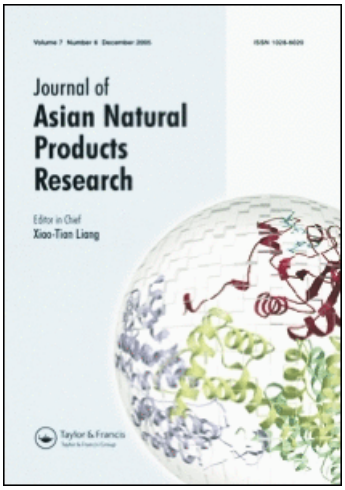


Journal of Asian Natural Products Research
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713454007

Synthesis of the anti-virus compound shuangkangsu's analogs

Di-Zao Li[a]; Yan-Bo Tang[a]; Zhi-Yun Kang[a]; Ruo-Yun Chen[a]; De-Quan Yu[a]
[a] The Key Laboratory of Bioactive Substances and Resources Utilization of Chinese Herbal Medicine, Peking Union Medical College, Ministry of Education, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

To cite this Article Li, Di-Zao , Tang, Yan-Bo , Kang, Zhi-Yun , Chen, Ruo-Yun and Yu, De-Quan(2009) 'Synthesis of the anti-virus compound shuangkangsu's analogs', Journal of Asian Natural Products Research, 11: 7, 613 — 620
To link to this Article: DOI: 10.1080/10286020902971029
URL: http://dx.doi.org/10.1080/10286020902971029

Journal of Asian Natural Products Research
Vol. 11, No. 7, July 2009, 613–620

Taylor & Francis
Taylor & Francis Group

Synthesis of the anti-virus compound shuangkangsu's analogs

Di-Zao Li, Yan-Bo Tang, Zhi-Yun Kang, Ruo-Yun Chen and De-Quan Yu*

The Key Laboratory of Bioactive Substances and Resources Utilization of Chinese Herbal Medicine, Peking Union Medical College, Ministry of Education; Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China

(*Received 23 March 2009; final version received 14 April 2009*)

Four novel cyclic peroxide glucosides **15a**, **15b**, **16a**, and **16b**, optically pure analogs of shuangkangsu (**1**), which is an anti-virus natural product with an unusual skeleton isolated from the buds of *Lonicera japonica* Thunb, were first synthesized totally in six steps including cycloaddition of furan with diethyl acetylenedicarboxylate and glycosylation.

Keywords: analogs of shuangkangsu; cyclic peroxide glucoside; reduction; oxidation; glycosylation

1. Introduction

Shuangkangsu (**1**; Figure 1) [1], a natural peroxide with significant anti-virus activities against the influenza virus in chicken embryo and the respiratory syncytial virus, was first isolated from the buds of *Lonicera japonica* Thunb, a famous traditional Chinese medicine used to treat influenza, pneumonia, and so on [2]. Shuangkangsu is a novel cyclic peroxide glucoside with an unusual 4,5-divinyl-3,6-dihydro-[1,2]dioxine-3,6-diol skeleton and a glycosyl bond formed from the hydroxyl of the peroxide hemiacetal, which had never been found in natural products before. Because of its unique molecular structure and significant anti-virus activities, shuangkangsu becomes a worthy target and a valuable lead compound for a new drug study. However, the synthesis of shuangkangsu is a great challenge. Here, we describe the synthesis of some shuangkangsu analogs (Figure 1). The retrosynthetic analysis of these analogs is shown as retrosynthetic cleavage of the glycosyl bond followed by removal of the peroxide bond linkage that led to oxepine-4,5-dicarbaldehyde or its derivatives and after the carboxyl group's transformation that led to furans by cyclic cleavage at the end (Figure 2).

2. Results and discussion

The synthetic route to compounds **15a**, **15b**, **16a**, and **16b**, analogs of shuangkangsu, is shown in Scheme 1. Here, we describe the synthesis and structural elucidation of these natural-like compounds.

Our results showed that the (2*Z*,4*Z*,6*Z*)-diethyloxepine-4,5-dicarboxylates (**4** and **5**) can be prepared directly by heating furans (**2A** and **2B**) with diethyl acetylenedicarboxylate (**3**) to reflux in boiling toluene under nitrogen for approximately 12 h [3]. The reduction of the diesters **4** and **5** to the corresponding diols **6** and **7**, respectively, was best carried out with

*Corresponding author. Email: dqyu@imm.ac.cn

ISSN 1028-6020 print/ISSN 1477-2213 online

DOI: 10.1080/10286020902971029
http://www.informaworld.com

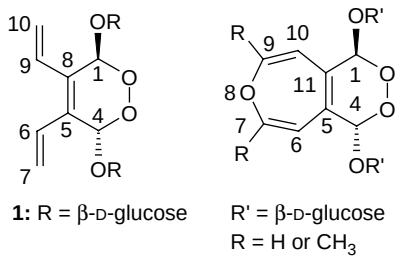


Figure 1. Structures of shuangkangsu and its analogs synthesized.

