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Practical Synthesis of a Renin Inhibitor via a Diastereoselective Dieckmann Cyclization

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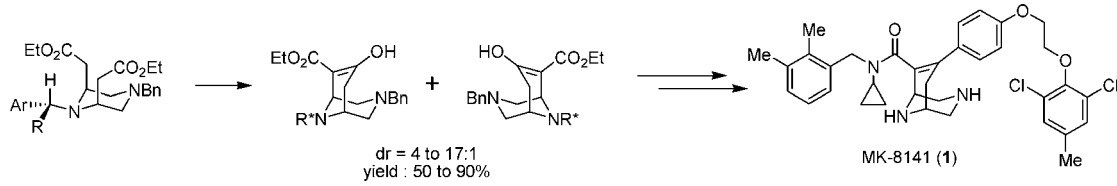
ABSTRACT



A scalable synthesis of a potent renin inhibitor (1) is described. The absolute stereochemistry is set via an unprecedented diastereoselective Dieckmann cyclization directed by a remote chiral protecting group. This transformation enables preparation of chiral 1,3-[3.3.1]-diazabicyclononenes by desymmetrization of alkyl-esters, with selectivities ranging from 4 to 17:1.

The renin−angiotensin system (RAS) is known to play an important role in cardiovascular diseases, renal diseases, and metabolic disorders.[1,2] Renin is an aspartyl protease that cleaves angiotensinogen to a decapeptide angiotensin I. This substrate is then further cleaved by the angiotensin-converting enzyme (ACE) to an octapeptide angiotensin II, a substance identified as a powerful vasoconstricting peptide. Recently, renin has been validated as a target in the regulation of high blood pressure and heart failure.[3]

MK-8141 (**1**) is a potent and selective, orally bioavailable renin inhibitor.[4] To support further development of this compound, we needed to develop a scalable synthesis suitable for the preparation of multigram to kilogram quantities. While a racemic synthesis of **1** has been reported,[4] there are no reports of a stereoselective approach to the chiral 1,3-[3.3.1]-diazabicyclononene core. We describe herein a practical stereoselective synthesis of **1** via an unprecedented diastereoselective Dieckmann cyclization, directed by a remote protecting group.[5]

Our retrosynthetic approach is outlined in Scheme 1. We envisioned that **1** could be assembled via an amide coupling between benzyl amine **2** and bicyclic acid **3**, followed by deprotection of both amines. Acid **3** could be obtained from the Suzuki cross-coupling between tosylate **4** and aryl boronate ester **5** to allow for a convergent approach. Finally,

(1) Skeggs, L. T.; Dovens, F. E.; Levins, M.; Lentz, K.; Kahn, J. R. *The Renin-Angiotensin System*; Jonhson, J. A., Anderson, R. R., Eds.; Plenum Press: New York, 1980; p 1. MacGregor, G. A.; Markandu, N. D.; Roulston, J. E.; Jones, J. C.; Morton, J. J. *Nature* **1981**, *291*, 329–331.

(2) For recent reviews, see: Carey, R. M.; Stragy, H. M. *Endocr. Rev.* **2003**, *24*, 261–271. Persson, P. B. *J. Physiol.* **2003**, *552*, 667–671. Re, R. N. *Med. Clin. North Am.* **2004**, *88*, 19–38. Brewster, U. C.; Perazella, M. A. *Am. J. Med.* **2004**, *116*, 263–272. Aneja, A.; El-Atat, F.; McFarlane, S. I.; Sowers, J. R. *Recent Prog. Horm. Res.* **2004**, *59*, 169–205.

(3) Maibaum, J.; Stutz, S.; Goschke, R.; Rigollier, P.; Yamagushi, Y.; Cumin, F.; Rahuel, J.; Baum, H. P.; Cohen, N. C.; Schnell, C. R.; Fuhrer, W.; Gruetter, M. G.; Schilling, W.; Wood, J. M. *J. Med. Chem.* **2007**, *50*, 4832–4844.

(4) Bezençon, O.; Bur, D.; Weller, T.; Richard-Bildstein, S.; Remen, L.; Sifferlen, T.; Corminboeuf, O.; Grisostomi, C.; Boss, C.; Prade, L.; Delahaye, S.; Treiber, A.; Strickner, P.; Binker, C.; Hess, P.; Steiner, B.; Fischli, W. *J. Med. Chem.* **2009**, *52*, 3689–3702.

(5) To the best of our knowledge, this type of desymmetrizing diastereoselective Dieckmann approach has not been previously disclosed in the literature. For a conceptually distinct diastereoselective Dieckmann approach, see: (a) Boger, D. L.; McKie, J. A.; Nishi, T.; Ogiku, T. *J. Am. Chem. Soc.* **1997**, *119*, 311. (b) Groth, U.; Kesenheimer, C.; Kreye, P. *Synlett* **2006**, *14*, 2223. (c) Kawabata, T.; Watanabe, T. *Heterocycles* **2008**, *76*, 1593.

