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A Brief and Convergent Synthetic Route to Defucogilvocarcin M Chromophore: The Formal Synthesis of WS-5995 A and C

Asit Patra, Pallab Pahari, Sutapa Ray, and Dipakranjan Mal*

Department of Chemistry, Indian Institute of Technology, Kharagpur 721 302, India

dmal@chem.iitkgp.ernet.in

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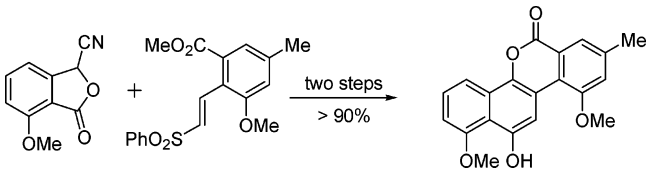

Densely substituted styryl sulfone **20** is shown to undergo double annulation with phthalide **21** to give, in one-pot operation and in excellent yield, the benzonaphthopyranone scaffold **22** of gilvocarcins.

The gilvocarcin family of polyketide natural products has stimulated considerable interest by virtue of their challenging structures and potent antitumor activities.[1,2] Since 1987, several research groups have pioneered the development of synthetic methodologies and total syntheses for this class of molecules.[3] Despite the classic solution to the synthesis of the gilvocarcins **1** by Suzuki et al., the synthetic interest in these molecules remains unabated.[4] In fact, the presence of the amino group in sugar moiety of ravidomycin (**2**) has necessitated a newer synthesis of its chromophore (**3**).[4a] Moreover, the synthesis of highly substituted arylnaphthoquinones present in naturally occurring quinonoids (e.g., **4** and angelmicin B[5]) could be more challenging than anticipated (Figure 1).

We report herein an efficient and new synthesis of benzonaphthopyranone chromophore of the gilvocarcin family.

Recently, we reported that the Hauser−Kraus annulation could be maneuvered for direct entry to the pentacyclic ring system (**7**) of chrymutasin (Scheme 1).[6] The ester group in the peri-position of partially dearomatized naphthalene derivative **6** served as a handle for in situ fabrication of the lactone ring following the first annulation. Recognizing the utility of such a strategy for the synthesis of gilvocarcin chromophores, we decided to investigate the reactivity of styryl sulfones toward Hauser−Kraus donors, because aryl sulfone moieties are both electron-withdrawing and easily removable by reductive procedures or base-induced elimination reactions.[7]

As a background study, we initially examined reactivity of styryl sulfone **10** toward Hauser−Kraus annulation (Scheme 2). The ester group ortho to the vinyl sulfone group in **10** was expected to undergo in situ lactone formation giving tetracyclic sulfone **15**. Accordingly, styryl sulfone **10**, prepared[8] from methyl anthranilate through Heck reaction of its diazonium salt with phenyl vinyl sulfone, was submitted to reaction with isobenzofuranone **8** in the presence of freshly prepared lithium *tert*-butoxide at −60 °C. After 2 h at room temperature, the reaction was quenched with a solution of ammonium chloride. Chromatographic purification of the crude product yielded three products as summarized in Scheme 2. Although we anticipated formation of the sulfone-containing tetracyclic compound **15**, all three products **11**, **13**,[9] and **16** were devoid of the phenylsulfonyl group. The desulfonylation possibly occurred after the initial Hauser−Kraus annulation and lactone ring formation. The structure of the major product (i.e., **11**; 68%) was established by its conversion to methyl ester **12**, which is known in the literature.[9] It may be noted that the benzonaphthopyranone skeleton represented by structure **16**[10] is found in many natural products, namely WS-5995 A. The reaction of isobenzofuranone **9**[11] with **10** similarly proceeded with a product profile similar to that of **8**. Since arylnaphthoquinones of the type **11** are convertible to benzonaphthopyranones (see **13**) through reduction followed by acid-catalyzed lactonization,[9] we were encouraged to examine the reactivity of styryl sulfone **20**, which would give the required substitution pattern of gilvocarcins.

