Synthesis and Biological Evaluation of Fully Functionalized *seco*-Pancratistatin Analogues[§]

James McNulty,*[,†] Jerald J. Nair,[†] Carly Griffin,[‡] and Siyaram Pandey[‡]

Department of Chemistry, McMaster University, 1280 Main Street West, Hamilton, Ontario, Canada, L8S 4M1, and Department of Chemistry and Biochemistry, University of Windsor, Windsor, Ontario, Canada, 9NB 3P4

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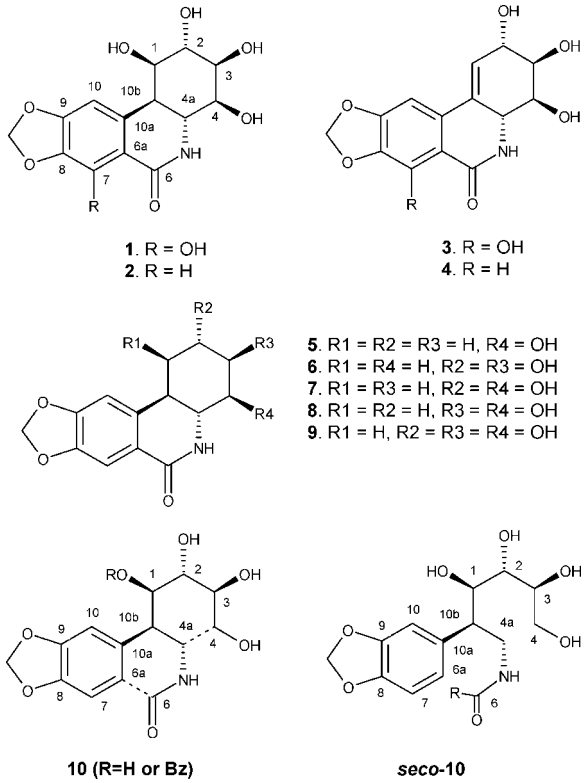
The total synthesis of fully functionalized polyhydroxyamide B,C-*seco*-analogues of the anticancer compound pancratistatin (PST) (**1**) is reported. Key steps include an Evans' $MgCl_2$-promoted *anti*-aldol reaction between a functionalized L-threose derivative and (*R*)-(+)-oxazolidinone to stereoselectively form the C-1/C-10b bond and a regiospecific radical-mediated oxidative fragmentation of a 1,3-benzylidene. The B,C-*seco* compounds **25** and **26** exhibited low activity (ED_{50} > 30 μg/mL) for inducing apoptosis in human cancer cells.

Plants belonging to the family Amaryllidaceae are widely distributed and of particular provenance in the tropics, South Africa, and Andean South America.[1] The plants are well-known for a variety of reasons including their ornamental appeal, use in traditional medicinal practices, and economic exploitation. The medicinal use of extracts from these plants can be dated to the times of Hippocrates and Pliny.[2] The constituents responsible for these biological properties have since been classed into three related major structural types, occurring exclusively within the Amaryllidaceae, all of which arise biogenetically from the common amino acid derived precursor norbelladine (Scheme 1). Representatives of the three structural types are recognized as to whether they possess the lycorane-, crinane-, or galanthamine-type skeleton (Scheme 1),[3] although several other types and more complex variations are also now well-known.[4] The advancement of Amaryllidaceae alkaloids and their synthetic derivatives as potential therapeutics over the past decade has been fueled mainly by the potent anticancer activity[2,5] of lycorane-type alkaloids pancratistatin (**1**), 7-deoxypancratistatin (**2**), narciclasine (**3**), and lycoricidine (**4**) as well as the selective, reversible acetylcholinesterase inhibitory activity[6] demonstrated by galanthamine and its analogues. Consequently, galanthamine has found use in the treatment of Alzheimer's and other neurodegenerative diseases. In fact, galanthamine represents the first alkaloid of the Amaryllidaceae to be approved as a prescription drug in the pharmaceutical treatment of a human disease; marketed as the hydrobromide salt under the generic name Reminyl. Among the crinane compounds of some note are crinamine, which was recently shown[7] by us to initiate apoptosis in cancer cells at the micromolar level, and 6-hydroxycrinamine, which was active against mouse melanoma cells.[8] Pancratistatin was first isolated from the spider lily *Pancratium littorale* when it was found to exhibit high levels of cancer cell growth inhibitory activity.[5] Due to this interesting biological property as well as its challenging molecular structure, it has attracted sustained research efforts over the past two decades. While the mechanism of its biological action remains unknown, recent work in our laboratories has revealed that pancratistatin induces apoptosis, or programmed cell death, selectively in cancer cells, with minimal effect on normal cells, and that the mitochondria in cancerous cells are the site of action.[9] An event leading to the apoptotic process was shown to involve early activation of caspase-3 followed by flipping of phosphatidyl serine.[9] Furthermore, pancratistatin showed greater specificity than etoposide (VP-16) or paclitaxel as an efficient inducer of apoptosis in human lymphoma (Jurkat) cells, with minimal effect on normal nucleated blood cells.[10] Targeted design and synthesis of Amaryllidaceae constituents has been partially driven by the limited supply of these compounds from natural sources. Pancratistatin and the related Amaryllidaceae constituents 7-deoxypancratistatin, narciclasine, and lycoricidine offer challenging targets for stereocontrolled synthesis,[11] and many of these SAR-based endeavors have sought to identify the pharmacophore and provide a synthetically accessible derivative or potential prodrug. To date, collectively, around 30 total syntheses of the four compounds and analogues have been reported and the area has recently been reviewed.[11] Briefly, milestone accomplishments include the first synthesis of racemic pancratistatin by Danishefsky and Lee in 1989[12] and the first asymmetric synthesis of this compound by Hudlicky et al. in 1995.[13] For a number of years now we have been interested in a systematic structural-based approach to unravel the anticancer pharmacophore of pancratistatin in order to define the minimum structural requirements for potent cytoxicity. Such requirements would guide the design of biological



[§] Dedicated to Dr. G. Robert Pettit of Arizona State University for his pioneering work on bioactive natural products.

* To whom correspondence should be addressed. E-mail: jmcnult@mcmaster.ca. Phone: +905-525-9140, ext. 27393. Fax: +905-522-2509.

[†] McMaster University.

[‡] University of Windsor.

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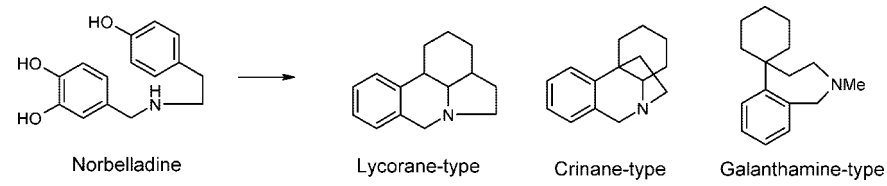
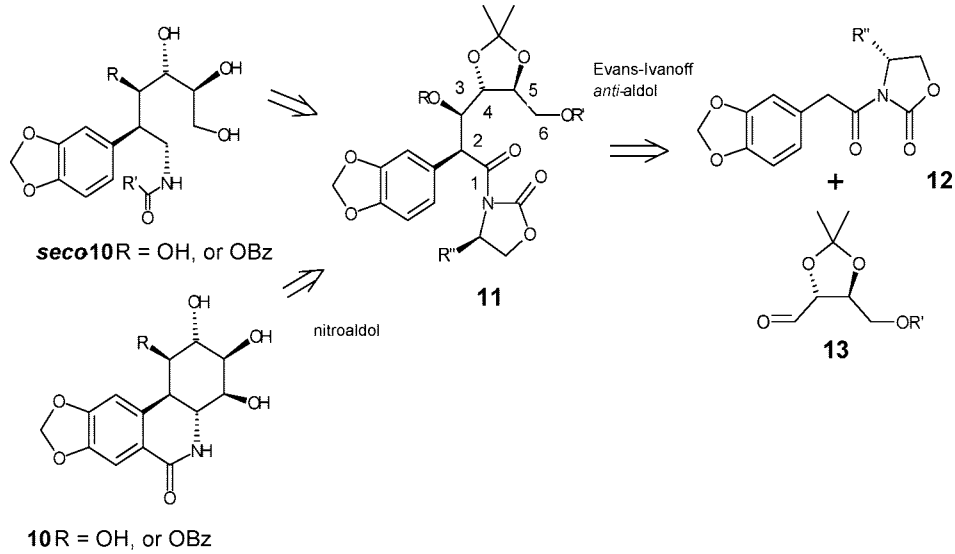
Scheme 1. Biosynthetic Origin of the Amaryllidaceae Alkaloids



