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Article

Total Synthesis of (*3S, 5R, 3'S, 5'R*)-Capsorubin

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Uma síntese total da (*3S, 5R, 3'S, 5'R*)-capsorubina (**1**) enriquecida enantiomericamente, através da condensação aldólica da (*1R*, *4S*)-1-(4-hidróxi-1,2,2-trimetil-ciclopentil)etanona (**2a**) e do crocetindial (**3**) é descrita. Uma síntese alternativa do composto **2a** opticamente ativo (*ee* 89%), com apenas oito etapas, também foi desenvolvida.

The total synthesis of enantiomerically enriched (*3S, 5R, 3'S, 5'R*)-capsorubin (**1**) by aldol condensation of (*1R, 4S*)-1-(4-hydroxy-1,2,2-trimethyl-cyclopentyl)ethanone (**2a**) and crocetindial (**3**) is described. An alternative, short eight-step synthesis of the optically active compound **2a** (*ee* 89%) is also reported.

Keywords: carotenoid, capsorubin, crocetindial, cyclopentane keto-alkohol, synthesis

Introduction

Carotenoid compounds are widely distributed among plants, animals and certain bacteria, and they are employed as natural pigments for foodstuffs.[1-3] It is well-known that certain carotenoids have important biochemical and biological functions, as well as nutritional importance as vitamin A precursors.[4-8] The use of carotenoids as chemoprevention agents against certain types of cancer has been reported,[9,10] and their use as antioxidants[11] and food additives has increased dramatically.[12-14]

Capsorubin (**1**) is a xanthophyll carotenoid[15] with a structure containing rather unusual five-membered ring end groups. It is the major pigment of red peppers and paprika *(Capsicum annuum)*, and it has been usually synthesized by adding two units of compound **2a** to crocetindial (**3**) through an aldol-condensation,[16] as shown in Figure 1. Recently, a new synthesis of capsorubin (**1**) from a known C_{10}-epoxy aldehyde has been described.[17]

Syntheses of compound **2a** have been previously described by Marquet *et al.*[18] and Weedon and co-workers,[19] producing either racemic or optically active (when (+)-camphor is employed as starting material) products. However, these syntheses are laborious, several-step procedures with reported overall yields varying from 0.03% to 4%. We have already described an eight-step synthesis of the racemic cyclopentane keto-alcohol **2a**, which has previously been converted into racemic capsorubin in one step.[20] More recently, we have also described a short, efficient synthetic route for the preparation of crocetindial (**3**) using two *in situ* procedures: a ketal hydrolysis/Wittig reaction and an allylic oxidation/Wittig reaction.[21]

In this paper we describe an alternative asymmetric route to the enantiomerically enriched compound **2a**. The total synthesis of (*3S, 5R, 3'S, 5'R*)-capsorubin (**1**) was achieved by a new experimental procedure involving the condensation of compounds **2a** and **3**.

Results and Discussion

The synthesis of keto-alcohol **2a** was achieved as depicted in Scheme 1.

Ketone **4** was prepared from commercially available isophorone.[22] The optically active alcohol **5** was obtained by the enantioselective reduction of **4** (90% yield) through a $LiAlH_4$ complex, methanol, and (+)-(*1S, 2R, 5S*)-menthol as the chiral auxiliary.[23] The enantiomeric excess of this reaction was found to be 89% as evaluated by chiral GLC analysis of **5** using a Chiraldex® β-cyclodextrin chiral column (30 m length × 0.30 mm i.d.). This was confirmed by comparison with the specific rotation of the well-known compound **5**.[24]

Reaction of compound **5** with sodium hydride and benzyl chloride in dioxane gave benzyl-ether **6** (98% yield).

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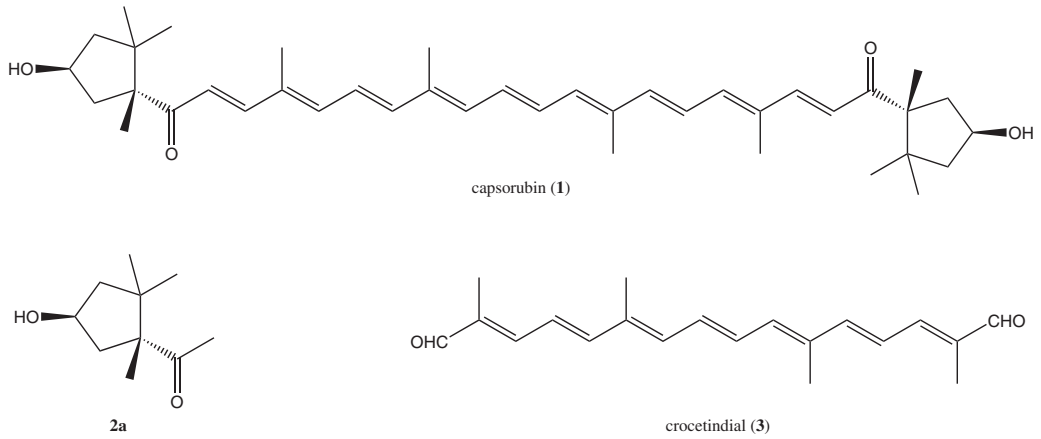
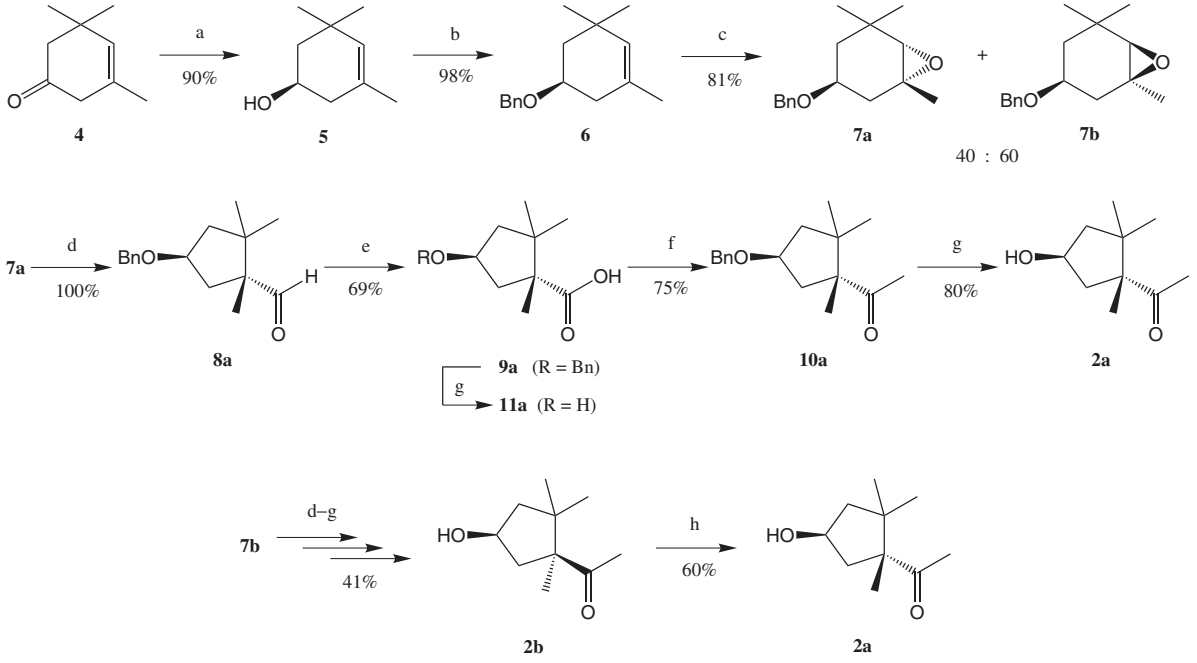


Figure 1. Structures of capsorubin (**1**), keto-alcohol **2a**, and crocetindial (**3**).



Reagents and conditions: (a) $LiAlH_4$, (+)-(*1S, 2R, 5S*)-menthol, MeOH, THF, −78 °C → reflux, 4h (90%); (b) NaH, BnCl, dioxane, 100 °C, 18 h (98%); (c) MCPBA, CH_2Cl_2, room temperature, 3 h (81% overall); (d) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 30 min (100% crude); (e) $NaClO_2$, NaH_2PO_4, H_2O, *t*-BuOH, 2-methyl-2-butene, 3 h (69%); (f) MeLi, THF, 0 °C to room temperature, 6h, (75%); (g) H_2, 5% Pd/C, MeOH, room temperature, 1h (80-85%); (h) $PhCO_2H$, $EtO_2CN{=}NCO_2Et$, PPh_3, THF, room temperature, 24 h, followed by NaOH 20%, MeOH, 2 h room temperature → 50 °C, 30 min (60% at two steps).

Scheme 1.

