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Synthesis of the (3*R*,6*S*)-3-Amino-6-(2,3-difluorophenyl)azepan-2-one of Telcagepant (MK-0974), a Calcitonin Gene-Related Peptide Receptor Antagonist for the Treatment of Migraine Headache

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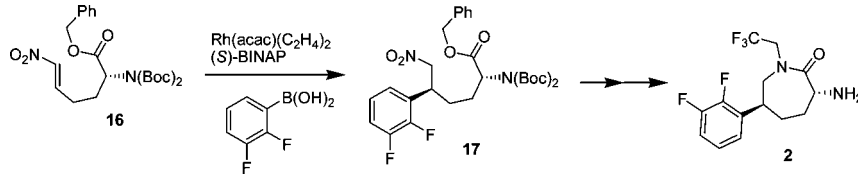
ABSTRACT



Two novel routes have been developed to the (3*R*,6*S*)-3-amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)azepan-2-one 2 of the CGRP receptor antagonist clinical candidate telcagepant (MK-0974, 1). The first employs a ring-closing metathesis of the styrene 7 as the key reaction, while the second makes use of a highly diastereoselective Hayashi−Miyaura Rh-catalyzed arylboronic acid addition to nitroalkene 16. The latter route has been implemented to produce multigram quantities of telcagepant for extensive preclinical evaluation.

Antagonists of the calcitonin gene-related peptide (CGRP) receptor represents a potential novel therapy for the treatment of migraine headaches devoid of the cardiovascular liabilities associated with current drugs.[1] A recent report from these laboratories detailed the identification of a series of potent, small-molecule, azepanone-based CGRP receptor antagonists potentially suitable for oral administration during a migraine attack.[2] Based on its potency, pharmacodynamic model efficacy, and pharmacokinetics in preclinical species, a member of this class of compounds was selected as a development candidate (Figure 1, **1**, telcagepant, MK-0974) and has recently demonstrated efficacy in migraine clinical trials.[3] In support of the preclinical evaluation of this molecule, a scaleable, stereoselective synthesis was required, and herein, we disclose our efforts toward this objective.

Among the challenges associated with the development of a successful synthesis of the (3*R*,6*S*)-3-amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)-azepan-2-one, **2**

(1) (a) Durham, P. L.; Russo, A. F. *Pharmacol. Ther.* **2002**, *94*, 77. (b) Edvinsson, L. *Expert Opin. Ther. Targets* **2003**, *7*, 377. (c) Durham, P. L. *N. Engl. J. Med.* **2004**, *350*, 1073. (d) Olesen, J.; Diener, H-C.; Husstedt, I. W.; Goadsby, P. J.; Hall, D.; Meier, U.; Pollentier, S.; Lesko, L. *N. Engl. J. Med.* **2004**, *350*, 1104–1110. Petersen, K. A.; Birk, S.; Lassen, L. H.; Krusse, C.; Jonassen, O.; Lesko, L.; Olesen, J. *Cephalalgia* **2004**, *25*, 139.

(2) Paone, D. V.; Shaw, A. W.; Nguyen, D. N.; Burgey, C. S.; Deng, Z. J.; Kane, S. A.; Koblan, K. S.; Salvatore, C. A.; Hershey, J., C.; Wong, B.; Roller, S. G.; Miller-Stein, C.; Graham, S. L.; Vacca, J. P.; Williams, T. M. *J. Med. Chem.* **2007**, *50*, 5564–5567.

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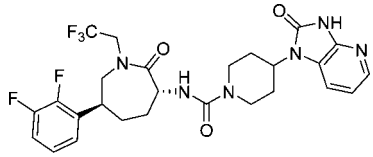

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Figure 1. Telcagepant.

