condition as for **17**, t_R of intermediate 6.6 min, of **18** 11.2 min). After the reaction was complete, most of the ethanol was removed under reduced pressure and the residue was diluted with a mixture of 250 mL of H_2O and 500 mL of ether. The ether layer was washed with saturated $NaHCO_3$ (2 × 250 mL), water (1 × 250 mL), and brine (1 × 250 mL). The ether layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was distilled to yield **18** (13.98 g, 60.7 mmol, 61%): $bp_{2.5}$ 81-84 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 1.15, 1.22, 1.25 (3 t, J = 7.0-7.4 Hz, 9 H, CH_3), 2.30-2.45 (m, 2 H, $CH_2C{=}C$), 2.78 (dt, 1 H, CHC=O), 3.45-3.80 (m, 4 H, OCH_2), 4.15 (q, J = 7.4 Hz, 2 H, OCH_2), 4.65 (d, 1 H, CH), 4.9-5.15 (m, 2 H, $H_2C{=}$), 5.75 (m, 1 H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.42, 15.29, 15.36 (CH_3), 32.84 (CH_2), 49.98 (CH) 60.44, 61.71, 62.74 (CH_2O), 102.96 (CH), 116.81 ($=CH_2$), 135.05 (=CH), 172.60 (C=O).

D,L-2-(Hydroxymethyl)-4-pentenal Diethyl Acetal (19). To a cold (0-5 °C) suspension of $LiAlH_4$ (12.25 g, 61 mmol) in 500 mL of ether was added dropwise **18** (13.98 g, 61 nmol) in 50 mL of ether. During the addition the temperature did not exceed 5 °C. After the addition was complete, the reaction mixture was allowed to warm to room temperature. GC analysis indicated the reaction was complete (same conditions as for **17**, t_R of **19** 9.6 min). Brine was added to quench the reaction. The ether was washed with H_2O (1 × 500 mL), 2 N H_2SO_4 (1 × 500 mL), saturated $NaHCO_3$ (1 × 500 mL), and brine (1 × 500 mL). The ether layer was dried over Na_2SO_4, and the solvent was removed under water aspirator vacuum to yield **19** (12.89 g, quantitative yield). This was used without further purification: ^1H NMR (200 MHz, $CDCl_3$) δ 1.23, 1.24 (2 t, J = 7.0 Hz, 6 H, CH_3), 1.85-2.33 (m, 3 H, $HCCH_2C{=}C$), 2.90 (br s, 1 H, OH), 3.45-3.89 (m, 6 H, CH_2O), 4.47 (d, J = 5.4 Hz, 1 H, CH), 5.00-5.13 (m, 2 H, $H_2C{=}$), 5.70-5.91 (m, 1 H, =CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.25, 15.32 (CH_3), 31.55 (CH_2), 43.19 (CH), 62.19, 62.37, 64.00 (CH_2O), 106.02 (CH), 116.54 ($C{=}CH_2$), 136.20 (=CH). Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.82; H, 10.71. Found: C, 63.50; H, 10.51.

5-Allyl-5-deoxy-L-*xylo*-hexulose (16). A solution containing **19** (0.75 g, 4 mmol), water (8 mL), DMSO (2 mL), and CH_3SO_2OH (100 μL) was stirred for 15 h at room temperature. The reaction was monitored by GC (same as **17**, t_R of **19** 9.5 min, **15** 5.1 min). FDP-Na_3 (0.560 g, 1.2 mmol) was added along with 5 mL of 20% DMSO in H_2O. The solution was adjusted to pH 6.8. Aldolase (350 units) and TPI (500 units) were added. The reaction was stopped after 48 h. The solution was extracted with ether (1 × 15 mL), and the aqueous layer was treated as before to remove the phosphate group. TLC (silica gel, ethyl acetate-methanol-H_2O, 12:6:2, R_f of the product 0.80) indicated no fructose (R_f 0.45). The solution was neutralized and freeze-dried. Trituration with ethanol, followed by removing solvent under reduced pressure, yielded a clean sample of **16**. Further purification was done (silica gel 20:4:1 ethyl acetate-methanol-water) to yield **16** (210 mg, 1.0 mmol, 50%). Residue was crystallized from CH_2Cl_2-ether: mp 112-3 °C; $[\alpha]^{26}_D$ -46.5° (*c* 0.37, water); ^1H NMR (200 MHz, D_2O) δ 1.56 (m, 1 H, CH), 1.74 (m, 1 H, C=CCH), 2.19 (m, 1 H, C=CCH), 3.20-3.90 (m, 6 H, CHOD), 4.87 (m, 2 H, $=CH_2$), 5.66 (m, 1 H, =CH); ^{13}C NMR (50 MHz, D_2O) δ 31.68 (C5), 41.63 (C7), 62.53, 63.69, 71.80, 71.99 (CHOD), 98.11 (C2), 116.81 ($=CH_2$), 135.70 (=CH). Anal. Calcd for $C_9H_{16}O_5$: C, 52.91; H, 7.92. Found: C, 52.82; H, 7.71. For X-ray structure, see Figure 1.

