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# Exploring the Chemistry of Bicyclic Isoxazolidines for the Multicomponent Synthesis of Glycomimetic Building Blocks

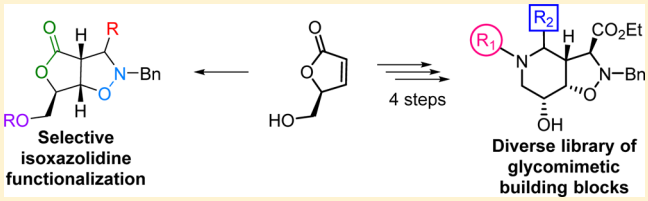
Jorin Hoogenboom,[†] Martin Lutz,[‡] Han Zuilhof,[†] and Tom Wennekes*[,†,§]

[†]Laboratory of Organic Chemistry, Wageningen University, Stippeneng 4, 6708 WE Wageningen, The Netherlands

[‡]Bijvoet Center for Biomolecular Research, Crystal and Structural Chemistry and [§]Department of Chemical Biology and Drug Discovery, Utrecht Institute for Pharmaceutical Sciences and Bijvoet Center for Biomolecular Research, Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands

Supporting Information

**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.

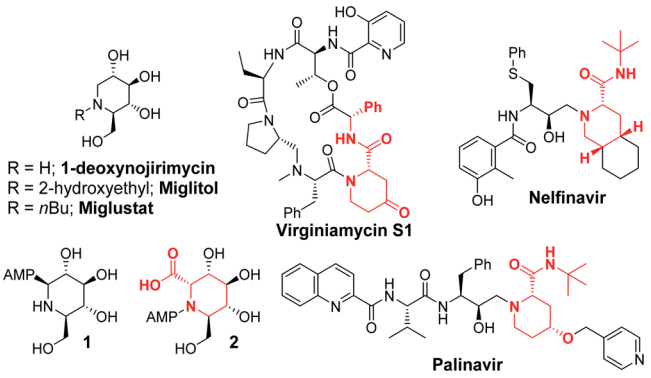



**Figure 1.** 1-Deoxynojirimycin with analogues thereof and notable examples of pipecolic acid derivatives (in red). AMP = 5-(adamantan-1-yl-methoxy)pentyl.

In our ongoing synthetic investigation toward 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 aglycon part and are therefore 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 toward glycomimetic building blocks, since it

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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 toward high regio- and enantiospecific products provide *C*-aryl-substituted isoxazolidines that often bear *N*-aryl groups. These products are synthetically less versatile for elaboration toward 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

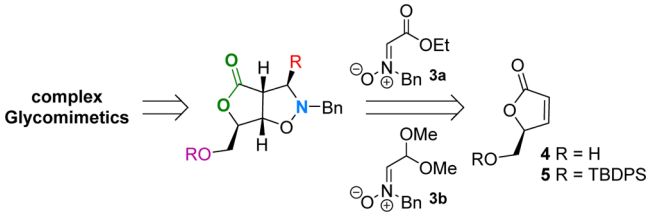



**Figure 2.** Complex glycomimetics may be obtained from bicyclic isoxazolidines, which provide many handles for further functionalization.

*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]

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 previously 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.

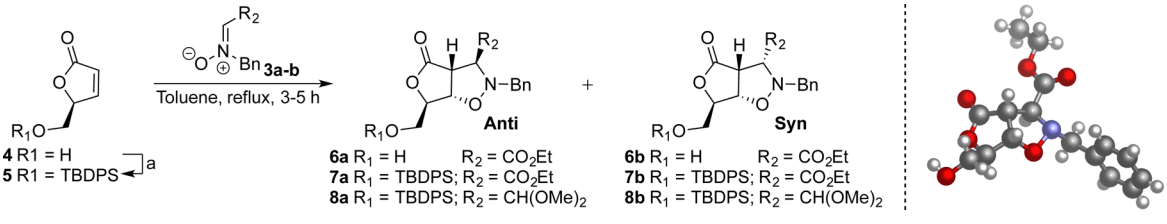
## RESULTS AND DISCUSSION

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 Ondruš et al. but has never been functionalized further.[25] Ondruš and co-workers 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 toward 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).

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 hydrolyze 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 favorable as treatment with $Me_3SnOH$ gave carboxylic acid **9** in almost quantitative yield (Scheme 2). The carboxylic acid could then be selectively reduced toward primary alcohol **10** in 94% over two steps by reducing an in situ formed mixed anhydride with sodium borohydride.

