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Research Article

Achmatowicz approach to the asymmetric synthesis of (+)- and (−)-monanchorin

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ABSTRACT

The full account of our development of a *de novo* asymmetric total synthesis of (+)-monanchorin has been reported. The optimized synthesis provided access to either enantiomer of the guanidine alkaloid natural product in nine steps from the commodity chemicals furan and caproic acid. The route relied upon the asymmetric Noyori hydrogen transfer reduction of an achiral acylfuran to introduce the absolute stereochemistry. In addition, an Achmatowicz rearrangement, a diastereoselective palladium-catalyzed glycosylation, a reductive amination and an acid-catalyzed bicyclic guanidine mixed acetal formation were used to complete the synthesis.

1. Introduction

In an effort to find natural products that selectively inhibit mast cell function, (+)-monanchorin was identified as a possible candidate in 2004 [1]. The novel bicyclic guanidine marine alkaloid was isolated from the sponge *Monanchora ungiculata*, which was collected off the coast near the Maldive islands by McKee and coworkers. Monanchorin was found to possess significant cytotoxicity (IC_{50} = 11.7 μg/mL) in an NCI high-throughput murine IC2 mast cell differential cytotoxicity assay [1]. In addition to this anticancer activity, it is believed that compounds like (+)-monanchorin have a therapeutic potential to restore normal immune responses in cancer patients [2–6].

2. Results and discussion

In combination with its promising activity, the unique shape and charge of (+)-monanchorin makes it a compelling structure for further medicinal chemistry exploration [7]. In particular, for its use in a medicinal chemistry study that focuses on the stereochemical structure-activity relationship (S-SAR) studies. For example, it has been suggested that these spherical ionic natural products could act as cellular mimics of cations, which suggests a potentially interesting activity for the enantiomer of monanchorin (*ent*)-**1**. Thus, our interest in monanchorin and related stereoisomers is as potential inhibitors of ion pumps (*e.g.*, Na^+/K^+-ATPase or Ca^{2+}-ATPase) [8–12]. In addition, we were also interested in monanchorin ability to stabilize the pro-apoptotic protein PDCD4 [13], which may also be the origins of its effects on mast cells. Previously, we [14–16] and others [17–19], have been interested in a polyketide based PDCD4 stabilizers, cryptocaryol, which showed interesting stereochemical flexibility in its S-SAR [20–23] toward its PDCD4 stabilizing activity. Similarly, we hypothesized that having access to both enantiomers of monanchorin, would serve as an interesting test of the origins of the structural bases of its PDCD4 activity and ion mimicry.

Of course, all discussions of the monanchorin SAR begins with its structure, which involved questions of both absolute and relative stereochemistry, as well as regiochemistry. The issue of regiochemistry revolved around two possible bicyclic aminal regioisomers **1** *vs.* **2** (Fig. 1). The assignment of regiochemistry and relative stereochemistry was made by a combination of 2D NMR analysis and computational modelling [1]. Finally, in 2009, the absolute stereochemistry of monanchorin was established with the asymmetric synthesis of its enantiomer, (−)-monanchorin (*ent*)-**1** by Snider [24].

There has been a total of four asymmetric syntheses of monanchorin reported in the literature (Scheme 1). Snider's synthesis began with 4*E*-decenal **4** (3 steps from hexanal) and used a combination of Shi epoxidation and azide opening to establish asymmetry [24]. The second

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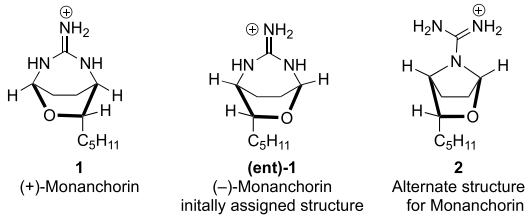
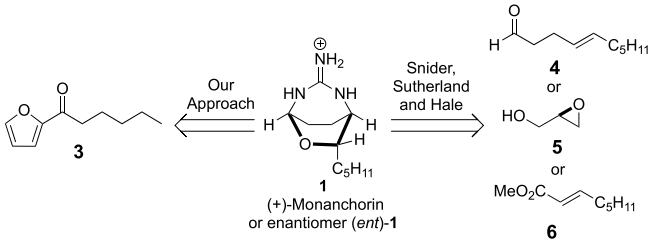


Fig. 1. (+)-Monanchorin and its enantiomer and regioisomer.

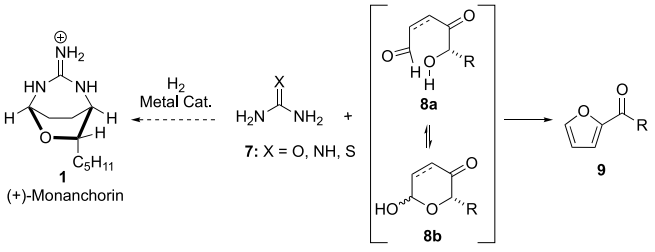


Scheme 1. Approaches to (+)-monanchorin.

