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TOTAL SYNTHESIS OF (±)-XYLOKETAL D AND MODEL STUDIES TOWARDS THE TOTAL SYNTHESIS OF (-)-XYLOKETAL A

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Abstract – A stereoselective total synthesis of (±)-xyloketal D (±-**2**) has been achieved using a cycloaddition reaction of an *ortho*-quinone methide and a dihydrofuran as a key step. Preliminary model studies towards the total synthesis of xyloketal A (**1**) are also reported.

INTRODUCTION

Xyloketals A (**1**) and D (**2**) are two of the metabolites that were isolated from a mangrove fungus of the *Xylaria* species (Ascomycota). The molecular structures of these natural products were determined by extensive spectroscopic studies and by X-Ray crystallography. Xyloketal A (**1**) has a unique chiral, C_3-symmetric molecular structure and was shown to be an inhibitor of acetylcholine esterase (**Figure 1**).[1]

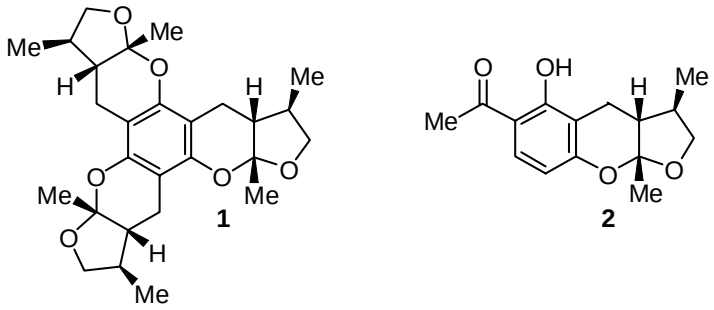
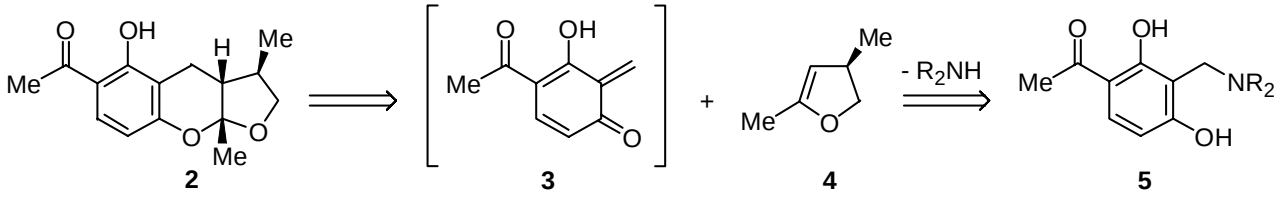


Figure 1. Molecular structures of xyloketals A (**1**) and D (**2**).

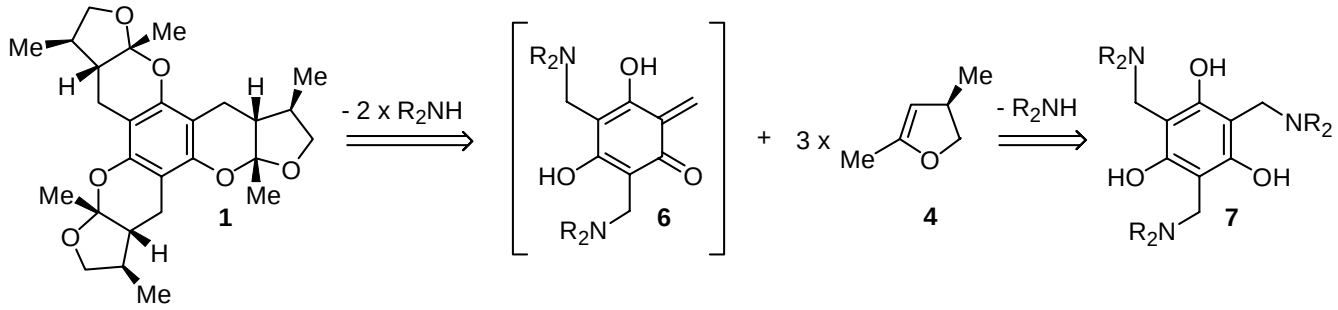
Retrosynthetic analysis of xyloketal D (**2**) suggested that it could be prepared by a [4+2] cycloaddition reaction of the *ortho*-quinone methide (**3**) and the dihydrofuran (**4**) (**Scheme 1**).[2] It was anticipated that this inverse electron demand Diels-Alder reaction would afford the target compound in a regio- and stereoselective manner.[3] The Mannich base (**5**) could serve as a precursor for the generation of the

o*rtho*-quinone methide (**3**).[4] Alkylation, oxidation, and photochemical reactions have been used to generate *ortho*-quinone methides from the Mannich bases of phenols.[2, 5]



Scheme 1. Proposed synthesis of xyloketal D (**2**).

