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Synthesis of the Common Propellane Core Structure of the Hasubanan Alkaloids

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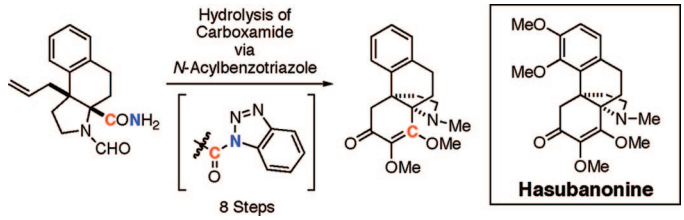

The racemic synthesis of the common propellane core structure found in various hasubanan alkaloids is reported. The successful completion hinged upon the stereocontrolled construction of the cis-substituted heterobicycle as a precursor for the intramolecular Dieckmann condensation. A novel strategy is introduced for the facile hydrolysis of a sterically demanding carboxamide under a mild condition. The 2-nitroanilide obtained by the Goldberg arylation of a carboxamide with 2-iodonitrobenzene was readily converted to the corresponding ester derivative by way of *N*-acylbenzotriazole. We expect that the reported synthetic route will allow the synthesis of a series of hasubanan alkaloids starting from the correspondingly functionalized 2-tetralone derivatives.

Introduction

A number of natural products bearing the unique propellane [4.4.3.0] core structure have been reported from plant sources.[1] The hasubanan alkaloids **1**−**5** share the 2,3-dimethoxycyclohexenone and *N*-methylpyrrolidine ring as a component of the hasubanan framework (Figure 1). These hasubanan alkaloids have initially received attention due to their close resemblance to the morphine alkaloids, although no reported analgesic bioactivities have been disclosed. The similar propellane framework is shared by acutumine (**6**), a chlorine-containing natural product that has recently been reported to inhibit T-cell growth and aid in memory by enhancing memorization and antiamnesic properties in mice and rats.[2] In light of the molecular complexity and promising bioactivity of acutumine, several groups have reported efforts toward the total synthesis of the alkaloid.[3] To date, there has been no reported total synthesis of acutumine, while the total synthesis of hasubanonine (**1**) has been published from a few groups, including the recent racemic synthesis by Castle in 2006.[1i] It is envisioned that a strategy toward the common propellane core skeleton found in the hasubanan alkaloids can be applied toward the synthesis of acutumine.

Results and Discussion

Retrosynthesis. We chose 3,4-didesmethoxyhasubanonine **7** as the synthetic target due to its shared tetracyclic core structure with the series of hasubanan alkaloids **1**−**5**, differing only in the positions of hydroxyl groups on the aromatic ring (Figure 1). The retrosynthetic analysis for the hasubanan skeleton **7** is shown in Scheme 1. It was envisioned that the propellane core could be constructed from a Dieckmann cyclization by the two substituents at the angular positions of cis-fused heterobicycle **A**. Each substituent must be installed in an appropriate order from precursor **B** under compatible conditions during each manipulation. We have foreseen the difficulty of hydrolysis of the sterically hindered cyano group at the angular position of the heterobicycle to the corresponding carboxylic acid derivative.

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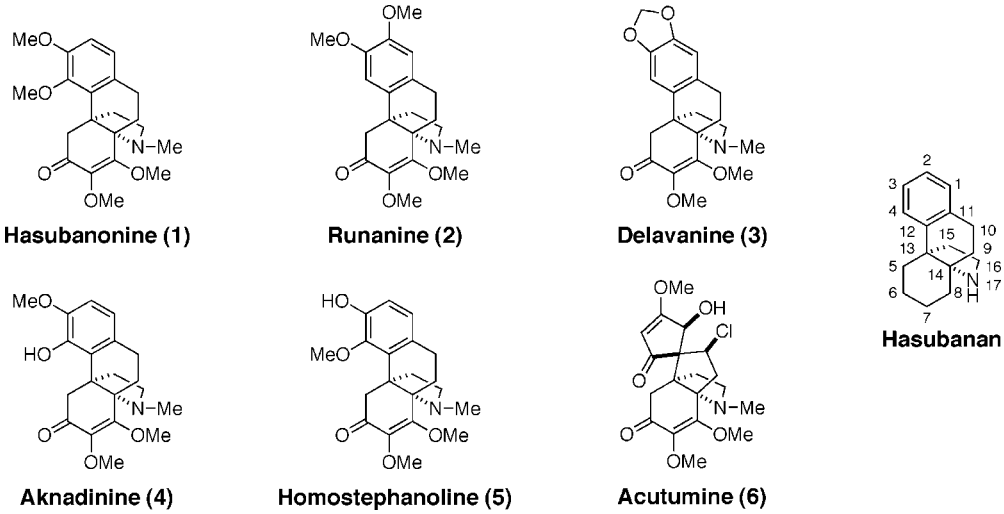
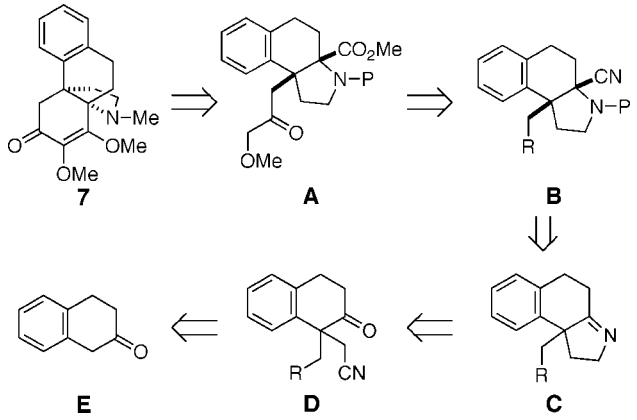


