Generation and *hetero*-Diels–Alder reactions of an *o*-quinone methide under mild, anionic conditions: rapid synthesis of *mono*-benzannelated spiroketals†

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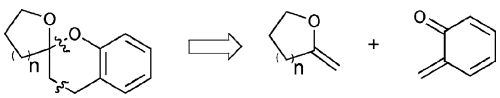
Deprotonation of *o*-hydroxybenzyl acetate with ^{i}PrMgCl provides a method of generating an *o*-quinone methide under mild, anionic conditions, such that highly sensitive *exo*-enol ethers can be employed as 2π partners in *hetero*-Diels–Alder reactions. This process results in *mono*-benzannelated spiroketals such as those found in the natural products berkelic acid, the chaetoquadrins or cephalostatin 6.

Introduction

Spiroketals are found in a large and diverse range of natural products. The complex structures and often interesting biological activity of such molecules has attracted the interest of many synthetic chemists.[1] Indeed, there is growing opinion that spiroketals are privileged pharmacophores.[2] By far the most common method of forming a spiroketal is the cyclodehydration of a keto-diol. Often, a large number of steps are required to synthesise these precursors, and in certain instances spiroketalisation does not occur.[3] Overall these factors can detract from the attractiveness of such an approach. An alternative, and often more step efficient strategy for the synthesis of spiroketals comprises the *hetero*-Diels–Alder reaction between an α,β-unsaturated carbonyl (4π) component and an *exo*-enol ether as a 2π partner. This method was introduced by Paul and Tchelitcheff in 1954,[4] when they showed that acrolein undergoes cycloaddition with 2-methylenetetrahydrofuran to give a [5,6]-spiroketal. Even so, the use of this reaction was almost completely overlooked until the early 1980's when Ireland and Häbich initially applied this method to the synthesis of insect pheromones.[5] Research by Ireland and his group continued to pioneer this reaction throughout the rest of that decade and on into the early 1990's.[6] Since then this process has been used in various forms by only a handful of groups,[7] and is, in general, underutilised. It was considered whether such an approach could be applied to *mono*-benzannelated spiroketals, since these motifs are found in a range of biologically interesting natural products, for example berkelic acid **1**,[8] chaetoquadrin A (**2**)[9] and cephalostatin 6 (**3**).[10]

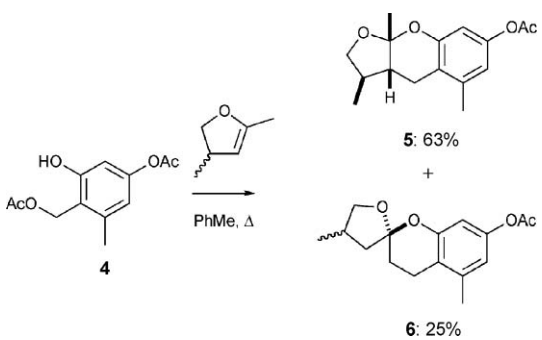
Within the context of such an approach, the α,β-unsaturated carbonyl (4π) component would be an *o*-quinone methide (Scheme 1).[11] The realisation of this concept is the basis of the current paper.



Scheme 1 Retrosynthesis of a *mono*-benzannelated spiroketal.

Results and discussion

Baldwin and co-workers have examined the generation of an *o*-quinone methide *via* thermolytic extrusion of AcOH from **4** in the presence of 4,5-dihydro-2,4-dimethylfuran (Scheme 2).[12] The major product was the expected benzopyran **5**, which was



Scheme 2 Unexpected observation of a *mono*-benzannelated spiroketal.

