Carbohydrate Research 346 (2011) 230–237

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Synthesis of C-glycosylated amino acids by hetero-Diels–Alder addition of ethyl 2-nitrosoacrylate to *exo*-glycals

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ARTICLE INFO

Article history:
Received 9 September 2010
Received in revised form 23 November 2010
Accepted 3 December 2010
Available online 9 December 2010

Keywords:
C-Glycosylated amino acids
Ethyl bromopyruvate
Ethyl 2-nitrosoacrylate
Hetero-Diels–Alder cycloaddition
exo-Glycals
Catalytic hydrogenation

ABSTRACT

C-Glycoamino acids bearing a variety of sugar moieties were prepared by the hetero-Diels–Alder addition of ethyl 2-nitrosoacrylate to *exo*-glycals. The reaction proceeds smoothly to yield spirocyclic oxazines that can be converted into useful products by several hydrogenolytic techniques.

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1. Introduction

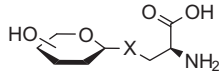
Glycosylation is one of the most common post- or co-translational modifications of proteins, which are involved in many important biological events, such as protein secretion and stability, cell–cell adhesion and signaling, innate immunity, embryogenesis, and morphogenesis. In fact, changes in oligosaccharide structure are associated with many pathological events, including cell migration, cell growth, cell differentiation, and tumor invasion. Two main types of protein glycosylation systems namely O-glycosylation modifying serine and threonine residues, and N-glycosylation modifying asparagines, are the most prevalent, and have been studied extensively. Glycosylation reactions are catalyzed by glycosyltransferases, which add sugar moieties to various glycoproteins, glycolipids, glycopeptides, and proteoglycans.[1]

In glycopeptides, the sugar units are connected to the peptide chain via *O*- or *N*-acetals (Fig. 1). Replacing the connecting heteroatom by a methylene unit (Scheme 1) offers great stability toward hydrolytic cleavage and affords stable *C*-glycosyl mimetics,[2] which may prove useful in biological studies and as potential therapeutic agents. While considering possible new routes to *C*-glycoamino acids (**3**) bearing a variety of sugar moieties, we were attracted by the possibility of adding ethyl 2-nitrosoacrylate **6** to *exo*-glycals **5**. In our previous works[3] we have demonstrated that the hetero-Diels–Alder addition of ethyl 2-nitrosoacrylate to *exo*-glycals proceeds smoothly to result high yields of spirocyclic oxazines, which can be converted into useful products, such as polyhydroxylated pyrrolidines, by several hydrogenolytic procedures. The oxazine cycloadducts are versatile intermediates possessing the necessary structural features to permit the preparation of another class of compounds, such as *C*-glycoamino acids.

2. Results and discussion

In this study we have successfully applied our previously reported methodology for the stereoselective synthesis of unnatural α-amino acids to *C*-glycoamino acids.[4] Our synthetic strategy employs the addition of ethyl 2-nitrosoacrylate **6** to *exo*-glycals **5**, as the key reaction (Scheme 1). The resulting oxazines **4** are suitable intermediates for a number of further transformations. It was expected that stereoselective reduction of adducts and further hydrogenolytic N–O bond cleavage would lead to the formation of the desired *C*-glycoamino acids **3**.

In a typical experiment, ethyl 2-nitrosoacrylate **6** (in situ generated from the oxime of ethyl bromopyruvate) readily undergoes



1, X = O, O-glycosylated serine
2, X = NHCO, N-glycosylated asparagine

Figure 1. General structure of glycosylated serine and asparagine.

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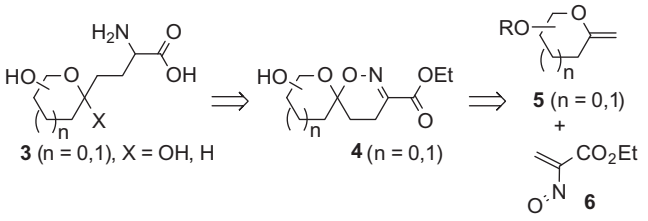
doi:10.1016/j.carres.2010.12.001



Scheme 1. Retrosynthetic approach to C-glycosylated amino acids.

cycloaddition reaction with the electron-rich sugar enol ether **7**[3] as indicated in Scheme 2. Treatment of **7** with 2 equiv of the oxime of ethyl bromopyruvate at room temperature in presence of Na_2CO_3 afforded cycloadduct **8** in fairly good yield as the only identifiable diastereoisomer. The resulting cycloadduct **8** was then first reduced with $NaBH_3CN$ to give a mixture of **9** and its epimer in very good yield, but with poor diastereoselectivity. As we previously noted,[3] the mixture of oxazines epimerises in the presence of Et_3N to the thermodynamically more stable isomer product **8**. In fact, the oxazine ring of epimer **8** adopts a chairlike conformation that brings the CO_2Et group equatorial and the EtO group axial, the latter being favoured by the anomeric effect.

At this frame, the free NH group was protected with $(Boc)_2O$ in the presence of triethylamine and DMAP and subsequently the product **10** underwent hydrogenolytic N–O bond cleavage. The N–O bond proved to be sterically hindered and stable under various conditions. Initial experiments including Pd/C, $Pd(OH)_2$ in MeOH or EtOH at rt or heating were rather disappointing. After a series of experiments the optimal conditions were found to be Ni/Raney/H_3BO_3 with MeOH in autoclave and heating for 2 days afforded lactol **14** in 50%. This compound was apparently formed by a domino reaction triggered by the N–O bond cleavage. The hemiacetal/acetal system thus formed was spontaneously converted into ketoaldehyde **12** by MeOH elimination, which upon the hydrogenation conditions led to reduction of the aldehyde group and formation of **14**. This hemiacetal system exists in $CDCl_3$ solution as a mixture of the two anomers in a ~10:1 ratio.

With these optimized conditions in hand, we turned our attention to the reduction of the lactol moiety in order to accomplish the synthesis of *C*-glycoamino acids of ribo-type. The reaction of **14** with triethylsilane in the presence of BF_3 gave the desired product **15** in 37% yield along with the spirocyclic product **16** in 43% yield. It is apparent that stereochemical control was achieved by hydride addition to the oxonium ion derived from the hemiketal **14** from its less hindered face (Fig. 2). Spiro-product **16** was obtained by a BF_3-promoted intramolecular ring closure with the amino group, also from the upper face.

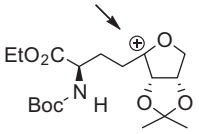


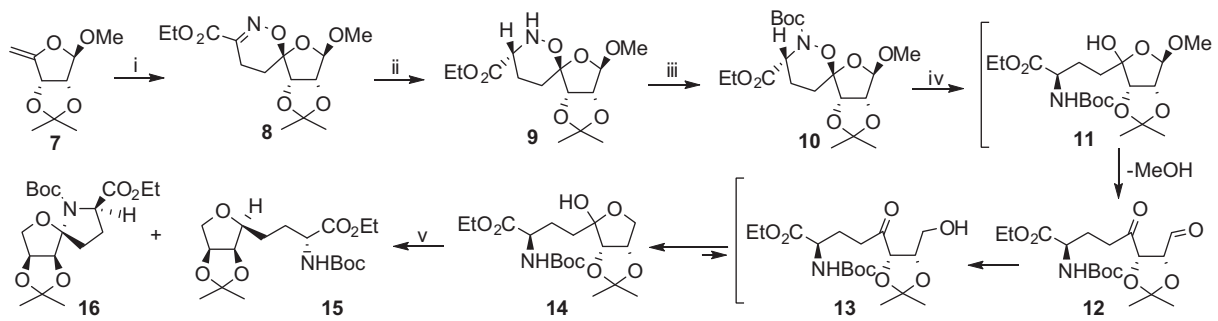
Figure 2.

