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Ring Contraction Through Epoxide Rearrangement: A Formal Synthesis of Capsorubin

Mauricio Gomes Constantino [a], Paulo Marcos Donate [a], Daniel Frederico [a], Tecia Vieira Carvalho [a], Luiz Eduardo Cardoso [a] & Julio Zukerman-Schpector [b]

[a] Departamento de Quimica, Faculdade de Filosofia, Ciéncias e Letras de Ribeirão Preto, Universidade de São Paulo, Avenida Bandeirantes 3900, 14040--901 - Ribeirão Preto-SP, Brazil Phone: +55/16 602 3747 Fax: +55/16 602 3747 E-mail:

[b] Departamento de Química, Centro de Ciéncias e Tecnologia, Universidade Federal de Säo Carlos, P. O. Box 676, 13565--905, Säo Carlos, SP, Brazil

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RING CONTRACTION THROUGH EPOXIDE REARRANGEMENT: A FORMAL SYNTHESIS OF CAPSORUBIN

Mauricio Gomes Constantino,* Paulo Marcos Donate, Daniel Frederico,
Tecia Vieira Carvalho, Luiz Eduardo Cardoso[1]

Departamento de Química, Faculdade de Filosofia, Ciências e Letras de Ribeirão Preto, Universidade de São Paulo, Avenida Bandeirantes 3900, 14040-901 - Ribeirão Preto-SP, Brazil. Fax +55/16 633 8151. Phone +55/16 602 3747. Email mgconsta@usp.br

and Julio Zukerman-Schpector

Departamento de Química, Centro de Ciências Exatas e Tecnologia, Universidade Federal de São Carlos, P. O. Box 676, 13565-905 – São Carlos – SP, Brazil

ABSTRACT: An eight-step synthesis of the cyclopentane keto-alcohol **2**, which has previously been converted in one step into the carotenoid pigment capsorubin (**1**), is described. The key step in our synthesis is a stereospecific epoxide rearrangement with ring contraction, thus producing the cyclopentane ring from an epoxide of a cyclohexene.

Capsorubin (**1**) (Figure 1) is a carotenoid pigment,[2, 3] a xanthophyll with a structure containing rather unusual five-membered ring end groups. It is found in red peppers (*Capsicum annuum*) and has been synthesized by adding two units of compound **2** to crocetindial (**3**) through aldol condensation.[4] Syntheses of compound **2** were described by Marquet *et al.*[5] and by Weedon *et al.*,[6] producing either racemic or, when (+)-camphor was used as starting material, optically active products. These syntheses are laborious several-step procedures with reported overall yields varying from 0.03 to 4%.

* To whom correspondence should be addressed

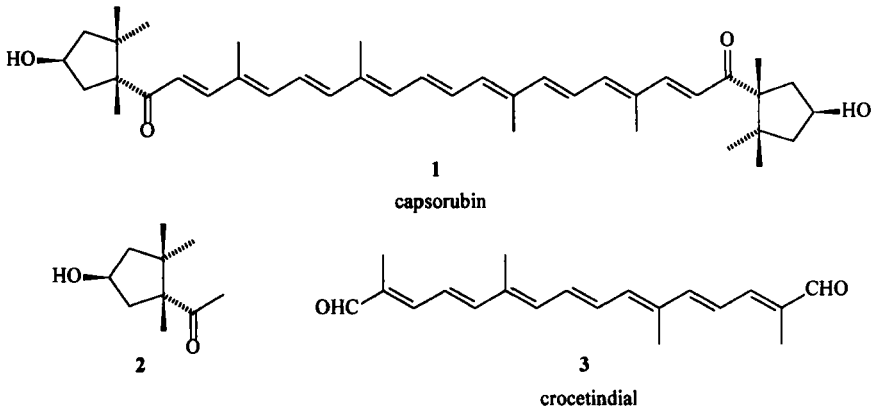
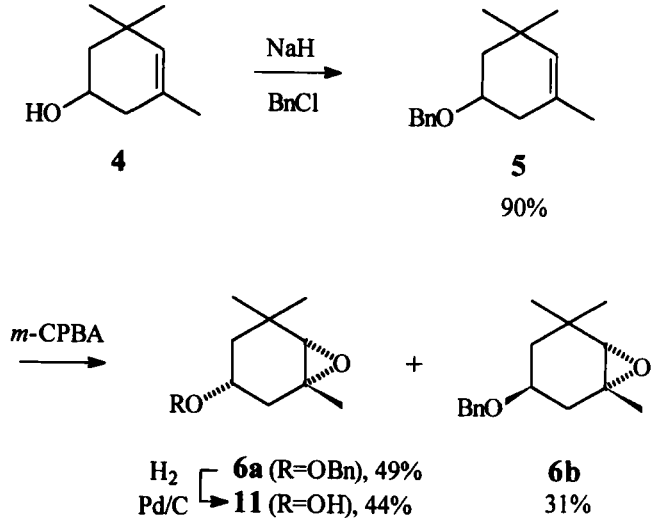