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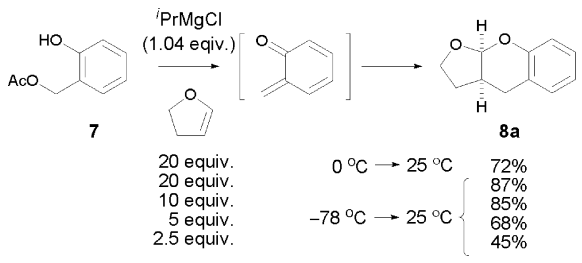
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra for **8a–g**. See DOI: 10.1039/b806593d

subsequently saponified to give the racemate of the natural product alboatrin. However, simple *exo*-enol ethers readily equilibrate with their *endo*-isomers under acidic and sometimes also thermal conditions. This may explain why they also observed the *mono*-benzannelated spiroketal **6** (as a mixture of diastereomers) in 25% yield. Presumably this was the result of cycloaddition of the intermediate *o*-quinone methide with 4-methyl-2-methylenetetrahydrofuran.[13]

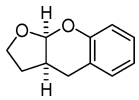
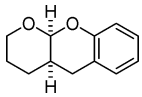
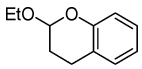
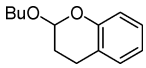
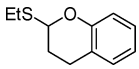
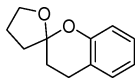
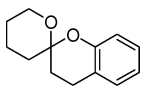
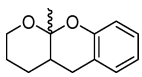
If this is the case, then equilibration needed to be avoided in the present work, since simple *exo*-enol ethers were to be employed as starting materials and are thermodynamically the less stable isomers.[14] Therefore the primary requirement was a method to generate an *o*-quinone methide under very mild, anionic conditions.[15] Pettus *et al.* have reported *hetero*-Diels–Alder reactions of β-substituted *o*-quinone methides generated from *O*-BOC-salicylic aldehydes upon addition of organometallic reagents. However, when simple enol ethers were employed as 2π partners, the reactions where almost exclusively carried out using the 2π partner as solvent.[16] In addition, in related work, when a fluoride initiated release of a β-unsubstituted *o*-quinone methide was investigated, the use of >35 equivalents of 2π partner was required for efficient cycloaddition.[17] Obviously, processes that require such large excesses of 2π partner do not lend themselves to natural product synthesis. Loubinoux *et al.* have reported that treatment of *o*-hydroxybenzyl acetate **7** with ^{t}BuOK in the presence of only 2 equiv. of a malonate nucleophile leads to overall nucleophilic substitution of the acetate group, presumably *via* an *o*-quinone methide intermediate.[18] However, not only are there no reports of this procedure being used in conjunction with a *hetero*-Diels–Alder reaction, but in addition, elevated temperatures were required for efficient reaction (>45 °C). Consequently, although this method was of interest, there was a need to identify an alternative base that would allow for the efficient generation of *o*-quinone methides at ambient temperature (or below). A solution of *o*-hydroxybenzyl acetate **7**[19] in THF was treated with a range of common bases at 0 °C in the presence of 2,3-dihydrofuran (20 equiv.), as an initial test 2π partner. The reactions were then warmed to 25 °C and stirred for 16 h. The use of either K_2CO_3 or Cs_2CO_3 as base did not lead to any reaction, whereas the use of *n*-BuLi led to precipitation of the phenolate anion. In stark contrast, the use of ^{i}PrMgCl (1.04 equiv.) led to benzopyran adduct **8a** in 72% yield following column chromatography (Scheme 3).



Scheme 3 Examining the number of equivalents of 2,3-dihydrofuran.

Ultimately, it was found to be most experimentally convenient and higher yielding to deprotonate the phenolic proton of **7** at −78 °C before addition of the 2π partner, the reaction then being allowed to warm slowly to 25 °C over 16 h. Using otherwise identical conditions, the expected *cis-fused* benzopyran adduct **8a** was obtained in 87% yield. The importance of the number of equivalents of the 2π partner was then investigated: the use of only 10 equivalents of 2,3-dihydrofuran led to only a small drop in the yield of **8a** to 85% (Table 1, entry 1), and on decreasing to only 5 equivalents, the yield of **8a** remained at a respectable 68%. Even when only 2.5 equivalents of the 2π partner were used, the yield was still 45%. The use of a range of other 2π partners was then examined; 3,4-dihydro-2*H*-pyran gave the *cis*-fused benzopyran adduct **8b** in 68% yield (entry 2), whereas the use of ethyl- and *n*-butyl vinyl ether gave **8c** and **8d** in 73% and 77% yields respectively (entries 3 and 4). When ethyl vinyl sulfide was used as the 2π partner, the *hemi*-thioacetal **8e** was obtained in 59% (entry 5). Finally, with a view to establishing methodology that would allow access to the natural products **1–3**, two *exo*-enol ethers were examined as the 2π partners. Gratifyingly, the use of 2-methylenetetrahydrofuran[5a] under the reaction conditions described above, led to the [5,6]-spiroketal **8f** [δ_C 106.6 (O_2C)] in 76% yield (entry 6), with no sign (as judged by ^{1}H NMR spectroscopy) of any products due to isomerisation of the 2π partner. Similarly the use of 2-methylenetetrahydropyran[5a] gave **8g** [δ_C 95.8 (O_2C)] in 59% yield (entry 8). It is particularly