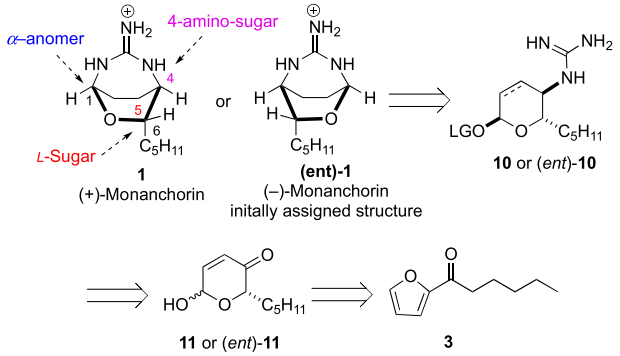
synthesis of monanchorin and the first route to the natural enantiomer, (+)-monanchorin, was completed by Sutherland [25], who started from (*R*)-glycidol **5** [26]. In 2014, Hale [27] reported an asymmetric synthesis of monanchorin from enoate **6** that used a Sharpless asymmetric dihydroxylation and azide opening of cyclic sulfate to establish the key amino-alcohol stereochemistry [28]. Most recently, in 2015, we communicated our asymmetric synthesis of monanchorin from achiral furan **3** [29], which used a Noyori hydrogen transfer reaction to establish its asymmetry [30–32].

A Noyori/Achmatowicz approach, in theory, should be a natural fit for the synthesis of monanchorin (Scheme 2). In theory, an idealized approach to monanchorin could be derived from the reductive amination reaction between guanidine or guanidine surrogate and Noyori/Achmatowicz [33–35] product **8**. Unfortunately, when the Achmatowicz products, like **8**, were exposed to amine and guanidine type nucleophiles only a complex mixture of Maillard like reaction products were observed [36]. We revised our approach building from the previous syntheses of monanchorin which relied upon azide ring-opening reactions to establish the *C*-4/5 amino alcohol stereochemistry (Scheme 3). Specifically, we envisioned that the key *C*-4/5 amino alcohol stereochemistry was coming from a *C*-4 aminosugar (Scheme 3), which in turn could enable control of the *C*-1 anomeric stereochemistry [37–39]. Thus, the stereochemistry of monanchorin could be viewed as possessing the stereochemistry of a *C*-4 amino-L-amicetose. Herein we describe the full account of our efforts to develop a *de novo* asymmetric synthetic route to both enantiomers of monanchorin.

Our revised retrosynthetic analysis envisioned monanchorin **1** would result from the cyclization/intramolecular glycosylation of a *C*-4 guanidine intermediate like **10** (Scheme 3). The stereochemistry of guanidine **10**, which in turn could come from a *C*-4 amination of **11**. Finally, pyranones like **11** can be readily assembled from acylfurans like **3**.



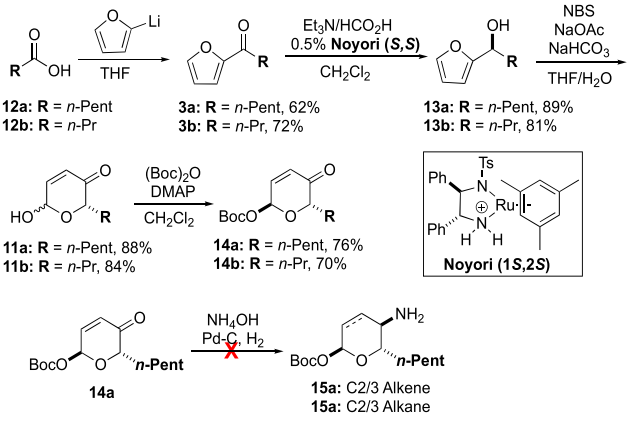
Scheme 2. Idealized Achmatowicz approach to (+)-monanchorin.



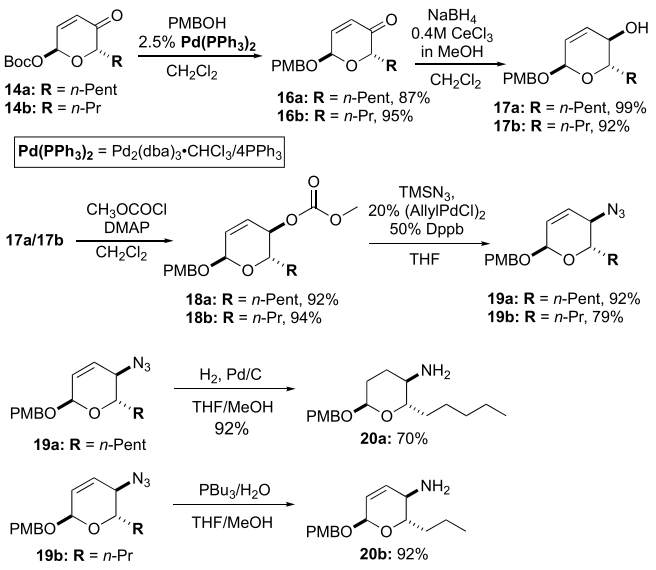
Scheme 3. Revised Achmatowicz retrosynthesis for (+)-**1**.

Our synthetic efforts began with the synthesis of pyranones **14a** and **14b** with a *C*-5 *n*-Pent and *n*-Pr group, respectively (Scheme 4). This synthesis started with the addition of excess 2-lithiofuran to carboxylic acids **12a/b** to form acylfuran **3a/b** (62%/72% yields). Noyori hydrogen transfer reduction of furyl ketones **3a/b** (0.5 mol% (*S,S*)-Noyori's catalyst, 1:2 (Et_3N/HCO_2H) [40] led to high yields (89%/81% yields) of furan alcohols **13a/b** with an excellent enantioselectivity (>96% *ee*) [41–44]. The furan alcohols **13a/b** were oxidatively rearranged under the typical Achmatowicz conditions (NBS in buffered THF/H_2O) to give pyranones **11a/b** (88%/84% yields). We diastereoselective protected/activated the anomeric position with a *t*-butylcarbonate group ($(Boc)_2O$/DMAP) which provided the Boc-protected pyranones **14a/b** (4:1 α/β-ratio) in excellent yields (76%/70%, for α-isomer). Unfortunately, all our efforts to perform a reductive amination of **14** lead to decomposition. This is presumably due to the base sensitivity of pyranones like **14**, with anomeric leaving groups.

