Benzolactams. 4. Reaction of 3′,4′- or 4′,5′-Dialkoxy-Substituted 1-(2′-Bromobenzyl)-2-ethoxycarbonyl-1,2,3,4-tetrahydroisoquinolines with Alkyllithium. 1,2 and 1,4 Additions of Alkyllithium to Benzolactams

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Treatment of 1-(2′-bromo-3′,4′-dialkoxybenzyl)-1,2,3,4-tetrahydroisoquinoline carbamates, **1a**,**c**, with excess alkyllithium gave 8-oxoberbines, **2a**,**c**, which were successively attacked in situ with another molecule of alkyllithium to give 1,2 and/or 1,4 addition products. A primary alkyllithium, such as MeLi or BuLi, gave a 1,2 addition product, 8-methyleneberbine **9a** or 8-butylideneberbine **3a**. *t*-BuLi preferred 1,4 addition, followed by elimination of the alkoxy group, to give 9-*tert*-butyl-8-oxoberbine **6a** or **7c**. *s*-BuLi gave a mixture of 1,2 and 1,4 addition products, 1-[2′-(2″-methylbutyryl)benzyl]-1,2,3,4-tetrahydroisoquinoline **4a** and 9-*s*-butyl-8-oxoberbine **5a**. Similar treatments of carbamate **1b** having no alkoxy group at its 3′ position gave 1,2 addition products, 8-butylideneberbine **3b**, 1-[2′-(2″-methylbutyryl)benzyl]-1,2,3,4-tetrahydroisoquinoline **4b**, and 1-(2′-pivaloylbenzyl)-1,2,3,4-tetrahydroisoquinoline **6b**, in all cases. Reactions of **1a** with *s*-BuMgCl and isoPrMgCl also gave the 1,4 adduct, **5a**, and its 9-isoPr analogue, **12a**. Treatment of **9a** with excess $NaBH_4$ in AcOH gave (±)-coralydine (**10b**).

Introduction

Berbines, which have a skeletal feature of protoberberine alkaloids,[1] have been shown to possess antitumor and antileukemic properties.[2] A practical and short route to the generation of 8-oxoberbines should be useful for the preparation of biologically important compounds. We have found that 8-oxoberbines can also be generated by a method based on the intramolecular addition of an aryl anion to a urethane carbonyl group.[3] However, we also found that it was quite difficult to obtain such benzolactams in high yields, in contrast to the experimental ease optimized in the reaction scheme, although Comins' group has recently achieved the synthesis of (−)-xylopinine by such a method.[4] In this paper, we report the interesting site selectivity upon the addition of alkyllithiums to the primary products, 8-oxoberbines. This addition reaction is considered to be one of the main reasons for their being consumed in situ.

Results and Discussion

A stirred solution of 1-(2-bromobenzyl)tetrahydroisoquinoline carbamate **1a** in THF was treated with 1 equiv of BuLi at 0 °C for 30 min and at room temperature for 2.5 h. The usual workup gave a mixture of **1a** and enamine **3a** in a 2:1 ratio. The structure of **3a** was determined by ^{1}H NMR analysis to be 8-butylideneberbine. Irradiation of an olefinic proton, δ 6.26, caused an NOE enhancement of a methoxy proton at 3.76 (25%). The use of excess BuLi (3 mol equiv) turned out to be a good method for the exclusive production of **3a** (92%), which was also obtained almost quantitatively by a similar treatment of 8-oxoberbine **2a**[5] with BuLi (2 mol equiv). This benzolactam (**2a**) was not detected in products of these reactions. Even though a similar treatment of **1a** was carried out at −78 °C and quenched by the addition of excess water 30 min later, **2a** was not obtained, but a mixture of **1a** and **3a** (BuLi) or **1a** and **6a** (*t*-BuLi) was obtained. This suggests that the second reaction (addition of RLi) was much faster than the first reaction (cyclization). When carbamate **1a** was treated with excess *t*-BuLi, benzolactam **6a** was obtained as a single product in 82% yield. The IR spectrum showed peaks at 1700 and 1613 cm^{-1}, owing to a benzolactam carbonyl group, and therefore it is reasonable to say that **6a** was formed in a reaction pathway based on the 1,4 addition of *t*-BuLi to **2a** followed by elimination of a methoxy group.[6,7,8] Treatment of **2a** with excess *t*-BuLi gave the same lactam **6a** almost quantitatively. These results suggest that the 1,2 addition reaction occurs owing to a higher nucleophilicity of a primary alkyl anion and that a more bulky alkyl anion is pushed away to the 1,4 addition.

(1) For recent reviews on protoberberine alkaloids, see: (a) Bhakuni, D. S.; Jain, S. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: Orlando, FL, 1986; Vol. 28, pp 95−184. (b) Hanaoka, M. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: Orlando, FL, 1988; Vol. 33, pp 141−230.

(2) See refs 3 and 12 cited in Matulenko, M. A.; Meyers, A. *J. Org. Chem*. **1996**, *61*, 573.

(3) Partly presented at the 69th National Meeting of the Chemical Society of Japan, Kyoto, Japan, 3/27−3/30, 1995.

(4) Comins, D. L.; Thakker, P. M.; Baevsky, M. F. *Tetrahedron* **1997**, *53*, 16327.

(5) Orito, K.; Miyazawa, M.; Kanbayashi, R.; Tokuda, M.; Suginome, H. *J. Org. Chem*. **1999**, *64*, 6583.

(6) For reviews, see: Reuman, M.; Meryers, A. I. *Tetrahedron* **1985**, *41*, 837. Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297. Hattori, T.; Miyano, S. *J. Synth. Org. Chem., Jpn*. **1977**, *55*, 121.

