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Practical synthesis of an orally active renin inhibitor aliskiren

Hua Dong, Zhi-Liu Zhang, Jia-Hui Huang, Rujian Ma,* Shu-Hui Chen and Ge Li

WuXi PharmaTech Co., Ltd, No. 1 Building, 288 FuTe ZhongLu, WaiGaoQiao Free Trade Zone, Shanghai 200131, PR China

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Abstract—A convergent synthesis of aliskiren was accomplished via the use of **Segment AB** as the key intermediate, which was prepared via the coupling of the Grignard reagent derived from **Segment B** with **Segment A**, followed by subsequent oxidative lactonization.

1. Introduction

The renin-angiotensin system (RAS) plays a central role in the regulation of blood pressure as well as in the maintenance of sodium and electrolyte balance. Thus, intervention of this cascade has been investigated as a treatment option for hypertension and congestive heart failure.[1,2] Since the formation of the end product of RAS, vasoconstrictor angiotensin II, is accomplished through two enzymatic events mediated, respectively, by renin (functioned at the first rate-limiting step) and angiotensin-converting enzyme (ACE), it is thus believed that inhibition of renin or ACE may result in antihypertensive effects. Furthermore, given the fact that angiotensinogen is the only known naturally occurring substrate for renin (in contrast to the multiple substrates known for ACE), this has rendered renin as an ideal target for the development of antihypertensive drugs.[3]

Aliskiren (also known as CGP60536B and SPP-100B) was discovered by Novartis Pharma AG as a non-peptidic orally active renin inhibitor after intensive research for many years.[4–6] Several recent publications detailed a number of approaches toward the synthesis of aliskiren.[7–11] Prompted by its fascinating biological activity and structural complexity, we became interested in the total synthesis of aliskiren.[12] In this letter, we report a convergent synthetic approach featuring **Segment AB** as the key intermediate, which was envisioned to be derived from the coupling of **Segment B** (via its Grignard reagent) and **Segment A** followed by a subsequent lactonization. We further envisioned that the opening of **Segment AB** with **Segment C** should provide the desired aliskiren (Scheme 1).

2. Synthesis of Segment A

The general synthetic route employed for this piece was based on an approach reported by Goschke and Mailbaum along with PharmaTech's modifications. As shown in Scheme 2, with the intention to devise a practical and cost-efficient synthesis for aliskiren, we replaced several expensive reagents used by Maibaum and his collaborators and streamlined the overall synthetic operations. Toward these goals, *O*-alkylation of the phenolic hydroxyl group in **1** (at 400 g scale) with the three-carbon side chain mesylate **2** (prepared from its corresponding alcohol) gave rise to aldehyde **3** (98%), which was reduced with $NaBH_4$ in ethanol to provide the corresponding alcohol **4**. PBr_3 mediated bromination of **4** led to the desired **Segment E** (91% from 3), which was allowed to react with the lithium enolate derived from Evan's chiral auxiliary **5** to afford adduct **6** in 76% yield. Standard alkaline peroxide mediated hydrolysis of **6** yielded the desired acid **7** (81%), which was further converted to the corresponding alcohol **8** via LAH reduction in almost quantitative yield. Subsequent treatment of **8** with PPh_3/NBS led to **Segment D** in 97% yield (at 460 g scale). Asymmetric alkylation of the lithium enolate derived from **9** with **Segment D** provided the expected product **10** (68%), which was further elaborated into its corresponding amino acid **11** via acidic hydrolysis. Compound **11** was

* Corresponding author. Tel.: +86 21 5046 1111; fax: +86 21 5046 3718; e-mail: marj@pharmatechs.com

