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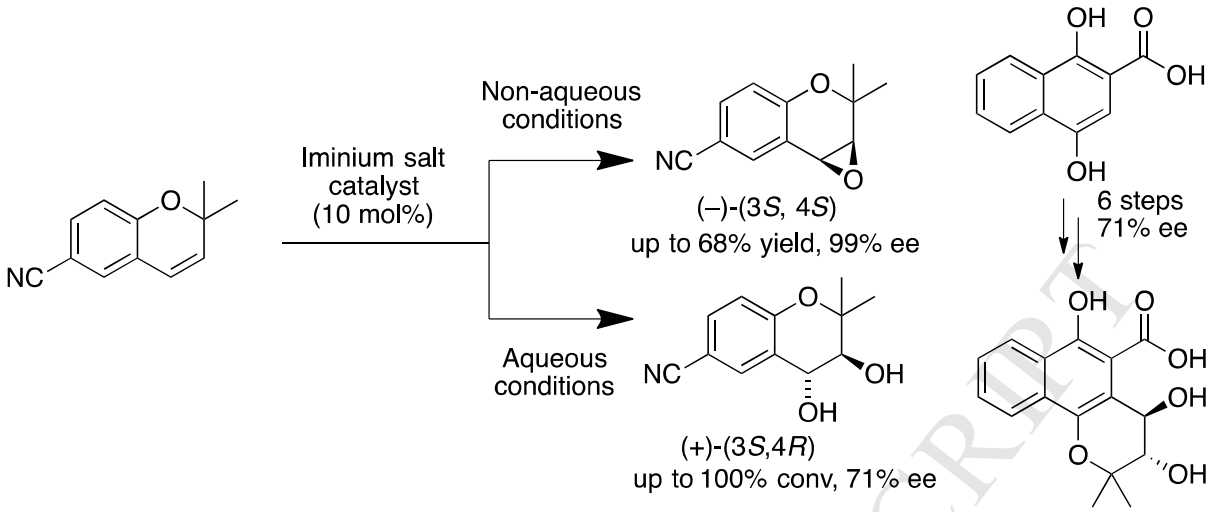
Graphical Abstract



Asymmetric Epoxidation of Chromenes Mediated by Iminium Salts: Synthesis of Mollugin and (3*S*,4*R*)-*trans*-3,4-Dihydroxy-3,4-Dihydromollugin

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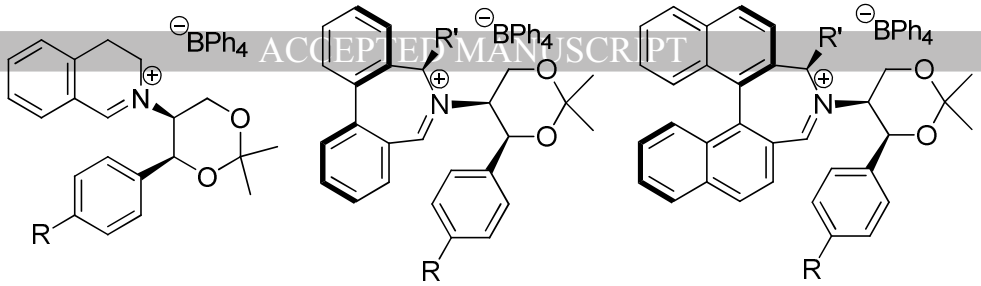
ABSTRACT: Organocatalytic asymmetric epoxidation of chromenes mediated by iminium salt catalysts under non-aqueous conditions provided *ee*s as high as 99%. Contrastingly, reaction under aqueous conditions can form the corresponding diol products with *ee*s as high as 71%. The process has been used for the synthesis of the East African medicinal plant metabolite (3*S*,4*R*)-*trans*-3,4-dihydroxy-3,4-dihydromollugin.

Introduction

The use of organocatalysts in the preparation of optically active compounds has attracted much attention over the last few years, although organocatalytic processes have been known for many decades. For example, one of the very early organocatalytic transformations was reported in 1860 by von Liebig, to form oxamide from cyanogen, catalysed by acetaldehyde;[1] the reaction was used on an industrial scale by Degussa. Many transformations have since been shown to be amenable to organocatalysis, including a number of enantioselective processes, including asymmetric epoxidation.[2] Two of the most successful organocatalyst types for asymmetric epoxidation are dioxiranes and oxaziridinium salts. Dioxiranes, derived from chiral ketones, such as those of Yang, Denmark, Armstrong, and Shi, have been reported to give enantioselectivities as high as 97% ee.[3] Oxaziridinium salts were first reported as reactive electrophilic oxygen transfer reagents by Lusinchi in 1976,[4] and may be derived in situ from iminium salts.[5] We have extensively investigated and developed iminium salt asymmetric epoxidation catalysts (Figure 1) based on dihydroisoquinolinium (e.g., **1**, **2**),[6,12] biphenylazepinium (e.g., **3**, **4** and **5**),[7] and binaphthylazepinium species (e.g., **6**, **7** and **8**);[8] these catalysts have shown excellent enantioselectivities of up to 99% ee.[9]



1 R = H
2 R = SO_2Me

3 R= R'= H
4 R= SO_2Me, R'= H
5 R= H, R'= CH_3

6 R= R'= H
7 R= SO_2Me, R'= H
8 R= H, R'= CH_3

Figure 1: Enantioselective iminium salt catalysts

We have generally used two sets of conditions, aqueous and non-aqueous, for iminium salt-catalysed asymmetric epoxidation processes. Aqueous conditions employ the triple salt oxone® as a stoicheiometric oxidant in the presence of Na_2CO_3 or $NaHCO_3$ as the base, and acetonitrile:water as the typical solvent mixture.[10] However, the use of aqueous media restricts the range of temperatures at which the epoxidation can be performed to above about –10 °C. An upper temperature limit is established by the stability of oxone, which decomposes relatively quickly under basic conditions at room temperature. Our non-aqueous system uses tetraphenylphosphonium monoperoxysulfate (TPPP) as the oxidant.[11] The use of TPPP eliminates the need for water as a co-solvent; in an organic solvent, typically chloroform, the reaction can be carried out at much lower temperatures, –40 °C or lower. We have found that the seven-membered ring catalysts are dramatically more reactive than the dihydroisoquinolinium species; further, the binap-derived catalysts are usually poorly effective under non-aqueous conditions. We were interested to examine the relative values of the two sets of conditions, and chose chromenes for the investigation as we have previously shown these to be excellent substrates for our systems; we have synthesized several biologically active chromene derivatives including levcromakalim **9**,[12] scuteflorin A **10**,[13] lomatin **11** and *trans*-khellactone **12** [14] (Figure 2) through highly enantioselective epoxidation reactions.

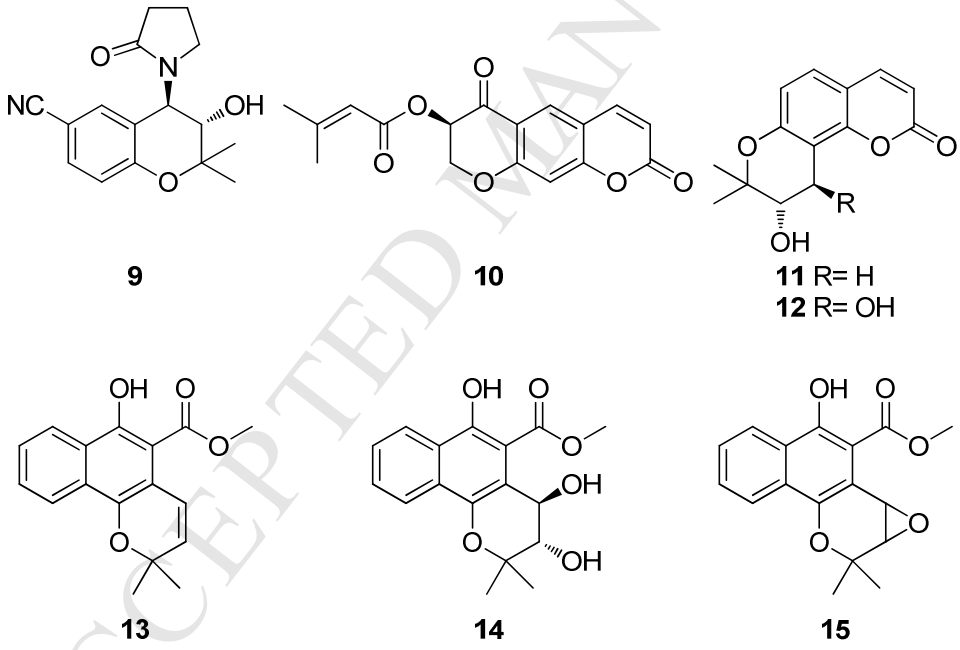
Chromene structural motifs are found in many natural products.[15] These compounds exhibit a wide range of biological properties such as anti-tumour,[16] anti-fungal,[17] anti-juvenile hormone in insects,[18] oestrogenic,[19] and anti-bacterial activities.[20]

