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Microbial reduction of 2-(6-*m*-methoxyphenyl-3-oxohexyl)-2,4,4-trimethylcyclopenta-1,3-dione with *Schizosaccharomyces pombe* (NRRL Y-164)

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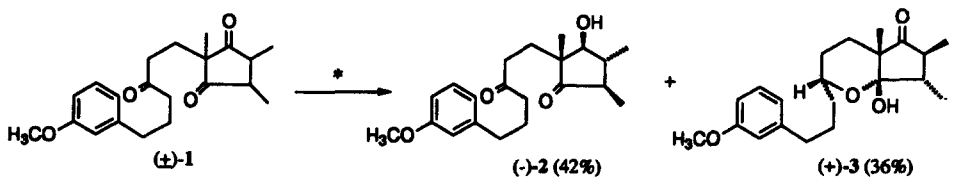
Abstract: Racemic 2-(6-*m*-methoxyphenyl-3-oxohexyl)-2,4,4-trimethylcyclopenta-1,3-dione **4** was resolved by reduction with *Schizosaccharomyces pombe* (NRRL Y-164) to give (−)-**5**, (+)-**6**, and (+)-**7** in 37, 12, and 19% yields, respectively. Chromic acid oxidation of (−)-**5** gave (+)-**4** while oxidation of (+)-**6** and (+)-**7** gave (−)-**4**, respectively. Sodium borohydride reduction of (+)-**4** followed by Oppenauer oxidation yielded (−)-**5** and (−)-**7**, and the same treatment of (−)-**4** yielded (+)-**5** and (+)-**7**, respectively. © 1997 Elsevier Science Ltd

Introduction

In a previous communication,[1] we reported the resolution of racemic 2-(6-*m*-methoxyphenyl-3-oxohexyl)-2,4,5-trimethylcyclopenta-1,3-dione **1** by microbial reduction with *Schizosaccharomyces pombe* (NRRL Y-164) to give **2** and **3** in 42 and 36% yields, respectively (Scheme 1). Racemic 2-(6-*m*-methoxyphenyl-3-oxohexyl)-2,4,4-trimethylcyclopenta-1,3-dione **4** was prepared earlier by us and subjected to an asymmetric cyclization reaction with L(−) and D(+)-phenylalanine as the asymmetry inducers,[2] respectively. In view of the successful resolution of **1** with *S. pombe* (NRRL Y-164), **4** was incubated with this same microorganism. We would like to report the results obtained together with the chemical correlation reactions performed during the characterization of transformation products.



* ***Schizosaccharomyces pombe* (NRRL Y-164)**

Scheme 1.

Results and discussion

From the incubation mixture of (±)-**4** with *S. pombe* (NRRL Y-164), (−)-**5**, (+)-**6**, and (+)-**7** were isolated in 37, 12, and 19% yields, respectively (Scheme 2).

Compound (−)-**5**, colorless oil with $[\alpha]_D^{25}$ −19.0 (c 0.94, $CHCl_3$), has a molecular formula $C_{21}H_{30}O_4$ as deduced from its HREIMS *m/z* 346.2146 (calcd 346.2144). Its IR absorption at 3500 cm^{-1} and a carbinoyl proton signal at δ 4.04 (dd, *J*=6.5 and 8.9 Hz) in its ^{1}H-NMR spectrum support the presence of a secondary hydroxyl group on the five-membered ring. The fact that (−)-**5**

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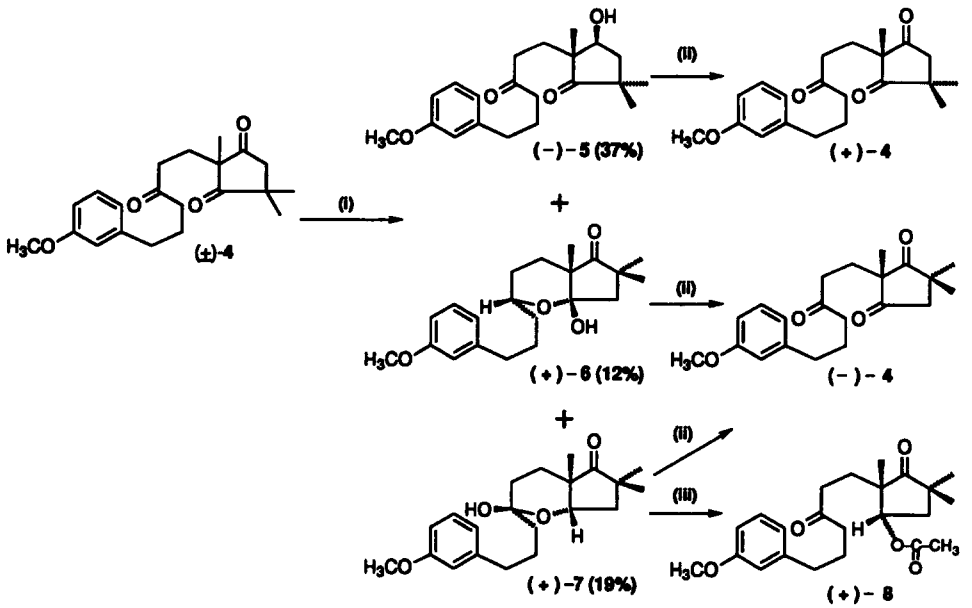


