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Synthesis of Enantiopure 10-Nornaltrexones in the Search for Toll-like Receptor 4 Antagonists and Opioid Ligands

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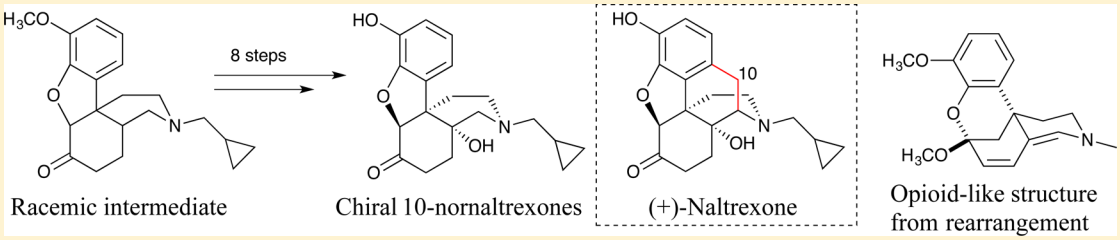
Supporting Information



ABSTRACT: 10-Nornaltrexones (3-(cyclopropylmethyl)-4a,9-dihydroxy-2,3,4,4a,5,6-hexahydro-1*H*-benzofuro[3,2-*e*]-isoquinolin-7(7a*H*)-one, **1**) have been underexploited in the search for better opioid ligands, and their enantiomers have been unexplored. The synthesis of *trans*-isoquinolinone **2** (4-aH, 9-*O*-*trans*-9-methoxy-3-methyl-2,3,4,4a,5,6-hexahydro-1*H*-benzofuro[3,2-*e*]isoquinolin-7(7a*H*)-one) was achieved through a nonchromatographic optimized synthesis of the intermediate pyridinyl compound **12**. Optical resolution was carried out on **2**, and each of the enantiomers were used in efficient syntheses of the "unnatural" 4a*R*,7a*S*,12b*R*-(+)-**1**) and its "natural" enantiomer (−)-**1**. Addition of a 14-hydroxy (the 4a-hydroxy) group in the enantiomeric isoquinolinones, (+)- and (−)-**2**), gave (+)- and (−)-10-nornaltrexones. A structurally unique tetracyclic enamine, (12b*R*)-7,9-dimethoxy-3-methyl-1,2,3,7-tetrahydro-7,12b-methanobenzo[2,3]oxocino[5,4-*c*]pyridine, was found as a byproduct in the syntheses and offers a different opioid-like skeleton for future study.

INTRODUCTION

Opiates have long been used as a standard treatment of both short-term and chronic pain. Their modes of action are known to occur mainly via the μ, δ, and κ opioid receptors.[1] The (−)-isomer of morphine (Figure 1), the natural plant product of opium, is a potent μ-receptor agonist and is widely used to treat acute and chronic pain. Unfortunately, when the natural (−)-morphine, and other opioids derived from (−)-morphine, interact with the opioid μ-receptor, and with other receptors, undesired physiological responses occur, such as respiratory depression,[2] tolerance,[3] and hyperalgesia[3] associated with chronic opioid use. One receptor interaction of some opioids that has recently been recognized is their activation of Toll-like 4 receptors (TLR-4). That interaction elicits an immune response linked to tolerance and hyperalgesia.[4,5] (+)-Naltrexone (Figure 1), the unnatural enantiomer which does not interact with opioid receptors, was proven to act as a functional TLR-4 antagonist[5] and has been shown to reduce the incubation period for cue-induced heroin seeking when administered during the withdrawal phase.[6]

Since (+)-naltrexone does not necessarily contain the ideal geometric shape for TLR-4 antagonism, we decided to synthesize simpler and more flexible analogues to see if they would display TLR-4 antagonism. These unnatural (stereochemistry relative to natural (−)-morphine and (−)-naltrexone), structurally simpler analogues could theoretically also be useful in the treatment of opioid dependence (e.g., (+)-naltrexone). (−)-Naltrexone has been examined as a treatment medication[7] for opioid dependence and alcohol abuse; its structurally simpler analogues in the "natural" series might have analgesic or narcotic antagonist activity.

Our initial targets of this study, the enantiomers of 3-(cyclopropylmethyl)-4a,9-dihydroxy-2,3,4,4a,5,6-hexahydro-1*H*-benzofuro[3,2-*e*]isoquinolin-7(7a*H*)-one (Figure 1, (+)- and (−)-**1**), were chosen because of their structural similarity to the enantiomers of naltrexone (in Figure 1, the C14-OH numbering system in naltrexone is from opioid nomenclature; in (+)-**1**, numbered using IUPAC convention, the C4a position is comparable to naltrexone's C14). In **1** (Figure 1), the benzylic carbon of naltrexone (C-10 in naltrexone) has been removed, and that, we reasoned, might be advantageous because of the somewhat increased flexibility offered by the structural simplification. In addition, we were aware that methods were available in the literature for the synthesis of an *N*-methyl relative of a precursor to the desired isoquinolinone

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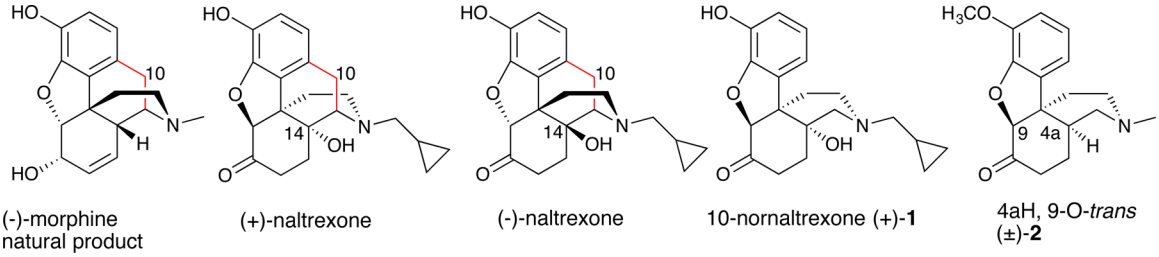
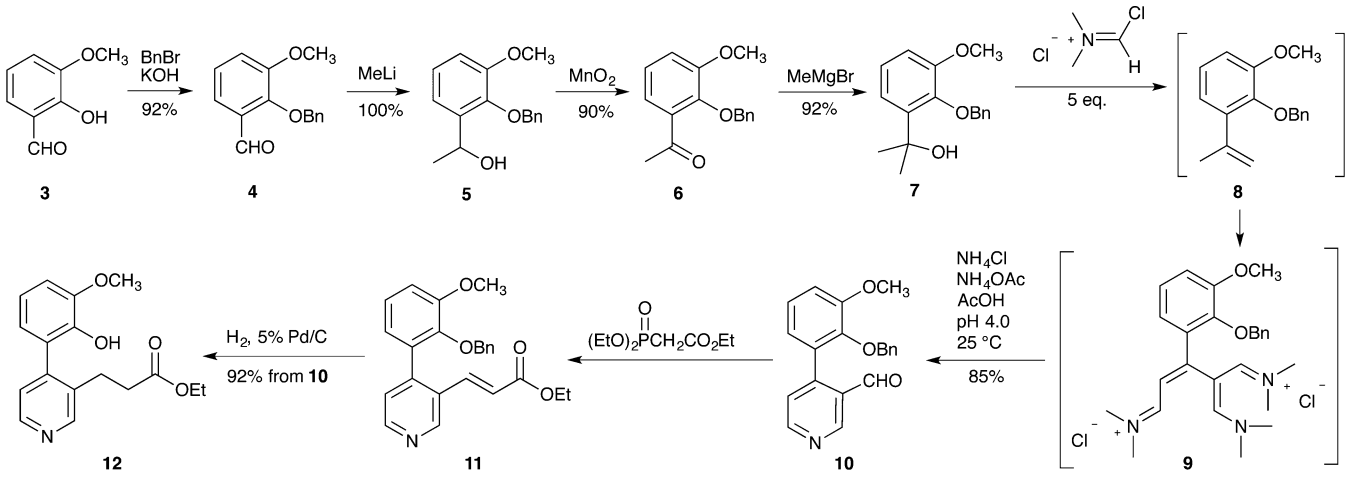


Figure 1. "Natural" and synthetic opioids.

Scheme 1. Nonchromatographic, Optimized Synthesis of Pyridine 12



2.[8] This racemic 4aH,9-*O*-*trans*-9-methoxy-3-methyl-2,3,4,4a,5,6-hexahydro-1*H*-benzofuro[3,2-*e*]isoquinolin-7-(7a*H*)-one ((±)-**2**, Figure 1) of Weller et al.[8] was prepared in a 13-step sequence from *o*-vanillin. It lacked our needed substituent on nitrogen and a 4a-hydroxyl group. It was, also, racemic, and their methodology was inadequate for our purposes. Cheng et al.[9] modified the route of Weller et al.[8] to make an *N*-cyclopropylmethyl analogue of (±)-**2** (Figure 1); however, their methods also did not meet our requirements. We needed to obtain a relatively large amount of material so that we could not only synthesize the enantiomers of **2** but, as well, create other structures, enabling the exploration of the structure−activity relationships of ligands that would and would not interact with the TLR-4 as antagonists. The chromatographic methods that had been used in preparing *trans* (±)-**2** could not easily produce sufficient material for our purposes.

Thus, we devoted our efforts, first, to improve the methodology leading to **2**. We succeeded in obtaining a nonchromatographic optimized synthesis of an intermediate to **2**, ethyl 3-(4-(2-hydroxy-3-methoxyphenyl)pyridin-3-yl)-propanoate (**12**, Scheme 1), and we obtained it on a multigram (ca. 200 g) scale. A route from the pyridinylpropanoate **12** to 4aH,9-*O*-*trans*-9-methoxy-3-methyl-2,3,4,4a,5,6-hexahydro-1*H*-benzofuro[3,2-*e*]isoquinolin-7(7a*H*)-one ((±)-**2**) was visualized as shown in Scheme 2. We thought that the *trans*-isoquinolinone **2** would prove to be a suitable compound for optical resolution from which we would eventually obtain the enantiomers of **1**. Introduction of the needed 4a-OH group in the diene (−)-**20** (7,9-dimethoxy-3-methyl-2,3,4,7a-tetrahydro-1*H*-benzofuro[3,2-*e*]isoquinoline) was achieved through the use of hydrogen peroxide in acidic media (Scheme 5). We now had the complete skeleton of the 10-nornaltrexone compound and it only remained to find a way to replace an *N*-methyl moiety with the 3-cyclopropylmethyl group in **1**, and that was done with cyanogen bromide, as shown in Scheme 6. After accomplishing that, we proceeded to shorten the procedure of Cheng et al.[9] for the synthesis of **36** from **12** (Scheme 7). The racemate **36** was optically resolved, and each of its hitherto-unknown enantiomers were used to prepare (+)- and (−)-**1**.

RESULTS AND DISCUSSION

Optimization of the Synthesis of the Key intermediate 12 from *o*-Vanillin (3). We optimized the synthesis of **2**, ethyl 3-(4-(2-hydroxy-3-methoxyphenyl)pyridin-3-yl)-propanoate (**12**), by eliminating chromatography (Scheme 1). Starting with the commercially available *o*-vanillin, we prepared 2-(2-(benzyloxy)-3-methoxyphenyl)propan-2-ol (**7**) in over 70% overall yield. Minor modifications in reagent choice were made to the literature route[8] to obtain high-yield transformations (Scheme 1). The low yield in the literature route[8] in going from alcohol **7** to 4-(2-(benzyloxy)-3-methoxyphenyl)-nicotinaldehyde (**10**, Scheme 1) had to be eliminated to allow significant mass throughput. Reaction of styrene with Vilsmeier reagent followed by treatment with hot aqueous NH_4Cl was shown by Jutz[10] to give 4-phenylnicotinaldehyde. Weller et al.[8] applied this reaction to **8**, presumably leading to intermediate **9**, which was cyclized to pyridine **10** upon heating in acidic workup. This reaction proceeded in a relatively poor yield of 41% (34% from **7**), possibly due to loss during chromatographic purification and significant decomposition during cyclization under their hot (100 °C), strongly acidic conditions. We determined that **10** could be efficiently accessed directly from alcohol **7** under modified Vilsmeier conditions. We utilized chloroform for formation of the Vilsmeier reagent, in situ,[11] for the dehydration of benzyl alcohol **7** and its conversion to Vilsmeier product **9**.

