

Application of intramolecular carbonyl-ene reaction towards the synthesis of idarubicinone scaffold

Shyam Basak, Sutapa Ray, and Dipakranjan Mal*

Department of Chemistry, Indian Institute of Technology Kharagpur, Kharagpur 721302, India

E-mail: dmal@chem.iitkgp.ernet.in

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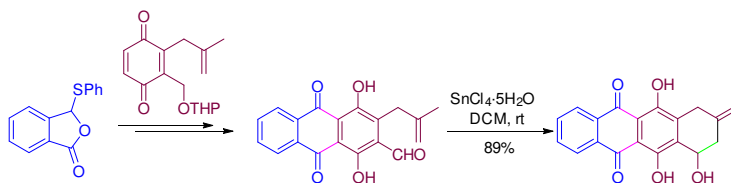
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Abstract

Intramolecular aromatic carbonyl-ene reaction (ICE)[†] has been combined with a modified Hauser annulation to offer a facile access to the tetracyclic idarubicinone core. The required key dihydroxyanthraquinone aldehyde precursor was assembled in one step by modified Hauser annulation of a functionalized benzoquinone. Its ene reaction in the presence of $\text{SnCl}_4 \cdot 5\text{H}_2\text{O}$ directly led to the formation of idarubicinone core. Also described are an unprecedented thermal cascade involving a thermal ICE en route to α -naphthols, and exploratory studies on model elaboration of anthracycline A rings.

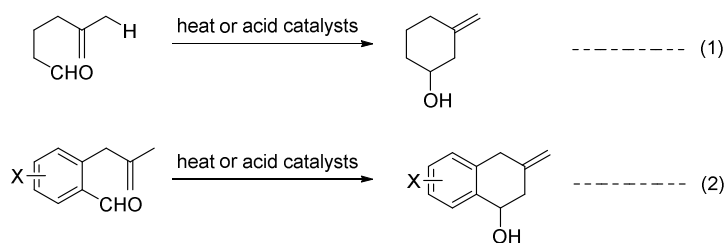
[†]By “aromatic carbonyl-ene reaction” we mean those reactions in which an aromatic ring is embedded in the transition state of a carbonyl-ene reaction.



Keywords: Intramolecular, carbonyl-ene, tetralin, anthracyclines

Introduction

The type-II intramolecular carbonyl-ene reaction (ICE) shown as eqn. 1 in Scheme 1 is an established process in the organic synthesis.¹⁻² It has allowed total synthesis of many bioactive natural products.³⁻⁸ However, its aromatic version (eqn. 2, Scheme 1) discovered in 1983 by Hauser and Mal in conjunction with their work on the total synthesis of (±)-γ-citromycinone, has been limited to anthracylines.⁹⁻¹⁵ It is a significant advancement in the area of ICE, in view of its success despite the conformational constraint imposed by a benzene ring. Furthermore, the placement of the benzylic hydroxyl group in the product obviates the problems of benzylic bromination under radical conditions on a large scale.^{16,17} However, its application to simple naphthalenes and anthracenes are problematic due to the susceptibility of the incipient ene products to aromatization. In a recent report¹⁸ from our laboratory, we have demonstrated that the ICE can be manoeuvred to prevent aromatization of the ene products, thus permitting synthesis of non-aromatized ene products i.e. hydroaromatic products. We also included development of a synthesis of *ortho* methallylbenzaldehydes based upon Suzuki coupling reactions.



Scheme 1. Type II carbonyl-ene reaction.

In seeking an application of the aromatic ICE in developing a simpler route to anthracyclines **1–5** (Figure 1), the most widely used anticancer drugs^{19–22}, we chose to assemble the tetracycline framework of idarubicinone (**3**) as shown in Scheme 2. The salient features of the retrosynthesis are i) modified Hauser annulation of **6** and **7** to assemble dihydroxy intermediate **8** and ii) its direct use as the ene substrate to produce tetracyclic intermediate **9**. It may be mentioned that the reactivity of the 1,4-dimethoxy analog of quinone **8**, prepared by Claisen rearrangement, was examined towards the aromatic ICE.²³ No further elaboration was attempted probably due to the problem with deprotection of the aromatic methoxy groups without affecting the A-ring. In devising the synthesis of **3**, we, therefore, envisioned investigations with dihydroxy intermediate **8**. It was anticipated that the corresponding ene product i.e. **9** would be sufficiently stable due to intramolecular hydrogen bonding for further elaborations without resorting to a deprotection.

In this study, the potential of the aromatic ICE approach in creating an asymmetric centre at C7 position of anthracyclines is proposed. Asymmetric epoxidations or hydroxylations or nucleophilic additions can be invoked for further elaborations, as indicated in Scheme 2. Asymmetric dihydroxylation of the ene product **9** is proposed to give **10** and then **3**. In the second approach, tetracycle **11** is expected to produce compounds **12** and **13** and **3** (Scheme 2).

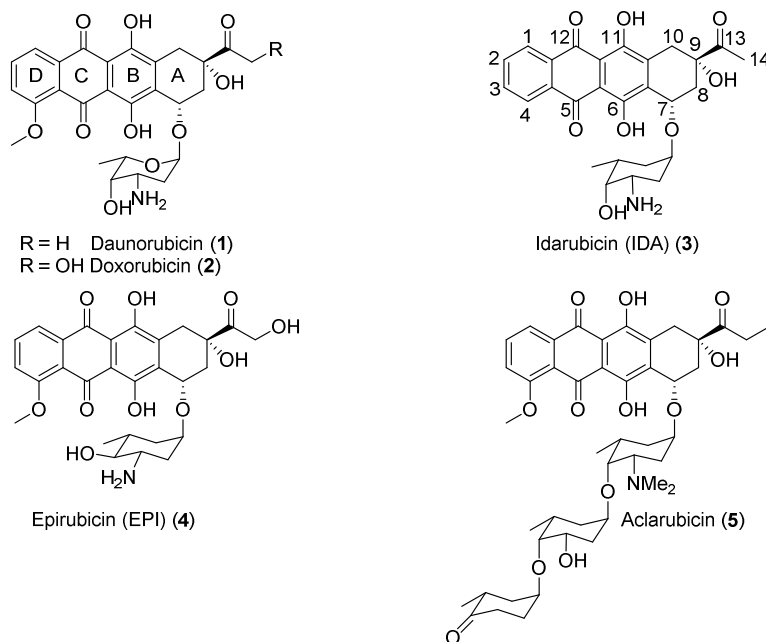
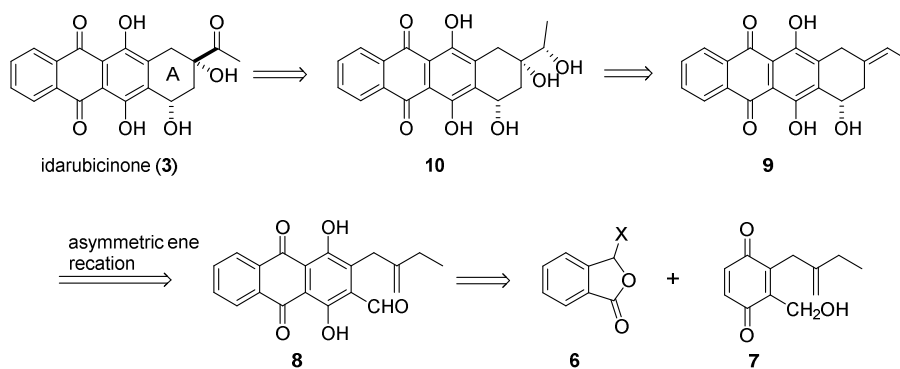
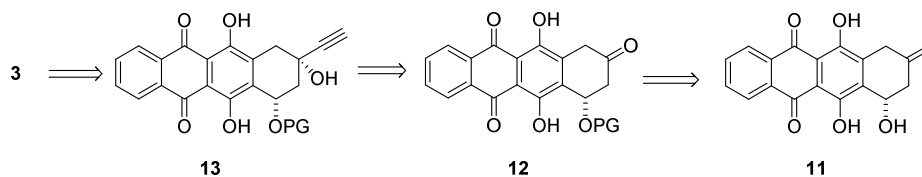