In a similar fashion, it can be envisioned that xyloketal A (**1**) could be prepared from the Mannich base (**7**) and three equivalents of the dihydrofuran (**4**) (**Scheme 2**).[6] This unprecedented and direct synthetic process would involve the stepwise generation and subsequent cycloaddition reaction of a series of *ortho*-quinone methide reaction intermediates [*c.f.* structure (**6**)].

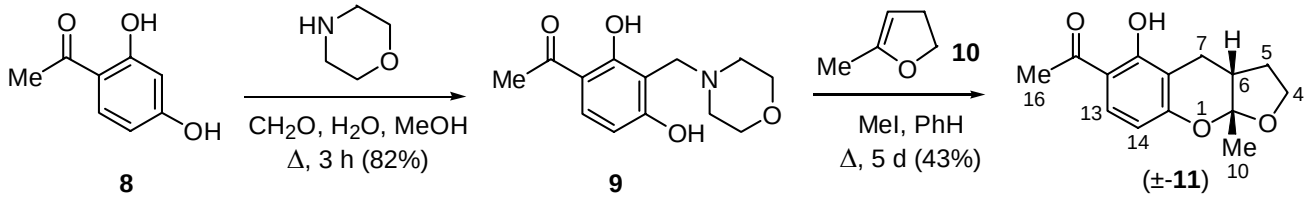


Scheme 2. Proposed synthesis of xyloketal A (**1**).

RESULTS AND DISCUSSION

The Mannich base (**9**) was prepared in good yield and as a single regioisomeric product from 2,4-dihydroxyacetophenone (**8**), formaldehyde, and morpholine. (**Scheme 3**).[4] The structure of the compound (**9**) and the regioselectivity of the aromatic substitution reaction were determined by analysis of the ^{1}H NMR spectrum. The aromatic protons of the product (**9**) were strongly coupled (J=8.9 Hz) which indicated that they were located on adjacent carbon atoms.[4] In order to determine the feasibility of the proposed cycloaddition reaction, commercially available 4,5-dihydro-2-methylfuran (**10**) was employed as a model substrate. On heating the Mannich base (**9**) and the dihydrofuran (**10**) (3 equivalents) with methyl iodide (1.05 equivalents) in benzene at reflux for 5 days, the xyloketal D analogue (±-**11**) was isolated in 43% yield.[2, 5a] Increasing the number of equivalents of methyl iodide lowered the yield of this reaction. This was caused by competing methylation reactions of one or more of the phenol groups of the Mannich base (**9**). The structure of the product and the regioselectivity of this cycloaddition reaction were determined on the basis of a sharp, downfield chemical shift (~13 ppm) of the unreacted phenolic proton. This indicated that the phenol group was adjacent to the carbonyl substituent.[1] In addition, the ^{13}C NMR spectrum showed a resonance that could be assigned to the

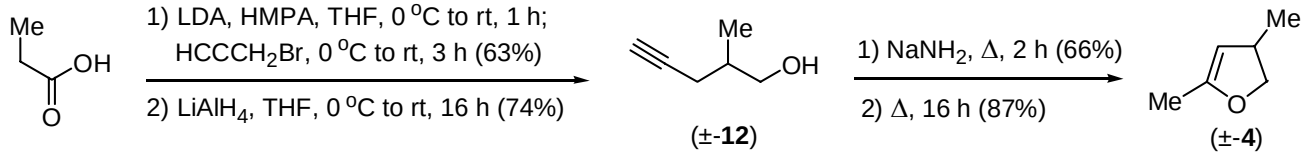
acetal carbon (C-2). The stereochemistry of the ring junction was assigned as *cis* based on the observation of a NOE contact between the bridgehead methyl group and H-6. In addition, a NOE contact was observed between H-7$_\beta$ and the bridgehead methyl group.



