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Formal Synthesis of (±)-Galanthamine and (±)-Lycoramine Using Rh(I)-Catalyzed [(3 + 2) + 1] Cycloaddition of 1-Ene−Vinylcyclopropane and CO

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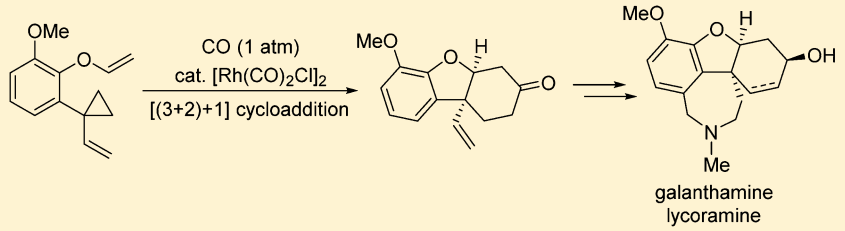
Supporting Information



ABSTRACT: An efficient strategy using Rh(I)-catalyzed [(3 + 2) + 1] cycloaddition of 1-ene−vinylcyclopropane and CO as a key step to build the *cis*-hydrodibenzofuran skeleton has been developed and applied for the formal synthesis of (±)-galanthamine and (±)-lycoramine.

Galanthamine (**1a**)[1,2] is an alkaloid isolated from the bulb of the Amaryllidaceae family with a fascinating tetracyclic structure containing an azepane ring and an all-carbon quaternary stereogenic center (Figure 1). It is a reversible

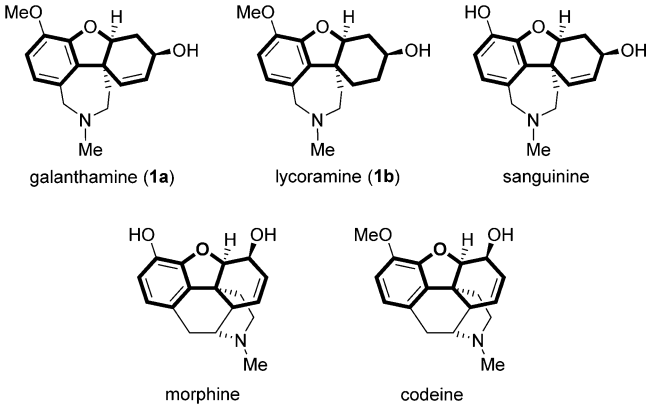


Figure 1. Representative galanthamine-type and morphine-type alkaloids.

and competitive acetylcholine esterase inhibitor[3] and has been used in the early treatment of Alzheimer's disease.[4] The splendid structure and biological activity of galanthamine are two major reasons synthetic chemists have been attracted to the synthesis of galanthamine and its analogues. Many elegant strategies[2,5] have been developed and applied in the synthesis of galanthamine. Development of a new strategy to access galanthamine and its other family members (Figure 1) with similar skeletons and significant biological activities is desirable for target- and function-oriented synthesis. The scarcity of these natural products is another driving force for developing more strategies for the synthesis of these natural products and analogues.

There is a *cis*-hydrodibenzofuran nucleus in galanthamine as well as other galanthamine-type and morphine-type biological alkaloids such as morphine. It is a challenge to form this *cis*-hydrodibenzofuran nucleus with an all-carbon quaternary stereogenic center. Recently, we developed a Rh(I)-catalyzed [(3 + 2) + 1] cycloaddition[6] of 1-ene/yne−vinylcyclopropanes (VCPs) and CO to construct the nucleus such as 5,6- and 6,6-bicyclic systems with this quaternary stereogenic center (Figure 2). The tether atom of the 1-ene/yne−VCP substrates can be

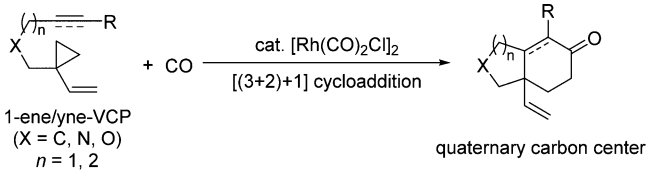


Figure 2. Rh(I)-catalyzed [(3 + 2) + 1] cycloaddition.

nitrogen, oxygen, and carbon. Consequently, the Rh(I)-catalyzed [(3 + 2) + 1] cycloaddition can be employed to construct hetero- and carbo-bicyclic skeletons. The impact of this Rh(I)-catalyzed [(3 + 2) + 1] reaction in synthesis has been demonstrated by us through its use in the total synthesis of agarofuran.[6] Building on our the previous success, we were

