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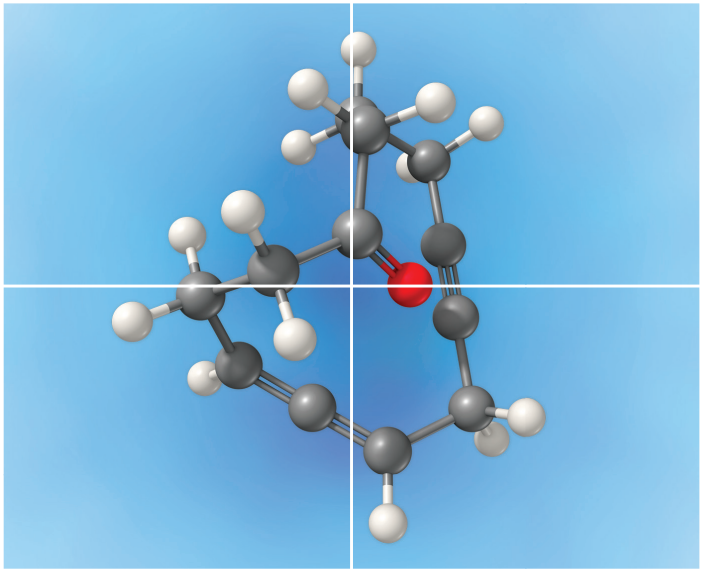

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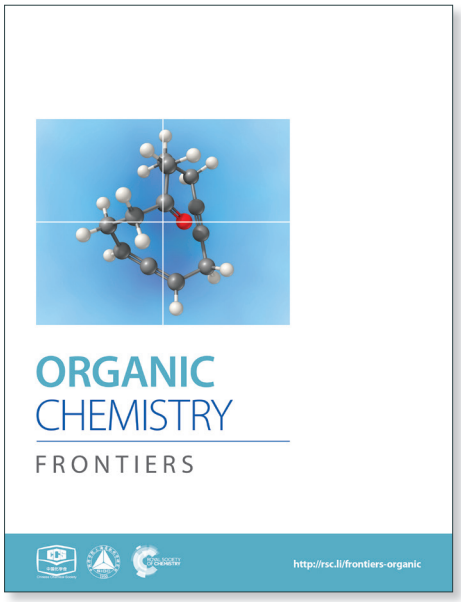

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ARTICLE

Metal-free Aerobic C-H Oxidation of Cyclic Enones †‡

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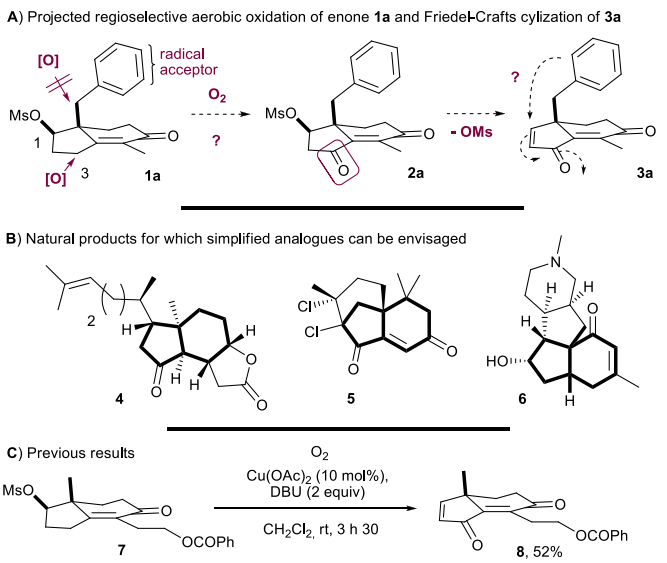
A metal-free procedure is described for the aerobic and complete C-H methylene oxidation of Hajos-Parrish enones into versatile dihydroindenediones. The synthetic utility of these substrates was illustrated by converting them into highly substituted indanes after an intramolecular Friedel-Crafts conjugate addition. Importantly, the aerobic oxidation was compatible with substrates sensitive to radicals.

Introduction

The construction of an all-carbon quaternary stereocenter in a polycyclic framework is a challenging field of investigation. Methyl hydrindenones, such as chiral cyclohexenones, are representative of this type of framework for which the preparation is facilitated by the desymmetrization of prochiral triketones derived from 2-methyl-1,3-cyclopentadione in the presence of an organocatalyst.[1] Further developments were reported to access the benzyl or allyl substituted hydrindenones from the corresponding 2-alkyl-1,3-cyclopentadiones, providing a rich platform for innovative and diversified synthetic developments.[2] In the context of a project of aerobic and regioselective γ-oxidation of the Hajos-Parrish's enones, we view these structures containing aromatic substituents such as **1a** as particularly interesting scaffolds (Scheme 1A). Indeed, selectively oxidizing the C3 position is a challenge: sp^3 benzylic carbons may undergo intramolecular H-abstraction while aromatic rings or the allyl group may suffer intramolecular radical attack.[3] It is nevertheless a rewarding task due to the functionalized and polycyclic cyclopentenone obtained after mesylate elimination. Furthermore, a conversion of **1a** into dihydroindenediones **3a** would give access not only to unique hydrindenones but also to highly substituted indanes after intramolecular Friedel-Crafts conjugate addition. Hence, the preparation of steroid subunits and simplified analogues of natural products such as aplykurodinone-1 (**4**),[4] gomerone C (**5**)[5] and magellanine (**6**)[6] could be projected (Scheme 1B). Herein, we report a metal-free methodology based on the generation of dienolate of Hajos-Parrish's enones containing various benzylic and allylic substituents to promote the regioselective aerobic oxidation, allowing direct access to versatile dihydroindenediones.

