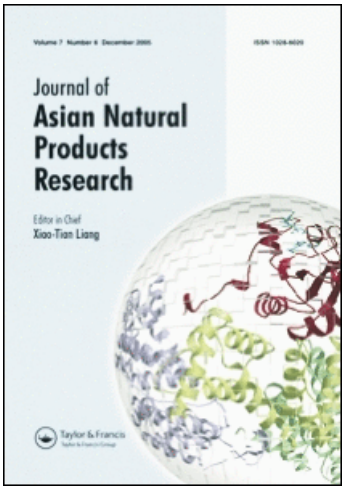

Journal of Asian Natural Products Research
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713454007

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To cite this Article Tang, Yan-Bo , Huang, Long-Jiang , Li, Di-Zao , Zhang, Qing-Jian , Chen, Ruo-Yun and Yu, De-Quan(2009) 'The synthesis of analogs of shuangkangsu, a novel natural cycloperoxide glucoside from *Lonicera japonica* Thunb', Journal of Asian Natural Products Research, 11: 2, 172 — 176
To link to this Article: DOI: 10.1080/10286020802618985
URL: http://dx.doi.org/10.1080/10286020802618985

Journal of Asian Natural Products Research
Vol. 11, No. 2, February 2009, 172–176

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The synthesis of analogs of shuangkangsu, a novel natural cycloperoxide glucoside from *Lonicera japonica* Thunb

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(*Received 15 July 2008; final version received 28 October 2008*)

Four novel optically pure cycloperoxide glucosides **9a**, **9b**, **10a**, and **10b**, analogs of shuangkangsu – a natural product with unusual skeleton and antivirus activity from the buds of *Lonicera japonica* Thunb, were firstly synthesized by employing peroxidation and glucosidation reactions from phthalaldehyde or 4,5-dichloro phthalaldehyde and glucose.

Keywords: shuangkangsu; cycloperoxide glucosides; shuangkangsu analogs; asymmetric synthesis

1. Introduction

Shuangkangsu (**1**) (Figure 1, [1]), a natural compound showed significant antivirus activities against influenza virus in chicken embryo and respiratory syncytial virus in cells, respectively, was isolated from the buds of *Lonicera japonica* Thunb, a famous traditional Chinese medicine that possesses functions of antipyretic and detoxical material and was used to treat influenza and pneumonia, etc. [2]. Shuangkangsu (**1**) is a novel cycloperoxide glucoside with unusual 2,3-dioxane-1,4-diol skeleton and glucosyl bond formed by hydroxyl of peroxide hemiacetal, which was found firstly in natural products. The unique molecular structure and significant antivirus activities render shuangkangsu a worthy target for chemical synthesis and structure modification. For initiating a synthetic program for shuangkangsu, we designed and synthesized analogs of shuangkangsu, and the structures of analogs are shown in Figure 1.

The retrosynthetic analysis that led to this approach is shown in Figure 2. Thus, retrosynthetic cleavage of the glucosyl bond followed by removal of the peroxide bond linkage led to phthalaldehyde.

2. Results and discussion

The synthetic route to compounds **9a**, **9b**, **10a**, and **10b**, analogs of shuangkangsu, is shown in Scheme 1.

4,5-Dichloro phthalaldehyde (**2**) or phthalaldehyde (**3**) reacted with H_2O_2 gave compound **4** or **5** in good yields. However, glucosylation of **4** or **5** was problematic. Firstly, peroxide **4** or **5** was not stable under acidic or basic conditions; next, according to previous reports [3–6], it was difficult to promote the yield of the reaction between compound **4** or **5** and glycosyl donors because of the low reactivity of hydroxyl of hemiacetal. So, it was better to select a suitable glucosylation method for **4** or **5**. Glycosyl donor trichloroacetimidate (**6**) reacted with **4** or **5**,

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ISSN 1028-6020 print/ISSN 1477-2213 online

