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Señor Director

DIRECCION DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Asunto : Solicitud de Patente para:
**DERIVADO DE ESPIROCETAL Y USO DEL MISMO COMO
MEDICINA PARA LA DIABETES**
Solicitante : **CHUGAI SEIYAKU KABUSHIKI KAISHA (CHUGAI
PHARMACEUTICAL CO. LTD).**
Clase : A61K 31/7048, A61P 003/004, A61P 003/010, A61P 043/000,
C07H 019/001
Fecha de Solicitud : 23 de Agosto de 2007

1. Yo, Luz Clemencia DE PÁEZ, en mi condición de apoderada de la sociedad solicitante de la patente de la referencia, me refiero al oficio No. **03401** notificado por fijación en lista del 25 de febrero de 2011.

2. Mediante oficio No. **03401** se puso en conocimiento del solicitante el informe que contiene el requerimiento efectuado por su Despacho para la presente solicitud de patente. Atiendo a las observaciones de la manera siguiente:

2.1. Presentación de documentos solicitados

Mediante oficio No. **03401** y de acuerdo con las disposiciones del Artículo 46 de la Decisión 486 su Despacho solicita el siguiente documento en inglés:

DANISHEFSKY: "A fully synthetic route to the Papulacandis. Stereospecific spiroacetalization of a C-1-arylated methylglucoside", Carbohydrate Research, 1987; Samuel, et Al., 171, páginas 317-327

Con el fin de atender a dicha solicitud, se presenta junto con este memorial copia del documento:

DANISHEFSKY: "A fully synthetic route to the Papulacandis. Stereospecific spiroacetalization of a C-1-arylated methyl glycoside", Carbohydrate Research, 1987; Samuel, et Al., 171, páginas 317-327

Con base en lo anterior, se desea poner de presente que el artículo solicitado por su Despacho contiene un error ortográfico en el título, puesto que el título en realidad hace referencia a C-1-arylated methyl **glycoside** y no a C-1-arylated methyl **glucoside**, como es afirmado en la acción oficial.

3. Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho sobre la presente solicitud de patente, atentamente solicito que se continúe su tramitación.

4. Anexos

- Copia en inglés del documento DANISHEFSKY: "A fully synthetic route to the Papulacandis. Stereospecific spiroacetalization of a C-1-arylated methyl glycoside".

Señor Director,


LUZ CLEMENCIA DE PÁEZ
C.C. No. 35.456.344 de Usaquén
T.P.A. No. 23.555

A FULLY SYNTHETIC ROUTE TO THE PAPULACANDINS. STEREO-SPECIFIC SPIROACETALIZATION OF A C-1-ARYLATED METHYL GLYCOSIDE*

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ABSTRACT

Lewis acid-catalyzed, hetero Diels-Alder reaction of (*E*)-1-methoxy-3-trimethylsilyloxy-1,3-butadiene with 6-benzoyloxymethyl-2,4-dibenzyloxy benzaldehyde afforded 2-(6-benzoyloxymethyl-2,4-dibenzyloxyphenyl)-2,3-dihydro-4*H*-pyran-4-one. This was converted into a derivative of papulacandin D by a stereo-specific, spiroacetalization of a C-1 methoxylated aryl glycoside, [3,5-dibenzoyloxy-(methyl 3-*O*-acetyl-4,6-di-*O*-benzoyl-DL-glucopyranosid-1-yl)phenyl]methyl benzoate.

INTRODUCTION

Papulacandins A-D are antibiotics which were isolated from a strain of *Papularia sphaerosperma*¹. The papulacandins inhibit the biosynthesis of a D-glucan in yeast spheroplasts. The mechanism of action of papulacandins B in the fungus *Geotrichum luteus* has been traced to its inhibition of the enzyme (1→3)-β-D-glucansynthase². The four antibiotics share several structural themes. A common feature is the spiroacetal type of engagement of a D-glucose residue with 5-hydroxymethyl resorcinol. The C-β-glycosyl bond joining the D-glucosyl residue to OH-4 of the resorcinol residue is a most provocative challenge from the synthetic standpoint¹.

Another common feature is the presence of a long-chain fatty acyl group at OH-3 of the D-glucose residue. The presence of this type of group is apparently crucial to biological activity². In the A, B, and C isomers, the OH-4 of the D-glucose residue is also linked to a β-D-galactopyranosyl group, OH-6 of which is acylated with a "short" [C₉C(O)] trienoyl residue. The D-galactosyl and "short" acyl groups are apparently not crucial for enzymic inhibition, but might well play a role in promoting transport to the active system². The configurations of the stereogenic centers within the long acyl chain are not known in either the absolute or the

