Pergamon

Tetrahedron 58 (2002) 4299–4309

TETRAHEDRON

Total synthesis of yahazunol, zonarone and isozonarone

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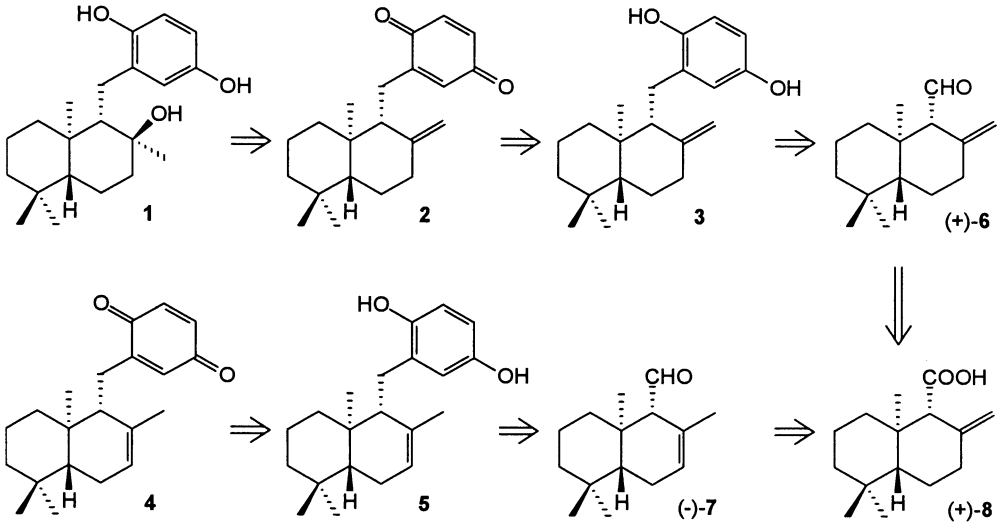
Received 14 January 2002; revised 15 March 2002; accepted 26 March 2002

Abstract—The synthesis of the marine natural products zonarone and isozonarone was achieved via (+)-albicanic acid, a sesquiterpene of the drimane type. Coupling of the appropiate drimane-synthon with lithiated hydroquinone ethers led to sesquiterpene arenes, which were further modified to the target molecules. Stereoselective epoxidation followed by regioselective opening of the oxirane ring yielded yahazunol.

1. Introduction

The five marine natural products yahazunol (**1**), zonarone (**2**), zonarol (**3**), isozonarone (**4**) and isozonarol (**5**) have been synthesised starting from (+)-albicanic acid ((+)-**8**) (Scheme 1). Due to their broad spectrum of biological activities[1–7] sesquiterpene arenes and sesquiterpene quinones[8] draw attention as synthethic targets to realize a thoroughly examination of their pharmacological properties. In this way the aim of this synthesis is a convenient synthetic pathway to sesquiterpene arenes possessing a drimane skeleton.

Yahazunol (**1**),[9] zonarone (**2**) and zonarol (**3**) have been obtained from the East Pacific brown algae *Dictyopteris undulata* Okamura.[10] Isozonarone (**4**) and isozonarol (**5**) have been isolated from the same species collected in the Gulf of California.[10] The key step of the synthesis (Scheme 2) was the coupling of the sesquiterpene part with the lithiated arene unit. The necessary aldehydes (+)-albicanal ((+)-**6**) and (−)-drim-7-en-11-al ((−)-**7**) were obtained from (+)-albicanic acid ((+)-**8**). This chiral synthon was prepared starting from β-ionone via a known route.[11–13] Several steps of this procedure could be improved.



Scheme 1. Retrosynthesis of the marine natural compounds **1**–**5**.

Keywords: terpenes; phenols; quinones; epoxidation.

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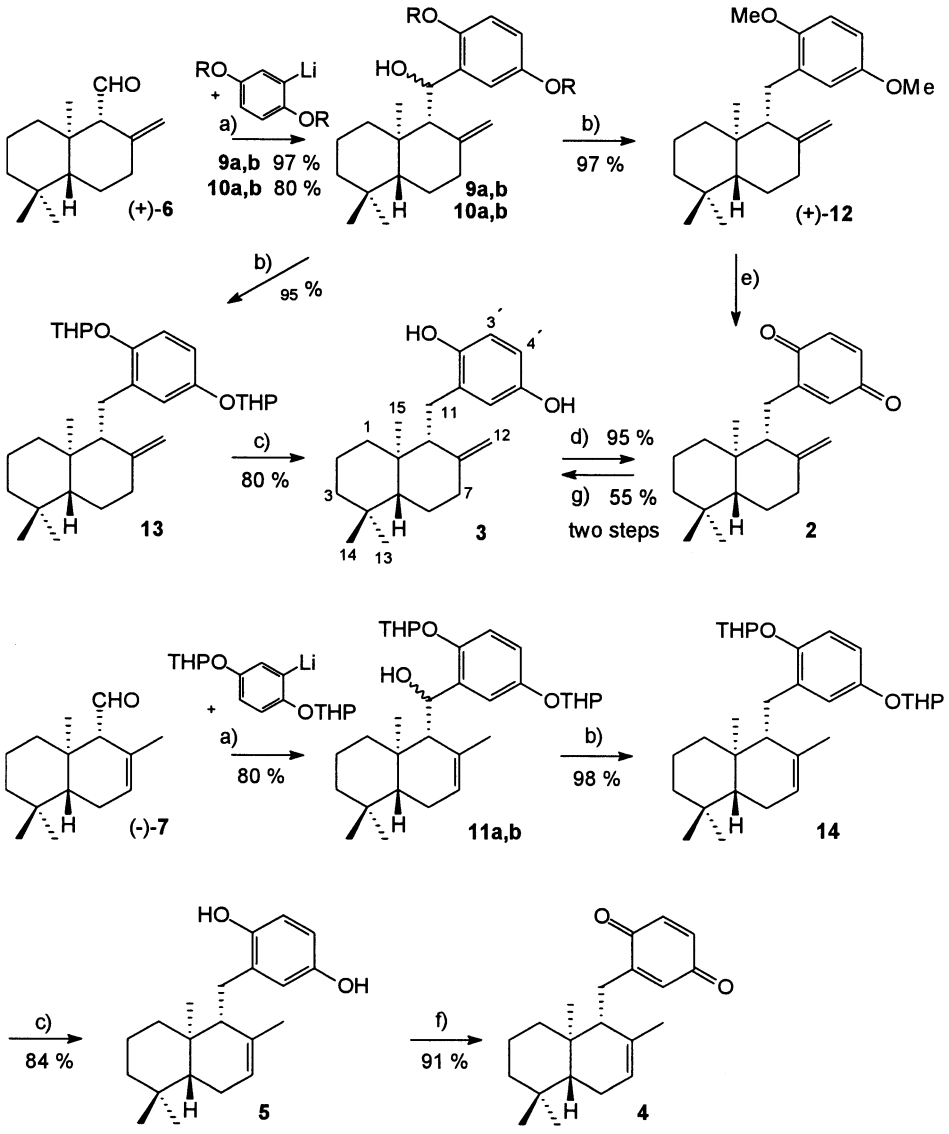


Scheme 2. (a) With (+)-**6**: R=Me: Et_2O, 0°C (**9a**, **b**); R=THP: THF, 0°C, (**10a**, **b**); with (−)-**7**: R=THP: THF, 20°C (**11a**, **b**); (b) 5.3 equiv. Li, liqu. NH_3, THF, NH_4Cl, −78°C; (c) oxalic acid, H_2O, MeOH, ethyl acetate; (d) 3.0 equiv. CAN, MeCN/H_2O (1:1); (e) 12.3 equiv. CAN, DMF/MeCN/H_2O (1:1:1), pyridine-2,6-dicarboxylic acid *N*-oxide; (f) 3.5 equiv. CAN, DMF/MeCN/H_2O (1:1:1); (g) THF/H_2O (3:2), $Na_2S_2O_4$, reflux.

2. Results and discussion

2.1. Synthesis of zonarol, zonarone, isozonarol and isozonarone[14]

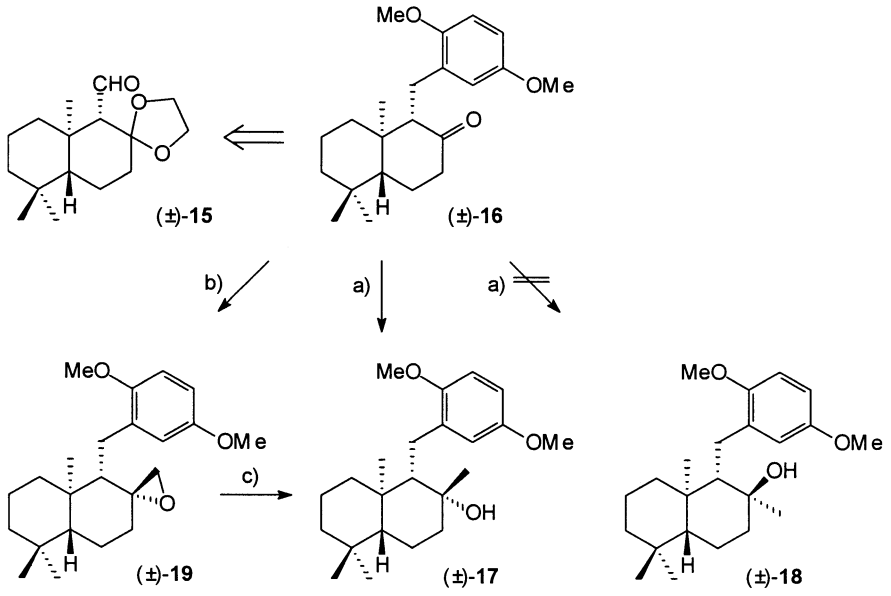
(+)-Albicanal ((+)-**6**) was coupled with 2-lithiohydroquinone dimethyl ether or 2-lithiohydroquinone di-THP-ether to obtain in case of (+)-**6** the benzylalcohols **9a**, **b**, **10a**, **b** or in case of (−)-**7** **11a**, **b** as a mixture of diastereomers (Scheme 2).

The benzylic desoxygenation of these compounds was achieved by reduction with lithium in liquid NH_3/THF followed by treatment with excessive NH_4Cl.[15] The zonarol di-THP-ether (**13**) (mixture of diastereomers) was deprotected following a procedure of Prelog et al.,[16] which offered mild conditions. Using stronger acids led to mixtures or decomposition. To avoid the annoying mixtures of diastereomers, obtained by using the THP moiety as protecting group, we also worked with the methyl group. The deprotection of (±)-zonarol dimethyl ether ((±)-**12**) was a challenge: Acidic conditions or Lewis acids (BBr_3, $BF_3{\cdot}Et_2O$, etc.) led to complex mixtures. Finally, we ended up with an one-pot-two-steps-procedure. Oxidative demethylation of (±)-**12** with CAN/pyridine-2,6-dicarboxylic acid *N*-oxide[17] yielded (±)-zonarone ((±)-**2**), which was reduced with sodium dithionite to (±)-zonarol ((±)-**3**) to give after purification a total yield of 55% over two steps. Zonarol (**3**) can easily be oxidised to the corresponding quinone zonarone (**2**) using CAN in H_2O/MeCN.

