# The Synthesis of Certain Phomentrioloxin A Analogues and Their Evaluation as Herbicidal Agents

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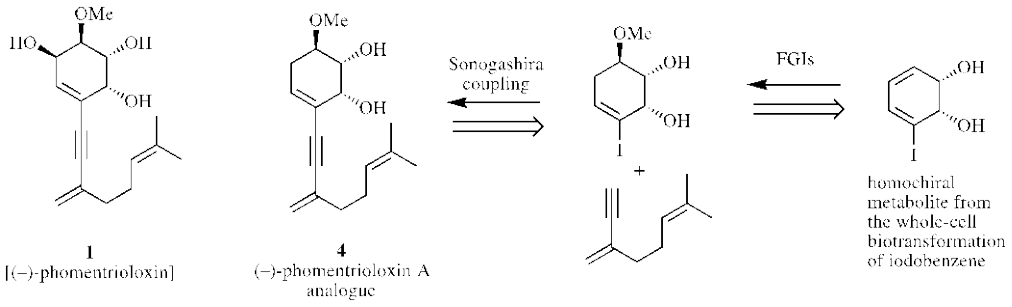



A series of 28 analogues of the phytotoxic geranylcyclohexentriol (–)-phomentrioloxin A (**1**) has been synthesised through cross-couplings of various enantiomerically pure haloconduritols or certain deoxygenated derivatives with either terminal alkynes or borylated alkenes. Some of these analogues display modest herbicidal activities and physiological profiling studies suggest that analogue **4** inhibits photosystem II in isolated thylakoids *in vitro*.

Among agricultural pests, weeds have the most significant adverse effects on crop productivity[1] and the absence of good means for controlling them is a primary source of

concern for farmers.[2] As a consequence, herbicidal applications outstrip the combined use of fungicides and insecticides in the USA and probably in many other countries as well.[3] The ongoing development of resistance to current herbicides has prompted an intense search for new ones with novel modes of action but there has been little recent success in this regard.[4]

Natural products (NPs) have attracted attention as potential sources of new agrochemicals or at least inspirations for them.[5] However, in contrast to the impressive contributions NPs have made to the development of new therapeutic agents,[6] they have not, thus far, been particularly useful sources of herbicides.[4,5] In an effort to redress this situation, certain studies have focussed on phytotoxic metabolites produced by fungi associated with economically significant weeds. For example, while seeking new agents to control the saffron thistle (*Carthamus lantus* L. ssp. *lanatus*), a widespread winter-growing annual weed of both pastures and crops that has been declared noxious throughout Australia, Evidente and co-workers[7] identified pathogenic strains of *Phomopsis* sp. and the teleomorph *Diaporthe gulyae* associated, respectively, with diseased strains of the saffron thistle and with the sunflower (*Helianthus annuus* L.). Three of the various phytotoxic metabolites produced by these fungi were identified as phomentrioloxins A-C (structures **1**-**3**, respectively, in Figure 1) that embody a polyoxygenated cyclohexene "core" and a geranyl-type "side-chain". The illustrated structure of the first of these metabolites, *viz*. compound **1**, was confirmed by our synthesis[8] of it from a homochiral *cis*-1,2-dihydrocatechol of defined absolute stereochemistry that is readily produced through the whole-cell biotransformation of iodobenzene. A key feature of our synthesis

was the linking of an iodinated mono-*O*-methylated conduritol with the relevant terminal alkyne using a Sonogashira cross-coupling reaction.

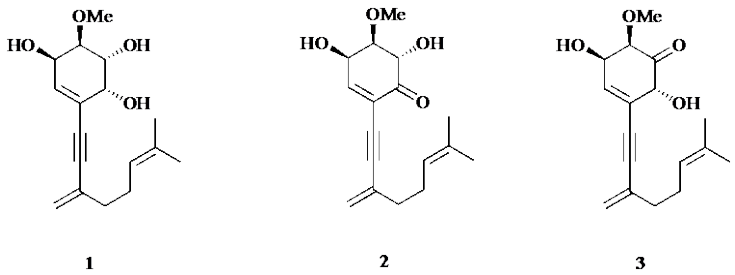



**Figure 1**: The Structures of Phomentrioloxins A-C (**1**-**3**, respectively)

Evidente and co-workers carried out a small structure-activity relationship study on derivatives of phomentrioloxin A. This revealed that various structural modifications of it led to changes in phytotoxic properties[7a,9] and, as a result, it was suggested that such natural products could form the basis for developing mycoherbicides for the biocontrol of noxious weeds including saffron thistle. Given the potential flexibility of our synthetic route to natural product **1** we sought to prepare a collection of otherwise difficult-to-access analogues and subject these to commercially-relevant screening regimes, including ones that could provide insights into their modes of action. The outcomes of such studies are reported here.

The first tranche of phomentrioloxin analogues to be prepared were compounds **4**-**14** (Figure 2) wherein variations were made to the nature of the oxygenation pattern in the cyclohexene core and, in parallel, to the degree of unsaturation in the geranyl-type tail (see structures **10**-**14**).

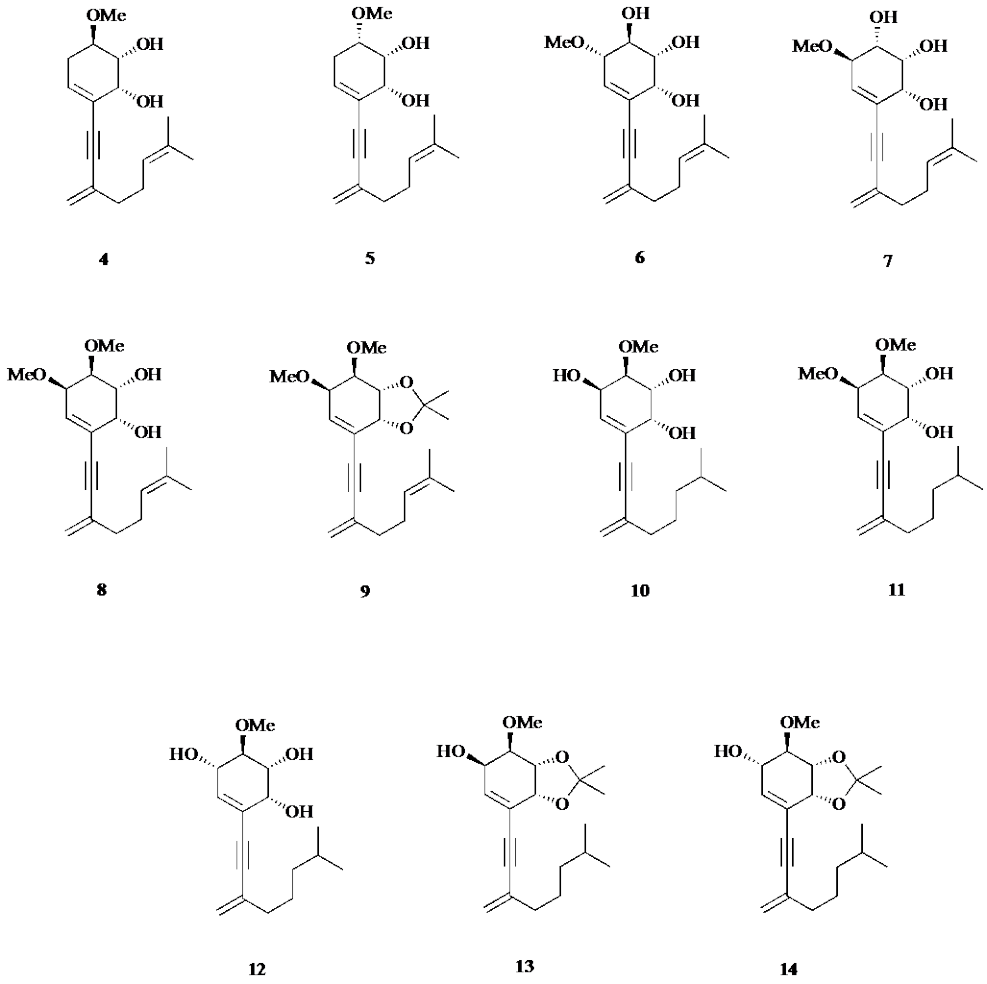



**Figure 2**: The Phomentrioloxin Analogues **4-14** Prepared for the Present Study that Retain the Geranyl-type Side-chain

The second tranche of analogues, namely compounds **15-22** (Figure 3), also involved variations in the nature of the oxygenation pattern within the core and, more significantly, variations to the side-chain. Specifically, the geranyl-type tail associated with the natural product **1** was replaced with a $C_{10}$-containing arylacetylene unit that it was thought would represent a similarly lipophilic but potentially more stable motif. Several 3,5-dimethoxy-substituted arylacetylene side-chains were introduced in an effort to explore

the impact of modifications to electron density within this part of the molecular framework.

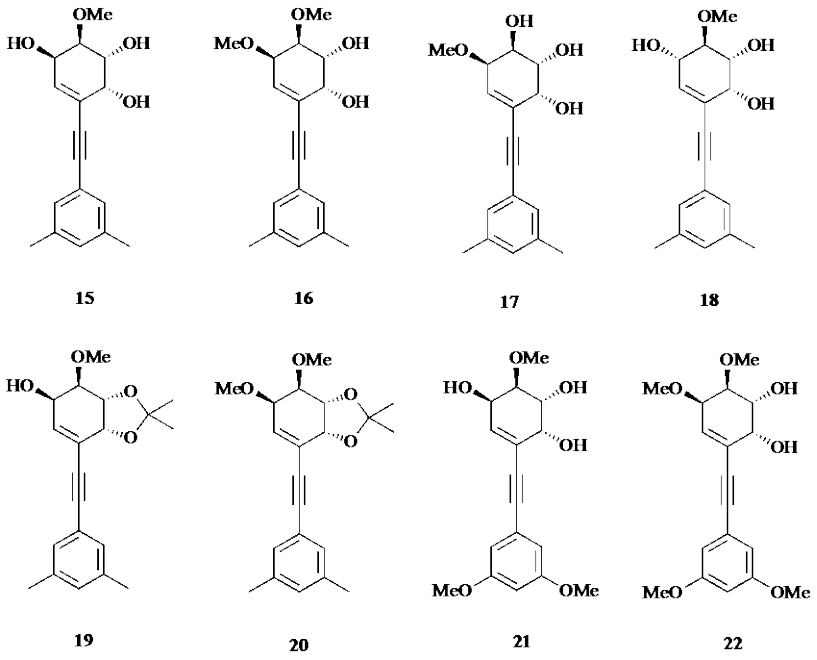



**Figure 3**: The Phomentrioloxin Analogues **15-22** Prepared for the Present Study and Incorporating a Phenylacetylene-type Side-chain.

The final tranche of analogues, namely compounds **23-31** (Figure 4), involved, *inter alia*, systems incorporating *E*- or *Z*-configured styrenyl or β-arylethyl-type side-chains as well as variations within the core. Throughout the collection of analogues certain acetonide-containing precursors were also tested as another means of investigating the impact of increased lipophilicity of the cyclohexene core on activity. The exhaustively protected precursor, **31**, to triol **29** was also subject to biological evaluation for the same reasons.

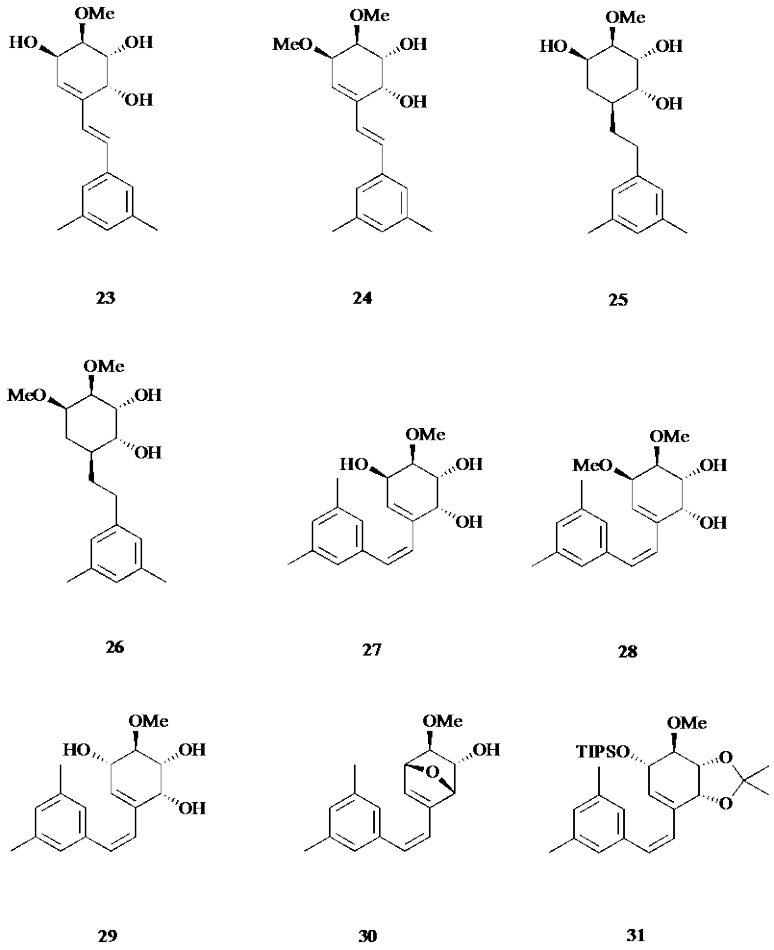
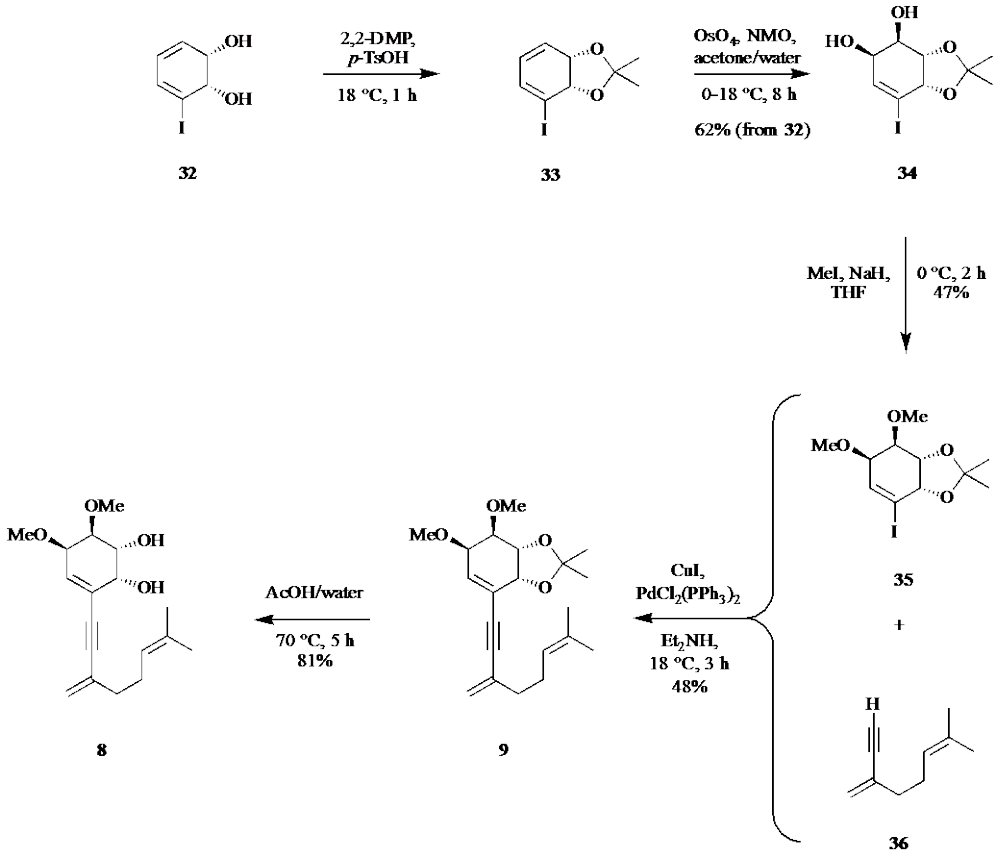



**Figure 4**: The Phomentrioloxin Analogues **23-31** Prepared for the Present Study and Incorporating a Styrenyl or Phenylethane-type Side-chain.

The reaction sequence shown in Scheme 1 is indicative of the protocols employed in the synthesis of the above-mentioned phomentrioloxin A analogues. It follows that employed in our synthesis of the "parent" system **1**.[8] Thus, the *cis*-1,2-dihydrocatechol **32**, which is readily obtained in enantiomerically pure form through the whole-cell biotransformation of iodobenzene,[10] was converted into the corresponding acetonide under previously defined conditions and thus affording the known[11] and rather unstable compound **33**. Regio- and diastereo-selective *cis*-dihydroxylation of the non-halogenated double bond within diene **33** proceeded readily under the UpJohn conditions[12] to give diol **34**[11] (62%

from **32**) that was subject to two-fold *O*-methylation using methyl iodide and thus providing the *bis*-ether **35** in 47% yield. Sonogashira cross-coupling of this last compound with the known[13] and readily accessible terminal alkyne **36** under standard conditions using cuprous iodide and $PdCl_2(PPh_3)_2$ in the presence of diethylamine then gave the targeted phomentrioloxin analogue **9** in 48% yield. Hydrolytic cleavage of the acetonide residue within the last compound could be achieved by heating it in an acetic acid/water mixture at 70 °C for 5 h and thus affording an *O*-methyl ether derivative, **8**, of phomentrioloxin in 81% yield.

**Scheme 1**: **Synthetic Sequence Used to Prepare Phomentrioloxin Analogues 8 and 9**

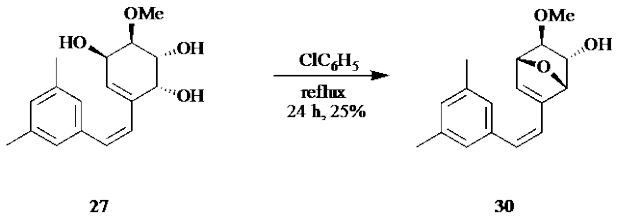


All the spectral data acquired on compounds **8** and **9** were in complete accord with the assigned structures.

The syntheses of remaining analogues used in this study are detailed in the Supporting Information (SI). These involved straightforward modifications of the protocols defined above with the head and tail "sections" of these analogues being linked through either Sonogashira or Suzuki-Miyaura cross-coupling protocols. Post-coupling chemical modifications included acetonide group cleavages, thermally induced *Z*- to *E*-olefin isomerizations, and/or exhaustive catalytic hydrogenations of the olefinic residues within compounds **23** and **24** (and thus affording, as single diastereoisomers, **25** and **26**, respectively). The assignment of the illustrated configurations at the cyclohexane ring carbon bearing the β-arylethyl group in the last pair of compounds is based on the assumption that the vicinally- and *cis*-related pair of hydroxyl groups within the precursors would direct the hydrogenation process.

The formation of the 7-oxobicyclo[2.2.1]heptene-containing analogue **30** from precursor **27** on thermolysis in refluxing chlorobenzene (Scheme 2) clearly involves a cyclodehydration reaction. Interestingly, under the conditions used there was no accompanying *Z*- to *E*-isomerisation of the styrenyl double bond.

**Scheme 2**: **Thermally Induced Cyclodehydration of Triol 27 Leading to Compound 30.**




27 30

Single-crystal X-ray analyses were secured on compounds **15**, **23** and **27** as well as certain precursors to congeners **7**, **8**, **9** and **17**. Details of these are provided in the Experimental Section and/or the SI.

The biological evaluations of compounds **1** and **4-31** were carried out at BASF's facilities at Limburgerhof in Germany. Preliminary evaluations of herbicidal activity were conducted in a green house. The plant species used for this purpose were *Setaria viridis* (SETVI, green foxtail) and *Amaranthus retroflexus* (AMARE, pigweed). The outcomes of conducting such tests are presented in Table 1 and represent the average rating for each of the two plant species involved. In broad terms, the active compounds caused a generalised necrosis of the aerial moieties of the plant species against which they were tested and suggesting they are eliciting their effects *via* a nonspecific pathway. In structure-activity terms, variations in the locations, configurations, degrees of *O*-methylation and/or deletions of oxygen-containing groups could have deleterious impacts on activity (see Entries 4 and 6) and certainly no obviously beneficial ones (relative to the parent system **1**). Increasing the degree of saturation in the geranyl-type side-chain also

had generally negative effects but replacement of such a moiety with an arylacetylene equivalent led to series of analogues with more pronounced herbicidal effects (see Entries 14, 16, 18 and 20).

**Table 1**: The Evaluation of Phomentrioloxin Derivatives as Non-specific Herbicides Against *A. retroflexus* and *S. viridis.*

| Entry | Compound[a] | Averaged Result[b] | Entry | Compound[a] | Averaged Result[b] |
|---|---|---|---|---|---|
| 1 | **1** [c] | + | 16 | **18** | ++ |
| 2 | **4** [c] | + | 17 | **19** | + |
| 3 | **5** [c] | + | 18 | **20** | ++ |
| 4 | **6** [c] | 0 | 19 | **21** | + |
| 5 | **7** [c] | + | 20 | **22** | ++ |
| 6 | **8** | 0 | 21 | **23** | 0 |
| 7 | **9** | + | 22 | **24** | 0 |
| 8 | **10** | 0 | 23 | **25** [d] | 0 |
| 9 | **11** [c] | + | 24 | **26** [d] | + |
| 10 | **12** | 0 | 25 | **27** | + |
| 11 | **13** | + | 26 | **28** | 0 |
| 12 | **14** | 0 | 27 | **29** [d] | + |
| 13 | **15** | + | 28 | **30** | + |
| 14 | **16** | ++ | 29 | **31** | + |
| 15 | **17** | + | – | – | – |

[a]Compounds applied at 2 kg a.i./ha unless otherwise specified; [b]Qualitative result over the two plant species used; [c] Compounds **1**, **4**, **5**, **6**, **7** and **11** were applied at 1 kg a.i./ha; [d] Compounds **25**, **26** and **29** were applied at 1.145, 1. 333 and 1.625 kg a.i./ha, respectively. Evaluation was carried out using a scale from 0–100. 100 means complete destruction of at least the aerial moieties, and 0 means no damage, or normal course of growth.) 0–25: 0 (no or very low activity); >25–50: + (moderate activity); >50–75: ++ (good activity); >75: +++ (very good activity).

In contrast, introduction of a styrenyl or β-arylethyl side-chain had a generally negative effect on activity – there were certainly no beneficial ones. A simple interpretation of these results is that those compounds containing the more stable/durable arylacetylenic side-chains probably had the longest half-lives under the extended testing conditions involved and were thus able to exert more sustained herbicidal effects.

Physiological profiling (PP) protocols were used for the purposes of trying to draw conclusions regarding the mode of action of the phomentrioloxin analogues as herbicides as well as for ranking their selectivities and potencies. PP[14] involves an array of physiological and bioassays that allow for differentiation between the distinct responses of different structures (whole plant, tissue, meristem cells, organelles), developmental stages (seed germination, vegetative growth), types of metabolism (phototrophic, heterotrophic) and physiological processes. The assays are designed to be sensitive, allow facilitated uptake and translocation of the applied compounds and include all potential herbicidal target sites. The bioassays included those involving heterotrophic cleaver (*Galium mollugo*) and photoautotrophic green alga (*Scenedesmus obliquus*) cell suspensions, isolated white mustard (*Sinapis alba*) shoots and germinating cress (*Lepidum sativum*) seeds. The physiological assays included studies of the Hill reaction of isolated wheat thylakoids, respiration measurements in cleaver cell suspensions, the formation of reactive oxygen species, chlorophyll fluorescence and ATP measurements in *Lemna* plants, carbon dioxide assimilation measurements in cleaver (*Galium aparine*) plants and toluidine blue staining of cress hypocotyls for detecting any inhibition of very long-chain fatty acid (VLCFA) biosynthesis.

