Regioselective Intramolecular Oxidation of Phenols and Anisoles by Dioxiranes Generated in Situ

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A novel method for regioselective oxidation of phenols and anisoles has been developed in which dioxiranes, generated in situ from ketones and Oxone, oxidize phenol derivatives in an intramolecular fashion. A series of ketones with electron-withdrawing groups, such as CF_3, COOMe, and CH_2Cl, were attached to phenols, anisoles, or aryl rings via a C_2 or C_3 methylene linker. In a homogeneous solvent system of CH_3CN and H_2O, oxidation of phenol derivatives **1**−**10** afforded spiro 2-hydroxydienones in 24−55% yields regardless of the presence of other substituents (ortho Me, meta Me or Br) on the aryl ring and the length of the linker. Experimental evidences were provided to support the mechanism that involves a regioselective π bond epoxidation of aryl rings followed by epoxide rearrangement and hemiketal formation.

Introduction

Oxidation of phenols has been recognized as an important area in organic chemistry since phenolic oxidation plays important roles in biosynthesis and total synthesis of many natural products such as quinoline and isoquinoline alkaloids.[1] In particular, *p*-quinols arised from oxidation of *p*-alkylphenols proved to be valuable building blocks in synthesis.[2] Thus, development of practical methods for selective oxidation of phenols to quinols has attracted a lot of attention.[3] Recently, a ruthenium-catalyzed oxidation method[4] using *t*-BuOOH as a co-oxidant was discovered to convert para-substituted phenols into *tert*-butyldioxy-dienones in a selective manner. Hypervalent iodine oxidants[5] such as (diacetoxyiodo)benzene (PIDA) and [bis(trifluoroacetoxy)iodo]-benzene (PIFA) have also been successfully used in selective oxidation of para-substituted phenols to *p*-quinols[6] and spiro cyclohexadienones,[6a,d−i] and the latter were employed as key intermediates in the synthesis of antibiotic aranorosin[7] (Scheme 1). A common feature of these methods involves oxidation of phenol hydroxyl groups and subsequent transformation to reactive electrophilic intermediates which are then trapped by nucleophiles. However, there is no chemical method available for regioselective π-bond oxidation of phenols and phenol ether derivatives.[8]

Dioxiranes,[9] a new class of versatile oxidants, have been used to oxidize phenols,[10] catechols,[11] hydroquinones,[12] anisoles,[13] and even aromatic hydrocarbons[14] under mild conditions. However, most of those oxidation reactions lack regioselectivity, which is partially overcome by using hindered phenols[11] or performing the reaction under acidic conditions.[13] Here we report an intramolecular method for regioselective oxidation of phenols and anisoles to spirocyclohexadienones, which utilizes dioxiranes generated in situ. These oxidation reactions may proceed via a regioselective π bond oxidation of phenols and anisoles followed by epoxide rearrangement and

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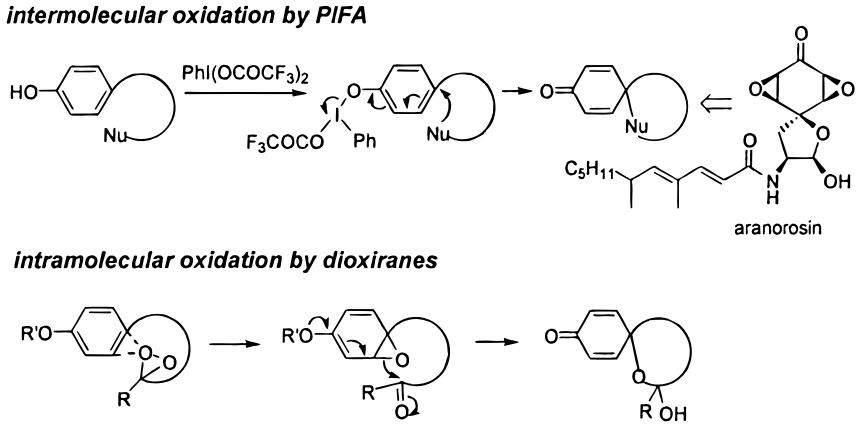
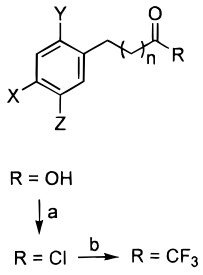
Scheme 1