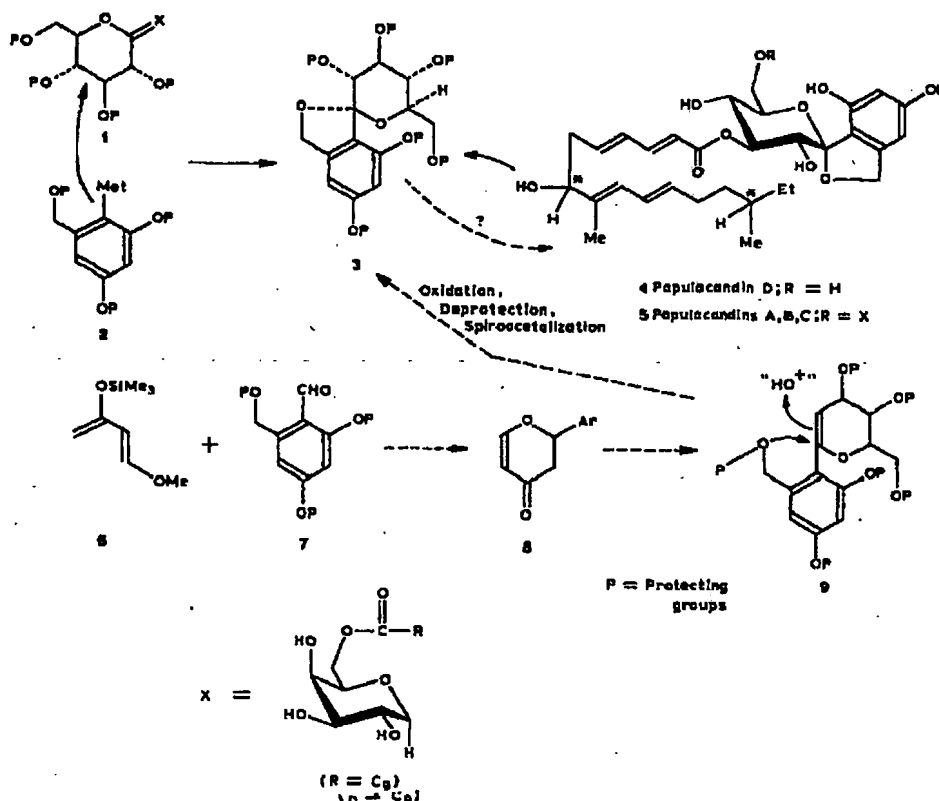
*This research was supported by PHS Grant HL-25848.

¹For an example of a synthesis of an arylated glycoside, see ref. 3.

relative sense. These uncertainties further complicate the goal of a total synthesis of any of the "intact" antibiotics.

We have engaged in various studies directed towards the synthesis of complex monosaccharides^{4,5}. Many of these compounds possess antibiotic activity and perform important bioregulatory missions. As part of this program, we have initiated some synthetic investigations in the papulacandin area. In this report, we describe a fully synthetic route to the desheptadecanoyl monosaccharide version of papulacandin D, characterized as its hexaacetyl derivative 28.

An obvious route to the papulacandins would involve coupling of a suitably protected derivative of D-glucose, such as 1, with a suitably protected organometallic compound 2. The challenges in such an approach would lie in developing good accesses to the subunits, and in achieving the coupling of the extensively functionalized and possibly hindered components. Of course, the precise nature of X and even the oxidation level of the formal structure 1 are deliberately left unspecified. Some early explorations of such an approach were not encouraging*.



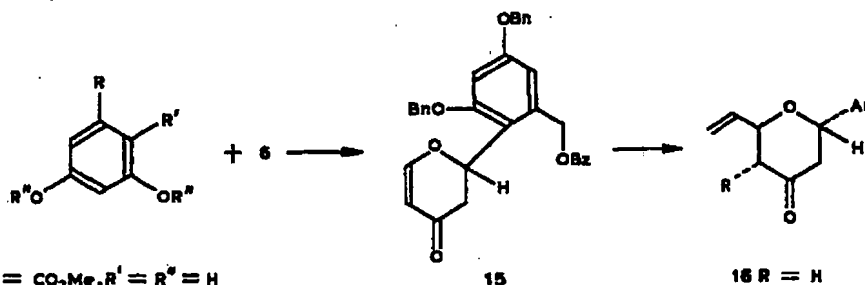
*The aromatic moiety has been metallated and treated with carbon dioxide⁶. Attempts at reacting the aryllithium moiety with pertrimethylsilylated glucunolactone gave starting material. Some other potential approaches which were not followed are implied in the work of Eade and Pham⁷.

The approach which we decided to follow was radically different in that it contemplated fashioning, by total synthesis, a dihydropyrone of the type 8. System 8 would be transformed to an intermediate such as 9. Oxidation of the double bond (in the desired stereochemical sense at C-2), followed by unveiling of the benzyl alcohol in the aromatic segment, would set the stage for spiroacetalization to produce 9*. The plan relied on the supposition that the stereochemical result of the spiroacetalization would be governed, at least at the thermodynamic level, by the anomeric effect³. In this way, the configuration at C-1 would conform to that required. Another central element of the projected route was the expectation that the dihydropyrone 8 would be accessible *via* a Lewis acid-catalyzed, hetero Diels-Alder reaction of a suitable benzaldehyde derivative 7 with the parent *trans*-1-methoxy-3-trimethylsilyloxydiene (6). The first phase of our inquiry concerned itself with the preparation of the required benzaldehyde and with the hetero Diels-Alder reaction⁹.

RESULTS AND DISCUSSION

Commercially available 3,5-dihydroxybenzoic acid was converted into the methyl ester 10. Bisbenzylation afforded 11, which upon reduction with lithium aluminum hydride gave rise 12 in 94% yield. Conversion of this compound into its benzoate derivative 13 set the stage for introduction of the crucial aldehyde function by means of a Villsmeier transformation. The key building block 14 was obtained in 66% yield.

Cyclocondensation of 14 with diene 6 occurred under catalysis¹⁰ by Yb(fod)₃. The reaction, which took place at 55° in (2H)chloroform over ~3 days, required only ~2 mol of catalyst /100 of the limiting reactant 14. The yield of apparently homogeneous pyrone 15, obtained initially as yellow syrup, was 92%.



