Syntheses of Antitumor Morphinane Alkaloids, Sinococuline and 6-*epi*-, 7-*epi*-, and 6-*epi*-7-*epi*-Sinococuline, from Sinomenine[1]

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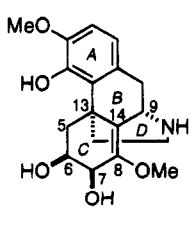
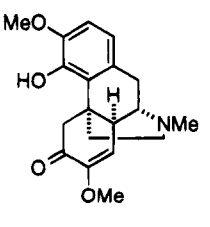
An antitumor alkaloid, sinococuline (**1**), and its C-6 and/or C-7 epimeric analogs **3**–**5** have been synthesized from sinomenine (**2**). The carbonyl transposition from **9** to **8** using selenoxide chemistry proceeded in an efficient manner. Successive C-6 hydroxylation through the potassium enolate oxidation with (−)-(2*S*,8a*R*)-(camphorsulfonyl)oxaziridine (**23**) predominantly produced the β-hydroxy enone **7a**, which allowed access to sinococuline (**1**) and the 7-*epi*-analog **4**. On the contrary, the oxidation of the lithium enolate with (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine (**22**) resulted in predominant formation of the α-hydroxy enone **7b**, which was converted to the 6-*epi*-analogs **3** and **5**. In contrast to the marked antitumor activity of **1**, analogs **3**–**5** showed no activity.

Introduction

We have previously reported[2] the isolation and structure elucidation of an antitumor alkaloid, sinococuline (**1**), from the native Japanese plant *Cocculus trilobus*. Sinococuline (**1**) is characterized by a morphinane skeleton possessing a unique oxidation state on ring C and promising antitumor activity against animal tumor models. However, the variable content in the plant and the difficult isolation and purification process due to its high-polar, noncrystallizable property prohibit further biological evaluations as an anticancer agent. To circumvent this problem, we sought to synthetically supply this alkaloid. We considered that sinomenine (**2**) would be a suitable starting material for sinococuline (**1**) since **2** is readily available in quantity from the rhizomes of the plant *Sinomenium acutum*[3] and possesses the same substitution pattern on ring A and the same absolute configurations at the C-9 and C-13 centers. Also, we thought that the establishment of this transformation will allow access to analogs not available from sinococuline, which will provide valuable information for a structure–activity relation study and the designing of analogs, some of which may express more promising biological properties. For these reasons, we developed a route to sinococuline (**1**) from sinomenine (**2**), and by using this methodology, we prepared three diastereomeric analogs, 6-*epi*-sinococuline (**3**), 7-*epi*-sinococuline (**4**), and 6-*epi*-7-*epi*-sinococuline (**5**) and compared their antitumor activities.



sinococuline (**1**)



sinomenine (**2**)

Results and Discussion

The key feature of this transformation lies in the construction of the C-6, C-7 β-*cis*-glycol and the C-8–C-14 methyl enol ether. We deemed that the C-6, C-7 *cis*-glycol could be constructed in two alternative ways: (1) the diene **6** formation and successive regio- and stereoselective *cis* hydroxylation using osmium-based reagents (path a) or (2) stereocontrolled β-hydroxylation at position 6 of enone **8** and the stereoselective reduction of the C-7 carbonyl group of **7a** (path b), and the C-8–C-14 enol ether would be placed *via* carbonyl transposition from **9** to **8** (Scheme 1). This transformation also needs *N*-demethylation which requires rather harsh conditions. Thus, this process must be done at an early stage, and the produced secondary amine should be protected until the C-ring substitution array is properly constructed. For the amine and C-4 hydroxyl protections, benzylic protective groups were considered to be suitable since they could be removed under mild and neutral conditions which will not affect the sensitive C-7 allylic alcohol and the C-8–C-14 enol ether.

Synthesis of Enone 8 from Sinomenine (2). Sinomenine (**2**) was *O*-benzylated under Mitsunobu conditions[4] [BnOH, diethyl azodicarboxylate (DEAD), Ph_3P, THF] to afford *O*-benzylsinomenine (**10**) in 89% yield (Scheme 2). Compound **10** was reacted with 1-chloroethyl chloroformate (ACE-Cl)[5] in 1,2-dichloroethane to afford the *N*-ACE intermediate, which was decomposed by refluxing in MeOH and successively treated with *N*-[(benzyloxycarbonyl)oxy]succinimide (Z-OSu) and $NaHCO_3$ in MeOH–H_2O to give **9** in 98% yield from **10**. The reduction of **9** with $NaBH_4$ in the presence of $CeCl_3$[6] in MeOH afforded **11a** and its C-6 epimer **11b** in a ratio of 1:1 in 97% yield. Since the β-configuration of the alcohol **11a** proved to be important for the successive transformations (vide infra), we examined the reduction of **9** under various conditions. The best result was obtained when 1.2 equiv of L-Selectride in THF was used as the reducing agent that exclusively (100% de) pro-

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(1) Preliminary communication: Hitotsuyanagi, Y.; Ikuta, H.; Nishimura, K.; Takeya, K.; Itokawa, H. *J. Chem. Soc., Chem. Commun.* **1994**, 2707.

(2) Itokawa, H.; Tsuruoka, S.; Takeya, K.; Mori, N.; Sonobe, T.; Kosemura, S.; Hamanaka, T. *Chem. Pharm. Bull.* **1987**, *35*, 1660.

(3) The rhizomes of *S. acutum* have been listed in the Japanese Pharmacopoeia and are available in the market. Sinomenine (**2**) is also commercially available from Aldrich Chemical Company, Inc., Milwaukee, WI.

(4) Mitsunobu, O. *Synthesis* **1981**, 1.

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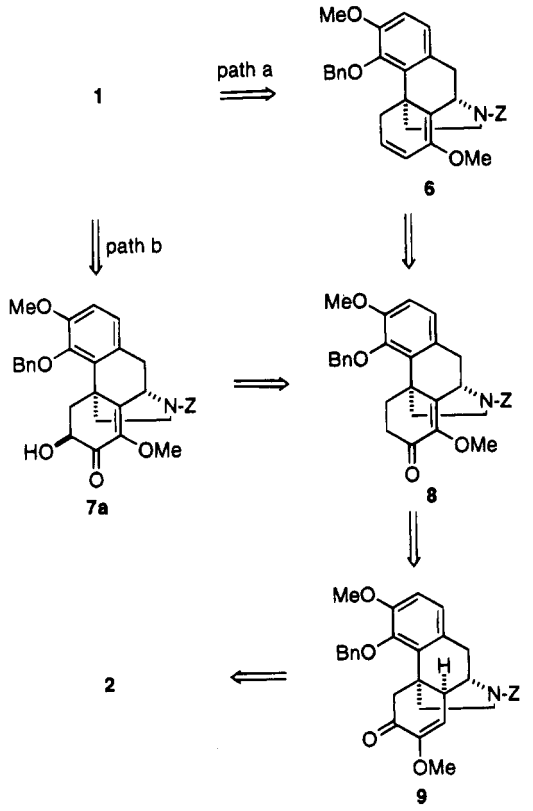
Scheme 1

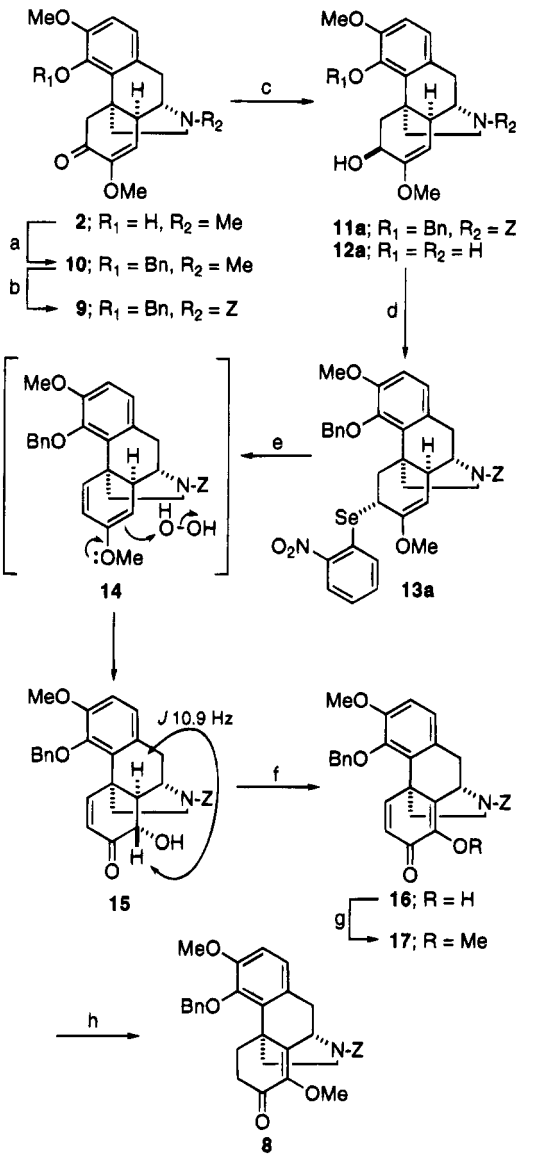


duced the alcohol **11a** in 91% yield. Interestingly, K-Selectride reduction produced a moderate yield (~50%) of **11a** and an unidentified product (~30%) in spite of being expected to give a similar result as L-Selectride for the reduction of substituted cyclohexanones.[7] The stereochemistry of the C-6 center of **11a** was determined by the following procedures. Alcohols **11a** and **11b** were separated by medium-pressure liquid chromatography and deprotected by Pearlman's palladium catalyst[8] to produce amines **12a** (74%) and **12b** (88%), respectively. This deprotection was necessary to avoid the complication caused by the urethane rotamers during the ^{1}H NMR analysis. A comparison of the coupling constants between H-5β and H-6 of **12a** with that of **12b** revealed **12a** possessing a β-hydroxyl group due to its smaller value (1.2 Hz), *i.e.*, the dihedral angle between H-5β and H-6 of **12a** is closer to 90° compared to **12b** (6.0 Hz) (Figure 1). The observation of NOE between H-5α and H-6 (4%) on **12a** supported this structure assignment.

The alcohol **11a** was selenylated with 2-nitrophenyl selenocyanate and tributylphosphine using Grieco's protocol[9] to afford α-selenide **13a** in 96% yield. Hydrogen peroxide (30 equiv) oxidation of **13a** did not give the expected diene **14** but further oxidized 8-hydroxy enone **15** in 89% yield. This rather unusual but clean transformation could be caused by the intermediate diene **14** being attacked from the less hindered α-face by an excess amount of hydrogen peroxide or (2-nitrophenyl)peroxyseleninic acid (o-NO_2PhSeO_3H) which would be generated in the reaction mixture. Although the α-alcohol **11b** gave the selenide **13b** in the same manner in excellent yield (97%), hydrogen peroxide treatment of **13b** afforded only

(7) Brown, C. A. *J. Am. Chem. Soc.* **1973**, *95*, 982.
(8) (a) Pearlman, W. M. *Tetrahedron Lett.* **1967**, 1663. (b) Hanessian, S.; Liak, T. J.; Vanasse, B. Synthesis **1981**, 396.
(9) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

Scheme 2



[a] Reagents: (a) BnOH, DEAD, Ph_3P, THF (89%); (b) ACE-Cl, $NaHCO_3$, 1,2-dichloroethane; MeOH, reflux; Z-OSu, $NaHCO_3$, MeOH (98%); (c) L-Selectride, THF, −78 °C (91%); (d) o-$NO_2PhSeCN$, n-Bu_3P, THF (96%); (e) H_2O_2, THF−H_2O (89%); (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (89%); (g) p-TsOMe, K_2CO_3, acetone (98%); (h) H_2, $(Ph_3P)_3RhCl$, benzene (97%).

