A CONVENIENT, ONE-POT SYNTHESIS OF AZULENES HAVING VERSATILE FUNCTIONAL GROUPS BY THE REACTION OF 2*H*-CYCLOHEPTA[*b*]FURAN-2-ONES WITH FURAN DERIVATIVES[1]

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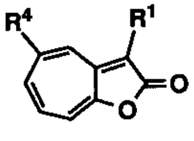
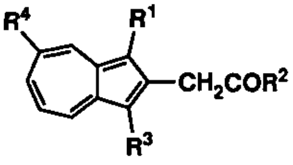
Abstract - 2-Acylmethyl- and 2-methoxycarbonylmethylazulene derivatives having versatile functional groups in the side chain, are synthesized in one-pot by the reaction of 2*H*-cyclohepta[*b*]furan-2-ones with furans on heating at 160-190 °C in aprotic solvent.

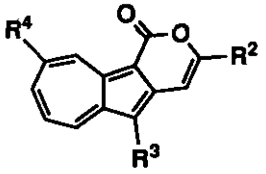
We recently reported[2] that variously functionalized azulene derivatives were synthesized in one-pot by the reaction of 2*H*-cyclohepta[*b*]furan-2-ones (**1** and **2**) with vinyl ether derivatives. This new method was further widened by the use of orthoesters and acetals of some aldehydes and ketones as reagents.[3,4]



1a-d: R^4=H
2a-d: R^4=iPr



3a-i: R^4=H
4a-g: R^4=iPr



5a-c: R^4=H
6a-c: R^4=iPr

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In this communication we wish to report another convenient method to prepare azulenes (**3** and **4**) having a versatile acylmethyl or methoxycarbonylmethyl group on C-2 and azulenes (**5** and **6**) with an annulated δ-lactone ring in one-pot by the application of the above azulene synthesis using some furans (**7a-d**) and 2,5-dihydro-2,5-dimethoxyfuran (**8**), as a precursor of 2-methoxyfuran (**7d**). Furylaldehyde and

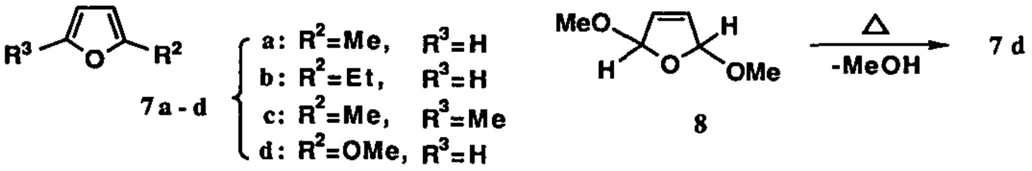


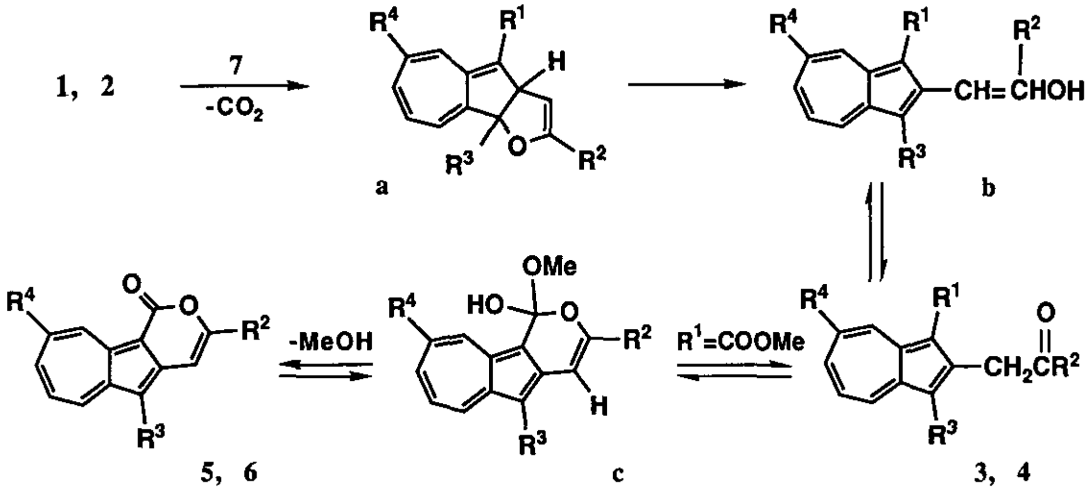
Table 1. Synthesis of Azulene Derivatives by the Reaction of **1** and **2** with **7** and **8**.