FIGURE 1. Structures of hasubanan alkaloids (**1**−**5**) and acutumine (**6**).

SCHEME 1. Retrosynthetic Analysis of Hasubanan Propellane Core



The cyclization hinged upon the successful diastereoselective construction of aminonitrile **B** from the cyclic imine **C**. We expected that the thermodynamic controlled condition will preferably give the cis-5,6-fused ring system in **B**.[4] The cyclic imine could be formed by chemoselective reduction of the cyano group in ketone **D**. The regioselective consecutive alkylation of 2-tetralone (**E**) gives 1,1-alkylated tetralone **D**.

For the synthesis of the hasubanan alkaloids, we envisioned that the enantioselective alkylation of 2-tetralone could be achieved by using a chiral phase transfer catalyst.[5] To obtain each hasubanan alkaloid **1**−**5** in Figure 1, the same synthetic route would be applicable starting from the corresponding 2-tetralone derivatives. According to this synthetic strategy, 7,8-dimethoxy-2-tetralone and 6,7-dimethoxy-2-tetralone would be the precursors for the synthesis of hasubanonine (**1**) and runanine (**2**), respectively. Conveniently, 7,8-dimethoxy-2-tetralone is a known compound in the literature and 6,7-dimethoxy-2-tetralone is commercially available.[6] We also expected the cyclopentanone derivative of **D** could be converted stereoselectively to the cis-5,5-fused ring system corresponding to **B**. Then, the following intramolecular Dieckmann condensation could provide the skeleton of the propellane [4.3.3.0] core structure of acutumine.

Synthesis of Cyclic Aminonitrile. In our initial synthetic planning, we focused our attention on the construction of the cis-substituted aminonitrile **B**. We chose to start our synthesis with the known (±)-1-allyl-2-tetralone (**8**),[7] because the allyl moiety provided the requisite three-carbon unit for the Dieckmann cyclization in **A**, and also because of the various literature precedents for transforming a tethered terminal olefin into the desired hydroxyl ketone regioselectively.[8] Regioselective alkylation of **8** with bromoacetonitrile afforded the 1,1-alkylated 2-tetralone **9** in 81% yield in a racemic form (Scheme 2).[9] In an attempt to directly access cyclic imine **13** from **9**, chemoselective reduction of the nitrile group with use of Raney Ni was explored.[10] Initial attempts cleanly gave the cyclic imine, although the tethered olefin was saturated under the hydrogena-

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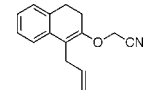
(9) The reaction was accompanied by 10% yield of the *O*-alkylated product below.



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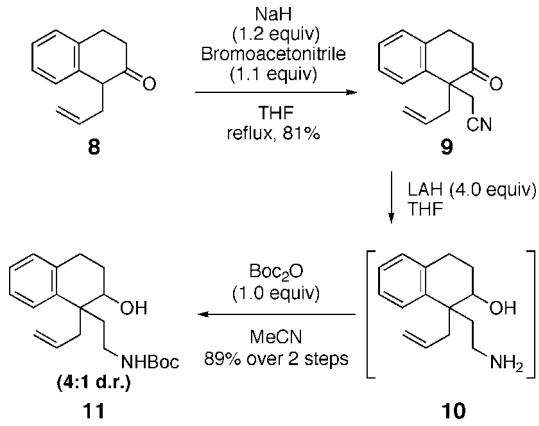
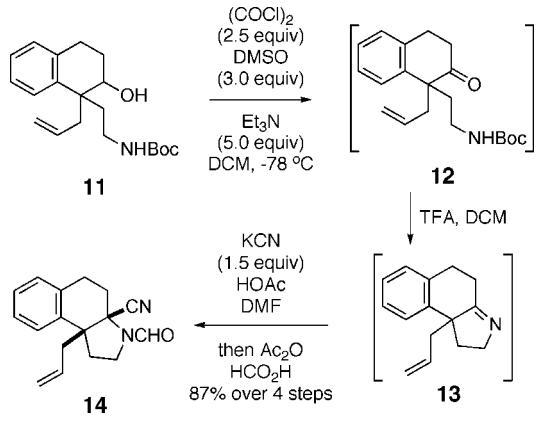
SCHEME 2. Preparation of the Precursor of Aminonitrile



