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Structure−Activity Relationship Studies of Illudins: Analogues Possessing a Spiro-cyclobutane Ring

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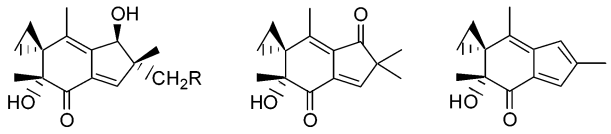
Bicyclic and tricyclic analogues of anticancer sesquiterpene illudin S have been synthesized. These contain a spiro-cyclobutane instead of spiro-cyclopropane structure. The cytotoxicity of the former is less than that of the corresponding cyclopropane-containing compounds.

Introduction

Illudins S (**1a**) and M (**1b**) are highly cytotoxic sesquiterpenes produced by the basidiomycete *Omphalotus illudens* (*Omphalotus olearius*, formerly *Clitocybeilludens*).[1−4] The toxicity and antitumor activity of these compounds can be explained by their behavior as alkylating agents. As shown in Scheme 1, Michael-type addition to the α,*β*-unsaturated ketone gives a highly reactive cyclohexadiene intermediate that undergoes cyclopropane ring opening with attack by nucleophiles (protein, DNA, H_2O). The driving force in this reaction is relief of ring strain when the cyclopropane opens. The stable aromatic structure that results is also a factor.[5,6]



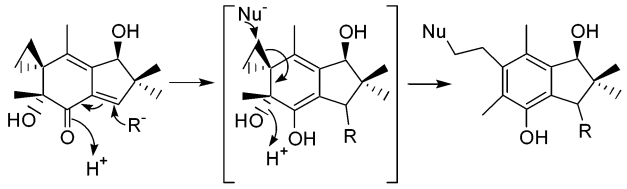
1a (R = OH)
1b (R = H)

2

3

The nucleophile in the Michael reaction can be a thiol such as cysteine or glutathione or the thiol group of a protein. It has also been found that reduction by cytosolic NADH- and NADPH-dependent enzymes can lead to similar aromatic products.[7,8]

SCHEME 1. Mechanism of Toxicity and Antitumor Activity of Illudins



R=GS or H (from NADPH)

Earlier SAR studies of illudins revealed that oxidation of illudin M to dehydroilludin M (**2**) resulted in lower toxicity but enhanced efficacy.[9,10] Also, treatment of illudin S with dilute H_2SO_4 gave acylfulvene (**3**), which was even less toxic than **2** and had superior efficacy.[11−13] Compounds **2** and **3** react with nucleophiles in the same way as Illudin S or M (cf. Scheme 1).

The increase in efficacy parallels reduction in reactivity of the compounds to thiols at neutral pH. Thus by modulating the reactivity it might be possible to prepare further useful analogues. Among the changes to the structure, we considered replacing the spiro-cyclopropane by a spiro-cyclobutane group, giving structures such as **4a** and **4b**. The cyclobutane would be expected to exhibit much less angle strain than the cyclopropane and would be less easily opened.[14] If a similar mechanism as in

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(14) Cyclopropanes and cyclobutanes are known to have similar enthalpies of reations in the gas phase. Howerer, cyclobutane is essentially inert toward eletrophiles, whereas cyclopropane has moderate activity; see: Wiberg, K. B.; Kass, S. R. *J. Am. Chem. Soc.* **1985**, *107*, 988−995.

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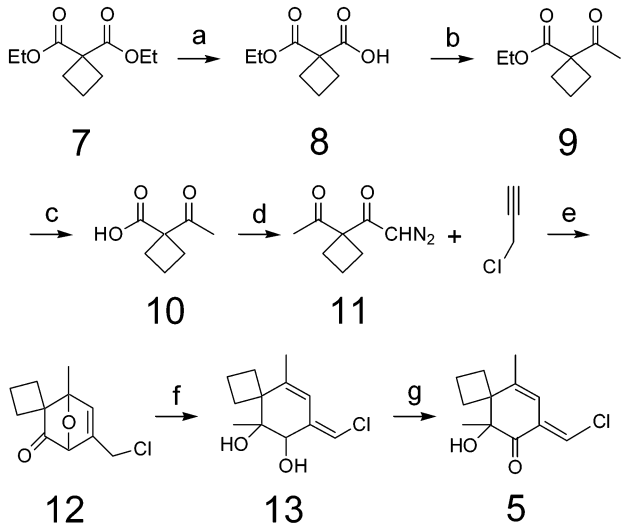
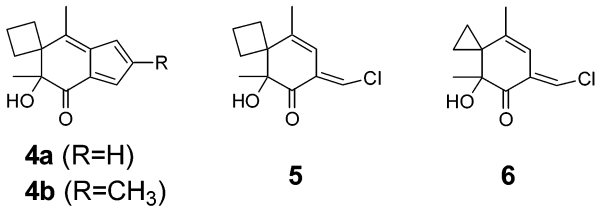
SCHEME 2. Synthesis of 5[a]



[a] Reagents and conditions: (a) KOH, EtOH, 0 °C, 94%; (b) (i) $SOCl_2$, 50 °C, (ii) MeLi, CuI, −25 °C, THF, 70% for two steps; (c) KOH, EtOH, 0 °C, 92%; (d) (i) $ClCO_2CH_3$, K_2CO_3, CH_2Cl_2, 0 °C, (ii) CH_2N_2, −10 °C, 64% for two steps; (e) $Rh_2(OAc)_4$, MS (4 Å), chlorobenzene, rt, 65%; (f) MeLi, ether, −78 to −0 °C, 62%; (g) IBX, DMSO, THF 43%.

Scheme 1 is assumed for alkylation by **4a**, reaction should be less favorable and might lead to enhanced efficacy.