Figure 1. Capsorubin and starting materials for the last step

In this paper we describe an alternate route to compound **2** which we have developed as a consequence of results obtained during our studies on the synthesis of abscisic acid[7,8] and related compounds.[9] Although this route produced compound **2** in racemic form, it is a short eight-step synthesis, it does not involve any particularly complex processes and uses readily available chemicals.

Scheme 1



We started with compound **4** (Scheme 1), easily prepared in two steps (79% overall yield) from commercially available isophorone.[10] In previous work[13] we found that the epoxides obtained from **4** gave a large number of by-products when treated with BF_3 etherate, and low yields of pure products; to overcome this difficulty, the alcohol group of **4** was now protected as its benzyl ether (90% yield). Oxidation of **5** with *m*-chloroperoxybenzoic acid furnished a mixture of stereoisomers **6a** and **6b**, easily separable by chromatography.

The relative stereochemistry of epoxides **6a** and **6b** could not be unambiguously determined by NMR measurements. We have thus submitted to an X-ray crystallographic analysis[14] the phenylurethan (**12**) of the alcohol (**11**) obtained from hydrogenolysis of **6a**. The ORTEP view of the molecule is shown in Figure 2.

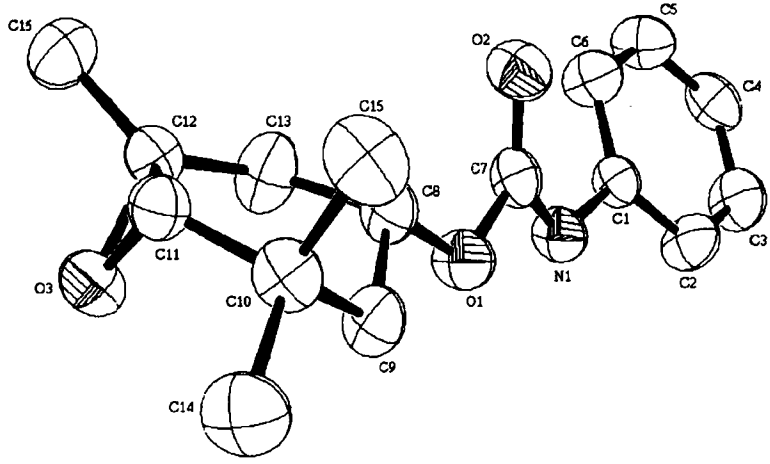
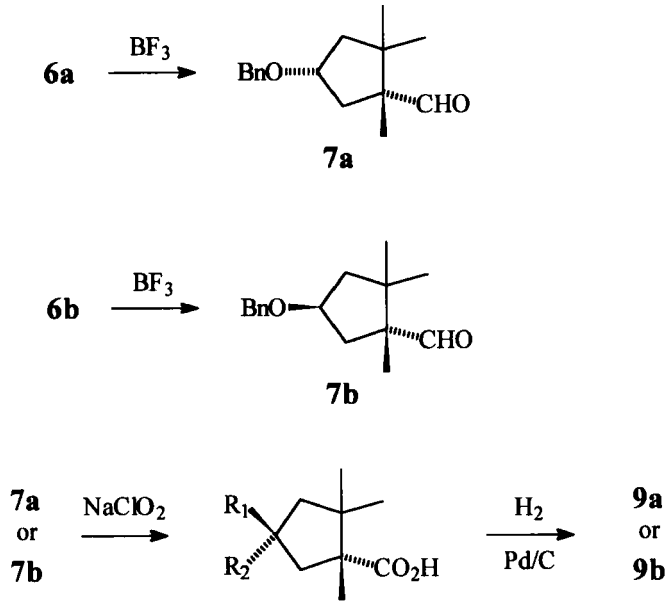


Figure 2. ORTEP view of the phenylurethan (**12**) prepared from **6a**

Upon treatment with BF_3 etherate, epoxides **6** (Scheme 2) produce aldehydes **7** together with a number of by-products. However, each isomer of aldehyde **7** is obtained almost exclusively (GLC) from the corresponding isomer of **6**, thus establishing the stereospecific nature of the epoxide rearrangement reaction.