SCHEME 3. Stereocontrolled Synthesis of Aminonitrile 14 via Cyclic Imine



tion conditions. Therefore, a protected amino ketone **12** was prepared in a stepwise fashion via a protected amino alcohol **11**. Reduction of tetralone **9** with LAH and concomitant chemoselective protection of the resulting amino alcohol **10** with Boc_2O gave carbamate **11** in 89% yield over two steps as an inconsequential 4:1 mixture of diastereomers.[11]

Swern oxidation of the diastereomixture of **11** cleanly gave tetralone **12**, although the attempted purification by silica gel chromatography induced formation of several compounds including a cyclic *N*,*O*-hemiketal (Scheme 3). The ^{1}H NMR of the crude mixture was clean, indicating the formation of **12** as the sole product. Deprotection of the Boc group of tetralone **12** allowed an entry into the cyclic imine **13**, which was also unstable under silica gel chromatography. Again, ^{1}H NMR of the crude mixture was clean and indicated that imine **13** had been formed. Isolation of the hydrocyanation product of the cyclic imine **13** proved to be difficult as the cyanide anion is extruded upon workup and purification, presumably due to the steric hindrance of the cis-5,6-fused ring juncture.

Our efforts then focused on finding conditions that allowed the capture of the unstable aminonitrile in situ. Hydrocyanation of the cyclic imine **13** followed by treatment with formic acetic anhydride[12] gave the *N*-formylated aminonitrile **14** in 87% over four steps from **11** as a single desired diastereomer without purification of **12** and **13**. *N*-Formylated aminonitrile **14** existed as a 1.8:1.0 mixture of rotational isomers about the formamide

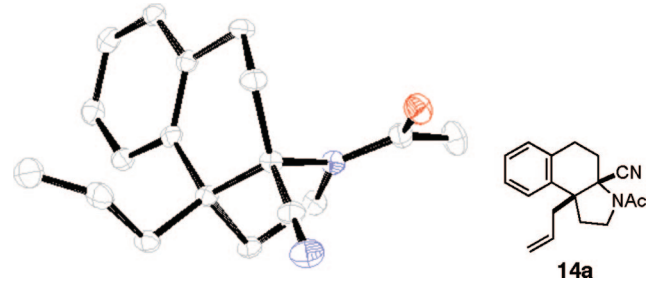
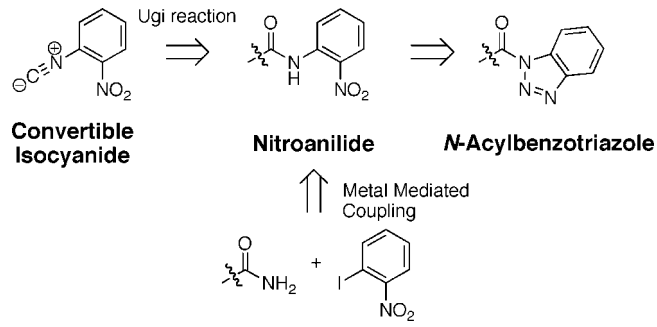


FIGURE 2. ORTEP figure of compound **14a**.

SCHEME 4. Facile Cleavage of an Amide Bond by Its Conversion to an *N*-Acylbenzotriazole



bond. We reasoned that the diastereoselective addition of hydrogen cyanide was due to the better stability of a cis-5,6-fused ring than a trans-5,6-fused ring juncture.[4]

The cis-substitution pattern of aminonitrile **14** was confirmed by X-ray crystal structure analysis of the corresponding *N*-acetylated aminonitrile **14a** (Figure 2).[13] For the X-ray crystal structure analysis, the acetamide **14a** was chosen instead of formamide **14** because we observed that it existed as a single rotational isomer regarding the amide bond by ^{1}H NMR.

Hydrolysis of Hindered Carboxamide. With the complete carbon skeleton in hand, we focused on accessing the Dieckmann cyclization precursor **A** from aminonitrile **14** (Scheme 1). The remaining agenda before the final ring closure to form the propellane core are the following: (1) to convert a sterically hindered nitrile into a methyl ester moiety (**14** to **19**, Scheme 4) and (2) oxidation of allylic side chain to α-methoxy ketone (Scheme 5). The cyanide ion is commonly used as a one-carbon synthon in organic synthesis. The versatility of the nitrile functional group has allowed for a facile entry into various carboxylic acid derivatives. However, one drawback to these conversions is the harsh acidic or basic conditions required to hydrolyze the nitrile. In our investigations, the simple hydrolysis of carboxamide **15** proved to be a stumbling block,[14] presumably due to its proximity to two fully substituted carbon centers, although a hindered aminonitrile **14** could be converted successfully to the corresponding carboxamide **15** in 91% yield (Scheme 5).

