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Conversion of lapachol to lomatiol: synthesis of novel naphthoquinone derivatives†

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Lapachol (**1**), a naphthoquinone isolated mostly from the plants of the bignoniaceae family has a broad spectrum of biological activities and as a consequence it has been the object of different chemical transformations. Lomatiol (**3**), another naturally occurring naphthoquinone having structural similarities to lapachol, has been obtained from chemical and microbial transformations of lapachol in very low yields. In the present study, an easy approach for the synthesis of lomatiol (**3**) from lapachol (**1**) has been developed using SeO_2 oxidation in 90% yield. Lomatiol, under epoxidation conditions afforded novel furano- and pyrano-naphthoquinone derivatives, which are analogues of anticancer agents, 2-acetylfuronaphthoquinone and β-lapachone. Most of the structures were unambiguously confirmed by single crystal X-ray analysis.

Introduction

Lomatiol (**3**), a naturally occurring naphthoquinone isolated mainly from plants of the lomatia species, particularly *L. denlab, L. ferrugiltea*, and *L. oblique*, has structural similarities to lapachol, a principal constituent of the Bignoniaceae family.[1,2] Lapachol (**1**), exhibits a wide spectrum of biological activities including antibacterial, antiplasmodial, antioxidant, neurological and trypanocidal activities.[3] Lapachol has also been used as anti-microbial and antiprotozoal agents and many of its derivatives have proved to be potent antimalarial and anti-HIV agents. β-Lapachone (Fig. 1) is an antibacterial agent from lapachol while atovaquone, a derivative of lapachol, has already been approved for the treatment of Pneumocystis pneumonia, toxoplasmosis and malaria.[4]

Despite their structural similarities, there is no direct chemical conversion of lapachol to lomatiol. However, leucolapachol triacetate has been converted to lomatiol in several steps and with poor yield.[5] Microbial transformation of lapachol has also been carried out using *Cunninghamella echinulata*, *Beauveria sulfurescens*, *Streptomyces albus*, and *Streptomyces griseus* to afford lomatiol and its derivatives in very low yields[5] (Fig. 2).

Furano- and pyrano-naphthoquinone derivatives are known to exhibit significant biological activities. Among those compounds,

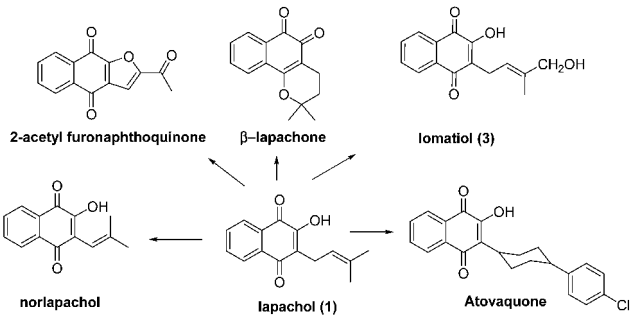

Fig. 1 Some biologically active compounds derived from lapachol.

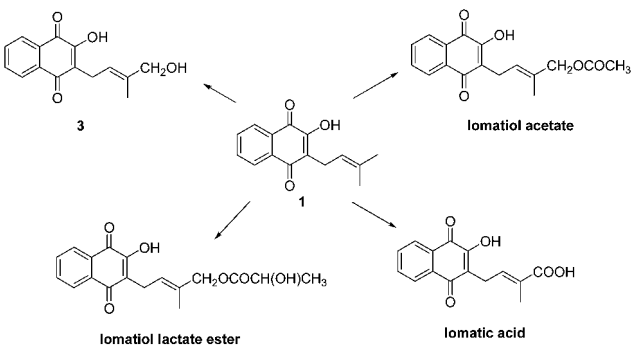

Fig. 2 Microbial transformation of lapachol to lomatiol and its derivatives.