Figure 1. Selected clinically used anthracyclines.

Retrosynthetic approach 1



Retrosynthetic approach 2

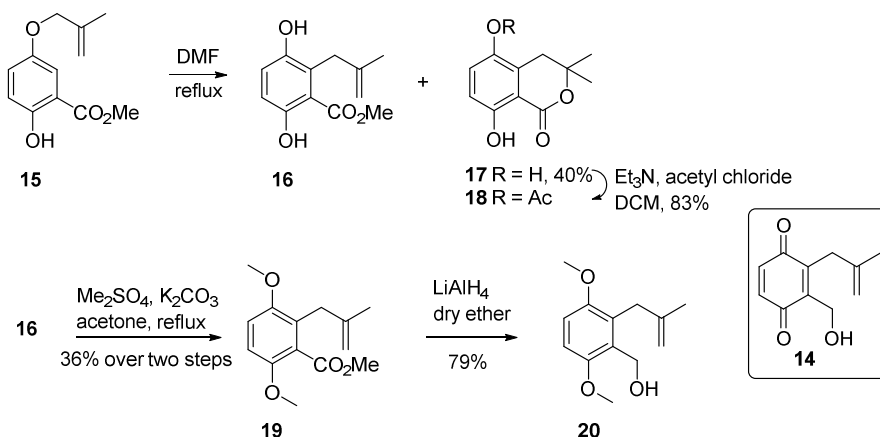


Scheme 2. Retrosynthetic analysis of idarubicinone (3).

Results and Discussion

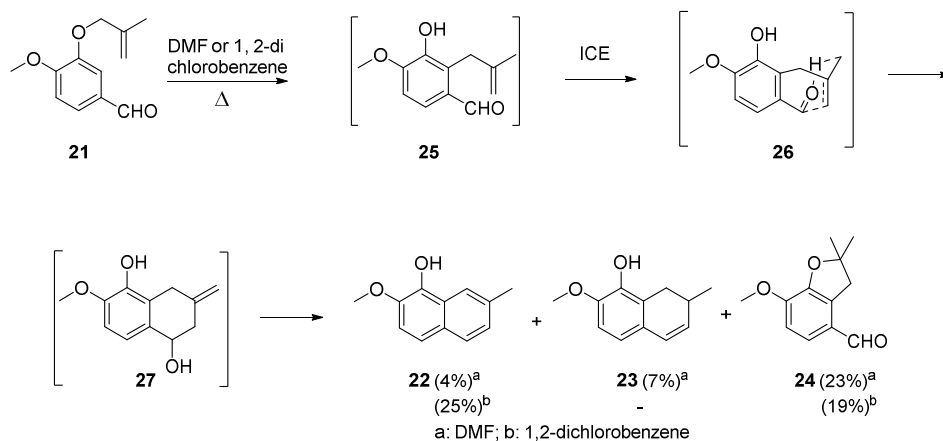
To perform a model study of idarubicinone (3) utilizing Hauser annulation, we first decided to synthesize the Michael acceptor **14** (cf **7**, Scheme 2) (Scheme 3). This proposal stemmed from our previous study on the

Hauser annulation of *p*-quinones for straightforward generation of 1,4-dihydroxyanthraquinone moieties.²⁴ Accordingly, *O*-methallyl substrate **15** was prepared by selective *O*-methallylation of methyl 2,5-dihydroxybenzoate with methallyl bromide in the presence of K₂CO₃ in acetone. Claisen rearrangement of **15** in boiling DMF gave two products **16** and **17** in 1:1 ratio. Appearance of a 2H singlet at δ 2.98 and a 6H singlet at δ 1.50 indicated the formation of **17**, which was confirmed by its acetylation to compound **18**. Quinol **16** was methylated to **19** by reaction with Me₂SO₄-K₂CO₃ in acetone. Compound **19** was then reduced to alcohol **20**²⁵ by lithium aluminium hydride.



Scheme 3. Preparation of alcohol **20**.

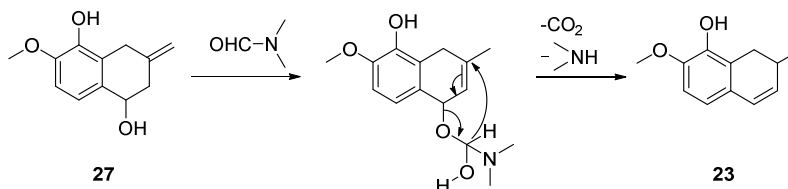
For an alternative route to **20**, we examined the possibility of Claisen rearrangement of a related aldehyde precursor, and for the model study we chose aldehyde **21**²⁶ (Scheme 4).



Scheme 4. Thermal rearrangement of aldehyde **21**.

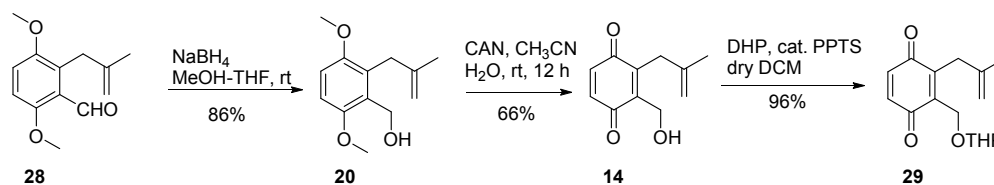
When it was heated in refluxing DMF, the desired Claisen product was not obtained. Instead, the reaction resulted in formation of three products **22** (4%), **23** (7%) and **24**²⁷ (23%) (Scheme 4). Formation of the naphthol **22** is accounted for by Claisen rearrangement of **21** to intermediate **25** followed by thermal ICE of **25** through **26** to **27**, its dehydration and isomerization. The formation of **23** is very striking in that its formation must involve a reduction, since there is a decrease in the oxidation level.²⁸ The probable mechanism is shown in Scheme 5, where DMF acts as the hydride donor. The structure of **23** is further confirmed by transforming it

into its acetate. It may be noted that the product **23** was not obtained when the reaction was carried out in 1,2-dichlorobenzene. Formation of **24** is explicable in terms of its Claisen rearrangement of **21** followed a 5-exo-trig cyclization of **25**.