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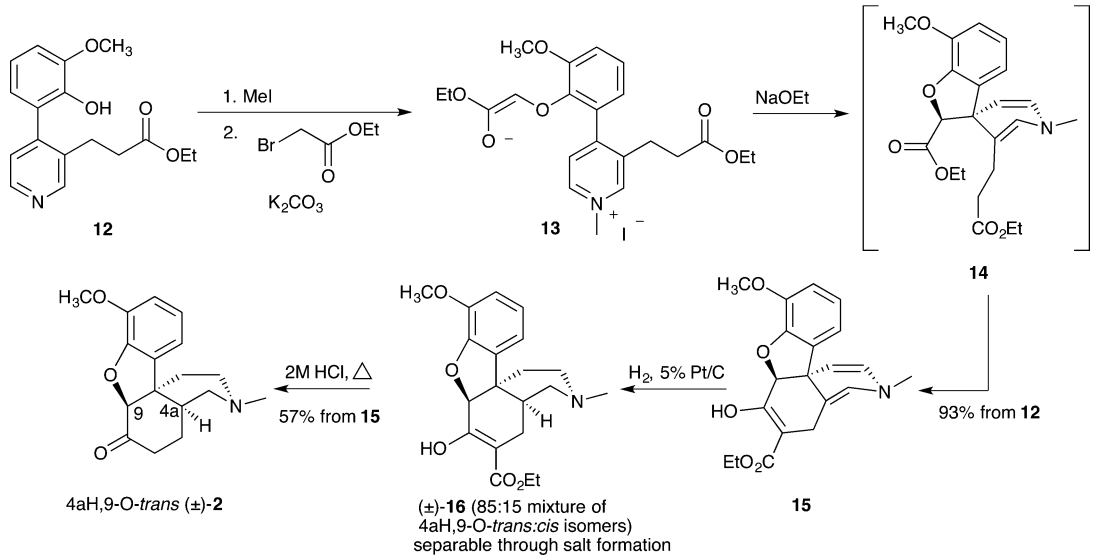
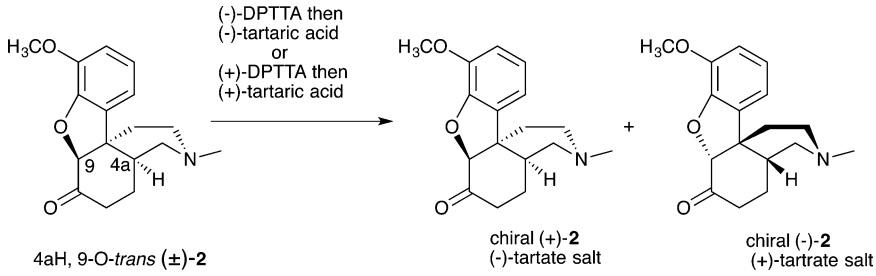
Scheme 2. Synthesis of 4aH,9-*O*-*trans*-(±)-2



Scheme 3. Optical Resolution of 4aH,9-*O*-*trans*-(±)-2



The use of refluxing chloroform instead of 1,2-dichloroethane[8] as a much superior solvent permitted a lower reaction temperature and complete solubilization of the Vilsmeier reagent, intermediate products, and the desired product **9**. By generating styrene **8** in situ from alcohol **7**, we eliminated the Weller et al.[8] isolation and purification of **8** for our large-scale synthesis. Attempted medium-scale purification of styrene **8** by high vacuum distillation resulted in a significant material loss from polymerization. By also controlling the pH, conducting the hydrolysis at 25 °C overnight (instead of 100 °C)[8] and carefully monitoring the reaction temperature during the acidic hydrolysis–cyclization event (**9** → **10**), a high yield (85%) was obtained (Scheme 1). In addition, by eliminating chromatography of alkene **11** and purifying the pyridinyl **12** through formation of the oxalate salt, the overall yield was greatly improved and large quantities of **12** (ca. 200 g batches) were readily prepared from *o*-vanillin (**3**) without the need for chromatography.

Synthesis of the Substrate for Optical Resolution, 4aH,9-*O*-*trans*-9-Methoxy-3-methyl-2,3,4,4a,5,6-hexahydro-1*H*-benzofuro[3,2-*e*]isoquinolin-7(7a*H*)-one ((±)-2). The synthesis of 4aH,9-*O*-*trans*-(±)-**2** from pyridinyl **12** was achieved following the Weller et al. route, with some modifications (Scheme 2). The stereoselective reduction of the trisubstituted alkene **15** was performed with 5% Pt/C rather than the more reactive PtO_2, while the resulting 85:15 mixture of 4aH,9-*O*-*trans*:*cis* ring juncture isomers **16** were separated by crystallization of the desired *trans* isomer as a tosylate salt. Weller et al.[9] reported a separation of the *cis* and *trans* isomers of racemic *trans*-(±)-**2** with recrystallization from benzene/hexane after subjecting crude **16** to acidic hydrolysis–decarboxylation. Acid hydrolysis led to the desired 4aH,9-*O*-*trans*-isoquinolinone **2**.

Having successfully improved the methodology leading to (±)-**2** on a sufficiently large scale (20 g) without the use of chromatograpy, we then focused on its optical resolution. We hoped to find a method that would result in the isolation in good yield of both enantiomers, since both were needed to obtain the corresponding enantiomers of **1** that would eventually be subjected to pharmacological evaluation. A chiral resolution of the racemic 4aH,9-*O*-*trans*-(±)-**2** (Scheme 3) was achieved by initially forming the (−)-*O*,*O*′-di-*p*-toluoyl-D-tartaric acid (DPTTA) salt in acetone, resulting in an ee of approximately 92% enriched in (+)-**2** (the ee was determined using ^{1}H NMR, through the addition of a chiral shift reagent ((*R*)-(−)-α-(trifluoromethyl)benzyl alcohol), which resolved the singlet at 4.34 ppm, as shown in the Supporting Information).[12,13] Formation of the (−)-tartaric acid salt in MeOH from the enriched free base enhanced the ee to >98%. Chiral (−)-**2** was isolated in >98% ee after treatment of the free-base filtrates with (+)-DPTTA and subsequently (+)-tartaric acid in an analogous fashion. In order to unambiguously determine the absolute stereochemistry of chiral (+)-**2**, the (*R*)-mandelic acid salt was prepared. Single-crystal X-ray diffraction determined that the absolute stereochemistry of the (+)-**2** enantiomer was analogous to that found in the unnatural (+)-isomer of morphine.

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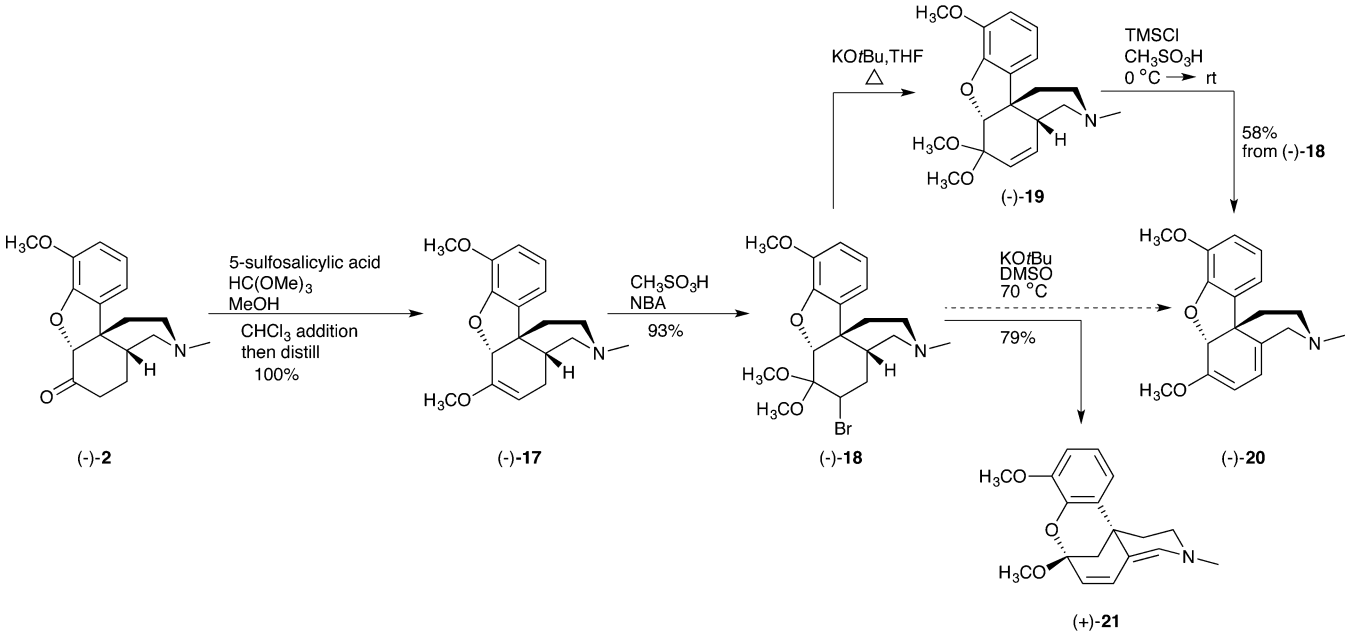
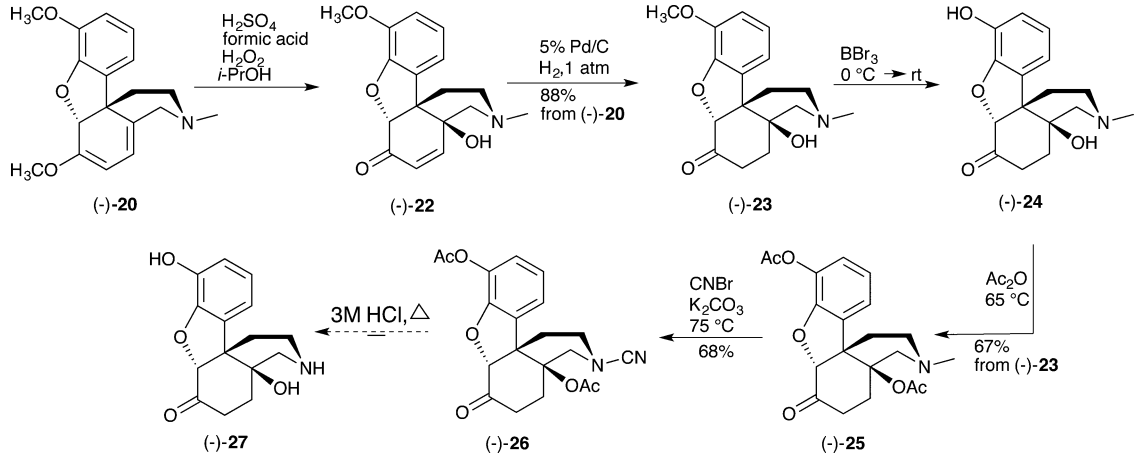
Scheme 4. Synthesis of 10-Northebaine (−)-20 and an Unusual Tetracyclic Enamine (+)-21



Scheme 5. Introduction of the 4a-OH in 22 and Attempted Deprotection of 26



Synthesis of Diene Intermediate 20 for Introduction of the 4a-OH and Isolation of Rearrangement Product 21. The enantiomers of **2** had the correct skeletal geometry of the targeted compound **1**. Missing, however, was a 4a-OH group, and we needed an *N*-cyclopropylmethyl replacement for the *N*-methyl moiety. We thought that the needed 4a-OH group could be easily introduced through a diene intermediate, 7,9-dimethoxy-3-methyl-2,3,4,7a-tetrahydro-1*H*-benzofuro[3,2-*e*]isoquinoline (**20**, 10-northebaine), because a comparable hydroxyl group had been successfully introduced in a structural analogue, *N*-northebaine (7,9-dimethoxy-2,3,4,7a-tetrahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline).[14] Unfortunately, the most direct route (Scheme 4) for this gave us a rearrangement product, a tetracyclic enamine 7,9-dimethoxy-3-methyl-1,2,3,7-tetrahydro-7,12b-methanobenzo[2,3]oxocino-[5,4-*c*]pyridine ((+)-**21**).

The route involved the synthesis of the trimethoxy bromide (−)-**18** (Scheme 4, 6-bromo-7,7,9-trimethoxy-3-methyl-2,3,4,4a,5,6,7,7a-octahydro-1*H*-benzofuro[3,2-*e*]isoquinoline). Its precursor, the methyl enol ether (−)-**17**, was formed from (−)-**2** and smoothly brominated giving a single stereoisomer (−)-**18**, under conditions that were successfully utilized in a synthesis of the isoquinolone, *N*-northebaine.[14] Treatment of the trimethoxybromide (−)-**18** with KO^{t}Bu in DMSO at 70 °C was expected to result in the 10-northebaine congener (−)-**20** (7,9-dimethoxy-3-methyl-2,3,4,7a-tetrahydro-1*H*-benzofuro-[3,2-*e*]isoquinoline) via double elimination, as also formerly reported in the synthesis of *N*-northebaine[14] (Scheme 4). However, under these reaction conditions, a high yield of a tetracyclic rearrangement product (+)-**21** was obtained as the only isolable reaction product. The unique structure of tetracyclic enamine (+)-**21** was verified by single crystal X-ray analysis of the free base. This novel molecule could possibly provide a new structure class of opioid-like analgesics.

