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Synthesis of the Natural Products 3-Hydroxymollugin and 3-Methoxymollugin

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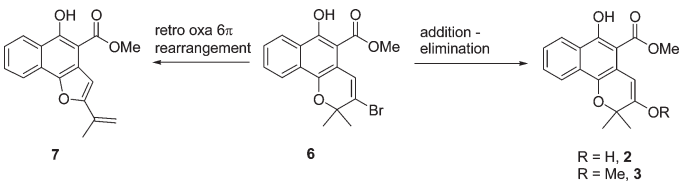

3-Hydroxymollugin **2** and 3-methoxymollugin **3** are cytotoxic compounds isolated as minor compounds from *Pentas longiflora* and *Rubia cordifolia*. Syntheses of 3-hydroxymollugin **2** and 3-methoxymollugin **3** were developed starting from easily available 3-bromomollugin **6**. Surprisingly, it was found that the reaction of 3-bromomollugin **6** with sodium methoxide in methanol resulted in the formation of 3-methoxymollugin **3** and the ring-contracted methyl isopropenylfuromollugin **7**. A mechanism for this ring contraction is proposed on the basis of a pericyclic retro oxa-6π ring-opening reaction. A second synthesis of 3-hydroxymollugin **2** was based on epoxidation of methyl 3-(3-methylbut-2-enyl)-1,4-naphthoquinone-2-carboxylate **17** and subsequent reduction of the quinone moiety, ring transformation, and DDQ oxidation. The latter oxidation process results in 3-hydroxymollugin **2** along with the rearranged furomollugin **4**, which is a ring-contracted analogue of the natural product mollugin **1**.

Introduction

Mollugin **1** is a naturally occurring benzochromene reputed for its anticarcinogenic[1,2] and antiviral activities.[3−5] This natural product **1** is well investigated, and several synthetic procedures were described in the last years.[2−8] Interesting analogues of mollugin **1** were also identified from plant sources, but in contrast to mollugin **1** itself, they were not synthesized hitherto (Figure 1). 3-Hydroxymollugin **2**, 3-methoxymollugin **3**, and furomollugin **4** are cytotoxic compounds which have been isolated from *Rubia cordifolia*[9] and *Pentas longiflora*.[10] In this paper, the first synthesis of 3-hydroxymollugin **2** and 3-methoxymollugin **3** along with a novel synthetic route toward furomollugin **7** are reported.

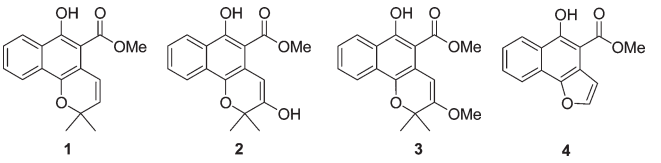

FIGURE 1. Compounds isolated from *R. cordifolia* and *P. longiflora*.

Results and Discussion

In a previous report, it was found that 3-bromomollugin **6** can easily be formed starting from 3,4-dihydromollugin **5** by

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SCHEME 1

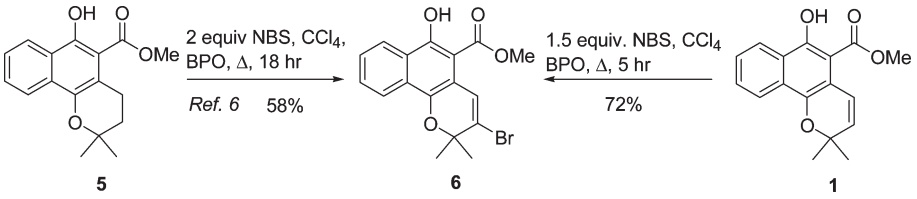
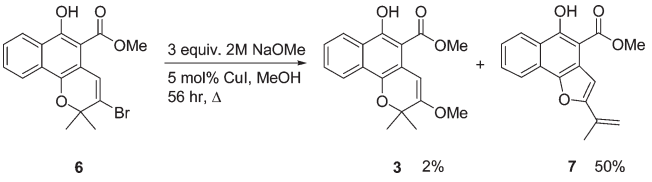


TABLE 1. Reaction Conditions for the Reactions with 3-Bromomollugin 6 Leading to Compounds 2, 3, and 7[a]

