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De Novo Asymmetric Synthesis of (+)-Monanchorin

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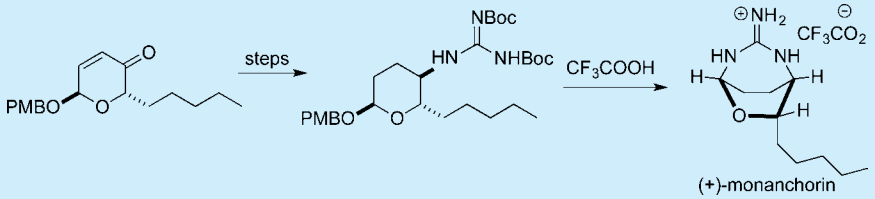
Supporting Information



ABSTRACT: A *de novo* asymmetric total synthesis of the guanidine alkaloid natural product (+)-monanchorin has been achieved in nine steps from the commodity chemicals furan and caproic acid. The asymmetry of the route was introduced by a Noyori reduction of an acylfuran. In addition, this route relies upon an Achmatowicz rearrangement, a diastereoselective palladium catalyzed glycosylation, reductive amination, and an acid catalyzed bicyclic guanidine mixed acetal formation.

As a stem cell, mast cells play an important role in the growth and establishment of human tumor cells.[1] Thus, scientists believed that tumor derived exosomes can reprogram mast cells to promote host immunosuppression, subvert T-regulatory cell function, and behave like malignant tumor cells.[1−7] This suggests the possibility of a specific antitumor drug therapy that returns the tumor-associated mast cells to their normal function by exposure to small molecules.[1]

To test this hypothesis, selective cytotoxic small molecules that inhibit mast cell function were sought. In this regard, (+)-monanchorin was recently identified as a possible candidate. Monanchorin was first isolated by McKee and co-workers in 2004 from the sponge *Monanchora ungiculata*, which was collected off the Maldive islands.[8] This structurally novel bicyclic guanidine alkaloid showed cytotoxicity (IC_{50} = 11.7 μg/mL) in an NCI high-throughput murine IC2 mast cell differential cytotoxicity assay.[8] The unique structure of this natural product makes it a very promising small molecular lead for further medicinal chemistry exploration.

Our interest in the guanidinium natural products was peeked by the suggestion that they stabilize the pro-apoptotic protein PDCD4,[9] which may be the origins of its effect on mast cells. Previously, we[10,11] and others[12−14] have studied polyketide type PDCD4 stabilizers and wanted to compare their activity to these structurally dissimilar cationic natural products. It has been suggested that these cationic natural products act by mimicking cellular ions and inhibiting ion pumps (e.g., Na^+/K^+-ATPase or Ca^{2+}-ATPase).[15] In this regard, we hypothesized that having access to both enantiomers of monanchorin would enable testing of the origins of the biological activity in regards to the structural bases of its ion mimicry.

In addition to the question of absolute and relative stereochemistry, the structure of monanchorin posed difficulties in terms of regiochemistry. Specifically, it was not trivial to assign which of the two possible bicyclic aminal structures **1** and **2** best fit (Figure 1). The regiochemistry and relative

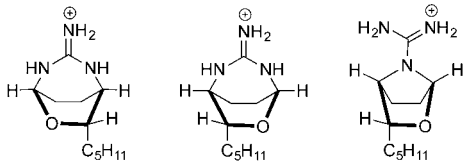


Figure 1. Monanchorin **1**, its enantiomer, and regioisomer **2**.

stereochemistry issues were largely settled by extensive use of a combination of 2D NMR analysis along with computational modeling. The absolute stereochemistry of monanchorin was finally established by Snider in 2009,[16] with his asymmetric synthesis of (−)-monanchorin (***ent*)-1**.

Including Snider's route, there has been three total syntheses of monanchorin (Scheme 1). Snider's synthesis began with a Shi epoxidation and azide opening of 4*E*-decenal, which in turn can be prepared from hexanal in three steps. The second route toward (+)-monanchorin was completed by Sutherland, which started from (*R*)-glycidol[17] and is available in either enantiomer as it comes from the Jacobsen resolution of the racemate.[18] The route also features the use of a MOM-ether directed palladium catalyzed Overman trichloroacetimidate rearrangement[19] to set the key aminoalcohol stereochemistry. The most recent asymmetric synthesis of monanchorin was reported in 2014 by Hale.[20] The Hale route uses a Sharpless asymmetric dihydroxylation and azide opening of cyclic sulfate[21] to establish the key amino-alcohol stereochemistry.