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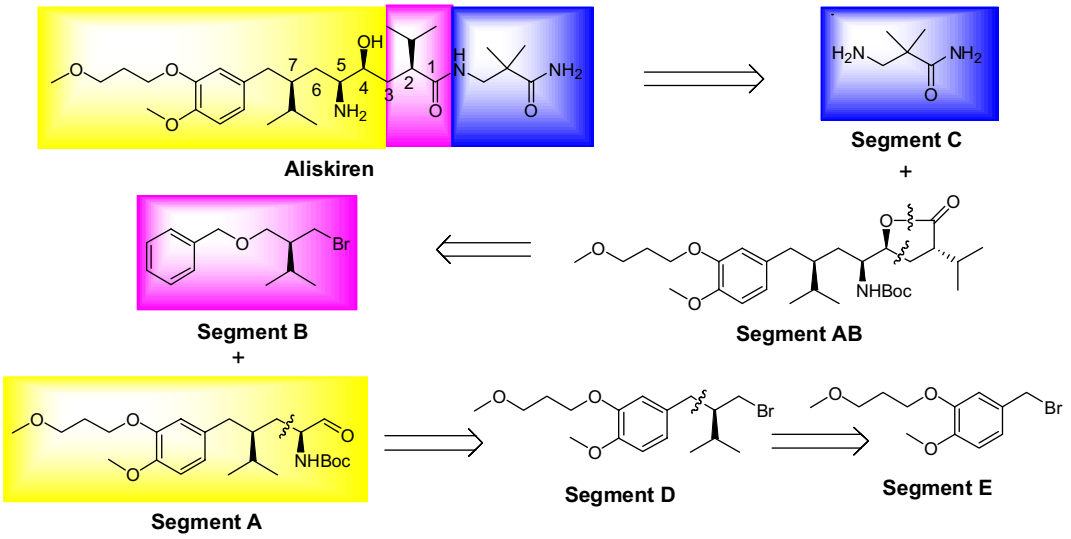
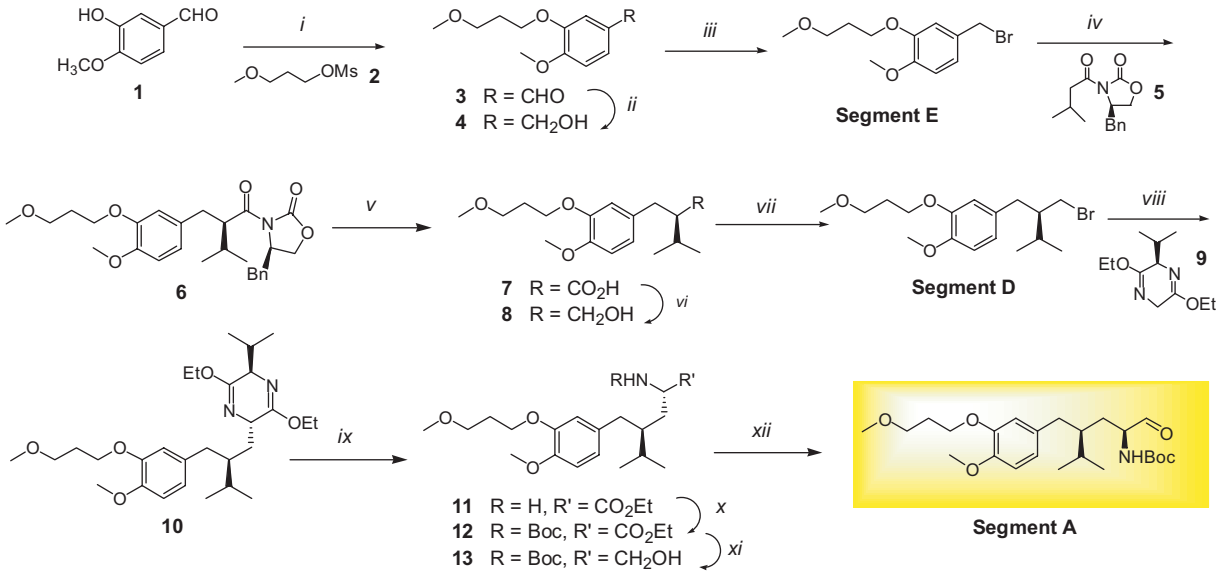


Scheme 1. PharmaTech's strategy for the synthesis of aliskiren.



