Preparation of Isopropylidenebenzocyclobutenes *via* the Photochemical Cyclization of 1-(*o*-Alkylaryl)-3-hydroxy-2,2-dimethylalkan-1-ones

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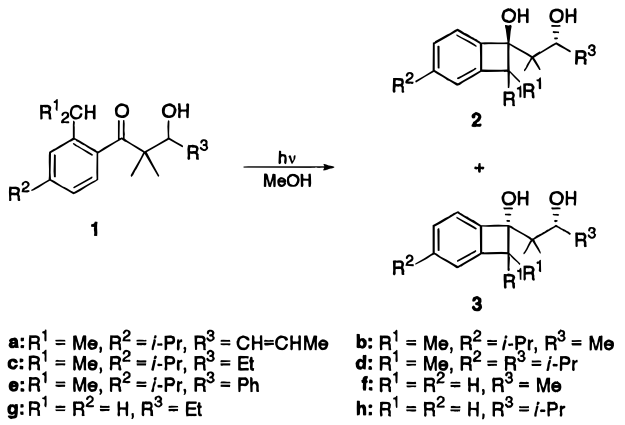
Photochemical cyclization of *o*-alkylaryl ketones to give benzocyclobutenols has been extensively investigated.[2] Some benzocyclobutenols are quite unstable and revert to the starting ketones even at ambient temperature.[3] We have previously reported that irradiation of 1-(*o*-methylaryl)-2,2-dimethylalkane-1,3-diones gave benzocyclobutenols which underwent thermal retro-aldol reaction at 150−180 °C to give benzocyclobutenones rather than C(1)−C(2) bond cleavage to revert to the starting diketones.[4] We report here that the benzocyclobutenols **2** and **3** obtained by the irradiation of 1-(*o*-alkylaryl)-3-hydroxy-2,2-dimethylalkan-1-ones **1** underwent acid-catalyzed reaction to give isopropylidenebenzocyclobutenes **4**.

Results and Discussion

We have previously reported that 1-aryl-2,2-dimethylalkane-1,3-diones with a methyl or ethyl group on an *ortho* position of the aromatic ring underwent photocyclization to give benzocyclobutenols, but those with an isopropyl group underwent no photoreaction.[4b] However, when a methanol solution of the 1-aryl-3-hydroxy-2,2-dimethylalkan-1-one with an *ortho*-isopropyl group (**1a**) was irradiated with a high-pressure mercury lamp through a Pyrex filter, two isomeric benzocyclobutenols **2a** and **3a** were obtained in 22 and 31% yields, respectively, at 60% conversion, though the rate of reaction was so slow as to necessitate long period irradiation. Compounds **2a** and **3a** were stereoisomers with respect to the two hydroxy groups and could be separated by repeated column chromatography. The ^{1}H NMR spectra of **2a** and **3a** showed four singlets due to four methyl groups at δ 0.77, 1.25, 1.39, and 1.61 for **2a** and δ 0.77, 1.13, 1.34, and 1.60 for **3a**. The two hydroxy groups of **2a** appeared at δ 3.25 and 3.69 as broad singlets, and those of **3a** appeared at δ 3.7−4.0. However, the configurations of **2a** and **3a** could not be assigned on the basis of their spectral data. The configuration of **2a** was determined by X-ray crystallographic analysis,[5] so the configurations of **2a** and **3a** were assigned as depicted in Scheme 1. The hydroxyketones **1b**−**e** also underwent photocyclization

Scheme 1



a: R^1 = Me, R^2 = *i*-Pr, R^3 = CH=CHMe **b:** R^1 = Me, R^2 = *i*-Pr, R^3 = Me
c: R^1 = Me, R^2 = *i*-Pr, R^3 = Et **d:** R^1 = Me, R^2 = R^3 = *i*-Pr
e: R^1 = Me, R^2 = *i*-Pr, R^3 = Ph **f:** R^1 = R^2 = H, R^3 = Me
g: R^1 = R^2 = H, R^3 = Et **h:** R^1 = R^2 = H, R^3 = *i*-Pr

Table 1. Photolysis of 1 in Methanol

			yield (%)[b]	
ketone	time (h)[a]	conv (%)	**2**	**3**
1a	24	60	22	31
1b	24	66	34	27
1c	24	48	35	2
1d	24	43	37	19
1e	24	62	25	37
1f	7.5	66	38	13
1g	15	78	28	19
1h	15	79	14	3

