quinoxaline-8,18-diol (2). Octol 1 (6.9 g, 11.7 mmol), 2,3-dichloroquinoxaline (7.0 g, 35.0 mmol), and K_2CO_3 (6.45 g, 46.7 mmol) in 150 mL of DMSO were stirred 8 h at rt and then 18 h at 50 °C. After the mixture was cooled to rt, 300 mL of water were added and the crude solid formed was filtered, washed with water (500 mL), and dried under reduced pressure. Purification by silica gel chromatography (CCl_4/EtOAc (85:15)) afforded cavitand **3** (4.3 g, 27%, R_f = 0.55) and the pure product **2** as a white solid (7.5 g, 53%, R_f = 0.25): mp 189–191 °C; DCI MS (isobutane) m/z 1202 ([M]$^{\bullet-}$); ^{1}H NMR ($CDCl_3$) δ 8.74 (bs, 2 H, OH), 8.22 (s, 2 H, ArH octol), 7.95–7.82 (m, 4 H, ArH), 7.66–7.29 (m, 10 H, ArH quinoxaline), 7.15 (s, 2 H, ArH octol), 7.12 (s, 2 H, ArH octol), 5.60–5.35 (m, 3 H, Ar*CH*), 4.34 (t, J = 7.1 Hz, 1 H, Ar*CH*), 2.45–2.05 (m, 8 H, CH*CH*$_2$), 1.60–1.10 (m, 32 H, CH_2), 0.92 (t, J = 6.1 Hz, 12 H, CH_3). Anal. Calcd for $C_{76}H_{78}N_6O_8$: C, 75.85; H, 6.53; N, 6.98. Found: C, 75.77; H, 6.61; N, 6.72.

(+)- and (−)-3-Carbo(−)menthoxy-*r*-9,*c*-11,*c*-13,*c*-15-tetrahexyl-7,17:8,16-dimetheno-9*H*,11*H*,13*H*,15*H*-quinoxalino[2‴,3‴:2‴,3‴][1,4]benzodioxonino[10‴,9‴:5,6]quinoxalino[2′,3′:2′,3′]quinoxalino[2″,3″:2″,3″][1,4]dioxonino[6″,5″:9′,10′][1,4]benzodioxonino[6′,5′:9,10][1,4]benzodioxonino[2,3-*b*]quinoxaline ((+)-4 and (−)-4). Cavitand **2** (6.2 g, 5.1 mmol), 2,3-dichloro-6-quinoxalinecarboxylic acid (−)-menthyl ester (1.9 g, 5.1 mmol), and K_2CO_3 (0.9 g, 6.5 mmol) were stirred 24 h at 50 °C in 75 mL of DMSO. After the mixture was cooled to rt, 150 mL of water was added. The crude precipitate was filtered, washed with water (200 mL), and dried under reduced pressure at 80 °C. *n*-Hexane (250 mL) was added and the solution refluxed 15 min and then filtered to remove some unreacted starting materials. Crystallization from the organic solution gave the pure product (5.9 g, 76%) as a colorless solid racemic mixture. The two diastereoisomers were separated through silica gel chromatography (*n*-hexane/EtOAc (9:1)). Before characterization the products were carefully dried (3 h, 130 °C (0.1 mmHg)). (+)-4: R_f = 0.28; mp 166–168 °C; $[\alpha]^{20}_D$ +9.0 (*c* 1.0, $CHCl_3$). (−)-4: R_f = 0.20; mp 153–155 °C; $[\alpha]^{20}_D$ −9.5 (*c* 1.0, $CHCl_3$); DCI MS (isobutane) m/z 1510 ([M]$^{\bullet-}$); IR (neat) ν 1717 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 8.65 (+)-4 and 8.62 (−)-4(d, J = 1.7 Hz, 1 H, H_a), 8.14 (m, 4 H, ArH octol), 8.09 (dd, J_1 = 8.7 Hz, J_2 = 1.8 Hz, 1 H, H_b), 7.85–7.70 (m, 7 H, ArH quinoxaline), 7.54–7.45 (m, 4 H, ArH quinoxaline), 7.40–7.35 (m, 2 H, Ar-H quinoxaline), 7.23–7.18 (m, 4 H, ArH octol), 5.60–5.40 (m, 4 H, Ar*CH*), 5.06 (td, J_1 = 10.8 Hz, J_2 = 4.2 Hz, 1 H, *CH*O), 2.34–2.15 (m, 8 H, ArCH*CH*$_2$), 2.10–1.12 (m, 41 H, CH and CH_2), 1.08–0.77 (m, 21 H, CH_3). Anal. Calcd for $C_{95}H_{98}N_8O_{10}$: C, 75.47; H, 6.53; N, 7.41. Found: C, 75.50; H, 6.58; N, 7.46.

