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Alternative routes to pterulone

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Abstract—Two new synthetic routes to pterulone, a fungal metabolite possessing potent antifungal activity as an inhibitor of NADH/ubiquinone oxidoreductase, are reported. © 2002 Elsevier Science Ltd. All rights reserved.

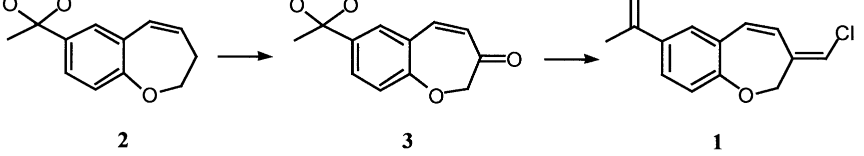
1. Introduction

Pterulone (**1**) (Scheme 1) is a chlorinated fungal metabolite produced by a *Pterula* species, on both natural[1] and artificial substrates.[2] It has received attention as a potent antifungal compound, exhibiting significant activity already at 1 μg/disc in the plate diffusion assay,[3] and has been shown to interfere with the NADH/ubiquinone oxidoreductase (complex I) inhibiting eucaryotic respiration.[3] As pterulone is free from functionalities commonly associated with toxicity, and is only weakly cytotoxic in vitro, it may be a useful lead compound for the development of novel antifungal compounds or of new molecular tools for studying interference with complex I.

Two syntheses of pterulone were recently reported.[4,5] One is based on 3(2*H*)-oxepinone to which the chlorovinyl group was attached by a Wittig reaction and the acetyl group was added by a Friedel–Craft's reaction,[4] while the other route is based on 2-hydroxy-5-bromobenzaldehyde that is reacted in a bidentate ether synthesis and Wittig reaction followed by a second Wittig reaction. The acetyl group is obtained from the bromo substituent via the nitrile obtained in a Rosenmund–von-Braun reaction.[5] With these routes, the synthesis of a number of derivatives and analogues that are used in an ongoing structure–activity relationship study was facilitated, but they are not suitable for the preparation of some crucial analogues. We therefore needed alternative ways to prepare pterulone (**1**), in which the dihydrooxepin ring was closed in a different way and where we had better control over the critical acetylation step. A desirable intermediate would be the dihydrobenzoxepin derivative **2**, containing a protected acetyl group in the correct position. Compound **2** is suitable for allylic oxidation to the ketone **3** which in principle could undergo any Wittig reaction and give a range of pterulone analogues after acetal hydrolysis (Scheme 1).

2. Results and discussion

Initially we prepared **2** by the procedure presented in Scheme 2. Methyl salicylate was acetylated with $AlCl_3$ and Ac_2O to give **4**, which was protected as the ethylene acetal **5**. **5** was coupled to ethyl 4-bromobutyrate to give **6**, and the Dieckmann condensation ring closure to yield **7** was accomplished with NaH in THF. **7** was reduced with $NaBH_4$ in MeOH to give the alcohol **8**, as a mixture of isomers. Ester hydrolysis of **8**, during which the ketone was deprotected in the work-up procedure, followed by dehydration and decarboxylation of the β-hydroxy acid **9** with DMF–DMA[6,7] gave **10**. The keto function of **10** was reprotected as



Scheme 1.

Keywords: condensations; metathesis; oxidation; Wittig reactions.

