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The Effect of Lewis Acids on the Stereochemistry in the Ugi Three-Component Reaction with D-*lyxo*-Pyrroline

Kimberly M. Bonger,[a][‡] Tom Wennekes,[a][‡] Dmitri V. Filippov,[a] Gerrit Lodder,[a] Gijsbert A. van der Marel,[a] and Herman S. Overkleeft*[a]

Dedicated to Professor Jan Reedijk on the occasion of his 65th birthday and retirement

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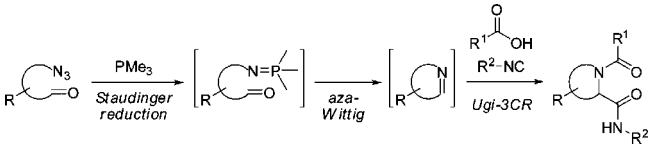
A library of polyhydroxylated pyrrolidines was obtained by performing a tandem Staudinger/aza-Wittig/Ugi three-component reaction on a L-ribose-derived 4-azido aldehyde. In this paper we describe the effect of Lewis acids on the diastereoselectivity of the final Ugi three-component reaction step that the intermediate (D-*lyxo*-pyrroline) cyclic imine undergoes. When the Ugi reaction was performed in methanol almost exclusively pyrrolidines with a 2,3-*cis* relationship were formed. However, a significant amount of 2,3-*trans* product was formed upon addition of Lewis acids to the Ugi reaction mixture. The scope of this effect is explored by evaluating a diverse set of Lewis acids in combination with variation of other reaction parameters and the carboxylic acid/isocyanide component.

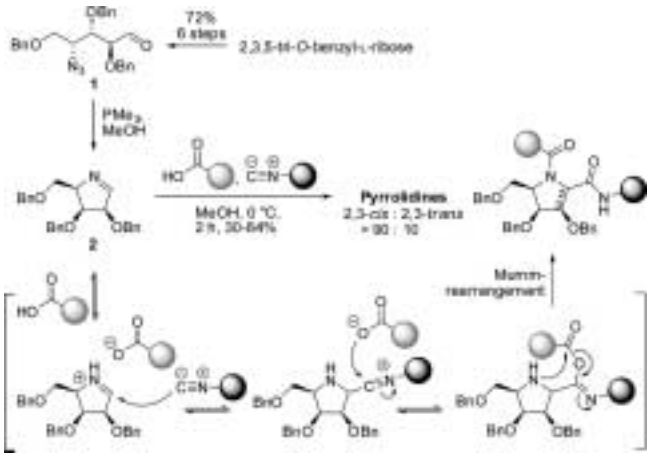
Introduction

Multicomponent reactions (MCRs) are frequently used as a powerful method to generate large families of structurally related molecules. Among MCRs, the Ugi reaction is one of the most explored to date.[1] We recently reported a variation on the Ugi reaction that we named the tandem Staudinger/aza-Wittig/Ugi three-component reaction (SAWU-3CR).[2] In this one-pot procedure, a carbohydrate-derived 4-azido aldehyde (Scheme 1) is subjected to Staudinger reduction with trimethylphosphane. The intermediate phosphazene thereupon undergoes an intramolecular aza-Wittig reaction with the aldehyde to form an imine. This cyclic imine is subsequently used as a component together with a carboxylic acid and an isocyanide in the Ugi three-component reaction (Ugi-3CR).



Scheme 1. Overview of the SAWU-3CR reaction sequence.

In our studies on the scope of the SAWU-3CR, we observed that the 4-azidoaldehyde **1** produces pyrrolidines with counter-intuitive 2,3-*cis* stereochemistry at the new stereogenic centre (Scheme 2).[3] This stereochemistry is established in the final Ugi-3CR step with the cyclic imine[4] (D-*lyxo*-pyrroline **2**). The Ugi-3CR mechanism consists of a series of successive equilibria where the C-2 stereogenic center is created upon attack of the isocyanide and fixed in the irreversible Mumm-rearrangement (Scheme 2).



Scheme 2. Synthesis of pyrrolidines from the 4-azidoaldehyde **1** with the tandem SAWU-3CR.

[a] Gorlaeus Laboratories, Leiden Institute of Chemistry, Leiden University,
PO Box 9502, 2300 RA Leiden, The Netherlands
Fax: +31-71-527-4307
E-mail: h.s.overkleeft@chem.leidenuniv.nl
[‡] K. M. Bonger and T. Wennekes contributed equally to this work.
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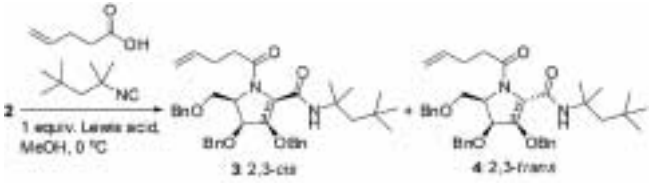
The preferred formation of 2,3-*cis* pyrrolidines in the Ugi-3CR with **2** is not influenced by the carboxylic acid or isocyanide component used.[3] Variation of the stoichiometry of the carboxylic acid and isocyanide component or of the reaction solvent and temperature also did not alter this preference for 2,3-*cis* products (unpublished results). In the study reported here we investigated what factors do influence the stereochemical outcome of the Ugi-3C reaction with D-*lyxo*-pyrroline **2**.

Results and Discussion

In related MCRs such as the Passerini-3CR, control of stereochemistry has been achieved by using Lewis acids combined with chiral ligands.[5] For the Ugi reaction, catalytic properties of Lewis acids on the yield and reaction rate have been reported.[6] In addition, $ZnCl_2$ has been shown to induce diastereoselectivity in the Ugi reaction when combined with chiral imines of glycosylamine derivatives.[7]

Consequently, we evaluated the effect of a diverse set of Lewis acids on the Ugi-3C reaction of **2** with pentenoic acid and 2,2,4,4-tetramethylbutyl isocyanide (*t*MB–NC). The reactions were performed by sequentially adding one equiv. of Lewis acid, carboxylic acid and isocyanide to a methanolic solution of **2** at 0 °C and stirring the reaction mixture for 2 h. The results are listed in Table 1 and it is apparent that Lewis acids have a considerable effect on the stereochemical outcome. In the presence of most Lewis acids, increased formation of 2,3-*trans* isomer **4** occurred. Among all Lewis acids tested, $InCl_3$[8] and $HgBr_2$ (Entries 11 and 15) gave the highest amount of the 2,3-*trans* product **4** with good overall yields. For the other Lewis acids that showed high amounts of the 2,3-*trans* product **4** [that is, $AlCl_3$, $SnCl_4$ and $Yb(OTf)_3$], a significantly lower yield was observed.

Table 1. The effect of Lewis acids on the Ugi-3C reaction of **2**.

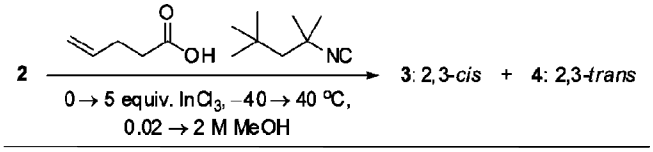


Entry	Lewis acid	2,3-*cis*	2,3-*trans*	Yield (%)[a]
1	none	> 90	10	72
2	$Ti(OiPr)_4$	> 90	10	50
3	CsF	81	19	53
4	$LiOCl_4$	76	24	87
5	LiBr	74	26	58
6	$MgBr_2$	63	37	91
7	$TiCl_4$	60	40	42
8	$Zr(OiPr)_4$	57	43	61
9	$BF_3{\cdot}Et_2O$	55	45	63
10	$ZnCl_2$	50	50	85
11	$InCl_3$	42	58	75
12	$AlCl_3$	40	60	47
13	$SnCl_4$	34	66	42
14	$Yb(OTf)_3$	33	67	58
15	$HgBr_2$	29	71	84

[a] Ratio and yield based on products purified by column chromatography.

In order to better understand what factors were causing the altered stereochemical outcome we further investigated the $InCl_3$-mediated Ugi-3CR. Table 2 presents the results of varying the amount of $InCl_3$, the temperature and the concentration at which the reaction is performed. These experiments show that formation of the 2,3-*trans* product is directly related to the amount of $InCl_3$. In the presence of a catalytic amount of $InCl_3$ the formation of 2,3-*cis* (**3**) was still dominant. However, upon increasing the amount of $InCl_3$ the formation of 2,3-*trans* (**4**) also increased. Variation of the reaction temperature had a slight effect on the stereochemical outcome and affected the overall yield. A clear trend of increased yields at lower reaction temperatures was observed. Variation of the concentration of the reaction had an effect on the stereochemical outcome of the Ugi-3CR, but the effect does not appear to be associated with the presence of a Lewis acid. Performing the reaction in very dilute solutions increased the formation of the 2,3-*trans* product **4**, both in the presence and absence of $InCl_3$.

Table 2. The effect of Lewis acid amount and the temperature and concentration of the Ugi-3C reaction.



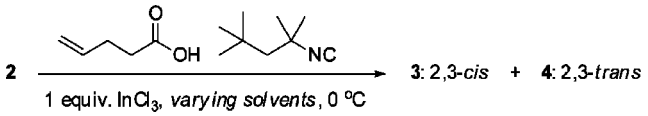
Entry	$InCl_3$ [equiv.]	*T* [°C]	Conc. [M]	2,3-*cis*/2,3-*trans*	Yield (%)[a]
Varying the amount of Lewis acid					
1	0	0	0.1	> 90 : 10	72
2	0.2	0	0.1	75 : 25	70
3	1	0	0.1	42 : 58	75
4	5	0	0.1	28 : 72	81
Varying the reaction temperature					
5	1	–40	0.1	48 : 52	85
6	1	0	0.1	42 : 58	75
7	1	20	0.1	33 : 67	63
8	1	40	0.1	60 : 40	44
Varying the reaction concentration (with $InCl_3$)					
9	1	0	2	45 : 55	74
10	1	0	0.2	42 : 58	62
11	1	0	0.02	30 : 70	52
Varying the reaction concentration (no $InCl_3$)					
12	0	0	2	> 90 : 10	58
13	0	0	0.2	> 90 : 10	66
14	0	0	0.02	78 : 22	80

[a] Ratio and yield based on products purified by column chromatography.

The influence of the solvent on the Lewis acid mediated Ugi reaction proved to be significant. Table 3 shows the obtained ratios and yields for the Ugi-3CR with **2** as performed in various solvents in the presence of one equiv. of $InCl_3$ at 0 °C. Only in DMF, methanol and acetonitrile a significant amount of the 2,3-*trans* product **4** was formed. The highest amount of the 2,3-*trans* product **4** was observed for acetonitrile (Entry 10). When $InCl_3$ was excluded from

the Ugi reaction in acetonitrile the 2,3-*cis* product was again the main product (Entry 11). This confirms that the solvent itself has no distinct effect on the stereochemical outcome. The other efficient 2,3-*trans* promoting Lewis acid in methanol from Table 1, $HgBr_2$, was also tested in acetonitrile (Entry 12). Interestingly, no improved 2,3-*trans* product formation was observed, but instead the formation of 2,3-*trans* decreased compared to the ratio obtained in methanol.

Table 3. The effect of the solvent of the Ugi-3C reaction.



Entry	Solvent	2,3-*cis*/2,3-*trans*	Yield (%)[a]
1	THF	> 90 : 10	16
2	dioxane	> 90 : 10	trace
3	CH_2Cl_2	83 : 17	41
4	2-propanol	81 : 19	27
5	hexane	77 : 23	66
6	toluene	77 : 23	56
7	EtOAc	70 : 30	39
8	DMF	57 : 43	32
9	MeOH	42 : 58	75
10	CH_3CN	16 : 84	63
11	CH_3CN without $InCl_3$	75 : 25	33
12	CH_3CN with $HgBr_2$	43 : 57	92

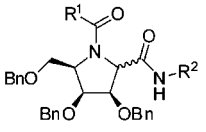
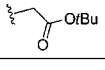
[a] Ratio and yield based on products purified by column chromatography.

There is literature evidence that addition of (catalytic amounts of) Lewis acid increases the reaction rate of Ugi-MCRs.[6] We therefore investigated whether this also holds true for our system with **2** and $InCl_3$ in methanol. Part A of Figure 1 depicts the formation of the 2,3-*cis* (**3**) and 2,3-*trans* (**4**) products over time as monitored by LC/MS in the presence and absence of $InCl_3$. As previously observed the addition of Lewis acid significantly increases the formation of 2,3-*trans* (**4**). However, no effect on the overall reaction rate was observed.