(I) *Schizosaccharomyces pombe* (NRRL Y-164)

(II) CrO_3-H^+ ; (III) Ac_2O-Py

Scheme 2.

is resistant to Oppenauer oxidation[3] but can be oxidized by Jones' reagent[4] to (+)-**4**, $[\alpha]_D^{24}$ +4.9 (c 1.0, $CHCl_3$), support this suggestion. Therefore, 1-hydroxy-2-(6-*m*-methoxyphenyl-3-oxohexyl)-2,4,4-trimethylcyclopenta-3-one was assigned to (−)-**5** and its (1*S*,2*R*)-stereochemistry was determined by chemical correlation which will be described later.

Compound (−)-**6**, $[\alpha]_D^{25}$ +83 (c 1.0, $CHCl_3$), mp 95–96°C, has a molecular formula $C_{21}H_{30}O_4$ as deduced from its HREIMS *m/z* 346.2141 (calcd 346.2144). Its IR absorption at 3420 and 1730 cm^{-1} suggested the presence of a hydroxyl and a carbonyl function. The ^{13}C-NMR spectrum revealed a sole carbonyl carbon (δ 223.3), a dioxygenated carbon (δ 102.2) and an oxygenated methine (δ 69.8, d) which couples directly to a carbinoyl proton (δ 3.70), identified by a HMQC spectrum. The molecular formula of (+)-**6** provided seven ring and double bond equivalents, six of which are easily identified from the presence of an aryl ring, a carbonyl group and the five-membered ring in the molecule. The HMBC spectrum (Figure 1) showed that the dioxygenated carbon coupled to 6-Me singlet (δ 1.01) and 9-H_2 (δ 1.94 and 2.10), and the carbonyl carbon coupled to 6-Me, 8α- and 8β-Me. This afforded the exact substitution pattern for the five-membered ring and the dioxygenated carbon to be a hemiketal carbon, probably ether-linked to C-3 to form a pyran ring accounting for the seventh equivalent. This suggestion was supported by the coupling pattern of the carbinoyl carbon (H-3, δ 3.70, ddt, *J*=11.4, 1.5, 5.6 Hz) which indicated H-3 to be an axial proton coupling to the flexible C-1′ proton (δ 1.40), and the axial proton (δ 0.96, *J*=11.4 Hz) and equatorial proton (δ 1.42, m) of C-4, clarified by a COSY-45 spectrum. Based on these analyses and supported by the X-ray diffraction analysis[5] the structure of (+)-**6** was established as (1*S*,3*R*,6*R*)-1-hydroxy-3-(3-*m*-methoxyphenylpropyl)-6,8,8-trimethyl-2-oxabicyclo[4,3,0]nonan-7-one.

Compound (+)-**7**, $[\alpha]_D^{25}$ +18.8 (c 1.0, $CHCl_3$), has a molecular formula $C_{21}H_{30}O_4$ as deduced from its HREIMS *m/z* 346.2144 (calcd 346.2144). Its IR absorption at 3450 and 1740 cm^{-1} suggested the presence of a hydroxyl and a carbonyl function as similar to (+)-**6**. The ^{13}C-NMR spectrum revealed a sole carbonyl carbon (δ 225.5), a dioxygenated carbon (δ 96.4, s) and an oxygenated methine (δ

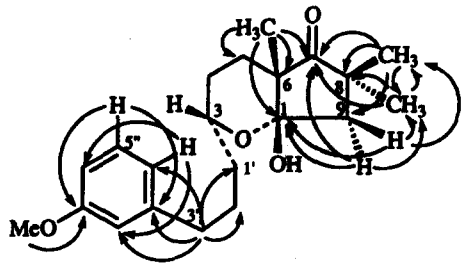


Figure 1. HMBC correlations for (+)-**6**.

