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Asymmetric Synthesis of Heterocyclic Analogues of a CGRP Receptor Antagonist for Treating Migraine

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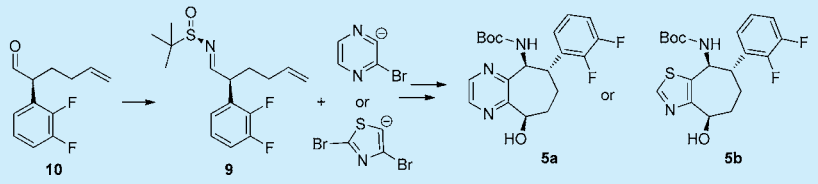
Supporting Information



ABSTRACT: An asymmetric synthesis of novel heterocyclic analogue of the CGRP receptor antagonist rimegepant (BMS-927711, **3**) is reported. The cycloheptane ring was constructed by an intramolecular Heck reaction. The application of Hayashi–Miyaura and Ellman reactions furnished the aryl and the amine chiral centers, while the separable diastereomeric third chiral center alcohols led to both carbamate and urea analogues. This synthetic approach was applicable to both 6- and 5-membered heterocycles as exemplified by pyrazine and thiazole derivatives.

Migraine is a painful, incapacitating disease that affects a large portion (12%) of the adult population and imposes a substantial economic burden on society (estimated to be $13 billion per year).[1] Calcitonin gene-related peptide (CGRP) is thought to play a causal role in migraine and may act via multiple mechanisms including pain transmission, neurogenic inflammation, and/or neurogenic vasodilation.[2] As current standard of care, the triptan class of 5-$HT_{1B/1D}$ receptor agonists actively constrict the dilated cranial arteries associated with a migraine and relieve migraine coincident with a reduction in CGRP levels.[3] However, triptans are also associated with a number of unpleasant, and potentially dangerous, cardiovascular side effects due to their nonselective smooth muscle vasoconstriction.[4] Because CGRP receptor antagonists block cranial vessel dilation, they are devoid of these undesirable cardiovascular effects of triptans and are emerging as new therapeutics for the effective treatment of migraine.[5]

An oral CGRP receptor antagonist, telcagepant (MK-0974)[6] (**1**, Figure 1), showed positive results in several phase II and phase III trials but was discontinued following a migraine-preventative study.[7] A recent publication from our laboratory disclosed the potent, oral CGRP receptor antagonist, BMS-846372, containing a cyclohepta[*b*]pyridine core (**2**, Figure 1), that was an attractive preclinical lead.[8] Poor aqueous solubility of **2** (<2 μg/mL) led us to install a primary amine in **3** (BMS-927711/rimegepant, Figure 1), which had even better potency and much improved aqueous solubility (50 μg/mL).[9] In a phase II clinical trial, compound **3** showed efficacy comparable to sumatriptan (Imitrex, 100 mg), but without the significant cardiovascular side effects associated with sumatriptan.[10] We wanted to further explore this core structure with other heterocycles such as pyrazine **4a** and thiazole **4b**, keeping the

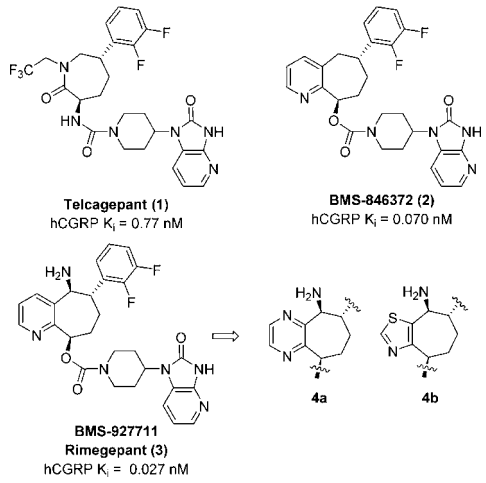


Figure 1. CGRP receptor antagonists.

spatial relationship of the pyridine sp_2 nitrogen, which is a critical pharmacophore for CGRP receptor affinity (Figure 1).

