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A Copper(II)-Mediated Regioselective Cyclization−Acetoxylation of 6,8-Dien-1-ones for the Synthesis of Functionalized Cyclopentanes

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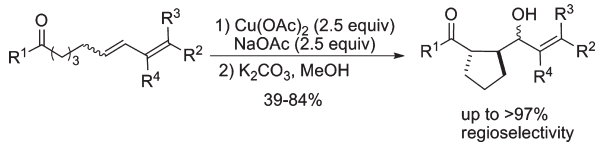

This paper describes a copper(II) acetate-mediated cyclization−acetoxylation of 6,8-dien-1-ones in the presence of sodium acetate as base. A variety of functionalized cyclopentanes containing synthetic useful allylic alcohol moieties with three contiguous stereogenic centers were synthesized in moderate to good yields with moderate to high regioselectivities.

Functionalized cyclopentanes are very important substructures which are present in many biologically active natural products, such as prostaglandins (PGs),[1] and have also been used as chiral ligands in asymmetric synthesis.[2] Metal-mediated radical cyclization of alkenes provides a powerful approach for the synthesis of highly functionalized cyclic compounds.[3] Metal oxidants play a crucial role in the cyclization process: producing radicals and/or interaction with intermediate radicals for subsequent transformations.[3] Various metal salts such as Mn(III), Fe(III), Ce(IV), and V(V) are efficient oxidants and have been widely used in the radical cyclization of carbonyl compounds.[3−8] Copper(II) salts are inexpensive and used as co-oxidants to terminate the radical species in most cases.[3] However, directly oxidizing carbonyl compounds, especially for monoketones, to generate reactive α-keto radicals with copper(II) salts have seldom been reported, and which still remains as a challenge.[3,9−11] In 1996, Snider and co-workers reported a successful free radical cyclization of unsaturated ketones by the Mn(III)-based oxidative generation of α-keto radicals directly from ketones with acetic acid as solvent.[9] Recently, Baran and co-workers reported a copper(II)-promoted cyclization of an enolate tethered with alkene to afford the cyclopentane product as isomeric mixture in 28% yield.[12] Very recently, Kündig and Taylor reported independently an efficient oxindole synthesis with copper(II) salts as oxidants in the presence of strong bases.[13] Employing inexpensive copper(II) salts as oxidants for the radical cyclization of 6,8-dien-1-ones **1** for the synthesis of cyclopentane derivatives attracts our interest for the following curiosities: (a) whether the relatively unstable α-keto radicals **2** can be formed; (b) whether the radicals **2** are active enough to react with conjugated dienes; and (c) what will occur to the allyl radicals **3**, forming diene like most reported oxidative radical cyclization processes[3] or trapping with other reagents (Scheme 1). Herein, we wish to report our results on this subject.

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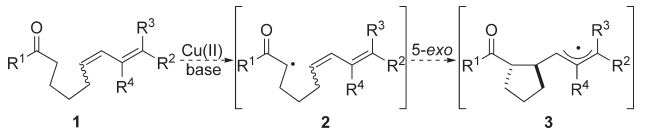
SCHEME 1



SCHEME 2. Initial Studies on Cyclization−Acetoxylation of 1a

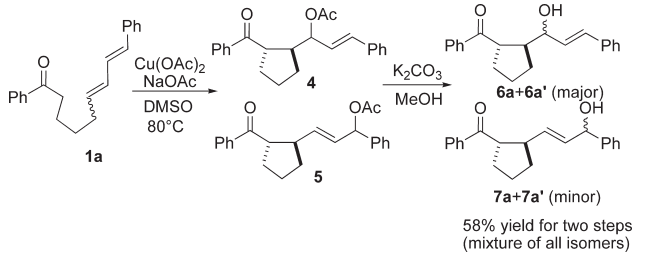


TABLE 1. Optimization of Reaction Conditions for Copper(II) Acetate-Mediated Cyclization−Acetoxylation of 1a[a]

