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Total synthesis of the tylophora alkaloids rusplinone, 13aα-secoantofine, and antofine using a multicatalytic oxidative aminochlorocarbonylation/Friedel–Crafts reaction

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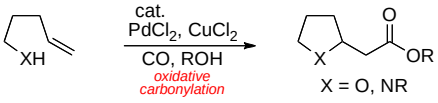
ABSTRACT

A rapid synthetic approach to the tylophora alkaloids antofine and 13aα-secoantofine is presented that makes use of a multicatalytic oxidative aminochlorocarbonylation/Friedel–Crafts reaction as the key step. This reaction, along with a one-pot, three-step telescoped process offers a three or four-pot sequence to access the title compounds in high overall yield.

1. Introduction

A primary goal of synthetic organic chemistry is to discover new approaches to rapidly achieve molecular complexity in a highly efficient manner. Traditional iterative synthetic approaches often lack economy of time, effort, and materials and tend to produce large amounts of waste. Of the many varied efforts to address these issues, the concept of multicatalytic reaction development offers an especially promising venue for process optimization and chemical discovery.[1] As such, multicatalysis, the execution of multiple distinct catalytic reactions in a single flask, has been garnering significant attention from the synthetic community. Our own multicatalytic program is focused on the development of new chemical technologies designed for integration into multicatalytic processes and the invention of multicatalytic strategies for the preparation of structurally complex molecular motifs.[2]

As part of this program we have been exploring new intramolecular oxidative carbonylation methods conceptually related to those developed by Semmelhack[3] and Hegedus.[4] Such reactions allow for the preparation of carbonyl-bearing complex heterocycles from simple alkenyl alcohols and amines and thus offer intriguing possibilities for incorporation into synthetically productive multicatalytic processes. Normally, oxidative carbonylations are terminated by the reaction of a penultimate acyl palladium intermediate with an equivalent of alcohol (often as solvent) or with a pendant hydroxyl or amino moiety to produce esters, lactones, or lactams, respectively (Scheme 1). Though the high utility of these transformations has been demonstrated, ester and amide functionalities lack broad utility as participants in catalytic reactions and thus are not ideal for the development of multicatalytic processes. Accordingly, we have aimed to develop novel oxidative carbonylation reactions that produce alternative carbonyl functionalities capable of undergoing further catalytic transformations.



Scheme 1. Oxidative carbonylation (Semmelhack, Hegedus).

In this regard, we recently reported the development a Pd(II)-catalyzed aminochlorocarbonylation reaction of alkenyl amines to produce reactive acid chloride intermediates.[2a] This method could be used to produce acid chlorides **2** or alternative acyl derivatives such as Weinreb amides by introduction of a suitable nucleophile (Scheme 2). More importantly, we found that this oxidative chlorocarbonylation method could be combined in tandem with

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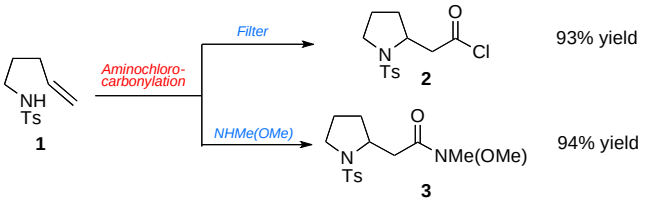
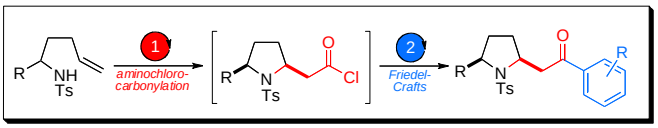
$In(OTf)_3$-catalyzed Friedel–Crafts reactions with electron rich arenes to produce complex α-aryl ketones (Scheme 3).

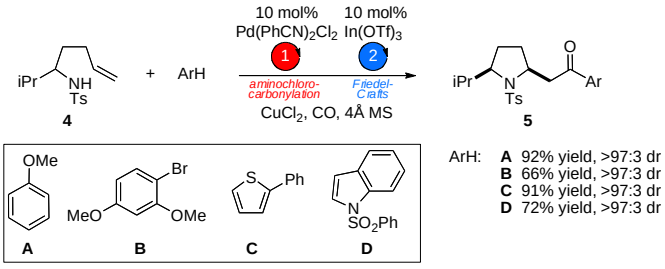


Scheme 2. Formation of acid chloride and Weinreb's amide.

