

Brigard & Castro
Abogados

As. 83.298

Apartado 3692

Cra. 7 16 -56
Bogotá - Colombia

Tel. Conm. 3802200
Tel./Fax (57-1) 2827976
(57-1) 3802700

E-Mail: bricas@brigardycastro.com.co

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 00-077048- -00009-0000
Fec: 2008-07-05 17:25:34 Dep. 2020 NUECREACIONES
Tia: 2 PATENTES
Eva: 1 REGDEPOSITO
Act 444 RESPUESTAREQUE Folios: 21

REF: Expediente No. 00 077.048 - Solicitud de Patente

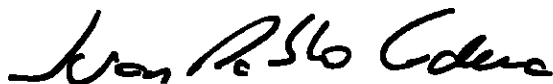
a favor de BRISTOL-MYERS SQUIBB COMPANY

Titulada: INHIBIDORES DE SGLT2 DE GLUCOSIDOS DE C-ARILO Y MÉTODO

JUAN PABLO CADENA SARMIENTO, vecino de Bogotá, portador de la tarjeta profesional No. 57492, obrando como apoderado de la Sociedad BRISTOL-MYERS SQUIBB COMPANY., según lo acredita el documento de poder presentado en esa División, dando alcance a mi escrito radicado el 20 de Junio de 2006, para dar respuesta al requerimiento notificado por fijación en lista el 23 de Marzo de 2006, me permito allegar los siguientes documentos:

1. T. KURIBAYASHI ET AL: "C-glycosilated aryl tins: versatile building blocks for aryl C-glycoside glycomimetics". JOURNAL OF CARBOHYDRATE CHEMISTRY, vol. 18, no. 4, 1999, pages 371 - 382. XP000978503.
2. W. GAFFIELD ET AL.: "Circular dichroism of C-glycosyl flavones. A chiroptical method for differentiating 6-C-, 8-C- and 6,8-C-beta-glycosyl isomers". TETRAHEDRON, Vol 34, no. 20, 1978, pages 3089 - 3096, XP000971951, page 3092, compound 5.

De la señora Jefe atentamente,



JUAN PABLO CADENA SARMIENTO

C.C. No. 80.410.337 de Usaquén

Cra 7a. No. 16-58 Piso 9

Julio 04, 2008

CHP/MEV/hsr.

1 ~~684~~
680
D₂

C-GLYCOSYLATED ARYL TINS: VERSATILE BUILDING BLOCKS FOR ARYL C-GLYCOSIDE GLYCOMIMETICS

Takashi Kuribayashi, Yumiko Mizuno, Sayako Gohya and Susumu Satoh*

Exploratory Chemistry Research Laboratories, Sankyo Co. Ltd.,
2-58 Hiromachi 1-chome, Shinagawa-ku, Tokyo 140-8710, JAPAN

Received October 8, 1998 - Final Form March 12, 1999

ABSTRACT

C-glycosylated aryl tins have been prepared as versatile building blocks of physiologically stable glycomimetics for glycoepitopes that have been recognized to serve biologically important roles in cell biochemistry.

INTRODUCTION

Glycoconjugates, also termed glycolipids, glycoproteins or proteoglycans, located on cell surfaces or extracellular matrices, have been recognized to be strongly involved in the basic phenomena governing multicellular society, such as cell differentiation and growth, recognition and adhesion, fertilization and implantation, growth of cancer cells, immunity, aging and so forth, and also in adhesion of bacteria and viruses through intercellular interaction.¹

Some of these phenomena are thought to depend on specific small motifs of oligosaccharides in huge glycoconjugates. In a sialyl Lewis^x which mediates leukocytes rolling on endothelial cells and results in leukocyte migration to the inflamed tissue, the carboxylic acid in the sialic acid, and the galactose and the fucose moieties are necessary to

interact with selectins.² A pentasaccharide constitutes the active site on heparin for the antithrombin III binding activity.³



In the course of our continuous effort to seek physiologically stable glycomimetics of these biologically important glycoepitopes, aryl C-glycosides have been proposed.⁴

We describe here the preparation of C-glycosylated aryl tins (1) that are versatile building blocks for aryl C-glycoside glycomimetics, coupled with palladium mediated C-C bond formation reactions. The palladium catalyzed cross-coupling reactions of organotin compounds with a variety of organic electrophiles were well documented⁵ because of the mildness of the reactions and of their compatibility with a wide range of functional groups on either coupling partners.

RESULTS AND DISCUSSION

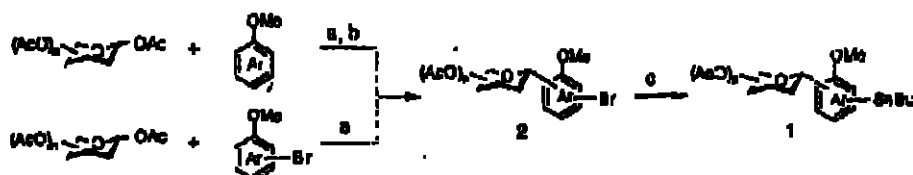
Although there are a couple of possible methods to introduce a stannyl group onto an aromatic ring,⁶ the palladium-catalyzed substitution reaction of the corresponding aromatic halide is considered to be a general purpose method and tolerable by a wide range of functional groups.^{6a,6d}

The general synthetic methods of the C-glycosylated aryl tins (1) are as follows (Scheme 1).

1. Peracetylated sugars were coupled with aromatics under SnCl_4 -AgOTf conditions to afford aryl C-glycosides (3).⁴ The conventional bromination of the aryl C-glycosides (3) afforded the C-glycosylated aryl bromides (2). Brominated aromatics with peracetylated sugars using SnCl_4 -AgOTf also afforded the C-glycosylated aryl bromides (2). Each method was selected depending on the utility or the reactivity of aromatic rings.

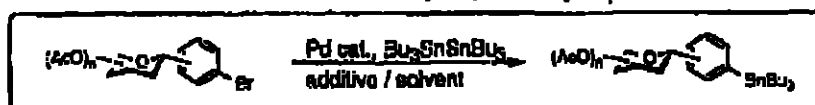
2. Subsequent stannylation of the C-glycosylated aryl bromides (2) was accomplished by C-glycosylated aryl bromides (2), bis(tributyltin), tetrakis(triphenylphosphine)palladium (0) and potassium carbonate (1 / 1.2 / 0.1 / 2) in refluxing toluene (condition A).^{6e} As some of the products (1) are labile to silica gel and give destannylation products, a rapid, short column is recommended for purification.

In the Table, some of the selected examples are arranged in order of orientation of sugar parts and tins.

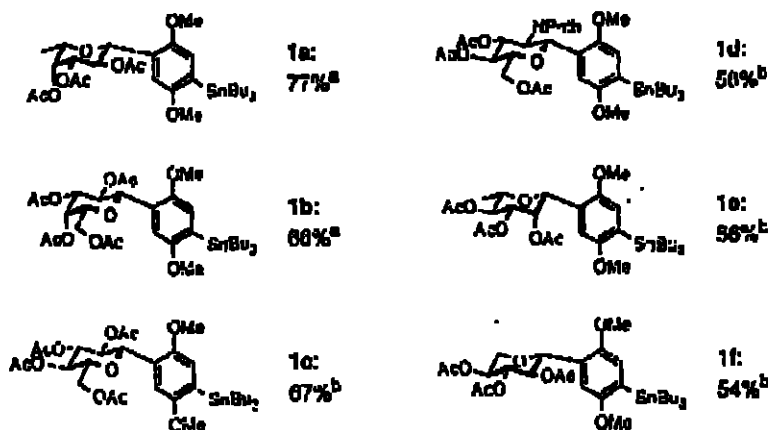


Scheme 1. General Synthetic Methods for C-Glycosylated Aryl Tins
a. SnCl₄, AgOTf / CH₂Cl₂. b. Br₂ / CCl₄. c. Bu₃SnSnBu₃, Pd(PPh₃)₄, K₂CO₃ / toluene.

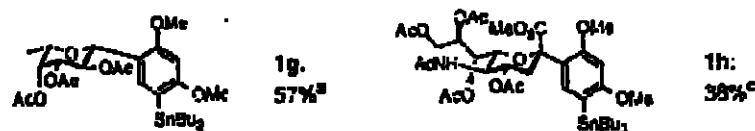
TABLE. Versatile C-Glycosylated Aryl Tins



1,4-Oriented C-glycosylated aryl tins



1,3-Oriented C-glycosylated aryl tins



a. Condition A; C-Glycosylated aryl bromide : Bu₃SnSnBu₃ : Pd(PPh₃)₄ : K₂CO₃ = 1 : 1.2 : 0.1 : 2 in refluxing toluene. b. Condition B; same as condition A but 1.8 eq of Bu₃SnSnBu₃ was used. c. Condition C; C-glycosylated aryl bromide : Bu₃SnSnBu₃ : Pd(OAc)₂ : P(nBu)₃ : K₂CO₃ = 1 : 1.2 : 0.1 : 2 in refluxing 1,4-dioxane.

Although condition A was effective for the preparation of C-fucosylated or C-galactosylated aryl tins, it failed to afford good yields in cases such as glucose-, glucosamine-, rhamnose- and xylose-derived aryl bromides. The addition of a slight excess bis(tributyltin) (1.6 eq) was found to afford a fairly good yield for each of the above cases (condition B).

Noteworthy is the attainment of a C-sialylated aryl tin (1h), which will be a promising building block to provide the glycomimetics of sialylated epitopes that are considered to play a key role in cell communications. However, the synthesis of the C-sialylated aryl tin (1h) using either condition led to some problems in purification. After several trials to find a condition that would provide the pure C-sialylated aryl tin (1h) in good yield, palladium acetate (II) (0.1 eq), tri-*n*-butylphosphine (0.2 eq) and potassium carbonate (2 eq) in refluxing 1,4-dioxane was found to afford the pure product (1h) in 38% yield (condition C).

The protective group was readily converted from the acetyl group to the benzyl group by the conventional methods without any problems (Scheme 2). The feasibility of the protective group conversion will expand the use of these building blocks.

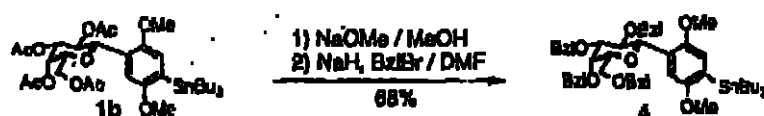
The palladium coupling of C-glycosylated aryl tins with a wide range of electrophiles like aryl halides, benzyl halides, vinyl halides, allyl halides, acid halides and so forth will be reported elsewhere.

EXPERIMENTAL

General methods. Analytical TLC was done on E. Merck precoated (0.25 mm) silica gel 60 F254 plates. Column chromatography was conducted using silica gel 60 (E. Merck 9385, 230-400 mesh). Melting points were measured with a Yanaco MP-500D and were uncorrected. Infrared (IR) spectra were recorded on a JASCO FT-IR-8900 spectrometer. ¹H NMR spectra were measured on a JEOL-JNM-EX-270 (270 MHz) or a JEOL JNM-GX-270 (270 MHz) spectrometer. Chemical shifts from ¹H NMR spectra are reported relative to tetramethylsilane (δ 0). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were recorded with a JEOL HX-100, a SX-102A or a JMS-AX-505H mass spectrometer. Optical rotation was measured on a Perkins-Elmer 241 polarimeter. All experiments were carried out under a nitrogen atmosphere. In experiments requiring dry solvents, dry CH₂Cl₂ and toluene were purchased from Kanto Chemical. 1M SnCl₄ CH₂Cl₂ solution was purchased from Aldrich. Other chemicals were used as purchased.

