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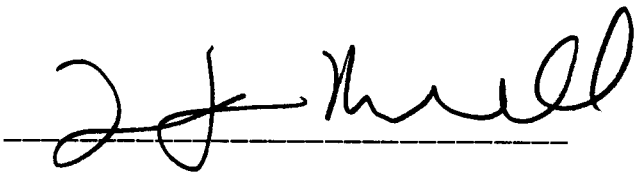
Signature 

Date 7-29-93

THE SYNTHESIS OF ALKYL-SUBSTITUTED BIPHENYL GLUCOPYRANOSIDES

A Thesis

Presented for the

Master of Science

Degree

The University of Tennessee, Knoxville

William Delany Murrell

August 1993

DEDICATION

This thesis is dedicated to my mother, father, Grandma Allen, grandparents, Bonita, Shamba, Jasmine, and most of all GOD. This would not be possible without their support.

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I would like to thank the following: Dr. G. Mamantov for going to bat for me and giving me a chance; the G. E. Foundation, the DuPont Co., and the University of Tennessee for financial support; Dr. D. Baker for all of his patience and guidance.

ABSTRACT

This account outlines the synthesis of three alkyl-substituted biphenyl glycosides **8a–8c** (α and β). The aryl–aryl couplings of the 4-bromo- or 4-iodoanisoles (**1a–1c**) and 1-alkyl-4-bromo- or 1-alkyl-4-iodobenzenes (**2a–2c**) were accomplished by utilizing an organometallic reagent to produce the biphenyl compounds **3a–3c**. Demethylation of compounds **3a–3c** was done via treatment with BBr_3 to yield analogs **4a–4c**. All of the starting materials were not available for purchase, so **2c** was made by diazotizing and halogenating **5**. The glycosidation reactions to produce α, β mixtures of condensation products **7a–7c** were catalyzed by $SnCl_4$. By varying the temperature and conditions of the reaction, both α and β products could be synthesized. Transesterification of products **7a–7c** (α and β) with NaOMe in MeOH yielded the desired adducts **8a–8c** (α and β).

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LIST OF SCHEMES

LIST OF ABBREVIATIONS

Ar	Aryl
aq	Aqueous
BPY	2,2'-Dipyridyl
cp	Clearing Point
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl Sulfoxide
EtOH	Ethanol
GLC	Gas–Liquid Chromatography
HREIMS	High Resolution Mass Spectroscopy in Electon Impact Mode
J	Spin-Spin Coupling Constant
MeOH	Methanol
MHz	Megahertz
NMR	Nuclear Magnetic Resonance Spectroscopy
R	Alkyl Group
Soln	Solution
THF	Tetrahydrofuran
TLC	Thin-layer Chromatography
UV	Ultraviolet Radiation

I. OVERVIEW OF THE DEVELOPMENT OF LIQUID CRYSTALS

A. Origin of Liquid Crystals

Liquid crystal research began with the discovery of mesogens,[1] where initial investigation was of only a descriptive nature. The discovery of liquid crystals is credited to Friedrich Reinitzer. Other major investigators during the early period of development were Otto Lehmann, Rudolf Schenck, and Daniel Vorländer. The original interest in liquid crystals was for the products of these compounds, namely soaps. R. Virchow, a biologist, was the next to investigate liquid crystals. His intense study of the structure of living cells described myelin for the first time in 1854.[2] It is now known that myelin structures in cells, lipid-water systems, are liquid crystalline structures. C. Mettenhiemer in 1875 was the first to describe liquid crystal birefringence, the characteristic that all liquid crystals share.

In 1888 Reinitzer was the first to give a detailed description of the liquid crystal phenomena of two cholesterol esters.[3] He reported that the compounds had two melting points. The first was characterized by the solid converting to a cloudy liquid. At a higher temperature the liquid would become transparent, and upon cooling a violet-blue color appeared and then immediately disappeared leaving a cloudy liquid. After additional cooling the violet-blue coloration reappeared, and subsequently the liquid turns into a white crystalline solid. Reinitzer was able to determine that this color

phenomenon was related to the liquid crystal's double refraction and optical activity.

B. General Structure of Mesogens

The objective of this section is to expound upon the general structure of liquid crystals. In order to convey an accurate picture of the structure of mesogens, the classification and characteristics of each liquid crystal type must be exemplified.

The logical place to start would be to discuss the structural features of liquid crystals.[4] Mesogens should be long (at least 1.3 to 1.4 mm), narrow and rod shaped. There should be permanent dipolar groups present which would lead to a high anisotropy of polarization. The majority of mesogens possess two or more aromatic rings, one or more bridging groups, and two terminal groups. The general formula is depicted in Figure 1.

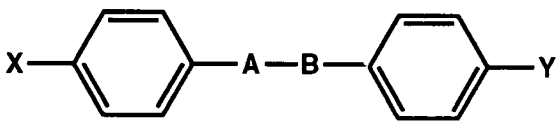
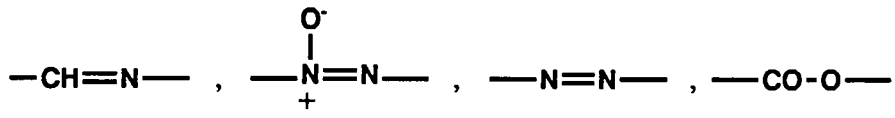
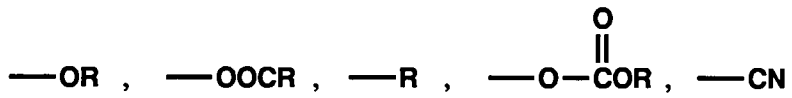


Figure 1. General structure of liquid crystals.

The "A" and "B" in Figure 1 indicate that the bridging group may not contain the same atom or functional group. The four standard bridging groups are the following:



The standard terminal groups are the following:



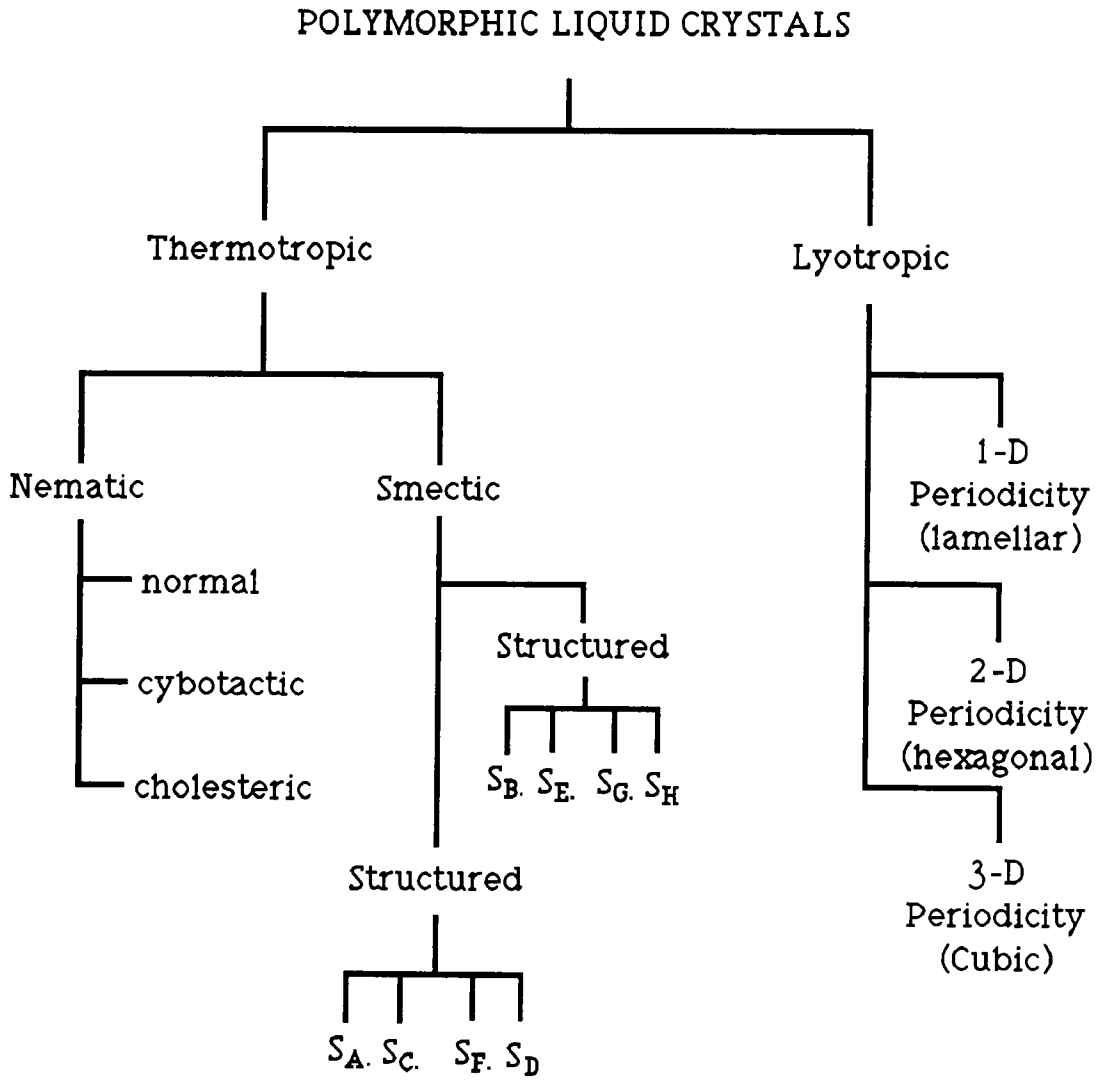
To assist the discussion of the classification and characterization of liquid crystals, Table I is presented to outline the major divisions within mesogens. There are two ways in which liquid crystals can be classified: (1) by their miscibility properties or phase type, and (2) by their structure type.

Thermotropic and lyotropic liquid crystals define the two major groups.[5] The thermotropic mesogen is formed when its crystal is heated. Lyotropic liquid crystals are formed through the penetration of a solvent between the molecules of a crystal lattice. The lyotropic system not only requires solvent, but is also sensitive to temperature change.

1. Thermogenic liquid crystals

There are two types of thermotropic liquid crystals which are classified as either nematic or smectic. Nematic liquid crystals (or nematogens) can be further divided into ordinary nematics, cybotactic nematics, and cholesteric nematics, while smectic liquid

Table 1. The Different Forms of Liquid Crystals.[5]



crystals (or smectogens) can exist in structured and unstructured forms.

The regular nematic liquid crystalline state is characterized by long-range orientational order that may connect thousands of molecules.[6] Within the mesophase, the long axes of the molecules are locally parallel to a given direction, which is called a director. When aligned, the mesophase is found to be uniaxial and is cylindrically symmetric to the director. Figure 2 illustrates the nature of an ordinary nematic liquid crystal.

Cybotactic nematic and regular nematic liquid crystals are similar but can be distinguished by their X-ray patterns.[7] The cybotactic has a greater inner ring intensity. Cybotactic nematics have virtually parallel molecules as in smectogens. The molecules are arranged in groups where the centers of the molecules of each group lie in a plane. The fact that layers do not form is what separates them from smectogens.