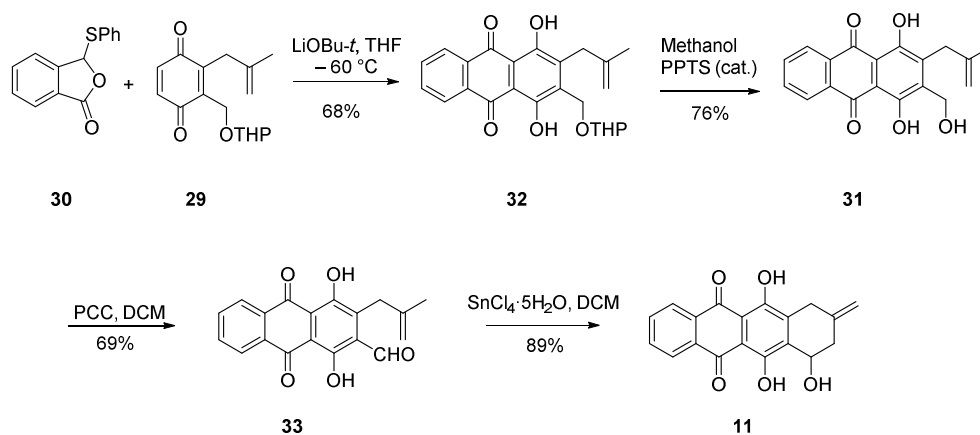
Scheme 5. Proposed mechanism for the transformation of **21** to **23**.

In view of the problems with above Claisen rearrangement methodology, the synthesis of quinone **14** was started from the known aldehyde **28**.¹⁸ It was converted into quinone **14** in two steps. NaBH₄ reduction of **28** gave alcohol **20** in 86% yield, which was oxidized with CAN to give **14** in 66% yield. It was then converted into THP ether **29** by treatment with DHP in dry DCM in the presence of a catalytic amount of PPTS (Scheme 6).



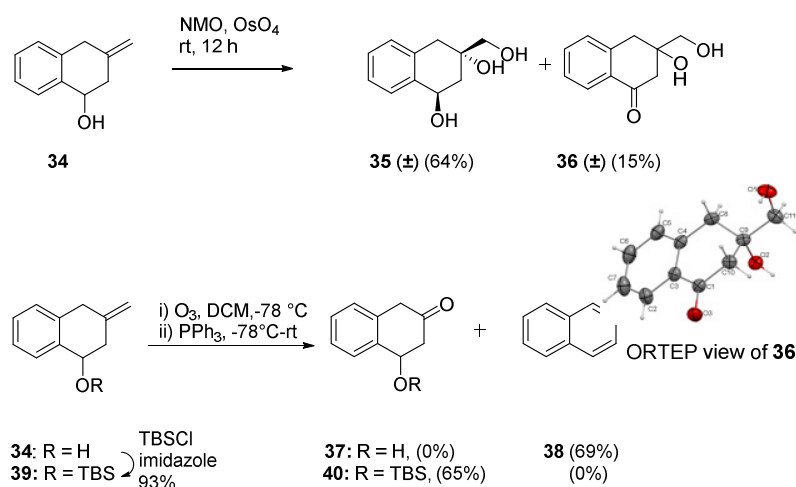
Scheme 6. Alternative synthesis of alcohol **20** and acceptor **29**.

Both the quinones **14** and **29** were subjected to Hauser annulations with phthalide **30**.²⁹ In the presence of LiOBu-*t*, the annulation²⁴ of **30** with **14** gave annulation product **31**, but in only 10% yield. Assuming that the free -OH in **14** interfered the annulation, we examined its protected form i.e. **29**. Annulation of phthalide sulfide **30** with **29** under similar conditions gave dihydroxyanthraquinone **32** in 68% yield. Deprotection of **32** with PPTS-MeOH provided alcohol **31** in 76% yield. PCC oxidation of **31** furnished aldehyde **33** in 69% yield. This was then subjected to ICE under a variety of conditions. Gratifyingly, we obtained tetracycle **11** as the sole product representing the core structure of idarubicinone (**3**) on treatment with SnCl₄·5H₂O. It was sufficiently stable to be purified by chromatography on silica gel (Scheme 7).



Scheme 7. Synthesis of the tetracycle core of idarubicinone (**3**).

In parallel with the synthesis of the tetracycle **11**, we performed few exploratory studies designed for functionalization of the A ring with model ene derivative **34**¹⁸ obtained from our previous work. Its NMO-mediated dihydroxylation afforded triol **35** in 64% yield along with diols **36** (15%). *Trans* stereochemistry of **35** was confirmed by analysis of coupling constants of C1 hydrogen and comparing them with those for similar compounds.²³ For 1,3-*cis* dihydroxy analogs, the corresponding coupling constants are less than 5 Hz. It is noteworthy that the dihydroxylation produced only one diastereomer. Ozonolysis of the ene product **34** followed by treatment with triphenylphosphine did not furnish product **37**. Instead, it produced aromatized product β -naphthol (**38**). But, its silyl derivative **39**, prepared by silylation with TBSCl/imidazole gave **40** in 65% yield on ozonolysis. It is sufficiently stable for a chromatographic purification (Scheme 8).

**Scheme 8.** Model study for functionalization of tetralin skeleton of anthracyclines.**Conclusions**

The modified Hauser annulation i.e. annulation of phenylthiophthalides with 1,4-quinones was combined with aromatic carbonyl-ene reaction to pave a simple entry to tetracyclic core of anthracyclines. Noteworthy is the fact that tetracycle **11** with free phenolic –OH group is not very sensitive to aromatization, and it should be amenable to selective dihydroxylation.

Experimental Section

General. All reactions utilizing moisture-sensitive reagents were performed under an inert atmosphere. All solvents namely DMF, DCM, THF, MeOH etc. were dried prior to use, according to the standard protocols. Melting points were determined in open capillary tubes and are reported as uncorrected. TLC was carried out on precoated plates (silica gel 60 F₂₅₄), and the spots were visualized with UV and fluorescent lights. Column chromatography was performed on silica gel (60–120 or 230–400 mesh). NMR spectra for all the compounds were recorded at 200/400/600 and 50/100/150 MHz (Bruker AVANCE 200, Bruker Ultrashield™ 400, Ascend™

600), respectively. IR spectra were recorded with a Perkin–Elmer FTIR instrument using a KBr pellet. HRMS spectra were obtained on XEVO-G2QTOF machine. The phrase “usual work-up” or “worked up in the usual manner” refers to washing of the organic phase with water (2 x 1/4 of the volume of the organic phase) and brine (1 x 1/4 of the volume of the organic phase), drying (Na₂SO₄), filtration, and concentration under reduced pressure.

