Total Synthesis of Hamigerans: Part 1. Development of Synthetic Technology for the Construction of Benzannulated Polycyclic Systems by the Intramolecular Trapping of Photogenerated Hydroxy-*o*-quinodimethanes and Synthesis of Key Building Blocks**

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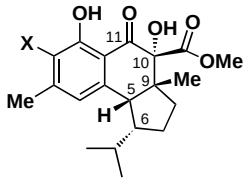
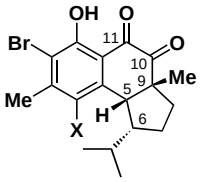
A recent report[1] disclosed the structures of a series of compounds isolated from the poecilosclerid sponge *Hamigera tarangaensis* Bergquist & Fromont (family Anchinoidae, syn. Phorbasidae) from the Hen and Chicken Islands off the coast of New Zealand. Termed hamigerans (e.g. **1**–**4**), these natural products contain a unique carbon skeleton in which

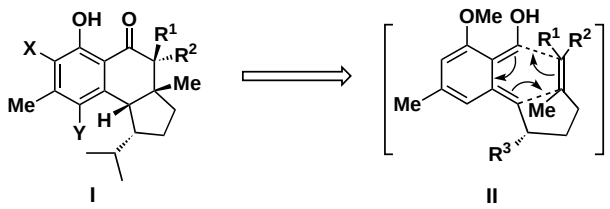


1: X = H: debromohamigeran A
2: X = Br: hamigeran A

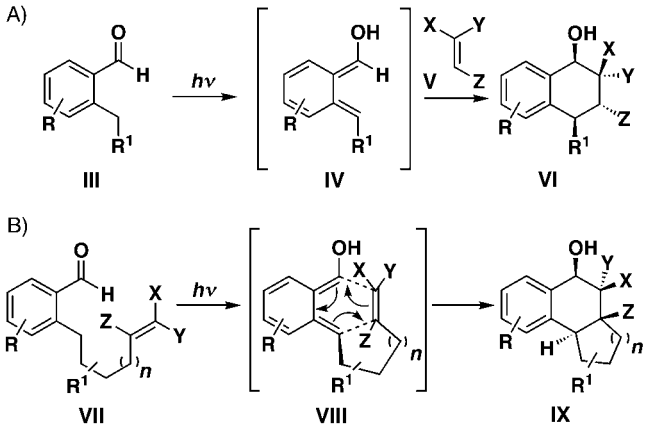


3: X = H: hamigeran B
4: X = Br: 4-bromohamigeran B

a substituted aromatic nucleus is fused onto a [4.3.0] carbocyclic system that contains three or four stereogenic centers and features an isopropyl group. The biological properties of these compounds range from moderate cytotoxicity (e.g. 4-bromohamigeran B (**4**)) against P-388 leukemia cells to strong antiviral activity (hamigeran B (**3**)) against herpes and polio viruses. Despite their relatively small size, the hamigerans offer both a challenge and an opportunity for the development of new synthetic technologies and chemical biology studies. In contemplating potential synthetic routes to these compounds, we considered the possibility of employing an intramolecular trapping strategy that involves the photochemically generated hydroxy-*o*-quinodimethane species **II** to form the benzannulated system **I** (Scheme 1). With a few notable exceptions,[2, 3] there are only scant examples of the potential use of this reaction in total synthesis,[4] despite the early work by Yang and Rivas[5] on the photochemical enolization of benzophenone. The few reports on this reaction have typically involved mechanistic studies and very simple substrates and/or rather special conditions.[6] In an effort to develop a streamlined and general method for the synthesis of benzannulated systems such as those found in the hamigerans, we undertook a systematic investigation of this process. In this and the following communication,[7] we wish to describe the details of our explorations in this area which led to the development of a general and practical entry into such systems (Scheme 2), and its application to the total synthesis of the hamigerans **1**–**4** and their analogues.



Scheme 1. Proposed *o*-enolquinodimethane route to the hamigerans.



Scheme 2. General strategy for the synthesis of benzannulated systems from substituted benzaldehydes by the photogeneration and trapping of hydroxy-*o*-quinodimethanes. A) Intermolecular variant. B) Intramolecular variant.