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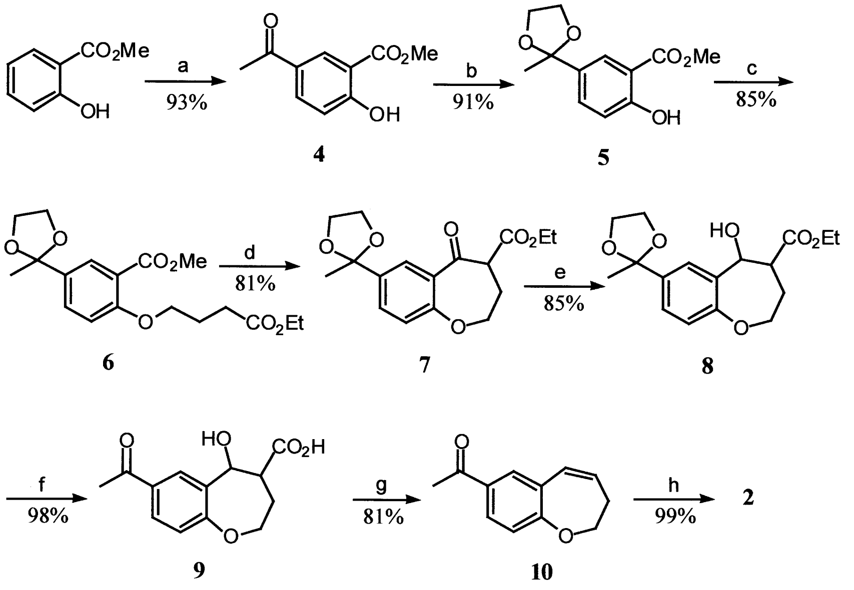
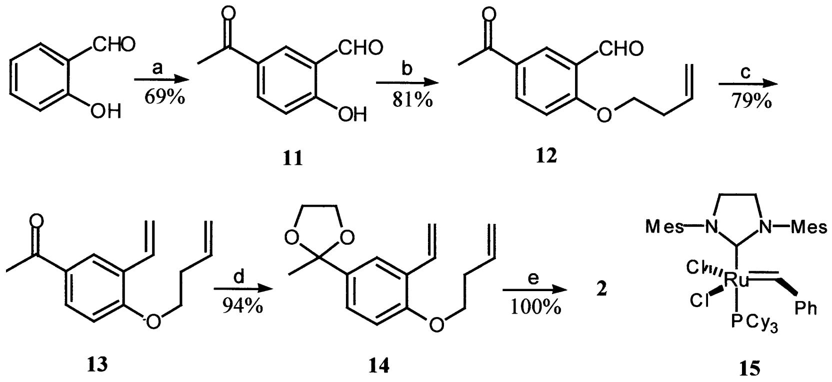


Scheme 2. (a) Ac_2O, $AlCl_3$, CH_2Cl_2, reflux. (b) Ethylene glycol, *p*TsOH, toluene, reflux. (c) Ethyl 4-bromobutyrate, K_2CO_3, DMF, reflux. (d) NaH, THF, reflux. (e) $NaBH_4$, MeOH. (f) LiOH, THF–H_2O 1:1. (g) Toluene, reflux DMF–DMA. (h) Ethylene glycol, *p*TsOH, toluene, reflux.

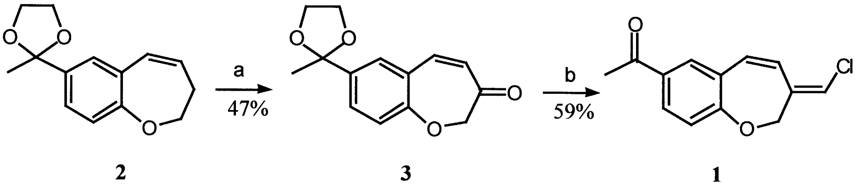


Scheme 3. (a) Ac_2O, $AlCl_3$, CH_2Cl_2, reflux. (b) 4-Bromobutene, K_2CO_3, DMF, reflux. (c) Ph_3PCH_3Br, KO*t*Bu, THF, −78°C. (d) Ethylene glycol, *p*TsOH, toluene, reflux. (e) **15** (5%), CH_2Cl_2, N_2, room temperature.

an ethylene acetal, and **2** was obtained in a 39% overall yield from methyl salicylate.

Another obvious way to obtain **2** is by ring-closing olefin metathesis of an acyclic diene catalysed by a metal carbene complex, a reaction that has been used for the synthesis of both six- and seven-membered oxacycles.[8–10] Salicylic aldehyde was acetylated with Ac_2O and $AlCl_3$ in CH_2Cl_2 to give **11**, which was reacted with 4-bromobutene in DMF/K_2CO_3 to give the ether **12**, after which the aldehyde functionality in **12** was transformed to a vinyl group in **13** by a Wittig reaction. The keto function of **13** was protected as the acetal **14** prior to the ring-closing reaction, in which the ruthenium catalyst **15** was used, to give **2** in 42% overall yield from salicylic aldehyde (Scheme 3).