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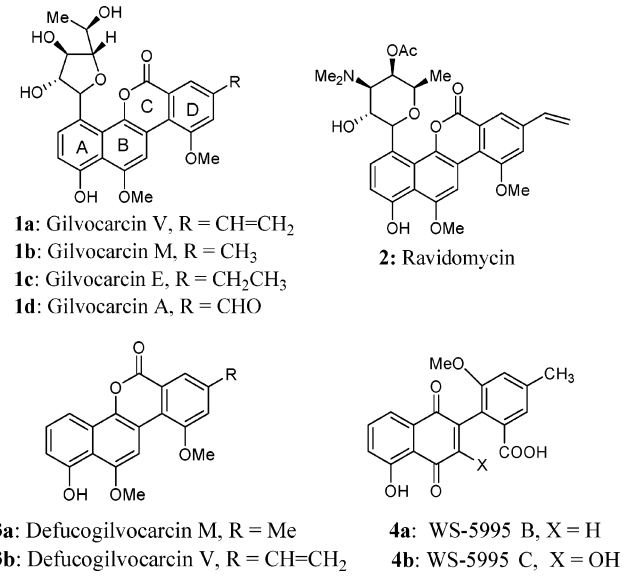
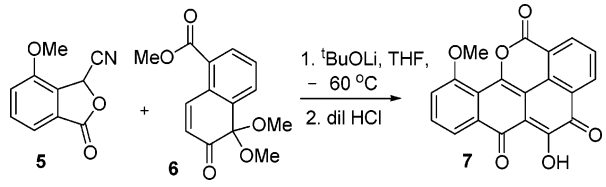
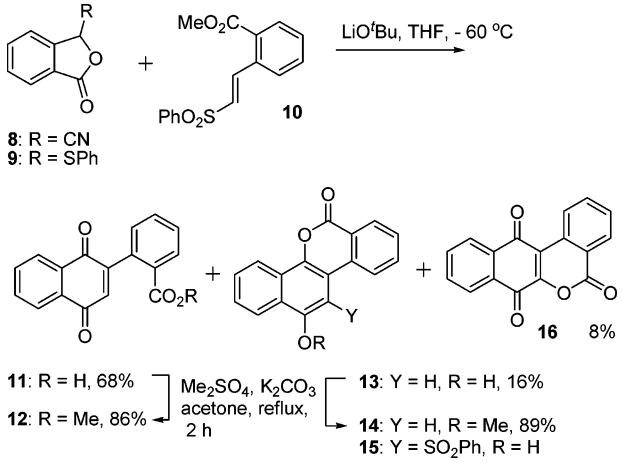


FIGURE 1. Gilvocarcin and WS-5995 antibiotics.

SCHEME 1. Strategy for Chrymutasins[6]



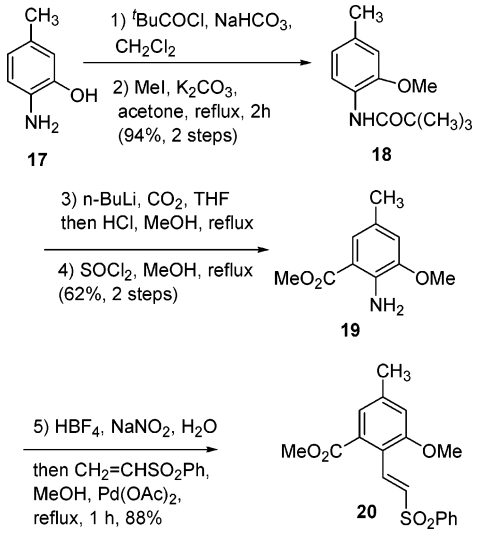
SCHEME 2. Annulation with Styryl Sulfone 10