Table 1 Examining the scope of 2π partners

Entry	2π partner[a]	Product		Yield[b]
1			**8a**	85%
2			**8b**	68%
3			**8c**	73%
4			**8d**	77%
5			**8e**	59%
6			**8f**	76%
8			**8g**	59%
9[c]			**8h**	11%[d]

[a] 10 equivalents. [b] Isolated yield following flash column chromatography. [c] 1.00 equiv. of ^{i}PrMgCl used. [d] 6 : 1 mixture of **8h** : **8g**.

noteworthy that when only 1.00 equivalent of ^{i}PrMgCl was employed in the attempted synthesis of **8g** (entry 9), a 6 : 1 mixture of **8h** : **8g** was obtained. The major product, **8h**, is that derived from cycloaddition of the intermediate *o*-quinone methide with 6-methyl-3,4-dihydro-2*H*-pyran, the *endo*-isomer of 2-methylenetetrahydropyran. This result serves to demonstrate the importance of ensuring that no phenolic protons from **7** are present when the *exo*-enol ether is added, lest isomerisation should occur.

Conclusion

The development of very mild, anionic reaction conditions for the generation of an *o*-quinone methide intermediate has allowed for the use of highly sensitive *exo*-enol ethers as 2π partners in *hetero*-Diels–Alder reactions. The ease with which the *o*-quinone methide is generated from a readily available precursor using a common base is of note. This rapid, and simple strategy is clearly applicable to the synthesis of a range of natural products including berkelic acid **1**, chaetoquadrin A (**2**) and cephalostatin 6 (**3**).[20]

Experimental

Commercially available reagents were used without further purification except THF which was distilled from Na–benzophenone ketyl. All reactions required anhydrous conditions and were conducted in flame-dried apparatus under an atmosphere of nitrogen. Analytical thin-layer chromatography (TLC) was performed on silica gel plates (0.25 mm) precoated with a fluorescent indicator. Standard flash chromatography procedures were performed using Kieselgel 60 (40–63 μm). Residual solvent was removed using a static oil pump (<1 mbar). Melting points were determined using a Gallenkamp melting point stage and are uncorrected. Infrared spectra were recorded on a Bruker Tensor 27 FTIR machine using a MIRacle ATR accessory. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 270 and 67.5 MHz respectively on a JeoL EX270. Chemical shifts are reported relative to $CHCl_3$ [^{1}H δ 7.27] or $CDCl_3$ [^{13}C δ 77.0]. Mass spectra were obtained by the EPSRC National Mass Spectrometry Service Centre (Swansea) using a high resolution double focussing mass spectrometer (Finnigan MAT 95 XP).

o-Hydroxybenzyl acetate[12a] 7

To a stirred solution of salicyl alcohol (1.00 g, 8.06 mmol) and Ac_2O (0.74 cm^3, 7.90 mmol, 0.98 equiv) in anhydrous THF (10 cm^3) at −10 °C was added $BF_3{\cdot}OEt_2$ (0.15 cm^3, 1.18 mmol, 0.15 equiv) dropwise over 1 min. The reaction was warmed to 4 °C and stirred for a further 16 h. The reaction was quenched at 4 °C by the addition of sat. aq. $NaHCO_3$ (10 cm^3). The layers were separated and the aqueous phase was extracted with EtOAc (10 cm^3). The combined organic phases were washed with water (10 cm^3), then dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* (bath temp. <20 °C) and the residue was purified by flash column chromatography (30% EtOAc in petrol) to give the title compound as a viscous oil, which solidified after approximately 1 week in the freezer leaving a white waxy solid (1.04 g, 80%); mp 35–36 °C (decomp) (lit.,[12a] oil); all other data as previously reported.