Scheme 2. Retrosynthetic Analysis of Pancratistatin Analogues



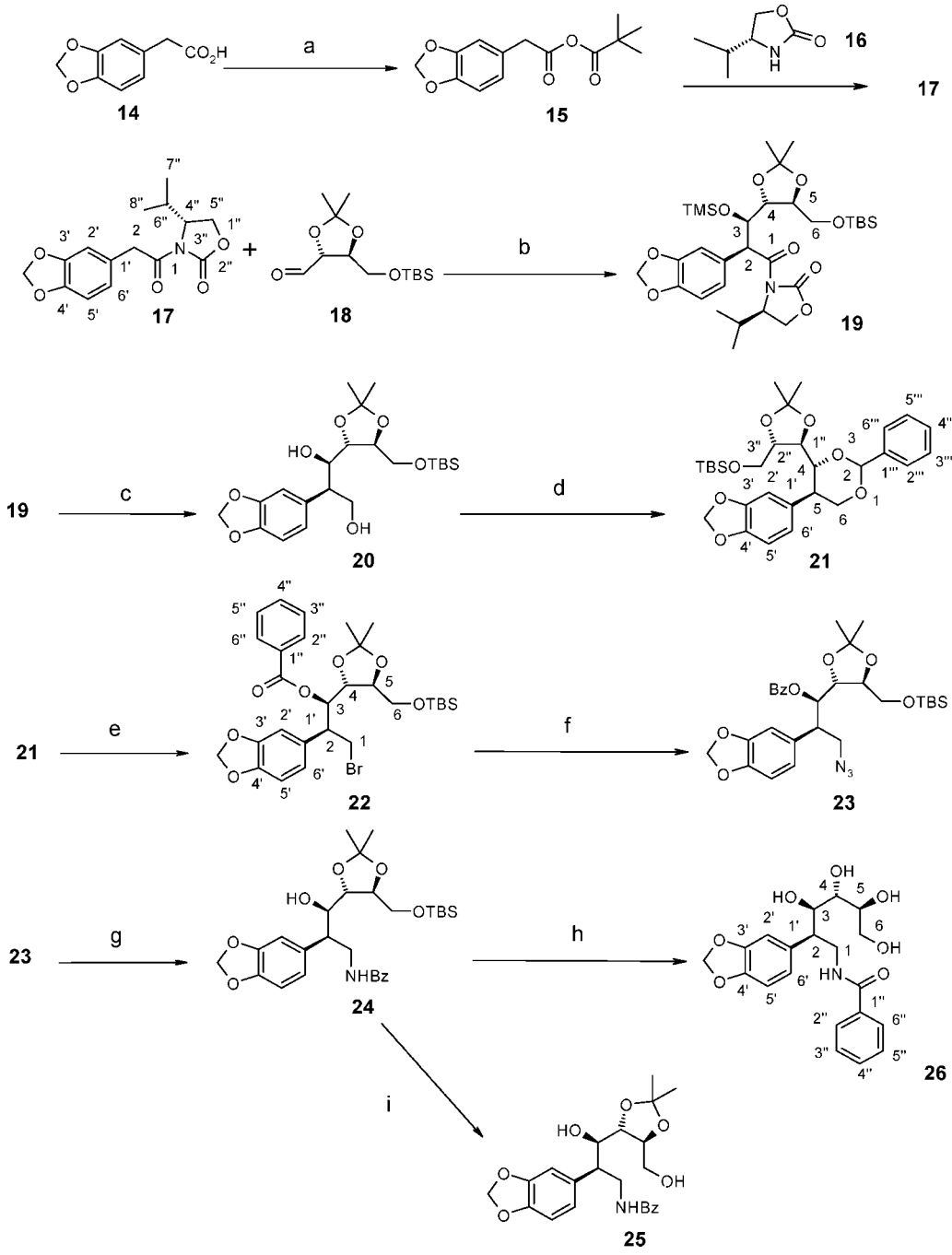
probes that may illuminate the biological target that is operative and allow synthetic access to a structurally simpler, active derivative. To this end we devised strategies[14–16] for the preparation of pancratistatin analogues **5**, **6**, and **7**, uncovering that only analogue **6** exhibited submicromolar activity in the P388 mouse leukemia cell line assay (ED_{50} = 0.45 μg/mL), an order of magnitude less than pancratistatin (ED_{50} = 0.039 μg/mL) and 2 to 3 orders of magnitude less potent than pancratistatin against some cell lines of the NCI 60 panel human tumor cell line assay. Furthermore, analogue **8** was shown by Hudlicky et al.[17] to be moderately active against P388 (ED_{50} = 1.39 μg/mL). These results point to the 2,3,4-triol compound **9** as containing the structurally minimum pharmacophore necessary for the full anticancer cytotoxic profile. The phenolic C7 hydroxyl is known to moderate the cytotoxicity slightly. Interestingly, while the C1 hydroxyl has been known to be noncrucial for potent cytotoxicity for some time, recently the C1-benzyloxy ester derivative was reported, which is the most potent anticancer derivative in the pancratistatin series known to date.[25] Finally, Pettit recently confirmed that an amide is also necessary at position 5 for full potency.[26] In summary then, structure **10** contains all of the known pharmacophoric elements required for potent anticancer activity. Considering these elements, and as part of an ongoing total synthesis program of benzoate **10**, we became interested in *seco*-analogues such as *seco*-**10**, containing both an amide opened form of the ring B/C lactam and a ring C/D opened cyclohexane. Such a derivative would allow a further understanding of the conformational requirements of the pharmacophore having all of the requisite functionality present but in a conformationlly mobile form. Herein, we report the first total synthesis and biological evaluation of such *seco*-derivatives.

Results and Discussion

In our general retrosynthetic analysis, outlined in Scheme 2, the natural products and derivatives **10** would be derived from intermediate **11** employing a nitroaldol cyclization as a key step.[14] Intermediate **11** would thus serve as a central intermediate also opening a route to the desired *seco*-**10** analogues described above. This central intermediate **11** could be derived from an Ivanoff-type reaction leading back to compounds **12** and **13**.