Both **15** and **16** were isolated as single diastereoisomers and their stereochemistry was deduced from their ^1H NMR spectra and NOE experiments. The assignment of the protons was made by COSY and/or decoupling experiments. In compound **15**, the 4-H (ribose numbering) proton at δ 3.38 of the newly formed stereocenter is coupled with the neighboring 3-H at δ 4.56 with a coupling constant J = 3.7 Hz, indicating a rather *cis*-disposition of these two protons. This was further confirmed by the strong mutual NOE enhancements observed between 4-H and 3-H (10% of 3-H upon saturation of 4-H and 8% of 4-H upon saturation of 3-H) verifying thus the configuration of C-4.

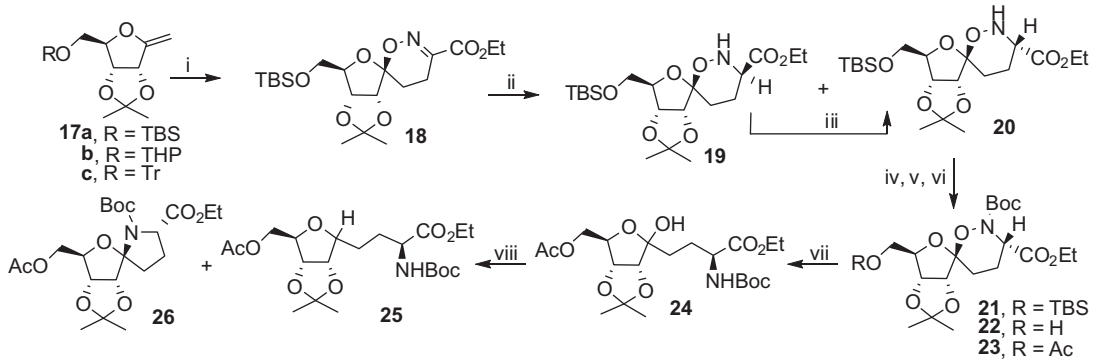
For compound **16**, NOE measurements were performed in C_6D_6 solution, where the signals were nicely separated and assigned. The lack of any hydrogen on the new stereocenter does not permit direct correlations, as in **15**. However, the absence of any significant NOE enhancement between the protons of the two spiro-rings strongly supports the proposed configuration, in which the methylene protons of the pyrrolidine ring as well as the one next to the nitrogen proton are at opposite sites of the plane with the 2-H and 3-H of the ribose ring. In the opposite configuration the mentioned protons are in proximity and are expected to give large mutual increments upon saturation.

We further explored generalized application of our synthetic strategy toward a series of *C*-glycoamino acids by changing the sugar part. Thus, *exo*-glycals **17a**–**c**[5] were prepared by Petasis olefination[6] on sugar lactones and further tested under the same reaction sequence as shown in Scheme 3. The cycloaddition reaction of **17a** with ethyl 2-nitrosoacrylate in CH_2Cl_2 gave cycloadduct **18** as a single diastereomer in 56% yield along with by-products that created problems in product purification. We could isolate from the reaction mixture and identify hemiacetal **27** (Scheme 4), resulting from the addition of water to the exocyclic double bond of glycal **17a**. Moreover, we found that enol ether **17a** decomposes partially to **27** during column chromatography on silica gel or by standing for several hours in chloroform solution.

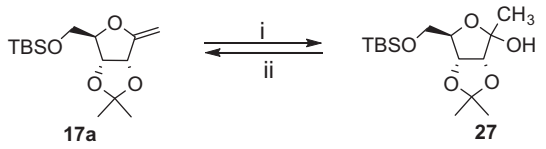
Attempts to regenerate **17a** by dehydrating hemiacetal **27** in acidic conditions did not result in the desired product, presumably because of TBS or acetonide removal. On the other hand, when $(CF_3CO)_2O$ (1.1 equiv) in pyridine[7] was used, alkene **17a** was obtained in 36% yield, whereas C-trifluoacetylation[8] on the double bond of **17a** occurred when excess of anhydride was used. Never-



Scheme 2. Reagents and conditions: (i) $BrCH_2C(NOH)CO_2Et$ (2 equiv), Na_2CO_3 (5 equiv), CH_2Cl_2, 20 °C, 24 h, 64%; (ii) $NaCNBH_3$ (4 equiv), AcOH glacial, 20 °C, 24 h, then $CHCl_3$, Et_3N (cat.), reflux, 30 min, 80%; (iii) Boc_2O, Et_3N, 20 °C, 65%; (iv) Raney Ni, H_2, reflux, 50%; (v) Et_3SiH, $Et_2O{\cdot}BF_3$, CH_2Cl_2, −40–20 °C, 37% for **11** and 43% for **12**.



Scheme 3. Reagents and conditions: (i) $BrCH_2C(NOH)CO_2Et$ (2 equiv), Na_2CO_3 (5 equiv), CH_2Cl_2, 20 °C, 24 h, 56%; (ii) $NaCNBH_3$ (4 equiv), AcOH glacial, 20 °C, 24 h, 80%; (iii) $CHCl_3$, Et_3N (cat.), reflux, 30 min, 100%; (iv) Boc_2O, Et_3N, 20 °C, 60%; (v) THF/AcOH/H_2O (4:13:7 v/v/v), 20 °C, 4 h, 98%; (vi) Ac_2O, pyridine, 0–20 °C, 8 h, 100%; (vii) Raney Ni, H_2, H_3BO_3, MeOH, $MgSO_4$ reflux, 24 h, 50%; (viii) Et_3SiH, $Et_2O{\cdot}BF_3$, CH_2Cl_2, −40–20 °C, 12% for **25** and 41% for **26**.



Scheme 4. Reagents and conditions: (i) $CDCl_3$ or CH_2Cl_2 or silica gel column (see text); (ii) $(CF_3CO)_2O$, pyridine, THF, −10 °C, 1 h, 45%.

theless, replacing dry CH_2Cl_2 by dry THF in the cycloaddition reaction improved the yield and decreased the amount of by-products. The only disadvantage of the method was the low reaction rate. Even after prolonged reaction time (1 week) enol ether **17a** was recovered in 37% yield.

Replacement of the TBS protective group to THP changes dramatically the reaction yield and a complex mixture of unidentified compounds is obtained. Furthermore, in the case of trityl ether **17c** the cycloaddition reaction occurred after 3 days in high yields, but with poor diastereocontrol essentially providing two cycloadducts in 1.4:1 diastereomeric ratio.

The stereochemistry of the addition to **17a** was confirmed by NOE measurements performed in a C_6D_6 solution of compound **18**, where the two methyl groups of the dioxolane ring appeared without overlappings. Thus, upon saturation of the *endo*-Me (δ 1.35), 3% and 2% enhancements were observed to the 4-H (ribose numbering) proton (δ 4.43) and to one methylene proton of the oxazine ring (δ 2.02) respectively, whereas saturation of the other methyl the *exo*-one (δ 1.09) caused 5% and 6% increments to the 2-H (δ 4.49) and 3-H (δ 4.81) (ribose numbering) protons.

