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Skeletal Diversity from Carbohydrates: Use of Mannose for the Diversity-Oriented Synthesis of Polyhydroxylated Compounds

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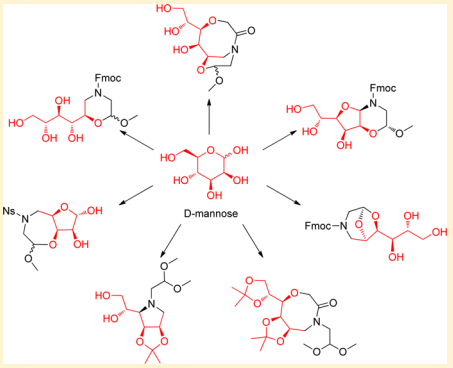
Supporting Information

ABSTRACT: The application of D-mannose as a multipurpose building block from the chiral pool enabled the diversity-oriented synthesis of an array of cyclic and bicyclic scaffolds with polyhydroxylated appendages with the aim to expand the skeletal diversity in the panorama of glycopeptidomimetic compounds.



INTRODUCTION

The screening of small molecule libraries represents a relevant and powerful approach in early stage drug discovery, with the aim of identifying hit candidates for the development of new drug leads. In this context, several approaches have been proposed to improve the quality and quantity of small molecules representing a library. Natural product structures have been taken into account for the construction of natural product-like libraries by virtue of the intrinsic chemical and structural diversity,[1] and the capability to exert potency, selectivity toward a wide number of targets, as well as the capability to cross biological membranes.

Diversity-Oriented Synthesis (DOS) was introduced by Schreiber in 2000[2] as a new paradigm for developing large collections of structurally diverse small molecules as probes to investigate biological pathways and to provide a larger array of the chemical space in drug discovery issues.[3] The objectives of DOS involve the development of synthetic pathways leading to the efficient production of small molecule collections having skeletal and stereochemical diversity within the chemical space. The principles of DOS have evolved from the concept of generating structurally diverse compounds through a complexity-generating reaction, followed by cyclization steps and appendage diversity, to the development of different cyclic structures through the build/couple/pair approach.[4] DOS concepts have been applied to create natural product-inspired libraries[5] by developing "drug-like" natural product-derived small molecule fragments capable of retaining the features of chemical and structural diversity and to fulfill the Lipinski's guidelines of drug-like properties.[6]

Carbohydrates are valuable scaffolds as molecular platforms for the generation of high-quality small molecule collections, taking advantage of their stereochemical diversity, structural bias, and polyfunctional opportunity, which has been exploited since the 90s in traditional combinatorial chemistry.[7] Some contributions on the application of carbohydrates or their derivatives in DOS have appeared in the literature recently, employing D-glucose,[8] D-mannitol,[9] C-glycosides,[10] glycals,[11] and vinyl sulfone-modified furanosides.[12] Nevertheless, only few of such papers accounted for the exploitation of carbohydrate scaffolds and their functionalities to develop skeletal diversity around such moieties.[9,10a]

Polyhydroxylated natural products (Figure 1) occupy a relevant position in biomedical issues, as they are carriers of attractive biological properties. Some examples include Hunanamycin A, which is a natural compound with a polyhydroxylated chain possessing antibiotic properties,[13] or 1-deoxynojirimycin (DNJ), and 1-deoxymannojirimycin, commonly known as iminosugars or iminocyclitols, which are widely found in plants and microorganisms and are valuable carbohydrate mimetics for their biological properties.[14] Pyrrolizidine alkaloids are other polyhydroxylated natural scaffolds that are considered as potential antibacterial, antiviral, antitumor, antidiabetic, immunostimulators, or anti-inflammatory agents.[15]

Our previous contribution to DOS consisted of the generation of peptidomimetic scaffolds according to a couple/pair approach, and one-pot approaches to generate skeletal diversity upon tuning the reaction process.[16] Representative peptidomimetic libraries proved to identify novel modulators of cell growth in yeast as a whole cell model for chemical genetics studies.[17] Thus, our interest in the development of DOS libraries of natural-inspired scaffolds

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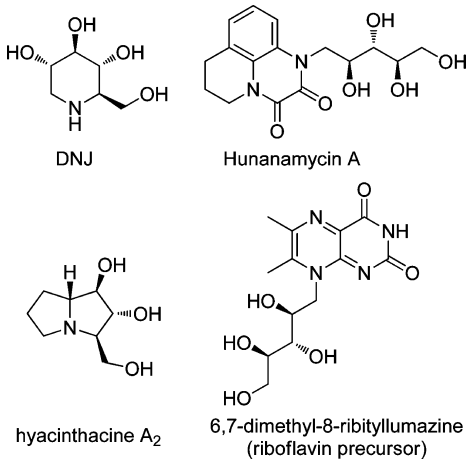


Figure 1. Representative small molecule polyhydroxylated natural products.

moved from the application of amino acid derivatives to build peptidomimetics, to the exploitation of sugar moieties so as to generate complex molecular scaffolds using building blocks from the two families of the chiral pool. Indeed, the application of carbohydrates allows for the generation of polyhydroxylated nitrogen-containing scaffolds bearing side-chain appendages, which incorporate both chemotypes from the domains of sugars and amino acids.

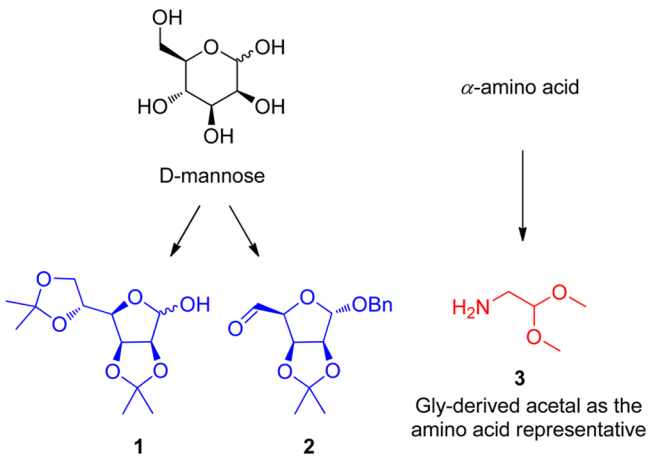
We reasoned to develop a DOS strategy[4] exploiting coupling and functional group-pairing approaches to integrate building blocks from D-mannose and glycine as a case study. The sugar moiety was exploited to address two diverse starting molecules being applied to different coupling reactions with glycine-derived aminoacetaldehyde dimethylacetal as the amino acid representative, in order to promote a *trans*-acetalization reaction as one of the possible pairing reactions.

RESULTS AND DISCUSSION

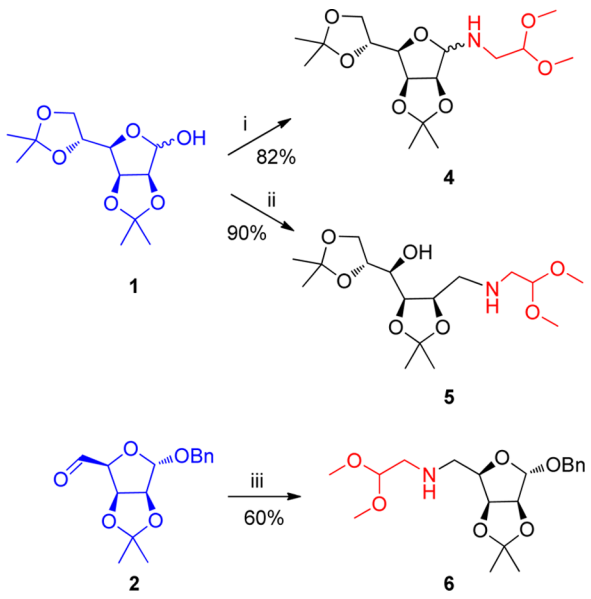
Di-isopropilidene-D-mannose compound **1**, and benzyl-isopropylidene lyxaric aldehyde **2**,[18] easily obtained from D-mannose, were taken into account for the generation of diverse building blocks exploiting D-mannose (Scheme 1).

In order to access compounds containing chemical moieties from both carbohydrates and amino acids, a coupling stage between **1** or **2** and **3**, as the glycine derivative, consisted of a reductive amination to exploit the reactivity of the carbonyl group with the amino acid-derived counterpart. The reaction of **1** with amino acetal **3** under standard reaction conditions for reductive amination resulted in the synthesis of aminal **4** as a 3:1 mixture of two unseparable anomers, as shown by the integration of NMR signals corresponding to the CH_2-N moiety. Upon addition of $LiAlH_4$ as a stronger reducing agent to the intermediate aminal, complete reduction of the aminal to the corresponding δ-amino alcohol **5** was achieved. Reductive amination of benzyl-isopropilidene lyxaric aldehyde **2** using $NaBH_3CN$ as the reducing agent resulted in clean conversion to the corresponding amine **6** in 60% yield (Scheme 2).

Scheme 1. Building Blocks Generation from D-Mannose and from Glycine as the Reference Amino Acid Counterpart



Scheme 2. Chemical Diversity Resulting from the Coupling Stage[a]



[a]Reagents and conditions: (i) $NH_2CH_2CH(OMe)_2$, $MgSO_4$, MeOH, reflux, 48 h; (ii) $NH_2CH_2CH(OMe)_2$, $MgSO_4$, MeOH, reflux, 48 h, then $LiAlH_4$, dry THF, r.t., 4 h; (iii) $NH_2CH_2CH(OMe)_2$, $NaBH_3CN$, 3 Å MS, dry CH_3CN, EtOH, r.t., 48 h.

The coupling stage was repeated on adducts **4**–**6** to introduce further diversity around such molecules and to enable subsequent DOS-driven pairing reactions (Scheme 3). Acylation of all mannose-derived amino acetals at the nitrogen atom was conceived to deactivate the basic character of the amino group for the subsequent pairing step under acid-catalized *trans*-acetalization conditions. Fmoc protection of **4** resulted in clean conversion, and successful chromatographic separation gave the corresponding anomers **7a** and **7b** in a 3:1 ratio. Higher diversity was introduced by reiterating the coupling stage on δ-amino alcohol **5**, taking advantage of both the amino and the hydroxylic functional groups. Acylation of the amino group with Fmoc, Cbz, or α-bromoacetyl group to achieve the corresponding compounds **8**–**10** in 60–67% yield was carried out for subsequent exploitation of the reactivity of the hydroxylic group as a nucleophile. Tosylation of the amino acetal **6** coming from lyxaric aldehyde produced the corresponding adduct **11** in 42% yield under standard reaction conditions. Also, the nosyl group was considered as a protecting group for the amine of **6**, giving compound **12** in 49% yield.