Epoxidation of **6** with *m*-chloroperoxybenzoic acid furnished a mixture of stereoisomers **7a** and **7b** (81% overall yield) in a 40:60 ratio. These stereoisomers were separated by column chromatography. In a previous work,[25] we described the stereospecific nature of the epoxide rearrangement reaction for compounds **7a** and **7b** upon treatment with $BF_3{\cdot}OEt_2$. For this reason, aldehyde **8a** can be obtained exclusively from **7a**. To avoid its decomposition, the aldehyde **8a** was directly oxidized to the carboxylic acid **9a** (69% yield from **7a**). Treatment of **9a** with methyl lithium at room temperature gave the methyl-ketone **10a** (75% yield). The optically active keto-alcohol **2a** was obtained by hydrogenolysis of compound **10a** (80% yield).

The optically active keto-alcohol **2b**, obtained from the corresponding stereoisomer **7b**, can be converted in the keto-alcohol **2a** by a Mitsunobu reaction,[26] increasing the overall yield of the desired stereoisomer **2a**.

For analytical purposes, compound **9a** was also converted by hydrogenolysis into the known hydroxy acid **11a** (80% yield), and the specific rotation of this compound was compared with literature data,[27] which confirmed the

enantiomeric excess of 89% for **9a**, in agreement with the optical purity of the starting compound **5**.

Crocetindial (**3**), the second intermediate to the synthesis of capsorubin (**1**), was prepared in 32% overall yield from fumaraldehyde dimethylacetal[28] through a new methodology developed in our laboratories for the construction of polyenic chains.[21]

Optically active capsorubin (**1**) was finally obtained by a new experimental procedure involving the condensation of compounds **2a** and **3**, using LDA as base, as depicted in Scheme 2. Under this condition, compound **1** was obtained in 43% yield after purification by recrystallization. This moderate yield can be due to crocetindial (**3**) polymerization or decomposition reactions but, in spite of that, it is higher than the yield cited in the literature for this kind of reaction.[16-19] Spectral data of compound **1** were identical to those previously described in the literature for capsorubin.[16,19]

Conclusions

In summary, we have developed a useful method for the synthesis of the optically active cyclopentane keto-alcohol **2a** with high optical purity (89% *ee*), and 12% overall yield from isophorone after 8 steps. The natural product capsorubin (**1**) can be synthesized in moderate overall yield (43%) from compound **2a** and crocetindial (**3**).

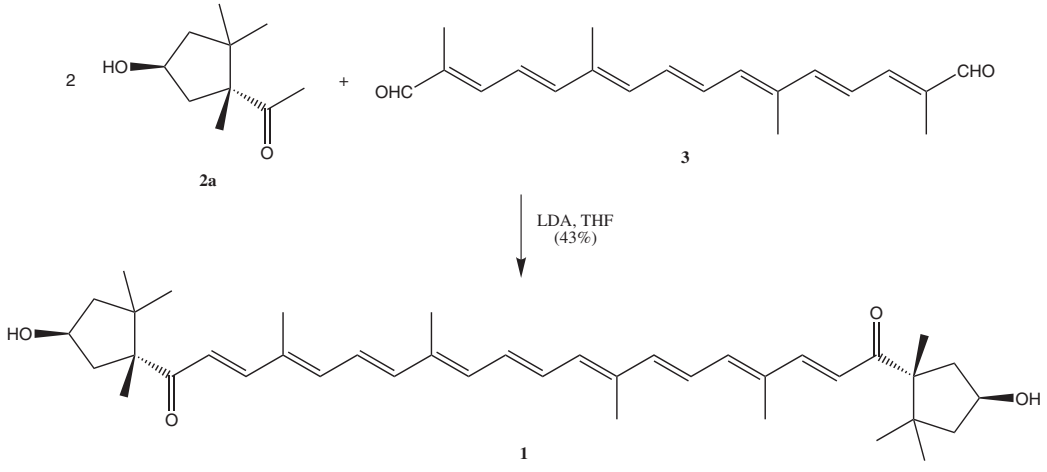
Experimental

General experimental procedures

NMR spectra were measured using a Bruker DPX 300 (300 MHz ^{1}H NMR and 75 MHz ^{13}C NMR) or a Bruker DRX 400 (400 MHz ^{1}H NMR and 100 MHz ^{13}C NMR) instrument; deuterochloroform was used as solvent and tetramethylsilane as internal standard. IR spectra (in KBr) were measured with a Perkin-Elmer Spectrum RX IFTIR spectrometer. Mass spectra were determined at an ionizing voltage of 70 eV, using an HP 5988-A or a Shimadzu QP 2010 spectrometer. Analytical gas chromatography (GLC) separations were performed on a Varian GC 3400 instrument with a fused silica capillary column (30 m length × 0.25 mm i.d.) coated with DB 1701 (phase thickness 0.25 μm), operating at temperatures in the 50-200 °C range. Chiral GC/MS analyses were performed in a Shimadzu QP 2010 instrument using a Chiraldex® β-cyclodextrin chiral column (30 m length × 0.30 mm i.d.). Optical rotations were measured on a Schmidt + Haensch model Polartronic HH8 or a Jasco model DM 370 polarimeter. Elemental analyses were performed with a Carlo Erba instrument EA 1110. TLC was performed on precoated silica gel 60 F254 (0.25 mm thick, Merck); silica gel 60, 70-230 mesh (Merck) was used for column chromatography.

*(−)-(1R)-3,5,5-Trimethylcyclohexen-3-ol (**5**)*

A solution of (+)-(*1S, 2R, 5S*)-menthol (6.00g, 39.0 mmol) in anhydrous THF (10 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (1.48 g, 39.0 mmol) in anhydrous THF (15 mL), maintained at −78 °C under N_2 atmosphere. The mixture was stirred for 30 min. before the dropwise addition of a solution of anhydrous methanol (1.5 mL, 39 mmol) in anhydrous THF (5 mL). After 1 h of stirring at −78 °C, a solution of compound **4** (1.79 g, 13.0 mmol) in anhydrous THF (10 mL) was added. The reaction mixture was heated under reflux for 4 h, and after this period the mixture was cooled and quenched with cold water (0.7 mL), NaOH 15% (0.7 mL), and finally water (1.4 mL). The precipitated hydroxides were removed by



Scheme 2.

filtration and washed with ethyl ether. The organic layer was filtered and dried over anhydrous magnesium sulfate, the solvents were evaporated, and the residue was purified by flash chromatography (*n*-hexane/ethyl acetate, from 9.5:0.5 to 1:1, v/v), producing **5** (1.63 g, 90%) as a colorless oil; $[\alpha]_D^{25}$ −9.2° (*c* 0.37, $CHCl_3$) or −128° neat, literature:[24] $[\alpha]_D^{25}$ (at 19 °C) −144° (homog); IR ν_{max}/cm^{-1}: 3345, 1742, 1467, 1394, 1359, 1049, 1014, 835; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.09 (br s, 1H), 3.95 (m, 1H), 2.45 (br s, 1H), 2.21 (dd, *J* 16.5, 5.7 Hz, 1H), 1.87 (dd, *J* 16.3, 9.5 Hz, 1H), 1.73 (two broad lines 12.1 Hz apart, 1H), 1.64 (s, 3H), 1.32 (t, *J* 11.9 Hz, 1H), 0.99 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.6 (CH), 128.5 (C), 66.0 (CHOH), 46.0 (CH_2), 39.7 (CH_2), 34.1 (C), 31.4 (CH_3), 29.5 (CH_3), 23.2 (CH_3); MS *m/z* 140 (M^+, 12%), 125 (100), 122 (7), 107 (36), 91 (23), 84 (47), 69 (42), 55 (30), 41 (35), 39 (27).

*(−)-(5R)-5-Benzyloxy1,3,3-trimethylcyclohexene (**6**)*

A solution of compound **5** (0.50 g, 3.57 mmol) in anhydrous dioxane (3 mL) was added to a suspension of sodium hydride (0.71 g of a 60% dispersion in mineral oil, previously washed with *n*-hexane, 18 mmol) in anhydrous dioxane (30 mL). The reaction mixture was heated to reflux for 3 h and then cooled at room temperature. Benzyl chloride (0.45 g, 3.57 mmol) in anhydrous dioxane (5 mL) was added, and the reaction mixture was heated again to reflux for 15 h. The reaction mixture was cooled, crushed ice was added, and the product was extracted with ethyl ether. The organic layer was dried over anhydrous magnesium sulfate, the solvents were removed under reduced pressure, and the residue was purified by column chromatography through silica gel (*n*-hexane/ethyl acetate, 9:1 v/v), yielding **6** (0.87 g, 98%) as a pale yellow oil; $[\alpha]_D^{25}$ −12.0° (*c* 0.40, $CHCl_3$); IR ν_{max}/cm^{-1}: 1453, 1360, 1239, 1094, 1073, 1028, 903, 734; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (br s, 5H), 5.10 (br s, 1H), 4.48 and 4.56 (AB system, *J* 12.7 Hz, 2H), 3.73 (m, 1H), 2.25 (dd, broad lines, *J* 16.5, 5.5 Hz, 1H), 1.95 (dd, broad lines, *J* 15.5, 9.4 Hz, 1H), 1.83 (two broad lines, 12.3 Hz, 1H), 1.62 (br s, 3H), 1.36 (t, *J* 11.9 Hz, 1H), 1.0 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0 (C), 131.7 (CH), 128.6 (C), 128.4 (CH), 127.5 (CH), 127.4 (CH), 73.0 (CHOR), 69.9 (CH_2OR), 42.6 (CH_2), 36.9 (CH_2), 33.8 (C), 31.1 (CH_3), 29.5 (CH_3), 23.4 (CH_3); MS *m/z* (M^+, 0.7%), 197 (3), 181 (27), 149 (2), 139 (3), 123 (23), 107 (19), 96 (20), 91 (100), 81 (15), 77 (12), 65 (12), 39 (5).