10 R = CO₂Me, R' = R'' = H

11 R = CO₂Me, R' = H, R'' = Bn

12 R = CH₂OH, R' = H, R'' = Bn

13 R = CH₂OBz, R' = H, R'' = Bn

14 R = CH₂OBz, R' = CHO, R'' = Bn

16 R = H

17 R = OBz

The product of the treatment of vinylmagnesium bromide in oxolane-dimethyl sulfide with cuprous iodide reacted with pyrone 15 to afford, after workup, a 70% yield of the tetrahydropyrone 16. The vinyl group was to serve as the

*For a recent synthesis of phyllanthocin based on a similar stereospecific spiroacetalization, see ref. 8.

precursor of the hydroxymethyl function (*i.e.*, C-6 of the C-1 arylated D-glycosyl residue). Clearly, it would be advantageous if the kinetically produced enolate resulting from the vinylation could be exploited for introduction of the C-4 oxygen function. While we have not studied the matter exhaustively, several attempts to achieve this result by use of benzoyl peroxide as the direct trapping agent produced only modest and irreproducible yields of the corresponding benzoyloxyketone **17***. Since we now know that the later steps of the synthesis can, in fact, be executed quite efficiently, and since the introduction of this function from the pyranone, in the absence of this kinetic predisposition, was far from satisfactory (*vide infra*), the advantages of oxidative trapping of the kinetically produced enolate from the vinylation of **15** are, in retrospect, apparent.

At this juncture, degradation of the vinyl group to the required C-1 fragment was undertaken. Oxidation of **16** with osmium tetroxide-sodium metaperiodate produced a very unstable ketoaldehyde, which was immediately treated with lithium tris(3-ethyl-3-pentyloxyaluminum)hydride¹³. The expected selective reduction of the aldehyde function was accomplished. Benzoylation of the primary alcohol afforded a 59% overall yield of **19**.

The next objective became the installation of the oxygen function at C-4. Reaction of ketone **20** with hexamethyldisilazine in the presence of iodotrimethylsilane¹⁴ afforded a two-component mixture of what was assumed to be the isomeric silylenol ethers **21**. This surmise could not be verified, since the gross n.m.r. spectral features of the two components of this unresolved mixture are quite similar. Rather, the crude material was subjected to the action of 4-chloroperoxybenzoic acid¹⁵. Subsequent treatment with methanol, and then with benzoyl chloride in pyridine, afforded the desired benzoyloxyketone **22**, though only in poor yield. Also isolated from the complex reaction mixture was a comparable quantity of an isomeric product of uncertain structure**.

Treatment of presumed **22** with lithium hexamethyldisilazide, followed by quenching of the reaction with chlorotrimethylsilane, gave a silylenol ether which, in crude form, was subjected to the action of palladium(II) acetate in acetonitrile¹⁶ to give, in 78% yield, enone **23**. Reduction, followed by acetylation, afforded the pseudoequatorial acetate **25**. Oxidation with 3-chloroperoxybenzoic acid in methanol gave the methoxyhydrin **26** having the *gluco*, rather than *manno*, configuration at C-2 (ref. 17).

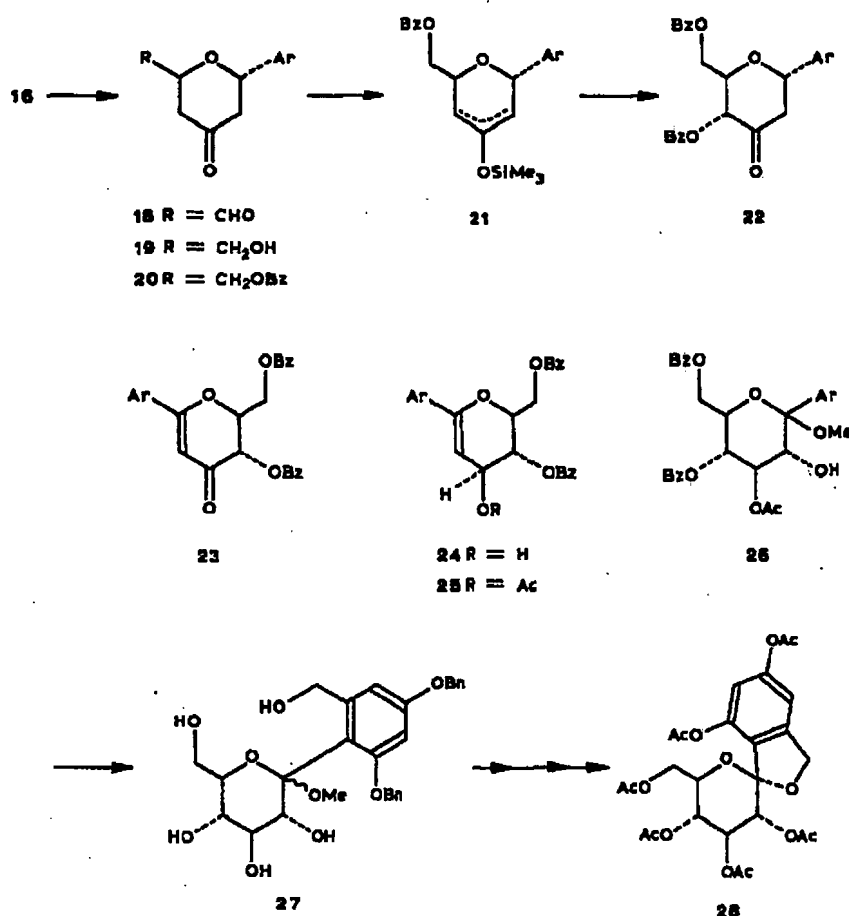
The final phase of the synthesis began with cleavage of all the acyl groups (with methanolic sodium hydroxide). Treatment of the presumed compound **27** with methanolic hydrogen chloride achieved spiroacetalization. The resultant product was acetylated and subjected to debenzoylation by hydrogenolysis in the presence of palladium(II) hydroxide¹⁸. Further acetylation afforded the racemic hexaacetate **28**. The same compound, in optically active form, was obtained as described from papulacandin D (**4**) hydrolysis and acetylation. The chromato-

*For a review on cuprate trapping reactions, see ref. 11; cf. *l.a.*, ref. 12.