8 9 (±-**11**)

Scheme 3. Synthesis of (±)-11-norxyloketal D (±-**11**).

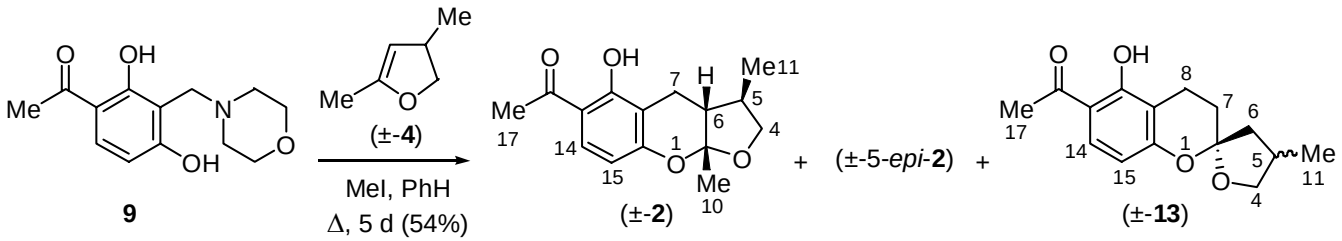
The racemic dihydrofuran (±-**4**) was prepared by modification of known synthetic procedures from the alcohol (±-**12**) in order to attempt the synthesis of (±)-xyloketal D (±-**2**) (**Scheme 4**).[7] The alcohol (±-**12**) was prepared in two steps, by standard synthetic methods, from propionic acid.[8]



(±-**12**) (±-**4**)

Scheme 4. Synthesis of racemic dihydrofuran (±-**4**).

The cycloaddition reaction of the Mannich base (**9**) with the dihydrofuran (±-**4**) (3 equivalents) afforded (±)-xyloketal D (±-**2**), (±)-5-*epi*-xyloketal D (±-5-*epi*-**2**), and the diastereomeric (±)-spiroacetals (±-**13**) as a mixture of products (11:1:3:3) in a combined yield of 54% (**Scheme 5**). It was possible to separate these compounds by repeated chromatography and the spectral data for synthetic (±)-xyloketal D (±-**2**) were in agreement with those reported for the natural product.[1] Thus, the relative stereochemistry of the major reaction product was firmly established. The formation of the (±)-spiroacetal products (±-**13**) in this reaction can be attributed to the isomerization and subsequent reaction of the corresponding exocyclic double bond isomer of dihydrofuran (±-**4**). It is of interest that a spiroacetal product was not identified in the cycloaddition reaction of 4,5-dihydro-2-methylfuran (**10**). Thus, it appears that the additional methyl substituent decreases the reactivity of the endocyclic double bond of the dihydrofuran (±-**4**) in this cycloaddition reaction.

