

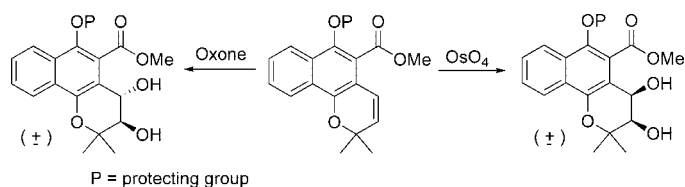
Efficient Synthesis of *cis*- and *trans*-3,4-Dihydroxy-3,4-dihydromollugin

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An efficient synthesis of naturally occurring compounds isolated from *Pentas longiflora*, *cis*-3,4-dihydroxy-3,4-dihydromollugin **2**, and *trans*-3,4-dihydroxy-3,4-dihydromollugin **3** is described. The *O*-protected mollugin derivatives were dihydroxylated using OsO_4 to achieve the corresponding *cis*-dihydroxy derivatives in excellent yield. The synthesis of *trans*-3,4-dihydroxy-3,4-dihydromollugin was achieved using Oxone in good yield. A mechanism for the formation of *cis*-3,4-dihydroxymollugin acetonide from the reaction of mollugin with Oxone is proposed.

1. Introduction

It has been estimated that 80% of the world population depends on alternative systems of medicine.¹ This traditional medicine is merely based on the knowledge of how to use medicinal plants. For instance, the African medicinal plant *Pentas longiflora* (Rubiaceae) is used to treat skin diseases such as pityriasis versicolor, itchy rashes, or mycoses.² The same plant is also used as medicine for treating diseases such as malaria, diarrhea, tapeworm, gonorrhea, and syphilis and is used as a purgative in Kenya and Rwanda.³ The plant *Galium mollugo* is phytochemically related to *Pentas longiflora* and is used as an herbal medicine with antitumor, antiviral, and other activities.⁴ An important constituent isolated from both plants

is mollugin **1**, which is a benzisochromene antibiotic.⁵ Compound **1** not only showed potent suppressive activity on hepatitis B surface antigen (HBsAg) secretion in human hepatoma Hep3B cells but also possessed strong inhibition of arachidonic acid (AA)-induced and collagen-induced platelet aggregation.⁶ Because of its importance, mollugin **1** has been synthesized by several groups (Figure 1).⁷

Next to mollugin **1**, several derivatives of mollugin **1** were isolated by us^{5h} and others^{5a-g} from *Pentas longiflora*, e.g., *cis*-3,4-dihydroxy-3,4-dihydromollugin **2** and *trans*-3,4-dihydroxy-3,4-dihydromollugin **3**. Recently, the synthesis of *trans*-3,4-dihydroxy-3,4-dihydromollugin **3** in 62% yield has been reported

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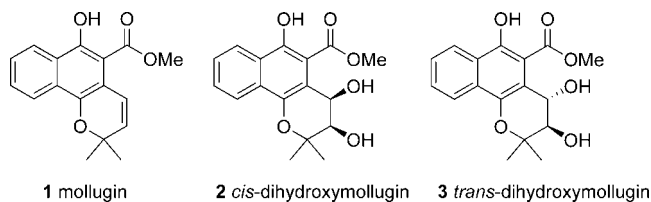
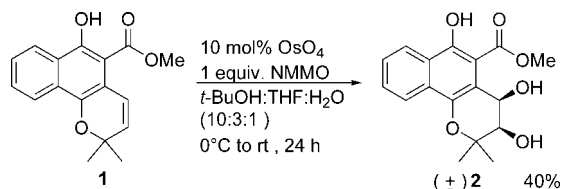


FIGURE 1. Benzisochromenes isolated from *Pentas longiflora*.

SCHEME 1



by Wang et al. by reacting dimethyldioxirane (DMD) with mollugin 1.⁸ However, in our hands, by employing the same reaction conditions the *trans*-3,4-dihydroxy-3,4-dihydromollugin 3 was only formed in 30% yield along with the formation of several side products. Therefore, a more detailed investigation was necessary which will be presented in this paper. This fact, taken together with the important biological activities and medicinal properties associated with these compounds, urged us to present our results in the synthesis of *cis*-3,4-dihydroxy-3,4-dihydromollugin 2 and *trans*-3,4-dihydroxy-3,4-dihydromollugin 3, respectively.

2. Results and Discussion

2.1. Synthesis of *cis*-3,4-Dihydroxy-3,4-dihydromollugin

2. Our initial aim was to synthesize *cis*-3,4-dihydroxy-3,4-dihydromollugin 2 by a direct dihydroxylation reaction onto mollugin 1 using various oxidizing agents. Mollugin 1 was prepared following the efficient three-step strategy recently reported by our group, by alkylation of methyl 1,4-dihydroxynaphthalene 1-carboxylate with 3-methyl-3-buten-1-ol and subsequent dehydrogenation using DDQ.^{7c} Starting from mollugin, several reactions were performed using oxidizing agents such as KMnO_4 (under neutral conditions as well as with 5 mol % of ruthenium (III) chloride), sodium periodate/lithium bromide, or phenyliodonium diacetate/lithium bromide for the dihydroxylation of mollugin. In most cases, complex reaction mixtures were obtained pointing to the complex nature of this reaction due to the presence of the free phenolic hydroxyl group. In the latter two cases, using lithium bromide under oxidizing conditions, 3-bromomollugin was formed in 18% and 17% yields, respectively.⁹ After considerable experimentation, it was observed that OsO_4 (4 wt % solution in H_2O) is the oxidant of choice. The reaction of mollugin 1 with 10 mol % of OsO_4 in the presence of 1 equiv of 4-methylmorpholine *N*-oxide monohydrate (NMMO) as co-oxidant resulted in *cis*-3,4-dihydroxy-3,4-dihydromollugin 2 for the first time in 40% yield (Scheme 1). In an effort to improve the yield of compound 2, several parameters were explored such as variation in the catalytic loading of OsO_4 , the number of equivalents of NMMO, and

TABLE 1. Effect of Various Parameters on the Dihydroxylation of Mollugin 1 Using OsO_4

entry	reaction conditions ^a	NMMO (equiv)	yield of 2 ^b (%)
	OsO_4 (4 wt % solution in H_2O)		
1	10 mol %	1.0	40
2	20 mol %	1.0	30
3	5 mol %	1.0	18
4	10 mol %	1.5	33
5	10 mol %	0.5	28
	OsO_4 (4 wt % solution in <i>t</i> -BuOH)		
6	10 mol %	1.0	15
	OsO_4 (solid) ^c		
7	10 mol %	1.0	0

^a All reactions were performed at 0.5 mmol scale in a solvent mixture of *t*-BuOH/THF/ H_2O (10:3:1). ^b Isolated yields. ^c Reaction performed in acetone/ H_2O (1:1) at 0 °C for 30 min.

SCHEME 2

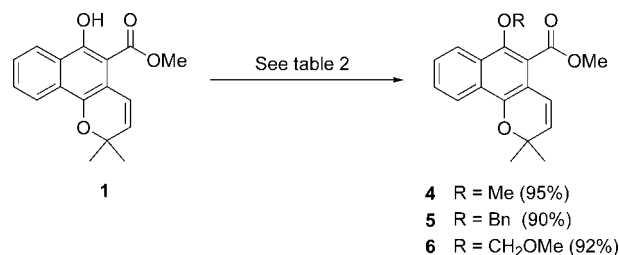


TABLE 2. Reaction Conditions for the Synthesis of *O*-Protected Mollugin Derivatives 4–6

entry	reaction conditions	result
1	1.5 equiv of MeI, 1.25 equiv of K_2CO_3 , acetone, rt, 24 h	R = Me, 4, 95%
2	1.2 equiv of BnBr, 1.25 equiv of K_2CO_3 , DMF, 60 °C, 4 h	R = Bn, 5, 90%
3	1.5 equiv of NaH, 1.5 equiv of MOM-Cl, DMF, 60 °C, 12 h	R = CH_2OMe , 6, 0%
4	1.5 equiv of $^i\text{PrNEt}_2$, 1.5 equiv of MOM-Cl, CH_2Cl_2 , 0 °C-rt, 18 h	R = CH_2OMe , 6, 92%

the reaction times. However, no appreciable improvement was observed in these cases (Table 1).

