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UNEXPECTED UNIQUE BEHAVIOR OF SPIRO-ISOQUINOLINES WITH A CYCLOHEXADIENONE SYSTEM IN ATTEMPTED DIENONE-PHENOL REARRANGEMENT

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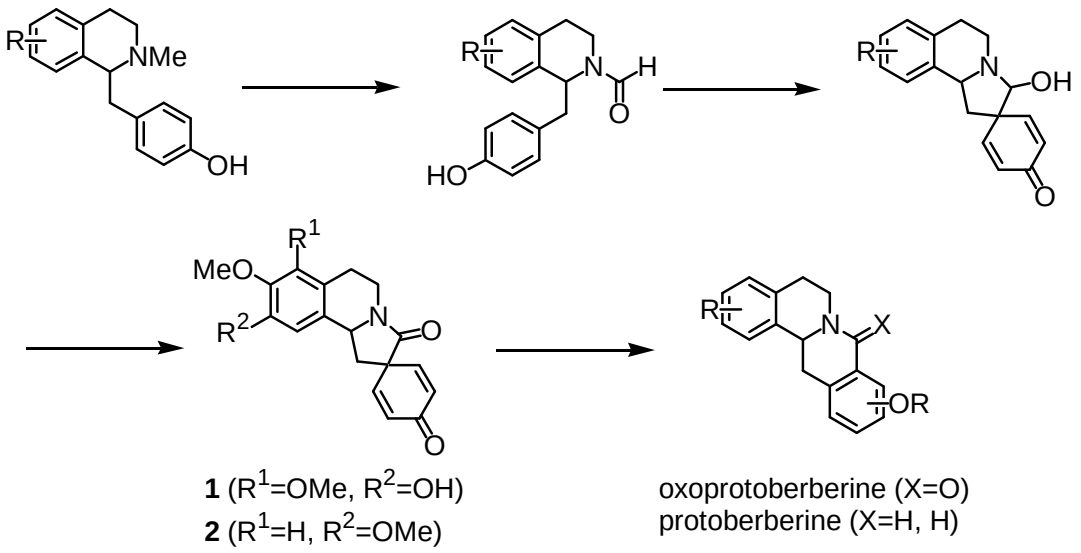
Abstract – 8',9'-Dimethoxy-1',5',6',10b'-tetrahydro-4*H*-spiro(cyclohexa-2,5-diene-1,2'-pyrrolo[2,1-a]isoquinoline)-3',4-dione **2** with a basic skeleton of a natural product, annnosqualine, exhibited unique behavior in a dienone-phenol rearrangement. Treatment of **2** with trifluoroacetic acid gave a simple 1-benzylisoquinoline alkaloid, norarmepavine **4**. Plausible reaction mechanism for the observed transformation is also described.

INTRODUCTION

Isoquinoline alkaloid stands as one of the most important natural products in terms of pharmaceutical development, synthetic chemistry, biosynthetic research and so on.

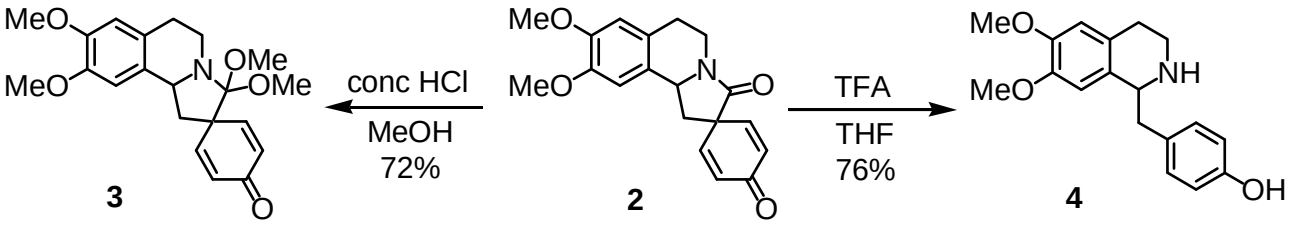


Scheme 1. **Proposed biogenetic pathway of annosqualine and oxoprotoberberine by Wu**

