The Efficient Synthesis of Morphinandienone Alkaloids by Using a Combination of Hypervalent Iodine(III) Reagent and Heteropoly Acid

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Abstract: The non-phenolic coupling reaction of benzyltetrahydroisoquinolines (laudanosine derivatives) by using a hypervalent iodine(III) reagent is described. In general, chemical oxidation of laudanosine gives glaucine. In contrast to general chemical oxidizing reagent systems, the novel use of reagent combination of phenyliodine bis(trifluoroacetate) (PIFA), and heteropoly acid (HPA) afforded morphinandienone alkaloids in excellent yields. In order to achieve the coupling reaction with simple reaction procedure, the use of HPA supported on silica gel instead of HPA was demonstrated and sufficient yield was exerted again. The present reagent system, PIFA/HPA, was also applied to the oxidation of other non-phenolic benzyltetrahydroisoquinolines and the high yield conversion to morphinandienones was accomplished.

Keywords: alkaloids · C–C coupling · heteropoly acids · hypervalent iodine reagents · spiro compounds

Introduction

The oxidative coupling reaction of benzyltetrahydroisoquinolines to morphinandienones has received considerable attention for a long time, since the proposal of alkaloid biosynthesis through the oxidative phenolic coupling reaction presented by Barton and Cohen in 1957.[1] A great deal of effort was invested in devising methodology for this purpose and several heavy metal oxidizing reagents such as thallium(III), vanadium(V), iron(III), ruthenium(IV) salts were developed.[1–6] In the early studies, the biomimetic phenolic coupling reaction using chemical oxidants[1b,c,2,3] or some other synthetic methods such as the Pschorr reaction,[1b,4] photochemical coupling reaction,[5] or benzyne reaction,[6] were continually employed. Despite large efforts, the yields of the coupling step were usually low and, in general, these methodologies did not afford practical routes to morphinandienone alkaloids.

However, a notable breakthrough to those low yields was reported by Miller in 1971.[7a] They investigated an electrooxidative method and reported the successful conversion of non-phenolic benzyltetrahydroisoquinoline to morphinandienones.[7,8] Such approaches by using convenient and stable non-phenolic substrates were found to have a significant advantage in the synthesis of morphinandienones or other spirodienone alkaloids.[7,8] Since then, much attention has been focused on the chemical oxidation of non-phenolic substrates toward morphinandienone synthesis.[9,10] Although two types of efficient non-phenolic coupling reactions, one leading to neospirinedienone alkaloids[9] and the other leading to aporphinic alkaloids,[10] have been developed, the transformation into morphinandienones (see for example Figure 1) by using chemical oxidation has not yet been accomplished. In this report, we wish to report the successful high-yield conversion of nonphenolic benzyltetrahydroisoquinoline to morphinandienones by using a combination of hypervalent iodine(III) reagent and heteropoly acid (HPA).

Results and Discussion

Due to the low toxicity, ready availability, easy handling, and their reactivities similar to that of heavy metal reagents, the use of the hypervalent iodine reagent is a dominant method for the oxidative coupling reaction of phenolic derivatives to date.[11] In continuation of our research on the use of hypervalent iodine(III) reagents for organic synthesis, we originally found that the reaction of phenol ethers with some nucleophiles in the presence of phenyliodine bis(trifluoroacetate) (PIFA)/$(CF_3)_2CHOH$ or PIFA/$BF_3{\cdot}Et_2O$ caused nucleophilic substitution reaction.[12] These reactions

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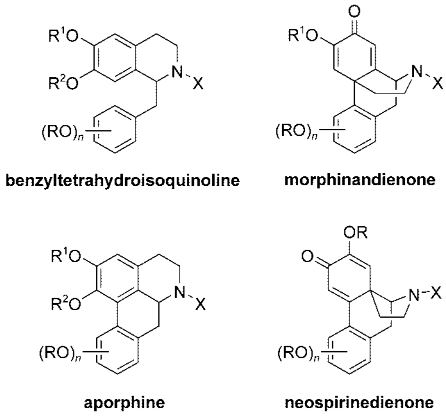


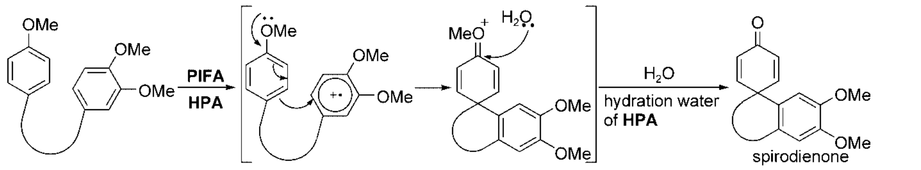
Figure 1. Some important isoquinoline and related alkaloids.

