Bioorganic & Medicinal Chemistry Letters 23 (2013) 5592–5598

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Insight into dihalogenation of E-ring of podophyllotoxins, and their acyloxyation derivatives at the C4 position as insecticidal agents

Zhiping Che [a,b], Xiang Yu [a], Lingling Fan [a], Hui Xu [a,*]

[a] Laboratory of Pharmaceutical Design & Synthesis, College of Sciences, Northwest A&F University, Yangling 712100, Shaanxi Province, China
[b] College of Forestry, Henan University of Science and Technology, Luoyang 471003, Henan Province, China

ARTICLE INFO

Article history:
Received 20 June 2013
Revised 20 July 2013
Accepted 8 August 2013
Available online 17 August 2013

Keywords:
Podophyllotoxin
Halogenation
Insecticidal activity
Botanical insecticide
Structural modification
Mythimna separata Walker

ABSTRACT

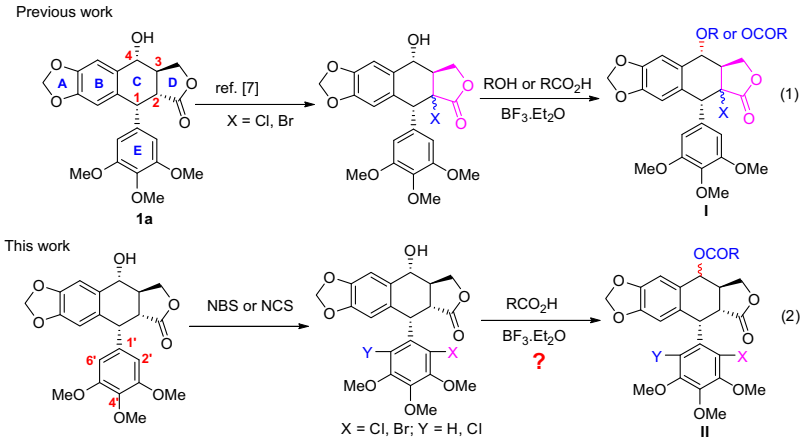
Unexpected sequential E-ring dihalogenation of podophyllotoxin analogues is reported. It demonstrated that a chlorine/bromine atom was prior introduced at the C2′ position of podophyllotoxin, and the corresponding free rotation of E-ring around the C1–C1′ bond of 2′-chloro or 2′-bromopodophyllotoxin was restricted. When 2′-chloro or 2′-bromopodophyllotoxin reacted with *N*-chlorosuccinimide (NCS), the chlorine atom was regioselectively introduced at their C6′ position on the E-ring. Whereas 2′-chloro or 2′-bromopodophyllotoxin reacted with NBS, the bromine atom was regioselectively introduced at their C5 position on the B-ring. When 2′-chloropodophyllotoxin reacted with different carboxylic acids in the presence of $BF_3{\cdot}Et_2O$, the steric effect of its E-ring for stereoselective synthesis of 4β-acyloxy-2′-chloropodophyllotoxin derivatives was observed. The insecticidal activity of 2′(2′,6′)-(di)halogen-substituted podophyllotoxin derivatives were evaluated with *Mythimna separata* Walker.

Podophyllotoxin (**1a**, Scheme 1), a naturally occurring cyclolignan, is the main secondary metabolite isolated from the roots and rhizomes of *Podophyllum* species such as *P. hexandrum* and *P. peltatum*. Besides its use as the lead compound for preparation of potent anticancer drugs such as etoposide, teniposide and etoposide phosphate,[1] compound **1a** also exhibited the interesting insecticidal,[2] antifungal[3] and antiviral activities.[4] Consequently, total synthesis[5] and structural modifications[6] of **1a** and its derivatives have been carried out in many research group worldwide. More recently, we have studied stereoselective synthesis of 4α-acyloxy/alkyloxy-2β-chloropodophyllotoxins and 4α-acyloxy/alkyloxy-2α/β-bromopodophyllotoxins (**I**) [Scheme 1, Eq. (1)],[7] and found some derivatives showed more potent insecticidal activity than toosendanin, a commercial insecticide isolated from *Melia azedarach*. Based upon the above-meantioned results, we envisioned that when the halogen atom at the C2 position on the C-ring of **I** was transferred to its C2′ or C2′ and C6′ position on the E-ring to afford 4-acyloxy-2′(2′,6′)-(di)halogen-substituted podophyllotoxin derivatives (**II**) [Scheme 1, Eq. (2)], whether the corresponding insecticidal activity of **II** could be improved. To our knowledge, although some examples of E-ring monohalogenation of **1a** and 4′-demethylepipodophyllotoxin (**1d**, Table 1) were pioneeringly reported by Ayres et al., Hu et al., Kofod et al., and Emmenegger et al., respectively,[8] E-ring dihalogenation of podophyllotoxin analogues has not been reported.