With the ultimate goal of applying the developed technology to complex molecule construction, we sought to include in our studies a diverse and polyfunctional collection of substrates for the intended photo-enolization-based reaction (Scheme 2). Thus, it was observed that a wide variety of dienophiles, including vinyl ketones,[8] acrylate esters,[9] acrylonitriles, and acroleins[4b] reacted with the electron-rich *o*-methylbenzaldehyde **7** (Table 1, entries 4–8) to afford a series of benzannulated systems in generally good yields. An initial exploration of the generality of the intermolecular Diels–Alder reaction of the photochemically generated hydroxy-*o*-quinodimethanes (Scheme 2 A) proved to be quite promising, except for the fact that some of the employed dienophiles showed an unacceptable propensity to photo-induced polymerization. We fine-tuned the reaction conditions and found that these reactions could be made quite efficient and practical (Table 1) by employing an excess of the polymerizable dienophiles, by performing the reaction in dilute

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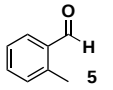
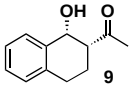
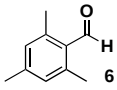
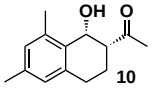
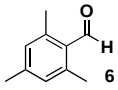
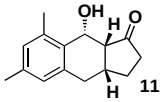
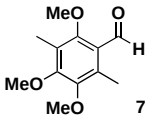
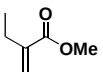
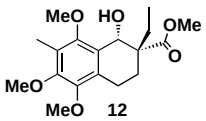
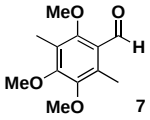
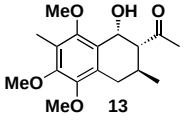
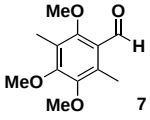
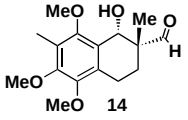
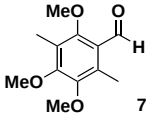
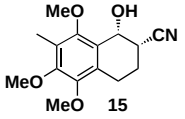
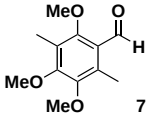
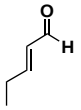
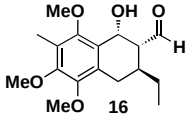
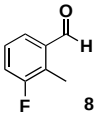
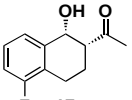
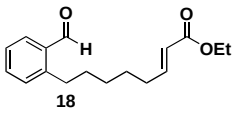
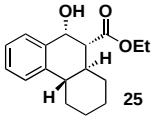
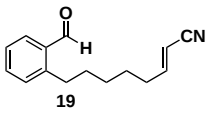
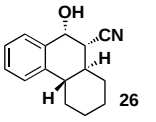
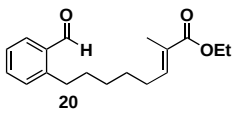
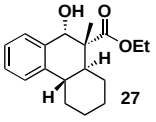
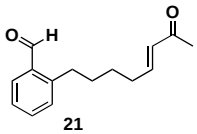
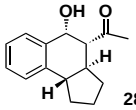
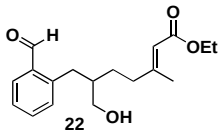
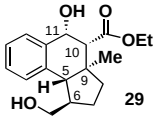
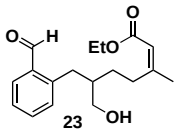
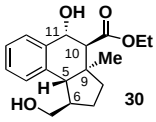
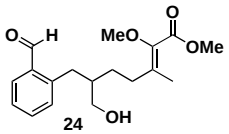
Table 1. Synthesis of benzannulated systems by the intermolecular trapping of hydroxy *o*-quinodimethanes (see Scheme 2A).[a]

Entry	Aldehyde	Dienophile	Product	*t* [h]	Yield [%]
1	 **5**		 **9**	12	55
2	 **6**		 **10**	8	72
3	 **6**		 **11**	8	71
4	 **7**		 **12**	2	83
5	 **7**		 **13**	4	82
6	 **7**		 **14**	2	89
7	 **7**		 **15**	2	75
8	 **7**		 **16**	4	84
9	 **8**		 **17**	2	88

[a] *O*-alkyl benzaldehyde (1 mmol) and olefin (5–20 equiv) were dissolved in deoxygenated toluene (0.025 M) in a pyrex flask and irradiated at ambient temperature with a 450-W Hanovia lamp at a distance of 10 cm. Products were obtained as separable mixtures of isomers in the following ratios, by entry number: 1) ≈4:1; 2) ≈4:1; 3) ≈8:1; 4) ≈3:1; 5) ≈8:4:1; 6) ≈6:1; 7) ≈7:1; 8) ≈9:3:1; 9) ≈6:1. The product shown is the major isomer (stereochemistry assigned by NMR spectroscopy).

