Organic LETTERS

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Kadcoccinones A–F, New Biogenetically Related Lanostane-Type Triterpenoids with Diverse Skeletons from *Kadsura coccinea*

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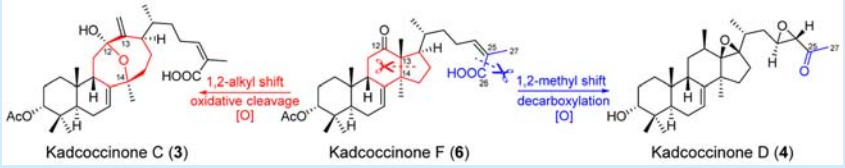
Supporting Information



ABSTRACT: Six new lanostane-related triterpenoids, kadcoccinones A–F (**1**–**6**), were isolated from *Kadsura coccinea*. Compound **3** possesses a novel 6/6/9-fused carbocyclic core containing a rare oxabicyclo[4.3.1]decane system. Compounds **4** and **5** are isomers representing the first example of the 18(13 → 12)-*abeo*-26-norlanostane triterpenoid. The absolute configurations of **1** and **4**–**6** were defined by X-ray diffraction and experimental ECD spectra, and that of **3** was elucidated by quantum chemical calculations. The plausible biogenetic pathway of **1**–**6** is postulated.

The economically and medicinally important plants of the family Schisandraceae, consisting of two genera *Schisandra* and *Kadsura*, are widely used in traditional Chinese medicine for their beneficial pharmacological effects, such as anticancer, antihepatitis, and anti-HIV-1 activities.[1] It is noteworthy that Schisandraceae triterpenoids characterized by complex polycyclic rings and multiple chiral centers have brought tremendous challenges and ambitious targets for synthetic organic chemists.[2]

Kadsura coccinea (Lem.) A. C. Smith is widely distributed throughout southwest China and well-known for treating cancer and dermatosis and as an anodyne to relieve pain.[3] In the last decades, our group has devoted itself to the discovery of structurally unique and bioactive triterpenoids from this plant. As were reported, several rearranged lanostane-type triterpenoids with novel skeletons, such as 6/6/5/5-, 6/6/6-, 6/6/5-, and 2,3-*seco*-6/6/5/6-fused ring systems, were isolated from the stems of *K. coccinea* from the Ziyuan prefecture of the Guangxi Province in China,[4] and highly oxygenated cycloartane-related triterpenoids were obtained from the stems of *K. coccinea* from the Honghe prefecture of the Yunnan Province in China,[5] wherein kadlongilactones A and B show potent cytotoxicity against K562, Bel-7402, and A549 cell lines with IC_{50} values less than 0.1, 0.1, and 1.0 μM, respectively.[5b] The above-mentioned results indicated that the different ecological environments might be an important external factor for structurally diverse natural products.

In our continuing endeavor to discover more novel bioactive analogues from this species, six new lanostane-related triterpenoids with diverse skeletons, namely kadcoccinones A–F (**1**–**6**), were isolated by a HPLC–UV-guided investigation on the EtOAc-soluble extract of the stems of *K. coccinea* collected in the Menglun district of the Yunnan Province in China. Herein, we describe the isolation, structure elucidation, biological evaluation, and possible biogenetic pathway of these compounds (Figure 1).

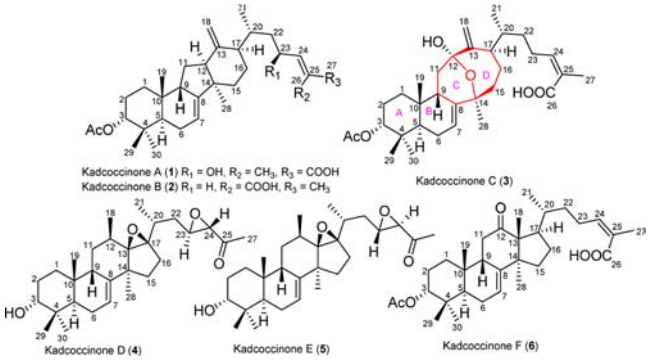


Figure 1. Structures of kadcoccinones A–F (**1**–**6**).