Procedure for aryl C-glycosidation of sugar acetates and *p*-dimethoxybenzene.

1,4-Dimethoxy-2-(2,3,4-tri-*O*-acetyl-β-*L*-fucopyranosyl)benzene (3a).
To a mixture of *L*-fucose tetraacetate (10 g, 30 mmol), *p*-dimethoxybenzene (6.2 g, 45



Scheme 2. Benzyl Protected C-Glycosylated Aryl Tins

nmol) and AgOTf (9.9 g, 45 mmol) in CH_2Cl_2 (150 mL) at 0 °C was added SnCl_4 1M CH_2Cl_2 solution (1.5 mL, 1.5 mmol) dropwise. After the reaction mixture was stirred for 2 h at 0 °C, 1N HCl aqueous solution (20 mL) was added and the aqueous layer was extracted with CH_2Cl_2 . The extract was washed with brine, dried over MgSO_4 , and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc 3:1) to provide the product (6.7 g, 16 mmol) in 54% yield: TLC R_f 0.50 (hexane/EtOAc 3:2); ^1H NMR (270 MHz, CDCl_3) δ 7.06 (s, 1H, Ar), 6.80 (s, 2H, Ar), 5.45 (d, 1H, $J = 3.3$ Hz, H_2), 5.21 (dd, 1H, $J = 9.9$ Hz and 3.3 Hz, H_1), 4.91 (d, 1H, $J = 9.9$ Hz, H_1), 3.96 (q, 1H, $J = 6.3$ Hz, H_3), 3.79 (s, 3H, OMe), 3.78 (s, 3H, OMe), 2.23 (s, 3H, OAc), 1.99 (s, 3H, OAc), 1.79 (s, 3H, OAc), 1.21 (d, 3H, $J = 6.3$ Hz, H_3); IR (KBr pellet) 2987, 2941, 2910, 2838, 1751, 1505 cm^{-1} ; FABHRMS m/z 410.1574 (410.1577 Calcd for $\text{C}_{19}\text{H}_{28}\text{O}_9$ [$\text{M}]^+$); $[\alpha]_D^{25} +6.1^\circ$ (c 0.833 CH_2Cl_2).

1,4-Dimethoxy-2-(2,3,4,6-tetra-*O*-acetyl- β -D-galactopyranosyl)-benzene (3b). 82% yield; mp 76-78 °C; TLC R_f 0.56 (CH_2Cl_2 /ether 5:1); ^1H NMR (270 MHz, CDCl_3) δ 7.04 (d, 1H, $J = 2.4$ Hz, Ar), 6.81 (d, 1H, $J = 2.4$ Hz, Ar), 6.81 (s, 1H, Ar), 5.52 (d, 1H, $J = 3.5$ Hz, H_2), 5.46 (t, 1H, $J = 9.9$ Hz, H_1), 5.21 (dd, 1H, $J = 9.9$ Hz and 3.5 Hz, H_1), 4.91 (d, 1H, $J = 9.9$ Hz, H_1), 4.21-4.04 (m, 3H, H_2 and H_3), 3.80 (s, 3H, OMe), 3.78 (s, 3H, OMe), 2.21 (s, 3H, OAc), 2.03 (s, 3H, OAc), 1.99 (s, 3H, OAc), 1.80 (s, 3H, OAc); IR (KBr pellet) 2940, 2800, 1752, 1505 cm^{-1} ; EHRMS m/z 468.1634 (468.1631 Calcd for $\text{C}_{23}\text{H}_{34}\text{O}_{11}$ [$\text{M}]^+$); $[\alpha]_D^{25} -2.2^\circ$ (c 1.04 CH_2Cl_2).

1,4-Dimethoxy-2-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyl)benzene (3c). 52% yield; TLC R_f 0.59 (hexane/EtOAc 3:2); ^1H NMR (270 MHz, CDCl_3) δ 6.95 (d, 1H, $J = 1.9$ Hz, Ar), 6.82-6.80 (m, 2H, Ar), 5.37 (t, 1H, $J = 9.0$ Hz, H_1), 5.29 (t, 1H, $J = 9.0$ Hz, H_1), 5.23 (t, 1H, $J = 9.0$ Hz, H_1), 4.92 (d, 1H, $J = 9.0$ Hz, H_1), 4.27 (dd, 1H, $J = 12.3$ Hz and 4.7 Hz, H_2), 4.14 (dd, 1H, $J = 12.3$ Hz and 2.2 Hz, H_2), 3.89-3.80 (m, 1H, H_3), 3.79 (s, 3H, OMe), 3.77 (s, 3H, OMe), 2.06 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.78 (s, 3H, OAc); IR (KBr pellet) 2999, 2949, 2838, 1754 cm^{-1} ; FABHRMS m/z 468.1638 (468.1631 Calcd for $\text{C}_{23}\text{H}_{34}\text{O}_{11}$ [$\text{M}]^+$); $[\alpha]_D^{25} -11.4^\circ$ (c 0.355 CHCl_3).

1,4-Dimethoxy-2-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido- β -D-glucopyranosyl)benzene (3d). 58% yield; TLC R_f 0.34 (hexane/EtOAc 3:2); ^1H NMR

(270 MHz, CDCl_3) δ 7.83–7.60 (m, 4H, Ar), 7.06 (d, 1H, $J = 3.0$ Hz, Ar), 6.71 (dd, 1H, $J = 8.9$ Hz and 3.0 Hz, Ar), 6.52 (d, 1H, $J = 8.9$ Hz, Ar), 6.17 (t, 1H, $J = 10.0$ Hz, H_1), 5.64 (d, 1H, $J = 10.0$ Hz, H_1), 5.28 (t, 1H, $J = 10.0$ Hz, H_2), 4.57 (t, 1H, $J = 10.0$ Hz, H_2), 4.35 (dd, 1H, $J = 12.1$ Hz and 4.7 Hz, H_3), 4.20 (dd, 1H, $J = 12.1$ Hz and 2.3 Hz, H_3), 4.09–4.00 (m, 1H, H_4), 3.77 (s, 3H, OMe), 3.36 (s, 3H, OMe), 2.11 (s, 3H, OAc), 2.07 (s, 3H, OAc), 1.88 (s, 3H, OAc); IR (KBr pellet) 2941, 2912, 2838, 1750, 1720 cm^{-1} ; FABHRMS m/z 555.1752 (555.1741 Calcd for $\text{C}_{21}\text{H}_{29}\text{O}_{11}\text{N}$ [M] $^+$); $[\alpha]_D^{25}$ -60.1° (c 0.22 CHCl_3).

1,4-Dimethoxy-2-(2,3,4-tri-*O*-acetyl- β -L-rhamnopyranosyl)benzene (3e). 58% yield; TLC R_f 0.72 (hexane/EtOAc 3:1); ^1H NMR (270 MHz, CDCl_3) δ 7.06 (d, 1H, $J = 2.8$ Hz, Ar), 6.77 (dd, 1H, $J = 8.9$ Hz and 2.8 Hz, Ar), 6.72 (d, 1H, $J = 8.9$ Hz, Ar), 5.58 (dd, 1H, $J = 3.4$ Hz and 1.2 Hz, H_2), 5.27 (dd, 1H, $J = 10.1$ Hz and 3.4 Hz, H_2), 5.14 (t, 1H, $J = 10.1$ Hz, H_2), 5.01 (s, 1H, H_1), 3.78 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.68 (dq, 1H, $J = 10.1$ Hz and 6.2 Hz, H_3), 2.08 (s, 3H, OAc), 1.98 (s, 3H, OAc), 1.90 (s, 3H, OAc), 1.32 (d, 3H, $J = 6.2$ Hz, H_4); IR (KBr pellet) 2984, 2941, 2839, 1748 cm^{-1} ; FABHRMS m/z 410.1575 (410.1573 Calcd for $\text{C}_{20}\text{H}_{28}\text{O}_9$ [M] $^+$); $[\alpha]_D^{25}$ +2.9° (c 1.00 CHCl_3).

1,4-Dimethoxy-2-(2,3,4-tri-*O*-acetyl- β -D-xylopyranosyl)benzene (3f). 49% yield; TLC R_f 0.30 (hexane/EtOAc 3:2); ^1H NMR (270 MHz, CDCl_3) δ 6.92 (d, 1H, $J = 2.3$ Hz, Ar), 6.82 (dd, 1H, $J = 9.1$ Hz and 2.3 Hz, Ar), 6.79 (d, 1H, $J = 9.1$ Hz, Ar), 5.36 (t, 1H, $J = 9.3$ Hz, H_2), 5.27 (t, 1H, $J = 9.3$ Hz, H_2), 5.15 (dt, 1H, $J = 9.3$ Hz and 5.8 Hz, H_2), 4.81 (d, 1H, $J = 9.3$ Hz, H_1), 4.22 (dd, 1H, $J = 11.2$ Hz and 5.5 Hz, H_3), 3.80–3.71 (m, 1H, H_4), 3.79 (s, 3H, OMe), 3.76 (s, 3H, OMe), 2.06 (s, 3H, OAc), 2.03 (s, 3H, OAc), 1.78 (s, 3H, OAc); IR (thin film) 2999, 2949, 2915, 2838, 1752 cm^{-1} ; FABHRMS m/z 396.1415 (396.1421 Calcd for $\text{C}_{19}\text{H}_{24}\text{O}_9$ [M] $^+$); $[\alpha]_D^{25}$ -29.6° (c 0.395 CHCl_3).

Procedure for bromination of aryl C-glycosides (3).

1-Bromo-2,3-dimethoxy-4-(2,3,4-tri-*O*-acetyl- β -L-fucopyranosyl)benzene (2a). Br_2 (0.62 mL, 12 mmol) was added dropwise to a solution of 1,4-dimethoxy-2-(2,3,4-tri-*O*-acetyl- β -L-fucopyranosyl)benzene (3a) (4.1 g, 10 mmol) in CCl_4 (100 mL) at 0 °C. After the reaction mixture was stirred for 2 h at 0 °C, H_2O (30 mL) was added and then extracted with CH_2Cl_2 (100 mL). The CH_2Cl_2 solution was washed by aqueous NaHCO_3 solution, aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution, and brine, dried over MgSO_4 , and concentrated *in vacuo*. The remainder was purified by column chromatography on silica gel (hexane/EtOAc 4:1) to provide the product (3.32 g, 6.78 mmol) in 68% yield; mp 172–173 °C; TLC R_f 0.36 (hexane/EtOAc 3:2); ^1H NMR (270 MHz, CDCl_3) δ 7.07 (s, 1H, Ar), 7.03 (s, 1H, Ar), 5.48 (t, 1H, $J = 10.1$ Hz, H_2), 5.37 (d, 1H, $J = 2.9$ Hz, H_2), 5.21 (dd,

689
685

1H, $J = 10.1$ Hz and 2.9 Hz, H_2), 4.87 (d, 1H, $J = 10.1$ Hz, H_1), 3.97 (q, 1H, $J = 6.6$ Hz, H_2), 3.89 (s, 3H, OMe), 3.80 (s, 3H, OMe), 2.24 (s, 3H, OAc), 1.99 (s, 3H, OAc), 1.81 (s, 3H, OAc), 1.22 (d, 3H, $J = 6.6$ Hz, H_3); IR (KBr pellet) 2985, 2966, 2943, 2851, 1752 cm^{-1} ; FABHRMS m/z 488.0684 (488.0682 Calcd for $\text{C}_{23}\text{H}_{29}\text{BrO}_6$, $[M]^+$); $[\alpha]_D^{25} +16.4^\circ$ (c 1.00 CH_2Cl_2).

