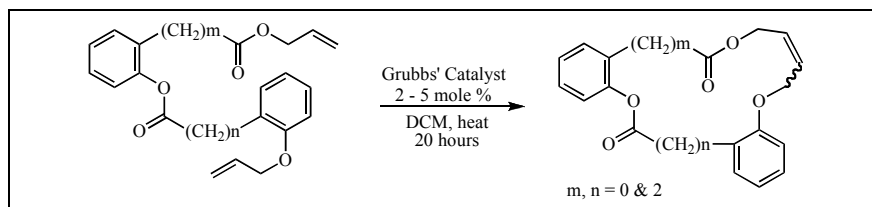


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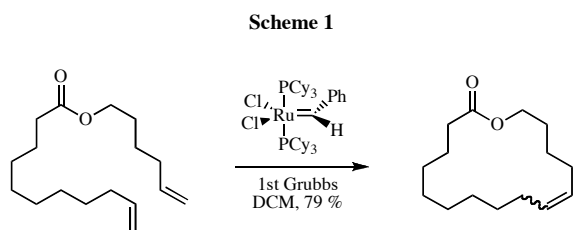
Stable aromatic macrolactones have been synthesized and characterized from 2- and 3-substituted phenylalkanoic acid systems in modest yields.

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## INTRODUCTION

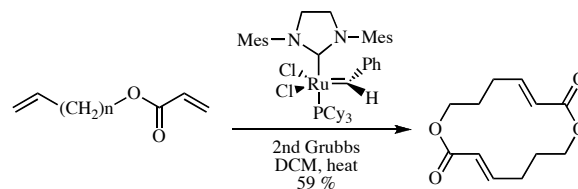
Macromolecules [1-5] have been the targets of the synthetic efforts of investigators, largely because of their widespread applications related to their medicinal, insecticidal and/or phytotoxic properties [6-14]. Accordingly, we endeavored to synthesize a new series of macrocyclic systems as possible candidates for biological screening.

Among the established macrocyclization approaches is the macrolactonization protocol [15-19], that has been employed in the synthesis of a wide variety of macromolecules of high significance. A more recent protocol employs olefin metathesis chemistry mediated by one of the reported metathesis catalysts. Indeed, Furstner and Langerman were the first to demonstrate that unsaturated esters could be cyclized by Ring Closing Metathesis (RCM) to the macrolactones, showing essentially that the RCM approach compares favorably with other macrocyclization methods, Scheme 1.



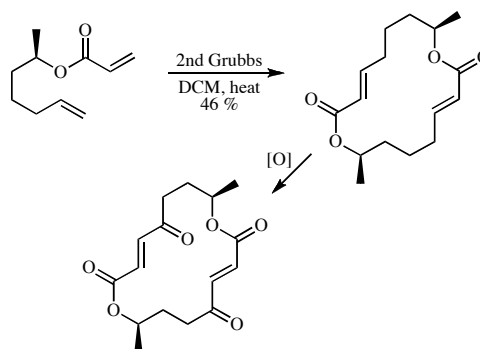
In a reported study, RCM reactions on dienes of the type shown in Scheme 2 have yielded macrocyclic "head-to-tail" dimers and trimers [15].

## Scheme 2



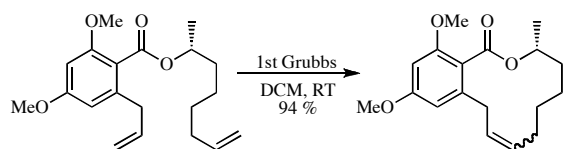
This discovery was subsequently applied by Grubbs in the synthesis of the antifungal antibacterial natural product (-)-pyrenophorin. Here, the cyclization step was achieved using the second generation Grubbs catalyst in modest yields, Scheme 3.

## Scheme 3



Of particular relevance, Furstner's synthesis of (+)-lasiodiplodin exemplifies the generation of aromatic macrolactones *via* the RCM strategy, Scheme 4. Cyclization using the first generation Grubbs catalyst gave excellent yields of the desired macrocycle as a mixture of double bond isomers.

Scheme 4



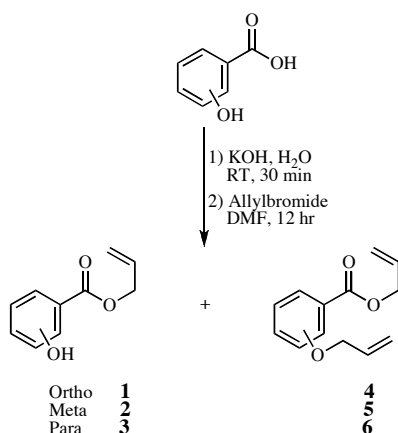
Recently, Nemoto *et al* have applied the RCM-based strategy in the synthesis of novel macrophelides with a thiazole side chain, some of which were found to exhibit apoptosis-inducing activity against specific mammalian tumor cell lines [20-23].

It is noteworthy that the above investigations in addition to other studies reveal that control of double bond geometry can be problematic in applying the RCM strategy to the synthesis of macrocycles. Accordingly, the effect of additives such as  $\text{Ti}(\text{OiPr})_4$ , and substituent groups on the geometric ratios must be examined on a case by case basis [10].

## RESULTS AND DISCUSSION

The current paper reports our preliminary findings on the synthesis of new aromatic macrolactones, employing the RCM strategy in the final macrocyclization step. Synthesis of the required RCM substrates 16 – 25, and 28, incorporated the conventional approach of reacting the requisite acid chloride with the appropriate phenol or the amino ester. These precursors were obtained through the transformations outlined below.

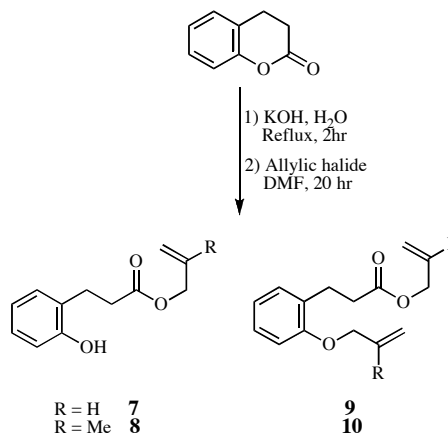
Scheme 5



Allylic esters 1 – 6 were synthesized by our previously reported approach [24,25] which involved treating the respective potassium carboxylate with allylbromide in DMF for about 12 hours, Scheme 5. For compounds 1–3, and 4–6, allylations were carried out using 1.1 and 2.2 equivalents of allylbromide respectively. Product yields averaged 80 %, for the preparation of 1–3, and about 95 % for compounds 4–6. Esters 7–10 were prepared from

dihydrocoumarin by refluxing with aqueous KOH, followed by allylation of the potassium carboxylate in DMF. These compounds were also obtained in good to excellent yields, Scheme 6.

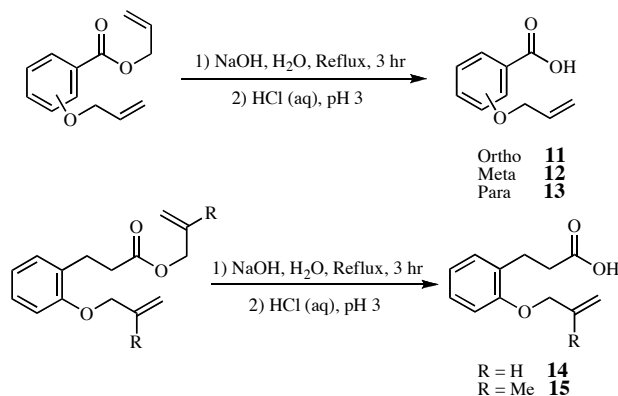
Scheme 6



In contrast, the amino ester **26**, Scheme 10, was obtained in much lower yield (~40 %) presumably because of the equally nucleophilic amino function when compared to the carboxylate group, thus accounting for the observed 35 % yield of compound **27**.

Conversion of the allyloxyesters to the corresponding carboxylic acid was achieved by refluxing in aqueous NaOH for about 3 hours, followed by acidification with 6 M HCl to pH 3, Scheme 7. The desired acids, **11** through **15**, were obtained in excellent yields ranging from 93 to 96 %.

