A Phosphine-Mediated Synthesis of 1,4-Oxazepine- and 1,5-Oxazocine-Based Sugar Hybrids from Deoxysugar Azides[1]

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Abstract: An efficient and convenient method was developed for the synthesis of novel 1,4-oxazepine- and 1,5-oxazocine-based sugar hybrids from readily available deoxysugar azides by means of tributylphosphine-mediated tandem reactions. The resulting glycoconjugates might be useful in increasing the diversity of sugar backbones, and could find applications as potential glycomimetics and in drug discovery.

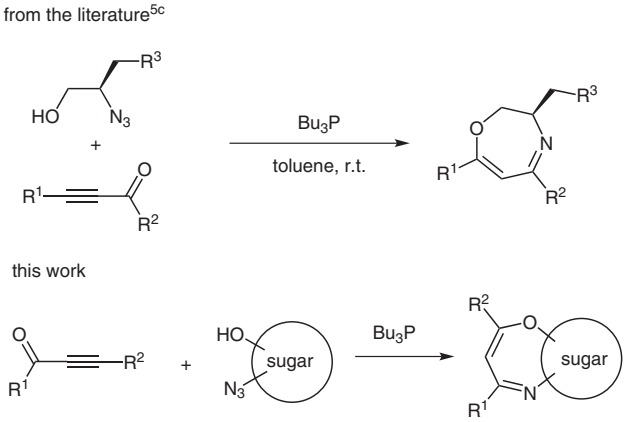
Key words: tandem reactions, heterocycles, carbohydrates, alkynes, oxazepines, oxazocines, azides

Synthesis of carbohydrate-based hybrids with biologically interesting scaffolds is an attractive area of research because of the wide range of applications of these compounds, especially in the area of drug discovery.[2] Apart from showing very different pharmacodynamic effects to those of their individual congeners, these hybrid molecules often exhibit unusual pharmacokinetic properties such as tissue permeability and improved aqueous solubility.[3] These considerations led us to initiate a research project into the design and synthesis of sugar hybrids based on well-documented biologically active oxazepine and oxazocine scaffolds.[4,5] While we were exploring various methods[6] for constructing oxazepine heterocycles, our attention was drawn to the recent serendipitous discovery of a simple and straightforward method for the preparation of 1,4-oxazepines from azido alcohols by François-Endelmond and co-workers.[5c] We applied this method to the synthesis of novel 1,4-oxazepine-based deoxysugar hybrids starting from readily available deoxysugar azides. Subsequently, we broadened the scope of this method to 1,5-oxazocine-based sugar hybrids.

Initially, we choose the readily accessible deoxysugar azide **1** (Table 1),[7] which we treated with a variety of ynones[8] in the presence of tributylphosphine under similar conditions to those previously described.[5c] To our delight, most of the ynones reacted with **1** and to give the desired 1,4-oxazepine-based sugar hybrids **2**–**11** in good yields (Table 1). Changing the nature of the substituents on the phenyl ring or replacing the phenyl in the ynone with a 2-thienyl group had little or no effect on the reaction. However, replacement of an aromatic R^1 group with a cycloalkyl group did not produce the desired compounds (results not shown), suggesting that aromatic groups may be necessary.

Having obtained encouraging results with various ynones, we next treated 1-(4-chlorophenyl)-3-phenylprop-2-yn-1-one with various sugar azides[2k,m,9] (Scheme 2). The 6-azido-3,6-dideoxysugar azides **12** and **13**, which have different stereochemistries at the C-4-position, reacted smoothly to give the corresponding 1,4-oxazepines **14** and **15**, respectively. To examine the reactivity of secondary azides in the present method, we treated the secondary sugar azide **16** with the ynone to form the desired product **17** in good yield.

To broaden the scope of our method, we attempted the corresponding reactions of 1,3-azido alcohol-containing sugar azides to form 1,5-oxazocine-based sugar hybrids, essentially under the same the conditions as described above. The reaction between deoxysugar azide **18** and ynones gave the corresponding 1,5-oxazocine-fused sugar hybrids **19** (Scheme 2). We prepared 6-deoxymannose azide derivative **20** from commercially available methyl α-D-mannopyranoside and we examined its reaction with various ynones. In all the cases, the corresponding 1,5-oxazocine-based mannose hybrids **21**–**25** were obtained in good yields (Table 2). It is noteworthy that we prepared 1,5-oxazocines from 1,3-azido alcohols for the first time



Scheme 1 Strategy for preparing oxazepine- and oxazocine-based sugar hybrids

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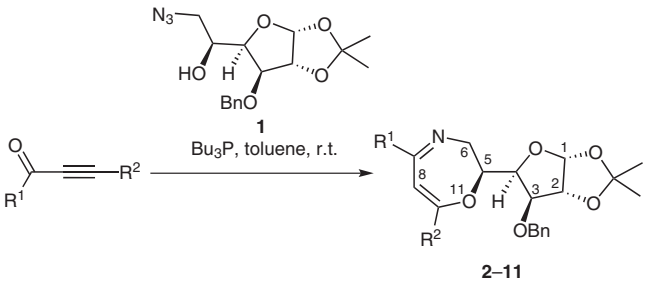
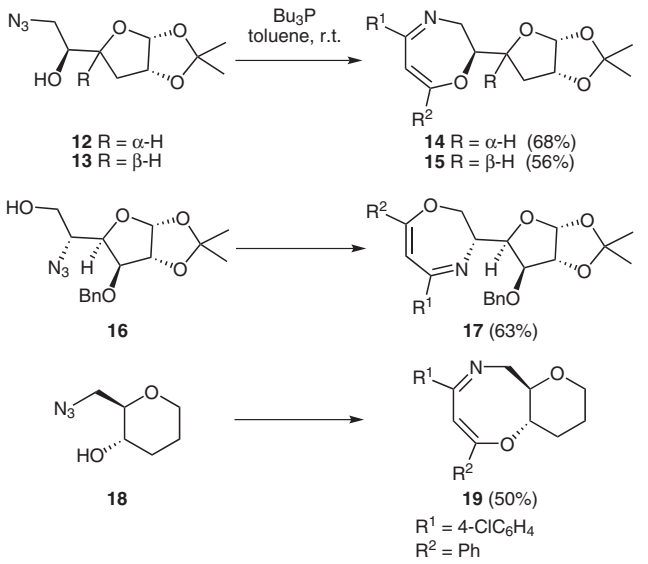
Table 1 Synthesis of 1,4-Oxazepine-Based D-Glucofuranoside Derivatives



Product	R^1	R^2	Yield (%)
2	Ph	Ph	61
3	4-ClC_6H_4	Ph	77
4	2-thienyl	Ph	72
5	3-FC_6H_4	Ph	68
6	2-thienyl	3-MeC_6H_4	60
7	Ph	4-*t*-BuC_6H_4	58
8	4-EtC_6H_4	4-*t*-BuC_6H_4	59
9	Ph	4-$MeOC_6H_4$	57
10	2-thienyl	4-$MeOC_6H_4$	70
11	4-$F_3CC_6H_4$	Ph	42

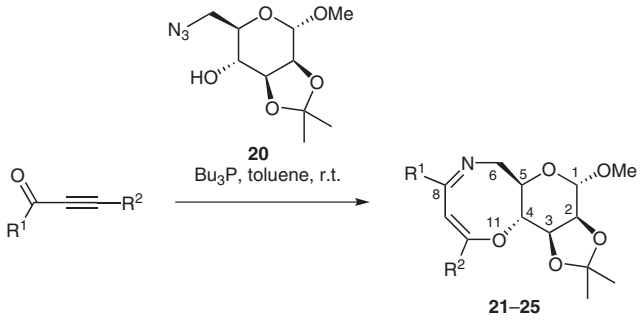


Scheme 2

by a tributylphosphine-mediated tandem aza-Wittig reaction and intramolecular cyclization.

To summarize, we have developed a simple method for preparing novel sugar hybrids based on 1,4-oxazepine and 1,5-oxazocine frameworks, starting from readily available deoxysugar azides by a tributylphosphine-mediated tandem reaction sequence. These compounds may be useful for screening in various biological targets or may be subjected to further manipulations to increase the diversity of available sugar frameworks. We have also broadened the range of methods available for the synthesis of the 1,5-oxazocine framework, starting from readily available azido deoxysugars with 1,3-azido alcohol functionalities.