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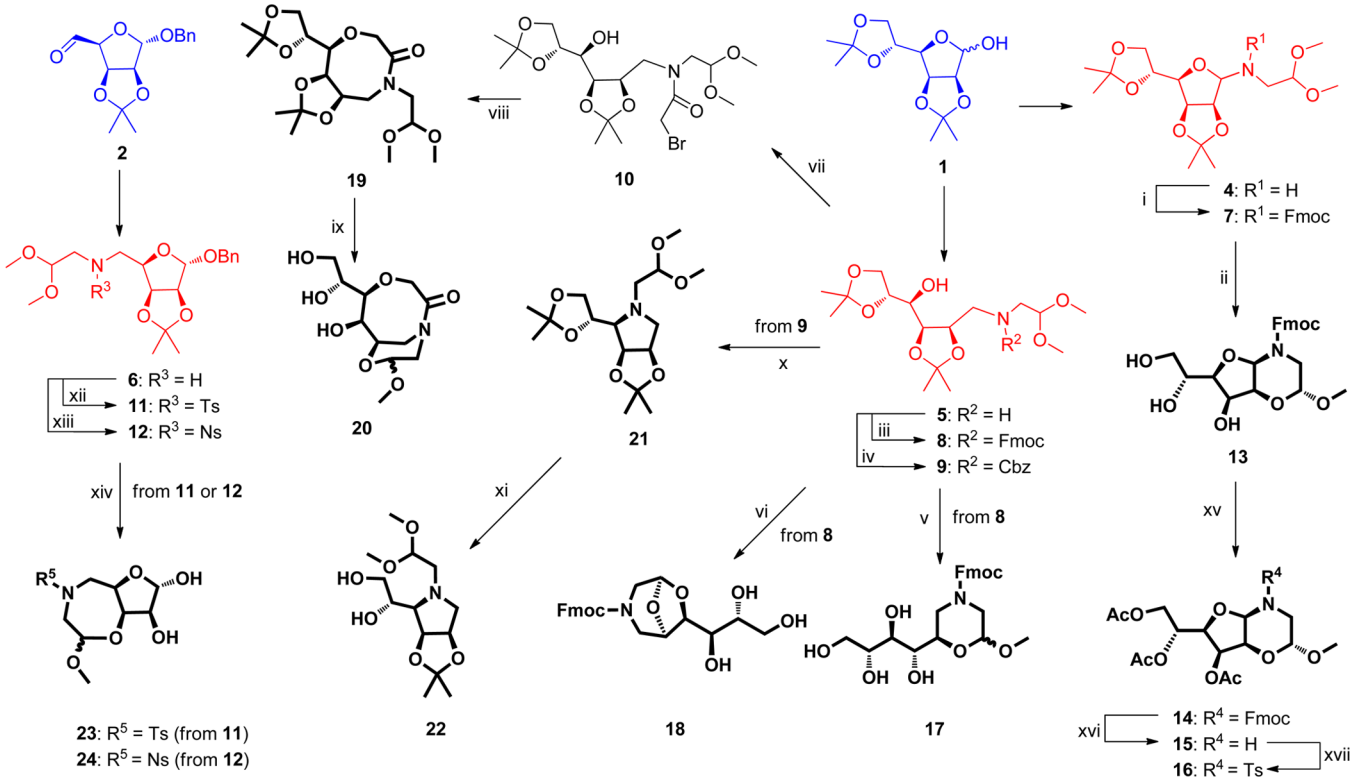
Scheme 3. Comprehensive Chart of DOS around D-Mannose: Building Blocks Are in Blue, Compounds Resulting from First Coupling Stage Are in Red, Final Scaffolds Are in Bold[a]



[a]Reagents and conditions: (i) Fmoc-Cl, H_2O−dioxane, $NaHCO_3$, 0 °C to r.t., 24 h, 87% (combined yield); (ii) TFA, neat, r.t., 2 h, 76% from **7a** and 73% from **7b**; (iii) Fmoc-Cl, H_2O−dioxane, $NaHCO_3$, 0 °C to r.t., 24 h, 61%; (iv) Cbz-Cl, TEA, dry THF, 0 °C to r.t., 24 h, 67%; (v) TFA−MeOH (99:1), r.t., 20 min, 73%; (vi) TFA−MeOH (99:1), r.t., 4 h, 50%; (vii) bromoacetyl bromide, Et_3N, dry CH_2Cl_2, −15 °C, 1 h, 60%; (viii) NaH, dry THF, 0 °C to r.t., 1 h, 78%; (ix) TFA, neat, r.t., 2 h, 42%; (x) PDC, Ac_2O, dry CH_2Cl_2, reflux, 90 min, then H_2, 10% Pd/C, MeOH, r.t., 16 h, 87%; (xi) TFA−MeOH (1:1), r.t., 2 h, 90%; (xii) TsCl, DIPEA, dry CH_2Cl_2, 0 °C to r.t., 18 h, 42%; (xiii) NsCl, DIPEA, dry CH_2Cl_2, 0 °C to r.t., 3 h, 49%; (xiv) TFA, neat, r.t., 2 h, 46% for **23** and 48% for **24**; (xv) Ac_2O, dry pyridine, r.t., 16 h, 55%; (xvi) Et_2NH−CH_3CN (3:7), r.t., 2 h, 85%; (xvii) TsCl, DIPEA, dry CH_2Cl_2, 0 °C to r.t., 24 h, 41%.

With all of this pool of compounds in hand, a series of pairing reactions were envisaged in order to achieve skeletal diversity around such mannose- and glycine-derived scaffolds (Scheme 3). The existence of polyhydroxylated species and the acetal moiety coming from the amino acid derivative **3** (Scheme 1) opened the way to intramolecular *trans*-acetalizations as the key pairing processes in the assembly of diverse scaffolds. The formation of cyclic acetals is an important issue in the development of small molecules as this chemical moiety is widespread in the panorama of bioactive natural products, especially those of the class of polyketides.

Upon treatment of the major anomer **7a** under neat TFA, the corresponding bicyclic *cis*-fused scaffold **13** was achieved in 76% yield as a single anomer, resulting from the acetalization of the C-3a hydroxyl group of **7a** to the dimethyl acetal carbon atom. Interestingly, the same scaffold was achieved similarly starting from the anomer **7b**, as a consequence of thermodynamic equilibration of *N*-Fmoc aminal intermediate species under acidic treatment, in agreement with similar *N*-acyl aminals as reported in the literature.[19] Benzoyl and tosyl analogues of **7a**/**7b** failed to give the corresponding bicyclic **13** and provided degradation products, as a consequence of the reduced stability of the *N*-acyl moiety (unpublished data). The existence of a single anomeric species for **13** consisting of a *cis*-adduct in a 1:1 mixture of rotamers around the C−N bond of the Fmoc group was established by detailed NMR study of the corresponding fully acetylated compound **14** (see Figure 2 and the Supporting Information for detailed NMR data).

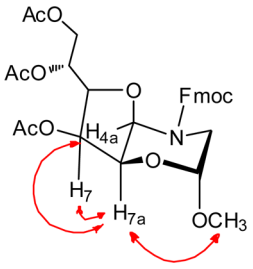


Figure 2. Selected NOE contacts from NOESY1D spectra of **14**.

In particular, the ^1H NMR signals at 5.37 and 4.99 ppm attributable to proton H-4a appeared as singlets and showed similar correlation to overlapping carbon signals at 77.3 ppm on the HSQC spectrum, suggesting the existence of a 1:1 ratio of rotamers possessing a similar NMR structure. This was ascertained by NOESY1D experiments carried out with a mixing time of 500 ms, which allowed for the identification of proton resonances from different rotameric species by the appearance of rotameric protons in the same phase as of the corresponding irradiated proton during chemical-exchange experiments, as reported in the literature.[20] The *cis*-fusion was

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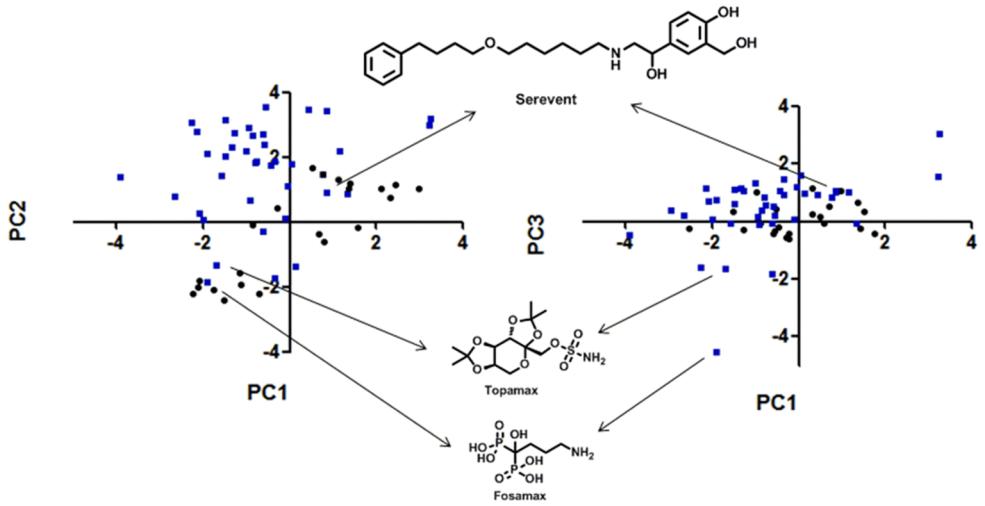

Figure 3. PCA plot resulting from the correlation between PC1 vs PC2 (left), and PC1 vs PC3 (right), showing the positioning in the chemical space of mannose-derived DOS compounds (black dots) with respect to the reference set of brand-name blockbuster drugs (blue squares).

evinced by NOESY1D experiments showing intense NOE effects between H-4a and H-7a protons, and the *endo* anomer was assessed by NOE effect between H-7a and OCH_3 protons, the latter being found in the axial orientation (see Figure 2 and the Supporting Information). The Fmoc-derivative **14** was successfully deprotected with a 30% solution of Et_2NH in acetonitrile, demonstrating full stability of the bicyclic aminal scaffold **15**. The potential of **15** for follow-up combinatorial chemistry was exemplified by sulfonylation at the amino group with TsCl, resulting in the synthesis of **16** in 41% yield.