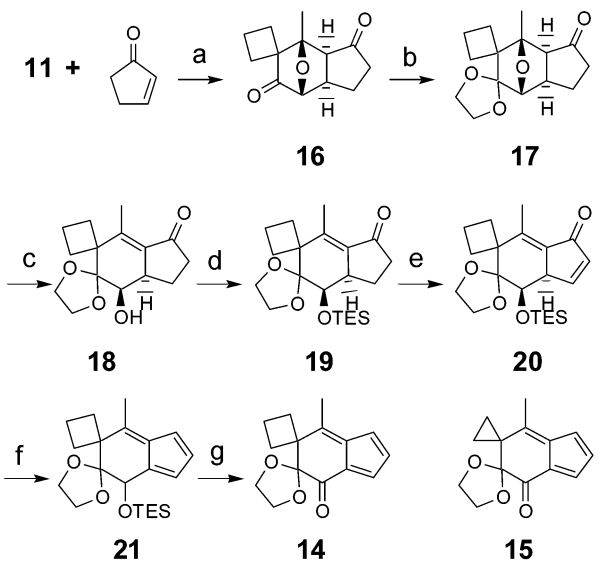


Results and Discussion

The approach to synthesis of **4a** follows that used for synthesis of acylfulvenes.[15] However we focused first on a simpler target molecule (i.e., **5**), because synthesis of the spiro-cyclopropane analogue (**6**) has been reported by Kinder et al.[16] and is straightforward. Moreover **6** was found to have IC_{50} values comparable to those of adriamycin in human tumor cell lines.

Synthesis of **5** is outlined in Scheme 2. Commercially available cyclobutane-1,1-dicarboxylic acid diethyl ester (**7**) on partial hydrolysis afforded the monoester carboxylic acid (**8**).[17] The latter was converted to the acid chloride, which on reaction with methyllithium and cuprous iodide afforded the ketoester (**9**) in high yield.[18] Hydrolysis of the ester and then reaction of the corresponding acid (**10**) with methyl chloroformate and K_2CO_3 in dichloromethane, followed by treatment with an ether solution of diazomethane, gave diazoketone (**11**) in 64% yield.[19]

SCHEME 3. Synthesis of 14[a]



[a] Reagents and conditions: (a) $Rh_2(OAc)_4$, chlorobenzene, rt, 37%; (b) TMSCl, CH_2Cl_2, ethylene glycol, rt, 77%; (c) KOH, CH_3OH, 53 °C, 75%; (d) TESCl, pyridine, 60 °C, 92%; (e) (i) TMSCl, LDA, Et_3N, THF, −78 °C, (ii) $Pd(OAc)_2$, CH_3CN, THF, rt, 65% for two steps; (f) (i) DIBALH, THF, −78 °C, (ii) HCl, $CHCl_3$, rt; (g) (i) TBAF, HOAc, THF, 0 °C, (ii) PDC, CH_2Cl_2, 0 °C, 51% for two steps.

The compound was employed in a 1,3-dipolar cycloaddition reaction with propargyl chloride following essentially the procedure of Padwa.[20] The oxabicyclo[2,2,1]-heptane (**12**) was obtained in 65% yield from diazoketone (**11**) in the reaction catalyzed by $Rh_2(OAc)_4$ and carried out in chlorobenzene at room temperature. There was no indication of any regioisomer formation.

Treatment of **12** with 3 equiv of MeLi gave the diol (**13**) resulting from attack at the ketone and also allylic proton abstraction and oxo-bridge opening. The exocyclic double bond is assigned the E configuration on the basis of NMR data (NOESY). Finally, oxidation of diol (**13**) with 2-iodoxybenzoic acid (IBX) gave the target compound (**5**) in 43% yield. The cyclopropane analogue (**6**) was also prepared according to Kinder et al.'s procedure,[16] for comparison of cytotoxicity.

Two acylfulvene analogues containing a cyclobutane ring were also synthesized. From our experience with acylfulvenes the most readily accessible target appeared to be spirocyclobutane (**14**) as shown in Scheme 3. In addition, the cyclopropane analogue **15** had previously been prepared and found to have biological activity similar to that of acylfulvene.[15] The synthesis of **14** involved the same diazoketone (**11**) that on cycloaddition reaction with 2-cyclopentenone afforded the tetracyclic adduct **16** though only in modest yield. An X-ray crystallographic analysis of **16** (see Figure 1) indicated the relative stereochemistry of the oxo-bridge and cyclopentanone ring fusion. Only the exo-isomer was isolated, although the endo-product may have been formed as well.

Selective ketalization of **16** was achieved with ethylene glycol and TMSCl in dichloromethane at room temperature. The oxo-bridge in **17** was then readily cleaved with

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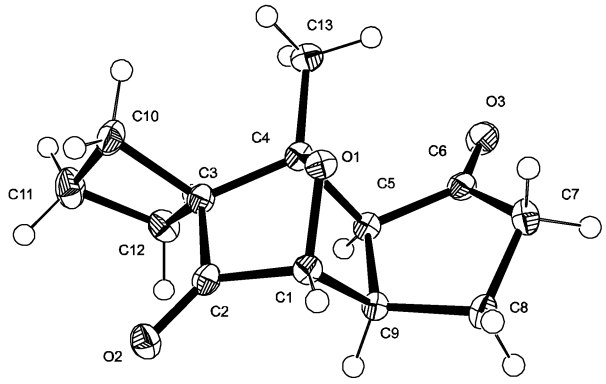
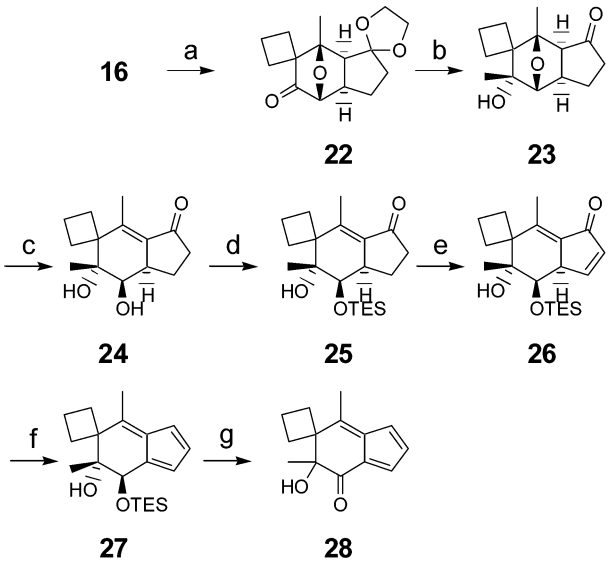


FIGURE 1. ORTEP view of X-ray molecular structure of **16**.