Scheme 2[a]



ketone	n	X	Y	Z
1	1	OH	H	H
2	1	OMe	H	H
5	1	OMe	H	Br
7	1	OMe	H	Me
9	1	OMe	Me	Me
10	2	OMe	H	H
11	1	H	H	H
12	1	Me	H	H
13	1	Cl	H	H
14	2	H	H	H

[a] (a) Oxalyl chloride, CH_2Cl_2, rt; (b) $(CF_3CO)_2O$, pyridine, CH_2Cl_2, −50 °C to −20 °C.

hemiketal formation, which constitutes a novel approach to selective oxidation of phenols and especially phenol ether derivatives (Scheme 1).

Results

Design and Synthesis of Ketones 1−14 for Intramolecular Oxidation of Phenols and Anisoles. We previously reported that unactivated C−H bonds at the δ site of ketones were oxidized selectively in good yields.[15] Ketones with electron-withdrawing groups, such as CF_3, COOMe, and CH_2Cl, showed higher activities in the oxidation reactions. Therefore, those reactive ketones were attached to phenols, anisoles, or aryl rings via a C_2 or C_3 methylene linker.[16] Following a literature procedure,[17] trifluoromethyl ketones **1**, **2**, **5**, **7**, and **9**−**14** were readily synthesized by stirring the corresponding carboxylic acid chlorides with trifluoroacetic anhydride and pyridine in CH_2Cl_2 from −50 to −20 °C for 5 h (Scheme 2). As shown in Scheme 3, ester **3c** was converted to ketoester **3** via α-hydroxylation[18] and TPAP-catalyzed oxidation,[19] whereas ketoesters **6** and **8** were prepared from the corresponding acids according to the procedures developed by Wasserman and co-workers.[20−22] Ketone **4** was synthesized by treatment of methyl ester **2b** with LDA and chloroiodomethane at −78 °C (Scheme 4).[23]

Intramolecular Oxidation of Ketones 1−14 (Table 1). Intramolecular oxidation reactions of ketones **1**−**14** were carried out with a 10 mM solution of ketones **1**−**14** in a 1.5:1 mixture of CH_3CN and aqueous Na_2·EDTA solution (4×10^{-4} M) containing 5.0 equiv of Oxone and 15.0 equiv of $NaHCO_3$ at room temperature. The results are summarized in Table 1.

Oxidation of phenol derivatives **1**−**10** gave novel spiro 2-hydroxydienones **1a** and **3a**−**10a** in 24−55% yields. Phenol **1** and anisole **2** gave the same product **1a** in similar yields. Compared with ketone **4** containing a CH_2-Cl group, ketones **1**−**3** and **5**−**10** with stronger electron-withdrawing groups CF_3 and COOMe exhibited higher activities (entry 4 vs entries 1−3 and 5−10). 4-(4-Hydroxyphenyl)butan-2-one failed to afford the desired oxidation product owing to the low reactivity of the methyl ketone (data not shown). Ketones with trifluoromethyl group as the activating group generally gave higher yields than those with COOMe group (entries 2 vs 3, 5 vs 6, and 7 vs 8). Anisoles **5** and **6** with a bromo substituent and **7**−**9** with methyl groups on the aryl ring were oxidized to the unsymmetrically substituted spiro dienones **5a**−**9a** (entries 5−9). Anisole **10** with a C_3 methylene linker furnished spiro dienones **10a** and 5-hydroxydodecenone **10b** (its structure was determined by X-ray analysis) (entry 10). Presumably **10b** came from intramolecular oxidation of **10a** as shown in Figure 1.[24] Under the reaction conditions, hemiketal **10a** was in equilibrium with its open form, hydroxy ketone **10c**. Owing to geometric constraints, the dioxirane generated from **10c** effected intramolecular enone epoxidation only at the face anti to the allylic hydroxy group. The resulting epoxide was opened by the adjacent hydroxy group to afford **10b**.

