Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2019, **17**, 655

A novel approach to oxazole-containing diterpenoid synthesis from plant roots: salviamines E and F†

Koichi Narita, Narumi Fujisaki, Yuta Sakuma and Tadashi Katoh *

Received 5th December 2018,
Accepted 16th December 2018

DOI: 10.1039/c8ob03030h

rsc.li/obc

In this study, salviamines E and F, which are structurally unique abietane-type diterpene alkaloids containing an oxazole ring, were efficiently synthesized from a known molecule, 5,7,8-trimethoxy-1-naphthol. The synthetic sequence involves the following crucial steps: (i) the assembly of a carbon skeleton by coupling a six-carbon homoprenyl unit with a naphthalene moiety (Kumada–Tamao–Corriu coupling); (ii) the construction of a tricyclic phenanthrene ring by acid-induced cyclization of a naphthalene derivative with a homoprenyl side chain; (iii) the formation of an oxazole ring by nucleophilic ring closure of a 2-aminophenylene-1,4-diyl-diformate or -diacetate moiety and (iv) Friedel–Crafts acetylation at the C13 position of the tetracyclic intermediates to obtain the two target molecules, salviamines E and F. To the best of our knowledge, salviamine synthesis is reported here for the first time.

Introduction

In 2006, Wu *et al.* reported the isolation and structural elucidation of six novel abietane-type diterpene alkaloids, salviamines A–F (**1–6**, Fig. 1) from the roots of *Salvia yunnanesis*,[1] which is a herbaceous perennial plant widely distributed throughout the provinces in southwestern China, including Yunnan, Guizhou and Sichuan.[1] The roots of this plant have been used in traditional Chinese herbal medicines.[1,2] Recently, pharmacological studies revealed that extracts from the roots of this plant exhibit anti-HIV,[3] antiproliferative[4] and antioxidant[5] properties. Structurally, salviamines possess unique fused pentacyclic (ABCDE rings) or tetracyclic (ABCD rings) skeletons, in which a characteristic hydroxy-substituted naphthoxazole moiety (*i.e.* **7**) serves as a common tricyclic core structure (BCD ring system).[1] The biological activity of **1–6** has not been established, which is probably due to the scarcity of samples from plant roots.[6] The total synthesis of salviamines has not been reported yet. In this study, we describe the total synthesis of salviamines E (**5**) and F (**6**) for the first time *via* strategic oxazole-ring formation.[7]

Results and discussion

Preliminary studies (part 1): attempted synthesis of model compound 7

Considering tricyclic naphthoxazole **7** as the model compound, we first attempted the synthesis of **7**, as shown in Scheme 1.[8]

We hypothesized that the requisite oxazole ring could be formed by the condensation of 2-aminonaphthalene-1,4-diol

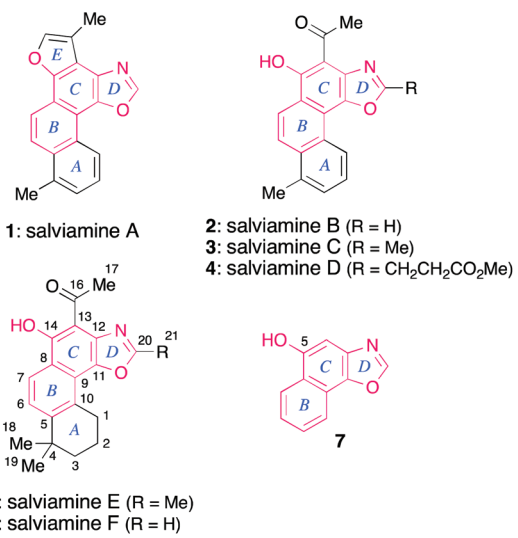
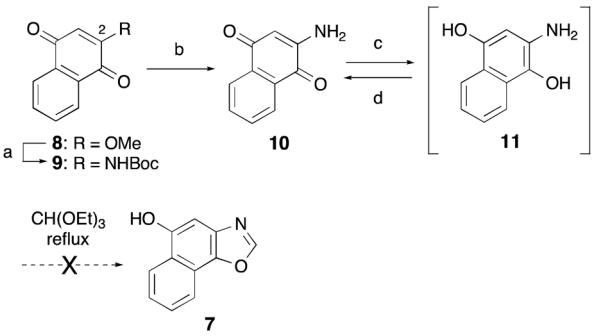


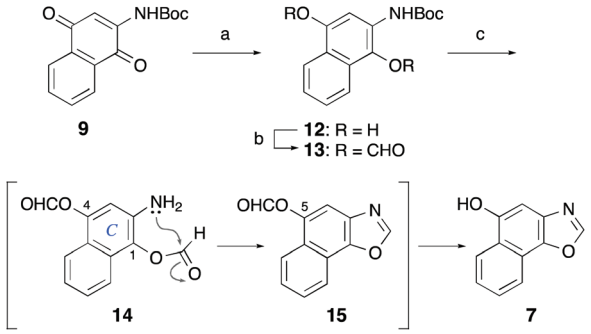
Fig. 1 Structures of salviamines A (**1**), B (**2**), C (**3**), D (**4**), E (**5**), F (**6**) and model compound **7** as a common tricyclic core structure (BCD ring system).

Faculty of Pharmaceutical Sciences, Tohoku Medical and Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai, 981-8558, Japan.
E-mail: katoh@tohoku-mpu.ac.jp

†Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. See DOI: 10.1039/c8ob03030h



Scheme 1 Attempted synthesis of model compound **7**. (a) $BocNH_2$, *t*-BuOK, THF, room temp., 10 min, 83%; (b) TFA, room temp., 1 h, 86%; (c) (i) Zn, AcOH, room temp., 1 h or (ii) $Na_2S_2O_4$, MeCN/H_2O (1 : 1), room temp., 24 h; (d) air oxidation. Boc = *tert*-butoxycarbonyl, *t*-Bu = *tert*-butyl, TFA = trifluoroacetic acid.



Scheme 2 Synthesis of model compound **7**. (a) Zn, AcOH, room temp., 30 min; (b) AcOCHO (prepared from HCO_2H and Ac_2O), $NaHCO_3$, room temp., 2 h, 88% (2 steps); (c) *p*-TsOH·H_2O, toluene, reflux, 1 h, 83%. Ac = acetyl, *p*-TsOH = *p*-toluenesulfonic acid.

(**11**) with triethyl orthoformate [$CH(OEt)_3$] under refluxing conditions (**11** → **7**).[9] The synthesis was initiated with amination of commercially available 2-methoxynaphthalene-1,4-dione (**8**) by substituting the C2 methoxy group with a NHBoc group,[10] which formed the desired NHBoc-substituted naphthalene-1,4-dione (**9**) in 83% yield. Subsequently, the deprotection of the *N*-Boc group in **9** provided 2-aminonaphthalene-1,4-dione (**10**) in 86% yield. Reduction of the *p*-quinone moiety in **10** under conventional conditions [*i.e.* (i) Zn in AcOH at room temperature[11] or (ii) $Na_2S_2O_4$ in MeCN/H_2O (1 : 1) at room temperature[12]] provided 2-aminonaphthalene-1,4-diol (**11**), which is a proposed substrate targeted for the crucial oxazole-ring formation. However, compound **11** was both unstable and easily susceptible to oxidation in an air atmosphere, thereby changing back into the reaction substrate (*i.e.* **10**). This outcome prompted us to modify our original method of synthesis to facilitate the crucial oxazole-ring formation.