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 toward reducing agents. When DiBAL-H, L-Selectride, or $NaBH_4$ was used as the reducing agent, mixtures of starting material, monoreduction toward the hemiacetal, overreduction toward the diol, and additional byproducts were observed. However, when $BH_3$−$SMe_2$ was used as the reducing agent, **7a** could be selectively reduced toward hemiacetal **11** in 78% yield, providing diol **12** (16%) as a minor product. In addition, diol **12** could be obtained

**Scheme 1. Cycloaddition Reaction of Furanones 4 and 5 with Nitrones 3a,b Providing Cycloadducts 6−8 (Left). Molecular Structure of Major *Anti*-Cycloadduct 6a in the Crystal (Right)[a]**




[a]Reaction conditions: TBDPSCl, imidazole, DMF, −10 to +20 °C, 4 h, 88%.



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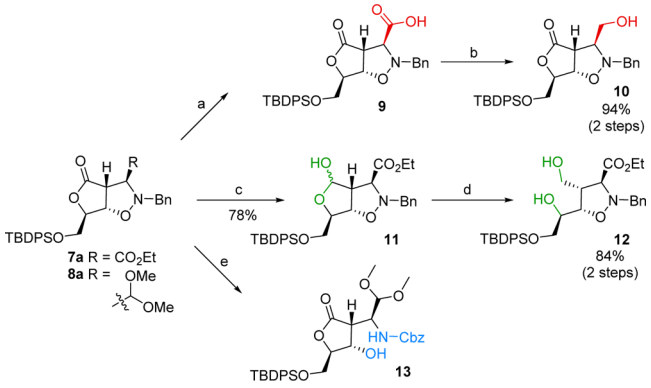
**Scheme 2. Selective Modification of Functional Positions in Bicyclic Isoxazolidine 7a and 8a**[a]




[a]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 two steps; (c) $BH_3$−$SMe_2$, THF, 4−20 °C, 3.5 h; (d) $NaBH_4$, MeOH, −3 to +7 °C, 100 min, 84% over two 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%.

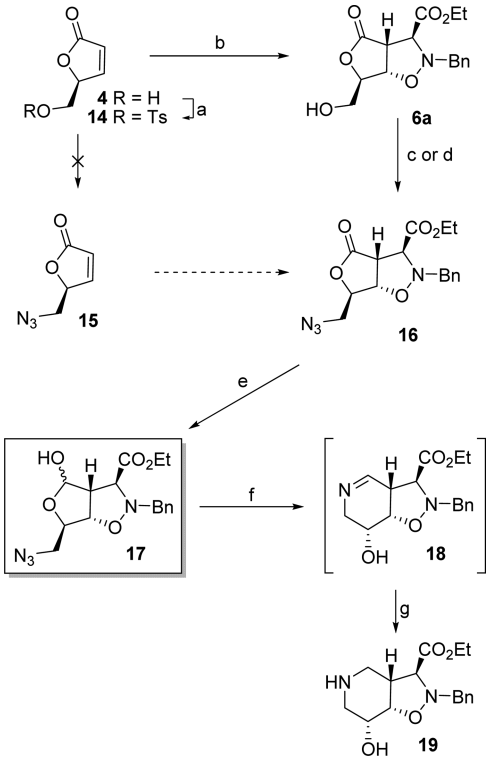
in 84% yield over two steps by reducing crude hemiacetal **11** with $NaBH_4$ in MeOH at 0 °C.

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 previously 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 an 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 synthesizing 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 toward **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

**Scheme 3. Synthesis of Azido-hemiacetal 17, Precursor for the SAWU-3CR**[a]




[a]Reaction conditions: (a) TsCl, pyridine, DCM, −15 to +5 °C, 1 h, 70%; (b) nitrone **3a**, toluene, reflux, 4.5 h, 55% (**6a**) and 31% (**6b**); (c) $(PhO)_2P(O)N_3$, diisopropyl azodicarboxylate, $PPh_3$, THF, −20 to +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 two 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 two steps.

previously obtained cycloadduct **6a**. However, this reaction proved less reliable at larger scales, but we could obtain compound **16** reliably at a 19 g 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 $BH_3$−$SMe_2$.