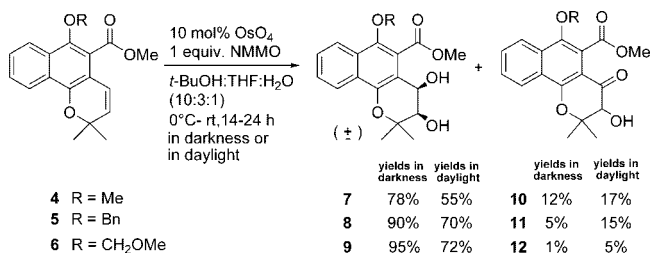
By increasing or decreasing the number of equivalents of NMMO, a decrease in the product yield was observed along with unidentified side products. Conducting the reaction at lower temperature or for prolonged periods of time did not alter the product yield to an appreciable amount. During the course of these investigations, mostly complex reaction mixtures with difficulty in isolating the required diol 2 were obtained. In view of the encountered failures to improve the yield in the *cis*-dihydroxylation of mollugin 1, a survey of the literature revealed that the dihydroxylation of a double bond using OsO_4 with substrates containing a free phenolic-OH made use of their *O*-protected ethers in most cases. Therefore, it was decided to protect the aromatic hydroxyl group of mollugin to avoid the assumed complex formation of the osmium species with the acidic phenolic hydroxyl moiety of mollugin 1. Based on this assumption, several protecting groups were chosen to protect the phenolate of mollugin after which the dihydroxylation reaction on *O*-protected mollugin was performed. The reaction of mollugin 1 with methyl iodide and potassium carbonate in acetone yielded the corresponding *O*-methylmollugin 4 in 95% yield (Scheme 2).

Using a standard protocol for dihydroxylation by means of OsO_4 (10 mol %, 4% in H_2O), the required *cis*-*O*-methyl 3,4-

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(9) 3-Bromomollugin was formed by direct bromination of mollugin 1 with bromine, generated in situ by the oxidation of LiBr, either with sodium periodate or phenyliodonium acetate.

SCHEME 3

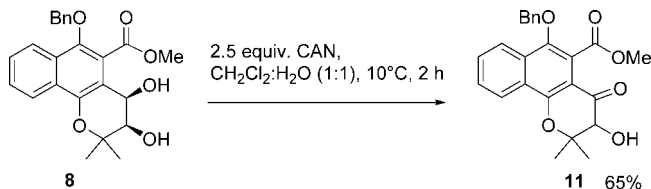


dihydroxy-3,4-dihydromollugin **7** was obtained in 55% yield accompanied by the corresponding α -hydroxy ketone **10** in 17% yield (Scheme 3). Although the improvement in the product yield was not successful, we were able to eliminate the undesired side reactions, except the formation of the overoxidized product **10**, and thus facilitated the product purification thoroughly. The formation of such α -hydroxy ketones is frequent in oxidation reactions of benzochromene derivatives, such as acronycine.¹⁰ To overcome these shortcomings, the hydroxy moiety of mollugin **1** was protected as the corresponding benzyl ether **5**. Using 1.2 equiv of benzyl bromide and potassium carbonate in *N,N*-dimethylformamide for 4 h at 60 °C, mollugin **1** afforded the benzyl ether of mollugin **5** in 90% yield. A similar protection of mollugin as methoxymethyl ether was also performed by use of 1.5 equiv of MOM chloride and *N*-ethyl-diisopropylamine in dichloromethane for 18 h resulting in the corresponding MOM ether of mollugin **6** in 92% yield (Table 2). The *O*-protected mollugin derivatives (**5** and **6**) were successfully dihydroxylated using 10 mol % of OsO₄ in the presence of 1 equiv of NMMO to afford the corresponding *O*-protected dihydroxylated mollugin derivatives (**8** and **9**) in 70% and 72% yields, respectively (Scheme 3). However, the corresponding *O*-protected α -hydroxy ketones were also formed as minor products (**11**, 15%, and **12**, 5%).

The formation of these α -hydroxy ketones was thought to depend on the interaction of light. Photochromism of 2-*H*-chromenes (2-*H*-1-benzopyrans) is well-known in which a reversible pyran ring opening would occur by the interaction of light.¹¹ A related photolability was found before at our department in the case of pentalongin (also isolated from *Pentas longiflora*), a 3,4-dehydropyranonaphthoquinone, which is known to degrade in alcoholic solvents in the presence of daylight.¹² A black coloration in the reaction flask was always observed after the addition of OsO₄ to a predissolved solution of NMMO and mollugin or *O*-protected mollugin in a solvent mixture of *t*-BuOH/THF/H₂O (10:3:1).

To avoid such undesired side reactions associated with light, a reaction of *O*-methylmollugin **4** with OsO₄ was carried out in darkness under identical experimental conditions. Interestingly, this dark coloration was not observed in the absence of light. In this way it was found that, conducting the reaction in darkness not only improved the yield of the required dihydroxylated compounds (**7–9**), but also reduced the amount of the corresponding α -hydroxy ketones (**10–12**). However, the characteristic reasons of this photochemical influence are not yet known and a degradation study of mollugin **1** in the presence of light in different alcoholic solvents is under progress to identify the related degradation products. Observing the benefits of performing the dihydroxylation reaction in darkness, prompted us to check the initial reaction of mollugin **1** with 10 mol% OsO₄, according to the conditions described in Scheme 1, in darkness. However, no significant improvements with respect to the yield were found. It is interesting to note that a decreasing trend in the formation of α -hydroxy ketone was observed with the increasing electron donating power of the protecting group. The increased electron donating property of MOM-protected mollugin **6** is responsible for obtaining the highest yield of dihydroxy compound **9** with OsO₄. With these vicinal dihydroxy compounds (**7–9**) in hand, efforts were made to obtain the required *cis*-diol **2** by deprotection (Scheme 4).

