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Synthesis of Xyloketal A, B, C, D, and G Analogues

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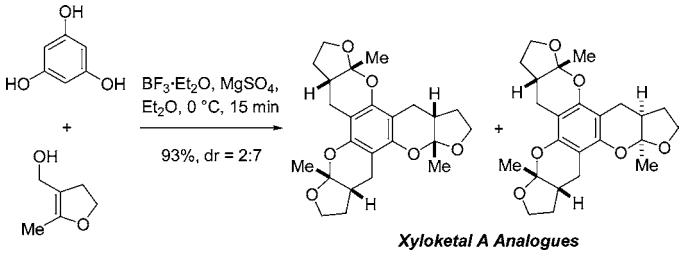

A series of demethyl analogues of the natural products xyloketal A, B, C, D, and G have been prepared in a notably direct manner from 3-hydroxymethyl-2-methyl-4,5-dihydrofuran and a series of corresponding phenols. These syntheses featured a boron trifluoride diethyl etherate-promoted electrophilic aromatic substitution reaction as a key step. In the case of the synthesis of analogues of xyloketal A, the process was found to be highly efficient (up to 93% yield). The optimized isolated yield of these reaction products is remarkable in view of the fact that this transformation involves, minimally, six individual reactions. Moreover, these synthetic studies provide significant insight into the possible biogenic origin of the xyloketal natural products.

Introduction

In 2001, Lin and co-workers reported the isolation and structural characterization of five related natural products, xyloketal A (**1**), B (**2**), C (**3**), D (**4**), and E (**5**), from a mangrove fungus of the *Xylaria* species (Figure 1).[1] More recently, Lin and co-workers have reported the isolation and structural characterization of two additional members of this family of natural products, xyloketal F (**6**) and G (**7**).[2,3] The molecular structures and relative stereochemistries of these natural products were determined by extensive spectroscopic studies and by X-ray crystallography.[1−3] The absolute stereochemistries of xyloketal A (**1**), D (**4**), F (**6**), and G (**7**) were determined by interpretation of their CD spectra. The absolute stereochemistries of the remaining members of this family of natural products were assigned by analogy. In addition, the semisynthesis of the C_2-symmetric natural product, xyloketal F (**6**), from xyloketal B (**2**), on condensation with formaldehyde under acidic reaction conditions, confirmed the common biogenic origin of all of these novel secondary metabolites.[2] The xyloketals incorporate identical 5,6-bicyclic acetal moieties that are fused to an aromatic core. In all cases, the hydrogen atoms of the cis-ring junctions of the bicyclic acetals are syn to the stereogenic methyl substituents at C5 of the five-membered rings.[4]

Xyloketal A (**1**) has a unique and remarkable C_3-symmetric molecular structure that incorporates three bicyclic acetal moieties. In the solid state, this molecule adopts a bowl-shaped conformation that is presumably enforced by anomeric effects.[1] Xyloketal B (**2**) and the minor C_2-symmetric component, xyloketal C (**3**) [that also readily rearranges to xyloketal B (**2**) in solution], incorporate two bicyclic acetal moieties.[5] Xyloketal D (**4**) and the corresponding regioisomer, xyloketal G (**7**), are the simplest members of this family of natural products in that they only contain one bicyclic acetal moiety. The isolation and structural characterization of xyloketal E (**5**), an additional derivative of xyloketal B (**2**) [cf. xyloketal F (**6**)], suggests that

(1) Lin, Y.; Wu, X.; Feng, S.; Jiang, G.; Luo, J.; Zhou, S.; Vrijmoed, L. L. P.; Jones, E. B. G.; Krohn, K.; Steingröver, K.; Zsila, F. *J. Org. Chem.* **2001**, *66*, 6252.

(2) Wu, X. Y.; Liu, X. H.; Lin, Y. C.; Luo, J. H.; She, Z. G.; Houjin, L.; Chan, W. L.; Antus, S.; Kurtan, T.; Elsässer, B.; Krohn, K. *Eur. J. Org. Chem.* **2005**, 4061.