2-acetylfuranonaphthoquinone and β-lapachone show superior antitumoral activity and the influence of the furan/pyran-ring on the antitumoral activity has recently been demonstrated.[6] As a consequence of its biological significance, lapachol and its

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derivatives have become important synthetic targets. Recently, a mechanistic study on the Hooker oxidation of lapachol to afford norlapachol, in one of its most intriguing transformations has been carried out in our group.[7] Our continued interest in converting lapachol (**1**) to various biologically active and pharmaceutically important molecules recently resulted in neurological and anti-tumor structure activity relationship studies of various naphthoquinones derived from lapachol.[8]

In the present study, we report SeO_2 oxidation of lapachol under different reaction conditions to afford the naturally occurring naphthoquinone, lomatiol (**3**). Subsequent chemical transformation of lomatiol afforded novel furano- and pyrano-naphthoquinone derivatives.

Results and discussion

In continuing our screening program of naphthoquinone derivatives of lapachol for bacterial, cancer and plasmodium activities, SeO_2 oxidation of lapachol (**1**), afforded the novel unsaturated aldehyde **2**, which was subsequently reduced with $NaBH_4$ to give lomatiol (**3**) in 30% yield. Nevertheless, lomatiol was obtained in 50% yield upon reduction of compound **2** with $NaBH_4/CeCl_3$. Compound **2** on catalytic hydrogenation over Pd/C followed by acid hydrolysis afforded the acetal **4** and the corresponding aldehyde **5** (Scheme 1). The structure of compound **2** was unambiguously confirmed by single crystal X-ray analysis (Fig. 3).[9a]

Interestingly, using the modified procedure of allylic oxidation reported by Tanis *et al.*,[10] lomatiol was obtained in 90% yield by the direct oxidation of lapachol using 0.08 instead of 0.02 equiv. of SeO_2. The generality of this methodology was further tested with the methyl ether derivative **1a** and the acetate derivative **1b** of lapachol to give the corresponding allyl alcohol derivatives of lomatiol **3a** and **3b**, respectively, in good yields (Scheme 2).

Subjecting lomatiol (**3**), under Sharpless asymmetric epoxidation conditions using (+)-DET as a catalyst,[11] afforded a mixture of furano-naphthoquinone derivatives (+)-**6** (20%) and (+)-**7** (40%), respectively, in 20% ee *via* epoxide ring opening (Scheme 3). Moreover, under these conditions, the starting material **3** was recovered in 30% yield.

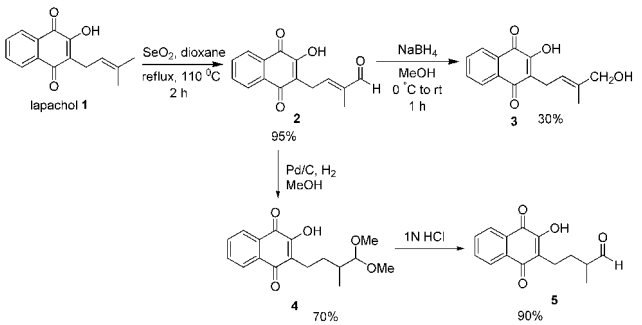
The stereochemistry of compounds **6** and **7** was assigned by single crystal X-ray structure determination (Fig. 4).[9b,c]

The *m*-CPBA epoxidation of lomatiol (**3**) afforded furano-naphthoquinone derivatives (±)-**6** (40%) and (±)-**7** (60%) as a mixture of diastereomers. The epoxidation reaction of lomatiol is regioselective since only the furano-naphthoquinone derivatives were formed in contrast to the *m*-CPBA epoxidation of lapachol which resulted in the formation of both furano- and pyrano-naphthoquinone derivatives[6] (Scheme 4).

The *m*-CPBA epoxidation of the acetate derivative of lomatiol **3b** afforded racemic epoxide (±)-**8** in 95% yield. Interestingly, under Sharpless asymmetric epoxidation conditions, compound **3b** furnished the corresponding optically active epoxide (+)-**8** in 80% yield with 90% ee (Scheme 5).

On the other hand, bromination of the lomatiol derivative **3b** afforded pyrano-bromoethers **9a** and **9b** and furano-bromoethers **10a** and **10b**, respectively, as a mixture of diastereomers (Scheme 6).

