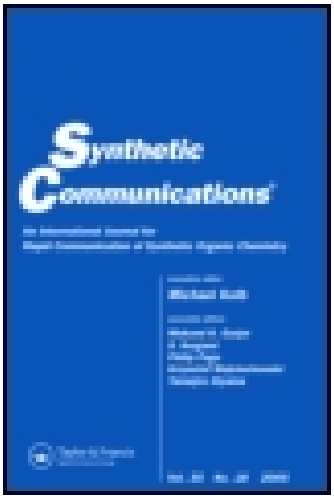

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Synthesis of 1,1-Dimethyl-4-indanol Derivatives

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Synthesis of 1,1-Dimethyl-4-indanol Derivatives

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Abstract: The synthesis of 1,1-dimethyl-4-indanols (**3a,b**) has been achieved by intramolecular Friedel–Crafts cyclization of 2-(3-methyl-2-butenyl)phenols (**5a**,**b**) or 1-methoxy-2-(3-methyl-2-butenyl)benzenes (**6a,b**) followed by demethylation, respectively.It was found that the solvent was critical for the formation of different products in the intramolecular Friedel–Crafts reactions of **6**. The unexpected product 4-methoxy-1,1,6,6-tetramethyl-*as*-hydrindacene (**11**) was obtained from the Friedel–Crafts reactions of **6a**, and its structure was confirmed by X-ray diffraction analysis. The key intermediates **5a,b** were prepared by *ortho*-alkenylation of phenols with 1-bromo-3-methyl-2-butene, and the reaction temperature exerted an obvious impact on the yield of 2-(3-methyl-2-butenyl)phenol (**5a**).

Keywords: 1,1-Dimethyl-4-indanols, intramolecular Friedel–Crafts reactions, 1-methoxy-2-(3-methyl-2-butenyl)benzenes, *ortho*-alkenylation of phenols

INTRODUCTION

3′,4′-Di-*O*-(−)-camphanoyl-(+)-*cis*-khellactone (DCK, **1**) and various its analogs have been reported to demonstrate extremely potent inhibitory activity against HIV-1 replication in H9 lymphocytic cells.[1–8] In our recent study on the structural modification of DCK (**1**), the oxygen atom in C ring and/or A ring of DCK have been replaced by other atoms, and some of these new analogs, such as 7-thia- and 1-thia-DCK, also inhibited potent anti-HIV activity.[5,6] Compared with DCK series, a different

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structure–activity relationship was implied in these DCK bioisosteres. In a continuing effort to identify the pharmacophores and clarify the mechanism of action in this class of potent anti-HIV agents, a new series of DCK analogs, namely 7-deoxy-DCK derivatives (**2a,b**) was designed, and the effect of the 7-oxygen atom of DCK (**1**) on the anti-HIV activity can be further explored. According to retrosynthetic analysis, 1,1-dimethyl-4-indanols (**3a,b**) are the key intermediates for the synthesis of **2a,b.** Additionally, the indanols are also useful as antioxidants, and more importantly, the indans are an important structural unit found in many natural and synthetic, biologically active molecules.[9] Herein, we report our study on the synthesis of 1,1-dimethyl-4-indanols (**3a,b**) (Fig. 1).

RESULTS AND DISCUSSION

As shown in Scheme 1, the synthetic route of 1,1-dimethyl-4-indanols (**3a,b**) was designed and tried by starting from an *ortho*-prenylation reaction of phenols (**4a,b**), followed by an intramolecular Friedel–Crafts cyclization of 2-(3-methyl-2-buteny1)phenols (**5a,b**). To avoid the formation of undesired by-products (**8a,b**) in the cyclization step, an alternative synthetic route was also examined. The phenol hydroxyl groups in compounds **5a,b** can be first blocked by the methyl group, and then cyclization of **6a,b** by intramolecular