diisobutylaluminum hydride (DIBAL) [4] in hexane under nitrogen below −70°C (Scheme 1). Oxidation of the seven-membered ring diols **6** and **7** with manganese dioxide (MnO_2) [4] supplied the corresponding dialdehydes **8** and **9**. Oxepine-4,5-dicarbaldehyde (**8**) or 2,7-dimethyloxepine-4,5-dicarbaldehyde (**9**) was reacted with H_2O_2 [5] and compound **10** or **11** was obtained with some difficulties because of the cyclic tensile force from the oxepine. When the reaction was performed under conditions such as H_2O_2–Ura, H_2O_2–MeOH–TsOH, or catalyzed by acid (H_2O_2–H_2SO_4–MeOH–H_2O), and so on, no new resultant was found. This may be attributable to the instability of the peroxide hemiacetal group of **10** or **11** under the conditions of either acid or alkalescence.

However, glycosylation of **10** or **11** was even more problematic. On the one hand, our results showed that peroxide **10** or **11** was not stable under heating and/or acidic conditions and was even more unstable under basic conditions. This is likely due to the high tendency to the cleavage of the dioxine ring in **10** or **11** under these conditions. On the other hand, our results also showed that it was difficult to promote the reaction between compound **10** or **11** and glycosyl donors. Therefore, it was important to select an appropriate glycosylation method for **10** or **11**. Glycosyl donor *O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-trichloroacetimidate (**12**) reacted with **10** or **11** in newly prepared anhydrous dichloromethane in the presence of a newly activated 4 Å molecular sieve, under nitrogen and in low temperature (−70°C) as well as in the presence of catalytic amounts of TMSOTf [6], in this work, to afford compound **13** or **14** in 5–8% yield. This may relate to the low reactivity of hydroxyl of hemiacetal [7–10] as well as the instability of the cyclic peroxide hemiacetal during the glycosylation.

According to the LC–MS analysis, compound **13** consisted of the diastereoisomers **13a** and **13b** (the ratio was 1:1) and compound **14** consisted of the diastereoisomers **14a** and **14b** (the ratio

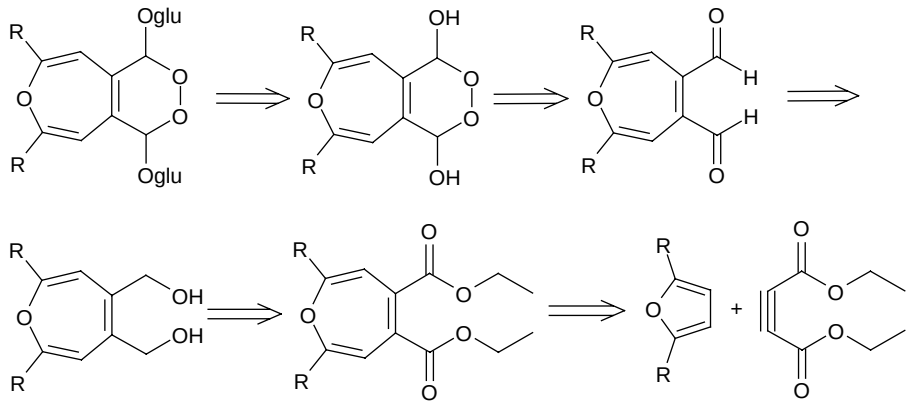
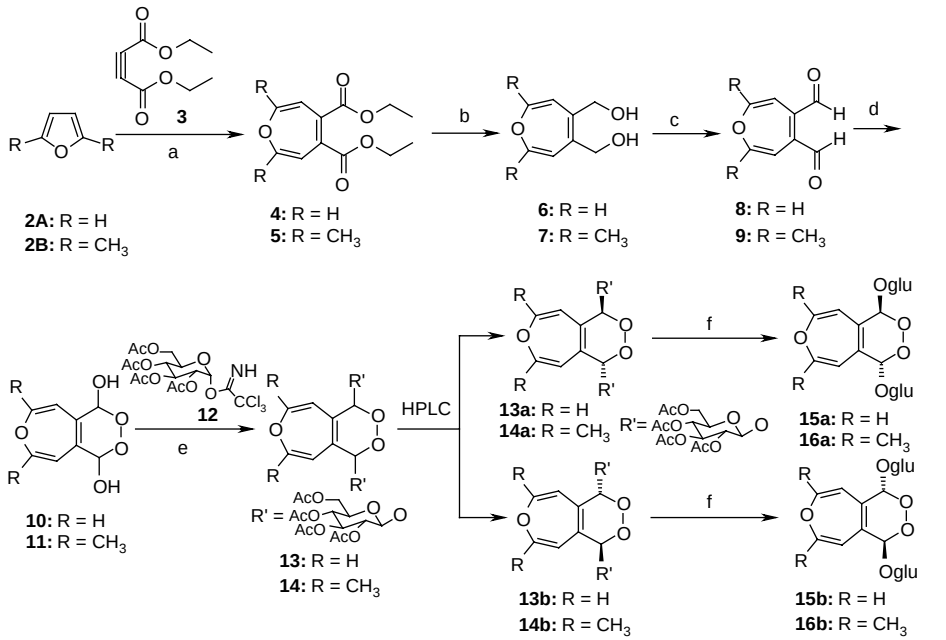


Figure 2. Retrosynthetic analysis of the analogs of shuangkangsu.



