Structure−Activity Relationship of Polyisoprenyl Benzophenones from *Garcinia pyrifera* on the Tubulin/Microtubule System

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Microtubule disassembly inhibitory properties have been established for the known polyisoprenylated benzophenones xanthochymol (**1a**) and guttiferone E (**1b**). The compounds were isolated from the fruits of *Garcinia pyrifera* collected in Malaysia. A structure−activity relationship study, including natural and semisynthetic derivatives, delineated some structural features necessary for the interaction with tubulin within this compound class.

The tubulin/microtubule system is involved in many biological phenomena, such as formation of the mitotic spindle, constitution of the cell cytoskeleton, and axonal transport. Therefore, any substance able to interact with this system represents a potential inhibitor of cell replication.[1] In the course of our ongoing search for anticancer agents in the plant kingdom, we have screened a large number of plants collected in Malaysia[2,3] and found that an EtOAc-soluble extract of the fruits of *Garcinia pyrifera* Ridley (Clusiaceae) exhibited significant inhibitory activity on the disassembly of microtubules into tubulin (63% inhibition at 6.67 μg/mL). This activity did not correlate with a positive cytotoxicity in KB cells (12% inhibition at 10 μg/mL).

The family Clusiaceae has numerous genera, including *Allanblackia, Calophyllum, Clusia, Garcinia, Rheedia,* and *Vismia*.[4] The genus *Garcinia*, which is mainly encountered in lowland rainforests of the tropical world, has been investigated extensively from phytochemical and biological points of view.[5] Prenylated xanthones,[6,7] triterpenes,[8,9] and biflavonoids[10,11] have been isolated from African and Southeast Asian *Garcinia* species. Previous investigations of the bark from *G. pyrifera* have afforded rubraxanthone, isocowanin, and isocowanol.[12] The present study deals with the isolation of known polyisoprenylated compounds (**1a**, **1b**, **2a**, and **2b**, Chart 1) from the fruits of this same species and a structure−activity study with isolated substances and semisynthetic analogues in the tubulin/microtubule system and against KB cells.

Results and Discussion

Bioassay-guided fractionation by chromatography on Si gel of an EtOAc-soluble extract of the fruits of *G. pyrifera* led to the isolation of various products, of which two, (+)-xanthochymol (**1a**) and (+)-guttiferone E (**1b**), were found to exhibit activity in the tubulin/microtubule system. A careful examination of the spectral data and their comparison with literature data[13,14] allowed the identification of **1a** and **1b**, first isolated as a mixture, together with (+)-cycloxanthochymol (**2a**) and (+)-isoxanthochymol (**2b**), also isolated as a mixture. In addition, fatty acids, morelloflavone, and the biflavanone GB2a were also isolated.[11]

The polyisoprenylated benzophenones **1a** and **1b** have been isolated previously as a mixture from *Clusia rosea*, and are claimed to be inseparable.[13] Pure xanthochymol (**1a**) has been isolated from *G. xanthochymus*,[15,16] *G. mannii*,[17] *G. staudtii*,[18] *Rheedia madrunno*,[19] and *G. subelliptica*,[14] and pure guttiferone E (**1b**) from *G. ovalifolia*.[13] Cycloxanthochymol (**2a**) has been found in *G. subelliptica*,[14] and isoxanthochymol (**2b**) in *G. xanthochymus*,[15,16] *G. ovalifolia*,[13,20] and *G. subelliptica*.[14] Various epimers or enantiomers of the preceding compounds have also been isolated from species in the Clusiaceae. Xanthochymol and (−)-camboginol, the well-known enantiomer of (+)-guttiferone E, have been shown to possess antibacterial[14] and anti-topoisomerase I and II activities.[21] Anti-HIV activity has been described for (+)-guttiferone E,[13] and (−)-guttiferone F, the C-30 epimer of (−)-camboginol [= (−)-guttiferone E] recently isolated from *Allanblackia stuhlmannii*.[22]

The xanthochymol/guttiferone E mixture (**1**), which constituted 40% of the *G. pyrifera* crude extract, showed a strong inhibitory activity of the disassembly of microtubules into tubulin, similar to that exhibited by paclitaxel (Taxol). Moreover, observation by electron microscopy of the microtubules assembled in the presence of mixture **1** and cooled to 0 °C showed a classical pattern for microtubules. In contrast to paclitaxel, mixture **1** did not promote the assembly of tubulin at 0 °C or in the absence of GTP. The IC_{50} value, measured as described previously,[23] was 2 μM. In the same test, paclitaxel displayed an IC_{50} of 0.5 μM.

Separation of the two regioisomers by HPLC of **1** on HPLC column Nucleodex, allowed isolation of the pure compounds xanthochymol (**1a**) and guttiferone E (**1b**), which showed the same activity as the mixture of the two compounds. Accordingly, chemical modifications were then performed on mixture **1**. Separation of **2a** and **2b** was not undertaken, as mixture **2** did not possess any activity on tubulin. The above results prompted us to undertake a SAR study in order to determine some structural features necessary for microtubule stabilizing activity among this class of polyisoprenyl benzophenones. The octahydro derivative **3** was prepared via catalytic hydrogenation of **1** (H_2, Pd/C). Most of the possible combinations of mono-, di-, and tri-*O*-methylated compounds were obtained using the following procedures: methylation of **1** (tautomeric equilibrium of OH-1 and OH-3 compounds) with trimethyl-

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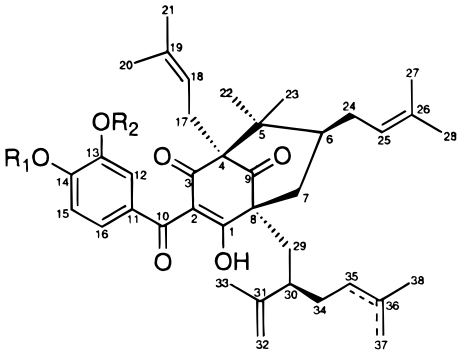
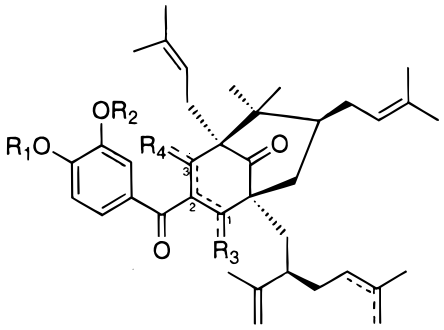
Chart 1

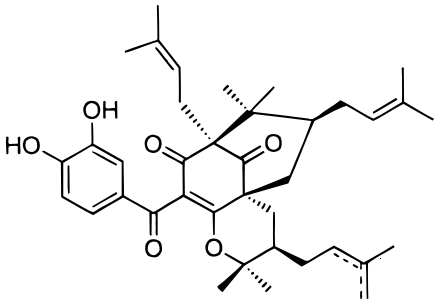


1 $R_1 = R_2 = H$
10 $R_1 = Me, R_2 = H$
11 $R_1 = R_2 = Me$
12 $R_1 = H, R_2 = Me$
13 $R_1 = Et, R_2 = H$
14 $R_1 = \beta$-D-Glc, $R_2 = H$

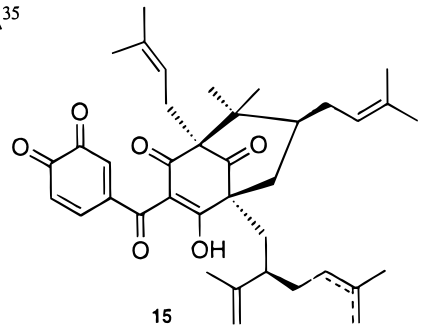


4 $R_1 = R_2 = H, R_3 = OMe, R_4 = O, \Delta^1$
5 $R_1 = R_2 = H, R_3 = O, R_4 = OMe, \Delta^2$
6 $R_1 = Me, R_2 = H, R_3 = OMe, R_4 = O, \Delta^1$
7 $R_1 = Me, R_2 = H, R_3 = O, R_4 = OMe, \Delta^2$
8 $R_1 = R_2 = Me, R_3 = OMe, R_4 = O, \Delta^1$
9 $R_1 = R_2 = Me, R_3 = O, R_4 = OMe, \Delta^2$

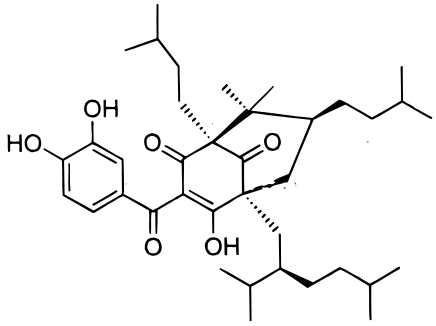
a Δ^{36}
b Δ^{35}



2



15



3

silyldiazomethane in acetone using increasing reaction times led at first to a 1:1 mixture of the C-1(C-3) enol-methylated derivatives **4** and **5**; then to the C-1(C-3),C-14 di-*O*-methylated compounds **6** and **7**, and finally to the C-1(C-3), C-13,C-14 tri-*O*-methylated derivatives **8** and **9**.[24] Partial demethylation of the mixtures **6**−**7** and **8**−**9** with 10% sodium hydroxide in methanol under reflux yielded the C-14 mono-*O*-methylated compound **10** and the C-13,C-14 di-*O*-methylated compound **11**, respectively. Methylation of **1** with MeI/NaH in THF afforded the C-13 *O*-methylated compound **12**, together with the C-14 isomer **10**. Compound **12** was purified from the mixture by preparative HPLC on Si gel.