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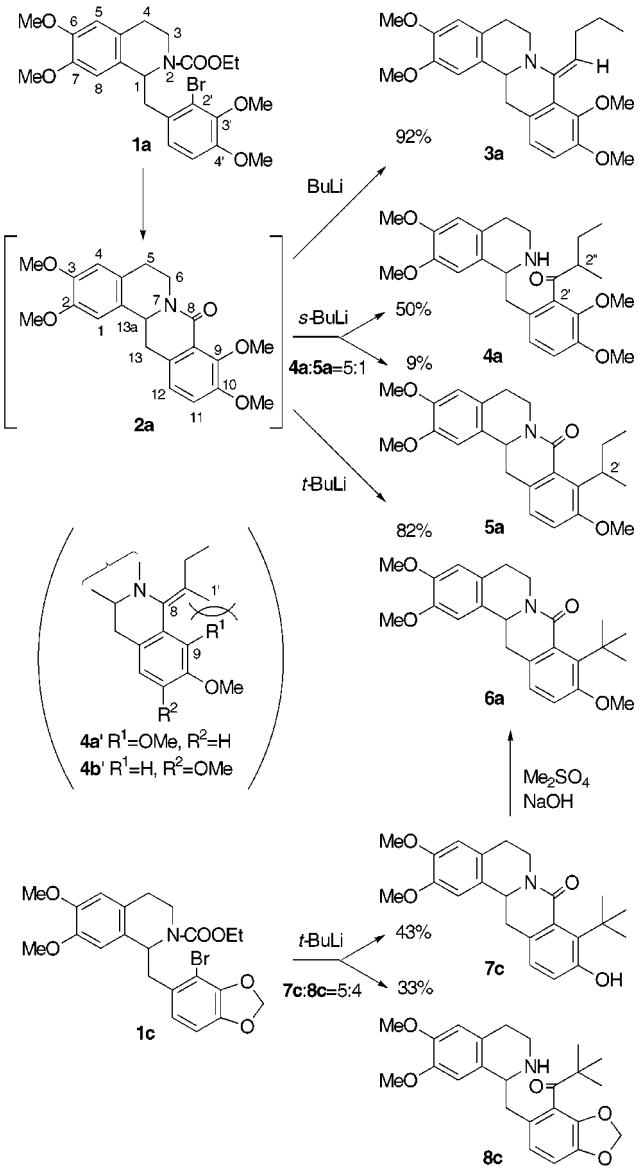
Next, we focused on the behavior of *s*-BuLi to **1a**. As shown in Scheme 1, the first molecule of *s*-BuLi also induced the efficient cyclization to 8-oxoberbine **2a**, as expected, and then the second molecule of *s*-BuLi underwent 1,2 and 1,4 additions on **2a** competitively to give two carbonyl compounds, **4a** and **5a** (5:1). This reaction scheme was also confirmed by treatment of **2a** with *s*-BuLi (see the Experimental Section). ^{1}H NMR spectrum of the compound **4a** showed no signal near δ 4.7−4.9, owing to a C-13a H or a C-6 equatorial-type H (trans to C-13a H) for the 8-oxoberbine structure, but showed a double doublet signal near δ 4.13, characteristic of a C-1 H of the 1-benzyltetrahydroisoquinoline ring system having no substituent on the N atom. Compound **5a** has a double doublet signal at δ 4.73 for the C-13a H of 8-oxoberbines and three MeO signals at δ 3.82, 3.89, and 3.90. The IR and ^{13}C NMR spectra also revealed that **4a** preferred an amino ketone structure [3346, 1693, and 1611 cm^{-1} and 211.3 (s) ppm] rather than a cyclic amino−alcohol or enamine structure like **3a**. Probably, in an enamine structure (**4a′**) assumed for **4a**, a C-1′ Me group of the inserted *s*-Bu group causes a bigger steric hindrance to a C-9 MeO group, compared with that allowed for a C-1′ H of a butylidene group of enamine **3a** or **3b**.

A similar treatment with *t*-BuLi of substrate **1c**, having a less-hindered methylenedioxy group at C-9 and C-10, gave not only a 1,4 addition product but also a 1,2 addition product competitively in a ratio of 5:4. This 1,4 addition proceeded with a loss of a methyleneoxy group, probably as a formaldehyde,[7u] to give phenol **7c** (43%), which was easily converted to the above-mentioned trimethoxyberbine **6a** by methylation with NaOH−Me_2SO_4. The accompanied 1,2 addition product (33%) was assigned to an amino ketone structure **8c** on the basis of its spectral data [IR 3340, 1686 cm^{-1}; ^{13}C NMR δ 213 (s)], which is similar to those described above for the compound **4a**.

Scheme 1



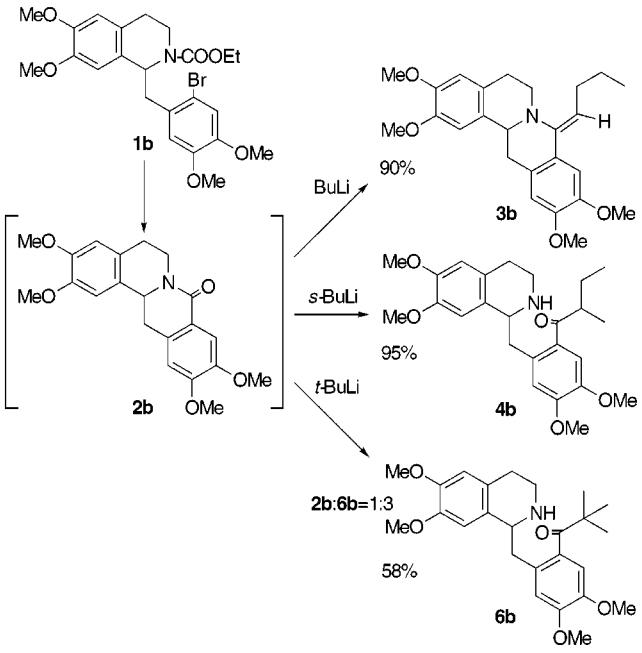
In contrast, carbamate **1b**[9] having no leaving group at its 3′ position preferred 1,2 addition. BuLi gave enamine **3b**. Both *s*-BuLi and *t*-BuLi produced ring-opened compounds, **4b** and **6b**, which have an amino ketone structure [3388, 1674, and 1607 cm^{-1} and 207.1 (s), 207.2 (s) ppm for **4b**; 3336, 1681, and 1607 cm^{-1} and 213.8 (s) ppm for **6b**], respectively (Scheme 2). The former amino ketone (**4b**) was probably formed in avoiding steric repulsion, which may be generated in an enamine structure **4b′** between its C-1′ Me and C-9 H groups. The latter addition reaction was not completed and gave a mixture of **2b**[10−12] and **6b** (1:3). Even with a large excess of the reagent (10 mol equiv of *t*-BuLi to **2b**), the ratio