We next evaluated the effect of a 25-fold excess of the isocyanide or carboxylic acid reaction partner on the Ugi-3CR reaction rate and the product ratio in methanol in the presence and absence of $InCl_3$ (shown in parts B and C of Figure 1, respectively). In the presence of an excess isocyanide and no $InCl_3$, formation of the 2,3-*cis* product remained dominant and a significant increase in the reaction rate was observed (Figure 1, B). When 25-fold isocyanide was used in the presence of $InCl_3$ the same increase in reaction rate was observed but now accompanied with an increase in 2,3-*trans* (**4**) product formation. When an excess carboxylic acid was subjected to the reaction without $InCl_3$, similar increased reaction rates were observed as with excess isocyanide (Figure 1, C). Upon addition of $InCl_3$, the reaction rate decreased significantly and the 2,3-*cis* isomer (**3**) was again the main product. The same set of experiments was also performed in acetonitrile with one equiv. of $InCl_3$. In this system, immediate formation of the Ugi-products was observed in all cases (data not shown). As in the experiments in methanol, a 25-fold excess of carboxylic acid in acetonitrile with $InCl_3$ altered the major product from 2,3-*trans* (**4**) to 2,3-*cis* (**3**).

Finally, the scope of the $InCl_3$-mediated Ugi-3C reaction with **2** in acetonitrile was evaluated with a diverse set of carboxylic acids and isocyanides. Table 4 gives an overview

Table 4. The effect of the carboxylic acid and isocyanide component on the $InCl_3$-mediated Ugi-3CR of **2** in CH_3CN.

Total yields (%)[a] and ratios 2,3-*cis*/2,3-*trans*				
	R¹: A	B	C	D
I: 	68 % 29 : 71	38 % 18 : 82	63 % 16 : 84	20 % 10 : > 90
II: 	53 % 26 : 74	38 % 50 : 50	72 % 33 : 67	35 % 32 : 68
R² III: 	56 % 14 : 86	31 % 45 : 55	51 % 42 : 58	32 % 43 : 57
IV: 	35 % 16 : 84	62 % 25 : 75	50 % 43 : 57	24 % 45 : 55
V: 	63 % 48 : 52	28 % 50 : 50	47 % 48 : 52	41 % 45 : 55

[a] Ratio and yield based on products purified by column chromatography.

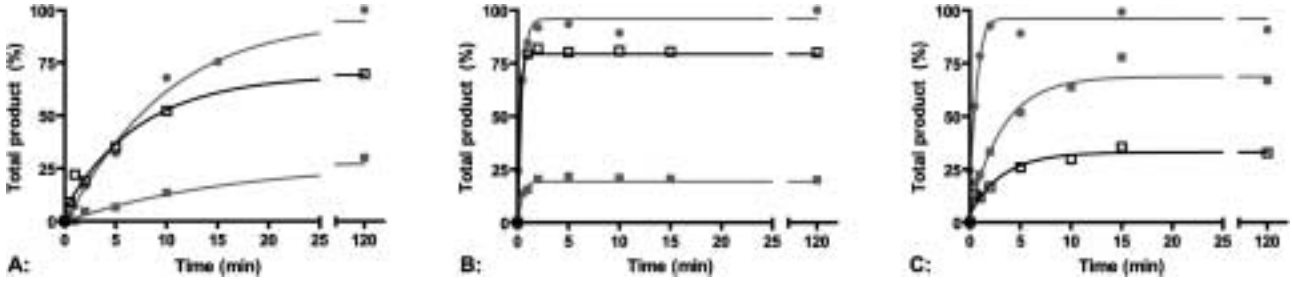


Figure 1. Formation of Ugi-3CR products over time as monitored by LC/MS. A: 1 equiv. 2,2,4,4-tetramethylbutyl isocyanide (*t*MB–NC) and 1 equiv. pentenoic acid, MeOH, 0.1 M, 0 °C; B: 25 equiv. *t*MB–NC and 1 equiv. pentenoic acid, MeOH, 0.1 M, 0 °C. C: 1 equiv. *t*MB–NC and 25 equiv. pentenoic acid, MeOH, 0.1 M, 0 °C. Filled gray circles: 2,3-*cis* (**3**) formed without $InCl_3$; filled gray squares: 2,3-*cis* (**3**) formed with 1 equiv. $InCl_3$; open black squares: 2,3-*trans* (**4**) formed with 1 equiv. $InCl_3$.

of the obtained products, 2,3-*cis*/*trans* ratios and overall yields. For comparison, when these reactions are performed in methanol without Lewis acid the 2,3-*cis* substituted pyrrolidines are almost exclusively formed, as reported previously.[3] In all cases for the Lewis acid mediated Ugi-3C reaction with **2** formation of the 2,3-*trans* product equaled or exceeded the formation of the 2,3-*cis* product. However, the 2,3-*cis*/*trans* ratio is highly dependent on the carboxylic acid and isocyanide used. In the case of isocyanide **V**, a ca. 1:1 mixture of products was observed that is independent of the used carboxylic acid. In contrast, the isocyanide **I** prefers formation of the 2,3-*trans* product in all cases. The overall yields are slightly lower than the reactions performed in methanol without a Lewis acid.[9] The lower yields could be caused by a known side reaction in which a second isocyanide adds to intermediate **7** (see Scheme 3) [10,5c] or by the possible promotion of other side reactions, such as the Ritter reaction,[11] by the Lewis acid in acetonitrile.

Scheme 3. Isocyanide addition via acyloxy/contact ion-pair intermediate **6**.

A possible explanation for the diastereoselective formation of 2,3-*cis* pyrrolidines in the Ugi-3C reaction with the D-*lyxo*-pyrroline **2** in the absence of Lewis acids may be found in the existence of an acyloxy intermediate in the course of the reaction (**6**; X = H, Scheme 3). This intermediate was first postulated by Ugi and its involvement in the Ugi reaction has subsequently been proposed by others.[1b,4d,12]

The intermediate **6** (X = H) would be formed after protonation of the imine by the attack of the nearby carboxylate anion from the least hindered side of **5** (X = H). After S_N2 displacement by the isocyanide yielding **7-*cis*** and subsequent Mumm-rearrangement this pathway would lead to the 2,3-*cis* pyrrolidine. Alternatively, the carboxylate anion might form a contact ion pair with the protonated cyclic imine and thereby shield the *trans*-face from isocyanide attack.

A Lewis acid can coordinate to the endocyclic nitrogen of the imine **2** and activate it. An explanation in the acyloxy model for the increased formation of the 2,3-*trans* products in the presence of Lewis acids may be that the Lewis acid activated imine **5** (X = LA) might favour direct attack of the isocyanide from the less hindered side to give **7-*trans***, which leads to 2,3-*trans*-pyrrolidines (Scheme 3).

Attempts to substantiate the acyloxy model by investigating the intermediates of the Ugi-3CR with ^{13}C-APT NMR measurements in CD_3OH were not conclusive. We did however observe an equilibrium of the imine **2** in CD_3OH with a second species that appears to be the CD_3O adduct **8**. Upon addition of one equiv. of $InCl_3$ to this solution the imine signals disappeared and the equilibrium fully shifted towards **8** (Figure 2). In the presence of $InCl_3$, **8** proved stable to the addition of a carboxylic acid. When in a final step isocyanide was added the species slowly disappeared (about 2 h) and the formation of 2,3-*trans* product **4** was observed.

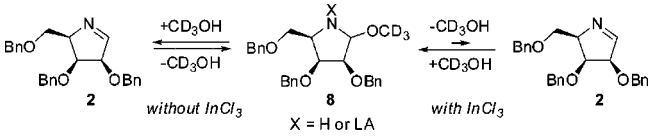


Figure 2. ^{13}C-APT NMR showed addition of the solvent, CD_3OH to the imine **2**. This equilibrium between **2** and **8** shifted towards **8** when $InCl_3$ was added.

A second ^{13}C-APT NMR experiment with **2** in CD_3OH in the absence of Lewis acid showed, upon addition of a carboxylic acid, an equilibrium between **2** and two other species that differed in their spectrum from putative **8**. These might be acyloxy intermediates, but could not be conclusively assigned as such. The earlier mentioned observation that in the presence of $InCl_3$, a 25-fold excess of carboxylic acid favours the formation of the 2,3-*cis* product (Figure 2, C) while 2,3-*trans* product formation dominated at a stoichiometric amount, might also indicate the involvement of an acyloxy intermediate. However, the excess carboxylic acid could also coordinate with $InCl_3$, thereby make it less available for interaction in the Ugi-3C reaction and thus result in 2,3-*cis* pyrrolidine formation.

Another plausible explanation for the 2,3-*cis* pyrrolidine formation in the absence of Lewis acids involves the influence of electronic effects on the conformation of the activated cyclic imine **5** (X = H, Figure 3, A). Woerpel and coworkers proposed a model for nucleophilic additions to five-membered ring oxocarbenium ion electrophiles.[13] In

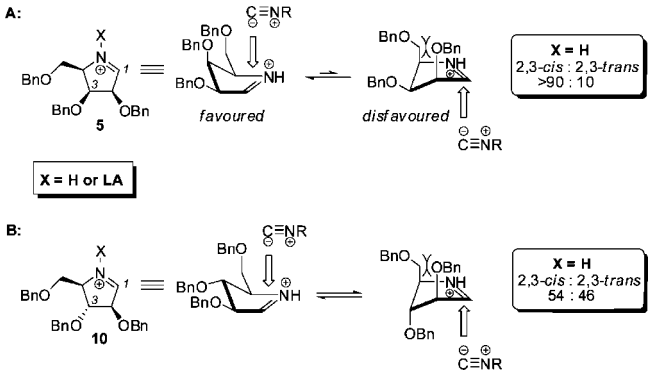


Figure 3. A: Formation of the 2,3-*cis* product from **5** by isocyanide attack from the concave face of the favoured conformer. B: Formation of ca. 1:1 mixture from **10** due to absence of a favoured conformer.

this model, a pseudoaxial position of alkoxy substituents at C-3 of the oxocarbenium ion produces the lowest energy conformer by maximizing favourable intramolecular electrostatic interactions. The nucleophile then attacks from the concave site of the envelope conformation giving a 1,3-*cis* product. The D-*lyxo*-pyrroline **2** also resides in an envelope conformation. The C-2/C-3 benzyloxy substituents in **2** also possess the required stereochemistry for the favoured pseudoaxial orientation after protonation to **5** (X = H). The favoured conformer of **5** (X = H) undergoes 1,3-*cis* attack of the isocyanide yielding 2,3-*cis* Ugi-3CR products (Figure 3, A).

Woerpel and co-workers further demonstrated the "critical" electronic effect of the pseudoaxial C-3 alkyloxy substituents by testing a C-3 inverted D-arabinose analogue.[13b] Adopting a C-3 pseudoaxial conformer for this oxocarbenium ion is disfavoured and a nucleophilic addition reaction with it produced a 1:1 mixture of 1,3-*cis* and 1,3-*trans* attack products. Analogously, we performed the Ugi-3CR on the D-*arabino*-pyrroline **9**, which is protonated to **10** (X = H; Figure 3, B). This reaction produced a 54:46 ratio of 2,3-*cis* (**11**) and 2,3-*trans* (**12**) products in 68% yield as opposed to the > 90:10 mixture obtained for D-*lyxo*-pyrroline **2**. The loss of selectivity observed for **9** is in agreement with the results obtained by Woerpel and co-workers for five-membered ring oxocarbenium ions. This result can also be explained by the acyloxy model, because the inverted C-3 position might lead to less stereoselective attack of the carboxylate on **10** (X = H).

Coordination and activation of the cyclic imine **2** by a Lewis acid at the nitrogen might disturb the above (Figure 3, A) discussed electronic effects of the C-3 position. Additionally, coordination of the Lewis acid with the benzyloxy ether substituents might stabilize the disfavoured conformer or shield the *cis*-face of the activated imine **5** (X = LA; Figure 3, A) and thereby lead to 2,3-*trans* products.

The increased formation of 2,3-*trans* pyrrolidines in the presence of Lewis acid does not appear to be a general effect for pyrroline cyclic imines in the Ugi-3CR. The D-*arabino*-pyrroline **9**, pentenoic acid and 2,2,4,4-tetramethylbutyl isocyanide were reacted in acetonitrile in the presence of $InCl_3$. In this Lewis acid mediated Ugi-3CR, a ca. 1:1 (44:56) 2,3-*cis*/*trans* product mixture was obtained (30% yield). This ratio is almost the same as the ratio (54:46) obtained for D-*arabino*-pyrroline **9** in methanol in the absence of Lewis acid.

Conclusions

At present there is no conclusive evidence to discount or confirm either of the above discussed models. However, if the acyloxy intermediate is incorporated in the C-3/electronic model, in the absence of Lewis acid, it would predict 1,3-*cis* attack of the carboxylate resulting in 2,3-*trans* pyrrolidines. This fact makes the two models mutually exclusive. It is challenging to further investigate the role of Lewis acids because of the multitude of instances where Lewis acids could have an effect in the complex interplay of equilibria between intermediates in the Ugi-3CR with **2** (Scheme 2).

