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Conjugate Addition−Dipolar Cycloaddition Cascade for the Synthesis of Benzo[*a*]quinolizine and Indolo[*a*]quinolizine Scaffolds: Application to the Total Synthesis of (±)-Yohimbenone

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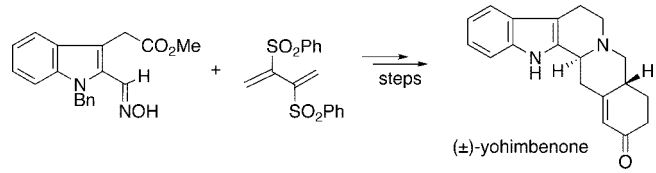

A highly efficient total synthesis of (±)-yohimbenone and a formal synthesis of (±)-emetine is described. The key element of the synthesis consists of a conjugate addition−dipolar cycloaddition of 2,3-bis(phenylsulfonyl)-1,3-butadiene with an appropriate oxime. The resulting cycloadducts are cleaved reductively to provide azapolycyclic scaffolds with strategically placed functionality for further manipulation to the target compounds.

Introduction

The tricyclic benzo[*a*]quinolizine ring system (**1**) is a common structural motif found in a wide variety of physiologically active compounds.[1−4] The core skeleton is present in berberine (**2**),[5] emetine (**3**),[6] and several other related ipecac alkaloids[7] that exhibit potent clinical activity such as glucosidase inhibition,[8] antiamebic properties,[9] as well as activity against breast cancer tumor cell lines.[10] In addition, benzo[*a*]quinolizines bind to the benzodiazepine receptor and mimic the physiological effects typical for benzodiazepine drugs.[11] In light of this broad array of biological activity, many methods for the construction of these polycyclic heterocycles are known.[12] Thus, more than two dozen syntheses of emetine have been described in the literature which showcase many elegant and important synthetic transformations.[3] Several of the emetine syntheses proceed by closure of ring B by a Bischler−Napieralski reaction[13] or by related palladium-catalyzed cyclizations.[14] Another method that has

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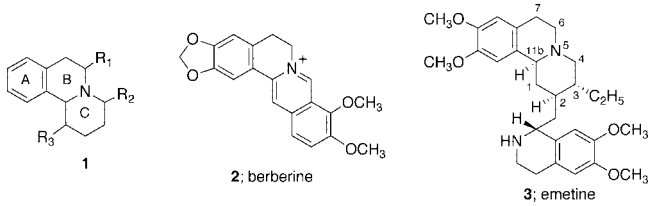


FIGURE 1. Some benzo[*a*]quinolizine alkaloids.

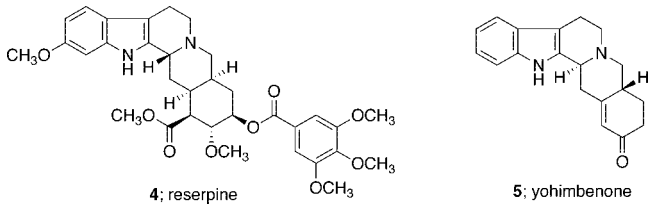


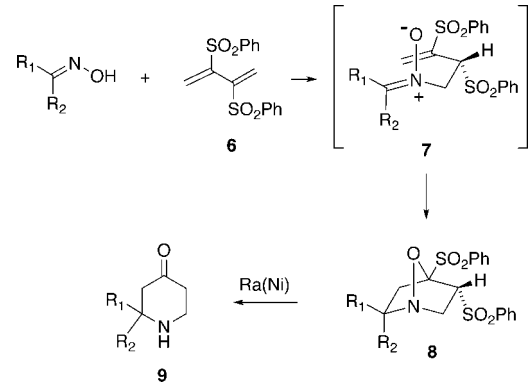
FIGURE 2. Some typical indolo[*a*]quinolizine alkaloids.

frequently been used involves the formation of the C_1-C_{11b} bond via a Mannich-type cyclization of a dihydroisoquinolinum ion.[15]

It has already been noted in several review articles[16] that a structural and biosynthetic parallelism exists between the ipecac and the rauwolfia class of indole alkaloids.[17] Representative examples of the rauwolfia family include reserpine (**4**) and yohimbenone (**5**). These alkaloids have attracted a great deal of attention from synthetic chemists as a consequence of their medicinal properties and intriguing molecular structures.[18] The historic total synthesis of reserpine by Woodward is often cited as a model of strategy in synthetic organic chemistry.[19] The challenges associated with the construction of the stereochemically complex indolo[*a*]quinolizine ring system have stimulated the development of a number of imaginative synthetic approaches.[20] A major problem in these syntheses is the generation of the proper stereochemistry at the C_3-position. Several studies have been conducted to understand and control this critical stereochemical issue.[21]

The rauwolfia alkaloid yohimbenone (**5**) has often served as a testing ground to evaluate the utility of different synthetic methodologies.[22] In this paper, we report on a formal synthesis of (±)-emetine (**3**) and a total synthesis of yohimbenone (**5**) by

SCHEME 1



a completely new method which is generally applicable to the synthesis of both the ipecac and yohimbine alkaloids. The approach to be described herein is based on our previous success utilizing the cycloaddition reaction of oximes with 2,3-bis(phenylsulfonyl)-1,3-butadiene (**6**).[23]

Results and Discussion

In previous work, we described the reaction of oximes with 2,3-bis(phenylsulfonyl)-1,3-butadiene (**6**) followed by a [3 + 2]-cycloaddition of the resulting nitrone as a method for constructing functionalized piperidone ring systems.[23] The first step in the cascade sequence was shown to involve conjugate addition to diene **6**, and this was followed by proton transfer to create a transient nitrone **7** that undergoes a subsequent 1,3-dipolar cycloaddition with the tethered vinyl sulfone (Scheme 1).[24] The regiochemistry of the cycloaddition is presumably controlled by nonbonded interactions in the transition state for the cycloaddition.

Reductive N−O cleavage of the resulting cycloadduct **8** provides functionalized piperidones of type **9**. Our laboratory has recently begun the exploration of this methodology as an efficient strategy to access a diverse group of azapolycyclic natural products.[25] As a further demonstration of its potential, we report herein on a flexible route that was devised to allow entry to both the isoquinoline and pentacyclic framework of the rauwolfia alkaloids. The principal advantage of the method is the presence of the vestigial sulfonyl substituent that allows further elaboration through site-specific enolate chemistry.

Our retrosynthetic analysis (Scheme 2) reveals a potentially convenient route to both of these alkaloids based on the above conjugate addition−dipolar cycloaddition cascade. Our plan involves formation of a dipolar cycloadduct (i.e., **12**) that can

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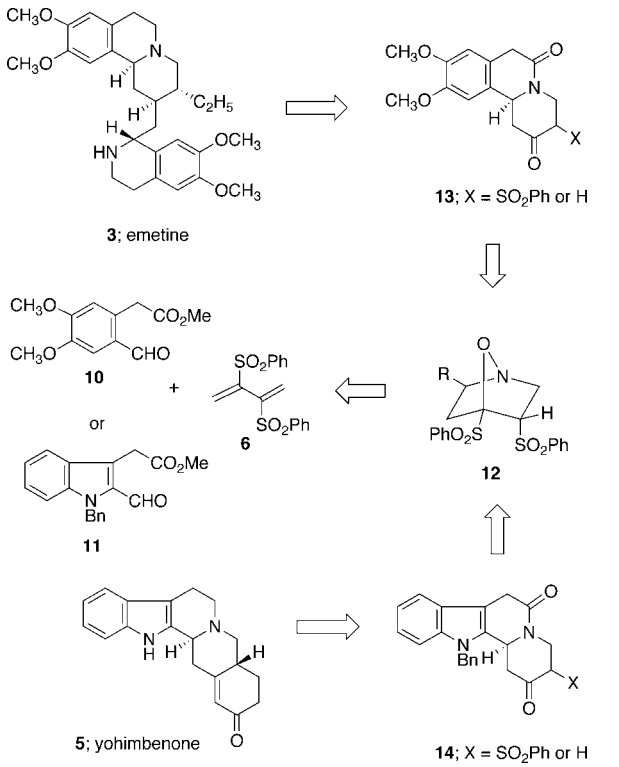
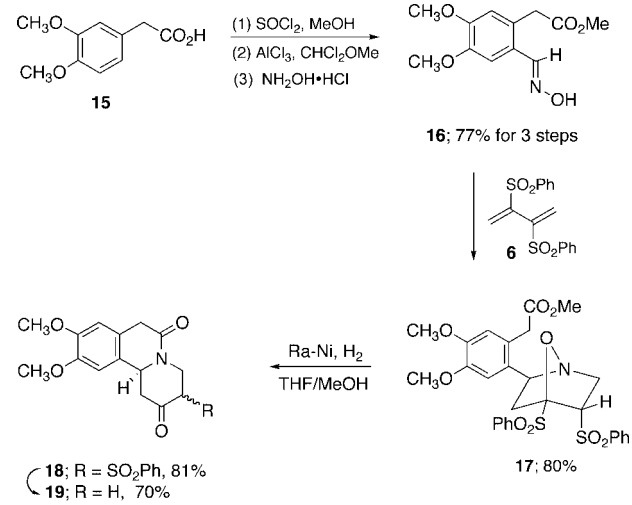
SCHEME 2



