Published in final edited form as:

Chem Biodivers. 2011 June ; 8(6): 1098–1111. doi:10.1002/cbdv.201000160.

An Entry to Curcuphenol/Elvirol Core Structures *via* a Retro-Aldol Procedure

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Abstract

Curcuphenol/elvirol analogues, the naturally occurring bisabolane sesquiterpenes were prepared in six steps from alkyl α -tetralones employing an aromatization reaction of cyclic dienone precursors and olefination of the key aldehyde intermediates. The *in vitro* antifungal activities of **6a**, **6b**, **6d** and **6g** are also reported.

Keywords

curcuphenol; elvirol; aromatic bisabolanenes; hydroxy-phenyl-butyraldehydes; 1,4-dienes; antifungal activity

Introduction

Substituted phenols play a crucial role in biosynthetic transformations [1], and they represent important building blocks for organic synthesis [2-5]. Hence, there is a continuing need for syntheses of phenolic substrates which are not available by conventional aromatic substitution chemistry.

The marine sesquiterpenes **1–2** (Figure 1), isolated from the sponges *Didiscus flavus* and *Epipolasis spp.*, were found to possess powerful antibacterial, antifungal, antitumor and antimalarial activities [6]. Elvirol **3**, which was isolated from the plant *Elvira biflora* (Compositae), is a structural isomer of curcuphenol whose structure does not obey the isoprene rule [7] [8]. Several synthetic pathways for these compounds have been reported in the literature [9-11]. On the biogenetic origin of bisabolene natural products, a hypothesis suggests that the phenolic sesquiterpenes could be formed by aromatization of its cyclic ketone precursors [12]. These molecular structures and their interesting bioactivities prompted us to undertake the syntheses of *meta* and *para* alkylated phenolic compounds, as a synthetic analogical approach to the natural products **1–3**.

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Results and Discussion

1. Synthetic Strategy

In a preliminary communication [13], we reported that an oxygenated functionality, vicinal to a quaternary C-atom of the cyclohexadienones **4**, causes ring-cleavage in K_2CO_3 -MeOH media at room temperature to afford the 4-phenyl-butyraldehydes **5a–g** (Scheme 1). A similar cleavage and a retro-Fries migration of an acyl group in different reaction conditions have been already observed by Zaidi, in the synthesis of 4-acylcyclohexa-2,5-dienone [14]. Hagiwara *et al.* have also achieved bisabolane terpenoids by another synthetic route through 1,4-addition of aldehydes to vinyl ketones, followed by an intramolecular condensation [15].

We used previously the 1,4-dienes chemistry of α -tetralones in the synthetic study of saudin [16–18] and of ouabain [19]. In this work we report the syntheses of curcuphenol/elvirol analogues **6** as biomimetic approach to bisabolane family employing the strategy of re-aromatization of the 1,4-dienones **4** (Figure 1). These compounds are positional isomers of **1** and **3** with diversity entries at the R, R¹ and R² groups what make them of particular interest to study the structural requirements needed for biological activity.

2. Syntheses of Analogues 6

As depicted in Scheme 2 each synthesis began with the introduction of R¹ substituents by means of the known Birch alkylation reaction (BAR) on **7a–c** and **7g**. The corresponding dienes with different degrees of oxidation were obtained in yields of 70–98%.

As an exception, 7-methoxy-tetralone gave on alkylation with MOMCl an aromatic product in low yield, probably derived from a retro Friedel-Crafts reaction. The carbonyl group was selectively reduced with NaBH₄ in MeOH at –78° to produce the β -configured alcohols **9** by axial attack of the hydride on the carbonyl group (60–95%). Protection of the alcohol group in **9** with benzoyl chloride furnished the corresponding *syn*-benzoates **10a–g** (80–98%). The α -configured alcohols were generated using L-selectride® in THF at –78° on dienes **8**, and acetates (as substitutes for the benzoates **10**) were also suitable compounds for the next steps.

Our initial efforts were directed towards the formation of the cross-conjugated system with the 3,5-dimethylpyrazol/CrO₃ method (cf. [20]). However, the yield of products **4** was moderate. On the other hand, the bis-allylic oxidation using PDC/*t*-BuOOH/Celite® in benzene or DCM afforded pure dienones **4a–g** in satisfactory yield (60–85%). Both protocols required careful control of reaction time, temperature, and product purification.

3. Conditions and Mechanism of Dienones Rearrangement

Preparation of 5—Experiments on the rearrangement of **4** to **5**, performed in acid media (such as H₂SO₄, polyphosphoric acid, supported-polyphosphoric acid on silicagel, and CF₃COOH) were not successful, in contrast to retro-aldol conditions, (treatment of **4** in MeOH with K₂CO₃), which led to the 4-aryl butanals **5a–g** in satisfactory yields (Scheme 3).

As outlined in Scheme 3, fragmentation of **4** is facile due to the stable phenolate system, which develops in the course of product **5** formation. Finally, we focused on Wittig olefination of **5** for the construction of hexenyl side-chain of **6** with 3-phenyl-propionaldehyde (**12**) as model compound and isopropyl triphenylphosphonium iodide (1 : 1, on a mmol scale) (Scheme 2). Alkene **13** was obtained by reaction of **12** in THF with the ylide of isopropyl triphenylphosphonium iodide, formed with NaH or *t*-BuOK (55–60°, 20% yield). Decreasing the reaction temperature to 30–25° and using BuLi, we were able to

isolate the β -hydroxy aldehyde and its dehydrated compound. Both products arose from an aldol self-condensation [21].

Better yields of **13** were obtained with the ylide of BuLi and the phosphonium salt and exact adjustment of the temperature in each addition reaction (from -78° to r.t., 82%). When this procedure was employed in case of the compounds without substitution at *ortho*-positions **5a**, **5e** and, **5h** (protected phenol) the α -tetralols **11a** (60% yield), **11e** (69%) and **11h**¹ were obtained (Scheme 4). With these results in hand, we investigated the BuLi/ylide role in this reaction.

Thus, submission of **5a**, **5b**, **5d**, and **5g** to an excess of the Wittig reagent (aldehyde : ylide (1 : 2)) at -78° , then r.t., for 30 min., provided **6a**, **6b**, **6d** and **6g** in good yields [22]. Under these reaction conditions and based on pKa value, phenols **5** can be deprotonated by the ylide, at least in part. Thus, phosphoranes formed between the phenoxides of **5** and triphenyl phosphonium ions have quaternary α -carbons and therefore a Wittig reaction on **5** is not feasible [23]. Therefore, we postulated that resonance anionic species of **5a**, **5e** derived from the deprotonation of phenols and, located on unoccupied *ortho*-positions, react more slowly to form α -tetralols **11a**, **11e** than undergo the olefination reaction (Scheme 4)². α -Tetralol **11h** is the product of an *ortho*-lithiation of **5h** (protected Ar-OH) in the presence of the strong base butyllithium and subsequent ring formation [24]. The presence of an excess of the Wittig reagent led to an intermolecular approach to be successful in producing the olefins **6a**, **6b**, **6d**, and **6g** which are not precursors of **11**.

Compounds **6** can be considered as basal structures of elvirol and curcuphenol **1–3**. In particular, the analogue **6g** has the most structural resemblance, whereas **6a** has no substitution on the side-chain. Compound **6b** is the most substituted analogue and **6d** contains an oxygenated function on the aromatic ring.

4. Antimicrobial Activity

The synthetic compounds **6** were evaluated for *in vitro* antimalarial, antifungal (Table 1) and antibacterial (Table 2) activity.

All compounds **6** proved to be inactive against *Plasmodium falciparum* at the highest concentration 4.8 $\mu\text{g/ml}$, in agreement with the behavior observed for curcudiol. As well, both compounds **6b** and **6g** were inactive against the Gram negative bacteria *E. coli* and *Pseudomonas aeruginosa*, in addition to *Mycobacterium intracellulare* at 20 $\mu\text{g/ml}$. Compound **6a** showed antifungal activity *in vitro* against *C. glabrata* (13.53 $\mu\text{g/ml}$), *C. neoformans* (5.45 $\mu\text{g/ml}$) and *A. fumigates* (19.53 $\mu\text{g/ml}$). Also **6a** was active against *S. aureus* (IC₅₀ = 11.18 $\mu\text{g/ml}$) and MRSA (IC₅₀ = 16.2 $\mu\text{g/ml}$).

Compound **6b** showed inhibitory activity against the fungi *Candida glabrata* and *Cryptococcus neoformans* (IC₅₀ = 7.4 $\mu\text{g/ml}$ for both), and the Gram positive bacteria *Staphylococcus aureus* and methicillin-resistant *S. aureus* (MRSA) (IC₅₀ 5.8 and 6.0 $\mu\text{g/ml}$, respectively). Compound **6g** exhibited antiproliferative activity against *C. glabrata* (IC₅₀ = 3.0 $\mu\text{g/ml}$), *Cryptococcus neoformans* (IC₅₀ = 5.0 $\mu\text{g/ml}$), and it was also active against *S. aureus* (IC₅₀ = 5.6 $\mu\text{g/ml}$) and MRSA (IC₅₀ = 5.9 $\mu\text{g/ml}$). The antifungal and antimicrobial bioactivity tests on compound **6d** showed only inhibitory activity against the fungi

¹)We speculate that the bicycle **9h** derived from the reaction control on **5h** was formed by the participation of the unoccupied *ortho*-position of the phenol.

²)This reaction resembles the combination of a phenol molecule which is capable of adding itself to the formaldehyde under base-catalysis (Lederer-Manasse reaction). W. J. Moran, E. C. Schreiber, E. Engel, D. C. Behn, J. L. Yamins, *J. Am. Chem. Soc.* **1952**, 74 (1), 127.

