HETEROCYCLES, Vol. 94, No. 5, 2017, pp. 949 - 956. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 11th January, 2017, Accepted, 30th March, 2017, Published online, 24th April, 2017
DOI: 10.3987/COM-17-13649

THREE NEW ISOBENZOFURANS FROM THE STEMS OF ORIENTAL TOBACCO AND THEIR BIOACTIVITIES

Pei He,[1] Shi-Yun Tang,[1] Zhen-Jie Li,[1,2] Chun-Bo Liu,[1] Qinpeng Shen,[1] Dang-Yu Tang,[1] Feng-Mei Zhang,[1] Zhi-Hua Liu,[1] Yong-Kuan Chen,[1] Jia-Qiang Wang,[2] Neng-Jun Xiang,[1,*] and Zhang-Jie Huang[2,*]

[1] Key Laboratory of Tobacco Chemistry of Yunnan Province, China Tobacco Yunnan Industrial Co., Ltd, Kunming 650231, P.R. China [2] School of Chemical Science and Technology, Yunnan University, Kunming 650091, P.R. China. E-mail: jszxtg_2015@163.com

Abstract – Three new isobenzofurans (**1-3**), together with four known furan derivatives (**4-7**) were isolated from the stems of oriental tobacco. Their structures were determined by means of HRESIMS and extensive 1D and 2D NMR spectroscopic studies. Compounds **1-7** were tested for their anti-tobacoo mosaic virus (TMV) activities and cytotoxicity activities. The results revealed that compounds **2** and **3** showed high anti-TMV activities with inhibition rates of 35.4, and 34.2%. These rates are higher than that of positive control. Other compounds also showed anti-TMV activities with inhibition rates in the range of 18.6~22.7%. These rates are close to that of positive control. Compounds **1-7** also showed moderate-to-weak inhibitory activities against some tested human tumor cell lines with IC_{50} values in the range of 2.8-9.3 μM.

Nicotiana tabacum, or cultivated tobacco, is an annually-grown herbaceous plant. It is found only in cultivation now, where it is the most commonly grown of all plants in the Nicotiana genus, and its leaves are commercially grown in many countries to be processed into tobacco.[1-3] In addition, *N. tabacum* is also used as insecticides, anesthetics, diaphoretics, sedatives, and emetic agents in Chinese folklore medicines. Phytochemical investigation revealed that *N. tabacum* was found to be rich in many useful chemical compounds, such as sesquiterpenes[4-6] alkaloids,[7,8] lignans,[9,10] flavonoids,[11-14] phenylpropanoids,[15,16] chromanones,[17,18] biphenyls,[19,20] benzolactones,[21-23] isocoumarins,[24] and furan-2-carboxylic acids.[25] Our previous investigation of this species led to the discovery of a number of new compounds that showed various bioactivities, such as anti-HIV-1, anti-TMV, and cytotoxicity.[4-15] Oriental tobacco is a

small-leafed variety of *Nicotiana tabacum* with highly aromatic. It is frequently referred to as "Turkish tobacco", as these regions were all historically part of the Ottoman Empire.[1,2] Now, its main use is in blends of pipe and especially cigarette tobacco (a typical American cigarette is a blend of bright Virginia, burley and Oriental). The roots and stems of oriental tobacco are the main by-product in tobacco planting, and the multipurpose utilization of them is an interesting topic and has attracted more and more attentions.[2,12] In the course of our search for new bioactive natural products from *Nicotiana tabacum*, three new isobenzofurans (**1**-**3**) and four known furan derivatives (**4**-**7**) were isolated from the stems of oriental tobacco. This paper deals with the isolation, structural elucidation, and their bioactivities of these compounds.

