room temperature under a current of nitrogen. The reaction mixture was then stirred for 1 h and poured into water (10 mL); isolation of the product by ether extraction gave the mesylate (186 mg). $BH_3$–THF complex (1.0 mL, 1.0 mmol) was added dropwise to a stirred solution of the mesylate in anhydrous tetrahydrofuran (3 mL) under a current of nitrogen at room temperature. After the reaction mixture was stirred for 2 h, 10% aqueous sodium hydroxide (0.5 mL) and 30% hydrogen peroxide (0.7 mL) were added; the resulting solution was further stirred for 20 min at the same temperature and diluted with ethyl acetate (20 mL). The organic layer was washed with brine and dried over $Na_2SO_4$. Evaporation of the solvent gave the 6-hydroxy compound (190 mg) whose solution in dichloromethane (8 mL) was treated with pyridinium chlorochromate (150 mg, 0.8 mmol) for 2 h at room temperature. The reaction mixture was diluted with ether (20 mL), and the organic layer was washed with brine and dried over $Na_2SO_4$. Evaporation of the solvent gave the 6-oxo compound **30** (153 mg), whose solution in *N,N*-dimethylformamide (3 mL) was treated with lithium bromide (54 mg, 0.51 mmol) for 1 h at 130 °C. The reaction mixture was poured into water (10 mL) and isolation of the product by ether extraction gave the residue which was purified by chromatography on silica gel (4 g) using dichloromethane as the eluant to give the 2-en-6-oxo compound **31** (95 mg, 63%) as colorless needles: mp 181–182 °C (MeOH), $[\alpha]_D$ +0.9° ($c$ = 0.21, $CHCl_3$), IR ($CHCl_3$) 1710 $cm^{-1}$, $^1H$ NMR (100 MHz) $\delta$ 0.70 (3 H, s, 18-$H_3$), 0.71 (3 H, s, 19-$H_3$), 1.34 (3 H, s, acetonide), 1.37 (3 H, s, acetonide), 3.73–4.08 (2 H, m, 22-H and 23-H), 5.40–5.80 (2 H, m, 2-H and 3-H). MS $m/z$ 470 ($M^+$). Anal. Calcd for $C_{30}H_{46}O_4$: 470.3759. Found: 470.3754.

**(22*S*,23*S*,24*R*)-2α,3α,22,23-Tetrahydroxy-5α-ergostan-6-one (32).** Osmium tetraoxide (7.5 mg, 0.03 mmol) in tetrahydrofuran (0.075 mL) was added dropwise to a stirred solution of the 2-ene-6-oxo compound **31** (75 mg, 0.16 mmol) in *tert*-butyl alcohol–tetrahydrofuran–water (10:8:1 v/v) (5 mL) containing *N*-methylmorpholine *N*-oxide (56.3 mg, 0.48 mmol) at room temperature. After 3 h at the same temperature, saturated aqueous sodium hydrogen sulfide (5 mL) was added to the reaction mixture and isolation of the product by ethyl acetate gave the diol (78 mg), whose solution in 80% aqueous acetic acid (2.7 mL) was refluxed for 3 h. After cooling, the reaction mixture was diluted with ethyl acetate (10 mL); and organic layer was washed with aqueous sodium bicarbonate solution and brine, and dried over $Na_2SO_4$. Evaporation of the solvent gave a white solid, which was purified by chromatography on silica gel (2 g) using chloroform containing 5% methanol as the eluant to give the tetraol **32** (62 mg, 84%) as colorless needles: mp 184–185 °C (EtOAc) (lit.[13,14] 184–185 °C; lit.[15] 182–183 °C). Its spectroscopic data were identical with those reported.

**Acknowledgment.** We are indebted to Professor N. Ikekawa, Tokyo Institute of Technology, for providing the NMR spectrum of **23**. A part of this work was financially supported by a grant-in-aid from the Ministry of Education, Science and Culture, Japan, and from the Sendai Institute of Heterocyclic Chemistry, which we gratefully acknowledge.

**Registry No. 2**, 145-13-1; **3**, 104336-29-0; **3** (Ts salt), 104336-30-3; **4**, 104336-32-5; **5**, 104336-31-4; **6**, 95042-54-9; **7**, 95042-55-0; **8**, 1522-46-9; **9**, 104336-33-6; **10**, 32249-55-1; **11a**, 104336-34-7; **11b**, 104336-35-8; **12a**, 104336-36-9; **12b**, 104336-37-0; **13a**, 104336-38-1; **13b**, 104336-39-2; **14**, 104336-40-5; **15**, 104336-41-6; **16**, 104336-42-7; **17**, 104336-43-8; **17** (mesylate), 104336-44-9; **18**, 104336-45-0; **19**, 104336-46-1; **19** (3β,22-diol), 104336-47-2; **20**, 90095-32-2; **21**, 85707-12-6; **23**, 104336-48-3; **24**, 104418-95-3; **25**, 104418-96-4; **26**, 104418-97-5; **27**, 104418-98-6; **28**, 104418-99-7; **29**, 104419-00-3; **29** (mesylate), 104419-01-4; **29** (6-hydroxymesylate), 104419-02-5; **30**, 104419-60-5; **31**, 104419-03-6; **31** (diol), 104336-49-4; **32**, 72050-69-2; 5-lithio-2-methoxyfuran, 104336-28-9.

# Interactivity of Chiral Catalysts and Chiral Auxiliaries in the Cycloaddition of Activated Dienes with Aldehydes: A Synthesis of L-Glucose

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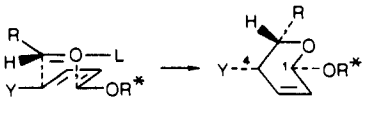
**Abstract:** $Eu(fod)_3$ and $Eu(hfc)_3$ catalyze the cycloaddition of a variety of aldehydes with oxygenated highly substituted butadienes. With achiral dienes, (+)-$Eu(hfc)_3$ shows only modest enantiofacial selectivities. Similarly, modest selectivities were observed in the reactions of several chiral dienes with aldehydes in the presence of the achiral $Eu(fod)_3$. However, the combination of chiral dienes with chiral (+)-$Eu(hfc)_3$ catalyst exhibited striking interactivities, resulting in some instances in diastereofacial excesses of 95%. Of the systems examined, only those dienes whose intrinsic facial selectivities are small and opposite in direction to that of the (+)-$Eu(hfc)_3$ catalyst exhibit useful interactivity of the two chiral components. Thus, the diastereomeric excesses observed here do not arise from strictly numerical factoring of componental preferences (simple double diastereoselectivity) but are a consequence of a "specific interactivity", inherent in the process itself. Application of these findings to the synthesis of optically pure substituted pyrans, L-glycolipids, and L-glucose is described.

The Lewis acid catalyzed aldehyde–diene cyclocondensation reaction (eq 1) has emerged as a useful implement in organic synthesis.[1] It has been successfully applied to reach various targets of interest in the carbohydrate[2a] and polypropionate[2b] areas. The




(1)

range of aldehydes and dienes which have participated in the process and the high levels of topographic and diastereofacial control which can be realized by careful management of variables (substrates, solvents, catalysts, temperatures) add to the utility of the method. Another feature of the reaction, when it operates in the pericyclic pathway,[3] is its suprafacial character. If the

(1) Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, D. *J. Am. Chem. Soc.* **1985**, *107*, 1246 and references cited therein.

(2) For two recent examples, see: (a) Danishefsky, S.; Maring, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 1269. (b) Danishefsky, S.; Harvey, H. F. *J. Am. Chem. Soc.* **1985**, *107*, 6647.

(3) (a) Larson, E. R.; Danishefsky, S. *J. Am. Chem. Soc.* **1982**, *104*, 6458. (b) For the initial report on $Eu(fod)_3$ catalysis, see: Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716.

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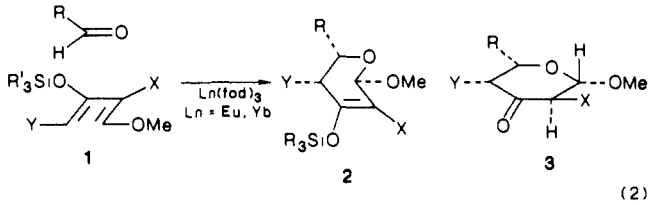
product of the process is viewed as a potential monosaccharide, this suprafaciality defines a connectivity between the trigonal stereochemistry of the diene and the $C_1$(glycoside)–$C_4$ relationship of the adduct (vide infra).

Given the biological activities of many of the goal systems available through this methodology, the importance of obtaining optically pure products can scarcely be exaggerated. From an efficiency standpoint, it would be desirable to reach this goal without recourse to resolution. The capacity to obtain optically pure (or highly enriched) products would also enhance the usefulness of the cyclocondensation reaction for producing chiral subunits which would be combined to synthesize larger chiral arrays. The practicality of such a "batching" strategy is critically dependent on the feasibility of obtaining subunits of reasonable enantiomeric purity.

This objective could be addressed by the use of aldehydes which might be available in the required enantiomeric sense. The attractiveness of this approach depends on the accessibility of the aldehyde in question and on the quality of transmission of stereochemical "information" from the chiral aldehyde to the emerging pyran. Indeed, several syntheses of optically pure products have been achieved in this fashion in our program.[4] The research described herein concerned itself with two other approaches. One involved the use of enantiomerically homogeneous auxiliaries installed in the 1-alkoxy group of the diene. The other focused on the use of enantiomeric homogenous Lewis acid catalysts. As matters transpired, considerable progress was attained by combining these chiral elements.

