An Oxidative Intramolecular Phenolic Coupling Reaction for the Synthesis of Amaryllidaceae Alkaloids Using a Hypervalent Iodine(III) Reagent

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The oxidative intramolecular phenolic coupling reaction of norbelladine derivatives (**1**) was investigated with the aim of preparing amaryllidaceae alkaloids. Spirodienone compounds (**2**), which are intermediates for the synthesis of an amaryllidaceae alkaloid, (+)-maritidine, or phenol ether derivatives containing the 5,6,7,8-tetrahydrobenzazocine systems (**9**), were selectively obtained by the reaction of **1** and the hypervalent iodine(III) reagent, phenyliodine(III) bis(trifluoroacetate) (PIFA). Both *p*−*p*′ coupling (**11**) and *p*−*o*′ coupling spirodienone compounds (**12**) were obtained by the reaction of phenol derivatives having an alkoxy group at the C-3′ position (**10**) with PIFA.

Introduction

The oxidative phenolic coupling reaction comprises a key step in the biosynthesis of a wide variety of natural products such as morphine or Amaryllidaceae alkaloids.[1] In 1957, Barton and Cohen suggested that the phenolic oxidation of diphenolic benzyltetrahydroisoquinoline precursors may generate the bond between the aporphine rings A and D, and this proposal has been amply supported by the results of numerous subsequent biosynthetic and synthetic studies.[2] Since that time, a number of biogenetic-type phenolic coupling reactions for the synthesis of Amaryllidaceae alkaloids using heavy metal oxidizing reagents (such as Tl(III)[3] or V(V)[4] salts) have been investigated. However, lack of regiocontrol during the cyclization and low yields of the coupling products have remained problematic. Moreover, Tl(III) or V(V) salts are highly toxic and must be handled very carefully. To solve these problems, oxidative phenolic coupling reactions using hypervalent iodine(III) reagents, which are safe and useful synthetic reagents,[5] were examined. Several phenolic coupling reactions using iodine(III) reagents have been reported,[6] but most of these reactions were only applicable to a limited substrate, and the obtained yields were generally low.

For the last decade, we have examined the oxidative reactions of phenol derivatives using hypervalent iodine reagents, phenyliodine(III) diacetate (PIDA) and phenyliodine(III) bis(trifluoroacetate) (PIFA), in poorly nucleophilic polar solvents such as 2,2,2-trifluoroethanol (CF_3CH_2OH) and 1,1,1,3,3,3-hexafluoro-2-propanol ($(CF_3)_2CHOH$), and found efficient phenolic oxidative reactions,[7] which lead to the convenient synthesis of azacarbocyclic spirodienones from phenol derivatives[7a] including to the total synthesis[7b] of the antitumor marine natural product, discorhabdin C (Scheme 1).[8]

We now report a novel and useful oxidative phenolic coupling reaction using the hypervalent iodine(III) reagent, PIFA. Treatment of norbelladine derivatives (**1**) and PIFA in $(CF_3)_2CHOH$ or CF_3CH_2OH caused a phenolic coupling reaction to give the spirodienone compound (**2**), which is the intermediate for the synthesis of Amaryllidaceae alkaloids (Scheme 2).[9]

Results and Discussion

Norbelladine derivatives **1** were readily prepared by a modification of the reported methods.[4a] Treatment of

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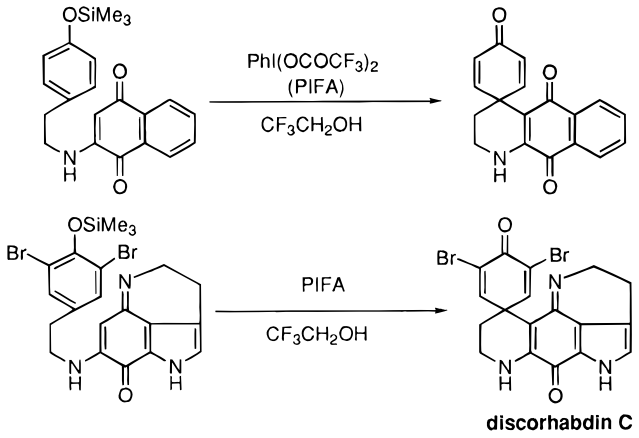
Scheme 1



Scheme 2

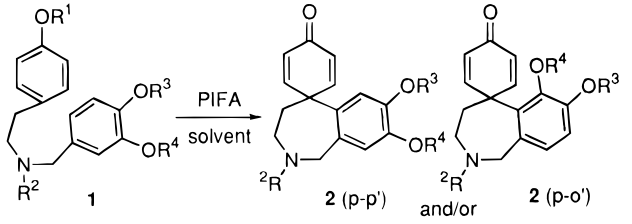
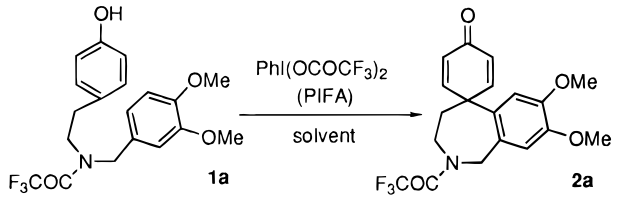
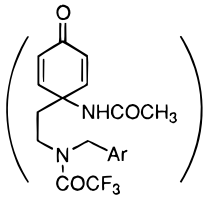


Table 1. Phenolic Coupling Reaction of 1a in Various Solvents



Solvent	Yield(%)	Solvent	Yield(%)
$(CF_3)_2CHOH$	70	Et_2O	30
CF_3CH_2OH	61	DMF	18
CH_3CN	50	THF	15
C_6H_6	44	$C_6H_5CH_3$	14
CH_2Cl_2	30		



3: Ar=3,4-dimethoxy phenyl

3′,4′-dimethyl-*N*-(trifluoroacetyl)norbelladine (**1a**) and PIFA in CF_3CH_2OH at −40 °C gave an aryl−aryl coupling product **2a** in 61% yield. The reaction of **1a** and PIFA at 25 °C gave **2a** in a slightly lower yield (50%). The reaction proceeds in poorly nucleophilic polar protic solvents such as $(CF_3)_2CHOH$ and CF_3CH_2OH. A reaction in polar nucleophilic solvents such as acetonitrile (CH_3CN) gave a mixture of **2a** (50%) and acetamido derivatives (**3**). In other solvents, an unsatisfactory result was obtained (Table 1).

We next investigated the reactivity of the *N*-protected norbelladine compounds. Although *N*-amide or *N*-carbamate protection caused a favorable aryl−aryl coupling reaction upon treatment with PIFA, no coupling products were obtained from the *N*-methylated or unprotected norbelladine compound (Table 2).

The amide group of **2a** and the carbamate group of **2b** could be cleaved by treatment with potassium carbonate[10]

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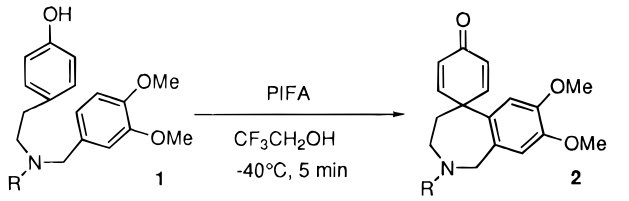
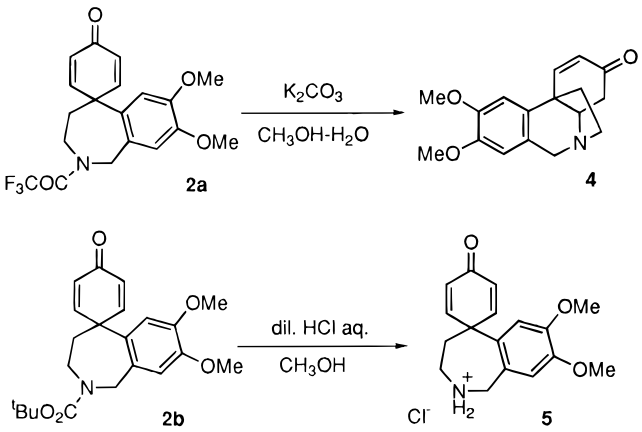
Table 2. Phenolic Coupling Reaction of 1 Protected as an Amide or a Carbamate

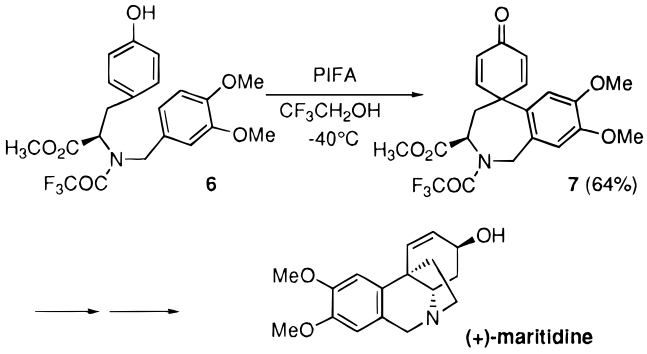


entry	R		product	yield (%)
1	COCF3	**1a**	**2a**	61
2	$CO_2{}^tBu$	**1b**	**2b**	49
3	TEOC	**1c**	**2c**	54
4	CO_2Et	**1d**	**2d**	48
5	COC_6F_5	**1e**	**2e**	50
6	CH_3	**1f**	**2f**	
7	H	**1g**	**2g**	

Scheme 3



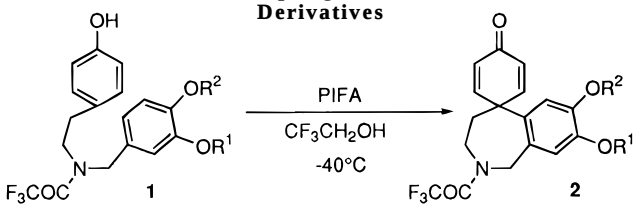
Scheme 4



or aqueous hydrogen chloride to give (±)-oxomaritidine (**4**) and **5**, respectively (Scheme 3). In the case of the norbelladine derivative (**6**) prepared from the L-tyrosine methyl ester and isovanilin,[3b] the intramolecular coupling reaction proceeded smoothly to give the coupling product (**7**), which is known as a key intermediate for (+)-maritidine (Scheme 4).[3b]

Furthermore, we investigated the reactivity of norbelladine derivatives having hydroxy groups protected as an ether or an ester at the C-3′ and C-4′ positions. The results are summarized in Table 3. The reaction of the *O*-silylated derivatives with PIFA afforded the corresponding coupling products in slightly lower yields than that of the methylated derivatives. Acetylated derivatives also reacted with PIFA to give the coupling products, although the yields were quite low. The reaction of the substrate having free hydroxy groups, however, gave no phenolic coupling product.

