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Article

Synthesis of Racemic and Chiral Albicanol, Albicanyl Acetate and Cyclozonarone: Cytotoxic Activity of *ent*-Cyclozonarone

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A síntese completa da mistura racêmica do cyclozonarone ((±)-**3**), foi obtida a partir do *E,E*-farnesol (**4**) em uma seqüência de oito passos com um rendimento geral de 6,6%. O albicanol ((±)-**1**) e seu acetato ((±)-**2**) são intermediários. Uma seqüência inicial, similar a partir do produto natural (-)-drimenol (**5**), produziu o(+)-albicanol (**1**) e o(+)-cyclozonarone (**3**) com 42% e 11%, respectivamente. A atividade citotóxica do composto(+)-cyclozonarone foi avaliada e mostrou alguma seletividade para MS-1 (células endoteliais de camundongos).

The total synthesis of racemic cyclozonarone ((±)-**3**) was achieved from *E,E*-farnesol (**4**) in an eight-step sequence in 6.6% overall yield. Albicanol ((±)-**1**) and its acetate ((±)-**2**) are intermediates. A similar sequence starting from natural (-)-drimenol (**5**) gave (+)-albicanol (**1**) and (+)-cyclozonarone (**3**) (42% and 11% yield, respectively). The cytotoxic activity of (+)-cyclozonarone was assayed and showed some selectivity towards MS-1 (mice endothelial cells).

Keywords: albicanol, albicanyl acetate, cyclozonarone, total synthesis, chiral synthesis

Introduction

Synthetic efforts towards naturally occurring drimane sesquiterpenes have been constant due to their interesting biological activities.

The drimane-type alcohol albicanol ((+)-**1**) (Figure 1) was isolated from the liverworts *Diplophyllum albilcans*[1] and later from the dorid nudibranch *Cadlina luteomarginata* together with its acetate ((+)-**2**) which has a potent fish antifeedant activity.[2]

Banerjee[3,4] has previously synthesized racemic albicanol in an eight-step sequence, in 13% yield, starting from a drimane keto alcohol, which in turn has to be prepared by a several-step route, in 58% yield, from a commercially available octalone.[5,6] The total synthesis of racemic (**1**) and (**2**) had already been accomplished, as well, by Weiler[7] through electrophilic cyclization of alkenic alkylsilanes, by a short three-step sequence in 30% yield, as a mixture of α and β isomers in C-9. Several asymmetric approaches to chiral **1** and **2** have been reported;[8-12] starting from higher terpenes with the *trans* decaline feature already constructed, such as manool,[8] or by routes involving optical resolution[9-11] and/or diasteroselective key steps, as reported by Shishido.[12]

Natural (-)-cyclozonarone (**3**) (Figure 1) has been isolated by Kurata *et al.*[13] from the Pacific brown algae *Dictyopteris undulata* and possesses a potent feeding-deterrent activity toward young abalones. We have previously established the absolute configuration of natural (-)-(5R,10R)-cyclozonarone ((**-**)**-3**) through a six-step route, starting from natural (-)-polygodial, leading us to the synthetic enantiomer (+)-(5S,10S)-cyclozonarone ((+)-**3**).[14] Later, (-)-cyclozonarone (**3**) was synthesized by Seifert *et al.*[15] starting from (+)-albicanol (**1**), which in turn was prepared in 9 steps from β-ionone.[16]

Results and Discussion

Our strategy started with *E,E*-farnesol where the cyclization of **4** led to (±)-drimenol (**5**) according to Welzel's procedure; Scheme 1.[17] Acetylation of drimenol ((±)**-5**) was performed as usually using Ac_2O and pyridine. The key step of the synthesis was the selenocatalytic allylic chlorination of drimenyl acetate ((±)-**6**);[18] leading to an

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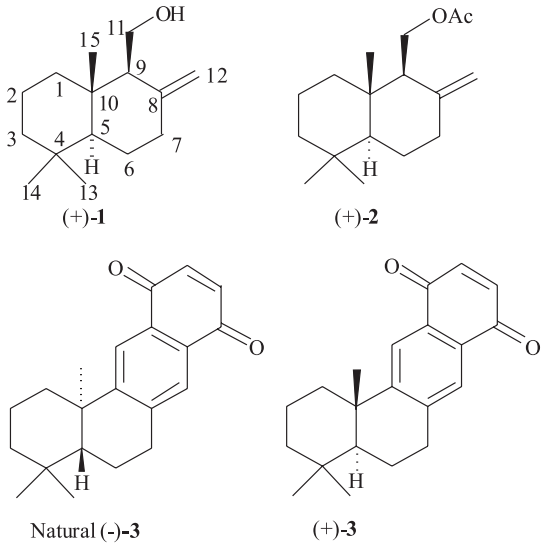


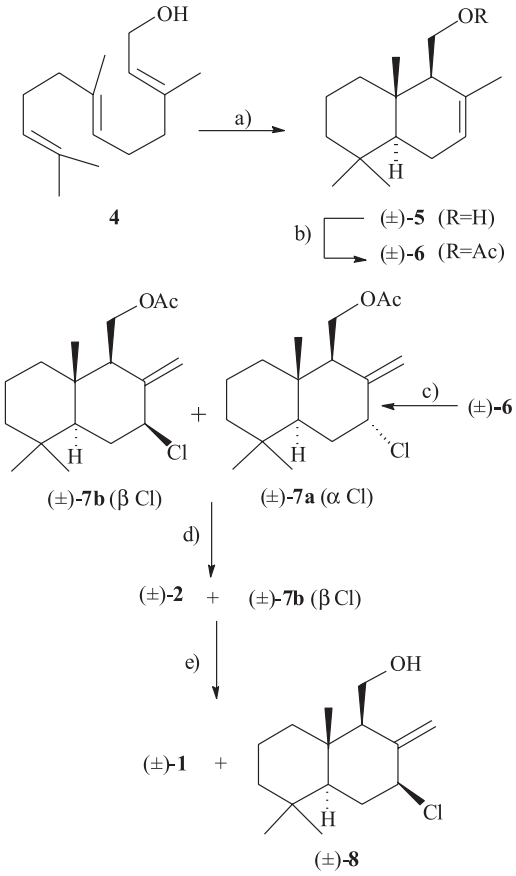
Figure 1. (+)-Albicanol (**1**), (+)-albicanyl acetate (**2**), cyclozonarone ((-)- **3**) and *ent*-cyclozonarone ((+)-**3**).

inseparable mixture of two chlorinated epimers (**7a** and **7b**) which was subjected to reduction with Zinc dust, to furnish racemic albicanyl acetate ((±)-**2**) and unchanged β- chlorinated epimer ((±)-**7b**). Treatment of the previous mixture ((±)-**2** and (±)-**7b**) with methanolic K_2CO_3 afforded (±)-**1** and (±)-**8** which were isolated and characterised by spectroscopic data analysis.

The more concluding data to establish (±)-**8** as the 7-β-chlorinated epimer, was the double doublet centred at 1.95 ppm for H-5, the constants (*J* 3.1 and 9.1 Hz) are corresponding to axial-equatorial and axial-axial couplings with each H-6. The signal centred at 2.29 ppm for H-6 eq (ddd, *J* 2.6, 5.0 and 12.6 Hz) evidenced an axial-equatorial coupling with H-5 and H-7ax, besides the geminal coupling. Moreover, the coupling constants for H-7 (signal centred at 4.35 ppm) suggest an axial disposition for this proton. Thus, confirming the equatorial disposition for the chloro atom in (±)-**8**. On the basis of a similar analysis for H-5, H-6 and H-7 on both chlorinated albicanyl acetate (**7a** and **7b**) the major epimer was assumed to have an axial chloro in C-7, while the minor epimer should correspond to the equatorial chloro in C-7.

The lack of reactivity for the equatorial chloro epimer towards Zn could be attributed to esteric hindrance for effective overlapping. Nevertheless, the ability of **7b** to react with Zn was confirmed submitting a sample of pure **7b** to the same experimental conditions as the epimeric mixture, although the reaction seems to be slower.

The possibility of readily preparing diene **9** from (±)-**1** prompted us to assay a different approach to (±)-cyclozonarone. (±)-Albicanol (**1**) was dissolved in pyridine and added to a mixture of Tf_2O in pyridine, the reaction yielded 62% of diene **9**. Racemic cyclozonarone

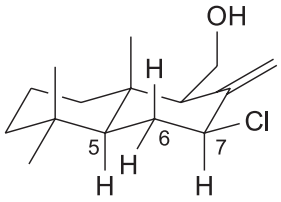


Scheme 1. Reagents and conditions. (a) HSO_3F, nitropropane:CH_2Cl_2 (5:1), -78°C, 1 h, 52% for (±)-**5**; (b) Ac_2O, Py, r.t. 91% for (±)-**6**; 86% for (+)-**6** from natural (-)-**5**; (c) PhSeCl, NCS, CH_2Cl_2, r.t., 3 h, 69% (for the epimeric mixture **7a** and **7b**) from (±)-**6**; 71% (for the epimeric mixture **7a** and **7b**) from (+)-**6**; (d) Zn dust, HOAc, THF, H_2O, r.t. 6 h (e) MeOH, K_2CO_3, r.t. 4 h, 71% (calculated from the epimeric mixture) for (±)-**1** after isolation from (±)-**8**; 69% (calculated from the epimeric mixture) for (+)-**1** after isolation from (-)-**8**.

was obtained from (±)-**9** and benzoquinone as previously described[14] (Scheme 2). Since racemic drimenol ((±)-**5**) has been previously resolved in its enantiomers[19] the sequence described represents a formal synthesis of both enantiomers of cyclozonarone.