Table 2 Synthesis of 1,5-Oxazocine-Based Mannose Hybrids



Product	R^1	R^2	Yield (%)
21	4-ClC_6H_4	Ph	66
22	2-thienyl	Ph	54
23	2-thienyl	4-$MeOC_6H_4$	49
24	Ph	Ph	43
25	3-FC_6H_4	Ph	51

All reagents, starting materials, and solvents (including dry solvents) were obtained from commercial suppliers and used without further purification. Reactions were carried out in oven-dried glassware under a positive pressure of argon, unless otherwise mentioned. Column chromatography was performed on silica gel (Rankem, 100–200 mesh). Deuterated solvents (Cambridge Isotope Laboratories) for NMR spectroscopic analyses were used as received. All NMR spectra were recorded on Varian 400-MHz spectrometer. All chemical shifts are quoted in ppm, relative to TMS, using the residual solvent peak as a reference standard. Optical rotation was recorded on a Rudolph Autopol-V Polarimeter at 589 nm (sodium D-line). Mass spectra were measured on an Agilent MSD/VL with ESI ionization. HRMS data were determined on a JEOL MS Route 600 H instrument or by MALDI-TOF using 2,5-dihydroxybenzoic acid as the solid matrix. IR spectra were recorded on a Perkin-Elmer 100 FT-IR spectrometer. Ynones were prepared from alkynes and acyl chlorides according to a previously described protocol.[8]

(2*R*)-2-[(3a*R*,5*S*,6*S*,6a*R*)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl]-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (2); Typical Procedure

Bu_3P (66 μL, 0.32 mmol) was added to a soln of 6-azido-3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidine-α-D-glucofuranose[7] (75 mg, 0.22 mmol) and BzC≡CPh (50 mg, 0.32 mmol) in anhyd toluene under argon. The mixture was stirred overnight at r.t. and then concentrated under reduced pressure to give a crude product that was purified by column chromatography (silica gel, EtOAc–hexanes, 4:1); yield: 61%; $[\alpha]_D^{24.9}$ –119.8 (*c* 0.25, MeOH).

IR (thin film): 697, 763, 801, 1026, 1076, 1163, 1216, 1260, 1374, 1450, 1566, 1623 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 3 H, acetonide CH_3), 1.51 (s, 3 H, acetonide CH_3), 3.76 (dd, *J* = 15.2, 6.0 Hz, 1 H, C=NCH_2), 4.18 (d, *J* = 3.2 Hz, 1 H, glucofuranose *H*-3), 4.36 (dd, *J* = 8.8, 3.2

Hz, 1 H, glucofuranose *H*-4), 4.54 (d, *J* = 11.6 Hz, 1 H, OCH_2Ph), 4.61 (dd, *J* = 8.8, 5.2 Hz, 1 H, OC*H* oxazepine), 4.68–4.72 (m, 2 H, OCH_2Ph and glucofuranose *H*-2), 4.94 (d, *J* = 14.4 Hz, 1 H, C=NCH_2), 5.98 (d, *J* = 3.6 Hz, 1 H, glucofuranose *H*-1), 6.26 (s, 1 H, oxazepine *H*-9), 7.18–7.25 (m, 5 H), 7.33–7.42 (m, 6 H), 7.55–7.58 (m, 2 H), 7.78–7.80 (m, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 166.1 (oxazepine *C*-10), 161.0 (oxazepine N=*C*-8), 141.6, 137.2, 136.0, 129.9, 129.4, 128.4 (4 C), 128.2 (2 C), 127.9, 127.7 (2 C), 127.3 (2 C), 126.4 (2 C), 111.9 [acetonide *C*(Me_2)], 105.3 (oxazepine *C*-9), 97.1 (glucofuranose *C*-1), 82.2 (glucofuranose *C*-2), 81.3 (glucofuranose *C*-4), 80.2 (glucofuranose *C*-3), 79.0 (O*C*H_2Ph), 72.1 (oxazepine O*C*H), 57.2 (=N*C*H_2), 26.8 [C(*C*H_3)$_2$], 26.3 [C(*C*H_3)$_2$].

HPLC-MS: *m/z* = 498.3 [M + 1]; t_R = 14.05 min.

HRMS (MALDI-TOF): *m/z* [M + H]$^+$ calcd for $C_{31}H_{32}NO_5$: 498.2280; found: 498.2279.

(2*R*)-2-[(3a*R*,5*S*,6*S*,6a*R*)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl]-5-(4-chlorophenyl)-7-phenyl-2,3-dihydro-1,4-oxazepine (3)

Yield: 77%; $[\alpha]_D^{24.2}$ –139.6 (*c* 0.5, MeOH).

IR (thin film): 667, 696, 755, 886, 1014, 1076, 1164, 1217, 1374, 1404, 1450, 1573, 1623, 1726 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ =1.34 (s, 3 H, acetonide CH_3), 1.51 (s, 3 H, acetonide CH_3), 3.75 (dd, *J* = 14.8, 5.6 Hz, 1 H, C=NCH_2), 4.18 (d, *J* = 2.0 Hz, 1 H, glucofuranose *H*-3), 4.35 (dd, *J* = 8.8, 3.2 Hz, 1 H, glucofuranose *H*-4), 4.54 (d, *J* = 11.6 Hz, 1 H, OCH_2Ph), 4.58 (dd, *J* = 8.4 Hz, 1 H, OC*H* oxazepine), 4.68–4.72 (m, 2 H, OCH_2Ph and glucofuranose *H*-2), 4.92 (d, *J* = 15.2 Hz, 1 H, C=NCH_2), 5.98 (d, *J* = 3.2 Hz, 1 H, glucofuranose *H*-1), 6.18 (s, 1 H, oxazepine *H*-9), 7.19–7.24 (m, 5 H), 7.33–7.42 (m, 5 H), 7.55 (d, *J* = 8.0 Hz, 2 H), 7.73 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 164.8 (oxazepine *C*-10), 161.3 (oxazepine N=*C*-8), 140.1, 137.2, 136.0, 135.4, 130.0, 128.7 (2 C), 128.5 (4 C), 128.4 (2 C), 128.0, 127.7 (2 C), 126.4 (2 C), 112.0 [acetonide *C*(Me_2)], 105.3 (oxazepine *C*-9), 96.6 (glucofuranose *C*-1), 82.2 (glucofuranose *C*-2), 81.3 (glucofuranose *C*-4), 80.3 (glucofuranose *C*-3), 79.0 (O*C*H_2Ph), 72.1 (oxazepine O*C*H), 57.3 (=N*C*H_2), 26.9 [C(*C*H_3)$_2$], 26.3 [C(*C*H_3)$_2$].

HPLC-MS: *m/z* = 532.2 [M + 1]; purity (%) = 95.3; t_R = 13.99 min.

HRMS (MALDI-TOF): *m/z* [M + H]$^+$ calcd for $C_{31}H_{31}ClNO_5$: 532.1890; found: 532.1926.

(2*R*)-2-[(3a*R*,5*S*,6*S*,6a*R*)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl]-7-phenyl-5-(2-thienyl)-2,3-dihydro-1,4-oxazepine (4)

Yield: 72%; $[\alpha]_D^{22.9}$ –150.9 (*c* 0.5, MeOH).

IR (thin film): 696, 765, 850, 886, 1076, 1114, 1163, 1215, 1277, 1571, 1618 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ =1.34 (s, 3 H, acetonide CH_3), 1.51 (s, 3 H, acetonide CH_3), 3.75 (dd, *J* = 14.8, 5.6 Hz, 1 H, C=NCH_2), 4.17 (d, *J* = 2.8 Hz, 1 H, glucofuranose *H*-3), 4.35 (dd, *J* = 8.8, 3.2 Hz, 1 H, glucofuranose *H*-4), 4.52 (d, *J* = 12.0 Hz, 1 H, OCH_2Ph), 4.60 (dd, *J* = 8.4, 6.0 Hz, 1 H, oxazepine OC*H*), 4.68–4.71 (m, 2 H, OCH_2Ph and glucofuranose *H*-2), 4.87 (d, *J* = 15.2 Hz, 1 H, C=NCH_2), 5.98 (d, *J* = 3.6 Hz, 1 H, glucofuranose *H*-1), 6.35 (s, 1 H, oxazepine *H*-9), 7.05 (app. t, *J* = 8.8, 4.0 Hz, 1 H), 7.17–7.25 (m, 5 H), 7.34–7.48 (m, 5 H), 7.57 (d, *J* = 7.6 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 160.8 (oxazepine *C*-10), 159.8 (oxazepine N=*C*-8), 147.3, 137.2, 136.0, 130.0, 128.6, 128.4 (4 C), 127.9, 127.7 (2 C), 127.3, 126.5 (2 C), 126.4, 111.9 [acetonide *C*(CH_3)$_2$], 105.3 (oxazepine *C*-9), 95.3 (glucofuranose *C*-1), 82.1 (glucofuranose *C*-2), 81.2 (glucofuranose *C*-4), 80.2 (glucofuranose C-3), 79.1 (O*C*H_2Ph), 72.0 (oxazepine O*C*H), 57.0 (oxazepine =N*C*H_2), 26.8 [C(*C*H_3)$_2$], 26.2 [C(*C*H_3)$_2$].