As shown in Table 1, the reaction of different podophyllotoxin analogues such as **1a**, epipodophyllotoxin (**1b**), picropodophyllotoxin (**1c**) and **1d**, with *N*-chlorosuccinimide (NCS) was examined first. When 0.4 mmol of **1a** reacted with 0.46 mmol of NCS at 0–28 °C, 2′-chloropodophyllotoxin (**2a**) and 2′,6′-dichloropodophyllotoxin (**3a**) were obtained in 79% and 16% yields, respectively (entry 1). If the amount of NCS was increased to 2 equiv of **2a**, only **3a** was obtained in a 90% yield (entry 2). Accordingly, when **1b** or **1c** reacted with NCS, the same results were also observed (entries 3–6). Interestingly, when **1d** reacted with NCS (1 or 2 equiv) at 0–28 °C, only monochlorination product, 2′-chloro-4′-demethylepipodophyllotoxin (**2d**), was obtained (entries 7 and 8). It is noteworthy that when the time of **1d** reacting with 2 equiv of NCS was prolonged from 4 to 7 h, the corresponding yield of **2d** was sharply decreased from 81% to 0% (entry 8 vs 9). Because NCS is also a mild oxidant besides its use as a chlorination agent, and 4′-hydroxy group of **2d** was very sensitive to the oxidant, so **2d** was further oxidized by excessive NCS. Compound **1d** reacting with 2 equiv of NCS at 0 °C was also investigated (entry 10). Although the oxidation process was delayed at 0 °C, and the reaction time was prolonged to 12 h, its dichlorination product, 2′,6′-dichloro-4′-demethylepipodophyllotoxin (**3d**), was still not obtained, and only **2d** was obtained in a 77% yield. The X-ray crystal structures of **2a**, **2b**, and **3a** were shown in Figure 1.

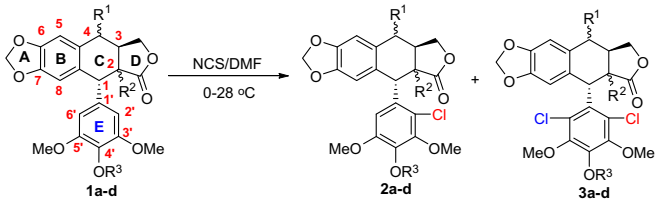
* Corresponding author. Tel./fax: +86 (0)29 87091952.
E-mail address: orgxuhui@nwsuaf.edu.cn (H. Xu).

0960-894X/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmcl.2013.08.044



Scheme 1. The chemical structures of compounds **I** and **II**.

Table 1
Investigation of **1a–d** reacting with NCS[a]



a: R^1 = α–OH; R^2 = β–H; R^3 = Me **b**: R^1 = β–OH; R^2 = β–H; R^3 = Me
c: R^1 = α–OH; R^2 = α–H; R^3 = Me **d**: R^1 = β–OH; R^2 = β–H; R^3 = H

Entry	Compd	Amount of (mmol)		*t* (h)	Isolated yield (%)	
		1	NCS		**2**	**3**
1	**1a**	0.4	0.46	24	**2a** (79)	**3a** (16)
2		0.4	0.8	24	**2a** (0)	**3a** (90)
3	**1b**	0.4	0.46	24	**2b** (81)	**3b** (10)
4		0.4	0.8	24	**2b** (0)	**3b** (91)
5	**1c**	0.4	0.46	24	**2c** (78)	**3c** (17)
6		0.4	0.8	24	**2c** (0)	**3c** (94)
7	**1d**	0.4	0.46	16	**2d** (85)	**3d** (0)
8		0.4	0.8	4	**2d** (81)	**3d** (0)
9		0.4	0.8	7	**2d** (0)	**3d** (0)
10		0.4	0.8	12[b]	**2d** (77)	**3d** (0)

[a] A solution of NCS in DMF (4 mL) was added dropwise to **1** in DMF (4 mL) at 0 °C. After adding, the mixture was allowed to warm from 0 to 28 °C.
[b] The reaction temperature was 0 °C.

Subsequently[9], **1a** reacting with *N*-bromosuccinimide (NBS) was examined in Scheme 2. When **1a** reacted with NBS (1 equiv) at 0–16 °C for 20 h, 2′-bromopodophyllotoxin (**2a**′) and 2′-bromopodophyllotoxone (**4**), the chemical structures of which were determined by the X-ray crystallography (Fig. 2),[9] were obtained in 88% and 7% yields, respectively. Interestingly, when **1a** reacted with 2 equiv of NBS at 0–16 °C for 46 h, besides **2a**′ (33% yield) and **4** (28% yield), an unusual 2′,5-dibromopodophyllotoxin (**5**, 15% yield, Fig. 2)[9] was obtained. However, the expected 2′,6′-dibromopodophyllotoxin (**5**′) was not produced. We assumed that the cavity between the B-ring and E-ring of **2a**′ was not big enough for introduction of a second bromine atom at the C6′ position. Therefore, the second bromine atom was regioselectively introduced at the C5 position on the B-ring of **2a**′.