Thus, in the synthetic direction, a non-Evans *anti*-aldol reaction of the methylenedioxy-functionalized phenylacetate-derived auxiliary **12** with L-threose chiron **13** would generate adduct **11**. Our synthesis (Scheme 3) started with pivaloyl chloride activation of 3,4-methylenedioxyphenylacetic acid, giving the mixed anhydride **15**, which was quenched with the lithium salt of (*R*)-(+)-oxazolidinone **16**, providing imide **17**. An Evans' aldol reaction[18] was next employed to stereoselectively couple imide **17** to L-threose aldehyde **18** (derived in four steps from L-tartaric acid), leading to the non-Evans *anti*-adduct **19** as the major diastereomer (95:5) in 98% yield. This catalytic *anti*-aldol operation is remarkable in that it connects the ring A aromatic moiety and, importantly, sets the stereochemistry at two (C-1 and C-10b) of the six contiguous stereocenters in PST with a further two (C-2 and C-3) preset by chiron **18**. In general, *syn*-aldol adducts are readily accessed through a variety of methods, whereas efforts to achieve such enantioselective *anti*-aldols are still difficult. Whereas most auxiliary-based aldol reactions require stoichiometric amounts of metal salt (B, Ti, Si, etc.) to generate the required enolate,[20] the present *anti*-aldol process[18] is distinguished by the use of a catalytic quantity (0.1–0.2 equiv) of magnesium halide. The Ivanoff reaction of magnesium carboxylate-derived enolates has previously[21] been documented to favor *anti*-aldols through induced stereoselectively, most likely as a consequence of *E*-enolate geometry. The selective formation (95:5) of the stereochemically proven (see below) non-Evans *anti*-aldol adduct **19**, which is easily separable on silica gel from the minor adduct identified as the Evans *anti*-aldol adduct,[22] is of interest, as it indicates that the facial selectivity of the auxiliary has an overriding influence on the stereochemical outcome of this reaction, overcoming any Felkin−Ahn bias on the part of the aldehyde. The large $^1H-^1H$ coupling (J = 10.2 Hz) observed between H-2 (δ 5.35) and H-3 (δ 4.41) in the NMR spectrum is in accord with a *trans* disposition of these protons. Lithium borohydride reaction of adduct **19** reductively cleaved the auxiliary and TMS group simultaneously, affording 1,3-diol **20**, which was smoothly con-

Scheme 3. Synthetic Strategy for Synthesis of Truncated Pancratistatin Analogues[a]



[a] (a) Pivaloyl chloride, triethylamine, diethyl ether, −78 °C to RT, 2 h, added to the lithium salt of **16**, THF, RT, 6 h (84%); (b) magnesium chloride, triethylamine, chlorotrimethylsilane in EtOAc, RT, 12 h, (98%); (c) $LiBH_4$, THF/MeOH, 0 °C to RT, 3 h (88%); (d) $PhCH(OMe)_2$, PTSA(cat.), CH_2Cl_2, RT, 1 h (91%); (e) NBS, AIBN, C_6H_6, 60 °C, 1 h (70%); (f) NaN_3, DMF, RT, 5 h (85%); (g) 10% Pd/C, H_2 (1 atm), THF, RT, 2 h (94%); (h) 2.0 M HCl, MeOH, RT, 2 h (87%); (i) $(Bu)_4NF$, THF, RT, 1 h (96%).

verted to benzylidene **21** with benzaldehyde dimethyl acetal (BDMA). Protection of the diol **20** as the benzylidene **21** at this stage served several purposes. First of all, it provided absolute confirmation of the stereochemical outcome of the aldol reaction. A single-crystal X-ray structural determination (Figure 1) of **21** confirmed its stereochemistry as shown in Scheme 3. Second, we reasoned that the NBS radical-mediated oxidative fragmentation of **21** would provide for the regioselective discrimination of the original primary and secondary alcohols from diol **20**. Installation of the benzoate at C-3 would also be achieved, which may prove crucial in the selective preparation of the very active C1-benzoate derivatives of pancratsitatin. In the event, we were delighted to find that the bromide **22** was obtained in 70% isolated yield from the reaction of **21** with *N*-bromosuccinimide (NBS) promoted with azoisobutyronitile (AIBN) as radical initiator. The oxidative fragmentation of benzylidene acetals with NBS provides a convenient regiocontrolled route to functionalized products and has been applied to a number of substrates, such as carbohydrates.[23] An interesting variant of the reaction having reversed regioslectivity was also recently described by our group.[24] A three-bond HMBC correlation linked H-3 (δ 5.38, d, $J = 9.6$ Hz) to the carbonyl group (δ 166.4, s) in bromide **22**, confirming the regiospecificity of the rearrangement. One further note of interest uncovered during this reaction was the finding that any trace of benzaldehyde remaining from the conversion of **20** to **21** was deleterious to the NBS-mediated oxidative fragmentation. We presume that traces of

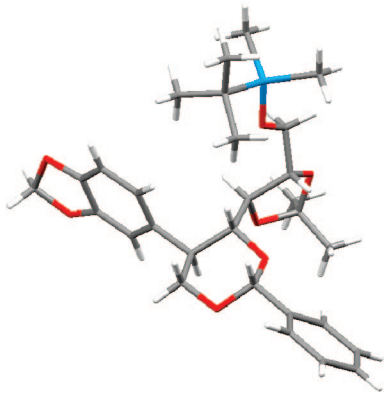


Figure 1. X-ray structure (stick diagram) of benzylidene **21**.

benzaldehyde function as radical chain transfer agents, quenching the radical chain process. No difficulty was encountered during the present fragmentation employing the pure benzylidene **21**. Nucleophilic substitution of bromide **22** using sodium azide proceeded without event to furnish azide **23**, which was subsequently reduced (Pd/C, H_2) to **24**, undergoing an *O,N*-benzoyl intramolecular migration as anticipated from our previous work with related derivatives.[14] The desired migration was indicated by the HMBC correlation of 2H-1 (δ 3.86 and 3.92) to the amide carbonyl (δ 167.7, s) as well as the upfield shift of H-3 (δ 3.77) from δ 5.40 in azide **23**. Desilylation of **24** with TBAF then afforded dihydroxybenzamide **25** in 96% yield. On the other hand, straightforward global deprotecion (2 M HCl) of **24** gave the tetrahydroxybenzamide **26**. Compound **26** represents the first member of the desired *seco*-**10** pancratistatin series possessing all of the essential elements of the known anticancer phamacophore, including the stereodefined 1,2,3,4-tetrahydroxy motif and the amide function.

The cytotoxicity of compounds **25** and **26** was evaluated alongside a standard of pancratistatin against human breast cell carcinoma (MCF-7) cells in serial dilution. Neither derivative **25** or **26** exhibited toxicity to MCF-7 cells even at the highest concentrations (ED_{50} > 30 μg/mL) tested, through live cell counting. In contrast, cells treated with pancratistatin suffered rapid apoptosis, as evidenced by nuclear condensation and annexin-V binding assays. At least one truncated pancratistatin analogue[11] is known to be mildly active in the human cancer screen: GI_{50} = 5.3 μg/mL (BXPC-3 cell line) and GI_{50} = 8.5 μg/mL (NCI-H460 cell line). The closest derivatives known to the present compounds **25** and **26** are the *seco*-derivatives reported by Chapleur and co-workers[27] containing an intact functionalized cyclohexane ring, but an amide-containing open ring B. These derivatives were also shown to be biologically inactive. The present results provide further valuable information on the anticancer pharmacophore. The indications now are that both a closed ring B lactam *and* a closed, 2,3,4-triol-functionalized cyclohexyl ring C are requirements for anticancer activity. The conformational restraints imposed by the lactam ring and cyclohexane appear to be critical for the correct positioning of the known pharmacophoric elements in binding to the still elusive biological target.[9,10] The synthesis of further derivatives of structural type **10** and studies on the mechanism of action of pancratistatin are ongoing in our laboratories.