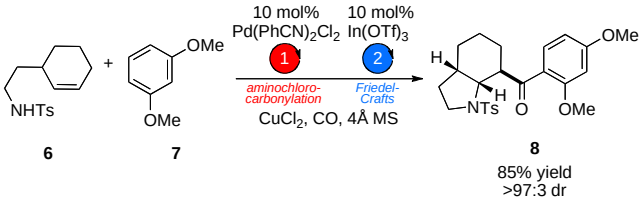


Scheme 3. Aminochlorocarbonylation/Friedel–Crafts.

A variety of alkenyl amine and aryl coupling partners proved to be compatible with this process. For example, when amine **4** was added slowly to a solution of anisole, catalytic $Pd(PhCN)_2Cl_2$, catalytic $In(OTf)_3$, and $CuCl_2$ under a CO atmosphere, the amino ketone **5A** was produced in high yield as essentially a single diastereomer (Scheme 4). A number of other electron-rich aromatic nucleophiles were productive in this transformation including both benzene derivatives and heterocycles (Scheme 4). Variations in the alkenyl substrate were also tolerated (Scheme 5).



Scheme 4. Scope of nucleophiles for aminochlorocarbonylation/Friedel–Crafts.



Scheme 5. Aminochlorocarbonylation/Friedel–Crafts of an internal olefin.

Given the high synthetic productivity of this process, we became interested in applying this tandem aminochlorocarbonylation/Friedel–Crafts reaction to the preparation of biologically active natural products. We were particularly drawn to the tylophora alkaloids, a group of approximately 60 alkaloids isolated from plants of the Ascelpiadaceae and Morceae family native to India and southeastern Asia (Fig. 1).[5] The tylophora alkaloids have long been of synthetic and medicinal interest due to the panoply of biological activities they possess, which include antibacterial, anticancer,

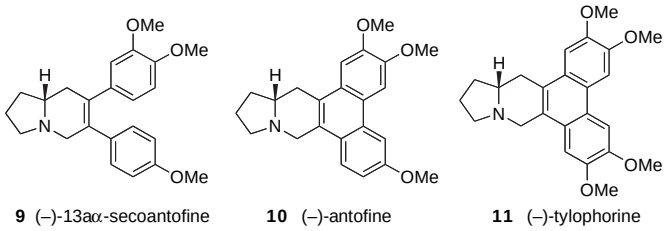


Figure 1. Structures of some tylophora alkaloids.

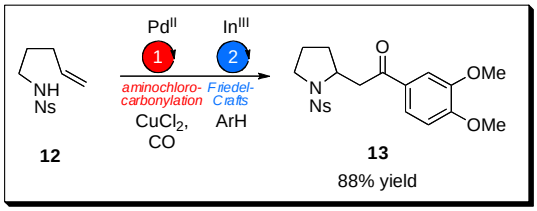
antifungal, antiviral, and *anti*-inflammatory properties.[6,7] Specifically, we surmised that a total synthesis of the tylophora alkaloid antofine would be an especially apt venue to apply our multicatalytic technology. Antofine is of particular interest because it has been shown to be very effective against multidrug-resistant cancer cell lines with IC_{50} values in the low nanomolar range.[8]

Due to their wide range of biological activity, there have been a number of total syntheses of tylophora alkaloids reported.[9] Recent approaches have included such key steps as Pt(II)-catalyzed cycloisomerization,[9a] [5+5]-cycloaddition,[9b] intramolecular alkene carboamination,[9c] and 1,3-dipolar cycloaddition,[9d] among others. Despite achievements made toward this class of molecules, it can be said that the reported strategies leave room for improvement in terms of the number of synthetic steps, overall yield, or potential for diverse analogue preparation. We recognized that our aminochlorocarbonylation/Friedel–Crafts reaction might allow for the rapid and easily diversifiable construction of a substantial portion of the phenanthroindolizidine skeleton common to the tylophora alkaloids. We thus set as our goal the realization of a total synthetic strategy toward this intriguing class of molecules.

