Synthesis of Phthalideisoquinoline and Protoberberine Alkaloids and Indolo[2,1-*a*]isoquinolines in a Divergent Route Involving Palladium(0)-Catalyzed Carbonylation[1]

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6,7,3′,4′-Alkoxy-substituted 1-(2′-bromobenzoyl)-3,4-dihydroisoquinoline methiodides **17** were treated with sodium borohydride in methanol or acetic acid to give *erythro*-1-(2′-bromo-α-hydroxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinolines **19**. Treatment of **17** with lithium aluminum hydride in tetrahydrofuran gave the *threo*-isomer **20** in preference to the *erythro* **19**. On the basis of studies on palladium(0)-catalyzed carbonylation of 2-bromo-3,4-dimethoxybenzyl alcohol to 6,7-dimethoxyphthalide, amino alcohol **19** or **20** was treated with a catalytic amount of palladium(II) acetate and triphenylphosphine in an atmosphere of carbon monoxide in the presence of chlorotrimethylsilane and potassium carbonate in boiling toluene to give the corresponding *erythro*- or *threo*-types of phthalideisoquinoline alkaloids **1** or **2**, respectively. One-pot cyclization of the *erythro*-amino alcohols **19** was achieved by heating in *N*,*N*-dimethylformamide containing potassium carbonate to give 2,3,8,9- or 2,3,9,10-alkoxy-substituted 5,6-dihydroindolo[2,1-*a*]isoquinolines **3**, which have a unique tetracyclic skeleton characteristic of dibenzopyrrocoline alkaloids. Similarly, palladium(0)-catalyzed carbonylation of 1-(2′-bromobenzyl)tetrahydroisoquinolines **21** in the presence of excess potassium carbonate was found to give 8-oxoberbines **22**, which on reduction with lithium aluminum hydride can be converted to protoberberine alkaloids **4**.

Introduction

Palladium-catalyzed carbonylation leading to the formation of benzolactams and benzolactones has recently been studied extensively.[2] These techniques have been applied to the preparation of heterocyclic compounds and some biologically active alkaloids.[3,4] We have also been interested in aromatic metalations, especially followed by carboxylation and carbonylation, to use them as synthetic tools for the construction of heterocyclic compounds. We have reported a method for the preparation of alkoxy-substituted benzolactones via halogen−lithium exchange followed by treatment of the resulting lithium salts with CO_2 gas.[5] In this paper, we report a new method involving palladium(0)-catalyzed carbonylation for the preparation of 5,6-dialkoxy-substituted phthalides from 3,4-dialkoxy-substituted 2-bromobenzyl alcohols and its application to the synthesis of phthalideisoquinoline alkaloids.[6]

Phthalideisoquinoline alkaloids are known to possess a variety of physiological activities, including the interesting roles of noscapine as a nonnarcotic cough cure and (+)-bicuculline **1d** as an effective antagonist of an inhibitory neurotransmitter, γ-aminobutyric acid (GABA).[7] The alkaloids comprise a 6,7- or 6,7,8-alkoxy-substituted 1,2,3,4-tetrahydroisoquinoline and a 6′,7′-alkoxy-substituted phthalide ring; these two units are linked together at their C-1 and C-3′ carbons to form either *erythro*- or *threo*-isomers in Berberidaceae, Fumariaceae, Papaveraceae, and Ranunculaceae plants.[8]

Among many approaches,[7,9,10] some methods for the selective synthesis of the *erythro*-form of these alkaloids, such as (±)-β-hydrastine (**1c**),[10c,11] (+)- and (−)-bicuculline (**1d**), (+)- and (−)-corytensine,[10g,h] or (+)-corlumine,[10d,h] have been reported. In contrast, the methods devised for synthesis of the *threo*-alkaloids have been based only on the inversion of the *erythro*-form.[12] We previously ob-

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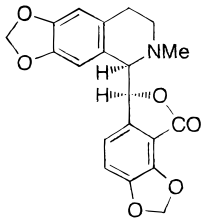
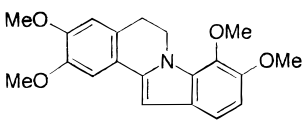
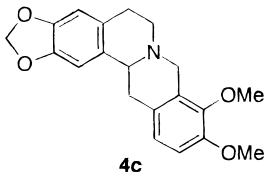


1d



3a



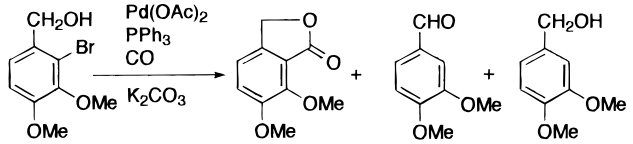
4c

tained an initial idea for the selective formation of each isomer from a common precursor[13] and have also studied some procedures for aromatic carboxylation and carbonylation starting with aromatic metalations.[5,6] In this paper, we deal with the selective hydride reductions of 1-(2′-bromobenzoyl)-3,4-dihydroisoquinoline methiodides **17** and the palladium(0)-catalyzed carbonylation of the resultant *erythro*- or *threo*-amino alcohols **19** or **20** in a new route to the synthesis of phthalideisoquinoline alkaloids. We also describe a similar carbonylation for the preparation of 8-oxoberbines, synthetic precursors of protoberberine alkaloids **4**, and one-pot conversion of *erythro*-amino alcohols **19** to an indolo[2,1-*a*]isoquinoline skeleton **3**, characteristic of dibenzopyrrocoline alkaloids.

Results and Discussion

Palladium(0)-Catalyzed Carbonylation of *o*-Bromobenzyl Alcohols. Carbonylative cyclization of 2-bromobenzyl alcohol **5a** to the corresponding phthalides **6a** was examined using $Pd(OAc)_2$ and Ph_3P for in situ generation of the Pd(0) catalyst,[14] on the basis of the Pd(0)-catalyzed carbonylation of *ortho*-bromobenzyl alcohols reported previously by Mori and Ban.[4a] Treatment with $Pd(OAc)_2-PPh_3$/CO gas in the presence of a powdered alkali, Na_2CO_3, K_2CO_3, K_2HPO_4, or K_3PO_4, using dry boiling toluene as a solvent caused the consumption of bromobenzyl alcohol **5a** (Scheme 1, Table 1). K_3PO_4 gave aldehyde **7a** in a higher yield than that of the desired phthalide **6a**, together with debromobenzyl alcohol **8a** (entry 4). K_2CO_3 may be a better base than K_3PO_4 for the present carbonylation−lactonization, as it gave the desired benzolactone **6a** in a relatively high yield (entries 5 and 8). Use of a large excess of these bases (20 mol equiv) clearly accelerated the consumption rate of **5a**, but gave the undesired benzaldehyde **7a** in a higher yield than that of **6a**, as shown in entries 6−8. Tertiary amines, such as Et_3N, *i*-Pr_2EtN, and Bu_3N, appeared to be less effective (entries 12−14).[15] Lack of selectivity in these reactions has been observed in those of the analogous bromides reported by the aforementioned pioneers.[4a,16]

Scheme 1



5a **6a** **7a** **8a**

Table 1. Pd(0)-Catalyzed Carbonylation of 2-Bromo-3,4-dimethoxybenzyl Alcohol 5a[a]

				products (%)			
entry	additives[b]	solvent	time, h	(**5a**)	**6a**	**7a**	**8a**
1	K_2CO_3	benzene	24	100	0	0	0
2	Na_2CO_3	toluene	24	66	7	14	8
3	K_2HPO_4	toluene	24	66	6	19	9
4	K_3PO_4	toluene	24	46	4	30	20
5	K_2CO_3	toluene	24	56	27	15	25
6	$20Na_2CO_3$	toluene	24	49	13	27	11
7	$20K_3PO_4$	toluene	24	21	0	59	20
8	$20K_2CO_3$	toluene	24	35	21	35	9
9	K_2CO_3-2TMSCl	toluene	26	30	40	21	9
10	$5K_2CO_3-2$TMSCl	toluene	24	18	13	66	4
11	$20K_2CO_3-2$TMSCl	toluene	24	0	23	75	2
12	Et_3N	toluene	24	90	5	0	4
13	i-Pr_2EtN	toluene	24	95	2	0	3
14	Bu_3N	toluene	24	94	6	0	0

[a] Reactions were carried out by heating a mixture of **5a** (25 mg, 0.1 mmol), $Pd(OAc)_2$ (4.4 mg, 0.02 mmol), PPh_3 (10.6 mg, 0.04 mmol), and the appropriate additives in boiling solvent (2 mL) in an atmosphere of CO gas. [b] Arabic numerals in front of the bases and TMSCl show their molar ratios to the substrate **5a**.

It has been reported that TMSCl accelerates the copper-catalyzed conjugate addition of Grignard reagents[17] and more recently some reactions involving other metal reagents, such as Zn,[18] Mg,[19] Mn,[20] $[RhCl(C_2H_4)_2]_2$,[21] $(CH_3)_2GaCl$,[22] NaH,[23] and LiH.[24] Assuming that TMSCl may have a similar effect on the present reaction, it was added into the system. In entry 9, a significant acceleration effect of carbonylation was observed by the addition of TMSCl. The dual addition of TMSCl and excess of K_2-

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(15) DBU, pyridine, 4-(dimethylamino)pyridine, and 2,2,6,6-tetramethylpiperidine were also ineffective.

(16) Other palladium catalysts were also examined. Under the typical reaction conditions for carbonylation of *o*-iodobenzyl alcohols $[PdCl_2(PPh_3)_2$, Et_3N, 1 atm of CO gas at 50−60 °C in DMF] reported by Stille,[4b,c] **5a** was unreactive. Treatments with $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$ using K_2CO_3 as a base in boiling toluene consumed **5a** slowly. The main product was aldehyde **7a**, accompanied with phthalide **6a** in 0−7% at most regardless of the presence or absence of TMSCl. Pd black and $Pd_2(dba)_3$ did not work at all, and **5a** was recovered unchanged.

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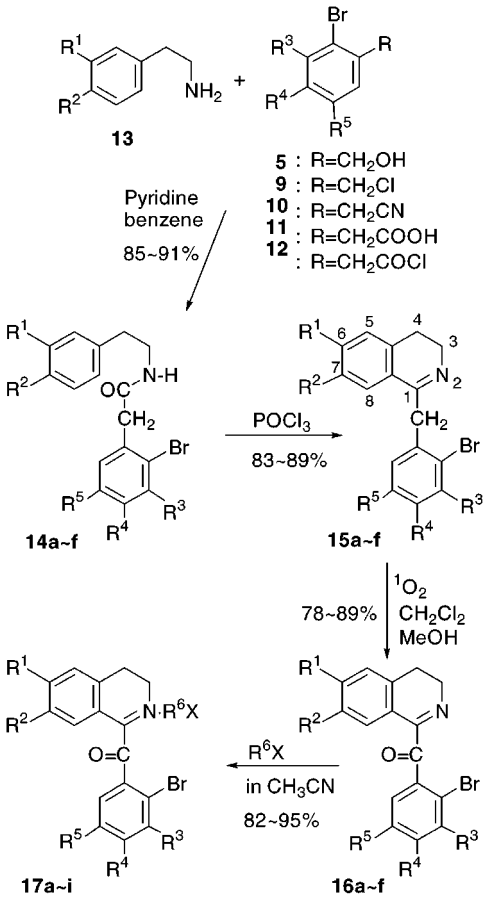
CO_3 induced faster consumption of **5a** (entries 10 and 11), though the formation of benzaldehyde **7a** again became predominant. Although these results are not satisfactory, it is notable that the aryl bromide (**5a**) was completely consumed within 24 h by the use of the palladium(0) catalyst in the presence of TMSCl and a large excess K_2CO_3 in refluxing toluene (entry 11).

Stereoselective Reduction of the Iminium Salts to *Erythro*- and *Threo*-Amino Alcohols. Use of aminobromobenzyl alcohols **19** and **20** carrying a tetrahydroisoquinoline ring as a key intermediate was planned for the synthesis of phthalideisoquinoline alkaloids by the carbonylative cyclization method. The isoquinoline substituent may act as an efficient internal trap of a liberated HBr molecule[25] and generate a steric repulsion to the OH and Br (or Pd) groups, which provides a favorable approach of both groups for the lactonization of **19** (or **20**) to a phthalideisoquinoline ring system. We started to prepare bromobenzyl alcohol **19a** as follows. Acid chloride **12a** was prepared from 2-bromo-3,4-dimethoxybenzaldehyde[26] by conventional methods via the corresponding benzyl alcohol **5a** (98%), benzyl chloride **9a**, benzyl cyanide **10a** (91%), and phenylacetic acid **11a** (92%). *N*-Acylation of 3,4-dimethoxyphenethylamine **13** with this acid chloride **12a** gave acetamide **14a** (91%), which was subjected to Bischler−Napieralski cyclization with $POCl_3$ in boiling toluene. The resultant dihydroisoquinoline (**15a**) (85%) was subsequently exposed to singlet oxygen[27] to produce **16a** in good yield. Methiodide **17a** was readily obtained in 82% yield by heating **16a** with excess CH_3I in CH_3CN (Scheme 2). Similar transformations yielded methiodides **17b**−**17f** in good yields. Additional iminium salts such as benzyl bromides **17g** and **17h** and propyl iodide **17i** were easily prepared from **16a** or **16d**, respectively.

Treatment of **17a** with excess fresh $NaBH_4$ in MeOH gave a mixture of *erythro*- (**19a**) and *threo*- (**20a**) amino alcohols in a ratio of 97:3,[28] in contrast to the results of $NaBH_4$ reduction of the analogous compounds reported.[27b,29] Changing the solvent to AcOH produced a remarkable exclusive *erythro*-selectivity even in the reduction of other methiodides **17** and ketone **16a** (Table 2). Treatment of *N*-benzyl bromide salt **17g** or **17h** with $NaBH_4$ in AcOH gave only *N*-benzyl *erythro*-amino alcohol (**19g** or **19h**) in good yield, though the reduction

Scheme 2



a : R^1=R^2= R^3=R^4=OMe, R^5=H (R^6X=MeI)
b : R^1=R^2=OMe, R^3+R^4=OCH_2O, R^5=H (R^6X=MeI)
c : R^1+R^2=OCH_2O, R^3=R^4=OMe, R^5=H (R^6X=MeI)
d : R^1+R^2= R^3+R^4=OCH_2O, R^5=H (R^6X=MeI)
e : R^1=R^2=R^4=R^5=OMe, R^3=H (R^6X=MeI)
f : R^1+R^2= R^4+R^5=OCH_2O, R^3=H (R^6X=MeI)
g : R^1=R^2= R^3=R^4=OMe, R^5=H (R^6X=BnBr)
h : R^1+R^2= R^3+R^4=OCH_2O, R^5=H (R^6X=BnBr)
h : R^1=R^2= R^3=R^4=OMe, R^5=H (R^6X=PrI)

Table 2. $NaBH_4$ Reduction of 3,4-Dihydroisoquinolines 16 and 17

	ratio of **19**:**20** (isolated yield of **19**)	
substrate	in MeOH[a]	in AcOH[b]
17a	97:3 (83%)	100:0 (89%)
17b	80:20	90:10 (80%)
17c	97:3 (92%)	
17d	95:5	100:0 (80%)
17e	97:3	100:0 (87%)
17f		100:0 (92%)
17g		100:0 (88%)
17h		100:0 (95%)
17i	95:5 (85%)	
16a	90:10 (80%)	

[a] 5 mol equiv of $NaBH_4$. [b] 10 mol equiv of $NaBH_4$.

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(28) When partially decomposed $NaBH_4$, such as that in an old bottle, was used for these reductions, the *erythro*-selectivity became lower.

(29) (a) Moniot, J. L.; Shamma, M. *J. Org Chem.* **1979**, *44*, 4337−4342. (b) McMahon, R. M.; Thornber, C. W. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2163−2167.

in MeOH failed. We were rather surprised that not only **17a**−**17f** and **16a** but also similar compounds with more bulky *N*-substituents such as **17g**, **17h**, and **17i** showed high *erythro*-selectivity on $NaBH_4$ reduction (Table 2), since it has been reported that the relative yields of the *threo*-alcohols were augmented consistently with the increasing size of the *N*-substituent of norhydrastine methyl ester.[29a]

Treatment of **17a** with 1 mol equiv of $NaBH_4$ gave ketone **18a** together with **19a** in a 70:30 ratio. This ketone **18a** (92%) was decomposed during separation from **19a** on preparative TLC. The quantitative reduction of **17a** to **18a** was best accomplished by catalytic hydrogenation in MeOH in the presence of the Adams catalyst, without further reduction to **19a** or **20a**. Ketone **18d** was also isolated as a colorless crystal in 90% yield by catalytic hydrogenation. Reduction of ketone **18a** with $NaBH_4$ in MeOH under the same conditions as those described above gave a mixture of **19a** and **20a** (94:6) [**19a** in 90% isolated yield (**19d** from **18d** in 80%)], proving that the reduction of **17** to **19** proceeded via the corresponding ketones **18**.