SCHEME 3



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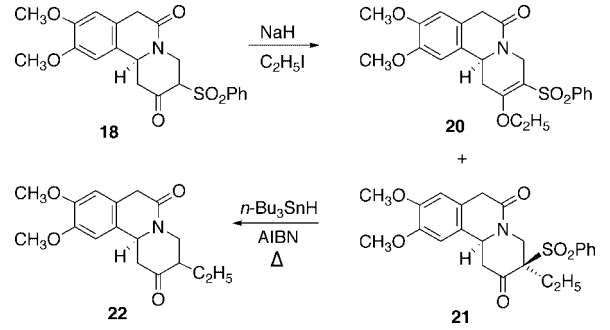

be obtained from the reaction of diene **6** with the oxime derived from either benzaldehyde **10** or the indole aldehyde **11**. We envisage that the appropriately positioned ester in the dipolar cycloadduct would undergo condensation with the resulting secondary amine after reductive N−O cleavage. This cyclization would provide either the pyrido[2,1-*a*]isoquinoline-2,6-dione **13** or the indolo[2,3-*a*]quinolizine-2,6-dione **14** which, after suitable modification, would be expected to give the desired natural products.

Our initial efforts focused on the benzo[*a*]quinolizine scaffold as we reasoned that this system might serve as a model for an eventual approach toward yohimbenone (**5**). Consequently, oxime **16** was prepared from commercially available carboxylic acid **15** by esterification followed by formylation with dichloromethyl methyl ether in the presence of aluminum chloride,[26] which afforded aldehyde **10** in 79% yield. Condensation of **10** with hydroxylamine hydrochloride in methanol provided oxime **16** in 97% yield. The addition of **16** to diene **6** afforded cycloadduct **17** as a single diastereomer in 80% yield. N,O-Reduction of cycloadduct **17** was readily accomplished using Ra−Ni under a hydrogen atmosphere in THF which furnished the cyclized lactam **18** in 81% yield as a 5:1 mixture of diastereomers. Further reduction of the phenylsulfonyl group present in **18** could be carried out using radical reduction conditions (i.e., *n*-Bu_3SnH, AIBN) which produced dihydroisoquinolinedione **19** in 70% yield (Scheme 3).[27]

Our initial attempts to introduce an ethyl group into the C_3-position (according to emetine numbering) involved using the enolate anion derived from **19** with ethyl iodide, and this led to a mixture of products. Instead, keto sulfone **18** was sequentially treated with NaH in DMF followed by the addition of EtI which afforded a 1:1 mixture of the *O*- and *C*-alkylated sulfones **20** and **21** in 86% yield. Radical reduction of **21** furnished **22** as a 7:1 mixture of diastereomers in 75% yield (Scheme 4).

With the key benzoquinolizine intermediate **18** in hand, a Robinson annulation strategy was next explored as a means of stitching together the D-ring.[28] To this end, the conjugate addition of **18** to methyl vinyl ketone was carried out using catalytic triethylamine, which afforded a 1:1 mixture of diastereomers of compound **23** in 84% yield. Treatment of the crude product with pyrrolidine and acetic acid furnished the unexpected benzoisoquinolinone **25** in 76% yield. We assume that the first step of this reaction involves generation of the expected enamine which then undergoes a subsequent addition to the neighboring carbonyl group to produce iminium ion **24** as a transient species. Proton loss followed by elimination of both water and phenylsulfonic acid nicely accounts for the formation of the observed product (Scheme 5).[30]

Considering the difficulty we encountered with the pyrrolidine-induced Robinson annulation reaction, we modified the cyclization conditions. Thus, cleavage of the phenylsulfonyl group in **23** was first carried out using *n*-Bu_3SnH/AIBN which afforded the desulfonylated product **26** as a 3:1 mixture of

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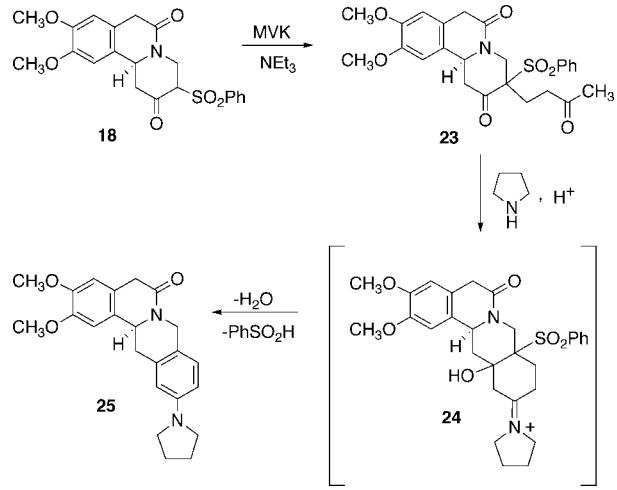
SCHEME 5



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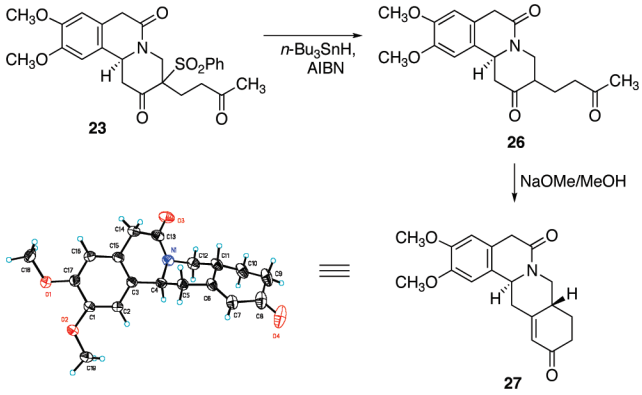
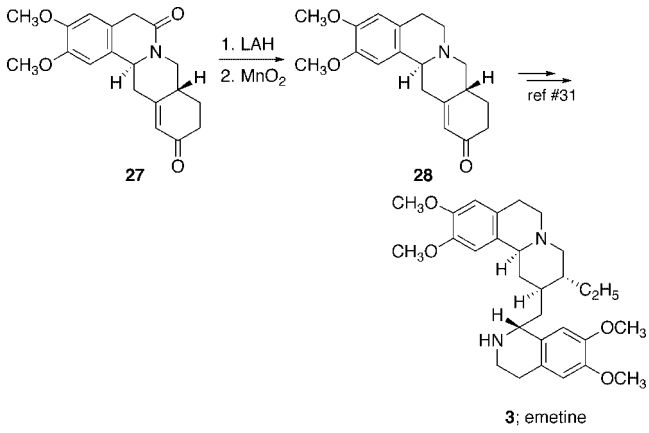


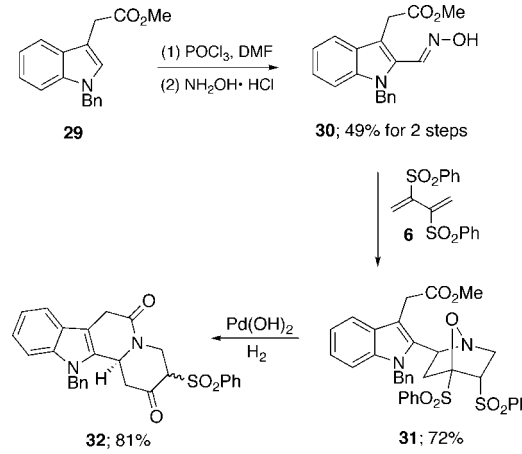
SCHEME 7



diastereomers in 87% yield. The intramolecular aldol cyclization of **26** with sodium methoxide in methanol at room temperature gave **27** in 70% yield. An X-ray crystal structure of **27** confirmed the stereochemical assignment. As anticipated, compound **27** has the same relative stereochemistry as emetine, with both alkyl groups of the piperidone ring occupying the thermodynamically more favorable equatorial position (Scheme 6).[29]

Reduction of the lactam functionality present in **27** by employing Lawesson's reagent for the initial conversion to the corresponding thioamide followed by Raney nickel reduction proved to be ineffective. Instead, lithium aluminum hydride was employed to reduce both the enone carbonyl group and amido

SCHEME 8



group. Reoxidation of the resulting allylic alcohol mixture with manganese oxide provided enone **28** (Scheme 7). The formation of intermediate **28** represents a formal synthesis of (±)-emetine (**3**) since **28** had been carried on to **3** by Takano and co-workers.[31] Most importantly, the above cascade method represents a viable approach toward synthesizing compounds containing an isoquinoline substructure. As further proof of principle we decided to pursue a synthesis of the structurally related yohimbenone alkaloid using this methodology.