2. Results and discussion

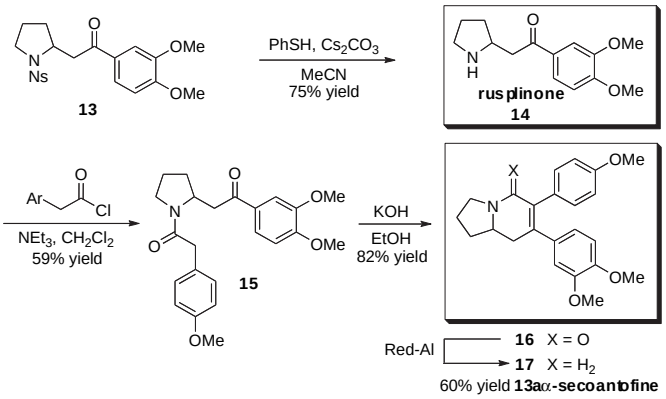
2.1. Synthesis of antofine

The key step in our synthetic strategy was the multicatalytic aminochlorocarbonylation/Friedel–Crafts acylation of a protected 4-pentenyl amine to provide a β-pyrrolidinyl ketone intermediate. Importantly, we discovered that the easily removable nosyl (Ns) group could be employed successfully for this chemistry instead of the tosyl group we had previously reported. Thus subjecting the readily available nosyl protected alkenyl amine **12** and veratrole to our standard aminochlorocarbonylation conditions, we were gratified to find that the β-pyrrolidinyl ketone **13** could be isolated in high yield (Scheme 6). Moreover, we have successfully scaled this reaction to produce 1.6 g of the product **13**.



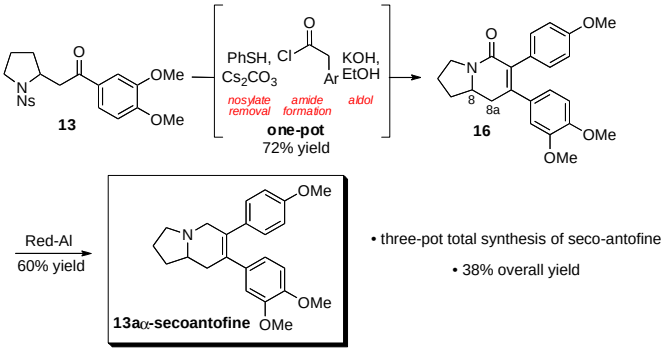
Scheme 6. Aminochlorocarbonylation/Friedel–Crafts key step.

Removal of the nosyl protecting group from **13** proved to be straightforward by treatment with thiophenol under basic conditions. This deprotection furnished the small alkaloid natural product rusplinone (**14**) in 75% yield. This material was acylated with *p*-methoxyphenylacetyl chloride to provide amide **15**, which was subjected to aldol condensation by warming in basic ethanol. Finally, reduction with sodium bis-(2-methoxyethoxy)aluminum hydride (Red-Al) furnished 13aα-secoantofine in 60% yield (Scheme 7). Thus the total synthesis of 13aα-secoantofine was achieved in a five-flask process with a 19% overall yield.



Scheme 7. Synthesis of rusplinone and 13aα-secoantofine.

Although the efficiency of this synthesis was acceptable, we wondered if the conversion of adduct **13** into indolizidine **16** could be executed as a single telescopic reaction, given that each individual step occurred under basic conditions. Indeed, a one-pot procedure was realized by the sequential addition of thiophenol, *p*-methoxyphenylacetyl chloride, and ethanolic potassium hydroxide to a solution of **13** and excess cesium carbonate in acetonitrile (Scheme 8). In addition to doubling the yield (72% vs 36% for the stepwise procedure), the telescopic procedure was considerably more simple and rapid to execute, requiring just 5 h of total

