Oxidative Intramolecular Phenolic Coupling Reaction Induced by a Hypervalent Iodine(III) Reagent: Leading to Galanthamine-Type Amaryllidaceae Alkaloids

Yasuyuki Kita,* Mitsuhiro Arisawa, Michiyo Gyoten, Makiko Nakajima, Ryuji Hamada, Hirofumi Tohma, and Takeshi Takada

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565-0871, Japan

Received April 28, 1998

By extending our oxidative phenol-coupling reactions using a hypervalent iodine(III) reagent, a versatile synthetic procedure for the galanthamine-type Amaryllidaceae alkaloids was accomplished. The first total synthesis of (±)-sanguinine and the total syntheses of (±)-galanthamine, (±)-narwedine, (±)-lycoramine, and (±)-norgalanthamine were also successfully carried out.

Introduction

Hypervalent iodine(III) reagents are now extensively used in the field of organic chemistry.[1] In particular, phenyliodine(III) diacetate (PIDA) or phenyliodine(III) bis(trifluoroacetate) (PIFA) have received a great deal attention because their reactivities are similar to those of heavy metal reagents or anodic oxidation, they have low toxicity, are readily available, and are easy to handle. The reaction of phenols themselves with hypervalent iodine(III) reagent leads to resinous products,[1a,b,2] while that of some phenols, bearing an electron-withdrawing group on the para site, leads to *p*-benzoquinones.[2] Phenols bearing electron-withdrawing *o*-nitro and *o*,*p*-dinitro groups react with PIDA to give the corresponding iodonium salts and related species.[3] On the other hand, some para-substituted phenols were observed to react with nucleophiles (alcohols,[4] enes,[5] amides,[6] carboxylic acids,[7] oximes,[8] fluoride ion,[9] water,[10] and electron-rich aromatic rings[11]) in the presence of PIFA to give the cross-conjugated cyclohexadienone by either an inter- or intramolecular reaction path (type I, Scheme 1). The type I reaction path involves the reactions of phenols, in which the oxygen reacts with the iodine center in the hypervalent iodine reagent. On the other hand, substituted phenol ethers react with nucleophiles (nitrogen,[12] oxygen, carbon,[13] and sulfur[14]) in the presence of PIFA to give

(1) Reviews see: (a) Banks, D. F. *Chem. Rev.* **1966**, *66*, 243−266. (b) Varvoglis, A. *Chem. Soc. Rev.* **1981**, *10*, 377−407. (c) Umemoto, T. *J. Synth. Org. Chem. Jpn.* **1983**, *41*, 251−265. (d) Koser, G. F. In *The Chemistry of Functional Groups*; Eds., Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: New York, 1983, Suppl. D, Chapter 18 and 25. (e) Varvoglis, V. *Synthesis* **1984**, 709−726. (f) Moriarty, R. M.; Prakash, O. *Acc. Chem. Res.* **1986**, *19*, 244−250. (g) Ochiai, M.; Nagao, Y. *J. Synth. Org. Chem. Jpn.* **1986**, *44*, 660−673. (h) Merkushev, E. B. *Russ. Chem. Rev. (Engl. Transl.)* **1987**, *56*, 826−845. (i) Ochiai, M. *Rev. Heteroatom Chem.* **1989**, *2*, 92−111. (j) Moriarty, R. M.; Vaid, R. K. *Synthesis* **1990**, 431−447. (k) Moriarty, R. M.; Vaid, R. K.; Koser, G. F. *Synlett* **1990**, 365−383. (l) Stang, P. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 274−285. (m) Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine*; VCH Publishers: New York, 1992. (n) Kita, Y.; Tohma, H.; Yakura, T. *Trends Org. Chem.* **1992**, *3*, 113−128, (o) Kita, Y.; Tohma, H. *Farumashia* **1992**, *28*, 984−989; *Chem Abstr.* **1992**, *117*, 233100 g. (p) Prakash, O.; Rani, N.; Tanwar, M. P.; Moriarty, R. M. *Contemp. Org. Synth.* **1995**, *2*, 121−131; *Chem. Abstr.* **1995**, *123*, 284824c. (q) Stang, P. J. In *The Chemistry of Triple-Bonded Functional Groups*; Patai, S., Ed.; John Wiley & Sons, Chichester, **1994**; Suppl. C2, Chapter 20. (r) Koser, G. F. In *The Chemistry of Halides, Pseudo-Halides and Azides*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: Chichester, 1995; Suppl. D2, Chapter 21. (s) Kitamura, T. *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 893−905. (t) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123−1178. (u) Stang, P. J. In *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH Publishers: Weinheim, 1995; Chapter 3. (v) Kita, Y.; Takada, T.; Tohma, H. *Pure Appl. Chem.* **1996**, *68*, 627−630. (w) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: San Diego, 1997. (x) Kitamura, T.; Fujiwara, Y. *Org. Prep. Proc. Int.* **1997**, *29*, 409−458.

(2) (a) Raju, R.; Rao, G. S. K. *Ind. J. Chem.* **1987**, *26B*, 469−471. (b) Murali, D.; Rao, G. S. K. *Ibid.* **1987**, *26B*, 668−670. (c) Tamura, Y.; Yakura, T.; Tohma, H.; Kikuchi, K.; Kita, Y. *Synthesis* **1989**, 126−127.

(3) (a) Fox, A. R.; Pausacker, K. H. *J. Chem. Soc.* **1957**, 295−301. (b) Kokil, P. B.; Nair. P. M. *Tetrahedron Lett.* **1977**, 4113−4116. (c) Kappe, T.; Korbuly, G.; Stadlbauer, W. *Chem. Ber.* **1978**, *111*, 3857−3866. (d) Page, S. W.; Mazzola, E. P.; Mighell, A. D.; Himes, V. L.; Hubbard, C. R. *J. Am. Chem. Soc.* **1979,** *101*, 5858−5860. (e) Spyroudis, S.; Varvoglis, A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 135−137.

(4) (a) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org, Chem.* **1987**, *52*, 3927−2930. (b) Lewis, N.; Wallbank, P. *Synthesis* **1987**, 1103−1106. (c) Pelter, A.; Elgendy, S. *Tetrahedron Lett.* **1988**, *29*, 677−680. (d) *Idem. J. Chem. Soc., Perkin Trans. 1* **1993**, 1891−1892. (e) Fleck, A. E.; Hobart, J. A.; Morrow, G. W. *Synth. Commun.* **1992**, *22*, 179−187. (f) Mitchell, A. S.; Russell, R. A. *Tetrahedron Lett.* **1993**, *34*, 545−548.

(5) Callinan, A.; Gary, Y. C.; Morrow, W.; Swenton, J. S. *Tetrahedron Lett.* **1990**, *31*, 4551−4552.

(6) Kita, Y.; Tohma, H.; Kikuchi, K.; Inagaki, M.; Yakura, T. *J. Org. Chem.* **1991**, *56*, 435−438.

(7) (a) Rama Rao, A. V.; Gurjar, M. K.; Sharma, P. A. *Tetrahedron Lett.* **1991**, *32*, 6613−6616. (b) Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, *33*, 5477−5480. (c) Hara, H.; Inoue, T.; Nakamura, H.; Endoh, M.; Hoshino, O. *Tetrahedron Lett.* **1992**, *33*, 6491−6494. (d) McKillop, A.; McLaren, L.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synlett* **1992**, 201−203. (e) Wipf, P.; Kim, Y.; Fritch, P. C. *J. Org. Chem.* **1993**, *58*, 7195−7203.

(8) (a) Kaçan, M.; Koyuncu, D.; McKillop, A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1771−1772. (b) Murakata, M.; Yamada, K.; Hoshino, O. *J. Chem. Soc., Chem. Commun.* **1994**, 443−444.

(9) Karam, O.; Jacquesy, J.; Jouannetaud, M. *Tetrahedron Lett.* **1994**, *35*, 2541−2544.

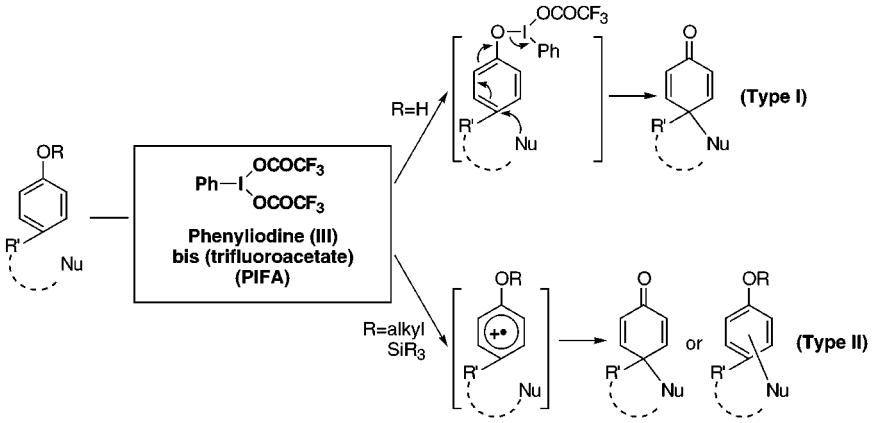
(10) McKillop, A.; McLaren, L.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2047−2048.

(11) (a) Szántay, C.; Blaskó, G.; Bárczai-Beke, M.; Péchy, P.; Dörnyei, G. *Tetrahedron Lett.* **1980**, *21*, 3509−3512. (b) White, J. D.; Chong, W. K.; Thirring, K. *J. Org. Chem.* **1983**, *48*, 2302−2304. (c) Kita, Y.; Yakura, T.; Tohma, H.; Kikuchi, K.; Tamura, Y. *Tetrahedron Lett.* **1989**, *30*, 1119−1120. (d) Rama Krishna, K. V.; Sujatha, K.; Kapil, R. S. *Tetrahedron Lett.* **1990**, *31*, 1351−1352. (e) Kita, Y.; Tohma, H.; Inagaki, M.; Hatanaka, K.; Yakura, T. *J. Am. Chem. Soc.* **1992**, *114*, 2175−2180. (f) Pelter, A.; Ward, R. S.; Abd-El-Ghani, A. *Tetrahedron: Asymmetry* **1994**, 5, 329−332. (g) Kita, Y.; Takada, T.; Ibaraki, M.; Gyoten, M.; Mihara, S.; Fujita, S.; Tohma, H. *J. Org. Chem.* **1996**, *61*, 223−227. (h) Swenton, J. S.; Callinan, A.; Chen. Y.; Rohde, J. J.; Kerns, M. L.; Morrow, G. W. *J. Org. Chem.* **1996**, *61*, 1267−1274. (i) Ward, R. S.; Pelter, A. Abd-El-Chani, A. *Tetrahedron* **1996**, *52*, 1303−1336. (j) Kita, Y.; Takada, T.; Gyoten, M.; Tohma, H.; Zenk, M. H.; Eichhorn, J. *J. Org. Chem.* **1996**, *61*, 5857−5864.