In case of D-*lyxo*-pyrroline **2**, the imine at the basis of the here presented study, we now do have considerable control over the stereochemical outcome when subjecting it to the Ugi-3CR. Increasing the amount of Lewis acid, performing the reaction at elevated temperature and in dilute solutions are factors that promote 2,3-*trans* pyrrolidine formation. Omitting the Lewis acid or performing the reaction in an apolar solvent with Lewis acid leads to the formation of the corresponding 2,3-*cis* pyrrolidines. The reaction conditions tolerate different carboxylic acids and isocyanides. However, the extent of diastereoselectivity for 2,3-*trans* products in the $InCl_3$ mediated Ugi-3CR in acetonitrile is dependent on the used pyrroline, carboxylic acid and isocyanide. The fact that Lewis acids influence the stereochemical outcome of the Ugi-3CR with D-*lyxo*-pyrroline **2** might provide some insight into the mechanism of the Ugi-3C reaction on prochiral imines.

We are currently investigating the (Lewis acid mediated) SAWU-3C reaction with a set of 4-azido aldehydes and 5-azido aldehydes derived from various furanose and pyranose carbohydrates. The pyrrolidine and piperidine bisamides obtained in these studies will be evaluated as iminosugar derivatives, with the potential to inhibit glycosyl processing enzymes,[14] or as polyhydroxylated proline or pipecolic acid derivatives, which may be incorporated into peptides to improve their biophysical properties.[15]

Experimental Section

General Methods: All solvents and reagents were obtained commercially and used as received unless stated otherwise. Methanol used for Ugi reactions was distilled from magnesium turnings and iodine, and stored over activated 3-Å molecular sieves under argon. Reactions were executed at ambient temperatures unless stated otherwise. All moisture sensitive reactions were performed under argon. Residual water was removed from starting compounds by repeated coevaporation with toluene. All solvents were removed by evaporation under reduced pressure. Column chromatography was performed on silica gel (40–63 μm). ^1H and ^{13}C-APT NMR spectra were recorded on a Bruker DMX 600 (600/150 MHz), Bruker DMX 500 (500/125 MHz), or Bruker AV 400 (400/100 MHz) spectrometer in $CDCl_3$. Chemical shifts are given in ppm (δ) relative to tetramethylsilane as internal standard (^1H NMR) or $CDCl_3$ (^{13}C NMR). Coupling constants (J) are given in Hz. All presented ^{13}C-APT spectra are proton decoupled. High-resolution mass spectra were recorded by direct injection (2 μL of a 2 μM solution in water/acetonitrile; 50:50; v/v and 0.1% formic acid) with a mass spectrometer (Thermo Finnigan LTQ Orbitrap) equipped with an electrospray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10, capillary temperature 250 °C) with resolution R = 60000 at m/z 400 (mass range m/z = 150–2000) and dioctylphthalate (m/z = 391.28428) as a "lock mass".[16] The high-resolution mass spectrometer was calibrated prior to measurements with a calibration mixture (Thermo Finnigan). Optical rotations were measured with a Propol automatic polarimeter (sodium D-line, λ = 589 nm). ATR-IR spectra were recorded with a Shimadzu FTIR-8300 fitted with a single bounce Durasample IR diamond crystal

ATR-element and are reported in cm^{-1}. R_f values were determined from TLC analysis using DC "fertigfolien" (Schleicher & Schuell, F1500, LS254), detection was performed by spraying with a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4\cdot 2H_2O$ (10 g/L) in 10% sulfuric acid or a solution of phosphomolybdic acid hydrate (7.5 wt.-% in ethanol) followed by charring at ca. 150 °C.

General Procedure for the SAWU-3CR Towards Substituted Pyrrolidines IA-D, IIA-D, IIIA-D, IVA-D, VA-D and 12-*trans*: The 4-azidopentanal **1** was coevaporated with toluene, dissolved in MeOH (0.05 M) and cooled (0 °C). After dropwise addition of a solution of trimethylphosphane (1 M in toluene, 2 equiv.), stirring was continued for 3 h at 0 °C when TLC analysis indicated complete consumption of the 4-azidopentanal and the appearance of the intermediate phosphazene (R_f = 0 in 1:1; EtOAc/toluene). The reaction mixture was concentrated and coevaporated with toluene, concomitant TLC analysis showed complete disappearance of the baseline phosphazene intermediate and emergence of the cyclic imine. Formation of the pyrroline **2** was confirmed by NMR analysis of the crude product. (3*R*,4*S*,5*R*)-3,4-di-*O*-benzyl-5-(benzyloxymethyl)-1-pyrroline (**2**). R_f = 0.34 (1:4; EtOAc/toluene). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.67 (s, 1 H, 2-H), 7.32–7.26 (m, 15 H, CH_{Ar} Bn), 4.72–4.50 (m, 7 H, 3×CH_2 Bn, 3-H), 4.35 (d, J = 4.7 Hz, 1 H, 4-H), 4.25–4.19 (m, 1 H, 5-H), 3.99–3.85 (m, 2 H, 6a-H, 6b-H) ppm. ^{13}C NMR (50.1 MHz, $CDCl_3$): δ = 166.9 (C-2), 138.0, 137.9, 137.2 (3×C Ar), 128.2, 127.9, 127.6, 127.4, 127.3 (9×CH Ar), 85.6, 77.7, 73.2 (C-3, C-4, C-5), 73.4, 73.1, 72.7 (3×CH_2 Bn), 68.5 (C-6) ppm. The crude pyrroline **2** is dissolved in MeOH or CH_3CN (0.1 M), divided in portions (0.2 mmol) and cooled (0 °C). The appropriate Lewis acid (1 equiv.) was added and subsequently the carboxylic acid (1 equiv.) and isocyanide (1 equiv.) were added. The reaction mixture was stirred for 2 h at 0 °C after which it was warmed to room temperature. Ethyl acetate was added to the mixture and the organic phase was washed with aq. satd. $NaHCO_3$. The organic phase was dried (Na_2SO_4), concentrated and the product was isolated by silica gel column chromatography (5→50% EtOAc in toluene) to afford the SAWU-3CR product as a light yellow oil.

Procedure for Monitoring the Formation of the 2,3-*cis* and 2,3-*trans* Pyrrolidines (3 and 4) by LC/MS Analysis: The crude pyrroline **2** was dissolved in MeOH or CH_3CN (0.1 M), and divided in portions containing 0.1 mmol of **2**. The solutions were cooled (0 °C) and (when needed) $InCl_3$ (0.1 mmol, 22.1 mg) was added. Subsequently, pentenoic acid (0.1 mmol, 10.2 μL or 2.5 mmol, 255 μL) and 2,2,4,4-tetramethylbutyl isocyanide (0.1 mmol, 17.6 μL or 2.5 mmol, 440 μL) were added. The reaction was stirred for 2 h at 0 °C. During the reaction, samples (50 μL) were taken at t = 0.1, 0.5, 1, 2, 5, 10, 15, 30, 60 and 120 min and quenched in 500 μL of a methanolic $NaBH_4$ solution (1 M). After standing for 1 h the samples were further diluted with 500 μL of an acetone/methanol (1:5) solution. For LC/MS analysis, 200 μL of the prepared samples was further diluted with 800 μL methanol-containing Fmoc-phenylalanine (0.08 mM) as an internal standard. The LC/MS UV-trace was measured at 214 nm and the peak surface areas of the 2,3-*cis* and 2,3-*trans* product were corrected to the internal standard. The total Ugi product formation was normalized to 100% and the curves were best-fitted by using a Boltzmann sigmoidal equation (GraphPad Prism V4.00, GraphPad Software, San Diego, CA).

2,5-Anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-2-formamido-*N*-(1,1,3,3-tetramethylbutyl)-D-*talo*-hexonamide (IA-2,3-*trans*): Yield 48% (54.1 mg, 92 μmol), >10:1 mixture of rotamers. R_f = 0.71 (1:1; toluene/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$, COSY), major rotamer: δ = 8.61 (s, 1 H, NC*H*O), 7.32–7.26 (m, 15 H, H_{Ar}), 6.72 (s, 1 H, CONH), 4.63 (d, $J_{Ha\text{-}Hb}$ = 12.0 Hz, 1 H, C*H*H Bn), 4.61 (d, $J_{Ha\text{-}Hb}$ = 12.0 Hz, 1 H, C*H*H Bn), 4.58 (d, $J_{Hb\text{-}Ha}$ = 12.0 Hz, 1 H, CH*H* Bn), 4.52 (d, $J_{Hb\text{-}Ha}$ = 12.0 Hz, 1 H, CH*H* Bn), 4.51–4.46 (m, 2 H, CH_2 Bn), 4.45 (s, 1 H, 2-H), 4.38–4.34 (m, 2 H, 4-H, 3-H), 4.21–4.17 (m, 1 H, 5-H), 3.91–3.84 (m, 2 H, 6a-H, 6b-H), 1.68 (dd, J = 14.4, 55.8 Hz, 2 H, CH_2 *t*Bu), 1.34 (s, 6 H, 2×CH_3), 0.95 (s, 9 H, 3×CH_3 *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, HSQC), major rotamer: δ = 167.3 (C), 163.8 (CHO), 137.8, 137.7, 137.4 (3×C Ar), 128.7, 128.5, 128.4, 127.9, 127.8, 127.7, 127.6 (15×CH Ar), 78.4 (C-4), 77.4 (C-3), 73.4, 72.6 (3×CH_2 Bn), 70.7 (C-6), 63.4 (C-2), 58.4 (C-5), 55.3 (C *t*Bu), 51.3 (CH_2 *t*Bu), 29.7, 29.2, 28.9 (5×CH_3) ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3339, 2956, 1726, 1652, 1455, 1365, 1284, 1125, 735, 698. $[\alpha]_D^{20}$ = –13.0 (c = 0.14, $CHCl_3$). HRMS: found 587.3476 $[M + H]^+$, calculated for $[C_{36}H_{46}O_5N_2 + H]^+$ 587.3480.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-2-formamido-*N*-(1,1,3,3-tetramethylbutyl)-D-*galacto*-hexonamide (IA-2,3-*cis*): Yield 20% (22.1 mg, 37 μmol), >10:1 mixture of rotamers. R_f = 0.26 (1:1; toluene/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$, COSY), major rotamer: δ = 8.33 (s, 1 H, NC*H*O), 7.36–7.23 (m, 15 H, H_{Ar}), 6.05 (s, 1 H, CON*H*), 4.78 (d, $J_{Ha\text{-}Hb}$ = 11.6 Hz, 1 H, C*H*H Bn), 4.68 (d, $J_{Hb\text{-}Ha}$ = 11.5 Hz, 1 H, CH*H* Bn), 4.60 (d, $J_{Ha\text{-}Hb}$ = 11.9 Hz, 1 H, C*H*H Bn), 4.56 (d, $J_{Ha\text{-}Hb}$ = 11.9 Hz, 1 H, C*H*H Bn), 5.52 (d, $J_{Hb\text{-}Ha}$ = 11.8 Hz, 1 H, CH*H* Bn), 4.46–4.39 (m, 3 H, 2-H, 3-H, CH*H* Bn), 4.18–4.15 (m, 1 H, 5-H), 4.06 (app. t, J = 10.3 Hz, 1 H, 6a-H), 3.93 (dd, J = 4.1, 14.2 Hz, 1 H, 4-H), 3.77 (dd, J = 3.3, 10.4 Hz, 1 H, 6b-H), 1.64 (d, J = 15.0 Hz, 1 H, C*H*H *t*Bu), 1.45 (d, J = 15.0 Hz, 1 H, CH*H* *t*Bu), 1.29 (app. d, J = 35.8 Hz, 6 H, 2×CH_3), 0.87 (s, 9 H, 3×CH_3 *t*Bu) . ^{13}C NMR (125 MHz, $CDCl_3$, HSQC), major rotamer: δ = 165.6 (C), 164.0 (CHO), 138.0, 137.7, 137.0 (3×C Ar), 128.5, 128.4, 128.1, 127.9, 127.6, 127.5 (15×CH Ar), 78.0 (C-4), 77.5 (C-3), 74.6, 73.2, 72.6 (3×CH_2 Bn), 69.0 (C-6), 63.2 (C-2), 59.0 (C-5), 55.3 [C, NH*C*$(CH_3)_2CH_2$*t*Bu], 51.8 (CH_2 *t*Bu), 31.5 (C *t*Bu), 31.3, 28.4, 27.7 (5×CH_3) ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3290, 2955, 2871, 1725, 1682, 1455, 1366, 1286, 1128, 737, 698 cm^{-1}. $[\alpha]_D^{20}$ = +29.6 (c = 0.83, $CHCl_3$). HRMS: found 587.3476 $[M + H]^+$, calculated for $[C_{36}H_{46}O_5N_2 + H]^+$ 587.3480.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-2-(*p*-nitrobenzamido)-*N*-(1,1,3,3-tetramethylbutyl)-D-*talo*-hexonamide (IB-2,3-*trans*): Yield 31% (43.9 mg, 62 μmol), 5:1 mixture of rotamers. R_f = 0.86 (1:1; toluene/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$, COSY), major rotamer: δ = 7.98 (d, J = 8.4 Hz, 1 H, H_{Ar}), 7.43 (d, J = 8.4 Hz, 1 H, H_{Ar}), 7.37–7.22 (m, 16 H, H_{Ar}), 6.93 (d, J = 8.4 Hz, 1 H, H_{Ar}), 5.87 (s, 1 H, CONH), 4.74 (d, $J_{Ha\text{-}Hb}$ = 12.0 Hz, 1 H, C*H*H Bn), 4.69 (s, 1 H, C*H*H Bn), 4.61 (d, J = 1.2 Hz, 1 H, CH*H* Bn), 4.57 (d, $J_{Hb\text{-}Ha}$ = 12.0 Hz, 1 H, CH*H* Bn), 4.52–4.50 (m, 1 H, 4-H), 4.46 (s, 1 H, 2-H), 4.38–4.35 (m, 1 H, 5-H), 4.16 (d, J = 4.2 Hz, 1 H, 3-H), 4.11 (d, $J_{Ha\text{-}Hb}$ = 10.8 Hz, 1 H, C*H*H Bn), 4.05 (d, J = 11.4 Hz, 1 H, CH*H* Bn), 3.74 (dd, J = 3.6, 10.2 Hz, 1 H, 6a-H), 3.67 (app. t, J = 9.6 Hz, 1 H, 6b-H), 1.68 (dd, J = 14.4, 34.2 Hz, 2 H, CH_2 *t*Bu), 1.33 (app. d, J = 3.0 Hz, 6 H, 2×CH_3), 0.97 (s, 9 H, 3×CH_3 *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, HSQC), major rotamer: δ = 170.2, 167.6 (2×C), 148.0, 142.8, 137.6, 137.4 (5×C Ar), 128.6, 128.5, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 123.3 (19×CH Ar), 79.0 (C-4), 78.2 (C-3), 73.1, 73.0, 72.9 (3×CH_2 Bn), 70.4 (C-6), 66.6 (C-2), 60.1 (C-5), 55.7 [C, NH*C*$(CH_3)_2CH_2$*t*Bu], 51.7 (CH_2 *t*Bu), 31.6 (C *t*Bu), 31.4, 28.9, 28.8 (5×CH_3) ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3342, 2952, 1682, 1635, 1522, 1345, 1097, 911, 863, 734, 698 cm^{-1}. $[\alpha]_D^{20}$ = –6.0 (c = 0.43, $CHCl_3$). HRMS: found 708.3643 $[M + H]^+$, calculated for $[C_{42}H_{49}O_7N_3 + H]^+$ 708.3643.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-2-(*p*-nitrobenzamido)-*N*-(1,1,3,3-tetramethylbutyl)-D-*galacto*-hexonamide (IB-2,3-*cis*): Yield

