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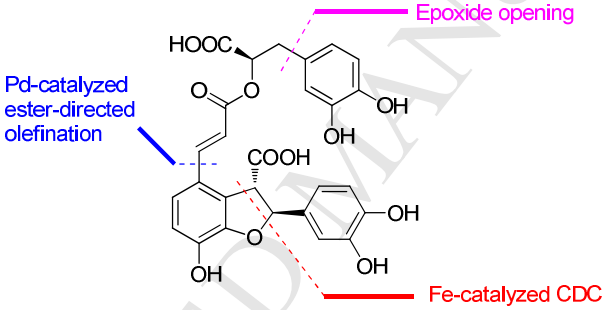
Total synthesis of lithospermic acid using Fe-catalyzed Cross-Dehydrogenative-Coupling reaction and Pd-catalyzed ester-directed C-H olefination

Yong Zheng, Weibin Song, Yefu Zhu, Bole Wei and Lijiang Xuan*
State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 501 Haike Road, Zhangjiang Hi-Tech Park, Shanghai 201203, China

*Corresponding Author. Email: ljxuan@mail.shcnc.ac.cn

The total synthesis of lithospermic acid has been accomplished employing two C-H activation reactions as key steps. Fe-catalyzed Cross-Dehydrogenative-Coupling reaction was used for the rapid construction of benzofuran framework. Pd-catalyzed ester-directed C-H olefination allowed the efficient assembly of the dihydrobenzofuran ester and acrylate moieties.



1. Introduction

Lithospermic acid (Figure 1) is originally isolated from *Lithospermum ruderale* in 1963, and its gross structure was fully elucidated in 1975.[1,2] It is one of the pharmaceutically active components of traditional Chinese medical plant Danshen (*Salvia miltiorrhiza*), which is used for the treatment of cardiovascular and cerebrovascular diseases.[3] Recently, lithospermic acid has been shown to exhibit HIV-1 integrase inhibition activity (IC_{50} = 1.4 μM).[4]

Owing to its remarkable biological profiles, limited availability from natural sources, and intriguing structural features, total synthesis of lithospermic acid have spurred considerable interest of the synthetic community. In 2005, Ellman and Bergman group reported the first total synthesis of (+)-lithospermic acid by exploiting Rh-catalyzed asymmetric intramolecular C-H alkylation as a key step.[5] Yu group also achieved total synthesis of lithospermic acid via Rh-catalyzed carbene C-H insertion and a late-stage Pd-catalyzed intermolecular C-H olefination.[6] Since then, Coster, Ghosh and Hyu groups have completed their total synthesis respectively.[7-9] It is still highly desirable to develop a concise synthetic route to lithospermic acid analogues for the evaluation of their potentials as lead compounds in drug research.

Recently, metal-catalyzed C-H activation has emerged as a powerful and economical tool for the total synthesis of natural products, owing to its remarkable potential for step and atom economy.[10] Our group has recently accomplished the first total synthesis of salvianoic acid A by employing Ru-catalyzed C-H olefination as a key step.[11] As part of our interest to explore synthesis and

structural modification of bioactive compounds from *Salvia miltiorrhiza*, we herein report a concise total synthesis of lithospermic acid using two C-H activation reactions as key steps. Fe-catalyzed Cross-Dehydrogenative-Coupling (CDC) was utilized for the rapid construction of benzofuran skeleton.[12] The dihydrobenzofuran ester and acrylate fragments were coupled by Pd-catalyzed ester-directed C-H olefination.[13]

