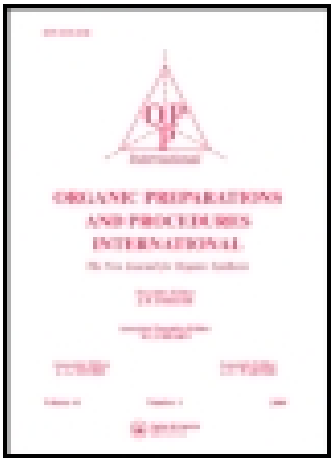

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EXPLOITATION OF CO-OPERATIVE DIRECTED ortho-METALLATION (DoM) BY 1,3-RELATED -OMOM GROUPS IN THE DEVELOPMENT OF A FULLY REGIO-CONTROLLED SYNTHESIS OF ATRANOL FROM ORCINOL

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EXPLOITATION OF CO-OPERATIVE DIRECTED *ortho*-METALLATION (DoM) BY 1,3-RELATED –OMOM GROUPS IN THE DEVELOPMENT OF A FULLY REGIO-CONTROLLED SYNTHESIS OF ATRANOL FROM ORCINOL

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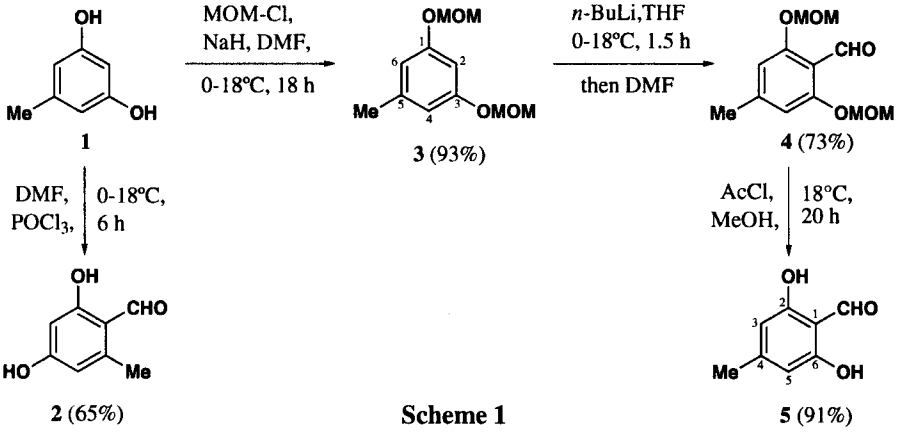
In connection with efforts to develop a total synthesis of the fungal metabolite diversonol[1] we required access to atranol (**5**, *Scheme 1*). The latter compound and its chloro derivative, both of which are powerful allergens, are themselves natural products and found as major components in oak moss absolute, an extract of the lichen *Everia prunatri* and an important ingredient in the perfumery industry.[2] Atranol also represents a key sub-structure associated with a wide-range of other lichen-derived natural products of polyketide origin. It has been prepared, albeit in very low yield, through Vilsmeier-Haack formylation of commercially available orcinol (**1**). The major product of this reaction is, in fact, the regioisomeric orcylaldehyde (**2**)[3] which we

have shown[4] can be elaborated, over a further five steps and using chemistry developed by Pulgarin and Tabacchi,[5] to atranol. Unfortunately, in our hands[4] this sequence proceeds in only 10% overall yield. As a consequence, we sought a more efficient means for obtaining compound **5** and considered trying to exploit the well-known capacity[6] of the –OMOM (O-*methoxymethyl*) group to direct metallation at *ortho*-positions on aromatic rings. In particular, it seemed possible that the *bis*-MOM ether **3** of orcinol might be expected to undergo regioselective lithiation at C2 by virtue of co-operativity[7] between these 1,3-related directed metallation groups (DMGs).[8] In 2003, Lepoittevin and co-workers exploited this concept in preparing target **5** from precursor **1**.[9] However, these researchers used –OMe-based DMGs in their synthesis and the cleavage of this moiety, so as to reveal the 2- and 6-hydroxy groups of compound **5**, was relatively inefficient and such that a modest 30% yield was realized over the three-step reaction sequence used. Furthermore, neither experimental procedures nor spectroscopic data were provided despite the lack of such in the earlier literature. Herein, therefore, we report on the successful exploitation of the *bis*-MOM ether, **3**, of orcinol (**1**) in establishing a significantly more efficient route (62% overall yield) to the title compound (**5**). ^{1}H and ^{13}C NMR data derived from synthetic atranol are also provided.