Vinylation-Electrophilic Cyclization of Aldopentoses: Easy and Stereoselective Access to *C*-Glycopyranosides of Rare Sugars

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A new C-glycosylation procedure, which involves vinylation of a properly protected aldopentose and mercuriocyclization of the obtained glycoenitol, is described; it allows *C*-glycopyranosides of rare sugars to be obtained from easily available pentoses. 2,3,5-Tri-*O*-benzyl-D-arabinose (**1a**) reacted with vinylmagnesium bromide to afford a mixture of D-gluco and D-manno 1,2-dideoxy-4,5,7-tri-*O*-benzyl-1-heptenitols **2a** and **2b** and with divinylzinc to afford only **2a**. 2,3,5-Tri-*O*-benzyl-D-ribose (**1b**) afforded mainly 1,2-dideoxy-4,5,7-tri-*O*-benzyl-D-*altro*-1-heptenitol (**2c**) with both vinylmetallic reagents, whereas 5-*O*-trityl-2,3-*O*-isopropylidene-D-ribose (**1e**) afforded 1,2-dideoxy-7-*O*-trityl-4,5-*O*-isopropylidene-D-*allo*-1-heptenitol (**2h**). Vinylation of 2,3,5-tri-*O*-benzyl-D-xylose (**1c**) afforded a mixture of D-iodo and D-gulo 1,2-dideoxy-4,5,7-tri-*O*-benzyl-1-heptenitols **2d** and **2e**, the first one being largely predominant when divinylzinc was employed. 2,3,5-Tri-*O*-benzyl-D-lyxose (**1d**) reacted only with vinylmagnesium bromide to afford a mixture of D-talo and D-galacto 1,2-dideoxy-4,5,7-tri-*O*-benzyl-1-heptenitols **2f** and **2g**. The enitols **2a-h** where cyclized with mercuric acetate and then processed with potassium chloride to afford the corresponding (D-glycopyranosylmethyl)mercurium chlorides **3a-h**. The cyclization was stereoselective except for **2e**, and in all cases, except **3d**, the anomeric substituent of the *C*-glycopyranoside was cis related with the alkoxy substituent at the adjacent carbon atom. So α-gluco, α-manno, β-altro, β-ido, α- and β-gulo, β-talo, α-galacto, and α-allo *C*-glycopyranosides were obtained.

The synthesis of *C*-glycosyl compounds has become an area of increasing interest as these compounds are useful chiral syntons[1] and potential inhibitors of metabolic processes.[2]

The C-glycosylation procedures reported until now generally involve the attack of a carbon nucleophile at the anomeric center of the parent sugar[3] or, more recently, the reaction of a glycosyl radical[4] or a glycosyl carbanion[5] with

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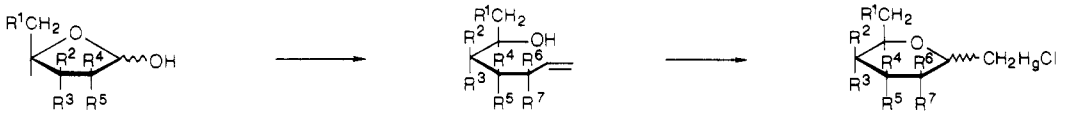
Scheme I



1a: $R^1 = R^3 = R^4 = OBn$; $R^2 = R^2 = H$
b: $R^1 = R^3 = R^5 = OBn$; $R^2 = R^4 = H$
c: $R^1 = R^2 = R^5$; OBn; $R^3 = R^4 = H$
d: $R^1 = R^2 = R^4 = OBn$; $R^3 = R^5 = H$
e: $R^1 = OTr$; $R^3 = R^5 = OC(CH_3)_2O$; $R^2 = R^4 = H$

2a: $R^1 = R^3 = R^4 = OBn$; $R^2 = R^5 = R^6 = H$; $R^7 = OH$ (gluco)
b: $R^1 = R^3 = R^4 = OBn$; $R^2 = R^5 = R^7 = H$; $R^6 = OH$ (manno)
c: $R^1 = R^3 = R^5 = OBn$; $R^2 = R^4 = R^7 = H$; $R^6 = OH$ (altro)
d: $R^1 = R^2 = R^5 = OBn$; $R^3 = R^4 = R^7 = H$; $R^6 = OH$ (ido)
e: $R^1 = R^2 = R^5 = OBn$; $R^3 = R^4 = R^6 = H$; $R^7 = OH$ (gulo)
f: $R^1 = R^2 = R^4 = OBn$; $R^3 = R^5 = R^7 = H$; $R^6 = OH$ (talo)
g: $R^1 = R^2 = R^4 = OBn$; $R^3 = R^5 = R^6 = H$; $R^7 = OH$ (galacto)
h: $R^1 = OTr$; $R^3 = R^5 = OC(CH_3)_2O$; $R^2 = R^4 = R^6 = H$; $R^7 = OH$ (allo)
i: $R^1 = R^3 = R^5 = OBn$; $R^2 = R^4 = R^6 = H$; $R^7 = OH$ (allo)
l: $R^1 = OTr$; $R^3, R^5 = OC(CH_3)_2O$; $R^2 = R^4 = R^7 = H$; $R^6 = OTr$ (altro)

3a: $R^1 = R^3 = R^4 = OBn$; $R^2 = R^5 = R^6 = H$; $R^7 = OH$; α
b: $R^1 = R^3 = R^4 = OBn$; $R^2 = R^5 = R^7 = H$; $R^6 = OH$; α
c: $R^1 = R^3 = R^5 = OBn$; $R^2 = R^4 = R^7 = H$; $R^6 = OH$; α
d: $R^1 = R^2 = R^5 = OBn$; $R^3 = R^4 = R^7 = H$; $R^6 = OH$; $\alpha + \beta$
e: $R^1 = R^2 = R^5 = OBn$; $R^3 = R^4 = R^6 = H$; $R^7 = OH$; $\alpha + \beta$
f: $R^1 = R^2 = R^4 = OBn$; $R^3 = R^5 = R^7 = H$; $R^6 = OH$; β
g: $R^1 = R^2 = R^4 = OBn$; $R^3 = R^5 = R^6 = H$; $R^7 = OH$; α
h: $R^1 = OTr$; $R^3, R^5 = OC(CH_3)_3O$; $R^2 = R^4 = R^6 = H$; $R^7 = OH$; α