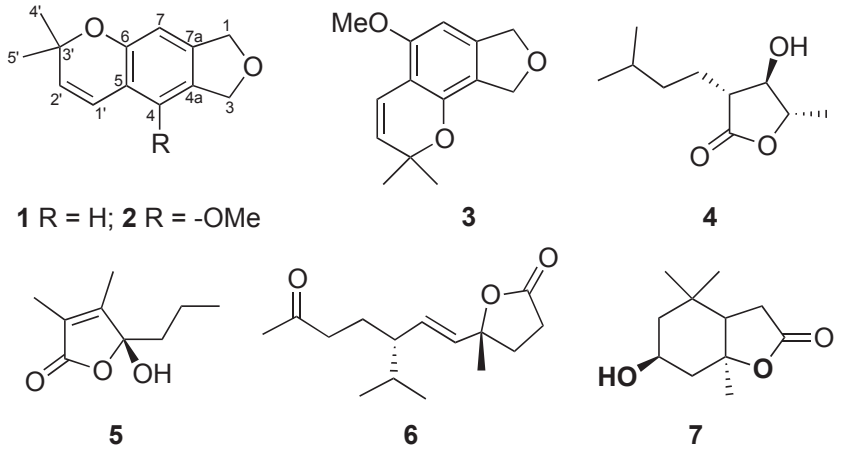

Figure 1. The structures of furan derivatives from the stems of oriental tobacco

A 70% aq. MeOH extract prepared from the stems of tobacco was subjected repeatedly to column chromatography and preparative HPLC to afford three new isobenzofurans, 2,2-dimethyl-6,8-dihydro-2*H*-furo[3,4-*g*]chromene (**1**), 5-methoxy-2,2-dimethyl-6,8-dihydro-2*H*-furo[3,4-*g*]chromene (**2**), and 5-methoxy-2,2-dimethyl-7,9-dihydro-2*H*-furo[3,4-*h*]chromene (**3**), and four known furan derivatives (**4**-**7**). The structures of the compounds **1**-**7** were as shown in Figure 1, and the ^{1}H and ^{13}C NMR data of **1**-**3** were listed in Table 1. The known compounds, compared with literature, were identified as MKN-004B (**4**),[26] (*S*)-5-hydroxy-3,4-dimethyl-5-pentylfuran-2(5*H*)-one (**5**),[27] (*R*)-5-((*S,E*)-3-isopropyl-6-oxohept-1-enyl)-5-methyldihydrofuran-2(3*H*)-one (**6**),[28] and (+)-isololiolide (**7**).[29]

Compound **1** was obtained as a pale-yellow gum. Its molecular formula was determined as $C_{13}H_{14}O_2$ by HRESIMS (*m/z* 2225.0898 $[M+Na]^+$; calcd 225.0891 for $C_{13}H_{14}O_2$), indicating the presence of seven degrees of unsaturation in the molecule. The UV spectrum showed absorption maxima at 210, 240 and 278 nm, and the IR spectrum showed absorption bands at 1610, 1561, and 1472 cm^{-1}, indicating the presence of aromatic ring. The ^{1}H and ^{13}C NMR spectra of **1** (Table 1) along with analysis of the DEPT

spectra displayed 13 carbon signals and 14 proton signals, respectively, corresponding to a 1,2,4,5-tetrasubstituted phenyl ring (C-4~C-7, C-4a, and C-7a; H-4 and H-7), an *gem*-dimethylchromene moiety,[30] and two oxygenated methylenes (C-1 and C-3, H_2-1 and H_2-3). On the basis of the molecular formula, in addition to four degrees of unsaturations for aromatic ring and two degree of unsaturations for *gem*-dimethylchromene moiety, the still one ring was needed to meet the required degrees of unsaturation. The HMBC correlations from H_2-1 to C-3, C-4a, C-7a, C-7, from H-7 to C-1, C-4a, C-7a, from H_2-3 to C-1, C-4, C-4a, C-7a, from H-4 to C-3, C-4a, C-7a, from H-1 to C-3, and from H-3 to C-1 (Figure 2) suggested that a isobenzofuran moiety was formed between aromatic ring, C-1, and C-3.[31] Since the nucleus of compound was determined, the additional carbons (*gem*-dimethylchromene) were accounted for the remaining substituents. Long-range correlations of H-1' to C-4, C-5, and C-6, of H-2' to C-5, and of H-4 to C-1' were observed. This led us to conclude that the *gem*-dimethylchromene moiety was fused in an angular manner at C-5 and C-6. Accordingly, the structure of **1** was determined, and gives the system name of 6,8-dihydro-2,2-dimethyl-2*H*-furo[3,4-*g*]chromene.