Chromenes extracted from rubiaceous plants across the world have similarly shown a wide range of biological activities.[21] Examples of chromenes isolated from this family of plants include mollugin **13** and its *trans*-diol **14** and epoxide **15** derivatives. Mollugin is one of the major chromenes isolated from Rubiaceae species such as Putoria calabrica and Rubia cordifolia, a medicinal plant used in China and India for the treatment of a range of conditions including arthritis, rheumatism, menstrual pain, and haemorrhage; anti-mutagenic and anti-viral activities have been reported.[22]

Both *cis*- and *trans*- 3,4-dihydroxy-3,4-dihydromollugin **14** have been isolated from the East African medicinal plant *Pentas longiflora*, used to treat tapeworm infections, rashes, malaria, and other conditions.[22b]

Synthetic approaches to chromenes including structures related to mollugin include high temperature cyclization of phenol propargyl ethers,[23] metal-catalysed cycloisomerization,[24] phenylboronic acid-mediated electrocyclization reaction of phenol with unsaturated aldehydes,[25] base-catalysed condensation of phenols with *α,β*–unsaturated aldehydes or their acetal derivatives,[26] Lewis acid-catalysed condensation of phenols with epoxides, *α,β*-unsaturated aldehydes or allylic alcohols,[27] and, recently, metalloradical activation.[28]

Mollugin and derivatives have been prepared using several of the methodologies described above, including Lewis acid-catalysed condensation of phenols with allylic alcohols,[29] Lewis acid-catalysed condensation of resorcinols with unsaturated aldehydes,[30] phenylboronic acid-mediated electrocyclization reaction of resorcinols with unsaturated aldehydes,[22,31] and electrocyclization of prenylated quinones.[32]



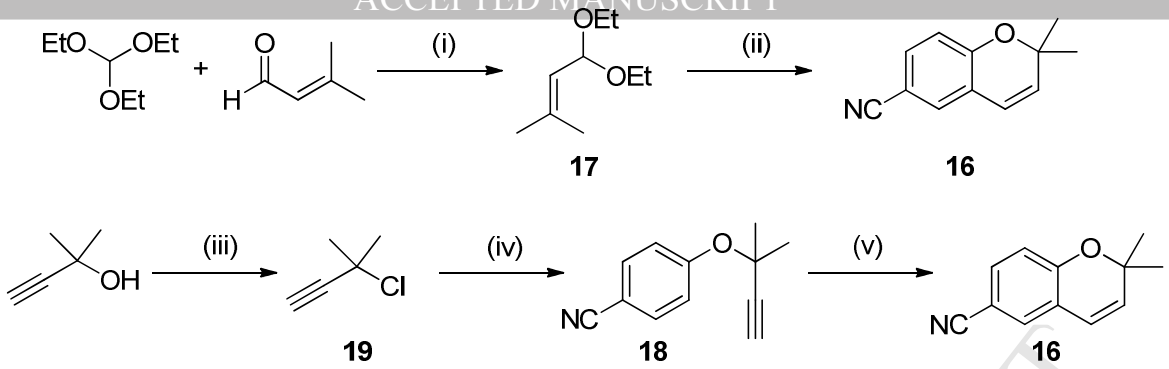
9 **10** **11** R= H **12** R= OH

13 **14** **15**

Figure 2: Biologically active compounds containing a chromene core

Results and Discussion

6-Cyano-2,2-dimethylchromene **16** is an intermediate in the synthesis of the anti-hypertensive agent, levcromakalim **9**.[12,33] We prepared the precursor 6-cyano-2,2-dimethylchromene **16** using two approaches: base-catalysed condensation of 4-cyanophenol and diethyl acetal **17**,[34] and cyclization of propargyl ether **18** (Scheme 1).[35] The synthesis of chromene **16** using the first method began with the preparation of the diethyl acetal **17** using North's procedure in 86% yield.[36] Acetal **17** was subsequently heated under reflux with 4-cyanophenol in *p*-xylene in the presence of 3-picoline as the base to give chromene **16** in 87% yield.



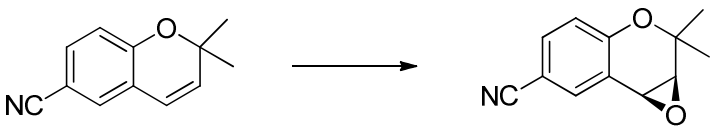
Reagents and conditions: (i) NH_4NO_3, EtOH, r.t., 24 h, 86%; (ii) 4-cyanophenol, 3-picoline, *p*-xylene, reflux, 24 h, 87%; (iii) $CaCl_2$, CuCl, Cu, cold aqueous HCl, 0 °C, 5 h; (iv) 4-cyanophenol, K_2CO_3, KI, acetone, reflux, 99%; (v) ethylene glycol, 210-215 °C, 24 h, quant.

Scheme 1: Syntheses of chromene 16

The rearrangement/cyclization of a propargyl ether is a general method for the synthesis of chromenes developed by Harfenist and Thom.[23c] 2-Methyl-3-butyn-2-ol was converted into propargyl chloride **19** using calcium chloride, cuprous chloride, a catalytic amount of copper powder and cold concentrated hydrochloric acid; the resulting chloride was used without purification due to its stability.[37] The O-alkylation of 4-cyanophenol was achieved by heating the phenol and 3-chloro-3,3-dimethylbutyne **19** with potassium carbonate and potassium iodide in acetone, giving propargyl ether **18** in up to 99% yield. Cyclization of ether **18** in ethylene glycol led to the formation of chromene **16** in quantitative yield (Scheme 1).

Asymmetric epoxidation reactions under both aqueous and non-aqueous conditions were then carried out on 6-cyano-2,2-dimethylchromene **16** using the selected iminium salts **1**-**4**, **6**, **7**. Under non-aqueous conditions, excellent enantioselectivity was observed for catalysts **2**, **3** and **4** for the asymmetric epoxidation reactions of chromene **16**, affording the corresponding epoxy-chromane (−)-(3*S*,4*S*)-**20** (Table 1). The highest ee was observed using biphenyl-derived iminium salt catalyst **3**, affording the corresponding epoxide in >99% ee under non-aqueous conditions. When catalysts **1**, **6** and **7** were used under non-aqueous conditions, no conversion to the epoxide was detected using 1H NMR spectroscopic analysis of the unpurified reaction mixtures. The reduced reactivity for these catalysts has been reported previously in our group for asymmetric epoxidation of commercially available alkenes.[38]

Table 1. Asymmetric epoxidation of 6-cyano-2,2-dimethylchromene **16** under non-aqueous conditions.[a]



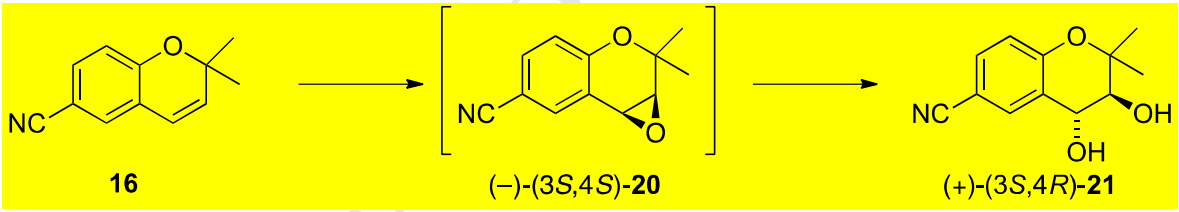
16 (–)-(3*S*,4*S*)-**20**

Catalyst	Yield/%	*ee*/% [b]
2	59	97
3	20	99
4	20	97

[a] *Reagents and conditions:* Iminium salt (10 mol%), TPPP (6 equiv.), $CHCl_3$, 0 °C, 1 d; [b] Enantiomeric excesses were determined by chiral HPLC on Chiralcel OD column; [c] The absolute configuration of the major enantiomers were determined by comparison of optical rotations with those reported in the literature[12,33]