Similarly, bromination[6] of acetyl lapachol **1b** afforded the corresponding bromopyrano-derivative **11a** and bromofurano-derivative **11b**, respectively, in 92% and 5% yields. Treatment of the bromopyrano-derivative **11a** with NaOH resulted in an unusual formylation reaction to give 3-bromo-3,4-dihydro-5-hydroxy-2,2-dimethyl-2*H*-benzo[*h*]chromene-6-carbaldehyde **13** along with the expected compounds **12** and **14** (Scheme 7).



Scheme 1 Synthesis of lomatiol from lapachol.

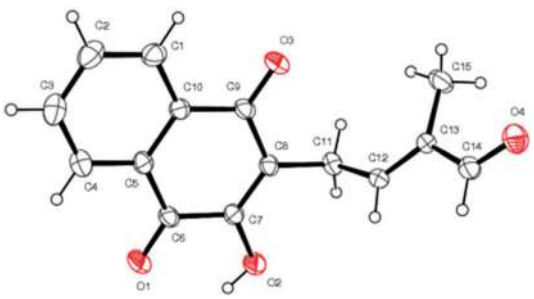
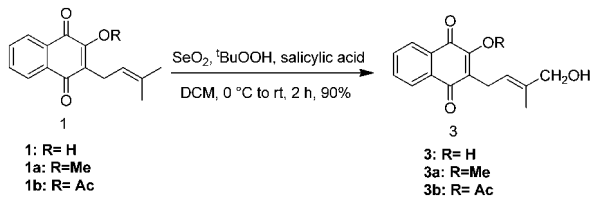
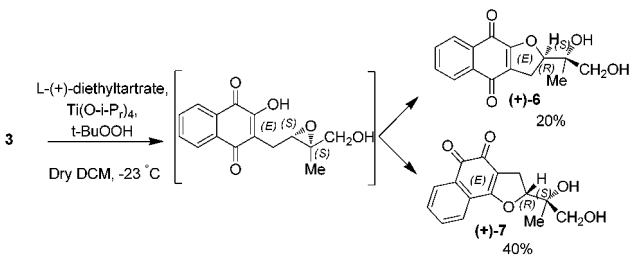


Fig. 3 ORTEP structure of compound **2**.



Scheme 2 SeO_2 oxidation of lapachol derivatives under modified conditions.



Scheme 3 Sharpless asymmetric epoxidation of lomatiol.

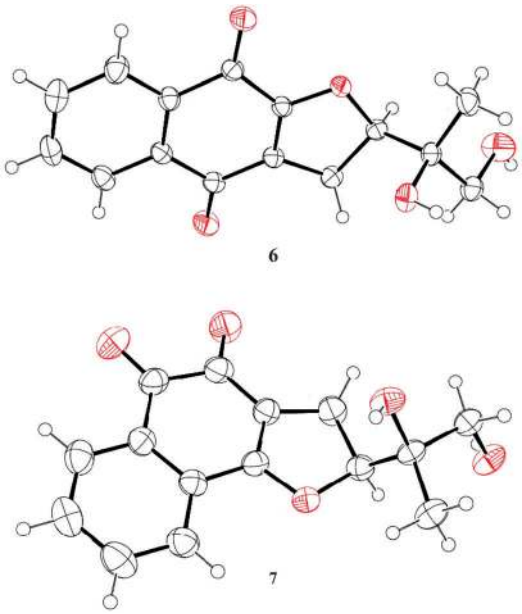
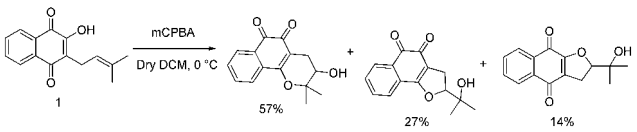
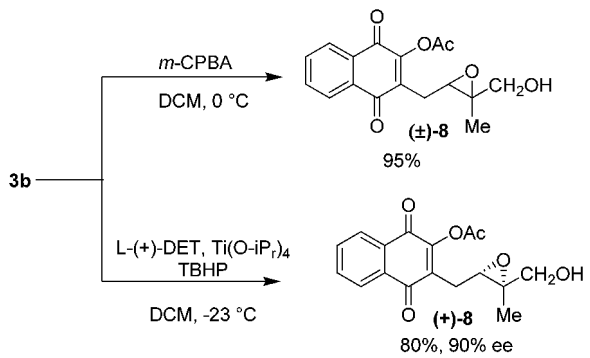