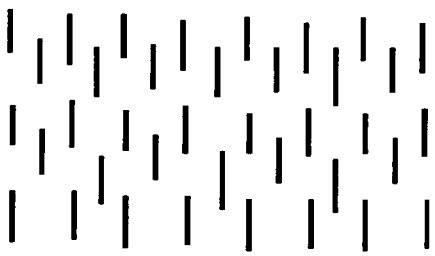


Figure 2. Ordinary nematic mesophase.

The third type of nematic liquid crystal is the cholesteric or twisted type. The cholesteric mesophase consists of chiral molecules which form a set of quasi-nematic layers.[8] The directors in this system are turned through a fixed angle from one layer to the next. Figure 3 illustrates this point. The most obvious difference between

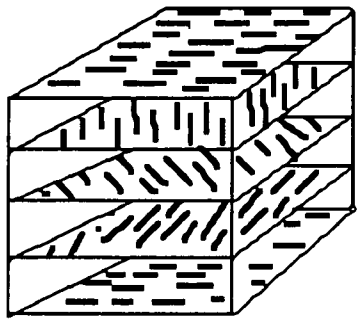


Figure 3. The "helical-like" cholesteric structure.

cholesterics and other nematics is that in cholesterics there is a radical change in optical properties, i.e., brightly colored mesophases.

Smectic liquid crystals are either structured or unstructured. These types are further divided into eight additional structures, smectic A through smectic H. Smectic does not define a characteristic, instead it describes all thermotropic liquid crystals that are not nematic.[9]

The characteristic feature of smectogens are that they are layered. The eight smectic phases will be briefly described in order to convey a skeletal understanding. The smectic A phase can be described as a layer of upright molecules with their centers not conforming to any regular spacing pattern. Of all smectogens, the

smectic A is the most disordered.[10] An example of a compound which forms a smectic A mesophase is ethyl *p*-azoxycinnamate. Figure 4 illustrates the smectic A structure.

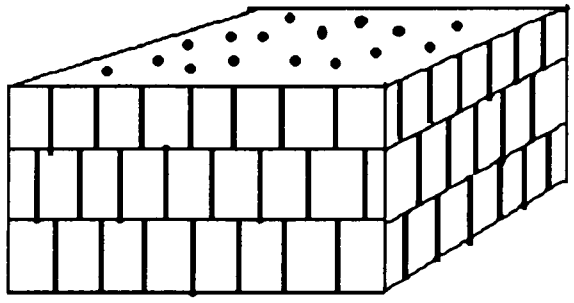


Figure 4. Structure of smectic A phase.

The smectic B structure is almost the same as A. The major difference is that the molecules in this phase arrange themselves in a hexagonal manner in each layer. An example of this type of compound is ethyl 4-ethoxybenzal-4'-aminocinnamate.

The smectic C structure is the tilted form of a smectic A mesophase. There is a moderate degree of disorder within the multiple layers. A structure with a temperature-independent tilt as well as structure with a temperature-dependent tilt can persist. There is also the possibility of a structure with a twist axis which displays similar optical properties to that of cholesteric nematogens.[11] An example of this type of compound is *p*-(*n*-octyloxy)benzoic acid. Figure 5 illustrates the structure of the smectic C phase.

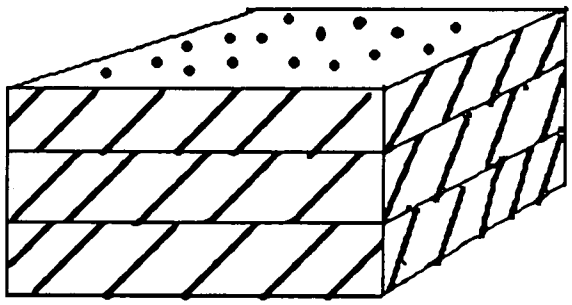


Figure 5. Structure of smectic C phase.

The smectic D phase can be described as a body-centered cubic structure. This is the only smectic structure that does not have a well-defined stratification. The smectic D plane is usually formed as a transition intermediate, and it is thus very difficult to study.[8] An example of a smectic D compound is 4'-*n*-(octadecyloxy)-3-nitrodiphenyl-4-carboxylic acid.

The smectic E state has a high molecule order as revealed by X-ray diffraction patterns. This phase orders itself in layers that conform to an orthorhombic cell, with long range two dimensional order as illustrated in Figure 6. An example of a smectic E compound

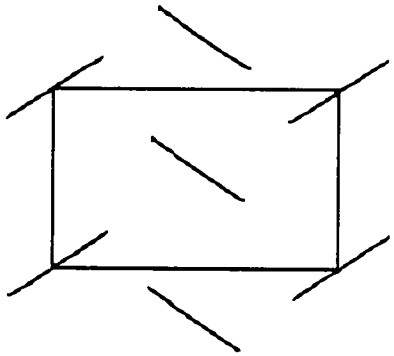


Figure 6. Structure of smectic E phase.

is diethyl-*p*-terphenyl-4,4'-dicarboxylate. There are two types, the normal and tilted species. Only the tilted type forms as a transitional intermediate.

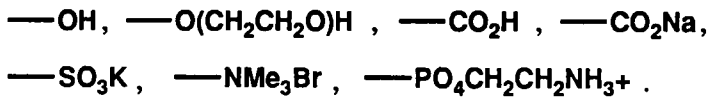
The smectic F phase is very similar to the smectic C phase, but occurs at lower temperature.[12] The molecules are arranged in tilted layers. The layer is easily deformed due to its low viscosity.

The smectic G phase is reminiscent of the E phase. The difference is that tilted layers are present, and the high level of molecular order is conserved.

The phase yet to be discussed is the smectic H phase, which was originally thought to be a smectic B phase. Upon X-ray analysis it was revealed that a high level of molecular order persisted, like that of a three-dimensional lattice. The compound 2-(4-*n*-pentylphenyl)-5-(4-*n*-pentyloxyphenyl)-pyrimidine forms both smectic H and smectic G mesophases.

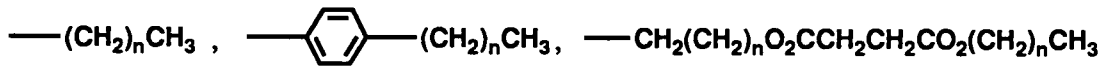
2. Lyotropic liquid crystals

As previously stated, the second major division of liquid crystals consists of Lyotropic mesogens. The characteristic lyotroph is an amphiphilic molecule. An amphiphile has two distinct regions, the polar hydrophilic head and the insoluble hydrophobic (zwitterionic, semi-polar, or polyhydrocarbon) tail. The two common types of amphiphiles are composed of one or two hydrophobic tails. The typical hydrophilic groups are the following:



—OH, —O(CH_2CH_2O)H , —CO_2H , —CO_2Na,
—SO_3K, —NMe_3Br , —$PO_4CH_2CH_2NH_3$+ .

Characteristic lipophilic groups are the following:[13]



—$(CH_2)_nCH_3$, —C$_6$H$_4$—$(CH_2)_nCH_3$, —$CH_2(CH_2)_nO_2CCH_2CH_2CO_2(CH_2)_nCH_3$

Lyotropic liquid crystals require solvent (such as water) to form. For the simplistic purposes of this manuscript, the discussion will be limited to two-compound systems composed of amphiphile and water. The common lyotropic mesophases display lamellar, hexagonal, and cubic molecular constitutions. The types of mesophases that form are dependent upon and are responsive to concentration as well as to temperature changes. Friberg has edited a comprehensive review of phase relationships and other

The nematic type of mesophase is known as the "middle", or "M_1" phase. X-ray studies indicate that the amphiphilic molecules are ordered in parallel arrangement of cylindrical fibrous micelles, or rod-like structures with indefinite length.[15] Further studies indicate that the rod structures then are arranged in a hexagonal fashion. (see Figure 7).

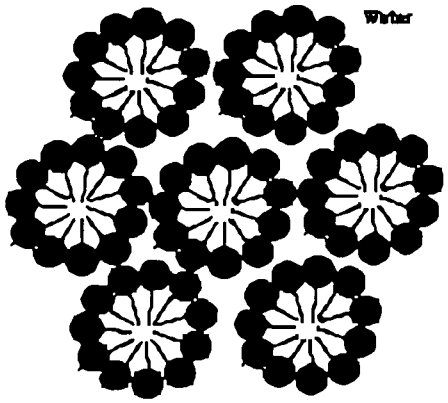


Figure 7. Schematic of "M_1" phase.

The smectic types of mesophases are known as "neat", "G", or "lamellar" phases. This mesophase exhibits lamellar packing with coherent double layers of molecules and ions separated by water (see Figure 8).

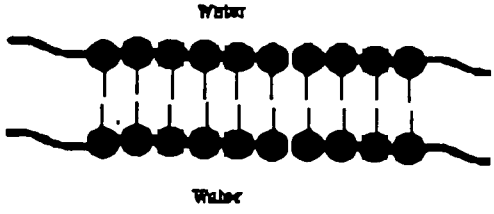


Figure 8. Smectic "neat" phase structure.

Mesophases of the cubic type are known as viscous "isotropic" or "V_1", phases. This type of mesophase is usually formed at a concentration intermediate of M_1, and G phases. X-ray diffraction studies indicate that the molecules are packed in spheres and conform to a face-centered cubic type lattice (see Figure 9).

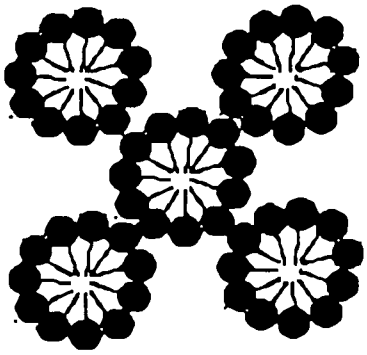


Figure 9. Illustration of cubic "V_1" (diametrical section) mesophase.

Mesophases of an "inverted" type also exist and are known as "V_2" and "M_2" phases. The major difference in the inverted phases is that the nonpolar organic environment predominates. The V_2 and M_2 are analogous to their respective counterparts except that their structures are inverted (see Figure 10).

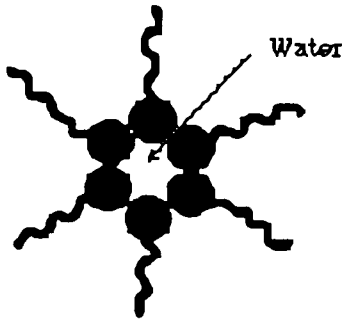


Figure 10. Cross section of M_2 and V_2 phases.

The determination of the structure of lyotropic crystals encompasses a wide array of instrumentation. Currently, the most widely used instrument is the electron microscope. Another popular method of structure determination is the utilization X-ray diffraction techniques.