Our synthesis of the yohimbane core starts with a Vilsmeier–Haack formylation[32] of the known indole **29**.[33] Conversion of the resulting aldehyde **11** to the corresponding oxime **30** was uneventfully accomplished with hydroxylamine hydrochloride. Treatment of **30** with diene **6** under conditions similar to those used in the emetine synthesis resulted in a smooth conjugate addition/[3 + 2]-cycloaddition cascade to give cycloadduct **31** in 72% yield (Scheme 8). Reductive N–O cleavage of **31** using $Pd(OH)_2$ with acetic acid in ethyl acetate under pressurized hydrogen (45 psi)[34] afforded the key ABCD yohimbane ring structure **32** in 81% yield as a 2:1 mixture of diastereomers. As was the case in the emetine synthesis, methyl vinyl ketone was added followed by reductive removal of the phenyl sulfonyl group to give **33** in 91% yield over the two steps. While satisfactory results were obtained for the intramolecular aldol condensation of **33** using NaOMe/MeOH, we found that the utilization of an enamine rather than an enolate anion was a more reliable method for forming the final E ring in **34** and the cyclization reaction occurred in 78% yield. Reduction of **34** with LAH followed by reoxidation with MnO_2 and then removal of the benzyl protecting group[35] provided (±)-yohimbenone (**5**)[36] in 72% yield over the three steps (Scheme 9).

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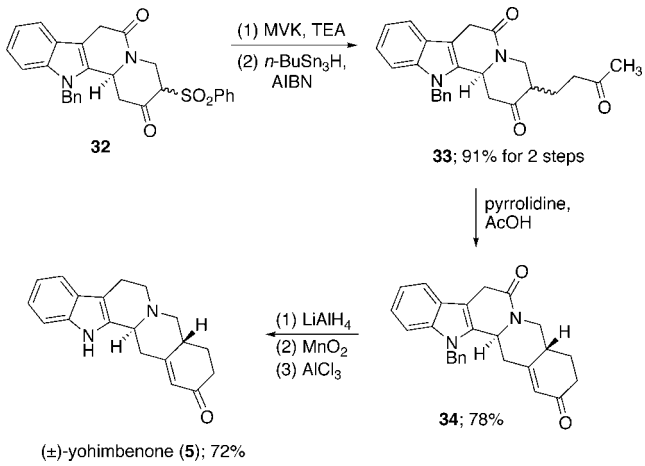
SCHEME 9



In conclusion, a synthesis of (±)-yohimbenone (**5**) has been accomplished. The key element of the synthesis consists of a conjugate addition−dipolar cycloaddition of 2,3-bis(phenylsulfonyl)-1,3-butadiene with the oxime derived from methyl 2-(1-benzyl-2-formyl-1*H*-indol-3-yl)acetate. The resulting cycloadduct was converted into (±)-yohimbenone by (1) reductive cleavage of the bicyclic isoxazolidine adduct, (2) cyclization of the resulting secondary amine onto the adjacent methyl ester, (3) conjugate addition with MVK and subsequent sulfone reduction, and (4) Robinson annulation followed by functional group manipulation. We have also achieved a formal synthesis of (±)-emetine (**3**) by intercepting Takano's intermediate **28** using a similar cascade strategy. The applicability of the new methodology to other alkaloid targets is currently under study and will be the subject of future reports.

Experimental Section

Methyl 2-(2-((Hydroxyimino)methyl)-4,5-dimethoxyphenyl)acetate (16). To a solution containing 10.0 g (51 mmol) of 2-(3,4-dimethoxyphenyl)acetic acid (**15**) in 100 mL of methanol at −78 °C was added 7.5 g (61 mmol) of thionyl chloride. The resulting solution was warmed to 25 °C and was stirred for 12 h before being concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with a saturated aqueous $NaHCO_3$ solution and brine. The organic layer was concentrated under reduced pressure to provide 10.1 g (94%) of methyl 2-(3,4-dimethoxyphenyl)acetate[37] which was used in the next step without further purification.

To a solution of 2.0 g (9.5 mmol) of the above compound in 50 mL of CH_2Cl_2 at 0 °C was added 2.5 g (19 mmol) of $AlCl_3$ in several portions over a 10 min period. To this mixture was added 1.7 g (13 mmol) of dichloromethyl methyl ether at 0 °C. The resulting solution was stirred for an additional 1 h at 0 °C, warmed to 25 °C, and stirred for 12 h. The reaction mixture was poured into ice−water and extracted with CH_2Cl_2. The combined organic layer was washed with a 5% aqueous KOH solution, dried over Na_2SO_4, and concentrated under reduced pressure yielding 1.8 g (79%) of methyl 2-(2-formyl-4,5-dimethoxyphenyl)acetate[37] (**10**) which was used in the next step without further purification.

To a solution containing 1.8 g (7.5 mmol) of the above aldehyde in 50 mL of methanol was added sequentially 0.6 g (8.2 mmol) of hydroxylamine hydrochloride and 1.2 g (15 mmol) of sodium acetate. After being stirred at 25 °C for 12 h, the solution was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with water and brine, and dried over Na_2SO_4. Concentration under reduced pressure left behind a residue which was purified using flash silica gel chromatography to provide 1.8 g (97%) of methyl 2-(2-((hydroxyimino)methyl)-4,5-dimethoxyphenyl)acetate (**16**) as a white solid: mp 120−122 °C; IR (neat) 3442, 1731, 1598, 1516, and 1275 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.69 (s, 3H), 3.74 (s, 2H), 3.89 (s, 3H), 3.91 (s, 3H), 6.74 (s, 1H), 7.20 (s, 1H), 8.22 (s, 1H), and 8.33 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 38.8, 52.5, 56.1, 109.8, 114.0, 123.5, 126.2, 148.5, 148.9, 150.4, and 172.0; HRMS calcd for [$C_{12}H_{15}NO_5$ + H^+] 254.1028, found 254.1033.

2-(4,5-Bis-benzenesulfonyl-7-oxa-1-azabicyclo[2.2.1]hept-2-yl)-4,5-dimethoxyphenyl]acetic Acid Methyl Ester (17). A mixture containing 3.7 g (11 mmol) of 2,3-bis(phenylsulfonyl)-1,3-butadiene[23] (**6**) and 2.6 g (10.1 mmol) of the above oxime **16** in 165 mL of toluene was heated for 24 h at 125 °C. The solution was concentrated under reduced pressure, and the resulting residue was purified using flash silica gel chromatography to provide 4.75 g (80%) of the titled compound **17** as a white solid: mp 186−187 °C; IR (neat) 2950, 1731, 1516, 1445, and 1327 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.08−2.14 (ddd, 1H, J = 19.2, 8.4, and 3.6 Hz), 3.41 (s, 3H), 3.56 (d, 1H, J = 16.0 Hz), 3.63 (d, 1H, J = 16.0 Hz), 3.68−3.71 (m, 1H), 3.74 (s, 3H), 3.77−3.78 (m, 2H), 3.80 (s, 3H), 4.58−4.62 (m, 2H), 6.40 (s, 1H), 6.59 (s, 1H), 7.49−7.53 (m, 2H), 7.63−7.68 (m, 3H), 7.72−7.76 (m, 1H), 7.85−7.87 (m, 2H), and 8.02−8.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 38.6, 40.8, 52.6, 55.8, 56.1, 61.4, 67.0, 68.1, 103.1, 109.2, 113.1, 123.3, 129.0, 129.2, 129.8, 130.6, 133.2, 134.9, 135.0, 139.0, 148.3, 148.9, and 171.9. Anal. Calcd for $C_{28}H_{29}NO_9S_2$: C, 57.23; H, 4.97; N, 2.38. Found: C, 56.85; H, 4.83; N, 2.37.

