

Preparation and Diastereoselective Birch Reduction–Alkylation of Chiral 3,4-Dihydro-1(2*H*)-isoquinolinones. Enantiospecific Syntheses and Opioid Receptor Affinities of Several Hydro-2,3-dimethyl-1*H*-7,12*a*-methanobenzo[6,7]cycloocta[1,2-*c*]pyridine-9-ols

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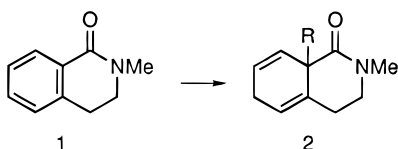
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Synthetic procedures have been developed to provide 2,3-disubstituted-3,4-dihydro-1(2*H*)-isoquinolinones **6**, **10**, and **15** from (1*R*,2*S*)-ephedrine, (1*R*,2*R*)-pseudoephedrine, and L-phenylalanine. Birch reduction of **6** and **10** gave enantiomerically related lactam enolates that were alkylated with methyl iodide, allyl bromide, benzyl bromide, *p*-benzyloxybenzyl bromide, and *p*-methoxybenzyl bromide to give **7a–7e**, **11a**, and **11b** with diastereoselectivities > 20:1. Birch reduction–methylation of **15** gave **19** with a diastereoselectivity of > 35:1. Selective reduction of the disubstituted double bond in **19** with diimide and cleavage of the *tert*-butyldimethylsilyl ether gave **20b**, from which iodoetherification under thermodynamic control gave the iodopyran **21a**; iodoetherification of **20b** under kinetic control gave the iodotetrahydrofuran **22**. Enantiospecific syntheses of analogues of **24** (Schultz, A. G.; Kirincich, S. J.; Rahm, R. *Tetrahedron Lett.* **1995**, *36*, 4551–4554) have been developed. Tetracycle **24** is isomeric with the potent analgesic agent levorphanol, but the bridging of the hydroisoquinoline ring by the hydroxybenzyl unit in **24** is at C(7, isoquinoline numbering) and C(8a) rather than at C(1) and C(4a) as in levorphanol. The key step in the transformation of **7d** and **7e** to tetracyclic phenolic amines (–)-**26** and (+)-**28** is the Grewe-type cyclization of **7d** to **25b** and **7e** to **25c**. *K_i* values for the inhibition of binding to the μ -, δ -, and κ -opioid receptors by (–)-**26**, (+)-**26**, (+)-**28**, (–)-**28**, and (+)-**32** are reported.

We recently reported the first Birch reduction–alkylations of 2-alkyl-3,4-dihydro-1(2*H*)-isoquinolinones, e.g., **1** → **2**.² This study was initiated because it appeared that bicyclic lactams such as **2** possess particularly well disposed functionality for utilization in the synthesis of alkaloids and related nitrogen-containing heterocyclic systems.

Dihydroisoquinolinone **1** is easily prepared from 2-phenylethylamine by literature procedures.³ Inexpensive, enantiomerically pure derivatives of 3-phenyl-2-propylamine were expected to provide chiral analogues of **1**. In this paper, we describe the preparation and diastereoselective Birch reduction–alkylation of several chiral 2,3-disubstituted-3,4-dihydro-1(2*H*)-isoquinolinones. Furthermore, we describe the utilization of this new chemistry to prepare structural analogues of the potent analgesic agent levorphanol.



(1) University of Rochester.

(2) (a) Schultz, A. G.; Kirincich, S. J.; Rahm, R. *Tetrahedron Lett.* **1995**, *36*, 4551–4554. (b) Kirincich, S. J. Ph.D. Thesis, Rensselaer Polytechnic Institute, Troy, NY, 1996.

(3) (a) Davies, R. V.; Iddon, B.; Suschitzky, H.; Gittos, M. W. *J. Chem. Soc., Perkin Trans. 1* **1978**, 180–184. (b) Gramain, J. C.; Simonet, N.; Vermeersch, G.; Febvay-Garot, N.; Caplain, S.; Lablanche-Combiere, A. *Tetrahedron* **1982**, *38*, 539–550.

Results and Discussion

Dihydro-1(2*H*)-isoquinolinone **6** could have been prepared from methamphetamine, but since the amphetamines are controlled substances, we decided to prepare **6** from the readily available (1*R*,2*S*)-ephedrine (**3**) (Scheme 1); the enantiomer **10** was prepared from (1*R*,2*S*)-pseudoephedrine (**8**) (Scheme 2).⁴

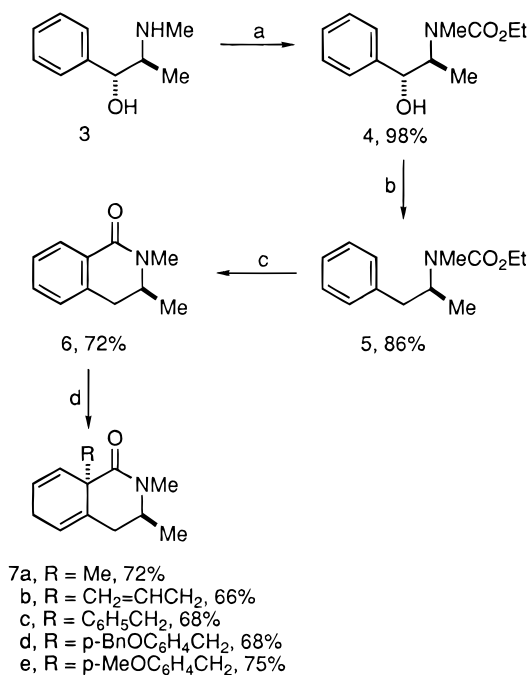
Reaction of **3** with ethyl chloroformate provided the urethane **4**, and hydrogenolysis of the OH group in **4** with Raney Ni in refluxing ethanol gave the methamphetamine derivative **5**. The cyclization of **5** to give **6** was carried out in methanesulfonic acid/P₂O₅ (10:1 by weight) at 120 °C.⁵

It was necessary to demonstrate that racemization had not occurred during hydrogenolysis with Raney Ni by a competing process involving dehydration followed by olefin hydrogenation. The racemate of **6** was prepared by reductive amination (NaBH₃CN/NH₄OAc) of phenylacetone, followed by acylation (ClCO₂Et), cyclization (MeSO₃H/P₂O₅), and *N*-methylation (NaH/THF, MeI). HPLC analyses verified that **6** had been prepared from **4** without racemization.

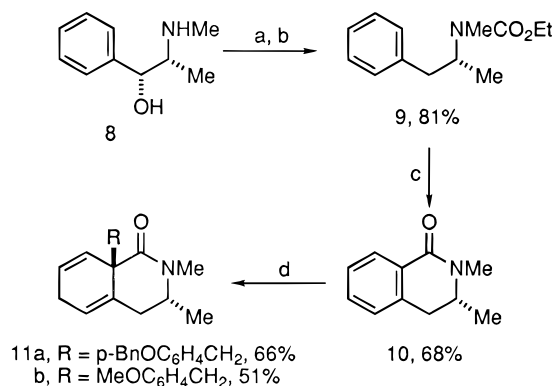
The Birch reduction–alkylations of **6** occurred with >20:1 diastereoselectivity to give **7a–7e** as the major diastereomers. Product diastereomer ratios were determined by HPLC analysis (μ Porasil; hexane/2-propanol,

(4) For the direct reduction of ephedrine and pseudoephedrine to methamphetamine, see: Emde, H. *Helv. Chim. Acta* **1929**, *12*, 365–376.

(5) Eaton, P.; Carlson, G. R.; Lee, J. T. *J. Org. Chem.* **1973**, *38*, 4071–4073.

Scheme 1^a

^a Reaction conditions: (a) ClCO₂Et, CH₂Cl₂, NaHCO₃, H₂O, 0 °C; (b) Raney Ni, H₂, EtOH, reflux; (c) MeSO₃H, P₂O₅, 120 °C; (d) Li, NH₃/THF, *t*-BuOH, -78 °C; piperylene; RX.

Scheme 2^a

^a Reaction conditions: (a) ClCO₂Et, CH₂Cl₂, NaHCO₃, H₂O, 0 °C; (b) Raney Ni, H₂, EtOH, reflux; (c) MeSO₃H, P₂O₅, 120 °C; (d) Li, NH₃/THF, *t*-BuOH, -78 °C; piperylene; RX.

9:1) before chromatographic separation. Stereochemical assignments were made with a high degree of confidence by comparison of experimentally determined coupling constants for protons at C(3) and C(4) with those determined by utilization of MacroModel. A small amount of the product of γ -alkylation was detected in the reaction mixture that provided **7b**.

Dihydro-1(2*H*)-isoquinolinone **10**, the enantiomer of **6**, was prepared from (1*R*,2*R*)-pseudoephedrine (**8**) (Scheme 2). Birch reduction-alkylation of **10** gave the enantiomers **11a** and **11b** of the (4'-benzyloxy)benzyl and (4'-methoxy)benzyl derivatives **7d** and **7e**.

The high degree of diastereoselectivity exhibited by alkylations of enolates generated from Birch reduction of **6** and **10** is striking in light of the modest stereoselectivities observed for enolates derived from 4-substituted cyclohexanecarboxylic acid derivatives.⁶ Stereocontrol is comparable to that found with alkylations of

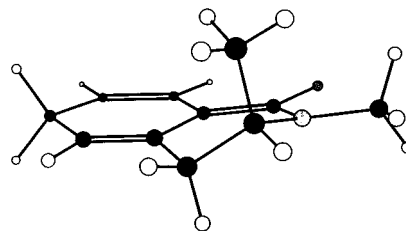
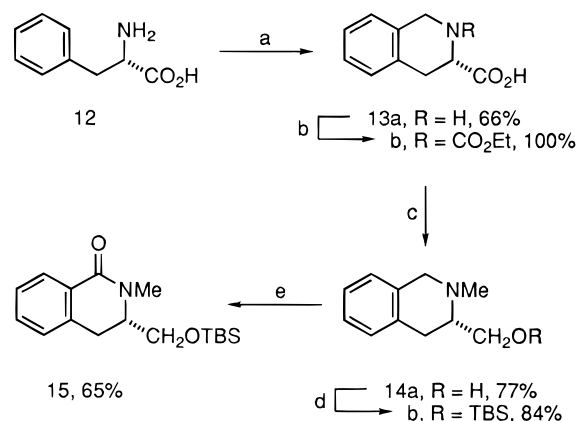


Figure 1. Most stable conformation of the enolate generated from Birch reduction of **6** (MM2, MacroModel).