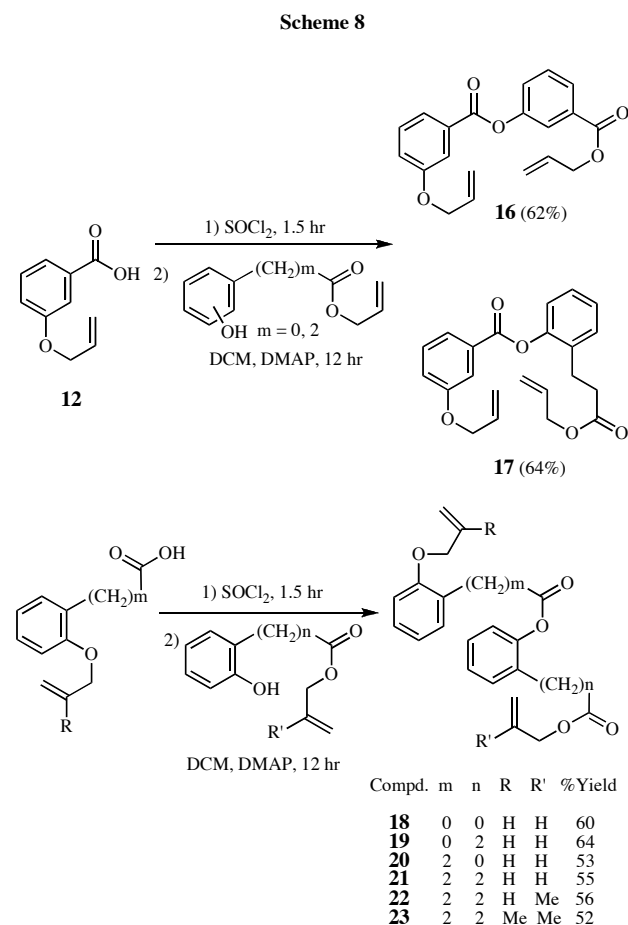
Scheme 7



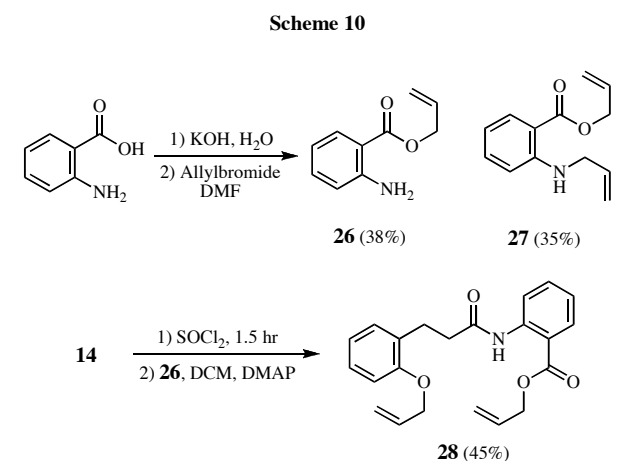
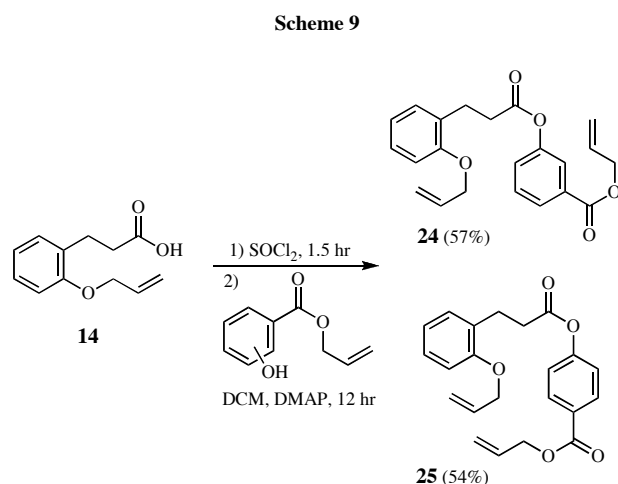
In synthesizing the RCM substrates **16–25**, and **28**, various reaction conditions were explored in an effort to optimize the product yield. We observed that best results were obtained when the reactions were performed in DCM at room temperature. In the absence of solvent and DMAP, a maximum yield of about 42 % was obtained

from these reactions. Similarly, reactions performed without the catalyst DMAP resulted in poor product yields, typically 20–25 %. We also observed that reactions done in THF generally gave lower yields than those done in DCM.

Schemes 8–10 depict the syntheses of the diene systems that were the subject of the subsequent RCM reactions.



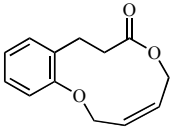
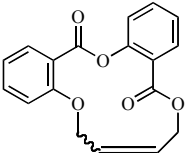
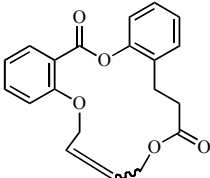
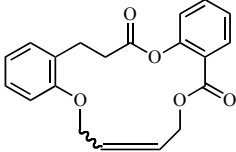
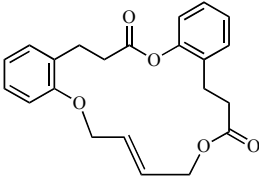
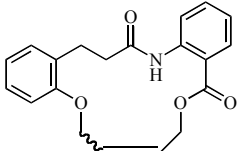
The RCM cyclizations using the 1<sup>st</sup> generation Grubbs catalyst occurred to give the expected heterocycle for most of the RCM substrates. Generally, the substrate dissolved in DCM was refluxed at 40 to 45 °C, with the progress of the reaction being monitored after each hour by TLC. Reactions were performed using either 2 mol or 5 mol percent of the catalyst. Our investigations revealed that there was no measurable difference in product yield when using more than 2 mol % of the catalyst. Also, a total reflux time of about 10 hours followed by stirring at room temperature overnight was optimal for these reactions. A reflux time in excess of 10 hours resulted in significant decomposition of the substrate and catalyst, thus having a deleterious effect on the product yield.



The heterocycles of the successful RCM reactions were obtained as clear solids with sharp melting points, in yields ranging from about 20 to 88 %. These systems were characterized, giving satisfactory analytical data consistent with their assigned structures [26]. Most of the isolated cyclization products were obtained as inseparable mixtures of double bond isomers, with an expected preference for the (*E*) isomer for the ring systems with 15 or more atoms, while those containing fewer atoms gave the (*Z*) isomer as the major product. Compound **29** was obtained exclusively as the (*Z*) isomer, while the 17-membered system **33** was obtained solely as the (*E*) isomer. Stereochemical ratios were determined by proton NMR. Table 1 outlines the structures and related physical data of the respective heterocycles along with the stereochemical outcome of the RCM reactions. All attempts at RCM cyclization on the substrates **16**, **17**, and **22** through **25** proved futile. For dienes **16** and **17**, the starting materials were recovered to the extent of 90%.

Compounds **23**, **24**, and **25** did not react at all, even with the more reactive second generation Grubbs catalyst. The starting dienes were completely recovered.

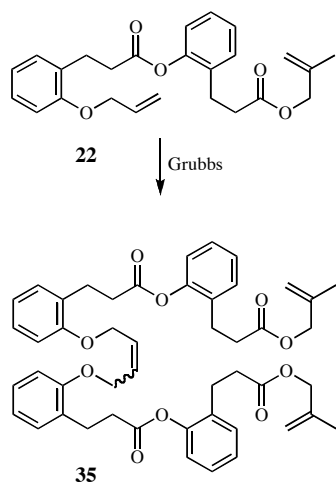
Table 1

RCM Substrate		Grubbs' 1st, 2 mol %		Product(s)			
		DCM, 10 hrs, Reflux		RT, 10 hrs			
RCM Substrate	RCM Product	Structure	Ring Size	% Yield	% (Z)	% (E)	MP (°C)
9	29		11	12	100	0	95 - 96
18	30		13	16	72	28	109 - 110
19	31		15	16	32	69	91 - 92
20	32		15	88	12	88	92 - 93
21	33		17	82	0	100	71 - 72
28	34		15	68	2	98	92 - 93

With respect to substrates **22** and **23**, the poor reactivity may be attributed to steric and/or electronic factors. For the other poorly reacting systems, connectivity across the benzene rings could be playing a more significant role. Additionally, one must also include the possibility that the right reaction conditions for these systems might not have

been found. Interestingly, substrate **22** was observed to undergo intermolecular olefin metathesis to produce the dimer **35** as a mixture of stereoisomers in about 78% yield, Scheme 11. The dimer **35** was found to have the same  $R_f$  value as the precursor diene, hence a pure sample was not obtainable for elemental analysis.

Scheme 11



In conclusion, the methodology of transforming substituted phenyl alkanolic acid allylic esters into novel aromatic macrocyclic systems has been demonstrated. The reaction seems to be more amenable to ring systems of 15 or more atoms, yielding the (*E*) isomer almost exclusively for the larger ring systems. Dienes possessing a methyl group on the penultimate carbons failed to give the expected cyclization products at all reactant concentrations. This might be attributed to steric as well as electronic factors in the olefin metathesis mechanism, and/or that the precise experimental conditions for ring closure might not have been found.

## EXPERIMENTAL

Melting points were determined on a Melt-Temp Melting Point Apparatus and are uncorrected. Infrared spectra were obtained on a Perkin Elmer 1000 Spectrometer as neat samples or  $\text{CCl}_4$  solutions.  $^1\text{H}$  nmr and  $^{13}\text{C}$  nmr spectra were recorded using a Bruker Spin Avance DPX 400 MHz spectrometer, with chemical shifts reported as parts per million ( $\delta$  ppm) downfield of the internal standard TMS. Gas Chromatography Mass Spectrometry (GC/MS) analyses were performed using the Shimadzu GCMS-QP5050A system. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA. All required compounds for the outlined syntheses were obtained from Aldrich Chemical Company. High purity *N,N*-dimethylformamide (DMF) was purchased from Aldrich and used without further purification. Dichloromethane (DCM) and Tetrahydrofuran (THF) were distilled from  $\text{CaH}_2$  and stored over 4 Å molecular sieves under nitrogen. High purity chromatographic solvents were obtained from Fisher or VWR Scientific Company. Thin layer chromatography (TLC) was performed using silica gel (200 – 400 mesh, 60 Å) on polystyrene support with fluorescent indicator. Flash chromatographic purification was performed using silica gel, 200–400 mesh, purchased from Aldrich.

