Bioorganic & Medicinal Chemistry 17 (2009) 1422–1427

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis and pharmacological activities of some sesquiterpene quinones and hydroquinones

Thorsten Laube [a], Andreas Bernet [a], Hans-Martin Dahse [b], Ilse D. Jacobsen [b], Karlheinz Seifert [a,*]

[a] Lehrstuhl für Organische Chemie, NW II, Universität Bayreuth, D-95440 Bayreuth, Germany
[b] Leibniz-Institut für Naturstoff-Forschung und Infektionsbiologie e.V., Hans-Knöll-Institut, Beutenbergstr. 11 a, D-07745 Jena, Germany

ARTICLE INFO

Article history:
Received 19 October 2008
Revised 13 January 2009
Accepted 14 January 2009
Available online 20 January 2009

Keywords:
Siphonodictyals
Terpenes
Phenols
Quinones

ABSTRACT

Synthesis of protected siphonodictyal C was achieved via drim-7-en-11-al. Some sesquiterpene quinones and hydroquinones were tested for their pharmacological activities in assays in search of antiproliferative, cytotoxic, antiphlogistic, antirheumatic and anti-inflammatory drugs. Wiedendiol B is a ten times stronger cyclooxygenase-2 inhibitor than the reference compound indomethacine. Cyclooxygenase-2 inhibitors are drugs with antiphlogistic and antirheumatic activity.

1. Introduction

Siphonodictyal C and further siphonodictyals have been obtained from the burrowing sponge *Siphonodictyon coralliphagum*.[1] The mucus exudation in the oscular chimney of *S. coralliphagum* contains these sesquiterpene hydroquinones which are toxic for coral polyps. Thus, the overgrowth of the oscular chimneys by coral polyps is prevented. Additionally, siphonodictyal C inhibits the growth of *Staphylococcus aureus* and *Bacillus subtilis*.

Siphonodictyal C has also been isolated from *Siphonodictyon* sp. and its structure differs from the one reported by an additional NaO_3S-group (Fig. 1).[2] This paper describes the synthesis of protected siphonodictyal C (±)-**8.** Compound (±)-**8**, the quinone (±)-**5** and 12 structurally similar sesquiterpene quinones and hydroquinones were tested for their antiproliferative, cytotoxic, antiphlogistic, antirheumatic and anti-inflammatory activities.

Recently, we published the synthesis of spongiaquinone methyl ether ((−)-**10**), spongiaquinone (**11**), hyatellaquinone (**12**)[3], wiedendiol B ((±)-**13**) and the sesquiterpene hydroquinone with a rearranged drimane skeleton (±)-**14.**[4] The sesquiterpene *o*-benzoquinone (±)-**15** and *p*-benzoquinone (±)-**16** with a rearranged drimane skeleton have been synthesized before.[5]

Our synthesis of zonarol (**17**), zonarone (**18**), isozonarol (**19**), isozonarone (**20**) and the building block drim-7-en-11-al (±)-**3** for the preparation of the protected siphonodictyal C was reported earlier.[6] Compounds **17**, **18** have been isolated from the East Pacific brown algae *Dictyopteris undulata* Okamura and **19**, **20** from the same species collected in the Gulf of California.[7]

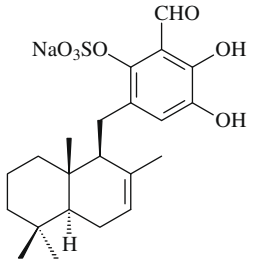
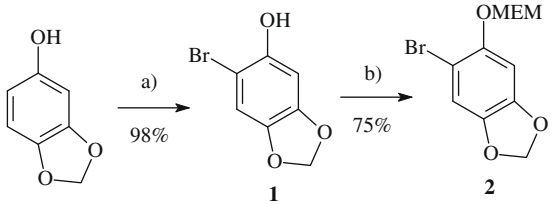