Table 1. ^{1}H and ^{13}C NMR data for compounds **1-3** ($CDCl_3$, 500 and 125 MHz)

No.	**1**		**2**		**3**	
	δ_C	δ_H (m, *J*, Hz)	δ_C	δ_H (m, *J*, Hz)	δ_C	δ_H (m, *J*, Hz)
1	74.6 t	5.14 s	75.0 t	5.11 s	75.3 t	5.19 s
3	75.0 t	5.11 s	73.0 t	5.14 s	72.2 t	5.15 s
4	126.1 d	7.01 s	156.3 s		152.4 s	
5	115.6 s		110.1 s		110.2 s	
6	155.3 s		154.1 s		156.8 s	
7	112.8 d	6.79 s	103.7 d	6.29 s	103.8 d	6.22 s
4a	132.1 s		124.3 s		124.9 s	
7a	138.5 s		140.9 s		140.2 s	
1′	118.1 d	6.63 (d) 9.8	116.6 d	6.65 (d) 9.8	116.3 d	6.60 (d) 9.8
2′	128.8 d	5.86 (d) 9.8	128.4 d	5.87 (d) 9.8	128.3 d	5.74 (d) 9.8
3′	76.0 s		76.0 s		76.2 s	
4′, 5′	26.5 q	1.57 s	27.0 q	1.57 s	26.6 q	1.55 s
-OMe			61.2 q	3.85 s	56.2 q	3.81 s

Compound **2** was also assigned the molecular formula of $C_{14}H_{16}O_3$ as supported by the HRESIMS (*m/z* 255.0990 $[M+Na]^+$). The ^{1}H and ^{13}C NMR spectroscopic data of **2** were also similar to those of compound **1**, except for the presence of a methoxy group (δ_C 61.2 q, δ_H 3.85 s), and the absence of an aromatic proton signal. This indicated that an aromatic proton in **1** was converted into a methoxy group in **2**. The HMBC correlations of the methoxy proton (δ_H 3.85 s) with C-4 suggested the methoxy

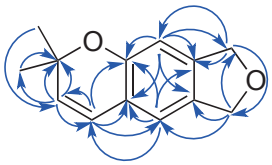

Figure 2. The HMBC (↷) correlations of **1**

group should be located at C-4. Thus, the structure of 2,2-dimethyl-6,8-dihydro-2*H*-furo[3,4-*g*]chromene (**2**) was established as shown.

Compound **3** was also assigned the molecular formula of $C_{14}H_{16}O_3$ as supported by the HRESIMS (*m/z* 255.1004 $[M+Na]^+$). The ^1H and ^{13}C NMR spectroscopic data of **3** were also similar to those of compound **2**, except for the substituents positions on the aromatic ring. The methoxy group located at C-6 was supported by the HMBC correlation of methoxy proton (δ_H 3.81 s) with C-6. The *gem*-dimethylchromene moiety fused in an angular manner at C-4 and C-5 was supported by the HMBC correlations of H-1' to C-4, C-5, and C-6, of H-2' to C-5, and on correlation was observed between H-4 and C-1'. Thus, the structure of 5-methoxy-2,2-dimethyl-7,9-dihydro-2*H*-furo[3,4-*h*]chromene (**3**) was established as shown.

Compounds **1-7** were tested for their anti-TMV activity at the concentration of 20 μM. The anti-TMV activity were tested using the half-leaf method.[32,33] Ningnanmycin (a commercial product for plant disease in China, with inhibition rate of 31.5%), was used as a positive control. The results showed that compounds **2** and **3** showed high anti-TMV activities with inhibition rates of 35.4, and 34.2%. These rates are higher than that of positive control. Other compounds also showed anti-TMV activities with inhibition rates in the range of 18.6~22.7%.

