described.[18] It was purified via three vacuum distillations at 30 Torr. The octadeuteriobicyclo[6.1.0]nona-2,4,6-triene was prepared in an identical manner with the use of perdeuteriated cyclooctatetraene as described above.

General Procedures. The reductions were carried out by allowing solutions of the bicyclo[6.1.0]nona-2,4,6-triene to come into contact with the freshly distilled metal mirrors at −78 °C in vacuo. The EPR spectra were recorded with an IBM (Bruker) ER-200D spectrometer equipped with an IBM variable-temperature unit.

(18) Katz, T. J.; Garratt, P. J. *J. Am. Chem. Soc.* **1964**, *86*, 5194.

Acknowledgment. We wish to thank the National Science Foundation (Grant CHE-9011801) and the donors of the Petroleum Research Fund, adminstered by the American Chemical Society, for support of this work.

A Route to Artificial Glycoconjugates and Oligosaccharides via Enzymatically Resolved Glycals: Dramatic Effects of the Handedness of the Sugar Domain Upon the Properties of an Anthracycline Drug

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Abstract: Racemic, fully synthetic glycals of considerable structural variety may be kinetically resolved via enzymatically mediated transesterification using Lipase PS-30 from *Pseudomonas cepacia* as catalyst and vinyl acetate as acyl donor. This methodology provides convenient access to a pool of optically enriched D- and L-glycals. These glycals may be employed as building blocks, both as glycosyl donors and glycosyl acceptors, to generate artificial oligosaccharides. Thus the D-glucal analogue **7**, bearing a phenyl group at C-5, was converted to the corresponding 1,2-anhydrosugar(s) **8/9**, which could be coupled directly to a second glycal. Alternatively, the 1,2-anhydrosugar could be converted to the corresponding β-glycosyl fluoride **14** or β-glycosyl sulfoxides **18a,b**. Both **14** and **18a,b** were glycosylated, with a glycal or a terminating sugar, in good yield. Conversely, the L-glucal analogue **3** was employed as a glycosyl acceptor, with L-fucosyl fluoride(s) ($\alpha:\beta$ = 1:1) as the glycosyl donor, to furnish the artificial "L,L"-disaccharide **17**. Enzymatically resolved L- and D-glycals were also used to construct novel glycoconjugates of daunomycinone with di-*sym*-collidinyliodonium perchlorate as the coupling reagent. By employing each antipode of the 5-phenyl analogue of galactal, (+)- and (−)-**25**, as glycosyl donor, a pair of diastereomeric 5'-phenyl analogues of daunomycin **22** and **23**, was obtained. These two compounds differ only in the handedness (L or D) of their carbohydrate sectors, yet exhibit markedly different biological properties. Interestingly, X-ray crystal structure determinations for **22** and **23** reveal fundamentally different overall molecular shapes for the two compounds.

Background

Whereas remarkable progress has been made in oligosaccharide assembly,[1] a fully satisfying, straightforward solution to oligosaccharide synthesis still remains to be achieved. With an eye toward this ultimate goal, it is well to pursue possibilities which might conveniently lend themselves to iteration and minimize the number of steps in the construction of the array. In this context, the use of glycals in the assembly of oligosaccharides and other glycoconjugates was seen to have considerable advantages.

It had long been known, primarily through the pioneering efforts of Lemieux and Thiem, that glycals function well as glycosyl donors, being activated by a variety of E^+ reagents.[2] The ability to transform glycals into 1,2-anhydrosugars,[3] 1,2-sulfonylaziridinosugar equivalents,[4] glycosyl fluorides,[5] phenylthio glycosides,[5] and *n*-pentenyl glycosides[5] has broadened their applicability as glycosyl donors. These earlier developments are summarized in Scheme I.[3-6]

A major advantage of glycals in complex constructions would lie in the simplification which they offer in protecting-group and activating-group strategies. These manipulations, as well as the coupling (glycosylation) reactions themselves, lie at the heart of oligosaccharide and glycoconjugate construction. Thus, in a glycal-based paradigm, only three hydroxyl groups need be differentiated. Furthermore, given the range of possibilities described above, the glycal linkage can be seen as a poised, readily actuatable glycosyl donor.

For the proposed new approach to gain full impact, it was necessary for glycals to be incorporated in syntheses, not only as glycosyl donors, as in the past, but as glycosyl acceptors. The overall logic of the approach is presented in Scheme II. In the first cycle, glycal A_1 functions as a glycosyl acceptor while glycal D_1, suitably activated, is the glycosyl donor. A coupling reaction would lead to disaccharide D_2, wherein the stereochemistry of the glycosidic bond and the nature of X are permutable from a menu of glycal assembly processes (see Scheme I above). Disaccharide

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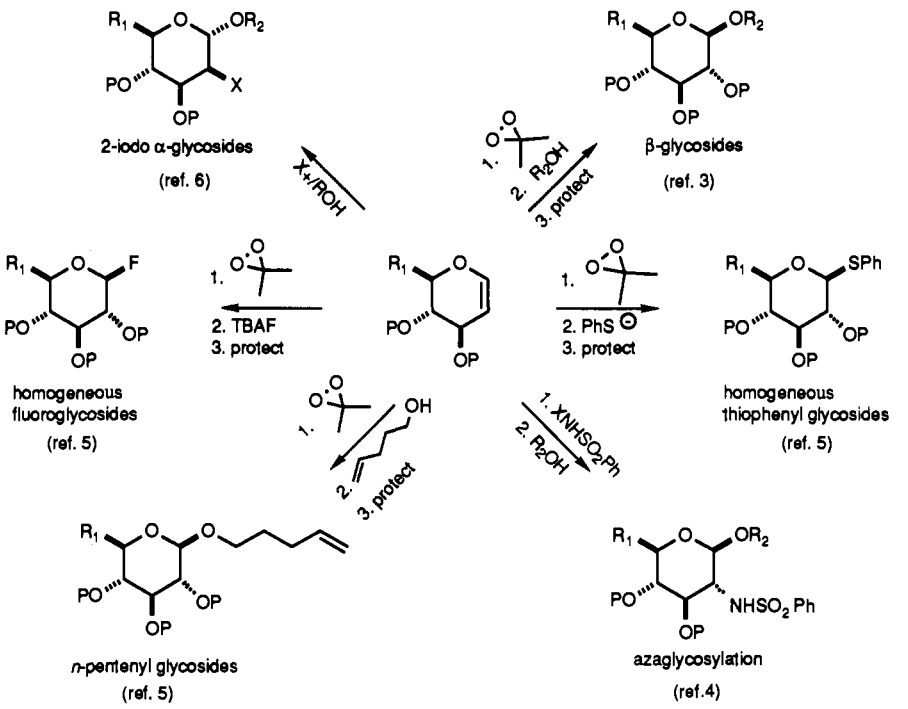
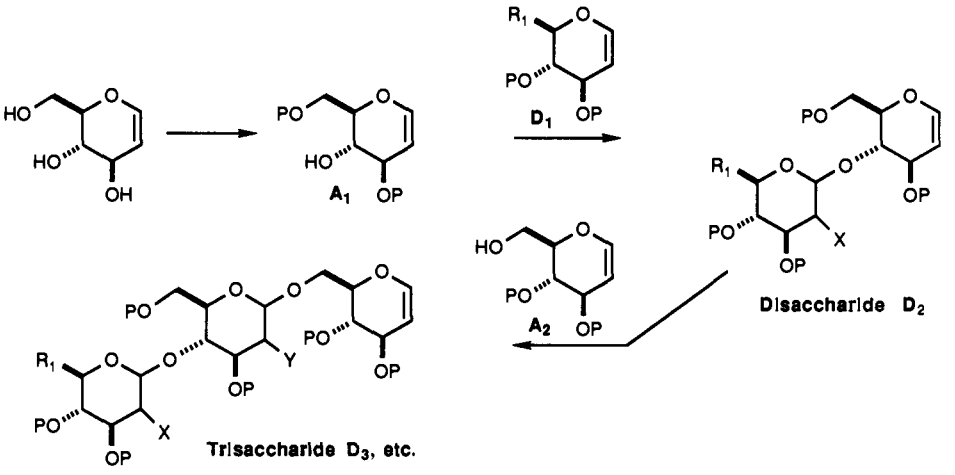
(1) For reviews of glycosylation methodology, see: (a) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212-235. (b) Paulsen, H. *Ibid.* **1982**, *21*, 155-173.
(2) (a) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2190-2198. (b) Thiem, J.; Karl, H.; Schwentner, J. *Synthesis* **1978**, 696-698. (c) Ramesh, S.; Kaila, N.; Grewal, G.; Franck, R. W. *J. Org. Chem.* **1990**, *55*, 5-7 and references cited therein.
(3) Halcomb, R. L.; Danishefsky, S. J. *Ibid.* **1989**, *206*, 6661-6666.
(4) (a) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 5811-5819. (b) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 5863-5864.
(5) Gordon, D. M.; Danishefsky, S. J. *Carbohydr. Res.* **1990**, *111*, 361-366.
(6) Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6656-6660.

0002-7863/92/1514-4518$03.00/0

Scheme I



Scheme II



D_2, itself a glycal, is now readied for its new role as a glycosyl donor with respect to the acceptor glycal A_2. This coupling produces trisaccharide D_3.

Given the vulnerability of glycals to Ferrier-like rearrangement,[7] it is perhaps understandable that they had not been used as glycosyl acceptors prior to our initiative. The recent discovery that an appropriate arrangement of protecting groups does allow for the use of glycals as glycosyl acceptors[6] opened the possibility for iterative oligosaccharide synthesis, with glycals serving as the monosaccharidic building blocks. This strategy is exemplified in the recent total syntheses of ciclamycin O,[8] allosamidin,[4b] and the oligosaccharide domain of the enediyne antibiotics.[9]

A particularly attractive feature of this approach is that a large variety of both natural and artificial racemic glycals are directly accessible via the Lewis acid catalyzed diene–aldehyde cyclocondensation (LACDAC) reaction[10] (see Scheme III). For these fully synthetic glycals to be useful as monosaccharidic building blocks, they must be obtained in optically pure, or at least highly enriched, form. Toward this end, an asymmetry element may be introduced into the heterocycloaddition reaction itself. Indeed, in ground-breaking work, Bednarski found that, with the proper combination of chiral auxiliaries and chiral lanthanide catalysts, diastereofacial excesses beyond 95% could be attained.[11] In subsequent ventures, catalysis by a variety of Lewis acidic vanadium,[12a] iron,[12b] and aluminum[12c] reagents bearing chiral ligands has been explored. With the aluminum binaphthol reagent, a high degree of asymmetric induction has been achieved in several cases.[12c]

Though promising, these demonstrations tended to be particularly impressive only with aromatic aldehydes. Moreover, neither

(7) (a) Ferrier, R. J.; Prasad, N. *J. Chem. Soc. C* **1969**, 570–575. (b) Ferrier, R. J. *Adv. Carbohydr. Chem. Biochem.* **1969**, *24*, 199.

(8) Suzuki, K.; Friesen, R.; Sulikowski, G. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 8895–8902.

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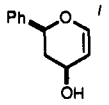
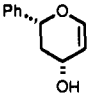
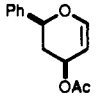
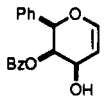
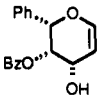
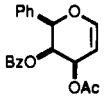
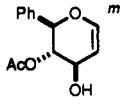
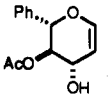
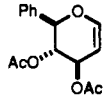
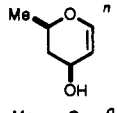
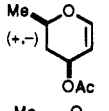
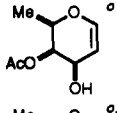
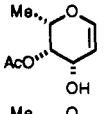
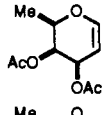
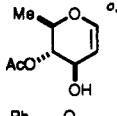
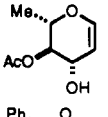
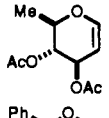
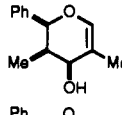
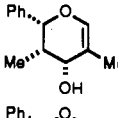
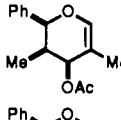
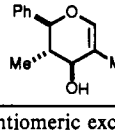
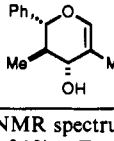
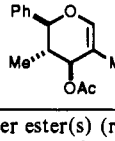
(10) For detailed discussions of the LACDAC reaction, see: (a) Danishefsky, S. J. *Chemtracts: Org. Chem.* **1989**, *2*, 273–289. (b) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15–23. (c) Danishefsky, S. J. *Aldrichimica Acta* **1986**, *19*, 59–69.

(11) Bednarski, M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1986**, *108*, 7060–7067.

(12) (a) Togni, A. *Organometallics* **1990**, *9*, 3106–3113. (b) Faller, J. W.; Smart, C. J. *Tetrahedron Lett.* **1989**, *30*, 1189–1192. (c) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310–312.

Table I. Enzymatically Mediated Resolutions of Glycals

racemic glycal	wt equiv enz, time	recovered alcohol	yield (%); ee (%)	product acetate	yield (%); ee (%)
 (2.0g)	2, 26 h		37; ≥97[a,d]		63; 60[b]
 (1.0g)	6, 7 days		48; ≥97[a,e]		50; 91[b]
 (1.0g)	2, 11 h		47; ≥97[a,d]		47; ≥97[b]
	2, 11 h				*f*
 (1.4g)	1, 33 h		51; 64[c]		37; ≥97[b,g]
	0.5, 37 h		44; ≥97[c,h]		48; ≥97[b,i]
	(a) 6, 4.5 days (b) 2, 3 days		41; ≥97[a] 54; 74[a,j]		59; 70[b] 44; 86[b]
	(a) 6, 10 days (b) 2, 4 days		44; ≥97[k] 74		50; 74[b] 26; ≥96[b]

[a] Enantiomeric excess determined by integration of the ^{1}H NMR spectrum of the correspondi.ig Mosher ester(s) (ref 29). [b] Enantiomeric excess determined from chiral shift experiments using (+)-Eu(hfc)$_3$ (ref 28). [c] Enantiomeric excess determined by conversion to the corresponding diacetate (Ac_2O, NEt_3, CH_2Cl_2, DMAP) and then incubation with (+)-Eu(hfc)$_3$ (ref 28). [d] Absolute configuration determined from the optical rotation of the corresponding dihydropyranone (ref 11) obtained by oxidation (PDC, CH_2Cl_2, HOAc, 4-Å MS). [e] Absolute configuration determined from the crystal structure of the daunomycin analogue **22** derived from this glycal. [f] Racemic, starting glycal was completely consumed (TLC), and the product displayed no optical rotation. [g] Absolute configuration determined from the measured optical rotation (ref 30). [h] Absolute configuration determined from the measured optical rotation (ref 31). [i] Absolute configuration determined from the measured optical rotation (ref 34). [j] Absolute configuration determined from the optical rotation of the corresponding dihydropyranone (ref 12c) obtained by oxidation (PDC, CH_2Cl_2, HOAc, 4-Å MS). [k] Enantiomeric excess determined by conversion to (2*S*,3*R*)-methyl 3-hydroxy-2-methyl-3-phenylpropanoate [(a) Dess-Martin periodinane (ref 37), CH_2Cl_2; (b) O_3, MeOH, −78 °C; (c) H_2O_2, KOH; (d) H_3O^+; (e) CH_2N_2] (ref 38) and incubation with (+)-Eu(hfc)$_3$ (ref 28). Absolute configuration determined from the optical rotation of this degradation product (ref 39). [l] Reference 27. [m] Reference 11. [n] Reference 40. [o] Reference 17. [p] Reference 31. [q] Reference 32.

the purely catalytic method nor the synergistic catalytic auxiliary combinations were effective with the very central diene **1**,[13] which leads to the galactose-like series (see Scheme III). Furthermore, the difficulties associated with synthesizing the Lewis acidic catalysts constituted a serious constraint. Thus, a need was perceived for a general, inexpensive, and operationally convenient route to optically enriched glycals.