The desired dimethoxydiene **20** was obtained using an extra step. By performing the elimination reaction on (−)-**18** (Scheme 4) in refluxing THF, the single elimination product (−)-**19** was cleanly obtained. Transformation of this intermediate to the desired 10-northebaine (−)-**20** was achieved utilizing trimethylsilyl chloride (TMSCl) and CH_3SO_3H. This route was initially carried out in the (−)-series and later repeated in the (+)-series. Having found a

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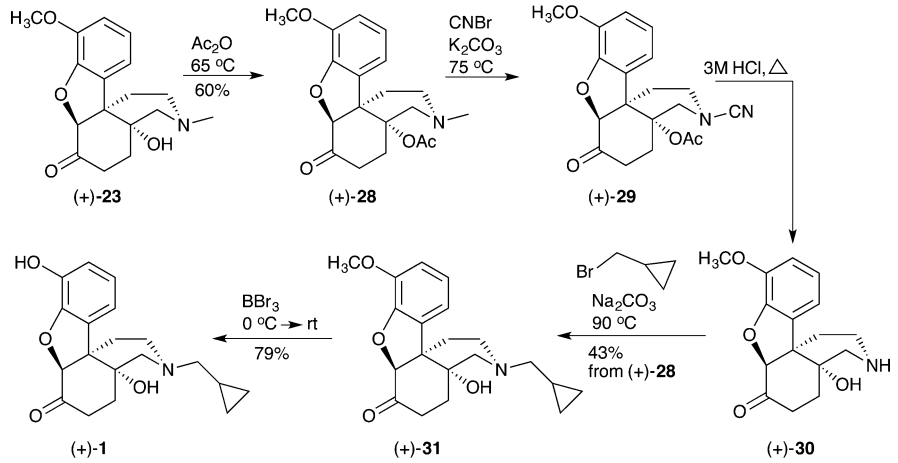
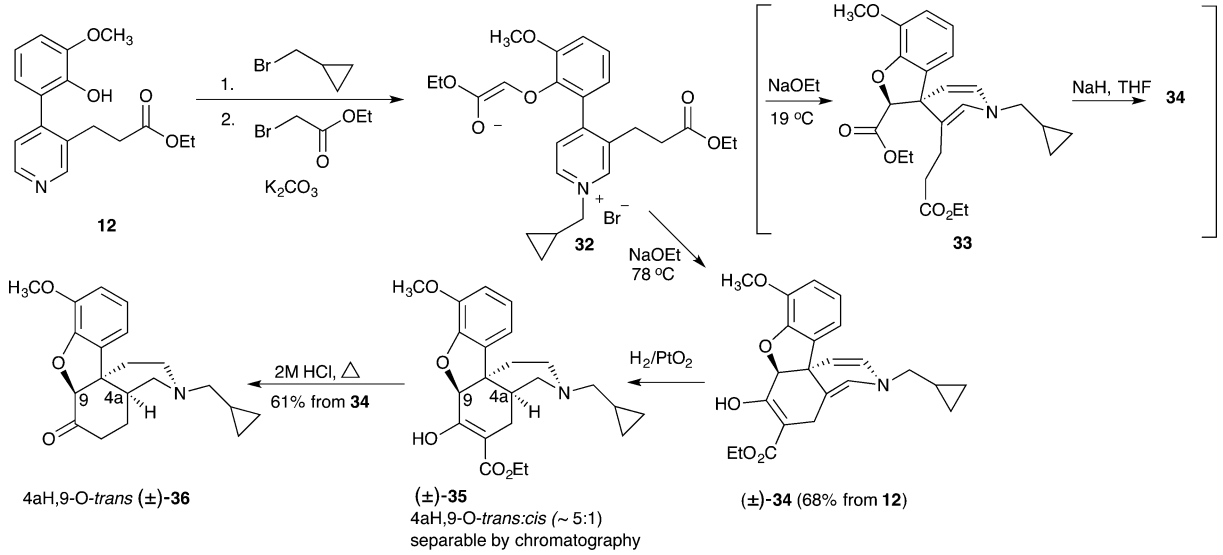
Scheme 6. Conversion to *N*-Cyclopropylmethyl Derivative



Scheme 7. Ring Closure Leading to Intermediate 4aH,9-*O*-*trans*-(±)-36



nonchromatographic route to the dimethoxydiene **20** that could be used for producing a sufficient quantity of product for further work, we concentrated on the final series of conversions to obtain both (−)- and (+)-**1**.

Introduction of the 4a-OH and Conversion of *N*-Methyl to *N*-Cyclopropylmethyl in the Synthesis of the Final Product (1). The 4a-OH (14-OH in opioid nomenclature) substituent was smoothly incorporated into the dimethoxydiene **20** (Scheme 5) with hydrogen peroxide under acidic conditions via epoxide formation/opening to form the 4a-hydroxyisoquinolinone **22** (4a-hydroxy-9-methoxy-3-methyl-2,3,4,4a-tetrahydro-1*H*-benzofuro[3,2-*e*]isoquinolin-7-(7a*H*)-one). The crude enone was catalytically reduced using Pd/C to ketone **23** (4a-hydroxy-9-methoxy-3-methyl-2,3,4,4a,5,6-hexahydro-1*H*-benzofuro[3,2-*e*]isoquinolin-7-(7a*H*)-one), initially in the (−)-series (Scheme 5), followed by the (+)-series.

Cleavage of the aromatic methoxy group in (−)-**23** gave the *N*-methyl analogue of the phenol, 4a,9-dihydroxy-3-methyl-2,3,4,4a,5,6-hexahydro-1*H*-benzofuro[3,2-*e*]isoquinolin-7-(7a*H*)-one (10-noroxymorphone ((−)-**24**). Subsequent protective acylation of the dihydroxyisoquinolinone (−)-**24** afforded (−)-**25**. *N*-Demethylation of the diacetyl compound **25** provided an *N*-cyano derivative (−)-**26**. In several trials, the hydrolysis of (−)-**26** to (−)-**27** proved problematic; thus, we conceptualized an alternate route to (+)- or (−)-**1** as shown in Scheme 6.

We determined that it was not necessary to cleave the aromatic methoxyl group in **23** and then protect it by acetylation; thus, we changed the reaction sequence. Only the 4a-OH in **23** was acetylated to give **28**, as shown in Scheme 6 for the (+)-series (the enantiomeric (−)-compounds were also synthesized). This was followed by *N*-demethylation of (+)-**28** to provide the monoacetylated *N*-cyano compound (+)-**29**. Under acidic conditions, the acetyl and cyano protecting groups were removed to give free amine (+)-**30**. *N*-Alkylation with cyclopropylmethyl bromide afforded (+)-**31**, which was O-demethylated to arrive at the target compound (+)-3-(cyclopropylmethyl)-4a,9-dihydroxy-2,3,4,4a,5,6-hexahydro-1*H*-benzofuro[3,2-*e*]isoquinolin-7(7a*H*)-one (10-nornaltrexone (+)-**1**) in a total of 24 steps from commercially available *o*-vanillin with an overall yield of 3.1%.

Alternate Route to 1 from 12 through Formation of Intermediate 36. While the desired target compound (+)-**1** could be obtained as shown in Scheme 6, we sought a shorter, more practical route. Using our improved route to the ethyl 3-

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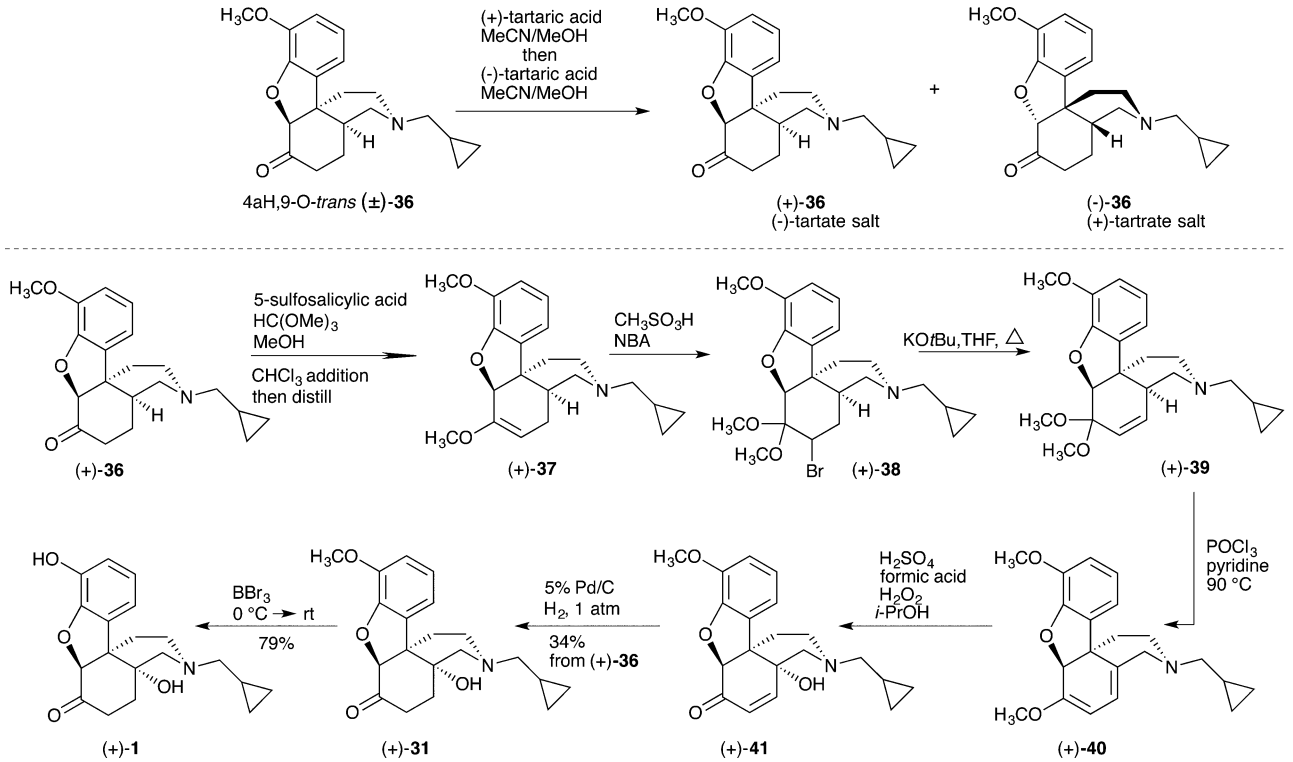
Scheme 8. Optical Resolution of 4aH,9-*O*-*trans*-(±)-36 and the Improved Synthesis of 10-Nornaltrexone (+)-1 or (−)-1



(4-(2-hydroxy-3-methoxyphenyl)pyridin-3-yl)propanoate (**12**, Scheme 1), we introduced the *N*-cyclopropylmethyl substituent at a much earlier stage, an approach that had been used by Cheng et al.[9] as an adaptation of the earlier work of Weller et al.[8] This obviated the necessity of using a difficultly accessible benzopyranopyridinone[15] and, as well, eliminated the four-step sequence required to transform the *N*-methyl into *N*-cyclopropylmethyl, since the latter moiety was introduced at an earlier stage of a reaction sequence that did not involve *N*-methyl-substituted intermediates (Scheme 7). The pyridinyl **12** was *N*-alkylated to the quaternary amine **32** using (bromomethyl)cyclopropane. Formerly, ring closure of the crude **32** was accomplished in two steps. First, basic conditions (NaOEt at 19 °C) gave **33**.[9] The latter was subjected to NaH in refluxing THF to afford product **34**. We have now found that the quaternary amine **32**, under basic conditions (NaOEt, at 78 °C), afforded the Dieckmann condensation product **34** (4aH,9-*O*-*trans*-ethyl 3-(cyclopropylmethyl)-7-hydroxy-9-methoxy-5,7a-dihydro-3*H*-benzofuro[3,2-*e*]isoquinoline-6-carboxylate) directly. The elimination of the isolation of the intermediate **33** enabled us to obtain **34** in 68% yield from **12**, rather than the <50% yield formerly obtained. The catalytic reduction of **34** (Scheme 7) and subsequent hydrolysis/de-esterification was performed as noted in the literature[9] and afforded 4aH,9-*O*-*trans*-(±)-**36** in 61% yield.