Attempts to prepare **4a** in a manner analogous to the synthesis of **2** and **3**[8,9,11] failed. Indeed, heterocycle-fused cycloheptane ring systems are rare in the literature.[12] A retrosynthetic analysis of target **4** is shown in Scheme 1 using the precedented carbamate formation from the alcohol **5**.[8,9,11,13] For the synthesis of **5**, we envisioned a key Heck cyclization at the position next to the heterocyclic nitrogen to afford **6**, which left a double bond for generation of the alcohol through the ketone intermediate. The Heck substrate **7**, a chiral amine intermediate, could be generated in a diastereoselective

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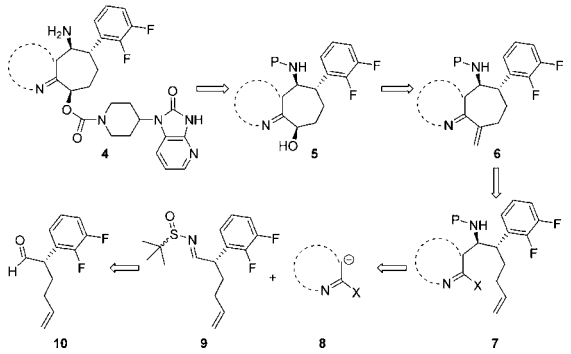
Scheme 1. Retrosynthetic Analysis for 4



fashion from a chiral sulfinamide intermediate **9**. The counterpart anion nucleophile **8** could be generated from a halogenated heterocycle. The sulfinamide **9** came from the α-aryl aldehyde **10** which had to be prepared enantioselectively and was expected to be prone to epimerization.

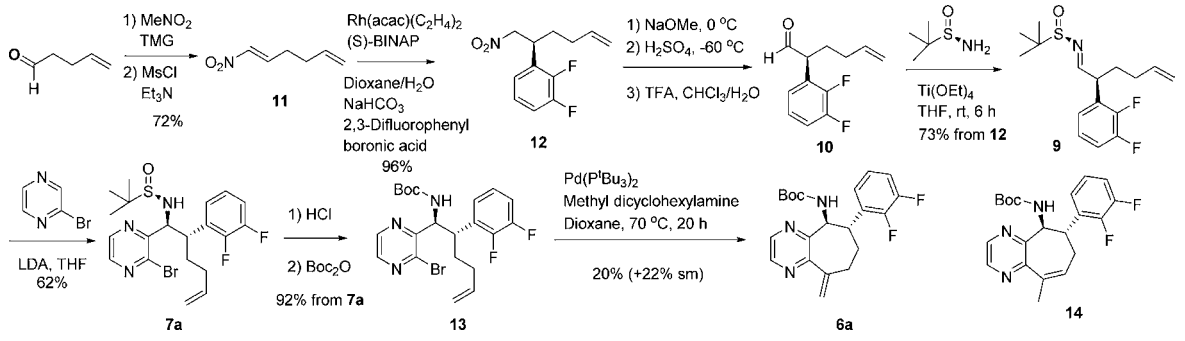
One proven approach to establish a chiral aryl center is the Hayashi–Miyaura Rh-catalyzed arylboronic acid addition to a nitroalkene.[14] In the asymmetric synthesis of **1**, 2,3-difluorophenylboronic acid was added successfully to an α-unsubstituted nitroalkene with good diastereoselectivity.[15] We were able to apply the reported conditions[15] to our synthesis of **12** as shown in Scheme 2. Nitroalkene **11** was prepared in 72% yield from 5-pentenaldehyde with nitromethane using tetramethylguanidine (TMG) as catalyst and followed by addition of methansulfonyl chloride and triethylamine to effect the elimination of nitro alcohol.[15] Compound **12** was then prepared in 96% yield using the reported conditions.[15] The Nef reaction[16] was successfully optimized to convert the nitroalkane to the desired aldehyde **10**, which was directly used in the next reaction without noticeable epimerization.[17] Enantiomerically pure (*R*)-(+)-2-methyl-2-propanesulfinamide reacted[18] with **10** to afford **9** in 73% yield from **12** with good diastereomeric ratio (>93:7 dr) as evidenced by ^{1}H NMR. Diastereoselective reaction of **9** with lithiated 2-bromopyrazine[19] went smoothly to afford mostly **7a** in 62% yield (~9:1 dr by ^{1}H NMR[20]).[18b] Several attempts at Heck cyclization of **7a** under mild conditions gave no product, while temperatures higher than 120 °C[21] caused decomposition of the sulfinyl group. Consequently, a protecting group swap with Boc was carried out using HCl in dioxane[22] and Boc anhydride, giving **13** in 92% yield. The minor diastereomer was easily removed by flash column chromatography at this stage. With **13**, a series of conditions for Heck cyclization were screened. Under the conditions shown in Scheme 2,[23] the desired product **6a** was obtained in 20% yield. However, higher reaction temperatures intended to effect better conversion gave **14** as the main product instead. For example, when the reaction was run at 100 °C for 20 h, 49% of **14** and only 13% of **6a** were obtained. Further optimization failed to improve the yield of **6a** for enough material to proceed.