As all the previous syntheses of monanchorin relied upon epoxide like ring-opening reactions to establish the stereochemistry (Scheme 1), we were intrigued by the possibility of

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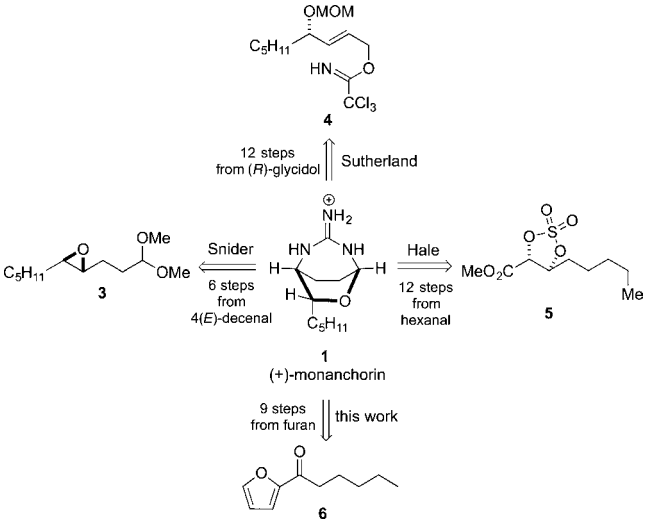
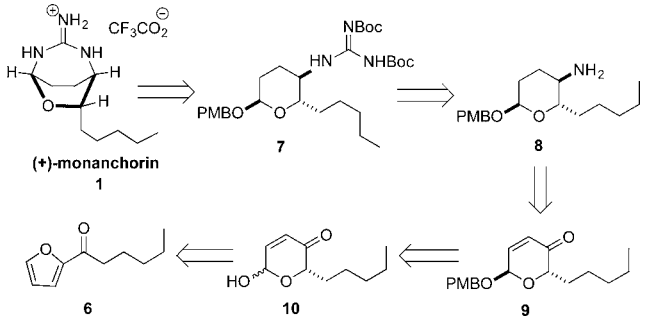
Scheme 1. Retrosynthesis of (+)-Monanchorin



exploring an alternative asymmetric approach. We were particularly interested in a *de novo* asymmetric approach,[22] as we would like to have access to both enantiomers. In this regard, we felt that an approach to monanchorin could be devised from our successful use of the Achmatowicz[23] approach to carbohydrates. This choice arose from the recognition that the pyran ring of (+)-monanchorin possessed *C*-4 amino-D-amicetose stereochemistry.[24] Herein we described our *de novo* synthetic route to (+)-monanchorin.

Retrosynthetically, we envisioned that monanchorin would result from the acid catalyzed deprotection/cyclization of the bis-Boc-protected guanidine **7** (Scheme 2). The stereo-

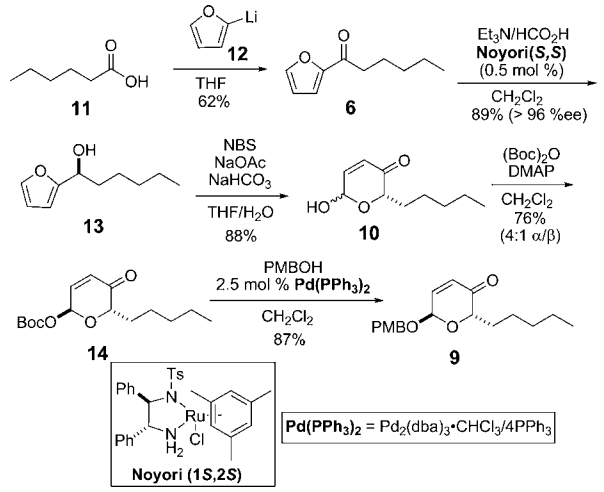
Scheme 2. Retrosynthesis of (+)-Monanchorin



chemistry of guanidine **7** could come from *C*-4 amino amicetose **8**, which in turn could come from a reductive amination of **9**. Previously we have shown that pyranones such as **9** can be readily assembled from acylfurans such as **6** via a Noyori reduction, Achmatowicz, and Pd-catalyzed glycosylation reaction sequence.[25−27]

Our synthesis started with the addition of excess 2-lithiofuran (**12**) to caproic acid (**11**) to form acylfuran **6** in a 62% yield (Scheme 3). The practicality of this reaction can be seen in that the acylfuran **6** formed can be used without the need for silica gel chromatography. Exposure of furyl ketone **6** to a catalytic amount (0.5 mol %) of the (*S*,*S*)-Noyori's catalyst[28] in a 1:2 ratio of Et_3N/HCO_2H led to high yields (89%) of furan alcohol **13** with excellent enantioselectivity (>96% ee). The furan alcohol **13** was rearranged into pyranone **10** when oxidized under the typical Achmatowicz conditions (NBS in buffered

Scheme 3. Synthesis of Pyranone 9

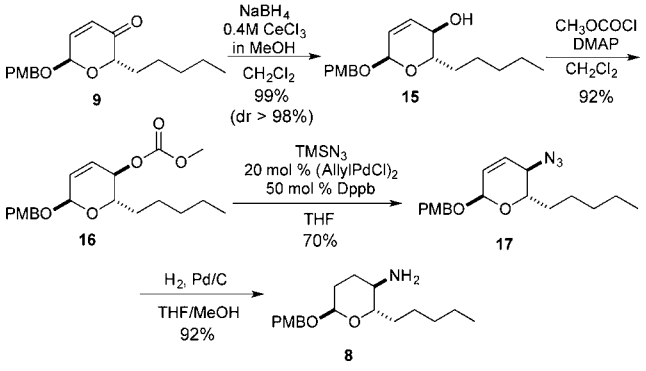


THF/H_2O). In order to diastereoselectively protect the anomeric position as a benzyl ether, we employed a two-step acylation/Pd-catalyzed glycosylation (**10** to **9**).

