Notes

Total Synthesis and Bioactivity of Some Naturally Occurring Pterulones

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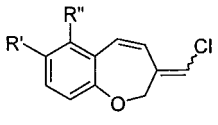
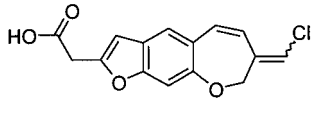
The naturally occurring pterulones **1**, **3**, and **13** were synthesized in high overall yield from readily available methyl 3-(2-propenyl)-4-(2-propenyloxy)benzoate (**6**) by employing ring-closing metathesis (RCM) as a key step. The biological activities of the synthesized pterulones were tested using cells of *Rhodotorula glutinis* and *Saccharomyces cerevisiae*.

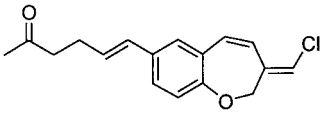
We recently reported the isolation of the novel chlorinated 2,3-dihydro-1-benzoxepin derivatives *E*/Z-**1** and *E*-**2** from the latex of the mushroom stipes of the forest litter-degrading agaric *Mycena galopus*.[1] The compounds referred to as pterulones are structurally related to pterulone (*E*-**3**), pterulinic acid (*E*/*Z*-**4**), and pterulone B (*E*-**5**), previously isolated from the litter-degrading coral fungus *Pterula* sp. strain 82168.[2,3] The compounds from *Pterula* were found to possess antibiotic activities,[3,4] and it might be possible that *E*/Z-**1** and *E*-**2** will show similar activities, as earlier studies have revealed antibiotic activity of culture filtrates of *M. galopus*.[5,6] Since the amounts of pterulones isolated from *M. galopus* were too small for bioactivity tests, we began a study toward synthesis of these types of compounds. A general, simple, and highly efficient procedure was developed and used in the total synthesis of several naturally occurring pterulones. The inhibitory effects of these synthetic pterulones on the growth of *Rhodotorula glutinis* and *Saccharomyces cerevisiae* were subsequently investigated.



(*E*/*Z*)-**1**: R' = CH_2OH; R" = H
(*E*)-**2**: R' = $COCH_3$; R" = OH
(*E*)-**3**: R' = $COCH_3$; R" = H



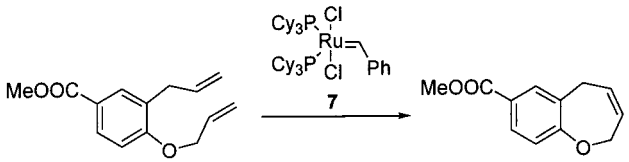
(*E*/*Z*)-**4**



(*E*)-**5**

The key step in our synthetic approach is the ring-closing metathesis (RCM) of the allyl ether **6** to 1-benzoxepin **8**

Scheme 1



6 **8**

mediated by the ruthenium benzylidene complex **7**[7] (Scheme 1). Reagent **7** is a very efficient and highly tolerant precatalyst for numerous metathesis reactions and has therefore found applications in the synthesis of complex target molecules.[8] The starting material **6** was easily prepared in high yield from commercially available methyl 4-hydroxybenzoate as previously described.[9] Treatment of **6** (6.25×10^{-3} M in CH_2Cl_2) with **7** (10 mol %) at room temperature for 2 h gave **8** in excellent yield (91%). An obvious way to convert **8** to allylic alcohol **10** would be epoxidation of the double bond in **8** followed by base-induced rearrangement of the resulting epoxide **9** (Scheme 2). When **8** was exposed to *m*-CPBA, however, only a modest yield of **9** (41%) was obtained. This unsatisfactory result was explained by opening of the epoxide ring through nucleophilic addition of the *m*-chlorobenzoate anion formed during the reaction.[10] A much better yield (86%) of **9** without formation of addition products was achieved upon treatment of **8** with in situ generated dimethyldioxirane.[11] Addition products were also obtained in the next step, rearrangement of epoxide **9** to allylic alcohol **10**, when lithium diethylamide[12] was used. However, with the more sterically hindered KHMDS as base, the reaction proceeded smoothly without formation of addition products and **10** was isolated in 89% yield. Swern oxidation[13] of **10** followed by treatment of the resulting ketone **11** with commercially available (chloromethyl)triphenylphosphonium chloride under Wittig conditions[14] afforded **12** as a 1:7.5 mixture of *E*/*Z* isomers[15] in 85% overall yield. Reduction of *E*/*Z*-**12** with LAH produced alcohol *E*/*Z*-**1** in 82% yield. The spectroscopic data for *E*-**1** and *Z*-**1** were identical with those reported for the natural alcohols from *M. galopus*.[1] Swern oxidation of the carbinol function in *E*/*Z*-**1** resulted in a high yield (93%) of aldehyde *E*/*Z*-**13**. The retention times and mass spectral data of *E*-**13** and *Z*-**13** were identical with those for two unknown minor compounds present in the crude extract of *M. galopus*. These findings strongly