## Results

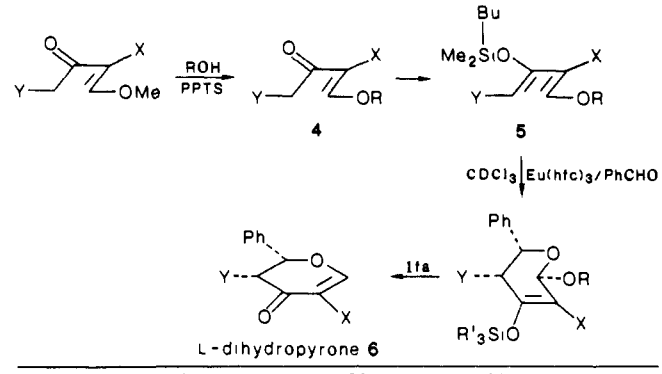
The first step in the discovery process[3b] was the finding that soluble lanthanide complexes such as $Eu(fod)_3$[5a] and $Yb(fod)_3$[5b] catalyze the cycloaddition reactions of activated dienes with a range of aldehydes. The advantage of this novel type of Lewis acid catalyst, for the goals set forth herein, is that it allows for ready isolation of the labile primary cycloadducts of the type **2**. These compounds can in turn be converted ($Et_3N$/MeOH) to ketonic methyl glycosides such as **3** (cf. eq 2).




(2)

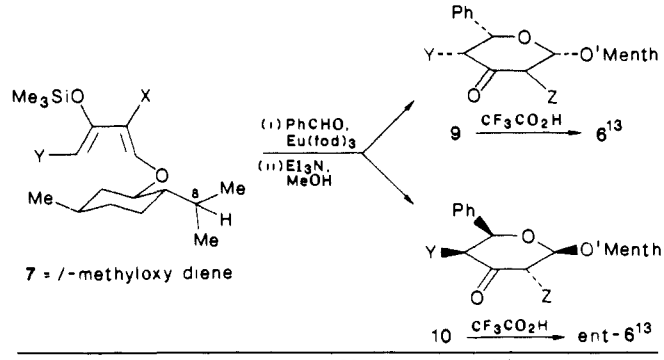
The efficacy of using lanthanide metals attached to resolved chiral ligands to promote enantiotopic selectivity in the cycloaddition reaction was examined.[3b] Commerically available (+)-$Eu(hfc)_3$,[6] used as an optical shift reagent in NMR spectroscopy,[7] was screened in several cycloaddition reactions. In the initial studies, the dienes all had 1-methoxy substituents as shown in system 1. While it was gratifying to find that (+)-$Eu(hfc)_3$ indeed functioned as a catalytic device for inducing enantiotopic preference in carbon–carbon bond-forming reactions, the magnitudes of the enrichments were modest.[8a] It seemed possible

Table I. Ratio of L-Dihydropyrone **6**/D-Dihydropyrone ent-**6** for the Reaction of Diene **5** with Benzaldehyde. Catalyst, (+)-$Eu(hfc)_3$; Solvent, $CDCl_3$ (R = *tert*-Butyl)




| X | Y | 6/ent-6 |
|---|---|---|
| (a) H | H | 69/31 |
| (b) Me | H | 70/30 |
| (c) Me | Me | 71/29 |
| (d) OAc | H | 66/32 |
| (e) $OSiMe_3$ | H | 71/29 |

Table II. Ratios of L-Pyranose **9**/D-Pyranose **10** from the Reaction of *l*-Menthyloxy Dienes **7a–d** with Benzaldehyde. Catalyst, $Eu(fod)_3$; Solvent, $CDCl_3$




| X | Y | 9/10 |
|---|---|---|
| (a) H | H | 33/67 |
| (b) Me | H | 45/55 |
| (c) OAc | H | 45/55 |
| (d) Me | Me | 49/51 |

that the extent of enantiotopic preference might be a function of the substitution pattern of the diene and of the nature of the alkoxy group at $C_1$. A vinylogous trans esterification reaction was de-

(4) Danishefsky, S.; Kobayashi, S.; Kerwin, J. F., Jr. *J. Org. Chem.* **1982**, *47*, 1981.

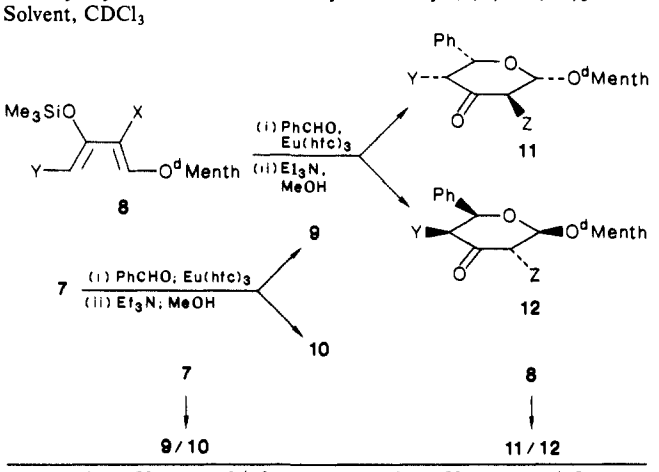
(5) (a) This is the trade name for tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III). (b) This is the trade name for tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium(III).

(6) Both antipodes of $Eu(hfc)_3$ are now commercially available from Aldrich: (+)-$Eu(hfc)_3$ is a tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) derivative; (−)-$Eu(hfc)_3$ is a tris[3-(heptafluoropropylhydroxymethylene)-(−)-camphorato]europium(III) derivative.

(7) For an excellent study of the effectiveness of various chiral lanthanide complexes as shift reagents see: McCreary, M.; Lewis, D.; Wernick, D. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 1038 and references cited therein.

(8) (a) General protocol for the determination of enantiomeric enrichments is as follows: Dihydropyrone **6** (ca. 117 mg, 0.68 mmol) was dissolved in methanol (7 mL), cooled to −78 °C, and treated with ozone in oxygen for 2 min. Excess ozone was removed by purging with dry $N_2$ at −78 °C. The solution was next treated with 30% hydrogen peroxide (320 μL, 2.7 mmol) and solid potassium hydroxide (80 mg, 1.36 mmol) and stirred at room temperature for 2.5 h. The mixture was diluted with brine (4 mL), acidified with dilute $H_2SO_4$ until pH 4, and extracted with ethyl acetate (4 × 1 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude material was chromatographed on silica gel to give *erythro*-2-methyl-3-phenyl-3-hydroxybutanoic acid. The optical rotation of this acid was recorded and compared to known values. The acid was next dissolved in $Et_2O$ (2 mL), and a solution of diazomethane in $Et_2O$ was added dropwise until a yellow color persisted. The solution was stirred for 0.5 h at room temperature; then the mixture was concentrated in vacuo. The residual oil was purified by chromatography on silica gel to give the known hydroxy methyl ester (ca. 63 mg). NMR shift studies ((+)-$Eu(hfc)_3$/$CDCl_3$) were carried out on this methyl ester. Resolution of the "enantiomeric" methyl singlets of the ester was observed, with the predominantly *R* enantiomer (L-pyrone) at lower field relative to its *S* counterpart (D-pyrone). (b) The terms D- and L-pyrone stem from the absolute stereochemistry at $C_5$ (sugar numbering) and anticipate the transformation of the oxygen heterocycle to a sugar by the conversion of the $C_6$ substituent to a hydroxy methyl group. (c) The absolute configuration of these acid esters have been previously established, see: (i) Cohen, S. G.; Winstein, S. Y. *J. Am. Chem. Soc.* **1964**, *86*, 725. (ii) Evans, D. A.; Taber, T. R. *Tetrahedron Lett.* **1980**, *21*, 4675. (iii) Evans, D. A.; Bartoli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

Table III. Ratios of D- and L-Pyranosides from the Reaction of Menthyloxy Dienes with Benzaldehyde. Catalyst, (+)-Eu(hfc)$_3$; Solvent, $CDCl_3$




| 7 | X | Y | 9/10 | 8 | X | Y | 11/12 |
|---|---|---|---|---|---|---|---|
| a | H | H | 75/25 (37/63) | a | H | H | 63/37 (63/37) |
| b | Me | H | 92/8 (45/55) | b | Me | H | 59/41 (55/45) |
| c | OAc | H | 93/7 (45/55) | c | OAc | H | 59/41 (55/45) |
| d | Me | Me | 87/13 (49/51) | d | Me | Me | 51/49 (51/49) |

veloped to allow for the introduction of a variety of alkoxy groups by exchange of a general alcohol, ROH, with the methoxy group of $\beta$-methoxyenones.[9] Enol silylation of the enones of the type **4**[10] produced the corresponding dienes **5**. Some improvement in enantiotopic preferences was realized by the use of larger alkoxy groups. The results with diene **5** (wherein R = *tert*-butyl) and benzaldehyde as the heterodienophile are shown in Table I.[11] While the enantiomeric enrichment (ee) was still not synthetically useful, there was noted a consistency, in that the commercially available (+)-Eu(hfc)$_3$ using D-camphorato ligands produced, in each case, an excess of L-dihydropyrone **6**.[8b]

Among the dienes which were synthesized via the exchange sequence were those bearing the enantiomeric *l* and *d*-menthyloxy groups **7** and **8**, respectively.[9] It was of interest to determine the efficacy of the chiral auxiliaries in expressing a diastereofacial preference in the cyclocondensation reaction.[12] To provide a basis figure for the inherent facial selectivity of the dissymmetric auxiliary, Eu(fod)$_3$[5a] bearing achiral ligands was employed as the lanthanide catalyst. The data in Table II reveal only modest preferences in the reactions of *l*-menthyloxy dienes **7a–d** with benzaldehyde. In each case the "principal" product was the D-pyranose[8b] **10**. Given the nearly equal formation of **9** and **10**, the significance of this apparent consistency is open to serious question.

For purposes of checking the consistency of the spectroscopic and degradative protocols used to establish the stereochemistry of the products,[8a] the same chemistry was carried out with the enantiomeric auxiliaries **8a–d** (**8** = ent-**7**). It need hardly occasion surprise that the ratios of L-pyranose derivative **11**/D-pyranose **12** (vide infra) were equal but opposite to those of the antipodal products **9** and **10** for corresponding X and Y substituents.