*Trans-(−)-(1R,3S,6S)-3-benzyloxy-1,5,5-trimethyl-7-oxabicyclo[4.1.0]heptane (**7a**)*

A solution of *m*-chloroperoxybenzoic acid (1.80 g of 50% MCPBA, 5.20 mmol) in methylene chloride (30 mL) was added dropwise to a solution of compound **6** (0.60 g, 2.60 mmol) in methylene chloride (10 mL). The reaction mixture was stirred at room temperature for 3 h. The resulting mixture was treated with 10% sodium sulfite solution (50 mL) and stirred for 1 h, to remove excess peracid. The organic layer was separated, and the aqueous layer was extracted with methylene chloride. The combined organic extracts were washed with 5% $NaHCO_3$, water and saturated brine, and dried over anhydrous magnesium sulfate. Solvent removal under reduced pressure gave a mixture of the *cis* and *trans* isomers of compounds **7a** and **7b** (0.52 g, 81%) in a 40:60 ratio. Isomers **7a** and **7b** were isolated by column chromatography through silica gel (*n*-hexane/methylene chloride/ethyl acetate 12:7:1, v/v/v), yielding *trans* isomer **7a** (0.20 g, 40%) and *cis* isomer **7b** (0.31 g, 60%).

*Trans isomer **7a***

$[\alpha]_D^{25}$ −6.0° (*c* 0.10, $CHCl_3$); IR ν_{max}/cm^{-1}: 1450, 1490, 1388, 1204, 1095, 1027, 916; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (br s, 5H), 4.48 and 4.56 (AB system, *J* 12.7 Hz, 2H), 3.60 (m, 1H), 2.60 (s, 1H), 2.41 (dd, *J* 14.4, 3.95 Hz, 1H), 1.64 (m, 2H), 1.37 (s, 3H), 1.15 (dd, *J* 14.3, 10.9 Hz, 1H),1.15 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7 (C), 128.3 (CH), 127.4 (CH), 71.8 (CHOR), 70.2 (CH_2OR), 67.3 (CH), 60.6 (C), 42.0 (CH_2), 36.8 (CH_2), 31.8 (C), 29.3 (CH_3), 25.5 (CH_3), 23.3 (CH_3); MS *m/z* 155 (M^+ − 91, 16%), 113 (14), 109 (9), 99 (9), 97 (16), 92 (33), 91 (100), 65 (15), 43 (40); Anal. Calc. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00; O, 12.99. Found: C, 77.62; H, 8,79.

*Cis isomer **7b***

$[\alpha]_D^{25}$ +5.8° (*c* 0.10, $CHCl_3$); IR ν_{max}/cm^{-1}: 1495, 1453, 1363, 1204, 1095, 1070, 1027, 916; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 4.48 and 4.56 (AB system, *J* 12.7 Hz, 2H), 3.56 (m, 1H), 2.55 (s, 1H), 2.14 (dd, J_1 6.8, J_2 14.7 Hz, 1H), 1.78 (dd, J_1 10.5, J_2 14.6 Hz, 1H), 1.37 (m, 2H), 1.32 (s, 3H), 1.08 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7 (C), 128.3 (CH), 127.4 (CH), 71.0 (CHOR), 69.8 (CH_2OR), 67.8 (CH), 58.3 (C), 37.2 (CH_2), 35.3 (CH_2), 31.8 (C), 27.9 (CH_3), 24.5 (CH_3), 24.2 (CH_3); MS *m/z* 245 (M^+ − 1, 5%), 155 (10), 139 (6), 123 (5), 105 (100), 95 (37), 91 (29), 69 (18), 43 (70). Anal. Calc. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00; O, 12.99. Found: C, 77.82; H, 8,92.

*Trans-(+)-(1R,4S)-4-benzyloxy-1,2,2-trimethyl-cyclopentanecarboxylic acid (**9a**)*

Freshly distilled boron trifluoride etherate (0.04 mL; 0.32 mmol) was added to a solution of compound **7a** (0.10 g, 0.4 mmol) in methylene chloride (10 mL). The reaction mixture was stirred at room temperature for 30 min

and then treated with a saturated sodium bicarbonate solution (20 mL). The organic layer was separated and washed with saturated brine, and it was then dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure. The crude product, obtained in quantitative yield, was used in the following step without further purification. A buffer solution (pH 4.5) was prepared by dissolving NaH_2PO_4 (0.33 g, 2.40 mmol) in water (5 mL) and then mixed with 30% aqueous $NaClO_2$ (1.44 mL, 4.80 mmol); the resulting solution was added to a previously prepared solution of the crude product **8a** (0.10 g) and 2-methyl-2-butene (1.0 mL) in *t*-butanol (3 mL). The reaction mixture was stirred for 3 h at room temperature. A 40% aqueous solution of NaOH was then added dropwise, to bring the pH to 11. The aqueous layer was extracted twice with *n*-hexane, acidified with concentrated HCl to pH 3.5, and then extracted with ethyl ether. The organic layer was dried over anhydrous magnesium sulfate, the solvents were removed under reduced pressure, and the solid product was recrystallized from *n*-hexane, yielding compound **9a** (0.073 g, 69%) as a white solid (mp 83-85°C); $[\alpha]_D^{25}$ +11.0° (*c* 0.08, $CHCl_3$); IR ν_{max}/cm^{-1}: 3405, 1680, 1350, 1314, 1100, 1105; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (br s, 1H), 7.32 (m, 5H), 4.50 and 4.41 (AB system, *J* 12.0 Hz, 2H), 4.55 (m, 1H), 2.59 (dd, *J* 14.1, 5.9 Hz, 1H), 2.03 (dd, *J* 9.7, 8.2 Hz, 1H), 2.01 (dd, *J* 9.8, 8.32 Hz, 1H), 1,80 (dd, *J* 14.2, 3.0 Hz, 1H), 1.15 (s, 3H), 1.10 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.3 (COOH), 138.5 (C), 128.3 (CH), 127.6 (CH), 127.5 (CH), 76.8 (CHOR), 70.9 (CH_2OR), 54.3 (C), 46.2 (CH_2), 42.0 (C), 42.4 (CH_2), 26.7 (CH_3), 24.1 (CH_3), 21.4 (CH_3). Anal. Calc. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45; O, 18.30. Found: C, 73.03; H, 8.09.

*Trans-(+)-(1R,4S)-1-(4-benzyloxy-1,2,2-trimethyl-cyclopentyl)ethanone (**10a**)*

Methyllithium (1.4 mL of a 1.0 mol L^{-1} solution in ethyl ether, 1.40 mmol) was added dropwise to a solution of compound **9a** (0.073 g, 0.27 mmol) in anhydrous THF (2 mL), kept at 0 °C under N_2 atmosphere. The resulting solution was warmed to room temperature and stirred for 6 h. Crushed ice and saturated ammonium chloride solution were then added, and the product was extracted with ethyl ether. The organic layer was dried over anhydrous magnesium sulfate, and the solvents were removed under reduced pressure. The residue was purified by column chromatography through silica gel (*n*-hexane/ethyl acetate, 9:1, v/v), giving compound **10a** (0.054 g, 75%) as a colorless oil; $[\alpha]_D^{25}$ +7.1° (*c* 0.02, $CHCl_3$); IR ν_{max}/cm^{-1}: 1697, 1462, 1458, 1350, 1100, 1084, 1066, 1028; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H), 4.47 and 4.43 (AB system, *J* 12.0 Hz, 2H), 4.10 (m, 1H), 2.63 (dd, *J* 14.4, 8.5 Hz, 1H), 2.11 (s, 3H), 1.93 (dd, *J* 13.6, 7.5 Hz, 1H), 1.82 (dd, *J* 13.5, 4.8 Hz, 1H), 1.63 (dd, *J* 14.4 Hz, 3.2 Hz, 1H), 1.30 (s, 3H), 1.17 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.7 ($COCH_3$), 138.8(C), 128.3 (CH), 127.5 (CH), 127.4 (CH), 77.2 (CHOR), 59.6 (C), 47.7 (CH_2), 43.4 (C), 42.1 (CH_2), 28.3 (CH_3), 25.8 (CH_3), 24.8 (CH_3), 21.2 (CH_3); MS *m/z* 154 (M^+ – 106, 4%), 113 (18), 111 (14), 110 (9), 109 (12), 95 (7), 92 (12), 91 (100), 65 (9), 43 (21). Anal. Calc. for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29; O, 12.29. Found: C, 78.21; H, 9.30.