The allylic oxidation of **2** with SeO_2 in xylene[11] gave **3** in a reasonable yield (47%). A number of other methods for allylic oxidation were tried: PCC and pyridine in CH_2Cl_2,[12] $Cr(CO)_6$, TBHP in acetonitrile,[13,14] CrO_3, 3,5-dimethylpyrazole in CH_2Cl_2,[15,16] DDQ in methanol,[17] SeO_2, and TBHP in acetonitrile[18] and SeO_2 in dioxane,[19] but were less successful. A Wittig reaction with chloromethyltriphenylphosphonium chloride and KO*t*Bu in dry THF transformed **3** to **1**, as a 1:5 *E*/*Z* mixture, and the isomerisation of the exocyclic double bond[4] gave the pure



Scheme 4. (a) SeO_2, xylene, reflux. (b) BuLi, (chloromethyl)triphenylphosphonium chloride, THF, room temperature, I_2/UV-light.

E-isomer identical to the natural product in all respects (Scheme 4).

3. Conclusion

From commercially available methyl salicylate or salicylic aldehyde, **2** was obtained in 8 or 5 steps in a total yield of 39 or 42%. **2** was then transformed to pterulone (**1**) in 2 steps with 27% yield. Although the total yields are not dramatically improved compared to the previously reported syntheses, the main advantage with the procedures presented here is that they give access to new pterulone analogues for quantitative structure–activity relationship (QSAR) studies.

4. Experimental

4.1. General

Materials were obtained from commercial suppliers and were used without further purification unless otherwise noted. THF was dried by refluxing over sodium/benzophenone ketyl immediately prior to use. CH_2Cl_2 and triethylamine were distilled from calcium hydride prior to use. All moisture and air-sensitive reactions were carried out under an atmosphere of dry nitrogen using oven-dried glassware. EIMS spectra (direct inlet, 70 eV) were recorded with a JEOL SX102 spectrometer, and the NMR spectra (in $CDCl_3$ or CD_3OD) with a Bruker DRX300 spectrometer at 300 MHz (^1H) and at 75 MHz (^{13}C), a Bruker DRX400 spectrometer (at 400/100 MHz) and a Bruker ARX500 spectrometer (at 500/125 MHz). The solvent signals (7.26 and 77.0 ppm in $CDCl_3$, and 3.31 and 49.1 ppm in CD_3OD) were used as reference. IR spectra were recorded with a Perkin–Elmer 298 spectrometer. Concentrations were made using rotary evaporation with bath temperatures at or below 40°C. Anhydrous $MgSO_4$ was used as drying agent for the organic extracts in the work-up procedures. All flash chromatography was performed on 60 Å 35–70 μm Matrex silica gel (Grace Amicon). HPLC separation was conducted on a HP1090 series I (column: Merck LiChroCART® 125-4, LiChrospher® 100, RP-18, 5 μm; linear water–acetonitrile gradient). TLC analyses were made on Silica Gel 60 F_{254} (Merck) plates and visualised with anisaldehyde/sulphuric acid and heating. Melting points (uncorrected) were determined with a Reichert microscope.

4.1.1. 5-Acetyl-2-hydroxybenzoic acid methyl ester (4). Anhydrous methylene chloride (45 mL) was added to a 100 mL round-bottom flask. $AlCl_3$ (8.4 g, 63.1 mmol) was added followed by acetic anhydride (2.42 mL, 25.6 mmol). The flask was put on an ice bath and methyl salicylate (2.54 mL, 19.7 mmol) was slowly added to the suspension. The reaction was allowed to stand for 3 h before the mixture was poured on ice, extracted with methylene chloride (3×40 mL), which was washed with brine (2×30 mL), dried and evaporated. The product was purified by chromatography (heptane–ethyl acetate 5:1) and isolated in 93% yield, 3.56 g, as white crystals: mp 60–63°C, lit. 60–62°C. Spectroscopic data were identical to those previously reported.[20]