DOI: 10.1080/10286020802618985
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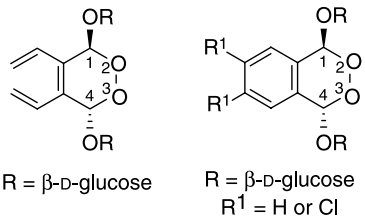


Figure 1. Structure of shuangkangsu and its analogs synthesized.

in this work, afforded compound **7** or **8** only in 5–8% yield under the usual condition using $BF_3{\cdot}Et_2O$ as the promoter. Additionally, when the glycosyl donor was changed to thioglycoside (**11**), which reacted with compound **5** on the condition of using AgOTf and NIS as the promoter, orthoester (**12**) was obtained in 10% yield. In the presence of $BF_3{\cdot}Et_2O$, **12** rearranged to compound **8** (Scheme 2).

The result identified by LC-MS showed that compound **7** consisted of two compounds **7a** and **7b** (in the ratio with 1:1), which were separated by using HPLC. According to the previous study [1], substituents on C-1 and C-4 of shuangkangsu and its analogs preferred the *trans*-relative stereochemistry. The absolute configurations of **7a** and **7b** were determined to (1*S*, 4*S*) and (1*R*, 4*R*), respectively, by the comparison of cotton effect in their CD spectra with shuangkangsu's [1]. Similarly, **8a** and **8b** were obtained and their absolute configurations were determined to (1*S*, 4*S*) and (1*R*, 4*R*), respectively.

As mentioned above, this kind of peroxide was not stable under basic conditions, so common reagents, such as $NaOCH_3$, K_2CO_3, etc., which were used to remove the acetyl groups in sugar moiety to yield free glycoside, were not suitable for this work. Finally, dibutyltin oxide [7], a near-neutral reagent, was employed to react with **7a**, **7b**, **8a**, and **8b** in the presence of CH_3OH, succeeded to afford desired compounds **9a**, **9b**, **10a**, and **10b**, respectively.

3. Experimental

3.1 General experimental procedures

Melting points were determined on an XT_4-100_X micro-melting apparatus and are uncorrected. Optical rotations were measured with PE-241 digital polarimeter. CD spectra were taken on JASCO J-725 spectrophotometer. The NMR spectra were recorded on Varian Mercury-300 spectrometer (300 MHz for ^1H and 75 MHz for ^{13}C). HR-FAB-MS and HR-ESI-MS spectra were obtained on AutoSpec Ultima-TOF and AccuTOF CS mass spectrometer, respectively.

3.2 General procedures for the synthetic compounds

*3.2.1 Compound **4***

To a solution of 4,5-dichloro phthalaldehyde (0.63 g, 3.1 mmol) in 10 ml CH_3OH was added 30% H_2O_2 (0.35 g, 3.1 mmol). The reaction mixture was stirred at room temperature for 2 h and then concentrated. The residue was washed by CH_2Cl_2, **4** was obtained as white powder in 98% yield; mp 145–148°C; ^1H NMR (300 MHz, acetone-d_6) δ (ppm): 7.58 (s, 2H) and 5.98 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 134.6, 132.3, 129.8, and 93.3.

*3.2.2 Compounds **7a**, **7b**, **8a**, and **8b***

Compound **4** (0.3 g, 1.27 mmol), glycosyl trichloroacetimidate (**6**) (3 g, 6 mmol), and freshly activated 4 Å molecule sieve (2 g) were added to a 250 ml three-necked flask, which

