A Novel Method for the Synthesis of Substituted Benzochromenes by Ethylenediamine Diacetate-Catalyzed Cyclizations of Naphthalenols to α,β-Unsaturated Aldehydes. Concise Synthesis of the Natural Products Lapachenole, Dihydrolapachenole, and Mollugin

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A new synthetic route for biologically interesting benzochromenes was developed starting from naphthalenols and α,β-unsaturated aldehydes in the presence of ethylenediamine diacetate. This methodology was applied for the total synthesis of the biologically important natural products lapachenole, dihydrolapachenole, and mollugin with a benzochromene moiety.

Introduction. – Molecules with the benzochromene (or naphthopyran) moiety are found widely in nature (*Fig.*) [1]. These compounds have been shown to have a range of significant biological and pharmacological properties. For example, lapachenole (**1**), tectol (**7**), acetylated tectol (**8**), and tecomaquinone (**9**) were isolated from *Lippia sidoides*, which is known as 'Alecrim pimenta', an odoriferous plant that grows wild in the northeastern region of Brazil [1a]. The aerial parts of this species are used traditionally as anti-infective and antiseptic agents, which contain thymol and carvacrol as the major constituents [2]. They also exhibit bactericidal and fungicidal activity [3]. Lapachenole (**1**) and dihydrolapachenole (**2**) were isolated from *Tabebuia chrysantha* [4]. Recently, lapachenole (**1**), isolated from *Avicennia rumphiana*, was shown to have a great cancer chemopreventive activity [5]. Mollugin (**3**) was isolated from the Chinese medicinal plant *Rubia cordifolia* [6] and has potential antitumor, antimutagenic, as well as antiviral activity against the hepatitis B virus [7]. In addition, mollugin (**3**) has been shown to strongly inhibit the arachadonic acid-induced and collagen-induced platelet aggregation [7]. Compounds **5a** and **5b** were isolated from *Pentas longiflora*, which is an important medicinal plant in Tropical East Africa [8]. 'Nekilango' or 'Segimbe' in Kenya and its root is used as a cure for tapeworm, itchy rashes, malaria, and pimples [9]. In Rwanda, this plant is also known as 'Isagara', and is used as an ointment to treat scabies and the skin disease pityriasis versicolar [9].

Compound **6** was isolated from *Pentas bussei* in Kenya, which is called 'Mdobe' or 'Mudobe' in the local dialect (Digo) [10]. A decoction of the roots is taken as a remedy for gonorrhea, syphilis, and dysentery. Microphyllaquinone (**10**) was isolated from the roots of *Lippia microphylla* [11], whereas rubioncolin B (**11**) was isolated from *Rubia cordifolia* [12] and *R. oncotricha* [13]. Both compounds have shown potent cytotoxic and antitumor activities. Compounds with a benzochromene skeleton are also used as important photochromic agents [14]. Lapachenole (**2**) and its derivatives are widely

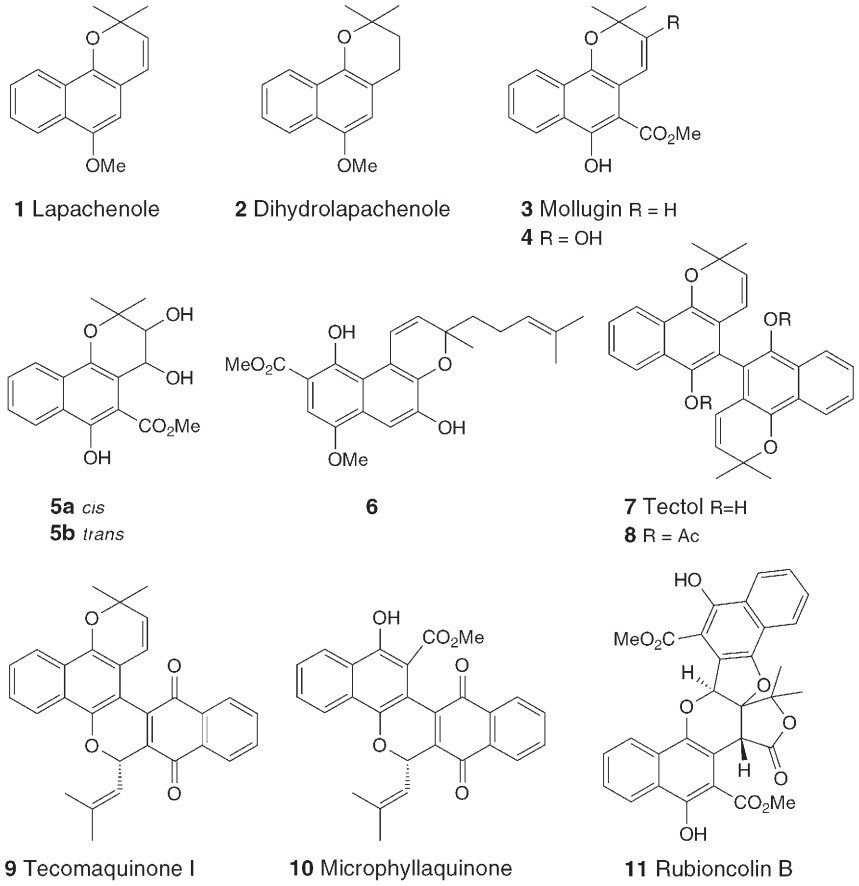


Fig. 1. *Selected natural products with benzochromene moiety*

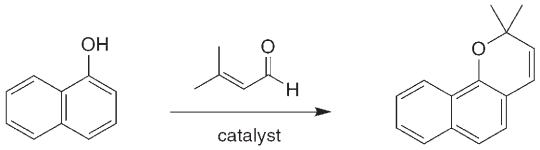
used as effective photoaffinity reagents of cytochrome P450 3A4 in protein-structure studies in the field of drug metabolizing enzymes [15].

Several synthetic approaches to benzochromenes have been reported [16–22]. These methods include the condensation of naphthalenol with propargylic alcohol in the presence of acid [16], a reaction of naphthalenols with titanium ethoxide [17], alumina-catalyzed reaction between 2-hydroxynaphthaldehyde and methyl cyanoacetate [18], and a reaction of 1-bromonaphthalen-2-ol with 3-methylbut-2-enal over organolithium [19]. As other methods, cycloaddition of phenol or naphthalenol to α,β-unsaturated aldehydes has also been reported in refluxing pyridine [20]. These reactions are limited by the harsh reaction conditions, unsatisfactory yields, and stoichiometric amounts of catalyst used. The cycloaddition of naphthalenols to dimethyl acetylenedicarboxylate in the presence of *tert*-butyl isocyanide [21] or trimethyl phosphate [22] has been reported as a useful strategy for synthesizing benzochromenes. However, there is still a demand for general methods that can efficiently provide various substituents on the benzochromene rings.