Starting with (−)-drim-7-en-11-al (−)-**7** and using the same procedures we were able to obtain isozonarol (**5**) and isozonarone (**4**) via **14**.

2.2. Synthesis of yahazunol

We tried to synthesise (±)-yahazunol ((±)-**1**) from (±)-**16**,

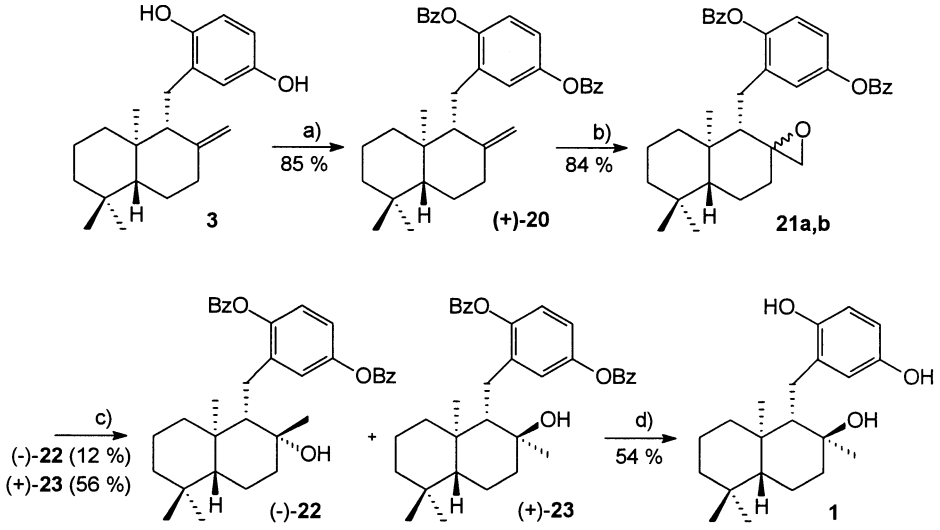


Scheme 3. Compound (±)-**16** could not be transformed into (±)-yahazunol dimethyl ether ((±)-**18**). (a) Metal organyls); (b) $Me_2S{=}CH_2$, THF/DMSO, −20°C, 30 min; (c) $LiAlH_4$, Et_2O, reflux.

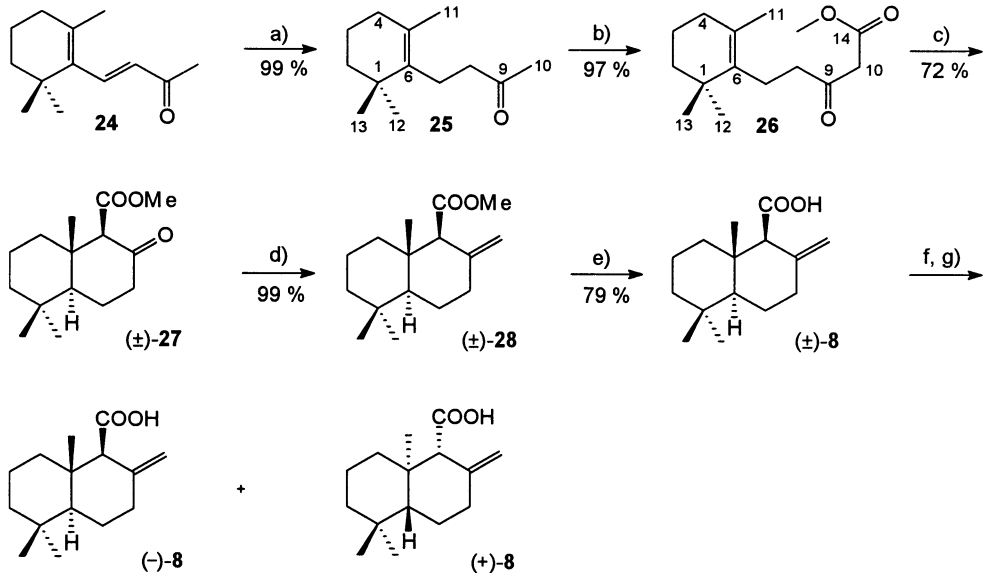
which could be obtained from the synthon (±)-**15** (Scheme 3). Due to the steric hindrance of the axial angular methyl group 15 in position 10 of the 12-nordrimane skeleton of (±)-**16**, the attack of metal organyls (cerium-,[18] samarium-,[19] titanium-[20] or ytterbium[21] organyls) gave compound (±)-**17**, which possesses an axial instead of the desired equatorial hydroxyl group in position 8 as (±)-yahazunol dimethyl ether ((±)-**18**).

The reaction of (±)-**16** with a sulfur ylide seemed to be a promising alternative: This reaction is usually taken to establish the oxygen of the carbonyl function in the equatorial position during the formation of the oxirane ring, because the ylide is attacking axial.[22] In opposite to the expected result we got the undesired product (±)-**19**. The stereochemistry of (±)-**19** was proved by opening the epoxide with $LiAlH_4$ in diethyl ether, which led exclusively to (±)-**17**. Due to these results, we started from zonarol (**3**) (Scheme 4). In the first step of the reaction sequence, the phenolic hydroxyl groups were benzylated.

The benzyl ether (+)-**20** was treated with MCPBA in CH_2Cl_2[23,24] to obtain the epoxides **21a**, **b** as a mixture of diastereomers. The ratio of **21a** (desired isomer) to **21b** was 82:18 (determined by ^1H NMR spectroscopy). The oxirane system in **21a**, **b** was opened with $LiAlH_4$ in refluxing diethyl ether to give (−)-**22** in 12% yield and (+)-**23** as major product in 56% yield. Compound (+)-**23** was debenzylated with H_2 and Pd/C in EtOH to the desired yahazunol (**1**) in 54% yield. A comparison of NMR data and optical rotations of synthetic **1** with natural **1**[9] showed good agreement. Using the same reaction sequence we synthesised in analogy to (+)-**23** yahazunol dimethyl ether (±)-**18**. In this case oxidative demethylation with CAN/pyridine-2,6-dicarboxylic acid *N*-oxide followed by reduction with sodium dithionite led to decomposition.



Scheme 4. Synthesis of yahazunol (**1**). (a) BzBr, K_2CO_3, acetone; (b) MCPBA, CH_2Cl_2; (c) $LiAlH_4$, Et_2O, reflux; (d) H_2, Pd/C, EtOH.



Scheme 5. (a) (i) $EtMe_2SiH$, $(Ph_3P)_3RhCl$ (0.5%), 50–55°C, (ii) MeOH, K_2CO_3; (b) dimethyl carbonate, NaH, toluene, 100°C; (c) 1.62 equiv. $SnCl_4$, CH_2Cl_2; (d) methylenetriphenylphosphorane, toluene; (e) NaSEt, DMF, 150°C; (f) and (g) separation of the racemate using (+)- and (−)-α-phenylethylamine as chiral auxiliary.[13]

We also tried an alternative strategy using the acetyl instead of the benzyl group as protecting group. We obtained (±)-zonarol diacetate in good yield. Further on, we got the epoxide but by opening the oxirane system to (±)-yahazunol diacetate with $LiAlH_4$ we were not able to reproduce the reaction sequence.

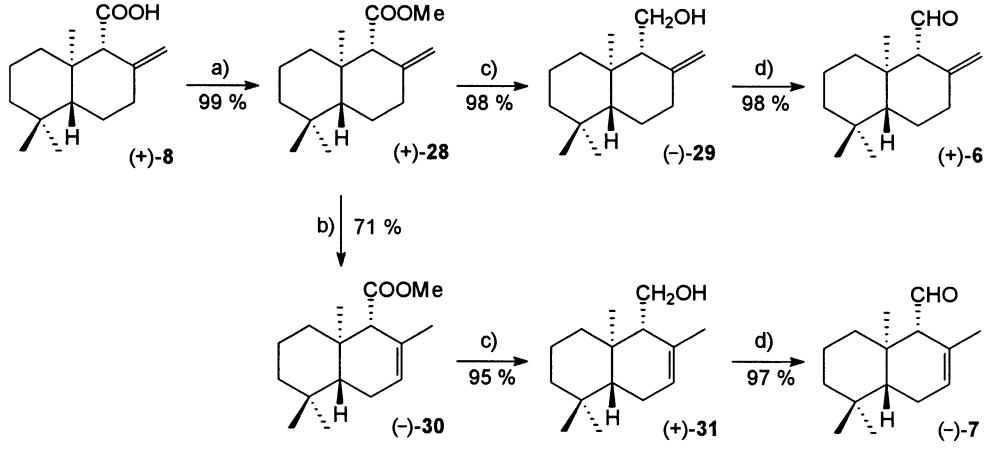
2.3. Preparation of (+)-albicanal and (−)-drim-7-en-11-al

The synthesis of described sesquiterpenes **1**–**5** needs the preparation of the chiral synthon (+)-albicanic acid ((+)-**8**) (Scheme 5).

This route was developed by Herlem et al.,[11] hence we only want to discuss some improvements. Herlem et al.[11] used Bu_3SnH for the regioselective hydrogenation of β-ionone (**24**) to dihydro-β-ionone. According to a procedure of Ojima and Kogure[25] we used Et_3SiH or $EtMe_2SiH$ and Wilkinson catalyst followed by $MeOH/K_2CO_3$ (solvolysis of the silyl enol ether) to obtain pure **25** in 99% yield. The yield of the cyclization of the β-ketoester **26** to (±)-**27** was 72%. (±)-8-Oxo-12-nordriman-11-acid methyl ester ((±)-**27**) was converted to (±)-**28** via a Wittig reaction.[12] The solvolysis of the obtained (±)-albicanic acid methyl ester ((±)-**28**) seems to be trivial but it is amazingly difficult. As reported before,[12] (±)-**28** is inert to normal saponification (KOH/MeOH, *t*-BuOK/*t*-BuOH, etc.). Using the described DMF/LiI-method[13] we obtained a maximum yield of 55% of the desired albicanic acid (±)-**8** after one recrystallization. Using NaSEt/DMF the reaction time shortened significantly from 36 to 1 h and yielded 79% of (±)-**8** after purification. For the cleavage of racemic (±)-**8** into its enantiomers we refer to the procedure described by Ragoussis et al.[13]

Now the chiral building block (+)-**8** had to be transformed into (+)-albicanal ((+)-**6**) and (−)-drim-7-en-11-al ((−)-**7**) (Scheme 6).

Quantitative esterification of (+)-**8** was carried out by transferring the free acid into its tetra-ethylammonium salt



Scheme 6. (a) (i) $[Et_4N]^+OH^-$, MeOH, ii) dimethyl sulfate, THF; (b) $Pd/CaCO_3$ (5% Pd), Ph_3P (2%), hydrogen atmosphere, room temperature, ethyl acetate; (c) DIBAH, CH_2Cl_2, 0°C; (d) PCC, CH_2Cl_2, room temperature.

followed by treatment with excessive dimethyl sulfate (CAUTION: Cancer hazard!). The obtained (+)-albicanic acid methyl ester ((+)-**28**) could be isomerised into drim-7-en-11-acid methyl ester ((−)-**30**) using $Pd/CaCO_3$ and Ph_3P under a hydrogen atmosphere. The esters (+)-**28** and (−)-**30** were reduced to the corresponding alcohols (−)-albicanol ((−)-**29**) and (+)-drim-7-en-11-ol ((+)-**31**) using diisobutylaluminium hydride (DIBAH) in CH_2Cl_2. Swern oxidation[26] of (−)-**29** did not work well. Finally, we obtained the desired (+)-albicanal ((+)-**6**) by oxidation of (−)-**29** with pyridinium chlorochromate (PCC) in CH_2Cl_2 in 98% yield. Similary the oxidation of (+)-**31** gave (−)-drim-7-en-11-al (−)-**7**) with 97% yield.

