Stereoselective Aziridination

Direct Stereoselective Aziridination of Cyclohexenols with 3-Amino-2-(trifluoromethyl)quinazolin-4(3H)-one in the Synthesis of Cyclitol Aziridine Glycosidase Inhibitors

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Abstract: Cyclophellitol aziridine and its configurational and functional isomers are powerful covalent inhibitors of retaining glycosidases, and find application in fundamental studies on glycosidases, amongst others in relation to inherited lysosomal storage disorders caused by glycosidase malfunctioning. Few direct and stereoselective aziridination methodologies are known for the synthesis of cyclophellitol aziridines. Herein, we present our studies on the scope of direct 3-amino-2-(trifluoromethyl)quinazolin-4(3H)-one-mediated aziridination on a variety of configurational and functional cyclohexenol isomers. We demonstrate that the aziridination can be directed by an allylic or homoallylic hydroxyl through H-bonding and that steric hindrance plays a key role in the diastereoselectivity of the reaction.

Introduction

Glycosidases are enzymes involved in the degradation of complex glycoconjugates in nature and are of relevance both in biomedicine and biotechnology.[1] Many glycosidases follow a two-step Koshland double displacement mechanism, which involves a covalent enzyme-glycoside intermediate.[2] The active site of such retaining glycosidases is usually composed of an aspartic acid or glutamic acid, termed the catalytic acid/base, and an aspartate/glutamate (or occasionally a tyrosine) termed the nucleophile. In the first step of substrate hydrolysis, the exocyclic oxygen is protonated by the acid/base residue. Next, the catalytic nucleophile attacks at the anomeric carbon and effects an SN2 displacement of the aglycon, yielding a covalent enzyme–glycoside complex with inversion of the anomeric stereochemistry.

In the second step, a water molecule is deprotonated by the acid/base carboxylate and hydrolyses the enzyme-substrate intermediate with a second inversion of the anomeric configuration (Figure 1A).[3] Cyclitol aziridines can mimic the conformation of the oxocarbenium ion transition state and irreversibly

![Figure 1. A) Koshland double displacement mechanism of retaining β-glycosidases. B) Cyclophellitol aziridines are 4H3 transition-state mimics and inhibit covalently and irreversibly retaining β-glycosidases.](image)

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201801703.

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Eur. J. Org. Chem. 0000, 0–0

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inactivate glycosidases by covalently reacting with the nucleophilic carboxylate (Figure 1B). Based on this virtue and the fact, as supported by several studies in recent years from our group,[4] that covalent and irreversible inhibition is often both very effective and highly selective, cyclolet aziridines and their corresponding activity-based probes (ABPs) are highly useful tools for chemical glycobiology research.[5]

An important step in the synthesis of cyclolet aziridine inhibitors and ABPs involves the stereoselective aziridination of a suitable cyclohexene precursor.[6] In contrast to epoxidations, synthetic methodologies for the direct and stereoselective aziridination of alkenes are scarce.[7] Our previous work on the synthesis of cyclophellit aziridines relied mostly on either intramolecular iodocyclization followed by aziridine formation (Figure 2A)[5a-c,d] or Staudinger-type ring closure of 1,2-azidoalcohols obtained from an epoxide precursor (Figure 2B).[5b] We also investigated the use of O-(2,4-dinitrophenyl)hydroxylamine (DPH) as nitrogen donor with Rh2(esp)2 as catalyst (Figure 2C).[8] However, some limitations were encountered with these methodologies. Although the iodocyclization/intramolecular substitution sequence gives complete stereochemical control with reasonable to good overall yields, this sequence is not an operationally simple sequence gives complete stereochemical control with reasonable to good overall yields, this sequence is not an operationally simple alternative (Scheme 1). Notably, the α-L-iduronidase inhibitors and ABPs, as we recently reported in a separate body of work,[13]