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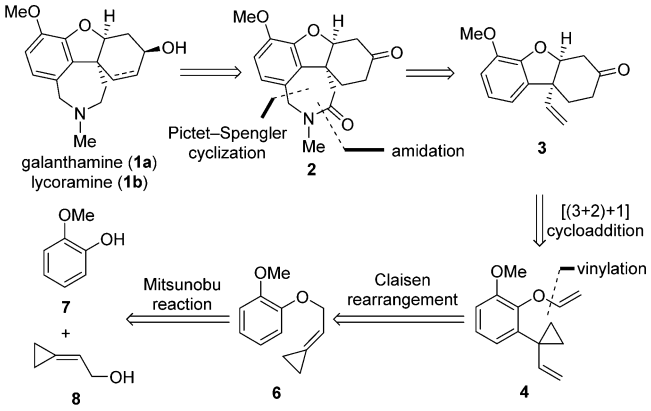
challenged to test whether our [(3 + 2) + 1] reaction can be used to construct the *cis*-hydrodibenzofuran nucleus and to realize the synthesis of galanthamine and lycoramine (Scheme 1). Major concerns were faced in our design stage: one is

Scheme 1. Synthetic Strategy for (±)-Galanthamine and (±)-Lycoramine



whether the tether of the 1-ene/yne−VCP substrate for the Rh-catalyzed [(3 + 2) + 1] reaction can be an aromatic ring; the other is whether the two-carbon unit for the cycloaddition can be an electron-rich enol ether.

Our strategy toward galanthamine and lycoramine is presented in Scheme 1. Galanthamine **1a** and lycoramine **1b** can be synthesized by known procedures[5l,7] from ketone **2** via Saegusa oxidation and reduction, which was reported by Xie and Zhou. Ketone **2** can be offered by traditional alkene functionalization of **3** to synthesize amide, followed by a Pictet−Spengler cyclization to form the seven-membered ring in **2**. The *cis*-hydrodibenzofuran nucleus in **3** can be prepared by Rh(I)-catalyzed [(3 + 2) + 1] cycloaddition from 1-ene−VCP **4**, which is prepared by Claisen rearrangement of **6** and vinylation of the corresponding phenol. Mitsunobu reaction from known compounds phenol **7** and alcohol **8** can be used to synthesize **6**.

The formal synthesis of racemic galanthamine is shown in Scheme 2. The phenol **7** and alcohol **8** underwent Mitsunobu reaction to form ether **6** overnight in 71% yield. Then Claisen rearrangement in naphthane at 188 °C for 3 h transformed **6** to **5** in 89% yield. We used Cu-catalyzed vinylation[8] to convert **5** to the 1-ene-VCP **4** with a reaction yield of 88%. Next, we tried the key Rh-catalyzed [(3 + 2) + 1] cycloaddition[6] of **4** and CO to **3** by using the previous reaction conditions under a balloon-pressured mixed gas of CO and N_2 (the ratio of CO/N_2 is 1/4, and this is usually labeled as 0.2 atm CO), finding that an unidentified byproduct contaminated the target product. When we increased the pressure from 0.2 atm CO to 1 atm CO (using balloon-pressured pure CO gas), the byproduct disappeared. However, the Rh-catalyzed [(3 + 2) + 1] reaction under these conditions needs 4 days to finish (for other conditions, see Table 1). This is not surprising because alkene is more reluctant to participate in the [(3 + 2) + 1] reaction than alkyne.[6] Gratifyingly, we obtained the [(3 + 2) + 1] cycloadduct **3** in 80% yield when we used 9.3 mg of compound **4**. We found that the [(3 + 2) + 1] reaction can be carried out by using 5 mol % catalyst loading using 246 mg of the substrate, but the reaction yield was 64% (entry 4, Table 1). We also attempted this key reaction on gram scale with only 1 mol % of

