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Synthesis of toxyloxanthone B

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ABSTRACT

A synthesis of the naturally occurring xanthone toxyloxanthone B is described, in which the key step is the regioselective addition of a methyl salicylate to a substituted benzyne, followed by cyclization of the intermediate aryl anion to form the xanthone, the regiochemistry of the aryne addition being confirmed by X-ray crystallography. Subsequent introduction of the pyran ring by [3,3]-rearrangement and deprotection completed the synthesis.

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1. Introduction

Xanthones are widely distributed in Nature, occurring in a wide range of organisms from bacteria to higher plants.[1] Not only are xanthones highly colored (Greek *xanthos*=yellow), they are also endowed with significant biological activity. Plants and trees of the *Garcinia* genus are a particularly rich source of bioactive xanthones, and recently isolated examples possess activity against platelet aggregation,[2] α-glucosidases,[3] cancer,[4] and MRSA.[5,6] In higher plants, xanthones are of mixed polyketide and shikimic acid biosynthetic origin, with many examples also possessing isoprene-derived side chains.[3–5] Indeed it was prenylated xanthones such as α-mangostin **1**, rubraxanthone **2**, and toxyloxanthone B **3a** (Fig. 1) that attracted our attention. α-Mangostin **1**, from *Garcinia mangostana*, is a potent inhibitor of sphingomyelinase,[7,8] whereas rubraxanthone **2**, isolated from various members of the *Garcinia* genus,[9,10] has a range of biological properties.[11,12] The cytotoxic xanthone toxyloxanthone B **3a** on the other hand is not *Garcinia*-derived being originally isolated from *Maclura pomifera* and *Toxylon pomiferum*,[13–16] and subsequently from the *Hypericum* genus, including *Hypericum perforatum* (St John's Wort).[17,18] Surprisingly, despite their relative structural simplicity, α-mangostin **1** is the only one of the three compounds to be synthesized.[8] We now report the synthesis of toxyloxanthone **3** that not only constitutes the first synthesis of the natural material, but also, as far as we are aware,

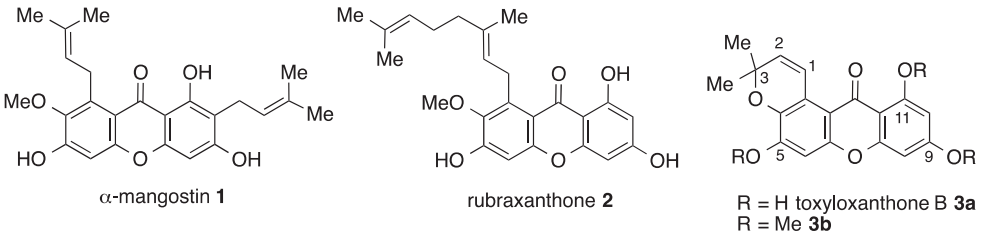

Fig. 1. Some naturally occurring prenylated xanthones.

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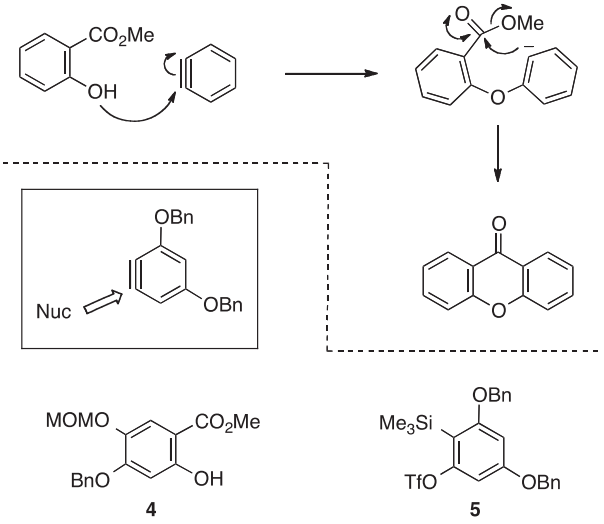
illustrates the first use of the aryne-based methodology developed by Larock[19,20] in the synthesis of bioactive natural products.