SCHEME 4



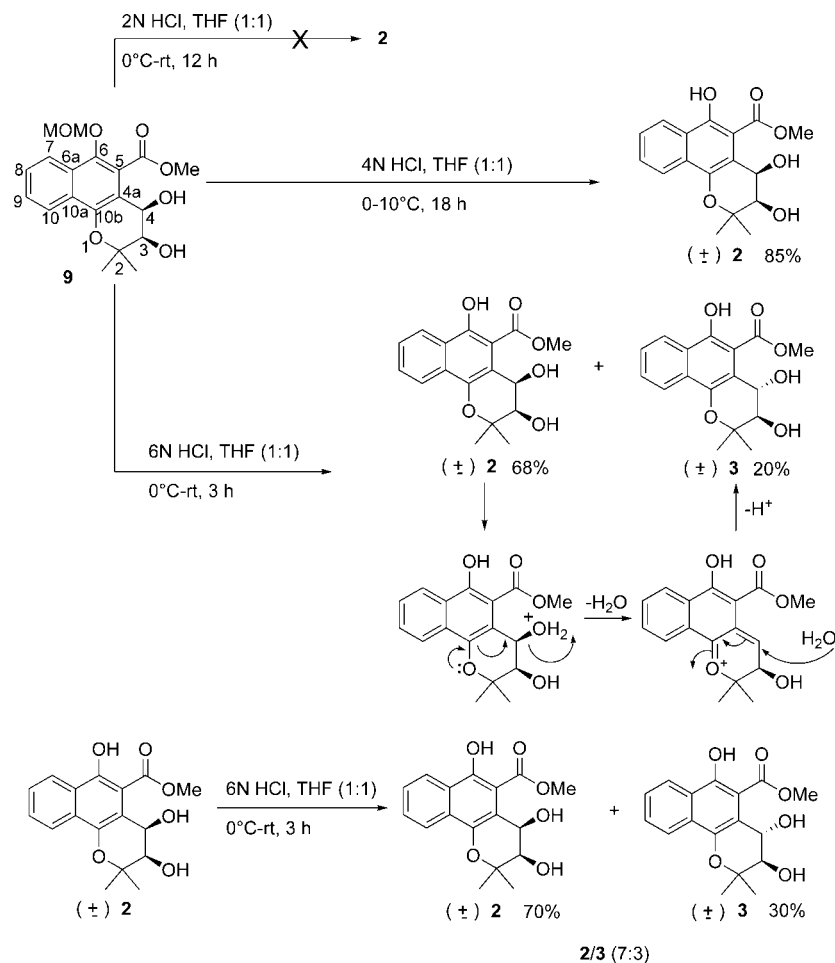
However, attempts to deprotect the methyl ether in compound **7** either by boron(III) bromide in dichloromethane or cerium(IV) ammonium nitrate (CAN) in acetonitrile failed, affording complex reaction mixtures only. The *O*-debenzylation reaction with compound **8** was carried out either in EtOH or in a solvent mixture of EtOH and EtOAc using 10 mol% of Pd(0) under H₂ atmosphere (4 bar) resulting in the recovery of starting material. The same reaction using 20 mol% of Pd(0) in MeOH, resulted in the formation of unidentified products. On the other hand, using 2.5 equiv of CAN under biphasic conditions in a solvent mixture of CH₂Cl₂/H₂O (1:1) at 10 °C for 2 h afforded the *O*-benzyl-protected α -hydroxy ketone **11** in 65% yield (Scheme 4). Although the deprotection of methyl and benzyl ethers failed, next it was focused on the deprotection of *O*-(methoxymethyl) group (MOM) of dihydroxy compound **9**. It is interesting to note that the concentration of the acid in fact influenced the deprotection of *O*-(methoxymethyl) group. Initially, the deprotection of compound **9** performed under mild reaction conditions using 2 N HCl (1:1) in THF either at 0 °C or at ambient temperature for several hours did not provide the required diol **2**. To our surprise, stirring compound **9** in an excess of 6 N HCl (1:1) in THF at 0 °C to room temperature for 3 h afforded both *cis*-3,4-dihydroxy-3,4-dihydromollugin **2** and *trans*-3,4-dihydroxy-3,4-dihydromollugin **3** in 68% and 20% yield, respectively. This unusual formation of a *trans*-diol **3** from *cis*-diol **9** can be explained as follows (Scheme 5). Deprotection of the MOM-ether **9** obviously results in *cis*-diol **2**. However, under excess acidic conditions the hydroxyl moiety at position 4 can be protonated and easily eliminated by an electron push mechanism starting from the electron lone pair of the pyran oxygen. In this way, a reactive charged *o*-quinomethide is formed to which water attacks and results in the formation of the thermodynamically more stable *trans* isomer **3**. The spectral data of compounds **2** and **3** were in accordance with those reported in literature.⁵ The *O*-(methoxymethyl) deprotection reaction of the compound **9** was successfully achieved using 4

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SCHEME 5



N HCl. Thus, a reaction between *O*-(methoxymethyl)dihydroxymollugin **9** and 4 N HCl at 0 °C for 18 h resulted in the exclusive formation of *cis*-diol **2** in 85% yield (Scheme 5). The hypothetical assumption of the transformation of *cis*-diol **2** to a thermodynamically more stable *trans* isomer **3** was also proved by conducting the reaction independently using *cis*-diol **2**. Thus, the reaction of *cis*-diol **2** using 6 N HCl in THF afforded a 7:3 mixture of *cis*- and *trans*-diols.

2.2. Synthesis of *trans*-3,4-Dihydroxy-3,4-dihydromollugin **3.** After the successful synthesis of *cis*-diol **2**, attention was focused toward the synthesis of the related *trans*-diol **3**, which was previously synthesized by Wang et al.⁸ As already stated, in our hands, applying these conditions gave rise to the formation of several side products. Therefore, a more detailed investigation of the synthesis of *trans*-3,4-dihydroxy-3,4-dihydromollugin **3** was necessary. The strategy for the synthesis of this *trans*-diol **3** is based on initial synthesis of the corresponding epoxide **14**, followed by anti ring opening of 3,4-epoxymollugin **14**. In an attempt to synthesize the target epoxide **14**, several epoxidation reactions were explored either by using hydrogen peroxide/base in nucleophilic conditions or by means of *m*-chloroperbenzoic acid (*m*-CPBA), sodium hypochlorite or Oxone under electrophilic conditions. Epoxidation of electron-poor alkenes such as α β -unsaturated carbonyl compounds are well-known with hydrogen peroxide.¹³ It was assumed that mollugin **1** with a γ δ -unsaturated ester in conjugation with an aromatic ring is more susceptible for epoxidation using H_2O_2 . However, the use of 6 equivalents of 30% H_2O_2 and 1.5 equiv of sodium carbonate in

SCHEME 6

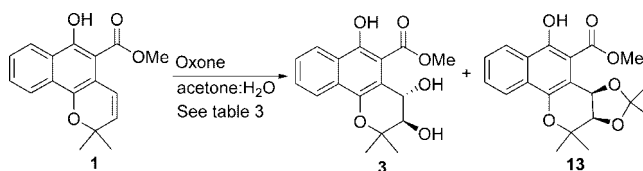


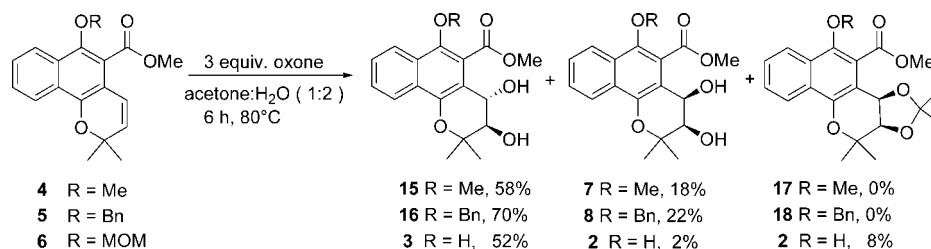
TABLE 3. Effect of Various Parameters in the Reaction of Mollugin **1** with Oxone

entry	Oxone (equiv)	<i>T</i> (°C)	time (h)	yield of 3 (%)	yield of 13 (%)	solvent
1	1.2	rt	96			THF/H ₂ O (1:1)
2	1.2	rt	96			MeOH/H ₂ O (1:1)
3	1.5	rt	96	15	10	CH ₃ COCH ₃ /H ₂ O (1:1)
4	2.0	rt	120	15	18	CH ₃ COCH ₃ /H ₂ O (1:1)
5	3.0	80	5	10	32	CH ₃ COCH ₃ /H ₂ O (2:1)
6	3.0	80	12	8	48	CH ₃ COCH ₃ /H ₂ O (2:1)
7	3.0	80	24	5	30	CH ₃ COCH ₃ /H ₂ O (2:1)
8	6.0	80	24	5	25	CH ₃ COCH ₃ /H ₂ O (2:1)
9	3.0	80	12	31	22	CH ₃ COCH ₃ /H ₂ O (1:2)

