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An expedient synthesis of salviadione

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ABSTRACT

An expedient synthesis of the alkaloid salviadione, the only to date isolated naturally occurring 1*H*-benzo[*def*]carbazole is described. The key step in the synthesis is a palladium-catalyzed, carbon monoxide-mediated reductive N-heterocyclization of a nitroarene with an adjacent alkene.

1. Introduction

The dried root of *Salvia miltiorrhiza* has been widely used in traditional Chinese medicine as Danshen or Tanshen for the treatment of a variety of ailments often in combination with other traditional medicinal plants. Numerous bioactive compounds have been isolated and characterized and they can be divided into two groups, water soluble phenolic acids and more lipophilic abietane-type diterpenes. Biological activity of isolated compounds includes, for example, antioxidant, anticoagulant, anti-HIV, antitumor, antibacterial, antifungal, and anti-inflammatory activities.[1] In addition to phenolic acids and abietane-type diterpenes, the unusual alkaloid salviadione, 1,1-dimethyl-6-(1-methylethyl)-1*H*-benzo[*def*]carbazole-3,5(2*H*,4*H*)-dione, was isolated in 2005 from the dried roots of *S. miltiorrhiza* (Fig. 1).[2] This is to our knowledge the only benzo[*def*]carbazole known isolated from a natural source[3] and one of a limited number of synthetic origin.[4] Intrigued by the unique structure of salviadione, we initiated a synthetic study.

From a synthetic viewpoint, the structure of salviadione is deceptively complex since the tricyclic diterpenoid carbon skeleton is readily assembled in a few synthetic steps according to Pan et al.[5] Thus, alkylation of the carbanion derived from **2**[6] with iodide **1**[7] afforded **3**[8,9] in excellent yield (Scheme 1). This compound was treated with polyphosphoric acid, resulting in a sequential intramolecular cyclization—Friedel–Crafts alkylation producing the known tricyclic diterpenoid **4**.[5] With the proper carbon skeleton in hand, the next step was to introduce a nitro-group adjacent to the methoxy group on the aromatic ring. Although the regioselectivity of the nitration was as expected *ortho* to the methoxy group,[10] the product(s) isolated depended on the reaction temperature, work up procedure, and speed of chromatographical purification. It should be stressed that the outcome of a given nitration, even under similar reaction conditions, was hard to control. Reaction of **4** with a mixture of fuming nitric acid–sulfuric acid at −78 °C gave not only the expected nitration product **5** but also nitro-phenol **6** (Scheme 1). The demethylation probably occurred after the nitro-group was introduced since the phenol derived from demethylation of **4** was not observed in reactions wherein the starting material was not completely consumed.

Nitro-phenol **6** was obtained as the major product in addition to a trace amount of **5** when the nitration was performed at −20 °C.

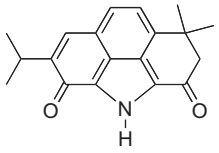

Fig. 1. Structure of Salviadione.

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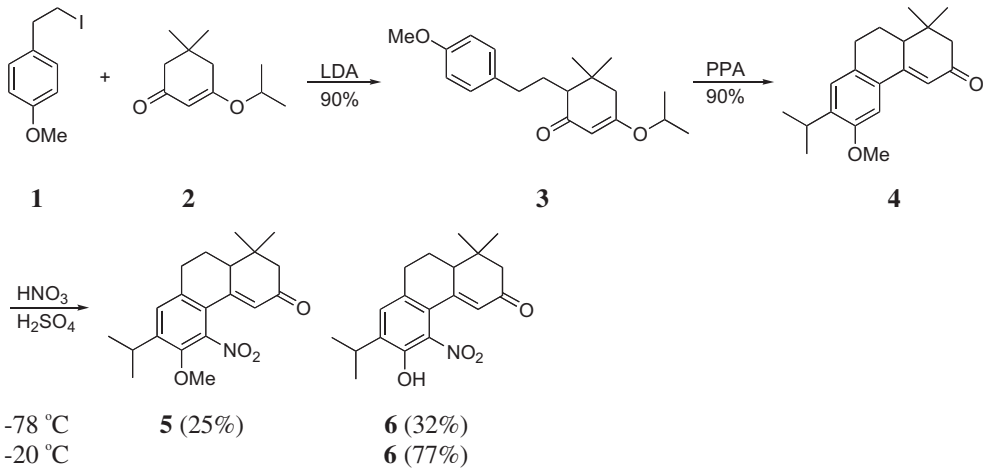
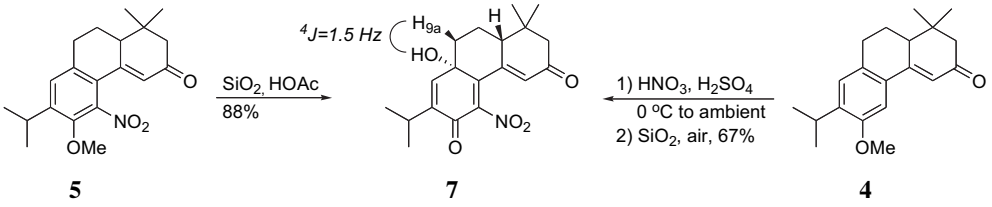