SCHEME 4. Synthesis of 28[a]



[a] Reagents and conditions: (a) TMSCl, CH_2Cl_2, ethylene glycol, −6 °C, 71%; (b) (i) MeLi, THF, −78 °C, (ii) TSA, acetone, reflux, 92% for two steps; (c) KOH, CH_3OH, 60 °C, 32%, (d) TESCl, pyridine, 80 °C, 90%; (e) (i) TMSCl, LDA, Et_3N, THF, −78 °C, (ii) $Pd(OAc)_2$, CH_3CN, THF, rt, 65% for two steps; (f) (i) DIBALH, THF, −78 °C, (ii) HCl, $CHCl_3$, 70% for two steps; (g) (i) TBAF, HOAc, THF, 0 °C, (ii) IBX, CH_2Cl_2, DMSO, rt, 77% for two steps.

KOH−methanol at 53 °C. Protection of the alcohol (**18**) as the triethylsilyl derivative (**19**) followed by formation of the trimethylsilyl ether and then treatment with palladium acetate in CH_3CN at room temperature[21] gave the unsaturated ketone (**20**) in good overall yield from **18**.

1,2-Reduction of key intermediate **20** with DIBALH in THF (−78 °C) gave an unstable alcohol, which on elimination of H_2O afforded the fulvene (**21**). Removal of the protecting TES group and oxidation of the resulting alcohol with pyridinium dichromate (PDC) in dichloromethane yielded target acylfulvene (**14**). The overall yield of **14** from **11** was 5%.

The tricyclic acylfulvene analogue (**28**) was synthesized as follows (Scheme 4). Selective ketalization of intermediate **16** at −6 °C (TMSCl, CH_2Cl_2) yielded the unstable monoacetal (**22**). The latter was immediately treated with methyllithium in THF at −78 °C to give the tertiary alcohol (**23**) (90%) after removal of the acetal protecting group. Treatment of **23** with KOH in methanol opened the oxo bridge, yielding unsaturated alcohol (**24**).

To form the fulvene ring, the secondary alcohol in **24** was protected as the triethylsilyl derivative and the compound **25** was treated with trimethylsilyl chloride and LDA (THF, −78 °C) followed by $Pd(0Ac)_2$ in CH_3-CN, THF at room temperature, giving the cross-conjugated ketone (**26**).[21] Reduction of the latter with DIBALH (THF, −78 °C) and 1,4-elimination of the resulting alcohol yielded fulvene (**27**). The triethylsilyl protecting group was then removed (TBAF, HOAC and THF, room temperature) and oxidation of the resulting secondary alcohol (PDC, CH_2Cl_2) gave target acylfulvene (**28**) in overall yield of 7% from **16**.

Bicyclic analogues **5** and **6** were first tested and were found to possess similar cytotoxicity (see Table 1) against several cell lines: MV 522 (lung adenocarcinoma), HL60 (human myeloid leukemia), 8392 (B cell lymphoma/leukemia), CHRF 2881 (normal megakaryocyte cell line). The cells were subjected to short exposure (2 h) and long exposure (48 h) to the compounds. (It is known that certain cells, e.g., MV522 and HL60, are sensitive to short exposure because of energy-dependent cellular accumulation.)[22,23]

Acylfulvene analogue **14** was found to be far less cytotoxic than the cyclopropane analogue **15** (Table 1), which had been prepared previously.[15] Because of the poor solubility of **14** we were unable to obtain an accurate measure of its efficacy. This led us to synthesize target **28**, which we hoped would be more soluble. Acylfulvene **28** had cytotoxicity similar to that found for acylfulvene **14**, except that **28** was more cytotoxic to MV522 cells in the 48 h assay. If a similar mechanism applies to both cyclopropyl and cyclobutyl compounds **14**, **15**, and **28**, it is possible that more facile ring opening in highly strained **15** will contribute to its greater cytotoxicity. Overall the results indicate that replacement of the cyclopropane by a cyclobutane moiety reduced the high cytotoxicity of acylfulvenes. Xenograft trials are now being carried out to test the efficacy of these compounds.

Experimental Section

Acid (8). An aqueous solution of KOH (360 mL, 0.648 mol, 1.8 M) was added to diester **7** (126.0 g, 0.630 mol), which was dissolved in 550 mL of EtOH at 0 °C. After 40 h, most of the EtOH was removed by evaporation, H_2O was added to dissolve all solids, then the solution was washed with 150 mL of ether, and the pH was carefully adjusted to 2 at 0 °C. The aqueous solution was extracted with EtOAc three times. The organic extracts were combined, washed with brine, dried, and evaporated to give **8 (**101.8 g, 94%) as a colorless liquid. IR (neat): 3189, 1729,1709 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 10.91 (1H, br s), 4.23 (2H, q, J = 6.8 Hz), 2.58 (4H, t, J = 8.0 Hz), 2.24−1.78 (2H, m), 1.27 (3H, t, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.7, 171.5, 61.9, 52.7, 29.0, 16.4, 14.3. HRMS (MALDI) (m/z) $[M + Na]^+$ calcd for $C_8H_{12}O_4Na$, 195.0628, found 195.0629.

Ketoester (9). $SOCl_2$ (50 mL, 0.685 mol) was added to **8** (50.5 g, 0.293 mol) at room temperature. The solution was heated gradually, bubbling started at 50 °C, and the solution

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TABLE 1. Analogue Cytotoxicity (IC_{50}, μM) in Select Cell Lines[a]

	MV522 lung		HL60 myeloid		8392 B cell		CHRF-2881 megakaryocyte	
	2 h	48 h	2 h	48 h	2 h	48 h	2 h	48 h
5	58.8 ± 6.6	15.8 ± 2.6	12.8 ± 1.8	2.9 ± 0.4	12.0 ± 2.3	2.7 ± 0.4	15.9 ± 1.6	11.7 ± 2.4
6	50.6 ± 6.0	28.0 ± 0.4	13.7 ± 0.9	5.3 ± 0.2	43.9 ± 5.1	8.5 ± 2.0	4.2 ± 1.2	5.0 ± 0.8
14	>400	>123	126 ± 4	24 ± 1	350 ± 20	13.1 ± 1.6	nt	nt
15	10.0 ± 1.1	4.6 ± 0.2	nt	nt	29.9 ± 3.3	nt	nt	nt
28	>140	49 ± 13	>140	24.0 ± 4.0	>140	15.0 ± 4.0	nt	nt