C. Application of Mesogens

1. Medical applications

Liquid crystals were first applied to the medical field as temperature sensors. Cholesteric liquid crystals can be used for the thermal studies of the circulatory system, detection of malignant tumors, as well as for the thermal mapping of human skin.[16] Cholesteryl esters have different mesogenic ranges, and over these ranges, color changes will occur simultaneously. This behavior is linked to the cholesteric liquid crystals structure. As mentioned earlier, when the molecular layers are uniformly aligned in such a way that the helical axis is normal to the substrate, the system displays unique optical properties. The brilliant colors are due to the structure's selective light reflection.

2. Scientific applications

Nematogens differ from isotropic liquids because of the parallel orientation of their flat, elongated molecules. As a result, a high

degree of magnetic anisotropy persists. The molecules can be homogeneously oriented by the magnetic field so that their optical axis turns parallel to the field. This property endows these mesogens with the ability to serve as anisotropic liquid solvents for NMR measurements. Anisotropy of the chemical shift and molecular geometry can be resolved by this method.[17]

In another case, the ordered arrangement of liquid crystals lead to some unusual solvent properties. Various substituted isomers of disubstituted benzenes easily dissolve in liquid crystal mediums because of their obvious similarities. Because of this property, liquid crystals make useful stationary phases in the gas–liquid chromatography of benzene isomers.[18]

The last type of chemical application that will be discussed is the use of liquid crystals to influence the rate of chemical reactions.[19] As mentioned earlier, liquid crystals make excellent anisotropic solvents. Bacon and Brown report an increase of the reaction rate of the Claisen rearrangement in the nematic state.[20]

3. Application of carbohydrate liquid crystals

a. Structure

The amount of research performed utilizing carbohydrate mesogens is not as voluminous as with conventional liquid crystals. Due to the fact that there is an abundance of carbohydrate starting materials, the potential for an enormous number of compounds

becomes very apparent. The goal of this section is to give a little insight into the general structure of carbohydrate mesogens.

The mesogenic structure of carbohydrate liquid crystals has been determined to be smectic A in the thermogenic state and lamellar in the lyotropic state.[21] There was much difficulty in placing these compounds in thermogenic groups because of their immiscibility in other smectic A compounds.[22] Because many of these compounds exhibit both amphiphilic and thermogenic behaviors, this is an excellent opportunity to explore both types of phenomena.

The crystal structure of the carbohydrate mesogen can exist in two modes. One mode is the head to head bilayer (see Figure 11) with interdigitized alkyl chains, which is characteristic of cyclic carbohydrate liquid crystals. The other mode is the head-to-tail monolayer packing with non-interdigitized alkyl chains, which is characteristic of acyclic carbohydrate liquid crystals.[23]

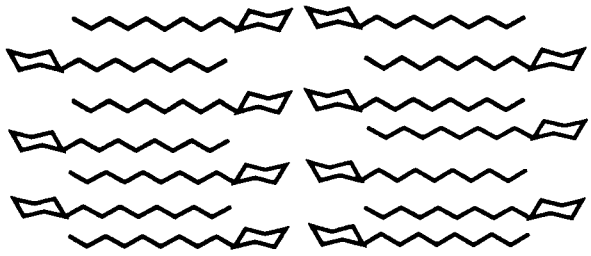


Figure 11. Carbohydrate mesogen bilayer

The head to head formation is essential for the formation of the carbohydrate mesogen bilayer. In other types of mesogens, hydrogen-bonded structures do not form liquid crystals. In this case, the hydrogen-bonding appears to play a critical role in the liquid crystal formation.[24]

As amphiphiles, α-, and β-D-glucopyranosides, as well as the α-D-glucothiopyranosides with alkyl chains longer than twelve carbons immediately form myelins.[25] Myelins are tubular structures formed when amphiphiles are placed in an aqueous medium. Myelins are cylindrical, helical, and form bilayers that constitute the lamellar phase. By carefully controlling the temperature and solvent concentration, all three lyotropic phases can be seen.[14]

b. Practical application

These compounds have been used as nonionic surfactants for extracting and crystallizing membrane proteins.[26] In one example[27] twenty-one soluble proteins, five tRNAs, and three protein-nucleic acid complexes were studied in a systematic manner with regard to their crystallization behavior from polyethylene glycol and ammonium sulfate solutions in the presence of 0-1.5% octyl β-D-glucopyanoside. This study indicated that this carbohydrate liquid crystal enhanced protein crystallization by as much as 30%.

II. STATEMENT OF PURPOSE

Carbohydrate liquid crystals are not available, but hold fruitful possibilities. This work represents an attempt to produce new carbohydrate liquid crystal candidates for structural and behavioral analysis. The biphenyl glucosides are new compounds that are a continuation of an existing series of alkyl and alkyl-substituted phenyl glucosides.

Since there is a large number of naturally occurring carbohydrate starting materials, they could be used to synthesize a considerable body of carbohydrate liquid crystals. These products would provide pure materials for the study of their complex phase transitions.

The opportunity also exists to study the effect of substitution on one functional part of the molecule, while holding the other functionality constant. The relationship between both functional sites (e.g., hydrophilic, and hydrophobic) has not been well established. In addition, to understand the behavior of these compounds, the following must also be addressed: the function of the carbohydrate moiety, the appropriate length of alkyl substitution, and the configuration effects as related to mesophase formation.

It is difficult to research carbohydrate mesogens because they are not available. There were only two publications that dealt with this class of compound before 1982. Considering the general

structure of mesogenic material, the synthesis of biphenyl glucosides seem to be next logical step in continuing in this area of research.

III. RESULTS AND DISCUSSION

A. Synthetic Strategy

The overall strategy for the synthesis of 4'-alkyl-substituted biaryl D-glucopyranosides involved in the synthesis of the aglycon and its coupling with the appropriately protected and activated D-glucopyranose derivative as shown by the retrosynthetic scheme in Figure 12. To this end, the strategy involved (1) the synthesis of the biaryl compound as is methyl ether, (2) its deprotection to give the biaryl phenol, (3) coupling of the penta-*O*-acetyl-D-glucopyranose under Lewis acid catalysis to give the 4'-alkyl-substituted biaryl D-glucopyranoside. Conditions that play on the concepts of kinetic and thermodynamic control of product mixtures would be invoked to provide both the α and β anomers. Deprotection (removal of Ac protecting groups) should the provide the desired biaryl α- and β-D-glucopyranosides.

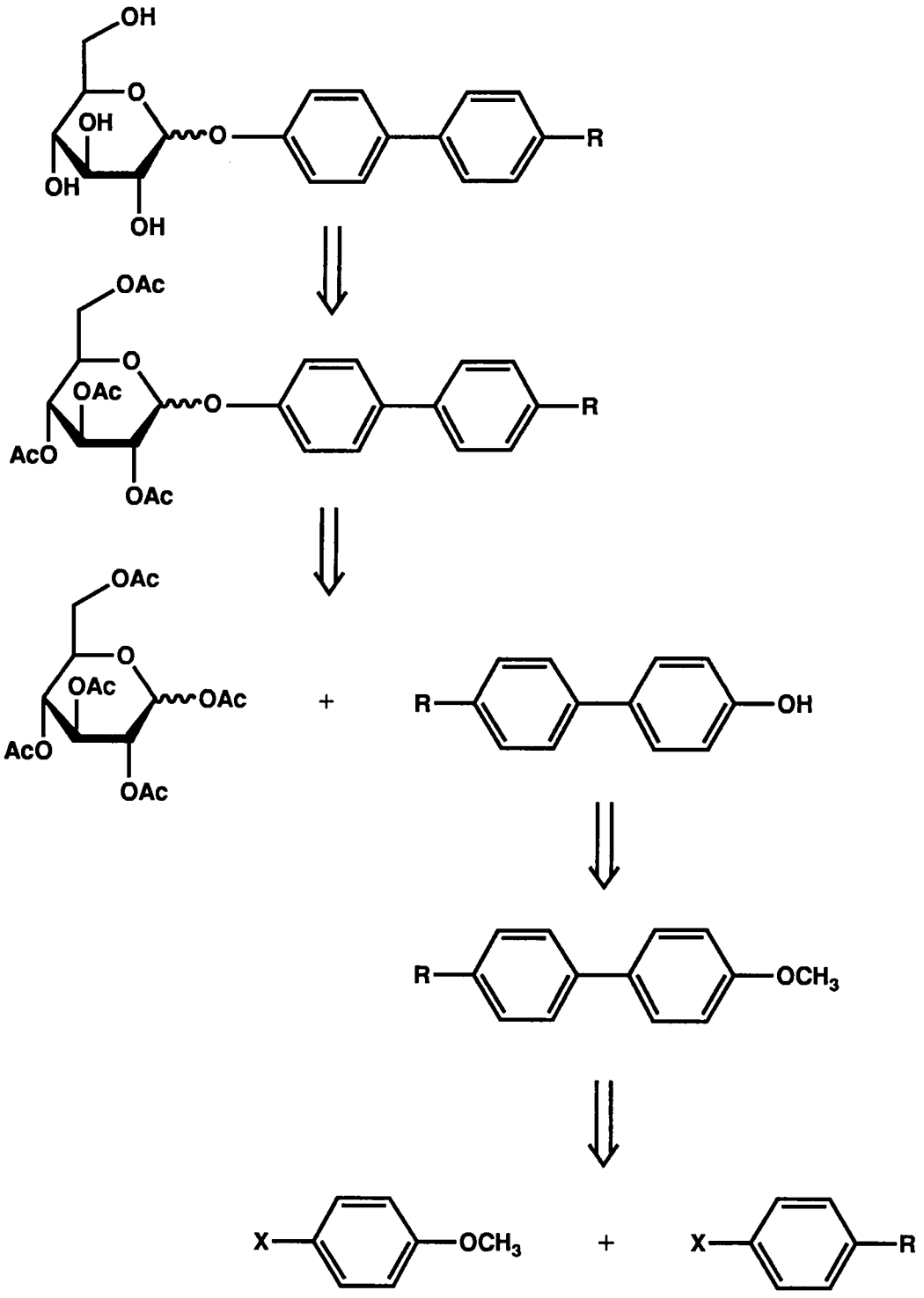


Figure 12. Retrosynthetic analysis for the synthesis of biaryl α- and β-D-glucopyranosides.

B. Synthesis and Characterization of Three Biaryl Analogs

1. Synthesis

The first attempt to produce the desired 4-alkyloxy-4'-alkyl biphenyl utilized the Ullmann coupling reaction.[28] A mixture of 1-iodo-4-(*n*-propyl)benzene, 4-iodoanisole, and copper powder was refluxed in DMF.[29] The reaction and allowed to continue for 120 h while monitoring the reaction by GLC. All of the starting material disappeared, while no crosscoupled or homocoupled condensation products were detected. Although the two iodo-substituted starting materials are highly reactive and should have led to the coupled product, the organometallic intermediates were probably more prone to reduction than to coupling. It is well known that the reactivity of aryl halides in coupling reactions follows the order: I > Br >> Cl >> F.[30]

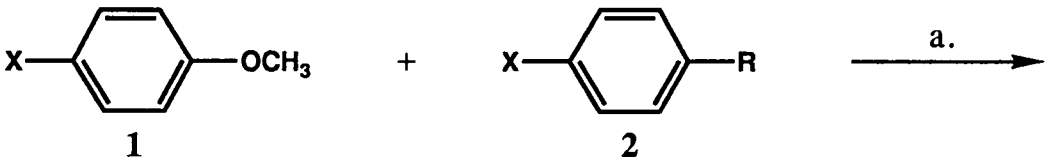
Alternatively, by following the procedure of Caubère and co-workers,[31] the three desired biphenyl methyl ethers **3a–3c** were successfully prepared. The 4-bromo- or 4-iodo-anisoles (**1a–1c**) and *p*-bromo- or *p*-iodoalkylbenzenes (**2a–2c**) were added to a prepared organometallic reagent (see Scheme 1) consisting of NaH, 2,2'-dipyridyl, $NiAc_2$, and *t*-amylONa in THF. (The resulting product mixture contained the two homocoupled products as well as the heterocoupled product in a 1:1:2 ratio.)