The next phase of the inquiry involved the study of the efficacy of combining a chiral catalyst, Eu(hfc)$_3$, with chiral diene **7** or **8**. Cycloadditions with benzaldehyde were carried out in $CDCl_3$. *A remarkable result was noted.* When the modestly L-selective diene **8** (see Table II for data on **7** which is ent-**8**) was used with the modestly L-selective (+)-Eu(hfc)$_3$ catalyst, meager ratios favoring L-pyranose were obtained. However, the combination of (+)-Eu(hfc)$_3$ with the modestly D-selective diene **7** provided substantial diastereotopic preferences for L-pyranose **9**/D-pyranose **10**.[8b] The results are given in Table III. The data in parentheses represent the "inherent" facial selectivities as derived from Table II.

Several features present themselves upon examination of the data in Tables I–III. It is seen that the "mismatched"[14] set (i.e., L-selective (+)-Eu(hfc)$_3$ with D-selective diene) produced the highest diastereotopic ratios of L/D-pyranose derivatives. Clearly, the selectivity of the overall process is benefitting from a "specific interactivity" among the dissymmetry elements of the catalyst and the auxiliary. *This specific interactivity is reflected in the production of diastereomeric excesses which do not arise from strictly numerical factoring* of *componental preferences.*

The estimation of the magnitude of this interactivity can be no more reliable than is the pertinence of the "basis" models. Thus, the presumption that the reaction of *tert*-butoxydiene **5** with (+)-Eu(hfc)$_3$ and benzaldehyde as the heterodienophile serves as a realistic model for the inherent enantiotopic catalyst selectivity for the menthyloxydienes cannot be quantitatively evaluated. Similarly, the use of Eu(fod)$_3$ as an achiral catalyst to provide the basis information about the inherent diastereofacial selectivity of dienes **7** and **8** with (+)-Eu(hfc)$_3$ introduces additional elements of uncertainty. Even less ground exists for speculating on the structural factors which govern either the enantiotopic biases of the catalysts or the inherent diastereofacial selectivity of the auxiliary, let alone the remarkably specific interactivity of these two elements. These matters will surely receive continuing attention.

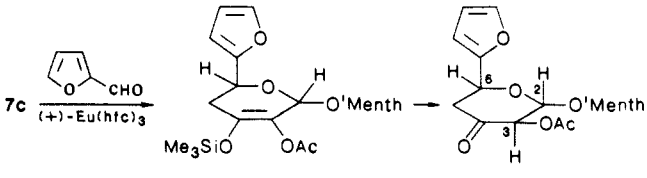
Nonetheless, while detailed interpretation is premature, a synthetically important result had been achieved. The introduction of an easily installed and easily retrieved auxiliary onto the diene, in concert with a catalytic quantity of commercially available lanthanide, allows for high diastereotopic excesses in the cycloaddition product. The major diastereomers bearing the auxiliaries can be readily purified either through direct crystallization or through chromatography. The enantiomerically pure dihydropyrones **6** and ent-**6** can be obtained either from the glycosides **9–12** or, more conveniently, directly from the silyl enol ether cycloadducts (cf. **23–24**) after treatment with tfa. The auxiliary is readily retrieved after this reaction.

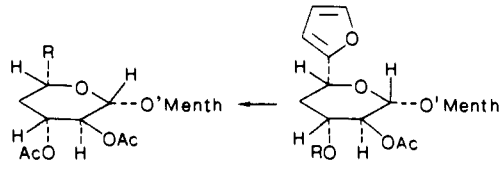
An application of this new methodology to the synthesis of a glycoside derivative of *l*-menthol was examined. Cyclocondensation of *l*-menthyloxy diene **7c** with furaldehyde in the presence of (+)-Eu(hfc)$_3$ followed by treatment with triethylamine in methanol afforded an excellent yield of *l*-menthyl glycoside. High-field NMR analysis indicated that this material was an 87/13 mixture of two products. The surmise was that both isomers arose from endo addition but differed only in the sense of the (D- or L-) pyranose component. On the basis rigorously proven precedents with benzaldehyde,[3b] the major component was formulated to be the L-glycoside derivative **14**, while the minor one was assigned as the D-sugar, **15**. One recrystallization produced a 75% yield of homogeneous **14**. Analysis of its high-field $^1H$ NMR spectrum establishes the acetoxy function to be equatorial, arising from axial protonation of the intermediate silyl enol ether. Reduction of the ketone with K-Selectride afforded the equatorial alcohol **16**. The connectivity between the nature and stereochemistry of anomeric centers and the sense of reduction of 4-pyranone derivatives has been the subject of a recent study in our laboratory.[15] The tendency toward formation of equatorial alcohol

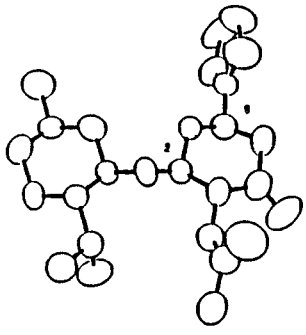
(9) Danishefsky, S.; Bednarski, M.; Izawa, T.; Maring, C. *J. Org. Chem.* **1984**, *49*, 2290.
(10) Emde, H.; Domsch, P.; Feger, H.; Gotz, H.; Hofmann, K.; Kober, W.; Krageloh, H.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, *1*.
(11) Bednarski, M.; Maring, C.; Danishefsky, S. *Tetrahedron Lett.* **1983**, *24*, 3451.
(12) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 6968.
(13) Compound **10d** would not convert to **6c** or ent-**6c** under tfa treatment. Thus, to obtain these pyrones one must cleave the silyl enol ether cycloadducts of the type **2** directly.
(14) Here we invoke the same term to address the individual tendencies of the chiral substrate and chiral catalyst. Cf. inter alia: (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (b) For an elegant use of double diastereoselectivity in total synthesis, see: Masamune, S.; Hirams, M.; Mori, S.; Ali, S. A.; Garvey, S. *J. Am. Chem. Soc.* **1981**, *103*, 1568. (c) Heathcock, C. H.; White, C. T. *J. Am. Chem. Soc.* **1979**, *101*, 7076. (d) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Marthre, D. J.; Bartroli, J. *Pure Appl. Chem.* **1981**, *53*, 1109. (e) Izumi, Y.; Tai, A *Stereodifferentiating Reaction*; Academic: New York, San Francisco, London, 1977; Chapter 8.
(15) Danishefsky, S.; Langer, M. E. *J. Org. Chem.* **1985**, *50*, 3672.

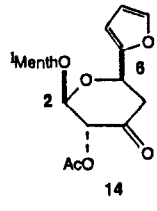
in the *cis*-methyl glycoside series is by now well precedented. Acetylation provided the diacetate **17**. Ozonolysis of the furan ring followed by oxidative workup afforded the acid **18**, best characterized as its methyl ester, **19**. Specific reduction of the carboxyl group of **18** was accomplished through the action of borane–THF. The resultant alcohol, upon acetylation, produced the triacetate **19**. This compound is seen to be an *l*-menthyl β-glycoside of peracetylated L-4-deoxyglucose. That the various stereochemical assignments are correct was established by an X-ray crystallographic determination of the triethylamine–methanol product **14**, as shown below.

It is seen that the new cycloaddition methodology leads to an L-glycolipid-type system without recourse to glycosylation or indeed to a carbohydrate building block. *The carbohydrate segment is created in a specific absolute configuration as part of the process itself.*[17]



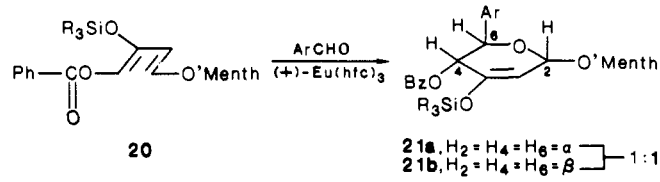






It is well to summarize the scope of the advance at this stage. Obviously, the use of the enantiomeric (−)-Eu(hfc)$_3$[6,18] along with the *d*-menthyl auxiliary would lead eventually to ent-**19** with the same selectivity as that manifested via the antipodal elements shown above. However, access to the D-glycoside of *l*-menthol or the L-glycoside of *d*-menthol would be possible only through the separation of a nearly 1:1 mixture of diastereomers (see entries in Table III for diene **8**). Another constraint to be noted is that, as a result of endo selectivity, only those glycosides with cis relationships between the anomeric oxygen and the side chain at position 5 (i.e., β-glycosides) are directly available through this methodology.

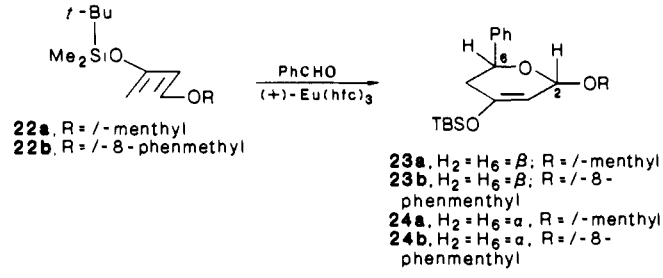
Another gap in the capability comes from the finding that dienes such as **20**, which function well in the cycloaddition reaction,[2] do not provide significant diastereotopic preferences using several dissymmetric auxiliaries with either of the Eu(hfc)$_3$ antipodes or via the achiral Eu(fod)$_3$ as catalysts. Thus, access to galactosides in homogeneous form requires separation of nearly 1:1 mixtures of products of the type **21**.

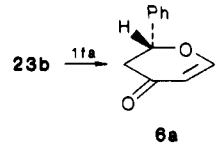



Another target which was addressed was that of a total synthesis of L-glucose (**28**). The uncommon enantiomers of the more common sugars are encountered in various important biological contexts.[19] Recently interest in L-glucose has increased as a result of the possibility that it might be of value as a low-caloric artificial sweetener.[20] Previous syntheses of L-hexoses had been achieved by transformation of the D-antipodes, through inversion of various stereogenic centers, either directly or by transposition of the "reducing" and "nonreducing" termini.[21] The recent breakthrough by Sharpless and Masamune via catalytically mediated asymmetric epoxidation was applied to a total synthesis of all of the L-hexoses from non-carbohydrate precursors.[22]

The cycloaddition of *l*-menthyloxy diene **7d** with benzaldehyde in the presence of (+)-Eu(hfc)$_3$ was conducted at room temperature in $CDCl_3$. A 3:1 ratio of L-pyranose (**9**)/D-pyranose (**10**) was obtained. When the TBS diene **22a** was treated with (+)-Eu(hfc)$_3$ and benzaldehyde in hexane at −20 °C, the ratio improved. A 7.2:1 ratio of L/D-pyranose derivatives **23** and **24** was obtained in 86% yield. Simple crystallization provides access to homogeneous **23a** in 58% yield.

