Chinese Chemical Letters 29 (2018) 1113–1115

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Communication

# Efficient preparation of β-hydroxy aspartic acid and its derivatives

Long Liu[a], Bo Wang[a], Cheng Bi[a], Gang He[a,b], Gong Chen[a,b,*]

[a] State Key Laboratory and Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, China
[b] Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300071, China

ARTICLE INFO

*Article history:*
Received 4 April 2018
Received in revised form 2 May 2018
Accepted 3 May 2018
Available online 5 May 2018

*Keywords:*
Amino acid
Natural product
Erythreo-β-OH-Asp
Erythreo-β-OMe-Asn
Antibiotics

ABSTRACT

We report an efficient and practical synthetic route to various properly-protected erythreo-β-OH-Asp compounds, which are key β-branched α-amino acid units in coralmycin A and other peptide natural products. Fmoc and cyclic ketal-protected erythreo-β-OH-Asp **7** is prepared from cheap chiral precursor L-diethyl tartrate in six steps without the need of column purification. The modified form of **7** serves as a versatile precursor to various β-alkoxyl analogs of erythreo-β-OH-Asp. In addition, we successfully performed a model study toward the total synthesis of coralmycin A, featuring a late stage installation of the side chain primary amide group of erythreo-β-OMe-Asn.


In 2014, Müller reported the isolation of an unusual group of antibacterial nonribosomal peptide natural products named cystobactamids featuring a central modified aspartic acid (Asp) or asparagine (Asn) residue and two flanking arms made of amide-linked para-aminobenzoic acid units [1]. More recently, Kim reported the isolation of coralmycins A and B, which have very similar structure with cystobactamid 919-2 (Scheme 1A) [2]. While coralmycin A shares the same central erythreo-β-methoxyasparagine (β-OMe-Asn) residue with cystobactamid 919-2, coralmycin B carries a central threo-β-methoxyaspartic acid (β-OMe-Asp) residue. Notably, these compounds show excellent antibacterial potency against several Gram-negative pathogens including *Escherichia coli*, *Pseudomonas aeruginosa, Acinetobacter baumanii,* and *Klebsiella pneumoniae,* with MICs of 0.1 – 4 μg/mL. Furthermore, cystobactamids have been identified as inhibitors of bacterial type IIa topoisomerases [3]. Intrigued by their unique structures, we started a synthetic study to understand how the central β-OMe-Asp or -Asp residue influences their antibacterial activity [4–6]. We speculated that varying the β-alkoxyl group might alter the spatial conformation of the parent scaffold and therefore influence its activity. Herein, we report the initial progress on an efficient and practical synthesis of erythreo-β-OH-Asp building block and its derivatives in various protected form.