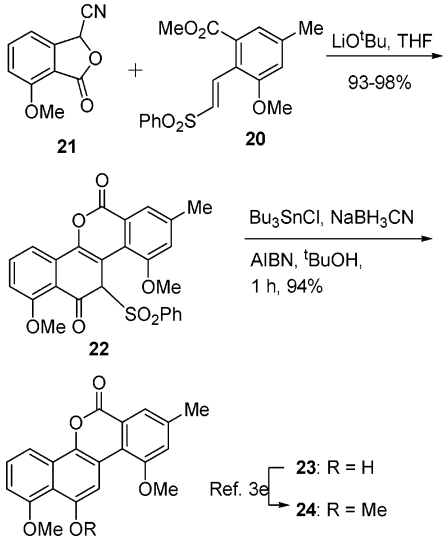
The preparation of sulfone **20** was achieved by extending Heck reaction[8] to the diazonium salt of amine **19**, which was, in turn, synthesized in four steps from commercially available amine **17** (Scheme 3) by a modification of the sequence[3d] developed by McKenzie et al. Though the amine group in **19** was flanked by two ortho substituents, in situ Heck coupling of its diazonium salt with phenyl vinyl sulfone in the presence of a catalytic amount of $Pd(OAc)_2$ smoothly provided the desired styryl sulfone **20** in 88% yield. The structure of styryl sulfone **20** was established by analysis of NMR data.

Results of the annulation study of sulfone **20** with isobenzofuranone **21** are presented in Scheme 4. The anion of cyanophthalide **21**, generated at −60 °C by reaction with lithium *tert*-butoxide, was treated with

SCHEME 3. Preparation of Styryl Sulfone 20



SCHEME 4. Preparation of Defucogilvocarcin Derivative 23



sulfone **20** for about 1 h. Subsequently, the reaction mixture was allowed to return to room temperature under ambient conditions during a period of 1 h. After quenching (aqueous NH_4Cl) and routine workup, we isolated a crystalline yellow solid as the sole product **22** in 93−98% yields, which was further purified by recrystallization. Unlike the products (i.e., **11**, **13**, and **16** from styryl sulfone **10**), compound **22** retained the phenyl sulfone group. In stark contrast to the fact that Hauser−Kraus annulation always provides 1,4-dihydroxynaphthalene derivatives,[12] the compound **22** exists in the keto form. The structure of **22** was confirmed by its X-ray crystallographic analysis as well as NMR data (Figure 2).

To arrive at the gilvocarcin nucleus, it was necessary to remove the $PhSO_2$ group in compound **22**. Of the many methods available for desulfonylation,[13] we chose to employ $Bu_3SnCl/NaCNBH_3$, considering the susceptibility of the lactone present in **22** to base-catalyzed ring opening. When compound **22** was subjected to reductive desulfonylation[14] with the above reagent, the product **23**,

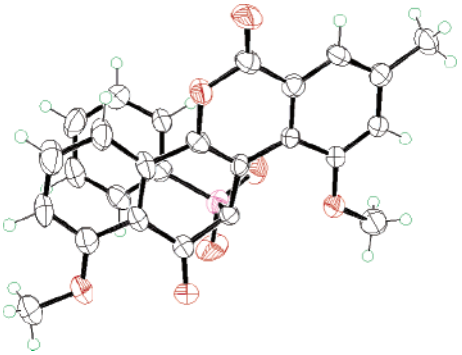


FIGURE 2. ORTEP plot of X-ray crystal structure of **22**.

an isomer of gilvocarcin M, was obtained in 94% yield. Comparison of the NMR data with those of the literature[15] authenticated the structure of the product. The synthesis of **23** could be regarded as the formal total synthesis of WS-5995 A and C (**4b**) antibiotics, which have been previously synthesized[10] from the methyl ether derivative **24**.

In summary, condensation of an appropriately substituted styryl sulfone with a phthalide has provided a regiospecific convergent synthesis of benzo[*d*]naphtho-[1,2-*b*]pyran-6-one nucleus of gilvocarcin antibiotics. This route has resulted in a brief and efficient synthesis of benzonaphthopyranone **23**, an established late-stage intermediate to WS-5995 A and C antibiotics. We believe that this work should be applicable to other polycyclic aromatic natural products, namely phenanthroviridins, jadomycin A, kinamycins, and *C*-glycosidic polyketides.[16]

