Asymmetric syntheses of (*R*)-4-halo-6,6a,7,8,9,10-hexahydro-5*H*-pyrazino[1,2-*a*][1,n]naphthyridines, important 5-HT_{2C} agonist precursors

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PII: S0040-4039(18)30487-8
DOI: https://doi.org/10.1016/j.tetlet.2018.04.030
Reference: TETL 49893

To appear in: *Tetrahedron Letters*

Received Date: 23 February 2018
Revised Date: 11 April 2018
Accepted Date: 12 April 2018

Please cite this article as: Schrader, T.O., Zhu, X., Kasem, M., Li, S., Liu, C., Ren, A., Wu, C., Semple, G., Asymmetric syntheses of (*R*)-4-halo-6,6a,7,8,9,10-hexahydro-5*H*-pyrazino[1,2-*a*][1,n]naphthyridines, important 5-HT_{2C} agonist precursors, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.04.030

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Asymmetric synthesis of (*R*)-4-halo-6,6a,7,8,9,10-hexahydro-5*H*-pyrazino[1,2-*a*][1,n]naphthyridines, important 5-HT$_{2C}$ agonist precursors

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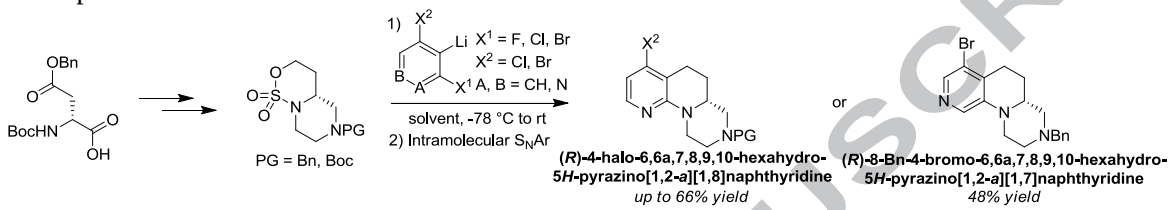

(*R*)-4-halo-6,6a,7,8,9,10-hexahydro-5*H*-pyrazino[1,2-*a*][1,8]naphthyridine
up to 66% yield

(*R*)-8-Bn-4-bromo-6,6a,7,8,9,10-hexahydro-5*H*-pyrazino[1,2-*a*][1,7]naphthyridine
48% yield

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ARTICLE INFO

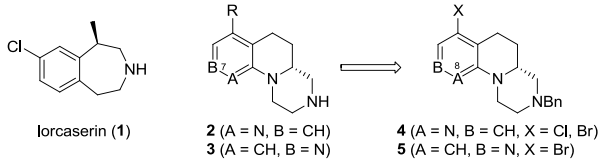
Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
5-HT$_{2C}$ agonists
asymmetric synthesis
Lorcaserin
sulfamidate
tetrahydronaphthyridines

ABSTRACT

Asymmetric syntheses of *N*-protected (*R*)-4-halo-6,6a,7,8,9,10-hexahydro-5*H*-pyrazino[1,2-*a*][1,n]naphthyridines, advanced intermediates for the synthesis of highly potent and selective 5-HT$_{2C}$ agonists, are described. The key transformation involves ring opening of *N*-protected bicyclic sulfamidate (*R*)-hexahydro-3*H*-pyrazino[1,2-*c*][1,2,3]oxathiazine 1,1-dioxide with (4-halo-2-fluoropyridin-3-yl)lithiums or (3-bromo-5-fluoropyridin-4-yl)lithium. *In situ* hydrolyses of the resultant sulfamic acids and subsequent intramolecular nucleophilic aromatic substitutions (S$_N$Ar) produce the enantiopure tricycles. The two step procedure represents new methodology for the stereoselective syntheses of tetrahydronaphthyridines.

