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Exploring the chemistry of bicyclic isoxazolidines for the multicomponent synthesis of glycomimetic building blocks

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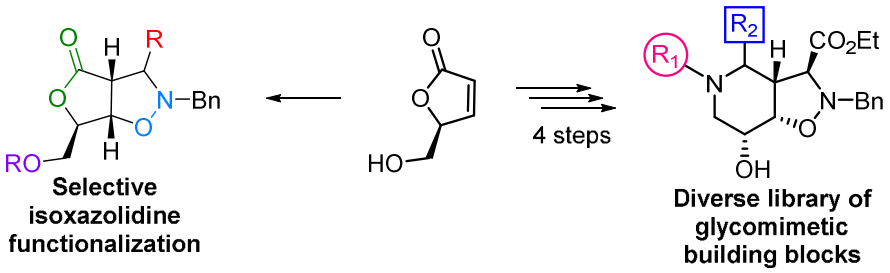
Abstract



Starting from a chiral furanone, the nitrone-olefin [3+2] cycloaddition can be used to obtain bicyclic isoxazolidines for which we report a set of reactions to selectively modify each functional position. These synthetically versatile bicyclic isoxazolidines allowed us to obtain complex glycomimetic building blocks, like iminosugars, *via* multicomponent chemistry. For example, a library of 20 pipecolic acid derivatives - a recurring motif in various prescription drugs - could be obtained *via* a one-pot Staudinger/aza-Wittig/Ugi three-component reaction of a bicyclic isoxazolidine-derived azido-hemiacetal. Notably, specific pipecolic acids in this library were obtained via hydrolysis of an unique tricyclic imidate side product of the Ugi-reaction. The azido-hemiacetal was also converted into an aza-*C*-glycoside iminosugar *via* an unprecendented one-pot Staudinger/aza-Wittig/Mannich reaction.

Introduction

Glycomimetics such as iminosugars and their derivatives are found in nature and display a wide variety of biological activities. For example, the archetypical glycomimetic 1-deoxynojirimycin (Figure 1), found in the leaves of the mulberry tree[1] and certain species of bacteria,[2] is a glycosidase inhibitor. Since the report of its identification and chemical synthesis in 1967,[3-5] the subsequent decades have witnessed a vast number of studies describing the synthesis and evaluation of biologically active glycomimetics. The value of these synthetic glycomimetics is evidenced by *N*-hydroxyethyl-1-deoxynojirimycin (Miglitol), a clinically used drug in the treatment of type 2 diabetes[6] that inhibits intestinal glucosidases, and by *N*-butyl-1-deoxynojirimycin (Miglustat), a glycosyl transferase inhibitor used in the clinic for the treatment of Gaucher disease.[7,8] Consequently, glycomimetics hold great promise for drug discovery. Key to enabling this is the development of synthetic methodology and novel glycomimetic building blocks to generate comprehensive and structurally diverse libraries of glycomimetics.

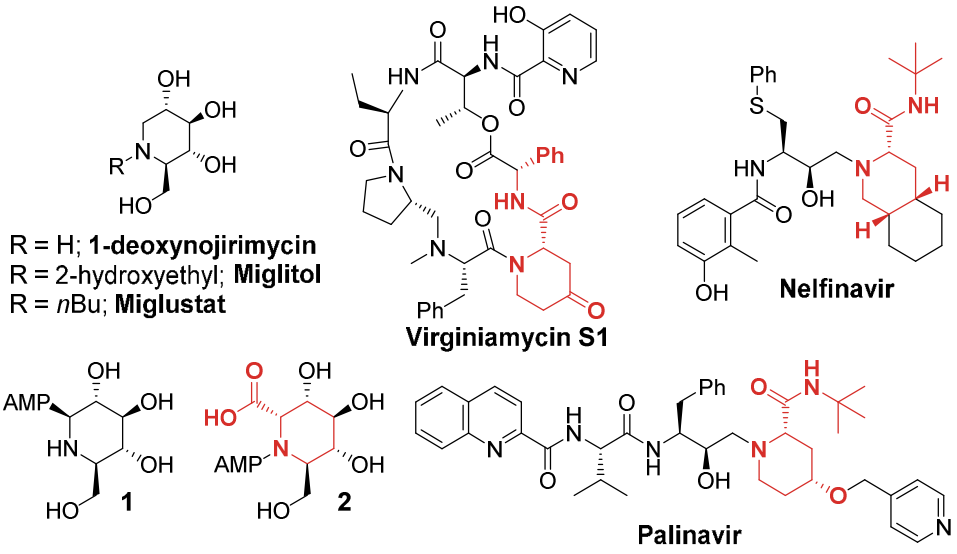


Figure 1. 1-Deoxynojirimycin with analogs thereof and notable examples of pipecolic acid derivatives (in red). AMP = 5-(adamantan-1-yl-methoxy)-pentyl.

In our ongoing synthetic investigation towards novel glycomimetics we are, among others, interested in developing aza-*C*-glycoside and pipecolic acid-based iminosugars. For example, we have previously reported on **1** and **2** (Figure 1), which are a more potent version of Miglustat[9] and a selective inhibitor of GBA2, respectively.[10] These types of iminosugars mimic the glycan and/or the aglycone part, and are thereby able to bind and inhibit the active site of specific carbohydrate-active enzymes. They can be constructed in several ways,[11-13] for example, we have shown previously that cyclic imines can be used in a Staudinger/aza-Wittig/Ugi three-component reaction (SAWU-3CR) to obtain pipecolic acid derivatives.[10] Alternatively, carbohydrate derived cyclic nitrones have also been used to obtain aza-*C*-glycosides through an 1,3-dipolar cycloaddition reaction.[14,15] However, this cycloaddition reaction has mainly been used to obtain bicyclic iminosugars. In contrast, the Ugi reaction, being a multicomponent reaction, is more suited to create libraries of diverse iminosugars.

The nitrone-olefin [3+2] cycloaddition could, in principle, be a useful reaction towards glycomimetic building blocks, since it can be used to install multiple neighboring stereogenic centers with high regio- and stereoselectivity in one step. The reaction has been studied extensively, however, most advances in its application towards high regio- and enantiospecific products provide *C*-aryl-substituted

isoxazolidines that often bear *N*-aryl groups. These products are synthetically less versatile for elaboration towards glycomimetics.[16,17]

One of the few examples of nitrones that do give rise to synthetically versatile cycloadducts are amino-acid derived nitrones **3a-b** (Figure 2). These nitrones bear a deprotectable *N*-substituent and either a masked carboxylic acid[18, 19] or masked aldehyde[20] that enable the synthesis of synthetically versatile isoxazolidines. In addition, the reaction has a large substrate scope, including several sugar-derived olefins. More specifically, olefin-containing D-mannitol-derived furanones **4** and **5** (Figure 2) functioned as the starting point for the current study.[21-24]

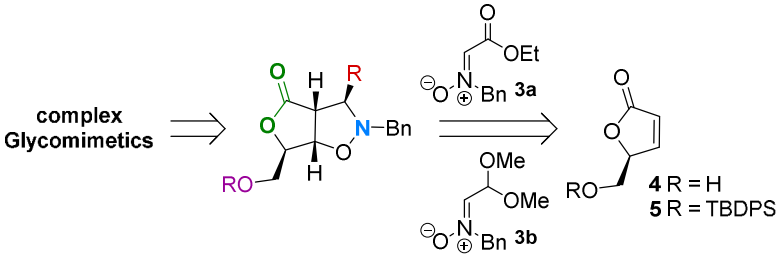


Figure 2. Complex glycomimetics may be obtained from bicyclic isoxazolidines, which provides many handles for further functionalization.

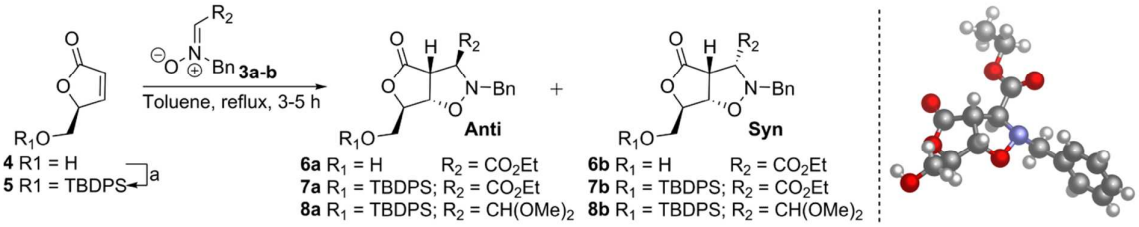
The nitrone-olefin [3+2] cycloaddition reaction with **4** and **5** has been reported to proceed with high regio- and diastereoselectivity, and to provide a chiral bicyclic isoxazolidine in good yield. We set out to explore the chemistry of these bicyclic isoxazolidines with the aim of creating a versatile chiral intermediate that can be used for the synthesis of glycomimetic building blocks based on pipecolic acid and aza-*C*-glycosides. Besides the earlier mentioned examples of clinically relevant iminosugars, these building blocks also represent important functional motifs in other drugs. Pipecolic acids are a recurring motif in, for example, Palinavir, Virginiamycin S1 and Nelfinavir (Figure 1). These drugs - used as protease inhibitors, antibiotics or in the treatment of HIV - all contain a piperidine-2-carboxamide motif, and are typically functionalized at the 4-position with either a chiral ether (Palinavir), ketone (Virginiamycin S1) or as part of a bicyclic system (Nelfinavir).

We here show that a versatile bicyclic isoxazolidine cycloadduct can be modified selectively at each functional position and subsequently transformed into a diverse range of pipecolic acid derivatives *via* a one-pot Staudinger/aza-Wittig/Ugi three-component reaction (SAWU-3CR). Finally, starting from the same isoxazolidine intermediate we synthesized an aza-*C*-glycoside via an unprecedented one-pot Staudinger/aza-Wittig/Mannich (SAWM) reaction.

Results and discussion

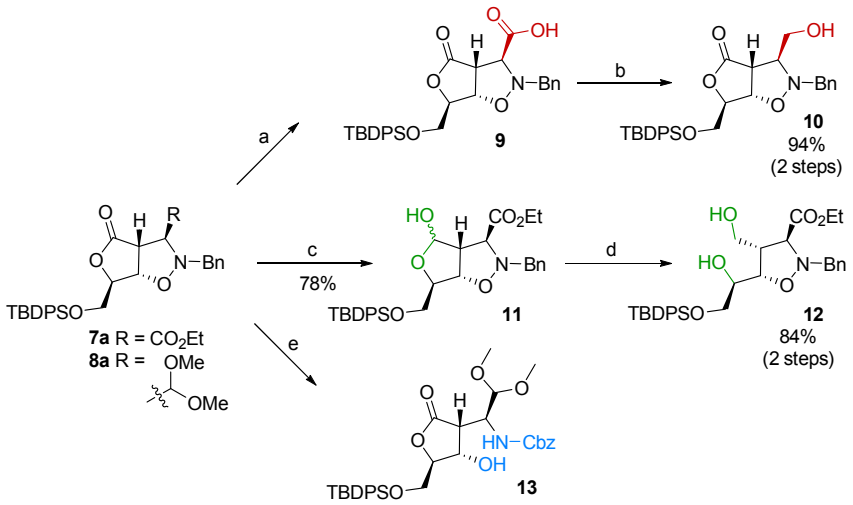
Our initial efforts focused on the product of the nitrone-olefin [3+2] cycloaddition between nitrone **3a** and furanone **5**, which provides known cycloadduct **7a** (Scheme 1, left). This bicyclic isoxazolidine was first reported by Ondrus et al., but has never been functionalized further.[25] Ondrus and coworkers reported that the selectivity of the cycloaddition reaction can be controlled by changing the *E*/*Z*-ratio of the nitrone, allowing the selective synthesis of either the *syn*- **7b** or *anti*-product **7a**. We explored if this selectivity could be further improved and succeeded in increasing the selectivity towards the main *anti*-product **7a** by using toluene as the solvent. By using this solvent compound **7a** was obtained in 68% yield, while providing **7b** (20%) as the minor compound (Scheme 1, left). Thus far the only reported assignment of the stereochemistry of this major diastereomer was based on NMR coupling constants.[25] We succeeded in crystallizing the closely related cycloadduct **6a** (Scheme 1) – obtained

through the reaction between furanone **4** and nitrone **3a** - that enabled the unequivocal assignment of the relative stereochemistry by X-ray crystal structure determination (Scheme 1, right).



Scheme 1. Cycloaddition reaction of furanone **4-5** with nitrone **3a-b** providing cycloadducts **6-8** (left). Molecular structure of major *anti*-cycloadduct **6a** in the crystal (right). Reaction conditions: a) TBDPSCl, imidazole, DMF, −10-20 °C, 4 h, 88%.

With the cycloaddition reaction optimized and the stereochemistry confirmed, we set out to selectively modify the newly created functional groups in the bicyclic isoxazolidine, namely the exocyclic ester, lactone and N-O bond. Initial attempts to hydrolyse the ethyl ester of cycloadduct **7a** under both basic (LiOH, ≤51% yield) and acidic conditions (HCl, 39% yield) provided the target carboxylic acid **9**, but only in mediocre yield due to degradation of the TBDPS group. Hydrolysis of the ester under neutral conditions proved more favourable as treatment with Me_3SnOH gave carboxylic acid **9** in almost quantitative yield (Scheme 2). The carboxylic acid could then be selectively reduced towards primary alcohol **10** in 94% over 2 steps by reducing an *in situ* formed mixed anhydride with sodium borohydride.