Scheme 3^a

^a Reaction conditions: (a) 37% CH₂O, concentrated HCl, 85 °C; (b) ClCO₂Et, THF, NaHCO₃, H₂O, 0 °C; (c) LiAlH₄, THF, reflux; (d) TBSCl, DMF, imidazole; (e) RuO₂ (cat.), NaIO₄, CH₃CN.

anions generated from bislactam ethers.⁷ The most stable conformation of the enolate generated from Birch reduction of **6**, as determined by molecular modeling experiments, is shown in Figure 1. It is obvious from the figure that the C(3) methyl substituent in a pseudoaxial environment provides very effective shielding of the β -face of the enolate. Placement of this methyl group in a pseudoequatorial position would result in serious eclipsing interactions with the neighboring *N*-methyl substituent (Figure 1).⁸

The conversion of L-phenylalanine (**12**) to (+)-(3*S*)-3,4-dihydro-3-(*tert*-butyldimethylsilyloxymethyl)-2-methyl-1(2*H*)-isoquinolinone (**15**) is shown in Scheme 3. (*S*)-1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic acid (**13a**) can be prepared from L-phenylalanine by a literature procedure⁹ or is available from commercial sources.¹⁰ Acylation of **13a** with ethyl chloroformate gave **13b**, and reduction of **13b** with LiAlH₄ in THF gave **14a** in 77% overall yield from **13a**. Protection of **14a** as the *tert*-butyldimethylsilyl

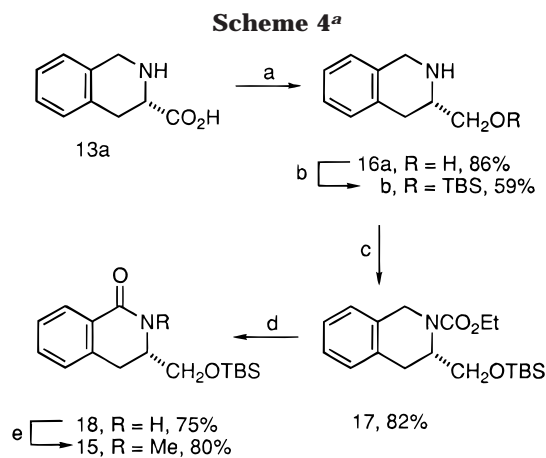
(6) (a) House, H. O.; Bare, T. M. *J. Org. Chem.* **1968**, *33*, 943–949. (b) Ziegler, F. E.; Wender, P. A. *J. Am. Chem. Soc.* **1971**, *93*, 4318–4319. (c) Van Bekkum, H.; Van Den Bosch, C. B.; Van Minnen Pathuis, G.; DeMos, J. C.; Van Wijk, A. M. *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 137–149. (d) Krapcho, A. P.; Dundulis, E. A. *J. Org. Chem.* **1980**, *45*, 3236–3245.

(7) (a) Schöllkopf, U.; Hartwig, W.; Groth, U. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 863–864. (b) Schöllkopf, U.; Groth, U. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 977–978.

(8) For a similar pseudoaxial conformation of the C(3) benzyl substituent of a N(4) methyl diketopiperazine observed in both the solid state and solution phase, see: Budesinsky, M.; Symersky, J.; Jecny, J.; VanHecke, J.; Hosten, N.; Angeunis, M.; Borremans, F. *Int. J. Peptide Protein Res.* **1992**, *39*, 123.

(9) Hayashi, K.; Ozaki, Y.; Nunami, K.-I.; Yoneda, N. *Chem. Pharm. Bull.* **1983**, *31*, 312–314.

(10) (*S*)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid (**13a**) is available in high enantiomeric purity from the Nutra Sweet Company and Aldrich Chemical Co.



^a Reaction conditions: (a) LiAlH₄, THF, reflux; (b) TBSCl, DMF, imidazole; (c) ClCO₂Et, THF, NaHCO₃, H₂O, 0 °C; (d) RuO₂ (cat.), NaIO₄, CH₃CN; NaOMe, MeOH; (e) *n*-BuLi, THF; MeI.

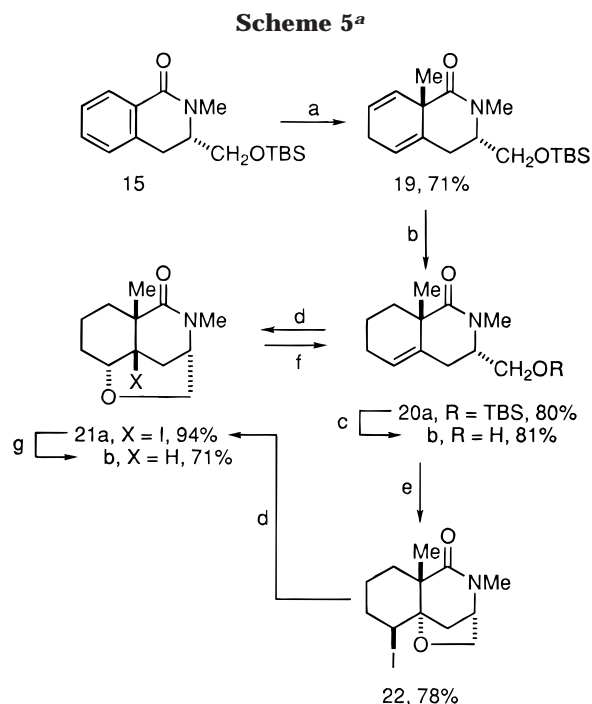
ether **14b** and oxidation of **14b** with catalytic ruthenium tetroxide and NaIO₄¹¹ gave **15**. A chiral HPLC analysis of **15** prepared from L-phenylalanine compared to racemic **15** demonstrated that (+)-**15** had been prepared with no detectable racemization.

Although the oxidation of **14b** to **15** was relatively successful on a small scale, attempts to scale-up the process were disappointing. For this reason, another preparation of **15** was developed (Scheme 4). The ruthenium tetroxide oxidation of carbamate **17** followed by carbamate cleavage with NaOMe provided lactam **18** in 75% yield; *N*-methylation gave **15**.

Birch reduction–alkylation (MeI) of **15** gave the 1,4-cyclohexadiene derivative **19** with a diastereoselectivity (>35:1) exceeding that observed for the conversion of **6** to **7a** (Scheme 5). It is believed that the higher diastereoselectivity is a result of the larger TBSOCH₂ group at C(3), which more effectively shields the α-face of the enolate from the alkylation reagent (see Figure 1).

Additional value from the C(3) stereodirecting group in **19** was expected by way of cyclization reactions with the C(4a)–C(5) double bond. Selective reduction of the disubstituted double bond with diimide gave **20a**, and cleavage of the silyl ether in **20a** gave **20b**. Treatment of olefinic alcohol **20b** with I₂ in THF and H₂O under conditions of thermodynamic control (25 °C, 96 h) gave the iodopyran **21a** in 94% isolated yield.^{12a} Reduction of **21a** with AIBN and Bu₃SnH in benzene gave pyran **21b**.

Treatment of **20b** under conditions of kinetic control with *N*-iodosuccinimide (1.1 equiv) in CH₂Cl₂ at 0 °C in the presence of NaHCO₃ gave a 9:1 mixture of **22** and **21a**, from which the iodotetrahydrofuran **22** was obtained in 78% yield by flash chromatography on silica gel. Thus, both the *cis*- and *trans*-perhydroisoquinolone ring systems **21** and **22** are available by experimentally simple iodoetherification reactions. Iodotetrahydrofuran **22** was cleanly converted to the iodopyran **21a** on treatment with I₂ in THF and H₂O at 25 °C. Furthermore, it was possible to reverse the iodoetherification^{12b} by treatment



^a Reaction conditions: (a) Li, NH₃/THF, *t*-BuOH, –78 °C; piperylene; RX; (b) *p*-TosNHNH₂, NaOAc, DME, reflux; (c) TBAF, THF; (d) I₂, THF, H₂O, 25 °C, 96 h; (e) NIS, CH₂Cl₂, NaHCO₃, 0 °C, 3 h; (f) MeLi, THF; (g) AIBN, Bu₃SnH, benzene, reflux.

of iodopyran **21a** with MeLi in THF to give **20b** in essentially quantitative yield.

Application to the Enantiospecific Synthesis of New Ligands for the Opioid Receptors. *N*-Methylmorphinan was first synthesized in 1946 by Grewe;¹³ the levo isomer called levorphanol (**23**) is 4 times as potent as morphine.^{13c} Tetracycle **24** is isomeric with levorphanol, but the bridging of the perhydroisoquinoline ring by the hydroxybenzyl unit in **24** is at C(7, isoquinoline numbering) and C(8a) rather than at C(1) and C(4a) as in levorphanol. The distance from the phenolic hydroxy group to the nitrogen atom in **24** is greater than that in **23**; that is, levorphanol can be considered to be an arylethylamine, while **24** is an arylpropylamine.¹⁴

Molecular models of levorphanol (**23**) reveal that the C(9, morphinan numbering)–N bond resides in a plane that is approximately orthogonal to the phenolic ring. The relatively high degree of chirality¹⁵ of **23** results in high stereospecificity for binding to the opioid receptors.¹⁶ Stereospecificity also has been observed for the unnatural enantiomers of codeine, morphine, and heroin, all of which showed no antinociceptive activity on subcutaneous injection in mice.¹⁷

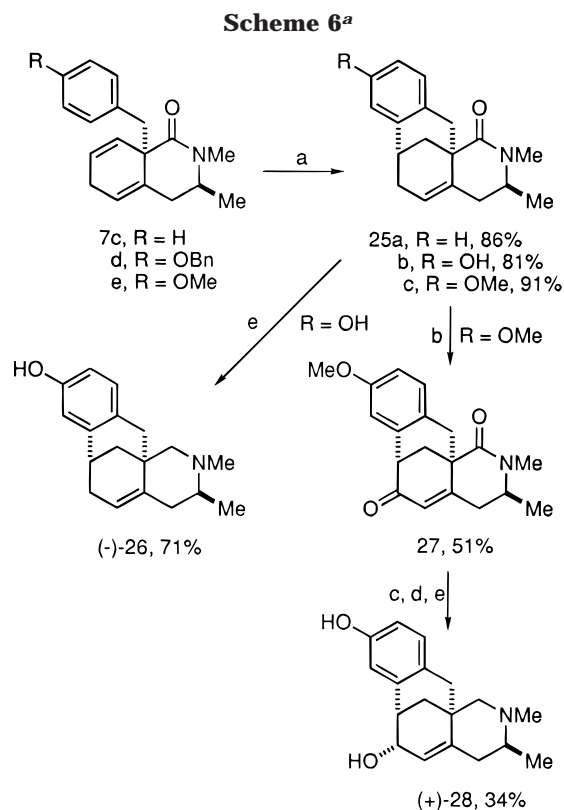
(13) (a) Grewe, R. *Naturwissenschaften* **1946**, *33*, 333–336. (b) Grewe, R.; Mondon, A. *Chem. Ber.* **1948**, *81*, 279–286. (c) Benson, W. M.; Stefko, P. L.; Randall, L. O. *J. Pharmacol. Exp. Ther.* **1953**, *109*, 189–194. The meperidines and methadons contain an arylpropylamine unit.

(15) (a) Avnir, D.; Katzenelson, O.; Zbrodsky Hel-Or, H. *Chem. Eur. J.* **1996**, *2*, 744–746, and references therein. (b) Seri-Levy, A.; Richards, W. G. *Tetrahedron: Asymmetry* **1993**, *4*, 1917–1923, and references therein. (c) Crossley, R. *Chirality and the Biological Activity of Drugs*; CRC Press: Boca Raton, FL, 1995; pp 21–47.

(16) Levorphanol and its inactive enantiomer dextrophan showed 4 orders of magnitude difference in their ability to displace ³H-labeled ligand; see: (a) Terenius, L. *Acta Pharmacol. Toxicol.* **1973**, *32*, 317. (b) Pert, C. B.; Snyder, S. H. *Science* **1973**, *179*, 1011–1014. (c) Simon, E. J.; Hiller, J. M.; Edelman, I. *Proc. Natl. Acad. Sci., U.S.A.* **1973**, *70*, 1947–1949.

(11) Tangari, N.; Tortorella, V. *J. Chem. Soc., Chem. Commun.* **1975**, 71–72.

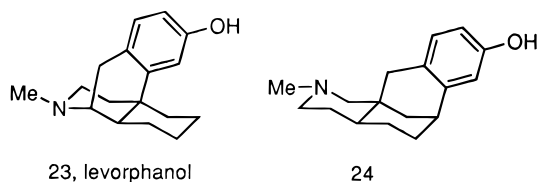
(12) (a) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York 1984; Vol. 3, pp 411–454. (b) Ireland, R. E.; Häbich, D.; Norbeck, D. W. *J. Am. Chem. Soc.* **1985**, *107*, 3271–3278.



^a Reaction conditions: (a) MeSO₃H, CH₂Cl₂, 0 °C; (b) PDC (cat.), Celite, *t*-BuOOH, benzene; (c) NaBH₄, CeCl₃, MeOH, 0 °C; (d) BBr₃, CH₂Cl₂, -78 °C to room temperature; (e) LiAlH₄, THF, reflux.