Methyl 2-hydroxy-5-(2-methylallyloxy)benzoate (15). To a stirred solution of methyl 2,5-dihydroxybenzoate (4 g, 23.8 mmol) in acetone (10 mL) potassium carbonate (3.2 g, 23.8 mmol) was added and stirred for 15 min. To this mixture methylallyl bromide (3.6 mL, 35.7 mmol) was added and stirred for 2.5 h. After the completion of the reaction, the mixture was concentrated under vacuum to remove excess acetone. The reaction mixture was then diluted with water and extracted with ethyl acetate (2 × 100 mL). The combined extracts were washed successively with water (50 mL), saturated aqueous solution of sodium thiosulfate (20 mL), brine (50 mL), dried (anhydrous Na₂SO₄), filtered and concentrated under reduced pressure. Column chromatography of the residue afforded ester **15** as oil (4.5 gm, 87%). *R_f* (1:5 EA(ethyl acetate)/hexane) 0.75; ¹H NMR (400 MHz, CDCl₃): δ 10.38 (s, 1H), 7.31 (d, *J* 3.2 Hz, 1H), 7.11 (dd, *J* 3.2, 8.8 Hz, 1H), 6.91 (d, *J* 8.8 Hz, 1H), 5.09 (s, 1H), 4.99 (s, 1H), 4.39 (s, 2H), 3.95 (s, 3H), 1.83 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 170.3, 156.1, 151.1, 140.8, 124.7, 118.5, 113.3, 112.9, 11.9, 72.5, 52.4, 19.5; IR (KBr): $\tilde{\nu}$ 3220, 2954, 2362, 1683, 1488, 1218, 771 cm⁻¹; HRMS (ESI): *m/z* calculated for C₁₁H₁₁O₃: requires: 191.0708 for [M-OMe]⁺; found: 191.0706.

Methyl 3,6-dihydroxy-2-(2-methylprop-2-enyl)benzoate (16). Compound **15** (4 g, 18.0 mmol) was dissolved in DMF (7 mL) and heated at reflux for 10 h. After completion of the reaction the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 × 100 mL). The combined extracts were washed successively with water (50 mL), brine (50 mL), dried (anhydrous Na₂SO₄), filtered and concentrated under reduced pressure. Column chromatography of the residue afforded ester **16** as white solid but in impure form. Since this compound was susceptible to aerial decomposition and could not be purified, it was directly subjected to methylation. *R_f* (1:3 EA/hexane) 0.4; mp 80 °C; ¹H NMR (400 MHz, CDCl₃): δ 10.39 (s, 1H), 7.01 (d, *J* 8.8 Hz, 1H), 6.91 (d, *J* 8.8 Hz, 1H), 4.83 (s, 1H), 4.53 (s, 1H), 3.95 (s, 3H), 3.68 (s, 2H), 1.82 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 171.3, 156.2, 147.6, 144.4, 126.3, 123.6, 116.8, 113.2, 110.6, 52.3, 36.1, 23.0; IR (KBr): $\tilde{\nu}$ 3496, 2954, 1681, 1497, 1178, 1027, 890, 825 cm⁻¹; HRMS (ESI): *m/z* calculated for C₁₁H₁₁O₃: requires: 191.0708 for [M – OMe]⁺; found: 191.0709.

Methyl 3,6-dimethoxy-2-(2-methylprop-2-enyl)benzoate (19). Dihydroxy compound **16** (0.67 g, 3.0 mmol) was dissolved in dry acetone (20 mL) under N₂-atmosphere. To this solution were added dry K₂CO₃ (2.1 g, 15 mmol) and Me₂SO₄ (0.57 mL, 6 mmol; freshly washed with cold water (10 mL), saturated NaHCO₃ solution (15 mL), brine (15 mL) and dried over anhydrous K₂CO₃). After 2 h of reflux, on completion of the reaction, the inorganic salts were filtered and the filtrate was concentrated. The residue was diluted with ethyl acetate (15 mL), treated with Et₃N (6 mmol) at room temperature and stirred for 30 min. The reaction mixture was then diluted with ethyl acetate (50 mL), washed with water (15 mL) and 5% aq. HCl solution (15 mL) then subjected to usual work-up (drying over anhydrous Na₂SO₄ and concentrating under reduced pressure) to obtain a crude residue. The crude product was purified by column chromatography on silica gel to furnish pure oil **19** in 36% yield over two steps. *R_f* (1:3 EA/hexane) 0.6; ¹H NMR (400 MHz, CDCl₃): δ 6.86 (d, *J* 8.8 Hz, 1H), 6.76 (d, *J* 8.8 Hz, 1H), 4.72 (s, 1H), 4.48 (s, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.34 (s, 2H), 1.70 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 168.2, 151.8, 150.1, 143.7, 127.1, 125.4, 112.4, 110.7, 109.7, 56.3, 56.3, 52.0, 34.6, 22.6; IR (KBr): $\tilde{\nu}$ 2925, 1733, 1560, 1457, 1263, 1066, 773 cm⁻¹; HRMS (ESI): *m/z* calculated for C₁₃H₁₅O₃: requires: 219.1021 for [M-OMe]⁺; found: 219.1016.

5,8-Dihydroxy-3,3-dimethylisochroman-1-one (17). Compound **17** was obtained along with **16** in 40% yield as a white solid from **15** as described above. R_f (1:3 EA/hexane) 0.37; IR (KBr): $\tilde{\nu}$ 3307, 2364, 1646, 1479, 1226, 1114, 883, 819, 686 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 10.74 (s, 1H), 6.99 (d, J 8.8 Hz, 1H), 6.79 (d, J 8.8 Hz, 1H), 2.98 (s, 2H), 1.50 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 169.5, 156.2, 144.4, 124.3, 123.4, 116.0, 107.9, 82.3, 32.9, 27.6, 27.6; HRMS (ESI): m/z calculated for $\text{C}_{11}\text{H}_{13}\text{O}_4$: requires: 209.0814 for $[\text{M} + \text{H}]^+$; found: 209.0812.