[a] A solution of the ketone (600 mg) in methanol (160 mL) was irradiated with a 100 W high-pressure mercury lamp through a Pyrex filter. [b] Based on converted starting material.

to give **2b**−**e** and **3b**−**e** under the same conditions. The configurations of **2b**−**e** and **3b**−**e** could not be assigned by comparison of their spectroscopic data with those of **2a** and **3a**. In this paper, the configurations of **2b**−**e** and **3b**−**e** were tentatively assigned by comparison of their chromatographic behavior with those of **2a** and **3a**. R_f values on a silica gel thin layer plate were higher in **2b**−**e** than in **3b**−**e**. The compound **2a** had higher R_f value than **3a**, so a similar relation would be expected for **2b**−**e** and **3b**−**e**. The photocyclization of hydroxy ketones **1f**−**h** which had an *ortho* methyl group to give **2f**−**h** and **3f**−**h** took place more rapidly than that of **1a**−**e**[6] under the same conditions. The C(2′)-methyl groups in **2a**−**e** and **3a**−**e** interact severely with the hydroxyalkyl group on C(1′). Therefore, the intermediate diradical from **1a**−**e** would prefer reversion to the starting ketone to cyclization to give the benzocyclobutenol. The lower photoreactivity of *o*-isopropyl substituted hydroxy ketones **1a**−**e** than that of *o*-methyl substituted hydroxy ketones **1f**−**g** is probably due to this steric interaction. Results of the photolysis of 1-(*o*-alkylaryl)-3-hydroxy-2,2-dimethylalkan-1-ones **1a**−**h** are given in Table 1.

When a benzene solution of the benzocyclobutenol **2f** in the presence of a catalytic amount of *p*-toluenesulfonic acid was heated under reflux for 6 h, isopropylidenebenzocyclobutene **4c** and the acetal **5c** were obtained in 52 and 48% yields, respectively (Scheme 2). Treatment of the benzocyclobutenol **3f** under the same conditions gave **4c** and the acetal **6c** in 50 and 50% yields, respectively. The ^{1}H NMR spectrum of **4c** was identical with reported

(1) (a) Saitama University. (b) Tokyo Gakugei University.
(2) Sammes, P. G. *Tetrahedron* **1976**, *32*, 405. Scaiano, J. C. *Acc. Chem. Res.* **1982**, *15*, 252.
(3) Arnold, B. J.; Sammes, P. G.; Wallace, T. W. *J. Chem. Soc., Perkin Trans. 1* **1974**, 409.
(4) (a) Yoshioka, M.; Nishizawa, K.; Arai, M.; Hasegawa, T. *J. Chem. Soc., Perkin Trans. 1* **1991**, 541. (b)Yoshioka, M.; Momose, S.; Nishizawa, K.; Hasegawa, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 499.
(5) Supporting Information contains the ORTEP diagram for compound **2a**.
(6) Two isomeric cyclopropane-1,2-diols were also yielded by the irradiation of **1h** through β-hydrogen abstraction. Yoshioka, M.; Miyazoe, S.; Hasegawa, T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2781.

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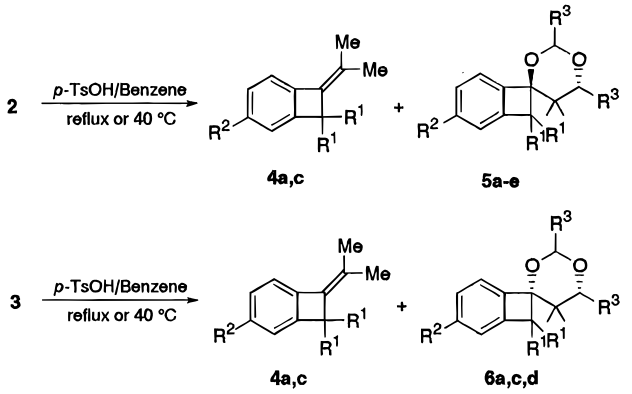
Scheme 2



a: R^1 = Me, R^2 = *i*-Pr, R^3 = Me **b:** R^1 = Me, R^2 = *i*-Pr, R^3 = Et
c: $R^1 = R^2$ = H, R^3 = Me **d:** $R^1 = R^2$ = H, R^3 = Et
e: $R^1 = R^2$ = H, R^3 = *i*-Pr