Cryptococcus neoformans (IC₅₀ 8.55 µg/ml). Therefore, analogues **6b** and **6g** are promising with regard to curcuphenol, and they are 1.3 times more active against Gram (+) *S. aureus* and *MRSa*. Based on the observation, these analogues may have improved *in vitro* antimicrobial activity relative to curcuphenol, the location of OH and Me groups on the aromatic ring of **6g**, may be possibly responsible for this change in the selectivity of inhibition.

In summary, we have developed a 6-step synthetic route to the curcuphenol as well as elvirol series, using a Wittig reaction to install the side-chain of seven aldehydes, which allow chemoselectivity with respect to the formation of products **6** or α -tetralols **11**. The formation of **11** could be useful as a method for preparing bicyclic precursors like 8-methoxy tetralones, otherwise difficult to obtain by any other means. Our findings may also be seen as a contribution to the aforementioned biogenic hypothesis or as a biomimetic approach to bisabolane/curcumane type substances by means of an aromatization step of dienones **4** and hydroxyphenyl butanals as precursors. Compounds **6b** and **6g** are functional analogues of curcuphenol, of which we have evidence of an improved antimicrobial activity as compared with the natural product. Moreover, our group is investigating improved synthetic proceedings in the quest for new and improved antimicrobial compounds.

Experimental Part

General

IR Spectra (in cm⁻¹) were recorded on Bruker FT I-25 spectrophotometer. ¹H- and ¹³C-NMR spectra (300 MHz and 75 MHz) were recorded on a Bruker AC-300-E spectrometer. The samples were dissolved in CDCl₃ as solvent and Me₄Si as internal standard; δ in ppm, J in Hz. High-resolution mass spectrometry (HR-ESI-MS) was performed at the UCR Mass Spectrometry Facility, Department of Chemistry, University of California, Riverside, U.S.A. M.p. were taken on a Ernst Leitz hot-stage microscope; and are uncorrected. All solvents were dried and distilled before use. All reactions were carried out under anhydrous conditions under N₂ atmosphere. All the organic extracts were dried over anhydrous sodium sulfate. Reactions were monitored by thin layer chromatography (t.l.c.) on aluminum-foil plates coated with 0.1-mm Analtech silica gel 60 GF254, and spot visualization under UV light. Column chromatography (CC): Analtech silica gel for flash chromatography, under a low pressure of N₂. Elution with hexane/EtOAc mixtures.

Typical procedures

Synthesis of dienones 4—To a solution of **10** (1 mmol) in benzene (16.6 ml), protected against light, was added pyridine dichromate (PDC) (1.6 mmol), Celite® (0.4 g), and *t*-BuOOH (3.3 mmol). The suspension was stirred vigorously at r.t. until t.l.c. indicated that the reaction was completed (3 h approx). The suspension was filtered through a Celite® and silicagel pad, washed by CH₂Cl₂ and evaporated to afford **4**.

(1S,8aS)-8a-methyl-6-oxo-1,2,3,4,6,8a-hexahydronaphthalen-1-yl benzoate (**4a**)

—Yellow oil (76%). *R*_f 0.60 (hexane/EtOAc 7 : 3). IR (film): 3050, 2977, 2942, 2869, 1732, 1660, 1600, 1560, 1492, 1450, 1368, 1314, 1249, 1177, 1071, 1027, 941, 812, 758, 720, 660. ¹H-NMR (CDCl₃) 8.08 (*d*, J = 6.9, 2H, H-Ar(2)); 7.62 (*t*, J = 7.3, 1H, H-Ar(4)); 7.48 (*t*, J = 7.7, 2H, H-Ar(3)); 6.95 (*d*, J = 9.9, 1H, H(8)); 6.25 (*dd*, J = 9.9, 1.9, 1H, H(7)); 6.20 (*d*, J = 1.5, 1H, H(5)); 4.84 (*dd*, J = 11.1, 4.9, 1H, H(1)); 2.51 (*dd*, J = 5.1, 1.7, 2H, H(4)); 2.45–2.42 (*m*, 2H, H(2)); 2.20–2.10 (*m*, 2H, H(3)); 1.47 (*s*, 3H, CH₃); ¹³C-NMR (CDCl₃) 186.0 (C=O); 165.3 (OC=O); 163.5 (C(4a)); 152.8 (C(8)); 133.3 (C(7)); 133.1 (ArC(1)); 129.5 (ArC(4)); 128.5 (ArC(2)); 128.1 (ArC(3)); 126.3 (C(5)); 77.0 (C(1)); 44.4 (C(8a));

31.7 (C(4)); 26.6 (C(2)); 23.9 (C(3)); 18.3 (CH₃); HR-ESI-MS: 283.1252 ([M + H]⁺, C₁₈H₁₉O₃; calc. 283.1256).

(1S,8aS)-5,7,8a-trimethyl-6-oxo-1,2,3,4,6,8a-hexahydronaphthalen-1-yl

benzoate (4b)—White crystals (62%), m.p. 131° (EtOAc/EtOH 9.5 : 0.5). *R*_f 0.45 (hexane/EtOAc 80 : 20). IR (film): 2980, 2948, 2939, 2867, 1720, 1670, 1633, 1601, 1451, 1395, 1369, 1314, 1273, 1111, 1098, 1070, 989, 810, 712, 690. ¹H-NMR (CDCl₃) 8.08 (*dt*, *J* = 4.7, 1.0, 2H, H-Ar(2)); 7.59 (*dt*, *J* = 4.5, 1.0, 1H, H-Ar(4)); 7.41 (*dt*, *J* = 4.5, 1.0, 2H, H-Ar(3)); 6.71 (*d*, *J* = 0.8, 1H, H(8)); 4.74 (*dd*, *J* = 7.6, 3.1, 1H, H(1)); 2.22–2.17 (*m*, 2H, H(4)); 2.15–1.96 (*m*, 2H, H(2)); 1.94 (*d*, *J* = 0.8, 3H, CH₃(5)); 1.84 (*d*, *J* = 1.9, 3H, CH₃(7)); 1.40 (*s*, 3H, CH₃(8a)); 1.26–1.23 (*m*, 2H, H(3)); ¹³C-NMR (CDCl₃) 186.2 (C=O); 165.4 (OC=O); 156.1 (C(4a)); 147.7 (C(8)); 133.3 (ArC(4)); 130.1 (ArC(1)); 130.7 (C(7)); 130.6 (C(5)); 129.6 (ArC(2)); 128.6 (ArC(3)); 77.6 (C(1)); 43.6 (C(8a)); 29.7 (C(2)); 26.9 (C(4)); 26.8 (C(3)); 19.1 (CH₃(7)); 16.4 (CH₃(8a)); 11.1 (CH₃(5)); HR-ESI-MS: 311.1567 ([M + H]⁺, C₂₀H₂₃O₃; calc. 311.1569).

(1S,8aS)-5-methoxy-8a-methyl-6-oxo-1,2,3,4,6,8a-hexahydro-naphthalen-1-yl

benzoate (4c)—Colorless oil (60%). *R*_f 0.23 (hexane/EtOAc 8 : 2). IR (film): 3060, 2941, 2869, 1718, 1690, 1665, 1635, 1584, 1452, 1316, 1211, 1177, 1109, 1071, 1026, 846, 711, 680. ¹H-NMR (CDCl₃) 8.08 (*d*, *J* = 5.6, 2H, H-Ar(2)); 7.61 (*t*, *J* = 5.0, 1H, H-Ar(4)); 7.47 (*t*, *J* = 5.3, 2H, H-Ar(3)); 6.94 (*d*, *J* = 6.6, 1H, H(8)); 6.30 (*d*, *J* = 6.6, 1H, H(7)); 4.85 (*dd*, *J* = 7.6, 3.1, 1H, H(1)); 3.75 (*s*, 3H, (OCH₃)); 2.10–2.07 (*m*, 2H, H(4)); 2.06–2.02 (*m*, 2H, H(2)); 1.90–1.84 (*m*, 2H, H(3)); 1.47 (*s*, 3H, (CH₃)); ¹³C-NMR (CDCl₃) 181.5 (C=O); 171.9 (OC=O); 165.4 (C(5)); 152.6 (C(8)); 147.9 (C(4a)); 133.7 (ArC(4)); 130.2 (ArC(2)); 129.8 (ArC(1)); 129.6 (C(7)); 128.5 (ArC(3)); 76.8 (C(1)); 60.5 (OCH₃); 45.1 (C(8a)); 26.7 (C(2)); 23.8 (C(4)); 22.8 (C(3)); 18.6 (CH₃).

(1S,8aS)-8a-(methoxymethyl)-6-oxo-1,2,3,4,6,8a-hexahydronaphthalen-1-yl

benzoate (4d)—White solid (73%), m.p. 120° (EtOAc). *R*_f 0.26 (hexane/EtOAc 7 : 3). IR (film): 2940, 2871, 1718, 1667, 1630, 1450, 1316, 1269, 1109, 1085, 1070, 1026, 986, 884, 751, 713. ¹H-NMR (CDCl₃) 8.03 (*d*, *J* = 4.7, 2H, H-Ar(2)); 7.59 (*t*, *J* = 4.9, 1H, H-Ar(4)); 7.46 (*dt*, *J* = 4.9, 1H, H-Ar(3)); 6.96 (*d*, *J* = 6.7, 1H, H(8)); 6.34 (*d*, *J* = 5.5, 1H, H(7)); 6.27 (*s*, 1H, H(5)); 4.85 (*dd*, *J* = 7.7, 3.2, 1H, H(1)); 4.13 (*d*, *J* = 6.2, 1H, CH₂OCH₃); 3.85 (*d*, *J* = 6.2, 1H, CH₂OCH₃); 3.31 (*s*, 3H, CH₂OCH₃); 2.12–2.09 (*m*, 2H, H(4)); 1.90 (*dq*, *J* = 7.9, 2.9, 2H, H(3)); 1.52 (*tt*, *J* = 7.7, 3.2, 2H, H(2)); ¹³C-NMR (CDCl₃) 186.4 (C=O); 165.2 (OC=O); 160.6 (C(4a)); 150.6 (C(8)); 133.5 (ArC(4)); 130.1 (ArC(1)); 130.6 (C(7)); 128.2 (C(5)); 129.6 (ArC(2)); 128.6 (ArC(3)); 77.4 (C(1)); 72.7 (CH₂OCH₃); 59.8 (CH₂OCH₃); 49.8 (C(8a)); 32.0 (C(4)); 27.2 (C(2)); 24.3 (C(3)); HR-ESI-MS: 313.1358 ([M + H]⁺, C₁₉H₂₁O₄; calc. 313.1362).