3. Experimental

3.1. General

All solvents were dried and purified prior to use. THF and diethyl ether were dried by distillation from Na/K under Ar. Flash chromatography: Merck silica gel 60, 0.040–0.063 mm (230–400 mesh).

IR: Perkin–Elmer 1420 Ratio Recording Spectrometer; solvent $CHCl_3$. Optical rotation values: JASCO Polarimeter P-1020 (589 nm). MS: Finnigan MAT 8500 and Finnigan MAT SS 300; 70 eV. NMR: Bruker Avance 360 and Bruker DRX 500, $CDCl_3/CHCl_3$, acetone-d_6/acetone, C_6D_6/C_6H_6 as internal standard. MPLC: Büchi B688 pump and Büchi B687 gradient former. For TLC runs, precoated silica-gel foils 60 F_{254} (5×10 cm^2) from Merck were used. Spots were visualised by irradiation under an UV lamp or by treatment with phosphomolybdic acid test spray.

3.2. Preparation, physical and spectroscopic data of the compounds

3.2.1. Yahazunol (1). To yahazunol dibenzyl ether ((+)-**23**) (150 mg, 0.29 mmol) in 50 ml of EtOH 5 mg of Pd/C (10%) was added. The solution was stirred for 2 h under H_2-atmosphere. After filtration through RP-material and removement of the solvent the residue was purified using MPLC (LiChrospher® 100 RP-18 (12 μm); MeCN/H_2O 3:1, 20 bar, 30 ml/min) to get **1** (52 mg, 0.16 mmol, 54%). Colourless crystals ($CHCl_3$); mp 126–128°C, $[\alpha]_D^{24}=-11$ (*c* 0.1, $CHCl_3$). Ref. 9: $[\alpha]_D^{27}=-12$ (*c* 0.1, $CHCl_3$). IR (cm^{-1}): 3560 (w), 3022 (m), 2923 (w), 1710 (m), 1500 (w), 1364 (w), 1216 (s). MS *m/z* (%): 332 (2, $M^{+\cdot}$), 314 (70), 191 (100), 178 (16), 161 (50), 123 (83), 95 (39) 69 (17). HRMS: Calcd for $C_{21}H_{32}O_3$ 332.2351. Found 332.2351. ^{1}H NMR (360 MHz, acetone-d_6): δ 6.64 (1H, d, *J*=2.7 Hz, H-6′), 6.53 (1H, d, *J*=8.5 Hz, H-3′), 6.49 (1H, dd, *J*=8.5, 2.7 Hz, H-4′), 2.85 (1H, dd, *J*=20.7, 2.7 Hz, H-11), 2.40 (1H, dd, *J*=20.7, 8.5 Hz, H-11), 1.92 (1H, ddd, *J*=16.9, 4.0 Hz, H-7), 1.84 (1H, m, H-1), 1.66 (1H, m, H-6), 1.62 (1H, m, H-2), 1.57 (2H, m, H-7, H-9), 1.34 (2H, m, H-2, H-6), 1.33 (1H, m, H-3), 1.30 (3H, s, H-12), 1.11 (1H, m, H-3), 0.97 (3H, s, H-15), 0.94 (1H, d, *J*=3.1 Hz, H-5), 0.86 (3H, s, H-13), 0.83 (3H, s, H-14), 0.72 (1H, ddd, *J*=4.4, 17.9 Hz, H-1). ^{13}C NMR (90 MHz, acetone-d_6): δ 150.4 (C-5′), 149.7 (C-2′), 131.2 (C-1′), 118.9 (C-6′), 117.4 (C-3′), 114.3 (C-4′), 75.1 (C-8), 62.4 (C-9), 57.0 (C-5), 44.6 (C-7), 42.6 (C-3), 41.4 (C-1), 40.6 (C-10), 33.9 (C-13), 33.8 (C-4), 28.0 (C-11), 24.6 (C-12), 21.9 (C-14), 21.2 (C-6), 19.1 (C-2), 15.9 (C-15).

3.2.2. Zonarone (2). To a well stirred solution of **3** (50 mg, 0.16 mmol) in 0.4 ml of MeCN was dropwise and slowly added 0.4 ml of 1.2 M CAN ($Ce(NH_4)_2(NO_3)_6$) (0.48 mmol) in H_2O. After stirring for 30 min the mixture was diluted with 10 ml of H_2O. The yellow precipitate was filtered off and washed with H_2O to give **2** (48 mg, 0.15 mmol, 95%). Yellow crystals (MeOH); mp 133–134°C, $[\alpha]_D^{23}=+65$ (*c* 0.48, MeOH). Ref. 27: $[\alpha]_D=+59$ (MeOH). IR (cm^{-1}): 2940 (s), 2865 (m), 2843 (m), 1650 (s), 1597 (s), 1459 (m), 1327 (m), 1258 (s), 1210 (s), 1154 (m), 1099 (m), 1044 (s). MS *m/z* (%): 312 (58, $M^{+\cdot}$), 297 (14), 282 (5), 256 (12), 216 (17), 201 (19), 189 (100), 175 (39), 161 (36), 147 (26), 137 (67), 124 (66), 119 (27), 95 (40), 81 (40). HRMS: Calcd for $C_{21}H_{28}O_2$ 312.2089. Found 312.2089. ^{1}H NMR ($CDCl_3$): δ 6.71 (1H, d, *J*=10.0 Hz, H-3′), 6.64 (1H, dd, *J*=10.0, 2.4 Hz, H-4′), 6.43 (1H, d, *J*=2.4 Hz, H-6′), 4.74 (1H, s, H-12), 4.28 (1H, s, H-12), 2.55 (2H, m, H-11), 2.33 (1H, m, H-7), 1.97 (1H, m, H-9), 1.73 (1H, m, H-1), 1.71 (1H, m, H-7), 1.70 (1H, m, H-6), 1.55 (1H, m, H-2), 1.48 (1H, m, H-2), 1.37 (1H, m, H-3), 1.31 (1H, m, H-6), 1.19 (1H, m, H-3), 1.10 (1H, m, H-5), 1.06 (1H, m, H-1), 0.85 (3H, s, H-13), 0.78 (3H, s, H-14), 0.74 (3H, s, H-15). ^{13}C NMR ($CDCl_3$): δ 187.8 (C-2′, C-5′), 149.3 (C-1′), 147.1 (C-8), 136.8 (C-3′), 136.0 (C-4′), 132.8 (C-6′), 108.0 (C-12), 55.4 (C-5), 53.9 (C-9), 41.9 (C-3), 39.7 (C-10), 39.1 (C-1), 37.8 (C-7), 33.6 (C-4, C-13), 24.1 (C-6), 23.0 (C-11), 21.1 (C-14), 19.3 (C-2), 14.5 (C-15).

3.2.3. Zonarol (3) via deprotection of 13. Zonarol di-THP-ether (**13**) (278 mg, 0.57 mmol) was dissolved in 200 ml of MeOH/ethyl acetate (3:2) and mixed with 60 ml of 2% oxalic acid. The mixture was stirred until the deprotection was complete (checked by TLC, 3 h). For workup 50 ml of saturated NaCl-solution and 50 ml of H_2O were added. The organic layer was separated and the aqueous layer extracted three times with 50 ml of *t*-butyl methyl ether. The combined organic layers were washed with brine, dried with Na_2SO_4 and filtered through silica gel. After evaporation of the solvent the residue was purified using the LOBAR®-system (column type A, LiChroprep® RP-18 (40–63 μm); MeOH/H_2O 75:25) to obtain **3** (145 mg, 0.46 mmol, 80%). Colourless crystals (MeCN); mp 154°C (sub.), $[\alpha]_D^{23}=+17$ (*c* 1.7, $CHCl_3$). Ref. 9: $[\alpha]_D=+18$ ($CHCl_3$). IR (cm^{-1}): 3590 (m), 3350 (w), 2930 (s), 2860 (m), 2840 (m), 1640 (w), 1595 (w), 1495 (s), 1450 (m), 1435 (m), 1385 (w), 1360 (m), 1315 (w), 1285 (w), 1255 (w), 1165 (s), 1140 (m), 1070 (w). MS *m/z* (%): 314 (68, $M^{+\cdot}$), 299 (8), 229 (6), 217 (6), 201 (6), 191 (100), 178 (23), 163 (24), 161 (28), 149 (17), 137 (20), 109 (19), 95 (29), 81 (17). HRMS: Calcd for $C_{21}H_{30}O_2$ 314.2246. Found 314.2246. ^{1}H NMR (C_6D_6): δ 6.63 (1H, d, *J*=2.5 Hz, H-6′), 6.31 (1H, dd, *J*=8.5, 2.5 Hz, H-4′), 6.24 (1H, d, *J*=8.5 Hz, H-3′), 4.87 (2H, s, H-12), 2.81 (1H, dd, *J*=15.5, 10.2 Hz, H-11), 2.73 (1H, dd, *J*=15.5, 1.9 Hz, H-11), 2.29 (1H, m, H-7), 2.17 (1H, d, *J*=10.2 Hz, H-9), 1.91 (1H, dd, *J*=12.8, 4.6 Hz, H-7), 1.74 (1H, d, *J*=12.6 Hz, H-1), 1.57 (1H, m, H-6), 1.52 (1H, m, H-2), 1.40 (1H, m, H-2), 1.34 (1H, d, *J*=13.2 Hz, H-3), 1.26 (1H, dd, *J*=12.8, 4.1 Hz, H-6), 1.14 (1H, m, H-3), 1.04 (1H, m, H-1), 1.02

(1H, m, H-5), 0.84 (3H, s, H-13), 0.80 (3H, s, H-15), 0.78 (3H, s, H-14). ^{13}C NMR (C_6D_6): δ 150.0 (C-5′), 148.6 (C-8), 147.8 (C-2′), 130.1 (C-1′), 116.9 (C-6′), 115.8 (C-3′), 112.7 (C-4′), 108.2 (C-12), 56.3 (C-9), 55.6 (C-5), 42.4 (C-3), 40.2 (C-10), 39.2 (C-1), 38.5 (C-7), 33.7 (C-4, C-13), 24.6 (C-6), 23.9 (C-11), 21.7 (C-14), 19.8 (C-2), 14.7 (C-15).

3.2.4. (±)-Zonarol ((±)-3) via (±)-12 and (±)-2. (±)-Zonarol dimethyl ether ((±)-**12**) (150 mg, 0.44 mmol) was dissolved in 42 ml of MeCN/DMF (1:1). To this solution 500 mg of pyridine-2,6-dicarboxylic acid *N*-oxide, 16.5 ml of H_2O, and 4.5 ml of an aqueous 1.2 M CAN-solution (5.4 mmol) were added under stirring. After 8 min 100 ml of H_2O was added and the solution extracted three times with *t*-butyl methyl ether. The solvent of the combined organic phases was removed and the residual oil dissolved in 50 ml of THF/H_2O (3:2), 762 mg $Na_2S_2O_4$ was added and the mixture heated under reflux for 30 min. The mixture was extracted three times with ethyl acetate. The combined organic layers were washed with saturated NaCl-solution and dried with Na_2SO_4. After filtration through silica gel and removing the solvent the residue was purified using MPLC (LiChrospher® Si-60 (15 μm); hexane/ethyl acetate 6:1, 20 bar, 30 ml/min) to give (±)-**3** (76 mg, 0.24 mmol, 55%).