We sought a procedure to transform a sterically hindered carboxamide functional group to the corresponding carboxylic acid derivative under mild conditions. In the course of our

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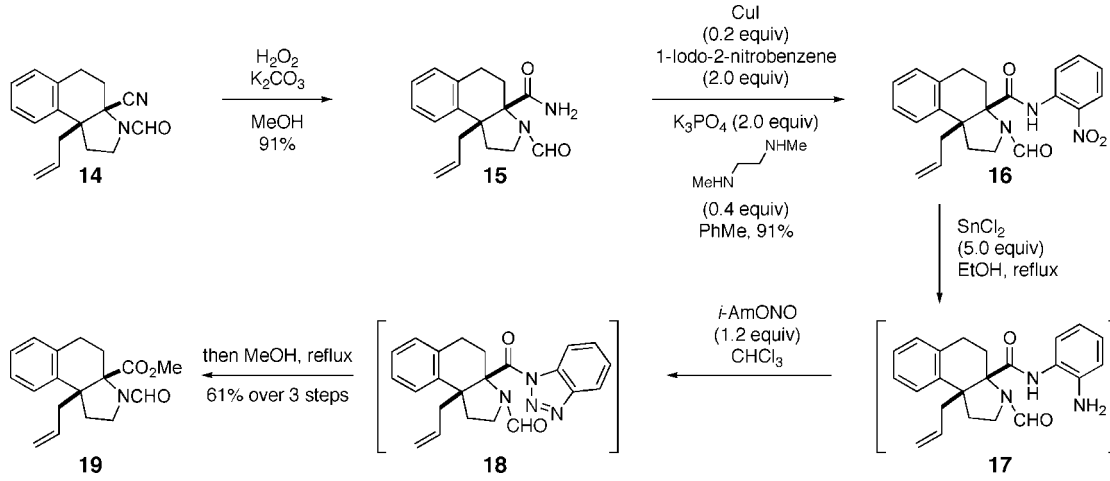
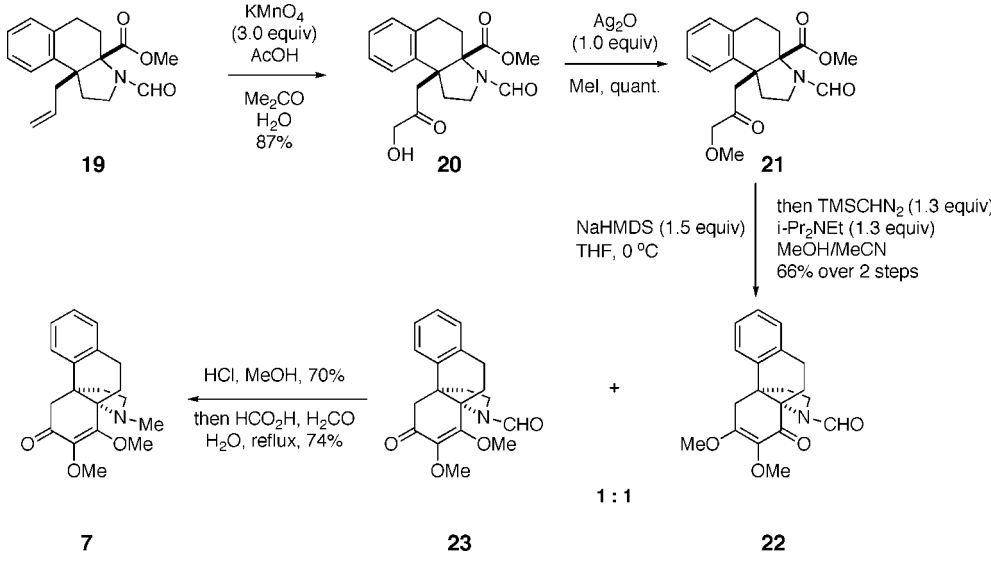
(13) Upon hydrocyanation of imine **13**, the unstable aminonitrile intermediate was acetylated by using AcCl (10.0 equiv) and TEA (1.0 equiv) in DCM as a 0.04 M solution to provide 56% yield of the desired **14a** over 4 steps from **11**.
(14) Attempts at cleaving carboxamide **15** led to decomposition of the starting material. The following conditions were explored for the cleavage of carboxamide **15**: (a) NaOH in refluxing MeOH. (b) H_2SO_4 in refluxing MeOH. (c) TMSCl in refluxing MeOH. (d) *N*,*N*-Dimethylformamide dimethyl acetal and $Sc(OTf)_3$ in MeOH.

SCHEME 5. Synthesis of Methyl Ester 19



SCHEME 6. Synthesis of the Hasubanan Propellane Core



synthetic studies on proteasome inhibitor omuralide, we recently reported 2-nitrophenyl isocyanide as a convertible isocyanide in the Ugi reaction (Scheme 4).[15] The hydrolysis of the resulting 2-nitroanilide was facilitated by its derivatization to *N*-acylbenzotriazole, which functioned as an acid chloride synthetic equivalent.[16] We realized the formation of 2-nitroanilide could be possible by metal-catalyzed *N*-arylation of a carboxamide derived from a nitrile.[17] We foresaw that the nitrogen atom of the carboxamide **15** could react to form the anilide despite the steric hindrance.