Recently, a new methodology was developed for the preparation of a variety of benzopyrans by ethylenediamine diacetate (EDDA)-catalyzed reactions between 1,3-dicarbonyl compounds or resorcinols, and α,β-unsaturated aldehydes [23]. These reactions involve a formal [3 + 3] cycloaddition of the resorcinols to α,β-unsaturated aldehydes *via* a 6π-electrocyclization. As part of an ongoing study of the synthetic efficacy of this methodology, we investigated ethylenediamine diacetate-catalyzed reactions of naphthalenols with α,β-unsaturated aldehydes. We report a mild and facile methodology for preparing biologically interesting benzochromene derivatives. Using this methodology as a key-step, we also report the concise synthesis of natural products lapachenole, dihydrolapachenole, and mollugin.

Results and Discussion. – The reaction between naphthalen-1-ol (**12**) and 3-methylbut-2-enal was first investigated using several catalysts (*Table 1*). Both $InCl_3$ (10 mol-%) and $Yb(OTf)_3$ (10 mol-%) as *Lewis* acid catalysts in refluxing MeCN did not provide any adducts. No products were obtained with pyridine as the reactant and solvent. Treatment of compound **12** with 3-methylbut-2-enal in the presence of 20 mol-% of $Ca(OH)_2$ according to the *Shigemasa* conditions [24] did not lead to any products. The use of pyridinium *p*-toluenesulfonate (PPTS) as a mild acid also gave no products. However, product **13** was formed with ethylenediamine diacetate (EDDA; 20 mol-%) as a catalyst. This reaction is solvent-dependent and the best yield (75%) was obtained in refluxing $CHCl_3$. Compound **13** was easily separated by column chromatography and identified by spectroscopic analyses.

Table 1. *Reaction of* **12** *with 3-Methylbut-2-enal with Several Catalysts*



12 **13**

Catalyst	Conditions	Yield [%]
$InCl_3$ (10 mol-%)	MeCN, reflux, 5 h	0
$Yb(OTf)_3$ (10 mol-%)	MeCN, reflux, 5 h	0
Pyridine (excess)	reflux, 5 h	0
$Ca(OH)_2$ (20 mol-%)	MeOH, reflux, 12 h	0
PPTS	CH_2Cl_2, reflux, 12 h	0
Ethylenediamine diacetate (20 mol-%)	THF, reflux, 10 h	10
Ethylenediamine diacetate (20 mol-%)	CH_2Cl_2, reflux, 10 h	51
Ethylenediamine diacetate (20 mol-%)	$CHCl_3$, reflux, 10 h	75

Additional reactions of naphthalenols with a variety of α,β-unsaturated aldehydes were carried out in the presence of EDDA (20 mol-%) in refluxing $CHCl_3$. The results are shown in *Table 2*. A reaction of naphthalen-1-ol (**12**) with 3,3-diphenylprop-2-enal

Table 2. *Additional Reactions of Naphthalenols with α,β-Unsaturated Aldehydes*

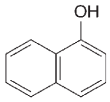
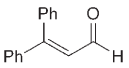
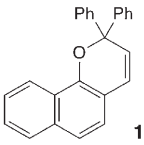
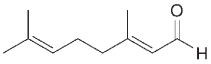
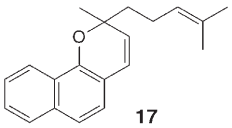
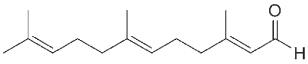
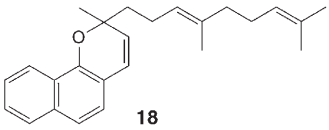
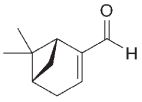
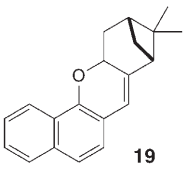
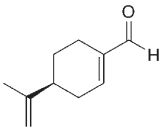
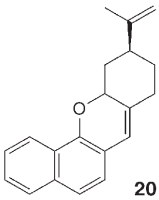
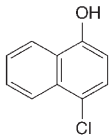
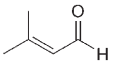
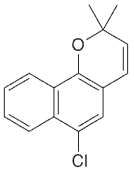
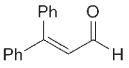
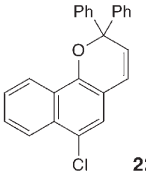
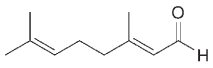
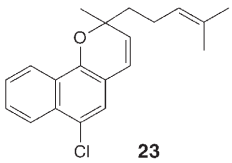
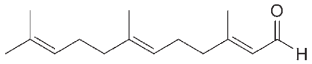
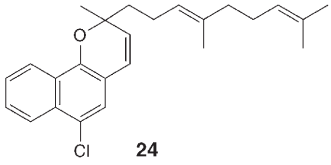
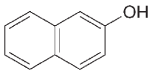
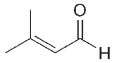
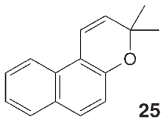
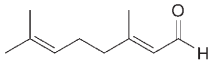
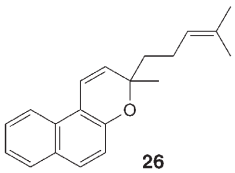
Entry	Starting material	α,β-Unsaturated aldehyde	Time [h]	Product	Yield [%]
1	 **12**		9	 **16**	70
2			8	 **17**	75
3			12	 **18**	83
4			12	 **19**	77
5			9	 **20**	70
6	 **14**		12	 **21**	62
7			8	 **22**	60

Table 2 (cont.)

