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An investigation of construction of chondroitin sulfate E (CS-E) repeating unit

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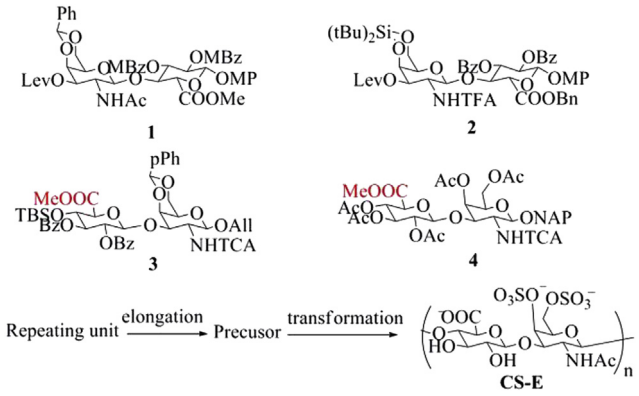
ABSTRACT

A series of the derivatives of chondroitin sulfate E (CS-E) disaccharide repeating unit were prepared by postglycosylation–oxidation strategy. The strategy showed excellent performance in glycosylation both on the reactivity and stereoselectivity. Different protecting methodologies were used for the manipulation of disaccharide building blocks. Substitutes at C-4 of glucosyl donors mildly influenced the glycosylation. The current synthesis afforded a feasible approach for the preparation of CS-E repeating unit.

1. Introduction

Chondroitin sulfate (CS) is a linear sulfated polysaccharide composed of repeating dimeric units GlcA-β(1→3)-GalNAc-β(1→4). Variation of sulfation position and number gives rise to different subtypes of CS polymer. CS-E is characterized by two sulfates at C-4 and C-6 positions of GalNAc residue, and it was reported to play critical roles in various physiological processes.[1] Precise molecular structure is essential for accurate pharmacological study. However, the complexity and heterogeneity of CS make it difficult to obtain structurally defined CS-E oligosaccharides in significant amounts from natural sources. To address the problem, well-defined synthetic CS-E oligosaccharides are required. Moreover, a further chemical structural modification of CS-E will give access to the examination of structure–activity relationship, providing more understanding of its biofunction on pharmacological targets.

Several reports of total synthesis of CS-E oligosaccharides have been published so far (Scheme 1).[2–10] Using a GalNAc donor and GlcA acceptor, Tamura, J. and co-workers successfully obtained disaccharide unit **1**, which was further elongated to give tetra-, hexa-, and octa-saccharides.[2–4] In the same sequence, repeating unit **2** was developed by Pedro M. Nieto and co-workers and it was employed for the further preparation of CS-E tetrasaccharides.[5] On the other hand, Hsieh-Wilson and co-workers described the synthesis of CS-E tetra- and hexa-saccharides having a GlcA–GalNAc motif came from **3**, which is in a reverse sequence.[6] Different with constructing disaccharide unit from two monosaccharide building blocks, Jacquinet and co-workers synthesized CS-E oligosaccharides starting from the key disaccharide unit **4**, which was obtained directly by hydrolysis of commercially available CS polymer.[7–10]



Scheme 1. Structures of key disaccharide used in total synthesis of CS-E oligosaccharides reported.

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0040-4020/

Besides, along with the development of total synthesis of CS-E, some derivatives were prepared and estimated in various biological activity studies.[11–19]

As illustrated in all these approaches, CS-E was prepared by 'oligomerization' of a key disaccharide repeating unit, to which an easy access was crucial to the efficient synthesis of CS-E oligosaccharides. According to the structural feature of CS-E, suitable protection and transformation strategy should be employed in the construction of the disaccharide repeating unit. However, their influence on glycosylation was poorly understood, although substituents may significantly affect yield and stereoselectivity in glycosylation reactions. In this article, we focused on the construction of CS-E repeating disaccharide unit in GlcA–GalNAc sequence, synthesized a small library of monosaccharide building blocks as donors and acceptors, compared their reactivity in glycosylation, and investigated the suitable strategies used in CS-E synthesis. At the same time, we explored the feasibility of post-glycosylation–oxidation strategy[20] at the disaccharide stage. In this approach, the disaccharide is assembled with nonoxidized glucosyl building block and the carboxylic acid moiety is introduced at the later stage. Since glucuronic acids are usually considered to be inactive glycosyl donors due to the presence of the electro-withdrawing carboxylic acid moiety,[20] we envisioned that the postglycosylation–oxidation strategy would be more effective for CS-E oligosaccharide glycosylation than the preglycosylation–oxidation strategy.

We initially designed a small library of monosaccharide building blocks containing eight donors and three acceptors, which presumably possess different reactivity in glycosylation (Fig. 1). In particular, to improve the utilization of compound library, all monosaccharides were enabled to be potentially useful building blocks for CS-E disaccharide fragments, and the corresponding basic structural characteristics were taken into account: (1) The β-stereoselectivity was controlled by the presence of a benzoyl participating group in the glucosyl unit. (2) A 4,6-*O*-benzylidene acetal was used to give an access to 4,6-sulfation of GalNAc residue in the future. (3) The anomeric hydroxyl group of galactosamine unit was masked with OMP, which could be oxidative deprotected by ceric ammonium nitrate (CAN) allowing further elongation. Apart from these common features, protection strategies at other positions were investigated of their influence on glycosylations. Firstly, thioglycoside and trichloroacetimidate were designed as anomeric group of glucosyl moiety. Secondly, nonoxidized glucosyl building blocks **5**–**8** were designed to investigate the difference of reactivity in glycosylation with their oxidized counterparts **9**–**12**. Thirdly, with respect to the C-4 position in glucosyl residue, the selectively removable Lev and TBS groups were chosen as representatives of orthogonal protecting groups which possess opposite electronic property. On the other hand, in galactosamine residue, three acceptor moieties **13**–**15** were designed differentiated by the amino types at C-2 position, as representatives of N-protection methods which were commonly used in CS-E synthesis.

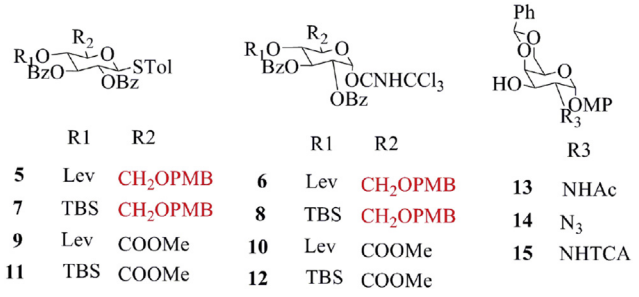
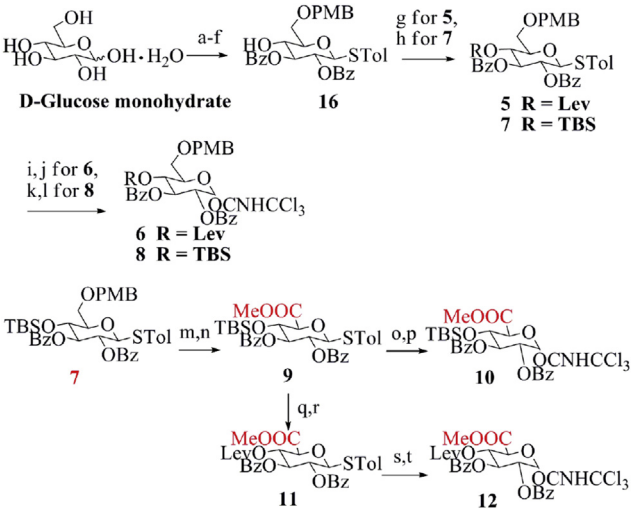


Fig. 1. A small library of monosaccharide building blocks.

2. Results and discussion

Synthesis of eight donors were carried out as shown in Scheme 2. Compound **16** was prepared from D-glucose monohydrate according to the traditional literature protocols for carbohydrates with select modifications.[6] Lev and TBS substitute were installed at the C-4 position of the glucosyl moiety to afford thioglycosides **5** and **7** in 96% and 66% yield, respectively. *p*-Methoxybenzyl ether (PMB) of **7** was subjected to oxidative removal with 2,3-dicyano-5,6-dichlorobenzoquinone (DDQ) to give alcohol in 96% yield. The primary alcohol was oxidized by pyridinium dichromate (PDC) followed by methyl esterification to afford the donor **9** in 77% yield (two steps). **9** was transformed into **11** through cleavage of the TBS group with HF·Py followed by levulinoylation in 69% yield (two steps). Conversion of donors **5**, **7**, **9**, and **11** to glycosyl trichloroacetimidate **6**, **8**, **10**, and **12** by cleavage of the anomeric thioether with NIS or NBS and subsequent treatment of the lactol with trichloroacetonitrile and catalytic amount of 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) or Cs_2CO_3 was readily achieved (69%–81%, two steps).

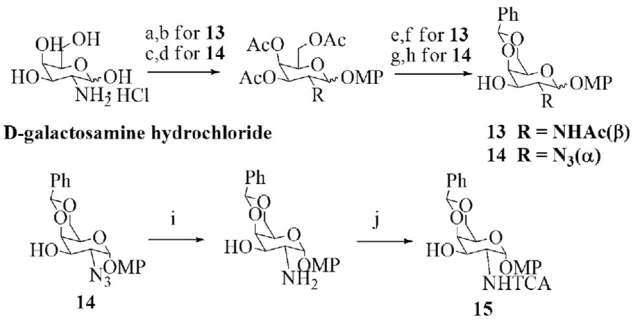


Scheme 2. Reagents and conditions: a. Ac_2O, cat. DMAP, 90 °C, 2.5 h, 94%; b. *p*-Toluenethiol, $BF_3{\cdot}Et_2O$, DCM, 40 °C, 8 h, 71%; c. NaOMe, MeOH, rt, 1 h, 93%; d. *p*-Methoxybenzaldehyde dimethyl acetal, cat. PTSA, 40 °C, reduced pressure, 6 h, 89%; e. BzCl, cat. DMAP, Py, rt, overnight, 70%; f. $NaBH_3CN$, TFA, molecular sieve, DMF, rt, 3 d, 93%; g. Levulinic acid, EDCI, cat. DMAP, DCM, rt, 2 h, 96%; h. TBDMSCl, imidazole, DMF, 2 d, 66%; i. NIS,TFA,DCM/H_2O, rt, 4 h; j. DBU, CCl_3CN, DCM, rt, overnight, 81% for two steps; k. NBS, acetone, 0 °C, 2 h, 77%; l. DBU, CCl_3CN, DCM, 9 h, 88%; m. DDQ, DCM/H_2O, rt, overnight, 96%; n. 1) PDC,DMF, rt, 3 d; 2) CH_3I, K_2CO_3, DMF, rt, 1 h, 77% for two steps; o. NIS, TfOH, DCM/H_2O, rt, 6 h, 98%; p. Cs_2CO_3, CCl_3CN, DCM, overnight, 84%; q. HF·Py, THF/Py, 18 h; r. Levulinic acid, EDCI, cat. DMAP, DCM, rt, 2 h, 69% for two steps; s. NIS, Tf_2O, DCM/H_2O, rt, 20 h, 97%; t. DBU, CCl_3CN, DCM, overnight, 80%.

It is worth noting that the four thioglycoside donors, bearing different substitutes, exhibited different performance in the process of hydrolysis of thioglycosides. Hydrolysis of thioglycoside **7** proceeded smoothly under a mild condition (NBS/Acetone, rt, 2 h), and it came into a mess of products with the presence of acid. Treated with traditional procedures (NIS/Acid/CH_2Cl_2, rt, 4–6 h), thioglycoside **5** and **11** were converted smoothly into corresponding hemiacetals. As for hydrolysis of thioglycoside **9**, it didn't work with the usual conditions such as NIS/TFA, NIS/trifilic acid or NIS/AgOTf. At last, the hydrolysis of **9** was conducted with NIS/Tf_2O at room temperature for 20 h.[21]

Synthesis of three acceptors were carried out as shown in Scheme 3. Peracetylated derivative of commercially available D-galactosamine hydrochloride was converted into corresponding OMP glycoside directly with $BF_3{\cdot}Et_2O$ in CH_2Cl_2. Then 4,6-*O*-

benzylidene acetal was installed after de-O-acetylation and acceptor **13** was obtained. However, **13** suffered from poor solubility in organic solvents such as dichloromethane, acetonitrile, and toluene. Acceptor **14** was prepared through a similar procedure of synthesis of **13**, accompanying with a β isomer in an α:β ratio of about 2:1. The azido derivative **14** was smoothly reduced with Lindlar catalyst under an H_2 atmosphere, followed by *N*-trichloroacetylation to give acceptor **15**.

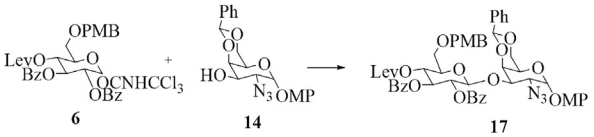


Scheme 3. Reagents and conditions: a. Ac_2O, Py, rt, overnight, 75%; b. *p*-Methoxyphenol, $BF_3{\cdot}Et_2O$, DCM, rt, overnight; N_2H_4-HOAc, DMF, rt, 3.5 h, 45%; c. 1) NaN_3, Tf_2O, DCM, H_2O, 0 °C, 3 h; 2) $CuSO_4{\cdot}5H_2O$, K_2CO_3, MeOH/DCM/H_2O, rt, 24 h; Gly, 24 h; 3) Ac_2O, Py, cat. DMAP, rt, overnight, 81% for three steps; d. *p*-Methoxyphenol, $BF_3{\cdot}Et_2O$, DCM, rt, 3 d; N_2H_4-HOAc, DMF, rt, 1.5 h, 86% (α:β, 2:1); e. NaOMe, MeOH/DCM, rt, 5 min, 86%; f. benzaldehyde dimethyl acetal, cat. PTSA, 40 °C, reduced pressure, 5 h, 70%; g. NaOMe, MeOH/DCM, rt, 30 min; h. benzaldehyde dimethyl acetal, cat. PTSA, 40 °C, reduced pressure, 10 h, 62% with 27% β isomer; i. Lindlar catalyst, MeOH, rt, overnight; j. TCACl, Et_3N,THF, 0 °C, 20 min, 73% for two steps.