At this juncture, the possibility of realizing still greater diastereofacial selectivity was examined. Mindful of the tremendous advance realized by Corey and associates via the 8-phenmenthol auxiliary,[23] we prepared diene **22b**.[9] *Reaction of* ***22b*** *with benzaldehyde in the presence of* (+)-*Eu(hfc)*$_3$ *in hexane from −78° to −20 °C, afforded a 25:1 ratio of* L-*pyranose* ***23b***/D-*pyranose* ***24b***. Treatment of homogeneous **23b**, obtained via crystallization, with tfa in methylene chloride afforded a 75% overall yield of optically pure L-dihydropyrone **6a**.




(16) The following library of crystallographic programs was used: MULTAN, University of York, York, England, 1980. Structure Determination Package V18.0, Enraf-Nonius Corporation, Delft, Holland, 1981. ORTEP-II, Oak Ridge National Laboratory, Oak Ridge, TN, 1970. See supplementary material for the fractional coordinates, temperature parameters, bond distances, bond angles, and an ORTEP drawing for **14**.

(17) For a previous report on the use of chiral dienes in the preparation of disaccharides see: David, S.; Eustache, J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2521.

(18) The antipodal (−)-Eu(hfc)$_3$ is now commercially available from Aldrich.

(19) (a) Sharon, N. *Complex Carbohydrates: Their Chemistry, Biosynthesi and Function*; Addison-Wesley: Reading, MA, 1975. (b) Candy, D. *Biological Functions of Carbohydrates*; Wiley: New York, 1980.

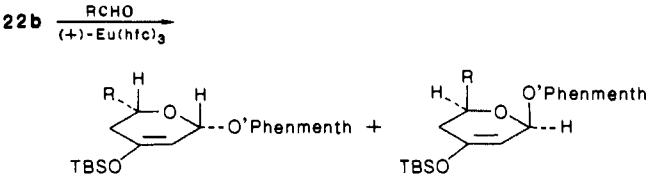
(20) (a) Shallenberger, R. S.; Acree, T. E.; Lee, C. Y. *Nature (London)* **1969**, *221*, 555. (b) Birch, G. G.; Latzmer, Z.; Hollaway, M. R. *Chem. Senses Flavor* **1980**, *5*, 63.

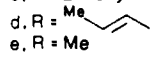
(21) (a) Szarek, W. A.; Hay, G. W.; Vyas, D. M.; Ison, E. R.; Hronowski, L. J. J. *Can. J. Chem.* **1984**, *62*, 671. (b) For a recent review on carbohydrate synthesis, see: McGarvey, G. J.; Kimua, M.; Oh, T.; Williams, M. F. *J. Carbohydr. Chem.* **1984**, *3*(2), 125.

(22) (a) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Science (Washington, D.C.)* **1983**, *220*, 949. For a radically different approach see: Root, R. L.; Durrwachter, R.; Wong, C. *J. Am. Chem. Soc.* **1985**, *107*, 2997.

(23) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.

Table IV. Reactions of Diene **22b** with RCHO. Catalyst, (+)-Eu(hfc)$_3$; Solvent, Hexane, Temperature, −10 to −50 °C

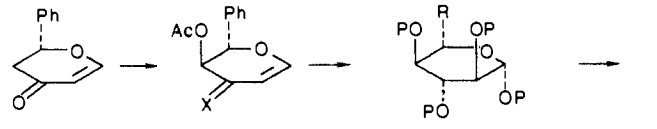



| 23, L-pyranose | 24, D-pyranose |
|---|---|
| b, R = Ph | L:D = 25:1 |
| c, R = 2-furyl | L:D = 22:1 |
| d, R =  | L:D = 6.4:1 |
| e, R = Me | L:D = 5.6:1 |

Before describing the conversion of **6a** to L-glucose, we digress to report the diastereofacial selectivities in the cycloadditions of phenmenthyloxy diene **22b** with some other aldehydes. The summary message which emerges from the data in Table IV is that a route to optically pure or highly enriched L-2,3-dihydropyrones is now available using very simple chemistry. Given the availability of *d*-8-phenmenthol[24] and the antipodal (−)-Eu(hfc)$_3$[6], with *l*-camphorato ligands, the D-pyrones can also be fashioned. Since the pyrones are convertible to a wide variety of other products, this new capability could well have broad impact in the synthesis of a variety of enantiomerically homogeneous products.

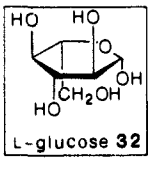
Illustrative of the power of the methodology set forth herein is the straightforward synthesis of L-glucose. Reaction of **6a** with manganese(III) acetate[25,26] achieves the required acetoxylation of the dihydropyrone, leading to **25** in 52% yield. Reduction of the keto group of **25** with sodium borohydride in the presence of cerric(III) chloride[27] afforded, after acetylation, the L-glucal anologue **26**. Osmylation of the double bond under the conditions of Van Rheenen[28] followed by acetylation gave **27**, as the β-anomer. The stage was now set for degradation of the benzene ring. Ozonolysis of **27** followed by oxidative treatment with hydrogen peroxide led to the protected L-glucuronic acid **28** which was in turn converted to **29** and finally to the free L-glucuronic acid **30**.

Alternatively, reduction of **28** with borane/THF followed by acetylation provided peracetyl L-glucose **31**. Total deacetylation gave free L-glucose shown (arbitrarily) as anomer **32**. A total synthesis of the unnatural antipode of glucose from non-carbohydrate precursors was thus achieved.




**25**, X = O
**26**, X = OAc, β-H

**27**, R = Ph; P = Ac
**28**, R = $CO_2H$, P = Ac
**29**, R = $CO_2Me$; P = Ac
**30**, R = $CO_2H$; P = H
**31**, R = $CH_2OAc$, P = Ac




L-glucose **32**

In summary, it is seen that a new and concise method has been developed for the synthesis of optically active carbohydrates and carbohydrate analogues without recourse to resolution. While several serious limitations exist at this writing, the ready access to novel new structural types in either the D or L series is most encouraging. Future research should be oriented toward finding catalysts of greater enantiotopic selectivity which would obviate the need for chiral auxiliaries. In the biological domain, it would be of great interest to ascertain whether the chemically novel structural types available through the chemistry described above can become involved in the various missions which naturally occurring carbohydrates perform.

## Experimental Section

**(2*S*,6*R*)-2-(*l*-Menthyloxy)-6-phenyl-2*H*-tetrahydropyran-4-one (9a).** To a solution of diene **7a** (200 mg, 0.68 mmol) and benzaldehyde (65 mg, 0.61 mmol) in $CDCl_3$ (2 mL) at room temperature was added a catalytic amount of (+)-Eu(hfc)$_3$ (10 mg, 0.01 mmol). The reaction was allowed to remain at room temperature and monitored by $^1$H NMR for the disappearance of the starting aldehyde and diene. After 5 h the reaction was complete at which time triethylamine (2 mL) and methanol (1 mL) were added. The reaction mixture was allowed to stir at room temperature for 2 h and then concentrated in vacuo to remove the volatiles. The crude material was then passed through a plug of silica gel and the plug washed with ethyl acetate. The organics were combined, dried over $MgSO_4$, and again concentrated in vacuo. Analysis of the reaction mixture by 250-MHz NMR indicated a 3:1 mixture of **9a**/**10a** (165 mg, 77%). This mixture was inseperable by both flash chromtography and HPLC ($SiO_2$, 5% ethyl acetate/hexane): $^1$H NMR ($CDCl_3$, 90 MHz) δ 7.5–7.2 (m, 5 H), 5.1–4.4 (m, 2 H), 3.9–3.2 (m, 1 H), 2.8–1.8 (m, 6 H), 1.8–0.5 (m, 16 H); MS *m/e* 330 ($M^+$).

**(2*S*,3*R*,6*R*)-2-(*l*-Menthyloxy)-3-methyl-6-phenyl-2*H*-tetrahydropyran-4-one (9b).** To a solution of diene **7b** (240 mg, 0.77 mmol) and benzaldehyde (80 mg, 0.75 mmol) in $CDCl_3$ (2 mL) at room temperature was added a catalytic amount of (+)-Eu(hfc)$_3$ (20 mg, 0.017 mmol). The reaction was allowed to remain at room temperature and monitored by $^1$H NMR for the disappearance of the starting aldehyde and diene. After 24 h the reaction was complete at which time triethylamine (2 mL) and methanol (1 mL) were added. The reaction mixture was allowed to stir at room temperature for 2 h and then was concentrated in vacuo to remove the volatiles. The crude material was then passed through a plug of silica gel and the plug washed with ethyl acetate. The organics were combined, dried over $MgSO_4$, and again concentrated in vacuo. Analysis of the reaction mixture by 250-MHz NMR and by HPLC ($SiO_2$, 5% ethyl acetate/hexane) indicated a 92:8 mixture of **9b**/**10b** (217 mg, 84%). Purification by either HPLC or crystallization from hexane gave optically pure ketone **9b**: mp 89–92 °C; $[\alpha]^{23}_D$ +71.2° (*c* 0.7, $CHCl_3$); $^1$H NMR (270 MHz, $CDCl_3$) δ 7.50–7.30 (m, 5 H), 4.64 (dd, *J* = 3.1, 11.5 Hz, 1 H), 4.49 (d, *J* = 8.6 Hz, 1 H), 3.34 (dt, *J* = 4.4, 10.6 Hz, 1 H), 2.75–2.52 (m, 3 H), 2.40–2.20 (m, 2 H), 1.76–0.70 (m, 19 H); IR ($CHCl_3$) 2960, 2820, 1700, 1200 cm$^{-1}$; Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.74; H, 9.30. Found: C, 77.02; H, 9.34.