proceed with the formation of a charge-transfer complex of phenol ethers with PIFA, followed by single electron transfer (SET), which leads to aromatic cation radical intermediates.[12a]

Recently, we developed a novel methodology for generating cation radical species using the combination of PIFA and HPA.[13] HPA is a readily available, economical, environmental, easy to handle, and odorless solid acid.[14] Interestingly, under this reagent system, the specific formation of spirodienones was observed in some cases during the investigation of the intramolecular coupling reaction of non-phenolic derivatives (Scheme 1).[13b] This finding prompts us to explore a new efficient procedure to introduce morphinandienones.

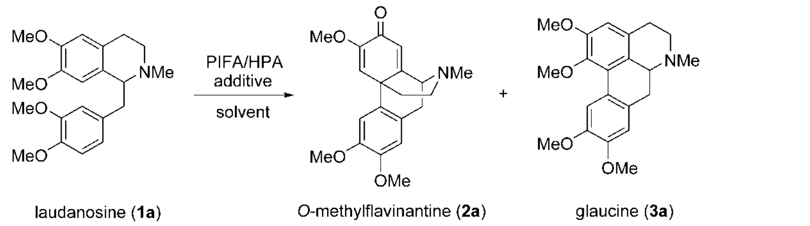
The study was performed on a commercial product, the laudanosine (**1a**) (Table 1). As for the chemical oxidation of **1a** with heavy metals, glaucine (**3a**) was usually obtained in moderate to good yields.[10] Similar to heavy metal oxidation, the reaction of **1a** with PIFA/BF_3·Et_2O in CH_2Cl_2 gave **3a** in 58% yield (entry 1).[12e] On the contrary, application of our prior conditions,[13b] the combination of PIFA and tungsto(IV) phosphoric acid ($H_3[PW_{12}O_{40}]$, ca. 0.25 mol%; 20 mg mL^{-1}) gave neither *O*-methyl flavinantine (**2a**) nor glaucine (**3a**) (entry 2). One possible factor which leads to this undesirable result is the influence of the tertiary amine. It is well known that the basicity of the nitrogen atom can play an important role in the oxidation of tetrahydroisoquinoline derivatives, and deactivation of the nitrogen atom often has an influence on the course of the coupling reaction.[2] To reduce the basicity of the nitrogen atom, the amount of HPA was increased and then the successful synthesis of the morphinandienones (**2a**) was achieved (entries 3, 4). Alternatively, some acid additives[15] to PIFA/$H_3[PW_{12}O_{40}]$ were investigated for the same purpose. In all cases, the dominant formation of **2a** was observed and the exclusive formation of **2a** in excellent yield occurred by using strong acid additive such as BF_3·Et_2O (entry 5). This is the first example to effectively produce morphinandienones by using chemical oxidation. Other commercially available HPAs, such as $H_3[PMo_{12}O_{40}]$, $H_4[SiW_{12}O_{40}]$, and $H_4[SiMo_{12}O_{40}]$, were also examined for this reaction, and all were found to give **2a** in good to excellent yields (entries 6–8). In order to achieve the coupling reaction with simple reaction procedure, the novel use of HPA supported on silica gel, which is prepared by known method,[16] was demonstrated and sufficient yield was exerted (entry 9).

Additionally, the reaction was carried out in the absence of HPA in wet solvent and also afforded **2a**. However, the yield of **2a** decreased and an inseparable mixture was obtained (entries 10, 11). This indicates that the presence of water plays an important role in producing **2a**, and the hy-



Scheme 1. Formation of spirodienones by treatment with PIFA/HPA.

Table 1. Oxidative coupling reaction of laudanosine (**1a**).