The cross-reaction of **2a**′ with NCS, or **2a** with NBS, was further investigated (Scheme 3). When **2a**′ reacted with 1 equiv of NCS at 0–16 °C for 24 h, only 2′-bromo-6′-chloropodophyllotoxin (**6**), the chemical structure of which was determined by the X-ray crystallography (Fig. 3),[9] was obtained in a 40% yield. On the contrary, when **2a** reacted with 1 equiv of NBS at 0–16 °C for 24 h, the expected 2′-chloro-6′-bromopodophyllotoxin (**9**) was not obtained. However, besides the oxidized product, 2′-chloropodophyllotoxone (**8**, 43% yield), which was confirmed by the X-ray crystallography (Fig. 3),[9] the unexpected 2′-chloro-5-bromopodophyllotoxin (**7**, 12% yield) was obtained. The configuration of **7** was confirmed according to the X-ray crystallography[9] of its ester, 2′-chloro-5-bromo-4α-propionyloxypicropodophyllotoxin (**7**′, Fig. 3), which was prepared by the reaction of **7** with propionic acid in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 4-*N*,*N*′-dimethylaminopyridine (DMAP) at 28 °C for 29 h. It also demonstrated that the *trans*-lactone of **7** was easily transferred into the *cis*-lactone in the presence of DMAP (a weak base). Although the E-ring of podophyllotoxin is free to rotate around its C1–C1′ bond, we here, based upon the above results, demonstrated for the first time

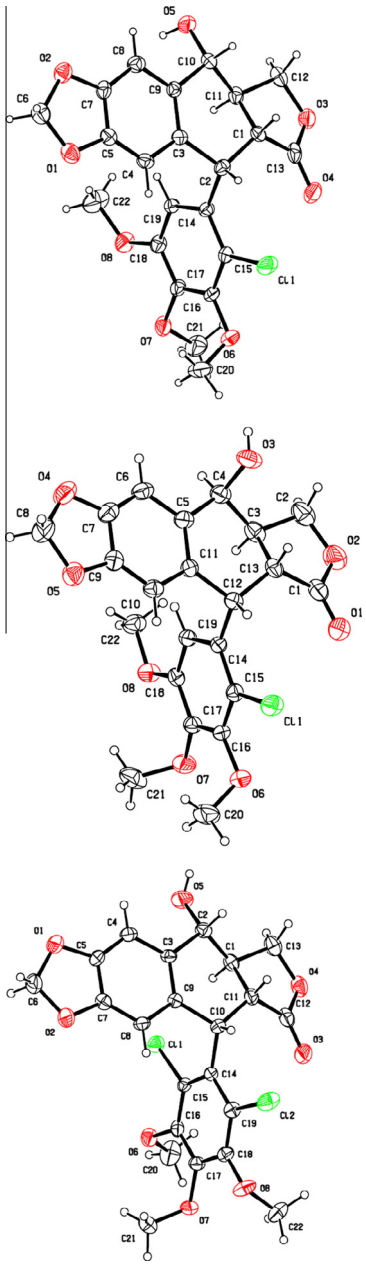
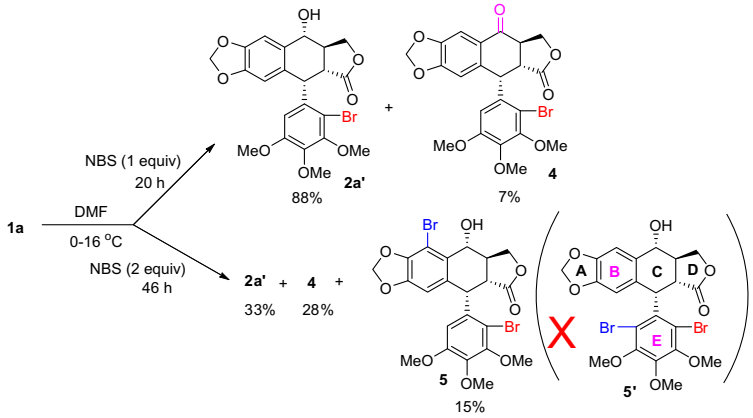


Figure 1. X-ray crystal structures of **2a** (top), **2b** (middle) and **3a** (bottom).

that free rotation of E-ring around the C1–C1′ bond of 2′-chloro or 2′- bromopodophyllotoxin is restricted. On the other hand, it further suggested that (a) a chlorine or bromine atom was preferentially introduced at the C2′ position of podophyllotoxin according to X-ray crystallography; (b) once a bromine atom was firstly introduced at the C2′ position of podophyllotoxin, its cavity between the B-ring and E-ring of **2a**′ was big enough for sequential introduction of a chlorine atom at the C6′ position to afford **6** (Scheme 3), and not big enough for introduction of a bromine atom at the C6′ position (Scheme 2); (c) similarly, once a chlorine atom was firstly introduced at the C2′ position of podophyllotoxin, its cavity between the B-ring and E-ring of **2a** was also big enough for sequential introduction of a chlorine atom at the C6′ position to give **3a** (Table 1), and not big enough for introduction of a bromine atom at the C6′ position (Scheme 3); (d) when 2′-chloro or 2′-bromopodophyllotoxin further reacting with NBS, the bromine atom was regioselectively introduced at their C5 position on the B-ring.