1-Bromo-2,5-dimethoxy-4-(2,3,4,6-tetra-*O*-acetyl- β -D-galactopyranosyl)benzene (2b). 70% yield; TLC R_f 0.33 (hexane/EtOAc 3:2); ^1H NMR (270 MHz, CDCl_3) δ 7.08 (s, 1H, OAc), 7.01 (s, 1H, OAc), 5.52 (d, 1H, $J = 3.4$ Hz, H_2), 5.48 (t, 1H, $J = 9.9$ Hz, H_2), 5.21 (dd, 1H, $J = 9.9$ Hz and 3.4 Hz, H_1), 4.89 (d, 1H, $J = 9.9$ Hz, H_1), 4.19-4.05 (m, 3H, H_3 and H_4), 3.88 (s, 3H, OMe), 3.80 (s, 3H, OMe), 2.21 (s, 3H, OAc), 2.04 (s, 3H, OAc), 1.99 (s, 3H, OAc), 1.81 (s, 3H, OAc); IR (KBr pellet) 3479, 2964, 2943, 1751, 1495, 1370, 1219 cm^{-1} ; FABHRMS m/z 547.0810 (547.0815 Calcd for $\text{C}_{23}\text{H}_{28}\text{O}_{11}^{19}\text{Br}$ $[M+H]^+$); $[\alpha]_D^{25} +22^\circ$ (c 0.80 CH_2Cl_2).

1-Bromo-2,5-dimethoxy-4-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyl)benzene (2c). 74% yield; TLC R_f 0.46 (hexane/EtOAc 3:2); ^1H NMR (270 MHz, CDCl_3) δ 7.07 (s, 1H, Ar), 6.95 (s, 1H, Ar), 5.36 (t, 1H, $J = 9.2$ Hz, H_2), 5.30 (t, 1H, $J = 9.2$ Hz, H_2), 5.23 (t, 1H, $J = 9.2$ Hz, H_2), 4.92 (d, 1H, $J = 9.2$ Hz, H_1), 4.27 (dd, 1H, $J = 12.4$ Hz and 4.9 Hz, H_3), 4.14 (dd, 1H, $J = 12.4$ Hz and 2.1 Hz, H_4), 3.87 (s, 3H, OMe), 3.87-3.77 (m, 1H, H_2), 3.80 (s, 3H, OMe), 2.07 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.80 (s, 3H, OAc); IR (KBr pellet) 2947, 1754 cm^{-1} ; FABHRMS m/z 546.0739 (546.0737 Calcd for $\text{C}_{23}\text{H}_{28}\text{O}_{11}^{79}\text{Br}$ $[M]^+$); $[\alpha]_D^{25} -18.7^\circ$ (c 1.00 CH_2Cl_2).

1-Bromo-2,5-dimethoxy-4-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido- β -D-glucopyranosyl)benzene (2d). 96% yield; TLC R_f 0.37 (hexane/EtOAc 3:2); ^1H NMR (270 MHz, CDCl_3) δ 7.88-7.65 (m, 4H, Ar), 7.04 (s, 1H, Ar), 6.82 (s, 1H, Ar), 6.13 (t, 1H, $J = 10.0$ Hz, H_2), 5.64 (d, 1H, $J = 10.0$ Hz, H_1), 5.29 (t, 1H, $J = 10.0$ Hz, H_2), 4.59 (t, 1H, $J = 10.0$ Hz, H_2), 4.35 (dd, 1H, $J = 12.3$ Hz and 4.9 Hz, H_3), 4.20 (dd, 1H, $J = 12.3$ Hz and 2.2 Hz, H_4), 4.10-4.00 (m, 1H, H_2), 3.88 (s, 3H, OMe), 3.41 (s, 3H, OMe), 2.10 (s, 3H, OAc), 2.08 (s, 3H, OAc), 1.87 (s, 3H, OAc); IR (KBr pellet) 2936, 1751, 1721 cm^{-1} ; FABHRMS m/z 633.0845 (633.0846 Calcd for $\text{C}_{25}\text{H}_{28}\text{O}_{11}^{79}\text{Br}$ $[M]^+$); $[\alpha]_D^{25} -75.1^\circ$ (c 0.23 CH_2Cl_2).

1-Bromo-2,5-dimethoxy-4-(2,3,4-tri-*O*-acetyl- β -L-rhamnopyranosyl)benzene (2e). 96% yield; TLC R_f 0.46 (hexane/EtOAc 1:1); ^1H NMR (270 MHz, CDCl_3) δ 7.07 (s, 1H, Ar), 7.00 (s, 1H, Ar), 5.57 (dd, 1H, $J = 3.3$ Hz and 1.1 Hz, H_2), 5.25 (dd, 1H, $J = 9.9$ Hz and 3.3 Hz, H_1), 5.14 (t, 1H, $J = 9.9$ Hz, H_1), 4.97 (s, 1H, H_1), 3.87 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.75-3.62 (m, 1H, H_2), 2.08 (s, 3H, OAc), 1.99 (s, 3H, OAc), 1.91 (s, 3H, OAc), 1.34 (d, 3H, $J = 6.1$ Hz, H_3); IR (KBr pellet) 2983, 2940, 2851, 1750 cm^{-1} ; FABHRMS m/z 488.0680 (488.0682 Calcd for $\text{C}_{23}\text{H}_{28}\text{O}_6^{79}\text{Br}$ $[M]^+$); $[\alpha]_D^{25} +33.9^\circ$ (c 1.00 CH_2Cl_2).

694
687

1-Bromo-2,5-dimethoxy-4-(2,3,4-tri-*O*-acetyl- β -D-xylopyranosyl)benzene (2f). 72% yield; TLC R_f 0.40 (hexane/EtOAc 3:1); ^1H NMR (270 MHz, CDCl_3) δ 7.27 (s, 1H, Ar), 7.06 (s, 1H, Ar), 5.35 (t, 1H, $J = 9.4$ Hz, H_2), 5.27 (t, 1H, $J = 9.4$ Hz, H_3), 5.22-4.97 (m, 1H, H_4), 4.81 (d, 1H, $J = 9.4$ Hz, H_1), 4.21 (dd, 1H, $J = 11.0$ Hz and 5.5 Hz, H_5), 3.86 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.46 (t, 1H, $J = 11.0$ Hz, H_6), 2.06 (s, 3H, OAc), 2.03 (s, 3H, OAc), 1.80 (s, 3H, OAc); IR (thin film) 3014, 2947, 2852, 1755 cm^{-1} ; FABHRMS m/z 474.0523 (474.0526 Calcd for $\text{C}_{17}\text{H}_{23}\text{O}_9^{79}\text{Br} [\text{M}]^+$); $[\alpha]_D^{25} -28.6^\circ$ (c 0.860 CH_2Cl_2).

Procedure for aryl C-glycosidation of sugar acetates and 1-bromo-2,4-dimethoxybenzene.

1-Bromo-2,4-dimethoxy-5-(2,3,4-tri-*O*-acetyl- β -L-fucopyranosyl)benzene (2g). A 1M SnCl_4 CH_2Cl_2 solution (75 mL, 75 mmol) was added to a mixture of L-fucose tetraacetate (16.6 g, 50 mmol), 1-bromo-2,4-dimethoxybenzene (15.2 g, 70 mmol) and AgOTf (16.6 g, 75 mmol) in CH_2Cl_2 (75 mL) at 0°C under N_2 atmosphere. After the reaction mixture was stirred for 4 h at 0°C , aqueous NaHCO_3 solution was added and stirred for 20 min. The inorganic material was filtered off over a Celite[®] pad and the filtrate was extracted several times with CH_2Cl_2 . The combined CH_2Cl_2 solution was washed with brine, and dried over anhydrous MgSO_4 , and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc 2:1) to provide the product (8.2 g, 17 mmol) in 34% yield; mp 172-173 $^\circ\text{C}$; TLC R_f 0.23 (hexane/EtOAc 2:1); ^1H NMR (270 MHz, CDCl_3) δ 7.59 (s, 1H, Ar), 6.41 (s, 1H, Ar), 5.41 (t, 1H, $J = 10.0$ Hz, H_2), 5.34 (d, 1H, $J = 4.3$ Hz, H_3), 5.18 (dd, 1H, $J = 10.0$ Hz and 4.3 Hz, H_4), 4.77 (d, 1H, $J = 10.0$ Hz, H_1), 3.92 (q, 1H, $J = 6.6$ Hz, H_5), 3.89 (s, 3H, OMe), 3.85 (s, 3H, OMe), 2.25 (s, 3H, OAc), 1.99 (s, 3H, OAc), 1.80 (s, 3H, OAc), 1.21 (d, 3H, $J = 6.6$ Hz, H_6); IR (KBr pellet) 3468, 2983, 2943, 2851, 1749, 1605, 1505 cm^{-1} ; FABHRMS m/z 489.0755 (489.0760 calcd for $\text{C}_{20}\text{H}_{24}\text{O}_{10}^{79}\text{Br} [\text{M}+\text{H}]^+$); $[\alpha]_D^{25} +23.3^\circ$ (c 0.56 CH_2Cl_2).

1-Bromo-2,5-dimethoxy-4-(methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy- α -D-glycero-D-galacto-2-neuropyranosinate)benzene (2h). 70% yield; TLC R_f 0.53 (EtOAc); ^1H NMR (270 MHz, CDCl_3) δ 7.73 (s, 1H, Ar), 6.42 (s, 1H, Ar), 5.52 (dd, 1H, $J = 10.9$ Hz and 5.2 Hz, H_2), 5.47-5.41 (m, 1H, amide NH), 5.35 (dd, 1H, $J = 5.8$ Hz and 2.0 Hz, H_7), 5.28 (dt, 1H, $J = 5.8$ Hz and 3.0 Hz, H_6), 4.41 (dd, 1H, $J = 12.4$ Hz and 3.0 Hz, H_4), 4.23-4.10 (m, 2H, H_3 and H_5), 3.93-3.80 (m, 1H, H_8), 3.90 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.71 (s, 3H, OMe), 2.94 (dd, 1H, $J = 13.3$ Hz and 5.2 Hz, H_9), 2.18 (s, 3H, NAc), 2.10 (s, 3H, OAc), 2.03 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.90 (s, 3H, OAc), 1.85 (t, 1H, $J = 13.3$ Hz, H_1); IR (KBr pellet) 3377, 2956, 1746 cm^{-1} ; FABHRMS m/z 690.1382 (690.1398 Calcd for $\text{C}_{27}\text{H}_{37}\text{O}_{14}\text{N}^{79}\text{Br} [\text{M}+\text{H}]^+$); $[\alpha]_D^{25} -4.6^\circ$ (c 0.72 CH_2Cl_2).