Scheme 2. Formal Synthesis of (±)-Galanthamine and (±)-Lycoramine

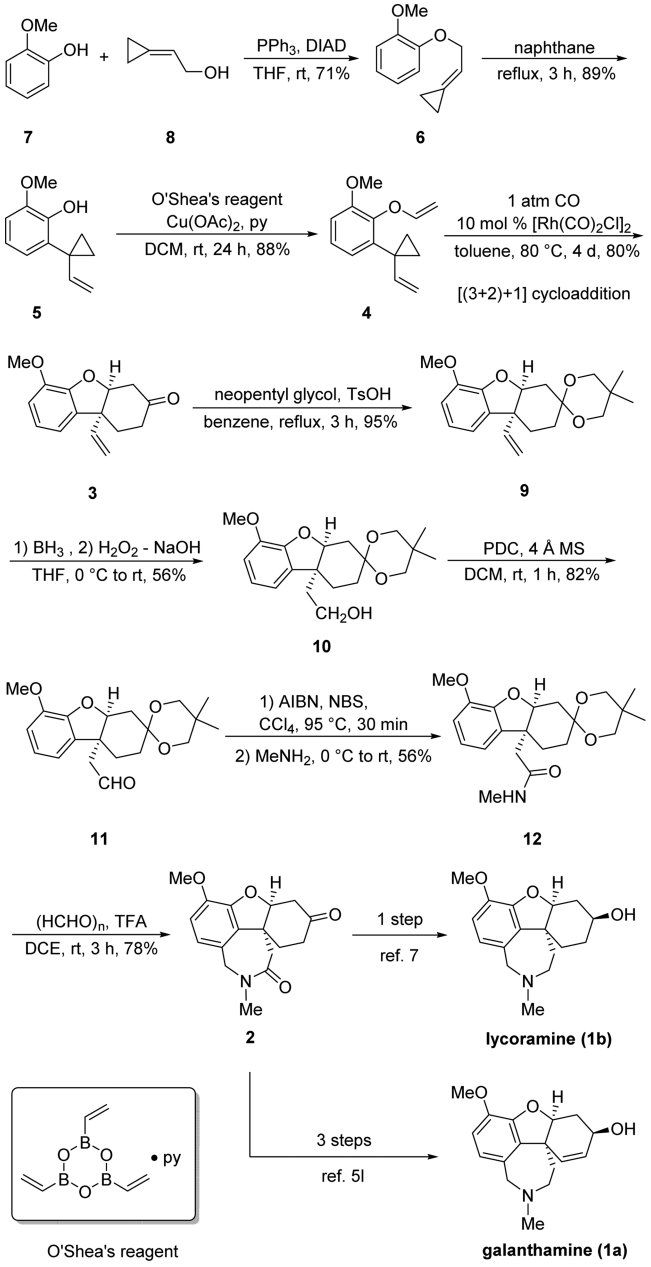


Table 1. $[Rh(CO)_2Cl]_2$-catalyzed [(3 + 2) + 1] Cycloaddition of 4 and CO

entry	starting material	catalyst loading (mol %)	time (d)	yield (%)
1	9.3 mg/0.043 mmol	10	4	80
2	20.2 mg/0.094 mmol	10	4	76
3	152 mg/0.70 mmol	10	4	64
4	246 mg/1.14 mmol	5	6	64
5[a]	1.36 g/6.30 mmol	1 + 1	7 + 7	53

[a]The reaction was carried out by adding 1 mol % of catalyst for 7 days, and then another 1 mol % of catalyst was added to continue the reaction for another 7 days.

catalyst loading, finding that the reaction was slower and another 1 mol % catalyst had to be added to the reaction system to get 53% yield of the target [(3 + 2) + 1] product

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(entry 5, Table 1).[9] Only a single diastereomer was observed in the [(3 + 2) + 1] reaction. This is common for the Rh-catalyzed reaction because the 5/6 bicyclic system often adopts *cis*-alkene insertion into the Rh−C bond of the key rhodacycle intermediate generated by vinylcyclopropane and rhodium catalyst.[10] The stereochemistry of [(3 + 2) + 1] cycloadduct **3** was further confirmed by both 2D NMR of **3** (see Supporting Information) and the synthesis of known compound **2** from **3** (see Scheme 2).

After the *cis*-hydrodibenzofuran nucleus was obtained, we continued to work on the azepane ring formation. At first, we protected carbonyl using glycol. However, the followed hydroboration−oxidation reaction for the vinyl group in the glycol-protected **3** gave a complex mixture. We attributed this to the relative less stability of the glycol-protecting group. Therefore, we protected the ketone in **3** by neopentyl glycol, and the corresponding product **9** was obtained in 95% yield. To our delight, neopentyl glycol protected **9** can undergo smoothly the hydroboration−oxidation reaction, giving rise to the corresponding alcohol **10** in 56% yield, together with 19% secondary alcohol (**10′**, see the Experimental Section) as a byproduct. We tried some other reagents such as 9-BBN and Cy_2BH for the hydroboration. However, no product was detected. Next, we used PDC to oxidize **10**, generating the corresponding aldehyde **11** in 82% yield. It was found that 4 Å molecular sieve can increase the oxidation reaction rate efficiently. Treating aldehyde **11** with NBS in the presence of a catalytic amount of AIBN as a radical initiator produced crude acyl bromide, which was then directly treated with an excess of dry methylamine gas (prepared *in situ*) to afford the expected amide **12** in 56% yield.[5a,11] To construct the azepane ring, the Pictet−Spengler reaction was carried out by adding paraformaldehyde and TFA to compound **12**.[12] We were happy to note that the Pictet−Spengler reaction took place cleanly to give compound **2** in 78% yield, in which the protecting group was deprotected under acidic reaction conditions. Compound **2** can be transformed to the desired galanthamine and lycoramine, as reported by previous works.[5l,7]