4.1.2. 2-Hydroxy-5-[2-methyl-1-(1,3-dioxolan)]-benzoic acid methyl ester (5). *p*TsOH (89.3 mg, 0.52 mmol) was added to a solution of **4** (3.36 g, 17.3 mmol) and ethylene glycol (1.93 mL, 34.6 mmol) in 100 mL of toluene, and the mixture was refluxed for 16 h with a Dean Stark trap. Et_3N (73 μL, 0.52 mmol) was added and the solvent was evaporated. The residue was purified by chromatography (heptane–ethyl acetate 6:1) and the product was isolated in 91% yield, 3.75 g, as a white solid: mp 43–45°C; ν_{max} (KBr) 3174, 2989, 2956, 2890, 1680, 1617 1592, 1488, 1443, 1340, 1210, 1097, 1040, 910, 875, 837; ^1H NMR ($CDCl_3$) 1.66 (s, 3H), 3.77 (m, 2H), 3.95 (s, 3H), 4.03 (m, 2H), 6.95 (d, 1H, J=8.6 Hz), 7.57 (dd, 1H, J=8.6, 2.3 Hz), 7.95 (d, 1H, J=2.3 Hz), 10.77 (s, 1H). ^{13}C NMR ($CDCl_3$) 27.5, 52.3, 64.4, 108.3, 111.7, 117.5, 126.6, 132.9, 134.3, 161.2, 170.5. MS *m/z* (% rel int) 238.0848 (M^+, 6, $C_{12}H_{14}O_5$ requires 238.0841), 224 (100%), 207 (11%), 192 (10%), 191 (98%), 147 (33%).

4.1.3. 2-(3-Ethoxycarbonyl-propoxy)5-(2-methyl-[1,3]-dioxolan-2-yl)-benzoic acid methyl ester (6). K_2CO_3 (10.5 g, 75.9 mmol) was added to a solution of **5** (12.8 g, 54.2 mmol) in DMF (120 mL) which was refluxed for 30 min. Ethyl 4-bromobutyrate (11.0 mL, 75.9 mmol) was added, and after an additional 2 h the mixture was extracted with diethyl ether (3×50 mL) which was washed with brine (2×50 mL). The organic phase was dried and evaporated and the crude product was purified by chromatography (heptane–ethyl acetate 6:1). **6** was obtained as white crystals in 85% yield, 16.2 g: mp 51–53°C; ν_{max} (KBr) 2986, 2950, 1730, 1499, 1375, 1262, 1226, 1200, 1097, 1078, 1039; ^1H NMR ($CDCl_3$) 1.25 (t, 3H, J=7.2 Hz), 1.63 (s, 3H), 2.14 (m, 2H), 2.58 (t, 2H, J=7.3 Hz), 3.77 (m, 2H), 3.89 (s, 3H), 4.04 (m, 2H), 4.09 (t, 2H, J=6.0 Hz), 4.13 (q, 2H, J=7.2 Hz), 6.92 (d, 1H, J=8.6 Hz), 7.55 (dd, 1H, J=8.6, 2.4 Hz), 7.88 (d, 1H, J=2.4 Hz). ^{13}C NMR ($CDCl_3$) 14.4, 24.7, 27.8, 30.6, 52.2, 60.6, 64.6, 67.8, 108.5, 113.1, 120.2, 128.8, 130.6, 135.5, 158.1, 166.8, 173.5. MS *m/z* (% rel int) 352.1524 (M^+, 7, $C_{18}H_{24}O_7$ requires 352.1522), 337 (97%), 307 (30%), 251 (20%), 223 (83%), 191 (49%), 115 (100%), 87 (46%).

4.1.4. 7-(2-Methyl-[1,3]dioxolan-2-yl)-5-oxo-2,3,4,5-tetrahydro-benzo[*b*]oxepin-4-carboxylic acid ethyl ester (7). Compound **6** (175 mg, 0.50 mmol) was added to a suspension of NaH 60% (23.8 mg, 0.60 mmol) in freshly distilled THF (12 mL) under N_2. After reflux for 17 h, the salt was discarded, and the solution was neutralised with 0.5 M $HCl_{(aq)}$, dried and evaporated. The product was purified by chromatography (heptane–ethyl acetate 3:1) and obtained as a mixture of keto and enol forms, as a yellowish oil in 81% yield, 130 mg; ν_{max} (liquid film) 2985, 2990, 1734, 1685, 1610, 1490, 1373, 1309, 1241, 1202, 1106, 1039, 873, 842; ^1H NMR ($CDCl_3$) of the major keto isomer (accounting for approximately 50%) 1.21 (t, 3H, J=6.9 Hz), 1.64 (s, 3H), 2.52 (m, 1H), 2.68 (m, 1H), 3.79 (m, 4H), 4.04 (m, 2H), 4.30 (q, 2H, J=6.9 Hz), 4.44 (dd, 1H, J=6.8, 4.0 Hz), 7.03 (d, 1H, J=8.8 Hz), 7.56 (dd, 1H, J=8.8, 2.4 Hz), 7.90 (d, 1H, J=2.4 Hz). It was not possible to assign which carbon signals belong to this isomer. MS *m/z* (% rel int) 320.1264 (M^+, 2, $C_{17}H_{20}O_6$ requires 320.1260), 305 (26%), 291 (15%), 267 (11%), 266 (57%), 259 (14%), 252 (14%), 251 (100%), 221 (13%), 207 (17%), 191 (34%), 147 (16%).