Table I. Reaction of Aldopentoses with Vinylmetallic Reagents

exp	compd	M	temp, °C	time, h	yield, %	products	ratio
1	**1a**	Mg	−30	15	95	**2a + 2b**	53/47
2		Mg	−50	20	90	**2a + 2b**	38/62
3		Zn	20	3	95	**2a**	
4	**1b**	Mg	−30	15	95	**2c + 2i**	75/25
5		Mg	−50	20	90	**2c + 2i**	87/13
6		Zn	20	20	80	**2c + 2i**	95/05
7	**1c**	Mg	−30	150	85	**2d + 2e**	67/33
8		Mg	20	16	100	**2d + 2e**	60/40
9		Zn	20	120	74	**2d + 2e**	85/15
10	**1d**	Mg	20	120	75	**2f + 2g**	41/59
11	**1e**	Mg	−30	20	85	**2l + 2h**	15/85

the proper acceptor. All the above procedures are hardly applicable to the synthesis of *C*-glycosyl compounds of rare sugars, such as D-altrose, D-allose, D-gulose, D-idose, or D-talose, because of the very high cost of the parent sugar.

In light of the fact that D-pentoses are all commercially available and cheap, we decided to investigate an alternative way to *C*-hexopyranosides that is based on the reaction of a pentofuranose with a vinylmetallic reagent (see Scheme I) to obtain an enitol **2**, which can be cyclized according to well-experimented procedures,[6] to afford a *C*-glycopyranoside **3**. It is worth noting that **3** has a free hydroxyl group, which enhances the potentiality of the method, as it allows its conversion, for example, to an amino or a fluoro group.

This procedure creates two new stereogenic centers, at C-2 and at the anomeric position of the *C*-glycosyl compounds. The stereochemistry of the first one depends on the stereochemical course of the attack at the carbonyl function of the aldopentose. In this regard some examples of stereoselective addition of organometallic reagents to carbohydrates are reported.[7] However, as the present work is dedicated to *C*-glycosyl compounds of rare sugars, both isomers are of interest. So also the experiments which afford both isomers are valuable. The second chiral center, which defines the anomeric configuration of the *C*-glycosyl compound, is formed during the ring closure. To effect this closure we decided to use the mercuriocyclization procedure, which has a good degree of stereoselectivity.[6]

Results and Discussions

2,3,5-Tri-*O*-benzyl-D-arabinofuranose (**1a**),[8] 2,3,5-tri-*O*-benzyl-D-ribofuranose (**1b**),[9] 2,3,5-tri-*O*-benzyl-D-xylofuranose (**1c**)[10] and 2,3,5-tri-*O*-benzyl-D-lyxofuranose (**1d**)[10] were treated with vinylmagnesium bromide in THF (see Table I). The reaction showed negligible stereoselectivity

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Table II. Mercuriocyclization of 2 and Diagnostic ^{1}H NMR Values of 3

compd	time, h	prod. (%)[a]	$J_{1,2}$, Hz	$J_{2,3}$, Hz	$J_{3,4}$, Hz	$J_{4,5}$, Hz	structure
2a	36	**3a** (51)	3	5	5	5	α-gluco
2b	200	**3b** (20)[b]	8	3			α-manno
2c	48	**3c** (71)	1	3	3	10	β-altro
2d	72	**3dβ** (73), **3dα** (7)	1	3	3	1.5	β-ido
			8	8	8	5.5	α-ido
2e	72	**3eα** (43), **3eβ** (30)	2	3	9	6.5	α-gulo
			10	3.5		1	β-gulo
2f	36	**3f** (61)	3.5	6.5		5	β-talo
2g	90	**3g**[d] (28)	3.5	9	2	6	α-galacto
2h	200	**3h**[d] (25)[c]	2	4.5	7	6	α-allo

[a] Unoptimized yields. [b] 50% of unreacted **2b** was recovered. [c] 55% of unreacted **2h** was recovered. [d] Traces of the β-anomer were also detected.

(experiments 1, 2, 7, 8, and 10) except in the case of 2,3,5-tri-*O*-benzyl-D-ribofuranose (**1b**) (experiments 4 and 5), which afforded predominantly the 1,2-dideoxy-4,5,7-tri-*O*-benzyl-D-*altro*-1-heptenitol (**2c**).[11] Small modifications of stereoselectivity were observed lowering the reaction temperature (experiments 2, 5, and 7). If an isopropylidene was employed instead of the benzyl groups to protect the hydroxyls at C-2 and C-3 of D-ribose, the stereochemistry of the reaction was overturned.[7a,b] The reaction of 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranose (**1e**) with vinylmagnesium bromide at −30 °C afforded the 1,2-dideoxy-4,5-*O*-isopropylidene-D-*allo*-1-heptenitol (**2h**)[11] in 70% de[12] (experiment 11 vs experiments 4 and 5).

Divinylzinc gave fairly better results, affording in each case predominantly or solely one diastereoisomer (see Table I):[12] 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**1a**) afforded only[12] the 1,2-dideoxy-4,5,7-tri-*O*-benzyl-D-*gluco*-1-heptenitol **2a**[11] (experiment 3), 2,3,5-tri-*O*-benzyl-D-ribofuranose (**1b**) afforded the 1,2-dideoxy-4,5,7-tri-*O*-benzyl-D-*altro*-1-heptenitol **2c** in 90% de[12] (experiment 6), 2,3,5-tri-*O*-benzyl-D-xylofuranose (**1c**) afforded the 1,2-dideoxy-4,5,7-tri-*O*-benzyl-D-*ido*-1-heptenitol **2d**[11] in 70% de[12] (experiment 9). 2,3,5-Tri-*O*-benzyl-D-lyxofuranose (**1d**) reacted with divinylzinc to negligible extent after 200 h.