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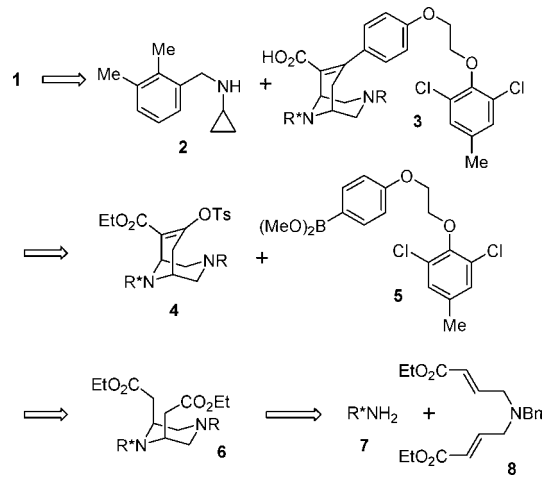
Scheme 1. *Retrosynthic* Approach to Renin Inhibitor **1**

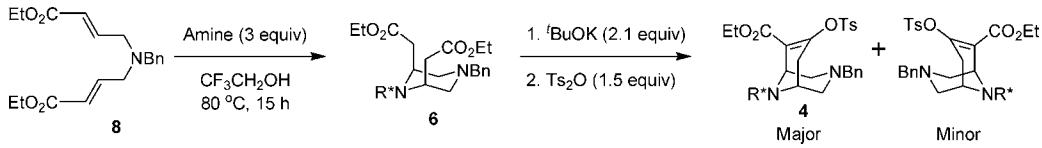


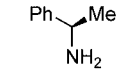
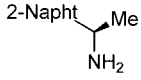
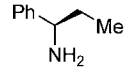
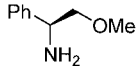
we imagined that the absolute stereochemistry of the bicyclic core could be installed via an unprecedented diastereoselective Dieckmann cyclization of piperazine **6**. To do so, we hypothesized that using a remote chiral protecting group on the bridged amine could direct the base-mediated cyclization. The piperazine **6** could be formed from a double 1,4-addition of a chiral amine **7** to the α,*β*-unsaturated ester **8**.

In the reported racemic synthesis of **1**,[4] piperazine **6** (R = Boc, R* = Me) was prepared by double-Michael addition of methyl amine to readily available dieneoate **8** (R = Bn) affording a 1.5:1 mixture of *trans* and *cis* (desired) **6** isomers. Treatment of **6** with ^{t}BuOK in toluene at 100 °C afforded complete conversion to the racemic Dieckmann cyclization product. We postulated that this strategy could be used with control of the absolute stereochemistry if a chiral amine replaced methylamine. Ideally, this amine would be easily installed and deprotected while being effective at inducing stereoselectivity in the subsequent base-mediated Dieckmann cyclization. Given the unprecedented nature of its potential enantiocontrol, this amine would have to be readily available in either antipode to maximize our probability of aquiring either diastereomer. On the basis of these criteria, we initially turned our attention to α-methylbenzyl amine which is available in bulk quantities at <$50/kg for either the *S* or *R* enantiomers and should be susceptible to straightforward removal by hydrogenolysis.

Prior to the evaluation of the diastereoselective Dieckmann cyclization, we needed to develop an efficient synthesis of piperazines **6**. The reported conditions used to prepare **6a** (R = Me) afforded <10% of the desired adduct **6c** after 24 h upon direct replacement of methylamine with an excess of (*R*)-methylbenzyl amine. Performing the reaction neat at 80 °C improved the yield of **6c** to 30% with modest selectivity (4:1) for the desired *cis* isomer. After an extensive solvent screen, we were pleased to find that running the reaction in a minimal amount of 1,1,1-trifluoroethanol (3 mL/g) in the presence of only 3 equiv of (*R*)-methylbenzyl amine allowed for the piperazine to be isolated in 80% yield as a 20:1 mixture of *cis*:*trans* isomers.[6] This protocol was also successful for the preparation of a series of analogous chiral alkyl aryl protected piperazines **6a**−**f** (Table 1).

Table 1. Double-Michael Addition of Chiral Amines and Diastereoselective Dieckmann Cyclization Results



entry	amine	1,4-addition yield (%)	ratio cis:trans	Dieckmann cyclization yield (%)[a]	dr[b]
1	$MeNH_2$	**6a** 20	1:1.5	**4a** nd	nd
2	$BnNH_2$	**6b** 65	12:1	**4b** 0	-
3		**6c** 90	>20:1	**4c** 90	8.5:1[c]
4		**6d** 45	>20:1	**4d** 59	17:1
5		**6e** 60	>20:1	**4e** 50	4:1
6		**6f** 52	>20:1	**4f** 67	11:1

[a] All reactions were performed at 20 °C in 1,4-dioxane. [b] dr measured by HPLC. [c] Reaction performed using ^{t}AmOK at −25 °C in DMF. The use of ^{t}BuOK in 1,4-dioxane lead to a 6:1 dr, 78% yield.

