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Synthesis of mollugin

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Abstract—The total synthesis of mollugin, a major constituent of rubiaceous herbs, using a straightforward synthetic approach starting from 1,4-naphthoquinone via a sequence of reactions, including selective prenylation, epoxidation, reduction of the quinone moiety, acid-catalysed ring expansion, bromination, dehydration and methoxycarbonylation is presented.

1. Introduction

The natural product mollugin **1** was isolated first from the rhizome of *Galium mollugo* (Rubiaceae) and identified as methyl 2,2-dimethyl-6-hydroxy-2*H*-naphtho[1,2-*b*]pyran-5-carboxylate.[1] Later, mollugin **1** together with several structurally related compounds such as 3-hydroxymollugin **2**, *cis*-3,4-dihydro-3,4-dihydroxymollugin **3a** and *trans*-3,4-dihydro-3,4-dihydroxymollugin **3b**[2] and also methyl 2,3-epoxy-3-prenyl-1,4-dioxonaphthalene-2-carboxylate **4**, a precursor in the biosynthesis of mollugin via the shikimate biosynthetic pathway,[3] have been reported as major constituents in many rubiaceous herbs including *Putoria calabrica*,[4] *Rubia cordifolia*,[5] *Rubia oncotricha*,[6] *Pentas longiflora*,[2b] *Rubia lanceolata*[7] and *Rubia tinctorum*.[8]

Mollugin **1** has been shown to possess antitumor activity,[5a] antimutagenic activity[8,9] and antiviral activity[10] against the hepatitis B virus (Fig. 1). Strong inhibition of arachidonic acid (AA)-induced and collagen-induced platelet aggregation has been shown for mollugin **1**.[11] As a result, many rubiaceous herbs are of great importance in the Chinese folk medicine for their blood circulation promoting, expectorant, cough-healing and antitumor properties.[5c,6,8] Particularly, in view of the antitumor activities of mollugin **1**, there is a renewed interest in the synthesis of 2*H*-naphtho[1,2-*b*]pyran-5-carboxylate derivatives related to mollugin **1**. Mollugin was synthesised previously according to the synthetic plan in Scheme 1. Condensation of diethyl 3,6-dihydroxyphthalate **5** and diethyl succinate **6** followed by acid-catalysed decarboxylation afforded 1,4-dihydroxynaphthalene-2-carboxylic acid **8**, which was further elaborated to mollugin **1** by reaction with 3-chloro-3-methyl-1-butyne in the presence of aluminium(III) chloride and subsequent esterification of the intermediate molluginic acid **9** with diazomethane.[12] This synthesis, although basically only four steps long, suffers from the disadvantage of a low overall yield, originating mainly from the variable yields of the double Claisen condensation (often as low as 5% and mounting to 48%, pointing to a tricky reaction).

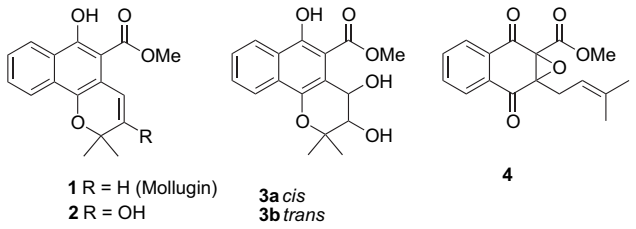

Figure 1.

Mollugin has also been synthesised starting from 1,4-dihydroxynaphthalene-2-carboxylic acid **8**. 3,4-Dihydromollugin **11** as a key step intermediate was obtained after electrophilic aromatic substitution of 2-methyl-3-buten-2-ol onto methyl 1,4-dihydroxynaphthalene-2-carboxylate **10**. Subsequent pyran ring closure in the presence of $BF_3 \cdot OEt_2$ resulted in 3,4-dihydromollugin **11** in 54% yield. Reflux of 3,4-dihydromollugin **11** in dioxane in the presence of DDQ yielded mollugin **1** in 72%.[13] Very recently, mollugin has been synthesised by treating methyl 3-(3-methyl-but-2-enyl)-1,4-dioxo-1,4-dihydro-naphthalene-2-carboxylate with triethylamine, which gave rise to an oxa-6π pericyclic reaction and subsequent formation of mollugin **1**.[14]

In this paper, the total synthesis of mollugin **1** is presented using a straightforward synthetic approach starting from

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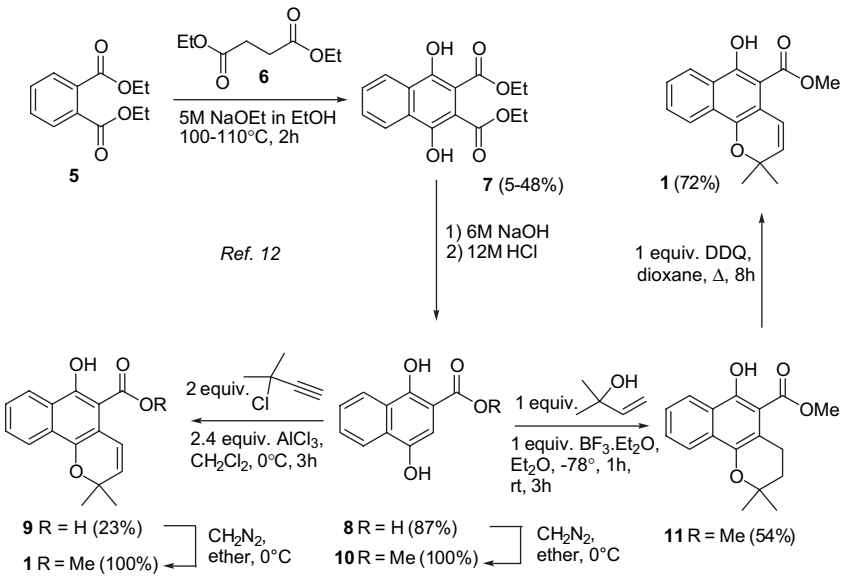


Scheme 1. Previous synthetic approach.