Kadcoccinone A (**1**) was determined to be $C_{32}H_{48}O_5$ by its HRESIMS at *m*/*z* 535.3395 ([M + Na]$^+$, calcd for 535.3394), indicating nine indices of hydrogen deficiency. The ^{1}H NMR spectrum of **1** showed signals of one secondary methyl at δ_H 1.19 (d, *J* = 6.2 Hz, H_3-21), six tertiary methyls at δ_H 0.82 (H_3-29), 0.90 (H_3-30), 1.11 (H_3-28), 1.14 (H_3-19), 2.22 (H_3-26), and 2.10 (−OAc), two oxygen-bearing methines at δ_H 4.80 (br s, H-3) and 5.10 (td, *J* = 4.7 and 9.5 Hz, H-23), and four olefinic protons at δ_H 5.51 (m, H-7), 4.82/4.84 (2H, d, *J* = 2.6 Hz, H-18), and 7.40 (dd, *J*

Received: August 15, 2015
Published: September 8, 2015

DOI: 10.1021/acs.orglett.5b02360
Org. Lett. 2015, 17, 4616–4619

= 1.1 and 9.5 Hz, H-24). The ^{13}C NMR spectrum resolved 32 carbon signals including five degrees of unsaturation occupied by two carbonyls and three double bonds, suggesting that **1** should be a tetracyclic structure.

A comprehensive analysis of the 1D and 2D NMR spectra revealed that **1** had an infrequent 14(13 → 12)-*abeo*-6/6/5/6-fused rearranged lanostane-type triterpenoid skeleton (Figure S3, Supporting Information). Luckily, we obtained the crystals of **1** from ethanol by repeated recrystallization, and a single-crystal X-ray diffraction experiment was carried out using Cu Kα radiation (see Scheme 1), allowing an explicit assignment of the absolute structure as 3*R*,5*R*,9*S*,10*R*,12*S*,14*R*,17*R*,20*R*,23*S* and an *E*-geometry of the double bond between C-24 and C-25 on the basis of the Flack parameter of 0.1(2) (CCDC 1405903).[6]

Kadcoccinone B (**2**) was assigned a molecular formula of $C_{32}H_{48}O_4$ by its HRESIMS at *m*/*z* 495.3481 ($[M-H]^-$, calcd for 495.3480). Comparison of the NMR data of **2** with those of **1** (Table S3, Supporting Information) suggested that they shared the same carbon skeleton, whereby an apparent difference at C-23 (δ_C 27.4 for **2**, δ_C 67.3 for **1**) implied that an oxygenated methine in **1** was replaced by a methylene in **2**. In addition, the C-24/C-25 double bond was undisputedly determined as having *Z*-geometry, judging from the ROESY correlation of H-24/H_3-27. The structure of **2** was fully established by detailed examination of $^1H-^1H$ COSY, HSQC, HMBC, and ROESY spectral analyses (Figures S3 and S4, Supporting Information).

Kadcoccinone C (**3**), with a molecular formula of $C_{32}H_{48}O_6$ and nine indices of hydrogen deficiency, was assigned on the basis of its HRESIMS at *m*/*z* 551.3345 ($[M + Na]^+$, calcd for 551.3343). The IR spectrum of **3** exhibited absorptions of hydroxyl (3432 cm^{-1}), carboxyl (1724 cm^{-1}), carboxyl ester (1694 cm^{-1}), and double bond (1639 cm^{-1}) functionalities. The ^1H NMR spectrum (Table 1) of **3** displayed signals for one secondary methyl at δ_H 0.82 (H_3-21), six tertiary methyls at δ_H 0.95 (H_3-29), 0.83 (H_3-30), 0.88 (H_3-19), 1.19 (H_3-28), 1.80 (H_3-27), and 2.03 (−OAc), one oxygenated methine at δ_H 4.57 (br s, H-3), and four olefinic protons at δ_H 5.61 (br d, *J* = 5.5 Hz, H-7), 4.81/5.15 (2H, br s, H-18), and 5.87 (br s, H-24). The ^{13}C NMR and DEPT spectra (Table 1) disclosed 32 carbon signals, including seven methyls, nine methylenes (one olefinic), seven methines (one oxygenated and two olefinic), and nine quaternary carbons (two carbonyl, three olefinic, and two oxygenated). Apart from five indices of hydrogen deficiency occupied by three double bonds and two carbonyls, a tetracyclic framework was assumed to exist.