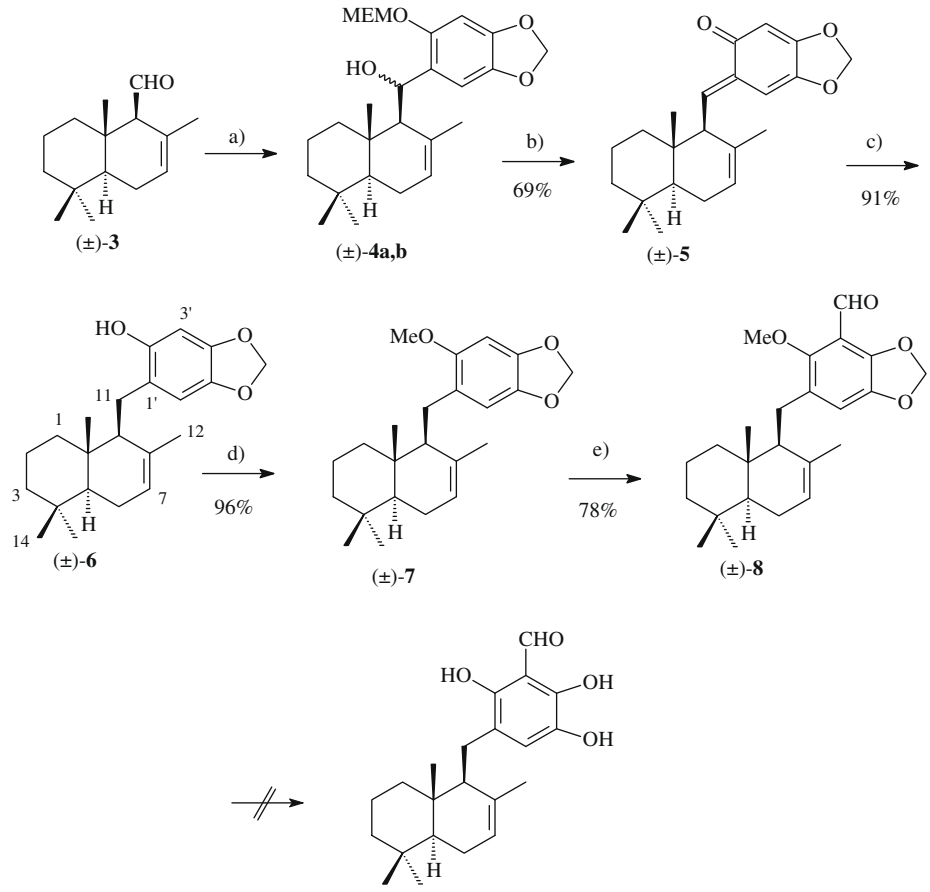
Figure 1. Siphonodytyal C.



Scheme 1. Synthesis of 5-bromosesamol MEM-ether (**2**): (a) Br_2, THF, 0 °C, 5 min; (b) NaH, MEMCl, THF, 0 °C, 15 min, room temperature, 45 min.

* Corresponding author. Tel.: +49 0921 553396; fax: +49 0921 555358.
E-mail address: karlheinz.seifert@uni-bayreuth.de (K. Seifert).

0968-0896/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2009.01.028



Scheme 2. Synthesis of protected siphonodityal C (±)-**8**: (a) 5-lithiumsesamol MEM-ether, THF, −100 °C, 5 min, −100 °C–room temperature, 2 h; (b) PTS, THF/H_2O 10:1, 40 °C, 30 min; (c) $NaBH_4$, EtOH, room temperature, 30 min; (d) *n*-Bu_4NOH, DMS, THF, room temperature; 30 min; (e) TMEDA, *n*-BuLi, THF, 0 °C, 30 min, DMF, room temperature, 16 h.

2. Results and discussion

2.1. Synthesis of protected siphonodictyal C

The arene part of the diastereomeric benzylic alcohol mixture (±)-**4a,b** was prepared starting with sesamol which was brominated with Br_2 in THF to 5-bromosesamol (**1**). Protection of the hydroxy function of **1** with the MEM-group (MEM = methoxyethoxymethyl) yielded 5-bromosesamol MEM-ether (**2**) (Scheme 1) which was transferred to 5-lithiumsesamol MEM-ether with *n*-BuLi at −100 °C.

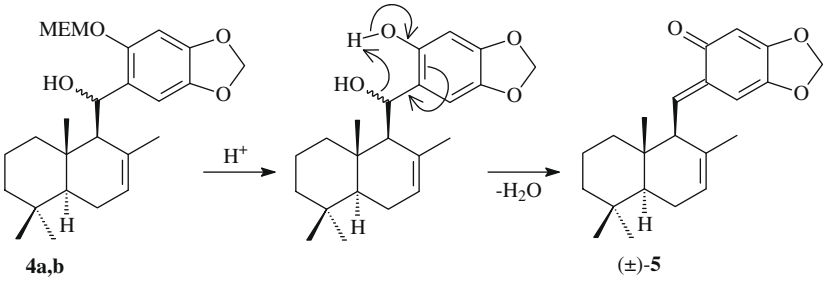
Drim-7-en-11-al ((±)-**3**) was coupled with 5-lithiumsesamol MEM-ether to the benzylic alcohols (±)-**4a,b** (Scheme 2). Treatment of (±)-**4a,b** with *p*-toluene sulfonic acid (PTS) in THF/H_2O led to the deprotection of the MEM-group and benzylic dehydration. Primarily the MEM-group was acid catalyzed removed. The formed phenol was rearranged in a six membered cyclic transition state to the alkylidenecyclohexadienone (±)-**5** (Scheme 3). This tendency to the rearrangement is probably responsible for the deprotection of the MEM-group of (±)-**4a,b** under these reaction conditions (PTS, THF/H_2O 10:1, 40 °C, 30 min). The sesamol MEM-ether being also present in the reaction mixture could not be deprotected under these conditions.

The reduction of (±)-**5** with $NaBH_4$ in EtOH yielded the phenol (±)-**6**. The free OH-group in (±)-**6** was deprotonated with *n*-Bu_4NOH and the phenolate was methylated with dimethylsulfate (DMS) to (±)-**7**. Compound (±)-**7** was deprotonated with *n*-BuLi in *o*-position to the methoxy-group and formylated with DMF to (±)-**8**. The deprotection of (±)-**8** with different reagents always led to decomposition.