The cytotoxicities of compounds **1-7** were also tested using a previously reported procedure.[34,35] The cytotoxic abilities against five human tumor cell lines (NB4, A549, SHSY5Y, PC3, and MCF7) by MTT-assay were summarized in **Table 2**. The results revealed that compounds **1-6** showed moderate-to-weak inhibitory activities against some tested human tumor cell lines with IC_{50} values in the range of 2.8-9.3 μM.

Table 2. Cytotoxic activity of compounds **1-6**

Compounds	Cell lines and IC_{50} (μM)				
	NB4	A549	SHSY5Y	PC3	MCF7
1	5.2	>10	8.7	>10	9.3
2	>10	6.7	>10	7.9	>10
3	6.8	>10	>10	8.5	9.2
4	>10	7.4	>10	8.2	>10
5	3.9	4.2	3.2	5.5	4.6
6	>10	8.9	7.4	>10	8.2
7	2.8	6.2	5.7	3.1	4.0
Taxol	0.03	0.02	0.05	0.05	0.05

NB4, human leukemia cell; A549, carcinomic human alveolar basal epithelial cell; SHSY5Y, human neuroblastoma cell; PC3, human prostate cancer cell; MCF7, human breast adenocarcinoma cell.

EXPERIMENTAL

General. UV spectra were obtained using a Shimadzu UV-2401A spectrophotometer. A Tenor 27 spectrophotometer was used for scanning IR spectroscopy with KBr pellets. 1D and 2D NMR spectra were recorded on DRX-500 spectrometers with TMS as internal standard, and the chemical shifts (δ) were expressed in ppm. HRESIMS was performed on an API QSTAR time-of-flight spectrometer and a VG Autospec-3000 spectrometer, respectively. Preparative HPLC was performed on a Shimadzu LC-8A

preparative liquid chromatograph with a ZORBAX PrepHT GF (21.2 mm × 25 cm, 7 μm) column or a Venusil MP C_{18} (20 mm × 25 cm, 5 μm) column. Column chromatography was performed with silica gel (200–300 mesh, Qing-dao Marine Chemical, Inc., Qingdao, China). The fractions were monitored by TLC, and spots were visualized by heating silica gel plates sprayed with 5% H_2SO_4 in EtOH.

Plant Material. The stems of oriental tobacco (Samsun, a variety of *Nicotiana tabacum*) were collected in Baoshan Prefecture, Yunnan Province, People's Republic of China, in September 2015. The identification of the plant material was verified by Prof. H. W. Yang (School of Tobacco, Yunnan Agriculture University).

Extraction and Isolation. The air-dried and powdered stems of oriental tobacco (5.2 kg) were extracted four times with 70% aqueous MeOH (3 × 5 L) at room temperature and filtered. The solvent was evaporated in vacuo, and the crude extract was dissolved in H_2O and partitioned with EtOAc. The EtOAc partition (156 g) was applied to silica gel (200–300 mesh) column chromatography, eluting with a $CHCl_3$-MeOH gradient system (9:1, 8:2, 7:3, 6:4, 5:5, 4:6), to give six fractions A–F. Further separation of fraction A (9:1, 30.6 g) by silica gel column chromatography, eluted with $CHCl_3$-Me_2CO (9:1-1:1), yielded mixtures A1–A6. Fraction A1 (9:1, 4.15 g) was subjected to silica gel column chromatography using petroleum ether-acetone and semi-preparative HPLC (66% MeOH-H_2O, flow rate 20 mL/min) to give **6** (10.2 mg). Fraction A2 (8:2, 3.26 g) was subjected to silica gel column chromatography using petroleum ether-acetone and semi-preparative HPLC (60% MeOH-H_2O, flow rate 20 mL/min) to give **1** (12.2 mg), **2** (9.8 mg), **3** (10.8 mg), **4** (8.2 mg), and **7** (14.6 mg). Fraction A3 (7:3, 4.14 g) was subjected to silica gel column chromatography using petroleum ether-acetone and semi-preparative HPLC (54% MeOH-H_2O, flow rate 20 mL/min) to give **5** (13.8 mg).