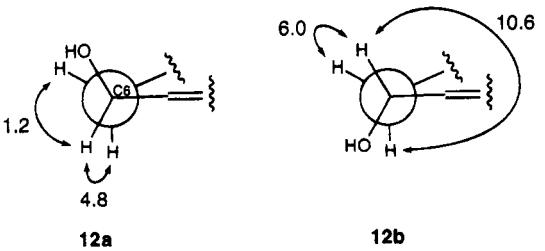
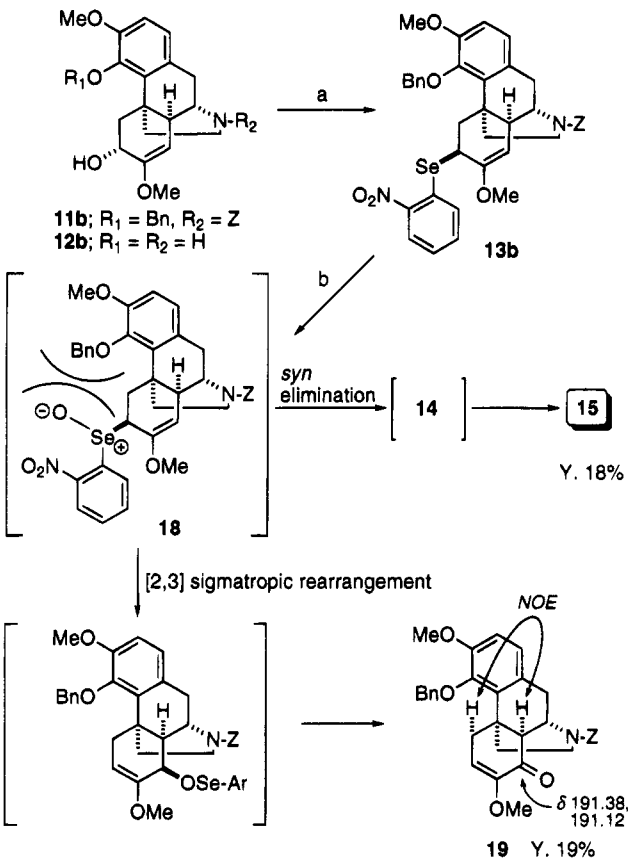


Figure 1. Coupling constants between H-5α,β and H-6 of **12a** and **12b** (J/Hz).

an 18% yield of **15** accompanied by a 19% yield of the unexpected enone **19** (Scheme 3). The structure of **19** was assigned by the molecular formula, $C_{33}H_{33}NO_6$, given by the high-resolution mass spectrum and the NMR measurements including the 2D NMR (COSY, NOESY) technique; the uniquely characteristic features being the enone carbonyl resonances (δ 191.38 and 191.12, ure-

Scheme 3

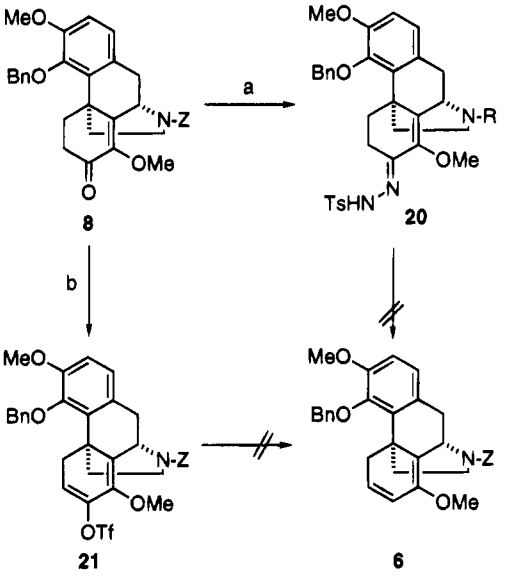


[a] Reagents: (a) *o*-$NO_2PhSeCN$, *n*-Bu_3P, THF (97%); (b) H_2O_2, THF–H_2O.

thane rotamers) in ^{13}C NMR and strong NOESY correlations between H-5α and H-14. The distinctive difference in the reaction course during the oxidation of the epimeric selenides **13a** and **13b** might be rationalized by the following considerations. The *syn* elimination of the α-selenoxide derived from **13a** would proceed without difficulty, but the β-selenoxide **18** suffers steric repulsion between the C-4 benzyloxy group and the phenylselenoxide moiety, which hampered the adoption of a suitable conformation required for the *syn* elimination, and the competing [2,3] sigmatropic rearrangement proceeded to afford the enone **19**.[10]

The Swern[11] oxidation of the hydroxy enone **15** gave diosphenol **16** in 89% yield which was *O*-methylated with methyl *p*-toluenesulfonate and K_2CO_3 in acetone to afford the dimethyl ether **17** in 98% yield. Selective hydrogenation of the C-5–C-6 olefinic bond of **17** was effected using Wilkinson's rhodium catalyst[12] in benzene to furnish the desired enone **8** in 97% yield.

Scheme 4



[a] Reagents: (a) *p*-$TsNHNH_2$, *p*-$TsOH{\cdot}H_2O$, THF (74%); (b) KHMDS, Tf_2NPh, THF (83%).

Attempts to Prepare the Diene 6. We initially examined the possibility of path a in Scheme 1 which is characterized by diene formation and subsequent selective *cis* dihydroxylation of the C-6–C-7 olefinic bond. To obtain the diene intermediate **6**, the enone **8** was converted to the tosylhydrazone **20** in 74% yield (Scheme 4). However, the Shapiro[13] reaction of **20** using MeLi (2 equiv) in THF at 0 °C for 24 h did not proceed at all. Only the slow decomposition of **20** was observed when the temperature was raised above room temperature. An alternative approach, the reduction of the enol triflate **21**, derived from **8** in 83% yield, using a palladium catalyst [$Pd(OAc)_2$ or $Pd(PPh_3)_4$; Et_3N or Bu_3N; PPh_3, HCO_2H; DMF or THF][14] did not proceed at 60 °C for 2 h. Elongation of the reaction time or temperature elevation caused decomposition of the substrate possibly due to the effect of the reagents on the benzylic protective groups. Other attempts such as DIBAL-H reduction of the enone **8** producing allylic alcohols and successive dehydration using Burgess's reagent[15] or Grieco's selenylation protocol[9] did not afford the diene **6**.

6-Hydroxylation of the Enone 8 and Conversions to Sinococuline (1) and Analogs 3–5. Since we could not obtain the diene **6**, we next examined the selective introduction of the β-hydroxyl group at the C-6 position of the enone **8** along the path b in Scheme 1. The 6-hydroxylation was achieved by the enolate oxidation (Scheme 5). The lithium, sodium, or potassium enolate was generated in THF using 2 equiv of lithium (LHMDS), sodium (NHMDS), or potassium bis(trimethylsilyl)amide (KHMDS), respectively. Two and one-half equivalents of Davis' oxaziridines, (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine (**22**),[16] (−)-(2*S*,8a*R*)-(camphorsulfonyl)-

(10) Although allyl phenylselenoxides generally favor the [2,3] sigmatropic rearrangement over the *syn* elimination,[10a–c] some examples of the diene formation have been reported.[10d,e] Also, the pseudoequatorial orientation of the α-selenoxide might be responsible for the exclusive *syn* elimination; the pseudoaxially oriented β-selenoxide **18** possibly rearranges more readily than the α-selenoxide. (a) Reich, H. J. *J. Org. Chem.* **1975**, *40*, 2570. (b) Clive, D. L. J.; Chittattu, G.; Curtis, N. J.; Menchen, S. M. *J. Chem. Soc., Chem. Commun.* **1978**, 770. (c) Davis, F. A.; Stringer, O. D.; Billmers, J. M. *Tetrahedron Lett.* **1983**, *24*, 1213. (d) Salmond, W. G.; Barta, M. A.; Cain, A. M.; Sobala, M. C. *Tetrahedron Lett.* **1977**, 1683. (e) Reich, H. J.; Wollowitz, S. *J. Am. Chem. Soc.* **1982**, *104*, 7051.

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Scheme 5

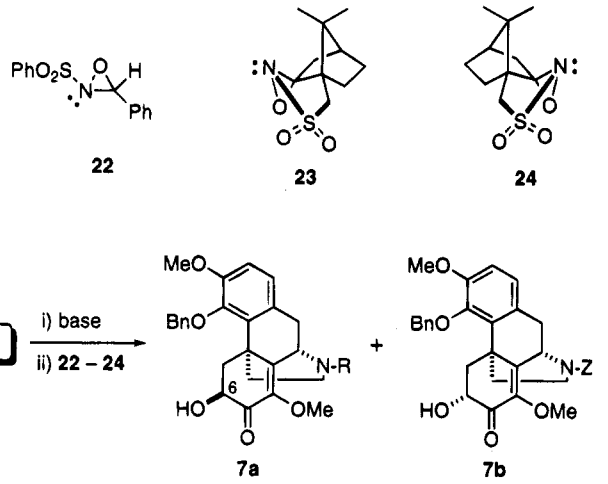


Table 1. 6-Hydroxylation of the Enone 8

entry	reagent[a]	base[b] (additive)[c]	result yield,[d] %	**7a**:**7b**[e]	recovered **8**, %
1	**22**	LHMDS	82	1:5	0
2	**22**	NHMDS	73	1:2	0
3	**22**	KHMDS	87	1:3	0
4	**22**	LHMDS (HMPA)	81	1:5	0
5	**23**	LDA	NR[f]		~quant
6	**23**	LHMDS	NR		~quant
7	**23**	NHMDS	65	1:3.7	31
8	**23**	KHMDS	67	3:1	21
9	**23**	LHMDS (HMPA)	NR		~quant
10	**23**	KHMDS (HMPA)	49	1:1	6
11	**24**	LHMDS	NR		~quant
12	**24**	NHMDS	31	2.5:1	49
13	**24**	KHMDS	52	2:3	22

[a] 2.5 equiv in THF, −78 °C, 1 h. [b] 2 equiv. [c] 2 equiv. [d] Isolated yield. [e] The ratio was determined by ^{1}H NMR (400 MHz) measurements. [f] NR = no reaction.

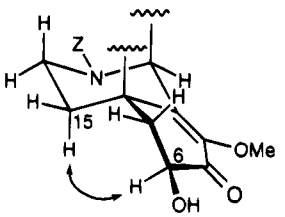


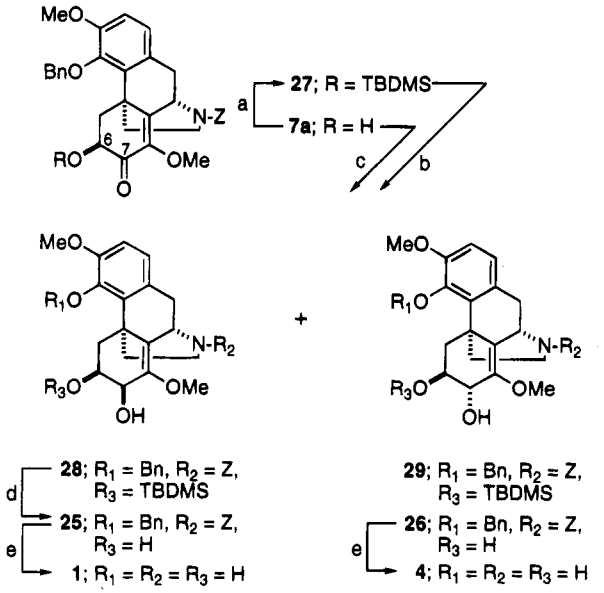
Figure 2. A diagnostic NOESYPH correlation for **7a**.

oxaziridine (**23**),[17] or (+)-(2*R*,8a*S*)-(camphorsulfonyl)-oxaziridine (**24**),[17] were used as the oxidizing agents and reacted at −78 °C for 1 h. The results are summarized in Table 1. The stereochemistry of the hydroxy enones **7a** and **7b** were determined from the NOESYPH[18] spectra. The β-hydroxy enone **7a** showed a strong NOESYPH correlation between H-6 and H-15α (Figure 2). Although the reaction with racemic **22** effectively proceeded irrespective of the species of the enolate metal cation, the **7a**/**7b** ratios were all in favor of **7b** due to the reagent attacking from the less hindered α-face (entries 1−3). The addition of HMPA did not alter the yield and the product ratio (entry 4). This predominant formation of **7b** was also needed for the syntheses of the analogs **3** and **5**. In the case of the chiral agents **23** and **24** the yields and the product ratios were greatly influenced by the enolate metal. The yields were generally lower than **22** due to the reduced reactivity, and the lithium enolate did not react at all (entries 5, 6, 9, and 11). A combination of KHMDS and **23** gave the best selectivity (**7a**/**7b** = 3:1, entry 8) among these experiments. The addition of HMPA resulted in inferior selectivity (entry 10). Interestingly, the change in the base, KHMDS to NHMDS, caused a reversal of the product ratio (entry 7). The same phenomena was observed when **24** was employed as the oxidizing agent (entry 12 *vs* 13). Although the effect of the metal cation is unclear, it does influence the diastereoselectivity in these cases.

