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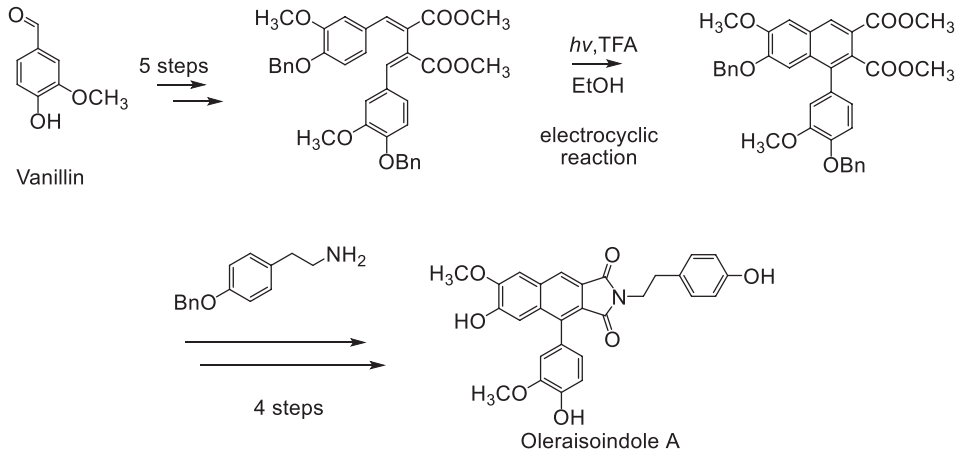
First Total Synthesis of Arylnaphthalene Lignan Oleraisoindole A

Weizeng Zhou, Chenglong Chen, Shuyu Sun, Shanpeng Chu, Mengying Li, Yamu Xia*

Department of Chemical Engineering, Qingdao University of Science and Technology, Qingdao 266042, PR China

ABSTRACT First total synthesis of arylnaphthalene lignan Oleraisoindole A, isolated from *Hyoscyamus niger*, has been reported here. Oleraisoindole A has been known for its certain inhibitory effects on the growth of breast tumor cells and white blood cells. Therefore, we design a 13-step strategy to synthesize Oleraisoindole A, involving hydrolysis, dehydration, acylation, and Pd/C catalyzed hydrogenation. The structures of all compounds were confirmed by ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR, and high-resolution mass spectra.



KEYWORDS Oleraisoindole A, Arylnaphthalene lignans, Electrocyclic reaction, Total synthesis, Lignans.

INTRODUCTION

Arylnaphthalene lignans, a class of natural compounds, are isolated from all parts of plants, for example, 1,2,3,4-tetradehydrodeoxypodophyllotoxin, from seeds of *Hernandia ovigera*;[1] daurinol, from roots, and epigeal part of *Haplophyllum dauricum*;[2] the prostalidins A, B, and C, from *Justicia*;[3] and justicinol, from the leaves of *Justicia flava vahl*.[4] This type of lignans own two C_6C_3 structural units, which build skeletal structures by all kind of resolve resolutions. From the bioactivity point of view, this type of lignans exhibit planty of incredible biological properties, including antimicrobial,[5,6] anti-inflammatory,[7] antiproliferative,[8] anti-HIV,[6] as well as other activities.

Arylnaphthalene lignans have been discovered earlier, it is disappointing that the current methods for synthesis are complicated, and the yield is unexpected. The key to synthesize arylnaphthalene lignans is the construction of the naphthalene ring. In 1979, Crescente *et al*. showed thermal and photocatalytic cyclization of succinic anhydride.[9] Nishii *et al*. developed a route by utilizing Lewis acid-promoted benzannulation of aryl

*Corresponding author: Email: xiayamu618@163.com

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(aryl')-2,2-dichlorocyclopropylmethanols aryl=aryl'; (abbreviated as AACMs) in 2004.[10] To simplify the synthesis of arylnaphthalene lignans, Eghbali *et al*. investigated a one-pot multicomponent coupling reaction between phenylacetylene, carbon dioxide, and 3-bromo-1-phenyl-1-propyne, in 2008.[11] Zhang *et al*. reported in 2013 the synthesis of sacidum lignan A employing Ueno-Stork radical cyclization reaction.[12] In 2013, Argade furnished the synthesis of justicidin B and retrojusticiding B, which builded arylnaphthalene frameworks through Pd-promoted [2+2+2] cyclization.[13] Electrocyclic reactions can be traced back to the 1960s.[14,15] Scientists all over the world have conducted in-depth studies on electrocyclization reactions, but in few cases, for the total synthesis of lignans, electrocyclic reactions have been applied. Therefore, we intend to use the strategy of electrocyclic reaction to construct naphthalene lignans.

Herein, we describe a total synthesis and characterization of naturally occurring bioactive arylnaphthalene lignin: Oleraisoindole A **[Figure 1]**, which was isolated from *Henbane* and *Portulaca oleracea* L.[16,17] The excellent anticancer activity of oleraisoindole A encouraged us to design an approach toward its core through employing a consequence of Stobbe condensation and photochemical reaction.