Results and Discussion

As the first research objective, D-glucos-configured cyclohexene 1a was used as starting material to screen the most promising aminoquinazolinolones described as nitrogen donors in the literature: 3-amino-2-ethylquinazolin-4(3H)-one (Et-Q-NH2), 3-amino-2-(trifluoromethyl)quinazolin-4(3H)-one (CF3-Q-NH2) and the chiral (S)-3-amino-2-(1-hydroxy-2,2-dimethylpropyl)quinazol-4(3H)-one (HO-Q-NH2), which all form in situ the reactive N-acetoxyaminoquinazolinolone in the presence of PIDA. In line with previous results,[12a] CF3-Q-NH2 gave superior yields (69–75% of 1b) when using cyclohexene 1a, PIDA and the quinazolinone in a 1:2:2 ratio respectively and by forming the reactive N-acetoxyaminoquinazolinolone at −78 °C prior to addition of the olefin at −23 °C. Aziridine intermediate 1d was isolated in 54% yield when using HO-Q-NH2 as aziridination agent, whereas reaction with Et-Q-NH2 returned starting material only (Scheme 1). Notably, the β-galacto-configured aziridine was formed stereoselectively in a 1.5 mmol reaction scale, indicating that hydrogen bonding from the homoallyl alcohol C7-OH guides the incoming Q+NHOAc, in agreement with the mechanistic proposal of Atkinson et al. (Scheme 2).[12a] These results...
led us to further investigate aziridinations with CF₃-Q-NH₂ on different cyclohexene substrates.

When gluco-configured cyclohexene 2a bearing a 4,6-benzylidene acetal and an allylic alcohol at C-2 was used, α-aziridine 2b was exclusively formed in 55% yield, providing further support for H-bonding guided delivery of the aziridinating reagent (Scheme 2). When perbenzylated gluco-cyclohexene 3a was subjected to the same reaction conditions no conversion was observed, indicating that the system is not reactive enough without the hydrogen bonding guided delivery and/or that the double bond, with relatively bulky substituents on either side of the alkene, is too crowded to allow for an effective addition. A similar pattern was observed with galacto-configured cyclohexenes. Galacto-configured cyclohexene 4a could be stereoselectively transformed into β-aziridine 4b while cyclohexene 5a afforded α-aziridine 5b in 61% yield (Scheme 3). These examples again illustrate the impact of neighboring (homo)allylic alcohol functionalities. Partially protected conduritol 6a was also amenable to stereoselective aziridination, affording β-aziridine 6b in 66% yield, whereas the starting material was recovered when the reaction was performed with perbenzylated conduritol 7a (Scheme 4).
In order to investigate whether an alcohol further away from the alkene could guide the reagent to one of the diastereotopic faces of the double bond, we examined the aziridination of partially protected xylo-configured cyclohexene \( 8a \). In this case only \( \beta \)-isomer \( 8b \) was obtained, indicating that the 4-\( \text{OH} \) is too distal for a productive H-bond interaction and that the aziridination takes place on the least hindered face of the double bond, opposite of the C-2-benzyl ether (Scheme 5).

Scheme 5. Proposed reaction transition state driven by steric hindrance of \( \alpha \)-ido-configured cyclohexenes in order to obtain \( \alpha \)-L-ido-configured aziridines as potential intermediates for the development of new iduronidase inhibitors.\(^{[15]} \) Partially protected cyclohexene \( 9a \) was not amenable to aziridination, possibly because the primary alcohol directs to the beta side while this region may be hindered by the allylic benzyl ether. Considering that \( \beta \)-D-xylo-configured aziridine \( 8a \) was obtained without H-bonding, we postulated H-bonding would not be essential for a satisfactory aziridination in case the double bond is readily accessible. To test this hypothesis, the free alcohols in \( 9a \) were benzylated (benzyl bromide, sodium hydride) to generate cyclohexene \( 10a \). From this fully protected cyclohexenol, \( \alpha \)-L-aziridine \( 10b \) was obtained in 43% yield together with 32% recovered starting material \( S.M. \). In this case a productive H-bond interaction and that the aziridination takes place on the least hindered face of the double bond, opposite of the C-2-benzyl ether (Scheme 5).