(3) Wu, X.; Liu, X.; Jiang, G.; Lin, Y.; Chan, W.; Vrijmoed, L. L. P. *Chem. Nat. Compd.* **2005**, *41*, 27.

(4) Herein, the numbering scheme is based on that described by Lin and co-workers (see refs 1 and 3).

(5) Xyloketal B (**2**) is presumably more stable than the regioisomeric natural product, xyloketal C (**3**), because destabilizing dipole−dipole interactions are minimized. In addition, xyloketal B (**2**) in principle can also form a hydrogen bonded dimer in solution [cf. xyloketal F (**6**), see ref 2].

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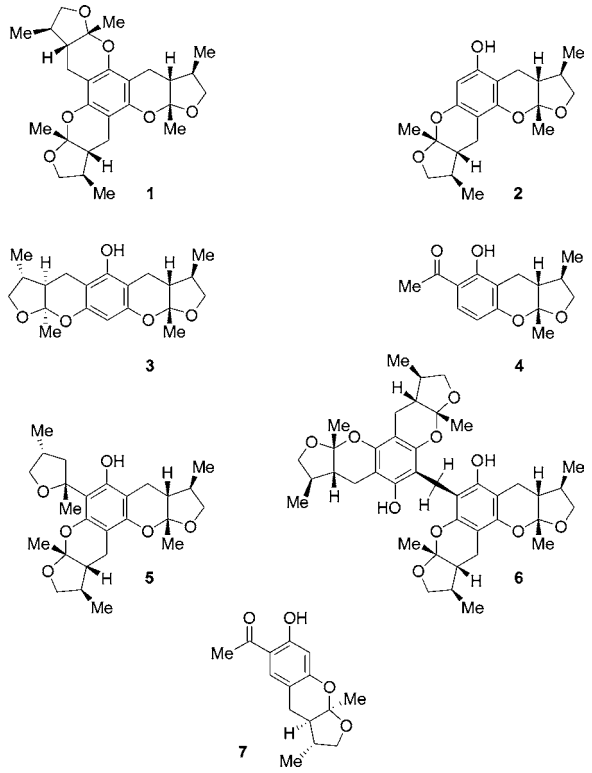


FIGURE 1. Molecular structures of xyloketal A (**1**), B (**2**), C (**3**), D (**4**), E (**5**), F (**6**), and G (**7**).

(4*R*)-4,5-dihydro-2,4-dimethylfuran (or the corresponding hydroxyketone) is the common biogenic precursor to all of these natural products. In the case of xyloketal E (**5**), it reasonable to conclude that this natural product is formed by a direct substitution reaction of the electron-rich aromatic ring of xyloketal B (**2**) on protonation of the aforementioned dihydrofuran precursor.[6] Xyloketal A (**1**) has also been shown to be a potent inhibitor of acetylcholine esterase and so it represents an important lead compound for the treatment of neurological diseases.[1,2] In addition, xyloketal A (**1**), B (**2**), and F (**6**) have been shown to have L-calcium channel blocking activity.[2] Thus, the total synthesis of these natural products and structural analogues is of notable significance.

We have previously reported the synthesis of (±)-11-norxyloketal D (**8**, R = H), the first total synthesis of (±)-xyloketal D (**4**, R = Me), and the synthesis of the two possible diastereoisomers of the tris-demethyl analogue of xyloketal A (**9** and **10**) (Figure 2).[7] These syntheses featured the cycloaddition reactions of appropriately functionalized *o*-quinone methides (generated by methylation of the readily available and corresponding Mannich bases **11** and **12**) and the dihydrofurans **13** and **14**. The Mannich base substrates **11** and **12** were prepared in one step from the corresponding commercially available aromatic phenols, 2,4-dihydroxyacetophenone and phloroglucinol (1,3,5-trihydroxybenzene), respectively.