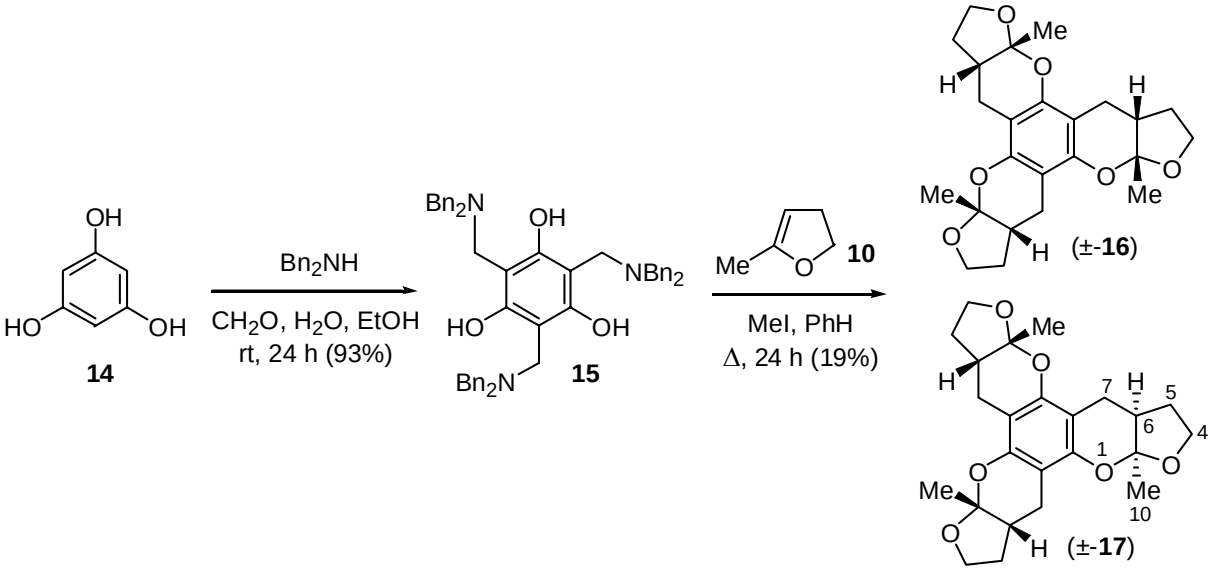


9 (±-**2**) (±-**13**)

Scheme 5. Synthesis of (±)-xyloketal D (±-**2**), diastereomer (±-5-*epi*-**2**), and (±)-spiroacetals (±-**13**).

The feasibility of using this cycloaddition strategy to prepare (-)-xyloketal A (**1**) was then demonstrated successfully in a model study (**Scheme 6**). The Mannich base (**15**) was prepared by adaptation of a

literature procedure from phloroglucinol (**14**), dibenzyl amine, and formaldehyde.[6a] A mixture of the Mannich base (**15**), 4,5-dihydro-2-methylfuran (**10**) (9 equivalents), and methyl iodide (3 equivalents) was heated at reflux to afford an inseparable mixture (1:4) of the desired symmetric xyloketal A analogue (±-**16**) and the diastereomer (±-**17**). This mixture of compounds was fully characterized by spectroscopic methods. Of note, the MS (CI) contained the parent molecular ion (M+H) as well as daughter ions that can be attributed to fragmentation by *retro* Diels-Alder reactions. In addition, a large signal for an ion that corresponded to the dihydrofuran (**10**) was observed. The ^{13}C NMR spectrum also clearly showed four signals that corresponded to the acetal carbons that would be expected for an inseparable mixture of compounds (±-**16**) and (±-**17**). The yield of this reaction (19%) is indeed respectable when one considers that this direct process involves nine individual reactions (three alkylation reactions, three elimination reactions, and three subsequent cycloaddition reactions).



Scheme 6. Synthesis of xyloketal A analogues (±-**16**) and (±-**17**).

We anticipate that the synthesis and use of the chiral, non-racemic (4*R*)-dihydrofuran (**4**) in this cycloaddition reaction will afford (-)-xyloketal A (**1**) in a diastereoselective manner. It is expected that this process will be controlled by the stereogenic centre of dihydrofuran (**4**). It remains to be determined if this process will be complicated by the formation of spiroacetal reaction byproducts. In view of this possibility, other synthetic routes to prepare this novel natural product are also being investigated.

EXPERIMENTAL

Mps were measured on a Gallenkamp capillary melting point apparatus and are uncorrected. IR spectra were recorded as evaporated films (EF) or as KBr discs (KBr) using a Perkin Elmer 599B IR spectrophotometer. NMR experiments were carried out on Bruker AMX 400 (400.1 MHz for ^1H and

100.6 MHz for ^{13}C), Varian AS500 (125.7 MHz for ^{13}C) and Bruker AMX 600 (600.1 MHz for ^{1}H) spectrometers. Chemical shifts (δ) are listed in parts per million downfield from tetramethylsilane using the NMR solvent peak as an internal reference. MS were recorded on a Hewlett Packard 5985 GC-mass spectrometer using chemical ionization (CI) with isobutene. Microanalyses (Anal.) were performed on a Carlo Erba Model 1106 CHN analyzer.