In general, ketones **18** were sensitive to air. *N*-Benzyl ketones **18g** and **18h** were thus labile and could not be isolated. When a stirred solution of **18a** in MeOH was treated with oxygen for 1 h at room temperature, it was transformed to *N*-methylcorydaldine[30] and 2-bromo-3,4-dimethoxybenzoic acid almost quantitatively. When **19a** and **20a** were heated under reflux in toluene in the presence of the mild oxidant $CuCl_2$ (2 equiv), a 3,4-dihydroisoquinolinium salt and the corresponding benzaldehyde were almost quantitatively formed.[31]

When **17a** was treated with 2 mol equiv of $LiAlH_4$ in THF at room temperature for 5 min, the *threo*-amino alcohol **20a** was obtained in preference to the *erythro*-amino alcohol **19a** in a 5:2 ratio (>90%). Because of the close R_f values of both isomers on TLC, a mixture was converted with Ac_2O−pyridine to the corresponding acetates which were separated on silica gel TLC as described in detail in the Experimental Section. Saponification of each acetate with 5% potassium hydroxide in MeOH at 50 °C for 5 min gave pure *threo*- (**20a**) and *erythro*- (**19a**) amino alcohols, respectively.

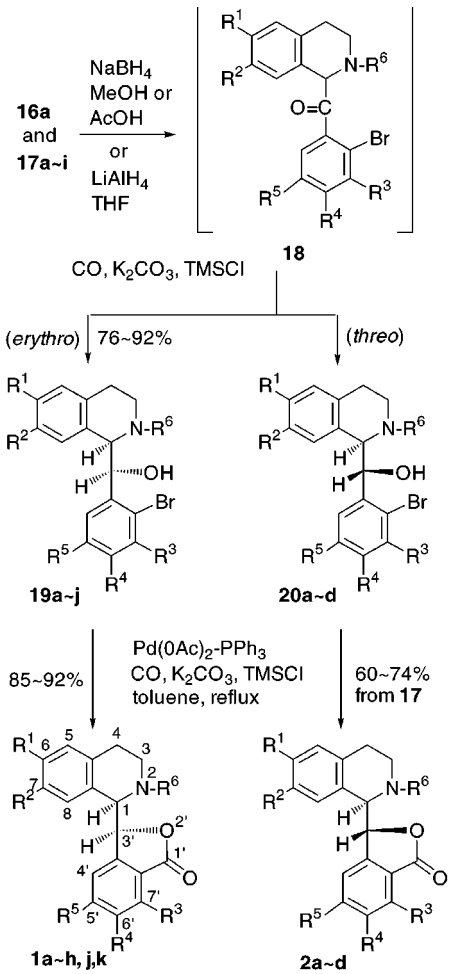
Reduction of **17a** was also examined using DIBALH and bis(2-methoxyethoxy)alminum hydride. As shown in Table 3, the latter reagent showed *threo*-selectivity similar to that of the $LiAlH_4$ reduction. The *erythro*-selectivity in the reduction of the salts **17a** with $NaBH_4$ can be well explained according to Cram's rule by the attack (route a, Scheme 4) of hydride from the open side.[32a] The opposite selectivity by aluminum hydride reduction has not yet been clearly explained, but the reduction may proceed via the formation of an oxygen−aluminum−nitrogen complex. Alternatively, there may be a similar chelation holding a lithium (or sodium) atom between the intermediate ketone (**18**) and aluminum hydride in accordance with Cram's chelate model,[32b] followed by the attack (route b) of "internal" hydride on the carbonyl group to give *threo*-alcohol **20** (Scheme 4). Reduction with DIBALH showed *erythro*-selectivity, prob-

Table 3. Reduction of Methiodides 17a−d and Ketone 18a with Hydride Reagents in THF

substrate	reagent	ratio of products **19**:**20**
17a	*i*-Bu_2AlH[a]	76:24
17a	$NaAl(OCH_2CH_2OCH_3)_2H_2$[a]	40:60
17a	$LiAlH_4$[b]	29:71
17b	$LiAlH_4$[b]	33:67
17c	$LiAlH_4$[b]	17:83
17d	$LiAlH_4$[b]	25:75
18a	$LiAlH_4$[b]	28:72

[a] 4 mol equiv at rt for 30 min. [b] 2 mol equiv at rt for 5 min.

Scheme 3



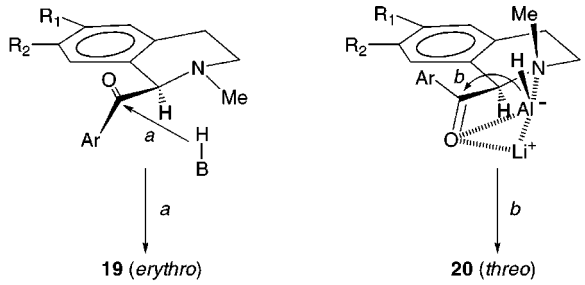
a : R^1=R^2= R^3=R^4=OMe, R^5=H, R^6=Me
b : R^1=R^2=OMe, R^3+R^4=OCH_2O, R^5=H, R^6=Me
c : R^1+R^2=OCH_2O, R^3=R^4=OMe, R^5=H, R^6=Me
d : R^1+R^2= R^3+R^4=OCH_2O, R^5=H, R^6=Me
e : R^1=R^2=R^4=R^5=OMe, R^3=H, R^6=Me
f : R^1+R^2= R^4+R^5=OCH_2O, R^3=H, R^6=Me
g : R^1=R^2= R^3=R^4=OMe, R^5=H, R^6=Bn
h : R^1+R^2= R^3+R^4=OCH_2O, R^5=H, R^6=Bn
i : R^1=R^2= R^3=R^4=OMe, R^5=H, R^6=Pr
j : R^1=R^2= R^3=R^4=OMe, R^5=R^6=H
k : R^1+R^2= R^3+R^4=OCH_2O, R^5=R^6=H

(30) (a) Späth, E.; Epstein, H. *Ber.* **1926**, *59*, 2791−2800. (b) Kupchan, S. M.; Kubota, S.; Fujita, E.; Kobayashi, S.; Block, J. H.; Telang, S. A. *J. Am. Chem. Soc.* **1966**, *88*, 4212−4218. (c) Reference 35b.

(31) A similar oxidative cleavage of laudanosine with ceric ammonium nitrate has been reported. See Ralph, I.; Bick, C.; Bremner, J. B.; Cava, M. P.; Wiriyachitra, P. *Aust. J. Chem.* **1978**, *31*, 321−326. With 2 mol equiv of $CuCl_2$, CuCl, $CuBr_2$, CuBr, CuI_2, or CuI in boiling toluene, oxidative cleavages of **19j**, the debromo derivative of **19a**, and *N*-methylephedrine were also observed.

(32) (a) Cram, J. D.; Abd Elhafez, F. A. *J. Am Chem. Soc.* **1952**, *74*, 5828−5835. (b) Cram, D. J.; Wilson, D. R. *J. Am. Chem. Soc.* **1963**, *85*, 1245−1249.

Scheme 4

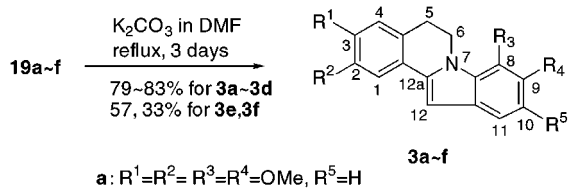


ably owing to the attack of hydride from the open side. Treatment of other methiodides, **17b**, **17c**, and **17d**, with $LiAlH_4$ gave the corresponding *threo*-alcohols **20** in preference to *erythro*-alcohols **19** in ratios of 2:1−5:1.

Synthesis of Phthalideisoquinoline Alkaloids. Carbonylation of **19a** (Scheme 3) with CO (1 atm) in the presence of $Pd(OAc)_2$ (20 mol %), PPh_3 (40 mol %), and K_2CO_3 (2 mol equiv) in boiling toluene under nearly standard conditions[2a] proceeded very slowly and 24 h later gave the lactone **1a** in a yield lower than 10%, contrary to the expectation described above. However, this was again overcome by the addition of TMSCl (2 equiv) and a large excess of K_2CO_3 (20 molar equiv), which dramatically accelerated the reaction rate to produce (±)-cordrastine II (**1a**) (from **19a**) and (±)-cordrastine I (**2a**) (from **20a**) in almost quantitative yields. The debromo derivative of **18a** or **19a**, which was the expected byproduct corresponding to the aldehyde **7a** or alcohol **8a** described above, was not detected. Application of this procedure to other *erythro*-amino alcohols **19b**−**f** gave almost the same results. When the aforementioned *threo*-amino alcohol-rich mixture (**19a**:**20a** = 1:2.5) was subjected to the accelerated lactonization, the products **1a** and **2a** were separable from each other on silica gel TLC, and **2a** was provided in 63% yield starting from methiodide **17a**. An attempt to perform the direct lactonization to norcordrastine (**1j**) of amino alcohol **19j** having a secondary amino group gave an intractable mixture including a small amount of **1j**. However, similar lactonizations of *N*-benzyl *erythro*-amino alcohols **19g** and **19h**, followed by removal of an *N*-benzyl group of the resultant phthalide **1g** (91%) and **1h** (75%) by palladium-catalyzed hydrogenolysis, gave (±)-norcordrastine II (**1j**)[33,34] and (±)-norbicuculline (**1k**), respectively, in good yields (Scheme 3).

Synthesis of Indolo[2,1-*a*]isoquinolines.[35] Indolo[2,1-*a*]isoquinolines have a structural feature of the so-called dibenzopyrrocoline alkaloids, such as cryptaustoline and cryptowoline, isolated from the bark of *Cryptocarya bowiei*.[36] Syntheses of these unique tetracyclic structures have been accomplished by several methods,[37] such as a benzyne reaction[38] of 1-(2′-bromo-4′,5′-dialkoxybenzyl)isoquinolines, oxidative coupling of 1-benzylisoquinolines,[39] enamine photocyclization,[40] addition of benzyl anion to 3,4-dihydroisoquinoline,[41] and radical cyclization and Bischler−Napieralski cyclization,[42] which give either 9,10-dialkoxyindolo[2,1-*a*]isoquinolines or a mixture of 9,10- and 10,11-dialkoxy-substituted derivatives. Our present method is able to produce 8,9-dialkoxy-substituted indolo[2,1-*a*]isoquinolines or their 9,10-dialkoxy regioisomers selectively.

Scheme 5



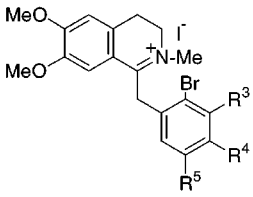
a: R^1=R^2= R^3=R^4=OMe, R^5=H
b: R^1=R^2=OMe, R^3+R^4=OCH_2O, R^5=H
c: R^1+R^2=OCH_2O, R^3=R^4=OMe, R^5=H
d: R^1+R^2= R^3+R^4=OCH_2O, R^5=H
e: R^1=R^2= R^4=R^5=OMe, R^3=H
f: R^1+R^2= R^4+R^5=OCH_2O, R^3=H

erythro-1-(2′-Bromo-3′,4′-dimethoxy-α-hydroxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **19a** was treated with $Pd(OAc)_2$, PPh_3, and excess K_2CO_3 in boiling DMF in an atmosphere of carbon monoxide. However, the expected carbonylation leading to the formation of a phthalide ring did not occur at all, and instead, a new compound **3a** with no *N*-methyl group was obtained. After careful examination to clarify the reaction pathway, it was found that this reaction took place slowly without CO gas, $Pd(OAc)_2$, and PPh_3, and it was completed in 3 days. On the basis of ^1H and ^{13}C NMR analysis in comparison with the spectral data reported for a similar system,[38d,g,40] the structure of the exclusive product was determined to be 2,3,8,9-tetramethoxy-5,6-dihydroindolo[2,1-*a*]isoquinoline **3a** (Scheme 5). This was also supported by measuring the nuclear Overhauser effect as follows. Irradiation of the signal of the proton at position 12 (δ 6.67) resulted in an enhancement of the signal areas of 1-H (20%, δ 7.18) and 11-H (10%, δ 7.24). Irradiation of the doublet signal of the proton at position 10 (δ 6.81) resulted in an enhancement of the signal areas of the aforementioned 11-H (19%) and the methoxy protons (14%, δ 3.95) at position 9.

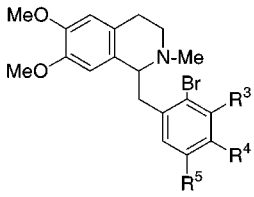
Methylenedioxy derivatives **19b**, **19c**, and **19d** were also transformed to the corresponding indolo[2,1-*a*]isoquinolines **3b**, **3c**, **3d** in good yields under the conditions described above. The N−H derivative of **19a** (**19j**) gave **3a** in 13% yield, while the *N*-benzyl derivative (**19g**) failed to give **3a**. This reaction appears to require a fairly

(33) Kerekes, P.; Gaál, G.; Bognár, R.; Töró, T.; Costisella, B. *Acta Chim. Acad. Sci. Hung.* **1980**, *105*, 283−291.
(34) Clarke, S. I.; Kasum, B.; Prager, R. H.; Ward, A. D. *Aust. J. Chem.* **1983**, *36*, 2493−2498.
(35) For a preliminary report, see Orito, K.; Miyazawa, M.; Suginome, H. *Heterocycl. Commun.* **1995**, *1*, 239−240.
(36) Ewing, J.; Hughes, G. K.; Ritchie, E.; Taylor, W. C. *Nature* **1952**, *169*, 618−619; *Aust J. Chem.* **1953**, *6*, 78−85.
(37) Elliott, I. W. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: Orlando, 1987; Vol. 31; pp 101−116.
(38) (a) Kametani, T.; Ogasawara, K. *J. Chem. Soc. (C)* **1967**, 2208−2212. (b) Benington, F.; Morin, R. D. *J. Org. Chem.* **1967**, *32*, 1050−1053. (c) Kametani, T.; Fukumoto, K.; Nakano, T. J. *Heterocycl. Chem.* **1972**, *9*, 1363−1366. (d) Kametani, T.; Shibuya, S.; Kano, S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1212−1214. (e) Ahmad, I.; Gibson, M. *Can. J. Chem.* **1975**, *53*, 3660−3664. (f) Kessar, S. V.; Batra, S.; Nadir, U. K.; Gandhi, S. S. *Ind. J. Chem.* **1975**, *13*, 1109−1112. (g) Mak, C.-P.; Brossi, A. *Heterocycles* **1979**, *12*, 1413−1416. (h) Ambros, R.; von Angerer, S.; Wiegrebe, W. *Arch. Pharm.* **1988**, *321*, 481−486. (i) Meyers, A. I.; Sielecki, T. M. *J. Am. Chem. Soc.* **1991**, *113*, 2789−2790.
(39) (a) Robinson, R.; Sugasawa, S. *J. Chem. Soc.* **1932**, 798−805. (b) Harley-Mason, J. *J. Chem. Soc.* **1953**, 1465−1466. (c) Hess, U.; Hiller, K.; Schroeder, R. S. *J. Prakt. Chem.* **1977**, *319*, 568−572.
(40) Ninomiya, I.; Yasui, J.; Kiguchi, T. *Heterocycles* **1977**, *6*, 1855−1860.
(41) Takano, S.; Satoh, S.; Ogasawara, K. *Heterocycles* **1987**, *26*, 1483−1485.
(42) (a) Mathew, K. K.; Menon, K. N. *Proc. Indian Acad. Sci.* **1949**, *29A*, 361−363. (b) Yasuda, S.; Hirasawa, T.; Yoshida, S.; Hanaoka, M. *Chem. Pharm. Bull.* **1989**, *37*, 1682−1683.

high nucleophilicity of the nitrogen atom but not a bulky *N*-substituent. When a mixture of **19a** and its *threo*-isomer **20a** was subjected to the present cyclization, the latter (**20a**) remained essentially unchanged, though a small amount of the *threo* **20a** may have been consumed with the production of **3a** through isomerization to the *erythro* **19a**.[12] 1-(2′-Bromo-3′,4′-dimethoxybenzyl)-2-methyltetrahydroisoquinoline **22f** and its regioisomer **22g** [(±)-6′-bromotetrahydrolaudanosine[38e]] (Scheme 5) were unreactive, while it was reported that the benzyne reaction converted **22e** and **22g** to a regioisomer of **3a**, 2,3,9,10-tetramethoxy-5,6-dihydroindolo[2,1-*a*]isoquinoline **3e** (from **22e**),[38a,d,g] and its *N*-methyl-5,6,12,12a-tetrahydro derivative (from **22g**).[38e] When methiodides



21a: R^3=R^4=OMe, R^5=H
21e: R^3=H, R^4=R^5=OMe[38e]

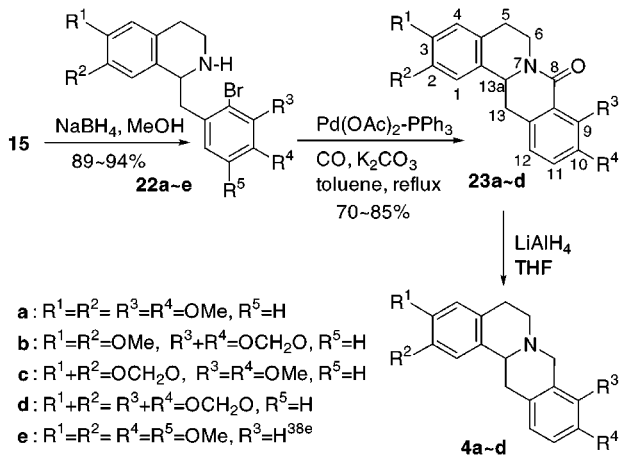


22f: R^3=R^4=OMe, R^5=H
22g: R^3=H, R^4=R^5=OMe[38e]

21a and **21e**[38e] were exposed to this K_2CO_3 treatment for 3 days, only traces of indolo[2,1-*a*]isoquinolines **3a** and **3e** (less than 3% yield for both) were observed on the ^{1}H NMR spectra of their reaction mixtures. These results appear to show that the cyclization does not start with the formation of *N*-methylenamine intermediate due to a simple dehydration of **19**. The reaction probably started with a nucleophilic attack of the nitrogen atom on the aromatic carbon bearing a bromine atom and may have proceeded with an efficient relief of steric repulsions between the Br atom, hydroxy, and *N*-methyl groups, for instance, in one possible pathway shown in a preliminary report.[35,43] We later found that even 4′,5′-dialkoxy derivatives **19e** and **19f** gave lower yields than those for **3a**−**d** the corresponding indolo[2,1-*a*]isoquinolines **3e** and **3f**, which have four alkoxy groups at the same 2, 3, 9, 10 positions as the aforementioned natural products. Nevertheless, these methods provided a new route to the indolo-[2,1-*a*]isoquinoline system.

