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Diversity-Oriented Synthesis of Chromenes via Metal-Free Domino Reactions from Ketones and Phenols

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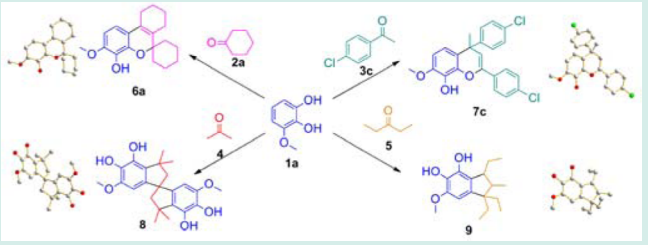
Supporting Information

ABSTRACT: Functionalized chromenes have been synthesized via highly selective metal-free domino reactions from ketones and phenols. 2H-Chromenes, 4H-chromenes, spiran and benzocyclopentane can be respectively prepared starting from the corresponding cyclic ketones, aryl methyl ketones, acetone, and 3-pentanone.



KEYWORDS: *diversity-oriented synthesis, metal-free, domino reaction*

INTRODUCTION

Chromenes and their derivatives are an important class of structural motifs present in many natural products and synthetic molecules.[1] They have also been applied in medicine,[2] health-promoting agents,[3] and photochromic materials.[4] Consequently, many synthetic methods have been developed for the construction of chromenes, including: (1) transition metal-catalyzed reactions;[5] and (2) organocatalyst-promoted reactions.[6] Despite extensive studies into the synthesis of chromenes, the development of a general strategy with high selectivity, which uses readily available starting materials under mild conditions, is still of great interest.

Diversity-oriented synthesis (DOS) as a tool for the discovery of novel and biologically active small molecules has drawn much attention from synthetic chemists.[7] DOS has many advantages including accessible complexity of molecules, consecutive reaction patterns, high reaction rate and efficiency, and minimal environmental impact.[8] Thus, DOS has received growing interest.

On the other hand, domino reactions are useful procedures for self-organized synthesis of organic compounds.[9] Compared with stepwise reactions, domino reactions should be more effective for the synthesis of complex organic compounds in one pot without separation and purification of the intermediates. Recently, we have developed a self-sorting domino reaction,[10] a focusing domino reaction[11] and a self-labor domino reaction.[12] Herein, we reported a highly selective synthesis of diverse chromenes via DOS-domino strategy from ketones and phenols in the presence of $TsOH{\cdot}H_2O$ without a metal catalyst as shown in Figure 1.

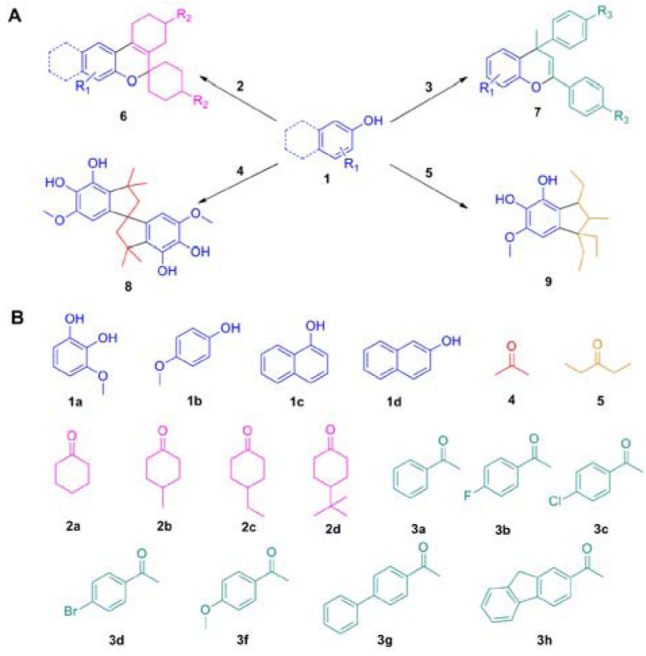


Figure 1. (A) Divergent DOS strategy for the construction of novel skeletons. (B) Chemical structures of the substances.