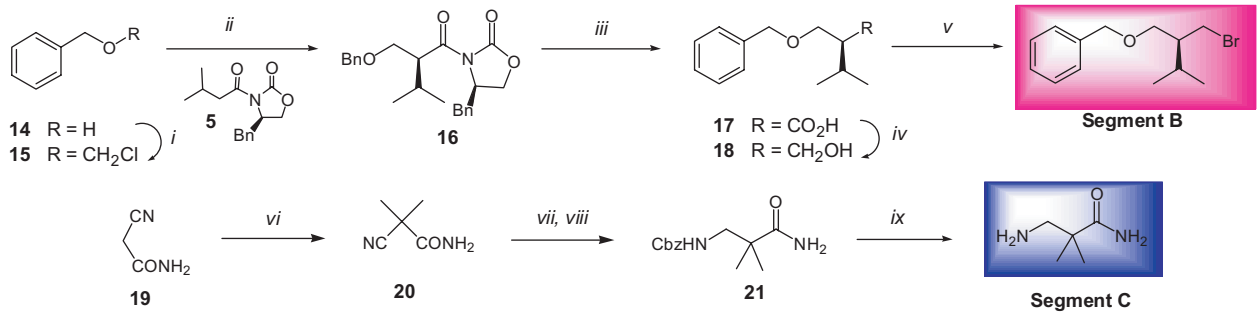
Scheme 2. Synthesis of Segment A: (i) K_2CO_3, CH_3CN, 98%; (ii) $NaBH_4$, EtOH; (iii) PBr_3, CH_2Cl_2, 91% (two steps); (iv) **5**, LiHMDS, THF, then **Segment E**, 76%; (v) LiOH, H_2O_2, 81%; (vi) LAH, THF, 95%; (vii) PPh_3, NBS, CH_2Cl_2, 97%; (viii) **9**, *n*-BuLi, then **Segment D**, 68%; (ix) HCl, MeCN; (x) Boc_2O, Et_3N; (xi) $NaBH_4$, EtOH, 91% (three steps); (xii) DMSO, ClC(O)C(O)Cl, Et_3N, CH_2Cl_2, 89%.

later converted to **12** (via *N*-Boc protection), thereafter **13** (via ester reduction) with an overall yield of 91% (three steps from **10**). The final Swern oxidation of **13** thus afforded the desired aldehyde **Segment A** in 89% yield.

3. Syntheses of Segments B and C

In accordance with the synthetic routes outlined in Scheme 3, benzyl alcohol **14** was first converted to its chloromethyl ether **15** (33%), which was engaged in the asymmetric *C*-alkylation with the titanium enolate derived from **5** to yield the desired adduct **16** in 50% yield. Upon standard alkaline peroxide mediated work-up and subsequent LAH reduction, compound **16** was converted to alcohol **18** through its acid intermediate **17** in an overall yield of 71%. Treatment of **18** with NBS and triphenyl phosphine thus afforded the desired bromo-derivative **Segment B**. It is worthwhile to mention that this reaction sequence was scaled up to produce 300 g of **Segment B**.