Scheme 1.

Compounds **5** and **6** are relatively stable in the pure state following chromatography. However, both compounds are slowly oxidized to quinol **7** (as a 14:1 mixture of diastereomers) in acidic solutions open to air or by simply leaving the crude product absorbed on silica gel for a period of time (Scheme 2). For example, oxidation of **5** absorbed on silica gel in the absence of solvent but in the presence of acetic acid gave **7** in 88% isolated yield. Quinole **7** was also obtained from nitration of **4** at 0 °C to ambient temperature followed by absorption of the crude product on silica gel (Scheme 2).

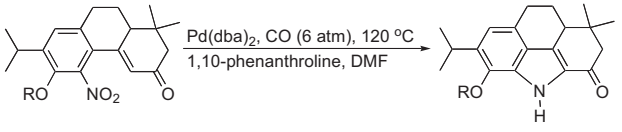


Scheme 2.

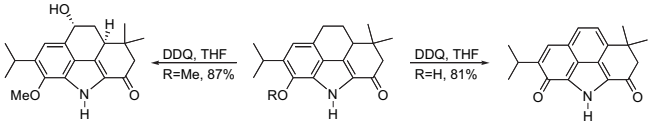
The proposed relative stereochemistry of the major diastereomer of **7** was supported by NOE, COSY, and selective decoupling NMR experiments. A four-bond spin–spin coupling between H9-axial and the hydroxy group was observed (J=1.5 Hz). Related coupling constants have been reported for similar compounds.[11] The same relative stereochemistry between the hydroxy group and H9-axial was reported for some related naturally occurring quinoles.[12]

The three nitration products **5**–**7** were reacted with carbon monoxide in the presence of a catalytic amount of palladium bis(dibenzylidenacetone) and 1,10-phenanthroline, conditions previously described for the preparation of indoles.[13] Cyclization of **5** and **6** smoothly gave the expected benzo[*def*]carbazoles **8** and **9** in 87% and 75% yield, respectively (Scheme 3). Both compounds were stable and did not oxidize using air-silica gel-acetic acid. Palladium-catalyzed cyclization of **7** did not furnish the expected product although the starting material was completely consumed in the reaction. Interestingly, a small amount (10%) of salviadione was isolated from the complex reaction mixture. Formation of salviadione directly from **7** was examined to some extent, however the yield never exceeded 10%.

In order to complete the synthesis of salviadione in a more synthetically useful fashion, both **8** and **9** were treated with a 4-fold excess of DDQ in THF. In the event, compound **8** resulted in exclusive benzylic oxidation forming the hydroxy substituted benzo[*def*]carbazole product **10** (Scheme 4).[14] It is interesting to note that **10** has the same relative stereochemistry between the hydroxy group and proton residing on the C9a carbon (see Table 1 for numbering) previously reported for some related naturally occurring compounds.[15] The relative stereochemistry was established by NOE NMR experiments. Since transformation of compound **10** into the target molecule required, at a minimum, demethylation, elimination of water, and oxidation, this compound was not further pursued. Gratifyingly, DDQ oxidation of **9** gave salviadione in 81% isolated yield (Scheme 4).



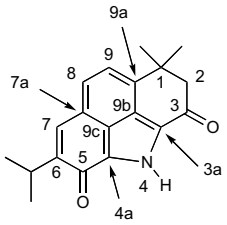
Scheme 3.



Scheme 4.