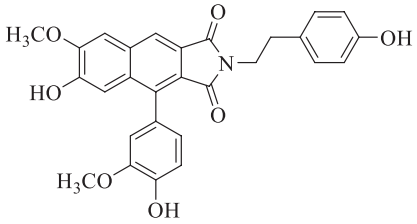
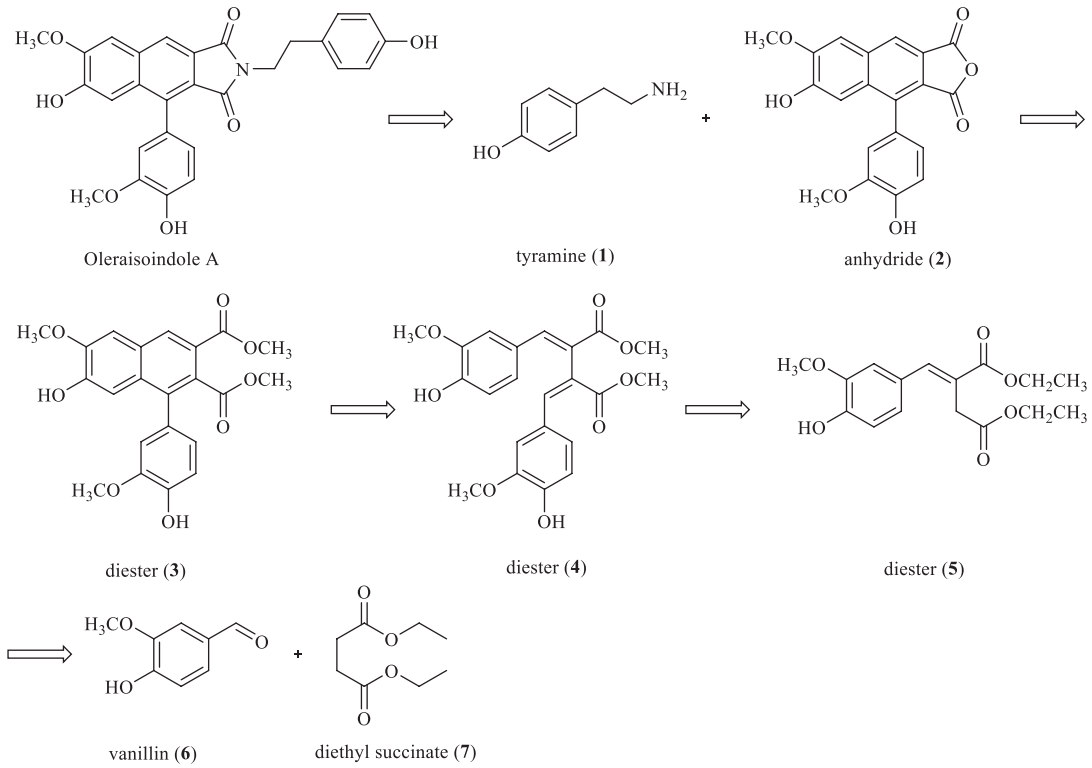