7% (9.9 mg, 14 μmol), complex mixture of rotamers. R_f = 0.40 (1:1; toluene/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$, COSY) broad peaks: δ = 8.13 (br.s ppm. 2 H, H_{Ar}), 7.76 (br. s, 2 H, H_{Ar}), 6.56 (br. s, 1 H, CONH), 6.27 (br. s, 1 H, CONH), 7.31–7.26 (m, 15 H, H_{Ar}), 4.90–4.30 (m, 7 H), 4.30–3.70 (m, 5 H), 1.80–1.53 (m, 2 H, CH_2 *t*Bu), 1.26 (s, 6 H, 2×CH_3), 0.88 (s, 9 H, 3×CH_3 *t*Bu) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, HSQC) broad peaks: δ = 128.4, 127.9, 127.8, 123.3 (CH Ar), 73.5 (CH_2 Bn), 55.4 [C, NH*C*$(CH_3)_2$-CH_2*t*Bu], 55.4 (CH_2 *t*Bu), 31.5 (C *t*Bu), 31.4, 27.9 (5×CH_3) ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3032, 2950, 2868, 1679, 1523, 1346, 1098, 910, 850, 735, 698 cm^{-1}. $[\alpha]_D^{20}$ = –10.2 (*c* = 1.05, $CHCl_3$). HRMS: found 708.3642 [M + H]$^+$, calculated for [$C_{42}H_{49}O_7N_3$ + H]$^+$ 708.3643.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-2-(pent-4-enoylamido)-*N*-(1,1,3,3-tetramethylbutyl)-D-*talo*-hexonamide (4, IC-2,3-*trans*): Yield 53% (67.9 mg, 106 μmol), 6:1 mixture of rotamers. R_f = 0.72 (3:2; toluene/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$, COSY), major rotamer: δ = 7.33–7.22 (m, 15 H, H_{Ar}), 6.28 (s, 1 H, CONH), 5.81–5.74 (m, 1 H, =CH), 4.97 (ddd, *J* = 1.2, 16.8, 37.2 Hz, 2 H, =CH_2), 4.65 (d, $J_{Ha\text{-}Hb}$ = 12.0 Hz, 1 H, C*H*H Bn), 4.63 (d, $J_{Ha\text{-}Hb}$ = 12.0 Hz, 1 H, C*H*H Bn), 5.58 (d, $J_{Hb\text{-}Ha}$ = 12.0 Hz, 1 H, CH*H* Bn), 4.55 (d, $J_{Hb\text{-}Ha}$ = 12.0 Hz, 1 H, CH*H* Bn), 4.47 (d, $J_{Ha\text{-}Hb}$ = 12.0 Hz, 1 H, C*H*H Bn), 4.44 (dd, *J* = 4.2, 7.8 Hz, 1 H, 3-H), 4.41 (d, $J_{Hb\text{-}Ha}$ = 12.0 Hz, 1 H, CH*H* Bn), 4.34–4.32 (m, 2 H, 4-H, 5-H), 4.16 (dd, *J* = 3.6, 10.8 Hz, 1 H, 6a-H), 4.08 (d, *J* = 4.2 Hz, 1 H, 2-H), 3.69 (dd, *J* = 5.4 Hz, 6b-H, 1 H, 10.8), 2.76–2.71 (m, 1 H, C*H*H pentenyl), 2.56–2.51 (m, 1 H, CH*H* pentenyl), 2.41–2.31 (m, 2 H, CH_2 pentenyl), 1.71 (d, *J* = 15.0 Hz, 1 H, C*H*H *t*Bu), 1.60 (d, *J* = 15.0 Hz, 1 H, CH*H* *t*Bu), 1.32 (d, *J* = 14.4 Hz, 6 H, 2×CH_3), 0.95 (s, 9 H, 3×CH_3 *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, HSQC), major rotamer: δ = 174.1, 168.1 (2×C), 137.8, 137.7, 137.6 (3×C Ar), 137.3 (=CH), 128.4, 128.3, 128.2, 128.0, 127.6, 127.5, 127.4 (15×CH Ar), 114.9 (=CH_2), 78.7 (C-3), 77.9 (C-2), 73.2, 72.4 (3×CH_2 Bn), 71.5 (C-6), 65.8 (C-4), 59.1 (C-5), 55.2 [C, NH*C*$(CH_3)_2CH_2$*t*Bu], 51.4 (CH_2 *t*Bu), 33.6 (CH_2 pentenyl), 31.4 (C *t*Bu), 31.3 (3×CH_3 *t*Bu), 29.0 (CH_2 pentenyl), 28.8, 28.6 (2×CH_3) ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3329, 2950, 1679, 1624, 1544, 1422, 1096, 733, 696 cm^{-1}. $[\alpha]_D^{20}$ = +22.3 (*c* = 6.06, $CHCl_3$). HRMS: found 641.3949 [M + H]$^+$, calculated for [$C_{40}H_{52}O_5N_2$ + H]$^+$ 641.3949.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-2-(pent-4-enoylamido)-*N*-(1,1,3,3-tetramethylbutyl)-D-*galacto*-hexonamide (3, IC-2,3-*cis*): Yield 10% (12.8 mg, 20 μmol), 2:1 mixture of rotamers. R_f = 0.24 (3:2; toluene/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$, COSY), major rotamer: δ = 7.32–7.25 (m, 15 H, H_{Ar}), 6.02 (s, 1 H, CONH), 5.85–5.73 (m, 1 H, =CH), 5.06–4.91 (m, 2 H, =CH_2), 4.75 (d, $J_{Ha\text{-}Hb}$ = 11.5 Hz, 1 H, C*H*H Bn), 4.69 (d, $J_{Hb\text{-}Ha}$ = 11.6 Hz, 1 H, CH*H* Bn), 4.58 (d, $J_{Ha\text{-}Hb}$ = 11.6 Hz, 1 H, C*H*H Bn), 4.53–4.47 (m, 3 H, 2-H, C*H*H Bn, CH*H* Bn), 4.44–4.36 (m, 2 H, 4-H, CH*H* Bn), 4.34–4.27 (m, 1 H, 5-H), 4.11 (app. t, *J* = 10.2 Hz, 1 H, 6a-H), 3.87 (app. d, *J* = 9.9 Hz, 1 H, 6b-H), 3.83 (app. t, *J* = 4.8 Hz, 1 H, 3-H), 2.89–2.84 (m, 1 H, C*H*H pentenyl), 2.46–2.31 (m, 3 H, CH*H* pentenyl, CH_2 pentenyl), 1.61 (d, *J* = 14.8 Hz, 1 H, C*H*H *t*Bu), 1.46 (d, *J* = 15.2 Hz, 1 H, CH*H* *t*Bu), 1.00 (d, *J* = 5.6 Hz, 6 H, 2×CH_3), 0.87 (s, 9 H, 3×CH_3 *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, HSQC), major rotamer: δ = 173.8, 166.3 (2×C), 138.0, 137.5 (2×C Ar), 137.1 (=CH), 137.0 (C Ar), 128.3, 128.1, 128.0, 127.8, 127.7, 127.4, 127.3, 127.2, 127.1 (15×CH Ar), 114.9 (=CH_2), 78.7 (C-4), 76.6 (C-3), 74.6, 73.3, 72.0 (3×CH_2 Bn), 69.8 (C-6), 64.7 (C-2), 59.0 (C-5), 55.6 [C, NH*C*$(CH_3)_2CH_2$*t*Bu], 53.3 (CH_2 *t*Bu), 33.3 (CH_2 pentenyl), 31.4 (C *t*Bu), 31.3, 31.2 (2×CH_3), 31.1 (3×CH_3 *t*Bu), 28.6 (CH_2 pentenyl) ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3323, 2951, 1666, 1521, 1400, 1098, 734, 697 cm^{-1}. $[\alpha]_D^{20}$ = +11.4 (*c* = 9.00, $CHCl_3$). HRMS: found 641.3949 [M + H]$^+$, calculated for [$C_{40}H_{52}O_5N_2$ + H]$^+$ 641.3949.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-2-{*N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-2-aminoacetamido}-*N*-(1,1,3,3-tetramethylbutyl)-D-*talo*-hexonamide (ID-2,3-*trans*): Yield 19% (31.8 mg, 38 μmol), >10:1 mixture of rotamers. R_f = 0.77 (1:1; toluene/EtOAc). ^{1}H NMR (600 MHz, $CDCl_3$, COSY), major rotamer: δ = 7.76 (d, *J* = 7.2 Hz, 2 H, H_{Ar}), 7.60 (d, *J* = 7.4 Hz, 2 H, H_{Ar}), 7.40–7.26 (m, 19 H, H_{Ar}), 5.76 (br. s, 1 H, CONH), 5.55 (br. s, 1 H, CONH), 4.68 (d, $J_{Ha\text{-}Hb}$ = 12.2 Hz, 1 H, C*H*H Bn), 4.58–4.49 (m, 5 H, CH_2 Bn, C*H*H Bn, CH*H* Bn, C*H*H Fmoc), 4.38–4.32 (m, 3 H, 5-H, 4-H, CH*H* Fmoc), 4.25–4.20 (m, 2 H, CH Fmoc, 3-H), 4.07–3.99 (m, 3 H, 2-H, 6a-H, CH*H* Bn), 3.81–3.77 (m, 1 H, 6b-H), 1.75 (d, *J* = 15.0 Hz, 1 H, C*H*H *t*Bu), 1.59 (d, *J* = 15.0 Hz, 1 H, CH*H* *t*Bu), 1.32 (s, 6 H, 2×CH_3), 0.95 (s, 9 H, 3×CH_3 *t*Bu) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, HSQC), major rotamer: δ = 170.1, 167.6, 156.2 (3×C), 143.9, 141.2, 137.8, 137.6, 137.3 (7×C Ar), 128.5, 128.3, 127.8, 127.7, 127.4, 127.0, 125.2, 119.9 (23×CH Ar), 78.5 (C-4), 78.0 (C-3), 73.3, 72.7, 72.6 (3×CH_2 Bn), 70.8 (C-6), 67.0 (CH_2 Fmoc), 66.7 (C-2), 58.6 (C-5), 55.6 [C, NH*C*$(CH_3)_2$-CH_2*t*Bu], 51.7 (CH_2 *t*Bu), 47.1 (CH Fmoc), 31.5 (C *t*Bu), 31.4, 28.8, 28.7 (5×CH_3) ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3335, 2951, 1718, 1667, 1453, 1098, 737, 698 cm^{-1}. $[\alpha]_D^{20}$ = +5.2 (*c* = 0.12, $CHCl_3$). HRMS: found 838.4428 [M + H]$^+$, calculated for [$C_{49}H_{61}O_{10}N_3$ + H]$^+$ 838.4399.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-2-{*N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-2-aminoacetamido}-*N*-(1,1,3,3-tetramethylbutyl)-D-*galacto*-hexonamide (ID-2,3-*cis*): Yield 1% (1.7 mg, 2 μmol), >10:1 mixture of rotamers. R_f = 0.24 (1:1; toluene/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$, COSY), major rotamer: δ = 7.75 (d, *J* = 7.6 Hz, 2 H, H_{Ar}), 7.60 (d, *J* = 7.4 Hz, 2 H, H_{Ar}), 7.39 (t, *J* = 7.4 Hz, 2 H, H_{Ar}), 7.31–7.13 (m, 13 H, H_{Ar}), 5.98 (br. s, 1 H, CONH), 5.64 (br. s, 1 H, CONH), 4.74 (d, $J_{Ha\text{-}Hb}$ = 11.5 Hz, 1 H, C*H*H Bn), 4.69 (d, $J_{Hb\text{-}Ha}$ = 11.3 Hz, 1 H, CH*H* Bn), 4.64 (d, $J_{Ha\text{-}Hb}$ = 12.0 Hz, 1 H, C*H*H Bn), 4.55–4.45 (m, 3 H, 2-H, C*H*H Bn, CH*H* Bn), 4.43–4.38 (m, 4 H, 4-H, CH*H* Bn, CH_2 Fmoc), 4.30–4.25 (m, 1 H, 5-H), 4.22 (t, *J* = 7.3 Hz, 1 H, CH Fmoc), 4.14–4.07 (m, 1 H, 6a-H), 3.87–3.78 (m, 2 H, 3-H, 6b-H), 1.62 (d, *J* = 15.0 Hz, 1 H, C*H*H *t*Bu), 1.45 (d, *J* = 15.0 Hz, 1 H, CH*H* *t*Bu), 1.36 (s, 3 H, CH_3), 1.20 (s, 3 H, 2×CH_3), 0.87 (s, 9 H, 3×CH_3 *t*Bu) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, HSQC), major rotamer: δ = 170.3, 165.9, 156.2 (3×C), 143.9, 141.2, 138.0, 137.5, 136.9 (7×C Ar), 128.5, 128.4, 128.1, 127.9, 127.6, 127.0, 125.1, 119.9 (23×CH Ar), 78.5 (C-4), 76.3 (C-3), 74.9, 73.6, 72.4 (3×CH_2 Bn), 69.1 (C-6), 67.1 (CH_2 Fmoc), 65.3 (C-2), 58.8 (C-5), 55.3 (C *t*Bu), 53.7 (CH_2 *t*Bu), 47.1 (CH Fmoc), 31.3, 28.9, 27.3 (5×CH_3) ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3303, 2951, 1718, 1667, 1453, 1097, 736, 698 cm^{-1}. $[\alpha]_D^{20}$ = +10.2 (*c* = 1.64, $CHCl_3$). HRMS: found 838.4428 [M + H]$^+$, calculated for [$C_{49}H_{61}O_{10}N_3$ + H]$^+$ 838.4399.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-*N*-(*tert*-butyl)-2-deoxy-2-formamido-D-*talo*-hexonamide (IIA-2,3-*trans*): Yield 39% (41.4 mg, 78 μmol), >10:1 mixture of rotamers. R_f = 0.51 (1:1; toluene/EtOAc). ^{1}H NMR (600 MHz, $CDCl_3$, COSY), major rotamer: δ = 8.57 (s, 1 H, NC*H*O), 7.34–7.27 (m, 15 H, H_{Ar}), 6.54 (br. s, 1 H, CONH), 4.65 (d, $J_{Ha\text{-}Hb}$ = 12.0 Hz, 1 H, C*H*H Bn), 4.62 (d, $J_{Ha\text{-}Hb}$ = 12.0 Hz, 1 H, C*H*H Bn), 4.56 (d, $J_{Hb\text{-}Ha}$ = 12.0 Hz, 1 H, CH*H* Bn), 4.53 (d, $J_{Hb\text{-}Ha}$ = 12.0 Hz, 1 H, CH*H* Bn), 4.49 (s, 2 H, CH_2 Bn), 4.41–4.39 (m, 1 H, 4-H), 4.37 (s, 1 H, 2-H), 4.30 (d, *J* = 3.7 Hz, 1 H, 3-H), 4.23 (dt, *J* = 2.8, 8.6 Hz, 1 H, 5-H), 3.89–3.83 (m, 2 H, 6a-H, H6b), 1.29 (s, 9 H, CH_3 *t*Bu) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, HSQC) mixture of rotamers: δ = 167.9 (C), 163.6 (CHO), 137.9, 137.6, 137.5 (3×C Ar), 128.5, 128.4, 127.9,