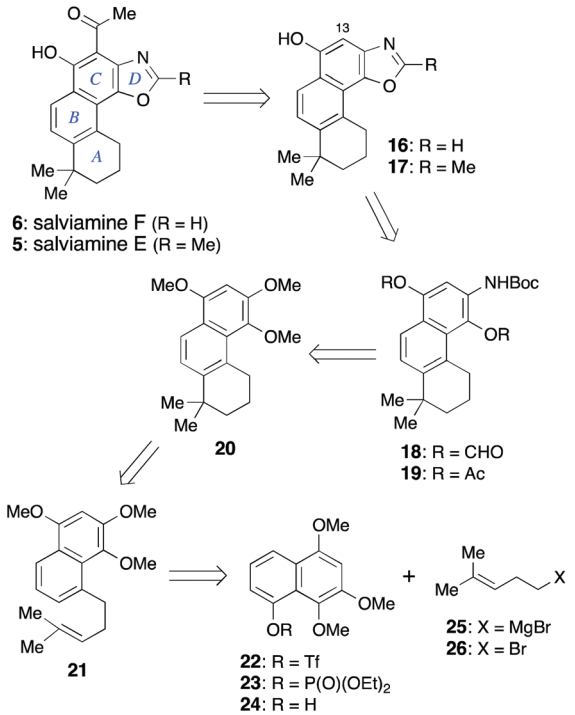
Preliminary studies (part 2): successful synthesis of model compound 7

As our initial attempts to synthesize model compound **7** were unsuccessful, we investigated an alternative method for synthesizing **7**, as shown in Scheme 2, which employed 2-aminonaphthalene-1,4-diyl diformate (**14**) as a promising substrate for oxazole-ring formation (**14** → **15**). We envisioned that the two electron withdrawing *O*-CHO groups at the C1 and C4 positions in **14** would decrease the electron density of the aromatic C ring, thereby avoiding the air oxidation responsible for changing the precursor back to the *p*-quinone derivative (*cf.* **10** in Scheme 1). In fact, naphthalene diformate **13** was obtained as a stable compound from **9** in good yield of 88% by reducing the *p*-quinone moiety in **9** with Zn in AcOH at room temperature followed by di-*O*-formylation of hydroquinone **12** using AcOCHO (prepared from HCO_2H and Ac_2O) in the presence of $NaHCO_3$ at room temperature.

It was then possible to achieve the crucial oxazole-ring formation[13] necessary for synthesizing **7**. Treatment of **13** with *p*-TsOH·H_2O [14] (3 equiv.) in toluene under refluxing conditions for more than an hour resulted in the direct formation of **7** in a relatively good yield of 83% (**13** → [**14** → **15**] → **7**). In this cascade reaction, it appeared that cyclized naphthoxazole **15** was produced from the intermediate, aminonaphthalene diformate **14**, which was initially generated *in situ* by deprotection of the *N*-Boc group in **13**, *via* internal nucleophilic ring closure accompanied by dehydration (**14** → **15**). This was followed by the deprotection of the remaining *O*-CHO group at C5 in **15** under acidic conditions using *p*-TsOH·H_2O,[15] which resulted in the formation of **7**. It should be noted that this is the first example of oxazole-ring formation employing 2-aminonaphthalene-1,4-diyl diformate (**14**) as a cyclization precursor.

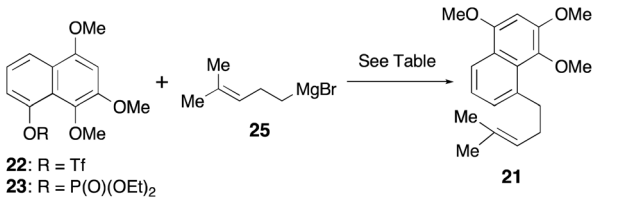
Synthetic plan for salviamines E (5) and F (6)

After successfully developing a novel method for constructing the tricyclic model compound **7**, we focussed on the synthesis of naturally occurring salviamines E (**5**) and F (**6**) by relying on the results from our preliminary studies. Our method of synthesizing **5** and **6** is outlined in Scheme 3. The key element of this approach was the construction of the oxazole-containing tetracyclic structure (*i.e.* the ABCD ring system in **5** and **6**). We hypothesized that the requisite oxazole moieties (*i.e.* the D ring) could be obtained through ring closure of the corresponding tricyclic amino-substituted diformate **18** and diacetate **19** (*i.e.* **18** → **16**; **19** → **17**). Furthermore, the cyclized products **16** and **17** were converted into target molecules **6** and **5**, respectively, *via* Friedel–Crafts acetylation at the C13 position. Intermediates **18** and **19** were obtained from the trimethoxyphenanthrene derivative **20** *via* successive *p*-quinone formation, amination (amine substitution) and reductive di-*O*-formylation or di-*O*-acetylation. The common tricyclic intermediate **20** was obtained from the naphthalene derivative **21** *via* acid-induced cyclization. Intermediate **21** was then formed from the Kumada–Tamao–Corriu coupling reaction[16] of triflate **22** or phosphate **23** [both were obtained from known 5,7,8-trimethoxy-1-naphthol (**24**)[17]] with homoprenyl Grignard reagent **25** [obtained from commercially available homoprenyl bromide (**26**, synonym: 5-bromo-2-methyl-2-pentene)].



Scheme 3 Plan for the synthesis of salviamines E (**5**) and F (**6**). Tf = trifluoromethanesulfonyl.

Table 1 Investigation on the Kumada–Tamao–Corriu coupling reaction of triflate **22** or phosphate **23** with Grignard reagent **25**



Entry	Substrate	Conditions	Yield[a] (%) **21**
1	**22**	$NiCl_2(dppp)$[b] (10 mol%), **25** (3 equiv.), THF, room temp., 7 h	17
2	**22**	$Pd(PPh_3)_4$ (10 mol%), **25** (3 equiv.), THF, room temp., 17 h	Dec.[c]
3	**23**	$NiCl_2(dppp)$[b] (10 mol%), **25** (3 equiv.), THF, room temp., 13 h	33
4	**23**	$NiCl_2(dppp)$[b] (25 mol%), **25** (3 equiv.), room temp., 2 h	40
5	**23**	$NiCl_2(dppp)$[b] (25 mol%), **25** (3 equiv.), Et_2O, room temp., 2 h	89
6	**23**	$NiCl_2(dppp)$[b] (25 mol%), **25** (3 equiv.), CPME,[d] room temp., 2 h	Dec.[c]
7	**23**	$Pd(PPh_3)_4$ (10 mol%), **25** (3 equiv.), THF, room temp., 5 h	Dec.[c]

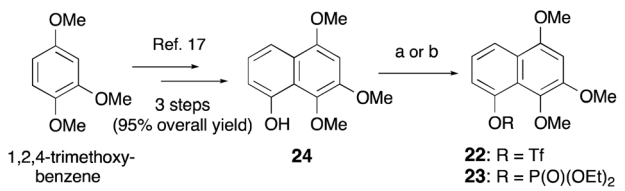
[a] Isolated yield. [b] dppp = 1,3-bis(diphenylphosphino)propane. [c] Decomposition. [d] CPME = cyclopentyl methyl ether.

Synthesis of intermediates 22 and 23

First, we prepared triflate **22** and phosphate **23**, which were both proposed substrates for the Kumada–Tamao–Corriu coupling reaction, starting from known compound **24**,[17] as shown in Scheme 4. Treatment of **24** with trifluoromethanesulfonic acid anhydride (Tf_2O) in the presence of i-Pr_2NEt provided the corresponding triflate **22** in 98% yield. Additionally, phosphate **23** was prepared in an excellent yield of 98% from **24** by phosphorylation using diethyl chlorophosphate [$ClP(O)(OEt)_2$] in the presence of NaH.