Reagent		Azulene Derivatives	R^1	R^2	R^3	Color /	Form	mp (°C)	Yield (%)
1a	**7a**	**3a**[7]	COOMe	Me	H	reddish violet	needles	76-77	25
		5a[18]	-----	Me	H	reddish violet	needles	149-150	47
1d	**7a**	**3b**[8]	CN	Me	H	violet	oil	---	36
1a	**7b**	**3c**	COOMe	Et	H	reddish violet	oil	---	14
		5b	-----	Et	H	reddish violet	needles	68-70	10
1a	**7c**	**3d**[9]	COOMe	Me	Me	violet	oil	---	15
		5c[19]	-----	Me	Me	reddish violet	needles	143-144	63
1c	**7c**	**3e**[10]	CN	Me	Me	violet	prisums	100-101	55
1a	**7d**	**3f**[11]	COOMe	OMe	H	violet	needles	71-72	58
1a	**8**	**3f**	COOMe	OMe	H	violet	needles	71-72	60
1b	**8**	**3g**[12]	COMe	OMe	H	reddish violet	oil	---	70
1d	**8**	**3h**[13]	CN	OMe	H	reddish violet	needles	91-92	41
2a	**7a**	**4a**	COOMe	Me	H	violet	oil	---	15
		6a[20]	-----	Me	H	reddish violet	oil	---	35
2d	**7a**	**4b**[14]	CN	Me	H	violet	oil	---	30
2a	**7b**	**4c**	COOMe	Et	H	violet	oil	---	15
		6b	-----	Et	H	reddish violet	oil	---	10
2d	**7b**	**4d**[15]	CN	Et	H	violet	oil	---	25
2a	**7c**	**4e**	COOMe	Me	Me	violet	oil	---	8
		6c[21]	-----	Me	Me	violet	needles	178-180	90
2c	**7c**	**4f**[16]	CN	Me	Me	violet	prisums	82-83	46
2a	**8**	**4g**	COOMe	OMe	H	reddish violet	oil	---	79
2b	**8**	**4h**[17]	COMe	OMe	H	reddish violet	oil	---	66

its dimethyl acetal did not react with **1** or **2** under the similar conditions.

Thus, 2*H*-cyclohepta[*b*]furan-2-ones (**1a-d** and **2a-d**) having various functional groups (a: R^1= COOMe, b: R^1=COMe, c: R^1=CN, d: R^1=$CONH_2$) on C-3 were heated *with 3-6 equivalents of furans* (**7a-d** *and* **8**) *at* 160-190 °C in toluene or THF in a sealed Pyrex tube for 20-100 h. After removal of the unreacted reagents and solvent in vacuo, azulenes formed were easily separated by silica gel column chromatography (benzene or 1: 50 MeOH-benzene as an eluent). The reaction of **1** and **2** with furans (**7a-c**) gave 2-acylmethylazulene derivatives (**3** and **4**) and δ-lactone-annulated azulenes (**5** and **6**). With furans (**7d** and **8**), the above reaction gave methoxycarbonylazulene derivatives (**3** and **4**) but no **5** and **6**. Compounds (**3** and **4**) gave **5** and **6**, respectively in nearly quantitative yields upon heating at 160 °C for 20 h in toluene. Alcoholysis of **5** and **6** with NaOMe in MeOH gave **3** and **4**, respectively as main product together with their hydrolyzed compounds.

The structures of these azulene derivatives were established on the basis of the ^{1}H nmr (see References) and other spectral data. The structures, properties, and yields of azulenes obtained by this method are shown in Table 1. The formation mechanism of the present azulenes (**3** and **4**) is believed to involve the [8+2] cycloadducts **a** (Scheme 1) between cyclohepta[*b*]furanones (**1** and **2**) and α,β-unsaturated ethers, similar to that proposed in a previous paper.[2] Then, the δ-lactone-annulated azulenes (**5** and **6**) were presumed to be derived by elimination of methanol from the intermediate **c**.



Scheme 1

Similarly, the reaction of 8-methoxycyclohepta[*b*]furan-2-ones (**9a-c**)[5,6] with **8** afforded 8-methoxyazulenes (**10a-d**) having methoxycarbonylmethyl group at the C-2 position. Product yields and structures of these 8-methoxyazulenes are summarized in Table 2.