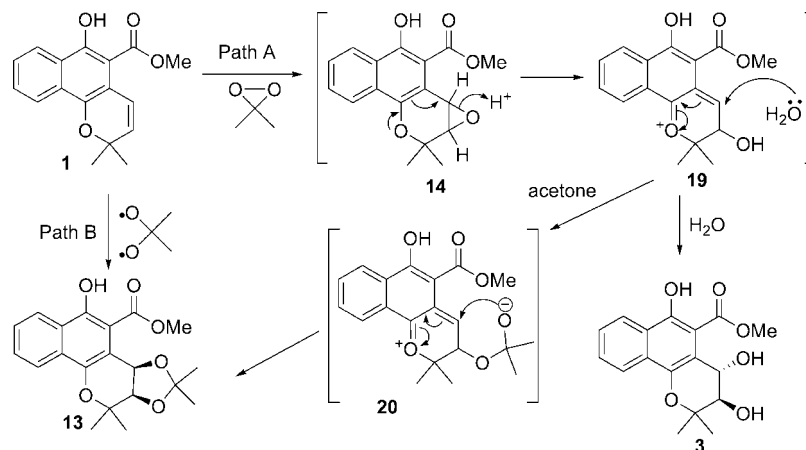
a solvent mixture of acetone/H₂O (5:2) did not afford the required epoxide **14**. Repeated endeavors by varying the amount of H_2O_2 using different bases in diverse solvents, e.g., acetone/H₂O (5:2) (2 equiv of Na_2CO_3), EtOH/H₂O (5:2) (1.5 equiv of Na_2CO_3), or THF/H₂O (3:1) (2 equiv of LiOH), failed. Sub-

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SCHEME 7



SCHEME 8. Mechanistic Proposal for the Dioxirane-Mediated Formation of 3,4-Dihydromollugin Acetonide 13



sequently, electrophilic epoxidizing agents such as *m*-CPBA, sodium hypochlorite, and Oxone (2KHSO₅, KHSO₄, K₂SO₄) were investigated. The reaction of mollugin **1** either with *m*-CPBA in the presence of base or using sodium hypochlorite/pyridine, did not lead to one distinct product. Interestingly, stirring of mollugin **1** with 2 equiv of Oxone in a solvent mixture of acetone/H₂O (1:1) for 120 h at ambient temperature resulted in the formation of a mixture of two compounds (Scheme 6). One of the compounds was identified as *trans*-3,4-dihydroxy-3,4-dihydromollugin **3** (15%), while the other was surprisingly identified as 3,4-dihydroxymollugin acetonide **13** on the basis of following evidence. The ¹H NMR spectrum of the tetracyclic compound **13** showed two singlets corresponding to two additional methyl groups and also an extra quaternary acetal carbon at δ 104.67 in its ¹³C NMR spectrum (CDCl₃).

In order to improve the yield of the required *trans*-diol **3**, various parameters have been examined (Table 3). The reaction did not work with solvent mixtures such as THF/H₂O and MeOH/H₂O. It is interesting to note that the increase in the amount of Oxone at elevated temperature led to an increment in the formation of 3,4-dihydroxymollugin acetonide **13** along with a simultaneous decrease in the amount of *trans*-diol **3**. It was observed that the temperature of the reaction also affected the rate of the reaction. The ratio of solvents (acetone/H₂O) also played an important role in determining the product formation. For instance, a solvent mixture of acetone/H₂O (2:1) favors the formation of acetonide **13** in 48% yield (entry 6), whereas the same reaction in acetone/H₂O (1:2) resulted in the formation of *trans*-diol **3** as the major product (31%, entry 9). The unsatisfactory results for the synthesis of compound **3** starting from mollugin turned the attention to look again for *O*-protected mollugin derivatives. It was thought that the same reasons which are preventing to obtain good yields in the *cis*-dihydroxylation of mollugin **1** using OsO₄ are also playing a role here. With this intention, the *O*-protected mollugin derivatives (**4–6**)

were subjected to a reaction with Oxone in aqueous acetone (Scheme 7). The reaction of *O*-methylmollugin **4** or *O*-benzylmollugin **5** with 3 equiv of Oxone in acetone/H₂O at 80 °C for 6 h resulted in the corresponding *trans*-diols **15** and **16** in 58% and 70%, respectively. Surprisingly, during these reactions the corresponding acetonides **17** (R = Me) and **18** (R = Bn) were not observed as expected, but their corresponding *cis*-diols (**10**, 18%; **11**, 22%) were obtained. These *cis*-diols (**10–11**) can be formed from their corresponding acetonides (**17** and **18**) due to the slight acidic conditions associated with Oxone. Interestingly, the MOM-ether of mollugin **6** reacted with Oxone under these conditions to afford the required *trans*-diol **3** in 52% yield along with 8% of 3,4-dihydroxymollugin acetonide **13**. This deprotection of MOM group may be due to the acidic character of oxone.

By considering the mechanistic features of this reaction, the formation of *cis*-3,4-dihydroxymollugin acetonide **13** is an important issue for discussion. In general, the mechanism of Oxone-mediated epoxidations of alkenes involves the initial *in situ* formation of an active species, i.e., 3,3-dimethyldioxirane, by the reaction of Oxone with acetone. The generated 3,3-dimethyldioxirane can react in two ways such that it follows either an ionic pathway or a radical path.¹⁴ Electrophilic attack of 3,3-dimethyldioxirane across mollugin **1** in a concerted way leads to 3,4-epoxymollugin **14** (Scheme 8).

Due to the instability of 3,4-epoxymollugin **14**, the epoxide readily opens to form the reactive *o*-quinomethide intermediate **19**. Antiattack of water as nucleophile across intermediate **19** leads to the corresponding *trans*-diol **3**. Addition of acetone to *o*-quinomethide **19** results in the formation of intermediate **20**, finally leading to *cis*-acetonide **13**. Alternatively, it is also suggested to be possible to generate bis(oxy)diradicals, which

(14) (a) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (b) Curci, R.; Dinioi, A.; Rubino, M. F. *Pure Appl. Chem.* **1995**, *67*, 811.

follow path B leading to 3,4-dihydroxymollugin acetonide **13**. Spectroscopic analysis by NOE study of compound **13** indicated a *cis*-configuration of the acetonide. In the NOE spectrum of 3,4-dihydroxymollugin acetonide **13**, a nuclear Overhauser effect between the two vicinal hydrogens indicated the *cis*-configuration. The formation of the *cis*-diols (**10** and **11**) from their corresponding *O*-protected mollugin (**4** and **5**) in the reaction with Oxone also stands as an indirect evidence for the *cis* configuration of acetonide **13**. Furthermore, literature studies revealed that the formation of such acetonide via a dioxygen radical with less reactive double bonds is feasible as is previously described in the case of patulin.¹⁵ It is also possible to explain why protected acetonides **17** (R = Me) and **18** (R = Bn) were not formed from their corresponding mollugin derivatives on the basis of the mechanism. The electron density associated with *O*-protected mollugin makes their double bond more electron rich and thereby facilitate DMD to react in an electrophilic manner to produce more of the *trans*-diol **3** rather than the acetonide **13**.

3. Conclusions

In conclusion, the natural products *cis*-3,4-dihydroxy-3,4-dihydromollugin **2** and *trans*-3,4-dihydroxy-3,4-dihydromollugin **3** were successfully synthesized in good to very good yield for the first time. The electronic properties and thus the reactivity of the double bond of mollugin is remarkably influenced by its protecting group. It is unequivocally important to conduct the *cis*-dihydroxylation reactions onto *O*-protected mollugin in darkness. In the reaction of mollugin **1** with Oxone afforded *trans*-3,4-dihydroxy-3,4-dihydromollugin **3** albeit together with the formation of the remarkable *cis*-3,4-dihydroxymollugin acetonide **13**. The formation of *cis*-3,4-dihydroxymollugin acetonide **13** in the reaction between mollugin **1** and Oxone clearly explains the less reactive nature of the double bond present in it. A plausible mechanism for the formation of *trans*-diol **3** and the *cis*-acetonide **13** from mollugin **1** using Oxone was proposed.