Table 2. Synthesis of benzannulated tricycles by the intramolecular trapping of hydroxy-*o*-quinodimethanes (see Scheme 2B).[a]

Entry	Aldehyde	Product	*t* [min]	Yield [%]
1	 **18**	 **25**	45	95
2	 **19**	 **26**	90	83
3	 **20**	 **27**	45	95
4	 **21**	 **28**	20	90
5	 **22**	 **29**	20	90[b]
6	 **23**	 **30**	20	88[c]
7	 **24**	**31**	60	75

[a] *O*-alkyl benzaldehydes (0.5–1 mmol) were dissolved in deoxygenated toluene or benzene (0.02 M) in a pyrex flask and irradiated at ambient temperature with a 450-W Hanovia lamp at a distance of 5 cm. Products were obtained as separable mixtures of isomers, which reflected the *E*:*Z* ratios of the starting olefins. The starting material and product shown are the major isomers (stereochemistry assigned by NMR spectroscopy). [b] Starting olefin: *E*/*Z* > 20:1; product: C10 epimers > 20:1. [c] Starting olefin: *Z*/*E* > 20:1; product: C10 epimers ≈ 3:1.

toluene solution, and by using ordinary pyrex vessels (as opposed to quartz glass). We also noted that in going from the parent 2-methylbenzaldehyde (**5**; Table 1, entry 1) to more substituted substrates, the efficiency of the reaction improved substantially (Table 1, entries 2–9). Interestingly, the more electron-rich benzaldehydes (Table 1, entries 2–8) proved to be excellent substrates in this reaction as did commercially available 3-fluoro-2-methylbenzaldehyde (**8**). The latter reacted with methyl vinyl ketone to afford the corresponding bicyclic fluoride **17** in high yield under the developed photolytic conditions (Table 1, entry 9).

A powerful extension of this methodology would be its intramolecular variant. This proposition assumed special priority in light of the many foreseeable applications of such synthetic technology. To test this, a rapid entry into a series of *ortho*-alkyl-substituted benzaldehydes was devised and employed to deliver substrates **18**–**24** (Table 2, entries 1–7). When these aldehydes were exposed to ultraviolet light (450-W Hanovia lamp, pyrex filter) at ambient temperature, a remarkably fast, stereoselective, and high-yielding ring closure took place in each case to furnish the tricycles **25**–**31** (Table 2, entries 1–7). These examples demonstrate that both [4.4.0] (Table 2, entries 1–3) and [4.3.0] bicyclic systems (Table 2, entries 4–7) can be fused onto the aromatic nucleus, and that the newly generated fusion in the cyclization product