(1S,8aS)-8a-allyl-6-oxo-1,2,3,4,6,8a-hexahydronaphthalen-1-yl benzoate (4e)—

Pale yellow oil (76%). *R*_f 0.38 (hexane/EtOAc 8 : 2). IR (film): 3072, 2948, 2868, 1718, 1666, 1451, 1315, 1268, 1110, 1070, 918, 750, 712. ¹H-NMR (CDCl₃) 8.09 (*t*, *J* = 8.8, 2H, H-Ar(2)); 7.61 (*dt*, *J* = 7.3, 1.5, 2H, H-Ar(3)); 7.48–7.46 (*m*, 1H, H-Ar(4)); 6.89 (*d*, *J* = 10.1, 1H, H(8)); 6.35 (*dd*, *J* = 10.1, 1.9, 1H, H(7)); 6.27 (*s*, 1H, H(5)); 5.37–5.29 (*m*, 1H, CH₂CH=CH₂); 5.11 (*br s*, 1H, CH₂CH=CH₂); 5.03 (*d*, *J* = 0.7, 1H, CH₂CH=CH₂); 4.91 (*dd*, *J* = 11, 4.9, 1H, H(1)); 2.93 (*dd*, *J* = 14.0, 7.5, 1H, CH₂CH=CH₂); 2.74 (*dd*, *J* = 14.0, 6.4, 1H, CH₂CH=CH₂); 2.39 (*dd*, *J* = 8.8, 3.2, 2H, H(4)); 2.16–2.12 (*m*, 2H, H(2)); 2.08–2.02 (*m*, 2H, H(3)); ¹³C-NMR (CDCl₃) 186.3 (C=O); 165.2 (OCO); 161.4 (C(4a)); 151.2 (C(8)); 133.4 (ArC(4)); 130.7 (CH₂CH=CH₂); 129.6 (ArC(1)); 129.5 (C(7)); 130.0 (ArC(2)); 128.4 (ArC(3)); 128.1 (C(5)); 118.4 (CH₂CH=CH₂); 77.0 (C(1)); 48.6 (C(8a)); 34.7 (CH₂CH=CH₂); 31.6 (C(4)); 26.5 (C(2)); 23.8 (C(3)).

(1S,8aS)-8a-allyl-5,7-dimethyl-6-oxo-1,2,3,4,6,8a-hexahydronaphthalen-1-ylbenzoate (4f)—White solid (79%), m.p. 154.5–155.5° (EtOAc). R_f 0.44 (hexane/EtOAc 9 : 1). IR (film): 3072, 2949, 2927, 2865, 1719, 1670, 1631, 1450, 1371, 1314, 1267, 1110, 1026, 997, 918, 712, 687. $^1\text{H-NMR}$ (CDCl_3) 8.09 (*dt*, $J = 4.7$, 1.0, 2H, H–Ar(2)); 7.49 (*dt*, $J = 4.9$, 1.0, 2H, H–Ar(3)); 7.61 (*dt*, $J = 4.9$, 1.0, 1H, H–Ar(4)); 6.66 (*d*, $J = 0.8$, 1H, H(8)); 5.04–4.99 (*m*, 1H, $\text{CH}_2\text{CH}=\text{CH}_2$); 4.91 (*dt*, $J = 6.6$, 0.8, 1H, $\text{CH}_2\text{CH}=\text{CH}_2$); 5.26–5.23 (*m*, 1H, $\text{CH}_2\text{CH}=\text{CH}_2$); 4.81 (*dd*, $J = 7.6$, 3.3, 1H, H(1)); 2.90 (*dd*, $J = 9.4$, 5.3, 1H, $\text{CH}_2\text{CH}=\text{CH}_2$); 2.69 (*dd*, $J = 9.4$, 4.1, 1H, $\text{CH}_2\text{CH}=\text{CH}_2$); 2.14–2.08 (*m*, 2H, H(4)); 2.07–2.02 (*m*, 2H, H(2)); 1.94 (*d*, $J = 0.6$, 3H, $\text{CH}_3(5)$); 1.87 (*d*, $J = 0.8$, 3H, $\text{CH}_3(7)$); 1.48–1.38 (*m*, 2H, H(3)); $^{13}\text{C-NMR}$ (CDCl_3) 186.5 (C=O); 165.4 (OC=O); 133.3 ($\text{CH}_2\text{CH}=\text{CH}_2$); 153.9 (C(4a)); 146.0 (C(8)); 131.7 (H–Ar(4)); 135.7 (C(7)); 132.7 (C(5)); 130.1 (H–Ar(1)); 129.7 (H–Ar(2)); 128.6 (H–Ar(3)); 117.8 ($\text{CH}_2\text{CH}=\text{CH}_2$); 78.0 (C(1)); 47.5 (C(8a)); 35.4 ($\text{CH}_2\text{CH}=\text{CH}_2$); 26.9 (C(2)); 26.7 (C(4)); 23.6 (C(3)); 16.3 ($\text{CH}_3(7)$); 11.0 ($\text{CH}_3(5)$).

(1S,8aS)-8a-(methyl)-4-methyl-6-oxo-1,2,3,4,6,8a-hexahydro naphthalen-1-ylbenzoate (4g)—Oil (69%). R_f 0.47 (hexane/EtOAc 8 : 2). IR (film): 3060, 2962, 2870, 1720, 1664, 1603, 1580, 1450, 1315, 1270, 1108, 1093, 1070, 1030, 989, 898, 760, 713. $^1\text{H-NMR}$ (CDCl_3) 8.07 (*d*, $J = 4.7$, 2H, H–Ar(2)); 7.60 (*dt*, $J = 4.8$, 1.0, 1H, H–Ar(4)); 7.48 (*t*, $J = 4.8$, 2H, H–Ar(3)); 6.95 (*d*, $J = 6.6$, 1H, H(8)); 6.26 (*dd*, $J = 6.6$, 1.2, 1H, H(7)); 6.21 (*s*, 1H, H(5)); 4.82 (*dd*, $J = 7.5$, 3.2, 1H, H(1)); 2.59 (*dd*, $J = 4.2$, 1.2, 1H, H(4)); 2.14–2.07 (*m*, 2H, H(2)); 1.96–1.88 (*m*, 2H, H(3)); 1.48 (*s*, 3H, $\text{CH}_3(8a)$); 1.19 (*d*, $J = 4.2$, 3H, $\text{CH}_3(4)$); $^{13}\text{C-NMR}$ (CDCl_3) 186.3 (C=O); 166.8 (OC=O); 165.4 (C(4a)); 153.5 (C(8)); 133.4 (C(7)); 129.9 (ArC(1)); 123.7 (C(5)); 129.6 (ArC(4)); 128.6 (ArC(2)); 127.8 (ArC(3)); 76.9 (C(1)); 44.6 (C(8a)); 33.4 (C(4)); 32.5 (C(2)); 26.7 (C(3)); 19.0 ($\text{CH}_3(4)$); 17.3 ($\text{CH}_3(8a)$); HR-ESI-MS: 319.1309 ($[\text{M} + \text{Na}]^+$, $\text{C}_{19}\text{H}_{20}\text{O}_3\text{Na}$; calc. 319.1310).

Synthesis of phenol-aldehydes 5—To a solution of dienone **4** (1 mmol) in MeOH (50 ml), K_2CO_3 (4 mmol) was added, and the reaction mixture was maintained with magnetic stirring at r.t. until complete. The reaction was quenched with brine and methanol was concentrated *in vacuo*. The aqueous layer was extracted with Et_2O (3 $\times$ 25 ml) and EtOAc (25 ml). Combined organic extracts were washed with brine, dried (anh. Na_2SO_4) filtered and evaporated *in vacuo* to give a residue which was purified by column chromatography to afford **5**.

4-(5-Hydroxy-2-methyl-phenyl) butyraldehyde (5a)—Pale orange solid (94%). R_f 0.48 (benzene/EtOAc 8 : 2). IR (film) 3347, 3021, 2935, 2865, 1716, 1609, 1595, 1501, 1467, 1451, 1272, 1150, 1070, 1027, 813, 720. $^1\text{H-NMR}$ 9.76 (*t*, $J = 1.5$, 1H, CHO); 7.20 (*dd*, $J = 5.7$, 3.6, 1H, H–Ar(4)); 6.98 (*d*, $J = 7.7$, 1H, H–Ar(3)); 6.61 (*s*, 1H, H–Ar(6)); 2.58 (*t*, $J = 7.3$, 2H, H(4)); 2.49 (*dt*, $J = 7.2$, 1.5, 2H, H(2)); 2.21 (*s*, 3H, CH_3); 1.90 (*q*, $J = 7.3$, 2H, H(3)); $^{13}\text{C-NMR}$ (CDCl_3) 202.5 (C(1)); 153.8 (ArC(5)); 140.6 (ArC(1)); 131.1 (ArC(3)); 126.5 (ArC(2)); 115.7 (ArC(6)); 112.9 (ArC(4)); 43.2 (C(2)); 32.3 (C(4)); 22.1 (C(3)); 18.2 (CH_3); HR-ESI-MS: 179.0990 ($[\text{M} + \text{H}]^+$, $\text{C}_{11}\text{H}_{15}\text{O}_2$; calc. 179.0994).