entry	reaction conditions	6[b] (%)	7 (%)	3 (%)	2 (%)
1	3 equiv of 2 M NaOMe, MeOH/DMF (1/1), 0.05 equiv of CuI, 56 h, Δ	0	50	2	0
2	4 equiv of 2 M NaOMe, MeOH/ DMF (1/1), 0.05 equiv of CuI, 56 h, Δ	0	40	5	0
3	3 equiv of 2 M NaOMe, MeOH/ DMF (1/1), 56 h, Δ	30	10	20	0
4	4 equiv of 4 M NaOMe, MeOH/DMF (1/1), 2 h, Δ	50	35	5	0
5	5 equiv of K_2CO_3, DMF, 24 h, rt	18	0	0	35
6	5 equiv of K_2CO_3, DMF, 4 h, 80 °C	25	10	0	42
7	5 equiv of K_2CO_3, DMF, 0.5% H_2O, 4 h, 80 °C	2	57	0	38
8	5 equiv of K_2CO_3, DMF, 5% H_2O, 4 h, 80 °C	2	49	0	47
9	5 equiv of K_2CO_3, MeOH/DMF (1/1), 24 h, rt	80	0	10	5
10	8 equiv of 4 M NaOMe, MeOH, 24 h, Δ	52	6	42	0
11	16 equiv of 4 M NaOMe, MeOH, 24 h, Δ	35	6	25	0
12	microwave, MeOH/DMF (1/1), 0.5 h	0	10	2	0

[a]A complete overview of all attempted reactions can be found in the Supporting Information. [b]Yields determined by ^{1}H NMR of the crude reaction mixtures.

SCHEME 2



reaction with 2 equiv of *N*-bromosuccinimide in CCl_4 in the presence of benzoyl peroxide (Scheme 1).[7] In the present paper, the synthesis of 3-bromomollugin **6** is improved from 58% to 72% by direct bromination of mollugin **1**, using *N*-bromosuccinimide in the presence of benzoyl peroxide (Scheme 1).

It was thought that the reaction of 3-bromomollugin **6** with sodium methoxide would lead to the target 3-methoxymollugin **3** via an addition−elimination reaction. Therefore, 3-bromomollugin **6** was reacted with 3 equiv of 2 M sodium methoxide and 0.05 equiv of copper(I) iodide in methanol[11] (Scheme 2, Table 1, entry 1). However, after 56 h of reflux only 2% of 3-methoxymollugin **3** was obtained together with 50% of a new compound, which was identified as methyl 5-hydroxy-2-isopropenylnaphtho[1,2-*b*]furan-4-carboxylate or 2-isopropenylfuromollugin **7**.

This rearranged compound **7** is an interesting compound as it can be viewed as a structural unit of the natural products rubicordifolin **8**, rubioncolin A **9**, and rubioncolin B **10** (Figure 2).[12] This statement, together with the finding that these compounds are often isolated together with mollugin **1** from Rubiaceae, led to the conclusion that these compounds **8**, **9**, and **10** might be biochemically related to mollugin **1**.

Several reaction conditions were verified in order to improve the yields of the reaction of 3-bromomollugin **6** with sodium methoxide (Table 1). Increasing the number of

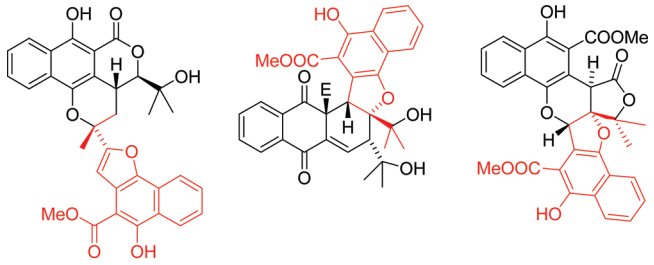


FIGURE 2. Natural products isolated from Rubiaceae.

equivalents of NaOMe resulted in a slight increase in the yield of 3-methoxymollugin **3** (entry 2). Surprisingly, in the absence of the catalyst copper(I) iodide, bromomollugin **6** and 3 equiv of 2 M sodium methoxide in methanol for 56 h under reflux resulted in an improvement in the yield of 3-methoxymollugin (20%) and with a decrease in the amount of isopropenylfuromollugin **7** (entry 3). Shifting the solvent to DMF and reacting 3-bromomollugin **6** with 4 M NaOMe in methanol (ratio MeOH/DMF 1/1) at 80 °C for 2 h afforded 35% isopropenylfuromollugin **7** along with 5% 3-methoxymollugin **3** (entry 4). Performing the reaction under similar basic conditions at room temperature gave no reaction, and only starting material was recovered. In order to investigate the mechanism of the formation of isopropenylfuromollugin **7**, which was thought to proceed via a thermochemical pericyclic ring-opening reaction, 3-bromomollugin **6** was heated in DMF. After heating at 100 °C for 16 h only starting material was recovered. However, this result completely changed upon addition of base. After reaction of 3-bromomollugin **6** with 5 equiv of potassium carbonate in DMF for 24 h at room temperature, the natural product 3-hydroxymollugin **2** was isolated in 35% yield (entry 5). The same reaction, when heated at 80 °C for 4 h, resulted in the formation of 3-hydroxymollugin **2** in 42% yield along with 5% isopropenylfuromollugin **7**