In broad terms, phomentrioloxin A (**1**) as well as analogues **9** and **20** generated weak/inconclusive PPs. Analogues **5**, **6**, **7** and **11** had minor effects on the growth of heterotrophic *Galium* suspension cells, unicellular algae and *Lemna* plants indicating uptake limitations or rapid metabolic detoxification. In addition, analogue **7** caused

moderate inhibition of cress germination in a light-dependant manner. The most consistent effect among these compounds was a moderate inhibition of carbon dioxide assimilation indicating a not-further-characterised inhibitory effect on photosynthesis. Analogues **15**, **16**, **19** and **22** caused moderate inhibition of cell division in heterotrophic suspension cells together with intensified green leaf pigmentation in *Lemna* plants. The origins of these effects remain unknown. The PP of compound **4** differed somewhat from the others as this analogue caused moderate inhibition of the Hill reaction and must thus be having an effect on photosynthetic electron-flow. In addition, light-dependant inhibition of cress germination was observed. Inhibition of the Hill reaction is a typical finding for photosystem II (PS II) inhibitors. However, such inhibitors are also usually strong inhibitors of algae and *Lemna* growth, a feature not observed for analogue **4**. This might indicate that the compound is able to inhibit PSII in isolated thylakoids *in vitro* but is rapidly detoxified in a cellular environment.

The present study serves to highlight the utility of our previously reported[8] synthesis of phomentrioloxin A in generating a diverse range of analogues. However, the biological evaluation of these analogues has revealed that, as a class and despite some earlier indications to the contrary,[7a,9] the phomentrioloxins are unlikely to be useful leads for the development of new herbicidal agents.

## EXPERIMENTAL SECTION

### General Protocols.

Unless otherwise specified, proton ($^{1}$H) and carbon ($^{13}$C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. The signal due to residual $CHCl_3$ appearing at $\delta_H$ 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at $\delta_C$ 77.0 were used to reference $^{1}$H and $^{13}$C NMR spectra, respectively. $^{1}$H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. Infrared spectra ($\nu_{max}$) were recorded on a FTIR Spectrometer. Samples were analyzed as thin films on KBr plates. Low-resolution ESI mass spectra were recorded on a single-quadrupole liquid chromatograph-mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Melting points were measured on an automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 $F_{254}$ plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid : ceric sulfate : sulfuric acid (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 mL), potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 20 g : 5 mL : 300 mL) ), *p*-anisaldehyde or vanillin: sulfuric acid (conc.): ethanol (15 g : 2.5 mL : 250 mL). Flash chromatographic separations were carried out following protocols defined by Still *et al.*[15]

with silica gel 60 (40–63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents, drying agents and other inorganic salts were generally commercially available and were used as supplied. Tetrahydrofuran (THF), methanol and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs *et al*.[16] Where necessary, reactions were performed under an nitrogen atmosphere.

**The Synthesis of Analogues 8 and 9 as Representative Chemical Transformations: (3a*S*,4*R*,5*R*,7a*S*)-7-Iodo-4,5-dimethoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*]-[1,3]dioxole (35)**. Sodium hydride (115 mg of a 60% dispersion in mineral oil, 2.88 mmol) was added to a magnetically stirred solution of compound **34**[11] (150 mg, 0.48 mmol) and iodomethane (300 μL, 4.80 mmol) in dry THF (25mL) maintained at 0 °C under a nitrogen atmosphere. Stirring was continued for 2 h at 0 to 18 °C then the reaction mixture was treated with ice/water (60 mL – CAUTION potential for evolution of hydrogen gas). The separated aqueous phase was extracted with ethyl acetate (1 × 25 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane gradient elution) to give, after concentration of the appropriate fractions ($R_f$ = 0.4 in 1:4 v/v ethyl acetate/hexane), compound **35** (77 mg, 47%) as a white, crystalline solid, mp = 46–49 °C; $[\alpha]^{20}_D = -33.8$ ($c$ = 3.0, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.50 (d, $J$ = 3.2 Hz, 1H), 4.60 (d, $J$ = 5.7 Hz, 1H), 4.39–4.36 (complex m, 1H), 3.88 (t, $J$ = 3.4 Hz, 1H), 3.77–3.74 (complex m, 1H), 3.48 (s, 3H), 3.40 (s, 3H), 1.39 (s, 3H), 1.35 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 137.5, 109.4, 100.2, 78.8, 77.7, 76.1, 74.5, 59.2, 57.3, 27.4, 25.9; IR $\nu_{max}$ 2984, 2929,

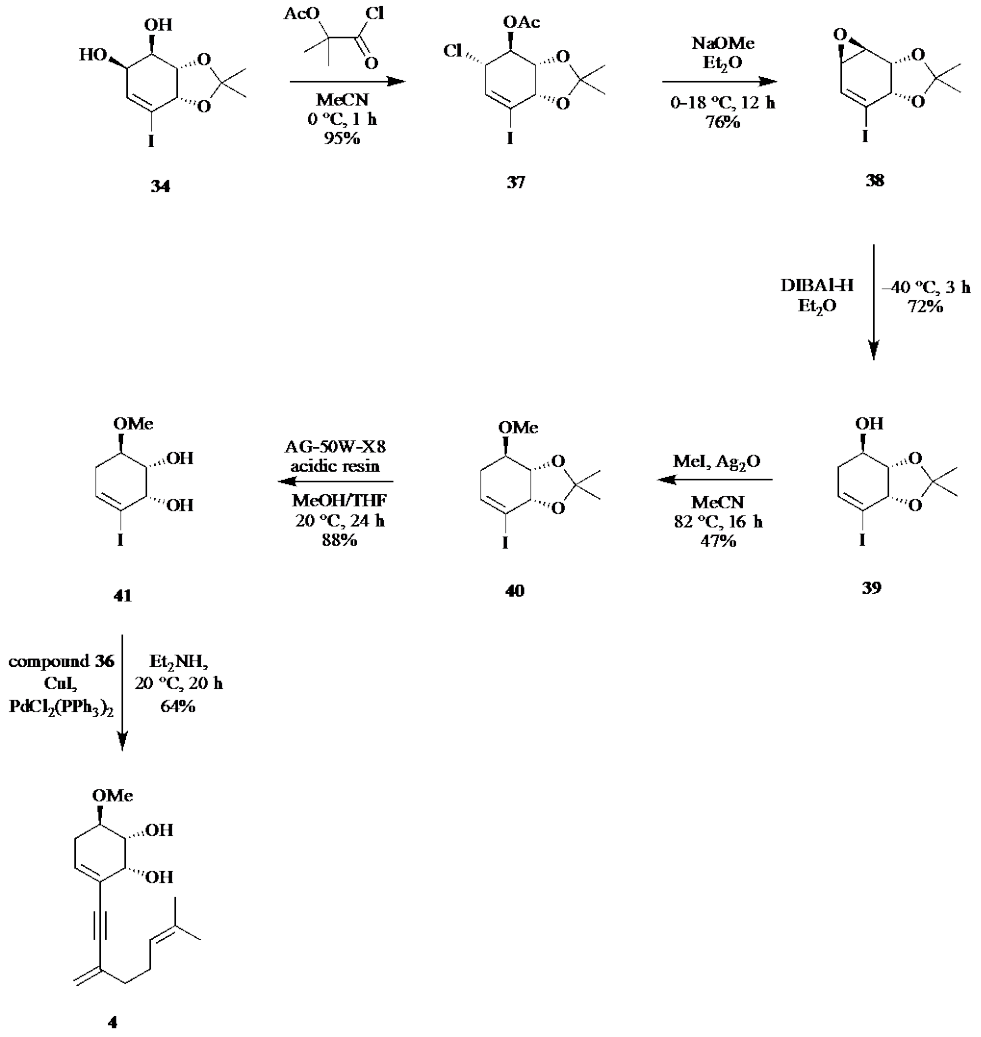
2826, 1630, 1459, 1381, 1371, 1237, 1101, 1079, 1039, 1005, 868 $cm^{-1}$; MS (EI, 70 eV) *m/z* 340 ($M^{+\bullet}$, 100%), 325 [$(M\text{-}CH_3\bullet)^+$, 78%], 311 (26), 282 (22); HRMS ($M^{+\bullet}$) calcd for $C_{11}H_{17}{}^{127}IO_4$ 340.0172, found 340.0173.

**(3a*R*,4*R*,5*R*,7a*R*)-4,5-Dimethoxy-2,2-dimethyl-7-(7-methyl-3-methyleneoct-6-en-1-yn-1-yl)-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxole (9)**. Cuprous iodide (11 mg, 0.05 mmol) and $PdCl_2(PPh_3)_2$ (25 mg, 0.04 mmol) were added to a magnetically stirred solution of compounds **35** (120 mg, 0.35 mmol) and **36**[13] (95 mg, 0.71 mmol) in anhydrous diethylamine (3 mL) maintained at 18 °C under a nitrogen atmosphere. After 3 h the reaction mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash chromatography (silica, 1:4 v/v ethyl acetate/ hexane gradient elution). Concentration of the appropriate fractions ($R_f$ = 0.3 in 1:4 v/v ethyl acetate/ hexane) afforded compound **9** (59 mg, 48%) as a clear, light-yellow oil, $[\alpha]^{20}_D = -17.7$ (*c* = 0.7, $CHCl_3$). $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 6.25 (d, *J* = 4.0 Hz, 1H), 5.37 (d, *J* = 2.0 Hz, 1H), 5.26 (d, *J* = 1.7 Hz, 1H), 5.12–5.08 (complex m, 1H), 4.64 (d, *J* = 6.2 Hz, 1H), 4.46 (t, *J* = 6.2 Hz, 1H), 4.04 (t, *J* = 3.8 Hz, 1H), 3.66 (dd, *J* = 6.0 and 3.4 Hz, 1H), 3.53 (s, 3H), 3.45 (s, 3H), 2.20 (s, 4H), 1.69 (s, 3H), 1.62 (s, 3H), 1.45 (s, 3H), 1.39 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 133.6, 132.2, 131.2, 123.4, 123.2, 121.7, 109.5, 90.8, 87.4, 79.0, 74.3, 74.0, 73.9, 58.9, 57.4, 37.3, 27.6, 26.8, 25.7, 25.5, 17.8; IR $\nu_{max}$ 2984, 2930, 2878, 2825, 1631, 1454, 1379, 1370, 1234, 1113, 1082, 1038, 961, 874 $cm^{-1}$; MS (EI, 70 eV) *m/z* [$(M\text{-}CH_3\bullet)^+$ 6%], 257 (14), 128 (9), 115 (100); HRMS $(M\text{-}CH_3\bullet)^+$ calcd for $C_{20}H_{27}O_4$ 331.1909, found 331.1947.

**(1*R*,2*R*,5*R*,6*S*)-5,6-dimethoxy-3-(7-methyl-3-methyleneoct-6-en-1-yn-1-yl)cyclohex-3-ene-1,2-diol (8)**. Compound **9** (33 mg, 0.09 mmol) was treated with acetic acid/water (3

mL of a 4:1 v/v mixture) and the solution thus obtained was heated at 70 °C for 5 h then cooled and concentrated under reduced pressure. Subjection of the ensuing light-yellow residue to flash chromatography (silica, 3:2 v/v ethyl acetate/hexane gradient elution) delivered, after concentration of the appropriate fractions ($R_f$ = 0.4 in 4:2 v/v ethyl acetate/ hexane), compound **8** (24 mg, 81%) as a clear, light-yellow syrup, $[\alpha]^{20}_D = -14$ ($c$ = 0.5, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.27 (d, $J$ = 4.5 Hz, 1H), 5.38 (d, $J$ = 1.9 Hz, 1H), 5.28 (d, $J$ = 1.9 Hz, 1H), 5.13–5.09 (complex m, 1H), 4.36 (d, $J$ = 4.2 Hz, 1H), 4.19–4.15 (complex m, 1H), 4.10 (t, $J$ = 4.2 Hz, 1H), 3.70 (dd, $J$ = 8.8 and 3.9 Hz, 1H), 3.51 (s, 3H), 3.48 (s, 3H), 2.79 (d, $J$ = 1.8 Hz, 1H), 2.69 (d, $J$ = 2.1 Hz, 1H), 2.20 (s, 4H), 1.69 (s, 3H), 1.62 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 132.4, 132.3, 130.9, 124.7, 123.2, 122.2, 91.4, 87.1, 77.4, 72.6, 68.6, 67.5, 58.1, 57.6, 37.2, 26.8, 25.7, 17.8; IR $\nu_{max}$ 3401, 2956, 2922, 1633, 1603, 1462, 1377, 1261, 1099, 995 cm$^{-1}$; MS (EI, 70 eV) *m/z* 306 ($M^{+\bullet}$, <1%), 275 (7), 259 (22), 217 (76), 189 (100), 69 (79); HRMS $(M+Na)^+$ calcd for $C_{18}H_{26}NaO_4$ 329.1729, found 329.1729.

**Reaction Sequence Leading to Phomentrioloxin A Analogue 4**




**(3a*S*,4*R*,7a*S*)-7-Iodo-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-ol (39)**. A magnetically stirred solution of epoxide **38**[17] (2.91 g, 9.88 mmol) in anhydrous diethyl ether (60 mL) was cooled to –40 °C then treated with DIBAL-H (11.9 mL of a 1 M solution in hexanes, 11.9 mmol) over 0.08 h. The ensuing mixture was maintained at this temperature for 3 h then treated with tartaric acid (50 mL of a saturated aqueous solution) and stirred for a further 0.5 h while being allowed to warm to 20 °C. The organic phase was separated and the aqueous layer extracted with diethyl ether (2 x 50 mL). The

combined organic layers were then washed with water (1 x 100 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane gradient elution) to furnish, after concentration of the appropriate fractions ($R_f$ = 0.4 in 1:1 v/v ethyl acetate/hexane), the title compound **39** (2.10 g, 72%) as a white, crystalline solid, mp = 101–103 °C, $[\alpha]^{20}_D$ = –9.3 ($c$ = 1.5, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.43 (dd, $J$ = 5.0 and 3.6 Hz, 1H), 4.65 (d, $J$ = 5.9 Hz, 1H), 4.09 (dd, $J$ = 7.1 and 5.9 Hz, 1H), 3.96 (td, $J$ = 7.2 and 4.6 Hz, 1H), 2.48 (dt, $J$ = 17.4 and 4.9 Hz, 1H), 2.12 (dddd, $J$ =17.4, 7.5, 3.6 and 1.3 Hz, 1H), 1.96 (broad s, 1H), 1.49 (s, 3H), 1.42 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 137.7, 109.4, 94.6, 79.4, 78.6, 67.5, 33.5, 28.1, 26.2; IR $\nu_{max}$ 3435, 2985, 2932, 1701, 1633, 1380, 1222, 1161, 1071, 1050, 867 cm$^{-1}$; MS (EI, 70 eV) *m/z* 296 ($M^{+\bullet}$, 12%), 281 (100); HRMS ($M^{+\bullet}$) calcd for $C_9H_{13}{}^{127}IO_3$, 295.9909, found 295.9913.

**(3a*S*,4*R*,7a*S*)-7-Iodo-4-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxole (40)**. Silver(I) oxide (1.81 g, 7.81 mmol) and methyl iodide (970 μL, 15.6 mmol) were added to a magnetically stirred solution of compound **39** (2.10 g, 7.10 mmol) in acetonitrile (40 mL) maintained under a nitrogen atmosphere. The ensuing mixture was heated at 82 °C for 16 h then cooled to 20 °C and filtered through a pad of diatomaceous earth that was washed with ethyl acetate (2 x 20 mL). The combined filtrates were concentrated under reduced pressure and the material so obtained subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane gradient elution). Concentration of the appropriate fractions ($R_f$ = 0.5 in 1.5:1 v/v ethyl acetate/hexane) gave the title

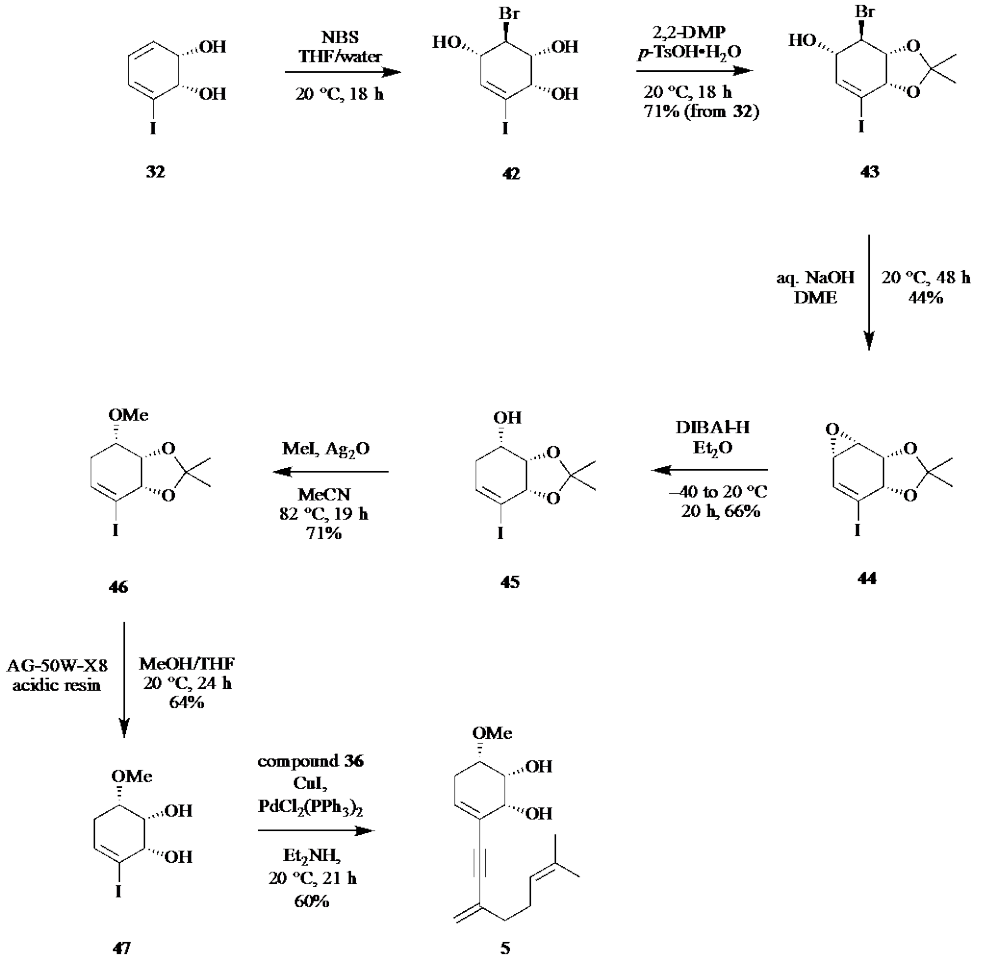
compound **40** (1.04 g, 47%) as a light-yellow oil, $[\alpha]^{20}_{D} = -14$ ($c$ = 1.0, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.37 (t, $J$ = 4.3 Hz, 1H), 4.59 (d, $J$ = 5.6 Hz, 1H), 4.21 (t, $J$ = 5.8 Hz, 1H), 3.61 (td, $J$ = 5.5 and 4.4 Hz, 1H), 3.43 (s, 3H), 2.43 (dtd, $J$ = 17.5, 4.2 and 1.5 Hz, 1H), 2.15 (dt, $J$ =17.6 and 4.4 Hz, 1H), 1.47 (s, 3H), 1.40 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 136.6, 109.3, 96.7, 78.9, 76.3, 75.7, 57.7, 29.9, 27.9, 26.3; IR $\nu_{max}$ 2985, 2932, 2896, 2824, 1749, 1728, 1636, 1455, 1379, 1370, 1339, 1213, 1163, 1104, 1071, 1032, 968 cm$^{-1}$; MS (EI, 70 eV) *m/z* 310 ($M^{+\bullet}$, 11%), 295 (100); HRMS ($M^{+\bullet}$) calcd for $C_{10}H_{15}{}^{127}IO_3$, 310.0066, found 310.0064.

**(1*R*,2*S*,6*R*)-3-Iodo-6-methoxycyclohex-3-ene-1,2-diol (41)**. A solution of compound **40** (1.04 g, 3.36 mmol) in methanol/THF (20 mL of a 1:1 v/v mixture) was treated with acidified AG-50W-X8 acidic resin (2.09 g, 200 wt%). The resulting mixture was stirred vigorously at 20 °C for 24 h then filtered through a pad of diatomaceous earth that was washed with ethyl acetate (2 x 10 mL). The combined filtrates were concentrated under reduced pressure and subjection of the residue to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane gradient elution) gave, after concentration of the appropriate fractions ($R_f$ = 0.2 in 1:1.5 v/v ethyl acetate/hexane), the title compound **41** (797 mg, 88%) as a light-cream colored solid, mp = 79–88 °C, $[\alpha]^{20}_{D} = -140$ ($c$ = 0.2, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.37 (dd, $J$ = 5.3 and 3.0 Hz, 1H), 4.40 (d, $J$ = 4.2 Hz, 1H), 3.84 (dd, $J$ = 9.3 and 4.2 Hz, 1H), 3.61–3.56 (complex m, 1H), 3.42 (s, 3H), 2.79 (broad s, 2H), 2.63 (dt, $J$ = 17.5 and 5.3 Hz, 1H), 2.01 (ddd, $J$ = 17.6, 8.2 and 3.0 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 137.7, 96.3, 74.7, 74.6, 72.2, 57.2, 33.1; IR $\nu_{max}$ 3391, 2971, 2926, 2821, 1633, 1432, 1395, 1196, 1097, 988, 961, 823, 684 cm$^{-1}$; MS (EI, 70 eV) *m/z*

270 ($M^{+\bullet}$, 8%), 252 (13), 74 (100); HRMS ($M^{+\bullet}$) calcd for $C_7H_{11}{}^{127}IO_3$ 269.9753, found 269.9757.

**(1*R*,2*R*,6*R*)-6-Methoxy-3-(7-methyl-3-methyleneoct-6-en-1-yn-1-yl)cyclohex-3-ene-1,2-diol (4)**. Alkyne **36** (594 mg, 4.43 mmol) was added to a solution of compound **41** (519 mg, 2.95 mmol) in anhydrous diethylamine (25 mL) and the ensuing solution sparged with nitrogen for 0.5 h. $PdCl_2(PPh_3)_2$ (207 mg, 0.30 mmol) and cuprous iodide (84 mg, 0.44 mmol) were then added and the resulting mixture stirred at 20 °C for 20 h before being concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:4 → 1:1 e v/v ethyl acetate/hexane gradient elution) to give, after concentration of the appropriate fractions ($R_f$ = 0.3 in 1:1 v/v ethyl acetate/hexane), the title compound **4** (519 mg, 64%) as a clear, light-yellow oil, $[\alpha]^{20}_D$ = +86 (*c* = 1.7, $CHCl_3$). $^1$H NMR ($CDCl_3$, 100 MHz) $\delta$ 6.10 (dd, *J* = 5.2 and 3.2 Hz, 1H), 5.33 (d, *J* = 2.0 Hz, 1H), 5.24 (d, *J* = 1.6 Hz, 1H), 5.12 – 5.08 (complex m, 1H), 4.34 (d, *J* = 4.1 Hz, 1H), 3.74 (dd, *J* = 9.2 and 4.0 Hz, 1H), 3.61 (ddd, *J* = 9.2, 7.9 and 5.4 Hz, 1H), 3.43 (s, 3H), 2.72 (dt, *J* = 18.7 and 5.3 Hz, 2H), 2.19 (m, 4H), 2.08 (dddd, *J* = 18.8, 8.0, 3.2 and 1.1 Hz, 2H), 1.68 (s, 3H), 1.61 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 134.0, 132.2, 131.2, 123.3, 121.6, 121.4, 89.4, 87.9, 75.2, 71.5, 69.1, 57.1, 37.4, 30.1, 26.8, 25.7, 17.8; IR $\nu_{max}$ 3401, 2918, 2191, 1671, 1605, 1443, 1376, 1196, 1101, 988, 903 $cm^{-1}$; MS (ESI, +ve) *m/z* 299 [$(M + Na)^+$, 100%]; HRMS $(M + Na)^+$ calcd for $C_{17}H_{24}NaO_3$ 299.1622, found 299.1623.