In summary, we have developed a new and efficient approach to the synthesis of galanthamine and lycoramine via Rh(I)-catalyzed [(3 + 2) + 1] cycloaddition of 1-ene−vinylcyclopropane and CO. It is the first time that we accomplished this cycloaddition with the benzene as a part of the tether of 1-ene−VCPs and electron-rich alkene (here an enol ether) as the two-carbon component. This strategy could be used to synthesize other natural products with a *cis*-hydrodibenzofuran structure. It is expected that an asymmetric version of the Rh-catalyzed [(3 + 2) + 1] reaction, which is not available at present and is our next research goal, could then realize the asymmetric synthesis of galanthamine. Further application of Rh-catalyzed [(3 + 2) + 1] reaction in synthesis is ongoing in our laboratory.

EXPERIMENTAL SECTION

General Information. Air- and moisture-sensitive reactions were carried out in oven-dried glassware sealed with rubber septa under a positive pressure of dry argon. Similarly, sensitive liquids and solutions were transferred via syringe. Reactions were stirred using Teflon-coated magnetic stir bars. Elevated temperatures were maintained using thermostat-controlled silicone oil baths. Organic solutions were concentrated using a rotary evaporator with a desktop vacuum pump. Tetrahydrofuran and toluene were distilled from sodium and benzophenone prior to use. Dichloromethane and 1,2-dichloroethane were distilled from CaH_2 prior to use. Synthetic reagents were purchased and used without further purification unless otherwise indicated. Analytical TLC was performed with 0.25 mm silica gel G plates with a 254 nm fluorescent indicator. The TLC plates were visualized by ultraviolet light and treatment with phosphomolybdic acid stain followed by gentle heating. Purification of products was accomplished by flash chromatography on silica gel, and the purified compounds showed a single spot by analytical TLC. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra data are reported as follows: chemical shift ppm, referenced to residual solvent peak, $CDCl_3$ = δ 7.26 ppm; C_6D_6 = δ 7.16 ppm; s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddt = doublet of doublet of triplets, dm = doublet of multiplet, m = multiplet, coupling constant (Hz), and integration. Data for ^{13}C NMR are reported in terms of chemical shift (ppm) relative to residual solvent peak ($CDCl_3$ = δ 77.0 ppm; C_6D_6, 128.0 ppm). IR spectra were reported in wavenumbers (cm^{-1}). HRMS were performed using the ESI ionization technique with an FT-ICR analyzer. Key: Ph = phenyl, DIAD = diisopropyl azodicarboxylate, THF = tetrahydrofuran, Py = pyridine, DCM = dichloromethane, TsOH = 4-methylbenzenesulfonic acid, PDC = pyridinium dichromate, MS = molecular sieve, AIBN = azodiisobutyronitrile, NBS = *N*-bromosuccinimide, TFA = trifluoroacetic acid, DCE = 1, 2-dichloroethane, PE = petroleum ether, EA = ethyl acetate.

1-(2-Cyclopropylideneethoxy)-2-methoxybenzene (6). To a stirred solution of **7** (310 mg, 2.5 mmol), **8** (42 mg, 0.5 mmol), and PPh_3 (262 mg, 1.0 mmol) in anhydrous THF (2 mL) was added DIAD (252 mg, 1.25 mmol) at 0 °C. After being stirred at room temperature overnight, the reaction solution was poured into 10 mL of 3 N NaOH solution. The aqueous mixture was extracted with 10 mL of diethyl ether. The combined organic phase was dried with anhydrous sodium sulfate and concentrated in vacuo. Purification of the residue through column chromatography on silica gel (eluted with PE/EA 20:1) afforded the product **6** as a colorless oil (67 mg, 71% yield).

6. Colorless oil. TLC R_f (PE/EA 10:1) = 0.59. ^{1}H NMR (400 MHz, C_6D_6): δ 0.74−0.86 (m, 4H), 3.42 (s, 3H), 4.57−4.61 (m, 2H), 6.11−6.16 (m, 1H), 6.64−6.70 (m, 1H), 6.85 (d, J = 3.2 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6): δ 1.9, 2.3, 55.6, 69.3, 112.9, 114.6, 114.8, 121.1, 121.3, 126.8, 149.5, 150.8. IR (neat): ν 2916, 2849, 1592, 1503, 1455, 1381, 1124, 1011 cm^{-1}. HRMS (ESI): calcd for $C_{12}H_{15}O_2$ ($M + H^+$) 191.1067, found 191.1067.