Scheme 1. Synthesis of the analogs of shuangkangsu. Reagents and conditions: (a) anhydrous toluene, N_2, reflux, 12 h; (b) N_2, DIBAL (1.0 M in hexane), anhydrous THF, $\leq -70°C$, 12 h; (c) MnO_2, anhydrous CH_2Cl_2, rt, 24 h; (d) H_2O_2, -20 to $-15°C$, 28–32 h; (e) TMSOTf, anhydrous CH_2Cl_2, N_2, $-70°C$, 6–12 h; (f) dibutyltin oxide, CH_3OH, reflux, 4 h.

was 1:1), which were separated by using HPLC, respectively.

Substituents on C-1 and C-4 of **13** or **14** exhibited possible *cis*- or *trans*-relative stereochemistry. But only *trans* isomers were obtained. Because the conformation of a *trans* isomer with both pseudo-equatorial substituents should be more stable than the *cis* isomer's conformation with one pseudo-axial substituent and one pseudo-equatorial substituent. The *trans* isomer exists as two possible diastereomers. According to its obvious Cotton effect in the CD spectra of **13a** ($\Delta\varepsilon_{232\,nm}$ $+2.7$, $\Delta\varepsilon_{212\,nm}$ -1.0) and optical rotation $[\alpha]_D^{25}$ $+120$, **13a** could be identified as an optically pure compound and its relative stereochemistry could be determined as *trans*. According to the reaction mechanism of glycosylation and the symmetry of the CD spectra of **13a**, the absolute configuration of **13a** was determined to be (1*S*, 4*S*) by comparison of the CD spectra with those of shuangkangsu ($\Delta\varepsilon_{240\,nm}$ $+19$, $\Delta\varepsilon_{210\,nm}$ -35) the absolute configuration of which was specific as (1*S*, 4*S*) [1]. Therefore, the structure of **13a** was formulated, as shown in Scheme 1. Similarly, the absolute configurations of **13b**, **14a**, and **14b** were determined to be (1*R*, 4*R*), (1*S*, 4*S*), and (1*R*, 4*R*) and their structures were formulated the same way as for **13a**, as shown in Scheme 1.

As mentioned above, this kind of peroxide was so unstable under basic conditions that common reagents such as $NaOCH_3$, NaOH, NH_3, $NH_2NH_2{\cdot}H_2O$, Na_2CO_3, K_2CO_3, and so on, which were used to remove the acetyl protective groups in sugar moiety to yield free glycoside, were all unsuitable for this work and our results made this sure. Finally, dibutyltin oxide [11,12], a near-neutral reagent, was used to react with **13a**, **13b**, **14a**, and **14b** in CH_3OH, succeeded to remove the acetyl groups in sugar

moiety and to afford the desired compounds **15a, 15b**, **16a**, and **16b**, respectively.

Substituents on C-1 and C-4 of **15** or **16** exhibited possible *cis*- or *trans*-relative stereochemistry and only *trans* isomers were obtained as same as that of **13** or **14**. The *trans* isomer exists as two possible diastereomers. According to its obvious Cotton effect in the CD spectrum of **15a** ($\Delta\varepsilon_{248\,nm}$ +3.5, $\Delta\varepsilon_{229\,nm}$ −1.3) and optical rotation $[\alpha]_D^{25}$ + 148, **15a** could be identified as an optically pure compound and its relative stereochemistry could be determined as *trans*. Based on the reaction mechanism of deacetylation and the symmetry of the CD spectrum of **15a**, the absolute configuration of **15a** was determined to be (1*S*, 4*S*) by comparison of the CD spectra with those of shuangkangsu ($\Delta\varepsilon_{240\,nm}$ +19, $\Delta\varepsilon_{210\,nm}$ −35) [1]. Therefore, the structure of **15a** was formulated, as shown in Scheme 1. Similarly, the absolute configuration of **15b**, **16a**, and **16b** was determined to be (1*R*, 4*R*), (1*S*, 4*S*), and (1*R*, 4*R*) by comparison of the CD spectra with those of shuangkangsu and their structures were elucidated in the same way as that of **15a**, as shown in Scheme 1.