We finally explored aziridination of L-ido-configured cyclohexenes in order to obtain \( \alpha \)-L-ido-configured aziridines as potential intermediates for the development of new iduronidase inhibitors.\(^{[15]} \) Partially protected cyclohexene \( 9a \) was not amenable to aziridination, possibly because the primary alcohol directs to the beta side while this region may be hindered by the allylic benzyl ether. Considering that \( \beta \)-D-xylo-configured aziridine \( 8a \) was obtained without H-bonding, we postulated H-bonding would not be essential for a satisfactory aziridination in case the double bond is readily accessible. To test this hypothesis, the free alcohols in \( 9a \) were benzylated (benzyl bromide, sodium hydride) to generate cyclohexene \( 10a \). From this fully protected cyclohexenol, \( \alpha \)-L-aziridine \( 10b \) was obtained in 43% yield together with 32% recovered starting material \( S.M. \) after direct aziridination reaction, and subsequent deprotection under Birch conditions. Reagents and conditions: (i) Ph(OAc)\(_2\), CF\(_3\)-Q-NH, DCM, r.t., 48 h; (ii) Li, NH\(_3\) (liq.), THF, –60 °C, 1 h.

In all cases, one step deprotection of the aziridine and hydroxyls in the aforementioned CF\(_3\)-Q functionalized aziridine intermediates was achieved under Birch conditions using lithium and liquid ammonia at –78 °C. The reactions were quenched with \( \text{H_2O} \) and impurities derived from CF\(_3\)-Q precipitated and were removed by filtration. The cyclitol aziridines were finally obtained in excellent yields after cation-exchange chromatography with Amberlite H\(^+\) resin to eliminate the lithium hydroxide salts (Table 1, 81–99%).

**Conclusions**

We have explored direct aziridination of both, partially protected and fully protected, configurational cyclohexenol using different substituted 3-aminoquinazolin-4(3H)-ones. From these studies we identified 3-amino-2-(trifluoromethyl)quinazolin-4(3H)-one as the superior aziridinating agent. Using this reagent, direct aziridination reaction can be applied on diverse glycoside configured cyclohexenes, and it appears that aziridination can be directed by allylic or homoallylic hydroxyls through H-bonding and that steric hindrance plays an essential role in the diastereoselectivity of the reaction. With this in mind, one could tune the cyclohexene scaffold depending on the desired configuration of the target aziridine and thus, synthesize diverse glycosidase inhibitors effectively in asymmetric fashion.

**Experimental Section**

**General methods and materials:** All reagents were of a commercial grade and were used as received unless stated otherwise. Dichloromethane (DCM), tetrahydrofuran (THF) and \( N,N \)-dimethylformamide (DMF) were stored over 4 Å molecular sieves, which were dried in vacuo before use. All reactions were performed under an argon atmosphere unless stated otherwise. Reactions were monitored by analytical thin-layer chromatography (TLC) using Merck aluminum sheets pre-coated with silica gel 60 with detection by UV absorption (254 nm) and by spraying with a solution of \((\text{NH}_4)_6\text{Mo}_7\text{O}_{24} \cdot \text{H}_2\text{O} (25 \text{ g/L}) \) and \((\text{NH}_4)_2\text{Ce(SO}_4)_3 \cdot \text{H}_2\text{O} (10 \text{ g/L})\) in 10% sulfuric acid followed by charring at ca. 150 °C or by spraying with an aqueous solution of KMnO\(_4\) (7 %) and K\(_2\)CO\(_3\) (2 %) followed by charring at ca. 150 °C. Column chromatography was performed manually or with a Biotage Isolera™ flash purification system using silica gel cartridges (Screening devices SiliaSep HR, particle size 15–
40 μm, 60A) in the indicated solvents. 1H NMR and 13C NMR spectra were recorded on Bruker AV-400 (400/101 MHz) and Bruker AV-500 (500/126 MHz) spectrometer in the given solvent. Chemical shifts are given in ppm relative to the chloroform residual solvent peak or tetramethylsilane (TMS) as internal standard. Coupling constants are given in Hz. All given 13C spectra are proton decoupled. The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), br (broad), Ar (aromatic), Cq (quaternary carbon), Q (quinoxaline). 2D NMR experiments (HSQC, COSY and NOESY) were carried out to assign protons and carbons of the new structures. High-resolution mass spectra (HRMS) of intermediates were recorded with a LTQ Orbitrap (Thermo Finnigan) and final compounds were recorded with an apex-QE instrument (Bruker). Optical rotations were measured on an Anton Paar MCP automatic polarimeter (Sodium D-line, λ = 589 nm). LC/MS analysis was performed on an LCQ Advantage Max (Thermo Finnigan) ion-trap spectrometer (ESI) coupled to a Surveyor HPLC system (Thermo Finnigan) equipped with a C18 column (Gemini, 4.6 mm × 50 mm, 3 μm particle size, Phenomenex) equipped with buffers A: H2O, B: acetonitrile (MeCN) and C: 1% aqueous TFA, or an Agilent Technologies 1200 Infinity LCMS with a 6120 Quadrupole MS system equipped with buffers A: H2O, B: acetonitrile (MeCN) and C: 100 mM NH4OAc. Buffers A: H2O, B: acetonitrile (MeCN) and C: 100 mM NH4OAc.