4.1.5. 5-Hydroxy-7-(2-methyl-[1,3]dioxolan-2-yl)-2,3,4,5-tetrahydro-benzo[*b*]oxepin-4-carboxylic acid ethyl ester (8). $NaBH_4$ (14.5 mg, 0.382 mmol) was added to a solution of **7** (123 mg, 0.382 mmol) in MeOH (25 mL) at 0°C. After the addition, the reaction was kept at room temperature for 4 h, before it was neutralized with 1 M $HCl_{(aq)}$ extracted with THF (3×40 mL) and washed with brine (2×40 mL). The organic phase was dried, evaporated and the product was purified by chromatography (heptane–ethyl acetate 3:1). **8** was obtained as 2:1 epimeric mixture, as a white solid in 85% yield, 105 mg: mp 58–60°C; ν_{max} (KBr) 3467, 2985, 2891, 1729, 1498, 1373, 1245, 1198, 1039, 987, 869, 837, 736; ^1H NMR ($CDCl_3$) of the major epimer 1.24 (t, 3H, J=7.1 Hz), 1.61 (s, 3H), 2.22 (m, 1H), 2.49 (m, 1H), 2.97 (ddd, 1H, J=9.5, 4.5, 1.8 Hz), 3.34 (d, 1H, J=6.8 Hz), 3.76 (m, 2H), 4.01 (m, 1H), 4.03 (m, 2H), 4.15 (m, 2H, J=7.1 Hz), 4.22 (m, 1H), 5.17 (d, 1H, J=6.8 Hz), 6.94 (d, 1H, J=8.2 Hz), 7.31 (dd, 1H, J=8.2, 2.3 Hz), 7.42 (d, 1H, J=2.3 Hz). It was not possible to assign which carbon signals belong to this isomer. MS *m/z* (% rel int) 322.1412 (M^+, 3, $C_{17}H_{20}O_6$ requires 322.1416), 308 (17%), 307 (100%).

4.1.6. 7-Acetyl-5-hydroxy-2,3,4,5-tetrahydro-benzo[*b*]oxepin-4-carboxylic acid (9). LiOH (0.305 g, 12.7 mmol) was added to a solution of **8** (1.60 g, 5.19 mmol) in THF–H_2O 1:1 (50 mL). After 16 h at room temperature, the solution was acidified (which caused removal of the protective group) with a few drops of 1 M $HCl_{(aq)}$, extracted with THF (3×30 mL) and washed with brine (2×30 mL). The organic phase was dried and evaporated, the product was purified by chromatography (heptane–ethyl acetate 1:1→0:1) and obtained as a white solid in 98% yield, 1.50 g: mp 139–141°C; ν_{max} (KBr) 3422, 3054, 2987, 1696, 1663, 1599, 1265, 985, 738, 705; ^1H NMR (MeOD) 2.25 (m, 1H), 2.44 (m, 1H), 2.56 (s, 3H), 2.95 (ddd, 1H, J=1.5, 5.6, 9.2 Hz), 4.11 (ddd, 1H, J=3.9, 5.6, 12.3 Hz), 4.33 (ddd, 1H, J=3.1, 9.2, 12.3 Hz), 5.27 (d, 1H, J=1.5 Hz), 6.99 (d, 1H, J=8.4 Hz), 7.82 (dd, 1H, J=8.4, 2.3 Hz), 8.02 (d, 1H, J=2.3 Hz). ^{13}C NMR (CD_3OD) 25.9, 28.4, 63.4, 71.6, 73.0, 121.5, 129.8, 132.1, 132.2, 133.4, 164.0, 175.7, 198.6. MS *m/z* (% rel int) 250.0841 (M^+, 81, $C_{13}H_{14}O_5$ requires 250.0841), 235 (64%), 333 (24%), 204 (54%), 189 (31%), 179 (33%), 173 (39%), 163 (34%), 161 (33%), 149 (100%).