The cyclization of the 1,2-dideoxy-*glyco*-1-heptenitols **2** was effected with mercuric acetate and showed, except for **2e**, a good stereoselectivity. We reported[6b] that the mercuriocyclization of 1,2-dideoxy-*glyco*-1-heptenitols such as **2** affords *C*-glycopyranosides with a 1,2-cis relationship. This agree with a preferential attack of the electrophile at the less hindered side of the double bond when this is eclipsed with the oxygen at C-3.[6d] According to these observations, the D-gluco, D-galacto, and D-allo 1,2-dideoxy-*glyco*-1-heptenitols **2a**, **2g**, and **2h** afforded solely[12] the α-*C*-D-glycopyranosides **3a**, **3g**, and **3h**, and the D-altro, D-ido, and D-talo 1,2-dideoxy-*glyco*-1-heptenitols **2c**, **2d**, and **2f** afforded, stereoselectively or solely[12] (see Table II), the β-*C*-D-glycopyranosides **3c**, **3dβ** and **3f**. The mercuriocyclization of the 1,2-dideoxy-4,5,7-tri-*O*-benzyl-D-*gulo*-1-heptenitol **2e** showed negligible stereoselection, affording a 6:4 mixture of α- and β-gulopyranosides **3eα** and **3eβ**. The 1,2-deoxy-4,5,7-tri-*O*-benzyl-D-*manno*-1-heptenitol **2b** showed a unique behavior, affording the α-*C*-D-mannopyranoside **3b** in which the anomeric substituent is trans with respect to the substituent at C-2. This different stereochemical behavior is not unexpected on the light of the known[14] difficulty to obtain β-mannopyranosides. Nevertheless, the fact that in the mercuriocyclization of the 1,2-dideoxy-3,4,5,7-tetra-*O*-benzyl-D-*manno*-1-heptenitol we obtained[6b] mainly a β-*C*-mannopyranoside suggests that the free hydroxyl group at C-3 in **2b** plays a role in the reaction. One hypothesis is that the allylic hydroxyl group attacks the mercurinium ion with formation of an oxirane intermediate, which in turn undergoes the cyclization by the hydroxyl group at C-6, the whole process resulting in a double displacement.

The anomeric configurations of the *C*-glycosyl compounds **3** were deduced from the coupling constants in the ^{1}H NMR spectra (see Table II). In particular the D-manno derivative **3b** showed a 8-Hz ax–ax coupling constant between H-1 and H-2, which can be due only to an α configuration in a $^1C_4$ conformation. The bulky methylmercury chloride substituent prefers to assume the equatorial orientation (with the exception of **3g**), in fact the *J* values (Table II) indicate that the α-*C*-glycopyranosides **3a**, **3b**, **3dα**, and **3eα** are mainly in a $^1C_4$ and the β-*C*-glycopyranosides **3dβ** and **3eβ** in a $^4C_1$ conformation. Assuming that also for the D-altro derivative **3c** and the D-talo derivative **3f** the methylmercury chloride group is in the equatorial position, the $J_{1,2}$ values indicate for **3c** and **3f** a β anomeric configuration.

The above described vinylation–electrophilic cyclization is a simple method which opens the way to the *C*-glycosyl compounds of some rare sugars from easily available pentoses through a simple two-step procedure.

Experimental Section

General Procedures. ^{1}H NMR spectra were recorded with a Varian XL200 spectrometer and ^{13}C NMR spectra with a Bruker WP80 spectrometer for solutions in $CDCl_3$. $[\alpha]_D$ were measured at 20 °C on a Perkin-Elmer 241 polarimeter. Preparative flash-chromatography was performed with Woelm 0–63 silica gel (<230 mesh) silica gel. Thin-layer chromatography (TLC) was performed on Merck silica gel-60 F-254 plates.

Vinylation with Vinylmagnesium Bromide, General Procedure. The aldofuranose **1** (0.4 mmol) dissolved in 1 mL of dry THF was added to 10 equiv of vinylmagnesium bromide[16] in 1 mL of THF at the temperature reported in the Table I. The reaction was monitored by TLC (hexane–ethyl acetate, 7:3, three elutions, for **1a** and **1c**; $CHCl_3$–CH_3CN, 8:2, for **1b**; hexane–benzene, 7:3, two elutions, for **1d** and hexane–ethyl acetate, 8:2, for **1e**). The reaction was quenched with aqueous NH_4Cl and extracted with CH_2Cl_2. The organic phase was washed with diluted HCl and then with water to neutrality, dried with Na_2SO_4, and evaporated. The isomeric products **2c–i**, **2d,e**, and **2f,g** were separated by careful flash-chromatography (hexane–ethyl acetate,

(11) The determination of the configuration of the new stereocenter was effected by conversion into the corresponding glycopyranose (ozonolysis and deprotection), which was gas-chromatographically identified (Sawardeker, J. S.; Sloneker, J. H.; Jeanes, A. *Anal. Chem.* **1965**, *37*, 1602) by comparison with an authentic sample.

(12) Deduced from the ^{13}C NMR spectrum of the reaction mixture.

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7:3; elution order: **2c** before **2i**, **2d** before **2e**, **2g** before **2f**); **2b** was separated from **2a** by crystallization. Nevertheless for preparative purposes it is better to submit the mixture to mercuriocyclization, as the mercurio derivatives are more easily separable.

Vinylation with Divinylzinc, General Procedure. The aldofuranose 1 (0.4 mmol) in 1 mL of dry THF was added to 10 equiv of divinylzinc (obtained by addition of the stoichiometric amount of $ZnBr_2$ in 2 mL of dry THF to vinylmagnesium bromide). The reaction was monitored by TLC and worked up as described for the Grignard reaction.