Figure 1: Oleraisoindole A

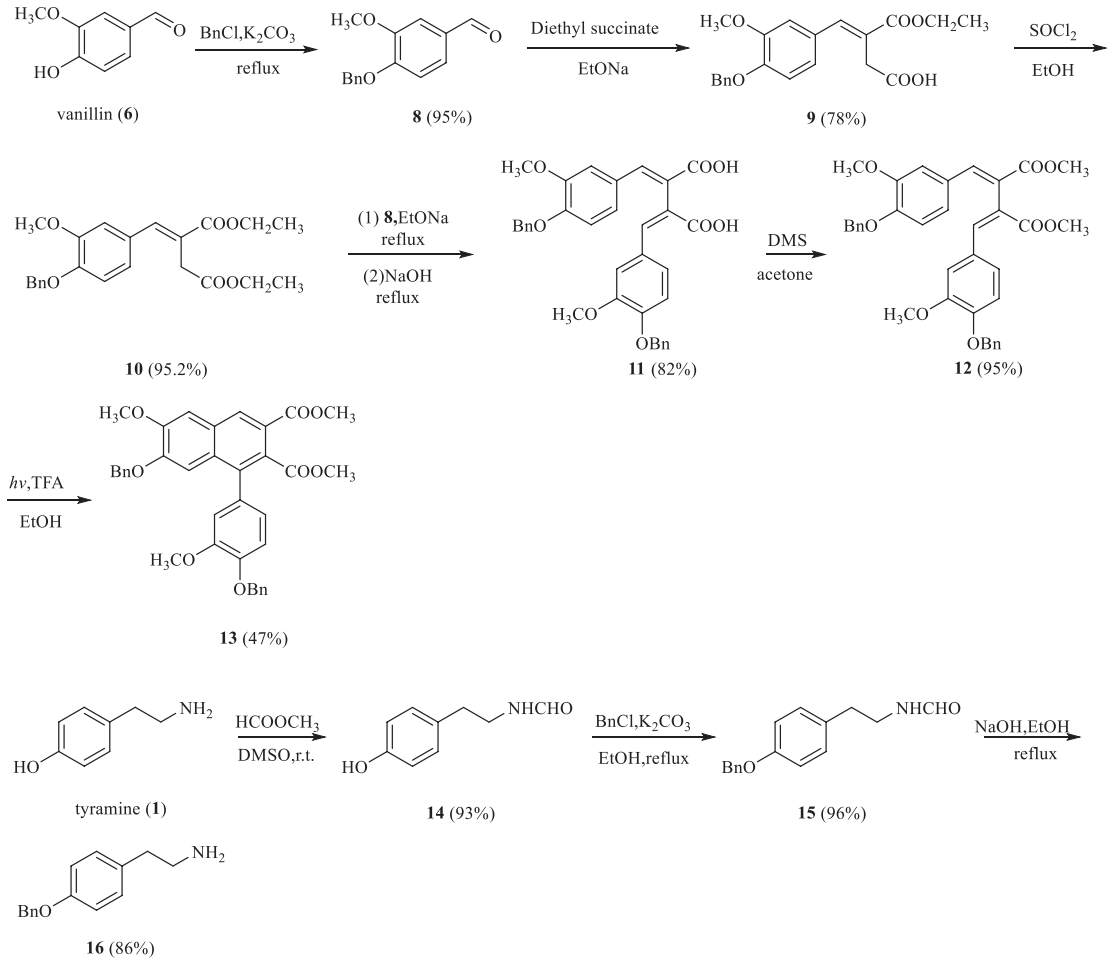
RESULTS AND DISCUSSION

A general design of our approach to Oleraisoindole A is depicted in **Scheme 1**. We can get Oleraisoindole A through acylation reaction of tyramine (**1**) and anhydride (**2**).[18] Anhydride (**2**) can be afforded by alkaline hydrolysis of diester (**3**) and dehydration.[19,20] We intend to adopt an electrocyclic reaction to construct the core of Oleraisoindole A and diester (**3**). In addition, diester (**4**) can be obtained by Stobbe condensation starting from vanillin and diethyl succinate.[19,21]

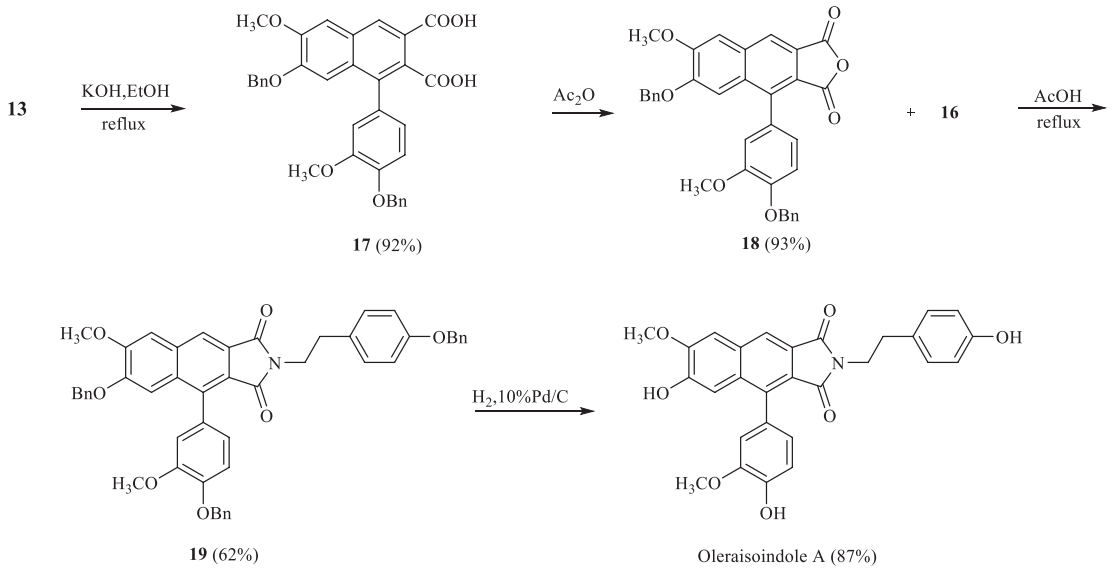
The first six synthetic steps of Oleraisoindole A are shown in **Scheme 2**. The first step was vanillin phenolic hydroxyl protection using benzyl chloride under basic conditions.[21] The second step was synthesis of an acid (**9**) through Stobbe condensation of **8** and diethyl succinate (**7**) in sodium ethoxide.[19,21] Then, synthesis of diethyl diester (**10**) was achieved by esterification of **9** with EtOH/$SOCl_2$ as acylating reagent[19]. In step four, dicarboxylic acid (**11**) was obtained by Stobbe condensation of **8** and **10,** followed by alkaline hydrolysis. To get our latter product easily, diester **12** was obtained by methylation with dimethyl sulfate (DMS).[22] Step six was the electrocyclic reaction of **12,** which was brought about by trifluoroacetic acid (TFA) and illuminating with high-pressure mercury lamp, resulting in intermediate **13** with 25.8% total yield.[23] Due to the instability of tyramine phenolic hydroxyl group, we designed a three-step synthesis for compound **16** in **Scheme 2**.[21,24] The first step was the amino group protection of tyramine. The second step was phenol hydroxyl protection, where the phenolic hydroxyl