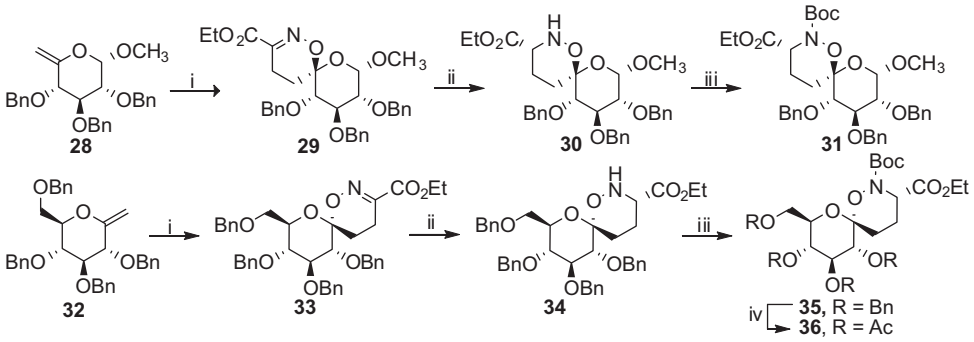
At this stage, we decided to retain the TBS ether as protective group to the primary hydroxyl and proceed to the next step of our synthesis. The conversion of cycloadduct **18** into the corresponding tetrahydro-oxazine **19** proceeded smoothly in high yields and isomerized to the thermodynamically more stable epimer **20**, which was subsequently protected to furnish Boc derivative **21**. The conformation of the epimer **20** was evident from the coupling constants of the 3-H oxazine proton which in $C_6D_6/CDCl_3$ 2:1 solution appears at δ 3.76 as dd with J = 11.0, 2.7 Hz. The large coupling is indicative of its axial disposition.

In an attempt to complete the synthesis, we had to find the most efficient catalyst for the hydrogenolysis of the N–O bond. Initial tests employing a variety of heterogeneous catalysts Pd/C, $Pd(OH)_2$ in MeOH or EtOH at rt or heating, either did not lead to any product or yielded unidentified side-products. We then performed the experiment with Ni/Raney in MeOH and heating under H_2 atmosphere, which led to desilylated oxazine **22**. In the present study, the steric bulk of TBS group was found to be critical for the observed reactivity of oxazine **21** under N–O bond hydrogenolysis conditions. Thus, we first changed the TBS group to acetyl, and oxazine **23** was exposed to the same hydrogenolysis conditions. Compound **24** was obtained in 50% yield, which was further reduced with the Et_3SiH, BF_3 system to give *C*-glycoamino acid **26** (41% yield) accompanied by small amounts of the open-chain amino acid **25**, which was isolated as a inseparable mixture of epimers in a ca. 3:1 ratio.

The absolute configuration of the newly formed stereocenter at the spiro-carbon of **26** is proposed on the basis of NOE measurements performed in $CDCl_3/C_6D_6$ 2:1 solution, where the methylene protons of the pyrrolidine ring of compound **26** appear as two multiplets at δ 2.00 and 2.14 without overlapping with the methyl of the acetoxy group (δ 1.77). Saturation of both multiplets does not cause any significant enhancement to the 5-methylene (ribose numbering) protons (δ 4.42), as it should be expected in the opposite configuration with the two groups being *cis* in proximity.

Our attention was then turned toward the synthesis of *C*-glycoamino acids of the gluco-type. In a previous publication[3] we reported the stereoselective synthesis of **29** and **30**, in an unsuccessful attempt to prepare indolizidine sugar mimics. *N*-Boc protection of **30** gave compound **31**. The synthesis of spirocyclic compounds **33**–**36** was performed in a fashion similar to the one described above starting from *exo*-glycal **32**. Unfortunately the preparation of the corresponding *C*-glycoamino acids was not possible, because compounds **31**, **35,** and **36** failed to undergo N–O hydrogenolysis under a large number of reducing agents, such as H_2 in the presence of Ni/Raney, Pd/C, $Pd(OH)_2$, PtO_2, SmI_2/AIBN, and $((CH_3)_3Si)_3SiH$–TTMS.[9] Compound **36** was prepared in an attempt to diminish the steric factor in the N–O cleavage.

The absolute configuration of the newly formed stereocenter at the spiro-carbon of compounds **33**–**36**, and therefore the stereoselectivity of the cycloadditions step in Scheme 5, was proposed on the basis of NMR studies on compound **35**. In the ^1H NMR spectrum of **35** ($CDCl_3/C_6D_6$, 3:2, solution) some of the proton chemical shifts, crucial for structure determination, could appear separately and were assigned by COSY and decoupling experiments. A significant through space interaction between one of the methylene protons of the oxazine ring (δ 1.60) and the 2-H (glucose numbering proton) proton (δ 3.37) was obvious in both NOESY and NOE difference experiments (7% enhancement of 2-H upon saturation of the methylene proton and 6% enhancement of the methylene proton upon saturation of the 2-H). These findings are in accordance with the proposed stereochemistry where the above mentioned protons are close to each other as it comes out from molecular models. A rational explanation of the observed stereoselectivity is that it is governed by the stability of the cycloadducts giving the most stable one with the oxygen atom at the axial position of glucose ring favored by the anomeric effect.



Scheme 5. Reagents and conditions: (i) $BrCH_2C(NOH)CO_2Et$ (2 equiv), Na_2CO_3 (5 equiv), CH_2Cl_2, 20 °C, 24 h, 38% for **29** (72% on the consumed **28**) and 35% for **33** (68% on the consumed **32**); (ii) $NaCNBH_3$ (4 equiv), AcOH glacial, 20 °C, 24 h, then $CHCl_3$, Et_3N (cat.), reflux, 30 min, 62% for **30** and 80% for **34**; (iii) Boc_2O, Et_3N, 20 °C, 50% for **31** and 50% for **35**; (iv) Pd/C (cat.), H_2, MeOH, reflux, overnight, then Ac_2O, pyridine, 0–20 °C, 8 h, 80% overall.

In conclusion, we investigated the synthesis of *C*-glycoamino acids derived by the hetero-Diels–Alder reaction of ethyl 2-nitrosoacrylate with *exo*-glycals. Interestingly, cycloadducts **7** and **14** could open a direct route to the synthetically useful aminoacid derivatives *C*-glycoamino acids after $NaBH_3CN$ reduction and N–O bond breaking. The conversion of cycloadducts **31**, **35**, and **36** to the corresponding gluco-derivatives proved to be tricky due to problems appearing in N–O cleavage. However and despite these problems, we have achieved the synthesis of several types of protected C-glyco amino acids either with (*R*)- (derived from **7** and **28**) or (*S*)-configuration (derived from **17a** and **32**): (i) spiro-oxazinane derivatives such as **9**, **20**, **30**, and **34**; (ii) open-chain amino acids such as **14**, **15**, **24**, and **25**; and (iii) unusual amino acids with a spiro-*N*,*O*-acetal structure like **16** and **26**. It is interesting that compounds **30** and **34** (Scheme 5) as well as compounds **9** and **16** (Scheme 2), **19**, **20**, and **26** (Scheme 3) are protected as novel representatives of conformationally constrained glucosylated amino acids.[10]

3. Experimental

3.1. General

Optical rotations were determined at room temperature on an A. Krüss P3000 Automatic Digital Polarimeter. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on a Bruker 300 AM spectrometer, with tetramethylsilane (TMS) as internal standard. High-resolution mass spectra (HRMS) were obtained on a VG ZAB-ZSE mass spectrometer under fast-atom bombardment (FAB) conditions with nitrobenzyl alcohol (NBA) as the matrix or on an IONSPEC FTMS spectrometer (matrix-assisted laser-desorption ionization, MALDI) with 2,5-dihydroxybenzoic acid (DHB) as matrix. Starting *exo*-glycals **7**, **17**, **28**, and **32** were prepared according to the literature procedures.[3,5]

3.2. General procedure for the hetero-Diels–Alder cycloadditions

A solution of $BrCH_2C(NOH)CO_2Et$ (2.96 g, 15 mmol) and the appropriate *exo*-glycal (15 mmol) was dissolved in CH_2Cl_2 (100 mL), Na_2CO_3 (3.975 g, 37.5 mmol) was added, and the mixture was stirred for 1–5 days at room temperature. During this period, additional amounts of the oxime of ethyl bromopyruvate and Na_2CO_3 were added if necessary, until the *exo*-glycal was consumed. The solids were removed by filtration through Celite and the filtrate was concentrated and chromatographed on a silica gel column with hexane/ethyl acetate as the eluent to give the hetero-Diels–Alder adducts as colorless or yellowish oils.