Recently, Wu and co-workers reported the isolation and structural elucidation of an unprecedented isoquinoline alkaloid, annosqualine **1**, which composed of tetracyclic core including tetrahydroisoquinoline, 5-membered lactam, and spirocyclohexadienone moieties.[1] As shown in Scheme 1, they suggested a hypothetic biogenesis of **1** together with a possibility of its biogenetic precursor for oxoprotoberberine and protoberberine alkaloids in the plant by focusing on its structural motif, although it is generally accepted that protoberberine alkaloids are biosynthetically derived from the corresponding *N*-methyl-1-benzylisoquinolines, where a berberine bridge carbon stems from *N*-methyl group via the *N*-oxide.[2] A proposed biogenesis of protoberberine and oxoprotoberberine from **1** by Wu involves well-recognized "dienone-phenol rearrangement" generally promoted by activation of cyclohexadienone carbonyl with acid catalysts.[3]

RESULTS AND DISCUSSION

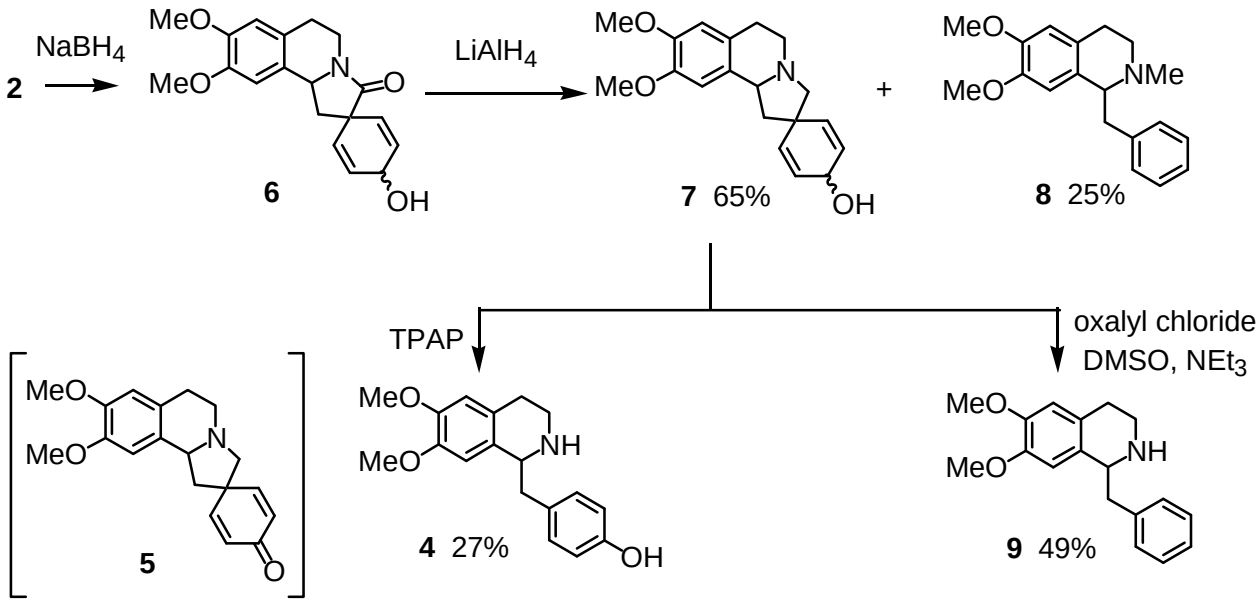
Very recently, we have achieved a total synthesis of annosqualine **1** and its analogue **2** using an oxidative enamide phenol coupling originally developed by us, as a key reaction.[4] As part of our continuing effort to synthesize biologically active natural products, we further investigated a conversion of annosqualine analogue **2** to a corresponding oxoprotoberberine-type product by following Wu's proposal via a dienone-phenol rearrangement.