1,4-naphthoquinone **12** via reductive acid-catalysed intramolecular cycylisation of 2-prenyl-1,4-naphthoquinone **13** as a key step for the construction of the 2*H*-naphtho[1,2-*b*]-pyran skeleton.

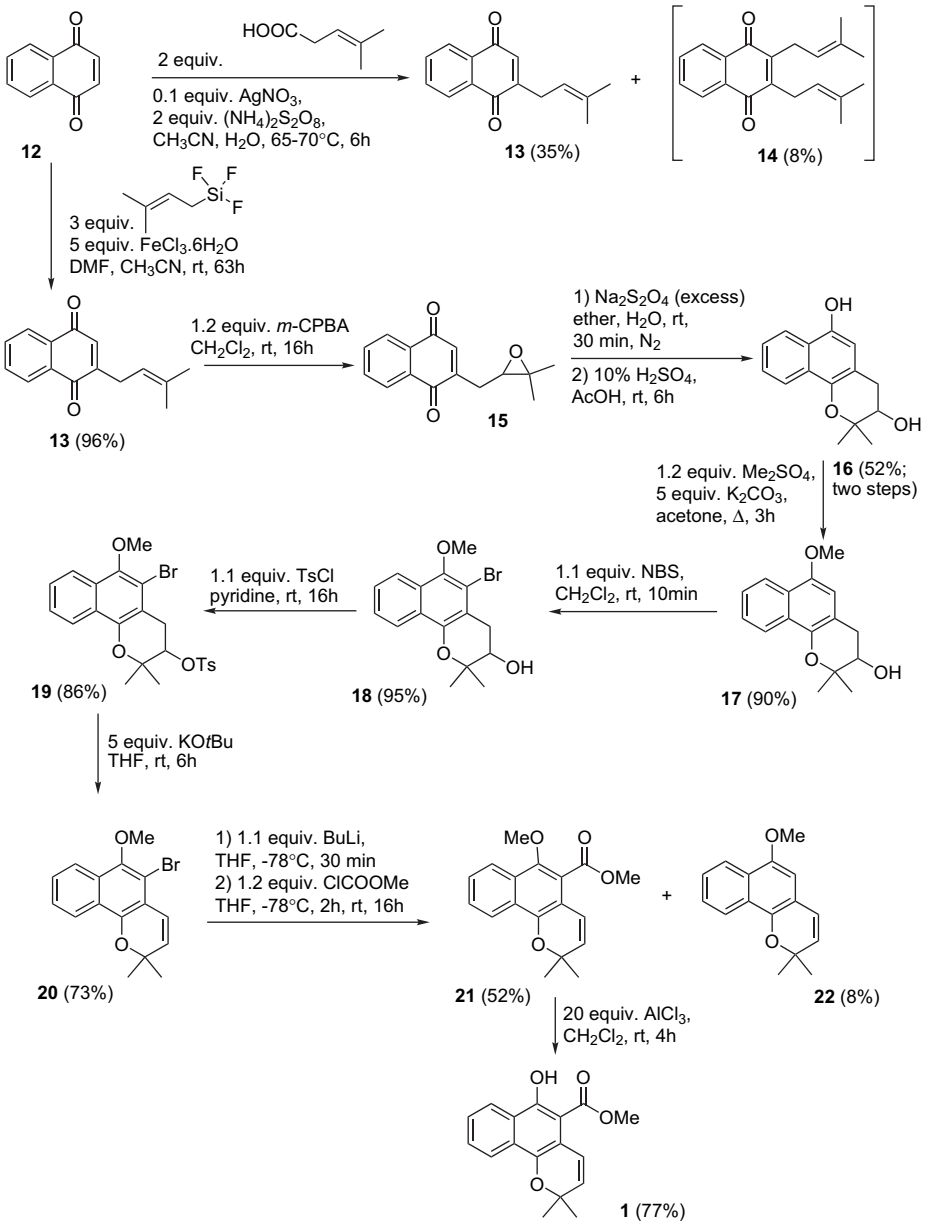
2. Results and discussion

The synthesis of mollugin **1** is presented in Scheme 2. 2-Prenyl-1,4-naphthoquinone **13**, the starting material for the synthesis of mollugin **1**, was reported previously to be available in a yield of 58% by radical prenylation of 1,4-naphthoquinone **12** with 4-methyl-3-pentenoic acid[15] in the presence of silver nitrate and ammonium persulfate.[16] In our hands, using these published reaction conditions, mixtures of starting material **12** together with the monoprenylated and diprenylated 1,4-naphthoquinones **13** and **14** were obtained in variable ratios depending on the applied reaction conditions. Optimisation of the reaction using an excess of allylating carboxylic acid, which was added in portions during the reaction, and purification of the resulting reaction mixtures via chromatography and subsequent recrystallisation afforded 2-prenyl-1,4-naphthoquinone **13** in a maximum yield of 35%. On the other hand, according to a recently published procedure for the monoallylation of quinones, reaction of 1,4-naphthoquinone **12** with prenyltrifluorosilane in the presence of $FeCl_3 \cdot 6H_2O$ as a Lewis acid, afforded the monoprenylated 1,4-naphthoquinone **13** in 98%.[17] Chemoselective epoxidation of the prenylic double bond with *m*-chloroperbenzoic acid in dichloromethane and subsequent reduction of the intermediate epoxide **15** using sodium dithionite in a biphase system with ether and water, followed by acid-catalysed intramolecular cyclisation of the intermediate hydroquinone epoxide with a solution of 10% sulfuric acid in acetic acid afforded 2*H*-naphtho[1,2-*b*]pyran-3,6-diol **16** in an overall yield of 52% (two steps). This diol **16**, which already reveals the basic skeleton of mollugin, was further elaborated via protection of the phenolic hydroxyl group as the methyl ether with dimethyl sulfate and potassium carbonate in refluxing acetone. Bromination of **17** in *ortho*-position of the methoxy substituent with *N*-bromosuccinimide in dichloromethane gave the brominated derivative **18** in 95% yield. However, the dehydration of alcohol **18**, with the objective of introducing a double bond between C(3) and C(4) in the pyran ring was quite troublesome. The alcoholic function of **18**, which is of a neopentylic nature could not be forced to dehydrate under acid-catalysed conditions using either *p*-toluenesulfonic acid or dry oxalic acid in refluxing anhydrous benzene or upon treatment with concentrated hydrochloric acid or sulfuric acid in acetic acid. The dehydration could, however, be accomplished via tosylation of alcohol **18** and subsequent treatment of the tosylate **19** with potassium *tert*-butoxide in dry THF to afford the dehydrated derivative **20** in 73% yield. For the introduction of the methoxycarbonyl group, compound **20** was treated with *n*-butyllithium in dry THF at −78 °C to afford, via bromine–lithium exchange and trapping of the intermediate lithium salt with methyl chloroformate, a mixture of the desired ester **21** in 52% yield, together with 8% of the debrominated naphthopyrane **22**.