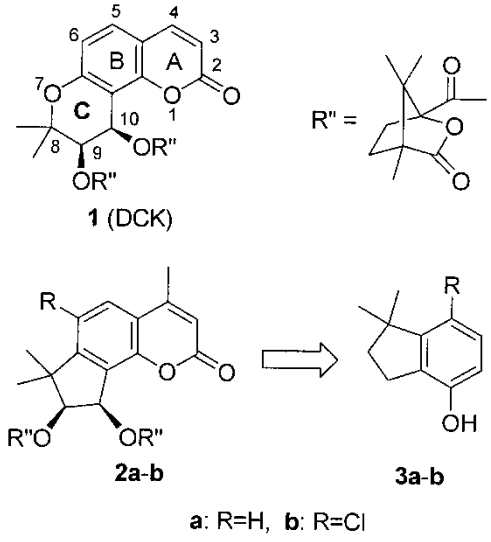
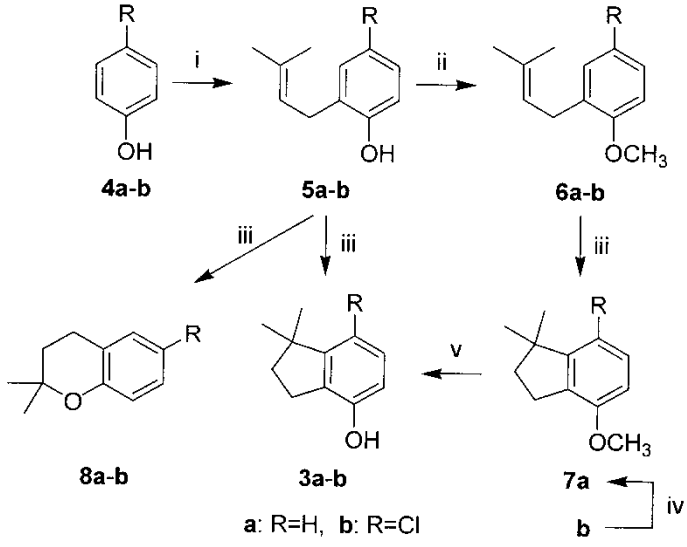


Figure 1. Structures of DCK (**1**), 7-deoxy-DCK analogs (**2a,b**), and 1,1-dimethyl-4-indanols (**3a,b**).



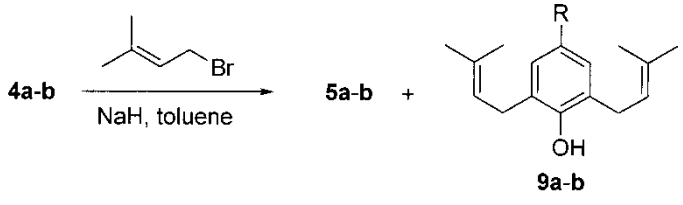
Scheme 1. The synthetic route of **3a,b**: (i) 1-bromo-3-methyl-2-butene, NaH, toluene; (ii) CH_3I, K_2CO_3/acetone, rt; (iii) HCl (g)/$AlC1_3$; (iv) $LiAlH_4$/THF; (v) BBr_3/CH_2Cl_2.

F-C reaction can give **7a,b**. The subsequent demethylation of **7a,b** with boron tribromide results in the convenient formation of target compounds **3a,b**. Although two more steps are needed in the later route, the chemo- and regioselectivity of the reaction can be more easily controlled. A more detailed investigation of the optimal conditions for these reactions is discussed as follows.

ortho-Prenylation of Phenols (4a,b) and Intramolecular Friedel–Crafts Cyclization of 2-(3-Methyl-2-butenyl) Phenols (5a,b)

The synthesis of *ortho*-prenylated phenols has been extensively studied because of their broad range of pharmacological activity, including anti-inflammatory, antifungal, antibacterial, antitumor, anti-HIV, and anti-Alzheimer activity.[10] *ortho*-Prenylphenols have been synthesized with many strategies, such as the Friedel–Crafts reaction of prenyl alcohols or prenyl halides with phenols, and direct alkylation of phenols with prenyl halides in the alkaline media or in the presence of an akali-metal catalyst. Because of competing side reactions such as *para*-prenylation, bis-prenylation, and oxygen-prenylation, *ortho*-prenylation of phenols proceeds with only moderate yield and regioselectivity.[10]

Following a literature method,[11] we tried the reaction of 1-bromo-3-methyl-2-butene with phenol (**4a**) or 4-chlorophenol (**4b**) in the presence of NaH in toluene at 35°C for 30 h (Eq. (1)). It is worthwhile to note that the reaction shows complete *ortho*-regioselectivity, but both mono- and dialkenylated phenols were furnished (Table 1). The formation of dialkenylated phenols might be attributed to the more electron-rich property of the aromatic system after the first introduction of a prenyl residue. In the case of **4a** as substrate, 2,6-bis-(3-methyl-2-butenyl)phenol (**9a**) dominated compared with mono-substituted phenol **5a**, whereas 4-chloro-2-(3-methyl-2-butenyl)phenol (**5b**) was the main product in the reaction of 4-chlorophenol (**4b**). The decrease of bis-prenylation product **9b** might be due to the weak electron-withdrawing property of C1 atom. To improve the yield of desired product **5a**, the reaction was then carried out at a lowered temperature (15°C). As expected, the mono-substituted phenol **5a** was obtained in satisfactory yield (60%), and the formation of dialkenylated phenol **9a** could be significantly reduced (23%).