Metal-free C-H aerobic α-oxidation of electron-withdrawing moieties presents several advantages. In addition to the simplicity of air or oxygen as the oxidant and the absence of metals, the preformation of an alkyl or silyl enol ether is not required as in the typical Rubottom oxidation.[7] The added-value of this methodology was demonstrated on ketones, nitriles, imines, esters and enones, leading to the corresponding peroxides, hydroxyl or fragmented products such as ketones depending on the moieties in the vicinity of the peroxide and the presence of reductants.[8] *Interestingly, when γ-oxidation of enones was performed, the corresponding peroxides or hydroxyls were obtained instead of the ketones.*[9] For the synthetic study of aplykurodinone-1 (**4**), we described the γ-aerobic oxidation of enone **7** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and a catalytic amount of $Cu(OAc)_2$ to produce dienedione **8** in 52% (Scheme 1C).[4b] The extension of this protocol to enones containing benzylic appendages such as **1a** was investigated and the results are presented herein.

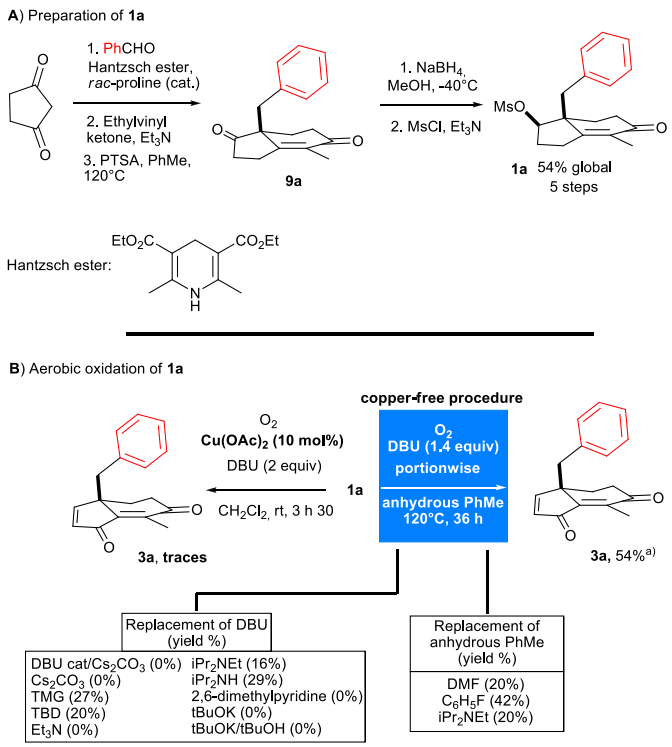


Scheme 1.

Results and discussion

The preparation of mesylate **1a** from 1,3-cyclopentadione and benzaldehyde was carried out first (Scheme 2A). Reductive coupling

(81%) with Hantzsch ester followed by quaternization (82%) with ethylvinyl ketone and Robinson annulation (88%) with *p*-toluenesulfonic acid delivered enone **9a**. Then, chemoselective reduction and mesylation afforded **1a** in 93% (2 steps). In line with our previous protocol optimized for substrates without benzylic appendages, we began treating **1a** with DBU in the presence of $Cu(OAc)_2$ in CH_2Cl_2 at rt under an atmosphere of oxygen (Scheme 2B). As a result, a complex mixture of products was formed from which **3a** could be isolated in no more than 10%. In order to limit side reactions, a copper-free process was tested. Harsher conditions were required to oxidize **1a** but, interestingly, with better results. Hence, **3a** was isolated in 22% by heating **1a** at 120°C for 5 days with DBU (1 equiv) in distillated toluene under an atmosphere of oxygen.

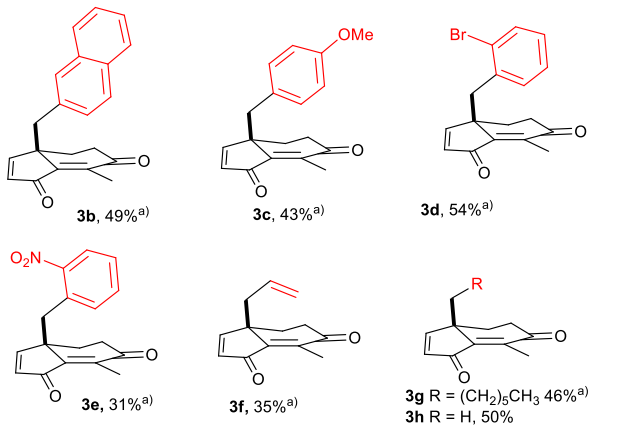


a) Average yield of two experiments

Scheme 2. PTSA: p-toluenesulfonic acid; TMG: *N,N,N',N'*-tetramethylguanidine; TBD: 1,5,7-Triazabicyclo[4.4.0]dec-5-ene

Increasing the amount of DBU (1.4 equiv) completed the reaction in 36 h and **3a** was isolated in 41%.[10] Increasing further to 1.5 equiv the amount of DBU led to lower yield and we assumed that **3a**, as a Michael acceptor, was to some extent sensitive to nucleophiles such as DBU.[11] While less nucleophilic bases than DBU are available, the strength and tolerance to oxygen are key requirements and a screening of bases such as guanidines, trialkylamines, lutidine, alkoxides or inorganic bases led to lower conversion or no oxidation at all (see Scheme 2B). Somewhat counterintuitively, solvent in which oxygen is more soluble such as DMF or fluorobenzene were less efficient to promote the reaction, indicating that polarity and oxygen solubility have to be finely tuned.[12] To reduce the concentration of DBU and limit therefore the risk of degradation, a sub-stoichiometric amount of DBU was introduced. After a screening of conditions, involving different concentrations, amounts of base, induction time and the use of syringe pump, we found that simply adding 0.2 equiv of DBU to **1a** followed by heating (12 h) and portionwise addition of DBU (0.2 equiv every 1.5 h, for a total of 1.4 equiv) provided the best result. Proceeding this way, we were able to isolate **3a** in 54% after 36 h (Scheme 2B). Noteworthy, the C3 methylene position is oxidised exclusively to the corresponding ketone during the process. Importantly, this procedure has been repeated several times by different experimentalists and provided consistent results.