[18] Treatment of the ester **21** with excess aluminium(III) chloride finally gave mollugin **1** in 77% yield. Recrystallisation from methanol afforded mollugin **1** as yellow-green flakes with physical and spectral data identical to those of the natural product.[1] In this way, mollugin **1** was prepared in 10 steps in a total yield of 11% from 1,4-naphthoquinone **12**.

3. Experimental

3.1. General

^{1}H NMR (270 MHz) and ^{13}C NMR (68 MHz) peak assignments were performed with the aid of the DEPT technique, 2D COSY spectra and HETCOR spectra. Dry tetrahydrofuran (THF) was obtained by distillation from sodium. Diethylether was dried and distilled from sodium. Other solvents were used as received from the supplier.



Scheme 2.

3.1.1. 2-(3-Methyl-2-butenyl)-1,4-naphthoquinone (13). Method A:[15] a solution of 1,4-naphthoquinone (**12**) (0.09 mol, 15.94 g), 4-methyl-3-pentenoic acid[15] (0.09 mol, 12.83 g of technical grade, i.e., 80% pure) and silver nitrate (9 mmol, 2 g) in acetonitrile (100 ml) and demineralised water (200 ml) were heated at 65–70 °C, and to the stirred solution was added dropwise, over a period of 2 h, a solution of ammonium persulfate (0.09 mol, 20.52 g) in demineralised water (50 ml). Stirring was continued at the same temperature for 1 h. A second portion of 4-methyl-3-pentenoic acid (0.045 mol, 6.40 g of 80% technical grade) was added and to the resulting mixture, a second portion of ammonium persulfate (0.09 mol, 20.52 g) in demineralised water (50 ml) was added dropwise over a period of 2 h and the stirred mixture was kept at the same temperature for 1 h. Afterwards the reaction mixture was cooled to room temperature, poured in water (500 ml) and extracted with ethyl acetate. The combined organic extracts were washed with a saturated solution of sodium hydrogen carbonate, dried ($MgSO_4$) and evaporated in vacuo. Flash chromatography over a short column of silica gel using ethyl acetate/petroleum ether (1:9) as eluent gave first a residual amount of 1,4-naphthoquinone (**10**) followed by a mixture of 2-(3-methyl-2-butenyl)-1,4-naphthoquinone (**13**) and 2,3-bis(3-methyl-2-butenyl)-1,4-naphthoquinone (**14**), which eluted together as a second fraction from the column (R_f=0.35). The latter fraction was further purified by recrystallisation from petroleum ether to afford *2-(3-Methyl-2-butenyl)-1,4-naphthoquinone* **13** (7.12 g, 35%) as yellow needles, mp 58–58.5 °C (lit.[16] mp 60–61 °C). ^{1}H NMR ($CDCl_3$): δ 1.67 (3H, s, CH_3), 1.79 (3H, s, CH_3), 3.28 (2H, m, CH_2), 5.19–5.26 (1H, m, CH=CMe_2), 6.77 (1H, t, J=1.6 Hz, H-3), 7.69–7.76 (2H, m, H-6 and H-7), 8.04–8.12 (2H, m, H-5 and H-8). ^{13}C NMR ($CDCl_3$): δ 17.81 (CH_3), 25.79 (CH_3), 28.01 (CH_2), 118.29 (CH=Me_2), 126.02 and 126.50 (C-5 and C-8), 132.15 (=C_{quat}), 132.33