Cavitands (±)-4 (One-Pot Procedure). Octol 1 (6.9 g, 11.7 mmol), 2,3-dichloroquinoxaline (7.0 g, 35.0 mmol), and K_2CO_3 (6.45 g, 46.7 mmol) in 150 mL of DMSO were stirred at rt for 8 h and successively 18 h at 50 °C. 2,3-Dichloro-6-quinoxalinecarboxylic acid (−)-menthyl ester (2.5 g, 6.6 mmol) and K_2CO_3 (0.9 g, 6.5 mmol) were then added and the resulting solution further heated for 24 h. After the mixture was cooled to rt, 150 mL of water were added. The crude precipitate was filtered, washed with water (400 mL), and dried under reduced pressure at 80 °C. Purification by silica gel chromatography (*n*-hexane/EtOAc (9:1)) afforded 4.2 g (27%) of cavitand **3** (R_f = 0.10), 3.1 g of (+)-4 (R_f = 0.28), 2.2 g of (−)-4 (R_f = 0.20), and 1.9 g of a (+)-4 and (−)-4 mixture (41% overall yield of 4).

(+)-3-(Hydroxymethyl)-*r*-9,*c*-11,*c*-13,*c*-15-tetrahexyl-7,17:8,16-dimetheno-9*H*,11*H*,13*H*,15*H*-quinoxalino[2‴,3‴:2‴,3‴][1,4]benzodioxonino[10‴,9‴:5,6]quinoxalino[2′,3′:2′3′]quinoxalino[2″,3″:2″,3″][1,4]dioxonino[6″,5″:9′,10′][1,4]benzodioxonino[6′,5′:9,10][1,4]benzodioxonino[2,3-*b*]quinoxaline (+)-5. A solution of cavitand (+)-4 (2.0 g, 1.3 mmol) in dry THF (50 mL) was added dropwise over 30 min to a solution of DIBALH (6 mL of a 1 M solution in THF) in 50 mL of dry THF under a nitrogen purge. The resulting solution was stirred 2 h at rt and then cooled to 0 °C and carefully quenched with a saturated aqueous solution of NH_4Cl and finally extracted with diethyl ether (3 × 100 mL). After drying (Na_2SO_4), the solvent was removed under reduced pressure and the residue chromatographed over silica gel (n-hexane/EtOAc 2:8) giving pure (+)-5 (1.7 g, 95%). Before characterization the products were carefully dried (3 h, 130 °C (0.1 mHg)): mp 206–207 °C; $[\alpha]^{20}_D$ +4.6 (*c* 1.0, $CHCl_3$); DCI MS (isobutane) m/z 1358 ([M]$^{\bullet-}$); ^{1}H NMR ($CDCl_3$) δ 8.17–8.14 (m, 4 H, ArH octol), 7.83–7.69 (m, 8 H, Ar-H quinoxaline), 7.51–7.42 (m, 7 H, ArH quinoxaline), 7.24–7.20 (m, 4 H, ArH octol), 5.57 (t, J = 7.9 Hz, 4 H, Ar*CH*), 4.81 (s, 2 H, *CH*$_2$OH), 2.31–2.23 (m, 8 H, CH*CH*$_2$), 1.6–1.2 (m, 32 H, CH_2), 0.93 (t, J = 6.4 Hz, 12 H, CH_3). Anal. Calcd for $C_{85}H_{82}N_8O_9$: C, 75.09; H, 6.08; N, 8.24. Found: C, 75.09; H, 6.10; N, 8.20.

Cavitand (−)-5. The same procedure employed for (+)-5 gave 1.7 g (95%) of pure (−)-5: mp 206–207 °C; $[\alpha]^{20}_D$ −4.6 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{85}H_{82}N_8O_9$: C, 75.09; H, 6.08; N, 8.24. Found: C, 75.12; H, 6.10; N, 8.23.

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Supplementary Material Available: Tables of final atomic coordinates, thermal parameters, bond distances, bond angles, and torsion angles (22 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Palladium-Mediated Arylation of Acetylated Enones Derived from Glycals. 4.† Synthesis of Aryl 2-Deoxy-β-D-*C*-glycopyranosides

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The palladium-mediated arylation of the peracetylated glycal-derived enones **1**, **2**, and **3** afforded mixtures of *C*-glycosides containing an arylated enone (**1a**, **2a**, or **3a**) and an arylated ketone (**1b**, **2b**, or **3b**). A rationale for the formation of these compounds is given. Reduction of the arylated enones proceeds in a stereospecific manner, thus affording aryl 2-deoxy-β-D-C-glycopyranosides in high yield.