(1)

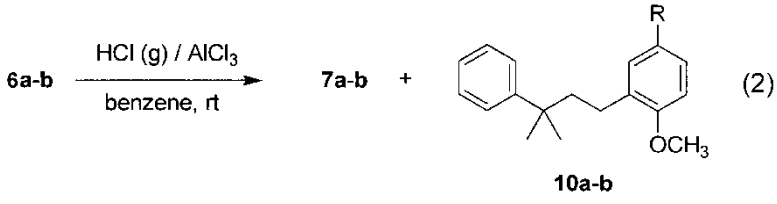
The initial trial on the cyclization of 2-(3-methyl-2-buteny1)phenol (**5a,b**) to 1,1-dimethyl-4-indanols (**3a,b**) in cyclohexane upon exposure to aluminum chloride in an HCl (g) atmosphere[12] proved to be inefficient (only 15% yield of **3a** and 12% yield of **3b**, respectively), mainly because of the formation of a large amount of undesired isomer **8a** (73%) and **8b** (39%). However, this process has provided an efficient method for the preparation of 2,2-dialkyl-2*H*-benzopyran derivatives, which exhibited an even broader range of interesting physiological properties.[13,14] Accordingly, we switched our attention to the synthesis of compounds **3** through an alternative approach by the protection of hydroxyl group of **5**.

Table 1. Product distributions obtained in the *o*-prenylation of phenols **4a,b**

	Products (isolated yield %)		
Temperature (°C)	**5**	**9**	Recovered **4**
35	**5a** (28)	**9a** (40)	**4a** (29)
15	**5a** (60)	**9a** (23)	—
35	**5b** (63)	**9b** (5)	—

Synthesis of 1,1-Dimethyl-4-indanols (3a,b) by an Indirect Pathway

As mentioned previously, the formation of by-products **8** in the intramolecular Friedel–Crafts cyclization of **5** is responsible for the low yields of **3**. In principle, the protection of the hydroxyl groups in **5** can completely avoid the formation of by-products **8** and as a result might enhance the yields of expected products. Accordingly, we subsequently tried an alternative stepwise strategy involving the blocking of the phenol hydroxyl group in compounds **5a,b** by the methyl group, followed by intramolecular Friedel–Crafts cyclization and demethylation reactions. Treatment of **5a,b** with methyl iodide under standard conditions (K_2CO_3/acetone) provided **6a,b** in 84% and 80% yields respectively as pale yellow oil. Fatope and Okogun reported that cyclization of 1-methoxy-2-(3-methyl-2-butenyl)benzene (**6a**) in the presence of aluminum chloride in an HCl (g) atmosphere in benzene gave 1,1-dimethyl-4-methoxyindan (**7a**) in 60% yield.[12] This result seems to be encouraging, but problems were encountered when we repeated this process. To our surprise, the desired **7a** was obtained in only 13% of yield using the literature procedure. However 1-methoxy-2-(3-methyl-3-phenylbutanyl)benzene (**10a**), an intermolecular Friedel–Crafts product with solvent benzene, was obtained as the major product (50% yield) [Eq. (2)]. A similar result was afforded in the cyclization of 4-chloro-1-methoxy-2-(3-methyl-2-butenyl)benzene (**6b**), and the yields of **7b** and **10b** were 32% and 23%, respectively.



(2)

Consequently, we tried hexane, cyclohexane, or CS_2 instead of benzene as the reaction solvent, respectively. The effects of the solvents on the yields and product distributions are summarized in Table 2. In case of