Mercuriocyclization, General Procedure. A 0.3-mmol portion of **2** in 3 mL of THF was stirred at room temperature under nitrogen and in the dark, with 1 equiv of $Hg(OAc)_2$. The reaction was monitored by TLC (hexane–ethyl acetate, 1:1). KCl (1 equiv) was then added, and the mixture was stirred for 1 *h* more. The THF was evaporated, and the residue was extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and evaporated. The products were purified by flash-chromatography (hexane–ethyl acetate, 6:4).

2a: oil, $[\alpha]_D$ +6.1° (*c* 1, $CHCl_3$); ^1H NMR δ 2.90 (2 H, OH), 3.59–3.76 (4 H), 4.06 (1 H, m, H-6), 4.41 (1 H, m, H-3), 4.50–4.84 (6 H, OCH_2Ph), 5.19 (1 H, dt, *J* = 10, 1.5, and 1.5 Hz, H-1a), 5.34 (1 H, dt, *J* = 17, 1.5, and 1.5 Hz, H-1b), 5.92 (1 H, ddd, *J* = 17, 10, and 5.5 Hz, H-2), 7.3 (15 H, Ar H); ^{13}C NMR 115.68 ppm (C-1). Anal. Calcd for $C_{29}H_{32}O_5$: C, 74.97; H, 7.19. Found: C, 74.68; H, 7.32.

2b: mp 71–73 °C (Et_2O); $[\alpha]_D$ +7.9° (*c* 1, $CHCl_3$); ^1H NMR δ 2.90 (2 H, OH), 3.62 (2 H, d, *J* = 5 Hz, H-7a and H-7b), 3.67 (1 H, dd, *J* = 5.5 and 4 Hz, H-4 or H-5), 3.85 (1 H, dd, *J* = 6.5 and 4 Hz, H-4 or H-5), 4.09 (1 H, m, H-6), 4.48 (1 H, m, H-3), 4.50–4.74 (6 H, OCH_2Ph), 5.24 (1 H, dt, *J* = 10.5, 1.5, and 1.5 Hz, H-1a), 5.41 (1 H, dt, *J* = 17, 1.5, and 1.5 Hz, H-1b), 5.95 (1 H, ddd, *J* = 17, 10.5, and 5 Hz, H-2), 7.3 (15 H, Ar H); ^{13}C NMR 115.92 ppm (C-1). Found: C, 74.82; H, 7.14.

2c: oil; $[\alpha]_D$ +24.8° (*c* 1, $CHCl_3$); ^1H NMR δ 3.00 (2 H, OH), 3.63 (2 H, d, *J* = 5 Hz, H-7a and H-7b), 3.72 (1 H, dd, *J* = 5 and 3.5 Hz, H-4), 3.79 (1 H, t, *J* = 5 Hz, H-5), 4.12 (1 H, q, *J* = 5 Hz, H-6), 4.44 (1 H, m, H-3), 4.50–4.70 (6 H, OCH_2Ph), 5.25 (1 H, dt, *J* = 10.5, 1.5, and 1.5 Hz, H-1a), 5.42 (1 H, dt, *J* = 17, 1.5, and 1.5 Hz, H-1b), 6.00 (1 H, ddd, *J* = 17, 10.5, and 5 Hz, H-2), 7.3 (15 H, Ar H); ^{13}C NMR 115.73 ppm (C-1). Found: C, 75.04; H, 7.33.

2d: oil; $[\alpha]_D$ +6.7° (*c* 1.5, $CHCl_3$); ^1H NMR δ 3.10 (2 H, OH), 3.42 (1 H, dd, *J* = 9.5 and 6.5 Hz, H-7a), 3.55 (1 H, dd, *J* = 9.5 and 6.5 Hz, H-7b), 3.58 (1 H, dd, *J* = 6.5 and 2 Hz, H-4), 3.72 (1 H, dd, *J* = 6.5 and 2 Hz, H-5), 4.11 (1 H, dt, *J* = 6.5, 6.5, and 2 Hz, H-6), 4.41 (1 H, m, H-3), 4.40–4.64 (6 H, OCH_2Ph), 5.18 (1 H, dt, *J* = 10.5, 1.5, and 1.5 Hz, H-1a), 5.35 (1 H, dt, *J* = 17, 1.5, and 1.5 Hz, H-1b), 5.92 (1 H, ddd, *J* = 17, 10.5, and 5 Hz, H-2), 7.3 (15 H, Ar H); ^{13}C NMR 115.29 ppm (C-1). Found: C, 74.78; H, 7.06.

2e: oil; $[\alpha]_D$ −14.3° (*c* 1.5, $CHCl_3$); ^1H NMR δ 3.00 (2 H, OH), 3.42 (1 H, dd, *J* = 9.5 and 6 Hz, H-7a), 3.50 (1 H, dd, *J* = 9.5 and 6 Hz, H-7b), 3.64 (1 H, t, *J* = 5 Hz, H-4), 3.76 (1 H, dd, *J* = 5 and 3 Hz, H-5), 4.06 (1 H, dt, *J* = 6, 6, and 3 Hz, H-6), 4.42 (1 H, m, H-3), 4.46–4.74 (6 H, OCH_2Ph), 5.23 (1 H, dt, *J* = 10.5, 1.5, and 1.5 Hz, H-1a), 5.37 (1 H, dt, *J* = 17, 1.5, and 1.5 Hz, H-1b), 6.00 (1 H, ddd, *J* = 17, 10.5, and 6 Hz, H-2), 7.3 (15 H, Ar H); ^{13}C NMR 116.19 ppm (C-1). Found: C, 75.05, H, 7.27.