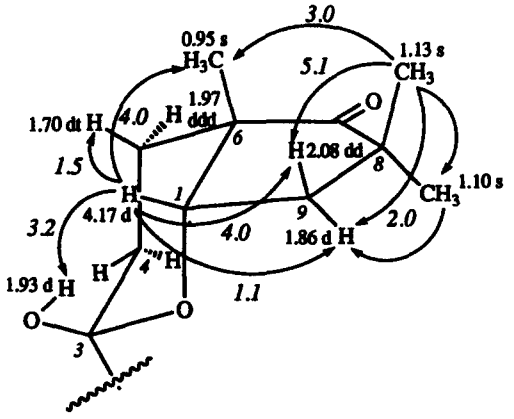


Figure 2. Partial ^{1}H-NMR data and NOED (arrow, %) of (+)-**7**.

75.5, d) which couples directly to a carbinoyl proton (δ 4.17), identified by an HMQC spectrum. These data suggested that (+)-**7** is structually related to (+)-**6**. The ^{1}H-NMR spectrum showed an D_2O exchangeable doublet at δ1.93 (J=2.0 Hz), which couples to H-4α (an axial proton) (δ 1.22, ddt, J=2.0, 4.18, 13.4 Hz), identified by the D_2O exchange experiment and double resonance at δ1.93, both of which collapsed H-4α to a double triplet (J=4.8, 13.4 Hz). These results locate 3β-OH which H-bonds to pyran oxygen (O-2) to make a W-shape coupling between O*H* and H-4α. An NOE study enhancing 3β-O*H*, 6-Me (δ 0.95, s), H-9α (δ 1.86, d) upon irradiation of H-1 (δ 4.17) also confirmed the *cis* relationship of H-1 to both 3β-OH and 6-Me (Figure 2). Treatment of (+)-**7** with Ac_2O–Py (r.t., 18h) yielded a needle shaped crystalline (+)-**8**, $[\alpha]_D^{25}$ +6.8 (c 1.25, $CHCl_3$), mp 58–59°C, having a molecular formula $C_{23}H_{32}O_5$ as deduced from its HREIMS *m/z* 388.2242 (calcd 388.2250). The structure of (+)-**8** was elucidated as (+)-(1*S*,2*S*)-1-acetoxy-2-(6-*m*-methoxyphenyl-3-oxohexyl)-2,4,4-trimethylcyclopenta-3-one based on X-ray diffraction analysis.[6] Based on the data obtained in (+)-**8**, the structure of (+)-**7** was concluded to be (1*S*,3*R*,6*S*)-3-hydroxy-3-(3-*m*-methoxyphenylpropyl)-6,8,8-trimethyl-2-oxabicyclo[4,3,0]nonan-7-one. Detailed ^{1}H- and ^{13}C-NMR assignments of (+)-**7** were made by analysis of COSY-45, HMQC, and HMBC spectra (Figure 3).

Chromic acid oxidation of both (+)-**6** and (+)-**7** yielded (−)-**4**, $[\alpha]_D^{25}$ −5.0 (c 1.0, $CHCl_3$), respectively. From earlier experience,[2] the carbonyl group flanked by four vicinal alkyl groups on the cyclopentane ring was not reduced under the condition of $NaBH_4$/MeOH/0°C.[7] This is a similar result to that which we obtained here with *S. pombe* (NRRL Y-164) and (±)-**4**. The $NaBH_4$ reduction of (+)-**4** followed by Oppenauer oxidation[3] yielded two mono-alcohols in 28 and 42% yields, respectively. The minor product with $[\alpha]_D^{25}$ −19.2 (c 1.04, $CHCl_3$) is identical in every respect (UV, IR and NMR) to (−)-**5** isolated from microbial reduction. The major product with $[\alpha]_D^{25}$ −18.9 (c 1.06, $CHCl_3$),

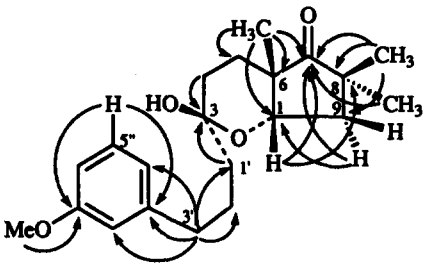
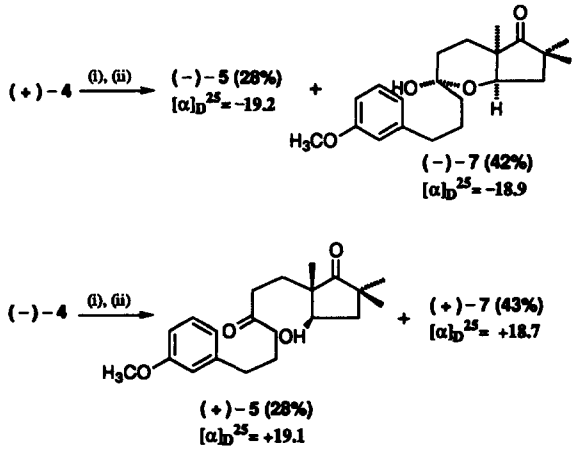