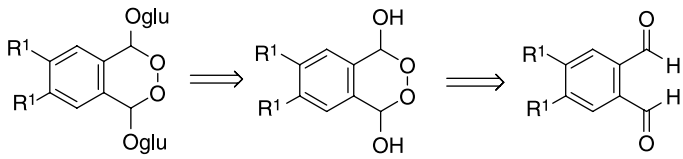
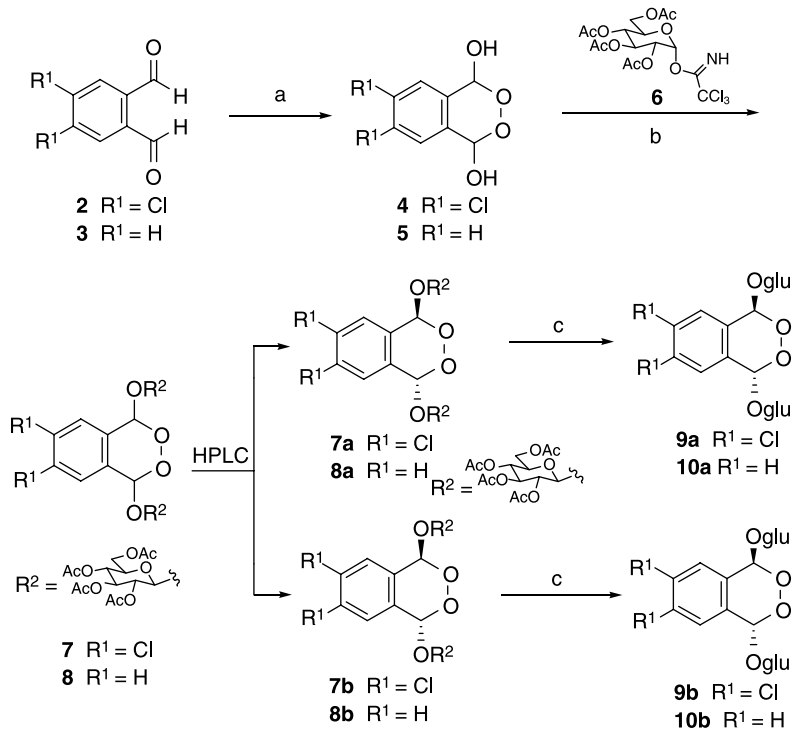
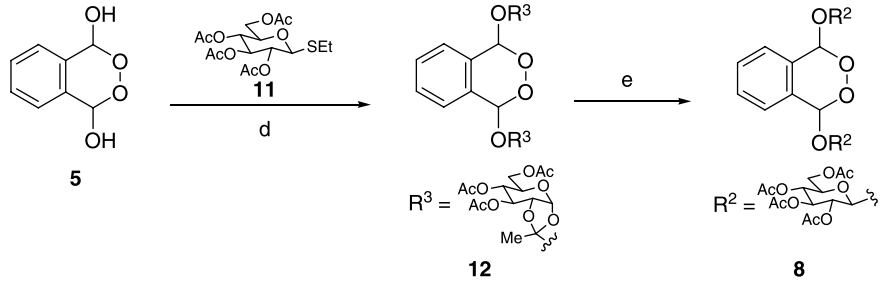


Figure 2. Retrosynthetic analysis of analogs of shuangkangsu.



Scheme 1. Synthesis of analogs of shuangkangsu. Reagents and conditions: (a) H_2O_2, CH_3OH, 2 h for **4** and 12 h for **5**; (b) $BF_3{\cdot}Et_2O$, CH_2Cl_2/Et_2O, 0°C, 12 h and (c) dibutyltin oxide, CH_3OH, reflux, 4 h.

was purged with nitrogen. Dried CH_2Cl_2/Et_2O (100 ml, 1:1) were injected to the flask. The mixture was stirred at room temperature for 1 h, and then $BF_3{\cdot}Et_2O$ (catalytic amount) was added at 0°C to the reaction mixture, which was allowed to stir at 0°C for another 12 h. The reaction mixture was diluted with CH_2Cl_2 (100 ml) and filtered through Celite. The filter cake was washed with CH_2Cl_2 and the combined filtrate was then washed with H_2O (3×50 ml), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (gradient elution, PE/EtOAc = 6:1 to 3:1) followed by Sephadex LH-20 column chromatography ($PE/CH_2Cl_2/CH_3OH = 5:5:1$) to give **7** as white solid in 5% yield, which was separated into compound **7a** and its diastereomer **7b** by using HPLC ($CH_3OH/H_2O = 60:40$).