2. Results and discussion

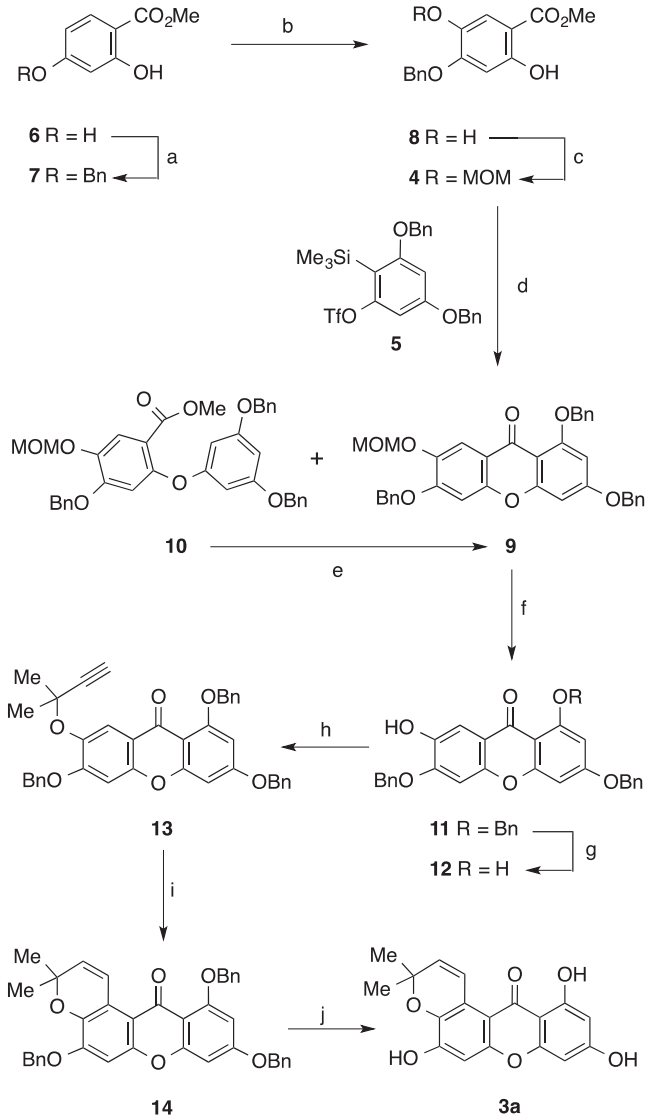
The toxyloxanthones were first isolated from *M. pomifera*,[13] although the originally assigned structure of toxyloxanthone B was corrected some two years later. Specifically, the position of the two methyl groups at C-3 was confirmed by NMR spectroscopy,[14] and subsequently confirmed by an unambiguous synthesis of the trimethyl ether **3b**,[15,16] although the natural product itself has not been synthesized. In common with many other routes to xanthones, the synthesis of toxyloxanthone B trimethyl ether **3b** was achieved in a classical sense by way of a suitably substituted benzophenone,[16] but we were attracted by the more contemporary aryne-based method introduced by Larock.[19,20] There has been a recent resurgence in interest in aryne chemistry, and their application in natural product synthesis is extremely topical.[21–23] The Larock method involves the nucleophilic addition of the hydroxy group of a methyl salicylate to a benzyne followed by cyclization of the resulting aryl anion onto the methyl ester (Scheme 1). In the case of toxyloxanthone B **3a**, the required coupling partners would be the methyl salicylate **4** and the *ortho*-trimethylsilyl triflate aryne precursor **5**, with benzyl protecting groups chosen for the three phenolic hydroxy groups, with the remaining phenol in **4** orthogonally protected as its MOM-ether. The substituted benzyne derived from precursor **5** is unsymmetrical and therefore could lead to two nucleophilic addition products. However, Stoltz and co-workers have previously shown that the aryne derived from **5** undergoes regioselective attack as indicated in Scheme 1,[24] and therefore we were confident that the correct xanthone would result from our projected coupling reaction.



Scheme 1. Larock benzyne-based route to xanthones, and the proposed precursors to toxyloxanthone B.

The methyl salicylate **4** was obtained from methyl 2,4-hydroxybenzoate **6** by selective protection of the non-hydrogen bonded phenol to give salicylate **7**. Subsequent Elbs persulfate oxidation[25] gave the hydroquinone **8** albeit in poor yield, although the 64% recovery of starting material **7** rendered the process viable. Selective protection of the non-hydrogen bonded phenol as its MOM-ether gave the required methyl salicylate **4** (Scheme 2). The aryne precursor **5** was prepared from phloroglucinol as described by Stoltz and co-workers,[24] setting the stage for the key step. Generation of the aryne from the triflate **5** with cesium fluoride in THF in the presence of the methyl salicylate **4** as described by Larock and co-workers gave the desired xanthone **9**, but in 1:1 admixture with the *ortho*-aryloxy benzoate **10** (Scheme 2). Reasoning that the only source of protonation of the intermediate aryl anion was the salicylate **4** itself, a change in conditions involving the addition of sodium hydride for prior deprotonation of the phenol resulted in an improved yield (40%) of the desired xanthone **9**, although the benzoate **10** was still formed (30%). As expected, the nucleophilic addition to the unsymmetrical benzyne derived from triflate **5** was highly regioselective resulting in the formation of the 1,3,6-tribenzyloxyxanthone **9**. The alternative regioisomer, the 2,4,6-tribenzyloxyxanthone, that would result from attack on the other aryne carbon was not observed. In terms of obtaining quantities of xanthone **9**, the formation of benzoate **10** was inconsequential since ester hydrolysis and cyclization onto the electron rich aromatic ring in the presence of trifluoroacetic acid anhydride provided further material.