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Scheme 2

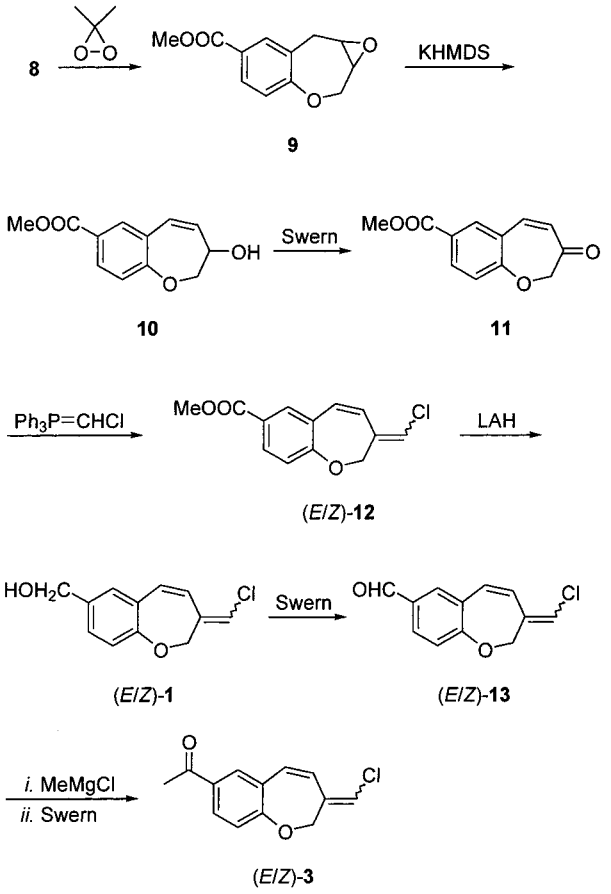

Table 1. Antimicrobial Activity of *Z*-**1**, *Z*-**3**, and *Z*-**13**

compound	concentration (μg/mL)	relative growth (%) of yeasts	
		R. glutinis	*S. cerevisiae*
blank		100	100
Z-**1**	50	5.5	89
	100	<1	≈1
Z-**3**	50	58	91
	100	40	84
Z-**13**	50	96	91
	100	65	87

suggest that *E*-**13** and *Z*-**13** are also metabolites from *M. galopus*. A quantitative conversion of *E*/*Z*-**13** to *E*/*Z*-**3** was achieved via a Grignard reaction with MeMgCl and subsequent Swern oxidation of the resulting alcohol. The spectroscopic data for *E*-**3** were identical with those reported for natural pterulone.[2] Recrystallization of *E*/*Z*-**3** from *n*-hexane provided a pure sample of isopterulone *Z*-**3**. Pure samples of *Z*-**1** and *Z*-**13** were obtained in a similar way.

The pterulones *Z*-**1**, *Z*-**3**, and *Z*-**13** were tested for biological activity using cultures of *Rhodotorula glutinis* and *Saccharomyces cerevisiae*. As summarized in Table 1, isopterulone (*Z*-**3**) and aldehyde *Z*-**13** showed weak inhibition of the growth of the yeast cultures tested. Previously, pterulone (*E*-**3**) was reported to exhibit weak activity to corresponding yeast strains.[4] In contrast to *Z*-**3** and *Z*-**13**, alcohol *Z*-**1** demonstrated a significant activity, with inhibitions of more than 99% at concentration of 100 μg/mL. At lower concentrations of *Z*-**1** (50 μg/mL) only the growth of *R. glutinis* was inhibited considerably (ca. 95%). Compounds **11** and *E*/*Z*-**12** were also tested, but had little if any effect on the growth of the organisms tested.

