Nat. Prod. Bioprospect. (2014) 4:181–188
DOI 10.1007/s13659-014-0022-6

ORIGINAL ARTICLE

Synthesis of L-Ascorbic Acid Lactone Derivatives

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Received: 13 April 2014 / Accepted: 28 April 2014 / Published online: 21 May 2014

Abstract A small focused library which comprised of L-AA lactone derivatives was built with a facile method. This reported method was optimized by modifying the acidity of the solvent. As a result, 12 L-AA lactones were synthesized. Among these lactones, lactones **8**–**12** were new compounds. The cytotoxicity of these synthetic compounds were investigated.

Keywords L-Ascorbic acid lactone · Cytotoxicity · Focused library

1 Introduction

L-Ascorbic acid (L-AA), one form of vitamin C, plays an important role in both plant and animal physiology. The foremost biologically functions of L-AA are centred around the antioxidant properties. Considerable evidence has been accruing in the last two decades about the importance of L-AA not only in protecting the plant from oxidative stress, but also in protecting mammals from various chronic diseases that have their origins in oxidative stress [1]. Derivatives of L-AA were found showing wide range of bioactivities including antiviral [2–5], cytotoxicity [6], inhibitory activities against tyrosinase-catalyzed melanin formation [7], increasing skin permeability [8, 9], and neurotropic activity [10]. Among them, octanoyl-6-*O*-ascorbic acid could enhance the solubility of many poorly water soluble drugs [11]. Because of these properties, L-AA derivatives were applicable in cosmetics and medicine [12, 13].

Many bioactive L-AA derivatives were found in nature [14–16]. For example, bioactive-oriented isolation of dilaspirolactone aglycon (**1**) and delesserrine (**2**) (Fig. 1) from Delesseriaceae family were reported [17, 18]. Our research group are interested in fern plants for a long time. A lot of species were systematically studied towards chemical components and their bioactivities [19–23], which led to the isolate of dichotomains A and B (**3**, **4**) (Fig. 1), two L-AA derivatives, from *Dicranopteris dichotoma*. And dichotomain B (**4**) was confirmed as a weak HIV-1 inhibitor [24]. These compounds with a fragment of L-AA lactone showed different bioactivities. Attracted by this difference and the unique structure of L-AA derivatives, we would like to build a small focused library of L-AA lactone derivatives to explore their bioactivities.

2 Results and Discussion

Tang et al. [25] reported a short total synthesis of L-AA lactone compounds leucodrin and leudrin through a

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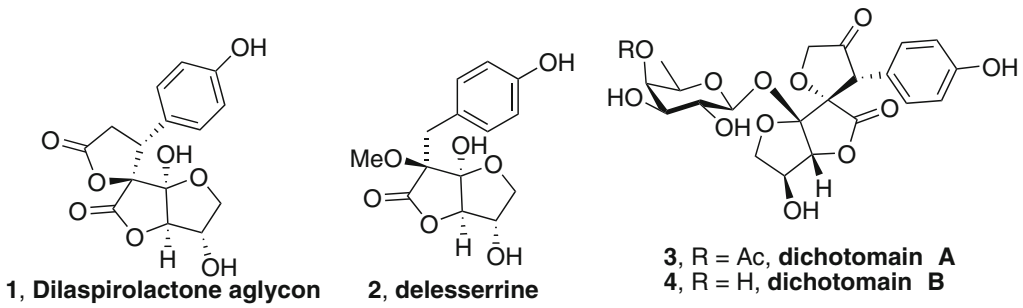
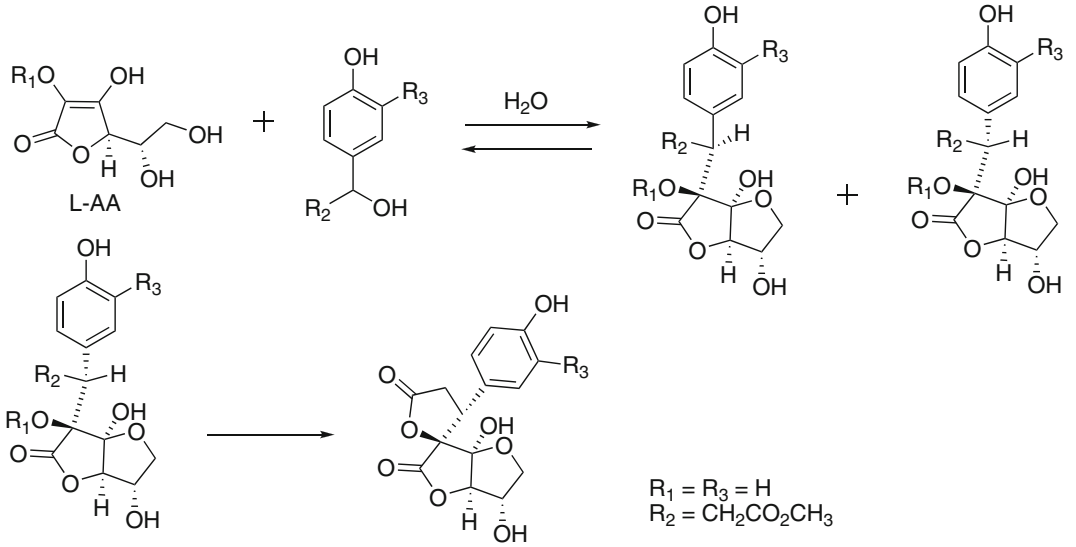


