Asian Journal of Chemistry; Vol. 27, No. 5 (2015), 1957-1958

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2015.18406

NOTE

Unexpected Facile Synthesis of Tetronic Acid During the Research on Stereospecific Total Synthesis of (+)-Biotin Starting from D-Erythorbic Acid as Chiral Pool

XIAO-KANG LI[1,2,3], FEI XIONG[1,2,*], ZHONG-YUAN SHEN[1], SHU-PING ZHANG[1,3], YI-HAO ZHOU[1], MING-LU XU[1] and ZI-QIAN ZHOU[1]

[1]Department of Chemistry, University of Shanghai for Science and Technology, Shanghai 200093, P.R. China
[2]Hubei Key Laboratory of Drug Synthesis and Optimization, Jingchu University of Technology, Jingmen, P.R. China
[3]School of Medical Instrument and Food Engineering, University of Shanghai for Science and Technology, Shanghai 200093, P.R. China

*Corresponding author: E-mail: fxiong@usst.edu.cn; feixiong09@fudan.edu.cn, fduxiong@gmail.com

Received: 4 July 2014; *Accepted*: 15 September 2014; *Published online*: 20 February 2015; AJC-16935

The reaction of D-erythronolactone (**8**) with the methanesulfonyl chloride in the presence of triethylamine afforded, after unexpected elimination reaction, the tetronic acid is obtained in excellent yield and chemical purity, instead of the dimesylates (**7**).

Keywords: (+)-Biotin, D-erythorbic acid, Tetronic acid.

A great deal of attention has been focused on (+)-biotin (vitamin H) because it plays essential roles in many aspects of human nutrition and animal health[1]. For example, (+)-biotin was used as a feed additive in traditional poultry industry and find uses for clinical treatment of hair loss, brittle nails and in tonic formulations for children. In addition, recent studies have revealed the potential applications of (+)-biotin as an anti-diabetic drug[2].

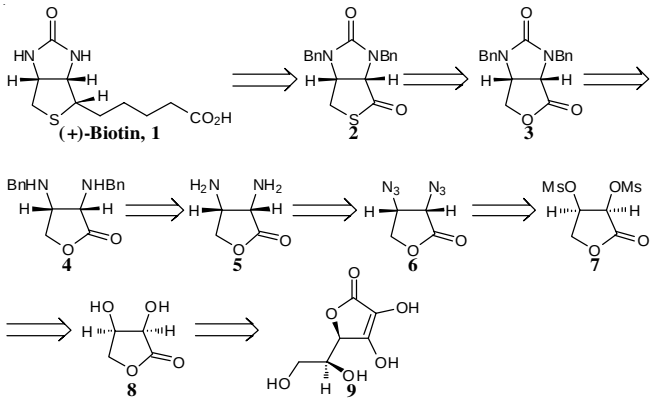
Despite their multiple functions, there are only a few industrially viable synthetic methods reported to date for the formal synthesis of (+)-biotin (**1**)[3,4]. During the past decades, much attention has been focused on developing various chiral agent-catalyzed enantioselective syntheses approach to prepare the (3a*S*, 6a*R*)-lactone (**3**), which is the crucial chiral building block of (+)-biotin[5-10]. However, these asymmetric synthesis methods suffer either harsh reaction conditions (the cryogenic temperature, long reaction time) or difficulties with organo-catalyst preparation. Therefore, as a part of the continuing work to explore new synthetic approaches to (+)-biotin[5-10], we devised a new synthetic approaches using D-erythorbic acid (**9**) and (3a*S*, 6a*R*)-lactone (**3**) as a chiral starting material and a key chiral building block, respectively, to realize the stereo-specific total synthsis of (+)-biotin (**1**).

Optical rotations were obtained on a JASCO P1020 digital polarimeter. Melting points were measured with a WRS-1B digital melting point apparatus and are uncorrected. NMR spectra were measured on Bruker AV 400 in DMSO-d_6 solution with tetramethylsilane as an internal standard. Chemical reagents were obtained from commercial sources and used as received.

D-Erythronolactone (8): To a solution of D-erythorbic acid (17.6 g, 0.1 mol) in 250 mL of deionized water was added anhydrous sodium carbonate (21.2 g, 0.2 mol) in three portions at 0 °C, followed by 31 % aqueous hydrogen peroxide (22 mL, 0.225 mmol) in dropwise. Active charcoal was then added to the resulting mixture, keep stirring at 75 °C for 0.5 h. Filtered the hot mixture, the combined filtrate are acidified with 6 N aqueous hydrochloric acid and concentrated the acidic solution. Treatment of the residue with boiling ethyl acetate, cooled the combined ethyl acetate solution to 0 °C and filtered. Air drying the collected solid gave D-erythronolactone (**8**) (10.7 g, 91 %) as colourless needles, m.p.: 104.3-104.7 °C; $[\alpha]_D^{20}$: -72.9° (c 0.533, H_2O). {Lit[11]. m.p.: 104-105 °C; $[\alpha]_D^{20}$: -73.2° (c 0.533, H_2O)}.

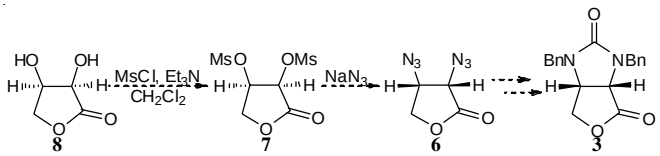
Tetronic acid (10): To a solution of **8** (4.4 g, 37.2 mmol) and triethylamine (12.4 mL, 89.4 mmol) in CH_2Cl_2 (120 mL) was added dropwise methanesulfonyl chloride (10.2 g, 89.4 mmol) at 0 °C. Then warmed the mixture to 25 °C, keep stirring at this temperature for 6 h. Ice water (80 mL) was then added to the reaction mixture, the organic phase was washed successively with 10 % HCl (50 mL), saturated $NaHCO_3$ (50 mL), brine (50 mL), and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave compound **10** (3.62 g, 97 %), which was generally used directly without further purification. Analytically pure (**10**) can be obtained by recrystallization from ethyl acetate. m.p.: 141.3-141.7 °C. [Lit[12]. m.p.: 141 °C]; ^{1}H NMR (DMSO): δ 4.65 (s, 2H), 4.97 (s, 1H).

