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Efficient syntheses of pterulone, pterulone B and related analogues †

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Received 9th June 2003, Accepted 24th September 2003
First published as an Advance Article on the web 23rd October 2003

An efficient synthesis of the three halogenated naturally occurring products, pterulone (**2**), pterulone B (**3**) and alcohol **5**, and of a wide range of related unnatural analogues has been achieved starting from the two readily available 1-benzoxepine sulfonyl-containing intermediates **6a** and **6b**. The biological activities of pterulone and some of the synthesized analogues were tested against a wide spectrum of phytopathogenic fungi.

Introduction

Pterulinic acid ((*E*/*Z*)-**1**), pterulone ((*E*)-**2**)[1] and pterulone B ((*E*)-**3**),[2] three novel halogenated antibiotics having a 2,3-dihydro-1-benzoxepine skeleton as a key structural element were isolated in 1997 from fermentations of the *Pterula* species (Fig. 1). These compounds are effective inhibitors of the eukaryotic respiratory chain at the NADH site of the ubiquinone oxidoreductase (complex I). Among them, pterulone has been shown to possess the most potent antifungal activity and to be only weakly cytotoxic *in vitro*.[3] More recently, two additional metabolites possessing the same chlorinated 2,3-dihydro-1-benzoxepine skeleton (*E*/*Z*)-**4** and (*E*)-**5**, have been isolated from the latex of the fungus *Mycena galopus*.[4] The limited availability of these products from the natural source, their significant biological activities as well as their unusual structures make them interesting synthetic targets.

To date, few approaches have been developed for the synthesis of two of these natural chlorinated products, namely pterulone (**2**) and alcohol **4** as well as of some of their unnatural analogues. The synthetic strategies employed in the sythesis of these compounds were based on ring-closing metathesis (RCM)[5] and an intramolecular Wittig reaction.[6] A reaction sequence similar to this last strategy was simultaneously developed by our group in an approach toward pterulone (**2**) and a great number of unsaturated analogues.[7]

Our main goal has therefore been to find a new method of preparation of the 2,3-dihydro-1-benzoxepine skeleton that is sufficiently flexible to be applied to the synthesis of several natural products and a wide range of related unnatural analogues in order to study their biological properties and the structure–activity relationships.

Considering the great utility of the sulfonyl group[8] in organic synthesis, we have envisioned a cycloannulation reaction involving a 2-hydroxybenzyl phenyl sulfone as a 1,4-dinucleophilic reactant and a 3-halo-2-halomethyl-1-propene as a 1,3-dielectrophilic reactant (Scheme 1). This synthetic sequence would provide ready access to the 1-benzoxepine intermediate **6** bearing a sulfone group which could then be subjected to a number of further transformations. For example, it could be used as a stabilizing carbanion in an alkylation reaction step and as a leaving group in nucleophilic displacements. Thus, for a given Y group, by varying the sulfone alkylation or/and sulfinate displacement, this procedure appeared to be suitable

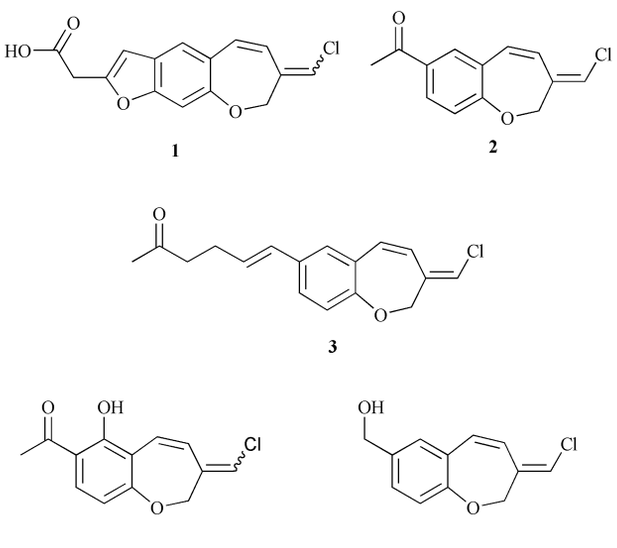
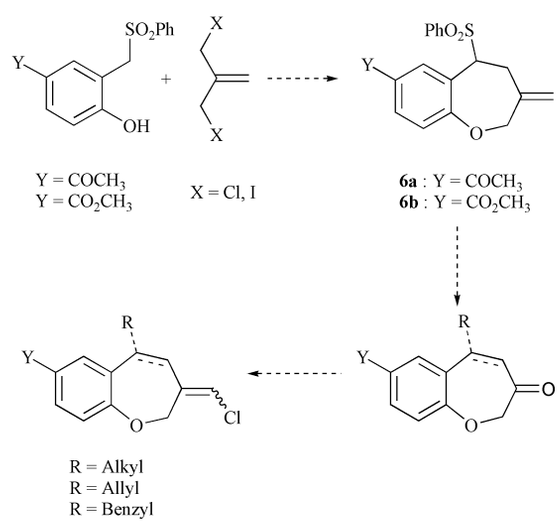


Fig. 1 Natural products recently isolated.

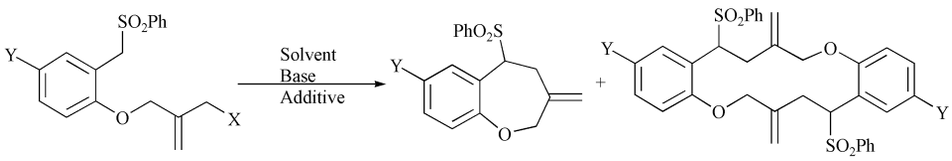


Scheme 1 Plan of the intended chemistry.

† Electronic supplementary information (ESI) available: further experimental details: synthesis and characterisation of compounds 6a, 9a–12a, 14, 19, 20, 22a,b, 23a,b, 25b, 27a,b, 28a,b, 29a,b, 30–33. See http://www.rsc.org/suppdata/ob/b3/b3/b306356a

DOI: 10.1039/b306356a

Table 1 Ring-closure studies



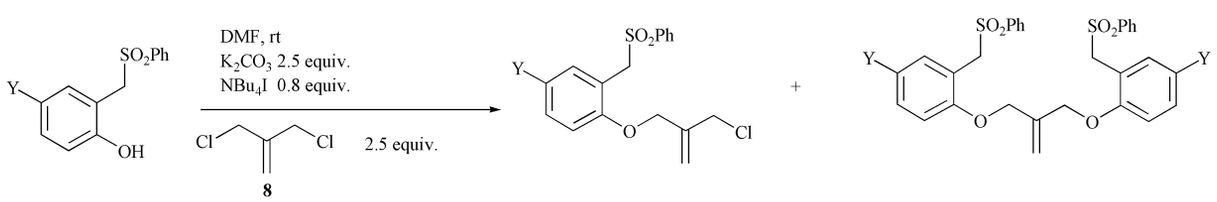
9a : Y = $COCH_3$ X = Cl
9b : Y = CO_2CH_3 X = Cl
11a : Y = $COCH_3$ X = I
11b : Y = CO_2CH_3 X = I

6a : Y = $COCH_3$
6b : Y = CO_2CH_3

12a : Y = $COCH_3$
12b : Y = CO_2CH_3

Entry	X	Y	Base, number equiv.	Solvent	Dilution/mol L^{-1}	Temperature	Additive	Yield of **6** (%)	Yield of **12** (%)
1	I	$COCH_3$	*t*-BuOK, 1.3	THF	0.05	−78 then −20 °C	*n*-Bu_4NI	No traces	62%[a]
2	I	$COCH_3$	LDA, 2	THF	0.05	rt		37[a]	Traces
3	Cl	$COCH_3$	NaH, 2	THF	0.05	rt		No reaction	
4	Cl	$COCH_3$	NaH, 2	DMF	0.05	0		60[b]	40[b]
5	Cl	$COCH_3$	LHMDS, 2	THF	0.05	rt		63	[d]
6	Cl	$COCH_3$	LHMDS, 2	THF	0.013	rt	LiBr	78[a]	Traces
7	I	CO_2CH_3	*t*-BuOK, 1.3	THF	0.05	−78 then −20 °C	*n*-Bu_4NI	No traces	73[a]
8	Cl	CO_2CH_3	*t*-BuOK, 1.3	THF	0.05	−78 then −20 °C	*n*-Bu_4NI	No traces	42[c]
9	Cl	CO_2CH_3	LHMDS, 1	THF	0.05	rt		60[a]	[d]
10	Cl	CO_2CH_3	LHMDS, 1	THF	0.01	rt		60[a]	[d]
11	Cl	CO_2CH_3	LHMDS, 1	THF	0.015	rt	LiBr	72[a]	Traces

[a] Isolated yield. [b] NMR ratios. [c] 13% of the starting material was also recovered. [d] Unisolated.



7a : Y = $COCH_3$
7b : Y = CO_2CH_3

9a : Y = $COCH_3$ Yield = 53%
9b : Y = CO_2CH_3 Yield = 49%

10a : Y = $COCH_3$ Yield = 24%
10b : Y = CO_2CH_3 Yield = 29%

Scheme 2 Phenol alkylation.

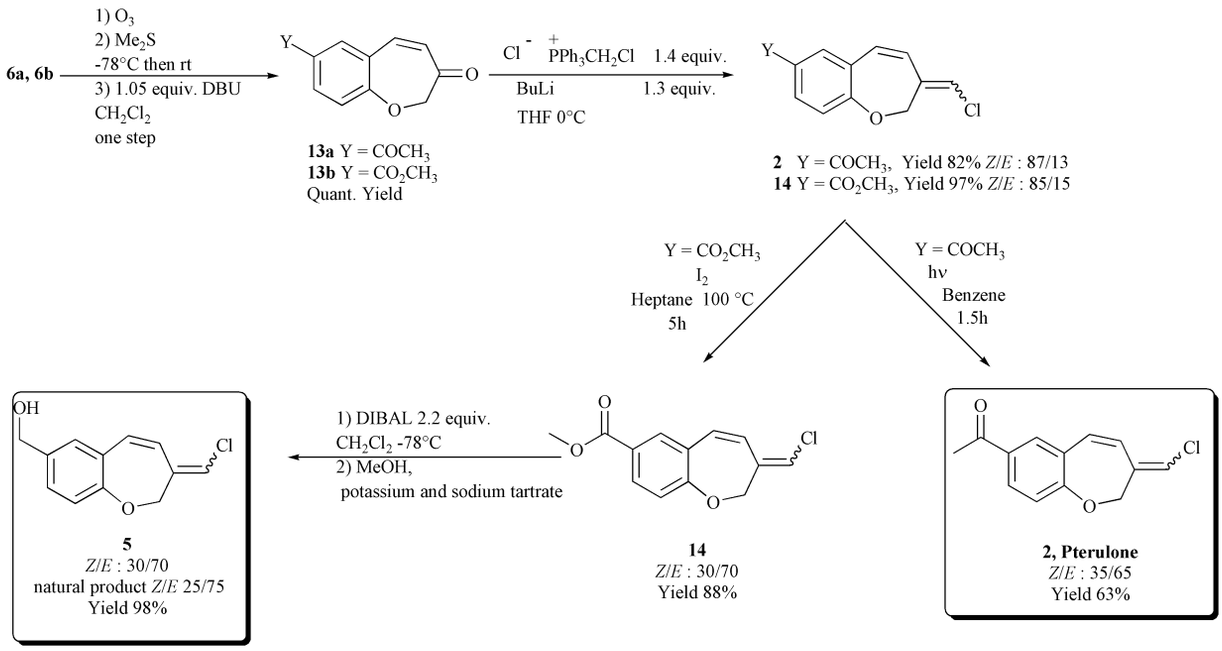
for the construction of a great variety of pterulone structures including more substituted analogues.