Fig. 1 Natural L-AA lactone derivatives



Scheme 1 A synthetic route to L-AA lactone derivatives reported by Poss et al

organocatalystic 1,4-conjugate addition of L-AA to α,β-unsaturated aldehydes. Although it effectively synthesized 5/5/5 spirodilactone L-AA derivatives, it could not access to other L-AA lactone derivatives. Poss et al. [26] reported that treating L-AA with different 4-hydoxy benzyl alcohols in hot water resulted in L-AA lactone derivatives (scheme 1). With this method, we obtained some L-AA lactone derivatives (**5**, **7**, **13**, **14**, **15**, Fig. 2), but a number of L-AA lactone derivatives (**6**, **8**, **9**, **10**, **11**, **12**, **16**, Fig. 2) could not formed by using this methods. The failure probably was caused by acidity of the solvent [25, 27], so, we modified the condition by applying the phosphate-citrate buffer solution (PH 5.0) as solvent. As a result, compounds **6**, **8**, **9**, **10**, **11**, **12**, **16** were successfully synthesized.

All 4-hydroxy benzyl alcohols were synthesized by reduction of corresponding aldehydes with $NaBH_4$ except **B9** and **B10** (Table 1). Without following the Ref. [26], 4-hydroxy benzaldehyde was protected with Bn group, and then reacted with methyl acetate through an aldol condensation. At last, removal of Bn group gave **B9** in 89 % yield. It is interesting that **B13** could not react with L-AA to yield lactone compound. However, it worked with methyl ether in stead of ethyl ether. An air oxidative product **B14** was detected in methanolysis reaction of **B13**, which was reducted by $NaBH_4$ to afford **B10** (Scheme 2).

With all designed 4-hydoxy benzyl alcohols in hand, we built a small focused library which contained L-AA lactone drivatives **5**–**16**. We found that 4-hydoxy benzyl alcohols like **B1**, **B4**, **B5**, **B7**, and **B11** with good water solubility could react well with L-AA to give lactone derivatives in good yield except **B3**. This might be that two phenolic hydroxyl groups in **B3** made it be easily oxidized by air. **B12** could not react with L-AA in all conditions applied in this article, probably because the reactivity of lone pair electron at S atom of **B12** was lower than that of phenol hydroxyl. So, it could not react like other 4-hydoxy benzyl alcohols. Furthermore, all L-AA lactones were obtained as a single compound except lactones **9** and **10** which were mixtures of two isomers at benzylic position. ^{1}H NMR indicated their ratio is about 10:1 for **9** and 3.4:1 for **10**, and we found that one isomer of **9** and **10** were unstable

