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Enantioselective, Biocatalytic Reduction of 3-Substituted Cyclopentenones: Application to the Asymmetric Synthesis of an hNK-1 Receptor Antagonist

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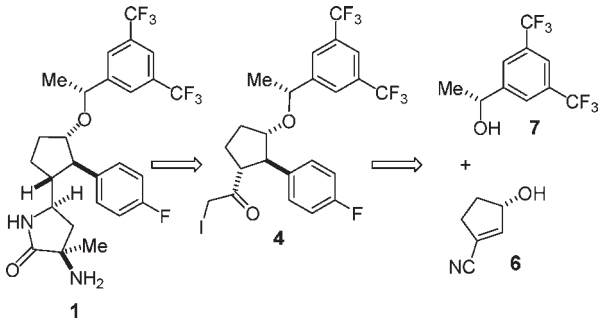
ABSTRACT



A convergent and enantioselective route to the hNK-1 receptor antagonist (1) is described, which sets all six stereogenic centers with high diastereoselectivity and delivers 1 in only 11 steps and 23% overall yield. The process was enabled by the development of the enantioselective enzymatic reduction of 3-functionalized cyclopentenones and stereospecific Pd-catalyzed etherification coupling of fragments 6 and 7.

Human neurokinin-1 (hNK-1) is a G-protein-coupled receptor, which is concentrated in the central nervous system and gastrointestinal tissue.[1] The neuropeptide substance P (SP) is the preferred ligand for the hNK-1 receptor and engages in the moderation of many biological processes.[2] Most notably, hNK1 receptor antagonists have been developed as therapeutic agents for treatment of chemotherapy-induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV).[3] Aprepitant (Emend)[4] is currently the only hNK1 antagonist on the market and is approved for the treatment of both CINV

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(2) (a) Guard, S.; Watson, S. P. *Neurochem. Int.* **1991**, *18*, 149. (b) Takeuchi, Y.; Shands, E. F. B.; Beusen, D. D.; Marshall, G. R. *J. Med. Chem.* **1998**, *41*, 3609 and references cited therein.

(3) (a) Tattersall, F. D.; Rycroft, W.; Cumberbatch, M.; Mason, G.; Tye, S.; Williamson, D. J.; Hale, J. J.; Mills, S. G.; Finke, P. E.; MacCoss, M.; Sadowski, S.; Ber, E.; Cascieri, M.; Hill, R. G.; MacIntyre, D. E.; Hargreaves, R. J. *Neuropharmacology* **2000**, *39*, 652. (b) Rupniak, N. M. J.; Tattersall, F. D.; Williams, A. R.; Rycroft, W.; Carlson, E. J.; Cascieri, M. A.; Sadowski, S.; Ber, E.; Hale, J. J.; Milles, S. G.; MacCoss, M.; Seward, E.; Huscroft, I.; Owen, S.; Swain, C. J.; Hill, R. G.; Hargreaves, R. J. *Eur. J. Pharmacol. Med. Chem.* **1997**, *326*, 201.

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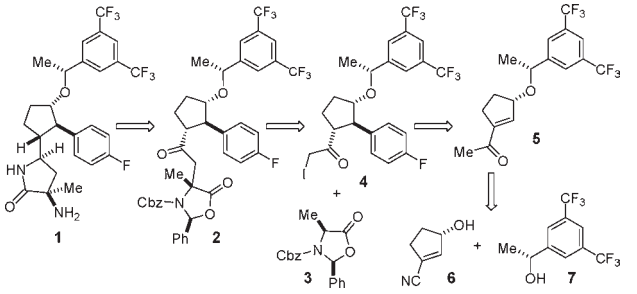
and PONV. As a result, there is ongoing pharmaceutical research to identify potent, selective, and orally bioavailable hNK-1 receptor antagonists as potential therapeutic agents.[5] Recently, structure **1** was identified as a potent, selective hNK-1 receptor antagonist, which warranted further development;[6] however, the reported synthesis was unsuitable to the large scale preparation of **1**, which was required to support the program. The development of a concise, stereoselective, and scalable synthesis of this structurally complex target constituted a considerable synthetic challenge. Herein we wish to report a convergent, stereocontrolled asymmetric synthesis of **1**.