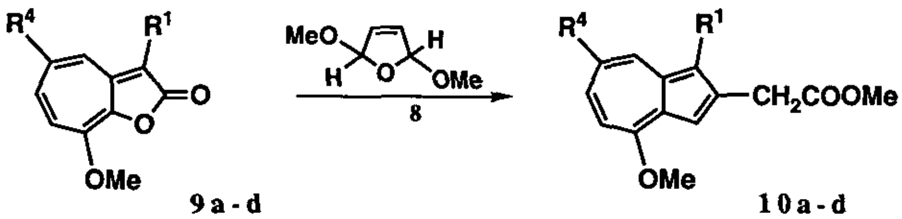


Table 2. Synthesis of Azulene Derivatives by the Reaction of **9** with **8**.

Reagent		Azulene Derivatives			Color / Form		mp	Yield
			R^1	R^4			(°C)	(%)
9a	**8**	**10a**[22]	COOMe	H	reddish violet	needles	189-191	45
9b	**8**	**10b**[23]	COMe	H	reddish violet	oil	---	48
9c	**8**	**10c**	CN	H	reddish violet	oil	---	62
9d	**8**	**10d**[24]	CN	ipr	reddish violet	oil	---	70

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7) **3a**: ^{1}H Nmr (270 MHz, $CDCl_3$) δ 2.24 (3H, s, CH_3), 3.95 (3H, s, OCH_3), 4.33 (2H, s, CH_2), 7.18 (1H, s, H-3), 7.46 (1H, t, J=10 Hz, H-5), 7.56 (1H, t, J=10 Hz, H-7), 7.78 (1H, t, J=10 Hz, H-6), 8.38 (1H, d, J=10 Hz, H-4), 9.55 (1H, d, J=10 Hz, H-8).
8) **3b**: ^{1}H Nmr (200 MHz, $CDCl_3$) δ 2.31 (3H, s, CH_3), 4.21 (2H, s, CH_2), 7.26 (1H, s, H-3), 7.50 (1H, d, J=9.8 Hz, H-5), 7.53 (1H, t, J=9.8 Hz, H-7), 7.83 (1H, t, J=9.8 Hz, H-6), 8.39 (1H, d, J=9.8 Hz, H-4), and 8.57 (1H, d, J=9.8 Hz, H-8); ^{13}C nmr (50.2 MHz, $CDCl_3$) δ 30.3 (q), 44.9 (t), 97.8 (s), 116.9 (s), 118.8 (d), 127.6 (d), 128.1 (d), 135.8 (d), 138.3 (d), 139.5 (d), 142.5 (s), 143.7 (s), 147.8 (s), and 203.9 (s).

9) **3d**: ^{1}H Nmr (270 MHz, CDCl$_3$) δ 2.22 (3H, s, CH$_3$), 2.52 (3H, s, CH$_3$), 3.94 (3H, s, OCH$_3$), 4.36 (2H, s, CH$_2$), 7.41 (1H, t, J=9.6 Hz, H-5), 7.47 (1H, t, J=9.6 Hz, H-7), 7.72 (1H, t, J=9.6 Hz, H-6), 8.36 (1H, d, J=9.6 Hz, H-4), 9.48 (1H, d, J=9.6 Hz, H-8); ^{13}C nmr (67.8 MHz, CDCl$_3$) δ 10.4, 29.9, 44.3, 50.9, 113.9, 125.6, 126.0, 127.3, 134.3, 136.7, 138.2, 140.4, 141.0, 147.1, 166.2, and 205.8.

10) **3e**: ^{1}H Nmr (300 MHz, CDCl$_3$) δ 2.25 (3H, s, COCH$_3$), 2.47 (3H, s, 3-Me), 4.16 (2H, s, CH$_2$), 7.41 (2H, t, J=10 Hz, H-5,7), 7.74 (1H, t, J=10 Hz, H-6), 8.30 (1H, d, J=10 Hz, H-4), and 8.47 (1H, d, J=10 Hz, H-8); ^{13}C nmr (50.2 MHz, CDCl$_3$) δ 10.6 (q), 30.1 (q), 43.9 (t), 97.0 (s), 117.3 (s), 118.8 (d), 125.7 (s), 126.8 (d), 135.3 (d), 135.5 (d), 139.3 (d), 143.2 (s), 147.8(s), 146.0 (s), and 203.5 (s).