*Trans-(+)-(1R,4S)-4-hydroxy-1,2,2-trimethyl-cyclopentanecarboxylic acid (**11a**)*

5% Palladium on activated carbon (20 mg) was added to a solution of compound **9a** (0.110 g, 0.44 mmol) in anhydrous methanol (3 mL), and the suspension was stirred under hydrogen atmosphere for about 1 h. The reaction mixture was filtered through silica gel, the solvent was removed under reduced pressure, and the solid product was recrystallized from toluene, producing compound **11a** (0.062 g, 85%) as a white solid (mp 214-216 °C, literature:[19] 216-217 °C); $[\alpha]_D^{25}$ +13.4° (*c* 0.09, EtOH), literature:[27] $[\alpha]_D^{25}$ +15° (*c* 0.034, CH_3OH), literature:[19] $[\alpha]_D^{25}$ (at 20 °C) +12.8° (*c* 1, EtOH); IR ν_{max}/cm^{-1}: 3441, 2967, 1731, 1651, 1451, 1373, 1242, 1142, 1046; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05 (br s, 2H), 4.39 (m, 1H), 2.22 (dd, J_1 2.91, J_2 14.9 Hz, 1H), 2.15 (dd, J_1 8.1, J_2 14.5 Hz, 1H), 2.09 (dd, J_1 8.7, J_2 15.1 Hz, 1H), 1.73 (dd, J_1 5.1, J_2 14.0 Hz, 1H), 1.14 (s, 3H), 1.05 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.3 (COOH), 70.5 (CHOH), 54.6 (CH_2), 50.7 (CH_2), 45.8 (CH_2), 44.8 (C), 25.2 (CH_3), 25.1 (CH_3), 19.1 (CH_3). Anal. Calc. for $C_9H_{16}O_3$: C, 62.77; H, 9.36; O, 27.87. Found: C, 63.14; H, 9.75.

*Trans-(+)-(1R,4S)-1-(4-hydroxy-1,2,2-trimethyl-cyclopentyl)ethanone (**2a**) from **10a***

5% Palladium on activated carbon (5 mg) was added to a solution of compound **10a** (0.050 g, 0.19 mmol) in methanol (5 mL), and the suspension was stirred under hydrogen atmosphere for 1 h. The mixture was filtered through Celite®, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography through silica gel (*n*-hexane/ethyl acetate 4:6, v/v), yielding compound **2a** (0.032 g, 80%) as a colorless oil; $[\alpha]_D^{25}$ +1.4° (*c* 0.010, EtOH), literature:[19] $[\alpha]_D^{25}$ (at 20 °C) +8.4° (*c* 1, EtOH); IR ν_{max}/cm^{-1}: 3357, 1700, 1457, 1357, 1200, 1114, 1064, 742, 700; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.50 (m, 1H), 2.82 (dd, *J* 14.4, 8.5 Hz, 1H), 2.13 (s, 3H), 2.04 (dd, *J* 13.7, 7.7 Hz, 1H), 2.03 (m, 1H), 1.67 (dd, *J* 13.7, 4.9 Hz, 1H), 1.43 (dd, *J* 14.3, 3.3 Hz, 1H), 1.30 (s, 3H), 1.19

(s, 3H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.9 ($COCH_3$), 70.0 (CHOH), 57.2 (C), 50.7 (CH_2), 45.3 (C), 43.7 (CH_2), 28.3 (CH_3), 25.8 (CH_3), 24.9 (CH_3), 21.5 (CH_3); MS *m/z* 114 (M^+ – 56, 24%), 95 (59), 85 (95), 83 (70), 67 (27), 55 (58), 43 (100), 41 (49), 39 (15), 29 (11).

*Trans-(+)-(1R,4S)-1-(4-hydroxy-1,2,2-trimethyl-cyclopentyl)ethanone (**2a**) from **2b** by Mitsunobu reaction*[26]

The *cis* keto-alcohol **2b** (0.460 g, 2.7 mmol) was dissolved in THF (10 mL), and the solution was cooled in an ice bath. Solid triphenylphosphine (0.839 g, 3.2 mmol) and benzoic acid (0.659 g, 5.4 mmol) were added to the solution of **2b**. Diethyl azodicarboxylate (0.610 g; 3.5 mmol) were dissolved in THF (5 mL), and this solution was added dropwise to the previously prepared solution. The reaction mixture was warmed to room temperature and stirred for 24 h. When the reaction was assumed by TLC analysis to be complete, THF was removed and petroleum ether was added. The mixture was stirred for 1 h at room temperature, filtered, and concentrated .The residue was used in the following reaction without purification. A solution of NaOH (20%) in methyl alcohol (1.0 mL, 3.6 mmol of NaOH) and the previously obtained crude compound (0.70 g) were warmed at 50 °C and stirred for 30 min. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography through silica gel (*n*-hexane/ethyl acetate, 1:1 v/v), producing compound **2a** (0.277 g, 60% overall yield).

*(3S,3S',5R,5R')-dihydroxy-*κ,κ*-carotene-6,6'-dione (**1**)*

n-Butyl lithium (0.06 mL of a 2.02 mol L^{-1} solution in *n*-hexane, 0.11 mmol) was added to a solution of diisopropylamine (0.02 mL, 0.12 mmol) in anhydrous THF (3 mL) kept at 0 °C, and the mixture was stirred at the same temperature for 20 min. The reaction mixture was cooled at –78 °C, and a solution of compound **2a** (0.08 g, 0.052 mmol) in anhydrous THF (1 mL) was added. The mixture was warmed at room temperature and stirred for 4 h, and again cooled to 0 °C. Crocetindial (**3**) (0.07g, 0.023 mmol) in THF (1 mL) was added, and the mixture was stirred for 1 h at 0 °C. A saturated ammonium chloride solution was then added, and the product was extracted with ether. The organic layer was dried over anhydrous magnesium sulfate, and the solvents were removed under reduced pressure. The solid product was recrystallized from methylene chloride:petroleum ether (9:1), yielding compound **1** (0.006 g, 43%) as a red solid (mp 214-216 °C, literature:[16,19] 216-217 °C); IR ν_{max}/cm^{-1}: 3430, 1685, 1640, 1598, 1085, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.1-6.41 (m, 14H), 4.48 (m, 2H), 2.82 (dd, *J* 14.4, 8.6 Hz, 2H), 1.99 (dd, *J* 13.7, 7.9 Hz, 2H), 1.92 (s, 12H), 1.68 (dd, *J* 13.5, 4.6 Hz, 2H), 1.46 (dd, *J* 14.9, 3.2 Hz, 2H), 1.32 (s, 6H), 1.18 (s, 6H), 0.85 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.98 (CO), 147.8 (CH), 143.5 (CH), 137.6 (C), 136.0 (CH), 133.1 (CH), 132.5 (CH), 126.6 (CH), 123.9 (CH), 122.7 (CH), 69.7 (CHOH), 58.9 (C), 50.5 (CH_2), 45.2 (C), 43.5 (CH_2), 25.8 (CH_3), 24.8 (CH_3), 20.7 (CH_3), 7.6 (CH_3), 7.2 (CH_3).

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Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br, as PDF file.

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Total Synthesis of (*3S, 5R, 3'S, 5'R*)-Capsorubin

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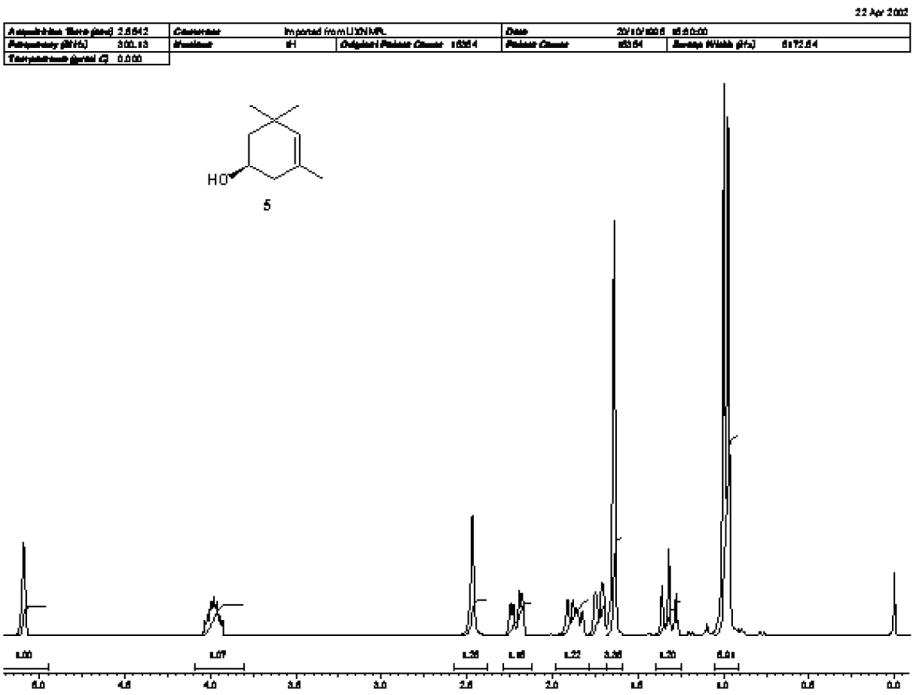

Figure S1. ^{1}H NMR spectrum of compound **5** (300 MHz, $CDCl_3$).

