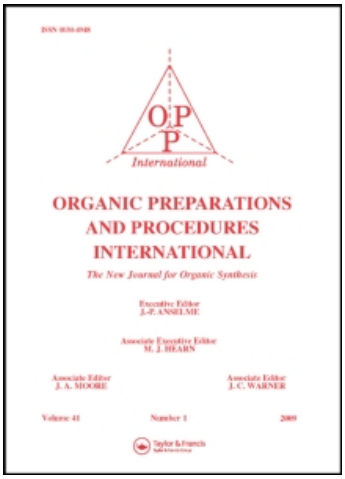


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

AN EFFICIENT SYNTHESIS OF (2R, 5R)- AND (2R, 5S)-2-METHYL-5-HYDROXYHEXANOIC ACID LACTONES

Ming-Jung Wu[a]; Jiann-Yih Yeh[b]
[a] School of Chemistry, Kaohsiung Medical College, Kaohsiung, Taiwan Republic of China [b] Graduate Institute of Pharmaceuticals, Kaohsiung Medical College, Kaohsiung, Taiwan Republic of China

To cite this Article Wu, Ming-Jung and Yeh, Jiann-Yih(1994) 'AN EFFICIENT SYNTHESIS OF (2R, 5R)- AND (2R, 5S)-2-METHYL-5-HYDROXYHEXANOIC ACID LACTONES', Organic Preparations and Procedures International, 26: 6, 671 — 674
To link to this Article: DOI: 10.1080/00304949409458164
URL: http://dx.doi.org/10.1080/00304949409458164

ORGANIC PREPARATIONS AND PROCEDURES INT., 26 (6), 671-711 (1994)

OPPI BRIEFS

AN EFFICIENT SYNTHESIS OF (2R, 5R)- AND (2R, 5S)-2-METHYL-5-HYDROXYHEXANOIC ACID LACTONES

Submitted by (11/19/93)

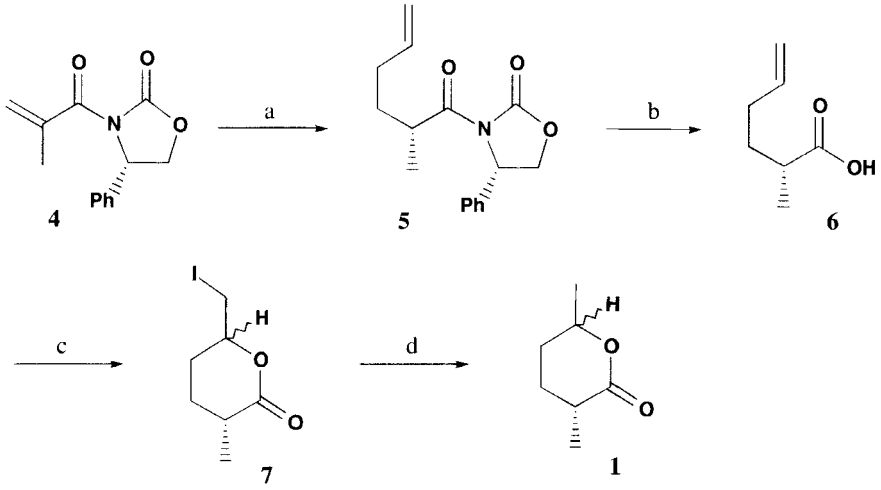
Ming-Jung Wu* and Jiann-Yih Yeh†

School of Chemistry, Kaohsiung Medical College
Kaohsiung, Taiwan, REPUBLIC OF CHINA

† *Graduate Institute of Pharmaceuticals, Kaohsiung Medical College*
Kaohsiung, Taiwan, REPUBLIC OF CHINA

cis-2-Methyl-5-hydroxyhexanoic acid lactone (**1**) is the major component of the sex pheromone of the carpenter bee *Xylocopa hirutissima*.[1] Although all of the enantiomers have been synthesized *via* various synthetic approaches,[2] we described herein an efficient synthesis of 2(R), 5(R,S)-2-methyl-5-hydroxyhexanoic acid lactone (**1**) that includes our recently developed asymmetric conjugate addition of allyltrimethylsilane to α,β-unsaturated *N*-acyloxazolidinone.[3,4]

