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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 antioxidants11 and food additives has increased dramatically.12-14

Capsorubin (1) is a xanthophyll carotenoid15 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 C10-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 LiAlH4 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).
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,\textsuperscript{25} we described the stereospecific nature of the epoxide rearrangement reaction for compounds 7a and 7b upon treatment with BF\textsubscript{3}OEt\textsubscript{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,\textsuperscript{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,\textsuperscript{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 through a new methodology developed in our laboratories for the construction of polyenic chains. 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. Spectral data of compound 1 were identical to those previously described in the literature for capsorubin.

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 Chiralpak® β-cyclodextrin chiral column (30 m length × 0.30 mm i.d.). Optical rotations were measured on a Schmidt + Haensch model PolaTronic 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 (6.00 g, 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 washed 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; [α]_D^25 −9.2° (c 0.37, CHCl_3) or −128° neat, literature: [24] [α]_D^25 at 19 °C −144° (homog); IR ν_{max}/cm⁻¹: 3345, 1742, 1467, 1394, 1359, 1049, 1014, 835; ^1H 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 16.5, 5.5 Hz, 1H), 1.83 (two broad lines, 12.3 Hz, 1H), 1.95 (dd, broad J 14.7 Hz, 1H), 1.37 (m, 2H), 1.33 (s, 3H), 1.15 (d, J 14.3, 10.9 Hz, 1H), 1.15 (s, 3H), 1.07 (s, 3H); ^13C NMR (75 MHz, CDCl_3) δ 138.7 (C), 128.3 (CH), 127.4 (CH), 71.8 (CHOH), 70.2 (CH), 39.7 (CH_3), 34.1 (C), 31.4 (CH), 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-Benzylxylo,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. Benzylic 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/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

[α]_D^25 −6.0° (c 0.10, CHCl_3); IR ν_{max}/cm⁻¹: 1450, 1490, 1388, 1204, 1095, 1027, 916; ^1H 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), 1.57 (s, 3H), 1.15 (d, J 14.3, 10.9 Hz, 1H), 1.15 (s, 3H), 1.07 (s, 3H); ^13C NMR (75 MHz, CDCl_3) δ 138.7 (C), 128.3 (CH), 127.4 (CH), 71.8 (CHOR), 67.3 (CH), 60.6 (C), 42.0 (CH), 36.8 (CH_3), 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

[α]_D^25 +5.8° (c 0.10, CHCl_3); IR ν_{max}/cm⁻¹: 1495, 1453, 1363, 1204, 1095, 1070, 916; ^1H NMR (300 MHz, CDCl_3) δ 7.35 (m, 5H), 4.48 and 4.56 (AB system, J 12.7 Hz, 2H), 3.60 (m, 1H), 2.55 (s, 1H), 2.14 (dd, J 6.8, J 14.7 Hz, 1H), 1.78 (dd, J 10.5, J 14.6 Hz, 1H), 1.37 (m, 2H), 1.32 (s, 3H), 1.08 (s, 3H), 1.02 (s, 3H); ^13C NMR (75 MHz, CDCl_3) δ 138.7 (C), 128.3 (CH), 127.4 (CH), 71.0 (CHOR), 69.8 (CHOR), 67.8 (CH), 58.3 (C), 37.2 (CH_2), 35.3 (CH_3), 31.8 (C), 27.9 (CH_3), 24.5 (CH_3), 24.2 (CH_3); MS m/z 245 (M^+ − 1%, 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,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%).
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 NaH₂PO₄ (0.33 g, 2.40 mmol) in water (5 mL) and then mixed with 30% aqueous NaClO₃ (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); [α]ₙ° +11.0° (c 0.08, CHCl₃); IR νmax/cm⁻¹: 3405, 1680, 1350, 1314, 1100, 1105; 'H NMR (300 MHz, CDCl₃) δ 9.70 (br s, 1H), 7.32 (m, 5H), 4.50 (m, 1H), 2.82 (dd, 1H), 2.09 (dd, 1H), 1.30 (s, 3H), 1.17 (s, 3H), 0.84 (s, 3H); 13C NMR (75 MHz, CDCl₃) δ 127.5 (CH), 127.4 (CH), 77.2 (CHOR), 54.3 (C), 47.7 (CH₂), 43.4 (C), 42.1 (CH₂), 28.3 (CH₃), 25.8 (CH₃), 24.8 (CH₃), 21.2 (CH₃); MS m/z 154 (M⁺–106, 4%), 113 (18), 111 (14), 110 (9), 109 (12), 97 (9), 92 (12), 91 (100), 65 (9), 43 (21). Anal. Calc. for C₁₁H₁₄O₂: C, 78.42; H, 9.29; O, 12.29. Found: C, 78.21; H, 9.50.