In summary, the results showed that cyclic peroxides hemiacetal such as **10** and **11** can be used to synthesize the optically pure analogs of shuangkangsu by means of their glycosylation.

3. Experimental

3.1 General experimental procedures

Melting points were determined on a XT_4-100X micro-melting apparatus and are uncorrected. The optical rotations were measured with a PE-241 digital polarimeter. The CD spectra were taken on a JASCO-712 spectrophotometer. The NMR spectra were recorded on a Varian Mercury-300 spectrometer (300 or 400 MHz for ^{1}H and 75 or 100 MHz for ^{13}C). The mass spectra were obtained on a ZAB-2F (EI) and Finnigan LTQ FTMS (ESI) spectrometer.

3.2 General procedures

3.2.1 Compounds **4** and **5**

During the dried three-necked round bottom flask, a solution of furans, for example furan **2A** (1.36 g, 20.0 mmol), in 8.0 ml newly distilled anhydrous toluene under a nitrogen atmosphere was cooled to 0–5°C in an ice bath. Diethyl acetylenedicarboxylate **3** (3.4 g, 20.0 mmol) was added dropwise slowly with stirring at such a rate that the temperature never rose above 50°C. After the addition, the reaction mixture was heated under gentle reflux for 8–12 h. The reaction was monitored by TLC (petroleum–acetone = 4:1–3:1) until one of the reactants disappeared. The reaction mixture was cooled to room temperature and the solvent was removed at reduced pressure leaving an oil residue as the crude product [3]. The pure compound **4** was obtained as a pale yellow oil by silica gel chromatographic separation (petroleum–acetone = 10:1–5:1); yield: 70.5%. Compound **5** was synthesized as a pale yellow oil by the same procedure; yield: 92.5%.

3.2.2 Compounds **6** and **7**

A solution of 1.0 M DIBAL in dry hexane (10 ml, 10 mmol) was added dropwise to a stirred solution of (2*Z*,4*Z*,6*Z*)-diethyloxepine-4,5-dicarboxylates (for example **4**, 1.0 g, 4.2 mmol) in dry tetrahydrofuran (20 ml) under nitrogen below −70°C. Then, 12 h later, the excess reagent was decomposed by careful addition into the strongly stirred mixture of ice and water (100 ml) and the mixture was stirred for 1 h. The aqueous layer was separated and extracted with ethyl acetate (200 ml). The combined organic layers were washed by saturated brine and dried with sodium sulfate. The dark yellow oil was gained after the removal of the solvent and purified by silica gel chromatographic separation to give **6**; yield: 10.0%.

Compound **7** was achieved by the same procedure; yield: 10.0%.

3.2.2.1 Compound **6**. A colorless gum; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.46–7.38 (m, 2H, H-2, and H-7), 7.15–7.08 (m, 2H, H-3, and H-6), 4.72 (s, 4H, 2 × CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 147.4 (C-2 and C-7), 129.7 (C-4 and C-5), 108.6 (C-3 and C-6), 64.2 (2 × CH_2); ESI-MS: *m/z* 177 $[M + Na]^+$, 155 $[M + H]^+$; HR-ESI-MS: *m/z* 177.0525 $[M + Na]^+$ (calcd for $C_8H_{10}NaO_3$, 177.0528).

3.2.2.2 Compound **7**. A colorless gum; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.06 (s, 2H, H-3, and H-6), 4.78 (s, 4H, 2 × CH_2), 2.39 (s, 6H, 2 × CH_3), ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 148.1 (C-2 and C-7), 134.9 (C-4 and C-5), 110.3 (C-3 and C-6), 59.4 (2 × CH_2), 19.5 (2- and 7-CH_3); ESI-MS: *m/z* 183 $[M + H]^+$, 205 $[M + Na]^+$; HR-ESI-MS: *m/z* 205.0859 $[M + Na]^+$ (calcd for $C_{10}H_{14}NaO_3$, 205.0841).

3.2.3 *Compounds* **8** *and* **9**

A solution of pure diol (such as **6**; 155 mg, 1.0 mmol) in dry dichloromethane (10 ml) was stirred at room temperature with newly prepared MnO_2 (1.05 g, 12.0 mmol, activated by keeping at 100°C for 4 h) for 24 h (TLC monitoring) and the reactant diol began to disappear. Filtration through Celite, evaporation of the solvent under reduced pressure, and purification of the residue by silica gel chromatography gave **8** as a yellow oil; yield: 15.0%. Compound **9** was synthesized by the same program; yield: 15.0%.

3.2.3.1 Compound **8**. A yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 10.63 (s, 2H, 2 × CHO), 7.98–7.90 (m, 2H, H-3, and H-6), 7.67–7.60 (m, 2H, H-2, and H-7); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 193.0 (2 × C═O), 147.0 (C-2 and C-7), 134.3 (C-4 and C-5), 111.0 (C-3 and C-6); ESI-MS: *m/z* 173 $[M + Na]^+$, 151 $[M + H]^+$; HR-ESI-MS: *m/z* 173.0229 $[M + Na]^+$ (calcd for $C_8H_6NaO_3$, 173.0215).