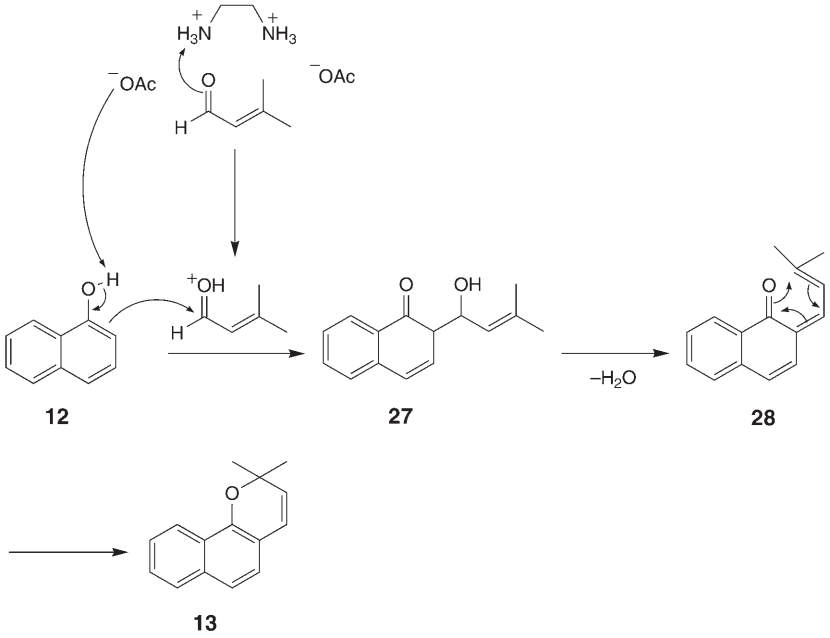
Entry	Starting material	α,β-Unsaturated aldehyde	Time [h]	Product	Yield [%]
8			12	 **23**	55
9			12	 **24**	77
10	 **15**		12	 **25**	75
11			12	 **26**	79

in refluxing $CHCl_3$ for 9 h produced the adduct **16** in 70% yield (*Entry 1*). A higher yield of products was obtained in the case of α,β-unsaturated aldehydes with a long chain. For example, treatment of **12** with citral and 20 mol-% of EDDA in refluxing $CHCl_3$ for 8 h gave compound **17** in 75% yield (*Entry 2*), whereas a reaction with (*E*,*E*)-farnesal for 12 h provided compound **18** in 83% yield (*Entry 3*). The cycloaddition reactions were also successful with other α,β-unsaturated aldehydes including the cyclic ring. Reactions between compound **12** and (−)-myrtenal provided the adduct **19** (77%), whereas treatment with (−)-perillaldehyde gave compound **20** in 70% yield (*Entries 4* and *5*). On the other hand, the process was also successful in reactions with a substituent on the naphthalen-1-ol ring. A reaction between compound **14** with 3-methylbut-2-enal under the same conditions for 12 h afforded the adduct **21** in 62% yield (*Entry 6*). Similarly, the reactions with 3,3-diphenypropenal, citral, and (*E*,*E*)-farnesal provided the products **22**–**24** in 60, 55, and 77% yields, respectively (*Entries 7–9*). To extend the utility of this methodology, further reactions with naphthalen-2-ol were examined. The reaction of naphthalen-2-ol (**15**) with 3-methylbut-2-enal in refluxing $CHCl_3$ for 12 h afforded compound **25** in 75% yield (*Entry 10*). Similarly, the reaction with citral provided the adduct **26** in 79% yield

(*Entry 11*). These reactions present a rapid route for the synthesis of benzochromene derivatives with a variety of substituents on the benzochromene rings.

Although the precise mechanism of the reaction is unclear, a likely mechanism is described in *Scheme 1*. The naphthalen-1-ol (**12**) first attacks the protonated enal to yield the alcohol **27**, which is directly dehydrated to give compound **28**. The intermediate **28** proceeds *via* oxa 6π-electrocyclization to give the product **13** [25].

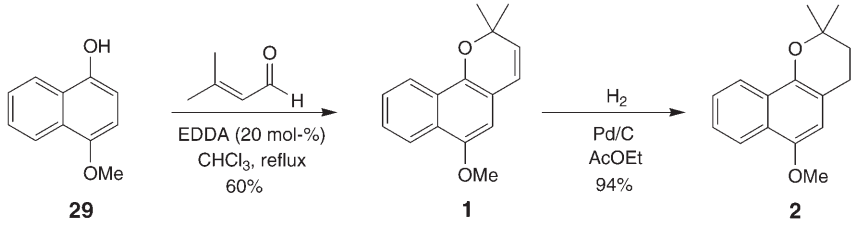
Scheme 1



As an application of this methodology, a concise synthesis of the natural products lapachenole (**1**), dihydrolapachenole (**2**), and mollugin (**3**) was attempted. Although several approaches for the synthesis of lapachenole (**1**) have been reported [26], there are no simple and efficient synthetic approaches. Our approach is shown in *Scheme 2*. A reaction between compound **29** and 3-methylbut-2-enal with 20 mol-% of EDDA in refluxing $CHCl_3$ for 24 h afforded lapachenole (**1**) in 60% yield. The structure of the synthetic material **1** was clearly assigned by comparing its spectroscopic properties with those reported in the literature [26]. The catalytic hydrogenation of compound **1** over Pd/C (20 psi) in AcOEt for 1 h gave the dihydrolapachenole (**2**) in 94% yield. The spectroscopic data of our synthetic material **2** are identical with those published in the literature [26d].

The total synthesis of mollugin (**3**) has also been reported by several groups [27]. These synthetic processes included 3–9 reaction steps and gave products in 10–61% overall yields. However, the known methods available suffer from the disadvantages of