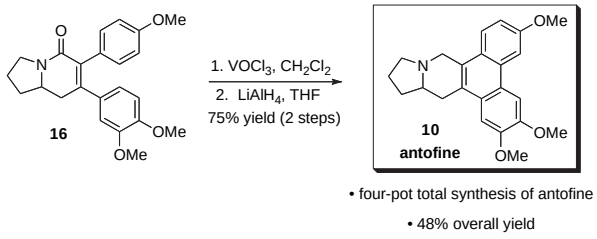


Scheme 8. Synthesis of 13aα-secoantofine.

reaction time with only one required chromatographic purification. Thus the combination of our multicatalytic synthesis of ketone **13** and the telescopic conversion of **13** to **16** has allowed us to realize a three-pot synthesis of 13aα-secoantofine in 38% overall yield.

It should be noted that during the one-pot conversion of **13** to **16**, an additional 8% yield of a pyridone product resulting from oxidation of the 8–8a bond was also isolated. When the final step of the telescopic reaction was carried out for extended periods or at temperatures above 60 °C, a significant amount of the desired product was transformed to this pyridone adduct. Rigorous exclusion of oxygen from the reaction did not fully attenuate the formation of this product. Nevertheless, the dramatically greater efficiency of the telescopic process versus the iterative one led us to consider this minor side product an acceptable loss of material.

Given the efficiency with which 13aα-secoantofine had been accessed, we decided to utilize our strategy to synthesize the related and biologically more interesting antofine, in which the two aryl substituents are joined to form a phenanthryl ring system. To accomplish this goal, we required a means to oxidatively couple the aryl groups of 13aα-secoantofine or its precursor. Fortunately, oxidative aryl coupling of diaryl indolizidine natural products has been achieved using a number of different conditions, including I_2/light,[10] Tl(TFA)$_3$,[9k] VOF_3/TFA,[9j,m] and $VOCl_3$.[11] After some experimentation, we found the $VOCl_3$ oxidation of **16** to be most effective, when care was taken to rigorously exclude oxygen. The crude reaction mixture produced by this coupling was subjected to deoxygenative reduction conditions using $LiAlH_4$ to furnish antofine in 75% yield over two steps (Scheme 9). Overall, the synthesis of antofine was achieved in four reaction pots in 48% yield.



Scheme 9. Synthesis of antofine.

3. Conclusions

Multicatalytic processes promise to provide novel and highly efficient approaches to prepare molecules of value. We have demonstrated the ability of one such multicatalytic process to facilitate the rapid and efficient production of several tylophora alkaloids, including 13aα-secoantofine and antofine, which were prepared in three and four-pot sequences, respectively. We believe the efficiency, convergency, and potential for structural variation our approach offers compares quite favorably with other reported syntheses of these molecules. Indeed, modification of the alkenyl amine, electron-rich aryl, and α-arylacetyl chloride components should provide ready access to a diverse library of novel tylophora analogues. Efforts in this regard are currently underway.

4. Experimental section

4.1. General information

All reactions were performed in base-washed, oven-dried glassware under an atmosphere of argon or carbon monoxide unless otherwise noted. Indium(III) triflate, bis-benzoni triledichloropalladium and copper(II) chloride (99.999%) were purchased from Aldrich then opened and stored in an inert atmosphere glovebox. Molecular sieves (4 Å) were finely ground then activated (300 °C, 10 mmHg) for several hours. 1,2-Dichloroethane was freshly distilled from calcium hydride just prior to use. All other reagents were used as received from commercial vendors.

^{1}H and ^{13}C NMR were recorded in $CDCl_3$ on Brucker DRX-300 and DRX-400 as noted, and are internally referenced to the residual solvent peak. Data from ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s=singlet, br s=broad singlet,

d=doublet, t=triplet, q=quartet, m=multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Nicolet Avatar 370 DTGS (Thermo) using NaCl salt plates and reported in terms of frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained from the Columbia University Mass Spectroscopy Facility on JOEL JMS-HX110 HF mass spectrometer using the FAB^+ ionization mode.