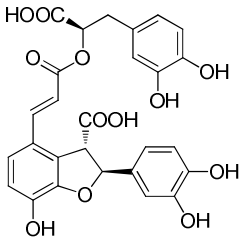
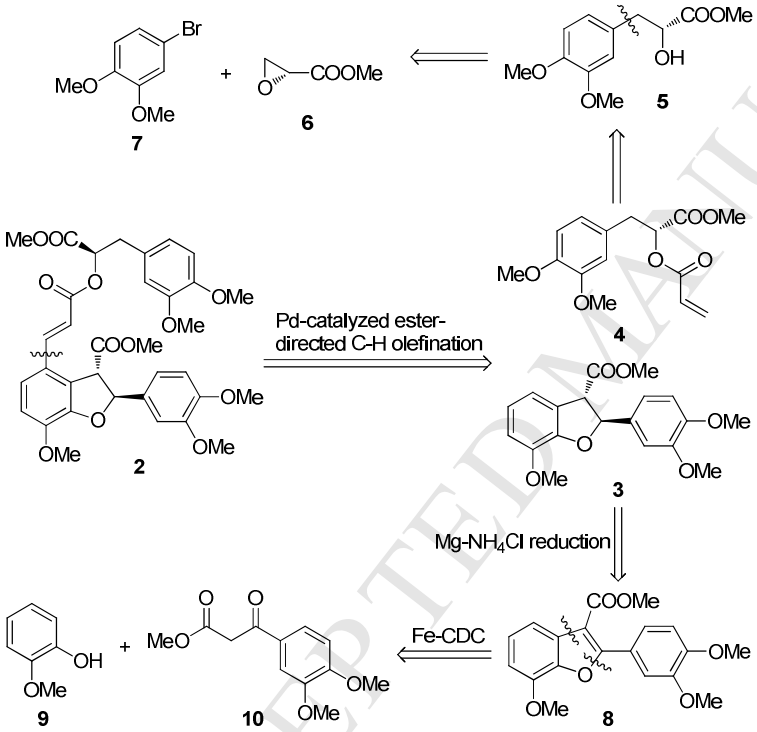


Figure 1. (+)-Lithospermic acid (**1**)



Scheme 1. Retrosynthetic analysis of heptamethyl lithospermic acid (**2**).

2. Results and discussion

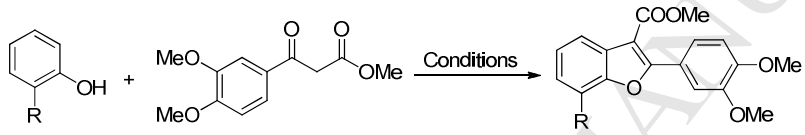
Our retrosynthetic analysis is depicted in Scheme 1. We envisioned that hepatmethyl lithospermic acid **2** could be assembled from dihydrobenzofuran ester **3** and acrylate subunit **4** by Pd-catalyzed ester-directed C-H olefination. Alcohol **5** was synthesized through metal-participated asymmetric reaction of **7** with the optically pure 2,3-epoxypropionate **6**, which has been reported in our previous work.[11] Dihydrobenzofuran ester **3** was prepared via Mg-NH_4Cl reduction of benzofuran ester **8**. Construction of **8** could be achieved by Fe-catalyzed CDC reaction of phenol **9** with *β*-keto ester **10**.

We initially began to synthesize benzofuran ester **8** from 2-methoxylphenol **9** and *β*-keto ester **10** by Fe-catalyzed CDC reaction. Disappointedly, by using $FeCl_3 \cdot 6H_2O$ as catalyst and $(t\text{-BuO})_2$ as oxidant, the desired product **8** resulted in 5% yield (Table1, entry 1). Other Fe catalysts and

oxidants failed to afford the desired product (Table1, entries 2-4). When oxygen was used as oxidant, **8** would be obtained in 20% yield (Table1, entry 5). The yield was increased to 35% when 1,10-phenanthroline was added as ligand (Table1, entry 6). Using other ligands, such as 2,2'-bipyridine and pyridine, did not further improve the yield (Table1, entries 7 and 8). All attempts to synthesize **8** by CDC reaction in acceptable yield were in vain. We suspected that the unsatisfactory yield of **8** arose from the presence of *ortho*-methoxyl group in phenol **9**. We then turned our attention to other 2-substituted phenols. Gratifyingly, the reaction between phenol **9a** and *β*-keto ester **10** gave **8a** in 72% yield (Table1, entry 9). 2-bromophenol **9b**, reacting with **10** under $FeCl_3$ and $(t\text{-BuO})_2$ conditions, afforded the desired product **8b** in 55% yield (Table1, entry 10). The yield was improved to 64% by adding 1,10-phenanthroline as ligand (Table1, entry 11).