In conclusion, the efficient procedure described herein gives easy access to compounds with a 1-benzoxepin skeleton. The key intermediate in this approach, the unsaturated ketone **11**, can serve as starting material not only for the synthesis of naturally occurring pterulones as demonstrated here for **1**, **3**, and **13** but also for the synthesis of a great number of unnatural analogues to obtain structure−activity relationships.

Experimental Section

General Experimental Procedures. Melting points were measured on an Olympus BH-2 polarizing optical microscope equipped with a Mettler FP82HT hot stage, controlled by a Mettler FP80HT central processor. ^{1}H and ^{13}C NMR spectra were obtained using $CDCl_3$ or benzene-d_6 solutions with a Bruker AC-E 200 spectrometer operating at 200 and 50 MHz, respectively, or a Bruker DPX 400 operating at 400 and 100 MHz, respectively, for ^{1}H and ^{13}C. Chemical shifts are reported in ppm (δ) using the residual $CHCl_3$ ($\delta_H = 7.24$, $\delta_C = 77.0$) or benzene ($\delta_H = 7.15$, $\delta_C = 128.5$) signals as references. EIMS data were determined at 70 eV on a Hewlett-Packard 5890B series mass selective detector, coupled with a DB-17 fused silica capillary column, 30 m × 0.25 mm i.d., film thickness 0.25 μm. HREIMS data were obtained with a Finnigan MAT 95 spectrometer. Flash chromatography was performed using Merck silica gel 60 (230−400 mesh). All reactions run in anhydrous conditions were carried out in oven-dried glassware under dry N_2 atmosphere. Solvents were dried by appropriate methods. All organic extracts were dried over anhydrous $MgSO_4$ prior to evaporation of the solvent under reduced pressure by using a rotary evaporator. Reagents were purchased from commercial suppliers and used without further purification.

Assay for Biological Activity. Biological activities of the compounds ***Z*-1**, ***Z*-3**, and ***Z*-13** were tested using the yeasts *Rhodotorula glutinis* ATCC 201718 and *Saccharomyces cerevisiae* CBS 1394. The bioassays were performed in a liquid growth medium, containing 0.4% (w/v) yeast extract (Oxoid), 1% (w/v) malt extract (Oxoid), and 0.4% (w/v) glucose dissolved in demineralized water and adjusted to pH 7.0. Cultivation of the yeasts was in 60 mL screw-capped bottles sealed with rubber septa. To the bottles were added increasing amounts of the appropriate compound, dissolved in CH_2Cl_2, to a final concentration of 50 and 100 μg/mL in a total volume of 10 mL, respectively. After removal of the solvent by evaporation, the bottles were filled with 10 mL growth medium and subsequently sterilized.

The bioassay was started by inoculation of 100 μL cells from a 24 h preculture. A suitable concentration of the cells for inoculation was obtained by a 50× dilution of the precultured yeast cells. The bottles were placed in a shaking incubator at 30 °C, and growth of the cells was monitored by sampling after 24 and 48 h of incubation. Concentration of the yeast cells was determined by reading the absorbance at 660 nm. Growth of inhibited cultures was related to samples from cultures grown in the absence of the tested compounds.

Methyl 3-(2-propenyl)-4-(2-propenyloxy)benzoate (6) was prepared in 89% overall yield from methyl 4-hydroxybenzoate as described,[9] except that the reactions with allyl bromide and K_2CO_3 were performed in DMF at room temperature.

Methyl 2,5-Dihydro-1-benzoxepine-7-carboxylate (8). To a stirred solution of 0.58 g (2.5 mmol) of **6** in 400 mL of CH_2Cl_2 was added 0.23 g (0.25 mmol) of ruthenium complex **7** at room temperature. After 3 h, the reaction mixture was concentrated under reduced pressure. Purification of the remaining residue by flash chromatography (25:1 petroleum ether (40−60 °C)/EtOAc) and Kugelrohr distillation gave 0.351 g (69%) of **8** as a stable, colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.45−3.51 (m, 2H), 3.84 (s, 3H), 4.55−4.60 (m, 2H), 5.47 (dm, J = 11.4 Hz, 1H), 5.84 (dm, J = 11.4 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 2.0 Hz, 1H), 7.83 (dd, J = 8.4,