Scheme 1: Retrosynthetic analysis of Oleraisoindole A



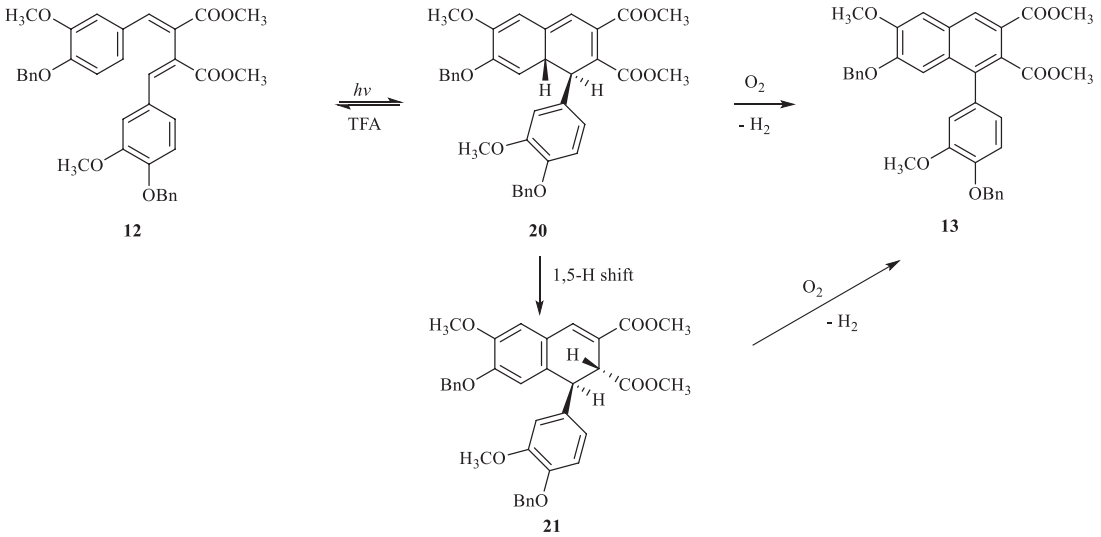
Scheme 2: Synthesis of 13 and 16 intermediates



Scheme 3: Synthesis of Oleraisoindole A

group of compound **14** was protected by benzyl chloride to give **15**. Basic hydrolysis of compound **15** afforded protected tyramine (**16**) in 76.8% total yield.

With the desired intermediates **13** and **16** in hand, the final four steps of the synthesis of Oleraisoindole A were carried out, as shown in **Scheme 3**. Alkaline hydrolysis of compound **13** yielded dicarboxylic acid **17**, which was dehydrated by acetic anhydride to give **18**.[20] The acylation reaction between **18** and **16**[18] gave **19**, which on reduction with 10% Pd/C yielded Oleraisoindole A with 46.20% total yield.[25]



Scheme 4: Possible mechanism of the electrocyclic reaction

Table 1: Comparison of different conditions and effects in electrocyclic reaction

Entry	Conditions	Yield (%) of **13**
1	*hv*, EtOH, TFA, 12 h, 60 (±5)°C	33
2	EtOH, TFA, 12 h, 100 (±5)°C	0
3	Toluene, TFA, 12 h, 110 (±5)°C	0
4	*hv*, EtOH, 12 h, 60 (±5)°C	5
5	*hv*, EtOH, TFA, 24 h, 60 (±5)°C	47
6	*hv*, EtOH, TFA, 48 h, 60 (±5)°C	46
7	*hv*, MeOH, TFA, 24 h,60 (±5)°C	25
8	*hv*, EtOH, TFA, 36 h, 60 (±5)°C	45

In addition, the possible mechanism of the electrocyclic reaction is predicted in **Scheme 4**.[9,14,26,27] Since diester **13** is a "4n+2" molecule, according to the Woodward–Hoffmann rules, we predict that the reaction happens in a conrotatory mechanism under the irradiation of a high-pressure mercury lamp to give intermediate **20** followed by a 1,5-hydrogen shift to give **21**. Diester **13** is obtained by oxidizing the intermediate with O_2 and losing H_2. A series of control experiments is shown in **Table 1**, EtOH is the best solvent, and the adjunction of TFA and ultraviolet light can promote the cyclization of **12**. The electrocyclic reaction cannot happen when the reaction temperature was raised to 100° without irradiation of high-pressure mercury lamp. Last but not least, reaction time is of significance to improve the yield of **13**. When the reaction time is longer than 24 h, the yield of **13** increases slowly.