HPLC-MS: *m/z* = 504.2 [M + 1]; purity (%) = 97.4; t_R = 12.89 min.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{29}H_{30}SNO_5$: 504.1844; found: 504.1844.

(2*R*)-2-[(3a*R*,5*S*,6*S*,6a*R*)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl]-5-(3-fluorophenyl)-7-phenyl-2,3-dihydro-1,4-oxazepine (5)

Yield: 68%; $[\alpha]_D^{24.3}$ –158.0 (*c* 0.5, MeOH).

IR (thin film): 696, 756, 788, 885, 1024, 1076, 1114, 1164, 1216, 1383, 1451, 1569, 1623, 1724 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ =1.34 (s, 3 H, acetonide CH_3), 1.51 (s, 3 H, acetonide CH_3), 3.75 (dd, *J* = 15.2, 6.0 Hz, 1 H, C=NCH_2), 4.18 (d, *J* = 2.4 Hz, 1 H, glucofuranose *H*-3), 4.36 (dd, *J* = 8.8, 2.8 Hz, 1 H, glucofuranose *H*-4), 4.52 (d, *J* = 12 Hz, 1 H, OCH_2Ph), 4.59 (dd, *J* = 8.4, 5.6 Hz, 1 H, oxazepine OC*H*), 4.68–4.72 (m, 2 H, OCH_2Ph and glucofuranose *H*-2), 4.94 (d, *J* = 14.8 Hz, 1 H, C=NCH_2), 5.98 (d, *J* = 4.0 Hz, 1 H, glucofuranose *H*-1), 6.20 (s, 1 H, oxazepine *H*-9), 7.09 (ddd, *J* = 10.8, 8.4, 2.8 Hz, 1 H), 7.18–7.24 (m, 5 H), 7.32–7.42 (m, 4 H), 7.50–7.58 (m, 4 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 164.7 (oxazepine *C*-10), 162.8 (d, *J* = 246 Hz), 161.3 (oxazepine N=*C*-8), 144.0 (d, *J* = 7.0 Hz), 137.2, 135.9, 130.0, 129.7 (d, *J* = 7.7 Hz), 128.5 (4 C), 128.0, 127.7 (2 C), 126.4 (2 C), 122.9, 116.2 (d, *J* = 21.7 Hz), 114.3 (d, *J* = 22.6 Hz), 111.9 [acetonide *C*(Me_2)], 105.3 (oxazepine *C*-9), 96.6 glucofuranose *C*-1), 82.2 (glucofuranose *C*-2), 81.3 (glucofuranose *C*-4), 80.2 (glucofuranose *C*-3), 79.0 (O*C*H_2Ph), 72.1 (oxazepine O*C*H), 57.4 (=N*C*H_2), 26.8 [C(*C*H_3)$_2$], 26.3 [C(*C*H_3)$_2$].

HPLC-MS: *m/z* = 516.2 [M + 1]; purity (%) = 95.5; t_R = 12.94 min.

HRMS (MALDI-TOF): *m/z* [M + H]$^+$ calcd for $C_{31}H_{31}FNO_5$: 516.2186; found: 516.2197.

(2*R*)-2-[(3a*R*,5*S*,6*S*,6a*R*)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl]-7-(3-methylphenyl)-5-(2-thienyl)-2,3-dihydro-1,4-oxazepine (6)

Yield: 60%; $[\alpha]_D^{22.6}$ –139.0 (*c* 0.5, MeOH).

IR (thin film): 699, 753, 787, 844, 886, 1076, 1025, 1164, 1216, 1243, 1382, 1433, 1571, 1601, 1618 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ =1.34 (s, 3 H, acetonide CH_3), 1.51 (s, 3 H, acetonide CH_3), 2.36 (s, 3 H, $C_6H_4CH_3$), 3.74 (dd, *J* = 15.2, 6.0 Hz, 1 H, C=NCH_2), 4.17 (d, *J* = 3.2 Hz, 1 H, glucofuranose *H*-3), 4.35 (dd, *J* = 8.8, 2.8 Hz, 1 H, glucofuranose *H*-4), 4.53 (d, *J* = 12.4 Hz, 1 H, OCH_2Ph), 4.58 (dd, actual merged in doublet *J* = 8.8, 6.0 Hz, 1 H, OC*H* oxazepine) 4.67–4.71 (m, 2 H, OCH_2Ph and glucofuranose *H*-2 are merged), 4.86 (d, *J* = 15.2 Hz, 1 H, C=NCH_2), 5.97 (d, *J* = 3.2 Hz, 1 H, glucofuranose *H*-1), 6.34 (s, 1 H, oxazepine *H*-9), 7.05 (app. t, *J* = 3.6 Hz, 1 H), 7.17–7.27 (m, 7 H), 7.33–7.39 (m, 3 H), 7.42 (d, *J* = 3.6 Hz, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 160.9 (oxazepine *C*-10), 159.8 (oxazepine N=*C*-8), 147.5, 138.1, 137.2, 136.0, 130.8, 128.5 (2 C), 128.4 (2 C), 127.9 (2 C), 127.6, 127.3, 127.1, 126.2, 123.7, 111.9 [acetonide *C*(Me_2)], 105.3 (oxazepine *C*-9), 95.2 (glucofuranose *C*-1), 82.2 (glucofuranose *C*-2), 81.3 (glucofuranose *C*-4), 80.2 (glucofuranose *C*-3), 79.1 (O*C*H_2Ph), 72.1 (oxazepine O*C*H), 57.1 (=N*C*H_2), 26.8 [C(*C*H_3)$_2$], 26.3 [C(*C*H_3)$_2$], 21.5 (*m*-*C*H_3-Ph).

HPLC-MS: *m/z* = 518.3 [M + 1]; purity (%) = 98.6; t_R = 13.62 min.

HRMS (MALDI-TOF): *m/z* [M + H]$^+$ calcd for $C_{30}H_{32}NO_5S$: 518.2001; found: 518.2041.

(2*R*)-2-[(3a*R*,5*S*,6*S*,6a*R*)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl]-7-(4-*tert*-butylphenyl)-5-phenyl-2,3-dihydro-1,4-oxazepine (7)
Yield: 58%; $[\alpha]_D^{24.5}$ –138.5 (*c* 1, MeOH).

IR (thin film): 698, 754, 824, 1024, 1076, 1113, 1163, 1216, 1279, 1374, 1570, 1582, 1623 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ =1.35 [s, 12 H, acetonide CH_3, and C(CH_3)$_3$], 1.51 (s, 3 H, acetonide CH_3), 3.75 (dd, *J* = 14.8, 5.6 Hz, 1 H, C=NCH_2), 4.20 (d, *J* = 2.8 Hz, 1 H, glucofuranose *H*-3), 4.36 (dd, *J* = 8.8, 3.2 Hz, 1 H, glucofuranose *H*-4), 4.58 (d, *J* = 11.6 Hz, 1 H, OCH_2Ph), 4.63 (dd actually merged in doublet, *J* = 9.5, 5.6 Hz, 1 H, oxazepine OC*H*), 4.69 (d, *J* = 3.6 Hz, 1 H, glucofuranose *H*-2), 4.72 (d, *J* = 12 Hz, 1 H, OCH_2Ph), 4.94 (d, *J* = 14.8 Hz, 1 H, C=NCH_2), 5.99 (d, *J* = 3.6 Hz, 1 H, glucofuranose *H*-1), 6.26 (s, 1 H, oxazepine *H*-9), 7.19–7.26 (m, 5 H), 7.37–7.44 (m, 5 H), 7.53 (d, *J* = 8.4 Hz, 2 H), 7.79–7.81 (m, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 166.2 (oxazepine *C*-10), 161.0 (oxazepine N=*C*-8), 153.4, 141.8, 137.3, 133.3, 129.3, 128.5 (2 C), 128.3 (2 C), 127.9, 127.8 (2 C), 127.3 (2 C), 126.3 (2 C), 125.4 (2 C), 111.9 [acetonide *C*(Me$_2$)], 105.3 (oxazepine *C*-9), 96.7 (glucofuranose *C*-1), 82.2 (glucofuranose *C*-2), 81.4 (glucofuranose *C*-4), 80.2, (glucofuranose *C*-3), 79.0 (O*C*H$_2$Ph), 72.2 (oxazepine O*C*H), 57.3 (=N*C*H$_2$), 34.8 [*C*(CH$_3$)$_3$], 31.3 [(3 C, *C*(CH$_3$)$_3$], 26.8 [C(*C*H$_3$)$_2$], 26.3 [C(*C*H$_3$)$_2$].