3.2.5. Isozonarone (4). Isozonarone (**4**) was prepared as **2** (91%), but 3.5 equiv. CAN, DMF/MeCN/H_2O (1:1:1) were used. Yellow crystals (MeOH); mp 130–132°C; $[\alpha]_D^{21}$=+89 (*c* 0.1, MeOH). Ref. 10: $[\alpha]_D^{30}$=+95 (MeOH). IR (cm^{-1}): 2925 (s), 1660 (s), 1600 (m), 1445 (m), 1385 (w), 1365 (w), 1300 (m), 1080 (w), 1065 (w), 910 (m). MS *m/z* (%): 314 (4), 312 (2, M^+), 189 (33), 124 (38), 119 (100), 109 (40), 95 (18), 91 (21), 81 (19), 69 (25). HRMS: Calcd for $C_{21}H_{28}O_2$ 312.2089. Found 312.2089. ^{1}H NMR (C_6D_6): δ 6.46 (1H, d, *J*=2.3 Hz, H-6′), 6.15 (1H, d, *J*=10.0 Hz, H-3′), 6.11 (1H, dd, *J*=10.0, 2.3 Hz, H-4′), 5.33 (1H, s, H-7), 2.48 (1H, m, H-11), 2.13 (1H, m, H-11), 1.94 (1H, m, H-9), 1.86 (1H, m, H-6), 1.77 (1H, m, H-6), 1.56 (1H, m, H-1), 1.43 (1H, m, H-2), 1.40 (3H, s, H-12), 1.34 (2H, m, H-2, H-3), 1.10 (2H, m, H-3, H-5), 0.84 (3H, s, H-13), 0.83 (3H, s, H-14), 0.80 (1H, m, H-1), 0.75 (3H, s, H-15). ^{13}C NMR (C_6D_6): δ 187.1 (C-5′), 187.0 (C-2′), 151.1 (C-1′), 136.5 (C-3′), 135.7 (C-4′), 133.8 (C-8), 132.8 (C-6′), 123.4 (C-7), 53.2 (C-9), 50.0 (C-5), 42.3 (C-3), 39.6 (C-1), 36.9 (C-10), 33.3 (C-13), 33.1 (C-4), 25.9 (C-11), 24.0 (C-6), 22.8 (C-12), 22.0 (C-14), 19.1 (C-2), 13.9 (C-15).

3.2.6. Isozonarol (5). Isozonarol di-THP-ether (**14**) (235 mg, 0.49 mmol) was dissolved in 140 ml of ethyl acetate/MeOH (1:1). To this mixture 25 ml of 2.8% oxalic acid was added. The mixture was stirred for 5 h at 40°C, diluted with saturated NaCl-solution and extracted four times with hexane/ethyl acetate (1:1). The combined organic layers were washed with saturated NaCl-solution and filtered through silica gel. After removing the solvent the residue was purified using MPLC (LiChrospher® Si-60 (15 μm); hexane/ethyl acetate 3:1, 20 bar, 30 ml/min) to give **5** (129 mg, 0.41 mmol, 84%). Colourless crystals; mp 150–152°C ($CHCl_3$), $[\alpha]_D^{22}$=+28 (*c* 1.0, $CHCl_3$). Ref. 9: $[\alpha]_D$=+30 ($CHCl_3$). IR (cm^{-1}): 3610 (m), 3350 (m), 2925 (s), 1500 (s), 1455 (s), 1385 (m), 1365 (m), 1290 (m), 1170 (s), 1095 (w), 1040 (w). MS *m/z* (%): 314 (96, $M^{+\cdot}$), 191 (100), 175 (18), 161 (13), 135 (17), 123 (36), 109 (37), 95 (27), 69 (13), 55 (14).). HRMS: Calcd for $C_{21}H_{30}O_2$ 314.2246. Found 314.2246. ^{1}H NMR ($CDCl_3$): δ 6.72 (1H, d, *J*=2.7 Hz, H-6′), 6.58 (1H, d, *J*=8.5 Hz, H-3′), 6.49 (1H, dd, *J*=8.5, 2.7 Hz, H-4′), 5.37 (1H, bs, H-7), 2.56 (2H, m, H-11), 2.32 (1H, bs, H-9), 1.97 (1H, m, H-6), 1.88 (1H, m, H-1), 1.87 (1H, m, H-6), 1.54 (1H, m, H-2), 1.45 (3H, s, H-12), 1.41 (2H, m, H-2, H-3), 1.26 (1H, m, H-5), 1.17 (1H, m, H-3), 1.08 (1H, m, H-1), 0.89 (3H, s, H-14), 0.86 (6H, s, H-13, H-15). ^{13}C NMR ($CDCl_3$): δ 149.2 (C-5′), 147.0 (C-2′), 135.3 (C-8), 131.3 (C-1′), 122.3 (C-7), 116.5 (C-6′), 116.1 (C-3′), 112.8 (C-4′), 54.2 (C-9), 50.3 (C-5), 42.2 (C-3), 39.5 (C-1), 36.8 (C-10), 33.3 (C-13), 33.0 (C-4), 26.2 (C-11), 23.7 (C-6), 22.2 (C-12), 21.9 (C-14), 18.9 (C-2), 13.9 (C-15).

3.2.7. (+)-Albicanal ((+)-6). Pyridinium chlorochromate (19.4 g, 90 mmol) was stirred for 15 min in 250 ml of CH_2Cl_2. A solution of (−)-albicanol ((−)-**29**) (1.91 g, 8.6 mmol) in 20 ml of CH_2Cl_2 was slowly added. The reaction was monitored, until the educt had completely disappeared (15–40 min). The mixture was filtered through a short silica gel column (12 cm) to separate the chromium salts. Removing the solvent in vacuo at room temperature gave (+)-**6** (1.85 g, 8.4 mmol, 98%) as a colourless oil. $[\alpha]_D^{26}$=+77 (*c* 1.0, $CHCl_3$). Ref. 28: (−)-**6** $[\alpha]_D$=−67.3 (*c* 1.83, $CHCl_3$). IR (cm^{-1}): 3025 (m), 2950 (s), 2860 (m), 1720 (s), 1470 (m), 1365 (m), 1100 (w). MS *m/z* (%): 220 (6, $M^{+\cdot}$), 207 (11), 193 (18), 177 (32), 137 (100), 123 (63), 109 (43), 95 (58), 81 (64), 69 (64), 55 (38). ^{1}H NMR ($CDCl_3$): δ 9.84 (1H, d, *J*=2.5 Hz, H-11), 4.88 (1H, s, H-12), 4.42 (1H, s, H-12), 2.41 (1H, m, H-9), 2.39 (1H, m, H-7), 2.02 (1H, m, H-7), 1.67 (1H, m, H-6), 1.54 (2H, m, H-1, H-2), 1.42 (1H, m, H-2), 1.40 (2H, m, H-3, H-6), 1.16 (1H, m, H-3), 1.15 (1H, m, H-1), 1.12 (3H, s, H-15), 0.99 (1H, m, H-5), 0.85 (3H, s, H-13), 0.83 (3H, s, H-14). ^{13}C NMR ($CDCl_3$): δ 206.6 (C-11), 145.0 (C-8), 109.2 (C-12), 67.8 (C-9), 53.9 (C-5), 41.8 (C-3), 39.8 (C-1), 39.0 (C-10), 36.7 (C-7), 33.5 (C-13), 33.4 (C-4), 23.0 (C-6), 21.9 (C-14), 18.7 (C-2), 16.0 (C-15).

3.2.8. (−)-Drim-7-en-11-al ((−)-7). (−)-Drim-7-en-11-al ((−)-**7**) was prepared starting from (+)-drim-7-en-11-ol ((+)-**31**) using the same procedure as described for (+)-**6** (97%). $[\alpha]_D$=−21 (*c* 1.0, $CHCl_3$). Ref. 29: $[\alpha]_D$=−19.2 (*c* 3.7, $CHCl_3$). IR (cm^{-1}): 2950 (s), 1725 (s), 1680 (w), 1465 (m), 1450 (m), 1400 (m), 1380 (w), 1280 (w), 1130 (w). MS *m/z* (%): 220 (39, $M^{+\cdot}$), 191 (57), 135 (20), 124 (47), 123 (38), 121 (23), 109 (100), 107 (20), 97 (29), 95 (38), 81 (21), 69 (24). ^{1}H NMR ($CDCl_3$): δ 9.65 (1H, d, *J*=5.2 Hz, H-11), 5.67 (1H, s, H-7), 2.55 (1H, bs, H-9), 2.04 (1H, m, H-6), 1.94 (1H, m, H-6), 1.64 (1H, m, H-1), 1.59 (3H, s, H-12), 1.50 (1H, m, H-2), 1.42 (2H, m, H-2, H-3), 1.25 (1H, m, H-1), 1.18 (1H, m, H-3), 1.11 (1H, m, H-5), 1.04 (3H, s, H-15), 0.89 (3H, s, H-14), 0.84 (3H, s, H-13). ^{13}C NMR ($CDCl_3$): δ 206.9 (C-11), 127.7 (C-8), 125.4 (C-7), 67.5 (C-9), 48.9 (C-5), 41.9 (C-3), 40.3 (C-1), 37.0 (C-10), 33.3 (C-13), 33.0 (C-4), 23.6 (C-6), 22.0 (C-14), 21.6 (C-12), 18.2 (C-2), 15.7 (C-15).

3.2.9. (±)-Albicanic acid ((±)-8). A mixture of (±)-albicanic acid methyl ester ((±)-**28**) (20 g, 79.9 mmol),

NaSEt (60 g, 72 mmol) and 250 ml of DMF was heated for 1 h at 150°C. After cooling the reaction mixture was poured into 0.5 l of conc. HCl and 1 kg of crushed ice. Saturated NaCl-solution (600 ml) was added and the solution was extracted three times with ethyl acetate. The solvent was removed and 60 g of a yellow oil was obtained, which was dissolved in 200 ml of MeOH. H_2O (800 ml) was slowly added. The precipitate was filtered off and washed with cold hexane to obtain 18 g of (±)-**8**. Recrystallization from MeOH gave (±)-**8** (14.9 g, 63.1 mmol, 79%); mp 129–130°C. IR (cm^{-1}): 3500 (w), 3020 (s), 2990 (s), 2940 (s), 2850 (s), 1720 (s), 1650 (m), 1460 (m), 1440 (m), 1390 (m), 1365 (m), 1225 (m), 1210, (s). MS *m/z* (%): 236 (22, $M^{+\cdot}$), 221 (20), 176 (15), 137 (100), 123 (42), 121 (25), 109 (33), 95 (45), 81 (40), 41 (56). HRMS: Calcd for $C_{15}H_{24}O_2$ 236.1780. Found 236.1780. ^{1}H NMR ($CDCl_3$): δ 4.87 (1H, s, H-12), 4.77 (1H, s, H-12), 2.63 (1H, s, H-9), 2.28 (1H, m, H-7), 1.93 (1H, m, H-7), 1.58 (1H, m, H-6), 1.49 (1H, m, H-1), 1.46 (1H, m, H-2), 1.31 (1H, m, H-2), 1.30 (1H, m, H-3), 1.28 (1H, m, H-6), 1.10 (1H, m, H-1), 1.09 (1H, m, H-3), 0.99 (1H, dd, J=12.5, 2.5 Hz, H-5), 0.91 (3H, s, H-15), 0.75 (3H, s, H-13), 0.72 (3H, s, H-14). ^{13}C NMR ($CDCl_3$): δ 175.2 (C-11), 145.5 (C-8), 108.7 (C-12), 64.5 (C-9), 55.8 (C-5), 43.2 (C-3), 40.3 (C-1), 40.0 (C-10), 37.4 (C-7), 34.4 (C-4), 34.0 (C-13), 24.5 (C-6), 22.2 (C-14), 20.0 (C-2), 14.7 (C-15).