The formation of a C–C bond at the anomeric center of a carbohydrate has become an increasingly important area of study in synthetic organic chemistry since a wide variety of *C*-glycosides have been isolated from natural sources.[1] Among them, aryl *C*-glycosides are of particular interest due to their antibiotic and antitumor activity.[1] Several

† For preceding paper see: Bellosta, V.; Czernecki, S.; Avenel, D.; El Bahij, S.; Gillier-Pandraud, H. *Can. J. Chem.* **1990**, *68*, 1364.

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(1) For a recent review see: Hacksell, C. V.; Daves, G. D., Jr. *Prog. Med. Chem.* **1985**, *22*, 1.

0022-3263/92/1957-4612$03.00/0

Scheme I

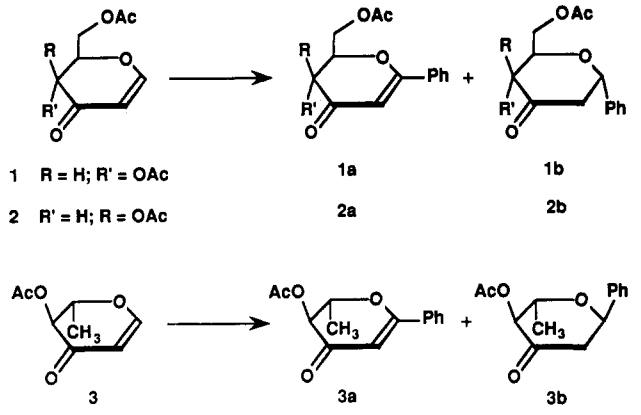


Table I. Influence of the Reaction Conditions on the a/b Ratio

entry	enone	AcOH (mL)	H_2O (mL)	temp (°C)	reaction time (h)	a/b	yield (%)
1	1	0	-	110	4	69/31	10
2	1	0.8	-	110	4	70/30	70
3	1	0.8	-	80	5	68/32	45
4	1	0.8	-	60	7	70/30	70
5	1	0.7	0.1	110	4	50/50	70
6	2	0.8	-	110	4	55/45	70
7	2	0.7	0.1	110	4	25/75	70
8	3	0.8	-	110	4	70/30	90

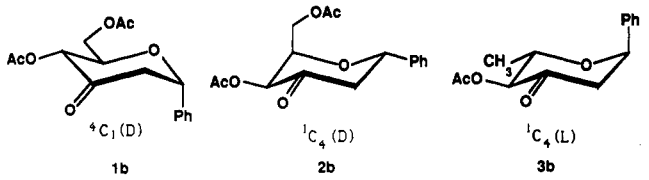
C-aryl glycosylation methods involving electrophilic substitutions[2] or the reaction of activated sugar derivatives with organometallic compounds[3] have been reported.

The high stereochemical control accompanying transition metal-mediated transformations[4] prompted us[5] and others[6,7] to investigate such methods for C-glycosylations. These reactions proceed by addition of a σ-arylpalladium complex to a protected glycal[5,6] or by reaction of a nucleophile with a π-allylpalladium complex generated from the glycal.[7]

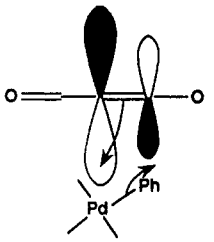
Since the palladium-mediated reactions are known to proceed more easily with electron-deficient double bonds[4] we decided to apply the title reaction to several readily-available peracetylated enones (**1–3**).[8]

Treatment of 4,6-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*erythro*-hex-1-en-3-ulose (**1**[8]) with benzene in the presence of acetic acid and palladium acetate, conditions which gave satisfactory results with peracetylated glycals,[5] led to a mixture of aryl *C*-glycosides: an arylated enone **1a** and an arylated ketone **1b**, in 70% yield. Under the same conditions, 4,6-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*threo*-hex-1-en-3-ulose (**2**[8]) and 4-*O*-acetyl-1,5-anhydro-2,6-dideoxy-L-*erythro*-hex-1-en-3-ulose (**3**[8]) led, respectively, to compounds **2a–2b** and **3a–3b**.

Chart I



Scheme II



The composition of the product mixture was dependent on the structure of the starting enone (Table I).

The structures of these compounds were unambiguously determined by 250-MHz ^1H NMR spectroscopy (Tables II and III) and by chemical transformations to known products.