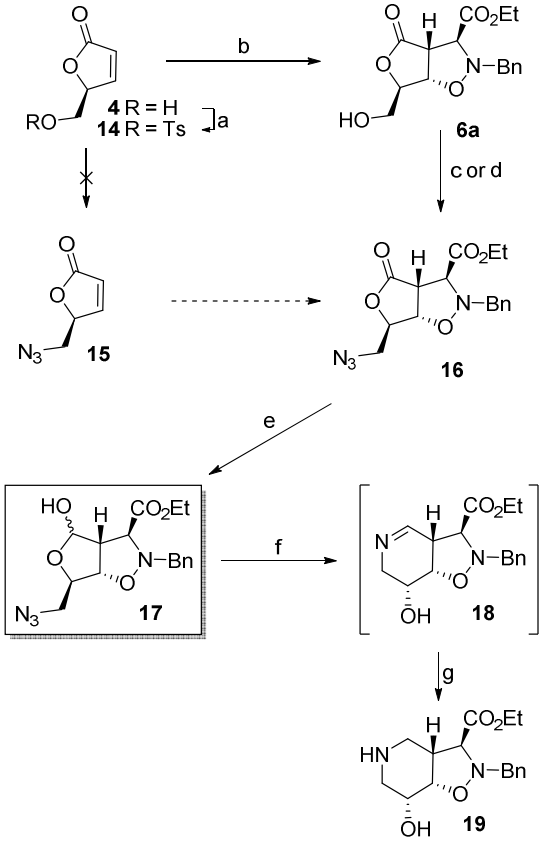
Scheme 2. Selective modification of functional positions in bicyclic isoxazolidine **7a** and **8a**. Reaction conditions: a) Me_3SnOH, $ClCH_2CH_2Cl$, reflux, 2.5 h; b) isobutyl chloroformate, $NaBH_4$, THF, DMF, −15 °C, 75 min., 94% over 2 steps; c) BH_3-SMe_2, THF, 4-20 °C, 3.5 h; d) $NaBH_4$, MeOH, −3-7 °C, 100 min., 84% over 2 steps; e) i. Raney-nickel, H_2 (1 bar), THF, rt, 7 h; ii. Pd/C, Cyclohexene, THF, reflux, 3 h; iii. CbzCl, $NaHCO_3$, THF/H_2O, rt, 14 h, 45%.

We next focused on selective modification of the lactone in **7a** and observed that its selective reduction is difficult due to the presence of the N-O bond, which is sensitive towards reducing agents. When employing DiBAL-H, L-selectride or $NaBH_4$ as reducing agents, mixtures of starting material, monoreduction towards the hemiacetal, overreduction towards the diol and additional byproducts were observed. However, by using BH_3-SMe_2 as the reducing agent, **7a** could be selectively reduced towards hemiacetal **11** in 78% yield, providing diol **12** (16%) as a minor product. In addition, diol **12** could be obtained in 84% yield over 2 steps by reducing crude hemiacetal **11** with $NaBH_4$ in MeOH at 0 °C.

Finally, we investigated cleaving the N-O bond in the isoxazolidine-ring through hydrogenation. Initial hydrogenolysis attempts on substrate **7a** with Pd/C or $Pd(OH)_2$ in MeOH under atmospheric pressure resulted in a very slow conversion. Complete hydrogenation of **7a** was only observed after several days at rt, at which point significant degradation had also occurred. Attempts to accelerate the reaction by using transfer hydrogenation conditions (HCO_2NH_4, Pd/C) or staged hydrogenation conditions, which we reported earlier for a similar compound,[20] resulted in side product formation and the target product proved to be unstable during isolation. MS analysis of the formed (side)products indicated that a significant amount of degradation could be attributed to β-elimination side reactions. We hypothesized that replacing one of the two carbonyl groups would prevent this side reaction and this spurred the development of our recently published novel nitrone **3b** bearing a acetal-masked aldehyde.[20] Cycloaddition of this nitrone with furanone **5** provided cycloadduct **8a** in 63% yield. Cycloadduct **8a** was then subjected to a staged hydrogenation with Raney-nickel, followed by a transfer hydrogenation with Pd/C in cyclohexene, to produce the amine that was protected *in situ* as a Cbz-carbamate to provide compound **13** in 45% yield over the three succesive transformations.

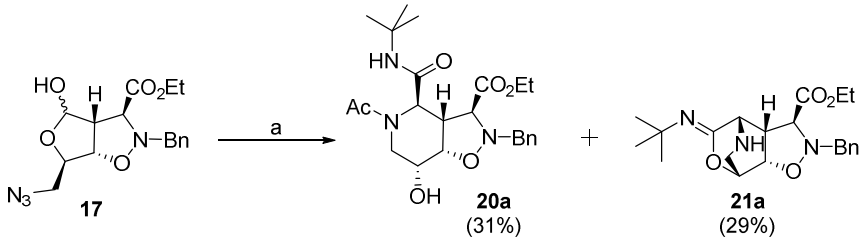
Encouraged by the versatile synthetic scope, our next aim was to synthesize a small library of functionalized glycomimetic building blocks from a common precursor derived from this bicyclic isoxazolidine. We envisioned that commercially available furanone **4** could be used to obtain azido-hemiacetal **17** in three to four steps (Scheme 3) that in turn could be used in the SAWU-3CR for the synthesis of a small library of pipecolic acid-based iminosugars.[26]

We initially focused on synthesising azido-cycloadduct **16** via azido-furanone **15** (Scheme 3), but it proved impossible to produce intermediate **15**, since conversion of **4** into **15** via a Mitsunobu reaction led to degradation. A two-stage reaction towards **15** via tosylate **14** was also unsuccessful. Compound **16** was however successfully prepared in 72% yield by installing the azide after the cycloaddition using a Mitsunobu reaction on the previously obtained cycloadduct **6a**. However, this reaction proved less reliable at larger scales, but we could obtain compound **16** reliably at a 19 gram scale in 89% yield by first converting compound **6a** to its mesylate, immediately followed by substitution with NaN_3. The lactone in **16** could then be selectively reduced to the target azido-hemiacetal **17** using BH_3-SMe_2.



Scheme 3. Synthesis of azido-hemiacetal **17**, precursor for the SAWU-3CR. Reaction conditions: a) TsCl, pyridine, DCM, −15-5 °C, 1 h, 70%; b) nitrone **3a**, toluene, reflux, 4.5 h, 55% (**6a**) & 31% (**6b**); c) $(PhO)_2P(O)N_3$, Diisopropyl azodicarboxylate, PPh_3, THF, −20-20 °C, 1.5 h, 72%; d) i. MsCl, Et_3N, DCM, 0 °C, 50 min. ii. NaN_3, DMF, 60 °C, 90 min., 89% over 2 steps; e) BH_3-SMe_2, THF, 4-20 °C, 7 h, 34%; f) PMe_3, THF, EtOH, 4 °C, 3 h; g) $(AcO)_3BHNa$, THF, 4 °C, 1.5 h, 66% over 2 steps.

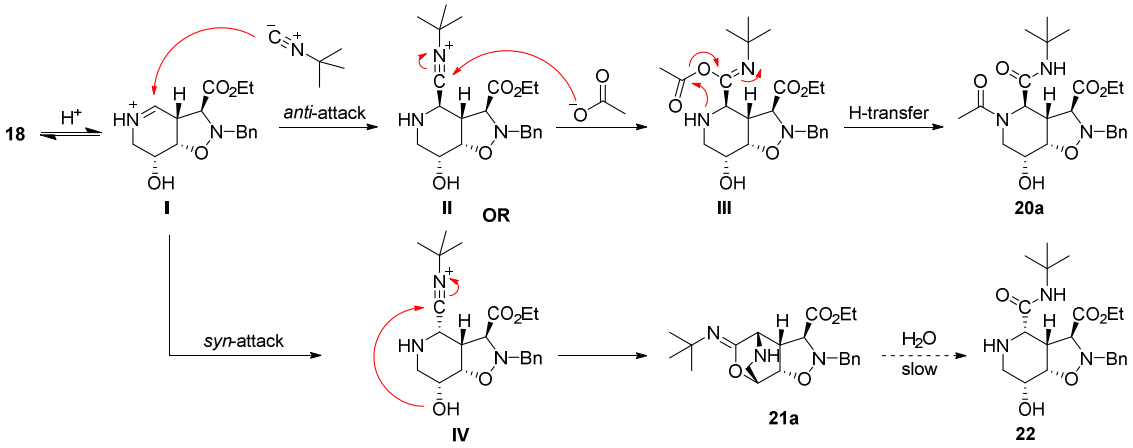
With the key intermediate (**17**) for the SAWU-3CR now in hand, the feasibility of this reaction was investigated by first attempting a tandem one-pot Staudinger/aza-Wittig-reaction. Hence, exposing compound **17** to PMe_3 gave cyclic imine **18** that could be directly converted to iminosugar **19** by reduction with $NaBH(OAc)_3$ in the same pot. Encouraged by these results, the complete SAWU-3CR sequence was performed on compound **17** with *tert*-butylisocyanide and acetic acid to give pipecolic acid **20a** as the major product (Scheme 4)**.**



Scheme 4. The SAWU-3CR with azido-hemiacetal **17.** Reaction conditions: a) i. PMe_3, EtOH, 4 °C, 3 h; ii. Acetic acid (1.25 equiv.), *t*butylisocyanide (1.25 equiv.), EtOH/TFE, 0-20 °C, 16 h, 60%, ratio **20a**:**21a** = 51:49.

However, in addition to the expected Ugi-product **20a** another product was also isolated in a considerable yield. Detailed analysis revealed this product to be compound **21a** that contains to the

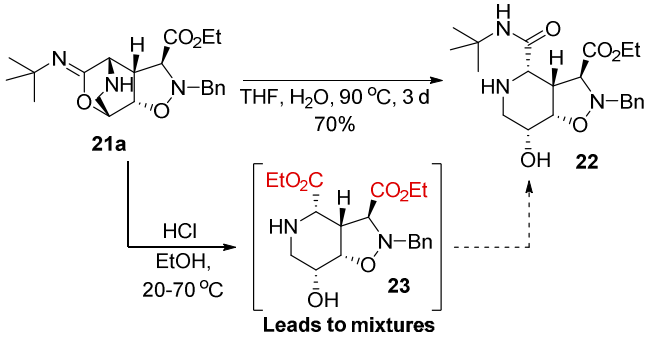
best of our knowledge an unprecedented tricyclic imidate (Scheme 4). We propose that **21a** results from an intramolecular side reaction during the Ugi-reaction. The different products obeserved in the Ugi-3CR of cyclic imine **18** result from the initial *syn*- or *anti*-attack of the isocyanide after imine protonation (Scheme 5). Compound **20a** is formed by an *anti*-attack by *tert*-butylisocyanide relative to the free alcohol. The resulting nitrilium ion intermediate **II** then undergoes the expected carboxylate attack and rearrangement seen in Ugi reactions.



Scheme 5. Reaction mechanism explaining the formation of *anti*-product **20a** and tricyclic imidate **21a**.

However, when the reaction proceeds *via* a *syn*-attack of the *tert*-butylisocyanide, the resulting nitrilium ion (**IV**) can also be attacked intramolecularly via a pseudo-boat conformation by the free alcohol instead of a carboxylate. Such a pseudo-boat conformation places the hydroxy group of **IV** in close proximity of the electrophilic carbon atom of the nitrilium ion, enabling the intramolecular attack. The required pseudo-boat conformation for the formation of cyclic imidate **21a** is actually the most stable conformation of the six-membered ring as determined by M11/6-311+g(d,p) density functional calculations (see supporting information for details and 3D images of this structure). We propose this is because of electrostatic stabilizing interactions between the lone pairs of the alcohol O atom and the partially positively charged C atom of the nitrilium group. In comparison, the chair conformations that have either the alcohol or the nitrilium moiety axial are several kcal/mol higher in energy. The resulting tricyclic compound **21a** is surprisingly stable, allowing purification by column chromatography and complete characterization.

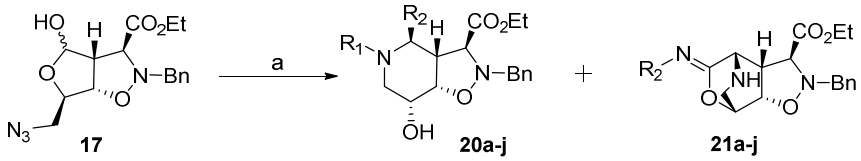
We serendipitously discovered that this side product (**21a**) hydrolyzed selectively over the course of several months towards amide **22**, the complementrary pipecolic acid with respect to **20a** (Scheme 5). We initially attempted to reproduce this process in a more practical time-frame using acid catalysis, which is typically used to convert imidates to the corresponding amides.[27-29] However, no conversion was observed at lower temperatures (20-25 °C), but the incomplete conversion to product **22** and a similar compound was observed at higher temperatures. We reasoned that the imidate of compound **21a** is first converted to an ethyl ester, similar to other published observations,[30-32] followed by the formation of the amide (Scheme 6). Indeed, by MS analysis the intermediate di-ester **23** was observed *in situ*, which was eventually converted to either the product **22**, or as we presume, the amide resulting from amide-bond formation with the original ester of compound **21a**, since the intermediate contains two ethyl esters that are probably equally reactive. Attempting the hydrolysis under basic conditions (NaOH), only led to degradation. However, when the hydrolysis of **21a** was performed under neutral conditions in a THF/water mixture at 90 °C in a closed vessel, product **22** was isolated in 70% yield.

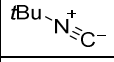
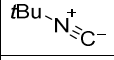
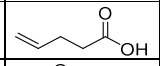
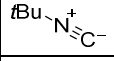
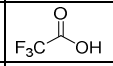
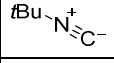
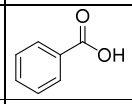
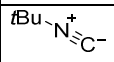
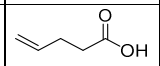
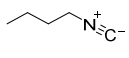
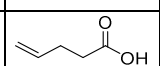
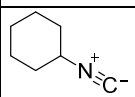
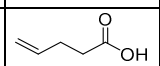
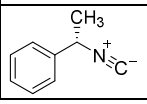


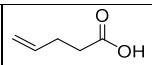
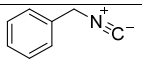
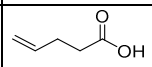
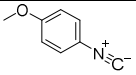
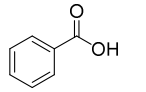
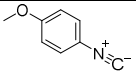
Scheme 6. Acid hydrolysis of imidate **21a** leads to mixtures, while hydrolysis under neutral conditions in THF/H_2O provides amide **22** in good yield.

These efficient conditions to obtain compound **22** from **21a** made it possible to obtain both pipecolic acid stereoisomers via the SAWU-3CR. Notably, the SAWU-3CR products **20** and **21** display very different retention times during chromatography, which makes purification relatively straightforward. Next, the scope of the SAWU-3CR was investigated with azido-hemiacetal **17**. To this end, we selected a diverse set of acids and isocyanides and subjected them to the SAWU-3CR with **17** (Table 1). We initially used a large excess of acid and isocyanide (3 equiv.; entry 1), but observed that the reaction actually benefited from using the acid and isocyanide in only a minor excess (1.25 equiv.; entry 2). These results were obtained by using acetic acid as the carboxylic acid, but when employing different acids similar or better yields were obtained (entries 3-5), indicating that the reaction tolerates a variety of acids.