**(2*S*,3*R*,6*R*)-3-Acetoxy-2-(*l*-menthyloxy)-6-phenyl-2*H*-tetrahydropyran-4-one (9c).** To a solution of diene **7c** (130 mg, 0.56 mmol) and benzaldehyde (55 mg, 0.52 mmol) in $CDCl_3$ (2 mL) at room temperature was added a catalytic amount of (+)-Eu(hfc)$_3$ (50 mg, 0.04 mmol). The reaction was allowed to remain at room temperature and monitored by $^1$H NMR for the disappearance of the starting aldehyde and diene. After 26 h the reaction was complete at which time triethylamine (2 mL) and methanol (1 mL) were added. The reaction mixture was allowed to stir at room temperature for 2 h and then was concentrated in vacuo to remove the volatiles. Next, the crude material was passed through a plug of silica gel, eluting with ethyl acetate. Concentration of the organics in vacuo and analysis of the reaction mixture by 250-MHz NMR and by HPLC ($SiO_2$, 5% ethyl acetate/hexane) indicated a 93:7 mixture of **9c**/**10c** (145 mg, 72%). Purification by crystallization from hexane gave optically pure ketone **9c**: mp 115–117 °C; $[\alpha]^{23}_D$ +119.6° (*c* 0.8, $CHCl_3$); $^1$H NMR (270 MHz, $CDCl_3$) δ 7.48–7.30 (m, 5 H), 5.21 (d, *J* = 8.1 Hz, 1 H), 4.87 (d, *J* = 8.1 Hz, 1 H), 4.68 (dd, *J* = 3.9, 10.3 Hz, 1 H), 3.34 (td, *J* = 4.4, 10.6 Hz, 1 H), 2.88–2.68 (m, 2 H), 2.30–2.22 (m, 2 H), 2.20 (s, 3 H), 1.80–0.75 (m, 16 H); IR ($CHCl_3$) 2930, 1745, 1730, 1370, 1210, 1130 cm$^{-1}$; Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 70.97; H, 8.36.

**(2*S*,3*R*,5*R*,6*R*)-3,5-Dimethyl-2-(*l*-menthyloxy)-6-phenyl-2*H*-tetrahydropyran-4-one (9d).** To a solution of diene **7d** (220 mg, 0.65 mmol) and benzaldehyde (65 mg, 0.61 mmol) in $CDCl_3$ (2 mL) at room temperature was added a catalytic amount of (+)-Eu(hfc)$_3$ (80 mg, 0.067 mmol). The reaction was allowed to remain at room temperature for 48 h and heated to 45 °C for an additional 12 h until the $^1$H NMR spectrum indicated the disappearance of the starting aldehyde and diene. The

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(25) Dunlap, N. K.; Sabol, M. R.; Watt, D. S. *Tetrahedron Lett.* **1984**, 5839.
(26) Danishefsky, S.; Bednarski, M. *Tetrahedron Lett.* **1985**, *26*, 3411.
(27) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
(28) Van Rheenen, V.; Kelly, R. C.; Cha, P. Y. *Tetrahedron Lett.* **1976**, *23*, 1973.

reaction was quenched with triethylamine (2 mL) and methanol (1 mL), was allowed to stir at room temperature for 2 h, and was then concentrated in vacuo to remove the volatiles. The crude material was then passed through a plug of silica gel, eluting with ethyl acetate. Concentration of the organics in vacuo and analysis of the reaction mixture by 250-MHz NMR and by HPLC ($SiO_2$, 5% ethyl acetate/hexane) indicated a 87:13 mixture of **9d**/**10d** (135 mg, 61%). Purification by chromotography on silica gel, eluting with 1:9 ethyl acetate/hexane, and crystallization from diethyl ether gave optically pure ketone **9d**: $[\alpha]^{23}_D$ +10.7° (*c* 0.6, $CHCl_3$); $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 7.45–7.25 (m, 5 H), 4.79 (d, *J* = 2.7 Hz, 1 H), 4.44 (d, *J* = 8.7 Hz, 1 H), 3.42 (td, *J* = 4.4, 10.6 Hz, 1 H), 2.90–2.75 (m, 1 H), 2.69 (dq, *J* = 2.8, 7.2 Hz, 1 H), 2.48–2.20 (m, 2 H), 1.74–0.70 (m, 22 H); IR ($CHCl_3$) 2930, 1710, 1448, 1210 $cm^{-1}$; MS, *m/e* 358 ($M^+$).

**(2*S*,3*R*,6*R*)-3-Acetoxy-2-(*l*-menthyloxy)-6-furyl-2*H*-tetrahydropyran-4-one (14).** To a solution of diene **7c** (530 mg, 1.5 mmol) and furfural (130 mg, 1.35 mmol) in $CDCl_3$ (5 mL) at room temperature was added a catalytic amount of (+)-Eu(hfc)$_3$ (240 mg, 0.20 mmol). The reaction was allowed to remain at room temperature and monitored by $^1H$ NMR for the disappearance of the starting aldehyde and diene. After 24 h the reaction was complete at which time triethylamine (4 mL) and methanol (3 mL) were added. The reaction mixture was allowed to stir at room temperature for 2 h and was then concentrated in vacuo to remove the volatiles. The crude material was passed through a plug of silica gel, eluting with ethyl acetate. Concentration of the organics in vacuo and NMR analysis of the reaction mixture indicated an 87:13 mixture of **14**/**15** (503 mg, 96%). Chromatography on silica gel, eluting with 1:3 ethyl acetate/hexane, and crystallization of the chromatographed material from hexane gave optically pure ketone **14** (380 mg, 75%); mp 126–127 °C; $[\alpha]^{23}_D$ +65.2° (*c* 1.3, $CHCl_3$); $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 7.45–7.42 (dd, *J* = 1.1, 2.2 Hz, 1 H), 6.40–6.35 (m, 2 H), 5.16 (dd, *J* = 1.1, 8.1 Hz, 1 H), 4.85 (d, *J* = 8.1 Hz, 1 H), 4.71 (dd, *J* = 2.4, 12.0 Hz, 1 H), 2.80 (dd, *J* = 2.5, 14.6 Hz, 1 H), 2.28–2.19 (m, 2 H), 2.17 (s, 3 H), 1.7–0.7 (m, 16 H); IR ($CHCl_3$) 2985, 2920, 1750, 1730, 1365, 1205 $cm^{-1}$. Anal. Calcd for $C_{21}H_{30}O_6$: C, 66.60; H, 8.09. Found: C, 66.86, H, 8.22.

**(2*S*,3*S*,4*R*,6*R*)-3,4-Diacetoxy-2-(*l*-menthyloxy)-6-furyl-2*H*-(3,4,5,6)-tetrahydropyran (17).** To a solution of ketone **14** (340 mg, 0.90 mmol) in THF (30 mL) at −78 °C under $N_2$ was added K-Selectride (1.34 mL of a 1 M solution in THF, 1.34 mmol) by syringe pump over a period of 1 h. The reaction was stirred an additional 1 h, quenched with a saturated solution of $NaHCO_3$ (20 mL), and allowed to warm to room temperature. The reaction mixture was transferred to a separatory funnel and the water layer extracted with ethyl acetate (4 × 20 mL). The organics were combined, dried over $MgSO_4$, and concentrated in vacuo. The crude alcohol was redissolved in $CH_2Cl_2$ (30 mL), and triethylamine (500 $\mu$L, 3.6 mmol), acetic anhydride (250 $\mu$L, 2.6 mmol), and a catalytic amount of (dimethylamino)pyridine were added at room temperature under $N_2$. After 24 h in the reaction mixture was concentrated in vacuo to remove volatiles and the crude material chromatographed on silica gel, eluting with 1:3 ethyl acetate/hexane to give **17** as a crystalline solid (290 mg, 79%): mp 127–129 °c; $[\alpha]^{23}_D$ −5.3° (*c* 0.8, $CHCl_3$); $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 7.38 (dd, *J* = 1.1, 2.2 Hz, 1 H), 6.36–6.28 (m, 2 H), 5.14–4.94 (m, 2 H), 4.61 (d, *J* = 7.7 Hz, 1 H) 4.59 (dd, *J* = 1.8, 11.8 Hz, 1 H), 3.52 (td, *J* = 4.4, 10.6 Hz, 1 H), 2.40 (ddd, *J* = 1.9, 6.2, 12.8 Hz, 1 H), 2.25–2.10 (m, 2 H), 2.08–1.92 (m, 7 H), 1.70–0.70 (m, 16 H); IR ($CHCl_3$) 2990, 1740, 1360, 1210 $cm^{-1}$. Anal. Calcd for $C_{23}H_{34}O_7$: C, 65.40; H, 8.05. Found: C, 65.62; H, 8.20.

***l*-Menthyl 4-Deoxy-2,3,6-tri-*O*-acetyl-$\beta$-L-glucopyranoside (19).** Furylpyranoside **17** (110 mg, 0.26 mmol) was dissolved in $CH_2Cl_2$ (25 mL) and methanol (8 mL), cooled to −78 °C, and treated with ozone in oxygen for 4 min (solution turns blue). Excess ozone was removed by purging with dry nitrogen at −78 °C. The reaction was allowed to come to room temperature, and the volatiles were removed by concentration in vacuo. The crude acid was redissolved in THF (10 mL) and a borane–THF complex (1.04 mL of a 1 M solution, 1.04 mmol) was added at room temperature under $N_2$. After 24 h the reaction was quenched with dilute HCl solution (5 mL) and transferred to a separatory funnel. The water layer was extracted with ethyl acetate (4 × 15 mL), and the organics were combined, dried over $MgSO_4$, and concentrated in vacuo. The crude alcohol was redissolved in $CH_2Cl_2$ (20 mL), and triethylamine (200 $\mu$L, 1.50 mmol), acetic anhydride (62 $\mu$L, 0.66 mmol) and a catalytic amount of (dimethylamino)pyridine were added at room temperature under $N_2$. After 12 h the reaction was concentrated in vacuo to remove volatiles and the crude material chromatographed on silica gel, eluting with 1:3 ethyl acetate/hexane to give the menthyl glycoside **19** (73 mg, 65%). Recrystallization from hexane gave white crystals: mp 103–105 °C; $[\alpha]^{23}_D$ −26.6° (*c* 0.7, $CHCl_3$); $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 5.10–4.80 (m, 2 H), 4.48 (d, *J* = 9.5 Hz, 1 H), 4.20 (dd, *J* = 6.7, 11.5 Hz, 1 H), 4.07 (dd, *J* = 4.3, 11.5 Hz, 1 H), 3.86–3.69 (m, 1 H), 3.30 (td, *J* = 4.4, 10.6 Hz, 1 H), 2.22–2.10 (m, 2 H), 2.08 (s, 3 H), 2.03 (s, 3 H), 2.02 (s, 3 H), 1.70–0.70 (m, 16 H); IR ($CHCl_3$) 2982, 2917, 1747, 1362, 1210 $cm^{-1}$. Anal. Calcd for $C_{22}H_{36}O_8$: C, 61.70; H, 8.50. Found: C, 60.98; H, 8.39.