(=C_{quat}), 133.55 and 133.60 (C-6 and C-7), 134.61 (C-3), 136.33 (=C_{quat}), 150.76 (=C_{quat}), 185.23 (2×C=O). IR (NaCl): ν_{max} 1659 (C=O), 1619 (C=O), 1595 (C=C) cm^{-1}. MS *m/z* (%): 226 (M+, 24), 211 (46), 183 (9), 146 (62), 41 (100). Anal. Calcd for $C_{15}H_{14}O_2$: C 79.62%, H 6.24%. Found: C 79.48%, H 6.33%

3.1.2. 2,3-Bis(3-Methyl-but-2-enyl)-1,4-naphthoquinone (14). ^{1}H NMR ($CDCl_3$): δ 1.68 (6H, d, J=1.3 Hz, 2×CH_3), 1.79 (6H, s, 2×CH_3), 3.36 (4H, d, J=6.9 Hz, 2×CH_2), 5.01 (2H, t×q, J=6.9, 1.3 Hz, 2×=CH), 7.68 (2H, m, 2×CH_{ar}), 8.07 (2H, m, 2×CH_{ar}). ^{13}C NMR ($CDCl_3$): δ 18.18 (2×CH_3), 25.87 (2×CH_3), 2.14 (2×CH_2), 119.94 (2×CH), 126.30 (2×CH_{ar}), 132.29 (2×C_{quat}), 133.39 (2×CH_{ar}), 133.89 (2×C_{quat}), 146.04 (2×C_{quat}), 185.26 (2×C=O). IR (KBr): ν_{max} 1659 (C=O), 1614 (C=C), 1592 (C=C). MS (ES^+) *m/z* (%): 295 ($M+H^+$, 100). Anal. Calcd for $C_{20}H_{22}O_2$: C 81.60%, H 7.53%. Found: C 81.48%, H 7.61%

Method B:[17] to a mixture of 1,4-naphthoquinone (**12**) (0.63 mmol, 100 mg) and $FeCl_3 \cdot H_2O$ (3 mmol, 810 mg) in DMF (9 ml) and acetonitrile (3 ml), was added prenyltrifluorosilane (1.8 mmol, 300 mg) and the mixture was stirred overnight at room temperature. The reaction mixture was poured in water and extracted with ethyl acetate. The extract was washed with water and dried ($MgSO_4$). Evaporation of the solvent in vacuo and purification of the residue by means of flash chromatography on silica gel using ethyl acetate/petroleum ether (1/9) as eluent gave **13** (140 mg, 96%) as a pale yellow solid.

3.1.3. 2-(2,3-Epoxy-3-methylbutyl)-1,4-naphthoquinone (15). To a cooled (0 °C) solution of 2-prenyl-1,4-naphthoquinone (**13**) (1 mmol, 0.23 g) in dichloromethane (10 ml) was added *m*-chloroperbenzoic acid (1.2 mmol, 0.28 g) and the mixture was stirred for 16 h at room temperature. The solvent was evaporated in vacuo and the residual white-yellow solid was dissolved in ether, washed with 2 M sodium hydroxide and then with water, dried ($MgSO_4$) and evaporated in vacuo to afford the crude epoxide **15** (170 mg, 70%, purity>95%) as a yellow oil, which was used as such in the next step. ^{1}H NMR ($CDCl_3$): δ 1.37 (6H, s, 2×CH_3), 2.63–2.73 (1H, m, C$H_a$$H_b$), 2.91–3.04 (2H, m, $CH_a$$H_b$ and CH–O), 6.93 (1H, s, H-3), 7.70–7.77 (2H, m, H-6 and H-7), 8.02–8.11 (2H, m, H-5 and H-8). ^{13}C NMR ($CDCl_3$): δ 18.83, 24.65, 29.33, 58.65, 61.45, 126.11, 126.56, 132.00, 133.69, 133.82, 135.85, 147.90, 184.62, 184.83. IR (NaCl): ν_{max} 1660 (C=O), 1623 (C=O). MS *m/z* (%): 242 (M+, 2), 184 (100), 156 (50).