2f: oil; $[\alpha]_D$ −12.2° (*c* 1, $CHCl_3$); ^1H NMR δ 2.95 (2 H, OH), 3.66–3.86 (5 H), 4.43 (1 H, m, H-3), 4.48–4.72 (6 H, OCH_2Ph), 5.22 (1 H, dt, *J* = 10.5, 1.5, and 1.5 Hz, H-1a), 5.40 (1 H, dt, *J* = 17.5, 1.5, and 1.5 Hz, H-1b), 6.00 (1 H, ddd, *J* = 17.5, 10.5, and 5 Hz, H-2), 7.3 (15 H, Ar H); ^{13}C NMR 115.67 ppm (C-1). Found: C, 74.79; H, 7.06.

2g: oil; $[\alpha]_D$ +1.5° (*c* 1, $CHCl_3$); ^1H NMR δ 3.00 (2 H, OH), 3.66–3.96 (5 H), 4.43 (1 H, m, H-3), 4.54–4.72 (6 H, OCH_2Ph), 5.18 (1 H, dt, *J* = 10.5, 1.5, and 1.5 Hz, H-1a), 5.33 (1 H, dt, *J* = 17.5, 1.5, and 1.5 Hz, H-1b), 5.97 (1 H, ddd, *J* = 17.5, 10.5, and 5.5 Hz, H-2), 7.3 (15 H, Ar H); ^{13}C NMR 115.77 ppm (C-1). Found: C, 74.69; H, 7.32.

2h: oil; ^1H NMR δ 1.26 (3 H, s, CH_3), 1.28 (3 H, s, CH_3), 3.2–4.4 (8 H), 5.25 (1 H, dt, *J* = 10, 1.5, and 1.5 Hz, H-1a), 5.42 (1 H, dt, *J* = 17, 1.5, and 1.5 Hz, H-1b), 6.02 (1 H, ddd, *J* = 17, 10, and 5 Hz, H-2), 7.3 (15 H, Ar H); ^{13}C NMR 115.78 ppm (C-1). And unseparated **2l**: ^{13}C NMR 115.47 ppm (C-1).

2i: oil; ^1H NMR δ 3.20 (2 H, OH), 3.45–3.90 (5 H), 4.18 (1 H, m, H-3), 4.35–4.75 (6 H, OCH_2Ph), 5.22 (1 H, dt, *J* = 10.5, 1.5, and 1.5 Hz, H-1a), 5.37 (1 H, dt, *J* = 17.5, 1.5, and 1.5 Hz, H-1b), 6.01 (1 H, ddd, *J* = 17.5, 10.5, and 5.5 Hz, H-2), 7.3 (15 H, Ar H); ^{13}C NMR 115.63 ppm (C-1).

3a: oil; $[\alpha]_D$ +3.4° (*c* 1, $CHCl_3$); ^1H NMR δ 1.74 (1 H, dd, *J* = 12 and 4 Hz, H-1′a), 2.01 (1 H, dd, *J* = 12 and 7 Hz, H-1′b), 3.25 (1 H, OH), 3.50 (1 H, dd, *J* = 5 and 3 Hz, H-2), 3.58 (1 H, t, *J* = 5 Hz, H-3 or H-4), 3.60 (1 H, dd, *J* = 10 and 5 Hz, H-6a), 3.72 (1 H, t, *J* = 5 Hz, H-3 or H-4), 3.80 (1 H, dd, *J* = 10 and 7 Hz, H-6b), 4.13 (1 H, dt, *J* = 7 and 5 Hz, H-5), 4.37 (1 H, ddd, *J* = 7, 4, and 3 Hz, H-1), 4.44–4.62 (6 H, OCH_2Ph), 7.3 (15 H, Ar H). Anal. Calcd for $C_{28}H_{31}O_5ClHg$: C, 55.72; H, 5.18. Found: C, 55.49; H, 4.99.

3b: oil; $[\alpha]_D$ + 14.6° (*c* 1, $CHCl_3$); ^1H NMR δ 2.00 (1 H, dd, *J* = 12 and 8 Hz, H-1′a), 2.16 (1 H, dd, *J* = 12 and 6.5 Hz, H-1′b), 2.44 (1 H, d, *J* = 9 Hz, OH), 3.51 (1 H, ddd, *J* = 9, 8, and 3 Hz, H-2), 3.60 (1 H, dd, *J* = 10 and 6 Hz, H-6a), 3.7–3.8 (3 H, H-3, H-4, and H-6b), 3.87 (1 H, dt, *J* = 8, 8, and 6.5 Hz, H-1), 4.07 (1 H, m, H-5), 4.32–4.70 (6 H, OCH_2Ph), 7.3 (15 H, Ar H). Found: C, 55.57; H, 5.03.

3c: mp 108–109 °C (from Et_2O); $[\alpha]_D$ +35.0° (*c* 1, $CHCl_3$); ^1H NMR δ 1.83 (1 H, dd, *J* = 12 and 5.5 Hz, H-1′a), 1.92 (1 H, dd, *J* = 12 and 5.5 Hz, H-1′b), 2.75 (1 H, OH), 3.46 (1 H, dd, *J* = 3 and 1 Hz, H-2), 3.72 (2 H, d, *J* = 2.5 Hz, H-6a and H-6b), 3.82 (1 H, dd, *J* = 10 and 3 Hz, H-4), 3.89 (1 H, t, *J* = 3 Hz, H-3), 3.98 (1 H, dt, *J* = 10, 2.5, and 2.5 Hz, H-5), 4.27 (1 H, dt, *J* = 5.5, 5.5, and 1 Hz, H-1), 4.38–4.80 (6 H, OCH_2Ph), 7.3 (15 H, Ar H). Found: C, 55.59; H, 4.98.

