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SYNTHESIS OF 2,3-DISUBSTITUTED INDOLES BY RADICAL CYCLIZATION WITH HYPOPHOSPHOROUS ACID AND ITS APPLICATION TO TOTAL SYNTHESIS OF (±)-CATHARANTHINE†

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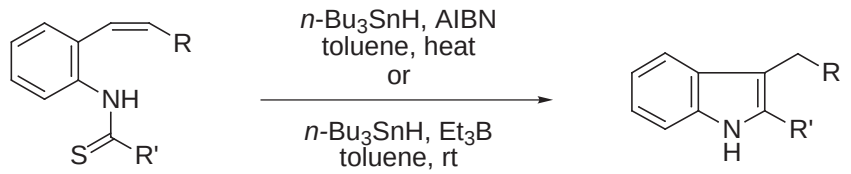
Abstract - Radical cyclization of *o*-alkenylthioanilides using hypophosphorous acid and AIBN in the presence of Et_3N proceeded smoothly to furnish the corresponding 2,3-disubstituted indoles in high yields. Utilizing the newly developed cyclization condition, a stereocontrolled total synthesis of (±)-catharanthine has been completed.

INTRODUCTION

The indole nucleus is an important constituent of a wide variety of natural products.[2] Since numerous indole derivatives display medicinally significant biological activities, the development of synthetic methods of this skeleton has steadily been an active area of research for many years.[3] Recently, we disclosed a novel indole synthesis by radical cyclization of *o*-alkenylthioanilides (**1**),[4] which is effected by tributyltin hydride in the presence of AIBN or Et_3B,[5] to furnish 2,3-disubsituted indoles (**2**) in high yields (Eq. 1). Although tin hydride is the most widely used agent in radical reactions, alternative reducing agents have been extensively investigated due to the toxicity of tin compounds and the difficulty in the removal of organotin impurities after the reaction.[6] Among them, hypophosphorous acid (*a.k.a.* phosphinic acid) reported by Barton *et al.* proved to be particularly effective as a radical reducing agent for organic halides.[7] We have found that hypophosphorous acid could also be employed in our indole synthesis. In particular, this reaction condition is quite effective for the construction of indoles bearing the sterically demanding substituents at 2-position. Taking advantage of this feature, we completed a convergent stereocontrolled total synthesis of (±)-catharanthine.[8] In this article, we describe an indole



1 **2** (1)

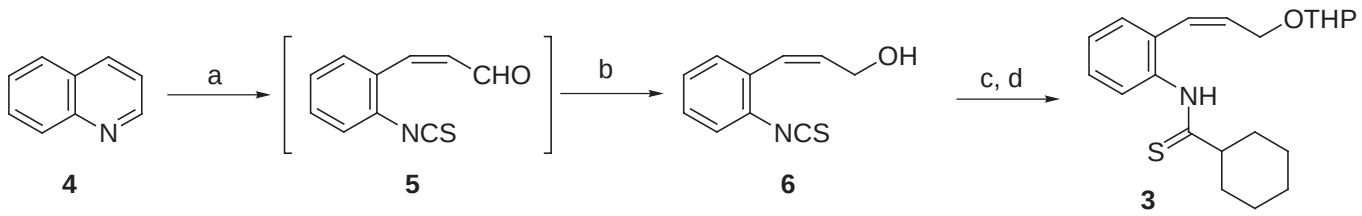
†This paper is dedicated to Professor James P. Kutney on the occasion of his 70th birthday.

synthesis by radical cyclization of *o*-alkenylthioanilides with combination of hypophosphorous acid and AIBN, and its application to the total synthesis of (±)-catharanthine.

RESULTS AND DISCUSSION

Radical Cyclization of *o*-Alkenylthioanilides using Hypophosphorous Acid

We chose thioanilide (**3**) bearing cyclohexyl group as a model compound, which was prepared according to our reported protocol.[4] Deannulation of quinoline (**4**) was carried out by a modified literature procedure[9] to give *cis*-alkenylphenyl isothiocyanate (**5**) (Scheme 1), which was immediately reduced to give the allylic alcohol (**6**). The following protection of the alcohol as THP ether, and addition of cyclohexyl Grignard reagent furnished the desired thioanilide (**3**).



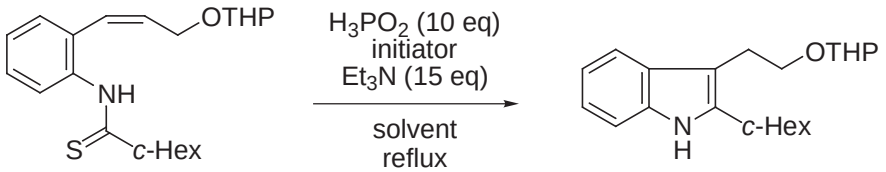
a) $CSCl_2$, $BaCO_3$, CH_2Cl_2/water, 0 °C, 40 min. b) $NaBH_4$, MeOH, 85% (2 steps). c) DHP, CSA, CH_2Cl_2, quant. d) *c*-HexMgBr, THF, 60%.

Scheme 1. Preparation of the Model Compound (**3**).

Having synthesized the model compound, we then examined hypophosphorous acid-mediated radical cyclization conditions. According to Barton's condition,[7a] compound (**3**) was treated with hypophosphorous acid (10 equiv., 50% aqueous solution), triethylamine (15 equiv.), and AIBN (0.4 equiv.) in 1,4-dioxane at 100 °C to afford the desired indole (**7**) in modest yield with recovery of *ca*. 60% of the starting material (Table 1, Entry 1). Reaction with stoichiometric amount of AIBN took place quite smoothly and completed in 20 min to give the indole in 65% yield (Entry 2). While comparable yields of the indole product were also obtained using 1-propanol or ethanol as solvent (Entries 3 and 4), the reaction in toluene proceeded quite slowly possibly because the reaction medium was heterogeneous (Entry 5). Reactions did not proceed using benzoyl peroxide, V-70,[10] or triethylborane as the radical initiator under heating or at room temperature (Entries 6-8).

The new condition provides several advantages over the previously reported tin-mediated reaction conditions. First, it is not necessary to remove organotin impurity after the reaction. The standard work-up is carried out by simple partition between ethyl acetate and 3N HCl, followed by 3N NaOH and brine. Second, since the reaction proceeds even in the presence of water in protic solvents, no special care is necessary to keep the reaction mixture anhydrous or oxygen-free. Unprotected hydroxyl group is, therefore, compatible with the reactions (Eq. 2). Third, this reaction condition is quite effective for installing bulky substituents at indole 2-position. Thus, thioanilide bearing 1-adamantyl group was

Table 1. Hypophosphorous Acid-mediated Radical Cyclization Reaction.

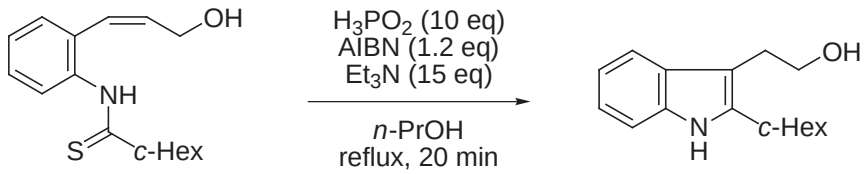


3 **7**

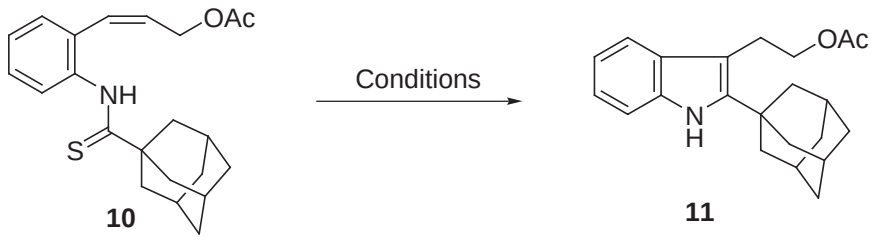
Entry	Initiator (eq)	Solvent	Time (min)	Yield (%)
1	AIBN (0.4)	1,4-dioxane	12 h	35[a]
2	AIBN (1.2)	1,4-dioxane	20	65
3	AIBN (1.2)	*n*-PrOH	20	70
4	AIBN (1.2)	EtOH	30	59
5	AIBN (1.2)	toluene	3 h	trace[g]
6	$(PhCOO)_2$ (0.3)	1,4-dioxane	no reaction	
7[b,c]	V-70[f] (0.1)	EtOH	no reaction	
8[b,d]	Et_3B (0.1)	EtOH	no reaction	
9[b,e]	Et_3B (0.1)	toluene	30	84

a) 57% of the starting thioanilide was recovered. b) The reaction was carried out at room temperature. c) H_3PO_2 (1.5 eq) and Et_3N (2.0 eq) were used. d) H_3PO_2 (5 eq) and Et_3N (6.3 eq) were used. e) *n*-Bu_3SnH (2.0 eq) was used. Without Et_3N. f) V-70 = 2,2'-azobis(4-methoxy-2,4-dimethylvaleronitrile). g) Conversion was slow.