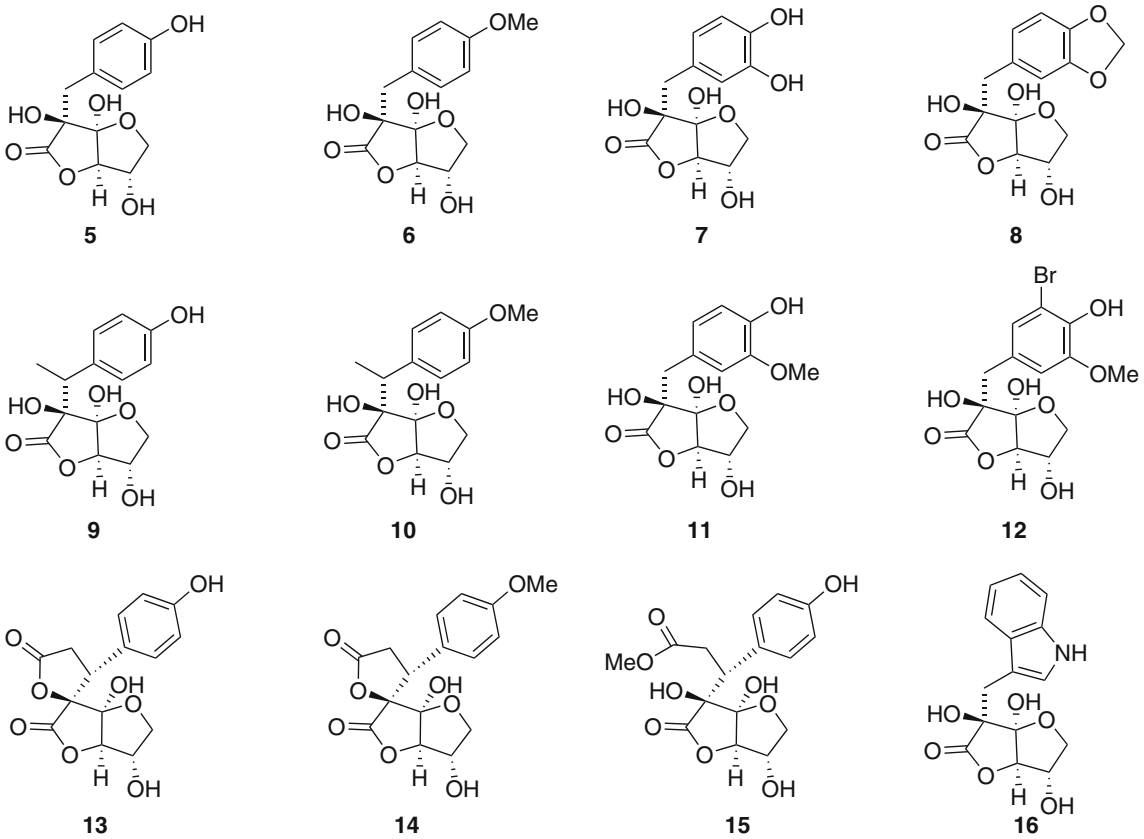


Fig. 2 Synthetic L-AA lactone derivatives

and could transform from semi-ketal into ketone at C3 position at room temperature or under NMR condition spontaneously.

All synthetic L-AA lactone derivatives were evaluated on five human tumor cell lines, including HL-60, SMMC-7721, A-549, MCF-7 and SW480, using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method (Table 2). Anticancer drug cisplatin (DDP) was used as the positive control. To our disappointment, none of these compounds showed cytotoxicity.

3 Experiment Section

3.1 General Experimental Procedures

HRESIMS were performed on a Agilent 6540 Q-TOF. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance III-400 and Bruker Avance III-600 MHz spectrometers. Chemical shifts (δ) were expressed in *ppm* with reference to the TMS resonance. Column chromatography was performed using Silica gel [(200–300) mesh, Qingdao Marine Chemical, Inc, Qingdao, China]. Reactions were monitored by TLC and spots were visualized by heating the silica gel plates sprayed with 10 % H_2SO_4 in EtOH.

3.2 Synthesis of 4-Hydroxy Benzyl Alcohols (**B1**–**B8**, **B11**–**B12**)

4-Hydroxy benzyl alcohols **B1**–**B8**, **B11**–**B12** were synthesized by reduction of corresponding commercial available aldehydes with $NaBH_4$ in MeOH at 0 °C for 1–4 h.

B3: Brown foam, 90 % yields, ^{1}H NMR (400 MHz, D_2O) δ 6.50–6.56 (m, 3H), 4.34 (s, 2H).

B5: Light yellow oil, 96 % yields, ^{1}H NMR (400 MHz, acetone-D6) δ 8.29 (s, 1H), 7.20 (d, $J = 8.4$ Hz, 1H), 6.77 (d, $J = 8.4$ Hz, 1H), 4.75 (m, 1H), 4.04 (d, $J = 4$ Hz, 1H), 1.36 (d, $J = 6.4$ Hz, 3H).

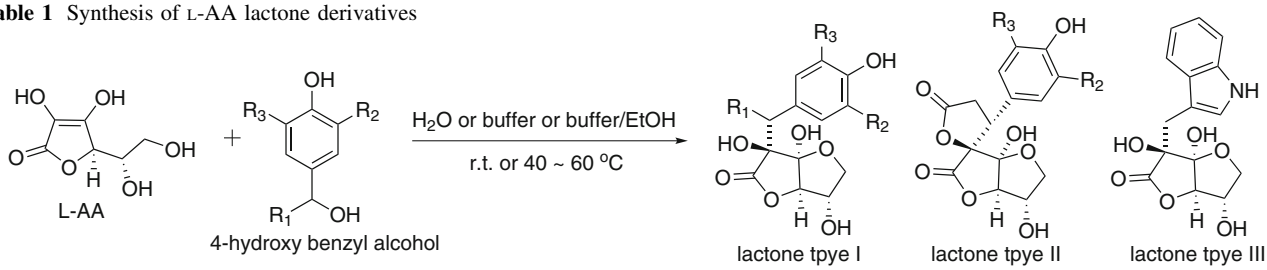
B7: White solid, 92 % yields, ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.57 (d, $J = 1.6$ Hz, 1H), 7.30 (d, $J = 1.6$ Hz, 1H), 6.48 (s, 1H), 3.91 (s, 3H).

