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An Efficient Process for the Synthesis of *trans*-2,3-Disubstituted-2,3-dihydro-4*H*-1-benzopyran-4-ones (Chroman-4-ones)

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Abstract—The piperidine catalyzed Knoevenagel condensation of 2′-aryl/alkyl-2-hydroxyacetophenones **7** and aryl/alkylaldehydes **8** in refluxing isopropyl alcohol with azeotropic removal of water affords, in high yield, equilibrium mixtures of *E*- and *Z*-chalcones **9** and *cis*- and *trans*-chroman-4-ones **10** which are effectively isomerized in situ to the *trans*-2,3-diaryl/alkylchroman-4-ones, following the addition of 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) to the cooled reaction mixture and may be isolated in high purities (91–99%) by simple filtration, with good to excellent yields (70–95%).

Introduction

2,3-Dihydro-4*H*-1-benzopyran-4-ones (chroman-4-ones) are widely distributed in nature.[1] 2-Arylchroman-4-ones (flavanones) and 3-arylchroman-4-ones (isoflavanones) are ubiquitous in the plant kingdom and many exhibit interesting and useful biological activities.[1] Although less common, natural 2,3-disubstituted chroman-4-ones also occur, for example, papuanic acid **1**,[2] isolated from the bark of *Calophyllum papuanum* Lauterb., *trans*-(+)-inophyllolide **2**,[3] a constituent of the tree *Calophyllum inophyllum* Linn., BE-14348B **3**,[4] a bacterial metabolite produced by *Streptomyces graminofaciens* and the rotenoids, such as munduserone **4**.[5] The 2,3-diarylchroman-4-one substructure also appears commonly in the more elaborate biflavonoids (Fig. 1).[6]

Chroman-4-ones are also important synthetic intermediates for chromans, chromenes and chromanols which themselves possess diverse pharmacological properties such as β-blockade, anticonvulsant, antiestrogen and antimicrobial.[7] More recently, complex 2,3-diarylchroman-4-ones have been prepared as valuable precursors to 2,3-diaryl-2*H*-1-benzopyrans, a class of compounds which exhibits potent antiestrogenic activity.[8–12] Our own interest has been focused on the synthesis of *trans*-2,3-dihydro-2-[4″-[2‴-(1-piperidinyl)ethoxy]phenyl]-7-[4-tetrahydro-2*H*-pyran-2-yl)oxy]-3-[(4′-[(tetrahydro-2*H*-pyran-2-yl)oxy]-phenyl]-4*H*-1-benzopyran-4-one, *trans*-**5**, which is a particularly convenient precursor to (S)-3-(4″-hydroxy)phenyl-4-methyl-2-[4″-[2-(1-piperidinyl)ethoxy]phenyl]-7-hydroxy-2*H*-1-benzopyran 4″,7-bistrimethylacetate **6** (Sch 57050, EM-800), a new anti-estrogenic compound, known to possess

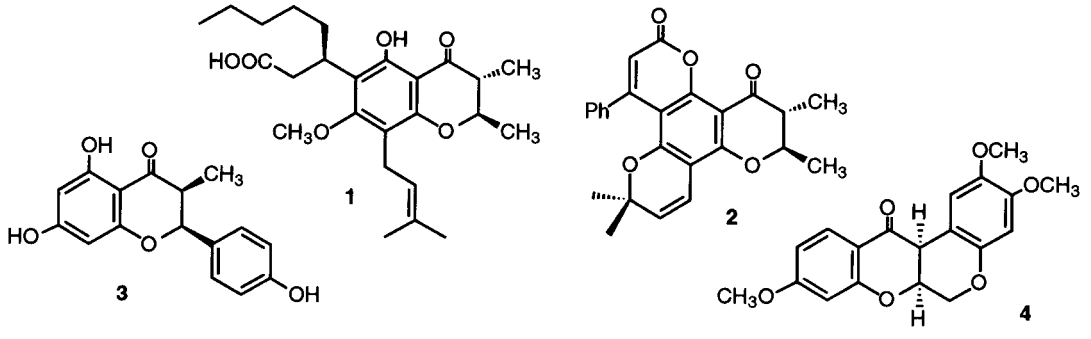

Figure 1.

Keywords: benzopyrans; chalcones; isomerization; rearrangements.

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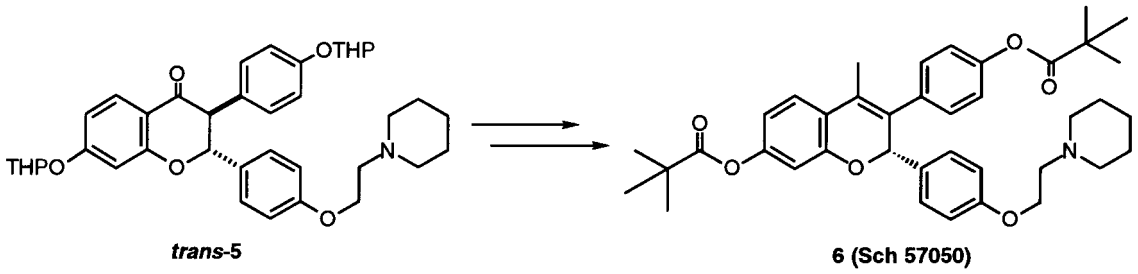
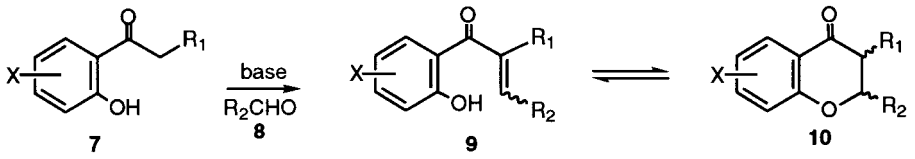


Scheme 1.