(Figure 2), of telcagepant is the remote C6 stereocenter. To address this problem, a route was envisioned in which olefin **3** would serve as a substrate to investigate diastereoselective reductions; implicit in this strategy is the potential utilization of the C3 amino group to establish the remote C6 stereocenter. A ring-closing metathesis carbon−carbon bond forming reaction of the α-styrene **4** would assemble the 7-member lactam ring, with a D-amino acid starting material serving to establish the required 3*R*-amino stereochemistry.

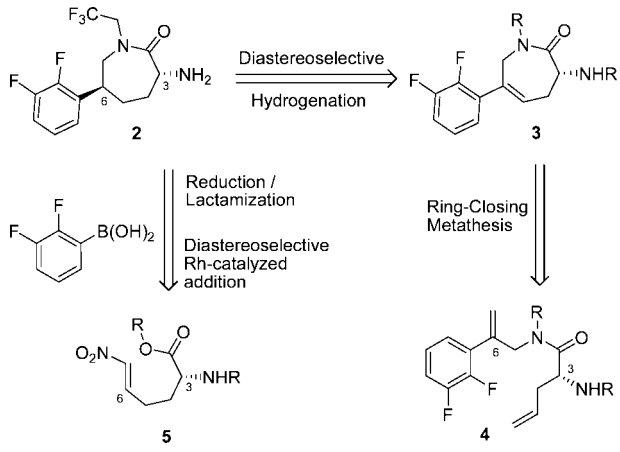


Figure 2. Two routes to azepanone **2**.

A Suzuki cross-coupling reaction of vinyl bromide **6** (Scheme 1), prepared in two steps from L-allylglycine,[2] with 2,3-difluorophenylboronic acid proceeded in good yield to afford the metathesis reaction precursor **7**. Cyclization of this challenging substrate was accomplished using 30 mol % of the Grubbs second-generation ruthenium catalyst[4] under moderately dilute conditions to deliver the azepenone **8** in 58% yield.[5] The metathesis product **8** served as the substrate to study diastereoselective olefin reduction conditions. Reaction of olefins such as **8** with an array of hydrogenation catalysts and solvents afforded the saturated caprolactams with *trans*/*cis* ratios ranging from 1:5 to 1:10. Molecular modeling studies indicated that the methylene of the DMB protecting group occludes reduction of the *re* face of the olefin that would produce the required *trans*-azepanone; accordingly, deprotection of the 2,4-dimethoxybenzyl group with trifluoroacetic acid afforded the alternative hydrogenation substrate **9**. Screening of a range of metal catalysts and solvents revealed that hydrogenation using Pd/C in toluene, with in situ Boc reprotection, afforded the desired product **10** in a 2: 1 *trans*/*cis* ratio (51% isolated *trans*). Treatment of the lactam **10** with 1 equivalent of sodium hydride followed by addition of 2,2,2-trifluoroethyltrichloromethane sulfonate at low temperature (−30 °C) afforded **11**. Deprotection to the targeted primary amine **2** followed by urea formation with piperidine **12**[6] gave telcagepant (**1**) in high yield.

The preceding route could be implemented to deliver limited quantities of **1** for preliminary characterization, but it suffered from several drawbacks. The key metathesis reaction was inefficient, requiring large amounts of the Ru catalyst (30 mol %) which would render scale-up prohibitive; additionally, the hydrogenation proceeded with only modest levels of diastereoselectivity to produce a *cis*/*trans* mixture. As a consequence, we sought to develop a more efficient, scaleable, and diastereoselective route.

A second-generation route was proposed which would employ an unprecedented diastereoselective Hayashi−Miyaura Rh-catalyzed arylboronic acid addition[7] to nitroalkene **5** to install the key C6 stereocenter (Figure 2, **5** to **2**). The efficiency of this transformation was difficult to predict due to the conspicuous lack of examples employing α-unsubstituted nitroalkenes; additionally, as the use of these Rh-catalyzed additions has been limited to achiral substrates, it was uncertain if the stereochemical outcome would be under catalyst control or be subject to substrate control due to the preexisting C3 stereocenter residing in **5**.