Once the optimization was completed, we investigated the compatibility of the chemistry with various substituents at the neopentyl position. Hence, mesylates **1b-e** containing naphtyl, *p*-methoxyphenyl, *o*-bromophenyl and *o*-nitrophenyl substituents were prepared and tested (see SI for details). Remarkably, dihydroindenediones **3b-e** were obtained with uniform efficiency in yields ranging from 43-54% at the exception of the *o*-nitrophenyl derivative **3e** which was isolated in 31% (Scheme 3). Applying the optimized protocol to the allyl-substituted **1f** led to the oxidised product **3f** in 35%. Still, substituted with an allyl group, **3f** is a promising substrate for synthetic transformations. As expected for alkane substituted substrates, **1g** and **1h** were converted more efficiently into **3g** (46%) and **3h** (50%). From a practical point, the crude mixture obtained was very clean in all cases, facilitating the purification of **3a-h**.[13]



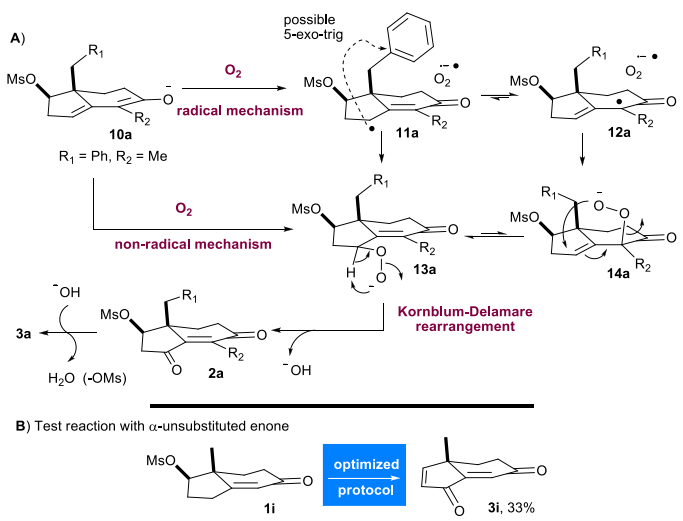
a) Average yield of two experiments

Scheme 3. Direct preparation of **3b-h** from the corresponding mesylates **1b-h** using the optimized protocol

Even though no detailed mechanistic study was conducted, some observations can be made from experiments. Hence, the oxidation at C3 appears to be the first step since there is no elimination of the mesylate when the reaction is conducted in the absence of oxygen.

To begin with, the formation of the thermodynamic dienolate **10a** (R_1=Ph, R_2=Me) can be reasonably postulated (Scheme 4A). A first mechanism could involve a single electron transfer (SET) to oxygen

to produce the radical species **11a** and **12a** which, after combination with the superoxide radical anion, could form the peroxides **13a** and **14a**. As a Mislow-Evans rearrangement of allylic sulfoxide, allylic peroxide **14a** could undergo [2,3]-sigmatropic rearrangement to produce **13a**.

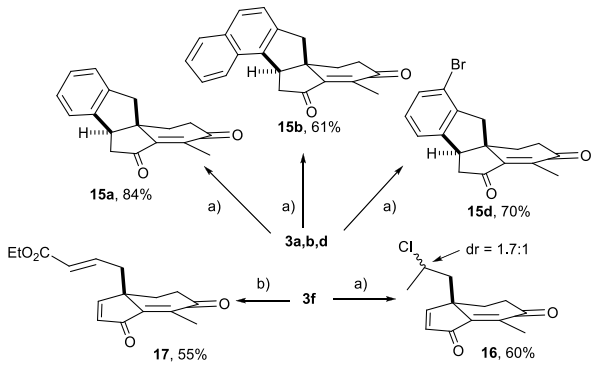


Scheme 4. Mechanistic discussions

To explain the unusual formation of ketone at C3, a Kornblum-DeLamare rearrangement of peroxide **13a** by intra- or intermolecular deprotonation (with DBU) could be invoked to generate **2a**.[14] The production of hydroxide would trigger the elimination of mesylate and conclude the process. As postulated by Gersmann, an alternative non-radical mechanism could involve the direct combination of dienolate **10a** and oxygen to provide the regioisomeric peroxides **13a** and **14a**.[9b,c] With the benzylic substrate **1a** and the methyl substrate **1h** being oxidised with the same efficiency (54% of **3a** and 50% of **3h**), it seems unlikely that radical species are involved since 1,5-hydrogen atom abstraction from the benzylic position of **11a**/**12a** or radical 5-exo-trig cyclization (see Scheme 4A) could probably occur. These side reactions would be favored on arenes substituted with electron withdrawing or donating groups stabilizing radical species. In this regard, the smooth oxidation of compounds **1c** and **1d** containing *p*-methoxy and *o*-bromo substituents into **3c** (43%) and **3d** (54%) uphold the hypothesis that an anionic scenario may predominate. Moreover, the process was unaffected by the exclusion of light. Therefore, it seems plausible that an anionic pathway is active during this process even if we can not completely rule out a competitive and parallel radical cage mechanism being operative since the oxidation of *o*-nitrobenzylic and allylic substituted enones **1e** and **1f** were less efficient, but these two appendages are very sensitive to radicals and bases.