To construct the C ring part of **1**, selective production of the *cis*-glycol **25** over the *trans*-glycol **26** from **7a** was required. Although we attempted the reduction using various reducing agents [$NaBH_4/CeCl_3$, DIBAL-H, L-Selectride, $LiBEt_3H$, $NaBH_4$, $NaBH(OAc)_3$], no satisfactory selectivity and/or yield was obtained. We proposed that the protection of the 6-β-hydroxyl group would alter the stereoselectivity since the free hydroxyl group might affect the selectivity through coordination to the reagent. Alcohol **7a** was protected as a *tert*-butyldimethylsilyl (TBDMS) ether **27** (89%, Scheme 6). The reduction of **27** with 1.2 equiv of $LiBEt_3H$ in THF at −78 °C proceeded with high diastereoselectivity that produced alcohols **28** (86%) and **29** (3%). Desilylation of **28** using a catalytic amount of *p*-toluenesulfonic acid in THF−H_2O at room temperature for 4 days gave the glycol **25** in 92% yield. Compound **25** was refluxed with one weight equivalent of Pearlman's catalyst in EtOH−cyclohexene (1:1) for 4.5 h to produce sinococuline (**1**) in 95% yield. This synthetic material was found to be identical with naturally occurring sinococuline based on ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), TLC, and optical rotation.

7-*epi*-Sinococuline (**4**) was prepared (98%) in the same manner from the *trans*-glycol **26** which was effectively produced (100% yield, **25**/**26** = 1:4.5) from **7a** using $NaBH_4/CeCl_3$ in EtOH. The configuration of **4** was

Scheme 6



[a] Reagents: (a) TBDMSCl, imidazole, DMF (89%); (b) $LiBEt_3H$, THF, −78 °C (**28**: 86% and **29**: 3%); (c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, EtOH (**25**: 18% and **26**: 82%); (d) *p*-TsOH·H_2O, THF−H_2O (92%); (e) $Pd(OH)_2$/C, cyclohexene−EtOH, reflux (95% for **1**; 98% for **4**).

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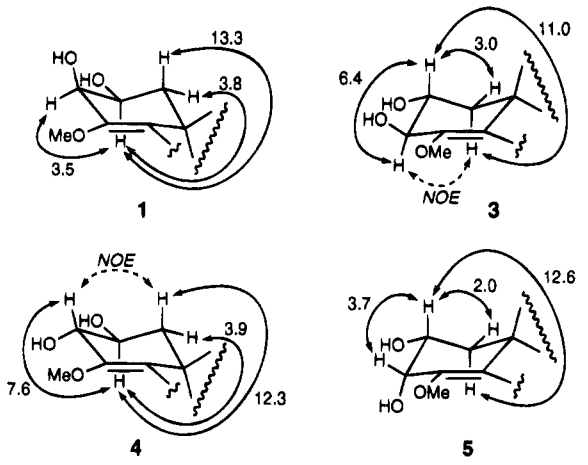
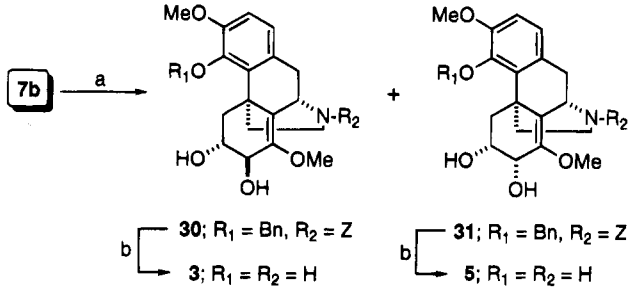


Figure 3. Selected coupling constants (*J*/Hz) and NOESYPH correlations for C ring part of compounds **1**, **3**, **4**, and **5**.

Scheme 7



[a] Reagents: (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH (**30**: 53% and **31**: 30%); (b) $Pd(OH)_2$/C, cyclohexene–EtOH (89% for **3**; 90% for **5**).

confirmed by comparing its ^1H NMR spectrum[19] with that of **1**. The coupling constant of **4** between H-6 and H-7 showed a larger value (7.6 Hz) than **1** (3.5 Hz) due to an axial–pseudoaxial relation (Figure 3).

6-*epi*-Sinococuline (**3**) and 6-*epi*-7-*epi*-sinococuline (**5**) were synthesized from the hydroxy enone **7b**. Sodium borohydride/$CeCl_3$ reduction of **7b** in MeOH afforded the *trans*-glycol **30** (53%) and the *cis*-glycol **31** (30%), which were similarly deprotected to give **3** and **5** in yields of 89% and 90%, respectively (Scheme 7). The stereochemistry was established by comparing their ^1H and ^{13}C NMR spectra as shown in structures **3** and **5**. The C ring of compounds **3** and **5** adopts the half-chair conformation shown in Figure 3, which was deduced from the large coupling constants (11.0 and 12.6 Hz, respectively) between H-5α and H-6. The coupling constant (6.4 Hz) of the *trans* analog **3** between H-6 and H-7 is larger than that (3.7 Hz) of the *cis* analog **5**, and a NOESYPH correlation was observed between H-5α and H-7 in **3**. Also, in ^{13}C NMR spectra, the C-5 resonance of **5** appeared higher (Δ ~4 ppm) field than that of **3** due to the γ-gauche effect.[20]

Antitumor Activity of Sinococuline (1) and Analogs 3–5. The antitumor activity of the analogs **3–5** was evaluated using P-388 lymphocytic leukemia in mice, and sinococuline (**1**) was reevaluated for comparison. Each sample was administered (25 mg/kg/day) intraperitoneally on days 1–5. Although sinococuline (**1**) showed marked antitumor activity (*T*/*C* = 166%), the other analogs showed no activity (**3**: 101%, **4**: 108%, **5**: 105%). This result suggests that the glycol moiety on ring C possessing the natural configuration (6*S*,7*S*) is essential for such activity.

Experimental Section

General. Evaporations of organic solutions dried over $MgSO_4$ were done under aspirator vacuum with a rotary evaporator. Benzene was distilled form calcium hydride, and THF was distilled form sodium. Melting points are uncorrected. Rotations are recorded in units of 10^{-1} deg cm^2 g^{-1}. ^1H Chemical shifts are referenced in $CDCl_3$ and methanol-d_4 to residual $CHCl_3$ (7.26 ppm) and CD_2HOD (3.34 ppm); ^{13}C chemical shifts are referenced to the solvent ($CDCl_3$, 77.03; methanol-d_4, 49.0 ppm). Medium-pressure liquid chromatography (MPLC) was performed with Kusano C.I.G. system. High-pressure liquid chromatography (HPLC) was performed with Shimadzu LC-6AD system.

***O*-Benzylsinomenine (10).** To a 0 °C solution of sinomenine (**2**, 0.680 g, 2.06 mmol) and triphenylphosphine (1.63 g, 6.20 mmol) in THF (10 mL) was added a solution of benzyl alcohol (0.64 mL, 6.18 mmol) and diethyl azodicarboxylate (0.97 mL, 6.16 mmol) in THF (2 mL) over a 15 min period. The mixture was stirred at room temperature for 10 h. After removal of the THF, the residue was purified by alumina column chromatography (0–1:5 EtOAc/CH_2Cl_2) and then silica gel column chromatography (1:10 MeOH/CH_2Cl_2). Crystallization from isopropyl ether gave 0.773 g (89%) of **10** as colorless prisms: mp 128–129 °C; $[\alpha]^{24}_D$ −19.3° (*c* = 0.56, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, 2H, *J* = 7.0, 1.3 Hz), 7.42–7.29 (m, 3H), 6.76 (d, 1H, *J* = 8.4 Hz), 6.73 (d, 1H, *J* = 8.4 Hz), 5.50 (d, 1H, *J* = 2.1 Hz), 5.27 (d, 1H, *J* = 11.1 Hz), 5.08 (d, 1H, *J* = 11.1 Hz), 4.15 (d, 1H, *J* = 16.0 Hz), 3.79 (s, 3H), 3.50 (s, 3H), 3.14 (dd, 1H, *J* = 5.2, 4.1 Hz), 3.00 (d, 1H, *J* = 18.1 Hz), 2.94 (m, 1H), 2.74 (dd, 1H, *J* = 18.1, 5.2 Hz), 2.46 (m, 1H), 2.44 (d, 1H, *J* = 16.0 Hz), 2.04 (s, 3H), 1.96 (ddd, 1H, *J* = 12.0, 12.0, 3.7 Hz), 1.92–1.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.95, 152.54, 151.55, 147.57, 138.39, 130.21, 128.25, 127.99, 127.49, 122.85, 115.43, 111.36, 73.16, 56.48, 55.68, 54.75, 49.80, 47.03, 46.07, 42.65, 40.92, 37.09, 24.63; IR (KBr) ν_{max} 2900, 1680, 1480, 1270, 1205, 1140, 1050, 1040 cm^{-1}; MS *m*/*z* (%) 328 (100, M − Bn$^+$). Anal. Calcd for $C_{26}H_{29}NO_4$: C, 74.44; H, 6.97; N, 3.34. Found: C, 74.48; H, 7.15; N, 3.28.

(9*S*,13*R*,14*S*)-7,8-Dehydro-4-(benzyloxy)-17-[(benzyloxy)carbonyl]-3,7-dimethoxymorphinan-6-one (9). To a suspension of **10** (4.035 g, 9.62 mmol) and $NaHCO_3$ (16.2 g, 193 mmol) in 1,2-dichloroethane (50 mL) was added 1-chloroethyl chloroformate (5.2 mL, 48.2 mmol) at 0 °C under an argon atmosphere. The mixture was stirred at this temperature for 0.5 h and then refluxed for 2 h. The reaction mixture was filtered and evaporated *in vacuo*. The residue was dissolved in MeOH (50 mL) and refluxed for 1 h. Aqueous $NaHCO_3$ (*ca.* 1 M, 19.3 mL, 19.3 mmol) and *N*-[[(benzyloxy)carbonyl]oxy]-succinimide (2.64 g, 10.6 mmol) was added to the mixture at room temperature and stirred for 0.5 h. The mixture was filtered and evaporated *in vacuo* to leave a residue, which was dissolved in CH_2Cl_2 (300 mL) and washed successively with H_2O (100 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed *in vacuo*. Medium-pressure liquid chromatography (SiO_2, 1:1 EtOAc/hexane) provided 5.09 g (98%) of **9** as a colorless gummy solid: $[\alpha]^{25}_D$ +78.5° (*c* = 0.33, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, 2H, *J* = 7.0 Hz), 7.44–7.28 (m, 8H), 6.81–6.70 (m, 2H), 5.53–5.42 (m, 1H), 5.35–5.06 (m, 4H), 4.73 (s, 0.6H), 4.61 (s, 0.4H), 4.15 (d, 1H, *J* = 16.0 Hz), 3.97–3.82 (m, 1H), 3.81 (s, 3H), 3.53 (s, 1.8H), 3.51 (s, 1.2H), 3.15 (ddd, 1H, *J* = 17.7, 17.7, 4.9 Hz), 2.86–2.66 (m, 2H), 2.61–2.46 (m, 1H), 2.43 (d, 1H, *J* = 16.0 Hz), 1.93 (br dd, 1H, *J* = 13, 13 Hz), 1.73–1.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.47, 128.98, 128.76, 128.53, 128.47, 128.33, 128.07, 127.99, 127.79, 127.64, 123.63, 113.75, 113.60, 111.82, 73.33, 67.33, 67.17, 55.72, 54.87, 49.25, 49.06, 48.83, 44.64, 40.90, 40.80, 38.59,

(19) All ^1H and ^{13}C NMR resonances of compounds **3–5** were assigned by the aid of 2D NMR (COSY, HMQC,[19a] and HMBC[19b]) spectra. (a) Müler, L. *J. Am. Chem. Soc.* **1979**, *101*, 4481. (b) Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093.

36.45, 36.17, 32.29, 31.79; IR ($CHCl_3$) ν_{max} 2950, 1685, 1630, 1480, 1420, 1270, 1130 cm^{-1}; MS *m/z* (%) 539 (3, M^+), 448 (7), 138 (29), 91 (100); HRMS calcd for $C_{33}H_{33}NO_6$ 539.2308, found 539.2302.