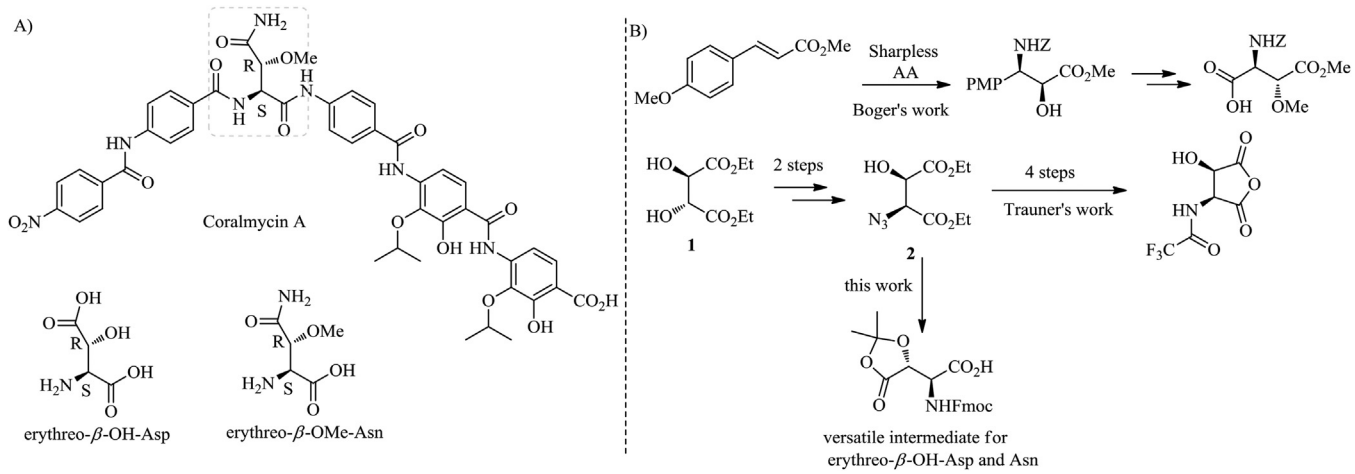
Erythreo-β-OH-Asp or Asn building blocks have been found in a wide range of peptide natural products. A number of methods have been investigated to construct these seemly simple β-oxygenated non-proteinogenic α-amino acid [7–16]: asymmetric Mannich type reaction [7], C-H bond hydroxylation [10], alkene dihydroxylation-intermolecular $S_N2$ reaction [11], reaction of optically pure Garner's aldehyde [12], halogenation-$S_N2$ reaction [13], resolution of racemic D,L-tHyAsp mixture [14], Sharpless asymmetric amino-hydroxylation of alkene [15] and conversion of tartaric acid [16]. However, most of these methods could not provide a practical synthesis of the properly protected β-OMe-Asp or Asn building blocks.

While our work is in progress, the groups of Trauner [17] and Müller [18] independently published their total syntheses of cystobactamids. As shown in Scheme 1B, Trauner used a substituted succinic anhydride as the key intermediate for β-OMe-Asn, which was prepared from L-diethyl tartrate **1**. However, the ring opening of the anhydride suffered from low regioselectivity [7]. On the other hand, Müller took advantage of the Sharpless asymmetric dihydroxylation route originally developed by Boger [8]. However, the need of oxidative degradation of phenyl ring to liberate the carboxyl group caused low atom economy.