Synthesis of intermediates 21 *via* the Kumada–Tamao–Corriu coupling reaction

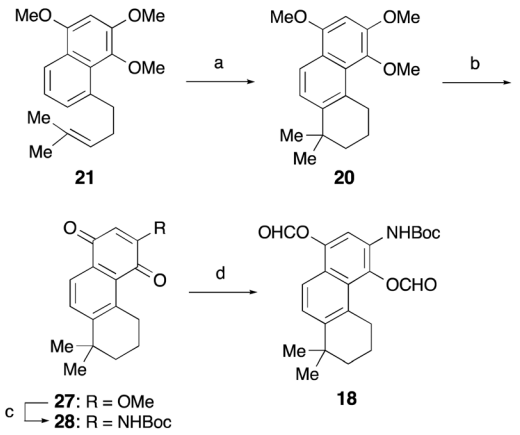
We then examined the Kumada–Tamao–Corriu coupling reaction of triflate **22** or phosphate **23** with Grignard reagent **25**, which was prepared *in situ* from commercially available **26**, under various conditions (Table 1, **22** or **23** + **25** → **21**). An initial screening was conducted using triflate **22** with nickel or palladium catalysts (entries 1 and 2); however, this resulted in a poor yield of the coupling product **21** (17%) or decomposition of **22** (or **21**). Further screening using phosphate **23** instead of triflate **22** under various conditions (entries 3–7) was also performed. The best result was obtained when the coupling reaction was employed with 25 mol% $NiCl_2(dppp)$ and 3 equiv. of Grignard reagent **25** in a solvent of Et_2O at room temperature over 2 hours (entry 5), which provided **21** in a higher yield of 89%. When less $NiCl_2(dppp)$ (10 mol%) in THF was used, the yield of **21** was significantly lower (33%, entry 3), and using of THF instead of Et_2O as a solvent also decreased the yield of **21** (40%, entry 4). When cyclopentyl methyl ether (CPME) was used as a solvent, the reaction was not clean, resulting in the formation of decomposition products (entry 6). Furthermore, using palladium catalysis [$Pd(PPh_3)_4$ (10 mol%)] instead of nickel catalysis [$NiCl_2(dppp)$ (10 mol%)] under the same conditions described in entry 3 also resulted in the formation of decomposition products (entry 7).



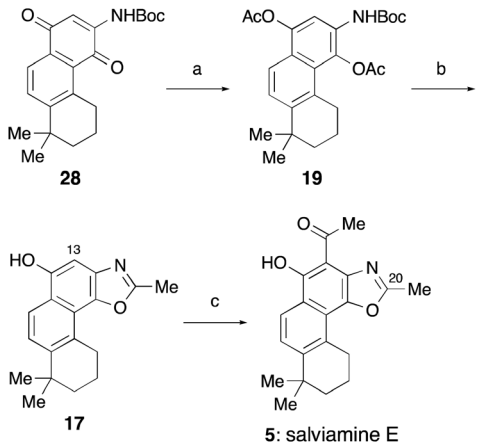
Scheme 4 Synthesis of triflate **22** and phosphate **23**. (a) Tf_2O, i-Pr_2NEt, CH_2Cl_2, 0 °C, 1 h, 98% for **22**; (b) $ClP(O)(OEt)_2$, NaH, THF, 0 °C, 50 min, 98% for **23**.

Synthesis of intermediate 18

Intermediate **18**, which is a substrate for the crucial oxazole-ring formation, was synthesized from the Kumada–Tamao–Corriu coupling product **21**, as shown in Scheme 5. The cyclization of **21** was efficiently achieved by reacting it with *p*-TsOH·H_2O in CH_2Cl_2 at the reflux temperature for 2 hours, and the requisite tricyclic phenanthrene derivative **20** was obtained in 84% yield. The subsequent oxidation of **20** with



Scheme 5 Synthesis of intermediate **18**. (a) *p*-TsOH·H_2O, CH_2Cl_2, reflux, 2 h, 84%; (b) CAN, MeCN/H_2O (1 : 1), 0 °C, 10 min, 74%; (c) $BocNH_2$, *t*-BuOK, THF, room temp., 10 min, 82%; (d) Zn, AcOCHO (prepared from HCO_2Na and AcCl), K_2CO_3, THF, room temp., 12 h, 94%. CAN = ceric ammonium nitrate.

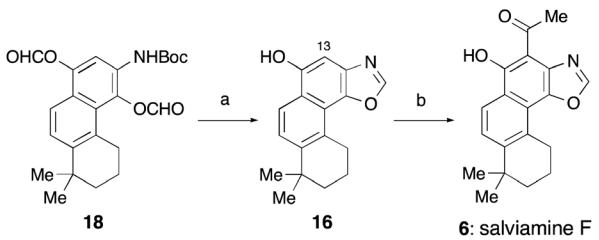


Scheme 7 Synthesis of salviamine E (**5**) through the methyl-substituted oxazole-ring formation. (a) Zn, Ac_2O, K_2CO_3, THF, room temp., 3 h, 72%; (b) *p*-TsOH·H_2O, toluene, reflux, 5 h, 86%; (c) AcCl, $AlCl_3$, benzene, reflux, 24 h, 77%.

ceric ammonium nitrate (CAN) produced the corresponding *p*-quinone **27** in 74% yield, which was then subjected to amination using $BocNH_2$ in the presence of *t*-BuOK to give the corresponding NHBoc-substituted *p*-quinone **28** in 82% yield. Reductive di-*O*-formylation of **28** with Zn and AcOCHO (prepared from HCO_2Na and AcCl[18]) in the presence of K_2CO_3 in THF at room temperature provided the requisite diformate **18** in an excellent yield of 94%.

Synthesis of salviamine F (6)

After intermediate **18** was obtained, we turned our attention to the synthesis of the first target molecule, salviamine F (**6**), as shown in Scheme 6. Oxazole-ring formation of **18** was efficiently achieved under the same conditions (*p*-TsOH·H_2O, toluene, reflux, 1 h) described in our preliminary studies (*cf.* Scheme 2, **13** → [**14** → **15**] → **7**). The desired cyclization product **16** was obtained in 68% yield. Finally, acetylation at the C13 position in **16** was effectively performed under Friedel–Crafts conditions (AcCl, $AlCl_3$, benzene, reflux, 20 h), which resulted in the formation of salviamine F (**6**) in 70% yield. The spectroscopic properties of **6** (IR, MS and both ^1H and ^{13}C NMR spectroscopy) were identical to those of naturally occurring **6**.[1]



Scheme 6 Synthesis of salviamine F (**6**) through the novel oxazole-ring formation. (a) *p*-TsOH·H_2O, toluene, reflux, 4 h, 68%; (b) AcCl, $AlCl_3$, benzene, reflux, 20 h, 70%.

Synthesis of salviamine E (5)

After successfully synthesizing salviamine F (**6**), we focused on producing the second target molecule, salviamine E (**5**), which possesses an additional methyl group at the C20 position, as shown in Scheme 7. Starting with **28**, the synthesis was performed in a similar manner to that of salviamine F (**6**) (*cf.* Schemes 5 and 6). Thus, reductive di-*O*-acetylation of **28** (Zn, Ac_2O, K_2CO_3, THF, room temp., 3 h) afforded the corresponding diacetate **19** in 72% yield. The crucial oxazole-ring formation of **19** proceeded smoothly and clearly under the aforementioned conditions (*p*-TsOH·H_2O, toluene, reflux, 5 h; *cf.* **18** → **16** in Scheme 6) to give the requisite tetracyclic product **17** in 86% yield. Finally, acetylation of **17** at the C13 position (AcCl, $AlCl_3$, benzene, reflux, 24 h) provided salviamine E (**5**) in 77% yield. The spectroscopic properties of **5** (IR, MS and both ^1H and ^{13}C NMR spectroscopy) were identical to those of naturally occurring **5**.[1]

Conclusions

In this study, we report on the total synthesis of salviamines E (**5**) and F (**6**) for the first time starting from known 5,7,8-trimethoxy-1-naphthol (**24**) (for **5** an overall yield of 19.9% requiring eight steps and for **6** an overall yield of 21.1% requiring eight steps). Key steps in the synthetic sequence were (i) the Kumada–Tamao–Corriu coupling reaction between naphthalene phosphate **23** and Grignard reagent **25** to assemble the requisite carbon skeleton (*cf.* **23** + **25** → **21** in Table 1); (ii) acid-induced cyclization of homoprenyl-substituted naphthalene derivative **20** to construct the tricyclic phenanthrene ring system (*cf.* **21** → **20** in Scheme 5); (iii) oxazole-ring formation of 2-aminophenylene-1,4-diyl-diformate **18** or -diacetate **19** by internal nucleophilic ring closure (*cf.* **18** → **16** in Scheme 6 and **19** → **17** in Scheme 7) and (iv) Friedel–Crafts acetylation at the C13 position in tetracyclic intermediates **16** and **17** to com-

plete the synthesis [*cf.* **16** → **6** (salviamine F) in Scheme 6 and **17** → **5** (salviamine E) in Scheme 7]. At present, we are conducting a biological evaluation of the synthesized salviamines E and F.