Having successfully prepared benzofuran ester **8b**, we next examined the possibility of transforming **8b** into **8** (Scheme 2). Fortunately, Ullman coupling of **8b** with MeONa in the presence of CuBr proceeded smoothly to furnish the desired product in 78% yield. Reduction of benzofuran ester **8** under Mg and NH_4Cl in MeOH successfully gave the corresponding (±)-*trans*-dihydrobenzofuran ester **3** in 67% yield without affecting ester group.

Table 1. Optimization of Fe-catalyzed CDC reaction[a]



9 R = OMe
9a R = H
9b R = Br

10

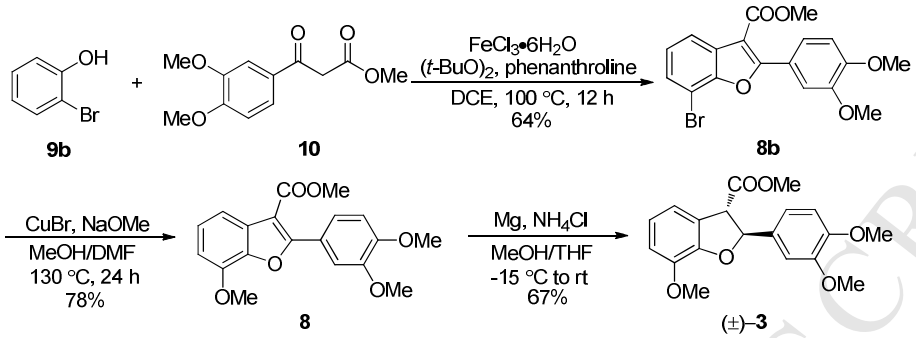
8 R = OMe
8a R = H
8b R = Br

Entry	R	Catalyst	Oxidant	Ligand	Yield (%)[b]
1	OMe	$FeCl_3\cdot 6H_2O$	$(t\text{-BuO})_2$		5
2	OMe	$FeSO_4$	$(t\text{-BuO})_2$		trace
3	OMe	$Fe(acac)_3$	$(t\text{-BuO})_2$		trace
4	OMe	$FeCl_3\cdot 6H_2O$	*t*-BuOOH		0
5	OMe	$FeCl_3\cdot 6H_2O$	O_2		20
6	OMe	$FeCl_3\cdot 6H_2O$	O_2	1,10-phenanthroline	35
7	OMe	$FeCl_3\cdot 6H_2O$	O_2	2,2'-bipyridine	19
8	OMe	$FeCl_3\cdot 6H_2O$	O_2	pyridine	10
9	H	$FeCl_3\cdot 6H_2O$	$(t\text{-BuO})_2$		72
10	Br	$FeCl_3\cdot 6H_2O$	$(t\text{-BuO})_2$		55
11	**Br**	**$FeCl_3\cdot 6H_2O$**	**$(t\text{-BuO})_2$**	**1,10-phenanthroline**	**64**

[a]Reaction conditions: phenol (0.3 mmol), **10** (0.2 mmol), Fe catalyst (10 mol%), oxidant (0.3 mmol) or O_2 (1 atm), ligand (20 mol %), DCE (2 mL), 100 °C, 12 h.
[b]Isolated yield.

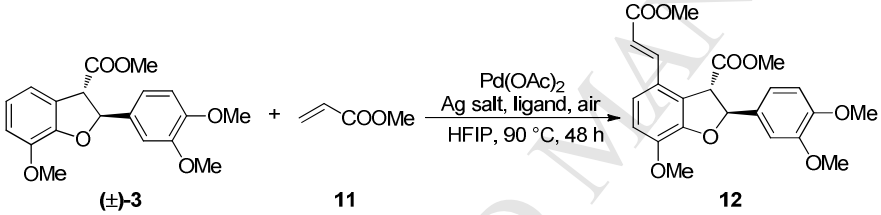
With (±)-dihydrobenzofuran ester **3** in hand, we next investigated Pd-catalyzed C-H olefination for coupling of (±)-dihydrobenzofuran ester **3** and acrylate **4**. In Yu's previous work, carboxylic acid group was employed as directing group for a late stage C-H olefination to construct the lithospermic acid.[6] Inspired by examples of phenylacetic ester-directed C-H olefination, we envisioned that phenylacetic ester group in (±)-**3** could be utilized as directing group for C-H