Synthesis of Protoberberine Alkaloids. Protoberberines are known to have a variety of biological activities, including antileukemic and antitumor activities.[44] Antitumor and anticancer activities of 8-oxoberbines have also been reported.[44b] The natural berbines occur in a 9,-10-alkoxy-substitution pattern[45] which is obtained with difficulty by the usual cyclization methods such as the traditional Bischler−Napieralski, Pictet−Spengler, or Pomeranz−Fritsch reactions, as briefly described by

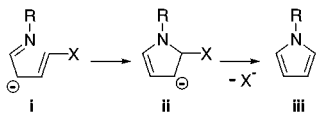
Scheme 6



Narasimuhan,[46] to give rather selectively 10,11-alkoxy derivatives. Therefore, considerable efforts have been directed toward the selective synthesis of berbines with the natural substitution pattern, and several synthetic methods,[9,47,48] including some enantioselective approaches,[48a,d,e,i] have been reported.

Palladium(0)-catalyzed carbonylation of 1-(2′-bromo-4′,5′-dialkoxybenzyl)tetrahydroisoquinolines was reported by Pandey.[3i,j] Carbonylation of a similar isoquinoline system was also reported to be catalyzed with $Fe_3(CO)_{12}$ and $Co_2(CO)_8$.[49] In the present study, we investigated the carbonylation using 1-(2′-bromo-3′,4′-dialkoxybenzyl)tetrahydroisoquinolines **22a**−**d** as substrates which were easily prepared by $NaBH_4$ reduction of the above-mentioned dihydroisoquinolines **15a**−**d** (Scheme 6). By treatment with CO in the presence of $Pd(OAc)_2$ (20 mol %), PPh_3 (40 mol %), and excess K_2CO_3 in boiling toluene, 2-bromo-3,4-dimethoxybenzyl derivatives **22a** and **22c** underwent relatively slow carbonylation and, 26 h later, gave 8-oxoberbines **23a** in 75% and **23c** in 85% isolated

(43) An alternative reaction pathway (**i** → **ii** → **iii**) with a leaving group X on a nitrogen-containing ring system **3**, based on the thermal electrocyclization of a pentadienyl anion to a cyclopentenyl anion, cannot be discarded. For selected references, see Stapp, P. R.; Kleinschmidt, R. F. *J. Org. Chem.* **1965**, *30*, 3006−3009; Slaugh, L. H. *J. Org. Chem.* **1967**, *32*, 108−113; Bates, R. B.: McCombs, D. A. *Tetrahedron Lett.* **1969**, 977−978; Shoppee, C. W.; Henderson, G. N. *J. Chem. Soc., Perkin Trans. 1* **1975**, 765−772.



(44) (a) See ref 3 cited in ref 48i. (b) See ref 12 cited in ref 48i.
(45) See ref 1 cited in ref 48i.

(46) Narasimhan, N. S.; Mali, R. S.; Kulkarni, B. K. *Tetrahedron* **1983**, *39*, 1975−1982.
(47) For reviews, see (a) Kametani, T.; Ihara, M. *Heterocycles* **1979**, *13*, 497−530. (b) Pandey, G. D.; Tiwari, K. P. *Heterocycles* **1980**, *14*, 59−82. (c) Bhakuni, D. S.; Jain, S. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: Orlando, 1986; Vol. 28; pp 95−171.
(48) Selected articles published on and after 1986; Synthesis based on the modified Pictet−Spengler, Bischler−Napieralski, or Pomerantz−Fritsch reaction, see (a) Czarnocki, Z.; Maclean, D. B.; Szarek, W. A. *Bull. Soc. Chim. Belg.* **1986**, *95*, 749−769. (b) Orito, K. Matsuzaki, T.; Suginome, H. *Org. Prep. Proc. Int.* **1989**, *21*, 309−314. (c) Sotomayor, N.; Domínguez, E.; Lete, E. *Synlett* **1993**, 431−433. (d) Czarnocki, Z.; Maclean, D. B.; Szarek, W. A. *J. Chem. Res. (C)* **1992**, 234−335; *J. Chem. Res. (M)* **1992**, 2801−2819. (e) Commins, D. L.; Thakker, P. M.; Baevsky, M. F. *Tetrahedron* **1997**, *53*, 16327−16340. Synthesis based on nucleophilic addition of carbanions to 3,4-dihydroisoquinolines, see (f) Warrener, R. N.; Lin, L.; Russell, R. A. *Tetrahedron* **1988**, *54*, 7485−7496. (g) Pyne, G. S.; Branko, D. *J. Org. Chem.* **1990**, *55*, 1932−1936. (h) Kessar, S. V.; Singh, P.; Vohra, R.; Kaur, N. P.; Venugopal, D. *J. Org. Chem.* **1992**, *57*, 6716−6720. Synthesis based on alkylation on a C-1 metalated tetrahydroisoquinoline, see (i) Matulenko, M. A.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 573−580. Synthesis based on photochemical cyclization of enamides, see (j) Weimar, C.; von Angerer, S.; Wiegrebe, W. *Arch. Pharm.* **1991**, *324*, 907−912. Synthesis based on radial cyclization, see (k) Dai-Ho, G.; Mariano, P. S. *J. Org. Chem.* **1987**, *52*, 706−707. (l) Takano, S.; Suzuki, M.; Ogasawara, K. *Heterocycles* **1990**, *31*, 1151−1156. (m) Takano, S.; Suzuki, M.; Kijima, A.; Ogasawara, K. *Tetrahedron Lett.* **1990**, *31*, 2315−2318. (n) Nimgirawath, S.; Ponghusabun, O.-a. *Aust. J. Chem.* **1994,** *47*, 951−955. Synthesis based on cycloaddition reaction of isoquinoline-pyrroline-2,3-dione with benzyne, see (o) Cobas, A.; Guitián, E.; Castedo, L. *J. Org. Chem.* **1992**, *57*, 6765−6769. Synthesis based on palladium-catalyzed cyclization, see (p) Bombrun, A.; Sageot, O. *Tetrahedron Lett.* **1997**, *38*, 1057−1060.
(49) Trifonov, L. S.; Orehovats, A. S. *Tetrahedron Lett.* **1985**, *26*, 3159−3162.

yield. Their methylenedioxy derivatives (**22b** and **22d**) were consumed within 18 h and gave the corresponding 8-oxoberbines **23b** and **23d** in good yields. Further, by treating with excess $LiAlH_4$ in the reported manner,[48h,i,50,51] these lactams were converted almost quantitatively to protoberberine alkaloids **4a**−**d**.

Conclusions

A general route for synthesis of phthalideisoquinoline alkaloids has been developed. The key steps are the stereoselective reduction of 1-(2′-bromobenzoyl)-3,4-dihydroisoquinoline methiodide **18** with sodium borohydride or lithium aluminum hydride, followed by a palladium(0)-catalyzed carbonylation of the resultant *erythro*- or *threo*-amino alcohols **19** and **20** aided by chlorotrimethylsilane. The synthesis of eight phthalideisoquinoline alkaloids having methoxy- and/or methylenedioxy-substituents together with nor- and iso-types of the alkaloids has been successfully demonstrated. Treatment of *erythro*-amino alcohols **19** with potassium carbonate in boiling DMF provided a new method for construction of the indolo[2,1-*a*]isoquinoline skeleton characteristic of the dibenzopyrrocoline alkaloids, such as cryptaustoline and cryptowoline, isolated from *Cryptocaria bowiei*. Palladium(0)-catalyzed carbonylation of 1-(2′-bromo-3′,4′-dialkoxybenzyl)tetrahydroisoquinolines **22** gave 8-oxoberbines **23**, which were treated with excess $LiAlH_4$ in boiling THF to give protoberberine alkaloids **4** in good yields.[52]

Experimental Section

General Procedures. Infrared spectra were recorded as Nujol mulls, unless otherwise specified. ^1H (90, 270, 400 MHz) and ^{13}C NMR (67.5 MHz) spectra were measured in $CDCl_3$ (99.8 atom % D, containing 0.03% v/v TMS, Aldrich). Mass spectra were recorded with EI at 70 eV. TLC was carried out on a Merck silica gel 60 PF_{254} (Nos. 7749 and 5554). The following solvents and reagents were distilled prior to use: THF (sodium benzophenone ketyl), benzene (P_2O_5), toluene (P_2O_5), CH_2Cl_2 (P_2O_5), pyridine (CaH_2), and Et_3N (CaH_2).

Palladium(0)-Catalyzed Carbonylation of 2-Bromo-3,4-dimethoxybenzyl Alcohol (5a). Bromo-3,4-dimethoxybenzyl alcohol **5a** (24 mg, 0.1 mmol), $Pd(OAc)_2$ (4.6 mg, 20 mol %), PPh_3 (10.6 mg, 40 mol %), and the appropriate additives in dry toluene (2 mL) were charged in a 10-mL pair-shaped flask, having a magnetic stirring bar in it, connected with a condenser, on which a three-way stopcock was attached for a CO gas balloon and an aspirator. After degassing with an aspirator followed by charging with CO gas three times, the reaction flask was dipped into an oil bath preheated at 140 °C, and the reaction mixture was refluxed with stirring for 24 h. The reaction mixture was allowed to cool to room temperature and was then filtered through a Celite pad. The solvent was removed on a rotary evaporator, and the ^1H NMR spectrum of the residue was measured for determination of the product ratio. When Me_3SiCl (22 mg, 0.2 mmol) was used as an additive, such as in entries 9−11, the residue was then dissolved in MeOH (3 mL) containing three drops of 2 N HCl, and, 30 min later, the solution was evaporated at room temperature. The oily residue was extracted with CH_2Cl_2 (5 mL) and water (5 mL), and the CH_2Cl_2 extracts were dried (Na_2SO_4) and evaporated to give the crude products for ^1H NMR analysis.

2-Bromo-3,4-dimethoxybenzyl Alcohol (5a). General Procedure. To a stirred solution of 2-bromo-3,4-dimethoxybenzaldehyde[26] (8.466 g, 34.546 mmol) in THF (45 mL) and MeOH (45 mL) was added $NaBH_4$ (0.653 g, 17.273 mmol) in portions. The mixture was stirred for 2 h and then concentrated to give an oily residue, which was dissolved in CH_2Cl_2 (150 mL) and water (50 mL) containing 2 N HCl (5 mL). The organic layer was washed with water (50 mL × 2), dried (Na_2SO_4), and condensed to give a solid (8.532 g), mp 76−79 °C. Recrystallization from Et_2O−petroleum ether gave **5a** (8.360 g, 98%); mp 78−80 °C; IR (neat) 3378, 1596, 1489 cm^{-1}; ^1H NMR (270 MHz) δ 2.18 (br s, 1H), 3.86, 3.87 (each br s, each 3H), 4.68 (s, 2H), 6.87, 7.16 (AB type, J = 8.4 Hz, each 1H); MS m/z (rel int) 248 (M^+, 94), 246 (M^+, 100), 231 [$(M - CH_3)^+$, 40], 229 [$(M - CH_3)^+$, 31], 167 [$(M - Br)^+$, 60]. Anal. Calcd for $C_9H_{11}O_3Br$: C, 43.75; H, 4.49; Br, 32.34. Found: C, 43.87; H, 4.63; Br, 32.27.

2-Bromo-3,4-(methylenedioxy)benzyl Alcohol (5b): 96% yield from 2-bromo-3,4-(methylenedioxy)benzaldehyde;[26] mp 114−115 °C (petroleum ether); IR 3270, 1617, 1497 cm^{-1}; ^1H NMR (270 MHz) δ 1.95 (br s, 1H), 4.67 (s, 2H), 6.05 (s, 2H), 6.75, 6.94 (AB type, J = 8.1 Hz, each 1H). Anal. Calcd for $C_8H_7O_3Br$: C, 41.59; H, 3.05; Br, 34.58. Found: C, 41.36; H, 2.97; Br, 34.58.

2-Bromo-3,4-dimethoxyphenylacetonitrile (10a). General Procedure. To a solution of benzyl alcohol **5a** (8.333 g, 33.7 mmol) in dry benzene (2 mL) was dropwise added $SOCl_2$ (6.02 g, 50.55 mmol). After the mixture was stirred at room temperature overnight, excess $SOCl_2$ was removed by azeotropic distillation with benzene under reduced pressure. The crude oily benzyl chloride **9a** [^1H NMR (90 MHz) δ 3.86, 3.89 (s, each 3H), 4.69 (s, 2H), 6.85, 7.20 (AB type, J = 8.4 Hz, each 1H] was dissolved in a mixture of DMSO (15 mL) and benzene (7 mL). To this solution was added NaCN (powdered, 3.303 g, 67.4 mmol) in portions. The mixture was stirred for 2 h, poured into water (100 mL), and extracted with benzene (15 mL × 5). The combined benzene layers were washed with saturated brine (20 mL × 5), dried (Na_2SO_4), and evaporated. The residue was distilled under reduced pressure to give **10a** as a colorless oil (7.824 g, 91%), bp 125−127 °C (0.2 mmHg). IR 2250, 1597, 1490 cm^{-1}; ^1H NMR (270 MHz) δ 3.79 (s, 2H), 3.86 (s, 3H), 3.89 (s, 3H), 6.90, 7.36 (AB type, J = 8.4 Hz, each 1H). Anal. Calcd for $C_{10}H_{10}NO_2Br$: C, 46.90; H, 3.94; N, 5.47; Br, 31.2. Found: C, 46.75; H, 3.98; N, 5.50; Br, 31.39.

2-Bromo-3,4-(methylenedioxy)acetonitrile (10b): 89% yield; mp 149−151 °C (CH_2Cl_2−Et_2O); IR 2250, 1621, 1499 cm^{-1}; ^1H NMR (270 MHz) δ 3.75 (s, 2H), 6.08 (s, 2H), 6.78, 6.99 (AB type, J = 8.1 Hz, each 1H). Anal. Calcd for $C_9H_6NO_2Br$: C, 45.03; H, 2.52; N, 5.84; Br, 33.29. Found: C, 44.87; H, 2.48; N, 5.82; Br, 33.49.

2-Bromo-3,4-dimethoxyphenylacetic Acid (11a). General Procedure. A solution of **10a** (7.760 g, 30.3 mol) in EtOH (100 mL) and 4 N NaOH (50 mL) was refluxed for 20 h. The cooled reaction mixture was diluted with water (200 mL) and then washed with CH_2Cl_2 (50 mL). The water layer was separated, acidified with concentrated HCl (20 mL), and extracted with CH_2Cl_2 (30 mL × 3). The extracts were washed with water (50 mL × 2), dried (Na_2SO_4), and concentrated to give a solid (8.881 g). Recrystallization from CH_2Cl_2−Et_2O gave **11a** (7.650 g, 92%): mp 154−155 °C; IR 3600−2800, 1710, 1596, 1490 cm^{-1}; ^1H NMR (270 MHz) δ 3.80 (s, each 1H), 3.86 (s, 3H), 3.87 (s, 3H), 6.85, 7.02 (AB type, J = 8.4 Hz, each 1H); (90 MHz) δ 5.30 (br s, 1H). Anal. Calcd for $C_{10}H_{11}O_4Br$: C, 43.66; H; 4.03; Br, 29.05. Found: C, 43.50; H, 3.97; Br, 29.07.

2-Bromo-3,4-(methylenedioxy)phenylacetic acid (11b): 89% yield; mp 183−185 °C (MeOH); IR 3200−2000, 1670 cm^{-1}; ^1H NMR (270 MHz) δ 3.76 (s, 2H), 6.05 (s, 2H), 6.73, 6.79 (AB q, J = 7.7 Hz, each 1H). Anal. Calcd for $C_9H_7O_4Br$: C, 41.73; H, 2.72; Br, 30.84. Found: C, 41.78; H, 2.76; Br, 30.67.