4.1.7. 1-(2,3-Dihydro-benzo[*b*]oxepin-7-yl)-ethanone (10). Compound **9** (1.97 g, 6.69 mmol) was dissolved in toluene (70 mL) and refluxed with a Dean Stark trap for 16 h, before DMF–DMA (2 mL, 15.1 mmol) was added. 10 min after the addition, the mixture was washed with brine (2×40 mL), dried and evaporated. The product was purified by chromatography (heptane–ethyl acetate 10:1) and obtained as a yellow oil in 81% yield, 1.02 g; ν_{max} (liquid film) 2965, 2929, 2893, 1678, 1597, 1497, 1360, 1277, 1245, 1129, 1117, 1037, 1000, 835, 774, 736, 705; ^1H NMR ($CDCl_3$) 2.56 (s, 3H), 2.69 (m, 2H), 4.28 (t, 2H, J=4.8 Hz), 6.05 (dt, 1H, J=11.7, 4.6 Hz), 6.38 (d, 1H, J=11.7 Hz), 6.99 (d, 1H, J=8.4 Hz), 7.73 (dd, 1H, J=8.4, 2.3 Hz), 7.82 (d, 1H, J=2.3 Hz). ^{13}C NMR ($CDCl_3$) 26.6, 34.1, 69.9, 120.3, 126.5, 128.6, 131.6, 131.9, 133.9, 134.0, 163.0, 197.0. MS *m/z* (% rel int) 188.0839 (M^+, 67, $C_{12}H_{12}O_2$ requires 188.0837), 173 (100%), 167 (17%), 149 (32%), 145 (14%), 115 (13%).

4.1.8. 7-(2-Methyl-[1,3]dioxolan-2-yl)-2,3-dihydro-benzo[*b*]oxepin (2). Compound **2** was prepared from **10** according to the procedure for transforming **4** to **5**. The product was purified by chromatography (heptane–ethyl acetate 10:1) and obtained as a yellow oil in 99% yield; ν_{max} (liquid film) 2987, 2889, 1610, 1496, 1373, 1240, 1200, 1123, 1039, 949, 871, 842, 706; ^1H NMR ($CDCl_3$) 1.65 (s, 3H), 2.68 (m, 2H), 3.79 (m, 2H), 4.04 (m, 2H), 4.23 (t, 2H, J=4.8 Hz), 5.99 (dt, 1H, J=11.7, 4.5 Hz), 6.34 (d, 1H, J=11.7 Hz), 6.93 (d, 1H, J=8.3 Hz), 7.23 (dd, 1H, J=8.3, 2.3 Hz), 7.29 (d, 1H, J=2.3 Hz). ^{13}C NMR ($CDCl_3$) 27.8, 34.4, 64.6, 69.6, 108.8, 119.9, 125.2, 126.5, 129.0, 129.8, 130.7, 137.4, 158.7. MS *m/z* (% rel int) 232.1103 (M^+, 15, $C_{14}H_{16}O_3$ requires 232.1099), 218 (13%), 217 (100%), 173 (21%).

4.1.9. 5-Acetyl-2-hydroxy-benzaldehyde (11). Acetic acid anhydride (1.51 mL, 16.0 mmol) was added to a stirred suspension of $AlCl_3$ (5.24 g, 39.3 mmol) in freshly distilled CH_2Cl_2 (30 mL). Salicylic aldehyde (1.5 g, 12.3 mmol) was added and the reaction was refluxed under nitrogen for 24 h. The solution was poured on a mixture of 1 M $HCl_{(aq)}$ and ice (50 g) and extracted with CH_2Cl_2 (3×40 mL). The organic phase was washed with brine (2×40 mL), dried and evaporated, and the crude product was purified by chromatography (heptane–ethyl acetate 6:1). **11** was obtained as a yellowish oil in 69% yield, 1.39 g. The product has previously been reported, produced by other methods.[21,22]

