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Bicyclic Hybrid Sugars as Glycosidase Inhibitors: Synthesis and Comparative Study of Inhibitory Activities of Fused Oxa-Oxa, Oxa-Aza, and Oxa-Carbasugar Hybrid Molecules

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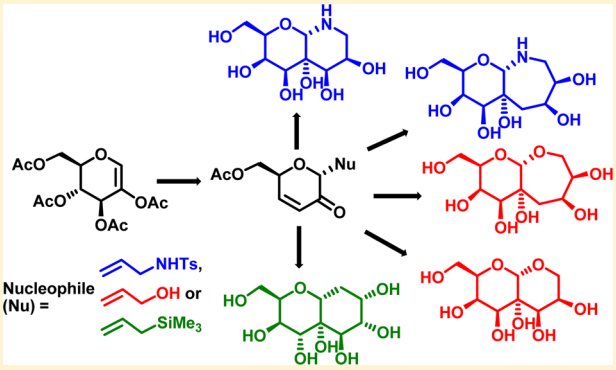
Supporting Information

ABSTRACT: A few bicyclic hybrid sugar molecules comprising of oxa-aza, oxa-oxa, and oxa-carbasugar fused skeletons were designed and synthesized from C-2 acetoxyglucal involving Ferrier rearrangement, Grignard addition, and ring-closing metathesis as key steps. The inhibitory activities of the synthesized molecules were tested against commercially available enzymes, which revealed the sugar−piperidine and sugar−pyran hybrids as potent and selective inhibitors.



INTRODUCTION

Glycosidase inhibitors have remained the focus of attention for glycochemists and synthetic organic chemists for decades due to their immense therapeutic potential as drugs against diseases such as diabetes, viral infections, cancer, lysosomal storage disorders, etc.[1] Most of the known glycosidase inhibitors, either naturally occurring or synthetic, are believed to function by mimicking the charge or shape of the transition state of the enzyme−substrate complex.[2] Although a tremendous deal of investigation is going on toward better understanding of facets required for the design and development of ideal glycosidase inhibitors, yet there is a need for improving the activity and selectivity of inhibitors. For this purpose, many synthetic glycosidase inhibitors are constantly being designed and evaluated for their inhibitory activities. While most of these efforts involve modification of position or stereochemistry of functional groups of naturally occurring inhibitors,[3] some new classes of glycosidase inhibitors have also emerged in the recent past.[3,4]

Among the various new kinds of glycosidase inhibitors reported, hybrid molecules have caught the fascination of several groups. The basis of design lies in the combination of 2 or more molecules that are individually potent inhibitors, so that the resulting molecule would display better inhibitory behavior than the parent molecules. Mehta et al.[5] first reported the conduritol−carbasugar hybrid molecule **1** (Figure 1), which showed selective α-glucosidase inhibition. Following this, our group has reported several sugar-fused hybrids molecules, for instance, hybrid of D-galactose with 1-deoxymannonojirimycin **2**,[6a] sugar−carbasugar hybrid **3**,[6b] sugar−pyrrolidine hybrid **4**,[6c] sugar−piperidine hybrid **5**,[6d] sugar−morpholino-triazole **6**,[6e] which were moderate to good and selective inhibitors (Figure 1). In addition, spiro compounds such as **7** and **8** have also been synthesized by our group.[6f,g]

Likewise, syntheses of other types of hybrid molecules such as bicyclic diazasugar **9**, sugar−β-lactam hybrid **10** and iminoalditol−amino acid hybrid **11** have appeared in the recent literature (Figure 2).[7a−c] A few similar hybrid molecules **12**−**14** bearing a heteroatom at the anomeric position of the sugar moiety[7d−f] have also been reported to exhibit interesting biological activities.

In view of these reports, we were interested to synthesize a new type of bicyclic sugar-fused molecules that bear an electronegative atom at the anomeric position and to study their inhibitory profile. The underlying idea was to mimic the oxacarbenium ion **B** or oxonium ion **C** (having a half-chair conformation) formed during the action of glycosidases closely resembling the well-accepted transition states dealing with glycosidases[1,2] (Figure 3). It was expected that form **B** (or **C**) will provide an additional electronegative center (X^-) in the vicinity, which may bring about better binding of the inhibitor to the active site of the enzyme via hydrogen bonding and thus leading to better/or specific inhibitions. It is likely that in the case of oxa-aza sugar hybrid molecules, form **B** could mimic the transition state better than **C**. It was of further interest to us to compare the behavior of these molecules by changing the groups (N, O, or CH_2) at the anomeric position of the sugar

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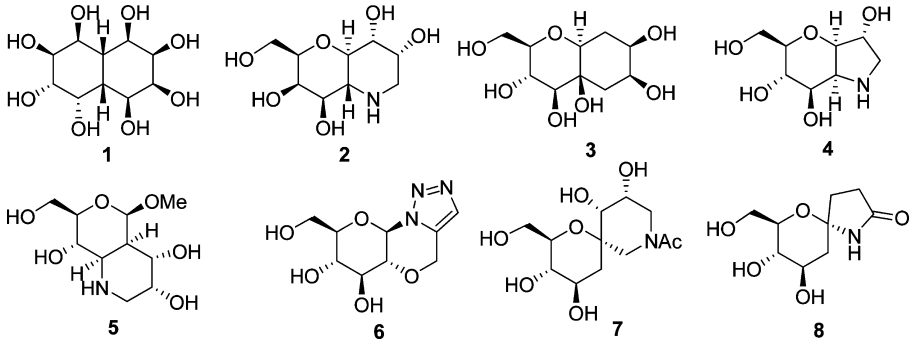

Figure 1. Hybrid molecules reported as glycosidase inhibitors.

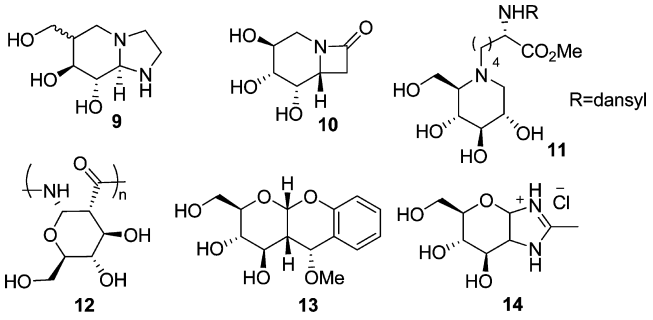

Figure 2.

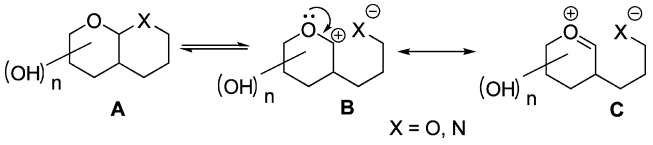

Figure 3. Basis of design of hybrid molecules.

part and also study the effect of ring size on the inhibition pattern.

RESULTS AND DISCUSSION

We planned the synthesis of molecules of the type **D** and **E** (Figure 4) for our investigation. We wished to further corroborate our theory by preparing a sugar−carbasugar hybrid **F**, since it cannot exist in form **B** (or **C**) (Figure 3). This would help to verify the role played by the electronegative center at the anomeric position in the inhibition of glycosidases.

The synthesis emanated from 2-acetoxyglucal **15** prepared using a literature method[8] via Ferrier rearrangement using suitable nucleophiles as depicted in Figure 4. The synthesis of sugar−azasugar hybrid molecules (type **D**) commenced with the addition of *N*-allyl-4-methylbenzenesulfonamide on 2-acetoxyglucal **15** using $BF_3{\cdot}Et_2O$ in CH_2Cl_2 following a reported method.[9] The major α-isomer **16** was then separated by column chromatography and subjected to further reactions (Scheme 1). The addition of excess of vinylmagnesium bromide on enone **16** resulted in the formation of a single isomer. During the course of this reaction, the acetate group was also deprotected to give the corresponding primary alcohol, which is in conformity with literature reports.[10] Silyl protection of the primary hydroxyl group using *tert*-butyldiphenylsilyl chloride (TBDPSCl) and Et_3N as a base gave **17a**. The triene **17a** was then treated with Grubbs' second generation catalyst in refluxing toluene to afford the diene **18a** in 86% yield. Dihydroxylation of **18a** was carried out using OsO_4 and NMO as reoxidant[11] followed by acetylation using Ac_2O/Et_3N in a 1:1 ratio to furnish the tetraacetate **19a**. The hydroxyl group at quaternary carbon remained unprotected, possibly because of the steric congestion around that center. The structure of compound **19a** was established by determining the absolute configuration of the newly generated stereocenters with the help of ^1H NMR, COSY, and NOESY experiments, which is shown in Figure 5 (positive NOESY correlations of H-2/H-4, H-4/H-5, H-5/H-7α, H-8a/H-7β and no NOESY correlations of H-8a/H-4, H-8a/H-5).[12] The deprotection of silyl ether as well as tosyl group deprotection on the amine was performed in one pot by refluxing overnight with tetra-*n*-butylammonium fluoride (TBAF) in THF.[13] The remaining acetate groups were removed by treatment with NH_3/MeOH leading to the fully deprotected molecule **20a**.

In a similar manner, sugar−azepane hybrid molecule **20b** was obtained by the addition of allylmagnesium chloride on the

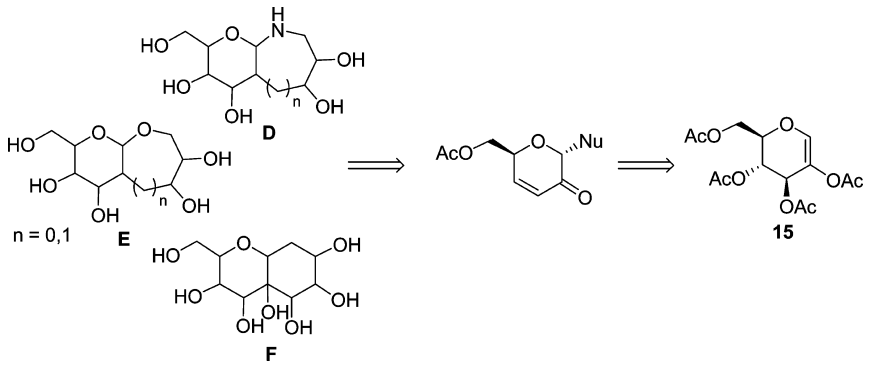

Figure 4.