C-GLYCOSYLATED ARYL TIN'S

Procedure for stannylation (Condition A and B).

Tri-*n*-butyl[2,5-dimethoxy-4-(2,3,4-tri-*O*-acetyl- β -L-fucopyranosyl)phenyl]stannane (1a). A suspended solution of 1-bromo-2,5-dimethoxy-4-(2,3,4-tri-*O*-acetyl- β -L-fucopyranosyl)benzene (2a) (6.9 g, 14.1 mmol), tetrakis(triphenylphosphine)palladium (810 mg, 0.7 mmol), potassium carbonate (1.98 g, 15 mmol) and bis(tributyltin) (9.23 g, 16 mmol) in toluene (150 mL) was refluxed for 10 h under a nitrogen atmosphere. After diluting the resulting mixture with EtOAc (150 mL), the organic solution was washed by aqueous KF solution, aqueous NaHCO₃ solution, and brine, dried over MgSO₄, and concentrated *in vacuo*. The remainder was purified by column chromatography on silica gel (hexane/EtOAc 9:1) to provide the product (7.60 g, 10.9 mmol) in 77% yield; TLC *R*_f 0.63 (hexane/EtOAc 2:1); ¹H NMR (270 MHz, CDCl₃) δ 6.88 (s, 1H, Ar), 6.87 (s, 1H, Ar), 5.56 (t, 1H, *J* = 9.9 Hz, H₂), 5.37 (d, 1H, *J* = 3.2 Hz, H₄), 5.21 (dd, 1H, *J* = 9.9 Hz and 3.2 Hz, H₃), 4.90 (d, 1H, *J* = 9.9 Hz, H₁), 3.98 (q, 1H, *J* = 6.6 Hz, H₅), 3.81 (s, 3H, OMe), 3.75 (s, 3H, OMe), 2.24 (s, 3H, OAc), 1.99 (s, 3H, OAc), 1.78 (s, 3H, OAc), 1.6-0.8 (m, 27H, Bu), 1.22 (d, 3H, *J* = 6.6 Hz, H₆); IR (KBr pellet) 2956, 2928, 2872, 2852, 1752 cm⁻¹; FABHRMS *m/z* 719.2527 (719.2526 Calcd for C₃₂H₅₂O₉Na¹¹⁸Sn [M+Na]⁺); [α]_D²⁵ +15.3° (c 0.91 CH₂Cl₂).

Tri-*n*-butyl[2,5-dimethoxy-4-(2,3,4,6-tetra-*O*-acetyl- β -D-galactopyranosyl)phenyl]stannane (1b). 60% yield; TLC *R*_f 0.67 (hexane/EtOAc 3:2); ¹H NMR (270 MHz, CDCl₃) δ 6.88 (s, 1H, Ar), 6.84 (s, 1H, Ar), 5.55 (t, 1H, *J* = 10.0 Hz, H₂), 5.51 (d, 1H, *J* = 3.4 Hz, H₄), 5.20 (dd, 1H, *J* = 10.0 Hz and 3.4 Hz, H₃), 4.91 (d, 1H, *J* = 10.0 Hz, H₁), 4.22-4.10 (m, 3H, H₅ and H₆), 3.80 (s, 3H, OMe), 3.73 (s, 3H, OMe), 2.20 (s, 3H, OAc), 2.02 (s, 3H, OAc), 1.98 (s, 3H, OAc), 1.76 (s, 3H, OAc), 1.59-1.46 (m, 6H, CH₂), 1.38-1.22 (m, 6H, CH₂), 1.04-0.98 (m, 6H, CH₂), 0.86 (t, 9H, *J* = 7.2 Hz, CH₃); IR (liquid film) 2956, 2928, 2872, 2851, 1754 cm⁻¹; FABHRMS *m/z* 777.2585 (777.2581 Calcd for C₃₄H₅₄O₉Na¹¹⁸Sn [M+Na]⁺); [α]_D²⁵ -6.1° (c 1.15 CH₂Cl₂).

Tri-*n*-butyl[2,5-dimethoxy-4-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyl)phenyl]stannane (1c). 67% yield; TLC *R*_f 0.71 (hexane/EtOAc 3:2); ¹H NMR (270 MHz, CDCl₃) δ 6.88 (s, 1H, Ar), 6.79 (s, 1H, Ar), 5.44-5.19 (m, 3H, H₂, H₃, and H₄), 4.95 (d, 1H, *J* = 9.7 Hz, H₁), 4.27 (dd, 1H, *J* = 12.3 Hz and 4.7 Hz, H₅), 4.14 (dd, 1H, *J* = 12.3 Hz and 2.2 Hz, H₆), 3.90-3.80 (m, 1H, H₂), 3.81 (s, 3H, OMe), 3.73 (s, 3H, OMe), 2.07 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.78 (s, 3H, OAc), 1.59-1.42 (m, 6H, CH₂), 1.31 (m, 6H, CH₂), 1.02 (t, 6H, *J* = 7.4 Hz, CH₂), 0.87 (t, 9H, *J* = 7.4 Hz, CH₃); IR (KBr pellet) 2956, 2927, 2872, 2851, 1755 cm⁻¹; FABHRMS *m/z* 777.2585 (777.2581 Calcd for C₃₄H₅₄O₉Na¹¹⁸Sn [M+Na]⁺); [α]_D²⁵ -53.1° (c 0.85 CH₂Cl₂).

Tri-*n*-butyl[2,5-dimethoxy-4-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido- β -D-glucopyranosyl)phenyl]stannane (1d). 58% yield; TLC *R*_f 0.35

(hexane/EtOAc 2:1); ^1H NMR (270 MHz, CDCl_3) δ 7.87-7.56 (m, 4H, Ar), 6.89 (s, 1H, Ar), 6.62 (s, 1H, Ar), 6.13 (t, 1H, $J = 10.0$ Hz, H_2), 5.68 (d, 1H, $J = 10.0$ Hz, H_1), 5.30 (t, 1H, $J = 10.0$ Hz, H_2), 4.65 (t, 1H, $J = 10.0$ Hz, H_2), 4.34 (dd, 1H, $J = 12.2$ Hz and 4.7 Hz, H_3), 4.21 (dd, 1H, $J = 12.2$ Hz and 2.1 Hz, H_4), 4.10-3.98 (m, 1H, H_1), 3.74 (s, 3H, OMe), 3.45 (s, 3H, OMe), 2.10 (s, 3H, OAc), 2.07 (s, 3H, OAc), 1.87 (s, 3H, OAc), 1.50-1.35 (m, 6H, CH_2), 1.35-1.18 (m, 6H, CH_2), 0.95 (t, 6H, $J = 7.1$ Hz, CH_3), 0.83 (t, 9H, $J = 7.2$ Hz, CH_3); IR (liquid film) 2956, 2928, 2871, 2852, 1752, 1722 cm^{-1} ; FABHRMS m/z 880.2441 (880.2453 Calcd for $\text{C}_{30}\text{H}_{45}\text{O}_{11}\text{K}^{116}\text{Sn}$ [$\text{M}+\text{K}$] $^+$); $[\alpha]_D^{25}$ -58.4° (c 0.55 CH_2Cl_2).

Tri-*n*-butyl[2,5-dimethoxy-4-(2,3,4-tri-*O*-acetyl- β -L-rhamnopyranosyl)phenyl]stannane (1e). 56% yield; TLC R_f 0.76 (hexane/EtOAc 2:1); ^1H NMR (270 MHz, CDCl_3) δ 6.94 (s, 1H, Ar), 6.79 (s, 1H, Ar), 5.56 (d, 1H, $J = 3.3$ Hz, H_2), 5.27 (dd, 1H, $J = 9.9$ Hz and 3.3 Hz, H_3), 5.15 (t, 1H, $J = 9.9$ Hz, H_2), 5.03 (s, 1H, H_1), 3.79 (s, 3H, OMe), 3.74 (s, 3H, OMe), 3.75-3.62 (m, 1H, H_2), 2.08 (s, 3H, OAc), 1.98 (s, 3H, OAc), 1.89 (s, 3H, OAc), 1.58-1.40 (m, 6H, CH_2), 1.40-1.20 (m, 6H, CH_2), 1.00 (t, 6H, $J = 8.1$ Hz, CH_3), 0.87 (t, 9H, $J = 7.2$ Hz, CH_3); IR (KBr pellet) 2953, 2928, 2869, 2854, 1750 cm^{-1} ; FABHRMS m/z 735.2246 (735.2266 Calcd for $\text{C}_{32}\text{H}_{42}\text{O}_9\text{K}^{116}\text{Sn}$ [$\text{M}+\text{K}$] $^+$); $[\alpha]_D^{25}$ +32.6° (c 0.99 CH_2Cl_2).

Tri-*n*-butyl[2,5-dimethoxy-4-(2,3,4-tri-*O*-acetyl- β -D-xylopyranosyl)phenyl]stannane (1f). 54% yield; TLC R_f 0.76 (hexane/EtOAc 3:1); ^1H NMR (270 MHz, CDCl_3) δ 6.87 (s, 1H, Ar), 6.78 (s, 1H, Ar), 5.36 (t, 1H, $J = 9.3$ Hz, H_2), 5.31 (t, 1H, $J = 9.3$ Hz, H_2), 5.23-5.09 (m, 1H, H_1), 4.84 (d, 1H, $J = 9.3$ Hz, H_1), 4.21 (dd, 1H, $J = 11.0$ Hz and 5.8 Hz, H_3), 3.81 (s, 3H, OMe), 3.72 (s, 3H, OMe), 3.48 (t, 1H, $J = 11.0$ Hz, H_2), 2.06 (s, 3H, OAc), 2.03 (s, 3H, OAc), 1.78 (s, 3H, OAc), 1.57-1.42 (m, 6H, CH_2), 1.42-1.23 (m, 6H, CH_2), 1.02 (t, 6H, $J = 8.0$ Hz, CH_3), 0.87 (t, 9H, $J = 7.3$ Hz, CH_3); IR (liquid film) 2956, 2927, 2871, 2853, 1758 cm^{-1} ; FABHRMS m/z 721.2078 (721.2109 Calcd for $\text{C}_{31}\text{H}_{39}\text{O}_9\text{K}^{116}\text{Sn}$ [$\text{M}+\text{K}$] $^+$); $[\alpha]_D^{25}$ -30.3° (c 0.73 CH_2Cl_2).

