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Efficient and Scalable Enantioselective Synthesis of a CGRP Antagonist

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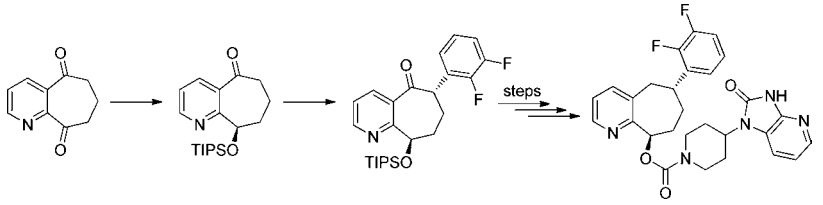
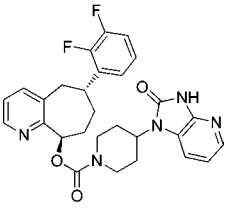
ABSTRACT



An enantioselective synthesis of the CGRP antagonist BMS-846372, amenable to large scale preparation, is presented. This new synthesis showcases a chemo- and enantioselective reduction of a cyclohepta[b]pyridine-5,9-dione as well as a Pd-catalyzed alpha-arylation reaction to form the key carbon−carbon bond and set the absolute and relative stereochemistry.

Calcitonin gene-related peptide (CGRP) is a 37-amino acid peptide associated with the pathophysiology of migraines.[1] Inhibition of the CGRP receptor with a small molecule has the potential to be an effective and safe treatment for people who suffer from migraines.[2] The current standard of care for migraines belongs to the triptan class of drugs, which are vascular constrictors and suffer from mechanism-based cardiovascular risks.[3] In contrast, a CGRP antagonist should prevent vasodilation thereby circumventing cardiovascular risks.[4] During the course of a program directed at using CGRP antagonists for the treatment of acute migraine, BMS-846372 (**1**) emerged as a potential clinical candidate (Figure 1).[5]



1

Figure 1. CGRP antagonist BMS-846372 (**1**).

Compound **1** is a cyclohepta[b]pyridine with a 2,3-difluorophenyl and an O-bound carbamate situated in a 1,4-*trans* disposition. The relative and absolute control of

† Chemical Development, Bristol-Myers Squibb Company
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(1) (a) Goadsby, P. J. *Drugs* **2005**, *65*, 2557. (b) Edvinsson, L. *Cephalalgia* **2004**, *24*, 611. (c) Williamson, D. J.; Hargreaves, R. J. *Microsc. Res. Tech.* **2001**, *53*, 167. (d) Goadsby, P. J.; Edvinsson, L.; Ekman, R. *Ann. Neurol.* **1990**, *28*, 183. (e) Goadsby, P. J.; Edvinsson, L. *Ann. Neurol.* **1993**, *33*, 48.

(2) Bell, I. M.; Bednar, R. A.; Fay, J. F.; Gallicchio, S. N.; Hochman, J. H.; McMasters, D. R.; Miller-Stein, C.; Moore, E. L.; Mosser, S. D.; Pudvah, N. T.; Quigley, A. G.; Salvatore, C. A.; Stump, C. A.; Theberge, C. R.; Wong, B. K.; Zartman, C. B.; Zhang, X.-F.; Kane, S. A.; Graham, S. L.; Vacca, J. P.; Williams, T. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6165.

(3) Goadsby, P. J.; Lipton, R. B.; Ferrari, M. D. *N. Eng. J. Med.* **2002**, *346*, 257.

(4) Olesen, J.; Diener, H. C.; Husstedt, I. W.; Goadsby, P. J.; Hall, D.; Meier, U.; Pollentier, S.; Lesko, L. M. *N. Eng. J. Med.* **2004**, *350*, 1104.

(5) Luo, G.; Chen, L.; Conway, C. M.; Denton, R.; Keavy, D.; Gulianello, M.; Huang, Y.; Kostich, W.; Lentz, K. A.; Mercer, S. E.; Schartman, R.; Signor, L.; Browning, M.; Macor, J. E.; Dubowchik, G. M. *ACS Med. Chem. Lett.* **2012**, *3*, 337.