converted into the corresponding indole in 75% yield, whereas tin hydride-mediated reaction gave only 35% of the desired product[4] (Eq. 3).



8 **9** (2)



10 **11** (3)

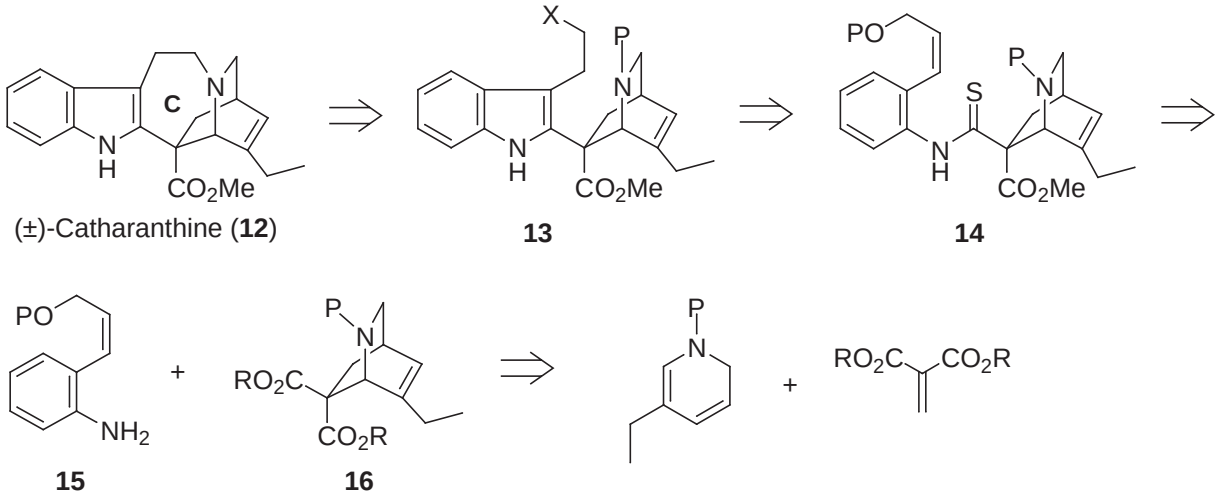
n-Bu_3SnH (1.5 eq), Et_3B (0.1 eq) 35%
toluene, rt, 2 h

H_3PO_2 (10 eq), AIBN (1.2 eq)
Et_3N(15 eq), *n*-PrOH, reflux, 30 min 75%

Stereocontrolled Total Synthesis of (±)-Catharanthine: Application of Hypophosphorous Acid-mediated Indole Formation Reaction

Catharanthine (**12**), is an important member of the *Iboga* class of alkaloids.[11,12] The dense, pentacyclic skeleton of **12** contains a tryptamine fragment substituted at the 2-position by a quaternary carbon center, and thereby represents an attractive challenge to our methodology.

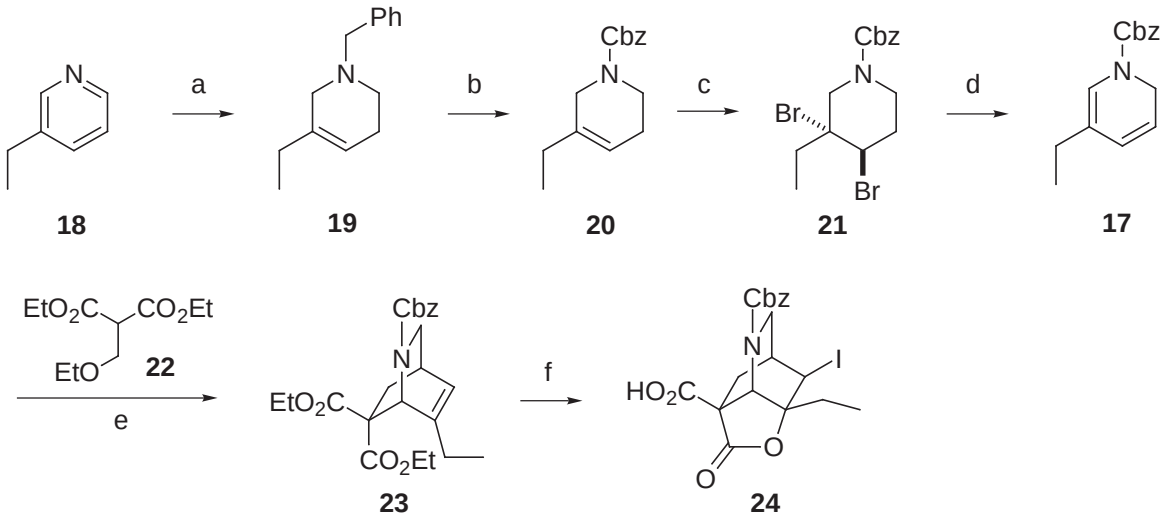
Our synthetic plan is depicted in Scheme 2. The 7-membered C-ring of **12** would be formed by intramolecular alkylation of a fully functionalized, highly preorganized molecule such as **13**. This precursor would be available from a late-stage radical-mediated indole formation reaction carried out upon a 2-alkenylthioanilide similar to **14**. The left and right halves of **14** could be joined by selective amide bond formation between fragments (**15**) and (**16**). The *cis*-2-alkenylaniline (**15**) was available *via* aforementioned deannulation reaction of quinoline.[9] The isoquinuclidine skeleton of **16** could most easily be assembled by a regioselective Diels-Alder reaction.



Scheme 2. Retrosynthetic Analysis of Catharanthine.

Our synthesis begins with the construction of the desired diene (**17**) from commercially available 3-ethylpyridine (**18**) by means of a high-yielding multistep sequence similar to one used by Szántay (Scheme 3).[12h] Pyridine (**18**) was benzylated in quantitative yield and then reduced to the corresponding tetrahydropyridine (**19**). The benzyl group was replaced by a benzyl carbamate to give **20** in 62% overall yield from the pyridinium salt. The trisubstituted double bond was then brominated in 97% yield to afford *trans*-dibromide (**21**). This compound was treated with DABCO to afford the desired diene (**15**) which was predictably somewhat oxygen-sensitive.[13] Diene (**17**) was thus immediately carried on without further purification.