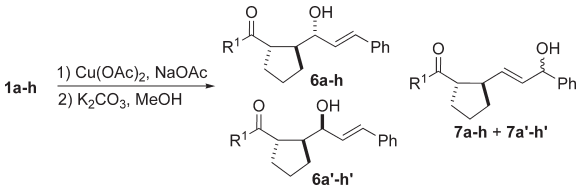
entry	$Cu(OAc)_2$ (equiv)	base (equiv)	yield (%)[b]	(**6a**+**6a′**)/(**7a**+**7a′**)[c]
1	1.0	NaOAc (1.0)	58	ND[d]
2	1.0	none	NR[e]	
3	2.5	NaOAc (2.5)	80	91/9
4	3.0	NaOAc (3.0)	74	ND
5[f]	2.5	NaOAc (2.5)	57	ND
6[g]	2.5	NaOAc (2.5)	76	ND
7	2.5	$NaHCO_3$ (2.5)	56	ND
8[h]	2.5	pyrrolidine (2.5)	64	96/4
9[h]	2.5	ethylenediamine (2.5)	39	83/17

[a]All the reactions were carried out with **1a** (0.30 mmol), $Cu(OAc)_2$, and base in DMSO (3.0 mL) at 80 °C under argon for 12 h unless otherwise stated. [b]Total yield for the isomeric mixture. [c]The ratio of (**6a** + **6a′**)/(**7a** + **7a′**) was determined by ^{1}H NMR of the isomeric mixture. [d]Not determined. [e]No reaction. [f]DMF was used as solvent. [g]$Cu(OAc)_2 \cdot H_2O$ was used. [h]4 Å MS (500 mg/mmol) was added.

The initial studies were carried out with 1,9-diphenylnona-6,8-dien-1-one (**1a**) (mixture of *E* and *Z*) as substrate with 1.0 equiv of $Cu(OAc)_2$ as oxidant and 1.0 equiv of NaOAc as base. We were pleased to find that the α-keto radicals **2** can be generated efficiently even in such a weak basic condition, and the reaction went smoothly in DMSO at 80 °C for 12 h via a cyclization−acetoxylation process to give 1,2-*trans*-cyclopentanes **4** and **5** which were further converted to **6** and **7** by the deprotection of acetyl groups in 58% yield for two steps with a good regioselectivity (Scheme 2).[14]

Encouraged by this promising result, the reaction conditions were further optimized in order to improve the yields, and some results are summarized in Table 1. It was found that no desired products were observed without base (Table 1, entry 2). When the amount of $Cu(OAc)_2$ and NaOAc was increased to 2.5 equiv, the total yield for the mixture of all isomers can be improved to 80% with a high regioselectivity (Table 1, entry 1 vs 3). Copper(II) acetate hydrate can also be used as oxidant with only a slightly lower yield. The reaction proceeded well with $NaHCO_3$ as base to give the desired product in a reasonable yield (Table 1, entry 7). Primary and secondary amines were also found to be effective bases for the current reaction in the presence of 4 Å molecular sieves, and up to 96/4 regioselectivity was obtained (Table1, entries 8 and 9).

TABLE 2. Copper(II) Acetate-Mediated Cyclization−Acetoxylation of 1a−h[a]



entry	R^1	time (h)[b]	**6**/**7**[c]	total yield of **6** and **7** (%)[d]	**6**/**6′** (dr)[e,f]
1	Ph (**1a**)	12	91/9	80	1.8/1.0
2	4-MeO-C_6H_4 (**1b**)	16	82/18	82	1.9/1.0
3	3,5-Me_2-C_6H_3 (**1c**)	9	82/18	75	2.0/1.0
4	2-Me-C_6H_4 (**1d**)	7	78/22	79	1.9/1.0
5	2-naphthyl (**1e**)	8	81/19	68	1.6/1.0
6	4−F-C_6H_4 (**1f**)	6	87/13	84	2.1/1.0
7[g]	4-CF_3−C_6H_4 (**1g**)	12	75/25	40	1.1/1.0
8	Cyclohexyl (**1h**)	96	64/36	50	1.0/1.0

[a]All the reactions were carried out with the substrate (0.30 mmol), $Cu(OAc)_2$ (0.75 mmol), and NaOAc (0.75 mmol) in DMSO (3.0 mL) at 80 °C under argon for the time indicated unless otherwise stated. [b]Time for the first step. [c]The ratio was determined by ^{1}H NMR of the isomeric mixture. [d]The average yield for two experiments. [e]The diastereomeric ratio was determined by ^{1}H NMR of the isomeric mixture. [f]Pure **6a−h** can be obtained while **6a′−h′** cannot be separated from **7**. [g]The reaction was carried out at 60 °C.