Tri-*n*-butyl[2,4-dimethoxy-5-(2,3,4-tri-*O*-acetyl- β -L-fucopyranosyl)phenyl]stannane (1g). 57% yield; TLC R_f 0.77 (hexane/EtOAc 2:1); ^1H NMR (270 MHz, CDCl_3) δ 7.30 (s, 1H, Ar), 6.35 (s, 1H, Ar), 5.60 (t, 1H, $J = 10.0$ Hz, H_2), 5.34 (d, 1H, $J = 2.3$ Hz, H_4), 5.18 (dd, 1H, $J = 10.0$ Hz and 2.3 Hz, H_1), 4.74 (d, 1H, $J = 10.0$ Hz, H_1), 3.93 (q, 1H, $J = 6.3$ Hz, H_2), 3.86 (s, 3H, OMe), 3.75 (s, 3H, OMe), 2.22 (s, 3H, OAc), 1.99 (s, 3H, OAc), 1.75 (s, 3H, OAc), 1.70-0.80 (m, 27H, Bu), 1.20 (d, 3H, $J = 6.3$ Hz, H_4); IR (liquid film) 2956, 2930, 2872, 2852, 1753, 1593, 1579 cm^{-1} ; FABHRMS m/z 723.2527 (723.2531 Calcd for $\text{C}_{31}\text{H}_{47}\text{O}_9\text{Na}^{110}\text{Sn}$ [$\text{M}+\text{Na}$] $^+$); $[\alpha]_D^{25}$ -22° (c 0.80 CH_2Cl_2).

694
690

Procedure for stannylation (Condition C).

Tri-*n*-butyl[2,5-dimethoxy-4-(methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy- α -D-glycero-D-galacto-2-neuropyranosinate)phenyl]-stannane (1h). A suspended solution of 1-bromo-2,5-dimethoxy-4-(methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy- α -D-glycero-D-galacto-2-neuropyranosinate)benzene (2h) (172.7 mg, 0.251 mmol), palladium (II) acetate (6.2 mg, 0.0276 mmol), tributylphosphine (20 μ L, 0.080 mmol), potassium carbonate (71.6 mg, 0.518 mmol) and bis(tributyltin) (170 μ L, 0.336 mmol) in 1,4-dioxane (5 mL) was refluxed for 8 h under a nitrogen atmosphere. After diluting the resulting mixture with EtOAc (10 mL), the organic solution was washed by aqueous KF solution, aqueous NaHCO₃ solution, and brine, dried over MgSO₄ and, concentrated *in vacuo*. The remainder was purified by column chromatography on silica gel (hexane/EtOAc 1:1) to provide the product (86.2 mg, 0.0967 mmol) in 38% yield: TLC *R_f* 0.59 (hexane/EtOAc 1:2); ¹H NMR (270 MHz, CDCl₃) δ 7.73 (s, 1H, Ar), 6.93 (s, 1H, Ar), 5.52 (dd, 1H, *J* = 10.6 Hz and 5.1 Hz, H₄), 5.42-5.37 (m, 2H, H₁ and amide NH), 5.21 (dd, 1H, *J* = 6.4 Hz and 2.8 Hz, H₂), 4.45 (dd, 1H, *J* = 12.4 Hz and 3.0 Hz, H₃), 4.24-4.10 (m, 2H, H₅ and H₆), 3.81-3.72 (m, 1H, H₇), 3.77 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.71 (s, 3H, OMe), 2.89 (dd, 1H, *J* = 13.3 Hz and 5.1 Hz, H₈), 2.17 (s, 3H, NAc), 2.05 (s, 3H, OAc), 1.99 (s, 3H, OAc), 1.98 (s, 3H, OAc), 1.90 (s, 3H, OAc), 1.73 (dd, 1H, *J* = 13.3 Hz and 11.3 Hz, H₉), 1.60-1.48 (m, 6H, CH₂), 1.40-1.23 (m, 6H, CH₂), 1.07-1.01 (m, 6H, CH₂), 0.90 (t, 9H, *J* = 7.2 Hz, CH₃); IR (liquid film) 3263, 3219, 3075, 3057, 3022, 3012, 2992, 2956, 2927, 1747 cm⁻¹; FABHRMS *m/z* 920.3160 (920.3164 Calcd for C₄₆H₅₃O₉Na¹¹³Sn [M+Na]⁺); [α]_D²⁵ -0.5° (c 0.82 CH₂Cl₂).

Tri-*n*-butyl[2,5-dimethoxy-4-(2,3,4,6-tetra-*O*-benzyl- β -D-galactopyranosyl)phenyl]stannane (4). NaOMe (28% MeOH solution, 0.5 mL) at it was added to a solution of tri-*n*-butyl[2,5-dimethoxy-4-(2,3,4,6-tetra-*O*-acetyl- β -D-galactopyranosyl)phenyl]stannane (1b) (1.03 g, 1.36 mmol) in MeOH (80 mL). After 1 h, the mixture was neutralized by Amberlite[®] CG-50. The insoluble materials were filtered, and solvent of the filtrate was removed *in vacuo*. NaH (55% oil; 0.36 g, 8.25 mmol) was added to the residue in DMF (10 mL) at 0 °C, the mixture was stirred for 15 min at rt. and then benzyl chloride (1 mL, 7.2 mmol) was added. After 4 h, the mixture was diluted with EtOAc (10 mL), washed with aqueous HCl solution (1N; 5 mL) and brine (5 mL), dried over MgSO₄, and concentrated under reduced pressure. A purification of the resulting residue by column chromatography with ethyl acetate/hexane (1:5) provided the compound (0.88 g, 0.93 mmol) in 68% yield: TLC *R_f* 0.61 (hexane/EtOAc 5:1); ¹H NMR (270 MHz, CDCl₃) δ 7.46-7.25 (m, 15H, Ar), 7.15-7.12 (m, 3H, Ar), 6.90-6.85 (m, 4H, Ar), 5.06

(d, 1H, $J = 11.5$ Hz, Bu), 4.79 (s, 3H, H₁ and Bu), 4.65 (d, 1H, $J = 11.5$ Hz, Bu), 4.50 (d, 1H, $J = 10.5$ Hz, Bu), 4.45 (d, 1H, $J = 12.5$ Hz, Bu), 4.43 (d, 1H, $J = 12.5$ Hz, Bu), 4.10 (d, 2H, $J = 2.5$ Hz, H₂ and H₃), 4.00 (d, 1H, $J = 10.5$ Hz, Bu), 3.76-3.74 (m, 2H, H₄ and H₅), 3.72 (s, 3H, OMe), 3.69-3.65 (m, 1H, H₆), 3.67 (s, 3H, OMe), 3.59 (dd, 1H, $J = 9.0$ Hz and 5.5 Hz, H₇), 1.55-1.49 (m, 6H, Bu), 1.35-1.27 (m, 6H, Bu), 1.05-1.02 (m, 6H, Bu), 0.86 (t, 9H, $J = 7.0$ Hz, Bu); IR (liquid film) 2925 cm⁻¹; FABHRMS m/z 969.4008 (969.4037 Calcd for C₃₁H₇₀O₇Na¹¹⁶Sn [M+Na]⁺; [α]_D²⁵ -14° (c 0.51 CH₂Cl₂).

REFERENCES AND NOTES

1. J. Lehmann, *Carbohydrates: Structure and Biology*, Thieme: New York, 1998, p 67.
2. (a) B. K. Brandley, M. Kiso, S. Abbas, P. Nikrad, O. Srivastava, C. Foxall, Y. Oda and A. Hasegawa, *Glycobiology*, **3**, 633 (1993); (b) J. Y. Ramphal, Z. -L. Zhong, C. Perez, L. E. Walker, S. A. DeFree and S. C. A. Gatta, *J. Med. Chem.*, **37**, 3459 (1994); (c) K. Yoshino, H. Ohmoto, N. Kondo, H. Tsujishita, Y. Hirumatsu, Y. Inoue, H. Kondo, H. Ishida, M. Kiso and A. Hasegawa, *J. Med. Chem.*, **40**, 455 (1997).
3. (a) R. W. Carroll, B. Skinner, M. R. Wardell and J. C. Whisstock, *Mol. Med. Today*, **1**, 226 (1995); (b) J. M. Walenga, W. P. Jeske, L. Bara, M. M. Samama and J. Fareed, *Thromb. Res.*, **86**, 1 (1997); (c) P. D. J. Grootenhuys and C. A. A. van Boeckel, *J. Am. Chem. Soc.*, **113**, 2743 (1991).
4. T. Kuribayashi, N. Ohkawa and S. Saich, *Tetrahedron Lett.*, **39**, 4537 (1998).
5. (a) J. Tsuji, *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: New York, 1995, p 228; (b) J. K. Stille, *Angew. Chem. Int. Ed. Engl.*, **25**, 508 (1986); (c) T. N. Mitchell, *Synthesis*, 803 (1992); (d) V. Farina, V. Krishnamurthy and W. J. Scott, in *Organic Reactions*; L. A. Paquette, Ed.; Wiley: New York, 1997, p 1.
6. (a) M. Kosugi, K. Shimizu, A. Ohtani and T. Migita, *Chem. Lett.*, 829 (1981); (b) T. Matsumoto, M. Katsuki, H. Iona and K. Suzuki, *J. Am. Chem. Soc.*, **113**, 6982 (1991); (c) K. Kato, H. Hayakawa, H. Tanaka, H. Kumamoto and T. Miyasaka, *Tetrahedron Lett.*, **36**, 6307 (1995); (d) J. Elguero, C. Jaramillo and C. Pardo, *Synthesis*, 563 (1997).

CIRCULAR DICHROISM OF C-GLYCOSYLFLAVONES

A CHIROPTICAL METHOD FOR DIFFERENTIATING 6-C-, 8-C- AND 6,8-DI-C- β -GLYCOSYL ISOMERS^{1a}

WILLIAM GAWNE^{1b}

Western Regional Research Laboratory,^{1b} Berkeley, CA 94719, U.S.A.

ROBERT M. HOROWITZ and BRINDO GENTILE

Fruit and Vegetable Chemistry Laboratory,^{1b} Pomona, CA 91106, U.S.A.

and

JEAN CHEPOT and MARIE-LOUISE BOUTILLANT

Laboratoire de Chimie Biologique, Université Claude Bernard, Lyon I, 69621, Villeurbanne, France

(Received in USA 21 February 1978; Received UK for publication 26 May 1978)

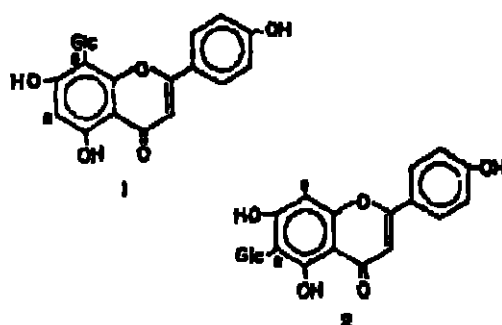
Abstract—Examination of a wide variety of C-glycosylflavones has shown that the sign of the CD band at 250–275 nm is diagnostic of the point of attachment of the glycosyl residue to the phenolic moiety. A positive CD band at 250–275 nm indicates a 6-C-linkage, as in hesperidin, whereas a negative CD band in this region indicates an 8-C-linkage, as in vitexin. 6,8-DI-C- β -glycosylflavones generally show two CD bands at 250–275 nm, a positive one at 265–275 nm and a negative one at 250–265 nm. Preliminary studies on C- α -glycosylflavones indicate that both 6-C- and 8-C- isomers show a negative CD band at 250–275 nm. The chiroptical properties of C- β -glycosylflavones are explained by proposing a quadrupole rule based upon the substituted benzoyl chromophore present in these molecules.