RESULTS AND DISCUSSION

Initially, we screened the acidic catalysts in various solvents (Table 1). A 15% yield of the chromene compound **6a** was obtained when $TsOH{\cdot}H_2O$ was used as the catalyst in benzene. However, the yield slightly increased to 20% when n-hexane was used as the solvent. Other popular solvents were found unsuitable for the reaction (Table 1, entries 4−11). The catalyst had an influence on the reaction. No product was obtained

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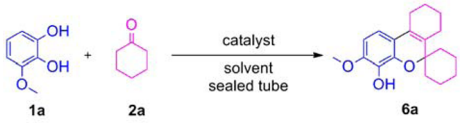
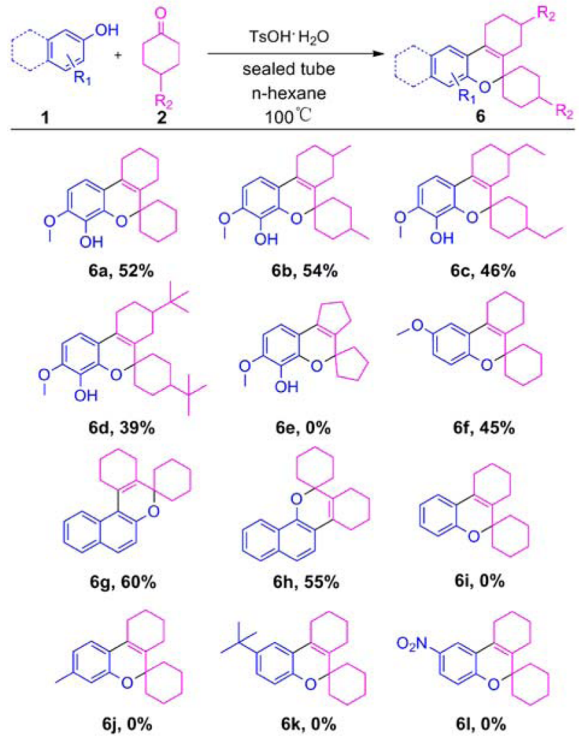
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	time (h)	T (°C)	yield (%)[b]
1	TsOH·H_2O	benzene	2	60	15
2	TsOH·H_2O	*n*-hexane	2	60	20
3	TsOH·H_2O	toluene	2	60	17
4	TsOH·H_2O	acetone	2	60	0
5	TsOH·H_2O	THF	2	60	0
6	TsOH·H_2O	DMSO	2	60	0
7	TsOH·H_2O	MeCN	2	60	0
8	TsOH·H_2O	DCE	2	60	0
9	TsOH·H_2O	dioxane	2	60	0
10	TsOH·H_2O	DMF	2	60	0
11	TsOH·H_2O	CH_3OH	2	60	0
12	$InCl_3$	*n*-hexane	2	60	0
13	$AlCl_3$	*n*-hexane	2	60	0
14	$AuCl_3$	*n*-hexane	2	60	0
15	CF_3SO_3H	*n*-hexane	2	60	6
16	HCl	*n*-hexane	2	60	0
17	AcOH	*n*-hexane	2	60	0
18	TsOH·H_2O	*n*-hexane	2	25	0
19	TsOH·H_2O	*n*-hexane	2	40	0
20	TsOH·H_2O	*n*-hexane	2	80	30
21	TsOH·H_2O	*n*-hexane	2	100	37
22	TsOH·H_2O	*n*-hexane	2	110	37
23	TsOH·H_2O	*n*-hexane	4	100	52

[a]Reaction conducted with 0.5 mmol of **1a**, 1.5 mmol of **2a**, and 0.5 mmol of TsOH·H_2O in 3 mL *n*-hexane. [b]Isolated yields.

Scheme 1. Reaction Scope of Phenols 1 and Ketones 2[a]



[a]Reaction was performed with phenols **1** (0.5 mmol), ketones **2** (1.5 mmol), and TsOH·H_2O (0.5 mmol) in *n*-hexane (3 mL) at 100 °C for 4 h. Isolated yields are given.

when TsOH·H_2O replaced by other protic or lewis acid (Table 1, entries 12−17). The reaction temperature was then optimized to increase the product yield, and 100 °C was found to be the optimal temperature (Table 1, entries 18−22). The effect of reaction time on the yield of **6a** was subsequently examined. Higher yields were observed when the reaction was carried out for 4 h (Table 1, entries 23). Ultimately, optimal conditions were identified as 1 equiv of phenol (**1a**), 3 equiv of ketone (**2**), and 0.5 equiv of TsOH·H_2O in n-hexane at 100 °C (Table 1, entry 23).