With the xanthone **9** available in quantity, the MOM-ether was cleaved under acidic conditions, and the resulting phenol **11** was



Scheme 2. Reagents and conditions: (a) BnBr, K_2CO_3, acetone, rt (82%); (b) $K_2S_2O_8$, NaOH, water, rt (15%+64% recovered **7**); (c) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt (70%); (d) NaH, CsF, THF, 65 °C (40%+30% **10**); (e) LiOH, MeOH, aq THF, then TFAA, CH_2Cl_2, rt (99%); (f) TFA, CH_2Cl_2, rt (94%); (g) $MgBr_2$, toluene, reflux (10%); (h) $HCCCMe_2Cl$, KI, K_2CO_3, acetone, reflux (75%); (i) toluene, reflux (100%); (j) BCl_3 (1 M in hexane), pentamethylbenzene, CH_2Cl_2, −78 °C, then rt (64%).

further deprotected by selective removal of the benzyl group *peri*- to the carbonyl by treatment with magnesium bromide in boiling toluene. The structure of the resulting phenol **12** was confirmed by X-ray crystallography (Fig. 2), providing unambiguous evidence for the regiochemistry of the aryne addition. Alkylation of phenol **11** with 3-chloro-3-methylbutyne gave the propargyl ether **13** in good yield. Claisen rearrangement under mild conditions[26] resulted in formation of the fused pyran ring to give protected toxyloxanthone **14** in quantitative yield (Scheme 2). The final step required the removal of three benzyl protecting groups, and although this could not be carried out under catalytic transfer hydrogenation with ammonium formate as hydrogen donor,[27] treatment with boron trichloride in dichloromethane in the presence of pentamethylbenzene[28] at −78 °C initially removed two of the benzyl groups. For full deprotection, the reaction mixture required warming to room temperature with extra boron trichloride, which pleasingly gave the xanthone **3a** (toxyloxanthone) in 64% yield.

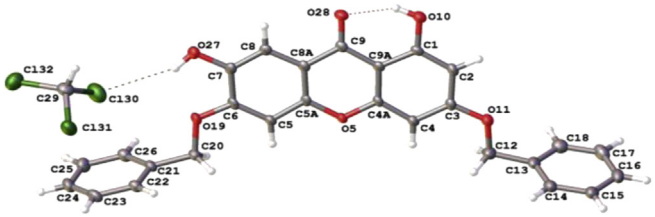


Fig. 2. X-ray crystal structure of 3,6-dibenzyloxy-1,7-dihydroxy-9*H*-xanthen-9-one **12** (with one molecule of chloroform) CCDC number 973933.

The ^{1}H spectroscopic properties of the synthetic material closely matched those described for the natural product,[17,18] although the ^{13}C NMR gave a systematic difference in the chemical shifts of 0.8–1.1 ppm. We assumed that this was due to incorrect calibration of the original spectrum, and indeed when we re-referenced the residual acetone peak, a near perfect match to the reported literature values was observed. Additionally, for further comparison, toxyloxanthone B **3a** was converted into the known trimethyl ether **3b** by reaction with dimethyl sulfate, the ^{1}H NMR spectroscopic data of which were identical with those reported.[16] The first synthesis of the naturally occurring xanthone toxyloxanthone B further demonstrates the use of arynes in synthesis, and in particular that the Larock xanthone methodology can be successfully applied in the synthesis of relatively complex natural products.

3. Experimental section

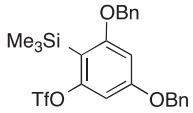
3.1. General information

Commercially available reagents were used throughout without purification unless otherwise stated. All anhydrous solvents were used as supplied, except tetrahydrofuran and dichloromethane that were freshly distilled according to standard procedures. Reactions were routinely carried out under an argon atmosphere unless otherwise stated, and all glassware was flame-dried before use. Light petroleum refers to the fraction with bp 40–60 °C. Ether refers to diethyl ether.

Analytical thin layer chromatography was carried out on aluminum backed plates coated with silica gel, and visualized under UV light at 254 and/or 360 nm and/or by chemical staining. Flash chromatography was carried out using silica gel, with the eluant specified.

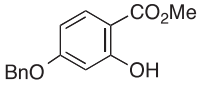
Infrared spectra were recorded using an FT-IR spectrometer over the range 4000–600 cm^{-1}. NMR spectra were recorded at 400 or 500 MHz (^{1}H frequency, 100 or 125 MHz ^{13}C frequency). Chemical shifts are quoted in parts per million (ppm), and are referenced to residual H in the deuterated solvent as the internal standard. Coupling constants, *J*, are quoted in hertz (Hz). In the ^{13}C NMR spectra, signals corresponding to CH, CH_2, or CH_3 groups are assigned from DEPT. Mass spectra were recorded on a time-of-flight mass spectrometer using electrospray ionization (ESI), or an EI magnetic sector instrument.