**Allyl salicylate (1).** A mixture of salicylic acid (1.50 g, 10 mmoles) and KOH (0.75 g, 11 mmoles) in water (10 mL) was stirred at room temperature for 10 minutes. The reaction

mixture was evaporated to dryness *in vacuo* leaving as residue the desired potassium salt. The salt was subsequently dissolved in dry DMF (25 mL), to which was added allylbromide (0.90 mL, 11 mmoles) and the mixture stirred at room temperature overnight. Work-up consisted of pouring the reaction mixture into cold brine (50 mL) and extraction with ether (50 mL). The organic layer was washed with water and then dried with  $\text{MgSO}_4$ . Flash chromatographic purification on silica gel using the solvent system hexanes:ethyl acetate 5:1 afforded compound 1 as a clear oil, (1.60 g, 83%); ir: 757, 1485, 1614, 1678 ( $\text{C}=\text{O}$ ), 2918, 3082, 3190  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  4.88 (d,  $J = 5.6$  Hz, 2H); 5.35 (d,  $J = 10.4$  Hz, 1H); 5.44 (d,  $J = 17.2$  Hz, 1H); 6.06 (ddt,  $J = 5.6, 10.6, 17.0$  Hz, 1H); 6.91 (t,  $J = 7.5$  Hz, 1H); 7.00 (d,  $J = 8.4$  Hz, 1H); 7.49 (t,  $J = 8.3$  Hz, 1H); 7.90 (d,  $J = 8.0$  Hz, 1H); 10.8 (s, 1H);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  66.2, 112.8, 118.0, 119.3, 130.3, 132.0, 136.2, 162.1, 170.2.

**Allyl 3-hydroxybenzoate (2).** Compound 2 was prepared according to the method outlined for 1 above and obtained as a pale yellow solid (81%); mp 50 – 51 °C, ir: 1169, 1226, 1444, 1588, 1603, 1673 ( $\text{C}=\text{O}$ ), 2918, 3225 (O-H)  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  4.85 (d,  $J = 5.6$  Hz, 2H); 5.32 (dd,  $J = 1.1, 10.4$  Hz, 1H); 5.43 (dd,  $J = 1.3, 17.2$  Hz, 1H); 6.04 (ddt,  $J = 5.6, 10.5, 17.1$  Hz, 1H); 7.11 (dd,  $J = 1.6, 8.4$  Hz, 1H); 7.34 (t,  $J = 8.1$  Hz, 1H); 7.65 (dd,  $J = 0.9, 6.4$  Hz, 2H).  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  66.3, 116.8, 118.9, 120.9, 122.4, 130.2, 131.7, 132.3, 156.4, 167.0.

**Allyl 4-hydroxybenzoate (3).** Compound 3 was prepared according to the method outlined for 1 above and obtained as a clear solid (80%); mp 104 – 105 °C, ir: 794, 1170, 1281, 1444, 1588, 1603, 1673 ( $\text{C}=\text{O}$ ), 2917, 2956, 3219, 3285  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  4.83 (d,  $J = 5.5$  Hz, 2H); 5.30 (dd,  $J = 1.1, 10.5$  Hz, 1H); 5.42 (dd,  $J = 1.4, 17.2$  Hz, 1H); 6.05 (ddt,  $J = 5.6, 10.4, 17.1$  Hz, 1H); 6.75 (s, 1H), 6.92 (d,  $J = 8.8$  Hz, 2H); 7.99 (d,  $J = 8.8$  Hz, 2H).  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  66.0, 115.8 (2 C's), 118.7, 122.5, 132.5 (2 C's), 132.6, 160.9, 167.2.

**Allyl 2-allyloxybenzoate (4).** Compound 4 was prepared according to the procedure outlined for compound 1, with the exception that 2.2 molar equivalents of KOH and the allylic halide were used. Thus, from 2.00 g salicylic acid compound 4 was obtained as a clear syrup (2.80 g, 90%); ir: 755, 1074, 1133, 1247, 1302, 1450, 1489, 1600, 1728, 2850, 2918, 3010, 3076  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  4.65 (dd,  $J = 1.3, 4.6$  Hz, 2H); 4.84 (dd,  $J = 1.0, 5.4$  Hz, 2H); 5.31 (dt,  $J = 1.0, 9.3$  Hz, 2H); 5.44 (d,  $J = 17.2$  Hz, 1H); 5.52 (d,  $J = 17.3$  Hz, 1H); 6.07 (m, 2H); 7.00 (d,  $J = 8.2$  Hz, 1H); 7.01 (t,  $J = 7.5$  Hz, 1H); 7.46 (dt,  $J = 1.5, 8.2$  Hz, 1H); 7.85 (dd,  $J = 1.4, 7.6$  Hz, 1H);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  65.9, 70.0, 114.0, 117.9, 118.5, 120.8, 121.0, 132.2, 132.7, 133.1, 133.8, 158.6, 166.3.

**Allyl 3-allyloxybenzoate (5).** Compound 5 was synthesized according to the procedure for compound 4, and was obtained as a clear oil (3.40 g, 96%); ir: 755, 1029, 1108, 1215, 1273, 1443, 1585, 1602, 1722, 2918, 3016, 3083  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  4.61 (d,  $J = 5.2$  Hz, 2H); 4.85 (d,  $J = 5.5$  Hz, 2H); 5.32 (dd,  $J = 1.2, 10.4$  Hz, 1H); 5.33 (dd,  $J = 1.3, 10.5$  Hz, 1H); 5.44 (dd,  $J = 1.4, 17.2$  Hz, 1H); 5.46 (dd,  $J = 1.5, 17.2$  Hz, 1H); 6.08 (m, 2H); 7.15 (dd,  $J = 0.8, 7.4$  Hz, 1H); 7.37 (t,  $J = 8.0$  Hz, 1H); 7.62 (s, 1H); 7.69 (d,  $J = 7.9$  Hz, 1H);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  66.0, 69.4, 115.5, 118.4, 118.7, 120.1, 122.6, 129.8, 131.8, 132.6, 133.3, 159.0, 166.5.

**Allyl 4-allyloxybenzoate (6).** Compound 6 was similarly obtained by the method outlined for 4 as a clear oil in 96% yield; ir: 757, 1029, 1100, 1280, 1443, 1585, 1602, 1724, 2918, 3016,

3080  $\text{cm}^{-1}$ .  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  4.62 (m, 2H); 4.82 (m, 2H); 5.29 (dd,  $J = 1.3, 10.5$  Hz, 1H); 5.34 (dd,  $J = 1.3, 10.5$  Hz, 1H); 5.43 (dd,  $J = 1.5, 17.2$  Hz, 1H); 5.45 (dd,  $J = 1.4, 17.2$  Hz, 1H); 6.06 (m, 2H); 6.95 (d,  $J = 9.0$  Hz, 2H); 8.03 (d,  $J = 9.0$  Hz, 2H).  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  65.7, 69.3, 114.7 (2 C's), 118.4, 118.5, 123.1, 132.1 (2 C's), 132.9, 133.0, 162.8, 166.4.

**Allyl 3-(2-hydroxyphenyl)propanoate (7).** A mixture of dihydrocoumarin (5.00 g, 33.7 mmol) and KOH (2.10 g, 37.1 mmol) in 50 mL water was refluxed for 2 hours. The water was removed *in vacuo*, and the resulting brown crystals dissolved in 50 mL DMF. Allyl bromide (4.59 g, 38.0 mmol) was then added in one portion followed by vigorous stirring at room temperature overnight. The reaction mixture was combined with brine (50 mL) and extracted with ether (50 mL). The combined organic extracts were dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to a pale yellow oil, which was purified by column chromatography on silica gel to yield compound **7** (84%); ir: 755, 1100, 1458, 1595, 1609, 1711 (C=O), 2851, 2919, 3036, 3408  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (DMSO, ppm):  $\delta$  2.60 (t,  $J = 8.0$  Hz, 2H); 2.79 (t,  $J = 7.9$  Hz, 2H); 4.54 (d,  $J = 5.4$  Hz, 2H); 5.19 (dd,  $J = 1.2, 10.5$  Hz, 1H); 5.26 (dd,  $J = 0.7, 17.3$  Hz, 1H); 5.89 (ddt,  $J = 5.5, 10.4, 17.2$  Hz, 1H); 6.70 (t,  $J = 7.4$  Hz, 1H); 6.78 (dd,  $J = 0.8, 8.0$  Hz, 1H); 7.02 (t,  $J = 7.7$  Hz, 1H); 7.05 (d,  $J = 7.4$  Hz, 1H); 9.37 (s, 1H).  $^{13}\text{C}$  nmr (DMSO, ppm):  $\delta$  26.3, 34.3, 65.1, 115.7, 118.5, 119.7, 127.3, 128.1, 130.6, 133.6, 156.0, 173.0.