EXPERIMENTAL SECTION

Melting points were determined with a Gallenkamp melting point apparatus without correction. High-pressure mercury lamp (125W) was purchased at Philips. All reactions were monitored by thin-layer chromatography that was performed on silica gel GF_{254} plates. Flash column chromatography was performed on silica gel (200–300 mesh). All nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AM-500MHz spectrometer (^{1}H NMR at 500 Hz, ^{13}C NMR at 125 Hz). High-resolution mass spectra (HRMS) data were recorded on a Bruker Daltonics APEXII47e spectrometer.

4-(Benzyloxy)-3-methoxybenzaldehyde (8)

A solution of vanillin (30.4 g, 199.93 mmol), benzyl bromide (25.31 g, 199.93 mmol), and potassium carbonate (27.63 g, 199.93 mmol) in dry ethanol (200 mL) was stirred at 90° for 11 h, the mixture was filtered immediately and cooled to −5° overnight. Crystals were filtered and washed by EtOH (2×30 mL) and dried to yield compound **8**: Faint yellow crystals; m. p. 64–65°; yield 45.98 g (95%); ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 3.84 s (3H, OCH_3), 5.16 s (2H, $ArCH_2O$), 6.87–7.54 m (8H, ArH), 9.85 s (1H, ArCHO); the spectral data for **8** are consistent with those in the literature.[21]

4-(4-(Benzyloxy)-3-methoxyphenyl)-3-(ethoxycarbonyl)but-3-enoic acid (9)

Compound **8** (30 g, 123.92 mmol) and diethyl succinate (21.57 g, 123.93 mmol) were added to a solution of EtONa (16.87 g, 247.84 mmol) in dry EtOH (500 mL). The mixture was refluxed for 6 h at 90° and then the EtOH was removed. About 20% HCl was added to the residue to adjust the pH to acidity. The mixture was extracted with EtOAc (3×50 mL) and the organic layer was washed with saturated brine solution and dried over anhydrous $MgSO_4$. Evaporation of EtOAc in *vacuo* gave product **9**: A brown oil, yield 35.78 g (78%); ^{1}H-NMR (500 Hz, $CDCl_3$): δ (ppm) 1.37 t (3H, OCH_2CH_3, J = 7 Hz), 3.63 s (2H, CH_2COOH), 3.92 s (3H, OCH_3), 4.32 q (2H, OCH_2CH_3, J = 7 Hz), 5.21 s (2H, $ArCH_2O$), 6.92–7.46 m (8H, ArH), 7.86 s (1H, ArCH=C); ^{13}C-NMR (125 Hz, $CDCl_3$): δ (ppm) 14.3 ($COOCH_2CH_3$), 34.1 ($C=CCH_2COOH$), 56.1 (OCH_3), 61.6 ($COOCH_2CH_3$), 70.9 (OCH_2Ar), 112.8, 113.5, 122.7, 123.3, 127.3, 127.7, 128.1, 128.7, 136.7, 142.6, 149.2, 149.6, 168.3 (C=O), 175.8 (C=O).

Diethyl 2-(4-(benzyloxy)-3-methoxybenzylidene) succinate (10)

Under an atmosphere of N_2, $SOCl_2$ (28.93 g, 24.32 mmol) was slowly added dropwise at 0° to a solution of **9** (30 g, 81.05 mmol) in dry EtOH (150 mL). The mixture was stirred for 10 h at room temperature. The EtOH and $SOCl_2$ were removed by rotary evaporation. After washing with a saturated solution of 30% Na_2CO_3 (2×100 mL), the mixture was extracted with EtOAc (3×100 mL) and the organic layer was washed with saturated brine solution and dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (EtOAc/petroleum ether = 1:3) to give product **10** as yellow oil, yield 30.72 g (95.2%); ^{1}H-NMR (500 Hz, $CDCl_3$): δ (ppm) 1.19 t (3H, OCH_2CH_3, J = 7 Hz,), 1.26 t (3H, OCH_2CH_3, J = 7 Hz), 3.52 s (2H, CCH_2COO), 3.80 s (3H, OCH_3), 4.12 q (2H, $COOCH_2CH_3$, J = 7 Hz), 4.21 q (2H, $COOCH_2CH_3$, J = 7 Hz), 5.09 s (2H, $ArCH_2O$), 6.81–7.37 m (8H, ArH), 7.77 s (1H, ArCH=C); ^{13}C-NMR (125 Hz, $CDCl_3$): δ (ppm) 14.0 ($COOCH_2CH_3$), 14.1 ($COOCH_2CH_3$), 33.7 ($C=CCH_2COO$), 55.7 (OCH_3), 60.7 ($COOCH_2CH_3$), 60.8 ($COOCH_2CH_3$), 70.5 (OCH_2Ar), 112.4, 113.2, 122.2, 124.3, 127.0, 127.7, 127.9, 128.4, 136.5, 141.4, 148.6, 149.1, 167.3(C=O), 171.1(C=O).