Fmoc-protected scaffold **8** was subjected to the same acid conditions to achieve pairing between the glycine-derived moiety and the hydroxyls of the parent mannose compound. In this event, accurate optimization of the reaction time enabled a divergent approach in the pairing phase to achieve two different scaffolds. Specifically, upon treatment of **8** with TFA containing 1% of methanol at room temperature, the corresponding morpholine derivative **17** containing a polyhydroxylated chain at position 5 was obtained in about 20 min, the process being followed by careful TLC monitoring. Upon prolonged treatment to 4 h under the same conditions, an intramolecular *trans*-acetalization between the hydroxyl group adjacent to the morpholine ring and the acetal carbon atom of **17** gave the corresponding bicyclic adduct **18** possessing the azabicyclo-[3.2.1]octane structure, together with a small amount of residual morfoline product **17**, easily separable by chromatography. The formation of the bicyclic product was clearly shown by the disappearance of the acetal proton signal of **17** at 3.44 ppm, and the appearance of the diagnostic bridgehead acetal proton signal at 5.45 ppm, in agreement with similar bicyclic compounds reported in the literature.[21]

Compound **10** was subjected to a pairing reaction exploiting the free OH group for the intramolecular nucleophilic substitution on the reactive α-bromoacetyl species upon treatment with NaH to attain the corresponding eight-membered ring lactam **19** in 78% yield. Attempts to selectively provide the free aldehyde function for further chemical manipulations using TFA in a biphasic water−chloroform solvent failed to proceed. A second pairing reaction on **19** to obtain a second cyclization through *trans*-acetalization was achieved in lower yield upon treatment with TFA, possibly due to ring strain of the resulting deprotected bicyclic scaffold **20** as a 1:1 mixture of anomers.

The pairing approach using the free OH as the nucleophile upon activation with NaH was also attempted on Cbz-protected compound **9** to achieve the corresponding seven-membered cyclic carbamate. Nevertheless, deprotected **5** was achieved after treatment with TFA, as a consequence of Cbz deprotection during the reaction of **9** with the hydride. Oxidation of the free hydoxyl group of Cbz-protected compound **9** with PDC to the corresponding ketone was considered to exploit the reactivity of the amino group as a nucleophile. The successful pairing reaction of the intermediate ketone was obtained upon hydrogenolysis of the Cbz group, which enabled the reductive amination of the carbonyl moiety with the free amino group under reducing conditions, giving the corresponding protected pyrrolidine **21** in 87% yield. The stereochemistry of the newly formed stereocenter was established by analyzing the values of the coupling constants between the protons of the pyrrolidine ring, according to data reported in the literature.[22] Selective deprotection of the terminal diol moiety was achieved by reacting compound **21** with a 1:1 TFA−MeOH mixture, giving the corresponding bicyclic compound **22** in 90% yield. Upon treatment of **22** under harsher acidic conditions, by refluxing the compound in 6 M HCl for 3 h, unidentified compounds were obtained, possibly resulting from elimination and rearrangement processes. As for **19**, attempts to provide the free aldehyde function from the dimethylacetal moiety using TFA in a biphasic water−chloroform solvent failed to proceed. Finally, the acetalization of lyxaric aldehyde-derived **11** and **12** by reaction under neat TFA conditions for 2 h gave the corresponding bicyclics scaffolds **23** and **24** in 46% and 48% yield, respectively, containing a seven-membered ring acetal.

Chemoinformatic Analysis. The structural features of this DOS library of mannose-derived scaffolds were analyzed in terms of chemical properties and shape analysis in the context of the chemical space[23] using principal component analysis (PCA) and principal moments of inertia (PMI) analysis. PCA is a statistical tool to condense multidimensional chemical properties (i.e., molecular weight, logP, ring complexity) into single dimensional numerical values (principal components), to simplify the comparison with different sets of compounds.[24]

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ChemGPS-NP[25] was chosen for the PCA analysis, as it is an easy web-based public tool useful for comprehensive chemical space navigation and exploration in terms of global mapping onto a consistent 8-dimensional map of structural characteristics.[26] The first four dimensions of the ChemGPS-NP map capture 77% of data variance. The first dimension PC1 (principal component one), represents size, shape, and polarizability (main contribution is size); PC2 is associated with aromatic and conjugation related properties (main influence is aromaticity); PC3 describes lipophilicity, polarity, and hydrogen-bond capacity (major contribution is lipophilicity); and PC4 expresses flexibility and rigidity. In our study, the chemical compounds **4**−**24** were positioned onto this map using interpolation in terms of PCA score prediction, and their chemical properties were analyzed using PCA and compared with a reference set of 40 brand-name blockbuster drugs using the protocols employed by Tan and co-workers,[27] specifically analyzing the positioning of the compounds in plots PC1 versus PC2 and PC1 versus PC3 (Figure 3).

The analysis of PC1 vs PC2 resulted in DOS compounds belonging to three clusters, the first being positioned in the negative direction of both axes, the second in the center of the graph, and the third in the opposite quadrant, due to diverse size (PC1) and aromaticity (PC2) content. Interestingly, the first cluster showed good overlapping with the structures of Fosamax and Topamax (Figure 3), both possessing OH moieties and the latter interestingly showing both acetal and diisopropylidene moieties. The third cluster showed good overlapping with Serevent (Figure 3), possessing a polyol structure and a hydrophobic chain, suggesting similarity of PC1 and PC2 descriptors with mannose-derived molecules in their *N*-protected form.

In the plot described by PC1 vs PC3 dimensions, a grouping into two clusters was observed, mainly due to the effect of the protecting groups, as PC1 is affected mainly by size and PC3 to the greatest degree by calculated log *P* values, and the number of rings, which together shift the protected compounds in a positive direction along both PC1 and PC3 axes. Although poorer in the number of elements of the library, the mannose-derived collection showed better diversity on the PC3 axis than BB drugs.

Principal moment of inertia (PMI) analysis was taken into account for the 3D molecular shape analysis of polyhydroxylated DOS compounds in the context of chemical space and compared to molecules of the above reference set of BB drugs.[27] PMI analysis was carried out by calculation of the lowest energy conformation of each representative compound of the mannose-derived DOS library, and of each molecule from the reference set using VegaZZ software.[28] Then, the three principal moments of inertia (I_{xx}, I_{yy}, I_{zz}) and the corresponding normalized principal moments of inertia were determined according to Sauer and Schwarz[29] for all polyhydroxylated DOS compounds and the reference blockbuster drugs. Specifically, the three calculated principal moments of inertia were sorted by ascending magnitude I_1, I_2, and I_3. All the normalized PMI ratios (I_1/I_3 and I_2/I_3) were plotted on a triangular graph where the vertices (0,1), (0.5,0.5), and (1,1) represent a perfect rod (i.e., 2-butyne), disc (i.e., benzene), and sphere (i.e., adamantane), respectively (Figure 4).

Mannose-derived compounds were found to lie along the center-left side of the triangle, with a preference for the rod−disc side. This positioning showed mannose-derived compounds possessing lower tendency to stay in the rod side of the triangle and major dispersion in the space, as compared to BB drugs, suggesting higher shape diversity for these compounds as compared to BB drugs, which showed higher tendency to lie along the rod−disc axis. Interestingly, compounds **6** and **20** proved to be positioned in the disc−sphere side of the triangle, demonstrating a quite diverse shape as compared to BB drugs and the other elements of the library. Also, compounds **13** and **17** proved to be positioned to the rod−sphere region, indicating good coverage within shape diversity as a function of extent of scaffold decoration with hydrophobic groups (i.e., Fmoc) and polyhydroxylated chains.

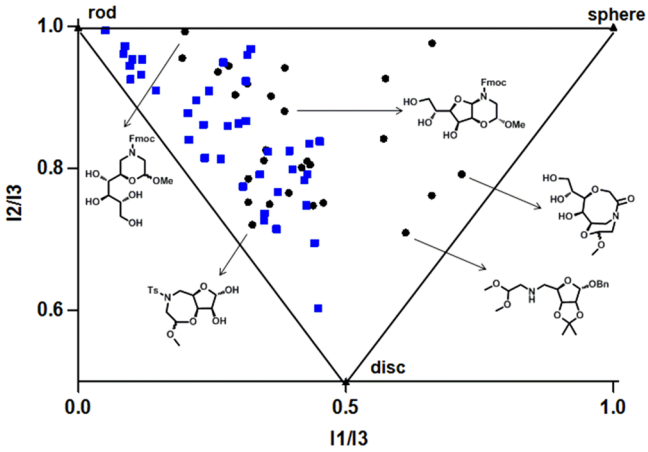

Figure 4. PMI plot showing the skeletal diversity of mannose-derived DOS compounds (black dots) with respect to the reference set of brand-name blockbuster drugs (blue squares).

The PMI analysis suggested that the skeletal diversity coming from the exploitation of mannose- and glycine-derived acetal according to the build-couple-pair approach resulted in an array of molecules spanning in the chemical space despite the limited number of representatives, as compared to brand-name blockbuster drugs. This feature is promising in view of expanding the array of reactions on such carbohydrate-derived building blocks and for generating natural product-like chemical libraries carriers of high molecular diversity and complexity.

■ CONCLUSIONS

Novel small molecule chemotypes are needed in modern phenotype screening to investigate biological mechanisms and to select both new targets and ligands for drug discovery issues. Diversity-Oriented Synthesis is the approach of choice to meet this issue as it enables innovative concept routes for chemical methodology and library development. The combination of carbohydrate and amino acid derivatives in building novel glyco- and peptidomimetic scaffolds is powerful for stereochemically dense skeletal diversity and follow-up combinatorial chemistry. Mannose was exploited as a case study to develop an array of skeletally diverse molecules in DOS fashion using the build-couple-pair approach. Specifically, the protected sugar derivative was subjected to coupling reaction with aminoacetaldehyde dimethyl acetal as a reference amino acid derivative possessing a protected carbonyl function for subsequent pairing steps. The diversity of the pool of scaffolds herein obtained was characterized in terms of shape and chemical properties using PMI and PCA analysis and compared to a reference set of BB drugs, demonstrating mannose as a powerful building block to generate highly diverse compounds

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when applied to DOS chemistry. Such an approach can be beneficial in generating high-quality combinatorial libraries in exploiting the hydroxyl groups for appendage diversity. Also, the combination of polyhydroxylated and hydrophobic moieties may result in novel and unexplored resources for addressing protein−protein interactions in drug discovery programs.