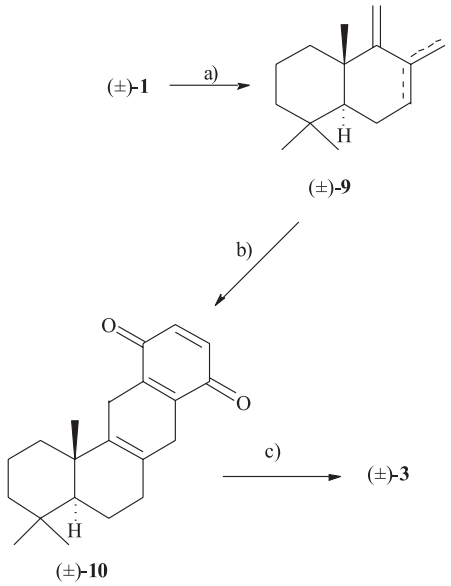
Starting from natural (-)-drimenol (**5**),[20] (+)-albicanol **1** and ent-cyclozonarone ((+)-**3**) were also prepared following the same sequence depicted in Schemes 1 and 2.

Our continuous interest in synthetic methods for cyclozonarone is grounded in the biological activities both enantiomers exhibit. Previously, the effect of *ent*-cyclozonarone ((+)-**3**), prepared in these laboratories, on the growth of *T. cruzi* epimastigotes, Tulahuen strains, was studied together with that of the reference drugs nifurtimox and benznidazole (made by Roche under the trade names Radanil™, Rochagan™ or Roganil™).[21] Compound (+)-**3** resulted ten times more active than the reference drugs. Recently, we have assayed cytotoxic



$J_{H5ax\text{-}H6eq}$ = 3.1 Hz; $J_{H5ax\text{-}H6ax}$ = 9.1 Hz;
$J_{H6eq\text{-}H7ax}$ = 5.0 Hz; $J_{H7ax\text{-}H6ax}$ = 12.6 Hz.

Figure 2. Significant coupling constants for (±)-**8**, characterised as 7β-chloro epimer.



Scheme 2. Reagents and conditions. (a) Tf_2O, Py, 0ºC→r.t., 40 min., 62% for (±)-**9** (mixture of *endo* and *exo* dienes 1:4); 60% for enantiopure **9** (mixture of *endo* and *exo* dienes 1:4); (b) *p*-benzoquinone, Bz, reflux, 28 h; (c) DDQ, reflux, 4 h, 46%, 2 steps (from (±)-**9** for (±)-**3**); 45%, 2 steps (for *ent*-cyclozonarone (+)-**3**).

activity of *ent*-cyclozonarone against cell lines A-549 (human lung carcinoma), HT-29 (human colon carcinoma), H-116 (human colon carcinoma), MS-1 (mice endothelial cells) and PC-3 (human prostate carcinoma), following the method reported by Bergeron *et al*.[22] The IC 50 obtained for the five mentioned cell lines are shown in Table 1, resulting that the activity against MS-1 cells is 10-50 times higher than towards other cell lines tested.

Table 1. Cytotoxic activity of *ent*-cyclozonarone **(+)-(11)**

Compound	A 549	HT 29	H 116	MS 1	PC 3
(+)-(**11**) IC_{50} /(μg mL^{-1})	5-1	1	5	0.5-0.1	5

Conclusions

Here, we have described a short total synthesis of racemic albicanol ((±)-**1**) (five steps, in 23% yield) and cyclozonarone ((±)-**3**) (eight steps, in 6.6% overall yield), starting from commercially available *E,E* farnesol. The key steps are the protonic cyclization of farnesol and the selenocatalytic allylic chlorination of drimenyl acetate ((±)-**6**)[18] to accomplish double bond isomerization. A similar sequence starting from natural (-)-drimenol (**5**) gave enantiopure (+)-**1** and (+)-**3** (42% and 11% respectively). Moreover, we have tested *ent*-cyclozonarone cytotoxic activity obtaining interesting IC50 values against all the cell lines assayed particularly MS-1 (the highest activity) and HT-29.

Experimental

General procedures

Melting points were determined on a Stuart Scientific SMP3 apparatus and are uncorrected. IR spectra were recorded on a Bruker Vector 22-FT in KBr disc or film. Optical rotations were obtained for $CHCl_3$ solutions in an Optical Activity, Ltd instrument in a 1 dm cell and their concentrations are expressed in g *per* mL. NMR spectra were recorded on a Bruker AC 200P (200.13 MHz for ^1H, 50.13 MHz for ^{13}C) in $CDCl_3$ solutions with TMS as internal standard. Carbon multiplicity was established by a DEPT pulse sequence and signals were assigned based on 2D experiments. All two-dimension spectra were acquired with a Bruker AVANCE 400 Spectrometer with a Bruker inverse 5 mm Z gradient probe. The HMBC spectra were obtained using the inv4gplrndqf pulse sequence in the Bruker software. HRMS were determined on a MAT 95XP, Thermo Finnigan spectrometer. Chromatographic separations were carried out on Merck silica gel 60 (230-400 Mesh) using hexane-ethylacetate gradients of increasing polarity. All organic extracts were dried over magnesium sulfate and evaporated under reduced pressure, below 65ºC.

*(±)-Drimenol (**5**)*

HSO_3F (0.08 mL, 1.35 mmol) was added, at –78 ºC, to a solution of (*E,E*)-farnesol (**4**) (300 mg, 1.35 mmol) in a mixture of nitropropane:CH_2Cl_2, 12:1 (13 mL). After stirring for 30 min the reaction mixture was quenched with $(C_2H_5)_3N$ (0.25 mL), diluted with water and extracted with EtOAc. The organic phase was dried ($MgSO_4$), filtered and the solvent was removed by simple distillation. The product was purified by column chromatography (hexane/EtOAc 8:2) to give (±)-**5** (156 mg, 52%) as a colourless oil. Spectroscopic characteristics (NMR) being identical to those of natural (-)-drimenol; IR (KBr) ν_{max}/cm^{-1}: 3356, 1032; HRMS (M^+) Found:222.19815. Calc. for $C_{15}H_{26}O$:222.19837.

*(±)- Drimenyl acetate (**6**)*

A mixture of (±)-**5** (474 mg, 2.1 mmol), pyridine (5 mL) and acetic anhydride (0.2 mL, 2.5 mmol) was stirred for 3 h at room temperature. The mixture was diluted with H_2O and extracted with EtOAc. The organic phase was washed with saturated aqueous solution of $KHSO_4$, dried ($MgSO_4$) and the solvent was evaporated. The residue was purified by column chromatography to afford (±)-**6** (513 mg, 91%) as a colourless oil, with identical spectroscopic characteristics as previously described for (+)-drimenyl acetate from natural (-)-drimenol.[23]

*7α and 7β-chloro-albicanyl acetate ((±)-**7a** and (±)-**7b**)*

Drimenyl acetate (±)-**6** (262 mg, 0.99 mmol) was added to a solution of commercially available phenylselenyl chloride (19 mg, 0.099 mmol) in CH_2Cl_2 (6 mL). N-chlorosuccinimide (146.38 mg, 1.1 mmol) in CH_2Cl_2 (5 mL) was added to the previously prepared mixture. After stirring for 2 h at room temperature, the solvent was removed and the residue was suspended in diethyl ether. The organic layer was decanted from the solid, washed with H_2O and brine, dried ($MgSO_4$) and the solvent was removed under reduced pressure. The resulting crude was purified by column chromatography to afford an inseparable C-7 epimeric mixture of (±)-**7a** and (±)-**7b** (204 mg, 69%). Signals assignable to the major epimer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.74 (s, 3H), 0.80 (s, 3H), 0.87 (s, 3H), 2.02 (s, CH_3COO, 3H), 2.60-2.66 (ddd, *J* 1.9 Hz, *J* 3.8 Hz and *J* 8.7 Hz, 1H), 4.09-4.19 (dd, *J* 8.7 Hz and *J* 11.3 Hz, 1H, H-11), 4.31-4.39 (dd, *J* 3.9 Hz and *J* 11.3 Hz,1H, H-11), 4.72 (d, *J* 1.7 Hz,1H, H-12), 4.84-4.87 (dd, *J* 2.8 Hz, 1H, H-7), 5.15 (d, *J* 1.7 Hz, 1H, H-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 33.4 (CH_2, C-1), 19.0 (CH_2, C-2), 38.6 (CH_2, C-3), 32.9 (C, C-4), 47.4 (CH, C-5), 41.7 (CH_2, C-6), 65.5 (CH, C-7), 145.6 (C, C-8), 49.0 (CH, C-9), 38.7 (C, C-10), 60.9 (CH_2, C-11), 111.6 (CH_2, C-12), 33.1 (CH_3, C-13), 21.8 (CH_3, C-14), 14.6 (CH_3, C-15), 171.2 (C=O, OAc), 21.6 (CH_3, CH_3COO). Signals assignable to the minor epimer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.78 (s, 3H), 0.83 (s, 3H), 0.92 (s, 3H), 2.02 (s, CH_3COO, 3H), 2.24-2.34 (ddd, *J* 2.5 Hz, *J* 5.1 Hz and *J* 12.5 Hz, 1H, H-6eq), 4.08-4.26 (dd, *J* 5.0 Hz and *J* 12.3 Hz, 1H, H-7), 4.17-4.27 (dd, *J* 9.1 Hz and *J* 11.2 Hz, 1H, H-11), 4.33-4.82 (dd, *J* 4.0 Hz and *J* 11.2 Hz,1H, H-11), 4.83 (d, *J* 1.4,1H, H-12), 5.51 (d, *J* 1.4, 1H, H-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.9 (CH_2, C-1), 19.0 (CH_2, C-2), 38.6 (CH_2, C-3), 33.6 (C, C-4), 54.6 (CH, C-5)*, 41.7 (CH_2, C-6), 63.5 (CH, C-7), 144.1 (C, C-8), 54.9 (CH, C-9)*, 38.7 (C, C-10), 61.1 (CH_2, C-11), 108.9 (CH_2, C-12), 33.5 (CH_3, C-13), 21.1 (CH_3, C-14), 15.1 (CH_3, C-15), 171.3 (C=O, OAc), 21.6 (CH_3, CH_3COO). *Signals may be interchanged. HRMS (M^+) (mixture of epimers) Found: 298.16976 . Calc. for $C_{17}H_{27}ClO_2$: 298.16996.