The lack of epimerization at C-4 in compounds **1a**, **2a**, and **3a** was confirmed by the values of the $J_{4,5}$ coupling constants which were 12.2 Hz for **1a** and 13.0 Hz for **3a** (axial–axial relationship) and 4.1 Hz for **2a** (axial–equatorial relationship). The configuration of C-4 in compounds **1b**, **2b**, and **3b** was confirmed also by the $J_{4,5}$ values: 9.7, 10.4, and 6.4 Hz, respectively.

In the spectra of **1b** and **3b**, the H-1 signal is a doublet of doublets and the coupling constants ($J_{1,2}$ = 3.5 Hz and $J_{1,2'}$ = 6 Hz) are too small to suggest an axial–axial relationship between H-1 and H-2_{ax}, indicating that H-1 is not in an axial position. The value of 6 Hz for $J_{1,2'}$, which may seem to be a little large for axial–equatorial coupling, has already been observed for other *C*-glycosyl compounds.[10] Therefore, only an α anomeric configuration in a $^4C_1$(D) conformation for **1b** and a $^1C_4$(L) conformation of **3b**, bearing two bulky groups in equatorial positions, is in reasonable agreement with these data.

In the case of ketone **2b**, the H-1 signal is a doublet of doublets with $J_{1,2}$ = 5.9 Hz and $J_{1,2'}$ = 8.2 Hz, suggesting an axial position for H-1 in a $^1C_4$(D) conformation.

These ^1H NMR data are also consistent with a C-1 epimer (β) in the $^4C_1$(D) conformation. But in the $^4C_1$(D) conformation a very small value is expected for $J_{4,5}$ according to Booth's rule[9] because H-4 and H-5 would be antiparallel to an electronegative atom (0–5 and 0–4 Hz, respectively). In similar cases, ^3J values of 1.3 Hz were observed for protons in this conformational arrangement.[10] Since the α configuration of **2b** was proven by chemical correlation (vide infra), these observations strongly suggest that a $^1C_4$(D) conformation, in which only one bulky group out of three is in the axial position, is preferred for this

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Table II. ^{1}H NMR Data for Arylated Enones[a]

compd	δ H-2	δ H-4	δ H-5	δ H-6	δ H-6′	δ CH_3CO	δ H (Ar)
1a	6.02 (s)	5.53 (d) $J_{4,5}$ = 13	4.85 (m) $J_{5,6}$ = 5 $J_{5,6'}$ = 2.9	4.51 (dd)	4.60 (dd) $J_{6,6'}$ = 12	2.08 (s) 2.15 (s)	7.4–7.8 (m)
2a	6.07 (s)	5.57 (d) $J_{4,5}$ = 4.1	4.90 (m) $J_{5,6}$ = 7.2 $J_{5,6'}$ = 4.8	4.42 (dd)	4.51 (dd) $J_{6,6'}$ = 12.2	2.08 (s) 2.16 (s)	7.4–7.75 (m)
3a	6.01 (s)	5.32 (d) $J_{4,5}$ = 12.2	4.65 (m) $J_{5,6}$ = 6.3	1.57 (CH_3) (d)		2.21 (s)	7.36–7.77 (m)

[a] Chemical shifts (δ) in ppm; coupling constants in Hz.

Table III. ^{1}H NMR Data for Arylated Ketones[a]

compd	δ H-1	δ H-2	δ H-2′	δ H-4	δ H-5	δ H-6	δ H-6′	δ CH_3CO	δ H(Ar)
1b	5.58 (dd) $J_{1,2}$ = 3.3 $J_{1,2'}$ = 5.6	3.2 (m) $J_{2,2'}$ = 10.2		5.32 (d) $J_{4,5}$ = 10.4	3.78 (ddd) $J_{5,6}$ = 2.2 $J_{5,6'}$ = 4.2	4.33 (m)		2.15 (s)	7.35–7.42 (m)
2b	5.21 (dd) $J_{1,2}$ = 5.9 $J_{1,2'}$ = 8.2	2.8 (m) $J_{2,2'}$ = 12.5		5.58 (d) $J_{4,5}$ = 6.4	4.20 (ddd) $J_{5,6}$ = 5.5 $J_{5,6'}$ = 8.3	4.75 (m)		2.05 (s) 2.02 (s)	7.35–7.45 (m)
3b	5.43 (dd) $J_{1,2}$ = 3.8 $J_{1,2'}$ = 6.3	3.14 (m) $J_{2,2'}$ = 14.4		4.97 (d) $J_{4,5}$ = 9.7	3.67 (m) $J_{5,6}$ = 6.1	1.25 (CH_3) (d)		2.11 (d)	7.28–7.40 (m)

[a] Chemical shifts (δ) in ppm; coupling constants in Hz.

compound. It has to be noted that, since C-3 is sp^2, destabilizing 1,3-diaxial interactions are limited. This flexibility in conformation is possible with *C*-glycosides because of the lack of any strongly directing anomeric effect.[10]

Several attempts were made to improve the overall yield and to modify the **a**/**b** ratio. They are summarized in Table I.