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*-butyl isocyanide and acetic acid to give pipecolic acid **20a** as the major product (Scheme 4).

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 observed 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*-butyl isocyanide relative to the free alcohol. The resulting



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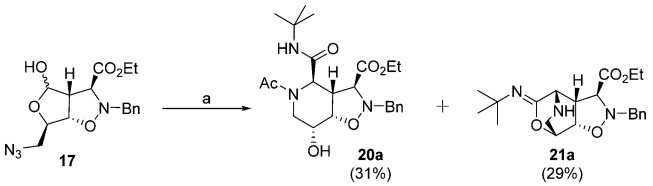
**Scheme 4. SAWU-3CR with Azido-hemiacetal 17**[a]



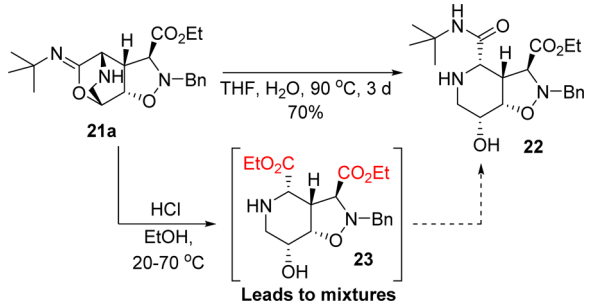

[a]Reaction conditions: (a) (i) $PMe_3$, EtOH, 4 °C, 3 h, (ii) acetic acid (1.25 equiv), *tert*-butylisocyanide (1.25 equiv), EtOH/TFE, 0–20 °C, 16 h, 60%, ratio **20a**:**21a** = 51:49.

nitrilium ion intermediate **II** then undergoes the expected carboxylate attack and rearrangement seen in Ugi reactions.

However, when the reaction proceeds via a *syn*-attack of the *tert*-butyl isocyanide, the resulting nitrilium ion (**IV**) can also be attacked intramolecularly via a pseudoboat conformation by the free alcohol instead of a carboxylate. Such a pseudoboat 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 pseudoboat 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 the Supporting Information for details and 3D images of this structure). We propose that 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 kilocalories per mole 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 toward 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 diester **23** was observed in situ,

**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**




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.

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 different acids were used similar or better yields were obtained (entries 3–5), indicating that the reaction tolerates a variety of acids.