Scheme 1. Retrosynthetic Analysis



The structural complexity of **1** could be divided into three distinct synthetic challenges: (1) the sterically congested ether which contained stereochemistry at both secondary stereogenic termini, (2) the *trans*,*trans*-1,2,3-trisubstituted cyclopentane core, and (3) the pyrrolidinone ring containing two stereogenic centers, one of which was a tertiary branched alkyl amine (Scheme 1). In order to address the stereochemistry of the remote, quaternary stereogenic center, we devised a strategy to produce **1** from ketone **2**, which would be acquired through diastereoselective alkylation of oxazolidinone **3** with iodoketone **4**. The most effective method to control the relative stereochemistry of the cyclopentane core in **4** would be via substrate-controlled conjugate addition of an aryl-metal species on allylic ether **5**, followed by isomerization of the ketone to the thermodynamically favored diastereomer. We envisioned that the most elegant approach to construct both secondary stereogenic centers in allylic ether **5** would be via convergent, stereospecific coupling of allylic alcohol **6** and alcohol **7**, both of which would need to be prepared in enantiomerically pure form.

Alcohol **7** is a common structural motif that exists in several hNK-1 antagonists reported by Merck[4,5] and is readily available via asymmetric reduction of the corresponding aryl methyl ketone.[7] In contrast, the enantioselective synthesis of allylic alcohol **6** has not been reported. Application of existing methodologies to the asymmetric reduction of 3-cyanocyclopentenone (**8**)[8] afforded **6** in variable yields and moderate enantioselectivities.[9] This is a historic problem with the enantioselective reduction of 2-unsubstituted cyclopentenones, presumably due to the lack of any functionality in these substrates that would interact with a chiral reagent or catalyst to offer significant enantiofacial discrimination. Although there was no precedent for the asymmetric, biocatalytic reduction of enones similar to **8**,[10] a ketoreductase library was screened. We discovered that alcohol dehydrogenase from *Rhodococcus erythropolis* (ADH RE) efficiently reduced enone **8** to (*S*)-allylic alcohol **6** in high yield (93%) and excellent enantioselectivity (>99% ee) (Scheme 2). In order to probe the scope of this novel biocatalytic transformation, two other 3-substituted cyclopentenones were also subjected to the same reaction conditions and afforded the (*S*)-allylic alcohol in good yield and >99% ee (Table 1). The extension of this method to other substrates suggests that broader application may be possible.

Scheme 2. Synthesis of Allylic Ether **10**[a]

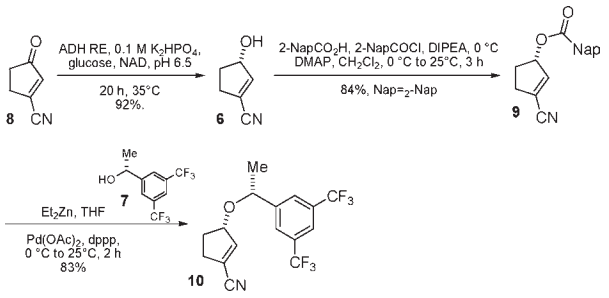
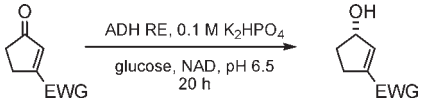


Table 1. Enantioselective, Biocatalytic Reduction of 3-Substituted Cyclopentenones



entry	EWG	conditions	% yield	% ee
1	CO_2Me	ADH RE, NADH, FDH	83	>99
2	CN	ADH RE, NADH, FDH	92	>99
3	SO_2Ph	ADH RE, NADH, FDH	87	>99

(6) Campos, K. R.; Chen, C-y; Ishibashi, H.; Kato, S.; Klapars, A.; Kohmura, Y.; Pollard, D. J.; Takezawa, A.; Waldman, J. H.; Wallace, D. J.; Yasuda, N. PCT Int. Appl. 2008021029, 2008.

