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Synthesis of Sialic Acids via Desymmetrization by Ring-Closing Metathesis

Eric A. Voight, Christian Rein, and Steven D. Burke*

Department of Chemistry, University of Wisconsin−Madison, 1101 University Avenue, Madison, Wisconsin 53706-1396

burke@chem.wisc.edu

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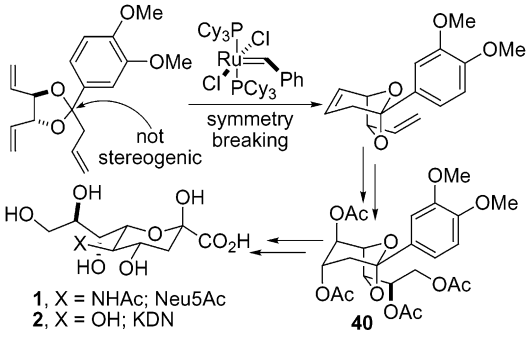
Formal total syntheses of the naturally occurring deaminated sialic acids KDN (**2**), a potential oncofetal antigen, and *N*-acetylneuraminic acid (Neu5Ac, **1**), the most naturally abundant sialic acid, have been accomplished in 46% and 9.3% overall yield, respectively, via a novel ketalization/ring-closing metathesis sequence. The rapid introduction of all oxygen and nitrogen functionality in a completely stereocontrolled manner exploited a rigid 6,8-dioxabicyclo[3.2.1]oct-2-ene template. The 2,7-anhydro-KDN derivative **40** served as an advanced intermediate in each of the two syntheses.

Introduction

The sialic acids are a family of 3-deoxy-2-ulosonic acids with approximately 40 naturally occurring members, most of which are *O*-acylated derivatives of 5-acetamido-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid [*N*-acetylneuraminic acid (Neu5Ac, **1**, Figure 1)].[1] In nature,



sialic acids are most frequently found as α-glycosidically linked terminal residues of glycoproteins and glycolipids. There are a wide range of biological properties endowed by sialic acids on natural glycoconjugate structure and function,[2] including direct involvement in cell-to-cell, and cell-to-microorganism, -toxin, and -antibody binding.[2a] The expression of sialic acid-recognizing proteins on the cell surface of pathogenic organisms allows them to attach themselves to host cell surface sialoglycoconjugates, a crucial part of the infection process. Since these

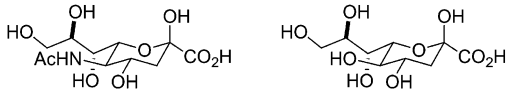


FIGURE 1. Sialic acids.

adhesion proteins likely play a key role in the organism's infection cycle, sialic acids provide useful drug design targets.[1] A particularly interesting sialic acid is the naturally occurring deaminated sialic acid (+)-3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (KDN, **2**, Figure 1), which was recently discovered at elevated levels in human fetal cord red blood cells and ovarian cancer cells.[3] This observation indicates potential oncofetal antigen properties that could be important in the early detection of disease and as a marker for detecting disease recurrence.[3b]

In synthesis, the sialic acids have elicited a great deal of interest due to their unique biological role and their densely functionalized, stereochemistry-rich frameworks. The enzyme-catalyzed condensation of hexoses with pyruvate has been demonstrated to give several natural and nonnatural sialic acids in good yields.[1,4] The chemical synthesis of sialic acids has been pursued to potentially produce compounds not accessible by enzyme-catalyzed routes.[1,4−6] These syntheses include enzyme-like routes that chain extend readily available hexose (usually D-mannose) derivatives and total syntheses from non-carbohydrate derived starting materials. Each mannose

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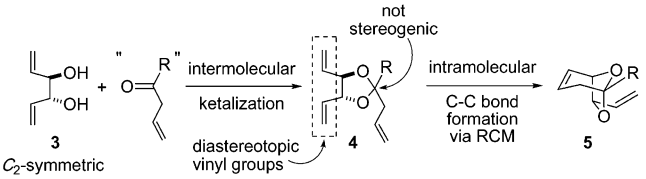

FIGURE 2. Desymmetrization strategy.

elongation strategy has utilized four starting material stereocenters and native functionality, while total synthesis routes have suffered from long and low-yielding reaction sequences. Therefore, the need for an efficient and versatile total synthesis route remained as an incentive for our studies.

We have recently been utilizing a ketalization/catalytic ring-closing olefin metathesis (RCM)[7] sequence as a novel method for subunit convergence and substrate desymmetrization in constructing the 6,8-dioxabicyclo[3.2.1]-octane ring system.[8−10] This strategy (Figure 2) involves intermolecular ketalization followed by intramolecular C−C bond formation, in contrast to the traditional route involving the complete construction of a fully functionalized carbon skeleton followed by late-stage ketodiol-to-acetal dehydration. The advantages of this route lie in the relative ease in which intermolecular C−O bond formation takes place relative to C−C bond formation and in the opportunity to desymmetrize C_2-symmetric diene−diol **3** by reaction of only one of the two diastereotopic vinyl groups of ketal **4** in the RCM step. This desymmetrization strategy differs from conventional C_2-symmetry breaking tactics that often involve intermolecular monofunctionalization of one of two identical chain termini, usually giving mixtures of starting material, monofunctionalized and difunctionalized products.[11] In addition to these features, the resulting 7-vinyl-6,8-dioxabicyclo[3.2.1]oct-2-ene (**5**) is a rigid template with two readily differentiable olefinic moieties for further synthetic manipulations.

Our first application of this strategy resulted in a short and efficient synthesis of (+)-*exo*-brevicomin (**11**, Figure 3), the aggregation pheromone of the western pine beetle, *Dendroctonus brevicomis*.[8] Commercially available ketone **6** and diene−diol **3** readily participated in an acid-catalyzed ketalization reaction, providing ketal **7** in excellent yield. Elimination of HCl gave triene RCM substrate **8**, which provided bicyclic acetal **10** upon reaction with 2 mol % of Grubbs' first generation ruthenium benzylidene catalyst **9**.[7] Hydrogenation furnished (+)-*exo*-brevicomin **11** in 61% overall yield from **3**.

Our initial interest in sialic acid synthesis began with a different desymmetrization strategy employed in total syntheses of 2-deoxy-β-KDO (**14**, Figure 4), a potent inhibitor of KDO incorporation into LPS, and 3-deoxy-D-*manno*-2-octulosonic acid (KDO, **15**), a component of the cell wall lipopolysaccharide (LPS) of Gram-negative bacteria.[12] Diene−diol **3** was converted to desymmetrized dioxanone **12** via an intermediate stannylene acetal. Conversion of **12** to a silyl ketene acetal, Ireland−Claisen rearrangement, and hydrolysis of the intermediate silyl ester provided **13** after reesterification. While this route gave good overall yields for two important octulosonic acids, the extensive protecting group shuffling, stereochemical inversion, and anomeric oxidation steps motivated us to pursue an alternate route to this densely functionalized class of molecules.

Our strategy for the synthesis of Neu5Ac (**1**) and KDN (**2**) is shown retrosynthetically in Figure 5. 2,7-Anhydrosialic acid derivatives **16** and **17** were envisioned as suitable precursors to **1** and **2**, respectively, requiring 2,7-anhydrosugar hydrolysis, carboxylate unmasking, and deprotection to deliver the natural products. The carboxyl surrogate (R) would be important in these final steps, since there is precedent indicating that electron-withdrawing substituents at this position inhibit hydrolysis.[13] The all-axial substitution pattern in **16** and **17** was expected to assist acetal hydrolysis. Both **16** and **17** would be derived from 7-vinyl-6,8-dioxabicyclo[3.2.1]oct-2-ene (**5**) via selective double bond functionalization, taking advantage of this rigid template for stereo- and regioselective introduction of all oxygen and nitrogen functionality. A key feature of this strategy arises from the presence of the opposite hydropyran chair conformations in bicyclic acetals **16** and **17** from those present in **1** and **2**. In the latter, the C4-, C5-, and C6-substituents are equatorially deployed, whereas in **16** and **17** they are all axial. Kinetic introduction of axial substituents on six-membered rings with regio- and stereochemical results matching our needs is generally preferred on stereoelectronic grounds. Bicyclic acetal **17** could be efficiently obtained from **5** via dihydroxylation of both olefins in one step, followed by inversion of the resulting C4 equatorial hydroxyl. Neu5Ac intermediate **16** could potentially be obtained from **17** by acetate cleavage and double inversion at C5. Diene **5** would be the product of intermolecular ketalization/intramolecular ring-closing metathesis, requiring a masked β,γ-unsaturated ketone or a suitably substituted olefin to avoid double bond migration in the acid-catalyzed ketalization step.

This improved route should (1) supply the correct oxidation state at the anomeric carbon, (2) require minimal protection/deprotection and stereochemical inversion steps, and (3) be amenable to the synthesis of nonulosonic acids (i.e. Neu5Ac, **1**, and KDN, **2**). The

(5) For recent chemical syntheses of Neu5Ac, see: (a) Liu, K.-G.; Yan, S.; Wu, Y.-L.; Yao, Z.-J. *J. Org. Chem.* **2002**, *67*, 6758. (b) Li, L.-S.; Wu, Y.-L.; Wu, Y. *Org. Lett.* **2000**, *2*, 891−894. (c) Banwell, M.; Savi, C. D.; Watson, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2251−2252. (d) Takahashi, T.; Tsukamoto, H.; Kurosaki, M.; Yamada, H. *Synlett* **1997**, 1065−1066.

(6) For recent chemical syntheses of KDN, see: (a) Warwel, M.; Fessner, W. D. *Synlett* **2000**, *6*, 865−867. (b) Banwell, M.; De Savi, C.; Watson, K. *J. Chem. Soc., Chem. Commun.* **1998**, 1189−1190. (c) Tsukamoto, H.; Takahashi, T. *Tetrahedron Lett.* **1997**, *38*, 6415−6418. (d) Salagnad, C.; Gödde, A.; Ernst, B.; Kragl, U. *Biotechnol. Prog.* **1997**, *13*, 810−813.

(7) For recent reviews, see: (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (b) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141−8153. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (d) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. I* **1998**, 371−388. (e) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036−2056.

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(13) Dondoni, A.; Marra, A.; Merino, P. *J. Am. Chem. Soc.* **1994**, *116*, 3324−3336.

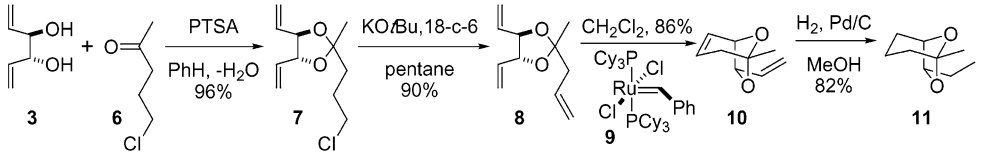


FIGURE 3. Total synthesis of (+)-*exo*-bremicomin.