***l*-Menthyl 2,3-Di-*O*-acetyl-4-deoxy-$\beta$-L-methylglucopyranuronate (18).** Furylpyranoside **17** (31 mg, 0.073 mmol) was dissolved in $CH_2Cl_2$ (1 mL) and methanol (1 mL), cooled to −78 °C, and treated with ozone in oxygen for 2 min (solution turns blue). Excess ozone was removed by purging with dry nitrogen at −78 °C. The reaction was allowed to come to room temperature, and the volatiles were removed in vacuo. The crude acid was redissolved in either (2 mL), and a solution of diazomethane in $Et_2O$ was added dropwise until a yellow color persisted. The solution was stirred for 10 min at room temperature and then concentrated in vacuo to remove the volatiles. The residue was chromatographed on silica gel, eluting with 1:3 ethyl acetate/hexane to give the $\beta$-menthyl glycoside of methyl glucuronate **18** (24 mg, 80%): mp 143–145 °C; $[\alpha]^{23}_D$ −32.0° (*c* = 0.6, $CHCl_3$); $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 5.10–4.85 (m, 2 H), 4.50 (d, *J* = 7.5 Hz, 1 H), 4.12 (dd, *J* = 2.2, 12.0 Hz, 1 H), 3.78 (s, 3 H), 3.31 (td, *J* = 4.4, 10.6 Hz, 1 H), 2.42 (ddd, *J* = 1.9, 5.2, 12.8 Hz, 1 H), 2.30–2.06 (m, 2 H), 2.03 (s, 3 H), 2.02 (s, 3 H), 1.70–0.70 (m, 16 H); IR ($CHCl_3$) 2995, 2930, 1750, 1360, 1220 $cm^{-1}$; MS (chemical ionization, ammonia), *m/e* (relative intensity) 432 ($M^+$ + 18, 1.8).

**(2*S*,6*R*)-2-(*l*-Menthyloxy)-6-phenyl-4-[(*tert*-butyldimethylsilyl)-oxy]-2*H*(5,6)-dihydropyran (23a).** A solution of benzaldehyde (740 mg, 6.90 mmol) and diene **22a** (2.30 g, 6.80 mmol) in hexane (20 mL) was cooled to −78 °C, and (+)-Eu(hfc)$_3$ (0.5 g, 0.42 mmol) was added. The reaction was kept at −78 °C for 72 h and then allowed to warm to −20 °C for an additional 12 h at which time NMR analysis showed no starting diene remained. The reaction was quenched with triethylamine (8 mL) and methanol (4 mL) and allowed to warm to room temperature. The volatiles were removed in vacuo, and the crude material was passed through a plug of silica gel and the plug washed with ethyl acetate. Concentration of the organics in vacuo gave silyl enol ethers **23a** and **24a** in a 7.2:1 ratio (2.5 g, 81%). Crystallization of this material from ethanol and recrystallization of the material obtained from mother liquors gave optically pure **22a** as white crystals (1.8 g, 58%): mp 62–64 °C; $[\alpha]^{23}_D$ 58.6° (*c* 0.6, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 250 MHz) $\delta$ 7.50–7.20 (m, 5 H), 5.39 (s, 1 H), 4.92 (s, 1 H), 4.75 (dd, *J* = 3.8, 9.0 Hz, 1 H), 3.55–3.35 (m, 1 H), 2.50–2.10 (m, 4 H), 1.70–0.70 [m, 25 H includes 0.93 (s, 9 H)], 0.22 (s, 3 H), 0.18 (s, 3 H); IR ($CHCl_3$) 2962, 2940, 1664, 1366, 1128, 1068 $cm^{-1}$; high-resolution MS (20 eV) calcd for $C_{27}$, $H_{44}$, $O_3$, Si 444.3060, found 444.3075.

**(2*S*,6*R*)-2-(*l*-Phenmenthyloxy)-6-furyl-4-[(*tert*-butyldimethylsilyl)-oxy]-2*H*(5,6)-dihydropyran (23c).** A solution of furfural (250 mg, 2.6 mmol) and diene **22b** (1.08 g, 2.56 mmol) in hexane (12 mL) was cooled to −20 °C and (+)-Eu(hfc)$_3$ (140 mg, 0.12 mmol) was added. The reaction was kept between −10 and −20 °C for 48 h at which time NMR analysis showed no starting diene remained. The reaction was quenched with triethylamine (8 mL) and methanol (4 mL) and allowed to warm to room temperature. The volatiles were removed in vacuo, and the crude material was passed through a plug of silica gel to give silyl enol ethers **23c** and **24c** in a 22:1 mixture (1.20 g, 92%). Crystallization of this material from ethanol and recrystallization of the material obtained for the mother liquors gave optically pure **23c** as white crystals: mp 84–86 °C; $[\alpha]^{23}_D$ +37.8° (*c* 1.0, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 250 MHz) $\delta$ 7.60–7.15 (m, 6 H), 6.50–6.30 (m, 2 H), 5.31 (s, 1 H), 4.83 (dd, *J* = 4.1, 11.2 Hz, 1 H), 4.62 (s, 1 H), 3.60–3.40 (m, 1 H), 2.80–1.90 (m, 4 H), 1.70–1.10 (m, 15 H), 1.04 (s, 9 H), 0.26 (s, 3 H), 0.26 (s, 3 H); IR ($CHCl_3$) 2954, 1672, 1365, 1134 $cm^{-1}$; MS, *m/e* 510 ($M^+$).

**(2*R*,6*S*)-6-Crotyl-2-(*l*-phenmenthyloxy)-4-[(*tert*-butyldimethylsilyl)-oxy]-2*H*(5,6)-dihydropyran (23d).** A solution of crotonaldehyde (34 mg, 0.48 mmol) and diene **22b** (200 mg, 0.48 mmol) in hexane (2 mL) was cooled to −20 °C and (+)-Eu(hfc)$_3$ was added (140 mg, 0.12 mmol). The reaction was kept between −10 and −20 °C for 48 h at which time NMR analysis showed no starting aldehyde or diene remained. The reaction was quenched with triethylamine (1 mL) and methanol (0.5 mL) and allowed to warm to room temperature. The volatiles were removed in vacuo, and the crude material was passed through a plug of silica gel to give silyl enol ethers **23d** and **24d** in a 6.4:1 mixture and some starting enone. Chromatography on silica gel, eluting with 1:9 ethyl acetate/hexane, gave compounds **23d** and **24d** (92 mg, 40%). HPLC ($SiO_2$, 2.5% ethyl acetate/hexane) separation gave optically pure **23d** as a viscous oil: $[\alpha]^{23}_D$ +44° (*c* 1.8, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 250 MHz) $\delta$ 7.50–7.10 (m, 5 H), 5.80–5.50 (m, 2 H), 5.11 (s, 1 H), 4.50 (s, 1 H), 3.70–3.50 (m, 1 H), 2.50–1.80 (m, 4 H), 1.72 (d, *J* = 5.4 Hz, 1 H), 1.70–1.10 (m, 15 H), 0.93 (s, 9 H), 0.18 (s, 3 H), 0.15 (s, 3 H); IR ($CHCl_3$) 2966, 2940, 1670, 1640, 1365, 1060 $cm^{-1}$; MS (chemical ionization, ammonia), *m/e* (relative intensity) 502 ($M^+$ + 18, 1.8).

**(2*R*,6*S*)-6-Methyl-2-(*l*-phenmenthyloxy)-4-[(*tert*-butyldimethylsilyl)oxy]-2*H*(5,6)-dihydropyran (23e).** A solution of acetaldehyde (100

μL, 1.80 mmol) and diene **22b** (200 mg, 0.48 mmol) in hexane (2 mL) was cooled to −20 °C, and (+)-Eu(hfc)$_3$ (100 mg, 0.08 mmol) was added. The reaction was kept between −10 and −20 °C for 48 h at which time NMR analysis showed no starting diene remained. The reaction was quenched with triethylamine (2 mL) and methanol (1 mL) and allowed to warm to room temperature. The volatiles were removed in vacuo, the crude material was passed through a plug of silica gel previously treated with triethylamine, and the plug was then washed with ethyl acetate. Concentration of the organics in vacuo gave silyl enol ethers **23e** and **24e** in a 5.6:1 mixture and some starting enone. Chromatography on silica gel, pretreated with triethylamine, eluting with 1:9 ethyl acetate/hexane, gave back a mixture of **23e** and **24e** (61 mg, 27%). Attempted HPLC separation ($SiO_2$, 2% ethyl acetate/hexane) and crystallization from ethanol failed to purify the mixture: $^1$H NMR ($CDCl_3$, 250 MHz) δ 7.50–7.10 (m, 5 H), 4.83 (s, 1 H), 4.15 (m, 1 H), 3.70–3.50 (m, 1 H), 2.50–1.80 (m, 4 H), 1.70–1.10 ((m, 18 H) includes a 1.15 (d, $J$ = 5.2 Hz, 3 H)), 0.90 (s, 9 H), 0.16 (s, 3 H), 0.14 (s, 3 H); IR ($CHCl_3$) 2968, 2944, 1645, 1370, 1062 cm$^{-1}$.