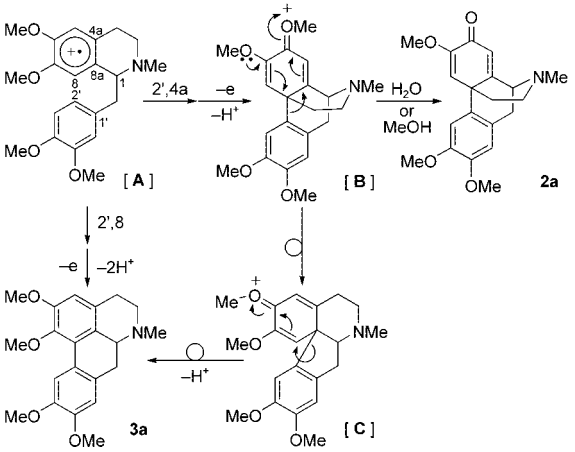


Entry	Additive[a] (5.0 equiv)	HPA[b] [mg mL^{-1}]	Solv.	*T* [°C]	*t* [h]	**2a** [%][c]	**3a** [%][c]
1	BF_3·Et_2O	none	CH_2Cl_2	−40	0.16	–	58
2	none	25 (PW)	CH_3CN	−20 to 0	12	–	–
3	none	100 (PW)	CH_3CN	−20 to 0	1	67	–
4	none	150 (PW)	CH_3CN	−20 to 0	1	70	–
5	BF_3·Et_2O	25 (PW)	CH_3CN	−20 to 0	0.5	90	–
6	BF_3·Et_2O	25 (PMo)	CH_3CN	−20 to 0	0.5	84	–
7	BF_3·Et_2O	25 (SiW)	CH_3CN	−20 to 0	0.5	71	–
8	BF_3·Et_2O	25 (SiMo)	CH_3CN	−20 to 0	0.5	66	–
9	BF_3·Et_2O	PW on SiO_2 (0.3 equiv)[d]	CH_3CN	−20 to 0	0.5	87	–
10	BF_3·Et_2O	none	0.5% H_2O/CH_3CN	−20 to 0	1	41	–
11	BF_3·Et_2O	none	1% MeOH/CH_2Cl_2	−20 to 0	1	41	–

[a] Further additives are given in ref. [15]. [b] PW = $H_3[PW_{12}O_{40}]$; PMo = $H_3[PMo_{12}O_{40}]$; SiW = $H_4[SiW_{12}O_{40}]$; SiMo = $H_4[SiMo_{12}O_{40}]$. [c] Yield of isolated products. [d] PW on SiO_2 = 20 wt% supported on silica gel (see ref. [16]).

dration water of HPA, which is present in the vicinity of the electrophilic site, and has a stabilizing effect on the cation radical species, due to the greater softness of the HPA anion,[17] may cause a preference for efficiently yielding **2a**.

A plausible reaction mechanism leading to **2a** and **3a** is envisaged as follows (Scheme 2). First, SET oxidation of the electron-rich aromatic ring leads to intermediate [**A**]. The formation of **2a** would be introduced by the hydration of the intermediate

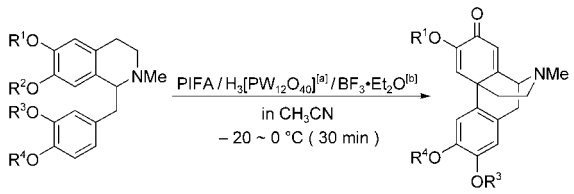


Scheme 2. Possible reaction formation mechanism for **2a** and **3a**.

[**B**]. On the other hand, as for **3a**, there are two possible pathways: direct *o*–*p* coupling[10b] (path a) versus bridgehead *p*–*p* coupling[18] via intermediate [**B**] and [**C**] followed by rearrangement (path b). In view of the isolation of **2a** and the absence of **3a** in entry 11, it seems reasonable to suggest that glaucine **3a** is formed by path b.

The remarkable result obtained in the reaction of laudanosine (**1a**) prompted us to extend our procedure to several morphinandienone syntheses. The benzyltetrahydroisoquinoline derivatives (**1b**–**e**) were prepared according to the reported method.[7b] The oxidation was investigated with PIFA/HPA/BF_3·Et_2O and the high yield conversion to morphinandienone derivatives, such as flavinantine, amurine, and pallidine was accomplished. The present result

Table 2. Syntheses of morphinandienones.



1 2

Substrate	OR^1	OR^2	OR^3	OR^4	Product	Yield [%][c]
1a	OMe	OMe	OMe	OMe	**2a** (*O*-methylflavinantine)	90
1b	OMe	OMe	$-OCH_2O-$		**2b** (amurine)	90
1c	OBn	OMe	OMe	OMe	**2c**	76
1d	OMe	OBn	OMe	OMe	**2d**	85
1e	OMe	OMe	OBn	OMe	**2e** (*O*-benzylpallidine)	79
1f	OMe	OMe	OMe	OBn	**2f** (*O*-benzylflavinatine)	82