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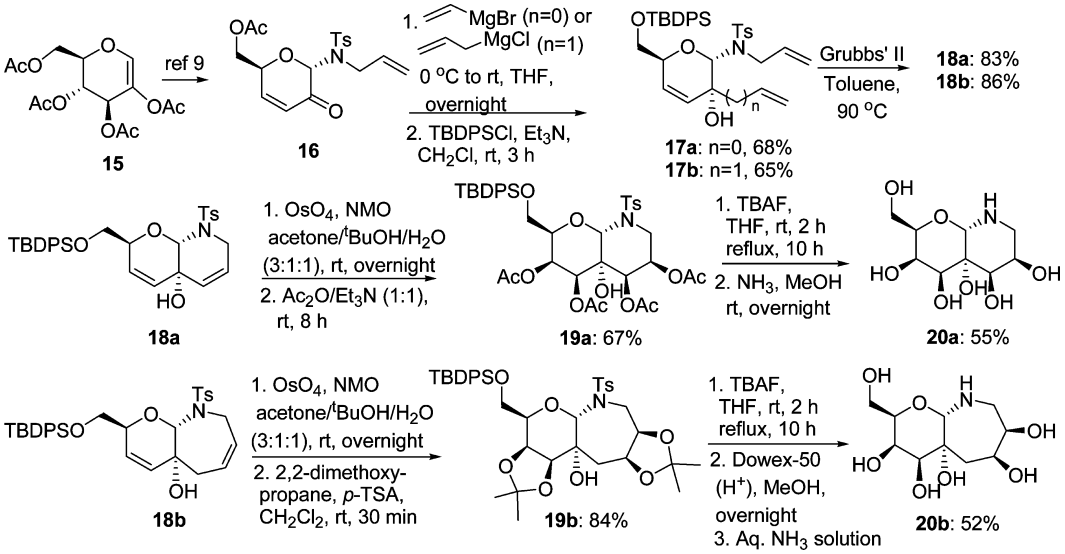
Scheme 1



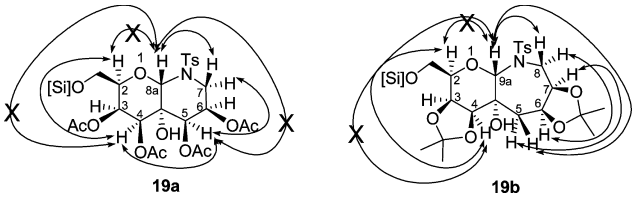


Figure 5.

enone **16** followed by ring-closing metathesis of the corresponding triene **17b** to give **18b**. In this case, after dihydroxylation, acetonide protection was done using 2,2-dimethoxypropane and a catalytic amount of *para*-toluenesulfonic acid (PTSA) in CH_2Cl_2, to provide diacetonide **19b**. This compound provided more convenient spectra for analysis of stereochemistry than the corresponding tetraacetate. The stereochemistry was established to be as shown in Figure 5, using ^{1}H NMR, COSY, and NOESY spectral studies (positive NOESY correlations of H-2/H-4, H-5α/H-7, H-6/H-8α, H-8β/H-9a, H-5β/H-9a and no NOESY correlations of H-9a/H-2, H-9a/H-4).[12] Finally complete deprotection of **19b** was carried out using TBAF in refluxing THF as described above, followed by treatment with acidic resin to afford **20b** (Scheme 1).

In a similar manner, allyl alcohol was added to the 2-acetoxyglucal **15** using $BF_3{\cdot}Et_2O$ (Scheme 2) to give hitherto unreported compounds **21a** and **21b**. The major α-isomer **21a** was subsequently subjected to the same series of reactions as described above, to afford sugar−pyran hybrid **25a** and sugar−oxepane hybrid **25b**. The stereochemistry of these compounds was determined from their acetate derivatives **24a** and **24b** by spectral means, and the same is illustrated in Figure 6 (**24a**:

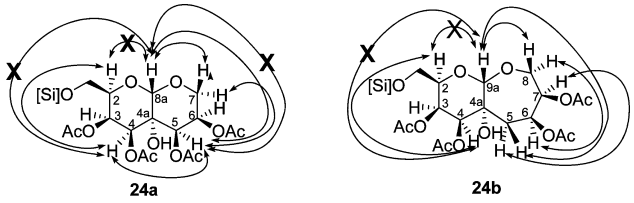
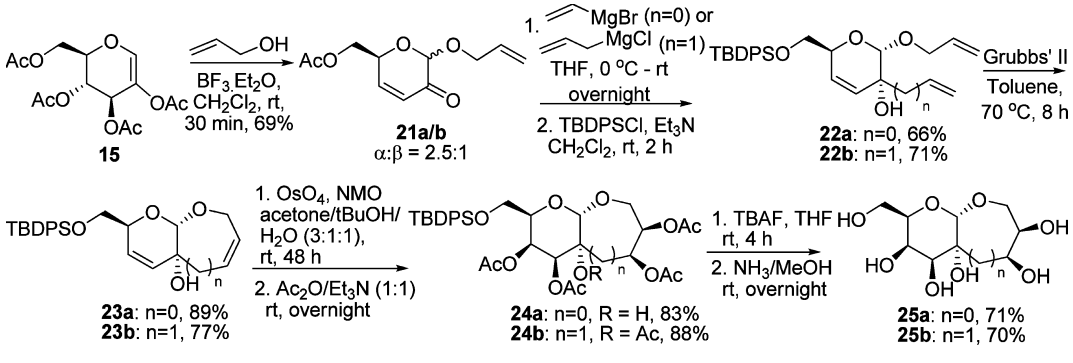


Figure 6.

positive NOESY correlations of H-2/H-4, H-4/H-5, H-5/H-7α, H-8a/H-7β and no NOESY correlations of H-8a/H-4, H-8a/H-5, **24b**: positive NOESY correlations of H-2/H-4, H-5α /H-7, H-6/H-8α, H-8β/H-9a, H-5β/H-9a and no NOESY correlations of H-9a/H-2, H-9a/H-4).[12]

Further, to synthesize the oxa-carbasugar hybrid molecule, allyltrimethylsilane was added onto glucal **15** using $HClO_4{\cdot}SiO_2$ in acetonitrile,[14] and the enone **26** obtained was treated with allylmagnesium chloride solution (Scheme 3) to give a mixture of tertiary alcohols. The primary alcohol was selectively

Scheme 2



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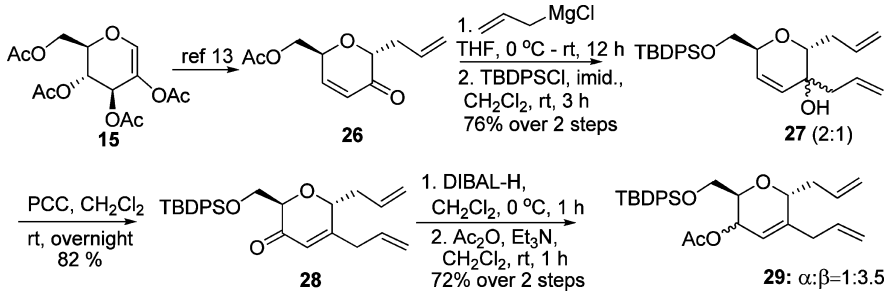
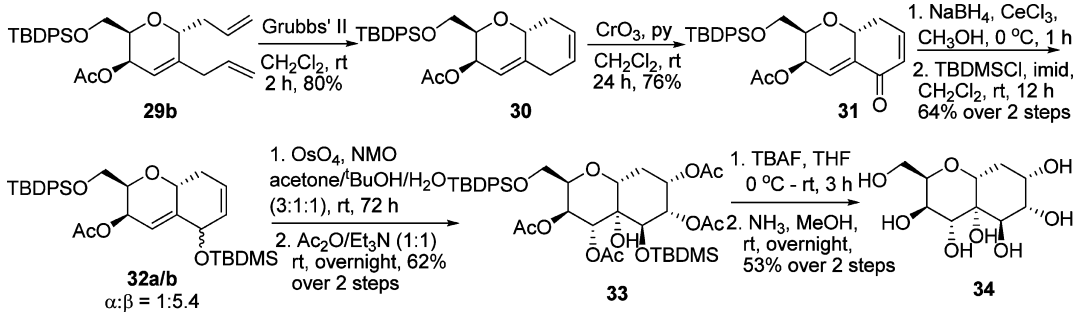
Scheme 3



Scheme 4



protected as its silyl ether using TBDPSCl and imidazole in CH_2Cl_2, and in this case, a 2:1 mixture of tertiary alcohols **27** was hence obtained. In order to overcome this loss of selectivity and make the synthesis more efficient, the mixture was subsequently oxidized with PCC under Dauben conditions[15] to furnish the enone **28** in 82% yield. The carbonyl group in **28** was reduced using DIBAL-H in dichloromethane at 0 °C, and subsequently the alcohols were protected as acetates. The acetates **29a**/**b** were obtained in a 3.5:1 ratio in 72% yield, which were easily separable by column chromatography at this stage.

The major isomer **29b** was then subjected to ring-closing metathesis reaction (Scheme 4), which took place in a facile manner using only 2.5 mol % of Grubbs' second generation catalyst in CH_2Cl_2 at room temperature to furnish the product **30** in 80% yield. Since we desired to increase the number of hydroxyl groups, the diene **30** was subjected to allylic oxidation using CrO_3/Py mixture,[16] wherein the double allylic position was selectively oxidized giving the dienone **31** in 76% yield. Next, the carbonyl group in **31** was reduced using $NaBH_4$/$CeCl_3$[17] followed by silyl protection of the secondary alcohols using TBDMSCl and imidazole as a base to provide a 1:5.4 mixture of **32a**/**b**. The major compound **32b** was subsequently subjected to dihydroxylation using OsO_4 and NMO as a reoxidant[11] giving a single tetraol, which was converted to the corresponding tetraacetate **33** for analytical purpose. The hydroxyl group at the quaternary carbon was again found to remain inert toward acetylation. The stereochemistry of the newly generated stereocenters in **33** was determined at this stage by ^{1}H NMR, COSY, proton decoupling, and NOE irradiation studies (Figure 7). Finally the deprotection of silyl groups was done using TBAF in THF followed by removal of the acetates using NH_3/MeOH. The heptahydroxylated oxa-carbasugar hybrid **34** was obtained in 53% over 2 steps.