Table 2. *p*-Toluenesulfonic Acid-Catalyzed Reaction of 2 and 3 in Benzene

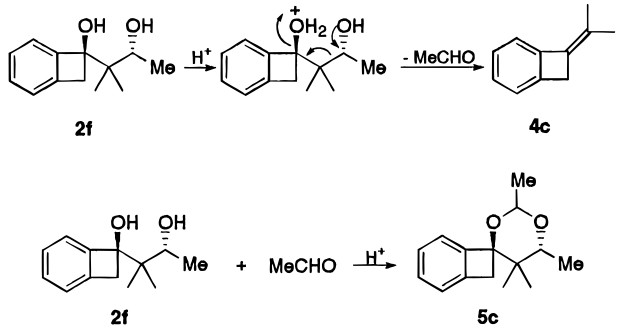
			yield (%)		
compd	temp (°C)	time (h)	**4**	**5**	**6**
2a	40	1	77		
3a	40	1	7		
2b	40	1	62	27	
3b	40	1	70		26
2c	40	1	78	7	
3c	40	1	82		
2d + **3d**[a]	40	1	77		
2e	40	1	97		
3e	40	1	9		
2f	reflux	6	52	48	
3f	reflux	6	50		50
2g	reflux	6	50	50	
3g	reflux	6	51		49
2h	reflux	1. 5	54	44	

[a] 2:1 mixture of **2d** and **3d**.

data.[7] The ^{1}H NMR spectrum of **5c** showed an AB-quartet at δ 2.98 and 3.39 (J = 14 Hz) due to methylene protons of the four-membered ring and two singlets (δ 0.56 and 1.14) and two doublets (δ 1.18 and 1.35) due to four methyl groups. The ^{1}H NMR spectrum of **6c** showed an AB-quartet at δ 3.11 and 3.47, two singlets at δ 0.62 and 1.28, and two doublets at δ 1.18 and 1.38. Treatment of benzocyclobutenols **2g,h** under the same conditions also gave isopropylidenebenzocyclobutene **4c** and acetals **5d,e**, and that of the benzocyclobutenol **3g** gave **4c** and the acetal **6d**. Treatment of 2,2-dimethylbenzocyclobutenols **2a**−**e** and their isomers **3a**−**e** under the same conditions, but at 40 °C, gave the 1-isopropylidene-2,2-dimethylbenzocyclobutene **4a** in high yield. Results of the acid-catalyzed reaction of **2** and **3** are given in Table 2. The benzocyclobutenols **2a**−**e** and **3a**−**e** have two methyl groups on C(2′) which interact with C(1′) substituents. This interaction would cause the acid-catalyzed reaction of **2a**−**e** and **3a**−**e** at lower temperature than that of **2f**−**h** and **3f,g**. The ^{1}H NMR spectrum of **4a** showed three singlets at δ 1.47, 1.77, and 1.90 due to C(2) methyl groups and two isopropylidene methyl groups. The formation of **4** can be explained by initial protonation at a C(1′) hydroxy oxygen of **2** or **3**. The protonated species from **2** or **3** would undergo dehydrative cleavage to form **4**. The aldehydes generated in this

(7) Frimer, A. A.; Weiss, J.; Gottlieb, H. E.; Wolk, J. L. *J. Org. Chem.* **1994**, *59*, 780.

Scheme 3



reaction course would react with **2** and **3** to form **5** and **6** (Scheme 3). The acid-catalyzed reaction of **2f,g** and **3f,g** gave acetals **5c,d** and **6c,d** in equal yield to isopropylidenebenzocyclobutene **4c**, but that of **2a,d,e** and **3a,c**−**e** gave only the 1-isopropylidene-2,2-dimethylbenzocyclobutene **4a**. This result indicates that **2f,g** and **3f,g** react rapidly with the aldehyde, and that the reaction of **2a,d,e** and **3a,c**−**e** with the aldehyde is slow probably owing to steric factors.