2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 31.6 (t), 52.0 (q), 70.8 (t), 121.5 (d), 125.5 (s), 126.0 (d), 127.0 (d), 129.8 (d), 130.6 (d), 135.4 (s), 162.7 (s), 166.7 (s); HREIMS *m*/z 204.0788 (calcd for $C_{12}H_{12}O_3$, 204.0786). A higher yield (91%) of **8** was achieved by omitting the Kugelrohr distillation, but then **8** had to be used immediately in the next reaction.[16]

Methyl 1a,2,8,8a-Tetrahydrooxireno[2,3-*c*][1]benzoxepine-6-carboxylate (9). To a stirred solution of 283 mg (1.39 mmol) of **8** in 25 mL of 1:1 CH_2Cl_2/acetone were added 40.0 mg (0.15 mmol) of 18-crown-6 and a solution of 1.20 g (14.4 mmol) of $NaHCO_3$ in 10 mL of water. The mixture was cooled to 0 °C, and a solution of 1.85 g (3.00 mmol) of Oxone in 10 mL of water was added dropwise. The reaction mixture was vigorously stirred at 0 °C for 16 h and then treated with an excess of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ for 30 min. After extraction with CH_2Cl_2, the combined organic layers were washed with brine, dried, and evaporated. The remaining residue was flash chromatographed (5:1 petroleum ether (bp 40−60 °C)/EtOAc) to yield 271 mg (89%) of **9** as a colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.02 (ddd, J = 4.4, 2.9, 2.0 Hz, 1H), 3.14−3.39 (m, 3H), 3.78 (s, 3H), 4.20 (dd, J = 14.2, 2.9 Hz, 1H), 4.38 (dd, J = 14.2, 2.0 Hz, 1H), 6.90 (d, J = 8.2 Hz, 1H), 7.72 (d, J = 2.0 Hz, 1H), 7.77 (dd, J = 8.2, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 32.5 (t), 52.1 (q), 53.3 (d), 54.0 (d), 68.7 (t), 121.2 (d), 126.2 (s), 130.0 (s), 130.4 (d), 131.9 (d), 161.8 (s), 166.5 (s); HREIMS *m*/z 220.0738 (calcd for $C_{12}H_{12}O_4$, 220.0736).

Methyl 3-Hydroxy-2,3-dihydro-1-benzoxepine-7-carboxylate (10). To a stirred solution of 319 mg (1.45 mmol) of **9** in 12 mL of toluene, cooled to −60 °C, was added dropwise KHMDS (3.2 mL of 0.5 M in toluene). After 1 h, the reaction mixture was quenched with ice-cold 0.5 M aqueous HCl and extracted with *tert*-butylmethyl ether. The combined organic layers were washed with brine, dried, and evaporated. The residue was flash chromatographed (3:1 petroleum ether (bp 40−60 °C)/EtOAc) to give 283 mg (89%) of **10** as a white solid: mp 107−108 °C (*n*-hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.08 (br s, OH), 3.86 (s, 3H), 4.05 (dd, J = 12.1, 1.9 Hz, 1H), 4.32 (ddd, J = 12.1, 4.5, 1.2 Hz, 1H), 4.44 (m, 1H), 6.13 (ddd, J = 11.9, 4.8, 0.8 Hz, 1H), 6.41 (d, J = 11.9 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 7.83 (dd, J = 8.4, 2.2 Hz, 1H), 7.91 (d, J = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.5 (q), 69.9 (d), 74.6 (t), 120.8 (d), 125.4 (s), 126.4 (s), 129.1 (d), 130.8 (d), 132.8 (d), 135.4 (d), 163.0 (s), 166.9 (s); HREIMS *m*/z 220.0740 (calcd for $C_{12}H_{12}O_4$, 220.0736).