3.2.3.2 Compound **9**. A pale yellow oil. ^{1}H NMR (300 MHz, CD_3COCD_3): δ (ppm) 10.00 (s, 2H, 2 × CHO), 7.60 (s, 2H, H-3, and H-6), 1.80 (s, 6H, 2-, and 7-CH_3); ^{13}C NMR (75 MHz, CD_3COCD_3): δ (ppm) 191.4 (2 × C═O), 148.3 (C-2 and C-7), 133.9 (C-4 and C-5), 112.3 (C-3 and C-6), 20.2 (2- and 7-CH_3); ESI-MS: *m/z* 201 $[M + Na]^+$, 179 $[M + H]^+$; HR-ESI-MS: *m/z* 201.0539 (calcd for $C_{10}H_{10}NaO_3$, 201.0528).

3.2.4 *Compounds* **10** *and* **11**

Compound **8** (30 mg, 0.2 mmol), for example, was stirred with 30% H_2O_2 (1.0 ml, 9.0 mmol) under −15 to −20°C for 28 h and then extracted with ethyl acetate (20 ml). The combined organic layers were dried with anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to afford a brown dope which became a colorless dope (**10**) after the purification by silica gel chromatographic separation; yield: 13.6%. Compound **11** was synthesized by the same program; yield: 15.6%.

3.2.4.1 Compound **10**. A colorless gum; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.37–7.29 (m, 2H, H-7, and H-9), 7.19–7.14 (m, 2H, H-6, and H-10), 5.93 (s, 2H, H-1, and H-4), 2.23 (brs, 1H, 2 × OH); ^{1}H NMR (300 MHz, $CDCl_3$ + D_2O) δ (ppm): 7.37–7.27 (m, 4H, H-6, H-7, H-9, and H-10), 5.92 (s, 2H, H-1, and H-4), 4.80 (brs, 0.4H, D_2O); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 149.7 (C-7 and C-9), 128.4 (C-5 and C-11), 117.0 (C-6 and C-10), 95.1 (C-1 and C-4); ESI-MS: *m/z* 223

$[M + K]^+$, 207 $[M + Na]^+$; HR-ESI-MS: *m/z* 207.1473 $[M + Na]^+$ (calcd for $C_8H_8NaO_5$, 207.1461).

3.2.4.2 Compound **11**. A colorless dope; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.12 (s, 2H, H-6, and H-10), 5.92 (s, 2H, H-1, and H-4), 2.25 (brs, 1H, OH), 1.77 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 150.0 (C-7 and C-9), 127.6 (C-5 and C-11), 116.0 (C-6 and C-10), 94.2 (C-1 and C-4), 18.7 (7- and 9-CH_3); ESI-MS: *m/z* 235 $[M + Na]^+$, 213 $[M + H]^+$; HR-ESI-MS: *m/z* 235.0593 $[M + Na]^+$ (calcd for $C_{10}H_{12}NaO_5$, 235.0582).

3.2.5 Compounds **13a**, **13b**, **14a**, *and* **14b**

Compound **10** (for example; 20.0 mg, 0.11 mmol), glycosyl trichloroacetimidate (**12**; 0.3 g, 0.6 mmol), and freshly activated 4 Å molecule sieve (0.2 g) were added to a 15 ml three-necked flask, which was purged with nitrogen. Dried CH_2Cl_2 (5.0 ml) was injected into the flask. The mixture was stirred at room temperature for 1 h, and then TMSOTf (catalytic amount) was added into the reaction mixture at -70°C, which was allowed to stir at -70°C for another 8 h. The reaction mixture was diluted with CH_2Cl_2 (10.0 ml) and filtered through Celite. The filter cake was washed with CH_2Cl_2 and the combined filtrate was then washed with H_2O (3×5.0 ml), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatographic separation (gradient elution, PE–EtOAc = 6:1–1:1) followed by Sephadex LH-20 column chromatography (PE–CH_2Cl_2–CH_3OH = 5:5:1) to give **13** as a white syrup in 5% yield, which was separated into compound **13a** and its diastereomer **13b** using HPLC (CH_3OH–H_2O = 70:30). The same procedure gave **14** as a white syrup in 8% yield, which was also separated into a pair of pure optical isomers **14a** and **14b** by HPLC (CH_3OH–H_2O = 70:30).