The corresponding epoxide product was indeed generated *in situ*, but the expected epoxy-chromane (3*S*,4*S*)-**20** was unstable under the aqueous reaction conditions, fully converting **16** into the corresponding diol (+)-(3*S*,4*R*)-**21** in up to 71% ee, presumably through trans-diaxial ring-opening at the benzylic position (Table 2). The data collected in Table 2 show that the biphenyl-derived catalysts **3** and **4** are the most reactive and selective, giving the best *ee*s of 68% and 71%, respectively. We were expecting that the reactions using binaphthyl-derived catalysts **6** and **7** under aqueous conditions would be more successful, as these catalysts are generally more reactive under aqueous conditions. The binaphthyl-derived catalysts **6** and **7**, however, gave zero and low enantioselectivity, respectively. This is a very surprising finding as we have previously found catalyst **6** to be one of the most enantioselective iminium catalysts that we have developed, giving as high as 95% *ee* for epoxidation of 1-phenyl-3,4-dihydronaphthalene.[8b]

Table 2. Formation of diol (+)-(3*S*,4*R*)-**21** under aqueous conditions.[a]

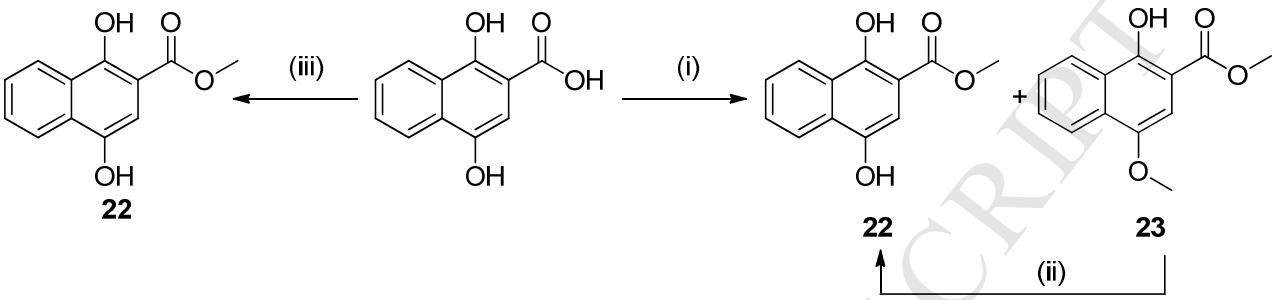


Catalyst	Conversion/%	*ee*/% [b]
1	65	60
2	44	57
3	100	68
4	100	71
6	25	0
7	52	20

[a] *Reagents and conditions:* Na_2CO_3 (4 equiv.), Oxone® (6 equiv.), iminium salt catalyst (10 mol%), MeCN/H_2O (1:1), 0 °C, 1 d; [b] Enantiomeric excesses were determined by chiral HPLC on Chiralcel OD column; [c] The absolute configuration of the major enantiomers were attributed by comparison of optical rotations with values reported in the literature [39]

We next turned our attention to the synthesis of mollugin **13**. Methylation of 1,4-dihydroxynaphthalene-2-carboxylic acid using sulfuric acid in methanol led to isolation of the desired 1,4-dihydroxynaphthalene-2-

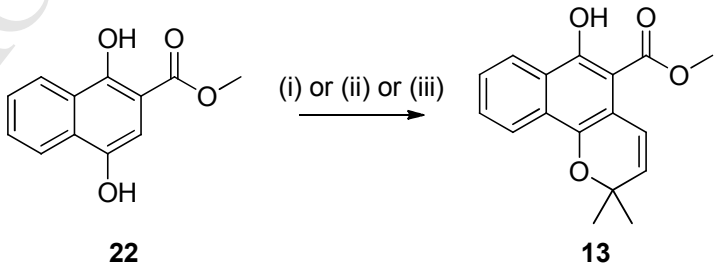
carboxylic ester **22** in a very low yield (5%) alongside dimethylated product **23**, formed in 90% yield.[40] Compound **23** could, however, be converted into **22** in 91% yield by treatment of a solution of **23** in anhydrous dichloromethane with aluminum chloride at 0 ºC (Scheme 2).[22a] Compound **22** was also formed in 96% yield when a solution of 1,4-dihydroxynaphthalene-2-carboxylic acid and methyl iodide in dimethylformamide was treated with anhydrous sodium hydrogen carbonate overnight at room temperature.[31,41]



Reagents and conditions: (i) CH_3OH, H_2SO_4, 8 h, 0 ºC-r.t., [**22**, 5%; **23**, 90%]; (ii) $AlCl_3$ (2 equiv.), 0 ºC, 2 h, 91%; (iii) MeI (2 equiv.), $NaHCO_3$ (2 equiv.), DMF, 0 ºC-r.t., overnight, 96%.

Scheme 2: Synthesis of **22**

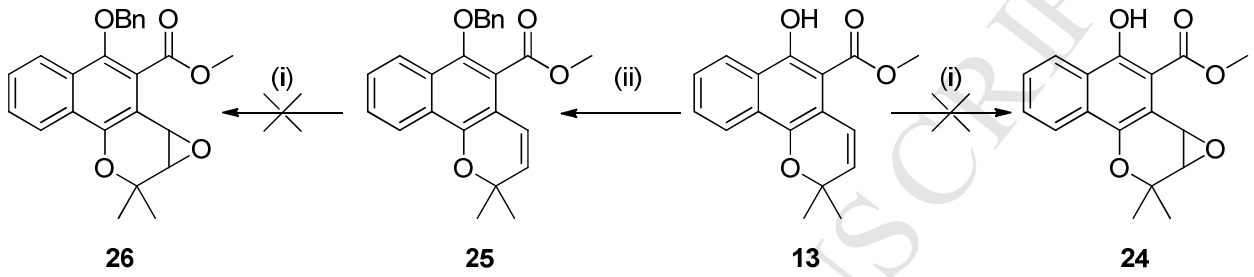
Jahng has described a synthesis of mollugin **13** from **22** using an *ortho*-directing intermolecular phenylboronic acid-mediated annelation with 3-methyl-2-butenal.[22a] In our hands, this annelation of 3-methyl-2-butenal with **22** was achieved in a reasonable 53% yield (Scheme 3). Using North's general procedure,[34] compound **22** was heated under reflux in *p*-xylene with *α,β*-unsaturated acetal **17** in the presence of 3-picoline to give mollugin in 64% yield. Alternatively, using Harfenist and Thom's general methodology,[23c] ester **22** was heated under reflux for 24 h with propargyl chloride **19** in the presence of potassium carbonate to yield mollugin **13** in 19% yield alongside recovered starting material **22** (79% recovery). Modification of the reaction conditions, replacing acetone by toluene and increasing the temperature from 50 °C to reflux, provided an experimentally convenient and high-yielding process, allowing isolation of mollugin **13** in 81% yield (Scheme 3).



Reagents and conditions: (i) 3-Methyl-2-butenal (2.2 equiv.), $PhB(OH)_2$ (1.1 equiv.), toluene/AcOH, reflux, 17 h, 53%; (ii) acetal **17** (1 equiv.), 3-picoline (0.25 equiv.), *p*-xylene, reflux, 24 h, 64%; (iii) 3-Chloro-3-methyl-1-butyne **19** (3.1 equiv.), CuCl (1 equiv.), Cu (5 mol%), K_2CO_3 (2 equiv.), KI (2 equiv.), toluene, reflux, 24 h, 81%.

Scheme 3: Synthesis of mollugin **13**

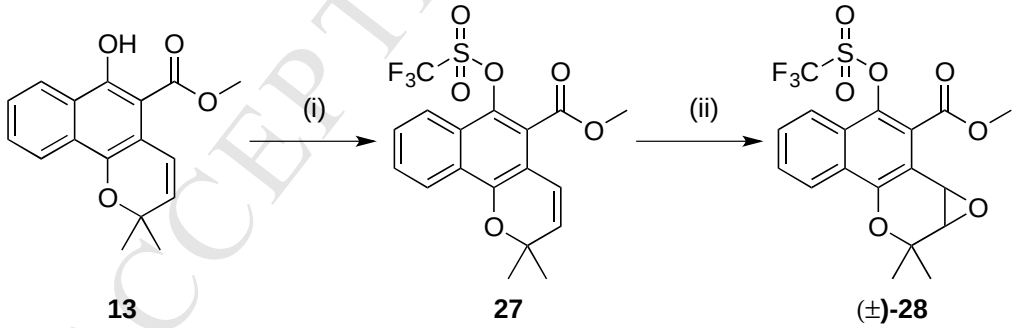
Synthesis of racemic mollugin oxide **15** was first attempted using standard epoxidation conditions. Unfortunately, *m*-CPBA oxidation of mollugin **13** in anhydrous dichloromethane was unsuccessful: epoxide **24** was not isolated and decomposition of the starting material was observed. Suspecting that the free phenolic hydroxyl may interfere with epoxidation or destabilize the epoxide moiety, we prepared the benzylated product **25** in 86% yield.[42] Attempts to oxidize **25** using *m*-CPBA and sodium hydrogen carbonate in anhydrous dichloromethane, however, again led only to the decomposition of the starting material (Scheme 4).