3.2.1. (3a*S*,4*R*,6*R*,6a*R*)-Ethyl 6-methoxy-2,2-dimethyl-4′,5′,6,6a-tetrahydro-3a*H*-spiro[furo[3,4-*d*][1,3]dioxole-4,6′-[1,2]oxazine]-3′-carboxylate (8)

This compound was prepared in 64% yield with spectral and analytical data identical to those reported in the literature.[3b]

3.2.2. (3a*R*,4*S*,6*R*,6a*R*)-Ethyl 6-((*tert*-butyldimethylsilyloxy)methyl)-2,2-dimethyl-4′,5′,6,6a-tetrahydro-3a*H*-spiro[furo[3,4-*d*][1,3]dioxole-4,6′-[1,2]oxazine]-3′-carboxylate (18)

This compound was prepared in 56% yield as a white solid whereas 17% of starting *exo*-glycal **17a** was recovered. Mp 62–63 °C; $[\alpha]_D$ −20.4 (*c* 0.52, MeOH); FTIR (film) 2949, 2928, 2855, 1743, 1722, 1469, 1458, 1375, 1288, 1256, 1208, 1136, 1108, 1010, 9556, 837, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.83 (d, 1H, *J* = 6.0 Hz), 4.62 (d, 1H, *J* = 6.0 Hz), 4.31 (q, 2H, *J* = 7.0 Hz), 4.19 (dd, 1H, *J* = 8.8, 5.8 Hz), 3.64 (m, 2H), 2.57 (m, 2H), 2.11 (m, 1H), 1.86 (m, 1H), 1.48 (s, 3H), 1.35 (s, 3H), 1.34 (t, 3H, *J* = 7.0 Hz), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^1H NMR (C_6D_6) δ 4.81 (d, 1H, *J* = 6.0 Hz), 4.49 (d, 1H, *J* = 6.0 Hz), 4.43 (dd, 1H, *J* = 9.0, 5.9 Hz), 3.98 (m, 1H), 3.83 (dd, 1H, *J* = 10.4, 9.0 Hz), 3.74 (dd, 1H, *J* = 10.4, 5.9 Hz), 2.45 (m, 2H), 2.02 (m, 1H), 1.61 (m, 1H), 1.35 (s, 3H), 1.09 (s, 3H), 0.94 (t, 3H, *J* = 7.2 Hz), 0.90 (s, 9H), −0.02 (s, 3H), −0.03 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.1, 150.9, 112.8, 107.9, 87.0, 84.0, 82.8, 63.6, 61.9, 26.3, 25.8, 25.0, 21.7, 18.6, 18.2, 14.1, −5.4; HRMS (*m*/*z*) calcd for $C_{20}H_{36}NO_7Si$ [$(M+H)^+$] 430.22556, found: 430.22566.

3.2.3. Ethyl (6*R*,8*S*,9*R*,10*R*,11*S*)-9,10,11-tris(benzyloxy)-8-methoxy-1,7-dioxa-2-azaspiro[5.5]undec-2-ene-3-carboxylate (29)

This compound was prepared in 38% yield (72% on the consumed **28**) with spectral and analytical data identical to those reported in the literature.[3b]

3.2.4. (6*R*,8*R*,9*R*,10*S*,11*R*)-Ethyl 9,10,11-tris(benzyloxy)-8-(benzyloxymethyl)-1,7-dioxa-2-azaspiro[5.5]undec-2-ene-3-carboxylate (33)

This compound was prepared in 35% yield as a colorless syrup. Although, 5 equiv of the $BrCH_2C(NOH)CO_2Et$ were added at a period of 5 days, the reaction did not complete and starting material that did not react was recovered after purification with flash chromatography (68% on the consumed **32**). $[\alpha]_D^{25}$ +24.3 (*c* 0.43, $CHCl_3$); FTIR (film) 3031, 2925, 2852, 1719, 1453, 1295, 1091 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25 (m, 18H), 7.18 (m, 2H), 4.85 (m, 4H), 4.66 (d, *J* = 11.6 Hz, 1H), 4.59 (d, *J* = 11.3 Hz, 1H), 4.53 (d, *J* = 12.2 Hz, 1H), 4.43 (d, *J* = 12.2 Hz, 1H), 4.24 (m, 3H), 3.65 (m, 5H), 2.48 (m, 2H), 1.95 (m, 1H), 1.66 (dd, *J* = 13.3, 6.3 Hz, 1H), 1.33 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 163.1, 151.3, 138.4, 138.0, 137.7, 128.3,

128.2, 128.1, 127.8, 127.6, 127.5, 127.4, 97.8, 82.5, 81.8, 78.1, 75.5, 75.4, 74.6, 73.2, 72.4, 68.3, 61.9, 22.5, 17.2, 14.0; HRMS (*m/z*) calcd for $C_{40}H_{44}NO_8$ [(M+H)$^+$] 666.30669, found: 666.30662.

3.2.5. 3a*R*,6*R*,6a*R*)-6-((*tert*-Butyldimethylsilyloxy)methyl)-2,2,4-trimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (27)

This compound was prepared in varying yield as a by-product in the preparation of **18** or in quantitative yield when a CH_2Cl_2 solution of *exo*-glycal **17a** was treated with a catalytic amount of HCl and was isolated chromatographically as an oil. $[\alpha]_D^{25}$ −35.2 (*c* 1.52, $CHCl_3$); FTIR (film) 3401, 2933, 2859, 1472, 1381, 1257, 1211, 1163, 1112, 1073, 837, 779 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.19 (s, 1H), 4.80 (dd, *J* = 6.7, 1.2 Hz, 1H), 4.44 (d, *J* = 6.1 Hz, 1H), 4.27 (d, *J* = 1.2 Hz, 1H), 3.79 (dd, *J* = 11.0, 4.9 Hz, 1H), 3.78 (dd, *J* = 11.0, 4.9 Hz, 1H), 1.53 (s, 3H), 1.51 (s, 3H), 1.35 (s, 3H), 0.93 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 112.5, 106.6, 88.0, 85.8, 82.0, 64.9, 26.7, 25.8, 25.2, 21.3, 18.2, −5.6, −5.7; HRMS (*m/z*) calcd for $C_{15}H_{30}O_5SiNa$ [(M+Na)$^+$] 341.17547, found 341.17553.

3.3. Dehydration of compound 27

A solution of **27** (3.1 g, 9.73 mmol) in dry THF (150 mL) was cooled to −10 °C under argon atmosphere, and then pyridine (7.75 mL, 25 equiv) and $(CF_3CO)_2O$ (1.13 mL, 1.1 equiv) were added. After stirring for 1 h at this temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, the solvent was evaporated, and the residue was chromatographed in a silica gel column with hexane/ethyl acetate (8:1) as the eluent to give 1.06 g of **17a** (36%), followed by unchanged **27** (45%).

3.4. General procedure for the $NaBH_3CN$ reduction of the hetero-Diels–Alder adducts

To a solution of the adducts **8**, **18**, **29** or **33** (6 mmol) in glacial acetic acid (40 mL), $NaBH_3CN$ (1.18 g, 19 mmol) was added at 0 °C with vigorous stirring under argon atmosphere and the resulting mixture was allowed to warm to room temperature, and stirred for 6–12 h. The reaction mixture was then poured into a saturated solution of Na_2CO_3 (200 mL) and extracted with ethyl acetate (2 × 50 mL). The organic layer was dried over Na_2SO_4, the solvent was evaporated, and the residue was dissolved in $CHCl_3$ (10 mL). After adding a few drops of Et_3N, this solution was refluxed for 3 h, the volatiles were evaporated off and the residue was chromatographed on a silica gel column with hexane/ethyl acetate as the eluent to give products **9**, **20**, **30** or **34** as colorless oils.