In this paper, we report our strategy of cleaving a sterically hindered carboxamide under mild conditions by way of an *N*-acylbenzotriazole. The Goldberg reaction of carboxamide **15** with 2-iodonitrobenzene gave nitroanilide **16** in 91% yield (Scheme 5).[17] Attempted base hydrolysis of **16**[18] only resulted in the recovery of the starting material, probably due to the steric hindrance of the amide. Tin-mediated chemoselective reduction of the nitro group of **16** gave anilide **17** without disturbing the allyl group. Upon treatment of the crude mixture with isoamyl nitrite, it provided *N*-acylbenzotriazole **18**, which was detected by TLC and ^{1}H NMR. The resulting isoamyl alcohol did not react with *N*-acylbenzotriazole to afford an isoamyl ester. It is probably due to the steric hindrance of **18** and so-called Newman's rule of six regarding the alcohol.[19] Without purification, heating **18** at refluxing temperatures in MeOH gave the desired methyl ester **19** in 61% yield over three steps from **16**. The resulting benzotriazole byproduct was conveniently removed simply by using a 1 N NaOH wash in the workup procedures.

Completion of Propellane Synthesis. The successful completion of the hasubanan skeleton was initiated with the regioselective hydroxy-carbonylation of the tethered olefin of methyl ester **19** with $KMnO_4$ (Scheme 6).[8] Methylation of alcohol **20** with silver oxide in MeI gave the methyl ether **21**. Our key cyclization employed NaHMDS. The resulting 1,3-dione (not shown) was detected by ^{1}H NMR as of approximately a 1:1 mixture of enol regioisomers, but it decomposed to unidentified compounds upon purification. We decided to capture the

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resulting dione with TMS-diazomethane, but this gave us a 1:1 mixture of methyl enol ether isomers as previously reported.[1j] The undesired **22** and desired **23**, the less polar product, were isolated in a combined 66% yield over two steps. The two isomers **22** and **23** were easily separable by column chromatography. Deformylation of **23** with HCl followed by *N*-methylation by treatment of the amine **23a** (not shown) with formaldehyde and formic acid allowed for the successful completion of the hasubanan propellane core **7**. Our ^{1}H NMR spectrum matched that of the partial chemical shifts that were reported in the literature.[1j] Attempted conversion of methyl enol ether **22** to the 1,3-dione to recycle for the enol ether formation step was not successful as the compound decomposed under acidic conditions.

Conclusions

In conclusion, we reported the racemic synthesis of the common propellane core found in various hasubanan alkaloids. The successful completion hinged upon the construction of the cis-substituted aminonitrile **14** and a strategy for converting the sterically demanding nitrile functional group into the corresponding ester under mild conditions by way of *N*-acylbenzotriazole, which is known as an acid chloride synthetic equivalent. Additionally, the regioselective formation of desired enol ether **23** is currently under investigation. We expect that the procedures reported will allow the synthesis of a series of hasubanan alkaloids starting simply from the corresponding 2-tetralone derivatives. These synthetic sequences could also be used in the construction of the propellane core structure of acutumine. The asymmetric total synthesis of hasubanonine will be reported in due course.

Experimental Section

Nitroanilide 16. A Schlenk tube was charged with CuI (21 mg, 0.11 mmol, 0.20 equiv), 1-iodo-2-nitrobenzene (270 mg, 1.08 mmol, 2.0 equiv), carboxamide **15** (154 mg, 0.54 mmol, 1.0 equiv), and K_3PO_4 (230 mg, 1.08 mmol, 2.0 equiv), evacuated, and backfilled with nitrogen. *N*,*N*′-Dimethylethylenediamine (23 uL, 0.22 mmol, 0.40 equiv) and toluene (1 mL) were added under nitrogen. The reaction mixture was stirred at 80 °C for 15 h. The resulting yellow-brown suspension was filtered through a pad of silica gel eluting with ethyl acetate (50 mL). The filtrate was concentrated in vacuo and the residue was purified by flash chromatography (SiO_2, 50% EtOAc in hexanes elution) to afford **16** (195 mg, 0.49 mmol, 91%) as a yellow solid. R_f (50% EtOAc in hexanes elution) 0.30; mp 175 °C; HRMS (EI) *m*/*z* calcd for $C_{23}H_{23}N_3O_4$ (M^+) 405.1689, found 405.1688; ^{1}H NMR (500 MHz, $CDCl_3$, a mixture of rotamers in 2.2:1.0 ratio) δ 11.19 (s, 0.69H), 11.01 (s, 0.31H), 8.99 (d, J = 8.5 Hz, 0.69H), 8.91 (d, J = 9.0 Hz, 0.31H), 8.39 (s, 0.63H), 8.34 (s, 0.39H), 8.29 (d, J = 8.0 Hz, 0.38H), 8.25 (d, J = 8.0 Hz, 0.62H), 7.67−7.74 (m, 1H), 7.34 (d, J = 7.5 Hz, 1H), 7.21−7.29 (m, 2H), 7.16−7.20 (m, 1H), 7.08−7.13 (m, 1H), 5.52−5.64 (m, 1H), 4.77−4.90 (m, 2H), 4.00 (dd, J = 8.0 Hz, 11.5 Hz, 0.32H), 3.87 (t, J = 9.0 Hz, 0.68H), 2.99−3.16 (m, 2H), 2.71−2.90 (m, 3H), 2.54−2.60 (m, 1H), 2.47−2.51 (m, 1H), 2.33−2.43 (m, 1H), 2.28 (dd, J = 6.0, 12.5 Hz, 0.32H), 2.11 (dd, J = 5.5, 13.0 Hz, 0.68 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 171.7, 161.8, 161.2, 138.7, 138.1, 137.5, 136.9, 136.65, 136.61, 136.5, 135.8, 134.9, 134.3, 134.1, 133.8, 129.1, 129.0, 127.43, 127.40, 127.38, 127.2, 127.0, 126.9, 126.4, 126.2, 124.4, 123.8, 122.1, 121.9, 118.6, 118.2, 73.2, 72.7, 53.40, 53.37, 45.3, 43.2, 43.0, 42.7, 38.3, 37.5, 27.6, 25.7, 24.9, 24.8; IR (film, cm^{-1}) 2969, 2925, 2104, 1658, 1606.