Reagents and conditions: (i) *m*-CPBA (1 equiv.), $NaHCO_3$ (2 equiv.), 0 °C, 50 min; (ii) BnBr (1.5 equiv.), K_2CO_3 (1.5 equiv.), DMF, 70 °C, 4h, 86%.

Scheme 4: Attempted oxidation of **13** and **25**

We conjectured that strongly electron-donating groups may destabilize the epoxide moiety under standard epoxidation conditions, and we therefore prepared the triflate derivative **27** in 98% yield by treatment of mollugin **13** with triethylamine and trifluoromethanesulfonic anhydride in anhydrous dichloromethane. Racemic epoxide **28** was prepared from **27** in 81% yield using *m*-CPBA (Scheme 5).

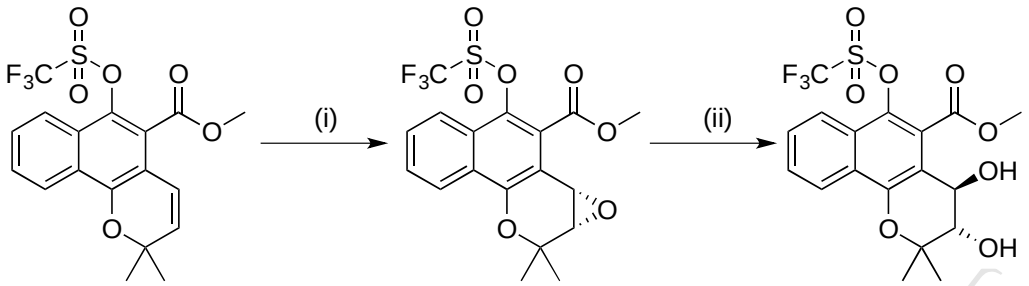


Reagents and conditions: (i) TEA (2 equiv.), $(CF_3SO_2)O$ (3 equiv.), DCM, 0 °C-r.t., 24 h, 91 %; (ii) *m*-CPBA (1 equiv.), $NaHCO_3$ (2 equiv.), 0 °C, 2 h, 81%.

Scheme 5: Synthesis of **27** & (±)-**28**

Biphenyl catalyst **3** was tested under aqueous conditions and non-aqueous conditions in the asymmetric epoxidation of **27**. Surprisingly, epoxidation of **27** under non-aqueous conditions was unsuccessful at −30, −10 and 0 °C even over 3 days, and the starting material was recovered in each case. Under aqueous conditions, however, the reactivity of catalyst **3** proved excellent, and full conversion to (−)-(3*S*,4*S*)-epoxide

28 was observed after 15 min (Scheme 6).



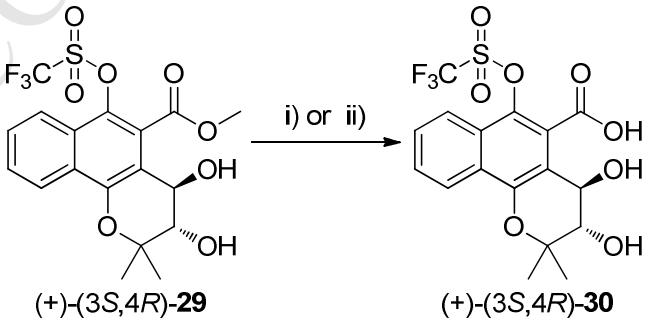
27 (–)-(3*S*,4*S*)-**28** (+)-(3*S*,4*R*)-**29**

Reagents and conditions: (i) catalyst **3** (10 mol%), Na_2CO_3 (5 equiv.), Oxone® (2 equiv.), MeCN:H_2O (1:1), 15 min, 91%; (ii) acetone/1M H_2SO_4 (2:1), r.t., 1 h, 74%.

Scheme 6: Synthesis of diol (+)-(3*S*,4*R*)-**29**

The reduced stability of developing positive charge at the benzylic position in **28** coupled with a reduced quantity of oxone® and an increased quantity of base allowed the epoxide product to be isolated in 91% yield and 71% ee, conversion into the diol under the reaction conditions not being observed under these conditions. Acid-catalysed ring-opening of the epoxide moiety of **28** with dilute sulfuric acid in aqueous acetone gave the corresponding (+)-(3*S*,4*R*)-*trans*-diol **29** in 74% yield.

Removal of the trifluoromethane sulfonate group was initially attempted with potassium hydroxide in a mixture of water and ethanol (1:1), the reaction was heated under reflux for 30 min until complete disappearance of **29** was observed using TLC. Preferential hydrolysis of the methyl ester had, however, occurred, leading to the formation of carboxylic acid **30**. Indeed the presence of the triflate group was confirmed using ^{19}F NMR spectroscopy. A selective triflate removal procedure was then attempted:[43] **29** was dissolved in dimethoxyethane in the presence of caesium carbonate and the reaction mixture heated to 80 °C. However, the saponification product **30** was the only product observed (62% yield) alongside recovered starting material (28%) (Scheme 7).

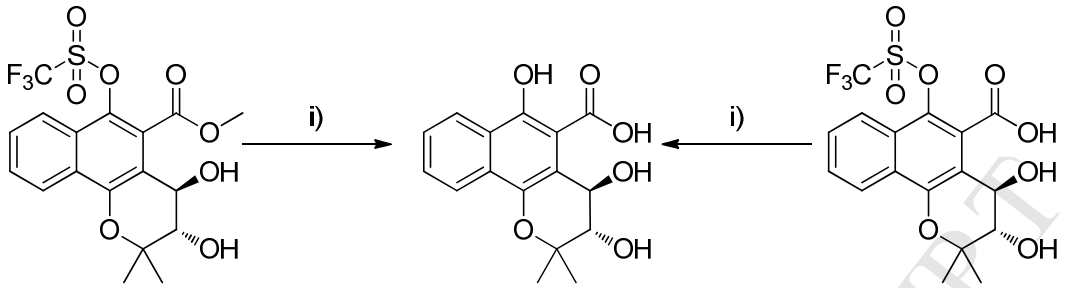


(+)-(3*S*,4*R*)-**29** (+)-(3*S*,4*R*)-**30**

Reagents and conditions: i) KOH (1 equiv), H_2O/EtOH (1:1), reflux, 30 min; ii) Cs_2CO_3 (1.2 equiv.), $MeOCH_2CH_2OMe$, 80 °C, 1 h.

Scheme 7: Attempted removal of the trifluoromethane sulfonate group

Finally, compound **29** was dissolved in methanol in the presence of caesium carbonate, leading to the formation of (3*S*,4*R*)-*trans*-3,4-dihydroxy-3,4-dihydromollugin **31** in quantitative yield. When triflate **30** was submitted to the same reaction conditions, **31** was also obtained in quantitative yield (Scheme 7).



Reagents and conditions: i) Cs_2CO_3 (2.5 equiv.), MeOH, 2 h.

Scheme 8: Triflate group removal

Conclusion

Aqueous and non-aqueous systems have been compared for the organocatalytic asymmetric epoxidation of chromenes mediated by several iminium salt catalysts. Under non-aqueous conditions, the epoxides were isolated with ees as high as 99%. Contrastingly, reaction under aqueous conditions could induce *in situ* hydrolysis of the epoxides, giving the corresponding diol products with ees of up to 71%. The reaction has been used for the synthesis of (3*S*,4*R*)-*trans*-3,4-dihydroxy-3,4-dihydromollugin **31** from mollugin.