The scheme below outlines our synthesis of 2(R), 5(R,S)-2-methyl-5-hydroxyhexanoic acid lactone (**1**). The starting (4S)-3-methacryloyl-4-phenyl-2-oxazolidinone (**4**) was prepared (99% yield) from methacryloyl chloride (**2**) and (4S)-3-lithio-4-phenyl-2-oxazolidinone (**3**) according to Evan's



a) Allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, -78° (93 %). b) LiOH, THF-H_2O, 25° (84 %).
c) I_2, $NaHCO_3$, CH_2Cl_2, 25° (84 %). d) Bu_3SnH, AIBN, benzene, 80° (30 %).

method.[5] Treatment of **4** with allyltrimethylsilane in the presence of 3 molar equivalent of $TiCl_4$ at -78° gave the conjugate allylation adduct **5** in 93% yield (88% diastereomeric excess). The optically pure **5** was isolated by flash column chromatography (silica gel, EtOAc-hexane, 1:9). The absolute configuration at C(2) was determined as **R**.[4] Compound **5** was then hydrolyzed with LiOH (aqueous THF) to give, after HCl acidification, (2R)-2-methyl-5-hexanoic acid (**6**) in 84% yield. Stereocontrolled iodolactonization of **6** under condition of kinetic control (I_2, $NaHCO_3$)[6] afforded iodolactone **7** in 82% yield with a *trans/cis* ratio of 1.6:1. Finally, free radical deiodination (Bu_3SnH, AIBN, benzene, 80°) gave **1** in 30% yield as a 1.8:1 mixture of (2R, 5R)- and (2R, 5S)-isomers. Thus, the overall yield of **1** from **4** was 20%.

EXPERIMENTAL SECTION

Melting points (uncorrected) were determined on a Yanaco MP apparatus. Infrared spectra were recorded on a Hitachi 260-30 spectrometer. ^1H NMR and ^{13}C NMR were recorded on a Varian XL-200E spectrometer. All chemical shifts are reported in ppm (TMS internal standard) and coupling constant are given in Hz. Elemental analyses were performed on a Hereus CHNO rapid analyzer. Low resolution mass spectra were recorded on a JEOL SX-102A and high resolution spectra were recorded on a JEOL JMX-HX 110 spectrometer.

(4S)-3-(2-Methyl-2-propenoyl)-4-phenyl-2-oxazolidinone (4).- To a stirred solution of (4S)-4-phenyl-2-oxazolidinone (**3**) (1.63 g, 10 mmol) and hydroquinone (0.012 g) in anhydrous THF (40 mL) was added nBuLi (1.6 M in hexane, 6.25 mL, 10 mmol) at 0°. After stirring for 15 min, the fresh distilled methacryloyl chloride (1.04 g, 10 mmol) was added. The reaction mixture was stirred for additional 90 min, quenched with saturated NH_4Cl solution, and extracted with ethyl acetate (25 mL x 3). The combined organic extracts were washed with saturated $NaHCO_3$, brine, and dried over anhydrous $MgSO_4$. After removal of solvent, the residue was purified by flash column chromatography (30% ethyl acetate in hexane as eluent) to give the product **4** (2.30 g, 99%) as a white solid, mp. 176-177°; ^1H NMR ($CDCl_3$): δ 7.33-7.41 (m, 5 H), 5.50 (s, 2 H), 5.47 (dd, 1 H, J = 8.8, 6.6), 4.72 (t, 1 H, J = 8.0), 4.26 (dd, 1 H, J = 8.8, 6.0), 2.01 (d, 3 H, J = 1.0); ^{13}C NMR ($CDCl_3$): δ 170.4, 153.2, 139.3, 137.9, 129.2, 128.9, 126.1, 122.0, 69.6, 58.1, 18.7.

