



# Chemical Studies on Antioxidant Mechanism of Tea Catechins: Analysis of Radical Reaction Products of Catechin and Epicatechin with 2,2-Diphenyl-1-picrylhydrazyl

Shengmin Sang,<sup>a,\*</sup> Xiaofang Cheng,<sup>b</sup> Ruth E. Stark,<sup>b</sup> Robert T. Rosen,<sup>a</sup>  
Chung S. Yang<sup>c</sup> and Chi-Tang Ho<sup>a</sup>

<sup>a</sup>Department of Food Science and Center for Advanced Food Technology, Rutgers University,  
65 Dudley Road, New Brunswick, NJ 08901-8520, USA

<sup>b</sup>Department of Chemistry, College of Staten Island, City University of New York, NY 10314, USA

<sup>c</sup>Laboratory for Cancer Research, College of Pharmacy, Rutgers University, 164 Frelinghuysen Road,  
Piscataway, NJ 08854-8020, USA

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**Abstract**—Tea catechins, an important class of polyphenols, have been shown to have wide spectrum of antitumor activity believed to be due mainly to their antioxidative effect. In this study, the radical scavenging behavior of catechins on 2,2-diphenyl-1-picrylhydrazyl (DPPH) was studied. Two reaction products of (+)-catechin, and two reaction products of (–)-epicatechin were purified and identified. Their structures were determined on the basis of detailed high-field 1-D and 2-D NMR spectral analysis. Structure elucidation of these products can provide insights into specific mechanisms of antioxidant reactions. A possible mechanism of the formation of reaction products is suggested. © 2002 Elsevier Science Ltd. All rights reserved.

## Introduction

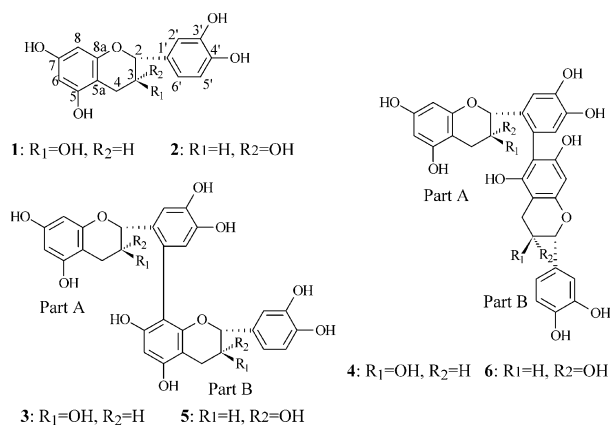
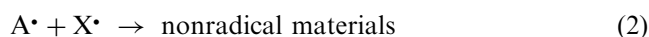
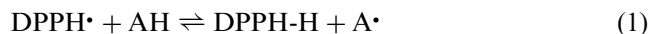
Tea is one of the most widely consumed beverages in the world. They belong to the theaceae family and come from two main varieties: *Camellia sinensis* var. *sinensis* and *C. sinensis* var. *assamica*.<sup>1</sup> The chemical composition of tea leaves has been thoroughly studied. The main constituents of green tea leaves belong to the polyphenol group which accounts for 25–35% on a dry weight basis.<sup>2</sup> Flavanols are important and characteristic tea polyphenols of which catechins (flavan-3-ols) are predominant and the major ones are: (+)-catechin (C), (+)-gallocatechin (GC), (–)-epicatechin (EC), (–)-epicatechin gallate (ECG), (–)-epigallocatechin (EGC), and (–)-epigallocatechin gallate (EGCG).<sup>3</sup> Recently, tea catechins have attracted considerable interest because of their associated beneficial health properties, including strong antioxidant activity<sup>4–9</sup> and remarkable cancer preventive effects in several animal models.<sup>10,11</sup> A number of studies attributed the cancer preventive effects to their antioxidant actions.<sup>4–7,9,12–15</sup> It is supposed that