Scheme 2

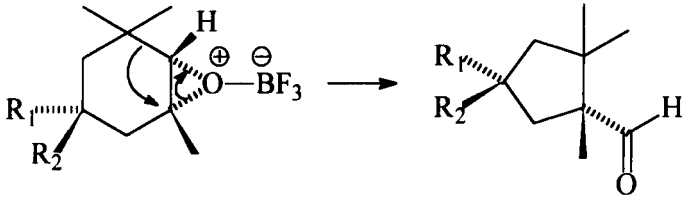


8a (R_1=H, R_2=OBn) (48% from **6a**)
8b (R_1=OBn, R_2=H) (62% from **6b**)
9a (R_1=H, R_2=OH) (74% from **8a**)
9b (R_1=OH, R_2=H) (85% from **8b**)

Aldehydes **7a** and **7b** can be isolated (yields 55% and 52%), but their purification has to be realized through column chromatography. As the carboxylic acids **8** can be easily purified by taking advantage of the water solubility of their sodium salts, we found it preferable to oxidize the crude aldehydes directly to the carboxylic acids **8** and then isolate the products (yields 48% and 62% from the epoxides **6**). The benzyl group of each isomer (**8a** and **8b**) was removed by hydrogenolysis (74% and 85% yield) to give the known[6, 13] compounds **9a** and **9b**, thus confirming the relative stereochemistry assigned to **8a** and **8b**. This stereochemistry shows that, in the epoxide rearrangement, the migrating group

approaches the carbon atom from the opposite side of the breaking C-O bond of the epoxide, strongly suggesting that no free carbocation is formed (Scheme 3).

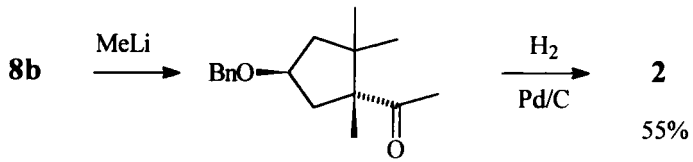
Scheme 3



6a : R_1 = OBn, R_2 = H **7a** : R_1 = OBn, R_2 = H

6b : R_1 = H, R_2 = OBn **7b** : R_1 = H, R_2 = OBn

Scheme 4



10b

69%

Compound **8b** was converted into **10b** (Scheme 4) by treatment with methyllithium at room temperature (69% yield). Hydrogenolysis of **10b** furnished the desired compound **2** (55% yield from **10b**, 5.2% overall yield from isophorone), thus completing the formal synthesis of capsorubin.

Experimental Section

NMR spectra were measured using a Bruker DPX-300 (300 MHz ^{1}H NMR

and 75 MHz ^{13}C NMR) instrument; deuterochloroform was used as solvent and tetramethylsilane as internal standard. IR spectra were measured with a Perkin-Elmer 1430 or a Perkin-Elmer 1600 FT spectrometers. TLC was performed on precoated silica gel 60 F_{254} (0.25 mm thick, Merck), and for column chromatography silica gel 60 70-230 mesh (Merck) was used. 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 range 50-200°C. Given yields correspond to materials with the same purity as the samples used in the subsequent steps.

5-Benzyloxy-1,3,3-trimethylcyclohexene (5).

A solution of 3,5,5-trimethylcyclohex-3-enol (**4**)[10] (2.00 g, 14.3 mmol) in dry dioxane (150 mL) was added to sodium hydride (4.20 g of a 60 % dispersion in mineral oil, previously washed with *n*-hexane, 105 mmol). The reaction mixture was heated to reflux for 3 h and then cooled to room temperature. Benzyl chloride (2.35 g, 18.6 mmol) in dry dioxane (15 mL) was added and the mixture was heated again to reflux for 24 h. The reaction mixture was cooled, crushed ice was added, and the product was extracted with ether. The combined ethereal extracts were dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the residue was purified by column chromatography through silica gel using a mixture of *n*-hexane and ethyl acetate (9:1) as eluent.