Methyl Ester 19. To a solution of **16** (1.89 g, 4.65 mmol, 1.0 equiv) in EtOH (18 mL) was added $SnCl_2$ (4.41 g, 23.3 mmol, 5.0 equiv). The solution was heated to reflux for 0.5 h, then quenched with H_2O (500 mL), and extracted with EtOAc (3 × 300 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo. Flash chromatography (SiO_2, 5% MeOH in DCM elution) afforded the anilide (1.62 g, 4.33 mmol, 93%). To a solution of the resulting anilide (464 mg, 1.24 mmol, 1.0 equiv) in $CHCl_3$ (6 mL) was added *i*-AmONO (0.33 mL, 1.48 mmol, 1.2 equiv). The reaction mixture was stirred for 15 h, then treated with MeOH (25 mL). The reaction mixture was heated to reflux for 15 h then quenched with 100 mL of NaOH (1N aqueous solution) and extracted with EtOAc (3 × 200 mL). The resulting benzotriazole was cleanly removed by extraction with the aqueous basic solution. The combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo. Flash chromatography (SiO_2, 30% EtOAc in hexanes elution) afforded **19** (261 mg, 0.88 mmol, 71%) as a colorless oil. R_f (50% EtOAc in hexanes elution) 0.31; HRMS (EI) *m*/*z* calcd for $C_{18}H_{21}NO_3$ (M^+) 299.1521, found 299.1519; ^{1}H NMR (500 MHz, $CDCl_3$, a mixture of rotamers in 1.4:1.0 ratio) δ 8.21 (s, 0.58H), 8.15 (s, 0.42H), 7.28 (t, J = 7.5 Hz, 1H), 7.17−7.20 (m, 1H), 7.10 (t, J = 7.0 Hz, 1H), 7.01−7.05 (m, 1H), 5.41−5.53 (m, 1H), 4.82−4.88 (m, 2H), 3.78 (s, 1.5H), 3.76 (s, 1.5H), 3.71 (dd, J = 9.5, 11.5 Hz, 0.5H), 3.63 (t, J = 9.0 Hz, 0.5H), 2.82−2.95 (m, 2H), 2.67−2.75 (m, 2H), 2.63−2.66 (m, 1H), 2.56−2.61 (m, 0.5H), 2.39−2.46 (m, 0.5H), 2.24−2.33 (m, 2H), 2.14−2.23 (m, 0.5H), 1.97−2.01 (m, 0.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 172.9, 161.6, 160.6, 138.4, 138.0, 137.6, 135.8, 133.6, 133.4, 128.9, 128.8, 127.29, 127.27, 127.0, 126.8, 126.7, 126.6, 118.3, 118.0, 71.2, 70.7, 52.8, 52.6, 52.4 (2×), 45.1, 43.3, 42.8, 42.7, 37.9, 37.1, 26.7, 25.3, 24.9, 24.4; IR (film, cm^{-1}) 2951, 2925, 2882, 2244, 1728, 1658, 1379.