11) **3f**: ^{1}H Nmr (270 MHz, CDCl$_3$) δ 3.73 (3H, s, CH$_3$), 3.94 (3H, s, CH$_3$), 4.27 (2H, br, CH$_2$), 7.24 (1H, br, H-3), 7.45 (1H, t, J=9.6 Hz, H-5), 7.56 (1H, t, J=9.6 Hz, H-7), 7.77 (1H, t, J=9.6 Hz, H-6), 8.38 (1H, d, J=9.6 Hz, H-4), and 9.58 (1H, d, J=9.6 Hz, H-8); ^{13}C nmr (67.8 MHz, CDCl$_3$) δ 37.3, 50.9, 52.0, 120.1, 127.3, 128.0, 137.4, 137.5, 138.5, 141.8, 143.1, 147.7, 166.0, and 171.9.

12) **3g**: ^{1}H Nmr (300 MHz, CDCl$_3$) δ 2.71 (3H, s, COCH$_3$), 3.70 (3H, s, CO$_2$CH$_3$), 4.20 (2H, s, CH$_2$), 7.18 (1H, s, H-3), 7.34 (1H, t, J=10 Hz, H-5), 7.39 (1H, t, J=10 Hz, H-7), 7.67 (1H, t, J=10 Hz, H-6), 8.29 (1H, d, J=10 Hz, H-4), and 9.07 (1H, d, J=10 Hz, H-8); ^{13}C nmr (75.5 MHz, CDCl$_3$) δ 31.9 (q), 37.1 (t), 51.9 (q), 120.7 (d), 125.7 (s), 127.3 (d), 127.7 (d), 136.4 (d), 137.4 (d), 138.3 (d), 140.2 (s), 142.7 (s), 146.8 (s), 171.4 (s), and 195.9 (s).

13) **3h**: ^{1}H Nmr (200 MHz, CDCl$_3$) δ 3.77 (3H, s, CO$_2$CH$_3$), 4.14 (2H, s, CH$_2$), 7.32 (1H, s, H-3), 7.49 (1H, t, J=10 Hz, H-5), 7.52 (1H, t, J=10 Hz, H-7), 7.82 (1H, t, J=10 Hz, H-6), 8.39 (1H, d, J=10 Hz, H-4), and 8.56 (1H, d, J=10 Hz, H-8); ^{13}C nmr (50.2 MHz, CDCl$_3$) δ 35.5 (t), 52.5 (q), 97.7 (s), 116.6 (s), 118.5 (d), 127.5 (d), 128.0 (d), 135.9 (d), 138.3 (d), 139.4 (d), 142.3 (s), 143.6 (s), 147.2 (s), and 170.3 (s).

14) **4b**: ^{1}H Nmr (300 MHz, CDCl$_3$) δ 1.39 (6H, d, J=6.9 Hz, CH(C$\underline{H}_3$)$_2$), 2.27 (3H, s, COCH$_3$), 3.19 (1H, m, J=6.9 Hz, C$\underline{H}$(CH$_3$)$_2$), 4.16 (2H, s, CH$_2$), 7.13 (1H, s, H-3), 7.44 (1H, d, J=10 Hz, H-5), 7.75 (1H, dd, J=10 and 1.8 Hz, H-6), 8.26 (1H, d, J=10 Hz, H-4), and 8.51 (1H, d, J=1.8 Hz, H-8); ^{13}C nmr (75.5 MHz, CDCl$_3$) δ 24.4 (q), 30.0 (q), 38.7 (d), 44.8 (t), 96.6 (s), 117.1 (s), 117.4 (d), 127.8 (d), 135.5 (d), 136.4 (d), 138.2 (d), 142.2 (s), 143.5 (s), 147.7 (s), 148.7 (s), and 203.7 (s).

15) **4d**: ^{1}H Nmr (200 MHz, CDCl$_3$) δ 1.09 (3H, t, J=7.2 Hz, CH$_2$C$\underline{H}_3$), 1.40 (6H, d, J=6.9 Hz, CH(C$\underline{H}_3$)$_2$), 2.62 (2H, q, J=7.2 Hz, C$\underline{H}_2$CH$_3$), 3.20 (1H, m, J=6.9 Hz, C$\underline{H}$(CH$_3$)$_2$), 4.17 (2H, s, CH$_2$), 7.15 (1H, s, H-3), 7.45 (1H, t, J=10 Hz, H-5), 7.76 (1H, dd, J=10 and 1.8 Hz, H-6), 8.28 (1H, d, J=10 Hz, H-4), and 8.52 (1H, d, J=1.6 Hz, H-8); ^{13}C nmr (75.5 MHz, CDCl$_3$) δ 7.9 (q), 24.6 (q), 36.3 (t), 38.9 (d), 43.9 (t), 96.7 (s), 117.4 (s), 117.6 (d), 127.8 (d), 135.6 (d), 136.5 (d), 138.3 (d), 142.4 (s), 143.7 (s), 148.2 (s), 148.8 (s), and 206.8 (s).