With all these building blocks in hand, we then preliminarily investigated the reactivity of monosaccharides library. Initially, condensations of acceptor **13** with thioglycoside **5** were conducted in the presence of NIS/TMSOTf or NIS/$BF_3{\cdot}Et_2O$, however, no desired product was obtained. Likewise, condensation between **13** and imidate **6** was also proved to be failed. The failures may be attributed to the poor solubility of acceptor **13**, just like a similar observation described by Susana Maza and co-workers.[22] As good solubility is essential for a reasonable comparison of reactivity, attention was then turned towards acceptor **13**, whose solubility was significantly improved by azido substitute instead of *N*-acetyl. Although glycosylation between acceptor **14** and thioglycoside **5** still didn't work, trichloroacetimidate **5** was coupled with acceptor **14** in excellent yield. Different reaction conditions was tested, and the optimal results were obtained with TMSOTf as catalyst and CH_2Cl_2 as solvent at temperature in a range of −80 °C to −40 °C, the outcomes were listed in Table 1. In all these TMSOTf or TESOTf-catalyzed glycosylations, donor **6** was consumed completed in less than 15 min, and plenty of hydrolysis product of donors were detected only when reaction was carried out at −20 °C. Besides, $BF_3{\cdot}Et_2O$-catalyzed reaction took a relative drastic condition (room temperature, 16 h) and led to a slightly lower yield (73%). All these results suggested the good reactivity of imidate **6** and acceptor **14**.

Encouraged by the good result, we then proceeded to examine the influence of protecting groups both on the reactivity and stereoselectivity towards assembling CS-E disaccharide unit. −60 °C was chosen as the reaction temperature, and if the reaction didn't work at −60 °C within 1 h, the reaction would be allowed to warm to room temperature and be stirred for several hours before being quenched. Then at the identical reaction condition (1.2 equiv donor, 0.12 equiv TMSOTf in dichloromethane), a series of condensations between acceptors **14**–**15** and donors **5**–**12** were carried out. As shown in Table 2, it is very clear that condensations with non-oxidized glucosyl donors were performed in a rapid way with excellent yields (79%–98%) and designed stereoselectivity. No formation of the isomeric α-linked disaccharide was observed.

Table 1
Glycosylations of donor **6** and acceptor **14** at varied reaction conditions



Entry	Promotor	Condition	Yield
1	TMSOTf	−20 °C, 15min	38%
2–4	TMSOTf	−40 °C, −60 °C, −80 °C, 15min	87%–90%
5	TESOTf	−60 °C, 15min	87%
6	$BF_3{\cdot}Et_2O$	−60 °C to rt, rt for 16 h	73%

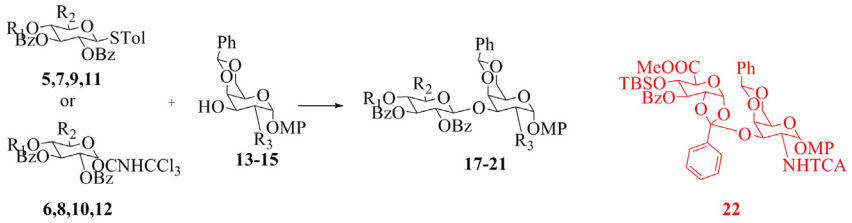
[a]The reaction was conducted in the identical process: To a mixture of donor **6** (1.2 equiv) and acceptor **14** (1.0 equiv) in dry CH_2Cl_2 (0.05 M) was added a solution of promoter (0.12 equiv) in CH_2Cl_2 (0.1 M). The reaction was monitored by TLC till a complete consumption of donor. Then the reaction was quenched by Et_3N and purified by column chromatography (petroleum ether/ethyl acetate 4/1).

Coupling acceptor **14** with nonoxidized glucosyl donors **6** and **8** were performed at −60 °C within 15 min to furnish the desired disaccharide **17** and **18** in 87% and 96% yield, respectively. In a similar manner, coupling reaction of acceptor **15** with non-oxidized glucosyl donors **6** and **8** afforded the expected disaccharide **19** and **20** in 79% and 98% yield, respectively. In contrast, glycosylation with oxidized glucosyl donors were performed in a very hard way. All of the relating entries were failed except for the condensation between **15** and **10**, affording the expected disaccharide **21** in 8% yield accompanied by its orthoester **22** ($\delta_{H\text{-}1}$ 6.01 ppm, $\delta_{C\text{-orthoester}}$ 121.08 ppm, $^1J_{H\text{-}1,H\text{-}2}$ 5.2 Hz) in 12% yield. Therefore, the reactivity order of imidate donors in the glycosylation was inferred as **8**>**6**>**10**>**12**. On the other hand, in this study thioglycoside donors either didn't work or gave only a trace of α disaccharide (Entry 1) under NIS/TMSOTf reaction condition. This was, however, not a surprise to us, because thioglycosides were never reported as an efficient donor in CS-E synthesis before, perhaps due to its poor reactivity.

Taken together, these results showed that, substitutes at C-5 position strongly influenced the reactivity of donors. Although glucuronic acid was universally adopted as donor in CS-E synthesis before, we thought nonoxidized glucosyl as superior. As a matter of fact, the reactivity of nonoxidized glucosyl donors were much higher than that of their oxidized counterparts in glycosylation, demonstrating that postglycosylation–oxidation strategy could significantly improve glycosylation efficiency in CS-E repeating disaccharide unit synthesis. The second impact factor on reactivity is the electronic property of substitutes at C-4 position. An electron-donating substitute TBS could mildly raise the reactivity of donors **7** and **10**. In contrast, Lev group exhibited a negative effect on the reactivity of donors **5** and **12** probably resulted from electron-withdrawing functionality. Except for donors, acceptors also playing a role in affecting glycosylation, especially when the donor was poor active. *N*-Trichloroacetylated acceptor **15** was proved to be slightly more reactive than azido type acceptor **14** in condensation with imidate **10**. And this may be due to the strong electron-withdrawing property of azido, which led a loss of the nucleophilicity of the neighboring hydroxyl group. To verify this speculation and further explore the extent of capability impact of increasing electron density of acceptors, we designed and synthesized three more acceptors **23**–**25**, bearing Cbz and 4,6-di-*tert*-butylsilylene group as electron-donating substitutes, and coupled them with trichloroacetimidate **10** at the same reaction condition used before. The synthesis of acceptors **23**–**25** was described in Scheme 4.

Acceptor **23** was prepared from **14** as described for **15**. Then 4,6-di-*tert*-butylsilylene group was installed after de-protection of 4,6-*O*-benzylidene acetal group and acceptor **24** was obtained.

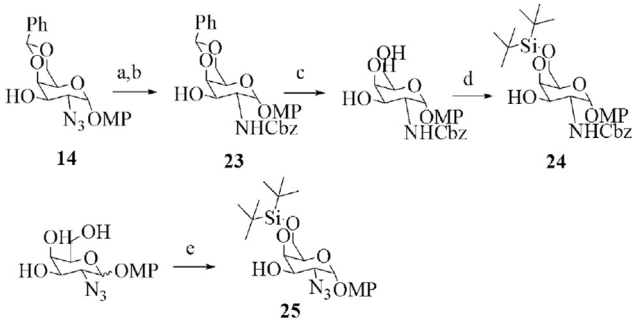
Table 2
Glycosylations of donors **5**–**12** and acceptors **13**–**15**



	R1	R2	R3
17	Lev	CH_2OPMB	N_3
18	TBS	CH_2OPMB	N_3
19	Lev	CH_2OPMB	NHTCA
20	TBS	CH_2OPMB	NHTCA
21	TBS	$COOCH_3$	NHTCA

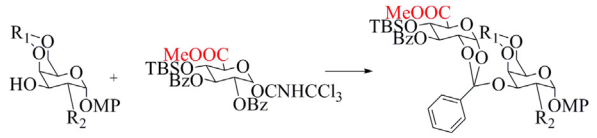
Entry	Donor	Acceptor	Promoter	Reaction condition	Product/Yield	
1	**5**	**13**	NIS/TMSOTf	−40 °C, 30 min	NR[a]	
2	**6**	**13**	TMSOTf	−40 °C, 30 min	NR[b]	
3	**6**	**14**	TMSOTf	−60 °C, 15 min	**17**/87%	
4	**8**	**14**	TMSOTf	−60 °C, 15 min	**18**/96%	
5–6	**10, 12**	**14**	TMSOTf	−60 °C to rt, 16 h	NR[c]	
7	**6**	**15**	TMSOTf	−60 °C, 15 min	**19**/79%	
8	**8**	**15**	TMSOTf	−60 °C, 15 min	**20**/98%	
9	**10**	**15**	TMSOTf	−60 °C to rt, 16 h	**21**/8%	**22**/12%
10	**12**	**15**	TMSOTf	−60 °C to rt, 16 h	NR[c]	
11–18	**5, 7, 9, 11**	**14, 15**	NIS/TMSOTf	−60 °C to rt, 16 h	NR[c]	

[a] The donor was completely hydrolyzed. The products were an α disaccharide (5%) and an orthoester (5%).
[b] No reaction, and the donor was completely hydrolyzed.
[c] No reaction, and the donor could be detected with its hydrolysis product.



Scheme 4. Reagents and conditions: a. Lindlar catalyst, H_2, MeOH, overnight; b. CbzCl, DCM, satd $NaHCO_3$, 0 °C—rt, overnight, 68% for two steps; c. MeOH, $TsOH·H_2O$, reflux, 1 h; d. $(t\text{-Bu})_2Si(OTf)_2$, Py, 0 °C—rt, 20 min, 29% for two steps; e. $(t\text{-Bu})_2Si(OTf)_2$, Py, 0 °C—rt, 20 min, 41% with 24% β isomer.

Table 3
Glycosylations between donor **10** and acceptors **23**–**25**



23 R_1=PhCH,R_2=NHCbz
24 R_1=$(tBu)_2Si$,R_2=NHCbz
25 R_1=$(tBu)_2Si$,R_2=N_3

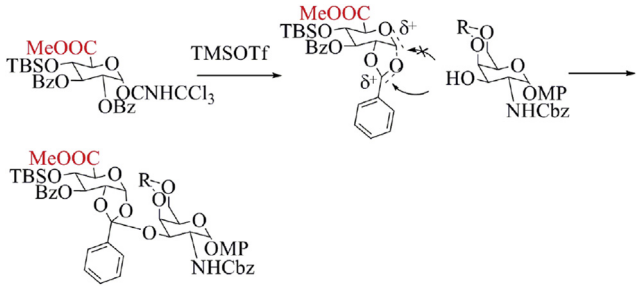
10

26 R_1=PhCH,R_2=NHCbz
27 R_1=$(tBu)_2Si$,R_2=NHCbz

Entry	Donor	Acceptor	Reaction condition	Product/Yield	
1	**10**	**23**	TMSOTf, −60 °C to rt, 16 h	**26**/42%	
2	**10**	**24**		**27**/31%	
3	**10**	**25**		No reaction	
4	**10**	**15**		**21**/8%	**22**/12%

Similarly, **25** was prepared from a 4,6-dihydroxy intermediate in the synthesis route of **14**.

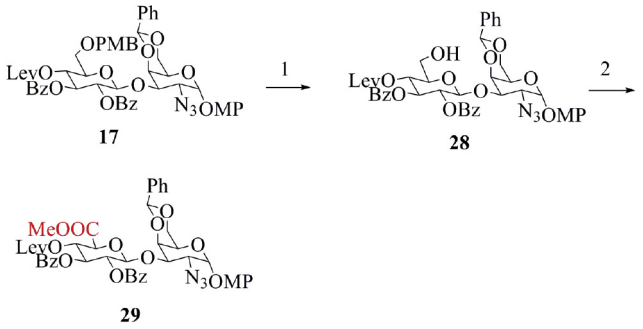
Much to our surprise, only orthoesters **26** and **27** were obtained without any of expected disaccharide product, at the yield of 42% for **26** ($\delta_{H\text{-}1}$ 5.86 ppm, $\delta_{C\text{-orthoester}}$ 120.61 ppm, $^1J_{H\text{-}1,H\text{-}2}$ 5.2 Hz) and 31% for **27** ($\delta_{H\text{-}1}$ 6.03 ppm, $\delta_{C\text{-orthoester}}$ 121.36 ppm, $^1J_{H\text{-}1,H\text{-}2}$ 4.4 Hz), respectively (Table 3). Combined with the result of glycosylation between donor **10** and acceptor **15**, it could be concluded that glucuronic acid donors tends to generate orthoesters as main products in glycosylations. Studies have found that acetylated trichloroacetimidate donors are known to give orthoesters as intermediates, especially when encountered in slow coupling reactions.[23] Thus it was speculated that, in a similar manner, the low reactivity of benzoylated imidate **10** led a slow reaction rate (room temperature, 16 h, and donor was not consumed completely), enabling the reaction to take orthoester pathway with good selectivity (See Scheme 5). With regard to high reactive imidates **6** and **8**, the reactions went very fast and were completed within 15 min at −60 °C, thus the glycosidic bond is formed quickly even for the less active acceptor **15**, leading to regioselectivity in desired β disaccharide way. As to acceptor **25**, the glycosylation didn't work. This may be due to the detrimental combination of the



Scheme 5. Formation of the orthoesters **26** and **27**.

electro-withdrawing N_3 substitute and the large steric hindrance 4,6-di-*tert*-butylsilylene group.

Next, we explored the applicability of post-glycosylation–oxidation strategy in the synthesis of CS-E disaccharide repeating unit. Compound **17** was chosen as the research object whose *p*-methoxybenzyl ether was easily removed by DDQ to give **28** (87%). Further oxidation of primary alcohol by TEMPO/BAIB following methyl esterification afforded C-5 carboxylic acid ester disaccharide derivative **29** in excellent yield (90% for two steps) (Scheme 6). **29** could be used as CS-E disaccharide unit for further elongation, as established by previous reports of synthesis of CS-E oligomers.[6,8,15] Subsequently, the efficiency of two glycosylation–oxidation approach was examined. In the application of postglycosylation–oxidation strategy, the total yield of glycosylation–oxidation reactions was 70% of **29** (glycosylation: 90%, oxidation: 87%, 90%), much higher than that of **26** (less than 8%) with employment of preglycosylation–oxidation strategy. We therefore believed that the former strategy is more favorable in the synthesis of CS-E disaccharide repeating unit. From this, a new synthesis approach was proposed that the nonoxidized disaccharide repeating unit is straightly elongated, and the carboxylic acid moiety is introduced at the CS-E oligosaccharide stage. This approach was expected to exhibit higher efficiency than the existed way with preglycosylation–oxidation strategy.