Discussion of Results

Our first approach was to evaluate the possibility that an early, racemic intermediate in the synthesis of artificial carbohydrates via the LACDAC reaction could be resolved by straightforward means. In the initial exploratory phase, it was particularly important to us that both antipodes be readily retrieved in highly enantiomerically enriched form. In this regard, a paper by Holla, which showed that the D-glucal system could be regiospecifically deacylated at C_3 by Lipase PS-30 from *Pseudomonas cepacia*, was of interest.[14] We went on to pose the question whether differential rates of acyl-transfer reactions for the two antipodal glycals might serve as the basis for a convenient kinetic resolution. For this purpose, we were attracted to a brilliant method developed by C.-H. Wong, wherein lipases could be mobilized to mediate acetylation via the use of vinyl acetate as an irreversible acylating agent.[15] Thus, we sought to merge the Holla finding as regards the C_3-hydroxy group of D-glycals with the Wong method for driving acetylation reactions.

A variety of racemic glycals were surveyed. As can be seen in Table I, the substrate specificity of Lipase PS-30 is quite broad, making this procedure applicable to a broad spectrum of artificial glycals.[16] For example, even the introduction of a bulky phenyl group in place of the usual methyl or hydroxymethyl substituent at the 5-position yields excellent substrates for the lipase (**2**, **3**, and **4**). The acylated D product is readily separated from the recovered L-glycal starting material by silica gel chromatography. Significantly, this methodology provides access to glycals of the galactal series, derived from diene **1**[13] (i.e., **3** and **5**), in a high degree of optical purity.

Through this methodology, in concert with the LACDAC reaction of diene **1** and the $Mn(OAc)_3$ oxidation of 4-deoxyglucal derivatives,[17] access to either D- or L-galactal and D- or L-glucal

(13) Danishefsky, S. J.; Maring, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 1269–1274.

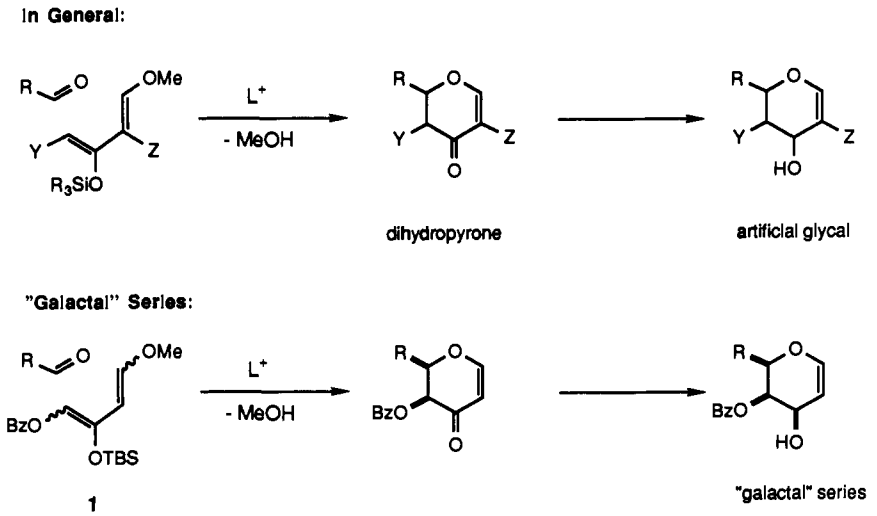
(14) Holla, E. W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 220–221.

(15) (a) Hsu, S.-H.; Wu, S.-S.; Wang, Y.-F.; Wong, C.-H. *Tetrahedron Lett.* **1990**, *31*, 6403–6406. (b) Wang, Y.-F.; Chen, S.-T.; Liu, K. K.-C.; Wong, C.-H. *Ibid.* **1989**, *30*, 1917–1920. (c) Wang, Y.-F.; Wong, C.-H. *J. Org. Chem.* **1988**, *53*, 3127–3129. (d) Sweers, H. M.; Wong, C.-H. *J. Am. Chem. Soc.* **1986**, *108*, 6421–6422.

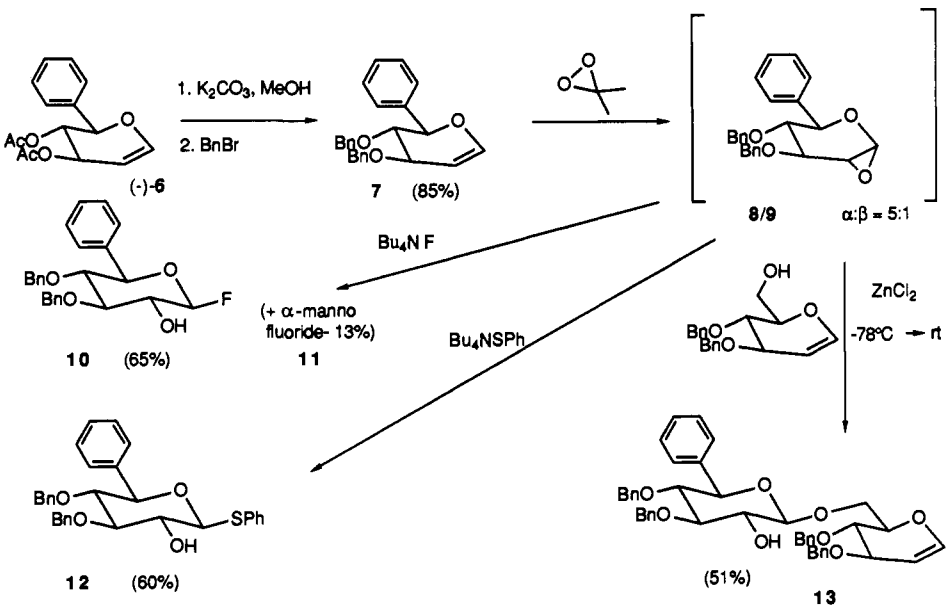
(16) For a preliminary account of the glycal resolution methodology, see: Berkowitz, D. B.; Danishefsky, S. J. *Tetrahedron Lett.* **1991**, *32*, 5497–5500.

(17) (a) Danishefsky, S. J.; Bednarski, M. *Tetrahedron Lett.* **1985**, *26*, 3411–3412. (b) Danishefsky, S. J.; Selnick, H. G.; Armistead, D. M.; Wincott, F. E. *J. Am. Chem. Soc.* **1987**, *109*, 8119–8120.

Scheme III



Scheme IV



derivatives has been provided. It is also well to note that, in previous studies, several galactal and glucal derivatives have been converted to the gulal and allal series, respectively, using a 3-step sequence [(i) thio-Ferrier rearrangement, (ii) oxidation of anomeric sulfide to sulfoxide, and (iii) rearrangement of axial anomeric sulfoxide to 3-axial glycal].[18]

Artificial Disaccharide Synthesis: Displacement Reactions of a 5-Phenyl-1,2-Anhydrosugar

With an established chemoenzymatic route to unnatural D- and L-glycals, we next examined their performance in glycosylation reactions, thereby providing a direct entry into structurally novel artificial oligosaccharides. Of particular interest in this endeavor were the analogues of galactal (i.e., **3** and **5**) and glucal (i.e., **4** and **6**), in which the hydroxymethyl substituent at C-5 had been replaced with a phenyl group. These glycals might be expected to confer a considerable degree of hydrophobicity on their derivative glycoconjugates.

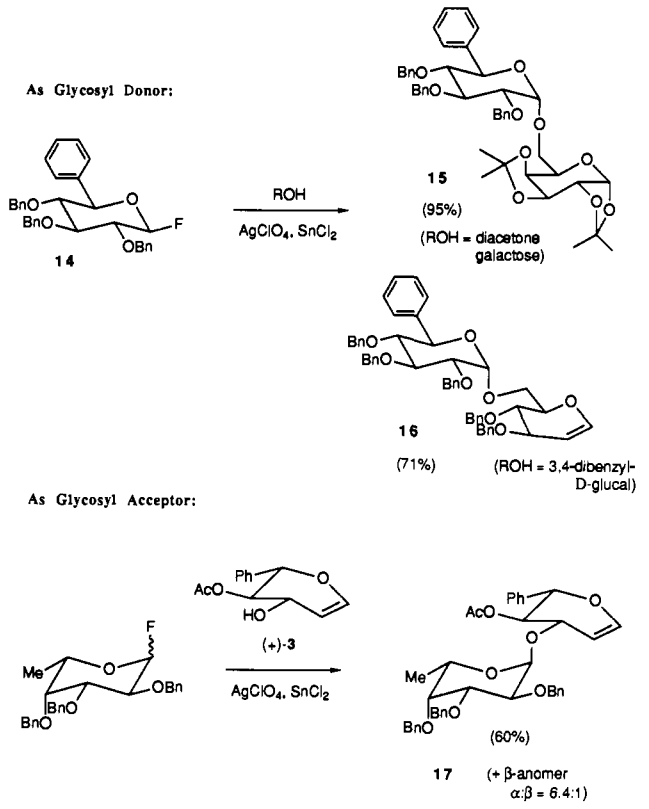
Initially, we set out to synthesize artificial disaccharides containing a 5(*R*)-phenyl-D-xylyl monosaccharidic unit derived from glycal **6**. We wished to exploit the 1,2-anhydrosugar method.[3,5] This method provides high margins of stereoselectivity in both the formation of the oxirane and its opening. While it is not convenient for synthesizing multigram levels of glycosides (due to the rather dilute solutions of anhydrous 2,2-dimethyloxirane which are employed), it is easily applied to gram scales. For maximum stereoselectivity in the glycosylations, nonparticipitory resident groups are required. Accordingly, diacetate (-)-**6** was saponified and benzylated to generate glycal **7** (Scheme IV). Epoxidation of **7** with dimethyldioxirane produced a 5:1 mixture of diastereomeric 1,2-anhydrosugars **8/9**. That the expected α-epoxide **8** was indeed the major component could be inferred from the results of several displacement reactions carried out on the mixture of epoxides.

Treatment of **8/9** with excess tetrabutylammonium fluoride[5] gave a mixture of chromatographically separable fluorohydrins **10** and **11** (5:1). The major product was the *β-trans*-diequatorial fluorohydrin **10** (anomeric H: δ 5.12–5.36, $J_{1,2}$ = 7 Hz, $J_{2,3}$ = 9 Hz). The minor product was the *α-trans*-diaxial fluorohydrin **11** (anomeric H: δ 5.63–5.84, $J_{1,2}$ = 1.7 Hz, $J_{2,3}$ = 3.5 Hz). Given that the fluorinolysis proceeds via an S_N2 displacement mechanism with complete inversion of configuration at C-1, the stereochemistry of epoxides **8** and **9** may be assigned as α and β, respectively.

An equatorially disposed phenylthio group at C-1 (i.e., **12**) could also be installed by the action of thiophenoxide anion on 1,2-anhydrosugar(s) **8/9** (Scheme IV). Indeed, the epoxide(s) could be glycosylated directly with 3,4-di-*O*-benzyl-D-glucal under zinc

(18) Wittman, M. D.; Halcomb, R. L.; Danishefsky, S. J.; Golik, J.; Vyas, D. *J. Org. Chem.* **1990**, *55*, 1979–1981.

Scheme V



chloride catalysis[3] to produce the β-coupled product **13** in 51% yield.

Glycosyl Fluoride Couplings

In light of the established success of glycosyl fluorides as glycosyl donors, in general, and their use in stereospecifically generating α-glycosidic linkages in particular,[19] we sought to explore a glycosyl fluoride route to the desired artificial disaccharides. The diastereomerically pure β-D-glycosyl fluoride **10** appeared to present an ideal entry into α-glycosides of "5-phenylxylose". Accordingly, **10** was benzylated at C-2 to give **14**. Treatment of **14** with diacetone galactose in diethyl ether under the Mukaiyama conditions ($SnCl_2$, $AgClO_4$)[19] gave the desired α-D-linked artificial disaccharide **15** in 95% yield (Scheme V). With the ultimate goal of developing an iterative process based upon glycal building blocks, it was of interest to examine the use of a glycal as the glycosyl acceptor in this reaction. In the event, **14** could be stereospecifically glycosylated with 3,4-di-*O*-benzyl-D-glucal to give the desired α-D-glycoside **16** in 71% yield. Note that this sequence nicely complements the direct coupling of the 1,2-anhydrosugar **8**/**9**, in which the corresponding β-D-glycoside **13** was produced stereospecifically.

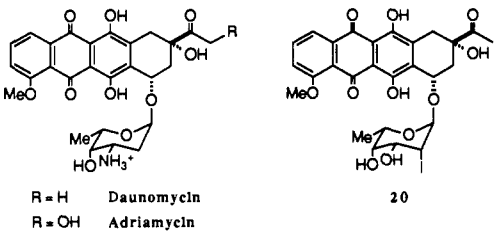
Encouraged by the success of these couplings with the 5-phenylxylyl fluoride **14** as glycosyl donor, we wondered if such a 5-phenylglycal might also be employed as glycosyl acceptor in this reaction. It will be recalled that glycals of the L configuration bearing a single free hydroxyl group at the 3-position are available directly from the enzymatic resolution step (see Table I). The differentially protected L-glycals (+)-**3** and (+)-**4**, for example, would appear to be ideally suited as glycosyl acceptors. In fact, treatment of 2,3,4-tri-*O*-benzyl-L-fucosyl fluoride(s) (α:β = 1:1) with (+)-**3** led to a mixture (6.4:1) of diastereomeric α- and β-coupled products in 74% yield. The major product, **17**, could be obtained in pure form by conventional chromatography. Significantly, no products reflecting migration of the acetyl group from C-4 to C-3 could be detected. The fact that α-stereoselectivity is slightly eroded in this case suggests that there may indeed be an advantage in employing diastereomerically pure β-glycosyl fluorides to generate α-glycosidic linkages (see the couplings with **14** as glycosyl donor; vide supra).

The Glycosyl Sulfoxide Approach

One of the more exciting new developments in glycosylation methodology is due to Kahne and associates and involves the treatment of glycosyl sulfoxides with triflic anhydride to produce an activated intermediate capable of glycosylating nucleophiles as weak as an amide nitrogen or a phenolic oxygen.[20] Given the ready availability of phenylthio β-D-glycoside **12** from the 5-phenylglycal **7**, we sought to tap into the Kahne chemistry. Protection of **12** as its C-2 pivaloyl ester, followed by oxidation with 1 equiv of dimethyldioxirane, led to a mixture (2.5:1) of diastereomeric sulfoxides **18a**,**b** (Scheme VI). When sulfoxides **18a**,**b** were treated with triflic anhydride, followed by diacetone galactose, a nearly quantitative yield of the desired β-D-glycoside **19** was obtained.

Synthesis of Analogues of Daunomycin

Previous studies from these laboratories had established that the daunomycin analogue **20**, featuring an α-glycosidic linkage, could be obtained by an iodonium ion mediated coupling reaction between 3,4-bis(trimethylsilyl)-L-fucal and daunomycinone.[8,21]



Our interest in exploring this chemistry further was heightened upon finding that **20** exhibits potent in vitro cytotoxic activity.[22] With optically pure D-fucal (**21**) and optically enriched L- (**3**) and D-5-desmethyl-5-phenylfucal (**5**) in hand, we decided to exploit the same strategy to generate three new daunomycin analogues **22**, **23**, and **24**. These analogues would allow us to probe the influences of the hydrophobicity of the drug, as well as the handedness of the sugar domain, upon biological activity in the daunomycin series. The compounds **22**–**24** were synthesized as shown in Scheme VII.