Several earlier syntheses of our target have made use of the regioselective Diels-Alder reaction of dienes such as **17** and 1,1-hetero-disubstituted acrylates.[12] This choice has generally led to diastereomeric



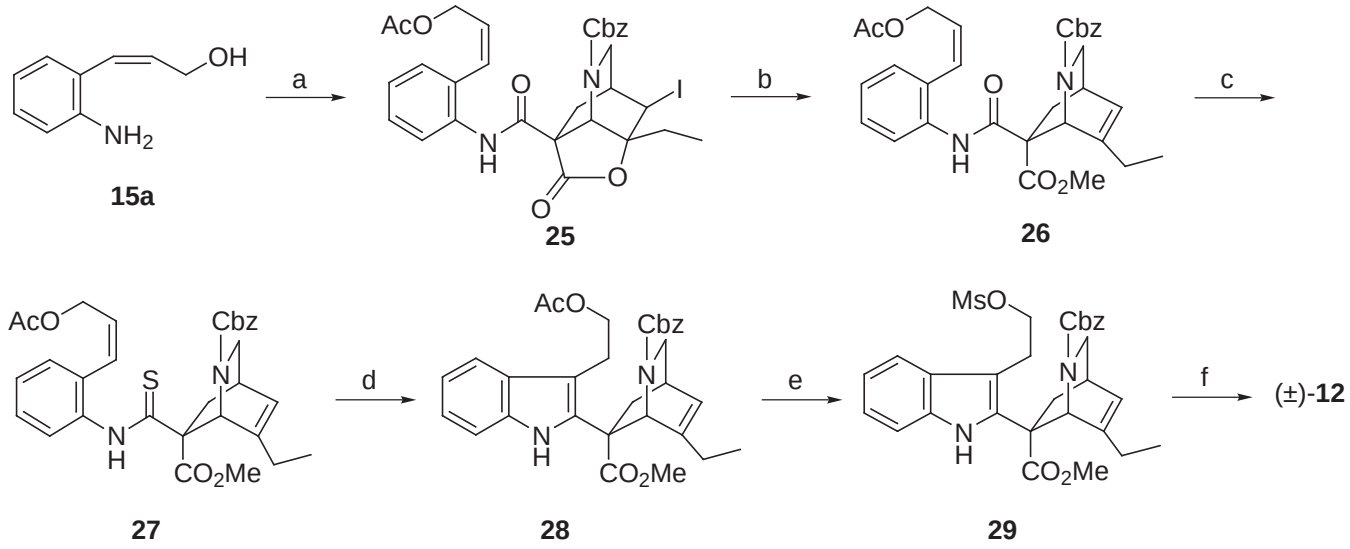
a) i) BnBr, 0 °C to rt. ii) $NaBH_4$, EtOH, 0 °C. b) CbzCl, PhH, 80 °C, 62% (3 steps). c) Br_2, CH_2Cl_2, rt, 97%. d) DABCO, MeCN, 80 °C. e) 100 °C. f) i) KOH, EtOH, H_2O, 80 °C. ii) I_2, $NaHCO_3$, H_2O, rt, 67% (4 steps).

Scheme 3. Synthesis of the Right-hand Fragment.

mixtures of cyclized products due to imperfect *exo/endo* selectivity. To circumvent this problem, we chose to use a 1,1-homo-disubstituted acrylate dienophile, i.e., diethyl methylenemalonate.[14] We found that the desired dienophile could be generated *in situ* from diethyl ethoxymethylmalonate, easily obtained by hydrogenation of commercially available diethyl ethoxymethylenemalonate at atmospheric pressure over palladium on carbon (Scheme 3). Thus, reaction with **17** at 100 °C under argon effected elimination of ethanol followed by cycloaddition to afford the desired diester isoquinuclidine (**23**) with complete regioselectivity. The diester was saponified, and the resulting diacid was then chemoselectively iodolactonized under kinetic conditions to give the desired *endo*-lactone (**24**) in 67% overall yield for the four steps from dibromide (**21**).

Following completion of the right-hand catharanthine precursor (**24**), the fragment (**24**) was condensed with aniline derivative (**15a**)[15] using standard carbodiimide coupling conditions (Scheme 4). After protection of the free primary hydroxyl group to afford anilide iodolactone (**25**) in 74% yield over two steps, iodolactonization was reversed by treatment with zinc and acetic acid, followed by immediate esterification of the free carboxylic acid with diazomethane, providing compound (**26**) in 83% yield. Anilide ester (**26**) was then treated with Lawesson's reagent in refluxing toluene to selectively afford the desired radical cyclization precursor, 2-alkenylthioanilide (**27**), in 86% yield.

Unfortunately, an attempt to construct indole skeleton by treatment of **27** with tributyltin hydride in the presence of triethylborane afforded only low and variable yields (12-22%) of the desired indole (**28**), even with modified procedure in which tin reagent was added slowly to the reaction mixture.[16] Gratefully, however, a marked improvement in yield was noted when cyclization reaction initiated with



a) i) **24**, WSCD, Et_3N, CH_2Cl_2, rt. ii) Ac_2O, pyridine, 74%. b) i) Zn, AcOH, CH_2Cl_2, rt. ii) CH_2N_2, Et_2O, rt, 83% (2 steps). c) Lawesson's reagent, pyridine, toluene, 110 °C, 86%. d) AIBN, H_3PO_2, Et_3N, *n*-PrOH, 90 °C, 40-50%. e) i) K_2CO_3, MeOH. ii) MsCl, Et_3N, CH_2Cl_2, rt, 82% (2 steps). f) Et_3SiH, $Pd(OAc)_2$, Et_3N, EtOH, EtOAc, rt, 96%

Scheme 4. Total Synthesis of (±)-Catharanthine

stoichiometric AIBN in the presence of excess aqueous hypophosphorous acid and triethylamine in refluxing 1-propanol, which reliably afforded the desired indole (**28**) in 40-50% yield.

Having completed the crucial indole cyclization, the final steps of the synthesis proceeded smoothly. The acetate in **28** was replaced with a mesylate to give **29** in 82% yield over two steps, and the benzyl carbamate was then removed under mild and highly selective conditions[17] to directly afford (±)-catharanthine (**12**) in 96% isolated yield.[18]

In summary, we have developed tin-free radical-mediated indole formation reaction by use of a combination of hypophosphorous acid and AIBN. In addition, this condition for the formation of indoles have been successfully applied to a completely stereocontrolled total synthesis of (±)-catharanthine, demonstrating the utility of this radical-based methodology for the construction of complex indole-containing natural products.

EXPERIMENTAL

General. Reagents were either commercially available and used as obtained, or were prepared as noted or according to published methods. Benzene, toluene, and dichloromethane were distilled from CaH_2 and stored over activated molecular sieves (4A). THF, ether, and acetonitrile, methanol, and ethanol were purchased anhydrous and stored over molecular sieves (4A) under argon. *t*-Butanol and 1-propanol were 99%+ reagent grade and used as received. 'Workup', unless otherwise noted, refers to partitioning the reaction mixture between the indicated aqueous and organic phases, followed by separation and extraction

of the aqueous phase and washing of the combined organic phases as indicated. Organic solutions were dried with powdered anhydrous magnesium sulfate. Preparative flash column chromatography was performed using a quantity of silica gel (Merck Silica gel 60, 230-400 mesh) equal to 30 to 50 times sample weight, with gradient elution over the indicated range of solvent mixtures. Preparative thin layer chromatography (PTLC) was carried out on 200 x 65 x 0.5 mm precoated glass plates (Merck Silica gel 60 F254). Yields, unless otherwise stated, refer to isolated yields of compounds judged greater than 95% pure by ^{1}H NMR. Previously reported compounds were identified on the basis of their ^{1}H NMR spectra, while new compounds were further characterized by ^{13}C NMR and IR, and gave satisfactory HRMS spectrographic analyses, unless noted otherwise. NMR spectra were obtained in $CDCl_3$ on a JEOL LA-400 400 MHz spectrometer. All ^{1}H NMR spectra are reported in ppm downfield from tetramethylsilane as an internal standard. All ^{13}C NMR spectra are reported in ppm relative to the central line of the triplet for $CDCl_3$ at 77 ppm. IR spectra were recorded on a JASCO FT/IR-410, and absorptions are reported in cm^{-1}. HRMS were obtained on a JEOL JMS-GCmate MS-DIP20 quadrupole at 70 eV, using direct probe insertion at temperatures of 70 to 330 °C.

