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[2+2] Photocycloaddition of [60]Fullerene with Podophyllotoxin Derivative Containing Cyclohexadienone Group

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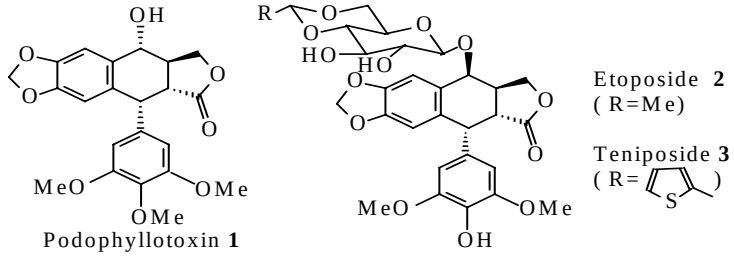
Abstract: Photochemical [2+2] cycloaddition of C_{60} with podophyllotoxin derivative containing a cyclohexadienone group in *o*-dichlorobenzene afforded an isomeric mixture of adducts and a pure adduct of C_{60}-fused podophyllotoxin derivatives. The structures of the products were characterized by MS, NMR and IR spectra.

Keywords: Podophyllotoxin, C_{60}-fused podophyllotoxin derivative, [60]fullerene, photocycloaddition.

The potential applications of fullerene derivatives make the study of the chemical, physical and biological properties of these compounds an important subject[1]. One of the most promising areas of application of fullerenes is the medicinal chemistry, namely as free radical scavengers[2,3] for the treatment of neurodegenerative diseases, as inhibitors of the HIV-1 protease[4-5] or the photodynamic therapy of neoplastic tissues[6]. On the other hand, podophyllotoxin **1** is a well-known natural product on account of its long history of use in folk medicine and the biological activity of its many derivatives[7,8]. In particular, its semisynthetic derivatives, etoposide **2** and teniposide **3**, are widely used as important anticancer drugs[9]. As a continuation of our and Guo *et al.*'s recent works in synthesis of the products of C_{60}-fused podophyllotoxin derivatives[10], herein we wish to report the results of our work on the synthesis of C_{60} with the podophyllotoxin derivative containing a cyclohexadienone group by photochemical [2+2] cycloaddition (as shown in **Scheme 1**).



Podophyllotoxin **1**

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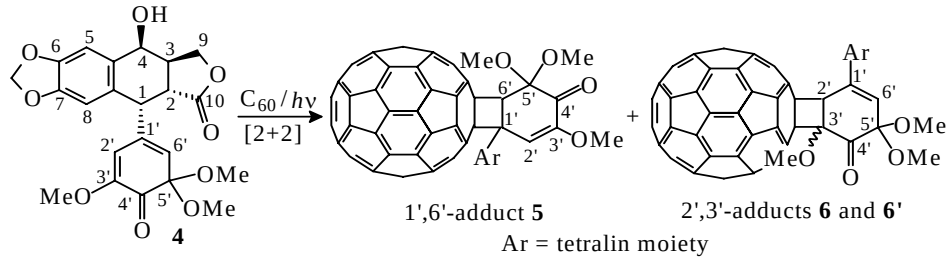
Scheme 1



Experimental

A solution of SM **4**[11] (145.5 mg, 0.34 mmol) and C_{60} (241.5 mg, 0.34 mmol) in *O*-dichlorobenzene (30 mL) was shoken under supersonic wave for 20 min to nearly desolve, then the reaction mixture was stirred and irradiated with a 450 W mercury-arc lamp for 120 min at room temperature. Purification by flash column chromatography on silica: elution with benzene afforded unreacted C_{60} (215.2 mg), then using gradient elution with C_6H_6/EtOAc afforded the pure 1′,6′-adduct **5** as a brown powder (3.0 mg, in 7.1% conversion yield) and further elution afforded a mixture of two isomers, 2′,3′-adducts **6** and **6′**, in an approx. 1.5:1.0 ratio, as a red powder (27.8 mg, in 66.2% conversion yield).

Table 1 ^{13}C-NMR spectral data[a] ($CDCl_3$, δ ppm), recorded on Bruker AV-400

Carbon	Adduct **5**	Adduct **6**	Adduct **6′**	SM**4**[11]
C-4′(C=O)	198.83	192.28	199.61	190.37
C-10(C=O)	175.76	176.16	179.09	175.33
C-6	*	*	*	149.18
C-7	*	*	*	148.59
C-3′	*	*	*	147.80
C-4a	*	*	*	137.50
C-8a	*	*	*	132.09
C-1′	55.05	130.08	129.90	129.92
C-2′	127.80	29.78	29.74	113.54
C-6′	29.79	128.80	127.80	127.71
C-5	110.42	110.50	110.05	109.86
C-8	109.43	109.33	109.01	109.22
OCH_2O	101.83	101.94	101.92	101.71
C-5′	89.41	95.92	95.92	93.07
C-9	68.53	68.23	68.11	68.02
C-4	67.13	67.13	66.23	66.23
3′-OMe	55.33	128.43	55.55	55.73
5′-OMe	51.59	50.64	54.38	50.34
	49.79	49.97	52.41	50.14
C-1	44.77	44.93	39.57	43.99
C-2	39.22	38.99	38.78	39.29
C-3	38.86	38.02	37.66	38.35
$C_{60}(SP^3)$	91.99	67.91	67.91	-
	95.97	89.78	89.78	-

[a] The data of *ca*. 50 peaks for sp^2 fullerene carbon between 130-160 ppm are not shown.
*Can not assign because of the data in the range of 130-160 ppm, in which C_{60}-sp^2 peaks occurred.