Variation of the acetic acid concentration (entry 1) had a noticeable effect on the reaction rate, suggesting that AcOH exerts a major influence on arylpalladium formation.

Varying the reaction temperature (entries 3 and 4) showed that a temperature equal to at least 100 °C is necessary to ensure the completion of the reaction within a few hours.

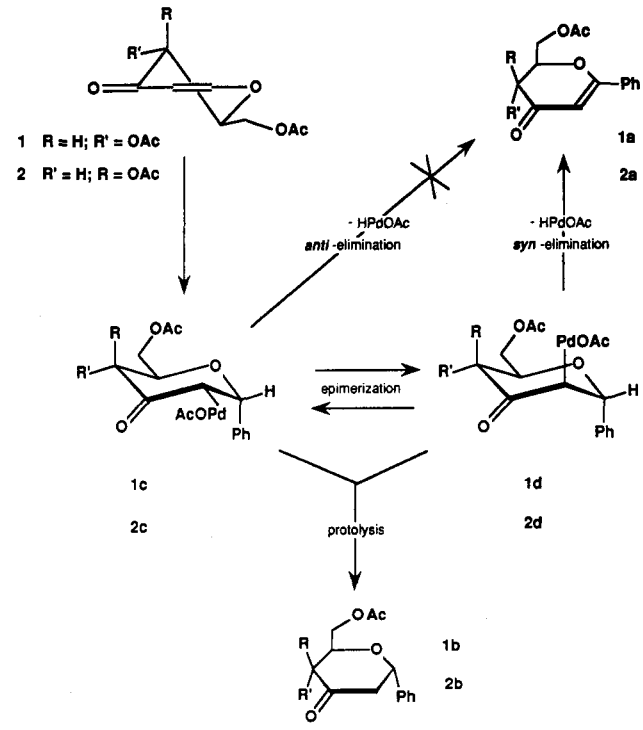
In no case did the **a**/**b** ratio vary with time, ruling out the formation of **a** from **b** under the reaction conditions, although such examples have been reported in the literature.[11]

These results raise some interesting questions about palladium chemistry.

As shown by Daves,[12] the regiochemistry of the arylation is determined by electronic factors in the absence of significant steric hindrance. Electronic interactions lead to a (presumably) concerted reaction where the electron-deficient palladium forms a σ-bond with the C-2 carbon, which is the site of the greatest electron density, and the relatively electron-rich aryl group bonds to the C-1 carbon, which carries the least electron density in the double bond.

As far as stereochemistry is concerned, if we admit that the first step of the arylation process is a *syn*-addition of an arylpalladium intermediate as is generally accepted for such a reaction,[13] and since it has been previously demonstrated[5] that the addition of the organometallic reagents occurs preferentially to the α-face, the resulting alkylpalladium should have the structure **1c** if derived from **1** and **2c** if derived from **2**.

Scheme III



In **1c** and **2c** there is no hydrogen atom to promote the usually observed syn-elimination of hydridoacetatopalladium.[14] So the formation of enones **1a** and **2a** could

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Table IV. ^{1}H NMR Data for Acetylated Phenyl 2-Deoxy-β-D-C-glycopyranosides[a]

compd	δ H-1	δ H-2	δ H-2′	δ H-3	δ H-4	δ H-5	δ H-6	δ H-6′	δ CH_3CO	δ H (Ar)
1e	4.57 (dd) $J_{1,2}$ = 11.6 $J_{1,2'}$ = 2.1	1.84 (ddd) $J_{2,2'}$ = 12.9 $J_{2,3}$ = 9.4 $J_{2',3}$ = 4.5	2.4 (ddd)	5.16 (ddd) $J_{3,4}$ = 9.4	5.10 (dd) $J_{4,5}$ = 9.4	3.78 (m) $J_{5,6}$ = 5 $J_{5,6'}$ = 2.2	4.32 (m) $J_{6,6'}$ = 12.2	4.16	2.03 (s) 2.07 (s) 2.09 (s)	7.35–7.22 (m)
2e	4.50 (dd) $J_{1,2}$ = 10.2 $J_{1,2'}$ = 3.6	1.82 (m) $J_{2,2'}$ = 12 $J_{2,3}$ = 10.8 $J_{2',3}$ = 5	2.38 (m)	5.10 (ddd) $J_{3,4}$ = 4.8	5.30 (dd) $J_{4,5}$ = 1.2	3.95 (m) $J_{5,6}$ = 7.7 $J_{5,6'}$ = 7.7	4.10 (m) $J_{6,6'}$ = 12	4.15	1.94 (s) 1.98 (s) 2.10 (s)	7.20–7.30 (m)
3e	4.50 (dd) $J_{1,2}$ = 11.5 $J_{1,2'}$ = 2.1	1.79 (m) $J_{2,2'}$ = 12.9 $J_{2,3}$ = 11.5 $J_{2',3}$ = 5.1	2.35 (ddd)	5.10 (ddd) $J_{3,4}$ = 9.5	4.84 (dd) $J_{4,5}$ = 9.5	3.63 (m) $J_{5,6}$ = 6	1.25 (CH_3) (d)		2.0 (s) 2.06 (s) 2.10 (s)	7.26–7.37 (m)