olefination, which avoids preparing acid by hydrolysis of ester.[13] To test our hypothesis, dihydrobenzofuran ester **3** and methyl acrylate **11** were chosen as standard substrates to test the C-H olefination. To our delight, the coupling product **12** was obtained in 17% yield with $Pd(OAc)_2$ and Ag_2CO_3 in HFIP (Table 2, entry 1). Further optimization of ligand revealed that the yield of **12** was improved to 81 % when Ac-Gly-OH was used as the ligand (Table 2, entries 2-4). Other silver salts gave lower yields than Ag_2CO_3 for the C-H olefination (Table 2, entries 5-7).



Scheme 2. Synthesis of (±)-dihydrobenzofuran ester **3**

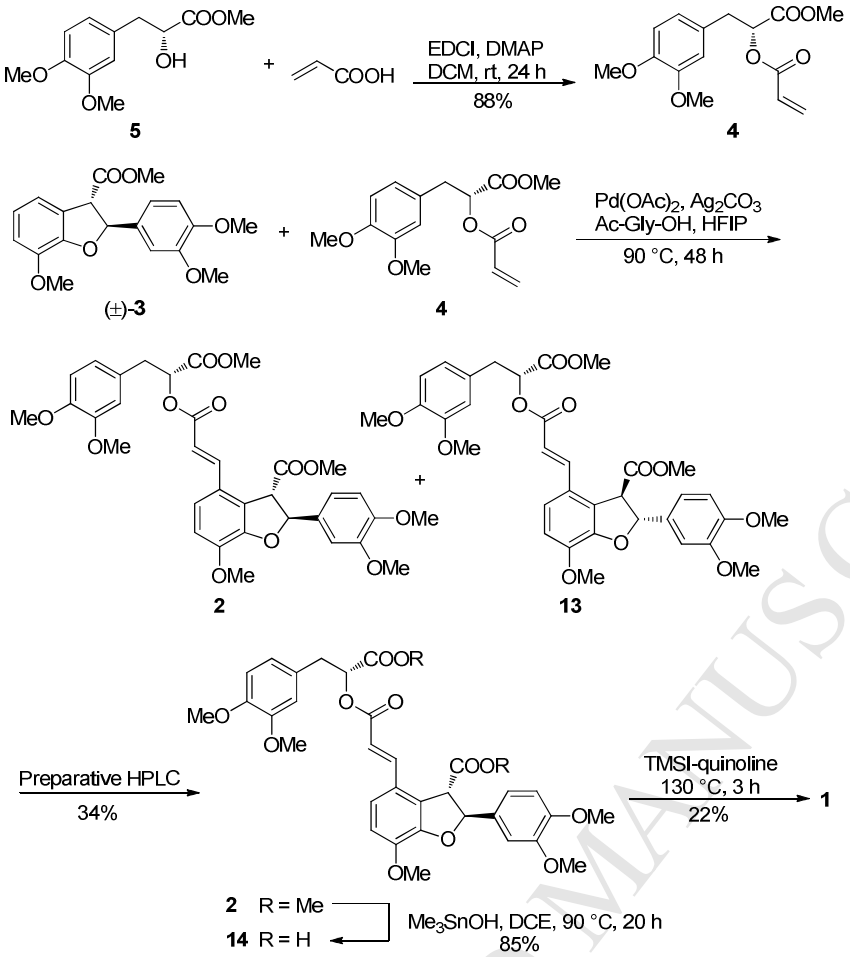
Table 2. Optimization of Pd-catalyzed ester-directed C-H olefination[a]



Entry	Ag salt	ligand	Yield(%)[b]
1	Ag_2CO_3		17
2	**Ag_2CO_3**	**Ac-Gly-OH**	**81**
3	Ag_2CO_3	Ac-Ala-OH	68
4	Ag_2CO_3	Ac-Leu-OH	54
5	AgOAc	Ac-Gly-OH	46
6	Ag_2O	Ac-Gly-OH	43
7	$AgNO_3$	Ac-Gly-OH	61

[a]Reaction conditions: **3** (0.2 mmol), **11** (0.4 mmol), $Pd(OAc)_2$ (5 mol%), Ag salt (0.4 mmol), ligand (20 mol%), HFIP (2 mL), air, 90 °C, 48 h.