4.2. General procedure for the aminochlorocarbonylation/Friedel–Crafts reaction

A dry screwcap vial fitted with a Teflon septum and magnetic stirbar was moved into the glovebox and charged with $In(OTf)_3$ (10 mol %), $PdCl_2(PhCN)_2$ (10 mol %), $CuCl_2$ (3.0 equiv), and 4 Å molecular sieves (1000 mg/mmol substrate). The sealed vial was removed from the glovebox and filled with carbon monoxide from a balloon by evacuating and back-filling three times. 1,2-Dichloroethane (1.65 mL/mmol substrate) was added to make a suspension, followed by the addition of the aromatic nucleophile. The substrate was then dissolved in 1,2-dichloroethane to make a 0.30 M solution—extra solution was prepared to account for the dead volume of the syringe. This solution was then added to the catalyst mixture via syringe pump at a rate of 0.075 equiv/hour unless otherwise noted. After complete addition of the substrate, the reaction was monitored by mass spectrometry or thin layer chromatography. Once complete, the reaction was quenched by the addition of ethyl acetate (2 mL for 0.12 mmol substrate), saturated aqueous ammonium chloride (1 mL), and water (1 mL) and stirred vigorously for several minutes. The mixture was then filtered through a short plug of Celite into ethyl acetate (5 mL) and washed further with saturated ammonium chloride (3 mL). The organic layer was dried on anhydrous sodium sulfate, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica gel, eluting with a gradient of 5–30% EtOAc/hexanes unless otherwise noted, afforded the title compound.

*4.2.1. N-Methoxy-N-methyl-2-(1-tosylpyrrolidin-2-yl)ethanamide (**3**).* Following general procedure but excluding $In(OTf)_3$ and aromatic nucleophile, a solution of *N*-tosylpentenamine **1**[12] (29.0 mg, 1.78 mmol, 1 equiv) in DCE (400 μL) was added via syringe pump at a rate of 0.03 mL/hour to a stirring suspension of $PdCl_2(PhCN)_2$ (68.3 mg, 10 mol %), $CuCl_2$ (718 mg, 3.0 equiv) and finely ground activated 4 Å molecular sieves (1.78 g) in DCE (200 μL) under an atmosphere of carbon monoxide and at 23 °C. After 15 h, the reaction mixture was cooled to 0 °C and solid *N*,*O*-dimethylhydroxylammonium chloride (58.7 mg, 0.605 mmol, 5 equiv) then 15% sodium hydroxide (600 μL) were added. The ice bath was removed and the heterogeneous mixture stirred at room temperature for two hours. Workup in the usual manner gave a residue that was purified by flash column chromatography on silica gel (20%→60% ethyl acetate/hexanes) to give the title compound **3** (37.2 mg, 94% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, 2H, *J*=8.1, Ar–*H*), 7.30 (d, 2H, *J*=8.0, Ar–*H*), 4.01–3.96 (m, 1H, NC*H*), 3.72 (s, 3H, NOCH_3), 3.49–3.44 (m, 1H, NCH_2), 3.22–3.18 (m, 1H, NCH_2), 3.16 (s, 3H, CH_3), 3.09–3.03 (m, 1H, CH_2C(O)), 2.66–2.58 (m, 1H, CH_2C(O)), 2.41 (s, 3H, CH_3), 1.84–1.67 (m, 3H, CH_2), 1.54–1.48 (m, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 143.4, 133.8, 129.7, 127.6, 61.3, 56.6, 49.2, 39.4, 31.8, 23.7, 21.5; IR: 2927, 1659, 1598, 1343, 1159, 1093, 817, 665 cm^{-1}. HRMS (FAB^+) exact mass calcd for $C_{15}H_{23}N_2O_4S$ $(MH)^+$ requires *m*/*z* 327.1373, found *m*/*z* 327.1394.