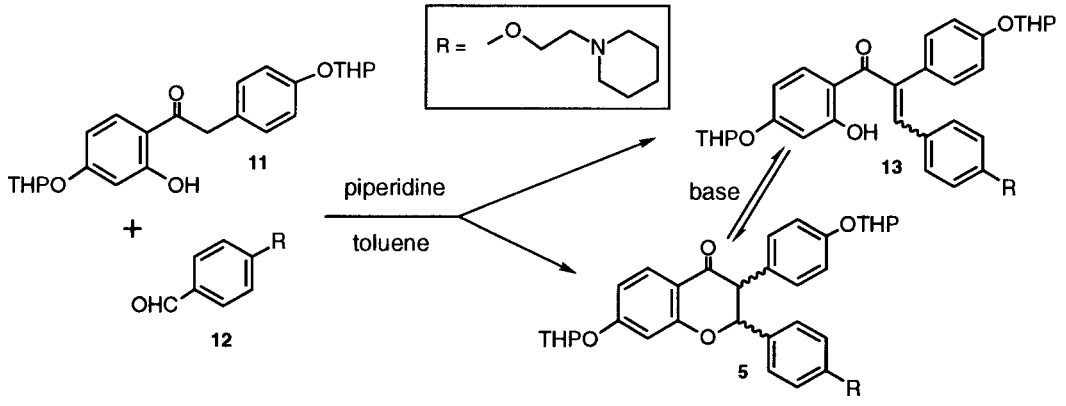
Scheme 2.

very strong affinity for the estrogen receptor site in human breast cancer cell cytosol and noted for its high oral bioavailability and lack of agonist activity (Scheme 1).[13]

Because of their widespread occurrence and valuable properties, numerous syntheses have been developed for the construction of chroman-4-ones.[14] Perhaps the most convenient and practical method is the base catalyzed Knoevenagel condensation between a 2-hydroxyacetophenone **7** and an aldehyde **8** (Kabbe reaction, Scheme 2).[15] In turn, the requisite acetophenones **7** are usually readily available[16] via a Fries rearrangement of the adduct obtained from an appropriate acid (or derivative thereof) and a substituted phenol. This route is saddled, however, with a major handicap, in that the product of the Knoevenagel reaction is normally an equilibrium mixture composed of *E* and *Z*-chalcones **9** and chroman-4-ones **10**.[17] If neither R_1 nor R_2 are hydrogen, the prospect of forming both *cis*- and *trans*-chroman-4-ones **10** also exists, generating a total of four isomers. The equilibrium position between the four potential products in Scheme 3 depends on several factors such as the catalyst and solvent employed, and the steric and electronic characteristics of X, R_1 and R_2 and the pendant substituents within the latter.[18] It is rare to find examples in which the chromanones **10** are the sole products of the reaction and thus to isolate pure samples of these compounds, chromatography[11,12] or fractional crystallization[8] is required, along with the attendant loss in efficiency and yield. This paper describes our efforts to identify a practical high yielding method for the preparation and isolation of chromanone *trans*-**5** without using chromatography and its application to the synthesis of other *trans*-2,3-disubstituted chroman-4-ones.

Results and Discussion

Our first sortie in attacking this synthetic problem was a study of the effect of a combination of various bases and solvents on the equilibrium between the α-arylchalcones **13** and the 2,3-diaryl-chromanones **5** (Scheme 3). The piperidine catalyzed Knoevenagel condensation of ketone **11**[10] and aldehyde **12**,[19] conveniently run in toluene with azeotropic distillation of water, permitted efficient construction of the carbon–carbon bond. Of the various cyclic and acyclic secondary amines, which were examined, only piperidine catalyzed the reaction. This base specificity in the Knoevenagel reaction has been noted previously.[15] After 24 h one equivalent of water had been produced and the reaction was complete. The molar ratio of *cis*-**5**: *trans*-**5**: *E*-**13**: *Z*-**13** in the crude product, as determined by HPLC,[20] was about 2.6:7:4.3:1 (chromanones/chalcones ~1.8:1).



Scheme 3.

Table 1. Effect of base and solvent on the ratio of **5**/**13**

Entry	Isomerization conditions[a]	Ratio of **5**/**13**[b]	Yield of **5**[c]
1	NaOAc/MeOH/reflux/20 h	5.9:1	43
2	KOAc/MeOH/reflux/20 h	5.9:1	47
3	DBU/toluene/reflux/20 h	1.6:1	58
4	DBU/DMF/rt/20 h	5.4:1	nm
5	DBU/DMF/rt/6 h	5.9:1	72
6	DBU/CH_3CN/rt/6 h	5.3:1	71
7	DBU/MeOH/rt/8 h	5.0:1	nm
8	DBU/THF/rt/16 h	3.1:1	nm
9	DBN/DMF/rt/8 h	7.0:1	85
10	DBN/CH_3CN/rt/8 h	7.7:1	85
11	CsF/DMF/rt/8h	6.2:1	81
12	CsF/DMF/4°C/20h	6.0:1	80
13	CsF/CH_3CN/rt/24h	8.5:1	87
14	CsF/IPA/rt/8h	2.0:1	nm
15	TMG/DMF/4°C/48h	10.8:1	79
16	TMG/CH_3CN/rt/54 h	11.8:1	76

[a] NaOAC or KOAc (4 equiv.), other catalysts (0.3 equiv.).
[b] Approximate molar ratio of (*cis*-**5**+*trans*-**5**) to (*E*-**13**+*Z*-**13**) by HPLC.[20]
[c] (%) in solution by HPLC; nm=not measured.

This crude material was then dissolved in various solvents and treated with a variety of catalysts. Table 1 reports the results of these experiments.

The use of sodium or potassium acetates in methanol resulted in substantial deprotection of the phenolic groups leading to low solution yields of **5** and **13** (entries 1 and 2). Fluoride has been used previously to catalyze this isomerization[21] and gave a high ratio of **5**–**13** in acetonitrile and DMF (entries 11–13) although in isopropyl alcohol (IPA), where its solubility is less, the ratio was lower (entry 14). The hindered bases DBU, DBN and tetramethylguanidine (TMG) also gave high ratios of **5**–**13** especially in solvents of high polarity. Several other bases were examined such as triethylamine, imidazole, dimethylaminopyridine and 1,8-bis-(dimethylamino)naphthalene, with IPA as solvent, but all of these led to a chromanone/chalcone ratio of the order of 1.6:1. Two acid catalysts which were tested (PTSA and $BF_3{\cdot}OEt_2$) almost completely converted the chromanones to chalcones and, not unexpectedly, caused substantial removal of the THP groups. No catalyst was found which effected complete cyclization of the α-arylchalcones **13** to give chromanones **5**.