On the basis of the successful synthesis of the 2H-chromene **6a**, the optimized conditions were applied to the range of other phenols and cyclic ketones, the results are listed in Scheme 1. Generally, moderate yields were obtained using substituted cyclohexanones (Scheme 1, **6b**, **6c**, and **6d**). No product was obtained when cyclopentanone was used (Scheme 1, **6e**), which indicated that the steric effect and the strain of cyclic ketone influenced the reaction. Encouraged by the results obtained with cyclohexanones, we focused our attention on phenols. The corresponding products were also obtained in moderate yields with naphthols as the substrates (Scheme 1, **6g** and **6h**). When 4-methoxyphenol was employed as the substrate, the corresponding product was isolated in moderate yield (Scheme 1, **6f**). No product was obtained when phenol, *m*-cresol, 4-(*tert*-butyl) phenol, and 4-nitrophenol were used (Scheme 1, **6i**, **6j**, **6k**, and **6l**), which indicated that electron rich aromatic substrates were necessary for the domino cyclization reaction. This may be because the Friedel-crafts alkylation reaction of phenol used electron rich aromatic substrates as starting materials in this condition.

In addition, aryl methyl ketones were employed to probe the scope of the reaction. As shown in Scheme 2, 4H-chromenes could be obtained when aryl methyl ketones were used as the substrates. Generally, good yields were obtained starting from the *p*-halogenated aryl methyl ketones (Scheme 2, **7b**, **7c**, and **7d**). The corresponding products were also in good yields with 4-methoxyacetophenone as substrate (Scheme 2, **7f**). No corresponding product was obtained with 4-nitroacetophenone as substrate (Scheme 2, **7e**), which indicated that the electronic effect of aromatic ketones influenced the reaction. This may be because the aldol reaction of electron withdrawing aromatic substrates as starting materials cannot occur in this condition. Corresponding products were obtained in good yields when aryl methyl ketones with an aromatic substituent were employed (Scheme 2, **7g** and **7h**).

When acetone was used as the substrate, a spiro compound **8** was obtained in 25% yield. We found a similar spiro compound was reported in the literature from the reaction of catechol and acetone.[13] However, benzocyclopentane **9** was obtained starting from 3-pentanone in 31% yield, which indicated that the steric effect of the alkyl ketone influenced the reaction. The mixture was too difficult to be purified when the 4-heptanone was used. Furthermore, the structures of **6a**, **6cm**, **7c**, **8**, and **9** were also confirmed by X-ray crystallography (Figure 2).[14]

To investigate the detailed reaction process, we used GC-MS to detect the proposed intermediates for this reaction. It was verified that the corresponding intermediates **6am**, **7am**, **8m**, and **9m** were present in the reaction mixture.[15] The corresponding intermediates are listed in Scheme 4.