***N*-(3,4-Dimethoxyphenethyl)-2-bromo-3,4-dimethoxyphenylacetamide (14a). General Procedure.** After a mixture of **11a** (550 mg, 2 mmol), $SOCl_2$ (480 mg, 4 mmol), and dry benzene (10 mL) was stirred at 50−60 °C for 2 h, excess $SOCl_2$ was removed under reduced pressure. The resulting acid chloride **12a** was dissolved in dry benzene (5 mL) and added

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(52) Asymmetric reduction of imines **15**−**17** is under investigation, and the results will be reported later.

dropwise to a stirred solution of 3,4-dimethoxyphenethylamine **13a** (290 mg, 1.8 mmol) and pyridine (237 mg, 3 mmol) in dry benzene (5 mL). The mixture was continuously stirred at room temperature overnight and then poured into water (30 mL). The benzene layer was separated. The water layer was extracted once with benzene (10 mL). The combined benzene layers were washed with 0.5 N HCl (10 mL), 0.5 N NaOH (10 mL), and water (20 mL) and dried (Na_2SO_4). Evaporation of benzene, followed by recrystallization of the crude product from benzene−Et_2O, afforded **14a** (710 mg, 91%): mp 103−105 °C; IR 3304, 1645, 1593, 1492 cm^{-1}; ^1H NMR (270 MHz) δ 2.70 (t, J = 7.0 Hz, 2H), 3.45, 3.47 (t, J = 7.0 Hz, each 1H), 3.63 (s, 2H), 3.83, 3.84, 3.85, 3.87 (each s, each 3H), 5.42 (br s, 1H), 6.60 (dd, J = 8.0, 1.8 Hz, 1H), 6.64 (d, J = 1.8 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.82, 6.98 (AB q, J = 8.4 Hz, each 1H). Anal. Calcd for $C_{20}H_{24}NO_5Br$: C, 54.81; H, 5.52; N, 3.20; Br, 18.23. Found: C, 54.98; H, 5.46; N, 3.12; Br, 18.24.

***N*-(3,4-Dimethoxyphenethyl)-2-bromo-3,4-(methylenedioxy)phenylacetamide (14b)**: 85% yield from **12b** and **13a**; mp 178−179 °C (benzene−Et_2O); IR 3290, 1647, 1593, 1519 cm^{-1}; ^1H NMR (270 MHz) δ 2.70 (t, J = 7.0 Hz, 2H), 3.46, 3.48 (t, J = 6.6 Hz, each 1H), 3.58 (s, 2H), 3.84, 3.86 (s, each 3H), 5.36 (br s, 1H), 6.07 (s, 2H), 6.60 (dd, J = 7.9, 2.0 Hz, 1H), 6.63 (d, J = 2.0 Hz, 1H), 6.74 (d, J = 7.9 Hz, 1H), 6.69, 6.74 (AB type, J = 7.9 Hz, each 1H). Anal. Calcd for $C_{19}H_{18}NO_5Br$: C, 54.04; H, 4.77; N, 3.32; Br, 18.92. Found: C, 53.82; H, 4.73; N, 3.37; Br, 19.13.

***N*-[(3,4-Methylenedioxy)phenethyl]-2-bromo-3,4-dimethoxyphenylacetamide (14c):** 86% yield from **12a** and **13b**; mp 163−165 °C (benzene); IR 3280, 1648, 1598, 1505, 1498 cm^{-1}; ^1H NMR (270 MHz) δ 2.66 (t, J = 6.9 Hz, 2H), 3.41, 3.43 (t, J = 6.8 Hz, each 1H), 3.63 (s, 2H), 3.85 (s, 3H), 3.88 (s, 3H), 5.39 (br s, 1H), 5.91 (s, 2H), 6.50 (dd, J = 7.8, 1.5 Hz, 1H), 6.56 (d, J = 1.5 Hz, 1H), 6.66 (d, J = 7.8 Hz, 1H), 6.83, 7.00 (AB type, J = 7.8 Hz, each 1H). Anal. Calcd for $C_{20}H_{24}NO_5Br$: C, 54.81; H, 5.52; N, 3.20; Br, 18.23. Found: C, 54.98; H, 5.46; N, 3.12; Br, 18.24.

***N*-[3,4-(Methylenedioxy)phenethyl]-2-bromo-3,4-(methylenedioxy)phenylacetamide (14d):** 86% yield from **12b** and **13b**; mp 103−105 °C (benzene−Et_2O); IR 3290, 1636, 1549, 1506, 1492 cm^{-1}; ^1H NMR (400 MHz) δ 2.66 (t, J = 6.8 Hz, 2H), 3.41, 3.44 (t, J = 6.8 Hz, each 1H), 3.59 (s, 2H), 5.33 (br s, 1H), 5.93, 6.07 (s, each 2H), 6.50 (d, J = 7.8 Hz, 1H), 6.71, 6.75 (AB type, J = 7.8 Hz, each 1H). Anal. Calcd for $C_{18}H_{16}NO_5Br$: C, 53.22; H, 3.97; N, 3.45; Br, 19.67. Found: C, 53.31; H, 4.01; N, 3.66; Br, 19.64.

1-(2-Bromo-3,4-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (15a). General Procedure. A mixture of acetamide **14a** (7.013 g, 16 mmol), $POCl_3$ (12.240 g, 80 mmol), and dry toluene (100 mL) was refluxed under N_2 for 3 h. The cooled mixture was poured into ice−water (100 mL) and stirred for 2 h. The organic layer was discarded. The water layer and precipitates were then basified with 2 N NaOH (200 mL) and extracted with CH_2Cl_2 (50 mL × 3). The extracts were washed with water (100 mL), dried (Na_2SO_4), and evaporated to give **15a** as a solid (5.731 g, 85%), mp 120−124 °C. Recrystallization from benzene−Et_2O gave an analytical sample, mp 123−125 °C; R_f 0.15 on silica gel TLC plate (5% MeOH−CH_2Cl_2): IR 1621, 1606, 1595, 1573, 1518 cm^{-1}; ^1H NMR (270 MHz) δ 2.67 (t, J = 7.6 Hz, 2H), 3.72 (t, J = 7.6 Hz, 2H), 3.79, 3.82, 3.85, 3.88 (each s, each 3H), 4.15 (s, 1H), 6.66, (s, 1H), 6.76, 6.98 (AB q, J = 8.4 Hz, each 1H). Anal. Calcd for $C_{20}H_{22}NO_4Br$: C, 57.15; H, 5.28; N, 3.33; Br, 19.01. Found: C, 57.16; H, 5.30; N, 3.37; Br; 18.91.

1-[2-Bromo-3,4-(methylenedioxy)benzyl]-6,7-dimethoxy-3,4-dihydroisoquinoline (15b): 89% yield; mp 162−164 °C (benzene); IR 1626, 1606 1576, 1519, 1502 cm^{-1}; ^1H NMR (270 MHz) δ 2.66 (t, J = 7.6 Hz, 2H), 3.71 (t, J = 7.6 Hz, 2H), 3.83 (s, 3H), 3.89 (s, 3H), 4.09 (s, 2H), 6.02 (s, 2H), 6.67, (s, 1H), 6.93 (s, 1H), 6.66, 6.77 (AB type, J = 8.2 Hz, each 1H). Anal. Calcd for $C_{19}H_{18}NO_4Br$: C, 56.45; H, 4.49; N, 3.48; Br, 19.77. Found: C, 56.39; H, 4.46; N, 3.33; Br; 19.72.

1-(2-Bromo-3,4-dimethoxybenzyl)-6,7-(methylenedioxy)-3,4-dihydroisoquinoline (15c): 89% yield; mp 154−157 °C (benzene); IR 1643, 1604, 1504, 1492 cm^{-1}; ^1H NMR (270 MHz) δ 2.64 (t, J = 7.6 Hz, 2H), 3.67 (t, J = 7.6 Hz, 2H), 3.83 (s, 3H), 3.87 (s, 3H,), 4.07 (s, 2H), 5.94 (s, 2H), 6.66, (s, 1H), 6.91 (s, 1H), 6.77, 6.91 (AB type, J = 8.4 Hz, each 1H). Anal. Calcd for $C_{19}H_{18}NO_4Br$: C, 56.45; H, 4.49; N, 3.48; Br, 19.77. Found: C, 56.51; H, 4.42; N, 3.33; Br; 19.89.

1-[2-Bromo-3,4-(methylenedioxy)benzyl]-6,7-(methylenedioxy)-3,4-dihydroisoquinoline (15d): 83% yield; mp 171−175 °C (MeOH); IR 1640, 1615, 1604, 1503 cm^{-1}; ^1H NMR (270 MHz) δ 2.63 (t, J = 7.6 Hz, 2H), 3.66 (t, J = 7.6 Hz, 2H), 4.01 (s, 2H), 5.95 (s, 2H), 6.03 (s, 2H), 6.67 (s, 1H), 6.66, 6.70 (AB type, J = 8.3 Hz, each 1H), 6.90 (s, 1H). Anal. Calcd for $C_{18}H_{14}NO_4Br$: C, 55.69; H, 3.63; N, 3.61; Br, 20.58. Found: C, 55.56; H, 3.60; N, 3.72; Br; 20.81.

1-(2-Bromo-4,5-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (15e): 89% yield from **14e** by the reported method;[53] a colorless oil [lit.[53] mp 192−193 °C (oxalate);[38e] 232−234 °C (HCl salt);[48b] 224−225 °C (HCl salt)]; IR (neat) 1645, 1625, 1607, 1561, 1508 cm^{-1}; ^1H NMR (270 MHz) δ 2.73 (t, J = 7.3 Hz, 2H), 3.62 (partly hiding t, J = 7.6 Hz, 2H), 3.74 (s, 3H), 3.84 (s, 6H), 3.87 (s, 3H), 4.11 (s, 2H), 6.66, 6.87, 7.00, 7.04 (each s, each 1H). This was subjected to $^1O_2$ oxidation without further purification.

1-[2-Bromo-4,5-(methylenedioxy)benzyl]-6,7-(methylenedioxy)-3,4-dihydroisoquinoline (15f): 89% yield from **14f**;[54] mp 120−126 °C (benzene−Et_2O); IR (neat) 1660, 1616, 1598, 1504 cm^{-1}; ^1H NMR (270 Hz) δ 2.66 (t, J = 7.6 Hz, 2H), 3.70 (t, J = 7.6 Hz, 2H), 4.05, 5.92, 5.96 (each s, each 2H), 6.67, 6.71, 6.93, 7.03 (each s, each 1H). Anal. Calcd for $C_{18}H_{14}NO_4Br$: C, 55.69; H, 3.63; N, 3.61; Br, 20.58. Found: C, 55.47; H, 3.63; N, 3.61; Br; 20.79.

1-(2-Bromo-3,4-dimethoxybenzoyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (16a). General Procedure. Dihydroisoquinoline **15a** (2.750 g) was dissolved in CH_2Cl_2 (250 mL) containing MeOH (7.5 mL) and methylene blue (7.5 mg) in a Pyrex test tube (25 mm × 250 mm) equipped with a sintered glass bubbler and was cooled with a stream of cold water on the side of the tube. Oxygen gas was introduced through the bubbler to the mixture, which was then irradiated with a 100-W tungsten lamp at 15 °C for 30 min, monitoring with TLC on silica gel with 5% MeOH−CH_2Cl_2. The mixture was treated with powdered activated charcoal (200 mg) and was then filtered through a thin pad of powdered $MgSO_4$. The filtrate was concentrated to give crude **16a** as a solid (2.943 g, ca. 100%), mp 120−125 °C. Recrystallization from benzene−Et_2O gave an analytical sample (2.708 g, 92%), mp 124−126 °C; R_f 0.6 with 5% MeOH−CH_2Cl_2; IR 1653, 1623, 1606, 1582, 1515 cm^{-1}; ^1H NMR (270 Hz) δ 2.75 (t, J = 7.7 Hz, 2H), 3.84 (t, J = 7.7 Hz, 2H), 3.86, 3.88, 3.93, 3.94 (each s, each 3H), 6.74, 7.22 (s, each 1H), 6.96, 7.48 (AB type, J = 8.5 Hz, each 1H). Anal. Calcd for $C_{20}H_{20}NO_5Br$: C, 55.31; H, 4.64; N, 3.24; Br, 18.40. Found: C, 55.19; H, 4.59; N, 3.26; Br, 18.18.

1-[2-Bromo-3,4-(methylenedioxy)benzoyl]-6,7-dimethoxy-3,4-dihydroisoquinoline (16b): 83% yield; mp 161−163 °C (benzene); IR 1672, 1605, 1568, 1516, 1466 cm^{-1}; ^1H NMR (270 Hz) δ 2.76 (t, J = 7.8 Hz, 2H), 3.87 (t, J = 8.0 Hz, 2H), 3.87 (s, 3H), 3.94 (s, 3H), 6.12 (s, 2H), 6.73 (s, 1H), 7.16 (s, 1H), 6.84, 7.34 (AB type, J = 8.5 Hz, each 1H). Anal. Calcd for $C_{19}H_{16}NO_5Br$: C, 54.56; H, 3.86; N, 3.35; Br, 19.10. Found: C, 54.43; H, 3.81; N, 3.53; Br, 19.03.

1-(2-Bromo-3,4-dimethoxybenzoyl)-6,7-(methylenedioxy)-3,4-dihydroisoquinoline (16c): 89% yield; mp 126−127 °C (MeOH−Et_2O); IR 1674, 1655, 1585, 1501, 1486 cm^{-1}; ^1H NMR (270 MHz) δ 2.70 (t, J = 7.8 Hz, 2H), 3.79 (t, J = 7.6 Hz, 2H), 3.85 (s, 3H), 3.92 (s, 3H), 5.99 (s, 2H), 6.71 (s, 1H), 7.15 (s, 1H), 6.96, 7.46 (AB type, J = 8.8 Hz, each 1H). Anal. Calcd for $C_{19}H_{16}NO_5Br$: C, 54.56; H, 3.86; N, 3.35; Br, 19.10. Found: C, 54.54; H, 3.95; N, 3.20; Br, 18.89.

1-[2-Bromo-3,4-(methylenedioxy)benzoyl]-6,7-(methylenedioxy)-3,4-dihydroisoquinoline (16d): 87% yield; mp 165−167 °C (benzene−Et_2O); IR 1675, 1662, 1603, 1589, 1503

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cm^{-1}; ^{1}H NMR (270 MHz) δ 2.72 (t, J = 7.8 Hz, 2H), 3.82 (t, J = 7.8 Hz, 2H), 6.00 (s, 2H), 6.11 (s, 2H), 6.71 (s, 1H), 7.09 (s, 1H), 6.84, 7.33 (AB type, J = 8.4 Hz, each 1H). Anal. Calcd for $C_{18}H_{12}NO_5Br$: C, 53.75; H, 3.01; N, 3.48; Br, 19.87. Found: C, 53.77; H, 2.82; N, 3.51; Br, 19.86.

1-(2-Bromo-4,5-dimethoxybenzoyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (16e): 87% yield: mp 184−186 °C (MeOH); IR 1671, 1595, 1570, 1509 cm^{-1}; ^{1}H NMR (270 Hz) δ 2.77 (t, J = 7.7 Hz, 2H), 3.82 (partly hiding t, J = 7.7 Hz, 2H), 3.87 (s, 3H), 3.92 (s, 6H), 3.94 (s, 3H), 6.74, 7.03, 7.15, 7.28 (each s, each 1H). Anal. Calcd for $C_{20}H_{20}NO_5Br$: C, 55.31; H, 4.64; N, 3.24; Br, 18.40. Found: C, 55.45; H, 4.50; N, 3.06; Br, 18.37.

1-[2-Bromo-4,5-(methylenedioxy)benzoyl]-6,7-(methylenedioxy)-3,4-dihydroisoquinoline (16f): 78% yield: mp 176−179 °C (MeOH−Et$_2$O); IR 1677, 1651, 1587, 1501 cm^{-1}; ^{1}H NMR (270 Hz) δ 2.71 (t, J = 7.9 Hz, 2H), 3.82 (t, J = 7.9 Hz, 2H), 6.00 (s, 2H), 6.05 (s, 2H), 6.71, 7.01, 7.13, 7.15 (each s, each 1H). Anal. Calcd. for $C_{18}H_{12}NO_5Br$: C, 53.75; H, 3.01; N, 3.48; Br, 19.87. Found: C, 53.90; H, 3.22; N, 3.20; Br, 19.72.

1-(2-Bromo-3,4-dimethoxybenzoyl)-6,7-dimethoxy-3,4-dihydroisoquinoline Methiodide (17a). General Procedure. The crude dihydroisoquinoline **16a** (3.680 g, 6.4 mmol) was refluxed in CH_3CN (25 mL) containing CH_3I (3.5 mL) for 75 min. Evaporation of the solvent and excess CH_3I, followed by recrystallization of the resultant solid from MeOH−Et$_2$O, gave methiodide **17a** as yellow crystals (4.02 g, 82%): mp 142−144 °C; IR 1638, 1601, 1572, 1560, 1525 cm^{-1}; ^{1}H NMR (270 MHz) δ 3.71 (s, 3H), 3.87, 3.90, 4.00, 4.02 (each s, each 3H), 3.80−4.20, 4.25−4.65 (br. m, each 2H), 6.66 (s, 1H), 6.91 (s, 1H), 7.25, 8.43 (AB type, J = 8.8 Hz, each 1H). Anal. Calcd for $C_{21}H_{23}NO_5BrI + H_2O$: C, 42.45; H, 4.23; N, 2.36; I + Br, 34.81. Found: C, 42.37; H, 4.05; N, 2.36; I + Br, 34.53.

1-[2-Bromo-3,4-dimethoxybenzoyl]-6,7-(methylenedioxy)-3,4-dihydroisoquinoline methiodide (17b): 85% yield; mp 197−198 °C (MeOH); IR 1600, 1648, 1617, 1598 cm^{-1}; ^{1}H NMR (270 MHz) δ 3.73 (s, 3H), 3.86, 4.03 (s, each 3H), 6.22 (s, 2H), 6.65 (s, 1H), 6.95 (s, 1H), 7.16, 8.25 (AB type, J = 8.4 Hz, each 1H). Anal. Calcd for $C_{20}H_{19}NO_5BrI$: C, 42.88; H, 3.42; N, 2.50; I + Br, 36.91. Found: C, 42.80; H, 3.55; N, 2.36; I + Br, 36.72.