8-Hydroxy-3,3-dimethyl-1-oxoisochroman-5-yl acetate (18). Et_3N (0.06 mL, 0.77 mmol) was added to a solution of **17** (80 mg, 0.38 mmol) in dry CH_2Cl_2 (3 mL) and stirred for 10 min. Acetyl chloride (0.05 mL, 0.77 mmol) was drop-wise added to this mixture at 0 °C and allowed to stir for 2.5 h at room temperature. The reaction was quenched with water (5 mL) and extracted with CH_2Cl_2 (50 mL). The combined extracts were successively washed with water (10 mL), brine (10 mL), dried (anhydrous Na_2SO_4), filtered and concentrated under reduced pressure. Column chromatography of the residue afforded **18** as a white solid (80 mg, 83%). R_f (1:3 EA/hexane) 0.4; mp 92 °C; ^1H NMR (400 MHz, CDCl_3): δ 11.11 (s, 1H), 7.19 (d, J 8.8 Hz, 1H), 6.91 (d, J 8.8 Hz, 1H), 2.81 (s, 2H), 2.32 (s, 3H), 1.48 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 169.1, 168.8, 160.0, 139.4, 130.2, 129.8, 116.7, 107.7, 82.0, 33.6, 27.3, 27.3, 20.6; IR (KBr): $\tilde{\nu}$ 3448, 2985, 1756, 1670, 1475, 1226, 1112, 902, 804 cm^{-1} .

[3,6-Dimethoxy-2-(2-methylprop-2-enyl)phenyl]methanol (20).²⁵ To a stirred solution of **19** (1.0 gm, 4 mmol) in dry ether (7 mL) under nitrogen atmosphere, cooled to 0 °C, lithium aluminium hydride (380 mg, 10 mmol) was added and stirred for 3 h at room temperature. After completion of the reaction, it was cooled and quenched by dropwise addition of saturated sodium sulfate until a white precipitate separated. This was filtered through celite and concentrated under reduced pressure. Column chromatography of the residue afforded pure **20** (700 mg, 79%) as colorless liquid. R_f (1:1 EA/hexane) 0.5; ^1H NMR (400 MHz, CDCl_3): δ 6.81 (d, J 8.8 Hz, 1H), 6.76 (d, J 8.8 Hz, 1H), 4.74 (s, 1H), 4.65 (s, 2H), 4.33 (s, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.46 (s, 2H), 1.81 (s, 3H).

4-Methoxy-3-(2-methallyloxy)benzaldehyde (21).²⁶ To a stirred solution of isovanillin (8.8 g, 57.9 mmol) in dry acetone (300 mL) was added solid K_2CO_3 (8.0 g, 57.9 mmol) at 0 °C followed by addition of methallyl bromide (8.8 mL, 86.9 mmol). The reaction mixture was stirred for 24 h and filtered. The filtrate was concentrated and extracted with ethyl acetate (250 mL). Organic layer was washed with H_2O (3 x 100 mL) and brine (100 mL). Combined organic layer was dried over Na_2SO_4 and evaporated under vacuum to afford the crude material. It was purified by performing flash column chromatography on silica gel with 1:5 ethyl acetate/hexane solvent to afford **21** (10.9 g, 52.7 mmol) in 91% yield. Yellow oil; ^1H NMR (200 MHz, CDCl_3) δ 9.75 (s, 1H), 7.41–7.32 (m, 2H), 6.91 (d, J 8.2 Hz, 1H), 5.06 (s, 1H), 4.94 (s, 1H), 4.49 (s, 2H), 3.88 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (50 MHz, CDCl_3) δ 190.8 (CH), 154.9, 148.7, 140.1, 130.0, 126.7 (CH), 113.2 (CH_2), 111.2, 110.8 (CH), 72.5 (CH_2), 56.1 (CH_3), 19.3 (CH_3); IR (KBr): $\tilde{\nu}$ = 3422, 2936, 1686, 1611, 1582, 1508, 1438, 1270, 1220, 1162, 1134, 1017, 905, 642 cm^{-1} .

Compound **21** (1.1 g, 5.33 mmol) was dissolved in DMF (5 mL) or 1, 2-dichlorobenzene and heated to reflux at 250 °C. Expected product was not obtained. From 1, 2-dichlorobenzene, products were **22** (0.245 g, 1.3 mmol, 25%), **23** (0.200 g, 1.00 mmol, 19%). From DMF, yields were **22** (0.035 g, 0.19 mmol, 4%), **23** (0.070 g, 0.37 mmol, 7%), **24** (0.255 g, 1.24 mmol, 23%).

2-Methoxy-7-methylnaphthalen-1-ol (22). Yellow liquid; ^1H NMR (200 MHz, CDCl_3) δ 8.06 (d, J 0.6, 1H), 7.73 (d, J 8.4 Hz, 1H), 7.42 (d, J 9.0, 1H), 7.28 (d, d, J 8.4, 1.6 Hz, 1H), 7.21 (d, J 9.0 Hz, 1H), 6.24 (bs, 1H), 3.97 (s, 3H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 141.5, 139.3, 135.2, 128.1, 127.5 (CH), 126.8 (CH), 124.3, 120.1 (CH), 119.5 (CH), 112.4 (CH), 57.1 (CH_3), 22.0 (CH_3); IR (KBr): $\tilde{\nu}$ 3422, 2927, 1741, 1608, 1459, 1275, 1220, 1051, 678

cm^{-1} . HRMS (ESI): m/z calculated for $\text{C}_{12}\text{H}_{12}\text{O}_2$: requires: 187.0759 for $[\text{M}-\text{H}]^+$, 188.0837 for $[\text{M}]$, 189.0916 for $[\text{M}+\text{H}]$, 191.1072 for $[\text{M}+3\text{H}]$; found: 187.0749, 188.0837, 189.0893, 191.1068.

2-Methoxy-7-methyl-7,8-dihydronaphthalen-1-ol (23). Yellow liquid; ^1H NMR (200 MHz, CDCl_3) δ 6.66 (d, J 8.0 Hz, 1H), 6.58 (d, J 8.0 Hz, 1H), 6.35 (dd, J 2.8, 9.6 Hz, 1H), 5.70 (s, 1H), 3.88 (s, 3H), 3.06–3.01 (m, 1H), 2.56–2.51 (m, 1H), 2.47–2.41 (m, 1H), 1.13 (d, J 6.8 Hz, 3H); ^{13}C NMR (50 MHz, CDCl_3): δ 146.1, 142.6, 133.2 (CH), 128.2, 126.5 (CH), 120.7, 117.5 (CH), 107.9 (CH), 56.2 (CH_3), 28.6 (CH_2), 28.4 (CH), 20.7 (CH_3); IR (KBr): $\tilde{\nu}$ 3454, 2956, 1636, 1491, 1275, 1079, 806, 772 cm^{-1} ; HRMS (ESI): m/z calculated for $\text{C}_{12}\text{H}_{14}\text{O}_2$: requires: 191.1072 for $[\text{M}+\text{H}]^+$; found: 191.1085.