With a reasonable synthesis of the piperazines in hand, efforts were undertaken to identify effective conditions for stereoselective Dieckmann cyclization using **6c** as a model substrate. The initial reaction conditions evaluated were those used in the racemic synthesis of **1** (NaH, in THF at 45 °C).[4] We were pleased that under these conditions a promising 3:1 diastereoselectivity of the desired bicycle **4c** was obtained. In constrast to the reactivity of **6a** which required 5 h to obtain complete conversion at 45 °C in THF, complete conversion with **6c** was achieved after only 30 min. Performing the reaction at ambient temperature improved the diastereoselectivity to 6:1, when ^{t}BuOK was used as base. An evaluation of solvent, base, and temperature revealed that performing the Dieckmann cyclization at −25 °C in DMF improved the diastereoselectivity up to 8.5:1 in the presence of 2.1 equiv of ^{t}AmOK (allowing the internal temperature to reach −5 °C over 2 h to achieved complete conversion), with an HPLC assay yield of 90%. Conveniently, the keto-ester was immediately trapped with tosyl anhydride to afford the tosylate required for the next step.

As outlined in Table 1, additional chiral α-alkyl-aryl amines were investigated to explore the effect of the chiral substituent on the selectivity of the Dieckmann cyclization. Increasing the size of the aryl versus the alkyl substituent had an opposite effect on the selectivity. The presence of a bulkier aryl group (2-naphtyl, **6d**, entry 4) improved the diastereoselectivity of the Dieckmann (17:1 ratio),[7] while the use of a more hindered alkyl group (α-ethylbenzyl, **6e**, entry 5) led to lower selectivities (4:1).

Interestingly, the use of methyl-protected *S*-phenylglycinols (entry 6, **6f**) lead to a slightly higher selectivity (11:1). Although these chiral amine substituents did afford higher levels of selectivity, weighing these modest improvements against the lower yields and higher cost of these amines made the use of α-(*R*)-methylbenzyl amine a superior selection. It is noteworthy that the addition of 2 equiv of methane sulfonic acid to the crude workup stream allowed for the bismesylate salt of **4c** which was isolated in 63% yield from **6c** and greater than 99:1 dr.

The unexpectedly high rate of reaction observed for the α-methylbenzyl-substituted compounds can be explained if the ester groups were fixed in a diaxial orientation. This is plausible if one invokes strain akin to the $A_{1,3}$ allylic strain observed with analogous 2,6-disubstituted *N*-Boc protected piperidines which are well-known to adopt such a conformation.[8] In support of this assertion, both computational and crystallographic studies show the preference for diaxial orientation of the ester functionalities of **6c** (Figure 1).[9] Interestingly, the unsubstituted benzyl-protected compound **6b** failed to undergo cyclization even under forcing conditions (refluxing toluene).[10]

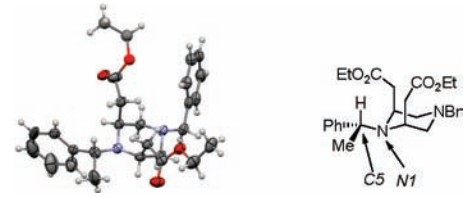


Figure 1. Preferential configuration of **6c** as observed by X-ray crystallography.

These studies shed some light on the observed sense of diastereoselectivity. In particular, the computational studies suggest hindered rotation about the *N1* (bridged-nitrogen)−*C5* (carbon of the chiral center) bond of 3.5 kcal with the *C5*-bound proton being oriented to minimize gauche interactions between the bulkier *C5* substituents and the axially oriented acetate groups (Figure 1). This orientation results in a preferential shielding of one of the methylene groups by the bulkier phenyl group with the other methylene proximal to the methyl group and thus more exposed. While it is tempting to suggest that the sense of selectivity derives from the selective deprotonation of the more accessible proton, attack of this enolate on the more hindered ester would lead to the minor diastereomer. Further studies are required to determine the mechanism of this transformation and will be conducted in due course.[11]

The end game of the synthesis required cross coupling of tosylate **4c** with a suitable coupling partner derived from aryl bromide **9**. Following extensive investigation, it was determined that Suzuki-type cross coupling was optimal. Aryl boronate **5** was accessed via trans-metalation of the aryl bromide **9**[12] to the corresponding triaryl lithium magnesiate[13] followed by quenching of this intermediate with trimethyl borate. Treatment of the resulting boronate ester **5** with 2 mol % $PdCl_2$, dppb, and the bismesylate salt of **4c** yielded **10** in 92% yield, isolated as its bis-HCl salt (Scheme 2). The ester moiety of **10** proved difficult to hydrolyze under standard saponification conditions.[14] Although the use of excess potassium trimethylsilanolate did give a high yield of **3a**, a cheaper alternative was desired. An investigation of hydrolysis conditions revealed that treatment of **10** with excess potassium *tert*-butoxide (7 equiv) in *tert*-butanol at 50 °C gave **3a** in 93% yield. Activation of this acid using

(6) It is believed that the acidity of the 1,1,1-trifluoroethanol allows for an easier proton exchange during the Michael addition.