3-Morpholin-4-yl-methyl-2,4-dihydroxyacetophenone (**9**)

To a solution of 2,4-dihydroxyacetophenone (**8**) (504 mg, 3.31 mmol) in methanol (9 mL) at rt were added morpholine (315 μL, 3.61 mmol) and an aqueous formaldehyde solution (37% w/v, 290 μL, 3.58 mmol). The reaction mixture was heated at reflux for 3 h and then concentrated *in vacuo* to afford a cream colored solid. Purification by column chromatography (ether:hexanes, 1:1) afforded the title compound (**9**) as a white solid (687 mg, 83%). mp 100-102 °C (ether:hexanes). R_f=0.22 (ether:hexanes, 4:1). IR (EF) 3432, 2948, 2854, 1615, 1493, 1274, 1260, 1116, 1060, 817 cm^{-1}. MS (CI) 252 (M+H, 100%), 88 (24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.53 (3H, s, *Me*), 2.65 (4H, m, NCH_2), 3.78 (4H, m, OCH_2), 3.87 (2H, s, ArCH_2), 6.36 (1H, d, *J*=8.9 Hz, *H*-5), 7.57 (1H, d, *J*=8.9 Hz, *H*-6), 8.64 (1H, br s, 4-O*H*), 13.15 (1H, s, 2-O*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.14, 52.98, 53.93, 66.76, 106.85, 108.54, 112.81, 131.89, 162.70, 165.98, 202.67. Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.84; H, 6.95; N, 5.25.

(±)-11-Norxyloketal D (±-**11**)

To a solution of the Mannich base (**9**) (199 mg, 0.792 mmol) in benzene (8 mL) at rt were added 4,5-dihydro-2-methylfuran (**10**) (220 μL, 2.41 mmol) and methyl iodide (52 μL, 0.84 mmol). The resultant solution was heated at reflux until TLC analysis indicated that the Mannich base had completely reacted (5 d). The reaction mixture was then cooled to rt, filtered, and concentrated *in vacuo*. Purification by column chromatography (hexanes:ether, 16:1) afforded the title compound (±-**11**) as a white solid (86 mg, 43%). mp 104-105 °C (hexanes:ether). R_f=0.25 (hexanes:ether, 4:1). IR (EF) 3487, 2973, 2938, 2904, 1621, 1491, 1421, 1370, 1330, 1271, 1177, 1107, 1086, 1004, 852 cm^{-1}. MS (CI) 249 (M+H, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.54 (3H, s, *Me*-10), 1.74 (1H, m, *H*-5), 2.08 (1H, m, *H*-5′), 2.47 (1H, m, *H*-6), 2.54 (3H, s, *Me*-16), 2.75 (1H, dd, *J*=17.9, 6.4 Hz, *H*-7$_\beta$), 3.02 (1H, dd, *J*=17.9, 1.1 Hz, *H*-7$_\alpha$), 3.98 (1H, apparent q, *J*=8.6 Hz, *H*-4), 4.06 (1H, apparent dt, *J*=9.5, 2.9 Hz, *H*-4′), 6.37 (1H, d, *J*=8.8 Hz, *H*-15), 7.52 (1H, d, *J*=8.8 Hz, *H*-14), 13.09 (1H, s, O*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.55, 22.39, 22.25, 28.62, 39.73, 67.09, 106.23, 107.51, 108.85, 113.30, 130.18, 159.73, 163.11, 202.82. Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.85; H, 6.61.

(±)-4,5-Dihydro-2,4-dimethylfuran (±-**4**)[7]

The alcohol (±-**12**) (3.95 g, 40.3 mmol) and sodium amide (150 mg, 3.84 mmol) were heated at reflux for 2 h. Direct distillation of the reaction mixture afforded the exocyclic double bond isomer of the title compound as a colorless liquid (2.60 g, 66%). A sample of this material (1.20 g, 12.2 mmol) was heated at reflux for 16 h and then distilled to afford the title compound (±-**4**) as a colorless liquid (1.04 g, 87%). bp ~100 ºC. IR (EF) 2961, 2875, 1674, 1453, 1383, 1243, 1043, 1008, 886 cm^{-1}. MS (CI) 99 (M+H, 100%). ^{1}H NMR (400 MHz, C_6D_6) δ: 0.84 (3H, d, *J*=6.6 Hz, *Me*-4), 1.68 (3H, apparent t, *J*=1.5 Hz, *Me*-2), 2.76 (1H, m, *H*-4), 3.71 (1H, dd, *J*=8.7, 6.5 Hz, *H*-5), 4.21 (1H, dd, *J*=9.5, 8.6 Hz, *H*-5′), 4.43 (1H, m, *H*-3). ^{13}C NMR (100 MHz, C_6D_6) δ: 13.59, 20.88, 37.88, 77.19, 101.39, 154.99.