Experimental Section

General Procedure for Annulation. To a stirred solution of lithium *tert*-butoxide (9.84 mmol) in THF (40 mL) at −60 °C (chloroform/liquid N_2 bath) under an inert atmosphere was added a solution of a phthalide (3.28 mmol) in THF (5 mL). The resulting yellowish solution was stirred at −60 °C for 25 min, after which a solution of a Michael acceptor (1.0−1.5 equiv unless otherwise stated) in THF (5 mL) was added to it. The cooling bath was removed after about 1 h at −60 °C, and the reaction mixture was brought to room temperature over a period of 1 h and further stirred for 2−6 h. The reaction was then quenched with 10% NH_4Cl (15 mL), and the resulting solution was concentrated. Generally, a bright yellow solid appeared, which was filtered and washed with 1:1 mixture (20 mL) of diethyl ether and petroleum ether. Otherwise, the residue was diluted with ethyl acetate (50 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 25 mL). The combined extracts were washed with brine and H_2O, dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography on silica gel or by recrystallization. This procedure was adopted for the preparation of compounds **11** and **22**.

2-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)benzoic Acid (11): Yellow solid. mp 193−195 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, J = 7.4 Hz, 2H), 8.08 (dd, J = 7.4 Hz, 1.3 Hz, 1H), 7.89−7.71 (m, 2H), 7.67 (dt, J = 7.5 Hz, 1.2 Hz, 1H), 7.56 (dt, J = 7.5 Hz, 1.2 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H), 6.91 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.3, 184.1, 169.6, 151.8, 136.1, 134.1, 134.0, 133.7, 133.7, 132.6, 132.5, 131.2, 130.5, 129.9, 129.3, 127.2, 126.3. MS EI (70 eV), *m/z*: 293 (100%), 278 (M^+), 262, 248, 233, 222, 206, 176, 162. Anal. Calcd for $C_{17}H_{10}O_4$: C, 73.38; H, 3.62. Found: C, 73.31; H, 3.37.

2-Methoxy-4-methylpivalanilide (18). Trimethylacetyl chloride (2.50 g, 20.75 mmol) was added dropwise to a stirred mixture of 2-amino-5-methylphenol (2.00 g, 16.26 mmol) and aqueous $NaHCO_3$ (1.65 g, 19.64 mmol, in 10 mL of H_2O) in dichloromethane (20 mL) at room temperature. Stirring was continued for 25 min, and then the resulting reaction mixture was diluted with water (50 mL) and extracted with dichloromethane (3 × 25 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated to provide 2-hydroxy-4-methylpivalanilide. Methyl iodide (2.27 mL, 5.15 g, 36.27 mmol) was added to a solution of 2-hydroxy-4-methylpivalanilide and K_2CO_3 (7.0 g, 50 mmol) in dry acetone (25 mL) at 0 °C, and stirring was continued for 3 h. After completion of the reaction, inorganic salts were filtered and the filtrate was concentrated. The residue was diluted with ether (100 mL) and successively washed with water (2 × 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated to give an oil. The crude liquid was further purified by column chromatography on silica gel (10% ethyl acetate−petroleum ether) to provide 2-methoxy-4-methylpivalanilide (**18**) (3.38 g, 94%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.25 (d, J = 8.1 Hz, 1H), 8.06−8.00 (brs, 1H), 6.75 (d, J = 8.1 Hz, 1H), 6.68 (s, 1H), 3.87 (s, 3H), 2.31 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.2, 147.8, 133.1, 125.2, 121.3, 119.3, 110.6, 55.7, 39.8, 27.6, 21.3.