Reduction of 9 with $NaBH_4/CeCl_3$. To a solution of **9** (1.174 g, 2.18 mmol) in MeOH (30 mL) was added $CeCl_3 \cdot 7H_2O$ (0.89 g, 2.39 mmol), and the mixture was stirred at room temperature for 10 min. $NaBH_4$ (89 mg, 2.35 mmol) was added to the solution, and the mixture was stirred for 1 h. Acetone (3 mL) was added to the mixture at 0 °C, and the mixture was stirred at this temperature for 0.5 h. The mixture was evaporated *in vacuo* to leave a residue, which was dissolved in CH_2Cl_2 (150 mL) and washed successively with H_2O (30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$ and filtered and the solvent removed *in vacuo*. The residue was chromatographed (MPLC, silica gel, 1:1 EtOAc/hexane) to provide **11a** (591 mg, 50%) and **11b** (558 mg 47%). **(6*S*,9*S*,13*R*,14*S*)-7,8-Didehydro-4-(benzyloxy)-17-[(benzyloxy)carbonyl]-3,7-dimethoxymorphinan-6-ol (11a):** A colorless gummy solid; $[\alpha]^{24}_D$ +27.9° (*c* = 0.23, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, 2H, *J* = 7.5 Hz), 7.44–7.28 (m, 8H), 6.83–6.71 (m, 2H), 5.47 (d, 1H, *J* = 11.5 Hz), 5.22–5.07 (m, 3H), 4.58–4.40 (m, 2H), 4.11 (t-like, 1H, *J* = 5 Hz), 3.94–3.82 (m, 1H), 3.80 (s, 3H), 3.56–3.45 (m, 1H), 3.50 and 3.48 (each s, 1.5H), 3.24–3.12 (m, 1H), 2.74–2.53 (m, 2H), 2.36 (br s, 1H), 1.98–1.89 (br m, 1H), 1.81 (dd, 1H, *J* = 14.0, 7.0 Hz), 1.60 (dd, 1H, *J* = 14.6, 5.0 Hz), 1.49 (ddd, 1H, *J* = 12.9, 12.5, 5.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.41, 157.27, 155.77, 155.59, 151.13, 151.06, 147.67, 138.21, 138.15, 136.84, 136.72, 131.04, 129.41, 129.07, 128.41, 128.32, 128.26, 127.86, 127.80, 127.78, 127.73, 127.61, 127.54, 127.50, 123.80, 111.90, 95.67, 73.57, 66.99, 66.85, 66.43, 55.80, 54.28, 50.40, 50.27, 44.03, 39.64, 39.37, 39.23, 36.98, 36.75, 34.40, 34.34, 31.96, 31.37; IR ($CHCl_3$) ν_{max} 3560, 2940, 1675, 1480, 1415, 1345, 1270, 1135, 1050, 1030 cm^{-1}; MS *m/z* (%) 541 (48, M^+), 342 (61), 91 (100); HRMS calcd for $C_{33}H_{35}NO_6$ 541.2464, found 541.2468. **(6*R*,9*S*,13*R*,14*S*)-7,8-Didehydro-4-(benzyloxy)-17-[(benzyloxy)carbonyl]-3,7-dimethoxymorphinan-6-ol (11b):** A colorless gummy solid; $[\alpha]^{28}_D$ +53.5° (*c* = 0.38, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, 2H, *J* = 7.1 Hz), 7.42–7.27 (m, 8H), 6.81–6.70 (m, 2H), 5.20–5.02 (m, 4H), 4.56–4.34 (m, 2H), 4.22 (br m, 1H), 3.94–3.86 (m, 1H), 3.83 (s, 3H), 3.53 (dd, 1H, *J* = 12.3, 5.8 Hz), 3.47 and 3.45 (each s, 1.5H), 3.15 (ddd, 1H, *J* = 13.1, 13.1, 4.9 Hz), 2.71–2.52 (m, 3H), 2.34–2.27 (m, 1H), 1.81 (br dd, 1H, *J* = 10, 10 Hz), 1.67–1.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.98, 156.80, 155.88, 155.71, 151.15, 147.76, 137.97, 137.00, 136.90, 131.01, 129.83, 129.51, 128.44, 128.03, 127.96, 127.84, 127.76, 123.59, 111.46, 95.48, 74.32, 67.13, 67.02, 66.38, 55.84, 54.48, 49.91, 49.76, 44.45, 41.09, 39.17, 39.12, 37.70, 36.73, 36.47, 31.80, 31.27; IR ($CHCl_3$) ν_{max} 3600, 2940, 1680, 1480, 1420, 1270, 1135, 1055, 1040 cm^{-1}; MS *m/z* (%) 541 (3, M^+), 105 (25), 91 (100); HRMS calcd for $C_{33}H_{35}NO_6$ 541.2464, found 541.2464.

Reduction of 9 with L-Selectride. To a solution of **9** (943 mg, 1.75 mmol) in THF (40 mL) was added 1 M L-Selectride (2.1 mL, 2.1 mmol) in THF during 10 min at −78 °C under an argon atmosphere, and the mixture was stirred at this temperature for 3 h. Thirty-five percent aqueous H_2O_2 (1 mL) was added to the solution, and the reaction was slowly warmed to room temperature and stirred for 1 h. Dimethyl sulfide (0.5 mL) was added to the solution, and the mixture was stirred for 10 min. The solvent was evaporated *in vacuo*, and the residue was chromatographed (MPLC, silica gel, 2:3 EtOAc/hexane) to provide the alcohol **11a** (864 mg, 91%).

(6*S*,9*S*,13*R*,14*S*)-7,8-Didehydro-4-hydroxy-3,7-dimethoxymorphinan-6-ol (12a). To a solution of **11a** (100.2 mg, 0.185 mmol) in EtOH–cyclohexene (1:1, 2 mL) was added Pearlman's catalyst (100 mg), and the mixture was refluxed for 45 min under an argon atmosphere. The reaction mixture was filtered and evaporated *in vacuo*. The residue was recrystallized from MeOH to provide **12a** (43.4 mg, 74%) as colorless prisms: mp 216–219 °C dec; $[\alpha]^{22}_D$ −185.1° (*c* = 0.10, pyridine); ^1H NMR (400 MHz, $CDCl_3$) δ 6.66 (d, 1H, *J* = 8.3 Hz), 6.58 (1H, d, *J* = 8.3 Hz), 4.47 (d, 1H, *J* = 2.4 Hz), 4.16 (m, 1H, H-6), 3.82 (s, 3H), 3.65 (dd, 1H, *J* = 14.8, 1.2 Hz, H-5β), 3.48 (s, 3H), 3.27 (dd, 1H, *J* = 5.3, 5.2 Hz), 3.20 (ddd, 1H, *J* = 17.3, 5.3, 0.8 Hz), 2.72 (ddd, 1H, *J* = 12.8, 4.7, 1.6 Hz), 2.66 (d, 1H, *J* = 17.3 Hz), 2.53 (ddd, 1H, *J* = 12.8, 12.6, 3.4 Hz), 2.43 (m, 1H), 1.88 (br d, 1H, *J* = 12 Hz), 1.74 (dd, 1H, *J* = 14.8, 4.8 Hz, H-5α), 1.49 (ddd, 1H, *J* = 12.6, 12.5, 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.57, 144.77, 144.31, 131.46, 125.28, 119.10, 108.82, 96.99, 66.55, 56.10, 54.37, 51.34, 45.57, 40.47, 39.84, 37.17, 35.18, 33.91; IR (KBr) ν_{max} 3420, 3070, 2850, 1650, 1225, 1050 cm^{-1}; MS *m/z* (%) 317 (29, M^+), 270 (47), 164 (100), 132 (35). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.31; H, 4.41. Found: C, 67.85; H, 7.31; N, 4.38.

(6*R*,9*S*,13*R*,14*S*)-7,8-Didehydro-4-hydroxy-3,7-dimethoxymorphinan-6-ol (12b). To a solution of **11b** (105.0 mg, 0.194 mmol) in EtOH–cyclohexene (1:1, 2 mL) was added Pearlman's catalyst (100 mg), and the mixture was refluxed for 45 min under an argon atmosphere. The reaction mixture was filtered and evaporated *in vacuo*. The residue was chromatographed (alumina, 50–3:1 CH_2Cl_2/MeOH) to provide **12b** (54.2 mg, 88%) as an amorphous solid: $[\alpha]^{23}_D$ −94.4° (*c* = 0.43, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 6.66 (d, 1H, *J* = 8.2 Hz), 6.54 (d, 1H, *J* = 8.2 Hz), 4.35 (s, 1H), 4.20 (ddd, 1H, *J* = 10.6, 6.0, 2.7 Hz, H-6), 3.80 (s, 3H), 3.63 (dd, 1H, *J* = 12.1, 6.0 Hz, H-5β), 3.41 (s, 3H), 3.21 (m, 1H), 3.15 (dd, 1H, *J* = 17.0, 5.3 Hz), 2.72 (ddd, 1H, *J* = 12.9, 4.8, 1.7 Hz), 2.65 (d, 1H, *J* = 17.0 Hz), 2.63 (br s, 1H), 2.57 (ddd, 1H, *J* = 12.9, 12.5, 3.4 Hz), 1.80 (ddd, 1H, *J* = 12.5, 3.4, 1.7 Hz), 1.61 (dd, 1H, *J* = 12.1, 10.6 Hz, H-5α), 1.60 (ddd, 1H, *J* = 12.5, 12.5, 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.54, 144.59, 144.50, 131.56, 124.63, 118.09, 108.41, 96.34, 66.57, 56.01, 54.28, 50.61, 45.66, 41.68, 39.46, 38.25, 36.42, 33.38; IR ($CHCl_3$) ν_{max} 3600, 3520, 2900, 1485, 1450, 1435, 1280, 1060, 1030 cm^{-1}; HRFAB-MS calcd for $C_{18}H_{24}NO_4$ [MH] 318.1705, found 318.1705.

(6*R*,9*S*,13*R*,14*S*)-7,8-Didehydro-4-(benzyloxy)-17-[(benzyloxy)carbonyl]-3,7-dimethoxy-6-[(2-nitrophenyl)seleno]morphinane (13a). To a solution of **11a** (1.95 g, 3.60 mmol) and 2-nitrophenyl selenocyanate (984 mg, 4.33 mmol) in THF (60 mL) under an argon atmosphere was added tributylphosphine (1.1 mL, 4.41 mmol) dropwise at 0 °C. The solution was stirred at room temperature for 4 h. After removal of the solvent under reduced pressure, the residue was chromatographed (MPLC, silica gel, 1:1 CH_2Cl_2/hexane → 5:5:1 CH_2Cl_2/hexane/EtOAc) to provide the selenide **13a** (2.51 g, 96%) as a yellow gummy solid: $[\alpha]^{27}_D$ +171.8° (*c* = 0.21, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, 1H, *J* = 8.3, 1.4 Hz), 7.73 (d, 1H, *J* = 8.1 Hz), 7.44–7.27 (m, 10H), 7.11 (ddd, 1H, *J* = 8.3, 8.3, 1.2 Hz), 6.89–6.76 (m, 3H), 5.22–5.05 (m, 3H), 4.95–4.85 (m, 1H), 4.62–4.44 (m, 2H), 4.07 (m, 1H) 4.00–3.89 (m, 1H), 3.88 (s, 3H), 3.77 (dd, 1H, *J* = 13.1, 5.8 Hz), 3.43 and 3.41 (each s, 1.5H), 3.21 (ddd, 1H, *J* = 18.1, 18.1, 5.1 Hz), 2.76–2.60 (m, 2H), 2.52 (br s, 1H), 1.88 (ddd, 1H, *J* = 12.8, 12.8, 3.8 Hz), 1.75 (br d, 1H, *J* = 13 Hz), 1.59 (ddd, 1H, *J* = 13.0, 13.0, 5.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.77, 155.71, 155.61, 155.53, 151.13, 147.85, 147.19, 137.63, 136.90, 136.79, 133.49, 133.13, 131.17, 130.29, 130.12, 129.83, 128.49, 128.04, 127.96, 127.76, 125.74, 125.18, 123.84, 111.71, 97.19, 74.83, 67.17, 67.05, 55.89, 54.75, 49.86, 49.71, 43.82, 41.22, 39.19, 38.94, 38.52, 36.88, 36.62, 31.72, 31.23; IR ($CHCl_3$) ν_{max} 2950, 1680, 1510, 1420, 1330, 1300, 1270 cm^{-1}; FAB-MS 727 (MH^+).