Table 2. Product distributions obtained in the cyclization of **6a–b**

	Products (isolated yield %)		
Solvent	**7**	**10**	**11**
Benzene	**7a** (13)	**10a** (50)	—
Hexane	**7a** (8)	—	—
Cyclohexane	**7a** (19)	—	—
CS_2	**7a** (38)	—	(3)
Benzene	**7b** (32)	**10b** (23)	

hexane or cyclohexane as the solvent, **7a** was obtained in low yields of 8–19%, probably due to their lower polarity and poor solubility of the substrates and catalysts. CS_2 seems to be the optimal solvent for the reaction, affording **7a** in 38% yield. It was found that low concentrations of the substrates **6a,b** in the reaction medium and rapid workup were preferable to avoid the intermolecular reaction. Small quantities of tricyclic compound were also separated from the reaction system in 3% yield, but it is difficult to determine its structure as **11**,**12** or **13** simply on the basis of its ^{1}H NMR, ^{13}C NMR, and MS spectra. Its structure was finally confirmed as 4-methoxy-1,1,6,6-tetramethyl-*as*-hydrindacene **(11)** by the X-ray single crystal diffraction analysis (Fig. 2), which was probably formed by the reverse F-C reaction of **6a** followed by cyclization of intermediate **14** (Scheme 2).

The dechlorination of **7b** was also tried by using lithium aluminum hydride (4 equiv.) in refluxing tetrahydrofuran for 72 h to provide **7a** in 30% yield. As reported in the literature,[15] the reductions of aromatic chlorides are more

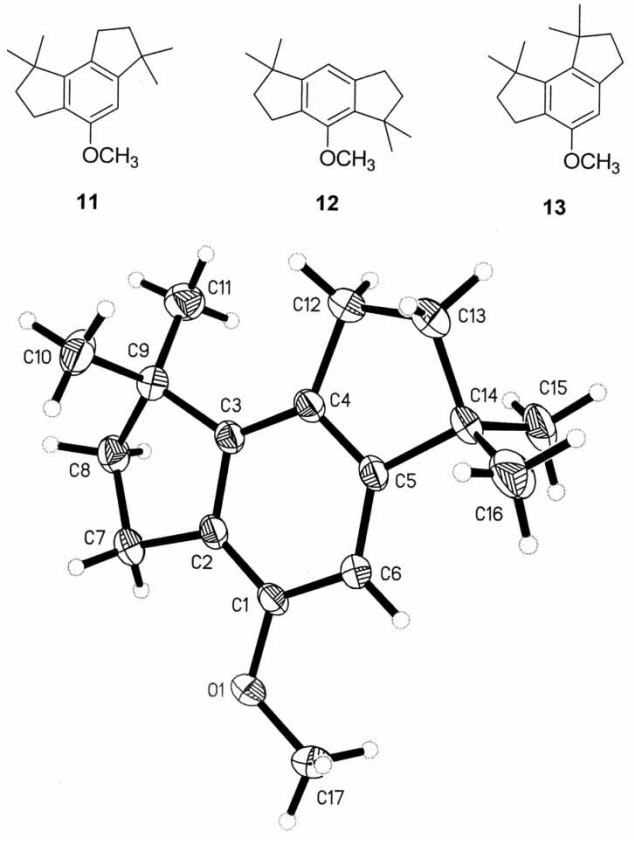
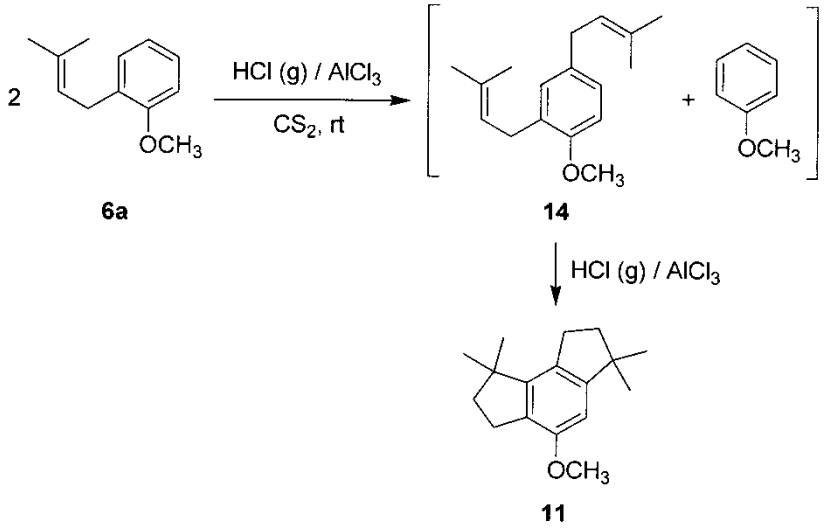


Figure 2. X-ray diffraction analysis of compound **11**.