Yield 2.95 g (12.8 mmol, 90%);

IR (neat film): 1453, 1360, 1239, 1094, 1073, 1028, 903, 833, 734, 696 cm^{-1};

^1H NMR ($CDCl_3$) δ 7.30 (br. s, 5H), 5.11-5.08 (br. s, 1H), 4.58 (s, 2H), 3.74 (m, 1H), 2.25 (dd, broad lines, J_1=5.5 Hz, J_2=16.5 Hz, 1H), 1.95 (dd, broad lines, J_1=9.4 Hz, J_2=15.5 Hz, 1H), 1.83 (two broad lines, 12.3 Hz apart, 1H), 1.62 (br. s, 3H), 1.36 (t, J=11.9 Hz, 1H), 1.00 (s, 3H), 0.94 (s, 3H);

^{13}C NMR ($CDCl_3$) 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 (rel. intensity) 124 (46) [M^+ - 106], 109 (46), 96 (58), 91 (100), 81 (28), 77 (11), 69 (16), 65 (16), 41 (23), 39 (5).

3-Benzyloxy-1,5,5-trimethyl-7-oxabicyclo[4.1.0]heptane (6).

To a solution of compound **5** (0.15 g, 0.65 mmol) in methylene chloride (3 mL), maintained at 25°C, was added dropwise a solution of *m*-chloroperoxybenzoic acid (0.30 g of 85% MCPBA, 1.6 mmol) in methylene chloride (10 mL). The reaction mixture was stirred at the same temperature for 3 h. The resulting mixture was treated with 10% sodium sulfite solution (20 mL) and stirred for 1 h to remove excess of peracid. The organic phase was separated and the aqueous phase was extracted with methylene chloride. The combined organic extracts were washed with 5% $NaHCO_3$, water, saturated brine, and dried over anhydrous magnesium sulfate. Removal of the solvent under vacuum. A mixture of the *cis* and *trans* isomers of compound **6** (0.14 mg, 89%) was obtained. Isomers **6a** and **6b** were isolated by column chromatography through silica gel, by using a mixture of *n*-hexane, methylene chloride and ethyl acetate (12:7:1) as eluent.

Cis-Isomer **6a**: yield 79 mg (0.32 mmol, 49% from **5**);

IR (neat film): 1737, 1453, 1363, 1094, 1066, 1027, 919, 816, 735, 697 cm^{-1};

^1H NMR ($CDCl_3$) δ 7.35 (br. s, 5H), 4.48 and 4.50 (AB system, J=12.1 Hz, 2H), 3.54 (m, 1H), 2.51 (s, 1H), 2.14 (dd, J_1=6.8 Hz, J_2=14.7 Hz, 1H), 1.78 (dd, broad lines, J_1=10.5 Hz, J_2=14.6 Hz, 1H), 1.38 (m, 2H), 1.32 (s, 3H), 1.08 (s, 3H), 1.02 (s, 3H);

^{13}C NMR ($CDCl_3$) δ 138.7 (C), 128.3 (CH), 127.5 (CH), 71.0 (CHOR), 69.9 (CH_2OR), 67.9 (CH), 58.3 (C), 37.3 (CH_2), 35.3 (CH_2), 31.9 (C), 27.9 (CH_3), 24.6 (CH_3), 24.3 (CH_3);

MS m/z (rel. intensity) 245 (4) [$M^{+\cdot}$- 1], 155 (10), 135 (15), 123 (12), 105 (100), 95 (36), 91 (32), 69 (21), 43 (66);

Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.82; H, 8.92.

Trans-Isomer **6b**: yield 49 mg (0.20 mmol, 31% from **5**);

IR (neat film): 1453, 1495, 1388, 1363, 1204, 1095, 1070, 1027, 916, 827, 735, 692 cm^{-1};

^1H NMR ($CDCl_3$) δ 7.40 (br. s, 5H), 4.47 and 4.56 (AB system, J=12.7 Hz), 3.60

(m, 1H), 2.63 (s, 1H), 2.41 (dd, broad lines, J_1= 3.95 Hz, J_2=14.3 Hz, 1H), 1.64 (m, 2H), 1.37 (s, 3H), 1.15 (dd, J_1=10.9 Hz, J_2=14.3 Hz, 1H), 1.15 (s, 3H), 1.07 (s, 3H);
^{13}C NMR ($CDCl_3$) δ 138.8 (C), 128.2 (CH), 127.4 (CH), 127.3 (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), 25.6 (CH_3), 23.3 (CH_3).
MS m/z (rel. intensity) 155 (16) [$M^{+\cdot}$-91], 137 (14), 113 (14), 109 (9), 99 (9), 97 (16), 95 (18), 92 (33), 91 (100), 65 (15), 43 (40), 41 (18);
Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.62; H, 8.79.