Results and discussion

The starting point for the synthesis of these various heterocyclic substrates was the sulfones **7a** and **7b** readily obtained from commercially available 4-hydroxyacetophenone and methyl 4-hydroxybenzoate using a slight modification of the procedure reported by Kaiser *et al.*[9] The challenging annulation of these dinucleophiles via *O*-alkylation with 3-halo-2-halomethyl-1-propene and subsequent intramolecular displacement of the allylic halide by the sulfone to provide the required seven-membered ring was then undertaken. The preparation of various nitrogen containing heterocycles Such related annulation reactions had been previously reported[10] but to our knowledge, the synthesis of oxygen heterocycles from bisalkylation of an hydroxysulfone is without precedent.

We began our studies by examining the alkylation of the phenol group of **7a** with the commercially available dichloride **8** (Scheme 2). Various reaction conditions have been reported for the *O*-alkylation of phenols with this dielectrophile. Our initial attempts using standard conditions[11] (K_2CO_3 in refluxing acetone) were complicated by formation of the diether **10a** along with the desired 2-(chloromethyl)-2-propenyl ether **9a**. This was not a surprise, since, as reported in the literature, the formation of this side product is known to be strongly influenced by the substituents on the benzene moiety.[12] A variety of conditions were tried in order to minimize the formation of this byproduct. The best results were obtained by treating **7a** with an excess of dichloride **8** (2.5 equiv.) in the presence of K_2CO_3 (2.5 equiv.) and *n*-Bu_4NI (0.8 equiv.) in DMF at room temperature,[13] in high dilution. Under these conditions, the chlorinated compound **9a** was isolated in 53% yield together with small amounts of the dimer easily separated by filtration. In a similar manner, **7b** was converted to **9b** in 49% isolated yield.

The intramolecular *C*-alkylation studies were then conducted on chlorides **9a** and **9b** and on the corresponding iodides **11a** and **11b** which are expected to be more reactive substrates for this seven-membered ring formation. The latter were prepared by halogen exchange of chlorides **9a** and **9b** with sodium iodide in refluxing acetone. One problem generally encountered with the cyclisation to medium-size rings is the formation of dimeric products due to entropic factors.[14] We have examined the cyclisation of these four sulfones and found the role of the counterion to be crucial. Table 1 summarizes some significant results under varied conditions. Thus, when a THF solution of *t*-BuOK was added dropwise to a THF solution of **11a** in the presence of *n*-Bu_4NI[15] at −78 °C, the exclusive formation of the dimeric product **12a** was observed. (entry 1). The reaction was also found to proceed in absence of *n*-Bu_4NI but at lower rate. The reaction of **11a** with sodium hydride did not proceed in THF (entry 3), whereas it afforded a 60 : 40 mixture of the mono and dimeric products in a polar solvent such as DMF (entry 4). In marked contrast, when the reaction was performed on **9a** in the presence of 2 equiv. of LDA, the expected annulation product **6a** was isolated in 37% yield (entry 2). A better result was obtained when the alkylation was conducted on **9a**, in THF, at room temperature in the presence of 2 equiv. of LHMDS (entry 5). It was possible to increase the yield of this seven-membered ring from 63% to 78% by carrying out the reaction in more dilute conditions (0.013 M) and in the presence of 1 equiv. of LiBr[16] (entry 6). Cyclisation of the corresponding sulfone ester **9b** under these optimized conditions



Scheme 3 Synthesis of pterulone (**2**) and alcohol **5**.

only needed 1 equiv. of base to provide the monomeric product **6b** in 72% yield (entry 11).

This two-reaction sequence, in which the previous chlorine–iodine exchange is not needed, allows a rapid entry into the 1-benzoxepine skeleton.

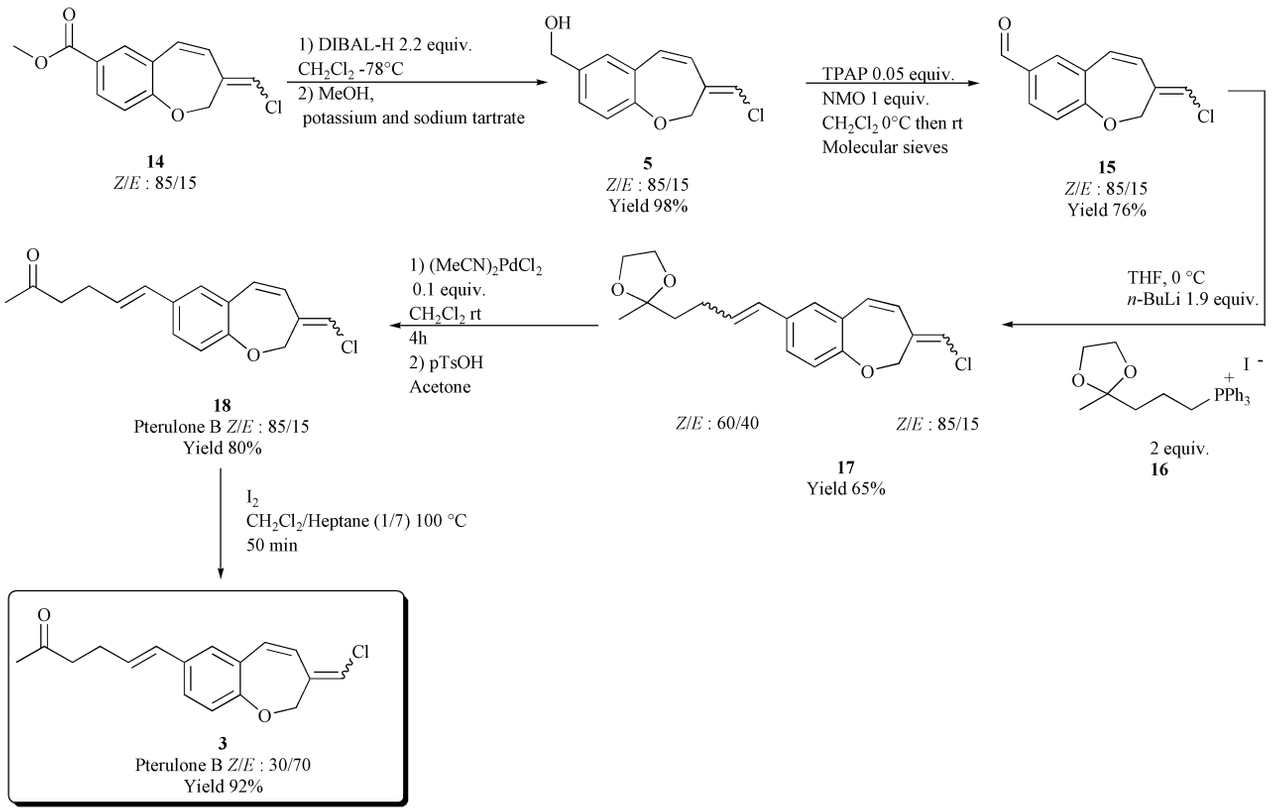
With the requisite intermediate **6a** in hand, we developed a synthetic approach to pterulone (**2**) as shown in Scheme 3. The key step to introduce the enone was accomplished in a single operation by oxidative cleavage of the exocyclic double bond followed by base-induced elimination of sulfinic acid.[17] Thus, ozonolysis of **6a** was performed at −78 °C, in CH_2Cl_2 and followed by reduction of the ozonide with dimethyl sulfide. *In situ* addition of DBU upon warming to room temperature cleanly effected the elimination of sulfinic acid to quantitatively give the expected unsaturated ketone **13a**.

The remaining step to complete the synthesis of pterulone (**2**) was to introduce the vinyl chloride moiety. To this end, we envisioned a direct Wittig reaction of **13a** with the ylide derived from the commercially available chloromethyltriphenylphosphonium chloride. Indeed, despite the presence of two carbonyl groups on intermediate **13a**, it was anticipated that the seven-membered ring ketone could be the more reactive one. We were delighted to see that the Wittig olefination of the seven-membered ring ketone proceeded, as expected. The chemoselectivity was excellent even when using an excess (1.3 equiv.) of the ylide prepared by treatment of chloromethyltriphenylphosphonium chloride (1.4 equiv.) with BuLi (1.3 equiv.) in THF.[18] The adduct **2**, isolated in 82% yield was a 87 : 13 *Z*–*E* olefinic mixture, a result consistent with related Wittig reaction products obtained from other pterulone intermediates.[5] Exposure of this chlorovinylated compound to UV irradiation (254 nm) in benzene or hexane[19] for 1.5 h led to an enrichment of the desired (*E*) isomer to give pterulone (**2**) as a 35 : 65 *Z*–*E* olefinic mixture.

We then turned our attention to the synthesis of two other naturally occurring 2,3-dihydro-1-benzoxepines, the alcohol **5** and pterulone B (**3**), from the same ester intermediate **6b**. The vinyl chloride **14** was readily synthesized in nearly quantitative yield (97%) by a sequence of two reactions similar to that previously discussed (Scheme 3). Isomerisation of the chlorinated double bond was here performed with I_2 in heptane[20] and reduction of the ester moiety with DIBAL-H afforded the expected natural product **5** in 87% yield over the last two steps as a 30 : 70 *Z*–*E* olefinic mixture. (natural product 25 : 75).