**2-Methylprop-2-en-1-yl-3-(2-hydroxyphenyl)propanoate (8).** Compound **8** was synthesized according to the procedure outlined for **7**, replacing the allyl bromide with 3-chloro-2-methyl-1-propene, and obtained as a clear syrup (79%); ir: 754, 1099, 1232, 1457, 1505, 1595, 1712, 2917, 2967, 3032, 3076, 3411  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  1.74 (s, 3H); 2.79 (t,  $J = 6.7$  Hz, 2H); 2.95 (t,  $J = 6.0$  Hz, 2H); 4.53 (s, 2H); 4.95 (d,  $J = 5.2$  Hz, 2H); 6.90 (d,  $J = 7.7$  Hz, 2H); 7.03 (s, 1H); 7.14 (m, 2H);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  19.9, 25.1, 35.1, 68.9, 113.8, 117.6, 121.3, 127.6, 128.4, 130.9, 140.0, 154.6, 175.7.

**Allyl 3-[2-(allyloxy)phenyl]propanoate (9).** Compound **9** was prepared according to the procedure outlined for compound **7**, with the exception that 2.2 molar equivalents of KOH and the allylic halide were used, and was obtained as a pale yellow syrup (4.60 g, 96%); ir: 753, 1112, 1243, 1454, 1494, 1588, 1602, 1737, 2865, 2918, 3022, 3082  $\text{cm}^{-1}$ .  $^1\text{H}$  nmr (DMSO, ppm):  $\delta$  2.62 (t,  $J = 7.9$  Hz, 2H); 2.87 (t,  $J = 7.5$  Hz, 2H); 4.53 (ddd,  $J = 1.4, 1.4, 5.4$  Hz, 2H); 4.58 (ddd,  $J = 1.5, 1.5, 4.9$  Hz, 2H); 5.20 (ddt,  $J = 1.4, 1.4, 10.4$  Hz, 1H); 5.24 (ddt,  $J = 1.8, 1.8, 14.5$  Hz, 1H); 5.26 (ddt,  $J = 1.5, 1.5, 15.4$  Hz, 1H); 5.41 (ddt,  $J = 1.7, 1.7, 17.3$  Hz, 1H); 5.89 (ddt,  $J = 5.5, 10.5, 17.2$  Hz, 1H); 6.06 (ddt,  $J = 4.9, 10.6, 17.3$  Hz, 1H); 6.86 (dt,  $J = 0.8, 7.4$  Hz, 1H); 6.94 (d,  $J = 8.0$  Hz, 1H); 7.17 (m, 2H).  $^{13}\text{C}$  nmr (DMSO, ppm):  $\delta$  26.4, 34.3, 65.2, 68.4, 112.7, 117.5, 118.5, 121.3, 128.4, 129.2, 130.5, 133.6, 134.7, 156.8, 172.9.

**2-Methylprop-2-en-1-yl 3-[2-[(2-methylprop-2-en-1-yl)oxy]phenyl]propanoate (10).** Using the procedure for compound **9**, **10** was synthesized and obtained as a clear oil (87%); ir: 752, 1111, 1240, 1452, 1494, 1602, 1659, 1737, 2850, 2918, 2972, 3076  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  1.75 (s, 3H); 1.87 (s, 3H); 2.71 (t,  $J = 8.1$  Hz, 2H); 3.03 (t,  $J = 7.5$  Hz, 2H); 4.46 (s, 2H); 4.52 (s, 2H); 4.93 (s, 1H); 4.96 (s, 1H); 5.00 (s, 1H); 5.13 (s, 1H); 6.84 (d,  $J = 8.3$  Hz, 1H); 6.90 (t,  $J = 6.7$  Hz, 1H); 7.18 (d,  $J = 7.2$  Hz, 1H); 7.19 (t,  $J = 6.0$  Hz, 1H);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  19.9, 26.7, 34.7, 68.0, 71.8, 110.4, 111.7, 112.6, 113.2, 121.0, 127.9, 129.4, 130.4, 140.5, 141.3, 156.9, 173.4.

**General Procedure for the Synthesis of the Carboxylic Acids.** A mixture of 3.00 g of the ester and 2.00 molar equivalent of NaOH in 100 mL water was refluxed for 3 hours. After cooling to room temperature, 50 mL diethyl ether was added to extract organic impurities. The aqueous layer was acidified with 50% aqueous HCl to pH 3 by drop-wise addition, and left to stand at room temperature overnight. The precipitated white crystals were collected by suction filtration and dried *in vacuo*.

**2-Allyloxybenzoic acid (11).** Compound **11** was obtained in 94% yield after re-crystallization from water, mp 60–61 °C; ir: 800, 996, 1458, 1603, 1690, 1736, 2520, 2919, 3076, 3259  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  4.82 (d,  $J = 5.5$  Hz, 2H); 5.45 (dd,  $J = 0.8, 10.5$  Hz, 1H); 5.51 (dd,  $J = 0.9, 17.2$  Hz, 1H); 6.13 (ddt,  $J = 5.6, 10.6, 17.1$  Hz, 1H); 7.07 (d,  $J = 8.3$  Hz, 1H); 7.16 (dt,  $J = 0.7, 7.8$  Hz, 1H); 7.57 (dt,  $J = 1.7, 9.0$  Hz, 1H); 8.20 (dd,  $J = 1.4, 7.7$  Hz, 1H); 11.0 (s, 1H).  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  71.2, 113.4, 118.4, 121.0, 122.8, 131.3, 134.2, 135.4, 157.6, 165.9.

**3-Allyloxybenzoic acid (12).** Compound **12** was obtained in 97% yield after re-crystallization from water, mp 69–70 °C; ir: 755, 1301, 1452, 1586, 1690, 1736, 2560, 2664, 2917, 3000, 3076  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  4.63 (d,  $J = 5.2$  Hz, 2H); 5.34 (dd,  $J = 1.2, 10.4$  Hz, 1H); 5.47 (dd,  $J = 1.3, 17.3$  Hz, 1H); 6.09 (ddt,  $J = 5.2, 10.6, 17.2$  Hz, 1H); 7.20 (dd,  $J = 1.6, 8.2$  Hz, 1H); 7.41 (t,  $J = 8.0$  Hz, 1H); 7.65 (s, 1H); 7.75 (d,  $J = 7.6$  Hz, 1H);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  69.4, 115.8, 118.5, 121.6, 123.2, 130.0, 130.9, 133.2, 159.0, 172.5.

**4-Allyloxybenzoic acid (13).** Compound **13** was obtained in 97% yield after re-crystallization from water, mp 160–161 °C; ir: 752, 1304, 1450, 1586, 1692, 1735, 2560, 2664, 2917, 3010, 3078  $\text{cm}^{-1}$ .  $^1\text{H}$  nmr (DMSO, ppm):  $\delta$  4.65 (d,  $J = 5.2$  Hz, 2H); 5.28 (dd,  $J = 1.3, 10.6$  Hz, 1H); 5.41 (dd,  $J = 1.5, 17.3$  Hz, 1H); 6.05 (ddt,  $J = 5.2, 10.6, 17.3$  Hz, 1H); 7.03 (d,  $J = 8.8$  Hz, 2H); 7.88 (d,  $J = 8.8$  Hz, 2H); 12.61 (s, 1H).  $^{13}\text{C}$  nmr (DMSO, ppm):  $\delta$  69.2, 115.3 (2 C's), 118.7, 123.9, 132.2 (2 C's), 134.1, 162.6, 167.8.

**3-(2-Allyloxyphenyl)propanoic acid (14).** Compound **14** was obtained in 93% yield after re-crystallization from water, mp 49–50 °C; ir: 751, 1113, 1240, 1452, 1493, 1602, 1711, 2648, 2847, 2918, 3076  $\text{cm}^{-1}$ .  $^1\text{H}$  nmr (DMSO, ppm):  $\delta$  2.49 (t,  $J = 7.5$  Hz, 2H); 2.82 (t,  $J = 7.5$  Hz, 2H); 4.58 (ddd,  $J = 1.5, 1.5, 4.9$  Hz, 2H); 5.25 (ddt,  $J = 1.6, 1.6, 10.6$  Hz, 1H); 5.42 (ddt,  $J = 1.7, 1.7, 17.3$  Hz, 1H); 6.06 (ddt,  $J = 4.9, 10.6, 17.3$  Hz, 1H); 6.86 (dt,  $J = 0.8, 7.4$  Hz, 1H); 6.94 (d,  $J = 7.9$  Hz, 1H); 7.15 (d,  $J = 7.4$  Hz, 1H); 7.17 (dt,  $J = 1.6, 7.5$  Hz, 1H); 12.15 (s, 1H).  $^{13}\text{C}$  nmr (DMSO, ppm):  $\delta$  26.4, 34.5, 68.8, 112.6, 117.5, 121.2, 128.3, 129.6, 130.5, 134.7, 156.8, 174.8.