Demethylation of the methyl ether moiety on the biphenyl presented no difficulty[32]. Compounds **3a–3c** were dissolved in

CH_2Cl_2, cooled to -78 °C, treated with BBr_3, and then the mixture was allowed to warm to room temperature. At the completion of the reaction, no additional purification was required, and the yields of compounds **4a–4c** were excellent (see Table II).

One of the desired biphenols was to be substituted with a 4'-heptyl group.[33] To produce one of the starting materials for this compound, **5** (see Scheme 2) was diazotized by the addition of HNO_2 at O °C, followed by treatment with aq KI, to produce 1-(*n*-heptyl)-4-iodobenzene (**2c**) in good yield (54%).

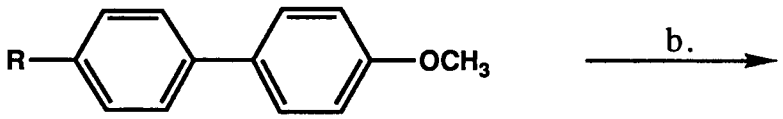
Synthesis of Biphenols



1 2

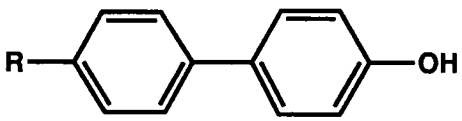
a. X = Br
b. X = Br
c. X = I

a. X = Br, R = Methyl
b. X = Br, R = Propyl
c. X = I, R = Heptyl



3

a. R = Methyl
b. R = Propyl
c. R = Heptyl



4

a. R = Methyl
b. R = Propyl
c. R = Heptyl

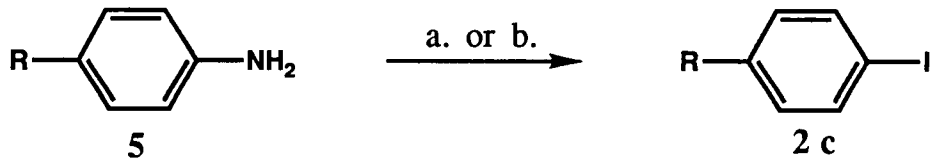
Scheme 1. Reagents and Conditions: **a.** NaH (12 equiv), Bpy (4 equiv), $Ni(Ac)_2$ (2 equiv), *t*-amyl-O-Na (4 equiv), THF, 63 °C, 4 h; **b.** BBr_3 (6 equiv), CH_2Cl_2, -78 °C, 1 h; rt, 10 h.

Table II. Yields, amounts and physicochemical data for compounds 3a–c and 4a–c.

Compound	mp (°C)	Amounts[a] (mmol)	Yield	Elemental Analysis
3a	107[b]	1a, 2.80 (15.0); 2a, 2.56 (15.0)	50%	
3b	72	1b, 6.54 (35.0); 2b, 6.96 (35.0)	41%	*Anal.* Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.98; H, 8.06.
3c	68	1c, 7.24 (31.0); 2c, 9.36 (31.0)	20%	HREIMS. Calcd for $C_{20}H_{26}O$: 282.19836. Found: 282.1964. Δ 1.96 mmass units.
4a	151–153[c]	3a, 1.26 (6.88)	94%	*Anal.* Calcd for $C_{13}H_{11}O$: C, 84.75; H, 6.56. Found: C, 84.62; H, 6.56
4b	148–150	3b, 2.54 (13.4)	94%	*Anal.* Calcd for $C_{15}H_{16}O$: C, 84.52; H, 7.97. Found: C, 84.97; H, 7.65
4c	142–145	3c, 0.664 (2.48)	93%	*Anal.* Calcd for $C_{19}H_{24}O$: C, 85.03; H, 9.01. Found: C, 84.97; H, 9.04

[a] Amounts in grams. [b] Lit.[29] mp = 107 °C. [c] Lit.[38] mp = 152–153 °C.

Synthesis of 1-Heptyl-4-iodobenzene (2c)



5 2 c

R = Heptyl

Scheme 2. Reagents and Conditions: a. HNO_2 (2 equiv), aq KI (3 equiv), 50% H_2SO_4, 0 °C, 4 h; **b.** HNO_2 (2 equiv), aq KI (3 equiv), 50% HCl, 0 °C, 4 h.

2. Characterization

The ^1H NMR spectral data for compounds **2c**, **3a–3c**, **4a–4c** is outlined in Table III. The spectra for these compounds in $CDCl_3$ were recorded and interpreted on a largely first-order basis.

The spectrum for **2c** shows typical first-order splitting except for the methylene protons on carbons C-3–C-6 which were displayed as an unresolved broad doublet. The four aromatic protons were displayed in an AA'BB' system with typical spin-spin coupling constants (see Table III).

The methoxy biphenyl analogs (**3a–3c**) also largely displays first-order splitting patterns (see Table III). The resonances for the alkyl substituents on analogs **3a** and **3b** were all first order. As in **2c**, all of the alkyl substituents in compound **3c** were first-order except for the methylene protons on carbons C-3–C-6 which were displayed as an unresolved broad doublet. The aromatic protons in compounds **3a–3c** followed the AA'BB' pattern in each of the two systems. The two protons adjacent to the methoxy group giving a doublet (J = 9 Hz) furthest upfield, followed by a doublet (J = 8 Hz) for the two protons adjacent to the various alkyl substituents. The other four protons are adjacent to the phenyl-phenyl linkage. The two protons on the ring containing the methoxy group probably give resonances further upfield than the two protons on the same ring as the alkyl group.

Table III. 250-MHz ^{1}H NMR Spectral Data for Compounds 2c, 3a–c, and 4a–c.[a]

Compound	Alkyl	Alkyloxy	Hydroxy	Aryl
2c	0.88 (t, CH_3, 3 H), 1.30 (br d, CH_2, 8 H), 1.58 (qt, CH_2, 2 H), 2.53 (t, CH_2, 2 H)			6.93 (d, 2 H, 9 Hz), 7.59 (d, 2 H, 8 Hz)
3a	2.38 (s, CH_3, 3 H)	3.35 (s, OCH_3, 3 H)	—	6.95 (d, 2 H, 9 Hz), 7.20 (d, 2 H, 8 Hz), 7.40–7.53 (m, 4 H)
3b	0.96 (t, CH_3, 3 H), 1.70 (sx, CH_2, 2 H), 2.61 (t, CH_2, 2 H)	3.81 (s, OCH_3, 3 H)	—	6.94 (d, 2 H, 9 Hz), 7.20 (d, 2 H, 8 Hz), 7.40–7.53 (m, 4 H)
3c	0.898 (t, CH_3, 3 H), 1.35 (br d, CH_2, 8 H), 1.64 (qt, CH_2, 2 H), 2.59 (t, CH_2, 2 H)	3.78 (s, OCH_3, 3 H)	—	6.93 (d, 2 H, 9 Hz), 7.20 (d, 2 H, 8 Hz), 7.48–7.59 (m, 4 H)
4a	2.38 (s, CH_3, 3 H)		4.85 (s, OH, 1 H)	6.90 (d, 2 H, 9 Hz), 7.25 (d, 2 H, 8 Hz), 7.40–7.60 (m, 4 H)
4b	0.96 (t, CH_3, 3 H), 1.68 (sx, CH_2, 2 H), 2.59 (t, CH_2, 2H)		4.70 (s, OH, 1 H)	6.88 (d, 2 H, 9 H), 7.21 (d, 2 H, 8 Hz), 7.45–7.57 (m, 4 H)
4c	0.898 (t, CH_3, 3 H), 1.30 (br d, CH_2, 8 H), 1.63 (qt, CH_2, 2 H), 2.64 (t, CH_2, 2 H)		4.77 (s, OH, 1 H)	6.90 (d, 2 H, 9 Hz), 7.24 (d, 2 H, 8 Hz), 7.47–7.59 (m, 4 H)

[a]Data are given in ppm downfield from internal Me_4Si for solutions in $CDCl_3$. Multiplicity, group, number of protons, and spin-spin splitting data (in Hz) are in parentheses. Multiplicities: br d, broad doublet; d, doublet; m, multiplet; q, quartet, qt; quintet; sx, sextet; s, singlet; t, triplet.

The hydroxy biphenyl compounds **4a–4c** produce almost identical spectra except that the methoxy resonance (a three-proton singlet) is now replaced by a hydroxy proton (one-proton singlet) peak.

C. Synthesis and Characterization of 4'-Alkyl-Substituted Biaryl α- and β-D-glucopyranosides

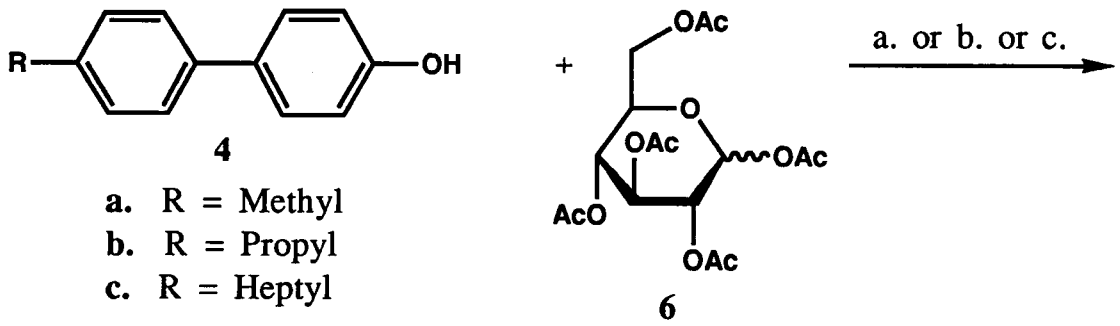
1. Synthesis

Helfrich and Schmitz-Hillebrecht[34] first proposed the $ZnCl_2$ catalyzed addition of alcohols to carbohydrates to form glucosides. Lemieux and coworkers[35], and Jahangir and Baker[36] adapted this method, but instead used the Lewis acid, $SnCl_4$, for the coupling. The preparation of the glucosides **7a–7c** was performed by coupling the various biphenols **4a–4c** to D-glucose pentaacetate (**6**) in CH_2Cl_2 (see Scheme 3). A mixture of α and β anomers was produced at higher temperatures (e.g., 40 °C or 52 °C) with longer reaction times, while the β isomer was produced at lower temperatures (e.g., -18 °C) with shorter reaction times. Although the α anomer is the thermodynamic product and is favored due to the anomeric effect, the acetyl group at C-2 forms a five-membered, positively charged dioxolenium intermediate that forces the nucleophile (ROH) to attack C-1 from the top side of the ring, forming the β anomer.[37] However, at higher

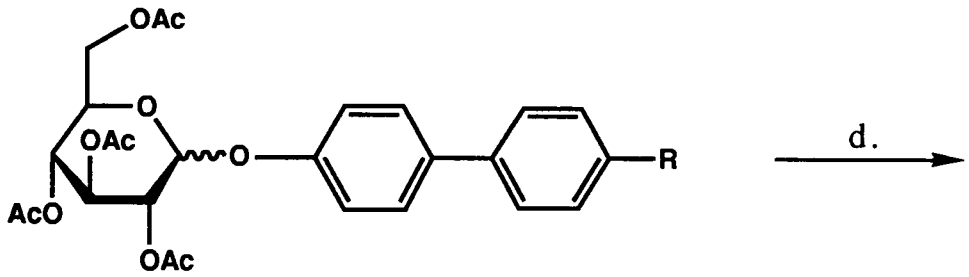
reaction temperatures, this is overcome and the α anomer forms. (The yield for this coupling varied with each biphenol to produce compounds **7a–7c**, see Table IV.) The best yield of the α anomer resulted when the temperature was 40 °C and the amount of solvent was kept to a minimum. In one instance the α anomer predominated (**7c**), which is attributed to the higher concentration, thus increased interaction of starting materials during the coupling. The α and β anomers were not separable in the acetylated form and had to be deprotected before they could be separated by column chromatography.