Table 3. Phenolic Coupling Reaction of Norbelladine Derivatives



entry	substrate	R^1	R^2	product	yield (%)
1	**1a**	Me	Me	**2a**	61
2	**1h**	$-CH_2-$		**2h**	56
3	**1i**	TBDMS	Me	**2i**	42
4	**1j**	TBDMS	TBDMS	**2j**	42
5	**1k**	Me	TBDMS	**2k**	35
6	**1l**	$PhCH_2$	Me	**2l**	49
7	**1m**	Me	^tBuCO	**2m**	32
8	**1n**	Me	CH_3CO	**2n**	37
9	**1o**	CH_3CO	Me	**2o**	trace
10	**1p**	H	Me	**2p**	19
11	**1q**	Me	H	**2q**	trace
12	**1r**	H	H	**2r**	trace

The oxidative cyclization of substrates having a hydroxy group protected as an ether at the C-4 position was also investigated. The reaction of the silyloxy derivatives with PIFA gave **2a** in good yield. Treatment of benzyloxy (**8d**) or methoxy derivatives (**8e**) with PIFA in CF_3CH_2OH, on the other hand, selectively afforded the coupling product (**9d** or **9e**) containing the 5,6,7,8-tetrahydrobenzazocine system. These results are summarized in Table 4.

Finally, we investigated the oxidative cyclization of the substrates having a methoxy or silyloxy group at the C-3′ position (**10**). Treatment of **10a** (R = Me) with PIFA in CF_3CH_2OH afforded both *p*−*p*′ coupling (**11a**) and *p*−*o*′ coupling products (**12a**). In the reaction of **10a** in CH_3CN, the formation ratio of **12a**/**11a** had increased although the overall yield of the coupling products had decreased (Table 5). **10b** (R = TBDMS) was also converted to the coupling products (**11b**, **12b**), which could not be separated by chromatography. Treatment of the mixture (**11b**, **12b**) with *n*-tetrabutylammonium fluoride in THF gave **11c** (R = H) and a narwedine[11] derivative (**13**), respectively, in good yield (95%) (Scheme 5).

The phenolic intramolecular coupling reaction using PIFA seems to proceed by either an ionic mechanism[7a] (**A**) or a radical mechanism[12] (**B**), which we reported very recently for the hypervalent iodine-induced nucleophilic substitution of *para*-substituted phenol ethers (Scheme 6). Although details of the mechanism remain unknown, the reaction of the substrate having a free hydroxy group (R = H) with PIFA is explained as follows: The reaction provides intermediates (**A**), which may induce a nucleophilic intramolecular cyclization. On the other hand, the reaction of substrates having no free hydroxy group or highly electron-donating methoxy groups in the aromatic ring with PIFA gave a cation radical intermediate (**B**), which may cause a nucleophilic intramolecular cyclization. In the case of the 4-methoxy and 4-(benzyloxy) compounds **8d** and **8e**, in which the carbon−oxygen ether bond at the 4-position is stable to cleavage, the reaction follows pathway b in poorly nucleophilic solvents.

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Conclusions

A novel oxidative phenolic coupling method has been developed using a hypervalent iodine(III) reagent instead of a heavy metal oxidizing reagent (Tl(III) or V(V) salt). This method can be applied to the intramolecular cyclization of norbelladine derivatives having various protecting groups. The nature of the substituents on the aromatic rings has an important effect on the outcome of the reaction. In addition, poorly nucleophilic polar protic solvents such as $(CF_3)_2CHOH$ or CF_3CH_2OH are very suitable for these phenolic coupling reactions. Further application of the reaction to the synthesis of other alkaloids is currently in progress.

Experimental Section

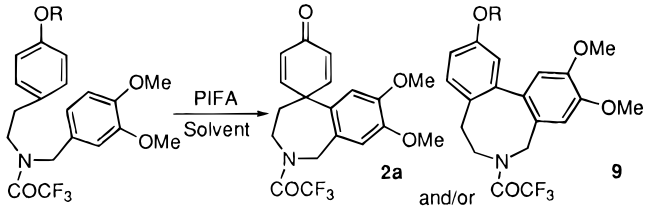
All melting points are uncorrected. Infrared (IR) absorption spectra (cm^{-1}) were recorded as a KBr pellet. ^1H NMR (and ^{13}C NMR) spectra were recorded in $CDCl_3$, unless otherwise noted, at 200, 250, 270, or 500 MHz with TMS as an internal standard. Most of the ^1H NMR spectra of amido compounds 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. Organic layers were dried with anhydrous $MgSO_4$ or Na_2SO_4. PIFA is commercially available. CF_3CH_2OH and $(CF_3)_2CHOH$ were obtained from commercial suppliers and were used without further purification. Compounds (**1a**,**g**,**h**,**p**, and **6**) were prepared by known methods.

***tert*-Butyl 1-(3,4-Dimethoxyphenyl)-4-(4-hydroxyphenyl)-2-azabutane-2-carboxylate (1b).** Di-*tert*-butyl dicarbonate (1.53 g, 7.00 mmol) was added to a suspension of **1g** (1.83 g, 6.36 mmol) and sodium carbonate (674 mg, 6.36 mmol) in H_2O (15 mL)−dioxane (15 mL) at 0 °C. After the mixture was stirred for 1 h, water was added to the reaction mixture. The mixture was extracted with AcOEt, and the organic layer was washed with water and brine and concentrated in vacuo. The residue was purified by chromatography on silica gel (*n*-hexane−AcOEt = 2:1) to give **1b** (2.42 g, 98%) as a colorless oil: IR 3350, 1690, 1670; ^1H NMR (500 MHz, $CDCl_3$) δ 1.48 (s, 9H), 2.67, 2.72 (brs, 2H), 2.28, 3.37 (brs, 2H), 3.84 (s, 3H), 3.86 (s, 3H), 4.30 (brs, 2H), 4.98 (s, 1H), 6.73−6.80 (m, 5H), 6.97 (brs, 2H); HRMS calcd for $C_{22}H_{29}NO_5$ (M^+) 387.2046, found 387.2070.

2-(Trimethylsilyl)ethyl 1-(3,4-Dimethoxyphenyl)-4-(4-hydroxyphenyl)-2-azabutane-2-carboxylate (1c). 2-(Trimethylsilyl)ethyl 4-nitrophenyl carbonate (242 mg, 0.857 mmol) was added to a solution of **1g** (223.8 mg, 0.779 mmol) and sodium bicarbonate (72.0 mg, 0.857 mmol) in H_2O (2 mL)−dioxane (5 mL) at rt. After the reaction mixture was stirred for 12 h, water was added. The mixture was extracted with AcOEt, and the extracts were washed with saturated $NaHCO_3$ solution, water, and brine and then concentrated in vacuo. The residue was purified by chromatography on silica gel (*n*-hexane−Et_2O = 1:1) to give **1c** (263.7 mg, 78%) as a colorless solid: mp 95−96 °C (from Et_2O−*n*-hexane): IR 3350, 2836, 1671; ^1H NMR (270 MHz, $CDCl_3$) δ 0.04 (s, 9H), 1.02 (t, 2H, J = 8.6 Hz), 2.69 (brs, 2H), 3.34 (brs, 2H), 3.84 (s, 3H), 3.86 (s, 3H), 4.22 (brs, 2H), 4.32 (s, 2H), 5.59 (s, 1H), 6.73−6.82 (m, 5H), 6.98 (d, 2H, J = 7.6 Hz). Anal. Calcd for $C_{23}H_{33}NO_5Si$: C, 64.01; H, 7.71; N, 3.25. Found: C, 63.89; H, 7.54; N, 3.29.