The regioselectivity of the reaction on enones that are not α-susbtituted such as **1i** was next investigated (Scheme 4B). Indeed, Kornblum-Delamare rearrangement of peroxide **14i** (R_2=R_1=H) could lead to 1,2-diketone unstable in these conditions. To investigate this scenario, **1i** was oxidised in the optimized conditions delivering **3i** in 33%. In comparison, the α-susbtituted enone **1h** was converted into **3h** in 50%, indicating clearly that α-substituted enones are more efficiently oxidised in γ-position with this protocol.

To illustrate the utility of these scaffolds, an internal Friedel-Crafts conjugate addition was implemented (Scheme 5). After a screening of Brønsted and Lewis acids, the best results were obtained with $AlCl_3$.[13] Hence, **3a** was efficiently converted into indane **15a** (84%) featuring all-carbon quaternary center embedded into a tetracyclic framework. Similarly, naphthyl derivative **3b** provided regioselectively **15b** in 61% yield by reaction at the sp^2 carbon with the highest electronic density.



Scheme 5. Reagents and conditions: a) $AlCl_3$ (5 equiv), CH_2Cl_2, rt; b) Grubbs 2nd generation (2 mol%), ethyl acrylate (6 equiv), CH_2Cl_2, rt

Interestingly, **3d** was converted into versatile **15d** (70%), a compound calling for various C-Br modifications toward molecular diversity. Unexpectedly, similar treatment of allylic substrate **3f** did not produce the cyclized product but yielded the Markovnikov hydrochloration adduct **16** (60%) with a modest stereoselectivity (dr = 1 : 1.7). As a further illustration of the potential of **3f**, cross-metathesis afforded acrylate **17** (55% yield not optimized) as a promising template for double Michael reactions.

Conclusion

In summary, an expedient and simple route to difficult-to-access dihydroindenediones containing various benzylic and allylic groups is described. Based on the aerobic oxidation of the dienolate of Hajos-Parrish's enones, the reaction proceeds with medium efficiency (31-54%) but remains useful in view of the number of transformations involved. Indeed, at least four transformations including deprotonation, oxygenation, rearrangement and elimination are occuring in one flask with an average yield of 75-85% for each one of them. The process led to the complete oxidation of the C-H methylene and is compatible with substrates sensitive to radicals. Further synthetic transformations of the oxidised products include their conversion into indanes displaying a highly substituted carbon network.

Experimental

All reactions were carried out under a nitrogen or argon atmosphere with dry solvents under anhydrous conditions, unless otherwise

noted. Dry methylene chloride and toluene were respectively obtained by distillation from CaH_2 and from sodium. Aerobic oxidations were carried out in two-neck flask fitted with a vertical condenser with a doubled balloon of oxygen at the top. After prolonged storage, mesylates **1a-i** were dried before engaging them in the oxidative process by azeotropic water removal with dry PhMe or by filtration on a pad of SiO_2. Reactions were monitored by thin-layer chromatography (TLC) on Merck silica gel plates with QF-254 indicator followed by one of these staining reagents: ammonium molybdate or potassium permanganate. Merck silica gel (60, 40-63 μm) was used for flash column chromatography. NMR experiments were recorded on Bruker Advance DMX -300 or -200 instruments and calibrated using residual undeuterated solvent as an internal reference (7.26 and 77.00 ppm for ^1H and ^{13}C NMR in $CDCl_3$). IR spectra were recorded on a PerkinElmer Spectrum 100 FT-IR-spectrometer with major peaks reported. High-resolution mass spectra (HRMS) were recorded by the mass spectrometry service at the IRCOF on an LCT Premier XE benchtop orthogonal acceleration time-of-flight (TOF) mass spectrometer (Waters Micromass).

General procedure for the preparation of dienedione. To a stirred solution of mesylate **1a-i** (1.0 equiv) in toluene (0.1 M) at rt was added DBU (0.2 equiv). The flask was first flushed with O_2 and then equipped with a vertical condenser fitted with a balloon of O_2. The resulting mixture was then stirred for 10 h at 110 ℃ (oil bath at 120 ℃). After 10 h, 0.2 equiv of DBU were successively added every 1.5 h (6 x 0.2 equiv, 1.4 equiv in total). Once 1.4 equiv of DBU were added, the reaction mixture was stirred at reflux for another 17 h before being concentrated in vacuo. Flash column chromatography of the residue afforded dienedione **3a-i**.

3a: According to the general procedure, the reaction of mesylate **1a** (201 mg, 0.60 mmol) and DBU (7 x 18 μL, 0.84 mmol) in toluene (6 mL) provided **3a** (83 mg, 55%) as a yellow amorphous solid (cyclohexane: EtOAc / 7:3). R_f = 0.5 (cyclohexane: EtOAc, 7:3); IR (film) ν 3027, 2937, 1690, 1668, 1639, 1451, 1181, 820, 738, 701, 469 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 6.1 Hz, 1H), 7.07 – 7.32 (m, 3H), 6.78 – 6.95 (m, 2H), 6.17 (d, *J* = 6.1 Hz, 1H), 2.71 – 3.01 (m, 3H), 2.58 (ddd, *J* = 19.4, 6.2, 1.5 Hz, 1H), 2.19 (ddd, *J* = 13.3, 5.8, 1.5 Hz, 1H), 2.10 (s, 3H), 1.86 (ddd~dt, *J* = 13.3, 6.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.0, 196.8, 162.8, 150.4, 135.7, 134.9, 134.3, 130.0 (2C), 128.4 (2C), 127.0, 47.8, 43.0, 33.9, 29.0, 9.8; HRMS (API): calcd for $C_{17}H_{17}O_2^+$ $[M+H]^+$: 253.1229, found 253.1227