tea catechins can react with reactive oxygen species, which may play important roles in carcinogenesis, thus terminating those chain reactions.<sup>16</sup> Previous structure–activity studies<sup>4,6</sup> indicated that flavonoids with an *o*-dihydroxy or trihydroxy B ring are the most effective antioxidants. Moreover, a gallate ester moiety at the 3-position of catechins (ECG and EGCG) has the highest antioxidant activity.<sup>4,6</sup> It is believed that characteristic reaction products may provide novel markers for antioxidant reactions of tea catechins in living systems. Therefore, detailed studies of the specific mechanisms of the antioxidation of catechins in different oxidation systems are of great scientific interest. Recently, Valcic et al.<sup>17,18</sup> reported the oxidation products of the reaction of EGC and EGCG with peroxy radicals, indicating that the principal site of antioxidant reaction in EGCG and EGC is the trihydroxyphenyl B-ring, regardless of the presence of a 3-galloyl moiety. We studied the oxidation products of EGCG and EGC in three different oxidant systems: peroxidase oxidant system, DPPH oxidant system, and H<sub>2</sub>O<sub>2</sub> oxidant system.<sup>19–21</sup> Depending on how the oxidation of catechins is achieved, the condensation products are different. Both the peroxidase oxidant system and the DPPH oxidant system showed that the most likely site of

\*Corresponding author. Tel.: +1-732-932-9611x346; fax: +1-732-932-6776; e-mail: smsang@hotmail.com

oxidation for EGCG and EGC occurs at B-ring rather than at gallate ester moiety, which is similar to the mechanism for the peroxy radicals system. However, the  $\text{H}_2\text{O}_2$  oxidant system provided an unambiguous proof that oxidation can occur at A-ring.

To continue our study on the antioxidant mechanisms of catechins, we reacted catechin and epicatechin, both with 2,2-diphenyl-1-picrylhydrazyl (DPPH). The DPPH system is a stable radical-generating procedure.<sup>22</sup> Because it can accommodate a large number of samples in a short period, and is sensitive enough to detect active principles at low concentrations, it was used in the present study. The antioxidant process of this reaction is thought to be divided into the following two stages:



**Figure 1.** Structures of compounds 1–6.

AH is the antioxidant,  $\text{A}^\bullet$  is the antioxidant radical, and  $\text{X}^\bullet$  is another radical species or the same species as  $\text{A}^\bullet$ .<sup>23,24</sup> Although the first stage is a reversible process, the second stage is irreversible and produces stable radical termination compounds. Structural information about these nonradical products would afford important contributions to antioxidant mechanism studies.

In this paper, we report the isolation and structure elucidation of two major oxidation products (**3** and **4**) formed by the reaction of (+)-catechin (**1**) with the stable radical DPPH, and two major oxidation products (**5** and **6**) from (–)-epicatechin (**2**) with DPPH.

## Results

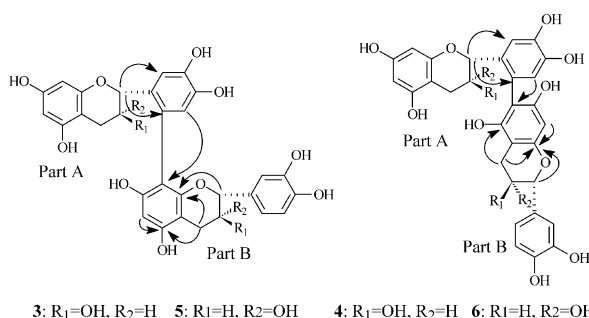
Two major oxidation products, compounds **3** and **4** were isolated and identified, on the basis of their spectral data, from the reaction of catechin **1** with DPPH. Similarly, the reaction of epicatechin (**2**) with DPPH also yielded two major oxidation products, compounds **5** and **6** (Fig. 1).

Compound **3**, a yellow amorphous solid was assigned the molecular formula of  $\text{C}_{30}\text{H}_{26}\text{O}_{12}$  determined by negative-ion APCI-MS ( $[\text{M}-\text{H}]^-$  at  $m/z$  577), as well as from its  $^{13}\text{C}$  NMR data. The  $^{13}\text{C}$  chemical shifts of **3** appeared as duplicated catechin carbon signals (Table 1), especially in the high field region ( $\delta$  27–83 ppm) associated with the heterocyclic C-ring, where the C-2, C-3 and C-4 carbon resonance showed up as twin peaks of comparable intensity. The major difference in the duplicated catechin is the presence of two additional quaternary carbons observed at  $\delta$  108.6 and 126.8 ppm at the expense of an unsubstituted aromatic carbon from the A-ring and B-ring. In addition, the  $^1\text{H}$  NMR