**It is not clear at this time whether the compound obtained was a regioisomer or a stereoisomer.

graphic mobility, i.r. and high-field n.m.r. spectra of the synthetic and naturally derived specimens were identical.

In summary, the basis for a synthetic attack on the papulacandins has been established. The spiroacetalization of the C-1 arylated methyl glycoside using a properly placed benzyl alcohol group has been shown to be viable and stereo-selective in the required sense. To achieve a practically useful synthesis would require the attainment of major improvements in going from 14 to 23, or the development of a new route to the late intermediates (*cf.*, 23-26).



EXPERIMENTAL

General methods. — Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. I.r. spectra were recorded with a Perkin-Elmer spectrophotometer 710 Band 1420. ¹H-N.m.r. spectra were recorded with a Varian EM-390 (90 MHz) or Bruker WM-250 (250 MHz) spectrometer.

Mass spectra were obtained with a Hewlett-Packard 5985 spectrometer. High-resolution, exact masses and chemical-ionization mass spectra were obtained with a Kratos MS 80 RFA spectrometer. Reagents and solvents were purified and dried by standard methods and all reactions were run under a nitrogen atmosphere. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

6-Benzoyloxymethyl-2,4-dibenzyloxybenzaldehyde (14). — 3,5-Dihydroxybenzoic acid (11.7 g, 75.9 mmol) was dissolved in methanol (100 mL) and concentrated H_2SO_4 (0.2 mL) added. After refluxing for 17 h, the methanol was evaporated and the residue (10) was dissolved in acetone (100 mL). Benzyl bromide (29 g, 0.17 mmol) and K_2CO_3 (23 g, 0.17 mmol) were added. After heating under reflux for 6 h, additional portions of benzyl bromide (2.9 g, 17 mmol) and K_2CO_3 (2.0 g, 14 mmol) were added. After stirring for another 10 h, the solid material was filtered off and washed with ether. The solvent was removed *in vacuo* to give methyl 5,5-dibenzyloxybenzoate (11; 25.9 g), m.p. 65–66°; $\nu_{\text{max}}^{\text{CHCl}_3}$ 3020, 1720, 1600, 1300, and 1160 cm^{-1} ; $^1\text{H-n.m.r.}$ (90 MHz, CDCl_3): δ (7.5–7.0 (m, 12 H), 6.70 (t, 1 H, J 3 Hz), 4.96 (s, 4 H), and 3.66 (s, 3 H); m.s.: m/z (%) 347 (M^+ , 33), 181 (26), and 91 (100). This material was used in the next experiment.

A slurry of lithium aluminum hydride (3.0 g, 79 mmol) in ether (200 mL) was prepared under N_2 and cooled to 0°. Crude 11 (25.9 g, 74 mmol) was added in portions and, after the addition was completed, stirring was continued for 2 h. Water (3 mL), 15% aqueous NaOH (3 mL), and water (9 mL) were added and the solid material was filtered off. Removal of the solvent *in vacuo* gave 3,5-dibenzoyloxybenzyl alcohol (12; 22.4 g, 95%) as a white solid, m.p. 73–77°; $\nu_{\text{max}}^{\text{CHCl}_3}$ 3610, 2920, 1600, and 1160 cm^{-1} ; $^1\text{H-n.m.r.}$ (90 MHz, CDCl_3): δ 7.3 (m, 10 H), 6.5 (m, 3 H, 4.91 (s, 4 H), 4.45 (br. s, 2 H), and 2.4 (br., 1 H); m.s.: m/z (%) 320 (M^+ , 72), 181 (36), and 91 (100). Compound 12 was used in the next experiment without further purification. Crude 12 (22.4 g, 70 mmol) was dissolved in dichloromethane (100 mL) and the solution cooled to 0°. Triethylamine (11 g, 0.11 mmol) and benzoyl chloride (11 g, 77 mmol) were added and the mixture was stirred for 1 h, at which time it was washed with M HCl, saturated NaHCO_3 , and NaCl solution, dried (MgSO_4), and the solvent removed to give (3,5-dibenzoyloxyphenyl)methyl benzoate (13; 29.5 g, 100%) as a white solid, m.p. 67–73°; $\nu_{\text{max}}^{\text{CHCl}_3}$ 3010, 1715, 1595, 1270, and 1155 cm^{-1} ; $^1\text{H-n.m.r.}$ (90 MHz, CDCl_3): δ 8.08 (dd, 2 H, J 8.2 Hz), 7.6–7.2 (m, 13 H), 6.69 (d, 2 H, J 2 Hz), 6.60 (+, 1 H, J 2 Hz), 5.28 (s, 2 H), and 5.03 (s, 4 H); m.s.: m/z (%) 24 (M^+ , 6), 181 (11), 105 (16), and 91 (100). This material was used in the next experiment without further purification.