127.8, 127.7, 127.6 (15 CH Ar), 78.5 (C-4), 77.8 (C-3), 73.3, 72.8, 72.7 (3×CH_2 Bn), 70.5 (C-6), 63.5 (C-2), 58.5 (C-5), 51.4 (C *t*Bu), 28.5 (CH_3 *t*Bu) ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3334, 2929, 1652, 1455, 1363, 1096, 735, 698 cm^{-1}. $[\alpha]_D^{20}$ = –4.9 (*c* = 0.41, $CHCl_3$). HRMS: found 531.2849 $[M + H]^+$, calculated for $[C_{32}H_{38}O_5N_2 + H]^+$ 531.2854.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-*N*-(*tert*-butyl)-2-deoxy-2-(*p*-nitrobenzamido)-D-*talo*-hexonamide (IIB-2,3-*trans*): Yield 19% (24.7 mg, 38 μmol), 5:1 mixture of rotamers. R_f = 0.73 (1:1; toluene/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$, COSY), major rotamer: δ = 7.97 (d, *J* = 8.4 Hz, 1 H, H_{Ar}), 7.42 (d, *J* = 8.4 Hz, 1 H, H_{Ar}), 7.34–7.14 (m, 16 H, H_{Ar}), 6.96 (d, *J* = 8.4 Hz, 1 H, H_{Ar}), 5.70 (s, 1 H, CONH), 4.78 (d, $J_{Ha\text{-}Hb}$ = 12.0 Hz, 1 H, C*H*H Bn), 4.62 (d, $J_{Ha\text{-}Hb}$ = 12.0 Hz, 1 H, C*H*H Bn), 4.59 (d, $J_{Hb\text{-}Ha}$ = 12.0 Hz, 1 H, CH*H* Bn), 4.55 (d, $J_{Hb\text{-}Ha}$ = 12.0 Hz, 1 H, CH*H* Bn), 4.51–4.49 (m, 1 H, 4-H), 4.39–4.35 (m, 2 H, 2-H, 5-H), 4.14–4.07 (m, 3 H, CH_2 Bn, 3-H), 3.71–3.64 (m, 2 H, 6a-H, 6b-H), 1.28 (s, 9 H, CH_3 *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, HSQC), major rotamer: δ = 170.0, 168.1 (2×C), 148.0, 142.8, 137.6, 137.4 (3×C Ar), 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.8, 123.3, 123.2 (19×CH Ar), 78.9 (C-4), 78.6 (C-3), 73.3, 73.0 (3×CH_2 Bn), 70.2 (C-6), 66.6 (C-2), 60.0 (C-5), 51.6 (C *t*Bu), 28.5 (3×CH_3 *t*Bu) ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3326, 2969, 1682, 1633, 1522, 1346, 1220, 1098, 1054, 909, 864, 735, 699 cm^{-1}. $[\alpha]_D^{20}$ = –9.5 (*c* = 0.32, $CHCl_3$). HRMS: found 652.3016 $[M + H]^+$, calculated for $[C_{38}H_{41}O_7N_3 + H]^+$ 652.3017.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-*N*-(*tert*-butyl)-2-deoxy-2-(pent-4-enoylamido)-D-*talo*-hexonamide (IIC-2,3-*trans*): Yield 48% (56.1 mg, 96 μmol), 4:1 mixture of rotamers. R_f = 0.66 (1:1; toluene/EtOAc). ^{1}H NMR (600 MHz, $CDCl_3$, COSY), major rotamer: δ = 7.35–7.16 (m, 15 H, H_{Ar}), 6.15 (s, 1 H, CONH), 5.78–5.74 (m, 1 H, =CH), 4.97 (ddd, *J* = 1.2, 17.4, 34.8 Hz, 2 H, =CH_2), 4.69 (d, $J_{Ha\text{-}Hb}$ = 12.0 Hz, 1 H, C*H*H Bn), 4.62 (d, $J_{Ha\text{-}Hb}$ = 12.0 Hz, 1 H, C*H*H Bn), 5.58 (d, $J_{Hb\text{-}Ha}$ = 12.0 Hz, 1 H, CH*H* Bn), 4.53 (d, $J_{Hb\text{-}Ha}$ = 12.0 Hz, 1 H, CH*H* Bn), 4.48–4.46 (m, 2 H, C*H*H Bn, 4-H), 4.42 (d, $J_{Hb\text{-}Ha}$ = 12.0 Hz, 1 H, CH*H* Bn), 4.36 (ddd, *J* = 3.5, 6.4, 7.6 Hz, 1 H, 5-H), 4.24 (s, 1 H, 2-H), 4.11 (dd, *J* = 3.6, 10.8 Hz, 1 H, 6a-H), 3.99 (d, $J_{H3\text{-}H4}$ = 4.2 Hz, 1 H, 3-H), 3.69 (dd, *J* = 6.6, 10.8 Hz, 1 H, 6b-H), 2.76–2.71 (m, 1 H, C*H*H pentenyl), 2.56–2.50 (m, 1 H, CH*H* pentenyl), 2.40–2.27 (m, 2 H, CH_2 pentenyl), 1.27 (s, 9 H, 3×CH_3 *t*Bu) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, HSQC), major rotamer: δ = 174.0, 168.8 (2×C), 137.9, 137.7 (3×C Ar), 137.6 (=CH), 128.3, 128.2, 127.8, 127.7, 127.6, 127.5 (15×CH Ar), 114.9 (=CH_2), 78.8 (C-4), 78.2 (C-3), 73.2, 72.6, 72.5 (3×CH_2 Bn), 71.4 (C-6), 65.9 (C-2), 58.9 (C-5), 51.2 (Cq *t*Bu), 33.5, 29.1 (2×CH_2 pentenyl), 28.4 (3×CH_3 *t*Bu) ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3324, 2970, 1668, 1624, 1454, 1433, 1362, 1096, 913, 734, 697 cm^{-1}. $[\alpha]_D^{20}$ = +28.1 (*c* = 2.06, $CHCl_3$). HRMS: found 585.3324 $[M + H]^+$, calculated for $[C_{36}H_{44}O_5N_2 + H]^+$ 585.3323.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-*N*-(*tert*-butyl)-2-deoxy-2-{*N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-2-aminoacetamido}-D-*talo*-hexonamide (IID-2,3-*trans*): Yield 24% (37.5 mg, 48 μmol); >10:1 mixture of rotamers. R_f = 0.57 (1:1; toluene/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$, COSY), major rotamer: δ = 7.76 (d, *J* = 7.5 Hz, 2 H, H_{Ar}), 7.60 (d, *J* = 7.4 Hz, 2 H, H_{Ar}), 7.40–7.25 (m, 19 H, H_{Ar}), 5.59 (br. s, 1 H, CONH), 5.54 (br. s, 1 H, CONH), 4.73 (d, $J_{Ha\text{-}Hb}$ = 12.2 Hz, 1 H, C*H*H Bn), 4.57–4.49 (m, 4 H, CH_2 Bn, C*H*H Bn, CH*H* Bn), 4.37–4.33 (m, 4 H, 5-H, 4-H, CH_2 Fmoc), 4.22 (t, *J* = 7.1 Hz, 1 H, CH Fmoc), 4.13 (m, 2 H, 2-H), 4.07–3.99 (m, 2 H, 6a-H, CH*H* Bn), 3.93 (s, 1 H, 3-H), 3.84–3.77 (m, 1 H, 6b-H), 1.26 (s, 9 H, CH_3 *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, HSQC), major rotamer: δ = 170.1, 168.2, 156.3 (3×C), 143.9, 141.2, 137.8, 137.6, 137.3 (7×C Ar), 128.5, 128.4, 128.0, 127.8, 127.7, 127.6, 127.0 125.2, 119.9 (23×CH Ar), 78.5 (C-4), 78.3 (C-3), 73.3, 72.8, 72.6 (3×CH_2 Bn), 70.7 (C-6), 67.0 (CH_2 Fmoc), 66.8 (C-2), 58.5 (C-5), 51.5 (C *t*Bu), 47.1 (CH Fmoc), 28.0 (3×CH_3 *t*Bu) ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3317, 2927, 2868, 1717, 1653, 1453, 1346, 1098, 1049, 909, 734, 698 cm^{-1}. $[\alpha]_D^{20}$ = +8.4 (*c* = 0.36, $CHCl_3$). HRMS: found 782.3802 $[M + H]^+$, calculated for $[C_{48}H_{52}O_7N_3 + H]^+$ 782.3800.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-*N*-cyclohexyl-2-deoxy-2-formamido-D-*talo*-hexonamide (IIIA-2,3-*trans*): Yield 48% (53.5 mg, 96 μmol), >10:1 mixture of rotamers. R_f = 0.43 (1:1; toluene/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$, COSY), major rotamer: δ = 8.58 (s, 1 H, NC*H*O), 7.30–7.26 (m, 15 H, H_{Ar}), 6.66 (br. s, 1 H, CONH), 4.64 (d, $J_{Ha\text{-}Hb}$ = 12.0 Hz, 1 H, C*H*H Bn), 4.62 (d, $J_{Ha\text{-}Hb}$ = 12.0 Hz, 1 H, C*H*H Bn), 4.57 (d, $J_{Hb\text{-}Ha}$ = 12.0 Hz, 1 H, CH*H* Bn), 4.52 (d, $J_{Hb\text{-}Ha}$ = 12.0 Hz, 1 H, CH*H* Bn), 4.50 (s, 2 H, CH_2 Bn), 4.45 (s, 1 H, 2-H), 4.39–4.37 (m, 1 H, 4-H), 4.34 (d, *J* = 3.8 Hz, 1 H, 3-H), 4.22 (d, *J* = 8.2 Hz, 1 H, 5-H), 3.90–3.83 (m, 2 H, 6a-H, 6b-H), 3.67–3.60 (m, 1 H, CH *c*Hex), 1.69–1.56 (m, 5 H, 5×CH_2 *c*Hex), 1.33–1.05 (m, 5 H, 5×CH_2 *c*Hex) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, HSQC), major rotamer: δ = 167.7 (C), 163.7 (CHO), 137.9, 137.6, 137.4 (3×C Ar), 128.5, 128.4, 128.0, 127.9, 127.8, 127.7, 127.6 (15×CH Ar), 78.3 (C-4), 77.6 (C-3), 73.3, 72.8, 72.7 (3×CH_2 Bn), 70.6 (C-6), 62.7 (C-2), 58.4 (C-5), 48.4 (CH *c*Hex), 32.7, 32.5 (2×CH_2 *c*Hex), 25.5, 24.6 (3×CH_2 *c*Hex) ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3318, 2929, 2857, 1725, 1652, 1455, 1276, 1124, 1074, 737, 698 cm^{-1}. $[\alpha]_D^{20}$ = –6.5 (*c* = 0.22, $CHCl_3$). HRMS: found 557.3007 $[M + H]^+$, calculated for $[C_{34}H_{40}O_5N_2 + H]^+$ 557.3010.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-*N*-cyclohexyl-2-deoxy-2-(*p*-nitrobenzamido)-D-*talo*-hexonamide (IIIB-2,3-*trans*): Yield 17% (23.0 mg, 34 μmol), 3:1 mixture of rotamers. R_f = 0.71 (1:1; toluene/EtOAc). ^{1}H NMR (600 MHz, $CDCl_3$, COSY), major rotamer: δ = 7.97 (d, *J* = 8.4 Hz, 1 H, H_{Ar}), 7.42 (d, *J* = 8.4 Hz, 1 H, H_{Ar}), 7.37–7.23 (m, 16 H, H_{Ar}), 6.96 (d, *J* = 8.4 Hz, 1 H, H_{Ar}), 5.78 (br. s, 1 H, CONH), 4.77 (d, $J_{Ha\text{-}Hb}$ = 12.0 Hz, 1 H, C*H*H Bn), 4.64–4.55 (m, 3 H, CH*H* Bn, CH_2 Bn), 4.52–4.50 (m, 1 H, 4-H), 4.46 (s, 1 H, 2-H), 4.36–4.33 (m, 1 H, 5-H), 4.14–4.12 (m, 2 H, 3-H, C*H*H Bn), 4.08 (d, *J* = 11.4 Hz, 1 H, CH*H* Bn), 3.72 (dd, *J* = 7.2 Hz, 10.2, 1 H, 6a-H), 3.68–3.64 (m, 2 H, 6b-H, CH *c*Hex), 1.82–1.56 (m, 5 H, 5×CH_2 *c*Hex), 1.33–1.05 (m, 5 H, 5×CH_2 *c*Hex) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, HSQC), major rotamer: δ = 170.1, 167.9 (2×C), 148.0, 142.8, 137.5, 137.4 (5×C Ar), 128.6, 128.5, 128.2, 128.1, 128.0, 127.8, 127.7, 123.2 (19×CH Ar), 78.8 (C-4), 78.5 (C-3), 73.3, 73.0, 72.9 (3×CH_2 Bn), 70.2 (C-6), 66.0 (C-2), 60.0 (C-5), 48.7 (CH *c*Hex), 32.7, 32.6 (2×CH_2 *c*Hex), 25.4, 24.7, 24.6 (3×CH_2 *c*Hex) ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3297, 2930, 2856, 1651, 1522, 1346, 1097, 1055, 910, 864, 734, 698 cm^{-1}. $[\alpha]_D^{20}$ = –6.9 (*c* = 0.23, $CHCl_3$). HRMS: found 678.3172 $[M + H]^+$, calculated for $[C_{40}H_{43}O_7N_3 + H]^+$ 678.3174.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-*N*-cyclohexyl-2-deoxy-2-(pent-4-enoylamido)-D-*talo*-hexonamide (IIIC-2,3-*trans*): Yield 30% (36.6 mg, 60 μmol), 1:3 mixture of rotamers. R_f = 0.62 (1:1; toluene/EtOAc). ^{1}H NMR (600 MHz, $CDCl_3$, COSY), major rotamer: δ = 7.35–7.25 (m, 15 H, H_{Ar}), 6.22 (d, *J* = 8.4 Hz, 1 H, CONH), 5.79–5.74 (m, 1 H, =CH), 4.99–4.92 (m, =CH_2), 4.69 (d, $J_{Ha\text{-}Hb}$ = 12.0 Hz, 1 H, C*H*H Bn), 4.61 (d, $J_{Ha\text{-}Hb}$ = 12.0 Hz, 1 H, C*H*H Bn), 4.57 (d, $J_{Hb\text{-}Ha}$ = 12.0 Hz, 1 H, CH*H* Bn), 4.54 (d, $J_{Hb\text{-}Ha}$ = 12.0 Hz, 1 H, CH*H* Bn), 4.48 (d, $J_{Hb\text{-}Ha}$ = 12.0 Hz, 1 H, CH*H* Bn), 4.46–4.42 (m, 2 H, C*H*H Bn, 4-H), 4.37–4.34 (m, 1 H, 5-H), 4.32 (s, 1 H, 2-H), 4.13 (dd, *J* = 3.0, 10.2 Hz, 1 H, 6a-H), 3.04 (d, *J* = 4.2 Hz, 1 H, 3-H), 3.70 (dd, *J* = 3.6, 10.2 Hz, 1 H, 6b-H), 3.63–3.58 (m, 1 H, CH *c*Hex), 2.76–2.71 (m, 1 H, C*H*H pentenyl), 2.57–