**Table 1.** NMR spectral data for compounds **3** and **4** ( $\text{CD}_3\text{OD}$ ) ( $\delta$  in ppm,  $J$  in Hz)

	3				4			
	A		B		A		B	
	$\delta_{\text{H}}$	$\delta_{\text{C}}$	$\delta_{\text{H}}$	$\delta_{\text{C}}$	$\delta_{\text{H}}$	$\delta_{\text{C}}$	$\delta_{\text{H}}$	$\delta_{\text{C}}$
2	4.73 d 7.4	80.4 d	4.69 d 7.4	82.2 d	4.80 d 7.4	80.4 d	4.50 d 7.4	83.1 d
3	3.92 m	68.1 d	3.96 m	68.6 d	4.09 m	67.5 d	3.95 m	68.7 d
4	2.36 dd 3.6, 16.8	27.1 t	2.54 dd 3.6, 16.8	27.3 t	2.54 dd 3.6, 16.8	26.2 t	2.54 m	29.1 t
	2.61 dd 4.8, 16.8		2.68 dd 4.8, 16.8		2.56 m		2.90 dd 4.8, 16.8	
5		157.7 <sup>a</sup> s		156.9 s		157.8 s		156.7 s
5a		100.7 s		101.0 s		100.5 s		101.6 s
6	5.78 d 2.2	95.7 d	6.04 s	96.7 d	5.85 d 2.2	95.6 d		108.6 s
7		157.8 <sup>a</sup> s		155.1 s		157.8 s		154.7 s
8	5.85 d 2.2	96.3 d		108.6 a	5.88 d 2.2	96.3 d	6.03 s	96.3 d
8a		157.2 s		153.6 s		157.1 s		154.4 s
1'		132.1 s		132.7 s		131.8 s		132.2 s
2'	6.78 s	114.4 d	6.66 d 1.8	114.8 d	6.78 s	114.1 d	6.72 d 1.8	115.8 d
3'		145.8 s		145.9 s		145.7 s		146.0 s
4'		146.1 s		145.9 s		145.8 s		146.2 s
5'	6.60 s	120.1 d	6.65 d 8.2	116.1 d	6.52 s	120.4 d	6.68 d 8.0	116.3 d
6'		126.8 s	6.54 dd 1.8, 8.2	119.6 d		126.6 s	6.60 dd 1.8, 8.0	120.0 d

<sup>a</sup>Assignments may be interchanged in each column.



**Figure 2.** Significant HMBC (H→C) correlations of compounds 3–6.

spectrum of **2** showed only three signals for A-ring at  $\delta$  5.78 d,  $J=2.2$  Hz, 5.85 d,  $J=2.2$  Hz, and 6.04 s, instead of the expected four; and five signals for B-ring at  $\delta$  6.54, dd,  $J=1.8$ , 8.2 Hz, 6.65 d,  $J=8.2$  Hz, 6.60 s, 6.66 d,  $J=1.8$  Hz, and 6.78 s, instead of the expected six. All of these suggest a biphenyl type linkage between the two catechin moieties. Since one of the A-ring signals and two of the B-ring signals in the  $^1\text{H}$  NMR spectrum of **3** are singlets, we presumed that the biphenyl linkage was between position C-6' of B-ring for part A and position C-6 or C-8 of A-ring for part B. The remaining outstanding issue was whether this linkage point in A-ring was at C-6 or C-8. To resolve this question, we carefully analyzed the cross peaks in the HMBC spectrum (Fig. 2). The HMBC spectrum showed correlations between  $\delta_{\text{C}}$  153.6 and H-2 ( $\delta_{\text{H}}$  4.73);  $\delta_{\text{C}}$  153.6 and H-4 ( $\delta_{\text{H}}$  2.36 and 2.61), and  $\delta_{\text{C}}$  156.9 and H-4 ( $\delta_{\text{H}}$  2.36 and 2.61), thus establishing the signal at  $\delta$  153.6 ppm as that of C-8a, and  $\delta$  156.9 ppm as that of C-5. This 153.6 ppm carbon was not coupled to the only A-ring proton ( $\delta$  6.04 ppm), while the 156.9 ppm carbon had a cross peak with the only A-ring proton in the HMBC spectrum. So the linkage was between position C-6' of B-ring for part A and position C-8 of A-ring for part B. Thus compound **3** was assigned as catechin [6'-8]-catechin. Full assignments of

the  $^1\text{H}$  and  $^{13}\text{C}$  NMR signals of **3** were accomplished using HMBC, HMQC, and TOCSY experiments (Table 1).