Careful analysis of the NMR data of **3** with those of **1** and **2** (Tables S2 and S3, Supporting Information) disclosed their structural similarities with regard to the side chain and six-membered A and B rings, which were further confirmed by 2D spectral analysis as shown in Figure 2. Two oxygenated sp^3 quaternary carbons at C-12 (δ_C 97.0) and C-14 (δ_C 76.4) were quite distinctive from **1** and those of kadcoccitone C.[4a] To account for the remaining two degrees of unsaturation, we deduced that **3** was likely to possess a unique oxabicyclo[4.3.1]-decane moiety replacing the 5/6-fused C/D rings. The aforesaid conjecturable ring system was confirmed by the $^1H-^1H$ COSY correlations of H-9/H-11 and H-16/H-17, coupled with the HMBC correlations of H-28 with C-8, C-14, and C-15, of H-18 with C-12, C-13, and C-17, of H-16 with C-14 and C-15, and of H-11 with C-12 and C-13.

The relative configuration of **3** was concluded from the 600 MHz ROESY spectrum in DMSO (Figure 2). According to the normal lanostane-type triterpenoid skeleton, H-5 was assigned as

Table 1. NMR Spectroscopic Data of 3 and Its Calculated ^{13}C NMR Data (δ in ppm, *J* in Hz)

no.	δ_H	δ_C		
	exptl[a,e]	exptl[b]	exptl[c]	calcd[d]
1	1.02 m; 1.87 m	28.3 CH_2	29.5	30.9
2	1.59 m; 1.91 m	22.3 CH_2	23.4	25.3
3	4.57 br s	77.6 CH	78.8	79.2
4	-	35.9 C	36.8	39.4
5	1.51 dd (4.5, 12.1)	38.3 CH	39.3	41.0
6	1.93 m	22.6 CH_2	23.7	25.9
7	5.61 br d (5.5)	117.8 CH	119.0	120.0
8	-	141.3 C	142.5	139.4
9	2.17 br d (13.0)	43.5 CH	44.7	45.2
10	-	34.1 C	35.2	38.8
11	1.38 dd (12.3, 14.2) 2.45 dd (3.3, 12.3)	37.6 CH_2	38.9	39.5
12	-	97.0 C	98.5	100.3
13	-	152.9 C	154.8	148.8
14	-	76.4 C	77.8	80.9
15	1.05 m; 2.02 m	32.5 CH_2	33.8	33.8
16	1.16 m; 1.96m	27.8 CH_2	29.3	29.9
17	2.54 m	40.8 CH	42.5	39.2
18	4.81 br s; 5.15 br s	107.8 CH_2	108.5	111.5
19	0.88 s	22.2 CH_3	23.0	23.2
20	1.53 m	35.3 CH	36.8	38.7
21	0.82 m	18.3 CH_3	19.4	18.0
22	1.17 m; 1.64 m	33.0 CH_2	34.3	33.6
23	2.38 m; 2.53 m	26.2 CH_2	27.8	30.5
24	5.87 br s	141.3 CH	143.0	138.3
25	-	128.3 C	129.3	129.0
26	-	169.9 C	171.2	163.8
27	1.80 s	21.0 CH_3	22.1	23.2
28	1.19 s	24.6 CH_3	25.7	25.4
29	0.95 s	22.3 CH_3	22.8	23.4
30	0.83 s	27.7 CH_3	28.2	28.3
-OAc	-	169.9 C	170.7	166.7
	2.03 s	21.0 CH_3	21.4	21.8

[a]Recorded in DMSO at 600 MHz. [b]Recorded in DMSO at 150 MHz. [c]Recorded in C_5D_5N at 150 MHz. [d]Calculated ^{13}C NMR data of **3** in DMSO. [e]"m" = overlapped or multiplet with other signals.

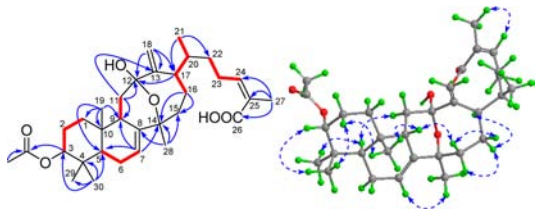


Figure 2. Selected $^1H-^1H$ COSY (bold), HMBC (arrow), and ROESY (dashed arrow) correlations of **3**.