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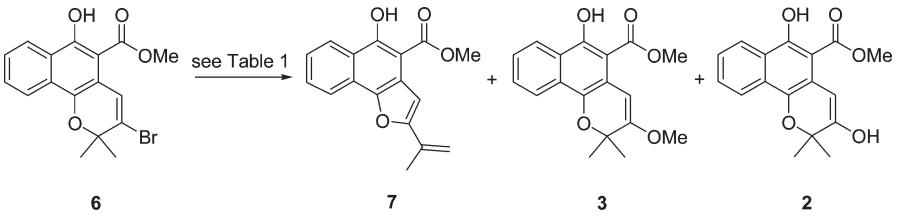
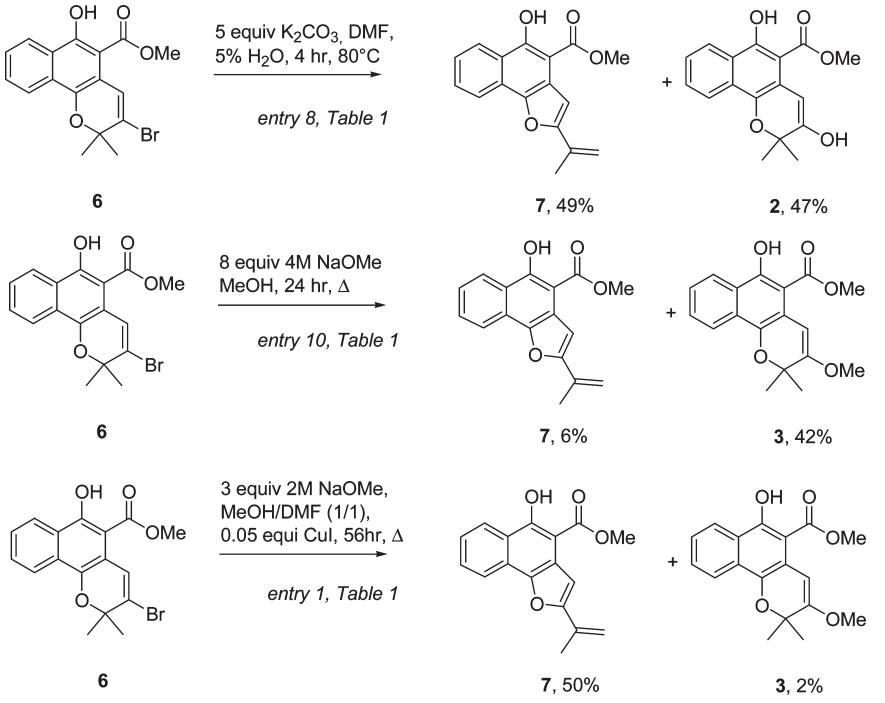
SCHEME 3