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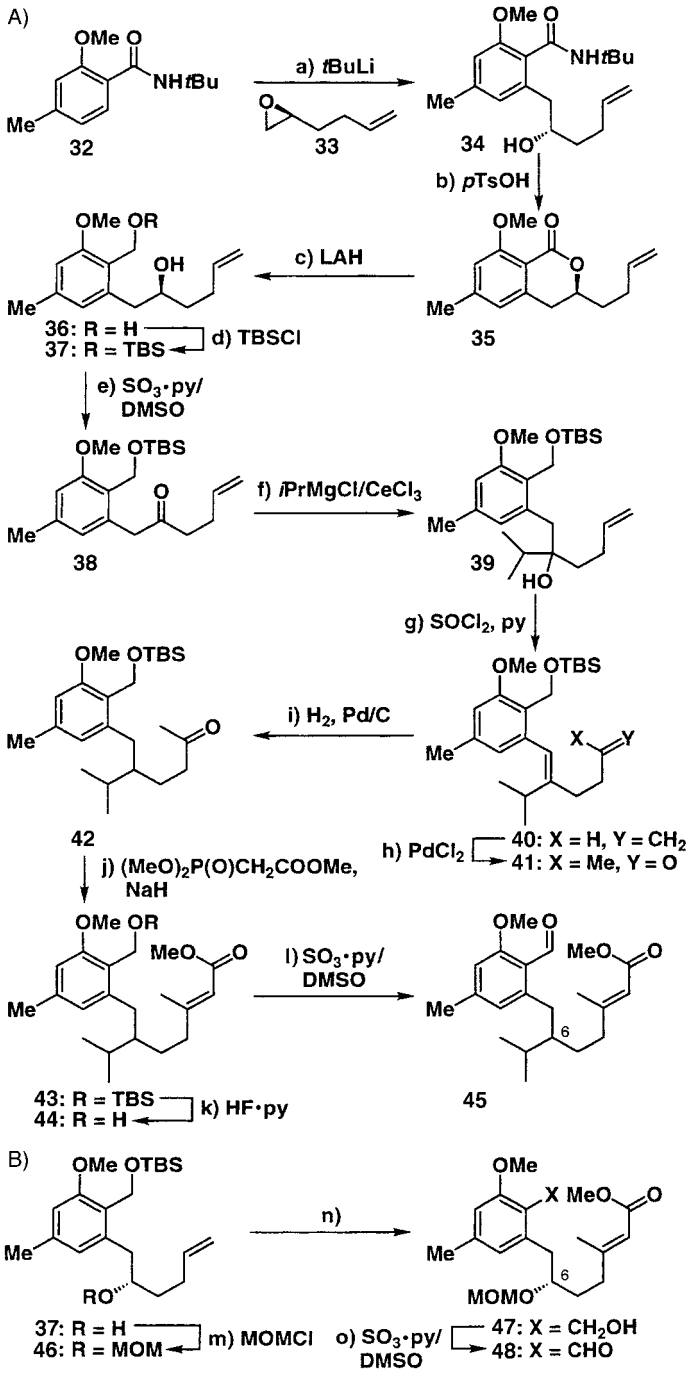
has a *trans*-fused stereochemistry. Furthermore, the three contiguous substituents that extend from the benzylic position (OH, electron-withdrawing group, and H or Me) were found to be *syn* to one another when di- or trisubstituted *E* olefins were employed (Table 2, entries 1–5). Also notable is the ability of this process to deliver quaternary centers (Table 2, entries 3, 5–7), including two such centers in adjacent positions (Table 2, entry 7). Furthermore, some interesting stereochemical aspects of this process are evident (Table 2, entries 5 and 6). When (*E*)-**22** was subjected to the reaction, the product with the *all-syn* stereochemistry at C9, C10, and C11 (**29**; Table 2, entry 5; for selected data, see Table 3) was obtained as the major product together with the isomeric compound **30** in which the ester group is *anti* to the two neighboring substituents (>20:1 ratio). An *endo* approach of the dienophile towards the hydroxy-*o*-quinodimethane accounts for this stereochemical outcome. Surprisingly, however, when pure (*Z*)-**23** was employed, a mixture of the same two products (**29**/**30** ≈1:3) was formed, with stereoisomer **30** now predominating. This observation requires an *exo* mode of approach of the incoming dienophile (to explain the formation of the major product **30** from **23**) and a *Z* to *E* isomerization under the irradiation conditions (to account for the formation of the *all-syn* isomer **29**). Molecular modeling confirms the highly strained nature of both the *exo* approach for the *E* isomer **22** and the *endo* arrangement for the *Z* isomer **23**, thus precluding the formation of the C5–C9 *syn* junction which would require transition states associated with such modes of interaction.

Having established the reaction as a reliable and efficient synthetic process and further defined its scope and generality, we then proceeded to the second phase of the program, which had as its ultimate aim the possible application of the intramolecular version of the developed technology to the total synthesis of the hamigerans. To this end, two cyclization precursors were designed, one in which the isopropyl group at the C6 position of the targeted structure (**45**, Scheme 3 A) was already installed prior to ring closure, and another in which this position was occupied by a protected oxygen functionality (**48**, Scheme 3 B). The latter functionality was chosen so as to serve as a handle to introduce the isopropyl group after cyclization, and to facilitate the desired epimerization at C5 (given the results of the model studies which led to the undesired C5–C9 junction).