[a] IC_{50} is the concentration of the compound at which 50% inhibition of colony formation occurs (in the 48-h assay) or 50% inhibition of tritiated thymidine into genomic DNA occurs (in the 2-h assay). Values are reported as the mean ± standard deviation for 3−5 experiments.[22,23]

was kept at this temperature for 3 h until the bubbling ceased and there was no further decrease in volume. A simple distillation (50−125 °C, 10 mmHg) gave 95 mL of the corresponding acid chloride as a yellow liquid. An ether solution of MeLi (137 mL, 191.8 mmol, 1.4M) was added to CuI (37.4 g, 196 mmol) in 400 mL THF at −25 °C. After 1 h, half of the acid chloride in 50 mL THF was added to the yellow solution of MeCu. After 1.5 h the mixture was warmed to room temperature. After a further 0.5 h, 300 mL aqueous citric acid (10%) was added to quench the reaction. Following evaporation of most of the THF, the liquid was filtered and the filtrate was extracted three times with EtOAc. The combined organic phase was washed successively with $Na_2S_2O_3$ (15%) solution and brine, then dried and evaporated. The procedure was repeated for the remainder of acid chloride. Fractional distillation (71−73 °C, 0.9 mmHg) of the residue gave **9 (**34.68 g, 70%) as a colorless liquid. IR (neat): 1735, 1711 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 4.21 (2H, q, J = 7.2 Hz), 2.47 (4H, t, J = 7.9 Hz), 2.13 (3H, s), 2.05−1.74 (2H, m), 1.27 (3H, t, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 203.1, 172.2, 61.6, 59.4, 27.8, 25.4, 15.7, 14.3. HRMS (CI) (*m*/*z*): $[M + H]^+$ calcd for $C_9H_{15}O_3$ 171.1014, found 171.1021.

Ketoacid (10). An aqueous solution of KOH (20.5 mL, 36.9 mmol, 1.8M) was added to **9** (5.7 g, 33.5 mmol) in 30 mL of EtOH at 0 °C. After 1 day, the ethanol was removed with a rotary evaporator, and the aqueous solution was washed with ether. The pH of the aqueous solution was carefully adjusted to 2 with HCl (6 M) at 0 °C, and then the aqueous solution was extracted with EtOAc three times. The combined organic phase was washed with brine, dried, and evaporated to give **10 (**4.4 g, 92%) as a colorless liquid. IR (neat): 3156, 1744, 1710 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 10.40−8.77 (1H, br s)), 2.54 (4H, t, J = 8 Hz), 2.23 (3H, s), 2.14−1.97 (1H, m), 1.95−1.78 (1H, m). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 203.0, 178.1, 59.1, 28.1, 25.7, 15.8. HRMS (MALDI) (*m*/*z*): $[M + Na]^+$ calcd for $C_7H_{10}O_3Na$ 165.0522, found 165.0523.

Diazoketone (11). $ClCO_2CH_3$ (5.9 mL, 76.36 mmol) was added slowly to a suspension of K_2CO_3 (20.1 g, 145.43 mmol) in 40 mL of CH_2Cl_2 at 0 °C. To the resulting suspension was added **10** (4.4 g, 30.9 mmol) in 30 mL of CH_2Cl_2 at −3 °C. After 5 h, the liquid was filtered through a pad of Celite, more CH_2Cl_2 was used to wash the Celite pad, and the filtrate was evaporated to remove the solvent and the excess $ClCO_2CH_3$. The residue was redissolved in 40 mL of CH_2Cl_2, to it was added 200 mL of an ether solution of diazomethane (61.2 mmol, 1 M) at −10 °C, and the mixture was kept for 12 h without stirring. (Caution! Diazomethane should be handled in an efficient fume hood behind a protection shield because of its toxicity and the possibility of explosions.) The liquid was then filtered, and the filtrate was evaporated to remove excess diazomethane and solvent. The residue was chromatographed (hexane/EtOAc 4:1) to give **11 (**3.28 g, 64%) as a yellow liquid. IR (neat): 2107, 1709, 1633 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 5.17 (1H, br s), 2.70−2.34 (4H, m), 2.08 (3H, s), 1.95−1.62 (2H, m). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 204.5, 191.4, 65.6, 53.2, 27.9, 25.1, 15.5. HRMS (CI) (*m*/*z*): $[M + H]^+$ calcd for $C_8H_{11}N_2O_2$ 167.0821, found 167.0820.

Cycloadduct (12). To a mixture of propargyl chloride (332 μL, 4.59 mmol), $Rh_2(OAc)_4$ (2 mg, 0.005 mmol), molecular sieves (1 g, 4 Å), and chlorobenzene (1 mL), was added 1 mL of chlorobenzene solution of **11** (100 mg, 0.60 mmol) slowly at room temperature. After half of the solution was added, another 2 mg of $Rh_2(OAc)_4$ was added. The total addition took 2 h. After evaporation of the excess propargyl chloride, the residue was eluted through a column of silica gel (CH_2Cl_2/hexane 2:3) to give **12 (**83 mg, 65%) as a colorless liquid. IR (neat): 1750 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 6.43−6.30 (1H, m), 4.61 (1H, s), 4.18 (2H, s), 2.28−2.10 (3H, m), 2.08−1.95 (1H, m), 1.95−1.83 (1H, m), 1.70 (3H, s) 1.60−1.46 (1H, m). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 210.7, 143.2, 139.9, 90.4, 83.9, 48.5, 38.7, 27.9, 26.3, 16.3, 15.3. HRMS (CI) (*m*/*z*): $[M + NH_4]^+$ calcd for $C_{11}H_{17}NO_2Cl$ 230.0948, found 230.0947.