Figure 3. Major HMBC correlation for (+)-7.

possessed identical spectral data to (+)-**7** but with opposite optical rotation. The same treatment of (−)-**4** also yielded a minor product (+)-**5** (28%) with $[\alpha]_D^{25}$ +19.1(c 1.02, $CHCl_3$), and a major product (+)-**7** (43%) with $[\alpha]_D^{25}$ +18.7 (c 0.99, $CHCl_3$) (Scheme 3). During these chemical correlation reactions with (+)- and (−)-**4** as the starting material, respectively, a pair of epimeric cyclopentanols formed in each case. In both instances, the major product was the one with the hydroxy group *trans* oriented in regard to the C-2 methyl which formed a pyrane ring involving the C-3′ side-chain carbonyl and leading to the formation of a hemiketal carbon. The minor product was the one with the hydroxy group *cis* oriented in regard to the C-2 methyl and remained unchanged. Based on results obtained on chemical correlation, the (1*S*,2*R*)-stereochemistry for (−)-**5** was assigned. These results also indicated the essential optical purity of these microbially reduced products.



(i) $NaBH_4$, MeOH, 0°C , 2h.
(ii) $Al(i\text{-}PrO)_3$, Me_2CO-C_6H_6, reflux, 21h.

Scheme 3.

Thus, in this study, we showed that resolution of (±)-**4**. could be achieved by microbial reduction with *S. pombe* (NRRL Y-164) in moderate yields. In both enantiomers, the less sterically hindered carbonyl group on the cyclopentane ring could be reduced to (*S*)-alcohol but to a different extent. In (+)-**4**, the less hindered carbonyl group is located in such a way that it is equivalent to the C-17 in steroid and was reduced more extensively. On the other hand, in (−)-**4**, the side-chain carbonyl was also reduced to a considerable extent.

Experimental

General

Melting points measured on a Buchi 510 melting point apparatus were uncorrected. Optical rotations were measured on a Jasco DIP-370 digital polarimeter. UV spectra were recorded on a Hitachi 150-20 double beam spectrometer. IR spectra were recorded on a Jasco A-100 infrared spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were obtained on Bruker AM-200 or Bruker AMX-400 spectrophotometer in $CDCl_3$ or CD_3OD using the solvent peaks as reference standards. 2D-NMR spectra were recorded by using Bruker's standard pulse program: in the HMQC and HMBC experiments, Δ=1 s and J=140, 8 Hz, respectively, the correlation maps consisted of 512×1K data points per spectrum, each composed of 16 to 64 transients. EIMS were recorded on Finnigan Mat 4500 GC/MS and HREIMS on JEOL JMX-HX-110 mass spectrometer at 70 eV. Normal phase silica gel for column chromatography were purchased from Merck, 7734 (70–230 mesh) and 9385 (230–400 mesh); TLC plates of Merck 573 (Si60 with F_{254}, 0.25 mm) were purchased from E. Merck, A.G., Darmstadt, Germany.

All of the solvents and inorganic chemicals were reagent grade. Sodium borohydride and aluminum isopropoxide were purchased from Aldrich chemical Co., Inc., Milwaukee, WI. Nutrient broth, maltose, proteose peptone #3 and bacto-agar were from Difco Laboratories, Detroit, MI. Dextrose was obtained from Wako Pure Chemical Industries, Ltd, Osaka, Japan.

The microorganism, *Schizosaccharomyces pombe* (NRRL Y-164), was maintained on an MP-#3 Agar (Maltose 4%, Proteose Peptone #3 1.5%, and Agar 3%) at 26°C for 11 days then transferred and grown in Nutrient broth–Dextrose medium (Nutrient broth 1.6% and Dextrose 4%) at 24–26°C on a rotary shaker (250 rpm, 1 in. stroke). Transformations were carried out in 2 L Erlenmyer flasks containing 400 mL of the same medium.

Microbiological reduction of (±)-4

The microorganism was grown in 8 L of Nutrient broth–Dextrose medium contained in twenty 2 L Erlenmyer flasks. (±)-**4** (1.83 g) dissolved in 40 mL DMF was added and the incubation was continued for 78 h. Extraction of the incubation mixture with $CHCl_3$ (3×2.7 L) and subsequent work-up gave a yellow oily residue (2.8 g). The residue was chromatographed over a silica gel column (400 g) and eluted with $CHCl_3$–Me_2CO mixture. The fractions (0.3 g) obtained from $CHCl_3$ elution were further purified over another silica gel column to recover unreacted substrate, (±)-**4** (240 mg, 13%). The fractions (0.25 g) obtained from $CHCl_3$–Me_2CO (99:1) were further purified over another silica gel column to give pure (+)-**6** (220 mg, 12%). The fractions (0.4 g) obtained from $CHCl_3$–Me_2CO (97:3) were further purified over another silica gel column to give pure (+)-**7** (349 mg, 19%). The fractions (0.7 g) obtained from $CHCl_3$–Me_2CO (95:5) were further purified over another silica gel column to give pure (−)-**5** (679 mg, 37%).