3b: According to the general procedure, the reaction of mesylate **1b** (354 mg, 0.92 mmol) and DBU (7 x 28 μL, 1.29 mmol) in toluene (9.2 mL) provided **3b** (136 mg, 49%) as a yellow amorphous solid (cyclohexane: EtOAc / 7:3). R_f = 0.45 (cyclohexane: EtOAc, 65:35); IR (film) ν 2965, 1692, 1670, 1258, 1072, 1012, 816, 734, 475 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 – 7.88 (m, 3H), 7.39 – 7.51 (m, 3H), 7.35 (d, *J* = 6.1 Hz, 1H), 7.08 (dd, *J* = 8.4, 1.7 Hz, 1H), 6.23 (d, *J* = 6.1 Hz, 1H), 3.15 (d, *J* = 13.4 Hz, 1H), 2.92 – 3.10 (m, 2H), 2.69 (ddd, *J* = 19.3, 6.1, 1.2 Hz, 1H), 2.26 (ddd, *J* = 13.3, 5.9, 1.2 Hz, 1H), 2.21 (s, 3H), 1.93 (ddd~dt, *J* = 13.3, 6.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1, 196.7, 162.8, 150.5, 134.9, 134.3, 133.2, 133.2, 132.2, 128.7, 128.0, 127.9, 127.6, 127.5, 126.3, 125.9, 47.9, 43.1, 34.0, 28.9, 9.8; HRMS (API): calcd for $C_{21}H_{19}O_2^+$ $[M+H]^+$: 303.1385, found 303.1387.

3c: According to the general procedure, the reaction of mesylate **1c** (200 mg, 0.55 mmol) and DBU (7 x 17 μL, 0.77 mmol) in toluene (5.5 mL) provided **3c** (66 mg, 43%) as a yellow amorphous solid (cyclohexane: EtOAc / 7:3). Rf = 0.4 (cyclohexane: EtOAc, 65:35); IR (film) ν 2921, 2854, 1692, 1670, 1613, 1510, 1445, 1305, 1245, 1176, 1030, 816, 516 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 6.1 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.73 – 6.82 (m, 2H), 6.23 (d, *J* = 6.1 Hz, 1H), 3.76 (s, 3H), 2.81 – 3.01 (m, 3H), 2.63 (ddd, *J* = 19.3, 6.1, 1.2 Hz, 1H), 2.20 (ddd, *J* = 13.3, 5.8, 1.2 Hz, 1H), 2.15 (s, 3H), 1.92 (ddd~dt, *J* = 13.3, 6.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1, 196.8, 162.9, 158.5, 150.5, 134.9, 134.1, 131.0 (2C), 127.6, 113.7 (2C), 55.1, 47.9, 42.1, 33.9, 28.9, 9.8; HRMS (API): calcd for $C_{18}H_{19}O_3^+$ $[M+H]^+$: 283.1334, found 283.1351.

3d: According to the general procedure , the reaction of mesylate **1d** (200 mg, 0.48 mmol) and DBU (7 x 14 μL, 0.67 mmol) in toluene (4.8 mL) provided **3d** (85 mg, 54%) as a yellow amorphous solid (cyclohexane: EtOAc / 7:3). Rf = 0.4 (cyclohexane: EtOAc, 65:35); IR (film) ν 2977, 2937, 1669, 1441, 1179, 1126, 1063, 1023, 950, 830, 764, 445 cm-1; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, J = 6.0 Hz, 1H), 7.45 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.14 (td, *J* = 7.5, 1.4 Hz, 1H), 7.02 (td, *J* = 8.0, 1.6 Hz), 6.87 (dd, *J* = 7.5, 1.6 Hz, 1H), 6.12 (d, *J* = 6.0 Hz, 1H), 3.38 (d, *J* = 13.4 Hz, 1H), 3.09 (d, *J* = 13.4 Hz, 1H), 2.99 (ddd, *J* = 19.3, 13.5, 5.8 Hz, 1H), 2.67 (ddd, *J* = 19.3, 6.1, 1.5 Hz, 1H), 2.31 (ddd, *J* = 13.5, 5.8, 1.5 Hz, 1H), 2.12 (s, 3H), 2.06 (ddd~dt, *J* = 13.3, 6.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 196.4, 161.3, 149.2, 135.1, 135.0, 134.8, 133.1, 132.2, 128.8, 127.1, 125.8, 48.5, 41.1, 33.9, 30.8, 9.8; HRMS (ESI): calcd for $C_{17}H_{16}O_2Br^+$ $[M+H]^+$: 331.0334 and 333.0313, found 331.0339 and 333.0320.