Unlike phenol derivatives **1**−**10**, ketones **11** and **12** with unactivated aryl rings (para H or CH_3) and a C_2

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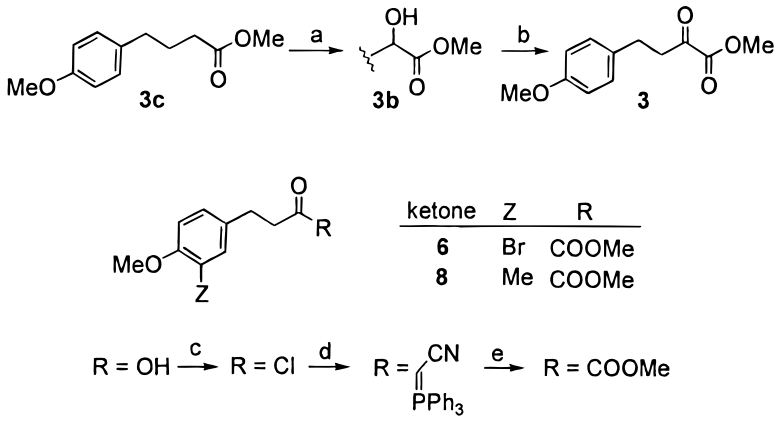
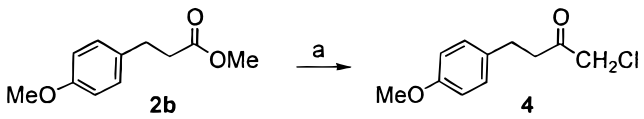
(24) To confirm this conjecture, **10a** was subjected to the reaction conditions as indicated in Table 1 for 24 h. ^{1}H NMR analysis indicated that the crude reaction mixture indeed contained **10a** and **10b** (ratio 1:0.25).

Scheme 3[a]



[a] (a) KHMDS, 2-(phenylsulfonyl)-3-phenyloxaziridine, THF, −78 °C; (b) tetrapropylammonium perruthenate (cat.), 4-methylmorpholine *N*-oxide, MS 4 Å, CH_2Cl_2, rt; (c) oxalyl chloride, CH_2Cl_2, rt; (d) $Ph_3P{=}CHCN$, *N*,*O*-bis(trimethylsilyl)acetamide, CH_2Cl_2, rt; (e) tetrabutylammonium−Oxone, CH_2Cl_2, MeOH, 50 °C.

Scheme 4[a]



[a] (a) LDA, CH_2ICl, THF, −78 °C, N_2; acetic acid, 48%.

methylene linker provided chroman-2-ols in 35−38% yield (entries 11 and 12). Oxidation of ketone **13** with an electron-withdrawing para Cl group proceeded sluggishly, and unsubstituted ketone **14** with a C_3 methylene linker failed to give any identifiable oxidation product after 24 h (entries 13 and 14).

Discussion

Oxidation of phenol derivatives **1**−**10** afforded spiro 2-hydroxydienones **1a** and **3a**−**10a** as the major products, independent of the reactivity of the ketones, the substituents on the aryl rings, and the length of the linker. The high regioselectivities reflect the intramolecular nature of the reaction. To account for the formation of spiro 2-hydroxydienones, we propose a mechanism which involves selective epoxidation of a π bond on the aryl ring ($\gamma-\delta$ π bonds for **1**−**9** and $\delta-\epsilon$ π bond for **10**) to the corresponding arene epoxide[14] followed by a *p*-hydroxy or -methoxy group-assisted epoxide opening and hemiketal formation (Figure 2).