Three further compounds involving modification of the OH groups were also prepared. The C-14 ethyl derivative **13** was the only product resulting from the action of EtI/NaH on **1**. To enhance the hydrophilic properties of the molecule, the C-14-α-D-glycosyl derivative **14** was prepared by treatment of **1** with 1,2,3,4-tetra-*O*-acetyl-α-D-glucopyranosyl bromide in the presence of NaH (reflux in toluene for 48 h), followed by catalytic alkaline deacetylation (MeONa−MeOH). Finally, the C-13,C-14 orthoquinone **15** was obtained by oxidation of **1** with $NaIO_4$. Cyclization of xanthochymol/guttiferone (**1**) into cycloxanthochymol/isoxanthochymol (**2**) was performed by refluxing in cyclohexane with *p*-toluenesulfonic acid (yield: 97%).

Biological results (Table 1) were obtained in terms of the inhibitory activity of microtubule disassembly and, in addition, on the cytotoxicity against KB cells. Etherification of the enol by methylation or cyclization led to a complete loss of activity on tubulin (compounds **2**, **4**−**9**). The same is true if both hydroxyls at C-13 and C-14 are methylated or oxidized (compounds **11** and **15**). However, some activity is preserved if only one of the hydroxyl groups at C-13 or C-14 is methylated (compounds **10** and **12**), ethylated (compound **13**), or glycosylated (compound **14**). Hydrogenation of the double bonds (compound **3**) also led to a total loss of activity. These results show that the catechol and enol portions of the molecule are not the entire pharmacophore responsible for the biological activity; the lipophilic

Table 1. Inhibitory Activity of Microtubule Disassembly and Cytotoxicity toward KB Cells

compound	microtubule disassembly inhibition[a] (IC_{50}, μM)	KB cells[b] (IC_{50}, μM)
1a	2	
1b	1.5	
1 mixture	2	10
2 mixture	inactive	5.8
3	inactive	20
4 and **5** mixture	inactive	20
6 and **7** mixture	inactive	16
8 and **9** mixture	inactive	50
10 mixture	15	64
11 mixture	inactive	6
12 mixture	8	37
13 mixture	80	5
14 mixture	17	70
15 mixture	inactive	12
paclitaxel	0.5	0.006

[a] Protocol used, see Zavala et al.[1] [b] Protocol used, see Tempête et al.[27]

domain having the unsaturated prenyl chains is also essential because the octahydro derivative **3** is not active, although the catechol and enol parts are not modified.

As for the cytotoxicity on KB cells, the IC_{50} values for the cell growth inhibition were similar for all the compounds (Table 1). It appears that cytotoxicity is probably not related to the interaction of the products with tubulin inside the cell.

In conclusion, the outstanding activity observed for compound **1** against tubulin in vitro and its similarity with data of paclitaxel have prompted us to continue our study of this series by preparing further xanthochymol derivatives and related synthetic compounds, with the aim of obtaining more potent cytotoxic compounds able to interact with cellular tubulin. Finally, it is interesting to note that these polyisoprenylated benzophenones are very often isolated not only from the fruits of *Garcinia* species but also from close genera of the same family Clusiaceae.

Experimental Section

General Experimental Procedures. Optical rotations at 20 °C were measured on a Perkin-Elmer 241 polarimeter. UV spectra were recorded on a Shimadzu UV-161 UV−vis spectrophotometer and IR spectra on a Perkin-Elmer Spectrum BX FT-IR instrument. The NMR spectra were recorded on Bruker AC-200, AC-250, AC-300, and AM-400 spectrometers, using TMS as internal standard. The NMR assignments were based on 2D COSY, HMQC, and HMBC NMR spectra. CIMS and HRCIMS were obtained on a Kratos MS-9 mass spectrometer, and EIMS on a Kratos MS-50 mass spectrometer. Column chromatography was performed using Si gel 60H (Merck, Darmstadt, Germany). Purification of compounds **1a** and **1b** was performed by HPLC on Nucleodex β-PM column (5 μm, 250 × 10 mm) (Macherey-Nagel). Compounds **10** and **12** were purified by HPLC on Novapak Silica (4 μm, 150 × 3.9 mm) (Waters). Compound **14** was purified by HPLC on Symmetry C_{18} (7 μm, 250 × 10 mm) (Waters).

Plant Material. Fruits of *G. pyrifera* were collected at Sungai Petani, Kedah, Malaysia, in July 1996, and were identified by O. Tarelli and L. E. Teo (University of Malaya, Kuala Lumpur, Malaysia). Voucher specimens (KL 4607) have been deposited at FRIM Kepong, Malaysia, and at the Herbarium of the Chemistry Department, University of Malaya, Kuala Lumpur, Malaysia.

Extraction and Isolation. The dried fruits of *G. pyrifera* (1.8 kg) were extracted by EtOAc, and the extract (63 g) was purified by column chromatography on Si gel (heptane−acetone, 95:5 to 60:40, CH_2Cl_2−MeOH, 50:50). Two fractions, A (heptane−acetone, 80:20) and B (heptane−acetone, 70:30), showed inhibition of microtubule disassembly. Fraction A (32.1 g) was subjected to repeated column chromatography on Si gel (heptane−acetone, 80:20) and afforded **1** (27.4 g). Fraction B (9.2 g) was purified in the same way, to give **1** (0.92 g).

Separation of Xanthochymol (1a) and Guttiferone E (1b). The mixture **1** of xanthochymol (**1a**) and guttiferone E (**1b**) (55:45) was separated by HPLC on a semipreparative Nucleodex β-PM column at 0 °C (CH_3CN−H_2O−TFA, 52.5:47.5:0.1%). A maximal amount of 1 mg of mixture **1** was injected each time, and the retention time was 90 min, which makes this separation difficult but successful. The HPLC fractions were neutralized with 1 N K_2CO_3 (SDS, Peypin, France) solution to avoid cyclization of **1a** and **1b** into **2a** and **2b**, respectively, extracted with Et_2O, and dried.

Mixture 1−Xanthochymol (1a)/Guttiferone E (1b): pale yellow amorphous powder; $[\alpha]_D$ +121° (*c* 0.83, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 230 (3.95), 277 (4.00), 346 (sh) nm, (EtOH + HCl 0.1 N) λ_{max} (log ϵ) 252 (3.93), 363 sh nm, (EtOH + NaOH 0.1 N) λ_{max} (log ϵ) 248 (3.94), 288 (4.11), 339 (4.00) nm; IR ($CHCl_3$) ν_{max} 3534, 3224, 3020, 2928, 1724, 1656, 1602, 1562, 1445, 1376, 1289, 1192, 895 cm^{-1}; EIMS *m*/*z* 602 $[M]^+$ (50), 533 (12), 465 (100), 449 (9), 411 (10), 341 (39), 231 (62), 137 (90), 69 (77); HRCIMS *m*/*z* 603.3703 $[MH]^+$ (calcd for $C_{38}H_{51}O_6$ 603.3686).

Xanthochymol (1a): $[\alpha]_D$ +141° (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, CD_3OD + 0.1% TFA) δ 1.51 (1H, m, H-6), 2.05 (1H, m, H-7), 2.26 (1H, m, H-7), 7.21 (1H, d, *J* = 2.1 Hz, H-12), 6.72 (1H, d, *J* = 8.0 Hz, H-15), 7.00 (1H, dd, *J* = 2.1, 8.0 Hz, H-16), 2.51 (1H, m, H-17), 2.77 (1H, m, H-17), 5.07 (1H, m, H-18), 1.74 (3H, s, H-20), 1.69 (3H, s, H-21), 1.17 (3H, s, H-22), 1.01 (3H, s, H-23), 2.03 (2H, m, H-24), 4.88 (1H, m, H-25), 1.67 (3H, s, H-27), 1.50 (3H, s, H-28), 1.93 (1H, m, H-29), 2.02 (1H, m, H-29), 2.51 (1H, m, H-30), 4.53 (2H, br s, H-32), 1.59 (3H, s, H-33), 1.46 (2H, m, H-34), 1.85 (2H, m, H-35), 4.65 (2H, br s, H-37), 1.69 (3H, s, H-38); ^{13}C NMR (75 MHz, CD_3OD + 0.1% TFA) δ 195.7 (C-1), 117.9 (C-2), 194.4 (C-3), 69.8 (C-4), 50.4 (C-5), 48.1 (C-6), 43.9 (C-7), 59.9 (C-8), 209.8 (C-9), 196.4 (C-10), 129.5 (C-11), 117.5 (C-12), 147.0 (C-13), 152.5 (C-14), 115.2 (C-15), 125.3 (C-16), 27.2 (C-17), 121.4 (C-18), 136.0 (C-19), 26.6 (C-20), 18.5 (C-21), 23.3 (C-22), 27.5 (C-23), 30.4 (C-24), 125.7 (C-25), 133.7 (C-26), 26.1 (C-27), 18.4 (C-28), 37.8 (C-29), 44.8 (C-30), 149.0 (C-31), 113.7 (C-32), 17.9 (C-33), 32.9 (C-34), 36.9 (C-35), 149.5 (C-36), 110.6 (C-37), 23.0 (C-38).