A number of methods for the preparation of alkylidenebenzocyclobutenes have been reported; methods include a Grignard reaction of benzocyclobutenones with alkylmagnesium bromide followed by dehydration,[7,8] a reaction of 1,2-bis(triphenylphosphonio)benzocyclobutene dibromide with base and aldehydes,[9] and a reaction of benzyne with allenes.[10] However, alkylidenebenzocyclobutenes with 2,2-dimethyl groups have not yet been reported. The photocyclization of 1-(*o*-alkylaryl)-3-hydroxyalkan-1-ones followed by acid-catalyzed reaction of the resulting benzocyclobutenols is a new route for the preparation of alkylidenebenzocyclobutenes, especially those with 2,2-dimethyl groups.

Experimental Section

Melting points were uncorrected and boiling points were measured from the oven temperatures in Kugelrohr distillation. ^{1}H NMR spectra were recorded at 200, 300, or 400 MHz using tetramethylsilane as an internal standard with $CDCl_3$ as solvent. ^{13}C NMR spectra were recorded at 50, 75, or 100 MHz with $CDCl_3$ as solvent. IR spectra were recorded for solutions in CCl_4 unless otherwise stated. A 100 W high-pressure mercury lamp was used as an irradiation source. The starting compounds **1** were prepared by the condensation of aryl ketone with the aldehyde according to previous described methods.[4b]

General Procedure for Photolysis of Hydroxy Ketones 1. A solution of 600 mg of **1** in 160 mL of methanol was irradiated with a high-pressure mercury lamp through a Pyrex filter under argon for 7.5−24 h. The photoproducts were isolated by silica gel column chromatography using hexane and ethyl acetate (6:1 to 12:1) or benzene and ethyl acetate (10:1) as eluent.

2-(1′-Hydroxy-4′-isopropyl-2′,2′-dimethyl-1′,2′-dihydrobenzocyclobuten-1′-yl)-2-methylhex-4-en-3-ol (2a): mp 133−134 °C (from hexane); IR ($CHCl_3$) 3600 and 3450 br cm^{-1}; ^{1}H NMR (400 MHz) δ 0.77 (3 H, s), 1.23 (6 H, d, J = 7 Hz), 1.25 (3 H, s), 1.39 (3 H, s), 1.61 (3 H, s), 1.72 (3 H, d, J = 6 Hz), 2.87 (1 H, sept, J = 7 Hz), 3.25 (1 H, br s), 3.96 (1 H, br s), 4.46 (1 H, d, J = 7 Hz), 5.60 (1 H, dd, J = 17 and 7 Hz), 5.70 (1 H, dq, J = 17 and 6 Hz), and 6.9−7.2 (3 H, m); ^{13}C NMR (100 MHz) δ 17.8 (q), 20.4 (q), 24.2 (2q), 24.3 (q), 25.5 (q), 27.3 (q), 34.7 (d), 43.4 (s), 55.3 (s), 78.9 (d), 91.0 (s), 117.8 (d), 122.2 (d), 125.7 (d), 128.7 (d), 130.7 (d), 143.2 (s), 150.2 (s), and 153.0 (s). Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.52; H, 10.12.

(8) Newsoroff, G. P.; Sternhell, S. *Aust. J. Chem.* **1972**, *25*, 1669. Landquist, J. K.; Stanier, A. *Tetrahedron Lett.* **1975**, 1611.
(9) Blomquist, A. T.; Hruby, V. J. *J. Am. Chem. Soc.* **1967**, *89*, 4996.
(10) Wasserman, H. H.; Keller, L. S. *J. Chem. Soc., Chem. Commun.* **1970**, 1483.

2-(1′-Hydroxy-4′-isopropyl-2′,2′-dimethyl-1′,2′-dihydrobenzocyclobuten-1′-yl)-2-methylhex-4-en-3-ol (3a):[11] IR ($CHCl_3$) 3600 and 3450 br cm^{-1}; ^1H NMR (400 MHz) δ 0.77 (3 H, s), 1.13 (3 H, s), 1.23 (6 H, d, J = 7 Hz), 1.34 (3 H, s), 1.60 (3 H, s), 1.72 (3 H, d, J = 6 Hz), 2.87 (1 H, sept, J = 7 Hz), 3.7−4.0 (2 H, br), 4.39 (1 H, d, J = 7 Hz), 5.45 (1 H, dd, J = 17 and 7 Hz), 5.70 (1 H, dq, J = 17 and 6 Hz), and 6.9−7.2 (3 H, m); ^{13}C NMR (100 MHz) δ 16.5 (q), 17.8 (q), 23.8 (q), 24.2 (2q), 25.0 (q), 28.0 (q), 34.8 (d), 43.1 (s), 55.8 (s), 80.0 (d), 91.2 (s), 117.7 (d), 122.3 (d), 125.8 (d), 128.9 (d), 130.4 (d), 143.3 (s), 150.5 (s), and 153.0 (s).