*(±)-Albicanol (**1**)*

Zn dust (433 mg, 6.62 mmol) was added to a solution of the mixture of epimers (±)-**7** (241 mg, 0.81 mmol) in HOAc (4.05 mL), THF (5.6 mL) and H_2O (2.3 mL). This mixture was stirred at room temperature for 6 h. The solution was diluted with diethyl ether and the organic phase was decanted from the solid, washed with saturated $NaHCO_3$ aqueous solution, water and dried ($MgSO_4$); the solvent was removed under reduced pressure. After column chromatography on silica gel, 192 mg of an inseparable mixture of albicanyl acetate ((±)-**2**) and the β chlorinated epimer ((±)-**7b**) was obtained. Saponification of the former mixture with K_2CO_3/ MeOH and usual work up, gave after column chromatography 40 mg of 7β-chloro-albicanol ((±)-**8**); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.73 (s, 3H), 0.80 (s, 3H), 0.90 (s, 3H), 1.05-1.65 (m, 8H, H-1, H-2, H-3, H-6ax and H-9), 1.94-1.97 (dd, *J* 3.1 Hz and *J* 9.1 Hz, 1H, H-5), 2.26-2.32 (ddd, *J* 2.6 Hz, *J* 5.0 Hz and *J* 12.6 Hz, 1H, H-6eq), 3.80-3.85 (dd, *J* 8.1 Hz and *J* 10.3 Hz, 1H, H-11), 3.87-3.91 (dd, *J* 3.7 Hz and *J* 10.3 Hz, 1H, H-11), 4.33-4.37 (dd, *J* 5.0 Hz and *J* 12.6 Hz, 1H, H-7ax), 4.92 (bs, 1H, H-12), 5.58 (bs, 1H, H-12). ^{13}C NMR ($CDCl_3$, 100MHz) δ 38.5 (CH_2, C-1), 19.0 (CH_2, C-2), 41.7 (CH_2, C-3), 33.6 (C, C-4), 58.8 (CH, C-5), 36.1 (CH_2, C-6), 63.6 (CH, C-7), 145.0 (C, C-8), 55.1 (CH, C-9), 38.6 (C, C-10), 58.5 (CH_2, C-11), 108.0 (CH_2, C-12), 33.4 (CH_3, C-13), 21.6 (CH_3, C-14), 15.3 (CH_3, C-15) and 128 mg (71% from mixture of epimers **7**) of (±)-albicanol (**1**); mp 68.2-68.8 ºC (hexane) (lit[2] mp 68-69 ºC); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.69 (s, 3H), 0.78 (s, 3H), 0.85 (s, 3H), 1.94-2.04 (m, 2H, H-7ax, H-9), 2.38-2.45 (ddd, *J* 2.4 Hz, *J* 4.2 Hz and *J* 12.9 Hz, 1H, H-7eq), 3.70-3.76 (d, *J* 11.0 Hz, 1H, H-11), 3.80-3.87 (dd, *J* 4.0 Hz and *J* 11.0 Hz, 1H, H-11), 4.64 (d, *J* 1.7 Hz, 1H, H-12), 4.94 (d, *J* 1.7 Hz, 1H, H-12); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 39.1 (CH_2, C-1), 19.2 (CH_2, C-2), 41.9 (CH_2, C-3), 33.5 (C, C-4), 55.2 (CH, C-5), 24.2 (CH_2, C-6), 37.9 (CH_2, C-7), 147.9 (C, C-8), 59.1 (CH, C-9), 39.0 (C, C-10), 58.8 (CH_2, C-11), 106.3 (CH_2, C-12), 33.6 (CH_3, C-13), 21.8 (CH_3, C-14), 15.3 (CH_3, C-15). HRMS (M^+) Found : 222.19726. Calc. for $C_{15}H_{26}O$: 222.19863.

*(±)-Albicanyl acetate (**2**)*

(±)-Albicanol (**1**) was acetylated as described for (±)-drimenol to give 220 mg (83%) of (±)-**2** as an oil with identical spectroscopic characteristics as previously described for natural (+)-albicanyl acetate.[2] HRMS (M^+) Found: 264.20887. Calc. for $C_{17}H_{28}O_2$: 264.20893.

Diene (±)-(**9**). A solution of triflic anhydride (0.22 mL) in pyridine was added dropwise to a solution of albicanol ((±)-**1**) (63 mg, 0.3 mmol) in pyridine (10 mL) at 0 ºC. The mixture was stirred for 40 min at room temperature.

An ice-water mixture was added and the solution was neutralized with $NaHCO_3$ and extracted with ethyl ether. The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuum. The crude was purified by column chromatography to afford an oily product (38 mg, 62%) as a mixture of *endo* and *exo* dienes (1:4). Spectral data of the major isomer is in good agreement with those reported for *exo*-diene (**9**).[14]

*(±)-Cyclozonarone (**3**)*

Benzoquinone (27.5 mg, 0.25 mmol) was added to a solution of diene (±)-**9** (1:4 mixture of *endo* and *exo* dienes) (40 mg, 0.19 mmol) in benzene (10 mL) and the mixture was refluxed under N_2 atmosphere for 28 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography to afford 21 mg of quinone **10**, which was eluted after the unchanged *endo*-diene. Quinone **10** was dissolved in benzene (10 mL) and DDQ (15 mg, 0.062 mmol) was added. The mixture was refluxed for 4 h and after removing the solvent under reduced pressure and column chromatography, (±)-cyclozanorone (**3**) 18.2 mg, (46% overall yield from (±)-**9**) was obtained as a yellow oil, with identical spectroscopic characteristics as previously described for natural (-)-cyclozonarone.[13] The same protocol was used for the synthesis of (+)-cyclozonarone (**3**) starting from natural (-)-drimenol.[20]

*(+)-Drimenyl acetate (+)-**6***

Acetylation of (-)-drimenol (1.5 g, 6.76 mmol) using standard condition furnished drimenyl acetate as colourless oil (1.53 g, 86%). Physical and spectroscopic characteristics were in good agreement with those previously described.[23] $[\alpha]^{28}_D$ + 7.69 (*c* 5.2, $CHCl_3$).

*7α and 7β-chloro-albicanyl acetate (**7a** and **7b**)*

Allylic chlorination of (+)-drimenyl acetate (200 mg, 0.09 mmol) gave an inseparable mixture of 7α and 7β-chloro-albicanyl acetate (**7a** and **7b**) (160.2 mg, 71%) as a white solid; mp 76.9-82.7 ºC; $[\alpha]^{22}_D$ – 57.8 (*c* 6.4, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr pellets): 1731, 1241, 918, 721; HRMS (M^+) Found: 298.16808. Calc. for $C_{17}H_{27}ClO_2$: 298.16995.

*Mixture of 7-β-chloro-albicanyl acetate (+)-**7b** and albicanyl acetate (+)-**2***

Reduction with Zn/HOAc/H_2O of **7** (mixture of epimers) (106 mg, 0.36 mmol) afforded 77 mg of a mixture of albicanyl acetate ((+)-**2**) and unchanged 7β-chloro-albicanyl acetate (**7b**), as an oil. Isolation by preparative TLC afforded 53 mg (66.3 %) of (+)-albicanyl acetate (**2**); $[\alpha]^{22}_D$ + 24.8º (*c* 4.83, $CHCl_3$); IR ν_{max}/cm^{-1} (film KBr): 2928, 1740, 1235 ; and 23mg (28.8 %) of unchanged 7β-chloro-albicanyl acetate ((+)-**7b**); $[\alpha]^{22}_D$ + 25.2º (*c* 1.59, $CHCl_3$); IR ν_{max}/cm^{-1} (KBr pellets): 2942, 1731, 1240, 907.

*(+)-Albicanol (+)-**1***

Saponification of the reduction mixture (250 mg) followed by column chromatography gave 170 mg of (+)-albicanol (**1**) as colourless needles; mp 67.5-68.3 ºC (lit[2] mp 68-69 ºC); $[\alpha]^{22}_D$ + 9.1º (*c* 2.21, $CHCl_3$) (lit[2] $[\alpha]^{25}_D$ + 13.0º (*c* 0.5, $CHCl_3$); HRMS (M+) Found: 222.19726. Calc. for $C_{15}H_{26}O$: 222.19836; IR ν_{max}/cm^{-1} (KBr pellets): 3371, 2941, 1691, 1644, 880; and 7-β-chlorol-albicanol ((-)-**8**) (52 mg) as colourless needles; mp 89.7-91.6 ºC; $[\alpha]^{28}_D$ – 2.8º (*c* 3.6, $CHCl_3$); IR (KBr): ν_{max}/cm^{-1} 3265, 2925, 1650, 1460.