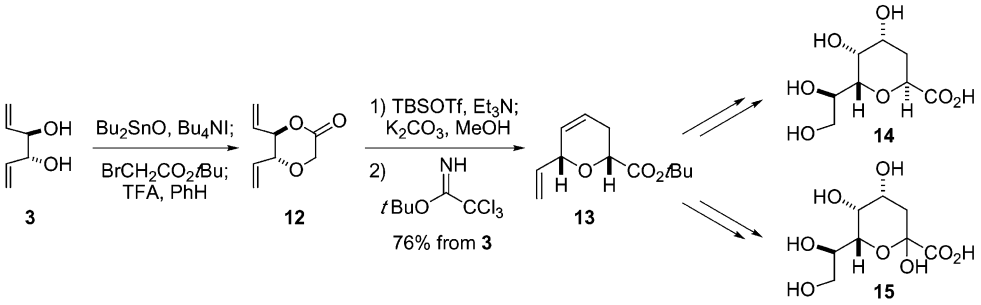


FIGURE 4. Total syntheses of KDO and 2-deoxy-β-KDO.

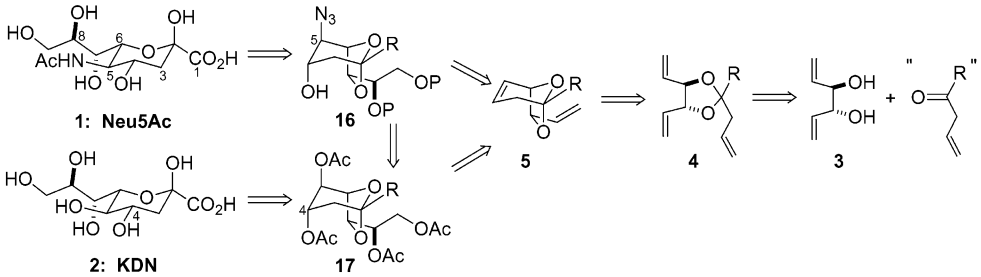
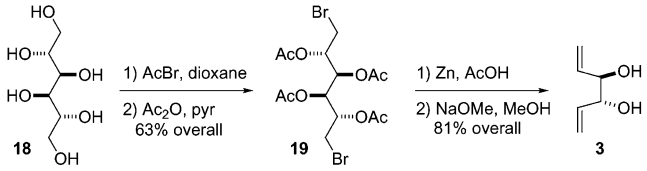


FIGURE 5. Retrosynthetic analysis.

SCHEME 1. Synthesis of (3*R*,4*R*)-3,4-Dihydroxy-1,5-hexadiene (3)

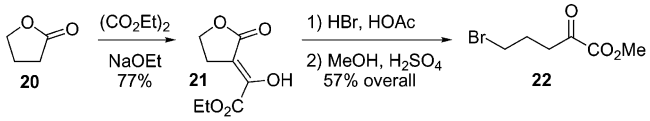


desymmetrization by ring-closing metathesis approach seemed ideally suited to meet all of these requirements, potentially delivering 2,7-anhydrosialic acid derivatives by choosing an appropriate carboxyl surrogate for R (Figure 5) and a suitable double bond functionalization strategy.

Results and Discussion

Synthesis of KDN. To begin the synthesis, known (*R*,*R*)-1,5-hexadiene-3,4-diol (**3**) was made from D-mannitol **18** via our recently published route (Scheme 1).[12] This sequence can be routinely carried out on a mole scale, but other efficient asymmetric crotylboration,[14] resolution by Sharpless asymmetric epoxidation,[15] enzymatic kinetic resolution,[16] and tartrate-derived[17] routes

SCHEME 2. Synthesis of α-Ketoester 22



to **3** have also been reported using non-carbohydrate-derived starting materials. Despite precedence indicating potentially problematic 2,7-anhydrosialic acid hydrolysis with a carboxyl functional group at C1,[13] the simplified synthetic route that would result by carrying an ester through the synthesis appeared very attractive. Known α-ketoester **22** was therefore made from γ-butyrolactone **20** via a literature route (Scheme 2).[18] Unfortunately, all attempts to perform ketalization reactions between **3** and **22** (or its dimethyl ketal) gave only decomposition of the unstable γ-bromoketone **22**, presumably due to the known instability of γ-haloketones[19] and inhibition of the reaction because of rapid hydrate formation when ketone **22** is exposed to aqueous acid.

In previous sialic acid total syntheses, both furan[20] and thiazole[13] heterocycles have been utilized as masked carboxylic acids. The furan ring can be converted to a carboxylic acid in one step using RuO_4 for oxidative cleavage, while the thiazole ring requires a two-step

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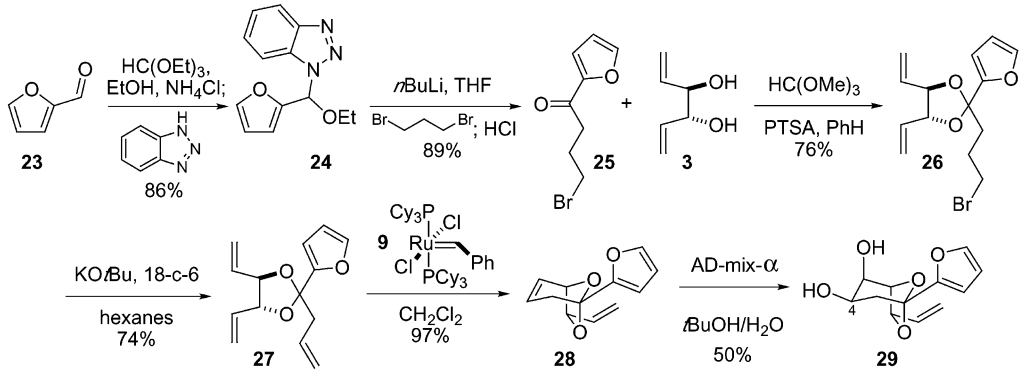
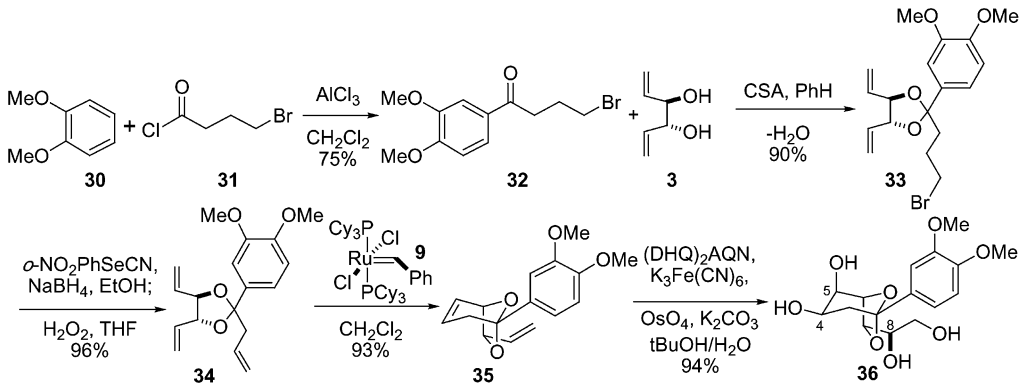
(19) Grandberg, I. I.; Zuyanova, T. I. *Khim. Geterotsikl. Soedin.* **1968**, *4*, 875−877.

SCHEME 3. Furan Carboxyl Surrogate



SCHEME 4. Synthesis of Tetraol 36



oxidation process. Furthermore, the γ-bromoketone **25** is a known compound that can be made in two steps from furfural (**23**, Scheme 3).[21] Ketone **25** was also resistant to ketalization, but ketal **26** could be obtained in 76% yield using trimethylorthoformate (3 equiv) as a dehydrating agent at room temperature in benzene with catalytic *p*-toluenesulfonic acid. Using similar conditions to those employed in the brevicomin synthesis,[8] potassium *tert*-butoxide (3 equiv) promoted elimination of HBr from **26** using 18-crown-6 (0.1 equiv) as phase transfer catalyst in hexanes, providing RCM substrate **27** (74%). The remaining mass balance consisted of double bond migration and *tert*-butyl ether S_N2 products. Using Grubbs' ruthenium benzylidene catalyst **9**,[7] RCM proceeded readily in 97% yield with 25 mol % catalyst (0.01 M in CH_2Cl_2, unoptimized catalyst loading), providing efficient access to 7-vinyl-6,8-dioxabicyclo[3.2.1]oct-2-ene (**28**). After many unsuccessful attempts at aziridination, epoxidation, halohydration, and aminohydroxylation, it was found that diene **28** could be converted to diol **29** using Sharpless' asymmetric dihydroxylation conditions[22] in 50% yield (63% based on recovered **28**). Unfortunately, all attempts to invert the C4 carbinol in **29** were unsuccessful. In most failed double bond functionalization reactions, the furan ring had apparently suffered oxidative or acid-catalyzed decomposition, so a more stable carboxyl surrogate was sought.

The electron-rich 3,4-dimethoxyphenyl carboxyl surrogate[23] was investigated because of the ready availability of ketone **32** (Scheme 4),[24] the ease with which the aromatic ring can be converted to a carboxylic acid with ozone or RuO_4, and the likely stability of the ring throughout the synthesis. Commercially available veratrole (**30**) and 4-bromobutyryl chloride (**31**) had been previously converted to ketone **32** in carbon disulfide, giving a 59% yield. Simply switching to CH_2Cl_2 (0.4 M) for the Friedel−Crafts reaction with aluminum(III) chloride (2 equiv) at 0 °C for 3 h gave highly crystalline **32** in 75% yield. For the acid-catalyzed ketalization between **32** and **3**, careful optimization was needed due to inhibition of the reaction by the electron-rich aromatic ring and the aforementioned instability of γ-haloketones.[19] Heating a benzene solution of diene diol **3** (1 equiv, 0.5 M), CSA (0.1 equiv), and ketone **32** (2 equiv) at reflux with azeotropic removal of water gave ketal **33** (90%) on a 10-g scale. Ketone **32** partially decomposed during the reaction, requiring a 2-fold excess to achieve complete conversion of diene−diol **3** to ketal **33**. Nucleophilic displacement of the bromide with selenide, oxidation, and eliminination following Sharpless' procedure[25] produced triene **34** (96%). All attempts to prepare **34** by ketalization between diene−diol **3** and the appropriate β,γ-unsaturated ketone gave only the product resulting from double bond conjugation. Terminally substituted olefins

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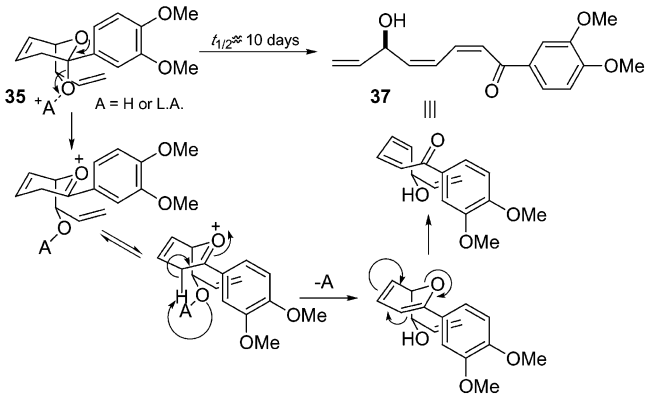


FIGURE 6. Metathesis product instability.