To a flame-dried flask under N_2 was added *N,N*-dimethylformamide (30 mL) and freshly distilled POCl_3 (21 g, 0.14 mol) at 0°. After being warmed to room temperature, the mixture was transferred to a flask containing 13 (29.5 g, 70 mmol), dissolved in *N,N*-dimethylformamide (50 mL). After being stirred for 2.5 h at 97°, the mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was separated, washed with water and NaCl solution, dried (MgSO_4),

and most of the solvent removed *in vacuo*. Ethyl ether was added and the resulting brown solid (20.9 g, 66%) was filtered off and used without further purification, m.p. 96–98°; $\nu_{\text{max}}^{\text{CHCl}_3}$ 3040, 1725, 1675, 1605, 1580, 1280, and 1160 cm^{-1} ; $^1\text{H-n.m.r.}$ (90 MHz, CDCl_3): δ 10.61 (s, 1 H), 8.08 (dd, 2 H, J 8, 2 Hz), 7.6–7.2 (m, 13 H), 6.74 (d, 1 H, J 2 Hz), 6.58 (d, 1 H, J 2 Hz), 5.79 (s, 2 H), 5.12 (s, 2 H), and 5.06 (s, 2 H); m.s.: m/z (%) 452 (M^+ , 9), 347 (63), 330 (97), 105 (19), and 91 (100).

Anal. Calc. for $\text{C}_{29}\text{H}_{24}\text{O}_5$: C, 76.97; H, 5.34. Found: C, 77.03; H, 5.51.

Cyclocondensation of aldehyde 14 with diene 6. — 2-(6-Benzoyloxymethyl-2,4-dibenzyloxyphenyl)-6-vinyl-2,3-dihydro-4H-pyran-4-one (16). To a slurry of the aldehyde 14 (4.42 g, 9.98 mmol) in CDCl_3 (15 mL) under N_2 , were added the diene 6 (2.0 g, 12 mmol) and $\text{Yb}(\text{fod})_3$ (204 mg, 0.19 mmol), and the mixture was heated at 55°. After 14 h, more diene 6 (0.44 g, 2.6 mmol) was added and, after 1 day, another portion (0.53 g, 3.1 mmol). After being heated for another 2 days, the mixture was cooled to room temperature and trifluoroacetic acid (0.5 mL) was added. After stirring for 10 min, the volatiles were removed and the residue chromatographed on silica gel (80 g) with 3:1 hexane–ethyl acetate, to give 2-(6-benzoyloxymethyl-2,4-dibenzyloxyphenyl)-2,3-dihydro-4H-pyran-4-one (15; 4.69 g, 92%) as a yellow syrup, $\nu_{\text{max}}^{\text{CHCl}_3}$ 3010, 1715, 1670, 1595, and 1270 cm^{-1} ; $^1\text{H-n.m.r.}$ (250 MHz, CDCl_3): δ 8.03 (dd, 2 H, J 2, 8 Hz), 7.7–7.3 (m, 14 H), 6.80 (d, 1 H, J 2.4 Hz), 6.67 (d, 1 H, J 2.4 Hz), 6.03 (dd, 1 H, J 15.4, 3.7 Hz), 5.57 (d, 1 H, J 12.9 Hz), 5.48 (dd, 1 H, J 6.1, 1 Hz), 5.42 (d, 1 H, J 12.9 Hz), 5.11 (d, 1 H, J 11.9 Hz), 5.07 (s, 2 H), 5.06 (d, 1 H, J 11.7 Hz), 3.48 (dd, 1 H, J 17.2, 15.4 Hz), and 2.52 (ddd, 1 H, J 1, 3.7, 17.2 Hz); m.s.: m/z (%), 520 (M^+ , 9), 398 (44), 307 (63), 237 (96), and 91 (100).

To a flame-dried flask under N_2 was added CuI (2.564 g, 13.5 mmol), oxolane (25 mL), and dimethyl sulfide (3.3 g, 51 mmol). The clear colorless solution was cooled to -78° , and vinylmagnesium bromide (27 mL of a M solution in oxolane (27 mmol)) was added. The dihydropyrone 15 (3.47 g, 6.7 mmol) was added in oxolane (20 mL), and the mixture stirred for 1.5 h. Ether and saturated NH_4Cl were added, the organic layer was separated, washed with 9:1 NH_4Cl – NH_4OH and NaCl solution, dried (MgSO_4), and the solvent removed. Chromatography on silica gel (90 g) with 2:1 hexane–ethyl acetate gave 16 (2.57 g, 70%) as a white solid, m.p. 115–117°; $\nu_{\text{max}}^{\text{CHCl}_3}$ 3005, 1715, 1605, 1270, and 1150 cm^{-1} ; $^1\text{H-n.m.r.}$ (250 MHz, CDCl_3): δ 8.04 (dd, 2 H, J 2, 8 Hz), 7.6–7.2 (m, 13 H), 6.76 (d, 1 H, J 2.4 Hz), 6.59 (d, 1 H, J 2.4 Hz), 5.90 (ddd, 1 H, J 4.4, 10.9, 17.5 Hz), 5.73 (d, 1 H, J 12.9 Hz), 5.64 (dd, 1 H, J 3.9, 10.4 Hz), 5.43 (d, 1 H, J 12.9 Hz), 5.3–5.1 (m, 2 H), 5.05 (d, 1 H, J 12.1 Hz), 5.00 (s, 2 H), 4.99 (d, 1 H, J 12.1 Hz), 4.85 (m, 1 H), 3.13 (dd, 1 H, J 10.4, 15.2 Hz), 2.70 (dd, 1 H, J 6.3, 15.1 Hz), and 2.4–2.7 (m, 2 H); m.s.: m/z (%) 548 (M^+ , 4), 426 (36), 357 (46), 335 (90), and 91 (100).