Our strategy to prepare pterulone B (**3**) involved the introduction of the (*E*)-olefin on the aryl moiety by Wittig olefination of the aldehyde **15** obtained by oxidation of alcohol **5** (Scheme 4). We anticipated that this approach would require another olefin isomerisation step.[21] In order to minimize the number of steps of this synthesis, we decided to examine the feasibility of the simultaneous isomerisation of the chloroolefin and the side chain double bond. Thus, the synthesis of **3** started from ester **14** (*Z* : *E*, 85 : 15) which was reduced with DIBAL-H. The resulting hydroxy group was oxidized using the procedure developed by Ley and Griffith[22] (catalytic TPAP, stoichiometric NMO) to give the corresponding aldehyde **15** in 76% yield. The Wittig reaction of **15** with the ylide derived from known phosphonium **16**[23] afforded the adduct **17** as an inseparable diastereomeric mixture of geometric isomers. Several attempts under classical conditions using iodine[20] or thermal thiophenol-AIBN system[24] failed to promote a clean isomerisation of both olefins in one step.[25] Consequently, we decided to develop a two-step procedure for these olefin isomerisations. The first step began with isomerisation of the side-chain olefin to give the pure (*E*)-olefin. We found that treatment of **17** under the mild conditions developed by Spencer and co-workers[26] (0.1 equiv. $(MeCN)_2PdCl_2$, CH_2Cl_2, rt, 4 h) produced the pure (*E*)-olefin with concomitant partial removal of the ketal protected group. Subsequent *in situ* acidic treatment of the crude product with pyridinium *p*-toluenesulfonate in aqueous acetone gave the ketone **18** in an 85 : 15 *Z*–*E* olefinic mixture with regard to the chlorinated double bond. The homogeneity of the (*E*)-isomer in the branched chain was confirmed by ^{1}H NMR analysis ($J_{HC=CH}$ = 12 Hz). Treatment of the chlorovinylated product with I_2 in heptane at 100 °C for 50 min led to an enrichment of the desired (*E*)-isomer to give pterulone B as a 30 : 70 *Z*–*E* olefinic mixture.

The next phase of this programme was to prepare various analogues from the two common synthetic substrates **6a**,**b** (Scheme 5). These versatile compounds may allow us to access saturated oxepanes by reductive removal of the sulfone group before oxidative cleavage of the exocyclic double bond. In addition, this functional group is also suitable for the introduction of diversity. As we were interested in examining the possibility of introducing alkyl groups at C_5 in order to prepare more substituted analogues, we began this study by investigating the synthesis of these compounds. To this end, **6b** was treated with 1 equiv. of LHMDS at room temperature in THF, in the



Scheme 4 Synthesis of pterulone B (**3**).

presence of 1 equiv. of DMPU. The resulting anion was quenched with ethyl bromide, allyl bromide or benzyl bromide to afford the corresponding alkylated products **19**, **20** and **21b** respectively in 58, 67 and 83% yield.[27] Under these conditions, the sulfone α-alkylation of the ketone analogue **6a** with benzyl bromide led to the formation of a complex mixture of products. Addition of a further equivalent of base to promote the dilithiation of the ketosulfone followed by addition of 2 equiv. of DMPU and of 1 equiv. of alkylating agent gave a single product **21a** isolated in 97% yield. Addition of more than 1 equiv. of alkylating agent afforded a mixture of products that resulted from *C*-alkylation at both the α position of the sulfone and of the ketone.

It is noteworthy that the synthesis of these alkylated products could be achieved by a one-pot, two-step procedure. Intermediate **9b** was first converted to **6b** by reaction with 1 equiv. of LHMDS in THF at room temperature followed by an additional equivalent of LHMDS and 1 equiv. of DMPU. Then addition of benzyl bromide to the resulting anion led to the formation of the expected compound **21b** in 61% isolated yield. This methodology was successfully applied to analogue **9a** but needed at least a twofold excess of base at the start of the reaction to provide **21a** in 53% yield.

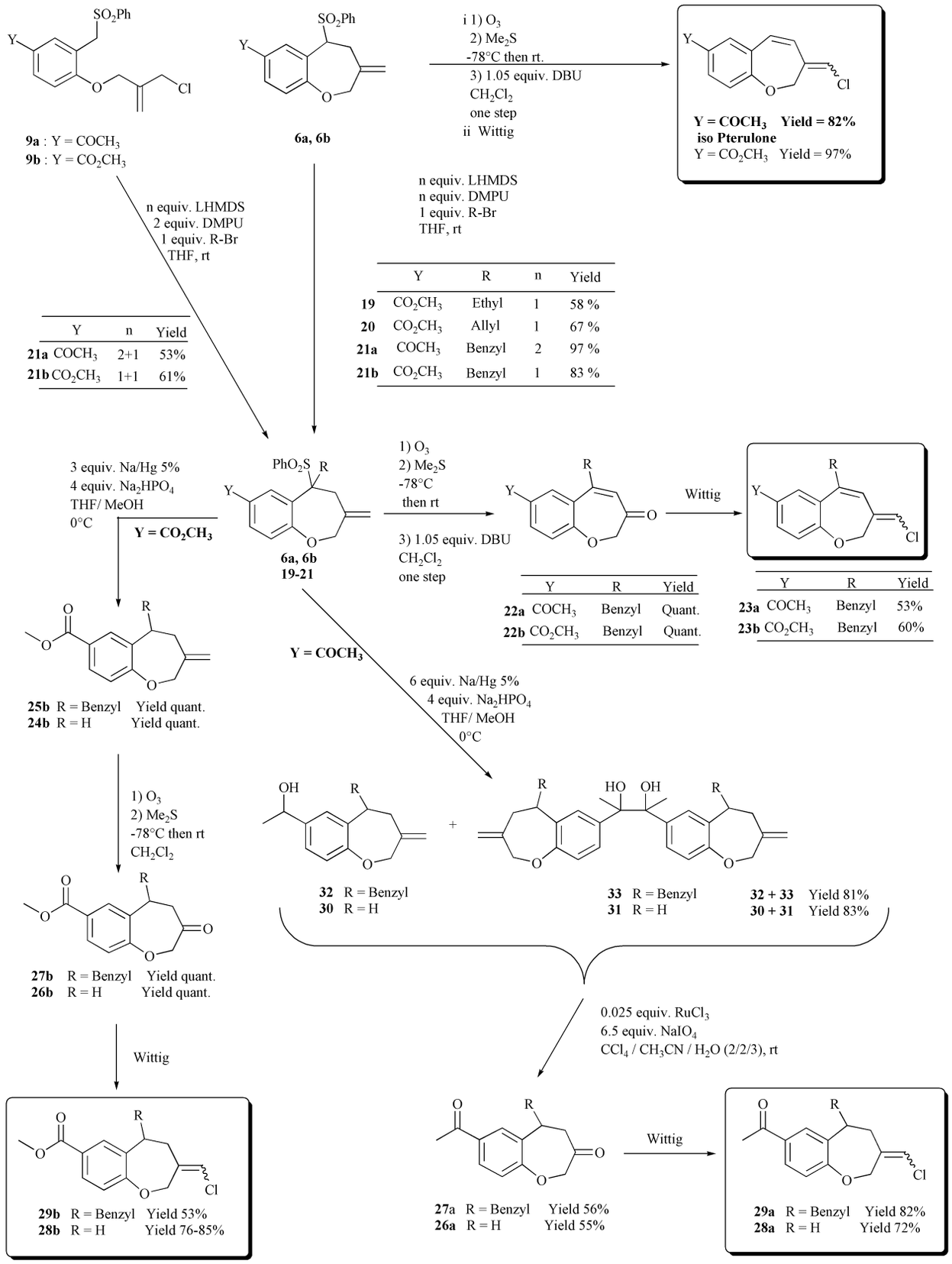
Ozonolysis of these two alkylated sulfones **21a** (resp. **21b**) followed by subsequent *in situ* base-induced elimination of sulfinic acid under the previously described conditions afforded the corresponding enone **22a** (resp. **22b**) in quantitative yield. Wittig reaction of **22a** (resp. **22b**) with chloromethylenetriphenylphosphorane occurred regioselectively at the seven-membered ring carbonyl group to give an 85 : 15 mixture of the (*E*/*Z*)-chlorovinyl derivatives **23a** (resp. **23b**) in 53% yield (resp. 60% yield).

The preparation of saturated analogues was then investigated (Scheme 5). To this end, the sulfone group of **6b** was submitted to reductive cleavage with excess sodium amalgam in MeOH (15 equiv. 5% Na–Hg, Na_2HPO_4, rt, 2 h). These conditions resulted in the cleavage of the sulfone group and in the reductive opening of the seven-membered ring by cleavage of the allylic C–C bond. This unanticipated problem was solved by using only 3 equiv. of sodium amalgam. Using these conditions, the expected seven-membered saturated oxacycle **24b** was isolated in quantitative yield. Ozonolytic cleavage of the double bond led to the ketone **26b** which was subjected to the previously described Wittig olefination and the expected chlorovinylated product **28b** was obtained in 76% yield over the three steps (85% yield based on recovered starting material). A similar reaction sequence starting from **21b** afforded **29b** in 53% overall yield.

Reductive desulfonylation of the corresponding ketosulfone **6a** with sodium amalgam (6 equiv. 5% Na–Hg, Na_2HPO_4, rt, 2 h) caused concomitant over-reduction of the keto group leading to a mixture of alcohol **30** and dimeric product **31**.[28] However, to our delight, when this mixture was treated under the conditions developed by Sharpless and co-workers[29] ($RuCl_3$, $NaIO_4$), oxidative cleavage of both the glycol and the double bond as well as oxidation of the secondary alcohol occurred simultaneously leading to the desired diketone **26a** in 55% isolated yield. The above two-step reaction was applied to sulfone **21a** and the saturated ketone **27a** was obtained in 45% overall yield. Finally, Wittig reaction of **26a** and **27a** with chloromethylenetriphenylphosphorane under conditions similar to those described for compound **22a** led to the saturated chlorinated analogues **28a** and **29a** in good yields.

Pterulone (**2**) and related analogues were tested against a wide spectrum of phytopathogenic fungi: *Botrytis cinerea*, *Septoria nodorum*, *Monilia fructigena*, *Magnaporthe grisea*, *Rhizoctonia solani* and *Septoria tritici*. Table 2 summarizes their biological activities expressed as a percentage of control of the fungi.

Pterulone (**2**) showed excellent control of all tested fungi at 50 ppm. Its activity was found to be slightly better for the Z enriched mixture than for the 35 : 65 mixture of the (*Z*/*E*)-isomer. Pterulone B (**3**) also showed good control, although weaker than for pterulone (**2**), of the different fungi. The natural alcohol **5** described as being strongly active against yeast cultures[5] was surprisingly found to be only moderately



Scheme 5 Synthesis of various analogues starting from **9a** and **9b**.

active against phytopathogenic fungi. The unnatural ethyl ester analogue **14** showed an activity almost as excellent as pterulone (**2**). In contrast, the aldehyde analogue **15** and the various analogues of pterulone (**2**) or its ethyl ester **14** (compounds **23a**, **23b**, **28a**, **28b**, **29a** and **29b**) were found to be poorly or moderately active against the various fungi, *S. nodorum* and *M. grisae* being the more sensitive fungi. All other compounds lacking the chlorovinyl moiety showed, with very few exceptions, no or poor activities demonstrating the importance of this functional group for fungicidal activity.