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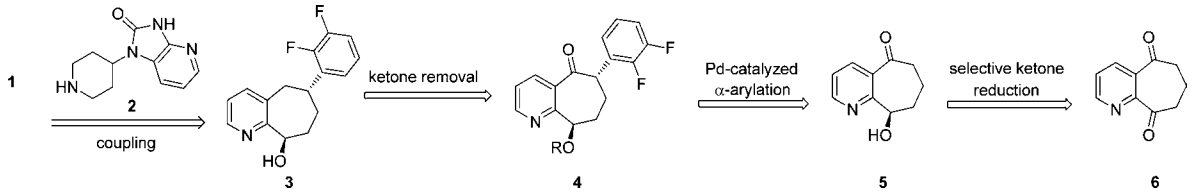
Scheme 1. Retrosynthetic Analysis for **1**

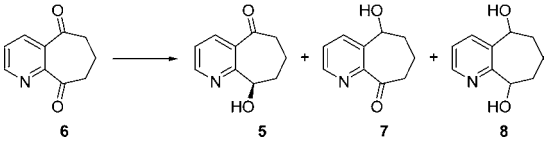


stereochemistry in this unusual cyclohepta[b]pyridine ring system was expected to be the paramount challenge in designing an efficient and scalable synthetic route to this molecule.

In a retrosynthetic direction, cleavage of the carbamate bond of compound **1** simplifies the target to chiral alcohol **3** and the known amine **2** (Scheme 1).[6] The addition of a carbonyl group to compound **3** reveals a key intermediate **4** containing a synthetic handle that allows for the installation of the difluoroaryl moiety. In the forward direction, compound **4** would be synthesized via a transition metal catalyzed α-arylation reaction between 1-bromo-2,3-difluorobenzene and ketone **5**.[7] The aryl group was anticipated to be installed in a *trans* disposition to the judiciously protected alkoxy group, thus relying on substrate control for the basis of relative stereoselectivity. In contrast, catalyst control would be employed to set the target molecule's first chiral center, as compound **5** would be produced via a chemo- and enantioselective reduction of the known 7,8-dihydro-5-*H*-cyclohepta[b]pyridine-5,9-dione, **6**.[8] Finally, the known dione **6** should be readily accessible on large scale via a Dieckmann cyclization−decarboxylation sequence starting from the readily available dimethyl 2,3-pyridinedicarboxylate.[9]

Following our synthetic strategy, we expected that an enantioselective ketone reduction would be complicated by the necessity to differentiate the two ketones present in compound **6**. As such, initial efforts were focused on an enzymatic approach, and high throughput screening efforts identified multiple enzymes that reduced diketone **6** to the corresponding alcohol with encouraging chemo- and enantioselectivity (Table 1, entry 1). Gratifyingly, when the reaction using the reductase enzyme ES-KRED-119 was run at 2 °C, enhanced enantioselectivity (98.0% ee) was realized (entry 2).[10] While these results were very promising, the formation of diol **8** and 5-hydroxy alcohol **7** could not be completely suppressed. An isolation protocol was developed to purge these impurities while upgrading the chiral purity. The chiral alcohol, **5**, was isolated as its HCl

Table 1. Chemo- and Enantioselective Reduction of **6**



entry	catalyst/enzyme	conversion (%)	ee (%)	ratio **5**:**7**:**8**
1	ES-KRED-119[a]	99	92.5	84:3:13
2	ES-KRED-119[b]	97	98.0	90:3:7
3	**9**[c,d]	100	≥99.9	100:0:0
4	**9**[e]	100	≥99.9	100:0:0
5	**9**[f]	100	≥99.9	100:0:0

[a] Reaction at rt. [b] Reaction at 2 °C. [c] **9** = Rh(*R*-binapine)(COD)BF_4. [d] Reaction in MeOH at 0.1 mol % catalyst loading. [e] Reaction in DCM at 0.1 mol % catalyst loading. [f] Reaction in DCM at 0.02 mol % catalyst loading.

salt in 99.2% ee in 81% yield with near complete rejection of impurities **7** and **8**. While the enzymatic approach gave us a path forward, a more direct and selective method was desired. Since the carbonyl at the 9-position is intrinsically more electrophilic than the one at the 5-position, differentiation of diketone **6** via an enantioselective hydrogenation was hypothesized to be feasible.[11] Hence, a screen of chiral rhodium complexes revealed Rh(*R*-binapine)(COD)BF_4 **9** as a highly chemo- and enantioselective catalyst for this transformation (entry 3).[12] This reaction could also be performed in DCM, which aids in downstream processing (vide infra), and could be carried out with as little as 0.02 mol % Rh while maintaining complete conversion and extremely high chemo- and enantioselectivity (≥99.9% ee; entries 4, 5).

