Accepted Manuscript

Multigram Scale, Chiron-Based Synthesis of Sacubitril

Yun Wang, Fen-Er Chen, Yong Shi, Wei-Sheng Tian

PII: S0040-4039(16)31559-3
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.11.078
Reference: TETL 48364

To appear in: *Tetrahedron Letters*

Received Date: 11 November 2016
Accepted Date: 18 November 2016

Please cite this article as: Wang, Y., Chen, F-E., Shi, Y., Tian, W-S., Multigram Scale, Chiron-Based Synthesis of Sacubitril, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.11.078

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ACCEPTED MANUSCRIPT

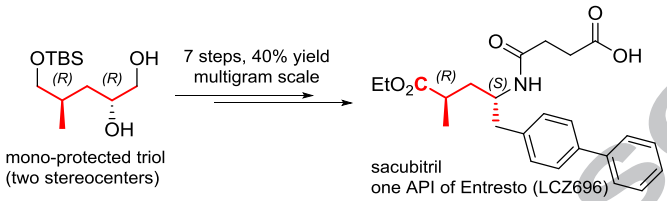
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Multigram Scale, Chiron-Based Synthesis of Sacubitril

Leave this area blank for abstract info.

Yun Wang, Fen-Er Chen, Yong Shi* and Wei-Sheng Tian*



ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Tetrahedron Letters
journal homepage: www.elsevier.com

Multigram Scale, Chiron-Based Synthesis of Sacubitril

Yun Wang [a, b], Fen-Er Chen [a], Yong Shi [b,] * and Wei-Sheng Tian [b,] *

[a] *Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China*
[b] *CAS Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
sacubitril
chiron approach
epoxide synthesis
Staudinger ligation
neprilysin inhibitor

ABSTRACT

Based on a chiron approach, sacubitril, a neprilysin inhibitor and API of Entresto, was synthesized in 7 steps with an overall yield of 40%. Two chiral centers of sacubitril are easily obtained from the starting material, one inherited and another inverted. Noteworthy steps are an efficient and mild preparation of epoxide from chiral vicinal diol using $C_4F_9SO_2F$/DBU, and a one-flask preparation of succinic amide from azide. All the reactions are performed on multigram scales.

2009 Elsevier Ltd. All rights reserved.

* Corresponding author. Tel.: +86-21-54925178; e-mail: shiong81@sioc.ac.cn

* Corresponding author. Tel.: +86-21-54925176; e-mail: wstian@sioc.ac.cn

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Sacubitril (**1**) is a neprilysin inhibitor developed by G. M. Ksander et al. in the early 1990s (Figure 1).[1] Combining sacubitril (**1**) with the angiotensin II receptor-blocker valsartan (**2**) by co-crystallization, Novartis developed a first-in-class combination drug (trade name Entresto) for use in heart failure (HF). Entresto was granted approval in 2015 by FDA to reduce the risk of cardiovascular death and hospitalization for HF in patients with chronic HF (NYHA Class II–IV) and reduced ejection fraction.[2]

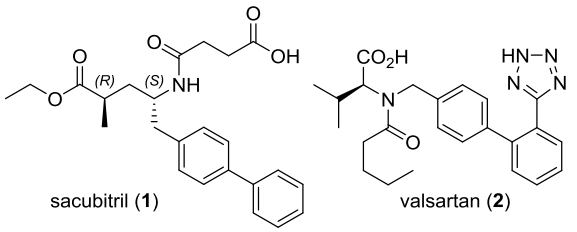
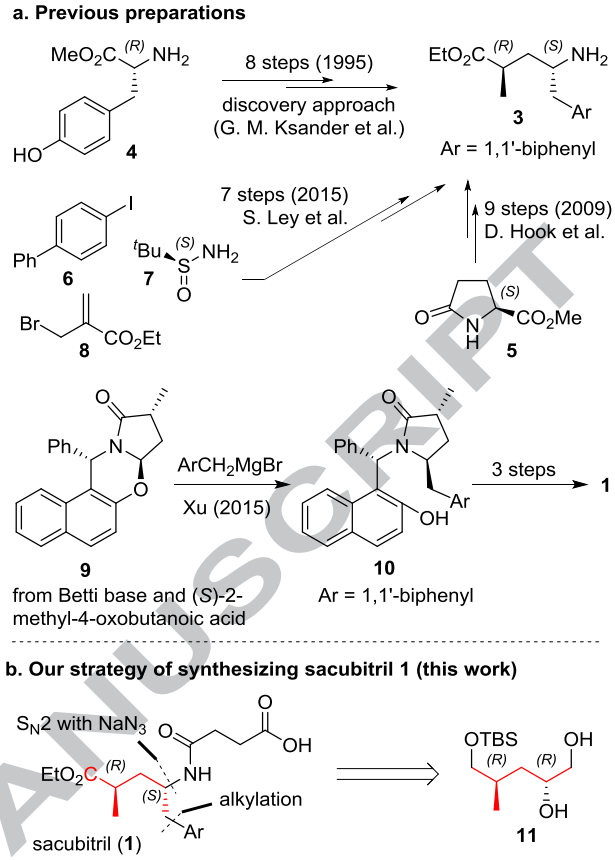