2-Methoxy-6-(1-vinylcyclopropyl)phenol (5). Substrate **6** (361 mg) was dissolved in 25 mL of naphthane. After reflux at 188 °C for 3 h, the reaction mixture was cooled to room temperature. Purification of the residue through column chromatography on silica gel (eluted with PE/EA 20:1) afforded the product **5** as a yellow oil (322 mg, 89% yield).

5. Yellow oil. TLC R_f (PE/EA 10:1) = 0.43. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00−1.06 (m, 2H), 1.06−1.12 (m, 2H), 3.89 (s, 3H), 4.61 (dd, J = 17.1, 1.2 Hz, 1H), 4.90 (dd, J = 10.3, 1.1 Hz, 1H), 5.57 (dd, J = 17.1, 10.3 Hz, 1H), 5.69 (br.s, 1H), 6.78−6.86 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.8, 24.6, 56.0, 109.6, 111.6, 119.4, 123.7, 127.8, 143.8, 145.1, 146.7. IR (neat): ν 3536, 3083, 1632, 1473, 1280, 1221 cm^{-1}. HRMS (ESI): calcd for $C_{12}H_{15}O_2$ ($M + H^+$) 191.1067, found 191.1066.

1-Methoxy-3-(1-vinylcyclopropyl)-2-(vinyloxy)benzene (4). Substrate **5** (19 mg, 0.1 mmol), O'Shea's reagent (24 mg, 0.1 mmol, see Scheme 2), $Cu(OAc)_2$ (20 mg, 0.1 mmol), and pyridine (79 mg, 1.0 mmol) in anhydrous DCM (1 mL) were stirred at room temperature for 24 h under a calcium chloride drying tube. Then the reaction mixture was treated with 3 M aqueous ammonium acetate and stirred for a further 30 min. The organic layers were separated, dried over anhydrous sodium sulfate, and concentrated in vacuo. Purification of the residue through column chromatography on silica gel (eluted with PE/EA 20:1) afforded the product **4** as a yellow oil (19 mg, 88% yield).

4. Yellow oil. TLC R_f (PE/EA 10:1) = 0.87. ^{1}H NMR (400 MHz, C_6D_6): δ 0.92 (dd, J = 6.6, 4.4 Hz, 1H), 1.09 (dd, J = 6.6, 4.4 Hz, 1H), 3.30 (s, 3H), 4.11 (dd, J = 6.3, 1.6 Hz, 1H), 4.53 (dd, J = 13.8, 1.6 Hz, 1H), 4.74 (dd, J = 17.0, 1.3 Hz, 1H), 4.91 (dd, J = 10.4, 1.3 Hz, 1H), 5.60 (dd, J = 17.0, 10.4 Hz, 1H), 6.50−6.58 (m 2H), 6.86−6.93 (m

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2H). ^{13}C NMR (100 MHz, C_6D_6): δ 15.0, 25.7, 55.5, 89.5, 111.7, 111.9, 124.3, 124.9, 136.7, 145.0, 145.6, 152.2, 152.7. IR (neat): ν 1637, 1466, 1267, 1225, 1150, 1065 cm^{-1}. HRMS (ESI): calcd for $C_{14}H_{17}O_2$ (M + H$^+$) 217.1223, found 217.1219.

(±)-(4a*S*,9b*R*)-6-Methoxy-9b-vinyl-1,2,4,4a-tetrahydrodibenzo[*b*,*d*]furan-3(9b*H*)-one (3). A solution of substrate **4** (9.3 mg, 0.043 mmol) and $[Rh(CO)_2Cl]_2$ (1.7 mg, 0.004 mmol) in anhydrous toluene (1 mL) was degassed by bubbling CO for 5 min. The reaction mixture was immersed in an 80 °C oil bath and stirred under balloon pressure gas of CO for 4 days. The reaction mixture was cooled to room temperature and concentrated in vacuo. Purification of the residue through column chromatography on silica gel (eluted with PE/EA 10:1) afforded product **3** as a yellow oil (8.4 mg, 80% yield).

3. Yellow oil. TLC R_f (PE/EA 10:1) = 0.08. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.98−2.10 (m, 2H), 2.21 (dd, J = 14.1, 3.6 Hz, 1H), 2.33 (dt, J = 6.7, 3.7 Hz, 1H), 2.70 (dd, J = 17.2, 3.3 Hz, 1H), 2.99 (dd, J = 17.2, 3.4 Hz, 1H), 3.87 (s, 3H), 5.01 (t, J = 3.3 Hz, 1H), 5.25 (d, J = 7.9 Hz, 1H), 5.29 (s, 1H), 6.11 (dd, J = 17.3, 10.8 Hz, 1H), 6.70 (dd, J = 7.5, 1.0 Hz, 1H), 6.79 (dd, J = 10.0, 2.6 Hz, 1H), 6.90 (t, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.7, 35.5, 41.0, 50.9, 55.9, 87.0, 111.9, 114.7, 116.3, 122.1, 132.7, 142.2, 144.5, 147.5, 208.6. IR (neat): ν 1721, 1492, 1458, 1283, 1200, 1113 cm^{-1}. HRMS (ESI): calcd for $C_{15}H_{17}O_3$ (M + H$^+$) 245.1172, found 245.1174.