We next turned to a more stereocontrolled approach to install the *C*-4 amine functionality. To accomplish this, we decided to explore the use of Pd-π-allyl chemistry to control stereochemistry at *C*-1 and *C*-4 (Scheme 5). This began with a Pd-catalyzed glycosylation (**14a/b** to **16a/b**) to diastereoselectively protect the anomeric position (5% triphenylphosphine, PMBOH and 1.25% $Pd_2(dba)\cdot CHCl_3$) as a *p*-methoxybenzyl acetal (87%/95% yields) [45–49]. We next investigated the stereoselective reduction of the *C*-4 ketones of **16a/b** with $NaBH_4$ (CH_2Cl_2/MeOH, −78 °C) forming the equatorial allylic alcohol **17a/b** in excellent yields (99%/92%). We then looked to convert the *C*-4 allylic alcohol of **17a/b** into a Pd-leaving group. This began with a carbonate formation with methyl chloroformate ($MeCO_2Cl$, DMAP) to form the mixed carbonates **18a/b** (92%/94% yields). The desired *C*-4 azide was then installed in **19a/b** upon exposure of **18a/b** to the Sinou conditions for Pd-π-allylic substitution ($TMSN_3$,$(Pd(ally)Cl)_2$/1,4-bis(diphenylphosphino)butane) [50–54]. This afforded both allylic azides **19a/b** as single regio- and



Scheme 4. Synthesis of pyranone **14** and attempted reductive aminations.



Scheme 5. Stereospecific synthesis of *C*-4 aminosugars **19** and **20**.

stereo-isomer and in good yields (92%/79%). The allylic azide intermediates could then be converted into the desired *C*-4 aminosugar both with a *C*-2/3-alkene **20b** and without **20a**. Thus, exposing allylic azide **19a** to hydrogenolysis (Pd/C, H_2, MeOH) in one-pot reduction reduced both the azide and allylic double bond, while leaving behind the PMB-group to give the 4-amino-amecito-sugar **20a** in 70% yield. In contrast, the azide in **19b**, was selectively reduced with PPh_3 in THF/MeOH/H_2O to give **20b** in 92% yield.

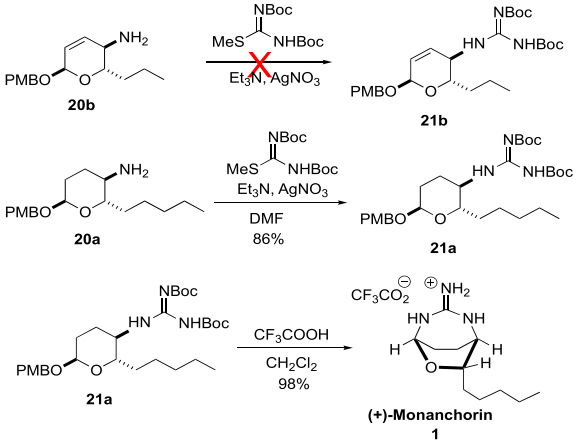
We next explored the stepwise installation of the *C*-4 guanidine group and the corresponding ring closure at the anomeric position to make the monanchorin bicycle (Scheme 6). This began with the reaction of *C*-4 amine **20b** with *N,N*-bis-Boc-*S*-methylisothiourea. Unfortunately, under these reaction conditions, no evidence of the desired product **21b** was observed. We surmised that the presence of the *C*-2/3 alkene made the anomeric position too susceptible to hydrolysis. Thus, we decided to explore the same transformation on *C*-4 amine **20a**, which lacked the *C*-2/3 alkene. To our delight, amine **20a** reacted with *N,N*-bis-Boc-*S*-methylisothiourea in the presence of silver nitrate and trimethylamine to give the desired bis-Boc-protected guanidine **21a** in 86% yield. The asymmetric synthesis of (+)-monanchorin completed when in one pot guanidine **21a** was treated with TFA to remove both Boc-protecting groups and to induce the final ring-closure furnishing (+)-monanchorin (**1**) in excellent yield (98%). The synthetic monanchorin so obtained had spectral data (^{1}H and ^{13}C NMR, IR and optical rotation) consistent with that recorded for the natural material [1].

With a synthesis of monanchorin in hand, we next looked to improve the efficiency of the overall route (Scheme 7). This began with an effort to review the number of steps required for the conversion of **16a** to **20a**, which required 4 steps (Scheme 5). In theory, this should be accomplished in one step with the reductive amination of **16a**. Unfortunately, in our hands, we were never able to isolate **20a** in a good yield and in stereochemically pure form from the direct reductive aminate of **16a**. In contrast, a very practical two-step reduction/reductive amination alternative was developed (Scheme 7). To our delight, the double bond in pyranone **16a** was successfully reduced (Pd/C, H_2, CH_2Cl_2) to cleanly give **22a** in excellent yield (97%). After a significant degree of screening of conditions for the reductive amination, we eventually found that the best results were obtained when ketone **22a** was exposed to both Zn and $NaCNBH_3$ [55]. Specifically, when exposing ketone **22a** to this combination of reducing agents (Zn and $NaCNBH_3$, NH_4OAc/NH_4OH, EtOH), 4-amino-amecito-sugar **20a** was produced in an 85% yield [56].