3.2. 3,5-Dibenzyloxy-2-trimethylsilylphenyl trifluoromethane sulfonate 5



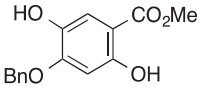
The title compound was prepared by the method of Stoltz and co-workers.[24]

3.3. Methyl 4-benzyloxy-2-hydroxybenzoate 7



A mixture of methyl 2,4-dihydroxybenzoate **6** (4.00 g, 23.8 mmol) and anhydrous potassium carbonate (4.90 g, 35.7 mmol) in acetone (22 mL) was stirred at room temperature for 5 min. Benzyl bromide (2.83 mL, 23.8 mmol) was added dropwise and the mixture was stirred at 10–15 °C for 3 h. Water (30 mL) and ethyl acetate (30 mL) were added and the two phases were separated. The aqueous phase was extracted with further ethyl acetate (3×40 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (9:1 light petroleum/ethyl acetate) to give the title compound (5.06 g, 82%) as a colorless solid, mp 103–105 °C (lit.,[29] mp 103–105 °C). Found: [M+Na^{+}], 281.0781. $C_{15}H_{14}NaO_4^{+}$ requires 281.0784; ν_{max} ($CHCl_3$)/cm^{-1} 3008, 2956, 1668, 1623, 1583, 1505, 1441, 1382, 1349, 1255, 1183, 1142, 1099, 1014; δ_H (400 MHz; DMSO-d_6) 10.78 (1H, s), 7.74 (1H, d, *J* 7.2), 7.47–7.36 (5H, m), 6.64–6.61 (2H, m), 5.18 (2H, s), 3.88 (3H, s); δ_C (100 MHz; DMSO-d_6) 169.8 (C), 164.7 (C), 163.0 (C), 136.8 (C), 131.8 (CH), 128.9 (CH), 128.5 (CH), 128.2 (CH), 108.5 (CH), 105.9 (C), 102.4 (CH), 70.1 (CH_2), 52.7 (Me).

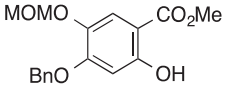
3.4. Methyl 4-benzyloxy-2,5-dihydroxybenzoate 8



To a stirred mixture of methyl 4-benzyloxy-2-hydroxybenzoate **7** (3.50 g, 13.5 mmol) in an aqueous solution of NaOH (1 M; 135 mL) at 0 °C was added over 30 min, a solution of potassium persulfate (7.70 g, 28.5 mmol) in water (135 mL). After stirring for 20 h at room temperature, the reaction mixture was acidified to pH 4 with concentrated hydrochloric acid. The mixture was filtered to remove the unreacted starting material (2.25 g, 64% recovery). Further concentrated hydrochloric acid (30 mL) was added to the aqueous phase and the mixture heated to 80 °C for 2 h. After cooling to room temperature, ethyl acetate (150 mL) was added, and then the aqueous layer was extracted with further ethyl acetate (3×200 mL). The combined organic phases were dried over $MgSO_4$ and

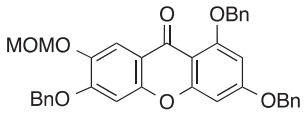
evaporated to give a dark oil that was purified by column chromatography (9:1 light petroleum/ethyl acetate). The product was crystallized from methanol to give the *title compound* as a colorless solid (560 mg, 15%), mp 165–167 °C. Found: [M+Na$^+$], 297.0716. $C_{15}H_{14}NaO_5^+$ requires 297.0733; ν_{max} ($CHCl_3$)/cm^{-1} 3684, 3555, 3011, 2956, 1669, 1635, 1509, 1440, 1399, 1374, 1276, 1239, 1168, 1082, 1000; δ_H (400 MHz; DMSO-d_6) 10.33 (1H, s), 8.94 (1H, s), 7.50–7.35 (5H, m), 7.18 (1H, s), 6.63 (1H, s), 5.18 (2H, s), 3.86 (3H, s); δ_C (100 MHz; DMSO-d_6) 170.0 (C), 156.1 (C), 154.2 (C), 140.1 (C), 136.9 (C), 128.9 (CH), 128.4 (CH), 128.2 (CH), 114.4 (CH), 103.7 (C), 102.1 (CH), 70.2 (CH_2), 52.6 (Me).