Anti-TMV Assays. The anti-TMV activities were tested using the half-leaf method,[32,33] and Ningnanmycin (20 μM), a commercial product for plant disease in China, was used as a positive control.

Cytotoxicity Assay. The cytotoxicity tests for the isolates were performed by against NB4, A549, SHSY5Y, PC3, and MCF7 tumor cell lines by MTT-assay (with taxol as the positive control).[34,35]

2,2-Dimethyl-6,8-dihydro-2*H*-furo[3,4-*g*]chromene (**1**), $C_{13}H_{14}O_2$, obtained as pale yellow gum; UV (MeOH), λ_{max} (log ε) 278 (3.82), 240 (3.68), 210 (4.05) nm; IR (KBr) ν_{max} 3080, 2918, 1610, 1561, 1472, 1328, 1275, 1147, 1051, 864 cm^{-1}; ^1H NMR and ^{13}C NMR data ($CDCl_3$, 500 and 125 MHz, respectively), see Table 1; ESI-MS (positive ion mode) *m/z* 225 $[M+Na]^+$; HR-ESI-MS (positive mode) *m/z* $[M+Na]^+$ 225.0898 (calcd 225.0891 for $C_{13}H_{14}NaO_2$).

5-Methoxy-2,2-dimethyl-6,8-dihydro-2*H*-furo[3,4-*g*]chromene (**2**), $C_{14}H_{16}O_3$, obtained as pale yellow gum; UV (MeOH), λ_{max} (log ε) 280 (3.90), 245 (3.64), 210 (4.12) nm; IR (KBr) ν_{max} 3070, 2963, 1612, 1568, 1464, 1334, 1269, 1159, 1046, 894 cm^{-1}; ^1H NMR and ^{13}C NMR data ($CDCl_3$, 500 and 125 MHz, respectively), see Table 1; ESI-MS (positive ion mode) *m/z* 255 $[M+Na]^+$; HR-ESI-MS (positive mode)

m/z $[M+Na]^+$ 255.1005 (calcd 255.0997 for $C_{14}H_{16}NaO_3$).

5-Methoxy-2,2-dimethyl-7,9-dihydro-2*H*-furo[3,4-*h*]chromene (**3**), $C_{14}H_{16}O_3$, obtained as pale yellow gum; UV (MeOH), λ_{max} (log ε) 282 (3.87), 246 (3.68), 210 (4.15) nm; IR (KBr) ν_{max} 3081, 2967, 1615, 1564, 1460, 1339, 1265, 1153, 1042, 879 cm^{-1}; ^1H NMR and ^{13}C NMR data ($CDCl_3$, 500 and 125 MHz, respectively), see Table 1; ESI-MS (positive ion mode) *m/z* 255 $[M+Na]^+$; HR-ESI-MS (positive mode) *m/z* $[M+Na]^+$ 255.1004 (calcd 255.0997 for $C_{14}H_{16}NaO_3$).

ACKNOWLEDGEMENTS

This research was supported by the National Natural Science Foundation of China (Nos. 21562049, 31360081 and 31400303), and the Applied Fundamental Foundation of Yunnan Province (Nos. 2014FB097, 2014FB163, and 2015FB162), and the Basic Research Foundation of Yunnan Tobacco Industry Co. Ltd (2013FL05 and 2012JC01).