Scheme 6. Reagents and conditions: 1. DDQ, DCM/H_2O, rt, overnight, 87%; 2. 1) TEMPO, BAIB, rt, 4 h; 2) CH_3I, K_2CO_3, DMF, rt, 2 h, 90% for two steps.

3. Conclusion

On the basis of the results, the following conclusions can be drawn: (1) the type of C-6 decisively affected glycosylation both on reactivity and stereoselectivity. The glucosyl donors performed excellently in glycosylation with good β stereoselectivity. In contrast, the oxidized type derivatives were proved to tend to generate orthoesters probably due to its poor reactivity. (2) The efficiency of glycosylation could be mildly improved by the raise of donors' reactivity mediated by substitutes at C-4. And the substitutes of acceptors also had some impact on coupling. (3) A smooth conversion of disaccharide **17** to **29**, demonstrated the feasibility of post-glycosylation–oxidation strategy in the synthesis of CS-E repeating unit, which has never been reported before. (4) Compared with preglycosylation–oxidation approach, postglycosylation–oxidation strategy was found preferable for the efficient construction of CS-E repeating disaccharide unit, and it was worthful to be applied in the synthesis of CS-E oligosaccharides or analogues.

4. Experimental section

4.1. General

All solvents and reagents were obtained from commercial sources and used without further purification unless otherwise noted. All NMR spectra were recorded on Mercury-400, 500 or 600 MHz spectrometers in $CDCl_3$, CD_3OD and DMSO. HRMS experiments were done with an Aglient 1100 series LC/MSD TOF and MS with a Thermo-Finnigan LCQ Advantage. Analytical thin chromatography (TLC) was carried out on TLC plates silica gel HSGF254 percolated by Branch of Qingdao Haiyang Chemical Plant. Chromatography was performed with silica gel H (HG/T2354-92).

4.2. 6-((4-Methoxybenzyloxy)methyl)-5-(4-oxopentanoyloxy)-2-(*p*-tolylthio)tetrahydro-2*H*-pyran-3,4-diyl dibenzoate, 5

EDCI·HCl (7.70 g, 40.19 mmol), DMAP (589 mg, 4.82 mmol) and Et_3N (5.6 mL, 40.19 mmol) were added into a solution of levulinic acid (4.67 g, 40.19 mmol) in CH_2Cl_2 (40 mL), and the solution was stirred at room temperature for 30 min. Then the resulting mixture was added to the solution of **16** (10.13 g, 16.07 mmol) in CH_2Cl_2 (50 mL), and the mixture was stirred at room temperature for 2 h. The reaction was diluted with CH_2Cl_2 and was washed by water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated, and purified by column chromatography (1:50 EtOAc/CH_2Cl_2) to afford **5** (11.24 g, 96%) as a white solid. ^{1}H NMR($CDCl_3$, 400 MHz): δ 7.88 (d, J=7.2 Hz, 2H, ArH-Bz), 7.80 (d, J=7.6 Hz, 2H, ArH-Bz), 7.19–7.46 (m, 10H, ArH-Bz, PMB, and SPhMe), 6.96 (d, J=7.6 Hz, 2H, ArH-SPhMe), 6.82 (d, J=8.4 Hz, 2H, ArH-PMB), 5.58 (t, J=9.6 Hz, 1H, H-3), 5.29 (t, J=9.6 Hz, 1H, H-2), 5.19 (t, J=9.6 Hz, 1H, H-4), 4.81 (d, J=10.0 Hz, 1H, H-1), 4.45 (d, J=11.6 Hz, 1H, CH_2-PMB), 4.41 (d, J=11.6 Hz, 1H, CH_2-PMB), 3.74–3.82 (m, 4H, H-5, OCH_3-PMB), 3.57–3.64 (m, 2H, H-$6_{a,b}$), 2.17–2.54 (m, 7H, H of Lev), 1.94 (s, 3H, CH_3-SPhMe); ^{13}C NMR($CDCl_3$, 100 MHz): δ 205.98 (CO-Lev), 171.24 (CO-Lev), 165.97 (CO-Bz), 165.22 (CO-Bz), 159.44 (ArC-PMB), 138.56 (ArC-SPhMe), 133.60 (2C, ArC-SPhMe), 133.47 (CO-Bz), 133.45 (CO-Bz), 130.39, 130.04 (2C), 130.03 (2C), 129.89 (2C), 129.70 (2C), 129.51, 129.21, 128.55 (4C), 128.47, 113.93 (2C, ArC-PMB), 86.48 (C-1), 77.98 (CH_2-PMB), 74.76, 73.43, 70.79, 69.40, 68.96, 55.43 (OCH_3-PMB), 37.91 (C-Lev), 29.68 (C-Lev), 28.05 (C-Lev), 21.36 (CH_3-SPhMe). HRMS (ESI) m/z: 735.2174 $[M+Na]^+$. Calcd for $C_{40}H_{41}NaO_{10}S$ 735.2240.

4.3. 6-((4-Methoxybenzyloxy)methyl)-5-(4-oxopentanoyloxy)-2-(2,2,2-trichloro-1-iminoethoxy)tetrahydro-2*H*-pyran-3,4-diyl dibenzoate, 6

To a solution of **5** (512 mg, 0.70 mmol) in CH_2Cl_2 (6 mL) and water (400 μL) was added *N*-iodosuccinimide (237 mg, 1.06 mmol). Then trifluoroacetic acid (50 μL, 0.70 mmol) was added dropwise to the mixture at 0 °C, and the reaction was allowed to warm to room temperature, and stirred for 4 h. Then the reaction was quenched with 5 M $Na_2S_2O_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford a yellow syrup containing the corresponding hemiacetal. ESI-MS m/z: 629.13 $[M+Na]^+$. Calcd for $C_{33}H_{34}O_{11}Na$ 629.20.

A mixture of the hemiacetal, Cl_3CCN (232 μL, 2.31 mmol), and DBU (28 μL, 0.19 mmol) in anhyd CH_2Cl_2 (3 mL) was stirred overnight at room temperature. Then the resulting mixture was concentrated. Column chromatography (1:10→1:5 EtOAc/PE+0.1% Et_3N) gave imidate **6** (210 mg, 81% for two steps) as a yellow syrup. ^{1}H NMR($CDCl_3$, 400 MHz): δ 8.59 (s, 1H, NH), 7.95–7.93 (m, 4H, ArH-Bz), 7.52–7.47 (m, 2H, ArH-Bz), 7.39–7.26 (m, 6H, ArH-Bz, PMB), 6.87 (d, J=8.4 Hz, 2H, ArH-PMB), 6.77 (d, J=3.6 Hz, 1H, H-1), 6.05 (t, J=10.0 Hz, 1H, H-3), 5.61 (t, J=10.0 Hz, 1H, H-4), 5.50 (dd, J=10.4, 3.6 Hz, 1H, H-2), 4.53–4.46 (m, 2H, CH_2-PMB), 4.35–4.27 (m, 1H, H-5), 3.79 (s, 3H, CH_3-PMB), 3.69 (dd, J=11.2, 2.0 Hz, 1H, H-6_a), 3.63 (dd, J=11.2, 4.0 Hz, 1H, H-6_b), 2.63–2.29 (m, 4H, CH_2CH_2-Lev), 2.02 (s, 3H, CH_3-Lev); ^{13}C NMR($CDCl_3$, 100 MHz): δ 205.92 (CO-Lev), 171.32 (CO-Lev), 165.80 (CO-Bz), 165.43 (CO-Bz), 160.62

(C=NH), 159.35 (ArC-PMB), 133.54 (ArC-Bz), 133.40 (ArC-Bz), 129.97, 129.91, 129.81, 129.20, 128.74, 128.50, 128.48, 128.08, 113.81 (2C, ArC-PMB), 93.44 (C-1), 73.29, 71.76, 70.76, 70.57, 68.24, 67.42, 55.33 (OCH_3-PMB), 37.85 (C-Lev), 29.61 (C-Lev), 27.92 (C-Lev). ESI-MS *m/z*: 750.12 $[M+H]^+$, 772.12 $[M+Na]^+$. Calcd for $C_{35}H_{35}Cl_3NO_{11}$ 750.13, $C_{35}H_{34}Cl_3NO_{11}Na$ 772.11.

4.4. 5-(*tert*-Butyldimethylsilyloxy)-6-((4-methoxybenzyloxy) methyl)-2-(*p*-tolylthio)tetrahydro-2*H*-pyran-3,4-diyl dibenzoate, 7

To a solution of alcohol **16** (23.73 g, 37.66 mmol) and imidazole (5.46 g, 80.23 mmol) in DMF (130 mL) was added *tert*-butyldimethylsilyl chloride (12.09 g, 80.23 mmol) at 0 °C. The mixture was stirred at room temperature for 2 days. It was then quenched with satd $NaHCO_3$ aq and diluted with CH_2Cl_2. The aqueous layer was separated and extracted with CH_2Cl_2 (3×). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. Column chromatography (1:10 EtOAc/PE) gave **7** (17.83 g, 66%) as a white foam. ^1H NMR($CDCl_3$, 400 MHz): δ 7.92–7.87 (m, 4H, ArH-Bz), 7.31–7.50 (m, 10H, ArH-Bz, PMB, and SPhMe), 7.04 (d, *J*=8.0 Hz, 2H, ArH-PMB), 6.93 (d, *J*=8.4 Hz, 2H, ArH-SPhMe), 5.60 (t, *J*=8.8 Hz, 1H, H-3), 5.30 (t, *J*=9.6 Hz, 1H, H-2), 4.89 (d, *J*=10.0 Hz, 1H, H-1), 4.60 (d, *J*=11.2 Hz, 1H, CH_2-PMB), 4.52 (d, *J*=11.2 Hz, 1H, CH_2-PMB), 4.01 (t, *J*=8.8 Hz, 1H, H-4), 3.81–3.84 (m, 4H, H-5, OCH_3-PMB), 3.65–3.77 (m, 2H, H-$6_{a,b}$), 2.31 (s, 3H, CH_3-SPhMe), 0.75 (s, 9H, CH_3-TBS), 0.03 (s, 3H, CH_3-TBS), −0.21 (s, 3H, CH_3-TBS); ^{13}C NMR($CDCl_3$, 100 MHz): δ 166.07 (CO-Bz), 165.49 (CO-Bz), 159.41 (ArC-PMB), 138.33 (ArC-SPhMe), 133.59 (2C, ArC-SPhMe), 133.27 (ArC-Bz), 133.18 (ArC-Bz), 130.67, 130.02 (3C), 129.94 (2C), 129.82 (2C), 129.66, 129.46 (2C), 128.74, 128.47 (2C), 128.45 (2C), 113.98 (2C, ArC-PMB), 86.15 (C-1), 81.05, 77.55 (CH_2-PMB), 73.34, 71.35, 69.42, 68.76, 55.51 (OCH_3-PMB), 25.84 (3C, CH_3-TBS), 21.41 (CH_3-SPhMe), 18.06 (C-TBS), −4.02 (CH_3-TBS), −4.52 (CH_3-TBS). ESI-MS *m/z*: 746.04 $[M+NH_4]^+$, 1478.92 $[2M+Na]^+$. Calcd for $C_{41}H_{52}NO_8SSi$ 746.32, $C_{82}H_{96}O_{16}S_2Si_2Na$ 1479.56.

4.5. 5-(*tert*-Butyldimethylsilyloxy)-6-((4-methoxybenzyloxy) methyl)-2-(2,2,2-trichloro-1-iminoethoxy)tetrahydro-2*H*-pyran-3,4-diyl dibenzoate, 8

A mixture of the hemiacetal **6′** (see Supplementary data, 177 mg, 0.29 mmol), Cl_3CCN (171 μL, 1.71 mmol), and DBU (17 μL, 0.11 mmol) in dry CH_2Cl_2 (7 mL) was stirred overnight at room temperature. Then the resulting mixture was concentrated. Column chromatography (1:10 EtOAc/PE+0.1% Et_3N) gave imidate **8** (193 mg, 88%) as a white foam. ^1H NMR($CDCl_3$, 400 MHz): δ 8.51 (1H, s, NH), 7.95–7.88 (4H, m, ArH of PMB and Bz), 7.49–7.28 (8H, m, ArH of Bz), 6.91 (2H, d, *J*=8.4 Hz, ArH of PMB), 6.73 (1H, d, *J*=3.6 Hz, H-1), 5.98 (1H, t, *J*=9.2 Hz, H-3), 5.39 (1H, dd, *J*=3.6, 10.4 Hz, H-2), 4.59–4.50 (2H, m, CH_2 of PMB), 4.27 (1H, t, *J*=9.2 Hz, H-4), 3.84–3.71 (6H, m, CH_3 of PMB, H-5, H-6), 0.76 (9H, s, CH_3 of TBS), 0.06 (3H, s, CH_3 of TBS), −0.14 (3H, s, CH_3 of TBS); ^{13}C NMR($CDCl_3$, 75 MHz): δ 165.92 (CO-Bz), 165.78 (CO-Bz), 161.05 (C=NH), 159.46 (ArC-PMB), 133.52 (ArC-Bz), 133.29 (ArC-Bz), 130.34, 130.07 (2C), 129.88 (2C), 129.53 (2C), 128.97, 128.60, 128.55 (2C), 128.52 (2C), 114.02 (2C, ArC-PMB), 93.82 (C-1), 75.02, 73.36, 73.31, 71.51, 68.76, 67.93, 55.48 (OCH_3-PMB), 25.92 (3C, CH_3-TBS), 18.19 (C-TBS), −3.98 (CH_3-TBS), −4.58 (CH_3-TBS). HRMS (ESI) *m/z*: 788.1575 $[M+Na]^+$. Calcd for $C_{36}H_{42}Cl_3NNaO_9Si$ 788.1592.