4.1.10. 5-Acetyl-2-but-3-enyloxy-benzaldehyde (12). K_2CO_3 (21.2 mg, 0.154 mmol) was added to a solution of **11** (21.0 mg, 0.128 mmol) and 4-brombut-1-en (16 μL, 0.154 mmol) in DMF (2 mL). The solution was refluxed for 6 h, cooled to room temperature and extracted with ether (3×10 mL). The organic phase was washed with brine (2×10 mL), dried and evaporated, and the crude product was purified by chromatography (heptane–ethyl acetate 6:1). **12** was obtained as white crystals in 81% yield, 22.6 mg: mp 71–73°C; ν_{max} (KBr) 2926, 1675, 1603, 1497, 1359, 1266, 1190, 986, 919, 821; ^1H NMR ($CDCl_3$) 2.58 (s, 3H), 2.62 (m, 2H), 4.21 (t, 2H, J=6.5 Hz), 5.14 (dd, 1H, J=10.2, 1.6 Hz), 5.19 (dd, 1H, J=17.1, 1.6 Hz), 5.88 (m, 1H), 7.05 (d, 1H, J=8.8 Hz), 8.19 (dd, 1H, J=8.8, 2.4 Hz), 8.37 (d, 1H, J=2.4 Hz), 10.47 (s, 1H). ^{13}C NMR ($CDCl_3$) 26.8, 33.7, 68.6, 113.1, 118.4, 124.6, 129.8, 130.4, 133.9, 136.1, 162.9, 189.4, 196.6; MS *m/z* (% rel int) 218.0934 (M^+, 22, $C_{13}H_{14}O_3$ requires 218.0943), 203 (83%), 177 (35%), 149 (100%), 55 (75%).

4.1.11. 1-(4-But-3-enyloxy-3-vinyl-phenyl)-ethanone (13). KO*t*Bu (39 mg, 0.344 mmol) was added to a stirred suspension of Ph_3PCH_3Br in freshly distilled THF (5 mL) under N_2. After stirring for 1 h at room temperature, the mixture was cooled to −78°C and slowly transferred to another cooled flask containing **12** (50 mg, 0.229 mmol) in THF (5 mL). The reaction mixture was allowed to reach room temperature, and 3 h later the mixture was extracted with diethyl ether (3×10 mL). The organic phase was washed with brine (2×10 mL), dried and evaporated, and the crude product was purified by chromatography (heptane–ethyl acetate 6:1). **13** was obtained as a yellow oil in 79% yield, 39 mg; $\nu_{\max}$ (liquid film) 2929, 1676, 1599, 1497, 1428, 1358, 1259, 1132, 1025, 916, 820; ^{1}H NMR ($CDCl_3$) 2.57 (s, 3H), 2.60 (m, 2H), 4.11 (t, 2H, J=6.6 Hz), 5.13 (m, 1H), 5.19 (dd, 1H, J=17.2, 1.6 Hz), 5.33 (dd, 1H, J=11.2, 1.4 Hz), 5.86 (dd, 1H, J=17.8, 1.4 Hz), 5.93 (m, 1H), 6.88 (d, 1H, J=8.7 Hz), 7.02 (dd, 1H, J=17.8, 11.2 Hz), 7.85 (dd, 1H, J=8.7, 2.3 Hz), 8.09 (d, 1H, J=2.3 Hz). ^{13}C NMR ($CDCl_3$) 26.4, 33.5, 67.7, 110.9, 115.8, 117.4, 126.6, 127.2, 129.7, 129.9, 130.9, 134.0, 159.7, 197.0; MS *m/z* (% rel int) 216.1149 (M^+, 30, $C_{14}H_{16}O_2$ requires 216.1150), 201 (15%), 188 (18%), 173 (39%), 147 (100%), 55 (54%), 43 (22%).