2-Methoxy-7-methyl-7,8-dihydro-naphthalen-1-yl acetate. ^1H NMR (600 MHz, CDCl_3) δ 6.88 (d, J 8.3 Hz, 1H), 6.73 (d, J 8.2 Hz, 1H), 6.35 (dd, J 2.2, 9.6 Hz, 1H), 5.75 (dd, J 3.3, 9.8 Hz, 1H), 3.81 (s, 3H), 2.77 (dd, J 6.6, 15.7 Hz, 1H), 2.51 (qd, J 3.4, 6.8 Hz, 1H), 2.35 (s, 4H), 1.09 (d, J 7.1 Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 169.1, 150.6, 137.5, 133.1, 128.7, 127.8, 126.1, 123.9, 109.4, 56.1, 29.6, 28.3, 20.7, 20.5. IR (KBr): $\tilde{\nu}$ 2921, 2851, 1764, 1463, 1275, 1219, 1191, 1077 cm^{-1} . HRMS (ESI): m/z calculated for $\text{C}_{14}\text{H}_{16}\text{O}_3$: requires: 233.1178 for $[\text{M}+\text{H}]^+$; found: 233.1193.

7-Methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-4-carbaldehyde (24).²⁷ ^1H NMR (200 MHz, CDCl_3) δ 9.85 (s, 1H), 7.27 (d, J 8.4 Hz, 1H), 6.83 (d, J 8.4 Hz, 1H), 3.91 (s, 3H), 3.35 (s, 2H), 1.49 (s, 6H); ^{13}C NMR (50 MHz, CDCl_3): δ 191.6 (CH), 149.5, 148.2, 128.6, 127.3 (CH), 126.9, 110.4 (CH), 89.3, 56.2 (CH_3), 43.4 (CH_2), 28.5 (2 \times CH_3); IR (KBr): $\tilde{\nu}$ 2972, 1686, 1611, 1582, 1508, 1438, 1270, 1220, 1162, 1134, 1017, 905, 642 cm^{-1} ; HRMS (ESI): m/z calculated for $\text{C}_{12}\text{H}_{14}\text{O}_3$: requires: 207.1021 for $[\text{M}+\text{H}]^+$; found: 207.1038.

[3,6-Dimethoxy-2-(2-methallyl)-phenyl]methanol (20).²⁵ To a stirred solution of compound **28** (0.44 g, 2 mmol) in THF (10 mL) and MeOH (3 mL) at 0 °C was added NaBH_4 (84 mg, 2.2 mmol) in portions. The resulting mixture was stirred at rt for overnight. Then it was quenched with saturated NH_4Cl (3 mL). Extraction of the reaction mixture with EA (3 \times 10 mL) followed by drying over Na_2SO_4 and removal of solvent gave a residue. Flash column chromatography of the residue on silica gel with 1:2 EA/hexane solvent afforded product **20** (0.38 g, 1.72 mmol) as colorless liquid in 86% yield.

2-Hydroxymethyl-3-(2-methylprop-2-enyl)-1,4-benzoquinone (14). To a stirred solution of **20** (280 mg, 1.26 mmol) in acetonitrile (7 mL), solution of ceric ammonium nitrate (2.07 gm, 3.78 mmol) in water (7 mL) was added drop-wise and stirred for 1 h. Then the reaction mixture was extracted with ethyl acetate (2 \times 50 mL). The combined extracts were washed successively with water (25 mL), brine (25 mL), dried (anhydrous Na_2SO_4), filtered and concentrated under reduced pressure. Column chromatography of the residue afforded **14** (160 mg, 66%). Yellow solid; R_f (1:1 EA/hexane) 0.4; ^1H NMR (400 MHz, CDCl_3): δ 6.74 (d, J 10 Hz, 1H), 6.70 (d, J 10 Hz, 1H), 4.73 (s, 1H), 4.47 (s, 2H), 4.45 (s, 1H), 3.21 (s, 2H), 2.46 (brs, 1H), 1.71 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 188.7, 187.0, 142.8, 142.2, 141.9, 136.8 (CH), 136.3 (CH), 111.9 (CH_2), 57.4 (CH_2), 32.7 (CH_2), 23.2 (CH_3); IR (KBr): $\tilde{\nu}$ 3448, 2933, 1654, 1297, 1018, 850 cm^{-1} .

2-(2-Methylprop-2-enyl)-3-(tetrahydropyran-2-yloxymethyl)-1,4-benzoquinone (29). To a stirred solution of **14** (40 mg, 0.21 mmol) in dry dichloromethane (5 mL) were added dihydropyran (0.04 mL, 0.42 mmol) and a catalytic amount of PPTS and stirred for 3 h. Then the reaction mixture was extracted with ethyl acetate (50 mL). The combined extracts were washed successively with water (10 mL), brine (10 mL), dried (anhydrous Na_2SO_4), filtered and concentrated under reduced pressure. Column chromatography of the residue afforded **29** (55 mg, 96%). Yellow semisolid; R_f (1:3 EA/hexane) 0.65; ^1H NMR (400 MHz, CDCl_3): δ 6.78 (s, 2H), 4.79 (s, 1H), 4.60 (d, J 10.8 Hz, 1H), 4.52 (s, 1H), 4.33 (d, J 10.8 Hz, 1H), 3.87 (t, J 9.6 Hz, 1H), 3.40–3.60 (m, 2H), 3.34 (s, 2H), 1.80 (s, 3H), 1.40–1.79 (m, 6H); IR (KBr): $\tilde{\nu}$ 2942, 1656, 1440, 1297, 1120, 1025, 771 cm^{-1} ; HRMS (ESI): m/z calculated for $\text{C}_{16}\text{H}_{20}\text{O}_4$: requires: 175.0759 for $[\text{M}-\text{OTHP}]^+$; found: 175.0761.