3.2.5.1 Compound **13a**. $[\alpha]_D^{25}$ + 120 ($c = 0.01$, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.46–7.34 (m, 2H, H-6, and H-10), 7.16–7.03 (m, 2H, H-7, and H-9), 6.13 (s, 2H, H-1, and H-4), 5.48 (t, 2H, $J = 9.6$ Hz, H-6′), 5.37 (t, 2H, $J = 9.6$ Hz, H-6′), 5.29 (d, 2H, $J = 7.8$ Hz, anomeric H), 5.27–5.20 (m, 2H), 4.31 (dd, 2H, $J = 12.0$, 5.4 Hz), 4.23 (dd, 2H, $J = 12.3$, 2.4 Hz), 3.98–3.92 (m, 2H), 2.08–2.04 (s, 24H, 8 × acetyl CH_3); ^{13}C NMR (75 MHz, CD_3COCD_3): δ (ppm) 170.6 (2 × C═O), 170.2 (2 × C═O), 170.0 (2 × C═O), 169.7 (2 × C═O), 152.3 (C-7 and C-9), 130.9 (C-5 and C-11), 119.4 (C-6 and C-10), 98.0 (C-1′), 96.6 (C-1 and C-4), 74.1 (C-5′), 73.5 (C-3′), 72.2 (C-2′), 69.5 (C-4′), 63.0 (C-6′), 20.6–20.3 (8 × acetyl CH_3); HR-ESI-MS: *m/z* 867.2195 $[M + Na]^+$ (calcd for $C_{36}H_{44}O_{23}Na$, 867.2171); CD spectra (THF): $\Delta\varepsilon_{232\,nm}$ +2.7, $\Delta\varepsilon_{212\,nm}$ −1.0.

3.2.5.2 Compound **13b**. $[\alpha]_D^{25}$ −115 ($c = 0.01$, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.47–7.33 (m, 2H, H-6, and H-10), 7.16–7.04 (m, 2H, H-7, and H-9), 6.14 (s, 2H, H-1, and H-4), 5.48 (dd, 2H, $J = 9.3$, 7.8 Hz, H-6′), 5.37 (t, 2H, $J = 9.3$ Hz, H-6′), 5.28 (d, 2H, $J = 8.1$ Hz, anomeric H), 5.26–5.20 (m, 2H), 4.31 (dd, 2H, $J = 12.3$, 5.4 Hz), 4.24 (dd, 2H, $J = 12.3$, 2.4 Hz), 3.98–3.91 (m, 2H), 2.09–2.05 (s, 24H, 8 × acetyl CH_3); ^{13}C NMR (75 MHz, CD_3COCD_3): δ (ppm) 170.6 (C═O), 170.1 (C═O), 170.0 (C═O), 169.8 (C═O), 152.1 (C-7 and C-9), 130.8 (C-5 and C-11), 119.3 (C-6 and C-10), 97.9 (C-1′), 96.7 (C-1 and C-4), 74.1 (C-5′), 73.6 (C-3′), 72.2 (C-2′), 69.4 (C-4′), 62.9 (C-6′), 20.6–20.2 (8 × acetyl CH_3); HR-ESI-MS: *m/z* 867.2157 $[M + Na]^+$ (calcd for $C_{36}H_{44}NaO_{23}$, 867.2171); CD spectra (THF): $\Delta\varepsilon_{231\,nm}$ −2.3, $\Delta\varepsilon_{214\,nm}$ +1.3.

3.2.5.3 Compound **14a**. $[\alpha]_D^{25}$ + 130 ($c = 0.01$, acetone); ^{1}H NMR (300 MHz,

$CDCl_3$): δ (ppm) 7.11 (s, 2H, H-6, and H-10), 6.11 (s, 2H, H-1, and H-4), 5.33–5.31 (m, 2H), 5.30 (d, 2H, $J = 7.8$ Hz, anomeric H), 5.20–5.13 (m, 4H), 4.24 (dd, 2H, $J = 12.6$, 5.7 Hz), 4.20 (dd, 2H, $J = 12.6$, 2.4 Hz), 3.95–3.89 (m, 2H), 2.12–2.05 (s, 24H, 8 × acetyl CH_3), 1.75 (7- and 9-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 170.9 (C═O), 170.6 (C═O), 169.6 (C═O), 169.4 (C═O), 153.0 (C-7 and C-9), 130.6 (C-5 and C-11), 119.2 (C-6 and C-10), 97.8 (C-1′), 96.3 (C-1 and C-4), 73.9 (C-5′), 73.1 (C-3′), 71.9 (C-2′), 68.8 (C-4′), 62.4 (C-6′), 21.3–20.9 (8 × acetyl CH_3), 17.5 (7- and 9-CH_3); HR-ESI-MS: *m/z* 895.2527 $[M + Na]^+$ (calcd for $C_{38}H_{48}NaO_{23}$, 895.2484); CD spectra (THF): $\Delta\varepsilon_{231\,nm}$ +3.0, $\Delta\varepsilon_{211\,nm}$ −1.6.