9,10-Dimethoxy-3-(phenylsulfonyl)-3,4-dihydro-1*H*-pyrido[2,1-*a*]isoquinoline-2,6(7*H*,11b*H*)-dione (18). A solution containing 2.8 g (4.8 mmol) of the above cycloadduct **17** and 0.28 g of freshly washed Raney nickel in 30 mL of THF was heated at reflux under an atmosphere of hydrogen for 12 h. The resulting solution was filtered through Celite and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to provide 1.6 g (81%) of the major diastereomer **18** as a white solid: mp 218−219 °C; IR (neat) 1721, 1654, 1521, 1465, 1450, and 1316 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) enol tautomer δ 2.91−2.99 (m, 1H), 3.13−3.25 (m, 2H), 3.59−3.65 (m, 2H), 3.83 (s, 3H), 3.87 (s, 3H), 4.76 (d, 1H, J = 12.0 Hz), 5.59 (d, 1H, J = 15.2 Hz), 6.56 (s, 1H), 6.60 (s, 1H), 7.55−7.62 (m, 2H), 7.67−7.72 (m, 1H), and 7.98−8.03 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.9, 41.2, 50.7, 56.1, 56.2, 59.3, 71.4, 107.8, 110.2, 122.6, 122.8, 129.3, 129.4, 129.5, 129.6, 134.8, 136.9, 148.5, 149.3, 167.5, and 197.0. Anal. Calcd for $C_{21}H_{21}NO_6S$: C, 60.71; H, 5.09; N, 3.37. Found: C, 60.32; H, 5.04; N, 3.33.

9,10-Dimethoxy-3,4-dihydro-1*H*-pyrido[2,1-*a*]isoquinoline-2,6-(7*H*,11b*H*)-dione (19). A solution containing 0.11 g (0.28 mmol) of keto sulfone **18** and 0.05 g (1.1 mmol) of *n*-Bu_3SnH in 8 mL of toluene was heated at reflux. Two portions of AIBN (0.051 g, 0.31 mmol) were subsequently added over a 20 min period. The reaction mixture was concentrated under reduced pressure, and the residue was purified using flash silica gel chromatography to provide 0.053 g (70%) of the titled compound **19** as a pale yellow oil: IR (film) 1721, 1644, 1516, 1250, and 1122 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.45−2.66 (m, 3H), 2.84 (d, 1H, J = 14.8 Hz), 2.95−3.03 (ddd, 1H, J = 12.8, 12.8, and 4.0 Hz), 3.71 (d, 2H, J = 3.2 Hz), 3.87 (s, 3H), 3.89 (s, 3H), 4.74 (d, 1H, J = 12.0 Hz), 5.08−5.13 (ddd, 1H, J = 13.2, 6.8, and 2.0 Hz), 6.57 (s, 1H), and 6.61 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.7, 40.8, 41.4, 51.2, 56.1, 56.2, 59.1, 107.7, 110.1, 122.3, 123.7, 148.5, 149.2, 167.4, and 206.1. Anal. Calcd. for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.28; H, 6.31; N, 5.25.

3-Ethyl-9,10-dimethoxy-3,4-dihydro-1*H*-pyrido[2,1-a]isoquinoline-2,6-(7*H*,11b*H*)-dione (22). To a solution of 0.1 g (0.24 mmol) of keto sulfone **18** in 1.5 mL of DMF at 0 °C was added 0.01 g (0.26 mmol) of NaH (60% dispersion in mineral oil). After the

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solution was stirred for 5 min, 0.06 g (0.36 mmol) of iodoethane was added via syringe, and the resulting solution was stirred at 25 °C for 1 h. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and purified using flash silica gel chromatography. The first fraction contained 0.048 g of enol ether **20** (45%) as a clear oil: IR (film) 1650, 1516, 1445, 1322, and 1245 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.19 (t, 3H, $J = 7.2$ Hz), 2.31−2.37 (m, 1H), 2.77 (d, 1H, 16.2 Hz), 3.56 (d, 1H, $J = 16.2$ Hz), 3.60 (d, 1H, $J = 16.2$ Hz), 3.74−3.79 (m, 1H), 3.86 (s, 3H), 3.87 (s, 1H), 3.86−3.89 (m, 1H), 3.95−4.00 (m, 1H), 4.65 (dd, 1H, $J = 11.4$ and 3.6 Hz), 5.62 (d, 1H, $J = 11.6$ Hz), 6.59 (s, 1H), 6.62 (s, 1H), 7.49−7.52 (m, 2H), 7.57−7.60 (m, 1H), 8.00 (s, 1H), and 8.01 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 10.6, 30.7, 31.7, 36.3, 51.9, 52.0, 52.1, 60.2, 104.0, 106.1, 118.4, 119.1, 123.8, 124.4, 128.8, 138.3, 144.2, 145.1, 153.5, and 162.4.

The second fraction contained 0.045 g (41%) of 3-ethyl-9,10-dimethoxy-3-(phenylsulfonyl)-3,4-dihydro-1*H*-pyrido[2,1-*a*]isoquinoline-2,6(7*H*,11b*H*)-dione (**21**) as a white solid: mp 219−220 °C; IR (film) 1721, 1655, 1516, 1450, and 1306 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, 3H), 1.78−1.87 (m, 1H), 1.95−2.04 (m, 1H), 2.65 (dd, 1H, $J = 16.8$ and 10.4 Hz), 3.72 (dd, 1H, $J = 16.8$ and 4.8 Hz), 3.63 (s, 2H), 3.88 (s, 6H), 4.19 (d, 1H, $J = 14.4$ Hz), 4.99 (d, 1H, $J = 14.4$ Hz), 5.13 (dd, 1H, $J = 10.4$ and 4.8 Hz), 6.62 (s, 1H), 6.63 (s, 1H), 7.58−7.62 (m, 2H), 7.71−7.75 (m, 1H), and 7.87−7.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.4, 27.4, 36.3, 43.1, 47.3, 55.0, 56.3, 56.4, 76.0, 107.4, 110.5, 123.1, 124.6, 129.1, 131.1, 134.8, 135.5, 148.5, 149.3, 167.8, and 201.3. Anal. Calcd for $C_{23}H_{25}NO_6S$: C, 62.29; H, 5.68; N, 3.16. Found: 62.04; H, 5.41; N, 3.08.

A solution containing 0.05 g (0.12 mmol) of keto sulfone **21** and 0.02 g (0.14 mmol) of *n*-Bu_3SnH in 9 mL of toluene was heated at reflux. Two portions of AIBN (0.021 g, 0.13 mmol) were subsequently added over a 20 min period. The reaction mixture was concentrated under reduced pressure, and the residue was purified using flash silica gel chromatography to provide 0.03 g (75%) of the titled compound **22** as a pale yellow oil: IR (film) 1716, 1644, 1516, 1454, and 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, 3H, $J = 7.6$ Hz), 1.92−2.02 (m, 1H), 2.10−2.21 (m, 1H), 2.49−2.54 (m, 2H), 2.87−2.97 (m, 2H), 3.60−3.63 (m, 1H), 3.87−3.94 (m, 7H), 4.69 (d, 1H, $J = 10.0$ Hz), 5.18−5.24 (m, 1H), 6.55 (s, 1H), and 6.61 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.0, 29.8, 41.4, 41.5, 45.3, 52.0, 56.3, 58.9, 107.5, 110.2, 123.9, 126.6, 148.5, 149.3,169.9, and 206.1; HRMS calcd for $[C_{17}H_{21}NO_4 + H^+]$ 304.1549, found 304.1545.