Scheme 2. Synthesis of compound **8** from thioglycoside. Reagents and conditions: (d) NIS/AgOTf, CH_2Cl_2/Et_2O, 0°C rt, 12 h and (e) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 10 h.

7a: White solid; $[\alpha]_D^{25}$ + 142 (c = 0.01, acetone); ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm): 7.49 (s, 2H), 6.13 (s, 2H), 5.40 (t, J = 9.0 Hz, 2H), 5.27 (d, J = 8.1 Hz, 2H), 5.05 (t, J = 9.0 Hz, 2H), 4.88 (d, J = 8.1 Hz, 2H), 4.32 (dd, J = 12.0, 2.4 Hz, 2H), 4.19 (dd, J = 12.3, 4.8 Hz, 2H), 4.09–4.05 (m, 2H), 2.09 (s, 6H), 2.04 (s, 6H), 2.02 (s, 6H), and 1.99 (s, 6H); ^{13}C NMR (75 MHz, acetone-d_6) δ (ppm): 170.6, 170.2, 170.0, 169.7, 132.3, 130.9, 129.3, 98.0, 96.6, 74.1, 73.5, 72.2, 69.5, 63.0, 20.6, 20.5, and 20.4; HR-FAB-MS m/z: 919.1448 $[M + Na]^+$ (calcd for $C_{36}H_{42}O_{22}Cl_2Na$, 919.1442); CD (acetone) $\Delta\varepsilon_{227\,nm}$ + 16 and $\Delta\varepsilon_{210\,nm}$ − 7.

7b: White solid; $[\alpha]_D^{25}$ − 105 (c = 0.01, acetone); ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm): 7.48 (s, 2H), 6.13 (s, 2H), 5.40 (t, J = 9.0 Hz, 2H), 5.27 (d, J = 8.1 Hz, 2H), 5.05 (t, J = 9.0 Hz, 2H), 4.88 (d, J = 8.1 Hz, 2H), 4.32 (dd, J = 12.0, 2.4 Hz, 2H), 4.19 (dd, J = 12.3, 4.8 Hz, 2H), 4.08–4.04 (m, 2H), 2.08 (s, 6H), 2.04 (s, 6H), 2.02 (s, 6H), and 1.99 (s, 6H); ^{13}C NMR (75 MHz, acetone-d_6) δ (ppm): 170.6, 170.1, 169.9, 169.7, 132.4, 130.8, 129.3, 97.9, 96.6, 74.1, 73.5, 72.2, 69.5, 63.0, 20.6, 20.5, and 20.4; HR-FAB-MS m/z: 919.1436 $[M + Na]^+$ (calcd for $C_{36}H_{42}O_{22}Cl_2Na$, 919.1442); CD (acetone) $\Delta\varepsilon_{226\,nm}$ − 20 and $\Delta\varepsilon_{210\,nm}$ + 9.

Compounds **8a** and **8b** were achieved by the same procedure.

8a: White solid; $[\alpha]_D^{25}$ + 170 (c = 0.01, acetone); ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm): 7.47–7.44 (m, 2H), 7.34–7.32 (m, 2H), 6.15 (s, 2H), 5.35 (t, J = 9.6 Hz, 2H), 5.30 (d, J = 8.1 Hz, 2H), 5.07 (t, J = 9.6 Hz, 2H), 4.97 (t, J = 8.1 Hz, 2H), 4.34 (dd, J = 12.0, 4.8 Hz, 2H), 4.20 (dd, J = 12.0, 2.4 Hz, 2H), 4.11–4.07 (m, 2H), 2.04 (s, 6H), 2.00 (s, 6H), 1.97 (s, 6H), and 1.94 (s, 6H); ^{13}C NMR (75 MHz, acetone-d_6) δ (ppm): 170.7, 170.2, 169.9, 169.7, 130.3, 130.0, 127.9, 97.8, 96.7, 73.4, 72.8, 71.7, 69.4, 62.6, 20.6, and 20.5; HR-ESI-MS m/z: 851.2263 $[M + Na]^+$ (calcd for $C_{36}H_{44}O_{22}Na$, 851.2222); CD (acetone) $\Delta\varepsilon_{220\,nm}$ + 11 and $\Delta\varepsilon_{210\,nm}$ − 5.