[a] Chemical shifts (δ) in ppm; coupling constants in Hz.

be explained by an unusual anti-elimintion or (and this is more likely) an epimerization of C-2, putting the palladium atom cis to H-1. It seems feasible that the carbon–palladium bond of **1c** and **2c** is ionizable because it is adjacent to the carbonyl group.[15c] The resulting intermediate enolate could epimerize by migration of the metal from the axial (β face) to the equatorial position (α face). Such an epimerization of a carbon–mercury bond has been reported in the literature.[15]

The formation of ketones **1b** and **2b** could result from a solvolysis of **1c** or **1d** and **2c** or **2d**, respectively. In fact, the amount of **1b** and was **2b** significantly greater when water was added to the reaction mixture (Table I, entries 5 and 7).

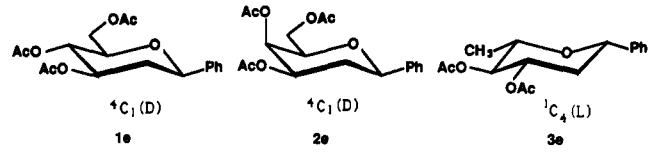
Attempts to verify this possibility by running the reaction with **1** in the presence of deuteriated acetic acid and water were unsuccessful. Polydeuteriated (at C-2 and C-3) arylated ketone **1b** was probably formed by deuteriation of **1b** after its formation. This was confirmed by exposure of **1b** to the same conditions.

Enones **1** and **3** afforded a similar 70:30 ratio of **a**/**b** whereas **2** gave a 55:45 **a**/**b** mixture under anhydrous conditions. This difference can be attributed to the fact that in **2c** the epimerization rate to **2d** is probably slow because of an unfavorable 2,4-diaxial interaction in the resulting intermediate. Therefore, protolysis of **2c** becomes predominant and leads to the formation of ketone **2b** in appreciable amount. In the presence of water, this occurrence is favored and ketone **2b** is the major product (75%, Table I, entry 7).

The reduction of the arylated ketones was previously studied and afforded 2-deoxy-α-D-C-glycopyranosides,[16] thus unambiguously proving the anomeric configuration of **1b**, **2b**, and **3b**.

Reduction of arylated enones **1a**, **2a**, and **3a** was achieved in a hydrogenation apparatus using 10% palladium on charcoal in ethyl acetate. After completion of the reaction (TLC), direct acetylation of the crude product was carried out (Ac_2O/pyridine) and the resulting product was analyzed by GLC, showing the presence of a single compound in each case. The structures were established by

Chart II



^{1}H NMR (Table IV) as phenyl 2-deoxy-β-C-glycosides **1e**, **2e**, and **3e**. These results are evidence for the simultaneous reductions of the C=C and C=O bonds from the α face of the enones. The absence of any allylic alcohol or arylated ketone from partial hydrogenation was verified by GLC.

The configurations at C-3 were confirmed by the values of the $J_{3,4}$ coupling constants which were, respectively, 9.4 Hz for **1e**, 9.5 Hz for **3e** (axial–axial relationship), and 4.8 Hz for **2e** (axial–equatorial relationship). In the three spectra, the H-1 signal was a doublet of doublets with a large $J_{1,2}$ constant (>10 Hz), indicating an axial–axial coupling. These data are consistent with a β anomeric configuration and a $^4C_1$(D) conformtion for **1c** and **2c** and a $^1C_4$(L) conformation for **3c**.