4-(3-Hydroxy-2,4,6-trimethyl-phenyl) butyraldehyde (5b)—Colorless oil (80%). R_f 0.51 (hexane/EtOAc 7 : 3). IR (film) 3474, 3007, 2949, 2882, 1716, 1480, 1456, 1410, 1386, 1246, 1212, 1094, 1012, 869. $^1\text{H-NMR}$ 9.81 (*t*, $J = 1.0$, 1H, CHO); 6.80 (*s*, 1H, H–Ar(5)); 4.71 (*s*, 1H, OH); 2.64 (*t*, $J = 5.4$, 2H, H(4)); 2.54 (*dt*, $J = 4.7$, 1.0, 2H, H(2)); 2.24 (*s*, 3H, $\text{CH}_3(6)$); 2.23 (*s*, 3H, $\text{CH}_3(2)$); 2.21 (*s*, 3H, $\text{CH}_3(4)$); 1.79 (*q*, $J = 4.8$, 2H, H(3)); $^{13}\text{C-NMR}$ (CDCl_3) 202.4 (CHO); 150.4 (ArC(3)); 137.0 (ArC(1)); 129.8 (ArC(5)); 127.5 (ArC(6)); 121.8 (ArC(2)); 120.4 (ArC(4)); 43.8 (C(2)); 29.2 (C(4)); 21.9 (C(3)); 19.3 ($\text{CH}_3(6)$); 15.7 ($\text{CH}_3(4)$); 11.8 ($\text{CH}_3(2)$); HR-ESI-MS: 207.1377 ($[\text{M} + \text{H}]^+$, $\text{C}_{13}\text{H}_{19}\text{O}_2$; calc. 207.1380).

4-(3-Hydroxy-2-methoxy-6-methyl-phenyl) butyraldehyde (5c)—Pale yellow oil (63%). R_f 0.56 (hexane/EtOAc 7 : 3). IR (film): 3405, 2921, 2850, 1717, 1603, 1488, 1464, 1292, 1237, 1165, 1093, 1001, 810, 716, 628. $^1\text{H-NMR}$ (CDCl_3) 9.79 (t , J = 1.0, 1H, CHO); 6.82 (dd , J = 5.5, 0.4, 1H, H-Ar(5)); 6.74 (d , J = 5.5, 1H, H-Ar(4)); 3.77 (s , 3H, OCH_3); 2.67 (t , J = 5.0, 2H, H(4)); 2.50 (dt , J = 4.7, 1.0, 2H, H(2)); 2.24 (s , 3H, CH_3); 1.86 (q , J = 4.7, 2H, H(3)); $^{13}\text{C-NMR}$ (CDCl_3) 202.5 (CHO); 146.9 (ArC(2)); 145.6 (ArC(3)); 133.0 (ArC(6)); 128.7 (ArC(1)); 126.5 (ArC(4)); 113.4 (ArC(5)); 61.2 (OCH_3); 43.3 (C(2)); 26.1 (C(4)); 22.0 (C(3)); 18.8 (CH_3); HR-ESI-MS: 231.0994 ($[\text{M} + \text{Na}]^+$, $\text{C}_{12}\text{H}_{16}\text{O}_3\text{Na}$; calc. 231.0997).

4-(5-Hydroxy-2-methoxymethyl-phenyl)-butyraldehyde (5d)—Colorless oil (87%). R_f 0.28 (hexane/EtOAc 7 : 3). IR (film): 3400, 2920, 2848, 1713, 1609, 1490, 1460, 1292, 1223, 1158, 1096, 1021, 815, 710, 627. $^1\text{H-NMR}$ (CDCl_3) 9.76 (s , 1H, CHO); 7.14 (d , J = 5.4, 1H, H-Ar(3)); 6.63 (s , 1H, H-Ar(6)); 6.60 (d , J = 5.5, 1H, H-Ar(4)); 4.38 (s , 2H, CH_2OCH_3); 3.36 (s , 3H, CH_2OCH_3); 2.64 (t , J = 4.9, 2H, H(4)); 2.50 (t , J = 4.9, 2H, H(2)); 1.92 (q , J = 4.9, 2H, H(3)); $^{13}\text{C-NMR}$ (CDCl_3) 202.7 (C=O); 155.7 (ArC(5)); 142.2 (ArC(1)); 131.5 (ArC(2)); 127.6 (ArC(3)); 116.1 (ArC(4)); 112.8 (ArC(6)); 72.3 (CH_2OCH_3); 57.7 (CH_2OCH_3); 43.2 (C(2)); 31.3 (C(4)); 23.1 (C(3)); HR-ESI-MS: 231.0996 ($[\text{M} + \text{Na}]^+$, $\text{C}_{12}\text{H}_{16}\text{O}_3\text{Na}$; calc. 231.097).

4-(2-Allyl-5-hydroxy-phenyl)-butyraldehyde (5e)—Pale yellow oil (94%). R_f 0.56 (hexane/EtOAc 7 : 3). IR (film): 3419, 3076, 3008, 2933, 2864, 1721, 1638, 1476, 1339, 1254, 1157, 991, 913, 820, 758, 667. $^1\text{H-NMR}$ (CDCl_3) 9.76 (s , 1H, CHO); 7.54 (d , J = 8.2, 1H, H-Ar(3)); 6.98 (d , J = 8.2, 1H, H-Ar(4)); 6.70 (s , 1H, H-Ar(6)); 6.01–5.98 (m , 1H, $\text{CH}_2\text{CH}=\text{CH}_2$); 5.05 (d , J = 1.3, 1H, $\text{CH}_2\text{CH}=\text{CH}_2$); 5.00 ($br\ s$, 1H, $\text{CH}_2\text{CH}=\text{CH}_2$); 3.26 (d , J = 6.2, 2H, $\text{CH}_2\text{CH}=\text{CH}_2$); 2.63 (t , J = 5.6, 2H, H(4)); 2.16–2.12 (m , 2H, H(2)); 1.95–1.75 (m , 2H, H(3)); $^{13}\text{C-NMR}$ (CDCl_3) 202.9 (C=O); 154.8 (ArC(5)); 140.8 (ArC(1)); 137.0 (ArC(3)); 131.0 ($\text{CH}_2\text{CH}=\text{CH}_2$); 129.7 (ArC(6)); 129.4 (ArC(2)); 115.4 ($=\text{CH}_2$); 113.4 (ArC(4)); 43.4 (C(2)); 36.9 (C(4)); 32.4 ($\text{CH}_2\text{CH}=\text{CH}_2$); 19.7 (C(3)); HR-ESI-MS: 227.1048 ($[\text{M} + \text{Na}]^+$, $\text{C}_{13}\text{H}_{16}\text{O}_2\text{Na}$; calc. 227.1041).

4-(6-Allyl-3-hydroxy-2,4-dimethyl-phenyl)-butyraldehyde (5f)—White solid (80%). R_f 0.30 (hexane/EtOAc 8 : 2). IR (film): 3476, 3077, 2932, 2870, 1717, 1637, 1579, 1480, 1412, 1389, 1212, 1095, 912, 874, 684. $^1\text{H-NMR}$ (CDCl_3) 9.81 (t , J = 0.8, 1H, CHO); 6.80 (s , 1H, H-Ar(5)); 6.01–5.88 (m , 1H, $\text{CH}_2\text{CH}=\text{CH}_2$); 5.04 (dd , J = 6.3, 1.0, 1H, $\text{CH}_2\text{CH}=\text{CH}_2$); 4.96 (dd , J = 2.0, 1.0, 1H, $\text{CH}_2\text{CH}=\text{CH}_2$); 4.69 (d , J = 1.6, 1H, OH); 3.33 (d , J = 4.1, 2H, $\text{CH}_2\text{CH}=\text{CH}_2$); 2.64 (t , J = 5.5, 1H, H(4)); 2.62 (d , J = 4.1, 1H, H(4)); 2.54 (dt , J = 4.7, 0.8, 2H, H(2)); 2.24 (s , 3H, Ar(4) CH_3); 2.22 (s , 3H, Ar(2) CH_3); 1.83–1.76 (m , 2H, H(3)); $^{13}\text{C-NMR}$ (CDCl_3) 202.3 (C=O); 150.8 (ArC(3)); 129.4 (ArC(6)); 138.2 ($\text{CH}_2\text{CH}=\text{CH}_2$); 137.0 (ArC(1)); 129.4 (ArC(5)); 121.9 (ArC(2)); 120.6 (ArC(4)); 115.6 ($\text{CH}_2\text{CH}=\text{CH}_2$); 43.9 (C(2)); 37.3 ($\text{CH}_2\text{CH}=\text{CH}_2$); 28.8 (C(4)); 22.6 (C(3)); 15.8 (Ar(4) CH_3); 11.9 (Ar(2) CH_3); HR-ESI-MS: 233.1542 ($[\text{M} + \text{H}]^+$, $\text{C}_{15}\text{H}_{21}\text{O}_2$; calc. 233.1537).

4-(5-hydroxy-2-methylphenyl)-pentanal (5g)—Pale yellow oil (60%). R_f 0.25 (hexane/EtOAc 8 : 2). IR (film): 3386, 2961, 2930, 2868, 1716, 1610, 1585, 1497, 1460, 1258, 1238, 1026, 994, 870, 813, 716. $^1\text{H-NMR}$ (CDCl_3) 9.70 (t , J = 1.0, 1H, CHO); 6.99 (d , J = 5.3, 1H, H-Ar(3)); 6.67 (d , J = 1.8, 1H, H-Ar(6)); 6.58 (dd , J = 5.4, 1.8, 1H, H-Ar(4)); 2.98–2.95 (m , 1H, H(4)); 2.36 (dt , J = 5.0, 1.1, 2H, H(2)); 2.22 (s , 3H, Ar(2) CH_3); 1.91 (t , J = 4.8, 2H, H(3)); 1.21 (d , J = 4.5, 3H, CH_3 (4)); $^{13}\text{C-NMR}$ (CDCl_3) 202.6 (C=O); 154.2 (ArC(5)); 145.7 (ArC(1)); 131.3 (ArC(3)); 127.5 (ArC(2)); 112.8 (ArC(6)); 112.2

(ArC(4)); 42.1 (C(2)); 33.9 (C(4)); 29.5 (C(3)); 21.6 (CH₃(4)); 18.6 (Ar(2)CH₃); HR-ESI-MS: 193.1154 ([M + H]⁺, C₁₂H₁₇O₂; calc. 193.1150).