2.50 (m, 1 H, CH*H* pentenyl), 2.46–2.28 (m, 2 H, CH_2 pentenyl), 1.69–1.56 (m, 5 H, 5×CH_2 *c*Hex), 1.33–1.05 (m, 5 H, 5×CH_2 *c*Hex) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, HSQC), major rotamer: δ = 174.2, 168.5 (2×C), 138.0, 137.7 (3×C Ar), 137.6 (=CH), 128.4, 128.3, 127.9, 127.8, 127.7, 127.5 (15×CH Ar), 115.0 (=CH_2), 78.7 (C-4), 78.2 (C-3), 73.3, 72.6, 72.5 (3×CH_2 Bn), 71.5 (C-6), 65.3 (C-2), 59.0 (C-5), 48.4 (CH *c*Hex), 33.6 (CH_2 pentenyl), 32.7, 32.5 (2×CH_2 *c*Hex), 29.1 (CH_2 pentenyl), 25.4, 24.7 (2×CH_2 *c*Hex) ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3301, 2930, 2856, 1650, 1637, 1623, 1420, 1096, 911, 733, 697 cm^{-1}. $[\alpha]_D^{20}$ = +25.2 (*c* = 1.34, $CHCl_3$). HRMS: found 611.3478 [M + H]$^+$, calculated for [$C_{38}H_{47}O_5N_2$ + H]$^+$ 611.3479.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-*N*-cyclohexyl-2-deoxy-2-{*N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-2-aminoacetamido}-D-*talo*-hexonamide (IIID-2,3-*trans*): Yield 18% (29.1 mg, 36 μmol), >10:1 mixture of rotamers. R_f = 0.54 (1:1; toluene/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$, COSY), major rotamer: δ = 7.76 (d, *J* = 7.5 Hz, 2 H, H_{Ar}), 7.60 (d, *J* = 7.4 Hz, 2 H, H_{Ar}), 7.41–7.25 (m, 19 H, H_{Ar}), 5.79 (d, *J* = 8.2 Hz, 1 H, CONH), 5.54 (br.t, 1 H, CONH), 4.71 (d, $J_{Ha\text{-}Hb}$ = 12.2 Hz, 1 H, C*H*H Bn), 4.56 (d, $J_{Hb\text{-}Ha}$ = 12.2 Hz, 1 H, CH*H* Bn), 4.53 (s, 2 H, CH_2 Bn), 4.50 (dd, *J* = 5.2, 10.4 Hz, 2 H, CH_2 Bn), 4.47–4.38 (m, 1 H, 5-H), 4.37–4.29 (m, 4 H, 2-H, 4-H, CH_2 Fmoc), 4.21 (t, *J* = 7.3 Hz, 1 H, CH Fmoc), 4.11–4.00 (m, 2 H, 6a-H, 3-H), 3.84–3.80 (m, 1 H, 6b-H), 3.65–3.56 (m, 1 H, CH *c*Hex), 1.82–1.56 (m, 5 H, 5×CH_2 *c*Hex), 1.33–1.05 (m, 5 H, 5×CH_2 *c*Hex) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, HSQC), major rotamer: δ = 170.3, 167.8, 156.5 (3×C), 143.9, 143.8, 141.2, 137.8, 137.5, 137.2 (7×C Ar), 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.0 125.1, 119.9 (23×CH Ar), 78.3 (C-4), 78.2 (C-3), 73.4, 72.6, 72.5 (3×CH_2 Bn), 70.4 (C-6), 67.1 (CH_2 Fmoc), 66.1 (C-2), 58.7 (C-5), 47.1 (CH Fmoc), 48.5 (CH *c*Hex), 32.7, 32.6 (2×CH_2 *c*Hex), 25.4, 24.8, 24.7 (3×CH_2 *c*Hex) ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3305, 2929, 2855, 1717, 1652, 1452, 1097, 911, 734, 698 cm^{-1}. $[\alpha]_D^{20}$ = +2.4 (*c* = 0.33, $CHCl_3$). HRMS: found 808.3959 [M + H]$^+$, calculated for [$C_{50}H_{53}O_7N_3$ + H]$^+$ 808.3956.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-*N*-butyl-2-deoxy-2-formamido-D-*talo*-hexonamide (IVA-2,3-*trans*): Yield 29% (30.8 mg, 58 μmol), 4:1 mixture of rotamers. R_f = 0.34 (1:1; toluene/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$, COSY), major rotamer: δ = 8.57 (s, 1 H, NC*H*O), 7.31–7.24 (m, 15 H, H_{Ar}), 6.78 (br. s, 1 H, CONH), 4.62 (d, $J_{Ha\text{-}Hb}$ = 12.0 Hz, 1 H, C*H*H Bn), 4.60 (d, $J_{Ha\text{-}Hb}$ = 12.0 Hz, 1 H, C*H*H Bn), 4.56 (d, $J_{Hb\text{-}Ha}$ = 12.0 Hz, 1 H, CH*H* Bn), 4.51–4.47 (m, 4 H, CH*H* Bn, CH_2 Bn, 2-H), 4.39–4.34 (m, 2 H, 4-H, 3-H), 4.21 (t, *J* = 7.4 Hz, 1 H, 5-H), 3.93–3.84 (m, 2 H, 6a-H, 6b-H), 3.17–3.13 (m, 1 H, CH_2 butyl), 1.42–1.38 (m, 2 H, CH_2 butyl), 1.32–1.26 (m, 2 H, CH_2 butyl), 0.97–0.85 (m, 3 H, CH_3 butyl) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, HSQC), major rotamer: δ = 167.7 (C), 163.7 (CHO), 137.8, 137.6, 137.4 (3×C Ar), 128.5, 128.4, 128.2, 127.9, 127.8, 127.7, 127.6 (15×CH Ar), 78.3 (C-4), 77.6 (C-3), 73.4, 72.7 (3×CH_2 Bn), 70.6 (C-6), 62.6 (C-2), 58.4 (C-5), 39.3, 31.3, 20.0 (3×CH_2 butyl), 13.7 (CH_3 butyl) ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3318, 2957, 2930, 2871, 1724, 1652, 1455, 1381, 1275, 1123, 1074, 736, 698 cm^{-1}. $[\alpha]_D^{20}$ = –4.5 (*c* = 0.22, $CHCl_3$). HRMS: found 531.2849 [M + H]$^+$, calculated for [$C_{32}H_{38}O_5N_2$ + H]$^+$ 531.2854.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-*N*-butyl-2-deoxy-2-*p*-nitrobenzamido-D-*talo*-hexonamide (IVB-2,3-*trans*): Yield 47% (61.2 mg, 94 μmol), 8:1 mixture of rotamers. R_f = 0.64 (1:1; toluene/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$, COSY), major rotamer: δ = 7.98 (d, *J* = 8.4 Hz, 1 H, H_{Ar}), 7.43 (d, *J* = 8.4 Hz, 1 H, H_{Ar}), 7.36–7.24 (m, 16 H, H_{Ar}), 6.95 (d, *J* = 8.4 Hz, 1 H, H_{Ar}), 6.00 (br. s, 1 H, CONH), 4.77 (d, $J_{Ha\text{-}Hb}$ = 12.0 Hz, 1 H, C*H*H Bn), 4.62–4.57 (m, 3 H, CH*H* Bn, CH_2 Bn), 4.53–4.52 (m, 2 H, 2-H, 4-H), 4.39–4.35 (m, 1 H, 5-H), 4.16 (d, *J* = 4.2 Hz, 1 H, 3-H), 4.12 (d, $J_{Ha\text{-}Hb}$ = 11.4 Hz, 1 H, C*H*H Bn), 4.07 (d, *J* = 11.4 Hz, 1 H, CH*H* Bn), 3.72 (dd, *J* = 3.6, 10.2 Hz, 1 H, 6a-H), 3.67 (app.t, *J* = 7.2, 10.2 Hz, 1 H, 6b-H), 3.16 (q, *J* = 6.6 Hz, 2 H, CH_2 butyl), 1.45–1.38 (m, 2 H, CH_2 butyl), 1.30–1.25 (m, 2 H, CH_2 butyl), 0.88 (t, *J* = 10.8 Hz, 3 H, CH_3 butyl) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, HSQC), major rotamer: δ = 170.1, 167.7 (2×C), 148.0, 142.7, 137.5, 137.4 (5×C Ar), 128.8, 128.6, 128.5, 127.8, 127.7, 127.5, 123.2 (19×CH Ar), 78.8 (C-4), 78.4 (C-3), 73.2, 73.0, 72.9 (3×CH_2 Bn), 70.2 (C-6), 65.8 (C-2), 60.1 (C-5), 39.3, 31.3, 20.0 (3×CH_2 butyl), 13.7 (CH_3 butyl) ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3341, 2957, 2929, 2871, 1724, 1274, 1124, 1074, 909, 864, 737, 699 cm^{-1}. $[\alpha]_D^{20}$ = –6.9 (*c* = 0.29, $CHCl_3$). HRMS: found 652.3016 [M + H]$^+$, calculated for [$C_{38}H_{41}O_7N_3$ + H]$^+$ 652.3017.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-*N*-butyl-2-deoxy-2-(pent-4-enoylamido)-D-*talo*-hexonamide (IVC-2,3-*trans*): Yield 29% (33.9 mg, 58 μmol), 3:1 mixture of rotamers. ^{1}H NMR (600 MHz, $CDCl_3$, COSY), major rotamer: δ = 7.35–7.24 (m, 15 H, H_{Ar}), 6.65–6.59 (br. s, 1 H, CONH), 5.80–5.73 (m, 1 H, =CH), 4.96 (ddd, *J* = 1.2, 17.4, 31.8 Hz, 2 H, =CH_2), 4.67 (d, $J_{Ha\text{-}Hb}$ = 12.0 Hz, 1 H, C*H*H Bn), 4.61–4.53 (m, 3 H, C*H*H Bn, 2×CH*H* Bn), 4.49–4.42 (m, 2 H, C*H*H Bn, CH*H* Bn, 4-H), 4.40 (s, 1 H, 2-H), 4.39–4.36 (m, 1 H, 5-H), 4.13 (dd, *J* = 3.6, 10.8 Hz, 1 H, 6a-H), 3.04 (d, *J* = 4.2 Hz, 1 H, 3-H), 3.70 (dd, *J* = 6.0, 10.8 Hz, 1 H, 6b-H), 3.22–3.17 (m, 1 H, CH*H* butyl), 3.08–3.05 (m, 1 H, CH*H* butyl), 2.78–2.72 (m, 1 H, C*H*H pentenyl), 2.56–2.51 (m, 1 H, CH*H* pentenyl), 2.40–2.28 (m, 2 H, CH_2 pentenyl), 1.42–1.38 (m, 2 H, CH_2 butyl), 1.32–1.26 (m, 2 H, CH_2 butyl), 0.97–0.85 (m, 3 H, CH_3 butyl) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, HSQC), major rotamer: δ = 174.1, 168.4 (2×C), 138.0, 137.7 (3×C Ar), 137.4 (=CH), 128.4, 128.3, 127.9, 127.8, 127.7, 127.5 (15×CH Ar), 115.0 (=CH_2), 78.7 (C-4), 78.2 (C-3), 73.3, 72.4 (3×CH_2 Bn), 71.5 (C-6), 65.2 (C-2), 59.0 (C-5), 39.2 (CH_2 butyl), 33.6 (CH_2 pentenyl), 31.1 (CH_2 butyl), 29.1 (CH_2 pentenyl), 20.0 (CH_2 butyl), 13.7 (CH_3 butyl) ppm. R_f = 0.51 (1:1; toluene/EtOAc). IR (thin film): $\tilde{\nu}_{max}$ = 3311, 2931, 1726, 1652, 1623, 1453, 1421, 1096, 734, 697 cm^{-1}. $[\alpha]_D^{20}$ = +26.5 (*c* = 1.24, $CHCl_3$). HRMS: found 585.3324 [M + H]$^+$, calculated for [$C_{36}H_{44}O_5N_2$ + H]$^+$ 585.3323.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-*N*-butyl-2-deoxy-2-{*N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-2-amino-acetamido}-D-*talo*-hexonamide (IVD-2,3-*trans*): Yield 13% (20.3 mg, 26 μmol), >10:1 mixture of rotamers. R_f = 0.46 (1:1; toluene/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$, COSY), major rotamer: δ = 7.76 (d, *J* = 7.2 Hz, 2 H, H_{Ar}), 7.58 (d, *J* = 7.4 Hz, 2 H, H_{Ar}), 7.41–7.25 (m, 19 H, H_{Ar}), 6.11 (br.t, 1 H, CONH), 5.56 (br.t, 1 H, CONH), 4.69 (d, $J_{Ha\text{-}Hb}$ = 12.0 Hz, 1 H, C*H*H Bn), 4.59 (d, $J_{Hb\text{-}Ha}$ = 12.0 Hz, 1 H, CH*H* Bn), 4.52 (s, 2 H, CH_2 Bn), 4.50–4.44 (m, 3 H, CH_2 Bn, 5-H), 4.37–4.27 (m, 4 H, 2-H, 4-H, CH_2 Fmoc), 4.20 (t, *J* = 7.3 Hz, 1 H, CH Fmoc), 4.05–4.00 (m, 2 H, 6a-H, 3-H), 3.85–3.80 (m, 1 H, 6b-H), 3.11 (q, *J* = 7.4 Hz, 2 H, CH_2 butyl), 1.42–1.35 (m, 2 H, CH_2 butyl), 1.28–1.25 (m, 2 H, CH_2 butyl), 0.86 (t, *J* = 7.3 Hz, 3 H, CH_3 butyl) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, HSQC), major rotamer: δ = 170.5, 168.6, 156.5 (3×C), 143.8, 141.2, 137.8, 137.5, 137.2 (7×C Ar), 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.1, 127.0, 125.1, 119.9 (23×CH Ar), 78.3 (C-4), 78.2 (C-3), 73.4, 72.5, 72.4 (3×CH_2 Bn), 70.8 (C-6), 67.1 (CH_2 Fmoc), 66.1 (C-2), 58.7 (C-5), 47.1 (CH Fmoc), 39.4, 31.3, 20.0 (3×CH_2 butyl), 13.7 (CH_3 butyl) ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3318, 2929, 2870, 1718, 1652, 1453, 1097, 910, 735, 698 cm^{-1}. $[\alpha]_D^{20}$ = +3.2 (*c* = 0.25, $CHCl_3$). HRMS: found 782.3802 [M + H]$^+$, calculated for [$C_{48}H_{51}O_7N_3$ + H]$^+$ 782.3800.