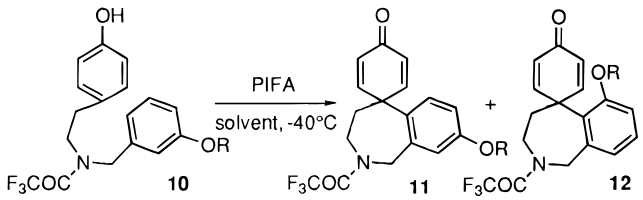
Ethyl 1-(3,4-Dimethoxyphenyl)-4-(4-hydroxyphenyl)-2-azabutane-2-carboxylate (1d). Ethyl chloroformate (0.499 mL, 5.21 mmol) was added to a suspension of **1g** (374 mg, 1.30 mmol) and potassium carbonate (1.08 g, 7.81 mmol) in acetone (12 mL) at rt. After being stirred for 1.5 h, the reaction mixture was refluxed for 12 h. Then the mixture was cooled and evaporated in vacuo. After general workup, the residue was purified by chromatography on silica gel (*n*-hexane−AcOEt = 2:1) to give *N*,*O*-diprotected compounds. A solution of the compound and NaOH (201 mg, 5.03 mmol) in EtOH (6.4 mL)−H_2O (0.5 mL) was stirred at 70 °C for 30 min. After cooling, the mixture was quenched with saturated NH_4Cl

Table 4. Reaction of the Substrates with a Hydroxy Group Protected as an Ether at the C-4 Position



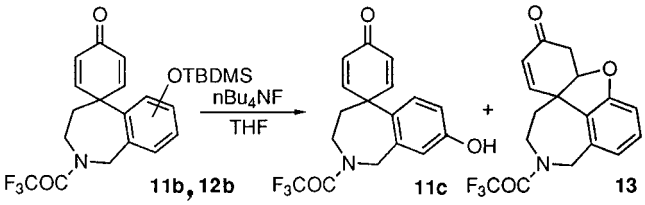
entry	substrate	R	solvent	reaction time	**2a** (%)	**9** (%)
1	**1a**	H	CF_3CH_2OH	5 min	61	
2	**8a**	TMS		30 min	57	
3	**8b**	TBDMS		4.5 h	66	
4	**8c**	TBDPS		4 h	23	12
5	**8d**	$PhCH_2$		24 h		48
6	**8e**	Me		30 min		47
7	**8e**		$(CF_3)_2CHOH$	1 h		42
8	**8e**		CH_3CN	3.5 h	33	23
9	**8e**		CH_2Cl_2	24 h	22	

Table 5. Reaction of Substrates Bearing a Methoxy or Silyloxy Group at the C-3′ Position



entry	R	solvent	yield (%)	ratio of **11/12**
1	CH_3 (**10a**)	CF_3CH_2OH	60	2.5
2	TBDMS (**10b**)	CF_3CH_2OH	40	3.6
3	TBDMS (**10b**)	CH_3CN	12	2.0

Scheme 5. Deprotection of the Silyl Ether



solution and concentrated in vacuo. The residue was extracted with AcOEt, and the extracts were washed with water and brine and then concentrated in vacuo. The residue was purified by chromatography on silica gel (*n*-hexane−AcOEt = 3:2) to give **1d** (396.7 mg, 85%) as a colorless oil: IR 3350, 1695, 1671; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.27 (t, 3H, J = 7.3 Hz), 2.70 (brs, 2H), 3.35 (brs, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 4.18 (brs, 2H), 4.32 (s, 2H), 5.31 (s, 1H), 6.73−6.82 (m, 5H), 6.99 (brs, 2H); HRMS calcd for $C_{20}H_{25}NO_5$ (M^+) 359.1733, found 359.1745.

***N*-(3,4-Dimethoxybenzyl)-*N*-(4-hydroxyphenethyl)pentafluorobenzamide (1e).** Pentafluorobenzoyl chloride (0.21 mL, 1.46 mmol) was added to a solution of **1g** (142 mg, 0.495 mmol) in pyridine (2 mL) at 0 °C. After being stirred for 45 min, the mixture was quenched with water and then extracted with CH_2Cl_2. The organic layer was washed with water and brine and then concentrated in vacuo. After general workup, the residue was purified by chromatography on silica gel (*n*-hexane−AcOEt = 3:1) to give *N*,*O*-diprotected compounds. A suspension of the compound (57.6 mg, 0.0852 mmol) in MeOH (6 mL)−H_2O (3 mL)−CH_2Cl_2 (2 mL) was stirred at rt for 1 h, and then the reaction mixture was concentrated in vacuo. The residue was purified by chromatography on silica gel (*n*-hexane−AcOEt = 3:2) to give **1e** (18.2 mg, 44%) as a colorless solid: IR 3350, 1653; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.66, 2.89 (t, 2H, J = 7.3 Hz), 3.28, 3.63 (t, 2H, J = 7.3 Hz), 3.84, 3.86, 3.87, 3.89 (s, 6H), 4.08, 4.69 (s, 2H), 4.84, 4.88 (s, 1H), 6.54 (s, 0.5H), 6.58 (dd, 0.5H, J = 8.8, 1.8 Hz), 6.70−6.88 (m, 5H), 7.09 (d, 1H, J = 8.5 Hz); HRMS calcd for $C_{24}H_{20}NO_4F_5$ (M^+) 481.1311, found 481.1311.

***N*-(3,4-Dimethoxybenzyl)-4-(hydroxyphenethyl)-*N*-methylamine (1f).** Formaldehyde (37% solution in H_2O, 6.3 mL) was added to a solution of **1g** (442,0 mg, 1.54 mmol) in MeOH (20 mL) at rt. After being stirred for 1.5 h, the mixture was cooled, $NaBH_4$ (1.05 g, 27.7 mmol) was added slowly under ice bath cooling, and the suspension was stirred at rt for 30 min. Evaporation of the solvent gave a residue, which was mixed with AcOEt and water. The resulting mixture was neutralized by addition of concd HCl and extracted with AcOEt. The extracts were washed with water and brine and concentrated in vacuo. The residue was purified by chromatography on silica gel (AcOEt) to give **1f** (422.7 mg, 91%) as a colorless solid: IR 3400; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.28 (s, 3H), 2.58−2.64 (m, 2H), 2.71−2.77 (m, 2H), 3.50 (s, 2H), 3.83 (s, 3H), 3.87 (s, 3H), 6.72 (d, 2H, J = 8.1 Hz), 6.80 (s, 2H), 6.86 (s, 1H), 7.03 (d, 2H, J = 8.4 Hz); HRMS calcd for $C_{18}H_{23}NO_3$ (M^+) 301.1678, found 301.1668.

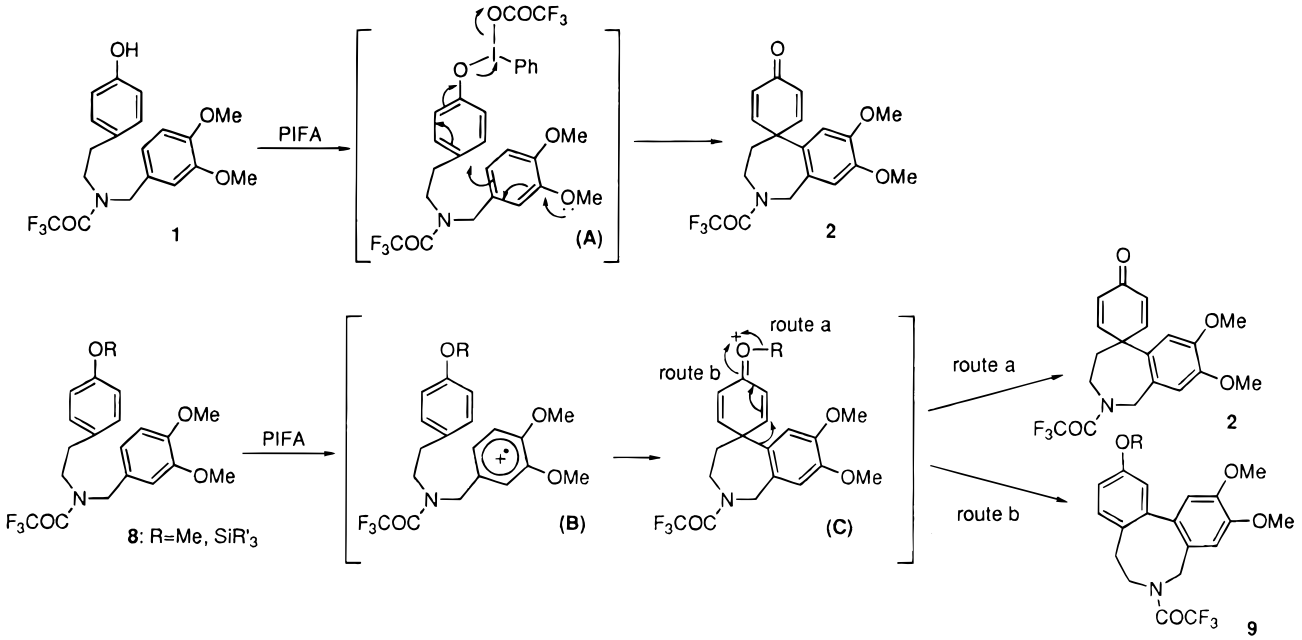
General Procedure of Preparing *N*-Trifluoroacetylated Compounds 1h−o. $(CF_3CO)_2O$ (2.0−3.0 mmol) was added to a solution of *O*-protected norbelladine derivative (1.0 mmol) in pyridine (5 mL) at 0 °C under nitrogen. Then the reaction mixture was stirred for 30 min, and water and AcOEt were added. The organic layer was separated, washed with 10% HCl, water, and brine, and concentrated in vacuo. The residue was purified with chromatography on silica gel (AcOEt−*n*-hexane) to give the corresponding *N*-trifluoroacetylated compounds in good yields.