3.1.4. 2,2-Dimethyl-3,4-dihydro-2*H*-naphtho[1,2-*b*]-pyran-3,6-diol (16). To a cooled (0 °C) solution of 2-prenyl-1,4-naphthoquinone (**13**) (10 mmol, 2.3 g) in dichloromethane (100 ml) was added *m*-chloroperbenzoic acid (12 mmol, 2,8 g) and the mixture was stirred for 16 h at room temperature. The solvent was evaporated in vacuo and the residual solid was dissolved in ether (100 ml), washed with 2 M sodium hydroxide and the ether solution, under a nitrogen atmosphere, was vigourously stirred for 30 min with a 20% solution of sodium dithionite in water (100 ml), while the yellow colour of the solution slowly became pale. The ether phase was separated by decantation and evaporated in vacuo. The residue was dissolved in acetic acid (100 ml) and the stirred solution was mixed with a 10% solution of sulfuric acid in water (50 ml), while stirring was continued for 6 h under a nitrogen atmosphere. The reaction mixture was poured in water and extracted with dichloromethane. The combined organic extracts were washed with a saturated solution of sodium hydrogen carbonate and then with brine, dried ($MgSO_4$) and concentrated in vacuo to a residual volume of 30 ml. The solution was kept overnight at −20 °C causing product **16** to precipitate as small white transparent cubes (1.26 g, 52%), mp 173.5–174.8 °C. ^{1}H NMR (acetone-d_6): δ 1.34 (3H, s, CH_3), 1.49 (3H, CH_3), 2.79 (1H, dd, J_{AB}=16.7 Hz, J_d=7.6 Hz, C$H_a$$H_b$), 3.06 (1H, dd, J_{AB}=16.7 Hz, J_d=5.6 Hz, $CH_a$$H_b$), 3.88–3.95 (1H, m, CH–OH), 4.26 (1H, d, J=5.6 Hz, CH–OH), 6.64 (1H, s, H-5), 7.43–7.51 (2H, m, H-8 and H-9), 8.12–8.19 (2H, m, H-7 and H-10), 8.43 (1H, s, phenolic-OH). ^{13}C NMR (acetone-d_6): δ 20.02 (CH_3), 26.19 (CH_3), 32.51 (CH_2), 70.22 (CHOH), 77.63 (CMe_2), 10.61 (C-5), 114.77 (=C_{quat}), 122.08 and 122.75 (C-7 and C-10), 125.08 and 125.95 (C-8 and C-9), 125.62 (=C_{quat}), 126.92 (=C_{quat}), 141.23 (=C–O), 146.97 (=C–O). IR (KBr): ν_{max} 3511 (OH), 3236 (OH), 1639, 1600, 1107, 1335, 1272, 1140, 1052, 766 cm^{-1}. MS *m/z* (%): 244 (M+, 63), 211 (49), 173 (81), 43 (100). Anal. Calcd for $C_{15}H_{16}O_3$: C 73.75%, H 6.60%. Found: C 73.42%, H 6.66%.

3.1.5. Synthesis of 6-methoxy-2,2-dimethyl-3,4-dihydro-2*H*-naphtho[1,2-*b*]pyran-3-ol (17). A mixture of 2,2-dimethyl-3,4-dihydro-2*H*-naphtho[1,2-*b*]pyran-3,6-diol (**16**) (4.5 mmol, 1.1 g), dimethyl sulfate (5.4 mmol, 0.68 g) and potassium carbonate (22.5 mmol, 3.1 g) in acetone (50 ml) was heated under reflux for 3 h, cooled to room temperature, filtered and evaporated in vacuo. Flash chromatography on silica gel using ethyl acetate/petroleum ether (1:4) gave pure **17** (1.05 g, 90%). Recrystallisation from ethyl acetate/petroleum ether (1:9) afforded **17** as white cubes, mp 122.3–122.8 °C. ^{1}H NMR ($CDCl_3$): δ 1.36 (3H, s, CH_3), 1.46 (3H, s, CH_3), 1.92 (1H, br s, OH), 2.85 (1H, dd, J_{AB}=17.2 Hz, J=4.6 Hz, C$H_a$$H_b$), 3.16 (1H, dd, J_{AB}=17.2 Hz, J=4.8 Hz, $CH_a$$H_b$), 3.85–3.89 (1H, m, CH–OH), 3.94 (3H, s, MeO), 6.45 (1H, s, H-5), 7.44–7.49 (2H, m, H-8 and H-9), 8.14–8.19 (2H, m, H-7 and H-10). ^{13}C NMR ($CDCl_3$): δ 22.32 (CH_3), 24.47 (CH_3), 32.15 (CH_2), 55.67 (MeO), 69.83 (CH–OH), 76.71 (CMe_2), 105.21 (C-5), 111.52 (=C_{quat}), 121.52 and 121.69 (C-7 and C-10), 125.21 and 125.87 (C-8 and C-9), 125.42 (=C_{quat}), 126.18 (=C_{quat}), 141.26 (=C–O), 149.27 (=C–O). IR (KBr): ν_{max} 3313 (OH), 1631, 1598, 1458, 1387, 1273, 769 cm^{-1}. MS *m/z* (%): 258 (M+, 6), 200 (19), 105 (100). Anal. Calcd for $C_{16}H_{18}O_3$: C 74.39%, H 7.02%. Found: C 74.28%, H 7.13%.

3.1.6. 5-Bromo-6-methoxy-2,2-dimethyl-2,3-dihydro-2*H*-naphtho[1,2-*b*]-pyran-3-ol (18). 6-Methoxy-2,2-dimethyl-3,4-dihydro-2*H*-naphtho[1,2-*b*]pyran-3-ol (**17**) (2 mmol, 0.51 g) was dissolved in dichloromethane (50 ml, dichloromethane was washed twice with concentrated sulfuric acid and filtered over sodium carbonate before use, to eliminate all traces of ethanol) and to this stirred solution, *N*-bromosuccinimide (2.2 mmol, 0.39 g) was added portionwise over a period of 10 min. The organic solution was washed successively with water, 5% solution of sodium hydrogen sulfite, saturated solution of sodium hydrogen carbonate