*Diene (**9**)*

Dehydration of (+)-albicanol (**1**) (94.1 mg, 0.42 mmol) afforded 52 mg, (60%) of diene **9** (mixture of *exo* and *endo* diene 1:4) as an oily product. Spectral data of the major isomer is in good agreement with those formerly reported by us for exo-diene (**9**).[14]

(+)-Ent-cyclozonarone

Diels Alder reaction of diene mixture (52 mg, 0.25 mmol) with *p*-benzoquinone (35.13 mg, 0.33 mmol) followed by oxidation of the corresponding quinone with DDQ (27.4 mg, 0.12 mmol) gave (+)-*ent*-cyclozonarone (35.3 mg, 45%) as oil. IR(KBr): ν_{max}/cm^{-1} 2924, 1669, 1600, 1460; ^{1}H-NMR and ^{13}C NMR spectra identical to those of natural (-)-cyclozonarone.[13]

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Supplementary Information

Available free of charge at http://jbcs.org.br, as PDF file.

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Synthesis of Racemic and Chiral Albicanol, Albicanyl Acetate and Cyclozonarone. Cytotoxic Activity of *ent*-Cyclozonarone

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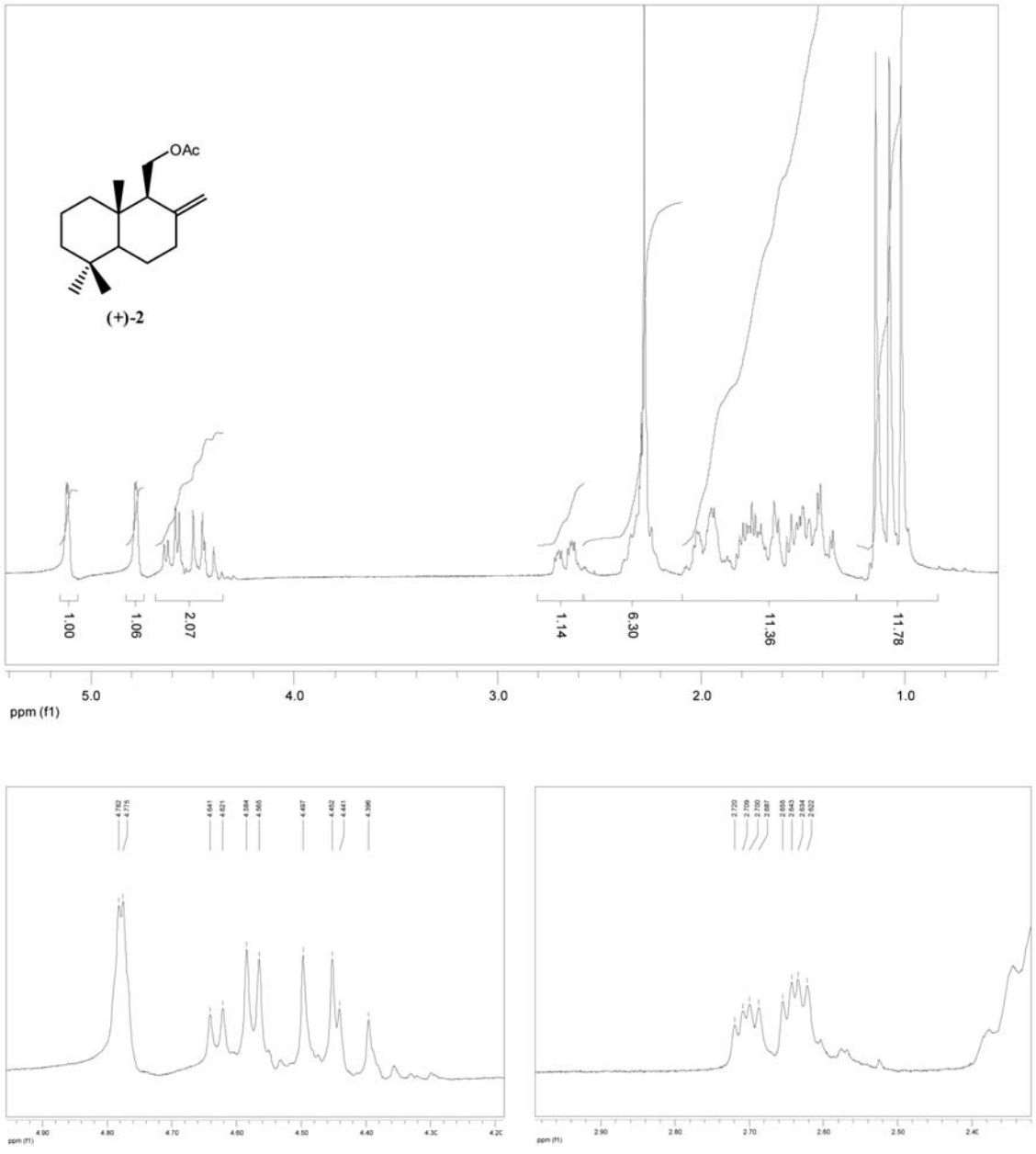

Figure S1. ^{1}H NMR for albicanyl acetate (+)-**2**.

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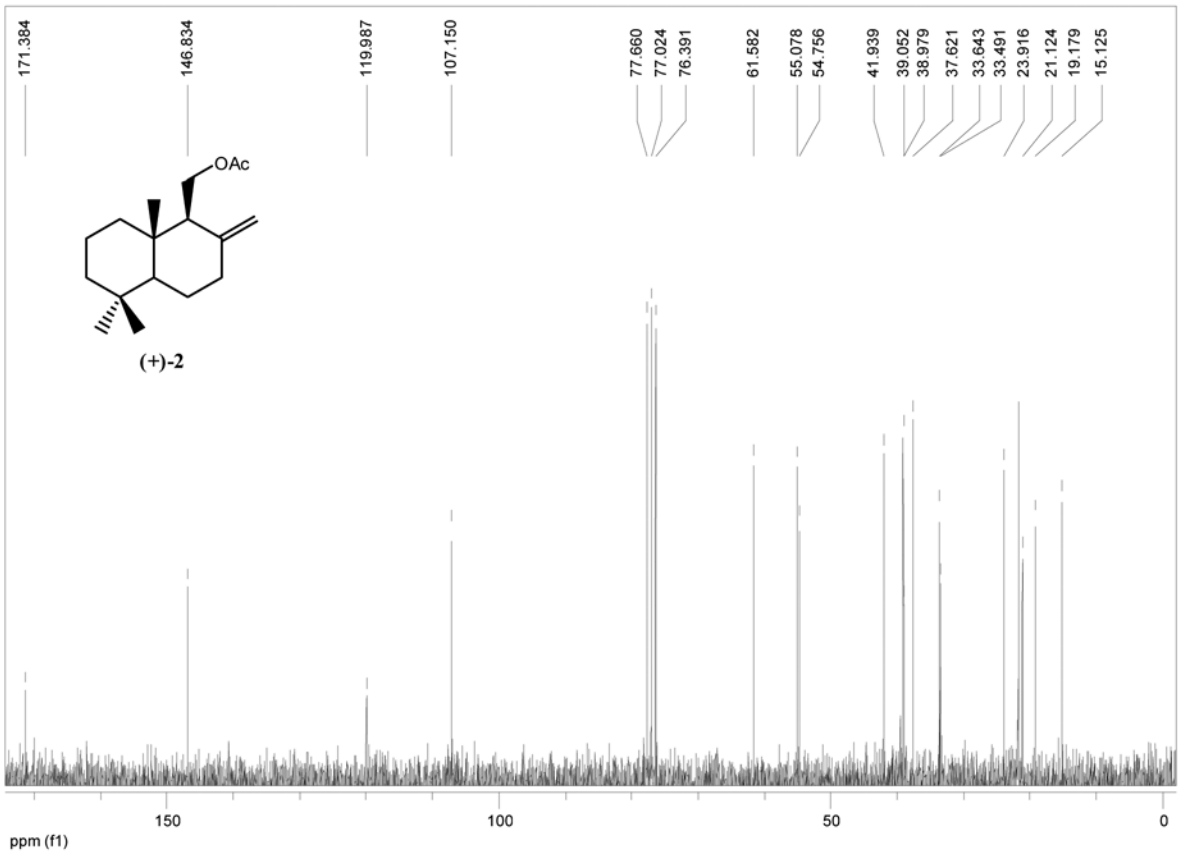

Figure S2. ^{13}C NMR for albicanyl acetate (+)-**2**.