**3-{2-[(2-Methylprop-2-en-1-yl)oxy]phenyl}propanoic acid (15).** Compound **15** was obtained as a colorless liquid after ether extraction and flash chromatography (96%); ir: 750, 1110, 1242, 1452, 1493, 1603, 1710, 2648, 2847, 2918, 3078  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  1.87 (s, 3H); 2.73 (t,  $J = 8.1$  Hz, 2H); 3.02 (t,  $J = 7.5$  Hz, 2H); 4.47 (s, 2H); 5.01 (s, 1H); 5.12 (s, 1H); 6.85 (d,  $J = 8.4$  Hz, 1H); 6.91 (t,  $J = 7.4$  Hz, 1H); 7.21 (m, 2H); 7.28 (s, 1H);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  19.9, 26.4, 34.4, 71.9, 111.7, 112.7, 121.0, 128.1, 129.1, 130.5, 141.3, 156.9, 179.9.

**General Procedure for the Synthesis of the RCM Substrates.** A 100 mL three-necked round-bottomed flask (RBF) fitted with a pressure-equalizing dropping funnel and a magnetic stir bar was flame-dried under a positive atmosphere of dry nitrogen for 10 minutes. After cooling to room temperature, a solution of the required phenol (1.05 eq) and 4-DMAP (2.00

eq) in 30 mL DCM was added *via* syringe through a pierced rubber septum. A separate RBF, equipped for magnetic stirring was similarly flame-dried under nitrogen. After cooling to room temperature, the flask was charged with the starting carboxylic acid (1.00 eq) and 1.5 equivalents of  $\text{SOCl}_2$ . The mixture was stirred for 1.5 hours while maintaining the flow of nitrogen, after which the excess  $\text{SOCl}_2$  was evaporated *in vacuo*. The resulting acid chloride was re-dissolved in 30 mL dry DCM and transferred *via* syringe to the dropping funnel, and subsequently added drop-wise over 10 minutes with stirring to the phenol solution. Stirring was continued for 12 hours at room temperature, after which the reaction mixture was transferred to an RBF and the solvent evaporated *in vacuo* to give the crude product as a yellow solid. The crude material was subsequently extracted with two 30 mL portions of ether, decanting the two liquid phases. The combined ether solutions were evaporated *in vacuo*, and the residue chromatographed on silica gel using hexanes:ethyl acetate; 3:1 as eluent to give the pure diene.

**3-(Allyloxy-carbonyl)phenyl 3-allyloxybenzoate (16).** Compound **16** was obtained as a clear solid after chromatography (62%), mp 34 °C; ir: 748, 933, 1100, 1260, 1441, 1486, 1586, 1648, 1725, 2850, 2918, 3079  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  4.65 (d, J = 4.9 Hz, 2H); 4.87 (d, J = 5.4 Hz, 2H); 5.32 (d, J = 11.0 Hz, 1H); 5.35 (d, J = 10.7 Hz, 1H); 5.44 (d, J = 17.0 Hz, 1H); 5.48 (d, J = 16.0 Hz, 1H); 6.08 (m, 2H); 7.24 (d, J = 6.0 Hz, 1H); 7.45 (m, 2H); 7.54 (t, J = 7.8 Hz, 1H); 7.74 (s, 1H), 7.84 (d, J = 7.3 Hz, 1H); 7.93 (s, 1H); 8.02 (d, J = 7.5 Hz, 1H).  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  66.3, 69.4, 115.9, 118.5, 119.0, 121.4, 123.2, 123.4, 126.9, 127.6, 129.9, 130.1, 130.8, 132.2, 132.4, 133.1, 151.3, 159.1, 165.2, 165.7; ms: m/z 338 ( $\text{M}^+$ ), 281, 161 (100%), 133, 105, 77, 65, 55, 41. *Anal.* Calcd. for  $\text{C}_{20}\text{H}_{18}\text{O}_5$  (338.35): C, 70.99; H, 5.36. Found: C, 70.99; H, 5.32.

**2-[3-Allyloxy-3-oxopropyl]phenyl 3-allyloxybenzoate (17).** Compound **17** was obtained as a clear oil after chromatography (64%); ir: 750, 924, 1102, 1216, 1441, 1489, 1584, 1593, 1737, 2917, 3016, 3076  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  2.69 (t, J = 7.6 Hz, 2H); 2.97 (t, J = 7.4 Hz, 2H); 4.56 (d, J = 4.8 Hz, 2H); 4.65 (d, J = 3.9 Hz, 2H); 5.20 (d, J = 10.4 Hz, 1H); 5.26 (d, J = 17.3 Hz, 1H); 5.35 (d, J = 10.5 Hz, 1H); 5.48 (d, J = 17.3 Hz, 1H); 5.86 (ddt, J = 5.4, 10.7, 16.3 Hz, 1H); 6.10 (ddt, J = 4.9, 11.0, 16.2 Hz, 1H); 7.27 (m, 5H); 7.45 (t, J = 7.8 Hz, 1H); 7.76 (s, 1H), 7.85 (d, J = 7.4 Hz, 1H);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  26.0, 34.9, 65.6, 69.4, 115.9, 118.5, 118.6, 121.4, 122.9, 123.1, 126.7, 128.1, 130.1, 130.6, 131.0, 132.5, 132.9, 133.2, 149.6, 159.2, 165.3, 172.7; ms: m/z 366 ( $\text{M}^+$ ), 348, 206, 161 (100%), 133, 105, 92, 79, 64, 41. *Anal.* Calcd. for  $\text{C}_{22}\text{H}_{22}\text{O}_5$  (366.41): C, 72.12; H, 6.05. Found: C, 72.19; H, 6.06.

**2-(Allyloxy-carbonyl)phenyl 2-allyloxybenzoate (18).** Compound **18** was obtained as a clear solid after chromatography (59%), mp 59 °C; ir: 750, 1199, 1252, 1449, 1487, 1601, 1724, 1747, 2850, 2918, 2983, 3016, 3076  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  4.68 (dd, J = 1.3, 3.2 Hz, 1H); 4.72 (dd, J = 0.8, 5.6 Hz, 2H); 5.16 (d, J = 10.3 Hz, 1H); 5.27 (dd, J = 1.3, 16.4 Hz, 1H); 5.29 (dd, J = 1.5, 12.2 Hz, 1H); 5.54 (d, J = 17.2 Hz, 1H); 5.87 (ddt, J = 5.7, 11.0, 16.5 Hz, 1H); 6.08 (ddt, J = 4.7, 10.7, 15.7 Hz, 1H); 7.03 (d, J = 8.4 Hz, 1H); 7.08 (t, J = 7.6 Hz, 1H); 7.26 (d, J = 8.1 Hz, 1H); 7.37 (t, J = 7.6 Hz, 1H); 7.54 (dt, J = 1.6, 7.4 Hz, 1H); 7.62 (dt, J = 1.5, 7.5 Hz, 1H); 8.10 (d, J = 7.7 Hz, 1H); 8.16 (d, J = 7.7 Hz, 1H);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  66.2, 69.9, 114.0, 118.0, 119.0, 119.7, 120.9, 124.2, 124.6, 126.3, 132.2, 132.3, 133.0, 133.2, 134.2, 134.6, 151.2, 159.4, 164.4, 164.8; ms: m/z 338 ( $\text{M}^+$ ), 178, 161 (100%),

133, 105, 92, 77, 64, 41. *Anal.* Calcd. for  $\text{C}_{20}\text{H}_{18}\text{O}_5$  (338.35): C, 70.99; H, 5.36. Found: C, 70.90; H, 5.25.

**2-[3-(Allyloxy)-3-oxopropyl]phenyl 2-allyloxybenzoate (19).** Compound **19** was isolated as a clear oil after chromatography (64%); ir: 750, 924, 1102, 1216, 1441, 1584, 1599, 1737, 2849, 2919, 3016, 3076  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  2.70 (t, J = 8.1 Hz, 2H); 3.00 (t, J = 7.5 Hz, 2H); 4.56 (d, J = 5.5 Hz, 2H); 4.70 (d, J = 4.6 Hz, 2H); 5.20 (d, J = 10.4 Hz, 1H); 5.26 (d, J = 16.2 Hz, 1H); 5.29 (d, J = 9.1 Hz, 1H); 5.52 (d, J = 17.2 Hz, 1H); 5.88 (ddt, J = 4.9, 10.5, 17.1 Hz, 1H); 6.10 (ddt, J = 5.7, 10.5, 17.0 Hz, 1H); 7.05 (d, J = 8.2 Hz, 1H); 7.08 (t, J = 7.4 Hz, 1H); 7.22 (m, 2H); 7.32 (m, 2H); 7.55 (dt, J = 1.6, 8.1 Hz, 1H); 8.05 (dd, J = 1.4, 7.6 Hz, 1H);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  26.1, 34.9, 65.5, 69.9, 114.0, 118.2, 118.5, 119.9, 120.9, 123.1, 123.1, 126.5, 128.0, 130.6, 132.6, 132.7, 132.9, 133.0, 134.6, 149.7, 159.1, 165.0, 172.9; ms: m/z 366 ( $\text{M}^+$ ), 219, 189, 178, 160, 147, 121, 91, 77, 65, 55, 41 (100%). *Anal.* Calcd. for  $\text{C}_{22}\text{H}_{22}\text{O}_5$  (366.41): C, 72.12; H, 6.05. Found: C, 72.13; H, 6.01.