and finally with brine, dried ($MgSO_4$) and evaporated in vacuo. Flash chromatography on silica gel using ethyl acetate/petroleum ether (1:4) afforded **18** (0.64 g, 95%) as a brown oil, which slowly solidified, mp 87–88 °C. ^{1}H NMR ($CDCl_3$): δ 1.36 (3H, s, CH_3), 1.43 (3H, s, CH_3), 2.09 (1H, br s, OH), 2.89 (1H, dd, J_{AB}=17.5 Hz, J=5.0 Hz, CH_aH$_b$), 3.10 (1H, dd, J_{AB}=17.5 Hz, J=5.3 Hz, CH$_a$$H_b$), 3.88 (1H, m, CH–OH), 3.93 (3H, s, MeO), 7.44–7.52 (2H, m, H-8 and H-9), 8.00–8.03 and 8.18–8.21 (each 1H, each m, H-7 and H-10). ^{13}C NMR ($CDCl_3$): δ 21.92 (CH_3), 24.40 (CH_3), 33.35 (CH_2), 61.28 (MeO), 77.10 (CMe_2), 112.88 (=C_{quat}), 116.12 (=C_{quat}), 121.74 and 122.30 (C-7 and C-10), 125.32 (=C_{quat}), 125.82 and 126.72 (C-8 and C-9), 127.62 (=C_{quat}), 145.08 (=C–O), 146.83 (=C–O). IR (KBr): ν_{max} 3313 (OH), 1574, 1450, 1366, 1350, 1142, 1082, 991, 767 cm^{-1}. MS *m/z* (%): 336/8 (M+, 40), 303/5 (17), 265/7 (28), 264/6 (33), 49 (100). Anal. Calcd for $C_{16}H_{17}BrO_3$: C 56.99%, H 5.08%. Found: C 57.28%, H 5.01%.

3.1.7. 5-Bromo-6-methoxy-2,2-dimethyl-3-tosyloxy-3,4-dihydro-2*H*-naphtho[1,2-*b*]pyran (19). A solution of 5-bromo-6-methoxy-2,2-dimethyl-2,3-dihydro-2*H*-naphtho-[1,2-*b*]-pyran-3-ol (**18**) (1.9 mmol, 0.64 g), and *p*-toluenesulfonyl chloride (2.1 mmol, 0.40 g) in pyridine (5 ml) was stirred for 16 h in a flask fitted with a calcium chloride tube. The solution was diluted with ether (100 ml), washed twice with 2 M HCl and then with a saturated solution of sodium hydrogen carbonate and then with brine, dried ($MgSO_4$) and evaporated in vacuo to afford **17** (0.80 g, 86%, purity>95%) as a brown oil, which was used without purification in the next step. An analytical sample of compound **19** was obtained using chromatography on silica gel with ethyl acetate/petroleum ether (1:4) as eluent to afford **19** as a light brown oil, which slowly solidified, mp 124 °C. ^{1}H NMR ($CDCl_3$): δ 1.32 (3H, s, CH_3), 1.36 (3H, s, CH_3), 2.45 (3H, s, CH_3-Ar), 2.87 (1H, dd, J_{AB}=17.8 Hz, J_d=6,1 Hz, CH_aH$_b$), 3.15 (1H, dd, J_{AB}=17.8 Hz, J_d=5.3 Hz, CH$_a$$H_b$), 3.92 (3H, s, MeO), 4.75 (1H, t, $J\approx$6 Hz, CH-OTs), 7.34 (2H, d, J=7.9 Hz, 2×=CH), 7.44–7.54 (2H, m, H-8 and H-9), 7.80 (2H, d, J=8.3 Hz, 2×=CH), 7.99–8.15 (2H, m, H-7 and H-10). ^{13}C NMR ($CDCl_3$): δ 21.67 (CH_3), 21.79 (CH_3), 24.67 (CH_3), 30.73 (CH_2), 61.28 (MeO), 75.27 (CH-OTs), 78.87 (CMe_2), 111.62 (=C_{quat}), 115.15 (C_{quat}), 121.76 and 122.23 (C-7 and C-10), 125.12 (=C_{quat}), 125.96 and 126.92 (C-8 and C-9), 127.71 (=C_{quat}), 127.85 (2×=CH), 129.94 (2×CH), 133.78 (=C_{quat}), 144.74 (=C_{quat}), 145.10 (=C–O), 147.01 (=C–O). IR (KBr): ν_{max} 1571, 1450, 1350, 1189, 906, 863, 765 cm^{-1}. MS *m/z* (%): 490/2 (M+, 40), 336/8 (12), 318/20 (23), 303/5 (62), 264/6 (30), 224 (30), 91 (53), 43 (100). Anal. Calcd for $C_{23}H_{23}BrO_5S$: C 56.22%, H 4.72%. Found: C 56.11%, H 4.91%.