(7) For a similar nucleophilic aromatic substitition based on an addition−elimination reaction sequence with oxazolines, see: (a) Meyers, A. I.; Lutomski, K. A. *J. Am. Chem. Soc.* **1982**, *104*, 879. (b) Wilson, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 881. (c) Wilson, J. M.; Cram, D. J. *J. Org. Chem.* **1984**, *49*, 4930. (d) Meyers, A. I.; Himmelsbach, R. J. *J. Am. Chem. Soc.* **1985**, *105*, 682. (e) Cram, D. J.; Bryant, J. A.; Doxsee, K. M. *Chem. Lett.* **1987**, 19. (f) Meyers, A. I.; Flisak, J. R. J.; Aitkin, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 5446. (g) Gant, T. G.; Meyers, A. I. *J. Am. Chem. Soc.* **1992**, *114*, 1010. (h) Baker, R. W.; Hockless, D. C. R.; Pocock, G. R.; Sargent, M. V.; Skeleton, B. W.; Sobolev, A. N.; Twiss, E.; White, A. H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2615. (i) Huchings, R. H.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 1004. For reaction with benzoates and naphthalenecarboxylates, see: (j) Tomioka, K.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 1739. (k) Suzuki, T.; Hotta, H.; Hattori, T.; Miyano, S. *Chem. Lett.* **1990**, 807−810. (l) Hattori, T.; Hotta, H.; Suzuki, T.; Miyano, S. *Bull. Chem. Soc. Jpn* **1993**, *66*, 613. (m) Hattori, T.; Satoh, T.; Miyano, S. *Bull. Chem. Soc. Jpn* **1993**, *66*, 3840. (n) Hattori, T.; Suzuki, T.; Hayashizaka, N.; Koike, N.; Miyano, S. *Bull. Chem. Soc. Jpn* **1993**, *66*, 3034. (o) Hattori, T.; Koike, N.; Miyano, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2273. (p) Hattori, T.; Hayasizaka, N.; Miyano, S. *Synthesis* **1995**, 41. (q) Hattori, T.; Koike, N.; Satoh, T.; Miyano, S. *Tetrahedron Lett.* **1995**, *36*, 4821. (r) Hattori, T.; Satoh, T.; Miyano, S. *Synthesis* **1996**, 514. (s) Wells, K. M.; Shi, Y.-J.; Lynch, J. E.; Humphrey, G. R.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1996**, *37*, 6439. (t) Hattori, T.; Suzuki, M.; Tomita, N.; Takeda, A.; Miyano, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1117. (u) Koike, N.; Hattori, T.; Takeda, A.; Okaishi, Y.; Miyano, S. *Chem. Lett.* **1997**, 641. (v) Hattori, T.; Takeda, A.; Suzuki, K.; Koike, B.; Koshiishi, E.; Miyano, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3661.

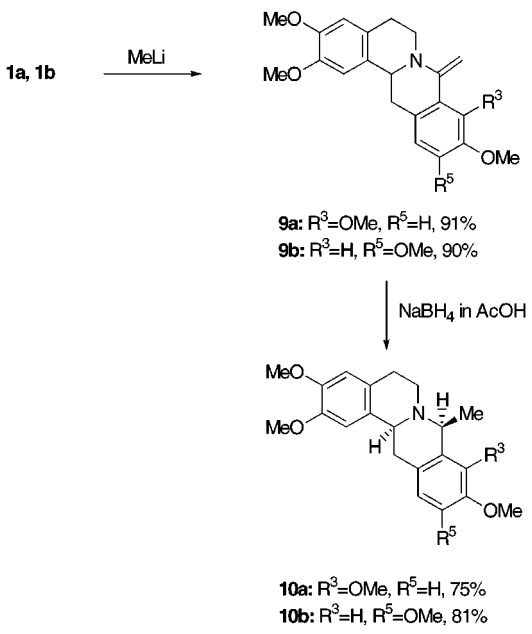
(8) For related nucleophilic additions to electron-deficient arenes, see: (a) Paradisi, C. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, Chapter 2.1. (b) Terrier, F. *Nucleophilic Aromatic Displacement: the Influence of the Nitro Group*; VCH Publisher: New York, 1991; p 257. (c) Vhupakhin, O. N.; Charushin, V. N.; van der Plas, H. C. *Nucleophilic Aromatic Substitution of Hydrogen*; Academic Press: San Diego, 1994. (d) Makosza, M.; Wojciechowski, K. *Liebigs Ann.* **1997**, 1805. (e) Golinski, J.; Makosza, M. *Tetrahedron Lett.* **1978**, 3495. (f) Hattori, T.; Sakamoto, J.; Hayashizaka, N.; Miyano, S. *Synthesis* **1994**, 199. (g) Maruoka, K.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 9091. (h) Seko, S.; Kawamura, N. *J. Org. Chem.* **1996**, *61*, 442. (i) Seko, S.; Miyake, K. *Chem. Commun.* **1998**, 1519. (j) Seko, S.; Miyake, K.; Kawamura, N. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1437.

(9) Gupta, S.; Bhakuni, D. S. *Synth. Commun.* **1989**, *19*, 393.
(10) Lentz, G. R. *J. Org. Chem.* **1974**, *39*, 2846.
(11) Pandey, G. D.; Tiwari, K. P. *Tetrahedron* **1981**, *37*, 1213.
(12) Ninomiya, I.; Naito, T.; Takasugi, H. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1720.

Scheme 2



Scheme 3

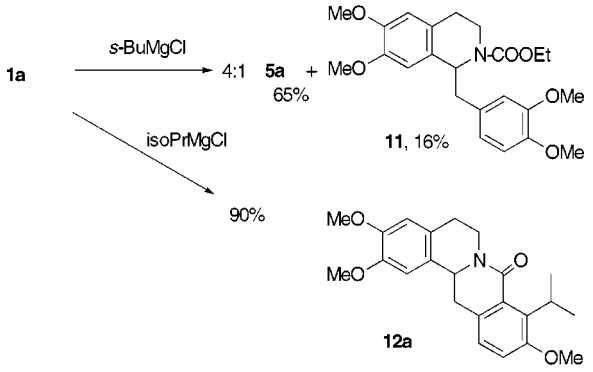


ended up at 1:5. This is the only case that the intermediate benzolactam, **2a** or **2b**, was obtained in this study. In addition, **3b** and **4b** were also obtained from **2b** in good yield (see the Experimental Section). No 1,6 addition products were obtained in this study.[7v]

Under the same conditions, MeLi also served as an efficient 1,2 addition reagent to produce enamine **9a** or **9b** in 91 or 90% isolated yield from **1a** or **1b**, and 92 or 90% yield from **2a** or **2b**, respectively. These compounds were further converted by treatment with excess $NaBH_4$ in AcOH to trans-fused berbine **10a** and **10b** exclusively (Scheme 3). The latter was identical with (±)-coralydine.[13]

Grignard reagents were also examined.[14] MeMgCl did not work at all for either the cyclization of **1a** or the addition to **2a**, and both substrates were recovered unchanged. Treatment of **1a** with *s*-BuMgCl in boiling

Scheme 4



THF gave only the 1,4 addition product **5a** together with the debrominated reactant **11** in a 4:1 ratio. Another secondary Grignard reagent isoPrMgCl[15] also gave the 1,4 addition product **12a** quantitatively (Scheme 4). However, neither benzolactam **2b** nor bromide **1b** reacted with *s*-BuMgCl, and both were recovered unchanged.