Scheme 2



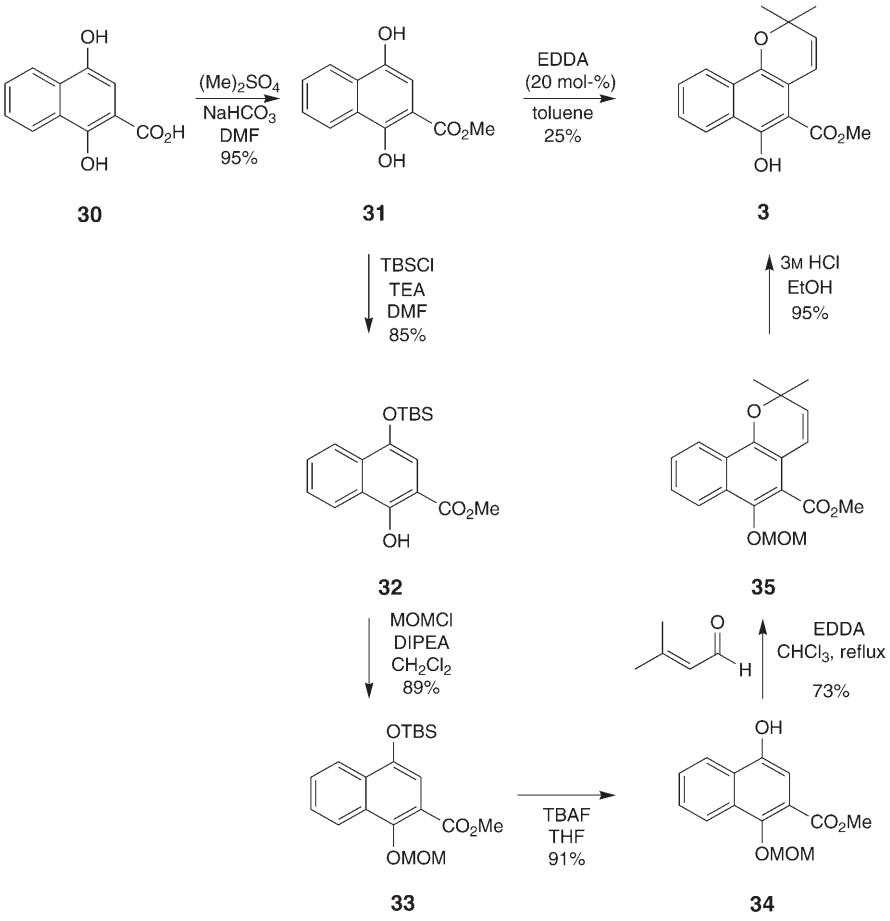
having a large number of reaction steps or low yields [27]. The synthetic strategy in this study is shown in *Scheme 3*. The esterification of compound **30** with $(Me)_2SO_4$ at room temperature for 10 h in DMF gave compound **31** in 95% yield. Treatment of compound **31** with 3-methylbut-2-enal in the presence of EDDA (20 mol-%) in refluxing toluene for 12 h gave the desired mollugin (**3**) in low yield (25%), along with unreacted and unidentified materials. Efforts to improve the yield of **3** in this reaction by varying the solvents and temperature were unsuccessful. Therefore, the OH group at C(4) of compound **31** was protected with chloromethyl methyl ether (MOMCl) in an attempt to increase the yield. First, a treatment of compound **31** with (*t*-Bu)Me_2SiCl (TBSCl) at room temperature for 10 h in DMF in the presence of Et_3N gave compound **32** in 85% yield, which was reacted directly with MOMCl at room temperature for 12 h in CH_2Cl_2 in the presence of EtN (i-Pr)$_2$ (DIPEA) to give compound **33** in 89% yield. The cleavage of the TBS group of compound **33** with Bu_4NF (TBAF) at room temperature for 3 h in THF provided compound **34** in 91% yield. Treatment of compound **34** with 3-methylbut-2-enal for 10 h in the presence of 20 mol-% of EDDA in refluxing $CHCl_3$ afforded compound **35** in 73% yield. The deprotection of the methoxymethyl (MOM) of compound **35** with 3M HCl at 50° for 1 h in EtOH afforded compound **3** in 95% yield. The spectroscopic data of our synthetic material **2** is the same as those published in the literature [27c].

Conclusions. – A new synthetic route for biologically interesting benzochromenes (= naphthopyrans) starting from naphthalenols was further developed. This methodology was applied successfully to the total synthesis of the biologically important natural products with a benzochromene moiety, *i.e.*, lapachenole, dihydrolapachenole, and mollugin. The key strategy in these synthetic routes is a formal [3 + 3] cycloaddition *via* 6π-electrocyclization of an intermediate quinone methide.

Experimental Part

General. All the experiments were carried out under N_2 atmosphere. *Merck* precoated silica gel plates (Art. 5554) with fluorescent indicator were used for anal. TLC. Flash column chromatography (CC) was performed with silica gel 9385 (*Merck*). IR Spectra: *Jasco FTIR-5300* spectrophotometer; in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker* model *ARX* (300 and 75 MHz, resp.) spectrometer in $CDCl_3$ using $\delta = 0$ and 77.0 ppm as the solvent chemical shift; δ in ppm, J in Hz. HR-MS and MS: carried out at the *Korea Basic Science Institute*; in m/z.

Scheme 3



Synthesis of **13** *and* **16**–**26**. *General Procedure.* Naphthalenols (1 mmol) and α,β-unsaturated aldehydes (2 mmol) were dissolved in $CHCl_3$ (10 ml) and ethylenediamine diacetate (EDDA; 36 mg, 0.2 mmol) was added at r.t. The mixture was refluxed for 8–12 h and then cooled to r.t. Removal of the solvent at reduced pressure left an oily residue, which was then purified by CC on silica gel to give the product.

*2,2-Dimethyl-2*H-*benzo[*h*]chromene* (**13**). Reaction of naphthalen-1-ol (**12**; 144 mg, 1 mmol) with 3-methylbut-2-enal (168 mg, 2 mmol) in $CHCl_3$ (10 ml) afforded **13** (158 mg, 75%). Liquid. IR (neat): 3052, 2976, 2926, 1645, 1618, 1566, 1508, 1460, 1373, 1339, 1275, 1219, 1194, 1165, 1123, 1090, 997, 949, 912, 864, 816, 752, 731. ^{1}H-NMR: 8.28–8.23 (*m*, 1 H); 7.78–7.74 (*m*, 1 H); 7.48–7.44 (*m*, 2 H); 7.37 (*d*, $J = 8.3$, 1 H); 7.17 (*d*, $J = 8.3$, 1 H); 6.46 (*d*, $J = 9.7$, 1 H); 5.66 (*d*, $J = 9.7$, 1 H); 1.55 (*s*, 6 H). HR-MS: 210.1044 (M^+, $C_{15}H_{14}O^+$; calc. 210.1045)

*2,2-Diphenyl-2*H-*benzo[*h*]chromene* (**16**). Reaction of **12** (144 mg, 1 mmol) with 3,3-diphenylprop-2-enal (417 mg, 2 mmol) in $CHCl_3$ (10 ml) afforded **16** (234 mg, 70%). Liquid. IR (neat): 3057, 2919, 1645, 1616, 1493, 1466, 1447, 1391, 1341, 1267, 1227, 1205, 1100, 970, 934, 816, 758. ^{1}H-NMR: 8.27–8.23 (*m*, 1 H); 7.59–7.56 (*m*, 1 H); 7.42–7.39 (*m*, 4 H); 7.34–7.28 (*m*, 2 H); 7.21–7.18 (*m*, 6 H); 7.11 (*d*, $J = 8.3$,

1 H); 7.01 (*d*, *J* = 8.3, 1 H); 6.59 (*d*, *J* = 9.7, 1 H); 6.05 (*d*, *J* = 9.7, 1 H). ^{13}C-NMR: 148.2; 145.6; 135.1; 128.6; 128.1; 128.0; 127.8; 127.3; 126.8; 126.1; 125.1; 125.0; 124.3; 122.5; 121.0; 115.9; 83.6. HR-MS: 334.1358 (M^+, $C_{25}H_{18}O^+$; calc. 334.1358).