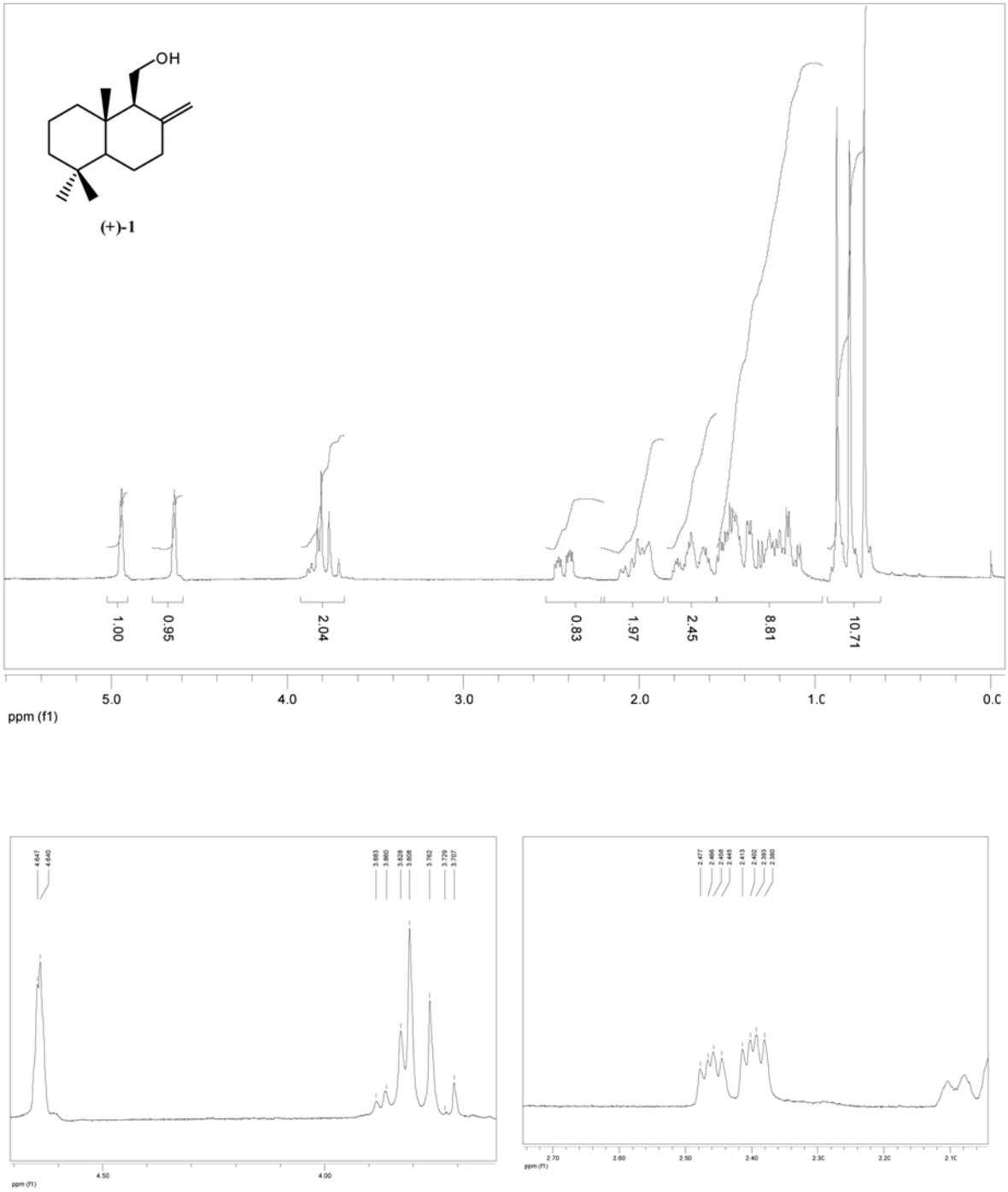

Figure S3. ^{1}H NMR for albicanol (+)-**1**.

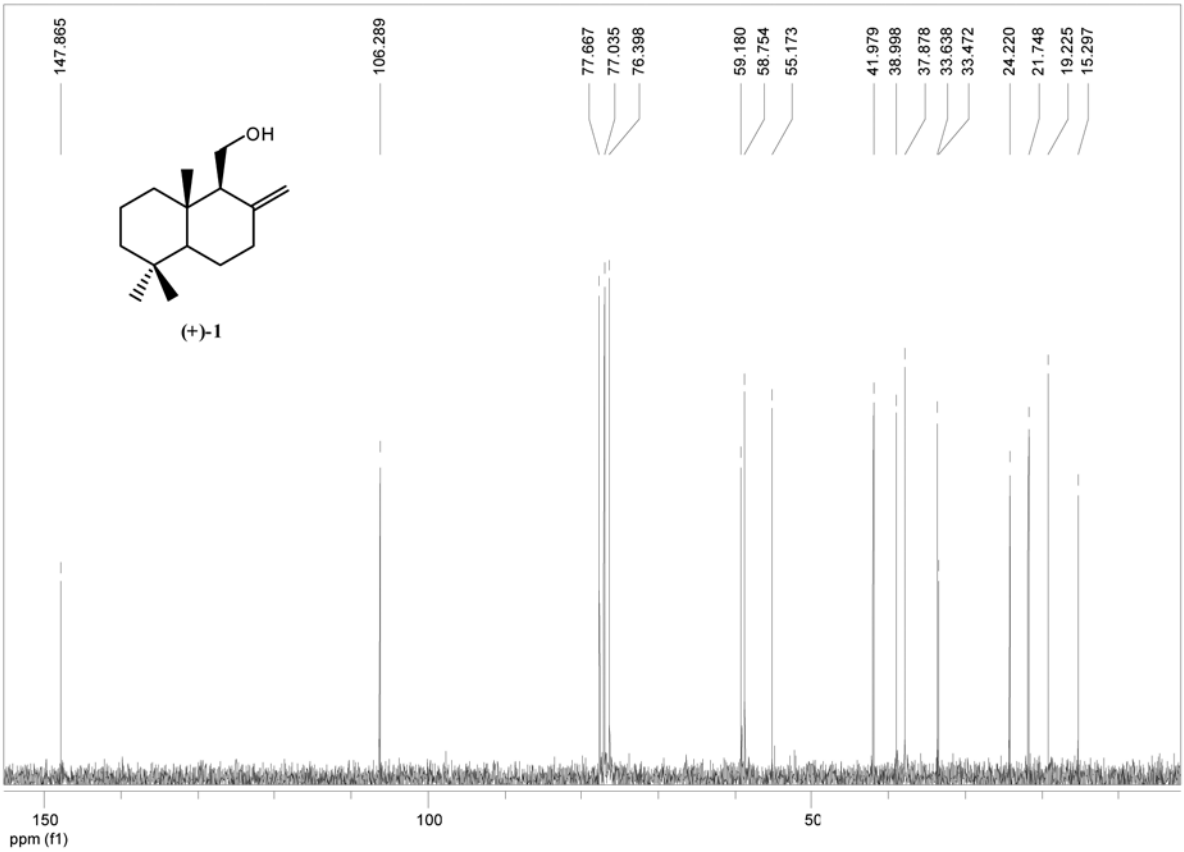

Figure S4. ^{13}C NMR for albicanol (+)-**1**.

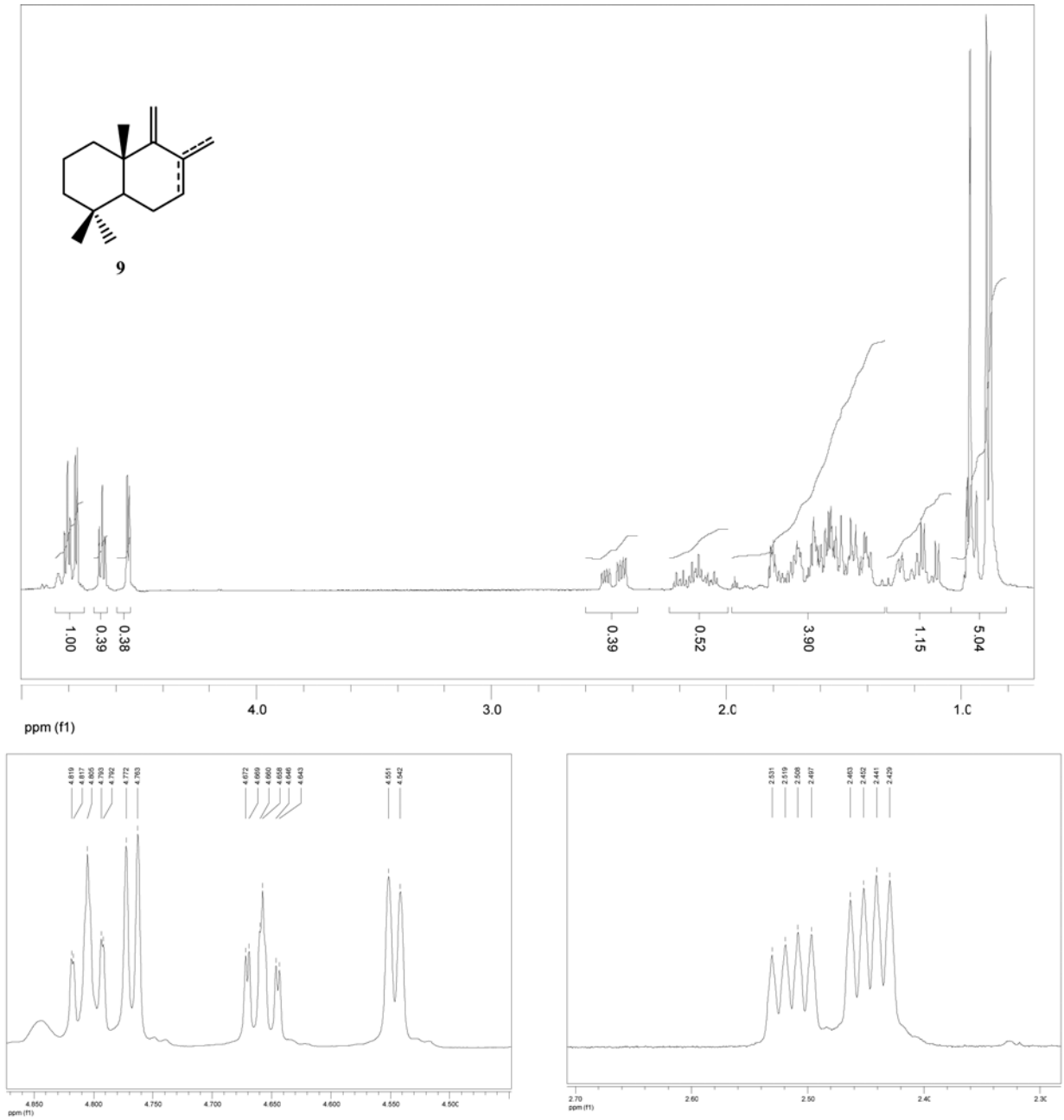

Figure S5. ^{1}H NMR for diene **9** (*endo*:*exo* / 1:4).