It was found that there are significant differences in the properties of the L-sugar drugs, **20** and **22**, relative to their D-sugar counterparts, **24** and **23**. In binding to various oligonucleotide constructs, the L-sugar drugs are bound substantially more tightly.[23] Interestingly, each of the L compounds exhibits much greater cytotoxicity than does its D counterpart. In fact, L-sugar analogues **20** and **22** are more cytotoxic versus a human colon tumor cell line (HCT-116) than adriamycin itself. Finally and most important, analogue **22** completely overcomes the resistance of the HCT-VM-46 and HCT-VP-35 cell lines where adriamycin fails. Compound **23**, on the other hand, bearing a constitutionally

(19) (a) Micheel, F.; Klemer, A. *Adv. Carbohydr. Chem.* **1961**, *16*, 85–103. (b) Mukaiyama, T.; Murai, Y.; Shoda, S. *Chem. Lett.* **1981**, 431–4321. (c) Mukaiyama, T.; Shoda, S. *Chem. Lett.* **1983**, 935–938. (d) Szarek, W. A.; Grynkiewicz, G.; Doboszewski, B.; Hay, G. W. *Chem. Lett.* **1984**, 1751–1754. (e) Nicolaou, K. C.; Dolle, R. E.; Papahatjis, D. P.; Randall, J. L. *J. Am. Chem. Soc.* **1984**, *106*, 4189–4192. (f) Hashimoto, S.; Hayashi, M.; Noyori, R. *Tetrahedron Lett.* **1984**, *25*, 1379–1382. (g) Thiem, J.; Wiesner, M. *Synthesis* **1988**, 124–127. (h) Nicolaou, K. C.; Dolle, R. E.; Chucholowski, A.; Randall, J. L. *J. Chem. Soc., Chem. Commun.* **1984**, 1153–1154. (i) Nicolaou, K. C.; Chucholowski, A.; Dolle, R. E.; Randall, J. L. *J. Chem. Soc., Chem. Commun.* **1984**, 1155–1156. (j) Nicolaou, K. C.; Randall, J. L.; Furst, G. T. *J. Am. Chem. Soc.* **1985**, *107*, 5556–5558.

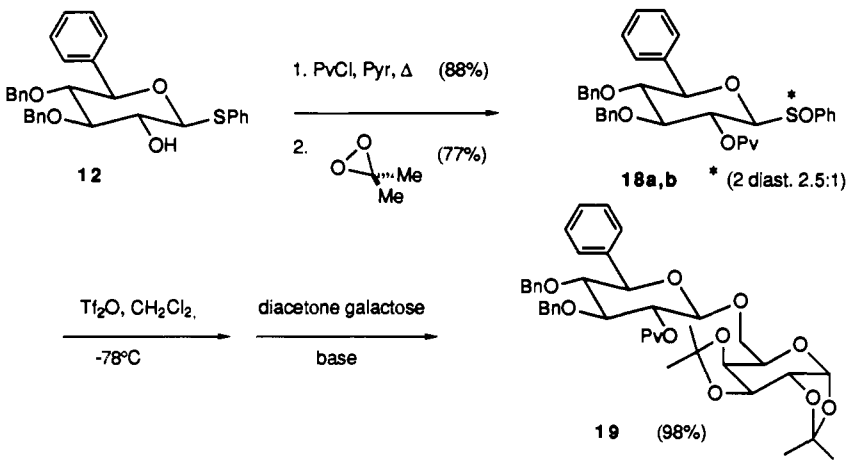
(20) Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881–6882.

(21) Sulikowski, G. A.; Danishefsky, S. J. Unpublished results.

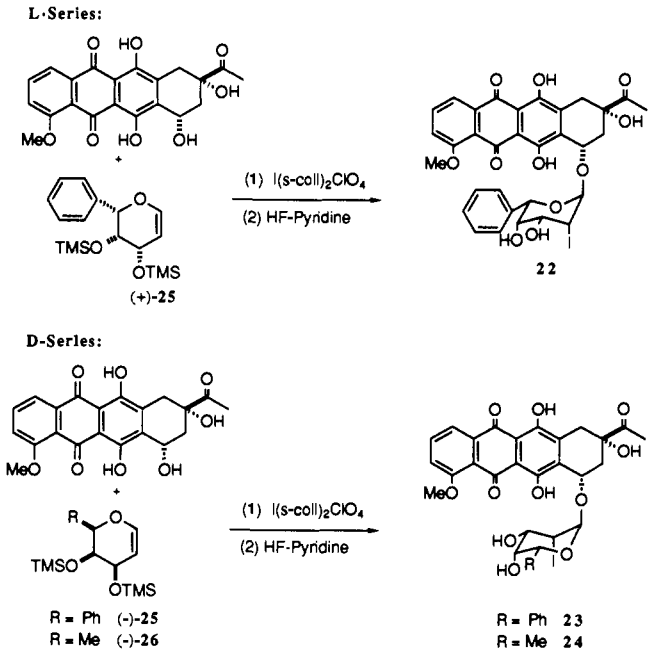
(22) Crosswell, A. R. Personal communication (Bristol-Myers-Squibb, Wallingford, CT).

(23) For a preliminary account of these findings, see: Roche, C. J.; Crothers, D. M.; Sulikowski, G. A.; Berkowitz, D. B.; Thomson, J. A.; Danishefsky, S. J. *The Site Selectivity of Anthracycline Drugs*, Book of Abstracts: Seventh Conversation in Biomolecular Stereodynamics, SUNY at Albany, June 18–23, 1991; Adenine Press: New York, 1991.

Scheme VI



Scheme VII

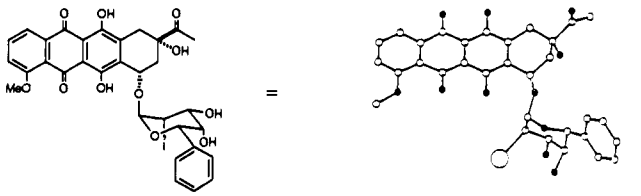


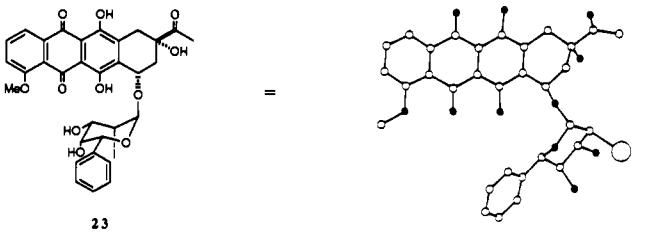
identical but D-configured carbohydrate sector, displays no useful level of cytotoxicity.[22] While the effects of modified iodinated daunosamine analogues on cytotoxicity had been disclosed by Horton,[24] the results described herein are the first which potentially implicate the sugar in the very important clinical question of multiple drug resistance. The biological importance of these findings is a matter of ongoing research and will be discussed elsewhere.

When the results of these studies became available, it was of interest to examine the consequences of the change of sugar handedness on the overall molecular structure. Toward this end, crystals of analogues **22** and **23** were grown and their structures determined by single-crystal X-ray analysis (see graphic representations of the structures). Both compounds feature three constitutional changes with respect to daunomycin itself. The axial hydrogen atom at $C_{2'}$ has been replaced with an iodine atom. A hydroxy function has been substituted for the equatorial amino group at $C_{3'}$. Finally, a $C_{5'}$-phenyl group is present in place of the usual $C_{5'}$-methyl group. The compounds differ only in the absolute configuration of their carbohydrate moieties.

The two crystal structures reveal fundamentally different shapes for the L- and D-configured analogues **22** and **23**. Both structures feature the characteristic hydrogen bond-locked, half-chair conformation of the A-ring of the aglycon.[25] The bioactive compound **22** crystallizes in an anti conformation with respect to rotations about the glycosidic bond and about the C_7–O bond; that is, the aglycon and the phenyl ring are on opposite sides of a plane bisecting the pyranose ring and passing through the ring oxygen atom and $C_{3'}$.

It would have been possible for the D compound **23** to crystallize in a spatially similar anti conformation. Indeed, starting with the crystal structure for **22**, by formally transposing (a) $C_{2'}$ and the ring oxygen and (b) $C_{3'}$ and $C_{5'}$, one arrives at a possible structure for **23** which would be "superimposable" upon the observed crystal structure for **22**. The actual crystal structure for **23**, however, reveals that this diastereomer prefers an alternative spatial arrangement of atoms, strikingly different from that observed for **22**. In the crystal, **23** assumes a syn conformation, wherein the aglycon and the phenyl ring lie relatively close in space. Thus, the overall molecular shape of the D compound **23** is clearly distinct from that of its bioactive L counterpart **22**.





Interestingly, several naturally occuring, L-configured anthracyclines, such as daunomycin hydrochloride,[25a] *N*-bromoacetyldaunomycin,[25b] carminomycin hydrochloride,[25c] and DNA-bound daunomycin[25d] crystallize in anti conformations similar to **22**, suggesting that this overall shape may be requisite for biological activity. To evaluate this notion further, one would like to establish to what extent the structural differences observed between **22** and **23** in the crystal accurately reflect structural differences in solution.

(24) Horton, D.; Priebe, W.; Varella, O. *Carbohydr. Res.* **1985**, *144*, 305.

(25) (a) Neidle, S.; Taylor, G. *Biochim. Biophys. Acta* **1977**, 450–459. (b) Anguili, R.; Foresti, E.; Riva Di Sanseverino, L.; Isaacs, N. W.; Kennard, O.; Motherwell, W. D. S.; Wampler, D. L.; Armacone, F. *Nature (London), New Biol.* **1971**, *234*, 78–80. (c) Von Dreele, R. B.; Einck, J. J. *Acta Crystallogr.* **1977**, *B33*, 3283–3288. (d) Wang, A. H.-J.; Ughetto, G.; Quigley, G. J.; Rich, A. *Biochemistry* **1987**, *26*, 1152–1163.

NMR studies directed toward elucidating the solution structures of **22** and **23** and the nature of their interactions with DNA are in progress.[26] Through these studies we would hope to establish the connectivity between carbohydrate stereochemistry, cytoxicity, and performance vis-ã-vis multiple drug resistance.

Summary

Racemic, fully synthetic glycals of considerable structural variety have been kinetically resolved via an enzymatically mediated transesterification reaction. This achievement marks a confluence of two lines of research in these laboratories, namely, (1) hetero-Diels–Alder methodology, by which racemic glycals of virtually unlimited structural diversity are accessible, and (2) the glycal-based assembly of oligosaccharides and glycoconjugates, which requires optically enriched glycals as building blocks.

The application of these optically enriched, artificial glycals toward the construction of a variety of both α- and β-linked "hydrophobic" disaccharides has been achieved. In so doing, the 5′-phenylglycal, **7**, could be converted into a variety of glycosyl donors, including the corresponding 1,2-anhydrosugar(s) **8**/**9**, β-glycosyl fluoride **10**, and β-glycosyl sulfoxides **18a,b**. Each of these glycosyl donors, in turn, participated successfully in glycosylation reactions with either glycals or terminating sugars as glycosyl acceptors.

The methodology described herein also provides a direct entry into novel glycoconjugates, wherein the configuration of the sugar moiety is readily varied. In this way, the effect of the handedness of carbohydrate sectors upon the conformation and biological properties of their derivative glycoconjugates (i.e., **22** and **23** in this study) may be conveniently examined. Further endeavors along these lines are being undertaken, and the application of the resolution methodology to a wide variety of more highly functionalized, synthetic glycals is being actively pursued.

Experimental Section

General Methods. Unless otherwise noted, all reagents were obtained from commercial sources and used without further purification, and all reactions were carried out under inert atmosphere. Lipase PS-30 (from *Pseudomonas cepacia*) was obtained from Amano. CH_2Cl_2 and $BF_3{\cdot}Et_2O$ were distilled from calcium hydride. THF was distilled from sodium–benzophenone. Ethanol was distilled from sodium–diethyl phthalate. Benzaldehyde was distilled under reduced pressure. Flash chromatography was performed on silica gel (Merck, 230–400 mesh).

^{1}H NMR spectra were recorded on a Bruker WM-250 or 490 instrument. Chemical shifts are reported in ppm relative to residual $CHCl_3$ (listed at 7.25 ppm). Infrared spectra were obtained on a Perkin-Elmer Model 1420 spectrometer. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter. Mass spectra [reported as m/z (relative intensity)] were recorded on a Kratos Model MS-80 RFA instrument. Melting points were determined using a Hoover capillary melting point apparatus and are uncorrected.

(2*R,3*S**)-3-(Benzoyloxy)-2-phenyl-2,3-dihydro-4*H*-pyran-4-one (36) and (2*R**,3*R**)-3-(Benzoyloxy)-2-phenyl-2,3-dihydro-4*H*-pyran-4-one (37).** To a solution containing the usual mixture of three isomeric dienes **1** (8.5 g, ca. 25.5 mmol, prepared according to Danishefsky and Maring[13]) and benzaldehyde (2.16 mL, 21.2 mmol) in CH_2Cl_2 (100 mL) at −78 °C was added $BF_3{\cdot}Et_2O$ (2.61 mL, 21.2 mmol) dropwise, with stirring. The reaction mixture was allowed to warm slowly to −40 °C over a period of 2 h, and then the reaction was quenched by the addition of $NaHCO_3$ (aqueous, 15 mL). After having been allowed to warm to room temperature, the two-phase mixture was poured into CH_2Cl_2 (250 mL)/$NaHCO_3$ (aqueous, 85 mL). The aqueous layer was extracted once more with CH_2Cl_2 (100 mL), and the combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), and evaporated. The crude cycloaddition product mixture was dissolved in CCl_4 (50 mL), and trifluoroacetic acid (2.13 mL, 27.6 mmol) was added dropwise with stirring at room temperature. After 1 h, the reaction was quenched by the addition of $NaHCO_3$ (aqueous, 10 mL), and then the mixture was poured into CH_2Cl_2 (200 mL)/$NaHCO_3$ (aqueous, 90 mL). The aqueous layer was extracted with a second portion of CH_2Cl_2 (100 mL), and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and evaporated. Flash chromatography (25–35% Et_2O/hexane) gave, in order of elution, **37** (401 mg, 6%) as a slightly yellow oil and **36** (3.39 g, 54%) as an off-white solid.

36: mp 89–91 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.63–5.66 (dd, J = 1.0, 6.2 Hz, 1 H), 5.67–5.68 (d, J = 3.3 Hz, 1 H), 5.78–5.80 (dd, J = 1.0, 3.3 Hz, 1 H), 7.30–7.43 (m, 7 H), 7.50–7.57 (m, 1 H), 7.59–7.62 (dd, J = 0.4, 6.2 Hz, 1 H), 7.88–7.92 (dd, J = 1.4, 8.4 Hz, 2 H); IR ($CHCl_3$) 3000, 1725, 1680, 1595, 1580, 1450, 1405, 1260 cm^{-1}; MS (CI) m/z 295 (66, MH^+), 224 (10), 213 (15), 173 (100, $PhCO_2$), 123 (35), 105 (76); HRMS (CI) m/z (MH^+) calcd for $C_{18}H_{14}O_4$ 295.0970, obsd 295.0988. Anal. Calcd for $C_{18}H_{14}O_4$: C, 73.46; H, 4.79. Found: C, 73.09; H, 4.78. **37**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.50–5.55 (d, J = 13 Hz, 1 H), 5.60–5.63 (d, J = 5.9 Hz, 1 H), 5.87–5.92 (d, J = 13 Hz, 1 H), 7.34–7.50 (m, 8 H), 7.50–7.52 (d, J = 6.6 Hz, 1 H), 7.89–7.93 (dd, J = 1.3, 8.4 Hz, 2 H); IR ($CHCl_3$) 3000, 1725, 1690, 1595, 1450, 1395, 1270, 1250 cm^{-1}; MS (CI) m/z 295 (60, MH^+), 213 (6.9), 173 (100, $PhCO_2$), 123 (58), 105 (24); HRMS (CI) m/z (MH^+) calcd for $C_{18}H_{14}O_4$ 295.0970, obsd 295.0966.

