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Synthesis of the isocoumarin portion of the rubromycins

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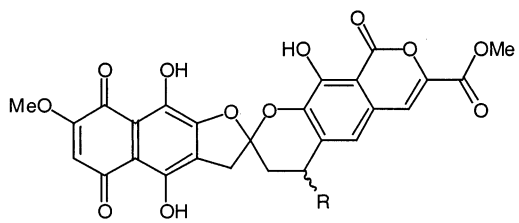
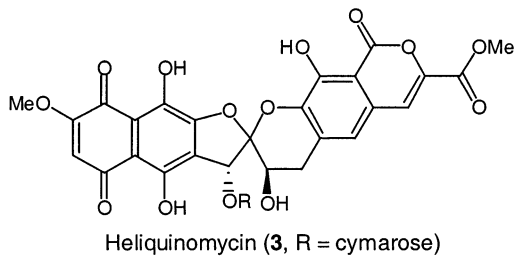
Abstract—A synthesis of the isocoumarin found in the rubromycin class of natural products is reported. The isocoumarin ring system is formed via Heck coupling of a pyruvate synthon with a terephthalic acid derivative followed by an intramolecular acid-catalyzed cyclization. The requisite terephthalic acid precursor is generated by carboxylation of catechol and then desymmetrization of the aromatic ring by halogenation. The isocoumarin derivative that has been produced is an appropriate precursor for the synthesis of γ-rubromycin, purpuromycin, and heliquinomycin.

γ-Rubromycin (**1**),[1] purpuromycin (**2**),[2] and heliquinomycin (**3**)[3] are a set of structurally related pigments consisting of naphthazarin and isocoumarin ring structures linked through a 5,6-spiroketal. The synthesis of this unique class of antitumor antibiotic compound has yet to be achieved although they display a range of biological activity. γ-Rubromycin (**1**) exhibits activity against the reverse transcriptase of human immunodeficiency virus-1[4] and against human telomerase which is overproduced in cancer cells;[5] purpuromycin (**2**) is a potential topical agent for vaginal infections[6] and heliquinomycin (**3**) is an inhibitor of DNA helicase.[3]





Keywords: isocoumarin; rubromycin; purpuromycin; antitumor; antibiotic.

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Due to the recent report of a synthesis of the isocoumarin portion of heliquinomycin,[7] we were prompted to report our efforts toward the synthesis of a common isocoumarin precursor **5** which could be employed in the syntheses of **1**–**3** (Fig. 1). Activation of **5** as the tosylate **4** would provide the isocoumarin precursor for γ-rubromycin and heliquinomycin, while oxidation of alcohol **5** to the aldehyde **6** would provide the requisite precursor for purpuromycin (**3**).

The synthesis of isocoumarin **5** began with catechol (**7**), which was subjected to carbon dioxide under high pressure to produce dihydroxyterephthalate **8** (Scheme 1).[8] Fischer esterification and protection of the phenols of **8** provided the dimethyl 2,3-dimethoxyterephthalate

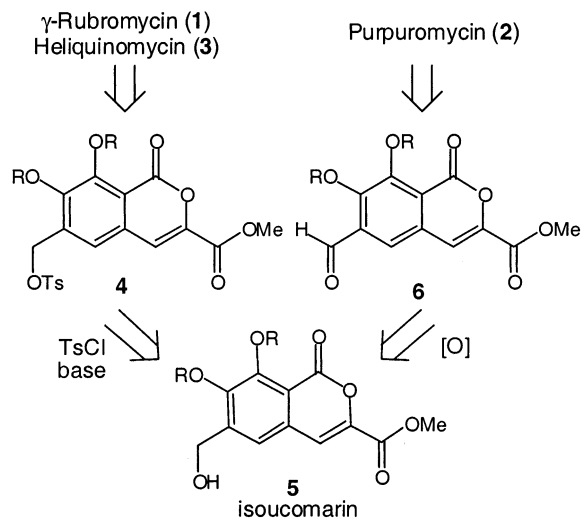

Figure 1.