*e-mail: pmdonate@usp.br

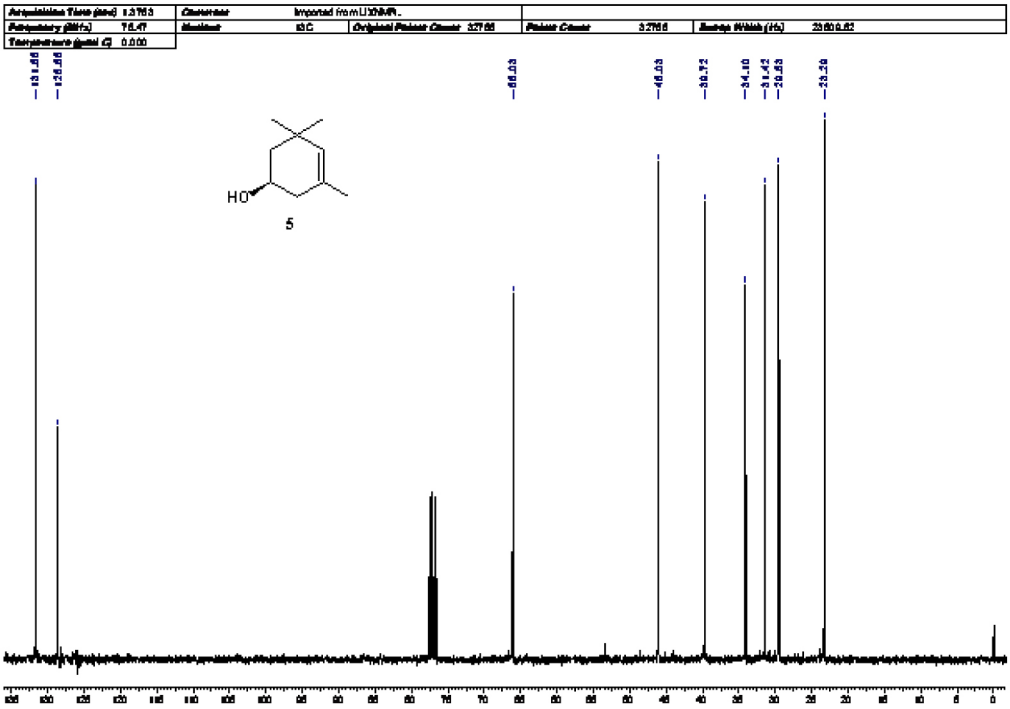

Figure S2. ^{13}C NMR spectrum of compound **5** (75 MHz, $CDCl_3$).

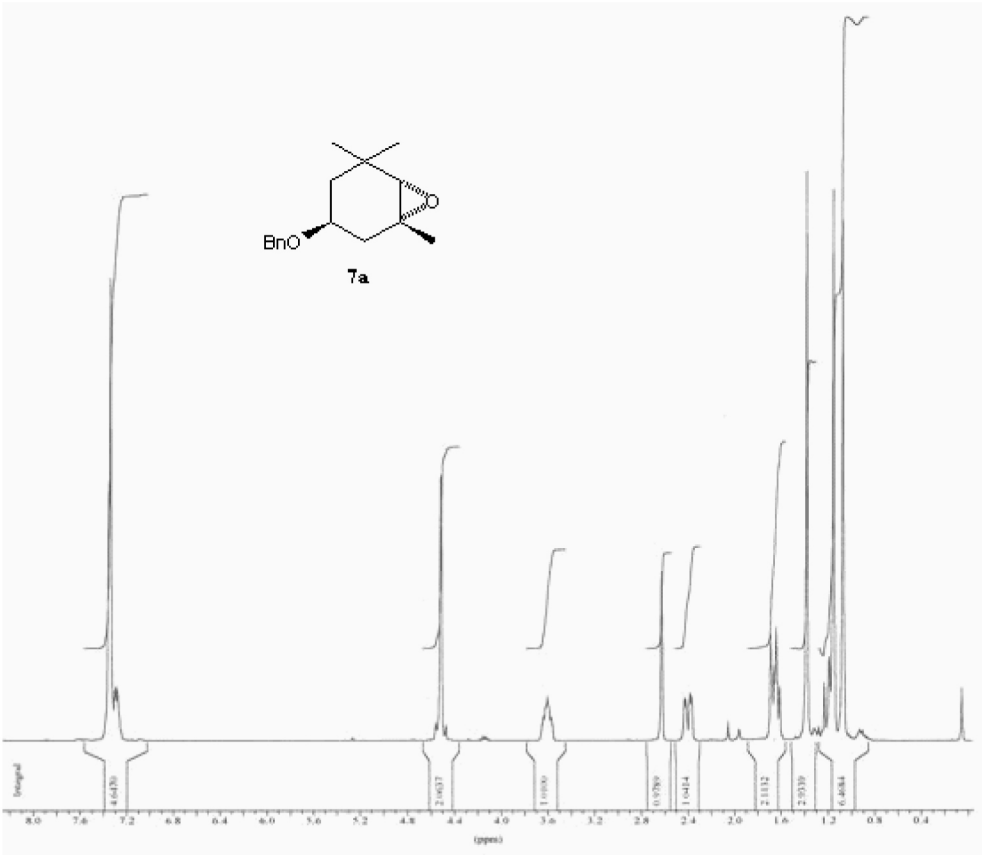

Figure S3. ^{1}H NMR spectrum of compound **7a** (300 MHz, $CDCl_3$).

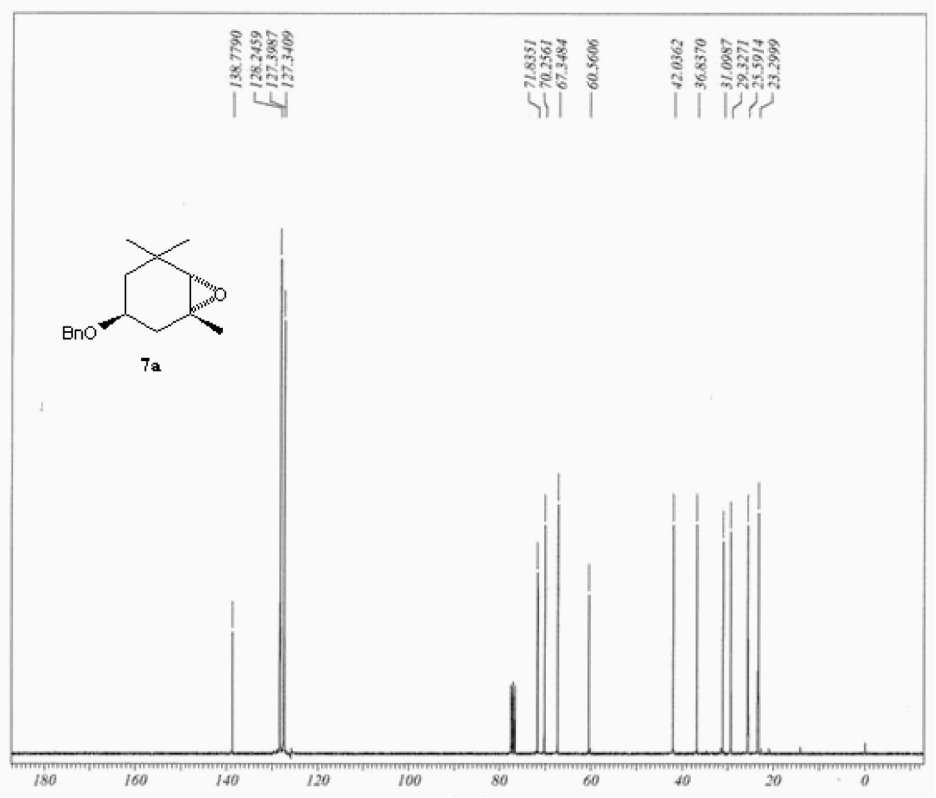

Figure S4. ^{13}C NMR spectrum of compound **7a** (75 MHz, $CDCl_3$).