1-[2-Bromo-3,4-(methylenedioxy)benzoyl]-6,7-dimethoxy-3,4-dihydroisoquinoline methiodide (17c): 85% yield; mp 163−164 °C (MeOH); IR 1648, 1617, 1598, 1574, 1506, 1491 cm^{-1}; ^{1}H NMR (270 MHz) δ 3.84 (s, 3H), 3.90 (s, 3H), 4.01 (s, 3H), 6.66 (s, 1H), 6.90 (s, 1H), 7.25, 8.41 (AB type, J = 8.9 Hz, each 1H). Anal. Calcd for $C_{20}H_{19}NO_5BrI$: C, 42.88; H, 3.42; N, 2.50; I + Br, 36.91. Found: C, 42.80; H, 3.55; N, 2.36; I + Br, 36.93.

1-[2-Bromo-3,4-(methylenedioxy)benzoyl]-6,7-(methylenedioxy)-3,4-dihydroisoquinoline methiodide (17d): 89% yield; mp 231−232 °C (benzene−Et$_2$O); IR 1672, 1650, 1610, 1595, 1498 cm^{-1}; ^{1}H NMR (270 MHz) δ 3.84 (s, 3H), 6.12 (s, 2H), 6.22 (s, 2H), 6.68 (s, 1H), 6.88 (s, 1H), 7.17, 8.29 (AB type, J = 8.6 Hz, each 1H). Anal. Calcd for $C_{19}H_{15}NO_5BrI$: C, 41.94; H, 2.78; N, 2.57; I + Br, 38.00. Found: C, 41.86; H, 2.65; N, 2.60; I + Br, 37.73.

1-(2-Bromo-4,5-dimethoxybenzoyl)-6,7-dimethoxy-3,4-dihydroisoquinoline methiodide (17e): 89% yield; mp 198−200 °C (MeOH); IR 1662, 1629, 1585, 1559, 1525, 1510 cm^{-1}; ^{1}H NMR (270 MHz) δ 3.67, 3.82, 4.01, 4.02, 4.05 (each s, each 3H), 7.61, 7.15, 7.04, 6.53 (each s, each 1H). Anal. Calcd for $C_{21}H_{23}NO_5BrI$: C, 43.77; H, 4.02; N, 2.43; I + Br, 35.89. Found: C, 43.57; H, 4.08; N, 2.34; I + Br, 35.92.

1-[2-Bromo-4,5-(methylenedioxy)benzoyl]-6,7-(methylenedioxy)-3,4-dihydroisoquinoline methiodide (17f): 86% yield; mp 202−205 °C (MeOH); IR 1646, 1610 cm^{-1}; ^{1}H NMR (270 MHz) δ 3.66, 4.54 (each br s, each 2H), 3.84 (s, 3H), 6.13 (s, 2H), 6.20 (s, 2H), 6.56, 6.91, 7.17, 7.76 (each s, each 1H). Anal. Calcd for $C_{19}H_{15}NO_5BrI$: C, 41.94; H, 2.78; N, 2.57; I + Br, 38.01. Found: C, 41.84; H, 2.85; N, 2.85; I + Br, 37.92.

1-(2-Bromo-3,4-dimethoxybenzoyl)-6,7-dimethoxy-3,4-dihydroisoquinoline Benzyl Bromide (17g). General Procedure. A mixture of dihydroisoquinoline **16a** (868 mg, 2.0 mmol) and benzyl bromide (359 mg, 2.1 mL, 0.25 mmol) in CH_3CN (8 mL) was refluxed for 2.5 h and was then evaporated. A yellow glassy residue was crystallized from MeOH−Et$_2$O to give benzyl bromide **17g** as yellow crystals (1.10 g, 91%): mp 153−154 °C. IR 1666, 1617, 1598, 1573, 1553 cm^{-1}; ^{1}H NMR (270 MHz) δ 3.74, 3.90, 3.99, 4.00 (each s, each 3H), 6.75 (s, 1H), 6.85 (s, 1H), 7.31(AB type, J = 8.8 Hz, 1H), 7.40−7.46 (m, 3H), 7.53−7.58 (m, 2H), 8.73 (AB type, J = 8.8 Hz, 1H). Anal. Calcd for $C_{27}H_{27}NO_5Br_2 + H_2O$: C, 52.03; H, 4.69; N, 2.25; Br, 25.64. Found: C, 52.06; H, 4.64; N, 2.15; Br, 25.72.

1-[2-Bromo-3,4-(methylenedioxy)benzoyl]-6,7-(methylenedioxy)-3,4-dihydroisoquinoline benzyl bromide (17h): 89% yield from **16d**; mp 162−164 °C (Et$_2$O); IR 1663, 1640, 1608, 1591 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.96, 3.61, 4.31, 4.83, 5.06, 5.86 (each br s, each 1H), 6.12 (s, 2H), 6.23 (s, 2H), 6.74 (s, 1H), 6.83 (s, 1H), 7.20 (AB type, J = 8.3 Hz, 1H), 7.40−7.45 (m, 3H), 7.49−7.55 (m, 2H), 8.57 (AB type, J = 8.3 Hz, 1H). Anal. Calcd for $C_{25}H_{19}NO_5Br_2$: C, 52.38; H, 3.34; N, 2.44; Br, 27.88. Found: C, 52.52; H, 3.33; N, 2.42; Br, 28.01.

1-(2-Bromo-3,4-dimethoxybenzoyl)-6,7-dimethoxy-3,4-dihydroisoquinoline Propyl Iodide (17i). A mixture of **16a** (218 mg, 0.5 mmol) and propyl iodide (0.2 mL, 1.8 mmol) in CH_3CN (1 mL) was refluxed for 4.5 h. Evaporation of the solvent and crystallization of the residue from MeOH gave benzyl bromide **17i** as a yellow crystalline solid (288 mg, 95%): mp 95−97 °C; IR 1671, 1628, 1602, 1574, 1555, 1522 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.99 (t, J = 6.6 Hz, 3H), 1.93 (six, J = 6.6 Hz, 2H), 3.71 (s, 3H), 3.86 (t, J = 6.6 Hz, 2H), 3.90, 3.99, 4.02 (each s, each 3H), 6.66 (s, 1H), 6.92 (s, 1H), 7.24, 8.42 (AB type, J = 8.9 Hz, each 1H). Anal. Calcd for $C_{23}H_{27}NO_5BrI$: C, 45.72; H, 4.50; N, 2.32; Br + I, 34.22. Found: C, 45.52; H, 4.64; N, 2.31; Br + I, 33.97.

General Procedure for Preparation of *Erythro*-Amino Alcohols 19a−j. *erythro*-1-(2-Bromo-3,4-dimethoxy-α-hydroxybenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (19a). Method A (in MeOH). To a stirred solution of **17a** (1.728 g, 3 mmol) in MeOH (75 mL) in water bath was added $NaBH_4$ (567 mg, 15 mmol) in portions for 5 min. After the mixture was continuously stirred at room temperature for 2 h, MeOH was evaporated. The residue was dissolved in water (30 mL) and CH_2Cl_2 (30 mL). The water layer was further extracted with CH_2Cl_2 (10 mL × 2). The combined CH_2Cl_2 layers were washed with water (10 mL × 2), dried (Na_2SO_4), and then evaporated. The resultant solid (1.400 g) was found to be a 97:3 mixture of amino-alcohols **19a** and **20a** by ^{1}H NMR analysis and treated with benzene−Et$_2$O to give **19a** (1.115 mg, 83%) as colorless crystals: mp 146−148 °C; IR 3302, 3315, 1615, 1591, 1518, 1482 cm^{-1}; ^{1}H NMR (270 MHz) δ 2.52−2.66 (m, 2H), 2.59 (s, 1H), 2.75 (s, 3H), 2.95−3.16 (m, 3H), 3.23 (s, 3H), 3.82, 3.83, 3.86 (each s, each 3H), 4.06 (d, J = 2.9 Hz, 1H,), 5.33 (d, J = 2.9 Hz, 1H), 5.26 (s, 1H), 6.65 (s, 1H), 6.67, 6.72 (AB type, J = 8.8 Hz, each 1H). Anal. Calcd for $C_{21}H_{26}NO_5Br$: C, 55.76; H, 5.79; N, 3.10; Br, 17.66. Found: C, 55.59; H, 5.77; N, 3.03; Br, 17.54.

Method B (in AcOH). $NaBH_4$ (2.3 g, 10 mmol) was added to a stirred solution of **17a** (576 mg, 1 mmol) in AcOH (10 mL) in water bath in portions for 1.5 h. After being stirred for 30 min, the mixture was treated with water (50 mL) and CH_2Cl_2 (25 × mL). The combined CH_2Cl_2 layers were washed with 2 N NaOH (5 mL) and water (10 mL × 2), dried (Na_2SO_4), and then concentrated. The oily residue (470 mg) showed no signals owing to **20a** in its ^{1}H NMR spectrum and was treated with benzene−Et$_2$O to give **19a** (398 mg, 89%), mp 146−148 °C.

Other solvent systems did not show significant selectivities [MeOH−THF (1:2), 46:54 for **19a**:**20a**; MeOH−DMSO (1:1), 50:50; DMF, 50:50; i-PrOH, 60:40].

***erythro*-1-(2-Bromo-3,4-dimethoxy-α-hydroxybenzyl)-2-methyl-6,7-(methylenedioxy)-1,2,3,4-tetrahydroisoquinoline (19b):** 92% yield (method B), mp 148−150 °C (MeOH−Et$_2$O); IR 3550, 1611, 1513 cm^{-1}; ^{1}H NMR (270 MHz) δ 2.55−2.70 (m, 2H), 2.74 (s, 3H), 2.90−3.20 (m, 2H), 3.35 (s, 3H), 3.83 (s, 3H), 4.00 (d, J = 3.0 Hz, 1H), 5.29 (d, J = 3.0 Hz, 1H), 5.40 (s, 1H), 6.04 (s, 2H), 6.57 (s, 1H), 6.51, 6.63 (AB type, J = 8.2 Hz, each 1H). Anal. Calcd for $C_{20}H_{22}NO_5Br$: C, 55.06; H, 5.08; N, 3.21; Br, 18.31. Found: C, 54.85; H, 4.94; N, 3.19; Br, 18.38.

***erythro*-1-[2-Bromo-3,4-(methylenedioxy)-α-hydroxybenzyl]-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (19c):** 92% yield (method A); mp 146−147 °C (MeOH−Et_2O); IR 3100, 1592, 1503 cm^{-1}; ^1H NMR (270 MHz) δ 2.50−2.63 (m, 2H), 2.72 (s, 3H), 2.88−3.16 (m, 2H), 3.86 (s, 3H), 3.89 (s, 3H), 3.97 (d, J = 3.3 Hz, 1H), 5.30 (d, J = 3.3 Hz, 1H), 5.29 (s, 1H), 5.76, 5.80 (each d, J = 1.5 Hz, each 1H), 6.54 (s, 1H), 6.72, 6.77 (AB type J = 8.7 Hz, each 1H). Anal. Calcd for $C_{20}H_{22}NO_5Br$: C, 55.06; H, 5.08; N, 3.21; Br, 18.31. Found: C, 54.97; H, 5.03; N, 3.20; Br, 18.03.

***erythro*-1-[2-Bromo-3,4-(methylenedioxy)-α-hydroxybenzyl]-2-methyl-6,7-(methylenedioxy)-1,2,3,4-tetrahydroisoquinoline (19d):** 80% yield (method B); mp 187−189 °C (benzene−Et_2O); IR 3570, 3080, 1617, 1500, 1489 cm^{-1}; ^1H NMR (270 MHz) δ 2.53−2.62 (m, 2H), 2.72 (s, 3H), 2.92−3.17 (m, 2H), 3.94 (d, J = 3.0 Hz, 1H), 5.26 (d, J = 3.0 Hz, 1H), 5.37 (s, 1H), 5.78, 5.82 (each d, J = 1.3 Hz, each 1H), 6.06, 6.10 (each d, J = 1.5 Hz, each 1H), 6.55 (s, 1H), 6.53, 6.65 (AB type J = 8.3 Hz, each 1H). Anal. Calcd for $C_{19}H_{18}NO_5Br$: C, 54.30; (H, 4.32; N, 3.33; Br, 19.02. Found: C, 54.12; H, 4.25; N, 3.26; Br, 19.32.

***erythro*-1-(2-Bromo-4,5-dimethoxy-α-hydroxybenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (19e):** 87% yield (method B); mp 141−142 °C (MeOH); IR 3540, 1612, 1600, 1571, 1519, 1499 cm^{-1}; ^1H NMR (270 MHz) δ 2.53−2.66 (m, 2H), 2.75 (s, 3H), 3.96−3.15 (m, 2H), 3.28, 3.57, 3.82, 3.87 (each s, each 3H), 4.00 (d, J = 3.0 Hz, 1H), 5.29 (d, J = 3.0 Hz, 1H), 5.39 (s, 1H), 6.49 (s, 1H), 7.06 (s, 1H). Anal. Calcd for $C_{21}H_{26}NO_5Br$: C, 55.76; H,5.79; N, 3.10; Br, 17.68. Found: C, 55.60; H, 5.76; N, 3.06; Br, 17.51.

***erythro*-1-[2-Bromo-4,5-(methylenedioxy)-α-hydroxybenzyl]-2-methyl-6,7-(methylenedioxy)-1,2,3,4-tetrahydroisoquinoline (19f):** 92% yield (method B); mp 169−171 °C (MeOH); IR 3584, 1621, 1610, 1503, 1471 cm^{-1}; ^1H NMR (270 MHz) δ 2.51−2.61 (m, 2H), 2.69 (s, 3H,), 2.88−3.13 (m, 2H), 3.96 (d, J = 3.0 Hz, 1H), 5.22 (d, J = 3.0 Hz, 1H), 5.42 (s, 1H), 5.80 (s, 2H), 5.92 (s, 2H), 6.51 (s, 1H), 6.55 (s, 1H), 7.02 (s, 1H). Anal. Calcd for $C_{19}H_{18}NO_5Br$: C, 54.30; H, 4.32; N, 3.33; Br, 19.02. Found: C, 54.32; H, 4.44; N, 3.22; Br, 19.26.

***erythro*-2-Benzyl-1-(2-bromo-3,4-dimethoxy-α-hydroxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (19g):** 88% yield (method B); mp 137−139 °C (benzene−Et_2O); IR 3530, 1609, 1594, 1514 cm^{-1}; ^1H NMR (270 MHz) δ 2.42−2.60 (m, 2H), 2.83−2.98 (m, 1H), 3.13−3.23 (m, 1H), 3.28, 3.82, 3.84, 3.87 (each s, each 3H), 3.79 (d, J = 13.2 Hz, 1H), 4.38 (d, J = 13.2 Hz, 1H), 4.32 (d, J = 3.3 Hz, 1H), 5.37 (s, 1H), 5.42 (d, J = 3.3 Hz, 1H), 6.57 (s, 1H), 6.69, 6.73 (AB type, J = 8.8 Hz, each 1H). Anal. Calcd for $C_{27}H_{30}NO_5Br$: C, 61.37; H, 5.72; N, 2.65; Br, 15.12. Found: C, 61.55; H, 5.73; N, 2.49; Br, 15.06. Crystallization from MeOH gave colorless crystals containing one molar equiv of MeOH, mp 80−82 °C; ^1H NMR (270 MHz) δ 3.48 (br s, 3H). Anal. Calcd for $C_{27}H_{30}NO_5Br{\cdot}CH_3OH$: C, 60.00; H, 6.11; N, 2.50; Br, 14.26. Found: C, 59.83; H, 6.11; N, 2.34; Br, 14.44.

***erythreo*-2-Benzyl-1-[2-bromo-3,4-(methylenedioxy)-α-hydroxybenzyl]-6,7-(methylenedioxy)-1,2,3,4-tetrahydroisoquinoline (19h):** 95% yield (method B); mp 77−79 °C (benzene−hexane); IR 3530, 1594, 1514, 1486 cm^{-1}; ^1H NMR (270 MHz) δ 2.47−2.63 (m, 2H), 2.74−2.92, 3.12−3.30 (m, each 1H), 3.78, 4.23 (AB type, J = 13.7 Hz, each 1H), 5.33 (d, J = 3.3 Hz, 1H), 5.57 (s, 1H), 5.80, 5.83 (each d, J = 1.5 Hz, each 1H), 6.06, 6.10 (each d, J = 1.2 Hz, each 1H), 6.17 (s, 1H), 6.55, 6.65 (AB type, J = 8.3 Hz, each 1H), 7.26−7.41 (m, 5H). Anal. Calcd for $C_{25}H_{22}NO_5Br$: C, 60.50; H, 4.47; N, 2.82; Br, 16.10. Found: C, 60.46; H, 4.49; N, 2.62; Br, 16.38.

***erythro*-1-(2-Bromo-3,4-dimethoxy-α-hydroxybenzyl)-6,7-dimethoxy-2-propyl-1,2,3,4-tetrahydroisoquinoline (19i):** 85% yield (method A); mp 95−97 °C (EtOH−hexane); IR 3390, 1610, 1594, 1517, 1488 cm^{-1}; ^1H NMR (270 MHz) δ 1.01 (t, J = 7.4 Hz, 3H), 1.65 (six, J = 7.4 Hz, 2H), 2.43−2.65 (m, 2H), 2.56−3.06 (m, 4H), 3.24, 3.82, 3.83, 3.87 (each s, each 3H), 4.16, 5.24 (d, J = 3.2 Hz, each 1H), 6.57 (s, each 1H), 6.64, 6.70 (AB type, J = 8.7 Hz, each 1H). Anal. Calcd for $C_{23}H_{30}NO_5Br$: C, 57.51; H, 6.29; N, 2.92; Br, 16.63. Found: C, 57.51; H, 6.30; N, 2.78; Br, 16.86.