B8: White solid, 82 % yields, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, $J = 1.0$ Hz, 1H), 6.79 (d, $J = 1.0$ Hz, 1H), 5.86 (br. s, 1H), 4.53 (s, 2H), 3.85 (s, 3H).

3.3 Synthesis of 4-Hydroxy Benzyl Alcohols (**B9**, **B10**)

B9: To a solution of 4-hydroxy benzldehyde (12.2 g, 0.1 mol) in 100 mL acetone, K_2CO_3 (20.7 g, 0.15 mol) and BnCl (12.6 mL, 0.11 mol) was added, which was

Table 1 Synthesis of L-AA lactone derivatives



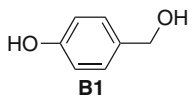
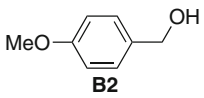
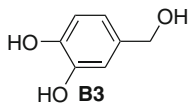
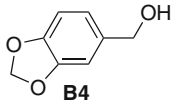
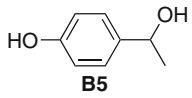
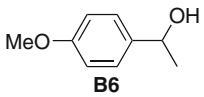
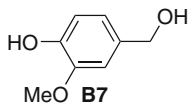
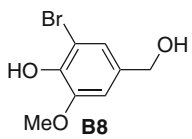
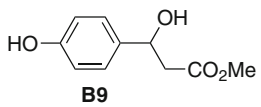
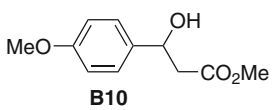
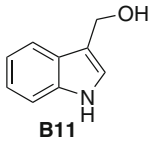
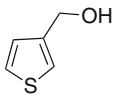
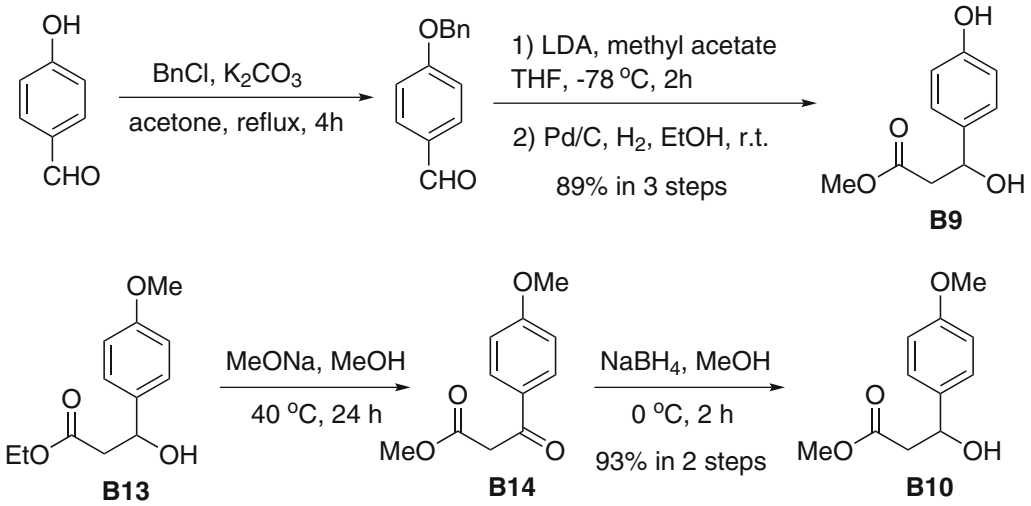
Entry	4-hydroxy benzyl alcohol	Condition	Product (yields)
1	 **B1**	H_20, 50 °C, 50 h	**5** (85 %)
2	 **B2**	buffer, 40 °C, 72 h	**6** (53 %)
3	 **B3**	H_20, 50 °C, 72 h	**7** (35 %)
4	 **B4**	buffer, 60 °C, 36 h	**8** (72 %)
5	 **B5**	buffer, 60 °C, 60 h	**9** (65 %) 10:1 of two benzylic siomers
6	 **B6**	buffer, 60 °C, 72 h	**10** (42 %) 3.4:1 of two benzylic siomers
7	 **B7**	buffer, 40 °C, 48 h	**11** (78 %)
8	 **B8**	buffer, 60 °C, 72 h	**12** (58 %)
9	 **B9**	H_20, 50 °C, 72 h	**13** (35 %) **15** (40 %)
10	 **B10**	H_20, 50 °C, 72 h	**14** (30 %)