***N*-[3-[(*tert*-Butyldimethylsilyl)oxy]-4-methoxybenzyl]-*N*-(4-hydroxyphenethyl)trifluoroacetamide (1i).** Reactants: NH-compound (704 mg, 1.82 mmol) in pyridine (5 mL); $(CF_3CO)_2O$ (0.51 mL, 3.64 mmol). **1i** (722 mg, 82%): colorless oil; IR 3400, 1670; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.14 (s, 6H), 0.98, 0.99 (s, 9H), 2.68−2.82 (m, 2H), 3.41−3.46 (m, 2H), 3.79, 3.80 (s, 3H), 4.29, 4.55 (s, 2H), 5.31 (s, 1H), 6.65 (d, 0.5H, J = 2.0 Hz), 6.70 (dd, 0.5H, J = 8.2, 2.0 Hz), 6.74−6.83 (m, 4H), 6.97 (d, 2H, J = 8.3 Hz). Anal. Calcd for $C_{24}H_{32}NO_4F_3Si$: C, 59.61; H, 6.67; N, 2.90. Found: C, 59.30; H, 6.64; N, 2.84.

***N*-[3,4-Bis[(*tert*-butyldimethylsilyl)oxy]benzyl]-*N*-(4-hydroxyphenethyl)trifluoroacetamide (1j).** Reactants: NH-compound (2.26 g, 4.63 mmol) in pyridine (15 mL); $(CF_3CO)_2O$ (1.31 mL, 9.26 mmol). **1j** (2.31 g, 85%): colorless solid; mp 107−108 °C (from Et_2O−*n*-hexane); IR 3400, 2955, 1678; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.17, 0.19 (s, 12H), 0.96, 0.97, 0.98 (s, 18H), 2.69−2.80 (m, 2H), 3.41−3.46 (m, 2H), 4.26, 4.52 (s, 2H), 4.76, 4.79 (s, 1H), 6.60, 6.67 (dd, 1H, J = 8.6, 7.7, 2.6, 1.7 Hz), 6.64 (d, 0.5H, J = 2.6 Hz), 6.72−6.81 (m, 3.5H), 6.98 (d, 2H, J = 8.6 Hz); HRMS calcd for $C_{29}H_{44}NO_4F_3Si_2$ (M^+) 583.2761, found 583.2775. Anal. Calcd for $C_{29}H_{44}NO_4F_3Si_2$: C, 59.66; H, 7.60; N, 2.40. Found: C, 59.65; H, 7.39; N, 2.46.

***N*-[4-[(*tert*-Butyldimethylsilyl)oxy]-3-methoxybenzyl]-*N*-(4-hydroxyphenethyl)trifluoroacetamide (1k).** Reactants: NH-compound (270.7 mg, 0.698 mmol) in pyridine (2

Scheme 6



mL); $(CF_3CO)_2O$ (0.20 mL, 1.40 mmol). **1k** (200.4 mg, 63%): colorless oil; IR 3400, 1640, 1630; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.15 (s, 6H), 0.99 (s, 9H), 2.69−2.80 (m, 2H), 3.44−3.48 (m, 2H), 3.77, 3.78 (s, 3H), 4.34, 4.58 (s, 2H), 5.12, 5.14 (s, 1H), 6.62−6.83 (m, 5H), 6.97 (d, 2H, J = 8.6 Hz). Anal. Calcd for $C_{24}H_{32}NO_4F_3Si$: C, 59.61; H, 6.67; N, 2.90. Found: C, 59.44; H, 6.70; N, 3.01.

***N*-[3-(Benzyloxy)-4-methoxybenzyl]-*N*-(4-hydroxyphenethyl)trifluoroacetamide (1l).** Reactants: NH-compound (327.8 mg, 0.902 mmol) in pyridine (1.5 mL); $(CF_3CO)_2O$ (0.25 mL, 1.80 mmol). **1l** (408.9 mg, 99%): colorless oil; IR 3400, 1686; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.62−2.71 (m, 2H), 3.30−3.37 (m, 2H), 3.88, 3.89 (s, 3H), 4.24, 4.51 (s, 2H), 4.94, 4.97 (s, 1H), 5.13 (s, 2H), 6.61, 6.76 (d, 1H, J = 1.7 Hz), 6.68, 6.78 (dd, 1H, J = 7.7, 1.7 Hz), 6.74, 6.76 (d, 2H, J = 8.6 Hz), 6.84, 6.85 (d, 1H, J = 7.7 Hz), 6.93 (d, 2H, J = 8.6 Hz), 7.27−7.41 (m, 5H); HRMS calcd for $C_{25}H_{24}NO_4F_3$ (M^+) 459.1658, found 459.1666.

4-[[*N*-(4-Hydroxyphenethyl)-*N*-(trifluoroacetyl)amino]-methyl]-2-methoxyphenyl Pivalate (1m). Reactants: NH-compound (170.0 mg, 0.476 mmol) in pyridine (1.5 mL); $(CF_3CO)_2O$ (0.20 mL, 1.43 mmol). **1m** (203.1 mg, 94%): colorless solid; mp 72−73 °C (from Et_2O−*n*-hexane); IR 3450, 1755, 1690; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.36 (s, 9H), 2.73−2.84 (m, 2H), 3.44−3.51 (m, 2H), 3.76 (s, 3H), 4.33, 4.59 (s, 2H), 4.99 (brs, 1H), 6.65−6.79 (m, 4H), 6.95 (d, 2H, J = 8.5 Hz), 6.97, 6.98 (d, 1H, J = 7.8 Hz); HRMS calcd for $C_{23}H_{26}NO_5F_3$ (M^+) 453.1763, found 453.1741.

***N*-[4-[(*tert*-Butyldimethylsilyl)oxy]phenethyl]-*N*-(3,4-dimethoxybenzyl)trifluoroacetamide (8b).** Reactants: NH-compound (167.9 mg, 0.418 mmol) in pyridine (1.0 mL); $(CF_3CO)_2O$ (0.088 mL, 0.627 mmol). **8b** (200.3 mg, 96%): colorless oil; IR 2950, 1692; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.17 (s, 6H), 0.97 (s, 9H), 2.72−2.84 (m, 2H), 3.43−3.51 (m, 2H), 3.85, 3.87, (s, 6H), 4.28, 4.57 (s, 2H), 6.61, 6.76 (d, 1H, J = 1.8 Hz), 6.65−6.85 (m, 2H), 6.77 (d, 2H, J = 8.5 Hz), 6.98 (d, 2H, J = 8.5 Hz). Anal. Calcd for $C_{25}H_{34}NO_4F_3Si$: C, 60.34; H, 6.89; N, 2.81. Found: C, 60.12; H, 6.78; N, 2.81.

***N*-(3,4-Dimethoxybenzyl)-*N*-(4-methoxyphenethyl)trifluoroacetamide (8e).** Reactants: NH-compound (469.9 mg, 1.56 mmol) in pyridine (1.5 mL); $(CF_3CO)_2O$ (0.66 mL, 4.68 mmol). **8e** (635.2 mg, quant): colorless oil; IR 1690; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.72−2.87 (m, 2H), 3.43−3.52 (m, 2H), 3.79 (s, 3H), 3.85 (s, 3H), 3.89 (s, 3H), 4.33, 4.59 (s, 2H), 6.62−6.86 (m, 5H), 7.05 (d, 2H, J = 8.4 Hz); HRMS calcd for $C_{20}H_{22}NO_4F_3$ (M^+) 397.1501, found 397.1503. Anal. Calcd for $C_{20}H_{22}NO_4F_3$: C, 60.45; H, 5.58; N, 3.52. Found: C, 60.24; H, 5.47; N, 3.53.

***N*-(4-Hydroxyphenethyl)-*N*-(3-methoxybenzyl)trifluoroacetamide (10a).** Reactants: NH-compound (199.2 mg, 0.774 mmol) in pyridine (1.5 mL); $(CF_3CO)_2O$ (0.33 mL, 2.32 mmol). **10a** (246.5 mg, 90%): crystals; IR 3400, 1688, 1682; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.75−2.83 (m, 2H), 3.45−3.51 (m, 2H), 3.79 (s, 3H), 4.36, 4.62 (s, 2H), 5.09, 5.12 (s, 1H), 6.66 (s, 0.5H), 6.72, 6.80 (d, 1H, J = 7.7, 6.8 Hz), 6.75−6.78 (m, 2.5H), 6.83−6.87 (m, 1H), 6.99 (d, 2H, J = 8.6 Hz), 7.25−7.28 (d, 1H, J = 7.7, 6.8 Hz); HRMS calcd for $C_{18}H_{18}NO_3F_3$ (M^+) 353.1238, found 353.1256.