(dimethyl and phenyl) did not migrate during ketalization, but inhibited subsequent ring-closing metathesis, requiring very high dilution and high catalyst loadings to achieve only partial conversion. Furthermore, the required ketone syntheses required three steps with chromatographic purification, rendering this route impractical for production of multigram quantities of **35**. Thus the selenoxide elimination to convert bromide **33** to triene **34** persisted as the best procedure.

Ring-closing metathesis of triene substrate **34** proceeded readily using Grubbs' ruthenium benzylidene catalyst **9** (0.01 equiv, Scheme 4).[7] This reaction was best performed by adding the catalyst in CH_2Cl_2 slowly over 10 h to a solution of **34** in CH_2Cl_2 (0.01 M) at 23 °C, giving 5-aryl-7-vinyl-6,8-dioxabicyclo[3.2.1]oct-2-ene (**35**, 93%). While attempted epoxidation and halohydration again failed, a double dihydroxylation using the conditions previously reported[12,22] provided tetraol **36** (94%) as white pellets after chromatography to remove iron salt impurities and recrystallization from EtOAc to remove co-eluting anthraquinone ligand. This reaction sequence provided 4-*epi*-2,7-anhydro-KDN derivative **36** in four steps and 76% overall yield from diene−diol **3**, a remarkably short and efficient route to this sialic acid precursor. No other stereoisomers were detected in the ^{1}H NMR of **36** before or after recrystallization. Use of the $(DHQ)_2AQN$ ligand,[22b] which has been shown to increase the rate and stereoselectivity of reactions with terminal alkenes, was needed for dihydroxylation of the terminal olefin to occur. When commercially available AD-mix-α was used, only the internal olefin experienced dihydroxylation as with furan substrate **28** (Scheme 3).

Metathesis product **35** proved to be rather unstable, cleanly decomposing to **37** (Figure 6) in an NMR tube over several days. Figure 6 shows a possible mechanism for this transformation. The electron-rich 3,4-dimethoxyphenyl carboxyl surrogate presumably facilitates ketal opening, which can lead to an eventual electrocyclic ring opening via the path shown to give **37**. This observation suggests a basis for the failure of many double bond functionalization attempts using electrophilic reagents. Fortunately, under the basic asymmetric dihydroxylation conditions yielding tetraol **36**, this decomposition pathway is suppressed.

While the rigid bicyclic framework of **36** clearly revealed the stereochemistry of the C4, C5 vicinal diol on the six-membered ring as evidenced by ^{1}H NMR coupling

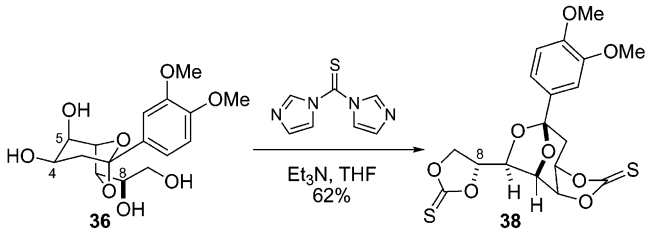


FIGURE 7. Determination of C-8 stereochemistry.

constants ($H3_{ax}$:H4, 11 Hz; $H3_{eq}$:H4, 6.5 Hz; H4:H5, 4 Hz), the C8 stereochemistry could not be determined by NMR. To confirm that this stereocenter had been correctly set, **36** was converted to dithionocarbonate derivative **38** (Figure 7). This material was recrystallized (acetone/MeOH) and its structure was confirmed by X-ray crystallography (see Supporting Information). The X-ray structure clearly shows the required C8(*R*) stereochemistry that is needed for the synthesis of natural nonulosonic acids and which is consistent with the Sharpless mnemonic for predicting the stereochemical result of asymmetric dihydroxylation reactions.[22a]

Inversion of the C4 stereocenter to establish the natural configuration of KDN required differentiation of the four hydroxyls in **36**. This was cleanly accomplished by a tin-catalyzed tosylation reaction (Scheme 5).[26] Stirring a suspension of **36** in methylene chloride (0.05 M) with *p*-toluenesulfonyl chloride (2.1 equiv), triethylamine (2.1 equiv), and dibutyltin oxide (0.05 equiv) for 12 h gave an unstable ditosylate that was peracetylated to give ditosylate diacetate **39**. While this recently reported reaction had only been used for the rapid monotosylation of the primary hydroxyl of an acyclic 2°, 1° vicinal diol, both the equatorial and primary hydroxyls of tetraol **36** were selectively sulfonylated without detection of any other disulfonylation products. The use of stoichiometric amounts of dibutyltin oxide for stannylene acetal formation to achieve selective equatorial protection of a sugar-derived cis vicinal diol is well-known,[27] but this is the first example using a catalytic amount of tin.[28]

Because of its limited stability, ditosylate **39** was routinely taken on to the next reaction by addition of toluene to the combined pure fractions of **39** after column chromatography. Following evaporation of the chromatography solvent (ether), cesium acetate (10 equiv) and 18-crown-6 (2 equiv) were added. Heating at reflux for 18 h gave inverted tetraacetate **40**[29] (81% overall from **36** after two recycles of recovered monotosylate triacetate). This sluggish S_N2 reaction failed when other solvents or oxygen nucleophiles were utilized. Many derivatives of tetraol **36**, including dithionocarbonate **38**

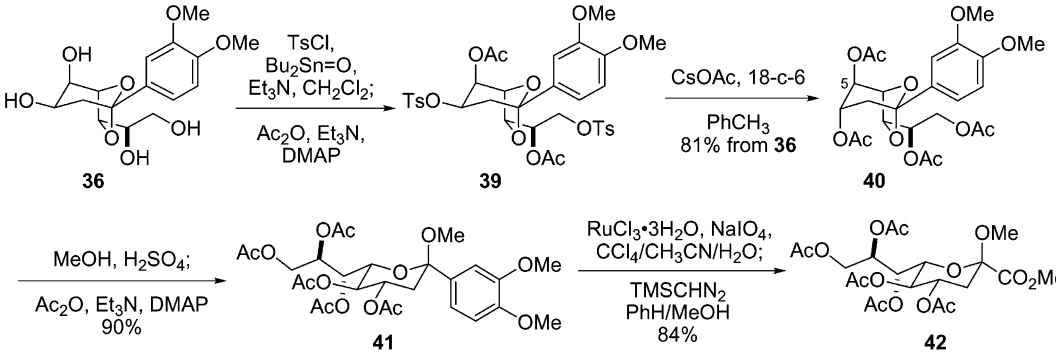
(25) Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947−949. Potassium *tert*-butoxide elimination (ref 8) provided **37** in 57% yield from **36** with ∼30% S_N2 displacement product.

(26) Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R. *Org. Lett.* **1999**, *1*, 447−450.

(27) For reviews, see: (a) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643−663. (b) Grindley, T. B. *Adv. Carbohydr. Chem. Biochem.* **1998**, *53*, 16−142.

(28) The tin-catalyzed monobenzoylation of various vicinal diols has been recently reported: (a) Maki, T.; Iwasaki, F.; Matsumura, Y. *Tetrahedron Lett.* **1998**, *39*, 5601−5604. (b) Iwasaki, F.; Maki, T.; Onomura, O.; Nakashima, W.; Matsumura, Y. *J. Org. Chem.* **2000**, *65*, 996−1002.

SCHEME 5. Completion of the Formal Total Synthesis of KDN



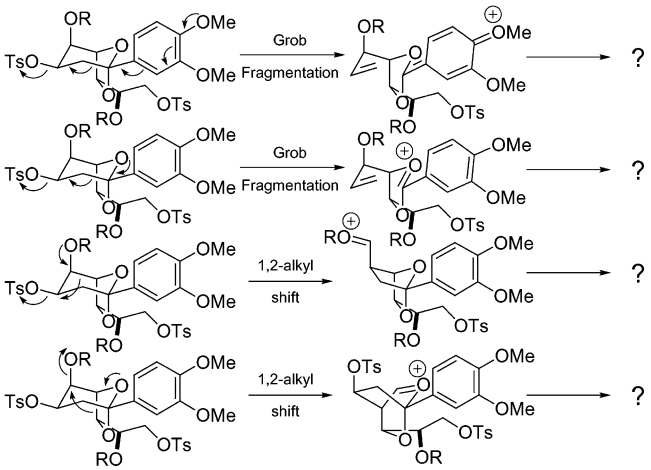


FIGURE 8. Possible decomposition pathways of activated equatorial hydroxyls.

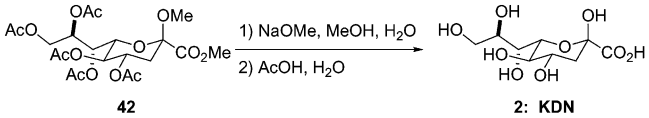


FIGURE 9. Previously reported conversion of **42** to KDN (**2**).[13,31a]

and ditosylate diacetate **39**, were found to be extremely acid sensitive. Attempted ditriflate formation failed completely because of rapid decomposition of any triflates formed. Any attempts to selectively protect tetraol **36** under acidic conditions (i.e. acetonide formation) gave only low yields of desired products. Decomposition pathways similar to those observed in the decomposition of diene **35** (Figure 6) could explain some of these difficulties, beginning with ring opening of one of the labile ketal C−O bonds. However, even with no acid, **39**, when concentrated after chromatography, decomposed rapidly to many (>10) compounds. Figure 8 shows possible decomposition pathways which could potentially be suffered by **39** or other activated C4 equatorial hydroxyls. The rigid template provides optimal orbital overlap for each of these Grob fragmentation and 1,2-alkyl shift reactions, giving cationic products that can further decompose in various ways. Fortunately, these problems could be avoided by simply not concentrating or storing **39**.

Cleavage of the bridged acetal and acquisition of the natural hydropyran conformation required only the addition of a drop of sulfuric acid to **40** in methanol at 0 °C, cleanly providing methyl glycoside **41** after 3 h (90%, 100% based on recovered **40**), following acetylation of the initially formed methanolysis product. Longer reaction time or increased temperature gave several polar acetate cleavage products which could all be converted to **40** and **41** after peracetylation, but this lowered the yield slightly and did not significantly improve the overall conversion. Other Lewis and protic acids (e.g. TESOTf, methanesulfonic acid, or trifluoroacetic acid) gave extensive decomposition of **40** with no isolable ketal-opened products. Final unmasking of the carboxylic acid function was best achieved using RuO_4, formed in situ by adding a catalytic amount of $RuCl_3 \cdot 3H_2O$ (0.05 equiv) to a 2:2:3 $CCl_4/CH_3CN/H_2O$ mixture containing **41** and $NaIO_4$ (12 equiv).[23b−e,30] After 6 h at ambient temperature, clean conversion to KDN pentaacetate methyl glycoside was achieved, isolated as methyl ester **42** (84%), for which all data (^{1}H NMR; melting point; IR; HRMS; and optical rotation) were in agreement with data in the literature.[31] Global deprotection of **42** has been achieved previously by moist methanol/sodium methoxide ester cleavage[31a] and methyl glycoside hydrolysis (refluxing $AcOH/H_2O$, Figure 9).[13]

The formal synthesis of KDN has thus been achieved in 46% overall yield from diene−diol **3**, employing our convergent ketalization/ring-closing metathesis strategy. This efficient and unique entry to KDN synthesis should make possible the stereocontrolled construction of various KDN derivatives due to the conformationally defined bicyclic acetal template and readily differentiated hydroxyls in the 2,7-anhydro sugar analogue **36**.