3.2.10. (+)-Albicanic acid) ((+)-8). Racemic albicanic acid ((±)-**8**) was separated into the two enantiomers (+)- and (−)-albicanic acid, as described in the literature.[13] We obtained (+)-**8** as colourless crystals; mp 130–132°C. $[\alpha]_D^{23}$=+27 (*c* 1.0, $CHCl_3$) Ref. 13: $[\alpha]_D^{25}$=+29 ($CHCl_3$).

3.2.11. (11*R*,*S*)-11-(2′,5′-Dimethoxy-1′-phenyl)-drim-8,12-en-11-ol (9a, b). Hydroquinone dimethyl ether (1.66 g, 12.0 mmol) dissolved in 25 ml of abs. Et_2O was mixed with 6.2 ml of 1.3 M sec-BuLi in cyclohexane (8.0 mmol) at 0°C. The ice bath was removed and the mixture was stirred for 3 h at room temperature. (+)-Albicanal ((+)-**6**) (880 mg, 4.0 mmol) in 5 ml of Et_2O was added and after stirring for 5 min 0.5 ml of saturated NH_4Cl-solution was dropped. Saturated NaCl-solution (5 ml) was added, the organic phase separated and dried with Na_2SO_4. The solvent was evaporated and the product was purified by MPLC (LiChroprep® RP-8 (15–25 μm); MeOH/H_2O 80:20, 4–6 bar, 25 ml/min) to obtain **9a**, **b** (1.39 g, 3.9 mmol, 97%).

3.2.12. (11*R*,*S*)-11-(2′,5′-Di-tetrahydropyranyloxy-1′-phenyl)-drim-8,12-en-11-ol (10a, b). Hydroquinone di-THP-ether (1.52 g, 5.4 mmol) was dissolved in 110 ml of abs. THF, cooled to 0°C, mixed with 3.4 ml of 1.3 M sec-BuLi in cyclohexane (4.4 mmol) and stirred for 2.5 h. (+)-Albicanal ((+)-**6**) (481 mg, 2.18 mmol), dissolved in 5 ml of abs. THF, was dropped to the obtained suspension and stirred for 15 min. To the reaction mixture 20 ml of saturated NH_4Cl-solution and 100 ml of ethyl acetate were added, the organic phase was separated, dried with Na_2SO_4 and evaporated. The product was prepurified by flash chromatography (CH_2Cl_2). Further purification by MPLC (LiChroprep® RP-8 (15–25 μm); MeCN/H_2O 83:17, 10 bar, 30 ml/min) yielded **10a**, **b** (870 mg, 1.74 mmol, 80%).

3.2.13. (11*R*,*S*)-11-(2′,5′-Di-tetrahydropyranyloxy-1′-phenyl)-drim-7-en-11-ol (11a, b). The drimenols **11a**, **b** were prepared in the same way as described for **10a**, **b**, but the hydroquinone di-THP-ether in abs. THF was not cooled to 0°C. Yield for **11a**, **b**: 80%.

3.2.14. (+)-Zonarol dimethyl ether ((+)-12). To a stirred mixture of 35 ml of liquid NH_3 and 18 ml of THF at −78°C Li (103 mg, 14.8 mmol, granulate, Merck) was added. After 15 min **9a**, **b** (1.00 g, 2.79 mmol), dissolved in 10 ml of THF, was added dropwise. After stirring for 15 min 2 g of NH_4Cl was added in portions (colour changed from dark blue to colourless). The NH_3 was allowed to evaporate (2 h). The residue was distributed in 150 ml of ethyl acetate and 100 ml of H_2O. The organic layer was dried with Na_2SO_4 and filtered through silica gel. Removing the solvent yielded (+)-**12** (927 mg, 2.71 mmol, 97%) as a colourless solid. Very pure (+)-**12** was obtained by MPLC (LiChrospher® Si-60 (15 μm); hexane/*t*-butyl methyl ether 10:1, 16 bar, 15 ml/min); mp 74–75°C. $[\alpha]_D^{21}$=+25 (*c* 1.0, $CHCl_3$). Ref. 30: $[\alpha]_D^{26}$=+27.9 ($CHCl_3$). IR (cm^{-1}): 3000 (m), 2940 (s), 2860 (m), 2830 (m), 1640 (w), 1605 (w), 1585 (w), 1495 (s), 1460 (m), 1440 (m), 1385 (w), 1365 (w), 1280 (w), 1210 (s), 1180 (w), 1160 (w), 1050 (m). MS *m/z* (%): 342 (100, $M^{+\cdot}$), 327 (10), 310 (14), 257 (1), 245 (2), 218 (1), 206 (9), 191 (15), 164 (16), 151 (77), 137 (23), 121 (32), 109 (11), 95 (16), 81 (11), 55 (8). HRMS: Calcd for $C_{23}H_{34}O_2$ 342.2559. Found 342.2558. ^{1}H NMR ($CDCl_3$): δ 6.72 (1H, d, J=9.0 Hz, H-3′), 6.71 (1H, d, J=2.8 Hz, H-6′), 6.63 (1H, dd, J=9.0, 2.8 Hz, H-4′), 4.74 (1H, s, H-12), 4.61 (1H, s, H-12), 3.78 (3H, s, MeO-2′), 3.72 (3H, s, MeO-5′), 2.74 (2H, m, H-11), 2.34 (1H, m, H-7), 2,20 (1H, m, H-7), 2.19 (1H, m, H-9), 1.87 (1H, m, H-1), 1.73 (1H, m, H-6), 1.62 (1H, m, H-2), 1.49 (1H, m, H-2), 1.41 (1H, m, H-3), 1.32 (1H, m, H-6), 1.24 (1H, m, H-5), 1.22 (1H, m, H-3), 1.15 (1H, m, H-1), 0.89 (3H, s, H-13), 0.83 (3H, s, H-14), 0.81 (3H, s, H-15). ^{13}C NMR ($CDCl_3$): δ 153.2 (C-5′), 151.7 (C-2′), 148.3 (C-8), 132.1 (C-1′), 116,2 (C-6′), 110.8 (C-3′), 109.6 (C-4′), 107.6 (C-12), 55.9 (C-9), 55.8 (MeO-2′, 55.7 (C-5), 55.5 (MeO-5′), 42.2 (C-3), 39.9 (C-10), 39.1 (C-1), 38.3 (C-7), 33.6 (C-4, C-13), 24.4 (C-6), 23.2 (C-11), 21.8 (C-14), 19.5 (C-2), 14.6 (C-15).

3.2.15. Zonarol di-THP-ether (13). The diastereomers **10a**, **b** were converted into **13** in the same way as described for preparation of **12**. Purification of **13** was possible by chromatography using the LOBAR®-system (column type A, LiChroprep® RP-18 (40–63 μm), MeCN/H_2O 9:1). Yield of **13**: 95%.

3.2.16. Isozonarol di-THP-ether (14). The drimene **14** was prepared as described for **13**. Yield of **14**: 98%.

3.2.17. (±)-8-Epiyahazunol dimethyl ether ((±)-17). Ytterbium(III) trifluoromethanesulfonate (330 mg, 0.56 mmol) was dissolved in 15 ml of THF and cooled to −78°C. To this solution MeLi (0.35 ml, 0.56 mmol) was added. After 30 min (±)-11-(2′,5′-dimethoxyphenyl)-8-oxo-12-nordrimane ((±)-**16**) (192 mg, 0.53 mmol) was added and stirred for 30 min. Saturated $NaHCO_3$-solution (15 ml) was added, the organic layer was separated and the aqueous layer extracted two times with 30 ml of ethyl

acetate. The combined organic layers were washed with saturated NaCl-solution and dried with Na_2SO_4. After filtration through silica gel and removing the solvent further purification was carried out by MPLC (LiChrospher® Si-60 (15 μm); hexane/ethyl acetate 15:1, 20 bar, 30 ml/min) to get (±)-**17** (45.2 mg, 0.12 mmol, 21%) and still (±)-**16** (135 mg, 0.37 mmol).

To a solution of samarium(II) iodide (9.1 ml, 0.91 mmol) in THF were added a solution of (±)-11-(2′,5′-dimethoxyphenyl)-8-oxo-12-nordrimane ((±)-**16**) (164 mg, 0.46 mmol) in 20 ml of THF, methyl iodide (0.02 ml, 0.46 mmol) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (0.55 ml, 4.55 mmol). After 30 min 20 ml of saturated NH_4Cl-solution was added, the organic layer was separated and the aqueous phase extracted two times with 30 ml of ethyl acetate. The combined organic layers were washed with saturated NaCl-solution and dried with Na_2SO_4. After filtration through silica gel and removing the solvent further purification was carried out by MPLC (LiChrospher® Si-60 (15 μm); hexane/ethyl acetate 15:1, 20 bar, 30 ml/min) to get (±)-**17** (15 mg, 0.04 mmol, 7%) and (±)-**16** (120 mg, 0.33 mmol).

IR (cm^{-1}): 3480 (s), 2950 (s), 2860 (m), 2840 (m), 1440 (s), 1390 (m), 1320 (m), 1270 (w), 1220 (w), 1170 (m), 1050 (w). MS *m/z* (%): 360 (100 $M^{+\cdot}$), 342 (1), 204 (70), 151 (73), 121 (13). ^{1}H NMR ($CDCl_3$): δ 6.80 (1H, d, *J*=2.6 Hz, H-6′), 6.72 (1H, d, *J*=8.8 Hz, H-3′), 6.62 (1H, dd, *J*=8.8, 2.6 Hz, H-4′), 3.78 (3H, s, MeO-2′), 3.75 (3H, s, MeO-5′), 2.93 (1H, dd, *J*=15.9, 7.7 Hz, H-11), 2.51 (1H, d, *J*=15.9 Hz, H-11), 1,78 (1H, m, H-7), 1.75 (1H, m, H-1), 1.56 (1H, m, H-6), 1.49 (1H, m, H-2), 1.46 (1H, m, H-9), 1.41 (2H, m, H-3, H-7), 1.32 (1H, m, H-6), 1.24 (1H, m, H-2), 1.22 (1H, m, H-3), 1.05 (3H, s, H-15), 0.95 (1H, m, H-1), 0.91 (1H, m, H-5), 0.88 (3H, s, H-12), 0.86 (3H, s, H-14), 0.84 (3H, s, H-13). ^{13}C NMR ($CDCl_3$): δ 153.5 (C-4′), 151.2 (C-2′), 134.3 (C-1′), 116.2 (C-6′), 111.0 (C-3′), 109.3 (C-4′), 73.3 (C-8), 58.8 (C-9), 56.0 (C-5), 56.0 (MeO-2′), 55.6 (MeO-5′), 42.6 (C-7), 42.0 (C-3), 39.9 (C-1), 39.0 (C-10), 33.6 (C-13), 33.5 (C-4), 31.2 (C-12), 23.0 (C-11), 21.8 (C-14), 18.4 (C-2, C-6), 15.3 (C-15).

