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Short synthesis of noscapine, bicuculline, egenine, capnoidine, and corytensine alkaloids through the addition of 1-siloxy-isobenzofurans to imines

Maria Del Pilar C. Soriano [a], Nagula Shankaraiah [a,b], Leonardo Silva Santos [a,*]

[a] Laboratory of Asymmetric Synthesis, Chemistry Institute of Natural Resources, Talca University, Talca, PO Box-747, Chile
[b] National Institute of Pharmaceutical Education and Research (NIPER), IDPL Township, Balanagar, Hyderabad 500037, India

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ABSTRACT

A concise diastereotioselective strategy for the synthesis of noscapine, bicuculline, and egenine (**1a**–**c**), as well as capnoidine and corytensine (**2a**,**b**), was developed using diastereoselective addition of 1-siloxy-isobenzofurans **4a** and **4b** to iminium ion **5** in a one-pot approach. The synthesis features the use of imine **13** obtained through Bischler–Napieralsky reaction from amine **11**. The addition of ionic liquids as addictives in the reactions afforded erythro configuration in major adduct compounds. The synthetic route can also be applied in the total synthesis of promising tubulin binding agent EM105 (**3**).

Noscapine (**1a**) is a known antitussive agent, commonly used without significant side effects,[1] and it has been found to bind to tubulin and alter its conformation, properties, and microtubule dynamics.[2] Noscapine presents good oral bioavailability in mice[3] being active against H460 NSCLC cells in nude mice.[4] The analogue EM105 (**3**) shows higher activity than **1a** and regresses breast cancer xenografts in nude mice without significant toxicity.[5] Noscapine and its analogues are thus interesting compounds, and noscapine is under phase I trials by Cougar Biotechnology.[6] On the other hand, *erythro* isomer as bicuculline (**1b**) is also a phthalide isoquinoline isolated by Manske[7] from *Dicentra cucullaria* in 1932 showing a different bioactivity: specific competitive antagonist of GABA.[8] Surprisingly, *threo*-Capnoidine (**2b**) is inactive when compared to *erithro*-**1b** isomer (Fig. 1).[9] GABA (γ-aminobutyric acid) is the major neuroinhibitory neurotransmitter of the central nervous system (CNS) and is likely present in about 60–70% of all CNS synapses.[10] Thus, compounds that posse affinity to the binding site for GABA itself, or allosteric modulatory sites, as the benzodiazepines, barbiturates, picrotoxines, and neurosteroid binding sites have been also pursued in the last years.[11]

These compounds show that chirality in molecules play an enormous role in medicine, and activity is governed by the asymmetry in molecules. However, after great developments in synthetic organic chemistry, there are still few methodologies that allow the selective construction of pre-determined moieties in some classes of compounds. In this context, we have pursued efficient synthetic routes for novel chemotypes when selectivity is required.

Over the last few years 2-trialkylsilyloxyfurans[12] have been used as versatile reagents for the preparation of several enantiomerically pure compounds of biological interest.[13] We have investigated the nucleophilic addition of carbon nucleophiles to cyclic *N*-acyliminium ions and found the relevant role played by the *N*-acyliminium ring size in the stereochemical outcome of the reaction.[14] As studies involving the intermolecular nucleophilic addition of 2-trialkylsilyloxyfurans to cyclic *N*-acyliminium ions

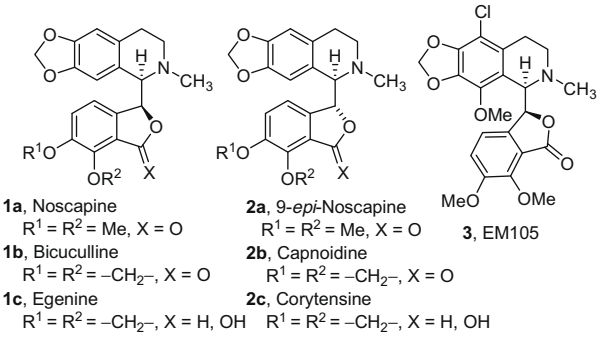

Figure 1. Isoquinoline alkaloids noscapine (**1a**) and its important analogue EM105 (**3**), bicucilline (**1b**), egenine (**1c**), 9-*epi*-noscapine (**2a**), capnoidine (**2b**), and corytensine (**2c**).