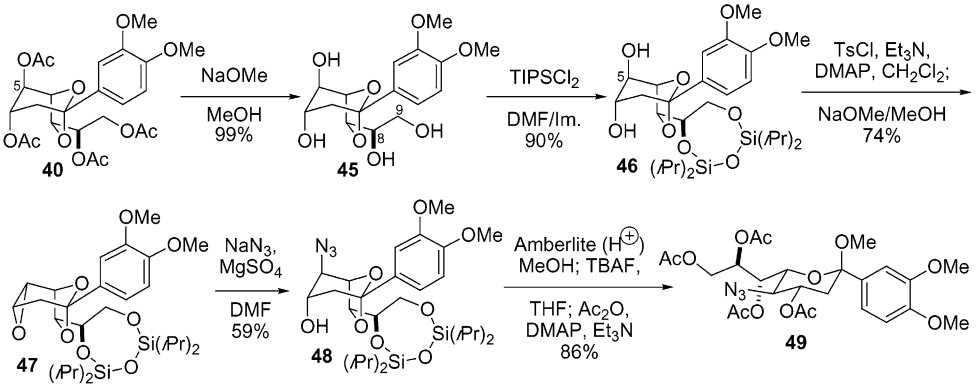
Synthesis of Neu5Ac. Neu5Ac differs from KDN only at C-5 (Figure 5) in the presence of an acetamido group in place of the C5 hydroxyl of KDN. Extensive attempts at selective aziridinination or aminohydroxylation of the internal olefin of diene **35** (Scheme 4) again failed to give any useful Neu5Ac intermediates. In our retrosynthesis of Neu5Ac (Figure 5), azido alcohol **16**, with its four axial

(29) (a) Huffman, J. W.; Desai, R. C. *Synth. Commun.* **1983**, *13*, 553−557. (b) Torisawa, Y.; Okabe, H.; Ikegami, S. *Chem. Lett.* **1984**, 1555−1556. (c) Sato, K.; Yoshitomo, A. *Chem. Lett.* **1995**, 39−40. (d) Shimizu, T.; Hiranuma, S.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6145−6148. (e) Pour, M.; Willis, A. C.; Furber, M.; Mander, L. N. *Tetrahedron* **1998**, *54*, 13833−13850.

(30) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938.

(31) (a) Mononen, I.; Lengstad, B.; Lönngren, J. *Acta Chem. Scand. B* **1980**, *34*, 775−776. (b) Nakamura, M.; Takayanagi, H.; Furuhata, K.; Ogura, H. *Chem. Pharm. Bull.* **1992**, *40*, 879−885.

SCHEME 6. Synthesis of Methyl Glycoside 49



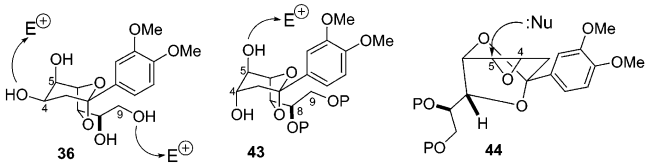


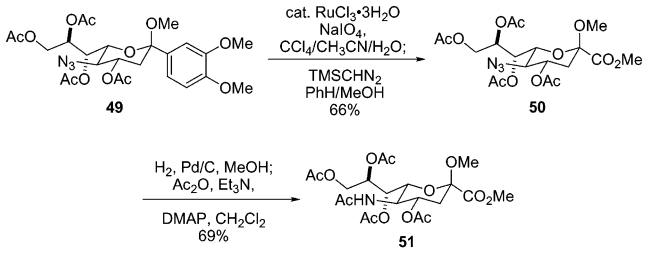
FIGURE 10. Chemo- and regioselectivities facilitated by rigid 6,8-dioxabicyclo[3.2.1]octane template.

substituents and electron-rich 3,4-dimethoxyphenyl carboxyl surrogate at the anomeric carbon, was seen as a suitable precursor to **1**. Tetraacetate **40** (Scheme 5), a late-stage KDN intermediate, was chosen as a suitable divergence point, requiring replacement of the C5 acetate by acetamido with retention (double inversion) via an intermediate epoxide to gain access to Neu5Ac (**1**).

Figure 10 highlights the chemo- and regioselectivities expected for hydroxyl sulfonylation (**36** and **43**) and epoxide nucleophilic ring opening (**44**) in the KDN and Neu5Ac intermediates. The rigid 6,8-dioxabicyclo[3.2.1]-octane template in **36** allowed complete selectivity for disulfonylation at the C4 equatorial hydroxyl and the C9 primary alcohol using a dibutyltin oxide-catalyzed tosylation reaction. In **43**, the axial C5 *exo*-hydroxyl was expected to be more reactive toward sulfonylation than the axial C4 *endo*-hydroxyl, allowing selective α-epoxide formation with a suitably protected C8, C9 diol. Epoxide **44** was expected to suffer nucleophilic attack selectively at C5 in order to allow a chairlike transition state via trans-diaxial ring opening.[32] The selectivity of each of these reactions is a direct consequence of the steric and conformational characteristics of the rigid 6,8-dioxabicyclo-[3.2.1]octane ring system.

With multigram quantities of inverted tetraacetate **40** in hand (Schemes 5 and 6), methanolysis proceeded readily employing NaOMe (0.25 equiv) in MeOH (99%, Scheme 6). Selective protection of the C8 and C9 hydroxyls of the resulting tetraol **45** was best achieved under basic conditions using 1,3-dichlorotetraisopropyl disiloxane (1.5 equiv) and imidazole (3 equiv) in DMF, affording the tetraisopropyl disiloxane **46** (90%).[33] Selective sulfonylation using *p*-toluenesulfonyl chloride (2.1 equiv) and triethylamine (4.2 equiv) with catalytic 4-(dimethylamino)pyridine gave a C-5 tosylate that could be displaced by the C4 hydroxyl using NaOMe (4.2 equiv) in MeOH to provide epoxide **47** (74%).[34,35] After some experimentation, it was found that epoxide azidolysis could best be accomplished using sodium azide (10.6 equiv) and magnesium sulfate (2.1 equiv) in DMF (0.1 M) at 90−95 °C, giving azido alcohol **48** (59%).[36] Without magnesium sulfate, only 50% conversion could be achieved after 2 d, giving a 2:1 ratio of epoxide-opening regioisomers. Once again, stronger Lewis or protic acids gave rapid decomposition of **48**. Methanolysis of 2,7-anhydro-Neu5Ac derivative **48** proceeded readily employing Amberlite IR-120 (plus) acid resin,[37] providing methyl glycoside **49** after removal of the TIPS group with TBAF and peracetylation in one pot.

SCHEME 7. Completion of the Formal Total Synthesis of Neu5Ac



To complete the synthesis of Neu5Ac, oxidative cleavage of the 3,4-dimethoxyphenyl carboxyl surrogate was achieved using the same conditions as for the conversion of **41** to **42** (Scheme 5) providing azidoNeu5Ac derivative **50** (66%, Scheme 7). Reductive acetylation of the azide in **50** gave **51** (69%),[5a] which had been previously converted to Neu5Ac (**1**) using 1 N aq sodium hydroxide followed by acidification with aq HCl (70%, Figure 11).[38a,d] The ^{1}H NMR, TLC R_f, IR, MS, and optical rotation of **51** matched those reported in the literature.[38] The formal total synthesis of Neu5Ac has thus been achieved in 9.3%

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(34) Takatori, K.; Kajiwara, M. *Synlett* **1995**, *3*, 280−282.

(35) Surprisingly, attempted epoxidation using Mitsunobu conditions gave almost exclusively the undesired *β*-epoxide despite close precedent suggesting that **10** should be the major product. Thomson, R.; von Itzstein, M. *Carbohydr. Res.* **1995**, *274*, 29−44.

(36) Monneret, C.; Risse, S.; Ardouin, P.; Gouyette, A. *Eur. J. Med. Chem. Chim. Ther.* **2000**, *35*, 137−146.

(37) (a) Baker, R.; Boyes, R. H. O.; Broom, D. M. P.; O'Mahony, M. J.; Swain, C. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1613−1621. (b) Kâlé, V. N.; Clive, D. L. J. *J. Org. Chem.* **1984**, *49*, 1554−1563.

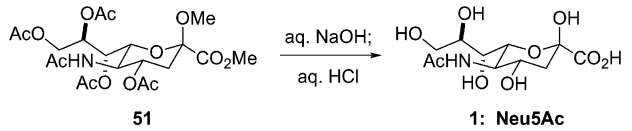

FIGURE 11. Previously reported conversion of **51** to Neu5Ac.[38a,d]

overall yield from diene−diol **3** employing our convergent ketalization/ring-closing metathesis strategy and exploiting the resulting rigid 6,8-dioxabicyclo[3.2.1]octane template.

Experimental Section

General Methods. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 300 MHz. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 75 MHz. Analytical thin-layer chromatography (TLC) was carried out on E. Merck (Darmstadt) TLC plates precoated with silia gel 60 F_{254} (0.25 mm layer thickness). Flash column chromatography (FCC) was performed on EM Science silica gel 60 (230−400 mesh).

Preparation of Compound 26. Ketone **25** (150 mg, 0.691 mmol) was dissolved in PhH (1 mL) and (*R*,*R*)-1,5-hexadiene-3,4-diol **3** (86.7 mg, 0.760 mmol), trimethylorthoformate (0.091 mL, 0.83 mmol), and *p*-toluenesulfonic acid (∼2 mg) were added. After stirring at rt for 2 h, additional trimethylorthoformate (0.8 equiv) was added. After an additional 0.5 h, more trimethylorthoformate (1 equiv) was added. After stirring overnight, the reaction mixture was poured into saturated aqueous sodium bicarbonate (30 mL), and the organic layer was diluted with Et_2O (30 mL). The organic phase was washed with saturated aqueous sodium bicarbonate (30 mL) and water (2 × 30 mL), dried ($MgSO_4$), and concentrated, and FCC (5% Et_2O/hexanes) gave pure **26** (164 mg, 76%) as a clear oil. ^{1}H NMR ($CDCl_3$) δ 7.40 (dd, J = 2, 1 Hz, 1H), 6.40 (dd, J = 3.5, 1 Hz, 1H), 6.35 (dd, J = 3.5, 1 Hz, 1H), 5.7−6.0 (m, 2H), 5.2−5.5 (m, 4H), 4.0−4.3 (m, 2H), 3.42 (t, J = 8.5 Hz, 2H), 1.8−2.3 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 154.1 (C), 142.5 (CH), 133.7 (CH), 132.5 (CH), 119.6 (CH_2), 119.5 (CH_2), 109.9 (CH), 107.3 (CH), 106.4 (C), 83.6 (CH), 82.1 (CH), 36.7 (CH_2), 33.6 (CH_2), 26.8 (CH_2); $[\alpha]^{24}_D$ +1.6° (*c* 0.61, $CHCl_3$).