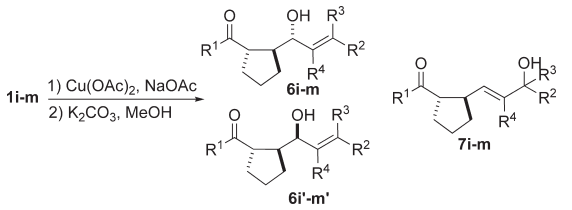
The substrate scope was then investigated with $Cu(OAc)_2$ (2.5 equiv) as oxidant and NaOAc (2.5 equiv) as base. As shown in Table 2, all the reactions of arylketone substrates (**1a−g**) went efficiently to give the desired cyclopentanes in moderate to good yields (40−84%) with good regioselectivities (75/25−91/9). However, the diastereoselectivities of **6** were very poor (Table 2, entries 1−7). Moreover, the reaction of cyclohexylketone substrate **1h** can also give the corresponding cyclopentanes in a reasonable yield for a longer time (Table 2, entry 8). In most cases, only pure stereoisomers **6a−g** can be isolated from the isomeric mixtures.

The effect of substituents on conjugated dienes was then studied, and the results are summarized in Table 3. For the reactions of **1i−m**, all stereoisomers (**6i−m**, **6i′−m′**, and **7k−m**) can be isolated as pure compounds. It was found that the regioselectivity could be reached to >97/3 for the cyclization−acetoxylation of substrate **1i** bearing 1,1-diphenyl substituents (Table 3, entry 1). Terminal dienes were also effective for the cyclization−acetoxylation to give moderate yields and good regioselectivities (Table 3, entries 3 and 4). However, when substrates bearing monoalkenes were subjected to this reaction, no desired products were obtained, which suggested that 1,3-diene moieties were necessary for current transformations.[15] The stereochemistry of ***6l*** was determined by the X-ray structure of **8**, which was derived from ***6l*** (see the Supporting Information). The relative stereochemistry between hydroxyl and cyclopentyl

(14) 1,2-*cis*-Cyclopentanes were barely detected by GC-MS and ^{1}H NMR of the crude reaction mixture if there was any.

(15) Two substrates bearing mono-alkenes (1-phenylhept-6-en-1-one and 1,7-diphenylhept-6-en-1-one) were subjected to this reaction, and no desired products were observed, which may be relevant to the radical stabilities. For a theoretical perspective on radical stability, see: Zipse, H. *Top. Curr. Chem.* **2006**, *263*, 163.

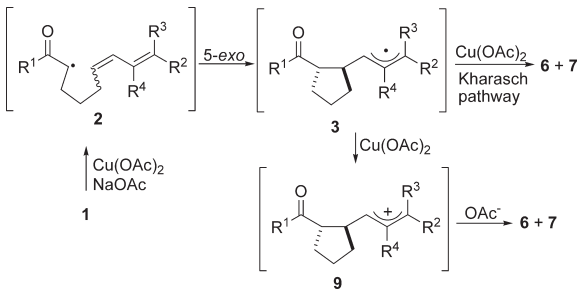
TABLE 3. Copper(II) Acetate-Mediated Cyclization−Acetoxylation of 1i−m[a]



entry	$R^1/R^2/R^3/R^4$	time (h)[b]	**6**/**7**[c]	total yield of **6** and **7** (%)[d,e]	**6**/**6′** (dr)[f]
1	4−F-C_6H_4/Ph/Ph/H (**1i**)	6	>97/3	39	2.1/1.0
2	4−F-C_6H_4/Ph/Me/H (**1j**)	8	95/5	56	2.0/1.0
3	4−F-C_6H_4/H/H/H (**1k**)	8	87/13	66	1.7/1.0
4	Ph/H/H/H (**1*l***)	7	85/15	59	1.6/1.0
5	Ph/H/H/Me (**1m**)	8	57/43	67	3.7/1.0

[a]All the reactions were carried out with the substrate (0.30 mmol), $Cu(OAc)_2$ (0.75 mmol), and NaOAc (0.75 mmol) in DMSO (3.0 mL) at 80 °C under argon for the time indicated. [b]Time for the first step. [c]The ratio was determined by ^{1}H NMR of the isomeric mixture. [d]The average yield for two experiments. [e]All stereoisomers can be separated by flash chromatography, while **7i** and **7j** (entries 1 and 2) cannot be obtained due to the trace amounts. [f]The diastereomeric ratio was determined by ^{1}H NMR of the isomeric mixture.