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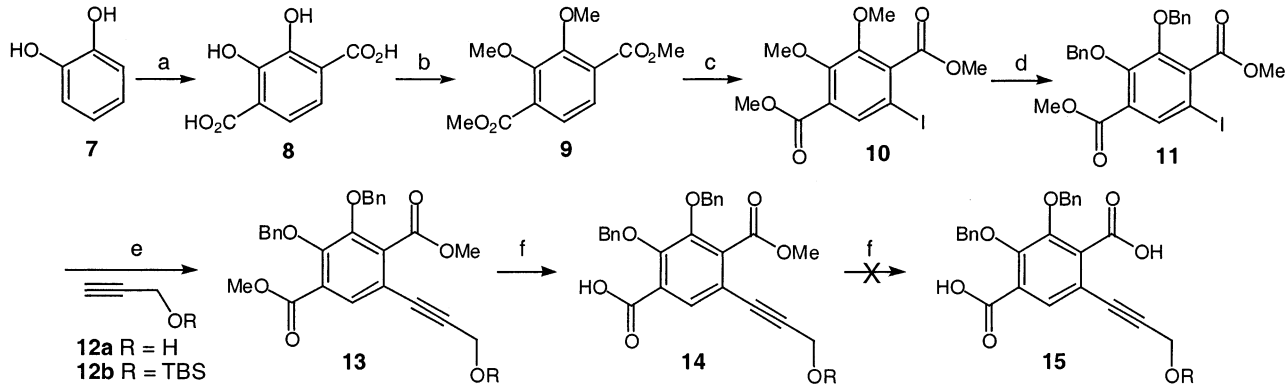


Scheme 1. (a) i. NaOH, ii. CO_2, 80 atm, 200°C, 48 h, 54% overall yield; (b) i. MeOH, HCl, 75%, ii Me_2SO_4, K_2CO_3, 100%; (c) i. $AgNO_3$, TFAA, ii. H_2, Raney Ni, iii. H^+, $NaNO_2$, KI, 86% overall yield; (d) i. BBr_3, ii. BnBr, K_2CO_3, 86% overall yield; (e) $Pd(PPh_3)_4$, CuI, Et_3N, 93–97%; (f) i. LiOH, H_2O/THF or KOH, H_2O/MeOH, Δ.

(**9**). At this point, the symmetry of **9** was broken via iodination to **10**. Direct iodination of arene **9** was not viable due to the deactivating influence of the aromatic ring substituents towards a positive source of iodine. Instead, a three-step sequence was employed: nitration of the ring according to the method of Crivello[9] was followed by reduction to the aniline and Sandmeyer reaction to afford aryl iodide **10** efficiently (86% yield for three steps).[10]

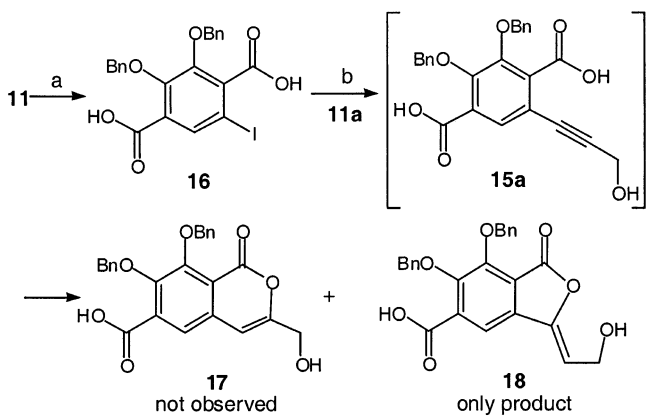
Initial efforts have been directed toward protecting the catechol derivatives as the corresponding bis-methyl ethers (i.e. **10**). However, difficulties may arise in removing the methyl ethers in any synthesis of **1**–**3**, due to the potential sensitivity of the molecule towards the standard Lewis acidic conditions (BBr_3, for example). Thus, we have shown that aryl iodide **10** can be transformed to its corresponding bis-benzyl ether **11** via a two-step sequence in 80% overall yield. The lability of benzyl ethers towards catalytic hydrogenolysis offers a mild alternative that should prove compatible with the remaining functionality in **1**–**3**.