These results further exemplify the utility of palladium-mediated reactions in carbohydrate chemistry. The arylated enones **1a**, **2a**, and **3a** should find application in the synthesis of natural products.[16] Furthermore, the arylated ketones **1b**, **2b**, and **3b** can be readily oxidized to the corresponding enones **1a**, **2a**, and **3a**.[17,18] Since the reduction of the latter affords only β-C-glycosylarenes, the sequence of reactions described constitutes a new synthetic pathway to aryl 2-deoxy-β-D-C-glycopyranosides.

Experimental Section

General Methods. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. IR spectra (KBr disk) were recorded on a Unicam SP3-300 spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$, using Me_4Si as internal standard at 250 MHz with a Bruker apparatus operating in the FT mode. Gas chromatographic analysis was carried out on a Girdel 75 FD2 instrument equipped with flame ionization detectors and fitted with a 1-m 3% w/w phenyldiethanolamine succinate (PDEAS) on Chromosorb W AW DMCS column at 155 °C. Analytical TLC was performed on precoated alumina plates (E. Merck silica gel $60F_{254}$) with ethyl acetate–cyclohexane (3:2 v/v) as eluent. For

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flash chromatography E. Merck silica gel 60 (230–400 mesh) was used.

Arylation. The general procedure is exemplified with arylation of 4,6-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*erythro*-hex-1-en-3-ulose (1). In a round-bottomed flask 684 mg (3 mmol) of enone 1 was dissolved in a solution of 20 mL of acetic acid and 36 mL of benzene, and 672 mg (3 mmol) of palladium acetate was added. The mixture was kept at 110 °C in a thermoregulated oil bath, and the reaction was followed by TLC.

After completion the solution was filtered on paper, in order to recover the palladium which can be reoxidized and reused, washed with water, and extracted with ether. The organic phase was then neutralized with a 5% solution of sodium bicarbonate.

The solution was cooled to 0 °C, and 100 mg of sodium borohydride was added to reduce the remaining traces of palladium salts (brown). The solution turned colorless, and a fine precipitate of Pd(0) was filtered off.

The organic phase was washed again, dried over anhydrous $MgSO_4$ and filtered. A crude mixture of arylated products was obtained by evaporating the solvent and purified by flash chromatography (ether–pentane).

The following new compounds were isolated and characterized as described below.

(4,6-Di-*O*-acetyl-2-deoxy-D-*erythro*-hex-1-enopyranos-3-ulos-1-yl)benzene (1a) could not be separated from **1b**, which was isolated only after hydrogenation of **1a** into **1e**.

(4,6-Di-*O*-acetyl-2-deoxy-α-D-*erythro*-hexopyranos-3-ulos-1-yl)benzene (1b): 191 mg (30% yield); oil; R_f 0.30; $[\alpha]^{20}_D$ 111.2° (*c* 1; EtOH); IR (cm^{-1}) 3040–3020, 1760 (C=O), 1740 (ester), 1250 (CO), 1100–1050, 740–710 (Ar). Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.88. Found: C, 62.51; H, 6.08.

Arylation of **2** afforded **(4,6-di-*O*-acetyl-2-deoxy-D-*threo*-hex-1-enopyranos-3-ulos-1-yl)benzene (2a)** [351 mg (38.5% yield); oil; R_f 0.49; $[\alpha]^{20}_D$ 46.3° (*c* 1.1; $CHCl_3$); IR (cm^{-1}) 3100–2900, 1740 (ester), 1670 (enone), 1600 (C=C), 1240 (CO), 1100–1050, 780–700 (Ar). Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.88. Found: C, 62.48; H, 5.78] and **(4,6-di-*O*-acetyl-2-deoxy-α-D-*threo*-hexopyranos-3-ulos-1-yl)benzene (2b)** [288 mg (31.5% yield); oil; R_f 0.51; $[\alpha]^{20}_D$ −53° (*c* 1.1; $CHCl_3$); IR (cm^{-1}) 3100–2900, 1760 (C=O), 1740 (ester), 1230 (CO), 1100–1050, 770–700 (Ar). Anal. Calcd for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 63.08; H, 5.40].

Arylation of **3** afforded **(4-*O*-acetyl-2,6-dideoxy-L-*erythro*-hex-1-enopyranos-3-ulos-1-yl)benzene (3a)** [463 mg (63% yield); mp 84–86 °C; R_f 0.38; $[\alpha]^{20}_D$ −321° (*c* 0.7; $CHCl_3$); IR (cm^{-1}) 3100–2900, 1720 (C=O), 1700 (enone), 1600 (C=C), 1240 (CO), 1140–1050, 790–700 (Ar). Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.29; H, 5.69. Found: C, 68.07; H, 5.68] and **(4-*O*-acetyl-2,6-dideoxy-α-L-*erythro*-hexopyranos-3-ulos-1-yl)benzene (3b)** [198 mg (27% yield); oil; R_f 0.4; $[\alpha]^{20}_D$ −110° (*c* 1; $CHCl_3$); IR (cm^{-1}) 3100–2900, 1750 (C=O), 1720 (ester), 1230 (CO), 1150–1050, 800–700 (Ar). Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.74; H, 6.45. Found: C, 67.59; H, 6.49].