(6*S*,9*S*,13*R*,14*S*)-7,8-Didehydro-4-(benzyloxy)-17-[(benzyloxy)carbonyl]-3,7-dimethoxy-6-[(2-nitrophenyl)seleno]morphinane (13b). Compound **13b** was prepared from **11b** in 97% yield by the same procedure used for **13a**. **13b**: $[\alpha]^{24}_D$ −206.6° (*c* = 0.55, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, 1H, *J* = 8.3, 1.4 Hz), 7.71 (d, 1H, *J* = 8.1 Hz), 7.43–7.16 (m, 10H), 7.09 (br s, 2H), 6.89–6.71 (m, 2H), 5.32–5.06 (m, 3H), 4.62–4.41 (m, 3H), 4.16 (d, 1H, *J* = 5.2 Hz), 3.95–3.84 (m, 1H), 3.83 (s, 3H), 3.78 (d, 1H, *J* = 14.4 Hz), 3.49 and 3.47 (each s, 1.5H), 3.29–3.17 (m, 1H), 2.81–2.55 (m, 2H), 2.49 (br s, 1H), 2.07 (m, 1H), 1.96 (ddd, 1H, *J* = 12.9, 12.9, 3.1 Hz), 1.46 (ddd, 1H, *J* = 12.9, 12.9, 5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.96, 155.82, 155.61, 155.44, 150.98, 149.46, 146.99, 138.21, 136.95, 136.80, 136.39, 132.77, 129.67, 129.18, 128.51, 128.42, 128.09, 127.98, 127.90, 127.79, 127.48, 127.40, 127.22, 125.99, 124.71, 123.72, 123.69, 112.82, 97.24, 73.61, 73.56, 67.10, 67.00, 56.20, 54.58, 50.71, 50.62,

43.83, 40.27, 40.03, 37.98, 37.05, 36.80, 36.56, 35.00, 34.93, 31.79, 31.14; IR ($CHCl_3$) ν_{max} 2940, 1680, 1510, 1415, 1330, 1300, 1275, 1130, 1035 cm^{-1}; FAB-MS 727 (MH^+).

(8*S*,9*S*,13*R*,14*S*)-5,6-Didehydro-4-(benzyloxy)-17-[(benzyloxy)carbonyl]-8-hydroxy-3-methoxymorphinan-7-one (15). To a solution of **13a** (3.05 g, 4.21 mmol) in THF (50 mL) was added 35% aqueous H_2O_2 (4.1 mL, 42 mmol) at 0 °C. The solution was stirred at room temperature for 21 h. Methyl sulfide (10 mL) was added to the solution at 0 °C and the mixture was stirred at this temperature for 0.5 h. The reaction mixture was diluted with toluene (200 mL), washed with water (2 × 100 mL), dried ($MgSO_4$), and filtered. After removal of the solvent under reduced pressure, the residue was chromatographed (MPLC, silica gel, 1:15 EtOAc/CH_2Cl_2 then 1:2 EtOAc/hexane) to provide **15** (1.96 g, 89%) as a colorless gummy solid: $[\alpha]^{27}_D$ +67.7° (*c* = 0.56, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, 1H, *J* = 10.1 Hz), 7.49–7.27 (m, 10H), 6.96–6.84 (m, 2H), 5.94 (d, 1H, *J* = 10.1 Hz), 5.34–5.09 (m, 3H), 4.99–4.84 (br m, 1H), 4.75 (d, 1H, *J* = 10.9 Hz), 4.16–3.90 (m, 2H), 3.87 (s, 3H), 3.50–3.30 (m, 2H), 2.93–2.62 (m, 2H), 2.24 (br d, 1H, *J* = 13 Hz), 1.98–1.87 (br m, 1H), 1.65 (ddd, 1H, *J* = 12.9, 12.9, 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.40, 160.34, 160.03, 155.43, 151.62, 145.76, 137.43, 136.78, 130.60, 129.32, 129.06, 128.55, 128.49, 128.42, 128.03, 127.90, 127.76, 123.92, 123.33, 123.22, 111.90, 74.12, 70.20, 67.12, 55.74, 51.03, 45.68, 38.06, 36.37, 36.12, 30.94, 30.58; IR ($CHCl_3$) ν_{max} 3530, 2950, 1680, 1480, 1420, 1280, 1120, 1060 cm^{-1}; MS *m*/*z* (%) 525 (52, M^+), 435 (31), 434 (100), 181 (57), 92 (89), 91 (71); HRMS calcd for $C_{32}H_{31}NO_6$ 525.2151, found 525.2136.

Oxidation of Selenide 13b. To a solution of **13b** (573 mg, 0.791 mmol) in THF (20 mL) was added 35% aqueous H_2O_2 (1.2 mL, 12 mmol) at 0 °C. The solution was stirred at room temperature for 21 h. Methyl sulfide (5 mL) was added to the solution at 0 °C, and the mixture was stirred at this temperature for 0.5 h. The reaction mixture was diluted with toluene (150 mL), washed with water (2 × 30 mL), dried ($MgSO_4$), and filtered. After removal of the solvent under reduced pressure, the residue was chromatographed (MPLC, silica gel, 1:15 EtOAc/CH_2Cl_2 then 1:2 EtOAc/hexane) to provide **15** (73.9 mg, 18%) and **19** (78.8 mg, 19%) as a pale yellow gummy solid. **(9*S*,13*S*,14*S*)-6,7-Didehydro-4-(benzyloxy)-17-[(benzyloxy)carbonyl]-3,7-dimethoxymorphinan-8-one (19):** a pale yellow gummy solid; $[\alpha]^{27}_D$ +138.1° (*c* = 0.79, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.51–7.27 (m, 10H), 6.80–6.70 (m, 2H, H-1 and 2), 5.72 (br s, 1H, H-6), 5.27–4.95 (m, 5H, PhCH_2 × 2 and H-9), 4.19 (dd, 1H, *J* = 17.3, 7.4 Hz, H-5β), 4.03–3.89 (m, 1H, H-16a), 3.83 (s, 3H, 3-OMe), 3.46 (s, 3H, 8-OMe), 3.44–3.32 (m, 1H, H-10a), 2.76–2.55 (m, 2H, H-10b and 16b), 2.50 (br s, 1H, H-14), 2.32 (dd, 1H, *J* = 7.3, 2.1 Hz, H-15b), 1.81 (ddd, 1H, *J* = 12.9, 1.9, 1.5 Hz, H-15a), 1.72 (ddd, 1H, *J* = 12.9, 12.9, 5.0 Hz, H-15b); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.38, 191.12, 155.36, 151.03, 146.75, 137.60, 136.81, 130.88, 130.69, 130.08, 128.52, 128.43, 128.01, 127.89, 127.85, 124.28, 114.41, 113.95, 111.65, 74.22, 67.08, 55.65, 55.54, 54.65, 45.04, 41.21, 38.23, 37.93, 37.82, 34.67, 31.70, 31.52; IR ($CHCl_3$) ν_{max} 2940, 1680, 1480, 1425, 1280, 1250, 1130, 1050, 1025 cm^{-1}; MS *m*/*z* (%) 539 (8, M^+), 449 (30), 448 (100), 404 (48); HRMS calcd for $C_{33}H_{33}NO_6$ 539.2308, found 539.2328.

(9*S*,13*S*)-5,6,8,14-Tetrahydro-4-(benzyloxy)-17-[(benzyloxy)carbonyl]-8-hydroxy-3-methoxymorphinan-7-one (16). Dimethyl sulfoxide (1.41 mL, 19.9 mmol) was added dropwise to a solution of oxalyl chloride (0.85 mL, 9.74 mmol) in CH_2Cl_2 (300 mL) at −78 °C under an atmosphere of argon. The mixture was stirred for 15 min followed by dropwise addition of a solution of **15** (2.60 g, 4.95 mmol) in CH_2Cl_2 (5 mL) over a 10 min period. The mixture was stirred at this temperature for 1 h. Triethylamine (5.5 mL, 39.5 mmol) was added, and the mixture was stirred for 5 min. The mixture was allowed to warm to 0 °C with stirring over a 15 min period. Water (100 mL) was added, and the organic layer was separated. The aqueous residue was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure, and the residue was chromatographed (MPLC, silica gel, 1:3 EtOAc/hexane) to provide the diosphenol **16** (2.31 g, 89%) as a colorless gummy solid: $[\alpha]^{27}_D$ −63.4° (*c* = 0.67, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, 1H, *J* = 10.3 Hz), 7.52–7.28 (m, 10H), 6.93–6.82 (m, 2H), 6.49 (br s, 1H), 6.39 (d, 1H, *J* = 10.3 Hz), 5.92–5.80 (m, 1H), 5.27–5.10 (m, 3H), 4.95 (d, 1H, *J* = 11.0 Hz), 4.07–3.91 (m, 1H), 3.88 (s, 3H), 3.33–3.22 (m, 1H), 3.19–3.00 (m, 1H), 2.95–2.80 (m, 1H), 2.21 (br d, 1H, *J* = 13 Hz), 1.52 (ddd, 1H, *J* = 12.8, 12.8, 5.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.48, 155.44, 155.32, 155.20, 151.82, 146.08, 140.16, 140.02, 137.20, 136.71, 129.62, 129.34, 128.67, 128.48, 128.27, 128.03, 127.78, 127.68, 125.56, 124.42, 112.26, 73.54, 67.63, 67.32, 55.98, 45.71, 43.50, 38.72, 37.82, 37.60, 37.30, 36.74, 36.58; IR ($CHCl_3$) ν_{max} 3440, 2940, 1680, 1645, 1600, 1480, 1430, 1405, 1325, 1280, 1125, 1060, 1035, 985 cm^{-1}; MS *m*/*z* (%) 523 (29, M^+), 389 (33), 388 (100), 269 (29), 92 (67), 91 (61); HRMS calcd for $C_{32}H_{29}NO_6$ 523.1995, found 523.2018.

(9*S*,13*S*)-5,6,8,14-Tetrahydro-4-(benzyloxy)-17-[(benzyloxy)carbonyl]-3,8-dimethoxymorphinan-7-one (17). To a solution of **16** (603 mg, 1.14 mmol) in acetone (20 mL) was added K_2CO_3 (318 mg, 2.30 mmol) and methyl *p*-toluenesulfonate (322 mg, 1.73 mmol), and the mixture was refluxed for 15 h. The reaction mixture was filtered and evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 mL), washed successively with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), and filtered. The solvent was removed under reduced pressure, and the residue was chromatographed (MPLC, silica gel, 1:2 EtOAc/hexane) to provide **17** (608 mg, 98%) as a colorless gummy solid: $[\alpha]^{24}_D$ −27.0° (*c* = 0.23, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, 1H, *J* = 10.3 Hz), 7.52–7.28 (m, 10H), 6.88 (br s, 2H), 6.28 (d, 1H, *J* = 10.3 Hz), 5.95–5.84 (m, 1H), 5.28–5.10 (m, 3H), 4.90 (d, 1H, *J* = 10.9 Hz), 4.08–3.90 (m, 1H), 3.88 (s, 3H), 3.84 and 3.75 (each s, 1.5H), 3.29–3.01 (m, 2H), 2.93–2.77 (m, 1H), 2.19 (ddd, 1H, *J* = 12.8, 3.5, 1.6 Hz), 1.57 (ddd, 1H, *J* = 12.9, 12.9, 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.50, 155.24, 155.09, 152.09, 151.92, 145.93, 145.20, 145.11, 142.06, 137.18, 136.57, 136.48, 130.69, 129.05, 128.81, 128.61, 128.46, 128.20, 128.04, 127.97, 127.86, 124.28, 124.17, 112.28, 74.76, 67.34, 60.45, 55.92, 45.80, 45.65, 44.08, 38.46, 38.09, 37.75, 36.97; IR ($CHCl_3$) ν_{max} 2950, 1685, 1665, 1640, 1480, 1420, 1290, 1125, 1060 cm^{-1}; MS *m*/*z* (%) 537 (14, M^+), 505 (31), 446 (36), 370 (30), 91 (100); HRMS calcd for $C_{33}H_{31}NO_6$ 537.2151, found 537.2166.

