An Approach to Benzannelated [5,6]-Spiroketals

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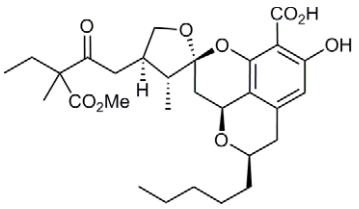
Abstract: Heating a variety of 2-hydroxybenzyl acetates bearing a range functional groups on the 4- or 5-position of the aromatic ring at 100 °C in neat γ-methylene-γ-butyrolactone (1.0 M) for 20 hours gives a series of benzannelated [5,6]-spiroketals in 75–89% yield.

Key words: Diels–Alder reactions, spiro compounds, heterocycles, natural products, *ortho*-quinone methide

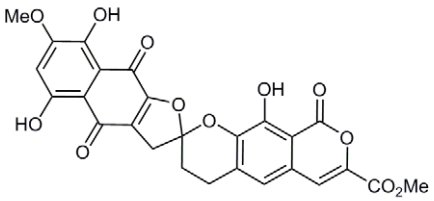
A number of natural products contain a 5,6-spiroketal moiety, where one, or both, of the rings is benzannelated e.g. berkelic acid (**1**), the rubromycins **2** and **3**, purpuromycin (**4**), heliquinomycin (**5**) and the griseorhodins **6** and **7** (Figure 1).[1]

All of the natural products **1**–**7** display a range of biological activities, which has contributed to the opinion that spiroketals are privileged pharmacophores.[2] A number of methods have been developed to access the key benzannelated 5,6-spiroketal of these molecules, however these have overridingly relied upon cyclodehydration of a ketodiol precursor, which have themselves required numerous synthetic steps to construct.[3,4] Another issue when considering the synthesis of a bisbenzannelated [5,6]-spiroketal from a bisphenolic ketone is the competitive formation of a benzofuran. This problem is a real concern when the aromatic rings bear electron-withdrawing groups,[3c] as would be required for the synthesis of **2**–**7**. It has been noted,[1b] that new methods are currently needed for the construction of benzannelated [5,6]-spiroketals.

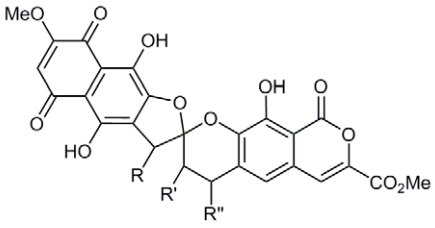
It was recently shown by the current author that a simple *ortho*-quinone methide (*o*-QM)[5] can be generated from 2-hydroxybenzyl acetate (**8a**) by deprotonation of the phenolic proton with *i*-PrMgCl at –78 °C and warming the resultant anion to room temperature.[6] This process was sufficiently mild that 2π partners which are highly sensitive to isomerisation, e.g. 2-methylenetetrahydrofuran, could be employed in ensuing hetero-Diels–Alder reactions. This resulted in a rapid and straightforward way of making monobenzannelated [5,6]- and [6,6]-spiroketals. The development of this process was based on an earlier report by Loubinoux et al.[7] who examined the base-mediated nucleophilic displacement of acetate from such precursors presumably via an intermediate *ortho*-quinone methide. However, more recently than the report by Loubinoux et al., Baldwin and his co-workers had shown that simply heating 2-hydroxybenzyl acetates led to elimination of acetic acid and the production of an *ortho*-quinone methide.[8,9] In the current authors hands, it was found that the application of 2-methylenetetrahydrofuran in this latter process unsurprisingly resulted in isomerisation of this sensitive 2π partner to the corresponding *endo* isomer. In the present work, it was considered whether the use of γ-



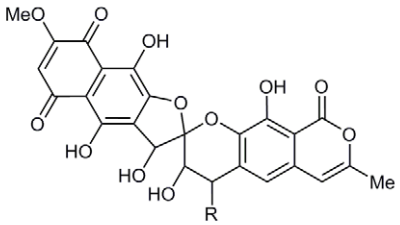
Berkelic acid **1**



β-Rubromycin **2**



γ-Rubromycin **3**: R = H, R' = H, R" = H
Purpuromycin **4**: R = H, R' = H, R" = OH
Heliquinomycin **5**: R = *O*-cymarose, R' = OH, R" = H



Griseorhodin C **6**: R = OH
Griseorhodin G **7**: R = H

Figure 1

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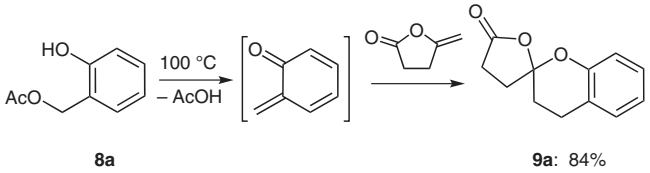
methylene-γ-butyrolactone as the 2π partner might be compatible with this latter procedure since it is far less likely to undergo isomerisation. This was indeed found to be the case, and simply heating 2-hydroxybenzyl acetate (**8a**) at 100 °C in neat γ-methylene-γ-butyrolactone (1.0 M) for 20 hours gave the benzannelated spiroketal **9a** in 84% yield (Scheme 1).[10] Perhaps surprisingly, as far as could be determined, none of the excess 2π partner had isomerised, even though under the reaction conditions, it had been exposed to acetic acid at 100 °C.