SCHEME 3. Proposed Mechanism for Copper(II) Acetate-Mediated Cyclization−Acetoxylation



moieties of **6a**−**m** and **6a′**−**m′** was tentatively assigned by NOE studies and NMR spectra comparison with **6*l*** and **6*l′*** (see the Supporting Information).

A plausible mechanism is proposed in Scheme 3 on the basis of the observed experiment results. α-Keto radicals **2** are generated by the oxidation of **1** with $Cu(OAc)_2$ as single electron oxidant under the assistance of NaOAc. Due to the relatively weak acidic α-CH_2 of monoketones, it is not easy to form anion with such a weak base (NaOAc or $NaHCO_3$) alone. Hence, $Cu(OAc)_2$ is supposed to act as a Lewis acid to activate the carbonyl group. Further 5-*exo* radical addition to the double bond gives allyl radical intermediate **3**. Radical species **3** will be further oxidized to cation intermediate **9** followed by the addition of acetate to afford products **6** and **7**. Alternatively, a Kharasch−Sosnovsky pathway involving trivalent copper intermediates[16] generated by the interaction of $Cu(OAc)_2$ with allyl radicals **3** is also possible. The observed regioselectivities may be relevant with the electronic, steric hindrance factors, and/or the radical and cation stabilities.

In conclusion, we have discovered a facile 5-*exo*-cyclization/acetoxylation of readily available 6,8-dien-1-ones mediated by inexpensive copper(II) acetate as efficient oxidant and sodium acetate as base. A variety of 1,2-*trans*-cyclopentanes containing synthetic useful allylic alcohol moieties with three contiguous stereogenic centers can be afforded in moderate to good yields with moderate to high regioselectivities.

Experiment Section

All cyclization−acetoxylation products are new compounds and give satisfactory spectroscopic characterization.

General Procedure for the Cyclization−Acetoxylation of 6,8-Dien-1-ones. To a Schlenk tube charged with the substrate **1** (0.30 mmol), $Cu(OAc)_2$ (0.136 g, 0.75 mmol), and NaOAc (0.062 g, 0.75 mmol) was added degassed DMSO (3.0 mL) under Argon. The resulting mixture was immersed into an oil bath (80 °C) and stirred until the reaction was complete as monitored by TLC. After cooling to room temperature, water (50 mL) was added and the mixture was extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After removal of solvents, the residue was treated with K_2CO_3 (0.065 g, 0.47 mmol) and MeOH (2.5 mL) and stirred at room temperature for 1 h, and then concentrated. The residue was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate = 15/1−5/1) to yield the corresponding isomeric mixture of **6** and **7**. Further careful isolation by flash chromatography on silica gel gave pure separable isomers.

Table 2, entry 1 (**6a**): colorless oil, R_f 0.12 (petroleum ether/ethyl acetate = 15/1); IR (film) 3462, 1676 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 7.2 Hz, 2H), 7.51 (dd, J = 7.6, 7.2 Hz, 1H), 7.41 (dd, J = 7.6, 7.2 Hz, 2H), 7.28−7.23 (m, 4H), 7.22−7.21 (m, 1H), 6.54 (d, J = 15.6 Hz, 1H), 6.20 (dd, J = 15.6, 6.4 Hz, 1H), 4.14 (dd, J = 7.2, 6.8 Hz, 1H), 3.85−3.79 (m, 1H), 2.89−2.81 (m, 1H), 2.57 (br s, 1H), 2.16−2.08 (m, 1H), 1.93−1.87 (m, 1H), 1.78−1.70 (m, 3H), 1.60−1.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 137.1, 136.8, 132.8, 131.7, 130.6, 128.6, 128.5, 128.5, 127.6, 126.5, 76.1, 49.4, 48.6, 32.4, 29.5, 25.7; HRMS (EI) calcd for $C_{21}H_{22}O_2$ (M) 306.1620, found 306.1623.