On the other hand, 4β-acyloxypodophyllotoxins (**10a** and **10b**) reacting with NCS was also examined. As described in Table 2, when 0.2 mmol of **10a** reacted with 0.23 mmol of NCS at 28 °C or 40 °C for 48 h, no product was obtained. When 0.2 mmol of **10a** reacted with 0.23 mmol of NCS at 50 °C for 48 h, 2′-chloro-4β-*n*-butanoyloxypodophyllotoxin (**11a**) was obtained in a 41% yield. When at 60 °C for 24 h, besides **11a** (72% yield), the dichlorination product, 2′,6′-dichloro-4β-*n*-butanoyloxypodophyllotoxin (**12a**), was also obtained (12% yield). When 0.2 mmol of **10a** reacted with 0.4 mmol of NCS at 60 °C for 24 h, the yields of **11a** and **12a** were 31% and 47%, respectively. The configuration of **11a** was determined by the X-ray crystallography (Fig. 4). Similarly, when 0.2 mmol of **10b** reacted with 0.23 mmol of NCS at 60 °C for 24 h, 2′-chloro-4β-*n*-octanoyloxypodophyllotoxin (**11b**) and 2′,6′-dichloro-4β-*n*-octanoyloxypodophyllotoxin (**12b**) were obtained in 68% and 8% yields, respectively. Obviously, the reaction conditions for chlorination of 4β-acyloxypodophyllotoxins in the presence of NCS would be more harsh as compared with those for **1a–d** (Table 1).

Meanwhile, as shown in Table 3, monochlorination products **11a** and **11b** further reacting with NCS was also investigated. For example, when 0.2 mmol of **11a** reacted with 0.23 mmol of NCS at 50 °C for 48 h, **12a** was obtained only in a 9% yield, and when at 60 °C for 48 h, **12a** was obtained in a 31% yield. When 0.2 mmol of **11a** reacted with 0.3 mmol of NCS at 60 °C for 48 h, the yield of **12a** was improved to 50%. Interestingly, when the molar ratio of NCS and **11a** was 2/1 at 60 °C for 24 h, **12a** was smoothly obtained in a 77% yield; whereas at 50 °C for 48 h, **12a** was afforded only in a 47% yield. In addition, when 0.2 mmol of **11b** reacted with 0.4 mmol of NCS at 60 °C for 24 h, **12b** was given in a 72% yield.



Scheme 2. Investigation of **1a** reacting with NBS.

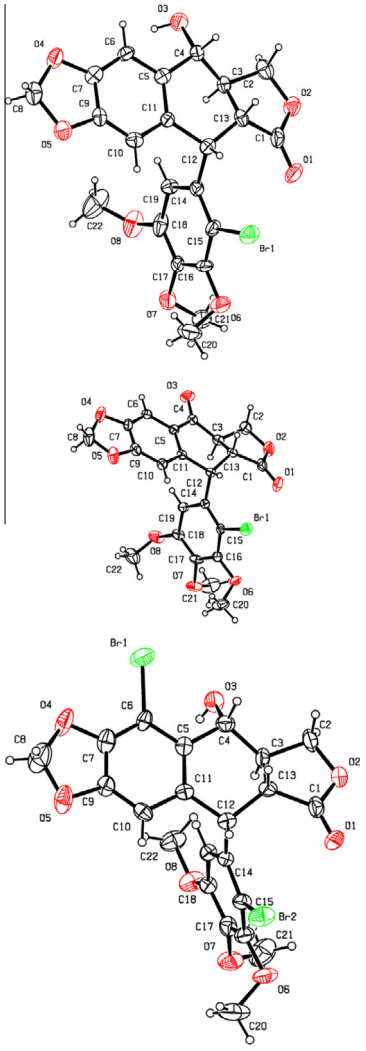
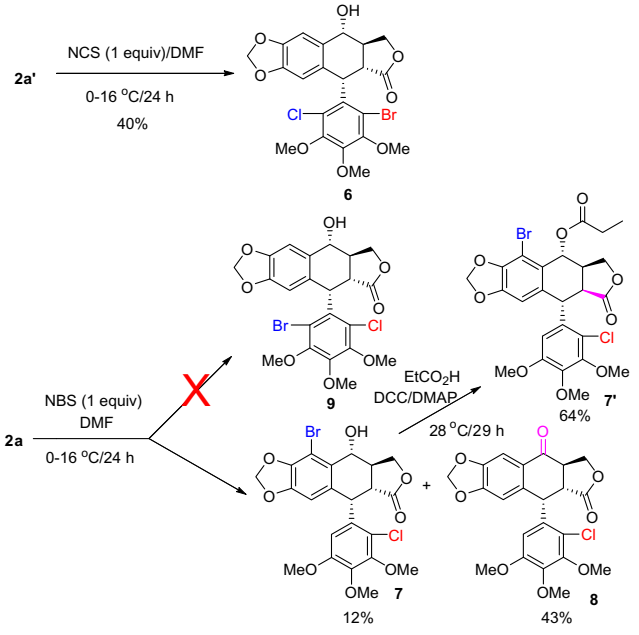


Figure 2. X-ray crystal structures of **2a′** (top), **4** (middle) and **5** (bottom).



Scheme 3. Investigation of reaction of **2a′** with NCS, and **2a** with NBS, respectively.