β-D-gluco-cyclitol CF3-Q-aziridine (1b): Obtained from cyclohexene 1a (487 mg, 1.40 mmol) as an orange oil in 75% yield (609 mg, 1.07 mmol). 1H NMR (400 MHz, CDCl3): δ = 8.15 (dt, J = 8.1, 1.1 Hz, 1H, CH-Q), 7.86–7.80 (m, 2H, 2 × CH Q), 7.60 (ddd, J = 8.2, 5.0, 3.3 Hz, 1H, CH-Q), 7.70–7.30 (m, 7H, 7 × CH Ar), 7.18 (t, J = 7.7, 2H, 2 × CH Ar), 6.99–6.91 (m, 1H, CH Ar), 4.97 (d, J = 11.2, 1H, CH-QPhPh), 4.75 (d, J = 11.4 Hz, 1H, CH-QPhPh), 4.69 (dd, J = 11.4, 3.4 Hz, 2H, 2 × CH-QPhPh), 4.42 (dd, J = 7.3, 3.4 Hz, 1H, CH-Q), 4.03 (dd, J = 11.0, 6.7 Hz, 1H, CH-Q), 3.92 (d, J = 8.2 Hz, 1H, CH-Q), 3.84 (dd, J = 11.0, 6.1 Hz, 1H-CH-Q), 3.70 (d, J = 7.3 Hz, 1H-CH-Q), 3.50 (t, J = 10.0 Hz, 1H-CH-Q), 3.38 (dd, J = 10.0, 8.2 Hz, 1H-CH-Q), 3.16 (br s, 1H, OH-Q), 2.96 (br s, 1H, OH-Q), 2.14 (dd, J = 10.0, 6.4, 3.4 Hz, 1H-CH-Q).

β-D-gluco-cyclitol OH-Q-aziridine (1d): Obtained from cyclohexene 1a (507 mg, 1.49 mmol) as an orange oil in 51 % yield (443 mg, 0.76 mmol). 1H NMR (400 MHz, CDCl3): δ = 8.21 (dd, J = 8.1 Hz, 1H-CH-Q), 7.81–7.73 (m, 1H, CH-Q), 7.71–7.66 (m, 1H, CH-Q), 7.54–7.47 (m, 1H, CH-Q), 7.74–7.42 (m, 2H, 2 × CH Ar), 7.37–7.30 (m, 8H, 8 × CH Ar), 5.06–5.01 (m, 1H, CH-QPhPh), 4.99 (d, J = 11.1 Hz, 1H, CH-QPhPh), 4.79 (s, 1H, OH-Q), 4.76–4.69 (m, 2H, 2 × CH-QPhPh), 4.27–4.06 (m, 3H, CH-QPhPh-b), 3.65–3.55 (m, 1H, OH-Q), 3.50–3.42 (m, 2H, CH-QPhPh-b), 2.76 (d, J = 8.0 Hz, 1H-CH-Q), 2.12 (ddd, J = 10.7, 7.4, 3.6 Hz, 1H-CH-Q), 1.02 (s, 9H, 3 × CH3).