Table 1. Substrate scope of the SAWU-3CR[a] with hemiacetal 17.



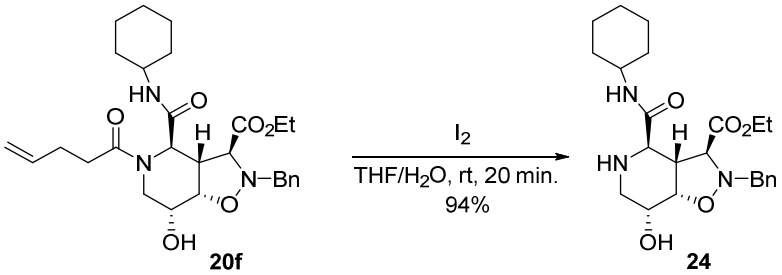
entry	acid	isocyanide	Product	yield[b]	ratio
1			**20a/21a**	53%[c]	56:44
2			**20a/21a**	60%	51:49
3			**20b/21a**	65%	46:54
4			**20c/21a**	76%	36:64
5			**20d/21a**	68%	48:52
6			**20e/21e**	54%	53:47
7a 7b			**20f/21f**	28% 79% (TFE)	1:0[d] 42:58
8			**20g/21g**	30%	56:44

9a 9b			**20h/21h**	20% 74% (TFE)	82:18 33:67
10a 10b			**20i/21i**	13% 59% (TFE)	1:0[d] 31:69
11			**20j/21i**	16%	1:0[d]

[a] Reaction conditions: a) i. PMe_3, EtOH, 4 °C, 3h; ii. Acid (1.25 equiv.), isocyanide (1.25 equiv.), EtOH/TFE, 0-20 °C, 16 h. [b] Isolated yield. [c] 3.00 equiv. of *t*butylisocyanide and acetic acid were used. [d] NMR showed only trace-amounts of the imidate when using EtOH as solvent. TFE = 2,2,2-trifluoroethanol

However, when primary, secondary and aromatic isocyanides were used we observed a significant drop in the reaction yields (entry 6-11). While the corresponding pipecolic acid derivatives **20e-j** could still be isolated in all cases, the tricyclic imidates **21e-j** were obtained in reduced yields or sometimes only observed as trace amounts in the reaction mixtures. It has been reported that unwanted side reactions during Ugi reactions can be suppressed by performing the reaction in the less nucleophilic solvent 2,2,2-trifluoroethanol (TFE) rather than in methanol.[33-36] The use of TFE as the solvent indeed resulted in significantly increased yields for the three selected reactions with a primary (entry 9b), secondary (entry 7b) and an even more challenging aromatic isocyanide (entry 10b), to 74, 79 and 59 % yield, respectively. Notably, the tricylclic imidates (**21f**, **21h**, **21i**) were now isolated as the major compounds. The observed effect of reaction conditions and components on the initial *syn*- or *anti*-attack of the isocyanides and resulting diastereoselectivity of the Ugi-3CR with cyclic imines has been reported before.[37,38] The complex multistep reaction mechanism and intermediates involved in the Ugi-3CR, however, prevent us from explaining the observed differences in the ratio of **20** and **21** when different solvents, carboxylic acids of isocyanides are employed. Remarkably, in a single case (entry 10b), a stable formamidine was isolated in 25% yield that probably resulted from attack of a second 4-methoxyisocyanide on the corresponding imidate **21i**, followed by a rearrangement (see supporting information for details).

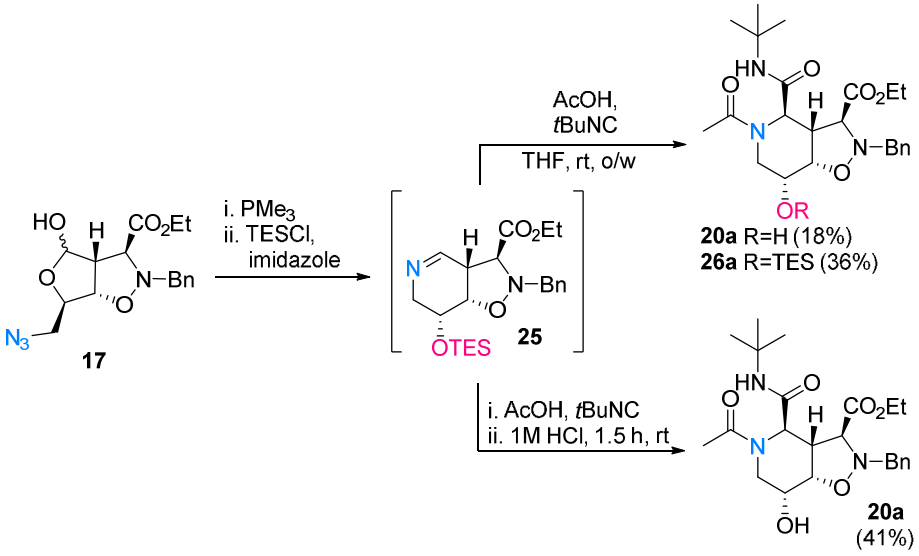
As shown above, imidate **21** can be conveniently hydrolyzed to provide the *syn*-product as a free amine, which provides a handle for further modification. Likewise, facile modification of the *anti*-product is also possible, since the 4-pentenoic handle – which is tolerated in the SAWU-3CR reaction – can be removed in almost quantitative yield (Scheme 7).



Scheme 7. Facile deprotection of *anti*-product **20f** to provide iminosugar **24**.

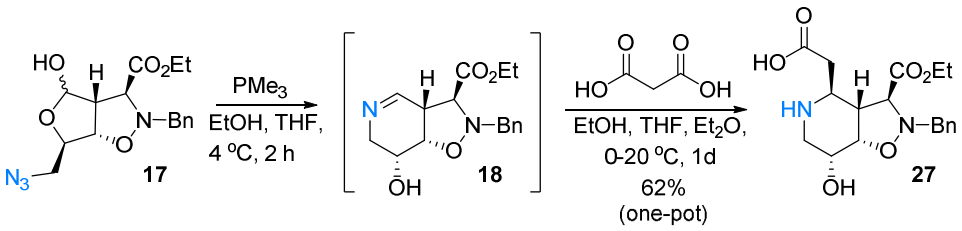
While the synthesis of both diastereomers *via* the SAWU-3CR is ideal for obtaining a diverse library of glycomimetic building blocks, we also wanted to explore the possibility of increasing the selectivity towards one of the SAWU-3CR products. We reasoned that the reaction could be made more selective towards the *anti*-product by introducing a bulky protecting group on the free hydroxyl group thus preventing *syn*-attack of an isocyanide. To this end, a one-pot procedure was developed in which the hydroxyl group that results from the Staudinger/aza-Wittig reaction was protected *in situ* as a TES

ether. The crude silyl-protected imine was then subjected to an Ugi reaction to selectively provide only *anti*-products in 53% as a mixture of **26a** and partially TES-deprotected **20a** (Scheme 8). *Anti*-product **20a** could also be obtained as the sole product in 41% by incorporating the TES-deprotection step *in situ*.



Scheme 8. *In situ* TES-protection of the cyclic imine results in selective *anti*-product formation.

Finally, we investigated if our Staudinger/aza-Wittig derived cyclic imine (**18**) could also be a suitable electrophile in other imine-mediated reactions, analogously to a recent paper describing the Staudinger/aza-Wittig/Grignard reaction.[39] To that end, we choose to investigate the Petasis and Mannich reaction, which both have not yet been used in conjunction with a Staudinger/aza-Wittig generated imine. While the Petasis reaction did not result in any conversion to the target product in our hands (see supporting information), we were able to modify imine **18** via a Mannich reaction. *In situ* treatment of **18** with malonic acid provided aza-C-glycoside **27** as a pure isomer in 62% yield after crystallization (Scheme 9).



Scheme 9. One-pot reaction of the Staudinger/aza-Wittig/Mannich (SAWM) reaction to give compound **27**.

Conclusion

In summary, the nitrone-olefin [3+2] cycloaddition reaction can be used to give highly functionalized bicylic isozazolidine cycloadducts in good yield and stereoselectivity. These cycloadducts are synthetically highly versatile and can be selectively modified at each functional position, which allows for the synthesis of a wide variety of glycomimetic building blocks. In this way it is possible to make a library of 20 pipecolic acid derivatives and an aza-*C*-glycoside by converting the bicyclic isozazolidine into an azido-hemiacetal, and using this in a one-pot Staudinger/aza-Wittig/Ugi three-component reaction (SAWU-3CR) or an unprecedented Staudinger/aza-Wittig/Mannich reaction

reaction. The SAWU-3CR on this azido-hemiacetal also produced an unprecedented tricyclic imidate that can be converted into corresponding pipecolic acid-based glycomimetic compounds.

Experimental Section

General information and methods

All moisture sensitive reactions were carried out under an argon atmosphere, using oven-dried glassware, unless otherwise stated. Dichloromethane (CH_2Cl_2, >99.8%) and toluene (>99.8%) were purified over aluminum oxide under argon using a solvent purification system. Reagents were obtained from commercial sources and used without further purification unless stated otherwise. Raney-Nickel was bought from commercial sources (W.R. Grace adn Co. Raney®; 2800, as a slurry in H_2O), which was washed with anhydrous THF three times before use. Palladium on carbon (Pd/C) was bought from commercial sources (10 wt. % loading, matrix activated carbon support). Analytical TLC was performed using prepared plates of silica gel (60 F-254 on aluminium) or aluminum oxide (60Å, F-254 on aluminum) and then, according to the functional groups present on the molecules, revealed with UV light or using staining reagents: ninhydrin (1.5% in *n*-BuOH with 3% AcOH) for amines or basic solution of $KMnO_4$ (1.0% in H_2O) for general staining. silica gel 60 (70–230 mesh) or aluminium oxide (0.05-0.15 mm particle size, neutral, Brockmann Activity grade I) was used for flash chromatography. ^{1}H NMR were recorded at 400 MHz and 500 MHz. ^{13}C NMR spectra were recorded at 100 MHz. Chemical shifts are reported in parts per million (ppm), calibrated on the residual peak of the solvent, whose values are referred to tetramethylsilane (TMS, $\delta_{TMS} = 0$) as the internal standard or the signal of the deuterated solvent. ^{13}C NMR spectra were performed with proton decoupling. Where indicated, NMR peak assignments were made using COSY and HSQC experiments. Electrospray ionization (ESI) mass analyses were performed on a mass spectrometer with a linear ion trap mass analyser, while high resolution ESI mass analyses were recorded on a Orbitrap high-resolution mass spectrometer. Infrared analyses were performed on a FT-IR spectrometer. Optical rotations were measured on a polarimeter (Sodium D-line, $\lambda = 589$ nm).

Ethyl (3a*R*,6*R*,6a*S*)-2-benzyl-6-(((tert-butyldiphenylsilyl)oxy)methyl)-4-oxohexahydrofuro[3,4-d]isoxazole-3-carboxylate (7)

A solution of nitrone **3a** (0.333 gr, 1.61 mmol, 1.14 equiv.) in toluene (9 mL) was heated to 40 °C for 2 hours, followed by the addition of furanone **2** (0.498 gr, 1.41 mmol, 1.0 equiv.) and additional toluene (3 mL). The reaction mixture was heated to reflux for 4 hours and then conc. *in vacuo*. The residue was purified via column chromatography (5-15% EtOAc in petroleum ether 40-60) afforded **7a** as a yellow oil (563 mg, 68%) R_F = 0.52 (8:2; PE:EtOAc) and **7b** (154 mg, 20%) as a yellow oil. R_F = 0.44 (8:2; PE:EtOAc). NMR signals of the major adduct **7a anti**:[a] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 – 7.55 (m, 4H), 7.51 – 7.23 (m, 11H), 4.87 (d, *J* = 6.3 Hz, 1H), 4.56 (d, *J* = 2.1 Hz, 1H), 4.26 (q, *J* = 7.2, 2H), 4.20 (s, 1H), 4.14 – 4.06 (m, 2H), 3.95 (s, 1H), 3.90 (dd, *J* = 11.6, 2.4 Hz, 1H), 3.73 (dd, *J* = 11.6, 1.9 Hz, 1H), 2.05 (s, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.04 (s, 9H). NMR signals of the major adduct **7b syn**:[a] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 – 7.54 (m, 4H), 7.48 – 7.27 (m, 11H), 4.91 (dd, *J* = 7.6, 1.7 Hz, 1H), 4.56 (q, *J* = 2.1 Hz, 1H), 4.35 – 4.24 (m, 3H), 3.92 – 3.76 (m, 3H), 3.76 – 3.66 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.02 (s, 9H). [a]NMR signals in accordance with NMR spectra by Ondrus et al.[25]

(3*S*,3a*R*,6*R*,6a*S*)-2-benzyl-6-(((tert-butyldiphenylsilyl)oxy)methyl)-3-(hydroxymethyl)tetrahydrofuro[3,4-d]isoxazol-4(2H)-one (10)