Preparation of Compound 27. To a suspension of KO*t*Bu (108 mg, 0.958 mmol) and 18-c-6 (8.4 mg, 0.032 mmol) in hexanes (4 mL) was added **26** (100 mg, 0.319 mmol) in hexanes (3 mL) dropwise. After the mixture was stirred for 4 h at rt, water (5 mL) was added, the aqueous was later extracted with Et_2O (3 × 20 mL), the organics were dried ($MgSO_4$) and concentrated, and FCC (0−2% EtOAc/hexanes, gradient elution) gave pure **27** (54.9 mg, 74%) as a slightly yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.40 (dd, J = 2, 1 Hz, 1H), 6.40 (dd, J = 3.5, 1 Hz, 1H), 6.32 (dd, J = 3.5, 2 Hz, 1H), 5.7−5.9 (m, 3H), 5.0−5.5 (m, 6H), 4.0−4.3 (m, 2H), 2.7−3.0 (m, 2H); ^{13}C ($CDCl_3$) δ 154.3 (C), 142.4 (CH), 133.7 (CH), 132.6 (CH), 131.6 (CH), 119.5 (CH_2), 119.4 (CH_2), 118.8 (CH_2), 109.8 (CH), 107.2 (CH), 106.1 (C), 83.6 (CH), 82.2 (CH), 42.6 (CH_2); $[\alpha]^{24}_D$ +0.5 (*c* 1.73, $CHCl_3$).

Preparation of Compound 28. Grubbs' catalyst (**9**, 48 mg, 0.058 mmol) and CH_2Cl_2 (15 mL) were combined, and triene **27** (54 mg, 0.23 mmol) was added in CH_2Cl_2 (8 mL). After 1 h, air was blown into the reaction flask for 1 d, and the resulting dark brown solution was poured through a pad of silica gel. The pad was washed with CH_2Cl_2 (200 mL), the combined organics were concentrated, and FCC (3% Et_2O/hexanes) gave **28** (46 mg, 97%) as an oil with light brown discoloration that did not appear as an impurity in any spectra. ^{1}H NMR ($CDCl_3$) δ 7.42 (dd, J = 2, 1 Hz, 1H), 6.54 (dd, J = 3.5, 1 Hz, 1H), 6.38 (dd, J = 3.5, 2 Hz, 1H), 6.17 (ddt, J = 10, 4.5, 2 Hz, 1H), 6.01 (ddd, J = 17, 10, 7 Hz, 1H), 5.85 (ddd, J = 10, 4, 2.5 Hz, 1H), 5.17 (ddd, J = 17, 2, 1.5 Hz, 1H), 5.09 (ddd, J = 10, 2, 1 Hz), 4.62 (ddd, J = 7, 1.5, 1 Hz, 1H), 4.56 (d, J = 4.5 Hz, 1H), 2.95 (ddd, J = 18, 2.5, 2 Hz, 1H), 2.49 (ddd, J = 18, 4, 2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 151.6 (C), 142.8 (CH), 137.2 (CH), 127.8 (CH), 124.9 (CH), 116.8 (CH_2), 110.0 (CH), 108.0 (CH), 103.1 (C), 86.1 (CH), 77.0 (CH), 35.8 (CH_2); $[\alpha]^{24}_D$ +143 (*c* 1.47, $CHCl_3$).

Preparation of Compound 29. Diene **28** (40.8 mg, 0.200 mmol) was dissolved in *tert*-butanol (1 mL) and water (1 mL). The yellow solution was cooled to 0 °C and AD-mix-α (280 mg) and methanesulfonamide (19.0 mg, 0.200 mmol) were added. After the mixture was warmed to rt and stirred overnight, sodium sulfite (0.3 g) was added and the reaction mixture was stirred 30 min. CH_2Cl_2 (5 mL) was added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were washed with 2 N KOH (5 mL), dried (Na_2SO_4), and concentrated, and FCC (75% EtOAc/hexanes) gave recovered **28** (8.0 mg, 5%) and pure **29** (24.0 mg, 50%, 63% based on recovered **28**). ^{1}H NMR ($CDCl_3$) δ 7.43 (dd, J = 2, 1 Hz, 1H), 6.54 (dd, J = 3.5, 1 Hz, 1H), 6.38 (dd, J = 3.5, 2 Hz, 1H), 5.92 (ddd, J = 17, 10, 7 Hz, 1H), 5.39 (dt, J = 17, 1.5 Hz, 1H), 5.22 (dt, J = 10, 1.5 Hz, 1H), 4.50 (br d, J = 2.5 Hz, 1H), 4.39 (dd, J = 6.5, 1 Hz, 1H), 4.13 (br s, 1H), 3.83 (br s, 1H), 2.90 (br s, 2H), 2.58 (dd, J = 13, 6.5, 1H), 2.05 (dd, J = 13, 10.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 150.5 (C), 143.2 (CH × 2), 136.3 (CH), 117.4 (CH_2), 110.3 (CH), 108.6 (CH), 103.5 (C), 82.1 (CH), 77.8 (CH), 68.5 (CH), 64.3 (CH), 38.5 (CH_2).

Preparation of Compound 32. 1,2-Dimethoxybenzene (veratrole, **30**, 9.93 mL, 77.1 mmol) was dissolved in CH_2Cl_2 (100 mL), the mixture was cooled to 0 °C, and $AlCl_3$ (18.6 g, 140 mmol) was added in portions over 10 min with vigorous stirring. After 5 min, 4-bromobutyryl chloride (13.68 g, 70.1 mmol) in CH_2Cl_2 (75 mL) was added dropwise via addition funnel. The resulting light yellow solution was stirred at 0 °C for 3 h, thenpoured into concentrated hydrochloric acid (50 mL) and ice (50 g), and the reaction flask was rinsed with CH_2Cl_2 (4 × 10 mL). The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 150 mL), and the combined organics were dried ($MgSO_4$) and concentrated to 50 mL. The resulting light yellow solution was poured into a 250-mL Erlenmeyer, rinsing with Et_2O (5 × 10 mL). The solution was swirled to mix solvents thoroughly, and recrystallization gave pure **32** (15.04 g, 75%) as white needles (mp 96−97 °C) which were used without prolonged storage or exposure to light for extended periods of time. ^{1}H NMR ($CDCl_3$) δ 7.63 (dd, J = 8.5, 2 Hz, 1H), 7.54 (d, J = 2 Hz, 1H), 6.91 (d, J = 8.5 Hz, 1H), 3.96 (s, 3H), 3.95 (s, 3H), 3.56 (t, J = 6.5 Hz, 2H), 3.15 (t, J = 6.5 Hz, 2H), 2.31 (quint, J = 6.5 Hz, 2H).

Preparation of Compound 33. Ketone **32** (15.04 g, 52.4 mmol) was dissolved in PhH (50 mL), (*R*,*R*)-1,5-hexadiene-3,4-diol **3** (2.99 g, 26.2 mmol) and camphorsulfonic acid (608 mg, 2.62 mmol) were added, and a Dean−Stark trap was attached. After refluxing 12 h with azeotropic removal of water, the reaction mixture was poured into saturated aqueous sodium bicarbonate (50 mL), and the organic layer separated. The aqueous phase was extracted with CH_2Cl_2 (4 × 50 mL), the combined organics were dried ($MgSO_4$)and concentrated, and FCC (15% Et_2O/hexanes) gave pure **33** (9.06 g, 90%) as a clear oil. ^{1}H NMR ($CDCl_3$) δ 7.07 (dd, J = 8.5, 2 Hz, 1H), 7.03 (d, J = 2 Hz, 1H), 6.84 (d, J = 8.5 Hz, 1H), 5.87 (ddd, J = 17.5, 10, 7 Hz, 1H), 5.67 (ddd, J = 17.5, 10, 7.5 Hz, 1H), 5.34 (ddd, J = 17.5, 1.5, 1 Hz, 1H), 5.31 (ddd, J = 17.5, 1.5, 1 Hz, 1H), 5.29 (ddd, J = 10, 1.5, 1 Hz, 1H), 5.20 (ddd, J = 10, 1.5, 1 Hz, 1H), 4.14 (ddt, J = 8, 7.5, 1 Hz, 1H), 3.96 (ddt, J = 8, 7, 1 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.3−3.5 (m, 2H), 1.8−2.1 (m, 4H);

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^{13}C NMR ($CDCl_3$) δ 148.6 (C × 2), 136.1 (C), 134.4 (CH), 133.0 (CH), 119.4 (CH_2), 119.1 (CH_2), 117.7 (CH), 110.5 (CH), 110.3 (C), 108.8 (CH), 83.9 (CH), 81.8 (CH), 55.9 (CH_3), 55.8 (CH_3), 40.0 (CH_2), 33.8 (CH_2), 27.2 (CH_2); IR (thin film) 3082, 2956 cm^{-1}; $[\alpha]^{24}_D$ −20 (*c* 1.4, $CHCl_3$); HRMS (FAB) calcd for $C_{18}H_{23}O_4BrNa$ (M + Na^+) 405.0677, found 405.0681.

Preparation of Compound 34. To a solution of *o*-nitrophenylselenocyanate (127 mg, 0.550 mmol) in ethanol (4 mL) was added sodium borohydride (23 mg, 0.60 mmol) slowly at 0 °C. After the solution was stirred for 15 min, ketal **33** (192 mg, 0.500 mmol) was added in ethanol (2 mL) over 20 min. After the mixture was stirred overnight at rt, additional *o*-nitrophenylselenocyanate (5 mg, 0.02 mmol) and sodium borohydride (2 mg, 0.05 mmol) were added, and the reaction was stirred an additional 3 h. The reaction was poured into water (10 mL), extracted with CH_2Cl_2 (3 × 10 mL), dried ($MgSO_4$), concentrated, and dissolved in THF (6 mL). The solution was cooled to 0 °C and hydrogen peroxide (30% in water, 0.07 mL, 0.6 mmol) was added slowly over 15 min. After being stirred at rt overnight, the reaction was diluted with CH_2Cl_2 (20 mL), the organic layer was washed with water (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), dried ($MgSO_4$), and concentrated. Purification by FCC (20−50% CH_2Cl_2/hexanes, gradient elution) gave pure **34** (145 mg, 96%) as a slightly yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.08 (dd, *J* = 8, 2 Hz, 1H), 7.04 (d, *J* = 2 Hz, 1H), 6.84 (d, *J* = 8 Hz, 1H), 5.88 (ddd, *J* = 17.5, 10.5, 7 Hz, 1H), 5.83 (ddt, *J* = 18, 9.5, 7 Hz, 1H), 5.68 (ddd, *J* = 18, 10, 7.5 Hz, 1H), 5.34 (ddd, *J* = 17.5, 1.5, 1 Hz, 1H), 5.31 (ddd, *J* = 17, 2, 1 Hz, 1H), 5.29 (ddd, *J* = 10, 1.5, 1 Hz, 1H), 5.20 (ddd, *J* = 10.5, 2, 1 Hz, 1H), 5.0−5.13 (m, 2H), 4.17 (ddt, *J* = 8, 7.5, 1 Hz, 1H), 3.96 (ddt, *J* = 8, 7, 1 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 2.68 (ABqdt, *J* = 14, 7, 1.5 Hz, 2H); ^{13}C ($CDCl_3$) δ 148.5 (C), 148.4 (C), 136.3 (C), 134.4 (CH), 133.2 (CH), 132.4 (CH), 119.4 (CH_2), 119.1 (CH_2), 118.4 (CH_2), 117.9 (CH), 110.4 (CH), 110.1 (C), 109.0 (CH), 84.0 (CH), 81.9 (CH), 55.9 (CH_3), 55.8 (CH_3), 46.1 (CH_2); IR (thin film) 3079, 2997 cm^{-1}; $[\alpha]^{24}_D$ −22 (*c* 0.58, $CHCl_3$); HRMS (EI) calcd for $C_{15}H_{17}O_4$ (M − allyl$^+$) 261.1127, found 261.1136.