2-(-4-(Benzyloxy)-3-methoxybenzylidene)-3-(4-(benzyloxy)-3-methoxybenzylidene)succinic acid (11)

Compounds **10** (30 g, 75.34 mmol) and **8** (18.24 g, 75.34 mmol) were added orderly to a solution of EtONa in dry EtOH (500 mL). The mixture was refluxed for 11 h, and then EtOH was removed by rotary evaporation. 30% aq. NaOH (50 mL) was added to the reaction mixture and refluxed for 3 h. Acid **11** was filtrated after adding HCl (50 mL) to the reaction mixture. White solid; m.p. 151–152°; yield 34.98 g (82%); ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 3.78 s (6H, 2×OCH_3), 5.16 s (4H, 2×$ArCH_2O$), 6.79-7.40 m (16H, ArH), 7.96 s (2H, 2×ArCH=C). ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) 55.8 (2×OCH_3), 70.7 (2×OCH_2Ar), 112.7, 113.1, 123.3, 124.9, 127.2, 127.3, 128.0, 128.6 (2×ArCH=**C**) 136.4 (2×Ar**C**H=C), 144.2, 149.2, 150.1, 172.7 (2×C=O). The spectral data for **11** are consistent with those in the literature.[21]

Dimethyl 2-(4-(benzyloxy)-3-methoxybenzylidene)-3-(4-(benzyloxy)-3-methoxybenzylidene)succinate (12)

A mixture of compound **11** (20 g, 35.32 mmol) and DMS (7.32 g, 52.96 mmol) in acetone (15 mL) was stirred at 60° for 2 h. The acetone was evaporated *in vacuo* and the residue was washed with ammonia (20 mL). The mixture was extracted with EtOAc, and the combined organic layers were washed with saturated brine solution and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (EtOAc/petroleum ether = 1:5) to afford compound **12**: Light yellow solid; m.p. 144–146°; yield 19.94 g (95%); ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 3.73 s (6H, 2×OCH_3), 3.79 s (6H, 2×$COOCH_3$), 5.18 s (4H, 2×$ArCH_2O$), 6.82–7.43 m (16H, ArH), 7.90 s (2H, 2×ArCH=C). ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) 52.4 (2×$COOCH_3$), 55.8 (2×OCH_3), 70.7 (2×OCH_2Ar), 112.4, 113.2, 124.4, 124.6, 127.2, 127.9, 128.0, 128.6 (2×ArCH=**C**), 136.6 (2×Ar**C**H=C), 142.3, 149.3, 149.7, 167.7 (2×C=O).

Dimethyl 7-(benzyloxy)-1-(4-(benzyloxy)-3-methoxyphenyl)-6-methoxynaphthalene-2,3-dicarboxylate (13)

Under the atmosphere of air, a solution of compound **12** (15 g, 25.2 mmol) and TFA (14.39 g, 126.21 mmol) in EtOH (50 mL) was stirred under the light of high pressure mercury lamp (125 W) for 24 h. The solvent was vaporated *in vacuo* and the residue was purified by column chromatography (EtOAc/petroleum ether = 1:8) to give compound **13**:white solid; m.p. 156–158°; yield 7.05 g (47%); ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 3.59 s (3H, OCH_3), 3.79 s (3H, OCH_3), 3.93 s (3H, OCH_3), 4.04 s (3H, OCH_3), 4.99–5.08 ABq (2H, $ArCH_2O$, J = 12.5Hz), 5.26–5.33 ABq (2H, $ArCH_2O$, J = 12.5Hz), 6.68–7.55 m (15H, ArH), 8.42 s (1H, ArCH=C). ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) 52.1 ($COOCH_3$), 52.4 ($COOCH_3$), 55.9 (OCH_3), 56.1 (OCH_3), 70.7 (OCH_2Ar), 71.0 (OCH_2Ar), 107.4, 107.9, 113.5, 113.7, 122.3, 122.6, 127.4, 128.0, 128.4, 128.6, 129.4, 129.8, 129.9, 130.5, 136.0, 136.7, 137.1, 147.5, 149.1, 150.5, 150.9, 166.5 (C=O), 169.7 (C=O).