**(2*R*,6*R*)-2-(*l*-Phenmenthyloxy)-6-phenyl-4-[(*tert*-butyldimethylsilyl)oxy]-2*H*(5,6)-dihydropyran (23b).** A solution of benzaldehyde (233 mg, 2.20 mmol) and diene **22b** (900 mg, 2.20 mmol) in hexane (12 mL) was cooled to −20 °C, and (+)-Eu(hfc)$_3$ (130 mg, 0.11 mmol) was added. The reaction was kept between −10 and −20 °C for 60 h at which time NMR analysis showed no strating aldehyde or diene remained. The reaction was quenched with triethylamine (8 mL) and methanol (4 mL) and allowed to warm to room temperature. The volatiles were removed in vacuo, the crude material was passed through a plug of silica gel, and the plug was washed with ethyl acetate. Concentration of the organics in vacuo gave silyl enol ethers **23b** and **24b** in a ratio of 25:1 (1.10 g, 95%). Crystallization of this material from ethanol and recrystallization of the residue from the mother liquors gave optically pure **23b** as white crystals (0.69 g, 60%); mp 59.5–60.8 °C; $[\alpha]^{23}_D$ +47.3° (*c* 1.1, $CHCl_3$); $^1$H NMR ($CDCl_3$, 250 MHz) δ 7.60–7.10 (m, 10 H), 5.23 (br s, 1 H), 4.71 (dd, $J$ = 3.7, 10.6 Hz, 1 H), 4.49 (br s, 1 H), 3.54 (dt, $J$ = 4.3, 10.3 1 H), 2.60–1.80 (m, 4 H), 1.70–1.10 [m, 15 H includes 1.32 (s, 3 H)], 1.44 (s, 3 H), 0.92 (s, 9 H), 0.19 (s, 3 H), 0.14 (s, 3 H); IR ($CHCl_3$) 2960, 2938, 1670, 1360, 1130, 1065 cm$^{-1}$; high-resolution MS (20 eV) calcd for $C_{33}$, $H_{48}$, $O_3$, Si 520.3373, Found 520.3382.

**(2*R*)-2-Phenyl-2,3-dihydro-4*H*-pyrone (6a).** To a solution of silyl enol ether **23b** (500 mg, 0.96 mmol) in $CH_2Cl_2$ (40 mL) at 0 °C was added trifluoroacetic acid (85 μL, 1.1 mmol). The reaction was stirred at 0 °C for 1 h, allowed to warm to room temperature, and stirred an additional 2 h at room temperature at which time saturated $NaHCO_3$ solution (20 mL) was added. The reaction mixture was transferred to a separatory funnel, and the organic layer was washed once with $NaHCO_3$ solution and once with brine and dried over $MgSO_4$. Evaporation of the solvent in vacuo and chromatography of the residue on silica gel, eluting with 1:3 ethyl acetate/hexane, gave optically pure dihydropyrone **6a** as a colorless oil (145 mg, 87%) and recovered 8-phenmenthol (191 mg, 85%). **6a**: $[\alpha]^{23}_D$ −96.3° (*c* 0.87, $CHCl_3$); $^1$H NMR ($CDCl_3$, 90 MHz) δ 7.55–7.25 (m, 6 H), 5.60–5.20 (m, 2 H), 3.20–2.40 (m, 2 H).

**(2*S*,3*S*)-3-Acetoxy-2-phenyl-2,3-dihydro-4*H*-pyrone (25).** To dihydropyrone **6a** (200 mg, 1.15 mmol) in dry benzene (20 mL) was added manganese triacetate ($Mn(OAc)_3$) (700 mg, 3.0 mmol), which was previously dried at 80 °C under high vacuum for 72 h. The reaction was heated to 90 °C for 12 h at which time an additional 500 mg of $Mn(OAc)_3$ was added. After 24 h of additional heating no starting material was observed by TLC at which time Florisil, Celite, and silica gel were added to the reaction. The mixture was allowed to cool to room temperature and filtered through a plug of silica gel, and the plug was washed with ethyl acetate (4 × 20 mL). The organics were combined, dried over $MgSO_4$, and concentrated in vacuo. Chromatography of the crude material on silica gel, eluting with 1:2.5 ethyl acetate/hexane, gave acetoxylated pyrone **25** (135 mg, 52%): $[\alpha]^{23}_D$ −106.3° (*c* 3.0, $CHCl_3$); $^1$H NMR ($CDCl_3$, 250 MHz) δ 7.48 (d, $J$ = 5.8 Hz, 1 H), 7.43 (s, 5 H), 5.68 (d, $J$ = 12.9 Hz, 1 H), 5.58 (d, $J$ = 5.8 Hz, 1 H), 5.36 (d, $J$ = 12.9 Hz, 1 H), 2.00 (s, 3 H); IR ($CHCl_3$) 2925, 1756, 1698, 1600, 1400, 1372, 1250, 1085, 1028 cm$^{-1}$; high-resolution MS (20 eV) calcd for $C_{13}H_{12}O_4$ 232.0737, found 232.0732.

**(2*S*,3*R*,4*S*)-3,4-Diacetoxy-2-phenyl-4*H*(2,3)-dihydropyran (26).** To a solution of dihydropyrone **25** (80 mg, 0.34 mmol) and cerium(III) chloride heptahydrate (130 mg, 0.35 mmol) in methanol (6 mL) at −78 °C under nitrogen was added sodium borohydride (15.0 mg, 0.40 mmol) in absolute ethanol (2 mL) slowly over a period of 2 h. The reaction was allowed to warm to 0 °C, diluted with diethyl ether (40 mL), and quenched with a pH 7 buffer (20 mL). The reaction mixture was transferred to a separatory funnel and the water layer extracted with ether (4 × 20 mL). The organics were combined, extracted with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude alcohol was next dissolved in $CH_2Cl_2$ (10 mL), and triethylamine (500 μL, 3.6 mmol), acetic anhydride (100 μL, 1.1 mmol), and a catalytic amount of (dimethylamino)pyridine were added at room temperature under nitrogen. After 24 h, a $NaHCO_3$ solution (5 mL) was added, and the reaction mixture was transferred to a separatory funnel. The water layer was extracted with $CH_2Cl_2$ (3 × 5 mL), and the organics were combined, washed with brine, and dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel, eluting with 1:3 ethyl acetate/hexane, gave glucal **26** (75 mg, 80%): $[\alpha]^{23}_D$ −3.3° (*c* 1.5, $CHCl_3$); $^1$H NMR ($CDCl_3$, 250 MHz) δ 7.50–7.30 (m, 5 H), 6.62 (dd, $J$ = 1.3, 6.1 Hz, 1 H), 5.65–5.50 (m, 1 H), 5.40 (dd, $J$ = 6.9, 9.3 Hz, 1 H), 4.95 (d, $J$ = 9.3 Hz, 1 H), 4.88 (dd, $J$ = 2.8, 6.1 Hz, 1 H), 1.96 (s, 3 H), 1.84 (s, 3 H); IR ($CHCl_3$) 3030, 1748, 1650, 1374, 1220 cm$^{-1}$; high-resolution MS (20 eV) calcd for $C_{15}O_5H_{16}$ 276.0998, found 276.1119; MS (chemical ionization, methane) *m/e* (relative intensity) 291 ($M^+$ + 15, 14), 251 (100), 233 (12), 217 (48).

**(2*S*,3*S*,4*R*,5*S*,6*R*)-3,4,5,6-Tetraacetoxy-2-phenyl-2*H*(2,3,4,5)-tetrahydropyran (27).** To a solution of glucal **26** (70 mg, 0.25 mmol), *N*-morpholine oxide (NMO) (44 mg, 0.32 mmol), *tert*-butyl alcohol (100 μL), and $H_2O$ (60 μL) in THF (4 mL) was added osmium tetroxide (40 μL of a 0.4 M solution in THF). After 32 h the reaction was complete by TLC analysis at which time 200 mg of solid sodium bisulfite ($NaHSO_3$) and 400 mg of Florisil were added. The reaction mixture was allowed to stir an additional 1 h and the crude reaction mixture passed through a silica gel plug, eluting with ethyl acetate (5 × 10 mL). The organics were combined and concentrated in vacuo. The crude diol was dissolved in $CH_2Cl_2$ (10 mL), and triethylamine (1.0 mL, 7.2 mmol), acetic anhydride (100 μL, 1.1 mmol), and a catalytic amount of (dimethylamino)pyridine were added at room temperature under nitrogen. After 32 h $NaHCO_3$ solution (5 mL) was added and the reaction mixture transferred to a separatory funnel. The water layer was extracted with $CH_2Cl_2$ (3 × 10 mL), and the organics were combined, washed with brine, and dried over $MgSO_4$. Concentration in vacuo and chromatography on silica gel, eluting with 1:3 ethyl acetate/hexane, gave phenyl glycoside **27** as a 5:1 mixture of β-/α-acetoxy anomers (78 mg, 80%). Recrystallization from ethanol gave the pure β-anomer **27** as white crystals: mp 165–167 °C; $[\alpha]^{23}_D$ −15.5° (*c* 1.9, $CHCl_3$); $^1$H NMR δ 7.34 (s, 5 H), 5.89 (d, $J$ = 8.2 Hz, 1 H), 5.50–5.10 (m, 3 H), 4.55 (d, $J$ = 9.8 Hz, 1 H), 2.10 (s, 3 H), 2.07 (s, 3 H), 2.02 (s, 3 H), 1.81 (s, 3 H); IR ($CHCl_3$) 3020, 1757, 1370, 1215, 1073, 1038 cm$^{-1}$; MS (chemical ionization, ammonia), *m/e* (relative intensity) 412 ($M^+$ + 18, 5.7), 335 (40.6), 274 (1.4), 215 (4.3), 173 (1.7).