3.2.5.4 Compound **14b**. $[\alpha]_D^{25}$ −125 ($c = 0.01$, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.10 (s, 2H, H-6, and H-10), 6.12 (s, 2H, H-1, and H-4), 5.33–5.30 (m, 2H), 5.29 (d, 2H, $J = 6.9$ Hz, anomeric H), 5.20–5.13 (m, 4H), 4.26 (dd, 2H, $J = 12.3$, 5.7 Hz), 4.20 (dd, 2H, $J = 12.3$, 2.1 Hz), 3.94–3.88 (m, 2H), 2.12–2.04 (s, 24H, 8 × acetyl CH_3), 1.73 (7- and 9-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 171.0 (C═O), 170.6 (C═O), 169.7 (C═O), 169.5 (C═O), 153.1 (C-7 and C-9), 131.6 (C-5 and C-11), 119.1 (C-6 and C-10), 97.9 (C-1′), 96.4 (C-1 and C-4), 73.8 (C-5′), 73.3 (C-3′), 71.8 (C-2′), 68.7 (C-4′), 62.3 (C-6′), 21.2–20.8 (8 × acetyl CH_3), 17.2 (7- and 9-CH_3); HR-ESI-MS: *m/z* 895.2507 $[M + Na]^+$ (calcd for $C_{38}H_{48}O_{23}Na$, 895.2484); CD spectra (THF): $\Delta\varepsilon_{230\,nm}$ −3.1, $\Delta\varepsilon_{212\,nm}$ +1.5.

3.2.6 Compounds **15a**, **15b**, **16a**, *and* **16b**

Compound **13a** (for example; 60.0 mg, 0.071 mmol) was dissolved in 5.0 ml CH_3OH and then dibutyltin oxide (3 mg, 0.012 mmol) was added into the mixture. After the addition, the mixture was heated under gentle reflux for 4 h and then concentrated. The residue was purified by silica gel column chromatography (gradient elution, $CHCl_3$–CH_3OH = 100:1–2:1) followed by Sephadex LH-20 column chromatography (PE–CH_2Cl_2–CH_3OH = 5:5:1) to afford **15a** as a white solid in 6.0% yield. Compounds **15b**, **16a**, and **16b** were synthesized in the same procedure (yield: 5.5, 8.0, 7.0%, respectively).

3.2.6.1 Compound **15a**. A white solid; mp 135–137°C; $[\alpha]_D^{25}$ +148 ($c = 0.005$, acetone); ^{1}H NMR (300 MHz, D_2O): δ (ppm) 7.50–7.37 (m, 2H, H-6, and H-10), 7.18–7.05 (m, 2H, H-7, and H-9), 5.82 (s, 2H, H-1, and H-4), 4.48 (d, 2H, $J = 9.9$ Hz, anomeric H), 4.37 (dd, 4H, $J = 10.5$, 4.5 Hz, H-6′), 3.82–3.45 (m, 8H, H-2′, H-3′, H-4′, H-5′); ^{13}C NMR (75 MHz, CD_3OD): δ (ppm) 151.6 (C-7 and C-9), 130.5 (C-5 and C-11), 118.2 (C-6 and C-10), 95.2 (C-1′), 92.7 (C-1 and C-4), 77.5 (C-5′), 76.3 (C-3′), 74.9 (C-2′), 71.8 (C-4′), 61.7 (C-6′); HR-ESI-MS: *m/z* 531.1322 $[M + Na]^+$ (calcd for $C_{20}H_{28}NaO_{15}$, 531.1326); CD spectra (H_2O): $\Delta\varepsilon_{248\,nm}$ +3.5, $\Delta\varepsilon_{229\,nm}$ −1.3.

3.2.6.2 Compound **15b**. A white solid; mp 133–135°C; $[\alpha]_D^{25}$ −163 ($c = 0.005$, acetone); ^{1}H NMR (300 MHz, D_2O): δ (ppm) 7.49–7.36 (m, 2H, H-6, and H-10), 7.18–7.04 (m, 2H, H-7, and H-9), 5.81 (s, 2H, H-1, and H-4), 4.47 (d, 2H, $J = 9.3$ Hz, anomeric H), 4.38–4.33 (m, 4H, H-6′), 3.82–3.45 (m, 8H, H-2′, H-3′, H-4′, H-5′); ^{13}C NMR (75 MHz, CD_3OD): δ (ppm) 151.6 (C-7 and C-9), 130.7 (C-5 and C-11), 118.2 (C-6 and C-10), 95.1 (C-1′), 92.6 (C-1 and C-4), 77.5 (C-5′), 76.2 (C-3′), 74.8 (C-2′), 71.9 (C-4′), 61.8 (C-6′); HR-ESI-MS: *m/z* 531.1370 $[M + Na]^+$ (calcd for $C_{20}H_{28}NaO_{15}$, 531.1326); CD spectra (H_2O): $\Delta\varepsilon_{246\,nm}$ −3.1, $\Delta\varepsilon_{231\,nm}$ +1.0.