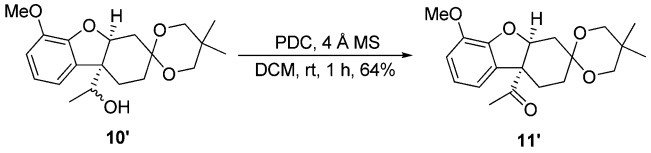
(±)-(4a*S*,9b*R*)-6-Methoxy-5′,5′-dimethyl-9b-vinyl-2,4,4a,9b-tetrahydro-1*H*-spiro[dibenzo[*b*,*d*]furan-3,2′-[1,3]dioxane] (9). To a stirred solution of **3** (723 mg, 3.0 mmol) in 30 mL of benzene were added neopentyl glycol (1.56 g, 15.0 mmol) and TsOH·H_2O (57 mg, 0.3 mmol). The resulting mixture was refluxed for 3 h. The reaction was cooled to room temperature, diluted with Et_2O, and quenched by addition of aqueous $NaHCO_3$. The aqueous layer was separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. Purification of the residue through column chromatography on silica gel (eluted with PE/EA 5:1) afforded the product **9** as a white solid (930 mg, 95% yield).

9. White solid. Mp = 80−82 °C. TLC R_f (PE/EA 4:1) = 0.57. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (s, 3H), 0.97 (s, 3H), 1.57−1.66 (m, 1H), 1.90−2.02 (m, 3H), 2.06 (dd, J = 14.3, 7.2 Hz, 1H), 2.36 (dd, J = 14.3, 5.7 Hz, 1H), 3.41−3.50 (m, 2H), 3.52−3.59 (m, 2H), 3.86 (s, 3H), 4.69 (t, J = 6.4 Hz, 1H), 4.91 (d, J = 17.3 Hz, 1H), 5.08 (d, J = 10.6 Hz), 5.93 (dd, J = 17.3, 10.6 Hz, 1H), 6.69 (d, J = 7.3 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.80−6.90 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 22.7, 27.7, 28.7, 30.0, 33.3, 50.8, 55.9, 69.9, 70.2, 87.0, 97.2, 111.7, 113.9, 115.6, 121.3, 134.0, 142.4, 145.3, 146.8. IR (neat): ν 2955, 2865, 1616, 1490, 1455, 1284 cm^{-1}. HRMS (ESI): calcd for $C_{20}H_{27}O_4$ (M + H$^+$) 331.1904, found 331.1894.

(±)-2-((4a*S*,9b*R*)-6-Methoxy-5′,5′-dimethyl-2,4,4a,9b-tetrahydro-1*H*-spiro[dibenzo[*b*,*d*]furan-3,2′-[1,3]dioxane]-9b-yl)-ethanol (10). To a stirred solution of **9** (910 mg, 2.8 mmol) in anhydrous THF (14 mL) was added 1 M BH_3−THF (14 mL, 14 mmol) at 0 °C. After the solution was stirred at room temperature for 3 h, 10 mL of 15% NaOH (aq) and 10 mL of 30% H_2O_2 (aq) were added to the reaction system at 0 °C sequentially. The resultant mixture was allowed to warm to room temperature. After 1 h, 10 mL of Et_2O was added to the reaction. The aqueous mixture was extracted with 10 mL of diethyl ether. The combined organic phase was dried with anhydrous sodium sulfate and concentrated in vacuo. Purification of the residue through column chromatography on silica gel (eluted with PE/EA 5:3) afforded product **10** as a white solid (539 mg, 56% yield) together with secondary alcohol **10′** (colorless oil, 181 mg, 19% yield, see below).

10. White solid. Mp = 109−111 °C. TLC R_f (PE/EA 5:3) = 0.23. ^{1}H NMR (400 MHz, C_6D_6): δ 0.65 (s, 3H), 0.78 (s, 3H), 0.96−1.04 (br.s, 1H), 1.41−1.51 (m, 1H), 1.55−1.64 (m, 1H), 1.69−1.82 (m, 3H), 1.89−1.99 (m, 2H), 2.54 (dd, J = 13.8, 6.0 Hz, 1H), 3.13−3.27 (m, 4H), 3.38 (br.s, 2H), 3.48 (s, 3H), 4.68−4.75 (t, J = 7.2 Hz, 1H), 6.58 (d, J = 7.3 Hz, 1H), 6.64 (d, J = 8.1 Hz, 1H), 6.79 (t, J = 7.7 Hz, 1H). ^{13}C NMR (100 MHz, C_6D_6): δ 22.4, 22.7, 28.8, 29.8, 29.9, 34.2, 44.0, 47.4, 56.0, 59.2, 69.9, 70.1, 87.2, 97.6, 113.5, 115.6, 121.5, 134.9, 146.4, 147.9. IR (neat): ν 3427, 2953, 2861, 1618, 1591 cm^{-1}. HRMS (ESI): calcd for $C_{20}H_{29}O_5$ (M + H$^+$) 349.2010, found 349.2014.