The mp, IR, HRMS, and ^{1}H NMR data obtained from synthetic salviadione were in agreement with the reported values for the natural product. A comparison of the ^{1}H NMR data is shown in Table 1. The broadbanddecoupled ^{13}C NMR spectrum of synthetic salviadione wasalso in good agreement the isolated compound (Table 2). Only one resonance (C3a) was observed with a $\Delta\delta$ larger than 1 ppm (1.2 ppm).

Table 1
^{1}H NMR data of synthetic and isolated salviadione



Proton	δ (ppm)[a]		
	Synthetic	Isolated	$\Delta\delta$ (ppm)
NH	13.24	14.23[b]	
H-2	2.95	2.95	0
H-6	7.55	7.56	0.01
H-8	7.66	7.66	0
H-9	7.31	7.30	−0.01
i-Pr−CH	3.49	3.54	0.05
i-Pr−Me	1.29	1.31	0.02
1-Me	1.51	1.49	−0.02

[a] In $CDCl_3$.
[b] In DMSO-d_6.

Table 2
^{13}C NMR data of synthetic and isolated salviadione

Carbon	δ (ppm)[a]		
	Synthetic	Isolated[b]	$\Delta\delta$ (ppm)
1	41.3	41.3	0
2	57.3	57.4	0.1
3	187.7	188.0	0.3
3a	127.0	128.2	1.2
4a	126.7	126.9	0.2
5	175.8	175.9	0.1
6	151.3	151.4	0.1
7	128.9	129.1	0.2
7a	128.2	*127.9*	−0.3
8	129.5	129.7	0.2
9	121.2	121.0	−0.2
9a	144.9	145.3	0.4
9b	124.0	*123.9*	−0.1
9c	124.2	124.3	0.1
i-Pr−Me	22.7	22.8	0.1
i-Pr−CH	27.3	27.4	0.1
C1−Me	30.0	30.1	−0.1

[a] In $CDCl_3$.
[b] Numbers in italic have been reversed compared to the original paper.

Extensive HMQC and HMBC NMR experiments suggest that the original assignment of the C7a and C9b resonances should be reversed.

2. Conclusion

Salviadione was efficiently synthesized in six linear steps from commercially available starting materials in 42% overall yield. The key indole forming step is a palladium-catalyzed reductive N-heterocyclization. The unexpected O-demethylation observed in the nitration ultimately proved beneficial to the synthetic scheme.

3. Experimental section

3.1. General procedures

NMR spectra were determined in $CDCl_3$ at 600 MHz (^{1}H NMR) and 150 MHz (^{13}C NMR) unless otherwise stated. The chemical shifts are expressed in δ values relative to $SiMe_4$ (0.0 ppm, ^{1}H and ^{13}C) or $CDCl_3$ (77.0 ppm, ^{13}C) internal standards.

Prior to use, hexanes and ethyl acetate were distilled from calcium hydride and THF was distilled from benzophenone ketyl. Chemicals prepared according to literature procedures have been footnoted the first time used; all other reagents were obtained from commercial sources and used as received. All reactions were performed under a nitrogen atmosphere in oven dried glassware. Solvents were removed from reaction mixtures and products on a rotary evaporator at water aspirator pressure unless otherwise stated. Melting points (uncorrected) were recorded directly from products obtained by chromatography on silica gel unless otherwise stated.