*4.2.2. 2-Nitro-N-(pent-4-enyl)aniline (**12**).* 2-Nitrobenzenesulfonamide (746 mg, 3.69 mmol, 1.1 equiv) and potassium carbonate (926 mg, 6.70 mmol, 2.0 equiv) were taken up in DMF (8.5 mL) under argon. 5-Bromopentene (500 mg, 3.35 mmol, 1 equiv) was added dropwise and the mixture stirred at 40 °C for 15 h. The reaction mixture was cooled to room temperature, quenched by addition of water (25 mL), poured into ether (25 mL) and hexanes (25 mL), and separated. The organic layer was washed further with water (2×20 mL), then brine (20 mL), then dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (20%→30% ethyl acetate/hexanes) to give the title compound **12** (541 mg, 60% yield) and *N*,*N*-dipent-5-enyl-2′-(nitrobenzene)sulfonamide (120 mg, 11%).[13]

*4.2.3. 1-(3,4-Dimethoxyphenyl)-2-(1-(2-nitrophenylsulfonyl)pyrrolidin-2-yl)ethanone (**13**).* Following general procedure but excluding $In(OTf)_3$ and aromatic nucleophile, a solution of *N*-nosylpentenamine **12** (480 mg, 1.78 mmol, 1 equiv) in DCE (6.6 mL) was added via syringe pump at a rate of 0.50 mL/hour to a stirring suspension of $PdCl_2(PhCN)_2$ (68 mg, 10 mol %), $CuCl_2$ (716 mg, 3.0 equiv) and finely ground activated 4 Å molecular sieves (1.78 g) in DCE (2.2 mL) under an atmosphere of carbon monoxide and at 23 °C. After 16 h, conversion to the acid chloride intermediate was complete as judged by ESIMS analysis of an aliquot diluted in methanol (observed methyl ester: $[MH^+]$ 329 *m*/*z*). Working quickly, the flask was opened to air and $In(OTf)_3$ (100 mg, 0.18 mmol, 10 mol %) was added in one portion followed by anhydrous veratrole (2.23 mL, 17.8 mmol, 10 equiv). The flask was fitted with a reflux condenser and heated at 70 °C for 42 h, then cooled to room temperature and worked up in the usual manner. Purification by flash column chromatography on silica gel (20%→50% ethyl acetate/hexanes) gave the title compound **13** (680 mg, 88% yield) as a colorless oil that solidified to a waxy solid on standing. ^1H NMR (300 MHz, $CDCl_3$) δ 8.04–8.00 (m, 1H, Ar–*H*), 7.79–7.53 (m, 5H, Ar–*H*), 6.92 (d, 2H, *J*=8.4, Ar–*H*), 4.55–4.44 (m, 1H, NC*H*), 3.95 (s, 6H, OCH_3), 3.74 (dd, 1H, *J*=16.2, 3.1, CH_2C(O)), 3.56–3.37 (m, 2H, NCH_2), 3.04 (dd, 1H, *J*=16.2, 10.5, CH_2C(O)), 2.11–1.92 (m, 2H, CH_2), 1.87–1.71 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 153.5, 148.9, 148.5, 133.6, 131.4, 131.3, 130.6, 129.6, 123.9, 123.0, 110.1, 110.1, 57.3, 56.0, 55.9, 48.9, 44.6, 31.7, 23.8, 14.1; IR: 3079, 2940, 1670, 1587, 1545, 1372, 1263, 1164, 1022, 730 cm^{-1}. HRMS (FAB^+) exact mass calcd for $C_{20}H_{23}N_2O_7S$ $(MH)^+$ requires *m*/*z* 435.1220, found *m*/*z* 431.1230.

*4.2.4. 1-(3,4-Dimethoxyphenyl)-2-(pyrrolidin-2-yl)ethanone (**14**).* Thiophenol (34 μL, 0.331 mmol, 1.2 equiv) was added dropwise to a stirring suspension of the nosylate **13** (120 mg, 0.276 mmol, 1 equiv) and cesium carbonate (135 mg, 0.414 mmol, 1.5 equiv) in acetonitrile (1.4 mL) under argon at 23 °C. After 5 h, the reaction was complete as judged by TLC (50% ethyl acetate/hexanes) and was diluted with ethyl acetate (1 mL). Solids were removed by filtration through a short plug of Celite and the filter cake washed with ethyl acetate (3×2 mL) then concentrated in vacuo. The residue was loaded onto a short plug of silica gel, washed with ethyl acetate (25 mL) to collect a fraction of mostly 2′-nitrodiphenylsulfide (80.1 mg) followed by elution with dichloromethane/methanol/triethylamine (80:18:2, 25 mL) to give rusplinone **14** (51.5 mg, 75% yield) as a clear oil.[14]