In summary, treatment of 1-(2′-bromo-3′,4′-dialkoxybenzyl)-1,2,3,4-tetrahydroisoquinoline carbamates with excess alkyllithium gave 8-oxoberbines, which were successively attacked in situ with another molecule of alkyllithium to give 1,2 and/or 1,4 addition products. A primary alkyllithium, such as MeLi or BuLi, gave a 1,2 addition product, 8-methylene- or 8-butylideneberbine. *t*-BuLi caused 1,4 addition, followed by an elimination of the alkoxy group, predominantly. *s*-BuLi gave a mixture of 1,2 and 1,4 addition products. Similar treatments of the carbamate having no alkoxy group at its 3′ position gave 1,2 addition products in all cases. One of the protoberberine alkaloids, (±)-coralydine, was easily obtained in this way.

Experimental Section

General Procedure for Preparation of Carbamates 1a−c. 1-(2′-Bromo-3′,4′-dimethoxybenzyl)-2-ethoxycarbonyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (1a). To a stirred solution of 1-(2′-bromo-3′,4′-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline[5] (300 mg, 0.71 mmol) in CH_2Cl_2 (5 mL) was added Na_2CO_3 (210 mg, 1.5 mmol) in water (3 mL), and then a solution of ClCOOEt (100 mg, 1 mmol) in CH_2Cl_2 (2 mL) was added dropwise. After the solution was stirred at room temperature for 1 h, a separated water layer was extracted with CH_2Cl_2. The extracts were combined, washed with water, and dried (Na_2SO_4). Evaporation of the solvent and crystallization of the residue (343 mg) from MeOH afforded the carbamate **1a** (273 mg, 78%): mp 116−117 °C; IR (Nujol) 1692, 1611, 1595, 1489 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.98, 1.21 (3:1, each t, J = 7.0 Hz, 3H), 2.62−3.70 (m, 6.75H), 3.84, 3.85, 3.87, 3.88 (each s, each 3H), 4.11 (dd, J = 6.9, 6.3 Hz, 0.5H), 4.34 (ddd, J = 13.1, 5.6, 2.3 Hz, 0.75 H), 5.38 (dd, J = 10.5, 4.5 Hz, 1H), 6.62, 6.71 (each s, each 1H), 6.77 (s, 2H); EI-MS m/z (rel int) 494 (M^+, 0.08), 492 (M^+, 0.06), 450 [($M - C_2H_4O)^+$, 0.4)], 264 (100). Anal. Calcd for $C_{23}H_{28}NO_6Br$: C, 55.88; H, 5.71; N, 2.83; Br, 16.16. Found: C, 55.79; H, 5.79; N, 2.79; Br, 15.90.

(13) (a) Hahn, G.; Schuls, H. J. *Ber. Dtsch. Chem. Ges.* **1938**, 2135. (b) Bruderer, H.; Metzger, J.; Brossi, A. *Helv. Chim. Acta* **1976**, *59*, 2793. (c) Dean, R. T.; Rapoport, H. *J. Org. Chem.* **1978**, *43*, 4183. (d) *Bull. Soc. Chim. Belg.* **1986**, *95*, 751−779. (e) Sotomayor, N.; Dominguez, E.; Lete, E. *Synlett* **1993**, 431.

(14) Treatment of **1a** with LDA in THF gave an intractable mixture. PhLi gave a mixture containing compounds originating from the 1,2 addition, and PhMgBr did not react with **1a** at all.

(15) Nishiyama, H.; Isaka, K.; Itoh, K.; Ohno, K.; Nagase, H.; Matsumoto, K.; Yoshiwara, H. *J. Org. Chem.* **1992**, *57*, 407.

1-(2′-Bromo-4′,5m′-dimethoxybenzyl)-2-ethoxycarbonyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (1b): colorless crystals (81%); mp 142−143 °C (MeOH) (lit.[9] 141−142 °C); IR (Nujol) 1689, 1511 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.05, 1.22 (1.8:1.2, each t, J = 6.9 Hz, 3H), 2.59−3.76 (m, 5H), 3.79, 3.82, 3.85, 3.86 (each s, each 3H), 4.09 (q, J = 6.9 Hz, 0.7H), 4.30 (ddd, J = 10.3, 5.5, 2.3 Hz, 0.6H), 5.32 (q, J = 4.6 Hz, 0.6H), 5.36 (t, J = 5.6 Hz, 0.4H), 6.40, 6.50, 6.59, 6.62, 6.64, 6.65, 6.97, 7.04 (0.4:0.6:0.4:0.6:0.4:0.6:0.4:0.6, each s, 4H).

1-[4′-Bromo-3′,4′-(methylenedioxy)benzyl]-2-ethoxycarbonyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (1c): colorless crystals (93%); mp 139−140 °C (MeOH); IR (Nujol) 1700, 1613, 1513 cm^{-1}; ^1H NMR (270 MHz) δ 1.02, 1.21 (2:1, each t, J = 7.1 Hz, 3H), 2.62−3.78 (m, 6.75H), 3.85, 3.87, 3.87, 3.88 (each s, each 3H), 4.11 (dd, J = 6.9, 6.3 Hz, 0.5H), 4.34 (ddd, J = 13.2, 7.9, 2.3 Hz, 0.75H), 6.62, 6.03 (2:1, each s, 2H), 6.66 (s, 1H), 6.55, 6.99 (AB type, J = 7.8 Hz, 2H), 6.70 (s, 1H); FD-MS m/z (rel int) 479 (M^+, 100), 477 (89.8), 264 (34.5). Anal. Calcd for $C_{22}H_{24}NO_6Br$: C, 55.24; H, 5.06; N, 2.93; Br, 16.70. Found: C, 54.96; H, 5.04; N, 2.96; Br, 16.90.