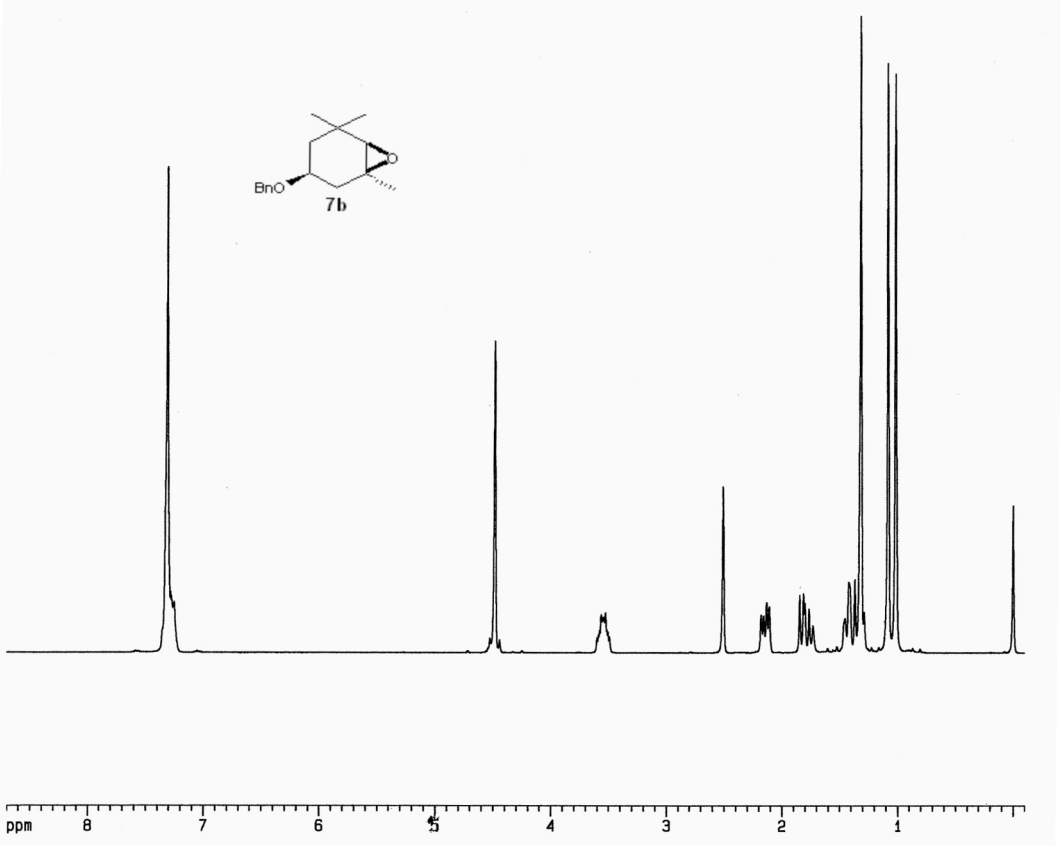

Figure S5. ^{1}H NMR spectrum of compound **7b** (75 MHz, $CDCl_3$).

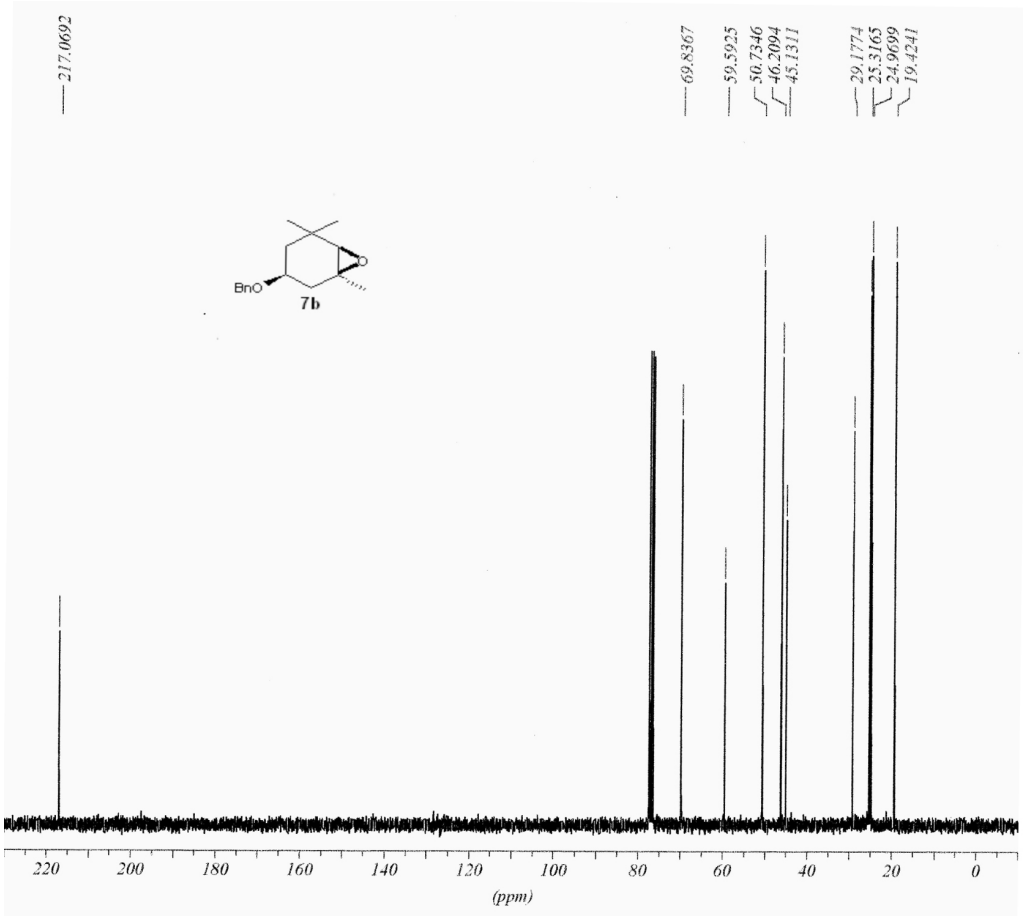

Figure S6. ^{13}C NMR spectrum of compound **7b** (75 MHz, $CDCl_3$).

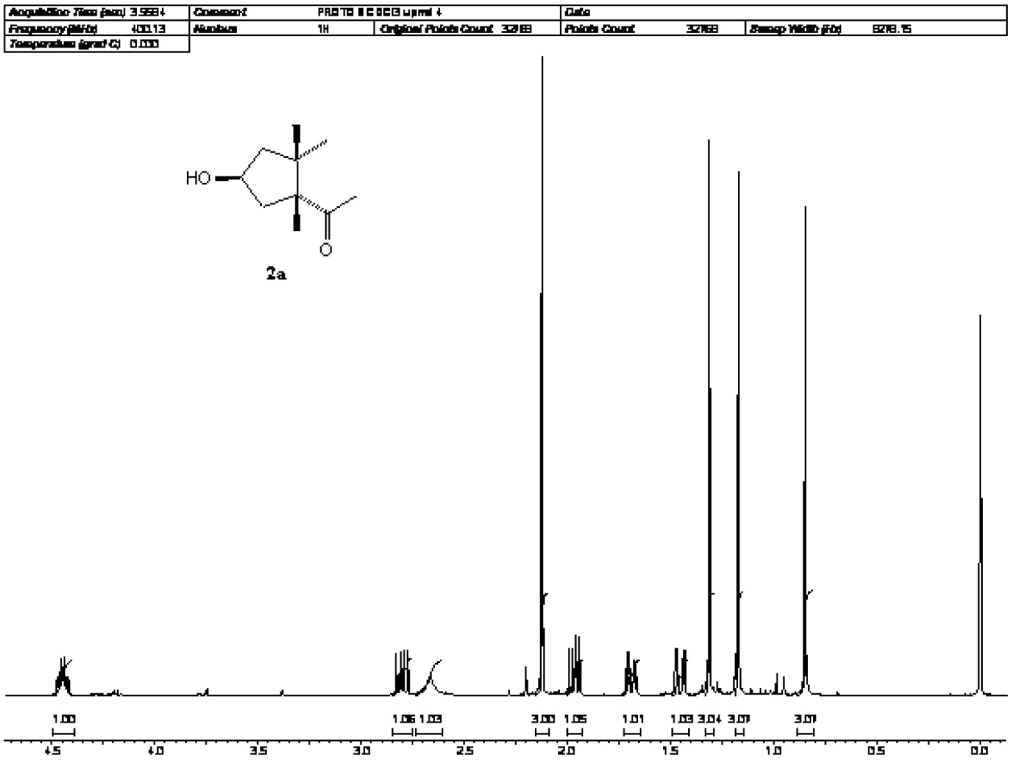

Figure S7. ^{1}H NMR spectrum of compound **2a** (300 MHz, $CDCl_3$).