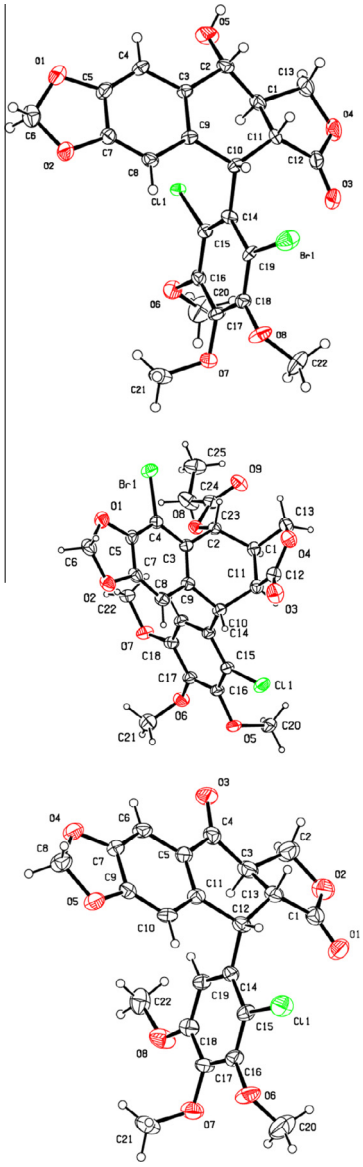
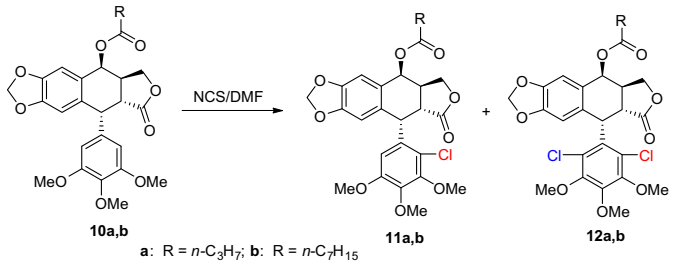


Figure 3. X-ray crystal structures of **6** (top), **7′** (middle), and **8** (bottom).

Therefore, the present dichlorination reaction depended on the reaction temperature and the amount of NCS.

As shown in Table 4, when **2a** reacted with different carboxylic acids (except R as Me or Et) in the presence of $BF_3{\cdot}Et_2O$, 4β-acyloxy-2′-chloropodophyllotoxin derivatives (**13c–n**) were stereoselectively obtained in 41–82% yields. It may be due to the steric hindrance of E-ring of 2′-chloropodophyllotoxin, **13c–n** were stereoselectively synthesized by the S_N1 reaction. The assignment of configuration of C4 position of **13a–b** was based on $J_{3,4}$ coupling constants: The C4β-substituted compounds have a $J_{3,4}$ ≈4.0 Hz due to a *cis* relationship between H3 and H4. If $J_{3,4}$ ≧10.0 Hz, it indicates that H3 and H4 is *trans* relationship, and the substituent at the C4 position of podophyllotoxin is α configuration.[10] For example, as described in Table 4, there were two H4 chemical shifts for **13a**, and two corresponding $J_{3,4}$ values of H4 were 9.5 and 3.0 Hz, respectively, so **13a** was a mixture of α and β isomers. Meanwhile, according to the peak areas of two H4, the ratio of α and β isomers of **13a** was 1/1. Similarly, the ratios of α and β isomers of **13b** were 1/1.27. Additionally, as the $J_{3,4}$ values of H4 of **13c–n** were 2.5 or 3.0 Hz, so the acyloxy groups at the C4 position of **13c–n** were all β configuration.

Table 2
Investigation of **10a** and **10b** reacting with NCS



Amount of (mmol)		T (°C)	t (h)	Isolated yield (%)		
10	NCS			**11**	**12**	**10**
0.2 (**10a**)	0.23	28	48	**11a** (0)	12a (0)	**10a** (100)
0.2 (**10a**)	0.23	40	48	11a (0)	12a (0)	**10a** (100)
0.2 (**10a**)	0.23	50	48	**11a** (41)	**12a** (0)	**10a** (40)
0.2 (**10a**)	0.23	60	24	**11a** (72)	**12a** (12)	**10a** (0)
0.2 (**10a**)	0.4	60	24	**11a** (31)	**12a** (47)	10a (0)
0.2 (**10b**)	0.23	60	24	**11b** (68)	**12b** (8)	**10b** (0)

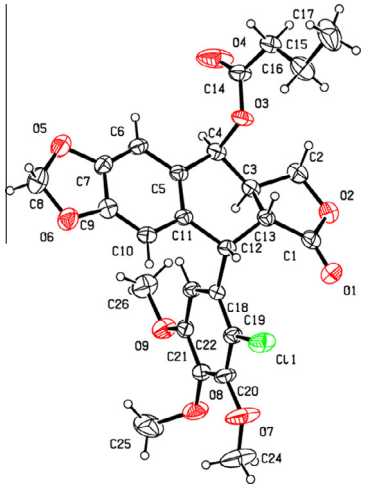
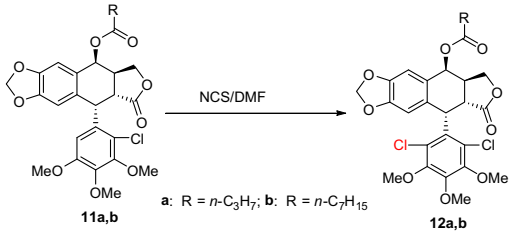


Figure 4. X-ray crystal structure of **11a**.