(9*S*,13*R*)-8,14-Didehydro-4-(benzyloxy)-17-[(benzyloxy)carbonyl]-3,8-dimethoxymorphinan-7-one (8). Compound **17** (306 mg, 0.569 mmol) in benzene (10 mL) was hydrogenated (1 atm) at room temperature for 3 days using tris(triphenylphosphine)rhodium(I) chloride (158 mg, 0.171 mmol) as a catalyst. The reaction mixture was filtered and concentrated, and the residue was chromatographed (MPLC, silica gel, 2:3 EtOAc/hexane) to provide **8** (297 mg, 97%) as a colorless gummy solid: $[\alpha]^{27}_D$ +17.8° (*c* = 0.57, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.47–7.28 (m, 10H), 6.89–6.76 (m, 2H), 5.81–5.69 (m, 1H), 5.27–5.07 (m, 3H), 5.01 (d, 1H, *J* = 11.1 Hz), 4.03–3.89 (m, 1H), 3.87 (s, 3H), 3.74 and 3.65 (each s, 1.5H), 3.19 (br dd, 1H, *J* = 17, 4 Hz), 3.13–2.95 (m, 2H), 2.89–2.74 (m, 1H), 2.49–2.29 (m, 3H), 1.96 (br d, 1H, *J* = 13 Hz), 1.86 (ddd, 1H, *J* = 12.9, 12.9, 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.76, 155.30, 155.13, 151.71, 146.44, 144.41, 136.68, 136.66, 132.63, 129.65, 129.35, 128.50, 128.46, 128.02, 127.88, 124.11, 123.97, 111.83, 74.37, 67.23, 60.66, 60.55, 55.83, 46.39, 46.22, 40.51, 39.08, 38.93, 38.21, 37.90, 37.00, 36.92, 35.31, 31.13; IR ($CHCl_3$) ν_{max} 2940, 1675, 1420, 1310, 1280, 1130, 1050, 1010 cm^{-1}; MS *m*/*z* (%) 539 (14, M^+), 482 (19), 479 (21), 404 (19), 388 (22), 92 (20), 91 (100); HRMS calcd for $C_{33}H_{33}NO_6$ 539.2308, found 539.2328.

(9*S*,13*R*)-8,14-Didehydro-4-(benzyloxy)-17-[(benzyloxy)carbonyl]-3,8-dimethoxymorphinan-7-one *p*-Toluenesulfonhydrazone (20). To a solution of **8** (16.4 mg, 0.0304 mmol) and *p*-toluenesulfonohydrazide (7.0 mg, 0.038 mmol) in THF (1.5 mL) was added *p*-toluenesulfonic acid monohydrate (*ca.* 1 mg, 0.005 mmol). The mixture was refluxed for 2 h. After removal of the THF under reduced pressure, the residue was dissolved in CH_2Cl_2 (20 mL) and washed successively with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$ and filtered and the solvent removed *in vacuo*. Silica gel

chromatography (MPLC, eluted with 1:2 EtOAc/hexane) provided **20** (15.9 mg, 74%) as an amorphous powder: $[\alpha]^{28}_D$ −34.4° (*c* = 0.27, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (br d, 2H, *J* = 7 Hz), 7.56 (br s, 1H), 7.48−7.20 (m, 12H), 6.87−6.70 (m, 2H), 5.75−5.65 (m, 1H), 5.25−5.01 (m, 3H), 4.97 (d, 1H, *J* = 11.0 Hz), 3.97−3.88 (m, 1H), 3.84 (s, 3H), 3.64 and 3.55 (each s, 1.5H), 3.17−3.04 (m, 1H), 3.01−2.86 (m, 1H), 2.85−2.69 (m, 2H), 2.38 (s, 3H), 2.30−2.02 (m, 3H), 1.83 (br d, 1H, *J* = 12 Hz), 1.75−1.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.15, 151.61, 146.14, 144.12, 143.09, 142.96, 137.56, 136.78, 135.23, 134.17, 133.27, 130.01, 129.75, 129.52, 128.55, 128.49, 128.21, 127.99, 127.86, 124.09, 123.94, 111.52, 74.27, 67.19, 60.92, 55.82, 46.16, 46.00, 39.39, 39.30, 39.05, 38.85, 38.04, 37.65, 37.29, 30.26, 21.58, 21.36; IR ($CHCl_3$) ν_{max} 2930, 1680, 1420, 1280, 1160, 1130, 1050 cm^{-1}.

(9*S*,13*R*)-6,7,8,14-Tetrahydro-4-(benzyloxy)-17-[(benzyloxy)carbonyl]-3,8-dimethoxy-7-[(trifluoromethanesulfonyl)oxy]morphinane (21). To a solution of **8** (55.9 mg, 0.104 mmol) in THF (7 mL) at −78 °C under an argon atmosphere was added potassium bis(trimethylsilyl)amide (0.5 M, 0.31 mL, 0.16 mmol) in toluene, and the mixture was stirred at this temperature for 30 min. A solution of *N*-phenyltrifluoromethanesulfonimide (92.9 mg, 0.26 mmol) in THF (2 mL) was added to the solution, and the mixture was stirred for 30 min. Saturated aqueous NH_4Cl (1 mL) was added, and the mixture was allowed to warm to 0 °C and stirred for 10 min. The reaction mixture was then diluted with CH_2Cl_2 (30 mL), washed with H_2O (5 mL) and brine (5 mL), dried and filtered. The solvent was removed under reduced pressure, and the residue was chromatographed (MPLC, silica gel, 1:2 EtOAc/hexane) to provide **21** (57.8 mg, 83%) as a colorless gummy solid: $[\alpha]^{28}_D$ −40.3° (*c* = 0.26, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.48−7.27 (m, 10H), 6.88−6.76 (m, 2H), 5.69−5.64 (m, 1H), 5.56−5.48 (m, 1H), 5.22 (d, 1H, *J* = 12.5 Hz), 5.17 (d, 1H, *J* = 12.5 Hz), 5.14−5.03 (m, 2H), 3.93−3.79 (m, 1H), 3.86 (s, 3H), 3.65 and 3.57 (each s, 1.5H), 3.31 (ddd, 1H, *J* = 19.3, 5.6, 3.4 Hz), 3.18−2.93 (m, 3H), 2.84−2.70 (m, 1H), 2.16−2.04 (m, 1H), 1.92−1.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.34, 155.17, 151.83, 151.75, 145.99, 140.64, 140.45, 138.62, 138.45, 137.66, 136.80, 136.60, 135.28, 135.17, 128.67, 128.57, 128.45, 128.30, 128.02, 127.84, 127.81, 127.74, 126.83, 124.27, 124.11, 120.10, 116.92, 115.84, 115.56, 113.74, 111.82, 74.28, 74.20, 67.21, 67.13, 61.63, 61.45, 55.89, 46.39, 46.14, 40.77, 39.58, 39.44, 38.23, 36.87, 36.22, 33.83, 33.70; IR ($CHCl_3$) ν_{max} 2940, 1685, 1415, 1275, 1135 cm^{-1}.

6-Hydroxylation of 8 (a typical procedure). To a solution of **8** (60.2 mg, 0.112 mmol) in THF (5 mL) at −78 °C under an argon atmosphere was added potassium bis(trimethylsilyl)amide (0.5 M, 0.44 mL, 0.22 mmol) in toluene, and the mixture was stirred at this temperature for 1 h. The mixture was allowed to warm to 0 °C. After 5 min stirring the mixture was cooled to −78 °C and a solution of (−)-(2*S*,8a*R*)-(camphorsulfonyl)oxaziridine (**23**, 64.3 mg, 0.28 mmol) in THF (2 mL) was added over a 5 min period. The mixture was stirred at this temperature for 1 h, and saturated aqueous NH_4Cl (1 mL) was added. The mixture was allowed to warm to room temperature. The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (30 mL), washed with H_2O (10 mL) and brine (10 mL), dried, and filtered. The solvent was removed under reduced pressure. Medium-pressure liquid chromatography (silica gel, 1:15 EtOAc/CH_2Cl_2) removed the unreacted **8** (14.0 mg, 23%), and the mixture of the hydroxy enones were separated by HPLC (Inertsil PREP-ODS (20 × 250 mm, 10 μ), 7:13 H_2O/MeOH, 10 mL/min) to provide **7b** (10.3 mg, 17%, t_R = 128.9 min) and **7a** (31.1 mg, 50%, t_R = 134.3 min). **(6*S*,9*S*,13*S*)-8,14-Dehydro-4-[(benzyloxy)carbonyl]-6-hydroxy-3,8-dimethoxymorphinan-7-one (7a):** a colorless gummy solid; $[\alpha]^{26}_D$ −22.7° (*c* = 0.68, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.53−7.27 (m, 10H), 6.89−6.73 (m, 2H), 5.78−5.65 (m, 1H), 5.28−5.07 (m, 3H), 5.00 (d, 1H, *J* = 10.9 Hz), 4.36 (ddd, 1H, *J* = 13.7, 6.4, 2.2 Hz, H-6), 4.03−3.88 (m, 1H), 3.86 (s, 3H,), 3.75 and 3.65 (each s, 1.5H), 3.58 (dd, 1H, *J* = 13.6, 6.4 Hz, H-5α), 3.43 and 3.41 (each br s, 0.5H, O*H*), 3.20−2.93 (m, 2H), 2.87−2.71 (m, 1H), 2.22 (dd, 1H, *J* = 13.7, 13.6 Hz, H-5β); 2.18−2.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.09, 155.32, 155.06, 151.95, 146.44, 143.48, 141.95, 141.82, 137.43, 136.59, 136.47, 133.93, 128.46, 128.19, 127.99, 127.85, 127.71, 123.90, 123.77, 112.08, 74.14, 69.84, 67.26, 59.99, 59.74, 55.84, 46.25, 46.02, 40.94, 39.94, 39.36, 36.01, 35.44; IR ($CHCl_3$) ν_{max} 3500, 2930, 1685, 1315, 1275, 1070 cm^{-1}; MS *m*/*z* (%) 555 (35, M^+), 432 (59), 420 (26), 388 (41), 348 (27), 275 (39), 92 (78), 91 (100); HRMS calcd for $C_{33}H_{33}NO_7$ 555.2257, found 555.2232. **(6*R*,9*S*,13*S*)-8,14-Dehydro-4-[(benzyloxy)carbonyl]-6-hydroxy-3,8-dimethoxymorphinan-7-one (7b):** a colorless gummy solid; $[\alpha]^{24}_D$ +51.3° (*c* = 0.17, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (br d, 2H, *J* = 7 Hz), 7.43−7.28 (m, 8H), 6.89−6.78 (m, 2H), 5.77 (d, 0.5H, *J* = 4.2 Hz), 5.72 (d, 0.5 H, *J* = 4.6 Hz), 5.26−4.95 (m, 4H), 4.09 (br d, 1H, *J* = 15 Hz), 4.04 (dd, 1H, *J* = 12.9, 4.7 Hz), 3.89 (s, 3H), 3.99−3.83 (m, 1H), 3.80 and 3.72 (each s, 1.5H), 3.39−3.32 (m, 1H), 3.27−3.17 (m, 1H), 3.12−2.98 (m, 1H), 2.85−2.70 (m, 1H), 1.91 (br d, 1H, *J* = 13 Hz), 1.73 (dd, 1H, *J* = 13.3, 13.3 Hz), 1.64 (ddd, 1H, *J* = 13.3, 13.3, 5.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.72, 155.30, 155.04, 151.85, 146.79, 146.69, 141.88, 136.63, 136.54, 131.11, 129.98, 129.73, 128.53, 128.40, 128.09, 127.93, 124.16, 124.02, 111.99, 74.49, 70.39, 67.35, 61.08, 55.90, 46.41, 39.88, 39.68, 39.47, 38.78, 38.38, 38.16; IR ($CHCl_3$) ν_{max} 3520, 2950, 1685, 1475, 1425, 1320, 1280, 1130, 1070, 1030 cm^{-1}; MS *m*/*z* (%) 555 (40, M^+), 432 (20), 420 (32), 91 (100); HRMS calcd for $C_{33}H_{33}NO_7$ 555.2257, found 555.2238.