SCHEME 4



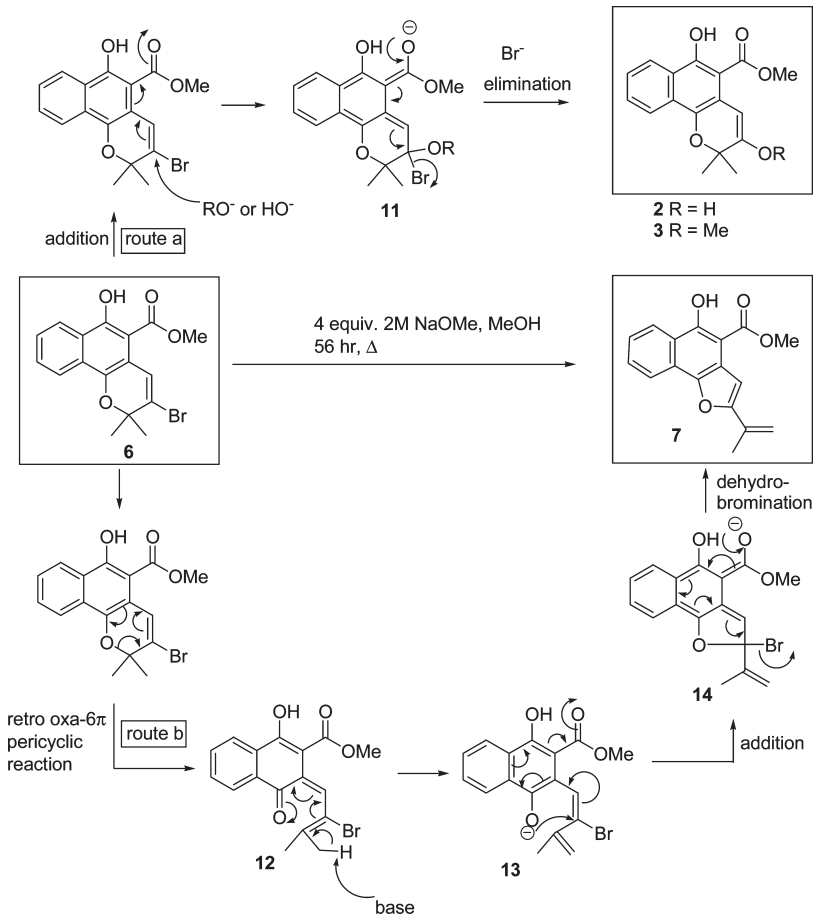
(entry 6). This result is explained by the inherent water content in DMF and K_2CO_3. In order to evaluate the role of water, two experiments were carried out with additional 0.5% and 5% of water. Surprisingly, both reactions proceeded smoothly, and the reaction carried out with 5% of water facilitated the formation of the required 3-hydroxymollugin **2** (47%) when compared to the reaction carried out with 0.5% water (38%) (entries 7 and 8). The experiments carried out with 5 equiv of K_2CO_3 as a base and 3-bromomollugin **6** either with 5% H_2O in DMF at 50 °C for 14 h (or 24 h) at ambient temperature or prolonged heating at 80 °C in DMF without H_2O (24 h) led to the formation of complex reaction mixtures. Using the same amount of base, the reaction of 3-bromomollugin **6** in methanol for 24 h at room temperature resulted in the recovery of starting material, whereas the same reaction under reflux conditions provided a complex reaction mixture. However, the reaction of 3-bromomollugin **6** in the presence of 5 equiv of K_2CO_3 in a solvent mixture of MeOH/DMF (1:1) for 24 h at room temperature resulted in the formation of 3-methoxymollugin **3** and 3-hydroxymollugin **2** in 10% and 5% yield, respectively (entry 9). Finally, by switching the base from potassium carbonate to NaOMe, 3-methoxymollugin **3** was obtained in an acceptable yield. Thus, when 8 equiv of a 4 M NaOMe in methanol under reflux for 24 h was used, 3-methoxymollugin **3** was obtained in 42% yield along with 6% of isopropenylfuromollugin **7** (entry 10). Under similar conditions, i.e., 8 equiv of 4 M NaOMe in MeOH and DMF (1:1), 3-bromomollugin **6** resulted in a complex reaction mixture. With an increase in the amount of base (8 equiv to 16 equiv of 4 M NaOMe), the reaction of compound **6** in methanol under reflux for 24 h decreased the formation of both 3-methoxymollugin **3** (only 25%) and **7** (6%) (entry 11) (Scheme 3). A microwave reaction was attempted, but the reaction of 3-bromomollugin **6** with 5 equiv of K_2CO_3 resulted only in a low yield of 3-methoxymollugin **3** (~2%) along with 10% of isopropenylfuromollugin 7 (entry 12). Further research under microwave conditions was abandoned.

These results allow the synthesis of the natural products 3-hydroxymollugin **2**, 3-methoxymollugin **3**, and isopropenylfuromollugin **7** in acceptable yields as represented in Scheme 4.

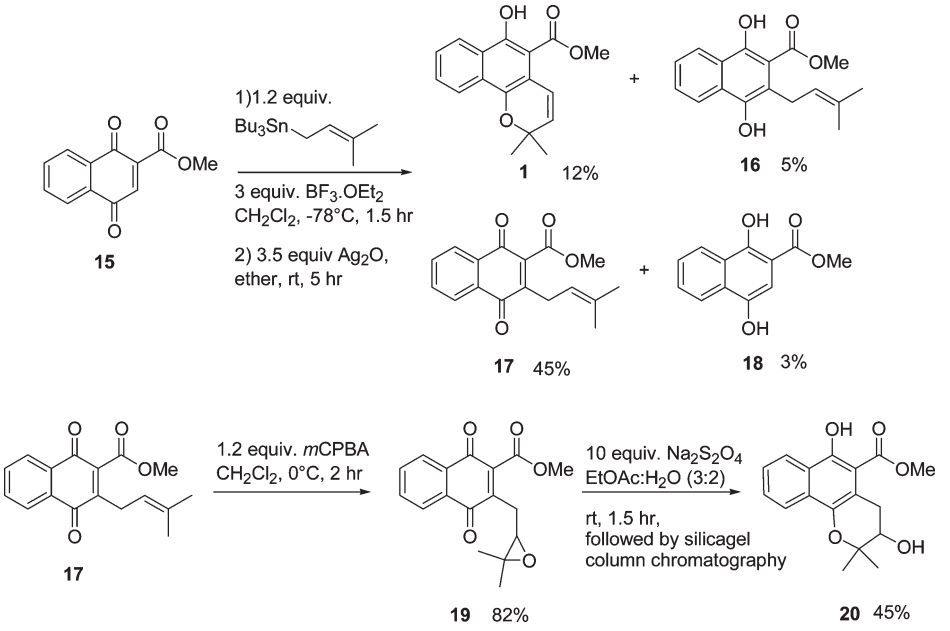
Based on these results, the following reaction mechanism for the formation of the ring contracted isopropenylfuromollugin **7** was proposed (Scheme 5). Apparently, thermal activation is necessary for the formation of isopropenylfuromollugin **7** as there is no formation of this compound **7** at room temperature versus its formation in 10% yield at 80 °C (entry 6).