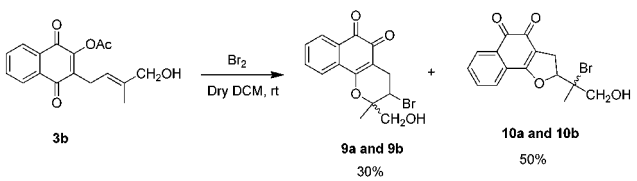
Fig. 4 ORTEP structure of compounds (+)-**6** and (+)-**7**.



Scheme 4 *m*-CPBA treatment of lapachol.

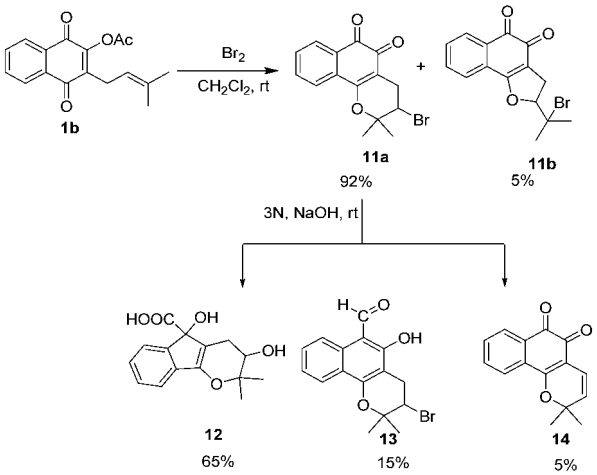


Scheme 5 *m*-CPBA and Sharpless asymmetric epoxidation of **3b**.



Scheme 6 Bromination of compound **3b**.

The structure of compound **13** was unambiguously confirmed by single crystal X-ray analysis (Fig. 5).[9d] while, the mechanism of formation is still under investigation.



Scheme 7 Unusual formylation reaction of compound **11a** with NaOH.

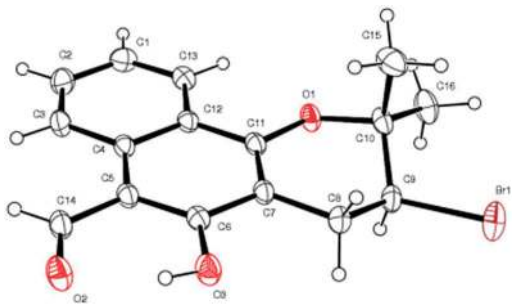


Fig. 5 ORTEP structure of compound **13**.

Conclusions

In conclusion, we have achieved the biomimetic synthesis of lomatiol (**3**) from lapachol (**1**) in 90% yield. The generality of this method was further shown using the methyl and acetyl derivatives of lapachol. Our efficient method for the synthesis of lomatiol (**3**) from lapachol (**1**) has provided an easy access to novel furano- and pyrano-napthoquinone derivatives in good yields. The biological significance of the newly synthesized lomatiol derivatives is being investigated.

Experimental

Synthesis of 4-(1,4-dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)-2-methylbut-2-enal 2

To a stirred solution of lapachol **1** (200 mg, 0.8 mmol) in dioxane (12 mL) was added SeO_2 (249 mg, 2.24 mmol) and the resultant mixture was stirred at reflux temperature for 1 h. After completion of the reaction, as indicated by TLC, the reaction mass was filtered through silica gel and washed with EtOAc/hexane (1 : 1). The solvent was removed under reduced pressure to give the crude product, which on column chromatographic purification over silica gel using 20–25% EtOAc in hexane as an eluent afforded the pure aldehyde **2** (201 mg, 95% yield) as yellow crystals. IR (neat) cm^{-1}: 3399, 3056, 2986,

2835, 2373, 2307, 1667, 1592, 1423, 1362, 1267, 1024, 896, 749; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.38 (s, 1H), 8.14 (d, J = 7.6 Hz, 1H), 8.11 (d, J = 7.6 Hz, 1H), 7.79 (td, J = 0.8, 7.6 Hz, 1H), 7.71 (td, J = 1.2, 7.6 Hz, 1H), 7.52 (s*, OH), 6.54 (td, J = 1.2, 7.6 Hz, 1H), 3.66 (d, J = 7.6 Hz, 2H), δ 1.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 184.2, 181.3, 153.7, 149.1, 140.6, 135.4, 133.4, 132.9, 129.5, 127.1, 126.5, 120.2, 23.5, 9.4; HRMS (ESI) m/z calcd for $C_{15}H_{13}O_4$ (M^+ + H) 257.2613, found 257.261.