**Reaction Sequence Leading to Phomentrioloxin A Analogue 5**




**(3a*R*,4*R*,5*S*,7a*S*)-4-Bromo-7-iodo-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-5-ol (43)**. A solution of compound **32**[10] (3 g, 12.6 mmol) in THF/water (38 mL of a 4:1 v/v mixture) was treated with *N*-bromosuccinimide (3.37 g, 18.9 mmol) and the ensuing mixture protected from light and stirred magnetically at 20 °C for 18 h then quenched with $Na_2S_2O_3$ (70 mL of a saturated aqueous solution) and extracted with diethyl ether (2 x 70 mL). The combined organic phases were washed with brine (1 x 70 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford an

orange solid **42**.[18] This material was dissolved in anhydrous 2,2-dimethoxypropane (30 mL) and the resulting solution maintained under a nitrogen atmosphere and, while being protected from light, was treated with *p*-TsOH•$H_2O$ (434 mg, 2.28 mmol). The resulting mixture was stirred at 20 °C for 18 h then treated with $NaHCO_3$ (30 mL of a saturated aqueous solution) and extracted with ethyl acetate (2 x 40 mL). The combined organic layers were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, hexane → 1:4 v/v ethyl acetate/hexane gradient elution) and gave, after concentration of the appropriate fractions ($R_f$ = 0.2 in 1:4 v/v ethyl acetate/hexane), the title compound **43** (3.38 g, 71%) as a voluminous, white solid, mp = 80–82 °C, $[\alpha]^{20}_D$ = +14 (*c* = 2.0, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.65 (dd, *J* = 4.4, 0.7 Hz, 1H), 4.67 (d, *J* = 5.1 Hz, 1H), 4.57 (t, *J*= 5.4 Hz, 1H), 4.30 (t, *J* = 5.0 Hz, 1H), 4.31–4.18 (complex m, 1H), 2.92 (dd, *J* = 9.3 and 0.7 Hz, 1H), 1.53 (s, 3H), 1.42 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 138.7, 111.8, 100.5, 78.3, 77.6, 71.1, 48.2, 27.9, 26.4; IR $\nu_{max}$ 3422, 3339, 2990, 2940, 2873, 1630, 1374, 1260, 1211, 1068, 1047, 1011, 857, 727 $cm^{-1}$; MS (EI, 70 eV) *m/z* 376 and 374 ($M^{+\bullet}$, both 6%) 361 and 359 (100 and 98), 302 (24), 299 (25), 174 (33), 172 (34); HRMS ($M^{+\bullet}$) calcd for $C_9H_{12}{}^{79}Br^{127}IO_3$, 373.9015, found 373.9018.

**(3a*S*,5a*S*,6a*S*,6b*S*)-4-Iodo-2,2-dimethyl-3a,5a,6a,6b-tetrahydrooxireno-[2',3':3,4]ben-zo[1,2-*d*][1,3]dioxole (44)**. NaOH (4.5 mL of a 2.0 M aqueous solution, 9.00 mmol) was added, dropwise, to a magnetically stirred solution of compound **43** (3.38 g, 9.00 mmol) in 1,2-dimethoxyethane (50 mL). The resulting mixture was protected from light and stirred at 20 °C for 48 h then concentrated under reduced pressure. The residue thus

obtained was partitioned between dichloromethane (50 mL) and water (50 mL) and the separated organic layer washed with brine (1 x 50 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Subjection of the material so obtained to flash chromatography (silica, 1:7 v/v ethyl acetate/hexane gradient elution) provided, after concentration of the appropriate fractions ($R_f$ = 0.1 in 1:9 v/v ethyl acetate/hexane), the title compound **44** (1.18 g, 44%) as a white, crystalline solid, mp = 46–47 °C, $[\alpha]^{20}_D$ = –82 (*c* = 1.3, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.00 (d, *J* = 4.2 Hz, 1H), 4.78 (dd, *J* = 6.7 and 1.8 Hz, 1H), 4.46 (dd, *J* = 6.7 and 2.7 Hz, 1H), 3.66 (ddd, *J* = 4.0, 2.7 and 1.8 Hz, 1H), 3.32 (t, *J* = 4.1 Hz, 1H), 1.55 (s, 3H), 1.41 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 138.2, 108.1, 100.1, 79.5, 73.7, 54.5, 50.9, 27.2, 25.3; IR $\nu_{max}$ 2987, 2937, 2881, 1626, 1371, 1208, 1159, 1056, 864 $cm^{-1}$; MS (EI, 70 eV) *m/z* 294 ($M^{+\bullet}$, 18%), 279 (100), 237 (26), 207 (22); HRMS ($M^{+\bullet}$) calcd for $C_9H_{11}{}^{127}IO_3$ 293.9753, found 293.9750.

**(3a*S*,4*S*,7a*S*)-7-Iodo-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-ol (45)**. A magnetically stirred solution of epoxide **44** (2.36 g, 8.06 mmol) in anhydrous diethyl ether (40 mL) was cooled to –40 °C then treated with a DIBAL-H (9.67 mL of a 1.0 M solution in hexanes, 9.67 mmol) over 0.08 h. The resulting solution was allowed to warm to 20 °C over 20 h before being treated with tartaric acid (50 mL of a saturated aqueous solution). After a further 1 h the aqueous layer was separated then extracted with diethyl ether (2 x 50 mL) and the combined organic layers were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane gradient elution) and concentration of the appropriate fractions ($R_f$ = 0.4 in 1:1 v/v ethyl acetate/hexane) afforded the title

compound **45** (1.57 g, 66%) as a colourless, micro-crystalline solid, mp = 101 °C, $[\alpha]^{20}_{D}$ = +41 (*c* =1.2, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.35 (dd, *J* = 6.0 and 2.8 Hz, 1H), 4.62 (d, *J* = 3.9 Hz, 1H), 4.39 (dd, *J* = 5.3 and 2.3 Hz, 1H), 3.99 (ddd, *J* = 8.9, 5.6 and 2.5 Hz, 1H), 2.39 (ddt, *J* = 12.1, 9.4 and 2.5 Hz, 1H), 2.30 (dt, *J* = 16.5 and 5.9 Hz, 1H), 1.45 (s, 3H), 1.43 (s, 3H), (signal due to hydroxyl group proton not observed); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 136.4, 110.2, 98.9, 80.6, 77.3, 66.6, 32.4, 27.3, 26.6; IR $\nu_{max}$ 3413, 2985, 2932, 2870, 1629, 1371, 1230, 1083, 1046, 864 $cm^{-1}$; MS (EI, 70 eV) *m/z* 296 ($M^{+\bullet}$, 6%), 281 (100); HRMS ($M^{+\bullet}$) calcd for $C_9H_{13}{}^{127}IO_3$ 295.9909, found 295.9909.

**(3a*S*,4*S*,7a*S*)-7-Iodo-4-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxole (46)**. Silver(I) oxide (1.35 g, 5.84 mmol) and iodomethane (730 μL, 11.7 mmol) were added to a magnetically stirred solution of alcohol **45** (1.57 g, 5.31 mmol) in anhydrous acetonitrile (40 mL). The ensuing mixture was stirred at 82 °C for 19 h then cooled to 20 °C and filtered through a pad of diatomaceous earth that was washed with ethyl acetate (2 x 50 mL). The combined filtrates were concentrated under reduced pressure and the residue thus obtained subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane gradient elution). Concentration of the appropriate fractions ($R_f$ = 0.6 in 1.5:1 v/v ethyl acetate/hexane) provided the title compound **46** (1.17 g, 71%) as a light-yellow oil, $[\alpha]^{20}_{D}$ = –32 (*c* = 1.2, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.35 (dd, *J* = 6.0 and 2.8 Hz, 1H), 4.59 (d, *J* = 4.9 Hz, 1H), 4.49 (ddd, *J* = 9.9, 7.2 and 2.2 Hz, 1H), 3.59 (ddd, *J* = 9.9, 7.2 and 2.2 Hz, 1H), 3.44 (s, 3H), 2.41–2.35 (complex m, 2H), 1.44 (s, 3H), 1.43 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 136.1, 110.6, 99.8, 80.8, 75.1, 75.0, 56.7, 28.8, 27.4, 26.8; IR $\nu_{max}$ 2984, 2932, 2822, 1626, 1454, 1380, 1370, 1233, 1168,

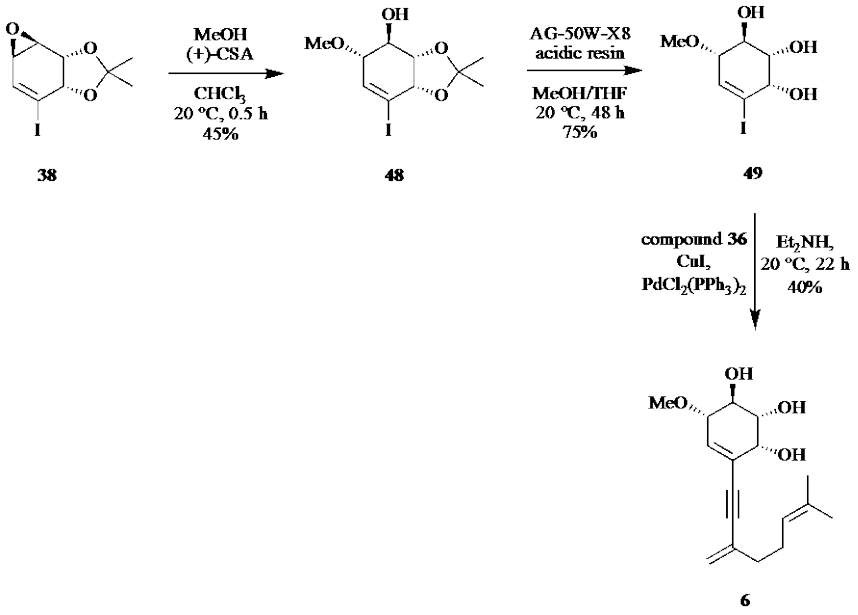
1111, 1066, 1035, 865 $cm^{-1}$; MS (EI, 70 eV) *m/z* 310 ($M^{+\bullet}$, 3%), 295 (100); HRMS ($M^{+\bullet}$) calcd for $C_{10}H_{15}{}^{127}IO_3$ 310.0066, found 310.0069.

**(1*R*,2*S*,6*S*)-3-Iodo-6-methoxycyclohex-3-ene-1,2-diol (47)**. A solution of acetonide **46** (1.17 g, 3.78 mmol) in methanol/THF (30 mL of a 1:1 v/v mixture) was treated with acidified AG-50W-X8 acidic resin (2.35 g, 200 wt%) and the ensuing mixture stirred vigorously at 20 °C for 24 h. The reaction mixture was then filtered through a pad of diatomaceous earth that was washed with ethyl acetate (2 x 10 mL). The combined filtrates were concentrated under reduced pressure and the residue thus obtained subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane elution) to give, after concentration of the appropriate fractions ($R_f$ = 0.2 in 1:2 v/v ethyl acetate/ hexane), the title compound **47** (650 mg, 64%) as a light-yellow oil, $[\alpha]^{20}_D$ = +1.5 (*c* = 0.8, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.33 (t, *J* = 4.0 Hz, 1H), 4.09 (d, *J* = 4.4 Hz, 1H), 3.99–3.88 (complex m, 1H), 3.71 (td, *J* = 4.3 and 1.7 Hz, 1H), 3.37 (s, 3H), 2.92 (broad s, 2H), 2.50 (dt, *J* =18.1 and 4.4 Hz, 1H), 2.19 (dt, *J* = 18.1 and 4.4 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 135.4, 100.0, 78.1, 75.0, 69.4, 57.5, 31.1; IR $\nu_{max}$ 3400, 2928, 2830, 1627, 1395, 1151, 1101, 1078, 980 $cm^{-1}$; MS (EI, 70 eV) *m/z* 270 ($M^{+\bullet}$, 100%), 252 (29). HRMS ($M^{+\bullet}$) calcd for $C_7H_{11}{}^{127}IO_3$ 269.9753, found 269.9750.

**(1*R*,2*R*,6*S*)-6-Methoxy-3-(7-methyl-3-methyleneoct-6-en-1-yn-1-yl)cyclohex-3-ene-1,2-diol (5)**. Alkyne **36** (485 mg, 3.62 mmol) was added to a magnetically stirred solution of compound **47** (650 mg, 2.41 mmol) in anhydrous diethylamine (20 mL). The resulting solution was sparged with nitrogen for 0.5 h then $PdCl_2(PPh_3)_2$ (169 mg, 0.24 mmol) and

cuprous iodide (68.8 mg, 0.36 mmol) were added. The ensuing mixture was stirred at 20 °C for 21 h then concentrated under reduced pressure and the residue thus obtained subjected to flash chromatography (silica, 1:4 →1:1 v/v ethyl acetate/hexane gradient elution). Concentration of the appropriate fractions ($R_f$ = 0.3 in 1:1 v/v ethyl acetate/hexane) gave the title compound **5** (400 mg, 60%) as a clear, light-yellow oil, $[\alpha]^{20}_D$ = +11 (*c* =1.1, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.05 (t, *J* = 4.1 Hz, 1H), 5.35 (d, *J* = 1.9 Hz, 1H), 5.25 (d, *J* = 1.6 Hz, 1H), 5.13–5.09 (complex m, 1H), 4.09 (m, 1H), 3.88 (m, 1H), 3.66 (td, *J* = 4.6 and 2.0 Hz, 1H), 3.38 (s, 3H), 2.95 (broad s, 1H), 2.89 (d, *J* = 10.0 Hz, 1H), 2.59 (dtd, *J* = 19.2, 4.6 and 1.3 Hz, 1H), 2.34–2.27 (complex m, 1H), 2.25–2.17 (complex m, 4H), 1.68 (s, 3H), 1.61 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 132.2, 132.0, 131.2, 123.3, 121.4, 89.6, 87.8, 78.4, 69.7, 68.7, 57.3, 37.4, 28.5, 26.8, 25.7, 17.8; IR $\nu_{max}$ 3427, 2931, 2190, 1717, 1667, 1446, 1376, 1217, 1085, 755 $cm^{-1}$; MS (ESI, +ve) *m/z* 299 [$(M + Na)^+$, 100%]. HRMS $(M + Na)^+$ calcd for $C_{17}H_{24}NaO_3$ 299.1622, found 299.1623.

**Reaction Sequence Leading to Phomentrioloxin A Analogue 6**



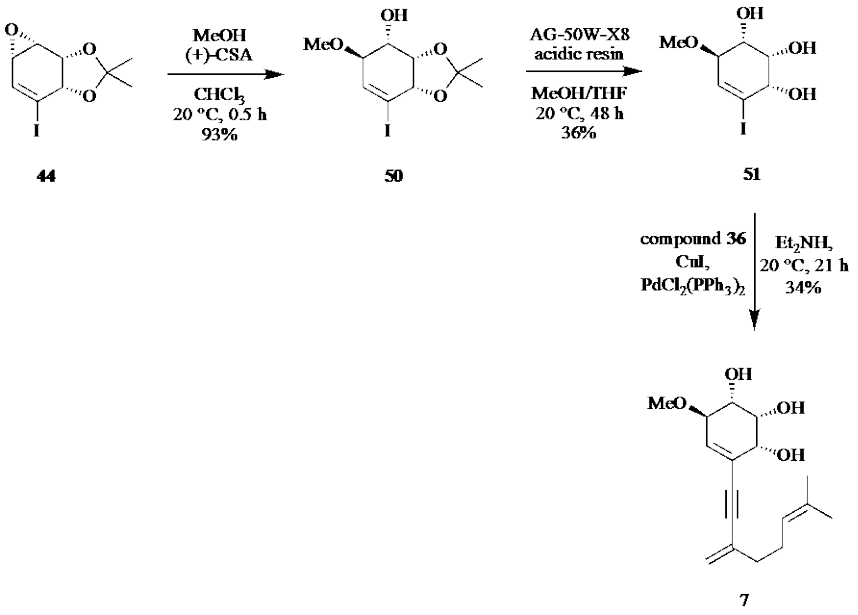

**(3aS,4R,5S,7aS)-7-Iodo-5-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]di-ox-ol-4-ol (48)**. A magnetically stirred solution of epoxide **38**[17] (326 mg, 1.11 mmol) in methanol/$CHCl_3$ (7.5 mL of a 1:1 v/v mixture) maintained at 20 °C was treated with (1*S*)-(+)-10-camphorsulfonic acid (52 mg, 0.22 mmol) and the ensuing mixture maintained in the dark for 0.5 h. After this time the reaction mixture was concentrated under reduced pressure and the residue subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane gradient elution). Concentration of the appropriate fractions ($R_f$ = 0.4 in 1.5:1 v/v ethyl acetate/hexane) then gave the title compound **48** (166 mg, 45%) as a clear, colourless oil, $[\alpha]^{20}{}_D$ = + 34° (*c* = 4.4, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.53 (s, 1H), 4.68 (d, *J* = 6.5 Hz, 1H), 4.13 (m, 1H), 3.64 (s, 1H), 3.63 (m, 1H), 3.47 (s, 3H), 2.67 (broad s, 1H), 1.54 (s, 3H), 1.41 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 140.3,

110.3, 93.1, 81.3, 79.5, 77.1, 72.4, 57.5, 28.1, 25.8; IR $\nu_{max}$ 3442, 2986, 2933, 2828, 1632, 1455, 1376, 1249, 1217, 1163, 1072, 972, 948, 912, 868, 790, 744 $cm^{-1}$; MS (EI, 70 eV) *m/z* 311 [$(M - CH_3\bullet)^+$, 100%], 251 (10), 239 (28), 226 (32). HRMS $(M - CH_3\bullet)^+$ calcd for $C_9H_{12}{}^{127}IO_4$ 310.9780, found 310.9781.

**(1*S*,2*S*,3*S*,6*S*)-4-Iodo-6-methoxycyclohex-4-ene-1,2,3-triol (49)**. A magnetically stirred solution of acetonide **48** (489 mg, 1.50 mmol) in a mixture of methanol/THF (10 mL of a 1:1 v/v mixture) was treated with acidified AG-50W-X8 acidic resin (979 mg, 200 wt%) and the ensuing mixture stirred vigorously while being protected from light at 20 °C for 48 h. The reaction mixture was then filtered through a pad of diatomaceous earth that was washed with ethyl acetate (2 x 20 mL). The combined filtrates were concentrated under reduced pressure and the residue so obtained subjected to flash chromatography (silica, ethyl acetate gradient elution) to give, after concentration of the appropriate fractions ($R_f$ = 0.3 in ethyl acetate), the title compound **49** (323 mg, 75%) as a white, crystalline solid, mp = 123–124 °C, $[\alpha]^{20}_D$ = –2.4 (*c* = 0.5, $CHCl_3$). $^1$H NMR ($CD_3OD$, 400 MHz) $\delta$ 6.43 (d, *J* = 2.4 Hz, 1H), 4.23 (d, *J* = 4.2 Hz, 1H), 3.70 (dd, *J* = 10.5 and 7.5 Hz, 1H), 3.59 (ddd, *J* = 7.5, 2.4 and 0.7 Hz, 1H), 3.52 (dd, *J* = 10.5 and 4.2 Hz, 1H), 3.45 (s, 3H). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.50 (d, *J* = 2.3 Hz, 1H), 4.41 (t, *J* = 4.3 Hz, 1H), 3.81 (ddd, *J* = 10.0, 7.5 and 2.2 Hz, 1H), 3.70–3.64 (complex m, 2H), 3.48 (s, 3H), 3.03 (d, *J* = 6.4 Hz, 1H), 2.87 (m, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 139.2, 98.4, 82.7, 75.3, 70.7, 70.2, 57.3; IR $\nu_{max}$ 3306, 2989, 2927, 2909, 2848, 1620, 1455, 1362, 1270, 1224, 1186, 1147, 1074, 993, 950, 877 $cm^{-1}$; MS (ESI, +ve) *m/z* 309 [$(M + Na)^+$, 100%]. HRMS $(M + Na)^+$ calcd for $C_7H_{11}{}^{127}INaO_4$ 308.9600, found 308.9600.

**(1*S*,2*R*,3*R*,6*S*)-6-Methoxy-4-(7-methyl-3-methyleneoct-6-en-1-yn-1-yl)cyclohex-4-ene-1,2,3-triol (6)**. Alkyne **36** (1.11 g, 8.28 mmol) was added to a magnetically stirred solution of iodide **49** (1.18 g, 4.14 mmol) in anhydrous diethyl amine (40 mL). The resulting solution was sparged with nitrogen for 0.5 h then $PdCl_2(PPh_3)_2$ (291 mg, 0.41 mmol) and cuprous iodide (118 mg, 0.62 mmol) were added. The ensuing mixture was stirred at 20 °C for 22 h then concentrated under reduced pressure and the dark brown residue so obtained subjected to flash chromatography (silica, hexane → 1:7:2 v/v/v methanol/ethyl acetate/hexane gradient elution). Concentration of the appropriate fractions ($R_f$ = 0.5 in 1:7:2 v/v/v methanol/ethyl acetate/hexane) gave the product **6** (484 mg, 40%) as a clear, light-yellow oil, $[\alpha]^{20}_D$ = +34 (*c* = 2.0, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.11 (d, *J* = 2.4 Hz, 1H), 5.36 (s, 1H), 5.26 (d, *J* = 1.1 Hz, 1H), 5.10 (m, 1H), 4.28 (d, *J* = 4.1 Hz, 1H), 4.05 (s, 2H), 3.89 (dd, *J* = 10.4 and 7.9 Hz, 1H), 3.80 (dd, *J* = 7.8 and 2.4 Hz, 1H), 3.63 (m, 1H), 3.56 (dd, *J* = 10.4 and 4.0 Hz, 1H), 3.48 (s, 3H), 2.19 (m, 4H), 1.68 (s, 3H), 1.61 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 134.2, 132.3, 131.0, 123.2, 123.1, 122.0, 90.6, 87.5, 81.2, 71.1, 70.2, 69.8, 57.1, 37.2, 26.7, 25.7, 17.8; IR $\nu_{max}$ 3400, 2925, 1631, 1605, 1438, 1376, 1083, 943, 894 cm$^{-1}$; MS (ESI, +ve) *m/z* 315 [(M + Na)$^+$, 100%]; HRMS (M + Na)$^+$ calcd for $C_{17}H_{24}NaO_4$ 315.1572, found 315.1571.

**Reaction Sequence Leading to Phomentrioloxin A Analogue 7**




**(3aS,4S,5R,7aS)-7-Iodo-5-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]-diox-ol-4-ol (50)**. A magnetically stirred solution of epoxide **44** (1.18 g, 3.99 mmol) in methanol/$CHCl_3$ (45 mL of a 2:1 v/v mixture) was treated with (1*S*)-(+)-10-camphorsulfonic acid (186 mg, 0.80 mmol) and the resulting mixture stirred in the dark for 0.5 h. The solvent was then removed under reduced pressure and the residue thus obtained subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane gradient elution). Concentration of the appropriate fractions ($R_f$ = 0.2 in 1:3 v/v ethyl acetate/hexane) gave the title compound **50** (1.21 g, 93%) as a clear, colorless solid, mp = 72–78 °C, $[\alpha]^{20}_D$ = –29 (*c* = 7.5, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.47 (d, *J* = 1.8 Hz, 1H), 4.63 (dd, *J* = 5.1 and 1.9 Hz, 1H), 4.47 (dd, *J* = 5.1 and 2.5 Hz, 1H), 3.94 (d, *J* = 8.3 Hz, 1H), 3.81 (dd, *J* = 8.3 and 2.6 Hz, 1H), 3.50 (s, 3H), 2.61 (broad s, 1H), 1.43

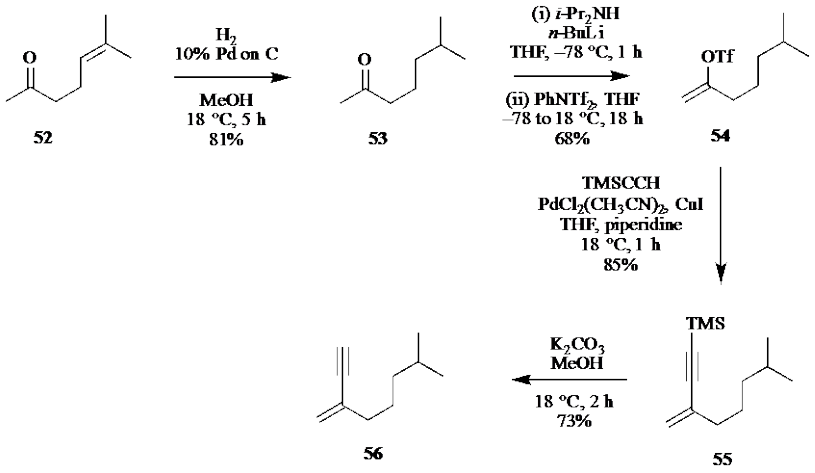
(s, 3H), 1.41 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 137.2, 110.6, 100.6, 80.6, 79.7, 76.3, 71.2, 57.6, 27.4, 26.4; IR $\nu_{max}$ 3390, 2984, 2918, 2843, 1697, 1618, 1381, 1217, 1073 cm$^{-1}$; MS (EI, 70 eV) *m/z* 311 [$(M - CH_3\bullet)^+$, 14%], 239 (23), 226 (100); HRMS $(M - CH_3\bullet)^+$ calcd for $C_9H_{12}{}^{127}IO_4$ 310.9780, found 310.9773.