4.6. 5-(*tert*-Butyldimethylsilyloxy)-6-(methoxycarbonyl)-2-(*p*-tolylthio)tetrahydro-2*H*-pyran-3,4-diyl dibenzoate, 9

To a solution of **7′** (8.51 g, 13.9 mmol) in DMF (139 mL) was added PDC (31.38 g, 83.41 mmol), and the mixture was stirred at room temperature for 3 days. The resulting mixture was filtered and concentrated. Column chromatography (1:2 EtOAc/PE) gave a white foam containing the corresponding carboxylic acid. The crude acid was dissolved in DMF (56 mL), then K_2CO_3 (5.76 g, 41.7 mmol) and CH_3I (6.9 mL, 111.2 mmol) were added. The reaction was stirred at room temperature for 1 h, and was quenched with water. The reaction was diluted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4, filtered, and concentrated. Column chromatography (1:10 EtOAc/PE) gave **9** (7.09 g, 77% for two steps) as a yellow solid. ^1H NMR($CDCl_3$, 400 MHz): δ 7.90–7.87 (m, 4H, ArH-Bz), 7.51–7.46 (m, 2H, ArH-Bz), 7.37–7.32 (m, 6H, ArH-Bz, SPhMe), 7.10 (d, *J*=8.0 Hz, 2H, ArH of SPhMe), 5.60 (t, *J*=9.2 Hz, 1H, H-3), 5.31 (t, *J*=9.2 Hz, 1H, H-2), 4.91 (d, *J*=10.0 Hz, 1H, H-1), 4.27 (t, *J*=9.2 Hz, 1H, H-4), 4.09 (d, *J*=9.2 Hz, 1H, H-5), 3.82 (s, 3H, CH_3-COOMe), 2.33 (s, 3H, CH_3-SPhMe), 0.72 (s, 9H, CH_3-TBS), −0.04 (s, 3H, CH_3-TBS), −0.21 (s, 3H, CH_3-TBS); ^{13}C NMR($CDCl_3$, 100 MHz): δ 168.30 (CO-COOMe), 165.90 (CO-Bz), 165.31 (CO-Bz), 138.77 (ArC-SPhMe), 133.72 (2C, ArC-SPhMe), 133.38 (ArC-Bz), 133.33 (ArC-Bz), 130.02 (2C), 129.96 (4C), 129.75, 129.49, 128.51 (4C), 128.19, 87.22 (C-1), 80.42, 76.63, 70.93, 70.77, 52.79 (CH_3-COOMe), 25.62 (3C, CH_3-TBS), 21.42 (CH_3-SPhMe), 17.96 (C-TBS), −4.20 (CH_3-TBS), −4.90 (CH_3-TBS). HRMS (ESI) *m/z*: 637.2272 $[M+H]^+$, 659.2083 $[M+Na]^+$. Calcd for $C_{34}H_{41}O_8SSi$ 637.2291, $C_{34}H_{40}NaO_8SSi$ 659.2111.

4.7. 5-(*tert*-Butyldimethylsilyloxy)-6-(methoxycarbonyl)-2-(2,2,2-trichloro-1-iminoethoxy)tetrahydro-2*H*-pyran-3,4-diyl dibenzoate, 10

A mixture of the hemiacetal **8′** (see Supplementary data, 151 mg, 0.28 mmol), Cl_3CCN (171 μL, 1.71 mmol), and Cs_2CO_3 (37 mg, 0.11 mmol) in anhyd CH_2Cl_2 (8 mL) was stirred overnight at room temperature, then it was concentrated. Column chromatography (1:10 EtOAc/PE+0.1% Et_3N) gave imidate **7** (161 mg, 84%) as a white foam. ^1H NMR($CDCl_3$, 400 MHz): δ 8.60 (s, 1H, NH), 7.95–7.87 (m, 4H, ArH-Bz), 7.50–7.26 (m, 6H, ArH-Bz), 6.74 (d, *J*=3.6 Hz, 1H, H-1), 5.97 (t, *J*=9.6 Hz, 1H, H-3), 5.41 (dd, *J*=3.6, 10.4 Hz, 1H, H-2), 4.51 (d, *J*=9.6 Hz, 1H, H-5), 4.39 (t, *J*=9.2 Hz, 1H, H-4), 3.79 (s, 3H, CH_3-COOMe), 0.74 (s, 9H, CH_3-TBS), −0.01 (s, 3H, CH_3-TBS), −0.15 (s, 3H, CH_3-TBS); ^{13}C NMR($CDCl_3$, 75 MHz): δ 168.65 (CO of COOMe), 165.71 (CO-Bz), 165.64 (CO-Bz), 160.77 (C=NH), 133.65 (ArC-Bz), 133.46 (ArC-Bz), 130.05 (ArC-Bz), 129.89 (2C, ArC-Bz), 129.74 (ArC-Bz), 128.72 (ArC-Bz), 128.62 (2C,ArC-Bz), 128.57 (2C,ArC-Bz), 93.38 (C-1), 74.65, 72.46, 70.90, 70.80, 52.91 (OCH_3-COOMe), 25.66 (CH_3 of TBS), 18.03 (C-TBS), −4.14 (CH_3-TBS), −4.88 (CH_3-TBS). HRMS (ESI) *m/z*: 696.0903 $[M+Na]^+$. Calcd for $C_{29}H_{34}Cl_3NNaO_9Si$ 673.1068.

4.8. 6-(Methoxycarbonyl)-5-(4-oxopentanoyloxy)-2-(*p*-tolylthio)tetrahydro-2*H*-pyran-3,4-diyl dibenzoate, 11

To a solution of **6** (1 g, 1.50 mmol) in anhyd THF (25 mL) and Py (25 mL) was added HF·Py (7.8 mL, 1.50 mmol) dropwise at 0 °C. The reaction was stirred at room temperature for 18 h. The mixture was washed with 10% $CuSO_4$ solution, and the aqueous layer was extracted with EtOAc (3×). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford a white solid containing desired de-protected product. ^1H NMR($CDCl_3$, 400 MHz): δ 7.97–7.95 (m, 4H, ArH-SphMe, Bz), 7.54–7.48 (m, 2H, ArH-Bz), 7.40–7.33 (m, 6H, ArH-Bz), 7.12 (d, *J*=7.6 Hz, 2H, ArH-SPhMe), 5.55 (t, *J*=9.2 Hz, 1H, H-3), 5.39 (t, *J*=9.6 Hz, 1H, H-2), 4.92 (d, *J*=10.0 Hz, 1H, H-1), 4.18–4.09 (m, 2H, H-4, H-5), 3.87 (s, 3H, OCH_3-COOMe), 3.39 (s, 1H, COOH), 2.04 (s, 3H, CH_3-SphMe); ^{13}C NMR($CDCl_3$, 75 MHz): δ 169.12 (CO of COOMe), 166.83 (CO-Bz), 165.33 (CO-Bz), 138.97 (ArC-SPhMe), 133.84 (2C, ArC-SPhMe), 133.63 (ArC-Bz), 133.56 (ArC-Bz), 130.16 (2C), 130.07 (2C), 129.99 (2C), 129.42, 129.18, 128.63 (2C), 128.60 (2C), 128.15,

87.42 (C-1), 78.34, 76.50, 70.65, 70.03, 53.22 (OCH_3-COOMe), 21.43 (CH_3-SPhMe). ESI-MS *m/z*: 544.94 $[M+Na]^+$. Calcd for $C_{28}H_{26}NaO_8S$ 545.12.

The crude product was added to a solution containing EDCI·HCl (719 mg, 3.75 mmol), DMAP (55 mg, 0.45 mmol), and levulinic acid (435 mg, 3.75 mmol). The reaction was stirred at room temperature for 2 h and poured into cold water. The resulting mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Column chromatography (1:20 EtOAc/CH_2Cl_2) gave **11** (642 mg, 69% for two steps) as a white solid. ^1H NMR($CDCl_3$, 400 MHz): δ 7.95 (d, *J*=8.0 Hz, 2H, ArH-Bz), 7.87 (d, *J*=7.6 Hz, 2H, ArH-SPhMe), 7.48–7.55 (m, 2H, ArH-Bz), 7.33–7.41 (m, 6H, ArH-Bz), 7.12 (d, *J*=7.6 Hz, 2H, ArH-SPhMe), 5.69 (t, *J*=9.6 Hz, 1H, H-3), 5.34–5.42 (m, 2H, H-2, H-4), 4.90 (d, *J*=10.0 Hz, 1H, H-1), 4.20 (d, *J*=10.0 Hz, 1H, H-5), 3.80 (s, 3H, $COOCH_3$), 2.38–2.64 (m, 4H, CH_2CH_2-Lev), 2.35 (s, 3H, CH_3-Lev), 2.03 (s, 3H, CH_3-SPhMe); ^{13}C NMR($CDCl_3$, 75 MHz): δ 205.95 (CO-Lev), 171.42 (CO-Lev), 167.17 (CO-COOMe), 165.85 (CO-Bz), 165.10 (CO-Bz), 139.23 (ArC-SPhMe), 134.29 (2C, ArC-SPhMe), 133.66 (ArC-Bz), 133.62 (ArC-Bz), 130.12 (2C), 130.10 (2C), 130.04 (2C), 129.30, 128.92, 128.65 (2C), 128.63 (2C), 127.45, 86.92 (C-1), 76.54 (C-2), 73.75, 70.14, 69.74, 53.32 (CH_3-COOMe), 37.87 (C-Lev), 29.84 (C-Lev), 27.91 (C-Lev), 21.50 (CH_3-SPhMe). ESI-MS *m/z*: 620.99 $[M+H]^+$, 643.06 $[M+Na]^+$. Calcd for $C_{33}H_{33}O_{10}S$ 621.18, $C_{33}H_{32}NaO_{10}S$ 643.16.

4.9. 6-(Methoxycarbonyl)-5-(4-oxopentanoyloxy)-2-(2,2,2-trichloro-1-iminoethoxy)tetrahydro-2*H*-pyran-3,4-diyl dibenzoate, 11

A mixture of **9′** (see Supplementary data, 152 mg, 0.30 mmol), Cl_3CCN (296 μL, 2.96 mmol), and DBU (13 μL, 0.09 mmol) in anhyd CH_2Cl_2 (2 mL) was stirred overnight at room temperature. Then it was concentrated. Column chromatography (1:5 EtOAc/PE+0.1% Et_3N) gave imidate **12** (155 mg, 80%) as a yellow syrup. ^1H NMR($CDCl_3$, 400 MHz) δ 8.66 (s, 1H, NH), 7.94–7.91 (m, 4H, ArH-Bz), 7.53–7.47 (m, 3H, ArH-Bz), 7.40–7.32 (m, 5H, ArH-Bz), 6.84 (d, *J*=3.2 Hz, 1H, H-1), 6.10 (t, *J*=9.6 Hz, 1H, H-4), 5.57–5.52 (m, 2H, H-3, H-2), 4.64 (d, *J*=10.0 Hz, 1H, H-5), 3.78 (s, 3H, CH_3-COOMe), 2.63–2.39 (m, 4H, CH_2CH_2-Lev), 2.03 (s, 3H, CH_3-Lev); ^{13}C NMR($CDCl_3$, 100 MHz): δ 205.75 (CO-Lev), 171.51 (CO-Lev), 167.39 (CO-COOMe), 165.72 (CO-Bz), 165.45 (CO-Bz), 160.44 (C=NH), 133.82 (ArC-Bz), 132.71 (ArC-Bz), 130.10 (2C, ArC-Bz), 130.06 (2C, ArC-Bz), 129.04 (ArC-Bz), 128.69 (2C, ArC-Bz), 128.66 (2C, ArC-Bz), 128.63 (ArC-Bz), 93.01 (C-1), 70.98, 70.39, 69.61, 69.31, 53.41 (CH_3-COOMe), 37.83 (C-Lev), 29.76 (CH_2-Lev), 27.92 (CH_3-Lev). HRMS (ESI) *m/z*: 680.0260 $[M+Na]^+$. Calcd for $C_{28}H_{26}Cl_3NNaO_{11}$ 680.0469.

4.10. *N*-(8-Hydroxy-6-(4-methoxyphenoxy)-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-7-yl)acetamide, 13

To a solution of **12′** (see Supplementary data, 1.91 g, 58.47 mmol) in DMF (25 mL) was added benzaldehyde dimethyl acetal (965 μL, 64.31 mmol) and *p*-toluene sulfonic acid monohydrate (45 mg, 2.34 mmol). The mixture was stirred at 40 °C for 5 h at reduced pressure. Then it was quenched by Et_3N, poured into 200 mL cold water, and stirred continuously for 2 h. Precipitate was filtered and washed by water and CH_2Cl_2 to afford **13** (1.72 g, 70%) as white solid. ^1H NMR(DMSO-d_6, 400 MHz): δ 7.77 (d, *J*=8.8 Hz, 1H, ArH-benzylidene), 7.50 (d, *J*=4.8 Hz, 2H, ArH-benzylidene), 7.40–7.38 (m, 3H, ArH-benzylidene, NH), 6.94 (*J*=9.2 Hz, 2H, ArH-OMP), 6.86 (*J*=8.8 Hz, 2H, ArH-OMP), 5.62 (s, 1H, CH), 5.00–4.95 (m, 2H, H-1, H-3), 4.16 (d, *J*=2.8 Hz, 1H, H-4), 4.08 (br s, 2H, H-5, OH), 4.00–3.93 (m, 1H, H-2), 3.79–3.70 (m, 5H, H-$6_{a,b}$, OCH_3-OMP), 1.82 (s, 3H, CH_3-NHAc); ^{13}C NMR(DMSO-d_6, 100 MHz): δ 169.48 (CO-NHAc), 154.49 (ArC-OMP), 151.40 (ArC-OMP), 138.53 (ArC-benzylidene), 128.66 (ArC-benzylidene), 127.92 (2C, ArC-benzylidene), 126.29 (2C, ArC-benzylidene), 117.87 (2C, ArC-OMP), 114.47 (2C, ArC-OMP), 100.21 (C-1), 99.74 (CH-benzylidene), 75.18, 69.35, 68.52, 66.10, 55.37 (OCH_3-OMP), 51.85 (C-2), 23.13 (CH_3-NHAc). HRMS (ESI) *m/z*: 416.1687 $(M+H)^+$, 438.1504 $[M+Na]^+$. Calcd for $C_{22}H_{26}NO_7$ 416.1709, $C_{22}H_{25}NNaO_7$ 438.1529.