Conclusion

In summary, we have established that the coupling of 2-hydroxybenzyl phenyl sulfone **7a** and **7b** with the commercially available 3-chloro-2-chloromethyl-1-propene may

Table 2 Fungicidal activities of pterulone and related analogues

Compound	*Z* : *E* ratio	Concentration/μg mL^{-1}	*B. cinerea*[a]	*S. nodorum*[b]	*M. fructigena*[a]	*M. grisea*[a]	*M. grisea*[b]	*R. solani*[a]	*S. tritici*[a]
Untreated			0	0	0	0	0	0	0
2	35 : 65	50	20	100	n.d.[c]	n.d.	20	100	90
2	87 : 13	50	100	100	100	100	100	100	100
3	30 : 70	50	0	80	80	100	n.d.	100	20
5	85 : 15	50	0	80	20	30	n.d.	100	0
6a	—	50	0	0	n.d.	n.d.	0	0	0
6b	—	50	0	10	n.d.	n.d.	10	0	20
14	85 : 15	50	0	90	90	100	100	100	100
15	85 : 15	50	0	80	n.d.	n.d.	40	0	30
19	—	50	0	20	n.d.	n.d.	0	0	0
13a	—	50	10	50	n.d.	n.d.	10	0	0
13b	—	50	0	40	n.d.	n.d.	10	0	10
21b	—	50	0	10	n.d.	n.d.	0	0	0
21b	—	50	0	50	n.d.	n.d.	10	0	0
22a	—	50	0	90	n.d.	n.d.	70	10	30
22b	—	50	0	70	n.d.	n.d.	100	0	0
23a	80 : 20	50	0	80	n.d.	n.d.	100	0	0
23b	50 : 50	50	10	70	n.d.	n.d.	100	0	0
24b	—	50	0	20	n.d.	n.d.	10	0	10
26a	—	50	0	0	20	0	n.d.	0	0
26b	—	50	0	20	n.d.	n.d.	10	0	10
27a	—	50	0	0	0	0	n.d.	0	0
27b	—	50	0	0	n.d.	n.d.	10	0	0
28a	65 : 35	50	0	0	20	0	n.d.	0	20
28b	65 : 35	50	10	80	n.d.	n.d.	30	0	50
29a	60 : 40	50	0	30	20	40	n.d.	0	0
29b	60 : 40	50	0	30	n.d.	n.d.	10	0	0

[a] Crushed mycelium. [b] Spore suspension. [c] n.d : not determined.

allow the rapid construction of the 1-benzoxepine skeleton (**6a** and **b**) that is present in several naturally occurring products. We have thus achieved the total synthesis of natural products such as pterulone, pterulone B and of a great variety of analogues.

Experimental

Synthesis

Commercially available starting materials were used without further purification. Solvents were dried according to standard procedures. All reactions were carried out under a nitrogen atmosphere. Melting points were determined on a Büchi apparatus and are uncorrected. NMR spectra were recorded on a Bruker ALS 300 using the solvent indicated. Chemical shifts δ are reported in ppm relative to the internal reference. High resolution mass spectra were obtained on a Thermofinnigan LCQ-advantage or on a Thermofinnigan MAT95XL. Flash chromatography was conducted using Merck silica gel 60 (40–63 μm). Thin layer chromatography was carried out on Merck silica 60/F-254 aluminium backed plates. The petroleum ether used was the fraction bp 40–60 °C. IR spectra were measured on a Perkin Elmer 681 spectrometer.

3-Benzenesulfonyl-4-(2-chloromethylallyloxy)benzoic acid methyl ester 9b and di-ether 10b

To a solution of 3-benzenesulfonylmethyl-4-hydroxybenzoic acid methyl ester (2.5 g, 8.16 mmol) in *N*,*N*-dimethylformamide (150 mL) was added tetrabutylammonium iodide (3.0 g, 8.16 mmol), potassium carbonate (2.90 g, 20.4 mmol) and 3-chloro-2-chloromethyl-1-propene (2.36 mL, 20.4 mmol). The mixture was stirred for 20 h at room temperature, and was then cooled to 0 °C. The reaction mixture was diluted with diethyl ether (100 mL) and 1 M hydrochloric acid was added until pH = 2. The di-ether **10b** came out of solution and was filtered off and washed with diethyl ether. The combined filtrates were extracted with diethyl ether (4 × 50 mL). The combined extracts were washed four times in acidic solution (1 M HCl, pH = 2) and twice with brine (extraction and washing were carried out in acidic solution to increase DMF solubility in the aqueous phase). The organic layer was dried over magnesium sulfate, concentrated under reduced pressure and the residue was purified by flash column chromatography (ethyl acetate–petroleum ether 35 : 65) to give the title compound **9b** (1.63 g, 50%) as a white solid, R_f 0.41 (ethyl acetate–petroleum ether, 2 : 3); mp: 92 °C (Found: C, 57.73; H, 5.00. $C_{19}H_{19}ClO_5S$ requires C, 57.79; H, 4.85%); ν_{max}(KBr)/cm^{-1} 3090, 2910, 1725, 1600, 1425, 1310, 1270, and 1140; δ_H(300 MHz; $CDCl_3$; Me_4Si) 3.80 (3H, s, OCH_3), 4.08 (s, 2H, CH_2Cl), 4.37 (2H, s, CH_2SO_2Ph), 4.47 (2H, s, OCH_2), 5.22 (1H, s, one of C=CH_2), 5.36 (1H, s, one of C=CH_2), 6.8 (1H, d, J = 8.67 Hz, C(5)–H), 7.41 (2H, m, SO_2Ph), 7.6 (3H, m, SO_2Ph), 7.89 (1H, s, C(2)–H), 7.98 (dd, J = 8.67, 2.2 Hz, C(6)–H); δ_C(75 MHz; $CDCl_3$; Me_4Si) 44.9, 52.05, 56.35, 68.3, 111.3, 117.2, 118.0, 123.05, 128.6, 128.8, 132.45, 133.65, 134.1, 138.45, 139.5, 160.0, 166.1.

Di-ether **10b**, yellow–white solid (934 mg, 29%), R_f 0.46 (ethyl acetate–petroleum ether, 3 : 2); mp: 114–116 °C; ν_{max}(KBr)/cm^{-1} 3080, 2990, 2940, 1720, 1605, 1500, 1420, 1310, 1270, and 1140; δ_H(300 MHz; $CDCl_3$; Me_4Si) 3.85 (3H, s, OCH_3), 4.45 (2H, s, CH_2SO_2Ph), 4.47 (2H, s, OCH_2), 5.34 (2H, s, C=CH_2), 6.88 (1H, d, J = 8.64 Hz, C(5)–H), 7.42 (2H, m, SO_2Ph), 7.6 (3H, m, SO_2Ph), 7.74 (1H, d, J = 2.07 Hz, C(2)–H), 7.98 (dd, J = 8.64, 2.2 Hz, C(6)–H); δ_C(75 MHz; $CDCl_3$; Me_4Si) 52.05, 56.9, 69.25, 111.8, 116.95, 117.4, 123.3, 128.95, 129.3, 132.9, 134.1, 134.4, 138.7, 138.8, 160.6, 166.45.

3-Benzenesulfonyl-4-(2-iodomethylallyloxy)benzoic acid methyl ester 11b

To a solution of **9b** (667 mg, 1.69 mmol) in acetone (17 mL) was added sodium iodide (380 mg, 2.53 mmol). The mixture was stirred for 14 h under reflux and was then cooled to room temperature and quenched with water. After extraction with dichloromethane, the combined organic layers were first washed with saturated sodium thiosulfate, and then with brine, dried over magnesium sulfate and concentrated under reduced pressure. Compound **11b** (808 mg, 98%) was obtained as a white solid, R_f 0.5 (ethyl acetate–petroleum ether, 1 : 1); ν_{max}(KBr)/cm^{-1} 3080, 3000, 2920, 1705, 1605, 1500, 1430, 1360, 1300,

1260, and 1140; δ_H(300 MHz; $CDCl_3$; Me_4Si) 3.82 (3H, s, OCH_3), 3.89 (s, 2H, CH_2I), 4.39 (2H, s, CH_2SO_2Ph), 4.45 (2H, s, OCH_2), 5.13 (1H, s, one of C=CH_2), 5.41 (1H, s, one of C=CH_2), 6.79 (1H, d, J = 8.82 Hz, C(5)–H), 7.38 (2H, m, SO_2Ph), 7.58 (3H, m, SO_2Ph), 7.89 (1H, d, J = 2.2 Hz, C(2)–H), 7.98 (dd, J = 8.67, 1.83 Hz, C(6)–H); δ_C(75 MHz; $CDCl_3$; Me_4Si) 4.95, 52.06, 56.37, 68.99, 111.28, 116.78, 117.16, 123.04, 128.61, 128.86, 132.44, 133.72, 134.12, 138.45, 140.86, 160.0, 166.11.

5-Benzenesulfonyl-3-methylene-2,3,4,5-tetrahydrobenzo[*b*]-oxepine-7-carboxylic acid methyl ester 6b and dimeric product 12b

To a solution of **9b** (100 mg, 0.253 mmol) in dry THF (17 mL) and lithium bromide (28.5 mg, 0.303 mmol), a 1.06 M solution of lithium bis(trimethylsilyl)amide (LHMDS) in THF (303 µL, 0.303 mmol) was added dropwise. The reaction mixture was stirred for 5 min, and the reaction was quenched by addition of water and acidified with dilute hydrochloric acid. After extraction with dichloromethane, the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate–petroleum ether, 35 : 65) to give the title compound **6b** (65 mg, 75%) as a white solid, R_f 0.41 (ethyl acetate–petroleum ether, 2 : 3); mp: 84–86 °C; ν_{max}(KBr)/cm^{-1} 3080, 2980, 2890, 1725, 1610, 1580, 1500, 1450, 1310, 1250, and 1140; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.98 (1H, dd, J = 13.9, 7.1 Hz, C(4)–Ha), 3.21 (1H, dd, J = 13.9, 7.1 Hz, C(4)–Hb), 3.86 (s, 3H, OCH_3), 4.21 (1H, d, J = 13.4 Hz, C(2)–Ha), 4.46 (1H, t, J = 7.35 Hz, C(5)–H), 4.73 (1H, d, J = 13.4 Hz, C(2)–Hb), 4.99 (1H, s, one of C=CH_2), 5.09 (1H, s, one of C=CH_2), 6.98 (1H, d, J = 8.28 Hz, C(9)–H), 7.43 (2H, m, SO_2Ph), 7.62 (3H, m, SO_2Ph), 7.76 (1H, d, J = 2.07 Hz, C(6)–H), 7.94 (1H, dd, J = 8.46, 2.0 Hz, C(8)–H); δ_C(75 MHz; $CDCl_3$; Me_4Si) 32.2, 52.5, 69.7, 77.4, 116.6, 123.35, 124.3, 126.25, 129.2, 129.85, 132.5, 134.30, 136.1, 137.05, 141.25, 162.85, 166.35; *m*/*z* (CI) 217 (MH − $PhSO_2H^+$, 100%), 359 (MH^+, 90). found MH^+ 359.09545. $C_{19}H_{19}O_5S$ requires 359.08749.