(6*S*,7*S*,9*S*,13*S*)-8,14-Didehydro-4-[(benzyloxy)carbonyl]-3,8-dimethoxymorphinane-6,7-diol (25) and (6*S*,7*R*,9*S*,13*S*)-8,14-Didehydro-4-[(benzyloxy)carbonyl]-3,8-dimethoxymorphinane-6,7-diol (26). To a solution of **7a** (323 mg, 0.581 mmol) in EtOH (10 mL) was added $CeCl_3 \cdot 7H_2O$ (326 mg, 0.875 mmol), and the mixture was stirred at room temperature for 10 min. $NaBH_4$ (44 mg, 1.16 mmol) was added to the solution, and the mixture was stirred for 1 h. Acetone (3 mL) was added to the mixture at 0 °C, and the mixture was stirred at this temperature for 0.5 h. The mixture was evaporated *in vacuo* to leave a residue, which was dissolved in CH_2Cl_2 (100 mL) and washed successively with H_2O (30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The residue was chromatographed (MPLC, silica gel, 20:1:1 CH_2Cl_2/hexane/MeOH) to provide **25** (59.0 mg, 18%) and **26** (267.2 mg, 82%). **25**: a colorless gummy solid: $[\alpha]^{25}_D$ −14.1° (*c* = 0.64, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.52−7.27 (m, 10H), 6.82−6.70 (m, 2H), 5.65 (m, 1H), 5.24−4.97 (m, 4H), 4.29 (m, 1H), 3.93−3.85 (m, 1H), 3.83 (s, 3H), 3.82−3.77 (m, 1H), 3.69 (s, 1.5H), 3.64 (s, 1.5H), 3.10 (br d, 1H, *J* = 17 Hz), 2.98−2.65 (m, 3H), 2.39 (br s, 1H), 2.16 (br dd, 1H, *J* = 13, 13 Hz), 2.11−2.04 (m, 1H), 1.93 (br d, 1H, *J* = 12 Hz), 1.77 (ddd, 1H, *J* = 12.7, 12.7, 5.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.52, 155.40, 151.73, 151.69, 146.42, 144.70, 144.56, 137.96, 137.04, 136.77, 135.41, 135.34, 129.22, 128.93, 128.46, 128.42, 128.10, 127.87, 127.65, 123.96, 123.83, 121.16, 111.47, 74.19, 67.05, 66.99, 65.26, 65.05, 56.99, 56.80, 55.83, 45.32, 45.14, 39.96, 38.72, 38.66, 36.84, 36.76, 36.33, 36.28; IR ($CHCl_3$) ν_{max} 3560, 2940, 1680, 1420, 1320, 1130, 1050 cm^{-1}; MS *m*/*z* (%) 557 (4, M^+), 482 (12), 481 (11), 390 (49), 91 (100); HRMS calcd for $C_{33}H_{35}NO_7$ 557.2414; found 557.2398. **26**: a colorless gummy solid; $[\alpha]^{27}_D$ +111.7° (*c* = 0.65, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.53−7.25 (m, 10H), 6.86−6.73 (m, 2H), 5.64−5.55 (m, 1H), 5.24−5.07 (m, 3H), 5.02 (d, 1H, *J* = 10.9 Hz), 4.15 (d, 1H, *J* = 7.3 Hz), 3.90 (m, 1H), 3.85 (s, 3H), 3.95−3.74 (m, 2H), 3.66 and 3.63 (each s, 1.5H), 3.14−2.86 (m, 3H), 2.78−2.60 (m, 2H), 2.52−2.39 (br m, 1H), 2.12 (br dd, 1H, *J* = 13, 13 Hz), 1.99−1.91 (br m, 1H), 1.86 (ddd, 1H, *J* = 12.6, 12.6, 5.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.45, 155.33, 151.73, 146.52, 144.05, 137.75, 136.92, 136.61, 135.27, 128.87, 128.63, 128.33, 128.05, 127.76, 127.57, 123.82, 123.72, 122.01, 121.87, 111.50, 74.00, 71.09, 70.95, 66.96, 59.23, 55.75, 45.57, 45.45, 39.93, 39.42, 38.52, 38.44, 37.45, 37.10, 36.95; IR ($CHCl_3$) ν_{max} 3580, 2930, 1680, 1480, 1420, 1320, 1270, 1130, 1055, 1020 cm^{-1}; MS *m*/*z* (%) 557 (13, M^+), 482 (34), 481 (33), 434 (21), 391 (44), 390 (93), 347 (20), 346 (22), 299 (21), 91 (100); HRMS calcd for $C_{33}H_{35}NO_7$ 557.2414, found 557.2389.

(6*S*,9*S*,13*S*)-8,14-Didehydro-4-(benzyloxy)-17-[(benzyloxy)carbonyl]-6-[(*tert*-butyldimethylsilyl)oxy]-3,8-dimethoxymorphinan-7-one (27). To a solution of **7a** (33.2

mg, 0.0598 mmol) in DMF (2 mL) was added *tert*-butyldimethylsilyl chloride (10.9 mg, 0.0723 mmol) and imidazole (8.2 mg, 0.12 mmol), and the mixture was stirred at room temperature for 24 h. The mixture was chromatographed (silica gel, 1:1 EtOAc/hexane) to provide **27** (35.8 mg, 89%) as a colorless gummy solid: $[\alpha]^{26}_D$ −20.3° (*c* = 0.44, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.51−7.27 (m, 10H), 6.87−6.73 (m, 2H), 5.76−5.65 (m, 1H), 5.26−5.04 (m, 4H), 4.35 (dd, 1H, *J* = 12.9, 5.7 Hz), 4.06−3.89 (m, 1H), 3.86 (s, 3H), 3.73 and 3.64 (each s, 1.5H), 3.32−3.22 (m, 1H), 3.19−2.92 (m, 2H), 2.89−2.74 (m, 1H), 2.49 (br dd, 1H, *J* = 13, 13 Hz), 2.15 (ddd, 1H, *J* = 12.5, 2.7, 1.5 Hz), 2.08 (ddd, 1H, 12.5, 12.5, 5.2 Hz), 0.85 (s, 9H), −0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.85, 155.36, 155.24, 151.99, 146.32, 142.61, 142.47, 141.41, 141.33, 137.66, 136.71, 136.60, 134.30, 128.55, 128.50, 128.05, 127.87, 127.70, 124.07, 123.91, 111.91, 73.76, 71.47, 67.28, 60.25, 60.00, 55.87, 46.31, 46.10, 41.94, 40.00, 39.92, 39.36, 36.43, 36.00, 35.75, 25.74, 18.46, −4.67, −5.47; IR ($CHCl_3$) 2940, 1685, 1270, 1085 cm^{-1}; FAB-MS 670 (MH^+).

Reduction of 27 with $LiBEt_3H$. To a solution of **27** (34.3 mg, 0.051 mmol) in THF (4 mL) was added Super-Hydride (1 M, 0.62 mL, 0.062 mmol) in THF at −78 °C under an argon atmosphere, and the mixture was stirred for 3 h. Saturated aqueous NH_4Cl (1 mL) was added to the solution, and the mixture was allowed to warm to room temperature. The solvent was evaporated *in vacuo*, and the residue was dissolved in CH_2Cl_2 (20 mL), washed successively with H_2O (5 mL) and brine (5 mL), dried, and filtered. The solvent was removed under reduced pressure, and the residue was chromatographed (MPLC, silica gel, 1:3 EtOAc/hexane) to provide **28** (29.5 mg, 86%) and **29** (1.2 mg, 3%). **(6*S*,7*S*,9*S*,13*S*)-8,14-Didehydro-4-(benzyloxy)-17-[(benzyloxy)carbonyl]-6-[(*tert*-butyldimethylsilyl)oxy]-3,8-dimethoxymorphinan-7-ol (28):** colorless needles; mp 135−136 °C; $[\alpha]^{24}_D$ +31.1° (*c* = 0.56, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.50−7.28 (m, 10H), 6.80−6.71 (br m, 2H), 5.69 (dd, 1H, *J* = 8.8, 5.0 Hz), 5.18−5.04 (m, 4H), 4.17 (d, 1H, *J* = 3.6 Hz), 3.91 (m, 1H), 3.89 (ddd, 1H, *J* = 12.2, 3.6, 3.6 Hz), 3.84 (s, 3H), 3.73 and 3.71 (each s, 1.5 H), 3.13 (br d, 1H, *J* = 17 Hz), 2.93−2.70 (m, 3H), 2.63 (d, 1H, *J* = 5.9 Hz), 2.22 (dd, 1H, *J* = 12.9, 12.9 Hz), 1.97 (br d, 1H, *J* = 12 Hz), 1.82 (ddd, 1H, *J* = 12.6, 12.6, 5.4 Hz), 0.86 (s, 9H), 0.03 (s, 3H), −0.36 (s, 3H); IR (KBr) ν_{max} 3490, 2960, 2890, 1690, 1680, 1480, 1260, 1070 cm^{-1}; HRFAB-MS calcd for $C_{39}H_{50}NO_7Si$ [MH] 672.3357, found 672.3339. Anal. Calcd for $C_{39}H_{49}NO_7Si$: C, 69.72; H, 7.35; N, 2.08. Found: C, 69.83; H, 7.50; N, 2.06. **(6*S*,7*R*,9*S*,13*S*)-8,14-Didehydro-4-(benzyloxy)-17-[(benzyloxy)carbonyl]-6-[(*tert*-butyldimethylsilyl)oxy]-3,8-dimethoxymorphinan-7-ol (29):** a colorless gummy solid; $[\alpha]^{27}_D$ +90.0° (*c* = 0.01, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.48−7.30 (m, 10H), 6.82−6.73 (m, 2H), 5.61 (br dd, 1H, *J* = 7, 7 Hz), 5.17−4.96 (m, 4H), 4.17 (dd, 1H, *J* = 7.4, 3.0 Hz), 3.92 (ddd, 1H, *J* = 13.4, 13.4, 4.9 Hz), 3.84 (s, 3H), 3.76 (ddd, 1H, *J* = 15.8, 7.4, 4.4 Hz), 3.65 and 3.63 (s, each 1.5H), 3.07 (m, 1H), 2.96 (br d, 1H, *J* = 17 Hz), 2.85 (dd, 1H, *J* = 13.9, 2.8 Hz), 2.82−2.70 (m, 1H), 2.25 (dd, 1H, *J* = 11.3, 3.0 Hz), 2.10 (br dd, 1H, *J* = 13, 13 Hz), 1.97 (br dd, 1H, *J* = 13, 3 Hz), 1.89 (ddd, 1H, *J* = 12.5, 12.5, 5.4 Hz), 0.82 (s, 9H), 0.03 (s, 3H), −0.67 (s, 3H); HRFAB-MS calcd for $C_{39}H_{50}NO_7Si$ [MH] 672.3357, found 672.3330.

Desilylation of 28. To a solution of **28** (42.0 mg, 0.0625 mmol) in THF−H_2O (3:1, 4 mL) was added *p*-toluenesulfonic acid monohydrate (1.2 mg, 0.0063 mmol), and the mixture was stirred at room temperature for 4 days. The mixture was cooled to 0 °C and neutralized with $NaHCO_3$. After removal of the solvent under reduced pressure, the residue was dissolved in CH_2Cl_2 (30 mL) and washed successively with H_2O (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$ and filtered and the solvent removed *in vacuo*. Medium-pressure liquid chromatography (SiO_2, 1:1:20 MeOH/hexane/CH_2Cl_2) provided **25** (32.1 mg, 92%).

Sinococuline (1). To a solution of **25** (155 mg, 0.278 mmol) in EtOH−cyclohexene (1:1, 4 mL) was added Pearlman's catalyst (155 mg), and the mixture was refluxed for 4.5 h under argon atmosphere. The reaction mixture was filtered and evaporated *in vacuo*. The residue was chromatographed (alumina, 30−3:1 CH_2Cl_2/MeOH) to provide sinococuline (**1**, 88.2 mg, 95%) as an amorphous powder: $[\alpha]^{25}_D$ −135.9° (*c* = 0.11, MeOH), [natural sinococuline: $[\alpha]^{25}_D$ −137.4° (*c* = 0.12 MeOH)];[21] ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, 1H, *J* = 8.3 Hz), 6.56 (d, 1H, *J* = 8.3 Hz), 4.36 (d, 1H, *J* = 6.1 Hz), 4.31 (dd, 1H, *J* = 3.5, 1.0 Hz), 3.88 (ddd, 1H, *J* = 13.3, 3.8, 3.5 Hz), 3.85 (s, 3H), 3.71 (s, 3H), 3.18 (ddd, 1H, *J* = 17.4, 6.1, 1.0 Hz), 2.92 (d, 1H, *J* = 17.4 Hz), 2.92 (ddd, 1H, *J* = 13.3, 3.8, 1.0 Hz), 2.70 (ddd, 1H, *J* = 13.2, 5.1, 1.7 Hz), 2.64 (ddd, 1H, *J* = 13.2, 12.2, 3.5 Hz), 2.19 (dd, 1H, *J* = 13.3, 13.3 Hz), 2.00 (ddd, 1H, *J* = 12.2, 3.5, 1.7 Hz), 1.88 (ddd, 1H, *J* = 12.2, 12.2, 5.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.36, 145.87, 145.56, 131.39, 130.35, 125.10, 119.20, 110.55, 68.67, 66.88, 57.41, 56.73, 46.74, 41.14, 39.98, 38.56, 37.38, 36.92; IR (KBr) ν_{max} 3420, 2945, 1485, 1280, 1215, 1060 cm^{-1}; MS *m*/*z* (%) 333 (11, M^+), 318 (19), 259 (24), 258 (100), 244 (19); HRMS calcd for $C_{18}H_{23}NO_5$ 333.1576, found 333.1571.