**Allyl 2-((3-[2-allyloxyphenyl]propanoyl)oxy)benzoate (20).** Compound **20** was isolated as a clear oil after chromatography (53%); ir: 753, 928, 1135, 1453, 1493, 1606, 1725, 1758, 2848, 2918, 3016, 3076  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  2.99 (t, J = 7.0 Hz, 2H); 3.14 (t, J = 7.0 Hz, 2H); 4.62 (d, J = 4.6 Hz, 2H); 4.78 (d, J = 4.5 Hz, 2H); 5.31 (m, 2H); 5.42 (dd, J = 1.3, 17.2 Hz, 1H); 5.48 (dd, J = 1.3, 17.3 Hz, 1H); 6.03 (ddt, J = 5.6, 10.4, 17.0 Hz, 1H); 6.13 (ddt, J = 5.0, 10.6, 17.2 Hz, 1H); 6.89 (d, J = 8.0 Hz, 1H); 6.94 (t, J = 6.8 Hz, 1H); 7.05 (d, J = 7.8 Hz, 1H); 7.27 (m, 2H); 7.33 (t, J = 7.4 Hz, 1H); 7.57 (dt, J = 0.8, 7.3 Hz, 1H); 8.06 (dd, J = 1.3, 7.7 Hz, 1H);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  26.4, 34.5, 66.1, 69.0, 111.9, 117.4, 119.1, 121.1, 123.9, 124.3, 126.3, 128.0, 129.3, 130.7, 132.2, 132.4, 133.8, 134.2, 151.1, 156.9, 164.7, 172.4. *Anal.* Calcd. for  $\text{C}_{22}\text{H}_{22}\text{O}_5$  (366.41): C, 72.12; H, 6.05. Found: C, 72.28; H, 6.10.

**2-(3-Allyloxy-3-oxopropyl)phenyl 3-(2-allyloxyphenyl)propanoate (21).** Compound **21** was isolated as a clear oil after chromatography (55%); ir: 753, 928, 1171, 1492, 1601, 1648, 1737, 1755, 2862, 2918, 3021, 3076  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  2.58 (t, J = 7.8 Hz, 2H); 2.82 (t, J = 7.4 Hz, 2H); 2.96 (t, J = 7.7 Hz, 2H); 3.14 (t, J = 7.4 Hz, 2H); 4.58 (d, J = 5.5 Hz, 2H); 4.62 (d, J = 4.6 Hz, 2H); 5.23 (d, J = 10.3 Hz, 1H); 5.29 (d, J = 17.2 Hz, 1H); 5.31 (d, J = 9.9 Hz, 1H); 5.47 (d, J = 17.2 Hz, 1H); 5.90 (ddt, J = 5.6, 10.7, 16.7 Hz, 1H); 6.11 (ddt, J = 4.8, 10.8, 16.9 Hz, 1H); 6.88 (d, J = 8.1 Hz, 1H); 6.93 (d, J = 7.4 Hz, 1H); 6.98 (d, J = 7.8 Hz, 1H); 7.21 (m, 5H);  $^{13}\text{C}$  nmr ( $\text{DMSO}$ , ppm):  $\delta$  25.5, 26.4, 34.2, 34.4, 65.3, 68.9, 112.8, 117.5, 118.6, 121.3, 123.3, 126.9, 128.3, 128.6, 128.9, 130.5, 130.9, 133.1, 133.5, 134.7, 149.6, 156.9, 172.1, 172.5. *Anal.* Calcd. For  $\text{C}_{24}\text{H}_{26}\text{O}_5$  (394.46): C, 73.08; H, 6.64. Found: C, 73.12; H, 6.61.

**2-Methylallyl-3-[[2-(2-allyloxyphenyl)propanoyl]oxyphenyl]propanoate (22).** Compound **22** was isolated as a clear oil after chromatography (56%); ir: 753, 923, 1171, 1453, 1492, 1587, 1601, 1738, 1755, 2917, 2967, 3021, 3071  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  1.73 (s, 3H); 2.60 (t, J = 8.2 Hz, 2H); 2.83 (t, J = 7.5 Hz, 2H); 2.96 (t, J = 8.0 Hz, 2H); 3.14 (t, J = 7.4 Hz, 2H); 4.50 (s, 2H); 4.61 (m, 2H); 4.92 (s, 1H); 4.95 (s, 1H); 5.30 (dd, J = 1.5, 10.6 Hz, 1H); 5.47 (dd, J = 1.6, 17.3 Hz, 1H); 6.10 (ddt, J = 4.9, 10.6, 17.3 Hz, 1H); 6.88 (d, J = 8.1 Hz, 1H); 6.92 (dt, J = 0.9, 7.5 Hz, 1H); 6.99 (dd, J = 1.1, 8.0 Hz, 1H); 7.20 (m, 5H);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  19.9, 25.9, 26.8, 34.5, 34.7, 68.2, 69.0, 111.9, 113.3, 117.4, 121.1, 122.9, 126.5, 128.0, 128.2, 129.0, 130.5, 130.7, 132.7, 133.8, 140.3, 149.4, 156.9, 172.2, 172.8; ms: m/z 188, 160, 145 (100%), 131, 120, 105, 91, 78, 57,

51, 24. *Anal.* Calcd. For  $C_{25}H_{28}O_5$  (408.19): C, 73.51; H, 6.91. Found: C, 72.58; H, 6.90

**2-Methylallyl 3-((2-[2-(2-methyl-allyloxyphenyl)propanoyl]-oxyphenyl)propanoate (23).** Compound **23** was isolated as a clear oil after chromatography (52%); ir: 752, 903, 1171, 1452, 1492, 1584, 1602, 1659, 1737, 1753, 2850, 2918, 2967, 3031, 3074  $cm^{-1}$ ;  $^1H$  nmr ( $CDCl_3$ , ppm):  $\delta$  1.74 (s, 3H); 1.89 (s, 3H); 2.61 (t, J = 8.0 Hz, 2H); 2.84 (t, J = 7.5 Hz, 2H); 2.97 (t, J = 7.8 Hz, 2H); 3.16 (t, J = 7.5 Hz, 2H); 4.51 (s, 4H); 4.93 (s, 1H); 4.96 (s, 1H); 5.03 (s, 1H); 5.16 (s, 1H); 6.89 (d, J = 8.1 Hz, 1H); 6.94 (t, J = 7.3 Hz, 1H); 6.99 (d, J = 7.7 Hz, 1H); 7.23 (m, 5H);  $^{13}C$  nmr ( $CDCl_3$ , ppm):  $\delta$  19.8, 19.9, 25.9, 26.9, 34.6, 34.7, 68.2, 71.9, 111.8, 112.6, 113.3, 121.0, 122.9, 126.5, 128.0, 128.2, 128.9, 130.5, 130.6, 132.7, 140.3, 141.3, 149.4, 157.0, 172.2, 172.8. *Anal.* Calcd. for  $C_{26}H_{30}O_5$  (422.51): C, 73.91; H, 7.16. Found: C, 73.80; H, 7.09.

**Allyl 3-((3-[2-allyloxyphenyl]propanoyl)oxy)benzoate (24).**

Compound **24** was isolated as a clear oil after chromatography (62%); ir: 753, 930, 1129, 1266, 1444, 1493, 1588, 1723, 1762, 2850, 2918, 3016, 3017  $cm^{-1}$ ;  $^1H$  nmr ( $CDCl_3$ , ppm):  $\delta$  2.95 (t, J = 7.7 Hz, 2H); 3.14 (t, J = 7.5 Hz, 2H); 4.62 (d, J = 4.8 Hz, 2H); 4.85 (d, J = 5.7 Hz, 2H); 5.32 (d, J = 10.6 Hz, 1H); 5.34 (d, J = 10.4 Hz, 1H); 5.44 (d, J = 15.8 Hz, 1H); 5.47 (d, J = 15.5 Hz, 1H); 6.09 (m, 2H); 6.89 (d, J = 8.1 Hz, 1H); 6.95 (t, J = 7.5 Hz, 1H); 7.25 (m, 3H); 7.46 (t, J = 8.0 Hz, 1H); 7.74 (s, 1H); 7.95 (d, J = 7.8 Hz, 1H);  $^{13}C$  nmr ( $CDCl_3$ , ppm):  $\delta$  26.8, 34.6, 66.2, 69.0, 112.0, 117.5, 119.0, 121.1, 123.3, 126.9, 127.4, 128.2, 128.9, 129.8, 130.7, 132.0, 132.5, 133.8, 151.1, 156.9, 165.8, 172.0; ms: m/z 366 ( $M^+$ ), 206, 161 (100%), 148, 133, 115, 105, 91, 77, 65, 41. *Anal.* Calcd. for  $C_{22}H_{22}O_5$  (366.41): C, 72.12; H, 6.05. Found: C, 71.93; H, 6.17.