[b]Isolated yield.



Scheme 3. Total synthesis of lithospermic acid **1**.

Having established the optimized conditions for Pd-catalyzed C-H olefination, we returned to the total synthesis of **1** (Scheme 3). C-H Olefination of (±)-*trans*-dihydrobenzofuran ester **3** with acrylate subunit **4** under the standard conditions to provide the desired coupling product **2** and its diastereomer **13**. Single diastereomer **2** could be separated in 34% yield from the mixtures of **2** and **13** by preparative HPLC. Next, treatment of **2** with Me_3SnOH in DCE provided diacid **14** in 85% yield.[14] Finally, subsequent removal of methyl groups in diacid **14** with TMSI-quinoline gave the natural product (+)-lithospermic acid **1**.

3. Conclusions

In summary, we have accomplished the total synthesis of lithospermic acid starting from 2-bromophenol, involving two metal-catalyzed C-H activation reactions. Fe-catalyzed Cross-Dehydrogenative-Coupling was utilized for the rapid construction of dihydrobenzofuran ester fragment. The dihydrobenzofuran ester and acrylate fragments were coupled by Pd-catalyzed ester-directed C-H olefination. This work provides a concise method towards the synthesis of lithospermic acid, which would facilitate further studies on the synthesis and biological evaluation of lithospermic acid analogues.

4. Experimental section

4.1. General information

All the reagents were used without further purification. The solvents were dried by the standard methods. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker NMR spectrometer with TMS as an internal standard. HRESIMS was measured on an Agilent G6224A TOF spectrometer. TLC was performed on pre-coated silica gel GF254 plates (Qingdao Marine Chemical Factory). Column chromatography was performed on silica gel (200−300 mesh, Qingdao Marine Chemical Factory). Visualization was carried out with UV or anisaldehyde staining.

4.2. Methyl 7-bromo-2-(3,4-dimethoxyphenyl)benzofuran-3-carboxylate (8b)

To a solution of **10** (4 mmol, 1.01 g) and **9b** (6 mmol, 720 mg) in DCE (10 mL) was added $FeCl_3 \cdot 6H_2O$ (10 mol%, 108 mg), 1,10-phenantroline (20 mol%, 144 mg) and $(t\text{-BuO})_2$ (8 mmol, 1.2 g) under N_2. The mixture was stirred at 100 °C for 12 h. The reaction mixture was cooled to room temperature and sat. $NaHCO_3$ was added. The mixture was extracted by DCM for three times. The organic layers were combined, and dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate) to give **8b** as white powder (998 mg, 64%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.71 – 7.64 (m, 2H), 7.40 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.11 (t, *J* = 7.9 Hz, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 161.3, 151.2, 150.5, 148.5, 128.6, 128.0, 125.2, 123.3, 121.8, 121.5, 112.6, 110.6, 108.3, 103.7, 56.1, 56.0, 51.8. HRMS-ESI (m/z): calcd for $C_{18}H_{15}BrNaO_5$ $[M + Na]^+$ 413.0001, found 413.0000.