Experimental section

General experimental procedures

All reactions involving air- and moisture-sensitive reagents were carried out using oven dried glassware and standard syringe-septum cap techniques. Routine monitorings of reaction were carried out using glass-supported Merck silica gel 60 F254 TLC plates. Flash column chromatography was performed on Kanto Chemical Silica Gel 60 N (spherical, neutral 40–50 nm) with the solvents indicated. All solvents and reagents were used as supplied with following exceptions. Tetrahydrofuran (THF) and Et_2O were freshly distilled from Na metal/benzophenone under argon. CH_2Cl_2 was distilled from calcium hydride under argon. ^1H and ^{13}C NMR spectroscopic data were recorded with a JEOL AL-400 (400 MHz) spectrometer. Chemical shifts were expressed in ppm using Me_4Si (δ = 0) as an internal standard. Infrared (IR) spectral measurements were carried out with a JASCO FT/IR-4100 spectrometer. Low- and High-resolution mass (HRMS) spectra were measured on a JEOL JMS-700 high resolution mass spectrometer.

tert-Butyl 1,4-dioxo-1,4-dihydronaphthalen-2-ylcarbamate (9)

Potassium *tert*-butoxide (345 mg, 3.1 mmol) was added to a stirred solution of 2-methoxynaphthalene-1,4-dione (**8**) (482 mg, 2.6 mmol) in THF (25 mL) containing *tert*-butyl carbamate ($BocNH_2$) (1.50 g, 12 mmol) at room temperature. After 10 min, the reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the resulting mixture was extracted with Et_2O (3 × 10 mL). The combined extracts were washed with brine (2 × 10 mL), then dried with Na_2SO_4. The mixture was concentrated *in vacuo*, and the residue was purified by column chromatography (hexane/EtOAc 5 : 1) to give **9** (578 mg, 83%) as a yellow solid. Recrystallization from hexane/EtOAc (3 : 1) gave an analytical sample of **9** as yellow granules. M. p. 179–180 °C. ^1H NMR (400 Hz, $CDCl_3$): δ = 1.54 (s, 9H), 7.48 (s, 1H), 7.68–7.80 (m, 2H), 8.10 (d, J = 7.8 Hz, 2H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 28.1 (3C), 82.6, 114.9, 126.3, 126.6, 130.1, 132.3, 133.0, 134.8, 141.1, 151.2, 180.8, 184.7 ppm. IR (KBr) ν = 3380, 2973, 1732, 1672, 1645, 1622, 1591, 1508, 1458, 1395, 1366, 1339, 1303, 1223, 1197, 1151, 1122, 967, 886, 788, 768, 725, 670, 634 cm^{-1}. HRMS (EI): calcd for $C_{15}H_{15}NO_4$ $[M]^+$ 273.1001; found 273.1005.

2-Aminonaphthalene-1,4-dione (10)

A solution of **9** (289 mg, 1.1 mmol) in trifluoroacetic acid (11 mL) was stirred at room temperature. After 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (130 mL) at 0 °C, and the resulting mixture was extracted with EtOAc (3 × 100 mL). The combined extracts were washed with brine (2 × 100 mL), then dried with Na_2SO_4. The mixture was concentrated *in vacuo*, and the residue was purified by column chromatography (hexane/EtOAc 1 : 1) to give **10** (158 mg, 86%) as an orange powder. Recrystallization from hexane/EtOAc (2 : 1) gave an analytical sample of **10** as orange needles. M.p. 205–206 °C. ^1H NMR (400 Hz, CD_3OD): δ = 5.90 (s, 1H), 7.67 (td, J = 7.6, 1.5 Hz, 1H), 7.76 (td, J = 7.6, 1.5 Hz, 1H), 7.99 (dd, J = 7.8, 1.0 Hz, 1H), 8.02 (dd, J = 7.8, 1.0 Hz, 1H) ppm. ^{13}C NMR (100 Hz, CD_3OD): δ = 103.3, 126.7, 127.1, 132.1, 133.3, 134.9, 135.6, 152.5, 183.0, 185.5 ppm. IR (KBr) ν = 3385, 3318, 3288, 3244, 1685, 1616, 1566, 1364, 1272, 1126, 986, 831, 778, 725 cm^{-1}; HRMS (EI): calcd for $C_{10}H_7NO_2$ $[M]^+$ 173.0477; found 173.0473.

2-(*tert*-Butoxycarbonylamino)naphthalene-1,4-diyl diformate (13)

A solution of **9** (57.4 mg, 0.21 mmol) in acetic acid (4 mL) was degassed by sonication. Zinc (0.11 g, 1.7 mmol) was added to the mixture, and the resulting mixture was stirred at room temperature for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) at 0 °C, and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (2 × 10 mL), then dried with Na_2SO_4. Concentration of the solvent *in vacuo* afforded *tert*-butyl (1,4-dihydroxynaphthalen-2-yl)carbamate (**12**) (57.8 mg), which was immediately used for the next reaction without further purification.

Acetic anhydride (1.60 mL, 17 mmol) was added dropwise to a stirred solution of formic acid (0.86 mL, 21 mmol) at 0 °C under argon, and the reaction mixture was stirred at 60 °C for 2 h. A solution of acetic formic anhydride (AcOCHO) prepared above was added dropwise to the crude product **12** (57.8 mg) containing $NaHCO_3$ (79 mg, 0.94 mmol) at room temperature. After 2 h, the reaction mixture was diluted with Et_2O (30 mL). The organic layer was washed with H_2O (3 × 5 mL), brine (2 × 5 mL), then dried with Na_2SO_4. The mixture was concentrated *in vacuo*, and the residue was purified by column chromatography (hexane/EtOAc 4 : 1 → 3 : 1) to give **13** (61 mg, 88% for 2 steps) as a colourless amorphous solid. Recrystallization from hexane/EtOAc (3 : 1) gave an analytical sample of **13** as colourless thin plates. M.p. 128–132 °C. ^1H NMR (400 Hz, $CDCl_3$): δ = 1.54 (s, 9H), 6.74 (s, 1H), 7.47–7.52 (m, 1H), 7.55–7.60 (m, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.91 (d, J = 8.3 Hz, 1H), 8.24 (s, 1H), 8.48 (s, 1H), 8.50 (s, 1H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$) δ = 28.2 (3C), 81.9, 111.9, 120.6, 121.7, 123.4, 125.9, 127.3, 127.9, 128.2, 130.9, 144.4, 152.2, 158.9, 159.0 ppm. IR (KBr) ν = 3350, 2979, 1742, 1643, 1608, 1584, 1525, 1503, 1455, 1428, 1368, 1259, 1233, 1152, 1114, 1030, 950, 882, 835, 755 cm^{-1}. HRMS (EI): calcd for $C_{17}H_{17}NO_6$ $[M]^+$ 331.1056; found 331.1055.