To a solution of ester **7a** (0.443 gr, 0.736 mmol, 1.0 equiv.) in 1,2-dichloroethane (11 mL) was added Me_3SnOH (0.540 gr, 2.99 mmol, 4.06 equiv.). The resulting suspension was heated to reflux for 2.5 h and then concentrated under a N_2 stream and then dissolved in EtOAc (50 mL). The organic layer was washed with 1M aq. HCl (5 mL, 2×), brine (5 mL), dried ($MgSO_4$) and then conc. *in vacuo*, affording crude compound **9**, which was used without further purification. A small sample of crude **9** was purified by flash column chromatography (5% MeOH in DCM) to obtain an analytically pure sample. R_F = 0.43 (10% MeOH in DCM). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.62 (ddd, *J* = 8.0, 2.6, 1.5 Hz, 4H), 7.49 – 7.30 (m, 11H), 4.83 (d, *J* = 6.5 Hz, 1H), 4.74 – 4.59 (m, 1H), 4.26 – 4.15 (m, 3H), 4.09 (d, *J* = 13.1 Hz, 1H), 3.92 (dd, *J* = 11.6, 2.6 Hz, 1H), 3.76 (dd, *J* = 11.6, 1.9 Hz, 1H), 1.04 (s, 9H). HRMS calcd for $C_{30}H_{32}O_6NSi - H^+$ [M−H$^+$]: 530.2004 Found 530.1997. Crude **9** was dissolved in dry THF (18 mL) and added to a flame-dried 3-neck round-bottom flask and cooled to −15 °C. To this solution was added isobutyl chloroformate (1.07 gr, 7.82 mmol, 10.0 equiv.), followed by the dropwise addition of a suspension of $NaBH_4$ (0.297 gr, 7.85 mmol, 10.0 equiv.) in DMF (7.0 mL) over 10 minutes. The resulting reaction mixture was stirred at −15 °C for 75 min. and then quenched with 1M aq. HCl (25 mL). The reaction mixture was extracted with EtOAc (75 mL, 25 mL, 2×). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$) and conc. *in vacuo*. The residue was purified by flash column chromatography (20-30% EtOAc in petroleum ether 40-60), affording compound **10** (385 mg, 94% over 2 steps) as a yellow oil, which crystallized upon standing. R_F = 0.32 (7:3; PE:EtOAc). mp = 109−110 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.67 – 7.58 (m, 4H), 7.50 – 7.37 (m, 6H), 7.37 – 7.27 (m, 5H), 4.73 (d, *J* = 6.5 Hz, 1H), 4.59 (t, *J* = 2.2 Hz, 1H), 4.12 – 4.00 (m, 2H), 3.91 (dd, *J* = 11.5, 2.5 Hz, 1H), 3.74 (dd, *J* = 11.6, 1.9 Hz, 1H), 3.72 – 3.62 (m, 3H), 3.44 (q, *J* = 3.8 Hz, 1H), 2.17 (s, 1H), 1.04 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.5, 136.5, 135.7, 135.6, 132.5, 132.0, 130.3, 130.2, 129.0, 128.7, 128.1, 128.1, 128.0, 83.0, 81.0, 70.6, 64.0, 62.2, 61.6, 52.8, 26.9, 19.2. FT-IR (neat): ν = 3282, 2931, 2859, 1775, 1427 cm^{-1}. HRMS calcd for $C_{30}H_{35}O_5NSi + Na^+$ [M+Na$^+$]: 540.2177 Found 540.2162. $[\alpha]_D^{20} = -32.0$ (*c* = 0.40, $CHCl_3$).

Ethyl (3*S*,3a*R*,6*R*,6a*S*)-2-benzyl-6-(((tert-butyldiphenylsilyl)oxy)methyl)-4-hydroxyhexahydrofuro[3,4-d]isoxazole-3-carboxylate (11) and **ethyl (3*S*,4*S*,5*S*)-2-benzyl-5-((*R*)-2-((tert-butyldiphenylsilyl)oxy)-1-hydroxyethyl)-4-(hydroxymethyl)isoxazolidine-3-carboxylate (12)**.

To a round-bottom flask containing cycloadduct **7a** (0.404 g, 0.722 mmol, 1.0 equiv.) at 4 °C was added a cold (4 °C) 2M solution of BH_3-SMe2 in THF (4.00 ml, 8.00 mmol, 11.1 equiv.). The mixture was allowed to warm to room temperature and stirred for 3.5 hours and quenched by carefully adding MeOH (0.30 ml). The mixture was concentrated *in vacuo* to afford the crude as a mixture of compound **11** and **12** (0.392 g) as a colourless oil, which was generally used to obtain compound **12** without further purification. Optionally, the crude could be purified by flash column chromatography (30-50% EtOAc in petroleum ether 40-60), affording an anomeric mixture of hemiacetal **11** (320 mg, 78%) as a colourless oil (HRMS calcd for $C_{32}H_{39}O_6NSi + Na^+$ [M+Na^+]: 584.2439 Found 584.2429) R_F = 0.57 (7:3; PE:EtOAc) and diol **12** (60 mg, 16%) as a colourless oil.

Hemiacetal **11** (0.100 g, 162 mmol, 1.0 equiv.) was dissolved in MeOH (3.0 ml) and cooled to −2 °C, $NaBH_4$ (13.5 mg, 0.357 mmol, 2.0 equiv.) was added and the resulting solution was then stirred at −3-7°C for 1 h. Additional $NaBH_4$ (3.4 mg, 0.5 equiv.) was added and the reaction mixture was stirred for an additional 40 min., followed by the portion-wise addition of 1M aq. HCl (10 mL). The reaction mixture was extracted with EtOAc (10 mL, 3×) and the combined organic layers were washed with sat. aq. NaHCO3 solution (10 ml) and brine (10 ml). Then it was dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (30-50% EtOAc in petroleum ether 40-60), affording diol **12** (87.2 mg, 87%) as a colourless oil. R_F = 0.27 (7:3; PE:EtOAc). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64 (ddt, *J* = 9.8, 6.8, 1.5 Hz, 4H), 7.50 – 7.30 (m, 6H), 7.24 (s, 5H), 4.18 (dd, *J* = 9.3, 7.1 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.99 (d, *J* = 13.2 Hz, 1H), 3.96 – 3.87 (m, 3H), 3.83 (dd, *J* = 10.5, 3.2 Hz, 1H), 3.76 – 3.63 (m, 3H), 3.28 (d, *J* = 4.6 Hz, 1H), 3.24 – 3.13 (m, 1H), 3.10 (d, *J* = 7.7 Hz, 1H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.06 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 135.8, 135.7, 135.6, 133.0, 132.7, 130.1, 130.1, 129.7, 128.3, 128.0, 127.7, 78.3, 69.8, 65.5, 62.3, 61.6, 60.6, 52.1, 27.0, 19.4, 14.2. FT-IR (neat): ν = 3385, 2931, 2857, 1738, 1472, 1428 cm^{-1}. HRMS calcd for $C_{32}H_{41}O_6NSi + H^+$ [M+H^+]: 564.2776 Found 564.2766. $[\alpha]_D^{20}$ = −22.7 (*c* = 1.00, $CHCl_3$).

Benzyl ((*S*)-1-((3*R*,4*S*,5*R*)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-4-hydroxy-2-oxotetrahydrofuran-3-yl)-2,2-dimethoxyethyl)carbamate (13)

A solution of cycloadduct **8a** (0.124 gr, 0.221 mmol, 1.00 equiv.) in dry THF (1.0 mL) was added to a round-bottom flask containing Raney-nickel (0.400 gr). The reaction mixture was placed under and hydrogen atmosphere (1 bar; balloon) and stirred vigorously for 5 h. TLC indicated incomplete conversion at this point so the reaction mixture was transferred to a round-bottom flask containing fresh Raney-nickel (0.500 gram) and stirred under an hydrogen atmosphere (1 bar; balloon) for an additional 2 hours. The reaction mixture was then placed under an argon atmosphere (1 bar) and Pd/C (0.100 gram) was added, followed by cyclohexene (2.5 mL). The resulting mixture was heated to reflux for 3 h and then cooled to 4 °C. Finally, H_2O (0.6 mL), $NaHCO_3$ (74 mg, 0.883 mmol, 4.00 equiv.) and CbzCl (0.094 mL, 0.662 mmol, 3.00 equiv.) were added sequentially and the resulting reaction mixture was stirred for 14 h, while allowing the mixture to warm to room temperature. The reaction mixture was filtered over Celite, the celite was subsequently washed with THF and the combined filtrate conc. *in vacuo*. The resulting residue was purified by flash column chromatography (20-30% EtOAc in petroleum ether 40-60), affording compound **13** (60.5 mg, 45%) as a yellow oil. R_F = 0.23 (7:3; PE:EtOAc). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.73 – 7.55 (m, 4H), 7.50 – 7.29 (m, 11H), 5.68 (d, *J* = 8.4 Hz, 1H), 5.25 – 5.03 (m, 3H), 4.69 (d, *J* = 2.5 Hz, 1H), 4.48 (dd, *J* = 5.3, 2.5 Hz, 1H), 4.43 (t, *J* = 2.5 Hz, 1H), 4.30 (td, *J* = 8.5, 2.4 Hz, 1H), 3.89 (dd, *J* = 11.8, 2.9 Hz, 1H), 3.77 (dd, *J* = 11.7, 2.1 Hz, 1H), 3.50 (s, 3H), 3.47 (s, 3H), 3.45 – 3.39 (m, 1H), 1.02 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.2, 157.8, 136.0, 135.8, 135.6, 132.6, 132.0, 130.2, 128.7, 128.5, 128.3, 128.0, 103.5, 85.3, 71.8, 67.6, 63.9, 57.0, 56.9, 50.5, 47.9, 26.8, 19.2. HRMS calcd for $C_{33}H_{41}O_8NSi + Na^+$ [M+Na^+]: 630.2494 Found 630.2483.

(*S*)-(5-oxo-2,5-dihydrofuran-2-yl)methyl 4-methylbenzenesulfonate (14).

To a solution of furanone **4** (215.6 mg, 1.890 mmol, 1.0 equiv.) in dry DCM (1.0 mL) at −15 °C was added pyridine (0.377 mL, 4.67 mmol, 2.5 equiv.), followed by the portion-wise addition of TsCl (0.540 gr, 2.83 mmol, 1.5 equiv.). The reaction mixture was stirred at −15 °C and allowed to warm to 5 °C over 1 hour. The reaction mixture was diluted with DCM (30 mL) and washed with 1M aq. HCl (10 mL, 3×), sat. aq. $NaHCO_3$ (10 mL), brine (10 mL). The organic phase was dried ($MgSO_4$) and then conc. *in vacuo*. The resulting residue was purified by flash column chromatography (0-100% MeOH in DCM), affording the product **14** (355 mg, 70%) as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.81 – 7.73 (m, 2H), 7.44 (dd, *J* = 5.8, 1.6 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 6.21 (dd, *J* = 5.8, 2.1 Hz, 1H), 5.19 (tt, *J* = 4.8, 1.9 Hz, 1H), 4.29 – 4.17 (m, 2H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 151.8, 145.7, 132.2, 130.2, 128.1, 123.9, 79.8, 67.5, 21.8. FT-IR (neat): ν = 3100, 2956, 2927, 1756, 1598, 1494, 1452, 1400 cm^{-1}. HRMS calcd for $C_{12}H_{12}O_5S + Na^+$ [M+Na^+]: 291.0298. Found 291.0290. $[\alpha]_D^{20}$ = −46.5 (*c* = 1.00, $CHCl_3$).

Ethyl (3a*R*,6*R*,6a*S*)-2-benzyl-6-(hydroxymethyl)-4-oxohexahydrofuro[3,4-d]isoxazole-3-carboxylate (6a) Nitrone **3a** (4.83 gr, 23.3 mmol, 1.09 equiv.) was added to a solution of furanone **4** (2.44 mg, 21.4 mmol, 1.00 equiv.) in toluene (10 mL) at 45 °C. The reaction mixture was heated to reflux for 4.5 hours and then conc. *in vacuo*. The residue was purified via column chromatography (30-40% EtOAc in heptane) to afford **6a** (80.5 mg, 55%) as a yellow oil (that crystallized upon standing) and **6b** (25.1 mg, 31%) as a yellow solid. NMR signals of the major adduct **6a anti**:[a] R_F = 0.27 (1:1; PE:EtOAc). mp = 83−84 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.04 (m, 5H), 4.73 (d, *J* = 6.4 Hz, 1H), 4.50 (d, *J* = 2.5 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 4.05 (q, *J* = 13.8 Hz, 2H), 3.95 – 3.75 (m, 3H), 3.67 (d, *J* = 12.3 Hz, 1H), 2.57 (s, 1H), 1.23 (t, *J* = 7.2 Hz, 3H). NMR signals of the minor adduct **6b syn**:[a] R_F = 0.22 (1:1; PE:EtOAc). mp = 144−145 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.26 (m, 5H), 4.86 (dd, *J* = 7.7, 2.2 Hz, 1H), 4.59 (q, *J* = 2.4 Hz, 1H), 4.32 – 4.19 (m, 3H), 3.94 (ddd, *J* = 12.4, 5.1, 2.5 Hz, 1H), 3.84 (d, *J* = 13.9 Hz, 1H), 3.80 – 3.70

(m, 2H), 3.67 (d, *J* = 7.6 Hz, 1H), 1.82 (dd, *J* = 6.8, 5.2 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H). $[\alpha]_D^{20}$ = +115.6 (*c* = 1.00, $CHCl_3$). [a] NMR signals in accordance with NMR spectra by Ondrus et al.[25]

Ethyl (3*S*,3a*R*,6*R*,6a*S*)-6-(azidomethyl)-2-benzyl-4-oxohexahydrofuro[3,4-d]isoxazole-3-carboxylate (16)

Method A:

To a solution of cycloadduct **6a** (31.0 mg, 0.0965 mmol, 1.00 equiv.) in dry THF (0.5 mL) at −20 °C was added PPh_3 (50.6 mg, 0.193 mmol, 2.00 equiv.), followed by the dropwise addition of diisopropyl azodicarboxylate (38.0 µL, 0.193 mmol, 2.00 equiv.) and $(PhO)_2P(O)N_3$ (41.5 µL, 0.193 mmol, 2.00 equiv.). The resulting reaction mixture was stirred at −20 to −15 °C for 30 min. and then allowed to warm to room temperature and stirred for 1 hour. H_2O (10 mL) and EtOAc (10 mL) were then added to the reaction mixture and the biphasic system was separated. The water layer was extracted with EtOAc (5 mL, 2×) and the combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and then conc. *in vacuo*. The residue was purified by flash column chromatography (2-5% MeOH in DCM), affording compound **16** (24.0 mg, 72%) as a yellow oil. R_F = 0.44 (7:3; PE:EtOAc).