Therefore, it is proposed that the reaction is initiated by a pericyclic retro oxa-6π ring-opening. Next, the allylic hydrogen in intermediate **12** is deprotonated by the base after which the phenolate **13** intramolecularly attacks the double bond which is activated by the electron-withdrawing ester

SCHEME 5



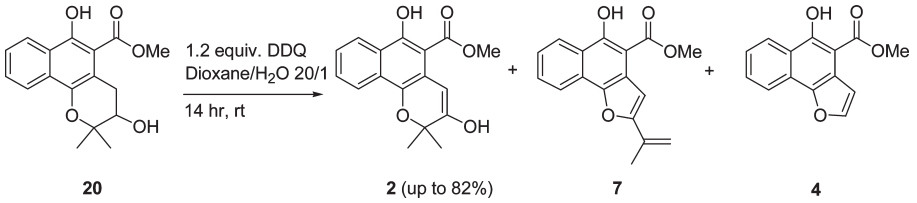
SCHEME 6



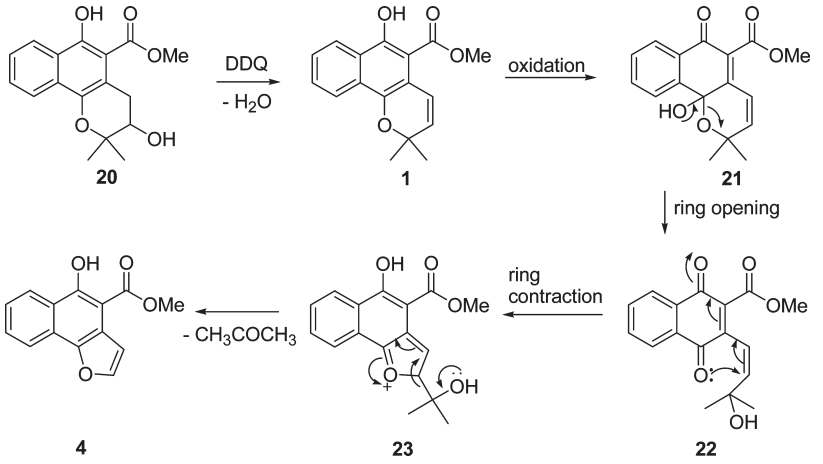
moiety. Addition−dehydrobromination results in the obtained isopropenylfuromollugin **7** (route b). Elimination of bromide in compound **11** occurs when sodium methoxide or hydroxide acts as a nucleophile across the conjugated vinyl bromide, leading to 3-methoxymollugin **3** or 3-hydroxymollugin **2**, respectively (route a).

Subsequently, an alternative route for the synthesis of 3-hydroxymollugin **2**, not starting from 3-bromomollugin **6**,

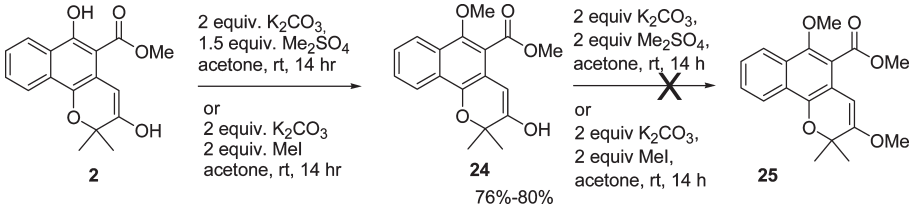
SCHEME 7



SCHEME 8. Plausible Mechanism for the Formation of Furomollugin 21



SCHEME 9



was evaluated (Scheme 6). This alternative synthesis of 3-hydroxymollugin **2** started from methyl 3-prenyl-1,4-naphthoquinone-2-carboxylate **17**,[6] which is considered to be the biochemical precursor of mollugin **1** and its analogues. Compound **17** was prepared by our previously disclosed method of prenylation of methyl naphthoquinone-2-carboxylate **15** with tributylprenyltin in the presence of boron(III) fluoride etherate and subsequent oxidation of the intermediate naphthol **16** with silver(I) oxide.[6] In this report, a more detailed investigation of the obtained reaction products is revealed. It has been found that the desired compound **17** is formed in 45% yield together with unoxidized naphthalene **16** (5%), reduced starting material **18** (3%), and mollugin **1** (12%). Epoxidation of the olefinic double bond in the prenyl side chain of methyl 3-prenyl-1,4-naphthoquinone **17** with *m*-CPBA in dichloromethane at 0 °C for 2 h resulted in epoxide **19** in excellent yield (82%). Reduction of the quinone **19** with sodium dithionite in ethyl acetate/H_2O (3/2)[7] afforded the corresponding naphthalene-1,4-diol as intermediate, which subsequently suffered ring opening of the epoxide by the proximate phenolic hydroxyl group during silica gel chromatography to give rise to chromanol **20**. In this way, the desired chromanol **20** was obtained in a moderate combined yield (57%). Surprisingly, oxidation of compound **20** using DDQ in different solvents afforded different products along with the required 3-hydroxymollugin **2**.