3-Benzenesulfonyl-9,10-dimethoxy-3-(3-oxobutyl)-3,4,7,11b-tetrahydro-1*H*-pyrido[2,1-*a*]isoquinoline-2,6-dione (23). To a suspension of 0.5 g (1.2 mmol) of keto sulfone **18** in 10 mL of a 9:1 mixture of THF/MeOH was added 0.6 g (8.5 mmol) of methyl vinyl ketone. After the mixture was stirred for 2 h, 0.01 g (0.12 mmol) of triethylamine was added as a 0.8 M solution in THF. The reaction mixture was stirred at 25 °C for an additional 18 h, poured into water, and extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and purified using flash silica gel chromatography to provide 0.49 g (84%) of the titled compound as a 1:1 mixture of diastereomers: mp 190−191 °C; IR (neat) 1716, 1650, 1511, 1445, and 1306 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) diastereomer A: δ 2.05 (s, 1H), 2.07−2.24 (m, 2H), 2.50−2.53 (m, 3H), 2.68−2.77 (m, 2H), 2.97 (dd, 1H, $J = 17.2$ and 5.2 Hz), 3.61 (d, 1H, $J = 20.4$ Hz), 3.70 (d, 1H, $J = 20.4$ Hz), 3.87 (s, 3H), 3.88 (s, 3H), 3.98 (d, 1H, $J = 14.8$ Hz), 5.01−5.05 (m, 2H), 6.59 (s, 1H), 6.62 (s, 1H), 7.59−7.63 (m, 2H), 7.71−7.75 (m, 1H), and 7.89−7.91 (m, 2H); diastereomer B: δ 1.76−1.84 (m, 1H), 2.14 (s, 3H), 2.26−2.34 (m, 1H), 2.50−2.60 (m, 2H), 2.98 (dd, 1H, $J = 15.2$ and 2.8 Hz), 3.16 (d, 1H, $J = 14.8$ Hz), 3.35 (dd, 1H, $J = 15.2$ and 12.4 Hz), 3.66 (d, 1H, $J = 20.0$ Hz), 3.87−3.90 (m, 7H), 4.79 (d, 1H, $J = 12.4$ Hz), 5.66 (d, 1H, $J = 15.6$ Hz), 6.57 (s, 1H), 6.64 (s, 1H), 7.58−7.62 (m, 2H), 7.70−7.73 (m, 1H), and 7.94−7.96 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) diastereomer A: δ 26.6, 30.1, 35.6, 37.6, 43.9, 47.5, 56.2, 56.3, 56.7, 75.1, 107.5, 110.4, 122.6, 124.0, 129.2, 131.1, 135.0, 135.5, 148.5, 149.3, 167.9, 201.0, and 207.0; diastereomer B: δ 24.8, 30.2, 35.4, 37.7, 44.2, 50.2, 56.2, 56.3, 58.7, 73.9, 107.7, 110.4, 123.0, 123.1, 129.4, 131.0, 134.7, 135.0, 148.6, 149.4, 167.7, 199.8, and 206.5. Anal. Calcd for $C_{25}H_{27}NO_7S$: C, 61.84; H, 5.60; N, 2.88. Found: C, 61.39; H, 5.77; N, 2.61.

2,3-Dimethoxy-11-pyrrolidin-1-yl-5,8,13,13a-tetrahydroisoquino[3,2-*a*]-isoquinolin-6-one (25). To a solution containing 0.1 g (0.21 mmol) of the above keto sulfone **23** in 1 mL of CH_2Cl_2 was added 0.01 g (0.18 mmol) of acetic acid and 0.01 g (18 mmol) of pyrrolidine. After being stirred for 12 h, the solution was concentrated under reduced pressure. The crude residue was dissolved in 3 mL of toluene, and 0.02 g (0.1 mmol) of *p*-toluenesulfonic acid was added. The resulting solution was heated at reflux for 1 h. Concentration under reduced pressure left a residue which was purified by silica gel chromatography to furnish 0.076 g (76%) of the titled compound **25** as a tan solid: mp 250−251 °C; IR (film) 1639, 1521, 1450, 1368, and 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.01 (brs, 5H), 2.92−2.99 (m, 1H), 3.13 (dd, 1H, $J =$ 15.6 and 3.2 Hz), 3.27 (brs, 4H), 3.65 (d, 1H, $J = 6.4$ Hz), 3.90 (s, 3H), 3.91 (s, 3H), 4.22 (d, 1H, $J = 16.0$ Hz), 4.72 (d, 1H, $J = 10.8$ Hz), 5.58 (d, 1H, 16.0 Hz), 6.32 (s, 1H), 6.50 (d, 1H, $J = 8.4$ Hz), 6.63 (s, 1H), 6.73 (s, 1H), and 7.05 (d, 1H, $J = 8.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 35.5, 39.3, 44.4, 48.0, 56.2, 56.3, 57.9, 108.4, 110.2, 111.3, 122.9, 125.8, 127.4, 129.8, 130.4, 134.2, 146.9, 148.3, 148.9, and 167.1. Anal. Calcd for $C_{23}H_{26}N_2O_3$: C, 72.98; H, 6.93; N, 7.41. Found: 72.87; H, 7.15; N, 7.46.

9,10-Dimethoxy-3-(3-oxobutyl)-3,4-dihydro-1*H*-pyrido[2,1-*a*]isoquinoline-2,6-(7*H*,11b*H*)-dione (26). A solution containing 0.15 g (0.3 mmol) of keto sulfone **23** and 0.35 g (1.2 mmol) of *n*-Bu_3SnH in 9 mL of toluene was heated at reflux. Two portions of AIBN (0.054 g, 0.33 mmol) were subsequently added over the course of 20 min. The reaction mixture was concentrated under reduced pressure and the residue was purified using flash silica gel chromatography to provide 0.09 g (87%) of the major diastereomer **26** as a white solid: mp 144−145 °C; IR (neat) 1716, 1644, 1516, 1445, and 1245 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.56−1.62 (m, 1H), 2.05−2.12 (m, 1H), 2.17 (s, 3H), 2.48−2.54 (m, 3H), 2.55−2.62 (m, 1H), 2.65−2.71 (m, 1H), 2.82 (dd, 1H, $J = 9.2$ and 2.0 Hz), 3.70 (d, 2H, $J = 4.0$ Hz), 3.86 (s, 3H), 3.88 (s, 3H), 4.70 (d, 1H, $J = 8.2$ Hz), 5.14 (dd, 1H, $J = 8.2$ and 4.0 Hz), 6.56 (s, 1H), and 6.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.4, 30.1, 34.6, 41.0, 46.8, 49.1, 51.6, 56.2, 60.1, 107.8, 110.1, 122.3, 123.5, 148.5, 149.3, 167.2, 207.1, and 208.0. Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 65.87; H, 6.62; N, 4.01.

2,3-Dimethoxy-8,8a,9,10,13,13a-hexahydro-5*H*-isoquino[3,2-*a*] isoquinoline-6,11-dione (27). To a solution containing 0.06 g (0.174 mmol) of the above compound **26** in 5 mL of THF was added 4.4 mL of a 0.08 M solution of sodium methoxide in methanol. The resulting mixture was stirred at 40 °C for 12 h, concentrated under reduced pressure, and purified using flash silica gel chromatography to provide 0.04 g (70%) of the titled compound **27** as a yellow solid: mp 237−238 °C; IR (neat) 1650, 1521, 1465, and 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.63−1.74 (m, 1H), 2.18−2.25 (m, 1H), 2.34−2.47 (m, 3H), 2.51−2.57 (m, 1H), 2.61−2.69 (m, 1H), 2.82 (dd, 1H, $J = 14.8$ and 2.8 Hz), 3.67 (s, 2H), 3.89 (s, 3H), 3.91 (s, 3H), 4.55 (d, 1H, $J = 10.8$ Hz), 5.05 (dd, 1H, $J = 13.2$ and 6.0 Hz), 6.01 (s, 1H), 6.6 (s, 1H), and 6.63 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.9, 34.7, 36.5, 36.7, 44.6, 48.1, 56.2, 56.4, 60.1, 108.2, 110.2, 122.5, 124.2, 126.9, 148.5, 160.4, 167.1, and 199.1. Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.79; H, 6.65; N, 4.03.