It was felt that of the two chromanones, *cis*-**5** would be the least stable due to the steric compression of the adjacent aryl groups. If conditions were identified under which *trans*-**5** could be induced to crystallize during isomerization, then perturbation of the chalcone/chromanone equilibrium would occur and the remaining components of the quaternary mixture, namely ***E*** and ***Z*** **13** and *cis*-**5**, would ultimately cycle over to the desired compound. The crude heterogeneous material from the Knoevenagel reaction, after removal of toluene, was partially purified by column chromatography on silica gel (mobile phase, ethyl acetate/hexane 3:2) and the chromanone *trans*-**5** eventually crystallized from ethyl acetate/hexane. The *trans* relationship of the vicinal aryl groups in **5** was established by the large coupling constant between the C-2 and C-3 protons ($J_{(2,3)}$=12 Hz), consistent with that in other *trans*-2,3-disubstituted chroman-4-ones.[2,4,22] In *trans*-**5** the signal for the C-2 proton appeared as a pair of doublets each with the same coupling constant and together integrating for one proton. This pattern appeared in several of the *trans*-2,3-disubstituted chromanones **10**, which we later prepared (vide infra) with, in some cases, similar doubling of the signal for the C-3 proton. COSY experiments on **10b** failed to reveal any additional coupling (other than to the C-3 proton). We initially thought the pair of doublets might be caused by the existence of more than one conformation of the 4*H*-1-pyran-4-one ring. However, one of the reviewers suggested the duplicity of these signals was more likely to arise from the additional stereogenic centers in the tetrahydopyranyl ethers and indeed this appears to be the case, as removal of the THP groups (acetic acid/water/rt) from compounds **10f**, **10g** and **10j** provided the corresponding phenols in which the pairs of doublets for the C-2 and C-3 protons had, in each compound, collapsed to solitary doublets, each integrating for one proton.

Subsequently the polar solvent, isopropyl alcohol, also fortuitously proved to be a superior medium for the crystallization of *trans*-**5** and thus was chosen for the isomerization. Indeed, when the toluene was removed from the crude product of the Knoevenagel reaction and the residue stirred at room temperature in isopropyl alcohol with DBU for 24 h, an excellent yield of pure crystalline chromanone *trans*-**5**, essentially free of its isomers, was isolated. DBU remained in the mother liquors, providing an advantage over fluoride, which would have been separated with the product. Further optimization indicated that highest yields of *trans*-**5** were obtained when about 0.3 equiv. of DBU was used and the concentration of products in the cyclization/crystallization was adjusted to about 30%. These observations thus provided the basis of a facile and efficient method for the construction of the *trans*-2,3-diarylchroman-4-one system in high yield.

A suspension of the ketone **11** and aldehyde **12** (1.05 equiv.) in toluene was refluxed with azeotropic removal of water in the presence of piperidine (0.3 equiv.) until the starting ketone was consumed. At the conclusion of the Knoevenagel reaction, toluene was removed by distillation under vacuum and replaced with isopropyl alcohol. DBU (0.3 equiv.) was added and the mixture stirred at ambient temperature for two days during which time crystallization of the product occurred. Filtration and washing with isopropyl alcohol afforded *trans*-**5** in 89% yield with 98% purity containing <1% of the other isomers.

To improve the manufacturing efficiency of this process it would be desirable to conduct both the Knoevenagel reaction and the cyclization in the same solvent. As chromanone *trans*-**5** was too soluble to crystallize from toluene, we examined the Knoevenagel reaction in isopropyl alcohol. Since water is miscible with isopropyl alcohol, the reaction was driven to completion by drying the reflux condensate via passage through 4 Å molecular sieves before returning to the reaction. Cooling the solution and addition of DBU as before led to *trans*-**5** in excellent yield. DBU could be added to the reaction at the start or the finish of the Knoevenagel condensation without affecting the final yield but this base, in the absence of piperidine, also failed to catalyze the latter process.

Table 2. Chroman-4-ones [*trans*-**5** and *trans*-**10a–l** (X=7-THPO)] prepared by this procedure

Compound	R_1	R_2	Reflux time (h)	Ratio of **9**/**10**[a]	mp °C	Chemical purity (%)[b]	Isolated yield (%)[c]
***trans*-5**	4-THPO-Ph	A[f]	24	1/1.6	90–92	95	89
10a	4-THPO-Ph	Ph	24	1/2.0	164–166	92	92
10b	4-THPO-Ph	4-CH_3-Ph	8	[d]	169–171	98	94
10c	4-THPO-Ph	4-CH_3O-Ph	24	1/2.0	162–164	91	95
10d	4-THPO-Ph	2-naphthyl	7	[d]	160–162	98	94
10e	Ph	*n*-heptyl	24	1/20.1	–	99	78[e]
10f	Ph	Ph	24	1/2.7	136–138	98	88
10g	Ph	4-CH_3O-Ph	24	1/2.5	130–132	96	92
10h	Ph	3,4-di-CH_3O-Ph	16	1/5.0	149–150	97	84
10i	Ph	A[f]	24	1/2.3	126–128	95	81
10j	CH_3	Ph	48	1/0.9	121–123	98	70
10k	CH_3	4-CH_3O-Ph	30	1/8.4	100–102	99	81
10l	CH_3	*n*-heptyl	72	1/11.1	–	92	80[e]

[a] In solution after Knoevenagel condensation and prior to adding DBU. HPLC area ratios.
[b] By HPLC area %.
[c] By filtration of product.
[d] Not measured. Chromanone crystallized during Knoevenagel condensation.
[e] Not crystalline—isolated by chromatography.
[f] A=4-[2-(1-piperidino)ethoxy]phenyl.

This procedure was then applied to the synthesis of other *trans*-2,3-disubstituted chroman-4-ones with generally excellent results (see Table 2). Some adjustment of concentration may be required in order to achieve efficient crystallization during the isomerization step. An obvious limitation of the method is a requirement that the desired chroman-4-one crystallizes, so that isomerization is driven beyond the point of equilibrium. In two cases (**10e** and **10l**), the products failed to solidify and were isolated by chromatography. Compound **10h** formed as a gum and some ethyl acetate was added during the isomerization step to promote crystallization, while **10d** crystallized during the Knoevenagel reaction prior to adding DBU.

Experimental

All reactions were carried out under nitrogen. Melting points were determined with a Mel-temp melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 (unless indicated otherwise) using either a Varian Associates XL-300 or Gemini 300 spectrometer operating at 300 MHz and internally locked to the deuterium frequency (15.4 MHz) of the solvent. Chemical shifts are in ppm downfield from TMS. IR spectra (in $CHCl_3$ unless noted otherwise) were obtained on a Mattson Galaxy Series FTIR 7000.