Diastereoselective acylation of hemiacetal **10** with $(Boc)_2O$/DMAP provided the Boc-protected pyranone **14** (4:1 α/β ratio) in excellent yield (76%). Coupling of pyranone **14** with *p*-methoxybenzyl alcohol in the presence of 2.5% palladium(0) and 5% triphenylphosphine gave PMB-protected pyranone **9** as a single diastereomer in excellent yield (87%).

With pyranone **9** suitably protected at the anomeric position, we next investigated the stereoselective azide incorporation at *C*-4 using π-allyl palladium catalysis (Scheme 4). The *C*-4

Scheme 4. Synthesis of Amine 8



ketone in **9** was diastereoselectively reduced with $NaBH_4$ (CH_2Cl_2/MeOH, −78 °C) forming the equatorial allylic alcohol **15** in excellent yield (99%). In order to convert the allylic alcohol of **15** into a better leaving group it was acylated with methyl chloroformate to form the mixed carbonate **16** (92%). Exposing carbonate **16** to the conditions developed by Sinou[29] ($TMSN_3$, $(Pd(ally)Cl)_2$/1,4-bis(diphenylphosphino)-butane) afforded a single regio- and stereoisomeric allylic azide **17** in a good yield (70%). Hydrogenolysis (Pd/C, H_2, MeOH) of allylic azide **17** via a one-pot reduction of both azide and the allylic double bond gave the 4-amino-amecito-sugar **8** in 92% yield.

In an effort to reduce the number of steps required for the conversion of **9** to **8**, we next investigated a two-step alkene reduction and ketone reductive amination (Scheme 5). To our delight, the double bond in pyranone **9** was successfully

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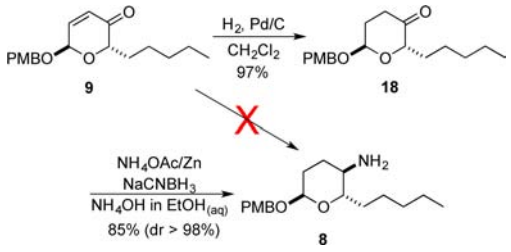
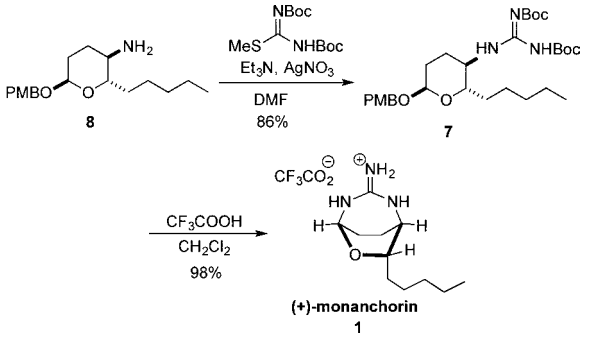
Scheme 5. Alternative Synthesis of Amine 8



reduced (Pd/C, H_2, CH_2Cl_2) to afford ketone **18** in an excellent yield (97%). After screening many potential conditions for the reductive amination, we found that the best results were obtained when ketone **18** was exposed to both Zn and $NaCNBH_3$.[30] Thus, when exposing ketone **18** to this combination of reducing agents (Zn and $NaCNBH_3$, NH_4OAc/NH_4OH, EtOH) 4-amino-amecito-sugar **8** was produced in 85% yield. Unfortunately, all further attempts at trying to obtain amine **8** more directly from pyranone **9** via one-pot reductive amination conditions were futile,[31] which may be a result of the base sensitivity of this type of pyranone.

The total synthesis of (+)-monanchorin was accomplished in two steps from amicetose **8** (Scheme 6). Reacting amine **8** with

Scheme 6. Synthesis of (+)-Monanchorin



N,*N*-bis-Boc-*S*-methylisothiourea in the presence of silver nitrate and trimethylamine resulted in bis-Boc protected guanidine **7**. Treatment of guanidine **7** with TFA in a one-pot reaction removed both Boc-protecting groups and induced the final ring closure furnishing (+)-monanchorin (**1**) in excellent yield (98%). Synthetic monanchorin so produced had spectral data (^1H and ^{13}C NMR, IR, and optical rotation) consistent with that recorded for the natural material.

In conclusion, a *de novo* asymmetric total synthesis of the guanidine alkaloids natural product (+)-monanchorin (**1**) has been achieved in nine steps from commercially available furan (**12**) and caproic acid (**11**) with an overall yield of 22%. The route is amenable for the synthesis of either enantiomer, as it relies on the use of a Noyori asymmetric reduction of acylfuran. The synthesis compares favorably in terms of length and overall yield with the previously reported routes. Our efforts to explore the biological properties of both enantiomers of monanchorin are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02651.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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