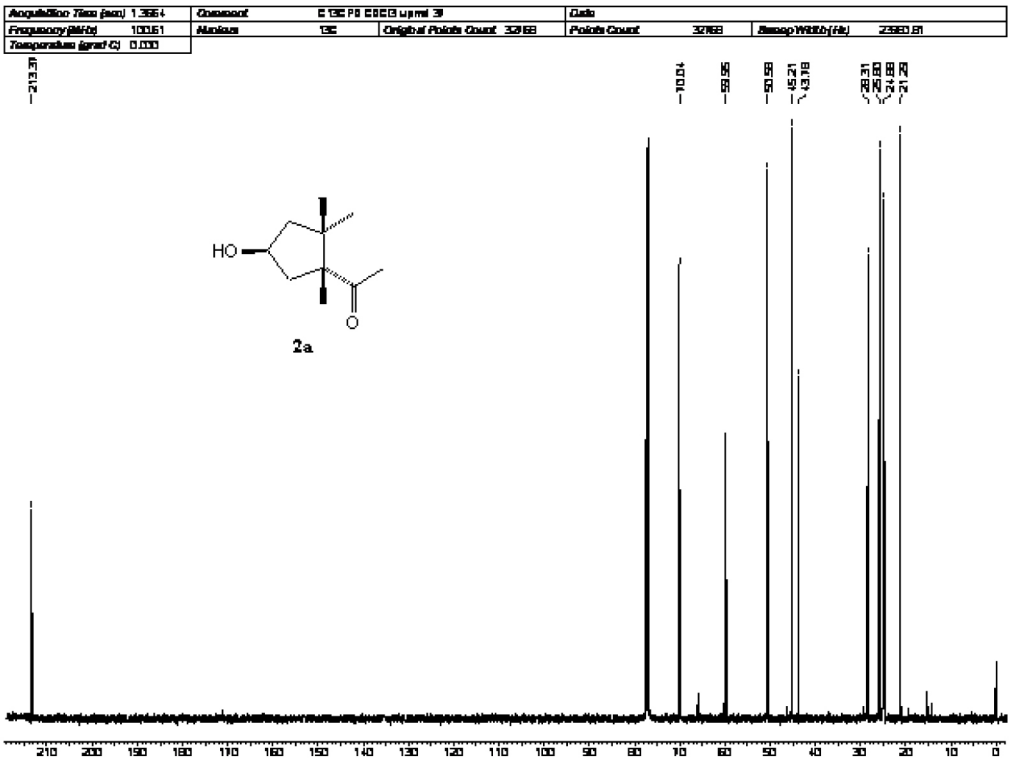

Figure S8. ^{13}C NMR spectrum of compound **2a** (75 MHz, $CDCl_3$).

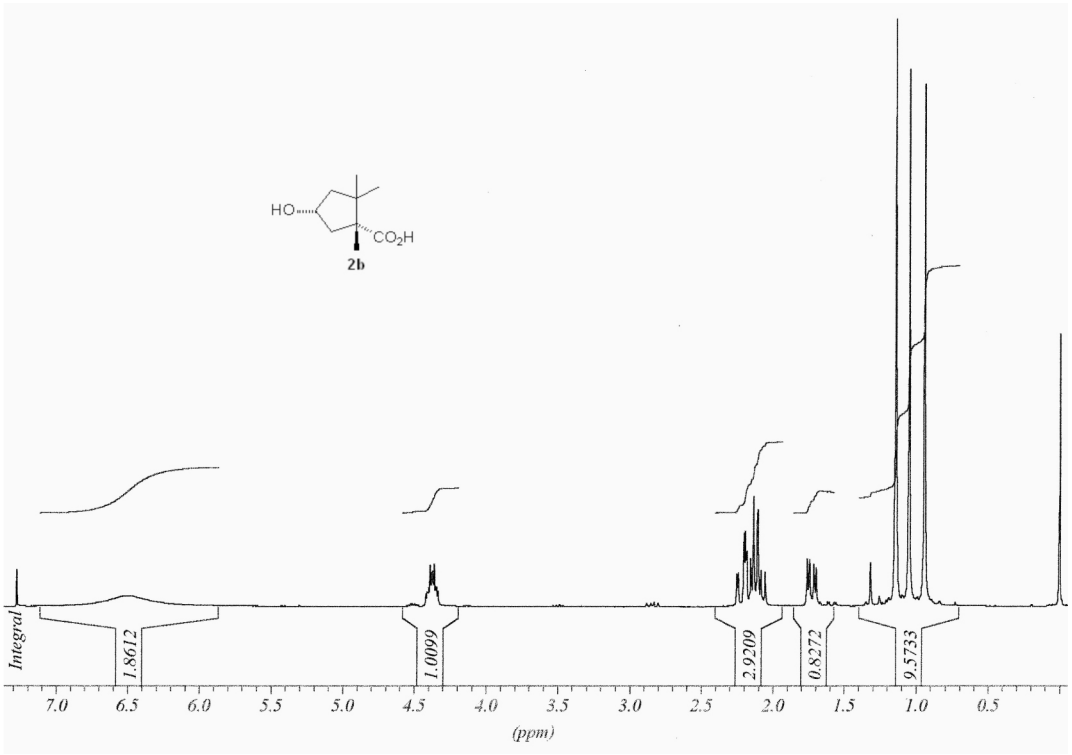

Figure S9. ^{1}H NMR spectrum of compound **2b** (75 MHz, $CDCl_3$).

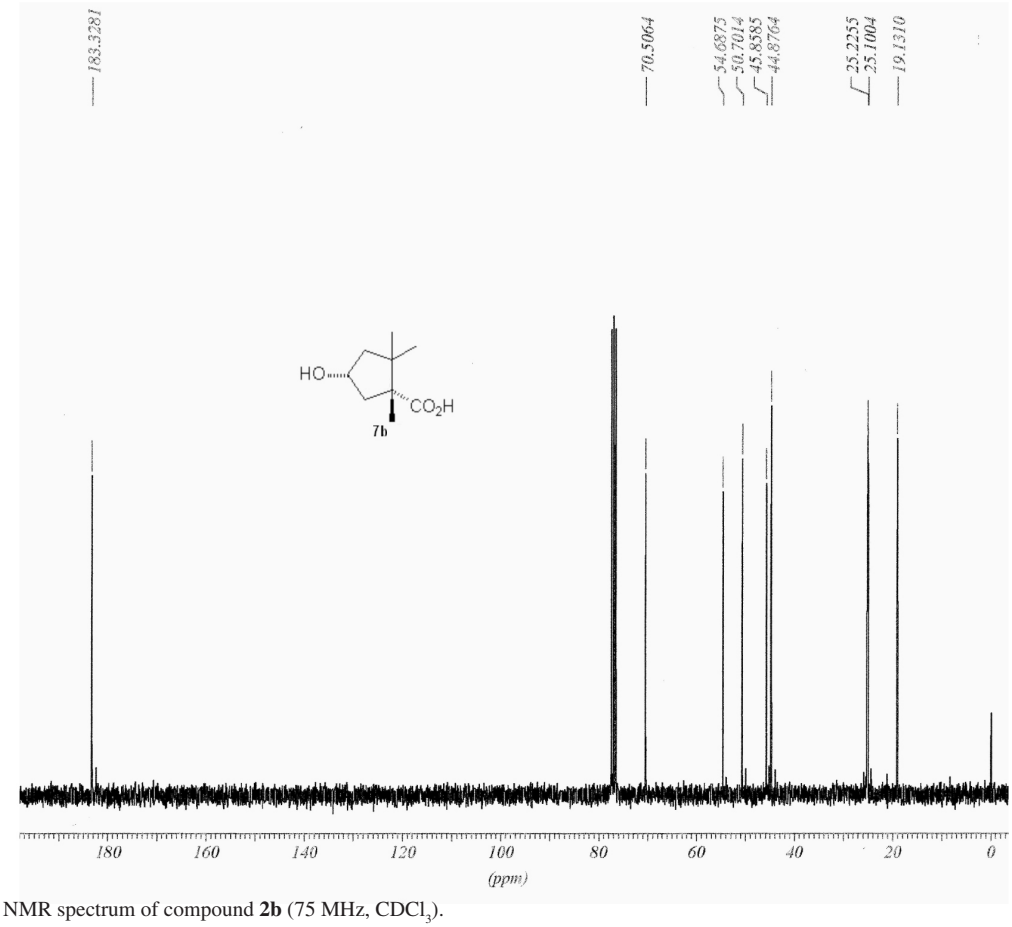

Figure S10. ^{13}C NMR spectrum of compound **2b** (75 MHz, $CDCl_3$).

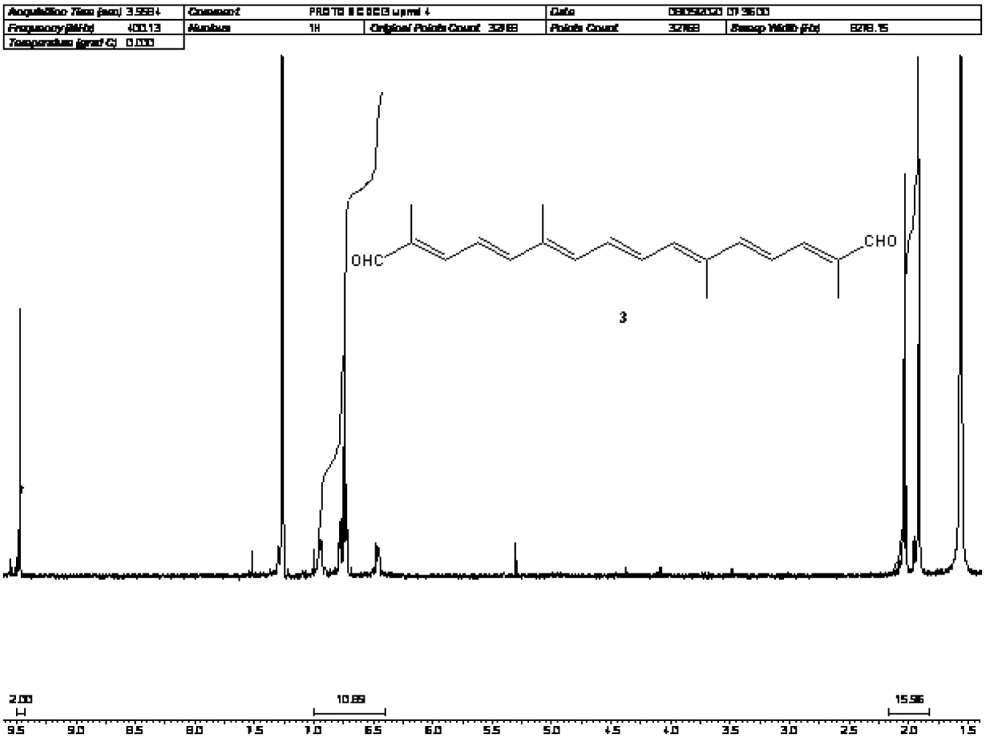

Figure S11. ^{1}H NMR spectrum of compound **3** (300 MHz, $CDCl_3$).