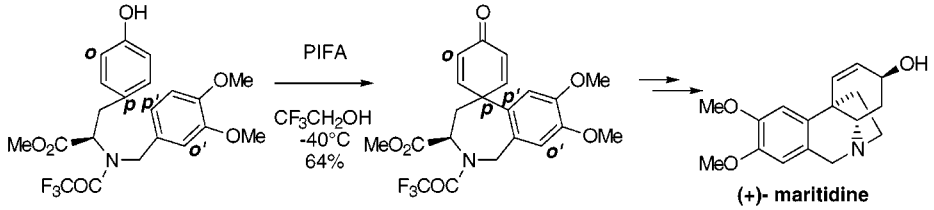
(12) Kita, Y.; Tohma, H.; Inagaki, M.; Hatanaka, K.; Yakura, T. *Tetrahedron Lett.* **1991**, *32*, 4321−4324.

S0022-3263(98)00786-5 CCC: $15.00
Published on Web 08/22/1998

Scheme 1. Hypervalent Iodine Oxidation: Oxidative Cyclization of Phenols and Phenol Ethers



Scheme 2



the more substituted phenol ethers by either an inter- or intramolecular reaction path (type II, Scheme 1). Type II involves the reactions of phenol ethers, wherein the aromatic ring reacts with the hypervalent iodine reagent and generates a cation radical intermediate.

Very recently, we have developed a biomimetic intramolecular para−para′ coupling reaction of norbelladine derivatives (type I) and the formal synthesis of (+)-maritidine, which belongs to the crinine-type Amaryllidaceae alkaloids (Scheme 2).[11j]

As an extension of our chemistry using hypervalent iodine(III) reagents, we were interested in developing a PIFA-induced para−ortho′ coupling reaction of norbelladine derivatives (type I) leading to the synthesis of galanthamine-type Amaryllidaceae alkaloids. These alkaloids have attracted much attention because of their diversity in pharmacology,[15] such as analgesic, anticholinergic, and anticholinesterase activities. Galanthamine (**1**) and related alkaloids have been evaluated as potential agents for the treatment of Alzheimer's disease and related illnesses. Although many chemists have synthesized these alkaloids [galanthamine (**1**),[16] narwedine (**2**),[17] lycoramine (**3**),[17] and norgalanthamine (**4**)[18]], the syntheses of those bases (e.g., sanguinine (**5**)[19] and leucotamine (**6**)[20]) with the phenolic hydroxy group have not been successful yet due to the limitations in their reported synthetic methods. Furthermore, the use of heavy metal reagents,[16] the lack of regiocontrol during the cyclization, and the low yields of the coupling products have remained problematic. Therefore, establishment of an effective synthetic method for various kinds of galanthamine-type Amaryllidaceae alkaloid derivatives will be very useful.

In this paper, we describe a PIFA-induced novel effective synthesis of the galanthamine-type Amaryllidaceae alkaloid derivatives (±)-galanthamine (**1**), (±)-

(13) (a) Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684−3691. (b) Kita, Y.; Gyoten, M.; Ohtsubo, M.; Tohma, H.; Takada, T. *Chem. Commun.* **1996**, 1481−1482. (c) Kita, Y.; Egi, M.; Okajima, A.; Ohtsubo, M.; Takada, T.; Tohma, H. *Chem. Commun.* **1996**, 1491−1492.

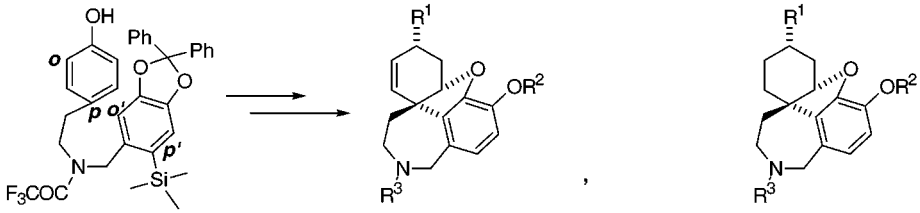
(14) (a) Kita, Y.; Takada, T.; Mihara, S.; Tohma, H. *Synlett* **1995**, 211−212. (b) Kita, Y.; Egi, M.; Ohtsubo, M.; Saiki, T.; Takada, T.; Tohma, H. *Chem. Commun.* **1996**, 2225−2226.

(15) (a) Bastida, J.; Viladomat, F.; Llabrés, J. M.; Codina, C.; Feliz, M.; Rubiralta, M. *J. Nat. Prod.* **1989**, *52*, 478−480. (b) Sweeney, J. E.; Bachman E. S.; Coyle, J. T. *Psychopharmacology* **1990**, *102*, 191−200. (c) Sweeney, J. E.; Puttfarcken, P. S.; Coyle, J. T. *Pharmacol. Biochem. Behavior* **1989**, *34*, 129−137. (d) Sweeney, J. E.; Höhmann, C. F.; Moran, T. H.; Coyle, J. T. *Ibid.* **1988**, *31*, 141−147. (e) Tonkopii, V. D.; Prozorovskii, V. B.; Konstorum, M. G. *Byull. Eksp. Biol. Med.*, **1975**, *80*, 120; *Chem. Abstr.* **1975**, *83*, 189728w. (f) Vasilenko, E. T.; Tonkopii, V. D. *Biolkhimiya* **1974** *39*, 301; *Chem. Abstr.* **1975**, *82*, 12913f. (g) Fisenko, V. P.; Mitsov, V. *Farma. Toksikol (Moscow)* **1975**, *38*, 34; *Chem. Abstr.* **1975**, *82*, 132979d. (h) Baraka, A.; Cozanitis, D. *Anesth. Analg.* **1973**, *52*, 832; *Chem. Abstr.* **1974**, *81*, 22842e. (i) Dolgushina, A. T. *Povysh. Rezistentnosti Organizma*, **1973**, 182; *Chem. Abstr.* **1974**, *81*, 72709h. (j) Cozanitis, D. A.; Nuuttila, K.; Karhunen P.; Baraka, A. *Anaesthesist* **1973**, *22*, 457. (k) Numata, A.; Takemura, T.; Ohbayashi, H.; Katsumo, T.; Yamamoto, K.; Sato, K.; Kobayashi, S. *Chem. Pharm. Bull.* **1983**, *31*, 2146. (l) Bazhenova, E. D.; Aliev, Kh. U.; Zakirov, U. B. *Farmakol. Alkaloidov Ikh. Proizvod.* **1972**, 74; *Chem. Abstr.* **1974**, *80*, 103864r. (m) Stichting Biomedical Research and Advice group, Neth. Appl. NL 88 00, 350; *Chem. Abstr.* **1990**, *112*, 112096y. (n) Ernir, S. US Patent 5, 589, 475; *Chem. Abstr.* **1997**, *126*, 54848. (o) Weniger, B.; Italiano, L.; Beck, J.; Bastida, J.; Bergonon, S.; Codina, C.; Lobstein, A.; Anton, R. *Planta Med.* **1995**, *61*, 77−79.

(16) (a) Crollner, L.; Frantsits, W.; Küenburg, B.; Hedenig, U.; Fröhlich, J.; Jordis, U. *Tetrahedron Lett.* **1998**, *39*, 2087−2088. (b) Szewczyk, J.; Wilson, J. W.; Lewin, A. H.; Carroll, F. I. *J. Hetrocycl. Chem.* **1995**, *32*, 195−199. (c) Vlahov, R.; Krikorian, D.; Spassov, G.; Chinova, M.; Vlahov, I.; Parushev, S.; Snatzke, G.; Ernst, L.; Kieslich, K.; Abraham, W.; Sheldrick, W. S. *Tetrahedron* **1989**, *45*, 3329−3345. (d) Shimizu, K.; Tomioka, K.; Yamada, S.; Koga, K. *Chem. Pharm. Bull.* **1978**, *26*, 3765−3771. (e) Shimizu, K.; Tomioka, K.; Yamada, S.; Koga, K. *Heterocycles* **1977**, *8*, 277−282. (f) Kametani, T.; Yamaki, K.; Yugi, H.; Fukumoto, K. *J. Chem. Soc. C* **1969**, 2602−2605. (g) Barton, D. H. R.; Kirby, G. W. *J. Chem. Soc.* **1962**, 806−817.

(17) (a) Chaplin, D. A.; Fraser, N.; Tifin, P. D. *Tetrahedron Lett.* **1997**, *38*, 7931−7932. (b) Essamkaoui, J. M.; Benharref, A.; Moskowitz, H.; Mayrargue, J.; Thal, C. *Heterocycl. Commun.* **1996**, *2*, 319−323. (c) Ishizaki, M.; Ozaki, K,; Kanematsu, A.; Isoda, T.; Hoshino, O. *J. Org. Chem.* **1993**, *58*, 3877−3885. (d) Parker, K. A.; Kin, H. J. *J. Org. Chem.* **1992**, *57*, 752−755. (e) Sánchez, I. H.; Soria, J. J.; López, F. J.; Lurraza, M. I.; Flores, H. J. *J. Org. Chem.* **1984**, *49*, 157−163. (f) Martin, S. F.; Garrison, P. J. *J. Org. Chem.* **1982**, *47*, 1513−1518. (g) Schults, A. G.; Yee, Y. K.; Berger, M. H. *J. Am. Chem. Soc.* **1977**, *99*, 8065−8067.

Scheme 3



1 : **galanthamine** R^1: OH, R^2=R^3: Me
2 : **narwedine** R^1: =O, R^2=R^3: Me
4 : **norgalanthamine** R^1: OH, R^2: Me, R^3:H
5 : **sanguinine** R^1: OH, R^2: H, R^3: Me
6 : **leucotamine** R^1:OCOCH$_2$CH(OH)CH$_3$ R^2: Me, R^3: H
3 : **lycoramine** R^1: OH, R^2=R^3: Me

narwedine (**2**), (±)-lycoramine (**3**), (±)-norgalanthamine (**4**), and (±)-sanguinine (**5**) (Scheme 3).