REFERENCES

1. The Editorial Committee of the Administration Bureau of Flora of China, 'Flora of China,' 67 vols., Beijing Science and Technology Press, Beijing, 2005.
2. A. Rodgman and T. A. Perfetti, 'The Chemical Components of Tobacco and Tobacco Smoke,' CRC Press, Taylor and Francis Group, Boca Raton, Florida, 2008.
3. A. Fuchs, W. Slobbe, P. C. Mol, and M. A. Posthumus, *Phytochemistry*, 1983, **22**, 1197.
4. S. Z. Shang, W. Zhao, J. G. Tang, X. M. Xu, H. D. Sun, J.-X. Pu, Z. H. Liu, M. M. Miao, Y. K. Chen, and G. Y. Yang, *Fitoterapia*, 2016, **108**, 1.
5. G. Y. Yang, W. Zhao, Y. K. Chen, Z. Y. Chen, Q. F. Hu, and M. M. Miao, *Asian J. Chem.*, 2013, **25**, 4932.
6. Q. P. Shen, X. M. Xu, L. Li, W. Zhao, N. J. Xiang, G. Y. Yang, Y. K. Chen, M. M. Miao, C. B. Liu, and Z. H. Liu, *Chin. Chem. Lett*., 2016, **27**, 753.
7. G.-H. Kong, Y.-P. Wu, W. Li, Z.-Y. Xia, Q. Liu, K.-M. Wang, P. He, R.-Z. Zhu, X.-X. Si, and G.-Y. Yang, *Heterocycles*, 2016, **92**, 331.
8. S. Z. Shang, Y. X. Duan, X. Zhang, J. X. Pu, H. D. Sun, Z. Y. Chen, M. M. Miao, G. Y. Yang, and Y. K. Chen, *Phytochem. Lett.*, 2014, **7**, 413.
9. Y. K. Chen, X. S. Li, G. Y. Yang, Z. Y. Chen, Q. F. Hu, and M. M. Miao, *J. Asian Nat. Prod. Res*., 2012, **14**, 450.
10. X.-M. Gao, X. Li, X. Yang, H. Mu, Y. Chen, G. Yang, and Q.-F. Hu, *Heterocycles*, 2012, **85**, 147.
11. M. M. Miao, L. Li, Q. P. Shen, C. B. Liu, Y. K. Li, T. Zhang, F. M. Zhang, P. He, K. M. Wang, R. Z. Zhu, Y. K. Chen, and G. Y. Yang, *Fitoterapia*, 2015, **103**, 260.