Anal. Calc. for $\text{C}_{35}\text{H}_{32}\text{O}_6$: C, 76.62; H, 5.87. Found: C, 76.94; H, 5.80.

trans-5-Benzoyloxy-6-benzoyloxymethyl-2-(6-benzoyloxymethyl-2,4-dibenzyloxyphenyl)-2,3,5,6-tetrahydro-4H-pyran-4-one (22). — The vinylpyranone 16 (1.04 g, 1.9 mmol) was dissolved in 1,4-dioxane (22 mL) and water (7 mL). Osmium

tetraoxide (0.5 mL of a 10 mg/mL solution in oxolane, 0.02 mmol) and NaIO_4 (1.34 g, 6.2 mmol) were added, and the mixture was stirred for 20 h. Water was added, and the mixture was stirred for 20 h. Water was added, and the mixture extracted with ether, the organic layer washed with water and NaCl solution, dried (MgSO_4), and most of the solvent removed *in vacuo*.

The crude aldehyde 18 was dissolved in oxolane (25 mL) under N_2 and cooled to -78° . Lithium tris(3-ethyl-3-pentyloxy)aluminum hydride (11 mL of a 0.57M solution in oxolane, 6.3 mmol) was added. After stirring for 2 h, the reaction was quenched with ethyl acetate and M HCl. The organic layer was washed with NaCl solution, dried (Na_2SO_4), and the solvent removed *in vacuo*. Chromatography on silica gel (20 g) with 2:1 hexane-ethyl acetate gave 6-benzoyloxymethyl-2-(6-benzoyloxymethyl-2,4-dibenzyloxyphenyl)-2,3,5,6-tetrahydro-4H-pyran-4-one (20) as a white foam (730 mg, 59%); $\nu_{\text{max}}^{\text{CHCl}_3}$ 3020, 3000, 1740, 1720, 1600, and 1270 cm^{-1} ; $^1\text{H-n.m.r.}$ (250 MHz, CDCl_3): δ 8.03 (dd, 2 H, J 2, 8 Hz), 7.98 (dd, 2 H, J 2, 8 Hz), 7.7–7.3 (m, 16 H), 6.77 (d, 1 H, J 2.4 Hz), 6.59 (d, 1 H, J 2.4 Hz), 5.85 (dd, 1 H, J 5.2, 7.9 Hz), 5.62 (d, 1 H, J 12.9 Hz), 5.48 (d, 1 H, J 12.9 Hz), 5.03 (s, 2 H), 5.02 (s, 2 H), 4.6–4.3 (m, 3 H), 3.17 (dd, 1 H, J 7.9, 16.0 Hz), 2.70 (dd, 1 H, J 5.2, 16.0 Hz), 2.6 (m, 1 H), and 2.53 (dd, 1 H, J 6, 16 Hz).

The pyranone 20 (508 mg, 0.77 mmol) was dissolved in benzene (5 mL) under N_2 . Hexamethyldisilazane (0.18 g, 1.1 mmol) and iodotrimethylsilane (6.17 g, 0.8 mmol) were added. The slurry was stirred for 40 min and the solvent removed *in vacuo*. The mixture was filtered through a plug of silica gel with 2:1 hexane-ethyl acetate and the solvent removed *in vacuo* to give two compounds (see 21) as a 2:1 mixture. The crude material was dissolved in benzene (5 mL), 3-chloroperbenzoic acid (171 mg, 1 mmol) added, and the mixture stirred for 30 min. The solvent was removed *in vacuo*, the gummy residue dissolved in methanol (2 mL) and oxolane (1 mL), and the solution stirred for 6 h. The solvent was removed *in vacuo*, the gum was dissolved in ethyl acetate, the solution washed with aqueous NaHCO_3 and NaCl, dried (Na_2SO_4), and the solvent removed *in vacuo*. Chromatography on silica gel (20 g) with 2:1 hexane-ethyl acetate gave a 1:1 mixture (240 mg) of two products which were dissolved in pyridine (1 mL) and benzoyl chloride (72 mg, 0.5 mmol). After being stirred for 2 h, the slurry was dissolved in ethyl acetate and washed with M HCl, saturated NaHCO_3 , and NaCl solution. Medium pressure liquid chromatography on silica gel with 5:2 hexane-ethyl acetate gave 22 (99 mg, 17%), m.p. 154–155°; $\nu_{\text{max}}^{\text{CHCl}_3}$ 3010, 1730, 1715, 1600, and 1265 cm^{-1} ; $^1\text{H-n.m.r.}$ (CDCl_3): δ 8.05 (dd, 2 H, J 2, 8 Hz), 7.95 (dd, 2 H, J 2, 8 Hz), 7.90 (dd, 2 H, J 2, 8 Hz), 7.7–7.3 (m, 19 H), 6.78 (d, 1 H, J 2.4 Hz), 6.51 (d, 1 H, J 2.4 Hz), 5.91 (t, 1 H, J 5.4 Hz), 5.78 (d, 1 H, J 9.4 Hz), 5.55 (d, 1 H, J 12.9 Hz), 5.46 (d, 1 H, 12.9 Hz), 5.16 (d, 1 H, J 14.1 Hz), 5.02 (d, 1 H, J 14.1 Hz), 4.96 (s, 2 H), 4.6–4.4 (m, 3 H), and 3.16 (d, 2 H, J 5.4 Hz).

Anal. Calc. for $\text{C}_{48}\text{H}_{40}\text{O}_{10}$: C, 74.26; H, 5.19. Found: C, 74.10; H, 5.29.

A comparable amount of an unidentified material was also obtained.