Results and Discussion

The conversion yield of 2′,3′-adducts with two stereoisomers (**6**/**6′**) is much higher than that of 1′,6′-adduct (**5,** a single product). The markedly different conversion yield between 2′,3′- and 1′,6′-adducts is reasonable for crowding of the 1′,6′-position in the molecule of dienone **4**. The molecular ion peaks at *m/z* 1150 ($C_{82}H_{22}O_9$) were found from the Maldi-TOF mass spectra (recorded on Bruker BIFLEX III) of both **5** and **6**/**6′**. The structures of the adducts were characterized by analysis of their NMR and IR spectra and by comparison with those of starting materials (SM). Each ^{13}C NMR spectrum of the adducts display *ca*. 50 resolved or partially resolved signals for sp^2 fullerene moiety carbons in the region of quaternary carbon atoms between 130 and 160 ppm, together with two signals of sp^3 bridgehead fullerene carbon at the range of 65-100 ppm. The number and chemical shifts of the fullerene moiety signals are only consistent with a closed 6,6-bridged structure for the adducts, and eliminate annulene-like open adduct structures from further consideration[12]. The remaining 22 signals belong to the dienone moiety carbon atoms, of which 5 signals (denoted as * in **Table 1**) are attributed to the quaternary carbon atoms within the area of fullerene signals. Most of them have downfield shifts compared to the starting dienone **4**, due to the electronwithdrawing influence of the carbon sphere. However, two signals of C-1′ and C-6′ for 1′,6′-aduct **5** appear at 55.05 and 29.79 ppm which are much higher fields than those of SM **4**, due to the changed hybridized orbitals from sp^2 to sp^3. Similar results can be observed from the spectrum of 2′,3′-aducts **6** and **6′**, in which the signals of C-2′ (29.78 and 29.74 ppm) and C-3′ (not shown in **Table 1**) have upfield shifts. Careful analysis of both ^{13}C and

Table 2 ^{1}H-NMR spectral data ($CDCl_3$, δ ppm), recorded on Bruker AV-300

Proton	Adduct **5**	Adduct **6**	Adduct **6'**	SM **4**[11]
H-5	6.94s	7.08s	6.78	6.84s
H-8	6.88s	6.96s	6.50s	6.60s
H-2′	6.20s	6.08d	5.95d	6.30d (*J*=1.65)
H-6′	5.46d (*J*=2.04)	5.52d	5.69d	5.08t (*J*=1.40)
OCH_2O	6.05ABq (*J*=1.21)	5.98s	6.00s	5.99ABq (*J*=1.20)
H-4	4.99d (*J*=4.27)	4.99d	4.83d	4.82d (*J*=3.20)
H-1	4.86d (*J*=2.62)	4.78d	4.68m	4.17d (*J*=5.20)
H-9	4.42m	4.66m	4.63m	4.43m
	4.50m	4.47m	4.43m	4.49m
5′-OMe	3.69s	3.54s	3.72s	3.26s
	3.64s	3.52s	3.72s	3.17s
3′-OMe	3.77s	7.36s	3.74s	3.71s
H-2	3.49m	3.37m	3.36m	3.29dd
H-3	3.43m	2.80m	2.80m	2.85m

Table 3 IR spectral data (cm^{-1}), recorded on Bruker Vector-22

Group	C_{60} (SM)	Adduct **5**	Adduct **6** / **6'**	SM **4**
C-4′ (C=O)	-	1638	1631	1685
C-10 (C=O)	-	1757	1760	1770
C_{60} moiety	1182, 1428, 527, 576	1187, 1433, 527	1189, 1433, 527	-

^{1}H NMR spectra of the mixture adducts, two sets of signals having an area ratio of *ca.* 1.5:1.0 are observed, and these are assigned to the stereoisomeric adducts **6** and **6′**, respectively, in which the methoxyl groups are located at different side of the four-membered ring. However, in the case of adduct **5**, no stereoisomer can be created although the tetralin moiety (Ar) can be located at two sides of the four-membered ring forming the same structure as **5**.

The ^{1}H NMR spectra (**Table 2**) of the adducts **5**, **6** and **6′** are similar to the starting dienone **4**. Most of the signals have a bit of downfield shifts as did in ^{13}C NMR spectra. It should be noted that the 7.36 ppm in the ^{1}H-NMR and 128.43 ppm in the ^{13}C-NMR of **6**, which are much lower field than usual, assigned to 3′-OMe in the molecule of **6** probably due to the influence of fullerene moiety to the protons of methoxyl. As shown in **Table 2**, for adduct **5**, H-1 and H-4 resonated at 4.86 (d, $J_{1,2}$ = 2.62 Hz) and 4.99 (d, $J_{3,4}$ = 4.27 Hz), respectively. Clearly, the $J_{1,2}$ and $J_{3,4}$ values of **5** are consistent with those of SM **4**[11], indicating the configurations of C-2 and C-4 remain, which are required for the anti-tumor activities. Similar *J* values in the ^{1}H NMR spectra of adducts **6**/**6′** should be presented but they are more complex due to the mixture compounds.

The IR spectra of the products show a carbonyl band of C-4′ (C=O) at 1638 cm^{-1} for adducts **5** and 1631 cm^{-1} for adduct **6/6'**, both of them are less than that of dienone **4** at 1685 cm^{-1} due to the less conjugation of the adducts. Moreover, three characteristic bands were found in the spectra of each adducts (**Table 3**), which assigned to the vibrations of C_{60} moiety.

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