Synthesis of (*E*)-2-hydroxy-3-(4-hydroxy-3-methylbut-2-enyl)-naphthalene-1,4-dione 3

To a stirred solution of compound **2** (50 mg, 0.2 mmol) in MeOH (2 mL) was added $CeCl_3{\cdot}7H_2O$ (4 mg, 0.01 mmol) and $NaBH_4$ (8 mg, 0.22 mmol) and the resultant mixture was stirred at room temperature for 1 h. After completion of the reaction as indicated by TLC, the reaction mass was filtered and the solvents were removed under reduced pressure which was acidified with 1 N HCl (4 mL) and extracted with DCM (2 × 5 mL). Combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product, which on column chromatographic purification over silica gel using 30–40% EtOAc in hexanes as an eluent afforded the pure lamatiol **3** (25 mg, 50% yield).

One-pot method for the synthesis of compound 3

To a suspension of SeO_2 (2.4 mg, 0.02 mmol) and salicylic acid (3.6 mg, 0.026 mmol) in dry DCM (2 mL) at 0 °C was added TBHP (163 μL, 6 M) and compound **1** (68 mg, 0.28 mmol) in dry DCM (2 mL) and the resulting solution was stirred at room temperature for 2 h. After completion of the reaction as indicated by TLC, water (5 mL) was added to the reaction mixture and extracted with DCM (2 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product, which on column chromatographic purification over silica gel using 30–40% EtOAc in hexane as an eluent afforded the pure lomatiol **3** (65 mg, 90% yield) as a light yellow solid. IR (neat) cm^{-1}: 3407, 3056, 2985, 2306, 1658, 1599, 1426, 1376, 1266, 1027, 897, 740; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 7.6 Hz, 1H), 8.05 (d, J = 7.2 Hz, 1H), 7.74 (t, J = 7.6 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.48 (s*, OH), 5.49 (t, J = 7.2 Hz, 1H), 3.99 (s, 2H), 3.48 (d, J = 7.2 Hz, 2H) and 1.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.6, 181.7, 153.1, 136.9, 135.1, 133.1, 132.9, 129.5, 126.9, 126.3, 122.9, 121.2, 68.7, 22.3, 13.9; HRMS (ESI) m/z calcd for $C_{15}H_{13}O_4$ (M^+ + H) 259.0970, found 259.0963.

Synthesis of 2-hydroxy-3-(4,4-dimethoxy-3-methylbutyl)naphthalene-1,4-dione 4 and 4-(1,4-dihydro-2-hydroxy-1,4-dioxonaphthalen-3-yl)-2-methylbutanal 5