Scheme 2. Acid treatment of 2

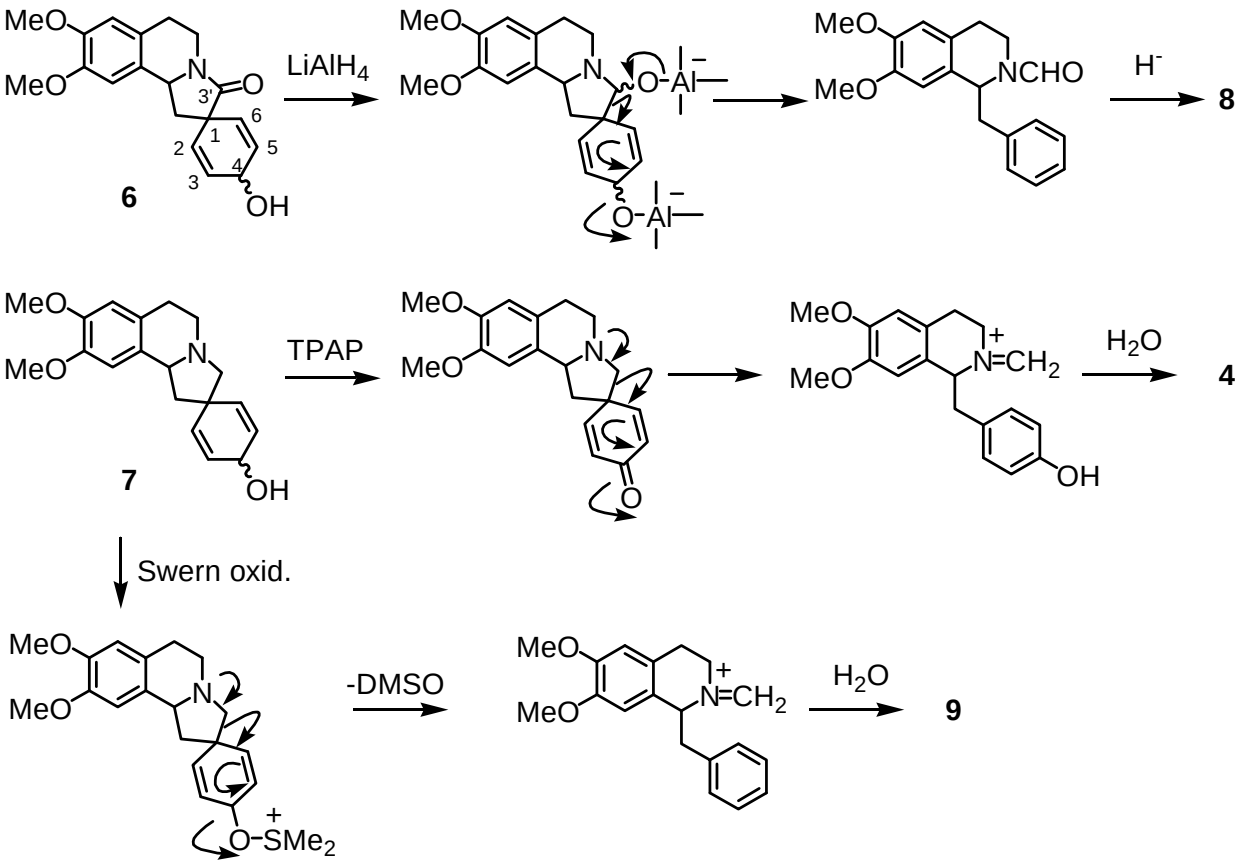
We first attempted a rearrangement of **2** by adopting a well recognized acidic reaction conditions as follows. When the dienone **2** was treated with concentrated hydrochloric acid in MeOH, unexpected dimethyl acetalization of the lactam carbonyl group occurred to afford **3** in 72% yield. Alternatively, decarbonylative aromatization to generate a natural product, norarmepavine **4**,[5] proceeded in the use of TFA as the acid.