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

**Scheme 5. Reaction Mechanism Explaining the Formation of *Anti*-Product 20a and Tricyclic Imidate 21a**

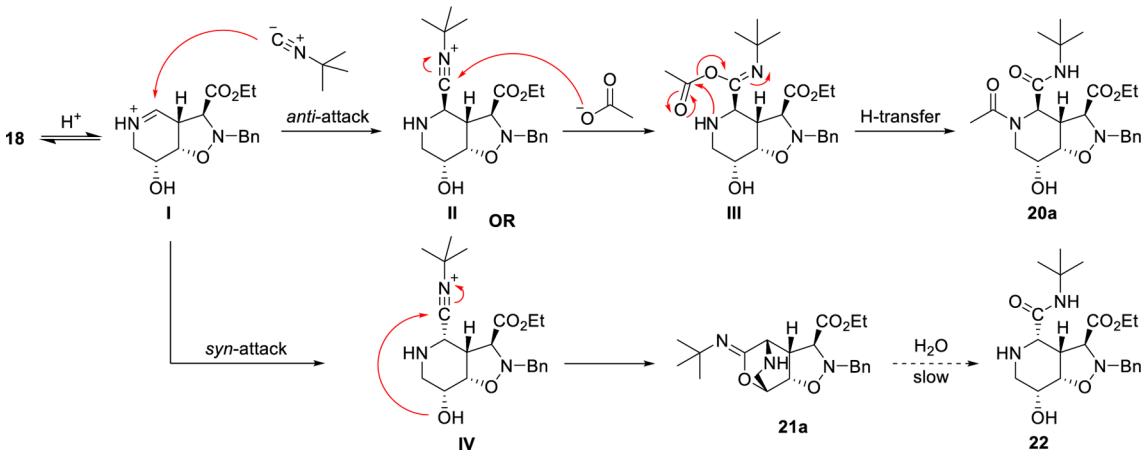





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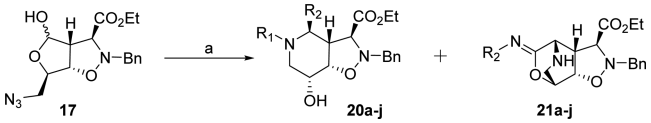
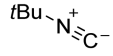
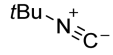
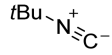
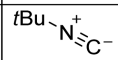
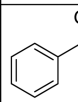
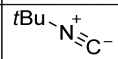
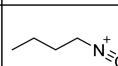
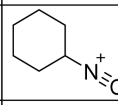
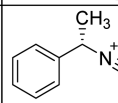
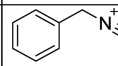
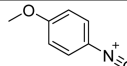
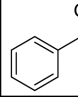
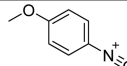
**Table 1. Substrate Scope of the SAWU-3CR[a] with Hemiacetal 17**



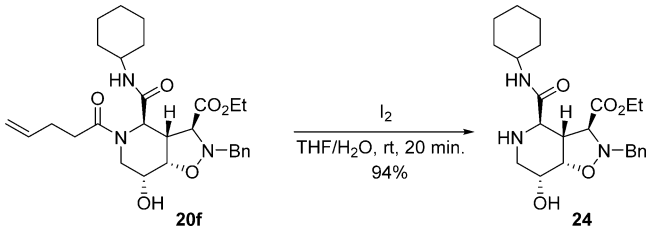

| entry | acid | isocyanide | Product | yield[b] | ratio |
|---|---|---|---|---|---|
| 1 |  |  | **20a/21a** | 53%[c] | 56:44 |
| 2 |  |  | **20a/21a** | 60% | 51:49 |
| 3 |  |  | **20b/21a** | 65% | 46:54 |
| 4 |  |  | **20c/21a** | 76% | 36:64 |
| 5 |  |  | **20d/21a** | 68% | 48:52 |
| 6 |  |  | **20e/21e** | 54% | 53:47 |
| 7a<br>7b |  |  | **20f/21f** | 28%<br>79%<br>(TFE) | 1:0[d]<br>42:58 |
| 8 |  |  | **20g/21g** | 30% | 56:44 |
| 9a<br>9b |  |  | **20h/21h** | 20%<br>74%<br>(TFE) | 82:18<br>33:67 |
| 10a<br>10b |  |  | **20i/21i** | 13%<br>59%<br>(TFE) | 1:0[d]<br>31:69 |
| 11 |  |  | **20j/21i** | 16% | 1:0[d] |

[a]Reaction conditions: (a) (i) $PMe_3$, EtOH, 4 °C, 3 h; (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

**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**, and **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 the 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).

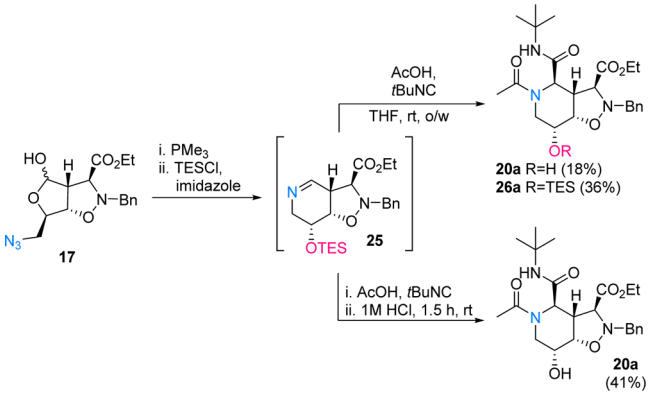
**Scheme 7. Facile Deprotection of *Anti*-Product 20f To Provide Iminosugar 24**




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 toward one of the SAWU-3CR products. We reasoned that the reaction could be made more selective toward 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.