To a stirred solution of compound **2** (30 mg, 0.12 mmol) in MeOH (2 mL) was added Pd/C (6 mg) and stirred under 1 atm hydrogen atmosphere for 2 h. The reaction mixture was filtered through a celite pad and the residue was washed with MeOH (2 × 5 mL). The filtrate was then concentrated under reduced pressure and the crude product was purified by column chromatography over silica gel (gradient elution with 12–15% EtOAc in hexane) to give the corresponding acetal **4**. Acetal **4** was then treated with 2 N HCl (2 mL) at 70 °C for 2 h. The reaction mixture was extracted with DCM (2 × 5 mL), the combined DCM layers were washed with water (5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude compound. Column chromatographic purification of the crude compound over silica gel (12–15% EtOAc in hexane) afforded the aldehyde derivative **5** (18 mg, 63% yield) as a yellow solid; compound **4** IR (neat) cm^{-1}: 3381, 2925, 2374, 1728, 1648, 1459, 1366, 1276, 1211, 1063, 938; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (dd, J = 0.8, 7.6 Hz, 1H), 8.07 (dd, J = 1.2, 7.6 Hz, 1H), 7.74 (td, J = 1.2, 7.6 Hz, 1H), 7.67 (td, J = 1.2, 7.6 Hz, 1H), 7.39 (s*, OH), 4.09 (d, J = 6.4 Hz, 1H), 3.36 (s, 3H), 3.35 (s, 3H), 2.67–2.58 (m, 2H), 1.85–1.70 (m, 2H), 1.39–1.31 (m, 1H) and 1.01 (d, J = 6.8 Hz, 3H); ^{13}C (100 MHz, $CDCl_3$): δ 184.7, 181.5, 153.2, 134.9, 133.1, 133.0, 129.6, 126.9, 126.2, 124.8, 108.8, 54.4, 54.2, 36.1, 30.5, 21.0, 14.3; HRMS (ESI) m/z calcd for $C_{17}H_{20}O_5Na$ (M^+ + Na) 327.1208, found 327.1222. Compound **5** was obtained as a yellow solid; IR (neat) cm^{-1}: 3440, 3057, 2986, 2367, 2307, 1645, 1428, 1265, 894, 742; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.68 (d, J = 1.6 Hz, 1H), 8.12 (d, J = 7.6 Hz, 1H), 8.09(d, J = 7.6 Hz, 1H), 7.77 (t, J = 7.6 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.38 (s*, OH), 2.69–2.64 (m, 2H), 2.44–2.39 (m, 1H), 2.04–1.95 (m, 1H), 1.18 (d, J = 6.8 Hz, 3H); HRMS (ESI) m/z calcd for $C_{15}H_{15}O_4$ (M^+ + H) 259.0970, found 259.0972.

(*R*)-2-((*S*)-1,2-Dihydroxypropan-2-yl)-2,3-dihydronaphtho[2,3-*b*]-furan-4,9-dione (+)-6 and (*R*)-2-((*S*)-1,2-dihydroxypropan-2-yl)-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (+)-7

To a stirred suspension of dried molecular sieves (60 mg) in dry CH_2Cl_2 (1 mL) was added L-(+)-diethyl tartrate (12 μL, 0.07 mmol) and titanium(IV) isopropoxide (17 μL, 0.06 mmol) at −23 °C. After 10 min, TBHP (6 M solution in decane, 581 μL, 0.348 mmol) was added. To this reaction mixture lomatiol **3** (30 mg, 0.116 mmol) dissolved in CH_2Cl_2 (1 mL) was added drop wise and the mixture was stirred for an additional 7 h at −23 °C under a nitrogen atmosphere. The reaction mass was allowed to reach 0 °C, diluted with CH_2Cl_2 (4 mL) and layers were separated. Then CH_2Cl_2 layer was washed with saturated solution of Na_2SO_3 (3 × 5 mL), brine solution (3 mL) and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude compound which was purified by column chromatography over deactivated silica gel (40–80% EtOAc in hexane) to afford pure compounds (+)-**6** (20% ee, 20% yield) and (+)-**7** (20% ee, 40% yield); Compound (+)-**6** was obtained as a yellow solid. $[\alpha]_D^{27}$ + 18.2 (c 0.1, $CHCl_3$); IR (neat) cm^{-1}: 3395, 2922, 2850, 2376, 1635, 1463, 1388, 1246,1199, 1049, 968; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, J = 7.5 Hz, 2H), 7.72 (td, J = 1.5, 7.5 Hz, 1H), 7.68 (td, J = 1.5, 7.5 Hz, 1H), 5.05 (dd, J = 9, 11 Hz, 1H), 3.81 (d, J = 11 Hz, 1H), 3.58 (d, J = 11 Hz, 1H), 3.29 (dd, J = 8.5, 17.5 Hz, 1H), 3.20 (dd, J = 11, 17.5 Hz, 1H), 2.46 (s*, OH), 2.01 (s*, OH), 1.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 182.3, 177.8, 159.9, 134.4, 133.2, 133.1, 131.6, 126.4, 126.2, 125.2, 87.5, 73.4, 66.8, 28.0, 19.0; HRMS (ESI) m/z calcd for $C_{15}H_{15}O_5$ (M^+ + H) 275.0919, found 275.0915. HPLC analysis of the compound **6** (Daicel AD-H,