3dβ: oil; $[\alpha]_D$ +13.4° (*c* 1.2, $CHCl_3$); ^1H NMR δ 1.77 (1 H, dd, *J* = 12.5 and 4 Hz, H-1′a), 2.09 (1 H, dd, *J* = 12.5 and 5.5 Hz, H-1′b), 3.36 (1 H, ddd, *J* = 11, 3, and 1 Hz, H-2), 3.44 (1 H, dd, *J* = 10 and 6.5 Hz, H-6a), 3.50 (1 H, dd, *J* = 3 and 1.5 Hz, H-4), 3.57 (1 H, dd, *J* = 10 and 6.5 Hz, H-6b), 3.72 (1 H, d, *J* = 11 Hz, OH), 3.75 (1 H, t, *J* = 3 Hz, H-3), 4.07 (1 H, dt, *J* = 6.5, 6.5, and 1.5 Hz, H-5), 4.29 (1 H, ddd, *J* = 5.5, 4, and 1 Hz, H-1), 4.40–4.58 (6 H, OCH_2Ph), 7.3 (15 H, Ar H). Found: C, 55.61; H, 5.07.

3dα: oil; $[\alpha]_D$ +15.4° (*c* 1.3, $CHCl_3$); ^1H NMR δ 1.96 (1 H, dd, *J* = 12 and 8 Hz, H-1′a), 2.22 (1 H, dd, *J* = 12 and 5.5 Hz, H-1′b), 2.66 (1 H, d, *J* = 3 Hz, OH), 3.09 (1 H, dt, *J* = 8, 8, and 3 Hz, H-2), 3.62 (1 H, t, *J* = 8 Hz, H-3), 3.69 (1 H, dd, *J* = 11 and 4 Hz, H-6a), 3.73 (1 H, dd, *J* = 8 and 5.5 Hz, H-4), 3.79 (1 H, dd, *J* = 11 and 7 Hz, H-6b), 3.91 (1 H, dt, *J* = 8, 8, and 5.5 Hz, H-1), 4.20 (1 H, ddd, *J* = 7, 5.5, and 4 Hz, H-5), 4.53–4.94 (6 H, OCH_2Ph), 7.3 (15 H, Ar H). Found: C, 55.68; H, 4.99.

3eβ: oil; ^1H NMR δ 2.01 (1 H, dd, *J* = 12 and 8.5 Hz, H-1′a), 2.15 (1 H, dd, *J* = 12 and 6 Hz, H-1′b), 2.29 (1 H, d, *J* = 11 Hz, OH), 3.39 (1 H, ddd, *J* = 11, 10, and 3.5 Hz, H-2), 3.52 (1 H, dd, *J* = 10 and 7 Hz, H-6a), 3.58 (1 H, dd, *J* = 10 and 6 Hz, H-6b), 3.65–3.72 (3 H, m, H-1, H-3 and H-4), 3.95 (1 H, ddd, *J* = 7, 6, and 1 Hz, H-5), 4.29–4.72 (6 H, OCH_2Ph), 7.3 (15 H, Ar H). Found: C, 55.57; H, 5.03.

3eα: oil; ^1H NMR δ 1.77 (1 H, dd, *J* = 12 and 3 Hz, H-1′a), 2.10 (1 H, dd, *J* = 12 and 6 Hz, H-1′b), 2.80 (1 H, OH), 3.67 (1 H, dd, *J* = 11 and 3.5 Hz, H-6a), 3.73 (1 H, dd, *J* = 3 and 2 Hz, H-2), 3.75 (1 H, dd, *J* = 9 and 3 Hz, H-3), 3.77 (1 H, dd, *J* = 11 and 6.5 Hz, H-6b), 3.96 (1 H, dd, *J* = 9 and 6.5 Hz, H-4), 4.18 (1 H, dt, *J* = 6.5, 6.5, and 3.5 Hz, H-5), 4.34 (1 H, ddd, *J* = 6, 3, and 2 Hz, H-1), 4.46–4.76 (6 H, OCH_2Ph), 7.3 (15 H, Ar H). Found: C, 55.54; H, 5.01.

3f: oil; $[\alpha]_D$ +3.7° (*c* 1, $CHCl_3$); ^1H NMR δ 1.80 (1 H, dd, *J* = 11.5 and 3.5 Hz, H-1′a), 2.02 (1 H, dd, *J* = 11.5 and 6.5 Hz, H-1′b), 2.36 (1 H, d, *J* = 4 Hz, OH), 3.52 (1 H, ddd, *J* = 5, 2.5 and 1 Hz, H-5), 3.75 (1 H, dd, *J* = 14 and 2.5 Hz, H-6a), 3.78 (1 H, ddd, *J* = 6.5, 4 and 3.5 Hz, H-2), 4.02 (1 H, d, *J* = 6.5 Hz, H-3), 4.05 (1 H, d, *J* = 5 Hz, H-4), 4.08 (1 H, dd, *J* = 14 and 1 Hz, H-6b), 4.31 (1 H, dt, *J* = 6.5 and 3.5 Hz, H-1), 4.44–4.76 (6 H, OCH_2Ph), 7.3 (15 H, Ar H). Found: C, 55.53; H, 5.00.

3g: oil; $[\alpha]_D$ +1.6° (*c* 0.7, $CHCl_3$); ^1H NMR δ 1.34 (1 H, dd, *J* = 13 and 4, H-1′a), 1.62 (1 H, dd, *J* = 13 and 5.5 Hz, H-1′b), 2.75 (1 H, OH), 3.63 (1 H, dd, *J* = 9 and 2 Hz, H-3), 3.77 (1 H, dt, *J* = 6, 4, and 3 Hz, H-5), 3.83 (1 H, dd, *J* = 12.5 and 3 Hz, H-6a), 3.90 (1 H, dd, *J* = 12.5 and 4 Hz, H-6b), 4.02 (1 H, dd, *J* = 9 and 3.5 Hz, H-2), 4.03 (1 H, dd, *J* = 6 and 2 Hz, H-4), 4.55–4.85 (6 H, OCH_2Ph), 5.38 (1 H, ddd, *J* = 5.5, 4, and 3.5, H-1), 7.3 (15

H, Ar H). Found: C, 55.70; H, 5.09.