Luche Reductions. (2*R,3*R**,4*R**)-3-(Benzoyloxy)-4-hydroxy-2-phenyl-2,3-dihydro-4*H*-pyran (3).** To a solution of **36** (1.92 g, 6.52 mmol) and $CeCl_3{\cdot}7H_2O$ (2.43 g, 6.52 mmol) in CH_2Cl_2 (55 mL)/EtOH (27 mL) at −78 °C was added dropwise a solution of $NaBH_4$ (271 mg, 7.18 mmol) in EtOH (27 mL). The addition took 20 min. After an additional 20 min at −78 °C, the reaction was complete (TLC) and so was quenched by the addition of $NaHCO_3$ (aqueous, 40 mL). The two-phase mixture was stirred, allowed to slowly warm to 0 °C, and then poured into EtOAc (250 mL)/Et_2O (250 mL)/$NaHCO_3$ (aqueous, 200 mL). The organic layer was washed with $NaHCO_3$ (aqueous, 3 × 150 mL) and brine (200 mL), dried ($MgSO_4$), and evaporated. Flash chromatography (20–40% EtOAc/hexane) gave **3** (1.87 g, 97%) as a white solid: mp 129 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.90–1.93 (d, J = 7.5 Hz, 1 H), 4.84–4.91 (m, 2 H), 5.19 (br s, 1 H), 5.63–5.65 (dd, J = 2, 4 Hz, 1 H), 6.65–6.67 (d, J = 5.9 Hz, 1 H), 7.20–7.57 (m, 8 H), 7.97–8.00 (d, J = 7.3 Hz, 2 H); IR ($CHCl_3$) 3560 (s, free OH), 3300–3600 (br), 3060, 3020, 2990, 1720, 1645, 1595, 1450, 1270, 1130 cm^{-1}; MS (CI) m/z 297 (64, MH^+), 279 (31), 211 (45), 175 (31), 157 (97), 123 (41), 105 (100); HRMS (CI) m/z (MH^+) calcd for $C_{18}H_{16}O_4$ 297.1127, obsd 297.1142. Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.84; H, 5.44.

(2*R,3*R**,4*R**)-3-Acetoxy-4-hydroxy-2-methyl-2,3-dihydro-4*H*-pyran (4-Acetylfucal) (29).** To a solution of the dihydropyrone[17] (200 mg, 1.18 mmol) and $CeCl_3{\cdot}7H_2O$ (438 mg, 1.18 mmol) in CH_2Cl_2 (12 mL)/EtOH (6 mL) at −78 °C was added, via syringe pump, a solution of $NaBH_4$ (49.0 mg, 1.30 mmol) in EtOH (6 mL). The addition took 2 h. After an additional 2.5 h at −78 °C, the reaction was complete (TLC) and so was quenched by addition of pH 7 buffer (aqueous KPO_4, 10 mL). The two-phase mixture was stirred, allowed to warm to −50 °C, and then poured into Et_2O (60 mL)/brine (10 mL). The aqueous layer was extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and evaporated to give **29** (160 mg, 79%) as a white solid of sufficient purity to be used directly in the next step (exposure of this compound to silica gel resulted in partial migration of the acetyl group from the 4- to the 3-position): mp 101 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.22–1.24 (d, J = 6.7 Hz, 3 H), 1.91–1.96 (d, J = 8 Hz, 1 H), 2.16 (s, 3 H), 4.07–4.16 (br q, J = 6.6 Hz, 1 H), 4.5–4.6 (m, 1 H), 4.64–4.68 (app dt, J = 1.8, 6.3 Hz, 1 H), 5.11–5.14 (dd, J = 0.6, 4.5 Hz, 1 H), 6.34–6.38 (dd, J = 1.5, 6.3 Hz, 1 H); IR (KBr) 3150–3500 (br, OH), 2990, 2940, 2900, 1740, 1650, 1460, 1385, 1250, 1170, 1100 cm^{-1}; MS (FAB, 3-NOBA) m/z 173 (13, MH^+), 155 (10), 129 (9), 115 (14), 95 (100). Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.50; H, 7.07.

(2*R,3*R**)-4-Hydroxy-2-phenyl-2,3-dihydro-4*H*-pyran (2).** To a solution of the corresponding dihydropyrone[27] (550 mg, 3.16 mmol) and $CeCl_3{\cdot}7H_2O$ (1.18 g, 3.16 mmol) in CH_2Cl_2 (24 mL)/EtOH (12 mL) at −78 °C was added, via syringe pump, a solution of $NaBH_4$ (140 mg, 3.70 mmol) in EtOH (12 mL). After 2.5 h at −78 °C, the reaction was complete (TLC) and so was worked up as for **3** (vide supra). Flash chromatography (30% Et_2O/hexane) gave **2** (554 mg, 100%) as a white solid: mp 54–56 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.44–1.46 (d, J = 7.2 Hz, 1 H), 1.93–2.07 (ddd, J = 9.2, 12, 13 Hz, 1 H), 2.34–2.43 (app ddt, J = 2, 6.5, 13 Hz, 1 H), 4.56–4.65 (m, 1 H), 4.84–4.88 (app dt, J = 2, 6.2 Hz, 1 H), 4.96–5.02 (dd, J = 2, 12 Hz, 1 H), 6.50–6.53 (d, J = 6.2 Hz, 1 H), 7.27–7.41 (m, 5 H); IR ($CHCl_3$) 3580, 3060, 3000, 2960, 2920, 2870, 1645, 1490, 1450, 1400, 1370, 1240 (s), 1120, 1040, 1000, 940, 880, 710 cm^{-1}; MS (FAB, 3-NOBA) m/z 176 (7, M^+), 175 (22), 159 (100, OH), 104 (28). Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.83; H, 6.90.

Typical Kinetic Resolution Procedure. (+)-(2*S*,3*S*,4*S*)-3-(Benzoyloxy)-4-hydroxy-2-phenyl-2,3-dihydro-4*H*-pyran (3) and (−)-(2*R*,3*S*,4*R*)-4-Acetoxy-3-(benzoyloxy)-2-phenyl-2,3-dihydro-4*H*-pyran (5). To a solution of racemic **3** (1.00 g, 3.38 mmol) in vinyl acetate (50

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mL, 542 mmol)/dimethoxyethane (25 mL) was added lipase PS-30 (6.0 g), and the resulting suspension was stirred vigorously in a stoppered round-bottom flask for 7 days. The reaction was stopped by the addition of Et_2O (50 mL) and filtration through a medium (ASTM 10–15) fritted funnel. The filtercake was washed with Et_2O (3 × 15 mL) and EtOAc (3 × 15 mL), and the combined filtrates were concentrated in vacuo. Flash chromatography (30–80% Et_2O/hexane) gave, in order of elution, (−)-**5** (568 mg, 50%) as a slightly yellow solid and (+)-**3** (480 mg, 48%) as a white solid.

(−)-**5**: mp 99 °C; $[\alpha]^{21}_D$ −147° (*c*, 1.16, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.94 (s, 3 H), 4.79–4.83 (ddd, J = 1.9, 3.7, 6.3 Hz, 1 H), 5.26 (br s, 1 H), 5.76–5.79 (m, 1 H), 5.88–5.92 (m, 1 H), 6.74–6.77 (dd, J = 1.8, 6.3 Hz, 1 H), 7.23–7.31 (m, 3 H), 7.39–7.45 (m, 4 H), 7.52–7.56 (m, 1 H), 8.00–8.02 (m, 2 H); IR (KBr) 3050, 3010, 2990, 2910, 2860, 1735, 1710, 1645, 1450, 1370, 1275, 1225, 1110 cm^{-1}; MS (CI) m/z 339 (7.2, MH^+), 279 (70, OAc), 216 (28), 211 (47), 157 (100), 123 (20), 105 (73); HRMS (CI) m/z (MH^+) calcd for $C_{20}H_{18}O_5$ 339.1232, obsd 339.1225. Anal. Calcd for $C_{20}H_{18}O_5$: C, 71.00; H, 5.36. Found: C, 70.82; H, 5.42. This compound was estimated to be 90–92% ee on the basis of its ^1H NMR spectrum [250 MHz, CCl_4/benzene-d_6 (4:1)] in the presence of the chiral shift reagent (+)-Eu(hfc)$_3$.[28] (+)-**3**: white needles from hexane/Et_2O; mp 121–122 °C; $[\alpha]^{21}_D$ +221° (*c* 1.06, $CHCl_3$); ^1H NMR and IR spectra were identical to those of racemic **3** (vide supra); HRMS (FAB, 3-NOBA/NaI) m/z (MNa^+) calcd for $C_{18}H_{16}O_4Na$ 319.0947, obsd 319.0977. Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.57; H, 5.31. It was judged to be ≥97% ee on the basis of the ^1H NMR spectrum (250 MHz, $CDCl_3$) of its Mosher ester(s) generated from (+)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride.[29]

(−)-(2*R*,3*S*,4*R*)-3,4-Diacetoxy-2-methyl-2,3-dihydro-4*H*-pyran (3,4-Diacetyl-D-fucal) (21) and (+)-(2*S*,3*R*,4*S*)-3,4-Diacetoxy-2-methyl-2,3-dihydro-4*H*-pyran (3,4-Diacetyl-L-fucal) (21). To a solution of racemic **29** (1.40 g, 8.10 mmol) in vinyl acetate (105 mL, 1.14 mol)/dimethoxyethane (52 mL) was added lipase PS-30 (1.40 g), and the resulting suspension was stirred vigorously in a stoppered round-bottom flask for 33 h. The reaction was stopped by the addition of Et_2O (100 mL) and filtration through a medium (ASTM 10–15) fritted funnel. The filtercake was washed with Et_2O (100 mL) and EtOAc (2 × 100 mL), and the combined filtrates were concentrated in vacuo. Flash chromatography (70% Et_2O/pentane) gave (−)-**21** (650 mg, 37%) as a colorless solid. Upon further elution, a mixture of (optically enriched) (+)-**29** and the corresponding 3-acetyl isomer (total of 712 mg, 51%) was obtained. This mixture (4.14 mmol) was dissolved in CH_2Cl_2 (40 mL) and 4-(dimethylamino)pyridine (51 mg, 0.41 mmol), and NEt_3 (6.92 mL, 49.7 mmol) and Ac_2O (2.35 mL, 24.8 mmol) were sequentially added. After 3 h at room temperature, the reaction mixture was concentrated in vacuo and chromatographed (30% Et_2O/hexane) directly to give (optically enriched) (+)-**21** (876 mg, 99%) as a colorless solid.

(−)-**21**: mp 49–51 °C; $[\alpha]^{21}_D$ −8.53° (*c* 0.950, acetone) [lit. (L antipode) $[\alpha]^{19}_D$ +9.9 ± 2° (*c* 1.01, acetone)[30]]; ^1H NMR (250 MHz, $CDCl_3$) δ 1.25–1.28 (d, J = 6.6 Hz, 3 H), 2.01 (s, 3 H), 2.15 (s, 3 H), 4.16–4.24 (br q, J = 6.6 Hz, 1 H), 4.61–4.65 (app dt, J = 1.9, 6.3 Hz, 1 H), 5.26–5.29 (br d, J = 4.7 Hz, 1 H), 5.55–5.59 (ddd, J = 1.0, 2.0, 4.7 Hz, 1 H), 6.43–6.47 (dd, J = 1.9, 6.3 Hz, 1 H); IR ($CHCl_3$) 3020, 3000, 2930, 1740 (br), 1650, 1375, 1200 (br), 1095, 1080 cm^{-1}; MS (FAB, 3-NOBA) m/z 215 (12, MH^+), 171 (6), 155 (48), 112 (13), 95 (100). Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 55.93; H, 6.60. This compound was judged to be ≥97% ee on the basis of its ^1H NMR spectrum [250 MHz, CCl_4/benzene-d_6 (4:1)] in the presence of the chiral shift reagent (+)-Eu(hfc)$_3$.[28] (+)-**21**: mp 47–50 °C; $[\alpha]^{21}_D$ +5.72° (*c* 1.35, acetone);[30] ^1H NMR (250 MHz, $CDCl_3$) data were identical to that of (−)-**21**. Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.28; H, 6.42. This compound was judged to be 64% ee on the basis of its ^1H NMR spectrum [250 MHz, CCl_4/benzene-d_6 (4:1)] in the presence of the chiral shift reagent (+)-Eu(hfc)$_3$.[28]

Kinetic resolutions of racemic glycals **2**, **4**,[11] **30**,[31] **32**,[32] and **34**[32] were carried out in an analogous manner under the conditions specified in Table I. Physical and spectral properties of the optically enriched products follow.

(2*R*,4*R*)-4-Hydroxy-2-phenyl-2,3-dihydro-4*H*-pyran (2): white solid, mp 70 °C; $[\alpha]^{21}_D$ +67.0° (*c* 1.03, $CHCl_3$). Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.63; H, 6.92. Spectral characteristics were the same as for racemic **2** (vide supra).

(2*S*,4*S*)-4-Acetoxy-2-phenyl-2,3-dihydro-4*H*-pyran (27): slightly yellow oil; $[\alpha]^{21}_D$ (60% ee) −16.6° (*c* 1.75, $CHCl_3$); racemic compound previously described.[33]

(2*S*,3*R*,4*S*)-3-Acetoxy-4-hydroxy-2-phenyl-2,3-dihydro-4*H*-pyran (4): white needles from EtOAc/hexane; mp 86 °C; $[\alpha]^{22}_D$ +25.9° (*c* 1.14, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.87 (s, 3 H), 2.21–2.24 (d, J = 6.5 Hz, 1 H), 4.41–4.48 (m, 1 H), 4.83–4.86 (d, J = 9.6 Hz, 1 H), 4.91–4.94 (dd, J = 2.6, 6.0 Hz, 1 H), 5.09–5.16 (dd, J = 6.8, 9.6 Hz, 1 H), 6.52–6.55 (dd, J = 0.5, 6.0 Hz, 1 H), 7.31–7.39 (m, 5 H); IR ($CHCl_3$) 3570, 3020, 1740 (br), 1645, 1375, 1230 (s), 1135, 1050, 710 cm^{-1}; MS (FAB, 3-NOBA) m/z 235 (7, MH^+), 233 (7), 217 (45, OH), 174 (27), 157 (100, Ph), 149 (57). Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.38; H, 5.77.

(2*R*,3*R*,4*R*)-3,4-Diacetoxy-2-phenyl-2,3-dihydro-4*H*-pyran (6): white solid, mp 77–78 °C; $[\alpha]^{22}_D$ −23.8° (*c* 0.975, $CHCl_3$); spectral characteristics previously described.[11]

(2*S*,3*R*,4*S*)-3-Acetoxy-4-hydroxy-2-methyl-2,3-dihydro-4*H*-pyran (3-acetoxy-L-rhamnal) (30): clear, colorless oil; $[\alpha]^{21}_D$ −43.4° (*c* 0.655, $CHCl_3$) [lit.[31] $[\alpha]^{26}_D$ −40.6° (*c* 0.093, $CHCl_3$)].

(2*R*,3*R*,4*R*)-3,4-Diacetoxy-2-methyl-2,3-dihydro-4*H*-pyran (3,4-diacetoxy-D-rhamnal) (31): clear, colorless oil; $[\alpha]^{21}_D$ −61.4° (*c* 0.650, $CHCl_3$) [lit. (D antipode)[34] $[\alpha]_D$ +58.2° ($CHCl_3$)].

(2*R*,3*S*,4*R*)-3,5-Dimethyl-4-hydroxy-2-phenyl-2,3-dihydro-4*H*-pyran (32): white solid, mp 117 °C; $[\alpha]^{22}_D$ +42.9° (*c* 1.03, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.78–0.81 (d, J = 7.0 Hz, 3 H), 1.32–1.35 (d, J = 8.1 Hz, 1 H), 1.65–1.66 (app t, J = 1.2 Hz, 3 H), 2.26–2.38 (app d quint, J = 2, 7 Hz, 1 H), 4.60–4.65 (app t, J = 7 Hz, 1 H), 5.05–5.06 (d, J = 1.8 Hz, 1 H), 6.29–6.30 (app t, J = 1.2 Hz, 1 H), 7.22–7.39 (m, 5 H); IR ($CHCl_3$) 3590, 3000, 2970, 2910, 2880, 1665, 1450, 1385, 1160 (s), 1050, 1000, 710 cm^{-1}; MS (FAB, 3-NOBA) m/z 204 (37, M^+), 203 (20), 187 (100, OH), 118 (96), 91 (33). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.08; H, 8.04.