The hence obtained hybrid molecules were then examined for their glycosidase inhibitory behavior. They were tested against 6 commercially available enzymes, and their activities

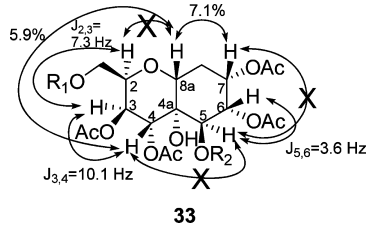


Figure 7.

are recorded in Table 1. In all the cases except with **34** (an oxa-carba hybrid), it was expected that they will mimic either form **B** or **C** (or possibly both in some cases) with however one common feature that the electronegative atom "**X**" (i.e., "**N**" or "**O**") will provide an additional binding with the active site of the enzyme leading to better and selective inhibition. This prediction was found to be true with **20a**, an oxa-aza hybrid, to a large extent, and with **25a**, an oxa-oxa hybrid, to a reasonable extent. Thus, **20a** was found to be quite potent and highly selective against β-glucosidase (almonds, IC_{50} = 38.8 μM), while the sugar−pyran hybrid **25a** showed good inhibition of β-galactosidase (bovine liver, IC_{50} = 36.5 μM). Both **20a** and **25a** are hybrids of two six membered rings, and thus the conformations do play a decisive role in both the cases, but more so with **20a**, which is likely to mimic **B** to a larger extent. The same selectivity, however, drops to some extent while dealing with seven membered ring hybrids **20b** and **25b**. This is not surprising considering more flexibility associated with the conformations of seven membered rings. Nonetheless, both **20b** and **25b** exhibited selectivity against α-glycosidases, **20b** being more active against α-glucosidase (Baker's yeast, IC_{50} = 26.2 μM) and α-mannosidase (Jack beans, IC_{50} = 29.4 μM). The bicyclic molecule **34** was not expected to mimic either forms **B** or **C**; instead, we expected it to behave somewhat similar to polycyclitols,[5] some of which are good to moderate glycosidase inhibitors. It did show a broad-range inhibition albeit in micromolar range. From these studies, it was apparent

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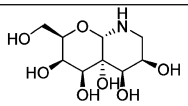
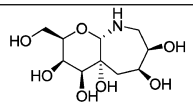
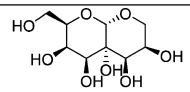
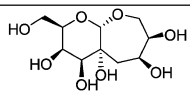
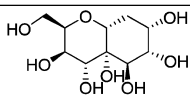
Table 1. Inhibition Values (IC_{50} in μM) of the Synthesized Compounds[a]

Compound	E_1	E_2	E_3	E_4	E_5	E_6
 **20a**	NI	38.8±9.7	NI	NI	NI	NI
 **20b**	26.2±13.0	512.0±151.6	NI	NI	29.4±2.9	NI
 **25a**	NI	NI	NI	36.5±6.1	383.2±202.4	NI
 **25b**	160.9±42.2	NI	36.7±15.1	NI	66.3±6.2	NI
 **34**	77.1±15.7	315.1±73.6	121.8±31.7	NI	NI	36.2±6.3

[a]E_1 = α-glucosidase (Baker's yeast), E_2 = β-glucosidase (almonds), E_3 = α-galactosidase (coffee beans), E_4 = β-galactosidase (bovine liver), E_5 = α-mannosidase (Jack beans), E_6 = β-mannosidase (*Helix pomatia*). NI = no inhibition at 1 mM. IC_{50} values have been given as mean ± standard deviation

that the amino-functionality exerted a stronger influence on the inhibitory properties of these hybrid molecules. This aspect could be further explored by introducing a lipophilic substituent on the nitrogen, which has proved advantageous to the glycosidase inhibition as can be seen in various reports in the literature.[18] There is an ample scope of variations in the structure and shape of hybrid molecules, which could possibly lead to the development of more effective glycosidase inhibitors.

In conclusion, we have synthesized a new class of glycosidase inhibitors that are hybrids of sugars with azasugars, sugars, or carbasugars, constructed in a way that the electronegative atom is situated at the anomeric position of the sugar. The synthesis of these molecules was achieved in a selective manner from C-2 acetoxyglucal via short reaction sequences and in good yields. Among the newly synthesized hybrid molecules, sugar–piperidine derivative **20a** and sugar–pyran derivative **25a** showed good and remarkably selective inhibition against β-glucosidase (almonds) and β-galactosidase (bovine liver) respectively.

EXPERIMENTAL SECTION

General Experimental Methods. All experiments were performed in oven-dried apparatus and under nitrogen atmosphere in dry solvents, unless indicated otherwise. Commercial grade solvents were dried by known methods, and dry solvents were stored over 4 Å molecular sieves. IR spectra were recorded as a thin film and expressed in cm^{-1}. Mass spectra were obtained using Q-TOF apparatus from high resolution ESI mass spectrometer. ^1H NMR (400 or 500 MHz) and ^{13}C NMR (100 or 125 MHz) spectra were recorded using $CDCl_3$ or D_2O as a solvent. Chemical shifts have been reported in ppm downfield to tetramethylsilane and coupling constants expressed in Hertz (Hz); splitting patterns have been assigned as s (singlet), d (doublet), dd (doublet of doublet), td (triplet of doublet), q (quartet), m (multiplet), br (broad), etc. Optical rotations were measured at 28 °C in indicated solvents. TLC plates were prepared using thin layers of silica gel on microscopic slides, and visualization of spots was effected by exposure to iodine or spraying with 10% H_2SO_4 and charring. Column chromatography was performed over silica gel (100–200 Mesh) using hexane and ethyl acetate as eluent.

General Procedure for Enzyme Inhibition Assay. All the enzymes and their corresponding substrates were procured from Sigma-Aldrich Chemical Co. The inhibition studies of compounds (**20a**, **20b**, **25a**, **25b**, **34**) were determined by measuring residual hydrolytic activities of the glycosidases. The substrates and enzymes were prepared as 0.025 M solutions in the respective pH buffer solutions of the corresponding enzyme. In all cases, the substrates used were the corresponding *p*-nitrophenyl glycopyranosides. The incubation mixture consisted of 100 μL of enzyme solution, 200 μL of 1 mg mL^{-1} aqueous solution of test compound and 100 μL of the appropriate buffer solution of the optimum pH for the enzyme. After incubation at 37 °C for 1 h, 100 μL of the substrate solution was added and allowed to react for 10 min. The reaction was quenched using 2.5 mL of 0.05 M borate buffer (pH = 9.8). In all cases, control experiments were run simultaneously in the absence of test compound. A series of blank experiments for the substrate were also carried out in the respective buffer solutions without the enzyme or test compounds. The absorbance of the liberated *p*-nitrophenol in each reaction (both test and control reactions) was recorded using spectrophotometer at 405 nm. Percentage inhibition was calculated as the ratio of the difference in the observed absorbances of the test and control reactions to the observed absorbance of the control reaction. Results have thus been reported as IC_{50} values, which is the concentration of the test compound that causes 50% inhibition of the enzyme. The assays were

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performed in triplicate, and the IC_{50} values have been reported as mean ± standard deviation, in Table 1.

N-Allyl-N-((2S,3R,6S)-6-((tert-butyldiphenylsilyloxy)methyl)-3-hydroxy-3-vinyl-3,6-dihydro-2H-pyran-2-yl)-4-methylbenzenesulfonamide ***17a***. The enone **16** (400 mg, 1.05 mmol) was dissolved in THF (4 mL) and cooled to 0 °C. The solution was treated with vinylmagnesium bromide solution (1 M in THF, 10.5 mL, 10.5 mmol), and the resulting solution was stirred overnight with gradual warming to room temperature. Saturated NH_4Cl (10 mL) was added carefully, and the contents were extracted using EtOAc (3 × 15 mL). The extracts were dried and concentrated using rotary evaporator. The crude compound was used for the next step without further purification. R_f = 0.5 (hexane/EtOAc = 1:1).

The crude alcohol was dissolved in dry CH_2Cl_2 (5 mL), and *tert*-butyldiphenylsilyl chloride (TBDPSCl, 0.29 mL, 1.16 mmol), Et_3N (0.44 mL, 3.15 mmol) and a catalytic amount of DMAP (16 mg, 0.11 mmol) were added. The solution was stirred at room temperature for 3 h. Then saturated $NaHCO_3$ solution (5 mL) was added, and extraction was done with CH_2Cl_2 (3 × 5 mL). The extracts were dried over Na_2SO_4 and concentrated in vacuo, and the crude alcohol was purified by silica gel chromatography to obtain **17a** (430 mg, 68% over 2 steps) as a colorless oil: R_f = 0.7 (hexane/EtOAc = 9:1); $[\alpha]_D^{28}$ = −47.1 (*c* 0.70, CH_2Cl_2); IR (neat) ν_{max} 3508, 3071, 2930, 2858, 1598, 1472, 1427, 1347, 1161, 1111 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69−7.62 (m, 6H), 7.50−7.38 (m, 6H), 6.92−6.91 (m, 2H), 6.06−5.97 (m, 2H), 5.86−5.80 (m, 2H), 5.64 (s, 1H), 5.42 (d, *J* = 17.1 Hz, 1H), 5.33 (d, *J* = 11.0 Hz, 1H), 5.24 (d, *J* = 17.7 Hz, 1H), 5.14 (d, *J* = 10.4 Hz, 1H), 4.32 (br s, 1H), 4.12 (dd, *J* = 6.1, 17.7 Hz, 1H), 3.79 (dd, *J* = 6.1, 10.4 Hz, 1H), 3.67 (dd, *J* = 2.4, 17.1 Hz, 1H), 3.61 (dd, *J* = 4.3, 10.4 Hz, 1H), 2.24 (s, 3H), 2.13 (s, 1H), 1.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3, 139.6, 137.3, 136.2, 135.8, 133.1, 133.0, 130.5, 130.0, 129.3, 129.2, 127.9, 127.8, 116.8, 116.0, 84.5, 75.4, 70.9, 65.4, 46.1, 26.9, 21.4, 19.2; HRMS calcd for $C_{34}H_{41}NNaO_5SSi$ $[M + Na]^+$ 626.2374, found 626.2374.