General Procedure. 9-*tert*-Butyl-2,3,10-trimethoxy-8-oxoberbine (6a). To an ice-cooled and stirred solution of **1a** (99 mg, 0.2 mmol) in dry THF (20 mL) under an atmosphere of nitrogen was added *t*-BuLi (1.7 M solution in pentane, 0.36 mL, 0.6 mmol). The mixture was kept at 0 °C for 30 min and then at room temperature for 2.5 h. THF was removed in a rotary evaporator, and the residue was treated with water and CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO_4), and concentrated. The residue (116 mg) was purified by preparative TLC on a Merck silica gel 60 PF_{254} developed with CH_2Cl_2. A main band with R_f 0.6 gave **6a**: colorless crystals (65 mg, 82%); mp 197−199 °C (EtOH); IR (Nujol) 1700, 1613 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.54 (s, 9H), 2.70−2.93 (m, 4H), 3.16 (ddd, J = 11.5, 8.6, 5.3 Hz, 1H), 3.83, 3.87, 3.90 (each s, each 3H), 4.77 (dt, J = 12.9, 4.0, 4.0 Hz, 1H), 4.82 (dd, J = 11.6, 3.0 Hz, 1H), 6.61, 6.69 (each s, each 1H), 6.89, 6.98 (AB type, J = 8.3 Hz, 2H); EI-MS m/z (rel int) 395 (M^+, 12.0), 204 (100), 192 (93.5), 161 (32.7). Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54. Found: C, 72.76; H, 7.50; N, 3.48.

A similar treatment with *t*-BuLi (1.7 M solution in pentane, 0.06 mL, 0.1 mmol) of (±)-8-oxotetrahydropalmatine **2a**[5] (18.5 mg, 0.05 mmol) gave the crude **6a** (19 mg). Crystallization from EtOH afforded colorless crystals (16 mg) of **6a**, mp 197−199 °C.

8-Butylidene-2,3,9,10-tetramethoxyberbine (3a). Carbamate **1a** (99 mg, 0.2 mmol) and BuLi (1.6 M solution in hexane, 0.38 mL, 0.6 mmol) were used. The crude product (79 mg) was purified through a column of Celite (2.0 g) and Mg_2SO_4 (2.0 g) with CH_2Cl_2 to give **3a** as a colorless oil (75.5 mg, 92%): IR (neat) 1698, 1611, 1517 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.97 (t, J = 6.6 Hz, 3H), 1.48 (q, J = 6.9 H, 2H), 2.20−2.48 (m, 3H), 2.82−3.00 (m, 4H), 3.29−3.39 (m, 1H), 3.76, 3.83, 3.85, 3.88 (each s, each 3H), 4.07 (dd, J = 10.0, 3.3 Hz, 1H), 6.26 (t, J = 6.9 Hz, 1H), 6.63, 6.67 (each s, each 1H), 6.74, 6.83 (AB type, J = 7.9 Hz, each 1H); EI-MS m/z (rel int.) 409 (M^+, 5.2), 352 (100), 192 (45.5); FD-MS m/z (rel int) 410 [$(M + H)^+$, 27.7), 409 (M^+, 100), 192 (45.5). HR-MS calcd for $C_{25}H_{31}NO_4$, 409.2253; found, 409.2235.

A similar treatment of **2a** (18.5 mg, 0.05 mmol) with BuLi (1.6 M solution in hexane, 0.063 mL, 0.1 mmol) gave **6a** (18 mg).

Reaction of Carbamate 1a with *s*-BuLi. A mixture of 1-[2′-(2″-methylbutyryl)-3′,4′-dimethoxybenzyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**4a**) and 9-(2-butyl)-2,3,10-trimethoxy-8-oxoberbine (**5a**) was obtained in a ratio of 5:1. **4a**: a colorless oil (50%); R_f 0.1 (5% MeOH−CH_2Cl_2); IR (neat) 3346, 1693, 1611, 1572, 1516 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0. 94, 0.95 (1:1, each dt, J = 7.3 Hz, 3H), 1.13, 1.14 (1:1, each d, J = 7.0 Hz, 3H), 1.32−1.45 (m, 1H), 1.77−1.92 (m, 2H), 2.62−2.74 (m, 3H), 2.83−2.98 (m, 3H), 3.15−3.24 (m, 1H), 3.81, 3.84, 3.85, 3.88 (each s, each 3H), 4.13−4.19 (m, 1H), 6.57, 6.65 (each s, each 1H), 6.92, 7.12 (AB type, J = 8.3 Hz, each 1H); ^{13}C NMR (270 MHz, $CDCl_3$) δ 11.84, 11.88 (1:1, each q), 15.1, 15.4 (1:1, each q), 25.18, 25.23 (1:1, each t), 29.4 (s), 39.55, 39.64 (1:1, each t), 39.8 (t), 49.13, 49.18 (1:1, each d), 55.9 (q, 3 MeO), 56.66, 56.69 (1:1, each d), 61.6 (q), 109.3 (d), 111.6 (d), 113.1, 113.2 (1:1, each d), 126.3 (s), 127.08, 127.13 (1:1, each d), 129.0 (s), 130.78, 130.83 (1:1, each s), 130.78, 130.83 (s), 136.7 (s), 145.9 (s), 147.1, 147.4 (1:1, each d), 150.9 (s), 211.3 (s); FAB-MS m/z (rel int) 428 [$(M + H)^+$, 29], 410 (38), 352 (100), 192 (52); FD-MS m/z (rel int) 427 (M^+, 100), 192 (24). HR-MS calcd for $C_{25}H_{34}NO_5$, 428.2437; found, 428.2426.

5a: colorless crystals (9.3%); mp 187−189 °C (Et_2O); R_f 0.8 (5% MeOH−CH_2Cl_2); IR (Nujol) 1639, 1515 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.70 (t, J = 3.5 Hz, 3H), 1.45 (d, J = 5.9 Hz, 3H), 1.67−1.85 (m, 2H), 2.73−3.01 (m, 5H), 3.82, 3.89, 3.90 (each s, each 3H), 3.39−4.02 (m, 1H), 4.73 (dd, J = 2.6 Hz, 1H), 4.99−5.04 (m, 1H), 6.68, 6.70 (each s, each 1H), 6.92, 7.03 (AB type, J = 8.3 Hz, each 1H); EI-MS m/z (rel int) 395 (M^+, 46), 204 (63), 192 (100), 175 (43). HR-MS calcd for $C_{24}H_{29}NO_4$, 395.2096; found, 395.2119. Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54. Found: C, 72.64; H, 7.51; N, 3.57.