3.2.18. (±)-8-Epiyahazunol dimethyl ether ((±)-17) via (±)-19. (±)-8-Epiyahazunol dimethyl ether ((±)-**17**) was prepared by reduction of (±)-**19** with $LiAlH_4$ as described for (−)-**22** and (+)-**23**, but the reaction time was reduced from 2 h to 30 min. Yield of (±)-**17**: 97%.

3.2.19. (±)-8,12-Epoxyzonarol dimethyl ether ((±)-19). Sodium hydride (60%, 43 mg, 1.08 mmol) was dissolved in 15 ml of DMSO and heated for 20 min to 75°C (until the formation of hydrogen has ended). After cooling to room temperature 20 ml of THF was added and the mixture was cooled to −20°C. To this solution trimethylsulfonium iodide (220 mg, 1.08 mmol), dissolved in 2 ml of DMSO, was added over a period of three min. After 1 min (±)-**11**-(2′,5′-dimethoxyphenyl)-8-oxo-12-nordrimane ((±)-**16**) (261 mg, 0.76 mmol), dissolved in 10 ml of THF, was added. After stirring for 15 min at −20°C and 45 min at room temperature, 10 ml of saturated $NaHCO_3$-solution was added. The organic layer was separated and the aqueous phase extracted two times with 5 ml of ethyl acetate. The combined organic layers were washed with saturated NaCl-solution and dried with Na_2SO_4. After filtration through silica gel and removing the solvent we obtained (±)-**19** (250 mg, 0.70 mmol, 92%). MS *m/z* (%): 358 (100, $M^{+\cdot}$), 340 (14), 220 (61), 204 (39), 203 (43), 189 (85), 159 (37), 152 (58), 151 (98), 121 (57). ^{1}H NMR ($CDCl_3$): δ 6.75 (1H), 6.68 (1H), 6.62 (1H), 3.77 (6H, MeO), 2.58 (1H), 2.35 (2H), 2.15 (1H), 2.0–1.85 (3H), 1.75–1.55 (3H), 1.50–1.20 (4H), 1.20–1.05 (2H), 1.02 (3H, s), 0.92 (3H, s), 0.89 (3H, s). ^{13}C NMR ($CDCl_3$): δ 153.4, 151.6, 132.9, 116.1, 110.9, 109.4, 57.9, 55.8, 55.6, 55.3, 51.5, 49.4, 42.1, 40.1, 39.2, 36.1, 33.6 (2 C), 21.8, 20.4, 20.2, 18.7, 14.7.

3.2.20. (+)-Zonarol dibenzyl ether ((+)-20). Zonarol ((+)-**3**) (385 mg, 1.22 mmol) was dissolved in 50 ml of acetone. To this solution 1.3 g of K_2CO_3 and benzyl bromide (0.75 ml, 6.24 mmol) were added. The mixture was heated under reflux for 36 h. The solution was filtered through silica gel and purified using MPLC (LiChrospher® Si-60 (15 μm); pentane/Et_2O 25:1, 20 bar, 30 ml/min) to get (+)-**20** (514 mg, 1.04 mmol, 85%) as colourless crystals. Mp 110–111°C (pentane/Et_2O), $[\alpha]_D^{24}$=+18 (*c* 1.05, $CHCl_3$). IR (cm^{-1}): 3020 (s), 2930 (m), 1495 (m), 12227 (m), 1205 (w), 1024 (w). MS *m/z* (%): 494 (72, $M^{+\cdot}$), 403 (6), 213 (8), 137 (7), 123 (8), 91 (100). HRMS: Calcd for $C_{35}H_{42}O_2$ 494.3185 Found 494.3184. ^{1}H NMR ($CDCl_3$): δ 7.44–7.30 (10H, m, benzyl), 6.81 (1H, d, *J*=2.8 Hz, H-6′), 6.78 (1H, d, *J*=8.7 Hz, H-3′), 6.68 (1H, dd, *J*=8.7, 2.8 Hz, H-4′), 5.01 (2H, bs, CH_2O-5′), 4.97 (2H, bs, CH_2O-2′), 4.72 (1H, s, H-12), 4.63 (1H. s, H-12), 2.81 (1H, m, H-11), 2.73 (1H, m, H-11), 2.32 (1H, m, H-7), 2.23 (1H, m, H-9), 1.95 (1H, m, H-7), 1.73 (2H, m, H-1, H-6), 1.55 (1H, m, H-2), 1.41 (1H, m, H-2), 1.32 (1H, m, H-3), 1.30 (1H, m, H-6), 1.10 (2H, m, H-3, H-5), 1.01 (1H, m, H-1), 0.86 (3H, s, H-13), 0.80 (3H, s, H-14), 0.76 (3H, s, H-15). ^{13}C NMR ($CDCl_3$): δ 152.7 (C-2′), 151.1 (C-5′), 148.4 (C-8), 137.5 (benzyl), 137.4 (benzyl), 132.5 (C-1′), 128.5 (benzyl), 128.4 (benzyl), 127.8 (benzyl), 127.7 (benzyl), 127.6 (benzyl), 127.5 (benzyl), 117.6 (C-6′), 112.5 (C-3′), 111.2 (C-4‘), 107.6 (C-12), 70.9 (CH_2O-2′), 70.5 (CH_2O-5′), 55.7 (C-9), 55.6 (C-5), 42.1 (C-3), 39.9 (C-10), 38.9 (C-1), 38.3 (C-7), 33.7 (C-13), 33.6 (C-4), 24.4 (C-6), 24.0 (C-11), 21.7 (C-14), 19.4 (C-2), 14.5 (C-15).

3.2.21. (8*R*,*S*)-8,12-Epoxyzonarol dibenzyl ether (21a, b). To a solution of (+)-zonarol dibenzyl ether ((+)-**20**) (500 mg, 1.01 mmol)) in 50 ml of CH_2Cl_2 1018 mg MCPBA (70–75%) was added. The reaction was monitored until the educt had completely vanished (90–120 min). A saturated solution of K_2CO_3 (20 ml) was added, the organic layer separated and the H_2O layer extracted three times with *t*-butyl methyl ether. The combined organic layers were washed with NaCl-solution, dried with Na_2SO_4 and filtered through silica gel. Further purification was achieved by MPLC (LiChrospher® 100 RP-18 (12 μm); MeCN/H_2O 4:1, 20 bar, 30 ml/min) to obtain **21a**, **b** (433 mg, 0.85 mmol, 84%) as a colourless oil.

3.2.22. 8-Epiyahazunol dibenzyl ether ((−)-22) and yahazunol dibenzyl ether ((+)-23). To a solution of **21a**, **b** (400 mg, 0.78 mmol) in 50 ml of Et_2O 950 mg $LiAlH_4$ was added. After heating under reflux for 2 h the reaction mixture was slowly poured into a mixture of 100 ml of conc.

HCl and 250 g of crushed ice. The organic layer was separated and the aqueous layer extracted two times with *t*-butyl methyl ether. The combined organic layers were washed with sat. $KHCO_3$-solution, saturated NaCl-solution and dried with Na_2SO_4. After filtration through silica gel and removing the solvent further purification was carried out by MPLC (LiChrospher® Si-60 (15 μm); hexane/*t*-butyl methyl ether 8:1, 20 bar, 30 ml/min) to get (−)-**22** (47 mg, 0.092 mmol, 12%) and (+)-**23** (226 mg, 0.44 mmol, 56%) as colourless oils. (−)-**22**: $[\alpha]_D^{23}=-10$ (*c* 1.0, $CHCl_3$). IR (cm^{-1}): 3490 (w), 3019 (m), 2925 (m), 1498 (w), 1460 (w), 1216 (s), 1026 (w). MS *m/z* (%): 512 (100, $M^{+\cdot}$), 404 (12), 313 (14), 191 (9), 91 (80). HRMS: Calcd for $C_{35}H_{44}O_3$ 512.3290. Found 512.3290. ^{1}H NMR ($CDCl_3$): δ 7.42–7.24 (10H, m, benzyl), 6.84 (1H, d, *J*=2.5 Hz, H-6′), 6.78 (1H, d, *J*=8.8 Hz, H-3′), 6.70 (1H, dd, *J*=8.8, 2.5 Hz, H-4′), 5.01 (2H, bs, CH_2O-2′), 5.00 (2H, bs, CH_2O-5′), 2.93 (1H, dd, *J*=16.2, 2.9 Hz, H-11), 2.56 (1H, d, *J*=16.2 Hz, H-11), 1.73 (1H, m, H-7), 1.71 (1H, m, H-1), 1.49 (2H, m, H-2, H-6), 1.42 (1H, m, H-9), 1.41 (1H, m, H-7), 1.39 (1H, m, H-3), 1.30 (2H, m, H-2, H-6), 1.11 (1H, m, H-3), 1.01 (3H, s, H-15), 0.89 (3H, s, H-12), 0.87 (3H, s, H-13), 0.84 (2H, m, H-1, H-5), 0.83 (3H, s, H-14). ^{13}C NMR ($CDCl_3$): δ 152.9 (C-5′), 150.5 (C-2′), 137.5 (benzyl), 137.4 (benzyl), 134.9 (C-1′), 128.6 (benzyl), 128.5 (benzyl), 127.9 (benzyl), 127.8 (benzyl), 127.6 (benzyl), 127.4 (benzyl), 117.2 (C-6′), 113.2 (C-3′), 111.2 (C-4′), 73.3 (C-8), 71.1 (CH_2O-2′), 70.6 (CH_2O-5′), 58.8 (C-9), 56.0 (C-5), 42.6 (C-7), 41.9 (C-3), 39.7 (C-1), 39.0 (C-10), 33.6 (C-13), 33.4 (C-4), 31.3 (C-12), 23.2 (C-11), 21.8 (C-14), 18.4 (C-2, C-6), 15.3 (C-15). (+)-**23**: $[\alpha]_D^{23}=+5$ (*c* 1.0, $CHCl_3$). IR (cm^{-1}): 3490 (w), 3019 (m), 2925 (m), 1498 (w), 1460 (w), 1216 (s), 1026 (w). MS *m/z* (%): 512 (100, $M^{+\cdot}$), 404 (12), 313 (14), 191 (9), 91 (80). HRMS: Calcd for $C_{35}H_{44}O_3$ 512.3290 Found 512.3290. ^{1}H NMR ($CDCl_3$): δ 7.42–7.23 (10H, m, benzyl), 6.86 (1H, d, *J*=2.8 Hz, H-6′), 6.80 (1H, d, *J*=8.8 Hz, H-3′), 6.70 (1H, dd, *J*=8.8, 2.8 Hz, H-4′), 5.00 (4H, m, CH_2O), 2.78 (1H, dd, *J*=14.6, 5.8 Hz, H-11), 2.57 (1H, dd, *J*=14.6, 4.0 Hz, H-11), 1.75 (1H, m, H-7), 1.69 (1H, m, H-1), 1.61 (1H, m, H-9), 1.60 (1H, m, H-6), 1.49 (1H, m, H-2), 1.31 (1H, m, H-7), 1.30 (2H, m, H-2, H-3), 1.25 (1H, m, H-6), 1.15 (3H, s, H-12), 1.04 (1H, m, H-3), 0.84 (3H, s, H-13), 0.81 (3H, s, H-15), 0.80 (1H, m, H-5), 0.76 (3H, s, H-14), 0.74 (1H, m, H-1). ^{13}C NMR ($CDCl_3$): δ 153.7 (C-5′), 151.2 (C-2′), 137.3 (benzyl), 136.8 (benzyl), 134.5 (C-1′), 128.6 (benzyl), 128.5 (benzyl), 128.2 (benzyl), 128.1 (benzyl), 127.9 (benzyl), 127.5 (benzyl), 118.2 (C-6′), 113.0 (C-3′), 111.8 (C-4′), 73.8 (C-8), 71.3 (CH_2O-2′), 70.5 (CH_2O-5′), 62.4 (C-9), 56.1 (C-5), 43.4 (C-7), 41.8 (C-3), 40.1 (C-1), 39.2 (C-10), 33.5 (C-13), 33.3 (C-4), 24.9 (C-11), 24.2 (C-12), 21.5 (C-14), 20.2 (C-6), 18.6 (C-2), 15.4 (C-15).