Having accomplished the strategic goal of differentiating the two ketones of compound **6** during the establishment of the first stereogenic center, we next set out to form the key C−C bond using the configuration of the substrate to impart the desired stereocontrol. We realized that the diastereoselectivity achieved in the key Pd-catalyzed α-arylation would be limited by the relative thermodynamic

(6) Leahy, D. K.; Desai, L. V.; Deshpande, R. P; Mariadass, A. V.; Rangaswamy, S.; Rajagopal, S. K.; Madhavan, L.; Illenddula, S. *J. Org. Process Res. Dev.* **2012**, *16*, 224.

(7) For a recent review of transition metal-catalyzed ketone arylations, see: Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082.

(8) Jones, G.; Jones, R. K. *J. Chem. Soc., Perkin. Trans. 1* **1973**, 27.

(9) Upon scale-up KO*t*Bu was used instead of sodium metal for safety considerations.

(10) ES-KRED-119 is a ketoreductase enzyme available from SyncoZymes.

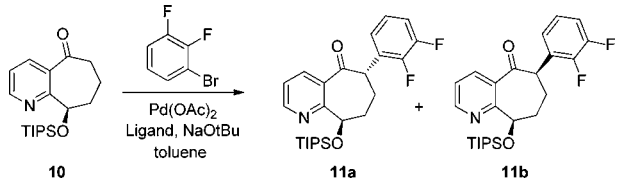
(11) For a discussion of reactivity of the substituents on the pyridine ring, see:Uff, R. C. In *Comprehensive Heterocyclic Chemistry*: Katritzky, A., Ed.; Pergamon Press: Oxford, 1997; Vol VII, Chapter 2.06.

(12) Tang, W.; Wang, W.; Chi, Y.; Zhang, X. *Angew. Chem., Int. Ed.* **2003**, *42*, 3509.

stability of the two diastereomers. However, because of the readily epimerizable nature of the newly formed stereocenter, an opportunity existed to convert the undesired stereoisomer to the desired product. Hence, a two stage approach could overcome this hurdle: in the first stage, the requisite C−C bond would be formed, and in the second, the stereochemistry could be controlled.

The choice of protecting group was expected to be of paramount importance for the success of both stages of α-arylation reaction. The triisopropylsilyl group was ultimately chosen, as we hypothesized that a bulky group would maximize the stereochemical control obtained. For its formation, the use of TIPSCl led to incomplete conversion; hence, the more reactive TIPSOTf with Et_3N was employed. Since both the asymmetric hydrogenation and the TIPS protection could be carried out in DCM (vide supra), a telescoped process was developed where the crude alcohol **5** was directly transformed to the TIPS protected **10** in 74% isolated yield. (Scheme 2).

Table 2. Optimization of Pd-Catalyzed α-Arylation Reaction[a]



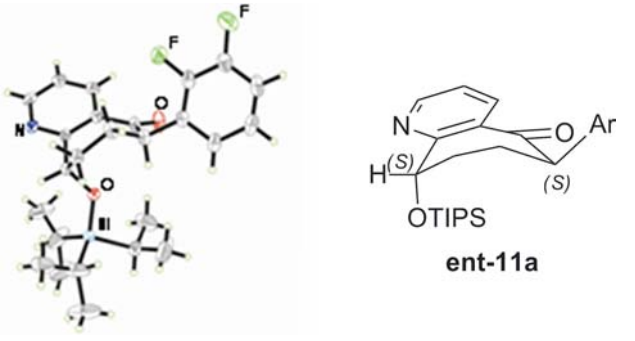
10 **11a** **11b**

entry	ligand (4 mol %)	conc (M)	temp (°C)	yield of **11a** + **11b** (%)
1	MePhos	0.43	120	55
2	SPhos	"	"	56
3	P*t*Bu$_3$	"	"	60
4	P*t*Bu$_3$HBF$_4$	"	"	60
5	"	1.0	"	71
6	"	"	95	80

[a] Reaction Conditions: 1 equiv of **10**, 1.2 equiv of 2,3-difluoro-1-bromobenzene, 1.3 equiv of NaOtBu, 4 mol % $Pd(OAc)_2$ in toluene.