*(1S,2R)-1-Hydroxy-2-(6-*m*-methoxyphenyl-3-oxohexyl)-2,4,4-trimethyl-cyclopenta-3-one (−)-5*

Colorless liquid; $[\alpha]_D^{25}$ −19.0 (c=0.94, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3500 (OH), 2960, 1735, 1715 (C=O), 1600, 1585, 1490, 1460, 1370, 1260, 1155 and 1045 cm^{-1}; UV (MeOH) λ_{max} (log ε) 272 (3.26), 279 (3.22) nm; ^{1}H-NMR δ ($CDCl_3$) 7.15 (1H, t, J=7.8 Hz, H-5″), 6.71 (1H, br d, J=7.8 Hz, H-6″), 6.70 (1H, br d, J=7.8 Hz, H-4″), 6.68 (1H, br s, H-2″), 4.04 (1H, dd, J=8.9, 6.5 Hz, H-1), 3.75 (3H, s, 3″-OMe), 2.54 (2H, t, J=7.5 Hz, 6′-H), 2.38 (4 H, t, J=7.2 Hz, H-2′ and H-4′), 2.05 (1H, dd, J=12.8, 6.5 Hz, H-5α), 1.85 (2H, quintet, J=7.5 Hz, H-5′), 1.76 (1H, dd, J=12.8, 8.9 Hz, H-5β), 1.74 (2H, m, H-1′), 1.12 (3H, s, 4β-Me), 0.94 (3H, s, 4α-Me), 0.93 (3H, s, 2-Me); ^{13}C-NMR δ ($CDCl_3$) 224.0 (s, C-3), 211.2 (s, C-3′), 159.6 (s, C-3″), 143.0 (s, C-1″), 129.3 (d, C-5″), 120.8 (d, C-6″), 114.2 (d, C-2″), 111.2 (d, C-4″), 73.0 (d, C-1), 55.0 (q, 3″-OMe), 52.8 (s, C-2), 44.6 (s, C-4), 42.7 (t, C-5), 41.8 (t, C-4′), 37.6 (t, C-2′), 35.0 (t, C-6′), 28.6 (t, C-1′), 24.9 (t, C-5′), 26.0 (q) and 25.2 (q) (4α- and 4β-Me), 15.8 (q, 2-Me); NOED ($CDCl_3$) 2-Me to H-1′ (17.1%), 4α-Me to H-1 (6.8%), H-5α (5.6%) and 4β-Me (7.3%), 4β-Me to H-5β (3.6%) and 4α-Me (9.1%); HREIMS m/z

346.2146 (calcd for $C_{21}H_{30}O_4$ 346.2144); EIMS m/z $[M]^+$ 346 (20), 328 (20), 212 (22), 197 (29), 177(25), 141 (50), 134 (100), 121 (18).

*(1S,2R,6R)-1-Hydroxy-3-(3-*m*-methoxyphenylpropyl)-6,8,8-trimethyl-2-oxabicyclo[4,3,0]nonan-7-one (+)-6*