General procedure for the preparation of compounds 8a–g

To a solution of *o*-hydroxybenzyl acetate **7** (165 mg, 1 mmol) in THF (0.50 cm^3) at −78 °C was added ^{i}PrMgCl (2.0 M in THF; 0.52 cm^3, 1.04 mmol). The solution was stirred for 15 min before the addition of the 2π partner (10 equiv.). The solution was then allowed to warm slowly to 25 °C over 16 h after which time, EtOAc (5 cm^3) was added and the resulting solution was filtered through a short plug of silica (~3cm^2 × 2 cm) using EtOAc (~20 cm^3) as eluent. The filtrate was reduced *in vacuo* and the residue was purified by flash column chromatography (SiO_2, EtOAc/40–60 petrol) to give the following compounds:

2,3,3*a*,9*a*-Tetrahydro-4*H*-1,9-dioxa-cyclopenta[*b*]naphthalene[21] 8a

According to the general procedure, *o*-hydroxybenzyl acetate **7** (167 mg, 1.00 mmol) and 2,3-dihydrofuran (0.76 cm^3) gave the title compound **8a** (150 mg, 85%) as white solid; mp 35–36 °C; R_f 0.74 (20% EtOAc in petrol); ν_{max} (film)/cm^{-1} 2954 w, 1584 m, 1487 m, 1453 m, 1232 m, 1181 m, 1095 s, 1061 s, 1040 s; δ_H (270 MHz; $CDCl_3$) 7.18–7.04 (2H, m, 2 × ArCH), 6.94–6.86 (2H, m, 2 × ArCH), 5.67 (1H, d, *J* 4.7, O_2CH), 4.07–3.86 (2H, m, OCH_2), 3.08 (1H, dd, *J* 16.4 and 5.5, O_2CHCH), 2.81–2.66 (2H, m, $ArCH_2$), 2.12–1.96 (1H, m, OCH_2CH(H)), 1.77–1.61 (1H, m, $OCH_2CH(H)$); δ_C (67.5 MHz; $CDCl_3$) 153.5 (ArCO), 129.2 (ArCH), 127.9 (ArCH), 121.6 (ArC), 121.4 (ArCH), 117.1 (ArCH), 101.8 (O_2C), 68.2 (OCH_2), 38.0 (CH), 28.3 (CH_2) and 26.4 (CH_2).

3,4,4*a*,10*a*-Tetrahydro-2*H*,5*H*-pyrano[2,3-*b*]chromene[21] 8b

According to the general procedure, *o*-hydroxybenzyl acetate **7** (166 mg, 1.00 mmol) and 3,4-dihydro-2*H*-pyran (0.91 cm^3) gave the title compound **8b** (129 mg, 68%) as white solid; mp 59–60 °C; R_f 0.70 (20% EtOAc in petrol); ν_{max} (film)/cm^{-1} 2926 m, 1582 w, 1486 m, 1240 m, 1128 m, 1078 s, 1032 m; δ_H (270 MHz; $CDCl_3$) 7.18–7.02 (2H, m, 2 × ArCH), 6.93–6.83 (2H, m, 2 × ArCH), 5.35 (1H, d, *J* 2.3, O_2CH), 4.09–3.96 (1H, m, OC*H*(H)), 3.79–3.68 (1H, m, OCH(*H*)), 2.95 (1H, dd, *J* 16.6 and 5.9, ArC*H*(H)), 2.68 (1H, dd, *J* 16.6 and 4.8, ArCH(*H*)), 2.26–2.12 (1H, m, OCHC*H*), 1.78–1.59 (4H, m, 2 × CH_2); δ_C (67.5 MHz; $CDCl_3$) 152.8 (ArCO), 129.4 (ArCH), 127.4 (ArCH), 120.8 (ArCH), 119.9 (ArC), 116.4 (ArCH), 96.6 (O_2C), 62.6 (OCH_2), 31.7 (CH), 28.9 (CH_2), 24.1 (CH_2) and 23.5 (CH_2).