Agonists of the 5-HT$_{2C}$ receptor, a centrally expressed G-protein coupled receptor (GPCR), have therapeutic potential across a range of conditions including obesity,[1] addiction,[2] urinary incontinence,[3] sexual dysfunction,[4] and psychiatric disorders.[5] The identification of 5-HT$_{2C}$ receptor agonists which possess high receptor selectivity is of critical importance, as agonism of related receptor subtypes 5-HT$_{2A}$ and 5-HT$_{2B}$ has been linked to hallucinations[6] and cardiac side effects[7] respectively. In 2012 the anti-obesity medication lorcaserin[8] (**1**, Belviq®, Scheme 1) became the first selective 5-HT$_{2C}$ receptor agonist to receive regulatory approval. As part of a program to identify additional agents for this clinically validated target, a number of selective (*R*)-4-substituted-6,6a,7,8,9,10-hexahydro-5*H*-pyrazino[1,2-*a*][1,8]naphthyridine (**2**, scheme 1) and (*R*)-4-substituted-6,6a,7,8,9,10-hexahydro-5*H*-pyrazino[1,2-*a*][1,7]naphthyridine 5-HT$_{2C}$ agonists (**3**) were discovered. Asymmetric syntheses of the chemically unique fused tricyclic precursors (**4** and **5**) of these agonists are reported herein.



Scheme 1. Selective 5-HT$_{2C}$ agonists lorcaserin (**1**) and tricyclic pyrazinonaphthyridines (**2** and **3**) with synthetic precursors **4** and **5**.

Our synthetic strategy toward compounds **4** and **5** was based on a previous report from these laboratories detailing the stereoselective synthesis of (*R*)-3-benzyl-7-bromo-2,3,4,4a,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinolines (**6**, Scheme 2),[9] a chemical precursor to a class of structurally related tricyclics which are differentiated from the tetrahydronaphthyridine based 5-HT$_{2C}$ agonists (**2** and **3**) by the absence of a pyridyl ring nitrogen.[10] Our convergent route to **6** involved the addition of (2-bromo-6-fluorophenyl)lithium (**8**) to optically pure aldehyde **7** and subsequent Swern oxidation which delivered *o*-fluorophenone **9**. After Boc-deprotection (to give **10**), a base-promoted intramolecular S$_N$Ar reaction followed by ketone removal with TFA and Et$_3$SiH produced the desired tricycle **6** in a respectable 84% yield (3 steps). The proposed route to tricycles **4** and **5** further exploits this methodology and includes modifications inspired Moss *et al.*[11] who described preparation of functionalized 5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidines via the ring opening of cyclic sulfamidates with magnesiated heterocycles and subsequent intramolecular S$_N$Ar reaction. We envisioned coupling of the optically pure bicyclic sulfamidate **11** with a 3-metallo-2,4-dihalopyridine (**12**) to produce ring opened sulfamic acid **13**, which could be hydrolyzed *in situ* to the cyclization precursor **14**. Chemoselective intramolecular S$_N$Ar substitution at the 2-position of pyridine **14** would yield the desired tricycles (**4** and **5**). It is noteworthy that in contrast to *o*-fluorophenone **10** which required a conjugated exocyclic ketone to promote S$_N$Ar reaction, oxygenation at the benzylic position of **14** would not be required for cyclization. This is a key feature of

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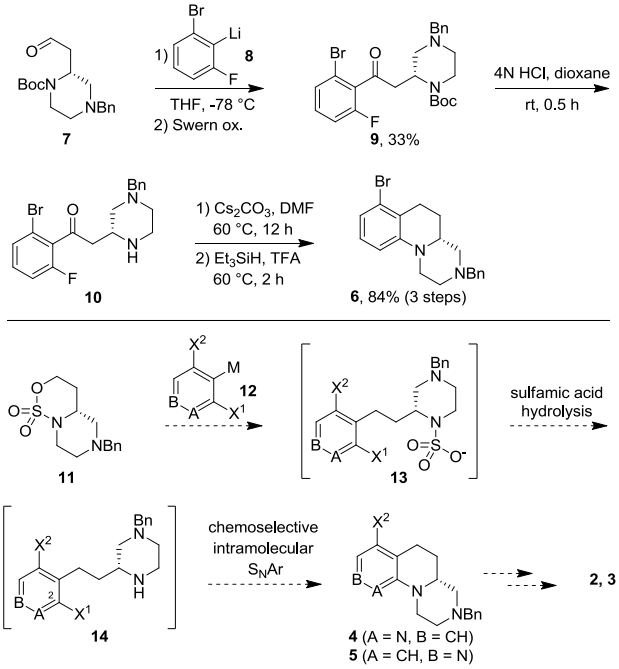
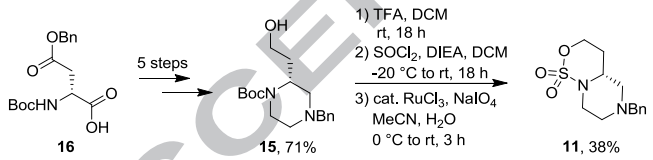
the proposed synthesis of **4** and **5**, as the oxidation-reduction sequence utilized in the previous route would be eliminated.