*2-Methyl-2-(4-methylpent-3-enyl)-2*H-*benzo[*h*]chromene* (**17**). Reaction of **12** (144 mg, 1 mmol) with citral (304 mg, 2 mmol) in $CHCl_3$ (10 ml) afforded **17** (209 mg, 75%). Liquid. IR (neat): 3054, 2971, 2924, 1645, 1618, 1568, 1508, 1449, 1383, 1338, 1271, 1188, 1098, 995, 924, 814, 754, 731. ^{1}H-NMR: 8.27–8.24 (*m*, 1 H); 7.77–7.74 (*m*, 1 H); 7.49–7.45 (*m*, 2 H); 7.44 (*d*, *J* = 8.3, 1 H); 7.35 (*d*, *J* = 8.3, 1 H); 6.49 (*d*, *J* = 9.8, 1 H); 5.62 (*d*, *J* = 9.8, 1 H); 5.19–5.14 (*m*, 1 H); 2.29–2.18 (*m*, 2 H); 1.91–1.77 (*m*, 2 H); 1.69 (*s*, 3 H); 1.60 (*s*, 3 H); 1.52 (*s*, 3 H). ^{13}C-NMR: 148.8; 134.9; 132.2; 128.8; 128.0; 126.5; 125.6; 125.3; 125.0; 124.6; 123.7; 122.4; 120.0; 115.5; 79.6; 41.6; 26.8; 26.1; 23.1; 18.0. EI-MS: 278 (M^+), 263, 196, 195, 194,166, 165, 152, 69. HR-MS: 278.1673 (M^+, $C_{20}H_{22}O^+$; calc. 278.1671).

*2-(4,8-Dimethylnona-3,7-dienyl)-2-methyl-2*H-*benzo[*h*]chromene* (**18**). Reaction of **12** (144 mg, 1 mmol) with (*E*,*E*)-farnesal (441 mg, 2 mmol) in $CHCl_3$ (10 ml) afforded **18** (289 mg, 83%). Liquid. IR (neat): 3054, 2967, 2924, 1645, 1618, 1568, 1508, 1449, 1381, 1271, 1188, 1101, 995, 924, 814, 754, 731. ^{1}H-NMR: 8.30–8.27 (*m*, 1 H); 7.79–7.76 (*m*, 1 H); 7.51–7.45 (*m*, 2 H); 7.37 (*d*, *J* = 8.3, 1 H); 7.18 (*d*, *J* = 8.3, 1 H); 6.51 (*d*, *J* = 9.8, 1 H); 5.63 (*d*, *J* = 9.8, 1 H); 5.21–5.16 (*m*, 2 H); 2.33–2.26 (*m*, 2 H); 2.16–2.00 (*m*, 4 H); 1.97–1.82 (*m*, 2 H); 1.75 (*s*, 3 H); 1.73 (*s*, 3 H); 1.66 (*s*, 3 H); 1.64 (*s*, 3 H). ^{13}C-NMR: 148.9; 135.8; 135.0; 131.8; 128.8; 128.1; 126.5; 125.7; 125.4; 125.1; 124.9; 124.5; 123.7; 122.5; 120.1; 115.6; 79.6; 54.0; 41.7; 40.2; 26.8; 26.2; 22.9; 18.2; 16.4. EI-MS: 346 (M^+), 196, 195, 165, 137, 107, 95, 93, 81, 69, 68, 67, 55. HR-MS: 346.2298 (M^+, $C_{25}H_{30}O^+$; calc. 346.2297).

*(8*R*,10*R*)-9,10,11,11a-Tetrahydro-9,9-dimethyl-8,10-methano-8*H-*benzo[*c*]xanthene* (**19**). Reaction of **12** (144 mg, 1 mmol) with (−)-(1*R*)-myrtenal (300 mg, 2 mmol) in $CHCl_3$ (10 ml) afforded **19** (213 mg, 77%). Liquid: IR (neat): 2926, 1566, 1462, 1387, 1263, 1192, 1101, 804, 745. ^{1}H-NMR: 8.09–8.04 (*m*, 1 H); 7.62–7.57 (*m*, 1 H); 7.33–7.26 (*m*, 2 H); 7.22 (*d*, *J* = 8.3, 1 H); 7.02 (*d*, *J* = 8.3, 1 H); 6.01 (*s*, 1 H); 5.07–5.01 (*m*, 1 H); 2.65–2.61 (*m*, 2 H); 2.27–1.91 (*m*, 5 H); 1.20 (*s*, 3 H); 0.85 (*s*, 3 H). HR-MS: 276.1515 (M^+, $C_{20}H_{20}O^+$; calc. 276.1514).

*(10*S*)-9,10,11,11a-Tetrahydro-10-(1-methylethenyl)-8*H-*benzo[*c*]xanthene* (**20**). Reaction of **12** (144 mg, 1 mmol) with (*S*)-(−)-perillaldehyde (300 mg, 2 mmol) in $CHCl_3$ (10 ml) afforded **20** (193 mg, 70%). Liquid. IR (neat): 3054, 2938, 1644, 1570, 1510, 1435, 1395, 1335, 1262, 1248, 1196, 1092, 1017, 889, 862, 804, 744. ^{1}H-NMR: 8.18–8.15 (*m*, 1 H); 7.73–7.70 (*m*, 1 H); 7.45–7.38 (*m*, 2 H); 7.32 (*d*, *J* = 8.3, 1 H); 7.06 (*d*, *J* = 8.3, 1 H); 6.15 (*s*, 1 H); 5.35–5.32 (*m*, 1 H); 4.98 (*s*, 1 H); 4.93 (*s*, 1 H); 2.69–2.56 (*m*, 2 H); 2.35–2.31 (*m*, 2 H); 2.25–2.16 (*m*, 1 H); 2.05–1.95 (*m*, 1 H); 1.88–1.68 (*m*, 1 H); 1.84 (*s*, 3 H). ^{13}C-NMR: 148.6; 146.7; 136.9; 134.4; 128.1; 126.1; 125.6; 124.8; 124.6; 122.1; 120.4; 117.8; 116.9; 111.7; 74.7; 39.5; 36.5; 32.2; 28.4; 22.8. EI-MS: 276 (M^+), 275, 261, 248, 247, 234, 233, 221, 220, 219, 208, 207, 195, 194, 181, 178, 165, 152. HR-MS: 276.1512 (M^+, $C_{20}H_{20}O^+$; calc. 276.1514)

*6-Chloro-2,2-dimethyl-2*H-*benzo[*h*]chromene* (**21**). Reaction of *4-chloronaphthalen-1-ol* (**14**; 179 mg, 1 mmol) with 3-methylbut-2-enal (168 mg, 2 mmol) in $CHCl_3$ (10 ml) afforded **21** (151 mg, 62%). Liquid. IR (neat): 3046, 2976, 2926, 1644, 1616, 1593, 1564, 1505, 1453, 1426, 1373, 1318, 1273, 1202, 1165, 1125, 957, 889, 760. ^{1}H-NMR: 8.24–8.21 (*m*, 1 H); 8.15–8.12 (*m*, 1 H); 7.57–7.46 (*m*, 2 H); 7.25 (*s*, 1 H); 6.36 (*d*, *J* = 9.7, 1 H); 5.63 (*d*, *J* = 9.7, 1 H); 1.55 (*s*, 6 H). ^{13}C-NMR: 147.7; 131.5; 130.5; 127.6; 126.5; 126.4; 124.7; 123.1; 122.8; 122.3; 116.1; 77.6; 28.3; 28.2. HR-MS: 244.0652 (M^+, $C_{15}H_{13}ClO^+$; calc. 244.0655).