Colorless needle crystals, mp 95–96°C; $[\alpha]_D^{25}$ +83.0 (c=1.0, $CHCl_3$); IR (KBr) ν_{max} 3420 (OH), 2950, 1730 (C=O), 1610, 1585, 1490, 1455, 1440, 1365, 1305, 1260, 1160, 1105 cm^{-1}; UV (MeOH) λ_{max} (log ε) 273 (3.36), 279 (3.32) nm; ^{1}H-NMR δ ($CDCl_3$) 7.16 (1H, dd, *J*=8.9, 7.6 Hz, H-5″), 6.74 (1H, br d, *J*=7.6 Hz, H-6″), 6.70 (1H, br d, *J*=7.6Hz, H-4″), 6.69 (1H, br s, H-2″), 3.77 (3H, s, 3″-OMe), 3.70 (1H, m, H-3), 2.55 (2H, t, *J*=7.7 Hz, H-3′), 2.10 (1H, d, *J*=12.8 Hz, H-9β), 2.02 (1H, ddd, *J*=13.6, 4.0, 2.8 Hz, H-5α), 1.94 (1H, d, *J*=12.8 Hz, H-9α), 1.42 (1H, m) and 0.96 (1H, m) (H-4), 2.00 (1H, m) and 1.50 (1H, m) (H-2′), 1.40 (2H, m, H-1′), 1.17 (3H, s, 8β-Me), 1.13 (3H, s, 8α-Me), 1.01 (3H, s, 6-Me); ^{13}C-NMR δ ($CDCl_3$) 223.3 (s, C-7), 159.7 (s, C-3″), 144.1 (s, C-1″), 129.2 (d, C-5″), 120.8 (d, C-6″), 114.3 (d, C-2″), 110.9 (d, C-4″), 102.2 (s, C-1), 69.8 (d, C-3), 55.1 (q, 3″-OMe), 51.8 (s, C-6), 48.7 (t, C-9) and 45.0 (s, C-8), 35.9 (t, C-3′), 35.5 (t, C-1′), 28.5 (t, C-4), 28.0 (q, 8α-Me), 27.7 (t, C-5), 26.9 (t, C-2′), 26.5 (q, 8β-Me), 21.8 (q, 6-Me); NOED ($CDCl_3$) 6-Me to H-5α (4.4%), H-5β (6.4%), 8β-Me (2.9%) and H-9β (5.8%), 8α-Me to H-9α (5.9%) and 8β-Me (5.0%), 8β-Me to 6-Me (2.6%), H-9β (7.0%) and 8α-Me (6.5%); HREIMS m/z $[M]^+$ 346.2141 (calcd for $C_{21}H_{30}O_4$ 346.2144); EIMS m/z $[M]^+$ 346 (15), 328 (12), 161 (30), 141 (20), 134 (100), 121 (30), 109 (8).

*(1S,3R,6S)-3-Hydroxy-3-(3-*m*-methoxyphenylpropyl)-6,8,8-trimethyl-2-oxabicyclo[4,3,0]nonane-7-one (+)-7*

Colorless liquid; $[\alpha]_D^{25}$ +18.8 (c=1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3450 (OH), 2950, 1740 (C=O), 1600, 1580, 1495, 1460, 1380, 1260, 1155, 1060 cm^{-1}; UV (MeOH) λ_{max} (log ε) 272 (3.26), 279 (3.21) nm; ^{1}H-NMR δ ($CDCl_3$) 7.16 (1H, t, *J*=7.8 Hz, H-5″), 6.72 (1H, br d, *J*=7.8 Hz, H-6″), 6.70 (1H, br d, *J*=7.8 Hz, H-4″), 6.68 (1H, br s, H-2″), 4.17 (1H, d, *J*=4.4 Hz, H-1), 3.76 (3H, s, 3″-OMe), 2.54 (2H, t, *J*=7.7 Hz, H-3′), 2.08 (1 H, dd, *J*=14.1, 4.4 Hz, H-9β), 1.97 (1H, ddd, *J*=13.4, 4.8, 2.8 Hz, H-5α), 1.93 (1H, d, *J*=2.0 Hz, 3-O*H*), 1.86 (1H, d, *J*=14.1 Hz, H-9α), 1.70 (1H, dt, *J*=4.6, 13.4 Hz, H-5β), 1.66 (2H, m, H-2′), 1.55 (2H, m, H-1′), 1.51 (1H, ddd, *J*=13.4, 4.6, 2.8 Hz, H-4β), 1.22 (1 H, ddt, *J*=2.0, 4.8, 13.4 Hz, H-4α), 1.13 (3H, s, 8β-Me), 1.10 (3H, s, 8α-Me), 0.95 (3H, s, 6-Me); ^{13}C-NMR δ ($CDCl_3$) 225.5 (s, C-7), 159.6 (s, C-3″), 143.6 (s, C-1″), 129.3 (d, C-5″), 120.8 (d, C-6″), 114.2 (d, C-2″), 111.1 (d, C-4″), 96.4 (s, C-3), 75.5 (d, C-1), 55.1 (q, 3″-OMe), 49.4 (s, C-6), 43.4 (s, C-8), 42.6 (t, C-1′), 41.1 (t, C-9), 35.8 (t, C-3′), 30.0 (t, C-4), 28.4 (q, 8β-Me), 27.1 (q, 8α-Me), 24.9 (t, C-5), 24.7 (t, C-2′), 22.5 (q, 6-Me); Major COSY 45: H_α-4↔3-O*H*, H_β-4, H_α-5, H_β-5; H_β-4↔H_α-4, H_α-5, H_β-5; H-1↔H_β-9↔H_α-9; H-1′↔H-2′↔H-3′; H-4″↔H-5″↔H-6″; HREIMS m/z $[M]^+$ 346.2144 (calcd for $C_{21}H_{30}O_4$ 346.2144); EIMS m/z $[M]^+$ 346 (8), 328 (4), 212 (10), 194 (8), 177 (12), 142 (54), 134 (100), 121 (22), 109 (12).