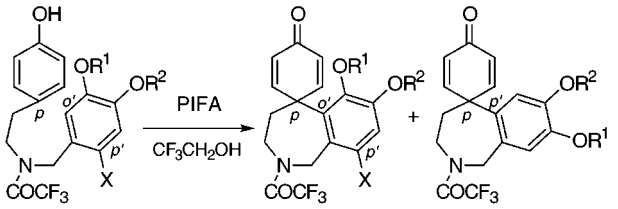
Results and Discussion

In the hypervalent iodine(III) reagent-induced oxidative intramolecular regioselective coupling reactions of norbelladine derivatives without any para′ site protection, no para−ortho′-coupled product was obtained at all. To establish the selective para−ortho′ coupling reaction of norbelladine derivatives instead of a para−para′ coupling reaction, we have synthesized many norbelladine derivatives(**13a**−**k**) by the reactions of tyramine and the corresponding aldehyde (Scheme 4) and have treated them with PIFA in some solvents. Only trifluoroethanol was found to be an effective solvent, while benzene or dichloromethane did not give the coupled product at all.

As indicated in Table 1, **13e**−**g**,**j**,**k**, whose para′ sites are protected with the trialkylsilyl groups, and catechol with methylendioxy derivatives gave para−ortho′ coupled products in moderate yields (runs 5−7, 10, and 11). It is interesting that these norbelladine derivatives did not react at all with K_3FeCN_6 or $Mn(acac)_3$, a previously reported oxidant. These reactions proceed, although hypothesized, via the mechanism of type I; the oxygen of the hydroxy group and the iodine center of hypervalent iodine reagent react and release electrons on the aromatic ring from oxygen, promoting the intramolecular ring-closing coupling reaction.

In the subsequent study to convert **14e**−**g**,**j**,**k** into a galanthamine ring, it was found that only **14f**,**j**,**k** gave the desired ring system. That is to say, using trifluoroacetic acid, the trimethylsilyl group at the para′ site and the diphenylmethylene group on catechol in **14f**,**j**,**k** could be removed easily, and the resulting phenolic hydroxy group promoted the Michael addition to the dienone and

Table 1. Intramolecular Coupling Reaction Using PIFA



13 **14** **15**

		substrate **13**			isolated yield (%)	
run		R^1	R^2	X	**14** (*p*−*o*′)	**15** (*p*−*p*′)
1	**a**	Me	Me	SPh	0	0
2	**b**	Me	Me	TMS	0	26
3	**c**	−CH$_2$−		Br	6	2
4	**d**	−CH$_2$−		SPh	0	0
5	**e**	−CH$_2$−		TMS	32	0
6	**f**	−CPh$_2$−		TMS	36	9
7	**g**	−CMe$_2$−		TMS	46	12
8	**h**	−CPh$_2$−		H	0	60
9	**i**	−CMe$_2$−		H	0	55
10	**j**	−CPh$_2$−		TES	37	0
11	**k**	−CPh$_2$−		TBS	28	0

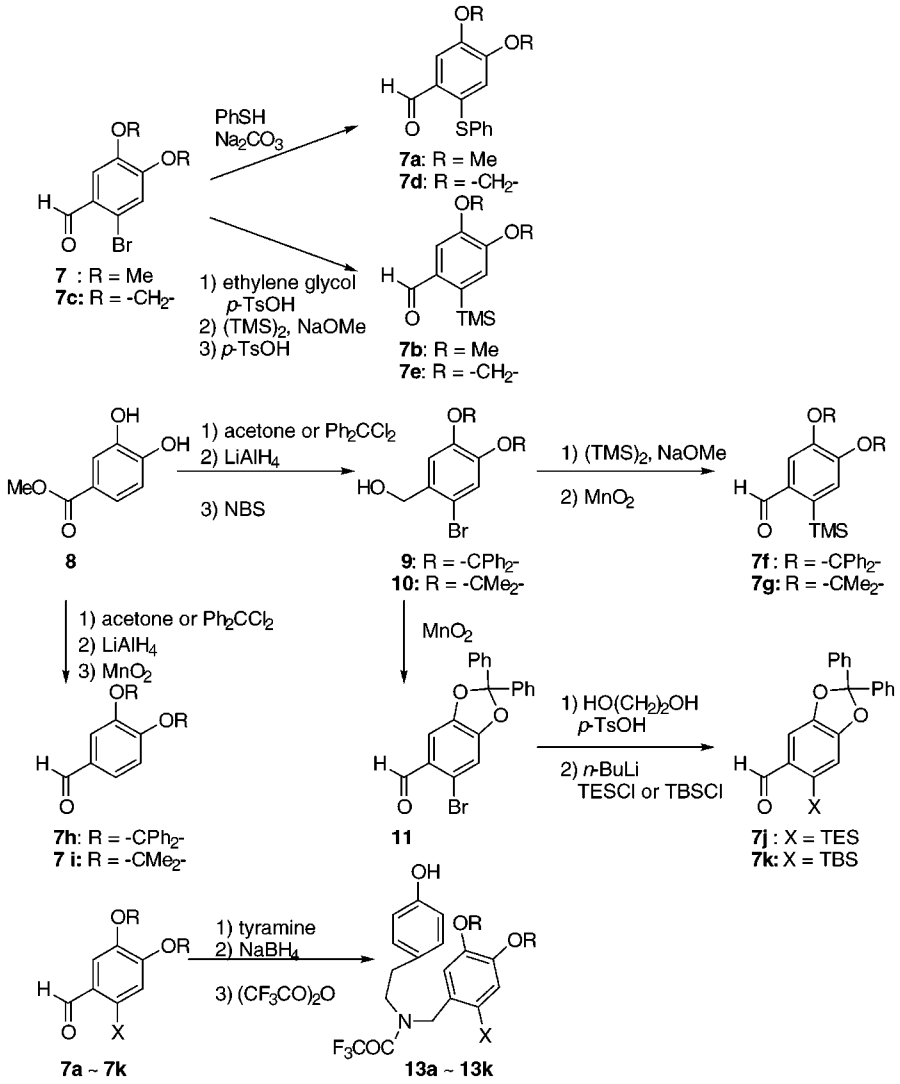
afforded the compound (**16**), which was methylated with Me_2SO_4/K_2CO_3 to give *N*-demethyl-*N*-(trifluoroacetyl)-narwedine (**17**), quantitatively (Scheme 5). It was also observed that with K_2CO_3−MeOH−H_2O, **14f** gave a crinine-type Amaryllidaceae alkaloid ring system (**18**) by the deprotection of trifluoroacetyl amide and the Michael addition of the generated secondary amine; that with concentrated hydrochloric acid or BCl_3 desilylated compound (**19**) was obtained from **14f**; and with 5 N hydrochloric acid-EtOH or BBr_3, **14f** was converted to a lignan ring system (**20**) through a dienone−phenol rearrangement (Scheme 6).

Encouraged by these results, we synthesized galanthamine (**1**), narwedine (**2**), lycoramine (**3**), norgalanthamine (**4**), and sanguinine (**5**) from **16** (Scheme 7). It is noteworthy to mention here that our synthetic method of galanthamine-type Amaryllidaceae alkaloids is superior to the previous ones for the following reasons: (1) In the para−ortho′ coupling reaction of norbelladine derivatives, the hypervalent iodine(III) reagent, which involves easy handling and has low toxicity, is used instead of heavy metal reagents. (2) Modifications of the secondary amine and the phenolic hydroxy groups in the galanthamine ring system are available.

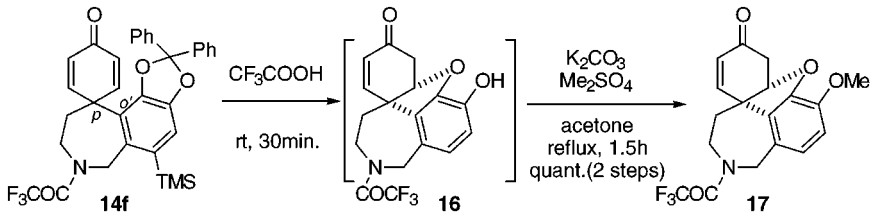
Narwedine (**2**) was synthesized by methylation of phenolic group in **16**, hydrolysis of trifluoroacetamide, and reductive methylation. Stereoselective reduction of

(18) Kametani, T.; Yamaki, K.; Terui, T. *J. Hetrocycl. Chem*. **1973**, *10*, 35−37.
(19) (a) Latvala, A.; Oenuer, M. A.; Goezler, T.; Linden, A.; Kivcak, B.; Hesse, M. *Phytochemistry* **1995**, *39*, 1229−1240. (b) Abdallah, O. M. *Phytochemistry* **1995**, *39*, 477−478. (c) Kihara, M.; Xu, L.; Konishi, K.; Kida, K.; Nagao, Y.; Kobayashi, S.; Shingu, T. *Chem. Pharm. Bull* **1994**, *42*, 289−292. (d) Kobayashi, S.; Satoh, K.; Numata, A.; Shingu, T.; Kihara, M. *Phytochemistry* **1991**, *30*, 675−677. (e) Kobayashi, S.; Takeda, S.; Ishikawa, H.; Matsumoto, H.; Kihara, M.; Shingu, T.; Numata, A.; Uyeo, S. *Chem. Pharm. Bull.* **1976**, *24*, 1537−1543.
(20) (a) Latvila, A.; Oenuer, M. A.; Goezler, T.; Linden, A.; Kivcak, B.; Hesse, M. *Phytochemistry* **1995**, *39*, 1229−1240. (b) Kobayashi, S.; Kihara, M.; Yuasa, K.; Imakura, Y.; Shingu, T.; Kato, A.; Hashimoto, T. *Chem. Pharm. Bull.* **1985**, *33*, 5258−5263. (c) Kobayashi, S.; Yuasa, K.; Soto, K.; Imakura, Y.; Shingu, T. *Heterocycles* **1982**, *19*, 1219−1222.