These observations invoke high basicity of the lactam nitrogen beyond that of the cyclohexadienone carbonyl, hence difficulties of dienone-phenol rearrangement were encountered under the usual acid conditions. Given these results, we next attempted the synthesis of amine **5** (deoxo **2**) to investigate its chemical reactivity under acidic conditions.



Scheme 3. Unexpected aromatization of a cyclohexadienol moiety in an annosqualine framework

Reduction of **2** with $NaBH_4$ gave **6** with 4:1 diastereoselectivity, which on further reduction with $LiAlH_4$ afforded **7** in 65% yield as a diastereomixure together with an unexpected aromatized compound **8** in 25 % yield. Oxidation of the resultant diastereomixture **7** was carried out under several reaction conditions; such as TPAP oxidation, Swern oxidation, PCC oxidation and MnO_2 oxidation. Among these experiments, only two oxidation reactions gave detectable products as follows. 1) TPAP oxidation (TPAP, NMO and MS4A) led to the formation of norarmepavine **4** in 27% yield that may possibly be generated through oxidation of a cyclohexadienol moiety followed by aromatization. 2) Swern oxidation (oxalyl chloride, DMSO and NEt_3) led to the isolation of aromatized product **9** in 49% yield that may be generated by activation of a dienol with protonation or sulfonium ion formation under the reaction conditions. The same product **9** was also produced by treatment of **7** with TFA in moderate yield. These results clearly indicated that the aromatization of cyclohexadienone or cyclohexadienol moiety occurred via the carbon-carbon bond cleavage between the 1 and 3' positions prior to the expected migration of the carbon bond for the unique annosqualine frameworks under the reaction conditions mentioned above. One of the most plausible reaction mechanisms for the formation of **4**, **8**, and **9** was depicted in Scheme 4. In summary, we disclose a unique reactivity of 8',9'-dimethoxy-1',5',6',10b'-tetrahydro-4*H*-spiro(cyclohexa-2,5-diene-1,2'-pyrrolo[2,1-a]isoquinoline)-3',4-dione **2** under acidic conditions. These results may provide some further information for the proposed biogenesis of protoberberine and oxoprotoberberine alkaloids by Wu and coworkers.



Scheme 4. **Plausible reaction mechanism for the formation of 4, 8, and 9.**

EXPERIMENTAL

Melting points were measured with a Yanagimoto MP apparatus and are uncorrected. IR spectra were obtained using a JASCO FT/IR-200 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were obtained on JEOL LAMBDA-270 (^{1}H-NMR: 270 MHz, ^{13}C-NMR: 67.8 MHz) instrument for solutions in $CDCl_3$ unless otherwise noted, and chemical shifts are reported on the δ scale from internal TMS. MS spectra were measured with a JEOL JMS-D 300 spectrometer. Elemental analyses were performed on a Yanaco-MT5.

3',3',8',9'-Tetramethoxy-1',5',6',10b'-tetrahydro-4*H*-spiro(cyclohexa-2,5-dien-1,2'-pyrrolo[2,1-*a*]-isoquinolin)-4-one (3): One drop of concentrated HCl was added to a stirred solution of **2** (56.0 mg, 0.172 mmol) in MeOH (1.0 mL). After being stirred for 30 min at 0 °C, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash silica gel column chromatography (AcOEt: hexane = 1 : 3) to give **3** (46.0 mg, 72%) as a pale yellowish oil. FT-IR (film) ν_{max} 2955, 1700, 1515, 1250 cm^{-1}; ^{1}H NMR (500 MHz, DMSO, 100 °C) δ 2.48 (dt, 1H, *J* = 1.8, 4.0 Hz), 2.59 (dt, 1H, *J* = 4.3, 16.0 Hz), 2.70 (ddd, 1H, *J* = 6.1, 10.1, 16.0 Hz), 2.95-3.01 (m, 1H), 3.27 (ddd, 1H, *J* = 4.9, 10.1, 13.4 Hz), 3.46 (s, 3H), 3.60 (s, 3H), 3.69 (s, 3H), 3.70 (s, 3H), 3.86-3.87 (m, 1H), 5.11 (t, 1H, *J* = 7.0 Hz), 6.55 (s,