**(1*R*,2*S*,3*S*,6*R*)-4-Iodo-6-methoxycyclohex-4-ene-1,2,3-triol (51)**. A magnetically stirred solution of acetonide **50** (1.21 g, 3.70 mmol) in methanol/THF (20 mL of a 1:1 v/v mixture) was treated with acidified AG-50W-X8 ion exchange resin (2.40 g, 200 wt%) and the ensuing mixture stirred vigorously at 20 °C and in the dark for 48 h. The solvent was then removed under reduced pressure and the residue thus obtained subjected to flash chromatography (silica, ethyl acetate gradient elution). Concentration of the appropriate fractions ($R_f$ = 0.2 in 0.5:9.5 v/v ethyl acetate/hexane) gave the title compound **51** (379 mg, 36%) as a white, crystalline solid, mp = 73–77 °C, $[\alpha]^{20}_D$ = –61 (*c* = 0.8, $CHCl_3$). $^1$H NMR ($CD_3OD$, 400 MHz) $\delta$ 6.48 (dd, *J* = 2.6 and 1.8 Hz, 1H), 4.10 (dt, *J* = 3.8 and 1.8 Hz, 1H), 4.00 (dd, *J* =3.8 and 2.1 Hz, 1H), 3.89 (dt, *J* =7.3 and 2.6 Hz, 1H), 3.69 (dd, *J* =7.3 and 2.1 Hz, 1H), 3.45 (s, 3H); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.56 (s, 1H), 4.20 (s, 2H), 3.93–3.86 (complex m, 2H), 3.46 (s, 3H), 3.26 (broad s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 136.5, 104.7, 80.1, 73.6, 72.1, 70.1, 57.4; IR $\nu_{max}$ 3217, 2918, 2861, 2821, 1660, 1620, 1415, 1336, 1099, 1081, 1045, 1028, 847 cm$^{-1}$; MS (EI, 70 eV) *m/z* 309 [$(M + Na)^+$, 100%]; HRMS $(M + Na)^+$ calcd for $C_7H_{11}{}^{127}INaO_4$, 308.9600, found, 308.9600.

**(1*R*,2*R*,3*R*,6*R*)-6-Methoxy-4-(7-methyl-3-methyleneoct-6-en-1-yn-1-yl)cyclohex-4-ene-1,2,3-triol (7)**. Alkyne **36** (684 mg, 5.10 mmol) was added to a magnetically stirred

solution of triol **51** (951 mg, 3.33 mmol) in diethylamine (30 mL) maintained at 20 °C. The ensuing mixture was sparged with nitrogen for 0.5 h then $PdCl_2(PPh_3)_2$ (234 mg, 0.33 mmol) and cuprous iodide (95.1 mg, 0.55 mmol) were added. After 21 h the reaction mixture was concentrated under reduced pressure and the brown residue thus obtained subjected to flash chromatography (silica, hexane → 9:1 ethyl acetate/hexane gradient elution). Concentration of the appropriate fractions ($R_f$ = 0.4 in 1:7:2 v/v/v methanol/ethyl acetate/hexane) gave the title compound **7** (331 mg, 34 %) as a clear, light-yellow oil, $[\alpha]^{20}_D$ = –15° (*c* = 0.8, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.17 (dd, *J* = 3.0 and 1.4 Hz, 1H), 5.38 (s, 1H), 5.29 (s, 1H), 5.10 (m, 1H), 4.21 (m, 2H), 4.06–4.03 (complex m, 1H), 3.81 (d, *J* = 6.8 Hz, 1H), 3.47 (s, 3H), 2.98 (broad s, 1H), 2.87 (broad s, 1H), 2.83 (broad s, 1H), 2.21 (m, 4H), 1.69 (s, 3H), 1.62 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 132.3, 131.8, 131.0, 124.4, 123.2, 122.0, 91.3, 86.8, 78.6, 72.0, 70.5, 69.2, 57.1, 37.2, 26.7, 25.2, 17.7; IR $\nu_{max}$ 3390, 2958, 2923, 2857, 1634, 1438, 1377, 1261, 1084 cm$^{-1}$; MS (ESI, +ve) *m/z* 315 [(M + Na)$^+$, 100%]; HRMS (M + Na)$^+$ calcd for $C_{17}H_{24}NaO_4$ 315.1572, found 315.1573.

**Reaction Sequence Leading to the Side-Chain Synthon 56 for the Preparation of Analogues 10-14**




**6-Methylheptan-2-one (53)**. A mixture of commercially available ketone **52** (2.00 g, 15.85 mmol) and Pd on carbon (100 mg of 10% material) in MeOH (5 mL) was placed under a balloon of hydrogen at 18 °C. After 5 h the reaction mixture was filtered through a short pad of diatomaceous earth and the filtrate concentrated under reduced pressure to give compound **53**[19] (1.64 g, 81%) as a clear, pale-yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 2.36 (t, $J$ = 7.5 Hz, 2H), 2.1 (s, 3H), 1.57–1.45 (complex m, 3H), 1.11 (complex m, 2H), 0.83 (d, $J$ = 6.4 Hz, overlapped 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 209.2, 43.9, 38.3, 29.7, 27.8, 22.4, 21.6; IR (KBr) $\nu_{max}$ 2955, 2872, 1717, 1468, 1365, 1168, 1079, 861 cm$^{-1}$; MS (EI, 70 eV) *m/z* 128 ($M^{+\bullet}$, 24%), 111 (45), 95 (57), 89 (48), 85 (100); HRMS ($M^{+\bullet}$) calcd for $C_8H_{16}O$ 128.1194, found 128.1201.

**6-Methylhept-1-en-2-yl trifluoromethanesulfonate (54)**. A magnetically stirred solution of diisopropylamine (2.9 mL, 20.69 mmol) in THF (30 mL) maintained between –15 and –20 °C under a nitrogen atmosphere was treated, dropwise, with *n*-BuLi (12 mL of a 1.6 M solution in hexanes, 19.2 mmol). After 0.25 h the cooling bath was removed and stirring was continued for 0.5 h. The reaction mixture thus obtained was cooled down to –78 °C then treated with compound **53** (1.66 g, 12.97 mmol). After stirring at –78 °C for 1 h, $PhNTf_2$ (5.6 g, 15.68 mmol) was added and the ensuing mixture was stirred for a further 18 h while being allowed to warm to 18 °C then poured into $NH_4Cl$ (80 mL of a saturated aqueous solution). The separated aqueous phase was extracted with diethyl ether (1 x 60 mL) and the combined organic phases were washed with brine (1 x 80 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Subjection of residue thus obtained to flash chromatography (silica, 1:50 v/v diethyl ether/pentane gradient elution) delivered, after concentration of the appropriate fractions ($R_f$ = 0.5 in 1:80 v/v ethyl acetate/hexane), compound **54** (2.31 g, 68%) as a clear, pale-yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.09 (d, $J$ = 3.5 Hz, 1H), 4.93 (m, 1H), 2.31 (t, $J$ = 7.6 Hz, 2H), 1.59–1.51 (complex m, 3H), 1.30–1.21 (complex m, 2H), 0.88 (d, $J$ = 6.8 Hz, overlapped 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 157.1, 118.6 (q, $J_{C\text{-}F}$ = 320 Hz), 103.9, 37.8, 34.0, 27.7, 23.8, 22.3; IR$\nu_{max}$ 2959, 2874, 1670, 1419, 1246, 1211, 937, 612 cm$^{-1}$; MS (EI 70 eV) *m/z* 111 [(M-TfO•)$^+$, 36%], 109 (32), 95 (67), 69 (100); HRMS (M-TfO•)$^+$ calcd for $C_9H_{15}F_3O_3S$ 111.1174, found 111.1173.

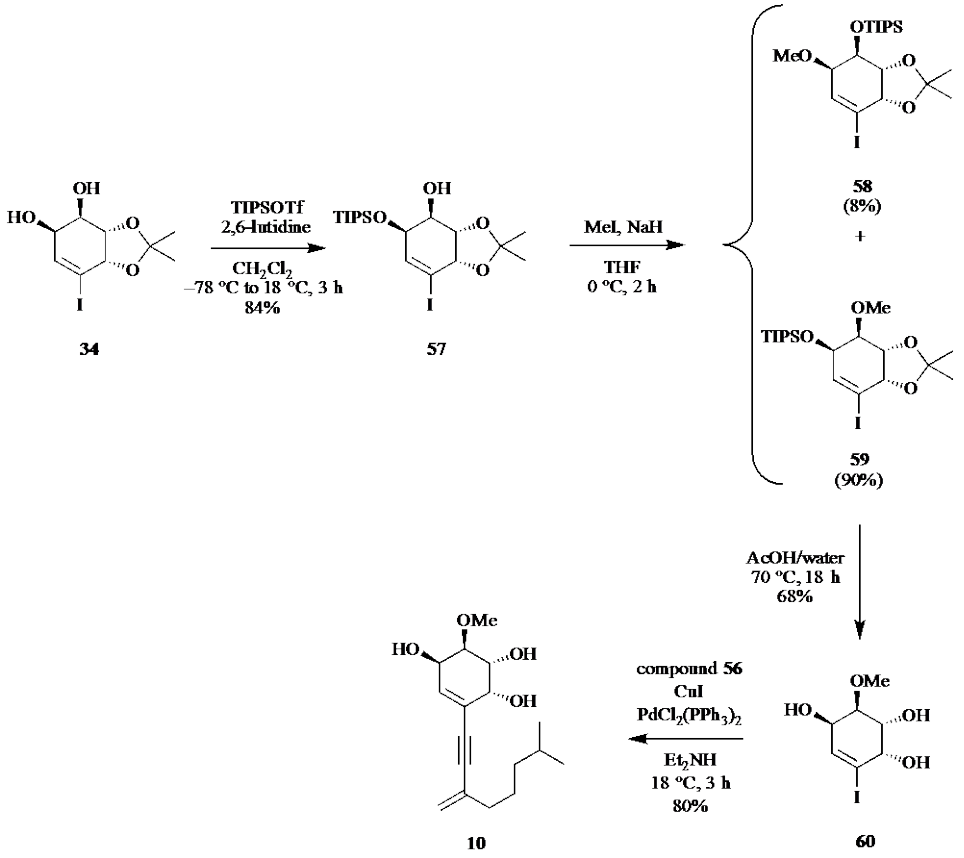
**Trimethyl(7-methyl-3-methyleneoct-1-yn-1-yl)silane (55)**. Trimethylsilylacetylene (1.9 mL, 13.45 mmol) was added to a magnetically stirred mixture of compound **54** (2.33 g,

8.94 mmol), cuprous iodide (255 mg, 1.34 mmol) and $PdCl_2(CH_3CN)_2$ (232 mg, 0.90 mmol) in piperidine (20 mL) and dry THF (10 mL) maintained under a nitrogen atmosphere. After stirring at 18 °C for 1 h the reaction mixture was treated with diethyl ether (40 mL) then $NH_4Cl$ (100 mL of a saturated aqueous solution). The separated aqueous phase was extracted with diethyl ether (40 mL) and the combined organic phases washed with $NH_4Cl$ (1 x 100 mL of a saturated aqueous solution) before being dried ($MgSO_4$), filtered then concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, pentane elution) delivered, after concentration of the appropriate fractions ($R_f$ = 0.6 in hexane), compound **55** (1.58 g, 85%) as a clear, pale-yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.35 (d, $J$ = 2.0 Hz, 1H), 5.22 (m, 1H), 2.12 (complex m, 2H), 1.58–1.49 (complex m, 3H), 1.21–1.16 (complex m, 2H), 0.88 (d, $J$ = 6.3 Hz, overlapped 6H), 0.19 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 132.0, 121.7, 105.8, 93.7, 38.1, 37.2, 27.8, 25.7, 22,6, –0.0(3); IR $\nu_{max}$ 2957, 2870, 2147, 1605, 1468, 1250, 842, 759 cm$^{-1}$; MS (EI 70 eV) *m/z* 208 ($M^{+\bullet}$, 33%), 193 (45), 123 (82), 73 (100); HRMS ($M^{+\bullet}$) calcd for $C_{13}H_{24}Si$ 208.1647, found 208.1642.

**7-Methyl-3-methyleneoct-1-yne (56)**. Compound **55** (1.25 g, 5.99 mmol) in methanol (5 mL) was treated with $K_2CO_3$ (2.48 g, 17.95 mmol). After stirring at 18 °C for 2 h the reaction mixture was filtered through a short pad of diatomaceous earth and the filtrate then concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, pentane elution) delivered, after concentration of the appropriate fractions ($R_f$ = 0.7 in hexane), compound **56** (594 mg, 73%) as a clear, pale-yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.41 (d, $J$ = 1.9 Hz, 1H), 5.29 (m, 1H), 2.88 (s, 1H), 2.16–

2.12 (complex m, 2H), 1.54–1.49 (complex m, 3H), 1.21–1.15 (complex m, 2H), 0.88 (d, $J$ = 6.8 Hz, overlapped 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 131.0, 122.6, 84.2, 76.7, 38.1, 37.2, 27.8, 25.7, 22.6; IR $\nu_{max}$ 3310, 2955, 2870, 1611, 1467, 1249, 902, 612 $cm^{-1}$; MS (EI , 70 eV) *m/z* 136 ($M^{+\bullet}$, 13%), 135 (47), 121 (25), 73 (100); HRMS ($M^{+\bullet}$) calcd for $C_{10}H_{16}$ 136.1252, found 136.1249.

**Reaction Sequence Leading to Phomentrioloxin A Analogue 10**




**(((3a*R*,4*R*,5R,7a*S*)-7-Iodo-5-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]-dioxol-4-yl)oxy)triisopropylsilane (58) and (((3a*S*,4*S*,5*R*,7a*S*)-7-Iodo-4-methoxy-2,2-dime-thyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-5-yl)oxy)triisopropylsilane (59)**. Sodium hydride (300 mg of a 60% dispersion in mineral oil, 7.50 mmol) was added to a magnetically stirred solution of compound **57**[8] (1.16 g, 2.48 mmol) and iodomethane (460 μL, 7.39 mmol) in dry THF (25 mL) maintained at 0 °C under a nitrogen atmosphere. Stirring was continued at 0 to 18 °C for 2 h then the reaction mixture was

treated with ice/water (60 mL). The separated aqueous phase was extracted with ethyl acetate (1 x 25 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuring light-yellow oil was subjected to flash chromatography (silica, 1:50 v/v ethyl acetate/hexane gradient elution) to give two fractions, A and B.

Concentration of fraction A ($R_f$ = 0.4 in 0.5:2.5:5.5 v/v/v ethyl acetate /dichloromethane/ hexane**)** gave compound **58** (100 mg, 8%) as a white, crystalline solid, mp = 66–67 °C, $[\alpha]^{20}_D$ = −27.5 (*c* = 0.16, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.44 (d, *J* = 1.9 Hz, 1H), 4.62 (dd, *J* = 5.3 and 1.6 Hz, 1H), 4.51–4.49 (complex m, 1H), 4.29 (t, *J* = 5.0 Hz, 1H), 3.85–3.83 (complex m, 1H), 3.41 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H), 1.11–1.03 (complex m, 21H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 137.7, 109.8, 98.9, 79.5, 77.9, 77.2, 69.7, 57.3, 27.5, 26.3, 18.1, 18.0, 12.6; IR $\nu_{max}$ 2940, 2888, 2865, 1636, 1462, 1383, 1335, 1241, 1221, 1198, 1139, 1122, 1081, 996, 881, 858, 681 cm$^{-1}$; MS (EI, 70 eV) *m/z* 467 [$(M\text{-}CH_3\bullet)^+$, 6%], 439 (35), 254 (100), 222 (55), 145 (88). HRMS $(M\text{-}CH_3\bullet)^+$ calcd for $C_{18}H_{32}{}^{127}IO_4Si$ 467.1115, found 467.1112.

Concentration of fraction B ($R_f$ = 0.3 in 0.5:2.5:5.5 v/v/v ethyl acetate /dichloromethane/ hexane**)** gave compound **59** (1.07 g, 90%) as a white, crystalline solid, mp = 81–83 °C, $[\alpha]^{20}_D$ = −36.0 (*c* = 0.5, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.44 (d, *J* = 2.9 Hz, 1H), 4.63 (dd, *J* = 5.6 and 1.3 Hz, 1H), 4.55–4.53 (complex m, 1H), 4.40 (t, *J* = 5.3 Hz, 1H), 3.74 (t, *J* = 4.2 Hz, 1H), 3.55 (s, 3H), 1.42 (s, 3H), 1.39 (s, 3H), 1.14–1.06 (complex m, 21H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 141.2, 109.6, 98.9, 80.2, 79.0, 75.0, 68.9, 59.7, 27.5, 26.1, 18.0(2), 18.0(0), 12.3; IR $\nu_{max}$ 2940, 2888, 2865, 1635, 1461, 1382, 1335, 1240, 1221, 1197, 1138, 1122, 1081, 954, 880, 858, 681 cm$^{-1}$; MS (EI, 70 eV) *m/z* 467

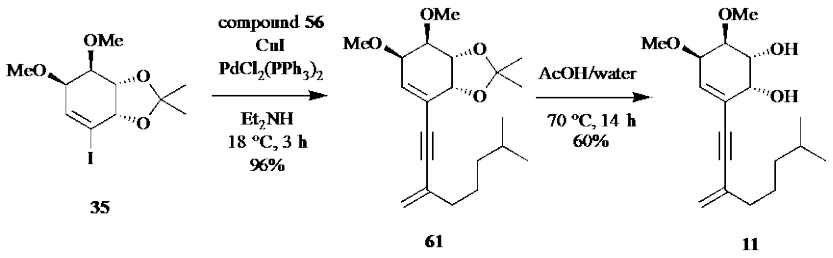
[(M-$CH_3$•)$^+$, 2%], 439 (55), 254 (100), 222 (44), 145 (63). HRMS (M-$CH_3$•)$^+$ calcd for $C_{18}H_{32}{}^{127}IO_4Si$ 467.1115, found 467.1116.

**(1*S*,2*R*,3*R*,4*R*)-6-Iodo-3-methoxycyclohex-5-ene-1,2,4-triol (60)**. Compound **59** (200 mg, 0.42 mmol) was treated with acetic/water (10 mL of a 7:1 v/v mixture) and the resulting solution was heated at 70 °C for 18 h then cooled and concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, 1:6:3 v/v/v methanol/ethyl acetate/ hexane gradient elution) gave, after concentration of the appropriate fractions ($R_f$ = 0.4 in 1:7:2 v/v/v methanol/ethyl acetate/hexane), compound **19** (81 mg, 68%) as a white, crystalline solid, mp = 145−147 °C, $[\alpha]^{20}_D$ = −82 ($c$ = 0.5, $CHCl_3$). $^1$H NMR [$(CD_3)_2SO$, 400 MHz)] $\delta$ 6.23 (d, $J$ = 3.4 Hz, 1H), 5.16 (dd, $J$ = 1.9 and 9.3 Hz, 1H), 4.94 (d, $J$ = 4.9 Hz, 1H), 4.86 (d, $J$ = 7.3 Hz, 1H), 4.19 (complex m, 1H), 3.92 (complex m, 2H), 3.42 (complex m, 1H), 3.36 (s, 3H); $^{13}$C NMR [$(CD_3)_2SO$, 400 MHz)] $\delta$ 140.4, 105.6, 79.8, 72.3, 68.3, 66.7, 58.2; IR $\nu_{max}$ 3412, 3351, 3306, 2994, 2925, 1630, 1446, 1289, 1117, 1097, 1078, 1034, 995, 914, 822 cm$^{-1}$; MS (ESI, +ve) *m/z* 309 [(M + Na)$^+$, 100%]; HRMS (M + Na)$^+$ calcd for $C_7H_{11}IO_4$ 308.9600, found 308.9600.

**(1*R*,2*R*,3*R*,4*R*)-3-Methoxy-6-(7-methyl-3-methyleneoct-1-yn-1-yl)cyclohex-5-ene-1,2,4-triol (10)**. Cuprous iodide (5 mg, 0.03 mmol) and $PdCl_2(PPh_3)_2$ (14 mg, 0.03 mmol) were added to a magnetically stirred solution of compounds **60** (120 mg, 0.42 mmol) and **56** (57 mg, 0.42 mmol) in anhydrous diethylamine (10 mL) maintained at 18 °C under a nitrogen atmosphere. After 3 h the reaction mixture was concentrated under reduced pressure and the residue obtained subjected to flash chromatography (silica,

1:6:3 v/v/v methanol/ethyl acetate/hexane gradient elution). Concentration of the appropriate fractions ($R_f$ = 0.5 in 1:7:2 v/v/v methanol/ethyl acetate/hexane) gave compound **10** (99 mg, 80%) as a clear, light-yellow oil, $[\alpha]^{20}_D = -49.1$ ($c$ = 2.6, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.15 (d, $J$ = 4.2 Hz, 1H), 5.36 (s, 1H), 5.28 (s, 1H), 4.49 (s, 1H), 4.33 (d, $J$ = 4.0 Hz, 1H), 4.19 (dd, $J$ = 8.0 and 3.8 Hz, 1H), 3.68 (dd, $J$ = 8.0 and 4.1 Hz, 1H), 3.53 (s, 3H), 2.73 ( broad s, 2H), 2.15 (t, $J$ = 7.5 Hz, 2H), 2.09 (s, 1H) 1.56–1.46 (complex m, 3H), 1.25–1.14 (complex m, 2H), 0.88 (s, 3H), 0.86 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 134.6, 131.3, 123.9, 122.0, 91.7, 86.7, 78.6, 68.4, 67.4, 64.0, 58.5, 38.1, 37.2, 27.8, 25.9, 22.6; IR $\nu_{max}$ 3400, 2949, 2927, 1629, 1604, 1461, 1384, 1230, 1107, 1094, 1035, 989 cm$^{-1}$; MS (EI, 70 eV) *m/z* 294 ($M^{+\bullet}$, 5%), 276 (15), 220 (100), 150 (53); HRMS ($M^{+\bullet}$) calcd for $C_{17}H_{26}O_4$ 294.1831, found 294.1832.