12. Z. Y. Chen, J. L. Tan, G. Y. Yang, M. M. Miao, Z. Y. Chen, and T. F. Li, *Phytochem. Lett*., 2012, **5**, 233.
13. Y. Li, Y. Zhao, N. Xiang, L. Yang, F. Wang, G. Yang, and Z. Wang, *Heterocycles*, 2014, **89**, 2771.
14. Y. Wang, C.-B. Liu, Q.-P. Shen, F.-M. Zhang, P. He, Z.-H. Liu, H.-B. Zhang, X.-D. Yang, M.-M. Miao, and G.-Y. Yang, *Heterocycles*, 2015, **91**, 1198.
15. H. Q. Leng, J. X. Chen, Y. Hang, Y. X. Duan, G. Y. Yang, Y. K. Chen, Y. D. Guo, Q. F. Hu, and M. M. Miao, *Chem. Nat. Compd.*, 2014. **49**, 1028.
16. J. Tan, Z. Chen, G. Yang, M. Miao, Y. Chen, and T. Li, *Heterocycles*, 2011, **83**, 2381.
17. D. Mou, W. Zhao, T. Zhang, L. Wan, G. Yang, Y. Chen, Q. Hu, and M. Miao, *Heterocycles*, 2012, **85**, 2485.
18. G. Yang, W. Zhao, T. Zhang, Y. Duan, Z. Liu, M. Miao, and Y. Chen, *Heterocycles*, 2014, **89**, 183.
19. S. Z. Shang, W. X. Xu, P. Lei, W. Zhao, J. G. Tang, M. M. Miao, H. D. Sun, J. X. Pu, Y. K. Chen, and G. Y. Yang, *Fitoterapia*, 2014, **99**, 35.
20. M. Zhou, K. Zhou, J. Lou, Y. D. Wang, W. Dong, G. P. Li, Z. Y. Jian, G. Du, H. Y. Yang, X. M. Li, and Q. F. Hu, *Phytochem. Lett*., 2015, **14**, 226.
21. Q. Shen, X. Xu, F. Zhang, N. Xiang, P. He, X. Si, R. Zhu, K. Wang, Z. Liu, C. Liu, and M. Miao, *Nat. Prod. Res*., 2016, **30**, 1464.
22. G.-H. Kong, Y.-P. Wu, J.-L. Shi, N.-J. Xiang, L.-X. Liu, G.-R. Yang, Y.-K. Li, X.-P. Lu, Q. Liu, and Q.-F. Hu, *Phytochem. Lett*., 2015, **14**, 230.
23. Q.-P. Shen, L. Li, X.-M. Xu, C.-B. Liu, N.-J. Xiang, F.-M. Zhang, P. He, Z.-H. Liu, S.-Z. Shang, M.-M. Miao, and G.-Y. Yang, *Heterocycles*, 2015, **91**, 1775.
24. S. Z. Shang, W. X. Xu, L. Li, J. G. Tang, W. Zhao, P. Lei, M.-M. Miao, H.-D. Sun, J. X. Pu, Y. K. Chen, and G. Y. Yang, *Phytochem. Lett.*, 2015, **11**, 53.
25. C.-B. Liu, X.-M. Xu, Q.-P. Shen, W. Zhang, X.-F. Shen, Y.-K. Yang, F.-M. Zhang, P. He, X.-X. Si, Y.-D. Guo, J.-J. Xia, and G.-Y. Yang, *Heterocycles*, 2016, **92**, 1095.
26. K. W. Cho, H. S. Lee, J. R. Rho, T. S. Kim, S. J. Mo, and J. H. Shin, *J. Nat. Prod*., 2001, **64**, 664.
27. J. Zhang, Y. Liang, X. J. Liao, Z. Deng, and S. H. Xu, *Nat. Prod. Res*., 2014, **28**, 150.
28. A. J. Aasen and C. R. Enzell, *Acta Chem. Scand. B*, 1975, **29**, 528.
29. D. Behr, I. Wahlberg, T. Nishida, and C. R. Enzell, *Acta Chem. Scand. B*, 1979, **33**, 701.
30. Q. F. Hu, B. Zhou, X. M. Gao, L. Y. Yang, L. D. Shu, Y. Shen, G. P. Li, C. T. Che, and G. Y. Yang, *J. Nat. Prod.*, 2012, **75**, 1909.
31. G. H. Kong, Y. P. Wu, J. L. Shi, N. J. Xiang, L. X. Liu, G. R. Yang, Y. K. Li, X. P. Lu, Q. Liu, and Q. F. Hu, *Phytochem. Lett*., 2015, **14**, 230.
32. M. Zhou, M. M. Miao, G. Du, S. Z. Shang, W. Zhao, Z.-H. Liu, G.-Y. Yang, C. T. Che, Q.-F. Hu,

and X.-M. Gao, *Org. Lett*., 2014, **16**, 5016.

33. M. Zhou, K. Zhou, X. M. Gao, Z. Y. Jiang, J. J. Lv, Z. H. Liu, G. Y. Yang, M. M. Miao, C. T. Che, and Q. F. Hu, *Org. Lett.*, 2015, **17**, 2638.
34. Q. F. Hu, B. Zhou, J. M. Huang, Z. Y. Jiang, X. Z. Huang, L. Y. Yang, X. M. Gao, G. Y. Yang, and C. T. Che, *J. Nat. Prod*., 2013, **76**, 1866.
35. Q. F. Hu, B. Zhou, Y. Q. Ye, Z. Y. Jiang, X. Z. Huang, Y. K. Li, G. Du, G. Y. Yang, and X. M. Gao, *J. Nat. Prod*., 2013, **76**, 1854.