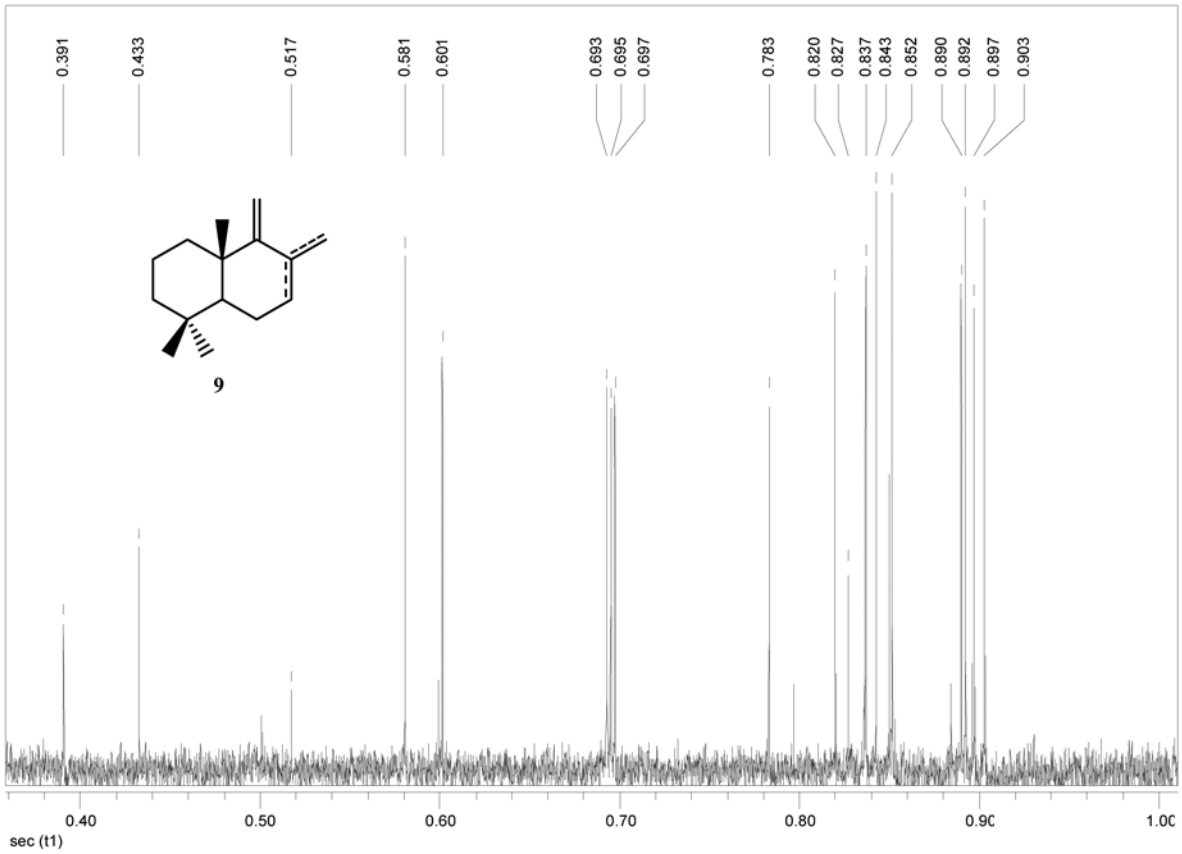

Figure S6. ^{13}C NMR for diene **9** (*endo*:*exo* / 1:4).

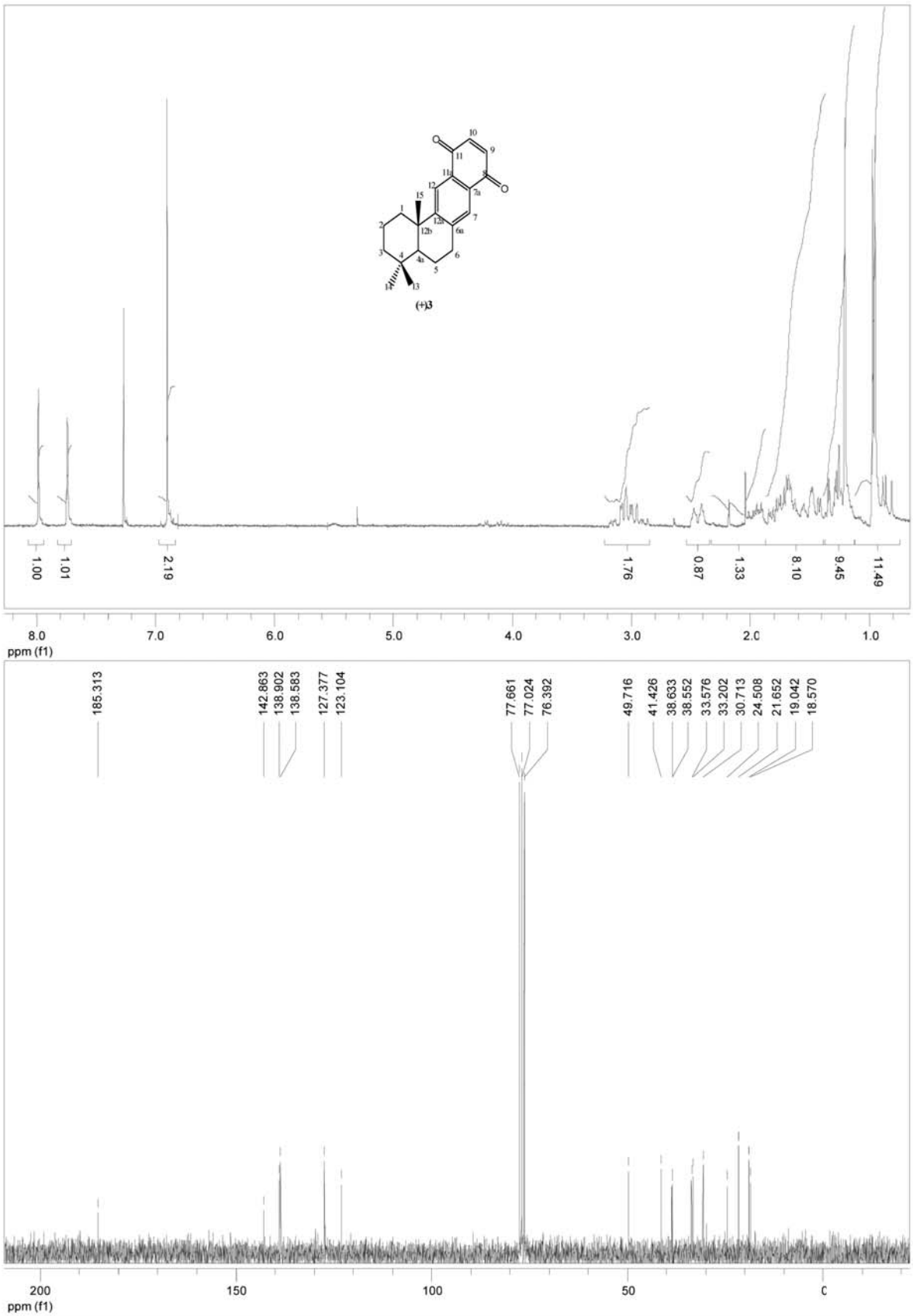

Figure S7. ^{1}H NMR and ^{13}C-NMR for *ent*-cyclozonarone (+)-**3**.