Guttiferone E (1b): $[\alpha]_D$ +104° (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, CD_3OD + 0.1% TFA) δ 1.50 (1H, m, H-6), 2.06 (1H, m, H-7), 2.26 (1H, m, H-7), 7.21 (1H, d, *J* = 2.1 Hz, H-12), 6.72 (1H, d, *J* = 8.0 Hz, H-15), 7.00 (1H, dd, *J* = 2.1, 8.0 Hz, H-16), 2.48 (1H, m, H-17), 2.70 (1H, m, H-17), 4.99 (1H, m, H-18), 1.74 (3H, s, H-20), 1.69 (3H, s, H-21), 1.13 (3H, s, H-22), 0.97 (3H, s, H-23), 2.06 (2H, m, H-24), 4.94 (1H, m, H-25), 1.67 (3H, s, H-27), 1.50 (3H, s, H-28), 1.92 (1H, m, H-29), 2.11 (1H, m, H-29), 2.48 (1H, m, H-30), 4.51 (2H, br s, H-32), 1.69 (3H, s, H-33), 2.03 (2H, m, H-34), 4.96 (1H, m, H-35), 1.63 (3H, s, H-37), 1.57 (3H, s, H-38); ^{13}C NMR (75 MHz, CD_3OD + 0.1% TFA) δ 195.7 (C-1), 117.9 (C-2), 194.4 (C-3), 69.8 (C-4), 50.0 (C-5), 48.1 (C-6), 43.9 (C-7), 59.9 (C-8), 209.8 (C-9), 196.1 (C-10), 129.6 (C-11), 117.5 (C-12), 146.3 (C-13), 152.5 (C-14), 115.2 (C-15), 125.3 (C-16), 27.2 (C-17), 121.4 (C-18), 136.0 (C-19), 26.6 (C-20), 18.5 (C-21), 23.3 (C-22), 27.5 (C-23), 30.4 (C-24), 125.7 (C-25), 133.7 (C-26), 26.1 (C-27), 18.4 (C-28), 37.5 (C-29), 45.3 (C-30), 149.0 (C-31), 113.2 (C-32), 17.9 (C-33), 33.6 (C-34), 124.2 (C-35), 132.8 (C-36), 27.2 (C-37), 18.3 (C-38).

Mixture 2−Cycloxanthochymol (2a)/Isoxanthochymol (2b): colorless amorphous powder; $[\alpha]_D$ +142° (*c* 0.60, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 227 (4.38), 277 (4.22), 317 (3.93) nm; IR ($CHCl_3$) ν_{max} 3530, 2932, 1727, 1667, 1640, 1600, 1442, 1374, 1286, 1123 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (1H, m, H-6), 1.81 (1H, m, H-7), 2.51 (1H, m, H-7), 7.41 (1H, d, *J* = 2.1 Hz, H-12), 6.70 (1H, d, *J* = 8.0 Hz, H-15), 7.03 (1H, dd, *J* = 2.1, 8.0 Hz, H-16), 2.51 (1H, m, H-17), 2.63 (1H, m, H-17), 4.83 (1H, m, H-18), 1.55 (3H, s, H-20), 1.66 (3H, s, H-21), 1.15 (3H, s, H-22), 0.99 (3H, s, H-23), 2.20 (1H, m, H-24), 2.59 (1H, m, H-24), 4.92 (1H, m, H-25), 1.68 (3H, s, H-27), 1.58 (3H, s, H-28), 1.88 (1H, m, H-29), 2.08 (1H, m, H-29), 3.06 (1H, m,

H-30), 1.17 (3H, s, H-32), 0.90 (3H, s, H-33), 1.47 (2H, m, H-34 **2a**), 2.11 (2H, m, H-34 **2b**), 1.85 (2H, m, H-35 **2a**), 5.09 (1H, m, H-35 **2b**), 4.76 (2H, br s, H-37 **2a**), 1.68 (3H, s, H-37 **2b**), 1.68 (3H, s, H-38 **2a**), 1.56 (3H, s, H-38 **2b**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4 (C-1), 119.6 (C-2), 193.1 (C-3), 68.3 (C-4), 51.5 (C-5 **2a**), 51.3 (C-5 **2b**), 46.3[25] (C-6 **2a**), 46.4[25] (C-6 **2b**), 39.9 (C-7), 53.4 (C-8), 209.0 (C-9), 194.8 (C-10), 130.0 (C-11), 114.9 (C-12), 144.1 (C-13), 150.1 (C-14), 114.3 (C-15), 124.0[25] (C-16 **2a**), 124.1[25] (C-16 **2b**), 25.6 (C-17), 121.3 (C-18), 134.7 (C-19), 26.1 (C-20), 18.1 (C-21), 22.5 (C-22), 26.7[25] (C-23 **2a**), 26.8[25] (C-23 **2b**), 28.0[25] (C-24 **2a**), 28.2[25] (C-24 **2b**), 124.8[25] (C-25 **2a**), 124.9[25] (C-25 **2b**), 133.6 (C-26), 25.7[25] (C-27 **2a**), 25.9[25] (C-27 **2b**), 17.9[25] (C-28 **2a**), 18.0[25] (C-28 **2b**), 39.8 (C-29 **2a**), 39.6 (C-29 **2b**), 42.1 (C-30 **2a**), 42.9 (C-30 **2b**), 86.9[25] (C-31 **2a**), 87.1[25] (C-31 **2b**), 21.1[25] (C-32 **2a**), 21.2[25] (C-32 **2b**), 28.4[25] (C-33 **2a**), 28.6[25] (C-33 **2b**), 29.4 (C-34 **2a**), 29.6 (C-34 **2b**), 35.2 (C-35 **2a**), 121.3 (C-35 **2b**), 144.9 (C-36 **2a**), 133.2 (C-36 **2b**), 110.6 (C-37 **2a**), 26.8 (C-37 **2b**), 22.5 (C-38 **2a**), 18.1 (C-38 **2b**); EIMS *m/z* 602 $[M]^+$ (40), 574 (24), 465 (65), 449 (24), 341 (50), 231 (33), 137 (86), 69 (100); HRCIMS *m/z* 603.3682 $[MH]^+$ (calcd for $C_{38}H_{51}O_6$ 603.3686).

Transformation of 1 into 2. A solution of the mixture xanthochymol/guttiferone E (**1**) (101.2 mg, 0.168 mmol) in cyclohexane (1 mL) and a small amount of TsOH was refluxed for 5 min. After cooling, the reaction mixture was washed with H_2O (5 mL) and extracted with Et_2O (5 mL). The organic layer was dried ($MgSO_4$) and the solvent evaporated. The residue, after purification by TLC on Si gel (heptane−acetone, 60:40), afforded **2** (98.3 mg).

Octahydroxanthochymol (3). A solution of the mixture xanthochymol/guttiferone E (**1**) (200.2 mg, 0.333 mmol) in MeOH (10 mL) and Pd/C (20 mg) was stirred under H_2 for 8 h. The reaction mixture was filtered through Celite, and the filtrate was evaporated to dryness. The residue, upon purification by column chromatography on Si gel (CH_2Cl_2−MeOH, 98:2), afforded **3** (196.6 mg) as a pale yellow amorphous powder: $[\alpha]_D$ +44° (*c* 1.0, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 228 (3.95), 278 (4.05), 348 (sh) nm; IR ($CHCl_3$) ν_{max} 3530, 3223, 2958, 1726, 1660, 1466, 1385, 1367, 1194 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD + 0.1% TFA) δ 1.37 (1H, m, H-6), 2.04 (1H, m, H-7), 2.23 (1H, m, H-7), 7.23 (1H, br s, H-12), 6.74 (1H, d, J = 8.1 Hz, H-15), 6.98 (1H, br d, J = 8.1 Hz, H-16), 1.31 (1H, m, H-17), 1.22 (2H, m, H-18), 1.37 (1H, m, H-19), 0.90 (3H, s, H-20), 0.93 (3H, s, H-21), 1.23 (3H, s, H-22), 0.99 (3H, s, H-23), 1.36 (2H, m, H-24), 1.57 (2H, m, H-25), 1.41 (1H, m, H-26), 0.85 (3H, s, H-27), 0.83 (3H, s, H-28), 1.19 (2H, m, H-29), 1.57 (1H, m, H-30), 1.86 (1H, m, H-31), 0.88 (3H, s, H-32), 0.94 (3H, s, H-33), 1.97 (2H, m, H-34), 1.99 (2H, m, H-35), 1.56 (1H, m, H-36), 0.82 (3H, s, H-37), 0.79 (3H, s, H-38); ^{13}C NMR (75 MHz, CD_3OD + 0.1% TFA) δ 195.8 (C-1), 117.3 (C-2), 195.0 (C-3), 69.8 (C-4), 49.6 (C-5), 46.4 (C-6), 43.3 (C-7), 59.9 (C-8), 208.8 (C-9), 195.3 (C-10), 128.7 (C-11), 115.9 (C-12), 145.1 (C-13), 151.2 (C-14), 113.6 (C-15), 123.5 (C-16), 29.4 (C-17), 34.0 (C-18), 28.8 (C-19), 21.6 (C-20), 21.7 (C-21), 21.8 (C-22), 26.1 (C-23), 30.0 (C-24), 37.0 (C-25), 28.8 (C-26), 21.2 (C-27), 22.0 (C-28), 39.4 (C-29), 39.8 (C-30), 28.3 (C-31), 15.4 (C-32), 19.7 (C-33), 24.4 (C-34), 31.3 (C-35), 28.0 (C-36), 21.5 (C-37), 22.2 (C-38); FABMS *m/z* 611 $[MH]^+$, 633 $[M + Na]^+$, 655 $[M + 2Na]^+$, 677 $[M + 3Na]^+$; HRCIMS *m/z* 611.4310 $[MH]^+$ (calcd for $C_{38}H_{59}O_6$ 611.4312).