Experimental Section

General Experimental Procedures. Reactions were carried out under an argon atmosphere in oven-dried glassware. All fine chemicals were obtained from Aldrich. Toluene, diethyl ether, and THF were distilled from sodium metal with benzophenone indicator. Dichloromethane and ethyl acetate were distilled over calcium hydride. Melting points (uncorrected) were measured on a Gallenkamp melting point apparatus. Optical rotations were determined on a Perkin-Elmer 241 polarimeter installed with a λ_{589} sodium lamp. IR spectra were measured on a Bio-Rad FTS-40 series spectrometer in dry film. CIMS were run on a Micromass Quattro Ultima spectrometer fitted with a direct injection probe (DIP) with ionization energy set at 70 eV, and HRMS (CI) were performed with a Micromass Q-Tof Ultima spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 600 or AV 700 spectrometer in $CDCl_3$ with TMS as internal standard, chemical shifts (δ) are reported in ppm downfield of TMS, and coupling constants (J) are expressed in Hz.

Preparation of (4″*R*)-Isopropyl-2″-oxazolidino-*N*-(3′,4′-methylenedioxy)phenyl Acetate (17). (3,4-Methylenedioxy)phenylacetic acid (0.500 g, 2.78 mmol) was dissolved in dry diethyl ether (30 mL) under argon and the stirred solution cooled to −78 °C when trimethylacetyl choride (0.342 mL, 2.78 mmol) and triethylamine (0.387 mL, 2.78 mmol) were added consecutively. After 1 h at −78 °C, the cold bath was removed and the solution allowed to warm to room temperature and filtered through a plug of Celite. The solvent was removed under reduced pressure to give the mixed anhydride (0.586 g, 80%) as a viscous yellow oil, which was subsequently used without further purification. (*R*)-(+)-4-Isopropyl-2-oxazolidinone **16** (0.286 g, 2.22 mmol) dissolved in dry THF (5.5 mL) was cooled to −78 °C, and lithium bis(trimethylsilyl)amide (1 M) (2.2 mL, 2.22 mmol) was then added dropwise under argon. After 30 min at this temperature, the anhydride dissolved in THF (5.5 mL) was introduced to the lithium oxazolidinone solution by rapid dropwise addition, and the stirred mixture was allowed to warm to room temperature. After 6 h, the reaction was complete (as indicated by TLC in 30% EtOAc in hexane) and quenched with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 10 mL). The organic fractions were dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The crude gum obtained was chromatographed (30% EtOAc in hexane) on silica gel to give imide **17** as a viscous yellow oil in overall 84% yield. Compound **17**: $[\alpha]^{25}_D$ −16.9 ($CHCl_3$, *c* 2.3); IR ν_{max} cm^{-1} (NaCl) 2965, 2925, 1770 (C═O), 1690 (Ph), 1492, 1304, 1114, 1060 (C−O), 935 (OCH_2O); CIMS 70 eV, *m*/*z* (rel int) 292 [M + 1]$^+$ (47), 231 (30), 162 (100), 130 (40); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.80 (3H, d, J = 6.6 Hz, CH_3(CH)CH_3), 0.88 (3H, d, J = 7.2 Hz, CH_3(CH)CH_3), 2.34 (1H, m, H-6″), 4.12 (1H, d, J = 15.6 Hz, H-2a), 4.20 (1H, dd, J = 3.0, 9.0 Hz, H-5a″), 4.26 (1H, d, J = 15.6 Hz, H-2b), 4.27 (1H, dd, J = 8.4, 9.0 Hz, H-5″b), 4.43 (1H, ddd, J = 3.0, 7.2, 8.4 Hz, H-4″), 5.94 (2H, s, OCH_2O), 6.75 (1H, d, J = 8.2 Hz, H-6′), 6.76 (1H, dd, J = 1.2, 8.2 Hz, H-5′), 6.81 (1H, d, J = 1.2 Hz, H-2′); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.1 (q, C-7″), 18.3 (q, C-8″), 28.4 (d, C-6″), 42.0 (t, C-2), 59.4 (d, C-4″), 63.6 (t, C-5″), 101.1 (t, OCH_2O), 108.9 (d, C-6′), 110.0 (d, C-2′), 123.2 (d, C-5′), 128.8 (s, C-1′), 147.3 (s, C-3′), 147.8 (s, C-4′), 153.2 (s, C-2″), 172.7 (s, C-1); HRMS (CI) calcd 292.1185 for $C_{15}H_{18}NO_5$, found 292.1175.

Preparation of (4″*R*,2*S*,3*R*,4*R*,5*S*)-4″-Isopropyl-2″-oxazolidino-*N*-[2-(3′,4′-methylenedioxy)phenyl-3-trimethylsilyloxy-4,5-isopropylidenedioxy-6-*tert*-butyldimethylsilyloxy] Hexanoate (19). Imide **17** (0.107 g, 0.368 mmol), $MgCl_2$ (7.00 mg, 0.074 mmol), and triethylamine (0.102 mL, 0.735 mmol) were dissolved in EtOAc (0.74 mL) at room temperature under an argon atmosphere. After 10 min, aldehyde **18** (0.100 g, 0.368 mmol) in EtOAc (0.74 mL) was added followed by trimethylsilyl chloride (0.069 mL, 0.551 mmol), and the solution was stirred until TLC (30% EtOAc/hexane) indicated total consumption of starting material (~12 h). The mixture was then quenched with saturated NH_4Cl solution (3 mL) and extracted with EtOAc (3 × 3 mL), and the organic fractions were dried over anhydrous Na_2SO_4. Following filtration and solvent removal, the crude material was eluted (30% EtOAc in hexane) on a silica gel column, which separated major adduct **19** (90%) from the minor adduct (5%), in overall 95% yield. Compound **19**: $[\alpha]^{25}_D$ −37.4 ($CHCl_3$, *c* 0.47); IR ν_{max} cm^{-1} (NaCl) 2966, 2920, 1785 (C═O), 1695 (Ph), 1495, 1303, 1257 ($SiCH_3$), 1120, 1065 (C−O), 936 (OCH_2O); CIMS 70 eV, *m*/*z* (rel int) 638 [M + 1]$^+$ (55), 580 (22), 548 (23), 522 (10), 490 (10), 393 (10), 363 (100), 275 (25), 202 (50), 130 (55); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.05 (9H, s, $Si(CH_3)_3$), 0.17 (6H, s, $Si(CH_3)_2$), 0.80 (9H, s, $SiC(CH_3)_3$), 0.87 (3H, d, J = 6.6 Hz, CH_3(CH)CH_3), 0.91 (3H, d, J = 7.2 Hz, CH_3(CH)CH_3), 1.22 (3H, s, O-C(CH_3)$_2$-O), 1.41 (3H, s, O-C(CH_3)$_2$-O), 2.54 (1H, m, H-6″), 3.44 (1H, dd, J = 1.2, 7.8 Hz, H-4), 3.49 (1H, dd, J = 3.6, 10.2 Hz, H-6a), 3.64 (1H, dd, J = 6.0, 10.2 Hz, H-6b), 3.90 (1H, ddd, J = 3.6, 6.0, 7.8 Hz, H-5), 4.04 (1H, dd, J = 9.0, 9.0 Hz, H-5″a), 4.11 (1H, dd, J = 2.4, 9.0 Hz, H-5″b), 4.30 (1H, ddd, J = 2.4, 6.0, 9.0 Hz, H-4″), 4.41 (1H, dd, J = 1.2, 10.2 Hz, H-3), 5.35 (1H, d, J = 10.2 Hz, H-2),