(2S,4aR,8aS)-2-((tert-Butyldiphenylsilyloxy)methyl)-8-tosyl-4a,5,8,8a-tetrahydro-2H-pyrano[2,3-b]pyridin-4a-ol ***18a***. The triene **17a** (410 mg, 0.68 mmol) was dissolved in dry toluene, and Grubbs' second generation catalyst (14 mg, 0.02 mmol) was added. The solution was refluxed for 1 h, and the solvent removed under a vacuum. The crude residue was purified by column chromatography giving **18a** (320 mg, 83%) as a pale yellow oil: R_f = 0.3 (hexane/EtOAc = 4:1); $[\alpha]_D^{28}$ = −30.0 (*c* 1.20, CH_2Cl_2); IR (neat) ν_{max} 3429, 3044, 2928, 2856, 1597, 1471, 1427, 1340, 1171, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76−7.74 (m, 2H), 7.62−7.60 (m, 4H), 7.45−7.38 (m, 6H), 7.08−7.06 (m, 2H), 5.97 (dd, *J* = 2.4, 9.8 Hz, 1H), 5.91−5.86 (m, 2H), 5.82 (dt, *J* = 2.4, 9.8 Hz, 1H), 4.67 (s, 1H), 4.46−4.43 (m, 1H), 4.36 (ddd, *J* = 2.1, 3.6, 17.1 Hz, 1H), 3.79 (dt, J = 2.4, 17.1 Hz, 1H), 3.74 (dd, *J* = 5.2, 10.4 Hz, 1H), 3.71 (dd, *J* = 6.1, 10.4 Hz, 1H), 2.43 (br s, 1H), 2.29 (s, 3H), 1.00 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.4, 137.2, 135.7, 133.0, 130.5, 130.0, 129.9, 129.3, 129.2, 128.6, 128.2, 128.0, 127.8, 85.9, 75.9, 64.4, 63.4, 47.6, 26.8, 21.5, 19.2; HRMS calcd for $C_{32}H_{37}NNaO_5SSi$ $[M + Na]^+$ 598.2059, found 598.2060.

(2R,3S,4S,4aR,5R,6R,8aS)-2-((tert-Butyldiphenylsilyloxy)methyl)-4a-hydroxy-8-tosyl-octa-hydro-2H-pyrano[2,3-b]pyridine-3,4,5,6-tetrayl tetraacetate ***19a***. The diene **18a** (200 mg, 0.35 mmol) was dissolved in acetone/^{t}BuOH/H_2O solvent system (3:1:1, 5 mL), and *N*-methyl morpholine *N*-oxide (100 mg, 0.87 mmol) followed by OsO_4 (0.04 mmol) were added in succession, and the resulting mixture was stirred at room temperature for 72 h. Then saturated $Na_2S_2O_5$ solution (5 mL) was added, and the mixture stirred for 1 h. The compound was extracted using EtOAc (3 × 5 mL), and the extracts were dried (Na_2SO_4) and concentrated.

The crude alcohol was dissolved in Ac_2O/Et_3N mixture (1:1, 4 mL) and allowed to react at room temperature overnight, following which the solvent was removed by evaporation, and the residue purified by column chromatography to obtain **19a** (190 mg, 67% over 2 steps) as a colorless oil: R_f = 0.3 (hexane/EtOAc = 4:1); $[\alpha]_D^{28}$ = −30.0 (*c* 1.20, CH_2Cl_2); IR (neat) $\nu_{max,}$ 3429, 3044, 2928, 2856, 1597, 1471, 1427, 1340, 1171, 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77−7.74 (m, 2H), 7.71−7.69 (m, 2H), 7.63−7.61 (m, 2H), 7.46−7.40 (m, 6H), 7.13−7.11 (m, 2H), 5.54 (d, *J* = 5.1 Hz, 1H, H-4), 5.43−5.37 (m, 3H, H-3, H-5, H-6), 5.10 (s, 1H, H-8a), 4.00 (dd, *J* = 6.0, 15.4 Hz, 1H, H-7α), 3.93 (dd, *J* = 7.0, 13.7 Hz, 1H, H-2), 3.83−3.80 (m, 1H, $-OCH_2Si$), 3.71 (d, *J* = 5.1, 14.3 Hz, 1H, $-OCH_2Si$), 3.21 (br s, 1H, $-OH$), 3.15 (dd, *J* = 11.7, 15.4 Hz, 1H, H-7β), 2.33 (s, 3H, $-OCOCH_3$), 2.07 (s, 3H, $-OCOCH_3$), 2.02 (s, 3H, $-OCOCH_3$), 1.97 (s, 3H, $-OCOCH_3$), 1.95 (s, 3H, $-OCOCH_3$), 1.07 (s, 9H, $-Si(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 169.3, 143.4, 138.3, 135.9, 135.7, 132.1, 131.9, 130.2, 130.1, 129.3, 128.0, 127.5, 83.1, 78.2, 72.3, 68.9, 66.2, 66.0, 65.6, 63.7, 43.0, 26.9, 21.6, 20.9, 20.7, 20.4, 19.0; HRMS calcd for $C_{40}H_{49}NNaO_{13}SSi$ $[M + Na]^+$ 834.2592, found 834.2594.

(2R,3R,4S,4aR,5R,6R,8aS)-2-(Hydroxymethyl)octahydro-2H-pyrano[2,3-b]pyridine-3,4,4a,5,6-pentaol ***20a***. Compound **19a** (170 mg, 0.20 mmol) was dissolved in dry THF (5 mL), and TBAF solution (1 M soln in THF, 0.80 mL, 0.80 mmol) was added. The reaction mixture was first stirred at room temperature for 2 h and then refluxed overnight. The solvent was removed in vacuo, and the residue dissolved in dry CH_3OH (3 mL). Liquor ammonia solution (25% w/v, 0.20 mL) was added to it, and the reaction mixture stirred at room temperature overnight. The solution was concentrated under a vacuum, and the residue purified by repeatedly washing with 50% EtOAc/Hexane and then with distilled chloroform. Compound **20a** was obtained in 55% yield (29 mg) as a thick whitish liquid: R_f = 0.7 (EtOAc/MeOH = 9:1); $[\alpha]_D^{28}$ = −2.4 (*c* 1.65, CH_3OH); IR (neat) ν_{max} 3514, 3072, 2930, 2858, 1161, 1112 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 5.16 (s, Hz, 1H), 4.08 (dd, *J* = 6.7, 17.1 Hz, 1H), 3.79−3.74 (m, 2H), 3.61−3.39 (m, 4H), 2.95−2.92 (m, 1H), 2.75−2.71 (m, 1H); ^{13}C NMR (125 MHz, D_2O) δ 91.2, 82.5, 82.2, 72.0, 71.6, 70.1, 66.4, 61.4, 46.4; HRMS calcd for $C_9H_{18}NO_7$ $[M + H]^+$ 252.1083, found 252.1084.

N-Allyl-N-((2S,3R,6S)-3-allyl-6-((tert-butyldiphenylsilyloxy)-methyl)-3-hydroxy-3,6-dihydro-2H-pyran-2-yl)-4-methylbenzenesulfonamide ***17b***. The enone **16** (500 mg, 1.32 mmol) was converted to **17b** using allylmagnesium chloride followed by TBDPS protection (as performed to obtain **17a**), to give **17b** (520 mg, 65% over 2 steps) as a colorless oil: R_f = 0.7 (hexane/EtOAc = 4:1); $[\alpha]_D^{28}$ = −59.4 (*c* 1.65, CH_2Cl_2); IR (neat) ν_{max} 3514, 3072, 2930, 2858, 1640, 1598, 1472, 1428, 1347, 1161, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69−7.66 (m, 4H), 7.62−7.61 (m, 2H), 7.50−7.38 (m, 6H), 6.89−6.87 (m, 2H), 6.09−6.01 (m, 1H), 5.97−5.90 (m, 3H), 5.84 (dd, *J* = 3.0, 10.3 Hz, 1H), 5.52 (s, 1H), 5.21−5.18 (m, 2H), 5.11 (dd, *J* = 1.2, 10.4 Hz, 1H), 4.28−4.25 (m, 1H), 4.14 (dd, *J* = 6.7, 17.1 Hz, 1H), 3.73−3.64 (m, 2H), 3.55 (dd, *J* = 4.9, 10.4 Hz, 1H), 2.57 (dd, *J* = 2.7, 14.0 Hz, 1H), 2.35 (dd, *J* = 7.9, 14.0 Hz, 1H), 2.22 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.4, 137.3, 136.1, 135.8, 133.0, 132.0, 130.0, 129.3, 128.9, 127.9, 127.8, 120.0, 116.7, 84.3, 75.0, 69.4, 65.4, 46.6, 41.9, 26.9, 21.4, 19.2; HRMS calcd for $C_{35}H_{43}NNaO_5SSi$ $[M + Na]^+$ 640.2529, found 640.2521.

(2S,4aR,9aS)-2-((tert-Butyldiphenylsilyloxy)methyl)-9-tosyl-2,4a,5,8,9,9a-hexahydro-pyrano-[2,3-b]azepin-4a-ol ***18b***. The triene **17b** (450 mg, 0.73 mmol) was subjected to ring-closing metathesis as done for triene **17a**, to furnish **18b** (370 mg, 86%) as a pale yellow oil: R_f = 0.7 (hexane/EtOAc = 9:1); $[\alpha]_D^{28}$ = −84.4 (*c* 0.45, CH_2Cl_2); IR (neat) $\nu_{max,}$ 3498, 3028, 2930, 2857, 1598, 1472, 1427, 1339, 1158, 1112, 1046 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78−7.76 (m, 2H), 7.69−7.66 (m, 4H), 7.44−7.36 (m, 6H), 7.11−7.10 (m, 2H), 5.86−5.80 (m, 2H), 5.75−5.71 (m, 1H), 5.53−5.49 (m, 1H), 5.46 (s, 1H), 4.51−4.49 (m, 1H), 4.27 (dt, *J* = 3.0, 17.7 Hz, 1H), 3.99 (dd, *J* = 6.1, 11.0 Hz, 1H), 3.87−3.82 (m, 2H), 2.40 (br s, 2H), 2.33 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 137.5, 135.7, 135.1, 133.3, 133.2, 129.9, 129.4, 128.8, 128.0, 127.8, 125.9, 83.2, 76.7, 69.1, 63.5, 42.3, 36.0, 26.9, 21.6, 19.3; HRMS calcd for $C_{33}H_{39}NNaO_5SSi$ $[M + Na]^+$ 612.2216, found 612.2214.