Optical Resolution of Intermediate 4aH,9-*O*-*trans*-(±)-36 and Completion of Alternate Synthesis of Final Product 1. An optical resolution of 4aH,9-*O*-*trans*-(±)-**36**[9] (3-(cyclopropylmethyl)-9-methoxy-2,3,4,4a,5,6-hexahydro-1*H*-benzofuro[3,2-*e*]isoquinolin-7(7a*H*)-one), Scheme 8, top) was achieved by formation of the (+)-tartrate salt in MeCN/MeOH 6:1 to give chiral (−)-**36** with an ee > 98%. The resultant filtrates enriched in the enantiomeric (+)-**36** were free based and treated with (−)-tartaric acid in MeCN/MeOH 6:1 to give chiral (+)-**36** with an ee > 98%. The same reaction conditions established in the *N*-methyl series **2** → **19** (Scheme 4) were exploited to synthesize (+)-**39** (3-(cyclopropylmethyl)-7,7,9-trimethoxy-2,3,4,4a,7,7a-hexahydro-1*H*-benzofuro[3,2-*e*]-isoquinoline) from (+)-**36** (Scheme 8, bottom). Transformation of (+)-**39** into (+)-10-northebaine ((+)-**40**, 3-(cyclopropylmethyl)-7,9-dimethoxy-2,3,4,7a-tetrahydro-1*H*-benzofuro[3,2-*e*]isoquinoline) scaled more effectively with $POCl_3$ in pyridine at 90 °C, while the remaining three steps were performed in an analogous fashion to the *N*-methyl series, **20** → **26** (Scheme 5), to give the desired 10-nornaltrexone (+)-**1** and, in the (−)-series, (−)-**1**, in a total of 20 steps from *o*-vanillin an overall yield of 6.6%.

Preliminary Pharmacological Data. In vitro TLR-4 antagonism studies with 10-nornaltrexone (+)-**1** are currently underway and will be the topic of a future report. In preliminary opioid receptor binding studies, (−)-**1** appeared to interact selectively with the μ receptor with roughly four times the affinity of morphine and had about 40 times less affinity for the κ receptor than naltrindole. It is important to note that additional studies must be conducted to determine the K_i's at each of the opioid receptors and to determine if the compound acts as an agonist or an antagonist at these receptors.

CONCLUSIONS

Enantiopure 10-nornaltrexone ((3-(cyclopropylmethyl)-4a,9-dihydroxy-2,3,4,4a,5,6-hexahydro-1*H*-benzofuro[3,2-*e*]-isoquinolin-7(7a*H*)-one) compounds (+)-**1** and (−)-**1**, which lack the bridging benzylic carbon commonly found in opiates, have been synthesized in 20 steps from *o*-vanillin in an effort to obtain TLR-4 antagonists and novel opioid ligands. Preliminary results show that (−)-10-nornaltrexone ((−)-**1**) binds to the μ opioid receptor with about four times the affinity of morphine. During these synthetic studies, a structurally unique tetracyclic

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enamine **21** was formed, which could provide a different type of skeleton for opioid analgesics. Further pharmacological work with these compounds is in progress and will be reported in the future.

EXPERIMENTAL SECTION

General Experimental Methods. All melting points are uncorrected. Proton and carbon nuclear magnetic resonance were recorded on a 400 or 500 MHz instrument in $CDCl_3$ (unless otherwise noted) with the values given in ppm and J (Hz) assignments of ^1H resonance coupling. Thin-layer chromatography (TLC) was performed on 0.25 mm Analtech GHLF silica gel.

*2-Benzyloxy-3-methoxybenzaldehyde (**4**).* The procedure of Cotterill et al.[16] was modified as follows: A mixture of deionized H_2O (1.25L), 85% KOH (234.2 g of 85%, 3.540 mol), and 100% ethanol (1 L) was refluxed for 10 min under a stream of nitrogen in a three-neck, 5 L flask with mechanical stirrer, reflux condenser, addition funnel, and nitrogen inlet. *o*-Vanillin (499.1 g, 3.280 mol) was melted and cautiously added to the solution. Neat benzyl bromide (421.9 mL, 606.7 g, 3.550 mol) was added to the solution in a thin stream to maintain a gentle reflux. At the end of the addition, 85% KOH (85.8 g, 1.30 mol) was cautiously added followed by benzyl bromide (154.5 mL, 222.2 g, 1.300 mol) at a rate sufficient to maintain gentle reflux. When the addition was complete, the mixture was refluxed for 0.5 h. Most of the ethanol was then stripped under aspirator vacuum using a high capacity condenser (ice water cooling) to collect about 1.25 L of ethanol−water mixture. The residual organic product layer was separated and the aqueous layer extracted with Et_2O (2 × 250 mL). The combined organic phase was washed with 10% NaCl solution (0.5 L) and the Et_2O evaporated under the aspirator. The residue was distilled from a 3-neck 2 L flask with a mechanical stirrer with an oil bath. A forerun was collected up to 85 °C and then a second forerun up to bp 135 °C/100 μm. The product 2-benzyloxy-3-methoxybenzaldehyde **4** (731.1 g, 92%) was then collected at bp 135 °C/100 μm as an oil that solidified to a white crystalline mass upon cooling to room temperature. Spectra matched those reported by Cotterill et al.[16]

*1-(2-(Benzyloxy)-3-methoxyphenyl)ethanol (**5**).* The melted aldehyde **4** (484.2 g, 2.0 mol) was dissolved under nitrogen in dry Et_2O (1.4 L) in a mechanically stirred, three-neck 5 L flask with condenser, addition funnel, and thermometer. The reaction flask was cooled to −78 °C, and methyllithium·LiBr (1.5M, 1.4 L, 2.1 mol) was added to the well-stirred mixture in a thin stream, keeping the temperature between −10 and −20 °C. At the end of the addition, an aliquot quenched with water and extracted with Et_2O showed complete reaction of starting material by TLC, and conversion to a lower R_f spot in (Et_2O/petroleum Et_2O 1:2). After 15 min, H_2O (800 mL) was cautiously added with cooling, resulting in a brisk evolution of gas. When the addition was complete, the temperature was allowed to rise to 5−10 °C, and two homogeneous phases resulted. The Et_2O layer was separated and extracted with water (250 mL). The aqueous layers were combined and extracted with Et_2O (2 × 250 mL). Et_2O extracts were combined and evaporated under aspirator vacuum in a mechanically stirred 5 L three-neck flask with a final batch temperature of 90 °C to remove water to afford **5** (518.2 g, 100%) as an oil that was used without further purification. TLC showed a single spot with traces of an unknown impurity at a slightly higher R_f. Spectra matched those reported by Weller et al.[9]

*1-(2-(Benzyloxy)-3-methoxyphenyl)ethanone (**6**).* To the well-stirred mixture of crude alcohol **5** (518.2 g, 2.006 mol) in 1,2-dichloroethane (DCE) (2 L) in a mechanically stirred 5 L three-neck flask was added activated MnO_2 (2.06 kg, 23.7 mol) in small portions. The stirred mixture was then refluxed with a universal water separator for 1.5 h, at which time TLC (Et_2O/petroleum Et_2O 1:2) showed complete conversion to the ketone; the product contained traces of benzaldehyde. The mixture was filtered on a 27 cm Buchner funnel, and the MnO_2 was washed thoroughly with DCE (10 × 500 mL). The combined filtrate and wash were evaporated under the aspirator. An identical run from 2.0 mol of aldehyde gave 519.1 g of alcohol that was oxidized as above and combined with the original batch. This combined material was stripped under high vacuum to a vapor temperature of 135 °C at 150 μm to give 918.2 g of **6**. The forerun collected under high vacuum was redistilled under aspirator vacuum to give 7.4 g of a fraction consisting largely of benzaldehyde. The remaining residue was combined with the first batch to afford pure **6** (921.6 g, 90%) as an oil. Spectra matched those reported by Weller et al.[8]

*2-(2-(Benzyloxy)-3-methoxyphenyl)propan-2-ol (**7**).* A mechanically stirred solution of MeMgBr (3 M in Et_2O, 763 mL, 2.29 mol) in a 5 L three-neck flask with a thermometer and mechanical stirrer was cooled to −15 °C under nitrogen. A solution of ketone **6** (477.3 g, 1.862 mol) in dry toluene (900 mL) was added in a thin stream to the mixture with efficient stirring while keeping the internal temperature between −15 and −20 °C. After 15 min, the stirred mixture was slowly and cautiously treated with H_2O (1500 mL) initially giving off gas. The resulting mixture consisted of an organic layer and thick aqueous slurry of inorganic material. The organic layer was separated and saturated aqueous NH_4Cl (1 L), solid NH_4Cl (250 g), and Et_2O (500 mL) were added to the mixture to give 2 phases containing a slight emulsion at the phase interface after stirring. The aqueous layer was separated from the emulsion and the remaining material easily filtered through Celite. The filter was washed with a little Et_2O, and the organic phase was separated and added to the original toluene−Et_2O solution. The combined organic phase was washed sequentially with half-saturated aqueous NH_4Cl (2 × 400 mL), H_2O (2 × 400 mL), 10% NaOH (2 × 200 mL), and H_2O (3 × 500 mL). The combined organics (about 3 L) were evaporated under aspirator vacuum and then distilled under high vacuum to give **7** (475.3 g, 94%) as an oil containing about 2% unreacted ketone. bp 140 °C/100 Torr. Spectra matched those reported by Weller et al.[8]

*4-(2-(Benzyloxy)-3-methoxyphenyl)nicotinaldehyde (**10**).* To a stirred solution of DMF (50.1 mL, 650 mmol) in anhydrous $CHCl_3$ (150 mL) at an internal temperature of 15 °C was added a solution of oxalyl chloride (53.1 mL, 600 mmol) in anhydrous $CHCl_3$ (100 mL) dropwise at a rate sufficient to maintain the internal temperature below 25 °C. Once the production of gas ceased, a solution of **7** (27.2 g, 100 mmol) in in anhydrous $CHCl_3$ (10 mL) was added. The mixture was refluxed under Ar for 3 h and cooled to room temperature. The mixture was cannulated into a solution of NaOAc·$3H_2O$ (108 g, 800 mmol), NH_4Cl (53 g, 1000 mmol), and AcOH (30 mL) in H_2O (250 mL) while simultaneously removing $CHCl_3$ by distillation from the quenched mixture under aspirator vacuum. The temperature of the quenched mixture was maintained at approximately 25 °C by external heating during the distillation. The reaction mixture was stirred overnight at room temperature and the product crystallized. The product was filtered affording a slightly sticky brown residue, which was dissolved in $CHCl_3$ (150 mL) and sequentially washed with H_2O (150 mL), 10% NaOH (100 mL), and H_2O (2 × 100 mL). The combined organic layers were distilled in a short path still under high vacuum bp ∼190 °C at 100 μm to give 4-(2-(benzyloxy)-3-methoxyphenyl)nicotinaldehyde **10** (27.1 g, 85% yield) as a yellow solid, which was used without further purification. Column chromatography of a small portion of this crude product with EtOAc/hexanes (gradient, 0 → 30%) gave an analytically pure sample of **10**. Spectra matched those reported by Cheng et al.[9]

*Ethyl (E)-3-(4-(2-(Benzyloxy)-3-methoxyphenyl)pyridin-3-yl)-acrylate (**11**).* To stirred pieces of clean, freshly cut sodium (13.7 g, 596 mmol) in a three-neck flask equipped with a reflux condenser was added anhydrous EtOH (700 mL). The mixture was refluxed until a homogeneous solution was obtained, and then the solution was cooled to room temperature. To the reaction mixture was added triethyl phosphonoacetate (118 mL, 133.1 g, 593 mmol), during which a drop in temperature to approximately 23 °C was observed. After the mixture was stirred for 10 min, crude **10** (172 g, 540 mmol) was added in portions maintaining the internal temperature at 20−25 °C with external cooling. After complete addition, the reaction mixture was stirred for 30 min and NH_4Cl (33.3 g) was added. The reaction mixture was concentrated under water vacuum aspiration, and Et_2O (500 mL) and H_2O (500 mL) were added. The aqueous layer was separated and extracted with Et_2O (200 mL). The organics were

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combined and washed with H_2O (3 × 250 mL) and brine (200 mL), filtered through Celite, and concentrated in vacuo to give a dark brown oil. The crude dark brown oil crystallized upon standing overnight and was vacuum oven-dried at 50 °C overnight to afford **11** (212.1 g), which was used without further purification. Column chromatography of a small portion of this crude product with EtOAc/hexanes (gradient, 0 → 25%) gave an analytically pure sample of **11**. Spectra matched those reported by Weller et al.[8]