Scheme 4. Synthesis of Starting Norbelladine Derivatives



Scheme 5. Construction of a Galanthamine Ring System



2 gave galanthamine (**1**). Hydrogenation of **1** gave lycoramine (**3**). Norgalanthamine (**4**) was synthesized by hydrolysis of trifluoroacetamide in **17** and stereoselective reduction of the carbonyl ketone (Scheme 7). To make sure the yielding of **4**, **4** was converted to galanthamine (**1**) by reductive N-methylation.

Sanguinine (**5**) was synthesized by *tert*-butyldimethylsilylation of **16**, stereoselective reduction, which proceeds via hydrolysis of trifluoroacetamide at the same time, and reductive methylation (Scheme 7).

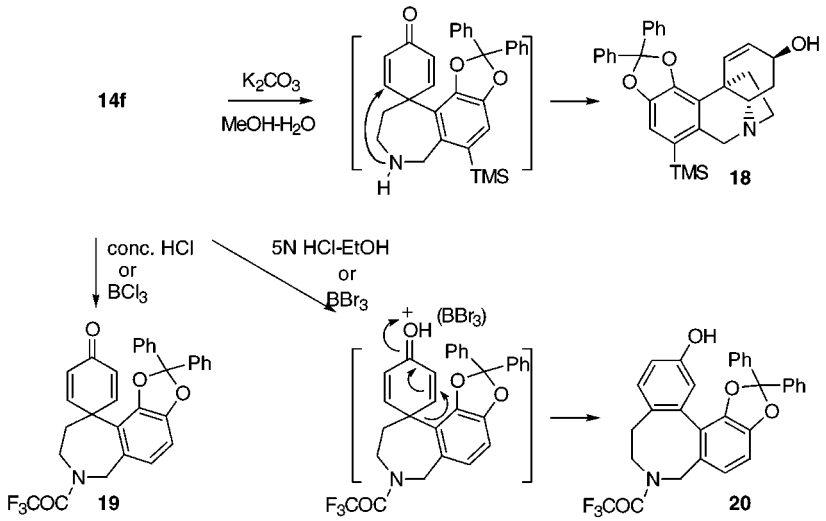
The synthesis of the chiral galanthamine-type alkaloids could also be achieved by using the reported methods; chiral galanthamine (−)-**1** was synthesized using chiral tyrosine derivatives instead of tyramine,[16d,16e] (−)-**1** and (+)-**1** were optically resolved from (±)-**1**,[16b] and chiral narwedine (−)-**2** and (+)-**2**, key intermediates in the synthseis of these alkaloids, were kinetically resolved from (±)-**2**.[22]

In summary, with this novel synthetic method using a hypervalent iodine(III) reagent, (±)-sanguinine (**5**), which has not been synthesized before, (±)-galanthamine (**1**), (±)-narwedine (**2**), (±)-lycoramine (**3**), and (±)-norgalanthamine (**4**) were successfully synthesized. The syntheses of other galanthamine-type alkaloids are currently in progress.

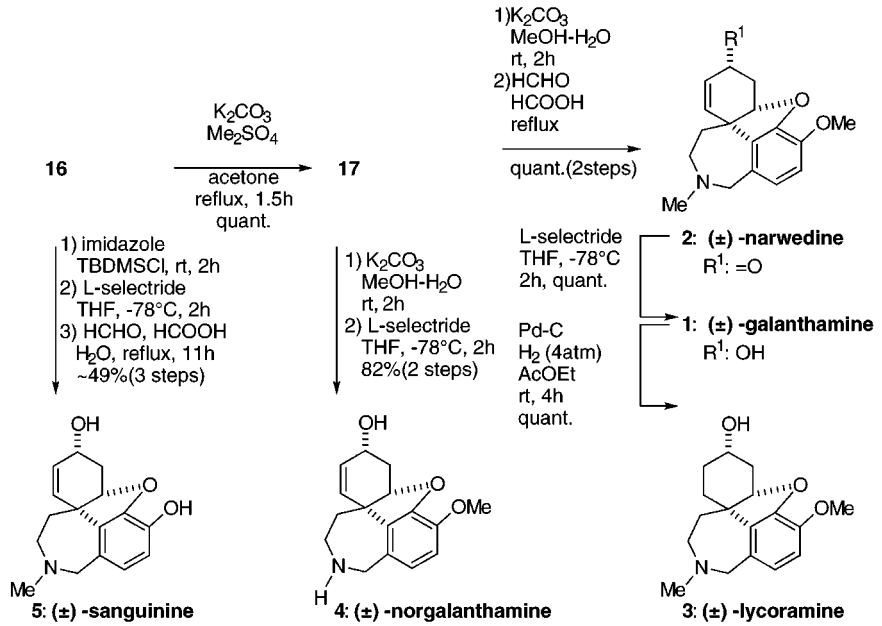
(21) (a) Laiho, S. M.; Fales, H. M. *J. Am. Chem. Soc.* **1964**, *86*, 4434−4437. (b) Kobayashi, S.; Ishikawa, H.; Kihara, M.; Shing, T.; Uyeo, S. *Chem. Pharm. Bull.* **1976**, *24*, 2553−2555. (c) Li, H.-Y.; Ma, G.; Xu, Y.; Hong, S. *Planta Med.* **1987**, *53*, 259−261. (d) Bastida, J.; Viladomat, F.; Llabrés, J. M.; Quiroga, S.; Codina, C.; Rubiralta, M. *Ibid.* **1990**, *56*, 123−124.

(22) Shieh, W.-C.; Carlson, J. A. *J. Org. Chem.* **1994**, *59*, 5463−5465.

Scheme 6. Deprotection of Coupling Products



Scheme 7. Synthesis of Galanthamine-Type Amaryllidaceae Alkaloids



Experimental Section

All melting points are uncorrected. Infrared (IR) absorption spectra (cm^{-1}) were recorded using a KBr pellet. ^1H NMR (and ^{13}C NMR) spectra were recorded in $CDCl_3$, unless otherwise mentioned, at 200, 250, 270, 300, or 500 MHz with TMS as an internal standard. Most of the ^1H NMR (and ^{13}C NMR) spectra of amido compounds exhibited the presence of two rotamers. E. Merck silica gel 60 for column chromatography and E. Merck precoated TLC plates, silica gel F_{254}, for preparative thin-layer chromatography were used. The organic layers were dried with anhydrous $MgSO_4$ or Na_2SO_4. PIFA is commercially available. CF_3CH_2OH was obtained from commercial suppliers and was used without further purification.

3,4-Dihydroxybenzoic Acid Methyl Ester (8). To a 300 mL round-bottom flask were added 3,4-dihydoxybenzoic acid (4.62 g, 30.0 mmol) and MeOH (60.0 mL), the mixture was stirred until a clear solution formed, concentrated sulfuric acid (3.00 mL) was added, and the resulting solution was refluxed for 9 h and cooled. The reaction mixture was concentrated using an evaporator, water (60.0 mL) was added, and the solution was extracted with ethyl acetate, washed with brine, dried, and filtered. The crude residue was subjected to column chromatography (*n*-hexane/AcOEt = 1:1), and **8** (4.82 g, 28.7 mmol) was isolated in 96% yield: mp 137.0−139.0 °C (from AcOEt, lit.[23] mp 138.5−139.5 °C); ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.61 (1H, d, J = 2.0 Hz), 7.56 (1H, dd, J = 8.5 Hz, 2.0 Hz), 6.89 (1H, d, J = 8.5 Hz), 5.87 (2H, brs), 3.87 (3H, s); LRMS (EI) *m/z* 168 (M^+); HRMS (EI) calcd for $C_8H_8O_4$ 168.0422, found 168.0425.

Preparation of (6-Bromo-2,2-diphenylbenzo[1,3]dioxol-5-yl)methanol (9). To **8** (101 mg, 0.600 mmol) was added α,α-dichlorodiphenylmethane (142 mg, 0.12 mL, 0.600 mmol) at 170−180 °C under nitrogen atmosphere and stirred at 170−180 °C for 10 min. To the cooled reaction mixture was added water and the mixture extracted with ethyl acetate. The organic layer was washed with brine, dried, filtered, and evaporated. Column chromatography (*n*-hexane/AcOEt = 10:1) yielded 2,2-diphenylbenzo[1,3]dioxole-5-carboxylic acid methyl ester (216 mg, 0.650 mmol, quant) as colorless needles. To a stirred suspension of $LiAlH_4$ (230 mg, 6.00 mmol) in ether (2.00 mL) was added a solution of 2,2-diphenylbenzo[1,3]-dioxole-5-carboxylic acid methyl ester (1.33 g, 4.00 mmol) in ether (2.00 mL) dropwise at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1.5 h and quenched with ethyl acetate followed by aqueous satu-

(23) Ikeda, Y.; Taguchi, H.; Yoshida, I. *Chem. Pharm. Bull.* **1981**, *29*, 2893−2898.

rated Rochelle salt. The mixture was extracted with ethyl acetate, washed with brine, dried, filtered, and evaporated. Column chromatography (*n*-hexane/AcOEt = 3:1) gave (2,2-diphenylbenzo[1,3]dioxol-5-yl)methanol (1.26 g, 4.15 mmol, quant) as a colorless clear oil. To a stirred solution of (2,2-diphenylbenzo[1,3]dioxol-5-yl)methanol (55.7 g, 0.180 mol) in DMF (100 mL) was added a solution of NBS (32.6 g, 0.180 mol) in DMF (100 mL) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 2 h, quenched with water, extracted with ether, washed with brine, dried, and filtered. Column chromatography (*n*-hexane/AcOEt = 2:1) yielded **9** (67.8 g, 0.177 mol, 98%) as white prisms.

2, 2-Diphenylbenzo[1,3]dioxole-5-carboxylic acid methyl ester: mp 98.0−99.5 °C (from AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.34−7.67 (12H, m), 6.88 (1H, d, J = 8.1 Hz), 3.84 (3H, s); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm) 166.4, 151.0, 147.2, 139.6, 129.2, 128.3, 126.1, 125.3, 124.1, 117.9, 109.6, 108.0, 52.0; IR (KBr) 1717, 1495, 1447, 1366 cm^{-1}; LRMS (EI) *m*/*z* 332 (M^+), 255 ($M^+ - Ph$), 165 ($M^+ - CHPh_2$); HRMS (EI) calcd for $C_{21}H_{16}O_4$ 332.1048, found 332.1043. Anal. Calcd for $C_{21}H_{16}O_4$: C, 75.89; H, 4.85. Found: C, 75.85; H, 4.58.