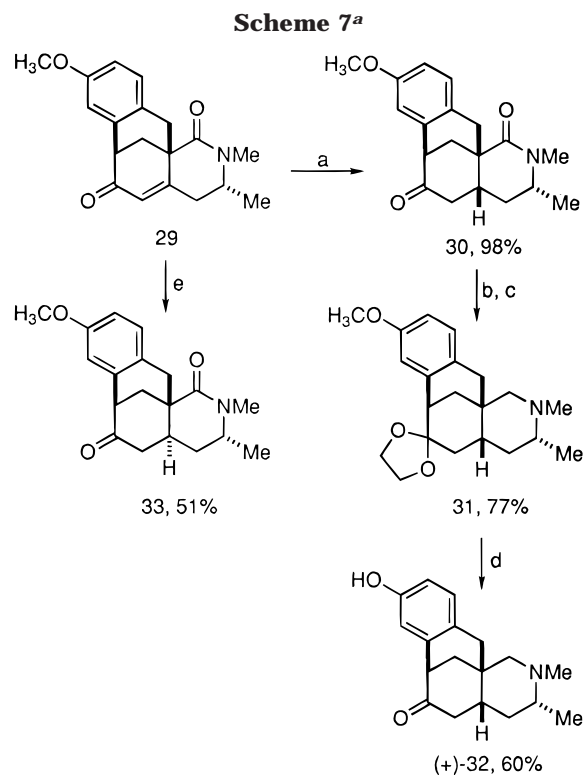
By contrast, the nitrogen atom in **24** resides very nearly coplanar with the phenolic ring. Thus, the polar binding elements in **24** and its enantiomer are spatially nearly equivalent; only hydrocarbon portions of the perhydroisoquinoline ring system reside on opposite faces of the aromatic ring in **24** and its enantiomer.^{18a} Another major difference between levorphanol and **24** is that the orientation of the electron pair on nitrogen in **23** is anti to the aromatic ring, whereas in **24** the orientation is syn.^{18b}

Tetracycle **24** was prepared as a racemate, and preliminary opiate receptor binding studies showed modest affinity for the μ - and κ -receptors: K_i (nM) > 100 at the μ -receptor, 2620 at the κ -receptor, and no binding detected at the δ -receptor.² With a lead structure established, we decided to make structural modifications that were expected to enhance opiate receptor affinity and selectivity (Schemes 6 and 7). Potential ligands were prepared as single enantiomers to test for stereoselectivity of binding to the opiate receptors.



Grewe cyclization of **7c–7e** with trifluoromethanesulfonic acid in CH₂Cl₂ gave the bridged cyclohexene

(17) Iijima, I.; Minamikawa, J.; Jacobson, A. E.; Brossi, A.; Rice, K. *J. Org. Chem.* **1978**, *43*, 1462–1463.



^a Reaction conditions: (a) H₂, 5% Pd/C, EtOAc, 79 psi; (b) *p*-TosOH, HO(CH₂)₂OH, benzene, reflux; (c) LiAlH₄, THF, reflux; (d) BBr₃, CH₂Cl₂, -78 °C to room temperature; (e) Li, NH₃/THF, *t*-BuOH, -78 °C.

derivatives **25a–25c**. A distinct advantage of the *O*-benzyl ether **7d** is that benzyl ether cleavage occurs along with cyclization to give the phenol **25b**. Reduction of the lactam with LiAlH₄ in THF gave the phenolic amine (–)-**26**.

Allylic oxidation of the methyl ether analogue **25c** provided keto lactam **27**; **27** was converted to the phenolic amine (+)-**28** containing the allylic alcohol moiety characteristic of morphine (Scheme 6). The enantiomers of (–)-**26** and (+)-**28**, (+)-**26** and (–)-**28**, were prepared from the corresponding 1,4-cyclohexadiene derivatives **11a** and **11b**.

The phenolic amino ketone (+)-**32** with a *cis*-perhydroisoquinoline ring fusion was prepared as shown in Scheme 7. The *cis* ring junction was obtained by hydrogenation of the enone double bond in **29**. It is clear that the axial methyl substituent is responsible for the observed stereoselectivity. In the absence of the axial methyl substituent, hydrogenation of the corresponding bridgehead olefin provides the *trans* ring junction.² The *trans*-perhydroisoquinoline (+)-**33** was obtained from **29** by the lithium in ammonia reduction (53% yield); however, a small amount of *cis*-fused **30** also was produced.

Opioid Receptor Affinities. Opioid receptor affinities for the enantiomerically pure ligands (–)-**26**, (+)-**26**, (+)-**28**, (–)-**28**, and (+)-**32** are shown in Table 1. Al-

(18) (a) For a discussion of μ -opiate receptor models, see: Aldrich, J. V. In *Burger's Medicinal Chemistry and Drug Discovery*; Wolff, M. E., Ed.; Wiley: New York, 1996; Vol. 3, pp 369–372. For a discussion of uncertainty associated with the importance of nitrogen lone pair orientation with respect to analgesic activity, see: (b) Belleau, B.; Conway, T.; Ahmed, F. R.; Hardy, A. D. *J. Med. Chem.* **1974**, *17*, 907–908. (c) Belleau, B.; Morgan, P. *J. Med. Chem.* **1974**, *17*, 908–909. (d) Shiotani, S.; Kometani, T.; Iitaka, Y.; Itai, A. *J. Med. Chem.* **1978**, *21*, 153–154.

Table 1. K_i Values (nM \pm SEM) for the Inhibition of Binding to μ -, δ -, and κ -Opioid Receptors on Bovine Striatal Membranes by (–)-**26**, (+)-**26**, (+)-**28**, (–)-**28**, and (+)-**32**^a

compound	[³ H]DAMGO (μ)	[³ H]naltrindole (δ)	[³ H]U69,593 (κ)
(–)- 26	2150 \pm 210	3540 \pm 310	244 \pm 37
(+)- 26	3320 \pm 230	5030 \pm 800	541 \pm 26
(+)- 28	4920 \pm 530	3770 \pm 470	1190 \pm 250
(–)- 28	4450 \pm 440	4260 \pm 1080	1080 \pm 100
(+)- 32	2080 \pm 150	928 \pm 85	887 \pm 69

^a Bovine striatal membranes, 0.5 mg of membrane protein, were incubated in a final volume of 1 mL of 50 mM Tris-HCl, pH 7.5, with at least six different concentrations of compounds in the presence of either 0.25 nM [³H]DAMGO, 0.2 nM [³H]naltrindole, or 1 nM [³H]U69,593 to measure binding to μ -, δ -, and κ -opioid receptors, respectively. Naloxone at a final concentration of 1 μ M was used to measure nonspecific binding. Samples incubated with either [³H]DAMGO or [³H]U69,593 were incubated at 25 °C for 60 min. To measure binding to δ -receptors, 5 mM MgCl₂ and 1 mM PMSF were included with [³H]naltrindole and the test compound. These samples were incubated at 25 °C for 3 h. Binding was terminated by filtering samples through Schleicher & Scheull No. 32 glass fiber filters. The filters were subsequently washed three times with 3 mL of cold 50 mM Tris-HCl, pH 7.5, and were counted in 2 mL of Ecoscint A scintillation fluid. For [³H]pCl-DPDPE and [³H]U69,593 binding, the filters were soaked in 0.25% polyethylenimine for at least 60 min before use. IC₅₀ values were determined using the least-squares fit to a logarithm-probit analysis. K_i values were calculated according to the equation

$$K_i = \frac{\text{IC}_{50} \text{ value of the test compound}}{1 + [\text{Concentration of } ^3\text{H-ligand}]/K_d \text{ value of } ^3\text{H-ligand}}$$

The equation was first reported by Cheng and Prusoff (*Biochem. Pharmacol.* **1973**, *22*, 3099–3108). The K_d values for [³H]DAMGO, [³H]naltrindole, and [³H]U69,593 binding to bovine striatal membranes were 0.99, 0.12, and 0.60 nM, respectively.

though none of these new ligands display high affinity for the opioid receptors, we believe that (–)-**26** and (+)-**26** deserve further study since the κ -receptor affinity of **26** is an order of magnitude greater than that determined for the lead structure **24**. Analogue **26** is prepared in only three steps from the chiral dihydro-1(2*H*)-isoquinolinones **6** or **10**, and it should be possible to modify the substituent on nitrogen to enhance κ -receptor affinity and selectivity.¹⁹ Utilization of the chemistry developed with phenylalanine (Schemes 4 and 5) will allow the installation of a hydroxymethyl or related polar substituent²⁰ at C(3) of the dihydroisoquinolin-1-one ring system. As alluded to in the discussion concerning the degree of chirality of **24**, the absence of significant stereospecificity for opioid receptor binding (Table 1) indicates that the out-of-plane hydrocarbon units of **24** play little if any role in the binding of **24** to the opioid receptors.

Experimental Section

General Procedures. Chemical ionization mass spectra were obtained on a Hewlett-Packard 5987A GC-MS system (isobutane). High-resolution mass spectra were obtained from the University of Illinois facilities at Urbana–Champaign. Thin-layer chromatography was performed with Merck Kieselgel 60 F-254 and Whatman Linear-K silica gel precoated glass plates. Melting points are reported without correction. Elemental analyses were obtained from Atlantic Microlab, Inc., Norcross, GA. Methylene chloride, methyl alcohol, *tert*-butyl alcohol, and triethylamine were dried over CaH₂ and distilled.

Tetrahydrofuran was dried over sodium/benzophenone ketyl and distilled. All other reagents were used as purchased. Reactions requiring anhydrous conditions were performed under a nitrogen atmosphere. Baker silica gel (40 μ m) was used for flash column chromatographies. All chiral HPLC analyses were carried out on a Chiralcel OD column using a 9:1 mixture of hexane and 2-propanol.

(–)-(1*R*,2*S*)-2-(Methyl)ethoxycarbonylamino-1-phenyl-1-propanol (4). To a solution of (1*R*,2*S*)-ephedrine (**3**) (4.28 g, 25.9 mmol) in CH₂Cl₂ (16 mL) was added a saturated solution of NaHCO₃ (24 mL). The resulting two-phase system was stirred vigorously at 0 °C, and ethyl chloroformate (2.81 g, 2.48 mL, 25.9 mmol) in CH₂Cl₂ (4 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 3 h, and then the CH₂Cl₂ layer was separated. The water phase was extracted with CH₂Cl₂ (2 \times 100 mL), and the combined CH₂Cl₂ layers were dried over MgSO₄. Concentration and crystallization of the viscous oil from hexane/ethyl acetate at 0 °C gave **4** as colorless crystals (6.03 g, 98%), mp 52–55 °C;²¹ IR (KBr) 3370, 1615 cm^{–1}; ¹H NMR δ (500 MHz, 60 °C, CDCl₃) 7.36–7.23 (m, 5 H), 4.82 (br s, 1 H), 4.14–4.06 (m, 3 H), 2.90–2.50 (br s, 1 H, exchangeable with D₂O), 2.73 (s, 3 H), 1.23 (d, J = 6.0 Hz, 3 H), 1.20 (t, J = 7.1 Hz, 3 H) ppm; ¹³C NMR δ (125.7 MHz, 60 °C, CDCl₃) 156.8, 142.3, 128.0, 127.3, 126.1, 76.7, 61.1, 58.5, 31.5, 14.4, 12.0; [α]_D²³ –40 (*c* 0.7, CHCl₃); CIMS, m/z (rel intensity) 238 (M⁺ + 1, 100). Anal. Calcd for C₁₃H₁₉NO₃: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.77; H, 7.95; N, 5.88.