Method B:

To a solution of cycloadduct **6a** (16.79 gr, 52.26 mmol, 1.00 equiv.) in DCM (86 mL) at 0 °C was added Et_3N (15.35 mL, 110 mmol, 2.10 equiv.), followed by the dropwise addition of MsCl (15.35 mL, 110 mmol, 2.10 equiv.). The resulting reaction mixture was stirred at 4 °C for 50 min.. Sat. aq. $NaHCO_3$ (400 mL) was added to the reaction mixture, followed by DCM (1 L). The resulting biphasic system was separated and the water layer was extracted with DCM (2×400 mL, 100 mL) and the combined organic layers were dried ($MgSO_4$) and then conc. *in vacuo*, affording the crude mesylated intermediate, which was dissolved in DMF (86 mL). NaN_3 (14.0 gr, 215 mmol, 4.00 equiv.) was added the reaction mixture was heated to 60 °C for 90 min. Additional DMF (50 mL) was added, followed by H_2O (400 mL). The reaction mixture was extracted with Et_2O (1 L, 400 mL, 2×200 mL) and the combined organic layers were washed with 5% aq. LiCl (200 mL, 2×), dried ($MgSO_4$) and conc. *in vacuo*. The residue was purified by flash column chromatography (10-25^EtOAc in petroleum ether 40-60), affording compound **16** (17.67 gr, 89% over 2 steps) as an orange oil. R_F = 0.44 (7:3; PE:EtOAc). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.24 (m, 5H), 4.66 (d, *J* = 6.5 Hz, 1H), 4.60 (t, *J* = 3.1 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 4.18 – 4.03 (m, 2H), 4.03 – 3.87 (m, 2H), 3.71 (dd, *J* = 13.3, 3.3 Hz, 1H), 3.56 (dd, *J* = 13.3, 3.0 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 167.9, 136.2, 128.8, 128.5, 127.8, 81.5, 79.8, 69.4, 62.1, 60.3, 52.7, 52.5, 14.2. FT-IR (neat): ν = 2983, 2108, 1779, 1734, 1606, 1497, 1455 cm^{-1}. HRMS calcd for $C_{16}H_{18}O_5N_4 + H^+$ [M+H$^+$]: 347.1350. Found 347.1344 $[\alpha]_D^{20}$ = +32.5 (*c* = 1.00, $CHCl_3$).

Ethyl (3*S*,3a*R*,6*R*,6a*S*)-6-(azidomethyl)-2-benzyl-4-hydroxyhexahydrofuro[3,4-d]isoxazole-3-carboxylate (17).

To a round-bottom flask containing lactone **15** (9.28 gr, 26.8 mmol, 1.0 equiv.) at 4 °C was added a 4 °C a 2M solution of BH_3-SMe_2 in THF (110 mL, 220 mmol, 8.2 equiv.). The resulting solution was stirred at 4 °C for 15 minutes and then allowed to warm to room temperature and stirred for 7 hours. The reaction mixture was cooled to 4 °C and quenched by the portion-wise addition of MeOH (200 mL). The reaction mixture was then conc. *in vacuo* and then purified by flash column chromatography (25-50 EtOAc in heptane) affording an anomeric mixture of compound **17** (3.16 gr, 34%) as a white solid. R_F = 0.58 (1:1; PE:EtOAc). mp = 96−98 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.22 (m, 5H), 5.57 (d, *J* = 5.3 Hz, 1H), 4.63 (dd, *J* = 7.1, 1.0 Hz, 1H), 4.32 (dd, *J* = 7.3, 4.8 Hz, 1H), 4.29 – 4.13 (m, 3H), 3.96 (d, *J* = 13.7 Hz, 1H), 3.58 (dd, *J* = 12.7, 7.4 Hz, 1H), 3.49 – 3.32 (m, 4H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 136.3, 136.2, 129.1, 128.9, 128.6, 128.4, 128.4, 127.9, 127.8, 103.4, 98.1, 83.9, 83.8, 83.4, 80.5, 70.9, 66.1, 61.8, 61.6, 61.0, 60.7, 55.6, 53.9, 52.5, 14.3, 14.2. FT-IR (neat): ν = 3436, 2981, 2936, 2099, 1734, 1497, 1455 cm^{-1}

HRMS calcd for $C_{16}H_{20}O_5N_4 + H^+$ [M+H$^+$]: 349.1506. Found 349.1496. $[\alpha]_D^{20}$ = −54.8 (*c* = 1.00, $CHCl_3$).

Ethyl (3a*R*,7*R*,7a*S*)-2-benzyl-7-hydroxyoctahydroisoxazolo[4,5-c]pyridine-3-carboxylate (19).

To a solution of azido-aldehyde **17** (0.106 gr, 0.304 mmol, 1 equiv.) in dry EtOH (1.6 mL) at 0 °C was added a solution of trimethylphosphine (1M in THF, 0.610 mL, 2 equiv.). The reaction mixture was stirred at 0 °C for 3 hours, then concentrated and subsequently co-evaporated with dry toluene (3×). The residue was dissolved in dry THF (1.6 mL) and cooled to 0 °C. $(AcO)_3BHNa$ (0.184 gr, 0.868 mmol, 2.86 equiv.) was added and the resulting reaction mixture was stirred for 1.5 h. The reaction was then quenched with sat. aq. $NaHCO_3$ (20 mL) and then extracted with EtOAc (20 ml, 2×10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and conc. *in vacuo*. The water layer was then additionally extracted with DCM (10 mL, 5×) and the combined organic layers were dried ($MgSO_4$) and conc. *in vacuo*. The residues from the EtOAc- and the DCM-extractions were both purified by flash column chromatography (5-10% MeOH in DCM) to afford compound **19** (61.1 mg, 66%) as white crystals. R_F = 0.14 (10% MeOH in DCM). mp = 120−122 °C. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.47 – 7.22 (m, 5H), 4.36 – 4.25 (m, 2H), 4.21 (d, *J* = 13.2 Hz, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.82 (ddd, *J* = 10.0, 4.8, 3.8 Hz, 1H), 3.41 (d, *J* = 3.1 Hz, 1H), 2.81 (dd, *J* = 12.7, 5.7 Hz, 2H), 2.77 – 2.63 (m, 2H), 2.38 (dd, *J* = 12.7, 9.5 Hz, 1H), 1.16 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 172.3, 137.0, 131.2, 129.3, 128.8, 78.4, 70.2, 67.6, 63.5, 62.3, 48.1, 47.6, 46.2, 14.4. FT-IR (neat): ν = 3308, 2847, 1734, 1498 ,1454, 1414 cm^{-1}. HRMS calcd for $C_{16}H_{23}O_4N_2 + H^+$ [M+H$^+$]: 307.1652. Found 307.1644. $[\alpha]_D^{20}$ = −43.0 (*c* = 1.00, $CHCl_3$).

General procedure A & B

To a roundbottom flask containing a 0.18M solution of azido-aldehyde **17** (1 equiv.) in dry EtOH at 0 °C was added a solution of trimethylphosphine (1M in THF, 2 equiv.). The reaction mixture was stirred at 0 °C for 3 hours, then concentrated and subsequenently co-evaporated with dry toluene (3×). The crude cyclic imine was dissolved dry EtOH (0.3M) (procedure **A)** or dry 2,2,2-trifluoroethanol (0.3M) (procedure **B)**, divided in the appropriate amount of portions and cooled to 0 °C. Next, the appropriate carboxylic acid (1.25 equiv.) and isocyanide (1.25 equiv.) were successfully added dropwise and the resulting reaction mixture was

stirred for 20 hours while allowing the mixture to warm to room temperature. Saturated $NaHCO_3$ was added to the mixture was extracted with EtOAc (3×). The combined organic layers were washed with sat. $NaHCO_3$ and brine, dried ($MgSO_4$) and conc. *in vacuo*. The SAWU-3-CR products were purified by silica gel flash column chromatography.

Ethyl (3*S*,3a*R*,4*R*,7*R*,7a*S*)-5-acetyl-2-benzyl-4-(tert-butylcarbamoyl)-7-hydroxyoctahydroisoxazolo[4,5-c]pyridine-3-carboxylate 20a and **ethyl (3*S*,3a*R*,4*S*,7*R*,7a*S*,*Z*)-2-benzyl-9-(tert-butylimino)octahydro-7,4-(epoxymethano)isoxazolo[4,5-c]pyridine-3-carboxylate 21a**

According to general procedure **A** the crude was obtained and purified via silicagel column chromatography (50-100% EtOAc in heptane then 0-100% EtOH in EtOAc) affording both **20a** (45.7 mg, 31%) and **21a** (40.3 mg, 29%) as light yellow oils. NMR signals and other experimental data of compound **20a**: R_F = 0.41 (100% EtOAc) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.23 (m, 5H), 6.41 (s, 1H), 5.05 (d, *J* = 1.4 Hz, 1H), 4.56 (dd, *J* = 9.3, 3.6 Hz, 1H), 4.27 (dd, *J* = 13.9, 9.1 Hz, 1H), 4.17 (qd, *J* = 7.1, 1.6 Hz, 2H), 4.08 – 3.98 (m, 2H), 3.64 (td, *J* = 9.4, 1.4 Hz, 1H), 3.36 – 3.20 (m, 2H), 3.18 (s, 1H), 2.53 – 2.44 (m, 1H), 2.05 (s, 3H), 1.31 – 1.21 (s, 12H, *t*Bu & $COOCH_2\underline{CH_3}$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 169.7, 168.7, 134.9, 130.1, 128.4, 128.0, 73.2, 68.1, 64.5, 61.9, 59.9, 52.5, 51.3, 45.2, 45.1, 28.7, 21.7, 14.2. FT-IR (neat): ν = 3333, 2968, 1746, 1685, 1641, 1538, 1455, 1406 cm^{-1}. HRMS calcd for $C_{23}H_{33}N_3O_6$+H^+ [M+H^+]: 448.2442. Found. 448.2425. $[\alpha]_D^{20}$ = +51.2 (*c* = 1.00, $CHCl_3$). NMR signals and other experimental data of compound **21a**: R_F = 0.42 (100% EtOH) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.36 (m, 2H), 7.39 – 7.30 (m, 2H), 7.35 – 7.24 (m, 1H), 4.55 (ddd, *J* = 4.3, 2.3, 0.9 Hz, 1H), 4.34 (d, *J* = 13.6 Hz, 1H), 4.29 – 4.17 (m, 2H), 4.21 – 4.10 (m, 1H), 3.81 (d, *J* = 13.6 Hz, 1H), 3.52 (d, *J* = 3.1 Hz, 1H), 3.39 – 3.23 (m, 3H), 2.88 (dd, *J* = 12.1, 0.9 Hz, 1H), 2.22 – 2.02 (m, 1H), 1.36 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 155.2, 136.9, 129.1, 128.4, 127.6, 75.0, 75.0, 70.3, 69.4, 61.9, 61.7, 53.4, 52.4, 51.1, 42.8, 30.0, 14.3. FT-IR (neat): ν = 3378, 3034, 2966, 1741, 1684, 1516, 1477, 1455 cm^{-1}. HRMS calcd for $C_{21}H_{29}N_3O_4$+H^+ [M+H^+]: 388.2231. Found. 388.2223. $[\alpha]_D^{20}$ = −32.4 (*c* = 1.00, $CHCl_3$).

Ethyl (3*S*,3a*R*,4*R*,7*R*,7a*S*)-2-benzyl-4-(tert-butylcarbamoyl)-7-hydroxy-5-(pent-4-enoyl)octahydroisoxazolo[4,5-c]pyridine-3-carboxylate 20b and **ethyl (3*S*,3a*R*,4*S*,7*R*,7a*S*,*Z*)-2-benzyl-9-(tert-butylimino)octahydro-7,4-(epoxymethano)isoxazolo[4,5-c]pyridine-3-carboxylate 21a.**

According to general procedure **A** the crude was obtained and purified via column chromatography (50-100% EtOAc in heptane then 0-100% EtOH in EtOAc) affording both **20b** (41.4 mg, 30%) and **21a** (39.2 mg, 35%) as yellow oils. NMR signals and other experimental data of compound **20b**: R_F = 0.76 (100% EtOAc). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.27 (m, 5H), 6.43 (s, 1H), 5.93 – 5.78 (m, 1H), 5.14 – 4.98 (m, 3H), 4.57 (dd, *J* = 9.3, 3.6 Hz, 1H), 4.30 (d, *J* = 14.1 Hz, 1H), 4.18 (qd, *J* = 7.2, 2.4 Hz, 2H), 4.11 – 3.98 (m, 2H), 3.70 – 3.61 (m, 1H), 3.40 – 3.22 (m, 2H), 3.17 (s, 1H), 2.56 – 2.27 (m, 5H), 1.31 – 1.24 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6, 169.8, 168.6, 137.0, 134.8, 130.1, 128.4, 128.0, 115.8, 73.3, 68.1, 64.6, 61.9, 59.9, 52.7, 51.3, 45.1, 44.7, 32.4, 28.9, 28.7, 14.2**.** FT-IR (neat): ν = 3338, 2976, 1737, 1677, 1635, 1537, 1498, 1454, 1415 cm^{-1}. HRMS calcd for $C_{26}H_{37}N_3O_6$+H^+ [M+H^+]: 488.2755. Found. 488.2741. $[\alpha]_D^{20}$ = +66.5 (*c* = 1.00, $CHCl_3$). NMR signals and other experimental data of compound **21a**: R_F = 0.42 (100% EtOH) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.36 (m, 2H), 7.39 – 7.30 (m, 2H), 7.35 – 7.24 (m, 1H), 4.55 (ddd, *J* = 4.3, 2.3, 0.9 Hz, 1H), 4.34 (d, *J* = 13.6 Hz, 1H), 4.29 – 4.17 (m, 2H), 4.21 – 4.10 (m, 1H), 3.81 (d, *J* = 13.6 Hz, 1H), 3.52 (d, *J* = 3.1 Hz, 1H), 3.39 – 3.23 (m, 3H), 2.88 (dd, *J* = 12.1, 0.9 Hz, 1H), 2.22 – 2.02 (m, 1H), 1.36 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 155.2, 136.9, 129.1, 128.4, 127.6, 75.0, 75.0, 70.3, 69.4, 61.9, 61.7, 53.4, 52.4, 51.1, 42.8, 30.0, 14.3. FT-IR (neat): ν = 3378, 3034, 2966, 1741, 1684, 1516, 1477, 1455 cm^{-1}. HRMS calcd for $C_{21}H_{29}N_3O_4$+H^+ [M+H^+]: 388.2231. Found. 388.2223. $[\alpha]_D^{20}$ = −32.4 (*c* = 1.00, $CHCl_3$).