(7) Hansen, K. B.; Chilenski, J. R.; Desmond, R.; Devine, P. N.; Grabowski, E. J. J.; Heid, R.; Kubryk, M.; Mathre, D. J.; Varsolona, R. *Tetrahedron: Asymmetry* **2003**, *14*, 3581.

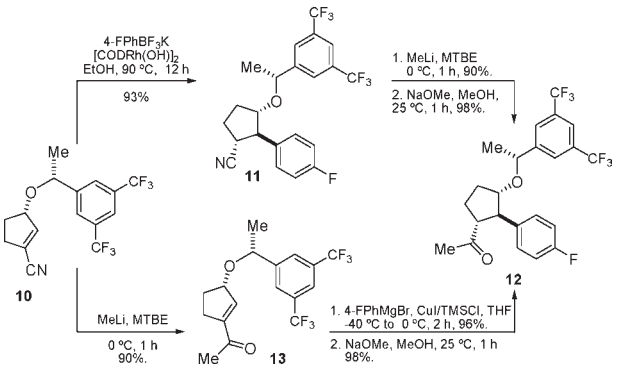
(8) Zimmerman, H. E.; Pasteris, R. J. *J. Org. Chem.* **1980**, 4864–4876. For an improved synthesis of **8**, please refer to the Supporting Information.

(9) (a) Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13529. (b) Corey, E. J.; Guzman-Perez, A.; Lazerwith, S. E. *J. Am. Chem. Soc.* **1997**, *119*, 11769. (c) Yun, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 5640. (d) Brown, H. C.; Ramachandran, P. V. *Acc. Chem. Res.* **1992**, *25*, 16–24. (e) Midland, M. M.; Tramontano, A.; Kazbubski, A.; Graham, R. S.; Tsai, D. J. S.; Cardin, D. *Tetrahedron* **1984**, *40*, 1371. (f) Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847.

(10) (a) For an excellent review of enzymatic reduction of ketones, see: Moore, J. C.; Pollard, D. J.; Kosjek, B.; Devine, P. N. *Acc. Chem. Res.* **2007**, 1412–1419. (b) Fonteneau, L.; Rosa, S.; Buisson, D. *Tetra-*

With alcohols **6** and **7** prepared in high optical purity, we sought a method to couple these partners without epimerization at either center. The documented stereospecificity of transformations which proceed via η^3-allylmetal intermediates made the Pd-catalyzed allylic etherification an attractive choice.[11,12] Although alcohol **7** was an unlikely candidate to participate in this coupling due to its steric congestion and poor nucleophilicity, we were able to develop conditions which effectively coupled **7** with allylic naphthoate ester **9** in good yield without compromising the integrity of either stereogenic center (Scheme 2). Under optimized conditions, **9** and **7** were coupled using $Pd(OAc)_2$ and dppp in the presence of 0.5 equiv of Et_2Zn to afford allylic ether **10** in 83% yield with net retention of configuration at both stereogenic centers.

Scheme 3. Synthesis of *trans*,*trans*-1,2,3 Cyclopentane Core[a]



Attempts to accomplish a cuprate conjugate addition on α,β-unsaturated nitrile **10** were unsuccessful; however we were able to demonstrate a Rh-catalyzed conjugate addition (3 mol % $[CODRh(OH)]_2$, EtOH, reflux) using 5.0 equiv of arylboronic acid or 1.5 equiv of aryl trifluoroborate (K salt).[13] Both procedures afforded **11** in 93% assay yield and high diastereoselectivity (>99:1 β-center, 90:10 α-center) after isomerization of the ketone to the thermodynamically favored diastereomer (NaOMe/MeOH). The nitrile was readily converted to the methyl ketone via treatment with MeLi in MTBE, delivering **12** in 90% assay yield (Scheme 3). Alternatively, methyl ketone **13** was readily produced from nitrile **10** (MeLi, MTBE), and as expected, Cu-catalyzed conjugate addition of an aryl Grignard delivered **12** in excellent yield (95%) and exceptional diastereoselectivity (>99:1 β-center) after isomerization of the ketone to the thermodynamically preferred diastereomer (NaOMe/MeOH, 98:2 α-center). Due to the improved diastereoselectivity, robustness, and improved cost the latter transformation was employed.