8a **9a**: 84%

Scheme 1

One advantage of this procedure over the previously developed base-mediated process[6a] is that the lactone functionality that is retained in the product, allows for further synthetic manipulation of the furan ring. Therefore, a range of substituted 2-hydroxybenzyl acetates **8b–k** were examined as *ortho*-quinone methide precursors.[11] It was found that electron-donating groups (OAc, Me, Cl) were tolerated during this process at the 4-position of the 2-hydroxybenzyl acetates to give the corresponding benzannelated spiroketals **9b–d** in 76–78% yield (Table 1). Importantly, an electron-withdrawing substituent (CO_2Me) could also be incorporated to give **9e** without detriment to the yield (79%). Electron-donating groups (Me and OMe) as well as halogens (Cl and Br) could also be introduced on to the 5-position and again notably, electron-withdrawing groups (NO_2, and CO_2Me) giving the spiroketals **9f–k** in good yield in every case (Table 1).

In conclusion, a rapid approach to the synthesis of aryl-substituted benzannelated [5,6]-spiroketals has been developed. A small array of such compounds has been synthesised, many in only two steps from the commercially available diols. This process proceeds via a series of *ortho*-quinone methides, the majority of which have never been described before. The yields for the hetero-Diels–Alder reactions were in the range 75–89%. The tolerance of electron-withdrawing substituents on the aromatic ring is of note, as is the formation of **9h**, since the bromide could be further elaborated via a Pd-catalysed cross-coupling reaction. Given the current interest in spiroketals as privileged biological motifs and the potential application of this process to the synthesis of natural products, the ease of entry to the compounds described here is noteworthy. Details on the biological activity of compounds **9a–k** will be reported in due course.

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References and Notes

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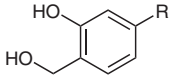
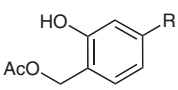
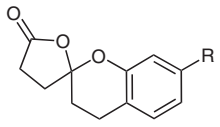
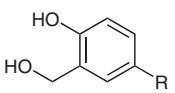
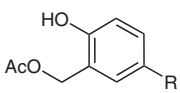
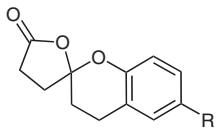
Table 1 Synthesis of Benzannelated Spiroketals **9** from 2-Hydroxybenzyl Acetates **8**

Diol		*o*-QM precursor		Yield (%)	Hetero-Diels–Alder product		Yield (%)
	R = H		**8a**	80		**9a**	84
	R = OAc		**8b**	91		**9b**	76
	R = Me		**8c**	48		**9c**	78
	R = Cl		**8d**	69		**9d**	76
	R = CO_2Me		**8e**	77		**9e**	79
	R = Me		**8f**	56		**9f**	77
	R = Cl		**8g**	62		**9g**	82
	R = Br		**8h**	60		**9h**	80
	R = OMe		**8i**	37		**9i**	75
	R = NO_2		**8j**	85		**9j**	82
	R = CO_2Me		**8k**	49		**9k**	89

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(10) **General Procedure**: 2-Hydroxybenzyl acetate (**8a**; 40 mg, 0.24 mmol) in γ-methylene-γ-butyrolactone (0.24 mL, 1.0 M) was heated at 100 °C for 20 h. The cooled reaction mixture was purified by flash column chromatography (SiO_2, 25% → 30% EtOAc in PE) to give **9a** as a white solid (36 mg, 84%); mp 107–108 ºC (lit.[12] 106 ºC); R_f 0.26 (EtOAc–PE, 3:7). IR: 2961, 2920, 1776 (C=O), 1582, 1489, 1447, 1251, 1220, 1170, 1093, 1055 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.07–7.17 (m, 2 H, 2 × ArCH), 6.93 (dt, *J* = 7.4, 1.1 Hz, 1 H, ArCH), 6.81 (dd, *J* = 8.1, 1.1 Hz, 1 H, ArCH), 3.06–3.18 (m, 1 H, 1 H of CH_2), 2.91–3.04 (m, 1 H, 1 H of CH_2), 2.79 (ddd, *J* = 16.5, 6.0, 2.5 Hz, 1 H, 1 H of CH_2), 2.64 (ddd, *J* = 17.6, 9.5, 2.5 Hz, 1 H, 1 H of CH_2), 2.52 (ddd, *J* = 13.1, 9.5, 2.5 Hz, 1 H, 1 H of CH_2), 2.19–2.35 (m, 2 H, 2 × 1 H of CH_2), 2.06–2.16 (m, 1 H, 1 H of CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.5 (C=O), 151.4 (ArCO), 129.0 (ArCH), 127.5 (ArCH), 121.6 (ArCH), 120.9 (ArC), 116.7 (ArCH), 106.2 (OCO), 33.8 (CH_2), 30.1 (CH_2), 28.2 (CH_2), 21.4 (CH_2). HRMS (EI): *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{12}O_3Na$: 227.0684; found: 227.0690.

(11) These were generally prepared in good yield by selective primary acetylation of the corresponding 2-hydroxybenzyl alcohols using Ac_2O (1.05 equiv) in the presence of catalytic $BF_3{\cdot}OEt_2$ (5 mol%), see: Weinert, E. E.; Frankenfield, K. N.; Rokita, S. E. *Chem. Res. Toxicol.* **2005**, *18*, 1364.

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