4.11. 7-Azido-6-(4-methoxyphenoxy)-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-8-ol, 14

To a solution of **15′** (see Supplementary data) in DMF (90 mL) was added benzaldehyde dimethyl acetal (4.8 mL, 31.82 mmol) and *p*-toluene sulfonic acid monohydrate (2.75 g, 14.47 mmol). The mixture was stirred at 40 °C for 10 h at reduced pressure. Then it was quenched by Et_3N, diluted with EtOAc, and washed with brine. The organic phase was dried over Na_2SO_4, filtered, concentrated and purified by column chromatography (1:5 EtOAc/PE) to afford desired product (9.89 g, 89% for two steps) as white solid which contained **14** (6.90 g, 62%) with its β isomer (2.99 g, 27%). α: ^1H NMR($CDCl_3$, 400 MHz): δ 7.52 (d, *J*=4.4 Hz, 2H, ArH-benzylidene), 7.39–7.38 (m, 3H, ArH-benzylidene), 7.06 (d, *J*=9.2 Hz, 2H, ArH-OMP), 6.85 (d, *J*=9.2 Hz, 2H, ArH-OMP), 5.58–5.56 (m, 2H, CH, H-1), 4.37 (dd, *J*=10.8, 3.2 Hz, 1H, H-3), 4.31 (d, *J*=2.8 Hz, 1H, H-4), 4.24 (d, *J*=12.4 Hz, 1H, H-6_a), 4.03 (d, *J*=12.4 Hz, 1H, H-6_b), 3.84 (s, 1H, H-5), 3.77 (s, 3H, OCH_3), 3.68 (dd, *J*=10.4, 3.2 Hz, 1H, H-2); ^{13}C NMR($CDCl_3$, 100 MHz): δ 155.51 (ArC-OMP), 150, 74 (ArC-OMP), 137.42 (ArC-benzylidene), 129.65 (ArC-benzylidene), 128.59 (2C, ArC-benzylidene), 126.43 (2C, ArC-benzylidene), 117.79 (2C, ArC-OMP), 114.96 (2C, ArC-OMP), 101.52 (CH), 98.36 (C-1), 75.58, 69.38, 67.64, 63.60, 60.73 (C-2), 55.90 (OCH_3). ESI-HRMS *m/z*: 400.1494 $(M+H)^{+\cdot}$ 422.1308 $[M+Na]^+$. Calcd for $C_{20}H_{22}O_6N_3$ 400.1509, $C_{20}H_{21}N_3NaO_6$ 422.1328. β: ^1H NMR($CDCl_3$, 400 MHz): δ 7.51 (d, *J*=4.4 Hz, 2H, ArH-benzylidene), 7.37–7.36 (m, 3H, ArH-benzylidene), 7.06 (d, *J*=8.8 Hz, 2H, ArH-OMP), 6.82 (d, *J*=8.8 Hz, 2H, ArH-OMP), 5.55 (s, 1H, CH), 4.73 (d, *J*=8.4 Hz, 1H, H-1), 4.33 (dd, *J*=12.4 Hz, 1H, H-6_a), 4.17 (d, *J*=3.2 Hz, 1H, H-4), 4.06 (d, *J*=12.4 Hz, 1H, H-6_b), 3.88 (t, *J*=8.4 Hz, 1H, H-2), 3.76–3.74 (m, 4H, H-5, OCH_3), 3.59 (dd, *J*=10.4, 1.6 Hz, 1H, H-3), 3.49 (s, 1H, OH); ^{13}C NMR($CDCl_3$, 100 MHz): δ 155.82 (ArC-OMP), 151.30 (ArC-OMP), 137.52 (ArC-benzylidene), 129.63 (ArC-benzylidene), 128.55 (2C, ArC-benzylidene), 126.68 (2C, ArC-benzylidene), 119.03 (2C, ArC-OMP), 114.73 (2C, ArC-OMP), 102.00 (C-1), 101.62 (CH), 74.68, 71.45, 69.10, 66.84, 63.86 (C-2), 55.88 (OCH_3). HRMS (ESI) *m/z*: 400.1485 $[M+H]^+$, 422.1301 $[M+Na]^+$, 438.1030 $[M+K]^+$. Calcd for $C_{20}H_{22}O_6N_3$ 400.1509, $C_{20}H_{21}N_3NaO_6$ 422.1328, $C_{20}H_{21}KN_3O_6$ 438.1067.

4.12. 2,2,2-Trichloro-*N*-(8-hydroxy-6-(4-methoxyphenoxy)-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-7-yl)acetamide, 15

To a solution of **16′** (see Supplementary data) in anhyd THF (20 mL) were added Et_3N (1.3 mL, 8.99 mmol) and trichloroacetyl chloride (670 μL, 6.03 mmol) successively at 0 °C. The reaction was stirred at 0 °C for 20 min, and was quenched by satd $NaHCO_3$ aq. The aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. Column chromatography (2:5 EtOAc/PE) to afford **15** (1.01 g, 73% for two steps) as white solid. ^1H NMR($CDCl_3$, 400 MHz): δ 7.57–7.49 (m, 2H, ArH-benzylidene), 7.44–7.35 (m, 3H, ArH-benzylidene), 7.09–7.02 (m, 3H, ArH-OMP, NH), 6.84 (d, *J*=8.8 Hz, 2H, ArH-OMP), 5.65 (d, *J*=3.2 Hz, 1H, H-1), 5.62 (s, 1H, CH), 4.52 (td, *J*=9.6, 3.2 Hz, 1H, H-2), 4.36 (d, *J*=2.8 Hz, 1H, H-4), 4.29 (d, *J*=12.8 Hz, 1H, H-6_a), 4.19 (d, *J*=9.2 Hz, 1H, H-3), 4.09 (d, *J*=12.4 Hz, 1H, H-6_b), 3.90 (s, 1H, H-5), 3.77 (s, 3H, OCH_3), 2.73 (s, 1H, OH); ^{13}C NMR($CDCl_3$, 75 MHz): δ 162.92 (CO-NH), 155.77 (ArC-OMP), 150.54

(ArC-OMP), 137.38 (ArC-benzylidene), 129.64 (ArC-benzylidene), 128.60 (2C, ArC-benzylidene), 126.47 (2C), 118.02 (2C, ArC-OMP), 115.07 (2C, ArC-OMP), 101.52 (CH), 97.77 (C-1), 75.30, 69.40, 68.32, 63.84, 55.91 (OCH_3), 52.83 (C-2). HRMS (ESI) *m*/*z*: 518.0513 $[M+H]^+$, 540.0321 $[M+Na]^+$. Calcd for $C_{22}H_{23}Cl_3NO_7$ 518.0540, $C_{22}H_{22}Cl_3NNaO_7$ 540.0360.

4.13. 5-Hydroxy-6-((4-methoxybenzyloxy)methyl)-2-(*p*-tolylthio)tetrahydro-2*H*-pyran-3,4-diyl dibenzoate, 16

To a solution of **5′** (see Supplementary data, 10 g, 48.78 mmol) in dry DMF (100 mL), $NaBH_3CN$ (5.1 g, 243.88 mmol) and 4 Å MS (10 g) were added. Trifluoroacetic acid (12.1 mL, 487.76 mmol) was added dropwise to the system at 0 °C. The mixture was stirred at room temperature for 3 days. Then it was filtered, diluted with CH_2Cl_2, and quenched with satd $NaHCO_3$ aq. The aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated, and purified by column chromatography (1:10 EtOAc/PE) to afford **16** (11 g, 93%) as white solid. ^{1}H NMR($CDCl_3$, 400 MHz): δ 7.90–7.85 (m, 4H, ArH-Bz), 7.45–7.18 (m, 10H, ArH-Bz, PMB, and SphMe), 6.98 (d, *J*=8.0 Hz, 2H, ArH-SphMe), 6.81 (d, *J*=8.8 Hz, 2H, ArH-PMB), 5.37 (t, *J*=9.2 Hz, 1H, H-3), 5.30 (t, *J*=9.6 Hz, 1H, H-2), 4.78 (d, *J*=9.6 Hz, 1H, H-1), 4.46 (s, 2H, CH_2-PMB), 3.83 (td, *J*=3.2, 9.6 Hz, 1H, H-4), 3.77–3.76 (m, 2H, H-6), 3.73 (s, 3H, OCH_3-PMB), 3.64–3.60 (m, 1H, H-5), 3.17 (d, *J*=3.2 Hz, 1H, OH), 2.24 (s, 3H, CH_3-SphMe); ^{13}C NMR($CDCl_3$, 100 MHz): δ 167.64 (CO-Bz), 165.48 (CO-Bz), 159.63 (ArC-PMB), 138.71 (ArC-SPhMe), 133.76 (CO-Bz), 133.71 (2C, ArC-SPhMe), 133.52 (CO-Bz), 130.18 (2C), 130.04 (2C), 129.94 (2C), 129.84, 129.77 (2C), 129.52, 129.08, 128.64 (2C), 128.62 (2C), 128.34, 114.13 (2C, ArC-PMB), 86.52 (C-1), 78.75 (C-5), 77.95 (CH_2-PMB), 73.71 (C-3), 71.11 (C-2), 70.33 (C-4), 69.89 (C-6), 55.51 (OCH_3-PMB), 21.41 (CH_3-SPhMe). ESI-MS *m*/*z*: 636.97 $[M+Na]^+$. Calcd for $C_{35}H_{34}O_8SNa$ 637.19.

4.14. 2-(7-Azido-6-(4-methoxyphenoxy)-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-8-yloxy)-6-((4-methoxybenzyloxy)methyl)-5-(4-oxopentanoyloxy)tetrahydro-2*H*-pyran-3,4-diyl dibenzoate, 17

A mixture of donor **6** (149 mg, 0.20 mmol) and acceptor **14** (63 mg, 0.17 mmol) was coevaporated with toluene (3×5 mL), dried under vacuum for 30 min. The mixture was dissolved in CH_2Cl_2 (4 mL), and activated 4 Å powdered molecular sieves were added. The reaction was stirred at room temperature for 30 min. The reaction was then cooled to −80 °C and stirred for an additional 15 min. Trimethylsilyl trifluoromethanesulfonate (0.1 M in CH_2Cl_2, 198 μL, 0.020 mmol) was added to the reaction dropwise. After 15 min, the reaction was quenched with TEA, and allowed to warm to room temperature. The reaction was filtered and concentrated to afford a yellow syrup. The product was purified by column chromatography (1:4 EtOAc/PE) to afford **17** (147 mg, 90%) as white foam. ^{1}H NMR($CDCl_3$, 400 MHz): δ 7.96 (d, *J*=7.6 Hz, 2H, ArH-Bz), 7.90 (d, *J*=7.2 Hz, 2H, ArH-Bz), 7.52–7.45 (m, 4H, ArH-Bz, benzylidene), 7.38–7.32 (m, 7H, ArH-Bz, benzylidene), 7.24 (d, *J*=8.4 Hz, 2H, ArH-PMB), 7.01 (d, *J*=9.2 Hz, 2H, ArH-OMP), 6.84–6.80 (m, 4H, ArH-PMB, OMP), 5.70 (t, *J*=9.6 Hz, 1H, HB-4), 5.57 (dd, *J*=9.6, 8.0 Hz, 1H, HB-3), 5.51 (d, *J*=3.2 Hz, 1H, HA-1), 5.46 (s, 1H, CH-benzylidene), 5.29 (t, *J*=9.6 Hz, 1H, HB-2), 5.10 (*J*=7.6 Hz, 1H, HB-1), 4.55–4.52 (m, 2H, CH_2-PMB, HA-4), 4.43 (d, *J*=11.2 Hz, 1H, CH_2-PMB), 4.34 (dd, *J*=10.4, 3.2 Hz, 1H, HA-2), 4.13 (dd, *J*=12.4, 1.2 Hz, 1H, HA-6_a), 4.00–3.95 (m, 1H, HB-5), 3.87 (dd, *J*=10.8, 3.6 Hz, 1H, HA-3), 3.76–3.65 (m, 10H, HA-6_b, HA-5, HB-$6_{a,b}$, CH_3-PMB, OMP), 2.67–2.30 (m, 4H, CH_2CH_2-Lev), 2.06 (s, 3H, CH_3-Lev); ^{13}C NMR($CDCl_3$, 100 MHz): δ 206.18 (CO-Lev), 171.73 (CO-Lev), 166.02 (CO-Bz), 165.30 (CO-Bz), 159.58 (ArC-PMB), 155.45 (ArC-OMP), 150.71 (ArC-OMP), 137.85 (ArC-benzylidene), 133.53 (ArC-Bz), 133.29 (ArC-Bz), 130.16, 130.08 (2C), 130.00 (2C), 129.73 (2C), 129.56, 129.17, 128.98, 128.61 (2C), 128.41 (2C), 128.32 (2C), 126.31 (2C, ArC-benzylidene), 117.81 (2C, ArC-OMP), 114.90 (2C, ArC-OMP), 114.03 (2C, ArC-PMB), 102.46 (CH-benzylidene), 100.68 (CA-1), 98.46 (CB-1), 76.94, 76.22, 75.62, 73.73, 73.58, 71.90, 69.72, 69.54, 69.08 (C-6), 63.85 (C-6), 58.55 (CA-2), 55.55 (OCH_3), 55.88 (OCH_3), 37.97 (C-Lev), 29.78 (C-Lev), 28.06 (C-Lev). HRMS (ESI) *m*/*z*: 988.3555 $[M+H]^+$, 1010.3317 $[M+Na]^+$, 1026.3093 $[M+K]^+$. Calcd for $C_{53}H_{54}N_3O_{16}$ 988.3504, $C_{53}H_{53}N_3NaO_{16}$ 1010.3324, $C_{53}H_{53}N_3KO_{16}$ 1026.3063.