3-(1′-Hydroxy-1′,2′-dihydrobenzocyclobuten-1′-yl)-3-methylbutan-2-ol (2f): mp 132−133 °C (from hexane); IR 3600 and 3450 br cm^{-1}; ^1H NMR (200 MHz) δ 0.69 (3 H, s), 1.01 (3 H, s), 1.16 (3 H, d, J = 7 Hz), 2.93 (1 H) and 3.58 (1 H) (AB-system, J = 15 Hz), 3.96 (1 H, br s), 4.12 (1 H, q, J = 7 Hz), 4.46 (1 H, br s), and 7.1−7.3 (4 H, m); ^{13}C NMR (50 MHz) δ 15.5 (q), 18.4 (q), 21.9 (q), 41.3 (s), 43.7 (t), 73.8 (d), 88.3 (s), 121.9 (d), 123.4 (d), 127.1 (d), 129.2 (d), 142.4 (s), and 148.6 (s). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.46; H, 8.71.

3-(1′-Hydroxy-1′,2′-dihydrobenzocyclobuten-1′-yl)-3-methylbutan-2-ol (3f): mp 84−85 °C (from hexane); IR 3600 and 3400 br cm^{-1}; ^1H NMR (200 MHz) δ 0.62 (3 H, s), 1.15 (3 H, s), 1.15 (3 H, d, J = 6 Hz), 3.01 (1 H) and 3.55 (1 H) (AB-system, J = 14 Hz), 3.85 (1 H, br s), 4.06 (1 H, q, J = 6 Hz), 4.40 (1 H, br s), and 7.1−7.3 (4 H, m); ^{13}C NMR (50 MHz) δ 15.5 (q), 18.3 (q), 21.6 (q), 41.5 (s), 42.8 (t), 73.2 (d), 88.8 (s), 121.8 (d), 123.5 (d), 127.1 (d), 129.2 (d), 142.4 (s), and 148.3 (s). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.47; H, 8.72.

General Procedure for Acid-Catalyzed Reaction of Benzocyclobutenols 2 and 3. A solution of 50 mg of **2** or **3** in 15 mL of benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid was heated under reflux or heated at 40 °C for 1−6 h. The solvent was evaporated, and the residue was chromatographed on silica gel (hexane and ethyl acetate 20:1 to 25:1) to give **4**, **5**, or **6**.

1-Isopropylidene-4-isopropyl-2,2-dimethyl-1,2-dihydrobenzocyclobutene (4a): bp 70 °C (0.4 Torr); ^1H NMR (200 MHz) δ 1.23 (6 H, d, J = 7 Hz), 1.47 (6 H, s), 1.77 (3 H, s), 1.90 (3 H, s), 2.87 (1 H, sept, J = 7 Hz), and 7.0−7.1 (3 H, m); ^{13}C NMR (50 MHz) δ 19.1 (q), 21.3 (q), 24.3 (2q), 25.1 (2q), 34.9 (d), 51.2 (s), 117.4 (d), 119.5 (d), 121.3 (s), 125.7 (d), 140.5 (s), 141.1 (s), 148.0 (s), and 155.0 (s). Anal. Calcd for $C_{16}H_{22}$: C, 89.65; H, 10.35. Found: C, 89.60; H, 10.28.

(11) These compounds were obtained as oils of high purity as determined on the basis of their ^1H and ^{13}C NMR spectra. However, their complete purification could not be achieved because they decomposed on distillation.