Inseparable mixture of **6a′**, **7a**, and **7a′**: colorless oil, R_f 0.08 (petroleum ether/ethyl acetate = 15/1); IR (film) 3454, 1676 cm^{-1}. **6a′**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94−7.89 (d, J = 7.6 Hz, 2H), 7.58−7.18 (m, 8H), 6.52 (d, J = 16.0 Hz, 1H), 6.17 (dd, J = 16.0, 6.8 Hz, 1H), 4.28 (dd, J = 6.4, 6.0 Hz, 1H), 3.73 (m, 1H), 2.91−2.82 (m, 1H), 2.25 (br s, 1H), 2.18−1.50 (m, 6H). **7a** (major epimer of **7**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94−7.89 (d, J = 7.6 Hz, 2H), 7.58−7.18 (m, 8H), 5.77 (dd, J = 15.6, 7.6 Hz, 1H), 5.64 (dd, J = 15.6, 6.4 Hz, 1H), 5.10 (d, J = 6.4 Hz, 1H), 3.56−3.49 (m, 1H), 3.06−2.96 (m, 1H), 2.18−1.50 (m, 6H).

Table 3, entry 1 (**6i**): colorless oil, R_f 0.25 (petroleum ether/ethyl acetate = 10/1); IR (film) 3462, 1676, 1597 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, J = 8.8, 5.6 Hz, 2H), 7.40−7.34 (m, 3H), 7.28−7.18 (m, 7H), 7.09 (dd, J = 8.8, 8.4 Hz, 2H), 6.04 (d, J = 9.6 Hz, 1H), 4.01 (dd, J = 9.2, 8.8 Hz, 1H), 3.67−3.62 (m, 1H), 2.84−2.76 (m, 1H), 2.06−2.00 (m, 1H), 1.92−1.86 (m, 2H), 1.76−1.67 (m, 2H), 1.65−1.59 (m, 1H), 1.42−1.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.3, 165.8 (d, J_{C-F} = 252.7 Hz), 144.5, 141.9, 139.6, 133.6 (d, J_{C-F} = 2.6 Hz), 131.5 (d, J_{C-F} = 9.1 Hz), 130.4, 123.1, 123.0, 128.4, 127.9, 127.6, 115.7 (d, J_{C-F} = 21.6 Hz), 73.3, 49.8, 49.5, 32.1, 29.6, 25.7; HRMS (EI) calcd for $C_{27}H_{25}FO_2$ (M) 400.1839, found 400.1843.

(16) For leading references on Kharasch−Sosnovsky reactions, see: (a) Kharasch, M. S.; Sosnovsky, G. *J. Am. Chem. Soc.* **1958**, *80*, 756. (b) Andrus, M. B.; Lashley, J. C. *Tetrahedron* **2002**, *58*, 845. (c) Eames, J.; Watkinson, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3567. (d) Mayoral, J. A.; Rodríguez-Rodríguez, S.; Salvatella, L. *Chem.—Eur. J.* **2008**, *14*, 9274.

6i′: colorless oil, R_f 0.21 (petroleum ether/ethyl acetate = 10/1); IR (film) 3460, 1676, 1597 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, J = 8.8, 5.6 Hz, 2H), 7.32−7.31 (m, 3H), 7.21−7.19 (m, 3H), 7.07−7.03 (m, 6H), 5.98 (d, J = 10.0 Hz, 1H), 4.11 (dd, J = 9.6, 6.8 Hz, 1H), 3.46−3.40 (m, 1H), 2.88−2.80 (m, 1H), 2.04−1.98 (m, 2H), 1.75−1.60 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 165.8 (d, J_{C-F} = 252.8 Hz), 144.2, 141.9, 134.1, 133.7 (d, J_{C-F} = 2.6 Hz), 131.3 (d, J_{C-F} = 9.2 Hz), 130.2, 123.1, 128.5, 128.3, 127.8, 127.7, 127.6, 115.7 (d, J_{C-F} = 21.6 Hz), 72.4, 49.0, 48.9, 32.4, 28.8, 25.8; HRMS (ESI) calcd for $C_{27}H_{25}FO_2Na$ (M + Na) 423.1731, found 423.1726.