C-Glycosylflavones are compounds in which the glycosyl residue is attached to the flavone by a C-C bond. The first crystalline C-glycosyl compound was isolated in 1851 but until the 1950's little progress had been made in establishing structures for these compounds.² Since then a large number of C-glycosylflavones have been isolated from various plant sources, including dicotyledons, monocotyledons, ferns, mosses and green algae. A recurring problem in the structure determination of isomeric C-glycosylflavones, such as vitexin (1) and hesperidin (2), is assignment of the position of attachment of the glycosyl residue to the flavone. Methods that have been used for this purpose include PMR spectra of acetyl derivatives³, mass spectra⁴ and IR values.⁵ These methods, however, require the preparation of derivatives of the parent compound, or may require that both isomers be on hand for comparison. We have found that CD measurements can be used to differentiate 6- and

8-C- β -glycosylflavones and we propose a benzoyl sector rule to account for the differing chiroptical properties.

INTRODUCTION

C-Glycosylflavones show absorption maxima in three regions of the UV spectrum. These maxima occur at 300–340 nm, at 250–275 nm and near 215 nm with extinction coefficients of 15,000–25,000. At least one CD band was observed in each of the three absorption regions. Examination of over 40 compounds (Chart 1, Table I) has shown that although CD bands at high and low wavelength are of little value in providing structural information, the sign of the CD band at 250–275 nm is determined by the position of the C- β -glycosyl residue on the flavone. A positive CD band at 250–275 nm indicates that the glycosyl residue is linked to C-6 of the flavone, whereas a negative band indicates that it is linked to C-8. These conclusions refer to β -D-glycosyl derivatives, which are almost always the naturally occurring isomers, and to α -L-rabinopyranosyl derivatives, which are structurally similar to β -D-glycosyl derivatives.⁶ Limited studies on C- α -L-glycosylflavones, where the glycosyl residue is attached to the flavone by an axial bond, have shown no correlation between CD and structure. In a previous report, we noted⁷ that 6,8-di-C-glycosylflavones showed CD bands at high and low wavelength of magnitude similar to those of monosubstituted C-glycosylflavones, while the CD band(s) at 250–275 nm was greatly reduced. Thus, a cancelling effect was observed upon disubstitution. Our subsequent studies have shown that the magnitude of the CD bands at 250–275 nm of di-C-glycosylflavones may be as large as those of mono-C-glycosylflavones. The di-C-glycosylflavones are usually characterized by two CD bands of opposite sign at 250–275 nm, whereas the monosubstituted isomers have only one CD band in this range.⁸ All subsequent discussion of CD bands in this paper refers to the 250–275 nm region.



^{1a}The sign of a CD band at 274–280 nm has been found to depend upon the enantiomeric configuration for some aryl α - and β -D-glycosylflavones⁸ and α -D-glucopyranosylflavonic acids.⁹ Also, CD bands at 245–275 nm in phenyl α - and β -D-glucopyranosides have been found¹⁰ to be positive and negative, respectively.

^{1b}For related CD studies on flavone glycosides, see Ref. 8.

Table 1. Circular Dichroism^a of C-glycosylflavones[illegible]

Table I (Contd)

A-Substituted Flavones			
Compound	λ_{max} nm	ϵ (M ⁻¹ cm ⁻¹)	$[\theta]_{25}^{\text{D}}$ deg dm ³ mol ⁻¹
6,8-di-O-glucosylquercetin (22) ^a	310(300)	-1500(200)	100(100)
6,8-di-O-glucosylquercetin (22) ^b	310(300)	---	100(100)
6,8-di-O-glucosylquercetin (22) ^c	310(300)	---	100(100)
6,8-di-O-glucosylquercetin (22) ^d	310(300)	---	100(100)
6,8-di-O-glucosylquercetin (22) ^e	310(300)	---	100(100)
6,8-di-O-glucosylquercetin (22) ^f	310(300)	---	100(100)
6,8-di-O-glucosylquercetin (22) ^g	310(300)	---	100(100)
6,8-di-O-glucosylquercetin (22) ^h	310(300)	---	100(100)
6,8-di-O-glucosylquercetin (22) ⁱ	310(300)	---	100(100)
6,8-di-O-glucosylquercetin (22) ^j	310(300)	---	100(100)
6,8-di-O-glucosylquercetin (22) ^k	310(300)	---	100(100)
6,8-di-O-glucosylquercetin (22) ^l	310(300)	---	100(100)
6,8-di-O-glucosylquercetin (22) ^m	310(300)	---	100(100)
6,8-di-O-glucosylquercetin (22) ⁿ	310(300)	---	100(100)
6,8-di-O-glucosylquercetin (22) ^o	310(300)	---	100(100)
6,8-di-O-glucosylquercetin (22) ^p	310(300)	---	100(100)
6,8-di-O-glucosylquercetin (22) ^q	310(300)	---	100(100)
6,8-di-O-glucosylquercetin (22) ^r	310(300)	---	100(100)
6,8-di-O-glucosylquercetin (22) ^s	310(300)	---	100(100)
6,8-di-O-glucosylquercetin (22) ^t	310(300)	---	100(100)
6,8-di-O-glucosylquercetin (22) ^u	310(300)	---	100(100)
6,8-di-O-glucosylquercetin (22) ^v	310(300)	---	100(100)
6,8-di-O-glucosylquercetin (22) ^w	310(300)	---	100(100)
6,8-di-O-glucosylquercetin (22) ^x	310(300)	---	100(100)
6,8-di-O-glucosylquercetin (22) ^y	310(300)	---	100(100)
6,8-di-O-glucosylquercetin (22) ^z	310(300)	---	100(100)
B-Substituted Flavones			
Compound	λ_{max} nm	ϵ (M ⁻¹ cm ⁻¹)	$[\theta]_{25}^{\text{D}}$ deg dm ³ mol ⁻¹
Quercetin (1a) ^b	310(300)	---	100(100)
Quercetin (1a) ^c	310(300)	---	100(100)
Quercetin (1a) ^d	310(300)	---	100(100)
Quercetin (1a) ^e	310(300)	---	100(100)
Quercetin (1a) ^f	310(300)	---	100(100)
Quercetin (1a) ^g	310(300)	---	100(100)
Quercetin (1a) ^h	310(300)	---	100(100)
Quercetin (1a) ⁱ	310(300)	---	100(100)
Quercetin (1a) ^j	310(300)	---	100(100)
Quercetin (1a) ^k	310(300)	---	100(100)
Quercetin (1a) ^l	310(300)	---	100(100)
Quercetin (1a) ^m	310(300)	---	100(100)
Quercetin (1a) ⁿ	310(300)	---	100(100)
Quercetin (1a) ^o	310(300)	---	100(100)
Quercetin (1a) ^p	310(300)	---	100(100)
Quercetin (1a) ^q	310(300)	---	100(100)
Quercetin (1a) ^r	310(300)	---	100(100)
Quercetin (1a) ^s	310(300)	---	100(100)
Quercetin (1a) ^t	310(300)	---	100(100)
Quercetin (1a) ^u	310(300)	---	100(100)
Quercetin (1a) ^v	310(300)	---	100(100)
Quercetin (1a) ^w	310(300)	---	100(100)
Quercetin (1a) ^x	310(300)	---	100(100)
Quercetin (1a) ^y	310(300)	---	100(100)
Quercetin (1a) ^z	310(300)	---	100(100)

^a Spectra obtained in methanol at 25°C unless otherwise noted.

^b Sample from the Fruit and Vegetable Chemistry Laboratory, Pasadena, CA.

^c Sample from the University of California, Davis, CA.

Mono-C-glycosylflavones

The CD bands of various heptacetate, 3, and isovitexin heptacetate, 4, differ in magnitude but not in sign from those of the parent flavones, 1 and 2, respectively. The CD band of 4-bromovitexin, 8, is about two-thirds the magnitude of the CD band of 1, but the sign is negative for both of them bands. Thus, a 6-C substitution does not greatly affect the CD of an 8-C-glycosylflavone when the substituent lies in the plane of the A-ring. Various B-ring substituents at positions 3 and 4 have little effect on the CD band as shown by the 8-C-glycosylflavones 6, 7, and 9 and the 6-C-glycosylflavones 9, 10, 11 and 12.

Forming a methyl or acetyl derivative of the glucosyl moiety in 8-C-isomers, (e.g., 3, 13 and 14) has little effect on the magnitude of the CD band relative to 1, whereas modification of the carbohydrate in 6-C-glycosylflavones (4, 15, 16 and 17) increases the CD band two or three fold over that of 1. This increase may be due to rotational isomerism of the carbohydrate about the C-4, C-1' bond (see below). Substitution of another carbohydrate residue on the glucosyl residue of either 6-C(18, 19 and 20)

or 8-C-glycosylflavones (21) does not markedly affect the CD.

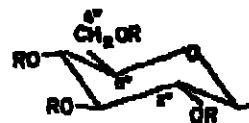
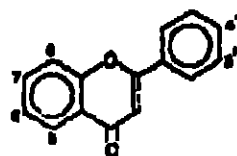
The effect of different C-2' substituents upon the CD is illustrated by 2'-O- β -D-xylopyranoside (22) and 2'-O- β -D-glucopyranoside (23). The CD of 22 differs little from that of 1, whereas the CD band of 23 is nearly three times as large as that of 1. This enhancement of the CD band may be due to an additional contribution from the *p*-hydroxybenzoyl chromophore, an alteration of the carbohydrate conformation, or from electronic interaction of the benzoyl chromophore at C-2' with the benzoyl chromophore of the A-ring.¹

Several glycosyl residues, other than β -D-glucosyl were examined as 6- or 8-substituents in C-glycosylflavones. 6-C- β -D-Galactopyranosyl (24), 6-C- β -D-Xylopyranosyl (25) and (26) and 6-C- α -L-Xylopyranosyl (27) derivatives of various flavones all gave a positive CD band (Fig. 1) although the intensity of the band varied widely among this group of compounds. 8-C- β -D-Galactopyranosyl (28) gave a negative CD band which was roughly one-half that of 1. Acetylation of the xylopyranosyl derivative 27, to yield 29, did not appreciably alter the CD compared to the effect that acetylation had on 2. CD studies on undervivified (30) and partially hydrolyzed (31 and 32) C- α -L-rhamnosylflavones have shown that both C-6 and C-8 isomers exhibit a negative CD band at 230-275 nm. Thus, to judge from

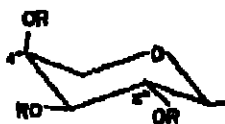
¹The study of such interactions between two benzene chromophores has resulted in the "excitonic chirality rule" of Harada and Watanabe.¹ However, 23 does not exhibit the split CD bands (couplet) characteristic of interacting benzoyl groups.