(±)-*trans*-2-(4″-[2‴-piperidinoethoxy]phenyl)-3-(4′-tetrahydropyranyloxyphenyl)-7-tetrahydropyranyloxy-2,3-dihydro-4*H*-1-benzopyran-4-one *trans*-5. A suspension of 2′-hydroxy-4′-tetrahydropyranyloxy-(4-tetrahydropyranyloxyphenyl)acetophenone (1 kg, 2.424 mol), 4-(2′-piperidinoethoxy)benzaldehyde (0.593 kg, 2.545 mol) and piperidine (62 g, 0.73 mol) in IPA (5.21 L) was heated at reflux while returning the condensate to the reaction through a bed of 4 Å molecular sieves (beads 8–12 mesh, 0.582 kg) and monitoring the reaction by HPLC.[20] After 24 h the mixture was cooled to 21°C, DBU (110.8 g, 0.73 mol) was added and the mixture stirred for 48 h during which time the product crystallized. The (±)-*trans*-2-(4″-[2‴-piperidinoethoxy]phenyl)-3-(4′-tetrahydropyranyloxyphenyl)-7-tetrahydropyranyloxy-2,3-dihydro-4*H*-1-benzopyran-4-one *trans*-**5** was filtered off, washed with IPA (2×500 mL) and dried under vacuum. Yield 1.414 kg (89%, corrected for purity of 95%). ^1H NMR; δ 1.30–1.95 (18H, m, $-CH_2-$); δ 2.38 (4H, m, $-CH_2N-$); δ 2.59 (2H, m, $-CH_2N-$); δ 3.55 (2H, m, $-CH_2O-$); δ 3.72 (2H, m, $-CH_2O-$); δ 3.98 (2H, t $-CH_2O-$); δ 4.53 (1H, d, $J_{H2,H3}$=12 Hz, H3); δ 5.36 (1H, t, –OCHO–); δ 5.61 (1H, t, –OCHO–); δ 5.78, 5.81 (1H, 2d, $J_{H2,H3}$=12 Hz, H2); δ 6.67 (1H, d, J=2 Hz, H8); δ 6.75 (1H, dd, J=2 Hz, J=9 Hz, H6); δ 6.82 (4H, d, J=9 Hz, H3′, H3″, H5′, H5″); δ 7.00 (2H, d, J=9 Hz, H2′, H6′); δ 7.31 (2H, d, J=9 Hz, H2″, H6″); δ 7.75 (1H, d, J=9 Hz, H5). ^{13}C NMR; δ 18.37; δ 18.74; δ 23.91; δ 24.48; δ 24.67; δ 25.54; δ 29.46; δ 29.88; δ 54.38; δ 56.13; δ 57.34; δ 61.65; δ 65.44; δ 83.42; δ 95.63; δ 103.38; δ 111.22; δ 113.98; δ 114.99; δ 115.82; δ 128.43; δ 128.77; δ 129.34; δ 129.92; δ 130.63; δ 155.18; δ 158.36; δ 162.43; δ 162.73; δ 191.64. IR; ν_{max} 2950, 1675, 1615, 1580, 1520, 1250 cm^{-1}. HR–MS: calcd for $C_{38}H_{46}NO_7$, $(M+H)^+$ 628.3274, found 628.3262.

General procedure for the preparation of *trans*-2,3-disubstituted-2,3-dihydro-4*H*-1-benzopyran-4-ones 10 (X=7-OTHP). A mixture of the ketone **7** (8.0 mmol) and aldehyde **8** (8.4 mmol) in IPA (8 mL) containing piperidine (2.67 mL, 2.7 mmol) was heated at reflux until the starting ketone was consumed (monitored by HPLC or TLC). The condensate was returned to the reaction through a bed of 4 Å molecular sieves (2 g). The reaction mixture was cooled, DBU (2.7 mmol) was added and the solution agitated for 48 h. The product 2,3-*trans*-disubstituted chroman-4-one **10** was filtered off, washed with IPA and dried under vacuum. Yield 80–92%.

10a. Anal. calcd for $C_{31}H_{32}O_6$: C, 74.38%; H, 6.44%, found: C, 74.09%; H, 6.56%; ^1H NMR δ 1.34–1.93 (12H, m, $-CH_2-$); δ 3.36–3.80 (4H, m, $-CH_2O-$); δ 4.52 (1H, d, $J_{H2,H3}$=12 Hz, H3); δ 5.33 (1H, t, –OCHO–); δ 5.60 (1H, t, –OCHO); δ 5.83, δ 5.87 (1H, 2d, $J_{H2,H3}$=12 Hz, H2); δ 6.67 (1H, d, J=2 Hz, H8); δ 6.72 (1H, dd, J=2 Hz, J=10 Hz, H6); δ 6.79 (2H, d, J=10 Hz, H3″, H5″); δ 6.98 (2H, d, J=10 Hz, H2′, H6′); δ 7.13–7.33 (3H, m,

H3′, H4′, H5′); δ 7.38 (2H, d, *J*=10 Hz, H2″, H6″); δ 7.74 (1H, d, *J*=10 Hz, H5). ^{13}C NMR; δ 18.37; δ 18.73; δ 24.49; δ 24.66; δ 29.46; δ 29.77; δ 29.87; δ 56.21; δ 61.65; δ 83.75; δ 95.64; δ 103.42; δ 103.52; δ 111.33; δ 115.02; δ 115.86; δ 116.15; δ 125.85; δ 127.92; δ 128.13; δ 128.40; δ 128.46; δ 129.99; δ 130.67; δ 137.89; δ 155.24; δ 162.35; δ 162.73; δ 162.79; δ 191.38. IR; ν_{max} 2950, 1680, 1615, 1580, 1520, 1450, 1250, 1175, 1115, 1035, 970 cm^{-1}. HR–MS: calcd for $C_{31}H_{33}O_6$, $(M+H)^+$ 501.2277, found 501.2275.