20% IPA/hexane, flow rate 1 mL min^{-1}, λ = 254 nm, 20% ee): t_R 10.35 min (major enantiomer) and 12.85 min (minor enantiomer). Compound (+)-**7** was obtained as a red solid. $[\alpha]_D^{27}$ + 54.5 (*c* 0.24, $CHCl_3$); IR (neat) cm^{-1}: 3448, 3056, 2986, 2924, 2853, 2685, 2306, 1647, 1426, 1266, 897, 739; ^1H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, *J* = 7.5 Hz, 1H), 7.64–7.62 (m, 2H), 7.58–7.56 (m, 1H), 5.16 (dd, *J* = 8.0, 10 Hz, 1H), 3.80 (d, *J* = 11 Hz, 1H), 3.62 (d, *J* = 11 Hz, 1H), 3.20 (dd, *J* = 7.5, 15.5 Hz, 1H), 3.12 (dd, *J* = 10, 15.5 Hz, 1H), 1.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 181.2, 175.5, 170.1, 134.7, 132.2, 130.7, 129.7, 127.4, 124.6, 116.2, 89.1, 73.5, 67.8, 27.1, 19.0; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{15}O_5$ (M^+ + H) 275.0919, found 275.0928. HPLC analysis of the compound **7** (Daicel AD-H, 20% IPA/hexane, flow rate 1 mL min^{-1}, λ = 254 nm, 20% ee): t_R 11.29 min (minor enantiomer) and 12.85 min (major enantiomer).

3-(((2*S*,3*S*)-3-(Hydroxymethyl)-3-methyloxiran-2-yl)methyl)-1,4-dioxo-1,4-dihydronaphthalen-2-yl acetate (+)-8

Sharpless asymmetric epoxidation of the compound **3b** (60 mg, 0.2 mmol) following the above procedure afforded (+)-**8** (50 mg, 80%) as a light yellow oil; $[\alpha]_D^{27}$ + 101.1 (*c* 0.2, $CHCl_3$); IR (neat) cm^{-1}: 3396, 3298, 2921, 2372, 1745, 1616, 1391, 1225, 1066; ^1H NMR (400 MHz, $CDCl_3$): δ 8.13–8.08 (m, 2H), 7.77–7.72 (m, 2H), 3.65 (d, *J* = 12 Hz, 1H), 3.55 (d, *J* = 12.4 Hz, 1H), 3.23 (t, *J* = 6 Hz, 1H), 2.94 (dd, *J* = 5.2, 13.6 Hz, 1H), 2.80 (dd, *J* = 6.8, 13.6 Hz, 1H), 2.40 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.3, 177.9, 168.0, 152.5, 135.5, 134.4, 134.1, 131.9, 126.9, 126.8, 65.1, 61.7, 58.0, 23.8, 20.6, 14.4; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{17}O_6$ (M^+ + H) 317.1025, found 317.1032. HPLC analysis of the compound (+)-**8** (Daicel AD-H, 20% IPA/hexane, flow rate 1 mL min^{-1}, λ = 254 nm, 90% ee): t_R 17.54 min (major enantiomer) and 19.82 min (minor enantiomer).