5.90–5.92 (2H, s, OCH_2O), 6.69 (1H, d, J = 8.4 Hz, H-6′), 6.83 (1H, dd, J = 1.2, 8.4 Hz, H-5′), 6.86 (1H, d, J = 1.2 Hz, H-2′); ^{13}C NMR (150 MHz, $CDCl_3$) δ −5.00 (3q, Si(CH_3)$_3$), 0.77 (2q, Si(CH_3)$_2$), 14.3 (q, C-7″), 18.2 (q, C-8″), 18.7 (s, SiC(CH_3)$_3$), 26.1 (3q, SiC(CH_3)$_3$), 26.7 (q, O-C(CH_3)$_2$-O), 27.2 (q, O-C(CH_3)$_2$-O), 28.2 (d, C-6″), 51.3 (d, C-2), 59.2 (d, C-4″), 62.4 (t, C-5″), 63.4 (t, C-6), 73.6 (d, C-3), 76.7 (d, C-5), 78.0 (d, C-4), 101.2 (t, OCH_2O), 107.9 (s, O-C(CH_3)$_2$-O), 108.5 (d, C-6′), 110.2 (d, C-2′), 123.6 (d, C-5′), 128.5 (s, C-1′), 147.5 (s, C-4′), 147.9 (s, C-3′), 153.7 (s, C-2″), 172.2 (s, C-1); HRMS (CI) calcd 638.3181 for $C_{31}H_{52}NO_9Si_2$, found 638.3170.

Preparation of [(2*R*,3*R*,4*S*,5*S*)-2-(3′,4′-Methylenedioxy)phenyl-4,5-isopropylidenedioxy-6-*tert*-butyldimethylsilyloxy]hexan-1,3-diol (20). A 98.1 mM solution of aldol adduct **19** (0.175 g, 0.275 mmol) in THF/MeOH (95:5) was cooled to 0 °C, and $LiBH_4$ (0.024 g, 1.099 mmol) was slowly added to the stirred mixture under positive argon pressure. After TLC (50:50, EtOAc/hexane) indicated consumption of all starting material (∼3 h), the reaction mixture was diluted with saturated NH_4Cl solution (3 mL) and extracted with EtOAc (3 × 3 mL). The pooled organic fractions were dried over anhydrous Na_2SO_4 and filtered to give an amorphous gum, which was subjected to column chromatography on silica gel with 50:50 EtOAc/hexane, affording diol **20** as a colorless oil in 88% yield. Compound **20**: $[\alpha]^{25}_D$ −80.0 ($CHCl_3$, c 0.2); IR ν_{max} cm^{-1} (NaCl) 3405 (OH), 2936, 2865, 1670 (Ph), 1492, 1445, 1362, 1255 (SiCH_3), 1130, 1074 (C-O), 934 (OCH_2O); CIMS 70 eV, m/z (rel int) 441 [M + 1]$^+$ (20), 383 (10), 307 (15), 255 (15), 219 (25), 155 (30), 135 (100). ^{1}H NMR (700 MHz, $CDCl_3$), δ 0.00 (6H, s, Si(CH_3)$_2$), 0.81 (9H, s, SiC(CH_3)$_3$), 1.31 (3H, s, O-C(CH_3)$_2$-O), 1.44 (3H, s, O-C(CH_3)$_2$-O), 2.96 (1H, ddd, J = 5.6, 7.0, 9.8 Hz, H-2), 3.56 (1H, dd, J = 3.5, 10.5 Hz, H-6a), 3.63 (1H, dd, J = 5.6, 10.5 Hz, H-6b), 3.78 (1H, d, J = 9.8 Hz, H-4), 3.84 (1H, dd, J = 9.8, 9.8 Hz, H-3), 3.87 (1H, dd, J = 7.0, 10.8 Hz, H-1a), 4.00 (1H, ddd, J = 3.5, 5.6, 9.8 Hz, H-5), 4.07 (1H, dd, J = 5.6, 10.8 Hz, H-1b), 5.92 (2H, s, OCH_2O), 6.67 (1H, dd, J = 1.4, 8.0 Hz, H-5′), 6.71 (1H, d, J = 1.4 Hz, H-2′), 6.74 (1H, d, J = 8.0 Hz, H-6′); ^{13}C NMR (176 MHz, $CDCl_3$) δ −5.51 (2q, Si(CH_3)$_2$), 18.3 (s, SiC(CH_3)$_3$), 26.0 (3q, SiC(CH_3)$_3$), 26.8 (q, O-C(CH_3)$_2$-O), 27.1 (q, O-C(CH_3)$_2$-O), 49.8 (d, C-2), 63.8 (t, C-6), 63.9 (t, C-1), 75.8 (d, C-3), 76.9 (d, C-5), 79.8 (d, C-4), 101.0 (t, OCH_2O), 108.4 (d, C-2′), 108.8 (d, C-6′), 109.2 (s, O-C(CH_3)$_2$-O), 122.0 (d, C-5′), 134.9 (s, C-1′), 146.5 (s, C-4′), 147.8 (s, C-3′); HRMS (CI) calcd 441.2309 for $C_{22}H_{37}O_7Si$, found 441.2301.

Preparation of [(2*R*,4*R*,1″*R*,2″*S*,5*R*)-2-Phenyl-4-(1″,2″-isopropylidenedioxy-3″-*tert*-butyldimethylsilyloxypropyl)-5-(3′,4′-methylenedioxy)phenyl]-1,3-dioxane (21). Benzaldehyde dimethyl acetal (BDMA) (0.041 mL, 0.273 mmol) was added slowly under an atmosphere of argon to a solution of diol **20** (0.120 g, 0.273 mmol) and *p*-toluenesulfonic acid monohydrate (5.00 mg, 0.0273 mmol) in dry dichloromethane (2.7 mL). After 15 min stirring at room temperature, TLC (15% EtOAc in hexane) indicated the reaction to be complete. The mixture was then diluted with 3 mL of saturated $NaHCO_3$ solution and extracted with dichloromethane (3 × 3 mL), and the combined organic fractions were dried over anhydrous Na_2SO_4 and filtered. The residue obtained after vacuum removal of solvent was loaded on a silica gel column and eluted with 15% EtOAc in hexane, giving benzylidene **21** (95%) as white crystals, which were recrystallized from EtOAc/hexane. Compound **21**: mp 73–75 °C. $[\alpha]^{25}_D$ −44.0 ($CHCl_3$, c 0.15); IR ν_{max} cm^{-1} (NaCl) 2930, 2875, 1673 (Ph), 1490, 1452, 1360, 1253 (SiCH_3), 1135, 1064 (C−O), 933 (OCH_2O). 70 eV, m/z (rel int) 529 [M + 1]$^+$ (15), 513 (30), 471 (35), 453 (25), 413 (20), 347 (30), 307 (65), 289 (35), 215 (35), 187 (40), 161 (90), 148 (100), 135 (40); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.00 (6H, s, Si(CH_3)$_2$), 0.84 (9H, s, SiC(CH_3)$_3$), 1.33 (3H, s, O-C(CH_3)$_2$-O), 1.42 (3H, s, O-C(CH_3)$_2$-O), 3.39 (1H, ddd, J = 4.8, 11.4, 12.0 Hz, H-5), 3.54 (1H, dd, J = 6.6, 10.2 Hz, H-3″a), 3.74 (1H, dd, J = 3.6, 10.2 Hz, H-3″b), 3.76 (1H, dd, J = 4.8, 10.8 Hz, H-6a), 3.94 (1H, dd, J = 10.8, 12.0 Hz, H-6b), 3.99 (1H, dd, J = 4.8, 9.0 Hz, H-1″), 4.26 (1H, dd, J = 4.8, 11.4 Hz, H-4), 4.29 (1H, ddd, J = 3.6, 6.6, 9.0 Hz, H-2″), 5.62 (1H, s, O-CH(Ph)-O), 5.95 (2H, s, OCH_2O), 6.74 (1H, dd, J = 1.8, 8.0 Hz, H-5′), 6.77 (1H, d, J = 1.8 Hz, H-2′), 6.78 (1H, d, J = 8.0 Hz, H-6′), 7.35 (1H, d, J = 8.4 Hz, H-4‴), 7.37 (2H, d, J = 8.4 Hz, H-3‴, H-5‴), 7.54 (2H, d, J = 8.4 Hz, H-2‴, H-6‴); ^{13}C NMR (150 MHz, $CDCl_3$) δ 1.05 (2q, Si(CH_3)$_2$), 18.3 (s, SiC(CH_3)$_3$), 26.0 (3q, SiC(CH_3)$_3$), 26.9 (q, O-C(CH_3)$_2$-O), 27.5 (q, O-C(CH_3)$_2$-O), 42.7 (d, C-5), 64.0 (t, C-3″), 72.4 (d, C-4), 74.9 (d, C-2″), 78.0 (t, C-6), 79.9 (d, C-1″), 101.2 (t, OCH_2O), 101.9 (d, O-CH(Ph)-O), 108.7 (d, C-6′), 108.9 (d, C-2′), 109.5 (s, O-C(CH_3)$_2$-O), 122.0 (d, C-5′), 126.3 (2d, C-3‴, C-5‴), 128.3 (2d, C-2‴, C-6‴), 129.1 (d, C-4‴), 131.2 (s, C-1′), 138.6 (s, C-1‴), 146.9 (s, C-4′), 148.0 (s, C-3′); HRMS (CI) calcd 529.2622 for $C_{29}H_{41}O_7Si$, found 529.2625.