HPLC-MS: *m/z* = 554.4 [M + 1]; purity (%) = 98.4; t_R = 15.71 min.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{35}H_{40}NO_5$: 554.2906; found: 554.2888.

(2*R*)-2-[(3a*R*,5*S*,6*S*,6a*R*)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl]-7-(4-*tert*-butylphenyl)-5-(4-ethylphenyl)-2,3-dihydro-1,4-oxazepine (8)
Yield: 59%; $[\alpha]_D^{24.2}$ –190.0 (*c* 0.5, MeOH).

IR (thin film): 697, 754, 825, 1024, 1074, 1113, 1163, 1216, 1279, 1575, 1607 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ =1.26 (t, *J* = 7.6 Hz, 3 H, CH$_2$CH_3), 1.34 [s, 12 H, acetonide CH_3, and C(CH_3)$_3$], 1.50 (s, 3 H, acetonide CH_3), 2.70 (q, *J* = 7.6 Hz, 2 H, CH_2CH$_3$), 3.67 (dd, *J* = 15.2, 5.2 Hz, 1 H, C=NCH_2), 4.20 (d, *J* = 2.0 Hz, 1 H, glucofuranose *H*-3), 4.40 (dd, *J* = 8.0, 2.4 Hz, 1 H, glucofuranose *H*-4), 4.56 (d, *J* = 12.4 Hz, 1 H, OCH_2Ph), 4.64–4.76 (m, 3 H, oxazepine OC*H*, glucofuranose *H*-2 and OCH_2Ph), 4.95 (d, *J* = 14.8 Hz, 1 H, C=NCH_2), 5.99 (d, *J* = 2.8 Hz, 1 H, glucofuranose *H*-1), 6.29 (s, 1 H, oxazepine *H*-9), 7.19–7.25 (m, 5 H), 7.29 (d, *J* = 7.6 Hz, 2 H), 7.40 (d, *J* = 8.4 Hz, 2 H), 7.52 (d, *J* = 8.0 Hz, 2 H), 7.75 (d, *J* = 7.6 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 168.4 (oxazepine *C*-10), 166.1 (oxazepine N=*C*-8), 155.1, 148.2, 137.1, 135.3, 132.1, 128.5 (2 C), 128.3 (2 C), 128.2 (2 C), 128.0, 127.9 (2 C), 126.9 (2 C), 125.7 (2 C), 112.1 [acetonide *C*(Me$_2$)], 105.4 (oxazepine *C*-9), 95.6 (glucofuranose *C*-1), 82.9 (glucofuranose *C*-2), 81.1 (glucofuranose *C*-4), 80.9 (glucofuranose *C*-3), 78.7 (O*C*H$_2$Ph), 72.0 (oxazepine O*C*H), 54.2 (=N*C*H$_2$), 35.0 [*C*(CH$_3$)$_3$], 31.2 [3 C, C(*C*H$_3$)$_2$], 28.8 (*C*H$_2$CH$_3$), 26.9 [C(*C*H$_3$)$_2$], 26.3 [C(*C*H$_3$)$_2$], 15.3 (CH$_2$*C*H$_3$).

HPLC-MS: *m/z* = 582.4 [M + 1]; purity (%) = 99.9; t_R = 17.53 min.

HRMS (MALDI-TOF): *m/z* $[M + H]^+$ calcd for $C_{37}H_{44}NO_5$: 582.3219; found: 582.3259.

(2*R*)-2-[(3a*R*,5*S*,6*S*,6a*R*)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl]-7-(4-methoxyphenyl)-5-phenyl-2,3-dihydro-1,4-oxazepine (9)
Yield: 57%; $[\alpha]_D^{24.4}$ –184.5 (*c* 1, MeOH).

IR (thin film): 699, 750, 846, 1026, 1074, 1178, 1256, 1484, 1509, 1539, 1604 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ =1.35 (s, 3 H, acetonide CH_3), 1.51 (s, 3 H, acetonide CH_3), 3.67 (dd, *J* = 14.4, 4.4 Hz, 1 H, C=NCH_2), 3.86 (s, 3 H, C_6H_4OCH_3), 4.20 (d, *J* = 2.8 Hz, 1 H, glucofuranose *H*-3), 4.43 (dd, *J* = 7.6, 2.4 Hz, 1 H, glucofuranose *H*-4), 4.53 (d, *J* = 12.0 Hz, 1 H, OCH_2Ph), 4.64 (app. t, *J* = 6.0 Hz, 1 H, OC*H* oxazepine), 4.70–4.76 (m, 2 H, glucofuranose *H*-2 and OCH_2Ph), 4.95 (d, *J* = 15.2 Hz, 1 H, C=NCH_2), 6.00 (d, *J* = 2.8 Hz, 1 H, glucofuranose *H*-1), 6.21 (s, 1 H, oxazepine *H*-9), 6.88 (d, *J* = 8.8 Hz, 2 H), 7.19–7.26 (m, 5 H), 7.44–7.55 (m, 5 H), 7.80 (d, *J* = 7.2 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 168.4 (oxazepine *C*-10), 166.9 (oxazepine N=*C*-8), 166.1, 162.3, 138.5, 137.1, 131.2, 128.9 (2 C), 128.7 (2 C), 128.6 (2 C), 128.1 (2 C), 127.9 (2 C), 127.1, 114.1 (2 C), 112.1 [acetonide *C*(Me$_2$)], 105.4 (oxazepine *C*-9), 94.8 (glucofuranose *C*-1), 82.0 (glucofuranose *C*-2), 81.1 (glucofuranose *C*-4), 80.8 (glucofuranose *C*-3), 78.7 (O*C*H$_2$Ph), 72.0 (oxazepine O*C*H), 55.6 (4-C_6H_4O*C*H$_3$), 54.4 (=N*C*H$_2$), 26.9 [C(*C*H$_3$)$_2$], 26.3 [C(*C*H$_3$)$_2$].

HPLC-MS: *m/z* = 528.3 [M + 1]; purity (%) = 98.9; t_R = 13.38 min.

HRMS (MALDI-TOF): *m/z* $[M + H]^+$ calcd for $C_{32}H_{34}NO_6$: 528.2386; found: 528.2421.

(2*R*)-2-[(3a*R*,5*S*,6*S*,6a*R*)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl]-7-(4-methoxyphenyl)-5-(2-thienyl)-2,3-dihydro-1,4-oxazepine (10)
Yield: 70%; $[\alpha]_D^{23.0}$ –171.7 (*c* 0.25, MeOH).

IR (thin film): 755, 838, 1027, 1075, 1116, 1178, 1255, 1278, 1385, 1435, 1510, 1567, 1608 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ =1.34 (s, 3 H, acetonide CH_3), 1.51 (s, 3 H, acetonide CH_3), 3.72 (dd, *J* = 15.2, 5.6 Hz, 1 H, C=NCH_2), 3.84 (s, 3 H, *p*-OCH_3), 4.16 (d, *J* = 3.2 Hz, 1 H, glucofuranose *H*-3), 4.35 (dd, *J* = 8.4, 2.8 Hz, 1 H, glucofuranose *H*-4), 4.52 (d, *J* = 12 Hz, 1 H, OCH_2Ph) 4.58 (dd, *J* = 8.4, 5.6 Hz, 1 H, OC*H* oxazepine), 4.68–4.71 (m, 2 H, OCH_2Ph and glucofuranose *H*-2), 4.85 (d, *J* = 15.2 Hz, 1 H, C=NCH_2), 5.97 (d, *J* = 3.6 Hz, 1 H, glucofuranose *H*-1), 6.29 (s, 1 H, oxazepine *H*-9), 6.87 (d, *J* = 8.8 Hz, 2 H), 7.05 (app. t, *J* = 4.4 Hz, 1 H), 7.17–7.26 (m, 5 H), 7.34 (d, *J* = 5.2 Hz, 1 H), 7.46 (br s, 1 H), 7.51 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 161.2 (oxazepine *C*-10), 159.8 (oxazepine N=*C*-8), 137.2, 128.6, 128.5 (3 C), 128.3, 128.0 (2 C), 127.9 (2 C), 127.7 (3 C), 127.4, 113.8 (2 C), 111.9 [acetonide *C*(Me$_2$)], 105.3 (oxazepine *C*-9), 93.9 (glucofuranose *C*-1), 82.2 (glucofuranose *C*-2), 81.3 (glucofuranose *C*-4), 80.2 (glucofuranose *C*-3), 79.1 (O*C*H$_2$Ph), 72.1 (oxazepine O*C*H), 56.9 (4-C_6H_4*C*H$_3$), 55.4 (=N*C*H$_2$), 26.8 [C(*C*H$_3$)$_2$], 26.3 [C(*C*H$_3$)$_2$].