Methyl 3-Oxo-2,3-dihydro-1-benzoxepine-7-carboxylate (11). To a stirred solution of 0.5 mL of $(COCl)_2$ in 10 mL of CH_2Cl_2, cooled to −78 °C, was added 0.65 mL of DMSO. After 2 min, a solution of 250 mg (1.14 mmol) of **10** in 8 mL of 3:1 CH_2Cl_2/DMSO was added dropwise and stirring was continued for 15 min. The reaction mixture was then mixed with 4.2 mL of Et_3N, allowed to come to room temperature, and diluted with ice-cold water. After extraction with CH_2Cl_2, the combined organic layers were washed with brine, dried, and evaporated. The remaining residue was flash chromatographed (5:1 petroleum ether (40−60 °C)/EtOAc) to give 242 mg (98%) of **11** as a white solid: mp 94−95 °C (*n*-hexane); ^{1}NMR ($CDCl_3$, 200 MHz) δ 3.90 (s, 3H), 4.56 (s, 2H), 6.40 (d, J = 12.1 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 12.1 Hz, 1H), 8.00 (dd, J = 8.4, 2.1 Hz, 1H), 8.08 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.4 (q), 77.6 (t), 121.1 (d), 126.4 (s), 127.0 (s), 130.0(d), 133.3 (d), 135.4 (d), 141.5 (d), 162.3 (s), 165.8 (s), 195.7 (s); HREIMS *m*/z 218.0579 (calcd for $C_{12}H_{10}O_4$, 218.0579).

Methyl (3*E*,*Z*)-3-(Chloromethylene)-2,3-dihydro-1-benzoxepine-7-carboxylate (12). To a stirred solution of 1.09 g (3.00 mmol) of (chloromethyl)triphenylphosphonium chloride in 15 mL of toluene was added dropwise KHMDS (5.2 mL of 0.5 M in toluene). The mixture was stirred at room temperature for 30 min and then cooled to 0 °C. A solution of 212 mg (0.972 mmol) of **11** in 10 mL of toluene was added dropwise over 10 min, and the mixture was allowed to come to room temperature. After 30 min of stirring, the reaction mixture was diluted with *tert*-butyl methyl ether, washed with brine, dried, and evaporated. The residue was flash chromatographed [25:1 petroleum ether (bp 40−60 °C)/EtOAc] to yield 212 mg (87%) of oily **12** as an inseparable 1:7.5 mixture of *E*/*Z* isomers: HREIMS *m*/z 250.0395 (calcd for $C_{13}H_{11}ClO_3$, 250.0397). (*Z*)-**12** (major isomer): ^{1}H NMR (C_6D_6, 400 MHz) δ 3.50 (s, 3H), 4.53 (s, 2H), 5.67 (s, 1H), 5.72 (d, J = 11.8 Hz, 1H), 5.92 (d, J = 11.8 Hz, 1H), 6.86 (d, J = 8.5 Hz, 1H), 7.85 (dd, J = 8.5, 2.3 Hz, 1H), 8.01 (d, J = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.08 (q), 68.0 (t), 120.4 (d), 121.2 (d), 125.2 (s), 127.4 (s), 127.6 (d), 128.6 (d), 130.2 (d), 134,5 (d), 137.6 (s), 162.6 (s), 166.4 (s). (*E*)-**12** (minor isomer): ^{1}H NMR (C_6D_6, 400 MHz) δ 3.51 (s, 3H), 3.96 (s, 2H), 5.36 (s, 1H), 6.11 (d, J = 12.0 Hz, 1H), 6.66 (d, J = 12.0 Hz, 1H), 6.86 (d, J = 8.3 Hz, 1H), 7.86 (dd, J = 8.3, 2.3 Hz, 1H), 8.00 (d, J = 2.3 Hz, 1H).[17]

[(3*E*,*Z*)-3-(Chloromethylene)-2,3-dihydro-1-benzoxepin-7-yl]methanol (1). To a stirred suspension of 47 mg of LAH in ether, cooled to 0 °C, was added dropwise a solution of 160 mg (0.64 mmol) of (*E*/*Z*)-**12**. After 2 h, another portion of LAH (6 mg) was added, and stirring was continued for 1 h. The reaction mixture was quenched with 1 M aqueous HCl, diluted with ether, and washed with brine. After drying and evaporation, the remaining residue was flash chromatographed [3:1 petroleum ether (bp 40−60 °C)/EtOAc] to yield 117 mg (82%) of **1** as a 1:7.5 mixture of *E*/*Z* isomers. The spectroscopic data for both isomers were identical with those reported in the literature.[1] Recrystallization from *n*-hexane provided an almost pure sample of (*Z*)-**1**: mp 73−75 °C; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 65.1 (t), 68.7 (t), 120.7 (d), 120.9 (d), 128.2 (d), 128.3 (s), 128.47 (d), 128.49 (d), 131.5 (d), 136.2 (s), 138.9 (s), 159.1 (s).