Ethyl 3-(4-(2-Hydroxy-3-methoxyphenyl)pyridin-3-yl)propanoate (12). To a solution of crude ethyl (*E*)-3-(4-(2-(benzyloxy)-3-methoxyphenyl)pyridin-3-yl)acrylate **11** (35.4 g, 90.8 mmol) in THF (180 mL) was added Pd/C (3.0 g). The mixture was degassed and subjected to hydrogenation under 60 psi of H_2. After 30 min, the reaction mixture was filtered through a pad of Celite, washing with additional THF (30 mL). The above procedure was repeated (5 × 35.4 g), combining product mixtures from each. The combined product mixtures were concentrated in vacuo and heated in acetone (400 mL). To the heated crude mixture was added oxalic acid (50 g) in warm acetone (150 mL). The oxalate salt began crystallizing immediately. The mixture was cooled to 0 °C, filtered, and rinsed with cold (0−5 °C) acetone (633 mL) followed by petroleum Et_2O (2 × 200 mL). The oxalate salt was air-dried overnight to afford the oxalate salt of **12** (193.83 g, 92% from **10**). The **12**·oxalate (193.21g, 0.49 mol) was converted to the free base in H_2O (1.3 L), $CHCl_3$ (600 mL), and 28% NH_4OH (100 mL) in a 3 L separatory funnel. The $CHCl_3$ was separated, and the aqueous solution was extracted with $CHCl_3$ (2 × 100 mL). The combined chloroform extracts were filtered through Celite leaving a small amount of purple sludge on the filter. The chloroform was evaporated, and the resulting syrup dissolved in Et_2O (560 mL) to rapidly give crystalline **12**. The **12** was filtered, washed with Et_2O, and dried to give 141.21 g. The filtrate and wash was evaporated to give a 3.90 g of second crop for a total of 145.11 g (97.3% from **12**·oxalate, 89.1% from crude **10**). Spectra matched those reported by Weller et al.[8]

Ethyl (12bR)-7-Hydroxy-9-methoxy-3-methyl-5,7a-dihydro-3H-benzofuro[3,2-e]isoquinoline-6-carboxylate (15). To a stirred solution of ethyl ester **12** (30.1 g, 99.9 mmol) in DMF (150 mL) was added iodomethane (8.25 mL, 133 mmol). The reaction mixture was heated at 50 °C for 1 h verifying the disappearance of starting material by TLC, cooled to room temperature, and concentrated in vacuo. To the crude intermediate was added DMF (150 mL) followed by K_2CO_3 (20.7 g, 150 mmol) and ethyl bromoacetate (12.2 mL, 110 mmol). The reaction mixture was stirred for 1 h at room temperature, filtered, and concentrated in vacuo. In a separate flask, anhydrous EtOH (150 mL) was added to freshly cut pieces of sodium (9.2 g, 400 mmol) and refluxed until a homogeneous solution was obtained. This freshly prepared NaOEt solution was cooled to room temperature and cannulated into the crude bis ethyl ester rinsing with THF (150 mL). The reaction mixture was refluxed for 1.5 h and cooled to −5 °C. The reaction mixture was cannulated into a rapidly stirred mixture of saturated aqueous NH_4Cl (147.6 g) and H_2O (147 g) at −5 °C, rinsing the reaction flask with THF (3 × 25 mL). The reaction mixture was concentrated in vacuo to ∼700 mL removing most of the organics. The aqueous layer was extracted with $CHCl_3$ (3 × 150 mL) and the combined organics were concentrated in vacuo to give a dark syrup. This dark syrup was dissolved in toluene (300 mL), and washed with H_2O (150 mL) and brine (100 mL). The aqueous washes were extracted with toluene (2 × 50 mL). The combined toluene extracts were concentrated in vacuo to ∼1/3 volume, filtered through Celite, and concentrated in vacuo to give **15** (32.1 g, 93%) as an orange solid. Spectra matched those reported by Weller et al.[8]

4aH,9-O-trans 9-Methoxy-3-methyl-2,3,4,4a,5,6-hexahydro-1H-benzofuro[3,2-e]isoquinolin-7(7aH)-one ((±)-2). To a solution of crude **15** (40.9 g, 115 mmol) in THF (200 mL) was added wet 5% Pt/C (40% in H_2O) (15 g), which was first dried by filtering a suspension of the catalyst in THF (60 mL) through Celite and rinsing with THF (5 × 50 mL). The mixture was degassed and subjected to hydrogenation under 60 psi of H_2. After 2 h, the reaction mixture was filtered through a pad of Celite with washing with additional THF (200 mL) and concentrated in vacuo. To the crude solution in 2-butanone (400 mL) was added anhydrous TsOH prepared by azeotropically distilling TsOH·H_2O (22.2 g) with a Dean−Stark trap. The tosylate salt formed almost immediately. The mixture was cooled to ∼20 °C, filtered, and rinsed with 2-butanone (200 mL) to give the ethyl ester **16** as the tosylate salt. The tosylate salt was free-based with concentrated NH_4OH (10 mL) in H_2O (100 mL), extracted with $CHCl_3$ (3 × 150 mL), and concentrated in vacuo. To the free base was added 3 M HCl (300 mL). The solution was refluxed for 2 h, cooled to room temperature, and extracted with $CHCl_3$ (300 mL). The aqueous layer was basified with 3 M NaOH to a pH ∼9 and extracted with $CHCl_3$ (3 × 200 mL). The combined organics were concentrated in vacuo to give racemic *trans*-(±)-**2** (18.04 g, 57% from **15**) as a yellow solid.

Optical Resolution of (4aS,7aS,12bR)-9-Methoxy-3-methyl-2,3,4,4a,5,6-hexahydro-1H-benzofuro[3,2-e]isoquinolin-7(7aH)-one (+)-2 and (4aR,7aR,12bS)-9-Methoxy-3-methyl-2,3,4,4a,5,6-hexahydro-1H-benzofuro[3,2-e]isoquinolin-7(7aH)-one (−)-2. To a crude solution of (±)-**2**[9] (20.5 g, 71.2 mmol) in acetone (150 mL) was added a solution of (−)-O,O′-di-*p*-toluoyl-L-tartaric acid (DPTTA) (30.3 g, 78.4 mmol) in acetone (100 mL). A precipitate formed almost immediately. The solution was cooled to 0 °C and maintained at that temperature for 15 min. The precipitate was filtered, rinsed with cold acetone, and free-based in H_2O (100 mL) containing concentrated NH_4OH (5 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 100 mL), washed with H_2O (100 mL), and concentrated in vacuo to afford a mixture of (+)-**2** and (−)-**2** (7.25 g, free base). To a solution of this mixture in MeOH (75 mL) was added a solution of (−)-tartaric acid (4.17 g, 27.8 mmol) in MeOH (25 mL). A white precipitate formed almost immediately. The suspension was cooled to 0 °C and maintained at that temperature for 15 min. The precipitate was filtered and rinsed with cold MeOH (75 mL), cold acetone (75 mL), and Et_2O (75 mL) to afford (+)-**2**-(−)-tartaric acid salt (10.5 g). >98% ee. The chiral shift reagent (*R*)-(−)-α-(trifluoromethyl)benzyl alcohol was added to the free base to determine the ee by examination of the resolved singlet at 4.34 ppm in the ^{1}H NMR.[12,13] All data were obtained on the free base: $[\alpha]^{20}_D$ +189.1 (*c* 0.9, $CHCl_3$); mp 156−158 °C; IR (thin film) 1721 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, *J* = 8.0 Hz, 1H), 6.75−6.69 (m, 2H), 4.34 (s, 1H), 3.78 (s, 3H), 2.76 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.61 (d, *J* = 12.0 Hz, 1H), 2.49 (t, *J* = 12.0 Hz, 1H), 2.42 (m, 1H), 2.32 (s, 3H), 2.30−2.20 (m, 3H), 1.90 (td, *J* = 12.0, 4.0 Hz, 1H), 1.78 (m, 1H), 1.66 (m, 1H), 1.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2, 148.9, 145.4, 130.5, 121.3, 118.7, 112.4, 91.8, 56.7, 56.0, 51.9, 50.3, 46.0, 40.2, 39.3, 38.7, 25.5; HRMS (TOF MS ES$^+$) calcd for $C_{17}H_{22}NO_3$ (M + H$^+$) 288.1600, found 288.1593. Anal. Calcd for ($C_{17}H_{21}NO_3$): C (71.06), H (7.37), N (4.87). Found: C (70.76), H(7.56), N (4.91).

The filtrate from above was concentrated in vacuo, free-based with concentrated NH_4OH (5 mL) in H_2O (100 mL), and extracted with $CHCl_3$ (3 × 100 mL). The combined organic fractions were washed with H_2O (100 mL) and concentrated in vacuo to give free base enriched in (−)-**2**. The above procedure was repeated using (+)-DPTTA (1.1 equiv) and (+)-tartaric acid (1.1 equiv) to afford (−)-**2**-(+)-tartaric acid salt, >98% ee. Free base $[\alpha]^{20}_D$ −192.3 (*c* 1.0, $CHCl_3$).

(4aR,7aR,12bS)-7,9-Dimethoxy-3-methyl-2,3,4,4a,5,7a-hexahydro-1H-benzofuro[3,2-e]isoquinoline ((−)-17). To a stirred solution of (−)-**2** (2.25 g, 7.82 mmol) in MeOH (35 mL) was added a premixed solution of 5-sulfosalicylic acid dihydrate (3.57 g, 14.1 mmol) and trimethyl orthoformate (8.5 mL, 78 mmol) in MeOH (20 mL). The reaction mixture was refluxed for 1 h, and then $CHCl_3$ (3 × 75 mL) was added and removed by distillation. The reaction mixture was cooled to 0 °C, and a precooled solution of 1.5 M NaOH (100 mL) at 0 °C was added. The aqueous layer was extracted with $CHCl_3$ (3 × 100 mL), washed with H_2O (100 mL), and concentrated in vacuo to afford (−)-**17** (2.36 g, 100%) as a yellow solid, which was used without further purification: $[\alpha]^{20}_D$ −168.5 (*c* 1.2, $CHCl_3$); mp 166−168 °C; IR (thin film) 1657 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (m, 1H), 6.78−6.76 (m, 2H), 4.77 (m, 1H), 4.70 (s, 1H), 3.79 (s, 3H), 3.45 (s, 3H), 2.78 (dd, *J* = 10.0, 4.0 Hz, 1H), 2.64 (d, *J* = 12.0

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Hz, 1H), 2.55 (t, J = 12.0 Hz, 1H), 2.37 (s, 3H), 2.29 (m, 1H), 2.12 (m, 1H), 1.92−1.81 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 148.1, 145.8, 132.0, 120.0, 119.0, 111.8, 98.3, 88.5, 57.0, 55.8, 54.5, 50.5, 48.0, 46.2, 38.6, 38.1, 25.4; HRMS (TOF MS ES$^+$) calcd for $C_{18}H_{24}NO_3$ (M + H$^+$) 302.1756, found 302.1760.

Optical rotation of enantiopure (+)-**17** (free base): $[\alpha]^{20}_D$ +161.9 (c 1.4, $CHCl_3$); mp 162−164 °C.

*(4aR,7aR,12bS)-6-Bromo-7,7,9-trimethoxy-3-methyl-2,3,4,4a,5,6,7,7a-octahydro-1H-benzofuro[3,2-e]isoquinoline ((−)-**18**).* To a stirred solution of (−)-**17** (2.61 g, 8.66 mmol) in MeOH (40 mL) and THF (20 mL) at −15 °C was added a solution of methanesulfonic acid (13.3 M, 717 μL, 9.50 mmol) in MeOH (3 mL) dropwise followed by a solution of *N*-bromoacetamide (1.16 g, 8.41 mmol) in MeOH (6 mL). After the mixture was stirred for 15 min at −15 °C, additional *N*-bromoacetamide (119 mg, 0.866 mmol) was added. After the mixture was stirred for an additional 15 min at −15 °C, NH_3 gas was bubbled through the solution. The reaction mixture was concentrated in vacuo, and to the resulting residue were added 3 M NaOH (50 mL) and concentrated NH_4OH (10 mL). The aqueous mixture was extracted with $CHCl_3$ (3 × 75 mL), washed with H_2O (75 mL), and concentrated in vacuo to afford bromide (−)-**18** (3.32 g) as a white foam that was used without further purification: $[\alpha]^{20}_D$ −133.4 (c 1.7, $CHCl_3$); mp 59−62 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (m, 1H), 6.80−6.79 (m, 2H), 4.41 (s, 1H), 3.97 (t, J = 9.5 Hz, 1H), 3.86 (s, 3H), 3.58 (s, 3H), 3.50 (s, 3H), 3.02 (m, 1H), 2.77 (dd, J = 11.5, 4.0 Hz, 1H), 2.66 (m, 1H), 2.52−2.44 (m, 2H), 2.43 (s, 3H), 2.20−2.14 (m, 1H), 1.94−1.79 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.9, 144.4, 131.6, 120.2, 118.7, 112.3, 98.0, 89.84, 89.75, 56.0, 55.7, 51.3, 49.8, 49.3, 47.4, 45.71, 45.69, 40.4, 35.4, 35.3, 34.8; HRMS (TOF MS ES$^+$) calcd for $C_{19}H_{27}NO_4Br$ (M + H$^+$) 412.1123, found 412.1117.