α-D-gluco-cyclitol CF3-Q-aziridine (2b): Obtained from cyclohexene 2a (40 mg, 0.161 mmol) as an orange oil in 55% yield (43 mg, 0.089 mmol). 1H NMR (500 MHz, CDCl3): δ = 8.21 (d, J = 7.7 Hz, 1H-CH-Q), 7.90–7.80 (m, 2H, 2 × CH-Q), 7.62 (ddd, J = 8.2, 6.2, 2.1 Hz, 1H, CH-Q), 7.50 (dd, J = 7.6, 2.1 Hz, 2H, 2 × CH Ar), 7.42–7.33 (m, 3H, 3 × CH Ar), 5.54 (s, 1H, CH-QPhPh), 4.47 (dd, J = 10.7, 4.7 Hz, 1H-CH-Q), 4.10 (d, J = 7.2 Hz, 1H-CH-Q), 4.06 (dd, J = 7.2, 4.5 Hz, 1H-CH-Q), 3.84 (dd, J = 11.8, 10.7 Hz, 1H-CH-Q), 3.73 (ddd, J = 10.3, 7.8 Hz, 1H-CH-Q), 3.66 (br s, 1H-CH-Q), 3.45 (d, J = 7.2 Hz, 1H-CH-Q), 3.30 (t, J = 10.5 Hz, 1H-CH-Q), 2.85 (br s, 1H-CH-Q), 2.38 (br d, J = 12.0, 10.5, 4.7, 1.8 Hz, 1H-CH-Q).

α-D-gluco-cyclitol CF3-Q-aziridine (2b): Obtained from cyclohexene 2a (40 mg, 0.161 mmol) as an orange oil in 55% yield (43 mg, 0.089 mmol). 1H NMR (500 MHz, CDCl3): δ = 8.21 (d, J = 7.7 Hz, 1H-CH-Q), 7.90–7.80 (m, 2H, 2 × CH-Q), 7.62 (ddd, J = 8.2, 6.2, 2.1 Hz, 1H, CH-Q), 7.50 (dd, J = 7.6, 2.1 Hz, 2H, 2 × CH Ar), 7.42–7.33 (m, 3H, 3 × CH Ar), 5.54 (s, 1H, CH-QPhPh), 4.47 (dd, J = 10.7, 4.7 Hz, 1H-CH-Q), 4.10 (d, J = 7.2 Hz, 1H-CH-Q), 4.06 (dd, J = 7.2, 4.5 Hz, 1H-CH-Q), 3.84 (dd, J = 11.8, 10.7 Hz, 1H-CH-Q), 3.73 (ddd, J = 10.3, 7.8 Hz, 1H-CH-Q), 3.66 (br s, 1H-CH-Q), 3.45 (d, J = 7.2 Hz, 1H-CH-Q), 3.30 (t, J = 10.5 Hz, 1H-CH-Q), 2.85 (br s, 1H-CH-Q), 2.38 (br d, J = 12.0, 10.5, 4.7, 1.8 Hz, 1H-CH-Q).
β-D-galacto-cyclitol CF₃-Q-aziridine (4b): Obtained from cyclohexene 4a (470 mg, 2.05 mmol) as an orange oil in 49% yield (225 mg, 1.00 mmol) and 15% starting material recovered. \[^{[\alpha]}_D^{20} = +69.4\ (c = 0.5, \text{CHCl}_3).\] \(^1\)H NMR (400 MHz, CDCl₃): δ = 8.22–8.16 (d, J = 7.6 Hz, 1H, CH-1), 7.78–7.88 (m, 2H, 2× CH Q), 7.62 (dd, J = 8.2, 6.3, 2.1 Hz, 1H, CH Q), 7.42–7.21 (m, 9H, CH Ar), 7.15–7.07 (m, 1H, CH Ar), 4.93 (d, J = 10.9 Hz, 1H, CH(PH)), 4.78 (d, J = 11.6 Hz, 1H, CH(PH)), 4.76 (d, J = 10.8 Hz, 1H, CH(PH)), 4.67 (d, J = 11.8 Hz, 1H, CH(PH)), 4.29 (d, J = 8.6 Hz, 1H, CH-2), 4.23 (dd, J = 11.6, 8.2 Hz, 1H, CH-7a), 4.10 (br s, 1H, CH-4), 3.99 (dd, J = 11.6, 5.8 Hz, 1H, CH-7b), 3.94 (dd, J = 7.9, 3.0 Hz, 1H, CH-6), 3.53 (br s, 1H, OH), 3.45–3.36 (m, 2H, CH-1, CH-3), 2.65 (d, J = 8.0 Hz, 1H, OH), 2.19 (s, 3H, CH₃-3), 1.22 (d, J = 6.3 Hz, 3H, CH₃-2). \(^{13}\)C NMR (101 MHz, CDCl₃): δ = 160.1 (C=O), 143.5 (C₃), 141.4 (q, J = 35.5 Hz, CCF₃), 138.0 (C₈ Ph), 137.9 (C₉ Ph), 135.3, 129.8, 128.6, 128.5, 128.4, 128.1, 127.9, 126.9 (10 × CH Ar, 4 × CH Q), 122.8 (C₇ Q), 118.1 (q, JCF₃ = 275.0 Hz, CF₃), 82.9 (C-3), 77.5 (C-2), 74.8 (CH(PH)), 71.9 (CH(PH)), 67.3 (C₄), 61.9 (C-7), 49.1 (C-1), 44.0 (C-6), 41.0 (C-5). HRMS: calcd. for [C₃₀H₂₈F₃N₃NaO₅]⁺: 568.2059, found 568.2061; calcd. for [C₃₀H₂₈F₃N₃NaO₅]⁺: 560.1879, found 550.1882.