***N*-[3-[(*tert*-Butyldimethylsilyl)oxy]benzyl]-*N*-(4-hydroxyphenethyl)trifluoroacetamide (10b).** Reactants: NH-compound (1.32 g, 3.68 mmol) in pyridine (5 mL); $(CF_3CO)_2O$ (1.04 mL, 7.36 mmol). **10b** (1.59 g, 96%): colorless oil; IR 3400, 1682; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.18 (s, 6H), 0.97 (s, 9H), 2.72−2.84 (m, 2H), 3.43−3.51 (m, 2H), 4.33, 4.60 (s, 2H), 4.76, 4.79 (s, 1H), 6.61 (d, 0.5H, J = 1.8 Hz), 6.69−6.82 (m, 2.5H), 6.76 (d, 2H, J = 8.8, 8.5 Hz), 6.99, 7.00 (d, 2H, J = 8.8, 8.5 Hz), 7.21 (ddd, 1H, J = 8.0, 7.3, 2.6 Hz). Anal. Calcd for $C_{23}H_{30}NO_3F_3Si$: C, 60.90; H, 6.67; N, 3.09. Found: C, 60.71; H, 6.63; N, 3.07.

4-[[*N*-(4-Hydroxyphenethyl)-*N*-(trifluoroacetyl)amino]-methyl]-2-methoxyphenyl Acetate (1n). An NH-compound prepared from [(*tert*-butyldimethylsilyl)oxy]tyramine and vanillin was trifluoroacetylated by the general method to give an *N*-$COCF_3$ compound (1.33 g, 97%). The *N*-$COCF_3$ compound (1.31 g, 2.71 mmol) was acetylated by a known method to give an *O*-acetylated compound (1.28 g, 90%). To both the *N*- and *O*-diprotected compounds (41.3 mg, 0.0786 mmol) was added tetra-*n*-butylammonium fluoride (1.0 M solution in THF, 0.086 mL) in THF (0.5 mL) containing AcOH (14.2 mg, 0.236 mmol) and the resulting mixture stirred for 5 min. The mixture was evaporated, and the residue was purified by chromatography on silica gel (CH_2Cl_2−MeOH = 50:1) to give **1n** (30.5 mg, 94%) as a colorless oil: IR 3400, 1767, 1685; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.31, 2.32 (s, 3H), 2.74−2.85 (m, 2H), 3.45−3.54 (m, 2H), 3.79 (s, 3H), 4.34, 4.59 (s, 2H), 5.48, 5.50 (s, 1H), 6.67, 6.74 (s, 1H), 6.73, 6.75 (d, 2H, J = 8.5 Hz), 6.81 (dd, 1H, J = 7.5, 2.0 Hz), 6.97 (d, 2H, J = 8.5 Hz), 7.00, 7.02 (d, 1H, J = 8.0 Hz); HRMS calcd for $C_{20}H_{20}NO_5F_3$ (M^+) 411.1290, found 411.1284. Anal. Calcd for $C_{20}H_{20}NO_5F_3$: C, 58.39; H, 4.90; N, 3.40. Found: C, 58.05; H, 4.95; N, 3.67.

***N*-[4-[(*tert*-Butyldiphenylsilyl)oxy]phenethyl]-*N*-(3,4-dimethoxybenzyl)trifluoroacetoamide (8c).** *tert*-Butyldiphenylsilyl chloride (1.60 mL, 0.622 mmol) was added to a solution of **1a** (159 mg, 0.415 mmol) and imidazole (57.0 mg, 0.830 mmol) in DMF (1.5 mL) at rt under nitrogen. After the mixture was stirred for 1 h, water and Et_2O were added. The

organic layer was separated, washed with water and brine, and concentrated in vacuo. The residue was purified by chromatography on silica gel (*n*-hexane−AcOEt = 10:1) to give **8c** (236 mg, 91%) as a colorless oil: IR 1690; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (s, 9H), 2.67−2.76 (m, 2H), 3.36−3.43 (m, 2H), 3.79, 3.81, 3.86 (s, 6H), 4.13, 4.48 (s, 2H), 6.54 (d, 0.5H, J = 1.7 Hz), 6.57 (d, 0.5H, J = 7.7 Hz), 6.69−6.71 (m, 3H), 6.78, 6.79 (d, 1H, J = 7.7 Hz), 6.85 (d, 2H, J = 8.6 Hz), 7.33−7.42 (m, 6H), 7.68−7.71 (m, 4H); HRMS calcd for $C_{35}H_{38}NO_4F_3Si$ (M^+) 621.2522, found 621.2522. Anal. Calcd for $C_{35}H_{38}NO_4F_3Si$: C, 67.61; H, 6.16; N, 2.25. Found: C, 67.45; H, 6.14; N, 2.34.

***N*-[4-(Benzyloxy)phenethyl]-*N*-(3,4-dimethoxybenzyl)-trifluoroacetamide (8d).** Benzyl bromide (0.057 mL, 0.472 mmol) was added to a suspension of **1a** (164.4 mg, 0.429 mmol) and potassium carbonate (65.2 mg, 0.472 mmol) in EtOH (3 mL). After being stirred for 30 min, the reaction mixture was filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel (*n*-hexane−AcOEt = 3:1) to give **8d** (197 mg, 97%) as a colorless oil: IR 1690; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.72−2.86 (m, 2H), 3.43−3.53 (m, 2H), 3.85 (s, 3H), 3.88 (s, 3H), 4.32, 4.59 (s, 2H), 5.05 (s, 2H), 6.65−6.93 (m, 5H), 7.05 (d, 2H, J = 8.4 Hz), 7.29−7.44 (m, 5H). Anal. Calcd for $C_{26}H_{26}NO_4F_3$: C, 65.95; H, 5.53; N, 2.96. Found: C, 65.74; H, 5.45; N, 2.93.

General Procedure for the Oxidative Cyclization of Norbelladine Derivatives Using PIFA. To a stirred solution of a norbelladine derivative (0.1 mmol) in CF_3CH_2OH (1 mL) was added a solution of PIFA (0.11 mmol) in CF_3CH_2OH (4 mL) at −40 °C under nitrogen, and the solution was stirred for 10 min. Then the solution was evaporated, and the residue was purified by column chromatography or preparative TLC to give a phenolic coupling compound in moderate yield.

2-(Trifluoroacetyl)-7,8-dimethyl-2,3,4,5-tetrahydro-1*H*-[2]benzazepine-5-spiro-1′-cyclohexa-2′,5′-dien-4′-one (2a). Reactants: **1a** (22.2 mg, 0.0579 mmol) in CF_3CH_2OH (1 mL); PIFA (27.4 mg, 0.0637 mmol) in CF_3CH_2OH (1.5 mL). **2a** (13.4 mg, 61%): colorless solid; mp 162−163 °C (from Et_2O−*n*-hexane); IR 1690, 1667, 1626; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.35−2.43 (m, 2H), 3.72, 3.87, 3.88 (s, 6H), 3.91−3.98 (m, 2H), 4.77, 4.81 (s, 2H), 6.31, 6.32 (d, 2H, J = 10.2 Hz), 6.52 (s, 1H), 6.61, 6.80 (s, 1H), 6.94, 7.05 (d, 2H, J = 10.2 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 33,8, 35.8, 42.6, 45.2, 45.3, 48.1, 48.3, 48.4, 48.6, 48.7, 112.6, 112.7, 113.1, 114.1, 116.2 (q, J = 288 Hz), 127.1, 127.2, 127.8, 127.9, 128.0, 148.1, 148.6, 148.7, 152.5, 152.9, 156.3 (m, J = 35 Hz), 185.0, 185.2; HRMS calcd for $C_{19}H_{18}NO_4F_3$ (M^+) 381.1185, found 381.1168.

***tert*-Butyl 7,8-Dimethoxy-4′-oxo-2,3,4,5-tetrahydro-1*H*-[2]benzazepine-5-spiro-1′-cyclohexa-2′,5′-diene-2-carboxylate (2b).** Reactants: **1b** (50.2 mg, 0.130 mmol) in CF_3CH_2OH (1 mL); PIFA (61.3 mg, 0.143 mmol) in CF_3CH_2OH (4 mL). **2b** (24.4 mg, 49%): colorless solid; mp 148−149 °C (from Et_2O); IR 1694, 1665, 1625; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36, 1.47 (s, 9H), 2.26−2.29 (m, 2H), 3.73 (s, 3H), 3.76−3.78 (m, 2H) 3.87 (s, 3H), 4.50, 4.62 (s, 2H), 6.29 (d, 2H, J = 10.3 Hz), 6.52, 6.82 (s, 1H), 6.64, 6.75 (s, 1H), 7.00, 7.03 (d, 2H, J = 10.3 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 28.2, 35.6, 43.5, 44.3, 47.6, 48.4, 48.6, 55.7, 79.9, 80.1, 112.7, 112.8, 113.2, 126.5, 127.7, 131.4, 147.4, 147.7, 153.7, 154.4, 154.8, 185.4. Anal. Calcd for $C_{22}H_{27}NO_5$ C, 68.55; H, 7.06; N, 3.63. Found: C, 68.48, H, 7.03; N, 3.62.