*6-Chloro-2,2-diphenyl-2*H-*benzo[*h*]chromene* (**22**). Reaction of **14** (179 mg, 1 mmol) with 3,3-diphenylprop-2-enal (417 mg, 2 mmol) in $CHCl_3$ (10 ml) afforded **22** (221 mg, 60%). Solid. M.p. 147–148°. IR (KBr) 2924, 1449, 1373, 1265, 1213, 1113, 978, 932, 760. ^{1}H-NMR: 8.36–8.35 (*m*, 1 H); 8.13–8.10 (*m*, 1 H); 7.54–7.47 (*m*, 6 H); 7.34–7.21 (*m*, 7 H); 6.67 (*d*, *J* = 9.7, 1 H); 6.21 (*d*, *J* = 9.7, 1 H). ^{13}C-NMR: 147.2; 145.1; 143.9; 131.7; 128.6; 128.1; 127.8; 127.3; 126.8; 126.3; 124.9; 124.7; 123.5; 122.8; 83.6. EI-MS: 368 (M^+), 333, 302, 293, 292, 291, 228, 226, 191, 178, 165. HR-MS: 268.0966 (M^+, $C_{25}H_{17}ClO^+$; calc. 368.0968).

*6-Chloro-2-methyl-2-(4-methylpent-3-enyl)-2*H-*benzo[*h*]chromene* (**23**). Reaction of **14** (179 mg, 1 mmol) with citral (304 mg, 2 mmol) in $CHCl_3$ (10 ml) afforded **23** (172 mg, 55%). Liquid. IR (neat): 2971, 2924, 1644, 1564, 1505, 1451, 1375, 1271, 1196, 1113, 995, 901, 877, 760. ^{1}H-NMR: 8.24–8.21 (*m*, 1 H); 8.15–8.12 (*m*, 1 H); 7.57–7.43 (*m*, 2 H); 7.24 (*s*, 1 H); 6.40 (*d*, *J* = 9.8, 1 H); 5.62 (*d*, *J* = 9.8, 1 H);

5.13–5.09 (*m*, 1 H); 2.22–2.15 (*m*, 2 H); 1.89–1.72 (*m*, 2 H); 1.64 (*s*, 3 H); 1.55 (*s*, 3 H); 1.48 (*s*, 3 H). ^{13}C-NMR: 171.5; 147.9; 132.2; 131.5; 129.5; 127.5; 126.4; 126.3; 124.7; 124.6; 124.4; 122.9; 122.7; 115.9; 80.0; 60.8; 26.7; 26.1; 21.5; 14.6. HR-MS: 312.1278 (M^+, $C_{20}H_{21}ClO^+$; calc. 312.1281).

*6-Chloro-2-(4,8-dimethylnona-3,7-dienyl)-2-methyl-2*H-*benzo[*h*]chromene* (**24**). Reaction of **14** (179 mg, 1 mmol) with (*E*,*E*)-farnesal (441 mg, 2 mmol) in $CHCl_3$ (10 ml) afforded **24** (293 mg, 77%). Liquid. IR (neat): 2969, 2924, 1644, 1593, 1505, 1451, 1375, 1271, 1204, 1111, 901, 878, 760. ^{1}H-NMR: 8.25–8.17 (*m*, 1 H); 8.15–8.12 (*m*, 1 H); 7.56–7.48 (*m*, 2 H); 7.24 (*s*, 1 H); 6.39 (*d*, *J* = 9.8, 1 H); 5.62 (*d*, *J* = 9.8, 1 H); 5.15–5.06 (*m*, 2 H); 2.22–2.16 (*m*, 2 H); 2.06–1.95 (*m*, 4 H); 1.86–1.80 (*m*, 2 H); 1.68 (*s*, 3 H); 1.59 (*s*, 3 H); 1.56 (*s*, 3 H); 1.49 (*s*, 3 H). ^{13}C-NMR: 147.9; 135.9; 131.8; 131.5; 129.6; 127.5; 126.4; 126.3; 124.8; 124.7; 124.2; 122.9; 122.7; 115.9; 80.0; 53.9; 41.6; 40.1; 26.7; 26.2; 22.9; 18.1; 16.4. EI-MS: 380 (M^+), 232, 231, 230, 229, 195, 165, 69. HR-MS: 380.1904 (M^+, $C_{25}H_{29}ClO^+$; calc. 380.1907).

*3,3-Dimethyl-3*H-*benzo[f]chromene* (**25**). Reaction of *naphthalen-2-ol* (**15**; 144 mg, 1 mmol) with 3-methylbut-2-enal (168 mg, 2 mmol) in $CHCl_3$ (10 ml) afforded **25** (158mg, 75%). Liquid. IR (neat): 3059, 2976, 2926, 1635, 1591, 1514, 1462, 1383, 1360, 1337, 1279, 1252, 1213, 1194, 1163, 1119, 1076, 992, 895, 814, 746, 733, 752, 731. ^{1}H-NMR: 7.97 (*d*, *J* = 8.4, 1 H); 7.77 (*d*, *J* = 8.1, 1 H); 7.67 (*d*, *J* = 8.8, 1 H); 7.48 (*dd*, *J* = 8.4, 8.1, 1 H); 7.36 (*dd*, *J* = 8.4, 8.1, 1 H); 7.11 (*d*, *J* = 8.8, 1 H); 7.04 (*d*, *J* = 9.9, 1 H); 5.73 (*d*, *J* = 9.9, 1 H); 1.52 (*s*, 6 H). EI-MS: 210 (M^+), 196, 195, 165, 152, 139, 98. HR-MS: 210.1047 (M^+, $C_{15}H_{14}O^+$; calc. 210.1045).