Preparation of [(2*R*,3*R*,4*S*,5*S*)-1-Bromo-2-(3′,4′-methylenedioxy)phenyl-3-(*O*)-benzoyl-4,5-isopropylidenedioxy-6-*tert*-butyldimethylsilyloxy]hexane (22). Benzylidene **21** (0.100 g, 0.189 mmol) was dissolved at room temperature in 1.9 mL of dry benzene (10 mL/mmol) under argon, and *N*-bromosuccinimide (NBS) (0.034 g, 0.189 mmol) and azoisobutyronitrile (AIBN) (3.1 mg, 0.0189 mmol) were added to the stirred solution, which was then heated to 60 °C. Within 1 h the reaction was complete, as indicated by TLC (10:90, EtOAc/hexane), whereupon the mixture was diluted with saturated $NaHCO_3$ solution (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic fractions were dried over anhydrous Na_2SO_4 and filtered, and solvent was removed under vacuum to give an amorphous residue, which was columned on silica gel with 10:90 EtOAc/hexane, affording bromide **22** as a pale yellow oil in 70% yield. Compound **22**: $[\alpha]^{25}_D$ +22.5 ($CHCl_3$, c 0.2); IR ν_{max} cm^{-1} (NaCl) 2858, 2338, 1719 (C═O), 1653 (Ph), 1559, 1507, 1490, 1456, 1376, 1248 (SiCH_3), 1041 (C−O), 936 (OCH_2O); CIMS 70 eV, m/z (rel int) 607 [M + 1]$^+$ (15), 551 (10), 529 (25), 471 (13), 407 (5), 349 (17), 291 (18), 279 (23), 201 (15), 149 (45), 105 (100), 77 (34); ^{1}H NMR (600 MHz, $CDCl_3$), δ −0.05 (6H, s, Si(CH_3)$_2$), 0.80 (9H, s, SiC(CH_3)$_3$), 1.30 (3H, s, O-C(CH_3)$_2$-O), 1.43 (3H, s, O-C(CH_3)$_2$-O), 3.56 (1H, ddd, J = 5.0, 7.0, 9.6 Hz, H-2), 3.61 (1H, dd, J = 7.0, 10.0 Hz, H-1a), 3.65 (1H, dd, J = 5.0, 10.0 Hz, H-1b), 3.67 (1H, dd, J = 4.8, 10.5 Hz, H-6a), 3.69 (1H, dd, J = 6.5, 10.5 Hz, H-6b), 3.71 (1H, ddd, J = 4.8, 6.5, 8.4 Hz, H-5), 3.90 (1H, d, J = 8.4 Hz, H-4), 5.38 (1H, d, J = 9.6 Hz, H-3), 5.97 (2H, s, OCH_2O), 6.80 (1H, d, J = 8.4 Hz, H-6′), 6.82 (1H, dd, J = 1.2, 8.4 Hz, H-5′), 6.84 (1H, d, J = 1.2 Hz, H-2′), 7.50 (2H, dd, J = 7.8, 7.8 Hz, H-3″, H-5″), 7.62 (1H, dd, J = 7.2, 1.2 Hz, H-4″), 8.13 (2H, dd, J = 1.2, 7.2 Hz, H-2″,H-6″); ^{13}C NMR (150 MHz, $CDCl_3$) δ 0.01 (2q, Si(CH_3)$_2$), 18.3 (s, SiC(CH_3)$_3$), 26.4 (3q, SiC(CH_3)$_3$), 27.0 (q, O-C(CH_3)$_2$-O), 27.2 (q, O-C(CH_3)$_2$-O), 34.9 (d, C-2), 49.7 (t, C-1), 61.9 (t, C-6), 73.8 (d, C-3), 76.6 (d, C-5), 76.8 (d, C-4), 101.3 (t, OCH_2O), 108.6 (d, C-6′), 108.7 (d, C-2′), 109.1 (s, O-C(CH_3)$_2$-O), 122.1 (d, C-5′), 128.8 (2d, C-3″, C-5″), 129.5 (s, C-1′), 130.1 (2d, C-2″, C-6″), 132.4 (s, C-1″), 133.7 (d, C-4″), 147.3 (s, C-4′), 148.1 (s, C-3′), 166.4 (s, C═O); HRMS (CI) calcd 607.1727 for $C_{29}H_{39}SiBrO_7$, found 607.1737.