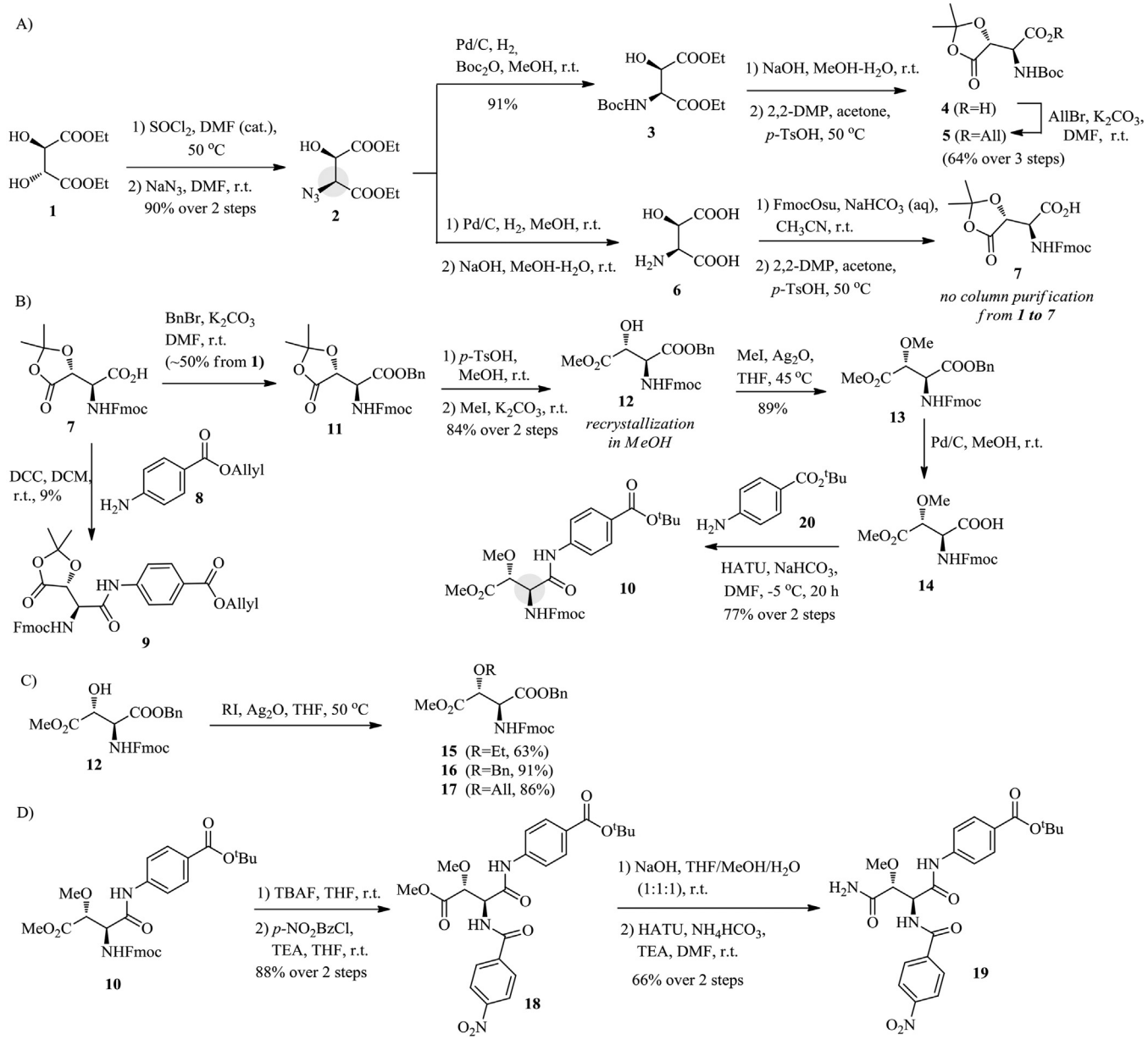
Similar to Trauner's approach, we wanted to use L-diethyl tartrate **1** as the starting material due to its low cost as an easily accessible chiral precursor. The key to achieve high efficiency of this strategy lies on the selective differentiation of the two carboxylate groups. As shown in Scheme 2A, **1** was first treated with $SOCl_2$ in the presence of catalytic amount of DMF in $CCl_4$ to furnish cyclic sulfate. Opening of the sulfate by $NaN_3$ in DMF led to azido alcohol **2** in 90% yield over two steps [19]. We initially attempted to hydrolyze **2** to the corresponding dicarboxylic acid,

* Corresponding author at: State Key Laboratory and Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Tianjin, 300071, China.
*E-mail address:* gongchen@nankai.edu.cn (G. Chen).

https://doi.org/10.1016/j.cclet.2018.05.012
1001-8417/




**Scheme 1.** Occurrence and strategy for synthesis of β-MeO-Asp/Asn building block.




**Scheme 2.** Synthesis of β-MeO-Asp and model study toward total synthesis of coralmycin A. (a) Preparation of Fmoc and Boc-protected β-OH-Asp. (b) Installation of para-aminobenzoic acid on C terminus of β-OMe-Asp. (c) Preparation of ether derivatives of β-MeO-Asp. (d) Installation of benzoic acid on N terminus and conversion of β-OH-Asp to β-MeO-Asn.

which could selectively react with boronic acid at the hydroxyl-substituted end. However, hydrolysis of **2** under basic conditions caused racemization of the azido-linked carbon.