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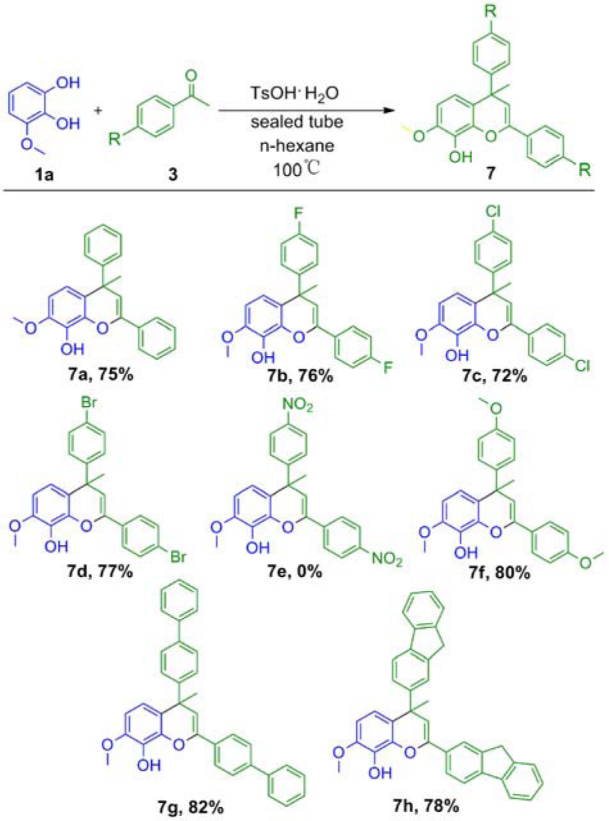
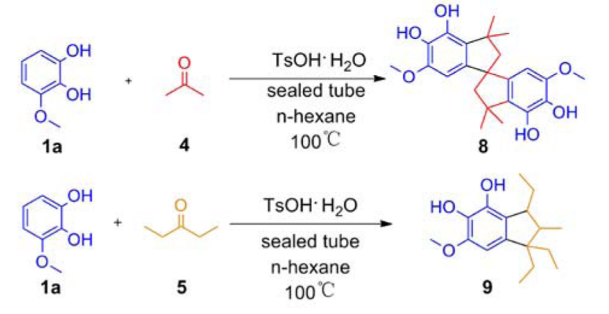
Scheme 2. Reaction Scope of Aromatic Ketones 3[a]



[a]Reaction was performed with phenol **1a** (0.5 mmol), ketones **2** (1.5 mmol), and TsOH·H_2O (0.5 mmol) in *n*-hexane (3 mL) at 100 °C for 4 h. Isolated yields are given.

Scheme 3. Reaction Scope of Ketones 4 and 5[a]



[a]Reaction was performed with phenol **1a** (0.5 mmol), ketones **4** (2.0 mmol), or **5** (1.5 mmol) and TsOH·H_2O (0.5 mmol) in *n*-hexane (3 mL) at 100 °C for 4 h.

On the basis of the above experiments, the possible mechanisms for the reactions are listed in Scheme 5. The intermediate **6am** is formed by the Friedel–Crafts alkylation reaction of **1a** with **2a**. Then **6am** reacts with **2a** to generate target the compound **6a** (Scheme 5a). The acetophenone **3a** reacts with itself to form intermediate **7am**, then **1a** undergoes intermolecular Michael addition reaction and dehydration reaction with **7am** to generate target compound **7a** (Scheme 5b).[6] **1a** reacts with **4** to form the intermediate **8m** by Friedel–Crafts alkylation reaction. Subsequently, **8m** reacts with **4** by double intermolecular alkylation, and double intramolecular Friedel–Crafts alkylation reaction and dehydration reaction to generate target compound **8** (Scheme 5c).[13] The intermediate **9m** is formed by the Friedel–Crafts alkylation reaction of **1a** with **5**. Consequently, the target compound **9** is generated by **9m** reacting with **5** (Scheme 5d). To verify the possible reaction mechanism, the reactions of **2c** with **6cm** and **1a** with **7am** were used to synthesize the corresponding target compounds. Fortunately, final products were obtained from the above reactions in 85% and 90% yields.

CONCLUSION

In conclusion, in this study, we have developed a novel method for the synthesis of functionalized chromenes from ketones and phenols based on metal-free domino reactions, which could be useful for generation of related compound library. The mild reaction conditions, simple operation and absence of metal catalyst make the described reactions an appropriate protocol for the synthesis of potentially bioactive compounds. Further studies on the applications of this reaction will be reported in due course.