(7) The 1-naphthyl susbtrate could not be evaluated in the Dieckmann cyclization since the double-Michael addition failed using (1-naphthyl)-ethylamine.

(8) Johnson, F. *Chem. Rev.* **1968**, *68*, 375. Quick, J.; Mondello, C.; Humora, M.; Brennan, T. *J. Org. Chem.* **1978**, *43*, 2705. Neipp, C.; Martin, S. F. *J. Org. Chem.* **2003**, *68*, 8867.

(9) See Supporting Information for X-ray and computational calculation data.

(10) Ho, T.-L.; Lin, Y.-J. *J. Chin. Chem. Soc.* **1997**, *44*, 261. Ho and Line have found Dieckmann cyclizations of analogous *N*-benzyl thiomorpholine substrates to be similarly challenging.

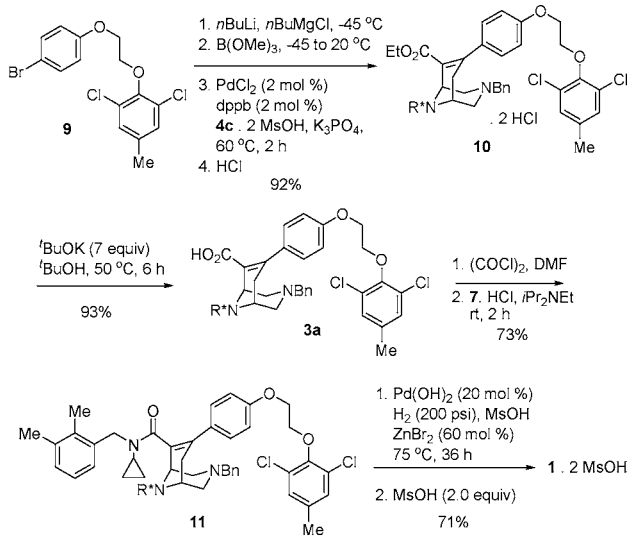
(11) Two plausible pathways allow to access the major diastereomer: (a) selective deprotonation of the less hindered methylene, followed by ketene formation, then deprotonation of the more hindered methylene and cyclization on the ketene; or (b) selective deprotonation of the less hindered methylene, followed by proton-transfer and cyclization.

(12) Gauvreau, D.; Huffman, M. A.; Hughes, G.; Itoh, T.; Yin, J.; Lau, S.; O'Shea, P. WO 2008088690 A2. July 24, 2008.

(13) Lau, S. Y. W.; Hughes, G.; O'Shea, P. D.; Davies, I. W. *Org. Lett.* **2007**, *9*, 2239.

(14) No hydrolysis occurred using excess $LiOH_{(aq)}$ in THF at 67 °C.

Scheme 2. Completion of the Synthesis of **1**



oxalyl chloride and catalytic DMF followed by amidation with amine **2** afforded **11** in 73% yield. The synthesis was completed by a global deprotection of the benzyl groups using $Pd(OH)_2$ under hydrogen atmosphere (200 psi). In this reaction, the presence of zinc bromide was key to avoid proto-dechlorination.[15] Following workup, **1** was isolated as its bis-MsOH salt in 71% yield with high purity, with spectroscopic properties and specific rotation matching those of an authentic sample.[16]

In conclusion, we have developed a practical stereoselective synthesis of renin inhibitor **MK-8141** in 9 steps and 23% overall yield from benzyl amine, without silica gel chromatography. The absolute stereochemistry is introduced by the use of a remote chiral auxiliary which directs an unprecedented diastereoselective Dieckmann cyclization.

Acknowledgment. We thank Dr. Richard G. Ball and Nancy N. Tsou (Merck Process Research, Rahway) for their support in X-ray crystallography.

Supporting Information Available: Procedures and spectra of compounds **1·2MsOH**, **2**, **3a**, **4c**−**4f**, **6a**−**6f**, **9**, **10·2HCl**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Wu, G.; Huang, M.; Richards, M.; Poirier, M.; Wen, X.; Draper, R. W. *Synthesis* **2003**, *11*, 1657.

(16) The use of (*S*)-α-methylbenzylamine lead to the preparation of the opposite enantiomer of MK-8141.