3.5. Methyl 4-benzyloxy-2-hydroxy-5-methoxymethoxybenzoate 4

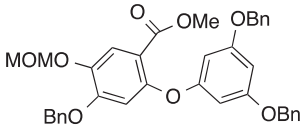


To a solution of methyl 4-benzyloxy-2,5-dihydroxybenzoate **8** (450 mg, 1.64 mmol) in dichloromethane (18 mL) at 0 °C, was added DIPEA (0.51 mL, 2.95 mmol), and after a few minutes, MOMCl (0.14 mL, 1.8 mmol). The mixture was stirred for 2 h at room temperature. Water (15 mL) was added and the mixture was extracted with ethyl acetate (3×15 mL). The combined organic extract was dried over $MgSO_4$, and evaporated. The residue was purified by flash column chromatography (9:1 light petroleum/ethyl acetate) to give the *title compound* as a colorless solid (410 mg, 70%), mp 103–105 °C. Found: [M+Na$^+$], 341.0994. $C_{17}H_{18}NaO_6^+$ requires 341.0996; ν_{max} ($CHCl_3$)/cm^{-1} 3154, 3011, 2955, 1668, 1620, 1511, 1497, 1441, 1355, 1259, 1192, 1162, 1097, 1070, 988; δ_H (400 MHz; DMSO-d_6) 10.58 (1H, s), 7.48–7.37 (6H, m), 6.73 (1H, s), 5.20 (2H, s), 5.09 (2H, s), 3.88 (3H, s), 3.39 (3H, s); δ_C (100 MHz; DMSO-d_6) 169.7 (C), 158.4 (C), 156.3 (C), 139.5 (C), 136.6 (C), 129.0 (CH), 128.6 (CH), 128.3 (CH), 117.8 (CH), 103.9 (C), 102.4 (CH), 96.2 (CH_2), 70.5 (CH_2), 56.2 (Me), 52.7 (Me).

3.6. 1,3,6-Tribenzyloxy-7-methoxymethoxy-9*H*-xanthen-9-one 9



To a solution of methyl 4-benzyloxy-2-hydroxy-5-methoxymethoxybenzoate **4** (409 mg, 1.28 mmol) in THF (15 mL) at room temperature was added sodium hydride ([60% dispersion in mineral oil] 52 mg, 1.29 mmol) and the mixture was left to stir for 45 min. The mixture was heated to 65 °C and cesium fluoride (780 mg, 5.14 mmol) was added, followed by a solution of 3,5-dibenzyloxy-2-trimethylsilylphenyl trifluoromethanesulfonate **5** (720 mg, 1.41 mmol) in THF (10 mL), over 30 min. The mixture was stirred for 24 h at 65 °C, then cooled, diluted with ether (100 mL), and washed with brine (100 mL). The aqueous layer was extracted with ethyl acetate (2×60 mL), the combined organic extracts dried over $MgSO_4$, filtered, and evaporated. The residue was purified by flash column chromatography (8:2 light petroleum/ethyl acetate) to give the *title compound* as a light brown solid (295 mg, 40%), mp 148–150 °C. Found: [M+H$^+$], 575.2062. $C_{36}H_{31}O_7^+$ requires 575.2064; ν_{max} ($CHCl_3$)/cm^{-1} 3068, 3010, 2931, 1715, 1644, 1624, 1606, 1499, 1453, 1438, 1376, 1268, 1182, 1156, 1122, 1076; δ_H (400 MHz; $CDCl_3$) 8.00 (1H, s), 7.67 (2H, d, *J* 7.1), 7.51–7.34 (13H, m), 6.87 (1H, s, H-5), 6.55 (1H, d, *J* 2.3), 6.50 (1H, d, *J* 2.3), 5.31 (2H, s), 5.27 (2H, s), 5.25 (2H, s), 5.14 (2H, s), 3.56 (3H, s); δ_C (100 MHz; $CDCl_3$) 174.3 (C), 163.3 (C), 160.7 (C), 159.7 (C), 154.6 (C), 151.6 (C), 143.9 (C), 136.4 (C), 135.9 (C), 135.8 (C), 128.8 (CH×2), 128.6 (CH), 128.4 (CH), 128.3 (CH), 127.7 (CH), 127.6 (CH), 127.2 (CH), 126.8 (CH), 116.6 (C), 113.2 (CH), 107.5 (C), 101.0 (CH), 97.2 (CH), 96.1 (CH_2), 94.0 (CH), 71.0 (CH_2), 70.8 (CH_2), 70.5 (CH_2), 56.4 (Me).



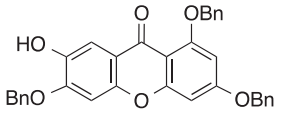
Also formed was *methyl 4-benzyloxy-2-(3,5-dibenzyloxy)phenoxy-5-methoxymethoxybenzoate* **10** (235 mg, 30%), mp 70–71 °C. Found: [M+Na$^+$], 629.2125. $C_{37}H_{34}NaO_8^+$ requires 629.2146; ν_{max} ($CHCl_3$)/cm^{-1} 3091, 3068, 3009, 1715, 1605, 1509, 1455, 1265, 1155, 1129; δ_H (400 MHz; $CDCl_3$) 7.73 (1H, s), 7.44–7.28 (15H, m), 6.60 (1H, s), 6.35 (1H, t, *J* 2.1), 6.12 (2H, d, *J* 2.1), 5.24 (2H, s), 5.05 (2H, s), 4.97 (4H, s), 3.75 (3H, s), 2.90 (3H, s); δ_C (100 MHz; $CDCl_3$) 165.0 (C), 160.7 (C), 160.3 (C), 153.6 (C), 151.5 (C), 143.1 (C), 136.7 (C), 135.8 (C), 128.7 (CH), 128.6 (CH), 128.2 (CH), 128.1 (CH), 127.6 (CH), 127.4 (CH), 120.1 (CH), 115.3 (C), 108.0 (CH), 96.9 (CH), 96.5 (CH), 96.1 (CH_2), 70.7 (CH_2), 70.1 (CH_2), 56.5 (Me), 52.0 (Me).