Mixture of 4 and 5—1-*O*-Methylxanthochymol (4a)/3-*O*-Methylxanthochymol (5a)/1-*O*-Methylguttiferone E (4b)/3-*O*-Methylguttiferone E (5b). A solution of the mixture xanthochymol/guttiferone E (**1**) (204.5 mg, 0.340 mmol) in acetone (1 mL), and Me_3SiCHN_2 (2 N) in *n*-hexane (255 μL, 0.510 mmol), was stirred at room temperature for 4 h. The reaction mixture was evaporated to dryness, and the residue, after purification by TLC on Si gel (heptane−diethyl ether, 40:60), afforded a mixture of **4** and **5** (169.7 mg) as a colorless amorphous powder: $[\alpha]_D$ +53° (*c* 1.0, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 236 (4.30), 275 (4.26), 319 (4.05) nm; IR ($CHCl_3$) ν_{max} 3527, 3020, 2930, 1724, 1663, 1641, 1595, 1444, 1289 cm^{-1}; ^{1}H NMR (250 MHz, CD_3OD)[26] δ 1.46 (1H, m, H-6), 1.98 (1H, m, H-7 **4a**, **4b**), 2.18 (1H, m, H-7 **4a**, **4b**), 2.01 (2H, m, H-7 **5a**, **5b**), 7.40[26] (1H, d, J = 2.1 Hz, H-12 **4a**, **4b**), 7.42[26] (1H, d, J = 2.1 Hz, H-12 **5a**, **5b**), 6.72 (1H, d, J = 8.0 Hz, H-15), 7.08[26] (1H, dd, J = 2.1, 8.0 Hz, H-16 **4a**, **4b**), 7.11[26] (1H, dd, J = 2.1, 8.0 Hz, H-16 **5a**, **5b**), 2.18 (1H, m, H-17 **4a**, **4b**), 2.41 (1H, m, H-17 **4a**, **4b**), 2.04 (1H, m, H-17 **5a**, **5b**), 2.20 (1H, m, H-17 **5a**, **5b**), 4.97 (1H, m, H-18 **4a**, **4b**), 4.87 (1H, m, H-18 **5a**, **5b**), 1.68[26] (3H, s, H-20 **4a**, **4b**), 1.70[26] (3H, s, H-20 **5a**, **5b**), 1.68[26] (3H, s, H-21 **4a**, **4b**), 1.70[26] (3H, s, H-21 **5a**, **5b**), 1.18 (3H, s, H-22 **4a**, **4b**), 1.06 (3H, s, H-22 **5a**, **5b**), 1.00 (3H, s, H-23 **4a**, **4b**), 0.97 (3H, s, H-23 **5a**, **5b**), 2.29 (1H, m, H-24), 2.44 (1H, m, H-24), 4.91 (1H, m, H-25), 1.66 (3H, s, H-27), 1.49 (3H, s, H-28), 1.86 (2H, m, H-29 **4a**, **4b**), 1.77 (2H, m, H-29 **5a**, **5b**), 2.49 (1H, m, H-30), 4.50 (2H, br s, H-32), 1.55 (3H, s, H-33 **4a**, **4b**), 1.38 (3H, s, H-33 **5a**, **5b**), 1.49 (2H, m, H-34 **4a**, **5a**), 2.04 (2H, m, H-34 **4b**, **5b**), 1.78 (2H, m, H-35 **4a**, **5a**), 4.95 (1H, m, H-35 **4b**, **5b**), 4.69 (2H, br s, H-37 **4a**, **5a**), 1.72 (3H, s, H-37 **4b**, **5b**), 1.73 (3H, s, H-38 **4a**, **5a**), 1.56 (3H, s, H-38 **4b**, **5b**), 3.66 (3H, s, *O*Me-1), 3.61 (3H, s, *O*Me-3); ^{13}C NMR (62.5 MHz, CD_3OD)[26] δ 174.5 (C-1 **4a**), 197.8 (C-1 **5a**), 174.5 (C-1 **4b**), 197.0 (C-1 **5b**), 113.3 (C-2 **4a**, **5a**), 113.7 (C-2 **4b**, **5b**), 195.4 (C-3 **4a**, **4b**), 173.4 (C-3 **5a**, **5b**), 70.6 (C-4 **4a**, **4b**), 65.7 (C-4 **5a**, **5b**), 50.0 (C-5), 48.0[26] (C-6 **4a**, **4b**), 47.7[26] (C-6 **5a**, **5b**), 41.9 (C-7 **4a**, **4b**), 45.0 (C-7 **5a**, **5b**), 57.7 (C-8 **4a**, **4b**), 62.3 (C-8 **5a**, **5b**), 209.1 (C-9), 196.1 (C-10), 132.2 (C-11), 115.7 (C-12), 146.8 (C-13), 152.8 (C-14), 115.3 (C-15), 126.5[26] (C-16 **4a**, **4b**), 126.8[26] (C-16 **5a**, **5b**), 26.6 (C-17 **4a**, **4b**), 26.1 (C-17 **5a**, **5b**), 121.7 (C-18 **4a**, **4b**), 121.3 (C-18 **5a**, **5b**), 135.0[26] (C-19 **4a**, **4b**), 135.4[26] (C-19 **5a**, **5b**), 26.2 (C-20), 18.3 (C-21), 24.1 (C-22 **4a**, **4b**), 23.0 (C-22 **5a**, **5b**), 27.6 (C-23 **4a**, **4b**), 27.2 (C-23 **5a**, **5b**), 31.6 (C-24), 125.8[26] (C-25 **4a**, **4b**), 125.9[26] (C-25 **5a**, **5b**), 133.3[26] (C-26 **4a**, **4b**), 133.7[26] (C-26 **5a**, **5b**), 26.0 (C-27), 18.3 (C-28), 36.6 (C-29 **4a**, **4b**), 38.0 (C-29 **5a**, **5b**), 44.4 (C-30 **4a**, **5a**), 46.2 (C-30 **4b**, **5b**), 148.8 (C-31), 112.6 (C-32 **4a**, **5a**), 111.9 (C-32 **4b**, **5b**), 17.4 (C-33 **4a**, **5a**), 18.0 (C-33 **4b**, **5b**), 32.4 (C-34 **4a**, **5a**), 33.3 (C-34 **4b**, **5b**), 37.6 (C-35 **4a**, **5a**), 124.3[26] (C-35 **4b**), 124.5[26] (C-35 **5b**), 149.3 (C-36 **4a**, **5a**), 132.6 (C-36 **4b**, **5b**), 110.6[26] (C-37 **4a**), 110.1[26] (C-37 **5a**), 26.6 (C-37 **4b**, **5b**), 22.7[26] (C-38 **4a**), 22.9[26] (C-38 **5a**), 18.3 (C-38 **4b**, **5b**), 60.5 (*O*Me−C-1), 60.1 (*O*Me−C-3); EIMS *m/z* 616 $[M]^+$ (30) 547 (8), 479 (100), 355 (17), 245 (28), 191 (22), 137 (83), 69 (58); HRCIMS *m/z* 617.3883 $[MH]^+$ (calcd for $C_{39}H_{53}O_6$ 617.3843).

Mixture of 6 and 7—1,14-Di-*O*-methylxanthochymol (6a)/3,14-Di-*O*-methylxanthochymol (7a)/1,14-Di-*O*-methylguttiferone E (6b)/3,14-Di-*O*-methylguttiferone E (7b). A solution of the mixture xanthochymol/guttiferone E (**1**) (153.4 mg, 0.255 mmol) in acetone (0.5 mL) and Me_3SiCHN_2 (2 N) in *n*-hexane (318 μL, 0.636 mmol) was stirred at room temperature for 10 h. The reaction mixture was evaporated to dryness. The residue, after purification by TLC on Si gel (heptane−acetone, 80:20), afforded a mixture of **6** and **7** (114.8 mg) as a colorless amorphous powder: $[\alpha]_D$ +31° (*c* 1.0, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 233 (4.31), 273 (4.20), 315 (4.00) nm; IR ($CHCl_3$) ν_{max} 3542, 3020, 2972, 1731, 1667, 1641, 1592, 1441, 1276 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD)[26] δ 1.49 (1H, m, H-6), 1.95 (1H, m, H-7 **6a**, **6b**), 2.14 (1H, m, H-7 **6a**, **6b**), 2.00 (2H, m, H-7 **7a**, **7b**), 7.34[26] (1H, d, J = 2.1 Hz, H-12 **6a**, **6b**), 7.39[26] (1H, d, J = 2.1 Hz, H-12 **7a**, **7b**), 6.88 (1H, d, J = 8.0 Hz, H-15), 7.25[26] (1H, dd, J = 2.1, 8.0 Hz, H-16 **6a**, **6b**), 7.29[26] (1H, dd, J = 2.1, 8.0 Hz, H-16 **7a**, **7b**), 2.50 (1H, m, H-17 **6a**, **6b**), 2.64 (1H, m, H-17 **6a**, **6b**), 2.27 (1H, m, H-17 **7a**, **7b**), 2.50 (1H, m, H-17 **7a**, **7b**), 4.98 (1H, m, H-18 **6a**, **6b**), 4.86 (1H, m, H-18 **7a**, **7b**), 1.69 (3H, s, H-20), 1.68 (3H, s, H-21), 1.22 (3H, s, H-22 **6a**, **6b**), 1.06 (3H, s, H-22 **7a**, **7b**), 1.00 (3H, s, H-23 **6a**, **6b**), 0.98 (3H, s, H-23 **7a**, **7b**), 2.32 (1H, m, H-24), 2.46 (1H, m, H-24), 4.89 (1H, m, H-25), 1.63 (3H, s, H-27), 1.49 (3H, s, H-28), 1.89 (2H, m, H-29 **6a**, **6b**), 1.79 (2H, m, H-29 **7a**, **7b**), 2.32 (1H, m, H-30), 4.55 (2H, br s, H-32 **6a**, **7a**), 4.52 (2H, br s, H-32 **6b**, **7b**), 1.57 (3H, s, H-33 **6a**, **6b**), 1.39 (3H, s, H-33 **7a**, **7b**), 1.51 (2H, m, H-34 **6a**, **7a**), 2.03 (2H, m, H-34 **6b**, **7b**), 1.84 (2H, m, H-35 **6a**, **7a**), 4.92 (1H, m, H-35 **6b**, **7b**), 4.70 (2H, br s, H-37 **6a**, **7a**), 1.69 (3H, s, H-37 **6b**, **7b**), 1.75 (3H, s, H-38 **6a**, **7a**), 1.57 (3H, s, H-38 **6b**, **7b**), 3.64 (3H, s, *O*Me-1), 3.60 (3H, s, *O*Me-3), 3.91 (3H, s, *O*Me-14); ^{13}C NMR (50 MHz, CD_3OD) δ 174.9 (C-1 **6a**, **6b**), 197.8 (C-1 **7a**, **7b**), 112.1 (C-2), 196.4 (C-3 **6a**, **6b**), 173.7 (C-3 **7a**, **7b**), 70.8 (C-4 **6a**, **6b**), 66.0 (C-4 **7a**, **7b**), 50.0 (C-5), 48.2[26] (C-6 **6a**, **6b**), 47.9[26] (C-6 **7a**, **7b**), 42.3