3e: According to the general procedure, the reaction of mesylate **1e** (569 mg, 1.5 mmol) and DBU (7 x 45 μL, 2.1 mmol) in toluene (15 mL) provided **3e** (136 mg, 31%) as a pale yellow amorphous solid (cyclohexane: EtOAc/7:3). R_f = 0.35 (cyclohexane: EtOAc, 6:4); IR (film) ν 2915, 2848, 1691, 1674, 1522, 1462, 1349, 1171, 1080, 841, 827, 784, 747, 710, 472 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.44 (td, *J* = 7.5, 1.5 Hz, 1H), 7.36 (d, *J* = 6.0 Hz, 1H), 7.36 (td, *J* = 7.8, 1.5 Hz, 1H), 6.94 (dd, *J* = 7.5, 1.3 Hz, 1H), 6.06 (d, *J* = 6.0 Hz, 1H), 3.58 (d, *J* = 13.3 Hz, 1H), 3.52 (d, *J* = 13.3 Hz, 1H), 2.94 (ddd, *J* = 19.4, 13.5, 5.8 Hz, 1H), 2.70 (ddd, *J* = 19.4, 6.1, 1.4 Hz, 1H), 2.32 (ddd, *J* = 13.5, 5.8, 1.4 Hz, 1H), 2.12 (s, 3H), 2.11 (ddd~dt, *J* = 13.5, 6.1 Hz, 1H);^{13}C NMR (75 MHz, $CDCl_3$) δ 199.5, 196.1, 160.9, 150.0, 148.7, 135.4, 135.1, 133.7, 132.7, 130.7, 128.4, 125.2, 48.6, 38.2, 33.8, 31.2, 9.8; HRMS (API): calcd for $C_{17}H_{16}NO_4^+$ $[M+H]^+$: 298.1079, found 298.1079.

3f: According to the general procedure, the reaction of mesylate **1f** (150 mg, 0.52 mmol) and DBU (7 x 16 μL, 0.73 mmol) in toluene (10 mL) provided **3f** (36 mg, 35%) as a pale yellow amorphous solid (cyclohexane: EtOAc / 8:2). R_f = 0.5 (cyclohexane: EtOAc, 6:4); IR (film) ν 2925, 2855, 1694, 1674, 1638, 1451, 1178, 1099, 1072, 1021, 824 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 6.1 Hz, 1H), 6.34 (d, *J* = 6.1 Hz, 1H), 5.50 – 5.71 (m, 1H), 5.11 (d, *J* = 10.0 Hz, 1H), 5.03 (dd, *J* = 16.9, 1.3 Hz, 1H), 2.76 (ddd, *J* = 19.4, 13.3, 5.7 Hz, 1H), 2.55 (ddd, *J* = 19.4, 6.2, 1.4 Hz, 1H), 2.46 (dd, *J* = 13.8, 7.9 Hz, 1H), 2.31 (dd, *J* = 13.9, 7.1 Hz, 1H), 2.21 (ddd, *J* = 13.3, 5.7,

1.4 Hz, 1H), 2.12 (s, 3H), 1.91 (ddd~dt, *J* = 13.3, 6.2 Hz, 1H);^{13}C NMR (75 MHz, $CDCl_3$) δ 200.2, 197.2, 162.8, 150.2, 135.1, 134.3, 132.3, 119.6, 46.8, 41.1, 33.6, 29.0, 9.8; HRMS (API): calcd for $C_{13}H_{15}O_2^+$ $[M+H]^+$: 203.1072, found 203.1072.

3g: According to the general procedure, the reaction of mesylate **1g** (357 mg, 1.0 mmol) and DBU (7 x 30 µL, 1.4 mmol) in toluene (10 mL) provided **3g** (117 mg, 46%) as a pale yellow amorphous solid (cyclohexane: EtOAc / 7:3). R_f = 0.4 (cyclohexane: EtOAc, 8:2); IR (film) ν 2925, 2856, 1694, 1674, 1638, 1456, 1178, 1072, 825 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 6.1 Hz, 1H), 6.35 (d, *J* = 6.1 Hz, 1H), 2.75 (ddd, *J* = 19.2, 13.2, 5.8 Hz, 1H), 2.54 (ddd, *J* = 19.2, 6.1, 1.5 Hz, 1H), 2.17 (ddd, *J* = 13.2, 5.8, 1.5 Hz, 1H), 2.12 (s, 3H), 1.90 (ddd~dt, *J* = 13.2, 6.1 Hz, 1H), 1.31 – 1.74 (m, 1H), 1.20 (br s, 10H), 0.95 – 1.10 (m, 1H), 0.84 (t, *J* = 6.8 Hz, 3H);^{13}C NMR (75 MHz, $CDCl_3$) δ 200.4, 197.5, 163.4, 150.9, 135.0, 133.6, 46.8, 36.5, 33.7, 31.6, 29.8, 29.7, 28.9, 25.2, 22.4, 13.9, 9.7; HRMS (API): calcd for $C_{17}H_{25}O_2^+$ $[M+H]^+$: 261.1855, found 261.1861.

3h: According to the general procedure, the reaction of mesylate **1h** (256 mg, 1.0 mmol) and DBU (7 x 30 µL, 1.4 mmol) in toluene (10 mL) provided **3h** (88 mg, 50%) as a yellow amorphous solid (cyclohexane: EtOAc / 7:3). R_f = 0.45 (cyclohexane: EtOAc, 6:4); IR (film) ν 2921, 2870, 1693, 1664, 1641, 1336, 1217, 1149, 1007, 950, 827, 468 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 6.0 Hz, 1H), 6.25 (d, *J* = 6.0 Hz, 1H), 2.78 (ddd, *J* = 19.1, 12.9, 6.1 Hz, 1H), 2.57 (ddd, *J* = 19.1, 5.8, 2.1 Hz, 1H), 2.10 (s, 3H), 2.04 (dd, *J* = 6.1, 2.1 Hz, 1H), 1.98 (ddd~dt, *J* = 12.9, 5.8 Hz, 1H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.2, 197.4, 165.2, 150.9, 133.6 (2C), 43.5, 33.9, 31.4, 23.8, 9.6; HRMS (ESI): calcd for $C_{11}H_{13}O_2^+$ $[M+H]^+$: 177.0916, found 177.0910.