Preparation of Compound 35. Triene **34** (7.32 g, 24. 2 mmol) was dissolved in CH_2Cl_2 (2.4 L) and the clear solution was stirred while Grubbs' catalyst (**9**, 199 mg, 0.242 mmol) was added via syringe pump in CH_2Cl_2 (50 mL) over 10 h. After an additional 4 h, Et_3N (5 mL) was added and air was blown into the reaction flask for 7 h. The resulting dark-brown solution was poured through a pad of silica gel. The pad was washed with CH_2Cl_2 (500 mL), the combined organics were concentrated, and FCC (25% Et_2O/hexanes) gave pure **35** (6.15 g, 93%) as an oil. ^{1}H NMR ($CDCl_3$) δ 7.14−7.2 (m, 2H), 6.8−6.9 (m, 1H), 6.17 (ddt, *J* = 10, 4.5, 2 Hz, 1H), 5.86 (ddd, *J* = 17, 10, 7 Hz, 1H), 5.85 (ddd, *J* = 10, 4, 2.5 Hz, 1H), 5.19 (ddd, *J* = 17, 2, 1.5 Hz, 1H), 5.09 (ddd, *J* = 10, 2, 1), 4.66 (ddd, *J* = 7, 1.5, 1 Hz, 1H), 4.56 (d, *J* = 4.5 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 2.73 (ddd, *J* = 18, 2.5, 2 Hz, 1H), 2.47 (ddd, *J* = 18, 4, 2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 148.9 (C), 148.6 (C), 137.5 (CH), 133.6 (C), 128.1 (CH), 125.8 (CH), 117.4 (CH), 116.6 (CH_2), 110.6 (CH), 108.4 (CH), 107.5 (C), 86.2 (CH), 77.1 (CH), 55.84 (CH_3), 55.81 (CH_3), 39.4 (CH_2); IR (thin film) 3039, 2998 cm^{-1}; $[\alpha]^{24}_D$ +97 (*c* 2.6, $CHCl_3$); HRMS (FAB) calcd for $C_{16}H_{18}O_4Na$ (M + Na^+) 297.1103, found 297.1089.

Preparation of Compound 36. Diene **35** (1.94 g, 7.07 mmol) was dissolved in *tert*-butanol (35 mL) and $(DHQ)_2AQN$ (320 mg, 0.354 mmol) was added. With vigorous stirring, water (35 mL), potassium carbonate (5.86 g, 42.4 mmol), and potassium ferricyanide (14.0 g, 42.4 mmol) were added, and the resulting yellow-orange biphasic mixture was cooled to 0 °C. Osmium tetroxide (2.5 wt % solution in *tert*-butanol, 0.93 mL, 0.071 mmol) was then added and the reaction was stirred vigorously at 0 °C for 31 h. Anhydrous sodium sulfite (21 g) was then added, the reaction was warmed to rt and stirred 30 min, water (50 mL) and ethyl acetate (150 mL) were added, and the aqueous layer was extracted with ethyl acetate (7 × 150 mL). The combined organics were dried ($MgSO_4$) and concentrated, and FCC (10−15% MeOH/EtOAc, gradient elution) gave **36** contaminated with co-eluting $(DHQ)_2AQN$ ligand. Recrystallization from ethyl acetate gave, after 3 crops of crystals, pure **36** (2.28 g, 94%) as white pellets (mp 138−139 °C). ^{1}H NMR (CD_3OD) δ 7.15 (d, *J* = 2 Hz, 1H), 7.10 (dd, *J* = 8.5, 2 Hz, 1H), 6.92 (d, *J* = 8.5 Hz, 1H), 4.70 (dd, *J* = 2.5, 0.5 Hz, 1H), 4.07 (ddd, *J* = 11, 6.5, 4 Hz, 1H), 3.86 (dd, *J* = 9, 0.5 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.79 (dd, *J* = 4, 2.5 Hz, 1H), 3.74 (dd, *J* = 11.5, 3 Hz, 1H), 3.58 (dd, *J* = 11.5, 5.5 Hz, 1H), 3.38 (ddd, *J* = 9, 5.5, 3 Hz, 1H), 2.20 (dd, *J* = 13, 6.5 Hz, 1H), 2.03 (dd, *J* = 13, 11 Hz, 1H); ^{13}C NMR (CD_3OD) δ 150.6 (C), 150.0 (C), 134.5 (C), 119.1 (CH), 112.4 (CH), 110.6 (CH), 109.2 (C), 81.2 (CH), 77.9 (CH), 73.3 (CH), 69.8 (CH), 66.0 (CH), 64.2 (CH_2), 56.5 (CH_3 × 2), 42.4 (CH_2); IR (thin film) 3362, 3002, 2934 cm^{-1}; $[\alpha]^{24}_D$ +43 (*c* 0.85, MeOH); HRMS (FAB) calcd. for $C_{16}H_{22}O_8Na$ (M + Na^+) 365.1212, found 365.1229.

Preparation of Compound 38. To a suspension of tetraol **36** (60.5 mg, 0.177 mmol) in THF (2 mL) was added thiocarbonyl diimidazole (175 mg, 0.884 mmol) and Et_3N (0.25 mL, 1.8 mmol). After being stirred at rt for 20 h, the reaction mixture was concentrated and FCC (Et_2O) gave **38,**which was recrystallized from acetone/MeOH to provide pure **38** (46.7 mg, 62%) as clear plates suitable for X-ray crystallographic analysis. ^{1}NMR (acetone-d_6) δ 7.14 (d, *J* = 2 Hz, 1H), 7.07 (dd, *J* = 8.5, 2 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 5.60 (td, *J* = 8, 4.5 Hz, 1H), 5.36 (ddd, *J* = 8.5, 5.5, 3.5 Hz, 1H), 5.33 (dd, *J* = 8, 1.5 Hz, 1H), 5.18 (br s, 1H), 4.77 (dd, *J* = 3.5, 1.5 Hz, 1H), 4.76 (dd, *J* = 9, 8,5 Hz, 1H), 4.55 (dd, *J* = 9, 5.5 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 2.73 (ddd, *J* = 15, 8, 1 Hz, 1H), 2.33 (dd, *J* = 15, 4.5 Hz, 1H); ^{13}C NMR (acetone-d_6) δ 192.6 (C), 191.8 (C), 150.7 (C), 149.8 (C), 131.7 (C), 118.5 (CH), 112.1 (CH), 103.4 (CH), 108.6 (C), 82.3 (CH), 79.1 (CH), 76.5 (CH), 75.9 (CH), 75.8 (CH), 70.4 (CH_2), 56.0 (CH_3), 55.9 (CH_3), 39.7 (CH_2). X-ray crystallography data are provided in the Supporting Information.

Preparation of Compound 40. To a suspension of tetraol **36** (963 mg, 2.81 mmol) in CH_2Cl_2 (56 mL) were added Et_3N (0.822 mL, 2.81 mmol), dibutyltin oxide (35 mg, 0.14 mmol), and TsCl (1.12 g, 5.90 mmol). The reaction was stirred for 16 h at rt, at which time a clear, homogeneous solution was observed. Et_3N (3.92 mL, 28.1 mmol), acetic anhydride (1.33 mL, 14.1 mmol), and 4-dimethylamino pyridine (34 mg, 0.28 mmol) were then added. After being stirred for 30 min at rt, the reaction mixture was washed with water (25 mL), the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), the combined organics were dried (Na_2SO_4) and concentrated, and FCC (0.5% Et_3N/Et_2O) gave pure **39**. $PhCH_3$ (10 mL) was added to the combined pure fractions of **39**, the clear solution concentrated to remove all Et_2O and Et_3N, and activated 4 Å molecular sieves (1 g) were added. After the mixture was stirred for 10 min at rt while flushing with a stream of nitrogen, CsOAc (5.39 g, 28.1 mmol) and 18-c-6 (1.49 g, 5.62 mmol) were added. The reaction was refluxed for 18 h and cooled to rt, and water (100 mL) and CH_2Cl_2 (100 mL) were added. The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and combined organics were dried (Na_2SO_4) and concentrated. Purification by FCC (0−10% Et_2O/CH_2Cl_2, gradient elution) gave monotosylate triacetate and pure **40** (608 mg). The recovered monotosylate triacetate was resubjected to the identical reaction conditions with CsOAc (2.70 g, 14.1 mmol) and 18-c-6 (0.745 g, 2.81 mmol), giving pure **40** (434 mg). A second recycling using CsOAc (1.35 g, 7.05 mmol) and 18-c-6 (0.373 g, 1.41 mmol) provided more pure **40** (121 mg, total = 1.16 g, 81%) as white flakes (mp 45−46 °C). ^{1}H NMR ($CDCl_3$) δ 7.08 (dd, *J* = 8, 2 Hz, 1H), 7.04 (d, *J* = 2 Hz, 1H), 6.86 (d, *J* = 8 Hz, 1H), 5.04 (ddd, *J* = 6, 2.5, 1.5 Hz, 1H), 4.98 (ddd, *J* = 8, 5.5, 3 Hz, 1H), 4.80 (d, *J* = 1.5 Hz, 1H), 4.58 (d, *J* = 1 Hz, 1H), 4.55 (dd, *J* = 8, 1 Hz, 1H), 4.46 (dd, *J* = 12.5, 3 Hz, 1H), 4.14 (dd, *J* = 12.5, 5.5 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 2.39 (dd, *J* = 15, 6 Hz,

1H), 2.18 (s, 3H), 2.17 (dd, J = 15, 2.5 Hz, 1H), 2.16 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.5 (C), 170.0 (C), 169.8 (C), 169.6 (C), 149.4 (C), 148.7 (C), 131.7 (C), 117.6 (CH), 110.7 (CH), 108.2 (CH), 107.6 (C), 77.2 (CH), 74.1 (CH), 71.1 (CH), 69.4 (CH), 68.2 (CH), 62.3 (CH_2), 56.0 (CH_3), 55.9 (CH_3), 37.4 (CH_2), 21.2 (CH_3), 21.0 (CH_3), 20.9 (CH_3), 20.7 (CH_3); IR (thin film) 2968, 1743, 1740, 1734 cm^{-1}; $[\alpha]^{24}_D$ +51 (c 1.1, $CDCl_3$); HRMS (FAB) calcd for $C_{24}H_{30}O_{12}Na$ (M + Na^+) 533.1635, found 533.1622.