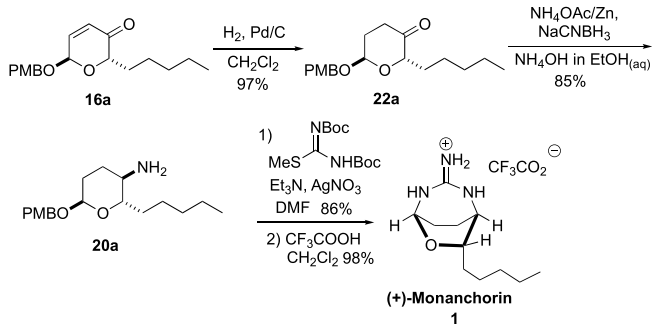
We then looked to extend the route to the synthesis of the enantiomer (−)-monanchorin (Scheme 8). This began with the asymmetric Noyori reduction of **3a** with the (*R,R*)-Noyori catalyst to provide the furyl alcohol (*ent*)-**13a** in excellent yield and enantioselectivity. Following an identical three steps protocol (Achmatowicz/*t*-Bu carbonate formation/Pd-glycosylation) (*ent*)-**13a** was converted into pyranone (*ent*)-**16a** in an excellent yield. Similarly, pyranone (*ent*)-**16a** was converted in 4 steps (hydrogenation/reductive amination/guanidine formation/cyclization) into the natural product enantiomer, (−)-monanchorin. Enantiomeric monanchorin possessed spectral data (^{1}H and ^{13}C NMR, IR) and opposite optical rotation as that for the isolated monanchorin.

This evolving synthetic effort offered an opportunity to evaluate our initial and revised retrosynthetic design (Scheme 9). Specifically, we could ask how good these approaches were at accessing monanchorin and how stereochemistry was installed. In this regard, all the successful approaches to monanchorin recognize the need to install the *C*-4/5 aminoalcohol stereochemistry. These stereocenters in turn can be used to control the bicyclic aminal formation (*i.e.*, 23 to **1**). Our first-generation approach hoped to use the *C*-5 alcohol stereochemistry, from the Noyori/Achmatowicz reaction, in **8a/b** to control the *C*-4 amine stereochemistry in a comprehensive reductive amination/bicyclic aminal formation. This effort failed, presumably due to the competing reactivity of the two carbonyls in **8a**. Our response was to use the *C*-5 stereocenter to control the C-1 α-stereochemistry (**8b** to **24a** then **24b** *via* **29**), which in turn could be used to control the *C*-4 stereochemistry *via* a highly selective Luche reduction (**24b** to **26**; *via* **28**).

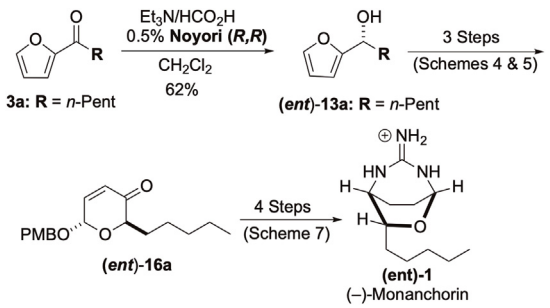
This newly installed *C*-4 alcohol stereochemistry in **26** was then stereospecifically converted into azide **27** (*via* a carbonate formation and Pd-π-allyl substitution; **26** to **27** *via* **30**). Then the *C*-4 azide in **27** can be reduced into the *C*-4 amine in **25**. This revised approach to **25** was fully stereocontrolled but at a cost of the addition of additional steps. In our final optimized approach, we found that the high facial selectivity of the Luche reduction (**24b** to **25** *via* **28**, **X** = O) held true to when we changed the enone reduction into a stereoselective reductive amination of the



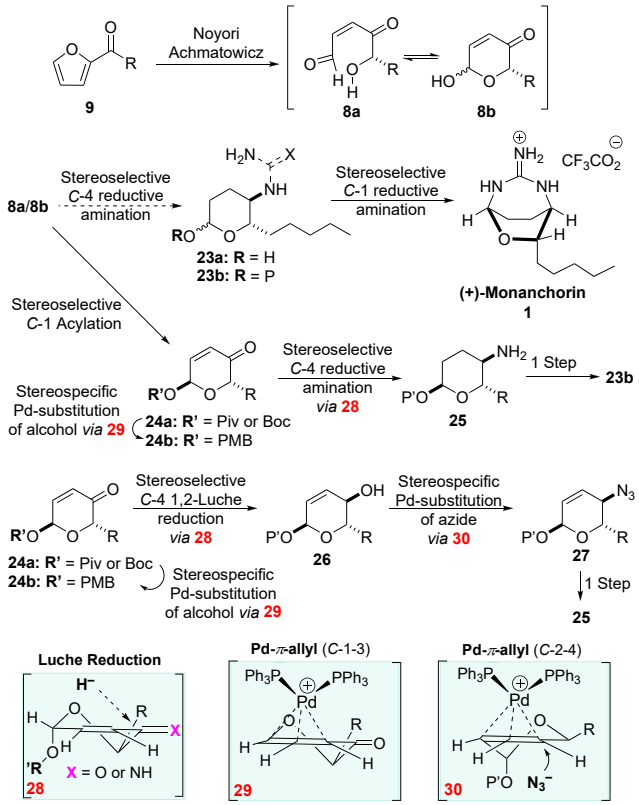
Scheme 6. Synthesis of (+)-monanchorin.



Scheme 7. Optimized synthesis of (+)-monanchorin.



Scheme 8. Synthesis of (−)-monanchorin.



Scheme 9. Stereochemical considerations.

enone **24b** to directly form **25** (*via* **28**, **X** = NH). The amine in **25** was then primed for guanidine introduction and bicyclic aminal formation to complete the synthesis of monanchorin.