(+)-(2*S*)-[*N*-2-(1-phenylpropyl)-*N*-methyl]ethylformate (5). To a mechanically stirred suspension of Raney Ni (wet, prepared from 200 g of aluminum–nickel alloy, Raney type Ni–Al 50:50)²² in ethanol (700 mL) was added **4** (29.55 g, 0.125 mol), and the mixture was heated to reflux for 2 h. After cooling to room temperature the mixture was filtered through Celite. Concentration, flash chromatography (hexane/ethyl acetate, 2:1) on silica gel (218 g), and distillation (88 °C/0.35 mmHg) gave **5** as a colorless liquid (23.80 g, 86%); IR (film) 1670, 1665 cm^{–1}; ¹H NMR δ (500 MHz, CDCl₃, 70 °C) 7.27–7.24 (m, 2 H), 7.18–7.15 (m, 3 H), 4.44 (br s, 1 H), 4.05 (broad q, 2 H), 2.75 (s, 3 H), 2.82 (dd, J = 13.7, 7.1 Hz, 2 H), 1.17 (t, J = 7.1 Hz, 3 H), 1.15 (d, J = 6.0 Hz, 3 H); ¹³C NMR (125.7 MHz, CDCl₃) δ 156.3, 138.7, 128.8, 128.2, 126.1, 60.8, 52.2, 40.5, 27.8, 17.9, 14.5; [α]_D²³ +37 (*c* 1.3, CHCl₃); CIMS, m/z (rel intensity) 222 (M⁺ + 1, 100). Anal. Calcd for C₁₃H₁₉NO₂: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.45; H, 8.28; N, 6.31.

(–)-(3*S*)-3,4-Dihydro-2,3-dimethyl-1(2*H*)-isoquinolinone (6). Urethane **5** (4.734 g, 20.82 mmol) was added to Eaton's acid (28.51 g, MeSO₃H/P₂O₅, 10:1.6 equiv by weight)⁵ at 120 °C. The reaction mixture was kept at 120 °C for 2 h, then cooled to room temperature, and then poured into a saturated solution of NaHCO₃. The mixture was stirred for 30 min and then extracted with CH₂Cl₂ (3 \times 100 mL). The combined CH₂Cl₂ layers were washed with water (100 mL), dried over MgSO₄, and concentrated. Flash chromatography (EtOAc) on silica gel and vacuum distillation (102 °C/0.35 mmHg) provided **6** as a colorless oil (2.63 g, 72%); IR (film) 1628, 1600 cm^{–1}; ¹H NMR δ (500 MHz, CDCl₃) 8.06 (m, 1 H), 7.39 (m, 1 H), 7.31 (m, 2 H), 7.15 (dd, J = 6.9 Hz, 0.5 Hz, 1 H), 3.72 (m, 1 H), 3.35 (dd, J = 15.9, 6.1 Hz, 2 H), 3.12 (s, 3 H), 2.66 (dd, J = 15.9, 2.5 Hz, 1 H), 1.15 (d, J = 6.6 Hz, 1 H); ¹³C NMR δ (125.7 MHz, CDCl₃) 163.6, 135.9, 131.4, 127.5, 126.6, 128.6, 53.5, 33.9, 33.1, 17.3. [α]_D²⁴ –300 (*c* 0.9, CHCl₃); HRMS calcd for C₁₁H₁₃NO (M + H⁺) 176.1075, found 176.1068. Anal. Calcd for C₁₁H₁₃NO: C, 75.40; H, 7.48; N, 7.99. Found: C, 74.69; H, 7.52; N, 7.89.

(+)-(3*S*,8*aR*)-3,4,6,8a-Tetrahydro-8a-[(4-methoxyphenyl)methyl]-2,3-dimethyl-1(2*H*)-isoquinolinone (7e). To a solution of **6** (1.156 g, 9.90 mmol) and *tert*-butyl alcohol (0.88

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solution was extracted with ether (2 × 25 mL). The aqueous layer was acidified with 10% HCl before extracting with EtOAc (3 × 25 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo to give colorless crystals (6.34 g, 100%), mp 129–130 °C: [α]_D²³ +74 (c 1.0, CHCl₃); ¹H NMR (CDCl₃) 7.22–7.09 (m, 4 H), 5.14 (q, *J* = 6.4, 3.2 Hz, 1 H), 4.77–4.71 (m, 1 H), 4.52–4.42 (m, 1 H), 4.24–4.20 (m, 2 H), 3.27–3.13 (m, 2 H), 1.31 (t, *J* = 7.1 Hz, 3 H); ¹³C NMR (CDCl₃) 176.5, 156.5, 132.2, 131.3, 128.4, 127.9, 126.8, 126.1, 62.1, 52.6, 44.1, 30.6, 14.5; IR (Nujol) 2968, 1733, 1645, 1462, 1350; CIMS *m/z* (rel intensity) 250 (M⁺ + 1, 100), 204 (12.5). Anal. Calcd for C₁₃H₁₅NO₄: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.57; H, 6.04; N, 5.67.

2-Methyl-1,2,3,4-tetrahydro-3-isoquinolinemethanol (14a). To a solution of LiAlH₄ (4.37 g, 5.0 equiv) in THF (100 mL) was added **13b** (5.75 g, 23.0 mmol). The solution was heated at reflux for 5 h and then was quenched by the sequential addition of water (4.37 mL), 10% NaOH (4.37 mL), and water (4.37 mL). Anhydrous Na₂SO₄ was added, and the resulting slurry was filtered through Celite. The pale yellow solution was concentrated under reduced pressure, and the residue was crystallized from CH₂Cl₂/hexanes to give colorless crystals (3.14 g, 77%), mp 104–106 °C: [α]_D²³ –64 (c 1.0, CHCl₃); ¹H NMR (CDCl₃) 7.15–7.11 (m, 2 H), 7.09–7.07 (m, 1 H), 7.03–7.01 (m, 1 H), 3.87 (d, *J* = 15.6 Hz, 1 H), 3.70–3.67 (m, 2 H), 3.59 (dd, *J* = 6.4, 1.3 Hz, 1 H), 3.34 (s, 1 H), 2.86–2.80 (m, 1 H), 2.77 (d, *J* = 6.9 Hz, 2 H), 2.41 (s, 3 H); ¹³C NMR (CDCl₃) 133.9, 133.6, 128.7, 126.5, 126.4, 125.9, 62.5, 60.0, 55.9, 40.0, 28.0; IR (Nujol) 2924, 1458, 1377, 1144, 723; CIMS *m/z* (rel intensity) 178 (M⁺ + 1, 100), 146 (10), 160 (6). Anal. Calcd for C₁₁H₁₅NO: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.63; H, 8.54; N, 7.94.

2-Methyl-1,2,3,4-tetrahydroisoquinoline-3-*tert*-butyldimethylsilyloxymethane (14b). To a solution of **14a** (1.00 g, 5.62 mmol) and imidazole (0.96 g, 2.5 equiv) in DMF (5 mL) was added *tert*-butyldimethylsilyl chloride (0.93 g, 1.1 equiv). The resulting solution was stirred at room temperature for 3 h. The reaction mixture was poured into saturated NaHCO₃ (20 mL), and the resulting solution was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The residue was chromatographed using ethyl acetate and hexane (65:35) as eluent to give a colorless oil (1.38 g, 84%): [α]_D²⁴ –97 (c 1.0, CHCl₃); ¹H NMR (CDCl₃) 7.14–7.09 (m, 4 H), 7.02 (d, *J* = 7.3 Hz, 1 H), 3.86–3.81 (m, 2 H), 3.65–3.59 (m, 2 H), 2.89 (dd, *J* = 16.4, 4.9 Hz, 1 H), 2.80 (dd, *J* = 16.3, 8 Hz, 1 H), 2.72–2.70 (m, 1 H), 2.51 (s, 3 H), 0.90 (s, 9 H), 0.06 (s, 6 H); ¹³C NMR (CDCl₃) 134.4, 133.9, 128.6, 126.1, 126.0, 125.8, 64.1, 60.8, 56.9, 42.0, 30.8, 25.8, 18.2, –5.5; IR (film) 1471, 1255, 1104, 1072, 776; CIMS, *m/z* (rel intensity) 292 (M⁺ + 1) 292 (100), 146 (18). Anal. Calcd for C₁₇H₂₉NOSi: C, 70.04; H, 10.03; N, 4.81. Found: C, 69.92; H, 10.00; N, 4.76.

(+)-(3S)-3,4-Dihydro-3-*tert*-butyldimethylsilyloxymethyl-2-methyl-1(2H)-isoquinolinone (15). To a well-stirred solution of **14b** (500 mg, 1.71 mmol) and NaIO₄ (1.49 g, 4.1 equiv) in CCl₄ (5 mL), CH₃CN (5 mL), and water (7.5 mL) was added RuO₂ (5 mg, 2.2 mol %). The resulting solution was stirred at room temperature for 3.5 h before diluting with CH₂Cl₂ (10 mL) and water (10 mL). The layers were separated and the aqueous layer extracted with CH₂Cl₂ (2 × 15 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography using a 5% acetone in CH₂Cl₂ solution as eluent gave a white solid (0.34 g, 65%), mp 57–59 °C: [α]_D²⁵ +190 (c 1.0, CHCl₃); ¹H NMR (CDCl₃) 8.10 (d, *J* = 7.8 Hz, 1 H), 7.44 (t, *J* = 7.3 Hz, 1 H), 7.35 (t, *J* = 7.6 Hz, 1 H), 7.19 (d, *J* = 7.6 Hz, 1 H), 3.72–3.69 (m, 2 H), 3.50 (t, *J* = 10 Hz, 1 H), 3.34 (dd, *J* = 16.1, 5.9 Hz, 1 H), 3.26 (s, 3 H), 3.05 (d, *J* = 16.1 Hz, 1 H), 0.9 (s, 9 H), 0.01 (s, 6 H); ¹³C NMR (CDCl₃) 163.9, 135.8, 131.6, 128.9, 127.7, 127.6, 126.8, 61.8, 59.4, 34.9, 28.7, 25.6, 18.0, –5.7, –5.8; IR (Nujol) 1660, 1262, 1107, 850; CIMS, *m/z* (rel intensity) 306 (M⁺ + 1, 100), 248 (10). An alternative preparation of **15** is described below. Anal. Calcd for C₁₇H₂₇NO₂Si: C, 66.84; H, 8.91; N, 4.59. Found: C, 66.90; H, 8.94; N, 4.65.

(3S)-1,2,3,4-Tetrahydro-3-isoquinolinemethanol (16a). To a slurry of LiAlH₄ (3.20 g, 2.5 equiv) in THF (120 mL) was added **13a** (6.30 g, 35.2 mmol). The resulting mixture was heated at reflux for 6 h. The reaction was quenched by addition of NaOH solution until a white precipitate was formed. More THF was added, and the mixture was heated at reflux for 10 min. The precipitate was filtered, and the remaining solution was dried over MgSO₄ and concentrated to give yellow crystals (86%), mp 105–107 °C: IR (film) 3300 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.12 (m, 2 H), 7.07 (m, 1 H), 7.00 (m, 1 H), 4.03 (s, 2 H), 2.06 (dd, *J* = 11.0, 3.7 Hz, 1 H), 3.51 (dd, *J* = 11.0, 7.8 Hz, 1 H), 3.09 (s, 1 H), 3.05 (m, 2 H), 2.68 (dd, *J* = 16.4, 4.4 Hz, 1 H), 2.59 (dd, *J* = 16.4, 11.0 Hz, 1 H); ¹³C NMR (CDCl₃) 135.1, 133.8, 129.2, 126.2, 126.0, 125.8, 65.3, 55.0, 47.6, 30.7; CIMS *m/z* 164 (M + 1).