1,4-Dihydroxy-2-(2-methylprop-2-enyl)-3-(tetrahydropyran-2-yloxymethyl) anthraquinone (32). A solution of **30** (242 mg, 1 mmol) in dry THF (5 mL) was added to suspension of LiOBu-*t* (240 mg, 3 mmol) in dry THF at -60 °C under an inert atmosphere. The resulting solution was stirred at -60 °C for 30 min after which a solution of **29** (331 mg, 1.2 mmol) in dry THF (5 mL) was added to it. The reaction was stirred for another 30 min at -60 °C followed by 6-8 h at room temperature. The reaction was then quenched with saturated ammonium chloride solution and THF was removed under reduced pressure. The residue was then extracted with ethyl acetate (3 x 20 mL). The combined extracts were washed with brine (3 x 1/3 vol), dried (Na₂SO₄) and concentrated to provide crude product. The crude product was purified by column chromatography to furnish quinone **32**. Red solid; *R_f* (1:3 EA/hexane) 0.7; mp 125–127 °C; ¹H NMR (400 MHz, CDCl₃): δ 13.62 (s, 1H), 13.50 (s, 1H), 8.34–8.40 (m, 2H), 7.70–7.90 (m, 2H), 4.88 (d, *J* 10.8 Hz, 1H), 4.80 (s, 1H), 4.65 (d, *J* 10.8 Hz, 1H), 4.39 (s, 1H), 3.98 (t, *J* 8.4 Hz, 1H), 3.67 (s, 2H), 3.50–3.65 (m, 2H), 1.89 (s, 3H), 1.50–1.83 (m, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 186.9, 186.5, 157.5, 156.8, 143.1, 142.2, 137.1, 134.3 (CH), 134.2 (CH), 133.6, 133.5, 126.9 (CH), 126.9 (CH), 111.8, 111.1, 110.9 (CH₂), 98.9 (CH), 62.2 (CH₂), 59.4 (CH₂), 33.5 (CH₂), 30.5 (CH₂), 25.4 (CH₂), 23.4 (CH₃), 19.3 (CH₂); IR (KBr): $\tilde{\nu}$ 2927, 2372, 1623, 1401, 1265, 1024, 773 cm⁻¹. HRMS (ESI): *m/z* calculated for C₂₄H₂₄O₆: requires: 431.1471 for [M+Na]⁺, 409.1651 for [M+H]⁺, 391.1546 for [M-H₂O+H]⁺, 325.1076 for [M-DHP+H]⁺, 307.0970 for [M-DHP-H₂O+H]⁺; found: 431.1483, 409.1667, 391.1545, 325.1082, 307.0992.

1,4-Dihydroxy-2-hydroxymethyl-3-(2-methylprop-2-enyl)anthraquinone (31). To a stirred solution of **32** (100 mg, 0.25 mmol) in methanol (5 mL), a catalytic amount of PPTS was added and stirred for 1 h. Then the reaction mixture was extracted with ethyl acetate (50 mL). The combined extracts were washed successively with water (10 mL), brine (10 mL), dried (anhydrous Na₂SO₄), filtered and concentrated under reduced pressure. Column chromatography of the residue afforded quinone **31** (60 mg, 76%). Red solid; mp 117–118 °C; *R_f* (1:3 EA/hexane) 0.6; ¹H NMR (400 MHz, CDCl₃): δ 13.68 (s, 1H), 13.51 (s, 1H), 8.35–8.40 (m, 2H), 7.90–7.70 (m, 2H), 4.83 (s, 1H), 4.79 (s, 2H), 4.45 (s, 1H), 3.63 (s, 2H), 2.70 (brs, 1H), 1.88 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 186.9, 186.9, 157.0, 156.9, 143.7, 139.9, 139.6, 139.6, 134.6 (CH), 134.5 (CH), 133.6, 133.5, 127.2 (CH), 127.0 (CH), 111.5, 111.4 (CH₂), 57.3 (CH₂), 33.4 (CH₂), 23.3 (CH₃); IR (KBr): $\tilde{\nu}$ 3426, 2923, 2370, 1587, 1401, 1263, 1020, 798 cm⁻¹; HRMS (ESI): *m/z* calculated for C₁₉H₁₆O₅: requires: 325.1076 for [M+H]⁺, 307.0970 for [M-H₂O+H]⁺; found: 325.1082, 307.0956.

1,4-Dihydroxy-3-(2-methyl-allyl)-9,10-dioxo-9,10-dihydroanthracene-2-carboxaldehyde (33). PCC (213 mg, 0.99 mmol) was added to a stirred solution of **31** (108 mg, 0.33 mmol) in DCM (5 mL) and stirring was continued for 3 h at rt. Solvent was evaporated and slurried with basic alumina. Column chromatography was done with basic alumina and 1:20 ethyl acetate/hexane solvent. Compound **33** (73 mg, 0.23 mmol) was obtained in 69% yield. Yellow solid; mp 100 °C; *R_f* (1:1 EA/hexane) 0.7; ¹H NMR (400 MHz, CDCl₃): δ 13.69 (s, 1H), 13.27 (s, 1H), 10.68 (s, 1H), 8.41–8.30 (m, 2H), 7.90–7.86 (m, 2H), 4.75 (s, 1H), 4.33 (s, 1H), 3.88 (s, 2H), 1.90 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 190.6 (CH), 186.7, 186.5, 159.3, 155.8, 143.7, 143.3, 134.9 (CH), 134.8 (CH), 133.0, 133.0, 131.0, 131.0, 127.3 (CH), 127.0 (CH), 112.0, 110.4 (CH₂), 32.6 (CH₂), 23.6 (CH₃); IR (KBr): $\tilde{\nu}$ 3375, 2372, 1585, 1218, 1052, 771 cm⁻¹. HRMS (ESI): *m/z* calculated for C₁₉H₁₄O₅: requires: 322.0841 for [M]⁺, 321.0763 for [M-H]⁺, 293.0814 for [M-HCHO+H]⁺; found: 322.0809, 321.0775, 293.0820.

6,7,11-Trihydroxy-9-methylene-7,8,9,10-tetrahydronaphthalene-5,12-dione (11). A stirred solution of **33** (0.145 g, 0.45 mmol) in dry DCM (4.5 mL) was treated with SnCl₄·5H₂O (0.079 g, 0.23 mmol) in stoppered reaction flask. After completion of the reaction, as monitored by TLC, it was quenched with saturated solution of sodium bicarbonate (2.5 mL/mmol). The reaction mixture was then extracted with DCM (3 x 5 mL). The combined extracts were washed with brine (3 x 1/3 vol), dried (Na₂SO₄) and concentrated to provide crude product. After flash column chromatography by silica gel with 1:2 ethyl acetate/hexane solvent compound **11** (0.129 g, 0.40 mmol) was obtained in 89% yield. *R_f* (1:1 EA/hexane) 0.65; ¹H NMR (400 MHz, CDCl₃): δ 13.72 (s,

1H), 13.37 (s, 1H), 8.40–8.32 (m, 2H), 7.80–7.88 (m, 2H), 5.30 (brs, 1H), 5.16 (s, 1H), 5.12 (s, 1H), 3.63 (ABd, *J* 20.4, 2H), 3.52 (ABd, *J* 20.4 Hz, 2H), 2.91 (brs, 1H), 2.71 (d, *J* 4.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 186.8, 186.7, 156.6, 156.0, 138.8, 138.3, 137.7, 134.4 (CH), 134.4 (CH), 133.5, 133.4, 127.0 (CH), 127.0 (CH), 113.4 (CH₂), 110.5, 63.8, 38.7, 32.1 (one quaternary carbon is missing); IR (KBr): $\tilde{\nu}$ 3450, 2370, 1583, 1403, 1222, 1024 cm⁻¹; HRMS (ESI): *m/z* calculated for C₁₉H₁₄O₅: requires: 323.0920 for [M+H]⁺; found: 323.0925.