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 chose to investigate the Petasis and Mannich

**Scheme 8. In Situ TES Protection of the Cyclic Imine Results in Selective *Anti*-Product Formation**



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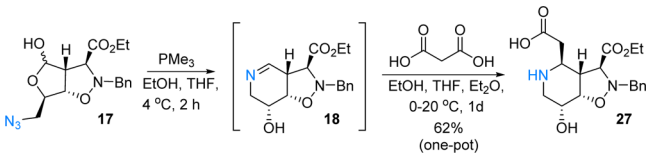
reaction, which both have not yet been used in conjunction with a Staudinger/aza-Wittig-generated imine. While the Petasis reaction did not result in any conversion to the target product in our hands (see the Supporting Information), we were able to modify imine **18** via a Mannich reaction. In situ 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 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 purchased from commercial sources (Raney 2800, as a slurry in $H_2O$), which was washed with anhydrous THF three times before use. Palladium on carbon (Pd/C) was purchased from commercial sources (10 wt % loading, matrix activated carbon support). Analytical TLC was performed using prepared plates of silica gel (60 F-254 on aluminum) or aluminum oxide (60 Å, 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 aluminum 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 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 analyzer, 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 (3aR,6R,6aS)-2-Benzyl-6-(((tert-butyldiphenylsilyl)oxy)-methyl)-4-oxohexahydrofuro[3,4-d]isoxazole-3-carboxylate (**7**).* A solution of nitrone **3a** (0.333 g, 1.61 mmol, 1.14 equiv) in toluene (9 mL) was heated to 40 °C for 2 h, followed by the addition of furanone **2** (0.498 g, 1.41 mmol, 1.0 equiv) and additional toluene (3 mL). The reaction mixture was heated to reflux for 4 h and then concentrated in vacuo. The residue was purified via column chromatography (5−15% EtOAc in petroleum ether 40−60) to afford **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*) $\delta$ 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*) $\delta$ 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 Ondruš et al.[25]

*(3S,3aR,6R,6aS)-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 g, 0.736 mmol, 1.0 equiv) in 1,2-dichloroethane (11 mL) was added $Me_3SnOH$ (0.540 g, 2.99 mmol, 4.06 equiv). The resulting suspension was heated to reflux for 2.5 h, then concentrated under a $N_2$ stream, and then dissolved in EtOAc (50 mL). The organic layer was washed with 1 M aq HCl (5 mL, 2×) and brine (5 mL), dried ($MgSO_4$), and then concentrated in vacuo to afford 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*) $\delta$ 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, three-neck, round-bottom flask and cooled to −15 °C. To this solution was added isobutyl chloroformate (1.07 g, 7.82 mmol, 10.0 equiv) followed by the dropwise addition of a suspension of $NaBH_4$ (0.297 g, 7.85 mmol, 10.0 equiv) in DMF (7.0 mL) over 10 min. The resulting reaction mixture was stirred at −15 °C for 75 min and then quenched with 1 M 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 concentrated in vacuo. The residue was purified by flash column chromatography (20−30% EtOAc in petroleum ether 40−60) to afford compound **10** (385 mg, 94% over two 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*) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ = 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 (3S,3aR,6R,6aS)-2-Benzyl-6-(((tert-butyldiphenylsilyl)oxy)-methyl)-4-hydroxyhexahydrofuro[3,4-d]isoxazole-3-carboxylate (**11**) and Ethyl (3S,4S,5S)-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) 2 M 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, stirred for 3.5 h, and quenched by careful addition of 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 colorless oil, which was generally used to obtain compound **12** without further purification. Optionally, the crude could be purified by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flash column chromatography (30−50% EtOAc in petroleum ether 40−60) to afford an anomeric mixture of hemiacetal **11** (320 mg, 78%) as a colorless 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 colorless 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 to +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 portionwise addition of 1 M aq HCl (10 mL). The reaction mixture was extracted with EtOAc (10 mL, 3×), and the combined organic layers were washed with satd aq $NaHCO_3$ solution (10 mL) and brine (10 mL), 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) to afford diol **12** (87.2 mg, 87%) as a colorless oil: $R_f$ = 0.27 (7:3; PE/EtOAc); $^1$H NMR (400 MHz, chloroform-*d*) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ = 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-((3R,4S,5R)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)-4-hydroxy-2-oxotetrahydrofuran-3-yl)-2,2-dimethoxyethyl)-carbamate (**13**).* A solution of cycloadduct **8a** (0.124 g, 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 g) and stirred under an hydrogen atmosphere (1 bar; balloon) for an additional 2 h. The reaction mixture was then placed under an argon atmosphere (1 bar), and Pd/C (0.100 g) 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 the mixture was allowed to warm to room temperature. The reaction mixture was filtered over Celite, the Celite was subsequently washed with THF, and the combined filtrate was concentrated in vacuo. The resulting residue was purified by flash column chromatography (20−30% EtOAc in petroleum ether 40−60) to afford 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*) $\delta$ 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, $CDCl_3$) $\delta$ 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 portionwise addition of TsCl (0.540 g, 2.83 mmol, 1.5 equiv). The reaction mixture was stirred at −15 °C and allowed to warm to 5 °C over 1 h. The reaction mixture was diluted with DCM (30 mL) and washed with 1 M aq HCl (10 mL, 3×), satd aq $NaHCO_3$ (10 mL), and brine (10 mL). The organic phase was dried ($MgSO_4$) and then concentrated in vacuo. The resulting residue was purified by flash column chromatography (0−100% MeOH in DCM) to afford the product **14** (355 mg, 70%) as a colorless oil: $^1$H NMR (400 MHz, chloroform-*d*) $\delta$ 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, $CDCl_3$) $\delta$ 171.7, 151.8, 145.7, 132.2, 130.2, 128.1, 123.9, 79.8, 67.5, 21.8; FT-IR (neat) $\nu$ = 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 (3aR,6R,6aS)-2-Benzyl-6-(hydroxymethyl)-4-oxohexahydrofuro[3,4-d]isoxazole-3-carboxylate (**6a**).* Nitrone **3a** (4.83 g, 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 h and then concentrated 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*) $\delta$ 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*) $\delta$ 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 Ondruš et al.[25]