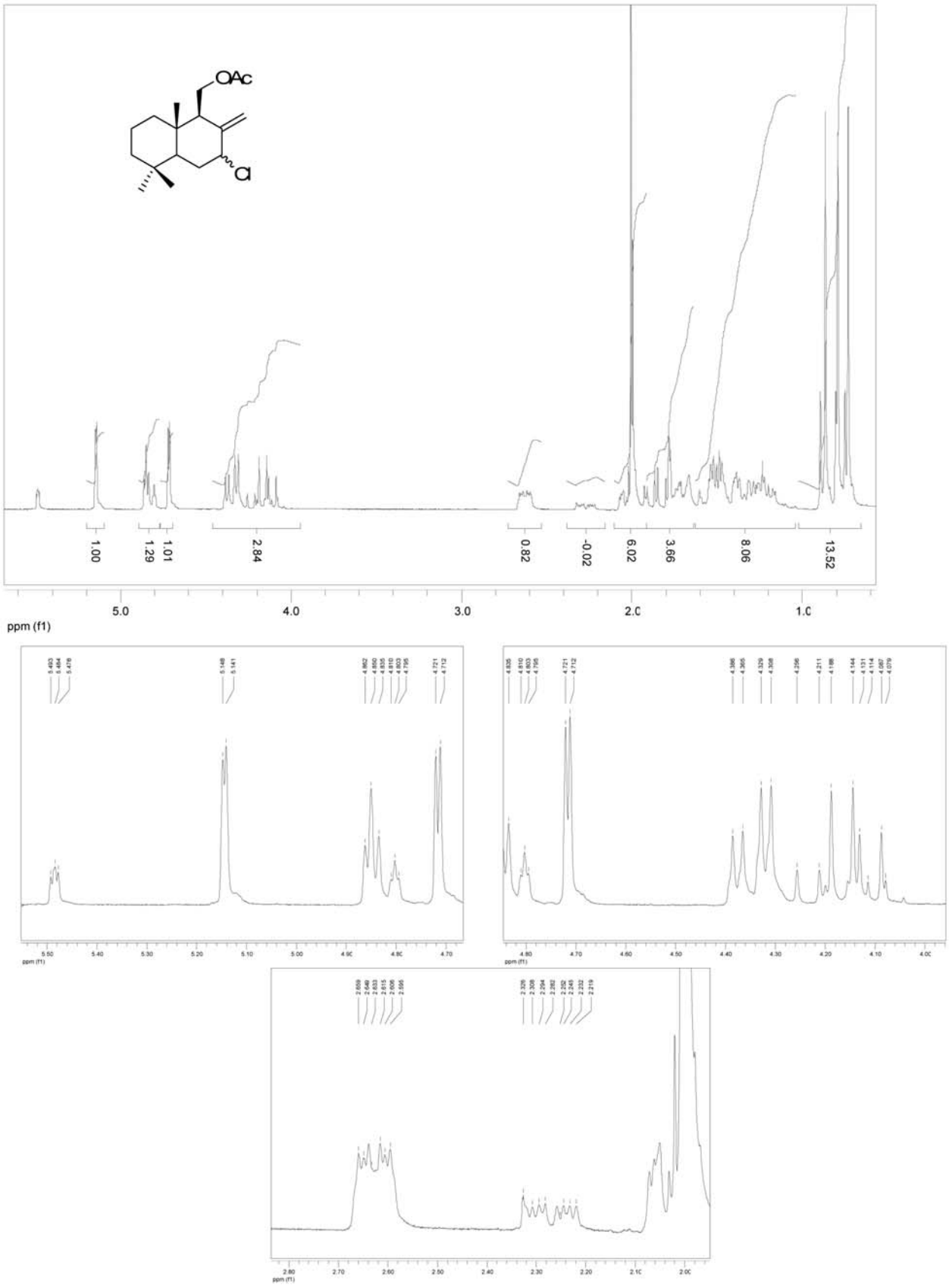

Figure S8. ^{1}H NMR for 7α and 7β-chloro-albicanyl acetate (±)-**7a** and (±)-**7b**.

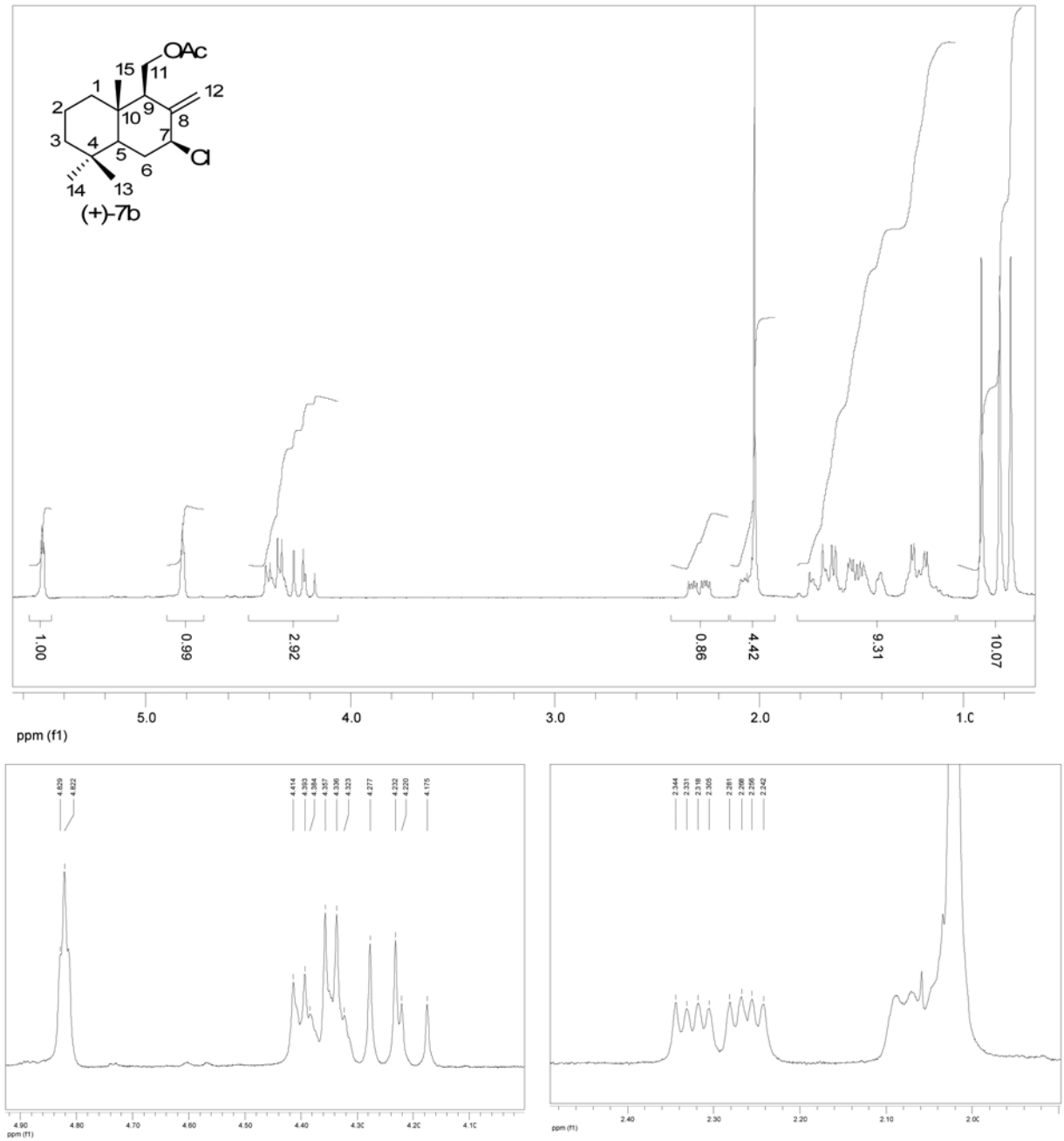

Figure S9. ^{1}H NMR for (+)-**7b** (unchanged epimer after 7α +7β reduction with Zn).

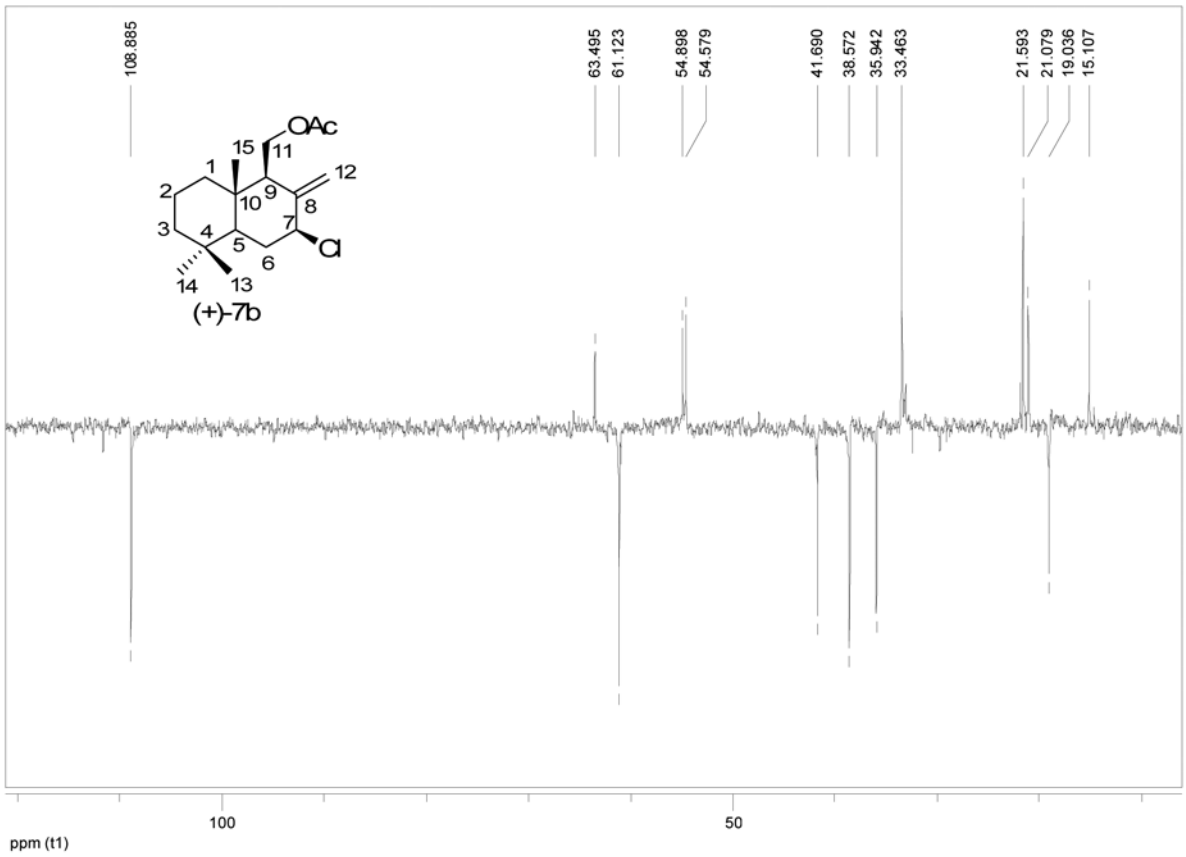

Figure S10. ^{13}C DEPT for (+)-**7b**.