* Corresponding author. Tel.: +56 71 201575; fax: +56 71 200448.
E-mail address: lssantos@utalca.cl (L.S. Santos).

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are so far restricted to five-membered *N*-acyliminium ion rings and mainly to *N*-carbobenzyloxy derivatives,[13] we decided to extend these studies to dihydro-carboline iminiums.

As part of our efforts in the field of biologically relevant carbolines, we turned our attention toward an alternative synthetic route for noscapine, figured out through the addition of siloxyfuran **4a** to key iminium intermediate **5**. Recently, we reported an enantioselective total syntheses of arborescidine alkaloids, (−)-quinolactacin B antibiotic, and PDE5 inhibitors.[6] Structurally, **1a** comprises a carboline framework attributing a common quinoline core. The retrosynthetic analysis for the basic framework of **1a** is depicted in Figure 2 and features the diastereoselective addition of 1-siloxy-isobenzofuran **4a** to the iminium ion **5** as the key step. Although demonstrated as a useful synthetic method, these asymmetric additions remain to be fully explored in the arena of total syntheses of alkaloid natural products.

We first explored the syntheses of 1-siloxy-isobenzofurans **4a** and **4b** that were readily available from isovanillin, (**6**, 3-hydroxy-4-methoxybenzaldehyde). Thus, bromobenzaldehyde **7a** was obtained in 76% yield from **6** by bromination of *N*-bromosuccinimide according to a modified procedure from Henry and Sharp.[15] Demethylation of **7a** with $AlC1_3$ and pyridine in CH_2C1_2 afforded **8**.[16] Then, methylenation of **8** with CH_2Br_2 in DMF in the presence of anhydrous KF gave **7b** (Scheme 1).[17] With the bromoaldehydes

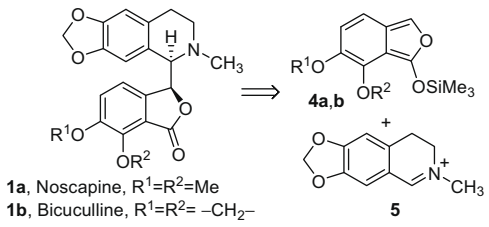
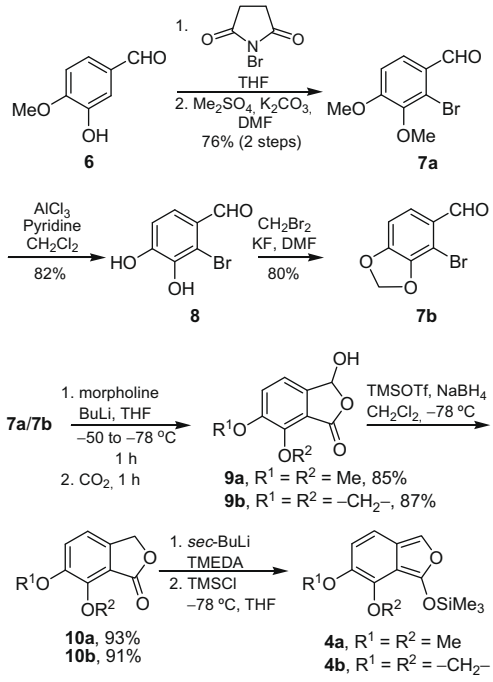


Figure 2. Retrosynthetic analysis for **1a** and **1b** through the addition of siloxyfurans **4a**,**b** to iminium ion intermediate.

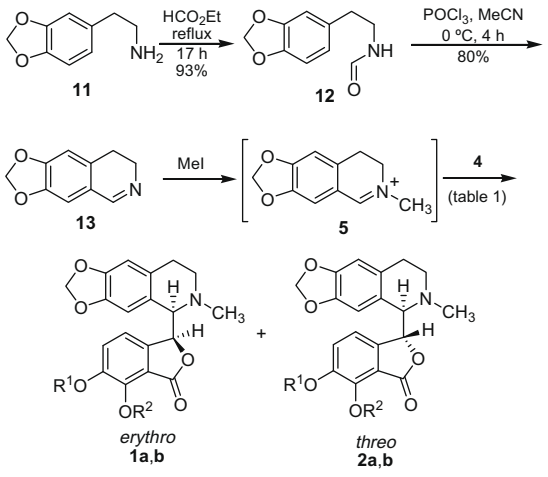


Scheme 1. Synthesis of 1-siloxy-isobenzofurans **4a** and **4b** from 3-hydroxy-4-methoxybenzaldehyde.