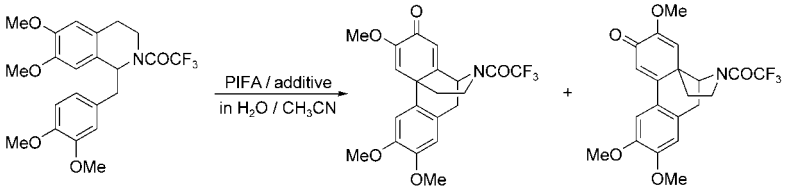
[a] 25 mg mL^{-1}. [b] 5 equiv. [c] Yield of isolated products.

listed in Table 2 clearly showed much preference to previous reports.[1–6,7b]

On the other hand, the oxidation of *N*-protected benzyltetrahydroisoquinoline derivatives, *N*-trifluoroacetylnorlaudanosine (**1g**), was also investigated (Table 3). When the reaction was carried out with PIFA/BF_3·Et_2O, the formation of neospirinedienone (**4**) was observed, similar to heavy metal oxidation (entry 1).[9b] On the contrary, the use of novel reagent combination, PIFA/HPA, afforded *N*-trifluoroacetylnorsebiferine (**2g**) and dominant formation of **2g** occurred in wet acetonitrile (entry 3). It is noteworthy that the reaction proceeds under such mild reaction conditions with a simple experimental protocol. In order to determine the effects of water, the PIFA/HPA mediated reactions were carried under anhydrous conditions and exclusive formation of **4** were encountered. We also carried out the reaction with PIFA/BF_3·Et_2O in wet acetonitrile and formation of **2g** was observed (entry 5). These results therefore suggest that the presence of water in the reaction medium plays an important role in its selectivity.

A plausible reaction mechanism leading to **2g** and **4** is envisaged as follows (Scheme 3). Initial SET oxidation of the aromatic ring reads to intermediate [**D**]. Nucleophilic cap-

Table 3. Oxidative coupling reaction of *N*-trifluoroacetylnorlaudanosine (**1a**).

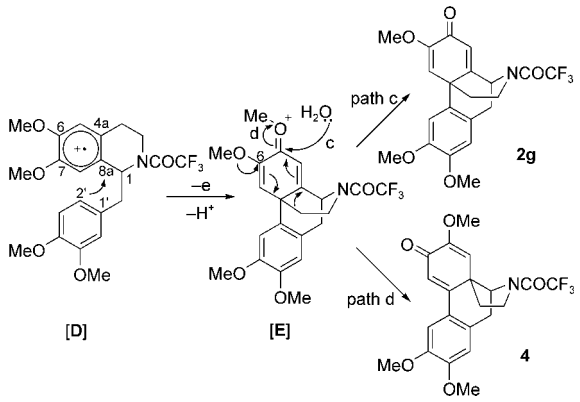


1g 2g 4

Entry	Additive	H_2O	*T* [°C]	*t* [h]	**2g** [%][a]	**4** [%][a]
1	BF_3·Et_2O[d]	none	–40 to 0	0.5	0	90
2	$H_3[PW_{12}O_{40}]$[b]	none	–20 to 0	0.5	63	32
3	$H_3[PW_{12}O_{40}]$[b]	2.5 %	–20 to 0	1	84	9
4	$H_3[PW_{12}O_{40}]$[b]/$(CF_3CO)_2O$[c]	none	–20 to 0	0.5	0	90
5	BF_3·Et_2O[d]	2.5 %	0 to RT	3	43	13

[a] Yield of isolated products. [b] ca. 30 mol %. [c] 4 equiv. [d] 2 equiv.

ture of [**D**] by the second aromatic ring gives intermediate [**E**]. The formation of [**E**] into **2g** occurs through the nucleophilic addition of H_2O (path c), while **4** is formed by rearrangement of [**E**] via path d.



Scheme 3. Possible reaction formation mechanism for **2g** and **4**.

Conclusion

The efficient and useful synthesis of morphinandienone alkaloids upon treatment with a combination of hypervalent iodine(III) reagent and heteropoly acid was accomplished. This high yielding conversion using less toxic reagent systems with simple reaction procedure may find several advantages for application to the synthesis of morphine types of skeletons and many other types of spirodienone alkaloids. Further applications along these lines are now in progress.