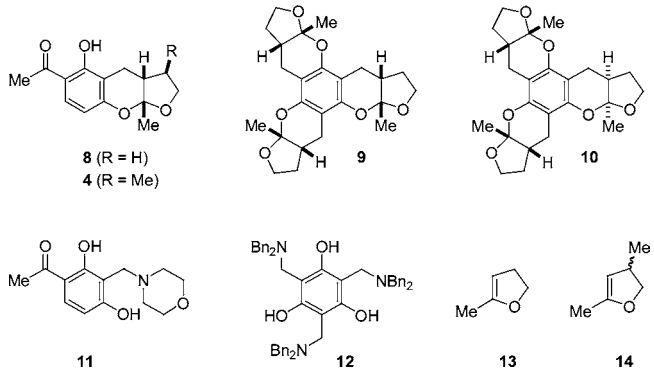


FIGURE 2. Synthesis of (±)-11-norxyloketal D (**8**, R = H), (±)-xyloketal D (**4**, R = Me), and the xyloketal A analogues **9** and **10**.[7]

Of note, the synthesis of (±)-xyloketal D (**4**, R = Me), although highly diastereoselective (11:1), was complicated by the formation of diastereoisomeric spiroacetals. These byproducts resulted from a nonstereoselective cycloaddition reaction (presumably following isomerization of the dihydrofuran **14** under the reaction conditions) of the corresponding exo-cyclic dihydrofuran. This complicating factor resulted in the formation of a highly complex mixture of reaction products on attempting the total synthesis of (±)-xyloketal A (**1**).[7]

We have subsequently reported the asymmetric syntheses of (−)-xyloketal D (**4**) and its enantiomer on preparing both enantiomers of 4,5-dihydro-2,4-dimethylfuran **14**.[8,9] These total syntheses confirmed the absolute stereochemistry of the natural product and thus the absolute stereochemistry of the xyloketals. Krohn and co-workers have also reported an asymmetric total synthesis of (−)-xyloketal D (**4**) from (3*R*)-3-methylbutyrolactone and 2,4-dihydroxyacetophenone.[10] This synthesis featured the conjugate addition reaction of the latter aromatic phenol to an α,*β*-unsaturated ketone [(4*R*)-5-hydroxy-4-methyl-3-methylenepentan-2-one], that was elaborated from the butyrolactone, on heating at reflux in toluene.[11,12] In addition, these researchers have also described the synthesis of demethyl analogues of xyloketal A (**1**) and B (**2**) (as well as a corresponding monoadduct) as mixtures of diastereoisomers from a model α,*β*-unsaturated ketone and phloroglucinol.[13] The ratio of these products was dependent on the ratio of the reactants employed and the reaction time.

(6) The stereochemistry of the quaternary benzylic center of xyloketal E (**5**), if this natural product is formed by an electrophilic aromatic substitution reaction of xyloketal B (**2**) and (4*R*)-4,5-dihydro-2,4-dimethylfuran, is opposite to what would be predicted on the basis of simple steric arguments. However, the level of diastereoselectivity of this proposed reaction is not predictable and it is possible that an epimer of xyloketal E (**5**) is also produced metabolically.

(7) Pettigrew, J. D.; Bexrud, J. A.; Freeman, R. P.; Wilson, P. D. *Heterocycles* **2004**, *62*, 445.

(8) Pettigrew, J. D.; Freeman, R. P.; Wilson, P. D. *Can. J. Chem.* **2004**, *82*, 1640.

(9) We have also outlined an alternative approach for the synthesis of the xyloketal natural products based on a novel phenylboronic acid-mediated condensation reaction of α,*β*-unsaturated aldehydes with aromatic phenols, see: Pettigrew, J. D.; Cadieux, J. A.; So, S. S. S.; Wilson, P. D. *Org. Lett.* **2005**, *7*, 467.