[3,5-Dibenzoyloxy-2-(methyl 3-O-acetyl-4,6-di-O-benzoyl-DL-glucopyranosid-

1-yl)phenyl methyl benzoate (26). — To a flame-dried flask under N₂ was added oxolane (2 mL), hexamethyldisilazane (69 mg, 0.49 mmol), and butyllithium (0.25 mL of a 1.6M solution in hexane, 0.4 mmol). After being stirred for 20 min, the solution was cooled to -78°, and a solution of 22 (105 mg, 0.14 mmol) in oxolane (1 mL) and hexamethylphosphoramide (75 mg, 0.42 mmol) was added. To this, freshly distilled chlorotrimethylsilane (86 mg, 0.79 mmol) was added and the reaction was quenched 15 min later with ether and saturated NaHCO₃. The organic layer was separated, washed with water and NaCl solution, dried (Na₂SO₄), and the solvent removed *in vacuo*. To the crude silylenol ether, dissolved in freshly distilled acetonitrile (2 mL), was added palladium (II) acetate (47 mg, 0.21 mmol), and the mixture stirred for 24 h. The solvent was removed *in vacuo* and the residue chromatographed on silica gel (8 g) with 3:1 hexane-ethyl acetate to give 3-benzoyloxy-2-benzoyloxymethyl-6-(6-benzoyloxymethyl-2,4-dibenzyloxyphenyl)-2,3-dihydro-4H-pyran-one (23; 82 mg, 78%) which contained ~10% of 22; $\nu_{\text{max}}^{\text{CHCl}_3}$ 3010, 1720, 1680, 1600, and 1265 cm⁻¹; ¹H-n.m.r. (250 MHz, CDCl₃): δ 8.2–8.0 (m, 6 H), 7.7–7.3 (m, 19 H), 6.77 (d, 1 H, *J* 2.0 Hz), 6.61 (d, 1 H, *J* 2.0 Hz), 6.01 (d, 1 H, *J* 12.8 Hz), 5.83 (s, 1 H), 5.47 (d, 1 H, *J* 12.8 Hz), 5.38 (d, 1 H, *J* 12.8 Hz), 5.08 (s, 2 H), 5.06 (s, 2 H), 5.0 (m, 1 H), 4.72 (dd, 1 H, *J* 2.4, 12.7 Hz), 4.54 (dd, 1 H, *J* 48, 12.7 Hz); m.s.c.i.: *m/z* (%) 775 (M⁺ + 1, 12), 244 (14), 140 (60), 105 (100), and 80 (69).

Compound 23 (82 mg, 0.11 mmol) was dissolved in oxolane (3 mL) under N₂, the solution cooled to -78°, diisobutyl aluminum hydride (0.6 mL of a M solution in hexane, 0.6 mmol) added, and the mixture stirred for 1 h. Some starting material remained and more diisobutyl aluminum hydride (0.5 mL of a M solution in hexane, 0.5 mmol) was added. After stirring for 1 h, the reaction was quenched with ethyl acetate and M HCl. The organic layer was separated, washed with NaCl solution, dried (Na₂SO₄), and the solvent removed. The crude residue (24) was dissolved in pyridine (0.5 mL) and acetic anhydride (0.05 mL) and the mixture stirred for 10 h. The solvent was removed and the residue chromatographed on silica gel (5 g) with 3:1 hexane-ethyl acetate to give [2-(3-acetyl-1,5-anhydro-4,6-di-*O*-benzoyl-2-deoxy-DL-arabino-hex-1-enit-3-yl)-3,5-dibenzoyloxyphenyl]methyl benzoate (25) (49 mg, 56%), $\nu_{\text{max}}^{\text{CHCl}_3}$ 3020, 1740, 1600, and 1270 cm⁻¹; ¹H-n.m.r. (250 MHz, CDCl₃): δ 8.2–7.9 (m, 6 H), 7.6–7.3 (m, 19 H), 6.75 (d, 1 H, *J* 2.2 Hz), 6.58 (d, 1 H, *J* 2.2 Hz), 5.70 (t, 1 H, *J* 5.5 Hz), 5.62 (t, 1 H, *J* 4 Hz), 5.45 (m, 2 H), 5.17 (d, 1 H, *J* 3.7 Hz), 5.07 (s, 3 H), 5.04 (s, 2 H), 4.74 (m, 1 H), 4.66 (dd, 1 H, *J* 4.1, 12.1 Hz), 4.55 (dd, 1 H, *J* 6.1, 12.1 Hz), and 1.94 (s, 3 H); m.s.c.i. (NH₃): *m/z* 836 (M⁺ + 18).

The glycol 25 (40 mg, 0.060 mmol) was dissolved in 10:1 methanol-oxolane (2 mL) and 3-chloroperoxybenzoic acid (13 mg, 0.07 mmol) was added. The mixture was stirred for 2 d, the solvent removed *in vacuo*, and the residue dissolved in ethyl acetate. The solution was washed with 10% NaHCO₃ and NaCl solution, dried (Na₂SO₄), and the solvent removed *in vacuo*. Chromatography on silica gel (3 g) with 2:1 hexane-ethyl acetate gave a mixture (43 mg, 82%) of methyl glyco-

sides (26) $\nu_{\text{max}}^{\text{CHCl}_3}$ 3020, 1725, 1605, and 1270 cm^{-1} ; $^1\text{H-n.m.r.}$ (250 MHz, CDCl_3): δ 8.1–7.9 (m, 6 H), 7.7–7.3 (m, 19 H), 6.79 (d, 1 H, J 2.3 Hz), 6.63 (d, 1 H, J 2.23 Hz), 5.87 (d, 1 H, J 13.6 Hz), 5.68 (t, 1 H, J 9.3 Hz), 5.5 (t, 1 H, J 9.2 Hz), 5.44 (d, 1 H, J 13.6 Hz), 5.07 (m, 2 H), 4.98 (s, 2 H), 4.63 (dd, 1 H, J 1.0, 11.8 Hz), 4.48 (dd, 1 H, J 4.7, 11.8 Hz), 4.3 (m, 1 H), 4.1 (m, 1 H), 3.30 (s, 3 H), and 1.94 (s, 3 H).