EXPERIMENTAL PROCEDURES

General Procedure for the Synthesis of 2H-Chromenes (6a–6h). TsOH·H_2O (0.5 mmol) was added to a stirred solution of 3-methoxybenzene-1,2-diol (70 mg, 0.5 mmol) and cyclohexanone (147 mg, 1.5 mmol) in *n*-hexane (3 mL). The reaction mixture was stirred at 100 °C in a sealed tube for 4 h. The mixture was concentrated under reduced pressure. The residue was purified by flash chromatography to give 3-methoxy-7,8,9,10-tetrahydrospiro[benzo[c]chromene-6,1′-cyclohexan]-4-ol (**6a**) (78 mg, 52% yield). mp = 115.4–119.5 °C; IR (KBr cm^{-1}) 3488, 2929, 2834, 1617, 1513, 1461, 1354, 1218, 1084; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.62 (d, J = 8.4 Hz, 1H), 6.46 (d, J = 8.4 Hz, 1H), 5.31 (s, 1H) 3.88 (s, 3H), 2.32 (d, J = 6 Hz, 2H), 2.07 (d, J = 6 Hz, 2H), 1.88 (d, J = 8.4 Hz, 2H), 1.75- 1.68 (m, 8H), 1.58- 1.49 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 146.6, 138.5, 133.9, 132.9, 123.7, 119.2, 112.2, 103.5, 79.2, 55.9, 31.8 (×2), 25.2, 24.8, 24.4, 22.7, 22.0, 21.6(× 2); HRMS (APCI) m/z $[M + H]^+$ calcd for $C_{19}H_{25}O_3$ 301.1798; found 301.1799.

General Procedure for the Synthesis of 4H-Chromenes (7a–7h). TsOH·H_2O (0.5 mmol) was added to a stirred solution of 3-methoxybenzene-1,2-diol (70 mg, 0.5 mmol) and acetophenone (180 mg, 1.5 mmol) in *n*-hexane (3 mL). The reaction mixture was stirred at 100 °Cin a sealed tube for 4 h. The mixture was concentrated under reduced pressure. The residue was purified by flash chromatography to give 7-methoxy-4-methyl-2,4-diphenyl-4H-chromen-8-ol (**7a**) (129 mg, 75% yield). mp = 116.4–120.2 °C; IR (KBr cm^{-1}) 3491, 3055, 2969, 2928, 1666, 1626, 1589, 1499, 1446, 1345, 1289, 1231, 1203, 1091, 1030; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.73 (t, J = 4 Hz, 2H), 7.40–7.26 (m, 6H), 7.19–7.14 (m, 2H), 6.53 (d, J = 8.8 Hz, 1H), 6.44 (d, J = 8.8 Hz, 1H), 5.59 (s, 1H), 5.45 (s, 1H), 3.02 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 149.8, 145.7, 145.2, 138.5, 133.9, 133.2, 128.4 (×2), 128.3 (×2), 128.1, 127.2 (×2), 125.9, 124.6 (×2), 122.7, 118.1, 107.3, 106.4, 56.1, 39.4, 30.3; HRMS (APCI) m/z $[M + H]^+$ calcd for $C_{23}H_{21}O_3$ 345.1485; found 345.1486.

Procedure for the Synthesis of 6,6′-Dimethoxy-3,3,3′,3′-tetramethyl-2,2′,3,3′-tetrahydro-1,1′-spirobi[indene]-4,4′,5,5′-tetraol (8). TsOH·H_2O (0.5 mmol) was added to a stirred solution of 3-methoxybenzene-1,2-diol (70 mg, 0.5 mmol) and acetone (232 mg, 2 mmol) in n-hexane (3