Sonagashira coupling of propargyl alcohol (**12a**) or its silyl ether derivative (**12b**) to arene **11** was readily accomplished; however, hydrolysis of the hindered ester group in **14** proved impossible at this stage (Scheme 1). Without the free carboxylate, cyclization to an isocoumarin did not proceed. As a solution to this problem, hydrolysis of the esters was undertaken prior to Sonagashira coupling (Scheme 2). Both methyl esters could be cleaved to provide bisacid **16** even though hydrolysis of the ester flanked by two *ortho* substituents required forcing conditions (KOH, H_2O/MeOH, Δ). Sonagashira coupling of the resultant iodide **16** with propargyl alcohol was then undertaken in the presence of $ZnCl_2$. Even though this protocol had been shown to provide the isocoumarins in related systems,[11] only the isophthalide product **18** from 5-*exo* dig cyclization was observed in this more functionalized case.

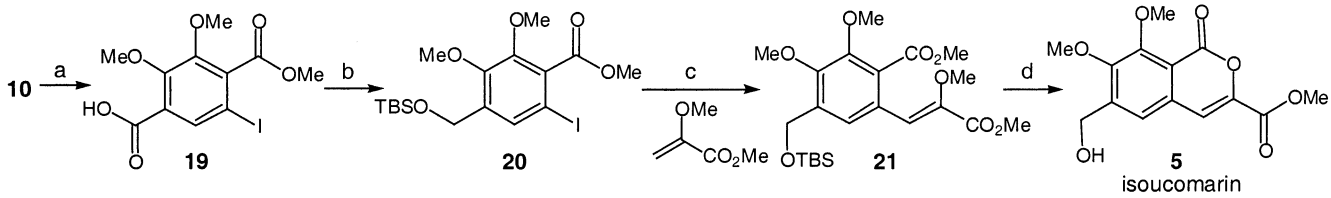
In order to generate the desired isocoumarin isomer, a modified approach was employed in which the latent lactone carbonyl would act as an electrophile instead of a nucleophile, thereby eliminating the regioselection problem during cyclization. A palladium catalyzed Heck-type coupling of *ortho*-iodo benzoates with acrylate derivatives provided the necessary construction (Scheme 3, **20** to **21**).[12] Exercising this strategy on diester **10** would lead to a compound with three methyl esters which would be difficult to selectively functionalize. As such, the regioselective saponification discovered earlier of the less hindered methyl ester (*meta* to the iodide) of **10** using LiOH in wet THF was applied to generate **19**. Chemoselective reduction of the resulting carboxylic acid to the corresponding alcohol[13] and subsequent protection as the silyl ether afforded **20** in 87% overall yield from **10**.

Application of the Heck coupling with the methyl enol ether of methyl pyruvate and **20** provided 71% of the coupled **21** along with 23% recovered starting material (Scheme 3). Acid catalyzed intramolecular condensation of **21** in 5% HCl/MeOH resulted in formation of isocoumarin along with concomitant removal of the silyl ether to provide isocoumarin precursor **5** directly in 83% yield.

At this point, **5** possesses the appropriate functionality for introduction of the isocoumarin subunit into **1**–**3** (Fig. 1). The isocoumarin portion of the griseorhodins[14]



Scheme 2. (a) i. LiOH, H_2O/THF, ii. KOH, H_2O/MeOH, Δ, 100% overall yield; (b) $Pd(PPh_3)_4$, $ZnCl_2$, Et_3N.



Scheme 3. (a) LiOH, THF/H_2O; (b) i. BH_3, THF, ii. TBSCl, imidazole, 87% from **10**; (c) $Pd(PPh_3)_4$, K_2CO_3, 71%+23% **20**; (d) 5% HCl/MeOH, 83%.

could also be obtained via this route by substituting acetone enol ether in place of methyl pyruvate enol ether during the Heck coupling. Further progress towards these natural products and derivatives thereof will be reported in due course.