(2*S*,3*S*,4*S*)-4-Acetoxy-3,5-dimethyl-2-phenyl-2,3-dihydro-4*H*-pyran (33): slightly yellow oil; $[\alpha]^{22}_D$ (86% ee) +30.9° (*c* 1.31, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.63–0.65 (d, J = 7.0 Hz, 3 H), 1.50 (app t, J = 1.1 Hz, 3 H), 2.02 (s, 3 H), 2.39–2.51 (app d quint, J = 2, 7 Hz, 1 H), 5.02 (d, J = 1.7 Hz, 1 H), 5.64–5.67 (app dq, J = 1.2, 6.4 Hz, 1 H), 6.30 (app t, J = 1.3 Hz, 1 H), 7.15–7.31 (m, 5 H); IR ($CHCl_3$) 3020, 2970, 2930, 2880, 1725 (s), 1670, 1450, 1370, 1250 (br), 1160, 1035, 710 cm^{-1}; MS (FAB, 3-NOBA) m/z 246 (9, M^+), 203 (12, Ac), 187 (100, OAc), 118 (18), 91 (18). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.32; H, 7.45.

(2*R*,3*R*,4*R*)-3,5-Dimethyl-4-hydroxy-2-phenyl-2,3-dihydro-4*H*-pyran (34): off-white solid, mp 100–101 °C; $[\alpha]^{22}_D$ +65.3° (*c* 1.22, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.83–0.85 (d, J = 6.7 Hz, 3 H), 1.27–1.30 (d, J = 8.0 Hz, 1 H), 1.67 (s, 3 H), 1.99–2.09 (ddq, J = 7, 8, 10 Hz, 1 H), 3.85–3.91 (app t, J = 8 Hz, 1 H), 4.50–4.55 (d, J = 10 Hz, 1 H), 6.31 (s, 1 H), 7.26–7.39 (m, 5 H); IR ($CHCl_3$) 3570, 3005, 2960, 2920, 2880, 1670 (s), 1455, 1375, 1160 (br), 1035, 1005, 710 cm^{-1}; MS (FAB, 3-NOBA) m/z 204 (37, M^+), 203 (41), 187 (100, OH), 118 (99), 91 (23). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.22; H, 7.96.

(2*S*,3*R*,4*S*)-4-Acetoxy-3,5-dimethyl-2-phenyl-2,3-dihydro-4*H*-pyran (35): white solid, mp 89–92 °C; $[\alpha]^{22}_D$ −47.4° (*c* 0.500, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.70–0.73 (d, J = 6.8 Hz, 3 H), 1.52 (app t, J = 1.0 Hz, 3 H), 2.05 (s, 3 H), 2.21–2.31 (ddq, J = 7, 8, 10 Hz, 1 H), 4.58–4.62 (d, J = 10 Hz, 1 H), 5.34–5.38 (dd, J = 0.8, 7.7 Hz, 1 H), 6.38 (s, 1 H), 7.27–7.38 (m, 5 H); IR ($CHCl_3$) 3020, 2960, 2920, 1720 (s), 1670, 1455, 1375, 1250 (br), 1160, 710 cm^{-1}; MS (FAB, 3-NOBA) m/z 246 (26, M^+), 203 (6, Ac), 187 (100, OAc), 118 (50), 91 (23). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 72.99; H, 7.40.

Synthesis of Artificial Disaccharides. (−)-(2*R*,3*S*,4*R*)-3,4-Dihydroxy-2-phenyl-2,3-dihydro-4*H*-pyran (38). To a solution of diacetate (−)-**6** (293 mg, 1.06 mmol) in MeOH (7 mL) was added K_2CO_3 (87.9 mg, 0.64 mmol). The reaction mixture was stirred at room temperature for 5 h and then concentrated in vacuo and chromatographed (3–5% MeOH/CH_2Cl_2) to yield (−)-**38** (193 mg, 95%) as a white solid: mp 136–140 °C; $[\alpha]^{26}_D$ −80.5° (*c* 0.215, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.83 (br s, 1 H), 2.09 (br s, 1 H), 3.73–3.80 (m, 1 H), 4.42–4.45 (m, 1 H), 4.65–4.69 (d, J = 10.0 Hz, 1 H), 4.83–4.86 (dd, J

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= 2.1, 6.1 Hz, 1 H), 6.45–6.48 (dd, J = 1, 6 Hz, 1 H), 7.36–7.43 (m, 5 H); IR ($CHCl_3$) 3580 (s, free OH), 3250–3500 (br), 3020, 1645, 1110, 1070, 1035 cm^{-1}; MS (FAB, 3-NOBA) m/z 192 (7, M^+), 191 (19), 175 (100, OH), 157 (32), 120 (41), 91 (24). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.73; H, 6.37.

(−)-(2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)-2-phenyl-2,3-dihydro-4*H*-pyran (7). To a solution of diol (−)-**38** (185 mg, 0.96 mmol) in DMF (5 mL) at 0 °C was added NaH (154 mg of a 60% dispersion in mineral oil, 3.85 mmol). The ice bath was removed and the reaction mixture was stirred for 10 min. Then benzyl bromide (458 μL, 3.85 mmol) was added dropwise. After 4.5 h at room temperature, the reaction mixture was poured into Et_2O (40 mL)/$NaHCO_3$ (aqueous, 40 mL). The aqueous layer was extracted with Et_2O (3 × 40 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. Chromatography (5% Et_2O/hexane) gave (−)-**7** (318 mg, 89%) as an oil that solidified upon thorough drying: mp 57–58 °C; $[\alpha]^{26}_D$ −30.9° (c 0.755, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 3.75–3.82 (dd, J = 7.2, 10.1 Hz, 1 H), 3.88–3.93 (d, J = 10.6 Hz, 1 H), 4.37–4.41 (app dt, J = 2, 7 Hz, 1 H), 4.40–4.44 (d, J = 10.6 Hz, 1 H), 4.62–4.66 (d, J = 11.6 Hz, 1 H), 4.67–4.72 (d, J = 11.6 Hz, 1 H), 4.71–4.75 (d, J = 10.1 Hz, 1 H), 4.92–4.95 (dd, J = 2.2, 6.1 Hz, 1 H), 6.48–6.51 (dd, J = 1.5, 6.1 Hz, 1 H), 6.90–6.93 (m, 2 H), 7.17–7.46 (m, 13 H); IR ($CHCl_3$) 3060, 3000, 2900, 2860, 1645, 1490, 1450, 1240, 1095 cm^{-1}; MS (FAB, 3-NOBA, for m/z > 300) m/z 372 (32, M^+), 371 (100), 355 (13, OH). Anal. Calcd for $C_{25}H_{24}O_3$: C, 80.62; H, 6.49. Found: C, 80.66; H, 6.43.

Epoxides 8 and 9. To a solution of glycal **7** (7.5 mg, 0.020 mmol) in CH_2Cl_2 (300 μL) at 0 °C was added a solution of dimethyldioxirane in acetone (1.2 equiv, 0.075 M). After 1 h at 0 °C, all of the glycal had been consumed (TLC), and so the volatiles were evaporated under a stream of nitrogen. The crude epoxide(s) were dried on the high vacuum to give a mixture (**8**:**9** = 5:1) of epoxides (7.8 mg, 100%).

8: ^1H NMR (250 MHz, $CDCl_3$) δ 3.16–3.17 (dd, J = 1.1, 2.4 Hz, 1 H), 3.43–3.50 (dd, J = 8.0, 10 Hz, 1 H), 3.75–3.79 (d, J = 10.5 Hz, 1 H), 4.06–4.10 (dd, J = 1.1, 8.0 Hz, 1 H), 4.28–4.32 (d, J = 10.5 Hz, 1 H), 4.54–4.58 (d, J = 10 Hz, 1 H), 4.72–4.77 (d, J = 11.5 Hz, 1 H), 4.81–4.86 (d, J = 11.5 Hz, 1 H), 5.07–5.08 (dd, J = 1.1, 2 Hz, 1 H), 6.83–6.90 (m, 2 H), 7.15–7.23 (m, 3 H), 7.30–7.46 (m, 10 H). **9**: ^1H NMR (250 MHz, $CDCl_3$) δ 3.39–3.42 (dd, J = 2.0, 2.8 Hz, 1 H), 3.68–3.72 (d, J = 10 Hz, 1 H), 3.83–3.91 (dd, J = 8.3, 10 Hz, 1 H), 4.02–4.05 (dd, J = 2.0, 8.3 Hz, 1 H), 4.31–4.35 (d, J = 10 Hz, 1 H), 4.47–4.52 (d, J = 10 Hz, 1 H), 4.72–4.85 (m, 2 H), 5.02–5.03 (d, J = 2.8 Hz, 1 H), 6.83–6.90 (m, 2 H), 7.15–7.23 (m, 3 H), 7.30–7.46 (m, 10 H).

(+)-3,4-Di-*O*-benzyl-5(*R*)-phenyl-β-D-xylopyranosyl Fluoride (10) and (+)-3,4-Di-*O*-benzyl-5(*R*)-phenyl-α-D-lyxopyranosyl Fluoride (11). Epoxides **8**/**9** were prepared from glycal (−)-**7** (150 mg, 0.403 mmol) as described above. The crude epoxide(s) was dissolved in dry THF (3 mL) and the resulting solution cooled to −20 °C. Tetrabutylammonium fluoride (TBAF) in THF (5 equiv of a 1.0 M solution) was added dropwise and the reaction mixture allowed to warm to room temperature. After 4 h, the reaction was quenched by pouring into EtOAc (40 mL)/H_2O (40 mL). The aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organics were washed with brine (40 mL), dried ($MgSO_4$), filtered, and evaporated. Flash chromatography (0.5–2% EtOAc/$CHCl_3$) gave, in order of elution, **11** (20.7 mg, 13%) and **10** (106 mg, 65%).

10: mp 91–93 °C; $[\alpha]^{26}_D$ +37.0° (c 0.535, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 2.1–2.5 (br s, 1 H), 3.54–3.62 (app t, J = 9 Hz, 1 H), 3.62–3.69 (app t, J = 9 Hz, 1 H), 3.77–3.81 (d, J = 10 Hz, 1 H), 3.73–3.85 (m, 1 H), 4.33–4.37 (d, J = 10 Hz, 1 H), 4.35–4.39 (d, J = 9 Hz, 1 H), 4.81–4.85 (d, J = 11 Hz, 1 H), 4.92–4.96 (d, J = 11 Hz, 1 H), 5.12–5.36 (dd, J = 7, 53 Hz, 1 H), 6.93–7.0 (m, 2 H), 7.19–7.23 (m, 3 H), 7.3–7.5 (m, 10 H); IR ($CHCl_3$) 3580 (free OH), 3260–3460 (br), 3020 (s), 2900, 1495, 1455, 1365, 1100 (s) cm^{-1}; MS (FAB, 3-NOBA/NaI) m/z 431 (100, MNa^+), 408 (10, M^+), 407 (40), 389 (18, F), 329 (55), 289 (49), 181 (64), 176 (94); HRMS (FAB, 3-NOBA/NaI) m/z (MNa^+) calcd for $C_{25}H_{25}O_4FNa$ 431.1635, obsd 431.1627. Anal. Calcd for $C_{25}H_{25}O_4F$: C, 73.51; H, 6.17. Found: C, 73.80; H, 6.07. **11**: $[\alpha]^{21}_D$ +31.2° (c 0.195, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 2.3–2.7 (br s, 1 H), 3.78–3.85 (app t, J = 9.5 Hz, 1 H), 3.81–3.85 (d, J = 10 Hz, 1 H), 3.94–3.99 (ddd, J = 1.4, 3.5, 9 Hz, 1 H), 4.17–4.20 (ddd, J = 1.7, 3.5, 5.1 Hz, 1 H), 4.36–4.40 (d, J = 10 Hz, 1 H), 4.70–4.75 (br d, J = 11 Hz, 2 H), 4.79–4.83 (d, J = 11.5 Hz, 1 H), 5.63–5.84 (dd, J = 1.7, 49 Hz, 1 H), 6.93–6.97 (m, 2 H), 7.17–7.24 (m, 3 H), 7.30–7.44 (m, 8 Hz), 7.46–7.51 (m, 2 H); IR ($CHCl_3$) 3570, 3010 (s), 2920, 2860, 1495, 1455, 1360, 1090 (br) cm^{-1}; MS (FAB, 3-NOBA/NaI) m/z 431 (20, MNa^+), 408 (8, M^+), 407 (32), 329 (20), 289 (44), 181 (100); HRMS (FAB, 3-NOBA/NaI) m/z (MNa^+) calcd for $C_{25}H_{25}O_4FNa$ 431.1635, obsd 431.1637. Anal. Calcd for $C_{25}H_{25}O_4F$: C, 73.51; H, 6.17. Found: C, 73.33; H, 6.40.

(−)-Phenyl 3,4-Di-*O*-benzyl-5(*R*)-phenyl-1-thio-β-D-xylopyranoside (12). Epoxides **8**/**9** were prepared from glycal (−)-**7** (44.0 mg, 0.118 mmol) as described above. The crude epoxide(s) was dissolved in dry THF (1 mL), and the resulting solution was added via cannula to a solution of tetrabutylammonium thiophenoxide (from TBAF and *S*-(trimethylsilyl)thiophenol, 5 equiv) at −20 °C in THF (0.5 mL). The cooling bath was removed, and after 3 h, the reaction was quenched by pouring into EtOAc (15 mL)/H_2O (15 mL) and worked up as for **10** and **11** (vide supra). Flash chromatography (5–30% EtOAc/hexane) gave **12** (35.6 mg, 60%) as a white solid: mp 85 °C; $[\alpha]^{26}_D$ −7.8° (c 0.49, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 2.47 (br s, 1 H), 3.40–3.47 (app t, J = 9 Hz, 1 H), 3.51–3.59 (app t, J = 9 Hz, 1 H), 3.64–3.72 (app t, J = 9.5 Hz, 1 H), 3.71–3.76 (d, J = 10 Hz, 1 H), 4.30–4.34 (d, J = 9.5 Hz, 1 H), 4.33–4.37 (d, J = 10 Hz, 1 H), 4.59–4.63 (d, J = 9.5 Hz, 1 H), 4.89 (br s, 2 H), 6.90–6.93 (m, 2 H), 7.15–7.46 (m, 16 H), 7.53–7.59 (m, 2 H); IR ($CHCl_3$) 3540 (br), 3010 (s), 2900, 2860, 1495, 1450, 1060 (s) cm^{-1}; MS (FAB, 3-NOBA, for m/z > 310) m/z 499 (74, MH^+), 481 (41, OH), 460 (51), 389 (100, SPh). Anal. Calcd for $C_{31}H_{30}O_4S$: C, 74.67; H, 6.06; S, 6.43. Found: C, 74.32; H, 6.21; S, 6.88.