A similar treatment of **2a** (18.5 mg, 0.05 mmol) with *s*-BuLi (1.0 M solution in pentane, 0.1 mL, 0.1 mmol) gave a mixture (20 mg) of **4a** and **5a** in a ratio of 5:1.

Reaction of Carbamate 1c with *t*-BuLi. 9-*tert*-Butyl-10-hydroxy-2,3-dimethoxy-8-oxoberbine (**7c**) and 1-[2′-trimethylacetyl-3′,4′-(methylenedioxy)benzyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**8c**) were obtained in a ratio of 5:4. **7c**: colorless crystals (43%); mp 183−185 °C (acetone), 212−215 °C ($CHCl_3$); R_f 0.4 (5% MeOH−CH_2Cl_2); IR (Nujol) 3198, 1612, 1573, 1511 cm^{-1}; ^1H NMR (270 MHz, CD_2Cl_2) δ 1.52 (s, 9H), 2.65−2.90 (m, 4H), 3.11 (ddd, J = 12.4, 8.9, 4.0 Hz, 1H), 3.79, 3.81 (each s, each 3H), 465 (dt, J = 12.9, 4.0, 4.0 Hz, 1H), 4.76 (dd, J = 3.0 Hz, 1H), 6.68 (AB type, partly hiding, J = 8.3 Hz, 1H), 6.68, 6.69 (each s, each 1H), 6.87 (AB type, J = 8.3 Hz, 1H); EI-MS m/z (rel int) 381 (M^+, 10.5), 192 (100), 190 (18.6), 85 (15.0), 83 (21.5). Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.60; H, 7.04; N, 3.62.

This phenol (6 mg) was treated with water (0.5 mL) containing KOH (6 mg, 0.1 mmol) and two drops of Me_2SO_4 at 80 °C for 30 min. The mixture was extracted with CH_2Cl_2. The organic layers were washed with water, dried (Na_2SO_4), and evaporated to give a single product (6 mg), whose IR and ^1H NMR spectral data were identical with those for **6a** in all respects.

8c: a colorless oil (33%); R_f 0.2 (5% MeOH−CH_2Cl_2); IR (neat) 3340, 1686, 1513 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.28 (s, 9H), 2.65−2.75 (m, 3H), 2.87−3.00 (m, 2H), 3.13−3.20 (m, 1H), 3.85 (s, 6H), 4.04 (dd, J = 3.3 Hz, 1H), 5.97, 5.99 (AB type, J = 1.3 Hz, each 1H), 6.57, 6.61 (each s, each 3H), 6.77, 6.81 (AB type, J = 8.0 Hz, each 1H); ^1H NMR (270 MHz, CD_2Cl_2) δ 1.23 (s, 9H), 2.58−2.67 (m, 3H), 2.80−2.92 (m, 2H), 3.05−3.13 (m, 1H), 3.75, 3.76 (each s, each 3H), 3.96 (dd, J = 3.3 Hz, 1H), 5.94, 5.95 (AB type, J = 1.3 Hz, each 1H), 6.54 (s, 2H), 6.75, 6.78 (AB type, J = 8.3 Hz, each 1H); ^{13}C NMR δ 27.2 (q), 29.4 (t), 39.6 (t), 40.0 (t), 44.9 (s), 55.8 (q), 56.8 (d), 101.1 (t), 108.6 (d), 109.6 (d), 111.6 (d), 123.6 (s), 123.9 (d), 127.1 (s), 129.8 (s), 130.7 (s), 143.1 (s), 145.9 (s), 147.1 (s), 147.4 (s), 213 (s); EI-MS m/z (rel int) 411 (M^+, 0.8), 396 (1.1), 354 (8.3), 192 (100). HR-MS calcd for $C_{24}H_{29}NO_4$, 411.2046; found, 411.2028.

8-Butylidene-2,3,10,11-tetramethoxyberbine (3b). The crude product (78 mg) was purified through a column of Celite (2.0 g) and Mg_2SO_4 (2.0 g) with CH_2Cl_2 to give **3b** as a colorless oil (74 mg, 90%): IR (neat) 1696, 1612, 1573, 1517 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.99 (t, J = 7.3 Hz, 3H), 1.49−1.56 (m, 2H), 2.10−2.50 (m, 2H), 2.51−3.30 (m, 6H), 3.87, 3.88, 3.89, 3.92 (each s, each 3H), 4.13 (dd, J = 11.6, 3.3 Hz, 1H), 5.58 (dd, J = 8.6, 5.6 Hz, 1H), 6.60, 6.64, 6.66, 7.16 (each s, each 1H); EI-MS m/z (rel int) 409 (M^+, 12.0), 352 (100). HR-MS calcd for $C_{25}H_{31}NO_4$, 409.2248; found, 409.2248. Irradiation of an aromatic proton signal at δ 7.16 caused an NOE enhancement of an olefinic proton signal at δ 5.58 (17.5%). Irradiation in the opposite way caused an NOE enhancement of the aromatic proton signal (25%).

A similar treatment with BuLi (1.56 M, 0.07 mL, 0.11 mmol) of (±)-8-oxoxylopinine **2b** (18.5 mg, 0.05 mmol) [mp 191−192

°C (MeOH) (lit.[10] 188−189 °C; lit.[11,12] 190−192 °C); prepared by the method reported by us[5]] gave **3b** (20 mg) as a single product.