3. Conclusion

In conclusion, a *de novo* asymmetric total synthesis of both enantiomers of the guanidine alkaloids natural product (+)-monanchorin (**1**) has been achieved in eight steps and 34% overall yield from achiral acyl furan **3a**. The route develops from the recognition that (+)-monanchorin (**1**) possesses a stereochemical relationship with α-L-amicetose aminosugar. As a result, either enantiomer can be equally prepared in the enantiomerically pure form *via* a Noyori/Achmatowicz approach. 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.

4. Material and methods

4.1. General methods

Triethylamine, ether, tetrahydrofuran, methylene chloride and methanol were dried by passing through an activated alumina column with argon. Hexanes refer to the petroleum fraction of boiling point 40–60 °C. Air- and/or moisture-sensitive reactions were carried out under an atmosphere of argon or nitrogen using oven-dried glassware and standard syringe/septa techniques. Commercial reagents were used without purification unless otherwise noted. Flash chromatography was performed using the indicated solvent system on silica gel standard grade 60 (230–400 mesh). R_f values are reported for analytical TLC using the specified solvents and 0.25 mm silica gel 60 F254 plates that were visualized by UV irradiation (254 nm) or by $KMnO_4$ or anisaldehyde staining. ^1H and ^{13}C spectra were recorded on 500 MHz and 150 MHz spectrometers. Chemical shifts are reported relative to $CDCl_3$ (δ: 7.26 ppm) for ^1H and $CDCl_3$ (δ: 77.0 ppm) for ^{13}C. Optical rotations were obtained using a digital polarimeter at sodium D line (589 nm) and were reported in the concentration of g/100 mL at 25 °C. IR was recorded on FT-IR spectrometer. Melting points are uncorrected.

4.2. Experimental procedures

Included below are the experimental procedures for all newly reported compounds. Full experimental details are included in the supporting information.

4.2.1. 1-(Furan-2-yl)butan-1-one (3b)

To 330 mL of furan (4.54 mol) was dropped *n*-BuLi (480 mL, 1.06 mol) at 0 °C. Then let it warm up to room temperature and the resulting solution was stirred at room temperature for 12 h. Then 400 mL of anhydrous THF was added to dissolve the solid mixture at RT, which was then transferred to butyric acid **12b** (48.3 mL, 0.528 mol) in 50 mL of THF at −78 °C. Then the resulting solution was stirred for 30 min at −78 °C followed by warming and stirring at 0 °C for another 12 h. Then into the reaction mixture, 30 mL of acetone was added to quit the reaction, followed by the addition of EtOAc (600 mL). At 0 °C 400 mL of saturated $NH_4Cl_{(aq)}$ was added to wash the organic layer. The aqueous layer was extracted with EtOAc (2 × 600 mL). The pooled organic layer was washed with 50 mL saturated brine, dried over Na_2SO_4 and then concentrated under reduced pressure to give a residue. Flush chromatography on silica gel eluting with 5% Et_2O/hexane gave furan acetone **3b** (52.27 g, 72%): light yellow oil; R_f = 0.69 (2:1 (v/v) hexane/EtOAc); IR (thin film, cm^{-1}): 3132, 2964, 2876, 1674, 1568, 1467, 1394, 1159, 1020, 881, 760; ^1H NMR (600 MHz $CDCl_3$): δ 7.51 (dd, J = 1.8, 0.6 Hz, 1H), 7.10 (dd, J = 3.6, 1.2 Hz, 1H), 6.45 (dd, J = 3.6, 1.8 Hz, 1H), 2.72 (dd, J = 7.8, 7.2 Hz, 2H), 1.68 (qdd, J = 7.8, 7.8, 7.2 Hz, 2H), 0.91(dd, J = 7.8, 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 189.6, 152.9, 146.2, 116.8, 112.1, 40.4, 17.8, 13.8.

4.2.2. (S)-1-(Furan-2-yl)butan-1-ol (13b)

To a solution of aqueous HCOONa (672 mL, 2.0 mol/L) was added furan ketone **3b** (52.27 g, 1.344 mol) and CH_2Cl_2 (34 mL). CTAB (13.6 g, 37.3 mmol) was then added. The mixture was stirred for 5 min. Noyori asymmetric transfer hydrogenation catalyst (*R*)-Ru(η^6-mesitylene)-(*S*,*S*)-TsDPEN (0.218 g, 0.1 mol%). The resulting solution was stirred at room temperature under argon for 24 h. Then the mixture was extracted with Et_2O (3 × 300 mL). The combined organic layer was washed with 50 mL saturated aqueous $NaHCO_3$, 50 mL saturated brine, dried over Na_2SO_4 and then concentrated under reduced pressure to give a residue. Flush chromatograph on silica gel eluting with 10% Et_2O/hexane gave furan alcohol **13b** (42.16 g, 81%): Colorless oil; R_f = 0.59 (2:1 (v/v) hexane/EtOAc); $[\alpha]_D^{21}$ −26 (*c* 1.5, CH_2Cl_2); IR (thin film, cm^{-1}) 3343, 2959, 2935, 2873, 1505, 1466, 1149, 1007, 732; ^1H NMR (600 MHz $CDCl_3$): δ 7.36 (dd, J = 1.8, 0.6 Hz, 1H), 6.32 (dd, J = 3.0, 1.8 Hz, 1H), 6.22 (d, J = 3.0,

1H), 4.68 (dd, $J = 7.2$, 6.6 Hz, 1H), 1.95 (s, 1H), 1.83 (m, 2H), 1.50–1.41 (m, 1H), 1.39–1.31 (m, 1H), 0.94 (dd, $J = 7.8$, 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 157.1, 142.0, 110.3, 105.9, 67.8, 37.8, 18.9, 14.0.