Diol (13). To an ether solution (2 mL) of **12** (60 mg, 0.28 mmol) was added a solution of MeLi (606 μL, 0.85 mmol, 1.4 M) in ether at −78 °C, and the temperature was raised to 0 °C after 40 min and kept there for 10 min before saturated NH_4Cl solution was added to quench the reaction. The reaction mixture was extracted with ether three times, and the combined organic phase was washed with brine, dried, and evaporated. The residue was chromatographed (CH_2Cl_2/EtOAc 4:1) to give **13 (**40 mg, 62%) as a liquid with a slight yellow color. IR (neat): 3442 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 6.14 (1H, br s), 6.12−6.02 (1H, m), 4.14 (1H, d, J = 2.0 Hz), 2.73−2.54 (1H, m), 2.38−2.24 (1H, m), 2.23−2.14 (1H, m), 2.11 (3H, s), 2.00−1.69 (3H, m), 0.92 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.9, 136.6, 116.5, 111.4, 76.1, 72.4, 51.2, 27.9, 23.6, 20.8, 15.8, 15.7. HRMS (CI) (*m*/*z*): $[M + NH_4]^+$ calcd for $C_{12}H_{21}NO_2Cl$ 246.1261, found 246.1265.

Keto Alcohol (5). IBX (2-iodoxybenzoic acid) (49 mg, 0.175 mmol) was added to 1 mL of DMSO. After 20 min the solution became clear, and then **13** (20 mg, 0.087 mmol) in 1 mL of THF was added to the IBX solution at room temperature. After 4 h, water was added to dilute the solution, and ether was used to extract the solution three times. The combined organic phase was washed with brine, dried, and evaporated. The concentrate was chromatographed (hexane/EtOAc 25:1) to give **5 (**8.5 mg, 43%) as a colorless liquid. IR (neat): 3496, 1698, 1559 cm^{-1}. UV (methanol) λ nm (ϵ): 233 (11580), 290 (7804). ^1H NMR ($CDCl_3$, 400 MHz): δ 6.99−6.82 (1H, m), 6.42−6.26 (1H, m), 4.02 (1H, s), 2.51−2.25 (3H, m), 2.23−2.21 (3H, m), 2.02−1,80 (2H, m), 1.78−1.64 (1H, m), 1.20 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 201.3, 149.7, 132.0, 124.3, 116.0, 79.1, 52.3, 29.2, 23.8, 21.8, 21.7, 16.2. HRMS (CI) (*m*/*z*): $[M + NH_4]^+$ calcd for $C_{12}H_{19}NO_2Cl$ 244.110, found 244.1097.

Diketone (16). A solution of **11** (2.83 g, 17.03 mmol) in 30 mL of chlorobenzene was added dropwise to 2-cyclopentenone (5 g, 60.9 mmol) dissolved in 3 mL of chlorobenzene with $Rh_2(OAc)_4$ (26.5 mg, 0.06 mmol) at room temperature during 12 h. After 1 h, the solvent and the excess 2-cyclopentenone were evaporated off at 50 °C. The residue was chromatographed (hexane/EtOAc 5:1−5:2) to give compound **16** (1.37 g, 37%) as a white solid: mp 111−113 °C. IR (KBr): 1756, 1737 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 4.30 (1H, s), 2.75−2.55 (1H, dt, J = 4.4 Hz, 8.4 Hz), 2.42−2.27 (2H, m), 2.27−2.13 (3H, m), 2.12−2.02 (2H, m), 2.02−1.91 (2H, m), 1.90−1.75 (2H, m), 1.52 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 217.4, 214.8, 90.7, 87.0, 56.1, 53.2, 42.0, 39.6, 26.0, 25.5, 25.2, 15.1, 14.0. HRMS (CI) (*m*/*z*) $[M + H]^+$ calcd for $C_{13}H_{17}O_3$ 221.1178, found 221.1177.

Ketone (17). Ethylene glycol (25 mL) was added to a CH_2Cl_2 (10 mL) solution of **16** (1.5 g, 6.90 mmol), and to this solution was added TMSCl (6.6 mL, 52.0 mmol) at 0 °C. The temperature was then raised to room temperature and kept for 27 h. The solution was poured into an aqueous solution of $NaHCO_3$ (150 mL, 0.63M) at 0 °C. The product was extracted with CH_2Cl_2 three times, and the combined organic phase was washed with brine and dried. After evaporation, the residue was chromatographed (hexane/EtOAc 5:2) to give **17** (1.4 g, 77%) as a white solid: mp 119−120 °C. IR (dry film): 1726 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 4.06 (1H, m), 4.01−3.88 (4H, m), 2.95−2.86 (1H, m), 2.35−2.19 (3H, m), 2.18−1.91 (4H, m), 1.89−1.52 (4H, m), 1.39 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 220.1, 113.5, 91.0, 87.7, 65.6, 65.0, 55.4, 53.3, 39.8, 39.6, 25.5, 25.5, 23.0, 15.5, 14.5. HRMS (CI) (*m*/*z*) $[M + H]^+$ calcd for $C_{15}H_{21}O_4$ 265.1440, found 265.1434.

Alcohol (18). Compound **17** (2.57 g, 9.72 mmol) was dissolved in a methanol solution of KOH (100 mL, 6%) at 53 °C. After 3 h the solvent was evaporated at 30 °C. The residue was partitioned between water and CH_2Cl_2. After separation, the aqueous phase was extracted with CH_2Cl_2, and the combined extracts were dried and evaporated. The residue was chromatographed (CH_2Cl_2/EtOAc 5:1) to give **18** (1.93 g, 75%) as a white solid: mp 178−180 °C. IR (dry film): 3442 (br), 1700, 1621 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 4.32−4.22 (1H, m), 4.16−4.00 (3H, m), 3.82 (1H, d, J = 3.6 Hz), 3.07−2.94 (1H, m), 2.80−2.67 (1H, m), 2.45 (3H, d, J = 2.8 Hz), 2.41−2.19 (3H, m), 2.19−2.07 (1H, m), 2.06−1.92 (3H, m,), 1.92−1.82 (3H, m). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.9, 150.1, 127.0, 110.9, 68.8, 66.8, 64.7, 49.3, 42.5, 39.7, 29.4, 23.5, 21.2, 17.1, 13.9. HRMS (CI) (*m*/*z*) $[M + H]^+$ calcd for $C_{15}H_{21}O_4$ 265.1434, found 265,1432.