8b: White solid; $[\alpha]_D^{25}$ − 120 (c = 0.02, acetone); ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm): 7.47–7.45 (m, 2H), 7.34–7.32 (m, 2H), 6.15 (s, 2H), 5.34 (t, J = 9.3 Hz, 2H), 5.30 (d, J = 8.1 Hz, 2H), 5.08 (t, J = 9.3 Hz, 2H), 4.97 (t, J = 8.1 Hz, 2H), 4.34 (dd, J = 12.0, 5.1 Hz, 2H), 4.20 (dd, J = 12.0, 2.4 Hz, 2H), 4.12–4.08 (m, 2H), 2.04 (s, 6H), 2.00 (s, 6H), 1.97 (s, 6H), and 1.94 (s, 6H); ^{13}C NMR (75 MHz, acetone-d_6) δ (ppm): 170.6, 170.2, 170.0, 169.7, 130.2, 129.9, 127.9, 97.7, 96.7, 73.2, 72.1, 71.6, 69.3, 62.5, 20.5, and 20.4; HR-ESI-MS m/z: 851.2221 $[M + Na]^+$ (calcd for $C_{36}H_{44}O_{22}Na$, 851.2222); CD (acetone) $\Delta\varepsilon_{219\,nm}$ − 11 and $\Delta\varepsilon_{209\,nm}$ + 4.

3.2.3 *Compounds **9a**, **9b**, **10a**, and **10b***

To a solution of **7a** (50 mg, 0.06 mmol) in 5 ml CH_3OH, was added dibutyltin oxide (3 mg, 0.012 mmol). The reaction mixture was slightly refluxed for 4 h and then concentrated. The residue was purified by silica gel column chromatography (gradient elution, CH_2Cl_2 / CH_3OH = 20:1 to 4:1) followed by Sephadex LH-20 column chromatography (PE/CH_2Cl_2 / CH_3OH = 5:5:1) to afford **9a** as white solid in 19% yield.

Compounds **9b**, **10a**, and **10b** synthesized by the same procedure.

9a: White solid; mp 173–175°C; $[\alpha]_D^{25}$ + 173 (c = 0.005, H_2O); ^{1}H NMR (300 MHz, CD_3OD) δ (ppm): 7.48 (s, 2H), 5.86 (s, 2H), 4.41 (d, J = 7.5 Hz, 2H), 3.74–3.61 (m, 8H), 3.32–3.28 (m, 2H), and 3.25–3.22 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ (ppm): 134.4, 133.3, 130.0, 98.2, 96.7, 78.0, 76.3, 74.9, 71.8, and 62.7; HR-FAB-MS m/z: 583.0581 $[M + Na]^+$ (calcd for $C_{20}H_{26}O_{14}Cl_2Na$, 583.0597); CD (H_2O) $\Delta\varepsilon_{240\,nm}$ + 4.5 and $\Delta\varepsilon_{219\,nm}$ − 1.8.

9b: White solid; mp 175–177°C; $[\alpha]_D^{25}$ − 128 (c = 0.005, H_2O); ^{1}H NMR (300 MHz, CD_3OD) δ (ppm): 7.48 (s, 2H), 5.86 (s, 2H), 4.42 (d, J = 8.4 Hz, 2H), 3.74–3.70 (m, 4H), 3.65–3.61 (m, 4H), 3.32–3.28 (m, 2H), and 3.24–3.21 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ (ppm): 134.4, 133.3, 130.0, 98.2, 96.7, 78.0, 76.3, 74.9, 71.8, and 62.7; HR-FAB-MS m/z: 583.0594 $[M + Na]^+$

(calcd for $C_{20}H_{26}O_{14}Cl_2Na$, 583.0597); CD (H_2O) $\Delta\varepsilon_{239\,nm}$ − 5.1 and $\Delta\varepsilon_{218\,nm}$ + 1.5.