(10) (a) Krohn, K.; Riaz, M. *Tetrahedron Lett.* **2004**, *45*, 293. (b) Krohn, K.; Riaz, M.; Flörke, U. *Eur. J. Org. Chem.* **2004**, 1261.

(11) This alternative high-yielding synthesis was also diastereoselective (8.5:1.5). However, the reported racemic synthesis of xyloketal D (**4**) and its diastereoisomer (80% combined yield) was also complicated by the formation of a diastereomeric mixture of the regioisomeric bicylic acetals (9%, combined yield). One of these latter diastereoisomers corresponds to xyloketal G (**7**) (see refs 10b and 3).

(12) These researchers have also described the synthesis of demethyl analogues of xyloketal D (**4**) and G (**7**) from a model α,*β*-unsaturated ketone and 2,4-dihydroxyacetophenone (see ref 10b).

(13) Krohn and co-workers have also attempted the synthesis of xyloketal A (**1**) from racemic 5-hydroxy-4-methyl-3-methylenepentan-2-one and phloroglucinol. In this instance, the desired tris-adducts were isolated in 6% yield as a mixture of eight diastereoisomers (the corresponding mono- and bis-adducts were also isolated) (see ref 10b).

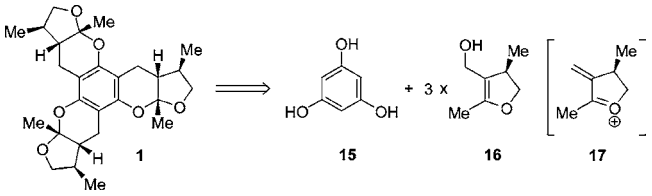


FIGURE 3. Retrosynthetic analysis of xyloketal A (**1**).

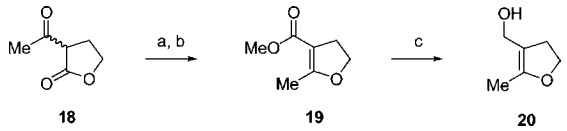
When we initiated our studies toward the total synthesis of the xyloketals, via *o*-quinone methide intermediates, we had also realized that xyloketal A (**1**) could in principle be prepared by a triple electrophilic aromatic substitution reaction of phloroglucinol **15** and the reactive intermediate **17** (Figure 3). The initial adducts of these substitution reactions would then be expected to rearrange, under the reaction conditions, to afford the thermodynamically stable cis-fused bicyclic acetal moieties of the natural product. The desired reactive intermediate **17** in this reaction could, in principle, be generated by ionization of the corresponding chiral nonracemic alcohol **16**. In a similar manner, xyloketal B (**2**) and C (**3**) could be prepared by executing selective double electrophilic aromatic substitution reactions of phloroglucinol **15** with the same reactive intermediate. In addition, xyloketal D (**4**) and the regioisomer, xyloketal G (**7**), could be prepared from the corresponding aromatic phenol, 2,4-dihydroxyacetophenone. In all of these reactions, it would be expected that the stereochemistry of the acetal formation reactions (that involve protonation of the dihydrofuran moieties) would be controlled, based on steric arguments, by the C4-methyl substituent of the parent alcohol **16**. Biogenically, the alcohol **16** could be derived from (4*R*)-4,5-dihydro-2,4-dimethylfuran **14** on reaction with a formaldehyde equivalent.[14]

In this paper, we describe the synthesis of analogues of xyloketal A (**1**), B (**2**), C (**3**), D (**4**), and G (**7**) from a model 3-(hydroxymethyl)dihydrofuran and a series of appropriate aromatic phenols. We believe that the exceedingly efficient and facile synthesis of these analogues, described herein, possibly reflects the biogenic origin of the xyloketal natural products.[15]