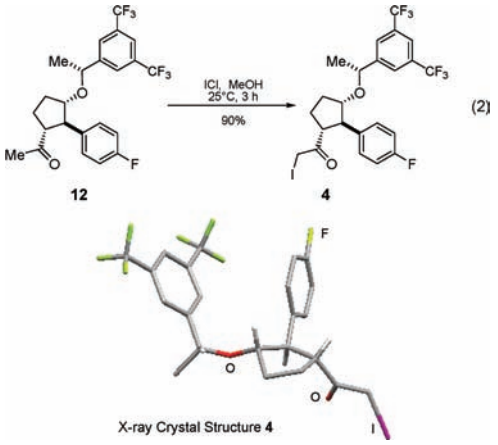
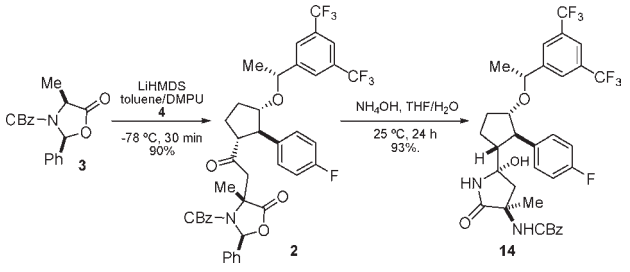


Figure 1. Synthesis and X-ray crystal structure of **4**.

Selective iodination of **12** with ICl in MeOH produced iodoketone **4** in 90% isolated yield (eq 2, Figure 1). An X-ray crystal structure of **4** verified both the relative and absolute chemistry of the four stereogenic centers assembled in this process.

Scheme 4. Convergent Coupling and Rearrangement to Lactam[a]



With a convergent and highly selective process to assemble iodoketone (6 steps, 58% yield), we focused our attention on the development of a stereocontrolled method to assemble the pyrrolidinone ring (Scheme 4). Alkylation of oxazolidinone **3** with iodoketone **4** was accomplished with LiHMDS at low temperature to afford **2** in 90% yield and >99:1 diastereoselectivity.[14] Aminolysis of oxazolidinone **2** with ammonium hydroxide resulted in formation of

hedron: Asymmetry **2002**, *13*, 579. (c) Attolini, M.; Bouguir, F.; Iacazio, G.; Peiffer, G.; Maffei, M. *Tetrahedron* **2001**, *57*, 537.

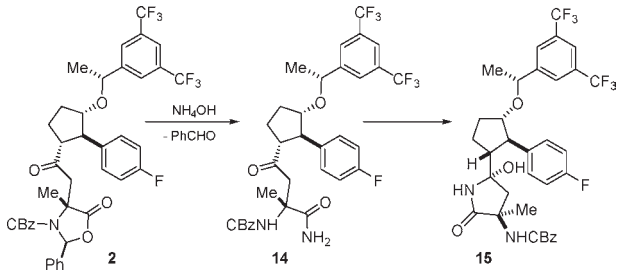
(11) (a) Kim, H.; Lee., C. *Org. Lett.* **2002**, 4369. (b) Leahy, D. K.; Evans, P. A. *Modern Rhodium-catalyzed Organic Reactions* **2005**, 191–214. (c) Muzart, J. *Tetrahedron* **2005**, 5955–6008 and references cited therein.

(12) Both the acetate and benzoate esters afforded similar yields, but the crystalline naphthoate ester was chosen for isolation purposes.

(13) (a) Wang, H.; Yang, D.-Q.; Mo, H.-H. *Youji Huaxue* **2007**, 806–818. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, 2829–2844. (c) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Org. Lett.* **1999**, 1683. (d) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229.