3.4.1. (3a*S*,3′*R*,4*R*,6*R*,6a*R*)-Ethyl 6-methoxy-2,2-dimethyldihydro-3a*H*-spiro[furo[3,4-*d*][1,3]dioxole-4,6′-tetrahydrooxazine]-3′-carboxylate (9)

This compound was prepared in 80% yield with spectral and analytical data identical to those reported in the literature.[3b]

3.4.2. (3a*R*,3′*S*,4*S*,6*R*,6a*R*)-Ethyl 6-((*tert*-butyldimethylsilyloxy)methyl)-2,2-dimethyldihydro-3a*H*-spiro[furo[3,4-*d*][1,3]dioxole-4,6′-tetrahydrooxazine]-3′-carboxylate (20)

This compound was prepared in 80% yield of two steps, as colorless oil. $[\alpha]_D^{25}$ −73.1 (*c* 2.9, $CHCl_3$); FTIR (film) 3460, 3243, 2924, 2855, 1740, 1733, 1471, 1463, 1373, 1328, 1303, 1106, 839, 778 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.82 (br d, *J* = 10 Hz, 1H, NH), 4.64 (d, *J* = 6.1 Hz, 1H), 4.41 (d, *J* = 6.1 Hz, 1H), 4.23 (dd as t, *J* = 7.5 Hz, 1H), 4.17 (q, *J* = 7.3 Hz, 2H), 3.80 (br m, 1H), 3.69 (dd, *J* = 10.8, 6.9 Hz, 1H), 3.61 (dd, *J* = 10.8, 8.1 Hz, 1H), 1.93 (m, 4H), 1.47 (s, 3H), 1.32 (s, 3H), 1.26 (t, *J* = 7.3 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{1}H NMR (C_6D_6/$CDCl_3$, 2:1) δ 6.00 (br, 1H, NH), 4.53 (d, *J* = 6.1 Hz, 1H), 4.38 (d, *J* = 6.1 Hz, 1H), 4.32 (dd as t, *J* = 7.7 Hz, 1H), 3.95 (q, *J* = 7.2 Hz, 2H), 3.76 (br dd, *J* = 11.0, 2.7 Hz, 1H), 3.69 (dd, *J* = 10.3, 7.7 Hz, 1H), 3.59 (dd, *J* = 10.3, 7.8 Hz, 1H), 1.90 (m, 4H), 1.41 (s, 3H), 1.19 (s, 3H), 1.00 (t, *J* = 7.2 Hz, 3H), 0.92 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.7, 112.5, 107.4, 86.4, 84.6, 82.0, 63.6, 61.0, 59.2, 27.5, 26.4, 25.9, 24.9, 23.6, 18.2, 14.1, −5.3, −5.4; HRMS *m/e* $C_{20}H_{37}NO_7Si$ [(M+H)$^+$] calcd (%): 432.2412, found 432.2431.

3.4.3. (3a*R*,3′*R*,4*S*,6*R*,6a*R*)-Ethyl6-((*tert*-butyldimethylsilyloxy)methyl)-2,2-dimethyldihydro-3a*H* spiro [furo[3,4-*d*][1,3]dioxole-4,6′-tetrahydrooxazine]-3′-carboxylate (19)

Small amount of this compound was isolated as an oil by careful chromatographic separation of the reaction mixture of **18** with $NaBH_3CN$ prior treatment with Et_3N. $[\alpha]_D^{25}$ −19.0 (*c* 1.03, $CHCl_3$); FTIR (film) 3117, 2955, 2933, 2857, 1744, 1472, 1375, 1256, 1212, 1189, 1163, 1109, 1074, 1050, 838 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.04 (br d, *J* = 10.4 Hz, 1H, NH), 4.5 (q, *J* = 6.1 Hz, 2H), 4.34 (dd, *J* = 11.5, 6.1 Hz, 1H), 4.20 (m, 2H), 3.91 (dt, *J* = 11.6, 4.3 Hz, 1H), 3.72 (m, 2H), 1.42 (s, 3H), 1.25 (s, 3H), 1.24 (t, *J* = 6.0 Hz, 3H), 0.87 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 176.8, 113.3, 111.0, 86.1, 83.7, 81.2, 63.4, 63.0, 62.4, 26.0, 25.8, 25.3, 24.4, 22.3, 18.5, 13.8, −5.3, −5.4; HRMS (*m/z*) calcd for $C_{20}H_{37}NO_7$-SiNa [(M+Na)$^+$] 454.2231, found 454.2233.

3.4.4. (3*R*,6*R*,8*S*,9*R*,10*R*,11*S*)-Ethyl 9,10,11-tris(benzyloxy)-8-methoxy-1,7-dioxa-2-azaspiro[5.5]undecane-3-carboxylate (30)

This compound was prepared in 62% yield with spectral and analytical data identical to those reported in the literature.[3b]

3.4.5. (3*S*,6*R*,8*R*,9*R*,10*S*,11*R*)-Ethyl 9,10,11-tris(benzyloxy)-8-(benzyloxymethyl)-1,7-dioxa-2-azaspiro[5.5]undecane-3-carboxylate (34)

This compound was prepared as an oil in 80% yield of two steps. $[\alpha]_D^{25}$ ~0 (*c* 1.2, $CHCl_3$); FTIR (film) 3064, 3031, 2921, 2860, 1738, 1455, 1329, 1090 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 18H), 7.18 (m, 2H), 4.97 (d, *J* = 11.7 Hz, 1H), 4.89 (s, 2H), 4.86 (d, *J* = 11.0 Hz, 1H), 4.68 (d, *J* = 11.3 Hz, 1H), 4.66 (d, *J* = 12.4 Hz, 1H), 4.58 (d, *J* = 11.0 Hz, 1H), 4.56 (d, *J* = 12.4 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.09 (d, *J* = 9.2 Hz, 1H), 3.75 (m, 6H), 3.38 (d, *J* = 9.5 Hz, 1H), 2.00 (m, 3H), 1.53 (m, 1H), 1.25 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 170.6, 138.5, 138.2, 137.8, 128.5, 128.4, 127.9, 127.8, 127.7, 127.6, 98.5, 82.9, 82.3, 79.5, 75.8, 75.7, 74.9, 73.5, 71.6, 68.6, 27.9, 22.9, 14.1; HRMS (*m/z*) calcd for $C_{40}H_6NO_8$ [(M+H)$^+$] 668.32234, found 668.32223.

3.5. General procedure for the protection of oxazinanes 9, 20, 30 and 34

To a solution of **9**, **20**, **30** or **34** (2.65 mmol), Et_3N (0.6 mL) and DMAP (20 mg) in dry CH_2Cl_2 (10 mL) $(Boc)_2O$ (1.16 g, 5.3 mmol) was added at 0 °C and the mixture was allowed to warm at room temperature, and was then stirred for 12 h. The resulting solution was washed with aqueous HCl 5% (10 mL); the aqueous layer was extracted with CH_2Cl_2 (10 mL) and the combined organic layer was dried over Na_2SO_4. The solvent was subsequently evaporated off and the residue was chromatographed on a silica gel column with hexane/ethyl acetate as the eluent to give products **10**, **21**, **31** or **35** as colorless or yellowish oils.