α-Lido-cyclitol CF₂-C-Q-aziridine (10b): Obtained from cyclohexene 10a (2.9 g, 5.57 mmol) as an orange oil in 43% yield 1.75 g, 2.40 mmol). \[^{[\alpha]}_D^{20} = +1.2 (c = 1, CHCl₃).\] \(^1\)H NMR (400 MHz, CDCl₃): δ = 8.25 (d, J = 7.9 Hz, 1H, CH Ar), 7.87 (d, J = 3.6 Hz, 2H, 2× CH Ar), 7.67–7.63 (m, 1H, CH Ar), 7.49–7.25 (m, 19H, 19× CH Ar), 7.14 (t, J = 7.4 Hz, 1H, CH Ar), 4.87 (d, J = 11.1 Hz, 1H, CH(PH)), 4.84 (s, 2H, 2× CH(PH)), 4.78 (d, J = 11.1 Hz, 1H, CH(PH)), 4.67–4.57 (m, 3H, 3× CH(PH)), 4.22 (d, J = 7.3 Hz, 1H, CH-6), 4.06 (d, J = 7.0 Hz, 1H, CH-7), 4.00 (d, J = 7.4 Hz, 1H, CH-1), 3.98–3.96 (m, 1H, CH(PH)), 3.78–3.69 (m, 3H, 3× CH-4, CH-4), 2.99–2.93 (m, 1H, CH-S). \(^{13}\)C NMR (101 MHz, CDCl₃): δ = 160.7 (C₇ O), 144.0 (C₉ Ar), 143.4 (q, J = 34.1 Hz, CCF₃), 139.0, 138.6, 138.3, 138.1 (C₄ Ar), 134.9, 129.3, 128.6, 128.4, 128.0, 127.9, 127.8, 127.7, 126.7, 126.6 (20 × CH Ar, 4 × CH Q), 123.2 (C₉ Q), 118.2 (q, JCF₃ = 276.8 Hz, CF₃), 80.7 (C-4), 80.2 (C-3), 76.0 (C-4), 75.2, 73.4, 73.2 (4 × CH(PH)), 67.6 (C-7), 44.2 (C-6), 41.2 (C-1), 38.0 (C-5). HRMS: calcd. for [C₃₀H₂₈F₃N₃NaO₅]⁺: 748.29983, found 748.29901. HRMS: calcd. for [C₃₀H₂₈F₃N₃NaO₅]⁺: 770.28123, found 770.28076. Data in agreement with those previously reported.[11]

General procedure for aziridine deprotection: Ammonia (10 mL/ mmol of starting material) was condensed at ~60 °C. Lithium (15 equiv.) was added and the mixture was stirred until the ammonia was completely dissolved and a bright blue solution was observed. Then, a solution of protected aziridine dissolved in anhydrous THF (5 mL/mmol) was added dropwise. The reaction mixture was stirred for 1 h at ~60 °C and subsequently quenched with MeOH and mil-Q-H₂O. The solution was warmed to room temperature and stirred until the ammonia was evaporated. The reaction crude was concentrated in vacuo, redissolved in MilliQ-H₂O and filtered to remove orange solid impurities from CF₃-Q. The filtrate was neutralized with Amberlite IR-120 H⁺ and the aziridine product bound to the resin was washed with water (3 times) to remove Li salts and subsequently eluted with an aqueous 1 M NaOH solution, and concentrated under reduced pressure to afford the fully deprotected aziridine.