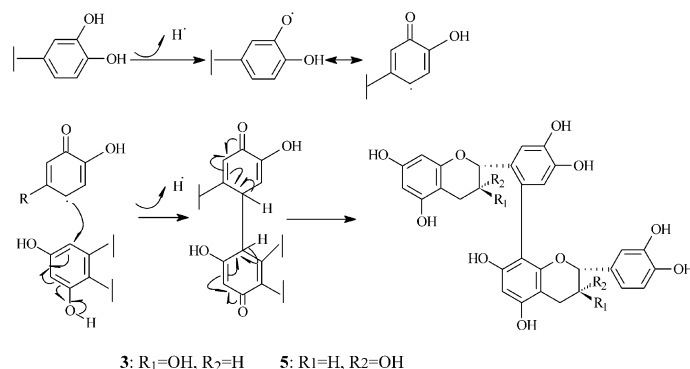
Compound **4** was isolated as a yellow amorphous solid. The negative-ion APCI-MS of **4** displayed a molecular ion peak at  $m/z$   $[\text{M}-\text{H}]^+ 577$ , supporting a molecular formula of  $\text{C}_{30}\text{H}_{26}\text{O}_{12}$ , which was the same as that of **3**. The NMR spectra of **4** displayed a signal pattern similar to that of **3**. The  $^1\text{H}$  NMR spectrum of **4** also showed three signals for A-ring at  $\delta$  5.85 d,  $J=2.2$  Hz, 5.88 d,  $J=2.2$  Hz, and 6.03 s; and five signals for B-ring at  $\delta$  6.52 s, 6.60, dd,  $J=1.8$ , 8.0 Hz, 6.68 d,  $J=8.0$  Hz, 6.72 d,  $J=1.8$  Hz, and 6.78 s. In the high field region (26–84 ppm) associated with C-ring, the  $^{13}\text{C}$  chemical shifts appeared as twin peaks of comparable intensity. The most apparent differences in the spectra of compounds **3** and **4** were at the chemical shifts of H-5' for structure part A. In the  $^1\text{H}$  NMR spectrum of **4**, the chemical shift of H-5' at B-ring for structure part A is in a higher field than those of H-5' and H-6' for structure part B, instead of in the lower field as in compound **3** (Table 1). All of this indicates that compound **4** is an isomer of **3**, the biphenyl linkage being between position C-6' of B-ring for part A and position C-6 of A-ring for part B. This was proved by the HMBC spectrum (Fig. 2). In the HMBC, it was C-8a ( $\delta$  154.4 ppm) that showed the correlation with the singlet peak ( $\delta$  6.03 s) at A-ring for part B, instead of C-5 ( $\delta$  156.7 ppm). Therefore, catechin [6'-6]-catechin was assigned to **4** (Fig. 1). Full assignments of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR signals of **4** were accomplished using HMBC, HMQC, and TOCSY experiments (Table 1).

Compounds **5** and **6** are the two major oxidation products of the reaction between (–)-epicatechin (**2**) and DPPH. They were assigned the same molecular formula of  $\text{C}_{30}\text{H}_{26}\text{O}_{12}$  determined by negative-ion APCI-MS ( $[\text{M}-\text{H}]^-$  at  $m/z$  577), as well as from their  $^{13}\text{C}$  NMR data, which was the same as those of **3** and **4**. Comparing

**Table 2.** NMR spectral data for compounds **5** and **6** ( $\text{CD}_3\text{OD}$ ) ( $\delta$  in ppm,  $J$  in Hz)

	<b>5</b>				<b>6</b>			
	A		B		A		B	
	$\delta_{\text{H}}$	$\delta_{\text{C}}$	$\delta_{\text{H}}$	$\delta_{\text{C}}$	$\delta_{\text{H}}$	$\delta_{\text{C}}$	$\delta_{\text{H}}$	$\delta_{\text{C}}$
2	4.68 brs	78.2 d	4.76 brs	79.8 d	4.75 brs	78.2 d	4.80 brs	79.8 d
3	4.01 m	66.0 d	4.18 m	67.0 d	4.21 m	66.1 d	4.22 m	67.0 d
4	2.43 dd	29.5 t	2.72 dd	29.1 t	2.46 dd	29.9 t	2.80 dd	29.4 t
	3.6, 16.8		3.6, 16.8		3.6, 16.8		3.6, 16.8	
	2.65 dd		2.88 dd		2.59 dd		2.91 dd	
	4.8, 16.8		4.8, 16.8		4.8, 16.8		4.8, 16.8	
5		158.0 <sup>a</sup> s		157.2 s		158.1 <sup>a</sup> s		157.0 s
5a		100.0 s		100.7 s		100.4 s		100.7 s
6	5.80 brs	96.2 d	6.09 s	96.3 d	5.84 brs	96.1 d		108.5 s
7		157.9 <sup>a</sup> s		155.1 s		158.0 <sup>a</sup> s		155.0 s
8	5.87 brs	96.4 d		108.3 s	5.84 brs	96.1 d	6.04 s	96.4 d
8a		157.6 s		153.8 s		157.4 s		154.0 s
1'		132.0 s		132.1 s		132.1 s		132.2 s
2'		116.2 d	6.77 d 1.8	115.2 d	7.29 s	116.0 d	6.72 d 1.8	115.2 d
3'		145.2 s		145.6 s		145.2 s		145.4 s
4'		145.5 s		145.8 s		145.7 s		145.8 s
5'	6.71 s	120.1 d	6.65 d 8.0	115.9 d	6.59 s	120.4 d	6.66 d 8.0	116.1 d
6'		125.4 s	6.59 dd	119.8 d		125.6 s	6.60 dd	119.4 d
			1.8, 8.0				1.8, 8.0	