Bromination of compound 3b

To a stirred solution of compound **3b** (30 mg, 0.1 mmol) in dry DCM (2 mL) at 0 °C was added bromine (6 μL, 2.4 mmol). The resultant reaction mixture was stirred for 15 min at room temperature. The reaction mixture was quenched with saturated solution of $Na_2S_2O_3$ and extracted with DCM (2 × 5 mL), the combined DCM layers were washed with water (5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude compound. Column chromatographic purification of the crude compound over silica gel (40–70% EtOAc in hexane) afforded the bromo derivatives **9a**, **9b**, **10a** and **10b**. Compounds **9a** and **9b**: IR (neat) cm^{-1}: 3058, 2985, 2874, 1741, 1656, 1445, 1375, 1268, 1239, 1097, 1047, 938, 847, 744, 705; ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (dd, *J* = 0.8, 8.0 Hz, 2H), 7.91 (td, *J* = 0.8, 8.0 Hz, 2H), 7.79 (qd, *J* = 1.2, 7.6 Hz, 2H), 7.63 (qd, *J* = 1.2, 8.0 Hz, 2H), 4.46 (d, *J* = 8.4 Hz, 1H), 4.36 (dd, *J* = 1.2, 5.6 Hz, 1H), 4.25 (dd, *J* = 1.2, 6.0 Hz, 1H), 4.20 (d, *J* = 8.4 Hz, 1H), 4.09 (d, *J* = 8.4 Hz, 1H), 3.93 (d, *J* = 8.4 Hz, 1H), 3.67 (dd, *J* = 1.2, 15.6 Hz, 1H), 3.46 (dd, *J* = 5.6, 18.0 Hz, 1H), 3.24 (dd, *J* = 6.0, 15.6 Hz, 1H), 2.91 (dd, *J* = 1.2, 17.6 Hz, 1H), 1.81 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.3, 180.8, 180.2, 179.1, 138.0, 137.8, 135.7, 131.3, 131.2 131.1, 130.9, 129.1, 128.8, 125.9, 125.3, 106.8, 84.2, 83.9, 77.5, 75.5, 74.2, 62.9, 58.6, 50.5, 47.9, 37.2, 34.9, 22.7, 22.6; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{14}O_4Br$ (M^+ + H) 337.0075, found 337.0075. Compound **10a**: IR (neat) cm^{-1}: 3410, 3357, 3284, 2920, 2369, 1643, 1402, 1078, 819, 629; ^1H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 7.2 Hz, 1H), 7.69–7.58 (m, 3H), 5.26 (t, *J* = 8.8 Hz, 1H), 4.44 (s, 2H), 3.30–3.27 (m, 2H), 2.16 (s, 3H), 1.25 (s, 3H); HRMS (ESI) *m*/*z* calcd for $C_{15}H_{14}O_4Br$ (M^+ + H) 337.0075, found 337.0092.

Synthesis of 3-bromo-3,4-dihydro-5-hydroxy-2,2-dimethyl-2*H*-benzo[*h*]chromene-6-carbaldehyde 13

To a stirred solution of compound **1b** (184 mg, 0.65 mmol) in DCM (4 mL) was added bromine (53 μL, 1.04 mmol) and the resultant reaction mixture was stirred at room temperature for 2 h. After completion of the reaction as indicated by TLC, the solvent was removed under reduced pressure to give the crude product, which on column chromatographic purification over silica gel using 40–45% EtOAc in hexane as an eluent afforded the pure compounds **11a** (93% yield) and **11b**[6] (5% yield). Compound **11a** (75 mg, 0.23 mmol) was treated with 3 N NaOH at rt for 2 h. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with DCM and extracted using DCM (2 × 5 mL) and water (5 mL). The combined DCM layers were washed with brine solution and dried over Na_2SO_4 and the solvent was removed under reduced pressure to give the crude product, which on chromatographic purification over silica gel using 15% EtOAc in hexane as an eluent afforded the pure compounds **12** (65% yield), **13** (15% yield) and **14** (5% yield). Compound **13** was obtained as white crystals. ^1H (500 MHz, $CDCl_3$) δ 14.04 (s, 1H), 10.49 (s, OH), 8.17 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.60 (t, *J* = 7.2 Hz, IH), 7.42 (t, *J* = 7.6 Hz, IH), 4.36 (dd, *J* = 5.5, 8.0 Hz 1H), 3.50 (dd, *J* = 8.0, 17.6 Hz, 1H), 3.26 (dd, *J* = 8.0, 17.6 Hz, 1H), 1.65 (s, 1H), 1.56 (s, 1H); ^{13}C (125 MHz, $CDCl_3$): δ 190.8, 165.7, 156.4, 132.7, 129.6, 123.9, 122.9, 120.4, 118.3, 106.2, 105.2, 79.1, 50.93, 28.4, 26.6, 22.8; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{16}BrO_3$ (M^+ + H) 335.0283, found 335.0280.

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