*Ethyl (3S,3aR,6R,6aS)-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 h. $H_2O$ (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 concentrated in vacuo. The residue was purified by flash column chromatography (2−5% MeOH in DCM) to afford 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 g, 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. Saturated aq $NaHCO_3$ (400 mL) was added to the reaction mixture, followed by DCM (1 L). The resulting biphasic system was separated, the water layer was extracted with DCM (2 × 400 mL, 100 mL), and the combined organic layers were dried ($MgSO_4$) and then concentrated in vacuo to afford the crude mesylated intermediate, which was dissolved in DMF (86 mL). $NaN_3$ (14.0 g, 215 mmol, 4.00 equiv) was added, and 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 concentrated in vacuo. The residue was purified by flash column chromatography (10−25 EtOAc in petroleum ether 40−60) to afford compound **16** (17.67 g, 89% over two steps) as an orange oil: $R_f$ = 0.44 (7:3; PE/EtOAc); $^1$H NMR (400 MHz, chloroform-*d*) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ = 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 (3S,3aR,6R,6aS)-6-(Azidomethyl)-2-benzyl-4-hydroxyhexahydrofuro[3,4-d]isoxazole-3-carboxylate (**17**).* To a round-bottom



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flask containing lactone **15** (9.28 g, 26.8 mmol, 1.0 equiv) at 4 °C was added a 4 °C a 2 M 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 min and then allowed to warm to room temperature and stirred for 7 h. The reaction mixture was cooled to 4 °C and quenched by the portionwise addition of MeOH (200 mL). The reaction mixture was concentrated in vacuo and then purified by flash column chromatography (25−50 EtOAc in heptane) to afford an anomeric mixture of compound **17** (3.16 g, 34%) as a white solid: $R_f$ = 0.58 (1:1; PE/EtOAc); mp = 96−98 °C; $^1$H NMR (400 MHz, chloroform-*d*) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ = 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 (3aR,7R,7aS)-2-Benzyl-7-hydroxyoctahydroisoxazolo[4,5-c]-pyridine-3-carboxylate (**19**).* To a solution of azido-aldehyde **17** (0.106 g, 0.304 mmol, 1 equiv) in dry EtOH (1.6 mL) at 0 °C was added a solution of trimethylphosphine (1 M in THF, 0.610 mL, 2 equiv). The reaction mixture was stirred at 0 °C for 3 h, concentrated, and subsequently coevaporated with dry toluene (3×). The residue was dissolved in dry THF (1.6 mL) and cooled to 0 °C. $(AcO)_3BHNa$ (0.184 g, 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 satd 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 concentrated in vacuo. The water layer was then additionally extracted with DCM (10 mL, 5×), and the combined organic layers were dried ($MgSO_4$) and concentrated 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-$d_4$) $\delta$ 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) $\delta$ 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) $\nu$ = 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 Procedures A and B.** To a round-bottom flask containing a 0.18 M solution of azido-aldehyde **17** (1 equiv) in dry EtOH at 0 °C was added a solution of trimethylphosphine (1 M in THF, 2 equiv). The reaction mixture was stirred at 0 °C for 3 h, concentrated, and subsequenently coevaporated with dry toluene (3×). The crude cyclic imine was dissolved dry EtOH (0.3M) (procedure A) or dry 2,2,2-trifluoroethanol (0.3 M) (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 h while the mixture was allowed to warm to room temperature. Saturated $NaHCO_3$ was added to the mixture, which was then extracted with EtOAc (3×). The combined organic layers were washed with satd $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. The SAWU-3-CR products were purified by silica gel flash column chromatography.