(3S)-1,2,3,4-Tetrahydro-3-*tert*-butyldimethylsilyloxymethylisoquinoline (16b). To a solution of **16a** (200 mg, 1.23 mmol) and imidazole (209 mg, 2.5 equiv) in DMF (1 mL) was added *tert*-butyldimethylsilyl chloride (203 mg, 1.1 equiv). The resulting solution was stirred at room temperature overnight and then was poured into saturated NaHCO₃, extracted with EtOAc, dried over MgSO₄, and concentrated to a yellow oil. Flash chromatography (1% acetone in CH₂Cl₂) gave a yellow oil (59%): IR (film) 1100 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.07 (m, 4 H), 4.08 (d, *J* = 4.2 Hz, 2 H), 3.77 (dd, *J* = 9.8, 3.9 Hz, 1 H), 3.61 (dd, *J* = 9.8, 6.9 Hz, 1 H), 3.02 (m, 1 H), 2.65 (m, 2 H), 2.37 (bs, 1 H), 0.90 (s, 9 H), 0.10 (s, 6 H).

(3S)-2-Carboethoxy-1,2,3,4-tetrahydro-3-*tert*-butyldimethylsilyloxymethylisoquinoline (17). To a solution of **16b** (2.72 g, 9.8 mmol) and NaHCO₃ (2.06 g, 2.5 equiv) in a 1:1 mixture of THF and water (40 mL) at 0 °C was added ethyl chloroformate (1.03 mL, 1.1 equiv). The resulting solution was warmed slowly to room temperature, stirred for 4 h, and then diluted with water. The mixture was extracted with EtOAc, dried over MgSO, and concentrated to a yellow oil. Flash chromatography using ethyl acetate and hexane (1:9) as eluent gave a colorless oil (82%): IR (film) 3300, 1680, 1100 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.23–7.17 (m, 4 H), 4.78 (t, *J* = 20 Hz, 1 H), 4.49 (m, 1 H), 4.35 (d, *J* = 16.6 Hz, 1 H), 4.24 (m, 2 H), 3.61 (m, 1 H), 3.38 (m, 1 H), 3.00 (m, 1 H), 1.34 (m, 1 H), 0.90 (s, 9 H), 0.02 (s, 6 H); CIMS *m/z* 350 (M⁺ + 1). Anal. Calcd for C₁₉H₃₁NO₃Si: C, 65.29; H, 8.94; N, 4.01. Found: C, 65.03; H, 8.93; N, 3.99.

(3S)-3,4-Dihydro-3-*tert*-butyldimethylsilyloxymethyl-1(2H)-isoquinolinone (18). To a stirred solution of **17** (6.02 g, 17.7 mmol) and NaIO₄ (15.6 g, 4.1 equiv) in CCl₄ (60 mL), CH₃CN (60 mL), and water (90 mL) was added RuO₂ (52 mg, 2.2 mol %). The resulting solution was stirred at room temperature for 1 h before diluting with CH₂Cl₂ and water. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated. Without further purification the residue was dissolved in a solution of CH₃ONa (1.13 g, 1.2 equiv) in MeOH (300 mL). The mixture was heated at reflux for 1 h before diluting with 10% NH₄Cl. The mixture was then extracted with CH₂Cl₂, after which the combined organic layers were dried over MgSO₄ and concentrated. Flash chromatography (2% acetone in CH₂Cl₂) gave off-white crystals (75%), mp 48–51 °C: IR (CHCl₃) 3185, 1665, 1600, 1100 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 8.08 (d, *J* = 7.5 Hz, 1 H), 7.45 (t, *J* = 7.6 Hz, 1 H), 7.35 (t, *J* = 7.6 Hz, 1 H), 7.20 (d, *J* = 7.3 Hz, 1 H), 6.28 (s, 1 H), 3.83 (m, 1 H), 3.74 (dd, *J* = 10, 4.7 Hz, 1 H), 3.60 (dd, *J* = 10, 8.5 Hz, 1 H), 2.86 (m, 2 H), 0.90 (s, 9 H), 0.07 (s, 6 H); ¹³C NMR (500 MHz, CDCl₃) 193.2, 165.8, 137.1, 132.1, 127.8, 127.4, 126.9, 65.3, 52.3, 29.9, 25.6, 18.0; CIMS *m/z* 292 (M⁺ + 1). Anal. Calcd for C₁₆H₂₅NO₂Si: C, 65.93; H, 8.71; N, 4.81. Found: C, 65.86; H, 8.71; N, 4.75.

Alternative Method for Preparation of 15. To a stirred solution of **18** (113 mg, 0.48 mmol) in THF (1 mL) at –78 °C was added *n*-BuLi (210 μ L, 1.1 equiv). The mixture was warmed to 0 °C and stirred for 45 min before MeI (89 μ L, 3 equiv) was added. The mixture was warmed to room temperature, diluted with water, and then extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and

concentrated. Flash chromatography (2% acetone in CH₂Cl₂) gave **15** (80%).

(+)-(3S,8aS)-3,4,6,8a-Tetrahydro-2,8a-dimethyl-3-tert-butylidimethylsiloxymethyl-1(2H)-isoquinolinone (19).

To a well-stirred solution of **15** (200 mg, 0.65 mmol) and *tert*-butyl alcohol (62.2 μ L, 1.05 equiv) in THF (4 mL) and NH₃ (20 mL) was added lithium until a blue coloration persisted for 15 min. Excess metal was quenched by the dropwise addition of piperylene, and then MeI (0.20 μ L, 5.0 equiv) was added. The resulting solution was stirred at -78 °C for 1 h, quenched with solid NH₄Cl, and warmed to room temperature. After evaporation of NH₃ was complete, the residue was diluted with CH₂Cl₂ (50 mL) and water (50 mL) and the layers were separated. The aqueous layer was extracted with CH₂-Cl₂ (2 \times 15 mL), and the combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. Flash chromatography using ether and hexane (20:80) as eluent gave a colorless solid (0.15 g, 71%), mp 47–48 °C: [α]_D²⁴ +88 (c 1.0, CHCl₃); ¹H NMR (CDCl₃) 6.15 (d, *J* = 10 Hz, 1 H), 5.75–5.71 (m, 1 H), 5.53 (bs, 1 H), 3.59 (dd, *J* = 9.5, 4.4 Hz, 1 H), 3.43 (t, *J* = 9 Hz, 1 H), 3.37–3.33 (m, 1 H), 2.97 (s, 3 H), 2.78–2.75 (m, 1 H), 2.66–2.65 (m, 2 H), 2.50 (d, *J* = 13.4 Hz, 1 H), 1.38 (s, 3 H), 0.90 (s, 9 H), 0.04 (s, 6 H); ¹³C NMR (CDCl₃) 173.5, 133.1, 130.6, 123.1, 120.9, 61.7, 59.5, 43.7, 35.3, 29.7, 28.6, 26.1, 25.6; IR (CHCl₃) 3000, 1610, 1200, 750, 655 cm⁻¹; CIMS, *m/z* (rel intensity) 322 (M⁺ + 1, 100), 176 (5).

Reduction of 19 with Diimide. Preparation of 20a. To a well-stirred solution of **19** (240 mg, 0.68 mmol) and *p*-TOSNHNH₂ (1.27 g, 10.0 equiv) in DME (20 mL) was added NaOAc (1.12 g, 20 equiv) in water (15 mL) over 2 h; the resulting solution was refluxed overnight. The reaction mixture was cooled to room temperature, poured into water (50 mL), and extracted with CH₂Cl₂ (3 \times 50 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash chromatography (EtOAc) gave a colorless oil (230 mg, 80%): [α]_D²² +65 (c 1.0, CHCl₃); ¹H NMR (CDCl₃) 5.42 (bs, 1 H), 3.59 (dd, *J* = 9.2, 4.4 Hz, 1 H), 3.38 (t, *J* = 9 Hz, 1 H), 3.34–3.31 (m, 1 H), 2.97 (s, 3 H), 2.62–2.59 (m, 1 H), 2.39 (d, *J* = 13.2 Hz, 1 H), 2.06–1.97 (m, 3 H), 1.72–1.67 (m, 2 H), 1.45 (ddd, *J* = 25.4, 12.70, 4.90 Hz, 1 H), 1.33 (s, 3 H), 0.90 (s, 9 H), 0.05 (s, 6 H); ¹³C NMR (CDCl₃) 175.6, 134.4, 123.6, 62.2, 59.7, 41.9, 35.3, 32.7, 30.4, 25.7, 25.3, 24.5, 17.9; IR (film) 1633.2, 1251.9, 1102.2, 837.4; HRMS calcd for C₁₈H₃₄NO₂Si (M + H⁺) 324.2359, found 324.2355.

Lactam Alcohol 20b. A solution of **20a** (100 mg, 0.31 mmol) in THF (2 mL) and TBAF (0.46 mL, 1.5 equiv) was stirred 3 h and then diluted with water (5 mL) and extracted with EtOAc (3 \times 5 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash chromatography (3% MeOH in CH₂Cl₂) gave **20b** (52 mg, 81%). An analytical sample was obtained by crystallization from EtOAc and hexane, mp 104–106 °C: [α]_D²⁴ -72 (c 0.40, CHCl₃); ¹H NMR (CDCl₃) 5.50 (bs, 1 H), 3.68 (dd, *J* = 10.7, 3.9 Hz, 1 H), 3.52 (t, *J* = 8.5 Hz, 1 H), 3.39–3.36 (m, 1 H), 2.98 (s, 3 H), 2.71–2.68 (m, 1 H), 2.41 (d, *J* = 13.5 Hz, 1 H), 2.21 (bs, 1 H), 2.07–1.95 (m, 3 H), 1.71–1.66 (m, 2 H), 1.46 (td, *J* = 13, 4.7 Hz, 1 H), 1.34 (s, 3 H); ¹³C (CDCl₃) 176.1, 134.9, 123.6, 62.1, 60.0, 42.1, 35.1, 32.6, 31.0, 25.3, 24.5, 17.9; IR (Nujol) 3297, 1602, 1048; CIMS, *m/z* (rel intensity) 210 (M⁺ + 1, 100), 178 (10). Anal. Calcd for C₁₂H₁₉NO₂: C, 68.86; H, 9.15; N, 6.69. Found: C, 68.58; H, 9.24; N, 6.56.

Iodopyran 21a. A solution of **20b** (10 mg, 0.048 mmol) and I₂ (30.35 mg, 2.5 equiv) in THF and H₂O was stirred at room temperature for 96 h. Saturated sodium thiosulfate was added, and the mixture was extracted with CH₂Cl₂ (3 \times 5 mL). The combined organic layers were dried over Na₂SO₄ and concentrated. Flash chromatography using EtOAc and hexane (80:20) as eluent gave **21a** (15 mg, 94%). An analytical sample was obtained by crystallization from EtOAc and hexane, mp 132–134 °C: [α]_D²⁴ +30 (c 0.5, CHCl₃); ¹H NMR (CDCl₃) 4.16 (t, *J* = 2.7 Hz, 1 H), 3.88 (dt, *J* = 11.2, 2.5 Hz, 1 H), 3.55 (d, *J* = 11.5 Hz, 1 H), 3.30–3.26 (m, 1 H), 3.18, 3.17 (m, 1 H), 2.89 (s, 3 H), 2.65 (dd, *J* = 13.2, 2.4 Hz, 1 H), 2.46–2.36 (m, 2 H), 1.86–1.83 (m, 1 H), 1.78–1.69 (m, 1 H), 1.49 (s, 3 H), 1.43–1.35 (m, 2 H); ¹³C NMR (CDCl₃) 171.5, 82.2, 66.8, 59.1, 58.2,

48.1, 42.1, 33.9, 33.0, 32.7, 28.9, 17.6; IR (Nujol) 1651, 1244, 1075; CIMS, *m/z* (rel intensity) 336 (M⁺ + 1, 100), 208 (45). Anal. Calcd for C₁₂H₁₈INO₂: C, 43.00; H, 5.41; N, 4.18. Found: C, 43.53; H, 5.26; N, 4.01.