(6*R*,7*S*,9*S*,13*S*)-8,14-Didehydro-4-[(benzyloxy)carbonyl]-3,8-dimethoxymorphinane-6,7-diol (30) and (6*R*,7*R*,9*S*,13*S*)-8,14-Didehydro-4-[(benzyloxy)carbonyl]-3,8-dimethoxymorphinane-6,7-diol (31). To a solution of **7b** (263 mg, 0.473 mmol) in MeOH (20 mL) was added $CeCl_3 \cdot 7H_2O$ (265 mg, 0.711 mmol), and the mixture was stirred at room temperature for 10 min. $NaBH_4$ (27 mg, 0.71 mmol) was added to the solution, and the mixture was stirred for 2 h. Acetone (3 mL) was added to the mixture at 0 °C, and the mixture was stirred at this temperature for 0.5 h. The mixture was evaporated *in vacuo* to leave a residue, which was dissolved in CH_2Cl_2 (100 mL) and washed successively with H_2O (30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$ and filtered and the solvent removed *in vacuo*. The residue was chromatographed (MPLC, silica gel, 1:1:20 MeOH/hexane/CH_2Cl_2) to provide **31** (77.9 mg, 30%) and **30** (139.9 mg 53%). **30**: a colorless gummy solid; $[\alpha]^{26}_D$ +1.0° (*c* = 0.39, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, 2H, *J* = 7.3 Hz), 7.43−7.27 (m, 8H), 6.82−6.70 (m, 2H), 5.62−5.54 (m, 1H), 5.26−5.01 (m, 4H), 4.19 (br s, 1H), 3.94−3.79 (m, 1H), 3.84 (s, 3H), 3.66 and 3.55 (each s, 1.5H), 3.63−3.49 (m, 2H), 3.19−3.08 (m, 1H), 2.93−2.65 (m, 2H), 2.55 (br s, 2H, O*H* × 2), 1.89 (br d, 1H, *J* = 13 Hz), 1.65−1.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.35, 155.17, 151.49, 145.83, 143.85, 143.73, 137.64, 136.90, 136.73, 133.85, 130.65, 130.40, 128.45, 128.21, 127.91, 127.78, 124.09, 123.97, 122.99, 111.23, 74.15, 71.66, 71.54, 71.30, 67.02, 58.72, 58.39, 55.76, 45.55, 45.44, 39.22, 39.13, 38.84, 38.66, 38.26, 37.93, 37.60, 37.50; IR ($CHCl_3$) ν_{max} 3600, 3450, 2940, 1680, 1420, 1320, 1275, 1135, 1055, 1025 cm^{-1}; MS *m*/*z* (%) 557 (12, M^+), 482 (15), 390 (15), 347 (10), 256 (12), 91 (100); HRMS calcd for $C_{33}H_{35}NO_7$ 557.2414, found 557.2423. **31**: a colorless gummy solid; $[\alpha]^{26}_D$ +90.8° (*c* = 0.32, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, 2H, *J* = 7 Hz), 7.43−7.27 (m, 8H), 6.83−6.73 (m, 2H), 5.68−5.61 (m, 1H), 5.22−5.01 (m, 4H), 4.28−4.20 (m, 1H), 3.94−3.80 (m, 1H), 3.85 (s, 3H), 3.71 and 3.69 (each s, 1.5H), 3.75−3.63 (m, 1H), 3.31−3.16 (m, 1H), 3.14−3.05 (m, 1H), 2.96−2.81 (m, 1H), 2.79−2.66 (m, 1H), 2.60 (br s, 1H), 2.33−2.20 (br m, 1H), 2.04−1.87 (m, 2H), 1.82−1.66 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.45, 155.32, 151.52, 146.23, 144.18, 137.63, 137.02, 136.78, 134.00, 133.87, 130.70, 130.55, 128.48, 128.41, 128.11, 127.96, 127.83, 127.64, 124.10, 124.02, 121.98, 111.25, 74.29, 74.24, 67.41, 66.99, 66.38, 66.19, 57.82, 55.79, 45.23, 45.16, 39.13, 39.06, 38.87, 38.70, 38.47, 38.10, 34.91, 34.82; IR ($CHCl_3$) ν_{max} 3570, 2940, 1685, 1425, 1325, 1270, 1130, 1050, 1025 cm^{-1}; MS *m*/*z* (%) 557 (24, M^+), 482 (25), 390 (22), 347 (14), 91 (100); HRMS calcd for $C_{33}H_{35}NO_7$ 557.2414, found 557.2437.

***7-epi*-Sinococuline (4).** To a solution of **26** (41.3 mg, 0.0741 mmol) in EtOH−cyclohexene (1:1, 2 mL) was added Pearlman's catalyst (41 mg), and the mixture was refluxed for 1 h under an argon atmosphere. The reaction mixture was filtered and evaporated *in vacuo*. The residue was chromatographed (alumina, 30−3:1 CH_2Cl_2/MeOH) to provide **4** (24.1

(20) Beierbeck, H.; Saunders, J. K.; ApSimon, J. W. *Can. J. Chem.* **1977**, *55*, 2813.

(21) We have previously reported −77° as a rotation for the natural sinococuline (**1**). However recent our reinvestigation revealed that the value should be corrected to that shown here.

mg, 98%) as an amorphous powder: $[\alpha]^{26}_D$ +25.3° (c = 0.18, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 6.79 (d, 1H, J = 8.3 Hz, H-2), 6.58 (d, 1H, J = 8.3 Hz, H-1), 4.33 (d, 1H, J = 5.3 Hz, H-9), 4.10 (d, 1H, J = 7.6 Hz, H-7), 3.85 (s, 3H, 3-OMe), 3.79 (ddd, 1H, J = 12.3, 7.6, 3.9 Hz, H-6), 3.63 (s, 3H, 8-OMe), 3.18 (ddd, 1H, J = 17.3, 6.2, 1.0 Hz, H-10a), 3.11 (dd, 1H, J = 14.1, 3.9 Hz, H-5α), 2.95 (d, 1H, J = 17.3 Hz, H-10b), 2.73 (ddd, 1H, J = 13.3, 4.7, 1.7 Hz, H-16a), 2.61 (ddd, 1H, J = 13.3, 12.2, 3.6 Hz, H-16b), 2.05 (ddd, 1H, J = 12.2, 3.6, 1.7 Hz, H-15β), 2.03 (dd, 1H, J = 14.1, 12.3 Hz, H-5β), 1.89 (ddd, 1H, J = 12.2, 12.2, 4.7 Hz, H-15α); ^{13}C NMR (126 MHz, CD_3OD) δ 147.39 (C-3), 145.61 (C-8), 145.57 (C-4), 131.12 (C-11), 130.00 (C-12), 125.85 (C-14), 119.31 (C-1), 110.62 (C-2), 72.18 (C-6), 71.72 (C-7), 59.13 (8-OMe), 56.70 (3-OMe), 47.08 (C-9), 41.19 (C-16), 41.00 (C-5), 39.76 (C-13), 39.10 (C-15), 37.85 (C-10); IR (KBr) ν_{max} 3400, 2920, 1485, 1440, 1280, 1220, 1060, 1020 cm^{-1}; MS m/z (%) 333 (27, M$^+$), 318 (38), 259 (30), 258 (100), 244 (24); HRMS calcd for $C_{18}H_{23}NO_5$ 333.1576, found 333.1559.

6-*epi*-Sinococuline (3). To a solution of **30** (65.1 mg, 0.117 mmol) in EtOH–cyclohexene (1:1, 2 mL) was added Pearlman's catalyst (65 mg), and the mixture was refluxed for 1 h under an argon atmosphere. The reaction mixture was filtered and evaporated *in vacuo*. The residue was chromatographed (alumina, 30–3:1 CH_2Cl_2/MeOH) to provide **3** (34.7 mg, 89%) as colorless prisms: mp 221–223 °C dec; $[\alpha]^{26}_D$ −126.5° (c = 0.21, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 6.78 (d, 1H, J = 8.3 Hz, H-2), 6.57 (d, 1H, J = 8.3 Hz, H-1), 4.35 (d, 1H, J = 5.7 Hz, H-9), 4.20 (d, 1H, J = 6.4 Hz, H-7), 3.86 (s, 3H, 3-OMe), 3.70 (s, 3H, 8-OMe), 3.57 (dd, 1H, J = 13.8, 3.0 Hz, H-5β), 3.56 (ddd, 1H, J = 11.0, 6.4, 3.0 Hz, H-6), 3.19 (ddd, 1H, J = 17.3, 6.4, 0.8 Hz, H-10a), 2.92 (d, 1H, J = 17.3 Hz, H-10b), 2.68 (ddd, 1H, J = 13.1, 5.7, 2.0 Hz, H-16a), 2.01 (ddd, 1H, J = 12.4, 3.1, 2.0 Hz, H-15a), 2.67 (ddd, 1H, J = 13.1, 12.4, 3.1 Hz, H-16b), 1.80 (dd, 1H, J = 13.8, 11.0 Hz, H-5α), 1.74 (ddd, 1H, J = 12.4, 12.4, 5.7 Hz, H-15b); ^{13}C NMR (126 MHz, CD_3OD) δ 147.15 (C-3), 145.21 (C-8), 145.03 (C-4), 133.06 (C-11), 129.17 (C-12), 126.03 (C-14), 119.44 (C-1), 110.44 (C-2), 72.38 (C-6), 72.03 (C-7), 58.17 (8-OMe), 56.71 (3-OMe), 46.99 (C-9), 40.42 (C-15), 40.07 (C-16), 39.96 (C-13), 39.15 (C-10), 38.72 (C-5); IR (KBr) ν_{max} 3450, 2940, 1485, 1440, 1280, 1220, 1035 cm^{-1}; MS m/z (%) 333 (5, M$^+$), 258 (100); HRMS calcd for $C_{18}H_{23}NO_5$ 333.1576, found 333.1587. Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.59; H, 7.03; N, 4.14.

6-*epi*-7-*epi*-Sinococuline (5). To a solution of **31** (88.1 mg, 0.158 mmol) in EtOH–cyclohexene (1:1, 2 mL) was added Pearlman's catalyst (88 mg), and the mixture was refluxed for 1 h under an argon atmosphere. The reaction mixture was filtered and evaporated *in vacuo*. The residue was chromatographed (alumina, 30–3:1 CH_2Cl_2/MeOH) to provide **5** (47.6 mg, 90%) as an amorphous powder: $[\alpha]^{26}_D$ +25.2° (c = 0.16, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 6.78 (d, 1H, J = 8.3 Hz, H-2), 6.57 (d, 1H, J = 8.3 Hz, H-1), 4.37 (d, 1H, J = 5.9 Hz, H-9), 4.19 (dd, 1H, J = 3.7, 0.8 Hz, H-7), 3.86 (s, 3H, 3-OMe), 3.74 (dd, 1H, J = 12.8, 2.0 Hz, H-5β), 3.72 (s, 3H, 8-OMe), 3.46 (ddd, 1H, J = 12.6, 3.7, 2.0 Hz, H-6), 3.12 (ddd, 1H, J = 17.3, 6.3, 0.8 Hz, H-10a), 2.92 (d, 1H, J = 17.3 Hz, H-10b), 2.69 (ddd, 1H, J = 13.1, 4.9, 1.8 Hz, H-16a), 2.64 (ddd, 1H, J = 13.1, 12.6, 3.1 Hz, H-16b), 2.07 (ddd, 1H, J = 12.6, 3.1, 1.8 Hz, H-15a), 1.77 (dd, 1H, J = 12.8, 12.6 Hz, H-5α), 1.63 (ddd, 1H, J = 12.6, 12.6, 5.0 Hz, H-15b); ^{13}C NMR (126 MHz, CD_3OD) δ 147.16 (C-3), 145.77 (C-8), 145.34 (C-4), 133.16 (C-11), 128.26 (C-12), 125.03 (C-14), 119.54 (C-1), 110.52 (C-2), 68.81 (C-6), 67.26 (C-7), 57.56 (8-OMe), 56.72 (3-OMe), 46.70 (C-9), 40.43 (C-13), 39.91 (C-16 or C-15), 39.90 (C-15 or C-16), 39.18 (C-10), 34.46 (C-5); IR ($CHCl_3$) ν_{max} 3520, 2940, 1480, 1450, 1435, 1280, 1060 cm^{-1}; HRFAB-MS calcd for $C_{18}H_{24}NO_5$ [MH] 334.1654, found 334.1659.

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Supporting Information Available: 400 or 500 MHz ^{1}H NMR spectra of **1**, **3–5**, **7a,b**, **8**, **9**, **11a,b**, **12b**, **13a,b**, **15–17**, **19–21**, **25–27**, and **29–31** (25 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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