3.2.6.3 Compound **16a**. A white solid; mp 138–139°C; $[\alpha]_D^{25}$ + 158 ($c = 0.005$, acetone); ^{1}H NMR (300 MHz, D_2O) δ (ppm): 7.11 (s, 2H, =CH), 5.80 (s, 2H, H-1, and H-4), 4.46 (d, 2H, $J = 8.1$ Hz, anomeric H), 4.38–4.33 (m, 4H, H-6′), 3.83–3.43 (m, 8H, H-2′, H-3′, H-4′, H-5′), 1.77 (s, 6H, 7-, and 9-CH_3); ^{13}C NMR (75 MHz, CD_3OD): δ (ppm) 152.4 (C-7 and C-9), 128.3 (C-5 and C-11), 117.0 (C-6 and C-10), 95.0 (C-1′), 93.6 (C-1 and C-4), 78.0 (C-5′), 76.3 (C-3′), 74.8 (C-2′), 71.8 (C-4′), 62.7 (C-6′), 18.0 (7- and 9-CH_3); HR-ESI-MS: *m/z* 559.1632 $[M + Na]^+$ (calcd for $C_{22}H_{32}NaO_{15}$, 559.1639); CD spectra (H_2O): $\Delta\varepsilon_{248\,nm}$ +3.2, $\Delta\varepsilon_{230\,nm}$ −1.5.

3.2.6.4 Compound **16b**. A white solid; mp 136–138°C; $[\alpha]_D^{25}$ −143 ($c = 0.005$, acetone); ^{1}H NMR (300 MHz, D_2O): δ (ppm) 7.10 (s, 2H, =CH), 5.80 (s, 2H, H-1, and H-4), 4.45 (d, 2H, $J = 9.6$ Hz, anomeric H), 4.35 (dd, 4H, $J = 10.8$, 6.0 Hz, H-6′), 3.82–3.43 (m, 8H, H-2′, H-3′, H-4′, H-5′), 1.77 (s, 6H, 7-, and 9-CH_3); ^{13}C NMR (75 MHz, CD_3OD): δ (ppm) 152.5 (C-7 and C-9), 128.4 (C-5 and C-11), 117.1 (C-6 and C-10), 95.1 (C-1′), 93.5 (C-1 and C-4), 78.0 (C-5′), 76.4 (C-3′), 74.9 (C-2′), 71.8 (C-4′), 62.7 (C-6′), 18.0 (7- and 9-CH_3); HR-ESI-MS: *m/z* 559.1642 $[M + Na]^+$ (calcd for $C_{22}H_{32}O_{15}Na$, 559.1639); CD spectra (H_2O): $\Delta\varepsilon_{246\,nm}$ −2.5, $\Delta\varepsilon_{230\,nm}$ +1.4.

Acknowledgement

This research work was financially supported by the National Natural Science Foundation of China (Grant No. 20372086).

References

[1] D.Q. Yu, R.Y. Chen, L.J. Huang, F.Z. Xie, D.S. Ming, K. Zhou, H.Y. Li, and K.M. Tong, *J. Asian Nat. Prod. Res.* **10**, 851 (2008).
[2] The eighth Chinese Pharmacopeia Commission, *Chinese Pharmacopeia 2005* (Chemical Industry Press, Beijing, 2006).
[3] D.Z. Li, Z.F. Zheng, Z.Y. Kang, and D.Q. Yu, *Chin. Chem. Lett.* **20**, 635 (2009).
[4] D. Butina and F. Sondheimer, *Synthesis* **39**, 543 (1980).
[5] H.S. Kim, Y. Shibata, Y. Wataya, K. Tsuchiya, A. Masuyama, and M. Nojima, *J. Med. Chem.* **42**, 2604 (1999).
[6] T.E.C.L. Ronnow, M. Morten, and B. Klaus, *Tetrahedron: Asymm.* **5**, 2109 (1994).
[7] A.J. Lin, L.Q. Li, S.L. Andersen, and D.L. Klayman, *J. Med. Chem.* **35**, 1639 (1992).
[8] M. Nishizama, D.M. Garcia, Y. Noguchi, K. Komatsu, S. Hatakeyama, and H. Yamada, *Chem. Pharm. Bull.* **42**, 2400 (1994).
[9] K. Ramu and J.K. Baker, *J. Med. Chem.* **38**, 1911 (1995).
[10] P.M. O'Neill, F. Scheinmann, A.V. Stachulski, J.L. Maggs, and B.K. Park, *J. Med. Chem.* **44**, 1467 (2001).
[11] W. Li, H.M. Liu, and Q.D. Yu, *Acta Chim. Sin.* **61**, 1516 (2003).
[12] Y.B. Tang, L.J. Huang, D.Z. Li, Q.J. Zhang, R.Y. Chen, and D.Q. Yu, *J. Asian Nat. Prod. Res.* **11**, 172 (2009).