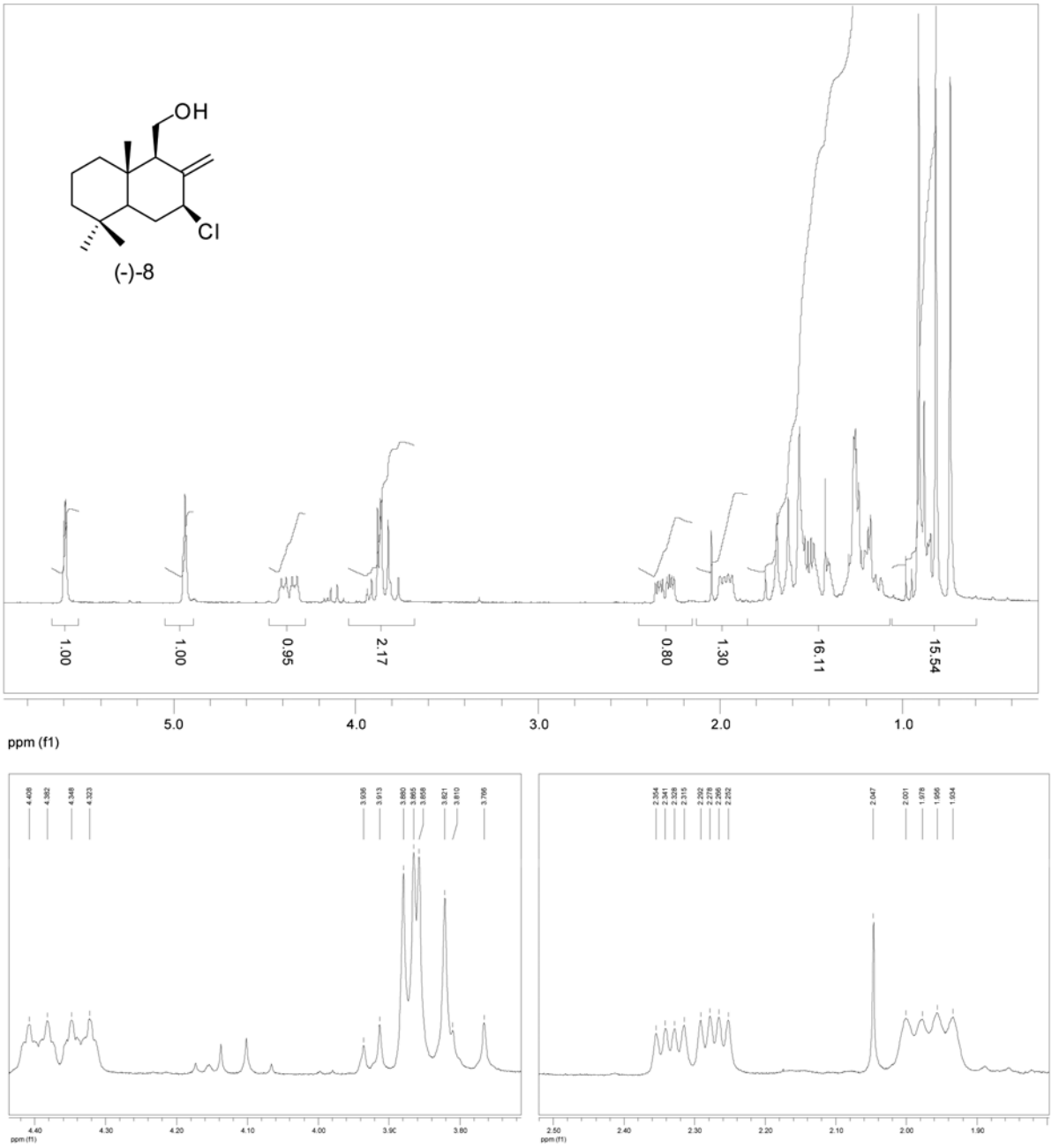

Figure S11. ^{1}H NMR for 7β-chloro-albicanol (-)-**8**.

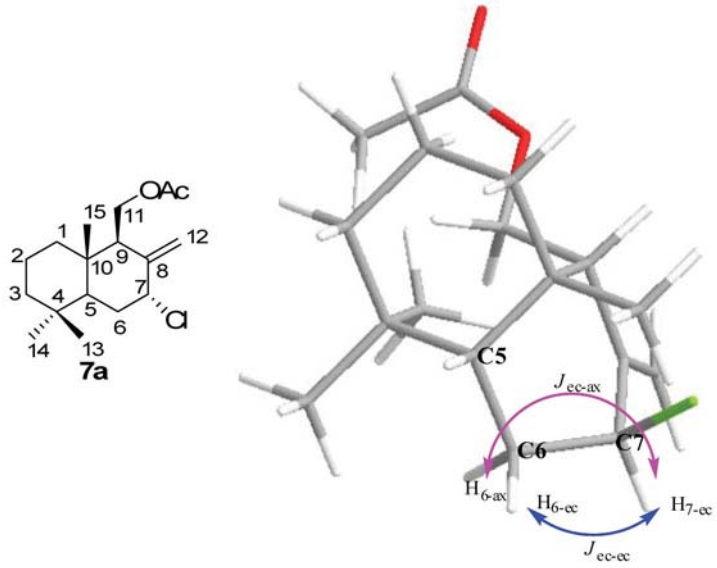

Figure S12. 3D structure for 7α-chloro-albicanyl acetate.

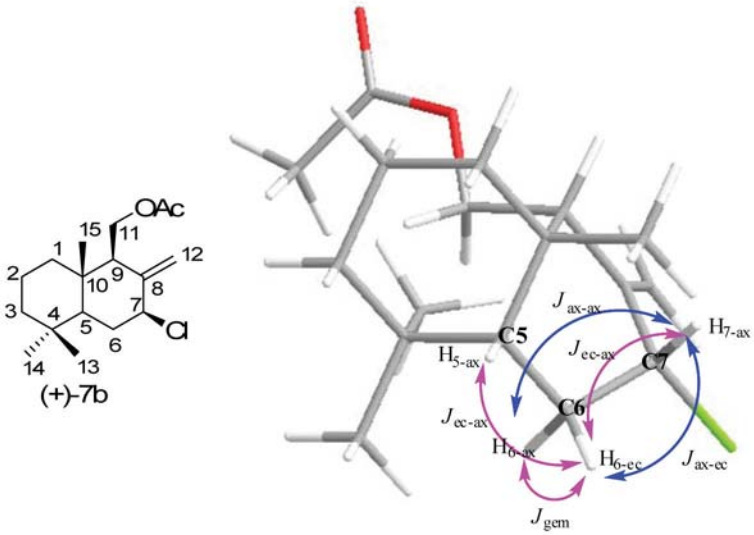

Figure S13. 3D structure for 7β-chloro-albicanyl acetate.

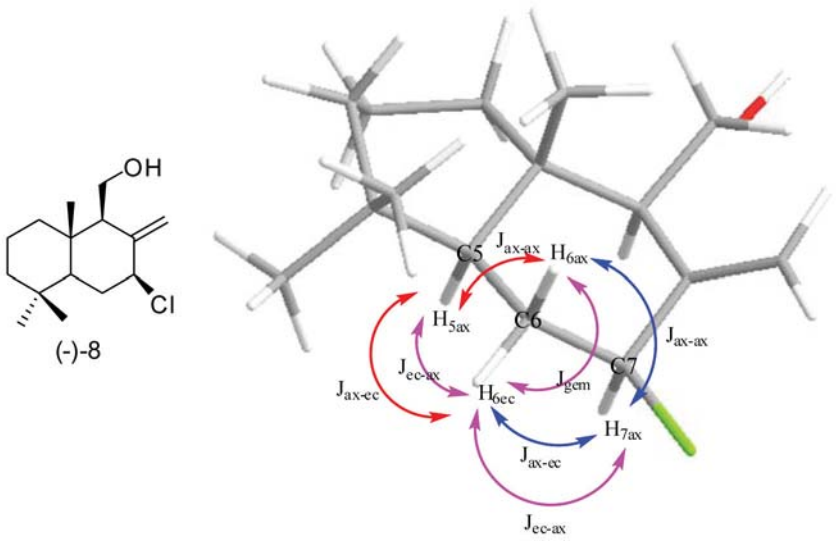

Figure S14. 3D structure for 7β-chloro-albicanol.