(±)-Xyloketal D (±-**2**)**, (±)-5-*epi*-xyloketal D** (±-5-*epi*-**2**) **and (±)-spiroacetals** (±-**13**)

To a solution of the Mannich base (**9**) (177 mg, 0.704 mmol) in benzene (7 mL) at rt were added the dihydrofuran (±-**4**) (207 mg, 2.11 mmol) and methyl iodide (46 μL, 0.74 mmol). The resultant solution was heated at reflux until TLC analysis indicated that the Mannich base had completely reacted (5 d). The reaction mixture was then cooled to rt, filtered, and concentrated *in vacuo*. Purification by column chromatography (dichloromethane:ether, 40:1) afforded a mixture (11:1:3:3) of (±)-xyloketal D (±-**2**), (±)-5-*epi*-xyloketal D (±-5-*epi*-**2**), and (±)-spiroacetals (±-**13**) as a yellow oil (99 mg, 54%). Further column chromatography (hexanes:ether, 4:1 on TLC grade silica gel) afforded an inseparable mixture (11:1) of (±)-xyloketal D (±-**2**) and (±)-5-*epi*-xyloketal D (±-5-*epi*-**2**) as a pale cream solid and an inseparable mixture (1:1) of the two (±)-spiroacetals (±-**13**) as a pale cream solid. (±)-Xyloketal D (±-**2**) and (±)-5-*epi*-xyloketal D (±-5-*epi*-**2**): mp 66-67 °C (hexanes:ether). R_f=0.24 (hexanes:ether, 4:1). IR (EF) 3399, 2968, 2898, 1621, 1491, 1421, 1382, 1370, 1332, 1272, 1117, 1070, 1006 cm^{-1}. MS (CI) 263 (M+H, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) for (±)-xyloketal D (±-**2**) δ: 1.08 (3H, d, *J*=6.5 Hz, *Me*-11), 1.52 (3H, s, *Me*-10), 1.98 (1H, ddd, *J*=11.3, 6.3, 1.2 Hz, *H*-6), 2.06 (1H, m, *H*-5), 2.53 (3H, s, *Me*-17), 2.71 (1H, dd, *J*=17.9, 6.2 Hz, *H*-7), 2.96 (1H, d, *J*=18.0, *H*-7′), 3.56 (1H, apparent t, *J*=8.4 Hz, *H*-4), 4.20 (1H, apparent t, *J*=8.3 Hz, *H*-4′), 6.36 (1H, d, *J*=8.9 Hz, *H*-15), 7.52 (1H, d, *J*=8.9 Hz, *H*-14), 13.10 (1H, s, O*H*). ^{13}C NMR (100 MHz, $CDCl_3$) for (±)-xyloketal D (±-**2**) δ: 15.76, 17.98, 22.68, 26.09, 35.10, 46.96, 74.28, 106.11, 108.25, 108.77, 113.12, 130.00, 159.49, 162.90, 202.65. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.88; H, 6.85. (±)-Spiroacetals (±-**13**): mp 57-59 °C (hexanes:ether). R_f=0.32 (hexanes:ether, 4:1). IR (EF) 3464, 2958, 2863, 1625, 1491, 1421, 1370, 1332, 1270, 1246, 1136, 1060, 1017, 853 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.10 (3H, d, *J*=6.6 Hz, *Me*-11), 1.18 (3H, d, *J*=6.6 Hz, *Me*-11), 1.55 (2H, dd, *J*=12.8, 9.5 Hz, 2 × *H*-6), 2.00 (5H, m, 3 × *H*-7, 2 × *H*-5), 2.28 (1H, dd, *J*=13.4, 9.5 Hz, *H*-6), 2.36 (1H, dd, *J*=12.9, 7.3 Hz, *H*-6), 2.46 (1H, m, *H*-7), 2.54

(3H, s, *Me*-17), 2.55 (3H, s, *Me*-17), 2.78 (4H, m, 4 × *H*-8), 3.54 (1H, t, *J*=7.7 Hz, *H*-4), 3.64 (1H, t, *J*=8.4 Hz, *H*-4), 4.09 (1H, t, *J*=7.9 Hz, *H*-4), 4.21 (1H, t, *J*=7.9 Hz, *H*-4), 6.34 (1H, d, *J*=8.9 Hz, *H*-15), 6.37 (1H, d, *J*=9.0 Hz, *H*-15), 7.50 (1H, d, *J*=8.9 Hz, *H*-14), 7.51 (1H, d, *J*=8.9 Hz, *H*-14), 13.01 (1H, s, O*H*), 13.02 (1H, s, O*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.29, 16.54, 17.67, 18.04, 26.13, 29.37, 29.65, 31.93, 33.04, 45.17, 45.34, 75.01, 75.36, 108.12, 108.86, 108.95, 109.98, 110.17, 113.18, 113.26, 129.56, 129.59, 159.60, 162.25, 202.70, 202.73. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.47; H, 7.16.