With compound **10** in hand, the first stage of the key α-arylation reaction was examined. Screening of various literature reaction conditions revealed the following trends.[7] Typically, strong bases and sterically demanding electron rich ligands (MePhos, SPhos, P*t*Bu$_3$, etc.) performed best for this reaction giving high conversion and superior impurity profile (Table 2, entries 1−3).[13] Additionally, the diastereoselectivity achieved was similar for all successful reactions (~6:1). Further experiments verified that resubjection of a pure sample of either the *trans* diastereomer **11a** or the *cis* diastereomer **11b** to the reaction conditions (or any basic conditions) did indeed epimerize the aryl stereocenter, resulting in the observed ~6:1 diastereoselectivity. We chose to focus our attention on the conditions outlined by Hartwig utilizing the relatively inexpensive and widely available P*t*Bu$_3$ ligand with NaO*t*Bu as the base, which resulted in ~60% in-process yield of compounds **11a** and **11b**.[13a] While these results were encouraging, the pyrophoric nature of this ligand was a concern to scale-up. Hence, the air stable and nonpyrophoric tetrafluoroborate salt of this ligand was examined and gave comparable results (entry 4).[14] Additional gains were realized by running the reaction more concentrated and at a lower temperature, leading to an in-process yield of up to ~85% (entries 5−6). Isolation of this compound proved to be challenging, and while losses to the workup and mother liquor were higher than desired, the product was isolated as a crystalline solid from NMP/water in 63% yield with improved diastereoselectivity of 12:1.

With the key C−C bond formed, stage two of the α-arylation sequence was examined in an effort to enhance the dr of compound **11a**. Since the desired *trans*-isomer **11a** was more readily crystallized than the *cis*-isomer **11b**, and the α-keto stereocenter was easily epimerized, we hypothesized that adding a base during crystallization may enable a crystallization-induced dynamic resolution.[15] Hence, subjection of the 12:1 mixture of compounds **11a** and **11b** to a catalytic amount of DBU in IPA/water for 48 h provided compound **11a** in 90% yield and 40:1 dr after isolation. The long crystallization age was utilized to maximize the stereochemical purity enhancement available via equilibration.



ent-11a

Figure 2. ORTEP drawing of **ent-11a**.

Having served its purpose as a handle for installing the aryl group, the carbonyl group needed to be removed. Surprisingly, many common methods for direct deoxygenation were unsuccessful.[16] The desired product **14** could only be obtained via a stepwise reduction: first ketone **11a** was reduced to the alcohol **12**, which was then converted to the corresponding mesylate **13** and subsequently reduced by lithium triethylborohydride to compound **14** (Scheme 2).[17]

(13) (a) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473. (b) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360.

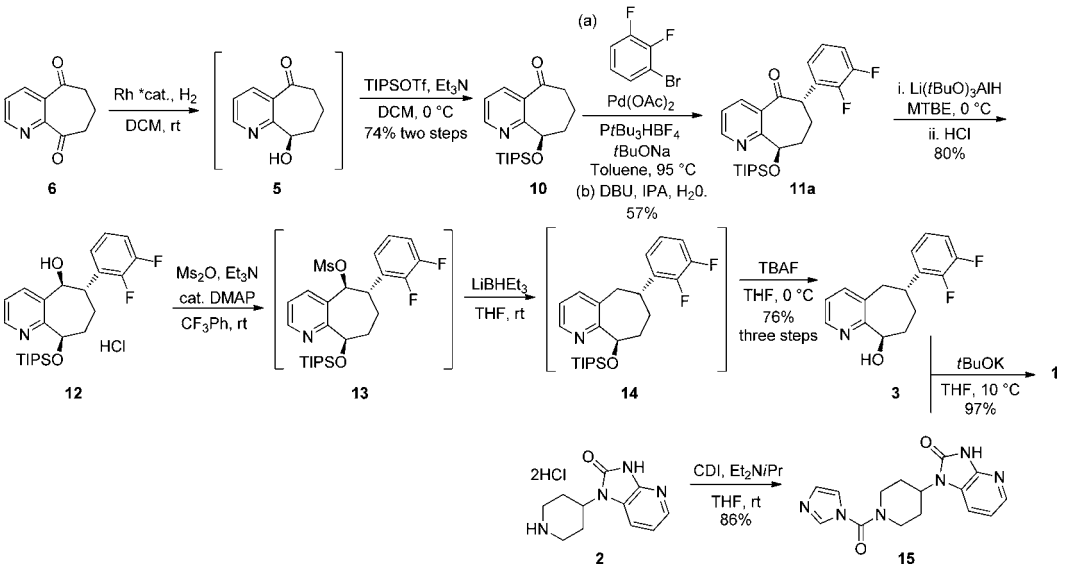
(14) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295.