α-oriented. The ROESY correlation of H-5/H_3-30 revealed that H-5 and H_3-30 were cofacial and α-oriented. On the contrary, the ROESY cross-peaks of H-3/H_3-29, H_3-29/H-2β/H_3-19, and H_3-19/H-9 suggested that H-3, H-9, H_3-19, and H_3-29 were on the same side with a β-direction. However, just like **1**, the same ROESY correlations of H-9β/H-15β (δ_H 2.02) and H-7/H_3-28 disclosed that H_3-28 should be α-oriented.

The nuclear Overhauser effect (NOE) is commonly regarded as one of the most effective methods in structural and conformational analyses. Yet, when the internuclear distance was more than 3 Å, the NOE correlations could not be observed even for the two spin systems bearing consistent orientations. Unfortunately, no evident ROESY correlations between HO-12 and other adjacent signals were observed in **3**. To ascertain the orientation of HO-12, the computer-generated 3D drawing and molecular structure model methods were conducted. First, we

DOI: 10.1021/acs.orglett.5b02360
Org. Lett. 2015, 17, 4616−4619

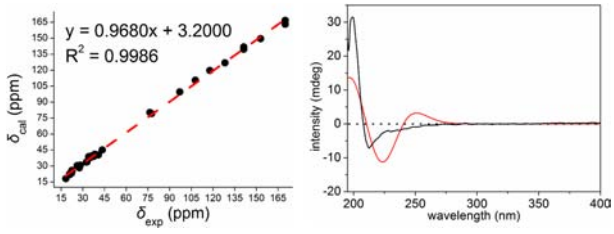


Figure 3. (a) Regression analysis of experimental vs calculated ^{13}C NMR chemical shifts of **3** (left). (b) Experimental (black) and calculated (red) ECD spectra of **3** in MeOH (right).

supposed the HO-12 was β-direction, in this case, the internuclear distances of H-9β/H-15β and H-5α/H-11α, were 3.77 and 3.99 Å, respectively (Figure S5, Supporting Information). However, the obvious ROESY correlations of H-5α/H-11α (δ_H 1.38) and H-9β/H-15β proved that the hypothesis was false. Thus, the HO-12 should be α-oriented, and the internuclear distances of H-9β/H-15β (1.99 Å) and H-5α/H-11α (2.39 Å) in the most stable conformer (Figure S5, Supporting Information) further demonstrated the reliability of the conclusion. In comparison with **2**, a considerable upfield signal shift (Δ 6.3 ppm) for C-17 occurred in **3** because of a γ-steric compression effect between HO-12 and H-17 (δ_H 2.54), indicating that H-17 should be α-oriented, which was further confirmed by the evidence that clear ROESY cross-peaks of H-15β/H-16β (δ_H 1.16), H-15α (δ_H 1.05)/H-16α (δ_H 1.96), and H-16α/H-17 were observed, and yet, no obvious signals of H-15β/H-16α and H-16β/H-17 were observed.

The extremely similar side chain with **1** and **2** indicated that C-20 in **3** was in the *R*-configuration, which was in accordance with the biogenetic point of view of the 20*R*-configuration in lanostane-type triterpenoids.[1] Additionally, the *Z*-configuration of the double bond between C-24 and C-25 in **3** was unequivocally elucidated by a clear ROESY correlation of H-24/H$_3$-27 (recorded in C_5D_5N). Consequently, the relative configuration of **3** was established.

All of the above-mentioned results were supported by the predominant conformer (60%, Figure 2) obtained by DFT calculation at the B3LYP/6-31G(d) level. Under the circumstances, the calculation of ^{13}C NMR chemical shifts of **3** at MPW1PW91-SCRF/6-31G(d,p) level with the PCM in DMSO was performed to verify the structure, and the results agreed well with the experimental data with R^2 = 0.9986 (Table 1 and Figure 3).

The calculated ECD spectrum at B3LYP/6-31G+(d,p) level with PCM in MeOH was compatible with the experimental ECD curve (Figure 3), allowing an explicit assignment of the absolute structure as 3*R*,5*R*,9*S*,10*R*,12*S*,14*S*,17*R*,20*R*.