(−)-*O*-[3,4-Di-*O*-benzyl-5(*R*)-phenyl-β-D-xylopyranosyl]-(1→6)-3,4-di-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enopyranose (13). Epoxides **8**/**9** were prepared from glycal (−)-**7** (30.0 mg, 0.081 mmol) as described above. To a solution of the crude epoxide(s) in THF (400 μL) was added a solution of 3,4-di-*O*-benzyl-D-glucal[35] (39.4 mg, 0.121 mmol) in THF (400 μL), and the resulting solution was cooled to −78 °C. Then a 1.0 M solution of $ZnCl_2$ in Et_2O (137 μL, 0.137 mmol) was added dropwise. The reaction mixture was allowed to gradually warm to room temperature overnight. After a total of 23 h, the reaction was quenched by pouring into EtOAc (30 mL)/$NaHCO_3$ (aqueous, 30 mL). The aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated. Chromatography (5–25% EtOAc/hexane) gave **13** (29.5 mg, 51%), as well as recovered glycosyl acceptor (25 mg). **13**: $[\alpha]^{20}_D$ −9.67° (c 1.35, $CHCl_3$); ^1H NMR (490 MHz, $CDCl_3$) δ 2.57 (d, J = 1.5 Hz, 1 H), 3.47–3.51 (app t, J = 9 Hz, 1 H), 3.64–3.67 (app t, J = 9 Hz, 1 H), 3.71–3.76 (m, 2 H), 3.77–3.79 (d, J = 10.3 Hz, 1 H), 3.84–3.87 (dd, J = 6.3, 11 Hz, 1 H), 4.12–4.14 (d, J = 11 Hz, 1 H), 4.12–4.16 (m, 2 H), 4.22–4.24 (d, J = 9.5 Hz, 1 H), 4.38–4.40 (d, J = 10.3 Hz, 1 H), 4.42–4.44 (d, J = 7.7 Hz, 1 H), 4.49–4.51 (d, J = 11.7 Hz, 1 H), 4.57–4.60 (d, J = 11.7 Hz, 1 H), 4.64–4.66 (d, J = 11.5 Hz, 1 H), 4.77–4.79 (d, J = 11.5 Hz, 1 H), 4.87–4.89 (dd, J = 2.9, 6.3 Hz, 1 H), 4.87–4.89 (d, J = 11.3 Hz, 1 H), 4.92–4.94 (d, J = 11.3 Hz, 1 H), 6.40–6.42 (dd, J = 1, 6.3 Hz, 1 H), 6.92–6.94 (m, 2 H), 7.20–7.40 (m, 21 H), 7.45–7.47 (m, 2 H); IR ($CHCl_3$) 3580 (br), 3060, 3000 (s), 2900, 2860, 1645, 1495, 1450, 1350, 1060 (s) cm^{-1}; MS (FAB, 3-NOBA/NaI) m/z 737 (8, MNa^+), 607 (7, OBn), 389 (5), 289 (13), 281 (18), 210 (18), 181 (100). Anal. Calcd for $C_{45}H_{46}O_8$: C, 75.61; H, 6.49. Found: C, 75.41; H, 6.20.

(+)-2,3,4-Tri-*O*-benzyl-5(*R*)-phenyl-β-D-xylopyranosyl Fluoride (14). To a solution of (+)-**10** (83.0 mg, 0.203 mmol) in DMF (2 mL) at 0 °C was added NaH (16.2 mg of a 60% dispersion in mineral oil, 0.406 mmol). The ice bath was removed and the reaction mixture was stirred for 10 min. The benzyl bromide (48.3 μL, 0.46 mmol) was added dropwise. After 2 h at room temperature, the reaction mixture was poured into Et_2O (30 mL)/$NaHCO_3$ (aqueous, 30 mL). The aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. Chromatography (5–10% EtOAc/hexane) gave (+)-**14** (92.0 mg, 100%) as a clear colorless oil: $[\alpha]^{21}_D$ +31.1° (c 0.280, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 3.58–3.65 (app t, J = 9 Hz, 1 H), 3.69–3.81 (m, 2 H), 3.77–3.81 (d, J = 10.2 Hz, 1 H), 4.35–4.39 (d, J = 10.2 Hz, 1 H), 4.37–4.41 (d, J = 9.6 Hz, 1 H), 4.72–4.77 (d, J = 11.1 Hz, 1 H), 4.80–4.85 (d, J = 10.9 Hz, 1 H), 4.86–4.90 (d, J = 11.1 Hz, 1 H), 4.87–4.91 (d, J = 10.9 Hz, 1 H), 5.28–5.52 (dd, J = 6.5, 53 Hz, 1 H), 6.88–6.92 (m, 2 H), 7.17–7.23 (m, 3 H), 7.26–7.48 (m, 15 H); IR ($CHCl_3$) 3040 (s), 3020 (s), 2900, 2860, 1495, 1450, 1355, 1100 (s) cm^{-1}; MS (FAB, 3-NOBA/NaI) m/z 521 (8, MNa^+), 498 (6, M^+), 497 (17), 407 (8, Bn), 271 (10), 223 (13), 193 (14), 181 (100). Anal. Calcd for $C_{32}H_{31}O_4F$: C, 77.09; H, 6.27. Found: C, 77.07; H, 6.43.

(+)-*O*-[2,3,4-Tri-*O*-benzyl-5(*R*)-phenyl-α-D-xylopyranosyl]-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (15). A mixture of glycosyl fluoride **14** (36.0 mg, 0.072 mmol) and diacetone galactose (56.4 mg, 0.217 mmol) in a flame-dried flask was azeotroped with benzene (3 × 2 mL). Freshly activated 4-Å molecular sieve powder (108 mg), then Et_2O (1.2 mL), and 2,6-di-*tert*-butylpyridine (33.4 μL, 0.144 mmol) were added. After rapid addition of anhydrous $AgClO_4$ (29.9 mg, 0.144 mmol) and $SnCl_2$ (27.4 mg, 0.144 mmol), the flask was flushed with nitrogen and stoppered. The reaction mixture was stirred for 5 days at

(35) Blackburne, I. D.; Fredericks, P. M.; Guthrie, R. D. *Aust. J. Chem.* **1976**, *29*, 381.

room temperature. The reaction was quenched by diluting with Et_2O (5 mL) and filtering through Celite. The filtercake was washed with Et_2O (10 × 5 mL). The combined filtrates were extracted with $NaHCO_3$ (aqueous, 25 mL), dried ($MgSO_4$), filtered, and evaporated. Chromatography (10–45% EtOAc/hexane) gave **15** (50.9 mg, 95%) as a foam, as well as recovered diacetone galactose (32.9 mg): $[\alpha]^{20}_D$ +1.70° (*c* 1.71, $CHCl_3$); ^1H NMR (490 MHz, $CDCl_3$) δ 1.32 (s, 3 H), 1.33 (s, 3 H), 1.43 (s, 3 H), 1.50 (s, 3 H), 3.49–3.53 (app t, *J* = 9.4 Hz, 1 H), 3.70–3.73 (dd, *J* = 3.7, 9.5 Hz, 1 H), 3.74–3.78 (dd, *J* = 8, 10 Hz, 1 H), 3.82–3.84 (d, *J* = 10.3 Hz, 1 H), 3.82–3.85 (dd, *J* = 6, 10 Hz, 1 H), 4.06–4.09 (dd, *J* = 6, 8 Hz, 1 H), 4.09–4.13 (app t, *J* = 9 Hz, 1 H), 4.31–4.32 (dd, *J* = 2.4, 50 Hz, 1 H), 4.37–4.39 (dd, *J* = 1.7, 7.9 Hz, 1 H), 4.42–4.44 (d, *J* = 10.3 Hz, 1 H), 4.60–4.62 (dd, *J* = 2.4, 7.9 Hz, 1 H), 4.67–4.69 (d, *J* = 9.8 Hz, 1 H), 4.75–4.77 (d, *J* = 12 Hz, 1 H), 4.81–4.84 (d, *J* = 12 Hz, 1 H), 4.85–4.87 (d, *J* = 11 Hz, 1 H), 4.98–5.00 (d, *J* = 11 Hz, 1 H), 5.08 (d, *J* = 3.7 Hz, 1 H), 5.52–5.53 (d, *J* = 5.0 Hz, 1 H), 6.91–6.93 (m, 2 H), 7.17–7.20 (m, 3 H), 7.28–7.45 (m, 15 H); IR ($CHCl_3$) 3000 (s), 2920, 1495, 1450, 1380, 1370, 1255, 1165, 1075 (s) cm^{-1}; MS (FAB, 3-NOBA) *m/z* 738 (26, M^+), 724 (12, Me), 523 (10), 421 (13), 387 (100), 349 (94), 327 (57). Anal. Calcd for $C_{44}H_{50}O_{10}$: C, 71.53; H, 6.82. Found: C, 71.36; H, 6.78.

(+)-*O*-[2,3,4-Tri-*O*-benzyl-5(*R*)-phenyl-α-D-xylopyranosyl]-(1→6)-1,5-anhydro-3,4-di-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enopyranose (16). To a mixture of glycosyl fluoride **14** (48.0 mg, 0.096 mmol), 3,4-di-*O*-benzyl-D-glucal[35] (126 mg, 0.385 mmol), and 4-Å molecular sieve powder (150 mg) in Et_2O (2 mL) was added 2,6-di-*tert*-butylpyridine (43.2 μL, 0.193 mmol). After addition of $AgClO_4$ (39.9 mg, 0.193 mmol) and $SnCl_2$ (36.5 mg, 0.193 mmol), the reaction mixture was stirred for 5 days at room temperature. Workup was carried out as for **15**. Chromatography (10–20% EtOAc/hexane) gave **16** (55.4 mg, 71%) as a white solid, as well as recovered glycosyl acceptor (48.2 mg): mp 87–90 °C; $[\alpha]^{20}_D$ +27.7° (*c* 2.26, $CHCl_3$); ^1H NMR (490 MHz, $CDCl_3$) δ 3.48–3.52 (app t, *J* = 9.5 Hz, 1 H), 3.68–3.71 (dd, *J* = 3.5, 9.6 Hz, 1 H), 3.80–3.83 (dd, *J* = 2.4, 11.6 Hz, 1 H), 3.81–3.84 (d, *J* = 10.3 Hz, 1 H), 3.89–3.91 (dd, *J* = 5.8, 8.0 Hz, 1 H), 3.96–3.99 (dd, *J* = 5.8, 11.6 Hz, 1 H), 4.10–4.14 (app t, *J* = 9.3 Hz, 1 H), 4.16–4.20 (m, 2 H), 4.43–4.45 (d, *J* = 10.3 Hz, 1 H), 4.51–4.53 (d, *J* = 12 Hz, 1 H), 4.60–4.62 (d, *J* = 12 Hz, 1 H), 4.70–4.72 (d, *J* = 10.6 Hz, 2 H), 4.72–4.74 (d, *J* = 12 Hz, 1 H), 4.75–4.78 (d, *J* = 12 Hz, 1 H), 4.84–4.87 (d, *J* = 11 Hz, 1 H), 4.85–4.87 (d, *J* = 11 Hz, 1 H), 4.87–4.89 (dd, *J* = 2.7, 6.2 Hz, 1 H), 4.98–4.99 (d, *J* = 3.5 Hz, 1 H), 4.97–4.99 (d, *J* = 11 Hz, 1 H), 6.37–6.38 (dd, *J* = 1, 6 Hz, 1 H), 6.91–6.93 (m, 2 H), 7.19–7.21 (m, 3 H), 7.26–7.40 (m, 25 H); IR ($CHCl_3$) 3060, 3000 (s), 2920, 2860, 1645, 1495, 1450, 1355, 1240, 1075 (s) cm^{-1}; MS (FAB, 3-NOBA) *m/z* 804 (2, M^+), 803 (7), 697 (5, OBn), 621 (9), 387 (100), 371 (67). Anal. Calcd for $C_{52}H_{52}O_8$: C, 77.59; H, 6.51. Found: C, 77.48; H, 6.40.

(−)-*O*-[2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl]-(1 → 3)-1,5-anhydro-4-*O*-acetyl-2-deoxy-5(*S*)-phenyl-L-*xylo*-pent-1-enopyranose (17). To a mixture of 2,3,4-tri-*O*-benzyl-L-fucosyl fluoride(s)[36] (α:β = 1:1, 47.0 mg, 0.107 mmol), (+)-**3** (50.3 mg, 0.214 mmol), and 4-Å molecular sieve powder in Et_2O (2 mL) was added 2,6-di-*tert*-butylpyridine (48.2 μL, 0.214 mmol). After addition of $AgClO_4$ (44.5 mg, 0.214 mmol) and $SnCl_2$ (40.7 mg, 0.214 mmol), the reaction mixture was stirred for 41 h at room temperature. Workup was carried out as for **15**. Chromatography (10–20% EtOAc/hexane) gave **17** (42.0 mg, 60%) as a white solid. This was followed by a second, mixed fraction (10.0 mg, 14%) containing both **17** and the corresponding β-coupled product (anomeric H δ 4.38–4.41, *J* = 7.6 Hz) in a ratio of 1:2.5. Further elution with 80% EtOAc/hexane gave recovered (+)-**3** (22.8 mg). **17**: mp 98–100 °C; $[\alpha]^{20}_D$ −11.1° (*c* 1.10, $CHCl_3$); ^1H NMR (490 MHz, $CDCl_3$) δ 1.10–1.11 (d, *J* = 6.5 Hz, 3 H), 1.65 (s, 3 H), 3.59–3.60 (br d, *J* = 2 Hz, 1 H), 3.74–3.77 (dd, *J* = 2.7, 10 Hz, 1 H), 3.85–3.89 (br q, *J* = 6.6 Hz, 1 H), 3.95–3.98 (dd, *J* = 3.7, 10 Hz, 1 H), 4.42–4.44 (app dt, *J* = 2, 6.8 Hz, 1 H), 4.60–4.63 (d, *J* = 11.6 Hz, 1 H), 4.61–4.63 (d, *J* = 11.8 Hz, 1 H), 4.65–4.69 (app t, *J* = 11 Hz, 2 H), 4.78–4.80 (d, *J* = 11.8 Hz, 1 H), 4.85–4.87 (d, *J* = 9.1 Hz, 1 H), 4.89–4.91 (dd, *J* = 2.6, 6.2 Hz, 1 H), 4.94–4.97 (d, *J* = 11.6 Hz, 1 H), 4.99–5.00 (d, *J* = 3.7 Hz, 1 H), 5.45–5.48 (dd, *J* = 6.8, 9.1 Hz, 1 H), 6.50–6.51 (dd, *J* = 1.5, 6.2 Hz, 1 H), 7.21–7.37 (m, 20 H); IR ($CHCl_3$) 3060, 3000 (s), 2900 (br), 1740 (s), 1645, 1495, 1450, 1370, 1240, 1100 (s), 1040 (s) cm^{-1}; MS (FAB, 3-NOBA, for *m/z* > 300) *m/z* 651 (31, MH^+), 573 (14, Ph), 543 (18, OBn), 433 (42), 417 (79), 325 (100). Anal. Calcd for $C_{40}H_{42}O_8$: C, 73.83; H, 6.50. Found: C, 73.84; H, 6.71.

(−)-Phenyl 3,4-Di-*O*-benzyl-5(*R*)-phenyl-2-*O*-pivaloyl-1-thio-β-D-xylopyranoside (39). To a solution of **12** (64.0 mg, 0.128 mmol) and 4-(dimethylamino)pyridine (1 crystal) in pyridine (3 mL) was added pivaloyl chloride (237 μL, 1.93 mmol), and the resulting mixture was heated at 70 °C. After 48 h, the reaction mixture was poured into $NaHCO_3$ (aqueous, 30 mL)/EtOAc (30 mL). The aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated. Chromatography, eluting with 5–10% EtOAc/hexane, gave **39** (65.8 mg, 88%) as a white solid which could be recrystallized from EtOAc/hexane (white needles): mp 142–143 °C; $[\alpha]^{20}_D$ −30.1° (*c* 2.27, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.26 (s, 9 H), 3.51–3.58 (app t, *J* = 9.3 Hz, 1 H), 3.70–3.74 (d, *J* = 10 Hz, 1 H), 3.75–3.83 (app t, *J* = 9 Hz, 1 H), 4.27–4.31 (d, *J* = 10 Hz, 1 H), 4.30–4.35 (d, *J* = 9.4 Hz, 1 H), 4.66–4.70 (d, *J* = 11 Hz, 1 H), 4.74–4.78 (d, *J* = 10 Hz, 1 H), 4.80–4.84 (d, *J* = 11 Hz, 1 H), 5.14–5.21 (dd, *J* = 9.1, 10 Hz, 1 H), 6.87–6.90 (m, 2 H), 7.16–7.51 (m, 16 H), 7.53–7.59 (m, 2 H); IR ($CHCl_3$) 3060, 3010 (s), 2900, 2860, 2820, 2800, 2760, 1730 (s), 1495, 1475, 1450, 1360, 1275, 1160 (s), 1130, 1070 cm^{-1}; MS (FAB, 3-NOBA, for *m/z* > 300) *m/z* 583 (2, MH^+), 531 (6), 473 (100, SPh), 383 (10). Anal. Calcd for $C_{36}H_{38}O_5S$: C, 74.20; H, 6.57; S, 5.50. Found: C, 74.15; H, 6.83; S, 5.17.