Secondary alcohol **10′** is stable but is a mixture of diastereomers (1:1), and characterization of it was difficult (its ^{1}H and ^{13}C NMR are given in the Supporting Information for reference). Therefore, we further oxidized it to ketone **11′**.



10′ 11′

(±)-1-((4a*S*,9b*R*)-6-Methoxy-5′,5′-dimethyl-2,4,4a,9b-tetrahydro-1*H*-spiro[dibenzo[*b*,*d*]furan-3,2′-[1,3]dioxan]-9b-yl)-ethanone (11′). To a solution of secondary alcohol **10′** (37.3 mg, 0.11 mmol) in DCM (2 mL) was added PDC (60 mg, 0.16 mmol) and 4 Å MS (50 mg). The mixture was then stirred for 1 h at room temperature. The resulting mixture was purified by flash column chromatography on silica gel (eluted with PE/EA 2:1) to afford the product **11′** as a yellow oil (23.7 mg, 64% yield).

11′. Yellow oil. TLC R_f (PE/EA 3:1) = 0.30. ^{1}H NMR (400 MHz, C_6D_6): δ 0.63 (s, 3H), 0.74 (s, 3H), 1.49−1.59 (m, 1H), 1.74−1.83 (m, 4H), 1.85−2.00 (m, 2H), 2.25 (ddd, J = 14.0, 9.7 4.2 Hz, 1H), 2.61 (ddd, J = 14.0, 9.7 4.2 Hz, 1H), 3.13 (d, J = 12.9 Hz, 3H), 3.21 (d, J = 11.3 Hz, 1H), 3.43 (s, 3H), 5.44 (dd, J = 9.1, 6.5 Hz, 1H), 6.60 (d, J = 7.4 Hz, 2H), 6.71 (dt, J = 11.7, 5.9 Hz, 1H). ^{13}C NMR (100 MHz, C_6D_6): δ 22.3, 22.6, 25.0, 25.7, 29.7, 29.8, 33.9, 55.9, 61.6, 69.9(2), 83.5, 97.3, 114.1, 116.2, 121.7, 130.8, 146.3, 148.8, 204.7. IR (neat): ν 2957, 2865, 1705, 1616, 1490, 1453, 1286 cm^{-1}. HRMS (ESI): calcd for $C_{20}H_{26}NaO_5$ (M + Na$^+$) 369.1672, found 369.1676.

(±)-2-((4a*S*,9b*R*)-6-Methoxy-5′,5′-dimethyl-2,4,4a,9b-tetrahydro-1*H*-spiro[dibenzo[*b*,*d*]furan-3,2′-[1,3]dioxan]-9b-yl)-acetaldehyde (11). To a solution of alcohol **10** (472.5 mg, 1.36 mmol) in DCM (25 mL) were added PDC (766 mg, 2.04 mmol) and 4 Å MS (800 mg). The mixture was then stirred for 1 h at room temperature. The resulting mixture was purified by flash column chromatography on silica gel (eluted with PE/EA 2:1) to afford product **11** as a yellow oil (384 mg, 82% yield).

11. Yellow oil. TLC R_f (PE/EA 5:3) = 0.65. ^{1}H NMR (400 MHz, C_6D_6): δ 0.65 (s, 3H), 0.75 (s, 3H), 1.37 (td, J = 13.0, 3.7 Hz, 1H), 1.64 (dd, J = 13.7, 9.1 Hz, 1H), 1.70−1.80 (m, 1H), 1.87 (d, J = 13.6 Hz, 1H), 1.96−2.10 (m, 2H), 2.26 (d, J = 15.1 Hz, 1H), 2.49 (dd, J = 13.8, 6.2 Hz, 1H), 3.07−3.23 (m, 4H), 3.45 (s, 3H), 4.55 (t, J = 7.6 Hz, 1H), 6.61 (d, J = 7.8 Hz, 2H), 6.76 (t, J = 7.7 Hz, 1H), 9.34 (s, 1H). ^{13}C NMR (100 MHz, C_6D_6): δ 22.4, 22.6, 28.0, 29.2, 29.8, 33.9, 46.8, 53.4, 55.9, 69.8, 70.1, 86.6, 97.2, 113.7, 115.7, 121.8, 133.8, 146.5, 147.6, 199.8. IR (neat): ν 2954, 2865, 1720, 1618, 1491, 1454, 1286 cm^{-1}. HRMS (ESI): calcd for $C_{20}H_{27}O_5$ (M + H$^+$) 347.1853, found 347.1855.