Synthesis of 6—Isopropyl triphenylphosphonium iodide (1.5–2 mmol) in THF (3.1 ml/mmole) was stirred and cooled at –78°. A solution of BuLi was added dropwise (1.6 M in THF, 1.5–2 mmol), and the reaction mixture was stirred for 0.5 h until it was let warmed to r.t. A typical orange-red coloration was observed as indication of deprotonation of the phosphonium salt. After 0.5 h, a solution of the corresponding aldehyde (1 mmol) in THF (0.94 ml/mmole) was added at –78° (0.5 h). The mixture was then kept warm 0.5 h more at r.t. and water was added. The mixture was extracted with Et₂O (3 × 10 ml). The combined organic extract was washed with brine, dried with anhydrous Na₂SO₄, and filtered. The filtrate was concentrated and the corresponding residues were purified by column chromatography to afford pure phenol olefins **6**.

4-Methyl-3-(5-methyl-hex-4-enyl)-phenol (6a)—Colorless oil (68%). *R*_f 0.56, (hexane/EtOAc 9 : 1), IR (film): 3347, 2935, 2865, 1609, 1595, 1467, 1376, 1221, 1150, 1070, 1027, 943, 867, 801. ¹H-NMR (CDCl₃) 6.97 (*d*, *J* = 8.1, 1H, H–Ar(5)); 6.63 (*br s*, 1H, H–Ar(2)); 6.56 (*dd*, *J* = 8.2, 2.2, 1H, H–Ar(6)); 5.16 (*t*, *J* = 6.8, 1H, H(4)); 2.52 (*t*, *J* = 7.8, 2H, H(1)); 2.21 (*s*, 3H, Ar(4)CH₃); 2.05 (*q*, *J* = 7.5, 2H, H(3)); 1.71 (*s*, 3H, CH₃(5)); 1.61 (*s*, 3H, H(6)); 1.59–1.54 (*m*, *J* = 7.3, 2H, H(2)); ¹³C-NMR (CDCl₃) 153.7 (ArC(1)); 142.4 (ArC(3)); 130.9 (ArC(5)); 127.9 (ArC(4)); 112.4 (ArC(6)); 115.7 (ArC(2)); 131.9 (C(5)); 124.3 (C(4)); 32.9 (C(1)); 30.2 (C(2)); 27.9 (C(3)); 25.7 (CH₃(5)); 17.7 (C(6)); HR-ESI-MS: 205.1516 ([M + H]⁺, C₁₄H₂₁O; calc. 205.1514).

2,4,6-Trimethyl-3-(5-methyl-hex-4-enyl)-phenol (6b)—Colorless oil (75%). *R*_f 0.74 (hexane/EtOAc 8 : 2). IR (film): 3502, 2964, 2920, 1581, 1476, 1447, 1374, 1205, 1086, 1010, 865. ¹H-NMR (CDCl₃) 6.78 (*s*, 1H, H–Ar(5)); 5.19 (*t*, *J* = 7.1, 1.3, 1H, H(4)); 4.47 (*br s*, 1H, OH); 2.58 (*dd*, *J* = 8.3, 3.1, 2H, H(1)); 2.22 (*s*, 3H, Ar(6)CH₃); 2.21 (*s*, 3H, Ar(4)CH₃); 2.20 (*s*, 3H, Ar(2)CH₃); 2.10 (*q*, *J* = 7.2, 2H, H(3)); 1.72 (*d*, *J* = 0.7, 3H, CH₃(5)); 1.64 (*s*, 3H, H(6)); 1.50–1.44 (*m*, 2H, H(2)); ¹³C-NMR (CDCl₃) 150.2 (ArC(1)); 138.4 (ArC(3)); 132.0 (C(5)); 129.6 (ArC(4)); 127.5 (ArC(5)); 124.3 (C(4)); 121.5 (ArC(2)); 119.7 (ArC(6)); 29.6 (C(1)); 29.5 (C(2)); 28.5 (C(3)); 25.7 (C(6)); 19.3 (C(6)CH₃); 17.8 (CH₃(5)); 15.7 (Ar(2)CH₃); 11.7 (Ar(4)CH₃); HR-ESI-MS: 233.1902 ([M + H]⁺, C₁₆H₂₅O; calc. 233.1827).

4-Methoxymethyl-3-(5-methyl-hex-4-enyl)-phenol (6d)—Oil (78%). *R*_f 0.22 (hexane/EtOAc 9 : 1). IR (film): 3354, 2928, 2861, 1610, 1586, 1502, 1451, 1377, 1227, 1161, 1096, 1074, 956, 930, 825. ¹H-NMR (CDCl₃) 7.14 (*d*, *J* = 8.4, 1H, H–Ar(5)); 6.64 (*d*, *J* = 2.5, 1H, H–Ar(2)); 6.58 (*dd*, *J* = 8.2, 2.6, 1H, H–Ar(6)); 5.32 (*br s*, 1H, Ar–OH); 5.16 (*tq*, *J* = 7.1, 1.4, 1H, H(4)); 4.39 (*s*, 2H, CH₂OCH₃); 3.37 (*s*, 3H, CH₂OCH₃); 2.60 (*t*, *J* = 7.9, 2H, H(1)); 2.05 (*q*, *J* = 7.2, 2H, H(3)); 1.71 (*d*, *J* = 1.1, 3H, CH₃(5)); 1.61 (*s*, 3H, H(6)); 1.61 (*q*, *J* = 7.3, 2H, H(2)); ¹³C-NMR (CDCl₃) 155.5 (ArC(1)); 143.6 (ArC(3)); 131.9 (ArC(4)); 131.1 (ArC(5)); 127.7 (C(5)); 124.3 (C(4)); 116.2 (ArC(2)); 112.5 (ArC(6)); 72.4 (CH₂OCH₃); 57.8 (CH₂OCH₃); 31.9 (C(1)); 31.2 (C(2)); 28.0 (C(3)); 25.7 (C(5)); 17.8 (C(6)); HR-ESI-MS: 235.1624 ([M + H]⁺, C₁₅H₂₃O₂; calc. 235.1620).

3-(1,5-Dimethyl-hex-4-enyl)-4-methyl-phenol (6g)—Colorless oil (64%). *R*_f 0.59 (hexane/EtOAc 8 : 2). IR (film): 3355, 2956, 2920, 1606, 1580, 1494, 1458, 1375, 1288, 1226, 1006, 945, 869, 808. ¹H-NMR (CDCl₃) 6.97 (*d*, *J* = 8.1, 1H, H–Ar(5)); 6.68 (*d*, *J* = 2.7, 1H, H–Ar(2)); 6.55 (*dd*, *J* = 8.1, 2.7, 1H, H–Ar(6)); 5.09 (*t*, *J* = 7.0, 1H, H–Ar(4)); 4.91 (*bs*, 1H, OH); 2.94–2.89 (*sextet*, *J* = 6.9, 1H, H(1)); 1.97–1.89 (*dt*, *J* = 7.4, 6.6, 2H, H(3)); 1.67 (*s*, 3H, CH₃(5)); 1.51 (*s*, 3H, H(6)); 1.63–1.54 (*dq*, *J* = 7.4, 1.2, 2H, H(2)); ¹³C-NMR

(CDCl₃) 154.0 (ArC(1)); 147.4 (ArC(3)); 131.6 (C(5)); 131.0 (ArC(5)); 127.5 (ArC(4)); 124.5 (C(4)); 112.3 (ArC(2)); 112.2 (ArC(6)); 37.7 (C(2)); 34.1 (C(1)); 26.1 (C(3)); 25.7 (Ar(5)CH₃); 21.5 (CH₃(1)); 18.6 (Ar(4)CH₃); 17.6 (C(6)); HR-ESI-MS: 219.1749 ([M + H]⁺, C₁₅H₂₃O; calc. 219.1671).

Synthesis of dienes 8—Ammonia (70 ml), was condensed into a flame, dried three-necked round bottom flask equipped with a dry-ice condenser, mechanical stirrer and maintained at −78°, under a positive pressure of dry nitrogen. A solution of **7** (2.4 g, 16.4 mmol) and *t*-BuOH (2 ml, 19 mmol) in ether (8 ml) was introduced *via* a double needle, and potassium (1.4 g, 36 mmol) was then added in small portions. The blue resulting suspension was stirred during 20 more min. To this suspension, anhydrous lithium bromide (3.14 g, 36 mmol) was then added and the mixture stirred vigorously for 30 min keeping the temperature at −78°. Finally, methyl iodide (32 mmol) was added, and the mixture was stirred for 15 min. The cooling bath was removed, and the ammonia was allowed to evaporate. The residue was diluted with brine (40 ml) and ether (30 ml), and the pH of the solution was adjusted to 7.5 by careful addition of 10% HCl. The aqueous layer was then separated and extracted with ether (4 × 25 ml) and EtOAc (4 × 25 ml). The combined ether extract was washed with brine, dried (anh. Na₂SO₄) filtered and evaporated to afford the corresponding diene-ketones **8**³⁾.

Synthesis of alcohols 9—The diene-ketone **8** (8.1 mmol) was solved in methanol (2 ml/mmole) and was cooled to −78°. NaBH₄ (9.7 mmol) was added portionwise, and the mixture was stirred until the reaction was completed (30 min., t.l.c.). The excess of reducing agent was destroyed by addition of water (4 ml) and brine (30 ml) at low temperature. The methanol was evaporated and the aqueous layer was extracted with ethyl ether (3 × 30 ml) and EtOAc (30 ml). The combined organic layer was washed with brine, dried, filtered and evaporated, affording the crude **9**.