2.2. Pharmacological activities

2.2.1. Antiproliferative and cytotoxic activities

Among the sesquiterpene quinones and hydroquinones alkylidenecyclohexadienone (±)-**5** shows the highest antiproliferative and



Scheme 3. Possible mechanism of the benzylic dehydration.

Table 1
Antiproliferative effect (GI_{50}) and cytotoxicity (CC_{50}) of doxorubicin, **5** and **8–16**

Compound	L-929 GI_{50}[a] (μM/l)	K-562 GI_{50}[a] (μM/l)	HeLa CC_{50}[b] (μM/l)
Doxorubicin	1.2 ± 0.6	1.0 ± 0.6	2.0 ± 0.8
Sesquit. cyclohexadienone (±)-**5**	6.2 ± 0.5	3.5 ± 0.4	7.4 ± 0.6
Sesquit. benzaldehyde (±)-**8**	24.0 ± 2.3	21.1 ± 2.1	41.4 ± 4.0
Sesquit. cyclohexadienone (±)-**9**	12.9 ± 1.1	6.2 ± 0.6	20.6 ± 1.9
Spongiaquinone methyl ether ((−)-**10**)	41.6 ± 4.1	20.7 ± 1.9	75.3 ± 6.9
Spongiaquinone ((±)-**11**)	27.1 ± 2.6	13.4 ± 1.1	75.1 ± 7.1
Hyatellaquinone ((±)-**12**)	20.9 ± 1.9	8.4 ± 0.7	72.1 ± 6.9
Wiedendiol B ((±)-**13**)	63.1 ± 5.9	35.8 ± 3.1	38.1 ± 3.1
Sesquit. hydroquinone (±)-**14**	59.9 ± 5.3	25.6 ± 2.1	41.3 ± 3.8
Sesquit. *o*-benzoquinone (±)-**15**	73.4 ± 6.9	26.6 ± 2.2	61.3 ± 5.9
Sesquit. *p*-benzoquinone (±)-**16**	14.0 ± 1.2	6.1 ± 0.5	62.3 ± 5.8

The GI_{50} and CC_{50} were determined from the mean dose-response curves (4 parallels per concentration).
[a] 50% Growth inhibition.
[b] Cytotoxic concentration for 50% of the cells exposed.

cytotoxic activity against the cell lines L-929 (murine fibroblasts), K-562 (human leukaemia) and HeLa (human cervix carcinoma) (Table 1). The antiproliferative and cytotoxic activity of (±)-**5** against L-929, K-562 and HeLa cells is 5.2, 3.5 and 3.7 times lower in comparison with doxorubicin which is used in cancer therapy for the treatment of leukaemia, lymphoma, sarcoma and carcinoma. The antiproliferative and cytotoxic activity was determined as described before[8].

The alkylidenecyclohexedienone (±)-**9** (Fig. 2) differs in its structure from (±)-**5** in the position of the double bond in the sesquiterpene part ((±)-**9**, 8,12-double bond, (±)-**5**, 7,8-double bond) only but its antiproliferative activity (L-929, K-562) is half time and the cytotoxicity (HeLa) three times lower in comparison with (±)-**5**. A similar antiproliferative effect as (±)-**9** possesses the sesquiterpene *p*-benzoquinone (±)-**16** with a rearranged drimane skeleton.

Spongiquinone (**11**) has been obtained from the sponges *Spongia* sp.[9] and *Stelospongia conulata.*[10] Hyatellaquinone (**12**) has been isolated from the alga *Peyssonnelia* sp. and the marine sponges *Hyatella intestinalis*[11] and *Spongia* sp.[9] Spongiaquinone ((±)-**11**) shows a higher cytostatic/cytotoxic activity against the cell lines HMO2 (gastric adenocarcinoma) GI_{50} 3.1 μg/ml and HepG2 (hepatocellular carcinoma) GI_{50} 3.6 μg/ml than hyatellaquinone ((±)-**12**) HMO2 GI_{50} 5.3 μg/ml, HepG2 GI_{50} 6.0 μg/ml. The cytostatic/cytotoxic activity against MCF7 (breast carcinoma) of (±)-**12** GI_{50} 2.4 μg/ml is slightly higher than of (±)-**11** GI_{50} 2.6 μg/ml.[12]

The antiproliferative (L-929, K-562) and cytotoxic (HeLa) activity of (±)-**12** is higher than of (±)-**11** (Table 1). Here we found the same effect as for the alkylidenenecyclohexadienones (±)-**5** and (±)-**9**. The position of the double bond in the sesquiterpene part of hyatellaquinone (8,12) and spongiaquinone (9,11) influences the activity. The methylation of spongiaquinone (**11**) to spongiaquinone methyl ether ((−)-**10**) reduces the antiproliferative effect (L-929, K-562) whereas the cytotoxicity (HeLa) is the same (Table 1).