Scheme 2. Possible mechanism for the formation of **11**.

difficult than those of aromatic iodides or bromides, especially for the substrates containing electron-donating substituents. Therefore, 4-methoxy in **7b** would be responsible for the slow reaction rate and low yield of product **7a**. Treatment of **7a,b** with boron tribromide under standard conditions (CH_2Cl_2, $-78^{\circ}C$ to rt, 2 h) smoothly cleaved the methyl ether and provided the target 1,1-dimethyl-4-indanols **(3a,b)** in 91% and 93% yield, respectively.

CONCLUSION

In conclusion, two approaches for the synthesis of indanols **3a,b** starting from corresponding phenols have been examined, and some unreported or unexpected reaction details were explored. The effects of solvents on the cyclization of **6a** and the reaction temperature on the yield of **5a** were optimized. We hope the results described in this work will be helpful for the synthesis of biologically interesting compounds with the indanols **3** as intermediates.

EXPERIMENTAL

Melting points were uncorrected. Reactions were monitored by TLC on 0.2-mm silica-gel plates, and the spots were visualized by ultraviolet light. Flash column chromatography was performed on silica-gel (300–400 mesh). ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 300 spectrometer at 300.13 and 75.47 MHz, respectively, and the solvent used was

$CDCl_3$ unless otherwise indicated. All chemical shifts were reported in δ units with reference to TMS (^1H) or the signals of the solvent (^{13}C). Mass spectra (EI) were taken on a Agilent 5973 N MSD spectrometer. HRMS data were determined on a Kratos Concept 1H spectrometer, Bruker APEXIII 7.0 Tesla FTMS or IonSpec 4.7 Tesla FTMS instrument.

2-(3-Methyl-2-butenyl)phenol (5a) and 2,6-bis-(3-Methyl-2-butenyl)phenol (9a)

Phenol (5 g, 53.13 mmol), NaH (60%, 2.81 g, 116.89 mmol) in anhydrous toluene (70 mL) was heated at 60°C for 0.5 h under argon. After being cooled to 15°C, 1-bromo-3-methyl-2-butene (11.87 g, 79.65 mmol) was added to the reaction mixture through a syringe. The mixture was stirred for 24 h and subsequently poured into water (200 mL). The mixture was extracted with EtOAc (3 × 30 mL), and the combined organic phase was washed with H_2O (3 × 20 mL) and brine (20 mL) and dried over anhydrous $MgSO_4$. After removal of the volatiles in vacuo, the residue was purified by flash column chromatography on silica gel (petroleum ether–EtOAc, 15:1) to give compound **5a** as a pale yellow oil (5.20 g, 60%): ^1H NMR (300 MHz, $CDC1_3$) δ 1.83 (s, 6H, CH_3), 3.41 (d, $J = 6.9$ Hz, 2H, CH_2), 5.36–5.41 (m, 2H, -OH, =CH-), 6.83–6.97 (m, 2H, 4-H, 6-H), 7.12–7.18 (m, 2H, 3-H, 5-H). A by-product **9a** was also obtained as a yellow oil (2.80 g, 23%): ^1H NMR (300 MHz, $CDCl_3$,) δ 1.76 (s, 12H, CH_3), 3.34 (d, $J = 6.9$ Hz, 4H, CH_2), 5.28–5.35 (m, 2H, =CH-), 5.36 (s, 1H, OH), 6.76–6.79 (m, 1H, 4-H), 6.96 (t, $J = 7.5$ Hz, 2H, 3-H, 5-H).

4-Chloro-2-(3-methyl-2-butenyl)phenol (5b) and 4-Chloro-2,6-bis-(3-methyl-2-butenyl)phenol (9b)

4-Chlorophenol (200 mg, 1.56 mmol), NaH (60%, 137 mg, 3.43 mmol) in anhydrous toluene (5 mL) was heated at 60°C for 2.5 h under argon. After being cooled to 35°C, 1-bromo-3-methyl-2-butene (349 mg, 2.34 mmol) was added to the reaction mixture through a syringe. Following the same workup procedure for **5a**, **5b** was obtained as a yellow oil (194 mg, 63%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.74 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 3.30 (d, $J = 6.9$ Hz, 2H, CH_2), 5.26–5.31 (m, 1H, =CH-), 5.38 (br, 1H, -OH), 6.71 (d, $J = 8.4$ Hz, 1H 6-H), 7.03–7.07 (m, 2H, 3-H, 5-H).^{13}C NMR (75 MHz, $CDC1_3$) δ 154.01, 134.30, 129.81, 127.31, 126.99, 121.81, 120.65, 115.52, 29.40, 25.66, 17.70. Similarly, product **9b** was yielded as a yellow oil (21 mg, 5%): ^1H NMR (300 MHz, $CDC1_3$) δ 1.76 (s, 6H, CH_3), 1.78 (s, 6H, CH_3), 3.30 (d, $J = 7.5$ Hz, 4H, CH_2), 5.25–5.30 (m, 2H, =CH-), 5.33 (s, lH, OH), 6.94 (s, 2H, 3-H, 5-H).