**Methyl 1,2,3,4-Tetra-*O*-acetyl-β-L-glucopyranuronate (29).** Phenyl acetoxyglycoside **27** (25 mg, 0.063 mmol) in acetic acid (5 mL) was treated with ozone in oxygen for 14 h at room temperature. The excess ozone was removed by purging with nitrogen and the solution was treated with 30% $H_2O_2$ (400 μL) and $H_2O$ (700 μL) and allowed to stir at room temperature for 12 h. The reaction mixture was concentrated in vacuo to remove volatiles, dissolved in $H_2O$ (2 mL), and extracted with $CH_2Cl_2$ (4 × 3 mL). The organics were combined and concentrated in vacuo. The residue was then redissolved in diethyl ether (2 mL), and a solution of diazomethane in $Et_2O$ was added dropwise until a yellow color persisted. The solution was stirred for 0.5 h at room temperature and then concentrated in vacuo. The residual oil was chromatographed on silica gel, eluting with 1:3 ethyl acetate/hexane to give the peracetylated glucuronic methyl ester **29** (12 mg, 52%); mp 107–109 °C; $^1$H NMR ($CDCl_3$, 250 MHz) δ 7.77 (d, $J$ = 8.0 Hz, 1 H), 4.4–4.1 (m, 3 H), 4.18 (d, $J$ = 10 Hz, 1 H), 3.75 (s, 3 H), 2.13 (s, 3 H), 2.05 (s, 6 H), 2.04 (s, 3 H); IR ($CHCl_3$) 3023, 1762, 1440, 1371, 1220, 1042 cm$^{-1}$; MS (chemical ionization, ammonia), *m/e* (relative intensity) 394 ($M^+$ + 18, 8.0).

**L-Glucuronic Acid (30).** To glucopyranuronate **29** (10 mg, 0.027 mmol) in water (1 mL) was added NaOH (10 μL of a 0.25 M solution) at room temperature. The reaction was stirred for 1 h at room temperature at which time IR-120 (Aldrich) acidic ion-exchange resin was added until the solution pH was neutral. After 1 h the solution was filtered and concentrated in vacuo to give the free L-glucuronic acid **30** (4 mg, 83%): $[\alpha]^{23}_D$ −32° (*c* 0.4, $H_2O$); $^1$H NMR ($D_2O$, 250 MHz) δ 5.18 (br dd, $J$ = 2.7, 8.3 Hz, 1 H), 3.80–3.60 (m, 1 H), 3.55–3.35 (m, 2 H), 3.30–3.15 (m, 1 H). A sample of D-glucuronic acid was obtained from Aldrich. Its $^1$H NMR was identical with compound **30** but opposite in optical rotation $[\alpha]^{23}_D$ +33 (*c* 1, $H_2O$).

**β-L(−)-Glucose Pentaacetate (31).** Phenyl acetoxyglycoside **27** (50 mg, 0.126 mmol) in acetic acid (5 mL) and ethyl acetate (15 mL) were treated with ozone in oxygen for 16 h at room temperature. The excess ozone was removed by purging with nitrogen, and the solution was then treated with 30% $H_2O_2$ (500 μL) and $H_2O$ (1 mL) and allowed to stir at room temperature for 24 h. The reaction mixture was concentrated in vacuo to remove volatiles and the residue dissolved in $H_2O$ (4 mL) and extracted with $CH_2Cl_2$ (5 × 5 mL). The organics were combined and concentrated in vacuo. The residue was then redissolved in THF (6 mL),

treated with a borane-THF ($BH_3$-THF) complex (500 μL of a 1 M solution), and stirred at room temperature under $N_2$. After 12 h an additional 300 μL of $BH_3$-THF solution was added, and after an additional 24 h of stirring at room temperature the reaction was quenched with saturated $NH_4Cl$ solution (6 mL). The water layer was extracted with $CH_2Cl_2$ (4 × 10 mL), and the organics were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude alcohol was then dissolved in $CH_2Cl_2$ (10 mL), and triethylamine (500 μL, 3.6 mmol), acetic anhydride (50 μL, 0.55 mmol), and a catalytic amount of (dimethylamino)pyridine were added at room temperature under $N_2$. After 8 h a $NH_4Cl$ solution (5 mL) was added and the reaction mixture transferred to a separatory funnel. The water layer was extracted with $CH_2Cl_2$ (3 × 10 mL), and the organics were combined, washed with brine, and dried over $MgSO_4$. Concentration in vacuo followed by chromatography on silica gel, eluting with 1:2.5 ethyl acetate/hexane, gave peracetylated L-glucose **31** (20 mg, 42% from **27**): mp 110-112 °C; $[\alpha]^{23}_D$ -4.8° (*c* 0.23, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 250 MHz) 5.72 (d, *J* = 8.08 Hz, 1 H), 5.35-5.05 (m, 2 H), 4.30 (dd, *J* = 14.48, 12.53 Hz, 1 H), 4.12 (dd, *J* = 2.23, 12.53 Hz, 1 H), 3.92-3.80 (m, 1 H), 2.12 (s, 3 H), 2.09 (s, 3 H), 2.04, (s, 6 H), 2.02 (s, 3 H); IR ($CHCl_3$) 3020, 1758, 1370, 1220, 1080, 1040 $cm^{-1}$; MS (chemical ionization, ammonia), *m/e* (relative intensity) 408 ($M^+$ + 18, 1.1), 242 (12.7), 157 (13.9), 114 (17), 97 (19.1). A sample of β-D(+)-glucose pentaacetate was obtained from Aldrich. It was identical with compound **31** by $^1H$ NMR, but opposite in optical rotation, $[\alpha]^{23}_D$ +4.2° (*c* 0.25, $CHCl_3$).

**L(-)-Glucose (32).** To β-L(-)-glucose pentaacetate (**31**) (20 mg, 0.051 mmol) in methanol (5 mL) at room temperature was added a catalytic amount of NaOMe (1 mg). The reaction was allowed to stir at room temperature for 6 h at which time acidic ion-exchange resin (Dowex H CR-S) was added until pH 6-7. The solution was filtered and then the volatiles were removed in vacuo to give the unprotected L-glucose **32** (8 mg, 86%): mp 128-142 °C; $[\alpha]^{23}_D$ -52° (*c* 0.8, $H_2O$); $^1H$ NMR ($D_2O$, 250 MHz) δ 5.20-4.40 (m, 1 H), 4.10-3.90 (m, 1 H), 3.80-3.00 (m, 5 H). A sample of D(+)-glucose was obtained from Aldrich. Its $^1H$ NMR was identical with compound **32** but opposite in optical rotation $[\alpha]^{23}_D$ 52.4° (*c* 1.0, $H_2O$).

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**Registry No. 6a**, 88198-68-9; **7a**, 104194-94-7; **7b**, 104194-95-8; **7c**, 104263-87-8; **7d**, 90130-49-7; **9a**, 87860-23-9; **9b**, 87860-24-0; **9c**, 87860-25-1; **9d**, 87860-26-2; **10a**, 87860-19-3; **10b**, 87860-20-6; **10c**, 87860-21-7; **10d**, 87860-22-8; **14**, 87804-49-7; **15**, 104194-96-9; **16**, 104130-15-6; **17**, 87804-50-0; **18**, 87804-52-2; **19** (R = COOH), 87804-51-1; **19** (R = $CH_2OH$), 104130-16-7; **19** (R = $CH_2OAc$), 87804-53-3; **22a**, 104130-17-8; **22b**, 104130-19-0; **23a**, 104130-18-9; **23b**, 104130-23-6; **23c**, 104130-20-3; **23d**, 104130-21-4; **23e**, 104130-22-5; **24a**, 104194-97-0; **24b**, 104195-01-9; **24c**, 104194-98-1; **24d**, 104194-99-2; **24e**, 104195-00-8; **25**, 104263-88-9; **26**, 104263-89-0; **26** (X = OH, β-H), 104130-24-7; **26** (diol), 104130-25-8; α-**27**, 104195-02-0; β-**27**, 104195-03-1; **28**, 104195-04-2; **29**, 104195-05-3; **30**, 104195-06-4; **31**, 66966-07-2; **31** (R = $CH_2OH$; P = Ac), 104195-07-5; **32**, 39281-65-7.

**Supplementary Material Available:** Data for the X-ray determination of the structure of compound **14** including protocols, positional and thermal parameters, bond distances, and bond angles (6 pages). Ordering information is given on any current masthead page.

# Anatomy of an $S_N1$ Reaction. Crystal Structure-Reactivity Correlations for 1-Arylethanol Derivatives

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**Abstract:** Crystal structures of 11 1-arylethanol derivatives show well-defined trends in bond length, angle, and conformation with changing patterns of substitution. The trends mirror changes in the reactivity of these compounds in the $S_N1$ reaction and show the benzylic system adjusting to accommodate developing positive charge during the early stages of C-O bond breaking. Bond length-reactivity correlations are more complicated than observed in systems previously studied, because the length of the C-OX bond depends on the dihedral angle with the aromatic ring. This dependence is systematic, and can be allowed for, but shows that bond lengths may be conformation-dependent. Thus, a compound cannot necessarily be characterized by a unique bond length R-X, as it can be by a unique rate constant for the cleavage of the R-X bond under standard conditions.

Penetrating mechanistic insights can be derived from the systematic study of crystal structures of suitable systems,[1] not least from trends in bond lengths.[2] We have demonstrated linear correlations between the lengths of C-O bonds in a range of systems R-OX and the rates at which the same bonds are broken heterolytically in solution—the longer the bond, the faster it breaks.[2-4]

In the systems we have studied so far, the group R has been held constant while the group X was varied, but there is convincing qualitative evidence[2] that the length of the R-OX bond depends also on the nature of R and specifically on its ability to stabilize a positive charge. This can be simply expressed in terms of a contribution to the ground-state structure from the valence tautomer $R^+{}^-OX$, which depends on the stability of both cation and oxyanion.[4]

We report an investigation of the crystal structures of 11 derivatives of 1-phenylethanol (**1**), where C-O bond cleavage (**1** ⇌ $1^{\pm}$) corresponds to an $S_N1$ reaction at a benzylic center

The system is chosen to allow systematic variation of the stability of both ionic fragments ($1^{\pm}$) by varying substituents X and Y. We can then analyze the dependence of the C-OX bond length

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