Cis-1,5,5-Trimethyl-7-oxabicyclo [4.1.0] heptan-3-ol (11).

A suspension of 5% palladium on activated carbon (10 mg) in dry methanol (10 mL) was stirred under a hydrogen atmosphere for 40 min. A solution of compound **6a** (200 mg, 0.82 mmol) in dry methanol (5 mL) was then added, and stirring was continued until 1 equivalent of hydrogen had been consumed. The mixture was then filtered and the solvent was removed under vacuum. The residue was purified by column chromatography through silica gel eluting with a mixture of *n*-hexane and ethyl acetate (4:6).
Yield 57 mg (0.36 mmol, 44%);
^{1}H RMN ($CDCl_3$) δ 3.7 (m, 1H), 3.0 (br. s, 1H), 2.58 (s, 1H), 2.03 (dd, J_1 = 14.6 Hz, J_2 = 6.1 Hz, 1H), 1.79 (dd, J_1 = 14.9 Hz, J_2 = 8.2 Hz, 1H); 1.41 (dd, J_1 = 12.9 Hz, J_2 = 9.7 Hz, 1H), 1.35 (s, 3H), 1.27 (dd, J_1 = 12.6 Hz, J_2 = 3.5 Hz, 1H), 1.1 (s, 3H), 1.0 (s, 3H);
^{13}C RMN ($CDCl_3$) δ 68.1 (CH), 64.8 (CHOH), 59.4 (C), 41.0 (CH_2), 37.1 (CH_2), 31.2 (C), 27.7 (CH_3), 26.2 (CH_3), 23.9 (CH_3).

N-Phenyl (1,5,5-trimethyl-7-oxabicyclo[4.1.0]hept-3-yloxy) carboxamide (12).

A mixture of compound **11** (1.0 g, 6.41 mmol) and phenyl isocyanate (1.0 mL, 9.15 mmol) was heated in a boiling water bath for 5 min. The reaction mixture was cooled to 0°C and the solid product thus obtained was washed with *n*-hexane and recrystallized from ethyl acetate.

Yield 1.09 g (3.96 mmol, 62%); mp 109-110°C;

^{1}H RMN ($CDCl_3$) δ 7.5-7.0 (m, 5H), 6.9 (s, 1H); 4.9 (m, 1H), 2.6 (s, 1H), 2.29 (dd, J_1 = 14.8 Hz, J_2 = 7.2 Hz, 1H), 2.1 (s, 3H); 1.86 (dd, J_1 = 14.6 Hz, J_2 = 10.1 Hz, 1H), 1.5 (m, 2H), 1.3 (s, 3H), 1.1 (s, 3H), 0.9 (s, 3H).

***Cis*-4-benzyloxy-1,2,2-trimethylcyclopentanecarbaldehyde (7a).**

To a solution of compound **6a** (500 mg, 2.03 mmol) in methylene chloride (25 mL) was added freshly distilled (58°C, 30 mm) boron trifluoride etherate (0.20 mL, 230 mg, 1.62 mmol). The solution was stirred for 30 minutes at room temperature and then treated with a saturated solution of sodium bicarbonate (35 mL). The resulting mixture was stirred for 30 minutes; the organic phase was then separated and the aqueous phase was extracted with methylene chloride. The combined organic extracts were washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the crude product, obtained in quantitative yield, was used in the following step without further purification.

For analytical purposes a similar preparation was carried out starting with compound **6a** (501 mg, 2.04 mmol); the crude product obtained as described above was purified by column chromatography through silica gel, by using a mixture of *n*-hexane and ethyl acetate (9:1) as eluent.