Wiedendiol B (**13**) has been isolated from the marine sponge *Xestospongia wiedemayeri*[13] and inhibits the cholesteryl ester transfer protein (CETP).[14] This is a plasma neutral glycoprotein which mediates the net transfer of cholesteryl ester from high density lipoprotein (HDL) into the low density lipoprotein (LDL). Since low levels of HDL and high levels of LDL are directly correlated with increased coronary artery diseases, CETP may play a role in the pathogenesis of atherosclerosis. The inhibition of CETP by compounds as wiedendiol B (**13**) may be used for reduction of the risks of coronary artery disease.

Wiedendiol B ((±)-**13**) and the sesquiterpene hydroquinone (±)-**14** differ strongly in their sesquiterpene part but their GI_{50} and CC_{50} values for the three cell lines L-929, K-562 and HeLa are similar and the activities are in the range from good (K-562) to moderate (L-929, HeLa) (Table 1).

2.2.2. Anti-inflammatory, antiphlogistic and antirheumatic activities

Inflammation is a complex process in living organisms, thereby limiting the availability of cell-free in vitro assays to predict anti-inflammatory and antiphlogistic activities of natural compounds. However, interference of natural compounds with some critical steps in the inflammatory process, such as the activity of key enzymes, can be tested in vitro.

3α-Hydroxysteroid dehydrogenase (3α-HSD), one of the key enzymes in the inflammatory cascade, is inhibited by the major types of nonsteroidal and steroidal agents.[15] Therefore, inhibition of 3α-HSD can be used in an assay in search for anti-inflammatory drugs.

3α-HSD catalyzes the reduction of 5β-dihydrocortisone under consumption of NADPH. The NADPH consumption can be determined photometrically by measuring the decrease of UV/vis extinction at 340 nm. Indomethacine and ibuprofene are used as reference compounds.

The sesquiterpene quinones (±)-**5** and (±)-**15** show very good inhibition of 3α-HSD comparable to indomethacine. The sesquiterpene benzaldehyde (±)-**8**, spongiaquinone ((±)-**11**), hyatellaquinone ((±)-**12**), wiedendiol B ((±)-**13**), zonarol ((+)-**17**)) and isozonarone ((+)-**20**)) show good inhibition, compound (±)-**14** with the same hydroquinone part as wiedendiol B ((±)-**13**) exhibits only moderate activity (Table 2). The shift of the double bond from the 7,8-position in the sesquiterpene part of (±)-**5** to the 8,11-position in (±)-**9** reduced the high activity observed in (±)-**5** (Table 2).

Another key enzyme in inflammation is cyclooxigenase-2 (COX2), which mediates the first step in prostaglandine synthesis. COX2 inhibitors are drugs with antiphlogistic and antirheumatic activities.[16] Wiedendiol B ((±)-**13**) and (±)-**15** were tested for their COX2 inhibition. The sesquiterpene *o*-benzoquinone (±)-**15** does not interact with COX2 whereas wiedendiol B ((±)-**13**) exhibits a selective COX2 inhibition with an IC_{50} value between 0.7 and 7 μM. COX2 inhibition by wiedendiol B ((±)-**13**) is ten times stronger than the reference compound indomethacine (data not shown).

Phagocytic cells such as granulocytes, monocytes and macrophages form the first line of defense against microbes. Upon attraction and activation by various inflammatory stimuli such as chemokines and binding of antigens to specialized receptors, granulocytes employ a number of mechanisms to attack and destroy microbes. One of these defense mechanisms is the production of reactive oxygen species (ROS).[17] ROS are generated by NADPH oxidase in a process termed 'respiratory burst'. The NADPH oxidase of phagocytes catalyzes the conversion of O_2 to O_2^- which is further