The construction of these two substrates is summarized in Scheme 3. Treatment of benzamide **32** with two equivalents of *t*BuLi in the presence of TMEDA (for abbreviations of reagents and protecting groups, see legends in schemes) led to the deep red colored dianion, which opened terminal epoxide **33** to afford secondary alcohol **34** in 69% yield (Scheme 3 A).[10] For the isopropyl substrate, the commercially available racemic epoxide (±)-**33** was utilized, whereas for the protected alcohol (Scheme 3 B), enantiomerically enriched (>99% *ee*) epoxide (*S*)-**33**, which was obtained by using the Jacobsen hydrolytic kinetic resolution method with the *S*,*S* cobalt catalyst,[11] was used (see below). Acid-induced (*p*TsOH) intramolecular attack of the newly generated alcohol at the amide group of **34** led to δ-lactone **35** in 91% yield.[10] Compound **35** was then reduced with $LiAlH_4$, the



Scheme 3. Synthesis of cyclization substrates **45** and **48**. Reagents and conditions: a) *t*BuLi (2.2 equiv), TMEDA (2.0 equiv), −78 → −20 °C, then **33** (1.0 equiv), THF, −78 → 0 °C, 2 h, 69%; b) *p*TsOH (2.0 equiv), toluene, reflux, 2 h, 91%; c) $LiAlH_4$ (2.0 equiv), THF, 25 °C, 30 min, 91%; d) TBSCl (1.1 equiv), Et_3N (2.0 equiv), 25 °C, 12 h, 89%; e) $SO_3 \cdot py$. (3.0 equiv), Et_3N (6.0 equiv), DMSO/CH_2Cl_2 (1:1), 0 °C, 2 h, 94%; f) *i*PrMgCl (2.0 equiv), $CeCl_3$ (2.0 equiv), −78 → 0 °C, 1 h, 94%; g) $SOCl_2$, py, CH_2Cl_2, −60 °C, 15 min, 80%; h) $PdCl_2$ (0.1 equiv), $Cu(OAc)_2$ (2.0 equiv), DMA/H_2O (10:1), O_2 (1 atm), 25 °C, 12 h, 80%; i) 10% Pd/C, H_2 (1 atm), EtOAc, 25 °C, 2 h, 92%; j) $(MeO)_2P(O)CH_2COOMe$ (3.0 equiv), NaH (3.0 equiv), THF, 60 °C, 3 h, 94% (mixture of *E*/*Z* isomers, ca. 3:1); k) HF·py (4.0 equiv), THF, 25 °C, 20 min, 91%; l) $SO_3 \cdot py$ (3.0 equiv), Et_3N (6.0 equiv), DMSO/CH_2Cl_2 (1:1), 0 °C, 2 h, 86%; m) MOMCl (2.0 equiv), iPr_2NEt (6.0 equiv), CH_2Cl_2, 25 °C, 4 h, 83%; n) same procedure as steps h, j, and k above, similar yields; o) same procedure as step l above, 88%. TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine. *p*TsOH = *p*-toluenesulfonic acid, TBS = *tert*-butyldimethylsilyl, py = pyridine, DMA = *N*,*N*-dimethylacetamide, MOM = methoxymethyl.

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resulting diol was selectively monosilylated ($TBSCl/Et_3N$, 89% yield), and the secondary alcohol was oxidized ($SO_3 \cdot py$/DMSO) to afford ketone **38** in 94% yield. Reaction of ketone **38** with *i*PrMgCl required prior addition of $CeCl_3$ to the Grignard reagent to generate the less basic cerium species, which reacted smoothly with the substrate to afford tertiary alcohol **39** in 94% yield. Elimination of the tertiary hydroxy group from **39** was effected regioselectively towards the aromatic nucleus by the action of $SOCl_2$/py at $-60\,^{\circ}C$, leading to olefin **40**, which was subjected to Wacker oxidation ($PdCl_2$, $Cu(OAc)_2$, H_2O, O_2) to afford the expected methyl ketone **41** as the major product (80% yield). Hydrogenation (Pd/C) of the remaining double bond led to compound **42** in 92% yield. Reaction of ketone **42** with $(MeO)_2P(O)CH_2COOMe$/NaH furnished the *E*-α,β-unsaturated ester **43** as the major product, together with its *Z* isomer (ca. 3:1) in 94% total yield. The silyl protecting group was then removed from **43** under carefully controlled conditions to afford the corresponding benzyl alcohol **44** (91% yield), which was smoothly oxidized to the targeted aldehyde **45** by treatment with $SO_3 \cdot py$/DMSO (86% yield).