Compound 12b. R_f 0.32 (ethyl acetate–petroleum ether, 1 : 1); mp: 190 °C (decomp.); ν_{max}(KBr)/cm^{-1} 3060, 2980, 2950, 2860, 1725, 1650, 1610, 1580, 1500, 1440, 1300, 1250, and 1140; δ_H(300 MHz; $CDCl_3$; Me_4Si) 3.0 (1H, dd, J = 13.74, 10.35 Hz, $PhSO_2CH$–CH_2a), 3.39 (1H, dd, J = 13.74, 5.28 Hz, $PhSO_2CH$–CH_2b), 3.56 (1H, d, J = 10.56 Hz, O–CH_2a), 3.84 (4H, m, OCH_3 and O–CH_2b), 4.98 (1H, s, one of C=CH_2), 5.13 (1H, s, one of C=CH_2), 5.28 (1H, dd, J = 10.17, 5.46 Hz, CH-SO_2Ph), 6.13 (1H, d, J = 8.85 Hz, C(9)–H), 7.24 (2H, m, SO_2Ph), 7.45 (1H, m, SO_2Ph), 7.59 (2H, m, SO_2Ph), 7.62 (1H, dd, J = 8.85, 2.07 Hz, C(8)–H), 7.94 (1H, d, J = 2.07 Hz, C(6)–H); δ_C(75 MHz; $CDCl_3$; Me_4Si) 32.4, 52.2, 60.55, 73.5, 110.2, 121.15, 122.7, 123.2, 128.35, 129.5, 131.05, 131.7, 133.3, 137.8, 138.0, 159.8, 166.3; *m*/*z* (CI) 217 (MH/2 − $PhSO_2H^+$, 100%), 359 (MH^+/2, 75), 717 (5). Found MH^+ 717.18320. $C_{38}H_{37}O_{10}S_2$ requires 717.17499.

7-Acetylbenzo[*b*]oxepine-3-one 13a

Ozone was bubbled through a solution of **6a** (50 mg, 0.175 mmol) in dichloromethane (20 mL) at −78 °C until a blue color persisted. Oxygen gas was then passed through the reaction mixture to remove excess O_3 until the solution became colorless. The ozonide was reduced by addition of 2 mL of dimethyl sulfide. The solution was allowed to warm up to room temperature and stirred for 14 h, then 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (28 µL, 0.183 mmol) was added. The reaction mixture was stirred for 5 min, and was quenched by addition of water and acidified with 1 M hydrochloric acid to increase dimethyl sulfoxide solubility in water. After extraction with dichloromethane, the combined organic layers were washed twice in acidic solution to remove dimethyl sulfoxide and then with brine, dried over magnesium sulfate and concentrated under reduced pressure to give the title compound **13a** (35 mg, 98%) as a white solid, R_f 0.61 (ethyl acetate–petroleum ether, 1 : 1); mp: 92–93 °C (Found: C, 71.33; H, 5.11. $C_{12}H_{10}O_3$ requires C, 71.28; H, 4.98%); ν_{max}(KBr)/cm^{-1} 3090, 2990, 1740, 1680, 1600 1360 and 1225; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.62 (3H, s, $COCH_3$), 4.60 (2H, s, C(2)–H), 6.44 (1H, d, J = 12.0 Hz, C(4)–H), 7.25 (2H, m, C(5)–H and C(9)–H), 8.0 (1H, dd, J = 8.49, 2.07 Hz, C(8)–H), 8.1 (1H, d, J = 2.07 Hz, C(6)–H); δ_C(75 MHz; $CDCl_3$; Me_4Si) 26.9, 77.9, 121.5, 127.4, 130.4, 132.6, 133.8, 134.5, 141.8, 162.7, 195.5, 195.9.

1-(3-Chloromethylene-2,3-dihydrobenzo[*b*]oxepin-7-yl)ethanone 2

To a suspension of (chloromethyl)triphenylphosphonium chloride (139.5 mg, 0.401 mmol) in dry THF (2.7 mL) at 0 °C was added a solution of 2 M *n*-BuLi in hexane (186 µl, 0.373 mmol). After 1 h of stirring at 0 °C, the resulting red solution, was added dropwise to a solution of **13a** (58 mg, 0.287 mmol) in THF (3.9 mL) at 0 °C. Stirring was continued for 30 min, and the reaction mixture was quenched by addition of water and acidified with dilute hydrochloric acid. The aqueous mixture was extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica (ethyl acetate–petroleum ether, 1 : 9) to give the title compound **2** as a 87 : 13 *Z*–*E* mixture (55 mg, 82%). White–yellow solid, R_f 0.4 (ethyl acetate–petroleum ether, 1 : 4); mp: 85–90 °C; ν_{max}(KBr)/cm^{-1} 3060, 2990, 2920, 2840, 1670, 1590, 1490, 1360, 1260 and 1230; δ_H(300 MHz; $CDCl_3$; Me_4Si) *Z* isomer 2.57 (3H, s, $COCH_3$), 4.89 (2H, s, C(2)–H), 6.39 (3H, s, C(4)–H and C(5)–H and C=CHCl), 7.08 (1H, d, J = 8.46 Hz, C(9)–H), 7.76 (1H, dd, J = 8.3, 2.25 Hz, C(8)–H), 7.86 (d, J = 2.25 Hz, 1H, C(6)–H); δ_H(300 MHz; $CDCl_3$; Me_4Si) *E* isomer 2.57 (3H, s, $COCH_3$), 4.59 (2H, s, C(2)–H), 6.17 (1H, s, C=CHCl), 6.87 (1H, d, J = 11.88 Hz, C(4)–H), 7.02 (1H, d, J = 11.88 Hz, C(5)–H), 7.08 (1H, d, J = 8.46 Hz, C(9)–H), 7.76 (1H, dd, J = 8.49, 2.25 Hz, C(8)–H), 7.90 (1H, d, J = 2.25 Hz, C(6)–H); δ_C(75 MHz; $CDCl_3$; Me_4Si) *Z* isomer 26.9, 68.5, 120.9, 121.8, 127.8, 128.1, 129.1, 129.6, 133.0, 133.7, 138.0, 163.2, 197.0.

Spectroscopic data were identical to those reported in literature.

A solution of the 87 : 13 *Z*–*E* mixture (42 mg, 0.179 mmol) was exposed to UV irradiation at 254 nm in benzene for 1.5 h. After purification by flash column chromatography (ether–petroleum ether, 2 : 3) compound **2** was obtained as a 35 : 65 *Z*–*E* mixture (26 mg, 63%).

(3-Chloromethylene-2,3-dihydrobenzo[*b*]oxepin-7-yl)methanol 5

To a solution of compound **14** (*Z* : *E* = 85 : 15, 115 mg, 0.459 mmol) in dichloromethane (3.4 mL) at −78 °C, was added a 1 M solution of diisobutylaluminium hydride (1.1 mL, 1.10 mmol) in hexane. After stirring the reaction mixture for 1 h 15 min at this temperature were added methanol (1 mL) and a 0.7 M solution of potassium and sodium tartrate (5 mL). The reaction mixture was allowed to reach room temperature and was stirred for 14 h then water and dichloromethane were added. After extraction with dichloromethane, the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The title compound **5** was obtained with no further purification as a 85 : 15 *Z*–*E* mixture. White–yellow solid (100 mg, 98%), R_f 0.22 (ethyl acetate–petroleum ether, 3 : 7); mp: 64–69 °C (Found: C, 64.50; H, 5.26. $C_{12}H_{11}ClO_2$ requires C, 64.73; H, 4.98%); ν_{max}(KBr)/cm^{-1} 3600, 3050, 2900, 1500, 1225 and 1000; δ_H(300 MHz; $CDCl_3$; Me_4Si) *Z* isomer 4.65 (2H, s, CH_2OH), 4.88 (2H, s, C(2)–H), 6.35 (3H, s, C(4)–H and C(5)–H and C=CHCl), 7.04 (1H, m, C(9)–H), 7.19 (2H, m, C(6)–H and C(8)–H); δ_H(300

MHz; $CDCl_3$; Me_4Si) *E* isomer 2.34 (1H, br s, OH), 4.56 (2H, s, C(2)–H), 4.65 (2H, s, CH_2OH), 6.13 (1H, s, C=CHCl), 6.55 (1H, d, J = 11.88 Hz, C(4)–H), 6.85 (1H, d, J = 11.88 Hz, C(5)–H), 7.04 (1H, m, C(9)–H), 7.19 (2H, m, C(6)–H and C(8)–H); δ_C(75 MHz; $CDCl_3$; Me_4Si) *Z* isomer 64.9, 68.7, 120.7, 120.8, 128.1, 128.4, 128.5, 128.2, 131.5, 136.3, 138.9, 159.0; δ_C(75 MHz; $CDCl_3$; Me_4Si) *E* isomer 64.9, 73.0, 119.6, 120.6, 128.1, 128.4, 128.5, 127.4, 131.5, 135.9, 138.9, 159.2.

Following the same procedure, compound **14** (*Z* : *E* = 30 : 70, 15 mg, 0.059 mmol), diisobutylaluminium hydride (125 µL, 0.125 mmol) and dichloromethane (0.4 mL) gave the title compound **5** as a 30 : 70 *Z*–*E* mixture. White–yellow solid (13.1 mg, 98%).