*3.1.1. 5,5-Dimethyl-6-(4-methoxyphenylethyl)-3-(1-methylethoxy)-cyclohex-2-enone (**3**)*[5]. 5,5-Dimethyl-3-(1-methylethoxy)-2-cyclohexen-1-one (**2**) (4.133 g, 22.68 mmol) was dissolved in THF (25 mL) and cooled to −78 °C under a positive flow of nitrogen. Lithium diisopropylamide (2.0 M, 13.6 mL, 27.21 mmol) was added drop wise via a cannula over 15 min. The resulting yellow solution was stirred for 1 h at −78 °C before slowly adding the solution drop wise via a cannula to a solution of 1-(2-iodoethyl)-4-methoxybenzene (**1**) (7.132 g, 27.21 mmol) in THF (25 mL) cooled to −78 °C. The solution was allowed to stir up to ambient temperature (12 h) followed by slow addition of a solution of NH_4Cl (satd aqueous, 50 mL). The phases were separated and the aqueous portion was extracted with EtOAc (3×200 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvents were removed under reduced pressure. The resulting orange oil was purified by chromatography (hexanes/EtOAc, 95:5 followed by 9:1) to afford **3** as a yellow oil (6.429 g, 20.32 mmol, 90%). ^{1}H NMR (270 MHz) δ 7.13 (d, J=8.5 Hz, 2H), 6.82 (d, J=8.3 Hz, 2H), 5.34 (s, 1H), 4.42 (sept, J=6.2 Hz, 1H), 3.78 (s, 3H), 2.76 (ddd, J=13.4, 9.7, 5.7 Hz, 1H), 2.54 (ddd, J=13.9, 9.7, 7.3, 1H), 2.26 (d, J=17.6 Hz, 1H), 2.18 (d, J=17.6 Hz, 1H), 1.97 (dd, J=8.7, 4.3 Hz, 1H), 1.83−1.69 (m, 2H), 1.28 (d, J=6.1 Hz, 6H), 1.02 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (67.5 MHz) δ 202.4 (+), 173.1 (+), 157.7 (+), 134.6 (+), 129.4 (−), 113.7 (−), 100.9 (−), 70.7 (−), 56.2 (−), 55.2 (−), 42.2 (+), 35.0 (+), 34.0 (+), 28.5 (−), 28.4 (+), 24.4 (−), 21.5 (−); IR (ATR) 2957, 2932, 1648, 1604, 1517, 1378, 1243, 1107 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{29}O_3$ ($M+H^+$) 317.2111, found 317.2107.

*3.1.2. 10,10a-Dihydro-1,1-dimethyl-6-methoxy-7-(1-methylethyl)-5-nitrophenanthren-3(1H,2H,9H)-one (**5**) and 10,10a-dihydro-1,1-dimethyl-6-hydroxy-7-(1-methylethyl)-5-nitrophenanthren-3(1H,2H,9H)-one (**6**).* Fuming nitric acid (5.0 mL, 144 mmol) was cooled to −78 °C and concentrated sulfuric acid (13 drops) was slowly added drop wise. After stirring for 20 min, **4** (166 mg, 0.556 mmol) was added in one portion to the nitration solution. The resulting dark red solution was removed from the cold bath and allowed to stir for 10 min at ambient temperature. The mixture was poured into 200 mL of ice, neutralized with Na_2CO_3 (s) and extracted with EtOAc (3×75 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The resulting crude product was purified by chromatography (hexanes/acetone, 6:4) to afford in order of elution **5** (47.9 mg, 0.140 mmol, 25%) as a colorless solid followed by **6** (59.6 mg, 0.181 mmol, 32%) as a yellow solid. Analytical data for **5**: mp 174−175 °C; ^{1}H NMR (600 MHz) δ 7.15 (s, 1H), 6.14 (d, J=0.8 Hz, 1H), 3.83 (s, 3H), 3.30 (sept, J=7.0 Hz, 1H), 2.81 (dddd, J=16.0, 7.3, 5.0, 0.6 Hz, 1H), 2.71 (dddd, J=16.0, 8.1, 5.0, 0.8 Hz, 1H) 2.61 (dt, J=7.1, 2.4 Hz, 1H), 2.35 (dd, J=16.0, 0.4 Hz, 1H), 2.27 (dd. J=16.0, 0.8 Hz, 1H), 1.99 (m, 1H), 1.87 (m, 1H), 1.26 (d, J=7.0 Hz, 3H), 1.24 (J=7.0 Hz, 3H), 1.16 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (150 MHz) δ 198.5, 151.8, 147.5, 145.5, 144.4, 137.4, 127.6, 125.3, 124.8, 63.9, 51.6, 45.7, 37.1, 29.4, 28.9, 26.6, 23.4, 23.4, 23.2, 22.0; IR (ATR) 2968, 1664, 1525, 1283, 1254 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{26}NO_4$ ($M+H^+$) 344.1862, found 344.1862. Analytical data for **6**: mp 154−156 °C (dec); ^{1}H NMR (270 MHz) δ 9.20 (br s, 1H), 7.17 (s, 1H), 5.84 (d, J=2.2 Hz, 1H), 3.37