7a and **7b**, the next step was accomplished according to a described procedure of Borchardt for protection of aldehydes in situ. Thus, **7a** and **7b**, respectively, reacted with lithium morpholide generated in situ in THF at −50 °C, followed by the addition of BuLi to exchange bromine with lithium, producing the *ortho*-lithiated morpholinoalkoxide intermediate in situ.[18] This step was conducted for 35 min strictly at −80 °C to avoid side reactions. Next, the addition of dry ice (solid CO_2) to morpholinoalkoxide intermediate followed by acidic workup gave **9a** and **9b** in 85% and 87% yield, respectively. Then, oxonion ion derived from **9a**,**b** were generated by TMSOTf at −78 °C, and reduced by $NaBH_4$ to achieve **10a** (93%) and **10b** (91%).[19] Trying to use $NaBH_4$ in EtOH afforded yields of **10a** around 55%. Finally, TMEDA was added to a solution of **10a** (or **10b**) in anhydrous THF at −78 °C, followed by the addition of a cyclohexane solution of *sec*-butyllithium over 30 min and stirring continued at 0 °C for 2 h. Then, trimethylsilyl chloride was added dropwise,[20] stirring was continued at 0 °C for 15 min then at rt for 16 h. The mixture was washed with saturated aqueous $NaHCO_3$, followed by saturated aqueous $CuSO_4$, dried over $MgSO_4$, and concentrated under reduced pressure. The resultant unstable dark orange oils obtained **4a** and **4b** were used without further purifications.

Furthermore, iminium ion **5** was obtained in situ from the addition of CH_3I to imine **13**.[21,22] Imine **13** was obtained by refluxing HCO_2Et with commercially available 3,4-methylenedioxy-phenethylamine **11** affording formamide **12** in 93% yield. Then, Bischler–Napieralski cyclization of **12** with $POCl_3$ in MeCN at 0 °C for 4 h achieving **13** in 80% yield, as depicted in Scheme 2. Having prepared imine **13**, the next stage was set to the model studies for the addition of siloxyfuran **4a** to the iminium ion **5** (Scheme 2, Table 1).

Next, we investigated the scope of the addition of **4a** to imine **13** with and without additives in different conditions (Table 1).[23] The *N*-methyl derivatives synthesized by quarternization of imine **13** with MeI followed by in situ formation of isoquinolinium salt **5** and subsequent addition of nucleophile **4a** in the absence of additives afforded *erythro* isomer in diatereoisomeric ratios ranging from 1.4 to 1.1:1 (*erythro:threo*). The reactions proceeded in reaction times around 30 h in low to moderate yields (45–78%), depending on the nature of the solvents employed (entries 1, 4, and 7 in Table 1). Then, CsF was added to the reactions (entries 2, 5, and 8 in Table 1) and after 12 h of reactions, diastereoselection were obtained favoring *erythro* isomer (1.6–3.1:1, *erythro:threo*). Finally, we tested the addition of butylmethylimidazolinium tetrafluoroborate (BMI·BF_4, entries 3, 6, 9, and 12 in Table 1) as addi-



Scheme 2. Total synthesis of noscapine (*erythro*-**1a**) and 9-epi-noscapine (*threo*-**2a**) by using siloxyfurans **4a** for the addition to iminium ion **5**. Synthesis of bicuculline (*erythro*-**1b**) and capnoidine (*threo*-**2b**) through the addition of **4b**–**5**.