The commercially available D-glutamic acid derivative **13** was elaborated, using a modification of the literature conditions,[8] to the orthogonally protected diester **14** in 81% yield over two steps (Scheme 2). DIBAL-H effected a selective half-reduction of the γ-ester to afford aldehyde **15**, which was used without purification in a Henry reaction with nitromethane (toluene, catalytic tetramethylguanidine). Subsequent addition of methanesulfonyl chloride and triethylamine to the intermediate nitro alcohol effected elimination to give the nitro olefin **16** in good overall yield.

With an established synthesis of the alkene **16** in place, experiments toward the execution of the key Hayashi−Miyaura Rh-catalyzed arylboronic acid addition could be under-

(4) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29.

(5) Both the Grubbs first-generation and the Grubbs−Hoveyda catalysts were ineffective for this transformation. The major byproducts detected in this reaction were dimerization of the substrate and an adduct incorporating the styrene from the Grubbs precatalyst.

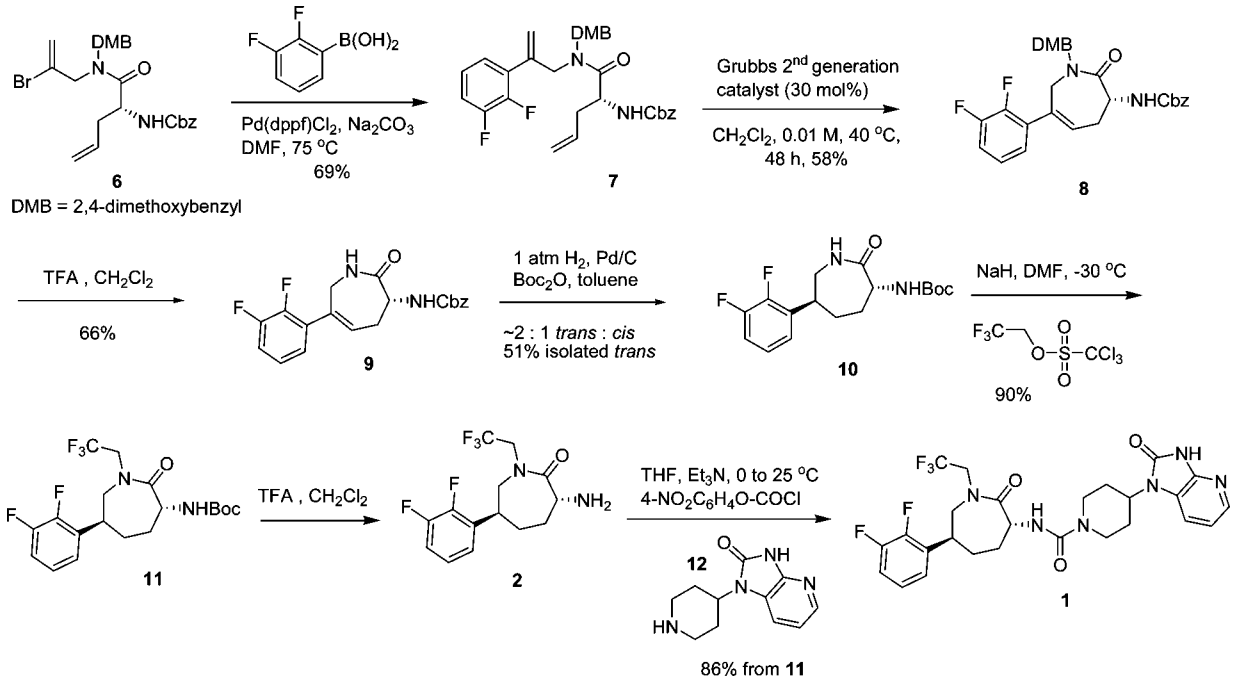
(6) Burgey, C. S.; Stump, C. A.; Nguyen, D. N.; Deng, Z. J.; Quigley, A. G.; Norton, B. R.; Bell, I. M.; Mosser, S. D.; Salvatore, C. A.; Rutledge, R. Z.; Kane, S. A.; Koblan, K; Vacca, J. P.; Graham, S. L.; Williams, T. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5052–5056.