Experimental Section

All melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. All NMR spectra were recorded in $CDCl_3$ with either TMS or residual $CHCl_3$ as the internal standard. IR absorption spectra were recorded as KBr pellets. UV spectra were taken on a SHIMADZU 2200 UV/Vis spectrometer. Aluminum oxide 60 (basic, Merck) and silica gel 60N (Kanto Chemical Company) were used for column chromatography. The organic layer was dried with anhydrous $MgSO_4$ or Na_2SO_4. PIFA is commercially available. $H_3[PW_{12}O_{40}]$ and $H_3[PMo_{12}O_{40}]$ were Kanto Chemical Company products. $H_4[SiW_{12}O_{40}]$, Montmorillonite K10, and Nafion NR50 (beads) were purchased from Aldrich. $H_4[SiMo_{12}O_{40}]$ was purchased from Wako Pure Chemical Industries. Compound **1a** is commercially available. Compounds **1b–g** were prepared by known methods.[7b] ^{1}H NMR and ^{13}C NMR spectra of the amide compounds **2g** and **4** exhibited the presence of two rotamers.[7d,21]

Typical coupling procedure leading to morphinandienone derivatives 2 by treatment with PIFA/HPA: HPA (2.8 g), PIFA (1.26 g, 2.94 mmol) and $BF_3{\cdot}Et_2O$ (1.4 mL, 11.2 mmol) were added at −20 °C to a stirred solution of laudanosine (**1a**, 1.00 g, 2.80 mmol) in CH_3CN (112 mL). Stirring was continued for 60 min at −20 to 0 °C. The solution was diluted with 10% Et_3N/EtOAc and then quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc and washed with brine. The organic extract was concentrated and the residue was purified by column chromatography on silica gel (EtOAc/Et_3N 20:1) to afford the *O*-methyl flavinantine (**2a**). The other laudanosine derivatives **1** were examined by a similar procedure by using 1.00 mmol of **1**.

Coupling procedure leading to *O*-methyl flavinantine (sebiferine) (2a) by treatment with PIFA/HPA supported on silica gel: HPA (20 wt% supported on silica gel) (500 mg), PIFA (43.0 mg, 0.10 mmol) and $BF_3{\cdot}Et_2O$ (63 μL, 0.50 mmol) were added at −20 °C to a stirred solution of laudanosine (**1a**, 35.7 mg, 0.10 mmol) in CH_3CN (4.0 mL). Stirring was continued for 30 min at −20 to 0 °C. The solution was filtered through a pad of alumina. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (EtOAc/Et_3N 20:1) to afford the *O*-methyl flavinantine (sebiferine) (**2a**, 29.6 mg, 87%).

***O*-Methyl flavinantine (sebiferine) (2a)**:[7b,19b,19d,20,21] Colorless solid; m.p. 162–163 °C (lit. [19d] 112–113 °C; lit. [19b] 158–160 °C; lit. [20] 161–162 °C); ^{1}H NMR: δ = 1.81–1.96 (m, 2H; CH_2), 2.45 (s, 3H; NMe), 2.56–2.59 (m, 2H; CH_2), 3.03 (dd, J = 18.0, 6.0 Hz, 1H; CH_2), 3.33 (d, J = 18.0 Hz, 1H; CH_2), 3.68 (d, J = 6.0 Hz, 1H; CH), 3.79 (s, 3H; OMe), 3.85 (s, 3H; OMe), 3.87 (s, 3H; OMe), 6.31 (s, 1H; ArH), 6.35 (s, 1H; ArH), 6.62 (s, 1H; ArH), 6.80 (s, 1H; ArH); ^{13}C NMR: δ = 32.6, 41.1, 41.7, 42.2, 45.7, 55.1, 55.9, 56.3, 60.8, 108.6, 110.4, 118.8, 122.2, 128.7, 130.0, 148.0, 148.3, 151.4, 161.7, 180.9; IR (KBr): $\tilde{\nu}$ = 1668, 1643, 1620 cm^{-1}; UV: λ_{max} (EtOH) = 283, 239 nm; HRMS-EI: *m/z*: calcd for $C_{20}H_{23}NO_4$: 341.1627; found: 341.1626; MS: *m/z* (%): 341 (100) [M^+]; elemental analysis calcd (%) for $C_{20}H_{23}NO_4$: C 70.36, H 6.79, N 4.10; found: C 70.20, H 6.86, N 4.05.