An alternative route for the Heck reaction to work is shown in Scheme 3. Compound **13** was converted to the α,ß-unsaturated ester **15** under standard reaction conditions with Grubbs II catalyst.[24] With the ester group in place, Heck cyclization could be run at higher temperatures (160 °C under microwave heating, 2 h) to effect the best conversion to the desired **17** (major product in 54% yield) with a smaller amount of the isomerized product **16** (24% yield). Ozonolysis of **17** led to the ketone **18** in 66% yield. Reduction of **18** by $NaBH_4$ afforded the two easily separable diastereomeric alcohols **5a** and **19** in good yield. Coupling of **5a** with compound **20** under the previously reported conditions,[11] followed by TFA-mediated Boc removal, gave the desired carbamate **4a**.

We also decided to prepare the corresponding urea analogue. Thus, alcohol **19** was converted to the key intermediate amine **21** in 77% overall yield as shown in Scheme 4 through Mitsunobu reaction with phthalimide, followed by treatment with hydrazine. However, **21** failed to react with **20** or our previous activated carbamate.[8,13] In the end, the carbamoyl chloride **24** was freshly prepared from **23**, which was in turn synthesized from **22** in three steps. Under these conditions, formation of the urea proceeded smoothly in 61% yield. A minor side product in which the SEM group transferred to the oxygen was also generated in 13% yield.[25] Removal of both Boc and SEM groups by TFA afforded the urea analogue **25** in 55% yield.

With this route successfully established, we applied it to the synthesis of the thiazole analogue **4b** as shown in Scheme 5. Starting with 2,4-dibromothiazole, we hoped that the 2-Br substituent could be retained to the end of the sequence as a handle for further functionalization. However, the 2-Br derivative of **27** was not well-behaved in the Heck cyclization. Hence, 2-Br was removed in one pot by lithium–halogen exchange after the lithiation of 2,4-dibromothiazole by LDA[26] and addition of **9** to generate compound **7b** as the major diasteeromer. Removal of the sulfinyl group followed by Boc protection afforded compound **26**, which was converted to acrylate **27** as described above. Under the conditions used for the pyrazine **15**, Heck cyclization yielded a majority of the undesired endocyclic alkene **28** (2:1 over the desired isomer **29**). For this synthesis, we discovered that the aldehyde **10** that had been used to prepare **9** had partially epimerized during