2-[(1*Z*)-3-Hydroxy-1-propenyl]phenylisothiocyanate (6)

To a rapidly stirred suspension of $BaCO_3$ (12.9 g, 65 mmol) and quinoline (**4**) (7.60 mL, 65.0 mmol) in a mixture of CH_2Cl_2 (45 mL) and water (45 mL) was added thiophosgene (3.30 mL, 43.3 mmol) at 0 °C under an argon atmosphere. After stirring for 40 min, the suspension was filtered through a pad of Celite and the filter cake was washed with ice-cold CH_2Cl_2 (50 mL) and brine (30 mL). The filtrate was extracted twice with ice-cold CH_2Cl_2 (100 mL). The combined organic extracts were diluted with MeOH (100 mL), followed by addition of $NaBH_4$ (630 mg, 19.3 mmol) in portions at –15 °C. Reaction was immediately quenched by addition of 3 N HCl and the mixture was neutralized with saturated aqueous $NaHCO_3$. After removal of the solvent on a rotary evaporator, the residue was dissolved in Et_2O (400 mL) and the resulting solution was washed with 3 N HCl, sat. $NaHCO_3$, and brine. The solution was then dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator. Purification of the crude product was carried out by recrystallization ($CHCl_3$-hexane) to obtain isothiocyanate (**6**) (5.05 g, 61%) as a yellow crystal. The mother liquor was further purified by flash column chromatography on silica gel (20% EtOAc in hexane) to afford additional product (1.96 g, 24%). mp 81.0-82.1 °C ($CHCl_3$/hexane); IR (film, cm^{-1}) 3323, 3075, 3028, 2870, 2097, 1593, 1567, 1480, 1446, 1018, 932, 764; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 (ddd, *J* = 6.6, 6.6, 1.4 Hz, 2 H), 6.08 (ddd, *J* = 11.7, 6.6, 6.6 Hz, 1H), 6.67 (br d, *J* = 11.7 Hz, 1 H), 7.19-7.29 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 59.6, 126.2, 126.4, 127.0, 128.5, 129.6, 130.1, 133.3, 133.9, 136.1; HRMS (EI) calcd for $C_{10}H_9NOS$: 191.0405, found 191.0403; Anal. Calcd for $C_{10}H_9NOS$: C, 62.80; H, 4.74 N, 7.32. Found: C, 62.85; H, 4.68; N, 7.17.

THP protection of allylic alcohol (6)

To isothiocyanate (**6**) (2.07 g, 10.9 mmol) in CH_2Cl_2 (20 mL) was added 3,4-dihydro-2*H*-pyran (3.0 mL, 32.7 mmol) and camphorsulfonic acid (253 mg, 1.09 mmol). The mixture was stirred at rt for 30 min. To the reaction mixture was added sat. $NaHCO_3$. The separated organic layer was washed with sat. NaCl, dried over $MgSO_4$, and concentrated. THP ether of compound (**6**) (3.01 g, quant.) was isolated by flash column chromatography on silica gel (5% EtOAc in hexane) as a yellow oil. IR (film, cm^{-1}) 2941, 2862, 2094, 1594, 1481, 1447, 1119, 1027, 933, 869, 765; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41-1.88 (m, 6H), 3.45-3.52 (m, 1H), 3.81-3.88 (m, 1H), 4.17 (ddd, *J* = 13.0, 6.8, 1.7 Hz, 1H), 4.41 (ddd, *J* = 13.0, 6.1, 1.7 Hz, 1H), 4.64-4.65 (m, 1H), 6.07 (ddd, *J* = 11.7, 6.8, 6.1 Hz, 1H), 6.69 (ddd, *J* = 11.7, 1.7, 1.7 Hz, 1H), 7.22-7.26 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 25.4, 30.6, 62.3, 64.0, 98.5, 126.4, 126.5, 127.0, 128.4, 129.7, 130.0, 131.9, 133.4, 136.1; HRMS (EI) calcd for $C_{15}H_{17}NO_2S$: 275.0980, found 275.0996.

2-[(1*Z*)-3-[(Tetrahydro-2*H*-pyran-2-yl)oxy]-1-propenyl]cyclohexanecarbothioanilide (3)

To a solution of THP ether of compound (**6**) (58.2 mg, 0.21 mmol) in THF (0.80 mL) was added ether solution of *c*-HexMgCl (2 equiv.) at 0 °C. After stirring for 10 min, the temperature was allowed to rise to rt. The reaction was terminated by addition of sat. NH_4Cl. The mixture was diluted with EtOAc and washed with brine, dried over $MgSO_4$, filtered and concentrated to afford the crude product. The desired thioanilide (**3**) (45.6 mg, 60%) was obtained by flash column chromatography on silica gel (15% EtOAc in hexane) as a yellow oil. IR (film, cm^{-1}) 3324, 2931, 2852, 1449, 1402, 1340, 1285, 1118, 1025, 905, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19-2.05 (m, 18H), 2.26-2.70 (m, 1H), 3.47-3.51 (m, 1H), 3.76-3.82 (m, 1H), 4.01 (ddd, *J* = 12.2, 7.0, 1.2 Hz, 1H), 4.25 (ddd, *J* = 12.2, 6.8, 1.5 Hz, 1H), 4.59 (m, 1H), 6.04 (ddd, *J* = 11.3, 7.0, 6.8 Hz, 1H), 6.55 (br d, *J* = 7.6 Hz, 1H), 7.11 (br d, *J* = 7.6 Hz, 1H), 7.23-7.36 (m, 2H), 7.82 (br d, *J* = 7.8 Hz, 1H), 8.98 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.6, 25.3, 25.6, 26.0, 30.6, 33.0, 55.6, 62.6, 64.0, 98.6, 126.7, 127.0, 127.9, 128.5, 129.7, 131.0, 132.2, 136.4, 210.7; HRMS (EI) calcd for $C_{21}H_{29}NO_2S$ 359.1919, found 359.1901.

2-[(1*Z*)-3-Hydroxy-1-propenyl]cyclohexanecarbothioanilide (8)

Yellow oil (prepared from THP ether (**3**) by treatment of CSA in MeOH). IR (neat, cm^{-1}) 3203, 2930, 2853, 1510, 1450, 1406, 1341, 1010, 729; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21-2.02 (m, 10 H), 2.64-2.70 (m, 1 H), 4.19 (d, *J* = 7.2 Hz, 2 H), 6.03 (dt, *J* = 7.2, 11.6 Hz, 1 H), 6.50 (d, *J* = 11.6 Hz, 1 H), 7.18 (d, *J* = 7.6 Hz, 1 H), 7.29-7.37 (m, 2 H), 7.76 (d, *J* = 8.0 Hz, 1 H), 8.72 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 25.9, 33.0, 55.6, 59.1, 127.0, 127.2, 127.3, 128.0, 130.0, 132.4, 133.3, 136.3, 211.2; LR-MS (EI) 275 (M^+); HRMS (EI) calcd for $C_{16}H_{21}NOS$: 275.1344, found 275.1345.

2-[(1*Z*)-3-(Acetyloxy)-1-propenyl](1-adamantane)carbothioanilide (10)

Yellow oil (synthesized as follows; condensation (**15a**, 1-adamanetanecarbonyl chloride, pyridine, cat. DMAP, CH_2Cl_2, 75%); Ac_2O, pyridine, 97%; Lawesson's reagent, pyridine, toluene, reflux, 84%). IR (film, cm^{-1}) 3327, 2904, 2849, 1736, 1498, 1450, 1346, 1233, 1011, 767; ^1H NMR (400 MHz, $CDCl_3$) δ 1.73-1.81 (m, 6 H), 2.04 (s, 3 H), 2.08-2.09 (m, 6 H), 2.14-2.20 (m, 3 H), 4.63 (dd, *J* = 6.8, 1.5 Hz, 1 H), 5.89 (ddd, *J* = 11.5, 6.8, 6.8 Hz, 1 H), 6.56 (br d, *J* = 11.5 Hz, 1 H), 7.19 (br d, *J* = 7.1 Hz, 1 H), 7.23-7.32 (m, 2 H), 7.70-7.75 (m, 1 H), 8.77 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 28.4, 36.2, 41.8, 46.6, 61.4, 126.4, 127.1, 127.9, 128.1, 128.4, 129.6, 132.1, 136.8, 170.8, 213.7; HRMS (EI) calcd for $C_{22}H_{27}NO_2S$: 369.1762, found 369.1759.