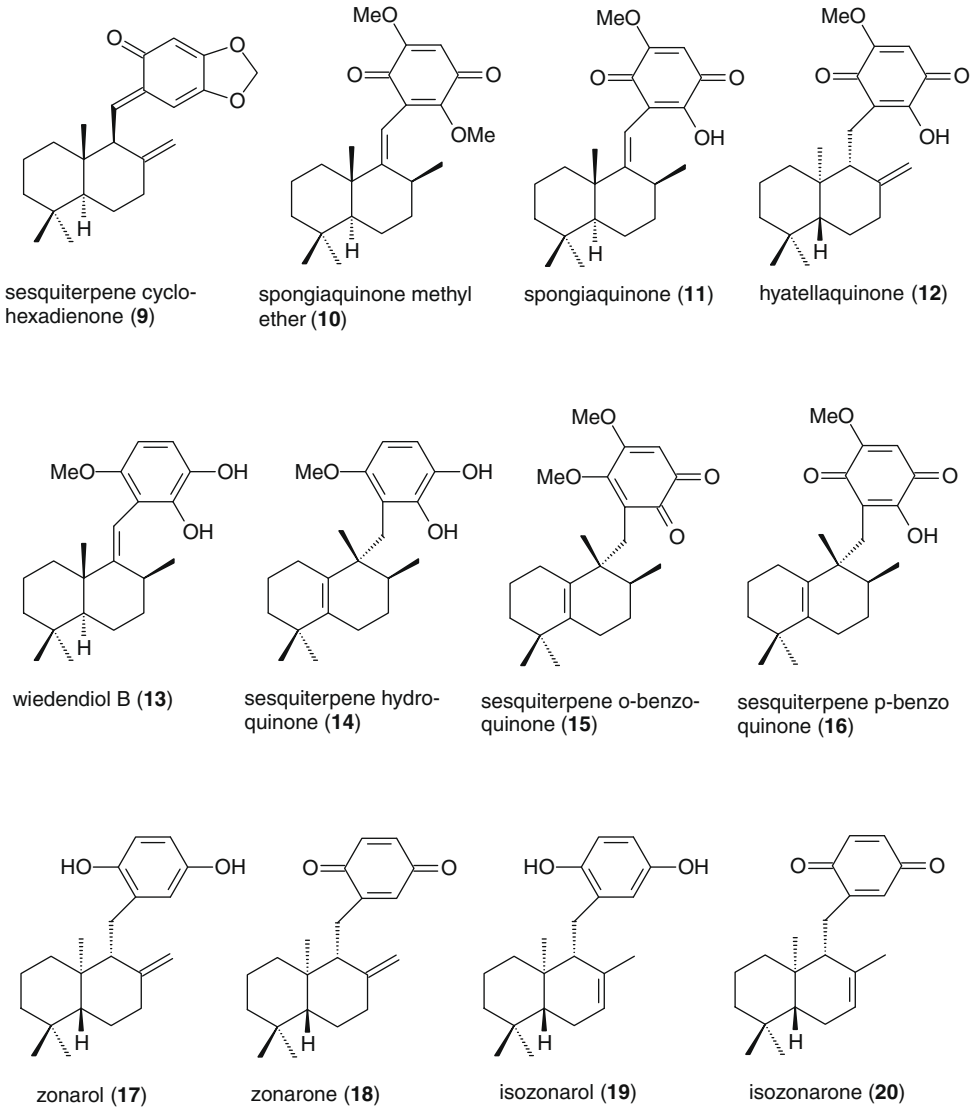


Figure 2. Pharmacologically tested sesquiterpene hydroquinones and sesquiterpene quinones.

converted into H_2O_2. Excessive ROS production and release into the extracellular compartment may be of importance in a number of inflammatory diseases, including arthritis, atherosclerotic lesions, and ischaemic tissue injury.[18,19] The degree of ROS release after activation of phagocytes can be modulated by compounds or drugs. In our experiments, we stimulated ROS production of granulocytes by serum-opsonized zymosan (SOZ). The influence of our compounds on ROS production was determined by measuring ROS by luminol-dependent chemiluminescence.[20]

Zonarol ((+)-**17**)), zonarone ((+)-**18**)), isozonarol ((+)-**19**)) show a very good, isozonarone ((+)-**20**)) a good and the quinones (±)-**9**, (±)-**11**, (±)-**12** and (±)-**16** a moderate inhibition of ROS release of ganulocytes (Table 3). The additional methoxy and hydroxy group in the quinone part of hyatellaquinone ((±)-**12**) in comparison with zonarone ((+)-**18**) strongly reduces the activity (Table 3).

Table 2
3α-Hydroxysteroid dehydrogenase (3α-HSD) activity[a]

Compound	Category
Sesquit. cyclohexadienone (±)-**5**	3
Sesquit. benzaldehyde (±)-**8**	2
Sesquit. cyclohexadienone (±)-**9**	1
Spongiaquinone methyl ether ((−)-**10**)	1
Spongiaquinone ((±)-**11**)	2
Hyatellaquinone ((±)-**12**)	2
Wiedendiol B ((±)-**13**)	2
Sesquit. hydroquinone (±)-**14**	1
Sesquit. *o*-benzoquinone (±)-**15**	3
Sesquit. *p*-benzoquinone (±)-**16**	1
Zonarol ((+)-**17**))	2
Isozonarone ((+)-**20**)	2

(3) High activity, comparable to indomethacine; (2) good activity; (1) moderate activity.

[a] In vitro assay for the search of nonsteroidal inhibitors of the 3α-HSD.

3. Experimental

3.1. General

MPLC: *Labomatic Laboprep-MPLC* unit *MD-50/80/100*. Flash chromatography (FC): silica gel *Si 60* (40-63 μ; *Merck*). TLC: *Merck* precoated plates silica gel *60 F_{254}*, detection by 5% molybdophosphoric acid in EtOH (*Aldrich Chemicals Ltd.*). NMR: *Bruker AC-300*; δ in ppm, *J* in Hertz; $CDCl_3$ as solvent and internal standard. MS: *Finnigan MAT 8500*, 70 eV; in *m/z* (rel.%).