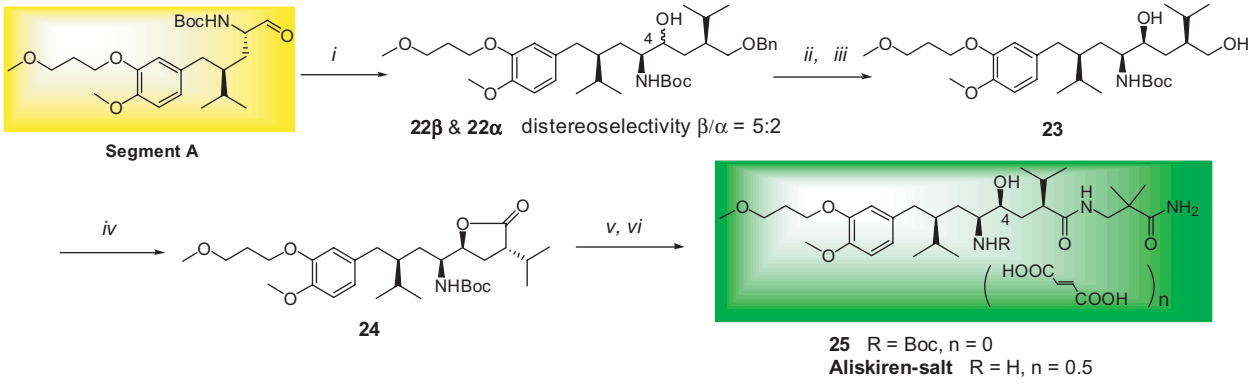
As also depicted in Scheme 3, **Segment C** was prepared via a four-step sequence consisting of (1) *C*-methylation, (2) LAH mediated cyano reduction, (3) *N*-Cbz protection (for easy purification), and (4) $Pd(OH)_2/C$ promoted *N*-deprotection. The overall yield of this sequence was quite low, this was primarily due to product loss occurred during isolation.



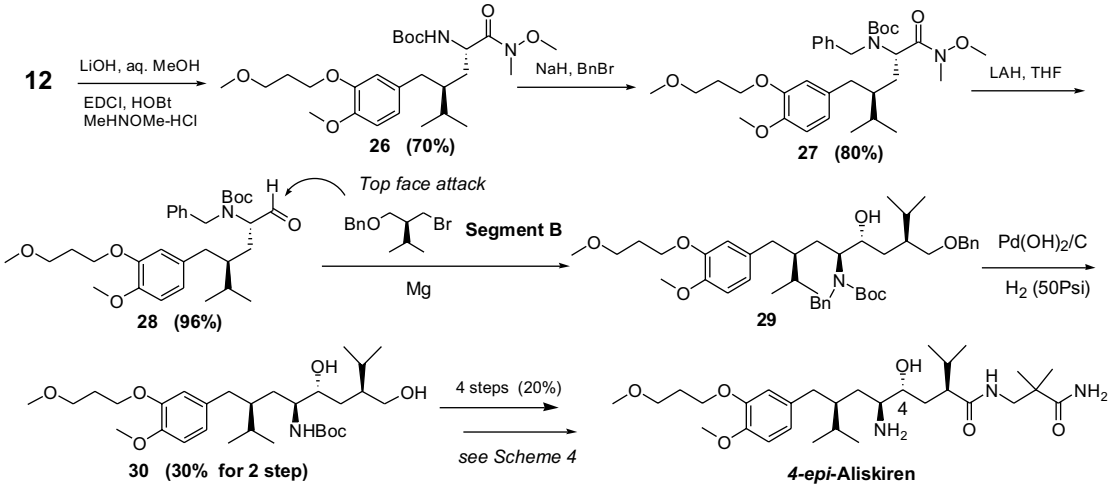
Scheme 3. Synthesis of Segments B and C: (i) HCHO, HCl (g), 33%; (ii) **5**, $TiCl_4$, CH_2Cl_2, then **15**, 50%; (iii) LiOH, H_2O_2, 82%; (iv) LAH, THF, 86%; (v) PPh_3, NBS, CH_2Cl_2, 61%; (vi) NaOEt, MeI, 64%; (vii) LAH, THF; (viii) CbzCl, Et_3N; (ix) $Pd(OH)_2/C$, H_2, 20% (three steps).

4. Final assembly of aliskiren

As shown in Scheme 4, treatment of **Segment A** (aldehyde) with the Grignard reagent prepared from **Segment B** provided two diastereoisomers, **22β** and **22α** in a ratio of 5:2 favoring the desired beta-isomer **22β**. Upon *O*-debenzylation and C-4 isomer separation, we obtained the pure desired diastereomer (at C-4 position) **23** in 23% yield. The following TPAP/NMMO mediated oxidation of diol **23** yielded the corresponding lactone **24** (38%) with all four chiral centers (at C-2, C-4, C-5, and C-7) correctly established. Further reaction of **24** with **Segment C** in the presence of 2-hydroxypyridine and triethylamine gave rise to the desired adduct **25** in 65% yield. Upon *N*-deprotection and final salt formation, compound **25** was converted to the target product aliskiren fumarate salt in 80% overall yield for two steps.