Table 1 continued

Entry	4-hydroxy benzyl alcohol	Condition	Product (yields)
11	 **B11**	buffer/EtOH, r.t, 8 h	**16** (57 %)
12	 **B12**	H_2O, 50 °C, 72 h buffer, 60 °C, 72 h buffer/EtOH, r.t., 72 h	nr



Scheme 2 Synthetic route to compounds **B9** and **B10**

refluxed for 4 h. Cooled to room temperature, 20 mL ice-water was added and extracted with EtOAc (3 × 100 mL). The organic layers were combined and washed by brine (3 × 50 mL), dried over Na_2SO_4 (s), then evaporated the solvent under the reduced pressure to give 4-benzyloxy benzldehyde as a light yellow solid (21 g, 99 %). This compound was used in next step without further purification.

To a solution of freshly distilled diisopropylamine (14 mL, 0.12 mol) in 100 mL dry THF at −78 °C was added *n*-BuLi (50 mL of 2 M in hexane, 0.1 mol) and stirred for 15 min. Freshly distilled methyl acetate (8.6 mL, 0.11 mol) was added. The reaction stirred for 1 h at −78 °C, and 4-benzyloxyl benzldehyde (21 g, 0.1 mol) in 100 mL dry THF was added. After 1 h at −78 °C, the reaction was quenched with saturated NH_4Cl aqueous solution (50 mL), warmed to room temperature, and stirred for an additional 6 h. The solution was extracted with EtOAc (3 × 100 mL), and the organic layers were combined and washed by brine (3 × 50 mL), dried over Na_2SO_4 (s), evaporated the solvent under the reduced pressure to give crude product as a yellow solid, which was purified by flash chromatography with petroleum ether/EtOAc (20/1) to give methyl 3-(4-(benzyloxy)phenyl)-3-hydroxypropanoate 26 g (91 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 7H), 6.96 (dd, $J = 1.9$, 8.0 Hz, 2H), 5.08 (dd, $J = 3.7$, 9.2 Hz, 1H), 5.06 (s, 2H), 3.72 (s, 3H), 2.66–2.80 (m, 2H).

To a solution of methyl 3-(4-(benzyloxy)phenyl)-3-hydroxypropanoate (5 g, 17.48 mmol) in 50 mL EtOH, 500 mg 10 % Pd/C was added, which then stirred under H_2 atmosphere overnight at room temperature. The reaction mixture was passed through a short pad of Celite to remove Pd/C and evaporated the solvent under the reduced pressure to give 3.4 g (100 %) of **B9** as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, $J = 8.5$ Hz, 2H), 6.78 (d, $J = 8.5$ Hz, 2H), 5.07 (dd, $J = 3.7$, 9.2 Hz, 1H), 3.72 (s, 3H), 2.66–2.81 (m, 2H).

Table 2 In vitro anti-tumor assay of the synthetic compounds

Entry	$IC_{50}(\mu M)$				
	HL-60	SMMC-7721	A-549	MCF-7	SW480
5	>40	>40	>40	>40	>40
6	>40	>40	>40	>40	>40
7	>40	>40	>40	>40	>40
8	>40	>40	>40	>40	>40
9	>40	>40	>40	>40	>40
10	>40	>40	>40	>40	>40
11	>40	>40	>40	>40	>40
12	>40	>40	>40	>40	>40
13	>40	>40	>40	>40	>40
14	>40	>40	>40	>40	>40
15	>40	>40	>40	>40	>40
16	>40	>40	>40	>40	>40
DPP	1.05	6.76	6.01	15.38	16.31
Taxol	<0.008	<0.008	<0.008	<0.008	<0.008

B10: To a solution of **B13** (10 g, 44.6 mmol) in anhydrous MeOH, MeONa (240 mg, 4.46 mmol) was added. The mixture was stirred at 40 °C for 24 h. Evaporated the solvent under the reduced pressure, the residue was dissolved in 100 mL EtOAc, washed by water (3 × 50 mL), brine (3 × 50 mL), dried over Na_2SO_4 (s). Evaporated the solvent under the reduced pressure to give 9.28 g (100 %) of **B14** as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 3.95 (s, 2H), 3.86 (s, 3H), 3.73 (s, 3H).

To a solution of **B14** (5 g, 24 mmol) in 30 mL MeOH at 0 °C was added $NaBH_4$ (1.82 g, 48 mmol), the mixture was stirred at 0 °C for 2 h. The reaction was quenched with saturated NH_4Cl aqueous solution (5 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 × 30 mL), and the organic layers were combined and washed by brine (3 × 50 mL), dried over Na_2SO_4 (s). Evaporated the solvent under the reduced pressure to give crude product as a colorless oil, and the crude product was purified by flash chromatography with petroleum ether/EtOAc (20/1) to give 4.7 g (93 %) of **B10** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, J = 2.8, 8.6 Hz, 2H), 6.90 (dd, J = 2.8, 8.6 Hz, 2H), 5.08 (dd, J = 3.7, 9.3 Hz, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 2.65–2.80 (m, 2H).