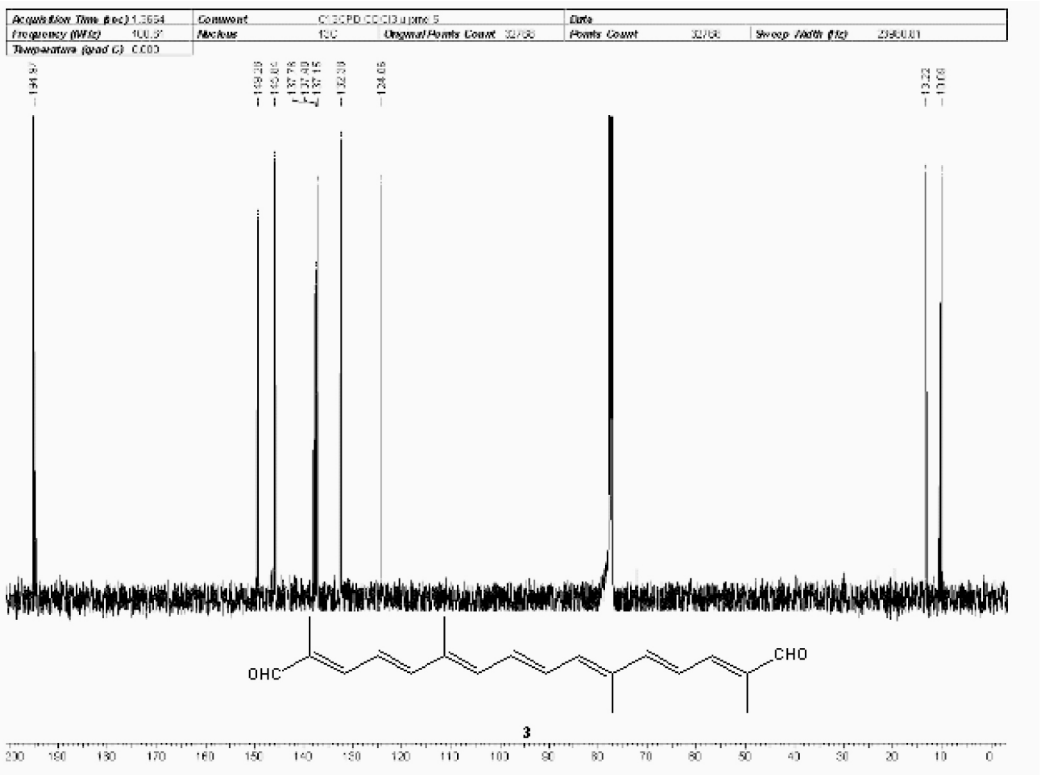

Figure S12. ^{13}C NMR spectrum of compound **3** (75 MHz, $CDCl_3$).

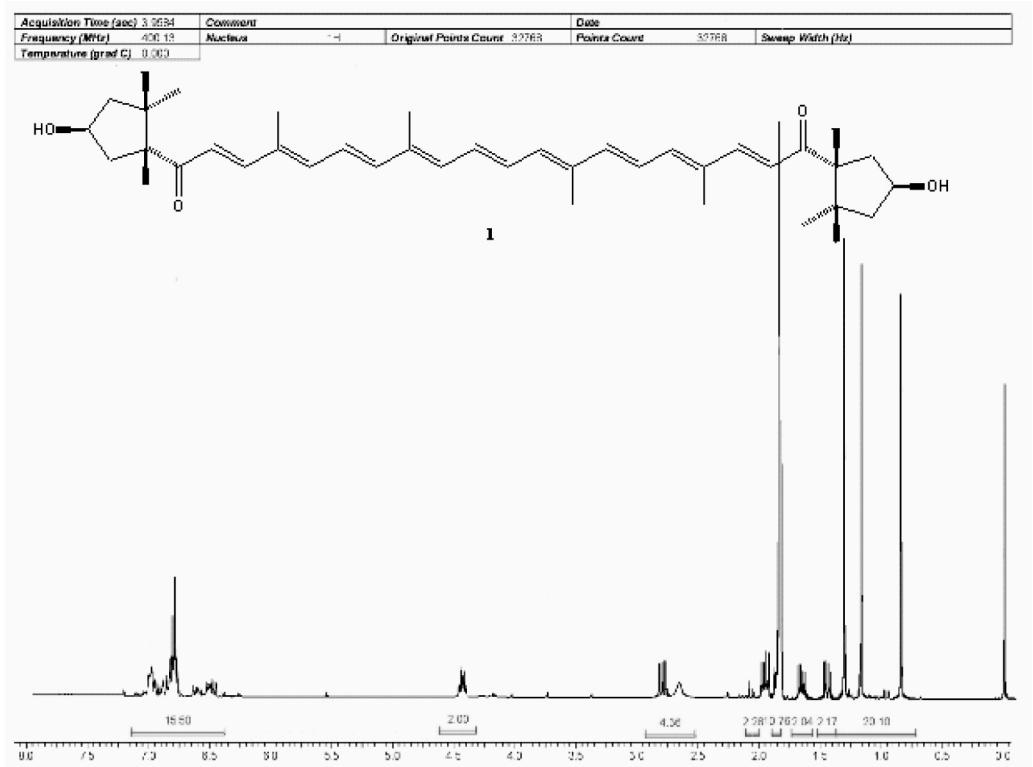

Figure S13. ^{1}H NMR spectrum of compound **1** (300 MHz, $CDCl_3$).

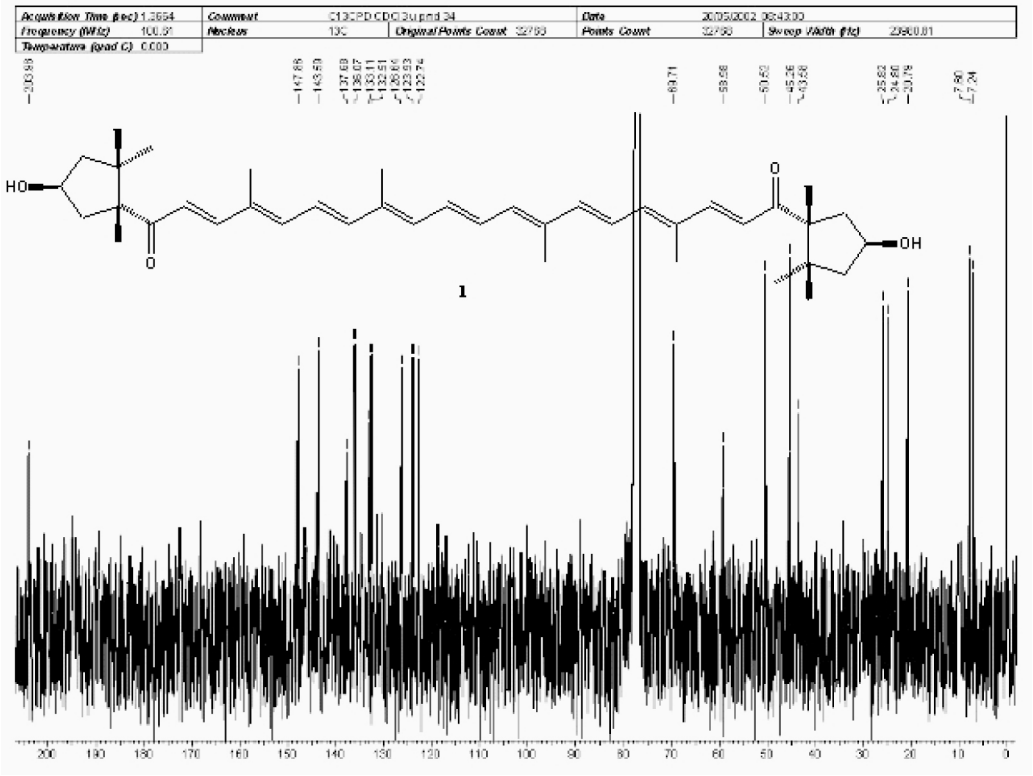

Figure S14. ^{13}C NMR spectrum of compound **1** (75 MHz, $CDCl_3$).