1-Methoxy-2-(3-methyl-2-butenyl)benzene (6a) and 4-Chloro-1-methoxy-2-(3-methyl-2-butenyl)benzene(6b)

Anhydrous K_2CO_3 (5.54 g, 40.1 mmol) and methyl iodide (2.6 mL, 5.91 g, 41.7 mmol) were added to a stirring solution of **5a** (2.60 g, 16.0 mmol) in dry acetone (10 mL). The mixture was stirred at room temperature for 18 h. The volatiles were removed in vacuo, and the residual solids were dissolved in H_2O (30 mL). The resulting mixture was extracted with EtOAc (3 × 30 mL), and the combined organic phase was dried over anhydrous Na_2SO_4. After the removal of the solvent, the residue was purified by flash column chromatography on silica gel (petroleum ether) to yield **6a** as a pale yellow oil (2.36 g, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 3.32 (d, $J = 7.5$ Hz, 2H, CH_2), 3.81 (s, 3H, CH_3O), 5.28–5.33 (m, 1H, -CH═), 6.81–6.94 (m, 2H, 4-H, 6-H), 7.12–7.20 (m, 2H, 3-H, 5-H). Following the same procedure for the preparation of **6a, 6b** was obtained from **5b** as a pale yellow oil (yield, 80%): ^{1}H NMR (300 MHz, $CDC1_3$) δ 1.70 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 3.28 (d, $J = 7.2$ Hz, 2H, CH_2), 3.81 (s, 3H, CH_3O), 5.24–5.30 (m, 1H, -CH═), 6.74 (d, J= 8.4 Hz, lH, 6-H), 7.08–7.13 (m, 2H, 3-H, 5-H). MS (EI) m/z (%): 210 (M^+, 100.00), 195 (78.78), 175(87.06), 160 (95.09), 155 (62.56), 125 (53.73), 115 (35.57), 77 (47.92), 41 (81.65). HRMS: calcd. mass for $C_{12}H_{15}ClO$ 210.0811; found 210.0806.

1,1-Dimethyl-1-4-methoxyindan (7a) and 1-Methoxy-2-(3-methyl-3-phenylbutanyl)benzene (10a)

Cyclization was carried out in a three-necked 250-mL flask equipped with an HCl (g) inlet tube and an air condenser with a $CaCl_2$ drying tube. The benzene solution of **6a** (1.80 g, 10.2 mmol) was added dropwise to a stirred suspension of powdered aluminium chloride (1.36 g, 10.2 mmol) in sodium-dried benzene (50 mL) at room temperature in an atmosphere of HCl (g). (HCl (g) was generated by dropping conc. sulphuric acid into NACl.) The reaction mixture was stirred for 2.5 h and then quenched by slow addition of 1 *N* hydrochloric acid. The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phase was dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by flash column chromatography on silica gel (petroleum ether) to provide **7a** as a pale yellow oil (226 mg, 13%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 6H, 1-CH_3), 1.93 (t, $J = 6.9$ Hz, 2H, 2-H), 2.85 (t, $J = 6.9$ Hz, 2H, 3-H), 3.84 (s, 3H, 4-CH_3O), 7.69 (d, $J = 8.4$ Hz, 1H, 5-H), 6.79 (d, J= 7.5 HZ, 1H, 7-H), 7.19 (t, J= 8.1 Hz, 1H, 6-H). In addition to **7a**, by-product **10a** was also obtained as a yellow oil (1.30 g, 50%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 6H, 3′-CH_3), 1.87–1.92 (m, 2H, 2′-CH_2), 2.35–2.40 (m, 2H, 1′-CH_2), 3.77 (s, 3H,

1-CH_3O), 6.79–6.87 (m, 2H, 4-H, 6-H), 7.03 (d, $J = 7.5$ Hz, 1H, 5-H), 7.11–7.22 (m, 2H, 4″-H, 3-H), 7.31–7.36 (t, $J = 7.8$ Hz, 2H, 3″-H, 5″-H), 7.43 (d, $J = 8.1$ Hz, 2H 2″-H, 6″-H). MS (EI) m/z (%): 254 (M^+, 43.95), 135 (71.96), 119 (91.72), 91 (100.00), 77 (21.08), 41 (21.09). HRMS (MALDI-DHB) calcd. mass for $C_{18}H_{22}O$ [$M^+ + Na$] 277.15633; found 277.1570.