10b. Anal. calcd for $C_{32}H_{34}O_6$: C, 74.69%; H, 6.66%, found: C, 74.23%; H, 6.68%. ^{1}H NMR; δ 1.35–1.95 (12H, m, $-CH_2-$); δ 2.24 (3H, s, $-CH_3$); δ 3.46–3.64 (2H, m, $-CH_2O-$); δ 3.64–3.82 (2H, m, $-CH_2O-$); δ 4.53 (1H, d, $J_{H2,H3}$=12 Hz, H3); δ 5.35 (1H, t, –OCHO–); δ 5.61 (1H, t, –OCHO–); δ 5.81, δ 5.86 (1H, 2d, $J_{H2,H3}$=12 Hz, H2); δ 6.67 (1H, d, *J*=2 Hz, H8); δ 6.76 (1H, dd, *J*=2 Hz, *J*=10 Hz, H6); δ 6.80 (2H, d, *J*=9 Hz, H3″, H5″); δ 7.01 (2H, d, *J*=10 Hz, H2′, H6′); δ 7.07 (2H, d, *J*=10 Hz, H3′, H5′); δ 7.28 (2H, d, *J*=9 Hz, H2″, H6″); δ 7.75 (1H, d, *J*=10 Hz, H5). ^{13}C NMR; δ 18.33; δ 18.76; δ 20.73; δ 24.49; δ 24.67; δ 29.44; δ 29.89; δ 56.05; δ 61.68; δ 83.52; δ 95.54; δ 95.63; δ 103.39; δ 103.50; δ 111.19; δ 114.99; δ 115.85; δ 127.93; δ 128.45; δ 128.71; δ 130.66; δ 134.97; δ 137.64; δ 155.21; δ 159.84; δ 162.38; δ 162.69; δ 191.53. IR; ν_{max} 2950, 1680, 1615, 1580, 1515, 1445, 1250, 1170, 1110, 1035, 970 cm^{-1}. HR–MS: calcd for $C_{32}H_{35}O_6$, $(M+H)^+$ 515.2434, found 515.2442.

10c. Anal. calcd for $C_{32}H_{34}O_7$: C, 72.44%; H, 6.46%, found: C, 72.30%; H, 6.57%; ^{1}H NMR; δ 1.37–1.90 (12H, m, $-CH_2-$); δ 3.44-3.62 (2H, m, $-CH_2O-$); δ 3.64–3.75 (2H, m, $-CH_2O-$); δ 3.67 (3H, s, $-OCH_3$); δ 4.52 (1H, d, $J_{H2,H3}$=12 Hz, H3); δ 5.33 (1H, t, –OCHO–); δ 5.59 (1H, t, –OCHO–); δ 5.77, δ 5.80 (1H, 2d, $J_{H2,H3}$=12 Hz, H2); δ 6.64 (1H, d, *J*=2 Hz, H8); δ 6.73 (1H, dd, *J*=2 Hz, *J*=10 Hz, H6); δ 6.80 (4H, d, *J*=9 Hz, H3′, H3″, H5′, H5″); δ 6.98 (2H, d, *J*=10 Hz, H2′, H6′); δ 7.32 (2H, d, *J*=10 Hz, H2″, H6″); δ 7.72 (1H, d, *J*=10 Hz, H5). ^{13}C NMR; δ 18.38; δ 18.76; δ 24.49; δ 24.67; δ 29.46; δ 29.90; δ 54.97; δ 56.14; δ 61.68; δ 83.41; δ 93.58; δ 95.65; δ 103.40; δ 111.24; δ 113.45; δ 115.01; δ 115.87; δ 128.44; δ 128.78; δ 129.37; δ 129.97; δ 130.64; δ 155.18; δ 159.08; δ 162.43; δ 162.74; δ 191.62. IR; ν_{max} 2950, 1680, 1615, 1580, 1515, 1450, 1250, 1180, 1110, 1035, 970 cm^{-1}. HR–MS: calcd for $C_{32}H_{35}O_7$, $(M+H)^+$ 531.2383, found 531.2384.

10d. Anal. calcd for $C_{35}H_{34}O_6$: C, 76.34%; H, 6.22%, found C, 76.11%; H, 6.33%, ^{1}H NMR; δ 1.40–1.97 (12H, m, $-CH_2-$); δ 3.30–3.53 (2H, m, $-CH_2O-$); 3.53–3.77 (2H, m, $-CH_2O-$); δ 4.68 (1H, d, $J_{H2,H3}$=12 Hz, H3); δ 5.30 (1H, t, –OCHO–); δ 5.62 (1H, t, –OCHO–); δ 6.01, 6.05 (1H, 2d, $J_{H2,H3}$=12 Hz, H2); δ 6.70 (1H, d, *J*=2 Hz, H8); δ 6.77 (1H, dd, *J*=2 Hz, *J*=9 Hz, H6); δ 6.77 (2H, d, *J*=9 Hz, H3″, H5″); δ 7.03 (2H, d, *J*=9 Hz, H2″, H6″); δ 7.49 (2H, m, 2-Naphth); δ 7.64 (1H, d, *J*=9 Hz, 2-Naphth); δ 7.78 (1H, d, *J*=9 Hz, H5); δ 7.75–7.90 (5H, m, 2-Naphth). ^{13}C NMR; δ 18.45; δ 18.49; δ 18.69 δ 18.74; δ 24.92; δ 25.09; δ 25.23; δ 25.36; δ 29.94; δ 30.25; δ 30.29; δ 30.62; δ 30.90; δ 57.93; δ 58.04; δ 58.12; δ 58.21; δ 62.01; δ 62.24; δ 62.42; δ 62.99; δ 63.42; δ 84.94; δ 85.07; δ 85.13; δ 85.24; δ 85.31; δ 94.74; δ 96.17; δ 96.20; δ 96.26; δ 96.43; δ 103.24; δ 103.67; δ 110.98; δ 111.07; δ 111.71; δ 111.78; δ 111.86; δ 114.54; δ 114.59; δ 115.35; δ 115.64; δ 116.46; δ 116.59; δ 124.39; δ 126.13; δ 126.16; δ 126.29; δ 126.59; δ 126.65; δ 126.75; δ 127.58; δ 127.90; δ 128.02; δ 128.11; δ 129.29; δ 129.80; δ 130.42; δ 130.48; δ 130.63; δ 132.84; δ 133.12; δ 135.24; δ 135.26; δ 135.31; δ 155.02; δ 156.15; δ 156.21; δ 162.88; δ 163.06; δ 163.23; δ 163.76; δ 163.95; δ 191.90; δ 192.58. IR; ν_{max} 2950, 1680, 1610, 1580, 1510, 1440, 1250, 1170, 1110, 1040, 970 cm^{-1}. HR–MS: calcd for $C_{35}H_{35}O_6$, $(M+H)^+$ 551.2434, found 551.2446.