(sept, J=6.9 Hz, 1H), 2.82–2.57 (m, 4H), 2.40 (d, J=16.0 Hz, 1H), 2.28 (d, J=15.8 Hz, 1H), 2.04–1.97 (m, 1H), 1.26 (d, J=6.7 Hz, 3H), 1.25 (d, J=6.9 Hz, 3H), 1.23 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (67.5 MHz) δ 198.2 (+), 154.2 (+), 149.2 (+), 139.7 (+), 134.0 (+), 133. 6 (+), 130.4 (−), 129.0 (+), 125.3 (−), 50.8 (+), 45.3 (−), 37.2 (+), 28.7 (−), 28.6 (+), 27.2 (−), 23.4 (+), 22.7 (−), 22.2 (−), 22.0 (−); IR (ATR) 3280, 2959, 1660, 1645, 1544, 726 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{24}NO_4$ (M+H$^+$) 330.1705, found 330.1705.

*3.1.3. Alternative procedure to **6**.* Fuming HNO_3 (500 μL, 12.0 mmol) was stirred at −20 °C for 5 min before concentrated H_2SO_4 (eight drops) was slowly added drop wise. The solution was stirred for 30 min before **4** (79 mg, 0.26 mmol) was added. The resulting dark red solution was stirred for 90 min before quenching with ice (30 mL). The mixture was neutralized with Na_2CO_3 (satd aqueous) and extracted with EtOAc (3×50 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The resulting brown oil was immediately purified by chromatography (hexanes/EtOAc, 9:1) affording **6** (66 mg, 0.20 mmol, 77%) as a yellow solid.

*3.1.4. 8a,9,10,10a-Tetrahydro-1,1-dimethyl-8a-hydroxy-7-(1-methylethyl)-5-nitrophenanthrene-3,6(1H,2H)-dione (**7**).* Fuming HNO_3 (6.9 mL, 164.0 mmol) was stirred at 0 °C for 5 min before concentrated H_2SO_4 (14 drops) was slowly added drop wise. After 30 min at 0 °C, the solution was added drop wise via a pipette to **4** (1.078 g, 3.61 mmol) at ambient temperature. The resulting dark red solution was stirred for 4 h where after H_2O (5 mL) and NH_4Cl (satd, aqueous, 40 mL) were added sequentially. The precipitate was removed by filtration, dissolved in acetone (50 mL) adhered to silica gel (≈1.0 g) and allowed to stand for 1 h. The solvent was removed under reduced pressure and purification by chromatography (hexanes/acetone, 9:1 followed by 7:3) gave **7** (0.832 g, 2.41 mmol, 67%, 14:1 diastereomeric ratio) as an orange solid. mp 239–240 °C; IR (ATR) 2952, 1663, 1530, 1266, 1253 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{24}NO_5$ (M+H$^+$) 346.1654, found 346.1655.

Spectral data of the major diastereomer **7** from the mixture: ^{1}H NMR (600 MHz, $CDCl_3$/DMSO-d_6) δ 6.66 (d, J=1.1 Hz, 1H), 6.02 (d, J=2.4 Hz, 1H), 5.49 (d, J=1.5 Hz, 1H), 2.94 (dsept, J=6.8, 1.0 Hz, 1H), 2.41 (ddd, J=12.3, 5.7, 2.4 Hz, 1H), 2.32 (ddd, J=13.8, 3.5, 2.3 Hz, 1H), 2.30 (d. J=15.3 Hz, 1H), 2.26 (d, J=15.3 Hz, 1H), 2.08 (dq, J=13.2, 4.0 Hz, 1H), 1.97–1.92 (m, 1H), 1.67 (ddt, J=13.2, 4.2, 1.2 Hz, 1H), 1.12 (d, J=7.2 Hz, 3H), 1.11 (d, J=7.2 Hz, 3H), 1.11 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$/DMSO-d_6) δ 198.0, 175.5, 152.1, 147.9, 145.6, 143.4, 142.2, 126.5, 68.9, 50.9, 49.0, 37.4, 35.6, 28.4, 26.4, 23.0, 21.3, 21.0, 20.5. Partial spectral data for minor diastereomer **7** from the mixture: ^{1}H NMR (600 MHz, $CDCl_3$/DMSO-d_6) δ 6.80 (d, J=1.0 Hz, 1H), 6.22 (d, J=2.8 Hz, 1H), 5.46 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$/DMSO-d_6) δ 198.1, 175.6, 153.4, 146.2, 145.8, 145.6, 139.8, 127.7, 67.7, 53.6, 45.1, 37.2, 37.1, 30.7, 28.7, 26.2, 23.0, 19.7, 19.6.