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-*N*-[(*tert*-butyloxycarbonyl)methyl]-2-deoxy-2-formamido-D-*talo*-hexonamide (VA-2,3-*trans*): Yield 33% (38.8 mg, 66 μmol), 1:1 mixture of rotamers. R_f = 0.59 (1:1; toluene/EtOAc). ^{1}H NMR (600 MHz, $CDCl_3$, COSY) mixture of rotamers: δ = 8.60 (s, 1 H, NC*H*O), 8.21 (s, 1 H, NC*H*O), 7.33–7.14 (m, 2×15 H, H_{Ar}), 6.28 (br. s, 2 H, CONH), 4.63–4.57 (m, 2×3 H, CH_2 Bn, 2-H), 4.51–4.46 (m, 2×2 H, CH_2 Bn), 4.36–4.35 (m, 2×2 H, 4-H, 3-H), 4.28–4.25 (m, 2×1 H, 5-H), 3.97 (d, J = 5.4 Hz, 2×2 H, NHCH_2CO$_2$*t*Bu), 3.91–3.81 (m, 2×2 H, 6a-H, 6b-H), 1.46 (s, 9 H, CH_3 *t*Bu), 1.44 (s, 9 H, CH_3 *t*Bu) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, HSQC) mixture of rotamers: δ = 168.8, 168.7, 168.3 (3×C), 163.6, 160.9 (2×CHO), 137.8, 137.4, 137.3 (2×3C Ar), 128.8, 128.4, 128.3, 128.1, 127.9, 127.8, 127.6 (2×15 CH Ar), 82.5, 82.1 (2×C *t*Bu), 78.0 (2×C-4), 77.7 (2×C-3), 73.3, 72.5, 70.5 (2×3 CH_2 Bn, 2×C-6), 62.3 (2×C-2), 58.3 (2×C-5), 42.1 (CH_2), 40.5 (CH_2), 30.0, 29.9 (2×3 CH_3 *t*Bu) ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3316, 2979, 1739, 1667, 1653, 1366, 1223, 1151, 735, 698 cm^{-1}. $[\alpha]_D^{20}$ = –1.8 (*c* = 1.44, $CHCl_3$). HRMS: found 589.2908 [M + H]$^+$, calculated for [$C_{34}H_{40}O_7N_2$ + H]$^+$ 589.2908.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-*N*-[(*tert*-butyloxycarbonyl)methyl]-2-deoxy-2-(*p*-nitrobenzamido)-D-*talo*-hexonamide (VB-2,3-*trans*): Yield 14% (19.9 mg, 28 μmol), 4:1 mixture of rotamers. R_f = 0.64 (1:1; toluene/EtOAc). ^{1}H NMR (600 MHz, $CDCl_3$, COSY), major rotamer: δ = 7.97 (d, J = 8.4 Hz, 1 H, H_{Ar}), 7.46 (d, J = 8.4 Hz, 1 H, H_{Ar}), 7.34–7.14 (m, 16 H, H_{Ar}), 6.96 (d, J = 8.4 Hz, 1 H, H_{Ar}), 6.57 (br. s, 1 H, CONH), 4.75 (d, $J_{Ha\text{-}Hb}$ = 12.0 Hz, 1 H, C*H*H Bn), 4.69 (s, 1 H, 2-H), 4.63 (d, $J_{Ha\text{-}Hb}$ = 12.0 Hz, 1 H, C*H*H Bn), 4.57 (dd, J = 11.4, 23.4 Hz, 1 H, CH_2 Bn), 4.49–4.47 (m, 1 H, 4-H), 4.42–4.39 (m, 1 H, 5-H), 4.26 (d, $J_{H3\text{-}H4}$ = 4.8 Hz, 1 H, 3-H), 4.10 (dd, J = 11.4, 33.6 Hz, 2 H, CH_2 Bn), 3.87 (ddd, J = 6.0, 18.0, 93.6 Hz, 2 H, NHCH_2CO$_2$*t*Bu), 3.71 (ddd, J = 3.6, 10.2, 48.6 Hz, 2 H, 6-H), 1.46 (s, 9 H, CH_3 *t*Bu) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, HSQC), major rotamer: δ = 170.2, 169.0, 168.3 (3×C), 148.0, 142.6, 137.3 (3×C Ar), 128.5, 128.3, 128.2, 128.1, 127.9, 127.6, 123.2 (19×CH Ar), 82.4 (C *t*Bu), 78.6 (C-4), 78.2 (C-3), 73.0, 72.7, 70.2 (3×CH_2 Bn, C-6), 65.5 (C-2), 60.1 (C-5), 42.1 (CH_2), 28.0 (3×CH_3 *t*Bu) ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3311, 2980, 1738, 1635, 1523, 1347, 1156, 912, 857, 735, 699 cm^{-1}. $[\alpha]_D^{20}$ = –5.8 (*c* = 0.76, $CHCl_3$). HRMS: found 710.3074 [M + H]$^+$, calculated for [$C_{40}H_{43}O_9N_3$ + H]$^+$ 710.3072.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-*N*-[(*tert*-butyloxycarbonyl)methyl]-2-deoxy-2-(pent-4-enoylamido)-D-*talo*-hexonamide (VC-2,3-*trans*): Yield 24% (30.8 mg, 48 μmol), 10:1 mixture of rotamers. ^{1}H NMR (600 MHz, $CDCl_3$, COSY), major rotamer: δ = 7.36–7.25 (m, 15 H, H_{Ar}), 6.68 (br. s, 1 H, CONH), 5.79–5.74 (m, 1 H, =CH), 4.95 (ddd, J = 1.8, 17.4, 35.4 Hz, 2 H, =CH_2), 4.69 (d, $J_{Ha\text{-}Hb}$ = 12.0 Hz, 1 H, C*H*H Bn), 4.61–4.56 (m, 3 H, C*H*H Bn, 2×CH*H* Bn), 4.49 (d, 1 H, C*H*H Bn), 4.47–4.38 (m, 5 H, C*H*H Bn, CH*H* Bn, 2-H, 4-H, 5-H), 4.14–4.10 (m, 2 H, 6a-H, 3-H), 3.94 (dd, J = 6.0, 18.6 Hz, 1 H, NHC*H*HCO$_2$*t*Bu), 3.76–3.71 (m, 2 H, NHCH*H*CO$_2$*t*Bu, 6b-H), 2.82–2.75 (m, 1 H, C*H*H pentenyl), 2.56–2.51 (m, 1 H, CH*H* pentenyl), 2.40–2.28 (m, 2 H, CH_2 pentenyl), 1.48 (s, 9 H, CH_3 *t*Bu) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, HSQC), major rotamer: δ = 174.0, 169.5, 168.5 (3×C), 137.9, 137.6 (3×C Ar), 137.5 (=CH), 128.4, 128.3, 127.8, 127.7, 127.6, 127.5 (15×CH Ar), 114.9 (=CH_2), 82.1 (C *t*Bu), 78.6 (C-4), 78.3 (C-3), 73.3, 72.6, 72.4 (3×CH_2 Bn), 71.5 (C-6), 65.1 (C-2), 59.0 (C-5), 42.0 (CH_2), 33.5 (CH_2 pentenyl), 29.0 (CH_2 pentenyl), 28.0 (3×CH_3 *t*Bu) ppm. R_f = 0.54 (1:1; toluene/EtOAc). IR (thin film): $\tilde{\nu}_{max}$ = 3306, 2933, 1739, 1636, 1416, 1366, 1223, 1151, 735, 698 cm^{-1}. $[\alpha]_D^{20}$ = +17.9 (*c* = 1.14, $CHCl_3$). HRMS: found 643.3379 [M + H]$^+$, calculated for [$C_{38}H_{46}O_7N_2$ + H]$^+$ 643.3378.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-*N*-[(*tert*-butyloxycarbonyl)methyl]-2-deoxy-2-{*N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-2-aminoacetamido}-D-*talo*-hexonamide (VD-2,3-*trans*): Yield 23% (38.6 mg, 46 μmol), 4:1 mixture of rotamers. R_f = 0.38 (1:1; toluene/EtOAc). ^{1}H NMR (600 MHz, $CDCl_3$, COSY), major rotamer: δ = 7.75 (d, J = 7.2 Hz, 2 H, H_{Ar}), 7.46 (d, J = 7.2 Hz, 2 H, H_{Ar}), 7.40–7.25 (m, 19 H, H_{Ar}), 6.57 (br. s, 1 H, CONH), 5.61 (br. s, 1 H, CONH), 4.68 (d, $J_{Ha\text{-}Hb}$ = 12.0 Hz, 1 H, C*H*H Bn), 4.61 (d, $J_{Hb\text{-}Ha}$ = 12.0 Hz, 1 H, CH*H* Bn), 4.55–4.45 (m, 6 H, 2×CH_2 Bn, 5-H, 2-H), 4.41–4.38 (m, 2 H, 4-H, FmocNHC*H*HCO), 4.35–4.29 (m, 2 H, CH_2 Fmoc), 4.19 (t, J = 7.2 Hz, 1 H, CH Fmoc), 4.16 (m, 2 H, 3-H, FmocNHCH*H*CO), 4.01–3.99 (m, 1 H, 6a-H), 3.85–3.74 (m, 2 H, 6b-H, NHCH_2CO$_2$*t*Bu), 1.40 (s, 9 H, CH_3 *t*Bu) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, HSQC), major rotamer: δ = 170.4, 168.8, 168.5, 156.5 (3×C), 143.8, 142.2, 137.8, 137.4, 137.3 (7×C Ar), 128.4, 128.0, 127.8, 127.7, 127.6, 127.0 125.1, 119.9 (23×CH Ar), 82.1 (C *t*Bu), 78.3 (C-4), 78.2 (C-3), 73.4, 72.6, 72.5 (3×CH_2 Bn), 70.7 (C-6), 67.0 (CH_2 Fmoc), 65.7 (C-2), 58.7 (2×C-5), 47.0 (CH Fmoc), 43.8, 42.0 (2×CH_2), 28.0 (3×CH_3 *t*Bu) ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3313, 2934, 1726, 1653, 1528, 1226, 1153, 738, 699 cm^{-1}. $[\alpha]_D^{20}$ = +8.0 (*c* = 0.82, $CHCl_3$). HRMS: found 840.3862 [M + H]$^+$, calculated for [$C_{50}H_{54}O_9N_3$ + H]$^+$ 840.3855.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-2-(pent-4-enoylamido)-*N*-(1,1,3,3-tetramethylbutyl)-D-*gluco*-hexonamide (11-*cis*): Yield 13% (15.7 mg, 26 μmol), 4:1 mixture of rotamers. R_f = 0.32 (3:1; toluene/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$, COSY), major rotamer: δ = 7.42–7.13 (m, 15 H, H_{Ar}), 6.98 (s, 1 H, CONH), 5.83 (ddd, J = 6.3, 11.3, 16.8 Hz, 1 H, =CH), 5.09–4.87 (m, 2 H, =CH_2), 4.73–4.33 (m, 7 H, 3×CH_2 Bn, 4-H/3-H/2-H), 4.22–4.19 (m, 2 H, 4-H/3-H/2-H), 4.17 (dd, J = 4.3, 9.7 Hz, 1 H, C*H*H-6), 3.94–3.91 (m, 1 H, 5-H), 3.49 (dd, J = 2.3, 9.7 Hz, 1 H, CH*H*-6), 2.40–2.36 (m, 4 H, 2×CH_2 pentenyl), 1.92 (d, J = 14.7 Hz, 1 H, C*H*H *t*Bu), 1.59 (d, J = 14.7 Hz, 1 H, CH*H* *t*Bu), 1.32 (d, J = 9.4 Hz, 6 H, 2×CH_3), 0.92 (s, 9 H, 3×CH_3 *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, HSQC), major rotamer: δ = 173.9, 167.9 (2×C=O), 138.0, 137.8, 137.6 (3×C_q Bn), 137.2 (=CH), 128.7, 128.6, 128.5, 128.3, 128.2, 128.0, 127.9 (15×CH Ar), 115.8 (=CH_2), 82.7 (C-2/C-3/C-4), 79.4 (C-2/C-3/C-4), 73.4, 73.0, 72.8 (3×CH_2 Bn), 66.2 (C-6), 64.5 (C-2/C-3/C-4), 64.0, 60.7 (C-5), 55.7 [C_q, NH*C*(CH$_3$)$_2$CH$_2$*t*Bu], 51.5 (CH_2-*t*Bu), 33.7 (CH_2 pentenyl), 31.7 (3×CH_3 *t*Bu), 31.6 (C_q *t*Bu), 29.4 (CH_3 *t*Bu), 28.9 (CH_3 *t*Bu), 28.8 (CH_2 pentenyl) ppm. IR (thin film): $\tilde{\nu}_{max}$ = 3328, 2949, 1668, 1537, 1453, 1365, 1205, 1117, 1026, 735, 698 cm^{-1}. $[\alpha]_D^{20}$ = –23.3 (*c* = 0.30, $CHCl_3$). HRMS: found 641.3949 [M + H]$^+$, calculated for [$C_{40}H_{52}O_5N_2$ + H]$^+$ 641.3949.

