Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 16 (2005) 2649–2651

An expeditious route to the antipode of harzialactone A

Ya-Jun Jian,[a,b] Yikang Wu,[b,*] Liang Li[b] and Jun Lu[a]

[a]*Department of Chemistry, The Northwest University, Xi'an 710069, China*
[b]*State Key Laboratory of Bio-organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China*

Received 7 June 2005; accepted 1 July 2005

Abstract—The antipode of the antitumor marine metabolite harzialactone A was synthesized from L-malic acid via a very efficient route in 40% overall yield involving only two chromatographic separations.

1. Introduction

Harzialactone A (+)-**1** is an antitumor marine metabolite isolated from a strain of *Trichoderma harianium* OUPS-N 115 made by Numata and co-workers.[1] In connection with establishing absolute configuration, Mereyala et al.[2] synthesized this compound from D-glucose (seven steps, 15% overall yield) and D-xylose (seven or eight steps, 24% overall yield). In these, the undesired extra oxygen atoms in the sugars were removed by radical-mediated reactions involving Bu_3SnH with the oxidation of the lactol to lactone being achieved with Ag_2CO_3. Herein, we report an expeditious route to (−)-harzialactone A, the antipode of the natural (+)-**1**, starting from L-malic acid. This has also been synthesized by Mereyala et al.[2] from D-glucose in <17% overall yield over nine steps.

2. Results and discussion

Our plan was very straightforward, making use of the readily accessible building block **2** by first converting it into the corresponding acid halide and then attaching a benzyl group to it. The stereogenic center at the benzylic position was planned to be established through a stereocontrolled reduction induced by the chiral OH in the malic residue. It should be noted that although the malic acid residue has been broadly used as a chiral pool in the asymmetric synthesis, in most cases it was reduced either partially or completely before other transformations were executed. Examples of making C–C bond selectively at the free carboxylic end of **2** are scant.[3] This approach needs further exploration to seek more applications for **2**.

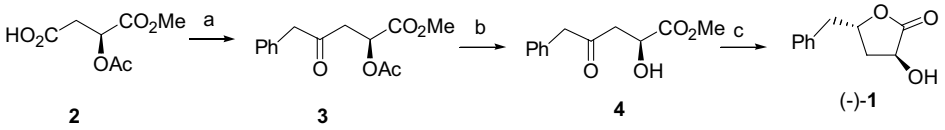
The starting material **2** was very conveniently derived from L-malic acid in 100% yield following the procedure of Larcheveque[4] (AcCl/40 °C/2 h, then MeOH/rt/overnight) without any need for chromatographic purification. Compound **2** was then converted[3] to the corresponding acid chloride by treatment with $SOCl_2$ at 42 °C and the crude product used directly in the next step after removal of excess $SOCl_2$.

In order to keep the two carbonyl groups in **2** intact, the introduction of a benzyl group was planned. We tried several reagents including $PhCH_2Cu(CN)ZnBr$,[5] $PhCH_2SbBu_4$,[6] $PhCH_2MgBr/Fe(acac)_3$,[7] and $PhCH_2MgBr/CuI$[8] that were known to react selectively with acid halides but not with esters. However, none of these worked well with our substrate. Under $PhCH_2Cu(CN)ZnBr$ conditions, the desired product **3** could be isolated albeit in 38% yield only. Other conditions mentioned above led to a very complicated product mixture. The problem was finally overcome by using $PhCH_2ZnBr/PdCl_2(PPh_3)_2$.[9] In this case, ketone **3** was obtained in 59% isolated yield (Scheme 1).

The acetyl protecting group was readily removed with a catalytic amount of *p*-TsOH in MeOH, giving **4** in 93% yield. The same alcohol could also be obtained in comparable yields (55% yield from malic acid) even from crude **3**. The ketone carbonyl group was then reduced using the procedure of Prasad et al.[10]

* Corresponding author. E-mail: yikangwu@mail.sioc.ac.cn

0957-4166/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2005.07.003



Scheme 1. Reagents and conditions: (a) (i) $SOCl_2$/42 °C/3 h, (ii) 2.5 equiv BnZnBr/0.1 equiv $PdCl_2(PPh_3)_2$/THF/rt/overnight, 59% from **2**; (b) *p*-TsOH/MeOH/rt/overnight/93%; (c) (i) Et_2BOMe/THF–MeOH (4:1)/$NaBH_4$/−78 °C/5 h, (ii) *p*-TsOH/CH_2Cl_2/rt/overnight, 73% from **4**.