Optical rotation of enantiopure (+)-**18** (free base): $[\alpha]^{20}_D$ +119.1 (c 1.9, $CHCl_3$).

*(7aR,12bS)-7,9-Dimethoxy-3-methyl-2,3,4,7a-tetrahydro-1H-benzofuro[3,2-e]isoquinoline ((−)-**20**).* To the crude solution of bromide (−)-**18** (3.32 g) in THF (60 mL) was added potassium *tert*-butoxide (3.88 g, 34.6 mmol). The reaction mixture was heated to reflux. After stirring for 4 h at reflux, the reaction mixture was cooled to room temperature and concentrated in vacuo. To the crude residue were added H_2O (50 mL) and concentrated NH_4OH to obtain a pH of 9.5, and the aqueous solution was extracted with $CHCl_3$ (3 × 50 mL). The combined organic fractions were washed with H_2O (100 mL) and concentrated in vacuo to afford (−)-**19** ((4a*R*,7a*R*,12b*S*)-7,7,9-trimethoxy-3-methyl-2,3,4,4a,7,7a-hexahydro-1*H*-benzofuro[3,2-*e*]isoquinoline), which was used without further purification. To the crude solution of (−)-**19** in $CHCl_3$ (40 mL) at 0 °C was added trimethylsilyl chloride (3.13 mL, 24.6 mmol), and the reaction mixture was warmed to room temperature. After the mixture was stirred 15 min at room temperature, a solution of CH_3SO_3H (480 μL, 7.39 mmol) in $CHCl_3$ (2 mL) was added dropwise. The reaction mixture was warmed to 35 °C and maintained at that temperature for 35 min. The solution was then cooled to 0 °C, and H_2O (50 mL) was added followed by concentrated NH_4OH to arrive at a pH of 9.5. The aqueous solution was extracted with $CHCl_3$ (3 × 50 mL), washed with H_2O (50 mL), and concentrated in vacuo to give a crude light brown solid. To a solution of this crude residue in MeOH (8 mL) was added a solution of (−)-tartaric acid (1.02 g, 6.78 mmol) in MeOH (4 mL). The (−)-tartaric acid salt of (−)-**20** began crystallizing almost immediately. The solution was cooled to 0 °C and maintained at that temperature for 15 min until crystallization was complete. The resulting solid was filtered and rinsed with cold MeOH to afford the (−)-tartaric acid salt of (−)-**20** (2.25 g, 58% over three steps). All spectral data reported on the free base: $[\alpha]^{20}_D$ −39.2 (c 1.6, $CHCl_3$); mp 160−163 °C; IR (thin film) 1667 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, J = 7.5 Hz, 1H), 6.79 (t, J = 7.5 Hz, 1H), 6.72 (d, J = 7.5 Hz, 1H), 5.69 (d, J = 6.0 Hz, 1H), 5.12 (s, 1H), 4.96 (d, J = 6.0 Hz, 1H), 3.81 (s, 3H), 3.56 (s, 3H), 3.26 (s, 2H), 2.74 (d, J = 11.0 Hz, 1H), 2.59 (t, J = 12.5 Hz, 1H), 2.39 (s, 3H), 1.98 (t, J = 12.5 Hz, 1H), 1.86 (d, J = 12.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.3, 146.2, 145.1, 133.8, 127.8, 120.7, 117.9, 117.6, 111.4, 94.3, 88.4, 59.6, 55.8, 55.0, 51.3, 49.8, 45.9, 40.4; HRMS (TOF MS ES$^+$) calcd for $C_{18}H_{22}NO_3$ (M + H$^+$) 300.1600, found 300.1607.

Optical rotation of enantiopure (+)-**20** (free base): $[\alpha]^{20}_D$ +30.5 (c 1.8, $CHCl_3$); mp 155−158 °C.

*(7R,12bS)-7,9-Dimethoxy-3-methyl-1,2,3,7-tetrahydro-7,12b-methanobenzo[2,3]oxocino[5,4-c]pyridine ((+)-**21**).* To a stirred solution of bromide (−)-**18** (0.366 g, 0.887 mmol) in DMSO (15 mL) was added potassium *tert*-butoxide (995 mg, 8.87 mmol). The reaction mixture was heated at 65 °C for 14 h and cooled to room temperature, and ice and H_2O were slowly added resulting in crystallization of (+)-**21**, which was filtered and rinsed to afford pure (+)-**21** (0.209 g, 79%) as a light brown solid: $[\alpha]^{20}_D$ +598.5 (c 1.9, $CHCl_3$); mp 214−217 °C; IR (thin film) 1639 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (d, J = 8.0 Hz, 1H), 6.82 (t, J = 8.0 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.12 (d, J = 9.5 Hz, 1H), 6.01 (s, 1H), 5.37 (d, J = 9.5 Hz, 1H), 3.83 (s, 3H), 3.57 (s, 3H), 3.47 (td, J = 13.0, 4.5 Hz, 1H), 3.30 (dd, J = 12.5, 6.0 Hz, 1H), 2.86 (s, 3H), 2.34−2.29 (m, 2H), 2.06 (td, J = 13.2, 6.5 Hz, 1H), 1.68 (d, J = 11.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.9, 143.6, 134.5, 131.7, 131.3, 119.8, 118.0, 117.2, 109.9, 109.8, 100.3, 56.0, 50.3, 47.2, 42.4, 40.3, 34.7, 33.5; HRMS (TOF MS ES$^+$) calcd for $C_{18}H_{22}NO_3$ (M + H$^+$) 300.1600, found 300.1591. Anal. Calcd for ($C_{18}H_{21}NO_3$·H_2O): C (68.12), H (7.30), N (4.41). Found: C (67.87), H (7.08), N (4.36).

Optical rotation of enantiopure (−)-**21** (free base): $[\alpha]^{20}_D$ −613.8 (c 0.9, $CHCl_3$); mp 214−218 °C

*(4aS,7aR,12bS)-4a-Hydroxy-9-methoxy-3-methyl-2,3,4,4a,5,6-hexahydro-1H-benzofuro[3,2-e]isoquinolin-7(7aH)-one ((−)-**23**).* To a stirred solution of (−)-**20** (free base, 0.860 g, 2.87 mmol) in 0.7% H_2SO_4 (11 mL), formic acid (11 mL), and *i*-PrOH (11 mL) at 0 °C was added H_2O_2 (5.46 M in H_2O, 580 μL, 3.17 mmol) dropwise. The reaction mixture was stirred for 1.5 h at 0 °C and warmed to 45 °C. After being stirred for 45 min at 45 °C, the reaction mixture containing crude (−)-**22** was cooled to 0 °C, 5% Pd/C (400 mg) was added, and the solution was subjected to an atmosphere of H_2 (1 atm). After being stirred for 1 h at 0 °C, the reaction mixture was warmed to room temperature. After being stirred at room temperature for 24 h, ice and 3 M NaOH were added until a pH of 9.5 was achieved. The slurry was filtered through Celite, rinsing with H_2O and $CHCl_3$. The organics and aqueous fractions were separated. The aqueous layer was extracted with $CHCl_3$ (3 × 100 mL), washed with H_2O (100 mL), and concentrated in vacuo to afford (−)-**25** as a crude white solid. Purification of this crude solid by SiO_2 column chromatography with 10% NH_4OH in MeOH/$CHCl_3$ (gradient, 0 → 10%) gave (−)-**23** (0.171 g, 20% from (−)-**20**) as a white solid. An 88% yield from (−)-**20** was obtained on a 28 mg scale: $[\alpha]^{20}_D$ −217.3 (1.4, $CHCl_3$); mp 134−137 °C; IR (thin film) 3438, 1723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 4.0 Hz, 1H), 6.86−6.80 (m, 2H), 4.55 (s, 1H), 4.25 (br s, 1H), 3.87 (s, 3H), 2.76 (d, J = 12.0 Hz, 1H), 2.72−2.63 (m, 3H), 2.43 (s, 3H), 2.41−2.28 (m, 3H), 1.82−1.72 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.3, 148.5, 145.1, 131.0, 121.2, 117.1, 112.1, 90.9, 70.0, 61.5, 55.8, 55.0, 49.8, 45.6, 34.5, 32.5, 30.4; HRMS (TOF MS ES+) calcd for $C_{17}H_{22}NO_4$ (M + H$^+$) 304.1543, found 304.1543.

Optical rotation of enantiopure (+)-**23** (free base): $[\alpha]^{20}_D$ +241.9 (c 1.1, $CHCl_3$)

*(4aS,7aR,12bR)-3-Methyl-7-oxo-1,2,3,4,5,6,7,7a-octahydro-4aH-benzofuro[3,2-e]isoquinoline-4a,9-diyl Diacetate ((−)-**25**).* Through a stirred solution of methyl ether (−)-**23** (0.171 g, 0.565 mmol) in CH_2Cl_2 (6 mL) was bubbled HCl gas until the pH of the solution was ∼3 on moist hydrion paper. The solution was cooled to 0 °C, and a solution of BBr_3 (166 μL, 1.75 mmol) in CH_2Cl_2 (2 mL) was added dropwise. After being stirred for 15 min at 0 °C, the reaction mixture was warmed to room temperature. After being stirred at room temperature for 1.5 h, the solution was cooled to 0 °C, and H_2O (6 mL) was added dropwise. The CH_2Cl_2 was removed by distillation, and the remaining aqueous solution was refluxed. After being refluxed for 30 min, the aqueous solution was cooled to 0 °C, and the pH was adjusted to 9.5 with concentrated NH_4OH. The aqueous solution was extracted with 9:1 $CHCl_3$/EtOH (5 × 10 mL). The combined organics were concentrated in vacuo to afford crude diol (−)-**24**,

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which was carried out without further purification. To crude diol (−)-**24** was added Ac_2O (4 mL). The reaction mixture was heated to 65 °C and maintained at that temperature for 1.5 h. The Ac_2O was removed by vacuum distillation. Purification of this crude solid by SiO_2 column chromatography with 10% NH_4OH in MeOH/$CHCl_3$ (gradient, 1 → 4%) afforded (−)-**25** (0.141 g, 67% from (−)-**23**) as a white solid: $[\alpha]^{20}_D$ −248.4 (*c* 2.4, $CHCl_3$); mp 118−122 °C; IR (thin film) 1774, 1735, 1725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 4.51 (s, 1H), 3.97 (d, *J* = 13.5 Hz, 1H), 2.88 (d, *J* = 11.0 Hz, 1H), 2.74 (m, 1H), 2.56 (d, *J* = 13.5 Hz, 1H), 2.51−2.45 (m, 3H), 2.42 (s, 3H), 2.29 (s, 3H), 2.03 (m, 1H), 2.02 (s, 3H), 1.79 (d, *J* = 11.5 Hz, 1H), 1.76 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 174.1, 169.9, 168.0, 151.4, 135.2, 130.3, 123.1, 121.4, 107.1, 90.7, 81.9, 55.2, 54.6, 48.7, 45.2, 33.4, 30.7, 26.1, 26.0, 22.0, 21.2, 20.4; HRMS (TOF MS ES$^+$) calcd for $C_{20}H_{24}NO_6$ (M + H^+) 374.1598, found 374.1599.

*(4aS,7aR,12bS)-3-Cyano-7-oxo-1,2,3,4,5,6,7,7a-octahydro-4aH-benzofuro[3,2-e]isoquinoline-4a,9-diyl Diacetate ((−)-**26**).* To a stirred solution of methylamine (−)-**25** (0.141 g, 0.378 mmol) in MeCN (4 mL) were added K_2CO_3 (0.053 g, 0.38 mmol) and CNBr (5.0 M, 84 μL, 0.42 mmol). The reaction mixture was heated to 75 °C and maintained at that temperature for 1.5 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. To the crude residue were added H_2O (10 mL) and concentrated NH_4OH to bring the pH to 9.5, and the aqueous mixture was extracted with $CHCl_3$ (3 × 10 mL). The combined organic fractions were washed with H_2O (20 mL) and concentrated in vacuo to give a yellow solid. Purification of this crude solid by SiO_2 column chromatography with 10% NH_4OH in MeOH/$CHCl_3$ (gradient, 1 → 3%) afforded (−)-**26** (0.099 g, 68%) as a white solid: $[\alpha]^{20}_D$ −231.0 (*c* 1.2, $CHCl_3$); mp 223−224 °C; IR (thin film) 2204, 1774, 1743, 1722 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22, (d, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 4.49 (s, 1H), 4.42 (d, *J* = 15.0 Hz, 1H), 3.47 (d, *J* = 15.0 Hz, 1H), 3.46 (m, 1H), 3.37 (m, 1H), 2.76 (m, 1H), 2.61−2.54 (m, 2H), 2.26 (s, 3H), 2.25 (s, 3H), 2.10 (s, 3H), 1.77−1.69 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.6, 169.9, 168.0, 151.4, 135.6, 128.8, 127.8, 122.1 (x2), 117.3, 90.4, 79.9, 55.1, 49.1, 44.5, 31.7, 30.9, 25.1, 21.7, 20.4; HRMS (TOF MS ES$^+$) calcd for $C_{20}H_{24}N_3O_6$ (M + NH_4^+) 402.1660, found 402.1661.