3.2.23. Dihydro-β-ionone (25). β-Ionone (**24**) (40.5 ml, 38.5 g, 20.0 mmol), ethyldimethylsilane (29 ml, 19 g, 22.0 mmol) and tris(triphenylphosphane)rhodium(I) chloride (0.20 mmol) were stirred for 2 h at 50–55°C. After cooling to room temperature 200 ml of 0.1% K_2CO_3 in MeOH was added. The mixture was stirred for 3 h, filtered through silica gel and the solvent was evaporated. The residue was dried for 2 h at 50°C and 20 mbar to obtain **25** (38.5 g, 19.8 mmol, 99%) as a pale yellow oil. IR (cm^{-1}): 3000 (m), 2950 (s), 2930 (s), 2870 (m), 1710 (s), 1475 (w), 1360 (m). MS *m/z* (%): 194 (9, $M^{+\cdot}$), 193 (25), 179 (7), 175 (44), 152 (40), 135 (39), 133 (46), 123 (30), 121 (42), 119 (35), 107 (36), 95 (40), 43 (100). ^{1}H NMR ($CDCl_3$): δ 2.46 (2H, m, H-8), 2.20 (2H, m, H-7), 2.10 (3H, s, H-10), 1.85 (2H, m, H-4), 1.52 (3H, s, H-11), 1.50 (2H, m, H-3), 1.36 (2H, m, H-2), 0.93 (6H, s, H-12, H-13). ^{13}C NMR ($CDCl_3$): δ 208.9 (C-9), 135.9 (C-6), 127.7 (C-5), 44.5 (C-8), 39.7 (C-2), 35.0 (C-1), 32.7 (C-4), 29.7 (C-10), 28.4 (C-12, C-13), 22.2 (C-7), 19.6 (C-11), 19.4 (C-3).

3.2.24. 5-(1,1,5-Trimethylcyclohex-5-en-6-yl)-3-oxo-pentanoic acid methyl ester (26). To a solution of dihydro-β-ionone (**25**) (52.0 g, 268 mmol) in 500 ml of toluene NaH (7.70 g, 480 mmol) and dimethyl carbonate (40.6 ml, 43.4 g, 480 mmol) were added and the mixture was heated for 2 h at 100°C. After cooling the solution was slowly poured into a mixture of 300 ml of conc. HCl and 600 g of ice. The organic layer was separated and the aqueous layer extracted two times with ethyl acetate. The combined organic layers were washed with saturated NaCl-solution and dried with Na_2SO_4. After filtration through silica gel and removing the solvent further purification was carried out by MPLC (LiChrospher® Si-60 (15 μm); hexane/ethyl acetate 12:1, 20 bar, 30 ml/min) to get **26** (65.5 g, 259.6 mmol, 97%). IR (cm^{-1}): 3020 (m), 2960 (s), 2930 (s), 2870 (m), 1740 (s), 1710 (s), 1435 (m), 1405 (w), 1380 (w), 1320 (m). MS *m/z* (%): 194 (19), 179 (39), 176 (55), 161 (73), 136 (56), 123 (51), 121 (100), 43 (28). ^{1}H NMR ($CDCl_3$): δ 3.71 (3H, s, CH_3O), 3.42 (2H, s, H-10), 2.58 (2H, m, H-8), 2.25 (2H, m, H-7), 1.86 (2H, m, H-4), 1.54 (2H, m, H-3), 1.53 (3H, s, H-11), 1.38 (2H, m, H-2), 0.94 (6H, s, H-12, H-13). ^{13}C NMR ($CDCl_3$): δ 202.7 (C-9), 167.6 (C-14), 135.5 (C-6), 128.1 (C-5), 52.3 (CH_3O), 48.9 (C-10), 43.8 (C-8), 39.7 (C-2), 35.0 (C-1), 32.7 (C-4), 28.4 (C-12, C-13), 22.0 (C-7), 19.7 (C-11), 19.4 (C-3).

3.2.25. (±)-8-Oxo-12-nordriman-11-acid methyl ester ((±)-27). A solution of 26 (15.7 g, 62.2 mmol) in 0.75 l CH_2Cl_2 was cooled to 0°C and pure $SnCl_4$ (26.3 g, 100.8 mmol) was slowly added within 15 min. The reaction was stirred for 2 h at 0°C followed by 16 h at 25°C. The mixture was washed three times with 250 ml of 10% HCl (0°C), 50 ml saturated $KHCO_3$-solution (0°C), 50 ml saturated NaCl-solution (0°C) and filtered through silica gel. Removement of the solvent gave an orange oil which was diluted with 30 ml of hexane. The mixture was left over night at 4°C to crystallise. After filtration and drying we obtained (±)-**27** (11.3 g, 44.8 mmol, 72%) as colourless needles; mp 85–86°C. IR (cm^{-1}): 3012 (m), 2955 (s), 2935 (s), 2850 (m), 1745 (s), 1710 (s), 1460 (m), 1440 (m), 1375 (m), 1355 (m), 1260 (m), 1200 (m), 1170 (s), 1115 (m). MS *m/z* (%): 252 (11, $M^{+\cdot}$), 237 (5), 234 (20), 221 (19), 219 (22), 206 (7), 205 (19), 177 (12), 163 (10), 137 (36), 136 (100), 123 (23), 116 (26). ^{1}H NMR ($CDCl_3$): δ 3.64 (3H, s, CH_3O), 3.18 (1H, s, H-9), 2.46 (1H, m, H-7), 2.31 (1H, m, H-7), 1.99 (1H, m, H-6), 1.70 (1H, m, H-6), 1.62 (1H, m, H-1), 1.52 (1H, m, H-2), 1.45 (2H, m, H-2, H-3), 1.39 (1H, dd, *J*=12.5, 2.7 Hz, H-5), 1.29 (1H, m, H-3), 1.23 (1H, m, H-1), 1.11 (3H, s, H-15), 0.93 (3H, s, H-13), 0.85 (3H, s, H-14). ^{13}C NMR ($CDCl_3$): δ 205.5 (C-8), 168.6 (C-11), 69.9 (C-9), 53.1 (C-5), 51.4 (CH_3O), 41.9 (C-10), 41.8 (C-3), 41.2 (C-7), 39.1 (C-1), 33.5 (C-4), 33.4 (C-13), 22.9 (C-6), 21.6 (C-14), 18.5 (C-2), 14.7 (C-15).

3.2.26. (±)-Albicanic acid methyl ester ((±)-28). The Wittig reagent was prepared by heating of methyltriphenylphosphonium bromide (35.7 g, 100 mmol) and $NaNH_2$ (4.88 g, 125 mmol) in 300 ml of toluene for 2.5 h. The mixture was allowed to cool to room temperature. After 6 h without any disturbance, the clear orange solution over the white solid was used for the described reaction.

A solution of (±)-**27** was dissolved in 50 ml of toluene and mixed slowly with the clear orange solution of the Wittig reagent. After 1 h the reaction mixture was filtered through silica gel. The solvent was removed and the obtained oil was taken up in 200 ml of hexane. The mixture is heated for 15 min under reflux and then left to cool to 20°C. The white precipitate of triphenylphosphine oxide was filtered off. Removing the solvent gave (±)-**28** (9.59 g, 38.3 mmol, 99%) as a colourless oil. IR (cm^{-1}): 3000 (m), 2940 (s), 2870 (m), 2850 (m), 1730 (s), 1650 (m), 1460 (m), 1440 (m), 1390 (m), 1375 (m), 1200 (m), 1170 (s). MS *m/z* (%): 251 (25), 250 (89, $M^{+\cdot}$), 235 (68), 219 (11), 191 (29), 179 (24), 176 (56), 161 (40), 137 (100), 123 (72), 121 (69). ^1H NMR ($CDCl_3$): δ 4.80 (1H, s, H-12), 4.64 (1H, s, H-12), 3.62 (3H, s, CH_3O), 2.78 (1H, s, H-9), 2.40 (1H, m, H-7), 2.04 (1H, m, H-7), 1.67 (1H, m, H-6), 1.54 (1H, m, H-1), 1.45 (1H, m, H-2), 1.41 (1H, m, H-2), 1.40 (1H, m, H-6), 1.39 (1H, m, H-3), 1.18 (1H, m, H-3), 1.16 (1H, m, H-1), 1.05 (1H, dd, J=12.7, 2.8 Hz, H-5), 1.03 (3H, s, H-15), 0.85 (3H, s, H-13), 0.81 (3H, s, H-14). ^{13}C NMR ($CDCl_3$): δ 172.0 (C-11), 143.8 (C-8), 108.3 (C-12), 63.1 (C-9), 54.6 (C-5), 50.8 (CH_3O), 42.2 (C-3), 39.1 (C-1, C-10), 36.3 (C-7), 33.5 (C-13), 33.4 (C-4), 23.3 (C-6), 21.7 (C-14), 18.9 (C-2), 14.2 (C-15).

3.2.27. (+)-Albicanic acid methyl ester ((+)-28). To a solution of (+)-**8** (2.00 g, 8.46 mmol) in 50 ml of MeOH tetraethylammonium hydroxide (20% in H_2O, 7.5 ml, 10.3 mmol) was added. The solvent was removed and the residue was dissolved in 40 ml of THF. To this solution dimethyl sulfate (2.4 ml, 26.4 mmol) (CAUTION: Cancer hazard!) and after 10 min 10 ml of 25% NH_3 in H_2O was added and the mixture was stirred for further 15 min. After addition of 100 ml of H_2O the mixture was extracted three times with Et_2O. The combined organic phases were dried with $MgSO_4$ and filtered through silica gel. Removing the solvent yielded (+)-**28** (2.09 g, 8.37 mmol, 99%) as a colourless oil; $[\alpha]_D^{24}$=+22 (*c* 1.00, $CHCl_3$).