Ethyl (3*S*,3a*R*,4*R*,7*R*,7a*S*)-2-benzyl-4-(tert-butylcarbamoyl)-7-hydroxy-5-(2,2,2-trifluoroacetyl)octahydroisoxazolo[4,5-c]pyridine-3-carboxylate 20c and **ethyl (3*S*,3a*R*,4*S*,7*R*,7a*S*,*Z*)-2-benzyl-9-(tert-butylimino)octahydro-7,4-(epoxymethano)isoxazolo[4,5-c]pyridine-3-carboxylate 21a.**

According to general procedure **A** the crude was obtained and purified via column chromatography (30-50% EtOAc in heptane then 0-40% EtOH in EtOAc) affording impure **20c** and pure **21a** (70 mg, 49%) as a crystalline solid. Impure **20c** was further purified via column chromatography (20% acetone in toluene) affording **20c** (50.5 mg, 27%) as a colorless oil. NMR signals and other experimental data of compound **20c**: R_F = 0.47 (1:1; PE:EtOAc). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.28 (m, 5H), 6.09 (s, 1H), 4.98 (d, *J* = 1.5 Hz, 1H), 4.56 (dd, *J* = 9.1, 3.9 Hz, 1H), 4.32 (d, *J* = 14.2 Hz, 1H), 4.21 (qd, *J* = 7.2, 6.5, 1.3 Hz, 2H), 4.12 – 3.98 (m, 2H), 3.67 – 3.58 (m, 2H), 3.36 (s, 1H), 2.25 (s, 1H), 1.35 – 1.27 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 168.0, 159.6, 159.2, 158.8, 158.4, 135.1, 129.7, 129.4, 128.6, 128.1, 120.6, 117.7, 114.9, 112.0, 72.9, 68.4, 63.6, 62.2, 60.4, 54.3, 51.9, 45.1, 44.1, 28.7, 14.2.

FT-IR (neat): ν = 3368, 2975, 1731, 1673, 1526, 1455 cm^{-1}. HRMS calcd for $C_{23}H_{30}F_3N_3O_6$+H^+ [M+H^+]: 502.2159. Found. 502.2143. $[\alpha]_D^{20}$ = +32.7 (*c* = 0.93, $CHCl_3$). NMR signals and other experimental data of compound **21a**: R_F = 0.42 (100% EtOH). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.36 (m, 2H), 7.39 – 7.30 (m, 2H), 7.35 – 7.24 (m, 1H), 4.55 (ddd, *J* = 4.3, 2.3, 0.9 Hz, 1H), 4.34 (d, *J* = 13.6 Hz, 1H), 4.29 – 4.17 (m, 2H), 4.21 – 4.10 (m, 1H), 3.81 (d, *J* = 13.6 Hz, 1H), 3.52 (d, *J* = 3.1 Hz, 1H), 3.39 – 3.23 (m, 3H), 2.88 (dd, *J* = 12.1, 0.9 Hz, 1H), 2.22 – 2.02 (m, 1H), 1.36 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 155.2, 136.9, 129.1, 128.4, 127.6, 75.0, 75.0, 70.3, 69.4, 61.9, 61.7, 53.4, 52.4, 51.1, 42.8, 30.0, 14.3. FT-IR (neat): ν = 3378, 3034, 2966, 1741, 1684, 1516, 1477, 1455 cm^{-1}. HRMS calcd for $C_{21}H_{29}N_3O_4$+H^+ [M+H^+]: 388.2231. Found. 388.2223. $[\alpha]_D^{20}$ = −32.4 (*c* = 1.00, $CHCl_3$).

Ethyl (3*S*,3a*R*,4*R*,7*R*,7a*S*)-5-benzoyl-2-benzyl-4-(tert-butylcarbamoyl)-7-hydroxyoctahydroisoxazolo[4,5-c]pyridine-3-carboxylate 20d and **ethyl (3*S*,3a*R*,4*S*,7*R*,7a*S*,*Z*)-2-benzyl-9-(tert-butylimino)octahydro-7,4-(epoxymethano)isoxazolo[4,5-c]pyridine-3-carboxylate 21a.**

According to general procedure **A** the crude was obtained and purified via column chromatography (50-100% EtOAc in heptane then 0-100% EtOH in EtOAc) affording **20d** (56.4, 33%) as a white turbid oil and **21a** (46.4 mg, 35%) as a yellow oil. NMR signals and other experimental data of compound **20d**: R_F = 0.30 (1:1; PE:EtOAc). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.49 – 7.30 (m, 10H), 6.85 (s, 1H), 5.23 (s, 1H), 4.58 (dd, *J* = 9.1, 4.0 Hz, 1H), 4.37 (d, *J* = 14.0 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.11 (d, *J* = 14.0 Hz, 1H), 3.93 – 3.83 (m, 1H), 3.70 (t, *J* = 9.5 Hz, 1H), 3.63 – 3.43 (m, 2H), 3.11 (d, *J* = 12.9 Hz, 1H), 2.61 (s, 1H), 1.33 (s, 9H), 1.31 – 1.26 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 169.5, 168.6, 135.0, 134.7, 130.5, 130.0, 128.5, 127.9, 127.7, 73.7, 67.6, 64.4, 61.9, 60.0, 53.4, 51.3, 46.7, 44.6, 28.8, 14.2. FT-IR (neat): ν = 3304, 2933, 1735, 1681, 1621, 1511, 1414 cm^{-1}. HRMS calcd for $C_{28}H_{35}N_3O_6$+H$^+$ [M+H$^+$]: 510.2599. Found. 510.2587. $[\alpha]_D^{20}$ = +71.9 (*c* = 1.00, $CHCl_3$).

Ethyl (3*S*,3a*R*,4*R*,7*R*,7a*S*)-2-benzyl-4-(butylcarbamoyl)-7-hydroxy-5-(pent-4-enoyl)octahydroisoxazolo[4,5-c]pyridine-3-carboxylate 20e and **ethyl (3*S*,3a*R*,4*S*,7*R*,7a*S*,*Z*)-2-benzyl-9-(butylimino)octahydro-7,4-(epoxymethano)isoxazolo[4,5-c]pyridine-3-carboxylate 21e.**

According to general procedure **A** the crude was obtained and purified via column chromatography (60-100% EtOAc in heptane then 0-100% EtOH in EtOAc) affording both **20e** (47.5 mg, 28%) and **21e** (26%)[a] as yellow oils. NMR signals and other experimental data of compound **20e**: R_F = 0.44 (75% EtOAc in PE). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.21 (m, 5H), 6.60 – 6.45 (m, 1H), 5.85 (ddt, *J* = 16.1, 10.7, 6.0 Hz, 1H), 5.19 – 4.96 (m, 3H), 4.58 (dd, *J* = 9.3, 3.6 Hz, 1H), 4.31 (d, *J* = 14.1 Hz, 1H), 4.17 (qt, *J* = 7.4, 3.7 Hz, 2H), 4.14 – 3.97 (m, 2H), 3.69 (t, *J* = 9.3 Hz, 1H), 3.37 – 3.23 (m, 2H), 3.16 (q, *J* = 6.7 Hz, 3H), 2.48 – 2.24 (m, 5H), 1.42 (p, *J* = 7.2 Hz, 2H), 1.35 – 1.20 (m, 5H), 0.89 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6, 170.6, 168.6, 137.1, 134.9, 130.1, 128.4, 128.0, 115.7, 73.2, 68.2, 64.6, 61.9, 59.9, 52.0, 45.3, 44.7, 39.4, 32.5, 31.6, 28.9, 20.1, 14.2, 13.8. FT-IR (neat): ν = 3340, 3034, 2959, 2931, 2873, 1735, 1636, 1529, 1497, 1454, 1415 cm^{-1}. HRMS calcd for $C_{26}H_{38}N_3O_6$+H$^+$ [M+H$^+$]: 488.2755. Found. 488.2745

$[\alpha]_D^{20}$ = +51.2 (*c* = 0.60, $CHCl_3$). NMR signals and other experimental data of compound **21e**[a]. R_F = 0.27 (100% EtOH). HRMS calcd for $C_{21}H_{29}N_3O_4$+H$^+$ [M+H$^+$]: 388.2231. Found. 388.2214. [a] The minor product could not be completely purified, but a relatively pure fraction was obtained for structure determination by NMR.

Ethyl (3*S*,3a*R*,4*R*,7*R*,7a*S*)-2-benzyl-4-(cyclohexylcarbamoyl)-7-hydroxy-5-(pent-4-enoyl)octahydroisoxazolo[4,5-c]pyridine-3-carboxylate 20f and **ethyl (3*S*,3a*R*,4*S*,7*R*,7a*S*,*Z*)-2-benzyl-9-(cyclohexylimino)octahydro-7,4-(epoxymethano)isoxazolo[4,5-c]pyridine-3-carboxylate 21f.**

According to general procedure **B** the crude was obtained and purified via column chromatography (50-100% EtOAc in heptane then 0-40% EtOH in EtOAc) affording **20f** (50.6 mg, 34%) as a light yellow oil and **21f** (55.5 mg, 46%) as a yellow oil. NMR signals and other experimental data of compound **20f**: R_F = 0.54 (75% EtOAc in PE). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.27 (m, 5H), 6.43 (d, *J* = 8.1 Hz, 1H), 5.85 (dddd, *J* = 16.2, 10.7, 5.8, 3.8 Hz, 1H), 5.18 – 4.99 (m, 3H), 4.57 (dd, *J* = 9.3, 3.6 Hz, 1H), 4.31 (d, *J* = 14.0 Hz, 1H), 4.22 – 4.13 (m, 2H), 4.12 – 3.98 (m, 2H), 3.73 – 3.58 (m, 2H), 3.40 – 3.25 (m, 2H), 3.20 (s, 1H), 2.39 (ddt, *J* = 16.7, 13.2, 8.5 Hz, 5H), 1.89 – 1.80 (m, 1H), 1.80 – 1.72 (m, 1H), 1.70 – 1.52 (m, 4H), 1.38 – 1.22 (m, 6H), 1.22 – 1.03 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6, 169.6, 168.7, 137.0, 135.0, 130.0, 128.4, 128.0, 115.8, 73.3, 68.2, 64.6, 61.9, 60.0, 52.1, 48.4, 45.2, 44.7, 32.9, 32.7, 32.5, 28.9, 25.6, 24.7, 14.2. FT-IR (neat): ν = 3338, 2932, 2856, 1735, 1636, 1525, 1452, 1416 cm^{-1}. HRMS calcd for $C_{28}H_{39}N_3O_6$+H$^+$ [M+H$^+$]: 514.2912. Found. 514.2898. $[\alpha]_D^{20}$ = +42.9 (*c* = 1.00, $CHCl_3$). NMR signals and other experimental data of compound **21f**: R_F = 0.47 (100% EtOH). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 (m, 5H), 4.55 – 4.43 (m, 1H), 4.27 (d, *J* = 13.8 Hz, 1H), 4.24 – 4.05 (m, 4H), 3.83 (d, *J* = 13.8 Hz, 1H), 3.65 – 3.54 (m, 1H), 3.54 – 3.49 (m, 1H), 3.37 – 3.20 (m, 3H), 2.86 (d, *J* = 12.1 Hz, 1H), 1.82 – 1.70 (m, 4H), 1.63 (d, *J* = 12.7 Hz, 1H), 1.36 – 1.18 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 155.9, 136.5, 129.2, 128.3, 127.6, 75.1, 70.5, 68.8, 61.6, 61.3, 53.4, 51.8, 51.2, 42.9, 34.0, 33.7, 25.9, 25.2, 25.1, 14.2. FT-IR (neat): ν = 2928, 2853, 1738, 1689, 1451 cm^{-1}. HRMS calcd for $C_{23}H_{31}N_3O_4$+H$^+$ [M+H$^+$]: 414.2387. Found. 414.2391. $[\alpha]_D^{20}$ = −24.1 (*c* = 1.00, $CHCl_3$).

Ethyl (3*S*,3a*R*,4*R*,7*R*,7a*S*)-2-benzyl-7-hydroxy-5-(pent-4-enoyl)-4-(((*S*)-1-phenylethyl)carbamoyl)octahydroisoxazolo[4,5-c]pyridine-3-carboxylate 20g and **ethyl (3*S*,3a*R*,4*S*,7*R*,7a*S*,*Z*)-2-benzyl-9-(((*S*)-1-phenylethyl)imino)octahydro-7,4-(epoxymethano)isoxazolo[4,5-c]pyridine-3-carboxylate 21g.**

According to general procedure **A** the crude was obtained and purified via column chromatography (50-100% EtOAc in heptane then 0-100% EtOH in EtOAc) affording both **20g** (30.1 mg, 17%) and **21g**[a] (19.2 mg, 13%) as yellow oils. NMR signals and other experimental data of compound **20g**: R_F = 0.17 (1:1; PE:EtOAc). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.18 (m, 9H), 7.15 (dd, *J* = 7.2, 1.9 Hz, 2H), 6.94 (d, *J* = 8.2 Hz, 1H), 5.89 – 5.73 (m, 1H), 5.20 (d, *J* = 1.4 Hz, 1H), 5.10 – 4.90 (m, 3H), 4.53 (dd, *J* = 9.2, 3.6 Hz, 1H), 4.29 (d, *J* = 14.0 Hz, 1H), 4.24 – 4.13 (m, 2H), 4.02 (d, *J* = 14.0 Hz, 1H), 3.97 – 3.86 (m, 1H), 3.75 – 3.59 (m, 1H), 3.29 – 3.09 (m, 3H), 2.46 – 2.26 (m, 5H), 1.42 (d, *J* = 7.0 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 169.7, 168.6, 143.5, 136.9, 134.9, 130.0, 128.8, 128.4, 127.9, 127.4, 125.7, 115.8, 73.2, 68.2, 64.3, 61.9, 59.9, 52.0, 49.2, 45.0, 44.6, 32.5, 28.8, 22.4, 14.2.

FT-IR (neat): ν = 3340, 2959, 2931, 2873, 1735, 1636, 1529, 1497, 1454, 1415 cm^{-1}. HRMS calcd for $C_{30}H_{37}N_3O_6$+Na$^+$ [M+Na$^+$]: 558.2575. Found. 558.2567. $[\alpha]_D^{20}$ = +64.5 (*c* = 1.00, $CHCl_3$). NMR signals and other experimental data of compound **21g**[a]: R_F = 0.37 (100% EtOH). HRMS calcd for $C_{25}H_{29}N_3O_4$+H$^+$ [M+H$^+$]: 436.2231. Found. 436.2211. [a] The minor product could not be completely purified, but a relatively pure fraction was obtained for structure determination by NMR.