The α, β mixtures of compounds **7a–7c** were treated with NaOMe (see Scheme 3) in anhydrous methanol[38] at rt for 12 h to yield products **8a–8c** (α and β). The crude products were isolated by gradient column chromatography on silica gel in good to fair yields (see Table IV).

Synthesis of 4'-Alkyl-Substituted Biaryl D-Glucopyranosides

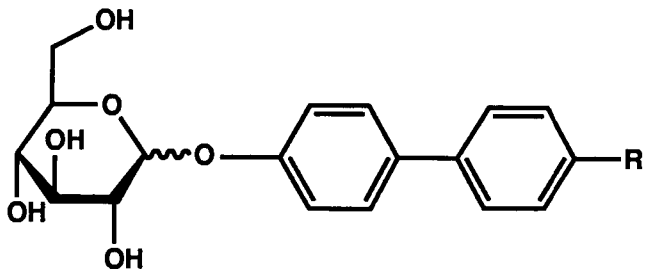


a. R = Methyl
b. R = Propyl
c. R = Heptyl



7

a. R = Methyl
b. R = Propyl
c. R = Heptyl



8

a. R = Methyl, α and β
b. R = Propyl, α and β
c. R = Heptyl, α and β

Scheme 3. Reagents and Conditions: **a.** (for β anomer): $SnCl_4$ (2 equiv), CH_2Cl_2, -18 °C, 4 h; **b.** (for α and β anomers): $SnCl_4$ (2 equiv), CH_2Cl_2, 3 Å sieves, 52 °C, 96 h; **c.** (for α and β anomers):

Table IV. Yields, amounts, and physicochemical data for compounds 7a–c and 8a–c.

Compound	mp (°C)	cp (°C)	Amounts[b] (mmol)	Yield	Elemental Analysis	$[\alpha]_D^{22}$ (degrees)
7a	158–160 (β)		4a 0.50 (2.70), 6 1.28 (3.30)	57%	*Anal.* Calcd for $C_{27}H_{30}O_{10}$: C, 63.03; H, 5.88. Found: C, 62.97; H, 5.91.	-3.07[c]
7b	152–154 (β)[a]		4b 0.20 (0.94), 6 0.68 (1.74)	62%	*Anal.* Calcd for $C_{29}H_{34}O_{10}$: C, 63.96, H, 6.66. Found: C, 63.51; H, 6.32	-1.29[c]
7c	140–142 (β)[a]		4c 0.20 (0.74), 6 0.38 (.970)	28%	*Anal.* Calcd for $C_{32}H_{46}O_{10}$: C, 66.21; H, 7.07. Found: C, 65.69; H, 7.03.	-1.10[c]
8a	(α)[d]188–190 (β)[d]198–200	(α) 218–220 (β) 204–206	7a 1.96 (3.80, α, β mixture)	55%	α product *Anal.* Calcd for $C_{19}H_{22}O_6 \cdot .45\ H_2O$: C, 64.38; H, 6.51. Found: C, 64.37; H, 6.52. β product *Anal.* Calcd for $C_{19}H_{22}O_6 \cdot 0.90\ H_2O$: C, 62.94; H, 6.62. Found: C, 62.93; H, 6.69.	(α) +0.20[e] (β) -1.10[e]
8b	(α)[d]158–160 (β)[d]192–194	(α) 224–226 (β) 236–238	7b 1.67 (2.94, α, β mixture)	47%	α product *Anal.* Calcd for $C_{21}H_{26}O_6 \cdot\ 0.45\ H_2O$: C, 64.38; H, 6.51. Found: C, 64.37; H, 6.52. β product *Anal.* Calcd for $C_{21}H_{26}O_6 \cdot\ 0.60\ H_2O$: C, 65.47; H, 7.12. Found: C, 65.47; H, 7.20.	(α) +11.76[e] (β) -4.80[e]
8c	(α)[d]134–136 (β)[d]136–138	(α) 242–244 (β) 244–246	7c 1.41 (2.35, α, β mixture)	73%	α product *Anal.* Calcd for $C_{25}H_{34}O_6 \cdot\ 0.70\ H_2O$: C, 67.70; H, 8.05. Found: C, 67.72; H, 8.03.	(α) +3.52[e] (β) -4.61[e]

[a] The α product was not isolable in the acetylated form, but it was possible to prevent it from being formed by limiting temperature and reaction time. [b]Amounts in grams. [c]10% in EtOAc. [d]At high reaction temperatures the α product formed in small amounts, and upon deprotection it was easily separated from the β (kinetic) product. [e]5% in MeOH.

2. Characterization

The ^1H NMR spectral data for compounds **7a–7c** and **8a–8c** are provided in Table 5. The spectra for these compounds in $CDCl_3$ and DMSO-d_6, respectively, were recorded and interpreted on a largely first-order basis.

The spectra for compounds **7a–7c** show virtually the same chemical shift and splitting patterns for all the alkyl and aromatic protons present in the earlier discussed precursors. The acetyl protons show their characteristic singlet signal for each of four acetyl groups. The chemical shift values for each of the pyranose protons were virtually identical in each compound. The pyranose protons (H-1, H-2, H-3, and H-4), could not be decoupled to elucidate their splittings due to their overlapping chemical shifts. H-6_a and H-6_b are diastereotopic and give two separate resonances that are split by H-5 into two doublets of doublets ($J_{6a,5}$ = 2 Hz, $J_{6b,5}$ = 3–5 Hz). The resonance for H-5 shows an interesting second-order splitting pattern. The H-5 proton is split into a doublet by each of the diastereotopic protons (H-6_a and H-6_b) adjacent to it, and is then split again into eight lines by the axial-axial coupling of H-4. (Such approximates an ABX system with the X-resonance again split by H-4.)

Compounds **8a–8c** (α and β) also displayed virtually the same splitting and chemical shift data for their respective alkyl and

Table V. 250-MHz ^{1}H NMR Spectral Data for Compounds 7a–c, and 8a–c.[a]

Compound	H-1	H-2	H-3	H-4	H-5	H-6_a,6_b	Acetate	Alkyl[b]	Aryl[c]
7a (β)	5.30d (8)	5.09–5.34m[d]			3.89m	4.17dd,[e] 4.30dd (2) (5)	2.04s, 2.06s, 2.08s, 2.09s	2.39 (s,CH_3, 3 H)	7.05 (d, 2 H, 9 Hz), 7.22 (d, 2 H, 8 Hz), 7.40–7.53 (m, 4 H)
7b (β)	5.31d (8)	5.10–5.41m			3.88m	4.18dd, 4.32dd (2) (5)	2.04s, 2.06s, 2.08s, 2.09s	0.9721 (t, CH_3, 3 H), 1.69 (sx, CH_2, 2 H), 2.62 (t, CH_2, 2 H)	7.04 (d, 2 H, 9 Hz), 7.24 (d, 2 H, 8 Hz), 7.42–7.54 (m, 4 H)
7c (β)	5.30d (8.5)	5.10–5.35m			3.89m	4.18dd, 4.31dd (2) (3)	2.04s, 2.06s, 2.08s, 2.09s	0.88 (t, CH_3, 3 H), 1.42 (br d, CH_2, 8 H), 1.64 (qt, CH_2, 2 H), 2.62 (t, CH_2, 2 H)	7.05 (d, 2 H, 9 Hz)), 7.24 (d, 2 H, 8 Hz), 7.40–7.51 (m, 4 H)
8a (α)	5.41d (3.5)	3.17–3.72m						2.32 (s, CH_3, 3 H)	7.15 (d, 2 H, 7 Hz), 7.24 (d, 2 H, 8 Hz), 7.50–7.58 (m, 4 H)
8a (β)	4.88d (7)	3.11–3.45m				3.46m, 3.71dd (4)		2.31 (s, CH_3, 3 H)	7.12 (d, 2 H, 9 Hz), 7.25 (d, 2 H, 8 Hz), 7.30–7.59 (m, 4 H)
8b (α)	5.41d (3.5)	3.20–3.70m						0.910 (t, CH_3, 3 H), 1.61 (sx, CH_2, 2 H), 2.57 (t, CH_2, 2 H)	7.15 (d, 2 H, 9 Hz), 7.24 (d, 2 H, 8 Hz), 7.51–7.59 (m, 4 H)
8b (β)	4.89d (7)	3.10–3.40m				3.51m, 3.72dd (4)		0.910 (t, CH_3, 3 H), 1.62 (sx, CH_2, 2 H), 2.59 (t, CH_2, 2 H)	7.09 (d, 2 H, 8 Hz), 7.25 (d, 2 H, 8 Hz), 7.51–7.58 (m, 4 H)
8c (α)	5.42d (3.5)	3.12–3.73m						0.854 (t, CH_3, 3 H), 1.26 (br d, CH_2, 8 H), 1.58 (qt, CH_2, 2 H), 2.59 (t, CH_2, 2H)	7.14 (d, 2 H, 9 Hz), 7.24 (d, 2 H, 8 Hz), 7.51–7.59 (m, 4 H)
8c (β)	4.89d (7)	3.12–3.75m				3.49m, 3.71dd (4)		0.855 (t, CH_3 3H) 1.28 (br d, CH_2, 8H), 1.59 (qt, CH_2, 2 H), 2.58 (t, CH_2, 2 H)	7.10 (d, 2 H, 8 Hz), 7.24 (d, 2 H, 8 Hz), 7.50–7.59 (m, 4 H)

[a] Data are given in ppm downfield from internal Me_4Si for solutions in DMSO-d_6. [b] Multiplicity, group, number of protons, and spin-spin splitting data (in Hz) are in parentheses. [c]Multiplicity, number of protons, and spin-spin splitting data (in Hz) are in parentheses. [d] In the acetylated glycoside H_1-H_4 gave resonances in the same region. [e]Multiplicities: br d, broad doublet; d doublet; dd, doublet of doublet; m, multiplet; q, quartet; qt, quintet; s, singlet; sx, sextet; t, triplet.

aromatic systems. The pyranose CH protons of the these spectra were mostly unidentifiable because their resonances overlapped and were partly concealed by the resonance of the HOD peak from exchange with the D_2O solvent.