($NaBH_4$/Et_2BOMe/THF–MeOH/−78 °C) to yield an intermediate diol. As the *syn*- and *anti*-diols generated at this step were inseparable on TLC, the crude product was directly cyclized by treatment with a catalytic amount of *p*-TsOH in CH_2Cl_2. (−)-Harzialactone A and the isomer derived from the *anti*-diol could be separated to obtain (−)-**1** in 73% isolated yield. From the ^1H NMR analysis (the integral ratio of the signal for the BnC*H*-O at δ 4.92 and 4.61, respectively) of the crude mixture, the *trans*/*cis* lactone ratio (and thus the *syn*/*anti* diol ratio) was estimated to be 20:1.

3. Conclusion

We have achieved an efficient synthesis of the antipode of the antitumor marine metabolite harzialactone A starting from L-malic acid. Only two chromatographic separations were needed in the whole synthesis. The overall yield (40%) was also significantly improved when compared to those reported in the literature. As the second stereogenic center at the benzylic position was constructed by substrate-induced stereoselective reduction, the natural harzialactone A should also be accessible by the same route by using D-malic acid as the starting material.

4. Experimental

The ^1H NMR spectra were recorded with a Varian Mercury 300 (300 MHz) spectrometer. The FT-IR spectra were scanned with a Nicolet Avatar 360 FT-IR. EI-MS spectra were recorded with an HP 5989A mass spectrometer. The ESI-MS spectra were recorded with a PE Mariner API-TOF or an Agilent Technologies LC/MSD SL instrument. The ESI-HRMS spectra were recorded with a APEX III (7.0 T) FTMS mass spectrometer. The melting points are uncorrected. The optical rotations were measured with a JASCO P-1030 polarimeter.

4.1. Methyl (*S*)-2-acetoxy-4-oxo-5-phenylpentanoate 3

A mixture of zinc dust (163 mg, 2.5 mmol) and 1,2-dibromoethane (22 μL, 0.5 mmol) in anhydrous THF (4 mL) was heated gently until boiling of the solvent was observed. The suspension was stirred at room temperature for a few minutes before being heated again (repeated three times). The mixture was then cooled to 0 °C and a solution of benzyl bromide (0.6 mL, 2.5 mmol) in THF (2 mL) was added dropwise over 30 min. The resulting mixture was stirred at room temperature for 1 h, and then added dropwise to a solution of the acid halide[4] [prepared from[11] **2** (187 mg, 1.0 mmol)] and $PdCl_2(PPh_3)_2$ (71 mg, 0.1 mmol) in THF (1 mL) cooled in a ice-water bath. After stirring at room temperature overnight, the reaction mixture was diluted with water (10 mL) and extracted with ether (3 × 10 mL). The extract was dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The residue was purified by column chromatography (silica gel, 5:4 *n*-hexane–Et_2O) to give **3** as a yellowish oil (153 mg, 59%): $[\alpha]_D^{25} = -19.3$ (*c* 1.17, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.29 (m, 3H), 7.23–7.18 (m, 2H), 5.47 (dd, $J = 4.0$, 3.6 Hz, 1H), 3.74 (s, 2H), 3.72 (s, 3H), 2.98 (m, 2H), 2.07 (s, 3H); IR (film) 1748, 701 cm^{-1}; ESI-MS 287.1 ($[M+Na]^+$); ESI-HRMS calcd for $C_{14}H_{16}O_5Na$ $[M+Na]^+$: 287.08899. Found: 287.08897.

4.2. Methyl (*S*)-2-hydroxy-4-oxo-5-phenylpentanoate 4

Compound **3** (130 mg, 0.5 mmol) was added to a solution of *p*-TsOH in MeOH (0.2 M, 3 mL) and the resulting mixture stirred at room temperature overnight. The mixture was evaporated in vacuo and the residue purified by column chromatography (silica gel, 1:2 *n*-hexane–Et_2O) to give **4** as a yellowish oil (102 mg, 93 %): $[\alpha]_D^{25} = +3.3$ (*c* 1.28, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.17 (m, 5H), 4.49 (m, 1H), 3.76 (s, 2H), 3.75 (s, 3H), 3.21 (br s, 1H, OH), 3.05–2.87 (m, 2H); IR (film) 3479, 1740, 1497, 701 cm^{-1}; ESI-MS 245.1 ($[M+Na]^+$); ESI-HR MS calcd for $C_{12}H_{13}O_4Na$ $[M+Na]^+$: 2245.07843. Found: 245.07826.