4. Experimental Section

4.1. Synthesis of *O*-Protected Mollugin 4–6. **4.1.1. Methyl 6-Methoxy-2,2-dimethyl-2*H*-benzo[*h*]chromene-5-carboxylate 4 (Mollugin 6-Methyl Ether).** Potassium carbonate (0.86 g, 6.25 mol) followed by methyl iodide (0.46 mL, 7.5 mol) were added to a stirred solution of mollugin **1** (1.42 g, 5 mol) in acetone (40 mL). The reaction mixture was stirred at room temperature for 18 h, after which K₂CO₃ was filtered and washed with acetone (10 mL). The combined organic layers were evaporated in vacuo, and the crude product was purified by flash column chromatography (petroleum ether/ethyl acetate 95/5 R_f 0.17) to give **4** as a thick viscous yellow liquid, which solidifies on standing for several days: yellow solid (1.41 g, 95%); mp 68–69 °C; ¹H NMR (CDCl₃) δ 1.51 (6H, s, 2 × CH₃), 3.96 (3H, s, COOCH₃), 3.99 (3H, s, OCH₃), 5.69 (1H, d, *J* = 9.9 Hz, CH-3), 6.42 (1H, d, *J* = 9.9 Hz, CH-4), 7.47–7.55 (2H, m, CH_{ar}), 8.00–8.08 (1H, m, CH_{ar}), 8.17–8.24 (1H, m, CH_{ar}); ¹³C NMR (CDCl₃): δ 27.7 (2 × CH₃), 52.5 (COOCH₃), 63.6 (OCH₃), 76.5 (C_{quat}), 77.5 (C_{quat}), 112.5 (C_{quat}), 119.9 (CH_{ar}), 120.6 (C_{quat}), 122.6 (CH_{ar}), 122.7 (CH_{ar}), 126.8 (CH_{ar}), 126.9 (CH_{ar}), 127.9 (C_{quat}), 130.3 (CH_{ar}), 145.0 (C_{quat}), 147.6 (C_{quat}), 167.9 (C=O); IR (KBr) ν_{max} 1713 (C=O); MS (ES⁺) *m/z* 299 (M + H⁺, 100). Anal. Calcd for C₁₈H₁₈O₄: C, 72.47; H, 6.08. Found: C, 72.83; H, 6.49.

4.1.2. Methyl 6-Benzoyloxy-2,2-dimethyl-2*H*-benzo[*h*]chromene-5-carboxylate 5 (Mollugin 6-Benzyl Ether). K₂CO₃ (0.86 g, 6.25 mol) followed by benzyl bromide (0.72 mL, 6.0 mol) were added to a stirred solution of mollugin **1** (1.42 g, 5 mol) in *N,N*-dimethylformamide (30 mL), and the reaction mixture was heated at 65 °C for 4 h. After completion of the reaction (monitoring with TLC), water (50 mL) was added and the aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over MgSO₄ and evaporated in vacuo, and the crude product was purified by flash column chromatography (petroleum ether/ethyl acetate 95/5 R_f 0.18) to give **5**: white solid (1.68 g, 90%); mp 72–73 °C; ¹H NMR (CDCl₃) δ 1.53 (6H, s, 2 × CH₃), 3.90 (3H, s, COOCH₃), 3.99 (3H, s, OCH₃), 5.10 (2H, s, OCH₂), 5.70 (1H, d, *J* = 9.9 Hz, CH-3), 6.44 (1H, d, *J* = 9.9 Hz, CH-4), 7.33–7.55 (2H, m, CH_{ar}), 8.03–8.10 (1H, m, CH_{ar}), 8.19–8.25 (1H, m, CH_{ar}); ¹³C NMR (CDCl₃) δ 27.8 (2 × CH₃), 52.5 (COOCH₃), 77.5 (C_{quat}), 77.9 (OCH₂), 112.6 (C_{quat}), 119.9 (CH_{ar}), 121.1 (C_{quat}), 122.6 (CH_{ar}), 122.8 (CH_{ar}), 126.8 (C_{quat}), 126.9 (CH_{ar}), 127.0 (C_{quat}), 127.9 (2 × CH_{ar}), 128.1 (C_{quat}), 128.2 (CH_{ar}), 128.6 (2 × CH_{ar}), 130.3 (CH_{ar}), 137.4 (CH_{ar}), 145.2 (C_{quat}), 146.4 (C_{quat}), 167.9 (C=O); IR (KBr) ν_{max} 1726 (C=O); MS (ES⁺) *m/z* 375 (M + H⁺, 100). Anal. Calcd for C₂₄H₂₂O₄: C, 76.99; H, 5.92. Found: C, 76.79; H, 6.14.

4.1.3. Methyl 6-Methoxymethoxy-2,2-dimethyl-2*H*-benzo[*h*]chromene-5-carboxylate 6 (Mollugin 6-Methoxymethyl Ether). *N,N*-Diisopropylethylamine (1.07 mL, 6.5 mol) was added at 0 °C under N₂ atmosphere to a stirred solution of mollugin **1** (1.42 g, 5 mol) in dry dichloromethane (10 mL). After the reaction mixture was stirred for 15 min at this temperature, MOM-Cl (0.569 mL, 7.5 mol) was added, and stirring was continued at room temperature. After 24 h, 2 N HCl (20 mL) was added, and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic layers were evaporated in vacuo, and the crude product was purified by flash column chromatography (petroleum ether/ethyl acetate 95/5 R_f 0.18) to give **6** as a thick viscous yellow liquid (1.50 g, 92%); ¹H NMR (CDCl₃) δ 1.51 (6H, s, 2 × CH₃), 3.61 (3H, s, COOCH₃), 3.98 (3H, s, OCH₃), 5.12 (2H, s, OCH₂), 5.69 (1H, d, *J* = 9.9 Hz, CH-3), 6.42 (1H, d, *J* = 9.9 Hz, CH-4), 7.45–7.55 (2H, m, CH_{ar}), 8.04–8.12 (1H, m, CH_{ar}), 8.16–8.23 (1H, m, CH_{ar}); ¹³C NMR (CDCl₃) δ 27.8 (2 × CH₃), 52.5 (COOCH₃), 57.8 (OCH₃), 76.6 (OCH₂), 77.5 (C_{quat}), 101.3 (C_{quat}), 112.5 (C_{quat}), 120.0 (CH_{ar}), 121.3 (C_{quat}), 122.4 (CH_{ar}), 123.0 (CH_{ar}), 126.8 (C_{quat}), 127.0 (CH_{ar}), 128.3 (C_{quat}), 130.3 (C_{quat}), 144.8 (C_{quat}), 145.5 (C_{quat}), 167.7 (C=O); IR (KBr) ν_{max} 1713 (C=O); MS (ES⁺) *m/z* 329 (M + H⁺, 100). Anal. Calcd for C₁₉H₂₀O₅: C, 69.50; H, 6.14. Found: C, 69.34; H, 6.18.

4.2. General Procedure for the Dihydroxylation of *O*-Protected Mollugin Derivatives 4–6 Using OsO₄ in Darkness. The dihydroxylation of compound **4** is taken as a representative example.

Compound **4** (149 mg, 0.5 mmol) was added to a stirred solution of osmium tetroxide (4% in H₂O, 0.317 mL, 0.05 mmol) and 4-methylmorpholine *N*-oxide monohydrate (NMMO) (58.5 mg, 0.5 mmol) in *t*-BuOH/THF/H₂O (10:3:1, 10 mL) at 0 °C in darkness. The reaction mixture was allowed to warm to room temperature, and stirring was continued for 14 h. After the addition of a saturated solution of aqueous sodium bisulfite (10 mL), the mixture was stirred for 1 h and then extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over magnesium sulfate, and evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 60/40 R_f 0.80) affording *O*-methyl-3,4-dihydroxy-3,4-dihydromollugin **7** (petroleum ether/ethyl acetate 80/20 R_f 0.60) and methyl 3-hydroxy-6-methoxy-2,2-dimethyl-4-oxo-3,4-dihydro-2*H*-benzo[*h*]chromene-5-carboxylate **10**.