For the free hydroxyl α glucosides, the H-1 proton was the only identifiable pyranose proton because it was shifted far downfield due to its proximity to the two adjacent electronegative oxygen atoms. The axial H-2 split the equatorial H-1 into a doublet (J = 3.5 Hz) with the spin-spin coupling data in good agreement with that in the literature.[39]

As in the α glucosides, the pyranose protons of the β glucosides were mostly concealed by solvent. The diastereotropic H-6_b displayed a doublet of doublets (J = 4 Hz) as split by H-5; H-6_a was located below the HOD peak. The chemical shift of H-1 was virtually the same in each β analog and displayed a doublet (J = 7 Hz) with the spin-spin coupling data in good agreement with that in the literature.[39]

IV. CONCLUSIONS

The 4'-alkyl-substituted biphenols (**4a–4c**) are known to be mesogenic. The newly synthesized biphenyl glycosides have not yet been tested to see if they exhibit any polymorphic behavior. Compounds **8a–8c** have displayed two physical changes in composition: a melting point as well as a clearing point which is characteristic of mesogenic compounds. But until optical and X-ray studies unmask the possible birefringence and liquid crystal structure, little can be said concerning their liquid crystal properties.

The importance of solvent became quite apparent in a glycosidation reaction to produce **7cαβ**. In all reactions of this type preceding this one, there was great difficulty encountered in obtaining the α product, which can now be directly attributed to the amount of solvent used. By decreasing the solvent by 75%, the α product was produced in greater amounts. As stated earlier, the dioxolenium ion formation directs formation of the "kinetic" β product. By increasing reaction temperature, the energetics of the system is such that the anomeric effect predominates. This action can be interpreted as increased forced interaction between the glucoside and Lewis acid which disfavors dioxolenium ion formation, resulting in the themodynamically favored α condensation product.

V. EXPERIMENTAL

A. General Methods

GLC–MS analyses were performed on a Hewlett-Packard gas–chromatograph (Model 5890) coupled to a Hewlett-Packard mass selective detector (Model 5970). ^{1}H NMR spectra were recorded on a Bruker AC 250 (250 MHz) spectrometer in solutions that were typically 1-2% (w/v) in substrate. Chemical shifts are reported in δ-units downfield from an internal tetramethylsilane (Me_4Si) standard in chloroform-*d*, and dimethyl sulfoxide-d_6. Standard multiplicity designations are as follows: b, broad; d, doublet; dd, doublet of doublets; m, multiplet; q, quartet; qt, quintet; s, singlet; sx, sextet; t, triplet. Melting points were determined using a Mel-Temp capillary melting point apparatus.

Silica gel (SiO_2) open column chromatography was performed on E. Merck Silica Gel-60 (63-212 μm). Thin-layer chromatography (TLC) was performed on E. Merck 0.2-mm aluminum-backed plates. Detection of products was achieved by using a UV lamp, and in the case of carbohydrate analogs, the general system used is an anisaldehyde–sulfuric acid spray followed by heat development.[40] Optical rotations were measured in the indicated solvent and concentration at the sodium D-line in a 1-dm cell at ambient temperature (22 °C), on a Perkin–Elmer model 241 spectro-polarimeter.

High-resolution mass spectrometry (HRMS) measurements in the electron-impact (EI+) mode determinations were made on a VG

ZAB-EQ (VG Analytical, Manchester, England) instrument at the Mass Spectrometry Center at The University of Tennessee. Atlantic Microlab, Inc., Norcross, GA performed all elemental analyses.

Tetrahydrofuran (THF) was distilled from potassium–benzophenone ketyl, while MeOH was distilled from magnesium turnings. Methylene chloride (CH_2Cl_2) was distilled from CaH. The above distillations were all performed under atmospheric conditions. All solvents were evaporated at ca. 40 °C/30 torr on a Büchi Rotovapor. "Concentration under high vacuum" refers to rotary evaporation at pressures of ≤ 5 torr. Reagents were reagent grade and used directly except for the following. Tertiary amyl alcohol (*t*-amyl-OH) was distilled from sodium metal. Sodium hydride (60% in oil) was used after three washings with hexane. Nickel acetate tetrahydrate [$Ni(Ac)_2 \cdot 4H_2O$] was dried *in vacuo* for 24 h with refluxing xylenes.

B. Procedure

Preparation of 4-methoxy-4'-methyl-1,1'-biphenyl, (3a).[31] To a suspension of degreased NaH (7.20 g, 180 mmol) was added THF (90 mL). 2,2'-Dipyridyl (9.36 g, 60.0 mmol) was next added, followed by the addition of $Ni(Ac)_2$ (5.28 g, 30.0 mmol) which changed the reaction color to green. The mixture was heated to 63 °C and was allowed to stir for 1 h. The dropwise addition of *t*-amylONa (12.0 mL of 5.00 M soln, 60.0 mmol) was carried out at reflux (63 °C), and the reaction mixture was allowed to stir for an additional 2 h.

With the organametallic reagent ready for use, a solution of **1a** (2.80 g, 15.0 mmol) and **2a** (2.56 g, 15.0 mmol) in THF (50 mL) was added to the reaction via syringe. The reaction was allowed to proceed for 4 h, until no starting material remained as determined by TLC. The reaction mixture was cooled to room temperature and quenched using 95% EtOH (150 mL) until H_2 evolution ceased and then acidified with 10% aq HCl (300 mL). The products were extracted with Et_2O (6 x 50 mL) and dried over $MgSO_4$. TLC indicated three products: two homocoupled, and the desired heterocoupled product. The solvent was evaporated and the product mixture was separated using column chromatography with silica gel as the stationary phase and petroleum ether/toluene (4:1) mixtures as eluent. The solvent was evaporated from the fractions containing the desired product to yield 1.49 g (50%), of 4-methoxy-4'-methyl-1,1'-biphenyl: mp 107 °C; lit.[31] mp 107 °C; ^{1}H NMR ($CDCl_3$): δ 2.38 (s, CH_3, 3 H), 3.35 (s, OCH_3, 3 H), 6.95 (d, J = 9 Hz, 2 H), 7.20 (d, J = 8 Hz, 2 H), 7.40–7.53 (m, 4 H). The ^{1}H NMR spectrum of the product is identical to the spectrum of the known compound.[31] GLC–MS (M^+) 199, r_t 6.27 min.

4-Methoxy-4'-propyl-1,1'-biphenyl, (3b).[31] To a suspension of degreased NaH (10.4 g, 260 mmol), was added THF (210 mL). 2,2'-Dipyridyl (21.9 g, 140 mmol) was next added, followed by the addition of $Ni(Ac)_2$ (12.3 g, 70.0 mmol) which changed the reaction color to green. The mixture was heated to 63 °C and was allowed to stir for 1 h. The dropwise addition of *t*-amylONa (28.0 mL of 5.00 M soln, 140 mmol) was carried out at reflux (63 °C), and the reaction mixture was allowed to stir for an additional 2 h.

With the organametallic reagent ready for use, a solution of **1b** (6.54 g, 35.0 mmol) and **2b** (6.96 g, 35.0 mmol) in THF (100 mL) was added to the reaction via syringe. The reaction was allowed to proceed for 4 h, until no starting material remained as determined by TLC. The reaction mixture was cooled to room temperature, and quenched using 95% EtOH (300 mL) until H_2 evolution ceased, and then acidified with 10% aq HCl (700 mL). The products were extracted with Et_2O (6 x 150 mL) and dried over $MgSO_4$. TLC indicated three products: two homocoupled, and the desired heterocoupled product. The solvent was evaporated and the product mixture was separated using column chromatography with silica gel as the stationary phase and petroleum ether/toluene (4:1) mixtures as eluent. The solvent was evaporated from the fractions containing the desired product to yield 3.24 g (41%), of 4-methoxy-4'-propyl-1,1'-biphenyl: mp 72 °C; ^{1}H NMR ($CDCl_3$): δ 0.96 (t, CH_3, 3 H), 1.70 (sx, CH_2, 2 H), 2.61 (t, CH_2, 2 H), 3.81 (s, OCH_3, 3 H), 6.94 (d, J = 9 Hz, 2 H), 7.20 (d, J = 8 Hz, 2 H), 7.41–7.53 (m, 4 H). GLC–MS (M^+) 226, r_t 9.95 min. *Anal.* Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.98; H, 8.06.

4'-Heptyl-4-methoxy-1,1'-biphenyl, (3c).[31] To a suspension of degreased NaH (14.8 g, 370 mmol), was added THF (180 mL). 2,2'-Dipyridyl (19.4 g, 124 mmol) was next added, followed by the addition of $Ni(Ac)_2$ (10.9 g, 62.0 mmol) which changed the reaction color to green. The mixture was heated to 63 °C and was allowed to stir for 1 h. The dropwise addition of *t*-amylONa (25.0 mL of 5.00 M soln, 124 mmol) was carried out at reflux (63 °C),

and the reaction mixture was allowed to stir for an additional 2 h. With the organametallic reagent ready for use, a solution of **1c** (7.24 g, 31.0 mmol) and **2c** (9.36 g, 31.0 mmol) in THF (60.0 mL) was added to the reaction via syringe. The reaction was allowed to proceed for 4 h, until no starting material remained as determined by TLC. The reaction mixture was cooled to room temperature, and quenched using 95% EtOH (250 mL) until H_2 evolution ceased, and then acidified with 10% aq HCl (500 mL). The products were extracted with Et_2O (6 x 100 mL) and dried over $MgSO_4$. TLC indicated three products: two homocoupled, and the desired heterocoupled product. The solvent was evaporated and the product mixture was separated using column chromatography with silica gel as the stationary phase and petroleum ether/toluene (4:1) mixtures as eluent. The solvent was evaporated from the fractions containing the desired product to yield 1.74 g (20%), of 4'-Heptyl-4-methoxy-1,1'-biphenyl: mp 68 °C; ^1H NMR ($CDCl_3$): δ 0.89 (t, CH_3, 3 H), 1.35 (br d, CH_2, 8 H), 1.64 (qt, CH_2, 2 H), 2.59 (t, CH_2, 2 H), 3.78 (s, OCH_3, 3 H), 6.93 (d, J = 9 Hz, 2 H), 7.20 (d, J = 8 Hz, 2 H), 7.48–7.59 (m, 4 H). GLC–MS (M^+) 282, r_t 10.07 min. HRMS in EI mode Calcd for $C_{20}H_{26}O$: 282.1983. Found: 282.1964. Δ 1.96 mmass units.