Dihydroxylation of 34. To a stirred solution of compound **34** (192 mg, 1.2 mmol) in THF (36 mL) and H₂O (18 mL) were added OsO₄ (2.4 mL 0.05 M solution in toluene, 0.12 mmol) and NMO (422 mg, 3.6 mmol). The reaction vessel was wrapped by a black paper and stoppered well. Reaction mixture was stirred for 15 h at rt. After the starting material disappeared, the reaction was quenched by adding sodium bisulfite. Then usual work-up was done with ethyl acetate. Crude material was subjected to column chromatography packed with basic alumina to give product **35** (149 mg, 0.77 mmol, 64%), **36** (35 mg, 0.18 mmol, 15%).

2,4-Dihydroxy-1,2,3,4-tetrahydronaphthalen-2-ylmethyl-oxonium (35). White solid; mp 98–100 °C; *R_f* (2:1 EA/hexane) 0.3; ¹H NMR (400 MHz, CDCl₃): δ 7.47 (d, *J* 7.2 Hz, 1H), 7.22–7.28 (m, 2H), 5.04 (t, *J* 5.4 Hz, 1H), 3.68 (d, *J* 11.2 Hz, 1H), 3.55 (d, *J* 11.2 Hz, 1H), 2.92 (d, *J* 16.8 Hz, 2H), 2.85 (d, *J* 16.8 Hz, 2H), 2.35 (bs, 2H), 2.21 (dd, *J* 5.2, 13.6 Hz, 1H), 2.05 (bs, 1H), 1.97 (dd, *J* 6.8, 13.6 Hz, 1H); ¹H NMR (400 MHz, acetone-*d*₆): δ 7.55 (d, *J* 7.2 Hz, 1H), 7.10–7.17 (m, 2H), 7.04 (d, *J* 7.6 Hz, 1H), 4.96 (d, *J* 3.6, 1H), 4.28 (s, 1H), 3.98 (bs, 1H), 3.59 (bs, 1H), 3.59 (s, 1H), 3.46 (s, 2H), 2.94 (s, 2H), 2.68 (d, *J* 16.8, 1H), 2.15–2.20 (m, 1H), 1.69–1.75 (m, 1H); ¹³C NMR (100 MHz, acetone-*d*₆): δ 141.5, 135.6, 129.6 (CH), 127.5 (CH), 127.5 (CH), 126.5 (CH), 72.7, 71.2 (CH₂), 67.2 (CH), 41.8 (CH₂), 39.3 (CH₂); IR (KBr): $\tilde{\nu}$ 3398, 2920, 1637, 1220, 1066 cm⁻¹; HRMS (ESI): *m/z* calculated for C₁₁H₁₄O₃: requires: 129.0704 for [M-CH₃OH-H₂O₂+H]⁺, 141.0704 for [M-3H₂O+H]⁺, 159.0810 for [M-2H₂O+H]⁺, 217.0841 for [M+Na]⁺; found: 129.733, 141.0746, 159.0839, 217.0913.

3-Hydroxy-3-hydroxymethyl-3,4-dihydro-2H-naphthalen-1-one (36). White solid; mp 43–45 °C; *R_f* (1:2 EA/hexane) 0.4; ¹H NMR (400 MHz, CDCl₃): δ 8.03 (d, *J* 7.6 Hz, 1H), 7.52 (t, *J* 7.6 Hz, 1H), 7.34 (t, *J* 7.6 Hz), 7.28 (d, *J* 7.6 Hz, 1H), 3.61 (s, 2H), 3.18 (d, *J* 16.8 Hz, 1H), 3.12 (d, *J* 16.8 Hz, 1H), 2.86 (d, *J* 16.8 Hz, 1H), 2.75 (d, *J* 16.8 Hz, 1H), 2.54 (bs, 1H), 2.23 (bs, 1H); ¹H NMR (400 MHz, acetone-*d*₆): δ 7.90–7.92 (m, 1H), 7.50–7.54 (m, 1H), 7.29–7.32 (m, 2H), 4.18 (t, *J* 5.6 Hz), 3.87 (s, 1H), 3.54 (d, *J* 5.6 Hz, 2H), 3.32 (d, *J* 16.6 Hz, 1H), 2.98 (d, *J* 16.6 Hz, 1H), 2.84 (dd, *J* 2.0, 16.6 Hz, 1H), 2.64 (dd, *J* 2.0, 16.6 Hz, 1H); ¹³C NMR (100 MHz, acetone-*d*₆): δ 197.4, 142.6, 134.3 (CH), 133.4, 130.8 (CH), 127.1 (CH), 126.8 (CH), 74.8, 70.2 (CH₂), 48.1 (CH₂), 39.0 (CH₂); IR (KBr): $\tilde{\nu}$ 3422, 2921, 1636, 1220 cm⁻¹; HRMS (ESI): *m/z* calculated for C₁₁H₁₂O₃: requires: 175.0759 for [M-H₂O+H]⁺, 193.0865 for [M+H]⁺; found: 175.0786, 193.0891.

4-(tert-Butyl-dimethylsilanyloxy)-3,4-dihydro-1H-naphthalen-2-one (40).³⁰ A stream of ozone was passed through a stirred solution of **39** (550 mg, 2.0 mmol) in dry DCM (10 mL) at -78 °C until resulting solution became blue-violet. The excess ozone was removed by passing a stream of oxygen followed by argon through the solution. The resulting mixture was allowed to reach -50 °C and carefully quenched by addition of Ph₃P (630 mg, 2.4 mmol) in dry DCM (2.5 mL). After 24 h at rt the reaction mixture was concentrated and the residue was subjected to chromatography on basic alumina and eluted with 1:30 ethyl acetate/hexane solvent. Product **40** (359 mg, 1.3 mmol) was obtained in 65% yield. Yellow liquid; *R_f* (1:20 EA/hexane) 0.5; ¹H NMR (600 MHz, CDCl₃) δ 7.38–7.33 (m, 1H), 7.30–7.26 (m, 2H), 7.18–7.12 (m, 1H), 5.06 (dd, *J* 3.8, 5.4 Hz, 1H), 3.77 (dd, 1H, *J* 1.0, 19.7 Hz), 3.51 (d, *J* 19.8 Hz, 1H), 2.75–2.63 (m, 2H), 0.86 (s, 9H), 0.13 (s, 3H), -0.05 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 208.6, 139.2, 133.1, 128.8 (CH), 128.4 (CH), 127.1 (CH), 126.5 (CH), 70.0 (CH), 48.0 (CH₂), 44.6 (CH₂), 25.9 (3 x CH₃), 18.3, -4.5 (CH₃), -4.6 (CH₃); IR (KBr): $\tilde{\nu}$ 2930, 2857, 1702, 1256, 1219, 1081, 952, 836, 670 cm⁻¹. HRMS (ESI): *m/z* calculated for C₁₆H₂₄O₂Si: requires: 277.1624 for [M+H]⁺; found: 277.1636.

Supplementary Materials

Analytical data (^1H NMR, ^{13}C NMR, single crystal X-ray diffraction) for all new compounds.

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