Iodofuran 22. To a solution of **20b** (18 mg, 0.086 mmol) in CH₂Cl₂ (0.5 mL) with suspended NaHCO₃ at 0 °C was added *N*-iodosuccinimide (21.4 mg, 1.1 equiv). The resulting solution was stirred at 0 °C for 3 h, diluted with CH₂Cl₂ (5 mL), washed with saturated Na₂S₂O₃ (2 \times 2 mL) and 10% NaOH (1 \times 2 mL), dried over Na₂SO₄, and concentrated under reduced pressure. An ¹H NMR spectrum of the resulting oil showed a 9:1 mixture of **22** and **21a**. Flash chromatography using EtOAc and hexane (80:20) as eluent gave **22** as a white solid (22.5 mg, 78%). An analytical sample was obtained by crystallization from EtOAc and hexane, mp 166–168 °C: [α]_D²⁶ +70 (c 0.5, CHCl₃); ¹H NMR (CDCl₃) 4.39 (bs, 1 H), 3.92 (d, *J* = 8 Hz, 1 H), 3.79 (d, *J* = 8 Hz, 1 H), 3.75 (s, 1 H), 2.91 (s, 3 H), 2.75 (d, *J* = 12 Hz, 1 H), 2.20–2.30 (m, 1 H), 2.04 (d, *J* = 14.1 Hz, 1 H), 1.90–1.87 (m, 3 H), 1.76–1.74 (m, 1 H), 1.70 (s, 3 H), 1.63–1.60 (m, 1 H); ¹³C NMR (CDCl₃) 176.3, 83.2, 73.6, 61.4, 49.6, 39.3, 34.2, 34.0, 30.9, 28.6, 26.8, 17.2; IR (Nujol) 1633, 1322, 1147; CIMS, *m/z* (rel intensity) 336 (M⁺ + 1, 100), 208 (30). Anal. Calcd for C₁₂H₁₈INO₂: C, 43.00; H, 5.41; N, 4.18. Found: C, 43.29; H, 5.45; N, 4.20.

Pyran 21b. A solution of **21a** (13.1 mg, 0.0389 mmol), *n*-Bu₃SnH (0.013 mL, 1.2 equiv), and AIBN (1 mg) in benzene (1.5 mL) was deoxygenated for 15 min prior to reflux. After 60 min, the solution was cooled, concentrated under reduced pressure, and diluted with ether (5 mL). The resulting solution was treated with DBU (1 equiv), filtered through silica gel, and concentrated. Flash chromatography (EtOAc) gave a white solid (5.8 mg, 71%), mp 119–121 °C: [α]_D²⁵ -170 (c 0.24, CHCl₃); ¹H NMR (CD₃CN) 3.82 (dt, *J* = 11.3, 2.4 Hz, 1 H), 3.71 (bs, 1 H), 3.47 (d, *J* = 11.3 Hz, 1 H), 3.36–3.35 (m, 1 H), 2.86 (s, 3 H), 2.48 (dq, *J* = 13.2, 6.6, 2.7 Hz, 1 H), 2.42–2.38 (m, 1 H), 1.83–1.79 (m, 2 H), 1.60–1.52 (m, 2 H), 1.48–1.42 (m, 1 H), 1.36–1.31 (m, 1 H), 1.21 (s, 3 H), 1.06–1.00 (m, 1 H); ¹³C NMR (CD₃CN) 177.2, 74.9, 66.8, 55.2, 41.1, 40.3, 35.9, 33.3, 31.8, 29.0, 27.1, 18.1; IR (CHCl₃) 1624, 1210, 764; HRMS calcd for C₁₂H₁₉NO₂ (M⁺) 209.1415, found 209.1416.

Regeneration of 20b from 21a. MeLi (0.12 mL of a 1.4M solution, 3.5 equiv) was added to a solution of **20b** (10 mg, 0.048 mmol) in THF (0.4 mL) at 0 °C. The resulting solution was stirred for 3 h at 0 °C and then warmed to room temperature and stirred an additional 2 h. The reaction mixture was quenched with water and extracted with EtOAc (3 \times 5 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure to give **20b** (quantitative, ¹H NMR analysis).

Cyclization of 7c to the Methanobenzo[6,7]cycloocta-[1,2-c]pyridine Ring System. Preparation of 25a. To a solution of **7c** (3.42 g, 12.7 mmol) in CH₂Cl₂ (80 mL) at 0 °C was added triflic acid (0.55 mL). The reaction mixture was stirred at 0 °C for 15 min and then allowed to warm to room temperature and stirred for 14 h. The yellow solution was diluted with additional CH₂Cl₂ (125 mL) and then was carefully washed with a saturated NaHCO₃ solution (120 mL). The CH₂Cl₂ layer separated, and the aqueous layer was extracted with CH₂Cl₂ (3 \times 80 mL). The combined CH₂Cl₂ layers were dried over MgSO₄ and concentrated. Flash chromatography (EtOAc) on silica gel gave **25a** as a colorless solid (2.98 g, 86%), mp 113–115 °C: IR (CHCl₃) 1610 cm⁻¹; ¹H NMR δ (500 MHz, CDCl₃) 7.14–7.09 (m, 3 H), 7.02 (d, *J* = 6.6 Hz, 1 H), 5.38 (m, 1 H), 3.49 (m, 1 H), 3.40 (d, *J* = 16.5 Hz, 1 H), 3.25–3.23 (m, 1 H), 2.97 (s, 3 H), 2.84 (dd, *J* = 16.5 Hz, 2.2 Hz, 1 H), 2.79–2.75 (m, 1 H), 2.60–2.55 (m, 1 H), 2.43 (ddd, *J* = 12.5 Hz, 4.0 Hz, 1.5 Hz, 1 H), 2.03 (m, 1 H), 2.00 (dd, *J* = 13.4 Hz, 1 H), 1.74 (dt, *J* = 12.5, 2.2 Hz, 1 H), 1.17 (d, *J* = 6.6 Hz, 3 H); ¹³C NMR δ (125.7 MHz, CDCl₃) 173.9, 140.2, 134.5, 132.9, 128.6, 128.5, 126.0, 125.8, 122.4, 53.9, 42.3, 38.9, 35.7, 35.5, 34.2, 33.0, 32.2, 18.6; [α]_D²³ -150 (c 1.0, CHCl₃); CIMS, *m/z* (rel intensity) 268 (M⁺ + 1, 100). Anal. Calcd for C₁₈H₂₁NO: C, 80.86; H, 7.92. Found: C, 80.46; H, 8.10.

(25b). 7d (0.739 g, 1.98 mmol) provided a colorless viscous oil (0.454 g, 81%): IR (CHCl₃) 3400, 1610 cm⁻¹; ¹H NMR δ

(500 MHz, CDCl₃) 6.86 (d, $J = 8.0$ Hz, 1 H), 6.62 (m, 2 H), 5.39 (m, 1 H), 3.51 (m, 1 H), 3.30 (d, $J = 16.5$ Hz, 1 H), 3.20–3.18 (bm, 1 H), 2.97 (s, 3 H), 2.77 (dd, $J = 16.5, 2.2$ Hz, 1 H), 2.79–2.75 (m, 1 H), 2.57–2.53 (m, 1 H), 2.40 (ddd, $J = 12.5, 4.0, 1.5$ Hz, 1 H), 2.05 (m, 1 H), 2.00 (dd, $J = 13.4, 0.5$ Hz, 1 H), 1.70 (dt, $J = 12.5, 2.2$ Hz, 1 H), 1.16 (d, $J = 6.6$ Hz, 3 H); ¹³C NMR δ (125.7 MHz, CDCl₃) 173.8, 157.4, 140.6, 131.6, 128.2, 127.3, 123.2, 111.1, 112.1, 54.9, 42.2, 37.9, 35.4, 35.2, 34.2, 33.4, 32.2, 18.5; [α]²⁵_D +240 (c 1.0, CHCl₃); CIMS, m/z (rel intensity) 284 ($M^+ + 1, 100$). Anal. Calcd for C₁₈H₂₁NO₂: C, 76.30; H, 7.47. Found: C, 76.35; H, 7.55.

25c. 7e (2.21 g, 7.07 mmol) provided a colorless viscous oil (2.01 g, 91%): IR (CHCl₃) 3400, 1610 cm⁻¹; ¹H NMR δ (500 MHz, CDCl₃) 6.91 (d, $J = 8.0$ Hz, 1 H), 6.68 (m, 2 H), 5.39 (m, 1 H), 3.86 (s, 3 H), 3.47 (m, 1 H), 3.30 (d, $J = 16.5$ Hz, 1 H), 3.20–3.18 (bm, 1 H), 2.95 (s, 3 H), 2.75 (dd, $J = 16.5, 2.2$ Hz, 1 H), 2.79–2.75 (m, 1 H), 2.57–2.53 (m, 1 H), 2.40 (ddd, $J = 12.5, 4.0, 1.5$ Hz, 1 H), 2.08 (m, 1 H), 1.98 (dd, $J = 13.4, 0.5$ Hz, 1 H), 1.69 (dt, $J = 12.5, 2.2$ Hz, 1 H), 1.15 (d, $J = 6.6$ Hz, 3 H); ¹³C NMR δ (125.7 MHz, CDCl₃) 173.8, 157.4, 141.1, 132.6, 129.2, 126.3, 122.2, 113.1, 112.1, 54.9, 53.7, 42.2, 37.9, 35.4, 35.2, 34.0, 33.2, 32.0, 18.4; [α]²⁵_D +210 (c 1.6, CHCl₃); CIMS, m/z (rel intensity) 298 ($M^+ + 1, 100$). Anal. Calcd for C₁₉H₂₃NO₂: C, 76.74; H, 7.80. Found: C, 76.71; H, 7.87.

(-)-(3*S*,7*S*,12*aS*)-2,3,4,6,7,12-Hexahydro-2,3-dimethyl-1*H*-7,12a-methanobenzo[6,7]cycloocta[1,2-*c*]pyridin-9-ol (**26**). A solution of **25b** (0.080 g, 0.29 mmol) in THF (5 mL) was added to a stirred suspension of LiAlH₄ (0.022 g, 0.58 mmol) in THF (5 mL). The mixture was heated to reflux for 2 h. Water (2 mL) was added, followed by a 10% KOH solution (2 mL) and some additional water (2 mL). The organic phase was separated, a precipitate was removed by filtration, THF (4 mL) was added, and the mixture was refluxed for 1 h. The mixture was washed with a saturated NaCl solution (2 mL), dried over MgSO₄, and concentrated. Chromatography (CH₂Cl₂/MeOH, 10:1) on neutral alumina gave **26** as a colorless foam (0.056 g, 71%): IR (CHCl₃) 3400, 2910, 1620, 1460; ¹H NMR δ (500 MHz, CDCl₃) 6.84 (d, $J = 8.0$ Hz, 1 H), 6.61–6.57 (m, 2 H), 5.26 (d, $J = 6.0$ Hz, 1 H), 3.29 (dd, $J = 8.0, 1.5$ Hz, 1 H), 3.09 (m, 2 H), 2.70 (m, 1 H), 2.54 (d, $J = 16.0$ Hz, 2 H), 2.45 (d, $J = 11.5$ Hz, 1 H), 2.41 (d, $J = 11.5$ Hz, 1 H), 2.34 (s, 3 H), 1.98 (dq, $J = 11.5, 2$ Hz, 1 H), 1.80 (dd, $J = 16.5, 2.5$ Hz, 1 H), 1.69 (dd, $J = 10.5, 2.5$ Hz, 1 H), 1.56 (dt, $J = 10.5, 2.0$ Hz, 1 H), 0.87 (d, $J = 7.0$ Hz, 3 H); ¹³C NMR δ (125.7 MHz, CDCl₃) 153.9, 142.6, 135.3, 129.9, 127.6, 121.1, 115.0, 113.7, 60.8, 55.0, 43.0, 39.8, 38.1, 36.0, 35.2, 35.0, 33.7, 7.9; [α]²⁴_D -210 (c 0.70, CHCl₃); CIMS, m/z (rel intensity) 270 ($M^+ + 1, 100$). Anal. Calcd for C₁₈H₂₃NO: C, 80.26; H, 8.61. Found: C, 80.31; H, 8.41.