**Reaction Sequence Leading to Phomentrioloxin A Analogue 11**

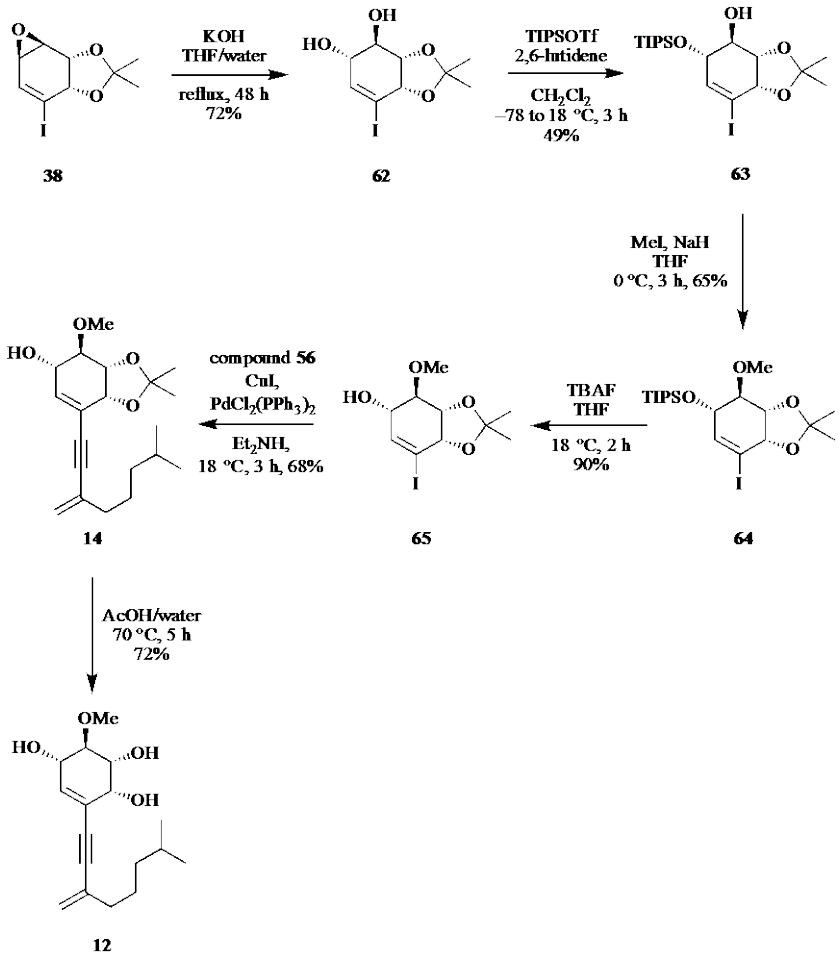



**(3a*R*,4*R*,5*R*,7a*R*)-4,5-Dimethoxy-2,2-dimethyl-7-(7-methyl-3-methyleneoct-1-yn-1-yl)- 3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxole (61)**. Cuprous iodide (26 mg, 0.14 mmol) and $PdCl_2(PPh_3)_2$ (63 mg, 0.09 mmol) were added to a magnetically stirred solution of compounds **35** (306 mg, 0.90 mmol) and **56** (184 mg, 1.35 mmol) in diethylamine (10 mL) maintained under under a nitrogen atmosphere. After stirring at 18 °C for 3 h the reaction mixture was concentrated under reduced pressure and the ensuing residue subjected to flash chromatography (silica, 1:5 v/v ethyl acetate/hexane gradient elution). Concentration of the appropriate fractions ($R_f$ = 0.5 in 2:2.5:5.5 v/v/v ethyl acetate/dichloromethane/hexane) then gave compound **61** (179 mg, 96%) as a pale-yellow oil, $[\alpha]^{20}_D = -54$ ($c$ = 0.5, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.23 (d, $J$ = 3.9 Hz, 1 H), 5.34 (d, $J$ = 2.0 Hz, 1 H), 5.24 (complex m, 1 H), 4.63 (d, $J$ = 6.2 Hz, 1 H), 4.44 (t, $J$ = 6.1 Hz, 1H), 4.02 (m, 1 H), 3.65 (dd, $J$ = 6.1 and 3.3 Hz, 1H), 3.51 (s, 3H), 3.43 (s, 3H), 2.14 (m, 2H), 1.56–1.49 (complex m, 3H), 1.44 (s, 3H), 1.38 (s, 3H), 1.19–1.15 (complex m, 2H), 0.87 (d, $J$ = 6.6 Hz, overlapped 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 133.5, 131.6, 123.2, 121.5, 109.4, 90.9, 87.2, 79.0, 74.2, 74.0, 73.8, 58.8, 57.3, 38.1, 37.3, 27.8, 27.5, 25.8, 25.5, 22.6; IR $\nu_{max}$ 2984, 2934, 2193, 1605, 1463, 1369, 1234, 1115,

1081, 974 $cm^{-1}$; MS (EI, 70 eV) *m/z* 348 ($M^{+\bullet}$, 3%), 333 (6), 234 (17), 115 (100), 75 (15); HRMS ($M^{+\bullet}$) calcd for $C_{21}H_{32}O_4$ 348.2316, found 348.2301.

**(1*R*,2*R*,5*R*,6*S*)-5,6-Dimethoxy-3-(7-methyl-3-methyleneoct-1-yn-1-yl)cyclohex-3-ene-1,2-diol (11)**. Compound **61** (121 mg, 0.35 mmol) was treated with acetic/water (10 mL of a 7:3 v/v mixture). The ensuing mixture was heated at 70 °C for 14 h then concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, 1:6:3 v/v/v methanol/ethyl acetate/hexane elution) delivered, after concentration of the appropriate fractions ($R_f$ = 0.5 in 1:4:5 v/v/v methanol/ethyl acetate/hexane), compound **11** (64 mg, 60%) as a light-yellow semi-solid, $[\alpha]^{20}_D = -135$ ($c$ = 0.5, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.24 (dd, $J$ = 4.5 and 0.6 Hz, 1H), 5.35 (d, $J$ = 2.0 Hz, 1H), 5.26 (dd, $J$ = 2.3 and 1.0 Hz, 1H), 4.34 (d, $J$ = 4.1 Hz, 1H), 4.16 (dd, $J$ = 8.8 and 4.1 Hz, 1H), 4.10 (t, $J$ = 4.4 Hz, 1H), 3.69 (dd, $J$ = 8.8 and 3.8 Hz, 1H), 3.50 (s, 3H), 3.46 (s, 3H), 2.94 (broad s, 2H), 2.16–2.12 (complex m, 2H), 1.57–1.49 (complex m, 3H), 1.19–1.15 (complex m, 2H), 0.87 (overlapping d, $J$ = 6.6 Hz, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 132.3, 131.4, 124.7, 121.9, 91.4, 87.0, 77.4, 72.6, 68.7, 67.5, 58.0, 57.6, 38.1, 37.2, 27.7, 25.8, 22.6; IR $\nu_{max}$ 3307 (broad), 2952, 2871, 1603, 1465, 1316, 1103, 885 $cm^{-1}$; MS (ESI, +ve) *m/z* 331 [$(M+Na)^+$, 100%]; HRMS $(M+Na)^+$ calcd for $C_{18}H_{28}O_4Na$, 331.1885, found 331.1888.

**Reaction Sequence Leading to Phomentrioloxin A Analogues 12 and 14**




**(3a*S*,4*S*,5*S*,7a*S*)-7-Iodo-2,2-dimethyl-5-((triisopropylsilyl)oxy)-3a,4,5,7a-tetrahydro-benzo[*d*][1,3]dioxol-4-ol (63)**. Trisopropylsilyl trifluoromethanesulfonate (1.02 mL, 3.78 mmol) was added, dropwise, to a magnetically stirred solution of compound **62**[17] (982 mg, 3.15 mmol) and 2,6-lutidine (1.5 mL, 12.90 mmol) in dichloromethane (25 mL) maintained at −78 °C under a nitrogen atmosphere. The ensuring mixture was allowed to warm to 18 °C over 3 h then treated with $NH_4Cl$ (60 mL of a saturated aqueous solution).

The separated aqueous phase was extracted with dichloromethane (1 x 40 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting light yellow-oil was subjected to flash chromatography (silica, 3:100 v/v ethyl acetate/hexane gradient elution) to give, after concentration of the appropriate fractions ($R_f$ = 0.3 in 0.5:2.5:5.5 v/v/v ethyl acetate/ dichloromethane/ hexane), compound **63** (722 mg, 49%) as a clear, colorless oil, $[\alpha]^{20}_D$ = +12.6 (*c* = 0.34, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.42 (d, *J* = 1.2 Hz, 1H), 4.67 (d, *J* = 6.6 Hz, 1H), 4.17 (d, *J* = 8.2 Hz, 1H), 4.11 (dd, *J* = 9.0 and 6.7 Hz, 1H), 3.56 (t, *J* = 8.6 Hz, 1H), 2.41 (broad s, 1H), 1.55 (s, 3H), 1.41 (s, 3H), 1.15–1.05 (complex m, 21H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 136.4, 117.7, 110.9, 77.4, 77.1, 74.6, 72.6, 28.1, 25.8, 18.0(0), 17.9(8), 12.4; IR $\nu_{max}$ 3416, 2943, 2892, 2867, 1644, 1463, 1383, 1336, 1248, 1070, 1015, 997, 882, 829, 682 cm$^{-1}$; MS (EI, 70 eV) *m/z* 453 [$(M\text{-}CH_3\bullet)^+$, 5%], 367 (41), 240 (100), 131 (33); HRMS $(M\text{-}CH_3\bullet)^+$ calcd for $C_{17}H_{30}{}^{127}IO_4Si$ 453.0958, found 453.0957.

**(((3a*S*,4*S*,5*S*,7a*S*)-7-Iodo-4-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]-dioxol-5-yl)oxy)triisopropylsilane (64)**. Sodium hydride (300 mg of a 60% dispersion in mineral oil, 7.50 mmol) was added to a magnetically stirred solution of compound **63** (1.16 g, 2.48 mmol) and iodomethane (460 μL, 7.39 mmol) in dry THF (25 mL) maintained at 0 °C under a nitrogen atmosphere. Stirring was continued at 0 to 18 °C for 3 h then the reaction mixture was treated with ice/water (60 mL) (CAUTION: possibility of hydrogen generation). The separated aqueous phase was extracted with ethyl acetate (1 x 25 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuring light-yellow oil was subjected to flash

chromatography (silica, 1:50 v/v ethyl acetate/hexane elution) to give, after concentration of the appropriate fractions ($R_f$ = 0.4 in 0.5:2.5:5.5 v/v/v ethyl acetate/ dichloromethane/ hexane), compound **64** (780 mg, 65%) as a clear, light-yellow oil, $[\alpha]^{20}_D$ = +33.1 (*c* = 1.0, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.55 (d, *J* = 3.2 Hz, 1H), 4.60 (d, *J* = 6.0 Hz, 1H), 4.18 (t, *J* = 6.0 Hz, 1H), 4.04 (t, *J* = 5.6 Hz, 1H), 3.58–3.48 (complex m, 1H), 3.40 (s, 3H), 1.48 (s, 3H), 1.38 (s, 3H), 1.15–1.06 (complex m, 21H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 137.9, 110.1, 99.5, 81.2, 78.4, 77.9, 71.1, 57.6, 27.7, 26.1, 18.1, 18.0, 12.5; IR $\nu_{max}$ 2941, 2866, 1635, 1463, 1381, 1251, 1214, 1125, 1075, 975, 882, 679 cm$^{-1}$; MS (EI, 70 eV) *m/z* 467 [(M-$CH_3$•)$^+$, 12%], 439 (46), 254 (100), 222 (64), 145 (73). HRMS (M-$CH_3$•)$^+$ calcd for $C_{18}H_{32}{}^{127}IO_4Si$ 467.1115, found 467.1110.

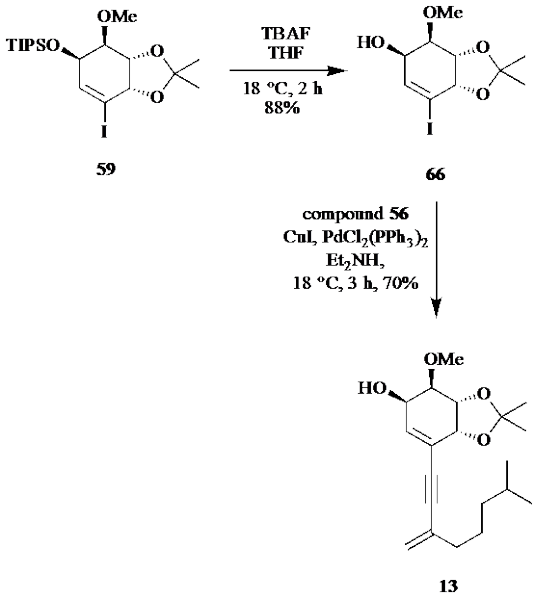
**(3a*S*,4*R*,5*S*,7a*S*)-7-Iodo-4-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]-diox-l-5-ol (65)**. A magnetically stirred solution of compound **64** (972 mg, 2.02 mmol) in THF (10 ml) maintained at 18 °C under a nitrogen atmosphere was treated with tetra-*n*-butylammonium fluoride (3 mL of 1.0 M solution in THF, 3.00 mmol). After 2 h the reaction mixture was concentrated under pressure and the residue so-formed subjected to flash chromatography (silica, 1:2 v/v ethyl acetate/hexane gradient elution). Concentration of the appropriate fractions ($R_f$ = 0.4 in 4:2.5:5.5 v/v/v ethyl acetate/dichloromethane/hexane) then gave compound **65** (592 mg, 90%) as a clear, light-yellow oil, $[\alpha]^{20}_D$ = +42.5 (*c* = 0.4, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.51 (s, 1H), 4.67 (d, *J* = 6.7 Hz, 1H), 4.12 (t, *J* = 6.7 Hz, 1H), 3.64–3.58 (complex m, 2H), 3.46 (s, 3H), 2.85 (broad s, 1H), 1.52 (s, 3H), 1.39 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 140.3, 110.3, 93.2, 81.3, 79.5, 77.2, 72.4, 57.5, 28.1, 25.8; IR $\nu_{max}$ 3399, 2987, 2932, 2830, 164

2, 1457, 1380, 1252, 1074, 945, 869 $cm^{-1}$; MS (EI, 70 eV) *m/z* 326 (8%), 310 [(M-$CH_3$•)$^+$, 73], 225 (32), 101 (100), 55 (51); HRMS (M-$CH_3$•)$^+$ calcd for $C_9H_{12}{}^{127}IO_4$ 310.9780, found 310.9778.

**(3a*R*,4*R*,5*S*,7a*R*)-4-Methoxy-2,2-dimethyl-7-(7-methyl-3-methyleneoct-1-yn-1-yl)-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-5-ol (14)**. Cuprous iodide (25 mg, 0.13 mmol) and $PdCl_2(PPh_3)_2$ (59 mg, 0.09 mmol) were added to a magnetically stirred solution of compounds **65** (275 mg, 0.85 mmol) and **56** (230 mg, 1.69 mmol) in anhydrous diethylamine (3 mL) maintained at 18 °C under a nitrogen atmosphere. After 3 h the reaction mixture was concentrated under reduced pressure and the residue obtained subjected to flash chromatography (silica, 2:5 v/v ethyl acetate/ hexane gradient elution). Concentration of the appropriate fractions ($R_f$ = 0.5 in 4:2.5:5.5 v/v/v ethyl acetate/ dichloromethane/hexane) then gave compound **14** (192 mg, 68%) as a clear, light-yellow oil, $[\alpha]^{20}_D$ = +11.5 (*c* = 0.2, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.19 (d, *J* = 1.8 Hz, 1H), 5.36 (s, 1H), 5.27 (s, 1H), 4.58 (d, *J* = 6.4 Hz, 1H), 4.10 (dd, *J* = 9.0 and 6.5 Hz, 1H), 3.73 (d, *J* = 8.9 Hz, 1H), 3.64 (t, *J* = 8.9 Hz, 1H), 3.47 (s, 3H), 2.75 (s, 1H), 2.16 (t, *J* = 7.6 Hz, 2H), 1.58–1.49 (complex m, 3H), 1.53 (s, 3H), 1.40 (s, 3H), 1.21–1.15 (complex m, 2H), 0.88 (s, 3H), 0.87 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 135.6, 131.4, 121.9, 119.5, 110.8, 91.0, 86.4, 79.7, 77.3, 74.5, 72.5, 57.3, 38.1, 37.2, 28.2, 27.8, 25.9, 25.8, 22.6; IR $\nu_{max}$ 3354, 2922, 2883, 2861, 1649, 1465, 1382, 1259, 1123, 1060, 1022, 988 $cm^{-1}$; MS (EI, 70 eV) *m/z* 319 [(M-$CH_3$•)$^+$, 23%,], 259 (42), 247 (63), 115 (18), 101 (100); HRMS ($M^{+\bullet}$) calcd for $C_{20}H_{30}O_4$ 334.2144, found 334.2140.

**(1*R*,2*R*,3*R*,4*S*)-3-Methoxy-6-(7-methyl-3-methyleneoct-1-yn-1-yl)cyclohex-5-ene-1,2,4-triol (12)**. Compound **14** (360 mg, 1.08 mmol) was treated with acetic/water (10 mL of a 4:1 v/v mixture) and the solution thus obtained was heated at 70 °C for 5 h then cooled and concentrated under reduced pressure. Subjection of the ensuring light-yellow residue to flash chromatography (silica, 1:6:3 v/v/v methanol/ethyl acetate/ hexane gradient elution) delivered, after concentration of the appropriate fractions ($R_f$ = 0.5 in 1:7:2 v/v/v methanol/ethyl acetate/ hexane), compound **12** (228 mg, 72%) as a clear, light-yellow oil, $[\alpha]^{20}_D = -31.7$ ($c$ = 0.7, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.15 (d, $J$ = 2.2 Hz, 1H), 5.37 (s, 1H), 5.28 (s, 1H), 4.32 (d, $J$ = 4.1 Hz, 1H), 3.89–3.84 (complex m, 1H), 3.80 (dd, $J$ = 7.9 and 2.3 Hz, 1H), 3.60 (d, $J$ = 10.0 Hz, 1H), 3.49 (s, 3H), 3.03 (broad s, 1H), 2.92 (broad s, 1H), 2.67 (broad s, 1H), 2.16 (t, $J$ = 7.7 Hz, 2H), 1.57–1.50 (complex m, 3H), 1.25–1.16 (complex m, 2H), 0.89 (s, 3H), 0.87 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 134.1, 131.4, 123.2, 121.8, 90.6, 87.4, 81.2, 71.1, 70.0, 69.9, 57.1, 38.1, 37.2, 27.8, 25.8, 22.6; IR $\nu_{max}$ 3399, 2954, 2928, 1627, 1462, 1384, 1234, 1185, 1096, 1081, 952 cm$^{-1}$; MS (EI, 70 eV) *m/z* 294 ($M^{+\bullet}$, 12%), 279 (14), 277 (100), 276 (43); HRMS ($M^{+\bullet}$) calcd for $C_{17}H_{26}O_4$ 294.1831 found 294.1833.

**Reaction Sequence Leading to Phomentrioloxin A Analogue 13**



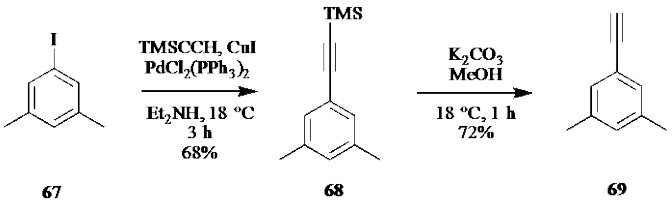

**(3a*S*,4*R*,5*R*,7a*S*)-7-Iodo-4-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]-dioxol-5-ol (66)**. A magnetically stirred solution of compound **59** (972 mg, 2.02 mmol) in THF (10 ml) maintained at 18 °C under a nitrogen atmosphere was treated with tetra-*n*-butylammonium fluoride (3 mL of 1.0 M solution in THF, 3.00 mmol). After 2 h the reaction mixture was concentrated under pressure and the residue so-formed subjected to flash chromatography (silica, 1:2 v/v ethyl acetate/hexane gradient elution). Concentration of the appropriate fractions ($R_f$ = 0.4 in 4:2.5:5.5 v/v/v ethyl acetate/dichloromethane/hexane) then gave compound **66** (578 mg, 88%) as a white, crystalline solid, mp = 65–66 °C, $[\alpha]^{20}_D$ = +51 ($c$ = 0.5, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.42 (d, $J$ = 2.9 Hz, 1H), 4.57 (d, $J$ = 5.3 Hz, 1H), 4.48–4.45 (complex m, 1H), 4.28–4.25 (complex m, 1H), 3.81–3.77 (complex m, 1H), 3.52 (s, 3H), 2.62 (broad s,

1H), 1.41 (s, 3H), 1.38 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 140.1, 110.0, 100.1, 78.6, 78.2, 73.6, 66.9, 59.3, 27.6, 26.3; IR $\nu_{max}$ 3455, 2985, 2933, 2830, 1631, 1456, 1380, 1372, 1230, 1108, 1076, 1039, 959, 867 cm$^{-1}$; MS (EI, 70 eV) *m/z* 326 (7%), 311 [(M-$CH_3$•)$^+$, 2%] 223 (9), 115 (100), 43 (15); HRMS (M-$CH_3$•)$^+$ calcd for $C_9H_{12}{}^{127}IO_4$ 310.9780, found 310.9781.

**(3a*R*,4*R*,5*R*,7a*R*)-4-Methoxy-2,2-dimethyl-7-(7-methyl-3-methyleneoct-1-yn-1-yl)-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-5-ol (13)**. Cuprous iodide (50 mg, 0.25 mmol) and $PdCl_2(PPh_3)_2$ (118 mg, 0.17 mmol) were added to a magnetically stirred solution of compounds **66** (550 mg, 1.68 mmol) and **56** (460 mg, 3.38 mmol) in anhydrous diethylamine (3 mL) maintained at 18 °C under a nitrogen atmosphere. After 3 h the reaction mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash chromatography (silica, 2:5 v/v ethyl acetate/ hexane gradient elution). Concentration of the appropriate fractions ($R_f$ = 0.5 in 4:2.5:5.5 v/v/v ethyl acetate/ dichloromethane/hexane) then gave compound **13** (397 mg, 70%) as a clear, light-yellow oil, $[\alpha]^{20}_D$ = −9.0 (*c* = 1.4, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.11 (d, *J* = 3.5 Hz, 1H), 5.35 (d, *J* = 2.0 Hz, 1H), 5.25 (d, *J* = 1.9 Hz, 1H), 4.57 (d, *J* = 5.7 Hz, 1H), 4.48 (t, *J* = 5.5 Hz, 1H), 4.39 (dt, *J* = 8.6, 4.0 Hz, 1H), 3.68–3.65 (complex m, 1H), 3.53 (s, 3H), 2.54 (d, *J* = 8.3 Hz, 1H), 2.15 (t, *J* = 7.5 Hz, 2H), 1.61–1.47 (complex m, 3H), 1.43 (s, 3H), 1.39 (s, 3H), 1.21–1.13 (complex m, 2H), 0.88 (s, 3H), 0.86 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 135.5, 131.6, 122.5, 121.5, 109.7, 90.7, 87.2, 79.6, 73.7, 73.1, 64.7, 58.9, 38.2, 37.3, 27.8, 27.7, 26.0, 25.8, 22.6; IR $\nu_{max}$ 3454, 2980, 2949, 2935, 2896, 2865, 1631, 1604, 1461, 1379, 1231, 1109, 1076, 1037, 985 cm$^{-1}$; MS (EI, 70 eV) *m/z* 334

($M^{+\bullet}$, 3%), 319 (7), 259 (5), 247 (12), 115 (100); HRMS ($M^{+\bullet}$) calcd for $C_{20}H_{30}O_4$ 334.2144, found 334.2142.

**Reaction Sequence Leading to the Side-Chain Synthon 69 for the Preparation of Analogues 15-20**



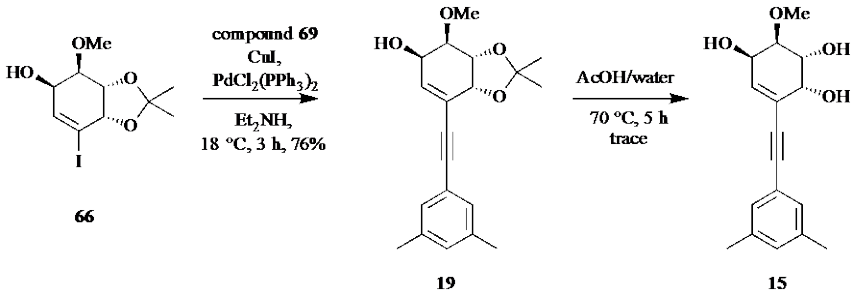

67 68 69

**((3,5-Dimethylphenyl)ethynyl)trimethylsilane (68)**. Commercially available 1-iodo-3,5-dimethylbenzene **67** (300 mg, 1.29 mmol), $PdCl_2(PPh_3)_2$ (45 mg, 0.07 mmol) and cuprous iodide (12 mg, 0.07 mmol) were placed in an oven-dried flask under a nitrogen atmosphere. Dry diethylamine was added and the resulting suspension stirred magnetically while being cooled at 0 °C. Trimethylsilylacetylene (0.28 mL, 1.94 mmol) was then added dropwise to the reaction mixture that was then allowed to warm to 18 °C and stirred at this temperature for 3 h. The reaction mixture was then concentrated under reduced pressure and diethyl ether (20 mL) added to the residue thus obtained. The ensuing mixture was filtered through a short pad of diatomaceous earth and the filtrate washed with brine (1 x 20 mL) before being dried ($Na_2SO_4$), filtered then concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, pentane elution) delivered, after concentration of the appropriate fractions ($R_f$ = 0.5 in hexane), compound **68**[20] (177 mg, 68%) as a clear, light-yellow syrup. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.11 (s, 2H), 6.95 (s, 1H), 2.28 (s, 6H), 0.24 (s, 9H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 137.7, 130.4, 129.6, 122.7, 105.5, 93.2, 21.1, 0.0(1); IR $\nu_{max}$ 2961,

2922, 2150, 2247, 2107, 1598 $cm^{-1}$; MS (EI, 70 eV) *m/z* 202 ($M^{+\bullet}$, 28%) 187 (100); HRMS ($M^{+\bullet}$) calcd for $C_{13}H_{18}Si$ 202.1178, found 202.1184.