*3.1.5. Alternative procedure to **7**.* To a solution of **5** (81 mg, 0.236 mmol) in acetone (5 mL) and acetic acid (1 mL) was added silica gel (0.5 g). The solvent was removed under reduced pressure and the yellow residue was allowed to stand open to air for 14 h. A slight yellow tint was noticed after this time and the residue was purified by chromatography (hexanes/acetone, 6:4) to afford **7** (72.0 mg, 0.208 mmol, 88%).

*3.1.6. 1,8,9,9a-Dihydro-1,1-dimethyl-5-methoxy-6-(1-methylethyl)-4H-benzo[def]carbazol-3(2H)-one (**8**).* To a solution of **5** (22 mg, 0.065 mmol) in anhydrous DMF (1.0 mL) in a threaded ACE glass pressure tube were added 1,10-phenanthroline monohydrate (1.6 mg, 0.008 mmol), 1,3-bis(diphenylphosphino)propane (1.7 mg, 0.004 mmol), and bis(dibenzylideneacetone)palladium (2.3 mg, 0.004 mmol). The tube was fitted with a pressure head, and the solution was saturated with carbon monoxide (4 cycles of 6 atm). The reaction mixture was heated at 120 °C under carbon monoxide (6 atm) for 168 h. The solvent was removed via bulb-to-bulb distillation affording a brown residue. Water (5 mL) was added to this residue and the mixture was extracted with ethyl acetate (3×30 mL). The combined organic phases were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The crude product was purified by chromatography (hexanes/acetone, 9:1) to give **8** (17.3 mg, 0.057 mmol, 87%) as a yellow solid. mp 228–230 °C; ^{1}H NMR (600 MHz) δ 8.64 (br s, 1H), 6.81 (s, 1H), 3.94 (s, 3H), 3.52 (sept, J=7.0 Hz, 1H), 3.03 (dd, J=12.1, 5.0 Hz, 1H), 3.02–2.95 (m, 2H), 2.77 (d, J=15.8 Hz, 1H), 2.33 (d, J=15.8 Hz, 1H), 2.21 (m, 1H), 1.62 (m, 1H), 1.27 (d, J=7.0 Hz, 3H), 1.27 (d, J=7.0 Hz, 3H), 1.24 (s, 3H), 0.85 (s, 3H); ^{13}C NMR δ 190.0, 140.9, 140.4, 134.3, 130.0, 129.5, 127.6, 126.4, 115.7, 60.9, 55.8, 41.8, 41.2, 28.4, 27.4, 26.8, 25.1, 24.2, 23.9, 20.4; IR (ATR) 3264, 2958, 2930, 1653, 1620 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{26}NO_3$ (M+H$^+$) 312.1964, found 312.1959.

*3.1.7. 1,8,9,9a-Tetrahydro-1,1-dimethyl-5-methoxy-6-(1-methylethyl)-8-hydroxy-4H-benzo[def]carbazol-3(2H)-one (**10**).* To a solution of **8** (39.0 mg, 0.124 mmol) in THF (4 mL) was added DDQ (115 mg, 0.496 mmol) over a period of 5 min. The resulting mixture was allowed to stir at ambient temperature for 4 h where after the solvent was removed under reduced pressure. The color of the residue changed from purple to orange over 30 min. The crude product was purified by chromatography (hexanes/EtOAc, 7:3) to give **10** (36.0 mg, 87%) as a brown solid. mp=141–143 °C; ^{1}H NMR (600 MHz) δ 8.60 (br s, 1H), 7.03 (s, 1H), 5.18 (t, J=2.7 Hz, 1H), 3.95 (s, 3H), 3.53 (sept, J=7.2 Hz, 1H), 3.37 (dd, J=12.0, 4.8 Hz, 1H), 2.81 (d, J=5.2, 0.6, 1H), 2.41 (ddd, J=13.8, 5.4, 3.0 Hz, 1H), 2.37 (d, J=16.8, 1H), 1.64 (ddd, J=16.8, 12.0, 3.0 Hz, 1H), 1.60 (br s, 1H), 1.28 (d, J=7.2 Hz, 3H), 1.27 (d, J=7.2, 3H), 1.26 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (150 MHz) δ 189.2, 143.0, 140.3, 132.8, 129.9, 128.9, 128.0, 125.5, 116.8, 67.7, 60.7, 55.9, 41.6, 35.7, 32.5, 28.3, 27.0, 24.1, 23.8, 20.7; IR (ATR) 3279 (br), 2959, 1650, 1624 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{26}NO_3$ (M+H$^+$) 328.1913, found 328.1909.