2,4,6-*Tris*[dibenzylaminomethyl]phloroglucinol (**15**)

To a solution of phloroglucinol (**14**) (3.00 g, 23.8 mmol) in ethanol (100 mL) at rt were added dibenzylamine (14.2 mL, 78.5 mmol) and an aqueous formaldehyde solution (37% w/v, 6.0 mL, 74 mmol). The reaction mixture was stirred overnight and the resultant precipitate was then collected by filtration, washed with ethanol (3 × 15 mL), and dried *in vacuo* to afford the title compound (**15**) as a white powder (16.68 g, 93%). mp 156-160 °C (ethanol). R_f=0.70 (hexanes:ether, 4:1) IR (KBr) 3454, 3093, 3067, 3031, 2897, 2830, 2794, 1743, 1630, 1491, 1450, 1383, 1352, 1254, 1115 cm^{-1}. MS (CI) 212 (96%), 198 (100%), 89 (18%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.60 (12H, s, 6 × PhCH_2), 3.78 (6H, s, 3 × ArCH_2), 7.22-7.33 (30H, m, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 49.24, 57.83, 99.50, 110.27, 127.39, 128.47, 129.57, 137.19, 155.90. Anal. Calcd for $C_{51}H_{51}N_3O_3$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.21; H, 7.04; N, 5.62.

(±)-11-Trinorxyloketal A (±-**16**) **and (±)-2,6-*epi* -11,11′,11″-trinorxyloketal A** (±-**17**)

To a solution of the Mannich base (**15**) (754 mg, 1.00 mmol) in benzene (10 mL) at rt were added 4,5-dihydro-2-methylfuran (**10**) (820 μL, 8.99 mmol) and methyl iodide (190 μL, 3.05 mmol). The resultant solution was heated at reflux until TLC analysis indicated that the Mannich base had completely reacted (24 h). The reaction mixture was then cooled to rt, filtered, and concentrated *in vacuo*. Purification by repetitive column chromatography (hexanes:ether, 1:1 then dichloromethane:ether, 18:1) afforded the title compounds (±-**16**) and (±-**17**) as a mixture of diastereomers (1:4) as a solid white foam (78 mg, 19%). mp 145-147 ºC [from petroleum ether (35-60 ºC)]. R_f=0.43 (ether:hexanes, 4:1), 0.27 (dichloromethane:ether, 9:1). IR (EF) 2983, 2933, 2894, 1617, 1460, 1380, 1106, 1004 cm^{-1}. MS (CI) 415 (M+H, 8%), 331 (9%), 253 (13%), 169 (28%), 85 (100%). ^{1}H NMR (600 MHz, C_6D_6) δ: 1.44, 1.45, 1.47 (3 × 3H of compound (±-**17**), s, *Me*-10, 10′, 10″), 1.48 (9H of compound (±-**16**), s, *Me*-10), 1.51 (6H, m, *H*-5), 1.65 (6H, m, *H*-5), 1.95 (6H, m, *H*-6), 2.73 (6H, m, *H*-7), 3.05 (6H, m, *H*-7), 3.62 (6H, m, *H*-4), 3.89 (6H, m, *H*-4). ^{13}C NMR (125 MHz, C_6D_6) δ: 20.81, 20.84, 20.88, 22.80, 22.93, 23.07, 23.22, 29.34, 29.36, 40.64, 40.66, 40.69, 66.56, 66.57, 66.59, 99.43, 99.57, 99.63, 99.65, 106.78, 106.91, 106.95,

107.12, 150.81, 150.88, 150.89, 151.07. Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.34; H, 7.30.

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This paper is dedicated to *Professor Leo A. Paquette* on the occasion of his 70th birthday.

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