3h: mp 208–210 °C (from Et_2O), $[\alpha]_D$ −9.1° (*c* 1, $CHCl_3$); ^1H NMR δ 1.33 (3 H, s, CH_3), 1.51 (3 H, s, CH_3), 1.88 (1 H, dd, *J* = 12 and 3.5 Hz, H-1′a), 2.23 (1 H, dd, *J* = 12 and 5.5 Hz, H-1′b), 2.72 (1 H, d, *J* = 4.5 Hz, OH), 3.21 (1 H, dd, *J* = 10 and 6 Hz, H-6a), 3.37 (1 H, dd, *J* = 10 and 3 Hz, H-6b), 3.76 (1 H, dt, *J* = 4.5, 4.5, and 2 Hz, H-2), 4.03 (1 H, dd, *J* = 7 and 6 Hz, H-4), 4.16 (1 H, dt, *J* = 6, 6, and 3 Hz, H-5), 4.22 (1 H, dd, *J* = 7 and 4.5 Hz, H-3), 4.32 (1 H, ddd, *J* = 5.5, 3.5, and 2 Hz, H-1), 7.3 (15 H, Ar H). Found: C, 55.68; H, 5.22.

Reactivity of 7,12-Dihydropyrido[3,2-*b*:5,4-*b*′]diindole with Electrophilic Reagents. Experimental and Computational Results

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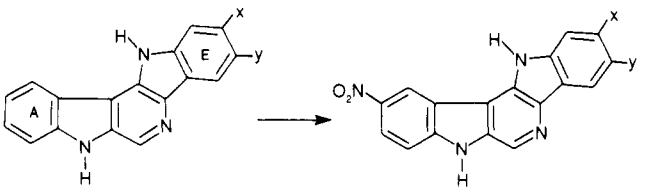
The reactivity of 7,12-dihydropyrido[3,2-*b*:5,4-*b*′]diindole (**1**) toward a variety of electrophiles ($^+NO_2$, Br^+, Cl^+, HSO_3^+) in acidic media has been investigated. Electrophilic attack on the protonated species **11** results in substitution at position 10 with high regioselectivity [i.e. **11** → **10** (92%), **11** → **13** (>73%)], effectively differentiating between the benzene nuclei, ring A and ring E of **1**. Attack of an electrophile (Br_2, HOAc/NaOAc) on the neutral molecule **1** results in a mixture of mono- and polysubstituted derivatives as predicted by MNDO calculations. The results of these electrophilic substitution reactions were compared to the p_z electron density populations and π-localization energies for the transition-state σ-complexes obtained from MNDO calculations. The experimental and theoretical results were in satisfactory agreement.

The heterocyclic base 7,12-dihydropyrido[3,2-*b*:5,4-*b*′]-diindole **1** was first reported in 1985.[1] It was later found that **1** possesses high affinity for the benzodiazepine receptor site in vitro and exhibits a broad range of biological profiles when the E-ring of the heterocycle is substituted with various functional groups.[2] These pyridodiindoles are the first completely rigid, planar benzodiazepine receptor ligands to have been prepared and provide a powerful tool with which to probe the topography of these receptors. It was, therefore, of interest to examine the reactivity of this heterocycle toward electrophiles and ultimately develop chemistry in which electrophiles could be introduced regioselectively, differentiating between the seemingly chemically similar benzene nuclei (ring A or E) of **1**. This would provide an entry into new, biologically active, high affinity ligands with which to further probe the pharmacophore of the benzodiazepine receptor.[3]

Results and Discussion

The synthesis of the pyridodiindoles is based on the Fischer–indole cyclization, as outlined in Scheme I. Treatment of the keto amide **2**[1] with phenylhydrazine at 160 °C followed by the concomitant [3,3] sigmatropic rearrangement[4] provided the diindole **3**, as illustrated. Cleavage of the benzoyl function of **3** with hydrazine, followed by an oxidation–disproportionation reaction across the 5–6 bond of the intermediate diindole **4** generated the fully aromatic pyridodiindoles in yields ranging from 50% and 88%. The process is illustrated for the 3-chloro (**5**)[5] and 3-bromo (**6**) analogues, respectively, in Scheme I.

Table I. Products of Nitration



1, x = H, y = H
5, x = H, y = Cl
8, x = Cl, y = H

10, x = H, y = H
7, x = H, y = Cl
9, x = Cl, y = H

compd	$NO_2(g)$/HNO_3[a]	70% HNO_3 (25 °C)	NO_2BF_4 (50 °C)	$NaNO_2$/TFA (25 °C)
1	PN	PN[a]	NR[a]	**10**, 92%[a]
5	PN	**7**, 67%	NR	**7**, 80%
8	PN	**9**, 66%	NR	**9**, 94%

[a] Reaction temperature = 0 °C; PN = polynitration products; NR = no reaction.

Since the 7,12-dihydropyrido[3,2–*b*:5,4–*b*′]diindole (**1**) has two para (3 and 10) and two ortho (1 and 8) positions with respect to the indole nitrogen atoms, which could undergo electrophilic attack, initial studies were directed toward the reactivity of the 3-chloro derivative **5**. The chlorine atom serves to block the 3-position from electrophilic attack, as well as deactivate ring E toward reaction with electrophiles.

Nitration. The 3-chloropyridodiindole **5** was stirred in a mixture of concentrated nitric acid/fuming nitric acid at 0 °C analogous to the conditions employed for the mononitration of 3-(alkoxycarbonyl)-β-carbolines at position 6.[6] This resulted in an inseparable mixture of

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