HPLC-MS: *m/z* = 534.3 [M + 1]; purity (%) = 96.7; t_R = 12.94 min.

HRMS (MALDI-TOF): *m/z* $[M + H]^+$ calcd for $C_{30}H_{32}NO_6S$: 534.1950; found: 534.1988.

(2*R*)-2-[(3a*R*,5*S*,6*S*,6a*R*)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl]-7-phenyl-5-[4-(trifluoromethyl)phenyl]-2,3-dihydro-1,4-oxazepine (11)
Yield: 42%; $[\alpha]_D^{24.9}$ –152.4 (*c* 0.25, MeOH).

IR (thin film): 766, 851, 887, 1068, 1109, 1123, 1216, 1325, 1385, 1494, 1566, 1622 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ =1.34 (s, 3 H, acetonide CH_3), 1.51 (s, 3 H, acetonide CH_3), 3.77 (dd, *J* = 14.8, 5.2 Hz, 1 H, C=NCH_2), 4.19 (d, *J* = 2.4 Hz, 1 H, glucofuranose *H*-3), 4.37 (d, *J* = 8.8 Hz, 1 H, glucofuranose *H*-4), 4.53–4.64 (m, 2 H, OCH_2Ph and OC*H* oxazepine), 4.69–4.74 (m, 2 H, glucofuranose *H*-2 and OCH_2Ph), 4.96 (d, *J* = 14.4 Hz, 1 H, C=NCH_2), 5.99 (d, *J* = 3.2 Hz, 1 H, glucofuranose *H*-1), 6.20 (s, 1 H, oxazepine *H*-9), 7.19–7.24 (m, 5 H), 7.31–7.45 (m, 3 H), 7.56 (d, *J* = 7.2 Hz, 2 H), 7.65 (d, *J* = 8.4 Hz, 2 H), 7.90 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 164.9 (oxazepine *C*-10), 161.6 (oxazepine N=*C*-8), 145.0, 137.2, 135.8, 130.2 (2 C), 128.6 (2 C), 128.5 (2 C), 128.0 (2 C), 127.7 (2 C), 127.7 (2 C), 126.5 (2 C), 125.3, 125.2, 112.0 [*C*(Me_2)], 105.3 (oxazepine *C*-9), 96.5 (glucofuranose *C*-1), 82.2 (glucofuranose *C*-2), 81.3 (glucofuranose *C*-4), 80.2 (glucofuranose *C*-3), 78.9 (O*C*H_2Ph), 72.2 (oxazepine O*C*H), 57.6 (=N*C*H_2), 26.9 [C(*C*H_3)$_2$], 26.3 [C(*C*H_3)$_2$].

HPLC-MS: *m/z* = 566.2 [M + 1]; purity (%) = 91.7.0; t_R = 14.72 min.

(2*R*)-5-(4-Chlorophenyl)-2-[(3a*R*,5*R*,6a*R*)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl]-7-phenyl-2,3-dihydro-1,4-oxazepine (14)
Yield: 68%; $[\alpha]_D^{23.5}$ –146.0 (*c* 1, MeOH).

IR (thin film): 755, 817, 890, 1014, 1059, 1092, 1162, 1216, 1373, 1449, 1572, 1593, 1622 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ =1.34 (s, 3 H, acetonide C*H*$_3$), 1.55 (s, 3 H, acetonide C*H*$_3$), 1.86–1.93 (m, 1 H, glucofuranose C*H*$_2$, H-3), 2.30 (dd, *J* = 4.4, 3.6 Hz, 1 H, glucofuranose C*H*$_2$, H-3), 3.61 (dd, *J* = 14.8, 5.2 Hz, 1 H, C=NC*H*$_2$), 4.21 (t, *J* = 4.8 Hz, 1 H, glucofuranose *H*-4), 4.51 (dd, *J* = 10.4, 5.2 Hz, 1 H, C=NC*H*$_2$), 4.68 (d, *J* = 15.2 Hz, 1 H, OC*H* oxazepine), 4.80 (app. s, 1 H, glucofuranose *H*-2), 5.89 (d, *J* = 2.8 Hz, 1 H, glucofuranose *H*-1), 6.15 (s, 1 H, oxazepine *H*-9), 7.32–7.44 (m, 5 H), 7.66–7.70 (m, 4 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 165.0 (oxazepine *C*-10), 161.9 (oxazepine N=*C*-8), 139.8, 135.9, 135.5, 130.2, 128.7 (2 C), 128.5 (2 C), 128.4 (2 C), 126.7 (2 C), 111.5 [acetonide *C*(Me_2)], 105.7 (oxazepine *C*-9), 96.4 (glucofuranose *C*-1), 84.0, (glucofuranose *C*-2), 80.4 (glucofuranose *C*-4), 77.9, (oxazepine O*C*H), 56.9 (=N*C*H_2), 35.1 (glucofuranose *C*-3), 26.8 [C(*C*H_3)$_2$], 26.2 [C(*C*H_3)$_2$].

HPLC-MS: *m/z* = 426.2 [M + 1]; purity (%) = 97.3; t_R = 11.70 min.

HRMS (MALDI-TOF): *m/z* [M + H]$^+$ calcd for $C_{24}H_{25}ClNO_4$: 426.1472; found: 426.1466.

(2*R*)-5-(4-Chlorophenyl)-2-[(3a*R*,5*R*,6a*R*)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl]-7-phenyl-2,3-dihydro-1,4-oxazepine (15)
Yield: 56%; $[\alpha]_D^{25.0}$ –147.5 (*c* 1, MeOH).

IR (thin film): 755, 817, 850, 1030, 1091, 1163, 1214, 1381, 1406, 1149, 1575, 1593, 1619 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ =1.32 (s, 3 H,, acetonide C*H*$_3$), 1.47 (s, 3 H, acetonide C*H*$_3$), 2.30–2.33 (m, 2 H, glucofuranose C*H*$_2$, H-3), 3.88 (dd, *J* = 15.2, 5.2 Hz, 1 H, C=NC*H*$_2$), 4.32 (app.q, *J* = 6.8 Hz, 1 H, glucofuranose *H*-4), 4.41 (d, *J* = 14.8 Hz, 1 H, C=NC*H*$_2$), 4.52 (dd, *J* = 7.2, 5.6 Hz, 1 H, OC*H* oxazepine), 4.77 (dd, *J* = 7.2, 3.6, 1 H, glucofuranose *H*-2), 5.83 (d, *J* = 7. 3.6 Hz, 1 H, glucofuranose *H*-1), 6.15 (s, 1 H, oxazepine *H*-9), 7.33–7.46 (m, 5 H), 7.67 (d, *J* = 8.4 Hz, 2 H), 7.77 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 165.3 (oxazepine *C*-10), 162.4 (oxazepine N=*C*-8), 140.0, 136.2, 135.5, 130.2, 128.7 (2 C), 128.4 (4 C), 127.1 (2 C), 113.2 [*C*(Me_2)], 106.5 (oxazepine *C*-9), 96.5 (glucofuranose *C*-1), 83.9 (glucofuranose *C*-2), 80.6 (glucofuranose *C*-4), 79.0 (oxazepine O*C*H), 57.3 (=N*C*H_2), 33.7 (glucofuranose *C*-3), 27.4 [C(*C*H_3)$_2$], 26.5 [C(*C*H_3)$_2$].

HPLC-MS: *m/z* = 426.2 [M + 1]; purity (%) = 95.2; t_R = 10.71 min.