The three-step reaction sequence leading from orcinol (**1**) to atranol (**5**) is shown in *Scheme 1* and the first two of these steps represent higher yielding modifications of those



Scheme 1

employed by Ohta *et al.*[10] in the early stages of their synthesis of the antibiotic grifolin. Thus, orcinol was converted into the previously reported[10] *bis*-MOM ether **3** (93%) using MOM-Cl in the presence of sodium hydride. A solution of compound **3** in THF was cooled to 0°C then treated with 1.2 molar equivalents of *n*-butyllithium. The ensuing mixture was left to stand at 0-18°C for 1.5 h then the resulting C2-lithiated derivative of *bis*-ether **3** quenched, at 18°C, with 2 mole equivalents of DMF. After work-up the targeted and previously reported[10] aldehyde **4** was obtained in 73% yield. The 75 MHz ^{13}C NMR spectrum of product **4** displayed only eight resonances thus indicating that the compound is C_2-symmetric and ruling out, therefore, the possi-

bility that the metallation of substrate **3** has taken place at the alternate site(s). The appearance of a singlet due to two equivalent aromatic protons at δ 6.64 in the 300 MHz ^{1}H NMR spectrum of compound **4** served to confirm this conclusion. The deprotection of *bis*-ether **4** was readily achieved using methanolic HCl (generated by the addition of acetyl chloride to MeOH) and in this manner atranol (**5**) was obtained in 91% yield and as light-yellow crystals. The spectral data derived from this material were in full accord with the assigned structure and are detailed below because of their previous absence in the literature.

EXPERIMENTAL SECTION

General experimental procedures have been described elsewhere.[11]

1,3-*bis*(Methoxymethoxy)-5-methylbenzene (3).- A magnetically stirred solution of orcinol (**1**) (800 mg, 5.6 mmol) in dry DMF (40 mL) maintained under an atmosphere of nitrogen at 0°C was treated with NaH (580 mg of a 60% suspension in mineral oil, 14.5 mmol) and the ensuing mixture stirred magnetically at this temperature until no further evolution of H_2 gas was observed (*ca.* 0.25 h). At this point the mixture was treated, dropwise, with MOM-Cl (1.10 mL, 14.5 mmol) and then allowed to warm to 18°C. Stirring was continued at this temperature for 18 h after which time the reaction mixture was poured into water (30 mL) and extracted with diethyl ether (5 x 30 mL). The combined ethereal extracts were washed with NaOH (3 x 20 mL of a 2 M aqueous solution) and brine (1 x 20 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. Subjection of the resulting light-yellow oil to flash chromatography (silica, 3:7 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions (R_f 0.7), compound **3**[10] (1.11 g, 93%) as a clear, colorless oil. ^{1}H NMR ($CDCl_3$): δ 6.47 (m, 3H, ArH), 5.15 (s, 4H), 3.48 (s, 6H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 158.1 (C), 140.3 (C), 110.3 (CH), 102.0 (CH), 94.3 (CH_2), 55.9 (OCH_3), 21.7 (CH_3); IR (NaCl): 2955, 2902, 2826, 2791, 1598, 1472, 1399, 1315, 1291, 1214, 1146, 1083, 1039, 996, 924, 840 cm^{-1}; MS *m/z*: 213 [(M+H)$^+$, 35%], 212 (M$^{+\bullet}$, 83), 182 (18), 181 (20), 152 (36), 136 (22), 108 (29), 55 (27), 45 (100); HRMS: $C_{11}H_{16}O_4$ requires M$^{+\bullet}$, 212.1049. Found: M$^{+\bullet}$, 212.1043.