Typical Procedure for Indole Formation using Hypophosphorous Acid and AIBN. 2-Cyclohexyl-3-(2-hydroxyethyl)indole (9)

To thioanilide (**8**) (101.1 mg, 0.367 mmol) in *n*-PrOH (1.8 mL) were added AIBN (66.3 mg, 0.404 mmol), Et_3N (0.77 mL, 5.52 mmol), and H_3PO_2 (50% aqueous solution, 0.40 mL, 3.64 mmol). The mixture was stirred at reflux for 20 min. After cooling to rt, EtOAc was added to the reaction mixture, then the solution was washed with a mixture of 3 N HCl and sat. NaCl (1:2) twice, a mixture of 3 N NaOH and sat. NaCl (1:2) twice, and finally brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. Compound (**9**) (63.8 mg, 71%) was isolated by preparative thin layer chromatography eluting EtOAc/hexane (4:6) as a yellow foam. IR (neat, cm^{-1}) 3538, 3413, 3321, 2927, 2852, 1464, 1294, 1041, 913, 743; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26-1.92 (m, 10 H), 2.87-2.92 (m, 1 H), 3.01 (t, *J* = 6.6 Hz, 2H), 3.83-3.89 (m, 1 H), 7.06-7.16 (m, 2 H), 7.31 (d, *J* = 7.6 Hz, 1 H), 7.54 (d, *J* = 7.8 Hz, 1 H), 7.89 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 26.6, 27.6, 33.4, 35.6, 62.9, 105.5, 110.4, 118.1, 119.2, 121.1, 128.5, 135.1, 141.8; HRMS (EI) calcd for $C_{16}H_{21}NO$: 243.1623, found 243.1621.

2-Cyclohexyl-3-[2-[(tetrahydro-2*H*-pyran-2-yl)oxy]ethyl]indole (7)

Slightly yellow oil. IR (film, cm^{-1}) 3416, 3338, 2926, 2851, 1462, 1350, 1294, 1118, 1024, 904, 808; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25-1.93 (m, 16 H), 2.87-2.94 (m, 1 H), 3.04 (dd, *J* = 7.8, 7.3 Hz, 2 H), 3.40-3.49 (m, 1 H), 3.60 (ddd, *J* = 15.4, 7.3, 7.3 Hz, 1 H), 3.83-3.88 (m, 1 H), 3.94 (ddd, *J* = 15.4, 7.8, 7.8 Hz, 1 H), 4.59-4.61 (m, 1 H), 7.06 (dt, *J* = 7.2, 1.2 Hz, 1 H), 7.10 (dt, *J* = 7.2, 1.5 Hz, 1 H), 7.28 (br d, *J* = 7.2 Hz, 1 H), 7.54 (br d, *J* = 7.2 Hz, 1 H), 7.82 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 24.9, 25.4, 26.0, 26.6, 30.7, 33.3, 35.7, 62.4, 68.1, 99.0, 106.7, 110.3, 118.2, 119.0, 120.8, 128.7, 135.0, 141.0; HRMS (EI) calcd for $C_{21}H_{29}NO_2$: 327.2198, found 327.2220.

2-(Adamane-1-yl)-3-[2-(acetoxy)ethyl]indole (11).

Slightly yellow oil. IR (film, cm^{-1}) 3414, 2905, 2849, 1724, 1462, 1239, 1030, 740; ^1H NMR (400 MHz, $CDCl_3$) δ 1.82 (s, 6 H), 2.08 (s, 3 H), 2.13 (s, 6 H), 2.13 (s, 6 H), (two singlet signals are overlapping),

3.26 (t, *J* = 7.8 Hz, 2 H), 4.29 (t, *J* = 7.8 Hz, 2 H), 7.08 (dt, *J* = 7.1, 1.2 Hz, 1 H), 7.13 (dt, *J* = 7.1, 1.5 Hz, 1 H), 7.29 (br d, *J* = 7.1 Hz, 1 H), 7.59 (br d, *J* = 7.1 Hz, 1 H), 7.97 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 24.8, 28.4, 35.1, 36.5, 41.9, 64.7, 105.0, 110.1, 117.8, 119.0, 121.0, 129.5, 133.7, 142.9, 170.9; HRMS (EI) calcd for $C_{22}H_{27}NO_2$: 337.2042, found 337.2052.

2-[(1*Z*)-3-Hydroxy-1-propenyl]aniline (15a)

Crude 2-(3-hydroxy-1-*cis*-propenyl)phenylisothiocyanate (**6**) (1.65 g, 8.63 mmol) was dissolved in *t*-BuOH (30 mL) and 5 M aqueous KOH (30 mL) and the reaction mixture was heated with vigorous stirring to 80 °C. When TLC analysis indicated complete hydrolysis of the isothiocyanate (and the intermediate 8-membered cyclic urea) had occurred, the mixture was cooled to rt. The reaction mixture was partitioned between Et_2O (30 mL) and sat. NH_4Cl (30 mL), and the aqueous layer was extracted (3 x 10mL Et_2O). The combined organic phases were washed with brine (30 mL), dried over $MgSO_4$ and filtered. The Et_2O was removed under reduced pressure, and flash column chromatography (70% AcOEt in hexane) gave **15a** (63%, 0.81 g, 5.43 mmol) as a slightly yellow oil which solidified on standing. IR (film, cm^{-1}) 3360, 3201, 3019, 2938, 2831, 2635, 1651, 1574, 1489, 1455, 1342, 1269, 1153, 1002, 953, 862, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (br s, 1H), 4.17 (d, *J* = 6.6 Hz, 2 H), 5.93 (dt, *J* = 11.2, 6.6 Hz, 1 H), 6.41 (d, *J* = 11.2 Hz, 1 H), 6.67 (d, *J* = 7.7 Hz, 1H), 6.74 (dd, *J* = 7.3, 7.3 Hz, 1H), 6.92 (d, *J* = 7.3 Hz, 1H), 7.08 (dd, *J* = 7.8, 7.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 59.5, 115.6, 118.5, 122.5, 127.2, 128.6, 129.8, 132.8, 143.7; HRMS (EI) calcd for $C_9H_{11}NO$: 149.0841, found 149.0837.

The conversion of 3-ethylpyridine (**18**) to dihydropyridine (**17**) was carried out by the following modified literature procedure.[12h] All the spectral data of **19**, **20**, **21**, and **17** were identical with those reported.[12h]

1-Benzyloxycarbonyl-3-ethyl-3,4-dehydropiperidine (17)

3-Ethylpyridine (**18**) (17.1 mL, 150 mmol) was cooled to 0 °C in an ice bath. Benzyl bromide (17.8 mL, 150 mmol) was added dropwise with stirring over several min. The reaction mixture evolved heat and turned yellow; after *ca*. 20 min, the reaction mixture grew viscous and rapidly solidified to a yellow glass. This was allowed to warm to rt and was left to stand overnight. The resulting opaque yellow-white solid was broken up with a spatula and ground in a mortar to produce a coarse, off-white powder. This powder was washed with several portions of ether and dried under vacuum to afford 1-benzyl-3-ethylpyridinium bromide as an off-white solid (41.58 g, 99.6%). The pyridinium salt (6.00 g, 21.6 mmol) was dissolved in ethanol (35 mL) in an addition funnel, and added dropwise over 15 min to a stirred suspension of $NaBH_4$ (3.22g, 86.3 mmol) in ethanol (60 mL) cooled to 0 °C on an ice bath. The resulting bright-yellow mixture was allowed to warm slowly to rt overnight with stirring. The solvent was then removed under vacuum and the residue was worked up between water and CH_2Cl_2 (3 x 50 mL, brine) and dried.