Phenyl 3,4-Di-*O*-benzyl-5(*R*)-phenyl-2-*O*-pivaloyl-1-thio-β-D-xylopyranoside Sulfoxides (18a,b). To a solution of **39** (14.5 mg, 0.025 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added a 0.08 M solution of dimethyldioxirane *in* acetone (1.0 equiv). The reaction mixture was stirred for 30 min and then evaporated under reduced pressure. Chromatography (25% EtOAc/hexane) gave a mixture (2.5:1) of sulfoxides **18a,b** (11.4 mg, 77%) as a white solid. (Only the major diastereomer and the corresponding sulfone were obtained if an excess of dimethyldioxirane was employed.)

18a (major diastereomer): ^1H NMR (250 MHz, $CDCl_3$) δ 1.27 (s, 9 H), 3.16–3.23 (app t, *J* = 9.3 Hz, 1 H), 3.54–3.58 (d, *J* = 10.2 Hz, 1 H), 3.78–3.85 (app t, *J* = 9 Hz, 1 H), 4.13–4.17 (d, *J* = 10.2 Hz, 1 H), 4.32–4.36 (d, *J* = 9.5 Hz, 1 H), 4.63–4.67 (d, *J* = 10.3 Hz, 1 H), 4.65–4.69 (d, *J* = 11 Hz, 1 H), 4.79–4.84 (d, *J* = 11 Hz, 1 H), 5.01–5.08 (dd, *J* = 9.0, 10 Hz, 1 H), 6.82–6.86 (m, 2 H), 7.00–7.04 (m, 2 H), 7.14–7.36 (m, 11 H), 7.60 (m, 3 H), 7.80–7.84 (m, 2 H); IR ($CDCl_3$) 2920, 2860, 1730 (s), 1155, 1130, 1045 (S=O) cm^{-1}. **18b** (minor diastereomer): C_2-H dd, δ 5.52–5.60 (*J* = 9, 10 Hz).

(−)-*O*-[3,4-Di-*O*-benzyl-5(*R*)-phenyl-2-*O*-pivaloyl-β-D-xylopyranosyl]-(1 → 6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (19). To a solution of trifluoromethanesulfonic anhydride (3.1 μL, 0.018 mmol, 2 equiv) in CH_2Cl_2 (100 μL) at −78 °C was added a solution of sulfoxides **18a,b** (11.0 mg, 0.018 mmol, 2 equiv) in CH_2Cl_2 (200 μL), and the mixture was stirred for 10 min. Then a solution of diacetone galactose (2.4 mg, 0.0092 mmol, 1.0 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (2.8 mg, 0.014 mmol) in CH_2Cl_2 (700 μL) was added dropwise, via cannula. The reaction mixture was allowed to gradually warm to −45 °C over the course of 4.5 h. The reaction mixture was then poured into $NaHCO_3$ (aqueous, 15 mL)/EtOAc (15 mL) and the aqueous layer extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated. Chromatography (5–25% EtOAc/hexane) gave **19** (6.6 mg, 98% based on glycosyl acceptor): $[\alpha]^{20}_D$ −47.1° (*c* 0.310, $CHCl_3$); ^1H NMR (490 MHz, $CDCl_3$) δ 1.21 (s, 9 H), 1.24 (s, 3 H), 1.29 (s, 3 H), 1.38 (s, 3 H), 1.48 (s, 3 H), 3.56–3.60 (app t, *J* = 9 Hz, 1 H), 3.57–3.60 (d, *J* = 10.5 Hz, 1 H), 3.74–3.79 (m, 2 H), 3.91–3.94 (m, 1 H), 4.00–4.03 (dd, *J* = 4.8, 11 Hz, 1 H), 4.18–4.20 (dd, *J* = 1.6, 8 Hz, 1 H), 4.23–4.24 (dd, *J* = 2.3, 4.9 Hz, 1 H), 4.27–4.29 (d, *J* = 9.6 Hz, 1 H), 4.31–4.33 (d, *J* = 10.4 Hz, 1 H), 4.51–4.53 (dd, *J* = 2.3, 8 Hz, 1 H), 4.58–4.60 (d, *J* = 8.1 Hz, 1 H), 4.68–4.71 (d, *J* = 11 Hz, 1 H), 4.78–4.80 (d, *J* = 11 Hz, 1 H), 5.17–5.21 (dd, *J* = 8.1, 9.2 Hz, 1 H), 5.45–5.46 (d, *J* = 4.9 Hz, 1 H), 6.89–6.91 (m, 2 H), 7.17–7.49 (m, 13 H); IR ($CHCl_3$) 3020 (s), 2970, 2930, 2900, 1730 (s), 1495, 1475, 1450, 1175, 1140, 1075 (s) cm^{-1}; MS (FAB, 3-NOBA/NaI) *m/z* 755 (20, MNa^+), 473 (100), 381 (8), 263 (48), 181 (36). Anal. Calcd for $C_{42}H_{52}O_{11}$: C, 68.83; H, 7.15. Found: C, 69.01; H, 6.99.

Synthesis of Analogues of Daunomycin. (−)-(2*R*,3*R*,4*R*)-3,4-Dihydroxy-2-phenyl-2,3-dihydro-4*H*-pyran (40). To a solution of diester (−)-**5** (413 mg, 1.22 mmol) in MeOH (15 mL) was added K_2CO_3 (101 mg, 0.733 mmol). The reaction mixture was stirred at room temperature for 3 h and then concentrated in vacuo and chromatographed (1–4% MeOH/CH_2Cl_2) to yield (−)-**40** (219 mg, 94%) as a white solid: mp 94–96 °C; $[\alpha]^{22}_D$ −103° (*c* 1.16, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 2.09–2.12 (d, *J* = 6.4 Hz, 1 H), 2.37–2.42 (d, *J* = 10 Hz, 1 H), 4.01–4.05 (app triplet, *J* = 5.1 Hz, 1 H), 4.55–4.60 (m, 1 H), 4.79–4.83 (ddd, *J* = 1.9, 3.0, 6.2 Hz, 1 H), 4.98 (br s, 1 H), 6.53–6.56 (dd, *J* =

(36) We wish to thank John M. Peterson (Yale University) for a sample of 2,3,4-tri-*O*-benzyl-L-fucosyl fluoride(s) (α:β = 1:1).

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0.9, 6.2 Hz, 1 H), 7.32–7.44 (m, 5 H); IR (KBr) 3550 (s, free OH), 3200–3500 (br), 3060, 3010, 2910, 2880, 1635, 1490, 1450, 1225, 1130, 1080, 1050 cm^{-1}; MS (EI) *m/z* 192 (2.6, M^+), 121 (11), 120 (100), 91 (59), 77 (7.9); HRMS (EI) *m/z* (M^+) calcd for $C_{11}H_{12}O_3$ 192.0786, obsd 192.0779. Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 69.00; H, 6.44.

(+)-(2*S*,3*S*,4*S*)-3,4-Dihydroxy-2-phenyl-2,3-dihydro-4*H*-pyran (40). To a solution of monoester (+)-**3** (400 mg, 1.35 mmol) in MeOH (10 mL) was added K_2CO_3 (112 mg, 0.810 mmol). The reaction mixture was stirred at room temperature for 2 h and then concentrated in vacuo and chromatographed (2–4% MeOH/CH_2Cl_2) to give (+)-**40** (221 mg, 85%) as a foam: $[\alpha]^{21}_D$ +96.3° (*c* 0.865, $CHCl_3$); this compound displayed ^1H NMR, IR, and mass spectra identical to those of (−)-**40** (vide supra). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.39; H, 6.34.

(−)-(2*R*,3*S*,4*R*)-2-Phenyl-3,4-bis[(trimethylsilyl)oxy]-2,3-dihydro-4*H*-pyran (25). To a solution of diol (−)-**39** (185 mg, 0.964 mmol) in CH_2Cl_2 (6 mL) was added TMS-imidazole (311 μL, 2.12 mmol) dropwise, with stirring. After 1 h, the reaction was complete (TLC). The solvent was removed in vacuo, and the residue was chromatographed directly (2–3% Et_2O/hexane) to give (−)-**25** (272 mg, 84%) as a clear, colorless oil: $[\alpha]^{21}_D$ −68.3° (*c* 1.15, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ −0.209 (s, 9 H), 0.163 (s, 9 H), 3.81–3.83 (dd, *J* = 1.9, 4.1 Hz, 1 H), 4.58–4.62 (app dt, *J* = 1.9, 6.2 Hz, 1 H), 4.64–4.66 (m, 1 H), 4.95 (br s, 1 H), 6.44–6.47 (dd, *J* = 1.8, 6.2 Hz, 1 H), 7.27–7.36 (m, 5 H); IR (film) 3050, 3020, 2940, 2880, 1645, 1490, 1450, 1390, 1250, 1085 cm^{-1}; MS (CI) *m/z* 337 (1.7, MH^+), 247 (100, OTMS), 217 (22), 193 (19), 192 (62), 187 (13), 145 (31), 91 (10), 73 (16); HRMS (CI) *m/z* (MH^+) calcd for $C_{17}H_{28}O_3Si_2$ 337.1655, obsd 337.1647.

(+)-(2*S*,3*R*,4*S*)-2-Phenyl-3,4-bis[(trimethylsilyl)oxy]-2,3-dihydro-4*H*-pyran (25). Diol (+)-**40** (192 mg, 1.00 mmol) was treated with TMS-imidazole (352 μL, 2.40 mmol), just as for the antipode (−)-**40** (vide supra), to give (+)-**25** (301 mg, 90%) as a clear, colorless oil: $[\alpha]^{21}_D$ +69.4° (*c* 1.25, $CHCl_3$); this compound displayed ^1H NMR, IR, and mass spectra identical to those of (−)-**25**. Anal. Calcd for $C_{17}H_{28}O_3Si_2$: C, 60.67; H, 8.38. Found: C, 60.47; H, 8.18.

(−)-(2*R*,3*R*,4*R*)-3,4-Dihydroxy-2-methyl-2,3-dihydro-4*H*-pyran (D-Fucal) (41). To a solution of diacetate (−)-**21** (500 mg, 2.34 mmol) in MeOH (20 mL) was added K_2CO_3 (194 mg, 1.40 mmol). The reaction mixture was stirred at room temperature for 2 h and then concentrated in vacuo and chromatographed (5% MeOH/CH_2Cl_2) to yield (−)-**41** (280 mg, 92%) as a white solid: mp 72–73 °C; $[\alpha]^{21}_D$ −18.9° (*c* 1.25, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.34–1.37 (d, *J* = 6.6 Hz, 3 H), 2.2–2.4 (br d, *J* = 6.9 Hz, 1 H), 2.5–2.65 (br s, 1 H), 3.65–3.75 (m, 1 H), 3.97–4.05 (q, *J* = 6.6 Hz, 1 H), 4.28–4.42 (m, 1 H), 4.64–4.68 (d, *J* = 6.2 Hz, 1 H), 6.34–6.36 (d, *J* = 6.2 Hz, 1 H); IR ($CHCl_3$) 3550, 3430, 3010, 2940, 1645, 1405, 1385, 1200, 1090, 1065 cm^{-1}; MS (FAB, 3-NOBA) *m/z* 131 (100, MH^+), 113 (67, OH), 95 (17), 85 (6), 69 (8). Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.74. Found: C, 55.09; H, 7.81.

(−)-(2*R*,3*S*,4*R*)-2-Methyl-3,4-bis[(trimethylsilyl)oxy]-2,3-dihydro-4*H*-pyran (3,4-Bis(trimethylsilyl)-D-fucal) (26). To a solution of diol (−)-**41** (235 mg, 1.81 mmol) in CH_2Cl_2 (13 mL) was added TMS-imidazole (637 μL, 4.34 mmol), and after 5 h a second portion was added (239 μL, 1.63 mmol). After a total of 6 h, the solvent was removed in vacuo, and the residue was chromatographed directly (5% Et_2O/hexane) to give (−)-**26** (447 mg, 90%) as a clear, colorless oil: $[\alpha]^{21}_D$ −39.2° (*c* 1.59, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.135 (s, 9 H), 0.145 (s, 9 H), 1.25–1.27 (d, *J* = 6.5 Hz, 3 H), 3.64–3.65 (br d, *J* = 4.3 Hz, 1 H), 3.96–4.03 Hz (q, *J* = 6.5 Hz, 1 H), 4.38–4.40 (m, 1 H), 4.47–4.51 (app dt, *J* = 1.8, 6.3 Hz, 1 H), 6.26–6.29 (dd, *J* = 1.8, 6.3 Hz, 1 H); IR (film) 3060, 2950, 2880, 1645, 1395, 1370, 1250, 1195, 1110 cm^{-1}; MS (FAB, 3-NOBA) *m/z* 274 (8, M^+), 273 (26), 259 (23, Me), 217 (86), 185 (100, OTMS), 169 (14). Anal. Calcd for $C_{12}H_{26}O_3Si_2$: C, 52.51; H, 9.55. Found: C, 52.67; H, 9.87.

(2′*S*,3′*S*,4′*S*,5′*S*,6′*R*)-7-*O*-[2′-[3′-Iodo-6′-phenyl-4′,5′-bis[(trimethylsilyl)oxy]tetrahydropyranosyl]]daunomycinone (42). A suspension of (−)-**25** (132 mg, 0.393 mmol), daunomycinone (188 mg, 0.471 mmol), and 4-Å molecular sieve powder (100 mg) in CH_2Cl_2 (18 mL) was stirred for 1 h at room temperature and then for 0.5 h at 0 °C in the dark. Di-*syn*-collidinyliodonium perchlorate[2a] [I(*s*-coll)$_2$$ClO_4$, ca. 90%] (205 mg, 0.393 mmol) was added in one portion, and stirring continued for 1 h at 0 °C in the dark. The reaction mixture was diluted (10 mL CH_2Cl_2) and filtered (Celite). The filtrate was washed with 10% NaS_2O_3 (aqueous, 5 mL), saturated $CuSO_4$ (aqueous, 2 × 5 mL), and brine (5 mL), then dried ($MgSO_4$), filtered, and evaporated. Chromatography (25–35% EtOAc/hexane) gave a mixture of isomeric coupling products (238 mg, 70%) consisting of >90% **42** (as judged by ^1H NMR). [Desilylation was carried out on the mixture of isomers to give a mixture of the corresponding isomeric triols, which could be separated by flash chromatography (vide infra)]. **42**: ^1H NMR (250 MHz, $CDCl_3$) δ 0.298 (s, 9 H), 0.126 (s, 9 H), 1.83–1.90 (dd, *J* = 3.5, 15 Hz, 1 H), 2.40 (s, 3 H), 2.40–2.46 (m, 1 H), 2.98–3.06 (d, *J* = 9.4 Hz, 1 H), 3.17–3.24 (d, *J* = 9.4 Hz, 1 H), 3.34–3.38 (dd, *J* = 3.3, 4.5 Hz, 1 H), 3.77 (br s, 1 H), 4.04–4.06 (d, *J* = 4.7 Hz, 1 H), 4.09 (s, 3 H), 4.59 (s, 1 H), 5.02 (br s, 1 H), 5.46–5.48 (app t, *J* = 2.6 Hz, 1 H), 5.96 (br s, 1 H), 6.95–7.22 (m, 5 H), 7.33–7.37 (d, *J* = 8 Hz, 1 H), 7.70–7.76 (app t, *J* = 8 Hz, 1 H), 7.92–7.95 (m, 1 H), 13.13 (s, 1 H), 13.99 (s, 1 H).