Ketone (19). TESCl (10.1 mL, 60.2 mmol) was added to a pyridine (90 mL) solution of **18** (1.6 g, 6.05 mmol) at 0 °C. The solution was heated to 60 °C and kept there for 2 h. After cooling to room temperature, it was poured into an aqueous solution of $NaHCO_3$ (150 mL, 0.7 M) at 0 °C. This solution was extracted with CH_2Cl_2 three times. The combined organic phase was dried and evaporated. The residue was chromatographed (hexane/EtOAc 5:1−4:1) to give **19** (2.1 g, 92%) as a white solid: mp 120−122 °C. IR (dry film): 1697, 1625 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 4.37−4.20 (1H, m), 4.17−3.90 (3H, m), 3.80 (1H, d, J = 4.0 Hz), 3.06−2.90 (1H, m), 2.89−2.72 (1H, m), 2.46 (3H, d, J = 2.8 Hz), 2.41−2.18 (3H, m), 2.18−2.02 (1H, m), 2.01−1.85 (3H, m,), 1.85−1.64 (2H, m) 0.94 (9H, t, J = 7.8 Hz), 0.74−0.46 (6H, m). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 207.1, 150.6, 127.5, 111.3, 69.6, 66.5, 64.7, 49.8, 44.1, 40.0, 29.7, 23.5, 22.2, 17.1, 13.9, 7.3, 5.3. HRMS (MALDI) (*m*/*z*) $[M + H]^+$ calcd for $C_{21}H_{35}O_4Si$ 379.2299, found 379.2299.

Cross Conjugated Ketone (20). TMSCl (400 μL, 3.15 mmol) was added to a solution of **19** (600 mg, 1.58 mmol) in THF (6 mL) at −78 °C. To this solution was added a solution of LDA (2.38 mmol, 2 M) in THF (1.19 mL). After 10 min, the solution was warmed to 0 °C for 15 min, and then it was cooled to −78 °C. After addition of Et_3N (1.5 mL), the solution was poured into 5 mL of saturated $NaHCO_3$ solution. The mixture was extracted with ether three times, and the combined organic phase was washed with aqueous citric acid (10%) until the pH of the aqueous phase became 4.5, washed with brine, dried, and evaporated. The residue was dissolved in mixed solution of CH_3CN and THF (8 mL, 5:3), to which $Pd(OAc)_2$ (356.2 mg, 1.59 mmol) was added. After 3 h, the suspension was filtered, and the filtrate was evaporated. The residue was chromatographed (hexane/EtOAc 5:1) to give recovered **19** (96 mg, 16%) and **20** (400 mg, 65%) as an oil. IR (dry film): 1688, 1629 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.37−7.20 (1H, m), 6.27 (1H, dd, J = 6, 2.4 Hz), 4.45−4.21 (1H, m), 4.18−3.96 (4H, m), 3.75−3.54 (1H, br s), 2.93−2.67 (1H, m) 2.52 (3H, d, J = 0.9 Hz), 2.39−2.20 (1H, m), 2.11−2.05 (1H, m), 2.04−1.84 (3H, m,), 0.88 (9H, t, J = 7.8 Hz) 0.53 (6H, m). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.1, 155.2, 148.5, 137.6, 126.0, 111.1, 69.7, 66.6, 64.7, 50.4, 48.0, 29.6, 23.6, 17.0, 13.3, 7.1, 5.2. HRMS (MALDI) (*m*/*z*) $[M + H]^+$ calcd for $C_{21}H_{33}O_4Si$ 377.2143, found 377.2151.

Fulvene (21). A toluene solution of DIBALH (532 μL, 0.798 mmol, 1.5M) was added to a solution of **20** (200 mg, 0.51 mmol) in THF (5 mL) at −78 °C. After 3.5 h, CH_3OH (1 mL) was added, and the solution was warmed to room temperature. After 10 min sodium potassium tartrate solution (10 mL, 1 M) was added. The solution was filtered, and the residue was washed with chloroform. The organic phases were combined, and a few drops of HCl (1.5%) were added. After stirring for a few hours, the solution was evaporated, and the residue chromatographed (hexane/EtOAc 5:0.4) to give **21** (160 mg, 87%) as a yellow oil. The proton and carbon NMR spectra indicated that it was a mixture of two isomers in a ratio of 1:0.24. At high temperatures the peaks on the proton spectrum coalesced, and at low temperature they separated. Major isomer: ^1H NMR (CD_2Cl_2, 500 MHz, −15 °C): δ 6.40−6.32 (1H, m), 6.31−6.27 (1H, m), 6.12−6.08 (1H, m), 4.76 (1H, d, J = 2.0 Hz), 4.28−4.20 (1H, m) 4.19−4.03 (2H, m), 3.99−3.92 (1H, m) 2.68−2.56 (1H, m), 2.32 (3H, s), 2.30−2.22 (1H, m), 2.22−2.08 (1H, m), 2.01−1.80 (3H, m), 0.97 (9H, t, J = 8.0 Hz), 0.73−0.62 (6H, m). ^{13}C NMR (CD_2Cl_2, 125 MHz, −15 °C): δ 154.4, 138.4, 136.9, 131.5, 123.2, 117.9, 116.0, 71.4, 67.6, 67.4, 52.2, 28.9, 23.4, 17.9, 15.9, 7.0, 4.9. HRMS(CI) (*m*/*z*) $[M + H]^+$ calcd for $C_{21}H_{33}O_3Si$ 361.2199, found 361.2195.

Ketone (14). HOAc (50 μL) was added to a THF solution of TBAF (1 mL, 1 M). The solution was in turn added to a solution of **21** (210 mg, 0.58 mmol) in THF (9 mL) at 0 °C. After 3 days, 50 mL of EtOAc was added, and the solution was washed with brine and saturated $NaHCO_3$. Then it was dried and evaporated. The residue was chromatographed (CH_2Cl_2/EtOAc 8:1−5:1) to give a yellow oil. Pyridinium dichromate (90 mg, 0.24 mmol) was added to a solution of 30 mg of the yellow oil in CH_2Cl_2 (3 mL) at 0 °C. After 18 h, 10 mL of CH_2Cl_2 was added, and the solution was filtered through a pad of Celite. The filtrate was evaporated, and the residue was chromatographed (CH_2Cl_2/EtOAc 5:0.15−5:0.20) to give **14** (24 mg, 51% in two steps) as a yellow oil. IR (dry film): 1681, 1622 cm^{-1}. UV (methanol) λ nm (ϵ): 317 (5847). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.40−7.31 (1H, m), 6.84−6.74 (1H, dd, J = 4.8, 1.5 Hz), 6.70−6.61 (1H, dd, J = 4.8, 2.4 Hz), 4.32−4.09 (4H, m), 2.56 (3H, s), 2.48−2.33 (2H, m) 2.32−2.21 (2H, m), 2.21−2.05 (1H, m), 2.02−1.88 (1H, m). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.4, 162.1, 139.0, 135.1, 132.3, 128.2, 125.5, 109.7, 66.6, 53.7, 27.7, 19.3, 16.4. HRMS (MALDI) (*m*/*z*) $[M + H]^+$ calcd for $C_{15}H_{17}O_3$ 245.1172, found 245.1175.