Synthesis of benzoates 10—To a solution of **9** (1.41 g, 8.7 mmol) in pyridine (5 ml) (cooled to 0°), was added benzoyl chloride (1.0 ml, 8.7 mmol) and catalytic amount of DMAP. The reaction mixture was stirred overnight, poured into cold 10% HCl solution (25 ml), extracted with ether (3 × 30 ml) and EtOAc (1 × 30 ml). The combined ether extract was washed with saturated solution of NaHCO₃, water, and a 10% CuSO₄ solution, dried with anhydrous Na₂SO₄, filtered and evaporated affording the ester **10**.

Benzoic acid 8a-methyl-1,2,3,4,6,8a-hexahydro-naphthalen-1-yl ester (10a)—Oil (94%). *R*_f 0.79 (hexane/EtOAc 8 : 2). IR (film): 2935, 2862, 1717, 1602, 1451, 1315, 1272, 1174, 1114, 1099, 1070, 1026, 988, 937, 711. ¹H-NMR (CDCl₃) 8.07 (*dd*, *J* = 8.4, 1.5, 2H, H-Ar(2), H-Ar(6)); 7.54 (*t*, *J* = 7.1, 1H, H-Ar(4)); 7.42 (*t*, *J* = 7.7, 2H, H-Ar(3), H-Ar(5)); 6.29–6.26 (*m*, 1H, H(8)); 6.02 (*t*, *J* = 2.8, 1H, H(5)); 5.60–5.45 (*m*, 1H, H(7)); 4.96 (*dd*, *J* = 11.0, 4.9, 1H, H(1)); 2.64 (*br s*, 2H, H(6)); 2.31–2.29 (*m*, 2H, H(4)); 2.07–2.02 (*m*, 2H, H(2)); 1.85–1.75 (*m*, 2H, H(3)); 1.34 (*s*, 3H, CH₃); ¹³C-NMR (CDCl₃) 166.0 (C(O)); 139.4 (C(4a)); 132.8 (ArC(4)); 131.4 (ArC(1)); 129.6 (ArC(2)); 128.4 (ArC(3)); 126.1 (C(7)); 122.5 (C(8)); 119.3 (C(5)); 78.8 (C(1)); 40.0 (C(8a)); 31.4 (C(4)); 27.4 (C(6)); 26.8 (C(2)); 24.7 (CH₃); 20.1 (C(3)); HR-ESI-MS: 269.1461 ([M + H]⁺, C₁₈H₂₁O₂; calc. 269.1463).

Benzoic acid 5,7,8a-trimethyl-1,2,3,4,6,8a-hexahydro-naphthalen-1-yl ester (10b)—White solid (98%), m.p. 119.5° (EtOAc). *R*_f 0.80 (hexane/EtOAc 9 : 1). IR (film):

³⁾Compounds **8a**, **8d**, **8e** and **9a**, **9d**, **9e** are described in “Studies of Birch alkylation of substituted α-tetralones”. G. R. Labadie, R. M. Cravero, M. González-Sierra. *Synth Commun.* **2000**, *30*, 4065.

2969, 2932, 2863, 2810, 1717, 1601, 1451, 1368, 1315, 1269, 1174, 1115, 1101, 1070, 986, 910, 846, 712, 688. ¹H-NMR (CDCl₃) 8.09 (*dd*, *J* = 8.5, 1.5, 2H, H-Ar(2), H-Ar(6)); 7.57 (*tt*, *J* = 7.3, 1.5, 1H, H-Ar(4)); 7.46 (*t*, *J* = 7.0, 1.2, 2H, H-Ar(3), H-Ar(5)); 5.33 (*s*, 1H, H(8)); 4.84 (*dd*, *J* = 11.4, 4.6, 1H, H(1)); 2.50 (*d*, *J* = 6.1, 2H, H(6)); 1.99 (*dd*, *J* = 11.1, 3.0, 2H, H(4)); 1.82 (*dq*, *J* = 12.6, 2.1, 1H, H(2)); 1.74 (*dd*, *J* = 12.3, 4.6, 1H, H(2)); 1.69 (*s*, 3H, CH₃(5)); 1.61 (*s*, 3H, CH₃(7)); 1.42–1.36 (*m*, 2H, H(3)); 1.30 (*s*, 3H, CH₃(8a)); ¹³C-NMR (CDCl₃) 166.0 (C=O); 132.7 (C(8)); 131.7 (C(4a)); 131.0 (C(7)); 129.6 (ArC(4)); 129.2 (ArC(1)); 128.4 (ArC(2)); 126.4 (ArC(3)); 123.9 (C(5)); 79.5 (C(1)); 41.7 (C(8a)); 38.2 (C(6)); 27.4 (C(2)); 24.2 (C(4)); 24.1 (C(3)); 22.7 (CH₃(7)); 20.5 (CH₃(5)); 18.7 (CH₃(8a)); HR-ESI-MS: 297.1774 ([M + H]⁺, C₂₀H₂₅O₂; calc. 297.1776).

Benzoic acid 5-methoxy-8a-methyl-1,2,3,4,6,8a-hexahydro-naphthalen-1-yl ester (10c)—Oil (80%). *R*_f 0.83 (hexane/EtOAc 8 : 2). ¹H-NMR (CDCl₃) 8.06 (*dd*, *J* = 8.4, 1.3, 2H, H-Ar(2), H-Ar(6)); 7.56 (*tt*, *J* = 7.3, 1.3, 1H, H-Ar(4)); 7.45 (*tt*, *J* = 8.2, 1.3, 2H, H-Ar(3), H-Ar(5)); 5.59 (*s*, 1H, H(8)); 5.58 (*s*, 1H, H(7)); 4.94 (*dd*, *J* = 11.5, 4.6, 1H, H(1)); 3.53 (*s*, 3H, OCH₃); 2.82–2.76 (*m*, 2H, H(6)); 2.10–1.90 (*m*, 2H, H(4)); 1.90–1.78 (*m*, 2H, H(3)); 1.75–1.70 (*m*, 2H, H(2)); 1.33 (*s*, 3H, CH₃); ¹³C-NMR (CDCl₃) 168.1 (OC=O); 157.0 (OCH₃); 132.8 (ArC(4)); 129.9 (ArC(2)); 129.3 (ArC(1)); 128.6 (ArC(3)); 126.4 (C(8)); 121.5 (C(7)); 109.1 (C(4a)); 72.4 (C(1)); 68.8 (C(8a)); 55.4 (OCH₃); 39.2 (C(6)); 28.7 (C(2)); 26.7 (C(4)); 25.6 (C(3)); 15.2 (CH₃); HR-ESI-MS: 299.1567 ([M + H]⁺, C₁₉H₂₃O₃; calc. 299.1569).

Benzoic acid 8a-methoxymethyl-1,2,3,4,6,8a-hexahydro-naphthalen-1-yl ester (10d)—White solid (99%), m.p. 89° (EtOAc). *R*_f 0.5 (hexane/EtOAc 8 : 2). IR (film): 3064, 2933, 2863, 1787, 1723, 1599, 1452, 1272, 1213, 1173, 1040, 1017, 997, 778, 703. ¹H-NMR (CDCl₃) 8.05 (*dd*, *J* = 7.6, 1.5, 2H, H-Ar(2), H-Ar(6)); 7.68 (*tt*, *J* = 7.6, 2.1, 1H, H-Ar(4)); 7.53 (*t*, *J* = 7.9, 2H, H-Ar(3), H-Ar(5)); 5.83 (*ddt*, *J* = 8.5, 3.3, 1.8, 1H, H(7)); 5.70 (*br s*, 1H, H(5)); 5.65 (*dt*, *J* = 7.6, 1.8, 1H, H(8)); 5.01 (*dd*, *J* = 11.4, 4.9, 1H, H(1)); 4.05 (*d*, *J* = 9.3, 1H, CH₂OCH₃); 3.61 (*d*, *J* = 9.4, 1H, CH₂OCH₃); 3.43 (*s*, 3H, OCH₃); 2.71–2.68 (*m*, 2H, H(6)); 2.34 (*t*, *J* = 13.8, 2H, H(4)); 2.16–2.11 (*m*, 2H, H(3)); 1.89–1.86 (*m*, 2H, H(2)); ¹³C-NMR (CDCl₃) 162.4 (OC(O)Ph); 136.1 (C(4a)); 134.6 (ArC(4)); 130.6 (ArC(1)); 129.6 (ArC(2)); 128.9 (ArC(3)); 128.4 (C(8)); 125.7 (C(7)); 121.9 (C(5)); 79.0 (C(1)); 73.7 (CH₂OCH₃); 59.9 (OCH₃); 45.2 (C(8a)); 31.7 (C(4)); 27.7 (C(2)); 26.9 (C(3)); 24.9 (C(6)); HR-ESI-MS: 299.1565 ([M + H]⁺, C₁₉H₂₃O₃; calc. 299.1569).