4.2.1. (±)-Methyl *cis*-3,4-dihydroxy-6-methoxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*h*]chromene-5-carboxylate 7: white solid (136 mg, 78%); mp 115–117 °C; ¹H NMR (CDCl₃) δ 1.42 (3H, s, CH₃), 1.54 (3H, s, CH₃), 2.64 (1H, br s, OH-3), 3.54 (1H, br s,

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OH-4), 3.79 (1H, d, $J = 4.4$ Hz, CH-3), 3.97 (3H, s, COOCH₃), 4.00 (3H, s, OCH₃), 4.97 (1H, d, $J = 4.4$ Hz, CH-4), 7.50–7.62 (2H, m, CH_{ar}), 8.04–8.10 (1H, m, CH_{ar}), 8.19–8.28 (1H, m, CH_{ar}); ¹³C NMR (CDCl₃) δ 23.3 (CH₃), 24.2 (CH₃), 52.9 (COOCH₃), 63.7 (OCH₃), 64.3 (CH-4), 71.5 (CH-3), 77.5 (C_{quat}), 78.4 (C_{quat}), 113.5 (C_{quat}), 122.7 (CH_{ar}), 123.1 (CH_{ar}), 127.1 (C_{quat}), 127.3 (CH_{ar}), 127.4 (CH_{ar}), 128.3 (C_{quat}), 144.2 (C_{quat}), 148.7 (C_{quat}), 169.3 (C=O); IR (KBr) ν_{\max} 1729 (C=O); MS (ES⁺) m/z 333 (M + H⁺, 10), 315 (M – OH⁻, 100). Anal. Calcd for C₁₈H₂₀O₆: C, 65.05; H, 6.07. Found: C, 65.29; H, 6.31.

4.2.2. Methyl 3-hydroxy-6-methoxy-2,2-dimethyl-4-oxo-3,4-dihydro-2H-benzo[h]chromene-5-carboxylate 10: yellow solid (20.7 mg, 12%); mp 122–123 °C; ¹H NMR (CDCl₃) δ 1.31 (3H, s, CH₃), 1.79 (3H, s, CH₃), 3.76 (1H, d, $J = 2.3$ Hz, OH), 3.98 (3H, s, COOCH₃), 4.02 (3H, s, OCH₃), 4.55 (1H, d, $J = 2.3$ Hz, CH-4), 7.59–7.66 (1H, m, CH_{ar}), 7.70–7.77 (1H, m, CH_{ar}), 8.08 (1H, d, $J = 8.4$ Hz, CH_{ar}), 8.34 (1H, d, $J = 8.4$ Hz, CH_{ar}); ¹³C NMR (CDCl₃) δ 17.3 (CH₃), 27.0 (CH₃), 53.0 (COOCH₃), 63.7 (OCH₃), 76.5 (CH-4), 85.2 (C_{quat}), 109.4 (C_{quat}), 119.7 (C_{quat}), 123.0 (CH_{ar}), 124.5 (CH_{ar}), 126.6 (C_{quat}), 127.7 (CH_{ar}), 130.7 (CH_{ar}), 132.1 (C_{quat}), 147.3 (C_{quat}), 155.4 (C_{quat}), 167.8 (C=O), 192.5 (C=O); IR (KBr) ν_{\max} 1691 (C=O), 1706 (COOMe); MS (ES⁺) m/z 331 (M + H⁺, 80), 299 (M – OMe, 100). Anal. Calcd for C₁₈H₁₈O₆: C, 65.45; H, 5.49. Found: C, 65.62; H, 5.78.

4.2.3. (±)-Methyl *cis*-3,4-dihydroxy-6-benzyloxy-2,2-dimethyl-3,4-dihydro-2H-benzo[h]chromene-5-carboxylate 8: white solid (184 mg, 90%) mp 91–93 °C; ¹H NMR (CDCl₃) δ 1.47 (3H, s, CH₃), 1.57 (3H, s, CH₃), 2.56 (1H, d, $J = 9.1$ Hz, OH-3), 3.55 (1H, d, $J = 7.3$ Hz, OH-4), 3.85 (1H, dd, $J = 9.1$ Hz, 4.7 Hz, CH-3), 3.91 (3H, s, OCH₃), 4.99 (1H, dd, $J = 7.3$ Hz, 4.7 Hz, CH-4), 5.06 (1H, d, $J = 11.0$ Hz, OCH₂), 5.16 (1H, d, $J = 11.0$ Hz, OCH₂), 7.34–7.47 (3H, m, CH_{ar}), 7.48–7.60 (4H, m, CH_{ar}), 8.07–8.15 (1H, m, CH_{ar}), 8.23–8.30 (1H, m, CH_{ar}); ¹³C NMR (CDCl₃) δ 23.1 (CH₃), 24.5 (CH₃), 52.9 (COOCH₃), 64.4 (OCH₂), 71.7 (CH-4), 78.0 (CH-3), 78.4 (C_{quat}), 113.7 (C_{quat}), 122.8 (CH_{ar}), 123.1 (CH_{ar}), 123.2 (C_{quat}), 127.2 (C_{quat}), 127.4 (CH_{ar}), 127.5 (CH_{ar}), 127.9 (2 × CH_{ar}), 128.2 (CH_{ar}), 128.6 (C_{quat}), 128.7 (2 × CH_{ar}), 137.3 (C_{quat}), 144.4 (C_{quat}), 147.6 (C_{quat}), 169.3 (C=O); IR (KBr) ν_{\max} 1718 (C=O); MS (ES⁺) m/z 391 (M – OH⁻, 100). Anal. Calcd for C₂₄H₂₄O₆: C, 70.57; H, 5.92. Found: C, 70.66; H, 6.09.

4.2.4. Methyl 3-hydroxy-6-benzyloxy-2,2-dimethyl-4-oxo-3,4-dihydro-2H-benzo[h]chromene-5-carboxylate 11: yellow crystals (10 mg, 5%); mp 133–134 °C; ¹H NMR (CDCl₃) δ 1.33 (3H, s, CH₃), 1.80 (3H, s, CH₃), 3.79 (1H, br s, OH), 3.96 (3H, s, COOCH₃), 4.58 (1H, s, CH-3), 5.07 (1H, d, $J = 10.7$ Hz), 5.15 (1H, d, $J = 10.7$ Hz), 7.34–7.48 (3H, m, CH_{ar}), 7.49–7.57 (2H, m, CH_{ar}), 7.58–7.76 (2H, m, CH_{ar}), 8.10 (1H, d, $J = 8.4$ Hz, CH_{ar}), 8.35 (1H, d, $J = 8.4$ Hz, CH_{ar}); ¹³C NMR (CDCl₃) δ 17.3 (CH₃), 27.1 (CH₃), 53.0 (COOCH₃), 76.5 (CH-4), 78.2 (CH-3), 85.3 (C_{quat}), 109.5 (C_{quat}), 120.4 (C_{quat}), 123.1 (CH_{ar}), 124.4 (CH_{ar}), 126.6 (C_{quat}), 127.8 (CH_{ar}), 128.1 (2 × CH_{ar}), 128.4 (CH_{ar}), 128.7 (2 × CH_{ar}), 130.8 (CH_{ar}), 132.4 (C_{quat}), 136.9 (C_{quat}), 146.2 (C_{quat}), 155.5 (C_{quat}), 167.9 (C=O), 192.5 (C=O); IR (KBr) ν_{\max} 1675 (C=O), 1733 (COOMe); MS (ES⁺) m/z 407 (M + H⁺, 100). Anal. Calcd for C₂₄H₂₂O₆: C, 70.92; H, 5.46. Found: C, 69.26; H, 5.31.