(2,2-Diphenylbenzo[1,3]dioxol-5-yl)methanol: ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.53−7.59 (4H, m), 7.30−7.35 (6H, m), 6.88 (1H, s), 6.78 (1H, d, J = 7.8 Hz), 6.74 (1H, d, J = 7.8 Hz), 4.45 (2H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 147.3, 146.6, 140.1, 134.8, 129.0, 128.2, 126.2, 120.5, 116.7, 108.2, 107.9, 65.0; IR (KBr) 3300, 1497, 1445 cm^{-1}; LRMS (EI) *m*/*z* 304 (M^+), 227 ($M^+ - Ph$); HRMS (EI) calcd for $C_{20}H_{16}O_3$ 304.1089, found 304.1099.

9: mp 99.0−99.5 °C (from AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.51−7.57 (4H, m), 7.35−7.42 (6H, m), 7.06 (1H, s), 7.03 (1H, s), 4.63 (2H, d, J = 6.2 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ (ppm) 147.3, 147.1, 139.6, 133.2, 128.4, 128.3, 126.2, 117.9, 113.0, 112.7, 109.2, 64.9; IR (KBr) 3340, 1483, 1450 cm^{-1}; LRMS (EI) *m*/*z* 383 (M^+), 382 ($M^+ - H$), 306 ($M^+ - Ph$), 305 ($M^+ - H - Ph$); HRMS (EI) calcd for $C_{20}H_{15}O_3Br$ 382.0205, found 382.0203. Anal. Calcd for $C_{20}H_{15}O_3Br$: C, 62.68; H, 3.94; Br, 20.85. Found: C, 62.71; H, 4.01; Br, 20.70.

Preparation of (6-Bromo-2,2-dimethylbenzo[1,3]dioxol-5-yl)methanol (10). To a stirred solution of **8** (840 mg, 5.00 mmol) and phosphorus pentoxide (1.06 g, 7.50 mmol) in toluene (10.0 mL) was added acetone (0.730 mL, 10.0 mmol) at 75 °C under nitrogen atmosphere. The mixture was stirred at 75 °C for 1 h, quenched with 25% aqueous NaOH, extracted with ethyl acetate, washed with brine, dried, filtered, and evaporated. Column chromatography (*n*-hexane/AcOEt = 5:1) gave 2,2-dimethylbenzo[1,3]dioxole-5-carboxylic acid methyl ester (784 mg, 3.77 mmol, 75%) as a clear yellow oil. To a stirred suspension of $LiAlH_4$ (1.00 g, 26.4 mmol) in THF (13.2 mL) was added a solution of 2,2-dimethylbenzo[1,3]dioxol-5-carboxylic acid methyl ester (3.66 g, 17.6 mmol) in THF (13.2 mL) dropwise at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 3 h and quenched with ethyl acetate followed by aqueous saturated Rochelle salt. The mixture was extracted with ethyl acetate, washed with brine, dried, filtered, and evaporated. Column chromatography (*n*-hexane/AcOEt = 3:1) yielded (2,2-dimethylbenzo[1,3]-dioxol-5-yl)methanol (2.83 g, 15.7 mmol, 89%) as a clear yellow oil. To a stirred solution of (2,2-dimethylbenzo[1,3]dioxol-5-yl)methanol (**13b**) (2.83 g, 15.7 mmol) in DMF (14.4 mL) was added a solution of NBS (2.79 g, 15.7 mmol) in DMF (14.4 mL) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 3 h, quenched with water, extracted with ether, washed with brine, dried, and filtered. Column chromatography (*n*-hexane/AcOEt = 5:1) yielded **10** (3.06 g, 11.8 mmol, 75%) as colorless needles.

2,2-Dimethylbenzo[1,3]dioxole-5-carboxylic acid methyl ester: ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.61 (1H, dd, J = 8.2 Hz, 1.6 Hz), 7.38 (1H, d, J = 1.6 Hz), 6.74 (1H, d, J = 8.2 Hz), 3.87 (3H, s), 1.69 (6H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ (ppm) 166.6, 151.4, 147.4, 124.8, 123.5, 119.1, 109.3, 107.7, 51.9, 25.8; IR(KBr) 1721 cm^{-1}; LRMS (EI) *m*/*z* 208 (M^+), 193 ($M^+ - Me$); HRMS (EI) calcd for $C_{11}H_{12}O_4$ 208.0732, found 208.0735.

(2,2-Dimethylbenzo[1,3]dioxol-5-yl)methanol: ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 6.77 (1H, s), 6.76 (1H, d, J = 8.0 Hz), 6.68 (1H, d, J = 8.0 Hz), 4.55 (2H, s), 1.67 (6H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ (ppm) 147.6, 147.0, 134.2, 120.0, 117.9, 108.0, 107.8, 65.4, 25.8; IR(KBr) 3300 cm^{-1}; LRMS (EI) *m*/*z* 180 (M^+), 165 ($M^+ - Me$); HRMS (EI) calcd for $C_{10}H_{12}O_3$ 180.0799, found 180.0786.

10: mp 81.0−81.5 °C (from AcOEt); ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm) 6.91 (1H, s), 6.87 (1H, s,), 4.63 (2H, s), 1.67 (6H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ (ppm) 147.7, 147.4, 132.3, 119.3, 112.6, 112.5, 109.2, 65.1, 25.8; IR (KBr) 3338 cm^{-1}; LRMS (EI) *m*/*z* 259 (M^+), 244 ($M^+ - Me$); HRMS (EI) calcd for $C_{10}H_{11}O_3Br$ 257.9693, found 257.9692. Anal. Calcd for $C_{10}H_{11}O_3Br$: C, 46.36; H, 4.28; Br, 30.84. Found: C, 46.38; H, 4.20; Br, 30.59.

Preparation of 2,2-Diphenyl-6-(trimethylsilanyl)benzo-[1,3]dioxole-5-carbaldehyde (7f). To a stirred solution of **9** (3.15 g, 8.20 mmol) and hexamethylphosphoric triamide (8.00 mL) were added sodium methoxide (1.33 g, 24.7 mmol) and hexamethyl disilane (3.61 g, 5.05 mL, 24.7 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 2 h, quenched with aqueous saturated NH_4Cl, extracted with ether, washed with brine, dried, filtered, and evaporated. Column chromatography (*n*-hexane/AcOEt = 5:1) yielded [2,2-diphenyl-6-(trimethylsilanyl)benzo[1,3]-dioxol-5-yl]methanol (1.73 g, 4.59 mmol, 56%) as white prisms. A stirred solution of [2,2-diphenyl-6-(trimethylsilanyl)benzo-[1,3]dioxol-5-yl]methanol (2.00 g, 5.30 mmol) and manganese oxide (MnO_2, activated for organic oxidation, 1.10 g, 12.7 mmol) in benzene (10.0 mL) was refluxed for 20 h. The reaction mixture was filtered through Celite 535, the mother liquor obtained was subjected to column chromatography (*n*-hexane/AcOEt = 5:1), and **7f** (1.71 g, 4.56 mmol, 86%) was isolated as colorless prisms.

[2,2-Diphenyl-6-(trimethylsilanyl)benzo[1,3]dioxol-5-yl]methanol: mp 130.0−131.0 °C (from AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.55−7.60 (4H, m), 7.35−7.38 (6H, m), 7.05 (1H, s), 7.02 (1H, s), 4.67 (2H, d, J = 5.9 Hz), 0.30 (9H, s); IR (KBr) 3330, 1451, 1180 cm^{-1}; LRMS (EI) *m*/*z* 376 (M^+), 361 ($M^+ - Me$), 302 ($M^+ - TMS + H$), 299 ($M^+ - Ph$); HRMS (EI) calcd for $C_{23}H_{24}O_3Si$ 376.1502, found 376.1522. Anal. Calcd for $C_{23}H_{24}O_3Si$: C, 73.37; H, 6.42. Found: C, 73.24; H, 6.49.

7f: mp 85.0−86.5 °C (from AcOEt); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 10.07 (1H, s), 7.55−7.57 (4H, m), 7.38−7.40 (6H, m), 7.26 (1H, s), 7.18 (1H, s), 0.34 (9H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ (ppm) 190.7, 151.3, 148.5, 140.5, 136.5, 129.6, 129.4, 128.3, 126.2, 118.1, 114.7, 110.4, 0.7; IR (KBr) 1698, 1450, 1210 cm^{-1}; LRMS (EI) *m*/*z* 374 (M^+), 359 ($M^+ - Me$), 300 ($M^+ - TMS + H$), 297 ($M^+ - Ph$); HRMS (EI) calcd for $C_{23}H_{22}O_3Si$ 374.1338, found 374.1361. Anal. Calcd for $C_{23}H_{22}O_3$-Si: C, 73.76; H, 5.92. Found: C, 73.54; H, 5.94.

Preparation of 2,2-Dimethyl-6-(trimethylsilanyl)benzo-[1,3]dioxole-5-carbaldehyde (7g). To a stirring solution of **10** (1.30 g, 5.00 mmol) in hexamethylphosphoric triamide (5.00 mL) were added sodium methoxide (810 mg, 15.0 mmol) and hexamethyl disilane (3.07 mL, 15.0 mmol) at 0 °C under nitrogen atmosphere. The mixture was stirred at 0 °C for 10 min and at room temperature for 2 h. The solution color turned from yellow to dark brown. The reaction was quenched with aqueous saturated NH_4Cl, extracted with ether, washed with brine, dried, filtered, and evaporated. Column chromatography (*n*-hexane/AcOEt = 5:1) yielded [2,2-dimethyl-6-(trimethylsilanyl)benzo[1,3]dioxol-5-yl]methanol (537 mg, 2.13 mmol, 43%) as a yellow oil. A stirred solution of [2,2-dimethyl-6-(trimethylsilanyl)benzo[1,3]dioxol-5-yl]methanol (807 mg, 3.20 mmol) and manganese oxide (MnO_2, activated for organic oxidation, 652 mg, 7.68 mmol) in benzene (7.80 mL) was refluxed for 11.5 h. The reaction mixture was filtered through Celite 535, and the mother liquor obtained was subjected to column chromatography (*n*-hexane/AcOEt = 10:1). **7g** (769 mg, 3.07 mmol, 96%) was isolated as colorless needles.