Amurine (2b):[7b,19b,19d,21] Colorless solid; m.p. 174 °C (lit. [21] 205–206 °C); ^{1}H NMR: δ = 1.73–1.94 (2H, m; CH_2), 2.45 (s, 3H; NMe), 2.49–2.59 (m, 2H; CH_2), 2.99 (dd, J = 17.7, 6.0 Hz, 1H; CH_2), 3.30 (d, J = 17.7 Hz, 1H; CH_2), 3.66 (d, J = 6.0 Hz, 1H; CH), 3.79 (s, 3H; OMe), 5.91 (s, 1H; OCH_2O), 5.95 (s, 1H; OCH_2O), 6.29 (s, 1H; ArH), 6.31 (s, 1H; ArH), 6.61 (s, 1H; ArH), 6.83 (s, 1H; ArH); ^{13}C NMR: δ = 33.0, 41.3, 41.7, 42.5, 45.7, 55.1, 60.8, 101.2, 105.1, 107.5, 118.7, 121.2, 129.6, 131.0, 146.8, 146.9, 151.4, 161.4, 180.9; IR (KBr): $\tilde{\nu}$ = 1668, 1643, 1618 cm^{-1}; UV: λ_{max} (EtOH) = 286, 246 nm; HRMS-EI: *m/z*: calcd for $C_{19}H_{19}NO_4$: 325.1314; found: 325.1314; MS: *m/z* (%): 325 (100) [M^+].

2,3-Dimethoxy-6-benzyloxymorphinandienone (2c):[7b] Colorless solid; m.p. 187–189 °C (lit. [7b] 227 °C); ^{1}H NMR: δ = 1.71–1.93 (m, 2H; CH_2), 2.45 (s, 3H, NMe), 2.53–2.55 (m, 2H; CH_2), 3.01 (dd, 1H, J = 17.7, 6.0 Hz; CH_2), 3.31 (d, J = 17.7 Hz, 1H; CH_2), 3.63 (s, 3H; OMe), 3.67 (d, J = 6.0 Hz, 1H; CH), 3.83 (s, 3H; OMe), 5.04 (d, J = 12.9 Hz, 1H; CH_2), 5.24 (d, J = 12.9 Hz, 1H; CH_2), 6.34 (s, 1H; ArH), 6.36 (s, 1H; ArH), 6.39 (s, 1H; ArH), 6.59 (s, 1H; ArH), 7.30–7.44 (m, 5H; ArH); ^{13}C NMR: δ = 32.6, 41.0, 41.7, 42.4, 45.5, 55.8, 56.1, 60.8, 70.0, 108.2, 110.2, 122.0, 122.4, 126.7 (2C), 128.0, 128.5, 128.7 (2C), 129.7, 136.3, 147.9, 148.2, 150.0, 161.2, 181.1; IR (KBr): $\tilde{\nu}$ = 1666, 1643, 1620 cm^{-1}; HRMS-EI: *m/z*: calcd for $C_{26}H_{27}NO_4$: 417.1940; found: 417.1936; MS: *m/z* (%): 417 (15) [M^+], 326 (41), 298 (38), 91 (100).

***O*-Benzylpallidine (2e)**:[4c,7b,22] Colorless solid; m.p. 173 °C (lit. [22] 165–167 °C; lit. [4c] 224–225 °C); ^{1}H NMR: δ = 1.82–1.97 (m, 2H; CH_2), 2.45 (s, 3H; NMe), 2.56–2.58 (m, 2H; CH_2), 2.99 (dd, J = 17.7, 5.7 Hz, 1 H: CH_2), 3.29 (d, J = 17.7 Hz, 1H; CH_2), 3.67 (d, J = 5.7 Hz, 1H; CH), 3.81 (s, 3H; OMe), 3.89 (s, 3H; OMe), 5.1 (s, 2H; CH_2), 6.31 (s, 1H; ArH), 6.36 (s, 1H; ArH), 6.67 (s, 1H; ArH), 6.84 (s, 1H; ArH), 7.30–7.44 (m, 5H; ArH); ^{13}C NMR: δ = 32.7, 40.8, 41.4, 42.2, 45.5, 55.1, 56.6, 60.7, 71.0, 109.5, 112.9, 118.7, 122.6, 127.3 (2C), 128.0, 128.5, 128.6 (2C), 130.5, 136.7, 147.7, 148.7, 151.4, 180.8; IR (KBr): $\tilde{\nu}$ = 1666, 1643, 1620 cm^{-1}; HRMS-EI: *m/z*: calcd for $C_{26}H_{27}NO_4$: 417.1940; found: 417.1942; MS: *m/z* (%): 417 (66) [M^+], 91 (100).