1H), 6.69 (s, 1H), 6.80 (d, 2H, *J* = 8.6 Hz), 7.01 (d, 2H, *J* = 8.6 Hz); ^{13}C NMR (125.6 MHz, $CDCl_3$) δ 28.0, 28.1, 38.1, 39.2, 41.7, 42.1, 52.4, 52.6, 53.0, 55.2, 55.3, 55.7, 55.78, 55.83, 56.2, 108.7, 110.2, 110.6, 111.0, 111.3, 113.56, 113.61, 126.1, 126.3, 128.1, 128.3, 130.3, 130.6, 130.8, 146.7, 146.9, 147.5, 147.7, 156.0, 158.3; MS [EI+] *m/z* 372 (M^++1); HR-MS[CI(+)] Calcd for $C_{21}H_{26}NO_5$ (M^++1):372.1811; Found 372.1824.

1-(4-Hydroxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**4**): TFA (0.15 mL) was added to a stirred solution of **2** (10.0 mg, 0.031 mmol) in THF (0.3 mL). After being stirred for 24 h at 60 °C, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash silica gel column chromatography (acetone : hexane = 2 : 1) to give **4** (7 mg, 76%) as a pale yellowish oil. FT-IR (film) ν_{max} 2930, 1615, 1515, 1260, 1220, 1110 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.79 - 3.02 (m, 4H), 3.12 - 3.32 (m, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 4.20 - 4.22 (m, 1H), 5.44 (brs, 1H), 6.59 – 6.63 (m, 4H), 7.00 (d, 2H, *J* = 8.1 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 28.4, 39.9, 41.2, 55.8, 55.6, 56.4, 109.4, 111.6, 116.0, 126.3, 128.4, 128.7, 130.3, 147.3, 147.7, 155.8; MS [EI+] *m/z* 300 (M^++1).

8',9'-Dimethoxy-1',5',6',10b'-tetrahydro-3'-oxospiro(cyclohexa-2,5-dien-1,2'-pyrrolo[2,1-*a*]isoquinolin)-4-ol (**6**): $CeCl_3 \cdot 7H_2O$ (344 mg, 0.923 mmol) was added to a stirred solution of **2** (300 mg, 0.923 mmol) in MeOH (5 mL) and $CHCl_3$ (5 mL) at rt. To this solution was added $NaBH_4$ (35 mg, 0.923 mmol) and the whole was stirred for further 3 h at rt. After treatment with saturated aqueous NH_4Cl, the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give a crude alcohol **6** as a diastereomixture. The purified sample for data collection was obtained by flash silica gel column chromatography.

More polar diastereomer 6 (white powder): Mp 182-184 °C; FT-IR (film) ν_{max} 3380, 2930, 1680, 1520 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.00 (dd, 1H, *J* = 9.1, 12.6 Hz), 2.69 - 3.17 (m, 5H), 3.87 (s, 3H), 3.88 (s, 3H), 4.28 (ddd, 1H, *J* = 1.9, 5.8, 12.8 Hz), 4.46 (brdt, 1H), 4.87 (brt, 1H), 5.65 (dd, 1H, *J* = 1.6, 9.7 Hz), 5.97 (dd, 1H, *J* = 1.6, 9.7 Hz), 6.19 (ddd, 1H, *J* = 1.6, 4.1, 9.7 Hz), 6.25 (ddd, 1H, *J* = 1.6, 4.1, 9.7 Hz), 6.57 (s, 1H), 6.64 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 27.9, 38.1, 41.7, 50.2, 53.5, 55.9, 56.0, 61.1, 107.4, 111.7, 125.3, 128.4, 129.1, 130.5, 131.5, 131.8, 148.1, 148.2, 172.3; MS [EI+] *m/z* 327 (M^+); Anal. Calcd for: $C_{19}H_{21}NO_4$: C 69.71, H 6.47, N 4.28; Found C 69.44, H 6.36, N 4.46.