Ethyl (3*S*,3a*R*,4*R*,7*R*,7a*S*)-2-benzyl-4-(benzylcarbamoyl)-7-hydroxy-5-(pent-4-enoyl)octahydroisoxazolo[4,5-c]pyridine-3-carboxylate 20h and **ethyl (3*S*,3a*R*,4*S*,7*R*,7a*S*,*Z*)-2-benzyl-9-(benzylimino)octahydro-7,4-(epoxymethano)isoxazolo[4,5-c]pyridine-3-carboxylate 21h.**

According to general procedure **B** the crude was obtained and purified via column chromatography (50-100% EtOAc in heptane then 0-100% EtOH in EtOAc) affording both **20h** (37.1 mg, 24%) and **21h** (61.4 mg, 50%) as yellow oils. NMR signals and other experimental data of compound **20h**: R_F = 0.59 (75% EtOAc in PE). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.21 (m, 8H), 7.21 – 7.12 (m, 2H), 6.94 (t, *J* = 6.0 Hz, 1H), 5.21 (d, *J* = 1.4 Hz, 1H), 5.06 – 4.90 (m, 2H), 4.57 (dd, *J* = 9.2, 3.6 Hz, 1H), 4.45 – 4.24 (m, 3H), 4.24 – 4.13 (m, 2H), 4.13 – 3.98 (m, 2H), 3.72 (td, *J* = 9.3, 1.4 Hz, 1H), 3.30 (q, *J* = 5.2, 4.3 Hz, 2H), 3.18 (s, 1H), 2.53 (s, 1H), 2.48 – 2.21 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 170.6, 168.6, 138.0, 136.9, 134.9, 130.1, 128.8, 128.4, 127.9, 127.6, 127.4, 115.7, 73.2, 68.2, 64.5, 61.9, 59.8, 52.0, 45.2, 44.6, 43.6, 32.4, 28.8, 14.2. FT-IR (neat): ν = 3339, 2980, 2929, 1734, 1634, 1524, 1497, 1454, 1416 cm^{-1}. HRMS calcd for $C_{29}H_{35}N_3O_6$+Na^+ [M+Na^+]: 544.2418. Found. 544.2411. $[\alpha]_D^{20}$ = +37.3 (*c* = 1.00, $CHCl_3$). NMR signals and other experimental data of compound **21h**: R_F = 0.38 (100% EtOH). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.20 (m, 10H), 4.62 – 4.54 (m, 1H), 4.50 – 4.34 (m, 2H), 4.27 – 4.07 (m, 4H), 3.71 (d, *J* = 13.9 Hz, 1H), 3.61 (d, *J* = 3.3 Hz, 1H), 3.34 – 3.23 (m, 2H), 3.19 (d, *J* = 8.3 Hz, 1H), 2.89 (d, *J* = 12.1 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 157.9, 140.7, 136.3, 129.4, 128.5, 128.3, 128.3, 127.6, 126.7, 75.0, 70.9, 68.4, 61.6, 60.9, 51.8, 51.2, 49.4, 43.0, 14.2. FT-IR (neat): ν = 3030, 2981, 2873, 1737, 1688, 1604, 1496, 1454 cm^{-1}. HRMS calcd for $C_{24}H_{27}N_3O_4$+H^+ [M+H^+]: 422.2074. Found. 422.2073. $[\alpha]_D^{20}$ = −49.5 (*c* = 0.80, $CHCl_3$).

Ethyl (3*S*,3a*R*,4*R*,7*R*,7a*S*)-5-benzoyl-2-benzyl-7-hydroxy-4-((4-methoxyphenyl)carbamoyl)octahydroisoxazolo[4,5-c]pyridine-3-carboxylate (20i) and **ethyl (3*S*,3a*R*,4*S*,7*R*,7a*S*,*Z*)-2-benzyl-9-((4-methoxyphenyl)imino)octahydro-7,4-(epoxymethano)isoxazolo[4,5-c]pyridine-3-carboxylate (21i)** and **ethyl (3*S*,3a*R*,4*S*,7*R*,7a*S*,*E*)-2-benzyl-9-((4-methoxyphenyl)imino)-5-((*E*)-((4-methoxyphenyl)imino)methyl)octahydro-7,4-(epoxymethano)isoxazolo[4,5-c]pyridine-3-carboxylate (S1)**.

According to general procedure **B** the crude was obtained and purified via column chromatography (50-100% EtOAc in heptane then 0-40% EtOH in EtOAc) affording both **20i** (29.0 mg, 18%), **21i** (52.6 mg, 41%) and **S1** (42.9 mg, 25%) as yellow oils. NMR signals and other experimental data of compound **20i**: R_F = 0.65 (75% EtOAc in PE). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.62 (s, 1H, NH), 7.43 – 7.28 (m, 7H), 6.88 – 6.76 (m, 2H), 5.93 – 5.75 (m, 1H), 5.26 (d, *J* = 1.4 Hz, 1H), 5.16 – 4.95 (m, 2H), 4.65 (dd, *J* = 9.3, 3.6 Hz, 1H), 4.33 (d, *J* = 14.0 Hz, 1H), 4.19 (qd, *J* = 7.1, 1.6 Hz, 3H), 4.05 (d, *J* = 14.0 Hz, 1H), 3.83 – 3.68 (m, 4H), 3.41 – 3.14 (m, 3H), 2.51 – 2.22 (m, 5H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 168.6, 168.5, 156.6, 136.9, 134.8, 130.8, 130.2, 128.4, 128.0, 121.5, 115.9, 114.3, 73.0, 68.2, 64.6, 62.0, 59.9, 55.6, 53.0, 45.1, 44.7, 32.5, 28.8, 14.2. FT-IR (neat): ν = 3308, 2935, 1738, 1683, 1634, 1512, 1415 cm^{-1}. HRMS calcd for $C_{29}H_{35}N_3O_7$+Na^+ [M+Na^+]: 560.2367. Found: 560.2360. $[\alpha]_D^{20}$ = +64.2 (*c* = 0.50, $CHCl_3$). NMR signals and experimental data of the major adduct **21i**: R_F = 0.51 (100% EtOH). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 (d, *J* = 6.7 Hz, 2H), 7.34 – 7.21 (m, 4H), 7.13 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 4.61 – 4.54 (m, 1H), 4.37 – 4.26 (m, 2H), 4.26 – 4.12 (m, 2H), 3.90 (d, *J* = 13.8 Hz, 1H), 3.81 (s, 3H), 3.72 (d, *J* = 3.1 Hz, 1H), 3.50 – 3.34 (m, 2H), 3.29 (dd, *J* = 12.2, 4.3 Hz, 1H), 2.92 (d, *J* = 12.1 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 157.0, 156.5, 138.4, 136.4, 129.3, 128.4, 127.7, 124.6, 114.0, 75.1, 71.1, 68.9, 61.8, 61.5, 55.6, 52.2, 51.4, 42.8, 14.3. FT-IR (neat): ν = 2935, 2836, 1737, 1679, 1606, 1504, 1455 cm^{-1}. HRMS calcd for $C_{24}H_{28}N_3O_5$+H^+ [M+H^+]: 438.2023. Found: 438.2023. $[\alpha]_D^{20}$ = +135.6 (*c* = 0.50, $CHCl_3$). NMR signals and other experimental data of compound **S1**: R_F = 0.53 (75% EtOAc in PE). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.72 (s, 1H), 7.37 (d, *J* = 7.4 Hz, 2H), 7.29 (dt, *J* = 11.6, 6.3 Hz, 3H), 7.21 – 7.12 (m, 2H), 6.96 – 6.89 (m, 2H), 6.90 – 6.82 (m, 4H), 4.87 – 4.73 (m, 1H), 4.41 (d, *J* = 8.0 Hz, 1H), 4.40 – 4.31 (m, 2H), 4.29 – 4.18 (m, 2H), 3.97 – 3.86 (m, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.56 – 3.43 (m, 3H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 157.0, 156.4, 152.7, 149.7, 144.1, 137.5, 136.1, 129.3, 128.4, 127.8, 124.9, 121.9, 114.6, 114.1, 75.1, 71.6, 68.1, 62.1, 61.4, 56.4, 55.6, 55.6, 51.7, 44.3, 14.3. FT-IR (neat): ν = 2934, 2835, 1736, 1689, 1625, 1577, 1505, 1464, 1426, 1408 cm^{-1}. HRMS calcd for $C_{32}H_{35}N_4O_6$+H^+ [M+H^+]: 571.2551. Found. 571.2548. $[\alpha]_D^{20}$ = −79.1 (*c* = 1.00, $CHCl_3$).

Ethyl (3*S*,3a*R*,4*R*,7*R*,7a*S*)-2-benzyl-7-hydroxy-4-(((4-methoxyphenyl)carbamoyl)carbamoyl)-5-phenyloctahydroisoxazolo[4,5-c]pyridine-3-carboxylate 20j and **ethyl (3*S*,3a*R*,4*S*,7*R*,7a*S*,*Z*)-2-benzyl-9-((4-methoxyphenyl)imino)octahydro-7,4-(epoxymethano)isoxazolo[4,5-c]pyridine-3-carboxylate 21i.**

According to general procedure **A** the crude was obtained and purified via column chromatography (50-100% EtOAc in heptane then 0-100% EtOH in EtOAc) affording both **20j** (26.5 mg, 16%) as a yellow oil, while **21i** was only formed in trace amounts under these conditions. NMR signals and other experimental data of compound **20j**: R_F = 0.21 (1:1; PE:EtOAc). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.10 (s, 1H), 7.52 – 7.33 (m, 12H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.44 (s, 1H), 4.68 (dd, *J* = 9.1, 4.0 Hz, 1H), 4.43 (d, *J* = 14.1 Hz, 1H), 4.25 (q, *J* = 6.8 Hz, 2H), 4.16 (d, *J* = 14.1 Hz, 1H), 4.02 – 3.91 (m, 1H), 3.85 – 3.76 (m, 4H), 3.70 – 3.47 (m, 2H), 3.13 (dd, *J* = 12.9, 3.1 Hz, 1H), 2.39 (s, 1H), 1.31 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 168.6, 168.2, 156.7, 134.9, 134.2, 131.0, 130.9, 130.2, 128.7, 128.6, 128.2, 128.1, 121.6, 114.4, 73.5, 67.4, 64.5, 62.2, 60.0, 55.7, 53.8, 46.9, 44.7, 14.3. FT-IR (neat): ν = 3304, 3064, 2933, 2837, 1735, 1681, 1621, 1601, 1577, 1511, 1454, 1414 cm^{-1}. HRMS calcd for $C_{31}H_{33}N_3O_7$+Na^+ [M+Na^+]: 582.2211. Found. 582.2189. $[\alpha]_D^{20}$ = +44.8 (*c* = 0.50, $CHCl_3$).

Ethyl (3*S*,3a*R*,4*S*,7*R*,7a*S*)-2-benzyl-4-(tert-butylcarbamoyl)-7-hydroxyoctahydroisoxazolo[4,5-c]pyridine-3-carboxylate (22).

To a solution of imidate **21a** (38.0 mg, 0.098 mmol) in tetrahydrofuran-d_8 (2.0 mL) was added D_2O (2.0 mL). The resulting solution was heated in a sealed vessel in an oil bath to 80 °C for 4 h and then heated at 90 °C for 3 days. The reaction mixture was then

concentrated *in vacuo* concentrated and co-evaporated with dry toluene to remove excess water. The residue was purified by flash column chromatography (30-50% acetone in toluene), affording amide **22** (28.0 mg, 70%) as a colorless oil. R_F = 0.18 (1:1; toluene:acetone). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 – 7.18 (m, 5H), 6.64 (s, 1H), 4.23 (dd, *J* = 7.0, 4.2 Hz, 1H), 4.15 – 4.03 (m, 3H), 3.98 (d, *J* = 13.8 Hz, 1H), 3.77 – 3.68 (m, 1H), 3.61 – 3.52 (m, 2H), 3.37 – 3.29 (m, 1H), 2.98 (dd, *J* = 14.2, 3.6 Hz, 1H), 2.51 (dd, *J* = 14.2, 2.1 Hz, 1H), 1.25 (s, 9H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 169.4, 135.8, 129.2, 128.6, 127.9, 76.9, 66.1, 65.3, 61.4, 58.9, 58.7, 51.0, 49.2, 45.8, 28.7, 14.1. FT-IR (neat): ν = 3378, 3297, 3034, 2966, 2931, 2874, 1741, 1684, 1515, 1477, 1455 cm^{-1}. HRMS calcd for $C_{21}H_{32}N_3O_5$+H$^+$ [M+H$^+$]: 406.2336. Found. 406.2334. $[\alpha]_D^{20}$ = −72.9 (*c* = 1.00, $CHCl_3$).

Ethyl (3*S*,3a*R*,4*R*,7*R*,7a*S*)-2-benzyl-4-(cyclohexylcarbamoyl)-7-hydroxyoctahydroisoxazolo[4,5-c]pyridine-3-carboxylate 24

To a solution of compound **20f** (37.0 mg, 0.072 mmol, 1.0 equiv.) in a THF/H_2O mixture (3:1, 1.4 mL) was added I_2 (54.9 mg, 0.22 mmol, 3.0 equiv.). The reaction mixture was stirred for 20 min and then quenched by the addition of 1M aq. $Na_2S_2O_3$ (4 mL) and stirred for 30 min. The reaction mixture was poured into a mixture of 1M aq. $Na_2S_2O_3$/sat. aq. NaCl (1/1, v/v, 10 mL) and then extracted with EtOAc (4×), dried ($MgSO_4$) concentrated *in vacuo*, affording a yellow oil. The residue was purified by flash column chromatography (0-20% EtOH in EtOAc) providing compound **24** (29.9 mg, 94%) as a yellow oil. R_F = 0.44 (20% EtOH in EtOAc). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.24 (m, 5H), 7.13 (s, 1H), 4.37 (d, *J* = 13.8 Hz, 1H), 4.33 – 4.20 (m, 2H), 4.18 – 4.06 (m, 2H), 3.98 – 3.80 (m, 2H), 3.79 – 3.64 (m, 2H), 3.64 – 3.51 (m, 1H), 3.32 – 3.19 (m, 1H), 3.00 – 2.86 (m, 2H), 1.94 – 1.78 (m, 2H), 1.78 – 1.65 (m, 2H), 1.65 – 1.52 (m, 1H), 1.40 – 1.10 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 169.4, 135.9, 130.0, 128.6, 128.0, 75.4, 69.3, 64.6, 61.9, 61.7, 56.6, 48.6, 46.3, 45.0, 32.9, 25.5, 24.9, 14.2. FT-IR (neat): ν = 3233, 2931, 2855, 1737, 1654, 1539, 1452 cm^{-1}. HRMS calcd for $C_{23}H_{33}N_3O_5$+H$^+$ [M+H$^+$]: 432.2493. Found. 432.2483. $[\alpha]_D^{20}$ = −42.5 (*c* = 0.40, $CHCl_3$).