**1-Ethynyl-3,5-dimethylbenzene (69)**. A magnetically stirred solution of compound **68** (850 mg, 4.21 mmol) in MeOH (5 mL) maintained at 18 °C was treated with $K_2CO_3$ (1.63 g, 8.41 mmol) and after 1 h the reaction mixture was filtered through a pad of diatomaceous earth and the filtrate concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, pentane elution) delivered, after concentration of the appropriate fractions ($R_f$ = 0.5 in hexane), compound **69**[20] (396 mg, 72%) as a clear, light-yellow syrup. $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.13 (s, 2H), 6.99 (s, 1H), 3.01 (s, 1H), 2.29 (s, 6H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 137.9, 130.7, 129.8, 121.7, 84.0, 76.4, 21.1; IR $\nu_{max}$ 3307, 3039, 2922, 2249, 2108, 1600, 1475 $cm^{-1}$; MS (EI, 70 eV) *m/z* 130 ($M^{+\bullet}$, 60%), 102 (100); HRMS ($M^{+\bullet}$) calcd for $C_{10}H_{10}$ 130.0783, found 130.9920.

**Reaction Sequence Leading to Phomentrioloxin A Analogues 15 and 19**

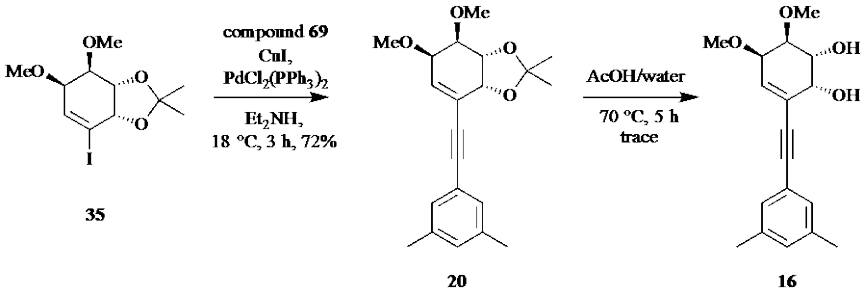



**(3a*R*,4*R*,5*R*,7a*R*)-7-((3,5-Dimethylphenyl)ethynyl)-4-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-5-ol (19)**. Compound **66** (250 mg, 0.77 mmol), $PdCl_2(PPh_3)_2$ (27 mg, 0.04 mmol) and cuprous iodide (7 mg, 0.04 mmol) were placed in an oven-dried flask under a nitrogen atmosphere. Dry diethylamine (10 mL) was then added and the resulting suspension cooled and stirred magnetically at 0 °C. After the dropwise addition of 1-ethynyl-3,5-dimethylbenzene **69** (166 µL, 1.15 mmol) was complete, the reaction mixture was stirred at 18 °C for 3 h then concentrated under reduced pressure and diethyl ether (20 mL) was added to the residue thus obtained. The ensuing mixture was filtered through a pad of diatomaceous earth and the filtrate washed with brine (1 x 30 mL) before being dried ($Na_2SO_4$), filtered and then concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) delivered, after concentration of the appropriate fractions ($R_f$ = 0.4 in 1:6 v/v ethyl acetate/hexane), compound **19** (191 mg, 76%) as a clear, yellow syrup, $[\alpha]^{20}_D$ = +54.5 ($c$ = 0.2, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.11 (s, 2H), 6.94 (s, 1H), 6.19 (d, $J$ = 3.5 Hz, 1H), 4.65 (d, $J$ = 5.7 Hz, 1H), 4.52 (t, $J$ =

5.5 Hz, 1H), 4.45–4.42 (complex m, 1H), 3.71 (t, $J$ = 4.7 Hz, 1H), 3.55 (s, 3H), 2.58 (d, $J$ = 8.6 Hz, 1H), 2.28 (s, 6H), 1.45 (s, 3H), 1.42 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 137.7, 135.6, 130.3, 129.5, 122.5, 122.5, 109.8, 90.4, 86.8, 79.6, 73.7, 73.1, 64.8, 59.0, 27.7, 26.0, 21.1; IR $\nu_{max}$ 3455, 2986, 2934, 2831, 1597, 1456, 1233, 1164, 1076, 955, 872, 689 cm$^{-1}$; MS (EI, 70 eV) *m/z* 328 ($M^{+\bullet}$, 100%), 313 (48), 296 (7); HRMS ($M^{+\bullet}$) calcd for $C_{20}H_{24}O_4$ 328.1675, found 328.1675.

**(1*R*,2*R*,3*R*,4*R*)-6-((3,5-Dimethylphenyl)ethynyl)-3-methoxycyclohex-5-ene-1,2,4-triol (15)**. Compound **19** (50 mg, 0.15 mmol) was treated with acetic/water (10 mL of a 7:3 v/v mixture) and the resulting solution heated at 70 °C for 5 h then cooled and concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, 1:6:3 v/v/v methanol/ethyl acetate/hexane gradient elution) gave, after concentration of the appropriate fractions ($R_f$ = 0.4 in 9:1 v/v ethyl acetate/hexane), compound **15** (trace) as a white, crystalline solid, mp = 157–159 ºC, $[\alpha]^{20}_D$ = −33.3 ($c$ = 0.35, $CHCl_3$). $^1$H NMR [$(CD_3)_2CO$, 400 MHz] $\delta$ 6.84 (s, 2H), 6.77 (s, 1H), 5.85 (d, $J$ = 3.8 Hz, 1H), 4.25–4.22 (complex m, 1H), 4.00 (dd, $J$ = 12.8 and 5.2 Hz, 1H), 3.92 (dd, $J$ = 7.6 and 3.8 Hz, 1H), 3.79 (d, $J$ = 4.0 Hz, 1H), 3.50 (d, $J$ = 7.2 Hz, 1H), 3.39 (dd, $J$ = 7.4 and 4.0 Hz, 1H), 3.26 (s, 3H), 2.68 (s, 6H) (signal due to hydroxyl group proton not observed); $^{13}$C NMR [$(CD_3)_2CO$, 100 MHz] $\delta$ 139.6, 137.7, 131.6, 130.7, 125.8, 124.7, 90.8, 89.8, 81.5, 69.9, 69.8, 66.3, 59.6, 21.8; IR $\nu_{max}$ 3389, 3303, 2915, 2848, 1597, 1432, 1381, 1251, 1093, 1060, 1034, 849, 686 cm$^{-1}$; MS (EI, 70 eV) *m/z* 288 ($M^{+\bullet}$, 100%), 277 (17), 270 (86), 255 (95); HRMS ($M^{+\bullet}$) calcd for $C_{17}H_{20}O_4$ 288.1362, found 288.1360.

**Reaction Sequence Leading to Phomentrioloxin A Analogues 16 and 20**

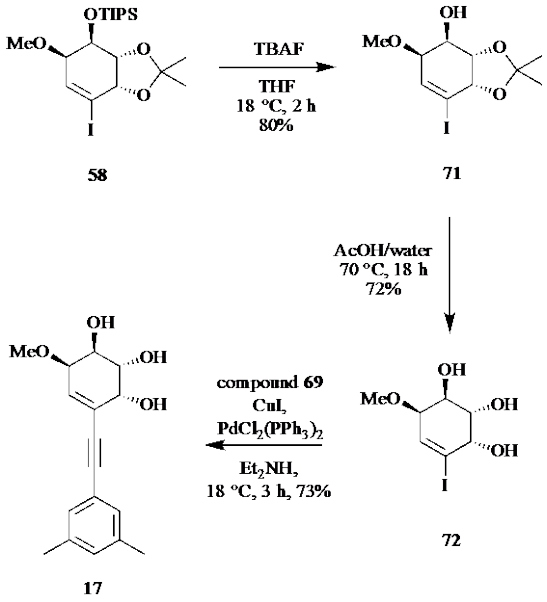



**(3a*R*,4*R*,5*R*,7a*R*)-7-((3,5-Dimethylphenyl)ethynyl)-4,5-dimethoxy-2,2-dimethyl-3a,4, -5,7a-tetrahydrobenzo[*d*][1,3]dioxole (20)**. Compound **35** (100 mg, 0.30 mmol), $PdCl_2(PPh_3)_2$ (11 mg, 0.02 mmol) and cuprous iodide (3 mg, 0.02 mmol) were placed in an oven-dried flask under a nitrogen atmosphere. Dry diethylamine (10 mL) was added and the resulting suspension was cooled and magnetically stirred at 0 °C. After the dropwise addition of 1-ethynyl-3,5-dimethylbenzene (**69**) (65 µL, 0.44 mmol) the reaction mixture was stirred at 18 °C for 3 h then concentrated under reduced pressure. The ensuing residue was treated with diethyl ether (10 mL) and the mixture thus obtained filtered through a pad of diatomaceous earth and the filtrate washed with brine (1 x 20 mL) before being dried ($Na_2SO_4$), filtered then concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane gradient elution) gave, after concentration of the appropriate fractions ($R_f$ = 0.5 in 1:5 v/v ethyl acetate/hexane), compound **20** (72 mg, 72%) as a clear, yellow syrup, $[\alpha]^{20}_D = -7.3$ ($c$ = 0.3, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.11 (s, 2H), 6.94 (s, 1H), 6.32 (d, $J$ = 3.9 Hz, 1H), 4.71 (d, $J$ = 6.1 Hz, 1H), 4.48 (t, $J$ = 6.1 Hz, 1H), 4.07

(t, $J$ = 3.6 Hz, 1H), 3.69 (dd, $J$ = 6.0 and 3.3 Hz, 1H), 3.54 (s, 3H), 3.46 (s, 3H), 2.28 (s, 6H), 1.48 (s, 3H), 1.42 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 137.7, 133.6, 130.3, 129.5, 123.2, 122.6, 109.5, 90.7, 86.9, 79.1, 74.3, 74.1, 74.0, 58.9, 57.4, 27.6, 25.6, 21.1; IR $\nu_{max}$ 2985, 2933, 2827, 1598, 1457, 1212, 1164, 1076, 932, 851, 689 cm$^{-1}$; MS (EI, 70 eV) *m/z* 342 ($M^{+\bullet}$, 100%), 327 (64), 300 (13); HRMS ($M^{+\bullet}$) calcd for $C_{21}H_{26}O_4$ 342.1831, found 342.1830.

**(1*R*,2*R*,5*R*,6*S*)-3-((3,5-Dimethylphenyl)ethynyl)-5,6-dimethoxycyclohex-3-ene-1,2-diol (16)** Compound **20** (50 mg, 0.15 mmol) was treated with acetic/water (10 mL of a 7:3 v/v mixture) and the resulting solution was heated at 70 °C for 5 h then cooled and concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, 9:1 v/v ethyl acetate/hexane gradient elution) gave, after concentration of the appropriate fractions ($R_f$ = 0.4 in 9:1 v/v ethyl acetate/hexane), compound **16** (trace) as light-yellow oil, $[\alpha]^{20}_D$ = −79.4 ($c$ = 0.82, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.10 (s, 2H), 6.96 (s, 1H), 6.35 (d, $J$ = 4.5 Hz, 1H), 4.43 (d, $J$ = 4.5 Hz, 1H), 4.21 (dd, $J$ = 9.0 and 3.7 Hz, 1H), 4.13 (t, $J$ = 4.2 Hz, 1H), 3.72 (dd, $J$ = 8.9 and 3.8 Hz, 1H), 3.53 (s, 3H), 3.50 (s, 3H), 2.80 (s, 1H), 2.74 (s, 1H), 2.29 (s, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 137.8, 132.3, 130.5, 129.4, 124.8, 122.2, 91.1, 86.7, 77.5, 72.7, 68.7, 67.6, 58.0, 57.6, 21.0; IR $\nu_{max}$ 3412, 2920, 2825, 1629, 1597, 1464, 1194, 1098, 990, 850, 689 cm$^{-1}$; MS (EI, 70 eV) *m/z* 302 ($M^{+\bullet}$, 4%), 254 (6), 228 (100), 157 (30); HRMS ($M^{+\bullet}$) calcd for $C_{18}H_{22}O_4$ 302.1518, found 302.1519.

**Reaction Sequence Leading to Phomentrioloxin A Analogue 17**




**(3aS,4R,5R,7aS)-7-Iodo-5-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]-dioxol-4-ol (71).** A magnetically stirred solution of compound **58** (100 mg, 0.21 mmol) in THF (10 ml) maintained at 18 °C under a nitrogen atmosphere was treated with tetra-*n*-butylammonium fluoride (0.3 mL of 1.0 M solution in THF, 0.30 mmol). After 2 h the reaction mixture was concentrated under pressure. The residue so-formed was subjected to flash chromatography (silica, 1:2 v/v ethyl acetate/hexane gradient elution) to provide, after concentration of the appropriate fractions ($R_f$ = 0.4 in 4:2.5:5.5 v/v/v ethyl acetate/dichloromethane/hexane), compound **71** (54 mg, 80%) as a white, crystalline solid, mp = 65–66 °C, $[\alpha]^{20}_D$ = −29.4 ($c$ = 0.35, $CHCl_3$).$^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.42 (d, $J$ = 2.6 Hz, 1H), 4.64 (dd, $J$ = 5.0 and 1.6 Hz, 1H), 4.41 (t, $J$ = 4.9 Hz, 1H), 4.39–4.36 (complex m, 1H), 3.88–3.86 (complex m, 1H), 3.46 (s, 3H), 2.42 (d, $J$ = 2.4 Hz,

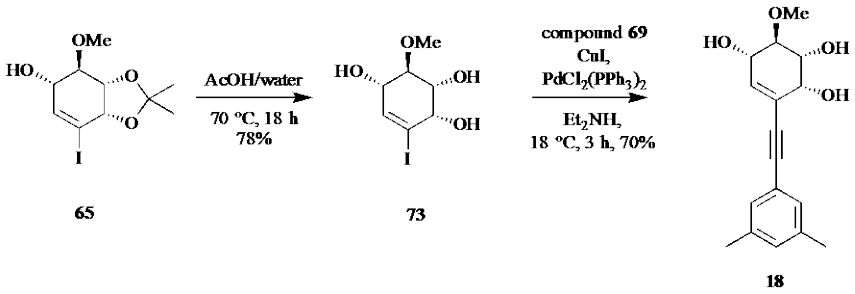
1H), 1.42 (s, 3H), 1.40 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 136.2, 109.8, 101.2, 78.3, 76.6, 75.8, 66.9, 57.1, 27.6, 26.2; IR $\nu_{max}$ 3520, 2998, 2988, 2934, 2872, 2828, 1627, 1458, 1379, 1148, 1082, 1051, 1025, 996, 930, 897 cm$^{-1}$; MS (EI, 70 eV) *m/z* 326 ($M^{+\bullet}$, 14%), 310 (21), 267 (20), 101 (100); HRMS ($M^{+\bullet}$) calcd for $C_{10}H_{15}{}^{127}IO_4$ 326.0015, found 326.0016.

**(1*S*,2*S*,3*S*,6*R*)-4-Iodo-6-methoxycyclohex-4-ene-1,2,3-triol (72)**. Compound **71** (50 mg, 0.10 mmol) was dissolved in acetic/water (10 mL of a 7:1 v/v mixture) and the resulting solution was heated at 70 °C for 18 h then cooled and concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, 1:6:3 v/v/v methanol/ethyl acetate/ hexane gradient elution) gave, after concentration of the appropriate fractions ($R_f$ = 0.4 in 1:7:2 v/v/v methanol/ethyl acetate/hexane), compound **72** (32 mg, 72%) as a white, crystalline solid, mp = 117 °C, $[\alpha]^{20}_D$ = −111.3 (*c* = 0.3, $CHCl_3$). $^1$H NMR [$(CD_3)_2SO$, 400 MHz] $\delta$ 6.29 (d, *J* = 1.4 Hz, 1H), 5.18–5.15 (complex m, 1H), 4.99 (s, 1H), 4.82 (d, *J* = 4.3 Hz, 1H), 3.99 (broad s, 2H), 3.83–3.77 (complex m, 2H), 3.36 (s, 3H); $^{13}$C NMR [$(CD_3)_2SO$, 400 MHz] $\delta$ 136.4, 106.9, 76.9, 70.5, 70.1, 67.7, 55.8; IR $\nu_{max}$ 3354, 2923, 2857, 2821, 1628, 1461, 1384, 1186, 1098, 1069, 967, 917, 878 cm$^{-1}$; MS (EI, 70 eV) *m/z* 326 ($M^{+\bullet}$, >1%), 267 (13), 225 (100), 99 (75); HRMS ($M^{+\bullet}$) calcd for $C_7H_{11}{}^{127}IO_4$ 285.9702, found 285.9696.

**(1*S*,2*R*,3*R*,6*R*)-4-((3,5-Dimethylphenyl)ethynyl)-6-methoxycyclohex-4-ene-1,2,3-triol (17)**. Compound **72** (100 mg, 0.35 mmol), $PdCl_2(PPh_3)_2$ (13 mg, 0.02 mmol) and cuprous iodide (4 mg, 0.02 mmol) were placed in an oven-dried flask under a nitrogen

atmosphere. Dry diethylamine (5 mL) was added and the resulting suspension was cooled and magnetically stirred at 0 °C. After the dropwise addition of 1-ethynyl-3,5-dimethylbenzene (**69**) (101 μL, 0.70 mmol) was complete the reaction mixture was stirred at 18 °C for 3 h then concentrated under reduced pressure and diethyl ether (10 mL) was added to the ensuing residue. The mixture thus obtained was filtered through a pad of diatomaceous earth and the filtrate was washed with brine (1 x 25 mL) then dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. Subjection of the residue so-formed to flash chromatography (silica, 1:6:3 v/v/v methanol/ethyl acetate/hexane gradient elution) delivered, after concentration of the appropriate fractions ($R_f$ = 0.4 in 9:1 v/v ethyl acetate/hexane), compound **17** (73 mg, 73%) as a clear, light yellow oil, $[\alpha]^{20}_D = -101.9$ ($c$ = 0.10, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.10 (s, 2H), 6.96 (s, 1H), 6.29 (d, $J$ = 4.3 Hz, 1H), 4.44 (s, 1H), 4.12–4.08 (complex m, 2H), 4.00 (t, $J$ = 4.2 Hz, 1H), 3.49 (s, 3H), 2.85 (s, 1H), 2.76 (s, 1H), 2.56 (d, $J$ = 5.9 Hz, 1H), 2.29 (s, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 137.9, 131.7, 130.7, 129.4, 125.1, 122.0, 91.6, 86.4, 74.8, 69.4, 68.4, 67.9, 57.4, 21.1; IR $\nu_{max}$ 3400, 2917, 2821, 1597, 1436, 1381, 1256, 1097, 1070, 1035, 849, 688 $cm^{-1}$; MS (EI, 70 eV) *m/z* 288 ($M^{+\bullet}$, 100%), 277 (74), 270 (50); HRMS ($M^{+\bullet}$) calcd for $C_{17}H_{20}O_4$ 288.1362, found 288.1361.

**Reaction Sequence Leading to Phomentrioloxin A Analogue 18**

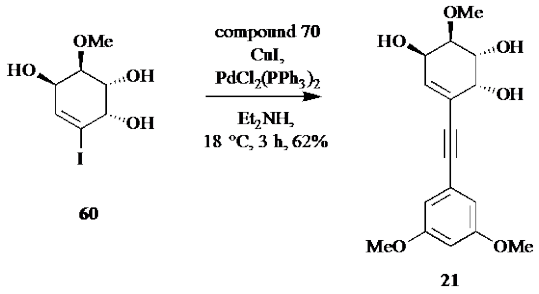



65 73 18

**(1*S*,2*R*,3*R*,4*S*)-6-Iodo-3-methoxycyclohex-5-ene-1,2,4-triol (73)**. Compound **65** (208 mg, 0.43 mmol) was dissolved in acetic/water (10 mL of a 7:1 v/v mixture) and the resulting solution heated at 70 °C for 18 h then cooled and concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, 1:6:3 v/v/v methanol/ethyl acetate/ hexane gradient elution) gave, after concentration of the appropriate fractions ($R_f$ = 0.4 in 1:7:2 v/v/v methanol/ethyl acetate/hexane), compound **73** (142 mg, 78%) as a clear, light-yellow oil, $[\alpha]^{20}_D$ = +2.0 ($c$ = 0.3, $CHCl_3$). $^1$H NMR [$(CD_3)_2CO$, 400 MHz] $\delta$ 6.14 (d, $J$ = 2.5 Hz, 1H), 4.54 (s, 1H), 4.25 (t, $J$ = 4.1 Hz, 1H), 4.14 (s, 1H), 4.02 (s, 1H), 3.73 (dd, $J$ = 10.2 and 7.4 Hz, 1H), 3.64–3.61 (complex m, 1H) 3.54 (apparent d, $J$ = 10.4 Hz, 1H), 3.43 (s, 3H); $^{13}$C NMR [$(CD_3)_2CO$, 100 MHz] $\delta$ 133.0, 125.6, 83.7, 74.9, 73.0, 72.0, 58.4; IR $\nu_{max}$ 3355, 2940, 2929, 2826, 1643, 1454, 1262, 1105, 1076, 1002, 942, 882 cm$^{-1}$; MS (ESI, +ve) *m/z* 309 [$(M+Na)^+$, 58%], 295 (20), 261 (100), 120 (5); HRMS $(M+Na)^+$ calcd for $C_7H_{11}{}^{127}I\ NaO_4$ 308.9600, found 308.9600.

**(1*R*,2*R*,3*R*,4*S*)-6-((3,5-Dimethylphenyl)ethynyl)-3-methoxycyclohex-5-ene-1,2,4-triol (18)**. Compound **73** (50 mg, 0.18 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol) and cuprous iodide (2 mg, 0.01 mmol) were placed in an oven-dried flask under a nitrogen atmosphere. Dry diethylamine (3 mL) was added and the resulting suspension was cooled at and magnetically stirred 0 °C. After the dropwise addition of 1-ethynyl-3,5-dimethylbenzene **69** (51 µL, 0.35 mmol) was complete the reaction mixture was stirred at 18 °C for 3 h then concentrated under reduced pressure and diethyl ether (10 mL) was added to the resulting residue. The mixture thus obtained was filtered through a pad of diatomaceous earth and the filtrate washed with brine (1 x 10 mL) before being dried ($Na_2SO_4$) filtered and then concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, 1:6:3 v/v/v methanol/ethyl acetate/hexane gradient elution) afforded, after concentration of the appropriate fractions ($R_f$ = 0.4 in 9:1 v/v ethyl acetate/hexane), compound **18** (35 mg, 70%) as a clear, light-yellow oil, $[\alpha]^{20}_D$ = +15.0 (*c* = 0.10, $CHCl_3$). $^1$H NMR [$(CD_3)_2CO$, 400 MHz] $\delta$ 7.07 (s, 2H), 7.01 (s, 1H), 6.11 (d, *J* = 2.6 Hz, 1H), 4.35 (d, *J* = 4.7 Hz, 1H), 4.24 (t, *J* = 4.4 Hz, 1H), 4.06 (d, *J* = 3.3 Hz, 1H), 3.86 (d, *J* = 6.3 Hz, 1H), 3.82–3.77 (complex m, 1H), 3.74 (dd, *J* = 7.6 and 2.5 Hz, 1H), 3.47 (s, 3H), 2.77 (s, 1H), 2.28 (s, 6H); $^{13}$C NMR [$(CD_3)_2CO$, 100 MHz] $\delta$ 139.6, 136.7, 131.8, 130.7, 125.2, 124.5, 90.7, 89.9, 83.1, 73.0, 72.3, 71.4, 58.5, 21.8; IR $\nu_{max}$ 3368, 2916, 2857, 2826, 1597, 1455, 1373, 1263, 1099, 1083, 952, 848, 688 $cm^{-1}$; MS (EI, 70 eV) *m/z* 288 ($M^{+\bullet}$, 17%), 277 (40), 228 (100), 185 (57); HRMS ($M^{+\bullet}$) calcd for $C_{17}H_{20}O_4$ 288.1362, found 288.1373.