2,3-Dimethoxy-5,6,8,8a,9,10,13,13a-octahydroisoquino[3,2-*a*]-isoquinolin-11-one (28). To a solution of 0.1 g (0.29 mmol) of lactam **27** in 12 mL of a 1:1 mixture of Et_2O/THF at 0 °C was added 0.1 g (2.6 mmol) of $LiAlH_4$. The resulting suspension was stirred for 30 min at 0 °C and then heated at 55 °C for 1.5 h. The reaction mixture was cooled to 0 °C and quenched with 0.12 mL

of water, followed by 0.12 mL of a 15% aqueous NaOH solution and finally an additional 0.36 mL of water. The resulting suspension was stirred vigorously for 1 h and then anhydrous $MgSO_4$ was added, and this was followed by an additional 30 min of stirring. The inorganic salts were removed by filtration, and the filtrate was concentrated under reduced pressure to give 0.1 g of 2,3-dimethoxy-5,8,8a,9,-10,11,13,13a-octahydro-6*H*-isoquino[3,2-*a*]isoquinolin-11-ol as a mixture of diastereomers. The crude residue was used in the next step without further purification.

To a solution of 0.1 g (0.29 mmol) of the above alcoholic mixture in 30 mL of a 1:1 CH_2Cl_2/THF mixture was added 0.4 g (4.6 mmol) of activated manganese dioxide. The resulting suspension was vigorously stirred for 72 h and then filtered through a Celite plug. The filtrate was concentrated under reduced pressure and purified using flash silica gel chromatography to give 0.07 g (75%) of the titled compound **28**[31] as a yellow solid: mp 182−185 °C; IR (neat) 1667, 1513, 1464, 1369, 1249, and 1146 cm^{-1}; ^1H NMR (C_6D_6, 600 MHz) δ 1.13−1.22 (m, 1H), 1.25−1.44 (m, 4H), 1.76 (t, 1H, J = 11.4 Hz), 1.96 (dt, 1H, J = 15.2 and 4.8 Hz), 2.23−2.35 (m, 4H), 2.44 (d, 1H, J = 16.2 Hz), 2.62 (d, 1H, J = 9.5 Hz), 2.63 (d, 1H, J = 11.4 Hz), 2.67−2.72 (m, 1H), 2.67−2.72 (m, 1H), 3.02−3.10 (m, 2H), 3.43 (s, 3H), 3.50 (s, 3H), 5.97 (s, 1H), 6.45 (s, 1H), and 6.56 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 25.9, 29.1, 36.6, 40.3, 51.3, 55.8, 56.1, 61.9, 62.3, 108.0, 111.4, 125.4, 126.5, 128.7, 147.4, 147.7, 163.4, and 199.5.

Methyl 2-(1-Benzyl-1*H*-indol-3-yl)acetate (29). To a solution of 9.0 g (34 mmol) of 2-(1-benzyl-1*H*-indol-3-yl)acetic acid[38] in 60 mL of dry MeOH at −78 °C was added 3.0 mL (40.7 mmol) of thionyl chloride. The suspension was slowly allowed to warm to 25 °C and was stirred for 17 h. The deep red solution was concentrated under reduced pressure and the residue was taken up in 100 mL of EtOAc. The solution was washed with a saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified using flash silica gel chromatography to furnish 8.3 g (88%) of the titled compound **29**[33] as a pale yellow oil: IR (neat) 1737, 1614, 1496, 1164, and 1013 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.71 (s, 3H), 3.80 (s, 2H), 5.25 (s, 2H), 7.12 (d, 3H, J = 7.6 Hz), 7.16 (t, 1H. J = 7.6 Hz), 7.21 (t, 1H, J = 7.6 Hz), 7.24−7.32 (m, 4H), and 7.66 (d, 1H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 31.0, 49.8, 51.8, 107.4, 109.7, 119.0, 119.3, 121.9, 126.7, 127.0, 127.5, 127.8, 128.6, 136.4, 137.3, and 172.3.

Methyl 2-(1-Benzyl-2-formyl-1*H*-indol-3-yl)acetate (11). A 100 mL flask was charged with 8 mL of dry DMF and 5.2 mL of $POCl_3$. The resulting solution was stirred at 0 °C for 1 h, and then a solution of 5.0 g of the above indole **29** in 32 mL of DMF was added dropwise. The orange solution was heated to 50 °C for 65 h, cooled to 25 °C, and slowly added to 800 mL of a prechilled 10% aqueous $NaHCO_3$ solution. The basic solution was stirred vigorously for 90 min and was then extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to furnish 0.19 g (5%) of recovered indole **29** and 2.4 g (56%) of the titled compound **11**: IR (neat) 1738, 1664, 1464, 1435, 1351, and 1167 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.72 (s, 3H), 4.16 (s, 2H), 5.82 (s, 2H), 7.10 (d, 2H, J = 7.1 Hz), 7.20−7.28 (m, 4H), 7.36−7.42 (m, 2H), 7.80 (d, 1H, J = 8.1 Hz), and 10.20 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 29.6, 47.7, 52.3, 110.9, 121.1, 121.2, 121.7, 126.4, 127.2, 127.5, 128.5, 131.0, 137.6, 139.2, 170.8, and 181.3.

[1-Benzyl-2-(hydroxyiminomethyl)-1*H*-indol-3-yl]acetic Acid Methyl Ester (30). To a solution of 5.3 g (17.2 mmol) of the above aldehyde in 130 mL of MeOH was added 1.6 g (22.4 mmol) of hydroxylamine hydrochloride and 3.6 g (43 mmol) of sodium acetate. The resulting solution was stirred for 23 h and then concentrated under reduced pressure. The residue was taken up in CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to yield 4.5 g (81%) of the titled compound **30** as a white solid: mp 121−122 °C; IR (neat) 3355, 1738, 1662, 1453, 1349, and 1256 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.69 (s, 3H), 3.94 (s, 2H), 5.68 (s, 2H), 7.03 (d, 1H, J = 8.3 Hz), 7.12−7.18 (m, 1H), 7.20−7.30 (m, 6H), 7.66 (d, 1H, J = 8.3 Hz) and 8.39 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.4, 48.2, 52.2, 110.1, 112.1, 119.6, 120.4, 124.3, 126.1, 127.2, 127.4, 128.2, 128.6, 137.8, 138.3, 142.4 and 171.7; HRMS calcd for [$C_{19}H_{18}N_2O_3$ + H^+] 323.1396, found 323.1394.

1-Benzyl-2-(4,5-bis-benzenesulfonyl-7-oxa-1-azabicyclo[2.2.1]-hept-2-yl)-1*H*-indol-3-yl]acetic Acid Methyl Ester (31). A 500 mL flask was charged with 5.5 g (17 mmol) of oxime **30**, 6.2 g (19 mmol) of 2,3-bis(phenylsulfonyl)-1,3-butadiene, and 200 mL of dry toluene. The mixture was heated at reflux for 41 h. After cooling, a small amount of silica gel was added, and the slurry was concentrated under reduced pressure. The resulting residue was subjected to flash silica gel chromatography to furnish 7.9 g (72%) of the titled compound **31** as a white solid: mp 142−143 °C; IR (neat) 1735, 1637, 1613, 1447, and 1324 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.35−2.40 (m, 1H), 3.38−3.44 (m, 2H), 3.47−3.62 (m, 3H), 3.65 (s, 3H), 4.48−4.54 (m, 1H), 4.83 (t, 1H, J = 7.6 Hz), 5.15 (d, 1H, J = 17.1 Hz), 5.30 (d, 1H, J = 17.1 Hz), 6.98 (d, 2H, J = 7.6 Hz), 7.09 (t, 1H, J = 7.6 Hz), 7.16 (t, 1H, J = 7.6 Hz), 7.18 (d, 1H, J = 7.6 Hz), 7.24−7.32 (m, 3H), 7.49 (dd, 1H, J = 17.1 and 7.6 Hz), 7.51 (d, 2H, J = 7.6 Hz), 7.65 (t, 2H, J = 7.6 Hz), 7.70 (t, 1H, J = 7.6 Hz), 7.75 (t, 1H, J = 7.6 Hz), 7.78 (d, 2H, J = 7.6 Hz), and 7.95 (d, 2H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.5, 39.5, 47.1, 51.9, 61.7, 65.0, 67.0, 103.1, 106.6, 109.6, 118.7, 119.9, 122.6, 126.3, 127.5, 127.9, 128.7, 129.1, 129.6, 130.2, 134.4, 134.7, 135.0, 136.7, 137.5, 138.5, and 172.4. Anal. Calcd for $C_{35}H_{32}N_2O_7S_2$: C, 64.01; H, 4.91; N, 4.27. Found: C, 63.86; H, 5.13; N, 4.18.