Less polar diastereomer 6 (colorless oil): FT-IR (film) ν_{max} 3380, 2930, 1680, 1520 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.96 (dd, 1H, *J* = 9.2, 12.5 Hz), 2.59 – 2.93 (m, 4H), 3.04 (dt, 1H, *J* = 4.5, 11.6 Hz), 3.81 (s, 3H), 3.82 (s, 3H), 4.23 (brdd, 1H), 4.71 (s, 1H), 4.81 (t, 1H, *J* = 7.7 Hz), 5.52 (brd, 1H), 5.85 (brd, 1H), 5.99 - 6.08 (m, 2H), 6.51 (s, 1H), 6.59 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 27.9, 37.8, 41.5, 49.3, 53.3, 55.8, 56.0, 61.6, 107.4, 111.6, 125.3, 126.3, 128.4, 129.3, 129.4, 130.8, 148.0, 148.1, 172.3; MS [EI+] *m/z* 327 (M^+); HR-MS [EI(+)] Calcd for $C_{19}H_{21}NO_4$ (M^+): 327.1470; Found 327.1496.

8,9-Dimethoxy-1',5',6',10b'-tetrahydrospiro(cyclohexa-2,5-dien-1,2'-pyrrolo[2,1-*a*]isoquinolin)-4-ol (**7**) **and 1-Benzyl-1,2,3,4-tetrahydro-2-methyl-6,7-dimethoxyisoquinoline (8):** $LiAlH_4$ (80%, 175 mg, 3.69 mmol) was added to a stirred solution of the crude alcohol **6** in THF (9.2 mL) at 0 °C, and the mixture was stirred for 15 h at rt. After careful addition of water (0.18 mL), followed by 4 N aqueous NaOH (0.18 mL) and water (0.54 mL), the resulting mixture was filtered through a pad of Celite, and the filtrate was concentrated to give a crude mixture. The residue was purified by silica gel column chromatography (EtOH : $CHCl_3$ = 1 : 30 ~ 10) to give **7** (187 mg, 65%, dr was not determined) as a pale yellow oil and **8** (68.7 mg, 25%) as a pale yellow oil.

More polar diastereomer 7: FT-IR (film) ν_{max} 3380, 1520, 1320 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.83 (dd, 1H, *J* = 9.8, 12.3 Hz), 2.27 (dd, 1H, *J* = 6.8, 12.3 Hz), 2.60 – 2.70 (m, 3H), 2.99 – 3.19 (m, 3H) 3.72 (brdd, 1H), 3.82 (s, 3H), 3.85 (s, 3H), 4.50 – 4.51 (m, 1H), 5.79 (ddd, 1H, *J* = 2.1, 3.1, 9.8 Hz), 5.85 – 5.90 (m, 2H), 6.03 (dt, 1H, *J* = 1.9, 10.1 Hz), 6.49 (s, 1H), 6.62 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 27.4, 41.9, 46.3, 48.2, 55.89, 55.93, 62.2, 62.3, 65.1, 108.5, 111.4, 125.2, 125.7, 126.2, 130.4, 135.6, 136.5, 147.3, 147.4; MS [EI+] *m/z* 313 (M^+); HR-MS [EI(+)] Calcd for $C_{19}H_{23}NO_3$ (M^+): 313.1678; Found 313.1700.