Ketoacetal (22). Diketone **16** (2.88 g, 13.08 mmol) was dissolved in a cooled solution (−6 °C) of CH_2Cl_2 (15 mL) and ethylene glycol (25 mL), to which TMSCl (16.50 mL, 130.0 mmol) was added. After 4.5 h the mixture was poured into an aqueous solution of $NaHCO_3$ (100 mL, 4.7 M) at 0 °C. The mixture was stirred for 0.5 h and extracted with CH_2Cl_2 three times, and the combined organic phase was washed with brine, dried, and evaporated. The residue was chromatographed (hexane/ether 5:2−5:4) to give **22** (2.45 g, 71%) as a liquid. IR (neat): 1753 cm^{-1}. ^1H NMR (CD_2Cl_2, 400 MHz): δ 4.04 (1H, s), 4.00−3.89 (2H, m), 3.88−3.76 (2H, m), 2.41−2.15 (2H, m), 2.06−1.69 (8H, m), 1.62 (3H, s), 1.61−1.53 (2H, m). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 216.4, 118.4, 88.8, 86.4, 65.7, 63.1, 56.8, 49.7, 43.3, 35.5, 27.5, 25.6, 25.1, 14.9, 13.7. HRMS (MALDI) (*m*/*z*): $[M + Na]^+$ calcd for $C_{15}H_{20}O_4Na$ 287.1254, found 287.1266.

Hydroxyketone (23). Ketoacetal **22** (5 g, 18.92 mmol) was dissolved in THF (40 mL) at −78 °C, to which a solution of MeLi (16.21 mL, 22.68 mmol, 1.4 M) in ether was added. After 2 h MeOH (5 mL) was added to the mixture and saturated ammonium chloride was used to neutralize the solution, after it was warmed to room temperature. The mixture was then evaporated, the residue was dissolved in EtOAc, and the solution was washed with brine, dried, and evaporated. The residue was added to acetone (10 mL) with toluenesulfonic acid (pH 1) and kept overnight. A saturated $NaHCO_3$ solution was

used to neutralize the mixture. It was extracted with EtOAc, and the organic phase was washed with brine, dried, and evaporated. The residue was chromatographed (hexane/EtOAc 5:4) to give **23** (4.1 g, 92%) as a white solid: mp 118−120 °C. IR (neat): 3448 (br), 1730 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 3.87 (1H, s), 3.28−3.09 (1H, m), 2.34 (1H, d, J = 7.2 Hz), 2.32−2.19 (1H, m), 2.18−1.89 (5H,m), 1.88−1.69 (2H, m), 1.68−1.49 (3H, m), 1.39 (3H, s), 1.37 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 220.8, 92.1, 92.0, 78.4, 55.9, 53.6, 39.6, 39.1, 27.3, 25.9, 25.7, 25.4, 15.8, 14.9. HRMS (MALDI) (*m*/*z*): $[M + H]^+$ calcd for $C_{14}H_{21}O_3$ 237.1485, found 237.1483.

Dihydroxyketone (24). Ketone **23** (50 mg, 0.21 mmol) was dissolved in a methanolic solution of KOH (15 mL, 6%) at 60 °C for 4 h. The methanol was then removed under reduced pressure at 40 °C. The residue was dissolved in EtOAc, and the solution was washed with brine, dried, and evaporated. The residue was chromatographed (hexane/EtOAc 1:1−1:3) to give recovered **23** (25 mg, 50%) and **24** (16 mg, 32%) as a white solid: mp 184−186 °C. IR (film): 3431 (br), 1691, 1615 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz): δ 3.63 (1H, d, J = 4.0 Hz), 3.21−2.99 (1H, m), 2.60−2.35 (5H, m), 2.35−2.13 (3H, m), 2.10−1.89 (3H,m), 1.89−1.72 (2H, m), 1.62 (3H, s). ^{13}C NMR (CD_3OD, 100 MHz): δ 210.1, 153.0, 128.5, 75.2, 75.1, 51.3, 42.0, 40.3, 29.6, 24.5, 23.6, 22.3, 17.2, 14.9. HRMS (MALDI) (*m*/*z*): $[M + H]^+$ calcd for $C_{14}H_{21}O_3$ 237.1485, found 237.1486.

Compound 25. To A pyridine solution (1 mL) of **24** (50 mg, 0.21 mmol) with DMAP (2.6 mg, 0.021 mmol) was added molecular sieves (100 mg, 3 Å) and TESCl (350.7 μL, 2.1 mmol). The mixture was kept at 80 °C overnight and then was cooled and poured into a saturated $NaHCO_3$ solution (10 mL). After filtration the mixture was extracted three times with EtOAc, and the combined organic phase was washed with brine, dried, and evaporated. The residue was chromatographed (hexane/EtOAc 1:3) to give **25** (66 mg, 90%) as an oil. IR (neat): 3465 (br), 1704, 1627 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 3.35 (1H, d, J = 8.4 Hz), 2.86−2.70 (1H, m), 2.53−2.40 (1H, m), 2.41 (3H, d, J = 2.8 Hz), 2.3−2.61 (4H, m), 2.12−1.91(5H, m), 1.43(3H, s), 1.42−1.32 (1H, m), 1.01 (9H, t, J = 8.0 Hz), 0.68 (6H, q, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 207.0, 151.2, 128.9, 77.5, 76.0, 52.5, 44.8, 39.5, 28.8, 26.8, 24.0, 22.4, 16.1, 15.1, 7.4, 5.7. HRMS (MALDI) (*m*/*z*): $[M + Na]^+$ calcd for $C_{20}H_{34}O_3Na$ 373.2169, found 373.2168.