Chromic acid oxidation of carbinols[4]

In a typical Jones oxidation procedure, a solution of Me_2CO (6 mL) containing the carbinol (60 mg, 0.173 mmol) was cooled to 0°–5°C, then 0.25 mL (0.6 mmol) of CrO_3–H_2SO_4 solution (prepared by dissolving 26.8 g of CrO_3 in 23 mL of conc. H_2SO_4 and H_2O added to make 100 mL) was added dropwise with stirring and the reaction mixture was stirred at room temperature for 30 min. Then EtOH (0.5 mL) and H_2O (10 mL) were added to terminate the reaction. The mixture was extracted with $CHCl_3$ (10 mL×3), and the combined $CHCl_3$ extract was washed with saturated NaCl solution and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure and purification of the product residue over silica gel column gave analytical sample.

(a) Oxidation of (−)-**5**: (−)-**5** (100 mg) was oxidized to give (+)-**4** (72.6 mg, 73%), $[\alpha]_D^{24}$ +4.9 (c=1.0, $CHCl_3$).

(b) Oxidation of (+)-**6**: (+)-**6** (50 mg) was oxidized to give (−)-**4** (35.2 mg, 70%), $[\alpha]_D^{25}$ −5.0 (c=1.0, $CHCl_3$).

(c) Oxidation of (+)-**7**: (+)-**7** (50 mg) was oxidized to give (−)-**4** (35 mg, 70%), $[\alpha]_D^{25}$ −5.0 (c=1.0, $CHCl_3$).

*(1S,2S)-1-Acetoxy-2-(6-*m*-methoxyphenyl-3-oxohexyl)-2,4,4-trimethyl-cyclopenta-3-one (+)-8*

The (+)-**7** (91 mg, 0.25 mmol) dissolved in pyridine (5 mL) was treated with Ac_2O (0.25 mL, 2.45 mmol) and left standing at r.t. for 18 h. To the reaction mixture, H_2O (40 mL) was added and the mixture was extracted with $CHCl_3$ (15 mL×3). The combined $CHCl_3$ was washed with H_2O, dried over $MgSO_4$ and the solvent evaporated to dryness to give crystalline residue. Purification of the residue over a small silica gel column and recrystallization from Me_2CO–Pet. ether gave (+)-**8** (76 mg, 74%), mp 58–59°C; $[\alpha]_D^{25}$ +6.8 (c=1.25, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2970, 2930, 1735 and 1715 (C=O and ester), 1600, 1580, 1455, 1370, 1240, 1150, 1030 cm^{-1}; UV (MeOH) λ_{max} (log ε) 273 (3.36), 279 (3.32) nm; ^{1}H-NMR δ ($CDCl_3$) 7.17 (1H, t, *J*=7.8 Hz, H-5″), 6.73 (1H, br d, *J*=7.8 Hz, H-6″), 6.70 (1H, br d, *J*=7.8 Hz, H-4″), 6.69 (1H, br s, H-2″), 5.12 (1H, t, *J*=5.9 Hz, H-1), 3.77 (3H, s, 3″-OMe), 2.56 (2H, t, *J*=7.6 Hz, H-6′), 2.47 (1 H, ddd, *J*=17.3, 10.6 and 5.5 Hz,) and 2.28 (1 H, ddd, *J*=17.3, 10.6 and 5.1 Hz,) (H-2′), 2.37 (2H, *J*=7.4 Hz, H-4′), 2.18 (1H, dd, *J*=13.9, 6.0 Hz, H-5β), 1.90 (1H, dd, *J*=13.9, 5.7 Hz, H-5α), 1.87 (2H, m, H-5′), 1.82 (1H, ddd, *J*=14.5, 11.5 and 5.4 Hz) and 1.70 (1H, ddd, *J*=14.5, 10.6 and 5.2 Hz) (H-1′), 1.11 (3H, s, 4α-Me), 1.07 (3H, s, 4β-Me), 1.03 (3H, s, 2-Me); ^{13}C-NMR δ ($CDCl_3$) 222.7 (s, C-3), 209.9 (s, C-3′), 170.3 (s, 1-O*C* (=O) Me), 159.6 (s, C-3″), 143.2 (s, C-1″), 129.3 (d, C-5″), 120.8 (d, C-6″), 114.2 (d, C-2″), 111.2 (d, C-4″), 77.7 (d, C-1), 55.1 (q, 3″-OMe), 51.3 (s, C-2), 44.5 (s, C-4), 42.0 (t, C-4′), 40.6 (t, C-5), 37.0 (t, C-2′), 35.1 (t, C-6′), 25.0 (t) and 25.1 (t) (C-1′ and C-5′), 26.5 (q, 4β-Me), 25.9 (q, 4α-Me), 21.05 (q, Me of OAc), 20.87 (q, 2-Me); NOED ($CDCl_3$) 2-Me to H-1′ (2.8%), H-2′ (d 2.28, 3.7%; d 2.47, 5.2%), H-3 (10.6%) and H-5β (3.7%), 4α-Me to H-5α (6.4%) and 4β-Me (9.6%), 4β-Me to H-1 (5.1%), H-5β (6.7%) and 4α-Me (19.1%); HREIMS m/z $[M]^+$ 388.2242 (calcd for $C_{23}H_{32}O_5$ 388.2250); EIMS m/z 389 (7), $[M]^+$ 388 (29), 370 (6), 254 (27), 194 (7), 184 (51), 177 (48), 151 (10), 134 (100), 124 (72), 109 (17).