HRMS (MALDI-TOF): *m/z* [M + H]$^+$ calcd for $C_{24}H_{25}ClNO_4$: 426.1472; found: 426.1466.

(3*R*)-3-[(3a*R*,5*R*,6*S*,6a*R*)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl]-5-(4-chlorophenyl)-7-phenyl-2,3-dihydro-1,4-oxazepine (17)
Yield: 63%; $[\alpha]_D^{24.6}$ +66.4 (*c* 1, MeOH).

IR (thin film): 767, 815, 1012, 1074, 1163, 1215, 1373, 1454, 1490, 1571, 1618 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ =1.36 (s, 3 H, acetonide C*H*$_3$), 1.53 (s, 3 H, acetonide C*H*$_3$), 3.96 (dd, *J* = 11.6, 5.2 Hz, 1 H, OC*H*$_2$ oxazepine), 4.08 (app. t, *J* = 10.4, 5.6 Hz, 1 H, C=NC*H*), 4.29 (d, *J* = 2.8 Hz, 1 H, glucofuranose *H*-3), 4.44 (d, *J* = 12.4 Hz, 1 H, OC*H*$_2$Ph), 4.62 (d, *J* = 11.6 Hz, 1 H, OC*H*$_2$Ph), 4.67 (d, *J* = 3.6 Hz, 1 H, glucofuranose *H*-2), 4.88 (dd, *J* = 6.0, 2.9 Hz, 1 H, glucofuranose *H*-4), 5.01 (d, *J* = 11.6 Hz, 1 H, OC*H*$_2$ oxazepine), 6.07 (d, *J* = 3.6 Hz, 1 H, glucofuranose *H*-1), 6.20 (s, 1 H, oxazepine *H*-9), 7.10–7.24 (m, 5 H), 7.34–7.40 (m, 5 H), 7.68 (d, *J* = 7.6 Hz, 2 H), 7.74 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 163.5 (oxazepine *C*-10), 162.5 (oxazepine N=*C*-8), 140.0, 137.3, 136.2, 135.3, 130.0, 128.8 (2 C), 128.4 (2 C), 128.4 (2 C), 128.3 (2 C), 127.8, 127.7 (2 C), 126.6 (2 C), 111.7 [acetonide *C*(Me_2)], 105.3 (oxazepine *C*-9), 96.0, (glucofuranose *C*-1), 82.4 (glucofuranose *C*-2), 82.0 (glucofuranose *C*-4), 81.8 (glucofuranose C-3), 74.7 (O*C*H_2Ph), 71.8 (oxazepine O*C*H), 65.0 (=N*C*H_2), 26.9 [C(*C*H_3)$_2$], 26.4 [C(*C*H_3)$_2$].

HPLC-MS: *m/z* = 532.3 [M + 1]; purity (%) = 97.3; t_R = 14.28 min.

HRMS (MALDI-TOF): *m/z* [M + H]$^+$ calcd for $C_{31}H_{31}ClNO_5$: 532.1890; found: 532.1840.

(6a*S*,10a*S*)-4-(4-Chlorophenyl)-2-phenyl-6,6a,8,9,10,10a-hexahydropyrano[3,2-*b*][1,5]oxazocine (19)
Yield: 50%; $[\alpha]_D^{24.7}$ –328.3 (*c* 1, MeOH).

IR (thin film): 764, 799, 986, 1089, 1125, 1273, 1350, 1448, 1487, 1575, 1593, 1618 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ =1.64–75 (m, 2 H, deoxysugar C*H*$_2$, H-3), 1.79 (d, *J* = 8 Hz, 1 H, deoxysugar C*H*$_2$, H-2), 2.25 (d, *J* = 10.4 Hz, 1 H, deoxysugar C*H*$_2$, H-2), 3.42 (dd, *J* = 23.6, 9.2 Hz, 2 H, deoxysugar C*H*$_2$, H-2), 3.98 (app. t, *J* = 13.2 Hz, 2 H, C=NC*H*$_2$), 4.15–4.21 (m, 1 H, deoxysugar C*H*$_2$, H-2), 4.34 (d, *J* = 11.2 Hz, 1 H, deoxysugar H-5), 5.60 (s, 1 H, oxazepine *H*-9), 7.33 (d, *J* = 8.4 Hz, 2 H), 7.36–7.42 (m, 3 H), 7.67 (d, *J* = 7.6 Hz, 2 H), 7.85 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 166.4 (oxazocine *C*-10), 160.6 (oxazocine N=*C*-8), 138.5, 136.3, 135.9, 129.9, 129.4 (2 C), 128.4 (2 C), 128.2 (2 C), 126.7 (2 C), 93.9 (oxazocine *C*-9), 75.6 (deoxyglucose *C*-5), 72.9 (deoxyglucose *C*-4), 68.2 (deoxyglucose *C*-1), 55.2 (oxazocine N*C*H_2), 30.0 (deoxyglucose *C*-3), 25.2 (deoxyglucose *C*-2).

HPLC-MS: *m/z* = 354.2 [M + 1]; purity (%) = 97.60; t_R = 10.76 min.

HRMS (MALDI-TOF): *m/z* [M + H]$^+$ calcd for $C_{21}H_{21}ClNO_2$: 354.1260; found: 354.1249.

(3a*S*,4*S*,5a*R*,11a*R*,11b*S*)-8-(4-Chlorophenyl)-4-methoxy-2,2-dimethyl-10-phenyl-3a,4,5a,6,11a,11b-hexahydro[1,3]dioxolo[4,5]pyrano[3,2-*b*][1,5]oxazocine (21)
Yield: 66%; $[\alpha]_D^{24.3}$ –252.3 (*c* 1, MeOH).

IR (thin film): 695, 762, 825, 988, 1088, 1136, 1244, 1382, 1488, 1593, 1622 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ =1.32 (s, 3 H, acetonide C*H*$_3$), 1.33 (s, 3 H, acetonide C*H*$_3$), 3.44 (s, 3 H, mannose OC*H*$_3$), 3.90 (app. t, *J* = 10.8 Hz, 2 H, C=NC*H*$_2$), 4.17 (d, *J* = 5.6 Hz, 1 H, mannose *H*-2), 4.25 (app. t, *J* = 9.2 Hz, 1 H, mannose *H*-4), 4.39–4.47 (m, 2 H, mannose *H*-3 and *H*-5), 4.99 (s, 1 H, mannose *H*-1), 5.62 (s, 1 H, oxazocine H-9), 7.33 (d, *J* = 8.4 Hz, 2 H), 7.35–7.42 (m, 3 H), 7.72 (d, *J* = 7.2 Hz, 2 H), 7.81 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 166.7 (oxazocine *C*-10), 161.1 (oxazocine N=*C*-8), 138.8, 136.0, 135.8, 130.1, 129.3 (2 C), 128.4 (2 C), 128.3 (2 C), 126.8 (2 C), 109.6 [acetonide *C*(Me_2)], 98.7 (oxazocine *C*-9), 94.3 (mannose *C*-1), 76.3 (mannose *C*-3), 76.1 (man-

nose *C*-5), 76.0 (mannose *C*-4), 62.2 (mannose *C*-2), 55.2 (mannose O*C*H$_3$), 53.5 (oxazocine N*C*H$_2$), 28.1 [C(*C*H$_3$)$_2$], 26.3 [C(*C*H$_3$)$_2$].

HPLC-MS: *m/z* = 456.3 [M + 1]; purity (%) = 94.9; t_R = 12.32 min.

HRMS (MALDI-TOF): *m/z* [M + H]$^+$ calcd for $C_{25}H_{27}ClNO_5$: 456.1577; found: 456.1606.

(3a*S*,4*S*,5a*R*,11a*R*,11b*S*)-4-Methoxy-2,2-dimethyl-10-phenyl-8-(2-thienyl)-3a,4,5a,6,11a,11b-hexahydro[1,3]dioxolo[4,5]pyrano[3,2-*b*][1,5]oxazocine (22)
Yield: 54%; $[\alpha]_D^{24.8}$ –145.9 (*c* 1, MeOH).