(2′*S*,3′*S*,4′*S*,5′*R*,6′*R*)-7-*O*-[2′-(4′,5′-Dihydroxy-3′-iodo-6′-phenyltetrahydropyranosyl)]daunomycinone (23). To a solution of **42** (and isomeric bisTMS ethers) (115 mg, 0.134 mmol) in THF (12 mL) at 0 °C was added HF–pyridine (600 μL). The reaction mixture was allowed to slowly reach room temperature. After 9 h, the reaction mixture was diluted with CH_2Cl_2 (75 mL) and quenched with $NaHCO_3$ (aqueous, 50 mL). The aqueous layer was extracted once more with CH_2Cl_2 (75 mL), and the combined organic layers were washed with saturated $CuSO_4$ (aqueous, 75 mL) and brine (75 mL). After the solvent was dried ($MgSO_4$), filtered, and evaporated in vacuo, the product mixture was chromatographed (0.5–1.5% MeOH/CH_2Cl_2) to give **23** (68.0 mg, 71%) as an orange powder. Later fractions contained the 2′*S*,3′*R* (daunomycinone axial, iodine equatorial) isomer (~5 mg, 5%) [^1H NMR (250 MHz, $CDCl_3$) anomeric proton δ 5.62–5.63 (d, *J* = 3.4 Hz)] and the 2′*R*,3′*R* (daunomycinone equatorial, iodine equatorial) isomer (~2 mg, 2%) [^1H NMR (250 MHz, $CDCl_3$) anomeric proton δ 5.27–5.30 (d, *J* = 8.3 Hz)], respectively. **23** gave orange needles from EtOAc/CCl_4 (see crystal structure in text): mp 191 °C dec; $[\alpha]^{22}_D$ +124° (*c* 0.080, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.67–1.71 (d, *J* = 8.7 Hz, 1 H), 1.93–2.00 (dd, *J* = 3.5, 15 Hz, 1 H), 2.38 (s, 3 H), 2.45–2.51 (br d, *J* = 15 Hz, 1 H), 2.76–2.80 (d, *J* = 11 Hz, 1 H), 3.02–3.09 (d, *J* = 19 Hz, 1 H), 3.18–3.26 (d, *J* = 19 Hz, 1 H), 3.43–3.49 (m, 1 H), 4.00–4.04 (ddd, *J* = 1.7, 3.3, 6.7 Hz, 1 H), 4.10 (s, 3 H), 4.31 (s, 1 H), 4.37–4.39 (d, *J* = 4.8 Hz, 1 H), 5.23 (br s, 1 H), 5.53–5.56 (m, 1 H), 6.02 (br s, 1 H), 7.03–7.28 (m, 5 H), 7.37–7.41 (d, *J* = 8.4 Hz, 1 H), 7.74–7.81 (app t, *J* = 8 Hz, 1 H), 7.96–7.99 (dd, *J* = 0.8, 7.5 Hz, 1 H), 13.14 (s, 1 H), 14.04 (s, 1 H); IR (KBr) 3200–3600 (br, OH), 2930, 2840, 1715, 1625, 1580, 1415, 1290, 1230, 1210 cm^{-1}; MS (FAB-NOBA/NaI) *m/z* 739 (2.2, MNa^+), 7.16 (2.9 M^+), 329 (24), 321 (22), 307 (100), 289 (53), 176 (62); HRMS (FAB, 3-NOBA/NaI) *m/z* (MNa^+) calcd for $C_{32}H_{29}O_{11}INa$ 739.0652, obsd 739.0672. Anal. Calcd for $C_{32}H_{29}O_{11}I$: C, 53.64; H, 4.08. Found: C, 53.68; H, 4.02.

(2′*R*,3′*R*,4′*R*,5′*R*,6′*S*)-7-*O*-[2′-[3′-Iodo-6′-phenyl-4′,5′-bis[(trimethylsilyl)oxy]tetrahydropyranosyl]]daunomycinone (43). A suspension of (+)-**25** (252 mg, 0.750 mmol), daunomycinone (358 mg, 0.900 mmol), and 4-Å molecular sieve powder (310 mg) in CH_2Cl_2 (34 mL) was treated with I(*s*-coll)$_2$$ClO_4$[2a] (390 mg, 0.750 mmol) in the same manner as for (−)-**25** (vide supra) to give a mixture of isomeric coupling products (412 mg, 64%) containing >90% **43** (by ^1H NMR). **43**: ^1H NMR (250 MHz, $CDCl_3$) δ −0.237 (s, 9 H), 0.113 (s, 9 H), 1.88–1.96 (dd, *J* = 4.2, 1.5 Hz, 1 H), 2.24–2.31 (br d, *J* = 15 Hz, 1 H), 2.31 (s, 3 H), 2.91–2.98 (d, *J* = 19 Hz, 1 H), 3.13–3.21 (dd, *J* = 1.5, 19 Hz, 1 H), 3.32–3.35 (dd, *J* = 3.2, 4.8 Hz, 1 H), 3.92–3.93 (d, *J* = 1.5 Hz, 1 H), 4.08 (s, 3 H), 4.14–4.16 (d, *J* = 4.8 Hz, 1 H), 4.59 (s, 1 H), 5.10 (br s, 1 H), 5.25–5.26 (br d, *J* = 2.1 Hz, 1 H), 6.14 (br s, 1 H), 7.28–7.43 (m, 6 H), 7.74–7.80 (app t, *J* = 8 Hz, 1 H), 7.99–8.02 (dd, *J* = 0.9, 8 Hz, 1 H), 13.24 (s, 1 H), 13.95 (s, 1 H).

(2′*R*,3′*R*,4′*R*,5′*S*,6′*S*)-7-*O*-[2′-(4′,5′-Dihydroxy-3′-iodo-6′-phenyltetrahydropyranosyl)]daunomycinone (22). A solution of **43** (and isomeric coupling products) (341 mg, 0.400 mmol) in THF (34 mL) was desilylated with HF–pyridine (1.8 mL) as for **42** above (11 h total). Chromatography yielded **22** (229 mg, 81%) as an orange powder. Later fractions contained the 2′*R*,3′*S* (daunomycinone axial, iodine equatorial) isomer (~10 mg, 4%) [^1H NMR (250 MHz, $CDCl_3$) anomeric proton δ 5.80–5.81 (d, *J* = 3.5 Hz)] and the 2′*S*,3′*S* (daunomycinone equatorial, iodine equatorial) isomer (~5 mg, 2%) [^1H NMR (250 MHz, $CDCl_3$) anomeric proton δ 5.22–5.25 (d, *J* = 8.0 Hz)], respectively. **22** gave orange needles from EtOAc/hexane (see crystal structure in text): mp 201 °C; $[\alpha]^{22}_D$ −123° (*c* 0.080, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.78–1.81 (d, *J* = 8.8 Hz, 1 H), 1.98–2.06 (dd, *J* = 4.4, 15 Hz, 1 H), 2.22–2.27 (br d, 1 H), 2.27 (s, 3 H), 2.73–2.78 (d, *J* = 11 Hz, 1 H), 2.93–3.00 (d, *J* = 19 Hz, 1 H), 3.16–3.24 (dd, *J* = 1.3, 19 Hz, 1 H), 3.41–3.48 (m, 1 H), 4.03 (s, 1 H), 4.10 (s, 3 H), 4.10–4.16 (m, 1 H), 4.45–4.47 (d, *J* = 4.8 Hz, 1 H), 5.28–5.29 (br d, *J* = 2.5 Hz, 1 H), 5.31 (d, *J* = 1.0 Hz, 1 H), 6.17 (br s, 1 H), 7.34–7.43 (m, 6 H), 7.76–7.83 (app t, *J* = 8 Hz, 1 H), 8.03–8.06 (dd, *J* = 0.8, 8 Hz, 1 H), 13.27 (s, 1 H), 14.06 (s, 1 H); IR (KBr) 3200–3600 (br, OH), 2930, 1715, 1620, 1580, 1415, 1285, 1235, 1210, 1000 cm^{-1}; MS (FAB-NOBA/NaI) *m/z* 739 (8.3, MNa^+), 381 (30), 321 (16), 307 (22), 289 (14), 176 (100). Anal. Calcd for $C_{32}H_{29}O_{11}I$: C, 53.64; H, 4.08. Found: C, 53.33; H, 3.90.

7-*O*-[2′,6′-Dideoxy-2′-iodo-3′,4′-bis[(trimethylsilyl)oxy]-α-D-talopyranosyl]daunomycinone (44). A suspension of (−)-**26** (300 mg, 1.09 mmol), daunomycinone (523 mg, 1.31 mmol), and 4-Å molecular sieve powder

(450 mg) in CH_2Cl_2 (50 mL) was treated with $I(s\text{-coll})_2ClO_4$[2a] (570 mg, 1.09 mmol) in the same manner as for (−)-**25** (vide supra) to give a mixture of isomeric coupling products (358 mg, 41%) containing >90% **44** (by ^1H NMR). **44**: ^1H NMR (250 MHz, $CDCl_3$) δ 0.127 (s, 9 H), 0.135 (s, 9 H), 1.24–1.27 (d, J = 6.5 Hz, 3 H), 1.88–1.95 (dd, J = 3.5, 15 Hz, 1 H), 2.41 (s, 3 H), 2.41–2.46 (br d, J = 15 Hz, 1 H), 2.99–3.06 (d, J = 19 Hz, 1 H), 3.19–3.27 (dd, J = 0.9, 19 Hz, 1 H), 3.4–3.5 (m, 1 H), 3.66–3.69 (app t, J = 2.8 Hz, 1 H), 3.97–4.00 (app t, J = 3.6 Hz, 1 H), 4.08 (s, 3 H), 4.22–4.30 (m, 1 H), 4.55 (br s, 1 H), 5.51–5.53 (m, 1 H), 5.65–5.66 (br d, J = 2.9 Hz, 1 H), 7.37–7.40 (d, J = 8.5 Hz, 1 H), 7.74–7.81 (app t, J = 8 Hz, 1 H), 8.01–8.04 (dd, J = 0.9, 7 Hz, 1 H), 13.27 (s, 1 H), 14.08 (s, 1 H).

7-*O*-(2′,6′-Dideoxy-2′-iodo-α-D-talopyranosyl)daunomycinone (24). A solution of **44** (and isomeric coupling products) (298 mg, 0.373 mmol) in THF (34 mL) was desilylated with HF–pyridine (1.7 mL) as for **42** above (18 h total). Chromatography (1–4% MeOH/CH_2Cl_2) gave **24** (195 mg, 80%) as a red glass. A later fraction contained the corresponding α-D-galacto-pyranosyl (daunomycinone equatorial, iodine equatorial) isomer (~3 mg, 1%) [^1H NMR (250 MHz, $CDCl_3$) anomeric proton δ 5.02–5.06 (d, J = 8.6 Hz)]. **24**: $[\alpha]^{22}_D$ +301° (*c* 0.095, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.31–1.34 (d, J = 6.6 Hz, 3 H), 1.84–1.89 (d, J = 11 Hz, 1 H), 1.93–2.00 (dd, J = 3.6, 15 Hz, 1 H), 2.39 (s, 3 H), 2.39–2.45 (br d, 1 H), 2.73–2.77 (d, J = 10 Hz, 1 H), 2.98–3.06 (d, J = 19 Hz, 1 H), 3.21–3.29 (br d, J = 19 Hz, 1 H), 3.27–3.35 (m, 1 H), 3.73–3.78 (dd, J = 1.8, 11 Hz, 1 H), 4.09 (s, 3 H), 4.26 (s, 1 H), 4.27–4.29 (d, J = 4.9 Hz, 1 H), 4.48–4.58 (br q, J = 6.6 Hz, 1 H), 5.52–5.54 (m, 1 H), 5.74 (br s, 1 H), 7.38–7.42 (d, J = 8.5 Hz 1 H), 7.76–7.82 (app t, J = 8 Hz, 1 H), 8.02–8.06 (dd, J = 0.8, 7.4 Hz, 1 H), 13.27 (s, 1 H), 14.14 (s, 1 H); IR (KBr) 3150–3600 (br, OH), 2980, 2940, 1715, 1620, 1580, 1415, 1385, 1355, 1290, 1240, 1215, 1000 cm^{-1}; MS (FAB-NOBA/NaI) *m/z* 677 (4.8, MNa^+), 654 (3.8, M^+), 321 (40), 307 (100), 289 (49), 176 (58); HRMS (FAB-NOBA/NaI) *m/z* (MNa^+) calcd for $C_{27}H_{27}O_{11}INa$ 677.0496, obsd 677.0519. Anal. Calcd for $C_{27}H_{27}O_{11}I$: C, 49.56; H, 4.16. Found: C, 49.20; H, 4.17.

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Registry No. (*E*,*E*)-**1**, 91861-09-5; (*Z*,*E*)-**1**, 91861-07-3; (*Z*,*Z*)-**1**, 91861-08-4; **2**, 138407-61-1; (±)-**2**, 138512-00-2; **3**, 138407-62-2; (±)-**3**, 138512-01-3; **4**, 104130-24-7; (±)-**4**, 138512-02-4; **5**, 138407-63-3; **6**, 138512-03-5; **7**, 138407-64-4; **8**, 138407-65-5; **9**, 138407-66-6; **10**, 138407-67-7; **11**, 138407-68-8; **12**, 138407-69-9; **13**, 138407-70-2; **14**, 138407-71-3; **15**, 138407-72-4; **16**, 138407-73-5; **17** (isomer 1), 138513-31-2; **17** (isomer 2), 138407-74-6; **18a**, 138407-75-7; **18b**, 138407-76-8; **19**, 138407-77-9; (−)-**21**, 75829-69-5; (+)-**21**, 54621-94-2; **22**, 138407-78-0; **23**, 138512-04-6; **24**, 138512-05-7; (−)-**25**, 138432-66-3; (+)-**25**, 138407-79-1; **26**, 138512-06-8; **27**, 138512-07-9; **28**, 138512-08-0; **29**, 104069-03-6; (±)-**29**, 138512-09-1; **30**, 95475-50-6; (±)-**30**, 138512-10-4; **31**, 76739-66-7; **32**, 138512-11-5; (±)-**32**, 138512-12-6; **33**, 109278-72-0; **34**, 138512-13-7; (±)-**34**, 138512-14-8; **35**, 106930-36-3; **36**, 138407-80-4; **37**, 138407-81-5; **38**, 138512-15-9; **39**, 138407-82-6; (−)-**40**, 138512-16-0; (+)-**40**, 138512-17-1; **41**, 134355-03-6; **42**, 138407-83-7; **43**, 138512-18-2; **44**, 138407-84-8; (±)-(2*R**,4*S**)-4-hydroxy-2-methyl-2,3-dihydro-4*H*-pyran, 80754-66-1.

Supplementary Material Available: Tables of fractional coordinates, bond distances, torsional angles, anisotropic temperature factors, and summaries of the X-ray crystallographic determinations for compounds **22** and **23** (38 pages). Ordering information is given on any current masthead page.

Synthetic Replicators and Extrabiotic Chemistry

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Abstract: Synthetic replicators can be generated by covalent attachment of two complementary structures to form a self-complementary molecule. The complementarity refers to sizes, shapes, and the weak, intermolecular forces that characterize molecular recognition phenomena. New self-complementary structures were obtained by coupling imides to synthetic receptors for imides, and their properties as replicators were explored. The new structures use hydrogen bonding of thymine derivatives to diaminotriazines as the recognition vehicle, and autocatalytic behavior is experimentally demonstrated during the covalent coupling step. Self-complementarity and molecular aggregation are discussed in terms of orientation of recognition surfaces with respect to one another. The development of other replicating systems based on alternative binding forces is discussed. The term *extrabiotic* is proposed for synthetic systems which exhibit lifelike behavior.

Synthetic replicators are at the interface of chemistry and biology, and they provide a means by which lifelike molecular behavior can be expressed in model systems. A recent example involves the coupling of adenine derivatives to suitably constructed imides.[1] Such systems can show sigmoidal growth,[2] reciprocity, and even mutation[3]—features characteristic of evolution at the molecular level. Here we present a new system based on thymine derivatives and propose that self-replicating molecules are a reasonable, perhaps inevitable, consequence of molecular recognition.

Self-complementarity represents the key feature of minimalist replicators,[4] and we have been much influenced by biological structures that show such properties. Most relevant are palindromic sequences of nucleic acids which can dimerize into double-stranded forms. However, the self-complementarity feature is so *economical* that a number of biological structures use it to advantage. For example, multisubunit enzymes, clathryn triskelions, and viral capsid proteins fit together in a 3-dimensional array; their subunits are self-complementary.[5]

Systems of manageable size for studies in solution that share this feature can be prepared by covalent coupling of two complementary fragments into a single unit. In this context, complementary refers to size, shape, and the weak intermolecular forces that characterize molecular recognition phenomena. The

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