4.2.5. (±)-Methyl *cis*-3,4-dihydroxy-6-methoxymethoxy-2,2-dimethyl-3,4-dihydro-2H-benzo[h]chromene-5-carboxylate 9: white solid (172 mg, 95%); mp 128–129 °C; ¹H NMR (CDCl₃) δ 1.45 (3H, s, CH₃), 1.56 (3H, s, CH₃), 2.46 (1H, d, $J = 9.2$ Hz, OH-3), 3.47 (1H, d, $J = 7.5$ Hz, OH-4), 3.63 (3H, s, COOCH₃), 3.82 (1H, dd, $J = 9.2$ Hz, 4.7 Hz, CH-3), 4.00 (3H, s, OCH₃), 4.99 (1H, dd, $J = 7.5$ Hz, 4.7 Hz, CH-4), 5.11 (1H, d, $J = 6.0$ Hz, OCH₂), 5.15 (1H, d, $J = 6.0$ Hz, OCH₂), 7.52–7.61 (2H, m, CH_{ar}), 8.07–8.15 (1H, m, CH_{ar}), 8.20–8.28 (1H, m, CH_{ar}); ¹³C NMR (CDCl₃) δ 23.4 (CH₃), 24.2 (CH₃), 52.9 (OCH₃), 57.9 (OCH₂), 64.4 (CH-4), 71.6 (CH-3), 78.4 (C_{quat}), 101.3 (C_{quat}), 113.5 (C_{quat}), 122.9 (CH_{ar}), 123.0 (CH_{ar}), 123.6 (C_{quat}), 127.0 (C_{quat}), 127.4 (CH_{ar}), 127.6 (CH_{ar}), 128.7 (C_{quat}), 144.5 (C_{quat}), 146.0 (C_{quat}), 169.1 (C=O); IR

(KBr) ν_{\max} 1706 (C=O); MS (ES⁺) m/z 345 (M – OH⁻, 100). Anal. Calcd for C₁₉H₂₂O₇: C, 62.97; H, 6.12. Found: C, 62.87; H, 6.20.

4.2.6. Methyl 3-hydroxy-6-methoxymethoxy-2,2-dimethyl-4-oxo-3,4-dihydro-2H-benzo[h]chromene-5-carboxylate 12: yellow solid (1.8 mg, 1%); mp 119–120 °C; ¹H NMR (CDCl₃) δ 1.30 (3H, s, CH₃), 1.79 (3H, s, CH₃), 3.65 (3H, s, COOCH₃), 3.80 (1H, d, $J = 2.0$ Hz, OH), 4.00 (3H, s, OCH₂OCH₃), 4.56 (1H, d, $J = 2.0$ Hz, CH-4), 5.12–5.22 (2H, m, OCH₂), 7.58–7.67 (1H, m, CH_{ar}), 7.70–7.78 (1H, m, CH_{ar}), 8.16 (1H, d, $J = 8.4$ Hz, CH_{ar}), 8.29–8.35 (1H, d, $J = 8.4$ Hz, CH_{ar}); ¹³C NMR (CDCl₃) δ 17.3 (CH₃), 27.0 (CH₃), 53.0 (OCH₃), 57.9 (OCH₃), 76.5 (C_{quat}), 85.3 (CH-4), 101.5 (C_{quat}), 109.5 (C_{quat}), 120.3 (C_{quat}), 123.5 (CH_{ar}), 124.2 (CH_{ar}), 126.5 (C_{quat}), 127.8 (CH_{ar}), 130.8 (CH_{ar}), 132.7 (C_{quat}), 144.9 (C_{quat}), 155.6 (C_{quat}), 167.7 (COOMe), 192.5 (C=O); IR (KBr) ν_{\max} 1684 (C=O), 1732 (COOMe); MS (ES⁺) m/z 361 (M + H⁺, 100). Anal. Calcd for C₁₉H₂₀O₇: C, 63.33; H, 5.59. Found: C, 62.98; H, 5.73.

4.3. Procedure for the O-Deprotection of the MOM Ether of (±)-Methyl *cis*-3,4-Dihydroxy-6-methoxymethoxy-2,2-dimethyl-3,4-dihydro-2H-benzo[h]chromene-5-carboxylate 9. To a stirred solution of compound **9** (362 mg, 1 mmol) in THF (2 mL) at 0 °C was added 4 N HCl (2 mL) dropwise. The reaction mixture was allowed to stir at 0–10 °C for 18 h, the solution was diluted with water (6 mL), and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over magnesium sulfate and evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 65/35 R_f 0.85) affording *cis*-3,4-dihydroxy-3,4-dihydromollugin **2** as a white solid.

4.3.1. (±)-Methyl *cis*-3,4,6-trihydroxy-2,2-dimethyl-3,4-dihydro-2H-benzo[h]chromene-5-carboxylate 2 (*cis*-3,4-dihydroxy-3,4-dihydromollugin): white solid (269 mg, 85%); mp 134–135 °C (hexane/CH₂Cl₂, 5/1) [lit.^{5b} mp 107.6–108 °C (CHCl₃)]; ¹H NMR (CDCl₃) δ 1.50 (3H, s, CH₃), 1.51 (3H, s, CH₃), 2.79 (1H, d, $J = 9.5$ Hz, OH-3), 3.53 (1H, d, $J = 6.6$ Hz, OH-4), 3.85 (1H, dd, $J = 9.5$ Hz, 5.2 Hz, CH-3), 4.06 (3H, s, COOCH₃), 5.22 (1H, dd, $J = 6.6$ Hz, 5.2 Hz, CH-4), 7.53–7.68 (2H, m, CH_{ar}), 8.20 (1H, d, $J = 8.3$ Hz, CH_{ar}), 8.37 (1H, d, $J = 8.3$ Hz, CH_{ar}), 11.23 (1H, s, OH); ¹³C NMR (CDCl₃) δ 22.1 (CH₃), 24.9 (CH₃), 52.9 (OCH₃), 64.4 (CH-4), 72.3 (CH-3), 77.5 (C_{quat}), 104.7 (C_{quat}), 112.9 (C_{quat}), 122.6 (CH_{ar}), 124.0 (CH_{ar}), 125.7 (C_{quat}), 127.1 (CH_{ar}), 128.9 (C_{quat}), 129.6 (CH_{ar}), 140.9 (C_{quat}), 155.9 (C_{quat}), 171.3 (C=O); IR (KBr) ν_{\max} 1654 (C=O), 3453 (OH); MS (ES⁻) m/z 317 (M – H⁺, 100). Anal. Calcd for C₁₇H₁₈O₆: C, 64.14; H, 5.70. Found: C, 64.63; H, 5.14.

4.3.2. (±)-Methyl *trans*-3,4,6-trihydroxy-2,2-dimethyl-3,4-dihydro-2H-benzo[h]chromene-5-carboxylate 3 (*trans*-3,4-dihydroxy-3,4-dihydromollugin): white solid (64 mg, 20%); mp 162–163 °C; ¹H NMR (CDCl₃) δ 1.40 (3H, s, CH₃), 1.58 (3H, s, CH₃), 2.41 (1H, br. s, OH-3), 3.18 (1H, br. s, OH-4), 3.80 (1H, d, $J = 6.2$ Hz, CH-3), 4.06 (3H, s, COOCH₃), 5.06 (1H, d, $J = 6.2$ Hz, CH-4), 7.53–7.68 (2H, m, CH_{ar}), 8.19 (1H, d, $J = 8.3$ Hz, CH_{ar}), 8.37 (1H, d, $J = 8.3$ Hz, CH_{ar}), 11.51 (1H, s, OH); ¹³C NMR (CDCl₃) δ 19.7 (CH₃), 25.6 (CH₃), 52.9 (OCH₃), 69.8 (CH-4), 76.1 (CH-3), 77.5 (C_{quat}), 103.8 (C_{quat}), 112.9 (C_{quat}), 122.6 (CH_{ar}), 124.1 (CH_{ar}), 125.7 (C_{quat}), 127.1 (CH_{ar}), 129.1 (C_{quat}), 129.7 (CH_{ar}), 141.0 (C_{quat}), 156.6 (C_{quat}), 171.4 (C=O); IR (KBr) ν_{\max} 1630 (C=O), 3325 (OH). MS (ES⁻) m/z 317 (M – H⁺, 100). Anal. Calcd for C₁₇H₁₈O₆: C, 64.14; H, 5.70. Found: C, 64.90; H, 6.32.