Compound ***19b***. The diene **18b** (150 mg, 0.25 mmol) was subjected to dihydroxylation by using the same procedure followed for converting **18a** to **19a**. The crude polyol was dissolved in dry CH_2Cl_2 (3 mL) and cooled to 0 °C. Then 2,2-dimethoxypropane (0.04 mL, 0.30 mmol) was added followed by PTSA (8 mg, 0.05 mmol). After 30

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min the reaction mixture was diluted with aq $NaHCO_3$ and extracted using CH_2Cl_2 (3 × 3 mL). Organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel column chromatography to furnish **19b** (185 mg, 84%) as a colorless oil: R_f = 0.5 (hexane/EtOAc = 9:1); $[\alpha]_D^{28}$ = +14.9 (*c* 1.65, CH_2Cl_2); IR (neat) ν_{max} 2923, 1744, 1702, 1368, 1234, 1043 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71−7.64 (m, 6H, aromatic), 7.44−7.35 (m, 6H, aromatic), 6.96−6.94 (m, 2H, aromatic), 5.56 (s, 1H, −O*H*), 5.02 (s, 1H, H-9a), 4.68 (dd, *J* = 1.8, 7.3 Hz, 1H, H-3), 4.54 (br s, 1H, H-6), 4.42−4.32 (m, 2H, H-2, H-7), 4.06 (d, *J* = 7.3 Hz, 1H, H-4), 3.86 (m, 1H, H-10), 3.64 (dd, *J* = 11.5, 14.6 Hz, 1H, H-8β), 3.49 (dd, *J* = 5.0, 9.2 Hz, 1H, H-10′), 3.27 (dd, *J* = 5.4, 14.6 Hz, 1H, H-8α), 2.34 (dd, *J* = 3.4, 16.2 Hz, 1H, H-5β), 2.24 (s, 3H, −NSO_2PhCH_3), 2.18 (dd, *J* = 3.4, 16.2 Hz, 1H, H-5α), 1.60 (s, 3H, −$OCOCH_3$), 1.42 (s, 3H, −$OCOCH_3$), 1.38 (s, 3H, −$OCOCH_3$), 1.32 (s, 3H, −$OCOCH_3$), 1.02 (s, 9H, −$Si(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 136.7, 135.7, 135.6, 133.6, 133.5, 129.7, 129.0, 128.1, 127.7, 127.6, 109.6, 108.4, 80.6, 79.2, 76.7, 75.9, 74.4, 73.3, 72.0, 62.4, 42.9, 28.9, 28.3, 26.9, 26.8, 25.6, 24.0, 21.4, 21.4, 19.3; HRMS calcd for $C_{39}H_{52}NO_9SSi$ $[M + H]^+$ 738.3132, found 738.3129.

(2R,3R,4S,4aR,6S,7R,9aS)-2-(Hydroxymethyl)decahydropyrano-[2,3-b]azepine-3,4,4a,6,7-pentaol ***20b***. Deprotection of tosyl and silyl groups of **19b** (150 mg, 0.20 mmol) was done in the same way as for **19a** followed by evaporation. The crude was dissolved in CH_3OH and stirred overnight with DOWEX-50 acidic resin (50 mg). The solution was treated with aq ammonia solution, concentrated, and the compound was purified in the manner described for **20a**, giving **20b** (24 mg, 52%) as a thick colorless liquid: R_f = 0.3 (EtOAc/MeOH = 19:1); $[\alpha]_D^{28}$ = +21.2 (*c* 0.40, CH_3OH); IR (neat) ν_{max} 3510, 3070, 2928, 1158, 1110 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 5.14 (s, 1H), 4.80−4.73 (m, 2H), 4.61−4.50 (m, 3H), 3.50−3.18 (m, 4H), 1.90−1.74 (m, 2H); ^{13}C NMR (125 MHz, D_2O) δ 94.2, 89.8, 88.6, 78.1, 64.2, 57.4, 55.0, 44.4; HRMS calcd for $C_{10}H_{20}NO_7$ $[M + H]^+$ 266.1240, found 252.1244.

((2S,6S)-6-(Allyloxy)-5-oxo-5,6-dihydro-2H-pyran-2-yl)methyl acetate ***21a*** *and ((2S,6R)-6-(Allyloxy)-5-oxo-5,6-dihydro-2H-pyran-2-yl)methyl acetate* ***21b***. Compound **15** (500 mg, 1.52 mmol) was dissolved in dry CH_2Cl_2 (8 mL) under N_2 atmosphere. To the solution was added allyl alcohol (0.11 mL, 1.67 mmol) followed by $BF_3{\cdot}Et_2O$ (0.47 mL, 3.8 mmol), and the resulting mixture was stirred at room temperature for 30 min. The mixture was then poured carefully into aq $NaHCO_3$ (10 mL) and shaken well followed by extraction using CH_2Cl_2 (3 × 5 mL). The combined extracts were dried over Na_2SO_4 and concentrated under a vacuum, and the residue was purified by column chromatography giving **21a** (65 mg, 19%) and **21b** (172 mg, 50%) as colorless oils.

21a: R_f = 0.5 (hexane/EtOAc = 3:1); $[\alpha]_D^{28}$ = +36.5.9 (*c* 1.25, CH_2Cl_2); IR (neat) ν_{max} 2923, 1744, 1702, 1368, 1234, 1043 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (dd, *J* = 1.7, 10.7 Hz, 1H), 6.19 (dd, *J* = 2.5, 10.7 Hz, 1H), 5.97−5.87 (m, 1H), 5.36−5.31 (m, 1H), 5.25 (dd, *J* = 1.7, 10.0 Hz, 1H), 4.93 (s, 1H), 4.78−4.75 (m, 1H), 4.39−4.17 (m, 4H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.3, 170.6, 147.0, 133.0, 126.3, 118.5, 96.9, 69.8, 66.9, 64.5, 20.7; HRMS calcd for $C_{11}H_{14}NaO_5$ $[M + Na]^+$ 249.0739, found 249.0737.

21b: R_f = 0.5 (hexane/EtOAc = 3:1); $[\alpha]_D^{28}$ = −137.1 (*c* 0.35, CH_2Cl_2); IR (neat) ν_{max} 2928, 1742, 1701, 1365, 1235, 1041 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (dd, *J* = 3.2, 10.6 Hz, 1H), 6.23 (dd, *J* = 2.2, 10.6 Hz, 1H), 5.96−5.87 (m, 1H), 5.36−5.31 (m, 1H), 5.25 (dd, *J* = 1.4, 10.0 Hz, 1H), 4.94 (s, 1H), 4.72−4.67 (m, 1H), 4.40−4.31 (m, 3H), 4.19 (ddd, J = 4.6, 5.9, 11.0 Hz, 1H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.3, 170.5, 146.4, 132.9, 126.2, 118.5, 96.6, 70.7, 69.5, 65.5, 20.8; HRMS calcd for $C_{11}H_{14}NaO_5$ $[M + Na]^+$ 249.0739, found 249.0739.

(2S,3R,6S)-2-(Allyloxy)-6-((tert-butyldiphenylsilyloxy)methyl)-3-vinyl-3,6-dihydro-2H-pyran-3-ol ***22a***. Following the procedure used for Grignard addition reaction and silyl protection for converting enone **16** to **17a**, enone **21a** (350 mg, 1.55 mmol) was converted to **22a** (460 mg, 66% over 2 steps) as a colorless oil: R_f = 0.5 (hexane/EtOAc = 3:1); $[\alpha]_D^{28}$ = +40.0 (*c* 0.70, CH_2Cl_2); IR (neat) ν_{max} 2928, 1642, 1365, 1235, 1041 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71−7.66 (m, 4H), 7.43−7.35 (m, 6H), 5.95−5.83 (m, 2H), 5.60 (d, *J* = 10.3 Hz, 1H), 5.32−5.26 (m, 2H), 5.20 (d, *J* = 10.3 Hz, 1H), 5.13 (dd, *J* = 1.2, 10.8 Hz, 1H), 4.68 (s, 1H), 4.23 (dd, *J* = 5.1, 12.6 Hz, 1H), 4.17 (t, *J* = 5.7 Hz, 1H), 4.08 (dd, *J* = 6.2, 12.6 Hz, 1H), 3.74 (dd, *J* = 5.7, 10.3 Hz, 1H), 3.66 (dd, *J* = 6.2, 10.3 Hz, 1H), 2.84 (br s, 1H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.4, 135.7, 134.8, 133.8, 133.5, 133.4, 129.8, 129.7, 129.4, 127.8, 127.7, 126.6, 117.9, 115.5, 99.3, 70.2, 69.4, 69.2, 66.1, 26.9, 26.6, 19.3; HRMS calcd for $C_{27}H_{34}NaO_4Si$ $[M + Na]^+$ 473.2124, found 473.2128.

(2S,4aR,8aS)-2-((tert-Butyldiphenylsilyloxy)methyl)-2,4a,7,8a-tetrahydropyrano[2,3-b]-pyran-4a-ol ***23a***. The ring-closing metathesis reaction of **22a** (425 mg, 0.94 mmol) was performed following the same procedure as used for triene **17a** affording **23a** (355 mg, 89%) as a pale yellow oil: R_f = 0.4 (hexane/EtOAc = 3:1); $[\alpha]_D^{28}$ = −40.0 (*c* 0.75, CH_2Cl_2); IR (neat) $\nu_{max,}$ 3468, 3070, 2930, 2857, 1472, 1427, 1347, 1176, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67−7.65 (m, 4H), 7.43−7.36 (m, 6H), 6.02 (dd, *J* = 2.3, 10.3 Hz, 1H), 5.96−5.92 (m, 2H), 5.86 (ddd, *J* = 1.7, 2.9, 9.7 Hz, 1H), 4.98 (s, 1H), 4.65−4.62 (m, 1H), 4.48 (dt, *J* = 2.6, 17.1 Hz, 1H), 4.35 (dt, *J* = 2.0, 17.1 Hz, 1H), 3.91 (dd, *J* = 5.1, 10.3 Hz, 1H), 3.81 (dd, *J* = 4.6, 10.3 Hz, 1H), 2.27 (br s, 1H), 1.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.7, 135.6, 133.2, 133.0, 131.6, 130.7, 129.9, 129.8, 129.1, 128.2, 127.8, 97.2, 76.5, 67.2, 65.4, 61.2, 26.8, 19.2; HRMS calcd for $C_{25}H_{30}NaO_4Si$ $[M + Na]^+$ 445.1811, found 445.1813.