For the oxidation of unsubstituted ketone **11**, there are two possible pathways for the formation of chroman-2-ol (**11a**), namely *$\gamma-\delta$ π bond epoxidation* or *δ C−H bond oxidation* (Figure 3). For the mechanism involving $\gamma-\delta$ π bond epoxidation, an unstable arene oxide is formed and then rearranges to a hydroxy trifluoromethyl ketone. In the alternative pathway, the same hydroxy trifluoromethyl ketone intermediate is formed via a δ C−H bond oxidation. Here these two mechanisms cannot be distinguished.

For *p*-methyl-substituted ketone **12**, a single 7-methyl chroman-2-ol (**12a**) would be expected to result from the reaction involving the δ C−H bond oxidation. However, a mixture of **12a** and **12b** were obtained, supporting the *$\gamma-\delta$ π bond epoxidation mechanism* (Figure 4). The rearrangement of arene oxide **12c** may proceed through the NIH shift,[13,25] i.e., hydroxylation-induced hydride and alkyl migration, to afford two dienones, which are then aromatized to the corresponding phenols **12d** and **12e**, respectively. Followed by a facile cyclization, a mixture of **12a** and **12b** were isolated as the major products.

The correlation between the reactivities of ketones and electronic properties of various substituents on the aryl ring lends further support to the π bond epoxidation mechanism. For ketones **1**−**10** and **12** with electron-donating substituents on the aryl ring (such as *p*-OH, -OMe, and -Me groups) and unsubstituted ketone **11**, the oxidation reactions were complete within 2 h (Table 1, entries 1−3 and 5−12). In contrast, oxidation of ketone **13** with strong electron-withdrawing Cl group on the aryl ring proceeded very slowly with the starting material remaining unaltered after 48 h (Table 1, entry 13). The difference in reactivity reveals the electrophilic nature of the oxidation reactions since the reaction rate decreases with the electron density on the aryl ring. This trend is in agreement with the mechanism involving *π bond epoxidation*, since para-substituents on the aryl ring exert more significant effect on the electron density of the $\gamma-\delta$ π bond than that of the δ C−H bond.

Recently a spiro transition state rather than a planar one has been established for dioxirane epoxidation.[26] This should also hold for intramolecular epoxidation of aryl rings. On the basis of the length of the linker, dioxiranes generated from ketones **1**−**12** and **14** can be classified into two classes: (a) Class I from ketones **1**−**9** and **11** with a C_2 methylene linker, and (b) Class II from ketones **10** and **14** with a C_3 methylene linker. Class I dioxiranes yielded either dienones or chromanols regardless of the electronic properties of the aryl ring (electron rich or unactivated) (Table 1, entries 1−9 and 11). However, the same scenario was not observed for Class II dioxiranes. Anisole **10** gave dienone **10a** via intramolecular oxidation (Table 1, entry 10), but ketone **14** without electronic-

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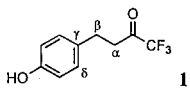
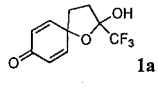
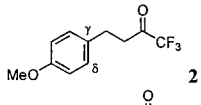
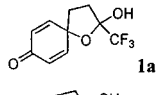
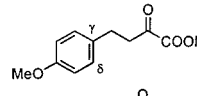
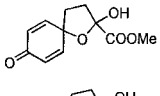
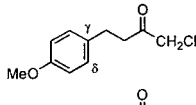
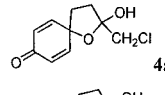
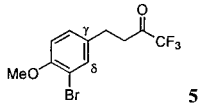
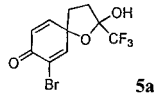
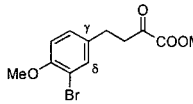
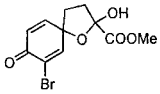
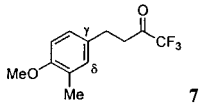
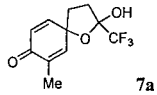
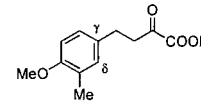
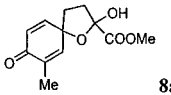
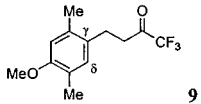
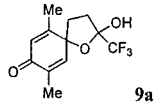
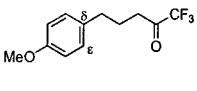
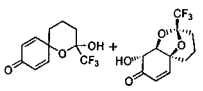
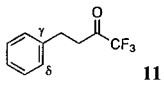
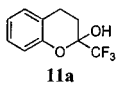
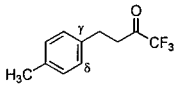
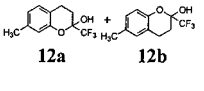
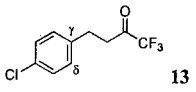
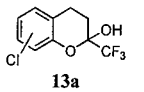
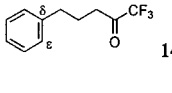
Table 1. Selective Oxidation of Ketones 1−14[a]