To circumvent this racemization issue, the azido group of **2** was first reduced to free amine *via* Pd/C-catalyzed hydrogenation and then protected by $Boc_2O$ to give **3** [20]. Hydrolysis of compound **3** by aq. NaOH gave the desired dicarboxylic acid without any racemization. The subsequent treatment of the di-acid with 2,2-dimethoxypropane (2,2-DMP) and catalytic amount of TsOH gave the desired cyclic acetal-protected mono acid **4** in excellent yield. Reaction of **4** with allyl bromide cleanly formed the allyl ester **5** [21]. By altering the order of ester hydrolysis and amino group protection, Fmoc and cyclic acetal-protected intermediate **7** was prepared in high yield (Scheme 2A). Notably, no flash chromatography purification was needed from **1** to **7**.

As shown in Scheme 2B, amide coupling of **7** with *para*-aminobenzoate ester **8** proceeded with low yield and considerable racemization under a variety of conditions tested presumably due to the steric congestion around the $\beta$ carbon. To alleviate the steric congestion, we decided to open the cyclic ketal and install the $\beta$-MeO group before the amide coupling. Benzyl protection of **7** [22], opening of the cyclic acetal with acid, and methyl esterification with MeI and $K_2CO_3$ gave compound **12** in good yield. Compound **12** can be recrystallized from MeOH. Treatment of **12** with MeI and $Ag_2CO_3$ at 45 °C gave the desired $\beta$ methyl ether **13** in excellent yield. The Bn group of **13** was deprotected by Pd-catalyzed hydrogenolysis, and the subsequent amide coupling with para-aminobenzoate ester **20** under the optimized conditions using HATU and $NaHCO_3$ at −5 °C proceeded in good yield to give **10** with excellent chiral integrity.

As shown in Scheme 2C, compound **12** can react with various alkyl halides under the same conditions for **13** to give the corresponding $\beta$-alkoxyl analogs, which would be useful for future structure activity relationship study.

As shown in Scheme 2D, Fmoc deprotection of **10** by the treatment of TBAF and the subsequent amide coupling with *para*-nitrobenzoyl chloride afforded the tripeptide **18** in 88% yield. Hydrolysis of the side chain methyl ester of **18** with aq. NaOH cleanly gave the carboxylic acid intermediate. The acid was then converted to the desired side chain primary amide of $\beta$-OMe-Asn *via* the treatment of HATU, $NH_4HCO_3$ in DMF at room temperatuer, finishing a successful model study toward the total synthesis of coralmycin A.

In conclusion, we developed an efficient and practical synthetic route to various properly-protected erythreo-$\beta$-OH-Asp compounds, which are key $\beta$-branched $\alpha$-amino acid units in coralmycin A and other peptide natural products. Fmoc and cyclic ketal-protected erythreo-$\beta$-OH-Asp **7** can be prepared from cheap chiral precursor L-diethyl tartrate in six step without the need of column purification. The modified form of **7** serves as a versatile precursor to various $\beta$-alkoxyl analogs of erythreo-$\beta$-OMe-Asp. In addition, we successfully performed a model study toward the total synthesis of coralmycin A, featuring a late stage installation of a side chain primary amide group of erythreo-$\beta$-OMe-Asn.

## Acknowledgment

We gratefully thank the National Natural Science Foundation of China (Nos. 21421062, 21672105, 91753124) for financial support of this work.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2018.05.012.