4.2.3. (S)-6-Hydroxy-2-propyl-2H-pyran-3(6H)-one (11b)

To a solution of 3.67 g furan alcohol **13b** (26.2 mmol) in 106 mL THF-H_2O (3:1) was added 4.4 g $NaHCO_3$ (52.4 mmol), 3.56 g $NaOAc{\cdot}3H_2O$ (26.2 mmol), and 4.66 g NBS (26.2 mmol) at 0 °C. The reaction mixture was kept stirring at this temperature for 1 h, then at 0 °C 60 mL saturated $NaHCO_3$ was added to quench the reaction. The reaction mixture was directly extracted with Et_2O (3 × 100 mL) and the organic layer was pooled, washed by 30 mL saturated brine, dried over Na_2SO_4 and then concentrated reduced pressure to give a residue, which was rapidly subjected to flush chromatography on silica gel. Elution with 20% EtOAc/hexane afforded pyranone alcohol **11b** (3.43 g, 84%): Colorless oil; $R_f = 0.41$ (2:1 (v/v) hexane/EtOAc); $[\alpha]_D^{21}$ +12 (*c* 1.6, CH_2Cl_2); IR (thin film, cm^{-1}) 3399, 2959, 2961, 2874, 1683, 1084, 1022, 968; ^{1}H NMR (600 MHz, $CDCl_3$) major isomer: δ 6.88 (dd, $J = 10.2$, 3.0 Hz, 1H), 6.07 (d, $J = 10.2$, 1H), 5.62 (s, 1H), 4.54 (dd, $J = 8.4$, 4.2 Hz, 1H), 3.83 (s, 1H), 1.89–1.83 (m, 1H), 1.70–1.63 (m, 1H), 1.47–1.36 (m, 2H), 0.91 (dd, $J = 7.8$, 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) major isomer: δ 197.2, 144.9, 127.7, 87.7, 74.1, 31.8, 18.4, 13.9.

4.2.4. (2S,6S)-t-Butyl-5,6-dihydro-6-propyl-5-oxo-2H-pyran-2-yl carbonate (14b)

To a solution of 4.0 g pyranone alcohol **11b** (25.8 mmol) in 26 mL CH_2Cl_2 was added 315 mg DMAP (2.58 mmol) at −78 °C. A pre-cooled solution of 11.2 g $(Boc)_2O$ (51.6 mmol) in 15 mL CH_2Cl_2 was added drop wise into the reaction mixture *via* a cannula. The reaction mixture was stirred at −78 °C for 12 h. The reaction was quenched by 150 mL saturated $NaHCO_3$ and then extracted with Et_2O (300 mL × 3). The organic layers were pooled, then washed by 50 mL saturated NaCl, dried over Na_2SO_4 and concentrated under reduced pressure to give a residue. Flush chromatograph on silica gel eluting with 5% Et_2O/hexane gave 5.61 g (85%) of two diastereomers of Boc-protected pyranone **14b** (α) and **14b** (β) in 2.7:1 ratio.

α-pyranone 14b: $R_f = 0.76$ (3:1 (v/v) hexane/EtOAc); $[\alpha]_D^{21}$ +55 (*c* 1.2, $CDCl_3$); IR (thin film, cm^{-1}) 2964, 2876, 1749, 1698, 1459, 1370, 1274, 1253, 1155, 1054, 936, 844; ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.86 (dd, $J = 10.2$, 3.6 Hz, 1H), 6.33 (d, $J = 3.6$ Hz, 1H), 6.19 (d, $J = 10.2$ Hz, 1H), 4.51 (dd, $J = 8.4$, 4.2 Hz, 1H), 1.92 (dddd, $J = 14.4$, 9.0, 7.8, 3.6 Hz, 1H), 1.70 (dddd, $J = 14.4$, 7.8, 7.8, 7.8 Hz, 1H), 1.51 (s, 9H), 1.48–1.40 (m, 2H), 0.91 (dd, $J = 7.8$, 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 195.8, 152.0, 141.0, 129.1, 89.4, 83.7, 75.6, 31.5, 27.9, 18.1, 13.8; HRMS (CI): calcd. for $[C_{13}H_{20}O_5 + Na]^+$: 279.1203, Found: 279.1204.

β-pyranone 14b: $R_f = 0.70$ (3:1 (v/v) hexane/EtOAc); $[\alpha]_D^{21}$ −78 (*c* 1.3, $CHCl_3$); IR (thin film, cm^{-1}) 2963, 2875, 1743, 1683, 1468, 1370, 1284, 1252, 1158, 1058, 946, 847; ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.85 (dd, $J = 10.2$, 3.0 Hz, 1H), 6.36 (dd, $J = 3.0$, 1.2 Hz, 1H), 6.20 (dd, $J = 10.2$, 1.2 Hz, 1H), 4.23 (dd, $J = 10.2$, 4.2 Hz, 1H), 1.94–1.87 (m, 1H), 1.79–1.73 (m, 1H), 1.52 (s, 9H), 1.56–1.51 (m, 1H), 1.49–1.41 (m, 1H), 0.95 (dd, $J = 7.8$, 7.2 Hz, 3H); ^{13}C NMR (150.8 MHz, $CDCl_3$): δ 196.2, 152.1, 142.0, 128.5, 89.6, 83.7, 79.7, 35.6, 27.9, 18.9, 13.8; HRMS (CI): calcd. for $[C_{13}H_{20}O_5 + Na]^+$: 279.1203, Found: 279.1204.