**Allyl 4-((3-[2-allyloxyphenyl]propanoyl)oxy)benzoate (25).**

Compound **25** was isolated as a clear oil after chromatography (54%); ir: 753, 927, 1110, 1270, 1493, 1603, 1722, 1759, 2918, 2983, 3016, 3071  $cm^{-1}$ ;  $^1H$  nmr ( $CDCl_3$ , ppm):  $\delta$  2.94 (t, J = 7.6 Hz, 2H); 3.13 (t, J = 7.4 Hz, 2H); 4.61 (d, J = 4.4 Hz, 2H); 4.85 (d, J = 5.3 Hz, 2H); 5.31 (d, J = 10.5 Hz, 2H); 5.43 (d, J = 16.6 Hz, 1H); 5.47 (d, J = 14.9 Hz, 1H); 6.08 (m, 2H); 6.89 (d, J = 8.4 Hz, 1H); 6.94 (t, J = 7.4 Hz, 1H); 7.13 (d, J = 8.5 Hz, 2H); 7.24 (m, 2H); 8.10 (d, J = 8.5 Hz, 2H);  $^{13}C$  nmr ( $CDCl_3$ , ppm):  $\delta$  26.7, 34.7, 66.0, 69.0, 112.0, 117.5, 118.7, 121.1, 122.1 (2 C's), 128.0, 128.3, 128.8, 130.7, 131.6 (2 C's), 132.6, 133.8, 154.9, 156.9, 165.9, 171.7. *Anal.* Calcd. for  $C_{22}H_{22}O_5$  (366.41): C, 72.12; H, 6.05. Found: C, 72.20; H, 6.09.

**Allyl 2-aminobenzoate (26).** Compound **26** was prepared according to the method outlined for compound **1** and isolated as a clear oil (38%); ir: 751, 1104, 1161, 1244, 1295, 1455, 1487, 1588, 1616, 1691, 2846, 2917, 3027, 3076, 3374, 3484  $cm^{-1}$ ;  $^1H$  nmr ( $CDCl_3$ , ppm):  $\delta$  4.81 (dt, J = 1.2, 5.5 Hz, 2H); 5.30 (dd, J = 1.2, 10.5 Hz, 1H); 5.42 (dd, J = 1.4, 17.2 Hz, 1H); 5.75 (s, 2H); 6.06 (ddt, J = 5.5, 10.5, 17.2 Hz, 1H); 6.68 (m, 2H); 7.30 (dt, J = 1.5, 8.3 Hz, 1H); 7.93 (d, J = 7.3 Hz, 1H);  $^{13}C$  nmr ( $CDCl_3$ , ppm):  $\delta$  65.3, 111.1, 116.7, 117.1, 118.3, 131.7, 132.9, 134.6, 151.0, 168.2.

**Allyl 2-(N-allylamino)benzoate (27).** Compound **27** was isolated alongside compound **26** as a pale yellow oil (35%);  $^1H$  nmr ( $CDCl_3$ , ppm):  $\delta$  3.90 (m, 2H); 4.80 (dt, J = 1.1, 5.5 Hz, 2H); 5.21 (dd, J = 1.4, 10.3 Hz, 1H); 5.30 (dd, J = 1.3, 10.4 Hz, 1H); 5.32 (dd, J = 1.3, 17.2 Hz, 1H); 5.43 (dd, J = 1.4, 17.2 Hz, 1H); 5.98 (ddt, J = 5.1, 10.3, 17.3 Hz, 1H); 6.06 (ddt, J = 5.5, 10.5, 17.2 Hz, 1H); 6.63 (t, J = 7.1 Hz, 1H); 6.69 (d, J = 8.5 Hz, 1H); 7.37 (dt, J = 1.4, 8.5 Hz, 1H); 7.90 (s, 1H); 7.99 (dd, J = 1.5, 8.0 Hz,

1H);  $^{13}C$  nmr ( $CDCl_3$ , ppm):  $\delta$  45.6, 65.2, 110.4, 111.9, 115.1, 116.5, 117.9, 118.2, 132.0, 133.0, 135.0, 151.5, 168.7.

**Allyl 2-((3-[2-(allyloxy)phenyl]propanoyl)amino)benzoate (28).** Compound **28** was prepared according to the method outlined for compound **16**, and isolated as a clear oil (45%); ir: 753, 930, 1162, 1253, 1526, 1588, 1602, 1688, 2846, 2917, 3010, 3076, 3312  $cm^{-1}$ ;  $^1H$  nmr ( $CDCl_3$ , ppm):  $\delta$  2.78 (t, J = 8.1 Hz, 2H); 3.13 (t, J = 7.5 Hz, 2H); 4.60 (d, J = 4.8 Hz, 2H); 4.83 (d, J = 5.5 Hz, 2H); 5.29 (dd, J = 0.6, 10.6 Hz, 1H); 5.34 (d, J = 10.4 Hz, 1H); 5.44 (d, J = 17.0 Hz, 1H); 5.46 (dd, J = 1.1, 17.3 Hz, 1H); 6.04 (ddt, J = 5.7, 10.6, 15.7 Hz, 1H); 6.13 (ddt, J = 5.1, 10.7, 16.9 Hz, 1H); 6.85 (d, J = 8.2 Hz, 1H); 6.90 (t, J = 7.3 Hz, 1H); 7.09 (t, J = 7.5 Hz, 1H); 7.19 (t, J = 8.3 Hz, 1H); 7.23 (d, J = 7.3 Hz, 1H); 7.57 (t, J = 7.5 Hz, 1H); 8.08 (d, J = 7.9 Hz, 1H); 8.77 (d, J = 8.5 Hz, 1H); 11.05 (s, 1H);  $^{13}C$  nmr ( $CDCl_3$ , ppm):  $\delta$  27.1, 39.0, 66.1, 69.0, 111.9, 115.2, 117.5, 119.1, 120.8, 121.1, 122.7, 127.9, 129.6, 130.5, 131.2, 132.1, 133.9, 135.1, 142.2, 156.9, 168.2, 172.2; ms: m/z 347, 307, 288, 272, 260, 248, 188, 174, 161, 145, 131, 119 (100%), 105, 91, 77, 65, 51, 41. *Anal.* Calcd. for  $C_{22}H_{23}NO_4$  (365.42): C, 72.31; H, 6.34; N, 3.83. Found: C, 72.29; H, 6.46; N, 4.00

**General Procedure for the RCM Cyclizations.** A 100 mL RBF fitted with a reflux condenser, a calcium chloride guard tube, and equipped for magnetic stirring was flame-dried under a positive atmosphere of dry nitrogen. After cooling to room temperature, the flask was charged with a solution of the RCM substrate in DCM (3 mM). To this solution was added the Grubbs catalyst (2–5 mol%) dissolved in 20 mL DCM. The reaction mixture was stirred under reflux (40 °C) for 10 hours on average, followed by another 10 hours at room temperature. Product isolation involved rotary evaporation of the reaction solvent and extraction of the reaction product by stirring with diethyl ether (40 mL). The ethereal solution was evaporated *in vacuo*, and the crude product purified by flash chromatography. Recrystallization in an appropriate solvent afforded the pure product.

**(Z)-Benzo[b]-1,6-dioxacycloundeca-3-ene-7-one (29).** Compound **29** was obtained as a clear solid after recrystallization from hexanes (12%), mp 95–96 °C; ir: 756, 977, 1113, 1241, 1451, 1495, 1601, 1729, 2851, 2918, 3022  $cm^{-1}$ ;  $^1H$  nmr (Acetone- $d_6$ , ppm):  $\delta$  2.64 (dd, J = 8.1, 8.6 Hz, 2H); 2.96 (dd, J = 8.1, 8.6 Hz, 2H); 4.64 (m, 4H); 6.09 (m, 2H); 6.89 (dt, J = 0.9, 7.4 Hz, 1H); 6.97 (d, J = 7.9 Hz, 1H); 7.21 (dt, J = 1.6, 8.1 Hz, 1H); 7.22 (d, J = 7.6 Hz, 1H);  $^{13}C$  nmr ( $CDCl_3$ , ppm):  $\delta$  27.5, 34.9, 64.6, 67.3, 111.4, 121.2, 126.4, 128.1, 129.3, 129.5, 130.7, 156.8, 173.5; ms:m/z 218 ( $M^+$ ), 188, 160, 145, 131, 115, 102, 91, 77, 65, 55 (100%). *Anal.* Calcd. for  $C_{13}H_{14}O_3$  (218.25): C, 71.54; H, 6.47. Found: C, 71.43; H, 6.47

**(E/Z)-dibenzo[b,f]-1,6,12-trioxacyclotrideca-3-ene-7,13-dione (30).** Compound **30** was obtained as a clear solid after recrystallization from hexanes (16%), mp 109–110 °C; ir: 751, 1043, 1126, 1197, 1293, 1450, 1486, 1600, 1712, 1750, 2846, 2918, 3038, 3071  $cm^{-1}$ ;  $^1H$  nmr ( $CDCl_3$ , ppm) (*E* isomer),  $\delta$  4.60 (d, J = 7.3 Hz, 2H); 4.70 (d, J = 5.9 Hz, 2H); 5.76 (dt, J = 6.1, 15.8 Hz, 1H); 6.17 (m, 1H); 7.14 (m, 1H); 7.27 (m, 2H); 7.55 (dt, J = 1.6, 8.4 Hz, 2H); 7.80 (dd, J = 1.7, 7.7 Hz, 1H); 7.94 (dd, J = 1.4, 6.3 Hz, 1H); 8.11 (m, 1H);  $^{13}C$  nmr ( $CDCl_3$ , ppm) (*E* isomer):  $\delta$  60.6, 64.5, 115.7, 123.0, 124.3, 124.9, 126.2, 126.6, 130.6, 131.5, 131.8, 132.6, 133.7, 134.1, 149.8, 157.2, 161.6, 166.1;  $^1H$  nmr ( $CDCl_3$ , ppm) (*Z* isomer),  $\delta$  4.78 (d, J = 7.5 Hz, 2H); 4.80 (d, J = 4.5 Hz, 2H); 6.18 (m, 1H); 6.30 (m, 1H); 7.15 (m, 2H); 7.28 (m, 2H); 7.39 (dt, J = 0.5, 7.3 Hz, 1H); 7.61 (m, 2H); 8.10 (m,



1H);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , ppm) (*Z* isomer):  $\delta$  62.5, 76.4, 121.9, 124.0, 124.4, 125.1, 126.3, 126.7, 130.7, 131.5, 132.5, 132.7, 133.8, 135.2, 150.3, 159.5, 163.2, 166.6. ms:  $m/z$  310 ( $\text{M}^+$ ), 241, 190, 173, 121 (100%), 105, 92, 77, 64, 53, 41. *Anal.* Calcd. for  $\text{C}_{18}\text{H}_{14}\text{O}_5$  (310.30): C, 69.67; H, 4.55. Found: C, 69.55; H, 4.38.