(2R,3S,4S,4aR,5R,6R,8aS)-2-((tert-Butyldiphenylsilyloxy)methyl)-4a-hydroxyoctahydro-pyrano[2,3-b]pyran-3,4,5,6-tetrayl tetraacetate ***24a***. The same method of dihydroxylation and acetylation that was used for compound **18a** was followed with **23a** (200 mg, 0.47 mmol) to yield **24a** (272 mg, 83%) as a pale yellow oil: R_f = 0.4 (hexane/EtOAc = 3:1); $[\alpha]_D^{28}$ = −40.0 (*c* 0.75, CH_2Cl_2); IR (neat) ν_{max} 3468, 3070, 2930, 2857, 1742, 1472, 1427, 1347, 1176, 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70−7.66 (m, 4H, aromatic), 7.44−7.38 (m, 6H, aromatic), 5.51 (d, *J* = 5.1 Hz, 1H, H-5), 5.43 (dd, *J* = 2.3, 4.0 Hz, 1H, H-3), 5.41−5.37 (m, 1H, H-6), 5.35 (d, *J* = 5.1 Hz, 1H, H-4), 5.03 (s, 1H, H-8a), 4.13 (t, *J* = 6.3 Hz, 1H, H-9), 3.98−3.91 (m, 2H, H-2, H-7), 3.82 (dd, *J* = 6.3, 13.1 Hz, 1H, H-9′), 3.60 (t, *J* = 13.7 Hz, 1H, H-7′), 3.21 (s, 1H, −OH), 2.13 (s, 3H, −$OCOCH_3$), 2.05 (s, 3H, −$OCOCH_3$), 1.93 (s, 3H, −$OCOCH_3$), 1.92 (s, 3H, −$OCOCH_3$), 1.09 (s, 9H, −$Si(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 169.4, 135.7, 132.2, 130.2, 130.1, 128.0, 127.8, 95.2, 78.0, 71.4, 69.0, 66.2, 65.0, 64.9, 64.2, 26.9, 21.0, 20.7, 20.4, 19.2; HRMS calcd for $C_{33}H_{43}O_{12}Si$ $[M + H]^+$ 659.2524, found 659.2525.

(2R,3R,4S,4aR,5R,6R,8aS)-2-(Hydroxymethyl)octahydropyrano-[2,3-b]pyran-3,4,4a,5,6-pentaol ***25a***. Compound **24a** (180 mg, 0.26 mmol) was dissolved in dry THF (5 mL), and TBAF solution (1 M soln in THF, 0.57 mL, 0.57 mmol) was added to it. The reaction mixture was first stirred at room temperature for 2 h. Solvent was removed in vacuo, and the residue dissolved in dry CH_3OH (4 mL). Liquor ammonia solution (25% w/v, 0.5 mL) was added, and the reaction mixture was stirred at room temperature overnight. The solution was concentrated under a vacuum, and the residue was purified by repeatedly washing with 50% EtOAc/Hexane and then distilled $CHCl_3$ to furnish **25a** (47 mg, 71%) as a colorless pasty liquid: R_f = 0.3 (EtOAc/MeOH = 19:1); $[\alpha]_D^{28}$ = +1.6 (*c* 0.50, CH_3OH); IR (neat) ν_{max} 3523, 3065, 2898, 1203, 1110 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 5.05 (s, 1H), 4.35 (dd, *J* = 2.4, 6.8 Hz, 1H), 4.14 (dd, *J* = 3.1, 9.2 Hz, 1H), 3.89−3.58 (m, 6H), 3.42 (m, 1H); ^{13}C NMR (125 MHz, D_2O) δ103.2, 72.1, 70.6, 67.7, 61.9, 61.8, 57.8, 56.9; HRMS calcd for $C_9H_{16}NaO_8$ $[M + Na]^+$ 275.0743, found 275.0742.

(2S,3R,6S)-3-Allyl-2-(allyloxy)-6-((tert-butyldiphenylsilyloxy)-methyl)-3,6-dihydro-2H-pyran-3-ol ***22b***. Following the procedure used for vinyl Grignard addition reaction and silyl protection for converting enone **16** to **17b**, enone **21b** (390 mg, 1.72 mmol) was converted to **22b** (565 mg, 71% over 2 steps) as a colorless oil: R_f = 0.5 (hexane/EtOAc = 9:1); $[\alpha]_D^{28}$ = +20.0 (*c* 0.40, CH_2Cl_2); IR (neat) ν_{max} 3557, 3071, 2930, 2857, 1472, 1428, 1112, 1048 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71−7.66 (m, 4H), 7.44−7.35 (m, 6H), 5.94−5.83 (m, 2H), 5.76 (dd, *J* = 1.8, 10.4 Hz, 1H), 5.69 (dt, *J* = 1.8, 10.4 Hz, 1H), 5.27 (dd, *J* = 1.8, 17.7 Hz, 1H), 5.19 (dd, *J* = 1.8, 10.4 Hz, 1H), 5.08−5.03 (m, 2H), 4.74 (s, 1H), 4.24−4.20 (m, 1H), 4.16−4.13

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(m, 1H), 4.10−4.06 (m, 1H), 3.72 (dd, J = 5.5, 10.4 Hz, 1H), 3.67 (dd, J = 5.5, 10.4 Hz, 1H), 2.68 (br s, 1H), 2.39 (dd, J = 6.7, 14.0 Hz, 1H), 2.33 (dd, J = 7.9, 14.0 Hz, 1H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.7, 135.2, 134.8, 133.9, 133.4, 132.9, 130.7, 129.7, 127.8, 127.7, 126.3, 118.2, 117.8, 99.2, 69.6, 69.1, 68.9, 66.1, 43.5, 26.9, 26.6, 19.3; HRMS calcd for $C_{28}H_{36}NaO_4Si$ $[M + Na]^+$ 487.2281, found 487.2285.

(2S,4aR,9aS)-2-((tert-Butyldiphenylsilyloxy)methyl)-4a,5,8,9a-tetrahydro-2H-pyrano-[2,3-b]oxepin-4a-ol ***23b***. The ring-closing metathesis reaction of **22b** (450 mg, 0.97 mmol) was performed following the same procedure as used for diene **17a**, affording **23b** (326 mg, 77%) as a pale yellow oil: R_f = 0.6 (hexane/EtOAc = 9:1); $[\alpha]_D^{28}$ = −21.4 (c 0.70, CH_2Cl_2); IR (neat) ν_{max} 3557, 3071, 2930, 2857, 1472, 1428, 1112, 1048 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67−7.65 (m, 4H), 7.43−7.35 (m, 6H), 6.04 (dd, J = 1.5, 10.7 Hz, 1H), 5.82−5.73 (m, 2H), 5.33 (s, 1H), 5.13−5.10 (m, 2H), 5.05 (t, J = 4.5 Hz, 1H), 4.40−4.35 (m, 1H), 3.78 (dd, J = 4.9, 10.3 Hz, 1H), 3.68 (dd, J = 5.7, 10.3 Hz, 1H), 2.46−2.37 (m, 1H), 1.71−1.65 (m, 2H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.7, 133.4, 132.1, 129.8, 129.7, 129.2, 127.9, 127.7, 119.0, 102.2, 101.0, 73.2, 68.6, 64.6, 40.7, 26.8, 19.3; HRMS calcd for $C_{26}H_{32}NaO_4Si$ $[M + Na]^+$ 459.1968, found 459.1965.

(2R,3S,4S,4aR,6S,7R,9aS)-2-((tert-Butyldiphenylsilyloxy)methyl)-octahydro-2H-pyrano-[2,3-b]oxepine-3,4,4a,6,7-pentayl pentaacetate ***24b***. The same method of dihydroxylation and acetylation that was used for compound **18a** was followed for **23b** (200 mg, 0.46 mmol) to yield **24b** (290 mg, 88%) as a colorless oil: R_f = 0.5 (hexane/EtOAc = 9:1); $[\alpha]_D^{28}$ = −12.8 (c 0.40, CH_2Cl_2); IR (neat) ν_{max} 3557, 3071, 2930, 2857, 1742, 1112, 1048 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61−7.57 (m, 4H, aromatic), 7.43−7.33 (m, 6H, aromatic), 5.49−5.46 (m, 1H, H-7), 5.36 (s, 1H, H-9a), 5.30 (m, 1H, H-4), 5.23−5.17 (m, 1H, H-8), 4.97 (dd, J = 5.2, 9.1 Hz, 1H, H-6), 4.30 (dd, J = 3.2, 11.9 Hz, 1H, H-8′), 4.24 (dd, J = 3.2, 11.9 Hz, 1H, H-2), 4.03 (ddd, J = 6.4, 11.9, 24.7 Hz, 1H, H-3), 3.74−3.71 (m, 1H, H-10), 3.58−3.56 (m, 1H, H-10′), 2.07 (s, 3H −OCOCαH_3), 2.03 (s, 3H −OCOCH_3), 2.02 (s, 3H −OCOCH_3), 2.00 (s, 3H −OCOCH_3), 1.95 (s, 3H, −OCOCH_3), 1.70 (dd, J = 5.0, 7.3 Hz, 1H, H-5β), 1.00 (s, 9H), 0.96 (m, 1H, H-5α); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 169.8, 135.6, 129.8, 127.8, 83.5, 76.5, 71.1, 70.2, 68.7, 60.8, 26.7, 26.6, 20.3, 20.2, 20.0; HRMS calcd for $C_{36}H_{46}NaO_{13}Si$ $[M + Na]^+$ 737.2605, found 737.2609.

(2R,3R,4S,4aR,6S,7R,9aS)-2-(Hydroxymethyl)octahydro-2H-pyrano[2,3-b]oxepine-3,4,4a,6,7-pentaol ***25b***. Following the same procedure used for deprotection of **24a** to **25a**, compound **24b** (270 mg, 0.38 mmol) was deprotected to provide **25b** in 70% yield (70 mg) as a thick whitish liquid: R_f = 0.3 (EtOAc/MeOH = 19:1); $[\alpha]_D^{28}$ = +1.6 (c 0.50, CH_3OH); IR (neat) ν_{max} 3523, 3065, 2898, 1203, 1110 cm^{-1}; ^{1}H NMR (500 MHz, D_2O) δ 5.07 (s, 1H), 4.25−4.12 (m, 2H), 3.90−3.62 (m, 6H), 3.52 (br s, 1H), 1.92−1.73 (m, 2H); ^{13}C NMR (125 MHz, D_2O) δ 104.2, 86.8, 79.6, 71.1, 69.2, 62.4, 58.0, 28.4, 27.5; HRMS calcd for $C_{10}H_{18}NaO_8$ $[M + Na]^+$ 289.0899, found 289.0901.

(2R,3R,6S)-2,3-Diallyl-6-((tert-butyldiphenylsilyloxy)methyl)-3,6-dihydro-2H-pyran-3-ol ***27a*** *and (2R,3S,6S)-2,3-Diallyl-6-((tert-butyldiphenylsilyloxy)methyl)-3,6-dihydro-2H-pyran-3-ol* ***27b***. To an ice-cooled stirred solution of enone **26** (800 mg, 1.97 mmol) in THF (10 mL) under N_2 atmosphere was added freshly prepared allylmagnesium chloride solution (19.7 mmol) in THF (30 mL), and the mixture was allowed to stir overnight with gradual warming to room temperature. The excess Grignard reagent was quenched with saturated NH_4Cl solution (20 mL), and the reaction mixture extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (1 × 40 mL), dried over Na_2SO_4, concentrated, and the residue was passed through a short column and eluted with 50% EtOAc. The eluent was concentrated and dissolved in dry CH_2Cl_2 (10 mL). Then TBDPSCl (0.55 mL, 2.17 mmol), followed by imidazole (343 mg, 5.91 mmol) were added, and the resulting solution was stirred for 3 h. Saturated $NaHCO_3$ was added to the reaction mixture and extracted with CH_2Cl_2. Extracts were dried (Na_2SO_4) and concentrated. The resulting residue was purified using column chromatography to yield a mixture of **27a** (122 mg, 14%) and **27b** (548 mg, 62%).