4-Methoxy-1,1,6,6-tetramethyl-*as*-hydrindacene (11)

Fllowing a similar procedure for the preparation of **7a**, except for the use of CS_2 as the solvent instead of benzene, **7a** was prepared in 38% yield, and **11** was obtained as colorless crystals (3%): mp 77–78°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 6H, 1-CH_3), 1.30 (s, 6H, 7-CH_3), 1.90–1.96 (m, 4H, 2-H, 6-H), 2.80 (t, $J = 7.2$ Hz, 2H, 3-H), 2.88 (t, $J = 7.2$ Hz, 2H, 5-H), 3.83 (s, 3H, 4-CH_3O), 6.51 (s, 1H, 8-H). ^{I3}C NMR (75 MHz, $CDCl_3$) δ 155.17, 153.49, 148.85, 129.25, 128.74, 102.36, 55.43, 55.31, 45.36, 43.51, 42.17, 42.13, 29.89, 28.98, 28.80, 27.46, 26.78. MS (EI) m/z (%): 244 (M^+, 25.27), 229 (100.00), 173 (67.04), 161 (17.31), 143 (13.11), 128 (14.49). HRMS (MALDI-DHB) calcd. mass for $C_{17}H_{24}O$ [$M^+ + H$] 245.1900; found 245.1902.

Single-Crystal X-ray Diffraction Data of 11

Compound **11** was dissolved in petroleum ether, and crystals were obtained by slow evaporation at room temperature after several days. Crystal with dimensions of 0.517 × 0.506 × 0.345 mm was selected and mounted on a Bruker Smart CCD diffractometer with graphite monochromatized Mo $K\alpha$ radiation ($\lambda = 0.71073$ Å). Diffraction data were collected using ω-2θ scans at room temperature (293 K). A perspective view of the structure is depicted in Fig. 2. Empirical formula: $C_{17}H_{24}O$. Formula weight: 244.36. Crystal system: monoclinic. Space group: $P2(1)/n$. Unit cell dimensions: $a = 9.1975$ (17) Å, $b = 17.430$ (3) Å, $c = 9.5062$ (17) Å, $\beta = 108.468(3)°$. $V = 1445.5$ (5) Å^3. Theta range for data collection is from 2.34 to 26.00°. $Z = 4$. $Dc = 1.123$ Mg/m^3. Absorption coefficient 0.067 mm^{-1}. $F(000) = 536$. Refinement method: full-matrix least-squares on F^2. Goodness-of-fit on F^2: 0.973. Final R indices [$I > 2\sigma$ (I)]: $R1 = 0$ 0708, wR2 = 0.1807. R indices (all data); R1 = 0.0931, wR2 = 0.1964. Largest diff. peak and hole: 0.260 and −0.240 e/Å^3.

7-Chloro-1,1-dimethyl-4-methoxyindan (7b) and 4-Chloro-1-methoxy-2-(3-methyl-3-phenylbutanyl)benzene (10b)

Following the same procedure for the preparation of **7a**, with benzene as the solvent, **7b** was afforded as a colorless liquid in 32% yield: ^{1}H NMR

(300 MHz, $CDC1_3$) δ 1.41 (s, 6H, 1-CH_3), 1.95 (t, $J = 7.5$ Hz, 2H, 2-H), 2.82 (t, $J = 7.5$ Hz, 2H, 3-H), 3.81 (s, 3H, 4-CH_3O), 6.62 (d, $J =$ 8.7 Hz, 1H, 5-H), 7.09 (d, $J =$ 8.4 Hz, 1H, 6-H). MS (EI) m/z (%): 210 (M^+, 28.46), 197 (34.66), 195 (100.00), 160 (53.67), 145 (10.56), 115 (11.39), 44 (13.93). HRMS calcd. mass for $C_{12}H_{15}OC1$ 210.0811; found 210.0823. By-product **10b** was obtained as a colorless liquid (23%): ^{1}H NMR (300 MHz, $CDC1_3$) δ 1.37 (s, 6H, 3′-CH_3), 1.83–1.88 (m 2H, 2′-CH_2), 2.29–2.34 (m, 2H, 1′-CH_2), 3.74 (s, 3H, 1-CH_3O), 6.68 (d, $J = 9.0$ Hz, 1H, 6-H), 6.98 (d, $J = 2.7$ Hz, 1H, 3-H), 7.05–7.09 (m, 1H, 5-H), 7.18–7.22 (m, 1H 4″-H), 7.30–7.42 (m, 4H, 2″-H, 3″-H, 5″-H, 6″-H). MS (EI) m/z (%): 288 (M^+, 25.33), 169 (11.76), 119 (100.00), 91 (44.39), 77 (9.48), 41 (10.53). HRMS (MALDI-DHB) calcd. mass for $C_{18}H_{21}OC1$ [$M^+ + Na$] 311.1173; found 311.1188.