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.40; H, 5.61; N, 6.09

(4S)-3-[(2R)-Methyl-5-hexenoyl)-4-phenyl-2-oxazolidinone (5).- To a cold (-78°) stirred solution of **4** (0.23 g, 1 mmol) in dry CH_2Cl_2 (10 mL) was added $TiCl_4$ (0.36 mL, 3 mmol).[7] The red-brown solution was stirred at -78° for 30 min. and then allyltrimethylsilane (0.48 mL, 3 mmol) was added into the reaction mixture. This solution was stirred at -78° (2 hrs), quenched with saturated NH_4Cl solution, and extracted with ethyl acetate (20 mL x 3). The combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. After removal of solvent, the residue was purified by flash column chromatography (10% ethyl acetate in hexane as eluent) to give **5** (0.24 g, 88% yield) as a white solid, mp. 53-54°; IR(KBr) 1780, 1695 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.27-7.43 (m, 5 H), 5.60-5.77 (m, 1 H), 5.43 (dd, 1 H, J = 8.8, 4.0), 4.85-4.95 (m, 2 H), 4.67 (t, 1 H, J = 8.8), 4.24 (dd, 1 H, J

=8.8, 4.0), 3.77 (sextet, 1 H, J = 6.8), 1.42-1.98 (m, 4 H), 1.14 (d, 3 H, J = 6.8); ^{13}C NMR ($CDCl_3$): δ 176.5, 153.3, 139.2, 137.9, 129.1, 128.7, 126.0, 114.9, 69.7, 57.8, 37.1, 32.8, 30.9, 16.4; MS (EI) 273 (M^+, 25.6), 219 (100); HRMS calcd for $C_{16}H_{19}NO_3$ 273.1366, found 273.1360.

Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.00; N, 5.12. Found: C, 70.00; H, 6.98; N, 5.15

(2R)-2-Methyl-5-hexenoic Acid (6).- The mixture of **5** (2.73 g, 10 mmol) and LiOH (0.29 g, 12 mmol) in aqueous THF (THF/H_2O, 4:1, 50 mL) was stirred at room temperature for 2 hrs. The reaction mixture was quenched with 10% aqueous HCl solution and extracted with CH_2Cl_2 (25 mL x 3). The combined organic extracts were washed with saturated $NaHCO_3$ solution. The organic layer was dried and evaporated to give the chiral oxazolidinone (1.52 g, 93%). The aqueous layer was acidified with concentrated HCl to pH =1 and extracted with CH_2Cl_2 (30 mL x 3). The combined organic extracts were dried and evaporated to give the acid **6** (1.08 g, 84%) as a yellow oil, $[\alpha]_D^{25}$ -8.2 (c 1.07, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 12 .1 (bs, 1 H), 5.78 (ddt, 1 H, J = 17.0, 10.2, 6.6), 4.94-5.09 (m, 2 H), 2.49 (sextet, 1 H, J = 7.0), 2.05-2.16 (m, 2 H), 1.46-1.89 (m, 2 H), 1.18 (d, 3 H, J = 7.0); ^{13}C NMR ($CDCl_3$): δ 183.2, 137.7, 115.2, 38.7, 32.5, 31.2, 16.7. These NMR data were identical to the literature value of racemic material.[8]

[2(R), 5(R,S)]-2-Methyl-5-hydroxy-6-iodohexanoic Acid Lactones (7).- The mixture of **6** (0.128 g, 1 mmol), $NaHCO_3$ (0.84 g, 10 mmol), and I_2 (0.5 g, 2 mmol) in CH_3CN (10 mL) was stirred at room temperature for 24 hrs. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2 (20 mL x 3). The combined organic extracts were washed with brine and dried ($MgSO_4$). Removal of solvent gave the iodolactone **7** (0.21 g, 84%, brownish oil), ^1H NMR ($CDCl_3$): δ 4.21-4.30 (m, 1 H), 3.25-3.36 (m, 2 H), 2.40-2.55 (m, 1 H), 2.02-2.20 (m, 2 H), 1.56-1.78 (m, 2 H), 1.26 (d, 1.85 H, J = 7.0, *trans* isomer), 1.20 (d, 1.15 H, J = 6.8, *cis* isomer) ; ^{13}C NMR ($CDCl_3$): δ 173.2, 76.8, 33.0, 26.6, 25.1, 16.1, 6.25 (*cis* isomer); 171.0, 79.3, 35.7, 29.2, 27.6, 17.0, 8.5 (*trans* isomer); MS (EI) 254 (M^+, 40.8), 41 (100); HRMS calcd for $C_7H_{11}O_2I$ 253.9804, found 253.9811.