(C-7 **6a**, **6b**), 45.2 (C-7 **7a**, **7b**), 57.8 (C-8 **6a**, **6b**), 62.5 (C-8 **7a**, **7b**), 210.4 (C-9), 197.2 (C-10), 133.4 (C-11), 116.3[26] (C-12 **6a**, **6b**), 116.4[26] (C-12 **6a**, **6b**), 147.0[26] (C-13 **6a**, **6b**), 147.4[26] (C-13 **6a**, **6b**), 154.2 (C-14), 111.5 (C-15), 126.7[26] (C-16 **6a**, **6b**), 127.0[26] (C-16 **7a**, **7b**), 26.5 (C-17 **6a**, **6b**), 26.3 (C-17 **7a**, **7b**), 121.8 (C-18 **6a**, **6b**), 121.4 (C-18 **7a**, **7b**), 135.1 (C-19), 26.8 (C-20), 18.6 (C-21), 24.2 (C-22 **6a**, **6b**), 22.8 (C-22 **7a**, **7b**), 27.8 (C-23 **6a**, **6b**), 27.4 (C-23 **7a**, **7b**), 31.7 (C-24), 127.0 (C-25), 133.3[26] (C-26 **6a**, **6b**), 133.8[26] (C-26 **7a**, **7b**), 26.2 (C-27), 18.5 (C-28), 36.7 (C-29 **6a**, **6b**), 38.2 (C-29 **7a**, **7b**), 44.6 (C-30 **6a**, **7a**), 45.4 (C-30 **6b**, **7b**), 149.0 (C-31 **6a**, **7a**), 149.5 (C-31 **6b**, **7b**), 114.0 (C-32 **6a**, **7a**), 112.8 (C-32 **6b**, **7b**), 17.5 (C-33 **6a**, **7a**), 18.1 (C-33 **6b**, **7b**), 32.7 (C-34 **6a**, **7a**), 33.5 (C-34 **6b**, **7b**), 37.8 (C-35 **6a**, **7a**), 124.6[26] (C-35 **6b**), 124.7[26] (C-35 **7b**), 148.0[26] (C-36 **6a**), 149.0[26] (C-36 **7a**), 135.6 (C-36 **6b**, **7b**), 110.2[26] (C-37 **6a**), 110.7[26] (C-37 **7a**), 26.7 (C-37 **6b**, **7b**), 23.0 (C-38 **6a**, **7a**), 18.5 (C-38 **6b**, **7b**), 60.8 (*O*Me-C-1), 60.4 (*O*Me-C-3), 56.7 (*O*Me-C-14); EIMS *m*/*z* 630 $[M]^+$ (46), 561 (19), 507 (13), 493 (33), 479 (16), 369 (33), 245 (28), 151 (56), 123 (29), 69 (100); HRCIMS *m*/*z* 631.3975 $[MH]^+$ (calcd for $C_{40}H_{55}O_6$ 631.3999).

Mixture of 8 and 9—1,13,14-Tri-*O*-methylxanthochymol (8a)/3,13,14-Tri-*O*-methylxanthochymol (9a)/1,13,14-Tri-*O*-methylguttiferone E (8b)/3,13,14-Tri-*O*-methylguttiferone E (9b). A solution of the mixture xanthochymol/guttiferone E (**1**) (426.4 mg, 0.708 mmol) in acetone (2 mL) and Me_3SiCHN_2 (2 N) in *n*-hexane (1.42 mL, 2.840 mmol) was stirred at room temperature for 48 h. The reaction mixture was evaporated to dryness. The residue, after purification by TLC on Si gel (heptane−acetone, 80:20), afforded a mixture of **8** and **9** (288.7 mg) as a colorless amorphous powder: $[\alpha]_D$ +54° (*c* 1.0, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 231 (4.38), 276 (4.24), 313 (4.03) nm; IR ($CHCl_3$) ν_{max} 3526, 3020, 2937, 1724, 1665, 1641, 1595, 1269, 1139 cm^{-1}; ^1H NMR (250 MHz, CD_3OD)[26] δ 1.46 (1H, m, H-6), 2.00 (1H, m, H-7 **8a**, **8b**), 2.12 (1H, m, H-7 **8a**, **8b**), 2.00 (2H, m, H-7 **9a**, **9b**), 7.43[26] (1H, d, J = 2.1 Hz, H-12 **8a**, **8b**), 7.47[26] (1H, d, J = 2.1 Hz, H-12 **9a**, **9b**), 6.79[26] (1H, d, J = 8.0 Hz, H-15 **8a**, **8b**), 6.75[26] (1H, d, J = 8.0 Hz, H-15 **9a**, **9b**), 7.16[26] (1H, dd, J = 2.1, 8.0 Hz, H-16 **8a**, **8b**), 7.18[26] (1H, dd, J = 2.1, 8.0 Hz, H-16 **9a**, **9b**), 2.50 (1H, m, H-17 **8a**, **8b**), 2.61 (1H, m, H-17 **8a**, **8b**), 2.21 (1H, m, H-17 **9a**, **9b**), 2.46 (1H, m, H-17 **9a**, **9b**), 5.00 (1H, m, H-18 **8a**, **8b**), 4.83 (1H, m, H-18 **9a**, **9b**), 1.66 (3H, s, H-20), 1,65 (3H, s, H-21), 1.21 (3H, s, H-22 **8a**, **8b**), 1.04 (3H, s, H-22 **9a**, **9b**), 1.00 (3H, s, H-23 **8a**, **8b**), 0.96 (3H, s, H-23 **9a**, **9b**), 2.33 (1H, m, H-24), 2.46 (1H, m, H-24), 4.92 (1H, m, H-25), 1.66 (3H, s, H-27), 1.46 (3H, s, H-28), 1.88 (2H, m, H-29 **8a**, **8b**), 1.80 (2H, m, H-29 **9a**, **9b**), 2.46 (1H, m, H-30), 4.50 (2H, br s, H-32 **8a**, **9a**), 4.46 (2H, br s, H-32 **8b**, **9b**), 1.54 (3H, s, H-33 **8a**, **8b**), 1.42 (3H, s, H-33 **9a**, **9b**), 1.50 (2H, m, H-34 **8a**, **9a**), 2.01 (2H, m, H-34 **8b**, **9b**), 1.83 (2H, m, H-35 **8a**, **9a**), 4.97 (1H, m, H-35 **8b**, **9b**), 4.71 (2H, br s, H-37 **8a**, **9a**), 1.64 (3H, s, H-37 **8b**, **9b**), 1.71 (3H, s, H-38 **8a**, **9a**), 1.56 (3H, s, H-38 **8b**, **9b**), 3.53 (3H, s, 1-*O*Me), 3.49 (3H, s, *O*Me-3), 3.78 (6H, s, *O*Me-13, *O*Me-14); ^{13}C NMR (50 MHz, CD_3OD) δ 174.8 (C-1 **8a**, **8b**), 196.0 (C-1 **9a**, **9b**), 113.1 (C-2 **8a**, **9a**), 113.6 (C-2 **8b**, **9b**), 195.4 (C-3 **8a**, **8b**), 173.8 (C-3 **9a**, **9b**), 70.7 (C-4 **8a**, **8b**), 65.8 (C-4 **9a**, **9b**), 50.3 (C-5), 48.2[26] (C-6 **8a**, **8b**), 47.8[26] (C-6 **9a**, **9b**), 42.1 (C-7 **8a**, **8b**), 44.4 (C-7 **9a**, **9b**), 57.7 (C-8 **8a**, **8b**), 62.4 (C-8 **9a**, **9b**), 210.3 (C-9), 197.8 (C-10), 133.3 (C-11), 111.2 (C-12), 150.7 (C-13), 155.6 (C-14), 111.2 (C-15), 126.6[26] (C-16 **8a**, **8b**), 126.9[26] (C-16 **9a**, **9b**), 26.7 (C-17 **8a**, **8b**), 26.4 (C-17 **9a**, **9b**), 121.7 (C-18 **8a**, **8b**), 121.4 (C-18 **9a**, **9b**), 135.3 (C-19), 26.3 (C-20), 18.4 (C-21), 24.1 (C-22 **8a**, **8b**), 23.3 (C-22 **9a**, **9b**), 27.7 (C-23 **8a**, **8b**), 27.2 (C-23 **9a**, **9b**), 31.6 (C-24), 127.1 (C-25), 132.9[26] (C-26 **8a**, **8b**), 133.7[26] (C-26 **9a**, **9b**), 26.1 (C-27), 18.0 (C-28), 36.5 (C-29 **8a**, **8b**), 37.9 (C-29 **9a**, **9b**), 44.5 (C-30 **8a**, **9a**), 45.3 (C-30 **8b**, **9b**), 149.1 (C-31 **8a**, **9a**), 149.4 (C-31 **8b**, **9b**), 113.6[26] (C-32 **8a**), 112.5[26] (C-32 **9a**), 113.1[26] (C-32 **8b**), 111.5[26] (C-32 **9b**), 17.4 (C-33 **8a**, **9a**), 17.9 (C-33 **8b**, **9b**), 32.3[26] (C-34 **8a**), 33.3[26] (C-34 **9a**), 33.3[26] (C-34 **8b**), 34.6[26] (C-34 **9b**), 37.6 (C-35 **8a**, **9a**), 124.3[26] (C-35 **8b**), 124.7[26] (C-35 **9b**), 146.9[26] (C-36 **8a**), 147.2[26] (C-36 **9a**), 135.3 (C-36 **8b**, **9b**), 110.6[26] (C-37 **8a**), 110.0[26] (C-37 **9a**), 26.6 (C-37 **8b**, **9b**), 22.7[26] (C-38 **8a**), 23.0[26] (C-38 **9a**), 18.4 (C-38 **8b**, **9b**), 60.7 (*O*Me-C-1), 60.4 (*O*Me-C-3), 56.6 (*O*Me-C-13, *O*Me-C-14); EIMS *m*/*z* 644 $[M]^+$ (50), 575 (11), 507 (100), 165 (29), 123 (4), 69 (39); HRCIMS *m*/*z* 645.4119 $[MH]^+$ (calcd for $C_{41}H_{57}O_6$ 645.4156).