Scheme 2. Previously reported stereoselective synthesis of (*R*)-3-benzyl-7-bromo-2,3,4,4a,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline (**6**) and proposed synthesis of (*R*)-8-benzyl-4-halo-6,6a,7,8,9,10-hexahydro-5*H*-pyrazino[1,2-a][1,n]naphthyridines **4** and **5**.

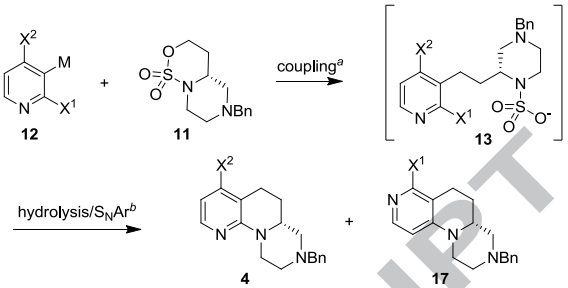
Synthesis of the requisite 6,6-bicyclic sulfamidate **11** is shown in Scheme 3. The differentially protected piperazine alcohol **15** was prepared in 5 steps from commercially available Boc-Asp(OBn)-OH (**16**) in 71% yield by optimization of a known procedure.[12] After Boc-deprotection, treatment with thionyl chloride and DIEA in DCM gave the intermediate sulfamidite. Oxidation to the sulfamidate was accomplished using catalytic (0.5 mol %) ruthenium chloride and sodium periodate as the stoichiometric oxidant which gave **11** in 38% yield (3 steps).



Scheme 3. Synthesis of bicyclic sulfamidate **11**.

Investigations of the arylation of sulfamidate **11** with 2,4-dihalo-3-metallopyridines is shown in Table 1. In an initial experiment (entry 1) the lithium anion **12a** (1.5 equiv), generated by deprotonation of 2-bromo-4-chloropyridine[13] with LiTMP at -78 °C in THF, was treated with sulfamidate **11** (1.0 equiv) at -78 °C and the reaction mixture was immediately warmed to 0 °C and stirred for 1 h to generate the ring opened sulfamic acid intermediate (**13**). Hydrolysis of the crude sulfamic acid (**13**) was accomplished upon addition of 1N aq. HCl diluted with MeOH and microwave heating at 60 °C for 2 h. Gratifyingly, the tricyclic products **4a** (39%) and **17a** (26%) were generated under the acidic conditions without the need for an additional cyclization step. However, the observed chemoselectivity was not optimal as there was only a slight preference for ring closure at the pyridyl 2-position (**4a** : **17a** = 1.5 : 1). To bias the system to favor S_NAr at the pyridyl 2-position

Table 1. Synthesis of (*R*)-8-benzyl-4-halo-6,6a,7,8,9,10-hexahydro-5*H*-pyrazino[1,2-*a*][1,8]naphthyridine (**4**) and (*R*)-3-benzyl-7-chloro-2,3,4,4a,5,6-hexahydro-1*H*-pyrazino[1,2-*a*][1,6]naphthyridine (**17**).

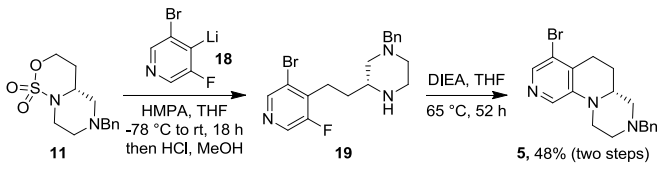


Entry	Nucleophile[c]	**4** (% yield)[d]	**17** (% yield)[d]	Additive[e]
1	**12a**	**4a** (39)	**17a** (26)	-
2	**12b**	**4b** (6)	-	-
3	**12c**	**4b** (9)	-	-
4	**12d**	**4b** (<5)	-	-
5	**12e**	**4a** (34)	**17b** (18)	-
6	**12b**	**4b** (66)	-	HMPA
7	**12f**	**4a** (66)	-	HMPA
8	**12d**	**4b** (23)	-	HMPA