2-Ethoxychroman[17] 8c

According to the general procedure, *o*-hydroxybenzyl acetate **7** (175 mg, 1.05 mmol) and ethyl vinyl ether (1.01 cm^3) gave the title compound **8c** (136 mg, 73%) as colourless oil; R_f 0.40 (10% EtOAc in petrol); ν_{max} (film)/cm^{-1} 2932 w, 1583 m, 1488 m, 1456 m, 1373 w, 1351 w, 1328 w, 1301 w, 1274 w, 1223 s, 1178 m, 1118 s, 1102 s, 1057 s; δ_H (270 MHz; $CDCl_3$) 7.19–7.05 (2H, m, 2 × ArCH), 6.94–6.80 (2H, m, 2 × ArCH), 5.28 (1H, t, *J* 2.8, O_2CH), 3.92 (1H, dq, *J* 9.6 and 7.1, OC*H*(H)), 3.67 (1H, dq, *J* 9.6 and 7.1, OCH(*H*)), 2.91 (1H, m, ArC*H*(H)), 2.66 (1H, ddd, *J* 5.7, 11.3 and 16.0, ArCH(*H*)), 2.14–1.90 (2H, m, CH_2), 1.22 (3H, t, *J* 7.1, Me); δ_C (67.5 MHz; $CDCl_3$) 152.3 (ArCO), 129.3 (ArCH), 127.3 (ArCH), 122.7 (ArC), 120.6 (ArCH), 117.0 (ArCH), 97.0 (O_2C), 63.7 (OCH_2), 26.7 (CH_2), 20.6 (CH_2) and 15.2 (Me).

2-Butoxychroman 8d

According to the general procedure, *o*-hydroxybenzyl acetate **7** (166 mg, 1.00 mmol) and butyl vinyl ether (1.29 cm^3) gave the *title compound* **8d** (158 mg, 77%) as colourless oil; R_f 0.46 (10% EtOAc in petrol); ν_{max} (film)/cm^{-1} 2932 s, 2871 m, 1583 m, 1489 s, 1457 s, 1224 s, 1213 m, 1177 w, 1119 m, 1103 s, 1064 s; δ_H (270 MHz; $CDCl_3$) 7.18–7.04 (2H, m, 2 × ArCH), 6.94–6.82 (2H, m, 2 × ArCH), 5.26 (1H, t, *J* 2.9, O_2CH), 3.87 (1H, dt, *J* 9.7 and 6.7, OC*H*(H)), 3.61 (1H, dt, *J* 9.7 and 6.7, OCH(*H*)), 3.09–2.93 (1H, m, ArC*H*(H)), 2.65 (1H, ddd, *J* 3.7, 5.7 and 16.2, ArCH(*H*)), 2.13–1.89 (2H, m, O_2CHCH_2), 1.64–1.50 (2H, m, OCH_2CH_2), 1.42–1.26 (2H, m, CH_2Me), 0.90 (3H, t, *J* 7.3, Me); δ_C (67.5 MHz; $CDCl_3$) 152.2 (ArCO), 129.1 (ArCH), 127.1 (ArCH), 122.5 (ArC), 120.4 (ArCH), 116.8 (ArCH), 96.9 (O_2C), 67.8 (OCH_2), 31.6 (CH_2), 26.5 ($ArCH_2$), 20.4 (CH_2), 19.1 (CH_2) and 13.7 (Me). *m*/*z* (EI) 206.1303 $[M]^+$, $C_{13}H_{18}O_2$ requires 206.1303.