Naphtho[2,1-*d*]oxazol-5-ol (7)

A solution of **13** (30.0 mg, 91 μmol) in toluene (9.0 mL) containing *p*-toluenesufonic acid monohydrate (51.7 mg, 0.27 mmol) was heated at reflux for 1 h. After cooling to room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (2 × 10 mL), then dried with Na_2SO_4. The mixture was concentrated *in vacuo*, and the residue was puri-

fied by column chromatography ($CHCl_3$/EtOAc 4 : 1) to give **7** (13.9 mg, 83%) as a pale yellow powder. Recrystallization from hexane/EtOAc (2 : 1) gave an analytical sample of **7** as pale yellow needles. M.p. 182–184 °C. ^{1}H NMR (400 Hz, CD_3OD): δ = 7.08 (s, 1H), 7.51–7.55 (m, 1H), 7.62–7.66 (m, 1H), 8.12 (d, J = 8.3 Hz, 1H), 8.34 (d, J = 8.8 Hz, 1H), 8.48 (s, 1H) ppm. ^{13}C NMR (100 Hz, CD_3OD): δ = 99.6, 120.6, 121.8, 124.8, 125.5, 126.0, 128.6, 137.3, 141.2, 153.0, 154.1 ppm. IR (KBr) ν = 3120, 1588, 1505, 1449, 1423, 1354, 1325, 1266, 1179, 1108, 1076, 823, 755 cm^{-1}. HRMS (EI): calcd for $C_{11}H_7NO_2$ $[M]^+$ 185.0477; found 185.0474.

5,7,8-Trimethoxynaphthalen-1-yl trifluoromethanesulfonate (22)

Trifluoromethanesulfonic anhydride (0.19 mL, 1.1 mmol) was added to a stirred solution of 5,7,8-trimethoxy-1-naphthol (**24**) (170 mg, 0.73 mmol) in CH_2Cl_2 (7 mL) containing *N*,*N*-diisopropylethylamine (0.14 μL, 1.1 mmol) at 0 °C under argon. After 1 h, the reaction was quenched with water (5 mL) at 0 °C, and the resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were washed with brine (2 × 5 mL), then dried with $MgSO_4$. The mixture was concentrated *in vacuo*, and the residue was purified by column chromatography (hexane/EtOAc 5 : 1) to give **22** (260 mg, 98%) as a pale brown solid. Recrystallization from hexane/$CHCl_3$ (10 : 1) gave an analytical sample of **22** as pale gray powders. M.p. 123–124 °C. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 3.87 (s, 3H), 3.98 (s, 3H), 4.01 (s, 3H), 6.72 (s, 1H), 7.26 (dd, J = 8.5, 7.1 Hz, 1H), 7.32 (d, J = 7.3 Hz, 1H), 8.22 (dd, J = 8.3, 1.5 Hz, 1H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 55.9, 57.1, 61.4, 96.1, 118.9 (q, J_{CF} = 320 Hz), 120.72, 120.73, 121.9, 122.5, 123.3, 134.8, 144.4, 151.0, 152.5 ppm. IR (KBr) ν = 3009, 2942, 2850, 1604, 1419, 1370, 1347, 1234, 1211, 1195, 1128, 1053, 1028, 978, 933, 894, 836, 817, 788, 758 cm^{-1}. HRMS (EI): calcd for $C_{14}H_{13}F_3O_6S$ $[M]^+$ 366.0385; found 366.0374.

Diethyl(5,7,8-trimethoxynaphthalen-1-yl) phosphate (23)

Sodium hydride (60% dispersion in paraffin liquid, 20.5 mg, 0.51 mmol) was added to a stirred solution of **24** (100 mg, 0.43 mmol) in THF (4 mL) at 0 °C under argon. After 30 min, diethyl chlorophosphate (67.9 μL, 0.47 mmol) was added dropwise to the mixture at 0 °C, and stirring was continued for 20 min at the same temperature. The reaction was quenched with water (3 mL) at 0 °C, and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined extracts were washed with water (2 × 5 mL) and brine (2 × 5 mL), then dried with Na_2SO_4. The mixture was concentrated *in vacuo*, and the residue was purified by column chromatography (hexane/EtOAc 3 : 1) to give **23** (155 mg, 98%) as a yellow oil. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 1.26–1.33 (m, 6H), 3.85 (s, 3H), 3.99 (s, 3H), 4.00 (s, 3H), 4.23–4.32 (m, 4H), 6.69 (s, 1H), 7.24 (dd, J = 15.9, 7.6 Hz, 1H), 7.50–7.52 (m, 1H), 8.01 (d, J = 8.8 Hz, 1H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 16.6, 16.1, 55.8, 57.2, 61.7, 64.32, 64.39, 95.8, 118.0, 119.2, 122.2, 122.8, 123.6, 145.5, 145.6, 150.2, 152.3 ppm. IR (neat) ν = 3481, 2983, 2935, 2843, 1600, 1510, 1456, 1421, 1363, 1267, 1250, 1208, 1056, 1035, 959, 848, 809, 761 cm^{-1}. HRMS (EI): calcd for $C_{17}H_{23}O_7P$ $[M]^+$ 370.1181; found 370.1194.

1,2,4-Trimethoxy-8-(4-methyl-3-penten-1-yl)naphthalene (21)

5-Bromo-2-methyl-2-pentene (3.30 mL, 24 mmol) was added slowly to a stirred suspension of magnesium turnings (654 mg, 27 mmol) in Et_2O (49 mL) under argon, and stirring was continued for 20 min, which resulted in the production of Grignard reagent **25**.

$NiCl_2$(dppp) (1.10 g, 2.0 mmol) and a solution of **23** (3.02 g, 8.2 mmol) in Et_2O (41 mL) were successively added to the above solution of **25** in Et_2O, and the resulting mixture was stirred at room temperature for 2 h. The reaction was quenched with 1 M HCl (30 mL) at 0 °C, and the resulting mixture was extracted with EtOAc (3 × 30 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (2 × 50 mL) and brine (2 × 50 mL), then dried with Na_2SO_4. The mixture was concentrated *in vacuo*, and the residue was purified by column chromatography (hexane/EtOAc 20 : 1) to give **21** (2.20 g, 89%) as a yellow oil. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 1.55 (s, 3H), 1.69 (s, 3H), 2.35 (q, J = 7.6 Hz, 2H), 3.16–3.18 (m, 2H), 3.85 (s, 3H), 3.99 (s, 3H), 4.00 (s, 3H), 5.24–5.28 (m, 1H), 6.68 (s, 1H), 7.21 (d, J = 6.8 Hz, 1H), 7.24–7.27 (m, 1H), 8.08 (dd, J = 8.3, 2.0 Hz, 1H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 17.6, 25.7, 31.0, 37.0, 55.8, 57.3, 61.2, 95.5, 120.4, 122.7, 123.1, 124.7, 127.6, 129.8, 131.4, 137.4, 139.1, 149.5, 152.7 ppm. IR (neat) ν = 2930, 2841, 1616, 1596, 1511, 1456, 1418, 1362, 1204, 1171, 1049, 980, 920, 808, 767, 713 cm^{-1}. HRMS (EI): calcd for $C_{19}H_{24}O_3$ $[M]^+$ 300.1725; found 300.1714.

5,6,8-Trimethoxy-1,1-dimethyl-1,2,3,4-tetrahydrophenanthrene (20)

p-Toluenesufonic acid monohydrate (217 mg, 1.1 mmol) was added to a stirred solution of **21** (311 mg, 1.0 mmol) in CH_2Cl_2 (21 mL) at room temperature, and the mixture was heated at reflux for 2 h. After cooling to room temperature, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ (10 mL), and the resulting mixture was extracted with $CHCl_3$ (3 × 10 mL). The combined extracts were washed with brine (2 × 15 mL), then dried with $MgSO_4$. The mixture was concentrated *in vacuo*, and the residue was purified by column chromatography (hexane/EtOAc 12 : 1) to give **20** (261 mg, 84%) as a colourless solid. Recrystallization from hexane gave an analytical sample of **20** as colourless needles. M.p. 72–73 °C. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 1.35 (s, 6H), 1.69–1.72 (m, 2H), 1.79–1.82 (m, 2H), 3.42 (t, J = 6.3 Hz, 2H), 3.77 (s, 3H), 3.96 (s, 3H), 3.98 (s, 3H), 6.63 (s, 1H), 7.33 (d, J = 9.3, 1H), 7.98 (d, J = 8.8 Hz, 1H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 20.4, 30.0, 31.9 (2C), 34.8, 38.8, 55.9, 57.4, 61.2, 95.2, 119.4, 120.4, 123.4, 128.7, 131.0, 140.2, 144.5, 150.3, 152.4 ppm. IR (neat) ν = 2929, 1614, 1512, 1453, 1420, 1409, 1362, 1314, 1259, 1203, 1154, 1127, 1071, 1038, 982, 926, 883 cm^{-1}. HRMS (EI): calcd for $C_{19}H_{24}O_3$ $[M]^+$ 300.1725; found 300.1732.