(7) (a) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829–2844. Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716–10717.

(8) Padron, J. M.; Kokotos, G.; Martin, T.; Markidis, T.; Gibbons, W. A.; Martin, V. S. *Tetrahedron: Asymmetry* **1998**, *9*, 3381–3394.

(9) Senda, T.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2001**, *66*, 6852–6856.

Scheme 1. Ring-Closing Metathesis Route



taken. Application of the standard literature conditions (3 mol % $Rh(acac)(C_2H_4)_2$/BINAP, 10:1 dioxane/water, 100 °C)[7] led to rapid hydrolysis of the 2,3-difluorophenylboronic acid to 1,2-difluorobenzene. Lowering the reaction temperature to 45 °C allowed olefin addition of the boronic acid to proceed competitively with decomposition;[9] however, addition of further quantities of metal/ligand (10−20 mol %, cumulative) and boronic acid were typically required for the reaction to reach completion.[10] These conditions could be implemented to deliver the desired adduct **17** with high levels of diastereoselection (93:7) and in good yield (80%; Table 1, entry 1).

Constrained by the propensity of the highly electron-deficient 2,3-difluorophenylboronic acid to decompose at elevated temperatures, the generation of more active catalysts was explored as a means to accelerate this reaction. The addition of inorganic bases to these Rh-catalyzed addition reactions has been shown to have a pronounced rate-accelerating effect,[11] presumably due to

Scheme 2. Hayashi−Miyaura Route

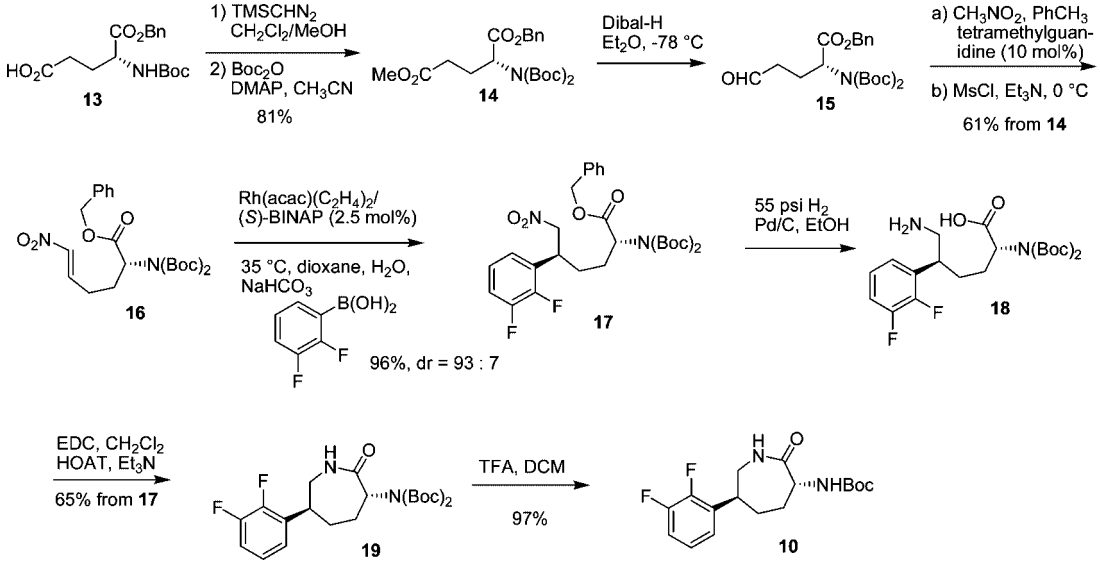
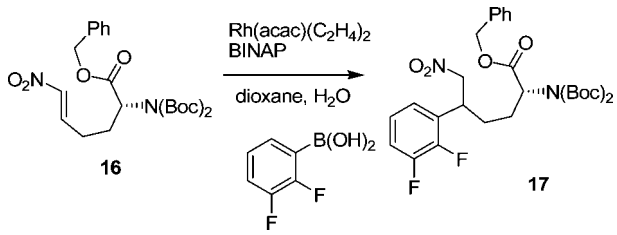