Table 3
Modulation of ROS production[a]

Compound	Category
Sesquit. cyclohexadienone (±)-**9**	1
Spongiaquinone ((±)-**11**)	1
Hyatellaquinone ((±)-**12**)	1
Sesquit. *p*-benzoquinone (±)-**16**	1
Zonarol ((+)-**17**))	3
Zonarone ((+)-**18**))	3
Isozonarol ((+)-**19**)	3
Isozonarone ((+)-**20**)	2

(3) High activity; (2) good activity; (1) moderate activity.
[a] In vitro chemiluminiscence assay detecting inhibition of ROS production in SOZ-stimulated granulocytes.

3.2. Preparation, physical and spectroscopic data of the compounds

3.2.1. 5-Bromosesamol (1)

A solution of sesamol (1.38 g, 10.0 mmol) in 60 ml of THF was cooled to 0 °C and Br_2 (0.51 ml, 10 mmol) was added. After stirring for 5 min at 0 °C saturated Na_2CO_3-solution was added and the reaction mixture was extracted three times with *t*-butyl methyl ether. The combined organic layers were washed with saturated NaCl-solution and filtered through silica gel/Na_2SO_4. Removing the solvent yielded **1** (2.13 g, 98%) as brownish oil. R_f: 0.57 (hexane/EtOAc 4:1). MS *m/z* (%): 218 (12, $M^{+?}$), 216 (12, $M^{+?}$), 91 (100). HRMS: calcd for $C_7H_5O_3Br$ 215.9422. Found 215.9422. ^{1}H NMR ($CDCl_3$): δ 6.90 (s, 1H, H-6), 6.74 (s, 1H, H-3), 5.89 (s, 2H, O–CH_2–O).

3.2.2. 5-Bromosesamol MEM-ether (2)

To a solution of **1** (1.53 g, 5.0 mmol) in 60 ml of THF was added at 0 °C NaH (370 mg, 10 mmol, 65% in mineral oil). After stirring for 10 min MEM-chloride (1.2 ml, 10.2 mmol) was added. The reaction mixture was left for 15 min at 0 °C and for 45 min at room temperature. Saturated NH_4Cl-solution was added and three times extracted with *t*-butyl methyl ether. The combined organic phases were washed with saturated NaCl-solution, filtered through silica gel/Na_2SO_4 and the solvent was evaporated under vacuum. The crude product was purified by flash chromatography on silica gel (hexane/EtOAc 6:1) to yield **2** (1.15 g, 75%) as light brownish oil. R_f: 0.68 (hexane/EtOAc 4:1). MS *m/z* (%): 306 (8, $M^{+\cdot}$), 304 (8, $M^{+\cdot}$), 218 (13), 216 (13), 150 (13), 89 (86), 59 (100). HRMS: calcd for $C_{11}H_{13}O_5Br$ 303.9946. Found 303.9946. ^{1}H NMR ($CDCl_3$): δ 6.91 (s, 1H, H-6), 6.78 (s, 1H, H-3), 5.88 (s, 2H, Ar–O–CH_2–O–Ar), 5.16 (s, 2H, O–CH_2–O), 3.87 (m, 2H, O–CH_2–CH_2), 3.55 (m, 2H, CH_2–CH_2–O), 3.33 (s, 3H, CH_3O).

3.2.3. 6-(11′-Hydroxy-7′-drimen-11′-yl)-3,4-methylendioxyphenol MEM-ether ((±)-4a,b)

To a solution of 5-bromosesamol MEM-ether (**2**, 1.22 g, 4.0 mmol) in 40 ml of THF was added at −100 °C *n*-BuLi (3 ml, 4.8 mmol, 1.6 M in cyclohexane). After 5 min a solution of drim-7-en-11-al ((±)-**3**, 386 mg, 1.75 mmol) in 5 ml of THF was added and the reaction mixture was warmed up to room temperature during 2 h. For workup saturated NH_4Cl-solution was added and the reaction mixture was extracted 3 times with *t*-butyl methyl ether. The combined organic phases were filtered through silica gel/Na_2SO_4 and the solvent was removed under vacuum. Flash chromatography on silica gel (hexane/EtOAc 9:1) gave the diastereomeric mixture of benzyl alcohols (±)-**4a,b** which was not further purified and characterized.

3.2.4. 6-(7′-Drimen-11′-yliden)-3,4-methylendioxy-2,4-cyclohexadienone ((±)-5)

To the mixture of diastereomeric benzyl alcohols (±)-**4a,b** in 50 ml of THF/H_2O 10:1 was added *p*-toluene sulfonic acid (100 mg). After heating at 40 °C for 30 min saturated Na_2CO_3-solution was added. The reaction mixture was extracted three times with *t*-butyl methyl ether, the combined organic phases were filtered through silica gel/Na_2SO_4 and the solvent evaporated under vacuum. Further purification was carried out by MPLC (LiChrospher RP-8, 15 μm; MeCN/H_2O 85:15) to yield (±)-**5** (411 mg, 69% over 2 steps) as yellow crystals. R_f: 0.68 (hexane/EtOAc 4:1). Mp 150–152 °C (MeCN/H_2O). IR (cm^{-1}): 2928, 1648, 1612, 1430, 1358, 890. MS *m/z* (%): 340 (40, $M^{+\cdot}$), 325 (16), 217 (100), 201 (43), 189 (47), 151 (24), 115 (8), 105 (8), 91 (7), 55 (20), 41 (28).