[a]Typical reaction conditions for arylation step (0.3 – 2.0 mmol scale): sulfamidate (1.0 equiv), 2,4-dihalo-3-metallopyridine (1.5 - 2.0 equiv), THF (0.1 M). Reactions performed at -78 °C followed by immediate warming to 0 °C, stirring was continued while warming to rt over 18 h with the exception of entries 1 and 5 which were stirred while warming to rt for 1 h and 2 h respectively.
[b]Hydrolysis conditions: 1 N aq. HCl /MeOH (1 : 1, 0.2M), 60 °C (microwave irradiation), 2 h.
[c]Aryllithiums **12a-c,e,f** (entries 1-3, 5-7) were generated by deprotonation of the corresponding 2,4-dihalopyridines with LiTMP at -78 °C.
Arylmagnesium reagent **12d** (entries 4 and 8) was generated from 4-bromo-2-fluoropyridine by treatment with TMPMgCl·LiCl at 0 °C.
[d]Isolated yields of product as a single isomer.
[e]For reactions performed with additive, 5.0-5.5 equiv of HMPA was used.

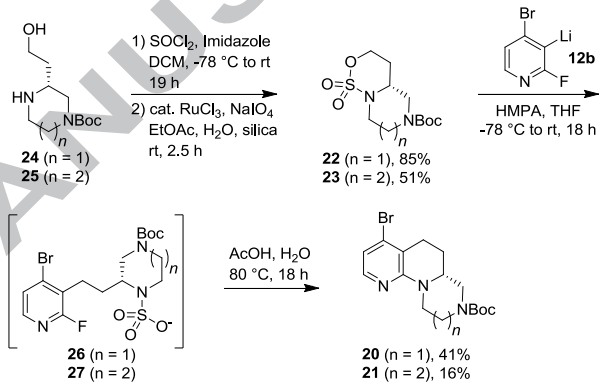
we attempted arylation of **11** with aryllithium **12b**, containing a 2-fluoro substituent (entry 2). Although the reaction produced solely the desired regioisomer (**4b**), the overall reaction efficiency was poor (6%). A similar result was also observed with the lithium anion (**12c**) generated from 4-bromo-2-chloropyridine (entry 3). Arylation of **11** under conditions reported by Moss *et al.*[11] (entry 4) which involved a counterion switch to the magnesium anion **12d** (entry 4) was also ineffective, affording only trace amounts of tricycle **4b**. Successful coupling of sulfamidate **11** with (2,4-dichloropyridin-3-yl)lithium (**12e**, entry 5) was achieved, unfortunately the 2-position chlorine atom did not significantly increase the selectivity for product **4a** over **17b** (compare with entry 1). A breakthrough was made when a literature search revealed reactivities of certain lithium acetylides in the ring opening of cyclic sulfamidates were improved when HMPA was used as a cosolvent.[14] Indeed, addition of HMPA (5.0 equiv) in the ring opening of sulfamidate **11** with (4-bromo-2-fluoropyridin-3-yl)lithium (**12b**) gave tricycle **4b** exclusively in 66% isolated yield (entry 6). A similar result was observed with anion **12f** which gave the desired chloro adduct **3a** in 66% yield (entry 7). This indicates that ring closure in these systems occurs preferentially at the 2-fluoro position regardless of which substituent (bromo or chloro) is in the 4-position. When the ring opening of sulfamidate **11** with magnesium anion **12d** was re-examined with HMPA as cosolvent (entry 8), product **4b** was obtained in a slightly improved 23% overall yield (compare with entry 4). This result suggested superior performance of aryllithium **12b** (versus **12d**) toward ring opening of **11** but incomplete metallation of 4-bromo-2-fluoropyridine could not be ruled out.[11] The diverse behavior of the various metallate species (**12a-f**) and the role of HMPA in these reactions is intriguing.[15] However, it was beyond the scope of this work to identify the basis for these discoveries as the focus was to identify useful synthons for our drug discovery program. Ultimately, the reaction was performed on multi-gram scale to give sufficient amounts of (*R*)-8-benzyl-4-bromo-6,6a,7,8,9,10-hexahydro-5*H*-pyrazino[1,2-*a*][1,8]naphthyridine (**4b**), a key intermediate for the preparation of a number of advanced preclinical selective 5-HT_{2C} agonists (**2**).