N-(4-hydroxyphenethyl)formamide (14)

A solution of tyramine (5 g, 36.48 mmol) and methyl formate (4.38 g, 72.95 mmol) in DMSO (30 mL) was stirred at room temperature for 6 h. The reaction mixture was poured into a 100-mL beaker containing 50 mL of deionized water and extracted with EtOAc (3×30 mL). The combined organic layers were washed with saturated brine solution and dried over anhydrous $MgSO_4$. Evaporation of the EtOAc *in vacuo* gave a crude product that was recrystallized (EtOAc/petroleum ether = 1:8) to give compound **14**: White solid, m.p. 96–98°; yield 5.60 g (93%); ^{1}H-NMR (500 MHz, $CDCl_3$): 2.82 t (2H, $ArCH_2CH_2$, J = 7 Hz), 3.57–3.61 m (2H, CH_2CH_2NH), 6.82–7.12 m (4H, ArH), 8.18 s (1H, NHC*H*O); ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) 31.1, 39.5, 116.9, 129.8, 156.0, 161.3, 207.2 (C=O).

N-(4-(benzyloxy) phenethyl)formamide (15)

Benzyl chloride (3.83 g, 30.29 mmol) was added dropwise to a solution of **14** (5 g, 30.29 mmol) and K_2CO_3 (4.19 g, 30.29 mmol) in EtOH (30 mL). The mixture was refluxed for 7 h. The reaction mixture was filtered at the moment when the reaction stopped. The filtrate was concentrated *in vacuo* and the residue was crystallized from EtOH to give compound **16**:White crystals, m.p. 100–101°; yield 4.02 g (96%); ^{1}H-NMR (500 MHz, $CDCl_3$): 2.83 t (2H, $ArCH_2CH_2$, J = 7 Hz), 3.46–3.63 m (2H, CH_2CH_2NH), 5.10 s (2H, $ArCH_2O$), 6.94–7.50 m (9H, ArH), 8.18 s (1H, NHC*H*O); ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) 34.6, 39.4, 70.1, 115.1, 115.2, 127.5, 128.0, 128.6, 129.8, 129.9, 130.9, 137.1, 157.6, 161.3 (C=O).

2-(4-(Benzyloxy) phenyl) ethan-1-amine (16)

A mixture of **15** (3 g, 11.76 mmol) and NaOH (0.71 g, 17.64 mmol) in EtOH were refluxed for 3 h. The reaction

mixture was cooled and the excess EtOH was vaporated in *vacuo*. The crude product was dissolved in EtOAc (30 mL) and washed with water (3×30 mL), saturated brine solution (3×30 mL) and dried over $MgSO_4$ to give product **16**: White solid, m.p. 113–115°; yield 2.30 g (86%); ^{1}H-NMR (500 MHz, $CDCl_3$): 2.73 t (3H, ArC*H*$_2$CH$_2$, *J* = 7 Hz), 2.97 t (2H, CH$_2$C*H*$_2$NH$_2$, *J* = 7 Hz), 5.09 s (2H, ArCH$_2$O), 6.96–7.48 m (9H, ArH); ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) 32.5, 39.8, 69.6, 115.4, 128.1, 128.3, 128.9, 129.9, 130.2, 137.6, 157.6. The spectral data for **10** are consistent with those in the literature.[21]

7-(Benzyloxy)-1-(4-(benzyloxy)-3-methoxyphenyl)-6-methoxynaphthalene-2,3-dicarboxylic acid (17)

A mixture of **13** (5 g, 8.41 mmol) and KOH (1.41 g, 25.19 mmol) in water (20 mL) was refluxed for 4 h. The mixture was cooled at room temperature and acidified with HCl (5 mol/L, 50 mL), whereby a white solid was obtained. The crude product was filtered, dried, and crystallized from EtOH to give compound **17**: White solid, m.p. 173–174°; yield 4.36 g (92%); ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 3.75 s (3H, OCH$_3$), 4.05 s (3H, OCH$_3$), 5.00–5.08 ABq (2H, ArCH$_2$O, *J* = 12.5 Hz), 5.21–5.33 ABq (2H, ArCH$_2$O, *J* = 12.5 Hz), 6.70–7.54 m (15H, ArH), 8.51s (1H, ArCH=C). ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) 55.8 (OCH$_3$), 56.0 (OCH$_3$), 70.6 (OCH$_2$Ar), 71.0 (OCH$_2$Ar), 107.5, 107.9, 113.4, 114.0, 122.2, 122.5, 127.3, 127.4, 127.5, 127.8, 128.0, 128.5, 128.6, 129.8, 130.1, 135.9, 136.3, 137.1, 147.6, 149.0, 150.6, 150.7, 169.9 (C=O), 174.1 (C=O).