3-Chloromethylene-2,3-dihydrobenzo[*b*]oxepine-7-carbaldehyde 15

To a suspension of compound **5** (92 mg, 0.413 mmol), 4-methylmorpholine *N*-oxide monohydrate (NMO) (84 mg, 0.620 mmol) and 4 Å molecular sieves (207 mg) in dichloromethane (1 mL) at 0 °C was added tetrapropylammonium peruthenate (14.6 mg, 0.041 mmol). The mixture was stirred for 1 h and was then filtered trough a silica pad and purified by flash column chromatography on silica (ethyl acetate–petroleum ether, 3 : 7) to give the title compound **15** as a 85 : 15 *Z*–*E* mixture. White solid (70 mg, 76%), R_f 0.58 (ethyl acetate–petroleum ether, 3 : 7); mp: 95–98 °C (Found: C, 65.60; H, 4.25. $C_{12}H_9ClO_2$ requires C, 65.35; H, 4.11%); ν_{max}(KBr)/cm^{-1} 3090, 2900, 1690, 1600, 1225 and 1000; δ_H(300 MHz; $CDCl_3$; Me_4Si) *Z* isomer 4.90 (2H, s, C(2)–H), 6.41 (3H, m, C(4)–H, C(5)–H and C=CHCl), 7.14 (1H, d, J = 8.3 Hz, C(9)–H), 7.70 (1H, dd, J = 8.3, 2 Hz, C(8)–H), 7.75 (1H, d, J = 2.07 Hz, C(6)–H), 9.91 (1H, s, HCO); δ_H(300 MHz; $CDCl_3$; Me_4Si) *E* isomer 4.6 (2H, s, C(2)–H), 6.2 (1H, s, C=CHCl), 6.9 (1H, d, J = 11.9 Hz, C(4)–H), 7.0 (1H, d, J = 11.9 Hz, C(5)–H), 7.14 (1H, d, J = 8.3 Hz, C(9)–H), 7.70 (1H, dd, J = 8.3, 2 Hz, C(8)–H), 7.75 (1H, d, J = 2.07 Hz, C(6)–H), 9.91 (1H, s, HCO); δ_C(75 MHz; $CDCl_3$; Me_4Si) *Z* isomer 68.5, 121.6, 122.2, 127.7, 129.5, 130.5, 128.4, 132.4, 135.2, 137.85, 162.2, 191.1.

3-Chloromethylene-7-[4-(2-methyl-1,3-dioxolan-2-yl)but-1-enyl]-2,3-dihydrobenzo[*b*]oxepine 17

To a suspension of phosphonium salt **16** (196 mg, 0.413 mmol) in dry THF (3.2 mL) at 0 °C was added a 2 M solution of *n*-BuLi in hexane (217 µl, 0.435 mmol). After being stirred for 1 h at 0 °C, this mixture was added dropwise to a solution of **15** (48 mg, 0.217 mmol) in THF (3.6 mL) at 0 °C. The reaction mixture was stirred for 25 min, and was quenched by the addition of water and acidified with dilute hydrochloric acid. After extraction with dichloromethane, the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate–petroleum ether, 1 : 9) to give the title compound **17** as a 85 : 15 and 60 : 40 mixture of four (*Z*)- and (*E*)-isomers. Colorless oil (47 mg, 71%), R_f 0.3 (ethyl acetate–petroleum ether, 1 : 9); δ_H(300 MHz; $CDCl_3$; Me_4Si) *Z*–*Z* isomer 1.32 (3H, s, CH_3), 1.81 (2H, m, C–CH_2), 2.44 (2H, m, H_2C–CH=CH), 3.9 (4H, m, OCH_2-CH_2O), 4.86 (2H, s, C(2)–H), 5.63 (1H, m, H_2C–C*H*=CH), 6.32 (4H, m, Ar–C*H*=CH, C=CHCl, C(4)–H and C(5)–H), 6.96 (1H, m, C(9)–H), 7.0 (2H, m, C(6)–H and C(8)–H); δ_H(300 MHz; $CDCl_3$; Me_4Si) *E*–*Z* isomer 1.32 (3H, s, CH_3), 1.81 (2H, m, C–CH_2), 2.35 (2H, m, H_2C–CH=CH), 3.9 (4H, m, OCH_2-CH_2O), 4.84 (2H, s, C(2)–H), 6.10 (1H, m, H_2C–C*H*=CH), 6.32 (4H, m, Ar–C*H*=CH, C=CHCl, C(4)–H, C(5)–H), 6.96 (1H, m, C(9)–H), 7.0 (2H, m, C(6)–H and C(8)–H); δ_H(300 MHz; $CDCl_3$; Me_4Si) *Z*–*E* isomer 1.35 (3H, s, CH_3), 1.81 (2H, m, C–CH_2), 2.44 (2H, m, H_2C–CH=CH), 3.9 (4H, m, OCH_2-CH_2O), 4.55 (2H, s, C(2)–H), 5.63 (1H, m, H_2C–C*H*=CH), 6.10 (1H, m, C=CHCl), 6.32 (1H, m, Ar–C*H*=CH), 6.52 (1H, d, J = 11.6 Hz, C(4)–H), 6.79 (1H, d, J = 11.6 Hz, C(5)–H), 6.96 (1H, m, C(9)–H), 7.0 (2H, m, C(6)–H and C(8)–H); δ_H(300 MHz; $CDCl_3$; Me_4Si) *E*–*E* isomer 1.35 (3H, s, CH_3), 1.81 (2H, m, C–CH_2), 2.35 (2H, m, H_2C–CH=CH), 3.9 (4H, m, OCH_2-CH_2O), 4.53 (2H, s, C(2)–H), 6.10 (2H, m, H_2C–C*H*=CH and C=CHCl), 6.32 (1H, m, Ar–C*H*=CH), 6.52 (1H, d, J = 11.6 Hz, C(4)–H), 6.79 (1H, d, J = 11.6 Hz, C(5)–H), 6.96 (1H, m, C(9)–H), 7.0 (2H, m, C(6)–H and C(8)–H); δ_C(75 MHz; $CDCl_3$; Me_4Si) *Z*–*Z* isomer 23.77, 24.31, 39.43, 65.10, 65.12, 68.69, 110.18, 120.45, 126.63, 127.88, 128.19, 128.22, 128.76, 129.01, 130.23, 133.11, 133.56, 138.94, 158.12.

85 : 15 and 0 : 100 *Z*–*E* 6-(3-chloromethylene-2,3-dihydrobenzo[*b*]oxepin-7-yl)hex-5-en-2-one 18

To a solution of compound **17** (79 mg, 0.237 mmol) in dichloromethane (1.5 mL) was added bis(acetonitrile)-palladium(II) (6 mg, 0.023 mmol) and the reaction mixture was stirred for 4 h at room temperature. Acetone (0.5 mL) and *p*-toluenesulfonic acid monohydrate (cat.) were then added to completely remove the ketal protected group. After being stirred for 15 min, the reaction mixture was filtered through a short pad of silica gel, and eluted with ethyl acetate. The solvent was removed under reduced pressure and the residue purified by flash column chromatography (ethyl acetate–petroleum ether, 1 : 9) to give the title compound **18** as an 85 : 15 and 0 : 100 mixture of (*Z*)- and (*E*)-isomers. Colorless oil (55 mg, 80%), R_f 0.33 (ethyl acetate–petroleum ether, 1 : 4).

30 : 70 and 0 : 100 *Z*–*E* 6-(3-chloromethylene-2,3-dihydrobenzo[*b*]oxepin-7-yl)hex-5-en-2-one 3

To a solution of compound **18** (55 mg, 0.190 mmol) in a mixture of heptane and dichloromethane (7 : 1) was added a crystal of iodine. The reaction mixture was warmed for 50 min at 100 °C after witch it was cooled to room temperature and hydrolysed by addition of saturated aqueous sodium thiosulfate and then extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate–petroleum ether, 1 : 9) to give the title compound **3** as a 30 : 70 and 0 : 100 mixture of *Z* and *E* isomers. Colorless oil (50 mg, 92%), R_f 0.33 (ethyl acetate–petroleum ether, 1 : 4); ν_{max}(film)/cm^{-1} 3090, 2910, 1725, 1600, 1500, 1225 and 960; δ_H(300 MHz; $CDCl_3$; Me_4Si) *E*-*E* isomer 2.15 (3H, s, CH_3), 2.47 (2H, m, H_2C–CH=CH), 2.59 (2H, m, $COCH_2$), 4.52 (2H, s, C(2)–H), 6.0 (2H, m, H_2C–C*H*=CH, C=CHCl), 6.33 (1H, m, Ar–C*H*=CH), 6.50 (1H, d, J = 11.6, C(4)–H), 6.79 (1H, d, J = 11.6 Hz, C(5)–H), 6.90 (1H, m, C(9)–H) 7.17 (2H, m, C(6)–H and C(8)–H); δ_H(300 MHz; $CDCl_3$; Me_4Si) *E*-*Z* isomer 2.18 (3H, s, CH_3), 2.47 (2H, m, H_2C–CH=CH), 2.59 (2H, m, $COCH_2$), 4.83 (2H, s, C(2)–H), 6.0 (1H, m, H_2C–C*H*=CH), 6.33 (4H, m, Ar–C*H*=CH, C=CHCl, C(4)–H, C(5)–H), 6.90 (1H, m, C(9)–H), 7.17 (2H, m, C(6)–H and C(8)–H); δ_C(75 MHz; $CDCl_3$; Me_4Si) *E*-*E* isomer 27.46, 30.45, 43.58, 73.02, 119.54, 120.54, 124.29, 127.05, 127.26, 128.54, 129.91, 131.31, 131.62, 132.92, 136.81, 158.84, 208.51; *m*/*z* (CI) 289 (MH^+, 93%), 279 (100), 291 (20); found MH^+ 289.0995. $C_{17}H_{18}ClO_2$ requires 289.0917

5-Benzenesulfonyl-5-benzyl-3-methylene-2,3,4,5-tetrahydrobenzo[*b*]oxepine-7-carboxylic acid methyl ester 21b

From compound 6b. To a solution of **6b** (195 mg, 0.543 mmol) in dry THF was added 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (0.072 mL, 0.605 mmol). This was followed by the dropwise addition of a 1.06 M solution of lithium bis(trimethylsilyl)amide in THF (0.6 mL, 0.605 mmol). After stirring for 15 min at room temperature benzyl bromide (73 µL, 0.605 mmol) was added and the reaction mixture was stirred for another 5 min. The reaction mixture was then hydrolysed with water. 1 M hydrochloric acid was added to neutralise the

mixture. After extraction with dichloromethane, the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography (dichloromethane–ethyl acetate–petroleum ether, 1 : 2 : 7) to give compound **21b** (211 mg, 86%) as a white solid.