Ketone (10 mM) —Oxone/$NaHCO_3$, CH_3CN/H_2O, rt→ Product

entry	ketone	time	product	yield (%)[b]
1	 **1**	15 min	 **1a**	53
2	 **2**	30 min	 **1a**	55
3	 **3**	1h	 **3a**	30
4	 **4**	24 h	 **4a**	24[c]
5	 **5**	2 h	 **5a**	47[d]
6	 **6**	1.5 h	 **6a**	24[d]
7	 **7**	1 h	 **7a**	55[d]
8	 **8**	1 h	 **8a**	24[d]
9	 **9**	1 h	 **9a**	50[d]
10	 **10**	1.4 h	 **10a** (26%) **10b** (22%)	48
11	 **11**	2 h	 **11a**	38
12	 **12**	2 h	 **12a** **12b**	35[e]
13	 **13**	48 h	 **13a**	–[f]
14	 **14**	24 h	–	–[g]

[a] Unless otherwise indicated, all reactions were carried out with a 1.0×10^{-2} M solution of ketone in a 1.5:1 mixture of CH_3CN and aqueous Na_2•EDTA solution (4×10^{-4} M) containing 5.0 equiv of Oxone and 15.0 equiv of $NaHCO_3$ at room temperature. [b] Isolated yield after flash column chromatography. [c] Isolated yield based on 76% conversion after 24 h. [d] Combined yield of a 1:1 mixture of diastereomers. [e] The ratio of **12a** and **12b** were not determined. [f] Only a trace amount of cyclized product can be isolated with 40% starting materials recovered. The ratio of the regioisomers could not be determined. [g] No identifiable oxidation product can be found.

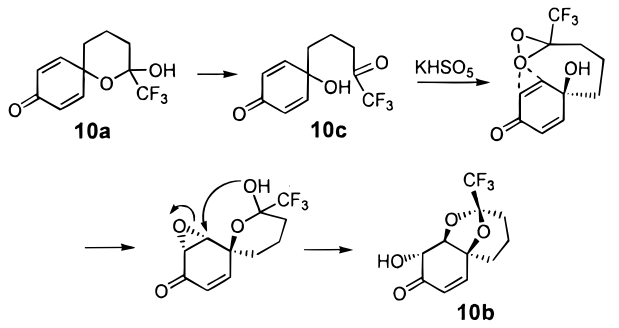


Figure 1.

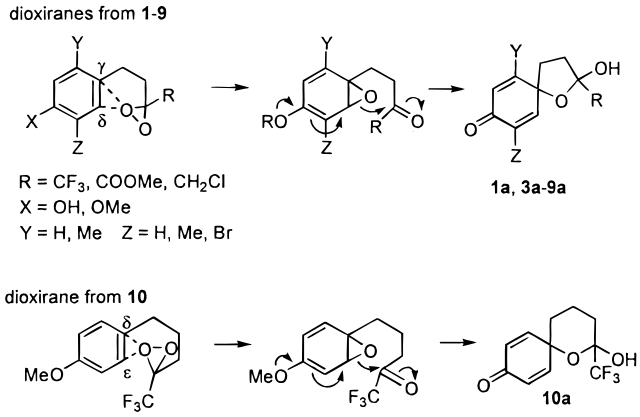


Figure 2.