2-(Trimethylsilyl)ethyl 7,8-Dimethoxy-4′-oxo-2,3,4,5-tetrahydro-1*H*-[2]benzazepine-5-spiro-1′-cyclohexa-2′,5′-diene-2-carboxylate (2c). Reactants: **1c** (53.7 mg, 0.124 mmol) in CF_3CH_2OH (1 mL); PIFA (58.9 mg, 0.137 mmol) in CF_3CH_2OH (4 mL). **2c** (28.9 mg, 54%): colorless solid; mp 167−169 °C (from Et_2O−CH_2Cl_2); IR 1694, 1666, 1626; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.01, 0.02 (s, 9H), 0.89−1.03 (m, 2H), 2.26 (brs, 2H), 3.70 (s, 3H), 3.75−3.82 (m, 2H), 3.86 (s, 3H), 4.09−4.22 (m, 2H), 4.57, 4.64 (s, 2H), 6.27 (d, 2H, J = 10.3 Hz), 6.48, 6.50 (s, 1H), 6.64, 6.74 (s, 1H), 6.99, 7.01 (d, 2H, J = 9.8, 10.3 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −1.5, 17.8, 35.6, 35.8, 44.1, 48.1, 48.7, 55.9, 63.9, 112.9, 113.3, 126.7, 130.9, 147.7, 148.0, 153.7, 155.7, 185.5. Anal. Calcd for $C_{23}H_{31}NO_5Si$: C, 64.31; H, 7.27; N, 3.26. Found: C, 64.13; H, 7.06; N, 3.27.

Ethyl 7,8-Dimethoxy-4′-oxo-2,3,4,5-tetrahydro-1*H*-[2]-benzazepine-5-spiro-1′-cyclohexa-2′,5′-diene-2-carboxylate (2d). Reactants: **1d** (203.5 mg, 0.566 mmol) in CF_3CH_2OH (4 mL); PIFA (267.8 mg, 0.623 mmol). **2d** (97.8 mg, 49%): colorless solid; mp 92−94 °C (from Et_2O); IR 1700, 1667, 1624; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.17−1.30 (m, 3H), 2.28 (brs, 2H), 3.72 (s, 3H), 3.76−3.83 (m, 2H), 3.88 (s, 3H), 4.09−4.19 (m, 2H), 4.58, 4.66 (s, 2H), 6.29 (d, 2H, J = 10.2 Hz), 6.52, 6.53 (s, 1H), 6.66, 6.76 (s, 1H), 7.02, 7.03 (d, 2H, J = 9.9, 10.2 Hz); HRMS calcd for $C_{20}H_{23}NO_5$ (M^+) 357.1576, found 357.1603.

2-(Pentafluorobenzoyl)-7,8-dimethoxy-2,3,4,5-tetrahydro-1*H*-[2]benzazepine-5-spiro-1′-cyclohexa-2′,5′-dien-4′-one (2e). Reactants: **1e** (32.1 mg, 0.0667 mmol) in CF_3CH_2OH (2 mL); PIFA (31.5 mg, 0.0733 mmol). **2e** (17.8 mg, 56%): colorless solid; mp 188−190 °C (from Et_2O); IR 1667, 1652; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.32−2.45 (m, 2H), 3.67 (s, 3H), 3.74, 3.75 (s, 3H), 3.92 (s, 1H), 4.08 (t, 1H, J = 6.0 Hz), 4.49, 4.94 (s, 2H), 5.97, 6.52, 6.55, 6.86 (s, 2H), 6.29, 6.34 (d, 2H, J = 10.3, 9.4 Hz), 7.01 (d, 2H, J = 10.3 Hz). Anal. Calcd for $C_{24}H_{18}NO_4F_5$: C, 60.13; H, 3.78; N, 2.92. Found: C, 59.92; H, 3.74; N, 2.93.

2-(Trifluoroacetyl)-7,8-(methylenedioxy)-2,3,4,5-tetrahydro-1*H*-[2]benzazepine-5-spiro-1′-cyclohexa-2′,5′-dien-4′-one (2h). Reactants: **1h** (30.8 mg, 0.0839 mmol) in CF_3CH_2OH (1 mL); PIFA (39.7 mg, 0.0923 mmol) in CF_3CH_2OH (1 mL). **2h** (17.3 mg, 56%): colorless solid; mp 143−145 °C (from Et_2O); IR 1690, 1667, 1626; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.34−2.43 (m, 2H), 3.89−3.98 (m, 2H), 4.74, 4.76 (s, 2H), 5.94, 5.96 (s, 2H), 6.30, 6.31 (d, 2H, J = 10.2, 10.4 Hz) 6.55 (s, 1H), 6.63, 6.81 (s, 1H), 6.90, 7.00 (d, 2H, J = 10.2, 10.4 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 33.7, 35.7, 44.2, 45.2, 45.3, 48.2, 48.3, 48.5, 48.6, 48.7, 101.7, 101.8, 109.7, 109.9, 110.0, 111.3, 117.3 (m), 127.1, 127.4, 129.0, 129.1, 129.3, 129.4, 147.2, 147.9, 148.0, 152.3, 152.7, 157.0 (m), 184.9, 185.1; HRMS calcd for $C_{18}H_{14}NO_4F_3$ (M^+) 365.0875, found 365.0880.

8-[(*tert*-Butyldimethylsilyl)oxy]-2-(trifluoroacetyl)-7-methoxy-2,3,4,5-tetrahydro-1*H*-[2]benzazepine-5-spiro-1′-cyclohexa-2′,5′-dien-4′-one (2i). Reactants: **1i** (54.4 mg, 0.119 mmol) in CF_3CH_2OH (1 mL); PIFA (56.5 mg, 0.131 mmol) in CF_3CH_2OH (5 mL). **2i** (22.5 mg, 42%): colorless solid; mp 154−155 °C (from Et_2O); IR 1692, 1671; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.13, 0.14 (s, 6H), 0.97, 0.98 (s, 9H), 2.33−2.41 (m, 2H), 3.65 (s, 3H), 3.90−3.94 (m, 2H), 4.71, 4.74 (s, 2H), 6.29, 6.32 (d, 2H, J = 10.2 Hz), 6.48, 6.49 (s, 1H), 6.62, 6.79 (s, 1H), 6.95, 7.06 (d, 2H, J = 9.9, 10.2 Hz). Anal. Calcd for $C_{24}H_{30}NO_4F_3Si$: C, 59.86; H, 6.28; N, 2.91. Found: C, 59.69; H, 6.24; N, 2.93.

7,8-Bis[(*tert*-butyldimethylsilyl)oxy]-2-trifluoroacetyl-2,3,4,5-tetrahydro-1*H*-[2]benzazepine-5-spiro-1′-cyclohexa-2′,5′-dien-4′-one (2j). Reactants: **1j** (146 mg, 0.250 mmol) in CF_3CH_2OH (3 mL); PIFA (108 mg, 0.250 mmol). **2j** (60.5 mg, 42%): colorless solid; mp 174−175 °C (from Et_2O); IR 1692, 1671; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.10, 0.18, 0.19 (s, 12H), 0.90, 0.91 (s, 18H), 2.33−2.40 (m, 2H), 3.92−3.95 (m, 2H), 4.69, 4.73 (s, 2H), 6.29, 6.30 (d, 2H, J = 10.3 Hz), 6.53, 6.54, 6.60, 6.76 (s, 2H), 6.92, 7.02 (d, 2H, J = 10.3, 9.4 Hz); HRMS calcd for $C_{29}H_{42}NO_4F_3Si_2$ (M^+) 581.2604, found 581.2620. Anal. Calcd for $C_{29}H_{42}NO_4F_3Si_2$: C, 59.87; H, 7.28; N, 2.41. Found: C, 59.71; H, 7.04; N, 2.35.

7-[(*tert*-Butyldimethylsilyl)oxy]-2-(trifluoroacetyl)-8-methoxy-2,3,4,5-tetrahydro-1*H*-[2]benzazepine-5-spiro-1′-cyclohexa-2′,5′-dien-4′-one (2k). Reactants: **1k** (89.9 mg, 0.186 mmol) in CF_3CH_2OH (3 mL); PIFA (87.9 mg, 0.204 mmol). **2k** (31.6 mg, 35%): colorless solid; mp 140−141 °C (from Et_2O−*n*-hexane); IR 1692, 1669; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.92 (s, 9H), 2.32−2.40 (m, 2H), 3.80, 3.81 (s, 3H), 3.90−3.97 (m, 2H), 4.76, 4,79 (s, 2H), 6.29, 6.30 (d, 2H, J = 9.9 Hz), 6.52 (s, 1H), 6.59, 6.77 (s, 1H), 6.91, 7.02 (d, 2H, J = 9.9, 10.2 Hz); HRMS calcd for $C_{24}H_{30}NO_4F_3Si$ (M^+) 481.1896, found 481.1900. Anal. Calcd for $C_{24}H_{30}NO_4F_3Si$: C, 59.86; H, 6.28; N, 2.91. Found: C, 59.97; H, 6.21; N, 2.87.

8-(Benzyloxy)-2-(trifluoroacetyl)-7-methoxy-2,3,4,5-tetrahydro-1*H*-[2]benzazepine-5-spiro-1′-cyclohexa-2′,5′-dien-4′-one (2l). Reactants: **1l** (61.6 mg, 0.134 mmol) in CF_3CH_2OH (1 mL); PIFA (63.4 mg, 0.147 mmol) in CF_3CH_2OH (4 mL). **2l** (29.9 mg, 49%): colorless solid; mp 172−174 °C (from CH_2-

Cl_2−*n*-hexane); IR 1692, 1667; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.33−2.40 (m, 2H), 3.73, 3.74 (s, 3H), 3.88−3.94 (m, 2H), 4.69, 4.76 (s, 2H), 5.13 (s, 2H), 6.31, 6.32 (d, 2H, J = 9.6, 10.2 Hz), 6.54, 6.56 (s, 1H), 6.65, 6.88 (1H, s), 6.93, 7.05 (d, 2H, J = 9.9 Hz), 7.31−7.40 (m, 5H); HRMS calcd for $C_{25}H_{22}NO_4F_3$ (M^+) 457.1501, found 457.1520.