EXPERIMENTAL SECTION

General. Analytical grade solvents and commercially available reagents were used without further purification. Reactions requiring an inert atmosphere were carried out under an argon atmosphere. Flash chromatography was performed using 32−63 μm silica gel (60 Å mesh) with the indicated solvent. Analytical thin-layer chromatography (TLC) was performed on 0.25 mm silica gel 60-F plates. Melting points are uncorrected. ^{1}H NMR spectra were acquired on 400 MHz spectrometers. ^{13}C NMR spectra were acquired at 100 and 50 MHz. All chemical shifts are reported in parts per million (δ) referenced to residual nondeuterated solvent. Data are reported as follows: chemical shifts, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constant(s) in Hz; integration). ESI mass spectra were carried out on a ion-trap double quadrupole mass spectrometer using electrospray (ES^+) ionization techniques, and a normalized collision energy within the range of 25−32 eV for MSMS experiments.

(3a*S*,4*R*/*S*,6*R*,6a*S*)-*N*-(2,2-Dimethoxyethyl)-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2dimethyltetrahydrofuro[3,4-*d*][1,3]-dioxol-4-amine (4). To a solution of di-isopropilidene-D-mannose **1** (200 mg, 0.77 mmol) and 2,2-dimethoxy-ethylamine (125 μL, 1.15 mmol) in MeOH (5 mL), $MgSO_4$ (200 mg, 1.18 mmol) was added, and the reaction mixture was left stirring at reflux for 48 h. $MgSO_4$ was then removed by filtration through Celite, and the filtrate was concentrated under vacuum to give a yellow crude product. Flash chromatography (EtOAc/Petr. et. = 1:2, buffered with 1% Et_3N; R_f = 0.17) afforded compound **4** (216 mg, 0.62 mmol, 82%) as a yellow oil. NMR spectroscopy revealed that compound **4** was obtained as a 3:1 mixture of α:β anomers. ^{1}H NMR (400 MHz, $CDCl_3$) 3:1 mixture of anomers: δ 4.71 (m, 0.5H, minor), 4.70 (s, 0.75H, Major), 4.63 (dd, J = 6.1, 3.3 Hz, 0.75H, Major), 4.58 (d, J = 5.6 Hz, 0.25H, minor), 4.53 (dd, J = 6.7, 3.3 Hz, 0.75H, Major), 4.47−4.30 (m, 3H), 4.05−4.01 (m, 2H), 3.87 (dd, J = 11.1, 7.8 Hz, 0.25H, minor), 3.38 (dd, J = 7.0, 3.4 Hz, 0.75H, Major), 3.36 (s, 3H), 3.34 (s, 3H), 2.99 (dd, J = 13.2, 5.7 Hz, 0.75H, Major), 2.80 (dd, J = 13.2, 5.7 Hz, 1H), 2.69 (dd, J = 12.9, 5.7 Hz, 0.25H, minor), 1.44 (s, 3H), 1.41 (s, 0.75H, minor), 1.40 (s, 2.25H, Major), 1.34 (s, 3H), 1.29 (s, 2.25H, Major), 1.28 (s, 0.75H, minor). ^{13}C NMR (50 MHz, $CDCl_3$) 3:1 mixture of anomers: δ 112.6 and 112.4, 109.2 and 109.0, 104.6 and 103.7, 95.1 and 92.0, 85.7 and 80.2, 79.8 and 79.6, 79.1 and 77.5, 73.4 and 73.3, 66.93 and 66.86, 54.2 and 54.0, 53.8, 48.3 and 47.0, 26.9 and 25.7, 26.0, 25.3 and 24.6, 25.2. MS (ESI) m/z (%): 348.05 [$(M + H)^+$, 100]; MSMS (ESI) m/z (%): 348.05 [$(M + H)^+$, 10], 316.01 (97), 285.97 (100), 257.92 (23). Anal. Calcd for $C_{16}H_{29}NO_7$: C, 55.32; H, 8.41; N, 4.03. Found: C, 55.38; H, 8.45; N, 4.00.

(*R*)-((4*S*,5*R*)-5-(((2,2-Dimethoxyethyl)amino)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-methanol (5). To a solution of di-isopropilidene-D-mannose **1** (115 mg, 0.43 mmol) and 2,2-dimethoxy-ethylamine (60 μL, 0.52 mmol) in MeOH (5 mL), $MgSO_4$ (100 mg, 0.86 mmol) was added, and the reaction mixture was left stirring at reflux for 48 h. $MgSO_4$ was then removed by filtration through Celite, and the filtrate was concentrated under vacuum to give a yellow crude product. The crude product was dissolved in dry THF (4 mL); then a stirred suspension of $LiAlH_4$ (49 mg, 1.30 mmol) in dry THF (4 mL) was added dropwise at 0 °C. The mixture was left reacting at room temperature for 4 h. $LiAlH_4$ was quenched with MeOH (5 mL) and H_2O (5 mL). The resulting salts were removed by filtration through Celite, and the filtrate was concentrated under vacuum, to give a crude product, which was purified by flash chromatography (EtOAc/Petr. et. = 3:1; R_f = 0.29), affording compound **5** (135 mg, 0.39 mmol, 90%), as a white powder. mp 83.7−84.8 °C. $[\alpha]_D^{24}$ = +14.5 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.48 (t, J = 5.5 Hz, 1H), 4.44 (d, J = 8.0 Hz, 1H), 4.40−4.32 (m, 1H), 4.16−4.12 (m, 2H), 4.07−4.04 (m, 1H), 3.50 (d, J = 8.0 Hz, 1H), 3.38 (s, 6H), 3.10 (dd, J = 12.9, 4.1 Hz, 1H), 2.84−2.81 (m, 1H), 2.78 (d, J = 5.5 Hz, 2H), 1.51 (s, 3H), 1.40 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 109.1, 107.8, 103.2, 76.3, 75.9, 75.3, 70.5, 67.8, 54.3, 54.2, 50.6, 47.9, 26.9, 26.2, 25.3, 24.4. MS (ESI) m/z (%): 350.10 [$(M + H)^+$, 100]; MSMS (ESI) m/z (%): 350.10 [$(M + H)^+$, 2], 318.11 (43), 285.97 (100), 259.99 (15), 228.02 (66). Anal. Calcd for $C_{16}H_{31}NO_7$: C, 55.00; H, 8.94; N, 4.01. Found: C, 55.11; H, 8.99; N, 3.92.

***N*-(((3a*S*,4*R*,6*S*,6a*S*)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)-2,2-dimethoxyethanamine (6).** To a solution of D-lixaric aldehyde[18] (500 mg, 1.80 mmol) in dry CH_3CN (3.5 mL), 2,2-dimethoxy-ethylamine (215 μL, 1.98 mmol) and 3 Å molecular sieves were added under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 1 h; then $NaBH_3CN$ (338 mg, 5.4 mmol) and EtOH (2.6 mL) were added. The reaction mixture was left stirring at room temperature for 2 days under a nitrogen atmosphere, and then concentrated under vacuum. The crude compound was purified by flash chromatography (EtOAc/Petr. et. = 2:1; R_f = 0.21) to obtain **6** (386 mg, 1.05 mmol, 60%) as a pure orange oil. $[\alpha]_D^{21}$ = +33.7 (c 0.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33−7.30 (m, 5H), 5.09 (s, 1H), 4.73−4.66 (m, 3H), 4.52−4.69 (m, 2H), 4.15 (q, J = 6.3 Hz, 1H) 3.40 (s, 6H), 3.40 (s, 2H), 2.98 (d, J = 6.3 Hz, 1H), 2.81 (d, J = 5.4 Hz, 1H), 1.45 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.4, 128.4 (2C), 128.0 (2C), 127.8, 112.4, 105.2, 103.7, 85.1, 80.1, 79.2, 68.9, 53.9 (2C), 51.3, 48.4, 26.0, 24.8. MS (ESI) m/z (%): 368.18 [$(M + H)^+$, 100]. Anal. Calcd for $C_{19}H_{29}NO_6$: C, 62.11; H, 7.96; N, 3.81. Found: C, 62.31; H, 7.99; N, 3.75.

(9*H*-Fluoren-9-yl)methyl-(2,2-dimethoxyethyl)-((3a*S*,4*R*,6*R*,6a*S*)-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)carbamate (7a) and (9*H*-Fluoren-9-yl)-methyl-(2,2-dimethoxyethyl)-((3a*S*,4*S*,6-*R*,6a*S*)-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)carbamate (7b). To a solution of **4** (214 mg, 0.61 mmol) in dioxane (3 mL) and water (6 mL) was added $NaHCO_3$ (103 mg, 1.23 mmol). The mixture was cooled to 0 °C; then a solution of Fmoc-Cl (159 mg, 0.61 mmol) in dioxane (3 mL) was added slowly. The mixture was left reacting at room temperature for 24 h under a nitrogen atmosphere; then it was diluted with EtOAc (20 mL). The organic phase was washed with 1 M HCl solution and brine, and dried over anhydrous Na_2SO_4. After solvent evaporation, the crude oil was purified by flash chromatography (EtOAc/Petr. et. = 1:3; R_f **7b** = 0.18, R_f **7a** = 0.32), thus affording compound **7b** (227 mg, 0.40 mmol, 65%) and compound **7a** (78 mg, 0.14 mmol, 22%), both as pure colorless oils. **7a**: $[\alpha]_D^{24}$ = +13.6 (c 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotamers: δ 7.76 (d, J = 7.4 Hz, 2H), 7.61 (br s, 2H), 7.40−7.33 (m, 4H), 5.03−4.93 (m, 2H), 4.56 (br, 2H), 4.42−4.22 (m, 4H), 4.12−3.98 (m, 4H), 3.28−3.26 (m, 1H), 3.24 (s, 6H), 1.45−1.24 (m, 12H). ^{13}C NMR (50 MHz, $CDCl_3$) mixture of rotamers: δ 156.0, 143.7 (2C), 141.4 and 141.3 (2C), 127.8 (2C), 127.2 (2C), 124.80 and 124.75 (2C), 120.0 (2C), 112.3, 108.8, 103.6, 96.6, 85.6, 84.3, 81.4, 76.5 and 76.3, 74.0, 66.7 and 66.5, 55.3, 54.9, 50.6, 47.4, 26.8, 26.1, 25.2, 24.4. MS (ESI) m/z (%):592.32 [$(M + Na)^+$, 100]. Anal. Calcd for $C_{31}H_{39}NO_9$: C, 65.36; H, 6.90; N, 2.46. Found: C, 65.49; H, 6.96; N, 2.39. **7b**: $[\alpha]_D^{24}$ = +40.3 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotamers: δ 7.75 (d, J = 7.4 Hz, 2H), 7.58 (br s, 2H), 7.34−7.29 (m, 4H), 5.40 (br s, 1H), 4.78−4.44 (m, 7H), 4.28 (t, J = 5.9 Hz, 1H), 4.12−3.81 (m, 3H), 3.60 (dd, J = 14.7, 5.3 Hz, 1H), 3.30 (s, 3H), 3.27 (s, 3H), 1.62−1.29 (m, 12H). ^{13}C NMR (50 MHz, $CDCl_3$) mixture of rotamers: δ 160.3 and 159.6, 143.9 (2C), 141.3 (2C), 127.7 and 127.6 (2C), 127.2 and 127.1 (2C), 124.9 (2C), 119.8 (2C), 112.6, 109.2, 105.3 and 102.8, 87.0 and 86.9, 79.3, 78.9, 78.5, 73.0, 67.4, 66.6, 53.1 (2C), 47.2, 45.5 and 45.4, 26.8, 25.5, 25.2, 23.9. MS (ESI) m/z (%): 592.32 [$(M + Na)^+$, 100]; MSMS (ESI) m/z (%): 592.32 [$(M + Na)^+$, 17], 382.15 (72), 370.17 (100), 338.13 (33). Anal. Calcd for $C_{31}H_{39}NO_9$: C, 65.36; H, 6.90; N, 2.46. Found: C, 65.52; H, 6.97; N, 2.37.