3.7. 1,3,6-Tribenzyloxy-7-methoxymethoxy-9*H*-xanthen-9-one 9 (method 2)

To a solution of methyl 4-benzyloxy-2-(3,5-dibenzyloxy)phenoxy-5-methoxymethoxybenzoate **10** (500 mg, 0.83 mmol) in methanol (14 mL) at 0 °C was added a solution of LiOH (395 mg, 16.5 mmol) in a mixture of THF/water (1:1, 7 mL), and the mixture was stirred at room temperature for 7 h. The mixture was concentrated under reduced pressure, the residue diluted with water (5 mL) and acidified to pH 6 with hydrochloric acid (2 M), and then extracted with ethyl acetate (3×20 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated under reduced pressure, to give the benzoic acid that was used immediately in the next step.

The above acid was taken up in dichloromethane (9 mL) and the solution cooled to 0 °C. Trifluoroacetic anhydride (0.69 mL, 4.95 mmol) was added slowly and the mixture was stirred for 3 h at room temperature. After this period, the mixture was concentrated under reduced pressure and diluted with a saturated solution of sodium hydrogen carbonate (10 mL). The mixture was extracted with dichloromethane (3×15 mL) and the combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure to give the title compound as a light brown solid (465 mg, 99%) that did not require further purification.

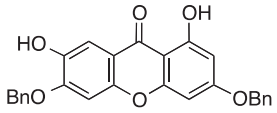
3.8. 7-Hydroxy-1,3,6-tribenzyloxy-9*H*-xanthen-9-one 11



To a solution of 1,3,6-tribenzyloxy-7-methoxymethoxy-9*H*-xanthen-9-one **9** (380 mg, 0.66 mmol) in anhydrous dichloromethane (24 mL) at 0 °C was added trifluoroacetic acid (4 mL), and the reaction mixture was stirred for 30 min at room temperature. Saturated aqueous sodium hydrogen carbonate (30 mL) was added slowly and the mixture extracted with ethyl acetate (3×30 mL). The combined organic extracts were washed with saturated brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residual oil was purified by flash column chromatography (7:3 light petroleum/ethyl acetate) to give the *title*

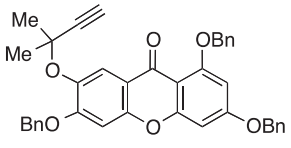
compound as a colorless solid (330 mg, 94%), mp 173–175 °C. Found: [M+H$^+$], 531.1814. $C_{34}H_{27}O_6^+$ requires 531.1802; ν_{max} ($CHCl_3$)/cm^{-1} 3687, 3603, 3011, 1630, 1602, 1500, 1438, 1272, 1239, 1174, 1118, 1017; δ_H (400 MHz; $CDCl_3$) 7.82 (1H, s), 7.62 (2H, d, *J* 7.3), 7.48–7.35 (13H, m), 6.91 (1H, s), 6.54 (1H, s), 6.48 (1H, s), 5.27 (2H, s), 5.24 (2H, s), 5.13 (2H, s); δ_C (100 MHz; $CDCl_3$) 175.0 (C), 163.5 (C), 160.7 (C), 159.8 (C), 151.2 (C), 150.2 (C), 143.0 (C), 136.3 (C), 135.7 (C), 135.0 (C), 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.4 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 126.8 (CH), 117.0 (C), 109.9 (CH), 107.3 (C), 99.6 (CH), 97.1 (CH), 94.0 (CH), 71.6 (CH_2), 70.8 (CH_2), 70.5 (CH_2).

3.9. 3,6-Dibenzyloxy-1,7-dihydroxy-9*H*-xanthen-9-one 12



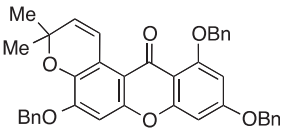
Anhydrous magnesium bromide (118 mg, 0.641 mmol) was added to 7-hydroxy-1,3,6-tribenzyloxy-9*H*-xanthen-9-one **11** (68 mg, 0.128 mmol) in toluene (2 mL) and the yellow suspension was heated to reflux and stirred for 15 h, turning deep red. Hydrochloric acid (5 mL) was added, and the aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography (2:3 ethyl acetate/light petroleum) to give the *title compound* as a pale yellow solid (5 mg, 10%); mp 173–174 °C. Found: [M+Na$^+$], 463.1149. $C_{27}H_{20}NaO_6^+$ requires 463.1200; ν_{max} ($CHCl_3$)/cm^{-1} 3632, 3550, 3071, 3013, 2947, 2890, 2852, 1654, 1614, 1488, 1289, 1174; δ_H (400 MHz; DMSO-d_6) 13.07 (1H, s), 9.87 (1H, s), 7.53–7.56 (10H, m), 7.23–7.21 (2H, m), 6.65 (1H, d, *J* 2.2), 6.46 (1H, d, *J* 2.2), 5.31 (2H, s), 5.25 (2H, s); δ_C (100 MHz; DMSO-d_6) 179.6 (C), 165.2 (C), 162.8 (C), 157.6 (C), 154.7 (C), 151.2 (C), 145.2 (C), 136.6 (C × 2), 129.0 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.43 (CH), 128.40 (CH), 113.3 (C), 108.2 (CH), 103.2 (C), 101.8 (CH), 97.9 (CH), 93.7 (CH), 70.8 (CH_2), 70.5 (CH_2).