10a: White solid; mp 152–155°C; $[\alpha]_D^{25}$ + 138 ($c = 0.005$, H_2O); ^1H NMR (300 MHz, D_2O) δ (ppm): 7.36–7.32 (m, 2H), 7.28–7.23 (m, 2H), 5.76 (s, 2H), 4.75 (d, $J = 6.9$ Hz, 2H), 3.84–3.70 (m, 4H), 3.65–3.61 (m, 4H), and 3.31–3.22 (m, 4H); ^{13}C NMR (75 MHz, CD_3OD) δ (ppm): 132.6, 131.7, 127.2, 99.2, 96.7, 77.8, 75.8, 74.1, 71.8, and 61.7; HR-ESI-MS *m/z*: 515.1372 $[M + Na]^+$ (calcd for $C_{20}H_{28}O_{14}Na$, 515.1377); CD (H_2O) $\Delta\varepsilon_{231\,nm}$ + 7.4 and $\Delta\varepsilon_{219\,nm}$ − 3.7.

10b: White solid; mp 151–153°C; $[\alpha]_D^{25}$ − 172 ($c = 0.005$, H_2O); ^1H NMR (300 MHz, D_2O) δ (ppm): 7.37–7.32 (m, 2H), 7.28–7.23 (m, 2H), 5.75 (s, 2H), 4.72 (d, $J = 7.2$ Hz, 2H), 3.85–3.61 (m, 8H), and 3.32–3.23 (m, 4H); ^{13}C NMR (75 MHz, CD_3OD) δ (ppm): 132.7, 131.7, 127.3, 99.3, 96.6, 77.8, 75.8, 74.2, 71.9, and 61.8; HR-ESI-MS *m/z*: 515.1380 $[M + Na]^+$ (calcd for $C_{20}H_{28}O_{14}Na$, 515.1377); CD (H_2O) $\Delta\varepsilon_{231\,nm}$ − 8.1 and $\Delta\varepsilon_{218\,nm}$ + 3.8.

3.2.4 *Compound **12***

Compound **5** (0.2 g, 1.2 mmol), thioglycoside **11** (1.88 g, 4.8 mmol), and freshly activated 4 Å molecule sieve (2 g) were added to a 250 ml three-necked flask, which was purged with nitrogen. Dried CH_2Cl_2/Et_2O (80 ml, 1:1) was injected to the flask. The mixture was stirred at room temperature for 1 h, and then NIS (1.35 g, 6 mmol) and a solution of AgOTf (0.12 g, 0.48 mmol) in 3 ml dried toluene were added at 0°C to the reaction mixture, which was allowed to stirred at room temperature overnight. The reaction mixture was filtered through Celite, and the combined filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE/acetone = 3:1) twice and finally gained pure compound **12** as white solid in 10% yield; mp 128°C; ^1H NMR (300 MHz, acetone-d_6) δ (ppm): 7.41–7.37 (m, 2H), 7.33–7.30 (m, 2H), 6.18 (s, 2H), 5.96 (d, $J = 5.2$ Hz, 2H), 5.16 (t, $J = 2.8$ Hz, 2H), 4.92 (dd, $J = 2.8$, 9.6 Hz, 2H), 4.57 (dd, $J = 5.2$, 2.8 Hz, 2H), 4.23–4.15 (m, 4H), 4.07–4.03 (m, 2H), 2.07 (s, 6H), 2.06 (s, 6H), 2.02 (s, 6H), and 1.91 (s, 6H); ^{13}C NMR (75 MHz, acetone-d_6) δ (ppm): 170.7, 170.1, 169.6, 131.4, 129.5, 127.6, 122.1, 97.9, 93.8, 73.9, 70.7, 69.1, 68.0, 63.9, 22.9, 20.7, 20.7, and 20.6; HR-ESI-MS *m/z*: 851.2212 $[M + Na]^+$ (calcd for $C_{36}H_{44}O_{22}Na$, 851.2222).

Acknowledgements

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

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