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(9*H*-Fluoren-9-yl)methyl-(2,2-dimethoxyethyl)(((4*R*,5*S*)-5-((*R*)-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)carbamate (8). To a solution of **5** (100 mg, 0.40 mmol) in dioxane (2 mL) and water (4 mL) was added $NaHCO_3$ (49 mg, 0.58 mmol). The mixture was cooled to 0 °C; then a solution of Fmoc-Cl (159 mg, 0.61 mmol) in dioxane (3 mL) was added slowly. The mixture was left reacting at room temperature for 24 h; then it was diluted with EtOAc (20 mL). The organic phase was successively washed with 1 M HCl solution and brine, and dried over anhydrous Na_2SO_4. After solvent evaporation, the crude oil was purified by flash chromatography (EtOAc/Petr. et. = 2:3; R_f = 0.32), giving compound **8** (102 mg, 0.18 mmol, 61%) as a pure colorless oil. $[\alpha]_D^{24}$ = +11.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotamers: δ 7.76 (d, *J* = 7.6 Hz, 2H), 7.61 (d, *J* = 7.3 Hz, 1H), 7.57 (d, *J* = 7.3 Hz, 1H), 7.42−7.38 (m, 2H), 7.34−7.30 (m, 2H), 4.61−4.53 (m, 2H), 4.46−4.33 (m, 2H), 4.23 (t, *J* = 5.6 Hz, 1H), 4.10−4.07 (m, 3H), 4.01−3.99 (m, 2H), 3.83−3.40 (m, 2H), 3.35 and 3.32 (s, 3H), 3.23 e 3.20 (s, 3H), 2.17 and 2.01 (d, *J* = 9.3 Hz, 2H), 1.57−1.21 (m, 11H), 0.89−0.84 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) mixture of rotamers: δ 156.1, 143.9 (2C), 141.3 (2C), 127.6 (2C), 127.1 (2C), 124.7, 124.5, 119.8 (2C), 109.3, 108.2, 103.5 and 103.0, 76.3, 76.1, 75.2, 70.2, 67.0, 66.5, 60.2, 54.7, and 54.3 (2C), 49.7 and 49.1, 48.2, 26.8, 25.2, 24.6, 14.1. MS (ESI) *m*/*z* (%): 1164.73 [(2M + Na)$^+$, 8], 594.33 [(M + Na)$^+$, 100]. MSMS (ESI) *m*/*z* (%): 594.33 [(M + Na)$^+$, 13], 536.23 (100), 384.21 (42). Anal. Calcd for $C_{31}H_{41}NO_9$: C, 65.13; H, 7.23; N, 2.45. Found: C, 65.28; H, 7.30; N, 2.40.

Benzyl-(2,2-dimethoxyethyl)(((4*R*,5*S*)-5-((*R*)-((*R*)-2,2-dimethyl-1,3-dioxolan-4yl)(hydroxy)-methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)carbamate (9). To a solution of **5** (500 mg, 1.43 mmol) and Et_3N (600 μL, 4.30 mmol) in anhydrous THF (5 mL), a solution of Cbz-Cl (408 μL, 2.86 mmol) in anhydrous THF (5 mL) was added at 0 °C. The mixture was allowed to reach room temperature and was left stirring under a nitrogen atmosphere for 24 h. Successively, the mixture was diluted with Et_2O, washed with $NaHCO_3$ saturated solution, 1 M HCl solution, and brine. Then, the organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by flash chromatography (EtOAc/Petr. et. = 1:3; R_f = 0.39) to give pure **9** (462 mg, 0.96 mmol, 67%) as a colorless oil. $[\alpha]_D^{20}$ = +30.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotamers: δ 7.35−7.32 (m, 5H), 5.16−5.12 (m, 2H), 4.54−4.25 (m, 3H), 4.08−3.87 (m, 3H), 3.76 and 3.72 (s, 1H), 3.65 and 3.62 (s, 1H), 3.49−3.21 (m, 7H), 2.16 and 2.08 (d, *J* = 11.6 Hz, 1H), 1.74 (d, *J* = 11.6 Hz, 1H), 1.45−1.30 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) mixture of rotamers: δ 156.2, 136.6, 128.5 (2C), 128.0 (2C), 127.9 and 127.7, 109.4, 108.3, 103.7 and 103.3, 76.3, 76.1, 75.3 and 75.2, 70.3, 67.3, 67.1 and 66.9, 54.7, 54.2, 50.0 and 49.8, 49.2 and 48.7, 26.9, 26.8, 25.2, 24.5. MS (ESI) *m*/*z* (%): 988.90 [(2M + Na)$^+$, 26], 506.38 [(M + Na)$^+$, 100]. Anal. Calcd for $C_{24}H_{37}NO_9$: C, 59.61; H, 7.71; N, 2.90. Found: C, 59.73; H, 7.82; N, 2.83.

2-Bromo-*N*-(2,2-dimethoxyethyl)-*N*-(((4*R*,5*S*)-5-((*R*)-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-(hydroxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)acetamide (10). To a solution of bromoacetyl bromide (50 μL, 0.57 mmol) and Et_3N (120 μL, 0.86 mmol) in CH_2Cl_2 (2 mL), a solution of **5** (200 mg, 0.57 mmol) in CH_2Cl_2 (2 mL), was added slowly at −15 °C. The resulting mixture was left stirring at the same temperature for 1 h. Then, the solvent was evaporated under reduced pressure, and the crude was purified by flash chromatography (EtOAc/Petr. et. = 1:1), affording pure compound **10** (161 mg, 0.34 mmol, 60%) as a yellow oil. $[\alpha]_D^{22}$ = +12.5 (*c* 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotamers: δ 4.51 (t, *J* = 5.8 Hz, 1H), 4.47−4.42 (m, 1H), 4.37−4.15 (m, 3H), 4.07−3.93 (m, 4H), 3.85−3.82 (m, 1H), 3.69−3.64 (m, 1H), 3.51−3.47 (m, 1H), 3.42 and 3.39 (s, 3H), 3.38 (s, 3H), 3.24−3.18 (m, 1H), 2.20 (br, 1H, OH), 1.47 and 1.45 (s, 3H), 1.39 and 1.37 (s, 3H), 1.32 and 1.31 (s, 5H), 1.11 and 1.09 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) mixture of rotamers: δ 168.2 and 168.1, 109.4, 108.6 and 108.3, 103.3 and 103.1, 76.0, 75.2 and 75.0, 74.9 and 74.3, 70.5 and 70.4, 66.9, 56. Three and 55.7, 55.3 and 55.2, 52.2, 50.3, 49.5 and 48.9, 27.3 and 27.2, 26.8 and 26.7, 25.3 and 25.2, 24.3, and 24.1. MS (ESI) *m*/*z* (%): 962.75 [(2M + Na)$^+$, 100], 492.17 [(M + Na)$^+$, 60], 469.92 [(M + H)$^+$, 90]). Anal. Calcd for $C_{18}H_{32}BrNO_8$: C, 45.96; H, 6.86; N, 2.98. Found: C, 46.09; H, 6.94; N, 2.90.

***N*-(((3a*S*,4*R*,6*S*,6a*S*)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)-*N*-(2,2-dimethoxyethyl)-4-methylbenzenesulfonamide (11).** To a solution of **6** (300 mg, 0.81 mmol) and DIPEA (306 μL, 1.62) in dry CH_2Cl_2 (7.5 mL), a solution of TsCl (200 mg, 1.06 mmol) in dry CH_2Cl_2 (7.5 mL) was added slowly at 0 °C. The mixture was allowed to reach room temperature and was left stirring under a nitrogen atmosphere overnight. Then, water was added slowly, and the resulting mixture was washed with a saturated solution of $NaHCO_3$ and brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by flash chromatography (EtOAc/Petr. et. = 1:4; R_f = 0.47) to give pure **11** (180 mg, 0.34, 42%). $[\alpha]_D^{20}$ = +40.7 (*c* 0.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.8 Hz, 2H), 7.36−7.25 (m, 7H), 4.98 (s, 1H), 4.67 (dd, *J* = 5.9, 3.9 Hz, 1H), 4.58 (d, *J* = 5.9 Hz, 1H), 4.58−4.57 (m, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.34 (d, *J* = 11.7 Hz, 1H), 4.20−4.16 (m, 1H), 3.75 (dd, *J* = 15.6, 3.4 Hz, 1H), 3.54−3.46 (m, 2H), 3.42 (dd, *J* = 11.2, 5.4 Hz, 1H), 3.37 (s, 3H), 3.35 (s, 3H), 2.37 (s, 3H), 1.40 (s, 3H), 1.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 137.2 (2C), 129.5 (2C), 128.5 (2C), 127.9 (2C), 127.8 (2C), 127.3, 112.5, 105.0, 103.8, 85.0, 80.1, 79.1, 68.7, 54.6, 54.4, 49.9, 47.9, 26.0, 24.8, 21.5; MS (ESI) *m*/*z* (%): 1064.50 [(2M + Na)$^+$, 100], 544.33 [(M + Na)$^+$, 82]. Anal. Calcd for $C_{26}H_{35}NO_8S$: C, 59.87; H, 6.76; N, 2.69. Found: C, 60.12; H, 6.80; N, 2.54.