Mixture 10—14-*O*-Methylxanthochymol (10a)/14-*O*-Methylguttiferone E (10b). Two methods were used. For method A, see Mixture 12 13-*O*-methylxanthochymol (12a)/13-*O*-methylguttiferone E (12b). For method B, a solution of the mixture of **6** and **7** (61.2 mg, 0.097 mmol) in 5% NaOH−EtOH (20 mL) was refluxed for 8 h. The solvent was evaporated, and the residue was dissolved in H_2O (50 mL). The aqueous layer was neutralized with HCl (10%) and extracted with Et_2O (3 × 20 mL). The organic layer was washed with H_2O (2 × 10 mL), dried ($MgSO_4$), and evaporated to dryness. The residue, after purification by TLC on Si gel (heptane−acetone, 70:30), afforded **10** (5.2 mg) as a pale yellow amorphous powder: $[\alpha]_D$ +36° (*c* 1.0, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 232 (3.99), 277 (3.94), 350 sh nm; IR ($CHCl_3$) ν_{max} 3546, 3020, 2930, 2857, 1725, 1654, 1602, 1512, 1458, 1376, 1279, 1131 cm^{-1}; ^1H NMR (400 MHz, CD_3OD + 0.1% TFA) δ 1.54 (1H, m, H-6), 2.06 (1H, m, H-7), 2.25 (1H, m, H-7), 7.11 (1H, d, J = 2.1 Hz, H-12), 6.74 (1H, d, J = 8.0 Hz, H-15), 7.08 (1H, J = 2.1, 8.0 Hz, H-16), 2.60 (1H, m, H-17), 2.69 (1H, m, H-17), 5.03 (1H, m, H-18), 1.69 (3H, s, H-20), 1.69 (3H, s, H-21), 1.16 (3H, s, H-22), 1.00 (3H, s, H-23), 2.04 (2H, m, H-24), 4.89 (1H, m, H-25), 1.65 (3H, s, H-27), 1.50 (3H, s, H-28), 1.92 (1H, m, H-29), 2.02 (1H, m, H-29), 2.59 (1H, m, H-30), 4.50 (2H, br s, H-32), 1.59 (3H, s, H-33 **10a**), 1.64 (3H, s, H-33 **10b**), 1.47 (2H, m, H-34 **10a**), 2.04 (2H, m, H-34 **10b**), 1.81 (2H, m, H-35 **10a**), 5.03 (1H, m, H-35 **10b**), 4.63 (2H, br s, H-37 **10a**), 1.65 (3H, s, H-37 **10b**), 1.69 (3H, s, H-38 **10a**), 1.58 (3H, s, H-38 **10b**), 3.93 (3H, s, *O*Me-14); ^{13}C NMR (50 MHz, CD_3OD + 0.1% TFA) δ 195.5 (C-1), 117.2 (C-2), 194.1 (C-3), 69.8 (C-4), 50.3 (C-5), 48.0 (C-6), 43.9 (C-7), 60.0 (C-8), 210.6 (C-9), 196.4 (C-10 **10a**), 196.1 (C-10 **10b**), 127.0 (C-11), 117.2 (C-12), 147.2 (C-13), 153.7 (C-14), 115.2 (C-15), 124.0 (C-16), 27.0 (C-17), 121.5 (C-18), 135.9 (C-19), 26.4 (C-20), 18.4 (C-21), 23.2 (C-22), 27.4 (C-23), 30.3 (C-24 **10a**), 30.7 (C-24 **10b**), 124.1 (C-25), 135.6 (C-26), 26.0 (C-27), 18.2 (C-28), 37.6 (C-29 **10a**), 37.3 (C-29 **10b**), 44.7 (C-30 **10a**), 45.2 (C-30 **10b**), 149.0 (C-31 **10a**), 149.5 (C-31 **10b**), 113.4 (C-32 **10a**), 113.0 (C-32 **10b**), 18.2 (C-33), 32.7 (C-34 **10a**), 33.4 (C-34 **10b**), 36.8 (C-35 **10a**), 124.0 (C-35 **10b**), 149.0 (C-36 **10a**), 133.6 (C-36 **10b**), 111.4 (C-37 **10a**), 26.4 (C-37 **10b**), 22.8 (C-38 **10a**), 18.4 (C-38 **10b**), 56.5 (OMe−C-14); EIMS *m*/*z* 616 $[M]^+$ (32), 547 (10), 479 (80), 355 (84), 231 (67), 151 (100), 123 (10), 69 (28); HRCIMS *m*/*z* 617.3819 $[MH]^+$ (calcd for $C_{39}H_{53}O_6$ 617.3843).

Mixture 11—13,14-Di-*O*-methylxanthochymol (11a)/13,-14-Di-*O*-methylguttiferone E (11b). A solution of the mixture of **8** and **9** (103.6 mg, 0.161 mmol) in 5% NaOH−EtOH (20 mL) was refluxed for 10 h. The solvent was evaporated, and the residue was dissolved in H_2O (50 mL). The aqueous layer was neutralized with HCl (10%) and extracted with Et_2O (3 × 20 mL). The organic layer was washed with H_2O (2 × 10 mL), dried ($MgSO_4$), and evaporated to dryness. The residue, after purification by TLC on Si gel (heptane−acetone, 80:20), afforded **11** (14.8 mg) as a pale yellow amorphous powder: $[\alpha]_D$ +32° (*c* 1.0, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 227 (4.00), 275 (3.96), 340 (sh) nm; IR ($CHCl_3$) ν_{max} 3543, 3020, 2936, 2857, 1724, 1655, 1599, 1515, 1464, 1376, 1279, 1144 cm^{-1}; ^1H NMR (250 MHz, CD_3OD + 0.1% TFA) δ 1.55 (1H, m, H-6), 2.03 (1H, m, H-7), 2.25 (1H, m, H-7), 7.34 (1H, d, J = 2.1 Hz, H-12), 6.84 (1H, d, J = 8.0 Hz, H-15), 7.19 (1H, dd, J = 2.1, 8.0 Hz, H-16), 2.59 (1H, m, H-17), 2.65 (1H, m, H-17), 5.02 (1H, m, H-18), 1.69 (3H, s, H-20), 1.69 (3H, s, H-21), 1.15 (3H, s, H-22), 1.00 (3H, s, H-23), 2.06 (2H, m, H-24), 4.83 (1H, m, H-25), 1.65 (3H, s, H-27), 1.52 (3H, s, H-28), 1.94 (2H, m, H-29), 2.59 (1H, m, H-30), 4.52 (2H, br s, H-32), 1.61 (3H, s, H-33), 1.52 (2H, m, H-34 **11a**), 2.05 (2H, m, H-34 **11b**), 1.85 (2H, m, H-35 **11a**), 5.02 (1H, m, H-35 **11b**), 4.64 (2H, br s, H-37 **11a**), 1.72 (3H, s, H-37 **11b**), 1.69 (3H, s, H-38 **11a**), 1.59 (3H, s, H-38 **11b**), 3.87 (3H, s, *O*Me-13), 3.90 (3H, s, *O*Me-14); ^{13}C NMR (62.5 MHz, CD_3OD + 0.1% TFA) δ 195.1 (C-1), 118.3 (C-2), 193.7 (C-3), 69.5 (C-4), 50.0 (C-5), 47.0 (C-6), 43.8 (C-7), 59.9 (C-8), 210.8 (C-9), 196.1 (C-10), 131.3 (C-11), 113.6 (C-12), 150.2 (C-13), 155.2 (C-14), 111.1 (C-15), 126.2 (C-16), 27.0 (C-17), 121.6 (C-18), 135.3 (C-19), 26.5 (C-20), 18.2 (C-21), 23.2 (C-22), 27.4 (C-