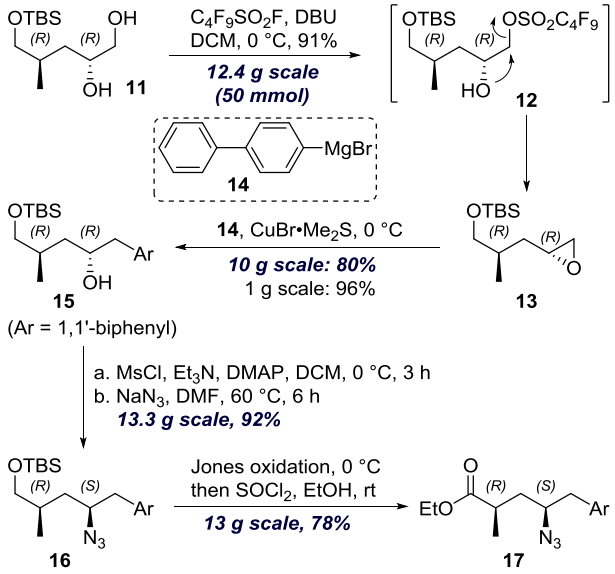
Figure 1. Sacubitril (**1**) and valsartan (**2**)

Sacubitril (**1**) is an α-methyl-γ-amino-δ-biphenyl valeric acid derivative with two stereocenters. The main synthetic challenge lies in the construction of the chiral intermediate **3**, and there have been four routes reported (Scheme 1a). The eight-step discovery route by Ksander and coworkers started with the unnatural *N*-Boc-D-tyrosine methyl ester **4**.[1] Therein, the chiral amine was inherited from **4** and the chiral methyl group was created by a stereoselective hydrogenation of an internal double bond. An alternative approach, by Hook et al., starting from l-pyroglutamic acid methyl ester, employed an alkylation of a chiral γ-lactam or a stereoselective hydrogenation of an α-methylene-γ-lactam to establish the chiral methyl group.[3] Ley et al. devised a flow chemistry methodology to enhance several steps in their synthesis which installed the chiral methyl group via a stereoselective hydrogenation of a *N*-sulfinyl protected acrylic acid and the chiral amine via a diastereoselective Reformatsky-type carbethoxyallylation of chiral *N*-sulfinyl imine.[4] Xu presented a synthesis of **1** featuring a stereoselective addition of Grignard reagent to oxazolidine **9**.[5] Herein, we report a multigram-scale synthesis of sacubitril (**1**) based on a chiron approach.

We have developed a series of chiral methyl-branched building blocks and used them in the syntheses of several commercially attractive compounds.[6] As depicted in Scheme 1b, we envisioned that mono-protected triol **11**, one of the chirons we developed, could be used as starting material to synthesize sacubitril (**1**). With an *R*-branched methyl group and an *R*-configured hydroxyl group, **11** could be easily transformed to **1** via an S_N2 reaction of the (*R*)-OH to introduce the *S*-configured amide-containing side chain and an alkylation of the terminal hydroxyl group with biphenyl metallic reagent.