Acknowledgments

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EXPERIMENTAL SECTION

General Experimental Methods

Commercially available reagents and solvents were used as supplied, without further purification, unless otherwise stated. Light petroleum (bp 40-60 °C), was distilled from calcium chloride prior to use. Ethyl acetate was distilled over calcium sulfate or chloride. Dichloromethane was distilled over phosphorus pentoxide or calcium hydride. Tetrahydrofuran was distilled under a nitrogen atmosphere from sodium-benzophenone ketyl radical. Triethylamine was stored over sodium hydroxide pellets. Air- and moisture-sensitive reactions were carried out using glassware that had been dried overnight in an oven at 240 °C, and allowed to cool in a desiccator over self indicating silica gel pellets, under a nitrogen atmosphere; the reactions were carried out under a slight positive pressure of nitrogen. Flash chromatography was carried out using Merck 9385 Kieselgel 60-45 (230-400 mesh), typically using ethyl acetate-petroleum ether mixtures, with the solvent polarity adjusted to provide an Rf of about 0.3. Thin layer chromatography (TLC) was

carried out on aluminium plates coated with a silica gel layer 0.25 mm thickness. Compounds were visualized by UV irradiation at a wavelength of 254 nm, or stained by exposure to an ethanolic solution of phosphomolybdic acid (acidified with concentrated sulfuric acid), followed by charring where appropriate. Infra-red absorption spectra were recorded on a Perkin-Elmer Paragon 2001 FT-IR spectrometer instrument in the range of 4000-600cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX 400 and Avance DPX 500 instruments.

1,1-Diethoxy-3-methyl-2-butene 17 [36]

3-Methylbut-2-enal (1.00 g, 11.90 mmol) and triethyl orthoformate (2.0 mL, 11.90 mmol) were dissolved in EtOH (20 mL) at room temperature. The mixture was stirred for 5 min and NH_4NO_3 (0.24 g, 2.97 mmol, 25 mol%) added. The mixture was stirred for 24 h. Saturated aqueous $NaHCO_3$ (20 mL) and brine (10 mL) were added. The mixture was extracted using Et_2O (3 x 20 mL), the organic layers were combined, dried and filtered, and the solvents were removed under reduced pressure to give the title compound **17** as a brown liquid, which was used without further purification. ν_{max} (film)/cm^{-1} 2975, 2930, 2914, 2879, 1682, 1447, 1377, 1358, 1348, 1206, 1142, 1115, 1083, 1053, 1017, 991. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.23 (m, 6H), 1.72 (d, 3H, J = 1.0 Hz), 1.75 (d, 3H, J = 1.0 Hz), 3.42 – 3.58 (m, 2H), 3.60 – 3.63 (m, 2H), 5.14 (d, 1H, J = 6.5 Hz), 5.30 (d, 1H, J = 6.5Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 15.5, 18.4, 25.6, 60.4, 98.6, 125.1, 137.6.

3-Chloro-3-methyl-1-butyne 19 [44]

$CaCl_2$ (56 g, 0.5 mol), CuCl (40 g, 0.3 mol), and Cu bronze powder (400 mg, 6.3 mmol) were suspended in cold concentrated aqueous HCl (37%, 430 mL). The mixture was flushed with argon several times and cooled in an ice bath with stirring. 2-Methylbut-3-yn-2-ol (96 mL, 1 mol) was added over 30 min. Stirring was continued for 1 h at 0 – 5 °C. The upper organic layer was separated and washed immediately with cold HCl (0-5 °C, 37%, 3 x 100 mL), water (2 x 100 mL), dried over anhydrous K_2CO_3, filtered, and the solvents were removed under reduced pressure to give propargyl chloride **19**, which was used without further purification. ν_{max} (film)/cm^{-1} 2983, 2927, 1739, 1666, 1616, 1447, 1370, 1111, 938, 836, 604; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.87 (s, 6H), 2.62 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 34.6, 56.9, 71.9, 86.5.

3-(3-Cyanophenoxy)-3-methylbut-1-yne 18 [35]

4-Cyanophenol (0.5 g, 4.2 mmol), anhydrous K_2CO_3 (0.58 g, 4.2 mmol) and KI (0.07 g, 0.42 mmol, 0.1 equiv.) were stirred in acetone (25 mL per gram of phenol) under a nitrogen atmosphere. 3-Chloro-3-methyl-1-butyne **19** (1.3 g, 8.8 mmol, 2.1 equiv) was added and the mixture heated under reflux for 18 h. The reaction was allowed to cool, and water (50 mL) added. The mixture was extracted with diethyl ether (3 x 25 mL), and the organic layers were combined, washed with NaOH (2N, 2 x 50 mL), HCl (2N, 50 mL), and

water (50 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent removed under reduced pressure to yield the title compound **18** as light yellow oil (0.77 g, 99%). ν_{max} (film)/cm^{-1} 3292, 3103, 3078, 3048, 2991, 2939, 2226, 2112, 1602, 1572, 1504, 1464, 1452, 1420, 1384, 1366, 1254, 1227, 1172, 1137, 956, 911, 839, 736, 696, 671, 651. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.70 (s, 6H), 2.65 (s, 1H,), 7.28 (d, 2H, J = 8.5 Hz), 7.57 (d, 2H, J = 8.5 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 29.5, 72.7, 75.3, 84.7, 105.1, 119.1, 120.0, 133.4, 159.4.

6-Cyano-2,2-dimethylchromene 16

Method A: 1,1-Diethoxy-3-methylbut-2-ene **17** (1.74 g, 11.0 mmol), 4-cyanophenol (2.65 g, 22.0 mmol) and 3-picoline (0.27 mL, 2.75 mmol) were dissolved in *p*-xylene (20 mL/g of phenol). The mixture was heated under reflux for 24 h, and the reaction mixture allowed to cool to ambient temperature. The clear, golden mixture was diluted with EtOAc (50 mL) and washed with HCl (1N, 2 x 25 mL). The aqueous layers were combined and washed with EtOAc (2 x 25 mL). The combined organic layers were washed with NaOH (1N, 25 mL), brine (25 mL), dried over anhydrous $MgSO_4$ and filtered. The solvents were removed under reduced pressure to give a bright yellow solid. The yellow solid was recrystallized from light petroleum to give the title compound **16** as a yellow powder (1.78 g, 87%).

Method B: Phenyl propargyl ether **18** (1.0 g, 5.40 mmol) was dissolved in ethylene glycol (5 mL/g of the propargyl ether) and the reaction mixture heated to 210-215 °C for 24 h. The mixture was allowed to cool to room temperature and water added. The mixture was extracted with Et_2O (2 x 25 mL), the organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solvents were removed under reduced pressure to give a bright yellow solid, recrystallized from light petroleum to give the title compound **16** as a yellow powder (1.0 g, quant.), mp 47-48 °C [Lit.[36] mp 47 °C]. ν_{max} (film)/cm^{-1} 3054, 2985, 2226, 1605, 1487, 1421, 1369, 1265, 1212, 1148, 1128, 1107, 961, 896, 828, 739, 705. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 6H), 5.70 (d, 1H, J = 11.6 Hz), 6.28 (d, 1H, J = 11.6 Hz), 6.78 (d, 1H, J = 8.4 Hz), 7.24 (d, 1H, J = 4.0 Hz), 7.37 (dd, 1H, J = 8.4 Hz, 4.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 28.4, 77.9, 103.8, 117.2, 119.3, 120.6, 121.7, 130.1, 132.2, 133.3, 156.8.

Preparation of Dimethyldioxirane (DMDO) [45]

Distilled H_2O (20 mL), acetone (30 mL), and $NaHCO_3$ (24 g, 0.285 mol) were combined and chilled in an ice/water bath with magnetic stirring for 20 min. Stirring was halted and oxone® (25 g, 0.164 mol) added in a single portion. The flask was loosely covered and the slurry was stirred vigorously for 15 min while still submerged in the ice bath. After 15 min, the stirrer bar was removed and rinsed with a small portion of distilled water. The flask containing the reaction slurry was attached to a rotary evaporator with the bath at room temperature. The rotary evaporator splash trap (250 mL) was chilled in a dry ice/acetone bath and a vacuum of 155 mmHg was applied *via* a benchtop diaphragm pump and an accompanying in-line vacuum

regulator. During this process, the flask was rotated vigorously (210 rpm) to prevent bumping of the slurry into the bump trap. After 15 min, the bath temperature was raised to 40 °C over the course of 10 min. When the bath reached 40 °C, the distillation was halted immediately by releasing the vacuum and raising the flask from the heated water bath. The pale yellow solution of DMDO was decanted from the rotary evaporator splash trap directly into a graduated cylinder to measure the total volume of the solution (an average of 25 mL) and the solution was dried over Na_2SO_4. The solution was filtered and rinsed with acetone (10 mL). The concentration of DMDO was determined by iodometric titration.