23), 30.4 (C-24), 125.7 (C-25), 133.5 (C-26), 26.0 (C-27), 18.0 (C-28), 37.6 (C-29 **11a**), 37.3 (C-29 **11b**), 44.6 (C-30 **11a**), 45.2 (C-30 **11b**), 149.1 (C-31 **11a**), 149.6 (C-31 **11b**), 113.4 (C-32 **11a**), 112.8 (C-32 **11b**), 17.8 (C-33), 32.6 (C-34 **11a**), 33.3 (C-34 **11b**), 36.8 (C-35 **11a**), 124.3 (C-35 **11b**), 147.0 (C-36 **11a**), 132.6 (C-36 **11b**), 110.4 (C-37 **11a**), 27.0 (C-37 **11b**), 22.8 (C-38 **11a**), 18.4 (C-38 **11b**), 56.9 (*O*Me−C-13), 56.5 (*O*Me-C-14); EIMS *m/z* 630 $[M]^+$ (34), 561 (11), 493 (100), 439 (14), 369 (29), 231 (23), 165 (44), 69 (27); HRCIMS *m/z* 631.4018 $[MH]^+$ (calcd for $C_{40}H_{55}O_6$ 631.3999).

Mixture 12−13-*O*-Methylxanthochymol (12a)/13-*O*-Methylguttiferone E (12b). A solution, under argon, of the mixture xanthochymol/guttiferone E (**1**) (300.2 mg, 0.499 mmol) in THF (2 mL) was cooled to 0 °C. Then NaH 60% (21.9 mg, 0.549 mmol) was added, and, after 15 min, MeI 99.5% (94 μL, 1.497 mmol) was also added. The reaction mixture was warmed to room temperature and stirred for 36 h. Water (5 mL) was added slowly, followed by 1 N HCl (5 mL) and Et_2O (2 × 10 mL). The organic layer was washed with H_2O (10 mL), dried ($MgSO_4$), and the solvent evaporated. The residue, after purification by TLC on Si gel (heptane−acetone, 70:30), afforded a 50:50 mixture of **10** and **12** (33.8 mg). This mixture was purified by HPLC on a Nova Pak Si gel column (heptane−EtOAc−HOAc, 97:3:0.05) to give **12** (16.2 mg) as a pale yellow amorphous powder: $[\alpha]_D$ +32° (*c* 0.5, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 227 (3.97), 280 (3.94), 346 (sh) nm; IR ($CHCl_3$) ν_{max} 3527, 3020, 2930, 2857, 1725, 1652, 1601, 1513, 1464, 1376, 1279, 1129 cm^{-1}; ^1H NMR (400 MHz, CD_3OD + 0.1% TFA) δ 1.54 (1H, m, H-6), 2.06 (1H, m, H-7), 2.25 (1H, m, H-7), 7.36 (1H, d, J = 2.1 Hz, H-12), 6.72 (1H, d, J = 8.0 Hz, H-15), 7.11 (1H, dd, J = 2.1, 8.0 Hz, H-16), 2.60 (1H, m, H-17), 2.69 (1H, m, H-17), 5.03 (1H, m, H-18), 1.69 (3H, s, H-20), 1.69 (3H, s, H-21), 1.16 (3H, s, H-22), 1.00 (3H, s, H-23), 2.04 (2H, m, H-24), 4.89 (1H, m, H-25), 1.65 (3H, s, H-27), 1.50 (3H, s, H-28), 1.92 (1H, m, H-29), 2.02 (1H, m, H-29), 2.59 (1H, m, H-30), 4.50 (2H, br s, H-32), 1.59 (3H, s, H-33 **12a**), 1.64 (3H, s, H-33 **12b**), 1.47 (2H, m, H-34 **12a**), 2.04 (2H, m, H-34 **12b**), 1.81 (2H, m, H-35 **12a**), 5.03 (1H, m, H-35 **12b**), 4.63 (2H, br s, H-37 **12a**), 1.65 (3H, s, H-37 **12b**), 1.69 (3H, s, H-38 **12a**), 1.58 (3H, s, H-38 **12b**), 3.89 (3H, s, *O*Me-13); ^{13}C NMR (50 MHz, CD_3OD + 0.1% TFA) δ 195.5 (C-1), 117.2 (C-2), 194.1 (C-3), 69.8 (C-4), 50.3 (C-5), 48.0 (C-6), 43.9 (C-7), 60.0 (C-8), 210.6 (C-9), 196.4 (C-10 **12a**), 196.1 (C-10 **12b**), 127.0 (C-11), 117.2 (C-12), 149.0 (C-13), 153.7 (C-14), 115.2 (C-15), 125.6 (C-16), 27.0 (C-17), 121.5 (C-18), 135.9 (C-19), 26.4 (C-20), 18.4 (C-21), 23.2 (C-22), 27.4 (C-23), 30.3 (C-24 **12a**), 30.7 (C-24 **12b**), 124.1 (C-25), 135.6 (C-26), 26.0 (C-27), 18.2 (C-28), 37.6 (C-29 **12a**), 37.3 (C-29 **12b**), 44.7 (C-30 **12a**), 45.2 (C-30 **12b**), 149.0 (C-31 **12a**), 149.5 (C-31 **12b**), 113.4 (C-32 **12a**), 113.0 (C-32 **12b**), 18.2 (C-33), 32.7 (C-34 **12a**), 33.4 (C-34 **12b**), 36.8 (C-35 **12a**), 124.0 (C-35 **12b**), 149.0 (C-36 **12a**), 133.6 (C-36 **12b**), 111.0 (C-37 **12a**), 26.4 (C-37 **12b**), 22.8 (C-38 **12a**), 18.4 (C-38 **12b**), 56.7 (*O*Me−C-13); EIMS *m/z* 616 $[M]^+$ (40), 547 (12), 479 (90), 355 (88), 231 (63), 151 (100), 123 (10), 69 (34); HRCIMS *m/z* 617.3851 $[MH]^+$ (calcd for $C_{39}H_{53}O_6$ 617.3843).

Mixture 13−14-*O*-Ethylxanthochymol (13a)/14-*O*-Ethylguttiferone E (13b). To a solution of the mixture xanthochymol/guttiferone E (**1**) (500.5 mg, 0.831 mmol) in DMF (1 mL) cooled to 0 °C was added NaH (60%) (36.5 mg, 0.914 mmol) and, after 15 min, EtI (99.5%) (73 μL, 0.914 mmol). The reaction mixture was refluxed for 12 h and, after cooling, hydrolyzed with H_2O (2 mL), neutralized with a solution of HCl (10%) (2 mL), and extracted with Et_2O (2 × 10 mL). The organic layer was washed with H_2O (5 mL), dried ($MgSO_4$), and the solvent evaporated. The residue, on purification by column chromatography on Si gel (heptane−acetone, 80:20), afforded **13** (43.2 mg) as a pale yellow amorphous powder: $[\alpha]_D$ +65° (*c* 1.0, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 228 (3.94), 276 (3.92), 346 (sh) nm; IR ($CHCl_3$) ν_{max} 3544, 3020, 2932, 1723, 1657, 1602, 1511, 1456, 1376, 1280, 1130 cm^{-1}; ^1H NMR (200 MHz, CD_3OD + 0.1% TFA) δ 1.50 (1H, m, H-6), 2.04 (1H, m, H-7), 2.26 (1H, m, H-7), 7.10 (1H, d, J = 2.1 Hz, H-12), 6.80 (1H, d, J = 8.0 Hz, H-15), 7.10 (1H, J = 2.1, 8.0 Hz, H-16), 2.56 (1H, m, H-17), 2.68 (1H, m, H-17), 5.08 (1H, m, H-18), 1.69 (3H, s, H-20), 1.69 (3H, s, H-21), 1.16 (3H, s, H-22), 0.99 (3H, s, H-23), 2.06 (2H, m, H-24), 4.87 (1H, m, H-25), 1.65 (3H, s, H-27), 1.49 (3H, s, H-28), 1.95 (1H, m, H-29), 2.02 (1H, m, H-29), 2.60 (1H, m, H-30), 4.53 (2H, br s, H-32), 1.59 (3H, s, H-33 **13a**), 1.62 (3H, s, H-33 **13b**), 1.46 (2H, m, H-34 **13a**), 2.04 (2H, m, H-34 **13b**), 1.85 (2H, m, H-35 **13a**), 5.08 (1H, m, H-35 **13b**), 4.63 (2H, br s, H-37 **13a**), 1.65 (3H, s, H-37 **13b**), 1.73 (3H, s, H-38 **13a**), 1.59 (3H, s, H-38 **13b**), 4.17 (2H, q, J = 7.1 Hz, H−CH_2), 1.45 (3H, t, J = 7.1 Hz, H−CH_3); ^{13}C NMR (50 MHz, CD_3OD + 0.1% TFA) δ 195.7 (C-1), 118.2 (C-2), 194.1 (C-3), 65.6 (C-4), 50.2 (C-5), 47.7 (C-6), 43.9 (C-7), 60.0 (C-8), 209.8 (C-9), 196.0 (C-10), 125.7 (C-11), 117.2 (C-12), 147.1 (C-13), 152.7 (C-14), 113.3 (C-15), 123.8 (C-16), 27.0 (C-17), 121.4 (C-18), 135.6 (C-19), 26.4 (C-20), 18.3 (C-21), 23.2 (C-22), 27.4 (C-23), 30.3 (C-24 **13a**), 30.5 (C-24 **13b**), 123.8 (C-25), 133.5 (C-26), 25.9 (C-27), 18.3 (C-28), 37.7 (C-29), 44.7 (C-30), 149.1 (C-31), 111.8 (C-32), 18.3 (C-33), 32.6 (C-34 **13a**), 33.1 (C-34 **13b**), 36.8 (C-35 **13a**), 123.9 (C-35 **13b**), 149.1 (C-36 **13a**), 131.4 (C-36 **13b**), 110.3 (C-37 **13a**), 26.2 (C-37 **13b**), 23.0 (C-38 **13a**), 18.3 (C-38 **13b**), 65.2 (C−CH_2), 14.9 (C−CH_3); CIMS *m/z* 631 $[MH]^+$; HRCIMS *m/z* 631.3957 $[MH]^+$ (calcd for $C_{40}H_{55}O_6$ 631.3999).