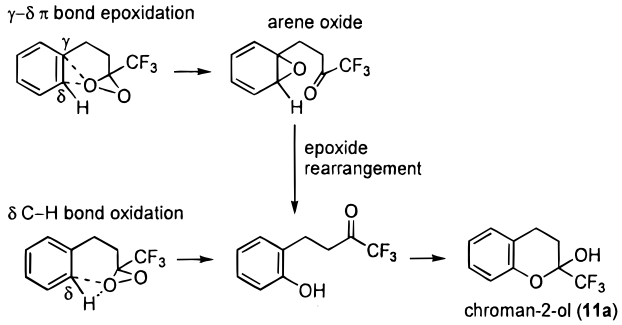


Figure 3.

activating MeO group on the aryl ring could not undergo intramolecular oxidation and afforded a mixture of unidentified products (Table 1, entry 14). Therefore, ketones with a C_2 methylene linker (Class I) are more suitable for regioselective intramolecular oxidation of aryl rings than those with a C_3 methylene linker (Class II), probably as a result of the geometric constraints of a spiro transition state.

To demonstrate the synthetic value of the spiro dienones, 2-hydroxy-2-trifluoromethyl dienone **1a** was converted in 85% yield under acidic conditions to 2-(trifluoromethyl)chroman-2,6-diol **1b** via dienone−phenol rearrangement with alkyl migration (Scheme 5).[27] This provides an easy access to trifluoromethyl-substituted chroman-2-ols. On the other hand, the trifluoromethyl group can be removed under basic conditions.[28] For example, chroman-2-ols **11a** and **12a**,**b** were transformed

(27) Davies, J. S.; Hassall, C. H.; Schofield, J. A. *J. Chem. Soc.* **1964**, 3126.

(28) Simons, J. H.; Ramler, E. O. *J. Am. Chem. Soc.* **1943**, *65*, 389.

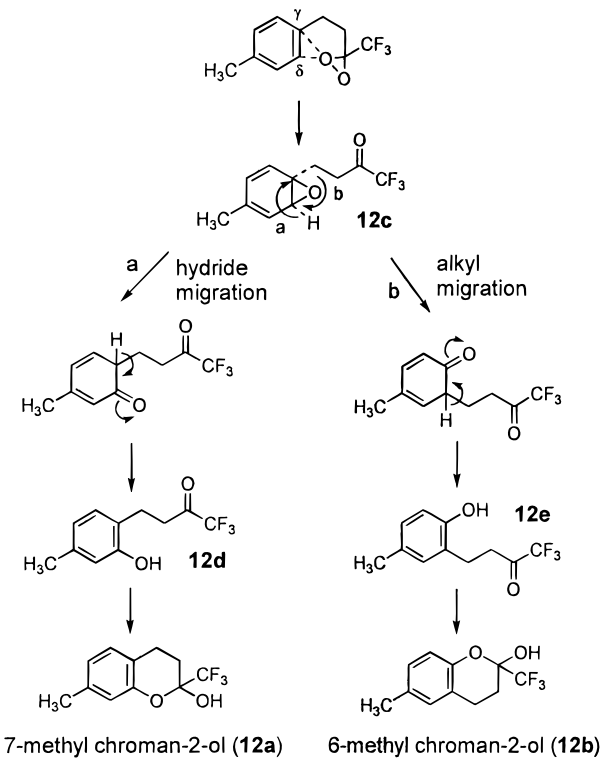
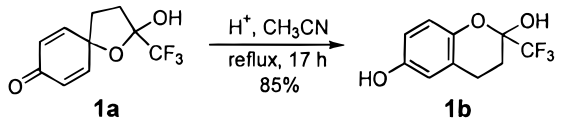
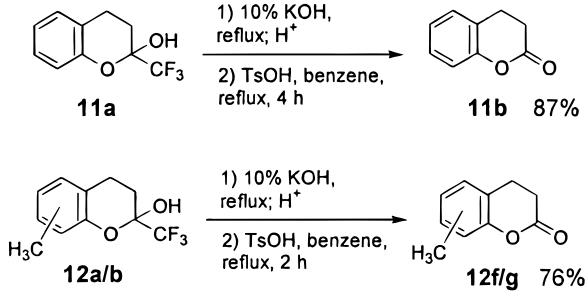