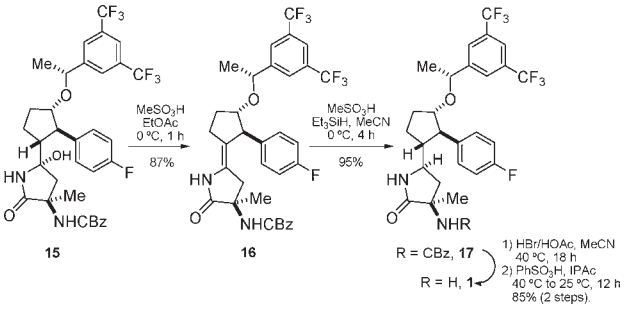
(14) (a) Seebach, D.; Sting, A. R. *Angew. Chem., Int. Ed.* **1996**, 2708–2748 and references cited therein. (b) Karady, S.; Amato, J.; Weinstock, L. *Tetrahedron Lett.* **1984**, *25*, 4337. (c) Szumigala, R. H., Jr.; Onofiok, E.; Karady, S.; Armstrong, J. D., III; Miller, R. A. *Tetrahedron Lett.* **2005**, 4403.

Scheme 5. Mechanism of Lactam Hydrolysis/Rearrangement



intermediate **14**, which underwent spontaneous cyclization to aminal **15** as a 1:1 mixture of diastereomers (Scheme 5).

Scheme 6. Endgame Chemistry



Dehydration of **15** with methanesulfonic acid afforded a 3:1 mixture of enamide isomers, favoring **16**, in 94% yield.[15] Reduction of the mixture of enamides with $Et_3SiH/MeSO_3H$ afforded **17** in excellent yield as a 90:10 mixture of diastereomers (Scheme 6). The unusually high diastereoselectivity achieved in the reduction could be rationalized through analysis of the PM3 minimized structure of acyliminium intermediate **18**, which suggests a less-hindered (*Re*) face (Figure 2). This conformation is further supported by analogy to that observed in the crystal

(15) Direct reduction of **15** to **17** generates 1 equiv of water which negatively impacts the yield and selectivity of the Et_3SiH reduction.

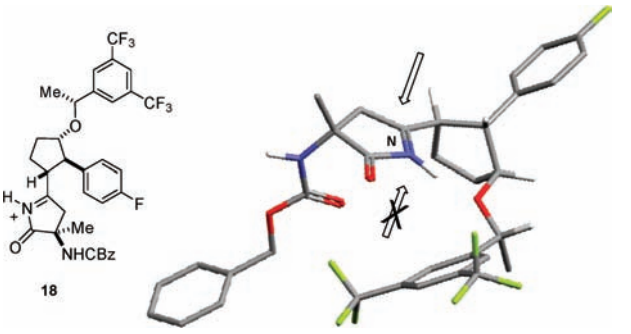


Figure 2. PM3-minimized structure of acyliminium **18**.

structure of intermediate **4**. Deprotection of the CBz-protected amine in **17** was accomplished with HBr/HOAc, and the hNK-1 antagonist, **1**, was isolated in 85% yield as the benzenesulfonate salt.

In conclusion, a convergent, highly selective route has been developed for the synthesis of the potent hNK-1 receptor antagonist **1**. Assembly of this highly functionalized candidate was accomplished with exceptional stereocontrol of all six stereogenic centers, in a total of 11 steps and 23% overall yield. The highlights of this synthesis are the discovery of an enantioselective, biocatalytic reduction of 3-substituted cyclopentenones and the development of a convergent and stereospecific Pd-catalyzed allylic etherification. The application of these two unique synthetic transformations in sequence, followed by substrate-controlled, diastereoselective conjugate additions, has general application to the enantioselective synthesis of highly functionalized cyclopentanoids with a high degree of stereocontrol. A detailed description of the generality of these methods will be disclosed shortly.

Acknowledgment. We thank J. Chilenski (Merck & Co.) for determination of absolute stereochemistry by single crystal X-ray diffraction as well as R. Reamer and L. DiMichele (Merck & Co.) for structural elucidation by NMR.

Supporting Information Available. Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.