(-)-(3*S*,7*S*,12*aS*)-2,3,4,6,7,12-Hexahydro-9-methoxy-2,3-dimethyl-1*H*-7,12a-methanobenzo[6,7]cycloocta[1,2-*c*]pyridine-1,6-dione (**27**). To a solution of **25c** (2.01 g, 6.76 mmol) in benzene at 10 °C (20 mL) was added Celite (0.20 g), pyridinium dichromate (0.23 g), and *tert*-butyl hydroperoxide (1.8 mL, 16 mmol). The mixture was stirred at 10 °C for 2 h and then allowed to warm to room temperature and stirred for 16 h. Filtration, concentration, and flash chromatography (EtOAc) on silica gel gave **27** as a colorless oil (1.08 g, 51%): IR (CHCl₃) 1663, 1652, 1640 cm⁻¹; ¹H NMR δ (500 MHz, CDCl₃) 6.95 (d, $J = 8.0$ Hz, 1 H), 6.80–6.75 (m, 2 H), 5.70 (s, 1 H), 3.76 (s, 3 H), 3.69–3.66 (m, 2 H), 3.57 (d, $J = 16.5$ Hz, 1 H), 3.03 (s, 3 H), 3.01–2.98 (m, 1 H), 2.81 (dd, $J = 16.6, 2.8$ Hz, 1 H), 2.66 (dd, $J = 13.5, 3.2$ Hz, 1 H), 2.31 (dd, $J = 13.5, 1.5$ Hz, 1 H), 2.22 (m, 1 H), 1.19 (d, $J = 6.6$ Hz, 3 H); ¹³C NMR δ (125.7 MHz, CDCl₃) 198.1, 171.3, 157.8, 157.5, 132.4, 130.1, 125.1, 125.0, 114.7, 112.7, 55.1, 52.4, 48.7, 44.1, 36.2, 35.9, 34.2, 33.4, 18.9; [α]²⁴_D +90 (c 1.0, CHCl₃); CIMS, m/z (rel intensity) 312 ($M^+ + 1, 100$). Anal. Calcd for C₁₉H₂₁NO₃: C, 73.29; H, 6.80. Found: C, 73.08; H, 6.58.

(+)-(3*S*,6*S*,7*S*,12*aS*)-2,3,4,6,7,12-Hexahydro-2,3-dimethyl-1*H*-7,12a-methanobenzo[6,7]cycloocta[1,2-*c*]pyridine-6,9-diol (**28**). A mixture of **27** (0.087 g, 0.27 mmol) and CeCl₃·4H₂O (0.075 g, 0.20 mmol) in MeOH (3 mL) was stirred at room temperature for 30 min. The resulting suspension was added NBH₄ (0.015 g). After 1.5 h, the reaction was quenched

by adding NH₄Cl (5 mL) and a few drops of HCl (10%). The resulting mixture was extracted with EtOAc (4 × 15 mL). The organic layers were combined, washed with brine (10 mL), dried over MgSO₄, and filtered. Evaporation in vacuo gave the alcohol (0.065 g, 74%) as a colorless foam: IR (CHCl₃) 3400, 1663, 1640 cm⁻¹; ¹H NMR δ (500 MHz, CDCl₃) 7.01 (d, $J = 8.0$ Hz, 1 H), 6.80–6.75 (m, 2 H), 5.34 (s, 1 H), 4.52 (d, $J = 6.0$ Hz, 1 H), 3.79 (s, 3 H), 3.53 (m, 1 H), 3.32 (d, $J = 16.5$ Hz, 1 H), 3.25 (m, 1 H), 2.97 (s, 3 H), 2.78 (d, $J = 16.5$ Hz, 2 H), 2.50 (dd, $J = 13.5, 3$ Hz, 1 H), 2.01 (dd, $J = 14.6, 1.5$ Hz, 1 H), 1.85 (dd, $J = 13.5$ Hz, 1 H), 1.17 (d, $J = 6.6$ Hz, 3 H); ¹³C NMR δ (125.7 MHz, CDCl₃) 173.1, 157.1, 134.7, 133.9, 129.8, 127.6, 127.3, 115.4, 113.2, 70.4, 55.1, 53.4, 42.7, 39.4, 38.0, 35.0, 34.2, 32.5, 18.7; CIMS, m/z (rel intensity) 314 ($M^+ + 1, 100$). Anal. Calcd for C₁₉H₂₃NO₃: C, 72.82; H, 7.40. Found: C, 72.72; H, 7.35.

The alcohol (0.065 g, 0.21 mmol) was dissolved in CH₂Cl₂ (5 mL) under N₂ and cooled to -78 °C. BBr₃ in CH₂Cl₂ solution (1 M, 1 mL) was added, and the reaction mixture was allowed to warm to room temperature. After stirring overnight at room temperature, the reaction was cooled to 0 °C and quenched with water. The resulting mixture was extracted with EtOAc (4 × 15 mL). The organic layers were combined, washed with brine (10 mL), dried over MgSO₄, and filtered. Flash chromatography (CH₂Cl₂/MeOH, 10:1) on silica gel afforded the phenol as a foam (0.041 g, 68%): IR (CHCl₃) 3500, 1661, 1637 cm⁻¹; ¹H NMR δ (500 MHz, (CD₃)₂CO) 8.02 (bs, exchangeable with D₂O), 6.83 (d, $J = 8.0$ Hz, 1 H), 6.70 (d, $J = 1.5$ Hz, 1 H), 6.53 (dd, $J = 8.0$ Hz, 1.5 Hz, 1 H), 5.30 (s, 1 H), 4.52 (bd, $J = 6.0$ Hz, 1 H), 3.58 (m, 1 H), 3.35 (d, $J = 9.5$ Hz, 1 H), 3.10 (d, $J = 16.5$ Hz, 1 H), 2.97 (s, 3 H), 2.87 (m, 1 H), 2.78 (d, $J = 16.5$ Hz, 2 H), 2.69 (m, 1 H), 2.32 (dd, $J = 13.5, 3$ Hz, 1 H), 1.78 (dt, $J = 13.5, 3.5$ Hz, 1 H), 1.14 (d, $J = 6.6$ Hz, 3 H); ¹³C NMR δ (125.7 MHz, (CD₃)₂CO) 173.1, 155.8, 136.4, 135.6, 130.4, 129.0, 127.0, 119.7, 115.5, 71.9, 55.6, 44.6, 41.4, 39.5, 36.0, 35.1, 34.1, 19.4; CIMS, m/z (rel intensity) 300 ($M^+ + 1, 100$). Anal. Calcd for C₁₈H₂₁NO₃: C, 72.72; H, 7.07. Found: C, 72.89; H, 6.81.

A solution of the phenol (0.080 g, 0.27 mmol) in THF (5 mL) was added to a stirred suspension of LiAlH₄ (0.022 g, 0.59 mmol) in THF (5 mL). The mixture refluxed for 2 h. Water (2 mL) was added, followed by a 10% KOH solution (2 mL) and some additional water (2 mL). The organic phase was separated, and a precipitate was removed by filtration. THF (4 mL) was added, and the mixture was refluxed for 1 h, then washed with saturated NaCl (2 mL), dried over MgSO₄, and concentrated. Chromatography (CH₂Cl₂/MeOH, 10:1) on neutral alumina gave **28** as a colorless foam (0.054 g, 71%): IR (CHCl₃) 3400, 2900, 1610, 1450 cm⁻¹; ¹H NMR δ (500 MHz, (CD₃)₂CO/CD₃OD (3:1)) 6.89 (d, $J = 8.5$ Hz, 1 H), 6.77 (d, $J = 1.5$ Hz, 1 H), 6.70 (d, $J = 8.5$ Hz, 1 H), 5.30 (s, 1 H), 4.50 (d, $J = 5.5$ Hz, 1 H), 3.77 (bs, 1 H), 3.52 (m, 1 H), 3.28 (d, $J = 17.5$ Hz, 2 H), 3.16 (s, 1 H), 2.98 (s, 3 H), 2.73 (m, 2 H), 2.48 (dd, $J = 8.0, 4.5$ Hz, 1 H), 1.97 (d, $J = 13.5$ Hz, 1 H), 1.97 (d, $J = 13.0$ Hz, 1 H), 1.17 (d, $J = 7.0$ Hz, 3 H); ¹³C NMR δ (125.7 MHz, (CD₃)₂CO/CD₃OD (3:1)) 153.9, 142.6, 135.3, 129.9, 127.6, 121.1, 115.0, 113.7, 60.8, 55.0, 43.0, 39.8, 38.1, 36.0, 35.2, 35.0, 33.7, 7.9; [α]²⁴_D +21 (c 0.98, CHCl₃); CIMS, m/z (rel intensity) 286 ($M^+ + 1, 100$). Anal. Calcd for C₁₈H₂₃NO₂: C, 75.76; H, 8.12. Found: C, 75.52; H, 8.38.

(+)-(3*R*,7*R*,12*aR*)-2,3,4,6,7,12-Hexahydro-9-methoxy-2,3-dimethyl-1*H*-7,12a-methanobenzo[6,7]cycloocta[1,2-*c*]pyridine-1,6-dione (**29**). **29** was prepared as described for the preparation of **27** (colorless oil, 55%): IR (CHCl₃) 1663, 1652 (C=O), 1640 (C=C) cm⁻¹; ¹H NMR δ (500 MHz, CDCl₃) 6.95 (d, $J = 8.0$ Hz, 1 H), 6.80–6.75 (m, 2 H), 5.70 (s, 1 H), 3.76 (s, 3 H), 3.69–3.66 (m, 2 H), 3.57 (d, $J = 16.5$ Hz, 1 H), 3.03 (s, 3 H), 3.01–2.98 (m, 1 H), 2.81 (dd, $J = 16.6, 2.8$ Hz, 1 H), 2.66 (dd, $J = 13.5, 3.2$ Hz, 1 H), 2.31 (dd, $J = 13.5, 1.5$ Hz, 1 H), 2.22 (m, 1 H), 1.19 (d, $J = 6.6$ Hz, 3 H); ¹³C NMR δ (125.7 MHz, CDCl₃) 198.1, 171.3, 157.8, 157.5, 132.4, 130.1, 125.1, 125.0, 114.7, 112.7, 55.1, 52.4, 48.7, 44.1, 36.2, 35.9, 34.2, 33.4, 18.9; [α]²⁴_D -93.0 ($c = 1.27$, CHCl₃); CIMS, m/z (rel intensity) 312 ($M^+ + 1, 100$). Anal. Calcd for C₁₉H₂₁NO₃: C, 73.29; H, 6.80. Found: C, 72.61; H, 6.77.