Table 4
^{1}H and ^{13}C NMR data of compounds (±)-**5**–(±)-**8** in $CDCl_3$, coupling constants *J* in Hertz

Pos.	(±)-**5**		(±)-**6**		(±)-**7**		(±)-**8**	
	δC	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
1	40.9	1.19 1.36	39.6	1.07 1.88	39.6	1.07 1.88	39.7	1.07 1.89
2	18.6	1.32 1.38	18.9	1.42 1.54	19.0	1.44 1.53	18.9	1.48 1.58
3	42.3	1.03 1.20	42.2	1.16 1.40	42.3	1.18 1.40	42.2	1.18 1.43
4	33.2	—	33.0		33.1		33.0	
5	49.8	1.25	50.3	1.28	50.3	1.25	50.2	1.24
6	23.7	1.85 2.06	23.7	1.88 1.93	23.8	1.88 1.93	23.7	1.87 1.92
7	123.0	5.55 br s	122.4	5.36 br s	122.0	5.38 br s	123.1	5.36 br s
8	131.7	—	135.1		135.9		134.9	
9	54.4	2.92 d (12.9)	54.4	2.25	54.6	2.25	54.9	2.21
10	38.4	—	36.9		36.9		36.8	
11	149.5	7.07 d (12.9)	26.1	2.51 d (6.1)	26.1	2.48 dd (15.3, 2.5) 2.64 dd (15.3, 9.2)	25.5	2.53 dd (15.3, 2.5) 2.63 dd (15.3, 9.2)
12	22.5	1.42 s	22.2	1.47 s	22.2	1.43 s	22.2	1.41 s
13	33.3	0.84 s	33.3	0.86 s	33.3	0.86 s	33.2	0.85 s
14	21.8	0.86 s	22.0	0.89 s	22.0	0.89 s	21.9	0.87 s
15	15.0	0.94 s	13.7	0.86 s	13.9	0.86 s	14.0	0.88 s
1′	133.5	—	121.6		124.6		129.8	
2′	184.2	—	147.2		151.8		153.3	
3′	101.7	5.87 s	98.1	6.32 s	94.6	6.47 s	114.3	
4′	162.0	—	145.4		145.4		146.1	
5′	145.2	—	141.4		140.9		144.8	
6′	98.0	6.36 s	109.0	6.68 s	109.3	6.73 s	114.2	6.95 s
OCH_2O	101.7	5.84 br s	100.8	5.85 br s	100.8	5.86 br s	102.8	6.06 s
OMe					56.3	3.74 s	63.6	3.77 s
CHO							188.5	10.24 s

Trivial numbering, see Scheme 2.

HRMS: calcd for $C_{22}H_{28}O_3$ 340.2038. Found 340.2040. ^{1}H and ^{13}C NMR: Table 4.

3.2.5. 6-(7′-Drimen-11′-yl)-3,4-methylendioxyphenol ((±)-6)

To a solution of (±)-**5** (240 mg, 0.70 mmol) in 25 ml of EtOH $NaBH_4$ (60 mg, 1.59 mmol) was added and the suspension was stirred for 30 min at room temperature. After addition of 2 N HCl (10 ml) the reaction mixture was three times extracted with *t*-butyl methyl ether. The combined organic phases were filtered through silica gel/Na_2SO_4 and the solvent was removed under vacuum. The crude product was purified by flash chromatography on silica gel (hexane/EtOAc 7:1) to give (±)-**6** (218 mg, 91%) as colourless oil. R_f: 0.39 (hexane/EtOAc 4:1). IR (cm^{-1}): 3390, 2925, 1611, 1500, 1448, 1180, 1110, 1075, 910, 730. MS *m/z* (%): 342 (9, $M^{+\cdot}$), 189 (8), 151 (100), 109 (34), 107 (16), 105 (15), 95 (19), 91 (19), 69 (22), 55 (24), 41 (30). HRMS: calcd for $C_{22}H_{30}O_3$ 342.2195. Found 342.2195. ^{1}H and ^{13}C NMR: Table 4.

3.2.6. 6-(7′-Drimen-11′-yl)-3,4-methylendioxyanisol ((±)-7)

Compound (±)-**6** (625 mg, 1.82 mmol) was dissolved in 20 ml of methanolic *n*-Bu_4NOH-solution and the solvent was removed under vacuum. To the residue in 12 ml of THF $(CH_3O)_2SO_2$ (1.2 ml, 13.2 mmol) was dropped and the reaction mixture was stirred for 30 min at room temperature. For workup NH_3-solution (10 ml, 25%) was added and the stirring continued for 15 min. Three times extraction with *t*-butyl methyl ether gave the organic phases which were combined, filtered through silica gel/Na_2SO_4 and evaporated in vacuum. Purification with flash chromatography on silica gel (hexane/EtOAc 12:1) yielded (±)-**7** (623 mg, 96%) as colourless oil. R_f: 0.74 (hexane/EtOAc 4:1). IR (cm^{-1}): 2920, 1615, 1490, 1455, 1165, 1125, 1070, 925. MS *m/z* (%): 356 (3, $M^{+?}$), 232 (2), 217 (3), 201 (2), 165 (100), 135 (21), 91 (24), 77 (42), 55 (36), 41 (63). HRMS: calcd for $C_{23}H_{32}O_3$ 356.2351. Found 356.2353. ^{1}H and ^{13}C NMR: Table 4.