4.15. 2-(7-Azido-6-(4-methoxyphenoxy)-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-8-yloxy)-5-(*tert*-butyldimethylsilyloxy)-6-((4-methoxybenzyloxy)methyl) tetrahydro-2*H*-pyran-3,4-diyl dibenzoate, 18

A mixture of donor **8** (122 mg, 0.16 mmol) and acceptor **14** (51 mg, 0.13 mmol) was coevaporated with toluene (3×5 mL), dried under vacuum for 30 min the mixture was dissolved in CH_2Cl_2 (3.2 mL), and activated 4 Å powdered molecular sieves were added. The reaction was stirred at room temperature for 30 min. The reaction was then cooled to −60 °C and stirred for an additional 15 min. Trimethylsilyl trifluoromethanesulfonate (0.1 M in CH_2Cl_2, 159 μL, 0.016 mmol) was added to the reaction dropwise. After 15 min, the reaction was quenched with TEA, and allowed to warm to room temperature. The reaction was filtered and concentrated to afford a yellow syrup. The product was purified by column chromatography (1:10 EtOAc/PE) to afford **18** (129 mg, 96%) as white foam. ^{1}H NMR($CDCl_3$, 400 MHz): δ 7.92–7.89 (m, 4H, ArH-Bz), 7.52–7.25 (m, 13H, ArH-Bz, benzylidene, PMB), 7.01 (d, *J*=9.2 Hz, 2H, ArH-OMP), 6.85–6.80 (m, 4H, ArH-PMB, OMP), 5.62 (t, *J*=9.2 Hz, 1H, HB-3), 5.52–5.44 (m, 3H, HA-1, HB-2, CH-benzylidene), 5.10 (d, *J*=8.0 Hz, 1H, HB-1), 4.59 (*J*=2.8 Hz, 1H, HB-4), 4.53 (s, 1H, CH_2-PMB), 4.51 (s, 1H, CH_2-PMB), 4.36 (dd, *J*=10.8, 3.2 Hz, 1H, HA-2), 4.14 (d, *J*=11.6 Hz, 1H, HA-6_a), 4.02 (t, *J*=8.8 Hz, 1H, HB-4), 3.87 (dd, *J*=10.8, 3.2 Hz, 1H, HA-3), 3.84–3.68 (m, 11H, HA-6_b, HA-5, HB-5, HB-$6_{a,b}$, CH_3-PMB, OMP), 0.76 (s, 9H, *t*-Bu-TBS), 0.02 (s, 3H, CH_3-TBS), −0.20 (s, 3H, CH_3-TBS); ^{13}C NMR($CDCl_3$, 100 MHz): δ 165.90 (CO-Bz), 165.44 (CO-Bz), 159.36 (ArC-PMB), 155.26 (ArC-OMP), 150.54 (ArC-OMP), 137.68 (ArC-benzylidene), 133.07 (ArC-Bz), 132.98 (ArC-Bz), 129.73, 129.82, 129.73, 129.70, 129.63, 129.42, 129.39, 128.89, 128.30, 128.16, 128.14, 126.20 (2C, ArC-benzylidene), 117.69 (2C, ArC-OMP), 114.70 (2C, ArC-OMP), 113.88 (2C, ArC-OMP), 102.28 (CH-benzylidene), 100.59 (CA-1), 98.36 (CB-1), 76.22, 76.09, 75.95, 75.53, 73.29, 72.27, 69.70, 69.28, 68.93, 63.63, 58.31 (CA-2), 55.64 (OCH3), 55.25 (OCH3), 25.64 (3C, *t*-Bu-TBS), 17.85 (C-TBS), −4.17 (CH_3-TBS), −4.64 (CH_3-TBS). HRMS (ESI) *m*/*z*: 1026.3788 $[M+Na]^+$, 1042.3530 $[M+K]^+$. Calcd for $C_{54}H_{61}N_3NaO_{14}Si$ 1026.3820, $C_{54}H_{61}N_3KO_{14}Si$ 1042.3560.

4.16. 6-((4-Methoxybenzyloxy)methyl)-2-(6-(4-methoxyphenoxy)-2-phenyl-7-(2,2,2-trichloroacetamido) hexahydropyrano[3,2-*d*][1,3]dioxin-8-yloxy)-5-(4-oxopentanoyloxy)tetrahydro-2*H*-pyran-3,4-diyl dibenzoate, 19

A mixture of donor **6** (129 mg, 0.17 mmol) and acceptor **15** (74 mg, 0.14 mmol) was coevaporated with toluene (3×5 mL), dried under vacuum for 30 min. The mixture was dissolved in CH_2Cl_2 (3.4 mL), and activated 4 Å powdered molecular sieves were added. The reaction was stirred at room temperature for 30 min the reaction was then cooled to −60 °C and stirred for an additional 15 min. Trimethylsilyl trifluoromethanesulfonate (0.1 M in CH_2Cl_2, 172 μL, 0.017 mmol) was added to the reaction dropwise. After 15 min, the reaction was quenched with TEA, and allowed to warm to room temperature. The reaction was filtered

and concentrated to afford a yellow syrup. The product was purified by column chromatography (2:5–1:2 EtOAc/PE) to afford **19** (126 mg, 79%) as white foam. ^{1}H NMR($CDCl_3$, 400 MHz): δ 7.91–7.88 (m, 4H, ArH-Bz), 7.52–7.46 (m, 4H, ArH-Bz, benzylidene), 7.38–7.23 (m, 7H, ArH-Bz, PMB, benzylidene), 6.96–6.92 (m, 3H, ArH-OMP, NH), 6.83–6.78 (m, 4H, ArH-PMB, OMP), 5.75 (d, J=2.0 Hz, 1H, HA-1), 5.63 (t, J=9.2 Hz, 1H, HB-4), 5.52 (d, J=8.8 Hz, 1H, HB-3), 5.46 (t, J=9.2 Hz, 1H, HB-2), 5.32 (s, 1H, CH-benzylidene), 5.19 (d, J=7.6 Hz, 1H, HB-1), 4.59–4.41 (m, 4H, CH_2-PMB, HA-4, HA-2), 4.18 (d, J=12.4 Hz, 1H, HA-6_a), 3.95–3.92 (m, 1H, HB-5), 3.86–3.74 (m, 10H, HA-6_b, HA-5, HB-$6_{a,b}$, CH_3-PMB, OMP), 3.66 (dd, J=10.8, 4.8 Hz, 1H, HA-3), 2.67–2.28 (m, 4H, CH_2CH_2-Lev), 2.05 (s, 3H, CH_3-Lev); ^{13}C NMR($CDCl_3$, 100 MHz): δ 206.05 (CO-Lev), 171.39 (CO-Lev), 165.80 (CO-Bz), 165.37 (CO-Bz), 161.79 (CO-NH), 159.43 (ArC-PMB), 155.44 (ArC-OMP), 150.65 (ArC-OMP), 137.44 (ArC-benzylidene), 133.54 (ArC-Bz), 133.46 (ArC-Bz), 129.97, 129.89, 129.84, 129.74, 128.91, 128.76, 128.50, 128.48, 128.08, 126.13 (2C, ArC-benzylidene), 118.08 (2C, ArC-OMP), 114.77 (2C, ArC-OMP), 113.89 (2C, ArC-PMB), 100.75 (CH-benzylidene), 99.58 (CA-1), 97.28 (CB-1), 74.69, 74.00, 73.58, 73.44, 71.58, 71.18, 69.11, 68.72, 68.27, 63.64, 50.70 (CA-2), 55.69 (OCH3), 55.31 (OCH3), 37.80 (C-Lev), 29.61 (C-Lev), 27.87 (C-Lev). HRMS (ESI) m/z: 1106.2357 $[M+H]^+$, 1128.2317 $[M+Na]^+$, 1144.2084 $[M+K]^+$. Calcd for $C_{55}H_{55}Cl_3NO_{17}$ 1106.2536, $C_{55}H_{55}Cl_3NNaO_{17}$ 1128.2355, $C_{55}H_{55}Cl_3NKO_{17}$ 1144.2094.

4.17. 5-(*tert*-Butyldimethylsilyloxy)-6-((4-methoxybenzyloxy) methyl)-2-(6-(4-methoxyphenoxy)-2-phenyl-7-(2,2,2-trichloroacetamido)hexahydropyrano[3,2-*d*][1,3]dioxin-8-yloxy)tetrahydro-2*H*-pyran-3,4-diyl dibenzoate, 20

A mixture of donor **8** (170 mg, 0.22 mmol) and acceptor **15** (96 mg, 0.19 mmol) was coevaporated with toluene (3×5 mL), dried under vacuum for 30 min the mixture was dissolved in CH_2Cl_2 (4.5 mL), and activated 4 Å powdered molecular sieves were added. The reaction was stirred at room temperature for 30 min. The reaction was then cooled to −60 °C and stirred for an additional 30 min. Trimethylsilyl trifluoromethanesulfonate (0.1 M in CH_2Cl_2, 222 μL, 0.022 mmol) was added to the reaction dropwise. After 15 min, the reaction was quenched with TEA, and allowed to warm to room temperature. The reaction was filtered and concentrated to afford a yellow syrup. The product was purified by column chromatography (1:5 EtOAc/PE) to afford **20** (204 mg, 98%) as white foam. ^{1}H NMR($CDCl_3$, 400 MHz): δ 7.88 (d, J=7.6 Hz, 2H, ArH-Bz), 7.84 (d, J=8.0 Hz, 2H, ArH-Bz), 7.49–7.42 (m, 2H, ArH-Bz, benzylidene), 7.36–7.23 (11H, m, ArH-Bz, benzylidene, OMP), 6.98 (d, J=4.4 Hz, 1H, NH), 6.94 (d, J=8.8 Hz, 2H, ArH-OMP), 6.80–6.78 (m, 4H, ArH-PMB, OMP), 5.79 (s, 1H, HA-1), 5.55 (t, J=8.8 Hz, 1H, HB-3), 5.41 (t, J=8.8 Hz, 1H, HB-2), 5.31 (s, 1H, CH-benzylidene), 5.17 (d, J=8.0 Hz, 1H, HB-1), 4.57–4.46 (m, 5H, HB-4, HA-4, HA-2, CH_2-PMB), 4.19 (d, J=11.2 Hz, 1H, HA-6_a), 3.90–3.75 (m, 12H, HA-6_b, HA-3, HA-5, HB-5, HB-$6_{a,b}$, CH_3-PMB, OMP), 0.75 (s, 9H, *t*-Bu-TBS), 0.03 (s, 3H, CH_3-TBS), −0.20 (s, 3H, CH_3-TBS); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.02 (CO-Bz), 165.82 (CO-Bz), 162.06 (CO-NH), 159.58 (ArC-PMB), 155.66 (ArC-OMP), 150.80 (ArC-OMP), 137.59 (ArC-benzylidene), 133.55 (ArC-Bz), 133.32 (ArC-Bz), 130.07 (2C), 130.00, 129.93 (2C), 129.81, 129.55 (2C), 129.12, 128.93, 128.56 (2C), 128.52 (2C), 128.22 (2C), 126.33 (2C, ArC-benzylidene), 118.56 (2C, ArC-OMP), 114.92 (2C, ArC-OMP), 114.13 (2C, ArC-PMB), 100.98 (CH-benzylidene), 99.63 (CA-1), 97.54 (CB-1), 77.12, 76.53, 74.81, 73.56, 72.20, 70.95, 69.31, 69.06, 68.74 (C-6), 63.77 (C-6), 55.85 (OCH_3), 55.52 (OCH_3), 50.92 (CA-2), 25.83 (3C, *t*-Bu-TBS), 18.08 (CH_3-TBS), −3.97 (CH_3-TBS), −4.56 (CH_3-TBS). HRMS (ESI) m/z: 1122.3018 $[M+H]^+$, 1144.2838 $[M+Na]^+$, 1160.2581 $[M+K]^+$. Calcd for $C_{56}H_{63}Cl_3NO_{15}Si$ 1122.3033, $C_{56}H_{62}Cl_3NNaO_{15}Si$ 1144.2852, $C_{56}H_{62}Cl_3NKO_{15}Si$ 1160.2591.

4.18. 5-(*tert*-Butyldimethylsilyloxy)-6-(methoxycarbonyl)-2-(6-(4-methoxyphenoxy)-2-phenyl-7-(2,2,2-trichloroacetamido)hexahydropyrano[3,2-*d*][1,3]dioxin-8-yloxy)tetrahydro-2*H*-pyran-3,4-diyl dibenzoate, 21

A mixture of donor **10** (170 mg, 0.21 mmol) and acceptor **15** (96 mg, 0.17 mmol) was coevaporated with toluene (3×5 mL), dried under vacuum for 30 min the mixture was dissolved in CH_2Cl_2 (4.5 mL), and activated 4 Å powdered molecular sieves were added. The reaction was stirred at rt for 30 min the reaction was then cooled to −60 °C and stirred for an additional 15 min. Trimethylsilyl trifluoromethanesulfonate (0.1 M in CH_2Cl_2, 206 μL, 0.021 mmol) at −60 °C was added to the reaction dropwise. The temperature was gradually raised to room temperature over 2 h, and the mixture was stirred overnight. Then the reaction was quenched with TEA, filtered and concentrated to afford a yellow syrup. The product was purified by column chromatography (1:10–1:5 EtOAc/PE) to afford a mixture of product (35 mg, 20%) containing **21** and **22** at a ratio of 2:3 as colorless syrup. ^{1}H NMR($CDCl_3$, 400 MHz): δ 7.93 (d, J=7.2 Hz, 2H, ArH-Bz), 7.88 (d, J=7.2 Hz, 2H, ArH-Bz), 7.52–7.20 (m, 11H, ArH-Bz, benzylidene), 7.06–7.02 (m, 3H, NH, ArH-OMP), 6.82 (d, J=9.2 Hz, 2H, ArH-OMP), 5.74 (d, J=2.4 Hz, 1H, HA-1), 5.54 (t, J=8.4 Hz, 1H, HB-3), 5.47 (t, J=8.4 Hz, 1H, HB-2), 5.32 (s, 1H, CH-benzylidene), 5.27 (d, J=7.2 Hz, 1H, HB-1), 4.67–4.58 (m, 2H, HA-3, HA-2), 4.53 (s, 1H, HA-4), 4.43 (t, 1H, J=8.8 Hz, HB-4), 4.27 (d, J=12.8 Hz, 1H, HA-6_a), 4.23 (d, J=9.2 Hz, 1H, HB-5), 4.06 (d, J=12.4 Hz, 1H, HA-6_b), 3.93 (s, 1H, HA-5), 3.81 (s, 3H, $COOCH_3$), 3.77 (s, 3H, CH_3-OMP), 0.74 (s, 9H, *t*-Bu-TBS), −0.06 (s, 3H, CH_3-TBS), −0.20 (s, 3H, CH_3-TBS); ^{13}C NMR($CDCl_3$, 150 MHz): δ 168.47 (CO-COOMe), 165.58 (CO-Bz), 165.52 (CO-Bz), 161.67 (CO-NH), 155.34 (ArC-OMP), 150.77 (ArC-OMP), 137.18 (ArC-benzylidene), 133.52 (ArC-Bz), 133.28 (ArC-Bz), 129.83, 129.74, 129.29, 128.74, 128.62, 128.43, 128.38, 127.98, 126.03 (2C, ArC-benzylidene), 117.87 (2C, ArC-OMP), 114.69 (2C, ArC-OMP), 100.87 (CH-benzylidene), 98.59 (CB-1), 97.44 (CA-1), 92.33 (C-Cl_3), 76.63, 75.38, 74.56, 71.19, 70.55, 69.90, 69.17, 63.54, 55.63 (OCH_3-OMP), 52.65 (OCH_3-COOMe), 50.47 (CA-2), 25.32 (3C, *t*-Bu-TBS), 17.67 (C-TBS), −4.43 (CH_3-TBS), −5.22 (CH_3-TBS). HRMS (ESI) m/z: 1052.2201 $[M+Na]^+$, 1068.1930 $[M+K]^+$. Calcd for $C_{49}H_{54}Cl_3NNaO_{15}Si$ 1052.2226, $C_{49}H_{54}Cl_3NKO_{15}Si$ 1068.1965.