General Procedure for the Formation of Racemic Epoxides using DMDO

The alkene was dissolved in $CHCl_3$ (2 mL per 0.1 g alkene) and the solution was cooled to 0 °C. The DMDO solution in acetone (0.03 M, 1.5 equiv) was gradually added. After the reaction had reached completion, the solvent was removed under reduced pressure at room temperature. The residue was purified by column chromatography.

General Procedure for the Formation of Racemic Diols

The racemic epoxide was dissolved in acetone (50 mL/g of epoxide) and stirred at room temperature for 5 min. Aqueous sulfuric acid (1 M, 5.5 equiv) was added to the solution, and the mixture stirred for 1 h at room temperature. After the reaction had reached completion, the reaction mixture was neutralized to pH 7 using sodium hydrogen carbonate. Dichloromethane (150 mL/g of epoxide) was added to the reaction mixture and the organic phase separated. The aqueous layer was extracted with dichloromethane (2 x 150 mL/g of epoxide), and the organic layers were combined and dried (Na_2SO_4). The solvents were removed under reduced pressure, and the residue purified by column chromatography.

General Procedure for the Catalytic Asymmetric Epoxidation of Alkenes Mediated by Iminium Salts using Oxone® under Aqueous Conditions

Oxone® (2 equiv.) was added with stirring to an iced-cooled solution of sodium carbonate (4 equiv.) in water (12 mL per 1.50 g of Na_2CO_3), and the resulting foaming solution was stirred for 5-10 min, until most of the effervescence had subsided. A solution of the iminium salt (10 mol%) in CH_3CN (6 mL per 1.50 g of Na_2CO_3), was added, followed by a solution of the alkene substrate (approx. 100 mg) in CH_3CN (6 mL per 1.50 g of Na_2CO_3). The suspension was stirred with ice-bath cooling until the substrate was completely consumed according to TLC. The mixture was diluted with ice-cooled diethyl ether (20 mL per 100 mg substrate), and the same volume of water added immediately. The aqueous phase was washed four times with diethyl ether, and the combined organic solutions were washed with brine and dried ($MgSO_4$). Filtration and removal of solvents gave a yellow or light brown residue, which was purified by column chromatography, typically using ethyl acetate/light petroleum (1:99), to provide the pure epoxide.

Tetraphenylphosphonium Monoperoxysulfate (TPPP) [46]

Tetraphenylphosphonium chloride (15.0 g, 40 mmol) was dissolved in CH_2Cl_2 (200 mL) and cooled in ice-water bath. A solution of oxone® (15.0 g, 48 mmol) in deionised water (300 mL) at 0 °C was added to the solution of tetraphenylphosphonium chloride over a period of 5 min. The resulting biphasic mixture was stirred vigorously for 1 h in the ice-water bath, the organic layer separated, and the solvents were removed under reduced pressure at room temperature. The white solid residue was transferred to a sintered glass funnel and washed with deionized water (3 x 80 mL). The solid was re-dissolved in CH_2Cl_2 (150 mL) and dried over $MgSO_4$; hexane was added to this solution until a solid precipitate just started to form, and the flask was placed in the freezer overnight, producing a colourless crystalline solid with 94% purity in peroxide. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.63 – 7.67 (m, 8H), 7.76 – 7.80 (m, 8H), 7.88 – 7.92 (m, 4H), 9.34 (s, 1H). The oxygen content was measured by comparing the integration of the aromatic signals with the hydroxyl proton.

General Procedure for Catalytic Asymmetric Epoxidation of Alkenes Mediated by Iminium Salts using Tetraphenylphosphonium Monoperoxysulfate (TPPP)

Tetraphenylphosphonium monoperoxysulfate (2 equiv.) was dissolved in the desired solvent (2 mL per 0.1 g oxidant) and the solution cooled to the required temperature. The iminium salt (10 mol%) was added dropwise over 15-20 min to the reaction mixture as a solution in the desired solvent (0.5 mL per 0.1 g oxidant) at the same temperature as the solution containing the oxidant. A solution of the alkene (approx. 100 mg) in the reaction solvent (0.5 mL per 0.1 g oxidant) was added dropwise. The mixture was stirred at the reaction temperature until the alkene was completely consumed according to TLC. Et_2O (pre-cooled to the reaction temperature, 20 mL per 0.1 g oxidant) was added to induce precipitation of the remaining oxidant, and the mixture filtered through Celite®. The solvents were removed, Et_2O (40 mL) was added to the residue, and the solution passed through a short pad of silica gel to remove catalyst residues. The solvents were removed under reduced pressure to give the epoxide. If the reaction did not reach completion, the epoxide was separated from the alkene by column chromatography, eluting with ethyl acetate/light petroleum 1:99.

6-Cyano-3,4-epoxy-2,2-dimethylchromane 20 [12]

Prepared according to the general procedure for the catalytic asymmetric epoxidation of alkenes mediated by iminium salts using TPPP under non-aqueous conditions from 6-cyano-2,2-dimethylchromene **16**. 6-Cyano-3,4-epoxy-2,2-dimethylchromane **20** was isolated as a colourless solid after purification by column chromatography eluting with EtOAc/light petroleum (5:95) plus 2% Et_3N. ν_{max} (film)/cm^{-1} 3055, 2987, 2305, 2228, 1616, 1580, 1494, 1466, 1421, 1385, 1369, 1344, 1265, 1236, 1207, 1162, 1133, 1100, 1040, 958,

935, 920, 896, 868, 828, 816, 737, 705. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.60 (s, 3H), 3.54 (d, 1H, J = 4.5 Hz), 3.91 (d, 1H, J = 4.5 Hz), 6.87 (d, 1H, J = 8.5 Hz), 7.53 (dd, 1H, J = 8.5, 2.0 Hz), 7.65 (d, 1H, J = 2.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 23.0, 25.5, 49.9, 62.3, 74.7, 104.3, 118.8, 119.1, 121.1, 133.8, 134.4, 156.5.

6-Cyano-3,4-dihydroxy-2,2-dimethylchromane 21 [39]

Prepared according to the general procedure for the catalytic asymmetric epoxidation of alkenes mediated by iminium salts using oxone under aqueous conditions from 6-cyano-2,2-dimethylchromene **16**. The product **21** was isolated as a yellow solid after purification by column chromatography eluting with EtOAc/light petroleum (50:50) plus 2% Et_3N, followed by drying at 60 °C under reduced pressure, m.p. 147-149 °C; ν_{max} (film)/cm^{-1} 3397, 2984, 2919, 2851, 2229, 1611, 1580, 1489, 1372, 1311, 1273, 1195, 1147, 1126, 1072, 1037, 1000, 952, 921, 836. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.25 (s, 3H), 1.52 (s, 3H), 3.62 (d, 1H, J = 9.0 Hz), 4.59 (d, 1H, J = 9.0 Hz), 6.85 (d, 1H, J = 8.5 Hz), 7.46 (ddd, 1H, J = 8.5, 2.5, 1.0 Hz), 7.81 (dd, 1H, J = 2.5, 1.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 19.3, 26.6, 68.6, 75.8, 79.8, 104.0, 118.0, 119.2, 124.4, 132.4, 133.3, 156.0.

Methyl 1-hydroxy-4-methoxy-2-naphthoate 23 [22a]

1,4-Dihydroxy-2-naphthoic acid (1.1 g, 5.38 mmol) was dissolved in methanol (12 mL), and dilute aqueous H_2SO_4 (1M, 5 mL) was added slowly at 0 °C. The resulting brown solution was heated under reflux for 2 h, allowed to cool, and water (6 mL) added slowly. The solvents were removed under reduced pressure and the residue dissolved in ethyl acetate (20 mL). The solution was transferred to a separating funnel and washed with brine (10 mL). The organic layer was isolated, dried over anhydrous $MgSO_4$, and filtered. The solvents were removed under reduced pressure and the residue was purified using silica gel column chromatography (petroleum ether / ethyl acetate, 5:1) to give **23** as a colourless solid (1.12 g, 90%) and **22** as a yellow solid (0.05 g, 5%). For **23**: mp 130-132 °C [Lit.[22a] mp 136-137 °C]; ν_{max} (neat)/cm^{-1} 3384, 2924, 1713, 1461, 846; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.97 (s, 3 H), 4.00 (s, 3 H), 7.03 (s, 1 H), 7.57 (ddd, 1 H, J = 8.2, 6.9, 1.3 Hz), 7.64 (ddd, 1 H, J = 8.3, 6.9, 1.3 Hz), 8.20 (ddd, 1 H, J = 8.4, 1.3, 0.7 Hz), 8.39 (ddd, 1 H, J = 8.3, 1.3, 0.7 Hz), 11.62 (s, 1 H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 52.4, 55.8, 100.6, 104.4, 122.0, 123.9, 125.7, 126.6, 129.2, 130.0, 147.8, 155.8, 171.5.