1-[4′,5′-Dimethoxy-2′-(2′′-methylbutyryl)benzyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (4b): chromatographed on Florisil (5% MeOH−CH_2Cl_2); a colorless oil (81 mg, 95%); IR (neat) 3380, 1674, 1607, 1515 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.92, 0.95 (1:1, each t, J = 7.3 Hz, 3H), 1.16, 1.19 (1:1, each d, J = 6.9 Hz, 3 H), 1.74−1.90 (m, 2H), 2.66−2.79 (m, 2H), 2.80−2.96 (m, 2H), 3.18−3.28 (m, 2H), 3.53−3.61 (m, 1H), 3.86 (s, 3H), 3.87, 3.88 (1:1, each s, 3H), 3.91, 3.93 (each s, each 3H), 4.15−4.21 (m, 1H), 6.58, 6.79 (each s, each 1H), 6.87, 6.91 (each s, 1:1, 1H), 7.20 (s, 1H); ^{13}C NMR (270 MHz) δ 11.9, 12.0 (1:1, each q), 16.7, 16.9 (1:1, each q), 26.7, 26.8 (1:1, each t), 29.6 (s), 40.5, 40.6 (1:1, each t), 40.9 (t), 45.1 (d), 55.8 (q), 55.9, 56.0 (q), 56.0 (q), 56.2 (q), 56.89, 56.95 (1:1, each d), 110.0 (d), 111.60, 111.63, 112.3, 112.4 (1:1:1:1, each d), 114.97, 115.01 (1:1, each d), 125.5 (d), 127.15, 127.19 (1:1, each d), 130.4 (s), 130.6 (s), 131.1 (s), 134.4 (s), 147.12 (a), 147.4 (s), 151.0 (s), 207.1, 207.2 (1:1, each s); EI-MS m/z (rel int) 409 [$(M - H_2O)^+$, 16.1], 394 (22.6), 352 (100), 336 (20.3), 264 (11.5), 192 (10.3), 176 (10.4). HR-MS calcd for $C_{25}H_{33}NO_5 \cdot H_2O$, 409.2253; found, 409.2278.

Treatment of this amine (42 mg) with Ac_2O (2 mL) and pyridine (0.5 mL) at room temperature gave the crude product (48 mg), which was purified by preparative TLC on a Merck silica gel 60 PF_{254} developed with 2% MeOH−CH_2Cl_2. A main band with R_f 0.2 gave an oil (30 mg), which was crystallized from Et_2O to give an N-acetyl derivative of **4b** as colorless crystals (25 mg, 53%): mp 122−124 °C; IR (Nujol) 1673, 1641, 1518 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.90, 1.03 (4:3, each t, J = 7.3 Hz, 3H), 1.16, 1.27 (3:4, d, J = 6.6 Hz, 3H), 1.40, 1.42, 2.06 (5:3:1, each s, 3H), 1.44−1.98 (m, 2H), 2.66−3.38 (m, 6H), 3.77−3.98 (m, 6H), 3.87 (s, 3H), 3.94 (s, 3H), 4.88−4.94 (m, 1H), 5.23−5.323 (m, 1H), 6.45, 6.46 (4:3, each s, 1H), 6.61 (s, 1H), 7.20 (s, 1H); EI-MS m/z (rel int) 496 (M^+, 1.2), 236 (100), 192 (33.5). HR-MS calcd for $C_{27}H_{35}NO_6$, 469.2469; found, 469.2459. Anal. Calcd for $C_{27}H_{35}NO_6$: C, 69.06; H, 7.51; N, 2.98. Found: C, 68.81; H, 7.50; N, 3.20.

A similar treatment of **2b** (18.5 mg, 0.05 mmol) with *s*-BuLi (1.0 M solution in pentane, 0.1 mL, 0.1 mmol) gave **4b** (22 mg).

1-(2-Trimethylacetyl-4,5-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (6b). Treatment of carbamate **1b** with *t*-BuLi gave a 1:3 mixture of 8-oxoberbine **2b** and **6b**. **2b**: colorless crystals (12 mg, 17%); mp 189−190 °C (AcOEt−Et_2O); R_f 0.6 (5% MeOH−CH_2Cl_2). **6b**: a colorless oil (50 mg, 58%); R_f 0.3 (5% MeOH−CH_2Cl_2); IR (neat) 3336, 1681, 1607, 1516 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.28 (s, 9H), 2.66−2.75 (m, 3H), 2.93 (quint, J = 6.1 Hz, 1H), 3.04 (dd, J = 13.9, 3.3 Hz, 1H), 3.18 (quint, J = 6.3 Hz, 1H), 3.85, 3.86, 3.87, 3.88 (each s, each 3H), 4.13 (dd, J = 9.2, 3.3 Hz, 1H), 6.58, 6.68, 6.78, 6.83 (each s, each 1H); ^{13}C NMR (270 MHz) δ 27.8 (q), 29.2 (t), 40.1 (t), 40.1 (t), 44.9 (s), 55.8 (q), 55.8 (q), 55.9 (q), 56.0 (q), 56.8 (d), 108.9 (d), 109.6 (d), 111.6 (d), 113.7 (d), 127.2 (s), 129.3 (s), 130.1 (s), 132.8 (s), 146.4 (s), 147.1 (s), 147.4 (s), 149.2 (s), 213.8 (s). EI-MS m/z (rel int) 427 (M^+, 0.5), 352 (15.4), 192 (100). HR-MS calcd for $C_{25}H_{33}NO_5$, 427.2358; found, 427.2386. Irradiation of an aromatic proton signal at 6.83 caused an NOE enhancement of a methoxy signal (10.0%) and a *t*-Bu signal at δ 1.28 (12.6%).

A similar treatment with *t*-BuLi (1.7 M solution in pentane, 0.6 mL, 0.5 mmol) of 8-oxoberbine **2b** (18.5 mg, 0.05 mmol) gave a mixture (19 mg) of **6b** and the unchanged **2b** in a ratio of 5:1.

General Procedure. 8-Methylene-2,3,9,10-tetramethoxyberbine 9a. To an ice-cooled and stirred solution of **1a** (49.4 mg, 0.1 mmol) in dry THF (10 mL) under an atmosphere of nitrogen was added MeLi (1.5 M solution in Et_2O, 0.2 mL, 0.3 mmol). The mixture was kept at 0 °C for 30 min and then at room temperature for 3 h. The solvents were removed in a rotary evaporator, and the residue was treated with water and CH_2Cl_2. The organic layers were washed with water, dried (Na_2SO_4), and evaporated. The residue (36 mg) was purified through a column of Celite (1.0 g) and Mg_2SO_4 (1.0 g) with CH_2Cl_2 to give **9a** as a colorless oil (33 mg, 91%): IR (neat) 1694, 1611, 1572, 1516 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.85−3.48 (m, 5H), 3.80, 3.87, 3.88 (each s, each 3H), 4.65, 5.79, 6.65, 6.68 (each s, each 1H), 6.83, 6.88 (AB type, J = 8.3 Hz, each 1H); EI-MS m/z (rel int) 367 (M^+, 5.2), 352 (100), 192 (45.5). HR-MS calcd for $C_{22}H_{25}NO_4$, 367.1819: found, 367.1794. FD-MS m/z (rel int) 410 [$(M + H)^+$, 25.7], 409 (M^+, 100), 192 (45.5). Irradiation of an olefinic proton signal at δ 5.79 caused an NOE enhancement of a methoxy signal at δ 3.80 (16%) and another olefinic proton signal at δ 4.65 (35%).