The enantioselective synthesis of the second required aldehyde **48** (Scheme 3B) started with epoxide (*S*)-**33** and proceeded through hydroxy silyl ether **37** (obtained as described above, Scheme 3A). Compound **37** was protected as its MOM ether ($MOMCl/iPr_2NEt$, 83% yield) and then carried through the same sequence as described for the preparation of racemic **45** to furnish, in similar yields, benzyl alcohol **47** (for selected data, see Table 3), which was oxidized with $SO_3 \cdot py$/DMSO to deliver the targeted intermediate **48** in enantiomerically enriched form.

Table 3. Selected data for compounds **29** and **47**.

29: colorless solid; $R_f = 0.3$ (silica gel, hexane/EtOAc 1:1); IR (film): $\tilde{\nu}_{max} =$ 3386, 2935, 1715, 1453, 1174, 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): $\delta =$ 7.48 (d, $J = 7.4$ Hz, 1H), 7.22–7.12 (m, 3H), 4.98 (t, $J = 7.0$ Hz, 1H), 4.18–4.08 (m, 2H), 3.92 (m, 1H), 3.63 (d, $J = 7.4$ Hz, 1H), 3.59 (m, 1H), 2.94 (d, $J = 7.0$ Hz, 1H), 2.45 (m, 1H), 2.29 (d, $J = 10.5$ Hz, 1H), 2.09 (m, 1H), 1.86 (dd, $J = 11.6$, 8.1 Hz, 1H), 1.68 (m, 1H), 1.58–1.45 (m, 2H), 1.12 (t, $J =$ 7.5 Hz, 3H), 0.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta = 173.2$, 139.0, 137.3, 127.3, 127.3, 126.4, 124.3, 67.9, 67.2, 60.6, 56.5, 52.0, 44.8, 39.8, 38.0, 21.1, 16.2, 14.2; HR-MS (MALDI): calcd for $C_{18}H_{24}O_4$ [M+Na^+]: 327.1567; found: 327.1562

47: colorless solid; $R_f = 0.5$ (silica gel, hexane/EtOAc 1:1); $[\alpha]_D^{22} = +5.27$ ($c = 0.168$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3465$, 2944, 1716, 1646, 1610, 1581, 1456, 1221, 1149, 1097, 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 6.62$ (s, 1H), 6.58 (s, 1H), 5.68 (s, 1H), 4.77 (m, 1H), 4.60 (m, 1H), 4.51 (d, $J =$ 7.0 Hz, 1H), 4.34 (d, $J = 7.0$ Hz, 1H), 3.82 (s, 3H), 3.78 (m, 1H), 3.67 (s, 3H), 3.06 (s, 3H), 2.94 (m, 2H), 2.74 (m, 1H), 2.30 (s, 3H), 2.24 (m, 1H), 2.14 (s. 3H), 1.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 167.1$, 159.7, 158.0, 138.6, 138.4, 125.3, 123.3, 115.3, 109.7, 95.5, 78.1, 55.9, 55.5, 55.4, 50.8, 39.7, 36.4, 32.3, 29.0, 21.5; HR-MS (MALDI): calcd for $C_{20}H_{30}O_6$ [M+ Na^+]: 389.1934; found: 389.1936

In summary, a highly efficient and direct approach to benzannulated systems has been developed by employing suitable aromatic aldehydes as starting materials and light as a reagent, and proceeding through a cascade reaction sequence that involved initial photo-enolization to afford reactive hydroxy-*o*-quinodimethane species, which were subsequently trapped by dienophiles in either inter- or intramolecular Diels–Alder fashion. The present technology holds considerable potential in the construction of complex molecules, as demonstrated by the accommodation of a diverse range of functional groups and its application to the total synthesis of the hamigerans described in the following communication.[7]

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