3i: According to the general procedure, the reaction of mesylate **1i** (100 mg, 1.0 mmol) and DBU (7 x 18 µL, 1.4 mmol) in toluene (4 mL) provided **3i** (22 mg, 33%) as a yellow amorphous solid (cyclohexane: EtOAc / 7:3). R_f = 0.45 (cyclohexane: EtOAc, 6:4); IR (film) ν 2928, 1680, 1351, 1173, 1074, 958, 845, 818, 530 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 6.0, 1.0 Hz, 1H), 6.34 (d, *J* = 6.0 Hz, 1H), 6.27 (br s, 1H), 2.80 (ddd, *J* = 19.0, 13.3, 5.7 Hz, 1H), 2.56 – 2.66 (m, 1H), 2.14 (ddd, J = 12.9, 5.6, 2.0 Hz), 2.05 (dd, *J* = 13.1, 5.5 Hz, 1H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1, 195.7, 166.4, 159.1, 133.2, 121.4, 43.1, 34.7, 32.3, 23.6; HRMS (ESI): calcd for $C_{10}H_9O_2^-$ $[M-H]^-$: 161.0603, found 161.0600.

General procedure for the Friedel-Crafts conjugate addition. To a stirred solution of dihydroindenedione **3a-c** in CH_2Cl_2 at rt was added $AlCl_3$ (5 equiv). The resulting reaction mixture was stirred until completion (monitored by TLC) before being quenched with HCl (1N, aq. sol.). The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were brined, dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography of the crude afforded indanes **15a-c** or chloroalkanes **16** and **16'**.

15a: According to the general procedure, the reaction of **3a** (50 mg, 0.2 mmol) and $AlCl_3$ (133 mg, 1.0 mmol) in CH_2Cl_2 (4 mL) provided **15a** (42 mg, 84%) as a yellow oil (cyclohexane: EtOAc / 8:2). R_f = 0.60 (cyclohexane: EtOAc, 7:3); IR (film) ν 2915, 1711, 1671, 1619, 1160, 1138, 1058, 813, 782, 760, 470, 425 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 – 7.27 (m, 5H), 3.29 (t, *J* = 9.7 Hz, 1H), 3.20 (d, *J* = 16.5 Hz, 1H), 2.93 (t, *J* = 4.6 Hz, 1H), 2.86 (d, *J* = 9.7 Hz, 1H), 2.67 (ddd, *J* = 19.4, 14.2, 5.4 Hz, 1H), 2.48 (ddd, *J* = 19.4, 4.8, 2.0 Hz, 1H), 2.23 (dd, *J* = 19.6, 9.0 Hz, 1H), 2.07 (s, 3H), 2.01 – 2.14 (m, 1H), 1.92 (ddd~dt, *J* = 14.2, 4.8 Hz, 1H);^{13}C NMR (75 MHz, $CDCl_3$) δ 208.1, 200.7, 151.2, 145.1, 140.3, 136.2, 127.4, 127.2, 125.4, 124.7, 52.4, 50.8, 45.3, 39.5, 33.8, 33.3, 10.0; HRMS (API): calcd for $C_{17}H_{17}O_2^+$ $[M+H]^+$: 253.1229, found 253.1230.

15b: According to the general procedure, the reaction of **3b** (20 mg, 0.07 mmol) and $AlCl_3$ (47 mg, 0.35 mmol) in CH_2Cl_2 (5 mL) provided indane **15b** (17 mg, 80%) as a yellow oil (cyclohexane: EtOAc / 8:2). R_f = 0.60 (cyclohexane: EtOAc, 65:35); IR (film) ν 3055, 2921, 2848, 1712, 1672, 1618, 1378, 1186, 1159, 1137, 1058, 811, 782, 730, 467 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 – 7.94 (m, 1H), 7.76 (t, *J* = 7.6 Hz, 2H), 7.45 – 7.58 (m, 2H), 7.38 (d, *J* = 8.4 Hz, 1H), 3.86 (t, *J* = 9.3 Hz, 1H), 3.47 (d, *J* = 16.6 Hz, 1H), 3.12 – 3.27 (m, 2H), 2.83 (ddd, *J* = 18.3, 14.1, 5.4 Hz, 1H), 2.60 (ddd, *J* = 18.3, 4.9, 2.1 Hz, 1H), 2.37 (dd, *J* = 19.7, 8.7 Hz, 1H), 2.24 (ddd, *J* = 14.1, 5.4, 2.1 Hz, 1H), 2.20 (s, 3H), 2.16 (ddd~dt, *J* = 14.1, 4.9 Hz, 1H);^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3, 200.8, 151.2, 140.9, 137.3, 136.2, 133.1, 130.1, 128.7, 128.2, 126.6, 125.4, 123.7, 123.5, 52.4, 49.3, 44.8, 40.8, 34.1, 33.9, 10.1; HRMS (API): calcd for $C_{21}H_{19}O_2^+$ $[M+H]^+$: 303.1385, found 303.1385.