3.5.1. (3a*S*,3′*R*,4*R*,6*R*,6a*R*)-2′-*tert*-Butyl 3′-ethyl 6-methoxy-2,2-dimethyldihydro-3a*H*-spiro[furo[3,4-*d*][1,3]dioxole-4,6′-morpholine]-2′,3′-dicarboxylate (10)

This compound was isolated in 62% yield. $[\alpha]_D^{25}$ 6.3 (*c* 3.6, $CHCl_3$); FTIR (film) 2921, 2860, 1738, 1455, 1329, 1090 cm^{-1}; ^{1}H NMR

($CDCl_3$) δ 5.05 (s, 1H), 4.81 (d, J = 5.5 Hz, 1H), 4.69 (m, 2H4.24 (q, J = 7.3 Hz, 2H), 3.37 (s, 3H), 2.30 (m, 1H), 2.05 (m, 2H), 1.70 (m, 1H), 1.50 (s, 9H), 1.46 (s, 3H), 1.32 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.6, 154.6, 113.3, 112.8, 109.4, 84.7, 81.6, 81.1, 61.4, 55.3, 55.1, 28.2, 26.3, 25.8, 24.9, 22.3, 14.2; HRMS (*m/z*) calcd for $C_{19}H_{31}NO_9Na$ [(M+Na)$^+$] 440.18910, found 440.18924.

3.5.2. (3a*R*,3′*S*,4*S*,6*R*,6a*R*)-2′-*tert*-Butyl 3′-ethyl 6-((*tert*-butyldimethylsilyloxy)methyl)-2,2-dimethyldihydro-3a*H*-spiro[furo[3,4-*d*][1,3]dioxole-4,6′-morpholine]-2′,3′-dicarboxylate (21)

This compound was isolated in 60% yield. $[\alpha]_D^{25}$ −46.4 (*c* 3.9, $CHCl_3$); FTIR (film) 2980, 2956, 2858, 1738, 1713, 1473, 1369, 1252, 1209, 1163, 1101, 838, 778 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.75 (two dd, J = 11.4, 6.1 Hz, 2H), 4.70 (m, 1H), 4.20 (m, 3H), 3.77 (d, J = 8.9 Hz, 1H), 3.75 (d, J = 3.7 Hz, 1H), 2.32 (br d, J = 11.8 Hz, 1H), 2.10 (m, 1H), 2.02 (m, 1H), 1.68 (ddd, J = 18.0, 13.3, 4.9 Hz, 1H), 1.51 (s, 9H), 1.47 (s, 3H), 1.34 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 154.6, 112.6, 87.3, 82.4, 81.8, 81.4, 63.7, 61.5, 54.9, 28.3, 26.4, 25.9, 25.5, 25.1, 22.4, 18.2, 14.1, −5.3, −5.4; HRMS (*m/z*) calcd for $C_{25}H_{46}NO_9Si$ [(M+H)$^+$] 532.29364, found 532.29378.

3.5.3. (3*R*,6*R*,8*S*,9*R*,10*R*,11*S*)-2-*tert*-Butyl 3-ethyl 9,10,11-tris(benzyloxy)-8-methoxy-1,7-dioxa-2-azaspiro[5.5]undecane-2,3-dicarboxylate (31)

This compound was isolated in 50% yield. $[\alpha]_D^{25}$ +48.1 (*c* 0.52, $CHCl_3$). FTIR (film) 2925, 2851, 1738, 1712, 1455, 1367, 1313, 1254, 1158, 1097 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 15H), 4.84 (d, J = 11.6 Hz, 1H), 4.83 (d, J = 8.9 Hz, 1H), 4.77 (d, J = 11.6 Hz, 1H), 4.75 (s, 1H), 4.70 (d, J = 8.9 Hz, 1H), 4.69 (d, J = 12.2 Hz, 1H), 4.59 (d, J = 11.3 Hz, 1H), 4.38 (dd, J = 6.1, 4.6 Hz, 1H), 4.25 (m, 2H), 3.98 (m, 2H), 3.80 (d, J = 5.5 Hz, 1H), 3.47 (s, 3H), 2.28 (m, 1H), 2.02 (m, 2H), 1.84 (m, 1H), 1.42 (s, 9H), 1.27 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 179.1, 155.2, 138.5, 138.2, 138.1, 128.4, 128.3, 128.1, 127.9, 127.7, 127.6, 105.2, 98.1, 82.1, 81.4, 78.3, 78.2, 74.6, 73.8, 73.5, 61.3, 58.0, 56.5, 28.1, 27.4, 21.7, 14.1; HRMS (*m/z*) calcd for $C_{38}H_{48}NO_{10}$ [(M+H)$^+$] 678.32782, found 678.32777.

3.5.4. (3*S*,6*R*,8*R*,9*R*,10*S*,11*R*)-2-*tert*-Butyl 3-ethyl 9,10,11-tris(benzyloxy)-8-(benzyloxymethyl)-1,7-dioxa-2-azaspiro[5.5]undecane-2,3-dicarboxylate (35)

This compound was isolated in 50% yield. $[\alpha]_D^{25}$ +26.1 (*c* 0.98, $CHCl_3$); FTIR (film) 3064, 3031, 2977, 2931, 2852, 1747, 1732, 1714, 1497, 1455, 1367, 1327, 1093 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.20 (m, 20H), 4.96 (d, J = 11.3 Hz, 1H), 4.88 (s, 2H), 4.86 (d, J = 13.5 Hz, 1H), 4.39 (m, 1H), 4.59 (m, 4H), 4.26 (dd, J = 7.3, 3.6 Hz, 1H), 3.75 (d, J = 9.15 Hz, 1H), 3.72 (d, J = 10.2 Hz, 1H), 3.47 (d, J = 9.5 Hz, 1H), 1.65 (m, 3H), 1.49 (m, 1H), 1.43 (s, 9H), 1.23 (t, J = 7.1 Hz, 3H); ^{1}H NMR ($CDCl_3$/C_6D_6, 3:2) δ 7.20 (m, 20H), 4.85 (d, J = 11.3 Hz, 1H), 4.82 (s, 2H), 4.80 (d, J = 10.8 Hz, 1H), 4.54 (m, 3H), 4.40 (m, 1H), 4.20 (dd, J = 7.3, 4.2 Hz, 1H), 4.14 (t, J = 9.7 Hz, 1H), 4.04 (m, 2H), 3.69 (m, 3H), 3.37 (d, J = 9.7 Hz, 1H), 2.05 (m, 1H), 1.75 (m, 2H), 1.60 (m, 1H), 1.36 (s, 9H), 1.08 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.4, 138.8, 138.8, 138.6, 138.4, 137.6, 128.8, 128.5, 128.4, 128.3, 128.2, 127.9, 127.7, 127.3, 127.2, 103.4, 83.3, 83.0, 82.1, 78.4, 76.0, 75.8, 74.4, 73.3, 72.6, 68.5, 61.0, 58.5, 29.7, 28.2, 22.8, 14.1; HRMS (*m/z*) calcd for $C_{45}H_{54}NO_{10}$ [(M+H)$^+$] 768.37477, found 768.37483.

3.6. (3a*R*,3′*S*,4*S*,6*R*,6a*R*)-2′-*tert*-Butyl 3′-ethyl 6-(hydroxymethyl)-2,2-dimethyldihydro-3a*H*-spiro[furo[3,4-*d*][1,3]dioxole-4,6′-tetrahydrooxazine]-2′,3′-dicarboxylate (22)

Compound **21** (0.446 g, 0.82 mmol) was dissolved in THF/AcOH/H_2O (4:13:7 v/v/v) and the mixture was stirred for 4 h at rt. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 0.35 g of **22** (60%) as a colorless oil. $[\alpha]_D^{25}$ −45.8 (*c* 4.47, $CHCl_3$); FTIR (film) 3480, 2982, 2940, 2873, 1738, 1715, 1455, 1372, 1314, 1212, 1161, 1020, 871 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.04 (d, J = 5.8 Hz, 1H), 4.80 (d, J = 5.8 Hz, 1H), 4.65 (br s, 1H), 4.4 (d, J = 2.7 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 3.86 (d, J = 13.1 Hz, 1H), 3.68 (m, 1H), 2.37 (m, 1H), 2.08 (m, 2H), 1.65 (m, 1H), 1.50 (s, 12H), 1.35 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.2, 155.5, 112.2, 87.6, 82.8, 81.8, 64.1, 61.8, 56.5, 28.1, 26.2, 26.1, 24.5, 22.3, 14.1; HRMS (*m/z*) calcd for $C_{19}H_{32}NO_9$ [(M+H)$^+$] 418.20771, found 418.20768.