3.4 General Procedure for the Preparation of L-AA Lactone Derivatives (5–16)

Method A [26] for lactones **5**, **7**, **13**, **14**, **15**: To L-AA (3 eq.) in 2 mL water was added corresponding alcohol **B1** or **B3** or **B9** or **B10** (0.5 mmol, 1 eq.), and the solution stirred at 50 °C for 72 h. The reaction was evaporated under reduced pressure and the residue was purified by column chromatography with DCM/MeOH (50/1–20/1) to afford lactone **5** or **7** or **13**, **15** or **14**, respectively.

5 (85 %), white foam: ^{1}H NMR (600 MHz, acetone-d_6) δ 8.31 (s, 1H), 7.14 (d, J = 8.5 Hz, 2H), 6.73 (d, J = 8.5 Hz, 2H), 5.86 (s, 1H), 4.66 (s, 1H), 4.45 (s, 1H), 4.30 (s, 1H), 4.09 (dd, J = 9.7, 5.5 Hz, 1H), 4.00 (dd, J = 9.7, 3.1 Hz, 1H), 3.77 (s, 1H), 3.09 (d, J = 13.5 Hz, 1H), 2.92 (d, J = 13.5 Hz, 1H). ^{13}C NMR (150 MHz, acetone-d_6) δ 175.88, 157.41, 132.83, 125.75, 115.60, 108.31, 86.97, 80.77, 75.51, 75.45, 55.05, 40.62. HRESIMS m/z 305.0636 (calcd for $C_{13}H_{14}O_7$ $[M + Na]^+$, 305.0632).

7 (35 %), yellow oil: ^{1}H NMR (600 MHz, acetone-d_6) δ 6.81 (d, J = 2.0 Hz, 1H), 6.70 (d, J = 8.1 Hz, 1H), 6.65 (dd, J = 8.1, 2.0 Hz, 1H), 5.85 (s, 1H), 4.66 (s, 1H), 4.42 (s, 1H), 4.30 (s, 1H), 4.09 (dd, J = 9.7, 5.5 Hz, 1H), 3.99 (dd, J = 9.7, 3.2 Hz, 1H), 3.04 (d, J = 13.4 Hz, 1H), 2.87 (s, 1H), 2.85 (d, J = 13.4 Hz, 1H). ^{13}C NMR (150 MHz, acetone-d_6) δ 175.95, 145.25, 145.17, 126.45, 123.30, 118.81, 115.60, 108.34, 86.97, 80.68, 75.49, 75.47, 40.90. HRESIMS m/z 333.0377 (calcd for $C_{13}H_{14}O_8$ $[M + Na]^+$, 333.0383).

13 (35 %), white foam: ^{1}H NMR (600 MHz, acetone-d_6) δ 8.67 (s, 1H), 7.29 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 6.56 (s, 1H), 4.79 (s, 1H), 4.25–4.40 (m, 2H), 4.21 (dd, J = 9.7, 6.0 Hz, 1H), 4.02 (dd, J = 9.7, 3.7 Hz, 1H), 3.90 (s, 1H), 3.17 (dd, J = 17.3, 13.2 Hz, 1H), 2.90 (dd, J = 17.3, 8.5 Hz, 1H). ^{13}C NMR (150 MHz, acetone-d_6) δ 174.37, 172.06, 158.70, 130.91, 124.09, 116.48, 106.38, 90.12, 88.98, 76.19, 74.81, 45.66, 33.97. HRESIMS m/z 321.0607 (calcd for $C_{15}H_{14}O_8$ $[M–H]^-$, 321.0616).

15 (40 %), light yellow oil: ^{1}H NMR (600 MHz, acetone-d_6) δ 8.46 (s, 1H), 7.25 (d, J = 9.0 Hz, 2H), 6.74 (d, J = 9.0 Hz, 2H), 5.78 (s, 1H), 4.72 (s, 1H), 4.26 (m, 1H), 4.02 (m, 2H), 3.62 (m, 1H), 3.47 (s, 3H), 3.29 (d, J = 1.5 Hz, 2H). HRESIMS m/z 377.0845 (calcd for $C_{16}H_{18}O_9$ $[M + Na]^+$, 377.0843).