4.19. Methyl 7-(benzoyloxy)-6-(*tert*-butyldimethylsilyloxy)-3*a*-(6-(4-methoxyphenoxy)-2-phenyl-7-(2,2,2-trichloroacetamido)hexahydropyrano[3,2-*d*][1,3]dioxin-8-yloxy)-2-phenyltetrahydro-3*aH*-[1,3]dioxolo[4,5-*b*]pyran-5-carboxylate, 22

^{1}H NMR($CDCl_3$, 400 MHz): δ 7.99 (d, J=7.2 Hz, 2H, ArH-Bz), 7.81 (d, J=7.2 Hz, 2H, ArH-Bz), 7.64–7.40 (m, 9H, ArH-Bz, benzylidene), 7.27–7.26 (m, 2H, ArH-Bz, benzylidene), 6.94 (d, J=8.8 Hz, 2H, ArH-OMP), 6.80–6.75 (m, 3H, NH, ArH-OMP), 6.01 (d, J=5.2 Hz, 1H, HB-1), 5.57 (d, J=3.6 Hz, 1H, HA-1), 5.47 (t, J=2.8 Hz, 1H, HB-3), 5.33 (s, 1H, CH-benzyl), 4.76 (t, J=3.6 Hz, 1H, HB-2), 4.68–4.63 (m, 1H, HA-2), 4.20–4.14 (m, 2H, HA-6_a, HB-4), 4.09 (dd, J=10.8, 3.2 Hz, 1H, HA-3), 4.03 (d, J=8.0 Hz, 1H, HB-5), 3.96 (d, J=2.8 Hz, 1H, HA-4), 3.89 (d, J=12.4 Hz, 1H, HA-6_b), 3.75 (s, 3H, CH_3-OMP), 3.72–3.66 (m, 4H, HA-5, CH_3-COOMe), 0.81 (s, 9H, *t*-Bu-TBS), 0.13 (s, 3H, CH_3-TBS), −0.02 (s, 3H, CH_3-TBS); ^{13}C NMR($CDCl_3$, 150 MHz): δ 169.71 (CO-COOMe), 164.79 (CO-Bz), 161.63 (CO-NH), 155.49 (ArC-OMP), 150.37 (ArC-OMP), 137.24 (ArC-benzylidene), 135.05 (ArC-Bz), 133.68 (ArC-Bz), 130.07, 129.94, 128.98, 128.86, 128.54, 128.42, 128.20, 126.42 (2C, ArC-benzylidene), 125.96, 121.08 [ArC-Bz(orthoester)], 118.03 (2C, ArC-OMP), 114.69 (2C, ArC-OMP), 100.73 (CH-benzylidene), 97.54 (CB-1), 97.44 (CA-1), 92.24 (C-Cl_3), 73.56, 73.51, 72.13, 71.79, 69.23, 69.11, 68.92, 63.06, 55.61 (OCH_3-OMP), 52.33 (OCH_3-COOMe), 50.21 (CA-2), 25.47 (*t*-Bu-TBS), 17.74 (C-TBS), −4.57 (CH_3-

TBS), −5.57 (CH_3-TBS). HRMS (ESI) *m/z*: 1052.2227 $[M+Na]^+$, 1068.1895 $[M+K]^+$. Calcd for $C_{49}H_{54}Cl_3NNaO_{15}Si$ 1052.2226, $C_{49}H_{54}Cl_3NKO_{15}Si$ 1068.1965.

4.20. Benzyl 8-hydroxy-6-(4-methoxyphenoxy)-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-7-ylcarbamate, 23

16′ (see Supplementary data) was prepared from **13** (406 mg, 1.06 mmol) as described for the preparation of **15**. This compound was suitable for the next step without purification. To a solution of **16′** in anhyd CH_2Cl_2 (10 mL) and satd $NaHCO_3$ aq (10 mL) was added CbzCl (281 μL, 1.97 mmol) at 0 °C. The reaction was stirred at room temperature overnight, poured into water and separated. The aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. Column chromatography (2:25 EtOAc/CH_2Cl_2) gave **23** (350 mg, 65% for two steps) as white solid. ^{1}H NMR($CDCl_3$, 100 MHz): δ 7.53 (m, 2H, ArH-benzylidene), 7.39–7.32 (m, 8H, ArH-benzylidene, Cbz), 7.00 (d, *J*=8.8 Hz, 2H, ArH-OMP), 6.83 (d, *J*=8.8 Hz, 2H, ArH-OMP), 5.62 (s, 1H, H-1), 5.60 (s, 1H, CH), 5.17 (d, *J*=9.2 Hz, 1H, NH), 5.11 (s, 2H, CH_2), 4.36 (td, *J*=10.8, 1.2 Hz, 1H, H-2), 4.30 (s, 1H, H-4), 4.25 (d, *J*=12.4 Hz, 1H, H-6_a), 4.06–4.03 (m, 2H, H-6_b, H-3), 3.81 (s, 1H, H-5), 3.77 (s, 3H, OCH_3); ^{13}C NMR($CDCl_3$, 100 MHz): δ 156.95 (CO-NH), 155.28 (ArC-OMP), 150.39 (ArC-OMP), 137.47 (ArH-benzylidene), 136.25 (ArH-Cbz), 129.39 (ArH-benzylidene), 128.68 (ArH-Cbz), 128.43 (ArH-Cbz), 128.36 (ArH-Cbz), 126.42 (ArH-benzylidene), 117.36 (2C, ArC-OMP), 114.85 (2C, ArC-OMP), 109.89 (ArH-benzylidene), 101.41 (CH), 97.81 (C-1), 75.45, 69.38, 68.96, 67.33 (CH_2), 63.66 (C-6), 55.81 (OCH_3), 52.32 (C-2). HRMS (ESI) *m/z*: 508.1961 $[M+H]^+$, 530.1776 $[M+Na]^+$. Calcd for $C_{28}H_{30}NO_8$ 508.1971, $C_{28}H_{29}NNaO_8$ 530.1791.

4.21. Benzyl 2,2-di-*tert*-butyl-8-hydroxy-6-(4-methoxyphenoxy)hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ylcarbamate, 24

To a solution of **17′** (see Supplementary data) in Py (25 mL) was added $Bu_2Si(OTf)_2$ (318 μL, 0.98 mmol) at 0 °C. The reaction was stirred at room temperature for 20 min, and was quenched by MeOH, diluted with EtOAc, washed with 1 M HCl aq, satd $NaHCO_3$ aq, and brine successively. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Column chromatography (1:5 EtOAc/PE) afforded **24** (260 mg, 29% for two steps) as white solid. ^{1}H NMR($CDCl_3$, 100 MHz): δ 7.40–7.28 (m, 5H, ArH-Cbz), 6.96 (d, *J*=8.8 Hz, 2H, ArH-OMP), 6.82 (d, *J*=8.8 Hz, 2H, ArH-OMP), 5.50 (d, 1H, *J*=2.0 Hz, H-1), 5.17–5.10 (m, 3H, NH, CH_2-Cbz), 4.50 (d, *J*=0.8 Hz, 1H, H-4), 4.30 (td, *J*=9.6, 3.2 Hz, 1H, H-2), 4.25 (d, *J*=13.6 Hz, 1H, H-6_a), 4.12 (*J*=12.4 Hz, 1H, H-6_b), 3.89–3.85 (m, 2H, H-5, H-3), 3.77 (s, 3H, OCH_3), 1.10 [s, 9H, (*t*-Bu)$_2$Si], 1.07 [s, 9H, (*t*-Bu)$_2$Si]; ^{13}C NMR($CDCl_3$, 100 MHz): δ 156.98 (ArC-OMP), 155.35 (CO-NH), 150.49 (ArC-OMP), 136.35 (ArC-Cbz), 128.71 (ArH-Cbz), 128.35 (ArH-Cbz), 128.28 (ArH-Cbz), 117.84 (2C, ArC-OMP), 114.84 (2C, ArC-OMP), 98.11 (C-1), 72.88, 70.14, 68.27, 67.04 (C-6), 55.82 (OCH_3), 52.01 (C-2), 27.69 [OCH_3-(*t*-Bu)$_2$Si], 27.48 [OCH_3-(*t*-Bu)$_2$Si], 23.53 [C-(*t*-Bu)$_2$Si], 20.96 [C-(*t*-Bu)$_2$Si]. HRMS (ESI) *m/z*: 560.2668 $[M+H]^+$, 582.2481 $[M+Na]^+$. Calcd for $C_{21}H_{34}N_3O_6Si$ 560.2680, $C_{21}H_{33}N_3NaO_6Si$ 582.2499.

4.22. 7-Azido-2,2-di-*tert*-butyl-6-(4-methoxyphenoxy) hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-8-ol, 25

To a solution of **15′** (see Supplementary data, 276 mg, 0.89 mmol) in Py (25 mL) was added $Bu_2Si(OTf)_2$ (318 μL, 0.98 mmol) at 0 °C. The reaction was stirred at room temperature for 20 min, and was quenched by MeOH, diluted with EtOAc, washed with 1 M HCl aq, satd $NaHCO_3$ aq, and brine successively. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Column chromatography (1:5 EtOAc/PE) afforded desired product (260 mg, 65%) as yellow syrup which contained **25** (164 mg, 41%) with its β isomer (96 mg, 24%). ^{1}H NMR($CDCl_3$, 100 MHz): δ 7.04 (d, *J*=8.8 Hz, 2H, ArH-OMP), 6.83 (d, *J*=9.2 Hz, 2H, ArH-OMP), 5.46 (d, *J*=3.2 Hz, 1H, H-1), 4.53 (d, *J*=3.2 Hz, 1H, H-4), 4.53 (dd, *J*=12.8, 1.6 Hz, 1H, H-6_a), 4.20 (dd, *J*=10.8, 2.8 Hz, 1H, H-3), 4.14 (*J*=13.2 Hz, 1H, H-6_b), 3.92 (s, 1H, H-5), 3.76 (s, 3H, OCH_3), 3.61 (s, 1H, OH), 3.56 (dd, *J*=10.4, 3.2 Hz, 1H, H-2), 1.07 [s, 9H, (*t*-Bu)$_2$Si], 1.05 [s, 9H, (*t*-Bu)$_2$Si]; ^{13}C NMR($CDCl_3$, 100 MHz): δ 155.45 (ArC-OMP), 150.73 (ArC-OMP), 118.05 (2C, ArC-OMP), 114.81 (2C, ArC-OMP), 98.43 (C-1), 72.88, 68.61, 67.93, 66.84, 60.58 (C-2), 55.76 (OCH3), 27.69 [OCH_3-(*t*-Bu)$_2$Si], 27.35 [OCH_3-(*t*-Bu)$_2$Si], 23.46 [C-(*t*-Bu)$_2$Si], 20.88 [C-(*t*-Bu)$_2$Si]. HRMS (ESI) *m/z*: 452.2197 $[M+H]^+$, 474.2005 $[M+Na]^+$. Calcd for $C_{21}H_{34}N_3O_6Si$ 452.2217, $C_{21}H_{33}N_3NaO_6Si$ 474.2036.