***N*-(((3a*S*,4*R*,6*S*,6a*S*)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)-*N*-(2,2-dimethoxyethyl)-4-nitrobenzenesulfonamide (12).** To a solution of **6** (120 mg, 0.33 mmol) and DIPEA (113 μL, 0.66 mmol) in dry CH_2Cl_2 (3 mL), a solution of *p*-NsCl (86 mg, 0.39 mmol) in dry CH_2Cl_2 (3 mL) was added slowly at 0 °C. The mixture was allowed to reach room temperature and was left stirring under a nitrogen atmosphere for 3 h. Then, water was added slowly, and the resulting mixture was washed with a saturated solution of $NaHCO_3$ and brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by flash chromatography (EtOAc/Petr. et. = 1:3; R_f = 0.51) to give pure **12** (90 mg, 0.16 mmol, 49%). $[\alpha]_D^{23}$ = +46.9 (*c* 1.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.6 Hz, 2H), 7.98 (d, *J* = 8.6 Hz, 2H), 7.27−7.17 (m, 5H), 4.90 (s, 1H), 4.63 (dd, *J* = 5.9, 3.7 Hz, 1H), 4.53 (d, *J* = 5.9 Hz, 1H), 4.49−4.45 (m, 1H), 4.42 (d, *J* = 11.8 Hz, 1H), 4.28 (d, *J* = 11.8 Hz, 1H), 4.17−4.13 (m, 1H), 3.69 (dd, *J* = 15.6, 3.4 Hz, 1H), 3.52 (dd, *J* = 15.6, 8.0 Hz, 1H), 3.46 (dd, *J* = 15.1, 5.1 Hz, 1H), 3.36 (dd, *J* = 15.1, 5.1 Hz, 1H), 3.28 (s, 3H), 3.27 (s, 3H), 1.35 (s, 3H), 1.22 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 149.8, 146.2, 137.0, 128.6 (2C), 128.5 (2C), 127.9 (2C), 127.7, 123.9 (2C), 112.7, 105.3, 103.5, 85.0, 80.0, 78.8, 69.0, 54.8, 54.3, 49.4, 47.7, 26.0, 24.8; MS (ESI) *m*/*z* (%): 575.26 [(M + Na)$^+$, 100]; MSMS (ESI) *m*/*z* (%): 575.26 [(M + Na)$^+$, 20], 388.21 (22), 314.17 (100). Anal. Calcd for $C_{25}H_{32}N_2O_{10}S$: C, 54.34; H, 5.84; N, 5.07. Found: C, 54.61; H, 5.89; N, 5.01.

(2*R*,4a*R*,6*R*,7*S*,7a*S*)-(9*H*-Fluoren-9-yl)methyl-6-((*R*)-1,2-dihydroxyethyl)-7-hydroxy-2-methoxy-tetrahydro-2*H*-furo-[3,2-*b*][1,4]oxazine-4(3*H*)-carboxylate (13). Compound **7b** (78 mg, 0.14 mmol) was dissolved in trifluoroacetic acid (1 mL) and stirred at room temperature for 2 h. After TFA evaporation, the crude powder was dissolved in MeOH and filtered through Amberlite XAD-2 resin. After solvent evaporation, the crude product was purified by flash chromatography (CH_2Cl_2/MeOH = 30:1, R_f = 0.22), thus affording compound **13** as a colorless oil (45 mg, 0.10 mmol, 73%). With the same procedure, compound **13** (45 mg, 0.10 mmol, 76%) was obtained also from the diastereomer **7a** (76 mg, 0.13 mmol). HPLC analysis revelead that compound **13** was achieved as a single anomer. $[\alpha]_D^{20}$ = −30.2 (*c* 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotamers: δ 7.68 (d, *J* = 7.6 Hz, 2H), 7.48 (br s, 2H), 7.33−7.30 (m, 2H), 7.22−7.20 (m, 2H), 5.27 and 4.93 (s, 1H), 4.84 and 4.67 (s, 1H), 4.78−3.98 (m, 5H), 3.98−3.02 (m, 6H), 3.45 and 3.32 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) mixture of rotamers: δ 155.6,

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143.7 (2C), 141.3 (2C), 128.0 (2C), 127.1 (2C), 124.8 (2C), 120.0 (2C), 95.7 and 95.2, 78.7, 77.9, 73.2, 68.2, 67.7, 66.9 and 66.3, 62.1, 54.9, 46.9, 42.7. MS (ESI) *m/z* (%): 480.23 [(M + Na)$^+$, 100], 457.87 [(M + H)$^+$, 27]; MSMS (ESI) *m/z* (%) = 480.23 [(M + Na)$^+$, 11], 360.09 (71), 258.10 (100). Anal. Calcd for $C_{24}H_{27}NO_8$: C, 63.01; H, 5.95; N, 3.06. Found: C, 63.12; H, 5.99; N, 3.00.

(1*R*)-1-((2*R*,4a*R*,6*R*,7*S*,7a*S*)-4-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)-7-acetoxy-2-methoxy-hexahydro-2*H*-furo[3,2-*b*][1,4]oxazin-6-yl)ethane-1,2-diyl Diacetate (14). Compound **13** (54 mg, 0.12 mmol) was dissolved in pyridine (2 mL) and Ac_2O (1 mL) and stirred at room temperature overnight. Then, the solvent was evaporated under reduced pressure, and the crude was purified by flash chromatography (Et_2O/Petr. et. = 1:1, R_f = 0.20), affording pure compound **14** (38 mg, 0.07 mmol, 55%) as a colorless oil. $[\alpha]_D^{20}$ = −32.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) 1:1 mixture of rotamers: δ 7.78−7.76 (m, 2H), 7.58−7.56 (m, 2H), 7.42−7.40 (m, 2H), 7.33−7.31 (m, 2H), 5.37 and 4.98 (s, 1H), 5.35 and 5.31 (t, *J* = 10.1 Hz, 1H), 5.05 and 4.94 (dd, *J* = 10.1, 3.2 Hz, 1H), 4.81 (d, *J* = 5.9 Hz, 1H), 4.67 and 4.37 (dd, *J* = 9.7, 6.2 Hz, 1H), 4.51 and 4.27 (dd, *J* = 9.7, 2.6 Hz, 1H), 4.38 and 4.20 (s, 1H), 4.28−4.27 (m, 1H), 4.12 and 4.04 (d, *J* = 10.1 Hz, 2H), 3.88 and 3.82 (d, *J* = 13.1 Hz, 1H), 3.72−3.70 and 3.52−3.50 (m, 1H), 3.52−3.50 (m, 1H), 3.36 and 3.30 (s, 3H), 2.10−2.05 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) 1:1 mixture of rotamers: δ 170.7, 170.1, 169.6 and 169.5, 155.2 and 154.7, 143.5 (2C), 141.3 (2C), 127.8 and 127.1 (2C), 125.5 and 125.0 (2C), 124.8 (2C), 120.0 (2C), 95.6 and 95.2, 77.6, 73.3, 72.2, 68.2 and 67.6, 65.1 and 64.9, 64.0, 62.2, 56.8 and 54.9, 46.9, 42.7 and 42.0, 20.8 (3C). MS (ESI) *m/z* (%): 1188.55 [(2M + Na)$^+$, 100], 606.31 [(M + Na)$^+$, 22]; MSMS (ESI) *m/z* (%): 606.31 [(M + Na)$^+$, 18], 546.24 (100), 486.31 (20), 384.24 (20). Anal. Calcd for $C_{30}H_{33}NO_{11}$: C, 61.74; H, 5.70; N, 2.40. Found: C, 62.01; H, 5.87; N, 2.31.

(*R*)-1-((2*R*,4a*R*,6*R*,7*S*,7a*S*)-7-Acetoxy-2-methoxyhexahydro-2*H*-furo[3,2-*b*][1,4]oxazin-6-yl)ethane-1,2-diyl Diacetate (15). Compound **14** (30 mg, 0.05 mmol) was treated with 30% solution of Et_2NH in CH_3CN (1 mL). The Fmoc deprotection was monitored by TLC. When complete conversion was obtained (after 2 h), volatiles were removed under reduced pressure, and the residue was purified by flash chromatography (AcOEt/Petr. et. = 1:2, buffered with 1% Et_3N; R_f = 0.14), affording pure compound **15** (15 mg, 0.047 mmol, 85%) as a yellow oil. $[\alpha]_D^{23}$ = −42.8 (*c* 0.4, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.30 (t, *J* = 9.9 Hz, 1H), 4.99 (dd, *J* = 9.9, 3.7 Hz, 1H), 4.72 (d, *J* = 2.2 Hz, 1H), 4.40 (s, 1H), 4.36 (d, *J* = 10.9, 1H), 4.20−4.18 (m, 2H), 3.64−3.61 (m, 2H), 3.40 (dd, *J* = 11.8, 2.9 Hz, 1H), 3.37 (s, 3H), 2.09 (s, 6H), 2.05 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.7, 170.1, 169.6, 96.5, 81.4, 73.1, 72.7, 66.1, 65.4, 63.0, 54.8, 41.9, 20.7 (3C). MS (ESI) *m/z* (%): 384.10 [(M + Na)$^+$, 100]; MSMS (ESI) *m/z* (%): 384.16 [(M + Na)$^+$, 10], 324.03 (100), 264.00 (10), 242.02 (20). Anal. Calcd for $C_{15}H_{23}NO_9$: C, 49.86; H, 6.42; N, 3.88. Found: C, 49.97; H, 6.49; N, 3.79.