***erythro*-1-(2-Bromo-3,4-dimethoxy-α-hydroxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (19j):** 80% yield (method A from **16a**); mp 153−155 °C (MeOH−Et_2O); IR 3302, 1607, 1590, 1512, 1485 cm^{-1}; ^1H NMR (400 MHz) δ 2.58−2.65 (m, 1H), 2.85−3.00 (m, 2H), 3.30−3.38 (m, 1H), 3.41, 3.84, 3.86, 3.87 (s, each 3H), 4.64, 5.12 (AB type J = 3.9 Hz, each 1H), 5.76, 6.58 (each s, each 1H), 6.83, 7.02 (AB type J = 8.3 Hz, each 1H). Anal. Calcd for $C_{20}H_{24}NO_5Br$: C, 54.81; H, 5.52; N, 3.20; Br, 18.23. Found: C, 54.66; H, 5.52; N, 3.18; Br, 18.09.

Reduction of Methiodide 17a by Catalytic Hydrogenation in the Presence of Adams Catalyst. General Procedure for Preparation of Ketones 18a and 18d. A stirred solution of **17a** (288 mg, 0.5 mmol) in MeOH (20 mL) was hydrogenated in the presence of PtO_2 (11.4 mg, 0.05 mmol) at 17 °C. Consumption of hydrogen ceased (16.0 mL, 1.04 M) 3 h later. The catalyst and solvent were removed, and the residue was dissolved in CH_2Cl_2 (20 mL), washed with water (20 mL), and dried (Na_2SO_4). Evaporation of the solvent gave the crude ketone **18a** (206 mg, 92%) as a colorless oil: IR (neat) 1674, 1608, 1585, 1520 cm^{-1}; ^1H NMR (270 MHz) δ 2.44 (s, 3H), 2.55−3.30 (m. 4H), 4.42 (s, 1H), 6.59, 6.65 (s, each 1H), 6.68, 7.21 (AB type, J = 8.4 Hz, each 1H); MS m/z (rel int) 451 (M^+, 0.5), 449 (M^+, 0.9), 206 {[M − $COC_6H_2(OCH_3)_2Br]^+$, 100}; HRMS m/z 449.0827 (calcd for $C_{21}H_{24}NO_5Br$: 449.0838). This oil was gradually decomposed in air to *N*-methylcorydaldine and 2-bromo-3,4-dimethoxybenzoic acid, as described below.

1-[2-Bromo-3,4-(methylenedioxy)benzoyl]-6,7-(methylenedioxy)-2-methyl-1,2,3,4-tetrahydroisoquinoline (18d): 90% yield from **17d**; mp 149−150 °C (MeOH−Et_2O); IR 1679, 1604, 1597, 1503 cm^{-1}; ^1H NMR (90 MHz) δ 2.40 (s, 3H), 2.50−3.20 (m, 4H), 4.35 (s, 1H), 5.89 (s, 2H), 6.05 (s, 2H), 6.59 (s, 1H), 6.61 (s, 1H), 6.59, 7.21 (AB type, J = 8.1 Hz, each 1H). Anal. Calcd for $C_{19}H_{16}NO_5Br$: C, 54.56; H, 3.86; N, 3.35; Br, 19.10. Found: C, 54.50; H, 3.76; N, 3.22; Br, 19.30.

Treatment of Methiodides 17a and 17d with 1 Mol Equiv of $NaBH_4$ in MeOH. From 17a: To a stirred solution of **17a** (288 mg, 0.5 mmol) in MeOH (16 mL) was added $NaBH_4$ (19 mg, 0.5 mmol). After 2 h, the mixture was worked up in the same manner as those noted above for reduction of **17a** using excess $NaBH_4$. The crude products (225 mg) were found to comprise essentially **18a** and **19a** in a 70:30 ratio by ^1H NMR analysis. Attempts to isolate **18a** by preparative TLC were unsuccessful.

From 17d: A similar treatment of **17d** (544 mg, 1 mmol), followed by two crystallizations of the crude reaction products (400 mg) from MeOH−Et_2O, gave ketone **18d** (233 mg, 56%), mp 149−150 °C.

$NaBH_4$ Reduction of 18a. 1-Benzoyltetrahydroisoquinoline **18a** (30 mg, 0.067 mmol) was treated with $NaBH_4$ (9 mg, 0.237 mmol) in method A. The crude product, a solid (30 mg), was found to be essentially *erythro*-amino alcohol (**19a**) in a 16:1 mixture of **19a** and **20a**. A fractional crystallization from benzene−hexane gave **19a** (27 mg, 90%) as colorless crystals, mp 146−148 °C.

$NaBH_4$ Reduction of 18d. 1-Benzoyltetrahydroisoquinoline **18d** (125 mg, 0.3 mmol) was treated with $NaBH_4$ (67 mg, 1.5 mmol) in method B. Recrystallization of the product (138 mg) from benzene−Et_2O gave *erythro*-amino alcohol **19d** (101 mg, 80%), mp 187−189 °C.

Treatment of 18a with Oxygen. Oxygen gas was introduced to a solution of the aforementioned crude ketone **18a** (30 mg) in MeOH for 1 h. After evaporation of MeOH, the residue was shaken with a mixture of CH_2Cl_2 (5 mL) and 0.5 N NaOH (4 mL). The CH_2Cl_2 layer was washed with water (5 mL), dried over anhydrous Na_2SO_4, and evaporated to dryness. The crude product was crystallized from petroleum ether to give *N*-methylcorydaldine (12 mg, 81%), mp 126−127 °C (lit.[30a] mp 123−124 °C;[27b,30b] 125−126 °C). The alkaline layer was once washed with CH_2Cl_2 (5 mL) and then acidified with 0.5 N HCl solution (2 mL). The resultant solid was collected and recrystallized from EtOH to give 2-bromo-3,4-dimethoxybenzoic acid (13 mg, 75%) as colorless crystals: mp 201−203 °C; IR 1700, 1694, 1665, 1588, 1563, 1491 cm^{-1}; ^1H NMR (90 MHz,

$CDCl_3$−DMSO-d_6) δ 3.84, 3.92 (each s, each 3H), 4.63 (br s, 1H), 6.87, 7.71 (AB type, J = 8.8 Hz, each 1H). Anal. Calcd for $C_9H_{90}O_4Br$: C, 41.40; H, 3.48; Br, 30.61. Found: C, 41.17; H, 3.52; Br, 30.40.

This acid was obtained in 76% yield by treatment of 2-bromo-3,4-dimethoxybenzaldehyde[26] (37 mg, 0.15 mmol) with Jones reagent (0.5 mL) in acetone (10 mL) at room temperature for 80 min.

Treatment of 19a with $CuCl_2$. A mixture of **19a** (23 mg, 0.05 mmol) and $CuCl_2$ (13.4 mg, 0.1 mmol) in toluene (1 mL) was heated in a test tube with shaking in an oil bath at 140 °C for 2 min. During this time, the color of the solution turned to green and then yellow, and it finally became colorless. The toluene layer, which was separated from the insoluble materials, was washed once with water (2 mL) and dried (Na_2SO_4). Toluene was evaporated to give 2-bromo-3,4-dimethoxybenzaldehyde as a crystalline solid (10 mg, 81%). The insoluble residue was dissolved in MeOH (4 mL), and then $NaBH_4$ (10 mg, 0.26 mmol) was added. After the mixture was stirred at room temperature for 2 h, MeOH was evaporated. The residue was extracted with CH_2Cl_2 (3 mL) and water (5 mL). The organic layer was washed with water (5 mL), dried (Na_2SO_4), and concentrated to give an oil (10 mg, 93%), which was identical in all respects with an authentic sample of 6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline.[31]

$LiAlH_4$ Reduction of Methiodide 17a. General Procedure. To a stirred solution of **17a** (288 mg, 0.5 mmol) in dry THF (50 mL) was added $LiAlH_4$ (40 mg, 1.0 mmol) at once. After 5 min, THF (5 mL) containing 1 mL of water was added to the stirred reaction mixture, which was then allowed to be stirred for 30 min. Precipitates were removed by suction filtration, and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (15 mL) and washed with water (10 mL). The CH_2Cl_2 layer was dried (Na_2SO_4) and concentrated to give an oil (233 mg), which comprised *erythro*- and *threo*-amino alcohols **19a** and **20a** (29:71) (>90%).

This was treated with acetic anhydride (1 mL) and pyridine (0.2 mL) at room temperature overnight, and then EtOH (5 mL) was added to decompose excess acetic anhydride. The solvents were removed by azeotropic distillation using benzene. The residue was dissolved in benzene (10 mL), washed with 5% $NaHCO_3$ solution (2 mL) and water (10 mL × 2), and dried (Na_2SO_4). Evaporation of the solvent gave an oil (271 mg), which was subjected to preparative TLC on silica gel (5% MeOH−CH_2Cl_2). A band with R_f 0.7 gave acetate of **19a** (63 mg) [IR (neat) 1745, 1683, 1596, 1518, 1490 cm^{-1}: ^1H NMR (270 MHz) δ 2.02, 2.60, 3.51, 3.85, 3.86, 3.87 (each s, each 3H), 3.96 (d, J = 4.4 Hz, 1H), 6.37 (d, J = 4.4 Hz, 1H), 5.82 (s, 1H), 6.60 (s, 1H), 6.72, 6.78 (AB type, J = 8.8 Hz, each 1H). MS m/z (rel int) 494, 492 [each $(M - H)^+$, each 0.04], 436, 434 [each $(M - OAc)^+$, each 0.80], 435, 433 [each $(M - HOAc)^+$, 2.4], 420, 418 [each $(M - HOAc - CH_3)^+$, 1.2], 206 [$(M$ − benzoyl group$)^+$, 100]. HRMS m/z 494.1001 (calcd for $C_{23}H_{27}O_6NBr$; 494.0974]. A less mobile band with R_f 0.5 gave acetate of **20a** (127 mg) [IR (neat) 1738, 1681, 1612, 1596, 1518, 1491 cm^{-1}: ^1H NMR (270 MHz) δ 2.06, 2.40, 3.55, 3.74, 3.83, 3.86 (each s, each 3H), 3.83 (partially hiding d, J = 6.6 Hz, 1H), 6.36 (d, J = 6.6 Hz, 1H), 6.04 (s, 1H), 6.53 (s, 1H), 6.85, 7.06 (AB type, J = 8.8 Hz, each 1H); EI-MS m/z (rel int) 494, 492 [each $(M - H)^+$, each 0.02), 436, 434 [each $(M - OAc)^+$, each 0.3], 206 [$(M$ − benzoyl group$)^+$, 100]; HRMS m/z 492.1001 (calcd for $C_{23}H_{27}O_6NBr$: 492.1021). Acetate of **19a** was dissolved in 5% KOH−MeOH (2 mL) and was heated to 50 °C for 5 min. MeOH was then evaporated, and the residue was treated with water (5 mL) and CH_2Cl_2 (10 mL × 3). The extracts were washed with water (10 mL), dried (Na_2SO_4), and evaporated. The resultant crude oily product (49 mg) was crystallized from benzene−Et_2O to give **19a** (41 mg, 16%), mp 146−148 °C. A similar treatment of acetate of **20a** afforded the crude alcohol (101 mg), which was crystallized from benzene−Et_2O to give **20a** (91 mg, 36%); mp 133−135 °C; IR 3380, 1609, 1596, 1516 cm^{-1}; ^1H NMR (270 MHz) δ 2.51 (s, 3H), 2.58−2.63 (m, 1H), 2.83−3.02 (m, 3H), 3.37 (s, 3H), 3.43 (d, J = 8.4 Hz, 1H), 3.75, 3.82, 3.89 (each s, each 3H), 4.99 (d, J = 8.4 Hz, 1H), 5.59 (s, 1H), 6.55 (s, 1H), 6.99, 7.41 (AB type, J = 8.8 Hz, each 1H). Anal. Calcd for $C_{21}H_{26}NO_5Br$: C, 55.76; H, 5.79; N, 3.10; Br, 17.66. Found: C, 55.78; H, 5.69; N, 2.98; Br, 17.54.

$LiAlH_4$ Reduction of 17b: 19b and **20b** (33:67) >90% yield; ^1H NMR spectrum (270 MHz) for *threo*-amino alcohol **20b**; δ 2.56 (s, 3H), 2.48−2.60 (m, 1H), 2.84−3.04 (m, 2H), 3.33−3.51 (m, 1H), 3.42 (d, J = 8.3 Hz, 1H), 3.42 (s, 3H), 3.83 (s, 3H), 4.91 (d, J = 8.3 Hz, 1H), 5.60 (s, 1H), 6.00 (dd, J = 8.9, 1.2 Hz, 2H), 6.56 (s, 1H), 6.88, 7.20 (AB type, J = 8.3 Hz, each 1H).

$LiAlH_4$ Reduction of 17c: 19c and **20c** (17:83) >90% yield; ^1H NMR spectrum (270 MHz) for *threo*-amino alcohol **20c**; δ 2.47 (s, 3H), 2.50−2.63 (m, 1H), 2.76−2.99 (m, 2H), 3.35−3.47 (m, 1H), 3.37 (d, J = 8.6 Hz, 1H), 3.77 (s, 3H), 3.91 (s, 3H), 4.96 (d, J = 8.6 Hz, 1H), 5.56 (s, 1H), 5.79 (dd, J = 4.0, 1.3 Hz, 2H), 6.54 (s, 1H), 6.98, 7.40 (AB type, J = 8.6 Hz, each 1H).

$LiAlH_4$ Reduction of 17d: 19d and **20d** (25:75) >90% yield; ^1H NMR spectrum (270 MHz) for *threo*-amino alcohol **20d**; δ 2.47 (s, 3H), 2.52−2.65 (m, 1H), 2.76−2.99 (m, 2H), 2.76−2.99 (m, 2H), 3.31−3.49 (m, 1H), 3.45 (d, J = 8.6 Hz, 1H), 4.84 (d, J = 8.6 Hz, 1H), 5.71 (s, 1H), 5.83 (dd, J = 7.3, 1.3 Hz, 2H), 6.04 (dd, J = 7.6 Hz, 2H), 6.55 (s, 1H), 6.87, 7.15 (AB type J = 8.3 Hz, each 1H).

$LiAlH_4$ Reduction of 18a. To a stirred solution of **18a** (12 mg, 0.027 mmol) in dry THF (2 mL) was added $LiAlH_4$ (2 mg, 0.053 mmol) at once in an atmosphere of N_2. After 30 min, workup in the same manner as that noted above for $LiAlH_4$ reduction of **17a** gave an oil (12 mg), which was found to be a mixture of **19a** and **20a** in a ratio of 28:72.

Reduction of Methiodide 17a with DIBALH. To a stirred solution of methiodide **17a** (28 mg, 0.05 mmol) in dry CH_2Cl_2 (5 mL) was added DIBALH (1.5 M in hexane, 0.133 mL, 0.2 mmol, Aldrich) under argon. After 30 min, water (0.1 mL) was added, and the mixture was allowed to be stirred for 30 min. Precipitates were removed by suction filtration, and the filtrate was concentrated. The residue was dissolved in CH_2Cl_2 (2 mL) and washed with water (3 mL). Dryness (Na_2SO_4) and evaporation of the solvent gave an oil (16 mg, ca. 100%), which comprised **19a** and **20a** in a ratio of 76:24.

Reduction of Methiodide 17a with Sodium Bis(2-methoxyethoxy)aluminum Hydride. To a stirred solution of methiodide **17a** (28 mg, 0.05 mmol) in dry THF (5 mL) was added sodium bis(2-methoxyethoxy)aluminum hydride (3.5 M in toluene, 0.057 mL, 0.2 mmol, Nippon Alkylaluminum Co.) in an atmosphere of argon. After 5 min, THF (1 mL) containing 0.2 mL of water was added, and the mixture was allowed to be stirred for 30 min. Precipitates were removed by suction filtration, and the filtrate was concentrated. The residue was dissolved in CH_2Cl_2 (2 mL), washed with water (3 mL), and dried (Na_2SO_4). Evaporation of the solvent gave an oil (23 mg, ca. 100%), which comprised **19a** and **20a** in a ratio of 40:60.