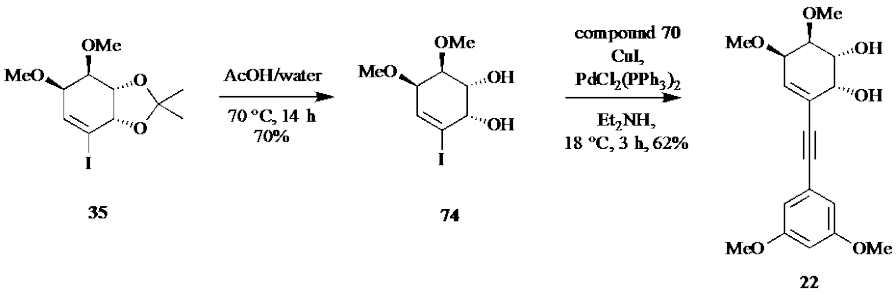
**Reaction Sequence Leading to Phomentrioloxin A Analogue 21**




**(1*R*,2*R*,3*R*,4*R*)-6-((3,5-Dimethoxyphenyl)ethynyl)-3-methoxycyclohex-5-ene-1,2,4-triol (21)**. Compound **60** (200 mg, 0.70 mmol), $PdCl_2(PPh_3)_2$ (25 mg, 0.04 mmol) and cuprous iodide (7 mg, 0.04 mmol) were placed in an oven-dried flask under a nitrogen atmosphere. Dry diethylamine (10 mL) was added and the resulting suspension was cooled and magnetically stirred at 0 °C. After the dropwise addition of commercially available 1-ethynyl-3,5-dimethoxybenzene **70** (252 µL, 1.40 mmol) was complete the ensuing mixture was stirred at 18 °C for 3 h then concentrated reduced pressure and diethyl ether (25 mL) was added. The mixture thus obtained was filtered through a pad of diatomaceous earth and the filtrate washed with brine (1 x 25 mL) before being dried ($Na_2SO_4$) filtered and concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, 1:6:3 v/v/v methanol/ethyl acetate/hexane gradient elution) delivered, after concentration of the appropriate fractions ($R_f$ = 0.4 in 9:1 v/v ethyl acetate/hexane), compound **21** (139 mg, 62%) as a clear, light-yellow oil, $[\alpha]^{20}_D = -38.3$ ($c$ = 1.1, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.62 (d, $J$ = 2.4 Hz, 2H), 6.46 (t, $J$ = 2.4 Hz, 1H), 6.26 (d, $J$ = 4.2 Hz, 1H), 4.52 (d, $J$ = 4.9 Hz, 1H), 4.41 (s,

1H), 4.24–4.21 (complex m, 1H), 3.78 (s, 6H), 3.71 (dd, J = 7.9 and 4.1 Hz, 1H), 3.55 (s, 3H), 2.69 (s, 1H), 2.67 (s, 1H), 2.51 (d, $J$ = 6.0 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 160.5, 135.3, 123.8, 123.7, 109.5, 102.2, 91.0, 86.5, 78.6, 68.3, 67.4, 64.0, 58.5, 55.4; IR $\nu_{max}$ 3400, 2936, 2839, 1589, 1455, 1420, 1205, 1156, 1095, 1063, 989, 869, 681 $cm^{-1}$; MS (EI, 70 eV) *m/z* 320 ($M^{+\bullet}$, 23%), 273 (18), 246 (100), 189 (39); HRMS ($M^{+\bullet}$) calcd for $C_{17}H_{20}O_6$ 320.1260, found 320.1260.

**Reaction Sequence Leading to Phomentrioloxin A Analogue 22**



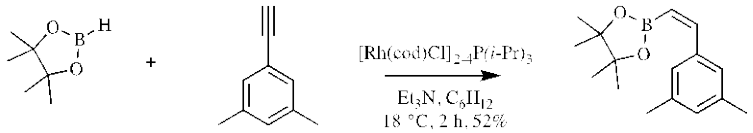

35 74 22

**(1*R*,2*S*,5*R*,6*S*)-3-Iodo-5,6-dimethoxycyclohex-3-ene-1,2-diol (74)**. Compound **35** (120 mg, 0.35 mmol) was treated with acetic/water (5 mL of a 7:1 v/v mixture) and the resulting solution heated at 70 °C for 14 h then cooled and concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, 4:1 v/v ethyl acetate/hexane gradient elution) gave, after concentration of the appropriate fractions ($R_f$ = 0.4 in 4:1 v/v ethyl acetate /hexane), compound **74** (75 mg, 70%) as a white, crystalline solid, mp = 78.3–83.3 °C, $[\alpha]^{20}{}_D = -162.5$ ($c$ = 0.2, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.62 (d, $J$ = 4.5 Hz, 1H), 4.40 (s, 1H), 4.22 (dd, $J$ = 8.8 and 4.1 Hz, 1H), 3.95 (t, $J$ = 4.1 Hz, 1H), 3.66 (dd, $J$ = 8.7 and 3.7 Hz, 1H), 3.49 (s, 3H), 3.46 (s, 3H), 3.12 (broad s, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 137.5, 103.5, 77.3, 74.9, 74.0, 68.0, 58.2, 57.8; IR $\nu_{max}$ 3401, 2980, 2929, 2826, 1629, 1455, 1369, 1344, 1195, 1097, 1051, 997, 865 cm$^{-1}$; MS (EI, 70 eV) *m/z* 300 ($M^{+\bullet}$, 18%), 282 (100%), 268 (36), 250 (32); HRMS ($M^{+\bullet}$) calcd for $C_8H_{13}{}^{127}IO_4$ 299.9859, found 299.9859.

**(1*R*,2*R*,5*R*,6*S*)-3-((3,5-Dimethoxyphenyl)ethynyl)-5,6-dimethoxycyclohex-3-ene-1,2-diol (22)**. Compound **74** (165 mg, 0.55 mmol), $PdCl_2(PPh_3)_2$ (20 mg, 0.03 mmol) and cuprous iodide (5 mg, 0.03 mmol) were placed in an oven-dried flask under a nitrogen

atmosphere. Dry diethylamine (10 mL) was added and the resulting suspension was cooled and magnetically stirred at 0 °C. After the dropwise addition of 1-ethynyl-3,5-dimethoxybenzene **70** (198 μL, 1.10 mmol) to the reaction mixture was complete it was stirred at 18 °C for 3 h then concentrated at reduced pressure and diethyl ether (25 mL) added to the residue thus obtained. The resulting mixture was filtered through a pad of diatomaceous earth and the filtrate washed with brine (1 x 25 mL) then dried ($Na_2SO_4$,), filtered and concentrated under reduced pressure. Subjection of the residue so-formed to flash chromatography (silica, 4:1 v/v ethyl acetate/hexane gradient elution) delivered, after concentration of the appropriate fractions ($R_f$ = 0.4 in 5:1 v/v ethyl acetate/hexane), compound **22** (114 mg, 62%) as a clear, light-yellow oil, $[\alpha]^{20}_D$ = −90.2 (*c* = 0.50, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.62 (d, *J* = 2.3 Hz, 2H), 6.45 (t, *J* = 2.3 Hz, 1H), 6.37 (d, *J* = 4.5 Hz, 1H), 4.44 (apparent dd, *J* = 4.3 and 2.2 Hz, 1H), 4.20 (ddd, *J* = 9.0, 4.2 and 1.8 Hz, 1H), 4.13 (t, *J* = 4.2 Hz, 1H), 3.77 (s, 6H), 3.71 (dd, *J* = 8.9 and 3.9 Hz, 1H), 3.52 (s, 3H), 3.49 (s, 3H), 2.87 (d, *J* = 1.9 Hz, 1H), 2.85 (d, *J* = 2.4 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 160.5, 133.0, 124.6, 123.9, 109.6, 102.2, 90.8, 86.9, 77.5, 72.6, 68.7, 67.6, 58.1, 57.7, 55.4; IR $\nu_{max}$ 3429, 2934, 2909, 2837, 1589, 1455, 1420, 1205, 1156, 1096, 1064, 990, 867, 681 cm$^{-1}$; MS (EI, 70 eV) *m/z* 334 ($M^{+\bullet}$, 93%), 319 (24), 304 (21), 285 (100); HRMS ($M^{+\bullet}$) calcd for $C_{18}H_{22}O_6$ 334.1416, found 334.1415.

**Reaction Sequence Leading to the Side-Chain Synthon 76 for the Preparation of Analogues 27-31**

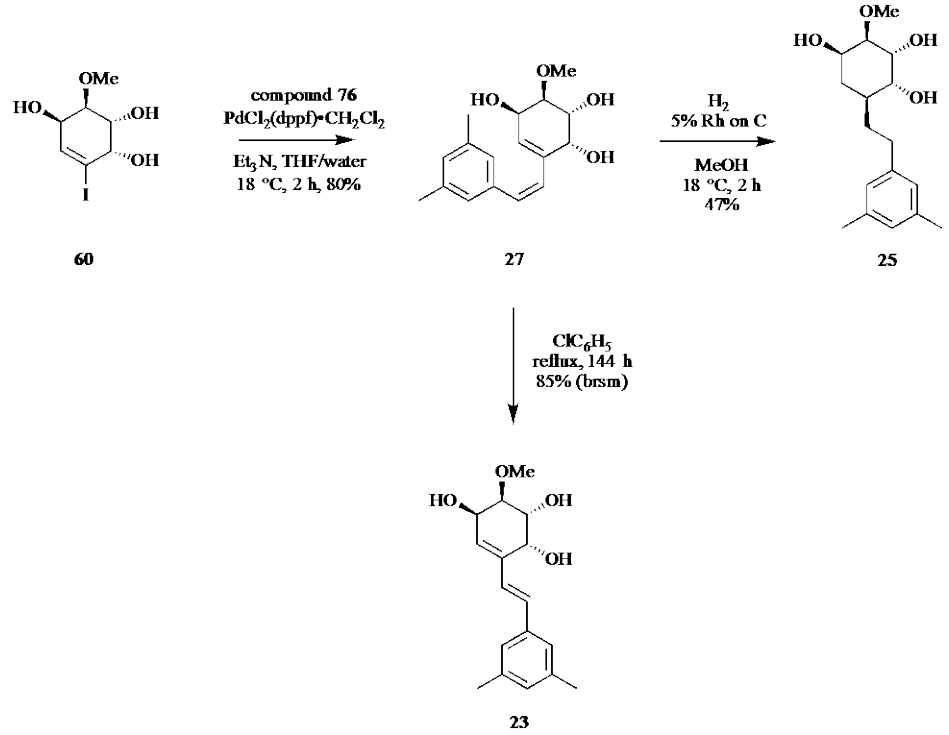



75 69 76

**(*Z*)-2-(3,5-Dimethylstyryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (76)**. A 50 mL Schlenk tube equipped with a magnetic stirring bar was charged with 1,5-cyclooctadienerhodium(I) chloride dimer {[RhCl(cod)]$_2$} (6 mg, 0.01 mmol) and the flushed with argon. Cyclohexanone (3 mL), tri-*iso*-propylphosphine [P(*i*-Pr)$_3$] (0.01 mL, 0.05 mmol), triethylamine (1 mL) and HB$_{pin}$ (**75**) (0.11 mL, 0.77 mmol) were then added in that order. After the reaction mixture had been stirred at 18 °C for 2 h 3,5-dimethylphenylacetylene (**69**) (200 mg, 1.54 mmol) was added in one portion and the ensuing mixture stirred at 18 °C for 2 h then quenched with methanol (5 mL). The ensuing mixture was filtered through a pad of diatomaceous earth and the filtrate concentrated under reduced pressure to give a light-brown oil. Subjection of this material to flash chromatography (silica, 5:95 v/v ethyl acetate/hexane gradient elution) delivered, after concentration of the appropriate fractions ($R_f$ = 0.3 in 1:9 v/v ethyl acetate/hexane), compound **76** (205 mg, 52%) as a clear, light-yellow oil, $[\alpha]^{20}_D$ = +4.7 (*c* = 0.9, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.15 (s, 3H), 6.91 (s, 1H), 5.54 (d, *J* = 14.9 Hz, 1H), 2.30 (s, 6H), 1.30 (s, 12H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 148.2, 138.4, 137.3, 129.7, 126.4, 83.4, 24.8, 21.2; IR $\nu_{max}$ 2978, 2918, 1627, 1601, 1458, 1379, 1349, 1262, 1144, 1085,

970, 897, 849 $cm^{-1}$; MS (EI, 70 eV) *m/z* 258 ($M^{+\bullet}$, 100%), 243 (32); HRMS ($M^{+\bullet}$) calcd for $C_{16}H_{23}BO_2$ 258.1791, found 258.1791.

**Reaction Sequence Leading to Phomentrioloxin A Analogues 23, 25 and 27**




**(1*R*,2*R*,3*R*,4*R*)-6-((*Z*)-3,5-Dimethylstyryl)-3-methoxycyclohex-5-ene-1,2,4-triol (27)**. A magnetically stirred solution of alcohol **60** (300 mg, 1.05 mmol), (*Z*)-2-(3,5-dimethylstyryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**76**) (271 mg, 1.05 mmol), $PdCl_2$dppf•$CH_2Cl_2$ (60 mg, 0.08 mmol) and triethylamine (2 mL) in THF/water (6 mL of a 9:1 v/v mixture) was purged with nitrogen for 0.5 h and then stirred at 18 °C for 2 h before being poured into water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were washed with brine (1 x 20 mL) then dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 1:6:3 v/v/v methanol/ethyl acetate/hexane gradient elution) and after concentration of the relevant fractions ($R_f$ = 0.3 in 9:1 v/v ethyl acetate/hexane) gave compound **27** (242 mg, 80%) as a white, crystalline solid, mp =

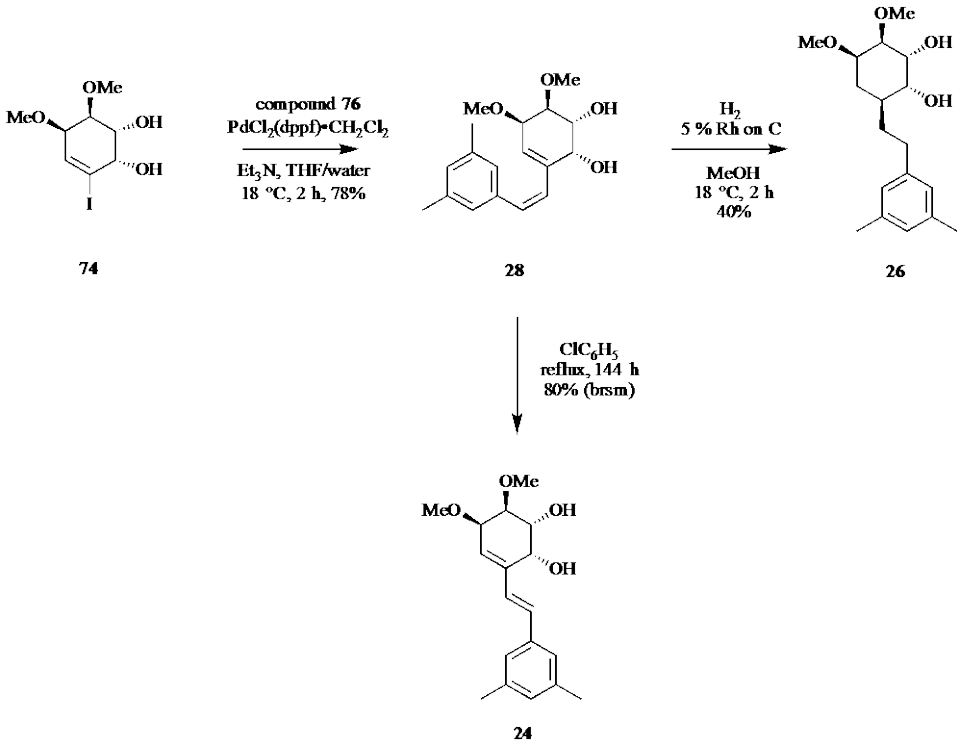
123–127 °C, $[\alpha]^{20}_D$ = −301.6 (*c* = 0.18, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.00 (s, 2H), 6.86 (s, 1H), 6.53 (d, *J* = 12.2 Hz, 1H), 6.11 (d, *J* = 12.5 Hz, 1H), 5.85 (dd, *J* = 4.6 and 1.5 Hz, 1H), 4.41 (t, *J* = 4.4 Hz, 1H), 4.33 (d, *J* = 4.1 Hz, 1H), 4.07 (dd, *J* = 8.9 and 4.0 Hz, 1H), 3.62 (dd, *J* = 8.9 and 4.2 Hz, 1H), 3.52 (s, 3H), 2.44 ( broad s, 3H), 2.27 (s, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 137.7, 137.5, 136.8, 132.4, 129.1, 128.4, 126.5, 78.7, 68.0, 67.9, 63.8, 58.2, 21.2; IR $\nu_{max}$ 3401, 2914, 2830, 1598, 1456, 1398, 1246, 1158, 1093, 1052, 988, 852 cm$^{-1}$; MS (EI, 70 eV) *m/z* 290 ($M^{+\bullet}$, 53%), 275 (1), 272 (100), 254 (49). HRMS ($M^{+\bullet}$) calcd for $C_{17}H_{22}O_4$ 290.1518, found 290.1518.

**(1*R*,2*R*,3*R*,4*R*)-6-((E)-3,5-Dimethylstyryl)-3-methoxycyclohex-5-ene-1,2,4-triol (23)**. A magnetically stirred solution of compound **27** (100 mg, 0.35 mmol) in chlorobenzene (5 mL) maintained under a nitrogen condition was heated under reflux for 144 h then cooled and concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, ethyl acetate gradient elution) gave, after concentration of the appropriate fractions ($R_f$ = 0.4 in 9:1 v/v ethyl acetate/hexane), compound **23** (33 mg, 85% brsm) as a white, crystalline solid, mp = 85 °C, $[\alpha]^{20}_D$ = −128.5 (*c* = 0.2, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.06 (s, 2H), 6.90 (s, 1H), 6.86 (d, *J* = 16.3 Hz, 1H), 6.73 (d, *J* = 16.3 Hz, 1H), 6.01 (d, *J* = 5.5 Hz, 1H), 4.74 (d, *J* = 4.0 Hz, 1H), 4.57 (t, *J* = 4.8 Hz, 1H), 4.04 (dd, *J* = 10.2 and 4.1 Hz, 1H), 3.65 (dd, *J* = 10.3 and 4.1 Hz, 1H), 3.56 (s, 3H), 2.74 (broad s, 1H), 2.31 (s, 6H) (signal due to hydroxyl group protons not observed); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 138.7, 138.0, 136.8, 131.4, 129.8, 127.6, 127.6, 124.6, 78.3, 67.8, 66.4, 63.3, 57.8, 21.3; IR $\upsilon_{max}$ 3395, 2916, 2827, 1597, 1446, 1384, 1242, 1104, 1094, 1066, 963, 851 cm$^{-1}$; MS (EI, 70 eV) *m/z* 290 (2%), 289 [(M-

H•)$^+$, 10], 272 (47), 254 (34), 211 (84), 183 (100); HRMS (M-H•)$^+$ calcd $C_{17}H_{21}O_4$ 289.1441, found 289.1440.

**(1*R*,2*R*,3*R*,4*R*,6*S*)-6-(3,5-Dimethylphenethyl)-3-methoxycyclohexane-1,2,4-triol (25)**. A magnetically stirred solution of compound **27** (30 mg, 0.10 mmol) in methanol (1 mL) was treated with rhodium on carbon (9 mg of 5% material). The reaction flask was connected to a balloon of hydrogen and after stirring the reaction mixture for 2 h at 18 °C the catalyst was removed by filtration through a pad of diatomaceous earth and the filtrate concentrated under reduced pressure on a rotatory evaporator. Subjection of the residue thus obtained to flash chromatography (silica, 1:6:3 v/v/v methanol/ethyl acetate/hexane gradient elution) gave, after concentration of the appropriate fractions ($R_f$ = 0.4 in 9.5:0.5 v/v ethyl acetate/hexane), compound **25** (14 mg, 47%) as a light-yellow oil, $[\alpha]^{20}_D$ = +21.9 (*c* = 0.57, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.81 (s, 3H), 4.09 (dd, *J* = 5.3 and 3.1 Hz, 1H), 4.04 (dt, *J* = 9.5 and 3.8 Hz, 1H), 3.65 (dd, *J* = 8.5 and 3.0 Hz, 1H), 3.53 (t, *J* = 4.3 Hz, 1H), 3.48 (s, 3H), 2.68 (ddd, *J* = 13.5, 10.7 and 5.3 Hz, 1H), 2.49 (ddd, *J* = 13.6, 10.5 and 6.1 Hz, 1H), 2.28 (s, 6H), 2.00 (broad s, 3H), 1.97–1.88 (complex m, 2H), 1.79 (dq, *J* = 8.9 and 4.4 Hz, 1H), 1.61–1.47 (complex m, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 142.3, 137.8, 127.4, 126.2, 82.1, 72.5, 69.5, 67.0, 58.4, 36.1, 34.2, 33.0, 31.5, 21.3; IR $\nu_{max}$ 3396, 2919, 2861, 2830, 1605, 1458, 1403, 1158, 1103, 1087, 1050, 972, 844 cm$^{-1}$; MS (EI, 70 eV) *m/z* 294 ($M^{+\bullet}$, 54%), 276 (30), 258 (57), 244 (100); HRMS ($M^{+\bullet}$) calcd $C_{17}H_{26}O_4$ 294.1831, found 294.1828.