Cross-Conjugated Ketone (26). Unsaturated ketone **25** (80 mg, 0.228 mmol) was dissolved in THF (2 mL) at −78 °C, to which triethylamine (0.5 mL), trimethylsilyl chloride (50.0 μL, 0.39 mmol) and a solution of LDA (0.342 mL, 0.684 mmol, 2 M) in ether were added in sequence. After 1 h a saturated $NaHCO_3$ solution (0.1 mL) was added, and the mixture was brought to room temperature. Ether was added followed by citric acid (5%) to bring down the pH of the solution to 4.5. After separation the organic phase was washed with brine, dried, and evaporated. The residue was dissolved in a mixture of THF and CH_3CN (1 mL, 1:1), and to this solution was added $Pd(OAc)_2$ (51.2 mg, 0.228 mmol) at room temperature. After 3 h CH_2Cl_2 was added, and the mixture was filtered through Celite. After evaporation the residue was chromatographed (hexane/EtOAc 3:1) to give recovered **25** (16 mg, 20%) and **26** (52 mg, 65%) as a colorless oil. IR (neat): 3446 (br), 1676, 1616 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.34 (1H, dd, J = 6.4, 2.4 Hz), 6.28 (1H, dd, J = 6.4, 2.4 Hz), 4.11 (1H, d J = 3.6 Hz), 3.87−3.64 (1H, m), 2.50 (3H, d, J = 0.8 Hz), 2.48−2.36 (1H, m), 2.35−2.24 (1H, m), 2.23−2.10 (1H, m), 2.09−1.84 (3H, m), 1.70−1.61 (1H, br s), 1.54 (3H, s), 0.87 (9H, t, J = 7.6 Hz), 0.61−0.42 (6H, m). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.4, 155.8, 148.8, 137.4, 126.4, 75.6, 75.4, 51.1, 45.6, 29.0, 24.1, 23.6, 16.5, 14.0, 7.2, 5.5. HRMS (MALDI) (*m*/*z*): $[M + H]^+$ calcd for $C_{20}H_{33}O_3Si$ 349.2193, found 349.2193.

Hydroxyfulvene (27). Ketone **26** (28 mg, 0.08 mmol) was dissolved in THF (2 mL) at −78 °C, and to this solution was added DIBALH (160.0 μL, 0.24 mmol, 1.5 M). After 15 min methanol (0.5 mL) was added, the temperature was raised to room temperature, and EtOAc (10 mL) and some Celite were added. After 0.5 h the mixture was filtered, and the filtrate was washed with brine, dried, and evaporated. The residue was dissolved in $CHCl_3$ (5 mL), and a few drops of 1.5% HCl were added. After 2 h, the mixture was neutralized with saturated $NaHCO_3$, dried, and evaporated. The residue was chromatographed (CH_2Cl_2/EtOAc 5:0.25) to give **27** (18.6 mg, 70%) as a yellow oil. IR (neat): 3599 (br), 1627, 1123, 1069, 1006 cm^{-1}. ^1H NMR (CD_2Cl_2, 500 MHz): δ 6.34 (1H, dd, J = 5.0, 2.0 Hz), 6.30 (1H, d, J = 5.0 Hz), 6.10−6.05 (1H, m), 4.64 (1H, s), 3.10−2.83 (1H, m), 2.53−2.41 (1H, m), 2.36 (3H, s), 2.32−2.20 (1H, m), 2.05 (1H, s), 2.03−1.83 (2H, m), 1.80−1.67 (1H, m), 1.01 (9H, t, J = 8.0 Hz), 0.82 (3H, s), 0.72 (6H, q, J = 8.0 Hz). ^{13}C NMR (CD_2Cl_2, 125 MHz): δ 155.5, 138.9, 137.1, 131.3, 122.6, 118.1, 80.0, 73.2, 53.9, 26.7, 23.8, 17.8, 16.3, 15.9, 7.1, 5.5). HRMS (EI) (*m*/*z*): $[M]^+$ calcd for $C_{20}H_{32}O_2Si$ 332.2172, found 323.2165.

Hydroxyketone (28). Silyl ether **27** (14 mg, 0.042 mmol) was dissolved in THF (0.8 mL) at 0 °C. To this solution was added a THF solution of TBAF (54.7 μL, 0.0547 mmol, 5% (v/v) CH_3COOH). The solution was kept overnight and then dissolved in EtOAc. The organic phase was washed with brine, dried, and evaporated to give an oily residue. The residue was chromatographed (CH_2Cl_2/EtOAc 5:2) to give an oily yellow residue. IBX (2-iodoxybenzoic acid) (22.1 mg, 0.08 mmol) was added to DMSO (0.5 mL). After the mixture became a clear solution, a CH_2Cl_2 solution (0.5 mL) of the above yellow residue was added at room temperature. After 40 min ether was added, and the resulting solution was washed with brine, dried ,and evaporated. The residue was chromatographed (CH_2Cl_2/EtOAc 5:0.2) to give **28** (7 mg, 77%) as an oil. IR (neat): 3457 (br), 1665, 1618 cm^{-1}. UV ($CHCl_3$) λ nm (ϵ): 317 (10177). ^1H NMR (CD_2Cl_2, 400 MHz): δ 7.19 (1H, br s), 6.88−6.73 (1H, m), 6.65 (1H, dd, J = 4.8, 2.4 Hz), 4.31 (1H, s), 2.56 (3H, s), 2.52−2.35 (3H, m), 2.08−1.87 (2H, m), 1.86−1.71 (1H, m), 1.26 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.0, 166.3, 139.4, 133.4, 132.0, 126.0, 125.1, 81.1, 57.2, 31.8, 24.5, 24.1, 19.5, 15.9. HRMS (MALDI) (*m*/*z*): $[M + H]^+$ calcd for $C_{14}H_{17}O_2$ 217.1223, found 217.1229.

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Supporting Information Available: NMR spectra of the synthesized compounds and X-ray files of **16** and **23** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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