Our planned synthetic strategy is depicted in **Scheme-I**, which is based upon the stereospecific preparation of classical Roche lactone (**3**), the direct precursor to key chiral intermediate (3a*S*, 6a*R*)-thiolactone (**2**) of (+)-biotin. The target molecule (+)-biotin (**1**) had earlier been readily elaborated from thiolactone (**2**)[5-9]. Lactone (**3**) would then be accessed from the cyclization of compound **4** in the presence of thiophosgene, which in turn would be visualized to be produced by a straightforward one-pot sequence from the introduction of benzyl group in compound **5**. Chiral diamine intermediate **5** was thought to be available from D-erythronolactone (**8**) with correct configuration *via* a series of inversion reactions. D-erythronolactone (**8**) could be directly available from the commercially available D-erythorbic acid (**9**) following a protocol reported earlier[13].



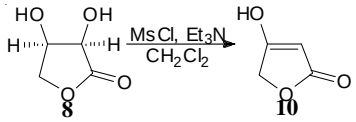
Scheme-I: Retrosynthetic analysis of (+)-biotin

With these considerations in mind, our stereospecific total synthsis of (+)-biotin (**1**) was undertaken starting from readily accessible D-erythorbic acid (**9**). Chiral starting material 9 was subjected to oxidation with hydrogen peroxide at 0 °C in the presence of sodium carbonate in deionized water, subsequent acid-catalyzed cyclization with 6 N aqueous hydrochloric acid furnish the desired D-erythronolactone (**8**) in 91 % yield.



Scheme-II: Synthetic route to (3a*S*, 6a*R*)-lactone (**3**)

We next set out to prepare the key chiral building block (3a*S*, 6a*R*)-lactone (**3**) steps from chiral intermediate **8**, using a configuration inversion strategy as outlined in **Scheme-II**. In combination with the experiences in the dimesylation of chiral diols[14], we attempted the dimesylation reaction of chiral diol (**8**) with 2.4 equivalent methanesulfonyl chloride in the presence of organic base (triethylamine). The reaction proceeded smoothly under stirring at room temperature for 6 h, and to our surprise only the elimination product **10** was isolated in 97 % yield, and no expected dimesylates (**7**) could be detected. However, the same product tetronic acid (**10**) was obtained under a range of other analogous reaction conditions (low temperature, using other organic base).



Scheme-III: Unexpected synthesis of tetronic acid (**10**)

It's noteworthy that the unexpected product tetronic acid (**10**) is also the efficient starting material application for the total synthesis of (+)-biotin (**1**)[15]. Therefore, we have developed a new and robust synthetic approach to the stereospecific total synthesis of (+)-biotin (**1**) starting from the known D-erythorbic acid (**9**), which exhibited advantage over the existing synthetic routes to **1** in terms of the readily accessible starting material.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the financial support from Shanghai Municipal Education Commission and the Open Project Program of Hubei Key Laboratory of Drug Synthesis and Optimization, Jingchu University of Technology (No. OPP2014ZD01).

REFERENCES

1. M.A. Boas, *Biochem. J.*, **21**, 712 (1927).
2. M.L. Lazo de la Vega-Monroy, E. Larrieta, M.S. German, A. Baez-Saldana and C. Fernandez-Mejia, *J. Nutr. Biochem*., **24**, 169 (2013).
3. M. Seki, *Med. Res. Rev*., **26**, 434 (2006).
4. P.J. De Clercq, *Chem. Rev*., **97**, 1755 (1997).
5. H.F. Dai, W.X. Chen, L. Zhao, F. Xiong, H. Sheng and F.E. Chen, *Adv. Synth. Catal*., **350**, 1635 (2008).
6. J. Huang, F. Xiong and F.E. Chen, *Tetrahedron Asymm.*, **19**, 1436 (2008).
7. F. Xiong, X.X. Chen and F.E. Chen, *Tetrahedron Asymm.*, **21**, 665 (2010).
8. X.X. Chen, F. Xiong, H. Fu, Z.Q. Liu and F.E. Chen, *Chem. Pharm. Bull. (Tokyo)*, **59**, 488 (2011).
9. F. Xiong, F.J. Xiong, W.X. Chen, H.Q. Jia and F.E. Chen, *J. Heterocycl. Chem*., **50**, 1078 (2013).
10. F. Xiong, X.K. Li, M. Xu, S.P. Zhang, F.E. Chen, B. Liao, H.J. Hua and J.H. He, *Asian J. Chem*., **26**, 3659 (2014).
11. H.K. Zhang, S.Q. Xu and P.Q. Huang, Patent CN 101139314, *Chem. Abstr*., 327110 (2008).
12. M.G. Scaros, P.K. Yonan, S.A. Laneman and P.N. Fernando, *Tetrahedron Asymm.*, **8**, 1501 (1997).
13. J. McGarrity and L. Tenud, Eur. Patent Appl. EP273270 A1 (1988); *Chem. Abstr*., 75168 (1989).
14. R. Weidenhagen and H. Wegner, *Chem. Ber*., **72**, 2010 (1939).
15. F. Micheel and W. Schulte, *Justus Liebigs Ann. Chem*., **519**, 70 (1935).