Preparation of [(2*R*,3*R*,4*S*,5*S*)-1-Azido-2-(3′,4′-methylenedioxy)phenyl-3-(*O*)-benzoyl-4,5-isopropylidenedioxy-6-*tert*-butyldimethylsilyloxy]hexane (23). Sodium azide (10.71 mg, 0.165 mmol) was added at room temperature under argon to a stirred solution of bromide **22** (0.100 g, 0.165 mmol) in dry DMF (1.7 mL, 10 mL/mmol), and the temperature was raised to 60 °C. TLC (10:90 EtOAc/hexane) indicated the reaction to be complete after ∼5 h. The reaction mixture was then diluted with saturated NaCl solution (3 mL) and extracted with EtOAc (3 × 3 mL). The pooled organic fractions were dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under vacuum to give a crude gum, which was eluted with 10:90 EtOAc/hexane on silica gel, affording azide **23** as a colorless oil in 85% yield. Compound **23**: $[\alpha]^{25}_D$ +25.3 ($CHCl_3$, c 0.2); IR ν_{max} cm^{-1} (NaCl) 2858, 2337, 2101 (N_3), 1719 (C═O), 1653 (Ph), 1559, 1507, 1490, 1457, 1376, 1250 (SiCH_3), 1064 (C-O), 938 (OCH_2O); CIMS 70 eV, m/z (rel int) 570 [M + 1]$^+$ (5), 526 (15), 420 (17), 344 (10), 286 (10), 232 (12), 213 (15), 135 (20), 122 (50), 105 (100), 77 (37); ^{1}H NMR (700 MHz, $CDCl_3$) δ −0.039 (6H, s, Si(CH_3)$_2$), 0.79 (9H, s, SiC(CH_3)$_3$), 1.30 (3H, s, O-C(CH_3)$_2$-O), 1.44 (3H, s, O-C(CH_3)$_2$-O), 3.52 (1H, ddd, J = 5.0, 7.0, 10.5 Hz, H-2), 3.58 (1H, dd, J = 7.0, 10.5 Hz, H-1a), 3.59 (1H, dd, J = 5.0, 10.5 Hz, H-1b), 3.61 (1H, dd, J = 4.8, 10.5 Hz, H-6a), 3.62 (1H, dd, J = 6.6, 10.5 Hz, H-6b), 3.67 (1H, ddd, J = 4.8, 6.6, 8.4 Hz, H-5), 3.89 (1H, dd, J = 1.4, 8.4 Hz, H-4), 5.40 (1H, d, J = 10.5 Hz, H-3), 5.96 (2H, s, OCH_2O), 6.80 (1H, d, J = 8.4 Hz, H-6′), 6.84 (1H, dd, J = 1.4, 8.4 Hz, H-5′), 6.86 (1H, d, J = 1.4 Hz, H-2′), 7.50 (2H, dd, J = 7.7, 8.4 Hz, H-3”, H-5″), 7.62 (1H, t, J = 7.7 Hz, H-4″), 8.13 (2H, dd, J = 1.4, 8.4 Hz, H-2”, H-6″); ^{13}C NMR (176 MHz, $CDCl_3$) δ −5.55 (q, Si(CH_3)$_2$), −5.47 (q, Si(CH_3)$_2$), 18.3 (s, SiC(CH_3)$_3$), 25.9 (3q, SiC(CH_3)$_3$), 27.0 (q, O-C(CH_3)$_2$-O), 27.2 (q, O-C(CH_3)$_2$-O), 47.2 (d, C-2), 53.6 (t, C-1), 61.9 (t, C-6), 72.7 (d, C-3), 76.2 (d, C-5), 76.7 (d, C-4), 101.3 (t, OCH_2O), 108.8 (d, C-6′), 108.9 (d, C-2′), 109.1 (s, O-C(CH_3)$_2$-O), 122.1 (d, C-5′), 128.9 (2d, C-3”, C-5″), 129.5 (s, C-1′), 130.1 (2d, C-2″, C-6″), 131.9 (s, C-1”), 133.7 (d, C-4″), 147.4

(s, C-4′), 148.3 (s, C-3′), 166.4 (s, C═O); HRMS (CI) calcd 570.2557 for $C_{29}H_{39}SiN_3O_7$, found 570.2550.

Preparation of [(2*R*,3*R*,4*S*,5*S*)-2-(3′,4′-Methylenedioxy)phenyl-3-hydroxy-4,5-isopropylidenedioxy-6-*tert*-butyldimethylsilyloxy] hexyl Benzamide (24). 10% Pd/C (18.7 mg, 0.0176 mmol) was suspended in a THF (1.8 mL, 10 mL/mmol) solution of azide **23** (0.100 g, 0.176 mmol) under hydrogen atmosphere, and the mixture was stirred for ∼2 h at room temperature. When TLC (EtOAc) showed the reaction to be complete, the solution was then filtered through a pad of Celite and the pad washed with EtOAc (3 × 3 mL), which was removed under vacuum, giving amide **24** as a transparent oil in 94% yield. Compound **24**: $[\alpha]^{25}_D$ +12.2 ($CHCl_3$, *c* 0.3); IR ν_{max} cm^{-1} (NaCl) 3500 (NH), 3400 (OH), 2860, 2337, 1684 (C═O), 1651 (Ph), 1558, 1507, 1489, 1458, 1249 ($SiCH_3$), 1040 (C-O), 936 (OCH_2O); CIMS 70 eV, *m*/*z* (rel int) 544 $[M + 1]^+$ (10), 526 (12), 468 (10), 336 (10), 289 (15), 268 (17), 219 (11), 161 (20), 148 (50), 122 (90), 105 (100), 77 (20); ^{1}H NMR (700 MHz, $CDCl_3$) δ −0.035 (3H, s, Si(CH_3)$_2$), −0.031 (3H, s, Si(CH_3)$_2$), 0.79 (9H, s, SiC(CH_3)$_3$), 1.28 (3H, s, O-C(CH_3)$_2$-O), 1.44 (3H, s, O-C(CH_3)$_2$-O), 3.06 (1H, ddd, *J* = 3.5, 6.3, 9.8 Hz, H-2), 3.55 (1H, dd, *J* = 3.5, 10.5 Hz, H-6a), 3.66 (1H, dd, *J* = 5.6, 10.5 Hz, H-6b), 3.74 (1H, dd, *J* = 0.7, 9.8 Hz, H-4), 3.77 (1H, dd, *J* = 9.8, 9.8 Hz, H-3), 3.86 (1H, dd, *J* = 7.0, 10.5 Hz, H-1a), 3.92 (1H, dd, *J* = 5.6, 10.5 Hz, H-1b), 4.06 (1H, ddd, *J* = 3.5, 5.6, 9.8 Hz, H-5), 5.95 (2H, s, OCH_2O), 6.55 (1H, bt, N*H*Bz), 6.68 (1H, dd, *J* = 1.4, 7.7 Hz, H-5′), 6.71 (1H, d, *J* = 1.4 Hz, H-2′), 6.76 (1H, d, *J* = 7.7 Hz, H-6′), 7.40 (2H, dd, *J* = 7.7, 7.7 Hz, H-3″, H-5″), 7.48 (1H, t, *J* = 7.7 Hz, H-4″), 7.67 (2H, dd, *J* = 1.4, 7.7 Hz, H-2″, H-6″); ^{13}C NMR (176 MHz, $CDCl_3$) δ −0.05 (2q, Si(CH_3)$_2$), 18.3 (s, Si*C*(CH_3)$_3$), 25.9 (3q, SiC(CH_3)$_3$), 27.1 (q, O-C(CH_3)$_2$-O), 27.2 (q, O-C(CH_3)$_2$-O), 43.4 (t, C-1), 49.9 (d, C-2), 63.1 (t, C-6), 72.2 (d, C-3), 76.9 (d, C-5), 78.4 (d, C-4), 101.2 (t, OCH_2O), 108.4 (d, C-6′), 108.8 (d, C-2′), 109.2 (s, O-*C*(CH_3)$_2$-O), 121.6 (d, C-5′), 127.0 (2d, C-3″, C-5″), 128.7 (2d, C-2″, C-6″), 131.6 (d, C-4″), 133.8 (s, C-1′), 134.6 (s, C-1″), 146.9 (s, C-4′), 148.3 (s, C-3′), 167.7 (s, C═O); HRMS (CI) calcd 544.2731 for $C_{29}H_{41}SiNO_7$, found 544.2725.