Table 3
Investigation of **11a** and **11b** reacting with NCS



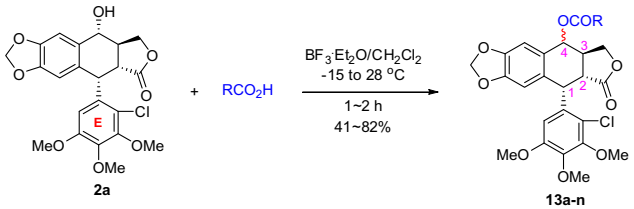
Amount of (mmol)		T (°C)	t (h)	Isolated yield (%)	
11	NCS			12	11
0.2 (**11a**)	NCS (0.23)	50	48	**12a** (9)	**11a** (67)
0.2 (**11a**)	NCS (0.23)	60	48	**12a** (31)	**11a** (43)
0.2 (**11a**)	NCS (0.3)	60	48	**12a** (50)	**11a** (20)
0.2 (**11a**)	NCS (0.4)	50	48	**12a** (47)	**11a** (30)
0.2 (**11a**)	NCS (0.4)	60	24	**12a** (77)	**11a** (0)
0.2 (**11b**)	NCS (0.4)	60	24	**12b** (72)	**11b** (0)

When **3a** reacted with different carboxylic acids in the presence of $BF_3{\cdot}Et_2O$ as shown in Table 5, only **14g–j** and **14l** were stereoselectively obtained. However, the relationships between the substituents introduced at the C4 position of **14a–m** and their configuration at the C4 position is not very obvious. The assignment of configuration of C4 position of **14a–m** was based on the above-mentioned Lee's rule.[10] The configuration of the substituents at the C4 position of **14a–m** and their corresponding $J_{3,4}$ coupling constants were reported in Table 5.

Finally, the insecticidal activity of some E-ring monohalogenation or dihalogenation products of podophyllotoxin against the pre-third-instar larvae of *Mythimna separata* Walker in vivo was tested by the leaf-dipping method at the concentration of 1 mg mL^{-1}.[2b] Toosendanin, a commercial insecticide isolated from *Melia azedarach*, was used as the positive control. Leaves treated with acetone alone were used as a blank control group. For podophyllotoxin derivatives showed delayed insecticidal activity in our previous papers,[2b,2f,7] the insecticidal activity of the tested compounds was recorded as the final mortality rate. As shown in Table 6, many compounds exhibited equal or higher insecticidal activity than toosendanin. Especially compounds **14d** and **14f** showed the highest insecticidal activity. In general, introduction of halogen atom on the E-ring of podophyllotoxins could lead to the more potent compounds (**1a–d** vs **2a–d** vs **3a–c**). The *trans*-lactone of podophyllotoxin derivatives is usually considered to be important for their insecticidal activity. But the final mortality rate of **7′** containing *cis*-lactone was 59.3%, so introduction of bromine and chlorine atoms on the B- and E-rings could improve the insecticidal activity. The insecticidal activity of **3a** containing 2′,6′-dichloro atoms, was more pronounced than that of **6** containing 2′-bromo and 6′-dichloro atoms. Similarly, the insecticidal activity of **12b** containing 2′,6′-dichloro atoms, was more promising than that of **11b** containing 2′-chloro atom. To alkylacyloxy series, the proper length of the side chain at the C-4 position is very important for the insecticidal activity. However, to alkylacyloxy series, the effect of the configuration of acyloxy at the C-4 position on the insecticidal activity was not very obvious.

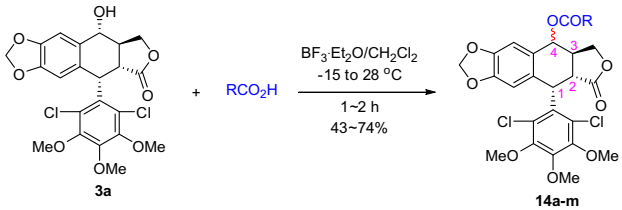
In summary, unexpected sequential E-ring double halogenation of podophyllotoxin analogues was investigated. Dichlorination of 4′-demethylepipodophyllotoxin in the presence of NCS was affected by its 4′-hydroxyl group. It should be pointed

Table 4
Investigation of **2a** reacting with carboxylic acids in the presence of $BF_3{\cdot}Et_2O$



Compound	R	$\delta_{H\text{-}4}$ (ppm)	$J_{3,4}$ (Hz)	Configuration	Isolated yield (%)
13a	Me	5.92/6.18	9.5/3.0	α:β = 1:1	79
13b	Et	5.93/6.18	9.0/3.0	α:β = 1:1.27	82
13c (**11a**)	*n*-Propyl	6.18	3.0	β	82
13d (**11b**)	*n*-Heptyl	6.18	2.5	β	81
13e	n-$(CH_2)_{10}CH_3$	6.18	2.5	β	67
13f	n-$(CH_2)_{14}CH_3$	6.18	2.0	β	60
13g	(*Z*)-9-n-$C_{17}H_{33}$	6.17	2.5	β	47
13h	CCl_3	6.25	2.0	β	73
13i	(m-NO_2)Ph	6.47	2.0	β	76
13j	(p-NO_2)Ph	6.46	2.5	β	41
13k	(m-Cl)Ph	6.42	2.5	β	63
13l	Ph	6.43	3.0	β	78
13m	(p-Me)Ph	6.41	2.0	β	68
13n	(m-Me)Ph	6.43	3.0	β	75