*Ethyl (3S,3aR,4R,7R,7aS)-5-Acetyl-2-benzyl-4-(tert-butylcarbamoyl)-7-hydroxyoctahydroisoxazolo[4,5-c]pyridine-3-carboxylate (**20a**) and Ethyl (3S,3aR,4S,7R,7aS,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 silica gel column chromatography (50−100% EtOAc in heptane then 0−100% EtOH in EtOAc) to afford 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*) $\delta$ 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 and $COOCH_2CH_3$); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 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) $\nu$ = 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*) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ = 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 (3S,3aR,4R,7R,7aS)-2-Benzyl-4-(tert-butylcarbamoyl)-7-hydroxy-5-(pent-4-enoyl)octahydroisoxazolo[4,5-c]pyridine-3-carboxylate (**20b**) and Ethyl (3S,3aR,4S,7R,7aS,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) to afford 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*) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ = 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*) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ = 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 (3S,3aR,4R,7R,7aS)-2-Benzyl-4-(tert-butylcarbamoyl)-7-hydroxy-5-(2,2,2-trifluoroacetyl)octahydroisoxazolo[4,5-c]pyridine-3-carboxylate (**20c**) and Ethyl (3S,3aR,4S,7R,7aS,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) to afford impure **20c** and pure **21a** (70 mg, 49%) as a crystalline solid. Impure **20c** was further purified via column chromatography (20% acetone in toluene) to afford **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*) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ = 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



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(100% EtOH); $^1$H NMR (400 MHz, chloroform-*d*) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ = 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 (3S,3aR,4R,7R,7aS)-5-Benzoyl-2-benzyl-4-(tert-butylcarbamoyl)-7-hydroxyoctahydroisoxazolo[4,5-c]pyridine-3-carboxylate (**20d**) and Ethyl (3S,3aR,4S,7R,7aS,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) to afford **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*) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ = 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 (3S,3aR,4R,7R,7aS)-2-Benzyl-4-(butylcarbamoyl)-7-hydroxy-5-(pent-4-enoyl)octahydroisoxazolo[4,5-c]pyridine-3-carboxylate (**20e**) and Ethyl (3S,3aR,4S,7R,7aS,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) to afford 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*) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ = 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 (3S,3aR,4R,7R,7aS)-2-Benzyl-4-(cyclohexylcarbamoyl)-7-hydroxy-5-(pent-4-enoyl)octahydroisoxazolo[4,5-c]pyridine-3-carboxylate (**20f**) and Ethyl (3S,3aR,4S,7R,7aS,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) to afford **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*) $\delta$ 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); C NMR (101 MHz, $CDCl_3$) $\delta$ 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) $\nu$ = 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*) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ = 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 (3S,3aR,4R,7R,7aS)-2-Benzyl-7-hydroxy-5-(pent-4-enoyl)-4-(((S)-1-phenylethyl)carbamoyl)octahydroisoxazolo[4,5-c]pyridine-3-carboxylate (**20g**) and Ethyl (3S,3aR,4S,7R,7aS,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) to afford 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*) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ = 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 (3S,3aR,4R,7R,7aS)-2-Benzyl-4-(benzylcarbamoyl)-7-hydroxy-5-(pent-4-enoyl)octahydroisoxazolo[4,5-c]pyridine-3-carboxylate (**20h**) and Ethyl (3S,3aR,4S,7R,7aS,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) to afford 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*) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ = 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*) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ = 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 (3S,3aR,4R,7R,7aS)-5-Benzoyl-2-benzyl-7-hydroxy-4-((4-methoxyphenyl)carbamoyl)octahydroisoxazolo[4,5-c]pyridine-3-carboxylate (**20i**), Ethyl (3S,3aR,4S,7R,7aS,Z)-2-Benzyl-9-((4-*