[2,2-Dimethyl-6-(trimethylsilanyl)benzo[1,3]dioxol-5-yl]methanol : ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm) 6.91 (1H, s), 6.88 (1H, s), 4.66 (2H, s), 1.67 (6H, s), 0.31 (9H, s); IR (KBr)

3300, 1250 cm^{-1}; LRMS (EI) *m/z* 252 (M^+), 237 ($M^+ - Me$); HRMS (EI) calcd for $C_{13}H_{20}O_3Si$ 252.1163, found 252.1173.

7g: mp 79.0−80.5 °C; ^1H NMR (270 MHz, $CDCl_3$) δ (ppm) 10.07 (1H, s), 7.35 (1H, s), 7.03 (1H, s), 1.71 (6H, s), 0.35 (9H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ (ppm) 190.8, 151.8, 148.7, 134.0, 136.1, 119.4, 114.4, 110.1, 26.0, 0.7; IR (KBr) 1663, 1447, 1177 cm^{-1}; LRMS (EI) *m/z* 250 (M^+), 235 ($M^+ - Me$); HRMS (EI) calcd for $C_{13}H_{18}O_3Si$ 250.1025, found 250.1027. Anal. Calcd for $C_{13}H_{18}O_3Si$: C, 62.37; H, 7.25,. Found: C, 62.28; H, 7.01.

Preparation of 2,2-Diphenyl-6-(triethylsilanyl)benzo-[1,3]dioxol-5-carbaldehyde (7j). A benzene (50.0 mL) solution of **9** (7.67 g, 20.0 mmol) and manganese oxide (activeted for organic oxidation, 4.17 g, 48.0 mmol) was refluxed for 14 h. The reaction mixture was filtered through Celite 535. Crystallization from ethyl acetate and column chromatography (*n*-hexane/AcOEt = 10:1) from resulted mother liquor yielded 6-bromo-2,2-diphenylbenzo[1,3]dioxole-5-carbaldehyde (7.27 g, 19.0 mmol, 95%) as pale yellow prisms. To a solution of 6-bromo-2,2-diphenylbenzo[1,3]dioxole-5-carbaldehyde (5.89 g, 15.5 mml) in benzene (40.0 mL), were added ethylene glycol (1.72 mL, 30.9 mmol) and *p*-toluenesulfonic acid monohydrate (53.0 mg, 0.278 mmol). The mixture was refluxed using Dean Stark equipment, at 110 °C for 2 h, quenched with aqueous $NaHCO_3$, extracted with ethyl acetate, washed with brine, and dried. Crystallization from ethyl acetate and column chromatography (*n*-hexane/AcOEt = 10:1) from resulted mother liquor yielded 6-bromo-3,4-[(diphenylmethylene)dioxy]benzaldehyde ethanediyl acetal (5.12 g, 78%) as pale yellow prisms. A stirring solution of 6-bromo-3,4-[(diphenylmethylene)dioxy]-benzaldehyde ethanediyl acetal (851 mg, 2.00 mml) in dried THF (15.0 mL) was cooled to −100 °C under nitrogen atmosphere. To the solution was added a solution (1.59 M) of *n*-butyllithium in *n*-hexane (1.38 mL, 2.20 mmol), and stirring was continued at −100 °C for 10 min. To the mixture was added triethylchlorosilane (0.37 mL, 22.0 mmol) and the resulting mixture stirred for 1 h with a gradual rise in temperature to room temperature. The mixture was quenched with H_2O, extracted with ethyl acetate, washed with brine and dried, filtered, and evaporated. The crude product was dissolved in acetone/H_2O (1:1) and refluxed for 20 min at 100 °C. The mixture was quenched with aqueous $NaHCO_3$, extracted with ethyl acetate, dried, filtered, and evaporated. Column chromatogtaphy (*n*-hexane/AcOEt = 9:1) yielded **7j** (739 mg, 1.77 mmol, 89%) as white prisms.

6-Bromo-2,2-diphenylbenzo[1,3]dioxole-5-carbaldehyde: mp 91.0−93.0 °C; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 10.16 (1H, s), 7.36−7.54 (10H, m), 7.44 (1H, s), 7.11 (1H, s); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ (ppm) 190.4, 152.8, 147.7, 138.9, 129.6, 128.4, 128.0, 126.1, 121.6, 119.5, 113.4, 108.4; IR (KBr) 1684 cm^{-1}; LRMS (EI) *m/z* 380 (M^+); HRMS (EI) calcd for $C_{20}H_{13}O_3$-Br 380.0048, found 380.0049. Anal. Calcd for $C_{20}H_{13}O_3Br$: C, 63.01; H, 3.44; Br, 20.96. Found: C, 63.08; H, 3.55; Br, 20.82.

6-Bromo-3,4-((diphenylmethylene)dioxy)benzaldehyde ethanediyl acetal: mp 150.0−152.0 °C; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.35−7.53 (10H, m), 7.13 (1H, s), 7.05 (1H, s), 6.00 (1H, s), 4.00−4.16 (4H, m); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ (ppm) 148.6, 147.1, 139.5, 129.9, 129.3, 128.3, 126.3, 118.2, 114.0, 112.8, 107.8, 102.6, 65.4; IR (KBr) 1152, 1080 cm^{-1}; LRMS (EI) *m/z* 424 (M^+), 347 ($M^+ - Ph$); HRMS (EI) calcd for $C_{22}H_{17}O_4Br$ 424.0310, found 424.0319. Anal. Calcd for $C_{22}H_{17}O_4Br$: C, 62.13; H, 4.03. Found: C, 61.82; H, 4.05.

7j: mp 57.0−58.0 °C; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 10.08 (1H, s), 7.37−7.59 (11H, m), 7.13 (1H, s), 0.85−0.97 (15H, m); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ (ppm) 190.7, 151.5, 148.5, 139.7, 138.2, 137.4, 129.4, 128.4, 126.1, 109.1, 7.6, 5.1; IR (KBr) 1684, 1451 1210 cm^{-1}; LRMS (EI) *m/z* 416 (M^+), 387 ($M^+ -$ Et); HRMS (EI) calcd for $C_{26}H_{28}O_3Si$ 416.1808, found 416.1797. Anal. Calcd for $C_{26}H_{28}O_3Si$: C, 74.96; H, 6.77. Found: C, 74.66; H, 6.85.

General Procedure for Norbelladine Derivatives 13 from Aldehyde 7. A stirred solution of **7g** (444 mg, 1.77 mmol) and tyramine (244 mg, 1.77 mmol) in MeOH (6.00 mL) was refluxed for 3 h. The solution was cooled, and $NaBH_4$ (356 mg, 9.40 mmol) was added at 0 °C and stirred at 0 °C for 30 min. The mixture was quenched with aqueous saturated NH_4Cl. The mixture was concentrated using an evaporator, extracted with ethyl acetate, washed with brine, and dried. To the residue were added pyridine (3.00 mL) and trifluoroacetic anhydride (0.550 mL, 3.88 mmol) at 0 °C and the mixture stirred for 1.5 h. The reaction mixture was quenched with saturated NH_4Cl, extracted with ethyl acetate, washed with brine, dried, filtered, and evaporated. Column chromatography (*n*-hexane/AcOEt = 3:1) yielded **13g** (795 mg, 1.70 mmol, 96%) as a white amorphous solid.

13g: ^1H NMR (270 MHz, $CDCl_3$) δ (ppm) 7.02 and 6.97 (2H, d, J = 8.5 Hz), 6.88 and 6.85 (1H, s), 6.76 and 6.74 (2H, d, J = 8.5 Hz), 6.48 and 6.45 (1H, s), 4.74 and 4.50 (2H, s), 3.50 and 3.48 (2H, t, J = 7.4 Hz), 2.86 and 2.80 (2H, t, J = 7.4 Hz), 1.65 and 1.58 (6H, s), 0.33 and 0.23 (9H, s); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ (ppm) 157.6 (m), 154.8 and 154.7, 149.0 and 148.9, 146.5 and 146.4, 134.1 and 133.9, 129.9 and 129.7, 129.8, 129.3 and 128.8, 118.3 and 118.2, 116.5 (m), 115.7 and 115.6, 113.9 and 113.9, 106.2 and 106.1, 51.3 and 49.9, 49.7 and 49.4, 34.8 and 31.9, 25.9, 0.4 and 0.2; IR (KBr) 3400, 1690, 1516, 1491, 1252, 1233, 1208, 1169, 1148 cm^{-1}; LRMS (EI) *m/z* 467 (M^+), 452 ($M^+ - Me$); HRMS (EI) calcd for $C_{23}H_{28}NO_4F_3Si$ 467.1739, found 467.1744.

13f: ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.32−7.56 (10H, m), 7.01 and 6.99 (2H, d, J = 8.0 Hz), 6.94 and 6.92 (1H, s), 6.72 and 6.71 (2H, d, J = 8.0 Hz), 6.63 and 6.59 (1H, s), 4.73 and 4.48 (2H, s), 3.51 (2H, m), 2.83 and 2.80 (2H, t, J = 7.3 Hz), 0.33 and 0.23 (9H, s); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ (ppm) 157.6 (m), 155.0 and 154.9, 148.7, 146.2, 140.1, 134.9 and 134.6, 130.6 and 130.0, 129.9 and 129.6, 129.5, 120.1, 128.5, 128.2, 126.2 and 126.1, 117.8 (m), 115.6 and 115.6, 114.1, 106.4 and 106.2, 51.3 and 49.8, 49.3 and 34.7, 31.8 and 31.5, 0.3 and 0.1; IR (KBr) 3551, 1694, 1485, 1250, 1221, 1208, 1145, 1021 cm^{-1}; LRMS (EI) *m/z* 591 (M^+), 576 ($M^+ - Me$), 514 ($M^+ -$ Ph); HRMS (EI) calcd for $C_{33}H_{32}NO_4F_3Si$ 591.2052, found 591.2065. Anal. Calcd for $C_{33}H_{32}NO_4F_3Si$: C, 66.99; H, 5.45; N, 2.37. Found: C, 66.89; H, 5.61; N, 2.29.