Preparation of [(2*R*,3*R*,4*S*,5*S*)-2-(3′,4′-Methylenedioxy)phenyl-3,6-dihydroxy-4,5-isopropylidenedioxy]hexyl Benzamide (25). A 1 M TBAF solution in THF (0.184 mL, 0.184 mmol) was added dropwise under argon to a stirred solution of hydroxybenzamide **24** (0.100 g, 0.184 mmol) in THF (1.8 mL, 10 mL/mmol). Stirring was continued for ∼1 h. When TLC (50:50 EtOAc/hexane) indicated that all starting material was consumed, the reaction mixture was then diluted with saturated NH_4Cl (3 mL) and extracted with EtOAc (3 × 3 mL). The pooled organic fractions were dried over anhydrous Na_2SO_4 and filtered, and solvent was removed under vacuum to give a crude gum, which was subjected to column chromatography on silica gel with 50:50 EtOAc/hexane, affording diol **25** as white flakes in 96% yield. Compound **25**: $[\alpha]^{25}_D$ +6.7 ($CHCl_3$, *c* 0.2); IR ν_{max} cm^{-1} (NaCl) 3361 (OH), 2927, 1685 (C═O), 1642 (Ph), 1540, 1488, 1442, 1375, 1248, 1040 (C−O), 934 (OCH_2O); CIMS 70 eV, *m*/*z* (rel int) 430 $[M + 1]^+$ (25), 412 (8), 372 (20), 338 (5), 298 (10), 277 (12), 232 (20), 214 (11), 148 (80), 122 (30), 105 (100), 77 (20); ^{1}H NMR (700 MHz, $CDCl_3$) δ 1.32 (3H, s, O-C(CH_3)$_2$-O), 1.43 (3H, s, O-C(CH_3)$_2$-O), 3.08 (1H, ddd, *J* = 3.5, 5.6, 8.4 Hz, H-2), 3.54 (1H, dd, *J* = 4.2, 11.9 Hz, H-6a), 3.69 (1H, dd, *J* = 4.2, 11.9 Hz, H-6b), 3.73 (1H, dd, *J* = 2.1, 8.4 Hz, H-4), 3.74 (1H, dd, *J* = 2.1, 8.4 Hz, H-3), 3.82 (1H, dd, *J* = 3.5, 10.5 Hz, H-1a), 3.90 (1H, dd, *J* = 5.6, 10.5 Hz, H-1b), 4.14 (1H, ddd, *J* = 4.2, 4.2, 8.4 Hz, H-5), 5.95 (2H, s, OCH_2O), 6.52 (1H, bt, N*H*Bz), 6.67 (1H, dd, *J* = 1.4, 7.7 Hz, H-5′), 6.74 (1H, d, *J* = 1.4 Hz, H-2′), 6.76 (1H, d, *J* = 7.7 Hz, H-6′), 7.40 (2H, dd, *J* = 7.7, 7.7 Hz, H-3″,H-5″), 7.48 (1H, t, *J* = 7.7 Hz, H-4"), 7.67 (2H, dd, *J* = 1.4, 7.7 Hz, H-2″,H-6″); ^{13}C NMR (176 MHz, $CDCl_3$), δ 27.1 (q, O-C(CH_3)$_2$-O), 27.2 (q, O-C(CH_3)$_2$-O), 43.1 (t, C-1), 49.4 (d, C-2), 61.9 (t, C-6), 71.8 (d, C-3), 76.8 (d, C-5), 76.9 (d, C-4), 101.2 (t, OCH_2O), 108.4 (d, C-6′), 108.8 (d, C-2′), 109.4 (s, O-*C*(CH_3)$_2$-O), 121.6 (d, C-5′), 127.0 (2d, C-3″, C-5″), 128.8 (2d, C-2″, C-6″), 131.8 (d, C-4"), 133.9 (s, C-1′), 134.3 (s, C-1″), 146.9 (s, C-4′), 148.3 (s, C-3′), 168.2 (s, C═O); HRMS (CI) calcd 430.1866 for $C_{23}H_{27}NO_7$, found 430.1860.

Preparation of [(2*R*,3*R*,4*S*,5*S*)-2-(3′,4′-Methylenedioxy)phenyl-3,4,5,6-tetrahydroxy]hexyl Benzamide (26). Hydroxyamide **24** (0.100 g, 0.184 mmol) was dissolved in 1.8 mL of MeOH (10 mL/mmol), to which was added 0.5 mL of 2 M HCl. The solution was stirred at room temperature for ∼2 h, during which time the reaction had run to completion as indicated by TLC (50:50 EtOAc/MeOH). The solution was then diluted with saturated $NaHCO_3$ solution (5 mL) and extracted with EtOAc (5 × 5 mL). The pooled organic fractions were dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under reduced pressure to give an amorphous gum, which was subjected to gel filtration on Sephadex LH-20 with MeOH, affording tetrahydroxybenzamide **26** as a white powder in 87% yield. Compound **26**: $[\alpha]^{25}_D$ −78.9 ($CHCl_3$, *c* 0.2); IR ν_{max} cm^{-1} (NaCl) 3340 (OH), 2927, 1690 (C═O), 1637 (Ph), 1541, 1488, 1441, 1311, 1248, 1039 (C−O), 934 (OCH_2O); CIMS 70 eV, *m*/*z* (rel int) 390 $[M + 1]^+$ (10), 338 (11), 322 (12), 298 (13), 268 (10), 232 (8), 200 (15), 176 (26), 148 (34), 122 (36), 105 (100), 77 (25); ^{1}H NMR (700 MHz, $CDCl_3$), δ 3.25 (1H, ddd, *J* = 4.2, 5.6, 9.8 Hz, H-2), 3.31 (1H, bs, H-3), 3.54 (1H, dd, *J* = 4.2, 9.1 Hz, H-6a), 3.61 (1H, dd, *J* = 3.5, 11.2 Hz, H-1a), 3.66 (1H, dd, *J* = 5.6, 11.2 Hz, H-1b), 3.79 (1H, bs, H-5), 3.93 (1H, d, *J* = 10.5 Hz, H-4), 4.08 (1H, dd, *J* = 5.6, 9.1 Hz, H-6b), 5.95 (2H, s, OCH_2O), 6.59 (1H, bt, N*H*Bz), 6.66 (1H, d, *J* = 7.7 Hz, H-5′), 6.70 (1H, s, H-2′), 6.76 (1H, d, *J* = 7.7 Hz, H-6′), 7.44 (2H, dd, *J* = 7.7, 7.7 Hz, H-3″,H-5″), 7.52 (1H, t, *J* = 7.7 Hz, H-4″), 7.72 (2H, d, *J* = 7.7 Hz, H-2″,H-6″); ^{13}C NMR (176 MHz, $CDCl_3$) δ 43.1 (t, C-6), 48.1 (d, C-2), 64.5 (t, C-1), 70.2 (d, C-3), 74.3 (d, C-5), 75.1 (d, C-4), 101.3 (t, OCH_2O), 108.6 (d, C-6′), 109.0 (d, C-2′), 121.6 (d, C-5′), 127.1 (2d, C-3″, C-5″), 129.0 (2d, C-2″, C-6″), 132.2 (d, C-4″), 133.6 (s, C-1′), 133.8 (s, C-1″), 147.0 (s, C-4′), 148.4 (s, C-3′), 169.0 (s, C═O); HRMS (CI) calcd 390.1539 for $C_{20}H_{23}NO_7$, found 390.1542.

Supplementary crystallographic data for compound **21** has been deposited at the Cambridge Crystallography Data Centre, CCDC data file 654288. This data can be obtained free of charge from www.ccdc.cam.ac.uk/data_requestcif.html.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **17** and **19**–**26** in pdf format is available free of charge on the Web at http://pubs.acs.org.

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