Table 1. Optimization of Hayashi−Miyaura Reaction



entry	BINAP	T (°C)	mol % catalyst	yield (%)	6*S*:6*R*
1	*S*	45	10−20	80	93:7[b]
2[a]	*S*	35	2.5	96	93:7[c]
3[a]	*rac*	35	3	50[d]	41:59[c]
4[a]	*R*	35	3	76[d]	3:97[c]

[a] 50 mol % of $NaHCO_3$ was added. [b] Ratio determined by NMR. [c] Ratio determined by HPLC. [d] Unoptimized.

the formation of a highly active BINAP-Rh-OH species.[12] Reaction optimization studies revealed that $NaHCO_3$ (0.5 equiv) was an efficacious additive, enabling the realization of an improved procedure that typically proceeded to completion within 6−12 h at 35 °C with practical amounts of catalyst (2.5 mol % Rh(acac)$(C_2H_4)_2$/BINAP) and boronic acid (2.5 equiv).[13] These improved reaction conditions reproducibly delivered the desired product in high yield and diastereoselectivity (96%, 93: 7, Table 1, entry 2) on a scale of up to 2 kg.

Exhaustive Pd/C-catalyzed hydrogenolysis of nitroalkane ester **17** gave amino acid **18** which was directly subjected to EDC-mediated lactamization to afford the diBoc caprolactam **19** in 65% average yield for the two steps (Scheme 2). Selective deprotection with trifluoroacetic acid in dichloromethane effected conversion of **19** to azepanone **10**, which was identical to the material from the ring-closing metathesis route and served to confirm the stereochemical outcome of the Hayashi−Miyaura reaction.

The production of the 6*S* stereocenter via the *S*-BINAP-Rh$(L)_n$ complex is consistent with the stereochemical model proposed by Hayashi for arylboronic acid additions to enones.[7] Alkene **16** contains a residing stereocenter that, in principle, could exert stereocontrol in this transformation. In order to confirm that the observed diastereoselectivity is the result of catalyst control, the reaction was performed with racemic BINAP. This experiment revealed a modest preference for the undesired 6*R* stereocenter (Table 1, entry 3); furthermore, use of the enantiomeric *R*-BINAP afforded the diastereomeric 6*R* product with excellent levels of selectivity (Table 1, entry 4). Thus, the slight inherent diastereofacial preference of the substrate can be easily overcome by the *S*-BINAP-Rh$(L)_n$ complex to afford the required 6*S* product.

In summary, we have developed two novel routes to the (3*R*,6*S*)-3-amino-6-(2,3-difluorophenyl)-1-(2,2,2-trifluoroethyl)azepan-2-one, **2**, of the CGRP receptor antagonist telcagepant (**1**). Ultimately, the highly stereoselective synthesis employing a key Hayashi−Miyaura nitro olefin addition was implemented to produce multigram quantities of telcagepant to support initial preclinical and clinical studies.

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Supporting Information Available: Experimental procedure and characterization data are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) A characteristic deep red color served as a visual indicator of the catalyst activity, and transition to a pale orange signaled that the reaction had stalled.

(11) Itooka, R.; Iguchi, Y.; Miyaura, N. *J. Org. Chem.* **2003**, *68*, 6000–6004.

(12) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052–5058.

(13) Notably, the characteristic deep red color of the active catalyst is maintained throughout the course of the reaction.