1′,2-*O*-Ethylidene-3-(1′-hydroxy-4′-isopropyl-2′,2′-dimethyl-1′,2′-dihydrobenzocyclobuten-1′-yl)-3-methylbutan-2-ol (5a):[11] ^1H NMR (400 MHz) δ 0.70 (3 H, s), 1.18 (3 H, d, J = 6 Hz), 1.23 (6 H, d, J = 7 Hz), 1.34 (3 H, s), 1.36 (3 H, d, J = 5 Hz), 1.45 (3 H, s), 1.67 (3 H, s), 2.87 (1 H, sept, J = 7 Hz), 3.95 (1 H, q, J = 6 Hz), 5.05 (1 H, q, J = 5 Hz), and 6.9−7.2 (3 H, m); ^{13}C NMR (100 MHz) δ 15.4 (q), 19.6 (q), 21.1 (q), 22.0 (q), 24.2 (q), 24.3 (q), 25.3 (q), 28.7 (q), 34.8 (d), 40.6 (s), 55.2 (s), 77.4 (d), 92.3 (s), 95.7 (d), 116.8 (d), 123.6 (d), 125.7 (d), 139.8 (s), 150.7 (s), and 152.5 (s).

1′,2-*O*-Ethylidene-3-(1′-hydroxy-4′-isopropyl-2′,2′-dimethyl-1′,2′-dihydrobenzocyclobuten-1′-yl)-3-methylbutan-2-ol (6a):[11] ^1H NMR (200 MHz) δ 0.70 (3 H, s), 1.16 (3 H, d, J = 7 Hz), 1.18 (3 H, s), 1.24 (6 H, d, J = 7 Hz), 1.29 (3 H, d, J = 5 Hz), 1.33 (3 H, s), 1.57 (3 H, s), 2.88 (1 H, sept, J = 7 Hz), 3.95 (1 H, q, J = 7 Hz), 5.16 (1 H, q, J = 5 Hz), and 7.0−7.3 (3 H, m); ^{13}C NMR (50 MHz) δ 14.7 (2q), 21.1 (q), 21.7 (q), 24.2 (2q), 25.0 (q), 26.2 (q), 34.7 (d), 38.6 (s), 54.2 (s), 78.2 (d), 91.6 (s), 94.8 (d), 117.5 (d), 124.2 (d), 124.9 (d), 141.0 (s), 150.5 (s), and 153.6 (s).

1′,2-*O*-Ethylidene-3-(1′-hydroxy-1′,2′-dihydrobenzocyclobuten-1′-yl)-3-methylbutan-2-ol (5c): bp 80 °C (0.5 Torr); ^1H NMR (300 MHz) δ 0.56 (3 H, s), 1.14 (3 H, s), 1.18 (3 H, d, J = 6 Hz), 1.35 (3 H, d, J = 5 Hz), 2.98 (1 H) and 3.39 (1 H) (AB-system, J = 14 Hz), 3.97 (1 H, q, J = 6 Hz), 5.22 (1 H, q, J = 5 Hz), and 7.1−7.4 (4 H, m); ^{13}C NMR (75 MHz) δ 15.1 (q), 15.4 (q), 20.3 (q), 21.1 (q), 37.2 (s), 39.8 (t), 77.4 (d), 89.5 (s), 95.8 (d), 123.3 (d), 123.4 (d), 126.5 (d), 129.1 (d), 142.6 (s), and 146.3 (d). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.67; H, 8.80.

1′,2-*O*-Ethylidene-3-(1′-hydroxy-1′,2′-dihydrobenzocyclobuten-1′-yl)-3-methylbutan-2-ol (6c): bp 90 °C (0.6 Torr); ^1H NMR (200 MHz) δ 0.62 (3 H, s), 1.18 (3 H, d, J = 6 Hz), 1.28 (3 H, s), 1.38 (3 H, d, J = 5 Hz), 3.11 (1 H) and 3.47 (1 H) (AB-system, J = 14 Hz), 3.75 (1 H, q, J = 6 Hz), 4.97 (1 H, q, J = 5 Hz), and 7.1−7.4 (4 H, m); ^{13}C NMR (50 MHz) δ 15.1 (q), 16.1 (q), 19.6 (q), 21.2 (q), 37.4 (s), 37.9 (t), 77.4 (d), 89.3 (s), 96.1 (d), 122.6 (d), 123.1 (d), 127.1 (d), 129.5 (d), 142.6 (s), and 144.9 (s). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.65; H, 8.84.

Supporting Information Available: Compound characterization data for **2b**−**e,g,h**, **3b**−**e,g,h**, **5b,d,e**, and **6d**, copies of NMR spectra, and ORTEP diagram of **2a** (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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