From compound 9b. To a solution of **9b** (200 mg, 0.507 mmol) in dry THF (33 mL) was added dropwise a 1.06 M solution of LHMDS in tetrahydrofuran (1.15 mL, 1.11 mmol). After stirring for 5 min 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (134 μL, 1.11 mmol) was added. The solution was stirred for 15 min when benzyl bromide (67 μL, 0.557 mmol) was added. The reaction mixture was stirred for another 5 min then quenched by addition of water and acidified with dilute hydrochloric acid. After extraction with dichloromethane, the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica (dichloromethane–ethyl acetate–petroleum ether, 1 : 2 : 7) to give the title compound **21b** (139 mg, 61%) as a white solid, R_f 0.33 (ethyl acetate–petroleum ether, 1 : 3); mp: 164–165 °C; ν_{max}(KBr)/cm^{-1} 3080, 2980, 2950, 2920, 1720, 1605, 1500, 1440, 1400, 1300, 1260, 1140 and 1120; δ_H(300 MHz; $CDCl_3$; Me_4Si) 3.0 (1H, d, J = 14.8 Hz, C(4)–Ha), 3.1 (1H, d, J = 14.8 Hz, C(4)–Hb), 3.5 (1H, d, J = 13.7 Hz, C(2)–Ha), 3.93 (3H, s, OCH_3), 4.0 (1H, d, J = 13.7 Hz, C(2)–Hb), 4.3 (2H, s, $PhCH_2$), 4.7 (2H, 2 × s, C=CH_2), 6.87 (3H, m, $PhCH_2$), 7.12 (3H, m, C(9)–H and CH_2Ph), 7.41 (2H, m, SO_2Ph), 7.60 (3H, m, SO_2Ph), 7.97 (1H, dd, J = 8.3, 1.9 Hz, C(8)–H), 8.55 (1H, d, J = 1.86 Hz, C(6)–H); δ_C(75 MHz; $CDCl_3$; Me_4Si) 38.3, 43.1, 52.7, 73.7, 76.8, 113.5, 123.8, 125.7, 126.1, 127.8, 128.6, 128.8, 131.3, 131.5, 132.2, 134.3, 134.8, 135.1, 136.3, 142.7, 165.3, 166.6; *m/z* (CI) 307 (MH − $PhSO_2H^+$, 100%), 449 (MH^+, 20). Found MH^+ 449.14237. $C_{26}H_{24}O_5S$ requires 449.13444.

1-(5-Benzenesulfonyl-5-benzyl-3-methylene-2,3,4,5-tetrahydrobenzo[*b*]oxepin-7-yl)ethanone 21a

From compound 6a. To a solution of **6a** (200 mg, 0.584 mmol) in dry THF, was added 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (0.152 mL, 1.27 mmol). This was followed by the dropwise addition of a 1.06 M solution of LHMDS in THF (1.28 mL, 1.27 mmol). After stirring for 15 min at room temperature benzyl bromide (70 μL, 0.584 mmol) was added and the reaction mixture was immediately quenched by addition of water and acidified with dilute hydrochloric acid. After extraction with dichloromethane, the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography (dichloromethane–ethyl acetate–petroleum ether, 1 : 2 : 7) to give the title compound **21a** (366 mg, 53%) as a white solid.

From compound 9a. To a solution of **9a** (600 mg, 1.58 mmol) in dry THF (50 mL) was added dropwise a 1.06 M solution of LHMDS in THF (3.17 mL, 3.17 mmol). After 5 min was added 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (134 μL, 3.17 mmol) and a 1.06 M solution of lithium bis-(trimethylsilyl)amide in THF (1.58 mL, 1.58 mmol). After stirring for 15 min, benzyl bromide (188 μL, 1.58 mmol) was added and the reaction was immediately hydrolysed by addition of water and acidified with dilute hydrochloric acid. After extraction with dichloromethane, the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography (dichloromethane–ethyl acetate–petroleum ether, 1 : 2 : 7) to give the title compound **21a** (366 mg, 53%) as a white solid, R_f 0.5 (ethyl acetate–petroleum ether, 2 : 3); mp: 131–132 °C (Found: C, 71.59; H, 5.70. $C_{26}H_{24}O_4S$ requires C, 72.20; H, 5.70%); ν_{max}(KBr)/cm^{-1} 3060, 2920, 2840, 1680, 1600, 1490, 1440, 1360, 1300, 1250, and 1140; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.6 (3H, s, $COCH_3$), 3.0 (1H, d, J = 14.8 Hz, C(4)–Ha), 3.1 (1H, d, J = 14.8 Hz, C(4)–Hb), 3.5 (1H, d, J = 13.7 Hz, C(2)–Ha), 4.0 (1H, d, J = 13.7 Hz, C(4)–Hb), 4.3 (1H, d, J = 14.7 Hz, $PhCH_2$a), 4.4 (1H, d, J = 14.7 Hz, $PhCH_2$b), 4.74 (2H, s, C=CH_2), 6.9 (3H, m, C(9)–H and CH_2Ph), 7.12 (3H, m, CH_2Ph), 7.42 (2H, m, SO_2Ph), 7.60 (3H, m, SO_2Ph), 7.9 (1H, dd, J = 8.4, 2.2 Hz, C(8)–H), 8.44 (1H, d, J = 2.1 Hz, C(6)–H); δ_C(75 MHz; $CDCl_3$; Me_4Si) 27.0, 38.5, 43.3, 52.7, 73.7, 76.8, 113.5, 123.8, 125.7, 127.8, 128.6, 128.9, 130.7, 131.3, 131.4, 132.7, 134.4, 134.6, 134.8, 136.3, 142.8, 165.7, 196.9.

1-(5-Benzyl-3-chloromethylene-2,3-dihydrobenzo[*b*]oxepin-7-yl)-ethanone 23a

Compound **23** was prepared following the same procedure as described for the preparation of pterulone (**2**), using (chloromethyl)triphenylphosphonium chloride (85.5 mg, 0.246 mmol), *n*-BuLi (0.226 mmol), compound **22a** (60 mg, 0.205 mmol). Purification (ethyl acetate–petroleum ether, 5 : 95) gave compound **23a** as an 80 : 20 *Z*–*E* mixture. Yellow–white solid (45 mg, 68%), R_f 0.53 (ethyl acetate–petroleum ether, 1 : 4); mp: 89–94 °C (Found: C, 73.52; H, 5.74. $C_{20}H_{17}ClO_2$ requires C, 73.96; H, 5.28%); ν_{max}(KBr)/cm^{-1} 3080, 3020, 2920, 2850, 1670, 1600, 1490, 1450, 1380 and 1270; δ_H(300 MHz; $CDCl_3$; Me_4Si) *Z* isomer 2.42 (3H, s, $COCH_3$), 3.95 (2H, s, $PhCH_2$), 4.91 (2H, s, C(2)–H), 6.26 (1H, s, C=CHCl), 6.42 (1H, s, C(4)–H), 7.09 (1H, d, J = 8.46 Hz, C(9)–H), 7.3 (5H, m, Ph), 7.7 (1H, dd, J = 8.4, 2.07 Hz, C(8)–H), 8.06 (1H, d, J = 2.07 Hz, C(6)–H); δ_H(300 MHz; $CDCl_3$; Me_4Si) *E* isomer 2.39 (3H, s, $COCH_3$), 4.10 (2H, s, $PhCH_2$), 4.59 (2H, s, C(2)–H), 6.12 (1H, s, C=CHCl), 7.0 (1H, s, C(4)–H), 7.09 (1H, d, J = 8.46 Hz, C(9)–H), 7.3 (5H, m, Ph), 7.7 (1H, dd, J = 8.4, 2.07 Hz, C(8)–H), 8.15 (1H, d, J = 2.07 Hz, C(6)–H); δ_C(75 MHz; $CDCl_3$; Me_4Si) *Z* isomer 26.4, 44.75, 70.4, 119.6, 121.4, 126.6, 128.26, 128.44, 128.7, 128.9, 130.3, 130.35, 132.85, 133.75, 138.5, 139.2, 163.6, 196.7.

3-Methylene-2,3,4,5-tetrahydrobenzo[*b*]oxepine-7-carboxylic acid methyl ester 24b

To a suspension of compound **6b** (175 mg, 0.488 mmol) and sodium phosphate dibasic (NaH_2PO_4) (277 mg, 1.95 mmol) in a 1 : 1 mixture of THF and methanol (10 mL) was added at 0 °C a 5% sodium amalgam (1.01 g, 2.2 mmol). The reaction mixture was stirred at room temperature until the reduction was complete (TLC). The reaction mixture was then hydrolysed with water and mercury was removed by filtration. After extraction with dichloromethane, the organic layer was dried over magnesium sulfate and evaporated under reduced pressure. Compound **24b** was obtained (108 mg, quantitative) as a colorless oil, R_f 0.73 (ethyl acetate–petroleum ether, 3 : 7); ν_{max}(film)/cm^{-1} 3090, 2980, 1725, 1610, 1500, 1430, 1280 and 1250; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.53 (2H, m, C(4)–H), 2.93 (2H, m, C(5)–H), 3.89 (3H, s, OCH_3), 4.49 (2H, s, C(2)–H), 5.0 (2H, 2 × s, C=CH_2), 7.0 (1H, d, J = 8.1 Hz, C(9)–H), 7.86 (2H, m, C(6)–H and C(8)–H). δ_C(75 MHz; $CDCl_3$; Me_4Si) 33.0, 34.4, 52.4, 77.3, 114.8, 121.4, 125.3, 129.8, 132.8, 133.8, 146.4, 164.0, 167.3; *m/z* (EI) 218 (M^+, 55%), 159 (70), 61 (80), 43 (100). Found $M^{+\cdot}$ 218.09429. $C_{13}H_{14}O_3$ requires 218.0943.

3-Oxo-2,3,4,5-tetrahydrobenzo[*b*]oxepine-7-carboxylic acid methyl ester 26b

Ozone was bubbled through a solution of **24b** (62 mg, 0.284 mmol) in dichloromethane (20 mL) at −78 °C until a blue color persisted. The solution was purged of excess ozone by bubbling oxygen through it until the solution became colorless, and the ozonide was reduced by the addition of 2 mL of dimethyl

$$\text{Activity (\%)} = 100 \times \frac{[\text{mean(final OD}_{\text{control wells}}) - \text{mean(initial OD}_{\text{control wells}})] - (\text{final OD}_{\text{treated well}} - \text{initial OD}_{\text{treated well}})}{\text{mean (final OD}_{\text{control wells}}) - \text{mean(initial OD}_{\text{control wells}})} \quad (1)$$

sulfide. The solution was allowed to warm up to room temperature and stirred for 14 h when it was hydrolysed with water. 1 M hydrochloric acid was added to increase dimethyl sulfoxide solubility in water. After extraction with dichloromethane, the organic layers were combined, washed twice in acidic solution (pH = 2) to remove dimethyl sulfoxide and then with brine, dried over magnesium sulfate and evaporated under reduced pressure to give the title compound **26b** (63 mg, 100%), R_f 0.38 (ethyl acetate–petroleum ether, 35 : 65); ν_{max}(film)/cm^{-1} 2970, 1725, 1610, 1580, 1490, 1430, and 1250; δ_H(300 MHz; $CDCl_3$; Me_4Si) 3.0 (2H, m, C(4)–H), 3.14 (2H, m, C(5)–H), 3.9 (3H, s, OCH_3), 4.55 (2H, s, C(2)–H), 7.0 (1H, d, J = 8.3 Hz, C(9)–H), 7.86 (2H, m, C(6)–H and C(8)–H); δ_C(75 MHz; $CDCl_3$; Me_4Si) 27.85, 40.2, 52.5, 78.3, 121.9, 126.3, 129.9, 130.0, 133.21, 162.0, 166.8, 210.0; *m*/*z* (EI) 220 (M^+, 100%), 161 (65), 147 (65). Found $M^{+\cdot}$ 220.07355. $C_{12}H_{12}O_4$ requires 220.0736.