4.4. General Procedure for the Dihydroxylation of O-Protected Mollugin Derivatives 4–6 Using Oxone. The dihydroxylation of compound **4** is taken as a representative example.

To a stirred solution of compound **4** (298 mg, 1.0 mmol) in acetone (10 mL) was added a solution of Oxone (2KHSO₅, KHSO₄, K₂SO₄) (1.84 g, 3 mmol) dissolved in water (20 mL). The reaction mixture was heated at 80 °C for 6 h and was then allowed to cool to room temperature. Aqueous saturated sodium bicarbonate was added (40 mL), and the aqueous phase was extracted into ethyl acetate (3 × 30 mL). The combined organic layers were washed

with water (2 × 20 mL), dried over magnesium sulfate, and evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 60/40 R_f 0.94) to afford the *trans*-*O*-methyl 3,4-dihydroxy-3,4-dihydromollugin **15** along with (petroleum ether/ethylacetate 65/35 R_f 0.82) *cis*-*O*-methyl 3,4-dihydroxy-3,4-dihydromollugin **7** (59 mg, 18%).

4.4.1. (±)-Methyl *trans*-3,4-dihydroxy-6-methoxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*h*]chromene-5-carboxylate **15:** white solid (193 mg, 58%); mp 82–83 °C; $^1\text{H NMR}$ (CDCl_3) δ 1.22 (3H, s, CH_3), 1.37 (3H, s, CH_3), 3.55 (1H, d, $J = 7.8$ Hz, CH-3), 3.88 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 4.15 (1H, brs, OH-3), 4.40 (1H, brs, OH-4), 4.81 (1H, d, $J = 7.8$ Hz, CH-4), 7.47–7.57 (2H, m, CH_{ar}), 7.97–8.03 (1H, m, CH_{ar}), 8.08–8.15 (1H, m, CH_{ar}); $^{13}\text{C NMR}$ (CDCl_3) δ 19.7 (CH_3), 25.9 (CH_3), 52.9 (OCH_3), 63.7 (Ar- OCH_3), 69.1 (CH-4), 76.1 (CH-3), 78.9 (C_{quat}), 113.5 (CH_{ar}), 122.0 (C_{quat}), 122.6 (C_{quat}), 123.1 (CH_{ar}), 127.0 (CH_{ar}), 127.2 (C_{quat}), 127.4 (CH_{ar}), 128.2 (CH_{ar}), 144.5 (C_{quat}), 148.5 (C_{quat}), 169.5 (C=O); IR (KBr) ν_{max} : 1712 (C=O); MS (ES^+) m/z 333 ($\text{M} + \text{H}^+$, 10), 315 ($\text{M} - \text{OH}^-$, 100). Anal. Calcd for $\text{C}_{18}\text{H}_{20}\text{O}_6$: C, 65.05; H, 6.07. Found: C, 64.78; H, 6.14.

4.4.2. (±)-Methyl *trans*-3,4-dihydroxy-6-benzyloxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*h*]chromene-5-carboxylate **16:** white solid (286 mg, 70%); mp 88–90 °C; $^1\text{H NMR}$ (CDCl_3) δ 1.40 (3H, s, CH_3), 1.60 (3H, s, CH_3), 2.36 (1H, br. s, OH-3), 3.08 (1H, br. s, OH-4), 3.82 (1H, d, $J = 7.2$ Hz, CH-3), 3.89 (3H, s, OCH_3), 4.82 (1H, d, $J = 7.2$ Hz, CH-4), 5.05 (1H, d, $J = 11.1$ Hz, OCH_2), 5.17 (1H, d, $J = 11.1$ Hz, OCH_2), 7.35–7.59 (7H, m, CH_{ar}), 8.07–8.13 (1H, m, CH_{ar}), 8.23–8.28 (1H, m, CH_{ar}); $^{13}\text{C NMR}$ (CDCl_3) δ 19.9 (CH_3), 25.9 (CH_3), 52.9 (OCH_3), 69.2 (Ar- OCH_3), 76.0 (CH-4), 77.9 (C_{quat}), 78.6 (C_{quat}), 113.7 (C_{quat}), 122.5 (C_{quat}), 122.7 (CH_{ar}), 123.1 (CH_{ar}), 127.1 (C_{quat}), 127.3 (CH_{ar}), 127.5 (CH_{ar}), 127.9 (2 × CH_{ar}), 128.2 (CH_{ar}), 128.5 (C_{quat}), 128.6 (2 × CH_{ar}), 137.3 (C_{quat}), 144.6 (C_{quat}), 147.4 (C_{quat}), 169.4 (C=O); IR (KBr) ν_{max} 1709 (C=O); MS (ES^+) m/z 391 ($\text{M} - \text{OH}^-$, 100). Anal. Calcd for $\text{C}_{24}\text{H}_{24}\text{O}_6$: C, 70.57; H, 5.92. Found: C, 69.93; H, 6.41.

4.5. Synthesis of (±)-*cis*-3,4-Dihydroxymollugin Acetonide **13 from Mollugin **1**.** To a stirred solution of mollugin **1** (284 mg,

1.0 mmol) in acetone (20 mL) was added a solution of Oxone (2KHSO₅, KHSO₄, K₂SO₄) (1.84 g, 3 mmol) dissolved in water (10 mL). The reaction mixture was heated at 80 °C for 12 h and then allowed to return to room temperature. Aqueous saturated sodium bicarbonate was added (40 mL) and the aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with water (2 × 20 mL), dried over magnesium sulfate and evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethylacetate 85/15 R_f 0.65) to afford *cis*-3,4-dihydroxymollugin acetonide **13** together with *trans*-3,4-dihydroxy-3,4-dihydromollugin **3** (26 mg, 8%; petroleum ether/ethyl acetate 60/40 R_f 0.94).

4.5.1. (±)-*cis*-3,4-Dihydroxymollugin acetonide **13:** yellow crystals (172 mg, 48%); mp 142–143 °C; $^1\text{H NMR}$ (CDCl_3) δ 1.01 (3H, s, CH_3), 1.38 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.55 (3H, s, CH_3), 4.02 (3H, s, COOCH_3), 4.18 (1H, d, $J = 6.1$ Hz CH-3), 5.80 (1H, d, $J = 6.1$ Hz CH-4), 7.50–7.66 (2H, m, CH_{ar}), 8.22 (1H, d, $J = 8.3$ Hz, CH_{ar}), 8.36 (1H, d, $J = 8.3$ Hz, CH_{ar}), 11.65 (1H, s, OH); $^{13}\text{C NMR}$ (CDCl_3) δ 23.2 (CH_3), 24.7 (CH_3), 26.9 (CH_3), 27.5 (CH_3), 52.4 (OCH_3), 70.9 (CH-3), 74.8 (C_{quat}), 78.1 (CH-4), 104.6 (C_{quat}), 109.5 (C_{quat}), 111.6 (C_{quat}), 122.7 (CH_{ar}), 123.8 (CH_{ar}), 125.6 (C_{quat}), 126.9 (CH_{ar}), 127.1 (CH_{ar}), 128.8 (C_{quat}), 129.2 (CH_{ar}), 140.9 (C_{quat}), 155.9 (C_{quat}), 172.4 (C=O); IR (KBr) ν_{max} 1645 (C=O), 3285 (OH); MS (ES^+) m/z 359 ($\text{M} + \text{H}^+$, 100). Anal. Calcd for $\text{C}_{20}\text{H}_{22}\text{O}_6$: C, 67.03; H, 6.19. Found: C, 67.48; H, 6.33.

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Supporting Information Available: Experimental procedures and characterization. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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