3.10. 7-(2,2-Dimethylbut-3-ynyl)-1,3,6-tribenzyloxy-9*H*-xanthen-9-one 13



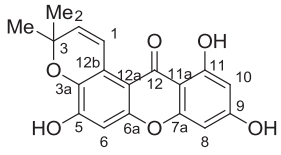
Potassium carbonate (82 mg, 0.594 mmol) and potassium iodide (82 mg, 0.49 mmol) were added to a solution of 7-hydroxy-1,3,6-tribenzyloxy-9*H*-xanthen-9-one **11** (150 mg, 0.283 mmol) in acetone (15 mL). 3-Chloro-3-methyl-1-butyne (80 μL, 0.707 mmol) was added in a single portion and the reaction mixture was heated to reflux and stirred for 48 h. After cooling, ether (60 mL) was added, and the ethereal solution was washed with aqueous NaOH (1 M; 3×10 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give a solid. This was purified by flash column chromatography (8:2 light petroleum/ethyl acetate) to give the *title compound* as a colorless solid (125 mg, 75%), mp 161–163 °C. Found: [M+H$^+$], 597.2287. $C_{39}H_{33}O_6^+$ requires 597.2272; ν_{max} ($CHCl_3$)/cm^{-1} 3305, 3011, 1645, 1623, 1605, 1498, 1443, 1379, 1270, 1182, 1119, 1048, 1028; δ_H (400 MHz; $CDCl_3$) 8.28 (1H, s), 7.65 (2H, d, *J* 7.3), 7.52 (2H, d, *J* 7.3), 7.46–7.34 (11H, m), 6.89 (1H, s), 6.55 (1H, d, *J* 1.8), 6.49 (1H, d, *J* 1.8), 5.28 (2H, s), 5.20 (2H, s), 5.13 (2H, s), 2.57 (1H, s), 1.72 (6H, s); δ_C (100 MHz; $CDCl_3$) 174.5 (C), 163.2 (C), 160.7 (C), 159.7 (C), 157.4 (C), 152.5 (C), 142.2 (C), 136.4 (C), 136.9 (C), 135.7 (C), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.1 (CH), 127.7 (CH), 127.6 (CH), 127.2 (CH), 126.8 (CH), 119.9 (CH), 116.4 (C), 107.6 (C), 100.7 (CH), 97.2 (CH), 94.1 (CH), 85.5 (C), 74.9 (C), 74.3 (CH), 70.9 (CH_2), 70.8 (CH_2), 70.5 (CH_2), 29.6 (Me).

3.11. 5,9,11-Tribenzyloxy-3,3-dimethylpyrano[3,2-*a*]xanthen-12(3*H*)-one 14



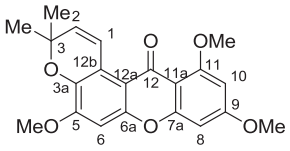
A solution of 7-(2,2-dimethylbut-3-ynyl)-1,3,6-tribenzyloxy-9*H*-xanthen-9-one **13** (10 mg, 0.02 mmol) in toluene (2 mL) was heated under reflux for 2.5 h. The solvent was evaporated and the residue purified by flash column chromatography (4:1 light petroleum/ethyl acetate) to give the *title compound* as a colorless solid (10 mg, 100%), mp 174–175 °C. Found: [M+H$^+$], 597.2283. $C_{39}H_{33}O_6^+$ requires 597.2272; ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2928, 1701, 1615, 1438, 1378, 1274, 1192, 1166, 1125, 1059, 1016; δ_H (400 MHz; $CDCl_3$) 8.14 (1H, d, *J* 9.8), 7.62 (2H, d, *J* 7.3), 7.49–7.35 (13H, m), 6.74 (1H, s), 6.48 (1H, d, *J* 2.1), 6.43 (1H, d, *J* 2.1), 5.85 (1H, d, *J* 9.8), 5.30 (4H, s), 5.09 (2H, s), 1.53 (6H, s); δ_C (100 MHz; $CDCl_3$) 176.9 (C), 162.9 (C), 160.5 (C), 158.8 (C), 152.3 (C), 151.3 (C), 139.8 (C), 136.6 (C), 136.4 (C), 135.8 (C), 131.8 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.0 (CH), 127.6 (CH×2), 126.9 (CH), 126.7 (CH), 121.6 (CH), 120.9 (C), 111.8 (C), 108.5 (C), 101.1 (CH), 97.3 (CH), 93.5 (CH), 75.3 (C), 70.8 (CH_2), 70.7 (CH_2), 70.4 (CH_2), 27.1 (Me).