Benzoic acid 8a-allyl-1,2,3,4,6,8a-hexahydro-naphthalen-1-yl ester (10e)—Pale green oil (99%). *R*_f 0.80 (hexane/EtOAc 9 : 1). IR (film): 3072, 2941, 2863, 1790, 1722, 1668, 1452, 1417, 1316, 1270, 1113, 913, 780, 711. ¹H-NMR (CDCl₃) 8.07 (*d*, *J* = 6.9, 2H, H-Ar(2), H-Ar(6)); 7.55 (*t*, *J* = 7.1, 1H, H-Ar(4)); 7.49 (*t*, *J* = 7.9, 2H, H-Ar(3), H-Ar(5)); 5.78–5.74 (*m*, 1H, CH₂CH=CH₂); 5.73–5.69 (*m*, 1H, H(8)); 5.68–5.58 (*m*, 1H, H(7)); 5.52–5.50 (*m*, 1H, H(5)); 5.12 (*br s*, 1H, CH₂CH=CH₂); 5.03 (*br s*, 1H, CH₂CH=CH₂); 5.0 (*d*, *J* = 1.3, 1H, H(1)); 2.80 (*dd*, *J* = 14.2, 7.9, 1H, CH₂CH=CH₂); 2.64 (*t*, *J* = 2.1, 2H, H(6)); 2.40 (*dd*, *J* = 14.2, 6.2, 1H, CH₂CH=CH₂); 2.30–2.10 (*tm*, *J* = 13.7, 1H, H(4)); 2.06–1.86 (*m*, 2H, H(2)); 1.87–1.78 (*m*, 2H, H(3)); 1.52 (*tt*, *J* = 13.5, 4.5, 1H, H(4)); ¹³C-NMR (CDCl₃) 165.8 (OC(O)Ph); 136.6 (C(4a)); 130.5 (ArC(1)); 130.4 (C(8)); 129.4 (ArC(4)); 129.2 (CH₂CH=CH₂); 128.7 (ArC(2)); 128.2 (ArC(3)); 128.7 (C(7)); 124.6 (C(5)); 116.0 (CH₂CH=CH₂); 78.9 (C(1)); 44.0 (C(8a)); 35.5 (CH₂CH=CH₂); 31.2 (C(4)); 27.0 (C(6)); 26.8 (C(2)); 24.5 (C(3)); HR-ESI-MS: 294.1616 ([M + H]⁺, C₂₀H₂₃O₂; calc. 294.1620).

Benzoic acid 8a-allyl-5,7-dimethyl-1,2,3,4,6,8a-hexahydro-naphthalen-1-yl ester (10f)—Pale yellow solid (95%), m.p. 82.5° (pentane/EtOAc 8 : 2). *R*_f 0.72 (hexane/EtOAc 9 : 1). IR (film): 3071, 2928, 2862, 1617, 1640, 1602, 1450, 1314, 1269, 1176, 1113,

1070, 1026, 989, 908, 869, 712, 688. $^1\text{H-NMR}$ (CDCl_3) 8.09 (*dd*, $J = 8.4, 1.2$, 2H, H–Ar(2), H–Ar(6)); 7.57 (*tt*, $J = 4.9, 1.2$, 1H, H–Ar(4)); 7.46 (*dt*, $J = 7.3, 1.2$, 2H, H–Ar(3), H–Ar(5)); 5.60–5.58 (*m*, 1H, $\text{CH}_2\text{CH}=\text{CH}_2$); 5.27 (*s*, 1H, H(8)); 5.02 (*dq*, $J = 17.2, 1.5$, 1H, $\text{CH}_2\text{CH}=\text{CH}_2$); 4.95 (*s*, 1H, $\text{CH}_2\text{CH}=\text{CH}_2$); 4.93 (*dd*, $J = 11.4, 4.9$, 1H, H(1)); 2.79 (*dd*, $J = 14.4, 8.2$, 1H, $\text{CH}_2\text{CH}=\text{CH}_2$); 2.48 (*d*, $J = 7.6$, 2H, H(6)); 2.58 (*d*, $J = 9.1$, 1H, H(4)); 2.38 (*dd*, $J = 14.4, 6.1$, 2H, $\text{CH}_2\text{CH}=\text{CH}_2$); 2.09–1.95 (*m*, 1H, H(4)); 1.95–1.80 (*m*, 3H, H(2), H(3)); 1.69 (*s*, 3H, $\text{CH}_3(5)$); 1.64 (*s*, 3H, $\text{CH}_3(7)$); 1.44–1.36 (*m*, 1H, H(3)); $^{13}\text{C-NMR}$ (CDCl_3) 165.9 (C=O); 135.2 ($\text{CH}_2\text{CH}=\text{CH}_2$); 132.8 (ArC(4)); 131.5 (C(4a)); 130.9 (C(7)); 129.0 (ArC(1)); 129.6 (ArC(2)); 128.4 (ArC(3)); 126.0 (C(5)); 124.4 (C(8)); 115.6 ($\text{CH}_2\text{CH}=\text{CH}_2$); 79.8 (C(1)); 45.7 (C(8a)); 36.2 ($\text{CH}_2\text{CH}=\text{CH}_2$); 38.5 (C(6)); 27.2 (C(2)); 24.1 (C(4)); 24.0 (C(3)); 22.7 ($\text{CH}_3(7)$); 18.6 ($\text{CH}_3(5)$); HR-ESI-MS: 323.1930 ($[\text{M} + \text{H}]^+$, $\text{C}_{22}\text{H}_{26}\text{O}_2$; calc. 323.1933).

Benzoic acid 4,8a-dimethyl-1,2,3,4,6,8a-hexahydro-naphthalen-1-yl ester (10g)

—Pale yellow oil (100%). R_f 0.84 (hexane/EtOAc 9 : 1). IR (film): 3025, 2962, 2933, 2873, 2858, 1718, 1601, 1585, 1491, 1452, 1376, 1335, 1313, 1173, 1109, 1039, 996, 985, 778, 710. $^1\text{H-NMR}$ (CDCl_3) 8.08 (*d*, $J = 5.6$, 2H, H–Ar(2)); 7.68 (*t*, $J = 5.0$, 1H, H–Ar(4)); 7.45 (*t*, $J = 5.0$, 2H, H–Ar(3)); 5.62 (*s*, 1H, H(8)); 5.72–5.56 (*m*, 1H, H(7)); 5.53–5.38 (*m*, 1H, H(5)); 4.94 (*ddd*, 1H, $J = 7.5, 6.3, 3.2$, H(1)); 2.67 (*d*, $J = 11.1$, 2H, H(6)); 2.48–2.32 (*m*, 1H, H(4)); 2.10–2.00 (*m*, 2H, H(2)); 1.92–1.76 (*m*, 2H, H(3)); 1.36 (*s*, 3H, $\text{CH}_3(8a)$); 1.06 (*d*, 3H, $J = 4.3$, $\text{CH}_3(4)$); $^{13}\text{C-NMR}$ (CDCl_3) 166.0 (C=O); 142.8 (C(4a)); 132.8 (ArC(4)); 130.8 (ArC(1)); 129.6 (ArC(2)); 128.9 (C(8)); 128.4 (ArC(3)); 122.2 (C(7)); 116.2 (C(5)); 79.1 (C(1)); 40.0 (C(8a)); 33.3 (C(6)); 31.9 (C(4)); 27.2 (C(2)); 26.9 (C(3)); 20.8 ($\text{CH}_3(4)$); 18.0 ($\text{CH}_3(8a)$); HR-ESI-MS: 283.1618 ($[\text{M} + \text{H}]^+$, $\text{C}_{19}\text{H}_{23}\text{O}_2$; calc. 283.1620).

Syntheses of 11—To a suspension of isopropyl triphenylphosphonium iodide (1 mmol) in THF (3 ml/mmol) at -78° , BuLi (1.6 M in THF, 1 mmol) was added dropwise. The reaction mixture was stirred at -78° for 1.5 h until it was slowly let warmed to r.t. After 1.5 h, the aldehyde **5** (1 mmol) dissolved in THF (0.94 ml/mmol) was added at -78° . 0.5 h later, the reaction mixture was then kept warm to r.t. for 1–3 h and water was added. The reaction was extracted with Et_2O (3×10 ml). The combined organic extract was washed with brine, dried (anhydrous Na_2SO_4), and finally filtered. The filtrate was concentrated *in vacuo* to afford phenol compounds **11a, e, h**.

5-Methyl-1,2,3,4-tetrahydro-naphthalene-1,8-diol (11a)—Pale yellow oil (60%). R_f 0.54 (hexane/EtOAc 7 : 3). IR (film): 3306, 2934, 2863, 1719, 1594, 1473, 1318, 1272, 1172, 1157, 1027, 991, 921, 837, 813, 756, 735. $^1\text{H-NMR}$ (CDCl_3) 7.51 (*s*, 1H, ArOH); 6.98 (*d*, $J = 8.1$, 1H, H(3)); 6.67 (*d*, $J = 8.4$, 1H, H(2)); 5.05 (*t*, $J = 6.3$, 1H, H(8)); 2.57 (*t*, $J = 5.4$, 2H, H(5)); 2.14 (*s*, 3H, CH_3); 1.92–1.83 (*m*, 2H, H(6)); 1.81–1.76 (*m*, 2H, H(7)); $^{13}\text{C-NMR}$ (CDCl_3) 154.5 (C(8)); 136.7 (C(4a)); 129.9 (C(6)); 27.6 (C(8a)); 123.9 (C(5)); 113.4 (C(7)); 67.9 (C(1)); 32.5 (C(2)); 27.1 (C(4)); 19.7 (C(3)); 19.0 (CH_3).

5-Allyl-1,2,3,4-tetrahydro-naphthalene-1,8-diol (11e)—Pale yellow oil (69%). R_f 0.51 (hexane/EtOAc 8 : 2). IR (film): 3351, 3077, 3005, 2935, 2866, 1637, 1593, 1473, 1333, 1271, 1252, 1158, 1071, 993, 913, 819, 757, 713, 667. $^1\text{H-NMR}$ (CDCl_3) 7.58 (*s*, 1H, ArOH); 7.00 (*d*, $J = 8.1$, 1H, H(3)); 6.71 (*d*, $J = 8.4$, 1H, H(2)); 5.91–5.85 (*m*, 1H, $\text{CH}_2\text{CH}=\text{CH}_2$); 5.05–5.01 (*m*, 1H, H(8)); 4.99–4.94 (*m*, 2H, $\text{CH}_2\text{CH}=\text{CH}_2$); 3.26 (*d*, $J = 6.0$, 2H, $\text{CH}_2\text{CH}=\text{CH}_2$); 2.64 (*t*, $J = 5.6$, 2H, H(5)); 2.17 (*s*, 2H, H(7)), 1.82–1.75 (*m*, 2H, H(6)); $^{13}\text{C-NMR}$ (CDCl_3) 155.0 (C(8)); 137.0 ($\text{CH}_2\text{CH}=\text{CH}_2$); 136.7 (C(4a)); 129.8 (C(6)); 123.7 (C(8a)); 115.4 ($\text{CH}_2\text{CH}=\text{CH}_2$); 114.3 (C(7)); 68.1 (C(1)); 36.9 ($\text{CH}_2\text{CH}=\text{CH}_2$); 32.7 (C(2)); 26.6 (C(4)); 19.8 (C(3)).