[2(R), 5(R,S)]-2-Methyl-5-hydroxyhexanoic Acid Lactone (1).- The solution of **7** (0.2 g, 0.8 mmol) and Bu_3SnH (0.32 g, 1.1 mmol) containing AIBN (5 mg) in benzene (5 mL) was heated to reflux and stirred at this temperature for 5 hrs. After cooling to room temperature, the solvent was removed, and residue purified by flash column chromatography (10% ethyl acetate in hexane as eluent) to give the lactone **1** (30 mg, 30%, colorless solid), mp. 49-50°; ^1H NMR ($CDCl_3$): δ 4.40-4.48 (m, 1 H), 2.40-2.46 (m, 1 H), 1.89-2.00 (m, 2 H), 1.52-1.68 (m, 2 H), 1.37 (d, 0.64 H, J = 6.2, *trans*), 1.36 (d, 0.36 H, J = 6.2, *cis*), 1.30 (d, 0.64 H, J = 7.0, *trans*), 1.22 (d, 0.36 H, J = 7.0, *cis*); ^{13}C NMR ($CDCl_3$): δ 174.4, 78.2, 35.8, 31.0, 28.6, 22.2, 17.4 (*trans* isomer); 176.2, 74.4, 33.0, 28.4, 25.6, 21.1, 16.2 (*cis* isomer). All data are in accord with published values.[2b]

Acknowledgment.- We are grateful to the National Science Council of the Republic of China for the financial support. We thank Dr. Lendon N. Pridgen, SmithKline Beecham Pharmaceuticals for the gift of chiral oxazolidinones.

REFERENCES

1. J. W. Wheeler, S. L. Evans, M. S. Blum, H. H. V. Velthius and J. M. F. de Camargo, *Tetrahedron Lett.*, 4029 (**1976**).

2. a) W. H. Pirkle and P. E. Adams, *J. Org. Chem.*, **43**, 378 (1978); **44**, 2169 (1979); b) K. Mori and S. Senda, *Tetrahedron*, **41**, 541 (1985); c) T. Katsuki and M.Yamaguchi, *Tetrahedron Lett.*, **28**, 651 (1987); d) R. Bernardi and D. Ghiringhelli, *Synthesis*, 938 (**1989**); e) K. Narasaka and Y. Ukagi, *Chemistry Lett.*, 81 (**1986**); f) T. Ibuka, M. Tanaka, S. Nishii and Y. Yamamoto, *J. Am. Chem. Soc.*, **111**, 4864 (1989); g) S. K. Kang, Y. W. Park, D. H. Lee, H. S. Sim and J. H. Jeon, *Tetrahedron: Asymmetry*, **3**, 705 (1992).

3. M. J. Wu, C. C. Wu and P. C. Lee, *Tetrahedron Lett.*, **33**, 2547 (1992).

4. M. J. Wu and J. Y.Yeh, *Tetrahedron*, **50**, 1073 (1994).

5 D. A. Evans, C. Chapman and J. Bisaha, *J. Am. Chem. Soc.*, **110**, 1238 (1988).

6. a) P. A. Bartlett, D. P. Richardson and J. Myerson, *Tetrahedron*, **40**, 2317 (1984); b) H.-S. Moon, N. E. Schore and M. Kurth, *J. Org. Chem*, **57**, 6088 (1992).

7. The amount of $TiCl_4$ (1.3 equiv.) was insufficient to promote these conjugate additions to completion.

8. M. Kawashima, T. Sato and T. Fujisawa, *Tetrahedron*, **45**, 403 (1989).

****

SIMPLIFIED CONDITION FOR SYNTHESIS OF CURCUMIN I AND OTHER CURCUMINOIDS

Submitted by (03/29/94)

K. V. D. Babu and K. N. Rajasekharan*

Department of Chemistry, University of Kerala
Trivandrum 695581, Kerala, INDIA

Curcumin I (**1a**), the yellow pigment of turmeric exhibits a variety of pharmacological properties including recently reported antitumour[1] and anticancer[2] properties. It has also been evaluated as a photodynamic agent useful in the destruction of bacteria[3] and tumor cells.[4] In connection with some of these studies we required several curcuminoids. A practical route for curcumin synthesis has been devised by Pabon.[5] Kashima[6] *et al.* have also synthesised curcumin using 2,3,5-trimethylisoxazolium salt as the starting material. Synthesis of curcumin has also been described in the patent literature.[7]