10e. ^{1}H NMR; δ 0.81 (3H, dt, $-CH_3$); δ 1.04–1.92 (12H, m, $-CH_2-$); δ 3.59 (1H, m, $-CH_2O-$); δ 3.69 (1H, m, $-CH_2O$); δ 3.93 (1H, d, $J_{H2,H3}$=12 Hz, H3); δ 4.74 (1H, d, $J_{H2,H3}$=12 Hz, H2); δ 5.62 (1H, t, –OCHO–); δ 6.66 (1H, d, *J*=2 Hz, H8); δ 6.70 (1H, dd, *J*=2 Hz, *J*=9 Hz, H6); δ 7.08 (5H, m, 3-Ph); δ 7.68 (1H, d, *J*=9 Hz, H5). ^{13}C NMR; δ 13.88; δ 18.23; δ 22.01; δ 23.99; δ 24.52; δ 28.40; δ 28.48; δ 28.58; δ 28.70; δ 29.46; δ 31.06; δ 32.56; δ 56.43; δ 56.49; δ 61.58; δ 81.33; δ 95.48 δ 95.56; δ 103.28; δ 111.06; δ 114.91; δ 127.06; δ 128.38; δ 128.61; δ 129.00; δ 129.36; δ 162.19; δ 162.73; δ 191.22. IR (neat on KBr); ν_{max} 2950, 1680, 1610, 1575, 1445, 1250, 1170, 1110, 1035, 950 cm^{-1}. HR–MS: calcd for $C_{27}H_{35}O_4$, $(M+H)^+$ 423.2535, found 423.2545.

10f. Anal. calcd for $C_{26}H_{24}O_4$: C, 77.98%; H, 6.04%, found C, 77.56%; H, 6.35%, ^{1}H NMR; 1.42–1.93 (6H, m, $-CH_2$); δ 3.57 (1H, m, $-CH_2O-$); δ 3.69 (1H, m, $-CH_2O-$); δ 4.59 (1H, d, $J_{H2,H3}$=12 Hz, H3); δ 5.60 (1H, t, –OCHO–); δ 5.88, 5.92 (1H, 2d, $J_{H2,H3}$=12 Hz, H2); δ 6.68 (1H, s, H8); δ 6.75 (1H, d, *J*=9 Hz, H6); δ 7.37 (2H, d, *J*=9 Hz, H2″H6″); δ 6.97–7.30 (8H, m, H2′, H3′, H4′, H3″, H5″); δ 7.75 (1H, d, *J*=9 Hz, H5). ^{13}C NMR; δ 18.34; δ 24.47; δ 29.42; δ 57.08; δ 61.67; δ 83.69; δ 95.55; δ 103.53; δ 111.29; δ 115.02; δ 125.81; δ 126.70; δ 127.93; δ 128.08; δ 128.24; δ 128.44; δ 129.04; δ 129.81; δ 135.66; δ 137.74; δ 162.38; δ 162.73; δ 191.15. IR; ν_{max} 2950, 1680, 1610, 1580, 1450, 1250, 1170, 1115, 1035, 950 cm^{-1}. HR–MS: calcd for $C_{26}H_{25}O_4$, $(M+H)^+$ 401.1753, found 401.1761.

10g. Anal. calcd for $C_{27}H_{26}O_5$: C, 75.33%; H, 6.09%, found C, 75.07%; H, 6.24%, ^{1}H NMR; 1.42–1.93 (6H, m, $-CH_2$); δ 3.59 (1H, m $-CH_2O-$); δ 3.68 (3H, s, $-OCH_3$); δ 3.72 (1H, m, $-CH_2O-$); δ 4.57 (1H, d, $J_{H2,H3}$=12 Hz, H3); δ 5.60 (1H, t, –OCHO–); δ 5.81, 5.86 (1H, 2d, $J_{H2,H3}$=12 Hz, H2); δ 6.68 (1H, d, *J*=2 Hz, H8); δ 6.75 (1H, dd, *J*=2 Hz, *J*=9 Hz, H6); δ 6.78 (2H, d, *J*=9 Hz, H3′, H5′); δ 7.00–7.20 (5H, m, 3-Ph); δ 7.32 (2H, d, *J*=9 Hz, H2′, H6′); δ 7.75 (1H, d, *J*=9 Hz, H5). ^{13}C NMR; δ 18.35; δ 24.46; δ 29.44; δ 54.95; δ 57.00; δ 61.71; δ 83.39; δ 95.64; δ 103.41; δ 111.27; δ 113.41; δ 115.01; δ 126.63; δ 127.95; δ 128.43; δ 129.34; δ 129.81; δ 135.93; δ 159.08; δ 162.47; δ 162.76; δ 191.39. IR; ν_{max} 3020, 2950, 1680, 1615, 1580, 1450, 1250, 1170, 1110, 1040, 950, 910 cm^{-1}. HR–MS: calcd for $C_{27}H_{27}O_5$ $(M+H)^+$ 431.1858, found 431.1855.

10h. Anal. calcd for $C_{28}H_{28}O_6$: C, 73.03%; H, 6.13%. Found C, 73.32%; H, 6.19%, ^{1}H NMR; δ 1.44–1.95 (6H, m,

–CH_2–); δ 3.60 (1H, m, –CH_2O–); δ 3.68 (6H, s, –OCH_3); δ 3.71 (1H, m, –CH_2O–); δ 4.65 (1H, d, $J_{H2,H3}$=12 Hz, H3); δ 5.63 (1H, t, –OCHO–); δ 5.79, δ 5.83 (1H, 2d, $J_{H2,H3}$=12 Hz, H2); δ 6.70 (1H, d, *J*=2 Hz, H8); δ 6.76 (1H, d, H5′); δ 6.76 (1H, q, H6); δ 6.85 (1H, q, H2′);δ 7.08 (1H, d, *J*=9 Hz, H6′); δ 7.10–7.26 (5H, 3-Ph); δ 7.77 (1H, d, *J*=9 Hz, H5). ^{13}C NMR; δ 18.35; δ 24.49; δ 29.45; δ 55.28; δ 55.48; δ 57.07; δ 61.70; δ 83.77; δ 95.52; δ 95.64; δ 103.46; δ 103.52; δ 110.87; δ 111.31; δ 115.02; δ 120.74; δ 126.62; δ 127.92; δ 128.43; δ 129.85; δ 130.08; δ 136.00; δ 148.25; δ 148.68; δ 162.47; δ 162.76; δ 191.44. IR; ν_{max} 2950, 1685, 1615, 1580, 1520, 1440, 1250, 1170, 1110, 1030, 960 cm^{-1}. HR–MS: calcd for $C_{28}H_{29}O_6$, $(M+H)^+$ 461.1964, found 461.1956.