Preparation of 4-hydroxy-4'-methyl-1,1'-biphenyl, (4a).[32] A flask containing **3a** (1.26 g, 6.88 mmol) in CH_2Cl_2 (50 mL) was cooled to -78 °C in an acetone–dry-ice bath. BBr_3 (42.0 mL of 1.00 M soln, 42.0 mmol) was added via syringe, and the mixture was allowed to warm to room temperature overnight. Upon completion, the reaction was quenched using MeOH (100 mL). The MeOH solution

was evaporated, and the residue was taken up in Et_2O (90 mL). H_2O (15 mL) was then added, and the organic layer containing the product was extracted and dried over $MgSO_4$. The solvent was evaporated giving 4-hydroxy-4'-methyl-1,1'-biphenyl that required no further purification (1.18 g, 94%): mp 151–153 °C; lit.[41] mp 152–153 °C; ^1H NMR ($CDCl_3$): δ 2.38 (s, CH_3, 3 H), 4.85 (s, OH, 1 H), 6.90 (d, J = 9 Hz, 2 H), 7.25 (d, J = 8 Hz, 2 H), 7.40–7.60 (m, 4 H). GLC–MS (M^+) 184, r_t 8.90 min. *Anal.* Calcd for $C_{13}H_{11}O$: C, 84.75; H, 6.56. Found: C, 84.97; H, 6.56.

4-Hydroxy-4'-propyl-1,1'-biphenyl, (4b).[32] A flask containing **3b** (2.54 g, 13.4 mmol) in CH_2Cl_2 (100 mL) was cooled to -78 °C in an acetone–dry-ice bath. BBr_3 (80.0 mL of 1.00 M soln, 80.0 mmol) was added via syringe, and the mixture was allowed to warm to room temperature overnight. Upon completion, the reaction was quenched using MeOH (200 mL). The MeOH solution was evaporated, and the residue was taken up in Et_2O (180 mL). H_2O (30 mL) was then added, and the organic layer containing the product was extracted and dried over $MgSO_4$. The solvent was evaporated giving 4-hydroxy-4'-propyl-1,1'-biphenyl that required no further purification (2.67 g, 94%): mp 148–150 °C; ^1H NMR ($CDCl_3$): δ 0.96 (t, CH_3, 3 H), 1.68 (sx, CH_2, 2 H), 2.59 (t, CH_2, 2 H), 4.70 (s, OH, 3 H), 6.88 (d, J = 9 Hz, 2 H), 7.21 (d, J = 8 Hz, 2 H), 7.45–7.57 (m, 4 H). GLC–MS (M^+) 212, r_t 10.10 min. *Anal.* Calcd for $C_{15}H_{16}O$: C, 84.52; H, 7.97. Found: C, 84.77; H, 7.65.

4'-Heptyl-4-Hydroxy-1,1'-biphenyl, (4c).[32] A flask containing **3c** (0.64 g, 2.48 mmol) in CH_2Cl_2 (30 mL) was cooled to

-78 °C in an acetone–dry-ice bath. BBr_3 (14.9 mL of 1.00 M soln, 14.9 mmol) was added via syringe, and the mixture was allowed to warm to room temperature overnight. Upon completion, the reaction was quenched using MeOH (60 mL). The MeOH solution was evaporated, and the residue was taken up in Et_2O (90 mL). H_2O (15.0 mL) was then added, and the organic layer containing the product was extracted and dried over $MgSO_4$. The solvent was evaporated giving 4-hydroxy-4'-heptyl-1,1'-biphenyl that required no further purification (0.62 g, 93%): mp 142–145 °C;. ^1H NMR ($CDCl_3$): δ 0.89 (t, CH_3, 3 H), 1.30 (br d, CH_2, 8 H), 1.63 (qt, CH_2, 2 H), 2.64 (t, CH_2, 2 H), 4.77 (s, OH, 3 H), 6.90 (d, J = 9 Hz, 2 H), 7.24 (d, J = 8 Hz, 2 H), 7.47–7.59 (m, 4 H). GLC–MS (M^+) 268, r_t 13.15 min. *Anal.* Calcd for $C_{19}H_{24}O$: C, 85.03; H, 9.01. Found: C, 84.97; H, 9.04.

Preparation of 1-(*n*-Heptyl)-4-iodobenzene, (2c).[33] To a mixture of concd H_2SO_4 (12.2 g) and H_2O (36.5 mL) was added **5** (5.00 g, 26.1 mmol), and the mixture was then cooled to 0 °C. A mixture of $NaNO_2$ (3.60 g, 52.2 mmol) and H_2O (7.56 mL) was then added, and the mixture was allowed to stir for 15 min. A soln of KI (12.8 g, 78.3 mmol) in H_2O (39 mL) was added slowly. The evolution of N_2 gas had already occurred during the reaction; therefore, it was unnecessary to warm the reaction in a water bath to initiate the reaction. The resulting product mixture was taken up in Et_2O and subsequently washed with aq sodium thiosulfate and then brine. The organic layer was separated, the solvent was evaporated, and the crude product mixture was separated using column chromatography with silica gel as the stationary phase and

petroleum ether/toluene (3:1) mixture as eluent Evaporation of the solvent from the fractions containing the desired product to yielded 4.22 g (54%) of the 1-(*n*-heptyl)-4-iodobenzene: bp 167 °C (10 mm Hg); lit.[33] bp 165 °C (10 mm Hg). ^{1}H NMR ($CDCl_3$): δ 0.88 (t, CH_3, 3 H), 1.30 (br d, CH_2, 8 H), 1.58 (qt, CH_2, 2 H), 2.53 (t, CH_2, 2 H), 6.93 (d, J = 9 Hz, 2 H), 7.59 (d, J = 8 Hz, 2 H). GLC–MS (M^+) 302, r_t 7.02 min.

4'-Methyl-1-1'-biphenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside, (7aβ)[35,36]. To a solution of **6** (1.28 g, 3.30 mmol), and **4a** (0.50 g, 2.70 mmol) in CH_2Cl_2 (220 mL) maintained under argon was added $SnCl_4$ (0.63 mL, 5.40 mmol). The reaction mixture stirred at -18 °C for 4 h and was then allowed to warm to room temperature at which time the reaction was quenched with 10% aq $NaHCO_3$ until the mixture was neutral. The product was extracted with $CHCl_3$ (6 x 75 mL), and the combined fractions were washed with H_2O (40 mL) and brine (40 mL), and then dried over $MgSO_4$. The solvent was evaporated, and the product mixture was separated using column chromatography with silica gel as the stationary phase with hexane/EtOAc (3:2) mixture as eluent The solvent was evaporated from the fractions containing the desired product to yield 0.79 g (57%) of the 4'-methyl-1-1'-biphenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside: mp 158–160 °C; ^{1}H NMR ($CDCl_3$): δ 2.39 (s, CH_3, 3 H), 2.04 (s, OAc, 3 H), 2.06 (s, OAc, 3 H), 2.08 (s, OAc, 3 H), 2.09 (s, OAc, 3 H), 3.89 (m, 1 H, H-5), 4.17 (dd, 1 H, H-6a, J = 2 Hz), 4.30 (dd, 1 H, H-6b, J = 5 Hz), 5.09–5.34 (m, 4 H, H-1, 2, 3, 4), 7.05 (d, J = 9 Hz, 2 H), 7.22 (d, J = 8 Hz, 2 H), 7.40–7.53 (m, 4 H). *Anal.* Calcd for $C_{27}H_{30}O_{10}$: C, 63.03; H, 5.88. Found: C, 62.97; H, 5.91.

4'-Propyl-1-1'-biphenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside, (7bβ)[35,36]. To a solution of **6** (0.68 g, 1.74 mmol), and **4b** (0.20 g, 0.74 mmol) in CH_2Cl_2 (100 mL) maintained under argon was added $SnCl_4$ (0.22 mL, 1.88 mmol). The reaction mixture stirred at -18 °C for 4 h and was then allowed to warm to room temperature at which time the reaction was quenched with 10% aq $NaHCO_3$ until the mixture was neutral. The product was extracted with $CHCl_3$ (6 x 40 mL), and the combined fractions were washed with H_2O (20 mL) and brine (20 mL), and then dried over $MgSO_4$. The solvent was evaporated, and the product mixture was separated using column chromatography with silica gel as the stationary phase with hexane/EtOAc (3:2) mixture as eluent The solvent was evaporated from the fractions containing the desired product to yield 0.32 g (62%) of the 4'-propyl-1-1'-biphenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside: mp 152–154 °C; ^{1}H NMR ($CDCl_3$): δ 0.97 (t, CH_3, 3 H), 1.68 (sx, CH_2, 2 H), 2.62 (t, CH_2, 2 H), 3.89 (m, 1 H, H-5), 4.18 (dd, 1 H, H-6a, J = 2 Hz), 4.31 (dd, 1 H, H-6b, J = 3 Hz), 5.10–5.41 (m, 4 H, H-1, 2, 3, 4), 7.04 (d, J = 9 Hz, 2 H), 7.24 (d, J = 8 Hz, 2 H), 7.40–7.51 (m, 4 H). *Anal.* Calcd for $C_{29}H_{34}O_{10}$: C, 63.96; H, 6.66. Found: C, 63.51; H, 6.32.

4'-Heptyl-1-1'-biphenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside, (7cβ)[35,36]. To a solution of **6** (0.38 g, 0.97 mmol), and **4c** (0.20 g, 0.74 mmol) in CH_2Cl_2 (180 mL) maintained under argon was added $SnCl_4$ (0.17 mL, 1.5 mmol). The reaction mixture stirred at -18 °C for 4 h and was then allowed to warm to room temperature at which time the reaction was quenched with 10% aq

$NaHCO_3$ until the mixture was neutral. The product was extracted with $CHCl_3$ (6 x 50 mL), and the combined fractions were washed with H_2O (20 mL) and brine (20 mL), and then dried over $MgSO_4$. The solvent was evaporated, and the product mixture was separated using column chromatography with silica gel as the stationary phase with hexane/EtOAc (3:2) mixture as eluent The solvent was evaporated from the fractions containing the desired product to yield 0.12 g (28%) of the 4'-heptyl-1-1'-biphenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside: mp 140–142 °C; ^1H NMR ($CDCl_3$): δ 0.88 (t, CH_3, 3 H), 1.42 (br d, CH_2, 8 H), 1.64 (qt, CH_2, 2 H), 2.62 (t, CH_2, 2 H), 3.89 (m, 1 H, H-5), 4.18 (dd, 1 H, H-6a, J = 2 Hz), 4.31 (dd, 1 H, H-6b, J = 3 Hz), 5.10–5.35 (m, 4 H, H-1, 2, 3, 4), 7.05 (d, J = 9 Hz, 2 H), 7.24 (d, J = 8 Hz, 2 H), 7.40–7.51 (m, 4 H). *Anal.* Calcd for $C_{32}H_{46}O_{10}$: C, 66.21; H, 7.07. Found: C, 65.69; H, 7.03.