Scheme 2. Enantioselective Synthesis of 13 and Attempted Heck Cyclization



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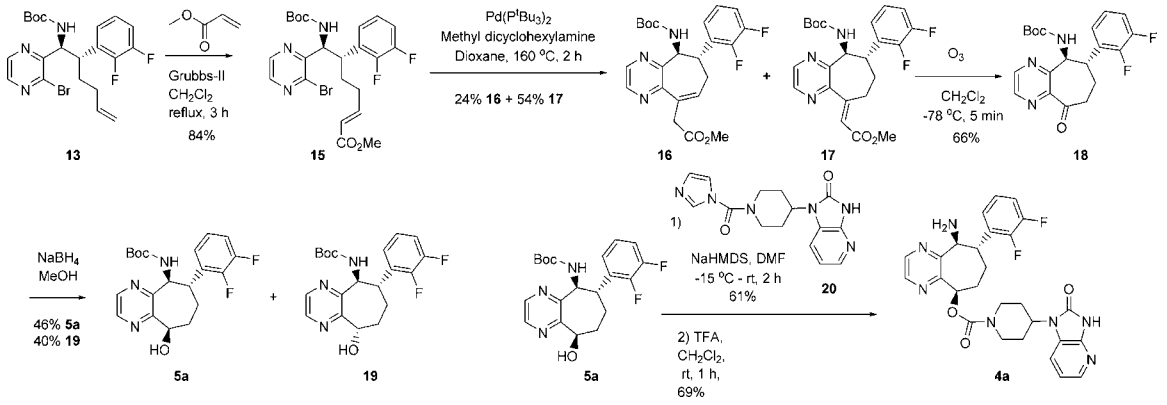
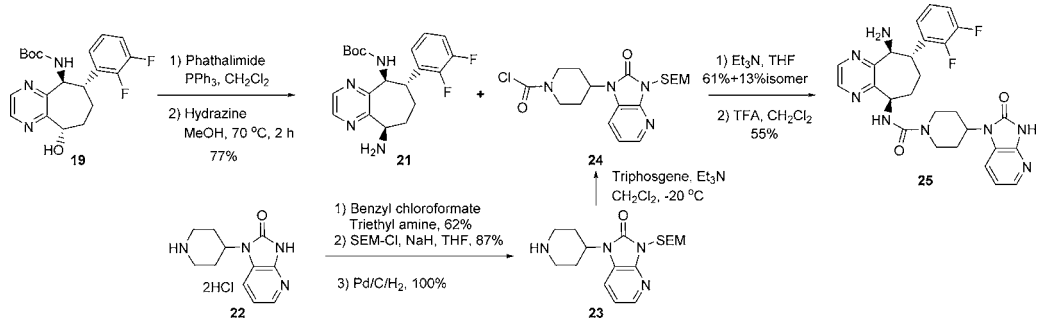
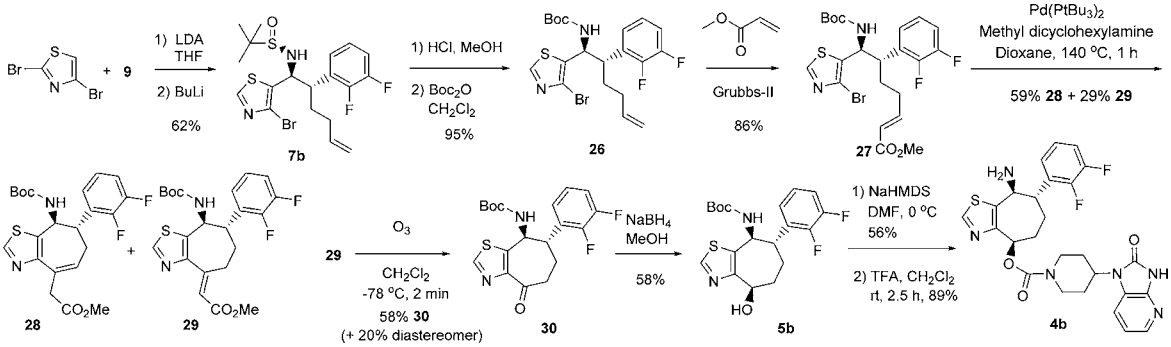
Scheme 3. Heck Cyclization and Synthesis of 4a