*3-Methyl-3-(4-methylpent-3-enyl)-3*H-*benzo[f]chromene* (**26**). Reaction of **15** (144 mg, 1 mmol) with citral (304 mg, 2 mmol) in $CHCl_3$ (10 ml) afforded **26** (220 mg, 79%). Liquid. IR (neat): 3059, 2971, 2924, 1676, 1636, 1591, 1516, 1462, 1381, 1337, 1275, 1250, 1186, 1090, 986, 814, 745. ^{1}H-NMR: 7.99 (*d*, *J* = 8.5, 1 H); 7.79 (*d*, *J* = 8.1, 1 H); 7.70 (*d*, *J* = 8.9, 1 H); 7.52 (*dd*, *J* = 8.5, 8.1, 1 H); 7.38 (*dd*, *J* = 8.5, 8.1, 1 H); 7.15 (*d*, *J* = 8.9, 1 H); 7.12 (*d*, *J* = 10.0, 1 H); 5.72 (*d*, *J* = 10.0, 1 H); 5.22–5.17 (*m*, 1 H); 2.26–2.18 (*m*, 2 H); 1.93–1.75 (*m*, 2 H); 1.75 (*s*, 3 H); 1.66 (*s*, 3 H); 1.53 (*s*, 3 H). ^{13}C-NMR: 151.6; 132.2; 130.3; 129.7; 129.5; 129.0; 128.9; 126.9; 124.6; 123.7; 121.6; 119.1; 118.9; 113.9; 78.8; 41.3; 26.5; 26.2; 23.3; 18.1. HR-MS: 278.1667 (M^+, $C_{20}H_{22}O^+$; calc. 278.1671).

Lapachenole (**1**). 4-Methoxynaphthalen-1-ol (**29**; 174 mg, 1 mmol) and 3-methylbut-2-enal (168 mg, 2 mmol) were dissolved in $CHCl_3$ (10 ml), and EDDA (36 mg, 0.2 mmol) was added at r.t. The mixture was refluxed for 24 h and then cooled to r.t. Removal of solvent at reduced pressure left an oily residue, which was then purified by CC (silica gel; hexane/AcOEt 20:1) to give **1** (144 mg, 60%). Solid. M.p. 63–64°. IR (KBr): 3071, 3011, 2975, 2934, 1645, 1597, 1456, 1406, 1389, 1370, 1337, 1277, 1208, 1165, 1130, 1117, 1096, 1030, 997, 984, 953, 943, 901, 841, 819, 768, 748. ^{1}H-NMR: 8.25–8.22 (*m*, 2 H); 7.56–7.46 (*m*, 2 H); 6.54 (*s*, 1 H); 6.44 (*d*, *J* = 9.6, 1 H); 5.68 (*d*, *J* = 9.6, 1 H); 3.97 (*s*, 3 H); 1.57 (*s*, 6 H). HR-MS: 240.1152 (M^+, $C_{16}H_{16}O_2^+$; 240.1150).

Dihydrolapachenole (**2**). To a soln. of **1** (48 mg, 0.2 mmol) in AcOEt (10 ml) in a *Parr* bottle was added 10% Pd/C (10 mg). The bottle was shaken for 1 h at 20 psi of H_2. Removal of the solvent at reduced pressure left an oily residue, which was then purified by CC (silica gel; hexane/AcOEt 20:1) to give **2** (46 mg, 94%). Solid. M.p. 77–78°. IR (KBr): 2930, 1634, 1599, 1458, 1387, 1318, 1273, 1206, 1157, 1121, 1100, 924, 768. ^{1}H-NMR: 8.20–8.10 (*m*, 2 H); 7.50–7.33 (*m*, 2 H); 6.47 (*s*, 1 H); 3.93 (*s*, 3 H); 2.83 (*t*, *J* = 6.7, 2 H); 1.87 (*t*, *J* = 6.7, 2 H); 1.39 (*s*, 6 H). HR-MS: 242.1306 (M^+, $C_{16}H_{18}O_2^+$; calc. 242.1307).

Methyl 1,4-Dihydroxynaphthalene-2-carbonylate (**31**). To a soln. of 1,4-Dihydroxynapthalene-2-carboxylic acid (**30**; 2.042 g, 10.0 mmol) in DMF (20 ml) was added $NaHCO_3$ (0.840 g, 10.0 mmol) and $(Me)_2SO_4$ (1.324 g, 10.5 mmol) at r.t. The mixture was stirred at r.t. for 10 h. The reaction was quenched by addition of 1N HCl (30 ml) soln., and the aq. soln. was extracted with AcOEt (3 × 40 ml). The combined org. extracts were washed with H_2O, dried ($MgSO_4$), and evaporated *in vacuo*. Flash CC (silica gel; hexane/AcOEt 3:1) afforded **31** (2.072 g, 95%). Solid. M.p. 198–199°. IR (KBr): 3387, 2953, 1647, 1599, 1516, 1478, 1441, 1356, 1298, 1256, 1150, 1100, 1073, 1026, 992, 847. ^{1}H-NMR: 11.45 (*s*, 1 H); 8.32 (*d*, *J* = 8.4, 1 H); 8.15 (*d*, *J* = 8.2, 1 H); 7.60–7.55 (*m*, 1 H); 7.52–7.47 (*m*, 1 H); 7.09 (*s*, 1 H); 3.91 (*s*, 3 H). HR-MS: 218.0582 (M^+, $C_{12}H_{10}O_4^+$; calc. 218.0579).

*Methyl 4-[(*tert*-Butyl)dimethylsilyloxy]-1-hydroxynaphthalene-2-carboxylate* (**32**). To a soln. of **31** (1.0 g, 4.59 mmol) in DMF (10 ml) were added 1*H*-imidazole (1.564 g, 23.0 mmol) and (*t*-Bu)Me_2SiCl (0.832 g, 5.50 mmol). The soln. was stirred at r.t. for 10 h, added to brine (50 ml), and extracted with AcOEt (3 × 40 ml). The combined org. phases were washed with H_2O (30 ml), dried ($MgSO_4$),, filtered,

and concentrated *in vacuo*. Flash CC (silica gel; hexane/AcOEt 10:1) afforded **32** (1.297 g, 85%). Solid. M.p. 94–95°. IR (KBr): 3445, 3073, 2955, 2857, 1669, 1632, 1599, 1441, 1387, 1352, 1254, 1233, 1154, 1084, 992, 858, 841, 781, 761, 737. ^{1}H-NMR: 11.6 (*s*, 1 H); 8.39–8.36 (*m*, 1 H); 8.10–8.07 (*m*, 1 H); 7.63–7.58 (*m*, 1 H); 7.55–7.50 (*m*, 1 H); 7.10 (*s*, 1 H); 3.98 (*s*, 3 H); 1.07 (*s*, 9 H); 0.25 (*s*, 6 H). ^{13}C-NMR: 171.2; 155.7; 143.3; 132.2; 128.8; 126.0; 125.7; 123.9; 122.4; 109.2; 104.6; 52.3; 25.9; 18.4; −4.4. HR-MS: 332.1444 (M^+, $C_{18}H_{24}O_4Si^+$; calc 332.1444).