Figure 4.

Scheme 5



Scheme 6



respectively to chroman-2-ones **11b** (87%) and **12f**,**g** (76%) through basic hydrolysis and lactonization under acidic conditions (Scheme 6).

In summary, we have developed a novel method for regioselective oxidation of phenols and anisoles to spiro 2-hydroxydienones by dioxiranes generated in situ under mild conditions. The oxidation reactions are proposed to proceed via a regioselective π bond epoxidation followed by epoxide rearrangement and hemiketal formation. This method allows convenient access to a series of novel CF_3-containing spiro 2-hydroxydienones, starting from anisoles without prior deprotection. Future work will be directed at exploring the potentials of substituted spiro dienones as building blocks in natural product synthesis.

Experimental Section

General Methods. All reactions were performed in oven-dried apparatus. Air and moisture-sensitive compounds were introduced via syringes through a rubber septum. THF was distilled from sodium−benzophenone. Dichloromethane was distilled over calcium hydride. Flash column chromatography was performed using the indicated solvent system on E. Merck silica gel 60 (230−400 mesh ASTM).

General Procedure for Intramolecular Oxidation (Table 1, Entry 2). To a solution of ketone **2** (0.232 g, 1.0 mmol) in CH_3CN (60 mL) was added an aqueous Na_2·EDTA solution (40 mL, 4×10^{-4} M) at room temperature. To this solution was added a mixture of Oxone (3.07 g, 5.0 mmol) and $NaHCO_3$ (1.30 g, 15.5 mmol). After stirring at room temperature for 30 min, the reaction mixture was poured into brine and extracted with EtOAc three times. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (30% EtOAc in *n*-hexane) to give **1a** (0.129 g, 55% yield) as a colorless syrup. Analytical TLC (silica gel 60), 50% EtOAc in *n*-hexane, $R_f = 0.45$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.04−2.27 (m, 1H), 2.36−2.55 (m, 3H), 6.17−6.21 (m, 2H), 6.83 (dd, J = 10.0, 3.0 Hz, 1H), 6.95 (dd, J = 10.0, 3.0 Hz, 1H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 33.17, 34.93, 81.08, 103.83 (q, $^2J_{C,F} = 34.0$ Hz), 122.44 (q, $^1J_{C,F}$ = 284.0 Hz), 127.91, 128.03, 147.39, 149.39, 185.39; IR (CH_2Cl_2) 3549.9, 1672.7 cm^{-1}; EIMS (20 eV) m/z 234 (M^+, 66), 165 (6), 147 (7), 109 (100); HRMS for $C_{10}H_9F_3O_3$ (M^+), calcd 234.0504, found 234.0500.