27a: Colorless oil; R_f = 0.7 (hexane/EtOAc = 9:1); $[\alpha]_D^{28}$ = −33.8 (c 2.50, CH_2Cl_2); IR (neat) ν_{max} 3436, 3071, 2930, 2851, 1471, 1427, 1112 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71−7.64 (m, 4H), 7.43−7.36 (m, 6H), 5.98−5.85 (m, 4H), 5.77 (dd, J = 2.1, 10.3 Hz, 1H), 5.16−5.03 (m, 4H), 4.20−4.18 (m, 1H), 3.79 (dd, J = 3.6, 10.7 Hz, 1H), 3.72−3.69 (m, 1H), 2.41−2.34 (m, 2H), 2.27−2.22 (m, 2H) 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.7, 135.2, 134.8, 133.1, 132.2, 129.7, 127.8, 118.5, 116.7, 78.5, 71.6, 65.3, 40.3, 33.0, 26.6, 19.2, 19.1; HRMS calcd for $C_{28}H_{36}NaO_3Si$ $[M + Na]^+$ 471.2331, found 471.2333.

27b: R_f = 0.6 (hexane/EtOAc = 9:1); $[\alpha]_D^{28}$ = −3.3 (c 1.05, CH_2Cl_2); IR (neat) ν_{max} 3432, 3071, 2929, 2856, 1639, 1472, 1427, 1112 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66−7.64 (m, 4H), 7.44−7.35 (m, 6H), 5.97−5.90 (m, 3H), 5.86 (dd, J = 2.7, 10.3 Hz, 1H), 5.15−5.03 (m, 4H), 4.25−4.23 (m, 1H), 3.82 (dd, J = 3.6, 9.5 Hz, 1H), 3.74−3.67 (m, 2H), 2.41−2.34 (m, 3H), 2.26 (dd, J = 8.5, 13.7 Hz, 1H), 1.89 (br s, 1H), 1.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1, 135.7, 133.3, 133.2, 132.7, 132.0, 129.8, 128.9, 127.7, 119.0, 116.4, 76.0, 73.0, 68.4, 64.8, 42.1, 32.7, 26.8, 19.2; HRMS calcd for $C_{28}H_{36}NaO_3Si$ $[M + Na]^+$ 471.2331, found 471.2338.

(2R,6R)-5,6-Diallyl-2-((tert-butyldiphenylsilyloxy)methyl)-2H-pyran-3(6H)-one ***28***. To a well-stirred suspension of PCC (620 mg, 2.90 mmol) in dry CH_2Cl_2 (5 mL) at room temperature was added a solution of mixture of alcohols **27a**/**b** (650 mg, 1.45 mmol) in CH_2Cl_2 (3 mL), and the mixture was stirred vigorously overnight. The resulting suspension was diluted with Et_2O (20 mL) and decanted. The residue was washed repeatedly with Et_2O (3 × 5 mL) leaving behind the brown solids. The eluent was washed with 1 N NaOH (1 × 20 mL), 1 N HCl (1 × 20 mL), aq $NaHCO_3$ (1 × 20 mL) and brine (1 × 20 mL). The organic layer was dried over Na_2SO_4, concentrated in vacuo, and the residue purified by column chromatography to obtain **28** (530 mg, 82%) as a colorless oil: R_f = 0.7 (hexane/EtOAc = 9:1); $[\alpha]_D^{28}$ = −32.7 (c 0.55, CH_2Cl_2); IR (neat) ν_{max} 3071, 2929, 2856, 1733, 1682, 1472, 1427, 1112 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67−7.63 (m, 4H), 7.43−7.36 (m, 6H), 5.99 (d, J = 1.2 Hz, 1H), 5.97−5.88 (m, 1H), 5.78−5.70 (m, 1H), 5.21−5.12 (m, 4H), 4.57 (t, J = 5.8 Hz, 1H), 4.28 (t, J = 3.7 Hz, 1H), 4.03−4.03 (m, 2H), 2.98−2.87 (m, 2H), 2.53−2.50 (m, 2H), 1.01 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.0, 164.1, 135.8, 135.6, 134.8, 133.9, 133.4, 133.0, 132.2, 129.7, 127.7, 124.1, 119.3, 117.8, 77.6, 73.9, 64.8, 37.6, 36.1, 26.8, 19.3; HRMS calcd for $C_{28}H_{34}NaO_3Si$ $[M + Na]^+$ 469.2175, found 469.2179.

(2R,3S,6R)-5,6-Diallyl-2-((tert-butyldiphenylsilyloxy)methyl)-3,6-dihydro-2H-pyran-3-yl acetate ***29a*** *and (2R,3R,6R)-5,6-Diallyl-2-((tert-butyldiphenylsilyloxy)methyl)-3,6-dihydro-2H-pyran-3-yl acetate* ***29b***. The enone **28** (510 mg, 1.14 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and cooled to 0 °C. To the solution was added DIBAL-H (1 M solution in toluene, 2.28 mL, 2.28 mmol), and the reaction mixture stirred for 1 h. Then CH_3OH (3 mL) was added slowly until the effervescence ceased. The resulting turbid solution was washed with saturated sodium potassium tartrate solution (5 mL) and extracted with EtOAc (3 × 10 mL). Combined organic extracts were washed with brine (1 × 20 mL), and dried over Na_2SO_4. The solvent was removed by evaporation, and the residue used without purification for the next step. The crude alcohol was dissolved in dry CH_2Cl_2 (5 mL), and Ac_2O (0.24 mL, 2.50 mmol) and Et_3N (0.48 mL, 3.42 mmol) were added to it, and the reaction mixture stirred for 1 h at rt. Solvent was evaporated under a vacuum, and the residue purified by column chromatography to afford alcohols **29a** (90 mg, 16%) and **29b** (312 mg, 56%).

29a: Colorless oil, R_f = 0.7 (hexane/EtOAc = 9:1); $[\alpha]_D^{28}$ = −3.0 (c 1.65, CH_2Cl_2); IR (neat) ν_{max} 3072, 2929, 2856, 1738, 1639, 1472, 1427, 1234, 1112 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67−7.65 (m, 4H), 7.42−7.35 (m, 6H), 5.99−5.91 (m, 1H), 5.71−5.65 (m, 1H), 5.52 (br s, 1H), 5.16−5.03 (m, 5H), 4.08 (dd, J = 3.6, 8.2 Hz, 1H), 3.87 (td, J = 4.6, 6.1 Hz, 1H), 3.73−3.68 (m, 2H), 2.71 (dd, J = 6.1, 15.9 Hz, 1H), 2.65 (dd, J = 7.3, 15.9 Hz, 1H), 2.46−2.35 (m, 1H), 1.97 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 143.1, 135.7, 134.9, 134.5, 133.4, 129.7, 127.7, 119.7, 117.6, 116.8,

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73.5, 72.2, 66.2, 63.5, 37.3, 35.9, 32.0, 26.8, 22.7, 21.3, 19.3; HRMS calcd for $C_{30}H_{38}NaO_4Si$ $[M + Na]^+$ 513.2437, found 513.2435.

29b: R_f = 0.7 (hexane/EtOAc = 9:1); $[\alpha]_D^{28}$ = +40.3 (*c* 0.85, CH_2Cl_2); IR (neat) ν_{max} 3072, 2930, 2857, 1737, 1639, 1472, 1428, 1370, 1238, 1111 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65−7.62 (m, 4H), 7.43−7.35 (m, 6H), 5.89−5.69 (m, 3H), 5.16 (dd, *J* = 2.1, 5.2 Hz, 1H), 5.10−5.00 (m, 4H), 4.16 (dd, *J* = 2.7, 9.7 Hz, 1H), 3.94 (td, *J* = 2.1, 6.7 Hz, 1H), 3.78−3.73 (m, 2H), 2.78−2.69 (m, 2H), 2.41−2.27 (m, 2H), 1.97 (s, 3H), 1.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 144.8, 135.6, 134.4, 129.8, 129.7, 127.7, 118.7, 117.7, 116.9, 74.9, 69.7, 64.7, 62.5, 37.6, 34.8, 32.0, 26.8, 22.7, 21.1, 19.2; HRMS calcd for $C_{30}H_{38}NaO_4Si$ $[M + Na]^+$ 513.2437, found 513.2437.

(2R,3R,8aR)-2-((tert-Butyldiphenylsilyloxy)methyl)-3,5,8,8a-tetrahydro-2H-chromen-3-yl acetate ***30***. The triene **29b** (290 mg, 0.59 mmol) was dissolved in dry CH_2Cl_2 and placed under N_2 atmosphere. To this solution was added Grubbs' second generation catalyst (19 mg, 0.023 mmol), and the reaction mixture stirred at room temperature for 2 h. The solvent was removed under a vacuum, and the residue purified by column chromatography to provide diene **30** (215 mg, 80%) as a colorless oil: R_f = 0.5 (hexane/EtOAc = 9:1); $[\alpha]_D^{28}$ = −104.3 (*c* 0.70, CH_2Cl_2); IR (neat) ν_{max} 3047, 2931, 2857, 1737, 1472, 1427, 1371, 1237, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65−7.62 (m, 4H), 7.43−7.35 (m, 6H), 5.89 (d, *J* = 5.7 Hz, 1H), 5.59 (br s, 2H), 5.16 (dd, *J* = 1.7, 5.7 Hz, 1H), 4.45 (dd, J = 7.1, 9.7 Hz, 1H), 3.87−3.76 (m, 3H), 2.96 (d, *J* = 19.7 Hz, 1H), 2.76 (d, *J* = 19.7 Hz, 1H), 2.45−2.27 (m, 2H), 1.98 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 143.1, 135.6, 134.9, 133.4, 129.8, 127.7, 125.5, 124.6, 115.1, 71.8, 70.8, 65.3, 62.5, 33.9, 30.5, 21.1, 19.2; HRMS calcd for $C_{28}H_{34}NaO_4Si$ $[M + Na]^+$ 485.2124, found 485.2123.

