto silica under reduced pressure. The resultant residue (adsorbed onto silica gel) was then purified by flash chromatography (4:1 Hexanes:EtOAc → 3:1 Hexanes:EtOAc) to furnish alcohol **32** (9 mg, 39% yield, 3 steps) in >20:1 diastereomeric excess. R_f 0.37 (7:3 Hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96–7.89 (m, 2H), 7.56–7.50 (m, 1H), 7.46–7.38 (m, 3H), 7.23–7.15 (m, 2H), 6.99 (td, *J* = 7.5, 1.1 Hz, 1H), 5.87 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.47 (s, 1H), 5.06 –4.94 (m, 2H), 3.11 (d, *J* = 4.9 Hz, 1H), 2.68 (ddd, *J* = 9.1, 6.7, 2.0 Hz, 1H), 2.61 (m, 4H), 2.34 (td, *J* = 9.7, 5.1 Hz, 1H), 1.79 (ddd, *J* = 11.8, 5.1, 2.0 Hz, 1H), 1.67 (d, *J* = 5.4 Hz, 1H), 1.00 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.2, 142.1, 140.1, 135.7, 132.9, 129.0, 128.6, 127.6, 126.8, 123.6, 115.0, 113.3, 89.3, 79.1, 63.0, 52.4, 43.4, 38.4, 36.9, 29.9, 26.6, 24.1; HRMS-APCI (*m/z*) $[M + H]^+$ calcd for $C_{23}H_{29}N_2O_3S^+$, 413.1893; found 413.1908.

Ketone 29 (Scheme 6). **32** (9.1 mg, 0.022 mmol, 1.0 equiv) was dissolved in a mixture of CH_2Cl_2 (0.8 mL) and MeCN (0.1 mL). NMO (11 mg, 0.094 mmol, 4.3 equiv) and 4 Å molecular sieves (10 mg) were added and the reaction mixture was cooled to 0 °C. TPAP (1.7 mg, 0.005 mmol, 20 mol%) was added as a solution in MeCN (0.2 mL). The reaction was warmed to 23 °C and stirred at 23 °C for 1h. The reaction was then diluted with a mixture of Hexanes and EtOAc (5 mL, 1:1 Hexanes:EtOAc), filtered through a silica plug (~ 1 x 1 cm), and rinsed with a mixture of EtOAc and Hexanes (1:1, 30 mL) as the eluent. The mixture was concentrated under reduced pressure and the resultant residue was purified by flash chromatography (9:1 Hexanes:EtOAc → 4:1 Hexanes:EtOAc) to furnish the ketone **29** (6.4 mg, 72% yield). R_f 0.52 (7:3 Hexanes:EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (dd, *J* = 8.5, 1.3 Hz, 2H), 7.56–7.49 (m, 1H), 7.48–7.40 (dd, *J* = 8.2, 0.8 Hz, 3H), 7.20 (ddd, *J* = 8.0, 7.4, 1.4 Hz, 1H), 7.06 (dd, *J* = 7.6, 1.3 Hz, 1H), 6.98 (td, *J* = 7.6, 1.1 Hz, 1H), 5.81 (s, 1H), 5.77 (dd, *J* = 17.5, 10.6 Hz, 1H), 5.13 (dd, *J* = 10.6, 0.5 Hz, 1H), 5.05 (d, *J* = 17.5 Hz, 1H), 2.79–2.67 (m, 2H), 2.61 (s, 3H), 2.51–2.39 (m, 1H), 2.02–1.80 (m, 1H), 1.09 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.1, 142.1, 141.8, 140.0, 133.3, 133.1, 129.0, 129.0, 127.6, 125.3, 123.8, 115.6, 114.6, 90.5, 69.7, 51.9, 39.0, 38.5, 29.9, 26.1, 25.5; HRMS-APCI (*m/z*) $[M + H]^+$ calcd for $C_{23}H_{27}N_2O_3S^+$, 411.1740; found 411.1761.

Salt 30 (**Scheme 6)**. Ketone **29** (19 mg, 0.046 mmol) was dissolved in CH_2Cl_2 (5 mL). DI H_2O (1.5 mL) followed by aq. HPF_6 (60% wt%, 5 drops) were added, the layers were separated, and the organic layer was concentrated under reduced pressure. The resultant residue was dissolved in $CDCl_3$ and salt **30** crashed out of solution as a white crystalline powder within 15 min. Crystals suitable for X-ray diffraction studies (CCDC xxxxxxx) were obtained using layer diffusion crystallization with $CHCl_3$ (bottom layer) and *n*Hexane (top layer).

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Supplementary Material

Supplementary data associated with this article, including NMR spectra, can be found in the online version.

References and notes

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