2-Ethylsulfanylchroman 8e

According to the general procedure, *o*-hydroxybenzyl acetate **7** (166 mg, 1.00 mmol) and ethyl vinyl sulfide (1.01 cm^3) gave the *title compound* **8e** (115 mg, 59%) as light yellow oil; R_f 0.30 (10% EtOAc in petrol); ν_{max} (film)/cm^{-1} 2926 s, 1582 s, 1480 s, 1456 s, 1273 s, 1208 s, 1183 s, 1109 s, 1074 s, 1043 s, 1022 s; δ_H (270 MHz; $CDCl_3$) 7.16–7.03 (2H, m, 2 × ArCH), 6.94–6.81 (2H, m, 2 × ArCH), 5.57 (1H, t, *J* 4.1, O(S)CH), 3.06–2.65 (4H, m, SCH_2 and CH_2), 2.38–2.24 (1H, m, C*H*(H)), 2.20–2.08 (1H, m, CH(*H*)), 1.34 (3H, t, *J* 7.4, Me); δ_C (67.5 MHz; $CDCl_3$) 152.5 (ArCO), 129.6 (ArCH), 127.4 (ArCH), 122.0 (ArC), 121.0 (ArCH), 117.5 (ArCH), 80.3 (SCO), 27.4 (CH_2), 24.7 (CH_2), 22.7 (CH_2) and 15.2 (Me); *m*/*z* 194.0764 $[M]^+$, $C_{11}H_{14}OS$ requires 194.0760.

mono-Benzannelated [5,6]-spiroketal 8f

According to the general procedure, *o*-hydroxybenzyl acetate **7** (190 mg, 1.14 mmol) and 2-methylenetetrahydrofuran[5a] (1.06 cm^3) gave the *title compound* **8f** (166 mg, 76%) as colourless oil; R_f 0.23 (5% EtOAc in petrol); ν_{max} (film)/cm^{-1} 2938 s, 2887 m, 1582 s, 1490 s, 1457 s, 1356 m, 1302 m, 1235 s, 1216 s, 1184 s, 1136 s, 1116 m, 1084 s, 1022 m; δ_H (270 MHz; $CDCl_3$) 7.15–7.04 (2H, m, 2 × ArCH), 6.90–6.73 (2H, m, 2 × ArCH), 4.14–3.93 (2H, m, OCH_2), 3.14–2.99 (1H, m, ArC*H*(H)), 2.76 (1H, dt, 4.9 and 16.3, ArCH(*H*)), 2.36–1.82 (6H, m, 3 × CH_2); δ_C (67.5 MHz; $CDCl_3$) 153.1 (ArCO), 129.2 (ArCH), 127.2 (ArCH), 121.9 (ArC), 120.5 (ArCH), 117.1 (ArCH), 106.7 (O_2C), 68.1 (OCH_2), 37.0 (O_2CCH_2), 30.0 ($ArCH_2$), 24.2 (CH_2) and 22.8 (CH_2); *m*/*z* (EI) $[M + NH_4]^+C_{12}H_{18}O_2N$ requires 208.1332, found 208.1332.

mono-Benzannelated [6,6]-spiroketal 8g

According to the general procedure, *o*-hydroxybenzyl acetate **7** (166 mg, 1.00 mmol) and 2-methylenetetrahydropyran[5a] (1.08 cm^3) gave the *title compound* **8g** (120 mg, 59%) as white solid; mp 53–54 °C; R_f 0.26 (5% EtOAc in petrol); ν_{max} (film)/cm^{-1} 2937 w, 1581 w, 1486 m, 1454 m, 1231 m, 1215 s, 1156 m, 1142 m, 1101 s, 1076 s, 1044 s, 1034 s; δ_H (270 MHz; $CDCl_3$) 7.19–7.06 (2H, m, 2 × ArCH), 6.95–6.87 (2H, m, 2 × ArCH), 3.86 (1H, dt, *J* 4.1 and 11.2, OC*H*(H)), 3.69–3.59 (1H, m, OCH(*H*)), 3.06 (1H, ddd, *J* 16.3, 13.0 and 6.3, ArC*H*(H)), 2.65 (1H, ddd, *J* 16.3, 6.3 and 2.0, ArCH(*H*)), 2.27–1.54 (8H, m, 4 × CH_2); δ_C (67.5 MHz; $CDCl_3$) 152.2 (ArCO), 129.1 (ArCH), 127.0 (ArCH), 122.7 (ArC), 120.5 (ArCH), 116.9 (ArCH), 95.8 (O_2C), 61.7 (OCH_2), 34.8 (CH_2), 31.9 (CH_2), 25.2 (CH_2), 21.0 (CH_2) and 18.4 (CH_2); *m*/*z* (EI) $[M + Na]^+$, $C_{13}H_{16}O_2Na$ requires 227.1043, found 227.1040.

Acknowledgements

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