3.1.8. 5-Bromo-6-methoxy-2,2-dimethyl-2*H*-naphtho-[1,2-*b*]pyran (20). To a cooled (0 °C) solution of 5-bromo-6-methoxy-2,2-dimethyl-3-tosyloxy-3,4-dihydro-2*H*-naphtho-[1,2-*b*]pyran (**19**) (1.3 mmol, 0.66 g) in dry tetrahydrofuran (20 ml) was added potassium *tert*-butoxide (6.5 mmol, 0.73 g), and the reaction mixture was kept at room temperature for 6 h in a flask fitted with a calcium chloride tube. The reaction mixture was quenched by the addition of 1 M HCl (100 ml) and the aqueous solution was extracted with ether. The combined organic extracts were washed with a saturated solution of sodium hydrogen carbonate, dried ($MgSO_4$) and evaporated in vacuo. Flash chromatography on silica gel using ethyl acetate/petroleum ether (5:95) afforded **20** (0.32 g, 73%) as a white solid. Recrystallisation from methanol gave **20** as light yellow needles, mp 59.5–60 °C. ^{1}H NMR ($CDCl_3$): δ 1.51 (6H, s, 2×CH_3), 3.95 (3H, s, MeO), 5.72 (1H, d, J=9.9 Hz, H-3), 6.81 (1H, d, J=9.9 Hz, H-4), 7.44–7.52 (2H, m, H-8 and H-9), 7.99–8.03 and 8.16–8.19 (each 1H, each m, H-7 and H-10). ^{13}C NMR ($CDCl_3$): δ 27.48 (2×CH_3), 61.28 (MeO), 76.48, (CMe_2), 112.65 (=C_{quat}), 115.18 (=C_{quat}), 121.81 and 122.51 (C-7 and C-10), 121.90 (C-4), 125.08 (=C_{quat}), 125.84 and 127.02 (C-8 and C-9), 128.30 (=C_{quat}), 130.31 (C-3), 145.60 (=C–O), 146.72 (=C–O). IR (KBr): ν_{max} 1632, 1556, 1355, 1270, 1163, 1129, 1081, 766 cm^{-1}. MS *m/z* (%): 318/20 (M+, 27), 303/5 (100), 288/90 (19), 225 (28). Anal. Calcd for $C_{16}H_{15}BrO_2$: C 60.21%, H 4.74%. Found: C 60.09%, H 4.91%.

3.1.9. Synthesis of 6-methoxy-2,2-dimethyl-2*H*-naphtho-[1,2-*b*]pyran (22) and methyl 6-methoxy-2,2-dimethyl-2*H*-naphtho[1,2-*b*]pyran-5-carboxylate (21). A solution of 5-bromo-6-methoxy-2,2-dimethyl-2*H*-naphtho[1,2-*b*]-pyran (**20**) (0.53 mmol, 170 mg) in dry tetrahydrofuran (5 ml) was cooled to −78 °C and to the stirred solution, in a nitrogen atmosphere, was added dropwise a solution of *n*-butyllithium (2.5 M) in hexane (0.58 mmol, 0.23 ml). After 30 min at this temperature, a solution of methyl chloroformate (0.64 mmol, 60 mg) in dry THF (1 ml) was added and the reaction mixture was kept for an additional 2 h at −78 °C. Afterwards, the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was poured in 1 M HCl and extracted with ether. The combined organic phases were washed with brine, dried ($MgSO_4$) and evaporated in vacuo. Flash chromatography on silica gel using ethyl acetate/petroleum ether (5:95) as eluent afforded first 6-methoxy-2,2-dimethyl-2*H*-naphtho-[1,2-*b*]pyran (**22**)[18] (R_f=0.29, 10 mg, 8%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.49 (6H, s, 2×CH_3), 3.94 (3H, s, MeO), 5.64 (1H, d, J=9.5 Hz, H-3), 6.39 (1H, d, J=9.5 Hz, H-4), 6.50 (1H, s, H-5), 7.42–7.49 (2H, m, H-8 and H-9), 8.13–8.16 (2H, m, H-7 and H-10). MS *m/z* (%): 240 (M+, 25), 225 (100), 210 (10). Using the same solvent combination, methyl 6-methoxy-2,2-dimethyl-2*H*-naphtho-[1,2-*b*]pyran-5-carboxylate (**21**) (R_f=0.13, 90 mg, 57%) was collected as a second fraction and appeared as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.51 (6H, s, 2×CH_3), 3.96 (3H, s, MeO), 3.99 (3H, s, MeO), 5.68 (1H, d, J=9.9 Hz, H-3), 6.42 (1H, d, J=9.9 Hz, H-4), 7.47–7.53 (2H, m, H-8 and H-9), 8.01–8.06 and 8.18–8.22 (each 1H, each m, H-7 and H-10). ^{13}C NMR ($CDCl_3$): δ 27.65 (2×CH_3), 52.40 (MeO), 63.49 (MeO), 76.44 (CMe_2), 112.36 (=C_{quat}), 119.80 (=CH), 120.52 (=C_{quat}), 122.46 (=CH), 122.59 (=CH), 126.75 (=CH), 126.83 (=CH), 127.78 (=C_{quat}), 130.24 (=CH), 144.89 (=C–O), 147.53 (=C–O), 167.78 (C=O). IR (NaCl): ν_{max} 1731 (C=O) cm^{-1}. MS *m/z* (%): 298 (M+, 7), 283 (13), 143 (88), 84 (92), 49 (100). Anal. Calcd for $C_{18}H_{18}O_4$: C 72.47%, H 6.08%. Found: C 72.22%, H 5.84%.

3.1.10. Mollugin (1). To a cooled (0 °C) solution of methyl 6-methoxy-2,2-dimethyl-2*H*-naphtho[1,2-*b*]pyran-5-carboxylate