Yield 275 mg (1.12 mmol, 55%);

IR (neat film): 2870, 2788, 2723, 1718, 1384, 1365, 1351 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 9.8 (s, 1H), 7.3 (br. s, 5H), 4.49 and 4.47 (AB system, J=11.7 Hz, 2H), 4.20 (m, 1H), 2.32 (dd, J_1=14.6 Hz, J_2=4.2 Hz, 1H), 2.06 (dd, J_1=13.8 Hz, J_2=7.8 Hz, 1H), 1.95 (dd, J_1=14.4 Hz, J_2=8.1 Hz, 1H), 1.83 (dd, J_1=13.8 Hz, J_2=4.8 Hz, 1H), 1.08 (s, 3H), 0.99 (s, 3H), 0.95 (s, 3H);

^{13}C NMR ($CDCl_3$) δ 206.3 (CHO), 138.5 (C), 128.3 (CH), 127.6 (CH), 127.5 (CH), 77.5 (CHOR), 71.0 (CH_2OR), 57.3 (C), 47.5 (CH_2), 43.8 (C), 40.7 (CH_2), 25.3 (CH_3), 24.5 (CH_3), 16.2 (CH_3);

MS m/z (rel. intensity) 155 (12) [M^+-91],109 (19), 110 (12), 99 (35), 92 (28), 91 (100), 71 (9), 65 (16), 43 (14), 41 (16).

***Trans*-4-benzyloxy-1,2,2-trimethylcyclopentanecarbaldehyde (7b).**

Compound **6b** (901 mg, 3.66 mmol) in methylene chloride (35 mL) was treated with boron trifluoride etherate (0.40 mL, 460 mg, 3.25 mmol) in the same way as described above. Crude product **7b**, similarly obtained in quantitative yield, was also used in the following step without further purification.

For analytical purposes a similar preparation was carried out starting with compound **6b** (503 mg, 2.04 mmol); the crude product obtained as described above was purified by column chromatography through silica gel, by using a mixture of *n*-hexane and ethyl acetate (1:1) as eluent.

Yield 262 mg (1.07 mmol, 52%);

^{1}H NMR ($CDCl_3$) δ 9.6 (s, 1H), 7.3 (br. s, 5H), 4.40 (s, 2H), 4.20 (m, 1H), 2.59 (dd, J_1=14.4 Hz, J_2=8.3 Hz, 1H), 1.89 (dd, J_1=13.8 Hz, J_2=7.2 Hz, 1H), 1.82 (dd, J_1=13.6 Hz, J_2=4.4 Hz, 1H), 1.67 (dd, J_1=14.2 Hz, J_2=3.9 Hz, 1H), 1.17 (s, 3H), 1.11 (s, 3H), 0.96 (s, 3H);

^{13}C NMR ($CDCl_3$) δ 206.7 (CHO), 139.5 (C), 128.4 (CH), 127.5 (CH), 127.3 (CH), 77.8 (CHOR), 71.0 (CH_2OR), 54.3 (C), 47.2 (CH_2), 43.6 (C), 42.4 (CH_2), 24.4 (CH_3), 21.5 (CH_3), 19.4 (CH_3).

***Cis*-4-benzyloxy-1,2,2-trimethylcyclopentanecarboxylic acid (8a).**

A buffer solution (pH 4.5) was prepared by dissolving $NaH_2PO_4 \cdot H_2O$ (1.38 g, 10.0 mmol) in water (10 mL), and then mixed with a 30% aqueous $NaClO_2$ (6 mL, ~ 20 mmol); the resulting solution was added dropwise to a previously prepared solution of the crude product **7a** (531 mg) and 2-methyl-2-butene (2.6 mL) in *t*-butanol (10 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, and the aqueous phase was extracted twice with *n*-hexane, acidified with concentrated hydrochloric acid to pH 3.5 and then extracted with ether. The combined ethereal extracts were dried over anhydrous magnesium sulfate and filtered, and the solvent was removed under reduced pressure. The residue was recrystallized from *n*-hexane to give compound **8a** as a white solid.