7-Acetyl-4,5-dihydrobenzo[*b*]oxepin-3(2*H*)-one 26a

To a well stirred solution of **30** and **31** (188 mg, 0.921 mmol calculated based on the molecular weight of **30**) in acetonitrile (1.9 mL), carbon tetrachloride (1.9 mL), and water (2.9 mL) was added sodium periodate ($NaIO_4$) (1.28 mg, 5.99 mmol). The resulting mixture was allowed to stir for 10 min at 0 °C when ruthenium chloride (4.7 mg, 0.023 mmol) was added. The mixture turned black and thick. The mixture was stirred for 14 h and then it was hydrolysed with a saturated sodium thiosulfate solution. 1 M hydrocloric acid was added to avoid emulsion. After extraction with dichloromethane, the combined organic layers were washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica (ethyl acetate–petroleum ether, 3 : 7) to give compound **26a** (104 mg, 55%) as a white solid, R_f 0.33 (ethyl acetate–petroleum ether, 35 : 65); mp: 80–82 °C (Found: C, 70.5; H, 5.95. $C_{12}H_{12}O_3$ requires C, 70.6; H, 5.92%); ν_{max}(KBr)/cm^{-1} 3040, 2980, 2920, 1720, 1670, 1590, 1490, 1420, 1360, 1310 and 1250; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.57 (3H, s, $COCH_3$), 3.02 (2H, m, C(5)–H), 3.13 (2H, m, C(4)–H), 4.55 (2H, s, C(2)–H), 7.05 (1H, d, J = 8.3 Hz, C(9)–H), 7.8 (2H, m, C(6)–H and C(8)–H); δ_C(75 MHz; $CDCl_3$; Me_4Si) 26.9, 28.0, 40.2, 78.2, 121.9, 129.0, 130.0, 132.0, 133.5, 162.2, 197.2, 209.9.

Biological tests

Each compound was dissolved in acetonitrile at a concentration of 7 mg mL^{-1} (7000 ppm). The solution was further diluted with methanol to 1/50th in order to give a final concentration for the test of 50 ppm. 50 µL of the resulting solution was dispensed in a 96-well microtiter plate and the solvent was evaporated at room temperature.

Compounds were tested against the phytopathogenic fungi *Botrytis cinerea*, *Monilia fructigena*, *Magnaporthe grisae*, *Rhizoctonia solani* and *Septoria tritici* as crushed mycelium, and *Septoria nodorum* and *Magnaporthe grisae* as spore suspensions.

S. tritici was grown on a medium containing 14.6 g of D-glucose, 7.1 g of bacteriological peptone (OXOID), 1.4 g of yeast extract (Merck) in demineralized water (1 L) and adjusted to pH 5.5. Other pathogens were grown on a medium containing 14.6 g of D-glucose, 7.1 g of mycological peptone (OXOID), 1.4 g of yeast extract (Merck) in demineralized water (1 L) and adjusted to pH 5.0.

S. nodorum (500 sp mL^{-1}) and *M. grisae* (5000 sp mL^{-1}) were inoculated as spore suspensions. Other pathogens were inoculated as crushed mycelium (1/10th of the final volume). The optical density (OD) was adjusted to 0.1 for *B. cinerea*, 0.5 for *M. fructigena*, 0.1 for *M. grisae*, 0.1 for *R. solani* and 0.5 for *S. tritici*.

The final OD was measured at the beginning of the levelling-off phase of the growth at 405 nm for *S. tritici* and at 620 nm for the other pathogens. The initial OD was estimated at 0.2 for *S. tritici* and at 0.08 for the other pathogens. The fungicidal activity of each compound was calculated according to the Abbott formula (eqn. (1)).

Acknowledgements

We are grateful to Dr Adeline Mousques and Ms Christine Martinez from Bayer CropScience (Lyon) for the design of the biological assay and the test of the various compounds.

References

1 M. Engler, T. Anke and O. Sterner, *J. Antibiot.*, 1997, **50**, 330–333.
2 M. Engler, T. Anke and O. Sterner, *Z. Naturforsch.*, 1998, **53c**, 318–324.
3 M. Engler, T. Anke, O. Sterner and U. Brandt, *J. Antibiot.*, 1997, **50**, 325–329.
4 J. B. P. A. Wijnberg, A. Van Veldhuizen, H. J. Swarts, J. C. Frankland and J. A. Field, *Tetrahedron Lett.*, 1999, **40**, 5767–5770.
5 B. W. T. Gruijters, A. Van Veldhuizen, C. A. G. M. Weijers and J. B. P. A. Wijnberg, *J. Nat. Prod.*, 2002, **65**, 558–561; P. Kahnberg, C. W. Lee, R. H. Grubbs and O. Sterner, *Tetrahedron*, 2002, **58**, 5203–5208; see also: P. Kahnberg and O. Sterner, *Tetrahedron*, 2001, **57**, 7181–7184.
6 S.-T. Huang, H.-S. Kuo and C.-T. Chen, *Tetrahedron Lett.*, 2001, **42**, 7473–7475.
7 G. Balme, I. Coudanne, P. Desbordes, N. Huser, P. Lemaire, A. Mousques, A. Nivlet and J.-P. Vors, PCT Int. Appl. WO 0314104 (priority date: 8th August 2001).
8 For reviews on the chemistry of sulfones: *The Chemistry of sulfones and sulfoxides*, Eds S. Patai, Z. Rappoport and C. Stirling, J. Wiley & Sons, New York, 1988; B. M. Trost, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 107–124; N. S. Simpkins, *Sulfones in Organic Synthesis*, Pergamon Press, Oxford, 1993; *The Synthesis of Sulfones, Sulfoxides and Cyclic Sulfides*, Eds S. Patai and Z. Rappoport, Wiley & Sons, New York, 1994; C. M. Rayner, *Contemp. Org. Synth.*, 1994, **1**, 191–203; C. M. Rayner, *Contemp. Org. Synth.*, 1995, **2**, 409–440; C. M. Rayner, *Contemp. Org. Synth.*, 1996, **3**, 499–533; R. Chinchilla and C. Nájera, *Recent Res. Dev. Org. Chem.*, 1997, **1**, 437; Nájera and J. M. Sansano, *Recent Res. Dev. Org. Chem.*, 1998, **2**, 637–683; C. Nájera and M. Yus, *Tetrahedron*, 1999, **55**, 10547–10658; E. N. Prilezhaeva, *Russ. Chem. Rev.*, 2000, **69**, 367–408.
9 C. Kaiser, M. S. Schwartz, D. F. Colella and J. R. Wardwell, *J. Med. Chem.*, 1975, **18**, 674–683 (sodium benzenesulfinate was used instead of magnesium toluenesulfinate).
10 J. C. Carretero, R. G. Arrayas and I. S. De Gracia, *Tetrahedron Lett.*, 1997, **38**, 8537–8539; J. C. Carretero and R. G. Arrayas, *J. Org. Chem.*, 1998, **63**, 2993–3005.
11 Z.-M. Wang, X.-L. Zhang and K. B. Sharpless, *Tetrahedron Lett.*, 1993, **34**, 2267–2270.
12 V. I. Levashova, V. A. Krasnov and L. I. Bunina-Krivorukova, *Zh. Org. Khim.*, 1989, **25**, 1463–1465.
13 H. Tsuda, Y. Takemura, Y. Suzuki and T. Kato, *Heterocycles*, 1997, **44**, 139; S. Czernecki, C. Georgoulis and C. Provelenghiou, *Tetrahedron Lett.*, 1976, **39**, 3535.
14 G. A. Molander, *Acc. Chem. Res*, 1998, **39**, 603–610.
15 S. Hanessian, L. D. Cantin and D. Andreotti, *J. Org. Chem.*, 1999, **64**, 4893–4900.
16 G. Guillena and C. Nájera, *J. Org. Chem.*, 2000, **65**, 7310–7322; M. Kanai, A. Muraoka, T. Tanaka, M. Sawada, N. Ikota and K. Tomiaka, *Tetrahedron*, 1995, **51**, 9349–9352.
17 B. M. Trost, P. Seoane, S. Mignani and M. Acemoglu, *J. Am. Chem. Soc.*, 1989, **111**, 7492.
18 Z. Song and P. Beak, *J. Am. Chem. Soc.*, 1990, **112**, 8126–8134.
19 E. N. Jacobsen, L. Deng, Y. Furakawa and L. E. Martinez, *Tetrahedron*, 1994, **50**, 4332.
20 J.-T. Zhang, W. Dai and R. G. Harvet, *J. Org. Chem.*, 1998, **63**, 8125–8132.

21 Wittig reaction products resulting from aromatic aldehydes are generally obtained as an *E*–*Z*-olefinic mixture: H. O. House, V. K. Jones and J. Frank, *J. Org. Chem*, 1964, **29**, 3327; B. E. Maryanoff and A. B. Reitz, *Chem. Rev.*, 1989, **89**, 863–927.
22 W. P. Griffith, S. V. Ley, G. P. Whitcombe and A. D. White, *J. Chem. Soc., Chem. Commun.*, 1987, 1625–1627; W. P. Griffith and S. V. Ley, *Adrichim. Acta*, 1990, **23**, No.1; S. V. Ley, J. Norman, W. P. Griffith and S. P. Marsden, *Synthesis*, 1994, 639–665.
23 G. Carr, C. Dean and D. Whittaker, *J. Chem. Soc., Perkin Trans. 2*, 1989, 71–76; J. A. Findlay, W. D. MacKay and W. S. Bowers, *J. Chem. Soc. (C)*, 1970, 2631–2635.
24 M. A. Ali and Y. Tsuda, *Chem. Pharm. Bull.*, 1992, **40**, 2842; S. H. Reich, M. Melnick, M. J. Pino, M. A. M. Fuhry, A. J. Trippe, K. Appelt, J. F. Davies II, B. W. Wu and L. Musick, *J. Med. Chem.*, 1996, **39**, 2781–2794.
25 Attempts to isomerise in a single operation led generally to decomposition of the material and resulted at best in only modest yields of the expected product.
26 J. Yu, M. J. Gaunt and J. B. Spencer, *J. Org. Chem.*, 2002, **67**, 4627–4629.
27 This alkylation reaction did not proceed in the absence of DBU.
28 When the reductive desulfonylation was carried out in the presence of less than 6 equimolar amounts of sodium amalgam, a significant amount of the starting material was recovered along with a mixture of **30** and **31**.
29 P. H. J. Carlsen, T. Katsuki, V. S. Martin and K. B. Sharpless, *J. Org. Chem.*, 1981, **46**, 3936–3938.