Alcohol 20. To a solution of **19** (241 mg, 0.81 mmol, 1.0 equiv) in acetone (4.94 mL), water (1.08 mL), and acetic acid (300 μL) was added a solution of $KMnO_4$ (382 mg, 2.42 mmol, 3.0 equiv) in acetone (6.51 mL) and water (1.45 mL). After 3 min a solution of H_2SO_4 (0.43 mL) in water (3 mL) was added, then $NaNO_2$ (181 mg, 2.62 mmol) was added whereupon the dark purple solution turned into a clear, colorless solution. The solution was diluted in water (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo. Flash chromatography (SiO_2, 70% EtOAc in hexanes elution) afforded **20** (232 mg, 0.70 mmol, 87%) as a colorless oil. R_f (5% MeOH in DCM elution) 0.23; HRMS (EI) *m*/*z* calcd for $C_{18}H_{21}NO_5$ (M^+) 331.1420, found 331.1410; ^{1}H NMR (500 MHz, $CDCl_3$, a mixture of rotamers in 1.3:1.0 ratio) δ 8.25 (s, 0.57H), 8.22 (s, 0.43H), 7.09−7.13 (m, 1H), 7.15−7.20 (m, 3H), 4.01 (d, J = 19.0 Hz, 0.5H), 3.93 (d, J = 18.5 Hz, 0.5H), 3.81−3.90 (m, 1H), 3.79 (s, 1.5H), 3.76 (s, 1.5H), 3.71 (dd, J = 5.0, 13.5 Hz, 0.5H), 2.98 (d, J = 16.5 Hz, 1H), 2.75−2.91 (m, 5.5H), 2.59−2.73 (m, 1H), 2.42−2.52 (m, 1H), 2.22−2.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.1, 207.0, 173.8, 172.9, 161.7, 161.1, 137.9, 137.5, 137.1, 135.3, 129.53, 129.47, 127.4 (2×), 127.3, 127.2, 126.34, 126.29, 71.3, 70.7, 69.3, 69.2, 53.4, 53.0, 51.2, 51.1, 46.3, 45.8, 45.2, 42.7, 37.1, 36.3, 26.4, 25.4, 24.5, 24.4; IR (film, cm^{-1}) 3417, 2920, 2850, 1734, 1657.

Methyl Ether 21. To a solution of **20** (30 mg, 0.10 mmol, 1.0 equiv) in MeI (4 mL) was added Ag_2O (31 mg, 0.14 mmol, 1.0 equiv). The solution was stirred for 15 h, then filtered through a pad of silica gel and concentrated in vacuo. Flash chromatography (SiO_2, 2% MeOH in DCM elution) afforded **21** (31 mg, 0.10 mmol, quant) as a colorless oil. R_f (5% MeOH in DCM elution) 0.37; HRMS (EI) *m*/*z* calcd for $C_{19}H_{23}NO_5$ (M^+) 345.1576, found 345.1576; ^{1}H NMR (500 MHz, $CDCl_3$, a mixture of rotamers in 1.3:1.0 ratio) δ 8.24 (s, 0.57H), 8.21 (s, 0.43H), 7.18−7.23 (m, 1H), 7.07−7.18 (m, 3H), 3.79 (d, J = 17.0 Hz, 0.5H), 3.78 (s, 1.5H), 3.76 (s, 1.5H), 3.65−3.75 (s, 1.5H), 3.31 (s, 3H), 3.02 (d, J = 17.5 Hz, 1H), 2.77−2.99 (m, 4H), 2.45−2.74 (m, 3H), 2.19−2.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.3, 205.2, 173.7, 172.9, 161.4, 160.9, 138.3, 137.8, 137.0, 135.3, 129.2, 129.1, 127.1, 126.9, 126.86, 126.83, 126.3, 126.2, 78.34, 78.27, 71.2, 70.6, 59.3 (2×),

53.2, 52.8, 51.0, 50.8, 46.2, 45.7, 45.1, 42.6, 37.1, 36.3, 26.5, 25.4, 24.5, 24.4; IR (film, cm^{-1}) 2982, 2948, 2887, 1733, 1672.

Enol Ether 23. To a solution of NaHMDS (0.37 mL, 0.37 mmol, 1.0 M in THF, 1.5 equiv) in THF (1 mL) at 0 °C was added **21** (86 mg, 0.25 mmol, 1.0 equiv) in THF (1 mL). The solution was warmed to rt and stirred for 30 min, then quenched with 1N HCl (5 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo. To the resulting dione in MeOH (0.20 mL) and MeCN (1.80 mL) was added iPr$_2$NEt (56 μL, 0.32 mmol, 1.3 equiv) then $TMSCHN_2$ (0.16 mL, 0.32 mmol, 0.20 M in diethyl ether, 1.3 equiv). The solution was stirred for 15 h, then quenched with 1 N HCl (5 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo. Flash chromatography (SiO_2, 2% MeOH in DCM elution) afforded **23** (27 mg, 0.083 mmol, 33%) as a colorless oil and the corresponding methyl enol ether isomer **22** (27 mg, 0.083 mg, 33%) as a colorless oil. Enol ether **23**: R_f (5% MeOH in DCM elution) 0.39; HRMS (ESI) m/z calcd for $C_{19}H_{21}NO_4$ (M^+) 327.1471, found 327.1462; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.43 (s, 1H), 7.26 (d, J = 8.5 Hz, 1H), 7.24 (t, J = 7.5 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 7.07 (d, J = 7.5 Hz, 1H), 4.15 (s, 3H), 3.70 (s, 3H), 3.53−3.57 (m, 1H), 3.00−3.05 (m, 1H), 3.00 (d, J = 17 Hz, 1H), 2.83−2.90 (m, 1H), 2.76−2.81 (m, 1H), 2.70 (d, J = 17 Hz, 1H), 2.56−2.61 (m, 1H), 2.27−2.30 (m, 2H), 2.16−2.22 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.2, 162.6, 161.6, 138.6, 136.3, 134.3, 129.4, 127.6, 127.3, 127.0, 66.8, 61.9, 61.0, 48.9, 46.9, 42.5, 34.0, 26.7, 24.5; IR (film, cm^{-1}) 2927, 2850, 1655, 1612, 1457, 1370. Other methyl enol ether regioisomer **22**: R_f (5% MeOH in DCM elution) 0.36; HRMS (ESI) m/z calcd for $C_{19}H_{21}NO_4$ (M^+) 327.1471, found 327.1468; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.49 (s, 1H), 7.28 (d, J = 7.6 Hz, 1H), 7.23 (t, J = 7.2 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.06 (d, J = 7.6 Hz, 1H), 4.00 (s, 3H), 3.66 (s, 3H), 3.47−3.52 (m, 1H), 2.98 (d, J = 19 Hz, 1H), 2.81−2.94 (m, 2H), 2.76 (d, J = 18 Hz, 1H), 2.71−2.77 (m, 1H), 2.20−2.27 (m, 2H), 2.05−2.15 (m, 1H), 1.81−1.86 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.7, 162.4, 160.8, 138.8, 134.3, 133.9, 129.6, 127.41, 127.37, 126.0, 68.3, 60.9, 58.5, 47.2, 41.5, 36.6, 32.9, 25.8, 23.9; IR (film, cm^{-1}) 3056, 2990, 2948, 1668, 1614, 1425, 1377.