3.7. (3a*R*,3′*S*,4*S*,6*R*,6a*R*)-2′-*tert*-Butyl 3′-ethyl 6-(acetoxymethyl)-2,2-dimethyldihydro-3a*H*-spiro[furo[3,4-*d*][1,3]dioxole-4,6′-tetrahydrooxazine]-2′,3′-dicarboxylate (23)

To a solution of **22** (0.2 g 0.48 mmol) in dry pyridine, were added 0.07 mL (1.5 equiv) Ac_2O at 0 °C, and the reaction mixture was stirred under argon atmosphere, at room temperature for 8 h. Pyridine was then concentrated in vacuo and the residue was dissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4, concentrated, and on a silica gel column with hexane/ethyl acetate 1:7 as the eluent to give 0.21 g of the acetylated derivative **23** in 95% yield. $[\alpha]_D^{25}$ −39.6 (*c* 6.6, $CHCl_3$); FTIR (film) 2982, 2940, 1747, 1712, 146, 1372, 1312, 1211, 1163, 1097, 1038, 1020, 973 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.83 (d, J = 6.1 Hz, 1H), 4.75 (d, J = 6.1 Hz, 1H), 4.70 (d, J = 4.0 Hz, 1H), 4.37 (dd, J = 8.6, 6.1 Hz, 1H), 4.32 (m, 2H), 4.23 (q, J = 7.2 Hz, 2H), 2.36 (m, 1H), 2.13 (m, 1H), 2.08 (s, 3H), 1.99 (m, 1H), 1.72 (m, 1H), 1.51 (s, 9H), 1.49 (s, 3H), 1.35 (s, 3H), 1.28 (t, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 170.3, 169.2, 154.6, 113.0, 112.7, 84.1, 82.4, 82.1, 81.3, 64.5, 61.5, 54.9, 28.2, 28.0, 25.0, 22.3, 20.7, 14.1; HRMS (*m/z*) calcd for $C_{21}H_{34}NO_{10}$ [(M+H)$^+$] 460.21827, found 460.21812.

3.8. (3*S*,6*R*,8*R*,9*R*,10*S*,11*R*)-2-*tert*-Butyl 3-ethyl 9,10,11-triacetoxy-8-(acetoxymethyl)-1,7-dioxa-2-azaspiro[5.5]undecane-2,3-dicarboxylate (36)

To a solution of **35** (30 mg, 0.04 mmol) in MeOH, a catalytic amount of Pd/C was added, and the mixture was stirred overnight under hydrogen atmosphere at the boiling point of the solvent. After total removal of all protecting benzyl groups, the catalyst was filtered through Celite and the filtrate was concentrated. Without further purification the crude residue was dissolved in 2 mL of pyridine. To this solution, 0.02 mL Ac_2O (2.5 equiv/OH group) were added at 0 °C. The reaction mixture was stirred at room temperature and under inert atmosphere for 8 h, then pyridine was removed under reduced pressure and the residue was diluted with CH_2Cl_2 and washed with brine. The aqueous phase was extracted with ethyl acetate and the combined organic layers were dried over Na_2SO_4 and concentrated. The residue was flash chromatographed to give 16 mg of the total acetylated derivative **36**, in 70% yield for the two steps. FTIR (film) 2927, 2854, 1755, 1369, 1219, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.5 (t, J = 9.6 Hz, 1H), 5.17 (d, J = 9.8 Hz, 1H), 5.13 (dd, J = 10.1, 3.7 Hz, 1H), 4.59 (m, 1H), 4.25 (m, 2H), 4.22 (q, J = 7.0 Hz, 2H), 4.10 (d, J = 12.5 Hz, 1H), 2.10 (s, 3H), 2.09 (s, 3H), 2.02 (s, 3H), 2.00 (m, 3H), 1.99 (s, 3H), 1.88 (m, 1H), 1.51 (s, 9H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.9, 170.0 (two peaks), 169.8, 169.7, 154.7, 101.8, 82.8, 73.1, 71.0, 69.3, 68.3, 61.7, 61.3, 58.3, 29.8, 28.1, 27.7, 22.1, 20.8, 20.7, 14.1; HRMS (*m/z*) calcd for $C_{25}H_{38}NO_{14}$ [(M+H)$^+$] 576.22923, found 576.22929.

3.9. General procedure for the synthesis of 14 and 24

To a solution of protected oxazinanes **10** or **23** (0.4 mmol) in MeOH (10 mL) H_3BO_3 (2.4 g, 38.7 mmol), catalytic amount of Raney Ni and $MgSO_4$ (200 mg) were added, and the mixture was refluxed under H_2 atmosphere for 24 h. H_3BO_3 was then neutralized by a satd aq Na_2CO_3, the mixture was extracted with CH_2Cl_2 (3×50 mL), and the organic layer was dried over Na_2SO_4. The solvent was then removed on a rotary evaporator and the residue was chromatographed on a silica gel column.

3.9.1. (2*R*)-Ethyl 2-(*tert*-butoxycarbonylamino)-4-((3a*S*,6a*S*)-4-hydroxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)butanoate (14)

This compound was isolated in 50% yield. $[\alpha]_D^{25}$ +55.6 (*c* 0.18, MeOH); FTIR (film) 3437, 338, 2980, 2924, 1738, 1716, 1695, 1515, 1449, 1370, 1164, 1096 cm^{-1}; ^1H NMR (major diastereoisomer) ($CDCl_3$) δ 5.34 (br d, J = 7.6 Hz, 1H, NH), 4.87 (dd, J = 5.8, 3.7 Hz, 1H), 4.50 (br s, 1H, OH), 4.46 (d, J = 5.8 Hz, 1H), 4.21 (q, J = 7.2 Hz, 1H), 4.20 (q, J = 7.0 Hz, 1H), 4.05 (dd, J = 10.4, 3.7 Hz, 1H), 3.92 (t, J = 11.2 Hz, 2H), 2.00 (m, 1H), 1.80 (m, 3H), 1.47 (s, 3H), 1.45 (s, 9H), 1.33 (s, 3H), 1.27 (t, J = 7.0 Hz, 3H); ^{13}C NMR (major diastereoisomer) ($CDCl_3$) δ 172.8, 156.3, 112.3, 107.4, 84.0, 80.7, 80.3, 70.7, 61.5, 52.9, 29.7, 28.3, 26.3, 24.9, 14.2; HRMS (*m/z*) calcd for $C_{18}H_{31}NO_8Na$ [(M+Na)$^+$], 412.19474, found 412.19403.

3.9.2. (2*S*)-Ethyl 4-((3a*R*,6*R*,6a*R*)-6-(acetoxymethyl)-4-hydroxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-2-(*tert*-butoxycarbonylamino)butanoate (24)

This compound was isolated in 59% yield as a colorless oil. $[\alpha]_D^{25}$ ~0 (*c* 0.4, $CHCl_3$); FTIR (film) 3379, 2980, 2932, 1742, 1718, 1513, 1454, 1371, 1244, 1163, 1038 cm^{-1}; ^1H NMR (major diastereoisomer) ($CDCl_3$) δ 5.32 (br d, J = 8.0 Hz, 1H), 4.74 (d, J = 5.8 Hz, 1H), 4.55 (d, J = 4.3 Hz, 1H), 4.54 (d, J = 5.8 Hz, 1H), 4.38 (m, 2H), 4,17 (m, 2H), 4.20 (q, J = 7.2 Hz, 2H), 2.10 (s, 3H), 2.01 (m, 1H), 1.78 (m, 3H), 1.48 (s, 3H), 1.45 (s, 9H), 1.34 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (major diastereoisomer) (C_6D_6) δ 172.8, 171.1, 156.4, 112.7, 109.1, 85.5, 83.9, 83.4, 79.8, 65.9, 61.2, 53.6, 28.4, 28.3, 28.2, 26.7, 25.2, 20.4, 14.0; HRMS (*m/z*) calcd for $C_{21}H_{35}NO_{10}Na$ [(M+Na)$^+$], 484.21587, found 484.21587.