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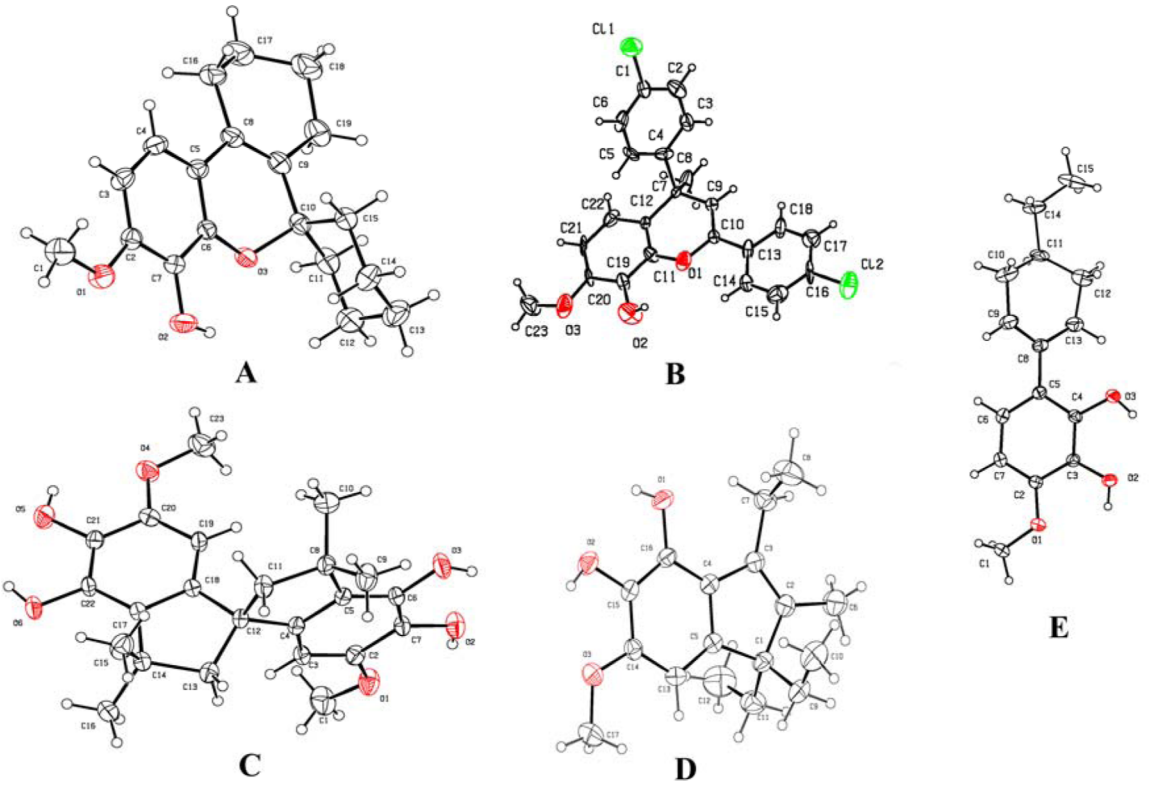
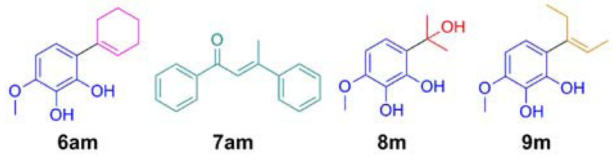
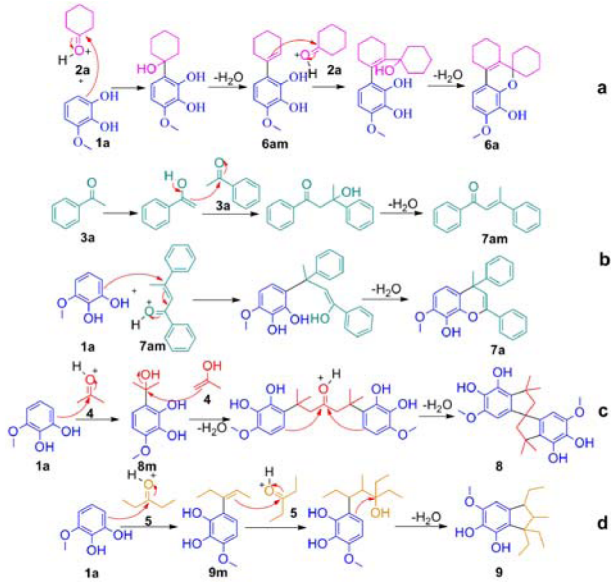


Figure 2. Crystal structures. (A) ORTEP drawing of **6a** (ORTEP drawing with 30% ellipsoids). (B) ORTEP drawing of **7c** (ORTEP drawing with 30% ellipsoids). (C) ORTEP drawing of **8** (ORTEP drawing with 30% ellipsoids). (D) ORTEP drawing of **9** (ORTEP drawing with 30% ellipsoids). (E) ORTEP drawing of **6cm** (ORTEP drawing with 30% ellipsoids).