3.2.28. (−)-Albicanol) ((−)-29). A solution of (+)-**28** (5.14 g, 20.5 mmol) in 100 ml of abs. CH_2Cl_2 was cooled to 0°C, DIBAH (Aldrich, 1.0 M in abs. CH_2Cl_2, 50 ml, 50 mmol) was added dropwise. After 30 min the solution was slowly poured into a mixture of 100 ml of conc. HCl and 250 g of ice. The organic layer was separated and the aqueous layer extracted two times with ethyl acetate. The combined organic layers were washed with sat. $KHCO_3$-solution, sat. NaCl-solution and dried with Na_2SO_4. Filtration through silica gel and removing the solvent yielded (−)-**29** (4.44 g, 20.0 mmol, 98%) as a colourless oil, which became a waxlike solid after several hours. Crystalline (−)-**29** was obtained using MeOH for crystallization; mp 68–70°C $[\alpha]_D^{24}$=−14 (*c* 1.0, $CHCl_3$). IR (cm^{-1}): 3600 (w), 3500–3300 (w), 3010 (s), 2930 (s), 2870 (s), 2850 (s), 1640 (m), 1460 (m), 1440 (m), 1390 (w), 1365 (w), 1260 (m), 1020 (s). MS *m/z* (%): 222 (12, $M^{+\cdot}$), 207 (8), 204 (9), 191 (6), 189 (13), 137 (100), 123 (25), 109 (21), 95 (41). ^1H NMR ($CDCl_3$): δ 4.92 (1H, s, H-12), 4.62 (1H, s, H-12), 3.81 (1H, dd, J=11.0, 9.5 Hz, H-11), 3.74 (1H, dd, J=11.0, 3.8 Hz, H-11), 2.40 (1H, m, H-7), 2.00 (1H, m, H-7), 1.95 (1H, m, H-9), 1.72 (1H, m, H-6), 1.64 (1H, m, H-1), 1.52 (1H, m, H-2), 1.47 (1H, m, H-2), 1.38 (1H, m, H-3), 1.32 (1H, m, H-6), 1.19 (1H, m, H-1), 1.17 (1H, m, H-3), 1.10 (1H, dd, J=12.6, 2.9 Hz, H-5), 0.85 (3H, s, H-13), 0.78 (3H, s, H-14), 0.69 (3H, s, H-15). ^{13}C NMR ($CDCl_3$): δ 147.8 (C-8), 106.3 (C-12), 59.2 (C-9), 58.7 (C-11), 55.2 (C-5), 42.0 (C-3), 39.0 (C-1), 38.9 (C-10), 37.9 (C-7), 33.6 (C-13), 33.4 (C-4), 24.1 (C-6), 21.7 (C-14), 19.2 (C-2), 15.3 (C-15).

3.2.29. (−)-Drim-7-en-11-acid methyl ester (−)-30). A mixture of (+)-**28** (614 mg, 2.45 mmol), $Pd/CaCO_3$ (5% Pd, 313 mg, 0.15 mmol) and Ph_3P (36 mg, 0.14 mmol) in 30 ml of ethyl acetate was stirred for 24 h under a H_2-atmosphere. After filtration through silica gel and removement of the solvents the residual oil is further purified by MPLC (LiChrospher® Si-60 (15 μm); hexane/toluene 3:2, 10 bar, 30 ml/min) to get (−)-**30** (437 mg, 1.75 mmol, 71%) as a colourless liquid. $[\alpha]_D^{24}$=−25 (*c* 1.2, $CHCl_3$). IR (cm^{-1}): 2940 (s), 1725 (s) 1465 (m), 1440 (m), 1395 (w), 1330 (w), 1220 (s), 1165 (m), 1040 (w). MS *m/z* (%): 250 (33, $M^{+\cdot}$), 127 (38), 124 (56), 109 (100), 105 (19), 95 (20), 91 (19), 81 (18). ^1H NMR ($CDCl_3$): δ 5.52 (1H, s, H-7), 3.63 (3H, s, CH_3O), 2.87 (1H, s, H-9), 1.98 (1H, m, H-6), 1.87 (1H, m, H-6), 1.58 (1H, m, H-1), 1.57 (3H, s, H-12), 1.49 (1H, m, H-2), 1.42 (1H, m, H-3), 1.40 (1H, m, H-2), 1.22 (1H, m, H-1), 1.16 (1H, m, H-5), 1.15 (1H, m, H-3), 0.91 (3H, s, H-15), 0.87 (3H, s, H-14), 0.84 (3H, s, H-13). ^{13}C NMR ($CDCl_3$): δ 173.3 (C-11), 129.1 (C-8), 124.2 (C-7), 62.1 (C-9), 51.0 (CH_3O), 49.3 (C-5), 42.0 (C-3), 40.3 (C-1), 36.1 (C-10), 33.3 (C-13), 32.9 (C-4), 23.6 (C-6), 21.9 (C-14), 21.3 (C-12), 18.6 (C-2), 14.8 (C-15).

3.2.30. (+)-Drim-7-en-11-ol ((+)-31). Compound (+)-**31** was prepared as described for (−)-**29**. After MPLC (LiChrospher® Si-60 (15 μm); hexane/ethyl acetate 7:1, 14 bar, 15 ml/min) we obtained (+)-**31** as waxlike solid (95%). $[\alpha]_D^{24}$=+20 (*c* 1.0, $CHCl_3$) Ref. 31: (−)-**31**: $[\alpha]_D^{20}$=−20 (*c* 1.0, $CHCl_3$). IR (cm^{-1}): 3640 (m), 3475 (w), 2940 (s), 1475 (m), 1460 (m), 1405 (w), 1380 (w), 1255 (s), 1065 (w). MS *m/z* (%): 222 (14, $M^{+\cdot}$), 124 (32), 123 (9), 109 (100), 95 (11). 91 (9), 81 (10), 69 (12), 55 (9). HRMS: Calcd for $C_{15}H_{26}O$ 222.1984. Found 222.1984. ^1H NMR ($CDCl_3$): δ 5.50 (1H, s, H-7), 3.82 (1H, dd, J=11.1, 2.4 Hz, H-11), 3.69 (1H, dd, J=11.1, 4.7 Hz, H-11), 1.94 (2H, m, H-1, H-6), 1.81 (2H, m, H-6, H-9), 1.52 (1H, m, H-2), 1.42 (1H, m, H-2), 1.38 (1H, m, H-3), 1.15 (2H, m, H-3, H-5), 1.03 (1H, m, H-1), 0.85 (3H, s, H-14), 0.83 (3H, s, H-13), 0.81 (3H, s, H-15). ^{13}C NMR ($CDCl_3$): δ 132.9 (C-8), 124.0 (C-7), 60.8 (C-11), 57.1 (C-9), 49.7 (C-5), 42.0 (C-3), 39.8 (C-1), 35.9 (C-10), 33.3 (C-13), 32.8 (C-4), 23.5 (C-6), 22.0 (C-14), 21.9 (C-12), 18.7 (C-2), 14.8 (C-15).

Acknowledgements

Support of this research by a grant of the Deutsche Forschungsgemeinschaft (Se-595/9-1) is gratefully acknowledged.

References

1. Loya, S.; Tal, R.; Kashman, R. Y.; Hizi, A. *Antimicrob. Agents Chemother.* **1990**, *34*, 2009–2012.
2. Bourguet-Kondracki, M.-L.; Longeon, A.; Morel, E.; Guyot, M. *Int. J. Immunopharmac.* **1991**, *13*, 393–399.
3. Barrero, A. F.; Alvarez-Manzaneda, E. J.; Mar Herrador, M.; Chahboun, R.; Galera, P. *Bioorg. Med. Lett.* **1999**, *9*, 2325–2328.
4. Radeke, H. S.; Digits, C. A.; Bruner, S. D.; Snapper, M. L. *J. Org. Chem.* **1997**, *62*, 2823–2831.
5. Mayer, A. M. S.; Paul, V. J.; Fenical, W.; Norris, J. N.; de Carvalho, M. S.; Jacobs, R. S. *Hydrobiologia* **1993**, *260/261*, 521–529.
6. Belisario, M. A.; Pecce, R.; Maturo, M.; De Rosa, S. *Toxicology* **1994**, *86*, 89–108.
7. Loya, S.; Hizi, A. *FEBS Lett.* **1990**, *269*, 131–134.
8. Capon, R. J. *Studies in Natural Products Chemistry, Structure and Chemistry (Part C)*; Atta-ur-Rahman, G., Ed.; Elsevier: Amsterdam, 1995; Vol. 15, pp 289–326.
9. Ochi, M.; Kotsuki, H.; Muraoka, K.; Tokoroyama, T. *Bull. Chem. Soc. Jpn* **1979**, *52*, 629–630.
10. Fenical, W.; Sims, J. J.; Squatrito, D.; Wing, R. M.; Radlick, P. *J. Org. Chem.* **1973**, *38*, 2383–2386.
11. Herlem, D.; Kervagoret, J.; Yu, D.; Khuong-Huu, F.; Kende, A. S. *Tetrahedron* **1993**, *49*, 607–618.
12. Liapis, M.; Ragoussis, V.; Ragoussis, N. *J. Chem. Soc., Perkin Trans. 1* **1985**, 815–817.
13. Ragoussis, V.; Liapis, M.; Ragoussis, N. *J. Chem. Soc., Perkin Trans. 1* **1987**, 987–992.
14. Schröder, J.; Magg, C.; Seifert, K. *Tetrahedron Lett.* **2000**, *41*, 5469–5473.
15. Small, G. H.; Engman Minnella, A.; Hall, S. S. *J. Org. Chem.* **1975**, *40*, 3151–3152.
16. Grant, H. N.; Prelog, V.; Sneeden, R. P. A. *Helv. Chim. Acta* **1963**, *46*, 415–421.
17. Syper, L.; Kloc, K.; Mlochowski, J.; Szulc, Z. *Synthesis* **1979**, *7*, 521–522.
18. Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904–3912.
19. Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698.
20. Rausch, M. D.; Gordon, H. G. *J. Organomet. Chem.* **1974**, *74*, 85–90.
21. Molander, G. A.; Burkhardt, E. R.; Weinig, P. *J. Org. Chem.* **1990**, *55*, 4990–4991.
22. Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353–1364.
23. Mc Donald, R. N.; Steppel, R. N.; Dorsey, J. E. *Org. Synth.* **1970**, *50*, 15–18.
24. Djura, P.; Stierle, D. B.; Sullivan, B.; Faulkner, D. J. *J. Org. Chem.* **1980**, *45*, 1435–1441.
25. Ojima, I.; Kogure, T. *Organometallics* **1982**, *1*, 1390–1399.
26. Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.
27. Mori, K.; Komatsu, M. *Bull. Soc. Chim. Belg.* **1986**, *95*, 771–781.
28. Poigny, S.; Huor, T.; Guyot, M.; Samadi, M. *J. Org. Chem.* **1999**, *64*, 9318–9320.
29. Arjona, O.; Garranzo, M.; Mahugo, J.; Maroto, E.; Plumet, J.; Saez, B. *Tetrahedron Lett.* **1997**, *38*, 7249–7252.
30. Akita, H.; Nozawa, M.; Shimizu, H. *Tetrahedron: Asymmetry* **1998**, *9*, 1789–1799.
31. Huneck, S. *Z. Naturforsch.* **1967**, *22b*, 462–463.