3-Methoxy-8,8-dimethyl-5,6,7,8-tetrahydrophenanthrene-1,4-dione (27)

A solution of ammonium cerium(IV) nitrate (5.48 g. 1.0 mmol) in MeCN/H_2O (1 : 1, 100 mL) was added to a stirred solution of

20 (1.00 g, 3.3 mmol) in MeCN (33 mL) at 0 °C. After 10 min, the reaction mixture was diluted with water (50 mL), and the resulting mixture was extracted with Et_2O (3 × 100 mL). The combined extracts were washed with brine (2 × 100 mL), then dried with Na_2SO_4. The mixture was concentrated *in vacuo*, and the residue was purified by column chromatography (hexane/EtOAc 3 : 1) to give **27** (668 mg, 74%) as a yellow powder. Recrystallization from hexane/EtOAc (5 : 1) gave an analytical sample of **27** as yellow granules. M.p. 155–156 °C. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 1.33 (s, 6H), 1.66–1.69 (m, 2H), 1.80–1.83 (m, 2H), 3.24 (t, J = 6.3 Hz, 2H), 3.88 (s, 3H), 6.08 (s, 1H), 7.73 (d, J = 8.3 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 19.2, 29.9, 31.8 (2C), 34.9, 37.8, 56.3, 107.7, 124.1, 128.6, 131.4, 132.6, 140.8, 153.3, 161.1, 181.9, 185.0 ppm. IR (neat) ν = 2930, 1674, 1649, 1616, 1567, 1470, 1457, 1358, 1316, 1247, 1189, 1169, 1151, 1057, 885, 851 cm^{-1}. HRMS (EI): calcd for $C_{17}H_{18}O_3$ $[M]^+$ 270.1256; found 270.1260.

tert-Butyl(8,8-dimethyl-1,4-dioxo-1,4,5,6,7,8-hexahydrophenanthren-3-yl)carbamate (28)

Potassium *tert*-butoxide (416 mg, 3.7 mmol) was added to a stirred solution of **27** (668 mg, 2.5 mmol) in THF (25 mL) containing *tert*-butyl carbamate ($BocNH_2$) (1.45 g, 12 mmol) at room temperature. After 10 min, the reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (2 × 10 mL), then dried with Na_2SO_4. The mixture was concentrated *in vacuo*, and the residue was purified by column chromatography (hexane/EtOAc 10 : 1) to give **28** (722 mg, 82%) as a yellow amorphous solid. Recrystallization from hexane/EtOAc (5 : 1) gave an analytical sample of **28** as yellow columnar crystals. M.p. 133–135 °C. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 1.33 (s, 6H), 1.53 (s, 9H), 1.67–1.70 (m, 2H), 1.80–1.86 (m, 2H), 3.22 (t, J = 6.3 Hz, 2H), 7.38 (s, 1H), 7.76 (d, J = 8.3 Hz, 1H), 7.82 (br s, 1H), 7.98 (d, J = 8.3 Hz, 1H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 19.2, 28.0, 30.0 (3C), 31.8 (2C), 34.8, 37.7, 82.2, 113.0, 124.3, 127.4, 131.6, 133.2, 140.8, 141.8, 151.2, 152.9, 182.0, 184.8 ppm. IR (neat) ν = 3376, 2933, 1740, 1567, 1497, 1368, 1320, 1285, 1241, 1221, 1160, 1141, 1128, 1067, 993, 879, 850, 820, 749 cm^{-1}. HRMS (EI): calcd for $C_{21}H_{25}NO_4$ $[M]^+$ 355.1784; found 355.1770.

3-(*tert*-Butoxycarbonylamino)-8,8-dimethyl-5,6,7,8-tetrahydrophenanthrene-1,4-diyl diformate (18)

Acetyl chloride (43.0 mL, 0.61 mol) was added slowly to a stirred solution of sodium formate (50.0 g, 0.74 mol) in Et_2O (160 ml) at room temperature under argon. After 12 h, the solids were separated by filtration and the solvent was removed *in vacuo*. The residue was purified by distillation (15 mbar, 35 °C) to afford acetic formic anhydride (AcOCHO) (25.1 g, 47%), which was stored in the freezer in a sealed vial under argon.

AcOCHO (1.37 g, 16 mmol) prepared above was added to a stirred solution of **28** (0.28 g, 0.78 mmol) in THF (16 mL) containing zinc (0.51 g, 7.8 mmol) and potassium carbonate (1.08 g, 7.8 mmol) at room temperature. After 12 h, the reaction mixture was diluted with EtOAc (80 mL) and the solids were separated by filtration. The filtrate was washed successively with 0.1 M HCl (20 mL), water (2 × 20 mL) and brine (2 × 20 mL), then dried with Na_2SO_4. The mixture was concentrated *in vacuo*, and the residue was purified by column chromatography (hexane/EtOAc 4 : 1) to give **18** (303 mg, 94%) as a colourless amorphous solid. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 1.34 (s, 6H), 1.49 (s, 9H), 1.67–1.70 (m, 2H), 1.78–1.83 (m, 2H), 3.07–3.15 (m, 1H), 3.24–3.32 (m, 1H), 7.13 (s, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.82 (d, J = 8.8 Hz, 1H), 8.18 (s, 1H), 8.47 (s, 1H), 9.36 (s, 1H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$) δ = 19.9, 27.8 (3C), 31.0, 31.7 (2C), 35.0, 38.1, 85.5, 117.3, 119.2, 124.7, 126.9, 128.4, 131.8, 141.6, 144.0, 146.7, 151.4, 158.6, 158.8, 162.0 ppm. IR (neat) ν = 2935, 2869, 1745, 1715, 1626, 1608, 1510, 1457, 1434, 1395, 1370, 1298, 1257, 1221, 1152, 1094, 918, 844, 756 cm^{-1}. HRMS (EI): calcd for $C_{23}H_{27}NO_6$ $[M]^+$ 413.1838; found 413.1838.

8,8-Dimethyl-8,9,10,11-tetrahydrophenanthro[3,4-*d*]oxazol-5-ol (16)

A solution of **18** (286 mg, 0.69 mmol) in toluene (14 mL) containing *p*-toluenesufonic acid monohydrate (0.39 g, 2.1 mmol) was heated at reflux for 4 h. After cooling to room temperature, saturated aqueous $NaHCO_3$ (10 mL) was added to the mixture, and the resulting mixture was extracted with EtOAc (3 × 20 mL). The combined extracts were washed with brine (2 × 20 mL), then dried with Na_2SO_4. The mixture was concentrated *in vacuo*, and the residue was purified by column chromatography (hexane/EtOAc 2 : 1) to give **16** (139 mg, 68%) as a colourless amorphous solid. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 1.39 (s, 6H), 1.76–1.79 (m, 2H), 1.96–2.02 (m, 2H), 3.45 (t, J = 6.6 Hz, 2H), 7.24 (s, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.64 (br s, 1H), 8.16 (d, J = 8.8 Hz, 1H), 8.19 (s, 1H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 19.5, 29.2, 31.6 (2C), 34.4, 38.5, 99.7, 120.6, 120.9, 122.6, 124.7, 129.5, 136.6, 141.8, 145.0, 150.4, 151.6 ppm. IR (neat) ν = 3128, 2927, 1597, 1507, 1454, 1415, 1360, 1301, 1248, 1192, 1158, 1119, 815, 759, 630 cm^{-1}. HRMS (EI): calcd for $C_{17}H_{17}NO_2$ $[M]^+$ 267.1259; found 267.1249.