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*methoxyphenyl)imino)octahydro-7,4-(epoxymethano)isoxazolo-[4,5-c]pyridine-3-carboxylate (**21i**), and Ethyl (3S,3aR,4S,7R,7aS,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) to afford 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*) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ = 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*) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ = 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*) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ = 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 (3S,3aR,4R,7R,7aS)-2-Benzyl-7-hydroxy-4-(((4-methoxy-phenyl)carbamoyl)carbamoyl)-5-phenyloctahydroisoxazolo[4,5-c]-pyridine-3-carboxylate (**20j**) and Ethyl (3S,3aR,4S,7R,7aS,Z)-2-Benzyl-9-((4-methoxyphenyl)imino)octahydro-7,4-(epoxymeth-ano)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) to afford **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*) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ = 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 (3S,3aR,4S,7R,7aS)-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 and coevaporated with dry toluene to remove excess water. The residue was purified by flash column chromatography (30−50% acetone in toluene) to afford 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*) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ = 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 (3S,3aR,4R,7R,7aS)-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, quenched by the addition of 1 M aq $Na_2S_2O_3$ (4 mL), and stirred for 30 min. The reaction mixture was poured into a mixture of 1 M aq $Na_2S_2O_3$/satd aq NaCl (1/1, v/v, 10 mL) and then extracted with EtOAc (4×), dried ($MgSO_4$), and concentrated in vacuo to afford a yellow oil. The residue was purified by flash column chromatography (0−20% EtOH in EtOAc) to provide 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*) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ = 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-((3S,3aR,4S,7R,7aS)-2-Benzyl-3-(ethoxycarbonyl)-7-hydroxy-octahydroisoxazolo[4,5-c]pyridin-4-yl)acetic Acid (**27**).* To a round-bottom flask containing a solution of azido-aldehyde **17** (0.106 g, 0.287 mmol, 1 equiv) in dry EtOH (1.6 mL) at 0 °C was added a solution of trimethylphosphine (1 M in THF, 0.575 mL, 2 equiv). The reaction mixture was stirred at 0 °C for 3 h, concentrated, and coevaporated 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 h, followed by the addition of MeOH (5 mL). The resulting solution was concentrated in vacuo to afford a yellow foam, which was purified by trituration with hot THF and subsequent trituration in hot MeOH, to afford 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-$d_4$) $\delta$ 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-$d_6$) $\delta$ 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) $\nu$ = 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 round-bottom flask containing a solution of azido-aldehyde **17** (0.104 g, 0.299 mmol, 1 equiv) in dry EtOH (1.6 mL) at 0 °C was added a solution of trimethylphosphine (1 M in THF, 0.600 mL, 2 equiv). The reaction mixture was stirred at 0 °C for 2 h, concentrated, and coevaporated 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 min at 0 °C and then another 50 min at room temperature. The mixture was then cooled to 0 °C,


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followed by the addition of acetic acid (86.0 μL, 1.50 mmol, 5.0 equiv) and *tert*-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 satd 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 satd aq $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), and then concentrated in vacuo. The residue was purified by flash column chromatography (20−100% EtOAc in heptane) to provide 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*) $\delta$ 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, $CDCl_3$) $\delta$ 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) $\nu$ = 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 and Deprotection.** To a round-bottom flask containing a solution of azido-aldehyde **17** (0.104 g, 0.299 mmol, 1 equiv) in dry EtOH (1.6 mL) at 0 °C was added a solution of trimethylphosphine (1 M in THF, 0.598 mL, 2 equiv). The reaction mixture was stirred at 0 °C for 2 h, concentrated, and coevaporated 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 min at 0 °C and then another 30 min at room temperature. The mixture was then cooled to 0 °C followed by the addition of *tert*-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 1 M HCl in $Et_2O$ (1.5 mL) were added, and the solution was stirred at rt for 2 h followed by the addition of satd 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 satd aq $NaHCO_3$ (8 mL) and brine (8 mL), dried ($MgSO_4$), and then concentrated in vacuo. The residue was purified by flash column chromatography (50−100% EtOAc in heptane) to provide compound **20a** (65.7 mg, 41%) as a yellow oil.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01515.

Characterization data and copies of $^1$H and $^{13}$C NMR spectra for all compounds (PDF)

X-ray crystallographic data for compound **6a** (CIF)

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: t.wennekes@uu.nl.


### Notes

The authors declare no competing financial interest.

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