10i. ^{1}H NMR; δ 1.26–1.92 (12H, m, –CH_2–); δ 2.37 (4H, m, –CH_2N–); δ 2.57 (2H, m, –CH_2N–); δ 3.51–3.80 (2H, m, –CH_2O–); δ 3.96 (2H, m, –CH_2O–); δ 4.57 (1H, d, $J_{H2,H3}$=12 Hz, H3); δ 5.59 (1H, t, –OCHO–); δ 5.81, 5.83 (1H, 2d, $J_{H2,H3}$=12 Hz, H2); δ 6.66 (1H, d, *J*=2 Hz, H8); δ 6.72 (1H, dd, *J*=2, 9 Hz, H6); δ 6.78 (2H, d, *J*=9 Hz, H3′, H5′); δ 7.02–7.20 (5H, m, 3-Ph); δ 7.28 (2H, d, *J*=9 Hz, H2′, H6′); δ 7.75 (1H, d, *J*=9 Hz, H5). ^{13}C NMR; δ 18.35; δ 23.90; δ 24.48; δ 25.54; δ 29.48; δ 54.41; δ 56.98; δ 57.34; δ 61.70; δ 65.43; δ 83.39; δ 95.64; δ 103.50; δ 103.82; δ 112.93; δ 113.95; δ 115.00; δ 126.63; δ 127.95; δ 128.43; δ 129.33; δ 129.79; δ 135.93; δ 158.37; δ 162.47; δ 162.76; δ 191.39. IR; ν_{max} 2950, 1680, 1615, 1580, 1520, 1450, 1250, 1170, 1110, 1040, 960 cm^{-1}. HR–MS: calcd for $C_{33}H_{38}NO_5$, $(M+H)^+$ 528.2750 found 528.2753.

10j. Anal. calcd for $C_{21}H_{22}O_4$: C, 74.54%; H, 6.55%. Found C, 74.30%; H, 6.91%, ^{1}H NMR; δ 0.82 (3H, d, *J*=7 Hz, –CH_3); δ 1.43–1.92 (6H, m, –CH_2–); δ 3.17 (1H, dq, *J*=7, 12 Hz, H3); δ 3.54 (1H, m, –CH_2O–); δ 3.67 (1H, m, –CH_2O–); δ 5.22, δ 5.26 (1H, 2d, $J_{H2,H3}$=12 Hz, H2); δ 5.56 (1H, t, –OCHO–); δ 6.60 (1H, d, *J*=2 Hz, H8); δ 6.71 (1H, dd, *J*=2, 9 Hz, H6); δ 7.35–7.56 (5H, m, 2-Ph); δ 7.71 (1H, d, *J*=9 Hz, H5). ^{13}C NMR; δ 10.00; δ 10.06; δ 18.32; δ 24.46; δ 29.46; δ 44.61; δ 61.65; δ 84.65 δ 84.71; δ 95.51 δ 95.66; δ 103.39; δ 111.21; δ 114.39; δ 127.73; δ 128.22; δ 128.52; δ 128.81; δ 138.10; δ 162.42; δ 162.52 δ 162.62; δ 192.42. IR; ν_{max} 2950, 1680, 1610, 1580, 1445, 1250, 1220, 1170, 1120, 1035, 970, 905 cm^{-1}. HR–MS: calcd for $C_{21}H_{23}O_4$, $(M+H)^+$ 339.1596, found 339.1607.

10k. Anal. calcd for $C_{22}H_{24}O_5$: C, 71.72%; H, 6.57%. Found C, 71.50%; H, 6.64%, ^{1}H NMR; δ 0.81 (3H, d, *J*=7 Hz, –CH_3); δ 1.42–1.91 (6H, m, –CH_2–); δ 3.15 (1H, dq, *J*=7, 12 Hz, H3); δ 3.54 (1H, m, –CH_2O–); δ 3.67 (1H, m, –CH_2O–); δ 3.76 (3H, s, –OCH_3); δ 5.15, δ 5.18 (1H, 2d, $J_{H2,H3}$=12 Hz, H2); δ 5.55 (1H, t, –OCHO–); δ 6.59 (1H, d, *J*=2 Hz, H8); δ 6.70 (1H, dd, *J*=2, 9 Hz, H6); δ 6.95 (2H, d, *J*=8.6, H3′, H5′); δ 7.44 (2H, d, *J*=8.6, H2′, H6′); δ 7.71 (1H, d, *J*=9 Hz, H5). ^{13}C NMR; δ 10.10; δ 18.37; δ 24.47; δ 29.46; δ 44.60; δ 55.13; δ 61.64; δ 84.37; δ 95.49 δ 95.64; δ 103.38; δ 111.11; δ 113.83; δ 114.39; δ 128.20; δ 129.12; δ 130.16; δ 159.49; δ 162.48; δ 192.66. IR; ν_{max} 2950, 1680, 1610, 1580, 1450, 1250, 1170, 1120, 1040, 970 cm^{-1}. HR–MS: calcd for $C_{22}H_{25}O_5$, $(M+H)^+$ 369.1702, found 369.1692.

10l. ^{1}H NMR; δ 0.82 (6H, m, –CH_3); δ 1.04–1.90 (18H, m, –CH_2–); δ 2.59 (1H, m, $J_{H2,H3}$=12 Hz, H3); δ 3.56 (1H, m, –CH_2O–); δ 3.67 (1H, m, –CH_2O–); δ 4.17 (1H, d, $J_{H2,H3}$=12 Hz, H2); δ 5.57 (1H, bt, –OCHO–); δ 6.56 (1H, d, *J*=2 Hz, H8); δ 6.66 (1H, dd, *J*=2 Hz, 9 Hz, H6); δ 7.64 (1H, d, *J*=9 Hz, H5). ^{13}C NMR; δ 10.23; δ 13.92; δ 18.25; δ 22.06; δ 23.98; δ 24.50; δ 28.62; δ 28.86; δ 29.46; δ 31.22; δ 32.13; δ 43.77; δ 61.57; δ 82.07; δ 95.42; δ 95.53; δ 103.16 δ 103.27; δ 110.88; δ 114.17; δ 128.12; δ 128.37; δ 129.35; δ 162.11; δ 162.51; δ 192.80. IR (neat on KBr); IR; ν_{max} 2950, 1680, 1615, 1575, 1445, 1355, 1250, 1175, 1105, 1040, 955, 910 cm^{-1}. HR–MS: calcd for $C_{22}H_{33}O_4$, $(M+H)^+$ 361.2379, found 361.2393.