3.12. 5,9,11-Trihydroxy-3,3-dimethylpyrano[3,2-*a*]xanthen-12(3*H*)-one (toxyloxanthone B) 3a



To a stirred solution of 5,9,11-tribenzyloxy-3,3-dimethylpyrano [3,2-*a*]xanthen-12(3*H*)-one **14** (2 mg, 0.005 mmol), and pentamethylbenzene (7 mg, 0.048 mmol) in dry dichloromethane (1 mL) at −78 °C was added BCl_3 (solution 1.0 M in dichloromethane; 0.03 mL) dropwise over 10 min. After 30 min at −78 °C, the reaction mixture was warmed to room temperature and stirred for 16 h. TLC and MS analysis showed the presence of the mono-benzylated compound, so extra BCl_3 (solution 1.0 M in dichloromethane; 0.03 mL) was added and the reaction mixture was stirred for a further 1 h, before being quenched with a mixture of chloroform and methanol (9:1, 2 mL). The excess solvent was removed under reduced pressure. The residue was purified by flash chromatography (4:1 light petroleum/ethyl acetate) to give the title compound as a pale yellow solid (1 mg, 64%), mp 318–319 °C (lit.,[17] mp 304–306 °C). Found: [M+H$^+$], 327.0864. $C_{18}H_{15}O_6^+$ requires 327.0863; ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3607, 1701, 1602, 1456, 1249, 1028, 850; δ_H (500 MHz; acetone-d_6) 13.38 (1H, s, 11-OH), 9.60 (1H, br s, 5-OH), 9.18 (1H, br s, 9-OH), 8.03 (1H, d, *J* 10.2, H-1), 6.82 (1H, s, H-6), 6.34 (1H, d, *J* 2.1, H-8), 6.21 (1H, d, *J* 2.1, H-10), 5.94 (1H, d, *J* 10.2, H-2), 1.46 (6H, s, Me-13); δ_C (125 MHz; acetone-d_6) 180.5 (C=O), 165.3 (C-7a), 163.3 (C-11), 157.0 (C-9), 157.0 (C-6a), 155.6 (C-5), 141.3 (C-4a), 129.6 (CH-2), 122.2 (CH-1), 118.0 (C-12b), 103.2 (CH-6), 102.0 (C-11a), 101.6 (C-12a), 97.6 (CH-10), 93.0 (CH-8), 74.9 (C-3), 26.2 (Me-13).

3.13. 5,9,11-Trimethoxy-3,3-dimethylpyrano[3,2-*a*]xanthen-12(3*H*)-one (toxyloxanthone B trimethyl ether) 3b



To a stirred solution of 5,9,11-trihydroxy-3,3-dimethylpyrano [3,2-*a*]xanthen-12(3*H*)-one **3a** (2 mg, 0.006 mmol), and anhydrous potassium carbonate (5 mg, 0.037 mmol) in acetone (1 mL) was added dimethyl sulfate (0.002 mL) and the mixture was heated to reflux and stirred for 16 h. The excess of solvents was removed under reduced pressure and the residue was purified by flash chromatography (4:1 light petroleum/ethyl acetate to 2:1 light petroleum/ethyl acetate) to give the title compound as a colorless solid (2 mg, 89%), mp 125–126 °C (lit.,[16] mp 192–193 °C). Found: $[M+H^+]$, 369.1343. $C_{21}H_{21}O_6^+$ requires 369.1333; ν_{max} ($CHCl_3$)/cm^{-1} 3156, 2903, 2254, 1795, 1618, 1467, 1383, 1097, 905, 650; δ_H (500 MHz; acetone-d_6) 8.10 (1H, d, *J* 10.2, H-1), 6.73 (1H, s, H-6), 6.42 (1H, d, *J* 2.3, H-8), 6.32 (1H, d, *J* 2.3, H-10), 5.77 (1H, d, *J* 10.2, H-2), 3.97 (3H, s, 11-OMe), 3.95 (3H, s, 5-OMe), 3.90 (3H, s, 9-OMe), 1.48 (6H, s, 3-Me); δ_C (125 MHz; acetone-d_6) 177.2 (C), 164.1 (C), 161.8 (C), 158.9 (C), 153.4 (C), 151.6 (C), 139.2 (C), 131.6 (CH), 121.5 (CH), 120.7 (C), 111.2 (CH), 107.9 (C), 98.7 (C), 95.0 (CH), 92.1 (CH), 75.4 (C), 56.3 (OMe), 56.2 (OMe), 55.6 (OMe), 27.1 (Me).

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Supplementary data

Copies of NMR spectra. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.12.055.

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