***O*-Benzylflavinantine (2f)**:[4b,7b,22] Colorless solid; m.p. 173–176 °C (lit. [22] 142–144 °C; lit. [7b] 203–204 °C; lit. [4b] 208–210 °C); ^{1}H NMR: δ = 1.81–1.92 (m, 2H; CH_2), 2.45 (s, 3H; NMe), 2.52–2.55 (m, 2H; CH_2), 3.00 (dd, J = 18.0, 6.6 Hz, 1H; CH_2), 3.33 (d, J = 18.0 Hz, 1H; CH_2), 3.62 (s, 3H; OMe), 3.64 (d, J = 6.6 Hz, 1H; CH), 3.88 (s, 3H; OMe), 5.12 (d, J = 12.6 Hz, 1H; CH_2), 5.20 (d, J = 12.6 Hz, 1H; CH_2), 6.08 (s, 1H; ArH), 6.29 (s, 1H; ArH), 6.65 (s, 1H; ArH), 6.75 (s, 1H; ArH), 7.30–7.44 (m, 5H; ArH); ^{13}C NMR: d = 32.6, 41.3, 41.7, 42.1, 45.7, 55.0, 56.0, 60.8, 72.0, 110.8, 112.5, 118.6, 122.2, 127.1 (2C), 128.0, 128.6 (2C), 129.6, 129.9, 137.3, 146.9, 149.1, 151.3, 161.6, 180.9; IR (KBr): $\tilde{\nu}$ = 1666, 1643, 1616 cm^{-1}; HRMS-EI: *m/z*: calcd for $C_{26}H_{27}NO_4$: 417.1940; found: 417.1941; MS: *m/z* (%): 417 (66) [M^+], 91 (100).

Procedure for the preparation of glaucine (3a): PIFA (43.0 mg, 0.10 mmol) and $BF_3{\cdot}Et_2O$ (63 μL, 0.50 mmol) were added at −20 °C to a stirred solution of laudanosine (**1a**, 35.7 mg, 0.10 mmol) in CH_2Cl_2 (4.0 mL). Stirring was continued for 30 min at −20 to 0 °C. The solution was diluted with CH_2Cl_2 and then quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 and washed with brine.

The organic extract was concentrated and the residue was purified by column chromatography on silica gel (hexane/EtOAc/Et_3N 20:10:1) to afford glaucine (**3a**, 20.6 mg, 58%).

Glaucine (3a):[9a,19b,23] Colorless solid; m.p. 134–137°C (lit. [23] 111–113°C; lit. [19b] 136–138°C; lit. [9a] 137–139°C); ^{1}H NMR: δ = 2.50–2.55 (m, 1H; CH_2), 2.57 (s, 3H; NMe), 2.58–2.70 (m, 1H; CH_2), 3.00–3.43 (m, 5H; CH, CH_2, CH_2), 3.65 (s, 3H; OMe), 3.89 (s, 3H; OMe), 3.90 (s, 3H; OMe), 3.93 (s, 3H; OMe), 6.59 (s, 1H; ArH), 6.78 (s, 1H; ArH), 8.09 (s, 1H; ArH); ^{13}C NMR: d = 29.0, 29.3, 34.5, 44.1, 53.3, 55.7, 55.8, 60.1, 62.5, 110.3, 110.7, 111.5, 124.7, 126.9, 127.2, 128.9, 129.3, 144.3, 147.4, 147.9, 151.8; IR (KBr): $\tilde{\nu}$ = 1597 cm^{-1}.

Procedure for the oxidative coupling reaction of *N*-trifluoroacetyl norlaudanosine by treatment with PIFA/HPA: HPA (100 mg) and PIFA (43.0 mg, 0.10 mmol) were added at −20°C to a stirred solution of **1g** (0.10 mmol) in 2.5% H_2O/CH_3CN (4.0 mL). Stirring was continued for 60 min at −20 to 0°C. The solution was dilute with AcOEt and filtered through a pad of alumina. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (hexane/EtOAc/Et_3N 10:15:0.5) to afford *N*-trifluoroacetylnorsebiferine (**2g**) and *N*-trifluoroacetylneospirinedioenone (**4**).

Procedure for the oxidative coupling reaction of *N*-trifluoroacetylnorlaudanosine by treatment with PIFA/BF_3·Et_2O: PIFA (43.0 mg, 0.10 mmol) and BF_3·Et_2O (25 μL, 0.20 mmol) were added at −20°C to a stirred solution of **1g** (0.10 mmol) in CH_3CN (4.0 mL). Stirring was continued for 30 min at −20 to 0°C. The solution was diluted with EtOAc and then quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc and washed with brine. The organic extract was concentrated and the residue was purified by column chromatography on silica gel (hexane/EtOAc/Et_3N 10:15:0.5) to afford the *N*-trifluoroacetyl neospirinedioenone (**4**).