2-((3*S*,3a*R*,4*S*,7*R*,7a*S*)-2-benzyl-3-(ethoxycarbonyl)-7-hydroxyoctahydroisoxazolo[4,5-c]pyridin-4-yl)acetic acid (27).

To a roundbottom flask containing a solution of azido-aldehyde **17** (0.106 gr, 0.287 mmol, 1 equiv.) in dry EtOH (1.6 mL) at 0 °C was added a solution of trimethylphosphine (1M in THF, 0.575 mL, 2 equiv.). The reaction mixture was stirred at 0 °C for 3 hours and then concentrated and co-evaporated with dry toluene (3×). The residue was dissolved in a 2:1 mixture of dry Et_2O/THF (3.0 mL) and malonic acid (38.5 mg, 0.370 mmol, 1.29 equiv.) was added. The resulting reaction mixture was stirred for 19 h, which resulted in the formation of a sticky oil. The oil was dissolved by the addition of dry EtOH (1.5 mL), providing a yellow solution that quickly formed a white precipitate. This reaction mixture was allowed to stir for another 2 hours, followed by the addition MeOH (5 mL). The resulting solution was conc. *in vacuo*, affording a yellow foam, which purified by trituration with hot THF and subsequent trituration in hot MeOH, affording compound **27** (66.0 mg, 62%) as an off-white solid. R_F = 0.10 (30% MeOH in DCM). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.45 – 7.24 (m, 5H), 4.33 – 4.20 (m, 3H), 4.20 – 4.01 (m, 3H), 3.56 (d, *J* = 2.6 Hz, 1H), 3.22 (dd, *J* = 12.1, 4.5 Hz, 1H), 3.00 (dd, *J* = 12.1, 10.4 Hz, 1H), 2.95 – 2.76 (m, 2H), 2.50 (dd, *J* = 17.3, 3.3 Hz, 1H), 2.29 (dd, *J* = 17.3, 7.9 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.8, 170.4, 136.9, 129.1, 128.0, 127.2, 77.1, 69.5, 66.0, 62.3, 60.5, 53.1, 50.9, 46.1, 37.4, 13.9. FT-IR (neat): ν = 2925, 2869, 1736, 1640, 1557, 1498, 1456, 1420 cm^{-1}. HRMS calcd for $C_{18}H_{24}N_2O_6$+H$^+$ [M+H$^+$]: 365.1707. Found. 365.1695. $[\alpha]_D^{20}$ = −44.8 (*c* = 0.50, $CHCl_3$).

Modified SAWU-3CR procedure with *in situ* alcohol-protection

To a roundbottom containing a solution of azido-aldehyde **17** (0.104 gr, 0.299 mmol, 1 equiv.) in dry EtOH (1.6 mL) at 0 °C was added a solution of trimethylphosphine (1M in THF, 0.600 mL, 2 equiv.). The reaction mixture was stirred at 0 °C for 2 hours and then concentrated and co-evaporated with dry toluene (3×). The residue was dissolved in dry THF (2.5 mL) and imidazole (23.5 mg, 0.345 mmol, 1.15 equiv.) was added. The resulting reaction mixture was cooled to 0 °C, followed by the dropwise addition of TESCl (58.0 µL, 0.345 mmol, 1.15 equiv.). The reaction mixture was stirred for 45 minutes at 0 °C and then another 50 minutes at room temperature. The mixture was then cooled to 0 °C, followed by the addition of acetic acid (86.0 µL, 1.50 mmol, 5.0 equiv.) and *t*butyl isocyanide (170 µL, 1.50 mmol, 5.00 equiv.). The resulting mixture was allowed to warm to rt and stirred for 3 days. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ (5 mL) and EtOAc (20 mL). The biphasic system was separated and the water layer was extracted with EtOAc (10 mL, 2×). The combined organic layers were washed with sat. aq. $NaHCO_3$ (10 mL), brine (10 mL), dried ($MgSO_4$) and then conc. *in vacuo*. The residue was purified by flash column chromatography (20-100% EtOAc in heptane), providing compound **26a** (61.6 mg, 36%) and compound **20a** (23.5 mg, 18%) as yellow oils. NMR signals and other experimental data of compound **26a**: R_F = 0.28 (7:3; PE:EtOAc). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.20 (m, 5H), 6.36 (s, 1H), 4.95 (s, 1H), 4.44 (dd, *J* = 9.1, 2.9 Hz, 1H), 4.28 – 4.18 (m, 2H), 4.17 – 4.02 (m, 3H), 3.65 (t, *J* = 9.2 Hz, 1H), 3.34 (t, *J* = 10.7 Hz, 1H), 3.19 (dd, *J* = 10.4, 5.6 Hz, 1H), 3.02 – 2.83 (m, 1H), 2.02 (s, 3H), 1.30 – 1.19 (m, 12H), 0.93 (t, *J* = 7.9 Hz, 9H), 0.59 (q, *J* = 8.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 170.0, 169.1, 135.0, 130.4, 128.1, 127.7, 73.8, 68.9, 65.3, 61.7, 60.1, 52.6, 51.2, 46.3, 45.6, 28.6, 21.6, 14.2, 6.8, 4.8. FT-IR (neat): ν = 3326, 2958, 2877, 1738, 1681, 1644, 1532, 1455, 1411 cm^{-1}. HRMS calcd for $C_{29}H_{48}N_3O_6Si$+H$^+$ [M+H$^+$]: 562.3307. Found. 562.3281.

Modified SAWU-3CR procedure with *in situ* alcohol-protection & deprotection

To a roundbottom containing a solution of azido-aldehyde **17** (0.104 gr, 0.299 mmol, 1 equiv.) in dry EtOH (1.6 mL) at 0 °C was added a solution of trimethylphosphine (1M in THF, 0.598 mL, 2 equiv.). The reaction mixture was stirred at 0 °C for 2 hours and then concentrated and co-evaporated with dry toluene (3×). The residue was dissolved in dry THF (2.5 mL) and imidazole (24.0 mg, 0.353 mmol, 1.15 equiv.) was added. The resulting reaction mixture was cooled to 0 °C, followed by the dropwise addition of TESCl (60.0 µL, 0.357 mmol, 1.19 equiv.). The reaction mixture was stirred for 55 minutes at 0 °C and then another 30 minutes at room temperature. The mixture was then cooled to 0 °C, followed by the addition of *t*butyl isocyanide (170 µL, 1.50 mmol, 5.00 equiv.)

and acetic acid (86.0 μL, 1.50 mmol, 5.0 equiv.). The resulting mixture was allowed to warm to rt and stirred for 17 h. Finally, H_2O (0.25 mL) and 1M HCl in Et_2O (1.5 mL) were added and the solution was stirred at rt for 2 h, followed by the addition of sat. aq. $NaHCO_3$ (5 mL) and EtOAc (20 mL). The biphasic system was separated and the water layer was extracted with EtOAc (10 mL, 2×). The combined organic layers were washed with sat. aq. $NaHCO_3$ (8 mL), brine (8 mL), dried ($MgSO_4$) and then conc. *in vacuo*. The residue was purified by flash column chromatography (50-100% EtOAc in heptane), providing compound **20a** (65.7 mg, 41%) as a yellow oil.

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Supporting information

X-ray crystallographic data for compound **6a** (CIF) and
Characterization data and copies of ^1H and ^{13}C NMR spectra for all compounds. (PDF)

References

1. Yagi, M., Kouno, T., Aoyagi, Y., and Murai, H. *Nippon Nogeikagaku Kaishi* **1976**, *50*, 571.
2. Murao, S. and Miyata, S. *Agric. Biol. Chem.* **1980**, *44*, 219.
3. Inouye, S., Tsuruoka, T., Ito, T., and Niida, T. *Tetrahedron* **1968**, *24*, 2125.
4. Paulsen, H. *Angew. Chem. Int. Ed.* **1966**, *5*, 495.
5. Paulsen, H., Sangster, I., and Heyns, K. *Chem. Ber.* **1967**, *100*, 802.
6. Jacob, G.S. *Curr. Opin. Struct. Biol.* **1995**, *5*, 605.
7. Butters, T.D., Dwek, R.A., and Platt, F.M. *Chem. Rev.* **2000**, *100*, 4683.
8. Platt, F.M., Neises, G.R., Dwek, R.A., and Butters, T.D. *J. Biol. Chem.* **1994**, *269*, 8362.
9. Wennekes, T., van den Berg, R.J.B.H.N., Donker, W., van der Marel, G.A., Strijland, A., Aerts, J.M.F.G., and Overkleeft, H.S. *J. Org. Chem.* **2007**, *72*, 1088.
10. Wennekes, T., Bonger, K.M., Vogel, K., van den Berg, R.J.B.H.N., Strijland, A., Donker-Koopman, W.E., Aerts, J.M.F.G., van der Marel, G.A., and Overkleeft, H.S. *Eur. J. Org. Chem.* **2012**, *2012*, 6420.
11. *Iminosugars: From Synthesis to Therapeutic Applications*; P. Compain and O.R. Martin. Wiley-VCH/ **2007**.
12. Wei, Z. *Curr. Top. Med. Chem.* **2005**, *5*, 1363.
13. Wennekes, T., van den Berg, R.J.B.H.N., Boltje, T.J., Donker-Koopman, W.E., Kuijper, B., van der Marel, G.A., Strijland, A., Verhagen, C.P., Aerts, J.M.F.G., and Overkleeft, H.S. *Eur. J. Org. Chem.* **2010**, *2010*, 1258.
14. Peer, A. and Vasella, A. *Helv. Chim. Acta* **1999**, *82*, 1044.
15. van den Broek, L.A.G.M. *Tetrahedron* **1996**, *52*, 4467.
16. Hashimoto, T. and Maruoka, K. *Chem. Rev.* **2015**, *115*, 5366.
17. Stanley, L.M. and Sibi, M.P. *Chem. Rev.* **2008**, *108*, 2887.
18. Inouye, Y., Watanabe, Y., Takahashi, S., and Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3763.
19. Nguyen, T.B., Beauseigneur, A., Martel, A., Dhal, R., Laurent, M., and Dujardin, G. *J. Org. Chem.* **2010**, *75*, 611.
20. Hoogenboom, J., Zuilhof, H., and Wennekes, T. *Org. Lett.* **2015**, *17*, 5550.
21. Diaz-Rodriguez, A., Sanghvi, Y.S., Fernandez, S., Schinazi, R.F., Theodorakis, E.A., Ferrero, M., and Gotor, V. *Org. Biomol. Chem.* **2009**, *7*, 1415.
22. Schmid, C.R., Bryant, J.D., Dowlatzedah, M., Phillips, J.L., Prather, D.E., Schantz, R.D., Sear, N.L., and Vianco, C.S. *J. Org. Chem.* **1991**, *56*, 4056.
23. Mann, J. and Weymouth-Wilson, A. *Carbohydr. Res.* **1992**, *216*, 511.
24. Fazio, F. and Schneider, M.P. *Tetrahedron: Asymmetry* **2000**, *11*, 1869.
25. Ondruš, V., Orság, M., Fišera, L.u., and Prónayová, N.a. *Tetrahedron* **1999**, *55*, 10425.
26. Timmer, M.S.M., Risseeuw, M.D.P., Verdoes, M., Filippov, D.V., Plaisier, J.R., van der Marel, G.A., Overkleeft, H.S., and van Boom, J.H. *Tetrahedron: Asymmetry* **2005**, *16*, 177.
27. Cook, G.R., Shanker, P.S., and Peterson, S.L. *Org. Lett.* **1999**, *1*, 615.
28. Endo, A. and Danishefsky, S.J. *J. Am. Chem. Soc.* **2005**, *127*, 8298.
29. Deng, X., Su, J., Zhao, Y., Peng, L.-Y., Li, Y., Yao, Z.-J., and Zhao, Q.-S. *Eur. J. Med. Chem.* **2011**, *46*, 4238.
30. Leca, D., Gaggini, F., Cassayre, J., Loiseleur, O., Pieniazek, S.N., Luft, J.A.R., and Houk, K.N. *J. Org. Chem.* **2007**, *72*, 4284.
31. Schulthess, A.H. and Hansen, H.-J. *Helv. Chim. Acta* **1981**, *64*, 1322.

32. Meise, W. and Mika, U. *Arch. Pharm.* **1989**, *322*, 573.
33. Thompson, M.J. and Chen, B. *J. Org. Chem.* **2009**, *74*, 7084.
34. Kazmaier, U. and Hebach, C. *Synlett* **2003**, *2003*, 1591.
35. Gulevich, A.V., Zhdanko, A.G., Orru, R.V.A., and Nenajdenko, V.G. *Chem. Rev.* **2010**, *110*, 5235.
36. Cristau, P., Vors, J.-P., and Zhu, J. *Org. Lett.* **2001**, *3*, 4079.
37. Katsuyama, A., Matsuda, A., and Ichikawa, S. *Org. Lett.* **2016**, *18*, 2552.
38. Bonger, K.M., Wennekes, T., Filippov, D.V., Lodder, G., van der Marel, G.A., and Overkleeft, H.S. *Eur. J. Org. Chem.* **2008**, *2008*, 3678.
39. Zoidl, M., Gonzalez Santana, A., Torvisco, A., Tysoe, C., Siriwardena, A., Withers, S.G., and Wrodnigg, T.M. *Carbohydr. Res.* **2016**, *429*, 62.