13j: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.33−7.58 (10H, m), 6.99 and 6.97 (2H, d, J = 8.0 Hz), 6.96 and 6.92 (1H, s), 6.74 and 6.73 (2H, d, J = 8.0 Hz), 6.62 and 6.57 (1H, s), 4.71 and 4.46 (2H, s), 3.52 (2H, t, J = 8.0 Hz), 2.84 and 2.81 (2H, t, J = 8.0 Hz), 0.67−0.99 (15H, m); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ (ppm) 157.6 and 157.7 (q, J = 36.0 Hz), 154.7 and 154.8, 148.6, 146.2, 140.2 and 140.3, 135.3 and 135.0, 129.7 and 129.9, 129.8 and 128.8, 129.0, 128.3, 126.9 and 127.4, 126.1 and 126.2, 116.9 and 117.0, 116.4 (q, J = 287 Hz), 115.5 and 115.6, 115.1, 106.1, 50.0 and51.3, 49.3 and 49.7, 31.9 and 34.8, 7.4 and 7.6, 4.1 and 4.3; IR(KBr) 3430, 1694, 1680, 1516, 1487, 1450, 1248, 1221, 1208, 1167, 1148, 1046, 1021 cm^{-1}; LRMS (FAB) *m/z* 634 ($M^+ + H$), 604 ($M^+ -$ Et); HRMS (FAB) calcd for $C_{36}H_{39}NO_4F_3Si$ 634.2601, found 634.2609.

General Procedure for PIFA-Induced Oxidative Coupling Reactions of Norbelladine Derivatives 13. To a stirred solution of **13g** (530 mg, 1.14 mmol) in trifluoroethanol (10.0 mL) was added a solution of phenyliodine bis(trifluoroacetate) (537 mg, 1.25 mmol) in trifluoroethanol (10.0 mL) at −40 °C under nitrogen atmosphere and the mixture stirred for 1.5 h. Soon the mixture turned to dark blue. The solvent was removed using an evaporator. Column chromatography (*n*-hexane/AcOEt = 2:1) yielded **14g** (245 mg, 0.524 mmol, 46%) and **15g** (53.3 mg, 0.141 mmol, 12%), both as brown amorphous solids.

14g: ^1H NMR (270 MHz, $CDCl_3$) δ (ppm) 6.79 (2H, d, J = 10.2 Hz), 6.77 (1H, s), 6.23 (2H, d, J = 10.2 Hz), 4.87 (2H, s), 3.84 (2H, t, J = 6.1 Hz), 2.30 (2H, t, J = 6.1 Hz), 1.42 (6H, s), 0.35 (9H, s); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ (ppm) 185.9, 156.1 (m), 150.5, 147.8, 146.4, 134.3, 133.4, 128.0, 118.2, 117.5, 115.0 (m), 113.2, 108.2, 48.2, 46.2, 45.0, 35.6, 25.7, 0.8; IR (KBr) 1694, 1667, 1495, 1242, 1142 cm^{-1}; LRMS (EI) *m/z* 465 (M^+), 450 ($M^+ - Me$); HRMS (EI) calcd for $C_{23}H_{26}NO_4F_3Si$ 465.1583, found 465.1589.

15g: ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.01 and 6.91 (2H, d, J = 10.2 Hz), 6.70 and 6.25 (1H, s), 6.41 and 6.44 (1H, s), 6.29 and 6.28 (2H, d, J = 10.2 Hz), 4.75 and 4.72 (2H, s), 3.94 and 3.91 (2H, t, J = 6.2 Hz), 2.34 and 2.35 (2H, t, J = 6.2 Hz),

1.64 and 1.63 (6H, s); IR (KBr) 1700, 1670, 1499, 1244, 1146 cm^{-1}; LRMS (EI) *m/z* 393 (M^+), 378 ($M^+ - Me$); HRMS (EI) calcd for $C_{20}H_{18}NO_4F_3$ 393.1188, found 393.1186.

14f: ^1H NMR (270 MHz, $CDCl_3$) δ (ppm) 7.30−7.39 (10H, m), 7.01 (1H, s), 6.91 (2H, d, J = 9.9 Hz), 6.41 (2H, d, J = 9.9 Hz), 4.93 (2H, s), 3.91 (2H, t, J = 5.9 Hz), 2.39 (2H, t, J = 5.9 Hz), 0.42 (9H, s); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ (ppm) 185.6, 156.5 (m), 150.6, 147.3, 146.2, 140.2, 134.8, 134.4, 129.2, 128.3, 126.1, 125.6, 117.9, 116.0 (m), 113.5, 48.1, 46.3, 45.0, 35.7, 0.8; IR (KBr) 1700, 1665, 1453, 1240, 1144, 1021 cm^{-1}; LRMS (EI) *m/z* 589 (M^+), 574 ($M^+ - Me$), 512 ($M^+ - Ph$); HRMS (EI) calcd for $C_{33}H_{30}NO_4F_3Si$ 589.1896, found 589.1898. Anal. Calcd for $C_{33}H_{30}NO_4F_3Si$: C, 67.22; H, 5.13; N, 2.38. Found: C, 67.50; H, 5.05; N, 2.26.

15f: ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.51−7.52 (4H, m), 7.35−7.37 (6H, m), 7.00 and 6.89 (2H, d, J = 10.0 Hz), 6.86 and 6.69 (1H, s), 6.61 and 6.60 (1H, s), 6.29 and 6.28 (2H, d, J = 10.0 Hz), 4.75 and 4.92 (2H, s), 3.92 and 3.89 (2H, t, J = 6 Hz), 2.37 and 2.33 (2H, t, J = 6.0 Hz); IR (KBr) 1669, 1626, 1497, 1451, 1242, 1199, 1167, 1146, 1046, 1021 cm^{-1}; LRMS (EI) *m/z* 517 (M^+), 440 ($M^+ - Ph$); HRMS (EI) calcd for $C_{30}H_{22}NO_4F_3$ 517.1501, found 517.1510.

14j: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.27−7.42 (10H, m), 6.96 (1H, s), 6.92 (2H, d, J = 10.0 Hz), 6.42 (2H, d, J = 10.0 Hz), 4.91 (2H, s), 3.89 (2H, t, J = 6.0 Hz), 2.37 (2H, t, J = 6.0 Hz), 0.95−0.97 (9H, m); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ (ppm) 185.7, 156.4 (q, J = 36.0 Hz), 150.8, 147.1, 146.1, 140.3, 135.2, 131.4, 128.9, 128.2, 128.1, 125.5, 117.9, 117.2 (m), 114.2, 47.8, 46.3, 44.9, 35.7, 7.6, 4.5; IR (KBr) 1700, 1667, 1453, 1262, 1238, 1206, 1181, 1144, 1049, 1021 cm^{-1}; LRMS (FAB) *m/z* 632 (M^+H); HRMS (EI) calcd for $C_{36}H_{37}NO_4F_3Si$ 632.2444, found 632.2427.

***N*-Demethyl-*N*-(trifluoroacetyl)narwedine (17).** To a 20-mL flask were added **14f** (11.8 mg, 0.020 mmol), a magnetic stirring bar, and trifluoroacetic acid (4.00 mL) and the mixture stirred at room temperature for 45 min. **14f** was quantitatively converted to **16**. The solvent was removed under vacuum, and acetone (5 mL), potassium carbonate (5.5 mg, 0.040 mmol), and dimethyl sulfate (0.0080 mL, 0.080 mmol) were added. The mixture was refluxed for 1.5 h, saturated $NaHCO_3$ was added, and the resulting mixture was extracted with ethyl acetate and dried. Column chromatography (*n*−hexane/AcOEt = 1:1) yielded **17** (7.5 mg, 0.020 mmol, quant) as a white amorphous solid: ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 6.93−6.92 (3H, m), 6.11 and 6.09 (1H, d, J = 10.4 Hz), 5.32 and 4.92 (1H, d, J = 15.8 Hz), 4.75 and 4.74 (2H, s), 4.55 and 4.14 (1H, d, J = 15.8 Hz), 4.63 and 4.36 (1H, d, J = 15.8 Hz), 3.86 (3H, s), 3.36−3.80 (1H, m), 3.26 and 3.17 (1H, d, J = 2.6 Hz), 2.80 and 2.71 (1H, t, J = 2.6 Hz), 2.13−2.21 (1H, m); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ (ppm) 193.6, 156.4 (m), 147.7 and 147.6, 144.9, 142.6 and 142.1, 129.5, 128.1 and 127.9, 126.6 and 126.1, 122.4 and 121.2, 116.3 (m), 112.1, 87.8 and 87.7, 56.0, 52.9 and 52.0, 48.8 and 48.8, 46.9 and 46.7, 37.8 and 34.8, 37.1 and 37.1; IR (KBr) 1693, 1512, 1439, 1281, 1252, 1208, 1169, 1143 cm^{-1}; LRMS (EI) *m/z* 367 (M^+); HRMS (EI) calcd for $C_{18}H_{16}NO_4F_3$ 367.1031, found 367.1024.

Narwedine (2). To a stirring solution of **17** (2.6 mg, 0.0074 mmol) in H_2O (1.00 mL) and MeOH (1.00 mL) was added potassium carbonate (10.2 mg, 0.074 mmol) and the mixture stirred at room temperature for 2 h. The reaction mixture was extracted with ethyl acetate. The organic layer was removed using an evaporator. To the stirring solution of the resultant residue in H_2O (2.00 mL) were added HCOOH (0.0020 mL, 0.0041 mmol) and 35% HCHO (0.0010 mL, 0.0089 mmol) and the mixture refluxed for 10 h. To the reaction mixture was added saturated $NaHCO_3$, and the resulting mixture was extracted with ethyl acetate, washed with brine, and dried. Column chromatography (Al_2O_3, AcOEt only) yielded **2** (2.5 mg, 0.0088 mmol, quant) as white crystals: mp 185−188 °C (from Et_2O, lit.[16h] mp 187−188 °C); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.95 (1H, d, J = 10.0 Hz), 6.70 (1H, d, J = 8.0 Hz), 6.65 (1H, d, J = 8.0 Hz), 6.04 (1H, d, J = 10.0 Hz), 4.73 (1H, brs), 4.09 (1H, d, J = 15.0 Hz), 3.84 (3H, s, OMe), 3.75 (1H, d, J = 15.0 Hz), 3.19 (3H, m), 2.75 (1H, dd, J = 15.0 Hz, 4.0 Hz), 2.44 (3H, s, NMe), 2.28 (1H, dt, J = 15.0 Hz, 4.0 Hz), 1.85 (1H, d, J = 15.0 Hz); IR (KBr) 1690, 1685, 1509, 1439, 1283 cm^{-1}; LRMS (EI) *m/z* 285 (M^+); HRMS (EI) calcd for $C_{17}H_{19}NO_3$ 285.1365, found 285.1332.