**Trans- (+)-(1R, 4S)-1-(4-benzyl oxy-1,2,2-trimethylcyclopentyl) ethanone (10a)**

Methylthiium (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 N₂ 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 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 4:6, v/v), yielding compound 2a (0.032 g, 80%) as a colorless oil; [α]ₙ° +1.4° (c 0.010, EtOH), literature:¹⁹ [α]ₙ° +13.4° (c 0.09, EtOH), literature:²² [α]ₙ° +15° (c 0.34, CH₃OH), literature:¹⁹ [α]ₙ° +22° (at 20 °C) +12.8° (c 1, EtOH); IR νmax/cm⁻¹: 3441, 2967, 2971, 1651, 1451, 1373, 1242, 1142, 1046; 'H NMR (300 MHz, CDCl₃), δ 6.05 (br s, 2H), 4.39 (m, 1H), 2.22 (dd, J = 2.91, J = 14.9 Hz, 1H), 2.15 (dd, J = 8.7, J = 14.5 Hz, 1H), 2.09 (dd, J = 8.7, J = 15.1 Hz, 1H), 1.73 (dd, J = 5.1, J = 14.0 Hz, 1H), 1.14 (s, 3H), 1.05 (s, 3H), 0.95 (s, 3H); 13C NMR (75 MHz, CDCl₃) δ 183.3 (COOH), 138.5 (C), 128.3 (C), 127.6 (CH), 127.5 (CH), 76.8 (CHOR), 70.9 (CH₂OR), 54.3 (C), 46.2 (CH₂), 42.0 (C), 42.4 (CH₂), 26.7 (CH₃), 24.1 (CH₃), 21.4 (CH₃). Anal. Calc. for C₁₉H₂₄O₂: C, 73.25; H, 8.45; O, 18.30. Found: C, 73.03; H, 8.09.

**Trans- (-)-(1R, 4S)-1-(4-hydroxy-1,2,2-trimethylcyclopentanecarboxylic 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); [α]ₙ° +13.4° (c 0.09, EtOH), literature:²² [α]ₙ° +15° (c 0.034, CH₃OH), literature:¹⁹ [α]ₙ° +22° (at 20 °C) +12.8° (c 1, EtOH); IR νmax/cm⁻¹: 3357, 1700, 1457, 1357, 1242, 1142, 1046; 'H NMR (300 MHz, CDCl₃), δ 6.05 (br s, 2H), 4.39 (m, 1H), 2.22 (dd, J = 2.91, J = 14.9 Hz, 1H), 2.15 (dd, J = 8.7, J = 14.5 Hz, 1H), 2.09 (dd, J = 8.7, J = 15.1 Hz, 1H), 1.73 (dd, J = 5.1, J = 14.0 Hz, 1H), 1.14 (s, 3H), 1.05 (s, 3H), 0.95 (s, 3H); 13C NMR (75 MHz, CDCl₃) δ 183.3 (COOH), 70.5 (CHOH), 54.6 (CH₂), 50.7 (CH₃), 45.8 (CH₂), 44.8 (C), 25.2 (CH₃), 25.1 (CH₃), 19.1 (CH₃). Anal. Calc. for C₁₉H₂₄O₃: C, 62.77; H, 9.36; O, 27.78. Found: C, 63.14; H, 9.75.

**Trans- (+)-(1R, 4S)-1-(4-hydroxy-1,2,2-trimethylcyclopentyl) 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; [α]ₙ° +1.4° (c 0.010, EtOH), literature:¹⁹ [α]ₙ° +22° (at 20 °C) +8.4° (c 1, EtOH); IR νmax/cm⁻¹: 3357, 1700, 1457, 1357, 1200, 1114, 1064, 742, 700; 'H NMR (300 MHz, CDCl₃) 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); $^1$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$_2$), 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)ethane (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,3'S,5R,5'R')-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) (0.07 g, 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); $^1$C NMR (100 MHz, CDCl$_3$) δ 203.98 (CO), 147.8 (CH$_2$), 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.

References


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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\(_3\)).
Total Synthesis of (3S, 5R, 3'S, 5'R)-Capsorubin

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$_3$).