*(4aR,7aS,12bR)-9-Methoxy-3-methyl-7-oxo-1,2,3,4,5,6,7,7a-octahydro-4aH-benzofuro[3,2-e]isoquinolin-4a-yl Acetate ((+)-**28**).* To alcohol (+)-**23** (0.445 g, 1.47 mmol) was added Ac_2O (10 mL). The reaction mixture was heated to 65 °C and maintained at that temperature for 1.5 h. The Ac_2O was removed by vacuum distillation. Purification of this crude solid by recrystallization in *i*-PrOH afforded (+)-**28** (0.306 g, 60%) as a white solid: $[\alpha]^{20}_D$ +250.2 (*c* 1.4, $CHCl_3$); mp 173−176 °C; IR (thin film) 1723 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.09 (d, *J* = 7.0 Hz, 1H), 6.90−6.83 (m, 2H), 4.54 (s, 1H), 3.90 (d, *J* = 14.0 Hz, 1H), 3.87 (s, 3H), 2.75−2.70 (m, 2H), 2.51 (d, *J* = 13.0 Hz, 1H), 2.47−2.42 (m, 3H), 2.37 (s, 3H), 2.03 (s, 3H), 1.81 (m, 1H), 1.71 (d, *J* = 9.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.6, 169.7, 148.4, 145.2, 129.3, 121.4, 117.8, 112.3, 90.4, 82.4, 55.8, 55.6, 54.8, 49.4, 45.8, 34.1, 31.6, 26.2, 22.0; HRMS (TOF MS ES$^+$) calcd for $C_{19}H_{24}NO_5$ (M + H^+) 346.1649, found 346.1649.

*(4aR,7aS,12bR)-3-(Cyclopropylmethyl)-4a-hydroxy-9-methoxy-2,3,4,4a,5,6-hexahydro-1H-benzofuro[3,2-e]isoquinolin-7(7aH)-one ((+)-**31**) from (+)-**28**.* To a stirred solution of *N*-methyl (+)-**28** (0.289 g, 0.836 mmol) in MeCN (9 mL) were added K_2CO_3 (0.116 g, 0.836 mmol) and CNBr (5.0 M in MeCN, 184 μL, 0.920 mmol). The reaction mixture was heated to 75 °C. After being stirred at 75 °C for 1 h, the reaction mixture was cooled to room temperature and concentrated in vacuo. To the residue were added H_2O (10 mL) and concentrated NH_4OH to arrive at a pH ∼9.5. The aqueous layer was extracted with $CHCl_3$ (3 × 15 mL), and the combined organics were washed with H_2O and concentrated in vacuo to afford (+)-**29** as a crude orange solid that was used without further purification. To the above crude mixture of (+)-**29** were added 3 M HCl (7 mL) and MeOH (1 mL). The reaction mixture was then heated to 110 °C. After being heated for 14 h at 110 °C, the reaction mixture was cooled to room temperature, and concentrated NH_4OH was added to arrive at a pH ∼9.5. The aqueous solution was extracted with 4:1 $CHCl_3$/MeOH (5 × 10 mL). The combined organics were washed with H_2O (10 mL) and concentrated in vacuo to afford amine (+)-**30** that was used without further purification. To the above crude amine (+)-**30** were added EtOH (7 mL), Na_2CO_3 (0.222 g, 2.09 mmol), and cyclopropylmethyl bromide (102 μL, 1.02 mmol). The reaction mixture was heated to 90 °C and maintained at that temperature for 2 h, at which time an additional 102 μL of cyclopropylmethyl bromide was added. After being stirred for an additional 1 h, the reaction mixture was concentrated in vacuo to afford a crude orange solid. Purification of this crude solid by SiO_2 column chromatography with 10% NH_4OH in MeOH/$CHCl_3$ (gradient, 1 → 4%) afforded (+)-**31** (0.101 g, 35% yield from (+)-**28**) as a tacky yellow foam. A 43% yield was obtained on a 35 mg scale: $[\alpha]^{20}_D$ +245.1 (*c* 4.1, $CHCl_3$); IR (thin film) 3428, 1723 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.00 (d, *J* = 7.0 Hz, 1H), 6.83−6.78 (m, 2H), 4.53 (s, 1H), 4.42 (br s, 1H), 3.85 (s, 3H), 2.85−2.82 (m, 3H), 2.68 (m, 1H), 2.47−2.37 (m, 4H), 2.31 (t, *J* = 11.0 Hz, 1H), 1.79−1.71 (m, 3H), 0.88 (m, 1H), 0.53 (d, *J* = 7.0 Hz, 2H), 0.12 (d, *J* = 2.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.7, 148.6, 145.2, 131.2, 121.3, 117.1, 112.2, 107.1, 91.2, 70.1, 62.6, 59.3, 55.9, 55.8, 47.8, 34.8, 32.9, 30.5, 8.2, 3.9, 3.7; HRMS (TOF MS ES$^+$) calcd for $C_{20}H_{26}NO_4$ (M + H^+) 344.1862, found 344.1856.

*(4aR,7aS,12bR)-3-(Cyclopropylmethyl)-4a,9-dihydroxy-2,3,4,4a,5,6-hexahydro-1H-benzofuro[3,2-e]isoquinolin-7(7aH)-one ((+)-**1**).* Through a stirred solution of methyl ether (+)-**31** (1.63 g, 4.75 mmol) in CH_2Cl_2 (40 mL) was bubbled HCl gas until the pH of the solution was ∼3. The solution was cooled to 0 °C, and a solution of BBr_3 (2.3 mL, 24 mmol) in CH_2Cl_2 (10 mL) was added dropwise. After being stirred for 15 min at 0 °C, the reaction mixture was warmed to room temperature. After being stirred at room temperature for 1.5 h, the solution was cooled to 0 °C, and H_2O (50 mL) was added dropwise. The CH_2Cl_2 was removed by distillation, and the remaining aqueous solution was refluxed. After being refluxed for 30 min, the aqueous solution was cooled to 0 °C, and the pH was adjusted to 9.5 with concentrated NH_4OH. The aqueous solution was extracted with 4:1 $CHCl_3$/MeOH (5 × 10 mL). The combined organics were concentrated in vacuo to afford a crude white solid. Purification of this crude solid by SiO_2 column chromatography with 10% NH_4OH in MeOH/$CHCl_3$ (gradient, 3 → 8%) afforded (+)-**1** (1.24 g, 79%) as a white solid: $[\alpha]^{20}_D$ +203.1 (*c* 3.0, $CHCl_3$); mp 175−177 °C; IR (thin film) 3398,1719 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.91 (d, *J* = 6.5 Hz, 1H), 6.82 (d, *J* = 7.5 Hz, 1H), 6.77 (t, *J* = 7.5 Hz, 1H), 5.78 (br s, 1H), 4.57 (s, 1H), 2.93−2.76 (m, 4H), 2.47−2.44 (m, 3H), 2.38−2.34 (m, 2H), 1.89−1.70 (m, 3H), 0.91 (m, 1H), 0.55 (d, *J* = 7.5 Hz, 2H), 0.14 (d, *J* = 3.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.8, 147.2, 141.7, 130.9, 121.8, 116.7, 116.5, 90.9, 70.2, 62.7, 59.4, 55.9, 47.7, 34.3, 33.5, 30.7, 8.0, 4.0, 3.9; HRMS (TOF MS ES$^+$) calcd for $C_{19}H_{24}NO_4$ (M + H^+) 330.1705, found 330.1698. Anal. Calcd for ($C_{19}H_{23}NO_4$): C (69.28), H (7.04), N (4.25). Found: C (68.88), H(6.94), N (4.47).

Optical rotation of enantiopure (−)-**1** (free base): $[\alpha]^{20}_D$ −184 (*c* 2.2, $CHCl_3$); mp 161−163 °C

*4aH,9-O-trans-Ethyl 3-(Cyclopropylmethyl)-7-hydroxy-9-methoxy-5,7a-dihydro-3H-benzofuro[3,2-e]isoquinoline-6-carboxylate ((±)-**34**).* To a stirred solution of ethyl ester **12** (2.0 g, 6.64 mmol) in DMF (10 mL) was added cyclopropylmethyl bromide (1.68 mL, 17.3 mmol) in two portions over 2 h. After the reaction mixture was heated at 50 °C for 2 h, an additional 0.84 mL of cyclopropylmethyl bromide was added to the reaction mixture, the temperature was increased to 60 °C, and the mixture was stirred for an additional 1 h. TLC analysis verified disappearance of the starting material, and the reaction mixture was concentrated in vacuo. To the crude intermediate was added DMF (10 mL) followed by K_2CO_3 (1.38 g, 10.0 mmol) and ethyl bromoacetate (0.810 mL, 7.30 mmol). The reaction mixture was stirred for 2 h at room temperature, filtered, and concentrated in vacuo to give crude **32**. In a separate flask, anhydrous EtOH (10 mL) was added to freshly cut pieces of sodium (0.611 g, 26.6 mmol) and refluxed until a homogeneous solution was obtained. This freshly prepared NaOEt solution was cooled to room temperature and cannulated into the crude bis-ethyl ester **32** rinsing with THF (150

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mL). The reaction mixture was refluxed for 12 h and cooled to −5 °C, and it was cannulated into a rapidly stirred mixture of saturated aqueous NH_4Cl (9.6 g) and H_2O (9.6 g) at −5 °C, rinsing the reaction flask with THF (3 × 10 mL). The reaction mixture was concentrated in vacuo to ∼7 mL, removing most of the organics. The aqueous layer was extracted with $CHCl_3$ (3 × 20 mL), and the combined organics were concentrated in vacuo to give a dark syrup. This dark syrup was dissolved in toluene (30 mL) and washed with H_2O (15 mL) and brine (10 mL). The aqueous washes were extracted with toluene (2 × 25 mL). The combined toluene extracts were concentrated in vacuo to ∼1/3 volume, filtered through Celite, and concentrated in vacuo to give **34** (1.79 g, 68%) as an orange solid. Spectra matched those reported by Cheng et al.[9]

*Optical Resolution of (4aS,7aS,12bR)-3-(Cyclopropylmethyl)-9-methoxy-2,3,4,4a,5,6-hexahydro-1H-benzofuro[3,2-e]isoquinolin-7-(7aH)-one ((+)-**36**) and (4aR,7aR,12bS)-3-(Cyclopropylmethyl)-9-methoxy-2,3,4,4a,5,6-hexahydro-1H-benzofuro[3,2-e]isoquinolin-7-(7aH)-one ((−)-**36**).* To a crude mixture of racemic *trans*-(±)-**36**[10] (22.4 g, 68.3 mmol) in MeCN (240 mL) and MeOH (40 mL) was added (+)-tartaric acid (5.12 g, 34.1 mmol). The mixture was heated to solution and subsequently cooled to room temperature. Upon cooling, crystallization occurred, and the solution was filtered. The filtrate was dissolved in $CHCl_3$ (200 mL) and H_2O (200 mL), and concentrated NH_4OH was added to a pH of ∼9.5. The aqueous layer was extracted with $CHCl_3$ (3 × 200 mL), washed with H_2O (250 mL), and concentrated in vacuo to afford (−)-**36** (3.05 g, >95% ee). The filtrates were concentrated, basified, and extracted with $CHCl_3$. To this mixture were added MeCN (160 mL), MeOH (30 mL), and (+)-tartaric acid (3.66 g, 24.4 mmol). The above crystallization procedure was repeated affording additional (−)-**36** (2.04 g, >95% ee). The remaining filtrate was concentrated in vacuo and purified by SiO_2 column chromatography with 10% NH_4OH in MeOH/$CHCl_3$ (gradient, 1 → 4.5%) to give recovered (±)-**36** (11.07 g) with an ee of 83% enriched in (+)-**36**. To this purified mixture was added MeCN (145 mL) followed by a warmed solution of (−)-tartaric acid (4.57 g, 30.4 mmol) in MeOH (24 mL). Crystallization occurred immediately, and the mixture was allowed to cool to room temperature. The solid was filtered, basified, extracted, and concentrated to afford (+)-**36** (7.50 g, >98% ee). The filtrate was concentrated, basified, extracted, and concentrated to give 3.95 g of a mixture enriched in (+)-**36** (86% ee). To this mixture were added MeCN (50 mL), MeOH (9 mL), and (+)-tartaric acid (1.63 g, 10.9 mmol). Upon heating, cooling, filtering, basifying, extracting, and concentrating an additional 2.69 g of (+)-**36** (>98% ee) was obtained. All spectral data was obtained on the (+)-**36** base containing 0.5·H_2O: $[\alpha]^{20}_D$ +173.4 (*c* 3.1, $CHCl_3$); mp 110−116 °C; IR (thin film) 1732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.04 (d, *J* = 7.0 Hz, 1H), 6.84−6.79 (m, 2H), 4.44 (s, 1H), 3.89 (s, 3H), 3.05 (dd, *J* = 11.5, 3.0 Hz, 1H), 2.93 (d, *J* = 12.0 Hz, 1H), 2.62 (t, *J* = 11.5 Hz, 1H), 2.54 (m, 1H), 2.44−2.32 (m, 5H), 2.02 (td, *J* = 12.8, 4.0 Hz, 1H), 1.91 (d, *J* = 13.0 Hz, 1H), 1.78 (m, 1H), 1.60 (dtd, *J* = 12.5, 12.0, 6.0 Hz, 1H), 0.92 (m, 1H), 0.55 (d, *J* = 7.5 Hz, 2H), 0.15 (d, *J* = 4.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.2, 148.8, 145.2, 130.5, 121.1, 118.6, 112.1, 91.8, 63.4, 55.9, 54.5, 52.3, 48.1, 40.0, 39.3, 38.5, 25.6, 8.3, 3.9, 3.8; HRMS (TOF MS ES$^+$) calcd for $C_{20}H_{26}NO_3$ (M + H^+) 328.1913, found 328.1912. Anal. Calcd for ($C_{20}H_{26}NO_{3.5}$): C (71.40), H (7.79), N (4.16). Found: C (71.73), H(7.49), N (4.10).