Preparation of Compound 41. Inverted tetraacetate **40** (223 mg, 0.437 mmol) was dissolved in MeOH (10 mL) and concentrated sulfuric acid (1 drop) was added at 0 °C. After being stirred at 0 °C for 3 h, the clear solution was poured into saturated aqueous sodium bicarbonate (15 mL), CH_2Cl_2 (30 mL) was added, layers separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organics were dried ($MgSO_4$), concentrated, and dissolved in CH_2Cl_2 (10 mL). Et_3N (0.488 mL, 3.50 mmol), acetic anhydride (0.165 mL, 1.75 mmol), and 4-dimethylamino pyridine (5.3 mg, 0.044 mmol) were then added at rt, and the reaction was stirred 2 h. After the mixture was poured into water (15 mL) and CH_2Cl_2 (20 mL) added, the separated aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organics were dried ($MgSO_4$) and concentrated, and FCC (20−50% Et_2O/hexanes, gradient elution) gave **40** (37 mg, ∼90% pure by ^{1}H NMR) and pure **41** (229 mg, 90%, 100% based on recovered **40**) as white flakes (mp 50−51 °C). ^{1}H NMR ($CDCl_3$) δ 7.04 (dd, J = 8, 2 Hz, 1H), 6.94 (d, J = 2 Hz, 1H), 6.87 (d, J = 8 Hz, 1H), 5.48 (dd, J = 6, 2 Hz, 1H), 5.43 (ddd, J = 11.5, 9.5, 5.5 Hz, 1H), 5.38 (td, J = 6, 2.5 Hz, 1H), 4.95 (t, J = 9.5 Hz, 1H), 4.54 (dd, J = 12.5, 2.5 Hz, 1H), 4.22 (dd, J = 12.5, 6 Hz, 1H), 4.19 (dd, J = 9.5, 2 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 2.95 (s, 3H), 2.54 (dd, J = 13, 5.5 Hz, 1H), 2.16 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 1.99 (s, 3H), 1.76 (dd, J = 13, 11.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 170.6 (C), 170.3 (C), 170.04 (C), 169.97 (C), 169.9 (C), 149.0 (C), 148.9 (C), 131.9 (C), 118.2 (CH), 110.8 (CH), 108.8 (CH), 101.2 (C), 70.2 (CH), 70.1 (CH), 69.2 (CH), 68.3 (CH), 67.6 (CH), 62.0 (CH_2), 55.9 (CH_3 × 2), 49.4 (CH_3), 42.0 (CH_2), 21.0 (CH_3), 20.9 (CH_3), 20.8 (CH_3), 20.7 (CH_3), 20.6 (CH_3); IR (thin film) 2940, 1751, 1734 cm^{-1}; $[\alpha]^{24}_D$ +13 (c 0.30, $CHCl_3$); HRMS (FAB) calcd for $C_{27}H_{36}O_{14}Na$ (M + Na^+) 607.2003, found 607.2033.

Preparation of Compound 42. Aryl methyl glycoside **41** (62 mg, 0.106 mmol) was dissolved in 2:2:3 carbon tetrachloride/acetonitrile/water (2.1 mL). Sodium periodate (272 mg, 1.27 mmol) and ruthenium(III)chloride trihydrate (1.1 mg, 0.0053 mmol) were then added, and the reaction was stirred at rt for 6 h. Ethyl acetate (50 mL), saturated aqueous ammonium chloride (10 mL), and water (10 mL) were then added, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (4 × 20 mL). The combined organics were dried ($MgSO_4$), concentrated, and dissolved in PhH (1.6 mL) and MeOH (0.5 mL). Trimethylsilyl diazomethane (2 M in hexanes, 0.11 mL, 0.21 mmol) was added and the reaction was stirred at rt for 2 h. Glacial acetic acid (0.5 mL) was then added and the yellow solution was stirred at rt an additional 30 min and concentrated, and FCC (25−50% Et_2O/hexanes, gradient elution) gave pure **42** (45 mg, 84%), which could be recrystallized from Et_2O/hexanes to give analytically pure clear square plates (mp 115−116 °C). ^{1}H NMR ($CDCl_3$) δ 5.42 (dd, J = 5.5, 2.5 Hz, 1H), 5.32 (ddd, J = 11.5, 10, 5 Hz, 1H), 5.31 (ddd, J = 6.5, 5.5, 2 Hz, 1H), 4.90 (t, J = 10 Hz, 1H), 4.71 (dd, J = 12.5, 2.5 Hz, 1H), 4.15 (dd, J = 12.5, 6.5 Hz, 1H), 4.06 (dd, J = 10, 2 Hz, 1H), 3.82 (s, 3H), 3.26 (s, 3H), 2.52 (dd, J = 13, 5 Hz, 1H), 2.12 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.84 (dd, J = 13, 11.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 170.6 (C), 170.2 (C), 170.00 (C), 169.92 (C), 169.8 (C), 167.1 (C), 98.7 (C), 70.8 (CH), 69.9 (CH), 69.1 (CH), 67.8 (CH), 67.4 (CH), 62.0 (CH_2), 52.7 (CH_3), 51.3 (CH_3), 36.9 (CH_2), 21.0 (CH_3), 20.8 (CH_3), 20.72 (CH_3), 20.67 (CH_3), 20.6 (CH_3); IR (thin film) 2956, 1748 cm^{-1}; $[\alpha]^{24}_D$ −6.8 (c 0.28, $CHCl_3$); HRMS (FAB) calcd for $C_{21}H_{30}O_{14}Na$ (M + Na^+) 529.1533, found 529.1555.

Preparation of Compound 45. Inverted tetraacetate **40** (680 mg, 1.33 mmol) was dissolved in MeOH (13 mL) and sodium methoxide (0.5 M solution in MeOH, 0.67 mL, 0.33 mmol) was added. After the solution was stirred at rt for 4 h, concentration and FCC (0−10% MeOH/EtOAc, gradient elution) gave pure **45** (452 mg, 99%) as a white solid that could be recrystallized from MeOH/EtOAc to give analytically pure clear needles (mp 116−117 °C). ^{1}H NMR (CD_3OD) δ 7.17 (d, J = 2 Hz, 1H), 7.12 (dd, J = 8.5, 2 Hz, 1H), 6.93 (d, J = 8.5 Hz, 1H), 4.63 (ddd, J = 1.5, 1, 0.5 Hz, 1H), 4.37 (dd, J = 9.5, 1 Hz, 1H), 3.93 (dddd, J = 5.5, 3.5, 1.5, 1.5 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.77 (dd, J = 11.5, 3 Hz, 1H), 3.67 (ddd, J = 3.5, 1, 0.5 Hz, 1H), 3.57 (dd, J = 11.5, 6 Hz, 1H), 3.38 (ddd, J = 9.5, 6, 3 Hz, 1H), 2.36 (dd, J = 14.5, 5.5 Hz, 1H), 1.99 (ddd, J = 14.5, 1.5, 0.5 Hz, 1H); ^{13}C NMR (CD_3OD) δ 150.7 (C), 150.2 (C), 135.5 (C), 119.1 (CH), 112.5 (CH), 110.6 (CH), 108.9 (C), 81.1 (CH), 77.3 (CH), 74.1 (CH), 72.0 (CH), 70.5 (CH), 64.7 (CH_2), 56.64 (CH_3), 56.59 (CH_3), 40.6 (CH_2); IR (thin film) 3291, 2916 cm^{-1}; $[\alpha]^{22}_D$ +31 (c 0.87, MeOH); HRMS (ESI) calcd for $C_{16}H_{22}O_8Na$ (M + Na^+) 365.1212, found 365.1206.

Preparation of Compound 46. Tetraol **45** (20.4 mg, 0.0596 mmol) was dissolved in DMF (1.2 mL) and cooled to 0 °C. Imidazole (12.2 mg, 0.179 mmol) and 1,3-dichlorotetraisopropyl disiloxane (29 μL, 0.089 mmol) were then added, and the reaction was slowly warmed rt over 2.5 h. MeOH (2 mL) was added, stirring was continued for 5 min, and the reaction was poured into water (20 mL) and Et_2O (50 mL). The aq layer was extracted with Et_2O (3 × 20 mL), the organics were dried ($MgSO_4$) and concentrated, and FCC (50−100% Et_2O/hexanes, gradient elution) gave pure **46** (31.4 mg, 90%) as a clear oil that could be recrystallized from Et_2O/hexanes to give a white solid (mp 87−89 °C). ^{1}H NMR (CD_3OD) δ 7.17 (d, J = 2 Hz, 1H), 7.13 (dd, J = 8.5, 2 Hz, 1H), 6.96 (d, J = 8.5 Hz, 1H), 4.70 (br s, 1H), 4.28 (br d, J = 8 Hz, 1H), 4.10−4.21 (m, 1H), 3.95 (dddd, J = 5.5, 3.5, 1.5, 1.5 Hz, 1H), 3.86 (s, 6H), 3.63−3.80 (m, 2H), 3.63 (br s, 1H), 2.39 (dd, J = 14.5, 5.5 Hz, 1H), 1.99 (br d, J = 14.5 Hz, 1H); ^{13}C NMR (CD_3OD) δ 150.8 (C), 150.3 (C), 135.3 (C), 119.1 (CH), 112.6 (CH), 110.6 (CH), 109.2 (C), 81.0 (CH), 77.7 (CH), 77.3 (CH), 72.0 (CH), 70.4 (CH), 68.5 (CH_2), 56.7 (CH_3), 56.5 (CH_3), 40.3 (CH_2), 17.8−18.2 (CH3 × 8), 14.7 (CH), 14.1 (CH), 13.92 (CH), 13.85 (CH); IR (thin film) 3294, 2941 cm^{-1}; $[\alpha]^{22}_D$ −10 (c 0.59, CHCl3); HRMS (ESI) calcd for $C_{28}H_{48}O_9Si_2Na$ (M + Na^+) 607.2735, found 607.2760.

Preparation of Compound 47. Diol **46** (1.50 g, 2.56 mmol) was dissolved in CH_2Cl_2 (27 mL), and Et_3N (1.51 mL, 10.8 mmol), TsCl (1.03 g, 5.41 mmol), and 4-dimethylamino pyridine (33 mg, 0.27 mmol) were added. After the mixture was stirred for 2 d at rt, NaOMe (0.5 M in MeOH, 22 mL, 10.8 mmol) was added and the reaction was stirred 30 min. Water (100 mL) was added, the aq layer was extracted with CH_2Cl_2 (4 × 50 mL), the combined organics were dried (Na_2SO_4) and concentrated, and FCC (10−20% Et_2O/hexanes, gradient elution) gave pure **47** (1.07 g, 74%) as a clear oil. ^{1}H NMR ($CDCl_3$) δ 7.05 (dd, J = 8, 2 Hz, 1H), 7.01 (d, J = 2 Hz, 1H), 6.84 (d, J = 8 Hz, 1H), 5.05 (d, J = 5 Hz, 1H), 4.00−4.16 (m, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.59−3.75 (m, 3H), 3.36 (dd, J = 4, 3 Hz, 1H), 2.37 (d, J = 15.5 Hz, 1H), 2.12 (dd, J = 15.5, 4 Hz, 1H), 0.80−1.11 (m, 28H); ^{13}C ($CDCl_3$) δ 149.1 (C), 148.7 (C), 133.5 (C), 117.3 (CH), 110.7 (CH), 108.2 (CH), 105.4 (C), 75.9 (CH), 75.4 (CH), 74.9 (CH), 67.1 (CH_2), 55.9 (CH_3), 55.8 (CH_3), 52.1 (CH), 49.1 (CH), 36.4 (CH_2), 17.2−17.5 (CH_3 × 8), 13.2 (CH), 12.6 (CH), 12.52 (CH), 12.45 (CH); IR (thin film) 2945 cm^{-1}; $[\alpha]^{22}_D$ +5.5 (c 0.51, $CHCl_3$); HRMS (ESI) calcd for $C_{28}H_{46}O_8Si_2Na$ (M + Na^+) 589.2629, found 589.2657.