698
694

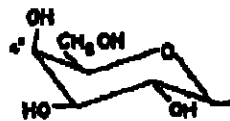
Chart I. Flavone inhibition patterns



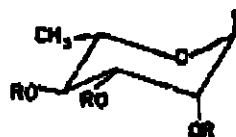
Glc, R = H
 AcGlc, R = Ac
 MeGlc, R = Me



ArG, R = H
 Ac-ArG, R = Ac



Gal



Fuc, R = H
 MeFuc, R = Me
 (CD₃)₂Fuc, R = CD₃



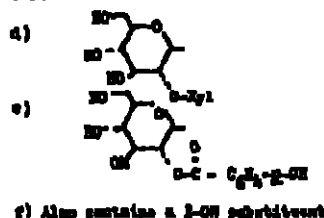
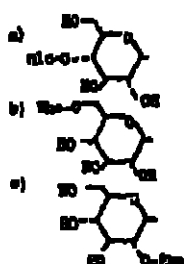
Xyl

Compound	2	6	7	8	3'	4'
1	OH	'''	OH	Glc	'''	OH
2	OH	Glc	OH	'''	'''	OH
3	OH	'''	OH	AcGlc	'''	OH
4	OH	AcGlc	OH	'''	'''	OH
5	OH	3r	OH	Glc	'''	OH
6	OH	'''	OH	Glc	'''	OH
7	OH	'''	OH	Glc	OH	OH
8	OH	'''	OH	Glc	'''	OH
9	OH	Glc	OH	'''	'''	OH
10	OH	Glc	OH	'''	OH	OH
11	OH	Glc	OH	'''	'''	'''
12	OH	Glc	OH	'''	'''	OH
13	OH	'''	OH	MeGlc	'''	OH
14	OH	'''	OH	AcGlc	Glc	OH
15	OH	AcGlc	OH	'''	'''	OH
16	OH	MeGlc	OH	'''	'''	OH
17	OH	AcGlc	OH	'''	Glc	OH
18	OH	a	OH	'''	'''	OH
19	OH	b	OH	'''	'''	OH
20	OH	a	OH	'''	'''	OH
21	OH	'''	OH	a	'''	OH
22	OH	'''	OH	a	'''	OH
23	OH	'''	OH	a	'''	OH

700
696

Chart 1 (Contd)

	5	6	7	8	3'	4'
26	OH	Gal	OH	...	...	OH
29	OH	Xyl	OH	...	OH	OH
36	OH	Xyl	OH	...	...	...
37	OH	Ara	OH	...	...	OH
20	OH	...	OH	Gal	...	OH
29	Gal	Ac ₂ Ara	Gal	...	...	Gal
30	OH	...	OH	Rha	...	OH
31	OH	...	OH	Me ₂ Rha	...	OH
32	OH	Me ₂ Rha	OH	...	...	OH
33	OH	Gal	OH	Gal	...	OH
34	OH	Gal	OH	Gal	OH	OH
35	OH	Me ₂ Gal	OH	Me ₂ Gal	OH	OH
36	OH	Xyl	OH	Gal	...	OH
37	OH	Xyl	OH	Gal	OH	OH
38	OH	Gal	OH	Ara	...	OH
39	OH	Ara	OH	Gal	...	OH
40	OH	Ac ₂ Gal	OH	Ac ₂ Gal	OH	OH
41	OH	Gal	OH	Rha	...	OH
42	OH	Rha	OH	Gal	...	OH
43	OC ₂ H ₅	(OC ₂ H ₅) ₂ Rha	OC ₂ H ₅	(OC ₂ H ₅) ₂ Rha	...	OC ₂ H ₅
44 ^a	OH	...	OH	O-Gal	OH	OH
45 ^a	OH	...	O-Gal	OH	OH	OH



these three examples, there is no change in sign with position of substitution if the glycosyl residues enter in the 1C conformation and is axially substituted at the 1-position.

di-C-glycosylflavones

All 6,8-di-C-glycosylflavones (33-43), except the isomeric derivative 42, and the rhamnosyl-containing compound 43, exhibited two CD bands at 250-275 nm, a positive CD band at 263-275 nm and a negative CD band at 250-262 nm (Fig. 2). The CD spectra of arabinosyl-containing diglycosyl compounds 33 and 39 were noteworthy since the arabinosyl residues gave rise to larger CD bands than the glycosyl residues. The negative lower wavelength band dominated the CD of the 8-C-arabinosyl compound 33, whereas the positive higher wavelength band dominated the CD of the 6-C-arabinosyl isomer 39. These findings may prove helpful in structural elucidation of di-C-glycosylflavones containing arabinose and glucose.

Miscellaneous glycosylflavones

Examination of two flavanone glycosides where the carbohydrate is bonded to a phenolic oxygen atom has shown that the 8-β-D-glucoside 44 gave a CD band 5-6 times greater than that of the 7-β-D-glucoside 45. CD measurements have been used recently to distinguish¹⁰ isomeric 7-O- and 4-O-β-glycosylflavones and 3-O-β-glycosylflavones.

Variable temperature studies

Variable temperature CD curves of vitisin heptacetate (3) and isovitisin heptacetate (4) are shown in Figs. 3 and 4, respectively.

The intensity of each CD band in the two isomers increases upon lowering the temperature. In particular, the 250-275 nm CD band increases in magnitude about twofold in 3 and nearly twofold in 4. At low temperatures (~-130 to -140°), most of the molecules of the isomeric C-glycosylflavones are probably frozen in a single preferred conformation. Since the 250-275 nm CD

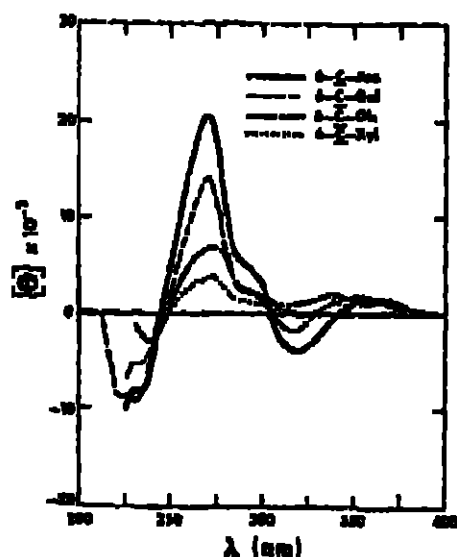


Fig. 1. Effect of different carbohydrates upon the CD of 6-C-glycosylflavones. CD spectra of 6-C- β -D-glucopyranosylflavone (17) (—), 6-C- β -D-galactopyranosylflavone (24) (---), 6-C- β -D-glucopyranosylchrysin (11) (·····), 6-C- β -D-glucopyranosylfisetin (25) (- - - - -).

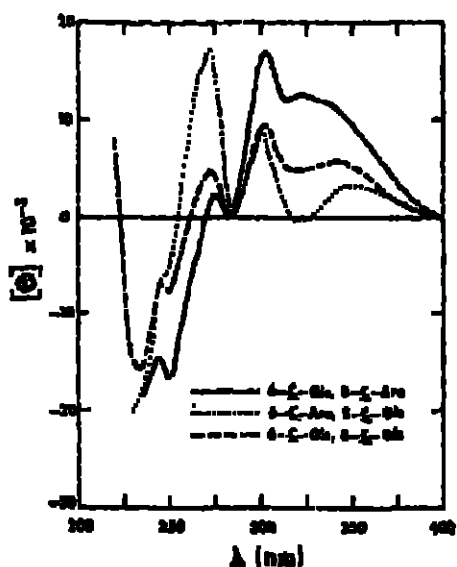


Fig. 2. Effect of different carbohydrates upon the CD of 6,8-di-C-glycosylflavones. CD spectra of 6-C- β -D-glucopyranosyl-8-C- β -D-glucopyranosylflavone (26) (·····), 6-C- β -D-glucopyranosyl-8-C- β -D-galactopyranosylflavone (27) (---), 6,8-di-C- β -D-glucopyranosylflavone (28) (—), 6,8-di-C- β -D-glucopyranosylchrysin (29) (- - - - -).

bands of 3 and 4 changed only in magnitude but not in sign upon warming to 20°, the predominance of one preferred conformation is indicated in the temperature range studied.

DISCUSSION

A probable explanation for the dissimilar chiroptical properties of 6-C- and 8-C-glycosylflavones is that the carbohydrate occurs on opposite sides of a symmetry plane of the substituted benzoyl chromophore. The ab-

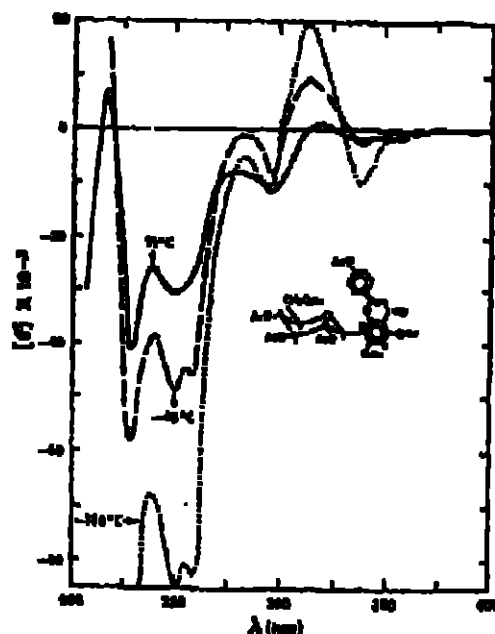


Fig. 3. Effect of temperature upon the CD of vitexin heptacetate (5). CD spectra at 23° (—), -65° (---) and -125° (·····) in 2:1 methanol-ethanol.

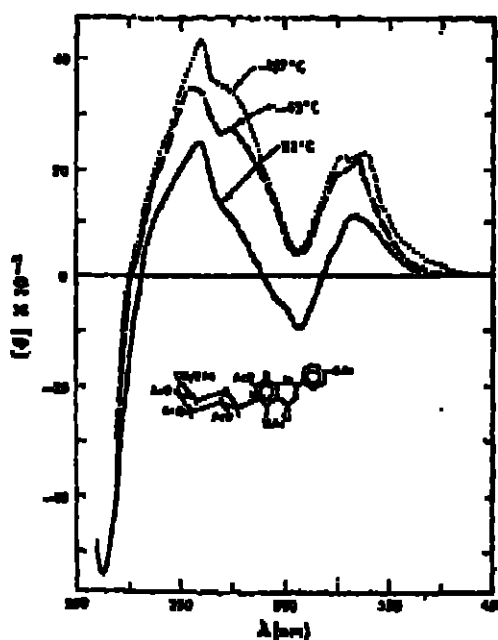
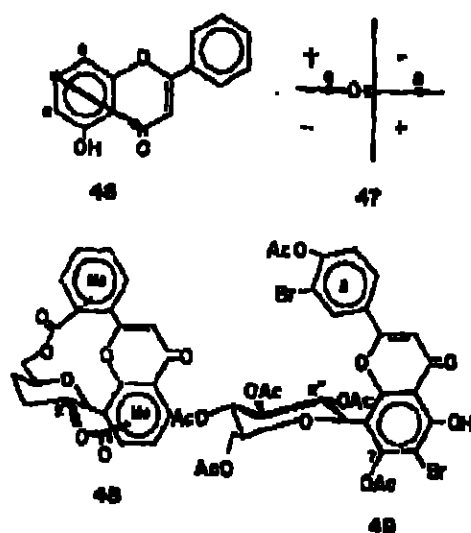


Fig. 4. Effect of temperature upon the CD of luteolin heptacetate (4). CD spectra at 23° (—), -65° (---) and -125° (·····) in 2:1 methanol-ethanol.

sorption band at 230–260 nm in substituted acetophenones has been tentatively assigned¹¹ as an intramolecular charge-transfer transition in which the transition moment is directed¹² from the para position of the acetophenone ring toward the CD group, as in 46. To define a quadrant, we take as symmetry planes of the benzoyl chromophore the plane of the aromatic A-ring



and a plane perpendicular to the A-ring and containing the transition moment.⁶ Viewing the flavone from the CO end of the transition moment, the sector diagram shown in 47 is obtained. The sign of the CD band related to the charge-transfer transition should be determined by whichever sector or sectors are predominantly occupied by the asymmetric substituent or perturbing group, which is the carbohydrate group in a C-glycosylflavone.