2-(Trifluoroacetyl)-8-methoxy-4′-oxo-2,3,4,5-tetrahydro-1*H*-[2]benzazepine-5-spiro-1′-cyclohexa-2′,5′-dienyl 7-Pivalate (2m). Reactants: **1m** (22.1 mg, 0.0487 mmol) in CF_3CH_2OH (0.5 mL); PIFA (23.1 mg, 0.0536 mmol) in CF_3CH_2OH (2 mL). **2m** (7.0 mg, 32%): colorless solid; mp 188−190 °C (from Et_2O); IR 2975, 1755, 1694, 1667, 1625; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (s, 9H), 2.35−2.42 (m, 2H), 3.81, 3.82 (s, 3H), 3.93−3.98 (m, 2H), 4.81, 4.84 (s, 2H), 6.30, 6.32 (d, 2H, J = 9.4, 10.3 Hz), 6.68, 6.70, 6.89 (s, 2H), 6.92, 7.04 (d, 2H, J = 10.3 Hz); HRMS calcd for $C_{23}H_{24}NO_5F_3$ (M^+) 451.1606, found 451.1607. Anal. Calcd for $C_{23}H_{24}NO_5F_3$: C, 61.19; H, 5.36; N, 3.10. Found: C, 61.11; H, 5.33; N, 3.26.

2-(Trifluoroacetyl)-8-methoxy-4′-oxo-2,3,4,5-tetrahydro-1*H*-[2]benzazepine-5-spiro-1′-cyclohexa-2′,5′-dienyl 7-Acetate (2n). Reactants: **1n** (31.0 mg, 0.754 mmol) in CF_3CH_2OH (3.5 mL); PIFA (356 mg, 0.829 mmol). **2n** (114 mg, 37%): colorless solid; mp 153−155 °C (from Et_2O); IR 1767, 1694, 1667, 1625; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.27 (s, 3H), 2.33−2.43 (m, 2H), 3.84, 3.85 (s, 3H), 3.92−4.01 (m, 2H), 4.82, 4.85 (s, 2H), 6.15, 6.31 (d, 2H, J = 10.4, 10.3 Hz), 6.72, 6.74, 6.92 (s, 2H), 6.92, 7.03 (d, 2H, J = 10.3 Hz); HRMS calcd for $C_{20}H_{18}NO_5F_3$ (M^+) 409.1137, found 409.1137. Anal. Calcd for $C_{20}H_{18}NO_5F_3$: C, 58.68; H, 4.43; N, 3.42. Found: C, 58.64; H, 4.48; N, 3.43.

2-(Trifluoroacetyl)-8-hydroxy-7-methoxy-2,3,4,5-tetrahydro-1*H*-[2]benzazepine-5-spiro-1′-cyclohexa-2′,5′-dien-4′-one (2o). Reactants: **1o** (22.1 mg, 0.0598 mmol) in CF_3CH_2OH (0.75 mL); PIFA (28.3 mg, 0.0658 mmol) in CF_3CH_2OH (0.5 mL). **2o** (4.1 mg, 19%): off-white amorphous powder; IR 1690, 1665, 1620; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.35−2.43 (m, 2H), 3.75, 3.76 (s, 3H), 3.89−3.97 (m, 2H), 4.74, 4.77 (s, 2H), 5.58, 5.60 (s, 1H), 6.31, 6.32 (d, 2H, J = 10.2 Hz), 6.51 (s, 1H), 6.74, 6.91 (s, 1H), 6.94, 7.05 (d, 2H, J = 10.2 Hz); HRMS calcd for $C_{18}H_{16}NO_4F_3$ (M^+) 367.1032, found 367.1007.

***N*-[2-[1-(Acetylamino)-4-oxo-2,5-cyclohexadienyl]ethyl]-*N*-(3,4-dimethoxybenzyl)trifluoroacetoamide (3a).** Reactants: **1a** (22.7 mg, 0.0592 mmol) in CH_3CN (1 mL); PIFA (28.0 mg, 0.0651 mmol). **3a** (6.8 mg, 27%): colorless amorphous powder; IR 3350, 1690, 1673, 1628; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.84−1.90, 2.04−2.38 (m, 2H), 1.98, 2.00 (s, 3H), 3.20−3.27, 3.31−3.37 (m, 2H), 3.87, 3.88, 3.90 (s, 6H), 4.53 (s, 2H), 6.25, 6.31 (d, 2H, J = 10.2, 9.9 Hz), 6.68 (s, 1H), 6.74, 6.91 (d, 2H, J = 10.2, 9.9 Hz), 6.79, 6.86 (d, 2H, J = 7.9 Hz); ^{13}C NMR (68.7 MHz, $CDCl_3$) δ 23.5, 36.5, 42.0, 51.9, 54.5, 56.0, 110.5, 111.3, 120.5, 125.9, 129.3, 130.0, 147.0, 149.2, 149.5, 149.6, 170.1, 184.7; HRMS calcd for $C_{21}H_{23}N_2O_5F_3$ (M^+) 440.1559, found 440.1566.

(3*S*)-(+)-Methyl 2-(Trifluoroacetyl)-7,8-dimethoxy-4′-oxo-2,3,4,5-tetrahydro-1*H*-[2]benzazepine-5′-spiro-1′-cyclohexa-2′,5′-diene-3-carboxylate (7). Reactants: **6** (22.0 mg, 0.0498 mmol) in CF_3CH_2OH (0.75 mL); PIFA (23.6 mg, 0.0548 mmol) in CF_3CH_2OH (0.5 mL). **7** (13.9 mg, 64%): colorless solid; mp 176−179 °C (from Et_2O−*n*-hexane): IR 1750, 1690, 1667, 1626; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.42 (dd, 1H, J = 14.9, 4.6 Hz), 2.85 (dd, 1H, J = 14.6, 13.4), 3.71, 3.73 (s, 3H), 3.80, 3.82 (s, 3H), 3.89, 3.90 (s, 3H), 4.75 (d, 1H, J = 17.5 Hz), 4.94 (d, 1H, J = 17.5 Hz), 5.11 (dd, 1H, J = 13.5, 4.6 Hz), 6.29, 6.39 (dd, 2H, J = 10.2, 9.9, 2.0, 1.7 Hz), 6.46, 6.49, 6.62 (s, 2H), 6.77, 6.94 (dd, 2H, J = 10.2, 9.9, 3.3, 3.0 Hz).

Spirocyclization of Silylated Compounds (8a and 8b) with PIFA. Reactants: **8a** (61.2 mg, 0.134 mmol) in CF_3CH_2OH (2 mL); PIFA (63.6 mg, 0.148 mmol) at rt. **2a** (29.3 mg, 57%); Reactants: **8b** (29.1 mg, 0.0585 mmol) in CF_3CH_2OH (1.2 mL); PIFA (27.7 mg, 0.0643 mmol) at rt. **2a** (14.8 mg, 66%).

11-(*tert*-Butyldiphenylsiloxy)-6-(trifluoroacetyl)-2,3-dimethoxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (9c). Reactants: **8c** (49.9 mg, 0.0803 mmol) in CF_3CH_2OH (1.5 mL); PIFA (38.0 mg, 0.0883 mmol) at rt. **9c** (6.0 mg, 12%) and **2a** (7.1 mg, 23%). **9c**: colorless solid; mp 213−214 °C (from Et_2O); IR 1690; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (s, 9H), 2.31 (dd, 1H, J = 14.5, 10.3 Hz), 2.89 (dd, 1H, J = 14.5, 6.8 Hz), 3.14 (dd, 1H, J = 14.5, 10.3 Hz), 3.22 (d, 1H, J = 13.7 Hz), 3.75 (s, 3H), 3.90 (s, 3H), 4.20 (dd, 1H, J = 14.5, 6.8 Hz), 5.12 (d, 1H, J = 13.7 Hz), 6.41 (s, 1H), 6.66 (d, 1H, J = 2.6 Hz), 6.81 (dd, 1H, J = 8.6, 2.6 Hz), 6.98 (d, 1H, J = 7.7 Hz), 7.33−7.42 (m, 7H), 7.70−7.74 (m, 4H); HRMS calcd for $C_{35}H_{36}NO_4F_3Si$ (M^+) 619.2366, found 619.2340.

11-(Benzyloxy)-6-(trifluoroacetyl)-2,3-dimethoxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (9d). Reactants: **8d** (79.7 mg, 0.168 mmol) in CF_3CH_2OH (2 mL); PIFA (79.6 mg, 0.185 mmol) at rt. **9d** (38.1 mg, 48%): colorless solid; mp 134−136 °C (from Et_2O); IR 1686; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.40 (dd, 1H, J = 14.9, 10.6 Hz), 2.98 (dd, 1H, J = 14.9, 6.9 Hz), 3.19 (dd, 1H, J = 14.2, 10.6 Hz), 3.31 (d, 1H, J = 13.9 Hz), 3.87 (s, 3H), 3.94 (s, 3H), 4.26 (dd, 1H, J = 13.9, 7.3 Hz), 5.11 (s, 2H), 5.18 (d, 1H, J = 13.5 Hz), 6.76 (s, 1H), 6.94 (d, 1H, J = 2.6 Hz), 7.00 (dd, 1H, J = 8.6, 2.6 Hz), 7.18 (d, 1H, J = 8.3 Hz), 7.31−7.47 (m, 6H). Anal. Calcd for $C_{26}H_{24}NO_4F_3$: C, 66.24; H, 5.13; N, 2.97. Found: C, 66.24; H, 5.17; N, 2.99.