*Methyl 4-[(*tert*-Butyldimethylsilyloxy]-1-(methoxymethoxy)naphthalene-2-carboxylate* (**33**). $MeOCH_2Cl$ (0.312 g, 3.9 mmol) was added to a soln. of **32** (1.0 g, 3.0 mmol) and $EtN(i\text{-}Pr)_2$ (1.939 g, 15.0 mmol) in dry CH_2Cl_2 (20 ml) at r.t. The mixture was stirred at r.t. for 12 h, and then H_2O (40 ml) was added. The mixture was extracted with CH_2Cl_2 (3 × 30 ml), and the combined org. extracts were washed with sat. NH_4Cl soln. (30 ml) and H_2O (30 ml), dried ($MgSO_4$), and evaporated *in vacuo*. Flash CC (silica gel; hexane/AcOEt 20:1) afforded **33** (1.005 g, 89%). Liquid. IR (neat): 2955, 2859, 1726, 1622, 1597, 1458, 1437, 1372, 1225, 1159, 1096, 1059, 986, 949, 862, 841, 770. ^{1}H-NMR: 8.31–8.28 (*m*, 1 H); 8.15–8.12 (*m*, 1 H); 7.57–7.54 (*m*, 2 H); 7.20 (*s*, 1 H); 5.18 (*s*, 2 H); 3.94 (*s*, 3 H); 3.63 (*s*, 3 H); 1.07 (*s*, 9 H); 0.28 (*s*, 6 H). ^{13}C-NMR: 166.4; 149.4; 147.6; 130.8; 129.9; 127.6; 126.7; 123.9; 122.5; 119.1; 111.9; 101.8; 57.7; 52.1; 25.8; 18.2; −4.5. HR-MS: 376.1705 (M^+, $C_{20}H_{28}O_5Si^+$; calc. 376.1706).

Methyl 4-Hydroxy-1-(methoxymethoxy)naphthalen-2-carboxylate (**34**). A soln. of **33** (0.791 g, 2.1 mmol) in THF (10 ml) was treated with Bu_4NF (1M in THF; 2.5 ml, 2.5 mmol). The resulting brown soln. was stirred at r.t. for 3 h, added to brine (50 ml), and extracted with AcOEt (3 × 50 ml). The combined org. phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Flash CC (silica gel; hexane/AcOEt 4:1) afforded **34** (0.501 g, 91%). Solid. M.p. 100–101°. IR (KBr): 3356, 2990, 2949, 1705, 1630, 1597, 1441, 1375, 1304, 1250, 1159, 1098, 1080, 1059, 992, 941, 855, 824, 781, 770, 708. ^{1}H-NMR: 8.32–8.26 (*m*, 1 H); 8.18–8.12 (*m*, 1 H); 7.61–7.56 (*m*, 2 H); 7.21 (*s*, 1 H); 5.17 (*s*, 2 H); 3.93 (*s*, 3 H); 3.62 (*s*, 3 H). ^{13}C-NMR: 167.2; 148.8; 148.2; 129.7; 127.7; 127.1; 123.9; 122.1; 118.9; 107.9; 101.8; 60.0; 52.5. EI-MS: 262 (M^+), 232, 217, 187, 186, 161, 130, 102. HR-MS: 262.0842 (M^+, $C_{14}H_{14}O_5^+$; calc. 262.0841).

*Methyl 6-(Methoxymethoxy)-2,2-dimethyl-2*H-*benzo[*h*]chromene-5-carboxylate* (**35**). Compound **34** (105 mg, 0.4 mmol) and 3-methylbut-2-enal (34 mg, 0.8 mmol) were dissolved in $CHCl_3$ (10 ml), and EDDA (14 mg, 0.08 mmol) was added at r.t. The mixture was refluxed for 10 h and then cooled to r.t. Removal of the solvent at reduced pressure left an oily residue, which was then purified by CC (silica gel; hexane/AcOEt 7:1) to give **35** (96 mg, 73%). Liquid. IR (neat): 2975, 1730, 1439, 1370, 1292, 1229, 1163, 1132, 1061, 1013, 961, 774. ^{1}H-NMR: 8.20–8.16 (*m*, 1 H); 8.08–8.05 (*m*, 1 H); 7.51–7.47 (*m*, 2 H); 6.41 (*d*, *J* = 9.9, 1 H); 5.67 (*d*, *J* = 9.9, 1 H); 5.11 (*s*, 2 H); 3.96 (*s*, 3 H); 3.60 (*s*, 3 H); 1.49 (*s*, 6 H). ^{13}C-NMR: 167.6; 145.3; 144.7; 130.2; 128.2; 126.9; 126.7; 122.9; 122.3; 121.2; 119.9; 112.3; 101.2; 76.5; 57.7; 52.4; 29.7; 27.8; 27.7. EI-MS: 328 (M^+), 313, 283, 253, 252, 251, 238, 237, 224, 223, 209, 205, 165, 152. HR-MS: calc. 328.1313 (M^+, $C_{19}H_{20}O_5^+$; 328.1311).

Mollugin (**3**). To a soln. of **35** (50 mg, 0.15 mmol) in MeOH (10 ml) was added 3M HCl (5 drops), and the mixture was heated at 50° for 1 h. The mixture was cooled, diluted with H_2O (20 ml), and extracted with AcOEt (3 × 30 ml). The combined org. phases were washed with sat. $NaHCO_3$ soln. and H_2O (30 ml), and dried ($MgSO_4$). Removal of solvent at reduced pressure left an oily residue, which was then purified by CC (silica gel; hexane/AcOEt 3:1) to give **3** (41 mg, 95%). Solid. M.p. 110–111°. IR (KBr): 3443, 2953, 1660, 1593, 1446, 1381, 1238, 1154, 1102, 1017, 770. ^{1}H-NMR: 11.31 (*s*, 1 H); 8.32 (*d*, *J* = 8.2, 1 H); 8.14 (*d*, *J* = 8.2, 1 H); 7.62–7.51 (*m*, 2 H); 4.95 (*d*, *J* = 4.8, 1 H); 3.99 (*s*, 3 H); 3.92 (*d*, *J* = 4.8, 1 H); 1.49 (*s*, 3 H); 1.43 (*s*, 3 H). HR-MS: 284.1047 (M^+, $C_{17}H_{16}O_4^+$; calc. 284.1049).

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