Methyl 1,4-dihydroxy-2-naphthoate 22 [22a]

Method A: Compound **23** (0.43 g, 1.85 mmol) was suspended in anhydrous dichloromethane under a nitrogen atmosphere. $AlCl_3$ (0.49 g, 3.70 mmol) was added at 0 °C, and the mixture stirred for 2 h at 0 °C. The reaction was quenched by slow addition of water (2 mL), followed by dilute aqueous HCl (1M, 1 mL). The title compound was extracted from the aqueous layer with dichloromethane (3×10 ml). The combined

organic layers were washed with brine (2 × 10 mL), dried over anhydrous Na_2SO_4 and filtered. The solvents were removed under reduced pressure and the residue purified using silica gel column chromatography (petroleum ether / ethyl acetate, 3:1) to give **22** as a yellow solid (0.36 g, 91%).

Method B: 4-Dihydroxy-2-naphthoic acid (0.20 g, 0.9 mmol) and anhydrous $NaHCO_3$ (0.10 g, 1.1 mmol) were suspended in anhydrous dimethylformamide and the suspension was stirred for 30 minutes under a nitrogen atmosphere at room temperature. Methyl iodide (0.20 g, 0.09 ml, 1.4 mmol) was added using a syringe. The mixture was stirred for 22 h, until all the starting material was consumed. Saturated brine (10 mL) was added, followed by dilute aqueous HCl (1M, 6 mL). The mixture was extracted with diethyl ether (3 x 30 mL), the organic phases were dried over anhydrous $MgSO_4$, and the solvents evaporated under reduced pressure. The residue was purified using flash column chromatography (petroleum ether / ethyl acetate, 4:1), to give **22** as a yellow solid (0.21 g, 96%), mp 191-193 °C [Lit.[9] mp 192-193 °C]; ν_{max} (neat)/cm^{-1} 3434, 2981, 1635, 1376, 929; ^{1}H-NMR (500 MHz, D_6-DMSO): δ 3.95 (s, 3 H), 7.10 (s, 1 H), 7.61 (ddd, 1 H, J = 8.2, 6.9, 1.3 Hz), 7.67 (ddd, 1 H, J = 8.3, 6.9, 1.3 Hz), 8.10-8.13 (m, 1 H), 8.24-8.27 (m, 1 H), 9.85 (s, 1 H), 11.32 (s, 1 H); ^{13}C-NMR (125 MHz, D_6-DMSO): δ 52.6, 103.8, 104.7, 122.2, 123.2, 124.8, 126.4, 128.7, 129.0, 145.1, 152.6, 170.5.

Mollugin 13 [30a]

Method A: Phenylboronic acid (0.25 g, 2.00 mmol) was added to a solution of methyl 1,4-dihydroxy-2-naphthoate (0.45 g, 2.00 mmol) in toluene, followed by glacial acetic acid (3 mL). 3-Methylbut-2-enal (0.30 ml, 3.00 mmol) was added dropwise. The reaction was heated under reflux using a Dean-Stark trap under a nitrogen atmosphere for 18 h. After cooling, aqueous sodium bicarbonate (30 mL) was added. The aqueous layers were extracted with ethyl acetate (3 x 30 mL) and washed with brine (10 mL); the combined organic extracts were dried over anhydrous $MgSO_4$. Removal of the solvents under reduced pressure afforded a brown solid. The residue was purified using silica gel column chromatography (petroleum ether / ethyl acetate, 11:1), to give **13** as a yellow solid (0.31 g, 56%).

Method B: Diethyl acetal 17 (0.55 mL, 6.6 mmol) and methyl 1,4-dihydroxy-2-naphthoate **22** (1.43 g, 6.6 mmol) were dissolved in *p*-xylene (10 mL). The mixture was stirred under a nitrogen atmosphere for 20 min. 3-Picoline (0.16 mL, 1.65 mmol) was added, and the reaction heated under reflux for 24 h. During the reflux, the solution turned black. The mixture was allowed to cool to room temperature, dissolved in diethyl ether, and washed with water. The organic layer was separated and charcoal added. The mixture was filtered through a pad of celite to afford an oily residue. The residue was purified using silica gel column chromatography (petroleum ether / ethyl acetate, 13:1), to give **13** as a yellow solid (1.2 g, 56%).

Method C: Methyl 1,4-dihydroxy-2-naphthoate 22 (0.53 g, 2.43 mmol), cuprous chloride (0.24 g, 2.43 mmol) and fine copper powder (7.7 mg, 0.12 mmol) were combined under a nitrogen atmosphere. Anhydrous toluene and K_2CO_3 (0.67 g, 4.86 mmol) were added. The mixture was stirred vigorously, and 3-

chloro-3-methyl-but-1-yne (0.7 g, 7.38 mmol) added. The mixture was heated under reflux until the starting material was consumed by TLC (24 h), allowed to cool to room temperature, and water (10 ml) added. The mixture was extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (5 mL), and dried over anhydrous $MgSO_4$. The solvents were removed removed under reduced pressure to yield a yellow oil, purified by column chromatography on silica gel (petroleum ether / ethyl acetate, 9:1) to furnish **13** as a yellow powder (0.56 g, 81%), mp 128-130 °C [Lit.[10] mp 131-133 °C]; ν_{max} (neat)/cm^{-1} 3435, 2986, 2305, 1712, 1264, 896; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.45 (s, 6 H), 3.91 (s, 3 H), 5.59 (dd, 1 H, J = 10.0 Hz), 7.03 (dd, 1 H, J = 10.0 Hz), 7.41-7,45 (m, 1 H), 7.51-7,54 (m, 1 H), 8.09 (d, 1 H, J = 8.3 Hz), 8.29 (d, 1 H, J = 8.3 Hz), 12.10 (s, 1 H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 26.9, 52.3, 74.5, 102.2, 112.5, 121.9, 122.3, 124.0, 125.0, 126.3, 128.8, 129.0, 129.3, 141.5, 156.5, 172.5.

Methyl-2,2-dimethyl-6-(((trifluoromethyl)sulfonyl)oxy)-2H-benzo[h]chromene-5-carboxylate 27

Mollugin **13** (0.45 g, 1.58 mmol) was dissolved in anhydrous dichloromethane (20 mL) at 0 °C under an argon atmosphere. Triethylamine (0.44 ml, 3.16 mmol) was added. The resulting yellow solution was stirred for 20 min. Trifluoromethanesulfonic anhydride (0.8 ml, 4.74 mmol) was added, causing the mixture to turn brown. After the addition was completed, the mixture was stirred at room temperature for 24 h. Water (5 ml) was added slowly, and the organic layer was separated, washed with brine (7 ml), dried over anhydrous Na_2SO_4, and filtered. The solvents were removed under reduced pressure, and the residue purified by column chromatography on silica gel using petroleum ether / ethyl acetate (7:1) to give the title compound **27** as a colourless oil (0.59 g, 91%), ν_{max} (neat)/cm^{-1} 2976, 1724, 1149, 819, 751; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.55 (s, 6H), 3.99 (s, 3H), 5.75 (d, 1H, J = 10 Hz), 6.62 (d, 1H, J = 10 Hz), 7.57-7.64 (m, 2H), 8.01-8.04 (m, 1H), 8.23-8.27 (m, 1H); ^{19}F-NMR (471 MHz, $CDCl_3$): δ −73.34; ^{13}C-NMR (125 MHz, $CDCl_3$): δ 28.0, 53.0, 77.5, 113.1, 118.7 (q, J= 318 Hz), 119.6, 121.7, 122.0, 122.6, 126.71, 126.74, 128.0, 128.7, 130.8, 135.8, 148.8, 165.1; *m/z* found for $[M+NH_4]^+$: 434.0872; $[C_{18}H_{15}F_3O_6S+NH_4]^+$ requires 434.0872.