(12b)-12-Benzyl-1,3,4,12b-tetrahydro-3-(phenylsulfonyl)indolo-[2,3-*a*]quinolizine-2,6-(7*H*,12*H*)-dione (32). A 30 mL sealed tube was charged with 0.34 g (0.52 mmol) of cycloadduct **31**, 0.15 g (0.16 mmol) of 20% $Pd(OH)_2$, 50 μL (0.78 mmol) of AcOH, and 3 mL of EtOAc. The resulting suspension was flushed with an atmosphere of hydrogen, pressurized with hydrogen (45 psi) and heated at 60 °C for 38 h. The solution was filtered through a plug of Celite and concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 and washed with a saturated aqueous $NaHCO_3$ solution. The resulting biphasic solution was stirred vigorously and the aqueous phase was separated and extracted with CH_2Cl_2 and EtOAc. The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to give 0.2 g (81%) of the titled compound **32** as a 2:1-mixture of diastereomers. The major diastereomer exhibited the following properties: mp 121−122 °C; IR (neat) 1698, 1658, 1449, 1322, and 1148 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.85 (d, 1H, J = 14.3 Hz), 3.14 (dd, 1H, J = 15.2 and 4.8 Hz), 3.17−3.22 (m, 1H), 3.81 (d, 1H, J = 4.8 Hz), 3.89 (d, 1H, J = 20.9 Hz), 3.99 (d, 1H, J = 20.9 Hz), 4.82 (d, 1H, J = 11.4 Hz), 5.22 (d, 1H, J = 17.2 Hz), 5.34 (d, 1H, J = 17.2 Hz), 5.68 (d, 1H, J = 15.2 Hz), 6.88 (d, 2H, J = 7.6 Hz), 7.15−7.31 (m, 6H), 7.56 (d, 1H, J = 7.6 Hz), 7.60 (t, 2H, J = 7.6 Hz), 7.70 (t, 1H, J = 7.6 Hz), and 8.03 (d, 2H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.3, 41.7, 47.1, 49.3, 54.7, 71.5, 106.2, 110.0, 118.8, 120.3, 123.2, 125.4, 125.6, 125.7, 127.9, 129.1, 129.2, 129.5, 134.7, 136.4, 136.7, 137.9, 167.8, and 196.1. Anal. Calcd for $C_{28}H_{24}N_2O_4S$: C, 69.40; H, 4.99; N, 5.78. Found: C, 69.58; H, 5.07; N, 5.68.

(12b)-12-Benzyl-1,3,4,12b-tetrahydro-3-(3-oxobutyl)indolo[2,3-*a*]quinolizine-2,6-(7*H*,12*H*)-dione (33). To a solution of 0.63 g (1.3 mmol) of keto sulfone **32** in 15 mL of a 9:1 THF/MeOH mixture was added 0.75 mL (9.0 mmol) of methyl vinyl ketone. After the mixture was stirred for 3 h, 0.35 mL of a 0.8 M solution of Et_3N in THF was added. The reaction mixture was stirred at 25 °C for 21 h and was concentrated under reduced pressure. The residue

(38) (a) Julia, M.; Tchernoff, G. *Bull. Soc. Chim. Fr.* **1960**, 741. (b) Capman, R. F.; Phillips, N. I. J.; Ward, R. S. *Tetrahedron* **1985**, *41*, 5229.

was purified using flash silica gel chromatography to furnish 0.7 g (97%) of the titled compound as a mixture of diastereomers. The diastereomeric mixture was separated by flash silica gel chromatography. Diasteromer A exhibited the following properties: mp 105−106 °C; IR (neat) 1715, 1658, 1600, 1447, 1308, and 1147 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 2.07 (s, 3H), 2.11−2.25 (m, 4H), 2.50−2.56 (m, 1H), 2.60 (dd, 1H, J = 18.1 and 11.4 Hz), 2.71−2.78 (m, 1H), 2.88 (dd, 1H, J = 17.1 and 4.8 Hz), 2.94 (t, 1H, J = 7.6 Hz), 3.38 (t, 1H, J = 7.6 Hz), 3.87 (d, 1H, J = 15.2 Hz), 3.77−3.90 (m, 2H), 5.18 (d, 1H, J = 14.3 Hz), 5.19−5.23 (m, 1H), 5.26 (d, 1H, J = 17.1 Hz), 5.32 (d, 1H, J = 17.1 Hz), 6.98 (d, 2H, J = 7.6 Hz), 7.16−7.20 (m, 1H), 7.22−7.33 (m, 5H), 7.53 (d, 1H, J = 7.6 Hz), 7.58 (d, 2H, J = 7.6 Hz), 7.71 (t, 1H, J = 7.6 Hz), and 7.85 (d, 2H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 26.7, 29.3, 29.9, 37.4, 44.6, 47.4, 47.8, 52.7, 75.1, 105.2, 110.1, 118.7, 120.3, 123.1, 125.4, 125.9, 128.0, 129.0, 129.1, 129.2, 129.4, 130.9, 133.9, 134.8, 135.0, 136.5, 137.9, 167.5, 199.6, and 206.6.

Diastereomer B exhibited the following properties: mp 102−103 °C; IR (neat) 1712, 1649, 1451, 1321, 1266, and 1240 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.73−1.79 (m, 1H), 2.11 (s, 3H), 2.21−2.27 (m, 1H), 2.44−2.57 (m, 2H), 2.89 (dd, 1H, J = 15.2 and 1.9 Hz), 3.04 (d, 1H, J = 15.2 Hz), 3.34 (dd, 1H, J = 15.2 and 12.4 Hz), 3.92 (d, 1H, J = 20.9 Hz), 3.99 (d, 1H, J = 20.9 Hz), 4.88 (d, 1H, J = 12.4 Hz), 5.25 (d, 1H, J = 17.1 Hz), 5.38 (d, 1H, J = 17.1 Hz), 5.82 (d, 1H, J = 15.2 Hz), 6.94 (d, 2H, J = 6.7 Hz), 7.17−7.33 (m, 6H), 7.59 (t, 3H, J = 8.6 Hz), 7.70 (t, 1H, J = 7.6 Hz), and 7.93 (d, 2H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 24.6, 29.4, 29.7, 30.1, 37.4, 44.7, 47.2, 49.0, 54.2, 73.8, 106.2, 110.1, 118.8, 120.3, 123.1, 125.5, 125.8, 127.9, 128.1, 129.1, 129.2, 130.7, 134.4, 134.8, 136.5, 137.9, 167.7, 198.8, and 206.2.

To a solution of 0.25 g (0.45 mmol) of the above diasteromeric mixture in 15 mL of toluene was added 0.5 mL (1.8 mmol) of n-Bu_3SnH. The reaction mixture was heated at reflux and then 0.1 g (0.61 mmol) of AIBN was added. After heating at reflux for 5 min, an additional 0.1 g (0.61 mmol) of AIBN was added, followed by an additional 0.1 g (0.61 mmol) after an additional 20 min. The resulting solution was further heated at reflux for 1 h, cooled to 25 °C and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to furnish 0.18 g (94%) of the titled compound **33** as a 3:2-mixture of diasteromers: mp 190−195 °C; IR (neat) 1729, 1648, 1463, 1452, 1236, and 1143 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.52−1.64 (m, 1H), 1.81−1.89 (m, minor), 1.89−1.97 (m, minor), 2.10−2.08 (m, 1H), 2.12 (s, minor), 2.16 (s, 3H), 2.44−2.58 (m, 4H), 2.63−2.72 (m, 1H), 2.74 (dd, 1H, J = 13.3 and 2.9 Hz), 3.01 (dd, minor, J = 14.3 and 3.8 Hz), 3.80−3.94 (m, 2H), 4.81 (dd, 1H, J = 12.4 and 2.9 Hz), 4.85 (dd, minor, J = 11.4 and 2.9 Hz), 4.96 (dd, minor, J = 14.3 and 2.9 Hz), 5.15 (d, 1H, J = 6.7 Hz), 5.24 (d, 1H, J = 18.1 Hz), 5.36 (d, 1H, J = 18.1 Hz), 6.91 (d, 2H, J = 7.6 Hz), 7.17−7.30 (m, 6H), and 7.55 (d, 1H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 20.2, 29.3, 30.0, 40.8, 47.1, 47.4, 49.3, 50.2, 55.3, 105.6, 110.1, 118.7, 120.3, 123.1, 125.4, 125.7, 127.9, 129.0, 129.1, 136.5, 137.8, 167.6, 206.1, and 207.8; HRMS calcd for [$C_{26}H_{26}N_2O_3$ + H^+] 415.2016, found 415.2010.