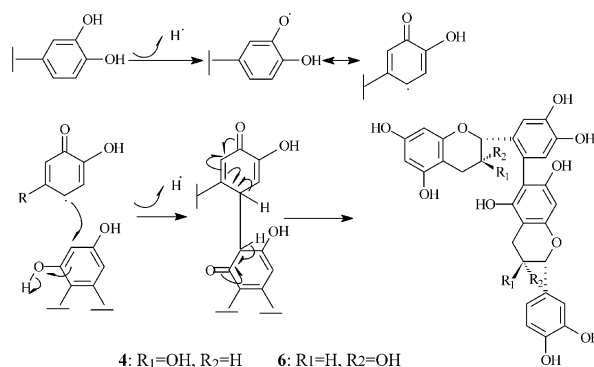
<sup>a</sup>Assignments may be interchanged in each column.



**Figure 3.** Proposed mechanism of compounds **3** and **5**.

the NMR data of these two compounds, like compounds **3** and **4**, they were also a pair of isomers. Both of them showed one singlet peak at A-ring for structure part B and two singlet peaks at B-ring for structure part A. So the biphenyl linkages for compounds **5** and **6** were also between position C-6' of B-ring for part A and position C-6 or C-8 of A-ring for part B. The HMBC spectrum of **5** showed the cross peaks between C-8a ( $\delta$  153.8 ppm) and H-2 ( $\delta$  4.76), C-8a and H-4 ( $\delta$  2.72 and 2.88 ppm), C-5 ( $\delta$  157.2 ppm) and the only singlet aromatic proton ( $\delta$  6.09 ppm) in the same A-ring (Fig. 2). The HMBC spectrum of **6**, C-8a ( $\delta$  154.0 ppm) showed a correlation with the singlet peak ( $\delta$  6.04 s) at A-ring for part B, instead of C-5 ( $\delta$  156.7 ppm). These relationships established C-8 as the point of linkage in the catechin moiety for compound **5** and C-6 for compound **6**. Thus, compound **5** was determined as epicatechin-(6'→8)-epicatechin, and epicatechin-(6'→6)-epicatechin was assigned to compound **6** (Fig. 1). Full assignments of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR signals of **5** and **6** were accomplished using HMBC, HMQC, and TOCSY experiments (Table 2).

Compound **3** corresponds to dehydrodicatechin B4 first reported by Weinges and Huthwelker<sup>25</sup> among the oxidation products of (+)-catechin obtained in the presence of peroxidase. It is difficult to differentiate between compounds **3** and **4** using only the 60 MHz proton NMR data and the MS data. Compound **3** was mentioned by Guyot and co-workers<sup>26</sup> using grape polyphenoloxidase on catechin. However, these authors could not distinguish the difference between C-6 as the point of linkage and C-8 as the point of linkage. On the other hand, compound **4** was also proposed by Guyot using the same NMR data as compound **3**, although that author preferred the structure of **3** matched with those NMR data. According to our present data, that structure should be assigned to compound **4**, instead of **3**. Compound **3** was also obtained by chemical oxidation of (+)-catechin with potassium ferricyanate.<sup>27</sup> But according to the  $^1\text{H}$  NMR data reported by Young et al.<sup>27</sup> for the methylation derivative of compound **3**, the author assigned the wrong structure. The NMR data matched with the structure of compound **4**, not **3**. So this is the first case to fully assign the structures of compounds **3** and **4**. More recently, compound **5** was reported by Foo and co-workers<sup>28</sup> from Chardonnay grape pomace. While compound **6** is a new compound.