An oxidation protocol using DDQ in dioxane/water (20/1) was found to oxidize chromanol **20** at room temperature resulting in the target 3-hydroxymollugin **2** in excellent yield (82%). Other conditions, which used DDQ in toluene, afforded mixtures of oxidation compounds **2**, **7**, and **21** (Scheme 7; see the Supporting Information for more details).

Mechanistically, the formation of furomollugin **4** is thought to proceed via the formation of mollugin **1**, which is successfully oxidized by DDQ to compound **21** (Scheme 8). Based on the observations by Trauner et al.,[13] it is believed that ring contraction and elimination of the elements of acetone lead to the formation of furomollugin **4**.

Having in hand a high-yielding synthesis of 3-hydroxymollugin **2**, methylation reactions were attempted in order to obtain 3-methoxymollugin **3** in high yield. Unfortunately, all attempted reaction conditions were unsuccessful (Scheme 9, see the Supporting Information). When 1.5 equiv of Me_2SO_4 or 2 equiv of iodomethane was used as methylating agent in the presence of 2 equiv of K_2CO_3 in acetone, only the

(13) Lumb, J.-P.; Choong, K. C.; Trauner, D. *J. Am. Chem. Soc.* **2008**, *130*, 9230–9231.

formation of *O*-methyl-3-hydroxymollugin **24** was observed. Attempts to further methylate *O*-methyl-3-hydroxymollugin **24** at the vinylic hydroxyl group were not successful using Me_2SO_4 or MeI. It was also observed that prolonged reaction times of more than 24 h led to a slow decomposition of the starting material.

Conclusion

In conclusion, the first synthesis of the natural products 3-hydroxymollugin **2** and 3-methoxymollugin **3** was successfully accomplished in acceptable yields. It was found that addition−dehydrobromination of 3-bromomollugin **6** is a feasible strategy to obtain compounds **2** and **3**. When 3-bromomollugin **6** is thermally activated, a retro-oxa-6π pericyclic reaction occurs with the formation of the interesting isopropenylfuromollugin **7**. In the case of 3-hydroxymollugin **2**, an alternative synthesis was presented based on epoxidation and subsequent ring closure of 3-prenyl-1,4-naphthoquinone-2-carboxylate **17**. DDQ-oxidation results in 3-hydroxymollugin **2** along with the rearranged furomollugin **4**, which is a ring-contracted analogue of mollugin **1**.

Experimental Section

3-Bromomollugin 6. To a stirred solution of mollugin **1** (2 mmol, 0.568 g) in CCl_4 (10 mL) were added benzoyl peroxide (0.2 equiv, 0.4 mmol, 96 mg) and *N*-bromosuccinimide (1.5 equiv, 3 mmol, 0.534 g). The reaction mixture was heated under reflux for 5 h and subsequently cooled in an ice bath. The reaction mixture was filtered and evaporated in vacuo to yield 3-bromomollugin **6**. The residue was purified by column chromatography (petroleum ether/ethyl acetate 97/3) to afford yellow crystals (0.78 g, 72% yield). Mp: 117.9−118 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.59 (6H, s), 4.03 (3H, s), 7.52 (1H, ddd, J = 8.3 Hz, J = 6.9 Hz, J = 1.4 Hz), 7.56 (1H, s), 7.62 (1H, ddd, J = 8.3 Hz, J = 6.9 Hz, J = 1.4 Hz), 8.11 (1H, ddd, J = 8.3 Hz, J = 1.4 Hz, J = 0.8 Hz), 8.36 (1H, ddd, J = 8.3 Hz, J = 1.4 Hz, J = 0.8 Hz), 12.27 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.8, 52.6, 78.7, 101.2, 113.1, 121.85, 123.8, 124.3, 125.2, 125.3, 126.7, 128.8, 129.8, 140.3, 157.3, 172.2. IR (KBr) ν_{max}: 1650 (C═O). MS (ES^+) m/z: 362/364 (M^+, 100).