(15) Caddick, S.; Jenkins, K. *Chem. Soc. Rev.* **1996**, *25*, 447.

(16) Only intractable byproducts were observed under Wolff–Kishner conditions. No reaction was observed with silane reducing agents. Lewis acid promoted thioketal formation was unsucessful.

(17) Holder, R. W.; Matturro, M. G. *J. Org. Chem.* **1977**, *42*, 2166.

Scheme 2. Synthesis of **1**



Interestingly, it was observed that the minor mesylate stereoisomer (*cis* to the aryl group) is reduced only at the O−S bond, and the corresponding alcohol was recovered from the reaction mixture. As such, it was necessary to develop a highly diastereoselective reduction of compound **11a**. The diastereoselectivity was found to be highly dependent on the choice of the hydride reducing agent. While sodium borohydride provided a disappointing dr of 3:1, the bulky lithium tri(*t*-butoxyalminum)hydride reduced ketone **11a** to alcohol **12** in 45:1 dr.[18]

The enhanced diastereoselectivity is likely due to synergistic steric effects exerted by the TIPS group. The crystal structural of ketone **ent-11a** provides substantial evidence for this hypothesis (Figure 2). In solid state, the TIPS group exerts a predominant influence on the overall structural features: the carbonyl is puckered up toward the TIPS group with a dihedral angle (O−C5−C11−C4) of 36 degrees, and as a result, the aryl group is pointed away from the carbonyl with a dihedral angle of (C−C−C−O) of 38 degrees. In this disposition, Si face attack on the carbonyl would be disfavored because of developing torsional strain between the emerging C−O bond and the C-aryl bond.[19] The accentuated steric repulsion between the bulky TIPS protecting group and the incoming hydride reagent would further discourage the Si face attack. Therefore when a stericly encumbered hydride reagent is employed, much enhanced diastereoselectivity is obtained.

The dr of alcohol **12** was further improved to greater than 99:1 when it was isolated in 80% yield as hydrogen chloride salt (Scheme 2). The mesylate **13** was formed cleanly with mesyl anhydride, Et_3N and catalytic DMAP and was subsequently reduced using lithium triethylborohydride at 0 °C to provide compound **14**. The deprotection of compound **14** using TBAF provided penultimate **3** cleanly. Since compounds **13** and **14** were noncrystalline, a telescoped, three-step-one-pot-isolation protocol was developed for the mesylation/reduction/deprotection sequence. Thus **3** was produced in 76% overall yield from **12** in >99.7% purity with one isolation.

The final step of the synthesis of compound **1** involves the late-stage coupling of alcohol **3** with amine **2** using a phosgene equivalent to form the final carbamate bond (Scheme 2).[6] We expected that CDI could be used as the phosgene equivalent, which reacted smoothly with amine **2** and Hünig's base to provide imidazyl-urea **15** in 86% isolated yield. Alcohol **3** was then treated with 1.1 equiv of imidazyl-urea **15** and KOtBu to provide the coupled product **1** in 97% yield and >99.9 HPLC area percent purity.

In conclusion we have developed an efficient and scalable enantioselective synthesis of the CGRP antagonist BMS-846372 (**1**). This synthesis featured a novel chemo- and enantioselective reduction of dione **6**, where electrophilicity differences between the two ketones were exploited. Also featured is a practical palladium catalyzed α-arylation, which in combination with a crystallization-induced dynamic resolution installed the final carbon−carbon bond with excellent stereocontrol. This route provided the target CGRP antagonist **1** in excellent chemical purity for use in preclinical and clinical trials.

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

(18) Haubenstock, H.; Eliel, E. *J. Am. Chem. Soc.* **1962**, *84*, 2362.
(19) Ashby, E. C.; Noding, S. A. *J. Am. Chem. Soc.* **1976**, *98*, 2010.

The authors declare no competing financial interest.