2,6-*bis*(Methoxymethoxy)-4-methylbenzaldehyde (4).- A magnetically stirred solution of compound **3** (950 mg, 4.5 mmol) in THF (50 mL) maintained at 0°C under an atmosphere of nitrogen was treated, dropwise, with *n*-BuLi (3.4 mL of a 1.6 M solution in hexane, 5.4 mmol). The resulting suspension was warmed to 18°C and stirred slowly at this temperature for 1.5 h then quenched with dry DMF (0.7 mL, 9.0 mmol). The ensuing mixture was poured into water (50 mL) and extracted with diethyl ether (4 x 30 mL). The combined organic phases were then washed with water (1 x 40 mL) and brine (1 x 40 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Subjection of the ensuing light-yellow oil to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions (R_f 0.2), compound **4**[10] (785 mg, 73%) as a pale-yellow solid, mp 38-39°C

(*lit.*[10] mp 40-42°C). ^{1}H NMR ($CDCl_3$): δ 10.46 (s, 1H, CHO), 6.64 (s, 2H, ArH), 5.23 (s, 4H), 3.48 (s, 6H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 188.7 (CHO), 159.4 (C), 147.3 (C), 113.7 (C), 109.2 (CH), 94.6 (CH_2), 56.4 (OCH_3), 22.6 (CH_3); IR (NaCl): 2955, 2829, 1687, 1608, 1573, 1458, 1392, 1240, 1154, 1113, 1050, 921 cm^{-1}; MS *m/z*: 240 ($M^{+\bullet}$, 58%), 209 (50), 195 (71), 194 (50), 179 (60), 178 (85), 165 (53), 164 (68), 136 (25), 77(22), 45 (100); HRMS: $C_{12}H_{16}O_5$ requires $M^{+\bullet}$, 240.0998. Found: $M^{+\bullet}$, 240.0996.

2,6-Dihydroxy-4-methylbenzaldehyde (5).- A magnetically stirred solution of compound **4** (102 mg, 0.4 mmol) in MeOH (10 mL) maintained under an atmosphere of nitrogen at 18°C was treated with AcCl (20 μL, 0.30 mmol) and the ensuing mixture stirred at this temperature for 20 h then concentrated under reduced pressure. HCl (10 mL of a 0.1 M aqueous solution) was added to the residue which was then extracted with ethyl acetate (3 x 15 mL). The combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Subjection of this material to flash chromatography (silica, 2:3 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions (R_f 0.5), compound **5** (59 mg, 91%) as light-yellow crystals, mp 119-121°C (*lit.*[12] mp 120-121°C). ^{1}H NMR [$(CD_3)_2CO$]: δ 10.72 (broad s, 2H, OH), 10.26 (s, 1H, CHO), 6.26 (s, 2H, ArH), 2.23 (s, 3H); ^{13}C NMR [$(CD_3)_2CO$]: δ 193.6 (CHO), 162.4 (C), 150.9 (C), 108.6 (C), 107.8 (CH), 21.7 (CH_3); IR (NaCl): 3305 (broad), 2887, 1655, 1605, 1457, 1428, 1358, 1310, 1277, 1207, 1135, 1029, 995, 910, 823, 727 cm^{-1}; MS *m/z*: 152 ($M^{+\bullet}$, 93%), 151 (100), 134 (6), 106 (16), 77 (10), 55 (13); HRMS: $C_8H_8O_3$ requires $M^{+\bullet}$, 152.0473. Found: $M^{+\bullet}$, 152.0471.

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METHYLTRIPHENYLPHOSPHONIUM PEROXYDISULFATE AND IODINE AS MILD REAGENTS FOR THE IODINATION OF ACTIVATED AROMATIC COMPOUNDS

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Aromatic iodides have been widely used in radiolabeling studies, and as synthetic intermediates in the formation of new carbon-carbon or carbon-heteroatom bonds *via* replacement of their iodine atoms with electrophiles.[1] Despite the importance of iodoarenes, there are few good methods in the literature for the iodination of aromatic compounds. Conventional methods for aromatic iodination involve the use of molecular iodine together with highly toxic heavy metal compounds, or mineral acids which are undesirable from the environmental point of view.[2] Other methods for iodination of aromatic compounds[3-12] involve environmental hazards such as handling and storage of molecular iodine, strongly acidic conditions, expensive and complex catalysts, toxic metallic compounds and the use of oxidizing reagents that are difficult to prepare.

In connection with our ongoing program to develop new reagents for iodination of aromatic compounds,[13] we herein report an efficient method for the iodination of activated