(±)-2-((4a*S*,9b*R*)-6-Methoxy-5′,5′-dimethyl-2,4,4a,9b-tetrahydro-1*H*-spiro[dibenzo[*b*,*d*]furan-3,2′-[1,3]dioxan]-9b-yl)-*N*-methylacetamide (12). To a solution of **11** (59 mg, 0.17 mmol) in dried CCl_4 (5 mL) were added, sequentially, AIBN (3 mg, 0.018 mmol) and NBS (36 mg, 0.20 mmol) under an argon atmosphere. The flask was then placed in an oil bath preheated at 95 °C, and the heterogeneous mixture was stirred for 30 min. The crude reaction mixture was cooled to 0 °C and then bubbled by $MeNH_2$ gas, which was prepared in situ from $MeNH_2$·HCl and NaOH and dried by basic drying tower. While under continuous $MeNH_2$ bubble, the suspension was stirred at room temperature for an additional 10 min. After direct removal of CCl_4 in vacuo, purification of the residue through column chromatography on silica gel (eluted with EA) afforded product **12** as syrupy oil (35.8 mg, 56% yield).

12. Syrupy oil. TLC R_f (EA) = 0.54. ^{1}H NMR (400 MHz, C_6D_6): δ 0.70 (s, 3H), 0.71 (s, 3H), 1.41−1.51 (m, 1H), 1.84 (dd, J = 13.8, 8.9 Hz, 1H), 2.02−2.18 (m, 3H), 2.23 (ddd, J = 14.4, 12.5, 4.1 Hz, 1H), 2.30 (d, J = 4.8 Hz, 3H), 2.41 (dt, J = 14.4, 4.4 Hz, 1H), 2.60 (ddd, J = 13.8, 6.2, 2.3 Hz, 1H), 3.16−3.25 (m, 4H), 3.49 (s, 3H), 4.20 (d, J = 3.8 Hz, 1H), 4.92 (dd, J = 8.8, 6.3 Hz, 1H), 6.64 (dd, J = 7.6, 1.6 Hz,

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1H), 6.75−6.83 (m, 2H). ^{13}C NMR (100 MHz, C_6D_6): δ 22.5, 22.6, 25.8, 27.7, 28.9, 29.8, 35.0, 46.7, 47.8, 56.0, 69.9, 70.1, 87.1, 97.6, 113.6, 116.2, 121.3, 134.9, 146.3, 147.8, 169.6. IR (neat): ν 3311, 2952, 1645, 1554, 1455, 1288 cm^{-1}. HRMS (ESI): calcd for $C_{21}H_{30}NO_5$ (M + H$^+$) 376.2118, found 376.2122.

(±)-Compound 2. To a solution of **12** (6.4 mg, 0.017 mmol) in dried DCE (2.5 mL) were added, sequentially, paraformaldehyde (2.0 mg, 0.07 mmol) and TFA (0.10 mL, 1.3 mmol) at room temperature. The reaction mixture was stirred at ambient temperature for 3 h and then quenched with saturated aqueous $NaHCO_3$, followed by addition of DCM. The organic layer was separated, and the aqueous phase was extracted with DCM. The combined organic phase was dried with anhydrous sodium sulfate and concentrated in vacuo. Purification of the residue through column chromatography on silica gel (eluted with EA) afforded the product **2** as a white solid (4.0 mg, 78% yield).

2. White solid. Mp = 149−150 °C. TLC R_f (EA) = 0.35. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.01−2.06 (m, 2H), 2.24−2.43 (m, 2H), 2.74 (dd, J = 17.6, 2.9 Hz, 1H), 2.86 (d, J = 13.8 Hz, 1H), 2.98−3.10 (m, 5H), 3.87 (s, 3H), 4.38−4.48 (m, 2H), 4.85 (t, J = 3.0 Hz, 1H), 6.72 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.7, 35.8, 36.2, 39.4, 42.3, 43.6, 52.1, 56.2, 88.4, 112.3, 120.0, 124.9, 132.5, 144.5, 146.9, 171.3, 207.3. IR (neat): ν 3359, 2920, 2850, 1722, 1508, 1438 cm^{-1}. HRMS (ESI): calcd for $C_{17}H_{20}NO_4$ (M + H$^+$) 302.1387, found 302.1390.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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