4.3. Methyl 2-(3,4-dimethoxyphenyl)-7-methoxybenzofuran-3-carboxylate (8)

8b (0.5 mmol, 185 mg), CuBr (0.05 mmol, 12 mg), freshly prepared NaOMe (2 mmol, 216 mg), MeOH (1 mL), and anhydrous DMF (3 mL) were added into sealed tube under N_2. The mixture was stirred at 130 °C for 24 h. The reaction mixture was cooled to room temperature and sat. NH_4Cl was added. The mixture was extracted by EtOAc for three times. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate) to give **8** as white powder (133 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.72 (m, 2H), 7.64 (dt, *J* = 7.9, 1.5 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 9.0 Hz, 1H), 6.88 (dd, *J* = 8.0, 1.0 Hz, 1H), 4.05 (s, 3H), 4.00 (s, 3H), 3.98 (s, 3H), 3.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 161.0, 150.8,

148.4, 145.1, 142.9, 129.0, 124.6, 123.1, 122.0, 114.7, 112.5, 110.5, 108.1, 107.1, 56.1, 56.0, 56.0, 51.6. HRMS-ESI (m/z): calcd for $C_{19}H_{18}NaO_6$ $[M + Na]^+$ 365.1001, found 365.1000.

4.4. (±)-Methyl 2-(3,4-dimethoxyphenyl)-7-methoxy-2,3-dihydrobenzofuran-3-carboxylate (3)

To a solution of **8** (1.2 mmol, 410 mg) in THF (15 mL) and MeOH (15 mL) was added freshly activated magnesium turning (3.6 mmol, 86 mg) and NH_4Cl (2.4 mmol, 127 mg) under N_2. The mixture was stirred at -15 °C for 5 h, and then stirred at room temperature for 24 h. Reaction was cooled to -15 °C before sat. NH_4Cl was added. The mixture was extracted by EtOAc for three times. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate) to give (±)-**3** as yellow oil (276 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 – 6.72 (m, 6H), 6.08 (d, *J* = 8.4 Hz, 1H), 4.36 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 149.2, 147.8, 144.6, 132.5, 125.1, 121.5, 118.8, 117.0, 112.5, 111.1, 109.3, 86.6, 56.1, 56.0, 56.0, 55.9, 52.7. HRMS-ESI (m/z): calcd for $C_{19}H_{20}NaO_6$ $[M + Na]^+$ 367.1158, found 367.1156.

4.5. (*R*)-3-(3,4-dimethoxyphenyl)-1-methoxy-1-oxopropan-2-yl acrylate (4)

To a solution of alcohol (2 mmol, 480 mg) and acrylic acid (3 mmol, 258 mg) in DCM (20 mL) was added DMAP (4 mmol, 488 mg) and EDCI (4 mmol, 764 mg) under N_2. The reaction mixture was stirred at room temperature for 24 h. After completion of reaction, 1N HCl was added at 0 °C. The mixture was extracted by EtOAc for three times. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate) to give **4** as colorless oil (517 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75-6.81 (m, 3H), 6.45 (d, *J* = 17.2 Hz, 1 H), 6.12-6.19 (m, 1H), 5.89 (d, *J* = 10.4 Hz, 1 H), 5.26-5.29 (m, 1H), 3.86 (s, 3H), 3.86 (s, 3H), 3.74 (s, 3H), 3.07-3.19 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 165.1, 148.6, 147.9, 131.9, 128.1, 127.4, 121.3, 112.3, 111.1, 73.2, 55.8, 52.4, 37.1. HRMS-ESI (m/z): calcd for $C_{15}H_{18}NaO_6$ $[M + Na]^+$ 317.1001, found 316.9997.

4.6. (±)-methyl 2-(3,4-dimethoxyphenyl)-7-methoxy-4-((E)-3-methoxy-3-oxoprop-1-en-1-yl)-2,3-dihydrobenzofuran-3-carboxylate (12)