**(*E/Z*)-Dibenzo[*b,m*]-1,7,12-trioxacyclopentadeca-9-ene-2,13-dione (31).** Compound **31** was obtained as a clear solid after recrystallization from low boiling petroleum ether (16%), mp 91–92 °C; ir: 754, 971, 1171, 1298, 1450, 1489, 1600, 1736, 2850, 2918, 3027, 3065  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , ppm) (*E* isomer):  $\delta$  2.71 (t,  $J = 7.4$  Hz, 2H); 3.05 (t,  $J = 7.3$  Hz, 2H); 4.56 (dd,  $J = 4.1, 5.6$  Hz, 2H); 4.66 (dd,  $J = 6.2, 7.3$  Hz, 2H); 6.00 (m, 2H); 7.13 (m, 6H); 7.54 (m, 2H);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , ppm) (*E* isomer):  $\delta$  25.0, 34.5, 60.0, 64.3, 114.0, 121.1, 122.0, 123.0, 126.6, 127.8, 128.8, 130.0, 130.9, 132.2, 132.9, 133.9, 149.4, 157.8, 166.0, 172.5.  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , ppm) (*Z* isomer):  $\delta$  2.71 (t,  $J = 7.4$  Hz, 2H); 3.05 (t,  $J = 7.3$  Hz, 2H); 4.72 (dd,  $J = 4.1, 5.6$  Hz, 2H); 4.85 (dd,  $J = 6.2, 7.3$  Hz, 2H); 6.13 (m, 2H); 7.29 (m, 6H); 7.90 (m, 2H);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , ppm) (*Z* isomer):  $\delta$  25.9, 36.0, 62.1, 71.1, 116.5, 121.4, 122.7, 123.1, 126.8, 128.0, 129.0, 130.4, 131.4, 132.3, 133.1, 134.2, 149.6, 158.4, 166.5, 173.1; ms:  $m/z$  338 ( $\text{M}^+$ ), 200, 190, 159, 145, 131, 121 (100%), 92, 77, 65, 55, 41. *Anal.* Calcd. for  $\text{C}_{20}\text{H}_{18}\text{O}_5$  (338.35): C, 70.99; H, 5.36. Found: C, 70.09; H, 5.39.

**(*E/Z*)-Dibenzo[*b,h*]-1,6,12-trioxacyclopentadeca-3-ene-7,13-dione (32).** Compound **32** was obtained as a clear solid after recrystallization from a 5:1 hexanes/ethyl acetate mixture (88%), mp 92–93 °C; ir: 753, 976, 1135, 1292, 1452, 1492, 1605, 1711, 1761, 2846, 2918, 3021, 3060  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , ppm) (*E* isomer):  $\delta$  2.94 (m, 2H); 3.04 (m, 2H); 4.65 (d,  $J = 2.8$  Hz, 2H); 4.85 (d,  $J = 6.3$  Hz, 2H); 6.14 (dt,  $J = 4.2, 15.6$  Hz, 1H); 6.28 (dt,  $J = 6.7, 15.6$  Hz, 1H); 6.96 (d,  $J = 8.3$  Hz, 1H); 6.98 (t,  $J = 7.7$  Hz, 1H); 7.13 (d,  $J = 7.6$  Hz, 1H); 7.23 (m, 2H); 7.36 (dt,  $J = 0.8, 7.7$  Hz, 1H); 7.57 (dt,  $J = 1.6, 8.0$  Hz, 1H); 8.03 (dd,  $J = 1.4, 7.8$  Hz, 1H);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , ppm) (*E* isomer):  $\delta$  26.2, 35.0, 65.7, 69.5, 115.9, 122.5, 124.5, 124.8, 126.5, 127.4, 128.5, 130.8, 131.0, 132.1, 132.5, 134.0, 150.1, 158.0, 165.8, 172.0; ms:  $m/z$  338 ( $\text{M}^+$ ), 200, 188, 172, 159, 145, 131, 121 (100%), 91, 77, 65, 55, 44. *Anal.* Calcd. for  $\text{C}_{20}\text{H}_{18}\text{O}_5$  (338.35): C, 70.99; H, 5.36. Found: C, 70.90; H, 5.39.

**(*E*)-Dibenzo[*b,h*]-1,6,14-trioxacycloheptadeca-3-ene-7,15-dione (33).** Compound **33** was obtained as a clear solid after recrystallization from hexanes (82%), mp 71–72 °C; ir: 753, 1009, 1132, 1243, 1491, 1583, 1599, 1737, 1753, 2851, 2918, 3021, 3060  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{DMSO}$ , ppm):  $\delta$  2.60 (m, 2H); 2.73 (m, 2H); 2.88 (m, 4H); 4.59 (d,  $J = 4.7$  Hz, 2H); 4.65 (d,  $J = 4.0$  Hz, 2H); 5.97 (dt,  $J = 5.1, 15.8$  Hz, 1H); 6.05 (dt,  $J = 4.6, 15.8$  Hz, 1H); 6.90 (t,  $J = 7.0$  Hz, 1H); 6.99 (d,  $J = 8.2$  Hz, 1H); 7.07 (dd,  $J = 1.1, 7.7$  Hz, 1H); 7.25 (m, 4H); 7.37 (dd,  $J = 1.4, 7.4$  Hz, 1H);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , ppm):  $\delta$  25.8, 27.5, 34.4, 35.2, 63.2, 67.7, 112.2, 121.4, 122.9, 126.7, 128.0, 128.3, 128.4, 129.2, 129.4, 129.6, 130.8, 132.7, 149.3, 157.0, 172.3, 172.5; ms:  $m/z$  366 ( $\text{M}^+$ ), 218, 188, 149 (100%), 120, 107, 91, 78, 65, 55, 41. *Anal.* Calcd. for  $\text{C}_{22}\text{H}_{22}\text{O}_5$  (366.41): C, 72.12; H, 6.05. Found: C, 72.15; H, 5.96.

**(*E/Z*)-Dibenzo[*b,h*]-1,6,12-dioxazacyclopentadec-3-ene-7,13-dione (34).** Compound **34** was obtained as a clear solid after recrystallization from low boiling petroleum ether (68%), mp 92–93 °C; ir: 751, 973, 1244, 1447, 1552, 1583, 1604, 1668, 1681, 1714, 2846, 2919, 3021, 3060, 3335, 3384  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , ppm) (*E* isomer):  $\delta$  2.63 (dt,  $J = 3.5, 8.6$  Hz, 2H); 3.04

(t,  $J = 8.0$  Hz, 2H); 4.63 (d,  $J = 5.1$  Hz, 2H); 4.94 (d,  $J = 6.0$  Hz, 2H); 6.33 (dt,  $J = 6.1, 9.4$  Hz, 1H); 6.39 (dt,  $J = 5.2, 10.4$  Hz, 1H); 6.93 (d,  $J = 7.7$  Hz, 1H); 6.95 (d,  $J = 7.4$  Hz, 1H); 7.15 (dt,  $J = 1.0, 8.0$  Hz, 1H); 7.25 (m, 2H); 7.57 (dt,  $J = 1.5, 8.7$  Hz, 1H); 8.04 (dd,  $J = 1.5, 7.9$  Hz, 1H); 8.60 (d,  $J = 7.7$  Hz, 1H); 9.60 (s, 1H);  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ , ppm) (*E* isomer):  $\delta$  29.2, 39.9, 65.4, 67.3, 113.4, 118.3, 121.7, 122.1, 123.7, 128.4, 128.8, 130.0, 131.1, 132.4, 134.1, 134.5, 139.3, 157.1, 166.2, 171.6; ms:  $m/z$  337 ( $\text{M}^+$ ), 190, 159, 145, 137, 120 (100%), 92, 77, 65, 55. *Anal.* Calcd. for  $\text{C}_{20}\text{H}_{19}\text{NO}_4$  (337.37): C, 71.20; H, 5.68; N, 4.15. Found: C, 71.20; H, 5.61; N, 4.18.

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