Acknowledgements

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10. All new compounds were characterized. **5**: IR (film) 3424, 2926, 2853, 1737 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.95 (s, 3H), 3.97 (s, 3H), 4.03 (s, 3H), 4.83 (s, 3H), 7.34 (s, 1H), 7.41 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.8, 60.7, 61.3, 61.9, 112.2, 116.3, 121.9, 132.3, 142.5, 143.3, 152.7, 157.0, 154.5, 160.8; HRMS (CI) m/z calcd for $C_{14}H_{15}O_7$ (MH^+) 295.0809, found 295.0810. **10**: IR (film) 2949, 1736, 1391, 1281 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.87 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 3.94 (s, 3H), 7.90 (s, 1H); ^{13}C NMR δ ($CDCl_3$, 125 MHz) δ 52.5, 52.9, 61.6, 61.8, 83.4, 128.6, 135.8, 139.3, 151.4, 153.2, 164.3, 166.5; HRMS (CI) m/z calcd for $C_{12}H_{13}IO_6$ (M+) 379.9738, found 379.9741. **11**: IR (film) 2949, 1735, 1278 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.87 (s, 3H), 3.89 (s, 3H), 5.10 (s, 2H), 5.11 (s, 2H), 7.32–7.43 (m, 10H), 8.00 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.5, 52.9, 76.4, 76.6, 84.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 129.2, 136.2, 139.8, 150.7, 152.1, 164.2, 166.5; HRMS (CI) m/z calcd for $C_{24}H_{21}IO_6$ (M^+) 532.0356, found 532.0360. **16**: mp 144°C, IR (film) 3331, 1737 cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz) δ 5.17 (s, 2H), 5.22 (s, 2H), 7.38–7.53 (m, 10H), 8.10 (s, 1H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 76.5, 76.7, 83.9, 128.6, 128.7, 128.8, 128.9, 129.8, 136.8, 137.1, 137.2, 141.3, 150.6, 152.7, 164.6, 167.0; HRMS (CI) m/z calcd for $C_{22}H_{17}IO_6$ (M^+) 504.0069, found 504.0072. **18**: IR (film) 3366, 1776, 1637 cm^{-1}; ^1H NMR (CD_3OD), 500 MHz) δ 4.35 (d, 2H, $J=7.0$ Hz), 5.02 (s, 2H), 5.21 (s, 2H), 5.77 (t, 1H, $J=7.1$ Hz), 7.19–7.37 (m, 10H), 7.47 (s, 1H). **19**: mp 149–150°C; IR (film) 3381, 1737, 1462, 1280 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.90 (s, 3H), 3.99 (s, 3H), 4.07 (s, 3H), 8.24 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 53.1, 62.1, 62.2, 84.7, 125.4, 137.5, 141.0, 150.6, 152.8, 164.9, 166.2; HRMS (CI) m/z calcd for $C_{11}H_{11}IO_6$ (M^+) 365.9600, found 365.9613. **20**: IR (film) 2951, 1739, 1396, 1269 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.11 (s, 6H), 0.94 (s, 9H), 3.83 (s, 3H), 3.84 (s, 3H), 3.94 (s, 3H), 4.70 (s, 2H), 7.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 5.5, 18.3, 25.9, 52.7, 59.3, 60.3, 61.5, 84.1, 132.9, 134.6, 138.9, 149.7, 149.9, 167.4; HRMS (CI) m/z calcd for $C_{17}H_{26}IO_5Si$ ($[M-H]^+$) 465.0593, found 465.0592. **21**: IR (film) 2951, 1726, 1282, 1284 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.13 (s, 6H), 0.95 (s, 9H), 3.72 (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 3.94 (s, 3H), 4.76 (s, 2H), 7.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.5, 18.4, 25.9, 52.2, 52.4, 59.4, 60.0, 60.4, 61.3, 119.2, 124.4, 126.4, 128.9, 137.2, 146.1, 149.2, 149.7, 164.6, 167.5; HRMS (CI) m/z calcd for $C_{22}H_{35}O_8Si$ (MH^+) 455.2099, found 455.2090.
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