Preparation of Compound 48. Epoxide **47** (610 mg, 1.08 mmol) was dissolved in DMF (11 mL). Sodium azide (741 mg, 11.4 mmol) and magnesium sulfate (274 mg, 2.28 mmol) were added and the reaction was heated at 90−95 °C for 20 h. The reaction was poured into 50% saturated sodium bicarbonate, extracted with Et_2O (5 × 75 mL), dried ($MgSO_4$), and concen-

trated, and FCC (10−40% Et_2O/hexanes) gave pure **48** (389 mg, 59%) as a clear oil. ^1H NMR ($CDCl_3$) δ 7.06 (dd, J = 8, 2 Hz, 1H), 7.03 (d, = 2 Hz, 1H), 6.86 (d, J = 8 Hz, 1H), 4.88 (br s, 1H), 4.22−4.35 (m, 1H), 4.03−4.19 (m, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 3.62−3.80 (m, 2H), 3.54 (br s, 1H), 2.92 (br d, J = 7.5 Hz, 1H), 2.41 (dd, J = 14.5, 5.5 Hz, 1H), 2.17 (br d, J = 14.5 Hz, 1H), 0.80−1.11 (m, 28H); ^{13}C NMR ($CDCl_3$) δ 149.4 (C), 148.8 (C), 132.3 (C), 133.6 (C), 117.5 (CH), 110.7 (CH), 108.8 (C), 108.2 (CH), 77.8 (CH), 77.0 (CH), 75.2 (CH), 68.2 (CH), 66.3 (CH_2), 61.4 (CH), 55.93 (CH_3), 55.88 (CH_3), 40.7 (CH_2), 17.2−17.5 (CH_3 × 8), 13.4 (CH), 12.63 (CH), 12.58 (CH), 12.5 (CH); IR (thin film) 3508, 2942, 2100 cm^{-1}; $[\alpha]^{22}_D$ −8.2 (*c* 0.39, $CHCl_3$); HRMS (ESI) calcd for $C_{28}H_{47}O_8Si_2N_3Na$ (M + Na^+) 632.2799, found 232.2779.

Preparation of Compound 49. Azido alcohol **48** (202 mg, 0.331 mmol) was dissolved in MeOH (7 mL) and Amberlite IR-120 (plus) (350 mg) was added. After being stirred for 2.5 h at rt, the reaction was filterred and concentrated, and the residue was dissolved in THF (7 mL). The clear solution was cooled to 0 °C, tetrabutylammonium fluoride (1 M in THF, 0.875 mL, 0.875 mmol) was added, and the reaction was stirred for 5 min. Et_3N (0.98 mL, 7.0 mmol), acetic anhydride (0.50 mL, 5.3 mmol), and 4-dimethylamino pyridine (4.3 mg, 0.035 mmol) were added, and the reaction was warmed to rt, stirred 45 min, and poured into water (40 mL). Extraction with CH_2Cl_2 (4 × 75 mL), drying ($MgSO_4$), concentration, and FCC (25−75% Et_2O/hexanes, gradient elution) gave pure **49** (162 mg, 86%) as a syrup that could be recrystallized from Et_2O/hexanes to give a white solid (mp 53−55 °C). ^1H NMR ($CDCl_3$) δ 7.02 (dd, J = 8.5, 2 Hz, 1H), 6.92 (d, J = 2 Hz, 1H), 6.86 (d, J = 8.5 Hz, 1H), 5.64 (dd, J = 7.5, 1.5 Hz, 1H), 5.40 (ddd, J = 11.5, 10, 5 Hz, 1H), 5.39 (ddd, J = 7.5, 5, 2.5 Hz, 1H), 4.49 (dd, J = 12.5, 2.5 Hz, 1H), 4.28 (dd, J = 12.5, 5 Hz, 1H), 3.89 (s, 6H), 3.76 (dd, J = 10.5, 1.5 Hz, 1H), 3.29 (dd, J = 10.5, 10 Hz, 1H), 2.89 (s, 3H), 2.57 (dd, J = 13, 5 Hz, 1H), 2.22 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 1.58 (dd, J = 13, 11.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 170.7 (C), 169.93 (C), 169.88 (C), 169.8 (C), 149.0 (C), 148.9 (C), 132.2 (C), 118.2 (CH), 110.8 (CH), 108.8 (CH), 100.9 (C), 71.7 (CH), 69.7 (CH), 69.3 (CH), 68.9 (CH), 61.8 (CH_2), 60.5 (CH), 55.9 (CH_3 × 2), 49.3 (CH_3), 42.0 (CH_2), 21.0 (CH_3 × 2), 20.7 (CH_3 × 2); IR (thin film) 2939, 2113, 1748 cm^{-1}; $[\alpha]^{22}_D$ +8.2 (*c* 0.61, $CHCl_3$); HRMS (ESI) calcd. for $C_{25}H_{33}O_{12}N_3Na$ (M + Na^+) 590.1962, found 590.1981.

Preparation of Compound 50. Methyl glycoside **49** (150 mg, 0.264 mmol) was dissolved in 2:2:3 carbon tetrachloride/acetonitrile/water (5.3 mL), sodium periodate (678 mg, 3.17 mmol) and ruthenium(III) chloride trihydrate (2.7 mg, 0.0132 mmol) were added, and the reaction was stirred at rt for 6 h. Ammonium chloride (50% saturated, 30 mL) was then added, the aqueous layer was extracted with EtOAc (5 × 75 mL), organics were dried ($MgSO_4$) and concentrated, and the residue was dissolved in 3:1 PhH/MeOH (5.3 mL). The dark solution was cooled to 0 °C and trimethylsilyl diazomethane (2 M in hexanes, 0.264 mL, 0.528 mmol) was added dropwise. After the mixture was stirred for 1 h, glacial acetic acid (0.5 mL) was added and the reaction was warmed to rt and stirred 30 min. Concentration and FCC (25−60% Et_2O/hexanes, gradient elution) gave pure **50** (84.7 mg, 66%) as a syrup that could be recrystallized from Et_2O/hexanes to give a white solid (mp 92−94 °C). ^1H NMR ($CDCl_3$) δ 5.57 (dd, J = 7, 1.5 Hz, 1H), 5.32 (ddd, J = 7, 5.5, 2.5 Hz, 1H), 5.27 (ddd, J = 11.5, 9.5, 5 Hz, 1H), 4.59 (dd, J = 12.5, 2.5 Hz, 1H), 4.22 (dd, J = 12.5, 5.5 Hz, 1H), 3.80 (s, 1H), 3.65 (dd, J = 10, 1.5 Hz, 1H), 3.26 (dd, J = 10, 9.5 Hz, 1H), 3.20 (s, 1H), 2.57 (dd, J = 13, 5 Hz, 1H), 2.20 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 1.69 (dd, J = 13, 11.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 170.6 (C), 170.0 (C), 169.8 (C), 169.6 (C), 167.1 (C), 98.7 (C), 70.6 (CH), 70.08 (CH), 69.96 (CH), 68.5 (CH), 61.8 (CH_2), 60.1 (CH), 52.7 (CH_3), 51.2 (CH_3), 36.7 (CH_2), 20.9 (CH_3 × 2), 20.7 (CH_3 × 2); IR (thin film) 2957, 2115, 1746 cm^{-1}; $[\alpha]^{22}_D$ −29 (*c* 0.63, $CHCl_3$); HRMS (ESI) calcd for $C_{19}H_{27}O_{12}N_3Na$ (M + Na^+) 512.1492, found 512.1509.

Preparation of Compound 51. AzidoNeu5Ac derivative **50** (16.9 mg, 0.0345 mmol) was dissolved in MeOH (0.35 mL) and Pd/C (10%, ∼5 mg) was added. A balloon filled with hydrogen was attached, the reaction was stirred for 20 h, filtered through Celite, and concentrated, and the residue was dissolved in CH_2Cl_2 (3.5 mL). Et_3N (0.10 mL, 0.69 mmol), acetic anhydride (0.033 mL, 0.345 mmol), and 4-dimethylamino pyridine (∼1 mg) were added, and the reaction was stirred for 16 h. Concentration and FCC (Et_2O, then EtOAc) gave pure **51** (12.0 mg, 69%) as a syrup that could be recrystallized from Et_2O/hexanes to give a white solid (mp 131−133 °C). ^1H NMR ($CDCl_3$) δ 5.41 (dd, J = 4, 2 Hz, 1H), 5.31 (d, J = 10 Hz, 1H), 5.25 (ddd, J = 11.5, 10.5, 5 Hz, 1H), 5.23 (ddd, J = 7.5, 2.5, 2 Hz, 1H), 4.81 (dd, J = 12.5, 2.5 Hz, 1H), 4.13 (ddd, J = 10.5, 10.5, 10 Hz, 1H), 4.12 (dd, J = 12.5, 7.5 Hz, 1H), 3.93 (dd, J = 10.5, 2.5 Hz, 1H), 3.82 (s, 3H), 3.27 (s, 3H), 2.44 (dd, J = 13, 5 Hz, 1H), 2.15 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 1.89 (s, 3H), 1.89 (dd, J = 13, 11.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 171.0 (C), 170.7 (C), 170.6 (C), 170.2 (C), 170.1 (C), 167.3 (C), 98.9 (C), 72.0 (CH), 71.7 (CH), 68.8 (CH), 68.4 (CH), 62.4 (CH_2), 52.7 (CH_3), 51.3 (CH_3), 49.3 (CH), 37.3 (CH_2), 23.2 (CH_3), 21.0 (CH_3), 20.9 (CH_3), 20.8 (CH_3 × 2); IR (thin film) 1745, 1664 cm^{-1}; $[\alpha]^{22}_D$ −12 (*c* 0.67, $CHCl_3$); HRMS (ESI) calcd for $C_{21}H_{31}O_{13}NNa$ (M + Na^+) 528.1693, found 528.1675.

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Supporting Information Available: Expanded general methods; X-ray crystallographic data for **38**; ^1H and ^{13}C NMR spectra for **32**−**36**, **40**−**42**, and **45**−**51**; and characterization data comparison to the literature for **42** and **51**. This material is available free of charge via the Internet at http://pubs.acs.org.

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