The $NaBH_4$ reduction[7] followed by Oppenauer oxidation[3] of (+)- and (−)-4

(a) Reaction of (+)-**4**: The starting material, (+)-**4** (302 mg, 0.87 mmol), was dissolved in MeOH (10 mL) and cooled to 0°C. $NaBH_4$ (340 mg, 8.7 mmol) was added to it in portions with stirring, the reaction was terminated after 2 h by addition of H_2O (40 mL) and extracted with $CHCl_3$ (20 mL×3). The combined $CHCl_3$ extract was washed with H_2O, dried over Na_2SO_4 and the solvent removed *in vacuo* to dryness. The residue was purified over a silica gel column (20 g) eluted with $CHCl_3$–Me_2CO mixture to give 300 mg of residue after evaporation of solvent. The residue was dissolved in Me_2CO–C_6H_6 (10:15 mL) and after addition of $Al(Me_2CHO)_3$ (244 mg, 1.0 mmol) the mixture was heated at reflux for 21 h. After cooling, H_2O (20 mL), 10% H_2SO_4 (20 mL), and C_6H_6 (15 mL) were added to it and the C_6H_6 layer was separated after shaking the mixture. The aqueous layer was further extracted with C_6H_6 (15 mL×2), and the combined C_6H_6 extract was washed with H_2O, dried over Na_2SO_4 and evaporated down to dryness. The residue was chromatographed over silica gel column (35 g) eluted with $CHCl_3$–Me_2CO mixture. The fractions eluted with $CHCl_3$–Me_2CO (99:1) were further purified with a small silica gel column to give (−)-**7** (126 mg, 42%) $[\alpha]_D^{25}$=−18.9 (c 1.06, $CHCl_3$). The fractions eluted with $CHCl_3$–Me_2CO (95:5) were further purified with a small silica gel column to give (−)-**5** (84 mg, 28%) with $[\alpha]_D^{25}$=−19.2 (c 1.04, $CHCl_3$).

(b) Reaction of (−)-**4**: The starting material, (−)-**4** (300 mg, 0.87 mmol) dissolved in MeOH (10 mL) was reduced with $NaBH_4$ (343 mg, 8.7 mmol) and then oxidized with $Al(Me_2CHO)_3$ (246 mg, 1.0 mmol) as mentioned above. Work-up of the reaction mixture gave (+)-**7** (130 mg, 43%) with $[\alpha]_D^{25}$ +18.7 (c 0.99, $CHCl_3$) and (+)-**5** (83 mg, 28%) with $[\alpha]_D^{25}$ +19.1 (c 1.02, $CHCl_3$) after column chromatographic separation and purification.

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5. Crystal data of (+)-**6**: orthorhombic p212121; a=6.755(3), b=8.846(7) Å, Z=4. Intensity data were collected on a CAD-4 diffractometer with θ/2θ scan mode, using monochromated MoKα radiation. Data were measured up to 2θ of 140.0°. A total of 2095 reflections were collected. Among them, 1787 were considered to be observed (>2.05 δ (I)). Final agreement indices are R(F)=0.049, RW=0.047, GoF=2.35, based on anisotropic refinement of all non-hydrogen atoms.
6. Crystal data of (+)-**8**: monoclinic p21; a=5.6743 (II), b=14.254 (6), c=13.857 (6) Å, Z=2. Intensity data were collected on a CAD-4 diffractometer with θ/2θ scan mode, using monochromated MoKα radiation. Data were measured with 2θ range of 30–44°. A total of 2534 reflections were collected. Among them, 1489 were considered to be observed (>2.05 δ (I)). Final agreement indices are RF=0.059, RW=0.062, GoF=1.23, based on anisotropic refinement of all non-hydrogen atoms.
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