Scheme 4. Synthesis of 25



Scheme 5. Asymmetric Synthesis of 4b



storage (~25% wrong diastereomer in **9**). Consequently, compounds **7b**, **26**, **27**, **28**, and **29** each consisted of two inseparable diastereomers in a 3:1 ratio, as evidenced by ^{1}H NMR analysis.[25] After ozonolysis of **29**, the undesired minor diastereomer was finally removed by flash column chromatography from ketone **30** (58% yield plus 20% diasteromeric ketone). After $NaBH_4$ reduction, the desired major alcohol **5b** was obtained in 58% yield, which was carried on to **4b** in good yield. Using a recently reported trifluoromethylation reaction,[27] we were able to convert **5b** to **31** in 24% yield, which led to analogue **4c** as shown in Scheme 6.

Binding affinities for the new CGRP receptor antagonists were determined by inhibition of ^{125}I-CGRP binding to SK-N-MC cell membranes, which endogenously express the receptor.[28] Binding data for compounds tested is shown in Table 1. Urethanes **4a**, **4b**, and **4c** all showed CGRP receptor binding activities that were comparable to those of **2** (BMS-846372) and rimegepant **3**. The urea analogue **25**, compared to **4a**, had 10-fold lower potency, which, however, was comparable to telcagepant **1**. Further profiling of these new compounds showed them to be inferior to **3** in terms of metabolic stability.

Scheme 6. Synthesis of 4c

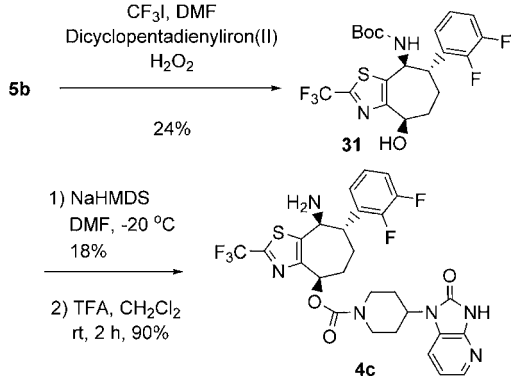


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Table 1. hCGRP K_i Data

compd	hCGRP K_i (nM)
rimegepant	0.027 ± 0.001
4a	0.056 ± 0.011
25	0.55 ± 0.094
4b	0.048 ± 0.011
4c	0.065 ± 0.011

In summary, we have developed a novel asymmetric synthesis of select heterocyclic analogues of the CGRP receptor antagonist rimegepant 3. These showed binding affinity against the CGRP receptor that was comparable to the rimegepant. Our approach to the novel core structures featured a 7-membered ring intramolecular Heck cyclization in which the critical location of the double bond was achieved by addition of an ester group. The aryl chiral center was constructed by a variant of the Hayashi–Miyaura reaction, and the amine chiral center was obtained by Ellman chiral sulfinamide chemistry in a diastereoselective reaction with nucleophiles generated by lithiation of bromo heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02921.

Experimental procedures and characterization of all intermediates and products (PDF)

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Notes

The authors declare no competing financial interest.

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(17) The Nef reaction (steps 1 and 2) afforded, in addition to **10**, the dimethyl acetal as the major product which could be recovered after the next sulfinamide reaction and deprotected by TFA in $CHCl_3/H_2O$ to generate **10**. The best approach was to directly treat the crude Nef reaction product with TFA and use the freshly prepared **10** in the following sulfinamide reaction. On one occasion when **10** was left under house vacuum overnight and used, it was found to be partially epimerized as evidenced in compound **9** as a mixture of two diastereomers. However, partially epimerized **10** could be used as diastereomers could be separated at later stage. See the Supporting Information for details.

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