Mixture 14−14-β-Glycosylxanthochymol (14a)/14-β-Glycosylguttiferone E (14b). A solution of the mixture xanthochymol/guttiferone E (**1**) (681.3 mg, 1.132 mmol) in toluene (7 mL) under argon and NaH (60%) (102 mg, 2.264 mmol) was stirred for 15 min, and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (98.5%) (945.3 mg, 2.264 mmol) was added. The reaction mixture was refluxed for 48 h. After cooling, it was hydrolyzed with H_2O (10 mL) and neutralized with a solution of 1 N AcOH. The mixture was extracted with EtOAc (3 × 20 mL). The organic layer was washed with H_2O (20 mL) then with brine; dried ($MgSO_4$); and the solvent evaporated. The residue was dissolved in MeOH (10 mL) under argon, and a solution of 1 N MeONa−MeOH (0.5 mL) was added. The reaction mixture was stirred at room temperature and under argon for 24 h and neutralized with a solution of 1 N HOAc. The solvent was evaporated, and the residue was dissolved in EtOAc. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated to dryness. The residue was purified by column chromatography on Si gel (CH_2Cl_2−MeOH, 90:10) followed by HPLC on a Symmetry column (MeOH−H_2O, 70:30), affording **14** (51.4 mg) as a pale yellow amorphous powder: $[\alpha]_D$ +4° (*c* 1.0, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 232 (4.04), 273 (3.92), 348 (sh) nm; IR ($CHCl_3$) ν_{max} 3691, 3384, 3020, 2932, 1720, 1602, 1507, 1452, 1375, 1284 cm^{-1}; ^1H NMR (300 MHz, CD_3OD + 0.1% TFA) δ 1.52 (1H, m, H-6), 1.92 (1H, m, H-7), 2.12 (1H, m, H-7), 7.36 (1H, d, J = 2.1 Hz, H-12), 7.23 (1H, d, J = 8.0 Hz, H-15), 7.00 (1H, dd, J = 2.1, 8.0 Hz, H-16), 2.35 (1H, m, H-17), 2.55 (1H, m, H-17), 4.98 (1H, m, H-18), 1.63 (3H, s, H-20), 1.63 (3H, s, H-21), 1.17 (3H, s, H-22), 0.92 (3H, s, H-23), 2.02 (2H, m, H-24), 4.78 (1H, m, H-25), 1.63 (3H, s, H-27), 1.28 (3H, s, H-28), 1.88 (1H, m, H-29), 1.97 (1H, m, H-29), 2.50 (1H, m, H-30), 4.59 (2H, br s, H-32), 1.59 (3H, s, H-33 **14a**), 1.63 (3H, s, H-33 **14b**), 1.45 (2H, m, H-34 **14a**), 2.04 (2H, m, H-34 **14b**), 1.81 (2H, m, H-35 **14a**), 4.98 (1H, m, H-35 **14b**), 4.64 (2H, br s, H-37 **14a**), 1.58 (3H, s, H-37 **14b**), 1.67 (3H, s, H-38 **14a**), 1.50 (3H, s, H-38 **14b**), 4.62 (1H, anomeric H), 3.30−3.90 (5H, β-LC); ^{13}C NMR (50 MHz, CD_3OD + 0.1% TFA) δ 195.9 (C-1), 118.1 (C-2), 195.0 (C-3), 71.3 (C-4), 50.8 (C-5), 48.0 (C-6), 43.6 (C-7), 61.0 (C-8), 209.2 (C-9), 197.1 (C-10 **14a**, 127.7 (C-11), 117.3 (C-12), 147.7 (C-13), 150.2 (C-14), 116.6 (C-15), 123.7 (C-16), 26.4 (C-17), 123.4 (C-18), 138.7 (C-19), 26.0 (C-20), 18.6 (C-21), 23.9 (C-22), 27.8 (C-23), 30.3 (C-24 **14a**), 30.7 (C-24 **14b**), 123.7 (C-25), 132.5 (C-26), 25.5 (C-27), 18.4 (C-28), 38.0 (C-29), 45.1 (C-30 **14a**, 149.5 (C-31), 111.7 (C-32 **14a**), 112.0 (C-32 **14b**), 18.4 (C-33), 32.3 (C-34 **14a**), 33.2 (C-34 **14b**), 37.4 (C-35 **14a**), 125.6 (C-35 **14b**), 147.7 (C-36 **14a**), 132.2 (C-36 **14b**), 109.9 (C-37 **14a**), 26.6 (C-37 **14b**), 23.0 (C-38 **14a**), 18.4 (C-38 **14b**), 103.8 (C-anomeric β-LC), 78.2, 77.5, 74.7, 70.9, 62.1 (5C-β-LC); FABMS (FAB+ [NBA+LiCl]) *m/z* 765 $[MH]^+$, 771 $[M + Li]^+$, 777 $[M - 1 + 2Li]^+$.

Mixture 15−13,14-*ortho*-Benzoquinone-Xanthochymol (15a)/13,14-*ortho*-Benzoquinone-Guttiferone E (15b). To a solution of the mixture xanthochymol/guttiferone E (**1**) (103.1

mg, 0.171 mmol) in CH_2Cl_2 (1 mL), a solution of $NaIO_4$ (36.6 mg, 0.171 mmol) in H_2O (200 μL) was added. The reaction mixture was stirred for 30 min at room temperature. Then water (5 mL) and EtOAc (5 mL) were added, and the aqueous layer was extracted with EtOAc (2 × 5 mL). The organic layers were combined, washed with H_2O (10 mL) and brine, dried ($MgSO_4$), and evaporated to dryness. The residue, after purification by TLC on Si gel (heptane−EtOAc, 60:40), afforded **15** (55.1 mg) as a colorless amorphous powder: $[\alpha]_D$ +39° (*c* 1.0, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 263 (4.30), 283 (4.19), 356 (sh) nm; IR ($CHCl_3$) ν_{max} 3508, 2929, 1729, 1687, 1619, 1468, 1376, 1291 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (1H, m, H-6), 1.94 (2H, m, H-7), 8.22 (1H, m, H-12), 6.94 (1H, m, H-15), 6.94 (1H, m, H-16), 2.72 (1H, m, H-17), 4.57 (1H, m, H-18), 1.61 (3H, s, H-20), 1.66 (3H, s, H-21), 1.12 (3H, s, H-22), 1.02 (3H, s, H-23), 1.84 (2H, m, H-24), 4.71 (1H, m, H-25), 1.53 (3H, s, H-27), 1.26 (3H, s, H-28), 1.87 (1H, m, H-29), 2.60 (1H, m, H-30), 4.41 (2H, br s, H-32), 1.49 (3H, s, H-33), 1.33 (2H, m, H-34), 1.79 (2H, m, H-35 **15a**), 4.94 (1H, m, H-35 **15b**), 4.49 (2H, br s, H-37 **15a**), 1.53 (3H, s, H-37 **15b**), 1.66 (3H, s, H-38); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.5 (C-1), 118.3 (C-2), 195.3 (C-3), 64.5 (C-4), 50.4 (C-5), 47.4 (C-6), 44.7 (C-7), 62.7 (C-8), 209.5 (C-9), 196.0 (C-10), 154.3 (C-11), 128.7 (C-12), 184.7 (C-13), 185.2 (C-14), 145.1 (C-15), 160.2 (C-16), 26.7 (C-17), 119.3 (C-18), 136.1 (C-19), 26.6 (C-20), 19.1 (C-21), 23.9 (C-22), 27.9 (C-23), 30.1 (C-24), 124.3 (C-25), 133.7 (C-26), 26.4 (C-27), 18.4 (C-28), 38.2 (C-29), 43.6 (C-30), 146.9 (C-31), 114.8 (C-32), 18.3 (C-33 **15a**), 18.6 (C-33 **15b**), 32.3 (C-34), 36.3 (C-35 **15a**), 123.6 (C-35 **15b**), 148.7 (C-36), 133.0 (C-36 **15b**), 110.3 (C-37 **15a**), 26.4 (C-37 **15b**), 23.3 (C-38 **15a**), 18.3 (C-38 **15b**); EIMS *m*/*z* 600 $[M]^+$ (60), 582 (40), 513 (63), 465 (33), 463 (60), 445 (100), 341 (53), 285 (73); HRCIMS *m*/*z* 601.3507 $[MH]^+$ (calcd for $C_{38}H_{49}O_6$ 601.3530).

Tubulin Assay. Compounds have been evaluated according to a published protocol.[1]

KB Cytotoxicity Assay. The assays were performed according to a published technique.[27] The control used for comparison was doxorubicin (IC_{50} 0.058 μg/mL).

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