13-Benzyl-3,4,4a,5,8,13,13b,14-octahydroindolo[2′,3′:3,4]pyrido-[1,2-*b*]isoquinoline-2,7-dione (34). To a solution of 0.05 g (0.12 mmol) of the above compound in 52 mL of CH_2Cl_2 was added 0.009 mL (0.10 mmol) of pyrrolidine and 0.006 mL (0.10 mmol) of AcOH. The resulting solution was stirred for 68 h and was then concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to furnish 0.04 g (78%) of the titled compound **34** as a yellow solid: mp 195−196 °C; IR (neat) 1713, 1668, 1464, 1454, 1246, and 1191 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.16−2.22 (m, 1H), 2.27−2.38 (m, 3H), 2.42 (t, 1H, J = 12.4 Hz), 2.50 (dt, 1H, J = 17.2 and 3.8 Hz), 2.55 (dd, 1H, J = 14.3 and 1.9 Hz), 2.60−2.68 (m, 1H), 3.79 (dd, 1H, J = 21.0 and 1.9 Hz), 3.88 (dd, 1H, J = 21.0 and 1.9 Hz), 4.63 (dd, 1H, J = 12.4 and 2.9 Hz), 5.06 (dd, 1H, J = 13.3 and 5.7 Hz), 5.31 (d, 1H, J = 17.2 Hz), 5.36 (d, 1H, J = 17.2 Hz), 5.72 (s, 1H), 6.98 (d, 2H, J = 6.7 Hz), 7.19 (t, 1H, J = 7.6 Hz), 7.24−7.33 (m, 5H), and 7.56 (d, 1H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.5, 29.2, 36.3, 36.4, 43.2, 47.1, 48.5, 55.1, 105.5, 109.8, 118.6, 120.2, 122.9, 125.3, 125.8, 126.7, 127.9, 129.1, 129.8, 136.9, 138.0, 159.1, 167.3, and 198.8; HRMS calcd for [$C_{26}H_{24}N_2O_2$ + H^+] 397.1911, found: 397.1905.

(±)-Yohimbenone (5). To a solution of 0.27 g (0.68 mmol) of lactam **34** in 12 mL of Et_2O at 0 °C was added 0.21 g (5.4 mmol) of $LiAlH_4$. The resulting suspension was stirred for 1 h at 0 °C, slowly warmed to 25 °C, and stirred for 24 h. The reaction mixture was cooled to 0 °C and quenched with 0.27 mL of water, followed by 0.27 mL of a 15% aqueous NaOH solution and finally an additional 0.82 mL of water. The resulting suspension was stirred vigorously for 1 h, anhydrous $MgSO_4$ was added, and the mixture was stirred for an additional 30 min. The inorganic salts were removed by filtration, the filtrate was concentrated, and the resulting residue was purified using flash silica gel chromatography to give 0.23 g (88%) of 13-benzyl-2,3,4,4a,5,7,8,13,13b,14-decahydroindolo[2′,3′:3,4]pyrido[1,2-*b*]isoquinolin-2-ol as a yellow solid: mp 183−184 °C; IR (neat) 3364, 1465, 1350, 1217, and 1182 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.77−1.84 (m, 1H), 2.03−2.10 (m, 1H), 2.26−2.35 (m, 2H), 2.40−2.48 (m, 2H), 2.76−2.83 (m, 1H), 2.87 (dt, 1H, J = 15.2 and 5.7 Hz), 2.96 (dt, 1H, J = 15.2 and 5.7 Hz), 3.12 (dd, 1H, J = 18.1 and 11.4 Hz), 3.24−3.29 (m, 1H), 3.65 (dd, 1H, J = 10.5 and 2.9 Hz), 4.22 (t, 1H, J = 6.7 Hz), 5.29 (s, 2H), 5.34 (s, 1H), 7.00 (d, 2H, J = 7.6 Hz), 7.09−7.16 (m, 3H), 7.21−7.31 (m, 3H), and 7.52−7.56 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 22.3, 24.6, 31.6, 33.7, 37.4, 47.4, 48.1, 58.1, 62.3, 67.4, 108.6, 109.6, 118.2, 119.3, 121.5, 125.3, 125.8, 127.0, 127.3, 128.8, 136.5, 137.6, 137.7, and 140.2.

To a solution of 0.08 g (0.21 mmol) of the above alcohol in 20 mL of a 1:1 CH_2Cl_2/THF mixture was added 0.2 g (2.1 mmol) of activated manganese dioxide. The resulting suspension was vigorously stirred for 65 h and then filtered through a Celite plug. The filtrate was concentrated under reduced pressure and purified using flash silica gel chromatography to yield 0.071 g (89%) of 13-benzyl-3,4,4a,5,8,13,13b,14octahydro-7*H*-indolo[2′,3′:3,4]pyrido[1,2-*b*]isoquinolin-2-one as a yellow solid: mp 149−150 °C; IR (neat) 1665, 1464, 1453, 1264, 1181, and 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.53−1.61 (m, 1H), 2.01−2.06 (m, 2H), 2.29−2.36 (m, 1H), 2.42−2.48 (m, 2H), 2.60 (t, 1H, J = 12.5 Hz), 2.70−2.77 (m, 1H), 2.84−2.89 (m, 1H), 2.91 (dt, 1H, J = 15.0 and 5.0 Hz), 2.98 (dt, 1H, J = 15.0 and 5.0 Hz), 3.24−3.31 (m, 2H), 3.77 (dd, 1H, J = 10.0 and 4.5 Hz), 5.27 (d, 1H, J = 17.5 Hz), 5.31 (d, 1H, J = 17.5 Hz), 5.70 (s, 1H), 6.99 (d, 2H, J = 7.5 Hz), 7.11−7.20 (m, 3H), 7.22−7.30 (m, 3H), and 7.55 (d, 1H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 22.3, 25.7, 34.4, 36.5, 37.8, 47.4, 48.0, 56.9, 61.4, 108.9, 109.6, 118.3, 119.5, 121.9, 125.3, 125.8, 126.8, 127.5, 128.9, 135.6, 137.5, 137.8, 163.0, and 199.3; HRMS calcd for [$C_{26}H_{26}N_2O$ + H^+] 383.2123, found 383.2119.

To a solution of 0.05 g (0.12 mmol) of the above compound in 10 mL of anhydrous toluene at 0 °C was added 0.6 g (0.47 mmol) of anhydrous $AlCl_3$. The resulting slurry was sonicated for 5 h, and then the solvent was removed under reduced pressure. The residue was diluted with EtOAc and washed with a 5% aqueous NaOH solution. The aqueous layer was separated and extracted with EtOAc. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography to give 0.03 g (92%) of (±)-yohimbenone (**5**) as a yellow solid: mp 242−244 °C (lit.[39] mp 244−245 °C); IR (neat) 3264, 1650, 1449, 1327, 1259, and 1164 cm^{-1}; ^1H NMR (DMSO-d_6, 600 MHz) δ 1.51−1.65 (m, 1H), 1.97−2.10 (m, 1H), 2.18 (t, 1H, J = 11.4 Hz), 2.26−2.43 (m, 3H), 2.62−2.69 (m, 1H), 2.70−2.89 (m, 2H), 3.04−3.15 (m, 3H), 3.19 (dd, 1H, J = 11.4 and 6.4 Hz), 3.35 (s, 1H), 5.83 (s, 1H), 6.95 (t, 1H, J = 7.3 Hz), 7.03 (t, 1H, J = 7.3 Hz), 7.29 (d, 1H, J = 8.3

(39) Szántay, C.; Honty, K.; Toke, L.; Szabo, L. *Chem. Ber.* **1976**, *109*, 1737.

Hz), 7.38 (d, 1H, $J = 7.3$ Hz), and 10.86 (s, 1H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 21.5, 25.6, 36.3, 36.6, 38.2, 51.7, 58.9, 60.9, 106.7, 111.1, 117.7, 118.5, 120.7, 124.6, 126.5, 134.7, 136.1, 163.6, and 198.6.

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Supporting Information Available: ^{1}H and ^{13}C NMR data of various key compounds lacking CHN analyses together with an ORTEP drawing for compound **27** as well as the corresponding CIF file. Atomic coordinates for compound **27** will be deposited with the Cambridge Crystallographic Data Centre. This material is available free of charge via the Internet at http://pubs.acs.org.

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