Table 5
Investigation of **3a** reacting with carboxylic acids in the presence of $BF_3{\cdot}Et_2O$



Compound	R	$\delta_{H\text{-}4}$ (ppm)	$J_{3,4}$ (Hz)	Configuration	Isolated yield (%)
14a	Me	5.97/6.12	9.0/2.0	α:β = 1:3.35	71
14b	Et	5.97/6.13	9.0/2.5	α:β = 1:3	70
14c	*n*-propyl	5.97/6.13	10.0/2.5	α:β = 1:2.7	74
14d	*n*-heptyl	5.97/6.12	10.0/2.0	α:β = 1:2.45	57
14e	n-$(CH_2)_{10}CH_3$	5.97/6.12	10.5/2.5	α:β = 1:2.33	73
14f	(*Z*)-9-n-$C_{17}H_{33}$	5.97/6.12	10.5/1.5	α:β = 1:2.13	54
14g	CCl_3	6.20	2.0	β	71
14h	(m-NO_2)Ph	6.42	2.0	β	71
14i	(p-NO_2)Ph	6.39	1.5	β	43
14j	(m-Cl)Ph	6.37	2.0	β	59
14k	Ph	6.22/6.37	9.5/2.0	α:β = 1:4.28	72
14l	(p-Me)Ph	6.35	2.0	β	67
14m	(m-Me)Ph	6.22/6.37	10.0/2.5	α:β = 1:3.2	72

out that no free rotation of E-ring around the C1–C1′ bond of 2′-chloro or 2′-bromopodophyllotoxin was demonstrated here. It is noteworthy that a chlorine or bromine atom prior introduced at the C2′ position of podophyllotoxin was confirmed by X-ray crystallography. When 2′-chloro or 2′-bromopodophyllotoxin further reacted with NCS, the chlorine atom was regioselectively introduced at their C6′ position on the E-ring. Whereas 2′-chloro or 2′-bromopodophyllotoxin further reacted with NBS, the bromine atom was regioselectively introduced at their C5 position on the B-ring. To our delight, it is the first time that regioselective bromination on the B-ring of podophyllotoxin is reported. Moreover, the reaction of 2′-chloropodophyllotoxin or 2′,6′-dichloropodophyllotoxin with different carboxylic acids in the presence of $BF_3{\cdot}Et_2O$ was also investi-

Table 6
Insecticidal activity of some E-ring monohalogenation or dihalogenation products of podophyllotoxin against *M. separata* on leaves treated with a concentration of 1 mg/mL[a]

Compound	Final mortality rate (%)	Compound	Final mortality rate (%)
1a	34.6 (±3.3)	**13e**	64.3 (±3.3)
1b	46.4 (±0)	**13f**	53.6 (±3.3)
1c	32.1 (±0)	**13g**	65.4 (±5.8)
1d	35.7 (±0)	**13h**	46.4 (±0)
2a	65.4 (±0)	**13i**	67.9 (±0)
2b	53.6 (±3.3)	**13j**	53.6 (±3.3)
2c	53.6 (±3.3)	**13k**	64.3 (±3.3)
2d	46.4 (±0)	**13l**	57.1 (±0)
3a	61.5 (±6.7)	**13m**	46.4 (±0)
3b	64.3 (±3.3)	**13n**	42.9 (±3.3)
3c	60.7 (±3.3)	**14a**	50.0 (±3.3)
2a′	55.6 (±0)	**14b**	32.1 (±3.3)
4	67.9 (±0)	**14c**	40.7 (±3.3)
5	55.6 (±0)	**14d**	71.7 (±3.3)
6	48.1 (±3.3)	**14e**	53.6 (±3.3)
7	59.3 (±3.3)	**14f**	69.2 (±3.3)
8	60.7 (±3.3)	**14g**	64.3 (±3.3)
7′	59.3 (±3.3)	**14h**	57.1 (±0)
11a	57.1(±0)	**14i**	50.0 (±3.3)
11b	42.3 (±0)	**14j**	46.4 (±0)
12a	55.6 (±6.7)	**14k**	53.6 (±3.3)
12b	59.3 (±3.3)	**14l**	42.9 (±3.3)
13a	39.3 (±3.3)	**14m**	50.0 (±3.3)
13b	50.0 (±3.3)	Toosendanin	53.8 (±0)

[a] Values are means ± S.D. of three replicate.

gated. The steric effect of E-ring for stereoselective synthesis of 4β-acyloxy-2′-chloropodophyllotoxin derivatives was observed. Especially some derivatives exhibited the more promising insecticidal activity as compared with toosendanin.

Acknowledgments

The present research was partly supported by National Natural Science Foundation of China (No. 31071737), and the Special Funds of Central Colleges Basic Scientific Research Operating Expenses (YQ2013008).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.08.044.