**Reaction Sequence Leading to Phomentrioloxin A Analogues 24, 26 and 28**




**(1*R*,2*R*,5*R*,6*S*)-3-((Z)-3,5-Dimethylstyryl)-5,6-dimethoxycyclohex-3-ene-1,2-diol (28)**. A magnetically stirred solution of alcohol **74** (100 mg, 0.33 mmol), compound **76** (86 mg, 0.33 mmol), $PdCl_2$dppf•$CH_2Cl_2$ (19 mg, 0.03 mmol), and triethylamine (1 mL) in THF/water (2 mL of a 9:1 v/v mixture) was purged with nitrogen for 0.5 h, stirred at 18 °C for 2 h then being poured into water (6 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were washed with brine (1 x 10 mL) then dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 3:2 v/v ethyl acetate/hexane gradient elution) and concentration of the relevant fractions ($R_f$ = 0.4 in 2:1 v/v ethyl acetate/hexane) gave compound **28** (79 mg, 78%) as a clear, light-yellow oil, $[\alpha]^{20}_D$ =

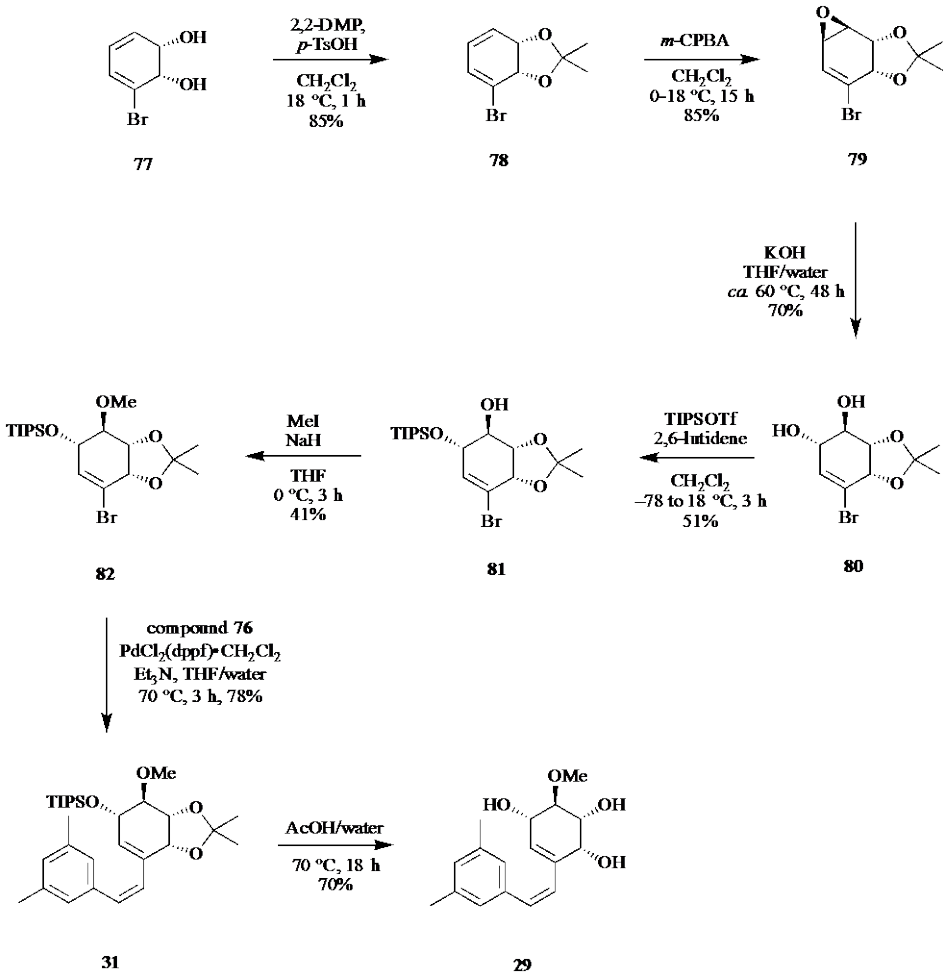
−178.6 ($c$ = 0.7, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.00 (s, 2H), 6.85 (s, 1H), 6.51 (d, $J$ = 12.2 Hz, 1H), 6.16 (d, $J$ = 12.2 Hz, 1H), 5.96 (dd, $J$ = 5.0 and 1.5 Hz, 1H), 4.36 (dd, $J$ = 4.2 and 1.6 Hz, 1H), 4.13 (dd, $J$ = 9.1 and 3.6 Hz, 1H), 3.99 (t, $J$ = 4.5 Hz, 1H), 3.62 (dd, $J$ = 9.7 and 3.9 Hz, 1H), 3.49 (s, 3H), 3.35 (s, 3H), 2.82 (d, $J$ = 1.7 Hz, 1H), 2.63 (d, $J$ = 2.1 Hz, 1H), 2.27 (s, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 138.6, 137.7, 136.7, 132.1, 129.0, 128.6, 126.6, 125.9, 77.5, 71.9, 68.4, 67.8, 57.4, 57.3, 21.2; IR $\nu_{max}$ 3411, 2971, 2916 2823, 1598, 1454, 1381, 1196, 1107, 1095, 1044, 989, 852 $cm^{-1}$; MS (EI, 70 eV) *m/z* 304 ($M^{+\bullet}$, 22%), 286 (25), 272 (100), 254 (98); HRMS ($M^{+\bullet}$) calcd for $C_{18}H_{24}O_4$ 304.1675, found 304.1673.

**(1*R*,2*R*,5*R*,6*S*)-3-((*E*)-3,5-Dimethylstyryl)-5,6-dimethoxycyclohex-3-ene-1,2-diol (24)**. A magnetically stirred solution of compound **28** (100 mg, 0.33 mmol) in chlorobenzene (5 mL) maintained under a nitrogen condition was heated under reflux for 144 h then cooled and concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane gradient elution) delivered, after concentration of the appropriate fractions ($R_f$ = 0.4 in 1:3 v/v ethyl acetate/hexane), compound **24** (36 mg, 80% brsm) as clear, light-yellow oil, $[\alpha]^{20}_D$ = +14.2 ($c$ = 1.4, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.07 (s, 2H), 6.88 (s, 1H), 6.90 (d, $J$ = 16.1 Hz, 1H), 6.73 (d, $J$ = 16.3 Hz, 1H), 6.09 (d, $J$ = 5.4 Hz, 1H), 4.74 (d, $J$ = 4.2 Hz, 1H), 4.15–4.11 (complex m, 2H), 3.66 (dd, $J$ = 10.5 and 4.0 Hz, 1H), 3.53 (s, 3H), 3.51 (s, 3H), 2.31 (s, 6H) (signal due to hydroxyl group protons not observed); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 139.2, 138.0, 136.9, 131.6, 129.7, 127.8, 125.9, 124.6, 77.7, 71.8, 67.8, 66.1, 57.8, 57.3, 21.3; IR $\nu_{max}$ 3400, 2917, 2831, 1599, 1463, 1383, 1257, 1114, 1093, 1046,

963, 851 $cm^{-1}$; MS (EI, 70 eV) *m/z* 304 ($M^{+\bullet}$, 100%), 286 (42), 254 (56); HRMS ($M^{+\bullet}$) calcd $C_{18}H_{24}O_4$ 304.1675, found 304.1674.

**(1*R*,2*R*,3*S*,4*R*,6*S*)-6-(3,5-Dimethylphenethyl)-3,4-dimethoxycyclohexane-1,2-diol (26)**. A magnetically stirred solution of compound **28** (30 mg, 0.10 mmol) in methanol (1 mL) was treated with rhodium on carbon (9 mg of 5% material). The flask was then connected to a balloon of hydrogen and after stirring for 2 h at 18 °C the catalyst was removed by filtration through a pad of diatomaceous earth and the filtrate concentrated under reduced pressure on a rotatory evaporator. Subjection of the residue thus obtained to flash chromatography (silica, 9:1 v/v ethyl acetate/hexane gradient elution) gave, after concentration of the appropriate fractions ($R_f$ = 0.4 in 4:1 v/v ethyl acetate/hexane), compound **26** (12 mg, 40%) as a clear, light-yellow oil, $[\alpha]^{20}_D$ = +16.6 (*c* = 0.75, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.82 (s, 1H), 6.81 (s, 2H), 4.07 (t, *J* = 4.2 Hz, 1H), 3.66 (td, *J* = 13.4, 12.0 and 7.6 Hz, 3H), 3.48 (s, 3H), 3.41 (s, 3H), 2.68 (ddd, *J* = 13.5, 10.9 and 5.3 Hz, 1H), 2.50 (ddd, *J* = 13.5, 10.6 and 5.9 Hz, 1H), 2.28 (s, 6H), 1.98–1.86 (complex m, 3H), 1.76 (dq, *J* = 8.7 and 4.2 Hz, 1H), 1.63–1.55 (complex m, 2H) (signal due to hydroxyl group proton not observed); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 142.3, 137.8, 127.4, 126.2, 79.4, 76.6, 72.4, 70.2, 58.4, 56.8, 36.4, 34.2, 33.1, 27.4, 21.3; IR $\nu_{max}$ 3401, 2924, 2826, 1606, 1455, 1383, 1195, 1108, 1095, 1055, 974, 844 $cm^{-1}$; MS (ESI, +ve) *m/z* 331 [$(M+Na)^+$, 100%]; HRMS $(M+Na)^+$ calcd $C_{18}H_{28}O_4Na$ 331.1885, found 331.1885.

**Reaction Sequence Leading to Phomentrioloxin A Analogues 29 and 31**




**(3a*S*,4*S*,5*S*,7a*S*)-7-Bromo-2,2-dimethyl-5-((triisopropylsilyl)oxy)-3a,4,5,7a-tetrahydrobenzo[d][1,3]dioxol-4-ol (81)**. Trisopropylsilyl trifluoromethanesulfonate (1.95 mL, 7.25 mmol) was added, dropwise, to a magnetically stirred solution of compound **80**[21] (1.4 g, 5.30 mmol) and 2,6-lutidine (2.50 mL, 21.5 mmol) in dichloromethane (30 mL) maintained at −78 °C under a nitrogen atmosphere. The ensuring mixture was allowed to warm to 18 °C over 3 h then treated with $NH_4Cl$ (60 mL of a saturated aqueous solution).

The separated aqueous phase was extracted with dichloromethane (1 x 50 mL) and the combined organic phases were dried ($MgSO_4$), filtered then concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 3:100 v/v ethyl acetate/hexane gradient elution) to give, after concentration of the appropriate fractions ($R_f$ = 0.3 in 0.5:2.5:5.5 v/v/v ethyl acetate/dichloromethane/hexane), compound **81** (1.15 g, 51%) as a yellowish oil, $[\alpha]^{20}_D$ = +23.2 ($c$ = 1.0, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.42 (d, $J$ = 1.6 Hz, 1H), 4.66 (d, $J$ = 6.6 Hz, 1H), 4.17 (d, $J$ = 8.2 Hz, 1H), 4.11 (dd, $J$ = 9.0 and 6.7 Hz, 1H), 3.55 (t, $J$ = 8.7 Hz, 1H), 2.45 (s, 1H), 1.54 (s, 3H), 1.40 (s, 3H), 1.15–1.04 (complex m, 21H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 144.5, 110.2, 92.2, 79.3, 77.0, 74.5, 73.6, 28.0, 25.7, 18.0(1), 17.9(9), 12.4; IR $\nu_{max}$ 3469, 2943, 2892, 2866, 1635, 1463, 1382, 1248, 1070, 1019, 997, 882, 866, 828 cm$^{-1}$; MS (ESI, +ve) *m/z* 445 and 443 [$(M+Na)^+$, 100 and 97%]; HRMS $(M+Na)^+$ calcd for $C_{18}H_{33}{}^{79}BrO_4NaSi$ 443.1229, found 443.1232.

**(((3a*S*,4*S*,5*S*,7a*S*)-7-Bromo-4-methoxy-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*]-[1,3]dioxol-5-yl)oxy)triisopropylsilane (82)**. Sodium hydride (257 mg of a 60% dispersion in mineral oil, 6.43 mmol) was added to a magnetically stirred solution of compound **81** (900 mg, 2.14 mmol) and iodomethane (294 μL, 4.73 mmol) in dry THF (20 mL) maintained at 0 °C under a nitrogen atmosphere. Stirring was continued at 0 to 18 °C for 3 h then the reaction mixture was treated with ice/water (60 mL) (CAUTION: possible evolution of hydrogen). The separated aqueous phase was extracted with ethyl acetate (1 x 25 mL) and the combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to

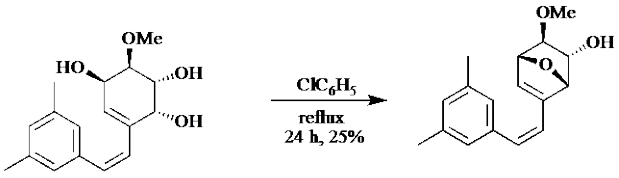
flash chromatography (silica, 1:50 v/v ethyl acetate/hexane gradient elution) to give, after concentration of the appropriate fractions ($R_f$ = 0.4 in 0.5:2.5:5.5 v/v/v ethyl acetate/dichloromethane/hexane), compound **82** (385 mg, 41%) as a light-yellow oil, $[\alpha]^{20}_D$ = +70.8 (*c* = 0.5, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.54 (d, *J* = 3.2 Hz, 1H), 4.60 (d, *J* = 6.1 Hz, 1H), 4.18 (t, *J* = 6.0 Hz, 1H), 4.03 (t, *J* = 5.6 Hz, 1H), 3.57–3.54 (complex m, 1H), 3.40 (s, 3H), 1.48 (s, 3H), 1.38 (s, 3H), 1.14–1.04 (complex m, 21H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 137.9, 110.1, 99.4, 81.2, 78.4, 77.9, 71.1, 57.5, 27.6, 26.1, 18.1, 18.0, 12.5; IR $\nu_{max}$ 2941, 2879, 2865, 1636, 1463, 1380, 1273, 1251, 1214, 1167, 1126, 1076, 952, 882, 865, 679 cm$^{-1}$; MS (ESI, +ve) *m/z* 459 and 457 [$(M+Na)^+$ 98 and 96%], 355 (100); HRMS calcd for $C_{19}H_{35}{}^{79}BrNaO_4Si$ 457.1386, found 457.1389.

**(((3a*R*,4*S*,5*S*,7a*R*)-7-((*Z*)-3,5-Dimethylstyryl)-4-methoxy-2,2-dimethyl-3a,4,5,7a-tetra-hydrobenzo[d][1,3]dioxol-5-yl)oxy)triisopropylsilane (31)**. A magnetically stirred solution of compound **82** (70 mg, 0.16 mmol), compound **76** (41 mg, 0.16 mmol), $PdCl_2$dppf•$CH_2Cl_2$ (9 mg, 0.01 mmol) and triethylamine (0.5 mL) in THF/water (3 mL of a 9:1 v/v mixture) was purged with nitrogen for 0.5 h, heated at 70 °C for 3 h then poured into water (6 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were washed with brine (1 x 10 mL) before being dried ($Na_2SO_4$), filtered then concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 3:97 v/v ethyl acetate/hexane gradient elution) and concentration of the relevant fractions ($R_f$ = 0.3 in 1:9 v/v ethyl acetate/hexane) afforded compound **31** (61 mg, 78%) as a clear, light-yellow oil, $[\alpha]^{20}_D$ = −73.0 (*c* = 0.2, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.02 (s, 2H), 6.83 (s, 1H), 6.51 (d, *J* = 12.3 Hz,

1H), 6.05 (d, *J* = 12.3 Hz, 1H), 5.81 (s, 1H), 4.61 (d, *J* = 6.5 Hz, 1H), 4.07 (t, *J* = 7.0 Hz, 1H), 3.85 (t, *J* = 7.3 Hz, 1H), 3.56 (dd, *J* = 7.3 and 1.8 Hz, 1H), 3.24 (s, 3H), 2.26 (s, 6H), 1.47 (s, 3H), 1.20 (s, 3H), 1.13–1.05 (complex m, 21H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 137.4, 137.1, 132.7, 132.0, 128.7, 128.2, 127.8, 126.5, 109.5, 80.2, 78.5, 73.9, 73.3, 56.7, 27.9, 25.5, 21.2, 18.1(8), 18.1(4), 12.7; IR $\nu_{max}$ 2941, 2865, 1600, 1463, 1379, 1250, 1137, 1098, 1063, 947, 883, 850 cm$^{-1}$; MS (EI, 70 eV) *m/z* 486 ($M^{+\bullet}$, 28%), 471 (100), 456 (5); HRMS *m/z* ($M^{+\bullet}$) calcd for $C_{29}H_{46}O_4Si$ 486.3165, found 486.3166.

**(1*R*,2*R*,3*R*,4*S*)-6-((*Z*)-3,5-dimethylstyryl)-3-methoxycyclohex-5-ene-1,2,4-triol (29)**. Com -pound **31** (50 mg, 0.10 mmol) was treated with acetic/water (10 mL of a 7:3 v/v mixture) and the resulting solution heated at 70 °C for 18 h then cooled and concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, 1:6:3 v/v/v methanol/ethyl acetate/hexane gradient elution) gave, after concentration of the appropriate fractions ($R_f$ = 0.4 in 9:1 v/v ethyl acetate/hexane), compound **29** (21 mg, 70%) as a clear, light-yellow oil, $[\alpha]^{20}_D = -93.0$ (*c* = 0.3, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.96 (s, 2H), 6.88 (s, 1H), 6.53 (d, *J* = 12.2 Hz, 1H), 6.10 (d, *J* = 12.2 Hz, 1H), 5.83 (s, 1H), 4.25 (d, *J* = 4.3 Hz, 1H), 3.87 (dd, *J* = 10.3 and 7.7 Hz, 1H), 3.75 (d, *J* = 7.8 Hz, 1H), 3.54–3.49 (complex m, 1H), 3.36 (s, 3H), 2.27 (s, 6H), 1.62 (broad s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 137.9, 136.9, 136.2, 132.1, 129.1, 128.3, 126.3, 80.8, 71.4, 70.6, 68.3, 56.3, 21.3; IR $\nu_{max}$ 3369, 2917, 2826, 1599, 1452, 1376, 1261, 1147, 1079, 945, 853 cm$^{-1}$; MS (EI, 70 eV) *m/z* 290 ($M^{+\bullet}$, 100%), 272 (17), 270 (13); HRMS ($M^{+\bullet}$) calcd for $C_{17}H_{22}O_4$ 290.1518, found 290.1523.

**Reaction Sequence Leading to Phomentrioloxin A Analogue 30**




27 30

**(1*S*,2*R*,3*S*,4*R*)-6-((*Z*)-3,5-Dimethylstyryl)-3-methoxy-7-oxabicyclo[2.2.1]hept-5-en-2-ol (30)**. A magnetically stirred solution of compound **27** (50 mg, 0.17 mmol) in chlorobenzene (5 mL) was heated under reflux for 24 h then cooled and concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, 3:2 v/v ethyl acetate/ hexane elution) gave, after concentration of the appropriate fractions ($R_f$ = 0.4 in 3:2 v/v ethyl acetate/hexane), compound **30** (14 mg, 30%) as light-yellow oil, $[\alpha]^{20}_D$ = −333.2 (*c* = 0.9, $CHCl_3$). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.98 (s, 3H), 6.54 (d, *J* = 9.7 Hz, 1H), 6.01 (dd, *J* = 9.8 and 4.9 Hz, 1H), 5.89 (s, 1H), 5.79 (d, *J* = 4.8 Hz, 1H), 4.96 (dt, *J* = 5.2 and 2.8 Hz, 1H), 4.23 (s, 1H), 3.87 (dd, *J* = 4.9 and 2.4 Hz, 1H), 3.49 (s, 3H), 2.31 (s, 6H), 2.20 (d, *J* = 1.9 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 140.5, 138.5, 135.1, 130.3, 127.5, 126.3, 125.2, 123.4, 87.5, 82.5, 77.5, 67.2, 57.6, 21.3; IR $\nu_{max}$ 3421, 2920, 2861, 1693, 1607, 1462, 1382, 1243, 1156, 1123, 1089, 957, 851 $cm^{-1}$; MS (ESI, +ve) *m/z* 295 [$(M+Na)^+$, 100%], 273 (10), 195 (12); HRMS [$(M+Na)^+$ calcd for $C_{17}H_{20}NaO_3$ 295.1310, found 295.1311.

**Crystallographic Studies.** *Crystallographic Data.*

*Compound **15***. $C_{17}H_{20}O_4$, $M$ = 288.34, $T$ = 200 K, monoclinic, space group $P2_1$, $Z$ = 2, $a$ = 4.6659(3) Å, $b$ = 11.9898(9) Å, $c$ = 13.673(1) Å; β = 90.470(4)°; $V$ = 764.89(9) Å$^3$, $D_x$ = 1.252 g cm$^{-3}$, 1423 unique data ($2\theta_{max}$ = 50°), $R$ = 0.036 [for 1295 reflections with $I > 2.0\sigma(I)$]; $Rw$ = 0.083 (all data), $S$ = 1.03.

*Compound **23***. $C_{17}H_{22}O_4$, $M$ = 290.36, $T$ = 150 K, monoclinic, space group $P2_1$, $Z$ = 2, $a$ = 4.7176(2) Å, $b$ = 11.7310(4) Å, $c$ = 13.7171(6) Å; β = 90.035(4)°; $V$ = 759.13(5) Å$^3$, $D_x$ = 1.270 g cm$^{-3}$, 1556 unique data ($2\theta_{max}$ = 143°), $R$ = 0.080 [for 1536 reflections with $I > 2.0\sigma(I)$]; $Rw$ = 0.220 (all data), $S$ = 1.01.

*Compound **27***. $C_{17}H_{22}O_4$, $M$ = 290.36, $T$ = 150 K, orthorhombic, space group $P2_12_12_1$, $Z$ = 4, $a$ = 4.5847(2) Å, $b$ = 11.7037(5) Å, $c$ = 29.754(3) Å; $V$ = 1596.54(19) Å$^3$, $D_x$ = 1.208 g cm$^{-3}$, 1901 unique data ($2\theta_{max}$ = 146.8°), $R$ = 0.065 [for 1563 reflections with $I > 2.0\sigma(I)$]; $Rw$ = 0.151 (all data), $S$ = 1.00.

*Compound **35***. $C_{11}H_{17}IO_4$, $M$ = 340.16, $T$ = 200 K, orthorhombic, space group $P2_12_12_1$, $Z$ = 4, $a$ = 7.8130(1) Å, $b$ = 11.5034(2) Å, $c$ = 14.4925(2) Å; $V$ = 1302.53(3) Å$^3$, $D_x$ = 1.735 g cm$^{-3}$, 3799 unique data ($2\theta_{max}$ = 60°), $R$ = 0.021 [for 3669 reflections with $I > 2.0\sigma(I)$]; $Rw$ = 0.051 (all data), $S$ = 1.00.

*Compound **51***. $C_7H_{11}IO_4 \cdot H_2O$, $M$ = 304.08, $T$ = 150 K, monoclinic, space group $C2$, $Z$ = 4, $a$ = 17.5832(15) Å, $b$ = 4.7115(1) Å, $c$ = 13.4131(8) Å; β = 111.360(12)°; $V$ = 1034.86(14) Å$^3$, $D_x$ = 1.952 g cm$^{-3}$, 1906 unique data ($2\theta_{max}$ = 143.8°), $R$ = 0.022 [for 1871 reflections with $I > 2.0\sigma(I)$]; $Rw$ = 0.059 (all data), $S$ = 1.00.

*Compound **72***. $C_7H_{11}IO_4 \cdot H_2O$, $M$ = 304.08, $T$ = 200 K, monoclinic, space group $C2$, $Z$ = 4, $a$ = 16.8154(8) Å, $b$ = 4.5652(2) Å, $c$ = 15.7010(8) Å; β = 120.5922°; $V$ = 1037.53(9) Å$^3$, $D_x$ = 1.947 g cm$^{-3}$, 3024 unique data ($2\theta_{max}$ = 60.2°), $R$ = 0.031 [for 2812 reflections with $I > 2.0\sigma(I)$]; $Rw$ = 0.073 (all data), $S$ = 0.99.

*Structure Determination.* Images for compound **15**, **35** and **72** were measured on a diffractometer (Mo Kα, mirror monochromator, λ = 0.71073 Å) fitted with an area detector and the data extracted using the DENZO/Scalepack package.[22] Images for compounds **23**, **27** and **51** were measured on a diffractometer (Cu Kα, mirror monochromator, λ = 1.54184 Å) fitted with an area detector and the data extracted using the CrysAlis package.[23] The structure solutions for all six compounds were solved by direct methods (SIR92)[24] then refined using the CRYSTALS program package.[25] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 1504203, 1504204, 1504205, 1504206, 1504207 and 1504208). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

**Biological Testing**. The test results shown in Table 1 derived from green house studies. The culture vessels used were plastic flowerpots containing loamy sand with approximately 3% of humus as the substrate. For the post-emergence treatment, the test plants were first grown separately as seedlings and several of these were transplanted into the culture vessels a few days prior to treatment. After they reached a height of 3 to 10

cm, depending on the plant habit, they were treated with the active ingredients which had been emulsified through the addition of 3.6 mL of a mixture of cyclohexanone/DMSO/Wettol EM31 (2:2:1 v/v/v mixture) and 2% Dash diluted with deionized water to the corresponding spray volume and sprayed on the plants via an ultrasonic spray nozzle. Unless otherwise specified, the application rate corresponded to 2 kg/ha with an application volume of 750 L/ha. The plants were kept and tended at 15-22 °C over a test period of 21 days. The responses of the plants to the individual treatments were visually evaluated after 21 days. The outcomes of these evaluation are presented in Table 1.

The physiological profiling (PP) studies were conducted using previously published protocols.[14a,26]

## ASSOCIATED CONTENT

### Supporting Information

Crystallographic data (including CIFs) and anisotropic displacement ellipsoid plots derived from the single-crystal X-ray analyses of compounds **15, 23**, **27**, **35**, **51** and **72**. $^{1}$H and $^{13}$C NMR spectra of phomentrioloxin analogues **4-7** and **10-31** as well as their precursors. This material is available free of charge via the internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest

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