(±)-**3** (0.2 mmol, 69 mg), methyl acrylate **11** (0.4 mmol, 35 mg), Ag_2CO_3 (0.4 mmol, 110 mg), Ac-Gly-OH (20 mol%, 10 mg), $Pd(OAc)_2$ (5 mol%, 5 mg) and HFIP (2 mL) was added into sealed tube. The mixture was stirred at 90 °C for 48 h. After the reaction was cooled to room temperature, the mixture was filtered by Celite and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate) to give **12** as colorless oil (70 mg, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 15.9 Hz, 1H), 7.21 (d, *J* = 8.6 Hz, 1H), 6.91 (dd, *J* = 7.8, 1.1 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 1H), 6.88 (d, *J* = 2.0 Hz, 1H), 6.83 (d, J = 8.3 Hz, 1H), 6.29 (d, *J* = 15.9 Hz, 1H), 6.04 (d, *J* = 5.8 Hz, 1H), 4.49 (d, *J* = 5.8 Hz, 1H), 3.95 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.86, 167.41, 149.29, 149.23, 148.43, 146.19, 141.12, 132.29, 125.00, 124.52, 120.56, 118.08, 117.35, 112.94, 111.11, 108.73, 87.53, 56.18, 55.96, 52.89, 51.70. HRMS-ESI (m/z): calcd for $C_{23}H_{24}NaO_8$ $[M + Na]^+$ 451.1363, found 451.1382.

4.7. (2S,3S)-methyl 2-(3,4-dimethoxyphenyl)-4-((E)-3-(((R)-3-(3,4-dimethoxyphenyl)-1-methoxy-1-oxopropan-2-yl)oxy)-3-oxoprop-1-en-1-yl)-7-methoxy-2,3-dihydrobenzofuran-3-carboxylate (2)

(±)-**3** (0.2 mmol, 69 mg), **4** (0.4 mmol, 118 mg), Ag_2CO_3 (0.4 mmol, 110 mg), Ac-Gly-OH (20 mol%, 10 mg), $Pd(OAc)_2$ (5 mol%, 5 mg) and HFIP (2 mL) was added into sealed tube. The mixture was stirred at 90 °C for 48 h. After the reaction was cooled to room temperature, the mixture was filtered by celite and concentrated *in vacuo*. The resulting residue was subjected to HPLC (YMC Diol-NP column, 150 mm × 20 mm, 5 µm particle size, 5:95 to 15:85 *i*-PrOH:hexanes over 65 min at 9 mL/min, detection: UV at 254 nm) to afford **2** (43 mg, 34%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 15.9 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 1H), 6.86-6.90 (m, 3H), 6.82 (d, *J* = 8.5 Hz, 1H), 6.75-6.79 (m, 3H), 6.32 (d, *J* = 16Hz, 1H), 6.02 (d, *J* = 5.6 Hz, 1H), 5.31 (dd, *J* = 8.5, 5.5 Hz, 1H), 4.45 (d, *J* = 5.6 Hz, 1H), 3.93 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.83 (s, 3H), 3.73 (s, 3H), 3.72 (s, 3H), 3.16 (dd, *J* = 14.3, 4.7 Hz, 1H), 3.09 (dd, *J* = 14.3, 8.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.80, 170.40, 166.21, 149.39, 149.32, 148.86, 148.55, 148.13, 146.49, 142.58, 132.39, 128.41, 125.07, 124.44, 121.53, 120.98, 118.13, 116.52, 112.98, 112.46, 111.20, 112.20, 108.81, 87.57, 73.19, 56.27, 56.04, 56.00, 56.00, 55.96, 55.92, 52.94, 52.47, 37.23. HRMS-ESI (m/z): calcd for $C_{34}H_{36}NaO_{12}$ $[M + Na]^+$ 659.2099, found 659.2099. $[\alpha]_D^{23}$ = +139 (c 0.39, CH_2Cl_2), lit. $[\alpha]_D$ = +134.5 (c 0.49, CH_2Cl_2),[5] $[\alpha]_D^{25}$ = +131.9 (c 0.079, CH_2Cl_2).[7] Melting point: 58-59 °C.

4.8.
(2S,3S)-4-((E)-3-((R)-1-carboxy-2-(3,4-dimethoxyphenyl)ethoxy)-3-oxoprop-1-en-1-yl)-2-(3,4-dimethoxyphenyl)-7-methoxy-2,3-dihydrobenzofuran-3-carboxylic acid (14)