Methyl 3-Methoxy-5-methylanthranilate (19). *n*-Butyllithium (1.6 M in hexane, 6.2 mL, 9.92 mmol) was added over a period of 5 min to a stirred solution of 2-methoxy-4-methylpivalanilide (1 g, 4.52 mmol) in THF (12 mL) at room temperature under dry N_2 atmosphere. After an additional 30 min, the solution was cooled to −78 °C (ethyl acetate/liquid N_2 bath), carbonated by passing dry CO_2 through the reaction mixture, and stirred continually for 2 h while maintaining an internal temperature of −78 °C. The reaction mixture was warmed to room temperature and was quenched with saturated $NaHCO_3$ solution (40 mL). The mixture was extracted with ethyl acetate (2 × 20 mL). The resulting aqueous layer was acidified with dilute HCl. The aqueous solution was successively extracted with ethyl acetate (3 × 40 mL), dried (Na_2SO_4), and concentrated. Purification of the crude product by recrystallization from ethyl acetate−petroleum ether gave a white crystalline solid. The white solid compound was refluxed with 10 mL of 25% aqueous HCl in methanol (5 mL) for 12 h. After cooling, the reaction mixture was diluted with H_2O (30 mL) and extracted with ethyl acetate (3 × 25 mL), washed with brine, dried (Na_2SO_4), and concentrated to afford a solid residue. The residue was dissolved in dry methanol (12 mL), and $SOCl_2$ (0.9 mL, 12 mmol) was added dropwise at 0 °C for 10 min. After being stirred for 1 h at 0 °C, the resulting reaction mixture was heated at reflux for 2 h. MeOH was removed, and the residue was diluted with aqueous $NaHCO_3$ solution (45 mL). The resulting mixture was extracted with ether (3 × 25 mL). The combined organic phases were washed with water and brine and concentrated. The residue on column chromatographic purification afforded **19** as an oil in 62% yield (550 mg). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27

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(d, J = 1.7 Hz, 1H), 6.69 (d, J = 1.7 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.6, 147.1, 139.2, 124.0, 121.6, 114.4, 109.9, 55.6, 51.3, 20.8.

Methyl 2-(2-Benzenesulfonylvinyl)-3-methoxy-5-methylbenzoate (20). A solution of $NaNO_2$ (170 mg, 2.46 mmol) in water (0.5 mL) was added dropwise to an ice-cold solution of **19** (390 mg, 2.00 mmol) in 40% aqueous HBF_4 (1.2 mL). Stirring was continued for 45 min at 0 °C, after which phenyl vinyl sulfone (370 mg, 2.20 mmol) in MeOH (0.5 mL) and $Pd(OAc)_2$ (10 mg, 0.043 mmol) were added to the above mixture. This was then heated on water bath for 1 h. The resulting mixture was cooled to room temperature and extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were successively washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography using petroleum ether−ethyl acetate (4:1) to give **20** (610 mg, 88%) as a white solid. mp 135−137 °C; IR (KBr) cm^{-1} 1716, 1599, 1461, 1438, 1323, 1296, 1223, 1169, 1142, 1065, 984, 887; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.09 (d, J = 15.4 Hz, 1H), 7.97 (dd, J = 7.4 Hz, 1.7 Hz, 2H), 7.61−7.46 (m, 3H), 7.22 (s, 1H), 7.15 (d, J = 15.4 Hz, 1H), 6.87 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.7, 158.9, 141.8, 141.1, 136.5, 133.5, 133.0, 130.9, 129.1, 127.6, 123.0, 118.0, 115.0, 55.8, 52.5, 21.6; MS ESI (70 eV): $[M + H]^+$, 347.0782, $[M - OCH_3]^+$, 315.0530; Anal. Calcd for $C_{18}H_{18}O_5S$: C, 62.41; H, 5.24. Found: C, 62.32; H, 5.47.

11-Phenylsulfonyl-1,10-dimethoxy-8-methyl-11*H*-dibenzo[*c*,*h*]chromene-6,12-dione (22): Yellow solid; mp 198−200 °C; IR (KBr) cm^{-1} 1732 (s), 1684 (s), 1622, 1583, 1471, 1444, 1322 (s), 1292, 1265, 1232, 1176, 1132, 1112, 1051, 1016, 784, 730, 686; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.59−7.15 (m, 7H), 7.08 (s, 1H), 6.94−6.85 (m, 1H), 6.63 (s, 1H), 3.99 (s, 3H), 3.93 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 186.7, 160.5, 159.3, 156.5, 146.2, 141.0, 136.9, 135.8, 134.2, 133.9, 129.1, 128.3, 122.3, 122.1, 118.5, 118.2, 115.9, 113.4, 105.6, 75.0, 56.2, 56.1, 21.7 (one predicted signal was not observed); HMRS ESI (70 eV): for $C_{26}H_{21}O_7S$ $[M + H]^+$ calcd 477.1008, found 477.1005.

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Supporting Information Available: Experimental details and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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