Methyl 3-(3,3-Dimethyloxiranylmethyl)-1,4-naphthoquinone-2-carboxylate 19. To a stirred solution of methyl 3-(3-methylbut-2-enyl)-1,4-naphthoquinone-2-carboxylate **17** (0.42 g, 1.47 mmol) in dichloromethane (20 mL) at 0 °C was added 1.2 equiv of 70% *m*-chloroperbenzoic acid (0.305 g, 1.77 mmol). Stirring was continued for 2 h after which time the reaction mixture was poured into water and the organic phase was separated, washed with a saturated aqueous solution of sodium bicarbonate (TLC monitoring), and dried over magnesium sulfate. Removal of the solvent in vacuo afforded 0.36 g of methyl 3-(3,3-dimethyloxiranylmethyl)-1,4-naphthoquinone-2-carboxylate **19** as a brown oil (82% yield), which was used directly in the next step, without purification. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.30 (3 H, s), 1.37 (3 H, s), 2.70 (1 H, dd, J = 12.9 Hz, J = 6.6 Hz), 2.96 (1 H, dd, J = 6.6 Hz, J = 4.7 Hz), 3.02 (1 H, dd, J = 12.9 Hz, J = 4.7 Hz), 3.95 (3 H, s), 7.77 (2 H, m), 8.10 (2 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.9, 24.6, 27.7, 53.0, 59.4, 62.2, 126.6, 126.9, 131.4, 134.4, 134.4, 140.7, 144.0, 164.9, 181.7, 184.5. IR (NaCl) ν_{max}: 1668, 1698, 1738. MS (ES+) m/z: 301 ($M + H^+$, 100).

Methyl 3,6-Dihydroxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*h*]chromene-5-carboxylate 20. A solution of methyl 3-(3,3-dimethyloxiranylmethyl)-1,4-naphthoquinone-2-carboxylate **19** (0.36 g, 1.19 mmol) in ethyl acetate (30 mL) was vigorously stirred at room temperature, and a solution of sodium dithionite (2.08 g, 11.98 mmol) in water (20 mL) was added. After 1.5 h of stirring at room temperature, the organic phase was separated, washed with water, and dried over magnesium sulfate, and the solvent was evaporated to afford a thick brown viscous liquid which was purified by flash chromatography using silica gel (petroleum ether/ethyl acetate 9/1) to afford 0.163 g of methyl 3,6-dihydroxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*h*]chromene-5-carboxylate **20** (45% yield) as a yellow crystals. Mp: 116−117 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.25 (3H, s), 1.39 (3H, s), 2.14 (1H, s_{broad}) 3.42 (2H, d, J = 9.4 Hz), 3.92 (3H, s), 4.68 (1H, t, J = 9.4 Hz), 7.46 (1H, t, J = 7.4 Hz), 7.56 (1H, t, J = 7.4 Hz), 7.85 (1H, d, J = 8.3 Hz), 8.32 (1H, d, J = 8.3 Hz), 11.77 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.1, 26.1, 34.2, 52.3, 72.1, 89.2, 103.3, 116.8, 121.2, 124.0, 124.5, 125.6, 129.2, 147.2, 156.1, 171.8. IR (NaCl) ν_{max}: 1645, 3456. MS (ES^-) m/z: 301 ($M - H^+$, 100). Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.79; H 6.14.

3-Hydroxymollugin (Methyl 3,6-Dihydroxy-2,2-dimethyl-2*H*-benzo[*h*]chromene-5-carboxylate) 2. To a solution of methyl 3,6-dihydroxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*h*]chromene-5-carboxylate **20** (0.25 g, 0.827 mmol) in a solvent mixture of dioxane/H_2O (20:1) (5 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.23 g, 0.278 mmol). After being stirred for 14 h at room temperature, the reaction mixture was poured into 30 mL of saturated sodium bicarbonate solution and extraction was performed with EtOAc (3 × 20 mL). The combined organic layers were dried and evaporated in vacuo to obtain crude 3-hydroxymollugin **2** as a brown solid which was flashed through a pad of silica gel to obtain 0.203 g of pure methyl 3,6-dihydroxy-2,2-dimethyl-2*H*-benzo[*h*]chromene-5-carboxylate **2** (82% yield) as a white solid. Mp: 142.3−143.5 °C (lit.[6] mp 143−145 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.57 (6H, s), 4.09 (3H, s), 7.21 (1H, d, J = 1.9 Hz), 7.53 (1H, ddd J = 8.3 Hz, J = 6.9 Hz, 1.4 Hz), 7.72 (1H, ddd J = 8.3 Hz, J = 6.9 Hz, J = 1.4 Hz), 7.74 (1H, d, J = 1.9 Hz), 8.20 (1H, dq, J = 8.3 Hz, J = 0.7 Hz), 8.47 (1H, dq, J = 8.3 Hz, J = 0.7 Hz), 12.28 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.7, 52.3, 74.7, 99.2, 109.4, 119.9, 120.0, 123.0, 125.0, 125.1, 125.2, 130.2, 144.4, 159.4, 162.6, 172.1. IR (KBr) ν_{max}: 1659, 3500. MS (ES^+) m/z: 301 ($M + H^+$, 100). Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.81; H 5.78.