4.1.12. 2-(4-But-3-enyloxy-3-vinyl-phenyl)-2-methyl-[1,3]-dioxolane (14). *p*TsOH (8.3 mg, 0.048 mmol) was added to a solution of **13** (0.35 g, 1.61 mmol) and ethylene glycol (0.5 mL, 8.96 mmol) in toluene (10 mL), and the mixture was refluxed for 16 h with a Dean Stark trap. Et_3N (8 μL, 0.053 mmol) was added and the solvent was evaporated. The residue was purified by chromatography (heptane–ethyl acetate 10:1), and **14** was isolated as a yellow oil in 94% yield, 0.39 g; $\nu_{\max}$ (liquid film) 2987, 2886, 1626, 1605, 1495, 1251, 1199, 1039, 911, 871, 816; ^{1}H NMR ($CDCl_3$) 1.67 (s, 3H), 2.59 (m, 2H), 3.79 (m, 2H), 4.04 (m, 4H), 5.12 (dd, 1H, J=10.3, 1.7 Hz), 5.19 (dd, 1H, J=17.2, 1.7 Hz) 5.23 (dd, 1H, J=11.2, 1.5 Hz), 5.82 (dd, 1H, J=17.8, 1.5 Hz), 5.94 (ddt, 1H, J=17.2, 10.3, 6.7 Hz), 6.84 (d, 1H, J=8.5 Hz), 7.05 (dd, 1H, J=17.8, 11.2 Hz), 7.34 (dd, 1H, J=8.5, 2.3 Hz), 7.60 (d, 1H, J=2.3 Hz). ^{13}C NMR ($CDCl_3$) 27.9, 34.0, 64.6, 67.9, 109.0, 111.8, 114.8, 117.3, 123.8, 126.0, 126.6, 131.8, 134.7, 135.6, 155.9; MS *m/z* (% rel int) 260.1406 (M^+, 12, $C_{16}H_{20}O_3$ requires 260.1412), 246 (17%), 245 (100%), 191 (28%), 147 (19%).

4.1.13. 7-(2-Methyl-[1,3]dioxolan-2-yl)-2,3-dihydro-benzo[*b*]oxepine (2). Compound **14** (10 mg, 0.04 mmol) was added to a solution of Ru complex **15** (1.6 mg, 0.002 mmol) in CH_2Cl_2 (8 mL), and the reaction mixture was refluxed under argon for 10 h at room temperature. **2** was obtained as the only product in quantitative yield, identical with that previously prepared (vide supra).

4.1.14. 7-(2-Methyl-[1,3]dioxolan-2-yl)-benzo[*b*]oxepin-3-one (3). SeO_2 (19.1 mg, 0.172 mmol) was added to a solution of **2** (20.0 mg, 0.086 mmol) in xylene (2 mL) which was refluxed for 25 h. The mixture was evaporated and the product purified by chromatography (heptane–ethyl acetate 6:1). **3** was obtained as a yellow oil in 47% yield, 8.8 mg; $\nu_{\max}$ (liquid film) 2988, 2891, 1717, 1668, 1615, 1490, 1259, 1200, 1039, 873, 843, 736; ^{1}H NMR ($CDCl_3$) 1.65 (s, 3H), 3.80 (m, 2H), 4.07 (m, 2H), 4.55 (s, 2H), 6.38 (d, 1H, J=12.1 Hz), 7.13 (d, 1H, J=8.1 Hz), 7.21 (d, 1H, J=12.1 Hz), 7.49 (dd, 1H, J=8.1, 2.3 Hz), 5.52, (d, 1H, J=2.3 Hz). ^{13}C NMR ($CDCl_3$) 27.8, 64.8, 78.0, 108.5, 120.9, 127.2, 129.5, 129.6, 130.5, 139.9, 142.5, 158.7, 196.9. MS *m/z* (% rel int) 246.0896 (M^+, 10, $C_{14}H_{14}O_4$ requires 246.0892), 232 (26%), 231 (100%), 188 (42%), 187 (42%), 173 (82%).

4.1.15. 1-[(3*E*)-3-(Chloromethylene)-2,3-dihydro-1-benzoxepin-7-yl]ethanone, pterulone (1). BuLi (560 μL, 1.40 mmol) was added to a solution of (chloromethyl)triphenylphosphonium chloride (649 mg 1.87 mmol) in freshly distilled THF (25 mL) under inert atmosphere (N_2) at −78°C. A solution of **3** (115 mg, 0.467 mmol) in THF (3 mL) was added after 1 h and the mixture was allowed to reach room temperature. After 2 h, the solution was acidified with a few drops of 2 M $HCl_{(aq)}$ and extracted with diethyl ether (3×10 mL). The organic phase was washed with brine (2×10 mL), dried and evaporated. The product was purified by chromatography (heptane–ethyl acetate 15:1) and obtained as a 1:5 *E*–*Z* mixture, which was isomerised with I_2/UV-light,[4] to obtain **1** identical in all respects with the natural product in 59% yield (from **3**).

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