(+)-(3*R*,4*aR*,7*R*,12*aR*)-2,3,4,4*a*,5,6,7,12-Octahydro-9-methoxy-2,3-dimethyl-1*H*-7,12a-methanobenzo[6,7]cycloocta[1,2-*c*]pyridine-1,6-dione (**30**). To a solution of **29** (0.500 g, 1.60 mmol) in EtOAc (20 mL) was added 5% Pd/C (0.220 g), and the suspension was shaken under an atmosphere of H₂ (79 PSI) for 72 h. The mixture was filtered through Celite and concentrated. Flash chromatography (EtOAc) on silica gel provided **30** as a colorless solid (0.498 g, 98%); IR (CHCl₃) 1703, 1612 cm⁻¹; ¹H NMR δ (500 MHz, CDCl₃) 7.10 (d, *J* = 8.0 Hz, 1 H), 6.72 (dd, *J* = 8.0, 2.5 Hz, 1 H), 6.58 (d, *J* = 2.5 Hz, 1 H), 4.25 (d, *J* = 13.0 Hz, 1 H), 3.72 (s, 3 H), 3.50 (m, 2 H), 2.93 (s, 3 H), 2.80 (dd, *J* = 15.0, 7 Hz, 1 H), 2.71 (d, *J* = 17.5 Hz, 1 H), 2.48 (br m, 1 H), 2.38 (d, *J* = 13.0 Hz, 1 H), 2.34 (d, *J* = 13.0 Hz, 1 H), 1.87 (d, *J* = 15.0 Hz, 1 H), 1.80 (d, *J* = 15.0 Hz, 1 H), 1.70 (q, *J* = 10.0, 4.5 Hz, 1 H), 1.27 (d, *J* = 6.6 Hz, 3 H); ¹³C NMR δ (125.7 MHz, CDCl₃) 210.1, 173.6, 157.2, 134.9, 130.0, 128.4, 114.1, 114.3, 112.4, 55.1, 53.3, 52.9, 41.2, 40.7, 38.1, 34.8, 33.3, 31.9, 21.6; [α]²⁵_D +12 (c 0.60, CHCl₃); CIMS, *m/z* (rel intensity) 314 (M⁺ + 1, 100). Anal. Calcd for C₁₉H₂₃NO₃: C, 72.82; H, 7.40. Found: C, 72.85; H, 7.41.

Ketal of 32: Preparation of 31. To the solution of **30** (0.498 g, 1.59 mmol) in benzene (15 mL) was added ethylene glycol (0.217 g, 3.32 mmol). PTSA (15 mg) was added, and the reaction mixture was refluxed overnight. After cooling to room temperature, the mixture was carefully poured into a saturated NaHCO₃ solution. The mixture was stirred for 30 min and then was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (150 mL), dried over MgSO₄, and concentrated. Flash chromatography (ethyl acetate/hexane, 2:1) on silica gel gave the ketal as a colorless foam (0.51 g, 90%); IR (CHCl₃) 2850, 1612 cm⁻¹; ¹H NMR δ (500 MHz, CDCl₃) 6.97 (d, *J* = 8.0 Hz, 1 H), 6.70 (dd, *J* = 8.0, 2.5 Hz, 1 H), 6.61 (d, *J* = 2.5 Hz, 1 H), 4.15–3.98 (m, 5 H), 3.73 (m, 1 H), 3.72 (s, 3 H), 3.50 (m, 1 H), 2.92 (s, 3 H), 2.54 (d, *J* = 17.5 Hz, 1 H), 2.48 (bm, 2 H), 2.12–1.96 (m, 2 H), 1.80 (dd, *J* = 15.0 Hz, 6 Hz, 1 H), 1.80 (dt, *J* = 15.0, 6 Hz, 1 H), 1.28 (q, *J* = 10.0, 4.5 Hz, 1 H), 1.26 (d, *J* = 6.6 Hz, 3 H); ¹³C NMR δ (125.7 MHz, CDCl₃) 175.3, 156.3, 136.8, 129.2, 128.6, 115.2, 112.4, 109.2, 64.6, 63.7, 54.9, 53.9, 43.4, 41.4, 39.4, 39.1, 35.0, 33.6, 31.7, 29.6, 21.6; [α]²⁵_D +52 (c 0.61, CHCl₃); CIMS, *m/z* (rel intensity) 358 (M⁺ + 1, 100). Anal. Calcd for C₂₁H₂₇NO₄: C, 70.56; H, 7.61. Found: C, 70.55; H, 7.63.

A solution of the ketal (0.51 g, 1.43 mmol) in THF (10 mL) was added to a stirred suspension of LiAlH₄ (0.076 g, 2.01 mmol) in THF (5 mL) at 0 °C, and the mixture was refluxed for 2 h. After cooling to room temperature, water (2 mL) was added, followed by a 10% KOH solution (2 mL) and some additional water (2 mL). The organic phase was separated, and a precipitate was removed by filtration. THF (4 mL) was added, and the mixture was refluxed for 1 h, washed with a saturated NaCl solution (2 mL), dried over MgSO₄, and concentrated. Chromatography (CH₂Cl₂/MeOH, 10:1) on neutral alumina afforded **31** as a colorless foam (0.407 g, 83%); IR (CHCl₃) 3500, 2930, 1590, 1410 cm⁻¹; ¹H NMR δ (500 MHz, CDCl₃) 6.95 (d, *J* = 8.0 Hz, 1 H), 6.72 (dd, *J* = 8.0, 2.5 Hz, 1 H), 6.62 (d, *J* = 2.5 Hz, 1 H), 4.08–3.97 (m, 3 H), 3.90 (m, 1 H), 3.76 (s, 3 H), 2.84 (d, *J* = 2.5 Hz, 1 H), 2.72 (dd, *J* = 13.0 Hz, 1 H), 2.58 (d, *J* = 17.5 Hz, 1 H), 2.50 (d, *J* = 17.5 Hz, 1 H), 2.48 (d, *J* = 13.0 Hz, 1 H), 2.20 (s, 3 H), 2.16 (m, 1 H), 1.97 (d, *J* = 10.5 Hz, 1 H), 1.75 (dt, *J* = 10.5, 6 Hz, 2 H), 1.60 (m, 1 H), 1.40 (ddd, *J* = 10.5, 6, 2.0 Hz, 1 H), 1.24 (m, 2 H), 1.26 (d, *J* = 6.6 Hz, 3 H); ¹³C NMR δ (125.7 MHz, CDCl₃) 156.4, 138.7, 129.1, 128.4, 115.2, 112.2, 109.6, 69.7, 64.4, 63.4, 59.6, 54.9, 43.6, 43.1, 42.7, 41.4, 37.4, 33.5, 32.7, 29.6, 20.2; [α]²⁴_D +20 (c 0.99, CHCl₃); CIMS, *m/z* (rel intensity) 344 (M⁺ + 1, 100). Anal. Calcd for C₂₁H₂₉NO₃: C, 73.44; H, 8.51. Found: C, 73.79; H, 8.25.

(+)-(3*R*,4*aR*,7*R*,12*aR*)-2,3,4,4*a*,5,6,7,12-Octahydro-9-hydroxy-2,3-dimethyl-1*H*-7,12a-methanobenzo[6,7]cycloocta[1,2-*c*]pyridin-6-one (**32**). **31** (0.407 g, 1.18 mmol) was dissolved in CH₂Cl₂ (5 mL) under N₂ and cooled to -78 °C. BBr₃ in CH₂Cl₂ (6 mL, 1 M) was added, and the reaction mixture was allowed to warm to room temperature. After stirring overnight, the reaction was cooled to 0 °C and quenched with water. The resulting mixture was extracted with EtOAc (4 × 15 mL). The organic layers were combined, washed with brine (10 mL), dried over MgSO₄, and filtered. Flash chromatography (CH₂Cl₂/MeOH, 10:1) on silica gel afforded **32** as a white foam (0.209 g, 60%); IR (CHCl₃) 3400, 3500, 1703 cm⁻¹; ¹H NMR δ (500 MHz, CD₃OD) 6.95 (d, *J* = 8.0 Hz, 1 H), 6.75 (d, *J* = 2.5 Hz, 1 H), 6.65 (dd, *J* = 8.0 Hz, 2.5 Hz, 1 H), 5.48 (bs, 1 H, exchangeable with D₂O), 3.53 (bs, 1 H), 3.27 (d, *J* = 18.5 Hz, 1 H), 3.10 (m, 1 H), 2.53 (d, *J* = 18.5 Hz, 1 H), 2.44 (d, *J* = 12.0 Hz, 1 H), 2.33 (d, *J* = 13.0 Hz, 1 H), 2.28 (s, 3 H), 2.22 (m, 3 H), 2.01–1.93 (m, 2 H), 1.66 (dd, *J* = 13.0, 3.5 Hz, 1 H), 1.30 (d, *J* = 13.0 Hz, 1 H), 1.07 (d, *J* = 6.6 Hz, 3 H); ¹³C NMR δ (125.7 MHz, CD₃OD) 213.1, 156.7, 138.1, 131.6, 128.4, 116.4, 115.6, 68.8, 68.5, 55.0, 49.8, 46.2, 43.5, 41.9, 39.0, 34.9, 33.7, 19.9; [α]²⁴_D +69 (c 0.23, CHCl₃); CIMS, *m/z* (rel intensity) 286 (M⁺ + 1, 100). Anal. Calcd for C₁₈H₂₃NO₂: C, 75.76; H, 8.12. Found: C, 75.50; H, 8.32.

(+)-(3*R*,4*aS*,7*R*,12*aR*)-2,3,4,4*a*,5,6,7,12-Octahydro-9-methoxy-2,3-dimethyl-1*H*-7,12a-methanobenzo[6,7]cycloocta[1,2-*c*]pyridine-1,6-dione (**33**). To a solution of **29** (3.00 g, 9.6 mmol) and *tert*-butyl alcohol (2.80 mL, 28.8 mmol) in THF (150 mL) was added NH₃ (~480 mL) at -78 °C. Lithium was added in small pieces until a blue coloration persisted. The solution was stirred at -78 °C for 120 min, and then the blue coloration was dissipated with piperylene. The mixture was stirred for an additional 30 min at -78 °C, and then solid NH₄Cl was added at -78 °C and the NH₃ was allowed to evaporate overnight. The resulting pale yellow residue was partitioned between CH₂Cl₂ (30 mL) and water (40 mL), and the water layer was extracted with CH₂Cl₂ (2 × 30 mL). The combined organic layers were washed with 10% sodium thiosulfate solution (20 mL), dried over MgSO₄, and concentrated. Flash chromatography (ethyl acetate/hexane, 2:1) on silica gel gave **30** (0.31 g, 10%) and then a second fraction which contained **33** (1.54 g, 51%); IR (CHCl₃) 1709, 1615 cm⁻¹; ¹H NMR δ (500 MHz, CDCl₃) 7.04 (d, *J* = 8.0 Hz, 1 H), 6.75 (dd, *J* = 8.0, 2.5 Hz, 1 H), 6.61 (d, *J* = 2.5 Hz, 1 H), 3.74 (s, 3 H), 3.63 (m, 1 H), 3.60 (p, *J* = 7 Hz, 1 H), 3.20 (d, *J* = 17.5 Hz, 1 H), 3.16 (d, *J* = 17.5 Hz, 1 H), 2.93 (s, 3 H), 2.80 (dd, *J* = 13.0, 3 Hz, 1 H), 2.42 (td, *J* = 13.0, 3 Hz, 1 H), 2.38 (d, *J* = 13.0 Hz, 1 H), 2.31 (ddd, *J* = 13.0, 6, 3 Hz, 1 H), 2.04 (dq, *J* = 15.0, 3 Hz, 2 H), 1.44 (dd, *J* = 12.0, 2 Hz, 1 H), 1.29 (d, *J* = 6.6 Hz, 3 H); ¹³C NMR δ (125.7 MHz, CDCl₃) 209.3, 174.1, 157.5, 135.4, 129.5, 127.6, 114.3, 112.4, 55.1, 53.9, 53.3, 41.0, 40.2, 37.6, 35.6, 34.3, 32.6, 31.8, 20.1; [α]²⁵_D +35 (c 1.6, CHCl₃); CIMS, *m/z* (rel intensity) 314 (M⁺ + 1, 100). Anal. Calcd for C₁₉H₂₃NO₃: C, 72.82; H, 7.40. Found: C, 72.87; H, 7.46.

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