16) **4f**: ^{1}H Nmr (300 MHz, CDCl$_3$) δ 1.36 (6H, d, J=6.9 Hz, CH(C$\underline{H}_3$)$_2$), 2.23 (3H, s, COCH$_3$), 2.42 (3H, s, 3-CH$_3$), 3.14 (1H, m, J=6.9 Hz, C$\underline{H}$(CH$_3$)$_2$), 4.13 (2H, s, CH$_2$), 7.37 (1H, t, J=10 Hz, H-5), 7.68 (1H, dd, J=10 and 1.8 Hz, H-6), 8.19 (1H, d, J=10 Hz, H-4), and 8.43 (1H, d, J=1.8 Hz, H-8); ^{13}C nmr (75.5 MHz, CDCl$_3$) δ 10.2 (q), 24.3 (q), 29.8 (q), 38.5 (d), 43.8 (t), 95.6 (s), 117.4 (s), 124.2 (s), 126.3 (d), 133.6 (d), 135.0 (d), 137.9 (d), 139.4 (s), 142.9 (s), 145.7 (s), 147.7 (s), and 203.4 (s).

17) **4h**: ^{1}H Nmr (200 MHz, $CDCl_3$) δ 1.39 (6H, d, J=6.9 Hz, $CH(C\underline{H}_3)_2$), 2.71 (3H, s, $COCH_3$), 3.17 (1H, m, J=6.9 Hz, $C\underline{H}(CH_3)_2$), 3.73 (3H, s, CO_2CH_3), 4.22 (2H, s, CH_2), 7.12 (1H, s, H-3), 7.36 (1H, t, J=10 Hz, H-5), 7.68 (1H, dd, J=10 and 1.6 Hz, H-6), 8.23 (1H, d, J=10 Hz, H-4), and 9.26 (1H, d, J=1.6 Hz, H-8); ^{13}C nmr (50.2 MHz, $CDCl_3$) δ 24.7 (q), 32.2 (q), 37.4 (t), 39.4 (d), 52.1 (q), 119.8 (d), 124.9 (s), 127.4 (d), 135.9 (d), 136.7 (d), 137.9 (d), 140.6 (s), 142.8 (s), 147.0 (s), 149.0 (s), 176.6 (s), and 195.8 (s).

18) **5a**: ^{1}H Nmr (270 MHz, $CDCl_3$) δ 2.42 (3H, d, J=0.7 Hz, CH_3), 6.60 (1H, m, J=0.7 Hz, H-4), 7.12 (1H, s, H-5), 7.51 (1H, t, J=10 Hz, H-7); 7.64 (1H, t, J=10 Hz, H-9), 7.74 (1H, t, J=10 Hz, H-8), 8.38 (1H, d, J=10 Hz, H-6), and 9.47 (1H, d, J=10 Hz, H-10); ^{13}C nmr (67.8 MHz, $CDCl_3$) δ 20.5, 96.1, 101.3, 111.1, 128.6, 129.8, 135.5, 136.6, 137.5, 141.6, 146.2, 149.8, and 159.4.

19) **5c**: ^{1}H Nmr (270 MHz, $CDCl_3$) δ 2.44 (3H, br, CH_3), 2.58 (3H, s, CH_3), 6.62 (1H, m, H-4), 7.46 (1H, t, J=10 Hz, H-7), 7.56 (1H, t, J=10 Hz, H-9), 7.68 (1H, t, J=10 Hz, H-8), 8.29 (1H, d, J=10.3 Hz, H-6), and 9.40 (1H, dd, J=9.1 and 1 Hz, H-10); ^{13}C nmr (67.8 MHz, $CDCl_3$) δ 9.7 (q), 20.6 (q), 99.7 (d), 105.4 (s), 118.2(s), 127.1 (d), 129.0 (d), 133.4 (d), 134.3 (d), 136.9 (d), 141.3 (s), 142.1 (s), 148.9(s), 158.9 (s), and 160.5 (s).