4.3. (3*S*,5*S*)-(−)-5-Benzyl-3-hydroxy-dihydro-furan-2-one (−)-1

To a cooled (−78 °C) stirred solution of **4** (48 mg, 0.22 mmol) in anhydrous THF (1.6 mL) and MeOH (0.4 mL) under a nitrogen atmosphere was injected a solution of $MeOBEt_2$ in THF (1 M, 0.24 mL, 0.24 mmol). Stirring was continued at −78 °C for 15 min before $NaBH_4$ (9 mg, 0.24 mmol) was added in one portion. After stirring at −78 °C for another 5 h, the reaction was quenched (at −78 °C) by the addition of AcOH (0.2 mL). The mixture was poured into saturated aqueous $NaHCO_3$ (7 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was dissolved in MeOH (5 mL) and evaporated to dryness with a rotary evaporator (repeated several times). To the oily residue were added *p*-TsOH (5 mg) and CH_2Cl_2 (2 mL) and the mixture stirred at room temperature overnight. After aqueous workup, the residue obtained was purified by column chromatography (silica gel, 2:1, *n*-hexane–EtOAc) to afford (−)-**1** (31 mg, 73%) as colorless transparent needles: mp 73–

75 °C (lit.[2b] 71–74 °C); $[\alpha]_D^{25} = -39.6$ (*c* 0.32, $CHCl_3$), {lit.[2b] $[\alpha]_D = -38$ (*c* 0.3, $CHCl_3$)}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.18 (m, 5H), 4.92 (m, 1H), 4.00 (dt, $J = 2.6$, 7.8 Hz, 1H), 2.99 (d, $J = 5.5$ Hz, 2H), 2.81 (br s, 1H, OH), 2.42–2.23 (m, 2H).

Acknowledgments

This work was supported by the National Natural Science Foundation of China (20025207, 20272071, 20372075, and 20321202), the Chinese Academy of Sciences ('Knowledge Innovation' project, KGCX2-SW-209), and the Major State Basic Research Development Program (G2000077502).

References

1. Amagata, T.; Usami, Y.; Minoura, K.; Ito, T.; Numata, A. *J. Antibiot.* **1998**, *51*, 33–40.
2. (a) Mereyala, H. B.; Gadikota, R. R. *Tetrahedron: Asymmetry* **1999**, *10*, 2305–2306; (b) Mereyala, H. B.; Joe, M.; Gadikota, R. R. *Tetrahedron: Asymmetry* **2000**, *11*, 4071–4081.
3. For the only precedents of this type in the literature we could find so far, see: Shi, X.-X.; Wu, Q.-Q.; Lu, X. *Tetrahedron: Asymmetry* **2002**, *13*, 2461–2464; Mori, S.; Takechi, S.; Shimizu, S.; Kida, S.; Iwakura, H.; Hajima, M. *Tetrahedron Lett.* **1999**, *40*, 1165–1168.
4. Henrot, S.; Larcheveque, M.; Petit, Y. *Synth. Commun.* **1986**, *16*, 183–190.
5. Berk, S. C.; Knochel, P.; Ye, M. C. P. *J. Org. Chem.* **1988**, *53*, 5789–5791.
6. Zhang, L.-J.; Huang, Y.-Z.; Jiang, H.-X.; Duan-Mu, J.; Liao, Y. *J. Org. Chem.* **1992**, *57*, 774–777.
7. Cardellicchio, C.; Fiandanese, V.; Marchese, G.; Ronzini, L. *Tetrahedron Lett.* **1987**, *28*, 2053–2056.
8. Reppy, M. A.; Gray, D. H.; Pindzola, B. A.; Smithers, J. L.; Gin, D. L. *J. Am. Chem. Soc.* **2001**, *123*, 363–371.
9. (a) Sengupta, S.; Sarma, D. S. *Tetrahedron: Asymmetry* **1999**, *10*, 4633–4637; (b) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189.
10. (a) Chen, K.-M.; Hardtmann, G.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155–158; (b) Evans, D. A.; Gauchet-Prunet, J. A.; Carreira, E. M.; Charette, A. B. *J. Org. Chem.* **1991**, *56*, 741–750.
11. The acid halide was obtained by dissolving **2** (187 mg, 1.0 mmol) in $SOCl_2$ (0.9 mL) and heating the mixture to 42 °C with stirring for 2.5 h, followed by removing the excess $SOCl_2$ under oil pump vacuum.