The sign of the rotational perturbation due to a group lying in a particular sector can be deduced experimentally by determining the preferred conformation of the C-glycosylflavone and then relating the observed CD band to the sector contribution given by this conformation. Two lines of evidence define the preferred conformation of C-glycosylflavones. First, pair studies^{1,2,10} have shown 48 to be the most likely conformation of vitexin heptacetate (7) because the 7'-O-acetyl group appears to be shielded by the A-ring and the 6'-O-acetyl group by the B-ring. In 48, most of the atoms of the carbohydrate, particularly those nearest the benzoyl chromophore, lie in the upper right quadrant. Second, an X-ray crystallographic study¹¹ of 3,5-dibromo-2',3',4',5',6',7'-hexaacetylflavone has shown that the plane of the pyranosyl ring is approximately perpendicular to the benzopyrone ring with the 2'-acetoxy group located over the heterocyclic ring, approximately halfway between the 1-acetoxy group and the B-ring, as in 49. In both conformations, the glycosyl residue of 48 and 49 predominantly occupies the upper right quadrant. Both 6-C- and 8-C-glycosylflavones have been shown by PMR to exhibit rotational isomerism with the 6-C-isomers more heavily weighted toward one conformer than the 8-C-isomers.

Since all the 8-C- β -glycosylflavones examined gave negative CD bands at 250-275 nm,⁶ the upper right quadrant may be assigned a negative sign.

The remaining sectors are assigned alternating signs,

resulting in the signed sector diagram 47. Thus, the oppositely signed 250-275 nm CD band of the 6-C substituted flavones would be due to the major conformer predominantly occupying the upper left quadrant. Further support for these conclusions is found in the CD spectra of the 6,8-di-C-glycosyl derivatives. These compounds apparently have a C-6 substituent primarily in one sector and a C-8 substituent primarily in another sector of opposite sign, resulting in the presence of two CD bands of opposite sign at 250-275 nm. Consequently, as a result of overlapping of oppositely signed adjacent CD bands,¹² the CD bands in di-C-glycosylflavones are often much weaker than those in the mono glycosides.

Our proposal for C-glycosylflavones is somewhat similar to the benzoin sector rule¹⁷ developed by Harada and Nakashita, who divided the isotropically symmetric benzoin chromophore into eight sectors and experimentally assigned signs to these sectors. The sign of the benzoyl sectors for C-glycosylflavones are the same as those of the inner sectors of Harada and Nakashita's benzoin.¹⁷

Acetylation or methylation of the carbohydrate hydroxyls increased the CD band two to three-fold in 6-C-glycosylflavones. Thus, derivatized 6-C-glycosylflavones (1) may possess conformations in which the glycosyl residue occupies the upper left quadrant to a greater extent than it does in the parent compounds or the increased CD may result from (2) an increased polarizability of the perturbing group due to a better substituent or (3) from altered electronic properties resulting in different perturbations on the aromatic chromophore transitions. No independent evidence exists on these points at present.

The CD of 6-C-galactopyranosylapigenin (34) is enhanced relative to that of 6-C-glucopyranosylapigenin (apigenin) (2). Models show that equatorial but not axial C-4' substituents lie near the plane of the benzoyl chromophore, regardless of conformation. Apparently a conformer is present in 24 in which the galactosyl residue is coplanar with the flavone such that the axial 4'-hydroxyl projects into the upper left quadrant. Similarly, arabidosyl derivatives 27 and 29 probably owe their strongly positive CD bands to conformations which project the hydroxyl and acetoxy groups at C-2' and C-4' into the upper left quadrant. The CD bands of xylosyl derivatives 25 and 26 are weak relative to those of 2, 27 and 29. This is probably due to the fact that (1) compounds 25 and 26 contain equatorial rather than axial C-4' hydroxyl groups and (2) loss of the hydroxymethyl group at C-5' probably allows the glycosyl group greater conformational mobility so that the upper left quadrant is less populated. Loss of the perturbing effect of this group at C-5' may be less important than loss of the bias it exerts upon the conformational equilibrium.

While the CD spectra of 8-C-rhamnosylflavones are consistent with those of all other 8-C-glycosyl compounds examined herein, even with a 6-C-glycosyl present in the molecule (see 47), the presence of a 6-C-rhamnosyl on a flavone results in a strong negative CD band at 250-275 nm. These observations suggest that 6-C-rhamnosylflavones adopt a preferred conformation in which the axially linked rhamnose predominantly occupies the lower left quadrant in 47.

CD results on O-glycosylflavones 44 and 45 are consistent with our benzoyl sector rule. The observation that the 8-glucoside 44 shows a stronger CD band than the 7-glucoside 45 suggests that the 7-substituent lies

⁶The transition moment for the 250-260 nm band of benzoin acid is tilted 6.5° toward the carbonyl group from the rule in question.¹⁰

¹¹In order to compare the chiroptical properties of 3 with the PMR data obtained in chloroform, we have measured the CD of 3 in chloroform and observed a negative CD band at 250 nm (Table I).

702
698

near symmetry plane of the chromophore and this results in a lesser contribution to the CD.

These findings show clearly that CD provides a useful,^{18,19} sensitive method for determining whether C-glycosylflavones contain 6-C-, 8-C-, or 6,8-di-C-glycosyl residues (see Experimental).

EXPERIMENTAL

The CD data recorded in Table I were obtained with the aid of a Cary 60 spectropolarimeter equipped with a 600 circular dichroism accessory calibrated as previously described.²⁰ Samples of C-glycosylflavones (0.1–0.5 mg) were weighed on a microanalytical balance and dissolved in 0.1–3.0 ml of solvent. Generally, CD measurements were performed using a 1 mm cell (2.3 ml volume), but, for samples possessing weak CD, either a 1 cm cell was used which required 0.6 ml of solution or a 1 mm cell was used which required 0.1 ml of solution. Measurements were obtained using the full range setting of either 0.01 or 0.04 d.

The variable temp. CD data recorded in Figs. 3 and 4 were obtained on a Jobin-Yvon Dichrograph Mark III. The low temperature data were corrected for solvent contraction by use of data reported²¹ for anthracene-glycol.

The acetyl derivative (28) of the arabinopyranosylglycoside (27), was prepared by allowing 27 to stand in acetic anhydride-pyridine on the steam bath for 1 hr followed by evaporation of the reagents under vacuum.

Acknowledgments.—The authors wish to thank Mr. W. Ungewer and Mme. Gagne, Jobin-Yvon, Longjumeau, France, for the low temperature CD data recorded in Figs. 3 and 4, and Profs. R. E. Park, J. B. Harborne and H. Wagner for samples of scutellarin, 6-C-palmitoylscutellarin and violacutin, respectively.

REFERENCES

- ¹ Presented in part at the 161st National Meeting of the American Chemical Society, Los Angeles, California (1974); CARR-21; ² Laboratoire de Science and Education Administration, U.S. Department of Agriculture.
- ³ L. J. Haynes, *Naturally Occurring C-Glycosyl Compounds in Adu. Carbohydrate Chem.* (Edited by M. L. Wolfrom and R. E. Tipson), Vol. 14, pp. 227–238. Academic Press, New York (1963); L. J. Haynes, *Ibid.*, Vol. 20, pp. 251–262. Academic Press, New York (1965); J. Chapin and M. L. Boulton, *C-Glycosylflavones. In The Flavonoids* (Edited by J. B. Harborne, T. J. Mabry and H. Mabry), Part 2, pp. 633–691. Chapman & Hall, London (1973).
- ⁴ R. Gentioli and R. M. Harowitz, *J. Org. Chem.* 33, 1371 (1968).
- ⁵ A. Fieser, *Tetrahedron* 24, 3497 (1968); M. L. Boulton, *J. Flavonoid Chem.* 14, 2267 (1973).
- ⁶ I. Kise and F. Saitoh, *Carbohydr. Res.* 12, 115 (1970).
- ⁷ T. Saitoh, C. Fieser and R. B. Smith, *Tetrahedron* 24, 3521 (1968); A. Lova, A. Liptak, I. Fieser and G. Saitoh, *Acta Chim. Budapest* 64, 99 (1973).
- ⁸ W. G. Gifford and R. M. Harowitz, *J. Chem. Soc. Chem. Commun.* 648 (1972).
- ⁹ W. Voelter, O. Oster, G. Jung and E. Brubaker, *Chimia* 25, 26 (1971); O. Oster, E. Brubaker, G. Jung and W. Voelter, *Proc. Conf. Appl. Phys. Chem.* (Edited by I. Buzas) Vol. 1, p. 213 (1971); *Chem. Abstr.* 76, 49429 (1972).
- ¹⁰ N. Harada and K. Nakashima, *Acta. Chem. Sci.* 2, 277 (1972).
- ¹¹ A. Lova, R. Bognar, C. Fieser, S. Ryschick and T. Saitoh, *Acta Chim. Budapest* 78, 345 (1973); T. Saitoh, S. Ryschick, C. Fieser, A. Lova and R. Bognar, *Chem. Zvesti* 29, 538 (1975).
- ¹² S. Nagakura and J. Tanioka, *J. Chem. Phys.* 22, 226 (1954); S. Nagakura, *Ibid.* 23, 1441 (1955); J. Tanioka and S. Nagakura, *Ibid.* 24, 1274 (1956); J. Tanioka, S. Nagakura and M. Kobayashi, *Ibid.* 24, 311 (1956).
- ¹³ J. Tanioka, *Bull. Chem. Soc. Japan* 36, 833 (1963).
- ¹⁴ R. M. Harowitz and B. Gentioli, *Chem. & Ind.* 625 (1966).
- ¹⁵ R. A. Hude, W. B. Hill, D. H. S. Hsu and J. J. R. Simon, *Appl. J. Chem.* 10, 715 (1967).
- ¹⁶ R. A. Jursch and D. H. Tompkins, *Acta Cryst.* B11, 1304 (1975).
- ¹⁷ K. M. Wolfrom, P. H. A. Lee, W. S. Briggs, A. Menonovitz and C. Djurdjevic, *J. Am. Chem. Soc.* 85, 66 (1963).
- ¹⁸ N. Harada, M. Ohachi and K. Nakashima, *Ibid.* 86, 7349 (1964); N. Harada and K. Nakashima, *Ibid.* 88, 7351 (1966).
- ¹⁹ R. M. Harowitz, R. Gentioli and W. G. Gifford, *Abstracts of Papers, 161st National Meeting of the American Chemical Society, Los Angeles, CA, 1974, CARR-21.*
- ²⁰ J. Chapin, M. L. Boulton, H. Wagner and K. Galla, *Phytochemistry* 13, 2383 (1974).
- ²¹ W. G. Gifford, Y. Tominaka, A. C. Olson and E. F. Jansen, *Arch. Biochem. Biophys.* 137, 405 (1973).
- ²² O. Kervin and I. Buzas, *Analyt. Chem.* 43, 1119 (1971).