References and notes

1. (a) Gupta, S.; Das, L.; Datta, A. B.; Poddar, A.; Janik, M. E.; Bhattacharyya, B. *Biochemistry* **2006**, *45*, 6467; (b) You, Y. J. *Curr. Pharm. Des.* **2005**, *11*, 1695; (c) Xu, H.; Lv, M.; Tian, X. *Curr. Med. Chem.* **2009**, *16*, 327; Gordaliza, M.; Garcia, P. A.; Miguel Del Corral, J. M.; Castro, M. A.; Gomez-Zurita, M. A. *Toxicon* **2004**, *44*, 441.
2. (a) Miyazawa, M.; Fukuyama, M.; Yoshio, K.; Kato, T.; Ishikawa, Y. *J. Agric. Food Chem.* **1999**, *47*, 5108; (b) Xu, H.; Wang, J.; Sun, H.; Lv, M.; Tian, X.; Yao, X.; Zhang, X. J. *J. Agric. Food Chem.* **2009**, *57*, 7919; (c) Di, X.; Liu, Y.; Liu, Y.; Yu, X.; Xiao, H.; Tian, X.; Gao, R. *Pestic. Biochem. Physiol.* **2007**, *89*, 81; (d) Gao, R.; Gao, C.; Tian, X.; Yu, X.; Di, X.; Xiao, H.; Zhang, X. *Pest Manag. Sci.* **2004**, *60*, 1131; (e) Wang, Y.; Shao, Y.; Wang, Y.; Fan, L.; Yu, X.; Zhi, X.; Yang, C.; Qu, H.; Yao, X.; Xu, H. J. *J. Agric. Food Chem.* **2012**, *60*, 8435.
3. Kumar, K. A.; Singh, S. K.; Kumar, B. S.; Doble, M. *Cent. Eur. J. Chem.* **2007**, *5*, 880.
4. (a) Castro, M. A.; del Corral, J. M. M.; Gordaliza, M.; Gomez-Zurita, M. A.; de la Puente, M. L.; Betancur-Galvis, L. A.; Sierra, J.; Feliciano, A. S. *Eur. J. Med. Chem.* **2003**, *38*, 899; (b) VanVliet, D. S.; Tachibana, Y.; Bastow, K. F.; Huang, E. S.; Lee, K. H. *J. Med. Chem.* **2001**, *44*, 1422.
5. (a) Stadler, D.; Bach, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 7557; (b) Engelhardt, U.; Sarkar, A.; Linker, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 2487; (c) Reynolds, A. J.; Scott, A. J.; Turner, C. I.; Sherburn, M. S. *J. Am. Chem. Soc.* **2003**, *125*, 12108; (d) Mingoia, F.; Vitale, M.; Madec, D.; Prestat, G.; Poli, G. *Tetrahedron Lett.* **2008**, *49*, 760; (e) Clayden, J.; Kenworthy, M. N.; Helliwell, M. *Org. Lett.* **2003**, *5*, 831.
6. (a) Passarella, D.; Peretto, B.; Yepes, R. B.; Cappelletti, G.; Cartelli, D.; Ronchi, C.; Snaith, J.; Fontana, G.; Danieli, B.; Borlak, J. *Eur. J. Med. Chem.* **2010**, *45*, 219; (b) Cappelletti, G.; Cartelli, D.; Peretto, B.; Ventura, M.; Riccioli, M.; Colombo, F.; Snaith, J. S.; Borrelli, S.; Passarella, D. *Tetrahedron* **2011**, *67*, 7354; (c) Xiao, Z.; Bastow, K.; Vance, J. R.; Sidwell, R. S.; Wang, H.; Chen, M.; Shi, Q.; Lee, K. H. *J. Med. Chem.* **2004**, *47*, 5140; (d) Xiao, Z.; Bastow, K. F.; Vance, J. R.; Lee, K. H. *Bioorg. Med. Chem.* **2004**, *12*, 3339.
7. (a) Xu, H.; Wang, Q.; Guo, Y. *Chem. Eur. J.* **2011**, *17*, 8299; (b) Xu, H.; Xiao, X.; Zhao, X.; Guo, Y.; Yao, X. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4008; (c) Xu, H.; Xiao, X.; Wang, Q. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5009; (d) Guo, Y.; Fan, L.; Wang, J.; Yang, C.; Qu, H.; Xu, H. *Tetrahedron* **2013**, *69*, 774.
8. (a) Ayres, D. C.; Lim, C. K. *J. Chem. Soc., Perkin Trans. I* **1972**, 1350; (b) Hu, H.; Wang, Z. Q.; Liu, S. Y.; Cheng, Y. C.; Lee, K. H. *J. Med. Chem.* **1992**, *35*, 866; (c) Kofod, H.; Jorgensen, C. *Acta. Chem Scand* **1955**, *9*, 1327; (d) Emmenegger, H. *Arzneim. Forsch.* **1961**, *11*, 459.
9. Ten crystallographic data (excluding structure factors) for the structures of **2a**, **2b**, **3a**, **2a′**, **4**–**6**, **7′**, **8**, and **11a** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as Supplementary publication number CCDC 894211, 901563, 894294, 901564, 900813, 901328, 901327, 901562, 901329, and 900812, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
10. Lee, K. H.; Imakura, Y.; Haruna, M.; Beers, S. A.; Thursto, L. S.; Dai, H. J.; Chen, C. H.; Liu, S. Y.; Cheng, Y. C. *J. Nat. Prod.* **1989**, *52*, 606.