6-(Trifluoroacetyl)-2,3,11-trimethoxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (9e). Reactants: **8e** (27.8 mg, 0.0700 mmol) in CF_3CH_2OH (1 mL); PIFA (33.1 mg, 0.0770 mmol) at rt. **9e** (13.1 mg, 47%): colorless solid; mp 134−136 °C (from AcOEt−*n*-hexane); IR 1686; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.41 (dd, 1H, J = 14.7, 9.7 Hz), 2.99 (dd, 1H, J = 14.7, 7.1 Hz), 3.19 (dd, 1H, J = 14.2, 10.6 Hz), 3.31 (d, 1H, J = 13.9 Hz), 3.85 (s, 3H), 3.90 (s, 3H), 3.94 (s, 3H), 4.26 (dd, 1H, J = 12.7, 6.4 Hz), 5.19 (d, 1H, J = 13.9 Hz), 6.82 (s, 1H), 6.86 (d, 1H, J = 2.6 Hz), 6.93 (dd, 1H, J = 8.6, 2.6 Hz), 7.18 (d, 1H, J = 8.6 Hz), 7.40 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 34.0, 48.4, 48.8, 55.4, 56.0, 112.0, 113.8, 114.0, 115.2, 118.9 (m), 127.1, 130.5, 131.2, 133.0, 140.9, 148.6, 148.8, 156.5 (m), 158.3; HRMS calcd for $C_{20}H_{20}NO_4F_3$ (M^+) 395.1341, found 395.1338. Anal. Calcd for $C_{20}H_{20}NO_4F_3$: C, 60.76; H, 5.10; N, 3.54. Found: C, 60.56; H, 5.07; N, 3.55.

2-(Trifluoroacetyl)-8-methoxy-2,3,4,5-tetrahydro-1*H*-[2]benzazepine-5-spiro-1′-cyclohexa-2′,5′-dien-4′-one (11a). Reactants: **10a** (38.0 mg, 0.109 mmol) in CF_3CH_2OH (1 mL); PIFA (51.6 mg, 0.120 mmol) in CF_3CH_2OH (1 mL). **11a** (16.4 mg, 43%): colorless solid; mp 149−150 °C (from Et_2O−CH_2Cl_2); IR 1694, 1669, 1620; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.36−2.42 (m, 2H), 3.80 (s, 3H), 3.93−3.99 (m, 2H), 4.80, 4.84 (s, 2H), 6.29, 6.30 (d, 2H, J = 9.8, 10.3 Hz), 6.72−7.04 (m, 3H), 6.92, 7.04 (d, 2H, J = 10.3 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 33.9, 35.9, 44.3, 45.4, 45.5, 47.8, 48.1, 49.0, 49.2, 49.3, 55.3, 113.6, 114.0, 116.0, 116.3 (q, J = 278 Hz), 116.7, 127.0, 127.1, 127.7, 131.1, 131.6, 136.6, 152.5, 152.8, 156.7 (q, J = 37 Hz), 158.8, 158.9, 185.2, 185.4; HRMS calcd for $C_{18}H_{16}NO_3F_3$ (M^+) 351.1083, found 351.1084. Anal. Calcd for $C_{18}H_{16}NO_3F_3$: C, 61.54; H, 4.59; N, 3.99. Found: C, 61.33; H, 4.71; N, 3.91.

2-(Trifluoroacetyl)-6-methoxy-2,3,4,5-tetrahydro-1*H*-[2]benzazepine-5-spiro-1′-cyclohexa-2′,5′-dien-4′-one (12a) was obtained by the same method as described above (6.6 mg, 17%) as a colorless solid: mp 135−137 °C (from Et_2O−*n*-hexane); IR 1690, 1663, 1622; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.35−2.41 (m, 2H), 3.58, 3.59 (s, 3H), 3.86−3.95 (m, 2H), 4.86, 4.89 (s, 2H), 6.30 (d, 2H, J = 10.3 Hz), 6.78−6.99 (m, 2H), 6.89, 6.94 (d, 2H, J = 10.3, 10.5 Hz), 7.25, 7.26 (dd, 1H, J = 8.0 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 36.9, 38.2, 44.9, 45.5, 45.6, 47.5, 47.8, 48.1, 49.1, 49.2, 55.7, 55.8, 112.4, 123.2, 124.2, 125.4, 127.6, 129.7, 137.6, 137.7, 154.0, 154.2, 159.6, 159.7, 186.2, 186.3; HRMS calcd for $C_{18}H_{16}NO_3F_3$ (M^+) 351.1083, found 351.1074. Anal. Calcd for $C_{18}H_{16}NO_3F_3$: C, 61.54; H, 4.59; N, 3.99. Found: C, 61.77; H, 4.64; N, 3.98.

Spirocyclization of Compounds 10b. PIFA (41.7 mg, 0.0970 mmol) in CF_3CH_2OH (1 mL) was added to a solution of **10b** (40.0 mg, 0.0882 mmol) in CF_3CH_2OH (1 mL) at −40 °C under nitrogen, and the solution was stirred for 30 min. The solution was concentrated in vacuo, and the residue was purified by preparative TLC to give the mixture of **11b** and **12b** (15.9 mg, 40%), which could not be separated by chromatography. Tetra-*n*-butylammonium fluoride (1.0 M solution in THF, 0.040 mL) was added to the solution of the mixture (16.7 mg, 0.0370 mmol) in THF (1 mL) at 0 °C under nitrogen, and the solution was stirred for 30 min. After removal of the

solvent, a residue was purified by preparative TLC to give **11c** (8.0 mg, 0.0237 mmol) and **13** (3.9 mg, 0.0115 mmol).

2-(Trifluoroacetyl)-8-hydroxy-2,3,4,5-tetrahydro-1*H*-[2]-benzazepine-5-spiro-1′-cyclohexa-2′,5′-dien-4′-one (11c): colorless solid; mp 220−222 °C (from EtOH); IR 3220, 1690, 1686, 1662; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.34−2.40 (m, 2H), 3.93−3.97 (m, 2H), 4.77, 4.80 (s, 2H), 6,29, 6.31 (d, 2H, J = 10.3 Hz), 6.68−6.71 (m, 1.5H), 6.86 (d, 0.5H, J = 2.6 Hz), 6.92, 7.04 (d, 2H, J = 10.3 Hz), 6.95 (d, 1H, J = 8.6 Hz). Anal. Calcd for $C_{17}H_{14}NO_3F_3$: C, 60.54; H, 4.18; N, 4.15. Found: C, 60.31; H, 4.29; N, 4.12.

(±)-7-Demethoxy-*N*-(trifluoroacetyl)narwedine (13): colorless amorphus: IR 1687, 1590; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.09−2.26 (m, 2H), 2.77 (ddd, 1H, J = 18.0, 6.8, 3.4 Hz), 3.10 (d, 1H. J = 18.0 Hz), 3.39 (dd, 0.5H, J = 12.8, 12.0 Hz), 3.73−3.79 (dd, 0.5H, J = 14.5, 13.6 Hz), 4.19 (d, 0.5H, J = 15.4 Hz), 4.37 (d, 0.5H, J = 15.4 Hz), 4.60 (d, 0.5H, J = 16.3 Hz), 4.68 (d, 0.5H, J = 2.6 Hz), 4.77 (d, 0.5H, J = 13.7 Hz), 4.95 (d, 0.5H, J = 16.2 Hz), 5.35 (d, 0.5H, J = 14.5 Hz), 6.07 (dd, 1H, J = 11.1, 10.3 Hz), 6.77−6.78 (d, 2H, J = 8.6 Hz), 6.81 (m, 0.5H), 6.87 (dd, 0.5H, J = 10.3, 1.8 Hz), 6.93 (d, 0.5H, J = 6.8 Hz), 7.16 (d, 1H, J = 7.7 Hz); HRMS calcd for $C_{17}H_{14}NO_3F_3$ (M^+) 337.0926, found 337.0923.

7,8-Dimethoxy-2,3,4,5-tetrahydro-1*H*-[2]benzazepinium-5-spiro-1′-cyclohexa-2′,5′-dien-4′-one Chloride (5). HCl (10%, 5 mL) was added to a solution of **2b** (391.8 mg, 1.02 mmol) in MeOH (10 mL) under ice bath cooling. After the mixture was stirred for 40 min at rt, 10% HCl (5 mL) was added at 0 °C. After an additional 30 min of stirring at rt, 10% HCl (15 mL) was added slowly to the stirred solution for 2 h at rt. After being stirred overnight, the mixture was concentrated and dried in vacuo to give **5** (337.2 mg, quant) as a colorless solid: IR 3382, 2150, 1663; ^{1}H NMR (250 MHz, CD_3OD) δ 2.40 (t, 2H, J = 5.0 Hz), 3.55 (t, 2H, J = 5.0 Hz), 3.75 (s, 3H), 3.87 (s, 3H), 4.55 (s, 2H), 6.34 (d, 2H, J = 9.8 Hz), 6.67 (s, 1H), 7.00 (s, 1H), 7.41 (d, 2H, J = 10.5 Hz).

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