3.10. General procedure for the deoxygenation of lactols 14 and 24

Lactol **14** or **24** (0.1 mmol) was dissolved in dry CH_2Cl_2 (1 mL), the mixture was cooled to −40 °C, and triethylsilane (0.3 mmol) was added followed by $BF_3{\cdot}OEt_2$ (0.3 mmol). The reaction mixture was stirred for 1 h at the same temperature, then allowed to warm at 25 °C, and maintained under stirring for an additional 4 h. The mixture was poured into water and extracted with CH_2Cl_2. The combined extracts were dried, evaporated, and the crude material was purified by flash chromatography (hexane/EtOAc 1:5) to afford **15** and **16** from **14** and **25** and **26** from **24**.

3.10.1. Ethyl 2(*R*)-(*tert*-butoxycarbonylamino)-4-((3a*R*,4*S*,6a*S*)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)butanoate (15)

This compound was isolated in 37% yield as a colorless oil. $[\alpha]_D^{25}$ +7.2 (*c* 0.1, $CHCl_3$); FTIR (film) 3360, 2979, 2924, 2852, 1738, 1716, 1515, 1455, 1369, 1164, 1101, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.18 (br d, J = 7.7 Hz, 1H, NH), 4.76 (dd. J = 6.1, 3.7 Hz, 1H), 4.56 (dd, J = 6.1, 3.7 Hz, 1H), 4.25 (m, 1H), 4.19 (m, 2H), 4.00 (d, J = 10.7 Hz, 1H), 3.44 (dd, J = 10.7, 3.7 Hz, 1H), 3.38 (td, J = 6.5, 3.7 Hz, 1H), 2.00 (m, 1H), 1.77 (m, 3H), 1.48 (s, 3H), 1.44 (s, 9H), 1.33 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.7, 155.4, 112.0, 81.9, 81.0, 80.8, 79.7, 72.5, 61.2, 53.5, 28.9, 28.3, 26.0, 24.9, 24.3, 14.2; HRMS (*m/z*) calcd for $C_{18}H_{31}NO_7Na$ [(M+Na)$^+$] 396.19982, found 396.19904.

3.10.2. (2′*S*,3a*S*,5′*R*,6a*S*)-1′-*tert*-Butyl 5′-ethyl 2,2-dimethyldihydro-3a*H*-spiro[furo[3,4-*d*][1,3]dioxole-4,2′-pyrrolidine]-1′,5′-dicarboxylate (16)

This compound was isolated in 43% yield as a colorless oil. $[\alpha]_D^{25}$ +79.9 (*c* 0.18, $CHCl_3$); FTIR (film) 1757, 1738, 1705. 1457, 1368, 1270, 1181, 1091, 1002 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.1, (m, 2H), 4.34 (m, 2H), 4.19 (m, 2H), 3.96 (d, J = 10.1 Hz, 1H), 2.15 (m, 4H), 1.49 (s, 3H), 1.38 (s, 9H), 1.34 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H); ^1H NMR (C_6D_6) δ 5.27 (dd, J = 5.7, 3.4 Hz, 1H), 5.21 (d, J = 5.7 Hz, 1H), 4.50 (dd, J = 9.7, 3.4 Hz, 1H), 4.19 (t, J = 7.8 Hz, 1H), 4.09 (d, J = 9.7 Hz, 1H), 3.96 (m, 2H), 2.03 (m, 3H), 1.85 (m, 1H), 1.44 (s, 3H), 1.39 (s, 9H), 1.21 (s, 3H), 0.95 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.7, 153.6, 111.7, 102.8, 84.5, 82.7, 80.7, 74.1, 61.4, 60.9, 34.7, 29.7, 28.1, 26.6, 26.3, 24.8, 14.2; HRMS (*m/z*) calcd for $C_{18}H_{29}NO_7Na$ [(M+Na)$^+$] 394.18417, found 394.18357.

3.10.3. (2*S*)-Ethyl 4-((3a*S*,6*R*,6a*R*)-6-(acetoxymethyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-2-(*tert*-butoxycarbonylamino)butanoate (25)

This diastereoisomeric mixture was isolated in 12% yield as a colorless oil. FTIR (film) 3383, 2980, 2932, 2856, 1743, 1723, 1515, 1455, 1371, 1244, 1162, 1075, 1039, 872 cm^{-1}. ^1H NMR (mixture of diastereoisomers) ($CDCl_3$) δ 5.38 (d, J = 8.0 Hz, 1H), 5.01 (br s, 0.5H), 4.85 (d, J = 5.8 Hz, 1H), 4.72 (m, 0.5H), 4.65 (d, J = 5.8 Hz, 1H), 4.59 (s, 1H), 4.55–4.45 (m, 3H), 4.32 (q, J = 7.0 Hz, 2H), 4.41–4.13 (m, 5H), 2.20 (s, 3H), 2.19 (s, 2H), 2.23–2.08 (m, 3H), 1.95–1.82 (m, 3H), 1.71 (s, 2H), 1.59 (s, 3H), 1.55 (s, 9H), 1.53 (s, 3H), 1.46 (s, 2H), 1.45 (s, 3H), 1.39 (t, J = 7.0 Hz, 3H), 1.38 (t, J = 7.0 Hz, 2H). HRMS (*m/z*) calcd for $C_{21}H_{35}NO_9Na$ [(M+Na)$^+$] 468.22095, found 468.22078.

3.10.4. (2′*R*,3a*R*,5′*S*,6*R*,6a*R*)-1′-*tert*-Butyl 5′-ethyl 6-(acetoxymethyl)-2,2-dimethyldihydro-3a*H*-spiro[furo[3,4-*d*][1,3]dioxole-4,2′-pyrrolidine]-1′,5′-dicarboxylate (26)

This compound was isolated in 41% yield as a colorless oil. $[\alpha]_D^{25} \approx 0$ (*c* 0.15, $CHCl_3$); FTIR (film) 2972, 2931, 2852, 1743, 1704, 1452, 1372, 1243, 1181, 1088, 1037 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.18 (d, J = 6.1 Hz, 1H), 5.06 (dd, J = 6.1, 2.1 Hz, 1H), 4.27 (m, 4H), 4.16 (m, 2H), 2.30 (m, 3H), 2.08 (s, 3H), 2.06 (m, 1H), 1.49 (s, 3H), 1.40 (s, 9H), 1.36 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); ^1H NMR ($CDCl_3/C_6D_6$ 1:1) δ 4.42 (m, 3H), 5.18 (br s, 2H), 4.16 (d, J = 7.9, 1H), 4.00 (m, 2H), 2.14 (m, 1H), 2.00 (m, 3H), 1.77 (s, 3H), 1.42 (s, 3H), 1.37 (s, 9H), 1.22 (s, 3H), 1.07 (t, J = 7.2 Hz, 3H); HRMS (*m/z*) calcd for $C_{21}H_{33}NO_9Na$ [(M+Na)$^+$] 466.20530, found 466.20456.

Acknowledgment

This work was co-funded by European Union and National fund PYTHAGORAS—EPEAEK II.

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