Galanthamine (1). To a stirring solution of **2** (3.0 mg, 0.011 mmol) in tetrahydrofuran (0.50 mL) was added 1 M solution of L-Selectride (Aldrich) in tetrahydrofuran (0.040 mL, 0.040 mmol) at −78 °C and the mixture stirred at the same temperature for 2 h. The mixture was then stirred at ice-bath temperature for 30 min, H_2O was added, and the resulting mixture was extracted with ethyl acetate and dried. Preparative thin-layer chromatography (SiO_2, $CHCl_3$/MeOH = 10:1) yielded **1** (3.2 mg, 0.011 mmol, quant) as white crystals: mp 119−120 °C (from Et_2O (lit.[24] mp 127−129 °C)); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.66 (1H, d, J = 8.0 Hz), 6.62 (1H, d, J = 8.0 Hz), 6.07 (1H, d, J = 10.5 Hz), 6.02 (1H, dd, J = 10.5 Hz, 5.0 Hz), 4.61 (1H, brs), 4.13 (1H, t, J = 5.0 Hz), 4.09 (1H, d, J = 15.0 Hz), 3.83 (3H, s, OMe), 3.68 (1H, d, J = 15.0 Hz), 3.27 (1H, t, J = 14.0 Hz), 3.05 (1H, d, J = 14.0 Hz), 2.68 (1H, d, J = 15.0 Hz), 2.40 (3H, s, NMe), 2.06−2.11 (1H, m), 1.99−2.04 (1H, m), 1.58 (1H, m); IR (KBr) 1507, 1439, 1283, 1266, 1048 cm^{-1}; LRMS (EI) *m/z* 287 (M^+); HRMS (EI) calcd for $C_{17}H_{21}NO_3$ 287.1521, found 287.1517.

Lycoramine (3). To a stirring solution of **1** (1.8 mg, 0.0060 mmol) in ethyl acetate (3.00 mL) was added Pd−C (3.0 mg) and the mixture stirred at room temperature for 4 h under hydrogen atmosphere (4.0 atm). Pd−C was removed by Celite filtration, and **3** (2.00 mg, 0.006 mmol, quant) was isolated as white crystals: mp 101−102 °C (from Et_2O (lit.[17c] mp 98−102 °C)); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.67 (1H, d, J = 8.3 Hz), 6.60 (1H, d, J = 8.0 Hz), 4.38 (1H, t, J = 2.8 Hz), 4.08−4.14 (1H, m), 4.61 (1H, brs), 4.04 (1H, d, J = 14.8 Hz), 3.86 (3H, s, OMe), 3.64 (1H, d, J = 14.8 Hz), 3.24 (1H, t, J = 14.0 Hz), 3.06 (1H, d, J = 14.0 Hz), 2.51 (1H, t, J = 15.8 Hz), 2.37 (3H, s, NMe), 1.58−2.04 (10H, m); IR (KBr) 3607, 2900, 1622, 1507, 1437, 1280, 1032 cm^{-1}; LRMS (EI) *m/z* 289 (M^+), 288 ($M^+ - H$); HRMS (EI) calcd for $C_{17}H_{23}NO_3$ 289.1678, found 289.1674.

Norgalanthamine (4). To a stirring solution of **17** (6.4 mg, 0.017 mmol) in H_2O (1.00 mL) and MeOH (1.00 mL) was added potassium carbonate (24.0 mg, 0.17 mmol) and the mixture stirred at room temperature for 2 h. Ethyl acetate was added to the reaction mixture. The solvent in the organic layer was removed using an evaporator. To a stirring solution of the resulting residue in tetrahydrofuran (2.00 mL) was added a 1 M solution of L-Selectride in tetrahydrofuran (0.070 mL, 0.070 mmol) at −78 °C and the mixture stirred at the same temperature for 2 h. The mixture was warmed to 0 °C and stirred for 30 min, H_2O was added, and the resulting mixture was extracted with ethyl acetate and dried. Preparative thin-layer chromatography (SiO_2, $CHCl_3$/MeOH = 5:1) yielded **4** (3.8 mg, 0.014 mmol, 82%) as white crystals: mp 158−159 °C (from Et_2O (lit.[21a] mp 156−158 °C, lit.[18] mp 149−152 °C, lit.[21b] mp 152.5−153 °C, lit.[21c] mp 171−173 °C, lit.[21d] mp 156−158 °C)); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.65 (1H, d, J = 8.0 Hz), 6.62 (1H, d, J = 8.0 Hz), 6.06 (1H, d, J = 10.0 Hz), 6.01 (1H, dd, J = 10.5, 5.0 Hz), 4.61 (1H, brs), 4.14 (1H, t, J = 5.0 Hz), 4.03 (1H, d, J = 15.0 Hz), 3.96 (1H, d, J = 15.0 Hz), 3.84 (3H, s, OMe), 3.37 (1H, d, J = 14.0 Hz), 3.23 (1H, t, J = 14.0 Hz), 2.70 (1H, d, J = 15.0 Hz), 1.73−2.04 (3H, m); IR (KBr) 1506, 1437, 1280, 1265 cm^{-1}; LRMS (EI) *m/z* 273 (M^+); HRMS (EI) calcd for $C_{16}H_{19}NO_3$ 273.1365, found 273.1390.

Sanguine (5). To a 20-mL flask were added **14f** (95.0 mg, 0.161 mmol), a magnetic stirring bar, and trifluoroacetic acid (4.00 mL), and the mixture was stirred at room temperature for 45 min. The solvent was removed under vacuum, and DMF (1.50 mL), imidazole (27.0 mg, 0.403 mmol), and *tert*-butyldimethylsilyl chloride (29.0 mg, 0.192 mmol) were added. The mixture was stirred at room temperature for 2 h, saturated $NaHCO_3$ was added, and the resulting mixture was extracted with ethyl acetate and dried. Column chromatography (*n*−hexane/AcOEt = 1:1) yielded *N*-demethyl-*O*-demethyl- *O*-(*tert*-butyldimethylsilyl)-*N*-(trifluoroacetyl)narwedine (54.0 mg, 0.115

(24) Biot, H. G. *Chem. Ber.* **1954**, *87*, 681−683.

mmol, 72%) as a white amorphous solid. To a stirring solution of the resulting *N*-demethyl-*O*-demethyl-*O*-(*tert*-butyldimethylsilyl)-*N*-(trifluoroacetyl)narwedine in tetrahydrofuran (10.0 mL) was added a 1 M solution of L-Selectride in tetrahydrofuran (0.48 mL, 0.485 mmol) at −78 °C and the mixture stirred at the same temperature for 2 h. The mixture was warmed to 0 °C using an ice bath and stirred at 0 °C for 30 min, H_2O was added, and the resulting mixture was extracted with ethyl acetate and dried. To a stirring solution of the resulting residue in H_2O (2.00 mL) were added HCOOH (0.020 mL, 0.538 mmol) and 35% HCHO (0.010 mL, 0.118 mmol), and the mixture refluxed for 12 h. To the reaction mixture was added saturated $NaHCO_3$, and the resulting mixture was then extracted with ethyl acetate, washed with brine, and dried. **5** (29.0 mg, 0.109 mmol, 68%) was isolated as white crystals.

***N*-Demethyl-*O*-demethyl-*O*-(*tert*-butyldimethylsilyl)-*N*-(trifluoroacetyl)narwedine**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.60−6.89 (3H, m), 6.05 and 6.07 (1H, d, J = 10.0 Hz), 5.29 and 4.88 (1H, d, J = 15.8 Hz), 4.75 and 4.34 (1H, d, J = 15.1 Hz), 4.66 and 4.65 (1H, s), 4.54 and 4.13 (1H, d, J = 15.8 Hz), 3.73 and 3.35 (1H, m), 3.14 and 3.08 (1H, d, J = 2.5 Hz), 2.79 and 2.73 (1H, m), 2.08−2.25 (2H, m), 0.86−0.98 (9H, m), 0.07−0.17 (6H, m); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ (ppm) 194.0 and 194.1, 156.3(m), 149.7 and 149.8, 142.4 and 142.8, 140.4, 129.8 and 129.8, 127.5 and 127.7, 126.9 and 127.3, 121.0 and 122.2, 121.6, 116.2(q, J = 287 Hz), 86.9 and 87.0, 51.9 and 52.8, 48.9 and 49.0, 46.7 and 46.8, 32.3 and 37.5, 34.5, 25.5, 18.3, −4.7; IR (KBr) 2932, 1694, 1507, 1435, 1310, 1285, 1252, 1206, 1169, 1146 cm^{-1}; LRMS (EI) m/z 467 (M^+); HRMS (EI) calcd for $C_{23}H_{28}NO_4F_3Si$ 467.1739, found 367.1710.

5: mp 210.0−215.0 °C (from acetone (lit.[21b] mp 211.5−213.0 °C)); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.59 (1H, d, J = 7.9 Hz), 6.50 (1H, d, J = 7.9 Hz), 6.03 (1H, d, J = 10.4 Hz), 5.90 (1H, dd, J = 10.4 Hz, 4.9 Hz), 4.48 (1H, brs), 4.17 (1H, t, J = 4.0 Hz), 4.05 (1H, d, J = 15.0 Hz), 3.64 (1H, d, J = 15.0 Hz), 3.23 (1H, t, J = 13.4 Hz), 3.03 (1H, d, J = 14.6 Hz), 2.63 (1H, s), 2.43 (1H, d, J = 15.3 Hz), 2.38 (3H, s, NMe), 2.05 (1H, t, J = 12.0 Hz), 1.91 (1H, d, J = 13.4 Hz), 1.52 (1H, d, J = 13.4 Hz); IR (KBr) 2926, 1506, 1456, 1300, 1258, 1044 cm^{-1}; LRMS (EI) m/z 273 (M^+); HRMS (FAB) calcd for $C_{16}H_{20}NO_3$ 274.1444, found 274.1461.

Acknowledgment. We thank Professor Shigeru Kobayashi and Professor Masaru Kihara (Tokushima University) for providing the NMR spectra of the isolated norgalanthamine, galanthamine, and sanguinine.

JO9807868