Optical rotation of enantiopure (−)-**36** (free base): $[\alpha]^{20}_D$ −156.5 (*c* 2.1, $CHCl_3$).

*(4aS,7aS,12bR)-3-(Cyclopropylmethyl)-7,9-dimethoxy-2,3,4,4a,5,7a-hexahydro-1H-benzofuro[3,2-e]isoquinoline ((+)-**37**).* To a stirred solution of (+)-**36** (7.73 g, 23.6 mmol) in MeOH (150 mL) was added a premixed solution of 5-sulfosalicylic acid dihydrate (10.8 g, 42.5 mmol) and trimethyl orthoformate (20.7 mL, 189 mmol) in MeOH (80 mL). The reaction mixture was refluxed for 1 h, and then $CHCl_3$ (3 × 50 mL) was added and removed by distillation. The reaction mixture was cooled to 0 °C, and a precooled solution of 1.5 M NaOH (500 mL) at 0 °C was added. The aqueous layer was extracted with $CHCl_3$ (3 × 500 mL), washed with H_2O (500 mL), and concentrated in vacuo to afford (+)-**37** (7.85 g, 100%) as a yellow solid that was used without further purification. An analytical sample was prepared through SiO_2 column chromatography with 10% NH_4OH in MeOH/$CHCl_3$ (gradient, 0.5 → 5%): $[\alpha]^{20}_D$ +134.5 (*c* 1.4, $CHCl_3$); mp 138−140 °C; IR (thin film) 1656 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.09 (t, *J* = 4.5 Hz, 1H), 6.78 (d, *J* = 4.0 Hz, 2H), 4.82 (d, *J* = 4.5 Hz, 1H), 4.75 (s, 1H), 3.84 (s, 3H), 3.50 (s, 3H), 3.01 (dd, *J* = 11.5, 4.0, Hz, 1H), 2.90 (d, *J* = 12.0 Hz, 1H), 2.62 (t, *J* = 12.0 Hz, 1H), 2.43−2.33 (m, 3H), 2.17 (m, 1H), 1.96−1.86 (m, 4H), 0.93 (m, 1H), 0.55 (d, *J* = 7.5 Hz, 2H), 0.15 (d, *J* = 4.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 148.0, 145.7, 132.0, 119.8, 118.8, 111.6, 98.2, 88.5, 63.8, 55.6, 54.9, 54.4, 48.4, 48.3, 38.3, 37.8, 25.5, 8.3, 3.95, 3.88; HRMS (TOF MS ES$^+$) calcd for $C_{21}H_{28}NO_3$ (M + H^+) 342.2064, found 342.2064.

*(4aS,7aS,12bR)-6-Bromo-3-(cyclopropylmethyl)-7,7,9-trimethoxy-2,3,4,4a,5,6,7,7a-octahydro-1H-benzofuro[3,2-e]isoquinoline ((+)-**38**).* To a stirred crude solution of (+)-**37** (7.76 g, 22.7 mmol) in MeOH (100 mL) and THF (50 mL) at −15 °C was added a solution of methanesulfonic acid (1.62 mL, 25.0 mmol) in MeOH (10 mL) dropwise followed by a solution of *N*-bromoacetamide (3.44 g, 25.0 mmol) in MeOH (10 mL). After the mixture was stirred for 15 min at −15 °C, additional *N*-bromoacetamide (157 mg, 1.14 mmol) was added. After the mixture was stirred for an additional 15 min at −15 °C, NH_3 gas was bubbled through the solution. The reaction mixture was concentrated in vacuo, and to the resulting residue were added concentrated NH_4OH (10 mL) and 3 M NaOH (100 mL). The aqueous mixture was extracted with $CHCl_3$ (3 × 125 mL), washed with H_2O (75 mL), and concentrated in vacuo to afford bromide (+)-**38** (10.81 g, 100%) as a tacky white foam that was used without further purification: $[\alpha]^{20}_D$ +120.0 (*c* 2.3, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 6.0 Hz, 1H), 6.80−6.77 (m, 2H), 4.42 (s, 1H), 3.97 (t, *J* = 9.5 Hz, 1H), 3.86 (s, 3H), 3.59 (s, 3H), 3.51 (s, 3H), 3.04−2.89 (m, 3H), 2.54 (t, *J* = 11.5 Hz, 1H), 2.49−2.38 (m, 3H), 2.19 (m, 1H), 1.95−1.87 (m, 2H), 1.81 (d, *J* = 12.5 Hz, 1H), 0.92 (m, 1H), 0.55 (d, *J* = 7.5 Hz, 2H), 0.15 (d, *J* = 3.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2, 144.7, 132.0, 120.4, 119.0, 112.4, 98.3, 90.2, 63.7, 56.1, 54.4, 51.7, 49.6, 48.3, 48.1, 47.8, 40.5, 35.6, 35.3, 8.4, 4.1, 3.9; HRMS (TOF MS ES$^+$) calcd for $C_{22}H_{31}NO_4Br$ (M + H^+) 452.1431, found 452.1433.

*(4aS,7aS,12bR)-3-(Cyclopropylmethyl)-7,7,9-trimethoxy-2,3,4,4a,7,7a-hexahydro-1H-benzofuro[3,2-e]isoquinoline ((+)-**39**).* To the crude solution of bromide (+)-**38** (10.8 g, 22.7 mmol) in THF (150 mL) was added potassium *tert*-butoxide (10.2 g, 90.9 mmol). The reaction mixture was heated to reflux. After being stirred for 4 h at reflux, the reaction mixture was cooled to room temperature and concentrated in vacuo. To the crude residue were added H_2O (100 mL) and concentrated NH_4OH to obtain a pH of ∼9.5, and the aqueous solution was extracted with $CHCl_3$ (3 × 100 mL). The combined organic fractions were washed with H_2O (200 mL) and concentrated in vacuo to afford (+)-**39** (7.14 g, 85%) as a tacky white foam, which was used without further purification: $[\alpha]^{20}_D$ +145.4 (*c* 4.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.07 (d, *J* = 7.0 Hz, 1H), 6.74−6.69 (m, 2H), 5.68 (dd, *J* = 9.5, 3.5 Hz, 1H), 5.64 (d, *J* = 9.5 Hz, 1H), 4.65 (s, 1H), 3.83 (s, 3H), 3.49 (s, 3H), 3.18−3.13 (m, 2H), 3.12 (s, 3H), 3.05−3.00 (m, 2H), 2.91 (t, *J* = 12.5 Hz, 1H), 2.78 (m, 1H), 2.54−2.49 (m, 2H), 2.06−2.01 (m, 2H), 0.97 (m, 1H), 0.58 (d, *J* = 7.5 Hz, 2H), 0.18 (d, *J* = 4.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.1, 144.3, 135.3, 131.9, 129.8, 119.5, 119.4, 111.8, 98.6, 90.6, 63.6, 56.0, 51.8, 51.0, 48.7, 48.5, 48.1, 38.8, 8.3, 4.0, 3.9; HRMS (TOF MS ES$^+$) calcd for $C_{22}H_{30}NO_4$ (M + H^+) 372.2169, found 372.2171.

*(7aS,12bR)-3-(Cyclopropylmethyl)-7,9-dimethoxy-2,3,4,7a-tetrahydro-1H-benzofuro[3,2-e]isoquinoline ((+)-**40**).* To a stirred solution of a portion of crude (+)-**39** (4.71 g, 12.7 mmol) in toluene (500 mL) was added pyridine (12.2 mL, 152 mmol) and $POCl_3$ (2.5 mL, 27 mmol). The reaction mixture was heated at 90 °C for 1.5 h and cooled to room temperature. To the reaction mixture were added $CHCl_3$ (200 mL), H_2O (400 mL), and concentrated NH_4OH to a pH of ∼9.5. The aqueous fraction was extracted with $CHCl_3$ (3 × 250 mL) and washed with H_2O (250 mL), and the combined organics were concentrated in vacuo to afford (+)-**40** (3.95 g, 91%) as a crude tacky light brown solid that was used without further purification: $[\alpha]^{20}_D$ +12.0 (*c* 2.2, $CHCl_3$); IR (thin film) 1615 cm^{-1}; ^1H NMR (500

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MHz, $CDCl_3$) δ 7.14 (d, J = 7.5 Hz, 1H), 6.81 (t, J = 7.5 Hz, 1H), 6.77 (d, J = 7.5 Hz, 1H), 5.75 (d, J = 6.5 Hz, 1H), 5.16 (s, 1H), 5.01 (d, J = 6.5 Hz, 1H), 3.86 (s, 3H), 3.61 (s, 3H), 3.53 (d, J = 13.0 Hz, 1H), 3.34 (d, J = 12.5 Hz, 1H), 3.02 (d, J = 11.5 Hz, 1H), 2.67 (t, J = 12.5 Hz, 1H), 2.43 (d, J = 6.5 Hz, 2H), 2.06 (td, J = 12.5, 4.0 Hz, 1H), 1.92 (d, J = 13.0 Hz, 1H), 0.95 (m, 1H), 0.56 (d, J = 2H), 0.17 (d, J = 4.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 146.1, 145.1, 133.9, 128.0, 120.7, 117.9, 117.5, 111.3, 94.3, 88.5, 63.5, 57.7, 55.8, 55.0, 50.3, 49.2, 40.4, 8.6, 4.1, 3.9; HRMS (TOF MS ES$^+$) calcd for $C_{21}H_{26}NO_3$ (M + H$^+$) 340.1907, found 340.1907.

(4aR,7aS,12bR)-3-(Cyclopropylmethyl)-4a-hydroxy-9-methoxy-2,3,4,4a,5,6-hexahydro-1H-benzofuro[3,2-e]isoquinolin-7(7aH)-one ((+)-31) from (+)-40. To a stirred solution of crude (+)-**40** (3.95 g, 11.6 mmol) in 0.7% H_2SO_4 (30 mL), formic acid (30 mL), and *i*-PrOH (30 mL) at 0 °C was added H_2O_2 (30% in H_2O, 2.4 mL, 23 mmol) dropwise. The reaction mixture was stirred for 1.5 h at 0 °C and warmed to 45 °C. After being stirred for 45 min at 45 °C, the reaction mixture was cooled to 0 °C. The solution of crude (+)-**41** was hydrogenated (40 psi) using 5% Pd/C (2 g). After being stirred for 1 h at 0 °C, the reaction mixture was warmed to room temperature. After the mixture was stirred at room temperature for 24 h, ice and 3 M NaOH were added until a pH of ∼9.5 was achieved. The slurry was filtered through Celite, rinsing with H_2O (100 mL) and $CHCl_3$ (100 mL). The organics and aqueous fractions were separated. The aqueous layer was extracted with $CHCl_3$ (3 × 100 mL), washed with H_2O (100 mL), and concentrated in vacuo to afford (+)-**31** as a crude white foam. Purification of this crude solid by SiO_2 column chromatography with 10% NH_4OH in MeOH/$CHCl_3$ (gradient, 1 → 4%) afforded (+)-**31** (1.73 g, 40% from (+)-**40**) as a tacky white solid. See the characterization data reported in (+)-**31** from (+)-**28**.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra. X-ray structures and data tables for (+)-**2** and (+)-**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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