**Figure 4.** Proposed mechanism of compounds **4** and **6**.

## Discussion

Two compounds (**3** and **4**) were isolated from the radical reaction products of catechin (**1**) and DPPH. From our elucidation of the chemical structures of these two compounds, we proposed an antioxidant mechanism of catechin as illustrated in Figures 3 and 4. As shown in Figures 3 and 4, an initial one-electron oxidation of catechin on B-ring by a DPPH radical generates a catechin phenoxyl radical. This phenoxyl radical can be tautomerised to the corresponding *o*-quinone, which was then followed by nucleophilic attack by the reactive C-8 (or C-6) carbon of another catechin unit in a Michael-type addition reaction to the quinone B-ring to form compound **3** (or **4**). Compounds **5** and **6** obtained from the reaction of epicatechin with DPPH are analogous to compounds **3** and **4**. So the proposed mechanisms for the formation of **5** and **6** are the same as that of **3** and **4**. This suggests that the configuration of position 3 for catechin and epicatechin does not affect the oxidative reaction. Both B-ring and A-ring are the principal site of antioxidant activity of catechin and epicatechin in the DPPH oxidant system.

On the basis of this work, as well as previous reports,<sup>17–21,25–27,29</sup> it can be concluded that using different oxidants can result in the formation of different oxidation products from catechins and that the main site of antioxidant action of catechins seems to not only depend on the oxidant used, but also on the structures of

catechins. The identification of oxidant-specific products may provide analytical approaches to evaluating the antioxidant actions of catechins in biological systems. Thus, it may provide a unique tool in the study of possible anticancer activity of catechins in the living system.

## Experimental

### General

$^1\text{H}$  (600 MHz),  $^{13}\text{C}$  (150 MHz) and all 2-D NMR spectra were run on Varian AM-600 NMR spectrometer, with TMS as internal standard. The APCI MS was performed on a Fisons/VG Platform II mass spectrometer. Preparative Thin-layer chromatography was performed on Sigma-Aldrich TLC plates (1000  $\mu\text{m}$  thickness, 2–25  $\mu\text{m}$  particle size), Thin-layer chromatography was performed on Sigma-Aldrich TLC plates (250  $\mu\text{m}$  thickness, 2–25  $\mu\text{m}$  particle size), with compounds visualized by spraying with 5% (v/v)  $\text{H}_2\text{SO}_4$  in ethanol solution. 1,1-diphenyl-2-picrylhydrazyl (DPPH), (+)-catechin and (–)-epicatechin were purchased from Sigma Chemical Co.  $\text{CD}_3\text{OD}$  was purchased from Aldrich Chemical Co.

### Oxidation of catechin (epicatechin) and isolation of reaction products 3 and 4 (5 and 6)

One gram catechin (0.8 g epicatechin) was reacted with 0.9 g (0.8 g) DPPH in acetone at room temp under darkness for 24 h. After evaporation of the solvent in vacuo, the residue was first applied to silica gel column eluted with chloroform to get rid of the DPPH and then subjected to Sephadex LH-20 column eluted with 95% ethanol to get the mixture of two major reaction products. The mixture of two reaction products was subjected to a preparative TLC plate eluted with ethyl acetate–methanol–water (20:1.2:0.8) solvent system to give 28 mg compound 3 and 20 mg compound 4 (20 mg compound 5 and 15 mg compound 6).

Compound 3 was isolated as a yellow amorphous substance:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 600 MHz): see Table 1;  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 150 MHz): see Table 1; negative APCI-MS  $m/z$  577  $[\text{M}-\text{H}]^-$ .

Compound 4 was isolated as a yellow amorphous substance:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 600 MHz): see Table 1;  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 150 MHz): see Table 1; negative APCI-MS  $m/z$  577  $[\text{M}-\text{H}]^-$ .

Compound 5 was isolated as a yellow amorphous substance:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 600 MHz): see Table 2;  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 150 MHz): see Table 2; negative APCI-MS  $m/z$  577  $[\text{M}-\text{H}]^-$ .

Compound 6 was isolated as a yellow amorphous substance:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 600 MHz): see Table 2;  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 150 MHz): see Table 2; negative APCI-MS  $m/z$  577  $[\text{M}-\text{H}]^-$ .

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