General Procedure for Synthesis of *Erythro*-Phthalideisoquinoline Alkaloides 1a−f and the *N*-Benzyl Derivatives 1g and 1h by Palladium(0)-Catalyzed Carbonylation of *Erythro*-Amino Alcohols 19a−h. Synthesis of (±)-Cordrastine-II (1a). A stirred mixture of **17a** (45 mg, 0.1 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), PPh_3 (10.5 mg, 0.04 mmol), K_2CO_3 (276 mg, 2 mmol), and Me_3SiCl (22 mg, 0.2 mmol) in toluene (2 mL) was refluxed in an atmosphere of carbon monoxide for 24 h in a manner similar to that described for carbonylation of benzyl alcohol **5a**. Precipitates were removed by suction filtration through a Celite pad, and the filtrate was concentrated to give an oily residue (60 mg), ^1H NMR analysis of which revealed that this was essentially a mixture of **1a**, PPh_3, and its oxide. The starting material was not detected. This was dissolved in MeOH (5 mL) containing 5% KOH and refluxed for 5 min. MeOH was removed on a rotary eveporator, and then water (5 mL) was added to the residue, which was washed with CH_2Cl_2 (3 mL × 2). The water layer, after addition of 2 N HCl (2 mL), was allowed to stand at room temperature for 3 h and was then basified with aqueous 2 N NaOH by adjusting to pH 9 and extracted with CH_2Cl_2 (3 mL × 3). The combined CH_2Cl_2 layers were washed with water (7 mL), dried (Na_2SO_4), and evaporated. The residue (43 mg) was crystallized from MeOH to give (±)-

cordrastine II (**1a**), (39 mg, 98%), as colorless crystals; mp 117−119 °C from MeOH (lit.[55] mp 110−114 °C;[34] 112−115 °C;[56] 117−118 °C;[33] 117−119 °C;[57] 118−119 °C). ^{1}H NMR (270 MHz) δ 2.30−2.40 (m, 1H), 2.58 (s, 3H), 2.55−2.70 (m, 2H), 2.90−3.00 (m, 1H), 3.67, 3.87, 3.88, 4.03 (each s, each 3H), 4.02, (d, J = 3.3 Hz, 1H), 5.54 (d, J = 3.3 Hz, 1H), 6.19 (s, 1H), 6.54 (s, 1H), 6.56, 7.09 (AB type, J = 8.3 Hz, each 1H).[12e,33,34,55,56,58,59]

(±)-Corlumine (1b): 80% yield from **19b**; mp 178−181 °C (MeOH) (lit.[34] 173−176 °C;[60] 174 °C;[61] 175−176 °C;[5,62] 178−181 °C;[63] 193.5−195 °C; ^{1}H NMR (270 MHz) δ 2.28−2.40 (m, 1H), 2.55−2.70 (m, 2H), 2.92−3.03 (m, 1H), 2.59 (s, 1H), 3.69 (s, 6H), 4.11 (d, J = 3.3 Hz, 1H), 5.67 (d, J = 3.3 Hz, 1H), 6.15 (s, 2H), 6.38 (s, 1H), 6.60 (s, 1H), 6.28, 6.95 (AB type, J = 7.9 Hz, each 1H).[10d,h,64]

(±)-*β*-Hydrastine (1c): 80% yield from **19c**; mp 135−137 °C (MeOH) (lit.[12a] mp 135 °C;[62] 136−140 °C;[10c] 135−137 °C;[65] 137−138 °C;[57,66] 138−139 °C;[67] 138−140 °C;[5] 150−151 °C;[11b,c] 151−152 °C). ^{1}H NMR (270 MHz) δ 2.22−2.32 (m, 2H), 2.42−2.65 (m, 2H), 2.85−2.94 (m, 1H), 2.55, 3.89, 4.06 (each s, each 3H), 3.99, (d, J = 3.6 Hz, 1H), 5.48 (d, J = 3.6 Hz, 1H), 5.90 (s, 2H), 6.38 (s, 1H), 6.58 (s, 1H), 6.52, 7.08 (AB type, J = 8.2 Hz, each 1H).[10c,56,64]

(±)-Bicuculline (1d): 85% yield from **19d**; mp 227−229 °C (MeOH−Et_2O) (lit.[68] mp 215 °C;[61] 215−216 °C;[60] 216 °C;[62] 217−220 °C;[5] 227−229 °C). ^{1}H NMR (270 MHz) δ 2.22−2.30 (m, 1H), 2.52−2.62 (m, 2H), 2.84−2.91 (m, 1H), 2.55 (s, 3H), 4.04, 5.56 (each d, J = 4.0 Hz, each 1H), 5.93 (d, J = 1.0 Hz, 1H), 6.16 (d, J = 1.7 Hz, 2H), 6.20, 6.92 (AB type, J = 7.9 Hz, each 1H), 6.46 (s, 1H), 6.58 (s, 1H).[12e,69]

(±)-Isocordrastine II (1e): 87% yield from **19e**; mp 167−169 °C (EtOH) (lit.[70] mp 157−159 °C;[59,71] 166−167 °C;[5] 167−169 °C;[62] 169−170 °C;[67] 169−171 °C;[72] 170−171 °C). ^{1}H NMR (270 MHz) δ 2.28−2.40 (m, 1H), 2.57−2.72 (m, 2H), 2.93−3.03 (m, 1H), 2.60 (s, 3H), 3.72, 3.79, 3.86, 3.91 (each s, each 3H), 4.12, 5.58 (each d, J = 4.0 Hz, each 1H), 6.23, 6.42, 6.62, 7.23 (each s, each 1H).[59,70−72]

(±)-Isobicuculline (1f): 89% yield from **19f**; mp 166−169 °C (MeOH−Et_2O); IR 1752, 1613, 1502 cm^{-1}; ^{1}H NMR (270 MHz) δ 2.27−2.43 (m, 1H), 2.58−2.64 (m, 2H), 2.91−2.98 (m, 1H), 2.53 (s, 3H), 3.93 (d, J = 4.6 Hz, 1H), 5.43 (d, J = 4.6 Hz, 1H), 5.92 (s, 2H), 6.08 (d, J = 4.9 Hz, 2H), 6.33, 6.50, 6.60, 7.17 (each s, each 1H). MS m/z (rel int) 190 (100). Anal. Calcd. for $C_{20}H_{17}NO_6$; C, 65.39; H, 4.66; N, 3.81. Found: C, 65.49; H, 4.58; N, 3.80.

***N*-Benzyl *erythro*-lactone 1g:** 91% yield from **19g**; mp 119−120 °C (MeOH−Et_2O); IR 1757, 1610, 1602, 1517, 1498 cm^{-1}; ^{1}H NMR (270 MHz) δ 2.24−2.45 (m, 1H), 2.65−2.83 (m, 2H), 2.90 (m, 1H), 3.81, 4.18 (AB type, J = 13.7 Hz, each 1H), 3.65, 3.87, 3.88, 4.04 (each s, each 3H), 4.16, 5.64 (each d, J = 3.7 Hz, each 1H), 6.19 (s, 1H), 6.62 (s, 1H), 6.57, 7.10 (AB type, J = 8.4 Hz, each 1H), 7.23−7.40 (m, 5H). Anal. Calcd for $C_{28}H_{29}NO_6$: C, 70.72; H, 6.15; N, 2.95. Found: C, 70.65; H, 6.16; N, 3.00.

***N*-Benzyl *erythro*-lactone 1h: 85**% yield from **19h**; mp 195−196 °C (MeOH−Et_2O) (lit.[5] mp 194−196 °C). This compound was identified on direct comparison with an authentic sample prepared by us.[5]

Palladium(0)-Catalyzed Carbonylation of *Threo*-Amino Alcohol 20a. Synthesis of (±)-Cordrastine I (2a). In a manner similar to the above, the aforementioned *threo*-alcohol **20a** (23 mg) was converted to (±)-cordrastine I (**2a**) (18 mg, 90%), mp 155−156 °C (MeOH) (lit.[34] mp 153−157 °C;[33] 154−155 °C;[57] 155−156 °C;[55,56,58,69] 156−157 °C). ^{1}H NMR (400 MHz) δ 2.30−2.40 (m, 1H), 2.55−2.70 (m, 2H), 3.00−3.10 (m, 1H), 2.65 (s, 3H), 3.71, 3.81, 3.82, 3.90 (each s, each 3H), 4.03, (d, J = 3.3 Hz, 1H), 5.51 (d, J = 3.3 Hz, 1H), 6.36, 6.69 (each s, each 1H), 7.00, 7.31 (AB type, J = 8.3 Hz, each 1H).[12e,33,55,56,58]

General Procedure for Synthesis of *Threo*-Phthalideisoquinoline Alkaloids 2a−d. Synthesis of (±)-Cordrastine I (2a). A stirred mixture (92 mg, 0.2 mmol) of *erythro*-(**19a**) and *threo*-alcohols (**20a**) in a ratio of 2:5 [prepared almost quantitatively by treatment of **17a** (119 mg, 0.2 mmol) with $LiAlH_4$ (15.2 mg, 0.4 mmol) in dry THF (20 mL) for 5 min], $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), PPh_3 (21.0 mg, 0.08 mmol), K_2CO_3 (552 mg, 4 mmol), and Me_3SiCl (44 mg, 0.4 mmol) in toluene (3 mL) was refluxed in an atmosphere of carbon monoxide for 24 h. The reaction mixture was allowed to be cooled to room temperature and filtered through a Celite pad. Toluene was removed on a rotary evaporator, and the residue was treated with water (10 mL) and CH_2Cl_2 (5 mL × 3). The organic layers were washed with water (10 mL), dried over anhydrous Na_2SO_4, and concentrated. An oily residue (148 mg, **19a**:**20a** = 29:71) was separated by preparative TLC (5% MeOH−CH_2Cl_2). A band with R_f 0.9 gave (±)-cordrastine I (**2a**, 50 mg, 62.5%) and another band with R_f 0.5 gave (±)-cordrastine II (**1a**, 18 mg, 22.5%).

(±)-Adlumine (2b): 60% yield; mp 195−198 °C (MeOH−$CHCl_3$) (lit.[34] mp 187−189 °C;[61] 189−190 °C;[63] 190 °C;[60] 191 °C;[62] 191.5−193.5 °C). ^{1}H NMR (270 MHz) δ 2.35−2.85 (m, 3H), 2.64 (s, 3H), 3.03−3.10 (m, 1H), 3.76 (s, 3H), 3.81 (s, 3H), 4.08, (d, J = 3.3 Hz, 1H), 5.68 (d, J = 3.3 Hz, 1H), 6.07 (s, 2H), 6.38 (s, 3H), 6.70 (s, 1H), 6.88, 7.17 (AB type, J = 7.9 Hz, each 1H).[64]

(±)-α-Hydrastine (2c): 74% yield, mp 152−154 °C (MeOH) (lit.[12a] mp 150 °C;[65] 150−151 °C;[62] 150−154 °C;[57,66] 151−152 °C). ^{1}H NMR (270 MHz) δ 2.40−2.80 (m, 3H), 2.55 (s, 3H), 3.00−3.10 (m, 1H), 3.84 (s, 3H), 3.98 (s, 3H), 4.00, (d, J = 3.3 Hz, 1H), 5.54 (d, J = 3.3 Hz, 1H), 5.78, 5.83 (each d, J = 1.3 Hz, each 1H), 6.37 (s, 1H), 6.65 (s, 1H), 7.04, 7.29 (AB type, J = 8.3 Hz, each 1H).[64]

(±)-Adlumidine (Capnoidine) (2d): (Capnoidine is optical antipode of adlumidine): 63% yield; mp 201−203.5 °C (MeOH−$CHCl_3$) (lit.[61] mp 198−199 °C;[62] 200−203 °C;[60] 199 °C). ^{1}H NMR (270 MHz) δ 2.40−2.80 (m, 1H), 2.53 (s, 3H), 3.00−3.10 (m, 1H), 4.03, (d, J = 3.3 Hz, 1H), 5.62 (d, J = 3.3 Hz, 1H), 5.84 (s, 2H), 6.10 (s, 2H), 6.40 (s, 1H), 6.67 (s, 1H), 6.94, 7.14 (AB q, J = 7.9 Hz, each 1H).[12e,73,74]

General Procedure for Hydrogenolysis of *N*-Benzyl Lactone 1g and 1h. Synthesis of (±)-Norcordrastine II (1j). A suspension of *N*-benzyl lactone **1g** (10 mg, 0.02 mmol) and 10% Pd−C (10 mg) in AcOEt (2 mL) was stirred in an atmosphere of hydrogen at room temperature for 8 h. Filtration of the catalyst and evaporation of the solvent in vacuo gave an oily residue, which was dissolved in CH_2Cl_2 (3 mL),

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washed with water (5 mL), and dried (Na_2SO_4). The solvent was evaporated to give (±)-norcordrastine II (**1j**) as a colorless oil [9 mg, lit.[33] mp 180−182 °C;[70] 183−185 °C;[34] 202−204 °C (HCl salt)], which appeared as one spot on silica gel TLC (5% MeOH−CH_2Cl_2, R_f 0.4). IR (neat) 1757 cm^{-1}; ^1H NMR (90 MHz) δ 2.43−2.60, 2.71−2.91 (m, each 2H), 3.82, 3.85, 3.89, 4.08 (each s, each 3H), 4.69 (d, J = 3.6 Hz, 1H), 5.72 (d, J = 3.6 Hz, 1H), 6.62 (s, 1H), 6.68 (s, 1H), 6.15, 6.97 (d, J = 8.2 Hz, each 1H).[33,34]

(±)-Norbicuculline 1k: 87% yield from **1h**; a colorless oil; IR (film) 3360, 1763, 1649, 1616, 1503, 1477 cm^{-1}; ^1H NMR (270 MHz) δ 2.40−2.58, 2.75−2.90 (each m, each 2H), 4.71 (d, J = 3.6 Hz, 1H), 5.92 (s, 2H), 5.95 (d, J = 7.9 Hz, 1H), 5.96, 5.98 (each s, each 1H), 5.75 (d, J = 3.6 Hz, 1H), 6.61 (s, 1H), 6.71 (s, 1H), 6.85 (d, J = 7.9 Hz, 1H); MS *m*/*z* (rel int) 353 (M^+, 6.1), 335 (21.2), 320 (14.8), 176 (100); HRMS *m*/*z* 353.0914 (calcd for $C_{19}H_{15}NO_6$: 353.0899).

2,3,8,9-Tetramethoxy-5,6-dihydroindolo[2,1-*a*]isoquinoline (3a). General Procedure. A mixture of **19a** (45 mg, 0.1 mmol) and K_2CO_3 (28 mg, 0.2 mmol) in DMF (2 mL) was refluxed under N_2 for 3 days. After evaporation of the solvent, the residue was extracted with CH_2Cl_2 (35 mL × 2), washed with water (10 mL × 3), and dried (Na_2SO_4). Evaporation of the solvent and crystallization of the oily residue (38 mg) from EtOH gave **3a** (27 mg, 79%), mp 190−194 °C, which gradually colored to dark green at room temperature. Recrystallization from EtOH gave the analytical sample (17 mg), mp 193−195 °C. IR 1609, 1575, 1556, 1508 cm^{-1}; ^1H NMR (270 MHz) δ 3.09, 4.63 (each t, J = 6.6 Hz, each 2H), 3.92, 3.93, 3.95, 3.97 (each s, aech 3H), 6.67 (s, 1H), 6.75 (s, 1H), 6.81, 7.24 (AB type, J = 8.6 Hz, each 1H), 7.18 (s, 1H); ^{13}C NMR (67.5 MHz) δ 29.3 (t), 42.1 (t), 56.0 (q), 56.0 (q), 57.0 (q), 61.5 (q), 95.5 (d), 107.1 (d), 108.3 (d), 111.1 (d), 115.4 (d), 121.6 (s), 125.0 (s), 126.0 (s), 130.1 (s), 135.6 (s), 136.3 (s), 148.0 (s), 148.2 (s), 148.6 (s); MS *m*/*z* (rel int) 339 (M^+, 100), 324 (68.7), 170 (23.5); FD-MS 340 [$(M + H)^+$, 24.1], 339 (M^+, 100). Anal. Calcd for $C_{20}H_{21}NO_4$; C, 70.78; H, 6.24; N,4.13. Found; C, 70.78; H, 6.28; N, 4.05.

2,3-Dimethoxy-8,9-(methylenedioxy)-5,6-dihydroindolo-[2,1-*a*]isoquinoline (3b): 80% yield; mp 198−200 °C (MeOH−Et_2O); IR 1596, 1552, 1503 cm^{-1}; ^1H NMR (270 MHz) δ 3.11, 4.39 (each t, J = 6.6 Hz, each 2H), 3.91 (s, 3H), 3.95 (s, 3H), 6.00 (s, 2H), 6.68 (s, 1H), 6.74 (s, 1H), 6.74, 7.06 (AB type, J = 8.6 Hz, each 1H), 7.18 (s, 1H); MS *m*/*z* (rel int) 323 (M^+, 100), 308 (17.5). Anal. Calcd for $C_{19}H_{17}NO_4$; C, 70.35; H, 4.26; N, 4.56. Found; C, 70.32; H, 4.36; N, 4.57.

8,9-Dimethoxy-2,3-(methylenedioxy)-5,6-dihydroindolo-[2,1-*a*]isoquinoline (3c): 82% yield; mp 177−180 °C (MeOH−Et_2O); IR 1623, 1576, 1502 cm^{-1}; ^1H NMR (270 MHz) δ 3.06, 4.58 (each t, J = 6.3 Hz, each 2H), 3.93 (s, 3H), 3.96 (s, 3H), 5.97 (s, 2H), 6.62 (s, 1H), 6.72 (s, 1H), 6.80, 7.20 (AB type, J = 8.6 Hz, each 1H), 7.19 (s, 1H); MS *m*/*z* (rel int) 323 (M^+, 100), 308 (93.0), 265 (35.2), 162 (20.5). Anal. Calcd for $C_{19}H_{17}NO_4$; C, 70.35; H, 4.26; N, 4.56. Found; C, 70.27; H, 4.30; N, 4.49.