Conversion of methyl glycosides 26 to spiro[5,7-diacetoxyisobenzofuran-1-(3H),1'-(2',3',4',6'-tetra-O-acetyl-DL-glycopyranose) (28). — The mixture 26 (32 mg, 0.037 mmol) was dissolved in 0.4M methanolic NaOH (1 mL) and stirred for 5 h; 1.1M methanolic HCl (1 mL) was added, followed by solid NaHCO_3 . The material was filtered through Na_2SO_4 with chloroform and the solvent removed *in vacuo*. Chromatography on silica gel (1 g) with 9:1 chloroform–methanol gave a material (22 mg) which was dissolved in ethyl acetate (2 mL). $\text{Pd}(\text{OH})_2$ on C (4 mg) was added and the mixture placed under an atmosphere of H_2 . After being stirred for 5 h, the mixture was filtered through Celite and the solvent removed *in vacuo*. The residue was dissolved in pyridine (0.5 mL) and acetic anhydride (50 μL), and stirred for 7 h. The solvent was removed *in vacuo* and the residue chromatographed on silica gel (1 g) with 1:1 hexane–ethyl acetate to give 8 mg (38%) hexaacetate 28; $\nu_{\text{max}}^{\text{CHCl}_3}$ 1755, 1380, and 1220 cm^{-1} ; $^1\text{H-n.m.r.}$ (250 MHz, CDCl_3): δ 7.01 (d, 1 H, J 1.8 Hz), 6.93 (d, 1 H, J 1.8 Hz), 5.71 (d, 1 H, J 10 Hz), 5.60 (t, 1 H, J 10 Hz), 5.25 (t, 1 H, J 10 Hz), 5.2 (m, 2 H), 4.3 (m, 2 H), 4.05 (m, 1 H), 2.41 (s, 3 H), 2.3 (s, 3 H), 2.07 (s, 3 H), 2.06 (s, 3 H), 2.02 (s, 3 H), and 1.80 (s, 3 H); n.s.: m/z (%) 552 (M^+ , 1), 450 (2), 366 (16), 176 (75), 119 (95), and 91 (100).

Anal. Calc. for $\text{C}_{25}\text{H}_{28}\text{O}_{14}$: Mol.wt. 552.1479. Found: 552.1483.

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REFERENCES

- 1 P. TRAXLER, H. FRITZ, AND W. F. RICHTER, *Helv. Chim. Acta*, 60 (1977) 578–584; P. TRAXLER, H. FRITZ, H. FUHRER, AND W. J. RICHTER, *J. Antibiot.*, 33 (1980) 967–978.
- 2 G. ROMMELE, P. TRAXLER, AND W. WEHRLI, *J. Antibiot.*, 36 (1983) 1539–1542.
- 3 S. J. DANISHEFSKY, B.-J. VANG, AND G. QUALLICH, *J. Am. Chem. Soc.*, 107 (1985) 1285–1293.
- 4 S. J. DANISHEFSKY, E. LARSEN, AND J. P. SPRINGER, *J. Am. Chem. Soc.*, 107 (1985) 1274–1280; S. J. DANISHEFSKY, W. H. PEARSON, AND B. E. SEGEMULLER, *J. Am. Chem. Soc.*, 107 (1985) 1280–1285.
- 5 S. J. DANISHEFSKY AND M. B. BARBACHYN, *J. Am. Chem. Soc.*, 107 (1985) 7761–7768.
- 6 B. M. TROST, G. T. RIVERS, AND J. M. GOLD, *J. Org. Chem.*, 45 (1980) 1835–1838; P. D. NOIRE AND R. W. FRANCK, *Synthesis*, (1980) 882–883.
- 7 R. A. EADE AND H.-P. PHAM, *Aust. J. Chem.*, 32 (1979) 2483–2493.

- 8 S. D. BURKE, I. E. COBB, AND K. TAKEUCHI, *J. Org. Chem.*, 50 (1985) 3420-3421.
- 9 S. J. DANEHEFSKY, E. LARSEN, D. ASKIN, AND N. KATO, *J. Am. Chem. Soc.*, 107 (1985) 1246-1255.
- 10 M. BEDNARSKI AND S. J. DANEHEFSKY, *J. Am. Chem. Soc.*, 105 (1983) 3716-3717.
- 11 R. J. K. TAYLOR, *Synthesis*, 364-392 (1985).
- 12 J. W. HUFFMAN, R. C. DESAI, AND G. F. HILLEBRAND, *J. Org. Chem.*, 49 (1984) 982-987;
J. C. MULLER AND G. OURISON, *Tetrahedron Lett.*, (1972) 3375-3378.
- 13 S. KRISHNAMURTHY, *J. Org. Chem.*, 46 (1981) 4628-4629.
- 14 R. D. MILLER AND D. R. MCKEAN, *Synthesis*, (1979) 730-732.
- 15 G. M. RUBOTTOM, M. A. VAZQUEZ, AND D. R. PELIGRINA, *Tetrahedron Lett.*, (1974) 4319-4322.
- 16 Y. ITO, T. HIRAO, AND T. SAEGUSA, *J. Org. Chem.*, 43 (1978) 1011-1013.
- 17 A. A. FRIMER, *Synthesis*, (1977) 578-579.
- 18 W. M. PERLMAN, *Tetrahedron Lett.*, (1967) 1663-1666.