Table 1
Addition of 1-silyloxy-isobenzofuran **4a** to iminium ion derivative **5** derived from imine **13** and MeI

Entry	Solvent	Additive	**1a**:**2a**[a]	Yield[b] (%)
1	CH_2Cl_2	—	1.1:1	45[c]
2	CH_2Cl_2	CsF	1.6:1	65
3	CH_2Cl_2	BMI·BF_4	1.9:1	72
4	MeCN	—	1.2:1	58[c]
5	MeCN	CsF	1.9:1	68
6	MeCN	BMI·BF_4	2:1	70
7	THF	—	1.4:1	50[c]
8	THF	CsF	1.3:1	65
9	THF	BMI·BF_4	3:1	66
10	THF/CH_2Cl_2	—	1.3:1	65[c]
11	THF/CH_2Cl_2	CsF	3:1	78
12	THF/CH_2Cl_2	BMI·BF_4	4:1	75

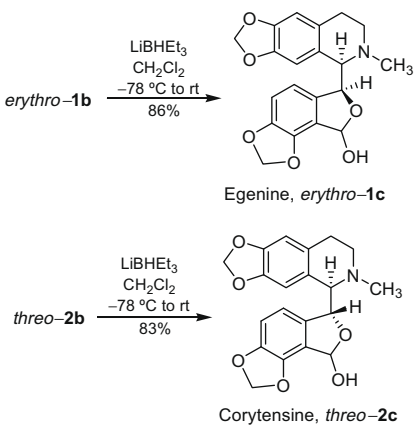
[a] Diastereomeric ratio (dr%) calculated based on HPLC.
[b] Isolated yields. All reactions were performed at −20 °C to 0 °C, 12 h.
[c] Reaction times around 30 h.

tive.[24] The diastereoselectivity of the reaction was not significantly affected by the nature of the solvent, but by the additives (CsF and BMI·BF_4). In fact, in the presence of CsF and BMI·BF_4 the preference for the *erythro* isomer **1a** increased (Table 1), when compared with no additive. The diastereoisomeric ratio of **1a**:**2a** obtained were determined by isolated products and confirmed by HPLC analysis.[25]

Then, the same reaction condition employed in entry 12 (Table 1) was used in the reaction of iminium intermediate **5** with 1-siloxy-isobenzofuran **4b** ($R^1 = R^2 = -CH_2-$). Thus, bicuculline **1b** and capnoidine **2b** were obtained in 65% yield and 3.5:1 *erythro*:*threo* selectivity.[26] Furthermore, reduction of *erythro*-**1b** and *threo*-**2b** with super hydride (LiBHEt$_3$) in CH_2Cl_2 afforded the alkaloids egenine (**1c**), and corytensine (**2c**) in 86 and 83% yield, respectively.[27] The relative configuration at the two newly generated stereogenic centers was established comparing with the reported compounds **1** and **2**. However, it was observed that the relative stereochemistry of compounds **1** and **2** could be deduced principally by comparison of their ^{13}C NMR spectra since it was noted that the ^{13}C chemical shifts of C-5′ and C-9 in the *threo* isomer are, respectively, further downfield and higher upfield than those of the corresponding carbons of the *erythro* isomer (Scheme 3).

The stereochemical outcome of the above-mentioned reaction came to us as not a surprise as previous results with 4-methyl-1-silyloxyfurans, which led us to predict the preferential formation of the *erythro* isomer.[14,28] Additionally, theoretical calculations of the transition state geometries associated with the addition of 1-silyloxy-isobenzofuran **4a** to the iminium ion **5** at DFT level (B3LYP/6-31G*) showed that array A (relative energy: 1.1 kcal mol^{-1}), expected to be the lowest energy transition state, displaying a synclinal approach of the π systems of the nucleophile and iminium ion was higher in energy than array C (relative energy: 0.0 kcal mol^{-1}), as depicted in Figure 3. Transition state C that affords to the lowest energy transition state for the *erythro* isomer with an antiperiplanar arrangement is preferred for the transition state due to an additional secondary orbital interaction. The same analysis can be done for the *threo* energies of transition states (arrays F and E). Martin and coworkers have found a similar result for the transition state calculations (RHF/3-21G*) in the addition of 2-methoxyfuran to five-membered *N*-carbomethoxy-*N*-acyliminium ion.[29] Generally, it is observed *threo* adduct in the addition of siloxyfurans to iminium ions as the major species.[12,14] Although at this point, we are not able to rationalize the reversal of the stereochemical outcome observed when 1-silyloxy-isobenzofuran **4** was employed, the unexpected preference for the *erythro* isomer may be due to the steric hindrance posed by the aromatic rings of the iminium ion and isobensofuran.