IR (thin film): 762, 855, 988, 1089, 1136, 1169, 1221, 1279, 1382, 1448, 1493, 1578, 1618 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ =1.32 (s, 3 H, acetonide C*H*$_3$), 1.33 (s, 3 H, acetonide C*H*$_3$), 3.44 (s, 3 H, mannose OC*H*$_3$), 3.88 (app. t, *J* = 10.4 Hz, 2 H, C=NC*H*$_2$), 4.17 (d, *J* = 5.6 Hz, 1 H, mannose, *H*-2), 4.27–4.33 (m, 2 H, mannose, *H*-3, *H*-4), 4.44 (app. t, *J* = 5.6 Hz, 1 H, mannose *H*-5), 5.01 (s, 1 H, mannose *H*-1), 5.83 (s, 1 H, oxazocine *H*-9), 7.02 (app. t, *J* = 4.8 Hz, 1 H), 7.36–7.46 (m, 5 H), 7.73 (d, *J* = 6.8 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 161.8 (oxazocine *C*-10), 160.5 (oxazocine N=*C*-8), 146.4, 136.0, 130.1, 128.8, 128.5 (2 C), 127.8, 127.2, 126.9 (2 C), 109.7 [acetonide *C*(Me$_2$)], 98.7 (oxazocine *C*-9), 93.3 (mannose *C*-1), 76.4 (mannose *C*-3), 76.3 (mannose *C*-5), 76.1 (mannose *C*-4), 62.5 (mannose *C*-2), 55.3 (mannose O*C*H$_3$), 53.0 (oxazocine N*C*H$_2$), 28.1 [C(*C*H$_3$)$_2$], 26.4 [C(*C*H$_3$)$_2$].

HPLC-MS: *m/z* = 428.2 [M + 1]; purity (%) = 96.5; t_R = 11.25 min.

HRMS (MALDI-TOF): *m/z* [M + H]$^+$ calcd for $C_{23}H_{26}NO_5S$: 428.1531; found: 428.1554.

(3a*S*,4*S*,5a*R*,11a*R*,11b*S*)-4-Methoxy-10-(4-methoxyphenyl)-2,2-dimethyl-8-(2-thienyl)-3a,4,5a,6,11a,11b-hexahydro[1,3]dioxolo[4,5]pyrano[3,2-*b*][1,5]oxazocine (23)
Yield: 49%; $[\alpha]_D^{24.9}$ –221.2 (*c* 0.25, MeOH).

IR (thin film): 752, 854, 979, 1027, 1055, 1075, 1177, 1255, 1382, 1430, 1510, 1611 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ =1.32 (s, 3 H, acetonide C*H*$_3$), 1.33 (s, 3 H, acetonide C*H*$_3$), 3.43 (s, 3 H, mannose OC*H*$_3$), 3.84 (s, 3 H, 4-C$_6$H$_4$OC*H*$_3$), 3.84–3.90 (m, actual triplet merged in singlet, 2 H, C=NC*H*$_2$), 4.17 (d, *J* = 5.6 Hz, 1 H, mannose *H*-2), 4.25–4.33 (m, 2 H, mannose, *H*-3, *H*-4), 4.43 (app. t, *J* = 6.0 Hz, 1 H, mannose *H*-5), 5.00 (s, 1 H, mannose *H*-1), 5.75 (s, 1 H, oxazocine *H*-9), 6.91 (d, *J* = 8.8 Hz, 2 H), 7.01 (app. t, *J* = 4.4 Hz, 1 H), 7.35 (d, *J* = 5.2 Hz, 1 H), 7.41 (d, *J* = 2 Hz, 1 H), 7.67 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 161.9 (oxazocine *C*-10), 161.2 (oxazocine N=*C*-8), 160.5 (4-C$_6$H$_4$O*C*H$_3$), 146.7, 128.6, 128.5 (2 C), 127.7, 127.2 (2 C), 113.8 (2 C), 109.7 [acetonide *C*(Me$_2$)], 98.7 (oxazocine *C*-9), 92.0 (mannose *C*-1), 76.4 (mannose *C*-3), 76.3 (mannose *C*-5), 76.1 (mannose *C*-4), 62.6 (mannose *C*-2), 55.5 (4-C$_6$H$_4$O*C*H$_3$), 55.2 (mannose O*C*H$_3$), 52.9 (oxazocine N*C*H$_2$), 28.1 [C(*C*H$_3$)$_2$], 26.4 [C(*C*H$_3$)$_2$].

HPLC-MS: *m/z* = 458.3 [M + 1]; purity (%) = 95.1; t_R = 11.85 min.

(3a*S*,4*S*,5a*R*,11a*R*,11b*S*)-4-Methoxy-2,2-dimethyl-8,10-diphenyl-3a,4,5a,6,11a,11b-hexahydro[1,3]dioxolo[4,5]pyrano[3,2-*b*][1,5]oxazocine (24)
Yield: 43%; $[\alpha]_D^{24.9}$ –237 (*c* 0.5, MeOH).

IR (thin film): 696, 762, 868, 987, 1016, 1090, 1054, 1136, 1221, 1382, 1447, 1497, 1574, 1624 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ =1.33 [s, 6 H, acetonide C(C*H*$_3$)$_2$], 3.44 (s, 3 H, mannose OC*H*$_3$), 3.92 (dd, *J* = 16, 9.6 Hz, 2 H, C=NC*H*$_2$), 4.17 (d, *J* = 5.6 Hz, 1 H, mannose *H*-2), 4.29 (t, *J* = 8.0 Hz, 1 H, mannose *H*-4), 4.42–4.48 (m, 2 H, mannose *H*-3, *H*-5), 4.99 (s, 1 H, mannose *H*-1), 5.68 (s, 1 H, oxazocine *H*-9), 7.35–7.42 (m, 6 H), 7.73 (d, *J* = 6.8 Hz, 2 H), 7.86 (d, *J* = 7.2 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 168.0 (oxazocine *C*-10), 160.8 (oxazocine N=*C*-8), 140.4, 136.0, 130.0 (2 C), 128.4 (2 C), 128.2 (2 C), 128.0 (2 C), 126.9 (2 C), 109.7 [acetonide *C*(Me$_2$)], 98.8 (oxazocine *C*-9), 95.0 (mannose *C*-1), 76.3 (mannose *C*-3), 76.3 (mannose *C*-5), 76.1 (mannose *C*-4), 62.3 (mannose *C*-2), 55.2 (mannose O*C*H$_3$), 53.4 (oxazocine N*C*H$_2$), 28.1 [C(*C*H$_3$)$_2$], 26.4 [C(*C*H$_3$)$_2$].

HPLC-MS: *m/z* = 422.3 [M + 1]; purity (%) = 92.0; t_R = 11.65 min.

HRMS (MALDI-TOF): *m/z* [M + H]$^+$ calcd for $C_{25}H_{28}NO_5$: 422.1967; found: 422.1962.

(3a*S*,4*S*,5a*R*,11a*R*,11b*S*)-8-(3-Fluorophenyl)-4-methoxy-2,2-dimethyl-10-phenyl-3a,4,5a,6,11a,11b-hexahydro[1,3]dioxolo[4,5]pyrano[3,2-*b*][1,5]oxazocine (25)
Yield: 51%; $[\alpha]_D^{24.9}$ –267.8 (*c* 0.5, MeOH).

IR (thin film): 698, 762, 866, 988, 1054, 1090, 1136, 1177, 1221, 1269, 1383, 1448, 1483, 1572, 1625 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ =1.34 [s, 6 H, acetonide C(C*H*$_3$)$_2$], 3.45 (s, 3 H, mannose OC*H*$_3$), 3.91 (t, *J* = 10.Hz, 2 H, C=NC*H*$_2$), 4.18 (d, *J* = 5.2 Hz, 1 H, mannose, *H*-2), 4.26 (t, *J* = 8.4 Hz, 1 H, mannose *H*-4), 4.41–4.78 (m, 2 H, mannose *H*-3, *H*-5), 5.00 (s, 1 H, mannose *H*-1), 5.64 (s, 1 H, oxazocine *H*-9), 7.10 (app. t, *J* = 8.4 Hz, 1 H), 7.30–7.44 (m, 4 H), 7.58–7.63 (m, 2 H), 7.72 (d, *J* = 6.8 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 166.7 (oxazocine *C*-10), 162.8 (d, *J* = 244.1 Hz), 161.2 (oxazocine N=*C*-8), 135.8, 130.1, 129.7, 129.6, 128.5 (2 C), 126.9 (2 C), 123.7, 117.0 (d, *J* = 21.3 Hz), 114.9 (d, *J* = 22.5 Hz), 109.7 [acetonide *C*(Me$_2$)], 98.8 (oxazocine *C*-9), 94.4 (mannose *C*-1), 76.4 (mannose *C*-3), 76.2 (mannose *C*-5), 76.1 (mannose *C*-4), 62.2 (mannose *C*-2), 55.2 (mannose O*C*H$_3$), 53.5 (oxazocine N*C*H$_2$), 28.1 [C(*C*H$_3$)$_2$], 26.3 [C(*C*H$_3$)$_2$].