A similar treatment of **2a** (18.5 mg, 0.05 mmol) with MeLi (1.5 M solution in Et_2O, 0.1 mL, 0.15 mmol) gave **9a** (17 mg).

8-Methylene-2,3,10,11-tetramethoxyberbine (9b): a colorless oil (90%); IR (neat) 1607, 1510 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.72−3.16 (m, 6H), 3.89 (s, 6H), 3.90, 3.92 (each s, each 3H), 4.17 (s, 1H), 4.17−4.23 (m, hiding, 1H), 4.73 (s, 1H), 6.64, 6.66, 6.69, 7.24 (each s, each 1H); EI-MS m/z (rel int) 367 (M^+, 27.1), 352 (51.9), 278 (25.1), 220 (28. 6), 205 (100), 192 (73.7). HR-MS calcd for $C_{22}H_{25}O_4N$, 367.1784; found, 367.1802.

A similar treatment of **2b** (18.5 mg, 0.05 mmol) with MeLi (1.5 M solution in Et_2O, 0.1 mL, 0.15 mmol) gave **9b** (16.5 mg).

General Procedure. *trans*-8-Methyl-2,3,9,10-tetramethoxyberbine (10a). To a stirred solution of **9a** (70 mg, 0.19 mmol) in AcOH (5 mL) was added $NaBH_4$ (76 mg, 1.9 mmol) in portions for 1 min. After the mixture was continuously stirred at room temperature for 3 h, AcOH was evaporated. The residue was dissolved in water and CH_2Cl_2. The water layer was further extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were washed with water, dried (Na_2SO_4), and evaporated to give an oily product (71 mg), which was crystallized from MeOH−Et_2O to give berbine **10a** (53 mg, 75%) as colorless crystals: mp 166−169 °C; IR (Nujol) 1608, 1515 cm^{-1}; ^1H NMR (270 Hz, $CDCl_3$) δ 1.51 (d, J = 5.9 Hz, 3H), 2.51−2.86 (m, 3H), 3.07−3.18 (m, 2H), 3.33−3.39 (m, 1H), 3.55−3.58 (m, 1H), 3.865 (s, 6H), 3.875, 3.881 (each s, each 3H), 6.62, 6.76 (each s, each 1H), 6.80, 6.91 (AB type, J = 8.25 Hz, each 1H); EI−MS m/z (rel int) 369 (M^+, 15.8), 354 (100), 338 (9.14), 178 (18.1). Anal. Calcd for $C_{22}H_{27}NO_4$; C, 71.52; H, 7.37; N, 3.79. Found; C, 71.30; H, 7.29; N, 3.81.

***trans*-8-Methyl-2,3,10,11-tetramethoxyberbine (10b), (±)-coralydine:** colorless crystals (81%); mp 89−91 °C (MeOH−ether), 122−124 °C (isoPr$_2$O) [lit.[14a] 115 °C; lit.[14b] 150.5−151 °C]; IR (Nujol) 1612, 1520 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.55 (d, J = 6.3 Hz, 3H), 2.42−2.51 (m, 1H), 2.68−2.76 (m, 1H), 2.82−2.92 (m, 1H), 3.02−3.16 (m, 2H), 3.35−3.42 (m, 1H), 3.69−3.76 (m, 2H), 3.87, 3.89 (each s, each 3H), 3.88 (s, 6H), 6.62, 6.65, 6.68, 6.75 (each s, each 1H).

Reaction of Carbamate 1a with *s*-BuMgCl. A similar treatment of **1a** (98.8 mg, 0.2 mmol) with *s*-BuMgBr (0.8 M solution in THF, 1.25 mL, 1.0 mmol) gave a crude product (88 mg), which was comprised of **5a** and the debrominated reactant, 1-(3,4-dimethoxybenzyl)-2-carbethoxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**11**) (4:1). Preparative TLC on silica gel (5% MeOH−CH_2Cl_2) gave **5a** as colorless crystals (51 mg, 65%): R_f 0.8; mp 187−190 °C (Et_2O). **11**: colorless crystals (13.3 mg, 16%); R_f 0.6; mp 91−93 °C (Et_2O); IR (Nujol) 1697, 1517 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.15, 1.65 (5:4, each t, J = 6.9 Hz, 3H), 2.49−3.28, 3.89−4.20 (each m, 8H), 3.63−3.85 (m, 12H), 5.11−5.27 (m, 1H), 6.20, 6.35 (4:5, each s, 1H), 6.54−6.80 (m, 4H); EI-MS m/z (rel int) 414 (M^+, 0.1), 370 [$(M - OEt)^+$, 0.9], 264 (100), 192 (19.7), 151 (7.0). Anal. Calcd for $C_{23}H_{29}NO_6$; C, 66.49; H, 7.04; N, 3.37. Found: C, 66.07; H, 7.03; N, 3.39.

Reaction of Carbamate 1a with isoPrMgCl. 9-Isopropyl-2,3,10-trimethoxy-8-oxoberbine (12a). A mixture of **1a** (49.4 mg, 0.1 mmol) and isoPrMgCl (2.0 M solution in THF, 0.15 mL, 0.3 mmol) was warmed in an oil bath at 40 °C for 2h. To the mixture was added 3 drops of MeOH, and the solvents were evaporated. The residue was treated with water and CH_2Cl_2. The CH_2Cl_2 layer was washed with water, dried (Na_2SO_4), and evaporated. The residue (46 mg) was purified by preparative TLC on a Merck silica gel 60 PF_{254} developed with 5% MeOH−CH_2Cl_2 to give **10a** as a colorless oil (34 mg, 90%): R_f 0.7; IR (neat) 1685, 1635, 1581 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.31, 1.46 (each d, J = 6.9 Hz, each 3H), 2.75−

2.99 (m, 5H), 3.84, 3.89, 3.90 (s, 3H), 4.30 (t, J = 6.9 Hz, 1H), 4.74 (dd, J = 12.5, 3.0 Hz, 1H), 4.99−5.04 (m, 1H), 6.68, 6.70 (each s, each 1H), 6.93, 7.03 (each d, J = 8.2 Hz, each 1H); EI-MS m/z (rel int) 381 (M^+, 61), 190 (100). HR-MS calcd for $C_{23}H_{27}NO_4$, 381.1941; found, 381.1920.

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