## References

[1] (a) S. Baumann, J. Herrmann, R. Raju, et al., Angew. Chem. Int. Ed. 53 (2014) 14605–14609;
(b) S. Cociancich, A. Pesic, D. Petras, et al., Nat. Chem. Biol. 11 (2015) 195–197.
[2] Y.J. Kim, H.J. Kim, G.W. Kim, et al., J. Nat. Prod. 79 (2016) 2223–2228.
[3] C. Mayer, Y.L. Janin, Chem. Rev. 114 (2014) 2313–2342.
[4] (a) D.J. Payne, M.N. Gwynn, D.J. Holmes, et al., Nat. Rev. Drug. Discovery 6 (2007) 29–40;
(b) H.W. Boucher, G.H. Talbot, J.S. Bradley, et al., Clin. Infect. Dis. 48 (2009) 1–12.
[5] (a) K. Tohdo, Y. Hamada, T. Shioiri, Synapse (Hoboken, NJ, United States) 4 (1994) 247–249;
(b) M. Sendai, S. Hashiguchi, M. Tomimoto, et al., Chem. Pharm. Bull. 33 (1985) 3798–3820.
[6] (a) S.K. Jia, Y.B. Lei, L.L. Song, et al., Chin. Chem. Lett. 28 (2017) 213–217;
(b) H.T. Jiang, H.L. Gao, C.S. Ge, Chin. Chem. Lett. 28 (2017) 471–475;
(c) X. Lu, B. Xiao, R. Shang, et al., Chin. Chem. Lett. 27 (2016) 305–311.
[7] X. Huang, X. Luo, Y. Roupioz, et al., J. Org. Chem. 62 (1997) 8821–8825.
[8] Z.M. Wang, H.C. Kolb, K.B. Sharpless, J. Org. Chem. 59 (1994) 5104–5105.
[9] (a) A.M. Hafez, T. Dudding, T.R. Wagerle, et al., J. Org. Chem. 68 (2003) 5819–5825;
(b) B.M. Trost, L.R. Terrell, J. Am. Chem. Soc. 125 (2003) 338–339.
[10] K. Chen, S.Q. Zhang, H.Z. Jiang, et al., Chem.-Eur. J. 21 (2015) 3264–3270.
[11] (a) J. Deng, Y. Hamada, T. Shioiri, J. Am. Chem. Soc. 117 (1995) 7824–7825;
(b) Z. Tang, Z.H. Yang, X.H. Chen, et al., J. Am. Chem. Soc. 127 (2005) 9285–9289;
(c) N. Shangguan, M. Joullie, Tetrahedron Lett. 50 (2009) 6748–6750.
[12] (a) K. Shimamoto, Y. Shigeri, Y. Yasuda-Kamatani, et al., Bioorg. Med. Chem. Lett. 10 (2000) 2407–2410;
(b) A. Wohlrab, R. Lamer, M.S. VanNieuwenhze, J. Am. Chem. Soc. 129 (2007) 4175–4177.
[13] (a) G. Campiani, M. De Angelis, S. Armaroli, et al., J. Med. Chem. 44 (2001) 2507–2510;
(b) D. Crich, A. Banerjee, J. Org. Chem. 71 (2006) 7106–7109.
[14] N. Bionda, M. Cudic, L. Barisic, et al., Amino Acids 42 (2012) 285–293.
[15] (a) D.L. Boger, R.J. Lee, P.Y. Bounaud, et al., J. Org. Chem. 65 (2000) 6770–6772;
(b) W. Jiang, J. Wanner, R.J. Lee, et al., J. Am.Chem. Soc 124 (2002) 5288–5290;
(c) W. Jiang, J. Wanner, R.J. Lee, et al., J. Am. Chem. Soc. 125 (2003) 1877–1887;
(d) D. Wong, C.M. Taylor, Tetrahedron Lett. 50 (2009) 1273–1275.
[16] J. Spengler, M. Pelay, J. Tulla-Puche, et al., Amino Acids 39 (2010) 161–165.
[17] B. Cheng, R. Muller, D. Trauner, Angew. Chem., Int. Ed. 56 (2017) 12755–12759.
[18] S. Huttel, G. Testolin, J. Herrmann, et al., Angew. Chem., Int. Ed. 56 (2017) 12760–12764.
[19] R. Hili, V. Rai, A.K. Yudin, J. Am. Chem. Soc. 132 (2010) 2889–2891.
[20] S. Saito, N. Bunya, M. Inaba, et al., Tetrahedron Lett. 26 (1985) 5309–5312.
[21] M. Tsakos, L.L. Clement, Eva S. Schaffert, et al., Angew. Chem. Int. Ed. 55 (2016) 1030–1035.
[22] B. France, V. Bruno, I. Nicolas, Tetrahedron Lett. 54 (2013) 158–161.