Amine 23a. To a solution of **23** (12 mg, 0.035 mmol) in MeOH (2 mL) was added concentrated HCl (30 μL) then the solution was heated to 65 °C for 15 h. The reaction mixture was quenched with 1 N NaOH (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo. Flash chromatography (SiO_2, 4% MeOH in DCM elution) afforded **23a** (7.4 mg, 0.025 mmol, 70%) as a yellow oil. R_f (5% MeOH in DCM elution) 0.33; HRMS (EI) m/z calcd for $C_{18}H_{21}NO_3$ (M^+) 299.1521, found 299.1517; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.10 (t, J = 7.0 Hz, 1H), 7.06 (d, J = 7.5 Hz, 1H), 4.14 (s, 3H), 3.68 (s, 3H), 3.08−3.15 (m, 1H), 2.97 (d, J = 17.0 Hz, 1H), 2.90−2.91 (m, 1H), 2.78−2.83 (m, 1H), 2.66−2.71 (m, 1H), 2.62 (d, J = 16.5 Hz, 1H), 2.39 (s, 1H), 2.21−2.31 (m, 2H), 2.16−2.20 (m, 1H), 1.84−1.90 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.8, 165.7, 142.6, 136.7, 134.7, 129.1, 127.9, 127.0, 126.3, 66.6, 61.6, 61.0, 48.2, 46.7, 42.4, 37.8, 26.9, 25.5; IR (film, cm^{-1}) 3350, 2922, 2854, 1716, 1670, 1609, 1449, 1328, 1243, 1061.

Propellane 7. To a solution of **23a** (7.4 mg, 0.025 mmol) in water (1 mL) was added formaldehyde (0.04 mL, 0.53 mmol) then formic acid (0.04 mL, 0.93 mmol). The reaction mixture was heated to reflux for 15 h, then cooled to rt, diluted with $NaHCO_3$ (10 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo. Flash chromatography (SiO_2, 5% MeOH in DCM elution) afforded **7** (5.7 mg, 0.022 mmol, 74%) as a white solid. R_f (5% MeOH in DCM elution) 0.34; mp 106 °C; HRMS (EI) m/z calcd for $C_{19}H_{23}NO_3$ (M^+) 313.1678, found 313.1668; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, J = 7.5 Hz, 1H), 7.17 (t, J = 7.5 Hz, 1H), 7.08 (t, J = 8.0 Hz, 1H), 7.02 (d, J = 7.0 Hz, 1H), 4.09 (s, 3H), 3.63 (m, 3H), 3.02 (d, J = 16 Hz, 1H), 2.74−2.87 (m, 3H), 2.64 (d, J = 16 Hz, 1H), 2.60−2.65 (m, 1H), 2.53 (s, 3H), 2.20−2.24 (m, 1H), 2.13−2.18 (m, 1H), 2.05−2.11 (m, 1H), 1.97−2.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 165.6, 143.0, 138.3, 135.1, 128.8, 128.0, 126.9, 126.1, 67.5, 61.0, 60.9, 51.6, 48.6, 48.4, 37.6, 36.5, 25.9, 23.0; IR (film, cm^{-1}) 2917, 2845, 2796, 1667, 1597, 1451, 1330, 1245, 1119, 1056.

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Supporting Information Available: Detailed experimental procedure for the synthesis of compounds **9**, **11**, **14**, and **15**, copies of ^{1}H and ^{13}C NMR spectra of **7**, **9**, **11**, **14**−**16**, **19**−**23**, and **23a**, and a CIF file for X-ray data of compound **14a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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