Yield 255 mg (0.976 mmol, 48% from **6a**); mp 85-88°C;

IR (KBr) 3443, 1671, 1442, 1357, 1300, 1242, 1114, 1050, 742 cm^{-1};

^1H NMR ($CDCl_3$) δ 9.4 (br. s, 1H), 7.32 (s, 5H), 4.50 and 4.41 (AB system, J=12.1 Hz, 2H), 4.08 (m, 1H), 2.59 (dd, J_1=5.9 Hz, J_2=14.3 Hz, 1H), 2.03 (dd, J_1=8.2 Hz, J_2=9.9 Hz, 1H), 2.01 (dd, J_1=8.3 Hz, J_2=10.1 Hz, 1H), 1.80 (dd, J_1=3.3 Hz, J_2=13.9 Hz, 1H), 1.17 (s, 3H), 1.13 (s, 3H), 1.07 (s, 3H);

^{13}C NMR ($CDCl_3$) 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), 43.0 (C), 41.3 (CH_2), 26.6 (CH_3), 24.1 (CH_3), 21.4 (CH_3);

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.23; H, 8.46. Found: C, 73.89; H, 8.11.

***Trans*-4-benzyloxy-1,2,2-trimethylcyclopentanecarboxylic acid (8b).**

Crude product **7b** (910 mg) was oxidized and purified in the same way as described for compound **7a**. After recrystallization from *n*-hexane compound **8b** was obtained as a white solid.

Yield 595 mg (2.27 mmol, 62% from **6b**); mp 82-85°C;

IR (KBr): 3457, 1685, 1350, 1457, 1314, 1142, 1100, 742 cm^{-1};

^1H NMR ($CDCl_3$) δ 9.77 (br. s, 1H), 7.32 (s, 5H), 4.50 and 4.41 (AB system, J=12.0 Hz, 2H), 4.50 (m, 1H), 2.59 (dd, J_1=5.9 HZ, J_2=14.1 Hz, 1H), 2.05 (dd, J_1=8.2 HZ, J_2=9.7 Hz, 1H), 2.01 (dd, J_1=8.32 Hz, J_2=9.8 Hz, 1H), 1.80 (dd, J_1=3.0 HZ, J_2=14.2 Hz, 1H), 1.17 (s, 3H), 1.12 (s, 3H), 1.06 (s, 3H);

^{13}C NMR ($CDCl_3$) 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. Calcd for $C_{16}H_{22}O_3$: C, 73.23; H, 8.46. Found: C, 73.03; H, 8.09.

***Cis*-4-hydroxy-1,2,2-trimethylcyclopentanecarboxylic acid (9a).**

A suspension of 5% palladium on activated carbon (20 mg) in dry methanol (5 mL) was stirred under a hydrogen atmosphere for 35 min. Then a solution of compound **8a** (212 mg, 0.811 mmol) in dry methanol (3 mL) was added and stirring was

continued until 1 equivalent of hydrogen had been consumed. The mixture was then filtered through silica gel and the solvent was removed under vacuum. The solid product was recrystallized from benzene.

Yield 101 mg (0.60 mmol, 74%); mp 200-203°C (lit.[5] mp 201°C);

IR (KBr): 3385, 1693, 1454,1264, 1037, 739 cm^{-1};

^1H NMR ($CDCl_3$) δ 6.68 (br. s, 2H), 4.32 (m, 1H), 2.22 (dd, J_1=6.6 Hz, J_2=18.0 Hz, 1H), 2.15 (dd, J_1=5.8 Hz, J_2=15.2 Hz, 1H), 2.00 (dd, J_1=2.9 Hz, J_2=18.0 Hz, 1H), 1.70 (dd, J_1=7.7 Hz, J_2=15.2 Hz, 1H), 1.15 (s, 3H), 1.06 (s, 3H), 0.96 (s, 3H);

^{13}C NMR ($CDCl_3$) δ 183.2 (COOH), 70.5 (CHOH), 54.7 (CH_2), 50.6 (C), 46.0 (CH_2 or C), 44.6 (C or CH_2), 25.3 (CH_3), 25.0 (CH_3), 19.2 (CH_3).

***Trans*-4-hydroxy-1,2,2-trimethylcyclopentanecarboxylic acid (9b).**

Isomer **8b** (117 mg, 0.44 mmol) was reduced in the same way as described above for compound **8a**, and the solid product was also recrystallized from benzene.