*3.1.8. 1,8,9,9a-Tetrahydro-1,1-dimethyl-5-hydroxy-6-(1-methylethyl)-4H-benzo[def]carbazol-3(2H)-one (**9**).* Reaction of **6** (140 mg, 0.566 mmol), bis(dibenzylideneacetone)palladium (20 mg, 0.034 mmol), 1,3-bis-(diphenylphosphino)propane (14 mg, 0.034 mmol), and 1,10-phenanthroline (13 mg, 0.068 mmol) were dissolved in anhydrous DMF (2 mL) in a threaded ACE glass pressure tube. The tube was fitted with a pressure head, and the solution was saturated with carbon monoxide (4 cycles of 6 atm of CO). The reaction was heated at 120 °C under CO (6 atm) for 32 h. DMF was removed via bulb-to-bulb distillation before water (10 mL) was added to the brown residue. The brown solution was extracted with ethyl acetate (3×40 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvent was removed. The resulting crude product was purified by chromatography (pentanes/acetone, 8:2 followed by 1:1) to afford **9** (91 mg, 0.423 mmol, 75%) as a light yellow solid. mp 234–236 °C; ^{1}H NMR (600 MHz, THF-d_8) δ 9.94 (s, 1H), 7.72 (s, 1H), 6.69 (s, 1H), 3.50 (sept, J=7.5 Hz, 1H), 3.03 (dd, J=12.6, 4.4 Hz, 1H), 2.96–2.88 (m, 2H), 2.7 (m, 1H), 2.20–2.14 (m, 2H), 1.53 (dq, J=11.9, 5.4 Hz, 1H), 1.24 (d, J=7.0 Hz, 3H), 1.22 (d, J=7.0 Hz, 3H), 1.19 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (150 MHz, THF-d_6) δ 187.9, 138.9, 133.6, 133.2, 129.5, 128.6, 126.8, 125.8, 115.7, 56.8, 42.4, 42.1, 28.7, 28.3, 27.8, 26.5, 24.0, 23.9, 20.6; IR (ATR) 3394 (br), 3260, 2962, 2928, 1617 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{24}NO_2$ (M+H$^+$) 298.1807, found 298.1802.

3.1.9. Salviadione. To a solution of **9** (35 mg, 0.118 mmol) in THF (5 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (107 mg, 0.471 mmol) slowly in 2 approximately equal portions with a 5 min interval. The reaction mixture was stirred for 4 h at ambient temperature. The solvent was removed under reduced

pressure from the resulting dark red-purple solution. The residue was dissolved in acetone (10 mL) and silica gel (≈1.0 g) was added. The solvent was removed under reduced pressure and the resulting solid was allowed to stand open to the air (4 h). Purification by chromatography (hexanes/acetone, 9:1) gave salviadione (28 mg, 0.095 mmol, 81%) as an orange solid. Physical (mp) and spectroscopical data (^{1}H, ^{13}C, COSY, HMBC, HMQC) were in accordance with literature values. HRMS (ESI) calcd for $C_{19}H_{20}NO_2$ ($M+H^+$) 294.1494, found 294.1494.

3.1.10. Alternative procedure. To a solution of **7** (101 mg, 0.29 mmol) in anhydrous DMF (7.0 mL) in a threaded ACE glass pressure tube were added dppp (7.7 mg, 0.019 mmol), phen (19 mg, 0.095 mmol), and $Pd(dba)_2$ (15 mg, 0.027 mmol). The tube was fitted with a pressure head and the solution was saturated with carbon monoxide (three cycles of 6 atm). The reaction mixture was heated at 120 °C under carbon monoxide for 168 h. The solvent was removed via bulb-to-bulb distillation affording a brown oil. Water (5 mL) was added to this residue and the mixture was extracted with ethyl acetate (3×25 mL). The combined organic phases were dried ($MgSO_4$), filtered, and solvent was removed under reduced pressure. The crude product was purified by chromatography (hexanes/ethyl acetate 7:3) to afford salviadione (8.7 mg, 0.029 mmol, 10%).

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