2,5-Anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-2-(pent-4-enoylamido)-*N*-(1,1,3,3-tetramethylbutyl)-D-*manno*-hexonamide (12-*trans*): 3:1 mixture of rotamers, yield 17% (21.5 mg, 34 μmol), R_f = 0.47 (3:1; toluene/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$, COSY), major rotamer: δ = 7.36–7.20 (m, 15 H, H_{Ar}), 6.13 (s, 1 H, CONH), 5.87–5.74 (m, 1 H, =CH), 5.09–4.91 (m, 2 H, =CH_2), 4.70–4.37 (m, 7 H, 3×CH_2 Bn, 5-H), 4.27–4.09 (m, 3 H, 2-H, 3-H, 4-H), 3.99 (dd, J = 4.3, 8.8 Hz, 1 H, C*H*H-6), 3.44 (dd, J = 8.9, 10.5 Hz, 1 H, CH*H*-6), 2.48–2.23 (m, 4 H, 2×CH_2 pentenyl), 1.44 (d, J = 14.7 Hz, 1 H, C*H*H *t*Bu), 1.35 (d, J = 14.7 Hz, 1 H, CH*H* *t*Bu), 1.22 (d, J = 14.4 Hz, 6 H, 2×CH_3), 0.86 (s, 9 H, 3×CH_3 *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, HSQC), major rotamer: δ = 172.9, 168.7 (2×C=O), 138.6 (C_q Bn), 137.2 (C_q Bn), 137.1 (=CH), 137.0 (C_q Bn), 128.8, 128.7, 128.7, 128.6, 128.5, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7 (15×CH Ar), 115.8 (=CH_2), 86.0 (C-5), 81.3 (C-2/C-3/C-4), 73.3 (CH_2 Bn), 71.8 (2×CH_2 Bn), 69.4 (C-2/C-3/C-4), 66.8 (C-6), 64.1 (C-2/C-3/C-4), 55.8 [C_q, NH*C*(CH$_3$)$_2$-CH$_2$*t*Bu], 53.5 (CH_2-*t*Bu), 34.3 (CH_2 pentenyl), 31.7 (3×CH_3 *t*Bu), 31.6 (C_q *t*Bu), 31.7 (3×CH_3 *t*Bu), 28.9 (CH_2 pentenyl), 28.3 (CH_3

*t*Bu), 27.4 (CH_3 *t*Bu) ppm. IR (thin film): $\tilde{\nu}_{max}$ = 2950, 1663, 1535, 1452, 1399, 1366, 1204, 1097, 736, 699 cm^{-1}. $[\alpha]_D^{20}$ = –33.3 (*c* = 0.24, $CHCl_3$). HRMS: found 641.3949 $[M + H]^+$, calculated for $[C_{40}H_{52}O_5N_2 + H]^+$ 641.3949.

Supporting Information (see also the footnote on the first page of this article): Copies of ^1H and ^{13}C-APT NMR spectra for all reported Ugi-3CR products. ^{13}C-APT NMR spectra of discussed intermediates in CD_3OH. Assignment of C-2 stereochemistry of the 2,3-*cis* (**3**) and 2,3-*trans* (**4**) diastereoisomers after depent-4-enoylation with ^1H-NOESY NMR spectra.

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