Procedure for the oxidative coupling reaction of *N*-trifluoroacetyl norlaudanosine by treatment with PIFA/HPA/$(CF_3CO)_2O$: HPA (100 mg) and PIFA (43.0 mg, 0.10 mmol) was added at −20°C to a stirred solution of **1g** (43.9 mg, 0.10 mmol) in 1.0% $(CF_3CO)_2O/CH_3CN$ (4.0 mL). Stirring was continued for 30 min at −20 to 0°C. The solution was diluted with EtOAc and then quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc and washed with brine. The organic extract was concentrated and the residue was purified by column chromatography on silica gel (hexane/EtOAc/Et_3N 10:15:0.5) to afford the *N*-trifluoroacetylneospirinedioenone (**4**).

***N*-trifluoroacetylnorsebiferine (2g)**:[7d,21,24] Colorless solid; m.p. 182–183°C (lit. [21] 203–204°C; lit. [24] 179.4–181.5°C); ^{1}H NMR: δ = 1.79–2.09 (m, 2H; CH_2), 2.89–3.29 (m, 3H; CH, CH_2), 3.44, 4.45 (2×dd, J =, 18.3, 5.7, 14.1, 5.4 Hz, total 1H; CH_2), 3.81 (s, 3H; OMe), 3.86 (s, 3H; OMe), 3.90 (s, 3H; OMe), 4.99, 5.60 (each d, J = 5.4, 5.7 Hz, total 1H; CH), 6.36, 6.37 (each s, total 1H; ArH), 6.41 (s, 1H; ArH), 6.62 (s, 1H; ArH), 6.84 (s, 1H; ArH); ^{13}C NMR: δ (major) = 37.9, 39.5, 41.6, 42.2, 52.0, 55.2, 55.9, 56.4, 108.7, 110.8, 117.4, 123.2, 126.7, 128.6, 148.7, 149.0, 151.9, 156.6, 180.1; δ(minor) = 37.0, 38.7, 41.0, 42.1, 52.0, 55.3, 55.9, 56.3, 108.7, 110.5, 117.6, 122.7, 126.4, 128.6, 148.7, 149.0, 151.8, 156.3, 180.1; IR (KBr): $\tilde{\nu}$ = 1649, 1678 cm^{-1}; HRMS-EI: m/z: calcd for $C_{21}H_{20}F_3NO_5$: 423.1293; found: 423.1292; MS: m/z (%): 423.2 (100) [M^+].

***N*-trifluoroacetylneospirinedioenone (4)**:[7d,25] Colorless solid; m.p. 250–251°C (lit. [25] 247–248°C); ^{1}H NMR: δ = 1.94–2.34 (m, 4H; CH_2, CH_2), 2.87, 3.10 (each dd, J = 18.3, 6.3, 17.4, 3.0 Hz, total 1H; CH_2), 3.21, 3.47 (each dd, J = 17.4, 7.2, 18.3, 9.3 Hz, total 1H; CH_2), 3.68, 3.73 (each s, total 3H; OMe), 3.91 (s, 6H; OMe, OMe), 4.49, 4.64 (each dd, J = 9.3, 6.3, 7.2, 3.0 Hz, total 1H; CH), 5.69, 5.83 (each s, total 1H; ArH), 6.60 (s, 1H; ArH), 6.65, 6.76 (each s, total 1H; ArH), 6.98, 7.07 (each s, total 1H; ArH); ^{13}C NMR: δ(major) = 31.7, 41.2, 45.1, 47.4, 55.2, 56.1 (2C), 60.6, 108.0, 111.1, 116.4, 116.2 (J = 287 Hz), 123.7, 125.2, 127.4, 148.7, 151.3, 151.8, 155.9 (J = 37 Hz), 156.8, 180.8; δ (minor) = 33.3, 36.2, 45.0, 48.1, 55.2, 56.0 (2C), 60.7, 107.4, 110.5, 114.4, 116.1 (J = 287 Hz), 122.6, 123.9, 127.0, 148.7, 151.8, 152.1, 154.4, 155.7(J = 37 Hz), 180.7; IR (KBr): $\tilde{\nu}$ = 1639, 1693 cm^{-1}; HRMS-EI: m/z: calcd for $C_{21}H_{20}F_3NO_5$: 423.1293; found: 423.1294; MS: m/z (%): 423.2 (100) [M^+]; elemental analysis calcd (%) for $C_{21}H_{20}F_3NO_5$: C 59.57, H 4.76, N 3.31; found: C 59.34, H 4.79, N 3.32.

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