Molecular orbital (MO) analyses (Figure 4) of the predominant conformer gave us an understanding of the

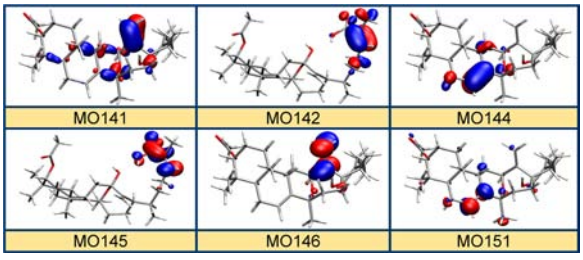


Figure 4. Most important orbitals involved in the key transitions of the conformer **3** in MeOH using PCM model.

experimental ECD spectrum. The experimental ECD spectrum showed a positive Cotton effect at 200 nm, which was caused by the electronic transitions from MO141 to MO146 and MO144 to MO151 involving a $\pi \rightarrow \pi^*$ transition of two double bonds. The negative curve peak at 212 nm was caused by the electronic transitions from MO142 to MO145 involving a $\pi \rightarrow \pi^*$ transition in the α,β-unsaturated carboxyl.

Kadcoccinone D (**4**) was deduced to be $C_{29}H_{44}O_4$ by its HRESIMS at *m*/*z* 479.3131 ([M + Na]$^+$, calcd for 479.3132), requiring eight degrees of unsaturation. Extensive analysis of 1D (especially two methyl doublets) and 2D NMR spectra revealed that **4** possessed a 18(13 → 12)-*abeo*-26-norlanostane skeleton. The proposed structure of **4** was fully determined by detailed interpretation of its HSQC, ^{1}H−^{1}H COSY, and HMBC spectra (Figure S3, Supporting Information), and its absolute configuration was finally deduced as 3*R*,5*R*,9*S*,10*R*,12*R*,13*R*,14*S*,17*R*,20*R*,23*R*,24*S* by X-ray diffraction (Scheme 1) with a Flack parameter of 0.07(18) (CCDC 1405902).[6]

Kadcoccinone E (**5**) had the same molecular formula as that of **4**. Side-by-side comparison of their NMR data indicated that **4** and **5** were a pair of isomers. The structure of **5** was further corroborated by HSQC, ^{1}H−^{1}H COSY, and HMBC spectra (Figure S3, Supporting Information), and its relative configuration was confirmed by single-crystal X-ray crystallographic analysis (Scheme 1) with a Flack parameter of 0.4(3) (CCDC 1405904).[6] To our surprise, the slight differences between **4** and **5** were the opposite configurations in H-23 and H-24, which were confirmed by comparison of their CD spectra (Figures S69 and S72, Supporting Information) showing the antipodal Cotton effects around 289 nm that were ascribed to the carbonyl group at C-25. Thus, the absolute configuration of **5** was deduced as 3*R*,5*R*,9*S*,10*R*,12*R*,13*R*,14*S*,17*R*,20*R*,23*S*,24*R*.

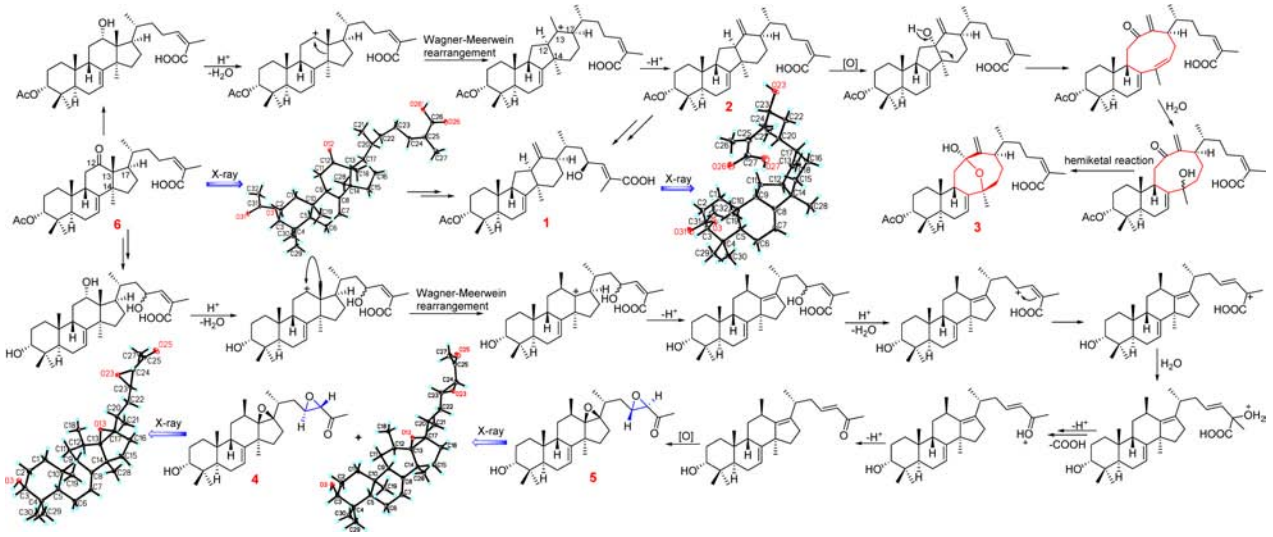
Kadcoccinone F (**6**) was determined to possess a molecular formula of $C_{32}H_{48}O_5$ by its HRESIMS at *m*/*z* 511.3400 ([M − H]$^-$, calcd for 511.3429). The NMR data of **6** closely resembled with those of kadpolysperin M,[7] indicating that it was a normal tetracyclic lanostane triterpene acid. A comprehensive examination of its HSQC, ^{1}H−^{1}H COSY, and HMBC spectra (Figure S3, Supporting Information) established the planar structure of **6**. Lastly, its absolute configuration (3*R*,5*R*,9*S*,10*R*,13*R*,14*S*,17*R*,20*R*) was undisputedly confirmed by single-crystal X-ray crystallographic analysis (Scheme 1) with a Flack parameter of 0.4(3) (CCDC 1405901).[6]