(2R,3R,8aR)-2-((tert-Butyldiphenylsilyloxy)methyl)-5-oxo-3,5,8,8a-tetrahydro-2H-chromen-3-yl acetate ***31***. To a vigorously stirred suspension of CrO_3 (90 mg, 0.9 mmol) in dry CH_2Cl_2 (2 mL) was added dry pyridine (0.08 mL, 0.9 mmol) slowly at 0 °C. The diene **30** (210 mg, 0.45 mmol) dissolved in dry CH_2Cl_2 (2 mL) was added to this suspension, and the mixture stirred for 24 h at room temperature. On consumption of starting material (TLC monitoring), Et_2O was added to the mixture and decanted, followed by washing of the residue with Et_2O. Extracts were concentrated, and the residue purified by column chromatography to give **31** (160 mg, 76%) as a colorless oil: R_f = 0.5 (hexane/EtOAc = 4:1); $[\alpha]_D^{28}$ = −55.2 (*c* 0.85, CH_2Cl_2); IR (neat) ν_{max} 3071, 2956, 2857, 1738, 1679, 1472, 1428, 1371, 1234, 1113 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64−7.61 (m, 4H), 7.44−7.36 (m, 6H), 7.06 (d, *J* = 9.7 Hz, 1H), 6.32 (dd, *J* = 2.0, 5.4 Hz, 1H), 6.00 (d, *J* = 9.7 Hz, 1H), 5.37−5.35 (m, 1H), 4.66 (dd, *J* = 4.9, 12.6 Hz, 1H), 3.98 (dd, *J* = 3.1, 6.6 Hz, 1H), 3.82−3.80 (m, 2H), 2.74 (dd, *J* = 5.7, 15.5 Hz, 1H), 2.66 (dd, *J* = 13.2, 15.5 Hz, 1H), 1.98 (s, 3H), 1.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.2, 170.6, 143.8, 138.6, 135.6, 133.2, 133.1, 129.9, 129.7, 127.8, 125.9, 71.9, 69.3, 64.8, 61.7, 43.8, 29.8, 26.8, 20.9, 19.2; HRMS calcd for $C_{28}H_{36}NO_5Si$ $[M + NH_4]^+$ 494.2363, found 494.2366.

(2R,3R,5S,8aR)-5-(tert-Butyldimethylsilyloxy)-2-((tert-butyldiphenylsilyloxy)methyl)-3,5,8,8a-tetrahydro-2H-chromen-3-yl acetate ***32a*** *and (2R,3R,5R,8aR)-5-(tert-Butyldimethylsilyloxy)-2-((tert-butyldiphenylsilyloxy)methyl)-3,5,8,8a-tetrahydro-2H-chromen-3-yl acetate* ***32b***. The enone (150 mg, 0.32 mmol) was dissolved in dry CH_3OH (4 mL) and cooled in an ice-bath. Then $CeCl_3{\cdot}7H_2O$ (237 mg, 0.63 mmol) followed by $NaBH_4$ (24 mg, 0.63 mmol) were added, and the resulting reaction mixture was stirred for 1 h. Subsequently, saturated NH_4Cl solution was added carefully until effervescence ceased and extraction was done with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (1 × 15 mL), dried over Na_2SO_4, and concentrated to obtain a residue (R_f = 0.4 (hexane/EtOAc = 3:1)).

The crude mixture was dissolved in dry CH_2Cl_2 (3 mL), and then imidazole (56 mg, 0.96 mmol) and TBDMSCl (58 mg, 0.38 mmol) were added in succession, and the reaction mixture allowed to stir overnight at room temperature. Saturated $NaHCO_3$ solution (5 mL) was added, and extraction was done with CH_2Cl_2 (3 × 5 mL). The combined extracts were washed with brine (1 × 15 mL), dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography to give **32a** (20 mg, 10%) and **32b** (102 mg, 54%) as colorless oils.

32a: R_f = 0.7 (hexane/EtOAc = 9:1); $[\alpha]_D^{28}$ = +10.9 (*c* 0.70, CH_2Cl_2); IR (neat) ν_{max} 3071, 2955, 2930, 2857, 1737, 1471, 1370, 1237, 1112, 1090 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64−7.61 (m, 4H), 7.42−7.35 (m, 6H), 6.09 (d, *J* = 6.1 Hz, 1H), 5.69−5.66 (m, 1H), 5.55−5.53 (m, 1H), 5.20 (dd, *J* = 1.8, 5.8 Hz, 1H), 4.84 (m, 1H), 4.44 (dd, *J* = 7.0, 9.5 Hz, 1H), 3.86 (td, *J* = 1.5, 6.7 Hz, 1H), 3.81−3.74 (m, 2H), 2.49−2.43 (m, 1H), 2.29−2.23 (m, 1H), 1.97 (s, 3H), 1.03 (s, 9H), 0.93 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.6, 131.0, 129.7, 127.7, 125.8, 70.9, 64.4, 62.6, 30.6, 29.7, 26.8, 25.9, 21.0, 0.08; HRMS calcd for $C_{34}H_{48}NaO_5Si_2$ $[M + Na]^+$ 615.2938, found 615.2936.

32b: R_f = 0.7 (hexane/EtOAc = 9:1); $[\alpha]_D^{28}$ = −103.9 (*c* 2.05, CH_2Cl_2); IR (neat) ν_{max} 3071, 2955, 2930, 2857, 1738, 1471, 1428, 1370, 1235, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66−7.61 (m, 4H), 7.43−7.35 (m, 6H), 6.02 (dd, *J* = 1.8, 10.1 Hz, 1H), 5.86 (d, *J* = 4.3 Hz, 1H), 5.67 (d, *J* = 10.1 Hz, 1H), 5.27 (dd, *J* = 2.7, 5.5 Hz, 1H), 4.49 (br s, 1H), 4.29 (d, *J* = 13.1 Hz, 1H), 3.89 (td, *J* = 2.7, 7.0 Hz, 1H), 3.81−3.73 (m, 2H), 2.21−2.17 (m, 1H), 1.96 (s, 3H), 1.82 (td, *J* = 10.3, 13.4 Hz, 1H), 1.04 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 140.5, 135.8, 135.6, 133.4, 129.8, 127.7, 126.5, 117.9, 72.1, 69.5, 68.5, 65.5, 62.0, 39.4, 26.8, 25.8, 21.0, 19.2, 18.2, −4.4, −4.6; HRMS calcd for $C_{34}H_{48}NaO_5Si_2$ $[M + Na]^+$ 614.3384, found 614.3383.

(2R,3S,4R,4aS,5R,6S,7S,8aR)-5-(tert-Butyldimethylsilyloxy)-2-((tert-butyldiphenyl-silyl-oxy)methyl)-4a-hydroxyoctahydro-2H-chromene-3,4,6,7-tetrayl tetraacetate ***33***. The diene **32b** (100 mg, 0.17 mmol) was dissolved in acetone/^{t}BuOH/H_2O solvent system (3:1:1, 3 mL) and *N*-methyl morpholine *N*-oxide (42 mg, 0.37 mmol) followed by OsO_4 (0.04 mmol) were added in succession, and the resulting mixture was stirred at room temperature for 72 h. Then saturated $Na_2S_2O_5$ solution (3 mL) was added and stirred for 1 h. The compound was extracted using EtOAc (3 × 5 mL), and the extracts were dried (Na_2SO_4) and concentrated.

The crude alcohol was dissolved in Ac_2O/Et_3N mixture (1:1, 3 mL) and stirred at room temperature overnight, following which the solvent was removed by evaporation, and the residue purified by column chromatography, to obtain **33** (82 mg, 62% over 2 steps) as a pale yellow oil: R_f = 0.4 (hexane/EtOAc = 4:1); $[\alpha]_D^{28}$ = +33.3 (*c* 0.15, CH_2Cl_2); IR (neat) ν_{max} 3454, 2955, 2926, 2854, 1753, 1463, 1428, 1370, 1235, 1112 cm^{-1}; ; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76−7.74 (m, 2H, aromatic), 7.69−7.67 (m, 2H, aromatic), 7.45−7.39 (m, 6H, aromatic), 5.50 (d, *J* = 10.3 Hz, 1H, H-4), 5.38 (dd, *J* = 7.4, 10.3 Hz, 1H, H-3), 5.26 (d, *J* = 3.5 Hz, 1H, H-5), 5.10 (dd, *J* = 3.5, 9.7 Hz, 1H, H-6), 4.33 (dd, *J* = 4.6, 12.0 Hz, 1H, H-8a), 4.24−4.20 (m, 1H, H-2), 3.91−3.82 (m, 3H, H-7, CH_2OSi), 2.51 (br s, 1H, −OH), 2.02 (s, 3H, −OCOCH_3), 1.94 (s, 3H, −OCOCH_3), 1.92 (s, 4H, H-8, −OCOCH_3), 1.87 (s, 4H, H-8′, −OCOCH_3), 1.11 (s, 9H, −Si(CH_3)$_3$), 0.85 (s, 9H, −Si(CH_3)$_3$), 0.06 (s, 3H, −SiCH_3), 0.03 (s, 3H, −SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 170.1, 169.5, 139.8, 135.6, 133.3, 129.8, 127.8, 122.1, 76.5, 72.3, 70.7, 68.4, 66.7, 63.6, 62.1, 36.9, 26.8, 25.6, 21.0, 20.9, 19.2, 17.9, −4.5, −4.7; HRMS calcd for $C_{40}H_{58}NaO_{12}Si_2$ $[M + Na]^+$ 809.3365, found 809.3372.

(2R,3R,4R,4aR,5R,6S,7S,8aR)-2-(Hydroxymethyl)octahydro-2H-chromene-3,4,4a,5,6,7-hexaol ***34***. The tetraacetate compound **33** (60 mg, 0.076 mmol) was subjected to deprotection and purification in the same manner as done using **24a**, to afford **34** (11 mg, 53%) as a colorless viscous oil: R_f = 0.3 (EtOAc/MeOH = 9:1); $[\alpha]_D^{28}$ = +35.6 (*c* 0.20, CH_3OH); IR (neat) ν_{max} 3507, 3080, 2905, 1203, 1165, 1110 cm^{-1}; ^1H NMR (500 MHz, D_2O)δ 3.91−3.78 (m, 5H), 3.68 (br s, 1H), 3.59−3.57 (m, 2H), 3.14 (dd, J = 3.7, 11.2 Hz, 1H), 1.67−1.54 (m, 2H); ^{13}C NMR (125 MHz, D_2O) δ 86.7, 77.8, 71.3, 68.5, 62.2, 60.9, 57.0, 55.3, 47.4, 25.8; HRMS calcd for $C_{10}H_{18}NaO_8$ $[M + Na]^+$ 289.0899, found 289.0895.

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■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra and additional spectra for all new compounds. 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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