Salviamine F (6)

Aluminium chloride (20.8 mg, 0.16 mmol) was added to a stirred solution of **16** (13.9 mg, 52 μmol) in benzene (5.2 mL) containing acetyl chloride (11 μL, 0.16 mmol) at room temperature, and the mixture was heated at reflux for 20 h. After cooling to room temperature, 3 M HCl (2 mL) was added to the mixture at 0 °C, and the resulting mixture was extracted with EtOAc (3 × 5 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (2 × 5 mL) and brine (2 × 5 mL), then dried with Na_2SO_4. The mixture was concentrated *in vacuo*, and the residue was purified by column chromatography (hexane/EtOAc 20 : 1) to give **6** (11.3 mg, 70%) as a yellow powder. Recrystallization from acetone gave an analytical sample of **6** as yellow needles {ref. 1 yellow syrup}. M.p. 197–198 °C {ref. 1 M.p. was not reported}. The ^{1}H and ^{13}C NMR, IR, and MS spectra (see below) were identical to those of

natural salviamine F.[1] ^{1}H NMR (400 Hz, $CDCl_3$): δ = 1.39 (s, 6H), 1.75–1.78 (m, 2H), 1.95–2.01 (m, 2H), 3.04 (s, 3H), 3.40 (t, J = 6.3 Hz, 2H), 7.58 (d, J = 8.8, 1H), 8.16 (s, 1H), 8.32 (d, J = 8.8 Hz, 1H), 14.66 (s, 1H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 19.4, 29.1, 31.2, 31.5 (2C), 34.7, 38.2, 106.1, 122.5, 122.8, 124.0, 125.4, 129.7, 134.9, 140.6, 149.3, 150.7, 162.2, 203.8 ppm. IR (neat) ν = 2964, 2931, 1619, 1585, 1509, 1459, 1422, 1392, 1364, 1308, 1289, 1244, 1115, 1060, 1025, 871, 828, 790, 616 cm^{-1}. HRMS (EI): calcd for $C_{19}H_{19}NO_3$ $[M]^+$ 309.1365; found 309.1366.

3-(*tert*-Butoxycarbonylamino)-8,8-dimethyl-5,6,7,8-tetrahydrophenanthrene-1,4-diyl diacetate (19)

Acetic anhydride (0.22 mL, 2.4 mmol) was added to a stirred solution of **28** (41.8 mg, 0.12 mmol) in THF (2.4 mL) containing zinc (76.9 mg, 1.2 mmol) and potassium carbonate (81.3 mg, 0.59 mmol) at room temperature. After 3 h, the solids were separated by filtration and the filtrate was diluted with EtOAc (20 mL). The organic layer was washed successively with 0.1 M HCl (5 mL), water (2 × 5 mL) and brine (2 × 5 mL), then dried with Na_2SO_4. The mixture was concentrated *in vacuo*, and the residue was purified by column chromatography (hexane/EtOAc 4 : 1) to give **19** (37.5 mg, 72%) as a colourless solid. Recrystallization from hexane/$CHCl_3$ (10 : 1) gave an analytical sample of **19** as colourless needles. Mp: 177–178 °C. ^{1}H NMR (400 Hz, $CDCl_3$): δ = 1.31 (s, 6H), 1.51 (s, 9H), 1.66–1.68 (m, 2H), 1.76–1.82 (m, 2H), 2.42 (s, 3H), 2.43 (s, 3H), 3.12 (br s, 2H), 6.46 (br s, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.97 (br s, 1H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$) δ = 20.2, 20.9, 21.2, 28.3 (3C), 30.1, 31.7 (2C), 34.5, 38.3, 81.1, 112.5, 119.2, 123.4, 125.7, 127.7, 128.5, 130.0, 134.1, 144.8, 145.3, 152.5, 168.8, 169.3 ppm. IR (neat) ν = 3357, 2928, 1762, 1745, 1720, 1655, 1636, 1501, 1371, 1267, 1217, 1170, 1140, 1065, 1017, 821 cm^{-1}. HRMS (EI): calcd for $C_{25}H_{31}NO_6$ $[M]^+$ 441.2151; found 441.2161.

2,8,8-Trimethyl-8,9,10,11-tetrahydrophenanthro[3,4-*d*]oxazol-5-ol (17)

A solution of **19** (31.8 mg, 72 μmol) in toluene (3.6 mL) containing *p*-toluenesufonic acid monohydrate (41.4 mg, 0.22 mmol) was heated at reflux for 5 h. After cooling to room temperature, saturated aqueous $NaHCO_3$ (2 mL) was added to the reaction mixture, and the resulting mixture was extracted with EtOAc (3 × 5 mL). The combined extracts were washed with brine (2 × 5 mL), then dried with Na_2SO_4. The mixture was concentrated *in vacuo*, and the residue was purified by column chromatography (hexane/EtOAc 1 : 1) to give **17** (17.5 mg, 86%) as a colourless solid. Recrystallization from $CHCl_3$ gave an analytical sample of **17** as colourless plates. M.p. 250–252 °C. ^{1}H NMR (400 Hz, $CDCl_3$/CD_3OD 10 : 1): δ = 1.38 (s, 6H), 1.75–1.78 (m, 2H), 1.95–201 (m, 2H), 2.70 (s, 3H), 3.42 (t, J = 6.3 Hz, 2H), 7.00 (s, 1H), 7.51 (d, J = 8.8 Hz, 1H), 8.16 (d, J = 8.8 Hz, 1H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$/CD_3OD 10 : 1): δ = 14.3, 19.4, 29.1, 31.4 (2C), 34.1, 38.5, 98.1, 120.6, 120.7, 121.9, 123.8, 128.8, 137.7, 141.5, 144.4, 150.9, 162.5 ppm. IR (neat) ν = 3138, 2940, 1569, 1451, 1412, 1317, 1280, 1248, 1215, 1193, 1173, 1153, 1122, 1057, 981, 952, 829, 754 cm^{-1}. HRMS (EI): calcd for $C_{18}H_{19}NO_2$ $[M]^+$ 281.1416; found 281.1411.

Salviamine E (5)

Aluminium chloride (24.0 mg, 0.18 mmol) was added to a stirred solution of **17** (16.9 mg, 60 μmol) in benzene (6.0 mL) containing acetyl chloride (13 μL, 0.18 mmol) at room temperature, and the mixture was heated at reflux for 24 h. After cooling to room temperature, 3 M HCl (2 mL) was added to the reaction mixture at 0 °C, and the resulting mixture was extracted with EtOAc (3 × 5 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (2 × 5 mL) and brine (2 × 5 mL), then dried with Na_2SO_4. The mixture was concentrated *in vacuo*, and the residue was purified by column chromatography (hexane/EtOAc 20 : 1) to give **5** (15.0 mg, 77%) as a yellow powder. Recrystallization from acetone gave an analytical sample of **5** as yellow needles {ref. 1 yellow powder}. M.p. 187–188 °C {ref. 1 M.p. 188–190 °C}. The ^{1}H and ^{13}C NMR, IR, and MS spectra (see below) were identical to those of natural salviamine E.[1] ^{1}H NMR (400 Hz, $CDCl_3$): δ = 1.38 (s, 6H), 1.74–1.77 (m, 2H), 1.94–2.00 (m, 2H), 2.70 (s, 3H), 3.02 (s, 3H), 3.36 (t, J = 6.3 Hz, 2H), 7.52 (d, J = 8.8, 1H), 8.29 (d, J = 8.8 Hz, 1H), 14.57 (s, 1H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 14.7, 19.4, 29.1, 31.2, 31.5 (2C), 34.7, 38.3, 106.2, 121.6, 122.6, 124.0, 124.6, 129.3, 136.3, 140.9, 148.8, 161.6, 161.8, 204.1 ppm. IR (neat) ν = 2959, 2926, 1624, 1583, 1459, 1393, 1309, 1280, 1243, 1137, 1066, 1023, 980, 865, 826, 790, 620 cm^{-1}. HRMS (EI): calcd for $C_{20}H_{21}NO_3$ $[M]^+$ 323.1521; found 323.1520.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This study was financially supported by a JSPS KAKENHI (Grant Number JP15K07865) and a Grant-in-Aid for the Strategic Research Foundation Program at Private Universities (Grant Number S15110010L) from MEXT.