4.23. 2-(7-(Benzyloxycarbonylamino)-6-(4-methoxyphenoxy)-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-8-yloxy)-5-(*tert*-butyldimethylsilyloxy)-6-(methoxycarbonyl)tetrahydro-2*H*-pyran-3,4-diyl dibenzoate, 26

A mixture of donor **10** (116 mg, 0.17 mmol) and acceptor **23** (73 mg, 0.14 mmol) was coevaporated with toluene (3×5 mL), dried under vacuum for 30 min the mixture was dissolved in CH_2Cl_2 (3.5 mL), and activated 4 Å powdered molecular sieves were added. The reaction was stirred at room temperature for 30 min. The reaction was then cooled to −60 °C and stirred for an additional 15 min. Trimethylsilyl trifluoromethanesulfonate (0.1 M in CH_2Cl_2, 173 μL, 0.017 mmol) was added to the reaction dropwise. The temperature was gradually raised to room temperature over 2 h, and the mixture was stirred overnight. Then the reaction was quenched with TEA, filtered and concentrated to afford a yellow syrup. The product was purified by column chromatography (1:5 EtOAc/PE) to afford **22** (61 mg, 42%) as colorless syrup. ^{1}H NMR($CDCl_3$, 400 MHz): δ 7.99 (d, *J*=7.6 Hz, 2H, ArH-Bz), 7.77 (d, *J*=7.2 Hz, 2H, ArH-Bz), 7.63–7.20 (m, 17H, ArH-Bz, benzylidene, Cbz, and NH), 6.95 (d, *J*=8.0 Hz, 2H, ArH-OMP), 6.78 (d, *J*=8.8 Hz, 2H, ArH-OMP), 5.86 (d, *J*=5.2 Hz, 1H, HB-1), 5.50 (s, 1H, HA-1), 5.43 (s, 1H, HB-3), 5.31 (s, 1H, CH-benzylidene), 4.98–4.90 (m, 2H, CH_2-Cbz), 4.81–4.70 (m, 2H, HB-2, HA-4), 4.49 (td, *J*=10.8, 3.2 Hz, 1H, HA-2), 4.16 (dd, *J*=8.0, 0.8 Hz, 1H, HB-4), 4.12 (d, *J*=12.4 Hz, 1H, HA-6_a), 4.06 (d, *J*=8.4 Hz, 1H, HB-5), 3.95 (dd, *J*=10.8, 2.0 Hz, 1H, HA-3), 3.83 (d, *J*=12.0 Hz, 1H, HA-6_b), 3.79–3.73 (m, 4H, OCH_3-OMP, HA-5), 3.69 (s, 3H, OCH_3-COOMe), 0.81 (s, 9H, *t*-Bu-TBS), 0.13 (s, 3H, CH_3-TBS), −0.01 (s, 3H, CH_3-TBS); ^{13}C NMR($CDCl_3$, 150 MHz): δ 169.68 (CO-COOMe), 165.11 (CO-Bz), 162.49 (CO-Bz), 155.71 (ArC-OMP), 155.06 (CO-NH), 150.44 (ArC-OMP), 137.46 (ArC-benzylidene), 136.26 (ArC-Cbz), 135.26 (CO-Bz), 133.60 (CO-Bz), 129.93, 129.03, 128.88, 128.81, 128.53, 128.43, 128.20, 128.15, 126.49, 126.07, 120.61 [ArC-Bz(orthoester)], 117.47 (2C, ArC-OMP), 114.57 (2C, ArC-OMP), 100.79 (CH-benzylidene), 98.05 (CB-1), 97.33 (CA-1), 73.87, 73.52, 73.13, 71.64, 69.61, 69.43, 69.19, 66.78 (CH_2-Cbz), 63.02, 55.63 (OCH_3-OMP), 52.30 (OCH_3-COOMe), 49.69 (CA-2), 25.47 (*t*-Bu-TBS), 17.74 (C-TBS), −4.55 (CH_3-TBS), −5.51 (CH_3-TBS). HRMS (ESI) *m/z*: 1020.3777 $[M+Na]^+$, 1042.3621 $[M+K]^+$. Calcd for $C_{55}H_{62}NO_{16}Si$ 1020.3838, $C_{55}H_{61}NNaO_{16}Si$ 1042.3657.

4.24. 2-(7-(Benzyloxycarbonylamino)-2,2-di-*tert*-butyl-6-(4-methoxyphenoxy)hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-8-yloxy)-5-(*tert*-butyldimethylsilyloxy)-6-(methoxycarbonyl) tetrahydro-2*H*-pyran-3,4-diyl dibenzoate, 27

A mixture of donor **10** (94 mg, 0.14 mmol) and acceptor **24** (65 mg, 0.12 mmol) was coevaporated with toluene (3×5 mL), dried

under vacuum for 30 min. The mixture was dissolved in CH_2Cl_2 (3.0 mL), and activated 4 Å powdered molecular sieves were added. The reaction was stirred at room temperature for 30 min the reaction was then cooled to −60 °C and stirred for an additional 15 min. Trimethylsilyl trifluoromethanesulfonate (0.1 M in CH_2Cl_2, 140 μL, 0.017 mmol) was added to the reaction dropwise. The temperature was gradually raised to room temperature over 2 h, and the mixture was stirred overnight. Then the reaction was quenched with TEA, filtered and concentrated to afford a yellow syrup. The product was purified by column chromatography (1:5 EtOAc/PE) to afford **27** (39 mg, 31%) as colorless syrup. ^{1}H NMR($CDCl_3$, 400 MHz): δ 8.03 (d, J=7.2 Hz, 2H, ArH-Bz), 7.75 (d, J=6.8 Hz, 2H, ArH-Bz), 7.60 (t, J=7.2 Hz, 1H, ArH-Bz), 7.47–7.24 (m, 11H, ArH-Bz, Cbz, and NH), 6.88 (d, J=8.8 Hz, 2H, ArH-OMP), 6.77 (d, J=8.4 Hz, 2H, ArH-OMP), 6.03 (d, J=4.4 Hz, 1H, HB-1), 5.46 (s, 1H, HA-1), 5.36 (s, 1H, HB-3), 5.00–4.91 (m, 2H, CH_2-Cbz), 4.83 (d, J=1.2 Hz, 1H, HB-2), 4.59 (d, J=9.6 Hz, 1H, HB-4), 4.45 (td, J=10.4, 2.0 Hz, 1H, HA-2), 4.20–4.13 (m, 2H, HA-4, HA-6_a), 4.07–3.99 (m, 3H, HB-5, HA-5, HA-6_b), 3.85 (dd, J=9.2, 0.8 Hz, 1H, HA-3), 3.75 (s, 3H, OCH_3-OMP), 3.67 (s, 3H, OCH_3-COOMe), 1.06 (s, 9H, *t*-Bu-TBS), 0.98 [s, 12H, *t*-Bu-(*t*-Bu)$_2$Si], 0.79 [s, 12H, *t*-Bu-(*t*-Bu)$_2$Si], 0.12 (s, 3H, CH_3-TBS), −0.02 (s, 3H, CH_3-TBS); ^{13}C NMR($CDCl_3$, 150 MHz): δ 169.84 (CO-COOMe), 165.12 (CO-Bz), 155.99 (ArC-OMP), 155.30 (CO-NH), 150.73 (ArC-OMP), 136.54 (ArC-Cbz), 135.85 (ArC-Bz), 133.77 (ArC-Bz), 130.10, 129.84, 129.20, 128.66, 128.61, 128.47, 128.23, 126.61, 121.36 [ArC-Bz(orthoester)], 118.29 (2C, ArC-OMP), 114.71 (2C, ArC-OMP), 98.59 (CB-1), 97.45 (CA-1), 73.89, 73.02, 72.28 (CA-4), 72.13, 70.78 (CA-3), 69.37, 68.31 (CA-5), 67.01 (CA-6), 66.82, 55.79 (OCH_3-OMP), 52.45 (OCH_3-COOMe), 49.31 (CA-2), 27.67 [CH_3-(*t*-Bu)$_2$Si], 27.55 [CH_3-(*t*-Bu)$_2$Si], 25.49 (CH_3-TBS), 23.49 [C-(*t*-Bu)$_2$Si], 20.93 [C-(*t*-Bu)$_2$Si], 17.88 (C-TBS), −4.42 (CH_3-TBS), −5.33 (CH_3-TBS). HRMS (ESI) m/z: 1094.4312 $[M+Na]^+$, 1110.3502 $[M+K]^+$. Calcd for $C_{56}H_{73}NNaO_{16}Si_2$ 1094.4366, $C_{56}H_{73}NKO_{16}Si_2$ 1110.4105.

4.25. 2-(7-Azido-6-(4-methoxyphenoxy)-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-8-yloxy)-6-(hydroxymethyl)-5-(4-oxopentanoyloxy)tetrahydro-2*H*-pyran-3,4-diyl dibenzoate, 28

In a flask covered with aluminum foil, **17** (469 mg, 0.48 mmol) was dissolved in CH_2Cl_2 (12 mL). Water (640 μL) and DDQ (130 mg, 0.57 mmol) were added. The reaction was stirred at room temperature overnight, and quenched with satd $NaHCO_3$ aq. The aqueous layer was separated and extracted with CH_2Cl_2 (3×). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. Column chromatography (1:1 EtOAc/PE) gave **28** (357 mg, 87%) as a white foam. ^{1}H NMR($CDCl_3$, 400 MHz): δ 7.96 (d, J=7.2 Hz, 2H, ArH-Bz), 7.91 (d, J=7.6 Hz, 2H, ArH-Bz), 7.51–7.33 (m, 11H, ArH-Bz, benzylidene), 7.03 (d, J=8.8 Hz, 2H, ArH-OMP), 6.82 (d, J=8.8 Hz, 2H, ArH-OMP), 5.75 (t, J=10.0 Hz, 1H, HB-4), 5.59–5.54 (m, 3H, HB-3, HA-1, H-benzylidene), 5.36 (t, J=9.6 Hz, 1H, HB-2), 5.21 (J=7.6 Hz, 1H, HB-1), 4.55 (J=1.6 Hz, 1H, HA-4), 4.42 (dd, J=10.8, 2.4 Hz, 1H, HA-2), 4.21 (d, J=12.4 Hz, 1H, HA-6_a), 4.04 (d, J=12.4 Hz, 1H, HA-6_b), 3.93–3.76 (m, 8H, HB-5, HB-$6_{a,b}$, HA-3, HA-5, CH_3-OMP), 2.74–2.30 (m, 4H, CH_2CH_2-Lev), 2.08 (s, 3H, CH_3-Lev); ^{13}C NMR($CDCl_3$, 75 MHz): δ 206.76 (CO-Lev), 172.39 (CO-Lev), 165.85 (CO-Bz), 165.21 (CO-Bz), 155.40 (ArC-OMP), 150.56 (ArC-OMP), 137.55 (ArC-benzylidene), 133.46 (ArC-Bz), 133.25 (ArC-Bz), 129.97, 129.92, 129.85, 129.31, 128.99, 128.95, 128.51, 128.34, 128.19, 126.21 (2C, ArC-benzylidene), 117.79 (2C, ArC-OMP), 114.80 (2C, ArC-OMP), 101.89 (CH-benzylidene), 100.70 (CA-1), 98.41 (CB-1), 76.84, 75.68, 74.78, 73.11, 71.86, 69.22, 69.05, 63.75 (CA-6), 61.39 (CB-6), 58.71 (CA-2), 55.74 (OCH_3-OMP), 37.90 (C-Lev), 29.64 (C-Lev), 28.00 (C-Lev). ESI-MS m/z: 890.28 $[M+Na]^+$. Calcd for $C_{45}H_{45}N_3NaO_{15}$ 890.27.

4.26. 2-(7-Azido-6-(4-methoxyphenoxy)-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-8-yloxy)-6-(methoxycarbonyl)-5-(4-oxopentanoyloxy)tetrahydro-2*H*-pyran-3,4-diyl dibenzoate, 29

Glucoside **28** (600 mg, 0.69 mmol) was dissolved in a mixture of CH_2Cl_2/buffer (Na_2CO_3/$NaHCO_3$, PH 9.5) (2/1, 4.5 mL). A CH_2Cl_2 solution of TEMPO (0.1 M, 1.4 mL, 0.14 mmol) was added, followed by addition of BAIB (557 mg, 1.73 mmol). The reaction mixture was stirred at room temperature for 4 h. Then the reaction was quenched by addition of satd $Na_2S_2O_3$ aq followed by separation of the layers. The aqueous layer was extracted with EtOAc (3×). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford a yellow syrup. The crude acid was dissolved in DMF (9 mL). Then K_2CO_3 (287 mg, 2.08 mmol) and CH_3I (345 μL, 5.54 mmol) were added. The reaction was stirred at room temperature for 2 h, and was quenched with water. The reaction was diluted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4, filtered, and concentrated. Column chromatography (1:1 EtOAc/PE) gave **29** (560 mg, 90% for two steps) as a white foam. ^{1}H NMR($CDCl_3$, 500 MHz): δ 7.97 (d, J=7.5 Hz, 2H, ArH-Bz), 7.91 (d, J=8.0 Hz, 2H, ArH-Bz), 7.54–7.33 (m, 11H, ArH-Bz, benzylidene), 7.03 (d, J=8.5 Hz, 2H, ArH-OMP), 6.81 (d, J=8.5 Hz, 2H, ArH-OMP), 5.75 (t, J=9.0 Hz, 1H, HB-4), 5.61–5.53 (m, 4H, HB-3, HB-2, HA-1, CH-benzylidene), 5.24 (d, J=7.5 Hz, 1H, HB-1), 4.62 (J=2.0 Hz, 1H, HA-4), 4.39 (dd, J=10.5, 2.5 Hz, 1H, HA-2), 4.35 (d, J=10.0 Hz, 1H, HA-5), 4.22 (d, J=12.5 Hz, 1H, HA-6_a), 4.05 (d, J=12.0 Hz, 1H, HA-6_b), 3.93 (dd, J=10.5, 3.0 Hz, 1H, HA-2), 3.84 (s, 1H, HA-5), 3.76 (s, 3H, CH_3-OMP), 3.73 (s, 3H, OCH_3-COOMe), 2.64–2.36 (m, 4H, CH_2CH_2-Lev), 2.03 (s, 3H, CH_3-Lev); ^{13}C NMR($CDCl_3$, 125 MHz): δ 205.63 (CO-Lev), 171.25 (CO-Lev), 167.25 (CO-COOMe), 165.61 (CO-Bz), 164.90 (CO-Bz), 155.33 (ArC-OMP), 150.47 (ArC-OMP), 137.65 (ArC-benzylidene), 133.43 (ArC-Bz), 133.24 (ArC-Bz), 129.89, 129.16, 129.81, 128.76, 128.43, 128.29, 128.06, 126.14 (2C, ArC-Ph), 117.69 (2C, ArC-OMP), 114.72 (2C, ArC-OMP), 101.77 (CH-benzylidene), 100.53 (CA-1), 98.19 (CB-1), 75.58 (CB-4), 75.42 (CA-4), 72.60 (CB-5), 72.39 (CA-5), 71.53 (CB-2), 69.62 (CB-3), 68.97 (CA-3), 63.68 (CA-6), 58.70 (CA-2), 55.62 (OCH_3-OMP), 53.01 (CH_3-COOMe), 37.55 (C-Lev), 29.56 (C-Lev), 27.69 (C-Lev). HRMS (ESI) m/z: 918.2641 $[M+Na]^+$, 934.2460 $[M+K]^+$. Calcd for $C_{46}H_{45}N_3NaO_{16}$ 918.2698, $C_{46}H_{45}N_3KO_{16}$ 934.2437.

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Supplementary data

Supplementary data (Experimental procedures for intermediates and compound characterizations were described) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.07.042.

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