To a solution of **2** (0.068 mmol, 43 mg) in DCE (2 mL) was added Me_3SnOH (0.34 mmol, 61 mg). The reaction mixture was stirred at 90 °C for 20 h. After completion of reaction, 1N HCl was added at 0 °C. The mixture was extracted by DCM for three times. The organic layers were combined, dried over Na_2SO_4, filtered through a small pad of silica gel, and concentrated *in vacuo.* The resulting residue purified by silica gel column chromatography (hexanes:EtOAc:HOAc 1:1:0.005) to give diacid **14** as white solid (35 mg, 85%). ^{1}H NMR (500 MHz, CD_3COCD_3) δ 7.84 (d, *J* = 16.0 Hz, 1H), 7.38 (d, *J* = 8.6, 1H), 7.07 (d, *J* = 1.9 Hz, 1H), 7.03 (d, *J* = 8.6 Hz, 1H), 6.98 – 6.91 (m, 3H), 6.89 – 6.82 (m, 2H), 6.42 (d, *J* = 16 Hz, 1H), 6.06 (d, *J* = 5.1 Hz, 1H), 5.25 (dd, *J* = 8.5, 4.2 Hz, 1H), 4.58 (d, *J* = 5.1 Hz, 1H), 3.92 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.74 (s, 3H) , 3.19 (dd, *J* = 14.3, 4.2 Hz, 1H), 3.09 (dd, *J* = 14.3, 8.5 Hz, 1H). ^{13}C NMR (126 MHz, CD_3COCD_3) δ 172.97, 171.16, 166.49, 150.57, 150.11, 149.49, 149.35, 147.40, 143.07, 133.92, 130.00, 126.99, 125.30, 122.56, 121.39, 118.83, 117.27, 114.31, 114.26, 112.71, 112.65, 110.59, 88.18, 73.75, 60.54, 56.50, 56.42, 56.11, 56.00, 37.62. HRMS-ESI (m/z): calcd for $C_{32}H_{32}NaO_{12}$ $[M + Na]^+$ 631.1786, found 631.1781. $[\alpha]_D^{23}$ = +170.2 (c 0.51, CH_2Cl_2).

4.9. Lithospermic acid (1)

14 (0.049 mmol, 30 mg) and trimethylsilylquinolinium iodide (50 equiv, 806 mg) was added into a seal tube. The reaction mixture was stirred at 130 °C for 3 h. The reaction was cooled to room temperature, and 1N HCl was added slowly. The mixture was extracted by EtOAc for four times. The combined organic layers were dried by Na_2SO_4, filtered and concentrated under vacuum. The resulting residue was subjected to HPLC separation (YMC C18 column, MeCN:H_2O:TFA 10:90:0.1 to 50:50:0.1 over 60 min at 1 mL/min, detection: UV at 254 nm). The collected fractions were concentrated under reduced pressure to give **1** as yellow powder (5.8 mg, 22%). ^{1}H NMR (500 MHz, CD_3COCD_3) δ 7.85 (d, *J* = 16.0 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 6.88 (m, 1H), 6.86 (d, *J* = 1.7 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.80 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.67 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.38 (d, *J* = 15.9 Hz, 1H), 5.98 (d, *J* = 4.7 Hz, 1H), 5.18 (dd, *J* = 8.6, 4.0 Hz, 1H), 4.53 (d, *J* = 4.7 Hz, 1H), 3.10 (dd, J = 14.4, 4.0 Hz, 1 H), 3.01 (dd, *J* = 14.3, 8.6 Hz, 1H). ^{13}C NMR (126 MHz, MeOD) δ 175.07, 173.43, 168.10,

148.81, 146.62, 146.06, 145.25, 144.08, 133.74, 129.18, 127.59, 124.56, 121.95, 121.66, 118.24, 117.57, 116.36, 116.31, 113.38, 88.74, 74.70, 57.48, 37.89. HRMS-ESI (m/z): calcd for $C_{27}H_{22}NaO_{12}$ $[M + Na]^+$ 561.1003, found 561.1005. $[\alpha]_D^{23}$ = +71 (c 0.16, MeOH), lit. $[\alpha]_D^{23}$ = +68.3 (c 0.8, CD_3OD),[6] $[\alpha]_D^{23}$ = +75 (c 0.2, MeOH).[8] Melting point: 180-182°C.

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Supplementary data

Supplementary data related to this article can be found at

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