4'-Methyl-1-1'-biphenyl α-D-glucopyranoside, (8a$_\alpha$).[35,36,38] To a solution **6** (2.88 g, 7.41 mmol) and **4a** (1.05 g, 5.70 mmol) in CH_2Cl_2 (230 mL), maintained under argon, was added $SnCl_4$ (1.33 mL, 11.2 mmol). The reaction stirred at 52 °C for 96 h and was allowed to cool to room temperature, at which time the reaction was quenched with 10% aq $NaHCO_3$ until the mixture was neutral. The product was extracted with $CHCl_3$ (6 x 75 mL), and the combined extracts were washed with H_2O (20 mL) and brine (50 mL), and then dried over $MgSO_4$. The solvent was evaporated, and the product mixture was separated using column chromatography with silica gel as the stationary phase with hexane/EtOAc (3:2) mixture as eluent The solvent was evaporated from the fractions containing the α and β

anomers to give 1.18 g (40%) of the mixture of anomers. To a solution of **7aα,β** (1.96 g, 3.80 mmol) in MeOH (50 mL), maintained under argon, was added MeONa (38.0 mL of 0.20 M soln). The reaction stirred at 25 °C for 12 h, and the reaction was neutralized with Dowex-50 X 2 H^+ ion exchange resin. After stirring for 10 min, the resin was removed via vacuum filtration. The solvent was evaporated, and the product mixture was separated using gradient column chromatography with silica gel as the stationary phase with EtOAc/(1–5%) MeOH mixture as eluent. The solvent was evaporated from the fractions containing the desired products to yield 0.73 g (55%) overall, and 0.04 g (3.3%) of the α product (R_f 0.30, 95:5 EtOAc/MeOH), 4'-methyl-1-1'-biphenyl α-D-glucopyranoside: mp 188–190 °C; cp 218–220 °C; ^{1}H NMR (DMSO-*d6*): δ 2.32 (s, CH_3, 3 H), 3.17–3.72 (m, H-2, 3, 4, 5, 6a, 6b, 6H), 4.50 (t, CH_2OH, 1 H), 4.78–5.10 (m, OH, 3 H), 5.41 (d, H-1, 1 H, J = 3.5 Hz), 7.15 (d, J = 7 Hz, 2 H), 7.24 (d, J = 8 Hz, 2 H), 7.50–7.58 (m, 4 H). *Anal.* Calcd for $C_{19}H_{22}O_6$•0.45 H_2O: C, 64.38; H, 6.51. Found: C, 64.37; H, 6.52.

4'-Methyl-1-1'-biphenyl β-D-glucopyranoside, (8aβ).[35,36,38] The solvent was evaporated from the fractions containing the desired product to yield 0.69 g (52%), R_f 0.40 (95:5 EtOAc/MeOH). The 4'-methyl-1-1'-biphenyl β-D-glucopyranoside: mp 198–200 °C; cp 204–206 °C; ^{1}H NMR (DMSO-*d6*): δ 2.31 (s, CH_3, 3 H), 3.46 (m, H-6a, 1 H), 3.71 (dd, J = 3 Hz, H-6b, 1 H), 4.68 (t, CH_2OH, 1 H), 4.88 (d, H-1, J = 7 Hz, 1 H), 5.03–5.33 (m, OH, 3 H), 7.12 (d, J = 9 Hz, 2 H), 7.25 (d, J = 8 Hz, 2 H), 7.50–7.59 (m, 4 H). *Anal.* Calcd for $C_{19}H_{22}O_6$•0.90 H_2O: C, 62.94; H, 6.62. Found: C, 62.93; H, 6.69.

4'-Propyl-1-1'-biphenyl α-D-glucopyranoside, (8bα). [35,36,38] To a solution **6** (2.40 g, 6.13 mmol) and **4b** (1.00 g, 4.71 mmol) in CH_2Cl_2 (200 mL), maintained under argon, was added $SnCl_4$ (1.13 mL, 9.50 mmol). The reaction stirred at 52 °C for 96 h and was allowed to cool to room temperature at which time the reaction was quenched with 10% aq $NaHCO_3$ until the mixture was neutral. The product was extracted with $CHCl_3$ (6 x 70 mL), and the combined extracts were washed with H_2O (40 mL) and brine (40 mL), and then dried over $MgSO_4$. The solvent was evaporated, and the product mixture was separated using column chromatography with silica gel as the stationary phase with hexane/EtOAc (3:2) mixture as eluent The solvent was evaporated from the fractions containing the α and β anomers to give 1.30 g (50%) of the mixture of anomers. To a solution of **7bα,β** (1.67 g, 2.94 mmol) in MeOH (50 mL), maintained under argon, was added MeONa (30.0 mL of 0.20 M soln). The reaction stirred at 25 °C for 12 h, and the reaction was neutralized with Dowex-50 X 2 H^+ ion exchange resin. After stirring for 10 min, the resin was removed via vacuum filtration. The solvent was evaporated, and the product mixture was separated using gradient column chromatography with silica gel as the stationary phase with EtOAc/(1–5%) MeOH mixture as eluent. The solvent was evaporated from the fractions containing the desired products to yield 0.52 g (47%) overall, and 0.05 g (4.2%) of the α product (R_f 0.31, 95:5 EtOAc/MeOH), 4'-propyl-1-1'-biphenyl α-D-glucopyranoside: mp 158–160 °C; cp 224–226 °C; ^1H NMR (DMSO-d_6): δ 0.91 (t, CH_3, 3 H), 1.61 (sx, CH_2, 2 H), 2.57 (t, CH_2, 2 H), 3.20–3.72 (m, H-2, 3, 4, 5, 6a,

6b, 6H), 4.49 (t, CH_2OH, 1 H), 4.75–5.63 (m, OH, 3 H), 5.41 (d, H-1, 1 H, J = 3.5 Hz), 7.15 (d, J = 9 Hz, 2 H), 7.24 (d, J = 8 Hz, 2 H), 7.51–7.59 (m, 4 H). *Anal.* Calcd for $C_{21}H_{26}O_6 \cdot 0.450\ H_2O$: C, 64.38; H, 6.51. Found: C, 64.37; H, 6.52.

4'-Propyl-1-1'-biphenyl β-D-glucopyranoside, (8bβ).[35,36,38] The solvent was evaporated from the fractions containing the desired product to yield 0.47 g (43%), R_f 0.42 (95:5 EtOAc/MeOH). The 4'-propyl-1-1'-biphenyl β-D-glucopyranoside: mp 192–194 °C; cp 236–238 °C; ^{1}H NMR (DMSO-$d6$): δ 0.91 (t, CH_3, 3 H), 1.62 (sx, CH_2, 2 H), 2.59 (t, CH_2, 2 H), 3.10–3.40 (m, H-2, 3, 4, 5, 4 H), 3.51 (m, H-6a, 1 H), 3.72 (m, H-6b, 1 H) 4.59 (t, CH_2OH, 1 H), 4.89 (d, H-1, J = 7 Hz, 1 H), 5.04–5.34 (m, OH, 3 H), 7.09 (d, J = 9 Hz, 2 H), 7.25 (d, J = 8 Hz, 2 H), 7.51–7.58 (m, 4 H). *Anal.* Calcd for $C_{21}H_{26}O_6 \cdot 0.60\ H_2O$: C, 65.47; H, 7.12. Found: C, 65.47; H, 7.20.

4'-Heptyl-1-1'-biphenyl α-D-glucopyranoside, (8cα).[35,36,38] To a solution **6** (2.74 g, 7.03 mmol) and **4c** (1.45 g, 5.40 mmol) in CH_2Cl_2 (50.0 mL), maintained under argon, was added $SnCl_4$ (1.28 mL, 10.8 mmol). The reaction stirred at 40 °C for 48 h and was allowed to cool to room temperature at which time the reaction was quenched with 10% aq $NaHCO_3$ until the mixture was neutral. The product was extracted with $CHCl_3$ (10 x 70 mL), and the combined extracts were washed with H_2O (40 mL) and brine (40 mL), and then dried over $MgSO_4$. The solvent was evaporated, and the product mixture was separated using column chromatography with silica gel as the stationary phase with hexane/EtOAc (3:2) mixture as eluent

The solvent was evaporated from the fractions containing the α and β anomers to give 1.41 g (43%) of the mixture of anomers. To a solution of **7cα,β** (1.41 g, 2.35 mmol) in MeOH (50.0 mL), maintained under argon, was added MeONa (30.0 mL of 0.20 M soln). The reaction stirred at 25 °C for 12 h, and the reaction was neutralized with Dowex-50 X 2 H^+ ion exchange resin. After stirring for 10 min, the resin was removed via vacuum filtration. The solvent was evaporated, and the product mixture was separated using gradient column chromatography with silica gel as the stationary phase with EtOAc/(1–5%) MeOH mixture as eluent. The solvent was evaporated from the fractions containing the desired products to yield 0.74 g (73%) overall, and 0.44 g (44%) of the α product (R_f 0.35, 95:5 EtOAc/MeOH), 4'-heptyl-1-1'-biphenyl α-D-glucopyranoside: mp 134–136 °C; cp 242–244 °C; ^{1}H NMR (DMSO-*d6*): δ 0.85 (t, CH_3, 3 H), 1.26 (br d, CH_2, 8 H), 1.58 (qt, CH_2, 2 H), 2.59 (t, CH_2, 2 H), 3.12–3.73 (m, H-2, 3, 4, 5, 6a, 6b, 6H), 4.48 (t, CH_2OH, 1 H), 4.96–5.10 (m, OH, 3 H), 5.42 (d, H-1, J = 3.5 Hz, 1 H), 7.14 (d, J = 9 Hz, 2 H), 7.24 (d, J = 8 Hz, 2 H), 7.51–7.59 (m, 4 H). *Anal.* Calcd for $C_{25}H_{34}O_6 \cdot 0.20\ H_2O$: C, 69.17; H, 7.99. Found: C, 69.13; H, 7.91.

4'-Heptyl-1-1'-biphenyl β-D-glucopyranoside, (8cβ). [35,36,38] The solvent was evaporated from the fractions containing the desired product to yield 0.28 g (29%), R_f 0.45 (95:5 EtOAc/MeOH). The 4'-heptyl-1-1'-biphenyl β-D-glucopyranoside: mp 134–136 °C; cp 242–244 °C; ^{1}H NMR (DMSO-*d6*): δ 0.85 (t, CH_3, 3 H), 1.28 (br d, CH_2, 8 H), 1.59 (qt, CH_2, 2 H), 2.58 (t, CH_2, 2 H), 3.12–3.54 (m, H-2, 3, 4, 5, 6a, 5 H), 3.66 (dd, H-6b, J = 2 Hz, 1 H), 4.59 (t, CH_2OH, 1 H), 4.89

(d, H-1, J = 7 Hz, 1 H), 5.04–5.34 (m, OH, 3 H), 7.10 (d, J = 9 Hz, 2 H), 7.24 (d, J = 8 Hz, 2 H), 7.50–7.59 (m, 4 H). *Anal.* Calcd for $C_{25}H_{34}O_6 \cdot 0.72\ H_2O$: C, 67.70; H, 8.05. Found: C, 67.72; H, 8.03.

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