Reduction of Arylated Enones. Three mmol of enone **1b**, **2b**, or **3b** was dissolved in 90 mL of ethyl acetate, and 200 mg of 10% palladium on charcoal was added. The mixture was vigorously stirred in a hydrogenating apparatus, and the course of the reaction was followed by TLC and GLC. After completion the catalyst was filtered off and the solvent was evaporated.

Direct acetylation of the reduction product was carried out using 2 mL (20 mmol) of acetic anhydride in 7 mL (86 mmol) of pyridine. After 24 h at room temperature, the solution was evaporated and treated with toluene in order to remove traces of pyridine or Ac_2O. The residue was dissolved in 30 mL of CH_2Cl_2, washed with water, and neutralized with a 5% solution of $NaHCO_3$. The organic phase was washed again and dried over $MgSO_4$. Filtration and evaporation of the solvent yielded the corresponding arylated triesters **1e** and **2e** and diester **3e**.

(3,4,6-Tri-*O*-acetyl-2-deoxy-β-D-*arabino*-hexopyranosyl)benzene (1e). A total of 280 mg (80% yield) was obtained from **1a**: oil; R_f 0.28; $[\alpha]^{20}_D$ 3.07° (*c* 1.5; EtOH); IR (cm^{-1}) 3040–3000, 1740 (ester), 1250 (CO), 1100–1050, 740–710 (Ar). Anal. Calcd for $C_{18}H_{22}O_7$: C, 61.71; H, 6.28. Found: C, 61.54; H, 6.08.

(3,4,6-Tri-*O*-acetyl-2-deoxy-β-D-*lyxo*-hexopyranosyl)benzene (2e). A total of 332 mg (95% yield) was obtained from **2a**: oil; R_f 0.8; $[\alpha]^{20}_D$ 16.7° (*c* 1; $CHCl_3$); IR (cm^{-1}) 3100–2900, 1740 (ester), 1230 (CO), 1100–1050, 770–700 (Ar). Anal. Calcd for $C_{18}H_{22}O_7$: C, 61.71; H, 6.28. Found: C, 61.85; H, 6.17.

(3,4-Di-*O*-acetyl-2-deoxy-β-L-*ribo*-hexopyranosyl)benzene (3e). A total of 277 mg (95% yield) was obtained from **3a**: oil; R_f 0.43; $[\alpha]^{20}_D$ −28° (*c* 1; $CHCl_3$); IR (cm^{-1}) 3100–2900, 1740 (ester), 1240 (CO), 1100–1050, 780–700 (Ar). Anal. Calcd for $C_{16}H_{20}O_4$: C, 65.75; H, 6.85. Found: C, 65.95; H, 6.98.

Tawicyclamides A and B, New Cyclic Peptides from the Ascidian *Lissoclinum patella*: Studies on the Solution- and Solid-State Conformations

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Two new cytotoxic cyclic peptides, tawicyclamides A and B (1–2), were isolated from the ascidian *Lissoclinum patella* collected in the Philippine Islands and their structures determined by NMR spectroscopy, oxidation studies, and tandem mass spectrometry. Absolute configurations were determined by HPLC analysis of derivatized constituent amino acids obtained from acid hydrolysis. X-ray crystallography confirmed the structure of tawicyclamide B and showed that the compound assumes an unusual conformation facilitated by a *cis*-valine–proline amide bond and stabilized by an intramolecular hydrogen bond. Tawicyclamides A and B represent a new family of cyclic octapeptides, possessing thiazole and thiazoline amino acids but lacking the oxazoline ring characteristic of previously reported cyclic peptides from *L. patella*. Isomerization of the valine–proline amide bond from cis to trans is among the conformational changes occurring upon oxidation of the thiazoline ring to a thiazole. A variety of NMR data supports these changes. Molecular modeling studies allowed us to establish the solution conformations of these compounds and to evaluate these conformational interpretations. Tawicyclamides A and B were weakly but equally cytotoxic against human colon tumor cells in vitro.

Ascidians have proven to be a rich source of bioactive amino acid-derived secondary metabolites.[2] The prolific Didemnidae family has produced several classes of peptide metabolites such as the didemnins[3] and the lissoclinum

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