1,1-Dimethyl-4-indanol (3a)

A solution of BBr_3 (3.0 M, 7.9 mL, 23.8 mmol) in CH_2Cl_2 was added dropwise to a cooled (−78°C) solution of **7a** (2.10 g, 11.9 mmol) in anhydrous CH_2Cl_2 (10 mL). The mixture was warmed over 2 h to room temperature, stirred for a further 1 h, and then decomposed by slow addition of water carefully. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3× 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. The resultant residue was purified by flash column chromatography on silica gel (petroleum ether–EtOAc, 20:1) to give the title compound **3a** as a pale yellow solid. Recrystallization from petroleum ether afforded **3a** as colorless needles (1.75 g, 91%): mp 81–83°C (lit.[16] mp 88–88.5°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 6H, 1-CH_3), 1.95 (t, $J =$ 7.2 Hz, 2H, 2-H), 2.82 (t, $J = 6.9$ Hz, 2H, 3-H), 4.68 (br, 1H, 4-OH), 6.62 (d, $J =$ 7.8 Hz, lH, 5-H), 6.75 (d, $J = 7.5$ Hz, lH, 7-H), 7.09 (t, $J = 7.8$ Hz, lH, 6-H). ^{13}C NMR (75 MHz, $CDC1_3$) δ 155.29, 151.80, 128.27, 127.83, 114.75, 112.86, 44.69, 41.31, 28.72, 26.05.

7-Chloro-1,1-dimethyl-4-indanol (3b)

Following a similar procedure for the preparation of **3a**, **3b** was obtained as a yellow oil (93%): ^{1}H NMR (300 MHz, $CDC1_3$) δ 1.41 (s, 6H, 1-CH_3), 1.96 (t, $J = 7.5$ Hz, 2H, 2-H), 2.78 (t, $J = 7.5$ HZ, 2H, 3-H), 4.96 (br, 1H, 4-OH), 6.56 (d, $J =$ 8.4 Hz, 1H, 5-H), 6.98 (t, $J =$ 8.4 Hz, 1H, 6-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.49, 149.05, 130.73, 129.24, 122.02, 114.45, 46.84, 41.88, 26.66, 26.04. MS (EI) m/z (%): 196 (M^+, 31.80), 183 (31.82), 181 (100.00), 146 (60.11), 145 (21.93), 115 (18.73), 77 (17.51), 41 (10.53). HRMS: calcd. mass for $C_{11}H_{l3}OC1$ 196.065; found 196.0654.

2,2-Dimethylchroman (8a)

Following a similar procedure for the preparation of **7a**, except for **5a** as the starting material and cyclohexane as the solvent, **3a** was afforded in 15% yield and **8a** was obtained as a colorless liquid (73%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 6H, 2-CH_3), 1.77 (t, $J =$ 6.6 Hz, 2H, 3-H), 2.74 (t, $J = 6.6$ Hz, 2H, 4-H), 6.76–6.82 (m, 2H, 6-H, 8-H), 7.02–7.09 (m, 2H, 5-H, 7-H).

6-Chloro-2,2-dimethylchroman (8b)

Following a similar procedure for the preparation of **7a**, except for **5b** as the starting material and cyclohexane as the solvent, **3b** was afforded in 12% yield, and **8b** was obtained as a colorless liquid (39%): ^{1}H NMR (300 MHz, $CDC1_3$) δ 1.31 (s, 6H, 2-CH_3), 1.78 (t, $J = 6.6$ Hz, 2H, 3-H), 2.74 (t, $J =$ 6.6 Hz, 2H, 4-H), 6.70 (d, $J = 9.3$ Hz, 1H, 8-H), 7.01–7.04 (m, 2H, 7-H, 5-H).

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