Less polar diastereomer 7: FT-IR (film) ν_{max} 3380, 1520, 1320 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.87 (dd, 1H, *J* = 9.8, 12.5 Hz), 2.29 (dd, 1H, *J* = 6.7, 12.5 Hz), 2.56 (d, 1H, *J* = 9.8 Hz), 2.63 - 2.71 (m, 2H), 2.95 - 3.05 (m, 2H), 3.12 - 3.17 (m, 1H), 3.72 (brdd, 1H), 3.83 (s, 3H), 3.85 (s, 3H), 4.47 – 4.49 (m, 1H), 5.77 (ddd, 1H, *J* = 2.1, 3.1, 9.8 Hz), 5.84 – 5.88 (m, 2H), 6.00 (dt, 1H, *J* = 1.9, 10.1 Hz), 6.50 (s, 1H), 6.62 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 27.3, 29.2, 41.9, 45.5, 48.1, 55.85, 55.92, 62.0, 62.4, 65.8, 108.5. 111.4, 125.3, 125.6, 126.1, 130.2, 135.3, 136.7, 147.3, 147.4; MS [EI+] *m/z* 313 (M^+); HR-MS [EI(+)] Calcd for $C_{19}H_{23}NO_3$ (M^+): 313.1678; Found 313.1668.

Compound 8: FT-IR (film) ν_{max} 2930, 1515, 1260, 1230 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.52 – 2.63 (m, 1H), 2.54 (s, 3H), 2.74 – 2.88 (m, 3H), 3.15 – 3.23 (m, 2H), 3.49 (s, 3H), 3.73 (*J* = 4.9, 8.3 Hz), 3.83 (s, 3H), 5.93 (s, 1H), 6.55 (s, 1H), 7.10 – 7.27 (m, 5H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 25.4, 29.7, 41.2, 42.6, 46.7, 55.4, 55.7, 64.8, 110.9, 111.1, 125.7, 125.9, 128.2, 128.6, 129.1, 129.9, 140.0, 146.2, 147.2; MS [ESI+] *m/z* 298 (M^++1).

TPAP oxidation of 7: MS4A (73 mg) and NMO (21.8 mg, 0.218 mmol) were added to a stirred solution of **7** (38.8 mg, 0.145 mmol) in MeCN (0.25 mL) and the mixture was stirred at rt for 4 h. The insoluble materials were filtrated off through a pad of Celite, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (EtOH : $CHCl_3$ = 1 : 10) to give **4** (10 mg, 27%) as a pale yellowish oil.

Swern oxidation of 7: A solution of DMSO (0.082 mL, 1.16 mmol) in CH_2Cl_2 (1 mL) was added to a stirred solution of oxalyl chloride (0.050 mL, 0.580 mmol) in CH_2Cl_2 (1 mL) at -78 °C. After being

stirred for 20 min at the same temperature, a solution of **7** (90.8 mg, 0.290 mmol) in CH_2Cl_2 (1 mL) was added to the mixture. The mixture was stirred for further 1 h at -40 °C and triethylamine (0.32 mL, 2.32 mmol) was added to the solution. The whole mixture was stirred for 20 min at the same temperature and poured into saturated aqueous NH_4Cl, and extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOH : $CHCl_3$ = 1 : 5) to give **9** (42.5 mg, 49%) as a pale yellowish oil; FT-IR (film) ν_{max} 2930, 1610, 1510, 1260 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.30 (brs, 1H), 2.63 – 2.83 (m, 2H), 2.92 (dd, 2H, *J* = 8.9, 13.4 Hz), 3.20 (dd, 2H, *J* = 4.6, 13.4 Hz), 3.80 (s, 3H), 3.85 (s, 3H), 4.16 (dd, 1H, *J* = 4.6, 9.5 Hz), 6.59 (s, 1H), 6.61 (s, 1H), 7.23 – 7.34 (m, 5H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 29.3, 40.5, 42.7, 55.7, 55.8, 56.7, 109.3, 111.7, 126.4, 127.1, 128.5, 129.3, 130.3, 139.0, 146.8, 147.3; MS [ESI+] *m/z* 284 (M^++1).

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