Scheme 1. Previous and our work on the synthesis of sacubitril



Scheme 2. Converting vicinal diol **11** to azido ester **17**

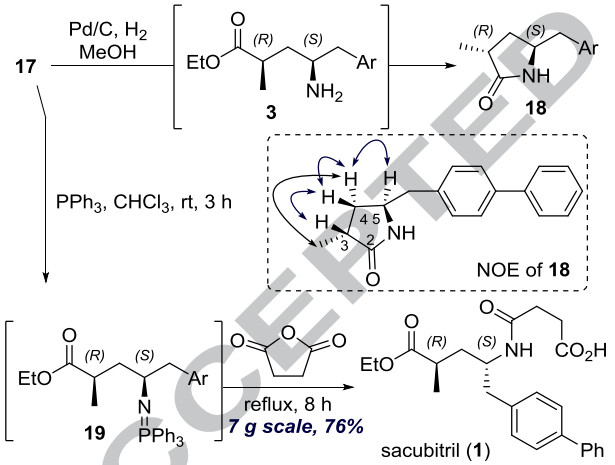
Our synthesis started with transforming **11** to chiral epoxide **13**, a good electrophile to react with metallic reagents (Scheme 2). We first tried to selectively convert the primary hydroxyl group of the vicinal diol unit to toluenesulfonate, but isolated the desired product in low yield (12–17%). The generated hydrochloric acid, although buffered with Et_3N (10 equiv) or pyridine (as solvent), removed the TBS group, thus making the reaction complex and low-yielding. After much experimentation, we found that treatment of **9** with $C_4F_9SO_2F$ and DBU in dichloromethane at 0 °C gave **13** in high yield on multigram scale.[7] The lower reactivity of $C_4F_9SO_2F$ (the reaction does not occur in the absence of DBU) guarantees the excellent selectivity, and the high leaving tendency of the resultant

ACCEPTED MANUSCRIPT

sulfonate leads to the spontaneous formation of epoxide **13** under mild conditions. Belonging to a class of highly valuable surfactants (R_FSO_3M), the perfluorobutanosulfonic acid salt from $C_4F_9SO_2F$ is water soluble, thus making the workup procedure easy to handle. The crude epoxide **13** could be used in the next step without purification, and, if on large scale, the $C_4F_9SO_2M$ could be collected from the aqueous phase.

Then, reacting with (1,1'-biphenyl)-4-ylmagnesium bromide (**14**) in the presence of a catalytic amount of CuBr•Me_2S, the epoxide of **13** was opened with exclusive regioselectivity to give **15** in high yield. The *R*-configured hydroxyl group was then converted into *S*-configured azide via a two-step process involving mesylation at 0 °C[8] and substitution of the resulting mesylate with sodium azide in DMF, providing azide **16** in 92% yield. Jones reagent removed the acid-sensitive TBS group of **16** and oxidized the newly exposed hydroxyl group in one flask; without purification, the resultant acid was treated with $SOCl_2$ in ethanol to afford ethyl ester **17** in good yield on multigram scale. Slight epimerization was occasionally observed during this process; ca. 5% of 2-*epi*-**17** was generated and could be readily separated via column chromatography on silica gel.

We then tried to convert **17** to **3**, which was reported to react with succinic anhydride to deliver sacubitril **1**.[1,9] Catalytic hydrogenation in the presence of Pd/C in MeOH, an efficient and clean method of reducing azide to primary amine, was first tried and gave exclusively lactam **18** in our hands. The NMR data of **18** matched those reported.[10] NOESY analysis confirmed the two substituents on the lactam ring to be *trans*, which should be 3*R*- and 5*S*-configured, according to the stereochemistry of the starting material.



Scheme 3. Completion of the synthesis of **1**

Reducing azides with triphenylphosphine (PPh_3), known as Staudinger reduction, is a standard process to yield primary amines. Interestingly, upon treating **17** with PPh_3, no lactam **18** was observed. The reaction system of **17** with PPh_3 was, however, not clean, giving a mixture of **3**, aza-ylide **19**, PPh_3, and triphenylphosphine oxide. But, even heating the reaction at reflux could not drive to completion the hydrolysis of iminophosphorane intermediate **19** to amine **3**. Since aza-ylides also react with carboxyl electrophiles, as demonstrated in the well-known Staudinger ligation[11], we assumed that treating the crude products with succinic anhydride would transform both **19** and **3** to sacubitril **1**, hence simplify the reaction outcome. Indeed, after running the reduction in THF, the solvent was switched to dichloromethane, to which succinic anhydride was added. After stirring at reflux for two days, both **3** and **19** were consumed to provide **1** in 82% yield. After optimization, the reaction proceeded in chloroform to give **1** in 76% yield on multigram scale. The analytical data of **1** matched those reported.[5]

In summary, we developed an easy and scalable synthesis of sacubitril (**1**) from chiron **11**. Key transformations include the one-step preparation of epoxide **13** from vicinal diol **11**, and the one-flask Staudinger reduction/succinic amide formation process. The former process ($C_4F_9SO_2F$/DBU system) provides an efficient method of preparing epoxides from chiral vicinal diols, and the latter process avoided the formation of lactam **18** and thus simplified the synthesis. All the reactions could proceed on multigram scales and only four purifications (**15**, **16**, **17**, and **1**) are needed.