14 (30 %), white foam: ^{1}H NMR (600 MHz, acetone-d_6) δ 8.67 (s, 1H), 7.38 (d, J = 9 Hz, 2H), 6.96 (d, J = 9 Hz, 2H), 6.56 (s, 1H), 4.79 (s, 1H), 4.25–4.40 (m, 2H), 4.21 (dd, J = 9.7, 6.0 Hz, 1H), 4.02 (dd, J = 9.7, 3.7 Hz, 1H), 3.90 (s, 1H), 3.81 (s, 3H), 3.17 (dd, J = 17.3, 13.2 Hz, 1H), 2.90 (dd, J = 17.3, 8.5 Hz, 2H). ^{13}C NMR (150 MHz, acetone-d_6) δ 174.32, 171.98, 160.88, 130.87, 125.34, 115.02, 106.38, 90.05, 88.95, 76.22, 74.78, 55.62, 45.57, 33.98. HRESIMS m/z 359.0740 (calcd for $C_{16}H_{16}O_8$ $[M + Na]^+$, 359.0737).

Method B for lactones **6**, **8**, **9**, **10**, **11**, **12**: To L-AA (4 eq.) in 4 mL phosphate-citrate buffer (pH = 5.0) was added corresponding alcohol **B2** or **B4** or **B5** or **B6** or **B7** or **B8** (1 mmol, 1 eq.), and the solution stirred at 40–60 °C

for 36–72 h. The reaction was evaporated under reduced pressure and the residue was purified by colum chromatography with DCM/MeOH (50/1–20/1) to afford lactone **6** or **8** or **9** or **10** or **11** or **12**, respectively.

6 (53 %), yellow foam: ^{1}H NMR (600 MHz, acetone-d_6) δ 7.22 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 5.90 (s, 1H), 4.68 (s, 1H), 4.50 (s, 1H), 4.31 (dd, J = 5.3, 3.2 Hz, 1H), 4.09 (dd, J = 9.7, 5.5 Hz, 1H), 4.01 (dd, J = 9.7, 3.1 Hz, 1H), 3.82 (s, 1H), 3.77 (s, 3H), 3.11 (d, J = 13.6 Hz, 1H), 2.96 (d, J = 13.6 Hz, 1H). ^{13}C NMR (150 MHz, acetone-d_6) δ 175.74, 159.76, 132.78, 127.07, 114.09, 108.30, 87.03, 80.64, 75.57, 75.44, 55.42, 40.51. HRESIMS *m/z* 319.0788 (calcd for $C_{14}H_{16}O_7$ $[M + Na]^+$, 319.0787).

8 (72 %), white foam: ^{1}H NMR (600 MHz, acetone-d_6) δ 6.83 (d, J = 1.4 Hz, 1H), 6.76 (dt, J = 16.3, 4.7 Hz, 2H), 5.96 (d, J = 1.7 Hz, 2H), 5.90 (s, 1H), 4.71 (s, 1H), 4.56 (s, 1H), 4.34 (dd, J = 4.6, 3.2 Hz, 1H), 4.11 (dd, J = 9.7, 5.5 Hz, 1H), 4.03 (m, overlaped, 2H), 3.08 (d, J = 13.7 Hz, 1H), 2.96 (d, J = 13.7 Hz, 1H). ^{13}C NMR (150 MHz, acetone-d_6) δ 175.49, 148.05, 147.55, 129.05, 124.87, 111.96, 108.47, 108.31, 101.88, 87.10, 80.48, 75.70, 75.41, 40.91. HRESIMS *m/z* 333.0586 (calcd for $C_{14}H_{14}O_8$ $[M + Na]^+$, 333.0581).

9 (65 %), colorless oil: main isomer: ^{1}H NMR (600 MHz, acetone-d_6) δ 8.35 (s, 1H), 7.17 (d, J = 8.8 Hz, 2H), 6.74 (d, J = 8.8 Hz, 2H), 5.71 (s, 1H), 4.57 (d, J = 3.7 Hz, 1H), 4.38 (s, 1H), 4.23 (d, J = 2.3 Hz, 1H), 4.04 (dd, J = 9.7, 5.4 Hz, 1H), 3.95 (dd, J = 9.7, 2.9 Hz, 1H), 3.34 (q, J = 7.2 Hz, 1H), 3.13 (s, 1H), 1.40 (d, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, acetone-d_6) δ 175.36, 157.37, 131.85, 129.12, 116.30, 115.48, 108.61, 86.28, 81.86, 75.30, 75.25, 43.24, 16.40. HRESIMS *m/z* 295.0816 (calcd for $C_{14}H_{16}O_7$ $[M - H]^-$,295.0823).