β-D-gluco-cyclitol aziridine (1c): Obtained from aziridine 1b (479 mg, 0.84 mmol) as an oil in 99% yield (146 mg, 0.83 mmol). \(^1\)H NMR (400 MHz, D₂O): δ = 3.94 (d, J = 10.9, 4.1 Hz, CH-7a), 3.70–3.58 (m, 2H, CH-7b, CH-2), 3.26 (dd, J = 10.2, 8.6 Hz, 1H, CH-3), 3.02 (t, J = 10.1 Hz, 1H, CH-4), 2.57 (dd, J = 6.1, 3.4 Hz, 1H, CH-6), 2.29 (d, J = 6.2 Hz, 1H, CH-1), 2.00 (m, 1H, CH-S). \(^{13}\)C NMR (101 MHz, D₂O): δ = 76.9 (C-3), 72.1 (C-2), 67.7 (C-4), 61.8 (C-7), 43.1 (C-5), 34.1 (C-1), 32.5 (C-6). Data in agreement with those previously reported.[22]

α-D-gluco-cyclitol aziridine (2c): Obtained from aziridine 2b (104 mg, 0.22 mmol) as an oil in 96% yield (37 mg, 0.21 mmol). \(^1\)H NMR (400 MHz, D₂O): δ = 3.87–3.77 (m, 2H), 3.69 (dd, J = 11.1, 6.4 Hz, 1H), 3.28 (dd, J = 10.3, 8.6 Hz, 1H), 3.19 (t, J = 10.1 Hz, 1H), 2.52 (dd, J = 6.4, 3.6 Hz, 1H), 2.30 (d, J = 6.4 Hz, 1H), 1.86–1.78 (m, 1H). Data in agreement with those previously reported.[23]
\(\beta\)-D-galacto-cyclitol aziridine (4c): Obtained from aziridine 4b (100 mg, 0.18 mmol) as an orange oil in 81% yield (25 mg, 0.14 mmol).\(^{1}\) H NMR (500 MHz, D\(_2\)O): \(\delta = 3.95\) (d, J = 8.4 Hz, 1H, CH-2), 3.83 (dd, J = 7.3, 1.0 Hz, 3H, CH\(_2\)OH, CH-4), 3.40 (dd, J = 8.3, 2.4 Hz, 1H, CH-3), 2.44–2.36 (m, 1H, CH-1), 2.35–2.27 (m, 1H, CH-6), 2.22–2.11 (m, 1H, CH-5).\(^{13}\) C NMR (126 MHz, D\(_2\)O): \(\delta = 76.0\) (C-3), 70.4 (C-2), 70.1 (C-4), 61.2 (CH\(_2\)), 39.2 (C-6), 34.4 (C-6), 31.9 (C-1). Data in agreement with those previously reported.\(^{[9]}\)

\(\alpha\)-D-galacto-cyclitol aziridine (5c): Obtained from aziridine 5b (622 mg, 1.31 mmol) as an oil in 85% yield (195 mg, 1.11 mmol).\(^{[1]}\) H NMR (400 MHz, D\(_2\)O): \(\delta = 6.3, 1.3\) Hz, 1H, CH-6), 1.93 (td, J = 7.5, 3.2, 1.3 Hz, CH-5).\(^{[13]}\) C NMR (126 MHz, D\(_2\)O): \(\delta = 72.6\) (C-3), 71.4 (C-4), 69.0 (C-2), 61.5 (C-7), 42.6 (C-5), 35.3 (C-1), 31.4 (C-6). Data in agreement with those previously reported.\(^{[20]}\)