(±)-Methyl-2,2-dimethyl-6-(((trifluoromethyl)sulfonyl)oxy)-2H-benzo[h]chromene-5-carboxylate oxide 28

Na_2CO_3 (0.13 g, 1.24 mmol) was added to a solution of **27** (0.26 g, 0.62 mmol) in anhydrous dichloromethane at 0 °C. A solution of *m*-CPBA (0.1 g, 0.62 mmol) was added slowly at 0 °C. Complete conversion of alkene was observed by TLC after 2 h. The residue was purified using column chromatography on silica gel, eluting with petroleum ether / ethyl acetate (4:1), buffered with 3% Et_3N, to furnish the racemic epoxide **28** as a colourless solid (0.21 g, 81%), mp 175-176 ˚C; ν_{max} (neat)/cm^{-1} 2976, 1724, 1149, 819, 751; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.38 (s, 3H), 1.73 (s, 3H), 3.62 (d, 1H, J = 4.5 Hz), 4.02 (s, 3H), 4.44 (d, 1H, J = 4.5 Hz), 7.61 (ddd, 1 H, J = 8.1, 6.9, 1.1 Hz), 7.67 (ddd, 1 H, J = 8.4, 6.9, 1.2

Hz), 8.03-8.07 (m, 1 H), 8.23-8.27 (m, 1 H); ^{19}F-NMR (471 MHz, $CDCl_3$): δ −73.18; ^{13}C-NMR (125 MHz, $CDCl_3$): δ 23.2, 25.7, 47.8, 53.3, 63.0, 74.8, 111.3, 118.7 (q, J= 318 Hz), 121.9, 122.8, 124.7, 127.3, 127.4, 128.3, 129.3, 135.9, 149.3, 164.6; *m/z* found for $[M+H]^+$: 433.0558; $[C_{18}H_{15}F_3O_7S+H]^+$ requires 433.0563.

(3*S*,4*S*)-Methyl-2,2-dimethyl-6-(((trifluoromethyl)sulfonyl)oxy)-2H-benzo[h]chromene-5-carboxylate oxide 28

Water (0.2 mL), acetonitrile (2 mL) and Na_2CO_3 (0.19 g, 1.80 mmol) were combined and cooled in an ice-bath at 0 °C. The mixture was stirred for 2 min, and oxone® (0.44 g, 0.72 mmol) and catalyst **3** (0.25g, 10 mol%) were added. After 5 min, a solution of **27** (0.15 g, 0.36 mmol) in acetonitrile was added dropwise. The mixture was stirred at 0 °C until complete conversion of the alkene was observed by TLC (15 min). The reaction mixture was diluted with diethylether (5 mL), and the resulting suspension filtered through a mixed pad of celite® and Na_2SO_3. The solvents were removed under reduced pressure. Epoxide (−)-(3*S*,4*S*)-**28** was obtained by flash column chromatography on silica gel eluting with petroleum ether / ethyl acetate (7:1), containing 3% TEA. (0.14 g, 91%). Chiral HPLC trace (99.5:0.5, hexane:iso-propanol, flow rate; 0.5 mL/min); 22.22 min (14.75 %), 32.60 min (85.25 %).

(+)-(*3S,4R*)-Methyl-3,4-dihydroxy-2,2-dimethyl-6-(((trifluoromethyl)sulfonyl)oxy)-3,4-dihydro-2H-benzo[h]chromene-5-carboxylate 29

Compound (−)-(3*S*,4*S*)-**28** (83 mg, 0.91 mmol) was dissolved in acetone (1 mL) at room temperature. Dilute sulfuric acid (1M, 0.5 mL) was added dropwise, and the mixture stirred for 1 h. Progress of the reaction was monitored by TLC until the starting material had been completely consumed. The mixture was neutralized to pH 7 using $NaHCO_3$. Dichloromethane (10 mL) and water (5 mL) were added, the layers separated, and the aqueous layer was extracted with dichloromethane (10 mL). The combined organic extracts were washed with brine (20 mL), and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure, and the residue was purified using column chromatography on silica gel using petroleum ether / ethyl acetate (1:1), to afford (+)-(3*S*,4*R*)-**29** as a colourless solid (68 mg, 74%). mp 186-188 ˚C; ν_{max} (neat)/cm^{-1} 3283, 2850, 1765, 1230, 893; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 3H), 1.60 (s, 3H), 3.79 (d, 1H, J = 6.8 Hz), 3.98 (s, 3H), 4.89 (d, 1H, J = 6.8 Hz), 7.59-7.70 (m, 2 H), 8.01-8.05 (m, 1 H), 8.24-8.28 (m, 1 H); ^{19}F-NMR (471 MHz, $CDCl_3$): δ −73.22; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.4, 25.7, 53.4, 68.8, 75.4, 79.3, 114.4, 115.7 (q, J = 318 Hz), 122.0, 123.2, 123.9, 127.0, 128.4, 129.1, 136.4, 148.3, 166.9; *m/z* found for $[M+NH_4]^+$: 468.0925; $[C_{18}H_{17}F_3O_8S+NH_4]^+$ requires 468.0934.

(+)-(*3S,4R*)-3,4-Dihydroxy-2,2-dimethyl-6-(((trifluoromethyl)sulfonyl)oxy)-3,4-dihydro-2H-benzo[h]chromene-5-carboxylic acid 30

(+)-(3*S*,4*R*)-**29** (50 mg, 0.11 mmol) was dissolved in dimethoxyethane (5 mL). Cs_2CO_3 (43 mg, 0.13 mmol) was added and the mixture heated to 80 °C for 1 h. The mixture was allowed to cool, and water (10 mL) added. The mixture was extracted using ethyl acetate (3 x 5 mL), and the combined organic layers were dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure, and the residue purified using column chromatography on silica gel using petroleum ether / ethyl acetate (1:1) to afford (+)-(3*S*,4*R*)-**30** as a yellow foam (40 mg, 84%). ν_{max} (neat)/cm^{-1} 3280, 1763, 1230, 1141, 1042, 942, 896; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.59 (s, 3H), 1.71 (s, 3H), 3.76 (d, 1H, *J* = 9.2 Hz), 5.45 (d, 1H, *J* = 9.2 Hz), 7.43 (s, 1H), 7.71-7.76 (m, 2 H), 8.12-8.17 (m, 1 H), 8.19-8.24 (m, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.0, 27.3, 74.1, 77.7, 84.0, 116.1, 118.9 (q, *J* = 319 Hz), 119.1, 122.6, 123.1, 127.7, 128.7, 129.1, 129.2, 135.0, 146.6, 165.7; *m/z* found for $[M+NH_4]^+$: 454.0773; $[C_{17}H_{15}F_3O_8S+NH_4]^+$ requires 454.0778.

(+)-(*3S,4R*)-3,4-Dihydroxy-2,2-dimethyl-6-(((trifluoromethyl)sulfonyl)oxy)-3,4-dihydro-2H-benzo[h]chromene-5-carboxylic acid 31

Method A: (+)-(3*S*,4*R*)-**30** (40 mg, 0.09 mmol) was dissolved in methanol (5 mL). Cs_2CO_3 (74 mg, 0.23 mmol) was added, and the mixture stirred for 2 h. The solvents were removed under reduced pressure, and water (10 mL) and ethyl acetate (5 mL) added to the residue. The layers were separated, and the aqueous layer was extracted with ethyl acetate (5 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford (+)-(3*S*,4*R*)-**31** as a yellow foam (28 mg, quant.).

Method B: (+)-(3*S*,4*R*)-**29** (65 mg, 0.14 mmol) was dissolved in methanol (10 mL). Cs_2CO_3 (117 mg, 0.36 mmol) was added, and the mixture stirred for 2 h. The solvents were removed under reduced pressure, and water (10 mL) and ethyl acetate (5 mL) added to the residue. The layers were separated, and the aqueous layer was extracted with ethyl acetate (5 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford (+)-(3*S*,4*R*)-**31** as a yellow foam (43 mg, quant.). ν_{max} (neat)/cm^{-1} 3280, 1760, 1213, 1195, 1158, 1042, 948; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.54 (s, 3H), 1.64 (s, 3H), 3.72 (d, 1H, *J* = 9.2 Hz), 5.42 (d, 1H, *J* = 9.2 Hz), 7.43 (s, 1H), 7.56-7.61 (m, 1 H), 7.63-7.70 (m, 1 H), 8.08 (d, 1 H, *J* = 8.4 Hz), 8.33 (d, 1 H, *J* = 8.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.8, 27.4, 74.7, 79.3, 82.3, 104.0, 116.4, 122.0, 124.4, 126.6, 126.7, 128.6, 129.2, 139.9, 148.2, 171.3; *m/z* found for $[M+NH_4]^+$: 322.1281; $[C_{16}H_{16}O_6+NH_4]^+$ requires 322.1285.

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