Table 3, entry 3 (**6k**): colorless oil, R_f 0.21 (petroleum ether/ethyl acetate = 10/1); IR (film) 3462, 1676, 1598 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, J = 8.4, 5.2 Hz, 2H), 7.11 (dd, J = 8.4, 7.2 Hz, 2H), 5.84 (ddd, J = 17.2, 10.4, 6.4 Hz, 1H), 5.19 (d, J = 17.2 Hz, 1H), 5.06 (d, J = 10.4 Hz, 1H), 3.95 (s, 1H), 3.72−3.66 (m, 1H), 2.75−2.67 (m, 1H), 2.12−2.04 (m, 1H), 1.91−1.83 (m, 1H), 1.79−1.65 (m, 4H), 1.52−1.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 165.8 (d, J_{C-F} = 252.6 Hz), 140.4, 133.6 (d, J_{C-F} = 2.7 Hz), 131.4 (d, J_{C-F} = 9.2 Hz), 115.7 (d, J_{C-F} = 21.8 Hz), 115.4, 76.8, 49.4, 48.1, 32.5, 29.6, 25.8; HRMS (EI) calcd for $C_{15}H_{17}FO_2$ (M) 248.1213, found 248.1215.

6k′: colorless oil, R_f 0.16 (petroleum ether/ethyl acetate = 10/1); IR (film) 3457, 1673, 1600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, J = 8.8, 5.6 Hz, 2H), 7.12 (dd, J = 8.0, 5.6 Hz, 2H), 5.89−5.80 (ddd, J = 17.2, 10.4, 6.4 Hz, 1H), 5.20 (d, J = 17.2 Hz, 1H), 5.08 (d, J = 10.4 Hz, 1H), 4.11 (s, 1H), 3.67−3.61 (m, 1H), 2.80−2.73 (m, 1H), 2.11−2.05 (m, 1H), 1.92−1.85 (m, 1H), 1.76−1.68 (m, 4H), 1.65−1.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7, 165.9 (d, J_{C-F} = 252.9 Hz), 139.9, 133.8 (d, J_{C-F} = 2.8 Hz), 131.2 (d, J_{C-F} = 9.2 Hz), 115.7 (d, J_{C-F} = 23.5 Hz), 74.8, 48.5, 47.5, 32.6, 27.6, 25.6; HRMS (EI) calcd for $C_{15}H_{17}FO_2$ (M) 248.1213, found 248.1215.

7k: colorless oil, R_f 0.12 (petroleum ether/ethyl acetate = 10/1); IR (film) 3337, 1677, 1597 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98−7.95 (m, 2H), 7.12 (dd, J = 11.2, 8.4 Hz, 2H), 5.71−5.57 (m, 1H), 4.04 (d, J = 5.2 Hz, 1H), 3.49−3.43 (m, 1H), 3.07−3.00 (m, 1H), 2.13−2.04 (m, 1H), 2.02−1.96 (m, 1H), 1.88−1.71 (m, 3H), 1.59−1.49 (m, 1H), 1.30 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 165.9 (d, J_{C-F} = 253.1 Hz), 135.0, 133.7 (d, J_{C-F} = 2.8 Hz), 131.3 (d, J_{C-F} = 9.1 Hz), 129.1, 115.8 (d, J_{C-F} = 21.7 Hz), 63.6, 52.7, 45.8, 33.4, 31.3, 25.2; HRMS (ESI) calcd for $C_{15}H_{17}FO_2Na$ (M + Na) 271.1105, found 271.1107.

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Supporting Information Available: The procedure for preparation of **1a** and copper(II)-mediated cyclization−acetoxylation of 6,8-dien-1-ones **1**, characterization of **1a**, **6**, **7**, and **8**, X-ray structure of **8**, NOE studies of **6a**, **6a′**, **6j**, **6j′**, **6*l***, and **6*l′***, along with NMR spectra of **6** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.