Concentration by rotary evaporation afforded crude 1-benzyl-3,4-dehydro-3-ethylpiperidine (**19**) as an orange oil. The crude dehydropiperidine was dissolved in benzene. Benzyl chloroformate (6.17 mL, 43.2 mmol) was added in one portion *via* syringe. The reaction mixture was heated at reflux for 4 h, at which time TLC analysis indicated complete conversion of the starting material. The solvent was removed under vacuum and the residue was purified by flash column chromatography (hexanes/ethyl acetate 15:1-5:1) to afford 1-benzyloxycarbonyl-3,4-dehydro-3-ethylpiperidine (**20**), as a colorless oil (3.28 g, 62% from the pyridinium salt). ^{1}H NMR δ 1.03 (t, *J* = 7.3 Hz, 3H), 1.92 (br s, 2H), 2.13 (br s, 2H), 3.52 (t, *J* = 5.6 Hz, 2H), 3.86 (br s, 2H), 5.22 (s, 2H), 5.52 (br s, 1H), 7.35 (m, 5H).

1-Benzyloxycarbonyl-3,4-*trans*-dibromo-3-ethylpiperidine (21)

The Cbz-protected dehydropiperidine (**20**) (3.28 g, 13.4 mmol) was dissolved in CH_2Cl_2 (50 mL). Bromine (*ca*. 0.69 mL, 13.4 mmol) was added dropwise until the red color persisted. The mixture was stirred an additional 5 min, then decolorized with aq $Na_2S_2O_3$. The mixture was worked up with brine (1 x 20 mL CH_2Cl_2) and dried. Concentration afforded a slightly yellow oil, 1-benzyloxycarbonyl-3,4-dibromo-3-ethylpiperidine (**21**) (5.33 g, 97%). ^{1}H NMR δ 1.14 (m, 3H), 2.02 (m, 3H), 2.78 (m, 1H), 3.33 (m, 2H), 4.19 (m, 2H), 4.62 (s, 1H), 5.17 (br s, 2H), 7.37 (m, 5H).

Diethyl 2-Carboxybenzyloxy-6-ethyl-2-azablcyclo[2.2.2]oct-5-ene-7,7-dicarboxylate (23)

Palladium on carbon (1.0 g, 10% Pd) was suspended in EtOAc (150 mL) and cooled to 0 °C on an ice bath with stirring. The mixture was then purged with hydrogen gas for 10 min. Diethyl ethoxymethylenemalonate (**22**, 10.7 g, 49.4 mmol) was then added *via* syringe in one portion. The reaction mixture was allowed to warm to rt. After 2 h, the reaction mixture was purged with bubbling argon, then filtered through a pad of Celite, and rinsed with CH_2Cl_2. Removal of the solvent under vacuum afforded diethyl ethoxymethylmalonate as a clear, colorless oil (11.0 g, 100%). ^{1}H NMR also indicated the presence of *ca*. 9% diethyl methylmalonate. The mixture was used as obtained in the following step. Dibromo compound (**21**) (5.33 g, 13.2 mmol) and DABCO (5.13 g, 45.7 mmol) were dissolved in acetonitrile (100 mL). The solution was heated to reflux; a white precipitate formed rapidly. After *ca*. 2 h, the mixture was cooled to rt (under argon) and the supernatant was decanted. The precipitate was rinsed (2 x 20 mL CH_2Cl_2) and the combined organic solutions were worked up between CH_2Cl_2 and water (2 x 20 mL CH_2Cl_2, brine), dried, and concentrated under vacuum to afford an orange, slightly cloudy oil (3.03 g, 94% crude yield). Although the ^{1}H NMR spectrum of this oil was consistent with structure (**17**), generally this material was not characterized but immediately used in the next step. Crude dihydropyridine (**17**) and diethyl ethoxymethylmalonate were mixed and pump/purged with argon (3 x). The slightly cloudy orange mixture was heated with stirring under argon under with a condenser at 100 °C overnight. The mixture was then cooled, and the volatiles were removed under vacuum. The

residue was purified by flash column chromatography (hexane/ethyl acetate 10:1-2:1) to afford Diethyl 2-carboxybenzyloxy-6-ethyl-2-azabicyclo[2.2.2]oct-5-ene-7,7-dicarboxylate (**23**), as a clear, slightly yellow oil (6.95 g, >100%). IR (cm^{-1}) 858, 1021, 1108, 1149, 1245, 1412, 1704, 1735, 2879, 2980; ^1H NMR (400 MHz, $CDCl_3$) δ 1.76-1.88 (m, 1H), 2.22-2.44 (m, 2H), 2.51-2.62 (m, 1H), 2.65-2.68 (m, 1H), 2.72-2.82 (m, 1H), 2.86-2.98 (m, 1H), 3.26-3.38 (m, 1H), 4.06-4.25 (m, 4H), 5.06-5.22 (m, 2H), 5.97 (br s, 1H), 7.27-7.37 (m, 5H); HRMS (EI) calcd for $C_{23}H_{29}NO_6$: 415.1995, found 415.2009.

4-Phenylmethyl *rel*-(3*R*,3a*S*,6*S*,7*R*,7a*R*)-7a-Ethyltetrahydro-7-iodo-2-oxo-3,6-methanofuro[3,2-*b*]-pyridine-3,4(2*H*,3a*H*)-dicarboxylate (24)

The diester (**23**) (6.95 g, *ca*. 13.2 mmol) was dissolved in ethanol (50 mL). An aq KOH solution (5 M, 50 mL) was added to give a homogeneous yellow solution, which grew warm to the touch. This mixture was refluxed under argon with stirring for 2 h, until TLC analysis (4:1:1 toluene/formic acid/ethyl formate eluant) showed complete conversion of the starting material The reaction mixture was cooled to rt and diluted with water (20 mL). The mixture was cooled to 0 °C on an ice bath, and acidified (below pH 1) with 4 N HCl (*ca*. 90 mL) with stirring. The mixture was then extracted with ether (50 mL) and the layers separated. The aqueous layer was saturated with NaCl, and extracted with ether (5 x 30 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated by rotary evaporation (bath temperature less than 30 °C) and exposure to vacuum to afford a viscous yellow oil. The crude diacid obtained above was dissolved in sat. $NaHCO_3$ (150 mL) to afford a cloudy white solution. Iodine (3.35 g, 13.2 mmol) was added and the mixture was stirred vigorously. The iodine slowly dissolved to afford a deep brown/purple solution. After stirring overnight, TLC (4:1:1 toluene/formic acid/ethyl formate eluant) showed complete consumption of the starting material. The mixture was carefully acidified with 4 N HCl until the pH was below 1. The mixture was extracted with ether (100 mL). The aqueous layer was saturated with NaCl and extract with ether (5 x 30 mL). The combined organic layers were then decolorized with a small amount of sat. $Na_2S_2O_3$ solution, and washed with brine (10 mL). The solution was dried and concentrated by rotary evaporation; the last traces of solvent were removed by prolonged exposure to vacuum to afford iodolactone (**24**) as a pale yellow foam (4.26 g, 67% over the four steps from dibromide (**21**)). ^1H NMR (400 MHz, $CDCl_3$) δ 1.85-2.02 (m, 2H), 2.28-2.35 (m, 1H), 2.50-2.69 (m, 2H), 3.40-3.58 (m, 2H), 3.93-4.01 (m, 1H), 4.58-4.62 (m, 1H), 5.08-5.27 (m, 2H), 7.26-7.43 (m, 5H); IR (film, cm^{-1}) 734, 930, 964, 1078, 1118, 1176, 1308, 1346, 1422, 1709, 1794, 2944, 2974.