To the best of our knowledge, kadcoccinone A (**3**), the first class of a novel 6/6/9-fused carbon skeleton, was very likely derived from the rare 14(13 → 12)-*abeo*-lanostane triterpenoid. Interestingly, **3** possesses an extraordinary nine-membered ring constructing a rare oxabicyclo[4.3.1]decane ring system. In addition, kadcoccinones D (**4**) and E (**5**), representing the first report of a 18(13 → 12)-*abeo*-26-norlanostane skeleton, might plausibly be traced back to the lanostane triterpenoid.[1]

The hypothetical biosynthetic pathway for **1**−**6** is proposed in Scheme 1. As a precursor, kadcoccinone F (**6**) underwent the reduction reaction and released one molecular H_2O to give the key intermediate, which further rearranged to form the kadcoccinone B (**2**) via a crucial Wagner−Meerwein rearrangement reaction.[1] Ultimately, **2** generated kadcoccinone C (**3**) by the key cleavage between C-12 and C-14 and a hemiketal reaction. Additionally, **1** was potentially derived from **2** by oxidation and double-bond flip reactions.[8] Beginning with **6**, the key steps of this biosynthesis route to **4** and **5** involve a series of redox, Wagner−Meerwein rearrangement, protonation transfer, decarboxylation, deprotonation, and epoxidation reactions.

DOI: 10.1021/acs.orglett.5b02360
Org. Lett. 2015, 17, 4616−4619

Scheme 1. Hypothetical Biogenetic Pathway for 1−6



The structure−activity relationships of **1**−**6** were initially discussed for their cytotoxicity against HL-60, SMMC-7721, A-549, MCF-7, SW-480, and HeLa human cancer cell lines (Table S1, Supporting Information) by using the MTT method.[9] Comparing **2** with **3**, we suspected the cleavage and hemiketal reactions between C-12 and C-14 might decrease the potency for cytotoxic activities. Besides, the cytotoxicity of **5** was greater than its isomer **4**, suggesting that the 23*S*,24*R* configuration might enhance the potency for cytotoxic activities in comparison to the 23*R*,24*S* configuration for the epoxide group.

In summary, Schisandraceae triterpenoids featuring numerous ring systems make them distinctive from other naturally occurring triterpenoids. In this paper, our findings on this species not only enrich the structural diversity of triterpenoids in the Schisandraceae family but also lay the foundation for further study on antitumor activity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02360.

Detailed experimental procedures, 1D and 2D NMR, HRESIMS, UV, and IR spectra of **1**−**6**, and computational data of **3** (PDF)

X-ray data of **1** (CIF)

X-ray data of **4** (CIF)

X-ray data of **5** (CIF)

X-ray data of **6** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Project supported financially by the National Natural Science Foundations of China (81373290 and 21322204) and the reservation-talent project of Yunnan Province (2011CI043).

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DOI: 10.1021/acs.orglett.5b02360
Org. Lett. 2015, 17, 4616−4619