Conduritol aziridine (6c): Obtained from aziridine 6b (100 mg, 0.16 mmol) as an oil in 99% yield (25 mg, 0.16 mmol).\(^{[1]}\) H NMR (500 MHz, D\(_2\)O): \(\delta = 3.90–3.84\) (m, 1H, CH-3), 3.71–3.67 (m, 1H, CH-5), 3.25–3.18 (m, 2H, CH-2, CH-4), 2.61 (dd, J = 6.2, 3.6 Hz, 1H, CH-3), 2.34 (d, J = 6.2 Hz, 1H, CH-1).\(^{[13]}\) C NMR (126 MHz, D\(_2\)O): \(\delta = 78.2\) (C-2/4), 74.7 (C-5), 74.1 (C-3), 73.5 (C-2/4), 37.9 (C-6), 37.4 (C-1). Data in agreement with those previously reported.\(^{[24]}\)

\(\beta\)-D-xylo-cyclitol aziridine (8c): Obtained from aziridine 8b (115 mg, 0.21 mmol) as an oil in 96% yield (30 mg, 0.20 mmol).\(^{[1]}\) H NMR (400 MHz, D\(_2\)O): \(\delta = 3.61\) (d, J = 8.3 Hz, 1H, CH-2), 3.34 (td, 1H, J = 10.5, 5.4 Hz, CH-4), 3.15 (dd, J = 10.3, 8.4 Hz, 1H, CH-3), 2.42 (br s, 1H, CH-6), 2.31 (dd, J = 13.8, 5.4, 1.6 Hz, 1H, CH-5a), 2.17 (d, J = 6.1 Hz, 1H, CH-1), 1.66 (dd, J = 14.0, 10.7, 3.3 Hz, 1H, CH-5b).\(^{[13]}\) C NMR (101 MHz, D\(_2\)O): \(\delta = 77.5\) (C-3), 72.6 (C-2), 66.2 (C-4), 34.5 (C-1), 31.3 (C-5), 30.8 (C-6). Data in agreement with those previously reported.\(^{[28]}\)

\(\alpha\)-Lido-cyclitol aziridine (10c): Obtained from aziridine 10b (1.79 g, 2.39 mmol) as an oil in 93% yield (389 mg, 2.22 mmol).\(^{[1]}\) H NMR (400 MHz, D\(_2\)O): \(\delta = 2.47\) (dd, 1H, J = 11.2, 4.4 Hz, 1H, CH-7a), 2.28–2.17 (m, 2H, CH-7b, CH-3), 2.11 (dd, J = 10.5, 5.6 Hz, 1H, CH-4), 1.98 (dd, J = 10.5, 7.4 Hz, 1H, CH-1), 1.07 (d, J = 6.0 Hz, 1H, CH-6), 1.01 (dt, J = 5.8, 5.1 Hz, 1H, CH-5), 0.77 (d, J = 6.0 Hz, 1H, CH-1).\(^{[13]}\) C NMR (101 MHz, D\(_2\)O): \(\delta = 76.0\) (C-2), 75.2 (C-3), 70.1 (C-4), 62.2 (C-7), 43.5 (C-5), 36.9 (C-1), 36.3 (C-6). HRMS: calcld. for [C\(_9\)H\(_8\)NO\(_2\)]\(^+\) 176.09228, found 176.09175. Data in agreement with those previously reported.\(^{[15]}\)

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

We thank The Netherlands Organization for Scientific Research (NWO-CW, ChemThem grant to J. M. F. G. A. and H. S. O.), the European Research Council (ERC-2011-AdG2920836 “Chembiospining”, to H. S. O.) and Sanofi Genzyme (research grant to J. M. F. G. A. and H. S. O. and postdoctoral contract to M. A.) for financial support.

Keywords: Stereoslective azidination - 3-amino-quinazolin-4(3H)-ones - Cyclopenhellit - Aziridines - Glycosidases - Glycosidase inhibitors
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Received: December 15, 2018
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Direct Stereoselective Aziridination of Cyclohexenols with 3-Amino-2-(trifluoromethyl)quinazolin-4(3H)-one in the Synthesis of Cyclitol Aziridine Glycosidase Inhibitors

This work describes direct aziridination reactions on differently substituted glycoside configured cyclohexenes with 3-amino-2-(trifluoromethyl)quinazolin-4(3H)-one as nitrogen donor. It is shown that aziridination can be directed by allylic or homoallylic hydroxyls through H-bonding, and that steric hindrance plays an essential role in the diastereoselective outcome of the final cyclitols aziridines.

DOI: 10.1002/ejoc.201801703