15d: According to the general procedure, the reaction of **3d** (10 mg, 0.03 mmol) and $AlCl_3$ (28 mg, 0.21 mmol) in CH_2Cl_2 (5 mL) provided **15d** (7 mg, 70%) as a yellow powder (cyclohexane: EtOAc / 8:2). R_f = 0.50 (cyclohexane: EtOAc, 7:3); IR (film) ν 2919, 2854, 1713, 1673, 1449, 1180, 1129, 1062, 959, 780 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.9 Hz, 1H), 7.21 (d, *J* = 7.4 Hz, 1H), 7.06 – 7.14 (m, 1H), 3.48 (t, *J* = 9.4 Hz, 1H), 3.38 (d, *J* = 17.1 Hz, 1H), 2.90 – 3.05 (m, 2H), 2.74 (ddd, *J* = 19.6, 14.1, 5.3 Hz, 1H), 2.59 (ddd, *J* = 18.3, 4.8, 1.9 Hz, 1H), 2.32 (dd, *J* = 19.6, 8.8 Hz, 1H), 2.21 (ddd, *J* = 13.1, 5.3, 1.9 Hz, 1H), 2.16 (s, 3H), 2.09 (ddd~dt, *J* = 14.1, 4.8 Hz, 1H);^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3, 200.8, 151.2, 140.9, 137.3, 136.2, 133.1, 130.1, 128.7, 128.2, 126.6, 125.4, 123.7, 123.5, 52.4, 49.3, 44.8, 40.8, 34.1, 33.9, 10.1; HRMS (API): calcd for $C_{17}H_{16}O_2Br^+$ $[M+H]^+$: 331.0334 and 333,0313, found 331.0331 and 333.0307.

16: According to the general procedure, the reaction of dihydroindenedione **3f** (24 mg, 0.12 mmol) and $AlCl_3$ (80 mg, 0.6 mmol) in CH_2Cl_2 (5 mL) provided a stereoisomeric mixture of diastereoisomer **16** (6 mg, 21%) and **16'** (11 mg, 39%) as colorless oil (cyclohexane: EtOAc / 8:2 to 7:3). **16**: R_f = 0.5 (cyclohexane: EtOAc, 6:4); IR (film) ν 3072, 2927, 2848, 1695, 1665, 1445, 1316, 1184, 1020, 844, 828, 710, 615, 506, 404 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 6.1 Hz, 1H), 6.42 (d, *J* = 6.1 Hz, 1H), 3.84 (m, 1H), 2.83 (ddd, *J* = 19.5, 13.2, 5.6 Hz, 1H), 2.60 (ddd, *J* = 19.5, 6.2, 1.2 Hz, 1H), 2.46 (ddd, *J* = 13.2, 5.6, 1.2 Hz, 1H), 2.32 (dd, *J* = 15.2, 8.5 Hz, 1H), 2.15 (s, 3H), 1.97 (dd, *J* = 15.2, 3.8 Hz, 1H), 1.88 (ddd~dt, *J* = 13.2, 6.2 Hz, 1H), 1.44 (d, *J* = 6.6 Hz, 3H);^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1, 196.9, 162.6, 149.9, 135.8, 134.8, 54.3, 46.8, 46.4, 33.9, 30.4, 27.1, 10.0; HRMS (API): calcd for $C_{13}H_{16}O_2Cl$ $[M + H^+]$: 239.0839, found 239.0834. **16'**: R_f = 0.35 (cyclohexane: EtOAc, 6:4); IR (film) ν 2926, 1674, 1186, 825, 617 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 6.1 Hz, 1H), 6.41 (d, *J* = 6.1 Hz, 1H), 3.78 – 4.05 (m, 1H), 2.69 (ddd, *J* = 19.3, 13.2, 5.3 Hz, 1H), 2.57 (ddd, *J* = 19.3, 6.6, 1.8 Hz, 1H), 2.21 (ddd, *J* =

13.2, 5.3, 1.8 Hz, 1H), 2.14 (s , *J* = 3.6 Hz, 3H), 2.08 – 2.17 (m, 2H), 1.95 (ddd~dt, *J* = 13.2, 6.6 Hz, 1H), 1.50 (d, *J* = 6.6 Hz, 3H);^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8, 196.7, 161.5, 150.5, 135.6, 133.8, 53.9, 46.7, 46.3, 33.7, 31.0, 26.5, 9.9; HRMS (API): calcd for $C_{13}H_{16}O_2Cl$ $[M+H]^+$: 239.0839, found 239.0845.

17: To a stirred solution of **3f** (24 mg, 0.060 mmol) and ethyl acrylate (40 µL, 0.360 mmol) in CH_2Cl_2 (5 mL) at rt was added Grubbs II catalyst (10 mg, 0.0012 mmol). The resulting mixture was stirred for 12 h before being concentrated in vacuo. Flash column chromatography (cyclohexane: EtOAc, 70:30) of the crude afforded acrylate **17** (18 mg, 55%) as a yellow oil. R_f = 0.55 (cyclohexane: EtOAc, 60:40); IR (film) ν 3029, 2927, 1653, 1352, 1331, 1173, 1017, 940, 843, 743, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 6.1 Hz, 1H), 6.76 (m, 1H), 6.39 (d, *J* = 6.1 Hz, 1H), 5.83 (d, *J* = 15.5 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.53 – 2.81 (m, 3H), 2.38 (dd, *J* = 14.0, 7.4 Hz, 1H), 2.23 (dd, *J* = 13.2, 4.3 Hz, 1H), 2.14 (s, 3H), 1.94 (ddd~dt, *J* = 13.2, 6.4 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.7, 196.5, 165.5, 161.9, 149.4, 141.8, 135.6, 135.0, 125.6, 60.6, 46.7, 39.5, 33.5, 28.9, 14.2, 9.9; HRMS (API): calcd for $C_{16}H_{19}O_4^+$ $[M+H]^+$: 275.1283, found 275.1276.

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Notes and references

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‡ Electronic Supplementary Information (ESI) available: procedures for the preparations of **1a-i** and spectra of all compounds. See DOI: 10.1039/c000000x/

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