HPLC-MS: *m/z* = 440.3 [M + 1]; purity (%) = 91.7; t_R = 12.03 min.

HRMS (MALDI-TOF): *m/z* [M + H]$^+$ calcd for $C_{25}H_{27}FNO_5$: 440.1873; found: 440.1836.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are copies of ^{1}H and ^{13}C NMR spectra of all final products and intermediates, together with experimental procedures for preparing the new deoxysugar azides.

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References

(1) Advinus Publication No. ADV-A-013.
(2) For selected reviews and publications on sugar hybrids, see: (a) Meutermans, W.; Le, G. T.; Becker, B. *ChemMedChem* **2006**, *1*, 1164. (b) Varki, A. *Glycobiology* **1993**, *3*, 97. (c) Reddy, B. G.; Vankar, Y. D. *Angew. Chem. Int. Ed.* **2005**, *44*, 2001. (d) Chakraborty, T. K.; Srinivasu, P.; Tapadar, S.; Mohan, B. K. *Glycoconjugate J.* **2005**, *22*, 83. (e) Dedola, S.; Nepogodiev, S. A.; Field, R. A. *Org. Biomol. Chem.* **2007**, *5*, 1006. (f) Nandurdikar, R. S.; Subrahmanyam, A.

V.; Kaliappan, K. P. *Eur. J. Org. Chem.* **2010**, 2788. (g) Stark, M.; Thiem, J. *Carbohydr. Res.* **2006**, *341*, 1543. (h) Sylvain, I.; Zerrouki, R.; Granet, R.; Huang, Y. M.; Lagorce, J. F.; Guilloton, M.; Blais, J. C.; Krausz, P. *Bioorg. Med. Chem.* **2002**, *10*, 57. (i) Kashyap, S.; Hotha, S. *Tetrahedron Lett.* **2006**, *47*, 3307. (j) Idutsu, Y.; Sasaki, A.; Matsumura, S.; Toshima, K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4332. (k) Abrous, L.; Jokiel, P. A.; Friedrich, S. R.; Hynes, J. Jr.; Smith, A. B. III; Hirschmann, R. *J. Org. Chem.* **2004**, *69*, 280. (l) Toshima, K.; Ozawa, T.; Kimura, T.; Matsumura, S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2777. (m) Kurhade, S. E.; Mengawade, T.; Bhuniya, D.; Palle, V. P.; Reddy, D. S. *Org. Biomol. Chem.* **2011**, *9*, 744; and references cited therein.

(3) (a) Monsigny, M.; Roche, A.-C.; Midoux, P.; Mayer, R. *Adv. Drug Delivery Rev.* **1994**, *14*, 1. (b) Poduslo, J. F.; Curran, G. L. *Mol. Brain Res.* **1994**, *23*, 157. (c) Polt, R.; Porreca, F.; Szabo, L. Z.; Bilsky, E. J.; Davis, P.; Abbruscato, T. J.; Davis, T. P.; Harvath, R.; Yamamura, H. I.; Hruby, V. J. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 7114. (d) Wadhwa, M. S.; Rice, K. G. *J. Drug Targeting* **1995**, *3*, 111. (e) Lerchen, H.-G.; Baumgarten, J.; Piel, N.; Kolb-Bachofen, V. *Angew. Chem. Int. Ed.* **1999**, *38*, 3680. (f) Egleton, R. D.; Mitchell, S. A.; Huber, J. D.; Janders, J.; Stropova, D.; Polt, R.; Yamamura, H. I.; Hruby, V. J.; Davis, T. P. *Brain Res.* **2000**, *881*, 37. (g) Davis, B. G.; Robinson, M. A. *Curr. Opin. Drug Discovery Devel.* **2002**, *5*, 279. (h) Jakas, A.; Horvat, S. *Bioorg. Chem.* **2004**, *32*, 516. (i) Sampathkumar, S.-G.; Campbell, C. T.; Weier, C.; Yarema, K. J. *Drugs Future* **2006**, *31*, 1099.

(4) (a) Serrano-Wu, M. H.; St. Laurent, D. R.; Chen, Y.; Huang, S.; Lam, K.-R.; Matson, J. A.; Mazzucco, C. E.; Stickle, T. M.; Tully, T. P.; Wong, H. S.; Vyas, D. M.; Balasubramanian, B. N. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2757. (b) Seto, S.; Tanioka, A.; Ikeda, M.; Izawa, S. *Bioorg. Med. Chem.* **2005**, *13*, 5717. (c) Seto, S.; Tanioka, A.; Ikeda, M.; Izawa, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1485. (d) Liao, Y.; Venhuis, B. J.; Rodenhuis, N.; Timmerman, W.; Wikstrom, H.; Meire, E.; Bartoszyk, G. D.; Bottcher, H.; Seyfried, C. A.; Sundell, S. *J. Med. Chem.* **1999**, *42*, 2235. (e) Robl, J. A.; Sun, C.-Q.; Stevenson, J.; Ryono, D. E.; Simpkins, L. M.; Cimarusti, M. P.; Dejneka, T.; Slusarchyk, W. A.; Chao, S.; Stratton, L.; Misra, R. N.; Bednarz, M. S.; Asaad, M. M.; Cheung, H. S.; Abboa-Offei, B. E.; Smith, P. L.; Mathers, P. D.; Fox, M.; Schaeffer, T. R.; Seymour, A. A.; Trippodo, N. C. *J. Med. Chem.* **1997**, *40*, 1570.

(5) To our knowledge, only three instances of related oxazepine-based sugar hybrids are documented in the literature, see: (a) Abrous, L.; Hynes, J. Jr.; Friedrich, S. R.; Smith, A. B. III; Hirschmann, R. *Org. Lett.* **2001**, *3*, 1089. (b) Tripathi, S.; Singha, K.; Achari, B.; Mandal, S. B. *Tetrahedron* **2004**, *60*, 4959. (c) François-Endelmond, C.; Carlin, T.; Thuery, P.; Loreau, O.; Taran, F. *Org. Lett.* **2010**, *12*, 40.

(6) (a) McEvoy, F. J.; Greenblatt, E. N.; Osterberg, A. C.; Allen, G. R. Jr. *J. Med. Chem.* **1970**, *13*, 295. (b) Yale, H. L.; Sowinski, F. *J. Med. Chem.* **1964**, *7*, 609. (c) Yale, H. L.; Beer, B.; Pluscec, J.; Spitzmiller, E. R. *J. Med. Chem.* **1970**, *13*, 713. (d) Yale, H. L.; Sowinski, F. *J. Med. Chem.* **1967**, *10*, 1022. (e) Allen, R. C.; Reitano, P. A.; Urbach, H. *J. Med. Chem.* **1978**, *21*, 838. (f) Mishra, J. K.; Panda, G. *J. Comb. Chem.* **2007**, *9*, 32. (g) Sridharan, V.; Maiti, S.; Menendez, J. S. *J. Org. Chem.* **2009**, *74*, 9365.

(7) Wang, J.; Li, J.; Tuttle, D.; Takemoto, J. Y.; Chang, C.-W. T. *Org. Lett.* **2002**, *4*, 3997.

(8) Cox, R. J.; Ritson, D. J.; Dane, T. A.; Berge, J.; Charmant, J.; Kantacha, A. *Chem. Commun.* **2005**, 1037.

(9) Procedures for the synthesis of new deoxysugar azides are described in the Supporting Information; see also: (a) Nicolaou, K. C.; Hwang, C. K.; Marron, B. E.; DeFrees, S.; Couladouro, E. A.; Abe, Y.; Carrol, P. J.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 3040. (b) Delgado, M.; Martin, J. D. *J. Org. Chem.* **1999**, *64*, 4798. (c) Yadav, J. S.; Prathap, I.; Tadi, B. P. *Tetrahedron Lett.* **2006**, *47*, 3773. (d) Kucera, D.; Haley, G. J.; Rueden, E. J.; Wang, T. WO 140549, **2008**; *Chem. Abstr.*, **2008**, *149*, 576804. (e) Wu, X.; Tang, X.; Xian, M.; Braunschweiger, P. G.; Wang, P. G. *Bioorg. Med. Chem.* **2002**, *10*, 2303. (f) Fan, Q.-H.; Ni, N.-T.; Li, Q.; Zhang, L.-H.; Ye, X.-S. *Org. Lett.* **2006**, *8*, 1007.