Phenylmethyl *rel*-(3*R*,3a*S*,6*S*,7*R*,7a*R*)-3-[[[2-[(1*Z*)-3-(Acetyloxy)-1-propenyl]phenyl]amino]-carbonyl]-7a-ethylhexahydro-7-iodo-2-oxo-3,6-methanofuro[3,2-*b*]pyridine-4(2*H*)-carboxylate (25)

Iodolactone acid (**24**) (3.9 g, 8.04 mmol), aniline (**15a**) (1.00 g, 6.74 mmol) and water-soluble carbodiimide (1.7 g, 8.75 mmol) were dissolved in CH_2Cl_2 (25 mL) under argon. Et_3N (1.4 mL, 10.11

mmol) was added and the mixture was stirred at rt until TLC indicated complete consumption of the aniline (1.5 h). The reaction mixture was partitioned between 1 N HCl and CH_2Cl_2 (50 mL each); the layers were separated and the organic layers were washed (1 x 50 mL each 1 N HCl, sat. $NaHCO_3$, brine), dried, and concentrated to afford the desired crude anilide as a white foam (4.55 g). The crude material was immediately dissolved in a mixture of Ac_2O (5 mL, 53 mmol) and pyridine (5 mL, 62 mmol) and stirred for 2 h at rt. The mixture was then partitioned between ether and 1 N HCl; the layers were separated and the organic layers were washed (2 x 20 mL sat. $NaHCO_3$, 1 x 10 mL brine), dried, and concentrated to afford a viscous orange-brown oil (4.95 g), which was purified by flash column chromatography (10:1-2:1 hexanes/EtOAc +0.5% Et_3N) to afford the anilide (**25**) as a colorless foam (3.29 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91-2.20 (m, 5H), 2.22-2.30 (m, 1H), 2.45-2.62 (m, 2H), 3.07-3.12 (m, 1H), 3.92-4.08 (m, 1H), 4.58-4.65 (m, 3H), 5.22-5.29 (m, 2H), 5.99-6.14 (m, 1H), 6.60-6.72 (m, 1H), 7.10-7.45 (m, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 9.12 (br s, 0.33H), 9.15 (br s, 0.67H); ^{13}C NMR (Since the compound was found to exist as a mixture of rotamers, the major rotamers was tentatively assigned) δ 8.4, 20.8, 33.4, 33.6, 37.0, 47.1, 50.2, 52.5, 52.9, 61.3, 67.7, 85.7, 121.6, 122.0, 124.7, 127.6, 128.0, 128.2, 128.5, 129.4, 129.7, 129.9, 129.9, 134.6, 134.6, 155.9, 165.5, 170.8, 175.3, 175.3; IR (cm^{-1}): 764, 963, 1234, 1305, 1420, 1535, 1708, 1737, 1764, 2943, 2975, 3325; HRMS (EI) calcd for $C_{30}H_{3l}N_2O_7I$: 658.1176, found: 658.1197.

2-Phenylmethyl 6-Methyl *rel*-(1*R*,4*R*,6*R*)-6-[[[2-[(1*Z*)-3-(Acetyloxy)-1-propenyl]phenyl]amino]-carbonyl]-7-ethyl-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (26)

Anilide (**25**) (3.29 g, 5.00 mmol) was dissolved in CH_2Cl_2 (25 mL) under argon. Powdered zinc (3.3 g, 50 mmol) was added, followed by glacial acetic acid (5.7 mL, 100 mmol) with rapid stirring. The reaction mixture warmed slightly, and was stirred at rt for 30 min. The reaction mixture was passed through Celite to remove excess zinc; the Celite pad was rinsed with several portions each of CH_2Cl_2 and ether. The filtrate was washed (3 x 20 mL 1N HCl), dried, and filtered. The solution volume was reduced to *ca*. 100 mL. To this gently swirled solution was added an ethereal solution of diazomethane (generated at 0 °C from *N*-methyl-*N*-nitrosourea using 50% aq NaOH). The diazomethane solution was added at rt until the bright yellow color persisted for 2-3 min. The yellow solution was quenched with a small amount of AcOH, and then stirred with sat. $NaHCO_3$. The layers were separated and the organic layer was washed (brine), dried, and concentrated to afford a bright yellow oil (3.02 g). This was purified by flash column chromatography (10:1-2:1 hexanes/EtOAc +0.5% Et_3N) to afford the desired methyl ester (**26**) as a clear, viscous, nearly colorless oil (2.26 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90-1.11 (m, 3H), 2.05 (br s, 3H), 2.08-2.30 (m, 2H), 2.60-2.75 (m, 1H), 2.76-3.01 (m, 1H), 3.80-3.95 (m, 1H), 3.75 (br s, 3 H), 4.48-4.83 (m, 3H), 4.99-5.33 (m, 3H), 5.80-6.10 (m, 2H), 6.35 (br d, *J* = 11.2 Hz, 0.3H), 6.67 (br d, *J* = 10.8 Hz, 0.7H), 7.00-7.42 (m, 9H), 7.69 (br d, *J* = 7.6 Hz, 0.7 H), 8.01 (br d, *J* = 6.8

Hz, 0.3 H), 8.24-8.90 (m, 1H); ^{13}C NMR: (Since the compound was found to exist as a mixture of rotamers, the major rotamer was tentatively assigned) δ 11.3, 20.9, 26.6, 30.1, 30.5, 46.8, 53.1, 55.1, 61.3, 61.6, 66.9, 123.4, 125.0, 127.1, 127.5, 127.9, 128.4, 128.4, 128.6, 129.1, 129.3, 134.9, 136.9, 145.3, 155.7, 166.0, 166.1, 170.8, 171.5; IR (cm^{-1}) 760, 1030, 1250, 1451, 1526, 1581, 1702, 1740, 2962, 3382; HRMS (EI) calcd for $C_{31}H_{34}N_2O_7$: 546.2366; found 546.2363.

2-Phenylmethyl 6-Methyl *rel*-(1*R*,4*R*,6*S*)-6-[[[2-[(1*Z*)-3-(Acetyloxy)-1-propenyl]phenyl]amino]-thioxomethyl]-7-ethyl-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (27)

Anilide (**26**) (2.26 g, 4.13 mmol) was dissolved in toluene (50 mL) under argon. Lawesson's reagent (5.02 g, 12.4 mmol) was added, followed by pyridine (0.17 mL, 2.1 mmol). The mixture was stirred at reflux under a condenser and argon balloon overnight. The mixture was cooled to rt, and worked up (sat. $NaHCO_3$/ether, brine), dried, and concentrated. The resulting bright-yellow oil was purified by flash column chromatography (5:1-1:5 hexanes/CH_2Cl_2 +1% MeOH) to afford thioanilide (**27**) as pale-yellow foam (2.00 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90-1.12 (m, 3H), 2.03 (s, 3H), 2.09-2.25 (m, 2H), 2.50-3.04 (m, 4H), 3.32-3.50 (m, 2H), 3.68-3.80 (m, 1H), 4.50-4.79 (m, 2H), 5.00-5.24 (m, 2H), 5.40 (br s, 1H), 5.77-5.89 (m, 1H), 6.04-6.18 (m, 1H), 6.40-6.58 (m, 1H), 7.01-7.43 (m, 9H), 10.00-10.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (Since the compound was found to exist as a mixture of rotamers, the major rotamer was tentatively assigned) δ 11.3, 20.9, 26.4, 30.8, 35.1, 47.8, 53.0, 54.7, 61.3, 67.5, 127.5, 127.6, 127.7128.1, 128.5, 128.5, 129.1, 129.8, 133.0, 136.1, 137.2, 144.1, 156.7, 170.4, 170.8, 201.7; IR (cm^{-1}) 761, 1101, 1238, 1370, 1417, 1507, 1699, 1739, 2962; HRMS (EI) calcd for $C_{31}H_{34}N_2O_6S$: 562.2138; found: 562.2125.