4.2.5. (2S,6R)-6-(4-Methoxybenzyloxy)-2-propyl-2H-pyran-3(6H)-one (16b)

To a solution of 7.74 g of 4-methoxybenzyl alcohol (56.0 mmol) and 7.18 g pyranone **14b** (28.0 mmol) in 17 mL CH_2Cl_2 was added a solution of 0.724 g $Pd_2(DBA)_3{\cdot}CHCl_3$ (0.70 mmol) and 0.734 g PPh_3 (2.80 mmol) in 3 mL CH_2Cl_2 at 0 °C. The reaction mixture was stirred at 0 °C for 10 h and then quenched by 35 mL saturated $NaHCO_3$, followed by extraction with Et_2O (100 mL × 3). The organic layer was pooled, then washed by 30 mL saturated NaCl, dried over Na_2SO_4 and concentrated under reduced pressure to give crude product. Chromatograph on silica gel, eluting with 10% EtOAc/hexane gave glycosylated pyranone **16b** (7.33 g, 95%): White solid, mp: 46.2–47.0 °C; $R_f = 0.72$ (2:1 (v/v) hexane/EtOAc); $[\alpha]_D^{21}$ 10 (*c* 1.41, $CHCl_3$); IR (thin film, cm^{-1}) 2960, 2873, 1693, 1612, 1513, 1464, 1247, 1090, 1026, 820; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29 (d, $J = 8.4$ Hz, 2H), 6.90 (d, $J = 9.0$ Hz, 2H), 6.80 (dd, $J = 10.2$, 3.6 Hz, 1H), 6.07 (dd, $J = 10.2$, 0.6 Hz, 1H), 5.26 (d, $J = 3.6$ Hz, 1H), 4.76 (d, $J = 11.4$ Hz, 1H), 4.59 (d, $J = 11.4$ Hz, 1H), 4.44 (dd, $J = 8.4$, 3.6 Hz, 1H), 3.80 (s, 3H), 1.96 (dddd, $J = 13.8$, 9.6, 6.0, 3.6 Hz, 1H), 1.69–1.63 (m, 1H), 1.59–1.51 (m, 1H), 1.50–1.41 (m, 1H), 0.97 (dd, $J = 7.8$, 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 196.8, 159.8, 143.6, 130.0, 129.3, 128.0, 114.1, 91.9, 74.1, 70.4, 55.4, 31.7, 18.6, 14.0; HRMS (CI): calcd. for $[C_{16}H_{20}O_4 + Na]^+$: 299.12538, Found: 299.12584.

4.2.6. (2S,3R,6R)-6-(4-Methoxybenzyloxy)-2-propyl-3,6-dihydro-2H-pyran-3-ol (17b)

A solution of 6.56 g pyranone **16b** (23.7 mmol) in 40.0 mL CH_2Cl_2–MeOH (3:1) was cooled down to −78 °C, then 0.90 g $NaBH_4$ (23.7 mmol) was added. The reaction mixture was kept stirring at −78 °C for 3 h. The reaction was then quenched by 10 mL saturated $NaHCO_3$, followed by extraction with Et_2O (3 × 30 mL). The organic layer was washed by 10 mL saturated NaCl, dried over Na_2SO_4, and concentrated under reduced pressure to give crude product. Chromatography on silica gel eluting with 30% EtOAc/hexane gave allylic alcohol **17b** (6.05 g, 92%): colorless oil; $R_f = 0.38$ (2:1 (v/v) hexane/EtOAc); $[\alpha]_D^{21}$ −51 (*c* 1.34, MeOH); IR (thin film, cm^{-1}) 3420, 3049, 2957, 2872, 1613, 1514, 1464, 1248, 1022, 821; ^{1}H NMR (600 MHz, CD_3OD): δ 7.23 (d, $J = 9.0$ Hz, 2H), 6.86 (d, $J = 9.0$ Hz, 2H), 5.87 (ddd, $J = 10.2$, 1.2, 1.2 Hz, 1H), 5.66 (ddd, $J = 9.6$, 3.0, 2.4 Hz, 1H), 4.97 (ddd, $J = 1.2$, 1.2, 0.6 Hz, 1H), 4.66 (d, $J = 11.4$ Hz, 1H), 4.45 (d, $J = 11.4$ Hz, 1H), 3.75 (ddd, $J = 9.6$, 3.0, 1.8 Hz, 1H), 3.60 (ddd, $J = 9.0$, 8.4, 2.4 Hz, 1H), 3.75 (s, 3H), 1.84–1.79 (m, 1H), 1.66–1.58 (m, 1H), 1.46–1.37 (m, 2H), 0.96 (dd, $J = 7.2$, 7.2 Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD): δ 161.0, 135.5, 131.4, 130.8, 127.3, 114.9, 94.6, 72.6, 70.7, 68.8, 55.8, 35.3, 20.0, 14.6; HRMS (CI): calcd. for $[C_{16}H_{22}O_4 + H]^+$: 279.15909, Found: 279.15954.