With optimized conditions established for the synthesis of tricycle **4**, the methodology was extended toward the synthesis of (*R*)-8-benzyl-4-bromo-6,6a,7,8,9,10-hexahydro-5*H*-pyrazino[1,2-*a*][1,7]naphthyridine (**5**), a synthon for the preparation of the structurally isomeric series of 5-HT_{2C} agonists (**3**). In this case, sulfamidate **11** was coupled with (3-bromo-5-fluoropyridin-4-yl)lithium (**18**) to generate free amine **19** after acidic quench of the reaction mixture. The intramolecular S_NAr reaction was accomplished using DIEA in THF at reflux for 52 h to generate tricycle **5** in 48% yield. No product that would have resulted from ring closure on the less electrophilic carbon atom at the 3-bromo position (of **19**) was obtained under these basic conditions.



Scheme 4. Synthesis of (*R*)-8-benzyl-4-bromo-6,6a,7,8,9,10-hexahydro-5*H*-pyrazino[1,2-*a*][1,7]naphthyridine (**5**).

The scope of the two step sulfamidate ring opening-intramolecular S_NAr reaction methodology was expanded to include the preparation of other useful 5-HT_{2C} agonist synthons, namely the Boc-protected 6,6,6 tricyclic (**20**) and 6,6,7-tricyclic (**21**) systems shown in Scheme 5. Synthesis of Boc-sulfamidates **22** and **23** was performed using an optimized two step sequence that involved treatment of amino alcohols **24**[16] and **25**[17] with *N*,*N*′-sulfinylbisimidazole formed *in situ*, followed by oxidation with wet silica gel-supported $RuCl_3/NaIO_4$[17] to furnish the desired sulfamidates in satisfactory yields (85% for **22** and 51% for **23**). Arylation of the 6,6-bicyclic sulfamidate **22** with aryllithium **12b** successfully gave the ring opened intermediate **26**. In order to prevent Boc-deprotection, hydrolysis of the sulfamic acid and intramolecular S_NAr reaction were accomplished by heating the intermediate (**26**) in acetic acid and water at 80 °C for 18 h to deliver the Boc-protected tricycle **20** in 41% yield. Similarly, the highly unique 6,6,7-tricyclic compound **21** was prepared from **23**, albeit in slightly reduced yield (16%). The improved yield observed for the synthesis of sulfamidate **22** (85%) and the compatibility of the Boc-protecting group in the tandem arylation/intramolecular S_NAr reaction sequence suggests the utility of these methodologies can be expanded and may warrant further exploration.



Scheme 5. Syntheses of the Boc-protected-6,6,6-tricycle **20** and Boc-protected-6,6,7-tricycle **21**.

In conclusion, the asymmetric syntheses of (*R*)-4-halo-6,6a,7,8,9,10-hexahydro-5*H*-pyrazino[1,2-*a*][1,n]naphthyridines have been accomplished using a two-step procedure which involved arylations of an optically pure bicyclic sulfamidates and subsequent intramolecular S_NAr reactions. This methodology was useful for preparing important preclinical selective 5-HT_{2C} agonists. Structure activity relationships (SARs) and biological activities of these unique tricyclic amines will be the subject of future reports from these laboratories.

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13. The ring opening of the cyclic sulfamidate *tert*-butyl 1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide with (2-bromo-4-chloropyridin-3-yl)lithium has been previously reported, see: Behnke, D.; Carcache, D.; Ertl, P.; Koller, M.; Orain, D. WO 2014030128, 2014.
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Supplementary Material

Supplementary data (experimental procedures and compound characterization data) associated with this article can be found, in the online version, at: .

Highlights:

- Novel chiral tricyclic tetrahydronaphthyridine-based tricyclic amines are described
- Compounds are valuable synthetic precursors to potent and selective 5-HT_{2C} agonists
- Ring opening of fused bicylic sulfamidate with dihalopyridinyllithiums
- Chemoselective intramolecular S_NAr reaction