*4.2.5. 1-(3,4-Dimethoxyphenyl)-2-(1-(2-(4-methoxyphenyl)ethanoyl)pyrrolidin-2-yl)ethanone (**15**).* To a solution of rusplinone **14** (48.0 mg, 0.192 mmol, 1.0 equiv) and triethylamine (80 μL, 0.576 mmol, 3.0 equiv) in dichloromethane (1 mL) was added a solution of *p*-methoxyphenylacetyl chloride (70.0 mg, 0.384 mmol, 2.0 equiv) in dichloromethane (1.0 mL) at 0 °C. The reaction was then warmed to room temperature and stirred for 12 h. The mixture was poured into ethyl acetate (10 mL) and washed with saturated ammonium chloride (2×3 mL) then brine (2 mL) then dried on sodium sulfate, filtered, and concentrated in vacuo. The residue was purified on silica gel (0%→10% acetone/

dichloromethane) to give amide **15** (44.9 mg, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, 1H, J=8.4, Ar–*H*), 7.61 (s, 1H, Ar–*H*), 7.17 (d, 2H, J=8.4, Ar–*H*), 6.89–6.83 (m, 3H, Ar–*H*), 4.53–4.49 (m, 1H, NC*H*), 3.92 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.85 (dd, 2H, J=13.8, 2.6, $CH_2C(O)$), 3.58 (s, 3H, OCH_3), 3.54–3.38 (m, 2H, NCH_2), 2.55 (dd, 1H, J=13.7, 10.6, $CH_2C(O)$), 2.01–1.73 (m, 3H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 170.0, 158.4, 153.2, 148.8, 129.9, 129.7, 126.6, 123.7, 114.0, 110.2, 110.1, 55.9, 55.3, 55.1, 47.2, 42.7, 42.0, 41.5, 29.1, 23.8. HRMS (FAB$^+$) exact mass calcd for $C_{23}H_{28}NO_5$ $(MH)^+$ requires m/z 398.1962, found m/z 398.1945.

*4.2.6. 7-(3,4-Dimethoxyphenyl)-6-(4-methoxyphenyl)-2,3,8,8a-tetrahydroindolizin-5(1H)-one (**16**).* A stock solution of 7.5% (w/w) potassium hydroxide in ethanol was prepared before initiating the reaction. The acid chloride was prepared by dropwise addition of thionyl chloride (440 μL, 6.02 mmol, 2.0 equiv) to a solution of *p*-methoxyphenylacetic acid (500 mg, 3.01 mmol, 1 equiv) and DMF (10 μL) in dichloromethane (5 mL) at 0 °C. After 5 min, the solution was warmed to 23 °C and stirred at this temperature for 4 h. Volatiles were removed by concentration in vacuo. Traces of hydrochloric acid were removed by dissolution in dichloromethane and concentration in vacuo. The acid chloride was carried forward without purification.