4.2.7. (2S,3R,6R)-6-(4-Methoxybenzyloxy)-2-propyl-3,6-dihydro-2H-pyran-3-yl methyl carbonate (18b)

To a solution of allylic alcohol **17b** (50 mg, 0.18 mmol) in dry CH_2Cl_2 (1.0 mL) at 0 °C, was added pyridine (73 μL, 0.90 mmol), DMAP (1.1 mg), and methyl chloroformate (87 mg, 0.90 mmol). After stirring 12 h at room temperature, water (1 mL) was added and then the mixture was extracted with EtOAc (3 × 5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 10% EtOAc/hexane to give carbonate **18b** (57.0 mg, 94%) as colorless oil. $R_f = 0.63$ (2:1 (v/v) hexane/EtOAc); $[\alpha]_D^{21}$ – 99.6 (*c* 0.99, $CHCl_3$); IR (thin film, cm^{-1}) 3010, 2958, 2879, 1747, 1514, 1441, 1260, 1026, 1004, 820, 790; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 (d, $J = 8.4$ Hz, 2H), 6.88 (d, $J = 8.4$ Hz, 2H), 5.92 (ddd, $J = 10.2$, 1.2, 1.2 Hz, 1H), 5.81 (ddd, $J = 10.2$, 2.4, 1.8 Hz, 1H), 5.04 (dd, $J = 1.2$, 0.6 Hz, 1H), 4.94 (dddd, $J = 9.0$, 1.8, 1.8, 1.2 Hz, 1H), 4.74 (d, $J = 11.4$ Hz, 1H), 4.49 (d, $J = 11.4$ Hz, 1H), 3.94 (ddd, $J = 9.0$, 9.0, 1.8 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 1.70–1.61 (m, 2H), 1.52–1.38 (m, 2H), 0.97 (dd, $J = 7.8$, 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 159.6, 155.6, 129.89, 129.88, 129.4, 128.4, 114.1, 93.1, 73.5, 69.8, 68.3, 55.5, 55.2, 34.2, 18.8, 14.2; HRMS (CI): calcd. for $[C_{18}H_{24}O_6 + Na]^+$: 359.14651. Found 359.14695.

4.2.8. (2S,3R,6R)-3-Azido-6-(4-methoxybenzyloxy)-2-propyl-3,6-dihydro-2H-pyran (19b)

To a mixture of carbonate **18b** (1.05 g, 3.11 mmol), allylpalladium chloride dimer (0.114 g, 0.31 mmol) and 1,4-bis(diphenylphosphino) butane (0.53 g, 1.24 mmol) in anhydrous THF (7.0 mL) was added $TMSN_3$ (2.1 mL, 15.5 mmol) under argon atmosphere. The solution was stirred at room temperature for 12 h. Then the mixture was evaporated under reduced pressure and purified using silica gel flash chromatography eluting with 5% EtOAc/hexane to give allylic azide **19b** (0.75 g, 79%) as colorless oil. $R_f = 0.81$ (2:1 (v/v) hexane/EtOAc); $[\alpha]_D^{21}$ − 125

(*c* 0.46, MeOH); IR (thin film, cm^{-1}) 3010, 2959, 2877, 2103, 1613, 1514, 1465, 1249, 1034, 821; ^1H NMR (600 MHz, $CDCl_3$): δ 7.28 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 9.0 Hz, 2H), 5.96 (ddd, J = 10.2, 1.2, 1.2 Hz, 1H), 5.89 (ddd, J = 9.6, 2.4, 1.8 Hz, 1H), 5.03 (s, 1H), 4.73 (d, J = 11.4 Hz, 1H), 4.49 (d, J = 11.4 Hz, 1H), 3.81 (s, 3H), 3.75 (ddd, J = 9.6, 9.0, 2.4 Hz, 1H), 3.60 (dddd, J = 9.6, 1.8, 1.8, 1.8 Hz, 1H), 1.82–1.77 (m, 1H), 1.69–1.62 (m, 1H), 1.53–1.43 (m, 2H), 1.00 (dd, J = 7.2, 7.2 Hz, 3H); ^{13}C NMR (150 MHz, CDCl3): δ 159.6, 129.9, 129.8, 129.1, 128.8, 114.1, 92.8, 69.8, 69.5, 59.0, 55.5, 34.8, 18.9, 14.2; HRMS (CI): calcd. for $[C_{16}H_{21}N_3O_3 + Na]^+$: 326.14751. Found 326.14801.

*4.2.9. (2S,3R,6R)-6-(4-Methoxybenzyloxy)-2-propyl-3,6-dihydro-2H-pyran-3-amine (**20b**)*

To a solution of azide **19b** (39 mg, 0.13 mmol) in THF/H_2O (9:1, v/v, 0.50 mL) was added PBu_3 (78 mg, 0.39 mmol), then the solution was stirred at room temperature for 1 h. Then the mixture was evaporated under reduced pressure, and the crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexane to give allylic amine **20b** (27 mg, 92%) as colorless oil. R_f (50% EtOAc/hexane) = 0.36; $[\alpha]_D^{21}$ −116 (*c* 0.87, $CHCl_3$); IR (thin film, cm^{-1}) 3323, 2962, 2936, 2876, 2484 (weak, broad), 1614, 1514, 1471, 1248, 1179, 1023, 1016, 824; ^1H NMR (600 MHz, CD_3OD): δ 7.26 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 9.0 Hz, 2H), 5.78 (ddd, J = 10.2, 0.6, 0.6 Hz, 1H), 5.75 (ddd, J = 10.2, 2.4, 2.4 Hz, 1H), 5.04 (s, 1H), 4.69 (d, J = 11.4 Hz, 1H), 4.49 (d, J = 11.4 Hz, 1H), 4.10 (dd, J = 9.6, 1.2 Hz, 1H), 3.78 (s, 3H), 3.61 (ddd, J = 9.6, 9.6, 1.8 Hz, 1H), 1.66–1.62 (m, 1H), 1.49–1.39 (m, 3H), 0.96 (dd, J = 7.2, 6.6 Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD): δ 161.1, 134.1, 131.4, 130.9, 127.8, 115.0, 94.6, 71.7, 70.8, 55.9, 50.1, 35.6, 20.1, 14.6; CIHRMS: calcd. for $[C_{16}H_{23}NO_3Na^+]$: 300.15701. Found 300.15704.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gresc.2022.03.003.

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