6-(Benzyloxy)-4-(4-(benzyloxy)-3-methoxyphenyl)-7-methoxynaphtho[2,3-c]furan-1,3-dione (18)

A solution of **17** (4 g, 7.09 mmol) in acetic anhydride (20 mL) was refluxed for 3 h. The mixture was cooled at room temperature. Compound **18** was obtained after filtration, evaporation, and recrystallization (toluene/petroleum ether = 1:10). Yellow solid, m.p. 190–193°; yield 3.60 g (93%); ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 3.83 s (3H, OCH$_3$), 4.09 s (3H, OCH$_3$), 5.09 s (2H, ArCH$_2$O), 5.26–5.39 ABq (2H, ArCH$_2$O, *J* = 12.5 Hz), 6.69–7.56 m (15H, ArH), 8.29 s (1H, ArCH=C). ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) 56.1 (OCH$_3$), 56.4 (OCH$_3$), 70.8(OCH$_2$Ar), 71.1(OCH$_2$Ar), 108.4, 109.3, 113.5, 113.6, 120.9, 122.0, 124.5, 124.7, 126.5, 127.4, 128.0, 128.1, 128.2, 128.7, 132.5, 132.9, 135.5, 137.0, 141.0, 148.6, 149.5, 151.4, 152.9, 162.4 (C=O), 163.6 (C=O).

6-(Benzyloxy)-4-(4-(benzyloxy)-3-methoxyphenyl)-2-(4-(benzyloxy)phenethyl)-7-methoxy-1*H*-benzo[f]isoindole-1,3(2*H*)-dione (19)

A mixture of **18** (3 g, 5.49 mmol) and **16** (1.25 g, 5.49 mmol) in glacial acetic acid (50 mL) was heated at reflux (oil bath temperature 120°) for 13 h. The mixture was cooled at room temperature and poured into a 500-mL beaker containing 100 mL of deionized water. The aqueous reaction mixture was extracted with ether (3×30 mL). The combined organic extracts were washed with saturated Na_2CO_3 and saturated brine solution and dried over $MgSO_4$ to afford crude product. The crude product was purified by column chromatography ($V_{EtOAc}/V_{petroleumether}$ = 1:5) to give compound **19**: Yellow solid, m.p. 144–146°; yield 2.57 g (62%); ^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) 2.93 t (2H, CH$_2$C*H*$_2$Ar, *J* = 8 Hz), 3.85–3.88 m (5H, OC*H*$_3$, NC*H*$_2$CH$_2$), 4.11 s (3H, OCH$_3$), 5.06–5.14 m (4H, 2×ArCH$_2$O), 5.30–5.39 ABq (2H, ArCH$_2$O, *J* = 12.5 Hz), 6.75–7.61 m (24H, ArH), 8.18 s (1H, ArC=C). ^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) 33.8 (CH$_2$*C*H$_2$Ar), 39.5 (N*C*H$_2$CH$_2$), 56.0 (OCH$_3$), 56.2 (OCH$_3$), 70.0 (OCH$_2$Ar), 70.7 (OCH$_2$Ar), 71.0 (OCH$_2$Ar), 108.6, 109.5, 113.3, 113.5, 114.9, 121.9, 122.0, 122.5, 126.7, 127.4, 127.5, 127.7, 127.9, 128.0, 128.5, 128.6, 128.7, 129.9, 130.7, 131.5, 131.7, 135.8, 137.1, 137.2, 138.1, 148.2, 149.3, 150.3, 151.8, 157.5, 167.6 (C=O), 168.1 (C=O). HRMS, m/z: 756.2881 $[M + H]^+$ (for $C_{49}H_{41}NO_7$ calculated: 756.2883).

Oleraisoindole A

Under an atmosphere of dry nitrogen, to a solution of **19** (1 g, 1.32 mmol) in anhydrous EtOH was added 10% Pd/C (100 mg), and then the nitrogen in the flask was replaced with hydrogen and stirred at room temperature for 2 h. The mixture was filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (EtOAc/petroleum ether/EtOH = 1:3:0.5) to get Oleraisoindole A: A light yellow oil, 0.56 g (87%); ^{1}H-NMR (500 MHz, CD_3OH): δ (ppm) 2.93 t (2H, CH$_2$C*H*$_2$Ar, *J* = 8 Hz), 3.87 t (2H, NC*H*$_2$CH$_2$, *J* = 8 Hz), 3.93 s (3H, OCH$_3$), 4.14 (3H, s, OCH$_3$), 6.76–7.37 m (9H, ArH), 8.20 s (1H, s, ArCH=C). ^{13}C-NMR (125 MHz, CD_3OH): δ (ppm) 38.5 (CH$_2$*C*H$_2$Ar), 39.0 (N*C*H$_2$CH$_2$), 55.0 (OCH$_3$), 55.2 (OCH$_3$), 108.4, 111.0, 113.7, 114.5, 114.8, 121.6, 121.8, 122.6, 129.5, 146.3, 147.3, 151.7, 151.8, 167.8 (C=O), 168.9 (C=O). HRMS, m/z: 486.1404 $[M + H]^+$.[17]

CONCLUSION

A concise and facile strategy for the synthesis of Oleraisoindole A has been developed with satisfying yields for the first time. This is an age-old but novel method to apply the electrocyclic reaction in constructing the skeleton of arylnaphthalene lignans. Additional studies to better understand the reaction mechanism and bioactivity of Oleraisoindole A derivatives are ongoing in our group.

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