The starting nosylate **3** (260 mg, 0.598 mmol, 1 equiv), azeotropically dried by three cycles of concentrating in vacuo from anhydrous benzene, and cesium carbonate (390 mg, 1.196 mmol, 2.0 equiv) were taken up in acetonitrile (2 mL). Thiophenol (64 μL, 0.628 mmol, 1 equiv) in acetonitrile (1 mL) was then added dropwise and the mixture stirred at 23 °C for 3 h. The yellow suspension was cooled to 0 °C and a solution of *p*-methoxyphenylacetyl chloride (166 mg, 0.897 mmol, 1.5 equiv) in acetonitrile (0.5 mL) was added dropwise. After 3 min, the reaction mixture was warmed to 23 °C and stirred for one hour. The solution of 7.5% (w/w) potassium hydroxide in ethanol (1.25 mL, 2.99 mmol, 5.0 equiv) was added causing the solution to turn black. The flask was quickly fitted with a reflux condenser and the reaction mixture heated at 60 °C for 1 h. Extended reaction time or elevated temperatures should be avoided at this step to minimize oxidation of the desired product. The reaction mixture was cooled to room temperature and quenched with a saturated aqueous solution of sodium thiosulfate (3 mL), a saturated aqueous solution of ammonium chloride (3 mL), and ethyl acetate (10 mL). The biphasic mixture was stirred at 23 °C for 30 min, then poured into ethyl acetate (30 mL): if necessary, dichloromethane (~5 mL) was added to the organic layer to form a clear solution. The layers were separated and the organic layer washed further with a saturated aqueous solution of ammonium chloride (15 mL), then dried on sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (5%→20% acetone/dichloromethane) to give the title compound **16** (165 mg, 72% yield) and the 2-pyridone resulting from oxidation of the product (18 mg, 8% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (d, 2H, J=8.7, Ar–*H*), 6.74–6.71 (m, 4H, Ar–*H*), 6.43 (d, 1H, J=1.2, Ar–*H*), 6.89–6.83 (m, 3H, Ar–*H*), 3.98–3.87 (m, 1H, NCH_2), 3.87 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.69–3.53 (m, 2H, NCH_2, and NC*H*), 3.48 (s, 3H, OCH_3), 2.85 (dd, 1H, J=22.2, 4.8, CH_2CH), 2.70 (dd, 1H, J=16.2, 13.8, CH_2CH), 2.32–2.25 (m, 1H, CH_2), 2.12–2.04 (m, 1H, CH_2), 1.97–1.63 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 158.4, 149.3, 147.9, 144.0, 132.6, 132.1, 131.8, 128.8, 120.8, 113.2, 112.7, 110.3, 55.7, 55.5, 55.4, 55.1, 44.7, 37.2, 22.8, 23.1. HRMS (FAB$^+$) exact mass calcd for $C_{17}H_{14}O_3$ $(MH)^+$ requires m/z 380.1856, found m/z 380.1851.

*4.2.7. 7-(3,4-Dimethoxyphenyl)-6-(4-methoxyphenyl)-1,2,3,5,8,8a-hexahydroindolizine (**9**).* To a solution of indolizidine **16** (190 mg, 0.501 mmol, 1.0 equiv) in dioxane (15 mL) was added a 65% (w/w) solution of Red-Al in toluene (2.20 mL, 7.01 mmol, 14 equiv) and the mixture heated at reflux for 2 h. The reaction mixture was cooled, volatiles removed in vacuo and excess hydride was quenched by careful addition of water (10 mL) then 15% NaOH (3 mL) then brine (20 mL). The aqueous mixture was extracted with chloroform (5×30 mL) and the combined organic fractions dried on sodium sulfate, filtered, and concentrated in vacuo. The residue was purified on silica gel (3% acetone/dichloromethane) to give 13aα-secoantofine **9** (109 mg, 60% yield).[15]

*4.2.8. Antofine (**10**).* To a solution of indolizidine **16** (20.0 mg, 0.053 mmol, 1.0 equiv) in degassed DCE (2 mL) at 0 °C was added $VOCl_3$ (15.0 μL, 0.158 mmol, 3.0 equiv). The solution was allowed to warm to room temperature and stir overnight. The reaction mixture was quenched with saturated ammonium chloride (1 mL). Then wash with 1 M ammonium hydroxide (3×1 mL) and brine (1 mL). Dry on sodium sulfate and filter through silica plug using 10% acetone/dichloromethane. The crude reaction mixture contains both desired coupled product and side product corresponding to the desired product containing an additional Cl atom [MH^+] 413 m/z. This mixture of products was then added as a THF solution (2 mL) to a suspension of $LiAlH_4$ (20.1 mg, 0.53 mmol, 10 equiv) in THF (3 mL) at 0 °C. The reaction mixture was then heated to reflux for 2 h. After cooling to 0 °C, three drops of 1 M NaOH was added (until bubbling subsided). This crude mixture was filtered through Celite followed by a silica plug to provide antofine **10** (14.5 mg, 75% yield over two steps).[9b]

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