(3*E*,*Z*)-3-(Chloromethylene)-2,3-dihydro-1-benzoxepine-7-carbaldehyde (13). Alcohol (*E*/*Z*)-**1** (53 mg, 0.24 mmol) was oxidized in a similar fashion as described above for **10**. Workup and flash chromatography [10:1 petroleum ether (bp 40−60 °C)/EtOAc] gave 49 mg (93%) of solid **13** as a 1:7.5 mixture of *E*/*Z* isomers: HREIMS *m*/z 220.0290 (calcd for $C_{12}H_9ClO_2$, 220.0291). (*E*)-**13** (minor isomer): ^{1}H NMR (C_6D_6, 200 MHz, main peaks) δ 3.95 (s, 2H), 5.38 (br s, 1H), 6.05 (d, J = 11.8 Hz, 1H), 6.70 (d, J = 11.8 Hz, 1H), 9.59 (s, 1H); EIMS *m*/*z* 222 [M^+ + 2] (26), 220 [M^+] (80), 185 (100), 157 (38), 145 (47), 129 (58), 128 (88), 127 (56), 63 (21), 51 (21). Recrystallization from *n*-hexane provided a pure sample of (*Z*)-**13** (major isomer): mp 107−108 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.90 (s, 2H), 6.40 (br s, 3H), 7.13 (d, J = 8.2 Hz, 1H), 7.69 (dd, J = 8.2, 2.0 Hz, 1H), 7.75 (d, J = 2.0 Hz, 1H), 9.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 68.1 (t), 121.3 (d), 121.9 (d), 127.3 (d), 128.0 (s), 129.2 (d), 130.7 (d), 132.0 (s), 134.8 (d), 137.4 (s), 163.9 (s), 190.8 (d); EIMS *m*/*z* 222 [M^+ + 2] (26), 220 [M^+] (80), 185 (100), 157 (42), 145 (51), 129 (64), 128 (95), 127 (56), 89 (16), 63 (20).

1-[(3*E*,*Z*)-3-Chloromethylene-2,3-dihydro-1-benzoxepin-7-yl]ethanone (3). To a stirred solution of 76 mg (0.34 mmol) of (*E*/*Z*)-**13** in 10 mL of ether, cooled to 0 °C, was added dropwise MeMgCl (0.5 mL of 3.0 M in THF). After 30 min, excess MeMgCl was destroyed with saturated aqueous NH_4Cl. The reaction mixture was mixed with 0.5 M aqueous HCl and extracted with ether. The combined organic layers were washed with brine, dried, and evaporated to give 99 mg of a light yellow oil. This oil was treated with $(COCl)_2$ and DMSO as described above for **10**. Workup and flash chromatography [10:1 petroleum ether (bp 40−60 °C)/EtOAc] gave solid **3** as a ca. 1:7.5 mixture of *E*/*Z* isomers in quantitative yield. The spectroscopic data for the minor component (*E*)-**3** (pterulone) were identical with those reported in the literature.[2] Recrystallization from *n*-hexane provided a pure sample of (*Z*)-**3** (isopterulone): mp 102−103 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.56 (s, 3H), 4.87 (s, 2H), 6.37 (s, 1H), 6.38 (s, 2H), 7.05 (d, J = 8.4 Hz, 1H), 7.76 (dd, J = 8.4, 2.2 Hz, 1H), 7.85 (d, J = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.5 (q), 68.1 (t), 120.5 (d), 121.4 (d), 127.5 (s), 127.7 (d), 128.8 (d), 129.2 (d), 132.6 (s), 133.4 (d), 137.7 (s), 162.8 (s) 196.7 (s); HREIMS *m*/z 234.0445 (calcd for $C_{13}H_{11}ClO_2$, 234.0448).

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Supporting Information Available: ^{1}H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The amount of the minor isomer in the sample was insufficient for ^{13}C NMR.

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