2,3,8,9-Bis(methylenedioxy)-5,6-dihydroindolo[2,1-*a*]-isoquinoline (3d): 83% yield; mp 205−206 °C (EtOH); IR 1598, 1562, 1544, 1502 cm^{-1}; ^1H NMR (270 MHz) δ 3.08, 4.37 (each t, J = 6.6 Hz, each 2H), 5.97 (s, 2H), 5.99 (s, 2H), 6.64 (s, 1H), 6.72 (s, 1H), 6.75, 7.06 (AB type, J = 8.3 Hz, each 1H), 7.16 (s, 1H); MS *m*/*z* (rel int) 308 [$(M + H)^+$, 23.2], 307 (M^+, 100), 248 (24.0), 153 (24.6). Irradiation of a signal at δ 6.64 caused a NOE enhancement (20 and 7%) of signals owing to 1-H and 11-H at δ 7.16 and 7.06, respectively. Anal. Calcd for $C_{18}H_{13}NO_4$; C, 70.35; H, 4.26; N, 4.56. Found; C, 70.23; H, 4.46; N, 4.79.

2,3,9,10-Tetramethoxy-5,6-dihydroindolo[2,1-*a*]isoquinoline (3e): 57% yield; mp 207−208 °C (MeOH−CH_2Cl_2) (lit.[36] mp 199 °C;[39a] 201−203 °C;[38d] 202−203 °C;[38a] 202−204 °C;[38g,h] 209−210 °C). IR 1623, 1609, 1547, 1503 cm^{-1}; ^1H NMR (270 MHz) δ 3.12 (t, J = 6.6 Hz, 2H), 3.91, 3.93 (each s, each 3H), 3.96 (s, 6H), 4.17 (t, J = 6.6 Hz, 2H), 6.64, 6.75, 6.80, 7.07, 7.17 (each s, each 1H).[38a]

2,3,9,10-Bis(methylenedioxy)-5,6-dihydroindolo[2,1-*a*]-isoquinoline (3f): 33%; mp 219.5−222.5 °C (MeOH); IR 1540, 1498 cm^{-1}; ^1H NMR (270 MHz) δ 3.07, 4.09 (each t, J = 6.6 Hz, each 2H), 5.93 (s, 2H), 5.96 (s, 2H), 6.59, 6.71, 6.77, 6.98, 7.12 (each s, each 1H); MS *m*/*z* (rel int) 308 [$(M + H)^+$, 24.9], 307 (M^+, 100), 248 (17.9), 154 (23.6). Anal. Calcd for $C_{18}H_{13}NO_4$; C, 70.35; H, 4.26; N, 4.56. Found; C, 70.47; H, 4.40; N, 4.37.

1-(2-Bromo-3,4-dimethoxybenzyl)-6,7-dimethoxy-3,4-hydroisoquinoline Methiodide (21a). To a stirred solution of **15a** (210 mg, 0.5 mmol) in CH_3CN (2 mL) was added CH_3I (0.2 mL, 3.2 mmol). After the mixture was gently refluxed for 10 min, the solvent was removed on a rotary evaporator. Crystallization of the residue from MeOH gave methiodide **21a** as yellow crystals (203 mg, 75%), mp 206−208 °C; [IR 1639, 1606, 1592, 1561, 1514 cm^{-1}; ^1H NMR (270 MHz) δ 3.42 (t, J = 7.7, 2H), 3.76 (s, 3H), 3.85, 3.86, 3.97, 3.99 (each s, each 3H), 4.34 (t, J = 7.7, 2H), 4.66 (s, 2H), 6.86, 7.05 (s, each 1H), 6.91, 7.10 (AB type, J = 8.8 Hz, each 1H). Anal. Calcd for $C_{21}H_{25}NO_4BrI$: C, 4.86; H, 4.48; N, 2.49; I + Br, 36.78. Found; C, 44.58; H, 4.47; N, 2.34; I + Br, 36.86.

1-(2-Bromo-3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (22f). To a stirred solution of methiodide **21a** (54.2 mg, 0.1 mmol) in MeOH (2 mL) was added $NaBH_4$ (10 mg, 0.25 mmol). After the mixture was continuously stirred for 30 min, MeOH was removed on a rotary evaporator, and the residue was treated with water (10 mL) and CH_2Cl_2 (5 mL). The water layer was further extracted with CH_2Cl_2 (3 mL). The combined CH_2Cl_2 layers were washed with water (10 mL) and dried (Na_2SO_4). Evaporation of the solvent gave a crystalline solid (43 mg), which was treated with benzene−Et_2O to give **22f** (39 mg, 87%), mp 126 °C; IR 1605, 1572, 1511 cm^{-1}; ^1H NMR (270 MHz) δ 2.58 (s, 3H), 2.61−2.73 (m, 1H), 2.84−2.97 (m, 3H), 3.26−3.40 (m, 1H), 3.52 (s, 3H), 3.85 (s, 9H), 3.85 (s, 2H), 5.89 (s, 1H), 6.58 (s, 1H), 6.71, 6.74 (AB type, J = 8.3 Hz, each 1H); MS *m*/*z* (rel int) 437, 435 [each $(M - H)^+$, 0.3], 231, 229 (each 2.5), 206 (100). Anal. Calcd for $C_{21}H_{26}NO_4Br$: C, 57.81; H, 6.01; N, 3.21; Br, 18.31. Found: C, 57.63; H, 5.95; N, 3.08; Br, 18.18.

Treatment of a Mixture of 19a and 20a with K_2CO_3 in Boiling DMF. A stirred suspension of an oily mixture (50 mg, >90% yield) of **20a** and **19a** (3:2) [obtained by treatment of methiodide **17a** (56 mg, 0.1 mmol) with $LiAlH_4$ (7.6 mg, 0.2 mmol) in the manner described above], K_2CO_3 (28 mg, 0.2 mmol), and DMF (2 mL) was refluxed in an atmosphere of nitrogen. After 36 h, a part of the reaction mixture (0.5 mL) was poured into brine (10 mL), extracted with CH_2Cl_2 (2 mL × 3), washed with brine (5 mL × 5), and dried (Na_2SO_4). The extract was concentrated to give an oil (13 mg), which was found to be a mixture of **20a**, **19a**, and **3a** in a ratio of 3:1:1 in its ^1H NMR (270 MHz) analysis. The other part of the reaction mixture was refluxed for an additional 24 h, and a similar workup to the above gave an oil, which comprised **20a**, **19a**, and **3a** in a ratio of 2:0:4.

General Procedure for Reduction of Dihydroisoquinoline 15a−e with $NaBH_4$. 1-(2-Bromo-3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (22a). To a stirred solution of freshly prepared 1-benzyldihydroisoquinoline **15a** (84 mg, 0.2 mmol) in MeOH (2 mL) was added $NaBH_4$ (3.8 mg, 0.1 mmol). After the mixture was stirred for 15 min, the solvents were evaporated at room temperature. The oily residue was dissolved in water (3 mL) and extracted with CH_2Cl_2 (3 mL × 3). The organic layers were washed with water (5 mL), dried (Na_2SO_4), and concentrated to give **22a** (84 mg, ca. 100%) as a colorless oil, IR (neat) 3380, 1601, 1492 cm^{-1}; ^1H NMR (270 MHz) δ2.76 (t, J = 5.9, 2H), 2.93 (dd, J = 13.6, 10.3 Hz, 1H), 2.98 (dd, J = 11.6, 5.9 Hz, 1H), 3.24 (dd, J = 12.15, 5.9 Hz, 1H), 3.34 (dd, J = 13.6, 3.7 Hz, 1H), 3.84, 3.87, 3.876, 3.881 (each s, each 3H), 4.23 (dd, J = 10.3, 3.7 Hz, 1H), 6.60 (s, 1H), 6.76 (s, 1H), 6.85, 6.99 (AB type, J = 8.4 Hz, each 1H); MS *m*/*z* (rel int) 422, 420 [each $(M - H)^+$, 0.2], 192 (100); HRMS *m*/*z* 421.0896 (calcd for $C_{20}H_{24}NO_4Br$: 421.0889).

1-[2-Bromo-3,4-(methylenedioxy)benzyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (22b): 94% yield; mp 187−187.5 °C (MeOH); IR (neat) 3312, 1612, 1518, 1502 cm^{-1}; ^1H NMR (270 MHz) δ2.75 (t, J = 5.6, 2H), 2.91 (dd, J = 10.2, 13.9 Hz, 1H), 2.97 (dd, J = 5.6, 12.8 Hz, 1H), 3.23 (1H, dd, J = 5.6, 12.8 Hz, 1H), 3.30 (dd, J = 13.9, 3.6 Hz, 1H), 3.86 (s,

3H), 3.87 (s, 3H), 4.19 (dd, J = 10.2, 3.6 Hz, 1H), 6.05 (s, 2H), 6.60 (s, 1H), 6.75 (s, 1H), 6.73, 6.77 (AB type, J = 7.3 Hz, each 1H); MS m/z (rel int) 406, 404 [each $(M - H)^+$, 0.2], 192 (100). Anal. Calcd for $C_{19}H_{20}NO_4Br$: C, 56.17; H, 4.96; N, 3.45; Br, 19.67. Found; C, 56.12; H, 5.01; N, 3.32; Br, 19.54.

1-(2-Bromo-3,4-dimethoxybenzyl)-6,7-(methylenedioxy)-1,2,3,4-tetrahydroisoquinoline (22c): 86% yield; a colorless oil; IR (neat) 3316, 1595, 1504 cm^{-1}; ^1H NMR (270 MHz) δ2.66 (t, J = 5.6, 2H), 2.81 (dd, J = 10.6, 13.9 Hz, 1H), 2.87 (dd, J = 5.6, 12.2 Hz, 1H), 3.13 (dd, J = 5.6, 12.2 Hz, 1H), 3.24 (dd, J = 13.9, 3.3 Hz, 1H), 3.81 (s, 6H), 4.12 (dd, J = 10.6, 3.3 Hz, 1H), 5.83 (s, 2H), 6.50 (s, 1H), 6.78 (s, 1H), 6.78, 6.92 (AB type, J = 8.6 Hz, each 1H); MS m/z (rel int) 406 [$(M - H)^+$, 0.5], 404 (0.4), 324 (6.1), 176 (100); HRMS m/z 404.0484 (calcd for $C_{19}H_{20}NO_4Br$: 404.0497).

1-[2-Bromo-3,4-(methylenedioxy)benzyl]-6,7-(methylenedioxy)-1,2,3,4-tetrahydroisoquinoline (22d): 97% yield; mp 173−175 °C (MeOH); IR 3318, 1617, cm^{-1}; ^1H NMR (270 MHz) δ2.67−3.19 (m, 5H), 4.74 (dd, J = 12.9, 3.3 Hz, 1H), 5.03 (d, J = 11.2 Hz, 3.0 Hz, 1H), 5.90 (s, 2H), 5.94 (s, 2H), 6.57 (s, 1H), 6.69 (s, 1H), 6.69 (d, J = 7.9, 1.6 Hz, 1H), 6.74 (d, J = 1.6 Hz, 1H), 6.77 (d, J = 7.9 Hz, 1H); MS m/z (rel int) 390, 388 [each $(M - H)^+$, 0.2], 308 (0.9), 213 (1.5), 176 (100). Anal. Calcd for $C_{18}H_{16}NO_4Br$: C, 55.40; H, 4.13; N, 3.59; Br, 20.48. Found; C, 55. 34; H, 4.02; N, 3.61; Br, 20.34.

General Procedure for Palladium(0)-Catalyzed Carbonylation of 1-(2-Bromobenzyl)-1,2,3,4-tetrahydroisoquinolines 22a−d. (±)-8-Oxotetrahydropalmatine (23a). A stirred mixture of freshly prepared tetrahydroisoquinoline **22a** (41 mg, 0.1 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), PPh_3 (10.5 mg, 0.04 mmol), and K_2CO_3 (14 mg, 0.1 mmol) in toluene (2 mL) was refluxed in an atmosphere of carbon monoxide for 26 h. The reaction mixture was allowed to cool to room temperature and filtered through a Celite pad. Toluene was removed on a rotary evaporator, and the residue was treated with water (5 mL) and CH_2Cl_2 (2 mL × 3). The organic layers were washed with water (5 mL), dried (Na_2SO_4), and concentrated. The oily residue (61 mg) was purified by preparative TLC (5% MeOH−CH_2Cl_2). A fraction with R_f 0.5 gave an oil (32 mg), which was crystallized from MeOH−Et_2O to give (±)-8-oxotetrahydropalmatine **23a**, as colorless crystals (28 mg, 75%), mp 171−172 °C (lit.[48h] mp 167−168 °C;[67,75] 170−171 °C); IR (neat) 1648, 1592, 1516, 1486 cm^{-1}; ^1H NMR (270 MHz) δ 2.70−3.15 (m, 1H), 3.87 (s, 9H), 3.89 (s, 3H), 4.73 (dd, J = 13.0, 3.3 Hz, 1H), 5.04 (dd, J = 8.6, 2.3 Hz, 1H), 6.68 (s, 1H), 6.69 (s, 1H), 6.95, 7.01 (AB type, J = 8.3 Hz, each 1H).[75]

(±)-8-Oxosinactine (23b): 18 h; 77% yield; mp 198−202 °C (MeOH) (lit.[76] mp 198−200 °C); IR (Nujol) 3004, 1646, 1600, 1514 cm^{-1}; ^1H NMR (270 MHz) δ 2.72−3.17 (m, 5H), 3.89 (s, 3H), 3.90 (s, 3H), 4.80 (dd, J = 12.9, 3.3 Hz, 1H), 4.98 (dd, J = 8.6, 3.0 Hz, 1H), 6.12, 6.17 (each d, J = 1.3 Hz, each 1H), 6.68 (s, 2H), 6.70, 6.87 (AB type, J = 7.9, each 1H); MS m/z (rel int) 353 (M^+, 100), 338 (31.7), 322 (11.0), 190 (22.4), 162 (85.2), 134 (71.5).

(±)-8-Oxocanadine (23c): 26 h, 85% yield; mp 209−211 °C (EtOH) (lit.[48h] mp 199−200 °C;[48h,i] 217−218 °C;[66] 222−223 °C); IR (Nujol) 1651, 1577, 1504, 1486 cm^{-1}; ^1H NMR (270 MHz) δ 2.70−3.06 (m, 5H), 3.84 (s, 3H), 4.01 (s, 3H), 4.70 (dd, J = 12.9, 3.3 Hz, 1H), 4.98 (dd, J = 8.6, 3.0 Hz, 1H), 6.66, 6.67 (s, each 1H), 6.93, 7.00 (AB type, J = 8.3, each H);[48h,i] MS m/z (rel int) 353 (M^+, 36.8), 178 (100), 176 (56.6), 135 (64.0), 120 (57.9), 90 (63.8).

(±)-8-Oxostylopine (23d): 18 h; 82% yield; mp 267−270 °C (MeOH); IR 1647, 1597, 1486 cm^{-1}; ^1H NMR (270 MHz) δ 2.69−3.14 (m, 5H), 4.75 (dd, J = 13.2, 3.3 Hz, 1H), 4.93 (dd, J = 9.2, 3.3 Hz, 1H), 5.95 (s, 2H), 6.07, 6.17 (each d, J = 1.3 Hz, each 1H), 6.66 (s, 1H), 6.69 (s, 1H), 6.68, 6.86 (AB type, J = 7.6 Hz, each 1H); MS m/z (rel int) 337 (M^+, 51.9), 174 (23.8), 162 (77.2), 134 (100). Anal. Calcd for $C_{19}H_{15}NO_5$: C, 67.65: H, 4.48; N, 4.15. Found: C, 67.65: H, 4.48; N, 4.15.

General Procedure for $LiAlH_4$ Reduction of 8-Oxoberbines 23a−d. (±)-Tetrahydropalmatine (4a). To a stirred solution of **23a** (35 mg, 0.1 mmol) in dry THF (10 mL) was added $LiAlH_4$ (19 mg, 0.5 mmol). This suspension was refluxed for 45 min under N_2, cooled to room temperature, and then treated with THF (2.5 mL) containing water (0.5 mL). The resultant precipitates were removed by suction filtration, and the filtrate was concentrated. The residue was shaken with water (5 mL) and CH_2Cl_2 (5 mL). The organic layer was dried (Na_2SO_4) and concentrated to give an oil (36 mg), which was crystallized from MeOH-Et_2O to give **4a** (31 mg, 87%), mp 150−151 °C (lit.[78] mp 145−146 °C;[79−81] 147 °C;[82] 148 °C;[83] 148−150 °C;[84] 149.5−150.5 °C;[48h] 150−151 °C;[85] 151−151.5 °C). The ^1H NMR spectrum of this sample was identical with the reported data.[78,81,82,85]

(±)-Sinactine (4b): 90% yield; mp 168−170 °C (MeOH) (lit.[86] mp 155−156 °C;[46] 163−165 °C;[81] 166 °C;[80,87] 167−168 °C;[84,88] 169−170 °C; lit.[56d] 257−258 °C (HCl salt). The ^1H NMR spectrum of this sample was identical with the reported data.[54j,59c,60c]

(±)-Canadine (4c): 82% yield; mp 172−174 °C (EtOH) (lit.[50] mp 163−165 °C;[51] 164−165 °C;[89] 165 °C;[87] mp 164−166 °C;[46] 167−168 °C;[76] 168−170 °C;[48h,i] 172−173 °C. The ^1H NMR spectrum of this sample was identical with the reported data.[46,48i,89]

(±)-Stylopine (4d): 86% yield: mp 211−214 °C (MeOH) (lit.[87] mp 191−192 °C;[46] 194−195 °C;[48p] 213−215 °C;[80] 217−218 °C;[88] 219 °C). The ^1H NMR spectrum of this sample was identical with the reported data.[46]

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Supporting Information Available: ^1H NMR spectra for compounds **1a**−**h**,**j**,**k**, **2a**−**d**, **3a**−**f**, **4a**−**d**, and **23a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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