In conclusion, we have explored an alternative and efficient route for the synthesis of several isoquinoline alkaloids. The employed method features the use of 1-siloxy-isobenzofuranes **4a** and **4b** to iminium ion **5** to introduce the chirality in products **1a**–**c** and **2a**–**c**. The reductions of **1b** and **2b** were performed using LiBHEt$_3$ affording **1c** and **2c** in good yields. The spectra data of our synthetic compounds, as well as the final products, were in accordance with the described ones.[19,25–27]



Scheme 3.

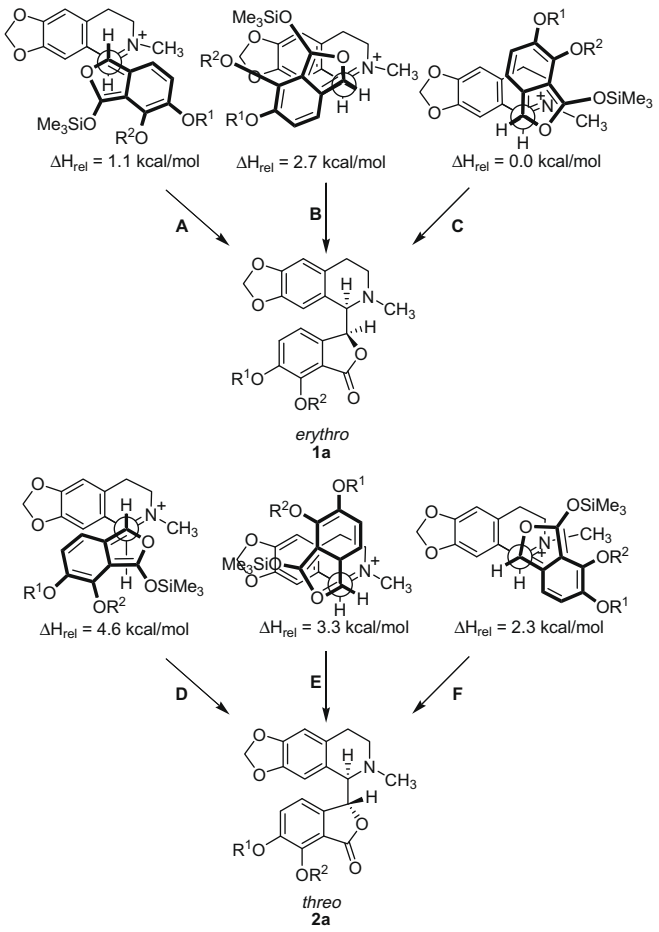


Figure 3. Transition state models for the production of *erythro*-**1a** and *threo*-**2a**.