3.2.7. 5-(7′-Drimen-11′-yl)-2,3-methylendioxy-6-methoxybenzaldehyd ((±)-8)

Compound (±)-**7** (225 mg, 0.63 mmol) was dissolved in 30 ml of THF and cooled to 0 °C. After addition of *N*,*N*,*N*′,*N*′-tetremethylethylenediamine (TMEDA, 0.15 ml, 0.95 mmol) and *n*-BuLi (0.6 ml, 0.95 mmol) the reaction mixture was stirred for 30 min at 0 °C. DMF (0.5 ml, 6.31 mmol) was dropped to the reaction mixture and the stirring was continued for 16 h at room temperature. For workup saturated NH_4Cl-solution was added and the mixture extracted three times with *t*-butyl methyl ether. The combined organic phases were filtered through silica gel/Na_2SO_4 and the solvent was removed under vacuum. After flash chromatography on silica gel (hexane/EtOAc 12:1) (±)-**8** (189 mg, 78%) was obtained as colourless oil. R_f: 0.66 (hexane/EtOAc 6:1). IR (cm^{-1}): 2925, 1620, 1540, 1495, 1450, 1150, 1120, 1075, 920. MS *m/z* (%): 384 (11, $M^{+\cdot}$), 193 (100), 121 (7), 109 (20), 69 (9), 41 (10). HRMS: calcd for $C_{24}H_{32}O_4$ 384.2301. Found 384.2301. ^{1}H and ^{13}C NMR: Table 4.

References and notes

1. Sullivan, B. W.; Faulkner, D. J.; Matsumoto, G. K.; Cun-heng, H.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 4568.
2. Mukku, V. J. R. V.; Edrada, R. A.; Schmitz, F. J.; Shanks, M. C.; Chaudhuri, B.; Fabbro, D. *J. Nat. Prod.* **2003**, *66*, 686.
3. Bernet, A.; Schröder, J.; Seifert, K. *Helv. Chim. Acta* **2003**, *86*, 2009.
4. Bernet, A.; Seifert, K. *Helv. Chim. Acta* **2006**, *89*, 784.
5. A. Bernet, Dissertation, University of Bayreuth, 2006.
6. Laube, T.; Schröder, J.; Stehle, R.; Seifert, K. *Tetrahedron* **2002**, *58*, 4299.
7. Fenical, W.; Sims, J. J.; Squatrito, D.; Wing, R. M.; Radlick, P. *J. Org. Chem.* **1973**, *38*, 2383.
8. Dahse, H.-M.; Schlegel, B.; Gräfe, U. *Pharmazie* **2001**, *56*, 489.
9. Capon, R. J.; Groves, D. R.; Urban, S.; Watson, R. G. *Aust. J. Chem.* **1993**, *46*, 1245.
10. Kazlauskas, R.; Murphy, P. T.; Warren, R. G.; Wells, R. J.; Blount, J. F. *Aust. J. Chem.* **1978**, *31*, 2685.
11. Talpir, R.; Rudi, A.; Kashman, Y.; Loya, Y.; Hizi, A. *Tetrahedron* **1994**, *50*, 4179.
12. Laube, T.; Beil, W.; Seifert, K. *Tetrahedron* **2005**, *61*, 1141.
13. Coval, S. J.; Conover, M. A.; Mierzwa, R.; King, A.; Puar, M. S.; Phife, D. W.; Pai, J.-K.; Burrier, R. E.; Ahn, H.-S.; Boykow, G. C.; Patel, M.; Pomponi, S. A. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 605.
14. Chackalamannil, S.; Xia, Y.; Wang, Y.; Tsai, H.; Czarniecki, M.; Wang, S.; Clemmons, A.; Ahn, H.-S.; Boykow, G. C. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2005.
15. Penning, T. M. *J. Pharm. Sci.* **1985**, *74*, 651.
16. Mutschler, E. *Lehrbuch der Pharmakologie und Toxikologie*; Wissenschaftliche Verlagsgesellschaft: Stuttgart, 1991; pp 176–183.
17. Hurst, N. P. *Ann. Rheum. Dis.* **1987**, *46*, 265.
18. Babior, B. M. *J. Clin. Invest.* **1984**, *73*, 599.
19. Morel, F.; Doussiere, J.; Vignais, P. V. *Eur. J. Biochem.* **1991**, *201*, 523.
20. Yu, P.-W.; Czuprynski, C. *J. Veterinary Immunol. Immunopathol.* **1996**, *50*, 29.