Acknowledgment

We thank the National Natural Science Foundation of China (21272258, 21572248) for financial support.

Supplementary data

Supplementary data (^{1}H NMR and ^{13}C NMR spectra) associated with this article can be found in the online version, at…

References and notes

1. Ksander, G. M.; Ghai, R. D.; deJesus, R.; Diefenbacher, C.; Yuan, A.; Berry, C.; Sakane, Y.; Trapani, A. *J. Med. Chem.* **1995**, *38*, 1689-1700.
2. McMurray, J. J. V.; Packer, M.; Desai, A. S.; Gong, J.; Lefkowitz, M. P.; Rizkala, A. R.; Rouleau, J. L.; Shi, V. C.; Solomon, S. D.; Swedberg, K.; Zile, M. R. *N. Engl. J. Med*, **2014**, *371*, 993-1004.
3. Hook, D.; Riss, B.; Kaufmann, D.; Napp, M.; Bappert, E.; Polleux, P.; Medlock, J.; Zanotti Gerosa, A. Process and intermediates for the preparation of 5-biphenyl-4-yl-2-methylpentanoic acid derivatives. World Patent, 2009090251 A2, 2009.
4. Lau, S.-H.; Bourne, S. L.; Martin, B.; Schenkel, B.; Penn, G.; Ley, S. V. *Org. Lett.* **2015**, *17*, 5436-5439.
5. Xu, X.-N. A preparation method of Sacubitril. CN 104557600 A, 2015.
6. (a) Tian, W.-S.; Zhang, S.-J.; Wang, Y. 4-methyl-2-oxopentanoates. CN 201010530595.3, 2013; (b) Song, Z.-J.; Shi, Y.; Jin, R.-H.; Lin, J.-R.; Tian, W.-S. *Chin. J. Chem.* **2012**, *30*, 2595-2597; (c) Zhang, S. J.; Shi, Y.; Tian, W. S. *Chin. J. Chem.* **2015**, *33*, 663-668; (d) Zhang, S. J.; Dong, H. D.; Gui, J. H.; Tian, W. S. *Tetrahedron Lett.* **2012**, *53*, 1882-1884; (e) Wang, Z.-K.; Xu, Q.-H.; Tian, W.-S.; Pan, X.-F. *Tetrahedron Lett.* **2007**, *48*, 7549-7551; (f) Shen, J.; Shi, Y.; Tian, W. *Chin. J. Chem.* **2015**, *33*, 683-687.
7. (a) Yan, Z.-H.; Wang, J.-Q.; Tian, W.-S. *Tetrahedron Lett.* **2003**, *44*, 9383-9384; (b) Yan, Z.-H.; Guan, C.-B.; Yu, Z.-X.; Tian, W.-S. *Tetrahedron Lett.* **2013**, *54*, 5788-5790.
8. Reaction of $C_4F_9SO_2F$ with diol **11** would release fluoride anion, which might cause the deprotection of TBS ether. In practice, we found it was important to keep the reaction system at or below 0 °C. However, running the reaction at ambient temperature would result in partial cleavage of TBS ether to give ((4*R*)-4-methyltetrahydrofuran-2-yl)methanol.
9. Hook, D.; Ruch, T.; Riss, B.; Wietfeld, B.; Sedelmeier, G.; Napp, M.; Baenziger, M.; Hawker, S.; Ciszewski, L.; Waykole Liladhar, M. Process for preparing 5-biphenyl-4-amino-2-methyl pentanoic acid. World Patent, 2008083967 A2, 2008.
10. The NMR data of our sample match those reported in references 3 and 9, except the signal of the methyl group. It was erroneously reported as 1.90 (s, 3H), which should be 1.19 (d, J = 7.2 Hz, 3H).
11. (a) Schilling, C. I.; Jung, N.; Biskup, M.; Schepers, U.; Brase, S. *Chem. Soc. Rev.* **2011**, *40*, 4840-4871; (b) van Berkel, S. S.; van Eldijk, M. B.; van Hest, J. C. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 8806-8827.

ACCEPTED MANUSCRIPT

Highlights

- ✓ A chiron-based synthesis of sacubitril was achieved on multigram scale.
- ✓ $C_4F_9SO_2F$/DBU converts terminal chiral vicinal diols to epoxides in high yields.
- ✓ Staudinger reduction avoids the formation of lactam.

ACCEPTED MANUSCRIPT