Scheme 4. Synthesis of aliskiren: (i) Mg, **Segment B**; (ii) $Pd(OH)_2/C$, H_2; (iii) C-4 hydroxy isomer separation; 23% for **23**; (iv) TPAP, NMMO, 38%; (v) **Segment C**, 2-hydroxypyridine, Et_3N, 65%; (vi) 0.33 N TMSCl, 1 N Phenol, CH_2Cl_2; (vii) $HO_2CCH{=}CHCO_2H$ (*trans*), MeOH, 80%.



Scheme 5. Synthesis of 4-*epi* aliskiren.

5. Synthesis of 4-*epi*-aliskiren

In contrast to the low selectivity obtained for **22** (Scheme 4), treatment of *N*-bis-protected aldehyde **28** (prepared from **12** via a four-step sequence outlined in Scheme 5) with the Grignard reagent derived from **Segment B** afforded a single C-4 isomer **29** (via Cram–Felkin mode), which was converted to diol **30** via $Pd(OH)_2/C$ mediated hydrogenation. Following the same reaction sequence as described for **23** shown in Scheme 4, compound **30** was converted to the 4-*epi*-aliskiren.

In summary, we have devised a new convergent route for the total synthesis of aliskiren and 4-*epi*-aliskiren. Since all of the key building blocks could be prepared in large scale, the synthetic route discussed herein may be used as a practical route for the synthesis of aliskiren.

References and notes

1. Reid, I. A.; Morris, R. J.; Ganong, W. F. *Ann. Rev. Physiol.* **1978**, *40*, 377–410.
2. Skeggs, L. T.; Doven, F. E.; Levins, M.; Lentz, K.; Kahn, J. R. The Biochemistry of the Renin–Angiotensin System. In *The Renin-Angiotensin System*; Johnson, J. A., Anderson, R. R., Eds.; Plenum Press: New York, 1980, pp 1–27.
3. Greenlee, W. J. *Med. Res. Rev.* **1990**, *10*, 173–236.
4. Goeschke, R.; Rasseti, V.; Cohen, N. C.; Rahuel, J.; Grutter, M.; Stutz, S.; Fuhrer, W.; Wood, J.; Maibaum, J. 15th Int. Symposium Med. Chem., 6–10 September, Edinburgh, 1998, Abst. p 229.
5. Maibaum, J. et al. 15th Int. Symposium Med. Chem., 6–10 September, Edinburgh, 1998, Abst. p 230 and 231.
6. Rahuel, J.; Rasetti, V.; Maibaum, J., et al. *Chem. Biol.* **2000**, *7*, 493–504.
7. Mealy, N. E.; Castaner, J.; Castaner, R. M.; Silverstre, J. *Drugs Fut.* **2001**, *26*, 1139–1148.
8. Rueger, H.; Stutz, S.; Goschke, R.; Spindler, F.; Maibaum, J. *Tetrahedron Lett.* **2000**, *41*, 10085–10089.
9. Sandham, D. A.; Taylor, R. J.; Carey, J. S.; Fassler, A. *Tetrahedron Lett.* **2000**, *41*, 10091–10094.
10. Dondoni, A.; De Lathauwer, G.; Perrone, D. *Tetrahedron Lett.* **2001**, *42*, 4819–4823.
11. Goschke, R.; Stutz, S.; Heinzelmann, W.; Maibaum, J. *Helv. Chim. Acta* **2003**, *86*, 2848–2870.
12. Dong, H.; Zhang, Z-L.; Huang, J-H.; Chen, S. H.; Li, G. Practical Synthesis of Aliskiren: An Orally Active Human Renin Inhibitor. 230th ACS National Meeting in Washington DC. Abst.# MEDI-893844; August 28–September 1, 2005.