Yield 62.3 mg (0.38 mmol, 85%); mp 214-216°C (lit.[5] mp 221.5°C);

IR (KBr): 3441, 2967, 1731, 1651, 1451, 1373, 1242, 1142, 1046 cm^{-1};

^1H NMR ($CDCl_3$) δ 6.50 (br. s, 2H), 4.38 (m, 1H), 2.22 (dd, J_1=2.91 Hz, J_2=14.9 Hz, 1H), 2.15 (dd, J_1=8.1 Hz, J_2=14.5 Hz, 1H), 2.09 (dd, J_1=8.7 Hz, J_2=15.1 Hz, 1H), 1.73 (dd, J_1=5.1 Hz, J_2=14.0 Hz, 1H), 1.14 (s, 3H), 1.05 (s, 3H), 0.95 (s, 3H).

***Trans*-1-(4-benzyloxy-1,2,2-trimethylcyclopentyl)ethanone (10b).**

Methyllithium (0.80 mL of a 1.49 M solution in ether, 1.18 mmol) was added dropwise to a solution of compound **8b** (0.103 mg, 0.393 mmol) in THF (5 mL), maintained at 0 °C under a nitrogen atmosphere. The resulting solution was warmed to room temperature and stirred for 6 h. Crushed ice and saturated solution of ammonium chloride was then added and the product was extracted with ether. The ethereal extract was dried over anhydrous magnesium sulfate and the solvent was removed under vacuum. The residue was purified by column chromatography through silica gel, using a mixture of *n*-hexane and ethyl acetate (9:1) as eluent.

Yield 70.5 mg (0.27 mmol, 69%);

IR (neat film): 1697, 1459, 1452, 1352, 1109, 1089, 1066, 1028, 802, 734, 697 cm^{-1};
^1H NMR ($CDCl_3$) δ 7.32 (br. s, 5H), 4.47 and 4.44 (AB system, J=12.1 Hz, 2H), 4.12 (m, 1H), 2.63 (dd, J_1=14.4 Hz, J_2=8.5 Hz, 1H), 2.12 (s, 3H), 1.93 (dd, J_1=13.6 Hz, J_2=7.5 Hz, 1H), 1.81 (dd, J_1=13.5 Hz, J_2=4.8 Hz, 1H), 1.61 (dd, J_1=14.4 Hz, J_2=3.2 Hz, 1H), 1.30 (s, 3H), 1.17 (s, 3H), 0.85 (s, 3H);
^{13}C NMR ($CDCl_3$) δ 212.4 ($COCH_3$), 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 (rel. intensity) 154 (4) [$M^{+\cdot}$-106], 113 (18), 111 (14), 110 (9), 109 (12), 95 (7), 92 (12), 91 (100), 65 (9), 43 (21);
Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.21; H, 9.30.

***Trans*-1-(4-hydroxy-1,2,2-trimethylcyclopentyl)ethanone (2).**

A suspension of 5% palladium on activated carbon (6 mg) in dry methanol (10 mL) was stirred under a hydrogen atmosphere for 40 min. Then a solution of compound **10b** (30 mg, 0.114 mmol) in dry methanol (5 mL) was added and stirring was continued until 1 equivalent of hydrogen had been consumed (60 min). The mixture was then filtered through silica gel and the solvent was removed under vacuum. The residue was purified by column chromatography through silica gel, using a mixture of *n*-hexane and ethyl acetate (4:6) as eluent.
Yield 10.8 mg (0.063 mmol, 55%);
IR (film) 3357, 1700, 1457, 1357, 1200, 1114, 1064, 742, 700;
^1H NMR ($CDCl_3$) δ 4.45 (m, 1H), 2.81 (dd, J_1=14.4 Hz, J_2=8.5 Hz, 1H), 2.12 (s, 3H), 2.04 (dd, J_1=13.7 Hz, J_2=7.7 Hz, 1H), 2.03 (m, 1H), 1.68 (dd, J_1=13.7 Hz, J_2=4.9 Hz, 1H), 1.45 (dd, J_1=14.3 Hz, J_2=3.3 Hz, 1H), 1.32 (s, 3H), 1.18 (s, 3H), 0.85 (s, 3H);
^{13}C NMR ($CDCl_3$) δ 213.2 ($COCH_3$), 70.2 (CHOH), 57.0 (C), 50.7 (CH_2), 45.3 (C), 43.8 (CH_2), 28.3 (CH_3), 25.8 (CH_3), 24.9 (CH_3), 21.3 (CH_3);
MS m/z (rel. intensity) 109 (81) [$M^{+\cdot}$-61], 95 (51), 85 (86), 83 (70), 69 (13), 67 (32), 55 (51), 43 (100), 41 (60), 39 (25), 29 (19).

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