***trans*-7-Hydroxy-2,3-diphenyl-2,3-dihydro-4*H*-1-benzopyran-4-one (10f, X=7-OH).** A suspension of *trans*-7-tetrahydropyranyloxy-2,3-diphenyl-2,3-dihydro-4*H*-1-benzopyran-4-one (400 mg, 1.0 mmol) in acetic acid (6 mL) and water (0.2 mL) was warmed gently to effect solution then maintained at room temperature for 18 h. The crystals which formed on standing were filtered off, washed with water and dried, 180 mg (57%), mp 221–222°C. Anal. calcd for $C_{21}H_{16}O_3$: C, 79.33%; H, 5.10%. Found C, 79.46%; H, 5.02%, ^{1}H NMR; δ 4.51 (1H, d, $J_{H2,H3}$=12 Hz, H3); δ 5.82 (1H, d, $J_{H2,H3}$=12 Hz, H2); δ 6.37 (1H, d, *J*=2 Hz, H8); δ 6.54 (1H, dd, *J*=2, 9 Hz, H6); δ 7.01–7.39 (10H, m, Ph); δ 7.68 (1H, d, *J*=9 Hz, H5); δ 10.65 (1H, s, OH). ^{13}C NMR; δ 57.09; δ 83.60; δ 102.47; δ 110.81; δ 113.51; δ 126.70; δ 127.89; δ 127.93; δ 128.12; δ 128.24; δ 128.36; δ 128.98; δ 129.12; δ 129.81; δ 135.98; δ 137.96; δ 162.72; δ 164.80; δ 190.79; IR; ν_{max} 2950, 1680, 1615, 1580, 1520, 1450, 1250, 1170, 1110, 1035, 970 cm^{-1}. HR–MS: calcd for $C_{21}H_{17}O_3$, $(M+H)^+$ 317.1178, found 317.1177.

***trans*-7-Hydroxy-3-phenyl-2-(4′-methoxyphenyl)-2,3-dihydro-4*H*-1-benzopyran-4-one (10 g, X=7-OH).** A suspension of *trans*-7-tetrahydropyranyloxy-3-phenyl-2-(4′-methoxyphenyl)-2,3-dihydro-4*H*-1-benzopyran-4-one (215 mg, 0.5 mmol) in acetic acid (3 mL) and water (0.1 mL) was warmed gently to effect solution then maintained at room temperature for 18 h. The reaction mixture was then added dropwise to aqueous $NaHCO_3$ solution (30 mL) and the precipitated solid filtered off, washed with water and dried, 138 mg (80%), mp 213–215°C. Anal. calcd for $C_{22}H_{18}O_4$: C, 76.29%; H, 5.24%. Found C, 75.76%; H, 5.24%, ^{1}H NMR; δ 3.67 (3H, s, –OCH_3); δ 4.45 (1H, d, $J_{H2,H3}$=12 Hz, H3); δ 5.74 (1H, d, $J_{H2,H3}$=12 Hz, H2); δ 6.27 (1H, d, *J*=2 Hz, H8); δ 6.48 (1H, dd, *J*=2, 9 Hz, H6); δ 6.78 (2H, d, *J*=9 Hz, H3′, H5′); δ 7.02–7.20 (5H, m, 3-Ph); δ 7.29 (2H, d, *J*=9 Hz, H2′, H6′); δ 7.63 (1H, d, *J*=9 Hz, H5). δ 10.60 (1H, s, OH). ^{13}C NMR; δ 54.99; δ 57.03; δ 83.24; δ 102.46; δ 110.78; δ 113.22; δ 113.44; δ 126.61; δ 127.32; δ 127.96; δ 128.25; δ 128.94; δ 129.35; δ 129.80; δ 130.07; δ 136.24; δ 159.07; δ 162.80; δ 164.91; δ 190.99. IR; ν_{max} 3890, 3340, 1680, 1620, 1590, 1465, 1250, 1180, 1120, 1035 cm^{-1}. HR–MS: calcd for $C_{22}H_{19}O_4$, $(M+H)^+$ 347.1283, found 347.1286.

***trans*-7-Hydroxy-3-methyl-2-phenyl-2,3-dihydro-4*H*-1-benzopyran-4-one (10j, X=7-OH).** A solution of *trans*-7-tetrahydropyranyloxy-3-methyl-2-phenyl-2,3-dihydro-4*H*-

1-benzopyran-4-one (110 mg, 0.295 mmol) in acetic acid (3 mL) and water (0.1 mL) was maintained at room temperature for 18 h and then added slowly to aqueous $NaHCO_3$ solution (30 mL). The precipitated solid was filtered off, washed with water and dried, 72 mg (87%). The product was recrystallized from diethylether, mp 173–174°C. Anal. calcd for $C_{16}H_{14}O_3$: C, 75.58%; H, 5.55%. Found C, 75.34%; H, 5.60%, ^{1}H NMR; δ 0.81 (3H, d, J=7 Hz, $-CH_3$); δ 3.09 (1H, dq, J=7, 12 Hz, H3); δ 5.18 (1H, d, $J_{H2,H3}$=12 Hz, H2) δ 6.29 (1H, d, J=2 Hz, H8); δ 6.50 (1H, dd, J=2, 9 Hz, H6); δ 7.31–7.58 (5H, m, Ph); δ 7.64 (1H, d, J=9 Hz, H5); δ 10.60 (1H, s, OH). ^{13}C NMR; δ 10.20; δ 44.60; δ 84.56; δ 102.35; δ 110.64; δ 112.84; δ 127.70; δ 128.50; δ 128.69; δ 128.72; δ 138.29; δ 162.72; δ 164.56; δ 192.04; IR; ν_{max} 3590, 1680, 1620, 1585, 1470, 1330, 1250, 1180, 1130, 1095, 1015 cm^{-1}. HR–MS: calcd for $C_{16}H_{15}O_3$, $(M+H)^+$ 255.1021, found 255.1023.

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