8-Methoxy-5-methoxymethyl-1,2,3,4-tetrahydro-naphthalen-1-ol (11h)—Oil (61%). R_f 0.87 (hexane/EtOAc 7 : 3). IR (film): 3305, 2930, 2860, 1594, 1471, 1318, 1272, 1173, 1156, 1117, 990, 921, 835, 812, 756, 735. $^1\text{H-NMR}$ (CDCl_3) 7.20 (d , $J = 8.4$, 1H, H(6)); 6.72 (d , $J = 8.4$, 1H, H(7)); 5.05 (t , $J = 4.4$, 1H, H(1)); 4.38 (d , $J = 0.7$, 2H, CH_2OCH_3); 3.88 (s , 3H, OCH_3); 3.36 (s , 3H, CH_2OCH_3); 2.84 (dt , $J = 17.3$, 5.0, H, H(4)); 2.64–2.61 (m , 1H, H(4)); 2.02–1.99 (m , 2H, H(2)); 1.83–1.77 (m , 2H, H(3)).

Antimicrobial Assay

All organisms were obtained from the American Type Culture Collection (Manassas, VA) and include the fungi *Candida albicans* ATCC 90028, *Candida glabrata* ATCC 90030, *Candida krusei* ATCC 6258, *Cryptococcus neoformans* ATCC 90113, and *Aspergillus fumigatus* ATCC 90906 and the bacteria *Staphylococcus aureus* ATCC 29213, methicillin-resistant *Staphylococcus aureus* ATCC 43300 (MRS), *Escherichia coli* ATCC 35218, *Pseudomonas aeruginosa* ATCC 27853, and *Mycobacterium intracellulare* ATCC 23068. Susceptibility testing was performed using a modified version of the CLSI methods [25–26] as described by Samoylenko *et al* [27]. All organisms are tested using modified versions of the CLSI (formerly NCCLS) methods. For all organisms excluding *M. intracellulare* and *A. fumigatus*, optical density is used to monitor growth [25], [26]. Media supplemented with 5% Alamar Blue™ (BioSource International, Camarillo, CA) is utilized for growth detection of *M. intracellulare* [28], [29] and *A. fumigatus* [30]. Samples (dissolved in DMSO) are serially-diluted in 20% DMSO/saline and transferred (10 μl) in duplicate to 96 well flat bottom microplates. Inocula are prepared by correcting the OD_{630} of microbe suspensions in incubation broth [RPMI 1640/0.2% dextrose/0.03% glutamine/MOPS @ pH = 6.0 (Cellgro) for *Candida spp.*, Sabouraud Dextrose for *C. neoformans*, cation-adjusted Mueller-Hinton (Difco) @ pH = 7.3 for *Staphylococcus spp.*, *E. coli*, and *P. aeruginosa*, 5% Alamar Blue™ (BioSource International, Camarillo, CA) in Middlebrook 7H9 broth with OADC enrichment, pH = 7.0 for *M. intracellulare*, and 5% Alamar Blue™/RPMI 1640 broth (0.2% dextrose, 0.03% glutamine, buffered with 0.165M MOPS at pH = 7.0) for *A. fumigatus* to afford an assay volume of 200 μl and final target inocula of: *Candida spp.* and *C. neoformans*: 1.5×10^3 , *M. intracellulare*: 2.0×10^6 , *Staphylococcus spp.*, *E. coli*, *P. aeruginosa*: 5.0×10^5 CFU/ml, and *A. fumigatus*: 2.7×10^4 CFU/ml. Final sample test concentrations are 1/100th the DMSO stock concentration. Drug controls [Ciprofloxacin (ICN Biomedicals, Ohio) for bacteria and Amphotericin B (ICN Biomedicals, Ohio) for fungi] are included in each assay. All organisms are read at either 530nm using the Biotek Powerwave XS plate reader (Bio-Tek Instruments, Vermont) or 544ex/590em, (*M. intracellulare*, *A. fumigatus*) using the Polarstar Galaxy Plate Reader (BMG LabTechnologies, Germany) prior to and after incubation: *Candida spp.* at 35°C for 46–50h, *Staphylococcus spp.*, *E. coli*, and *P. aeruginosa* at 35°C for 16–20h, *C. neoformans* at 35°C for 70–74h, *A. fumigatus* at 35°C for 46–50h, and *M. intracellulare* at 37°C and 10% CO_2 for 70–74h. IC_{50} s (concentrations that afford 50% inhibition relative to controls) are calculated using XLfit 4.2 software (IDBS, Alameda, CA) using fit model 201. The MIC is defined as the lowest test concentration that allows no detectable growth (for *M. intracellulare* and *A. fumigatus*, no color change from blue to pink). Minimum fungicidal or bactericidal concentrations are determined by removing 5 μl from each clear (or blue) well, transferring to agar and incubating as previously mentioned. The MFC/MBIC is defined as the lowest test concentration that kills the organism (allows no growth on agar). Drug controls ciprofloxacin (ICN Biomedicals, Ohio) for bacteria and amphotericin B (ICN Biomedicals, Ohio) for fungi were included in each assay.

Acknowledgments

The authors wish to express their gratitude to UNR (Universidad Nacional de Rosario) and Fundación J. Prats. This work was supported by CONICET (Consejo Nacional de Investigaciones Científicas y Técnicas) and ANPCYT

(Agencia Nacional de Promoción Científica y Técnica). M. F. P. thanks CONICET and UNL (*Universidad Nacional del Litoral-Santa Fe*) for a fellowship. We also thank Ms. Marsha Wright and Mr. John Trott at the National Center for Natural Products Research (University of Mississippi) for biological testing, which was supported by the NIH, NIAID, Division of AIDS, Grant No. AI 27094 and the USDA Agricultural Research Service Specific Cooperative Agreement No. 58-6408-2-0009. This investigation received financial support from the UNICEF/UNDP/WORLD BANK/WHO Special Programme for Research and Training in Tropical Diseases (TDR) to GRL.

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Figure 1. Retrosynthetic Plan towards Bisabolane Phenolic Sesquiterpenes

Scheme 1. Preparation of 4-phenylbutyraldehydes 5

Scheme 2. Synthesis of analogues 6

a) i. NH_3 , K, Et_2O , $t\text{-BuOH}$, -78° ; ii. LiBr; iii. RX, from -78° to r.t. b) NaBH_4 , MeOH, -78° , 30 min. c) PhCOCl , Py, DMAP, 0° , 2 h. d) PDC, $t\text{-BuOOH}$, Celite®, DCM. e) K_2CO_3 , MeOH, r.t., 36 h. f) Isopropyl triphenylphosphonium iodide (1.5–2 mmol), THF at -78° , 1.6 M BuLi (1.5–2 mmol) 0.5 h, r.t. 0.5 h., aldehyde (1 mmol) -78° (0.5 h), then 0.5 h. at r.t.

Scheme 3. Reaction Mechanism for the Preparation of 5

Scheme 4. Preparation of α -Tetralols 11

Isopropyl triphenylphosphonium iodide (1 mmol), THF, -78° , 1.6 M BuLi (1 mmol) 1.5 h, r.t., 1.5 h., aldehyde (1 mmol) dissolved in THF (0.94 ml/mmol) at -78° , 0.5 h, then r.t. for 1–3 h.

Table 1

Inhibitory Activities of Compounds 6a, 6b, 6d and 6g against C. albicans, C. glabrata, C. krusei, C. neoformans and A. fumigatus

Compound	IC ₅₀ /MIC/MFC (μg/ml) ^a				
	<i>C. albicans</i>	<i>C. glabrata</i>	<i>C. krusei</i>	<i>C. neoformans</i>	<i>A. fumigatus</i>
6a	NA/NA/NA	13.53/20.0/20.0	NA/NA/NA	5.45/20.0/20.0	19.53/NA/NA
6b	NA/NA/NA	7.4/20.0/20.0	NA/NA/NA	7.4/20.0/20.0	NA/NA/NA
6d	NA/NT/NT	NA/NT/NT	NA/NT/NT	8.55/NT/NT	NA/NT/NT
6g	11.0/20.0/20.0	3.0/10.0/10.0	13.6/NA/NA	5.0/10.0/10.0	10.2/NA/NA
Amphotericin B	0.5/1.25/2.5	0.7/1.25/1.25	0.8/1.25/2.5	0.8/2.5/2.5	0.8/1.25/5.0

^a) IC₅₀: concentration that affords 50% inhibition growth; *Minimum Inhibitory Concentration* (MIC): lowest concentration that allows no detectable growth; *Minimum Fungicidal Concentration* (MFC): lowest concentration that kills the organism; NA: not active at 20μg/ml; NT: not tested.

Table 2*IC₅₀, MIC and MBC of Compounds 6a, 6b, 6d and 6g toward S. aureus and MRSA*

Compound	IC ₅₀ /MIC/MBC (μg/ml) ^{a)}	
	<i>S. aureus</i>	MRSA
6a	11.18/20.0/NA	16.2/20.0/NA
6b	5.8/10.0/20.0	6.0/10.0/NA
6d	NA/NT/NT	NA/NT/NT
6g	5.6/10.0/10.0	5.9/10.0/NA
Ciprofloxacin	0.1/0.25/1.0	0.1/0.25/1.0

^{a)}IC₅₀: concentration that affords 50% inhibition growth; *Minimum Inhibitory Concentration* (MIC): lowest concentration that allows no detectable growth; *Minimum Bactericidal Concentration* (MBC): lowest concentration that kills the organism; NA: not active at 20μg/ml; NT: not tested.