Procedure for the Synthesis of 3-Methoxymollugin 3 Using NaOMe. To a solution of freshly prepared 4 M sodium methoxide in methanol (2.2 mL, 4.4 mmol) was added 3-bromomollugin **6** (0.20 g, 0.55 mmol). The reaction mixture was heated under reflux for 24 h. Then methanol was removed in vacuo and the residue partitioned between ethyl acetate and water. The organic phase was separated, washed with water, and dried over $MgSO_4$, and the solvent was removed in vacuo. Purification by silica gel column chromatography using petroleum ether/ethyl acetate (90:10) as eluent afforded 72 mg of 3-methoxymollugin **3** (42% yield, white crystals) along with 9 mg of methyl 5-hydroxy-2-isopropenylnaphtho[1,2-*b*]furan-4-carboxylate **7** (6% yield).

3-Methoxymollugin (Methyl 6-Hydroxy-3-methoxy-2,2-dimethyl-2*H*-benzo[*h*]chromene-5-carboxylate) 3. Mp: 119.5−121 °C (lit.[6] mp 121−123 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.70 (6H, s), 3.17 (3H, s), 4.09 (3H, s), 7.04 (1H, s), 7.50 (1H, ddd, J = 8.3 Hz, J = 6.9 Hz, J = 1.4 Hz), 7.69 (1H, ddd, J = 8.3 Hz, J = 6.9 Hz, J = 1.4 Hz), 8.23 (1H, d, J = 8.3 Hz), 8.45 (1H, d, J = 8.3 Hz), 12.25 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.6, 51.2, 52.4, 73.7, 99.2, 106.6, 120.0, 120.3, 122.9, 124.9, 125.0, 125.1, 130.1, 144.1, 159.3, 159.6, 172.1. IR (KBr) ν_{max}: 1656. MS (ES^-) m/z: 313 ($M - H^+$, 100). Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.52; H, 5.98.

Procedure for the Synthesis of 3-Hydroxymollugin 2 Using K_2CO_3. To a solution of 3-bromomollugin **6** (0.20 g, 0.55 mmol) in DMF (6 mL) were added potassium carbonate (0.380 g, 2.75 mmol) and water (0.15 mL). The reaction mixture was heated at 80 °C for 4 h and then poured into 30 mL of water. The aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were washed with water (2 × 50 mL), dried over $MgSO_4$, and evaporated. Purification of

the crude residue by column chromatography using petroleum ether/ethyl acetate (90:10) as eluent afforded 76 mg of 3-isopropenylfuromollugin **7** as white crystals (49% yield), and petroleum ether/ethyl acetate (70:30) as eluent afforded 77 mg of 3-hydroxymollugin **2** (yield 47%).

2-Isopropenylfuromollugin (Methyl 5-Hydroxy-2-isopropenylnaphtho[1,2-*b*]furan-4-carboxylate) 7. Mp: 96.3−98 °C (lit.[12] mp 95−100 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.19 (3H, s), 4.09 (3H, s), 5.18 (1H, s), 5.86 (1H, s), 7.01 (1H, s), 7.51 (1H, ddd, J = 8.3 Hz, J = 7.2 Hz, J = 1.1 Hz), 7.68 (1H, ddd, J = 8.3 Hz, 7.2 Hz, 1.1 Hz), 8.26 (1H, dt, J = 8.3 Hz, J = 0.6 Hz), 8.45 (1H, dt, J = 8.3 Hz, 0.6 Hz), 12.27 (1H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.5, 52.4, 99.1, 105.6, 112.5, 112.0, 121.3, 123.1, 124.7, 125.1, 125.1, 130.1, 133.0, 144.0, 156.6, 159.3, 172.1. IR (KBr) ν_{max}: 1654, 3434. MS (ES^+) m/z: 283 ($M + H^+$, 100). Anal. Calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 71.98; H, 5.11.

***O*-Methyl 3-Hydroxymollugin 24.** To a 10 mL acetone solution of 3-hydroxymollugin **2** (0.20 g, 0.67 mmol) were added potassium carbonate (0.184 g, 1.33 mmol) and MeI (0.189 g, 1.33 mmol). The reaction mixture was stirred at ambient temperature for 14 h, and the acetone was evaporated. The crude residue was partitioned between EtOAc and water and extracted with (3 × 20 mL) of EtOAc. The combined organic extracts were dried and evaporated to give a dark viscous liquid which was purified by flash chromatography to afford methyl 3-hydroxy-6-methoxy-2,2-dimethyl-2*H*-benzo[*h*]chromene-5-carboxylate **25** (0.167 g, 80% yield, brown crystals). Mp: 122−123 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.75 (6H, s), 4.05 (3H, s), 4.03 (3H, s), 7.04 (1H, s), 7.50−7.57 (1H, m), 7.61−7.69 (1H, m), 8.22−8.30 (2H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.0, 52.3, 64.0, 69.5, 103.1, 113.8, 120.3, 122.6, 123.8, 124.6, 125.7, 126.1, 128.8, 146.6, 154.8, 163.1, 166.4. IR (KBr) ν_{max}: 1656. MS (ES^-) m/z: 313 ($M - H^+$, 100). Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.93; H, 6.02.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of newly synthesized and target compounds. This material is available free of charge via the Internet at http://pubs.acs.org.