(**21**) (0.69 mmol, 220 mg) in dry dichloromethane (20 ml) was added aluminium(III) chloride (13.8 mmol, 1.84 g) and the reaction mixture was stirred for 4 h in a flask fitted with a calcium chloride tube. The reaction mixture was quenched by the addition of water (50 ml) (cooling!) and the aqueous solution was further diluted with 1 M HCl (50 ml), extracted with dichloromethane, dried ($MgSO_4$) and evaporated in vacuo. Flash chromatography on silica gel using ethyl acetate/petroleum ether (5:95) afforded mollugin (**1**) (150 mg, 77%) as a yellow powder. Recrystallisation from methanol gave mollugin (**1**) as yellow-green flakes, mp 129.5–131 °C (lit.[1] mp 128.8 °C). The spectral data of mollugin (**1**) were in complete accordance with those reported for the natural mollugin. ^{1}H NMR ($CDCl_3$): δ 1.48 (6H, s, 2×CH_3), 4.00 (3H, s, MeO), 5.66 (1H, d, J=9.9 Hz, H-3), 7.09 (1H, d, J=9.9 Hz, H-4), 7.46–7.53 and 7.57–7.63 (each 1H, each m, H-8 and H-9), 8.15–8.18 and 8.34–8.38 (each 1H, each m, H-7 and H-10), 12.17 (1H, s, OH), ^{13}C NMR ($CDCl_3$): δ 26.83 (2×CH_3), 52.29 (MeO), 74.61 (CMe_2), 102.19 (=C_{quat}), 112.54 (=C_{quat}), 121.90 (=CH), 122.30 (=CH), 124.06 (=CH), 125.05 (=C_{quat}), 126.27 (=CH), 128.98 (=C_{quat}), 129.32 (=CH), 141.54 (=C–O), 156.48 (=C–O), 172.49 (C=O), IR (KBr): ν_{max} 1651 (C=O), 1449, 1360, 1342, 1238, 769 cm^{-1}. MS m/z (%): 284 (M+, 23), 252 (32), 237 (85), 84 (69), 49 (100). Anal. Calcd for $C_{17}H_{16}O_4$: C 71.82%, H 5.67%. Found: C 71.63%, H 5.77%.

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References and notes

1. Schildknecht, H.; Straub, F.; Scheidel, V. *Liebigs Ann. Chem.* **1976**, 1295–1306.
2. (a) Hari, L.; De Buyck, L. F.; De Pooter, H. L. *Phytochemistry* **1991**, *30*, 1726–1727; (b) De Kimpe, N.; Van Puyvelde, L.; Schripsema, J.; Erkelens, C.; Verpoorte, R. *Magn. Reson. Chem.* **1993**, *31*, 329–330; (c) El-Hady, S.; Bukuru, J.; Kesteleyn, B.; Van Puyvelde, L.; Nguyen Van, T.; De Kimpe, N. *J. Nat. Prod.* **2002**, *65*, 1377–1379.
3. Inoue, K.; Shiobara, Y.; Nayenshiro, H.; Inouye, H.; Wilson, G.; Zenk, M. H. *Phytochemistry* **1984**, *73*, 307–311.
4. Gonzalez, A. G.; Barroso, J. T.; Cardona, R. J.; Medina, J. M.; Rodriguez Luis, F. *An. Quim.* **1977**, *73*, 538–545.
5. (a) Itokawa, H.; Mihara, K.; Takeya, K. *Chem. Pharm. Bull.* **1983**, *31*, 2353–2358; (b) Itokawa, H.; Qiao, Y.; Takeya, K. *Phytochemistry* **1989**, *28*, 3465–3568; (c) Koyama, J.; Ogura, T.; Tagahara, K.; Konoshima, T.; Kozuka, M. *Phytochemistry* **1992**, *31*, 2907–2908; (d) Itokawa, H.; Ibraheim, Z. Z.; Qiao, Y.; Takeya, K. *Chem. Pharm. Bull.* **1993**, *41*, 1869–1872.
6. Itokawa, H.; Qiao, Y.; Takeya, K. *Phytochemistry* **1991**, *30*, 637–640.
7. Kuo, S.-C.; Chen, P.-R.; Lee, S.-W.; Chen, Z.-T. *J. Chin. Chem. Soc.* **1995**, *42*, 869–871.
8. Kawasaki, Y.; Goda, Y.; Yoshihira, K. *Chem. Pharm. Bull.* **1992**, *40*, 1504–1509.
9. Marec, F.; Kollarova, I.; Jegorov, A. *Planta Med.* **2001**, *67*, 127–131.
10. Ho, L.-K.; Don, M.-J.; Chen, H.-C.; Yeh, S.-F.; Chen, J.-M. *J. Nat. Prod.* **1996**, *59*, 330–333.
11. Chung, M. I.; Jou, S. J.; Cheng, H. C.; Lin, C. N.; Ko, F. N.; Teng, C. M. *J. Nat. Prod.* **1994**, *57*, 313–316.
12. Schildknecht, H.; Straub, F. *Liebigs Ann. Chem.* **1976**, 1307–1312.
13. Ho, L.-K.; Yu, H.-J.; Ho, C.-T.; Don, M.-J. *J. Chin. Chem. Soc.* **2001**, *48*, 77–79.
14. Lumb, J. P.; Trauner, D. *Org. Lett.* **2005**, *7*, 5865–5868.
15. Ragoussis, N. *Tetrahedron Lett.* **1987**, *28*, 93–96.
16. Jacobsen, N.; Torssell, K. *Acta Chem. Scand.* **1973**, *27*, 3211–3216.
17. (a) Hagiwara, E.; Hatanaka, Y.; Gohda, K.-L.; Hiyama, T. *Tetrahedron Lett.* **1995**, *36*, 2773–2776.
18. (a) See Ref. 4; (b) Costa, S. M. O.; Lemis, T. L. G.; Pessoa, O. D. L.; Pessoa, C.; Montenegro, R. C.; Braz-Filho, R. *J. Nat. Prod.* **2001**, *64*, 792–795.