(*R*)-1-((2*R*,4a*R*,6*R*,7*S*,7a*S*)-7-Acetoxy-2-methoxy-4-tosyl-hexahydro-2*H*-furo[3,2-*b*][1,4]oxazin-6-yl)ethane-1,2-diyl Diacetate (16). To a solution of **15** (15 mg, 0.047 mmol) and DIPEA (25 μL, 0.14 mmol) in dry CH_2Cl_2 (0.7 mL), a solution of TsCl (18 mg, 0.094 mmol) in dry CH_2Cl_2 (0.7 mL) was added slowly at 0 °C. The mixture was allowed to reach room temperature and was left stirring under a nitrogen atmosphere for 24 h. Then, water was added slowly, and the resulting mixture was washed with a saturated solution of $NaHCO_3$ and brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by flash chromatography (EtOAc/Petr. et. = 1:3; R_f = 0.21) to give pure **16** (10 mg, 0.019, 41%). $[\alpha]_D^{20}$ = −27.8 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 5.23 (s, 1H), 5.19 (t, *J* = 10.1 Hz, 1H), 5.01 (dd, *J* = 10.1, 3.4 Hz, 1H), 4.75 (d, *J* = 2.3 Hz, 1H), 4.38 (d, *J* = 3.3 Hz, 1H), 4.05−4.03 (m, 2H), 3.67−3.64 (m, 1H), 3.36 (d, *J* = 11.8 Hz, 1H), 3.31 (s, 3H), 3.03 (dd, *J* = 11.7, 2.3 Hz, 1H), 2.40 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.3, 169.8, 169.5, 143.9 (2C), 129.3 (2C), 128.3 (2C), 95.2, 78.5, 73.5, 72.0, 65.9, 65.6, 62.6, 54.7, 42.9, 29.6, 21.5, 20.6 (2C). MS (ESI) *m/z* (%): 538.24 [(M + Na)$^+$, 100]; MSMS (ESI) *m/z* (%): 538.12 [(M + Na)$^+$, 20], 478.11 (100), 418.01 (20). Anal. Calcd for $C_{22}H_{29}NO_{11}S$: C, 51.26; H, 5.67; N, 2.72. Found: C, 51.33; H, 5.70; N, 2.66.

(6*R*)-(9*H*-Fluoren-9-yl)methyl-2-methoxy-6-((1*R*,2*R*,3*R*)-1,2,3,4-tetrahydroxybutyl)-morpholine-4-carboxylate (17). A solution of compound **8** (76 mg, 0.13 mmol) in trifluoroacetic acid (1 mL) and MeOH (100 μL) was left stirring at room temperature for 20 min, until complete disappearance of the starting material (TLC control) was observed. Then, TFA was rapidly quenched by adding a saturated aqueous solution of $NaHCO_3$ (20 mL) until pH = 7. The crude product was extracted in EtOAc and, after solvent evaporation, purification by flash chromatography (EtOAc/MeOH = 10:1, R_f = 0.20), afforded compound **17** as an amorphous solid (44 mg, 0.09 mmol, 73%). HPLC analysis revealed that **17** was obtained as a 10:1 mixture of anomers. ^{1}H NMR (400 MHz, CD_3CN) major anomer, major rotamer: δ 7.81 (d, *J* = 7.4 Hz, 2H), 7.60 (d, *J* = 7.4 Hz, 2H), 7.40−7.38 (m, 2H), 7.33−7.31 (m, 2H), 4.82 (s, 1H), 4.80 (br s, 1H, OH), 4.43 (dd, *J* = 10.0, 6.5 Hz, 1H), 4.40 (br s, 1H, OH), 4.36 (s, 1H), 4.25 (t, *J* = 6.3 Hz, 1H), 4.10 (br s, 1H, OH), 4.03 (d, *J* = 13.2 Hz, 1H), 3.87 (d, *J* = 13.4 Hz, 1H), 3.81 (br s, 1H, OH), 3.66−3.53 (m, 5H), 3.40 (s, 3H), 3.31−3.30 (m, 2H), 3.21 (s, 1H). ^{13}C NMR (100 MHz, DMSO) major anomer, major rotamer: δ 154.6, 144.2 (2C), 141.1 (2C), 128.2 (2C), 127.6 (2C), 125.6 (2C), 120.7 (2C), 99.1, 95.0, 71.3, 70.0, 67.3, 66.2, 64.2, 55.8, 54.4, 47.0, 46.4. MS (ESI) *m/z* (%): 940.64 (20, [2 M + Na]$^+$), 482.31 [(M + Na)$^+$, 100]; MS (ESI) *m/z* (%): 482.31 [(M + Na)$^+$, 30], 450.10 (60), 304.26 (32), 272.05 (34), 260.19 (62), 228.14 (100). Anal. Calcd for $C_{24}H_{29}NO_8$: C, 62.73; H, 6.36; N, 3.05. Found: C, 62.97; H, 6.39; N, 3.01.

(1*R*,5*R*,7*S*)-(9*H*-Fluoren-9-yl)methyl-7-((1*R*,2*R*)-1,2,3-trihydroxypropyl)-6,8-dioxa-3-aza bicyclo[3.2.1]octane-3-carboxylate (18). A solution of compound **8** (90 mg, 0.16 mmol) in trifluoroacetic acid (1 mL) and MeOH (100 μL) was left stirring at room temperature for 4 h, until most of the starting material was converted to the bicyclic product, with respect to the monocyclic product (TLC control). Then, TFA was quenched with a saturated $NaHCO_3$ solution (20 mL) until neutral pH. The crude product was extracted in EtOAc and, after solvent evaporation, purification by flash chromatography (EtOAc/MeOH = 100:1, R_f = 0.41), afforded compound **18** as a pure colorless oil (33 mg, 0.07 mmol, 50%). $[\alpha]_D^{20}$ = +49.5 (*c* 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotamers: δ 7.75 (d, *J* = 7.3 Hz, 2H), 7.56−7.54 (m, 2H), 7.39−7.28 (m, 4H), 5.50 and 5.46 (s, 1H), 4.46−4.39 (m, 3H), 4.20 (s, 1H), 4.11−4.08 (m, 1H), 3.95 (dd, *J* = 9.0, 4.6 Hz, 1H), 3.80 (s, 1H), 3.74−3.48 (m, 3H), 3.38−3.19 (m, 2H), 3.04 (d, *J* = 7.3 Hz, 1H), 3.02−3.00 (br s, 2H, OH). ^{13}C NMR (50 MHz, $CDCl_3$) mixture of rotamers: δ 155.7, 143.3 (2C), 140.9 (2C), 127.5 (2C), 126.7 (2C), 124.6 (2C), 119.7 (2C), 97.1 and 97.0, 80.3 and 80.2, 72.5 (2C), 70.1, 67.4, 63.4 and 63.3, 47.9, 46.8, 43.8. MS (ESI) *m/z* (%): 876.58 [(2M + Na)$^+$, 34], 450.14 [(M + Na)$^+$, 100]. Anal. Calcd for $C_{23}H_{25}NO_7$: C, 64.63; H, 5.90; N, 3.28. Found: C, 64.97; H, 6.02; N, 3.21.

(3a*R*,4*R*,9a*R*)-8-(2,2-Dimethoxyethyl)-4-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-tetrahydro-3a*H*-[1,3]dioxolo-[4,5-*f*][1,4]oxazocin-7(4*H*)-one (19). Sodium hydride (60% in oil, 22 mg, 0.56 mmol) was added to a solution of **10** (130 mg, 0.28 mmol) in anhydrous THF (5 mL) at 0 °C, and the mixture was left stirring for 1 h at room temperature. NaH was quenched with MeOH (2 mL) and filtered through Celite. The filtrate was concentrated under vacuum, to yield a yellow oil which was purified by flash chromatography (EtOAc/Petr. et. = 1:1; R_f = 0.39). Compound **19** (83 mg, 0.21 mmol, 78%) was thus obtained as a pure colorless oil. $[\alpha]_D^{22}$ = +28.9 (*c* 1.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.60 (dd, *J* = 5.8, 4.3 Hz, 1H), 4.51 (d, *J* = 16.4 Hz, 1H), 4.49 (dd, *J* = 14.4, 11.4 Hz, 1H), 4.36 (d, *J* = 16.4 Hz, 1H), 4.30 (dd, *J* = 5.8, 3.1 Hz, 1H), 4.28−4.20 (m, 2H), 4.07−3.97 (m, 2H), 3.67 (dd, *J* = 5.9, 1.2 Hz, 1H), 3.53 (dd, *J* = 13.7, 4.3 Hz, 1H), 3.40 (s, 3H), 3.39 (s, 3H), 3.31 (dd, *J* = 13.7, 6.2 Hz, 1H), 3.11 (dd, *J* = 14.4, 2.7 Hz, 1H), 1.42 (s, 3H), 1.38 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 108.9, 108.3, 102.4, 76.7, 75.7, 74.1, 73.5, 73.0, 65.7, 55.1, 54.9, 50.8, 49.4, 27.8, 26.5, 25.5, 25.2; MS (ESI) *m/z* (%): 800.93 [(2M + Na)$^+$, 100], 412.33 [(M + Na)$^+$, 30]. Anal. Calcd for

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$C_{18}H_{31}NO_8$: C, 55.51; H, 8.02; N, 3.60. Found: C, 55.64; H, 8.09; N, 3.52.

(1*R*,6*R*,7*R*,9*R*/*S*)-5-((*R*)-1,2-Dihydroxyethyl)-6-hydroxy-9-methoxy-4,8-dioxa-1-azabicyclo[5.3.1]undecan-2-one (20). A solution of compound **19** (100 mg, 0.27 mmol) in trifluoroacetic acid (0.5 mL) was left stirring at room temperature for 2 h. Then, TFA was evaporated under vacuum, and the crude residue was purified by flash chromatography (CH_2Cl_2/MeOH/NH_4OH (10%) = 4:2:2, R_f = 0.17), affording compound **20** as a colorless oil (36 mg, 0.12 mmol, 42%). ^{1}H NMR (400 MHz, D_2O) 1:1 mixture of anomers: δ 5.42 (s, 0.5H), 5.11−5.08 (m, 0.5H), 4.98 (s, 0.5H), 4.44−4.21 (m, 3H), 4.05−4.02 (m, 0.5H), 3.87−3.75 (m, 2H), 3.72 (s, 1.5H), 3.68−3.55 (m, 2H), 3.51 (s, 1H), 3.45−3.38 (m, 1H), 3.28 (s, 1.5H), 3.23−3.21 (m, 0.5H), 3.10−3.05 (m, 0.5H), 2.98−2.95 (m, 0.5H), 2.82−2.80 (m, 0.5H). ^{13}C NMR (100 MHz, D_2O): δ 174.4 and 172.8, 95.0 and 94.0, 90.1 and 87.2, 78.3 and 78.2, 70.6 and 70.5, 70.2, 70.0, 64.4 and 63.4, 62.5 and 62.3, 57.0 and 55.3, 45.9, and 44.9. MS (ESI) *m*/*z* (%): 277.19 [(M + H)$^+$, 100]; MSMS (ESI) *m*/*z* (%): 277.19 [(M + H)$^+$, 8], 246.03 (100), 228.04 (20), 186.02 (22), 170.06 (18), 152.03 (12). Anal. Calcd for $C_{11}H_{19}NO_7$: C, 47.65; H, 6.91; N, 5.05. Found: C, 47.87; H, 7.01; N, 4.97.