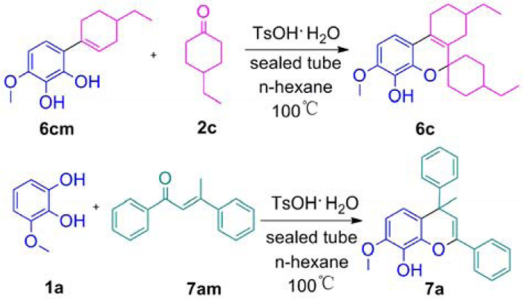
Scheme 4. Intermediates of the Reactions



Scheme 5. Proposed Reaction Pathway



Scheme 6. Intermediates Reactions[a]



[a]Reaction was performed with **6cm** (0.5 mmol) and **2c** (0.5 mmol), **1a** (0.5 mmol) and **7am** (0.5 mmol), and TsOH·H_2O (0.5 mmol) in *n*-hexane (3 mL) at 100 °C for 4 h.

mL). The reaction mixture was stirred at 100 °Cin a sealed tube for 4 h. The mixture was concentrated under reduced pressure. The residue was purified by flash chromatography to give 6,6′-dimethoxy-3,3,3′,3′-tetramethyl-2,2′,3,3′-tetrahydro-1,1′-spirobi[indene]-4,4′,5,5′-tetraol (**8**) (100 mg, 25% yield). mp = 160.2−165.1 °C; IR (KBr cm^{-1}) 3514, 3482, 2965, 2929, 2852, 1627, 1493, 1448, 1339, 1311, 1225, 1198, 1144, 1107, 832; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.96 (s, 2H), 5.28 (s, 2H), 5.26 (s, 2H), 3.74 (s, 6H), 2.26 (d, J = 13.2 Hz, 2H), 2.14 (d, J = 12.8 Hz, 2H), 1.58 (s, 4H), 1.51 (s, 6H), 1.43 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 148.4 (×2), 141.9 (×2), 141.4 (×2), 132.3 (×2), 129.6 (×2), 97.7 (×2), 60.7 (×2), 58.4 (×2), 55.9, 43.2 (×2), 29.4 (×2), 28.8 (×2); HRMS (APCI) m/z $[M + H]^+$ calcd for $C_{23}H_{29}O_6$ 401.1959; found 401.1959.

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Procedure for the Synthesis of 1,1,3-Triethyl-6-methoxy-2-methyl-2,3-dihydro-1H-indene-4,5-diol (9). $TsOH{\cdot}H_2O$ (0.5 mmol) was added to a stirred solution of 3-methoxybenzene-1,2-diol (70 mg, 0.5 mmol) and 3-pentanone (129 mg, 1.5 mmol) in n-hexane (3 mL). The reaction mixture was stirred at 100 °C in a sealed tube for 4 h. The mixture was concentrated under reduced pressure. The residue was purified by flash chromatography to give 1,1,3-triethyl-6-methoxy-2-methyl-2,3-dihydro-1H-indene-4,5-diol (**9**) (43.1 mg, 31% yield). mp = 110.8−114.5 °C; IR (KBr cm^{-1}) 3501, 2965, 2929, 1629, 1486, 1456, 1377, 1285, 1241, 1153, 1117, 792; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.34 (s, 1H), 5.31 (s, 1H), 5.25 (s, 1H), 3.88 (s, 3H), 2.68−2.62 (m, 2H), 1.71 (s, 3H), 1.67−1.59 (m, 2H), 1.23−1.08 (m, 6H), 0.31−0.24 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 144.2, 141.8, 138.7, 130.8, 97.1, 97.0, 58.3, 56.5, 30.4 (×4), 20.1, 14.7, 9.1, 7.8 (×2); HRMS (APCI) m/z $[M + H]^+$ calcd for $C_{17}H_{25}O_3$ 277.1798; found 277.1799.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data including GC/MS analysis and X-ray crystal data for **6a**, **6am**, **7c**, **8**, and **9**. This information is available free of charge via the Internet at http://pubs.acs.org/.

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Author Contributions

A.-X.W. conceived and designed the experiments, W.-J.X., Q.L., and F.-F.G. performed the experiments, W.-J.X., Y.-P.Z., and J.-G.W. cowrote the manuscript and Supporting Information.

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Notes

The authors declare no competing financial interest.

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