20) **6a**: ^{1}H Nmr (270 MHz, $CDCl_3$) δ 1.44 (6H, d, J=7.0 Hz, $CH(C\underline{H}_3)_2$), 2.41 (3H, m, J=1.1 Hz, CH_3), 3.28 (1H, m, J=7.0 Hz, $C\underline{H}(CH_3)_2$), 6.57 (1H, d, J=1.1 Hz, H-4), 7.02 (1H, s, H-5), 7.46 (1H, t, J=10 Hz, H-7), 7.68 (1H, dd, J=10 and 2 Hz, H-8), 8.26 (1H, d, J=10 Hz, H-6), and 9.52 (1H, d, J=2 Hz, H-8).

21) **6c**: ^{1}H Nmr (270 MHz, $CDCl_3$) δ 1.42 (6H, d, J=7.0 Hz, $CH(C\underline{H}_3)_2$), 2.43 (3H, d, J=0.8 Hz, CH_3), 2.53 (3H, s, CH_3), 3.25 (1H, m, J=7.0 Hz, $C\underline{H}(CH_3)_2$), 6.58 (1H, q, J=0.8 Hz, H-4), 7.40 (1H, t, J=10.0 Hz, H-7), 7.62 (1H, ddd, J=10.0, 1.8, and 0.7 Hz, H-8), 8.16 (1H, dd, J=10.0 and 0.7 Hz, H-6), and 9.44 (1H, d, J=1.8 Hz, H-8).

22) **10a**: ^{1}H Nmr (300 MHz, $CDCl_3$) δ 3.72 (3H, s, CO_2CH_3), 3.87 (3H, s, CO_2CH_3), 4.10 (2H, s, CH_2), 4.18 (3H, s, OCH_3), 7.10 (1H, d, J=10.8 Hz, H-5), 7.25 (1H, t, J=10 Hz, H-7), 7.37 (1H, s, H-3), 7.65 (1H, t, J=10 Hz, H-6), and 9.50 (1H, d, J=10 Hz, H-8); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 37.3 (t), 50.6 (q), 51.8 (q), 56.5 (q), 111.1 (d), 114.5 (s), 116.2 (d), 123.0 (d), 131.3 (s), 136.9 (d), 138.3 (d), 141.5 (s), 143.9 (s), 163.2 (s), 166.1 (s), and 172.1 (s).

23) **10b**: ^{1}H Nmr (300 MHz, $CDCl_3$) δ 2.70 (3H, s, $COCH_3$), 3.71 (3H, s, CO_2CH_3),4.12 (2H, s, CH_2), 4.17 (3H, s, OCH_3), 7.11 (1H, d, J=10.8 Hz, H-5), 7.25 (1H, t, J=10 Hz, H-7), 7.40 (1H, s, H-3), 7.66 (1H, t, J=10 Hz, H-6), and 9.13 (1H, d, J=10 Hz, H-8); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 32.0 (q), 37.2 (t), 52.1 (q), 56.6 (q), 111.2 (d), 116.7 (d), 123.0 (d), 126.1 (s), 131.0 (s), 137.0 (d), 138.0 (d), 138.8 (s), 142.6 (s), 163.4 (s), 171.7 (s), and 196.3 (s).

24) **10d**: ^{1}H Nmr (300 MHz, $CDCl_3$) δ 1.34 (6H, d, J=6.9 Hz, $CH(C\underline{H}_3)_2$), 3.11 (1H, m, J=6.9 Hz, $C\underline{H}(CH_3)_2$), 3.72 (3H, s, CO_2CH_3), 4.03 (2H, s, CH_2), 4.13 (3H, s, OCH_3), 7.13 (1H, d, J=11.4 Hz, H-5), 7.33 (1H, s, H-3), 7.69 (1H, dd, J=11.4 and 1.8 Hz, H-6), and 8.41 (1H, d, J=1.8 Hz, H-8); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ 24.4 (q), 35.4 (t), 38.1 (d), 52.2 (q), 56.5 (q), 96.7 (s), 111.6 (d), 113.5 (d), 117.5 (s), 130.1 (s), 135.9 (d), 137.4 (d), 141.4 (s), 143.1 (s), 143.3 (s), 162.6 (s), and 170.6 (s).

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