(3a*S*,4*R*,6a*R*)-5-(2,2-Dimethoxyethyl)-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-tetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole (21). Compound **9** (170 mg, 0.35 mmol), Ac_2O (115 μL, 1.23 mmol), and 3 Å molecular sieves (10 mg) were dissolved in anhydrous CH_2Cl_2 (10 mL); then pyridinium dichromate (93 mg, 0.25 mmol) was slowly added. The mixture was left stirring under reflux for 90 min, and then filtrated through silica gel (EtOAc/Petr. et. = 1:1), affording the intermediate ketone as a colorless oil [^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotamers: δ 7.38−7.35 (m, 5H), 5.31 and 5.17−5.11 (m, 2H), 4.79−3.62 (m, 8H), 3.40−3.27 (m, 7H), 3.17−3.06 (m, 1H), 1.59−1.19 (m, 12H)]. The Cbz-protected ketone (140 mg, 0.29 mmol) was then dissolved in MeOH (20 mL), Pd/C (25 mg, 0.23 mmol) was added, and the resulting mixture was left stirring overnight at room temperature under a hydrogen atmosphere. The catalyst was filtered through Celite, and the filtrate was concentrated under vacuum, to yield a yellow oil, which was purified by flash chromatography (EtOAc/Petr. et. = 1:2; R_f = 0.65). Compound **21** (100 mg, 0.30 mmol) was obtained as a pure yellow oil in 87% yield. $[\alpha]_D^{20}$ = −23.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.60−4.45 (m, 4H), 4.25 (t, *J* = 7.0 Hz, 1H), 3.97 (t, *J* = 7.7 Hz, 1H), 3.39 (s, 3H), 3.37−3.30 (m, 2H), 3.35 (s, 3H), 2.76 (d, *J* = 4.4 Hz, 1H), 2.32−2.22 (m, 2H), 1.44 (s, 3H), 1.42 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 112.3, 110.0, 103.2, 80.2, 77.5, 72.4, 65.3, 59.3, 56.3, 54.6, 52.4, 44.6, 26.0, 25.8, 25.6, 23.8; MS (ESI) *m*/*z* (%): 354.30 [(M + Na)$^+$, 80], 332.14 [(M + H)$^+$, 100]. Anal. Calcd for $C_{16}H_{29}NO_6$: C, 57.99; H, 8.82; N, 4.23. Found: C, 58.09; H, 8.95; N, 4.09.

(*S*)-1-((3a*S*,4*R*,6a*R*)-5-(2,2-Dimethoxyethyl)-2,2-dimethyl-tetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]-pyrrol-4-yl)ethane-1,2-diol (22). A solution of compound **21** (105 mg, 0.32 mmol) in trifluoroacetic acid (0.5 mL) and MeOH (0.5 mL) was left stirring at room temperature for 2 h. Then, TFA was quenched with $NaHCO_3$ saturated solution (20 mL) until neutral pH. The crude product was extracted in EtOAc and, after solvent evaporation, purification by flash chromatography (CH_2Cl_2/MeOH = 20:1, R_f = 0.35), afforded compound **22** as a pure orange oil (84 mg, 0.29 mmol, 90%). $[\alpha]_D^{20}$ = −25.9 (*c* 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.69 (dd, *J* = 6.3, 4.3 Hz, 1H), 4.60 (dd, *J* = 6.3, 5.1 Hz, 1H), 4.51 (t, *J* = 5.7 Hz, 1H), 4.01−3.98 (m, 1H), 3.84 (dd, *J* = 11.3, 6.6 Hz, 1H), 3.73 (dd, *J* = 11.3, 4.3 Hz, 1H), 3.46 (s, 2H, OH), 3.39 (s, 3H), 3.37 (s, 3H), 3.35 (d, *J* = 10.9 Hz, 1H), 3.04 (dd, *J* = 13.2, 5.4 Hz, 1H), 2.33−2.25 (m, 3H), 1.50 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 111.5, 103.1, 80.8, 78.0, 69.7, 67.6, 64.9, 59.6, 54.4, 53.8, 53.2, 25.9, 24.6. MS (ESI) *m*/*z* (%): 604.87 [(2M + Na)$^+$, 30], 314.25 [(M + Na)$^+$, 70], 292.12 [(M + H)$^+$, 100]. Anal. Calcd for $C_{13}H_{25}NO_6$: C, 53.59; H, 8.65; N, 4.81. Found: C, 53.81; H, 8.78; N, 4.65.

(5a*R*,7*S*,8*S*,8a*R*)-2-Methoxy-4-tosyloctahydrofuro[2,3-*f*][1,4]-oxazepine-7,8-diol (23). A solution of compound **11** (50 mg, 0.10 mmol) in trifluoroacetic acid (1 mL) was left stirring at room temperature for 2 h. Then, TFA was evaporated under vacuum, and the crude product was purified by flash chromatography (EtOAc/Hexane = 2:1, R_f = 0.20), affording compound **23** as a pure colorless oil (16 mg, 0.04 mmol, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) 3:1 mixture of anomers: δ 7.64 (d, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 2H), 5.31 (s, 0.25H, minor), 5.19 (s, 0.75H, Major), 4.57−4.55 (m, 0.5H, minor), 4.46 (dd, *J* = 8.7, 8.6 Hz, 1.5H, Major), 4.24−4.17 (m, 2H), 3.98 (d, *J* = 12.1 Hz, 0.75H, Major), 3.90 (dd, *J* = 13.7, 6.4 Hz, 0.75H, Major), 3.49 (s, 2.25H, Major), 3.45 (s, 0.75H, minor), 3.43−3.34 (m, 0.5H, minor), 2.86 (dd, *J* = 13.7, 11.2 Hz, 0.75H, Major), 2.77 (dd, *J* = 12.7, 10.4 Hz, 0.25H, minor), 2.67−2.61 (m, 1H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9 (2C), 129.9 (2C), 126.9 (2C), 107.6, 96.5, 80.7, 76.7 and 76.4, 72.3, 56.4 and 54.9, 50.9, 29.7, 21.5. MS (ESI) *m*/*z* (%): 382.17 [(M + Na)$^+$, 100]; MSMS (ESI) *m*/*z* (%): 382.21 [(M + Na)$^+$, 10], 364.18 (70), 350.16 (100), 332.02 (8), 292.06 (30). Anal. Calcd for $C_{15}H_{21}NO_7S$: C, 50.13; H, 5.89; N, 3.90. Found: C, 50.39; H, 5.97; N, 3.79.

(5a*R*,7*S*,8*S*,8a*R*)-2-Methoxy-4-((4-nitrophenyl)sulfonyl)-octahydrofuro[2,3-*f*][1,4]oxazepine-7,8-diol (24). A solution of compound **12** (40 mg, 0.072 mmol) in trifluoroacetic acid (0.5 mL) was left stirring at room temperature for 2 h. Then, TFA was evaporated under vacuum, and the crude product was purified by flash chromatography (EtOAc/Hexane = 1:1, R_f = 0.21), affording compound **24** as a pure white solid (13 mg, 0.035 mmol, 48%). ^{1}H NMR (200 MHz, $CDCl_3$) 3:1 mixture of anomers: δ 8.34 (d, *J* = 8.4 Hz, 2H), 7.93 (d, *J* = 8.4 Hz, 2H), 5.21 (d, *J* = 3.6 Hz, 0.25H, minor), 5.15 (d, *J* = 3.6 Hz, 0.75H, Major), 4.46−4.41 (m, 2H), 4.24−4.14 (m, 2H), 3.87 (d, *J* = 13.2 Hz, 0.75H, Major), 3.77 (dd, *J* = 13.6, 6.2 Hz, 0.75H, Major), 3.47 (s, 2.25H, Major), 3.44 (s, 0.75H, minor), 3.37−3.34 (m, 0.5H, minor), 3.01 (dd, *J* = 13.9, 10.6 Hz, 1H), 2.70 (dd, *J* = 12.7, 10.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) major anomer: δ 149.7, 145.2, 128.0 (2C), 124.5 (2C), 107.2, 96.1, 80.6, 76.3, 72.3, 56.0, 54.6, 50.0. MS (ESI) *m*/*z* (%): 413.16 [(M + Na)$^+$, 100]. Anal. Calcd for $C_{14}H_{18}N_2O_9S$: C, 43.07; H, 4.65; N, 7.18. Found: C, 43.16; H, 4.68; N, 7.12.

PCA Analysis. The web-based public tool ChemGPS-NP[25] was used for PCA analysis of compounds **4**−**24**, to compare their chemical properties with those of a reference set of 40 brand-name blockbuster (BB) drugs as reported by Tan and co-workers.[27] ChemGPS-NP can be applied for comprehensive chemical space navigation and exploration in terms of global mapping on to a consistent 8-dimensional map of structural characteristics. The first four dimensions of the ChemGPS-NP map capture 77% of data variance. Chemical compounds were positioned onto this map using interpolation in terms of PCA score prediction. SMILES codes for all compounds **4**−**24** and the 40 BB drugs of the reference set were retrieved using ChemBioDraw Ultra 12.0 and submitted to ChemGPS-NP for achieving the corresponding PC scores (see the Supporting Information). The PCA data were then used for the construction of PC1 vs PC2 and PC1 vs PC3 plots.

PMI Analysis. Principal moment of inertia analysis was carried out by calculation of the lowest energy conformation of each compound **4**−**24**, and each compound from the reference set of 40 brand-name blockbuster (BB) drugs.[27] The conformation calculation was performed using the built-in AMMP molecular mechanics algorithm with default parameters of the VEGA ZZ molecular modeling software package v.3.0.1. Once the lowest energy conformer was calculated, the three principal moments of inertia (I_{xx}, I_{yy}, I_{zz}) and normalized principal moments of inertia, npr1 (I_{xx}/I_{zz}) and npr2 (I_{yy}/I_{zz}) were determined, and PMI ratios were calculated for **4**−**24** and each compound from the reference set of BB drugs, as reported by Sauer and Schwarz (see the Supporting Information).[29] The ratios were plotted on a triangular graph with the vertices (0,1), (0.5,0.5), and (1,1) representing a perfect rod, disc, and sphere, respectively.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds, copies of NOESY1D and additional NMR data of compound

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14, and PCA and PMI data for compounds **4**−**24** and reference set of BB drugs. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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