Notes and references

1 F.-W. Lin, A. G. Damu and T.-S. Wu, *J. Nat. Prod.*, 2006, **69**, 93–96.
2 D. J. Cousins, in *Medicinal, Essential Oil, Culinary Herb and Pesticidal Plants of the Labiatae*, ed. D. J. Cousins, CAB International, Wallingford, Oxford, U.K., 1994, (Part 2), pp. 244–284.
3 (*a*) Z.-F. Zhang, Z.-G. Peng, L. Gao, B. Dong, J.-R. Li, Z.-Y. Li and H.-S. Chen, *J. Asian Nat. Prod. Res.*, 2008, **10**, 391–396; (*b*) Z.-F. Zhang, H.-S. Chen, Z.-G. Peng, Z.-R. Li and J.-D. Jiang, *J. Asian Nat. Prod. Res.*, 2008, **10**, 252–255.

4 C.-Y. Wu, Y. Liao, Z.-G. Yang, X.-W. Yang, X.-L. Shen, R.-T. Li and G. Xu, *Phytochemistry*, 2014, **106**, 171–177.
5 J. Liu, J. Zhao, Z. Dai, R. Lin, G. Wang and S. Ma, *Molecules*, 2014, **19**, 1786–1794.
6 It has been reported that salviamines A–F (0.5–3.4 mg) were isolated from the dried roots of *Salvia yunnanesis*, (9.1 kg, see: ref. 1); the isolated yields were estimated to be 0.0000055–0.000037%.
7 Recently, we have reported an approach to marine sesquiterpenoid benzoxazoles, nakijinols A, B and E–G, *via* an alternative method for the construction of benzoxazole ring system, see: Y. Takeda, K. Nakai, K. Narita and T. Katoh, *Org. Biomol. Chem.*, 2018, **16**, 3639–3647.
8 To the best of our knowledge, the method for synthesizing naphtho[2,1-*d*]oxazole-5-ol (**7**) was previously unheard of.
9 Condensation of 2-aminophenol with $CH(OEt)_3$ under refluxing conditions is a typical procedure for benzoxazole synthesis. See: (*a*) S. Rajasekhar, B. Maiti and K. Chanda, *Synlett*, 2017, **28**, 521–541; (*b*) C. S. Demmer and L. Bunch, *Eur. J. Med. Chem.*, 2015, **97**, 778–785; (*c*) R. V. Kumar, *Asian J. Chem.*, 2004, **16**, 1241–1260; (*d*) R. J. Bergeron, S. Singh and N. Bharti, *Tetrahedron*, 2011, **67**, 3163–3169; (*e*) M. M. Heravi, B. Baghernejad and H. A. Oskooie, *Chin. J. Chem.*, 2009, **27**, 379–383; (*f*) I. Mohammadpoor-Baltork, A. R. Khosropour and S. F. Hojati, *Catal. Commun.*, 2007, **8**, 1865–1870.
10 Recently, we have developed a novel and efficient method for the amination of a methoxy-*p*-quinone derivative by substitution with an amino group, see: T. Katoh, S. Atsumi, R. Saito, K. Narita and T. Katoh, *Eur. J. Org. Chem.*, 2017, 3878–3849.
11 (*a*) A. C. Benniston, T. P. L. Winstanley, H. Lemmetyinen, N. V. Tkachenko, R. W. Harrington and C. Wills, *Org. Lett.*, 2012, **14**, 1374–1377; (*b*) B. J. D. Wright, C. Chan and S. J. Danishefsky, *J. Nat. Prod.*, 2008, **71**, 409–414.
12 (*a*) K. M. Schmid, L. Jensen and S. T. Phillips, *J. Org. Chem.*, 2012, **77**, 4363–4374; (*b*) M. J. Smith, C. C. Nawrat and C. J. Moody, *Org. Lett.*, 2011, **13**, 3396–3398; (*c*) A. P. Kostikov, N. Malashikhina and V. V. Popik, *J. Org. Chem.*, 2009, **74**, 1802–1804; (*d*) R. H. Munday, R. M. Denton and J. C. Anderson, *J. Org. Chem.*, 2008, **73**, 8033–8038; (*e*) N. Kawai, Y. Fujibayashi, S. Kuwabara, K. Takao, Y. Ijuin and S. Kobayashi, *Tetrahedron*, 2000, **56**, 6467–6478; (*f*) A. T. Watson, K. Park and D. F. Wiemer, *J. Org. Chem.*, 1995, **60**, 5102–5106; (*g*) N. Harada, T. Sugioka, Y. Ando, H. Uda and T. Kuruki, *J. Am. Chem. Soc.*, 1988, **110**, 8483–8487.
13 Recently, the oxazole-ring formation from the related precursor [*i.e.* 2-(*tert*-butoxycarbonylamino)phenyl carboxylate derivative] has been reported, see: L.-M. Yu, Z. Hu, Y. Chen, A. Ravji, S. Lopez, C. B. Plescia, Q. Yu, H. Yang, M. Abdelmalak, S. Saha, K. Agama, E. Kiselev, C. Marchand, Y. Pommier and L.-K. An, *Eur. J. Med. Chem.*, 2018, **151**, 777–796.
14 The use of $BF_3{\cdot}EtO_2$ instead of *p*-TsOH·H_2O under standard conditions [*i.e.* $BF_3{\cdot}EtO_2$ (3 equiv.), CH_2Cl_2, −10 °C to room temp., 7 h] resulted in the production of intermediate **15** in 69% yield. In this reaction, the requisite product **7** was not obtained at all.
15 We believed that the hydrated water of *p*-TsOH·H_2O assisted hydrolysis of the *O*-CHO group in intermediate **15**, leading to the requisite product **7**.
16 For selected recent reviews, see: (*a*) A. Labande, E. Deydier, E. Manoury, J.-C. Daran, C. Audin and R. Poli, *Turk. J. Chem.*, 2015, **39**, 1158–1170; (*b*) W.-N. Li and Z.-L. Wang, *RSC Adv.*, 2013, **3**, 25565–25575; (*c*) M. Schnurch, R. Flasik, A. F. Khan, M. Spina, M. D. Mihovilovic and P. Stanetty, *Eur. J. Org. Chem.*, 2006, 3283–3307; (*d*) J.-P. Corbet and G. Mignani, *Chem. Rev.*, 2006, **106**, 2651–2710.
17 5,7,8-Trimethoxy-1-naphthol (**24**) was prepared from commercially available 1,2,4-trimethoxybenzene according to the reported method, which involved the following three steps: (i) Br_2, CH_2Cl_2, 0 °C, 1 h, 98%; (ii) furan, LiNi-Pr_2, THF, −78 °C, 4 h; then room temperature, 15 h and (iii) $HClO_4$, THF, room temperature, 1.5 h, 97% (2 steps); see: T. Ogata, Y. Sugiyama, S. Ito, K. Nakano, E. Torii, A. Nishiuchi and T. Kimachi, *Tetrahedron*, 2013, **69**, 10470–10476.
18 Acetic formic anhydride (AcOCHO) was prepared from HCO_2Na and AcCl according to the reported method, see: J. Doulcet and G. R. Stephenson, *Chem. – Eur. J.*, 2015, **21**, 13431–13436. It is known that this method is simpler than others previously described, gives better yields of the formylated products, and is easily adapted to the preparation of large quantities with an increase in yield. Note that when AcOCHO was prepared from HCO_2H and Ac_2O under the same conditions described for the model synthesis (*cf.* Scheme 2, **12** → **13**), poor yield of the product **18** was obtained (~10%) probably due to the incompletion of the expected double *O*-formylation.