Acknowledgments

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19. Morpholine (12 mmol) and THF (20.0 mL) were placed in a 100 mL flask, and a solution of the bromoaldehyde (**7a** or **7b**, 10 mmol) in 20.0 mL of THF was placed in a dropping funnel. The mixture in the flask was cooled with stirring to 50 °C, and *n*-butyllithium (1.6 M in hexane, 7.5 mL, 12 mmol) was added all at once. After 5 min, the solution of the aldehyde was added from the dropping funnel over a period of 1 min, and the resulting mixture was cooled to 80 °C over 15 min. *n*-Butyllithium (1.6 M in hexane, 10 mL, 16 mmol) was then added dropwise, keeping the temperature at or below 75 °C. After the addition was over (5 min), the mixture was stirred at 80 °C for 35 min, and then a large excess of solid CO_2 was added at once. After 1 h, the mixture was allowed to reach room temperature and was acidified to pH 1 with 6 M HCl. The solution after dilution with brine was extracted with Et_2O (4 × 30 mL) and then exhaustively with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated in vacuo to give the crude phthalaldehydic acids **9a**,**b**. The crude product was recrystallized from H_2O to give 85% of **9a**: mp 142–145 °C; FTIR (KBr): 3443, 1762, 1605 cm^1; ^1H NMR (400 MHz, acetone-d_6), δ: 3.93 (6H, s), 6.51 (1H, br s), 7.35 (2H, br s). Next, to a stirred solution or suspension of the **9a** (2 mmol) in 15 mL of CH_2Cl_2 and $NaBH_4$ (3.2 mmol) at 78 °C was added TMSOTf (2 mmol) dropwise. The mixture was stirred at 78 °C for 2 h and then at 25 °C for 12 h. Then the mixture was evaporated in vacuo and the residue was treated, diluted with brine, and then exhaustively extracted with CH_2Cl_2. The combined CH_2Cl_2 solutions were washed with brine, dried (Na_2SO_4), and then evaporated in vacuo to give an essentially pure **10a** in 93% yield. Mp 98–100 °C (lit., mp 97–100 °C); FTIR (KBr): 1760 cm^1, ^1H NMR (400 MHz, $CDCl_3$), δ: 3.90 (3H, s), 4.07 (3H, s), 5.22 (2H, s), 7.21 (1H, d, J = 7.8 Hz), 7.47 (1H, d, J 7.8 Hz). Compound **10b** was obtained following the same procedure in 91% yield.
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22. *Imine **4** was synthesized as described by Ref.* 15: yellow solid. ^1H NMR (300 MHz, $CDCl_3$), δ: 2.58–2.72 (2H, m), 3.65–3.74 (2H, m), 6.00 (2H, s), 6.61 (1H, s), 6.74 (1H, s), 8.17 (1H, t, J = 2.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$), δ: 25.2, 47.1, 101.3, 107.6, 108.1, 122.6, 131.8, 146.5, 149.2, 159.5.
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25. *(a) Noscapine (erythro-**1a**) data is in accordance with*: Smula, V.; Cundasawmy, N. E.; Holland, H. L.; MacLean, D. B. *Can. J. Chem.* **1973**, *51*, 32873293. Mp 135–137 °C (lit., mp 136–140 °C). ^1H NMR (400 MHz, $CDCl_3$), δ: 2.21–2.33 (2H, m), 2.42–2.66 (2H, m), 2.55 (3H, s), 2.83–2.95 (1H, m), 3.90 (3H, s), 4.00, (1H, d, J = 3.5 Hz,), 4.05 (3H, s), 5.49 (1H, d, J = 3.5 Hz), 5.89 (2H, s), 6.39 (1H, s), 6.58 (1H, s), 6.52 (1H, d, J = 7.0 Hz), 7.08 (1H, d, J = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 26.7, 44.7, 49.0, 56.7, 62.0, 66.0, 82.7, 100.5, 107.3, 108.1, 117.3, 118.5, 119.4, 124.5, 130.0, 140.4, 145.4, 146.0, 147.5, 152.6, 167.0. HRMS, ESI(+)MS: m/z calcd for $[C_{21}H_{21}NO_6+H]^+$: 384.1447, found: 384.1439. *(b) epi-Noscapine (threo-**2a**) is in accordance with*; Seitanidi, K. L.; Yagudaev, M. R.; Israilov, I. A.; Yunusov, M. S. *Khim. Prirodu. Soedin.