2-Phenylmethyl 6-Methyl *rel*-(1*R*,4*R*,6*R*)-6-[3-[2-(Acetyloxy)ethyl]-1*H*-indol-2-yl]-7-ethyl-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (28)

Thioanilide (**27**) (414 mg, 0.74 mmol) was dissolved in 1-propanol (5 mL) under argon along with AIBN (133 mg, 0.81 mmol), hypophosphorous acid (30% aqueous solution, 1.4 mL, 7.4 mmol), and Et_3N (1.55 mL, 11.1 mmol). The mixture warmed slightly, and was stirred in a 90 °C oil bath under a reflux condenser and argon balloon. After 45 min, TLC indicated complete consumption of the starting material. The mixture was cooled to rt and diluted with ether (20 mL). Workup (1 N HCl, 1N NaOH, brine), drying, and concentration afforded a yellow oil, which was purified by flash column chromatography (10:1-5:1 hexanes/EtOAc +0.5% Et_3N) to give the desired indole (**28**) as a clear, faintly yellow oil (198 mg, 50%). IR (film, cm^{-1}) 737, 1083, 1244, 1419, 1457, 1672, 1698, 1738, 2962, 3298; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (t, *J* = 7.6 Hz, 3H), 1.91 (d, *J* = 10.8 Hz, 1H), 2.04 (s, 3H), 2.18 (m, 2H), 2.90-3.20 (m, 5H), 3.54 (s, 3H), 3.60 (m, 1H), 4.14 (m, 1H), 4.25 (m, 1H), 5.12 (q, *J* = 15.6, 10.8 Hz, 2H), 5.48 (s, 1H), 6.11 (d, *J* = 5.6 Hz, 1H), 7.09 (t, *J* = 8.0 Hz, 1H), 7.17 (t, *J* = 7.2 Hz, 1H), 7.38 (d, *J* = 8.0 Hz,

1H), 7.60 (d, *J* = 8.0 Hz, 1H), 9.96 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4, 21.1, 23.4, 24.3, 25.1, 26.5, 30.8, 34.9, 48.4, 52.6, 53.5, 63.8, 67.6, 108.4, 111.6, 118.5, 119.3, 121.8, 126.7, 127.7, 128.1, 128.5, 128.7, 135.2, 135.5, 136.1, 144.5, 156.9, 171.0, 171.4, (1 obscured peak); HRMS (EI) calcd for $C_{31}H_{34}N_2O_6$: 530.2417, found 530.2406.

2-Phenylmethyl 6-Methyl *rel*-(1*R*,4*R*,6*R*)-7-Ethyl-6-[3-[2-[(methylsulfonyl)oxy]ethyl]-1*H*-indol-2-yl]-2-azabicyclo[2.2.2]oct-7-ene-2,6-dicarboxylate (29)

Acetate-indole (**28**) (166 mg, 0.29 mmol) was dissolved in dry methanol (5 mL) under argon. K_2CO_3 (powdered anhydrous, 200 mg, 1.45 mmol) was added and the mixture was stirred vigorously for 30 min at rt. The mixture was partitioned between ether and water, and worked up (ether, brine), dried, and concentrated to afford a white foam (152 mg). The crude material was immediately dissolved in dry CH_2Cl_2 (2 mL) and treated with mesyl chloride (27 μL, 0.35 mmol) and Et_3N (53 μL, 0.38 mmol). The mixture was stirred for 20 min at rt. The mixture was partitioned between 1N HCl and ether, and worked up (ether, $NaHCO_3$, brine), dried, and concentrated to afford the crude product as a yellow oil (176 mg). This material was purified by flash column chromatography (10:1-2:1 hexanes/EtOAc +0.5% Et_3N) to afford the desired mesylate (**29**) as a white foam (135 mg, 82%). IR (cm^{-1}) 737, 952, 1174, 1355, 1421, 1458, 1671, 1735, 2962, 3296; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (t, *J* = 6.8 Hz, 3H), 1.88 (d, *J* = 12.8 Hz, 1H), 2.17 (m, 2H), 2.78 (s, 3H), 2.93 (m, 2H), 3.21 (m, 5H), 3.57 (s, 3H), 4.25 (m, 1H), 4.35 (m, 1H), 5.17 (s, 2H), 5.62 (s, 1H), 6.12 (br d, *J* = 6.0 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 10.06 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.3, 24.9, 26.5, 30.7, 34.9, 37.2, 48.4, 52.7, 53.4, 53.5, 67.6, 68.9, 106.6, 111.8, 118.0, 119.6, 122.0, 126.8, 127.7, 128.1, 128.3, 128.4, 135.1, 136.0, 136.1, 144.4, 157.0, 171.5 (2 obscured peaks); HRMS (EI) calcd for $C_{30}H_{34}N_2O_6S$: 566.2087, found 566.2088.

(±)-Catharanthine (12)

Mesylate (**27**) (82 mg, 0.14 mmol) was dissolved in EtOAc (passed through Al_2O_3, 0.5 mL) along with $Pd(OAc)_2$ (11 mg, 0.05 mmol) under argon. Dry ethanol (0.5 mL) was added and the mixture was stirred at rt for 3 min (orange solution slowly turned red/brown). Triethylsilane (50 μL, 0.29 mmol) was added, and the mixture bubbled, warmed, and rapidly turned black. Et_3N (20 μL, 0.14 mmol) was added immediately. The mixture was stirred at rt for 15 min. The reaction mixture was diluted with CH_2Cl_2, and filtered through Celite to remove the precipitated palladium. The filtrate was worked up (CH_2Cl_2, $NaHCO_3$), dried, and concentrated. The crude material was purified by PTLC (two 200 x 65 x 0.5 mm plates, double elution with 1:1 hexanes/EtOAc +0.5% Et_3N) to afford (±)-catharanthine (**12**), as a white powder (45 mg, 96%). mp 163-166 °C decomp (recrystallized from $CHCl_3$; lit., mp 163-164 °C from Et_2O[12g]; mp 175-176 °C decomp from MeOH[12f]); IR (cm^{-1}) 741, 909, 1078, 1267, 1460, 1713, 2844, 2961, 3375; ^{1}H

NMR (400 MHz, $CDCl_3$) δ 1.07 (t, *J* = 6.8 Hz, 3H), 1.77 (dd, *J* = 13.6, 3.6 Hz, 1H), 2.09 (m, 1H), 2.31 (m, 1H), 2.72 (br d, *J* = 6.8 Hz, 1H), 2.81-2.94 (m, 3H), 3.25-3.40 (m, 3H), 3.56 (m, 1H), 3.73 (s, 3H), 4.17 (s, 1H), 5.92 (br d, 1H), 7.08-7.16 (overlapping triplets, 2H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.68, (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.6, 21.4, 28.2, 30.7, 88.7, 49.3, 52.3, 53.0, 55.4, 61.9, 110.4, 110.7, 118.2, 119.4, 121.8, 123.5, 129.0, 134.9, 136.4, 149.4, 174.2; HRMS (EI) calcd for $C_{21}H_{24}N_2O_2$: 336.1838, found 336.1846. The structure was further confirmed by ^1H-^1H COSY, DEPT, and HMQC (^1H-^{13}C correlation) NMR measurements (data not shown).

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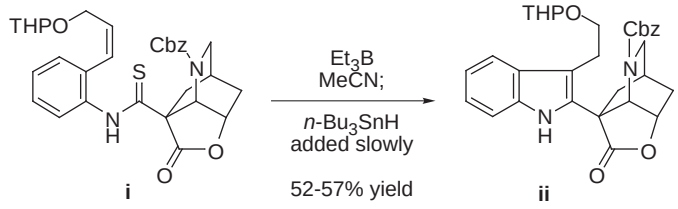
13. Compound (**17**) could be handled briefly (<1 h) in air and was stable to neutral aqueous workup. Exposure to air over longer periods resulted in decomposition.

14. This compound, while known, readily polymerizes even at low temperature. The reference calls for hydrogenation over Raney nickel at 1000 psi and 45 °C. This procedure results in the formation of appreciable amounts (~20%) of diethyl methylmalonate from *in situ* elimination of ethanol and subsequent hydrogenation. The milder conditions reported here afford the desired compound in greater than 90% purity (by ^{1}H NMR integration). W. Feely and V. Boekelheide, *Org. Synth., Coll. Vol. IV*, 1963, 298.

15. The aniline derivative (**15a**) was prepared by alkaline hydrolysis of isothiocyanate (**6**) (see, experimental).

16. A model study using compound (**i**) indicated that indole formation could be successfully executed in acceptable yields by a modified procedure in which THF solution of *n*-Bu_3SnH was added to the reaction mixture over *ca.* 10 min at rt.



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of the Cbz group. (M. T. Reding and T. Fukuyama, unpublished results.)

18. The analytical data of the material obtained by this route was in accord with that reported in the literature for (±)-catharanthine (ref. 12f).