Rearrangement of 1a to 1b in Acidic Medium. A solution of **1a** (0.053 g, 0.23 mmol) in CH_3CN (2 mL) and 6 N hydrochloric acid (4 mL) was refluxed for 17 h. The reaction mixture was diluted with EtOAc (30 mL) and washed with saturated $NaHCO_3$ solution (20 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (30% EtOAc in *n*-hexane) to afford **1b** (45 mg, 85%) as a syrup. Analytical TLC (silica gel 60), 30% EtOAc in *n*-hexane, $R_f = 0.18$; ^{1}H NMR (300 MHz, CD_3CN) δ 1.85−1.96 (m, 1H), 2.12 (dd, J = 13.5, 5.0 Hz, 1H), 2.70 (dd, J = 16.0, 5.0 Hz, 1H), 2.90 (ddd, J = 16.0, 13.5, 5.0 Hz, 1H), 5.18 (d, J = 1.8 Hz, 1H), 6.58−6.70 (m, 3H); ^{13}C NMR (75.5 MHz, CD_3CN) δ 20.69, 25.26, 94.99 (q, $^2J_{C,F} = 32.0$ Hz), 115.60, 116.05, 118.35, 123.58, 124.19 (q, $^1J_{C,F} = 285.0$ Hz), 145.10, 152.45; EIMS (20 eV) m/z 234 (M^+, 100), 165 (4); HRMS for $C_{10}H_9O_3F_3$ (M^+), calcd 234.0504, found 234.0500.

Preparation of Dihydrocoumarin 11b from 11a. A mixture of **11a** (0.045 g, 0.21 mmol) and 10% KOH (4 mL) was heated to reflux for 19 h. The reaction mixture was acidified with 2 N HCl and extracted with CH_2Cl_2 three times. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to give crude 3-(2-hydroxyphenyl)propionic acid. The crude acid was dissolved in benzene (5 mL) and refluxed with TsOH (4 mg) for 4 h. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ solution. The organic phase was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (30% EtOAc in *n*-hexane) to provide dihydrocoumarin (**11b**) (27 mg, 87% yield). The spectroscopic data of **11b** was found to be consistent with the authentic dihydrocoumrain as shown in Aldrich NMR library. Analytical TLC (silica gel 60), 30% EtOAc in *n*-hexane, $R_f = 0.51$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.79 (d, J = 7.7 Hz, 2H), 3.01 (d, J = 7.7 Hz, 2H), 7.04−7.28 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.72, 29.24, 116.95, 122.63, 124.40, 128.01, 128.27, 152.00, 168.58.

Preparation of 7- and 6-Methyl 3,4-Dihydrocoumrains 12f/g from 12a/b. A solution of a mixture of **12a** and **12b** (186 mg, 0.80 mmol) in an 10% KOH solution (6 mL) was stirred at refluxing temperature overnight. After being cooled to room temperature, the reaction mixture was acidified with 2 N HCl, saturated with NaCl, and extracted with Et_2O three times. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated to give the crude acid. A mixture of the crude acid in benzene (10 mL) containing TsOH (20 mg) was stirred at refluxing temperature for 2 h. After evaporation of the solvent, the residue was purified by flash column

chromatography (5% EtOAc in *n*-hexane) to afford a 1:1 mixture of 7-methyl 3,4-dihydrocoumrain **12f** and 6-methyl 3,4-dihydrocoumrain **12g** as a colorless syrup (99 mg, 76% yield), which showed consistent spectroscopic data as reported in the literature.[29] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H), 2.32 (s, 3H), 2.75 (t, J = 7.0 Hz, 4H), 2.94 (t, J = 7.0 Hz, 4H), 6.83−7.01 (m, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) **12f**: δ 21.02, 23.28, 29.33, 117.25, 119.42, 125.05, 127.67, 138.37, 151.81, 168.76; **12g**: δ 20.63, 23.63, 29.24, 116.52, 122.26, 128.42, 128.62, 133.91, 149.86, 168.76.

(29) Yates, P.; Macas, T. S. *Can. J. Chem.* **1988**, *66*, 1.

Acknowledgment. This work was supported by The University of Hong Kong and Hong Kong Research Grants Council.

Supporting Information Available: Experimental details for preparation of ketones **1**−**14**; characterization data of **3a**−**9a**, **10a**/**b**, **11a**, **12a**/**b**, and **13a**; X-ray structural analysis of **10b** containing tables of atomic coordinates, thermal parameters, bond lengths, and bond angles. This material is available free of charge via the Internet at http://pubs.acs.org.

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