10 (42 %), colorless oil, main isomer: ^{1}H NMR (600 MHz, acetone-d_6) δ 7.29 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 5.69 (s, 1H), 4.70 (s, 1H), 4.39 (d, J = 6.1 Hz, 1H), 4.32 (dd, J = 5.0, 3.1 Hz, 1H), 4.05–4.08 (m, overlaped, 1H), 3.97 (dd, J = 11.5, 3.0 Hz, 1H), 3.83 (s, 1H), 3.77 (s, 3H), 3.23 (q, J = 7.3 Hz, 1H), 1.51 (d, J = 7.3 Hz, 3H). ^{13}C NMR (150 MHz, acetone-d_6) δ 176.34, 159.64, 131.76, 130.42, 114.69, 113.74, 109.15, 87.03, 86.29, 75.31, 75.10, 55.41, 43.25, 16.39. HRESIMS *m/z* 333.0949 (calcd for $C_{15}H_{18}O_7$ $[M + Na]^+$,333.0945).

11 (78 %), colorless oil: ^{1}H NMR (600 MHz, acetone-d_6) δ 7.57 (s, 1H), 6.92 (d, J = 1.9 Hz, 1H), 6.80–6.67 (m, 2H), 5.87 (s, 1H), 4.69 (s, 1H), 4.51 (s, 1H), 4.31 (m, 1H), 4.09 (dd, J = 9.8, 5.4 Hz, 1H), 4.01 (dd, J = 9.7, 3.0 Hz, 1H), 3.82 (s, 1H), 3.78 (s, 3H), 3.11 (d, J = 13.5 Hz, 1H), 2.94 (d, J = 13.5 Hz, 1H). ^{13}C NMR (150 MHz, acetone-d_6) δ 175.94, 147.61, 146.55, 126.16, 124.37, 115.33, 115.21, 108.30, 86.97, 80.79, 75.48, 75.34, 56.14, 41.03. HRESIMS *m/z* 335.0742 (calcd for $C_{14}H_{16}O_8$ $[M + Na]^+$,335.0737).

12 (58 %), white foam: ^{1}H NMR (600 MHz, acetone-d_6) δ 8.22 (s, 1H), 7.05 (d, J = 1.9 Hz, 1H), 6.92 (d, J = 1.8 Hz, 1H), 5.93 (s, 1H), 4.73 (s, 1H), 4.60 (s, 1H), 4.35 (dd, J = 5.2, 3.3 Hz, 1H), 4.11 (dd, J = 9.8, 5.5 Hz, 1H), 4.03 (dd, J = 9.8, 3.0 Hz, 2H), 3.81 (s, 3H), 3.07 (d, J = 13.8 Hz, 1H), 2.97 (m, overlaped, 1H). ^{13}C NMR (150 MHz, acetone-d_6) δ 175.50, 148.28, 143.97, 127.58, 127.50, 114.28, 108.59, 108.29, 87.26, 80.38, 75.67, 75.38, 56.61, 40.46. HRESIMS *m/z* 388.9870, 390.9851 (M + 2-H) (calcd for $C_{14}H_{15}BrO_8$ $[M - H]^-$, 388.9878).

Method C [27] for lactone **16**: To L-AA (2.3 eq.) in 10 mL phosphate-citrate buffer (PH 5.0) was added corresponding alcohol **B11** (1 mmol, 1 eq.) in 1 mL EtOH, and the solution stirred at room temperature for 8 h. The reaction mixture was extracted with EtOAc, the extract was washed with water, dried over Na_2SO_4 (s), and the solvent was evaporated under reduced pressure and the residue was purified by column chromatography with DCM/MeOH (10/1) to afford lactone **16** (57 %) a gray foam. ^{1}H NMR (600 MHz, acetone-d_6) δ 10.18 (s, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 2.3 Hz, 1H), 7.07 (t, J = 8.0, 1.0 Hz, 1H), 6.98 (t, J = 8.0, 1.0 Hz, 1H), 5.92 (s, 1H), 4.65 (s, 1H), 4.50 (s, 1H), 4.28 (m, 1H), 4.10 (dd, J = 9.7, 5.5 Hz, 1H), 4.01 (dd, J = 9.7, 3.2 Hz, 1H), 3.91 (s, 1H), 3.39 (d, J = 14.3 Hz, 1H), 3.25 (d, J = 14.3 Hz, 1H). ^{13}C NMR (150 MHz, acetone-d_6) δ 176.47, 137.13, 129.06, 126.46, 122.00, 120.06, 119.52, 111.99, 108.53, 107.89, 87.24, 80.22, 75.47, 75.45, 31.22. HRESIMS *m/z* 328.0795 (calcd for $C_{15}H_{15}NO_6$ $[M + Na]^+$, 328.0792).

Acknowledgments This work was financially supported by the National Natural Science Foundation of China (No. U0932602) and the National Basic Research Program of China (973 Program No. 2011CB915503). All authors do not have any financial/commercial conflicts of interest.

Conflict of interest The authors declare no conflict of interest.

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