* **1978**, 465–471; *Chem. Abstr.* **1979**, *90*, 6585z. Mp 151–153 °C (lit., mp 150–151 °C). ^1H NMR (400 MHz, $CDCl_3$), δ: 2.40–2.81 (3H, m), 2.54 (3H, s), 2.99–3.10 (1H, m), 3.85 (3H, s), 3.99 (3H, s), 4.01, (1H, d, J = 3.4 Hz), 5.53 (1H, d, J = 3.4 Hz), 5.78 (1H, d, J = 1.3 Hz), 5.83 (1H, d, J = 1.3 Hz), 6.37 (1H, s), 6.65 (1H, s), 7.04 (1H, d, J = 8.4 Hz), 7.29 (1H, d, J = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 29.2, 44.9, 51.3, 56.7, 62.2, 66.2, 81.8, 100.7, 107.4, 108.2, 118.1, 118.4, 119.3, 125.3, 130.0, 141.1, 145.8, 146.3, 147.6, 152.3, 168.0. HRMS, ESI(+)MS: m/z calcd for $[C_{21}H_{21}NO_6+H]^+$: 384.1447, found: 384.1455.
26. *(a) Bicuculline (erythro-**1b**) data is in accordance with*: Teitel, S.; O'Brien, J.; Brossi, A. *J. Org. Chem.* **1972**, *37*, 1879–1881. Mp 225–227 °C (lit., mp 227–229 °C). ^1H NMR (400 MHz, $CDCl_3$), δ: 2.23–2.31 (1H, m), 2.51–2.62 (2H, m), 2.83–2.90 (1H, m), 2.54 (3H, s), 4.05 (1H, d, J = 4.3 Hz), 5.56 (1H, d, J = 4.3 Hz), 5.92 (1H, d, J = 1.1 Hz), 6.17 (2H, d, J = 1.7 Hz), 6.19 (1H, d, J = 8.0 Hz), 6.91 (1H, d, J = 8.0 Hz), 6.47 (1H, s), 6.58 (1H, s). HRMS, ESI(+)MS: m/z calcd for $[C_{20}H_{17}NO_6+H]^+$: 368.1134, found: 368.1145. *(b) Capnoidine (threo-**2b**) data is in accordance with Ref. 26a*: mp 202–204 °C (lit., mp 200–203 °C). ^1H NMR (400 MHz, $CDCl_3$), δ: 2.39–2.80 (1H, m), 2.53 (3H, s), 3.01–3.10 (1H, m), 4.04, (1H, d, J = 3.4 Hz), 5.62 (1H, d, J = 3.4 Hz), 5.83 (2H, s), 6.11 (2H, s), 6.40 (1H, s), 6.66 (1H, s), 6.94 (1H, d, J = 8.0 Hz), 7.14 (1H, d, J = 8.0 Hz). HRMS, ESI(+)MS: m/z calcd for $[C_{20}H_{17}NO_6+H]^+$: 368.1134, found: 368.1142.
27. *(a) Egenine* (**1c**): ^1H NMR (400 MHz, $CDCl_3$), δ: 1.75–1.85 (1H, m), 1.96–2.04 (1H, m), 2.35–2.43 (1H, m), 2.50 (3H, s), 2.66–2.75 (1H, m), 3.89 (1H, d, J = 3.5 Hz), 5.41 (1H, d, J = 3.5 Hz), 5.66 (1H, d, J = 7.7 Hz), 5.95 (2H, d, J = 1.2 Hz), 6.02 (2H, d, J = 1.2 Hz), 6.35 (1H, s), 6.52 (1H, d, J = 7.7 Hz), 6.59 (1H, s), 6.81 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 22.3, 44.0, 45.9, 65.0, 87.0, 98.0, 100.9, 101.6, 107.5, 108.4, 108.5, 114.5, 124.0, 124.2, 128.6, 133.1, 141.5, 146.4, 146.7, 148.2. HRMS, ESI(+)MS: m/z calcd for $[C_{20}H_{19}NO_6+H]^+$: 370.1291, found: 370.1299. *(b) Corytensine* (**2c**): ^1H NMR (400 MHz, $CDCl_3$), δ: 1.95 (3H, s), 2.36–2.48 (2H, m), 2.91–2.93 (1H, m), 3.10–3.14 (1H, m), 3.69 (1H, s), 5.25 (1H, s), 5.88 (1H, s), 5.95 (1H, s), 6.05 (1H, s), 6.08 (1H, s), 6.27 (1H, s), 6.60 (1H, s), 6.70 (1H, s), 6.83 (2H, d, J = 8.5). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 29.1, 46.6, 53.8, 68.5, 89.9, 97.6, 100.7, 101.8, 106.7, 108.3, 108.8, 113.9, 124.1, 128.7, 130.5, 135.2, 141.5, 146.0, 146.3, 148.1. HRMS, ESI(+)MS: m/z calcd for $[C_{20}H_{19}NO_6+H]^+$: 370.1291, found: 370.1283.
28. (a) Shono, T.; Hamaguchi, H.; Sasaki, M.; Fujita, S.; Nagami, K. *J. Org. Chem.* **1983**, *48*, 1621–1628; (b) Shono, T.; Miyamoto, T.; Mizukami, M.; Hamaguchi, H. *Tetrahedron Lett.* **1981**, *22*, 2385–2388; (c) Slemon, C. E.; Hellwig, L. C.; Ruder, J.-P.; Hoskins, E. W.; MacLean, D. B. *Can. J. Chem.* **1981**, *59*, 3055–3060.
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