Results and Discussion

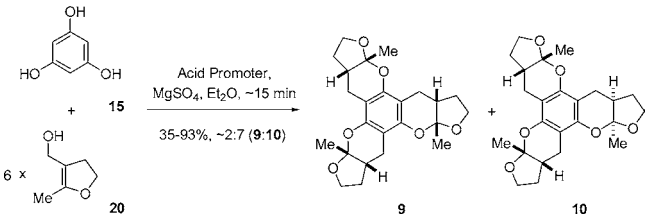
Synthesis of Xyloketal A Analogues. The required model 3-(hydroxymethyl)dihydrofuran, the alcohol **20**, was prepared by reduction of the known ester **19** with lithium aluminum hydride (Scheme 1).[16,17] Of note, the volatile alcohol **20** is a relatively unstable compound and so it was used immediately in subsequent experiments. The ester **19** was prepared from the commercially available lactone **18** on heating in methanol in the presence of hydrogen chloride (which was bubbled into the reaction mixture) and following redistillation of the resultant product from a catalytic amount of concentrated sulfuric acid.[16]

SCHEME 1. Synthesis of 3-Hydroxymethyl-2-methyl-4,5-dihydrofuran 20[a]



[a] Reagents and conditions: (a) HCl (g), methanol, reflux, 4 days then distill; (b) H_2SO_4 (cat.), distill, 19% (over two steps); (c) $LiAlH_4$, ether, 0 °C to room temperature, 20 min, 96%.

TABLE 1. Synthesis of Xyloketal A Analogues 9 and 10



entry	acid promoter (equiv)	temp (°C)	yield[a] of **9** and **10** (%)
1	$BF_3{\cdot}Et_2O$ (2.7)	0	36
2	$BF_3{\cdot}Et_2O$ (2.7)	−78	35
3	$BF_3{\cdot}Et_2O$ (1.3)	0	69
4	**$BF_3{\cdot}Et_2O$ (1.0)**	**0**	**93**
5	$BF_3{\cdot}Et_2O$ (0.5)	0	77
6	$BF_3{\cdot}Et_2O$ (0.25)	0	77
7	HF (cat.)	0	77
8	p-TsOH (1.0)	0	71

[a] Combined isolated yield of xyloketal A analogues **9** and **10** after purification by flash chromatography.

The initial reaction conditions selected for the triple electrophilic aromatic substitution reaction of phloroglucinol **15** with the alcohol **20** were based on a report by Razdan and co-workers on the synthesis of Δ^1-tetrahydrocannabinol (THC) from *p*-mentha-2,8-dienol and olivetol.[18] A two-fold excess of the unstable alcohol **20** was employed per phenolic reaction site and the initial reaction involved stirring a mixture of the phloroglucinol **15** (1 equiv) and the alcohol **20** (6 equiv), in ether at 0 °C, in the presence of anhydrous magnesium sulfate and boron trifluoride diethyl etherate (2.7 equiv) (Table 1, entry 1).[18,19] The known xyloketal A analogues **9** and **10** were formed rapidly

(14) The isolation of xyloketal F (**6**) suggests, as commented on by Lin and co-workers (and demonstrated by semisynthesis), that a formaldehyde equivalent is involved in the biosynthesis of this particular natural product (see ref 2). It can also be inferred that a formaldehyde equivalent could also be involved in additional steps in the biosynthesis of the xyloketals in view of this new synthetic proposal.

(15) After the reports of our original syntheses of xyloketal D (**4**) (see: ref 7 and 8), Lin and co-workers have also commented that the biosynthesis of the xyloketals involves *o*-quinone methide intermediates (see ref 3). In view of the findings reported in this paper, in addition to our earlier observations, we believe that this conclusion is incorrect. Of note, the α,β-unsaturated ketone reported by Krohn and co-workers is a synthetic equivalent of the alcohol **16** (see ref 10). We believe that the former compound is not directly involved in the biosynthesis of the xyloketal natural products because relatively forcing conditions are required for this compound to react (nor was the reactivity of this compound influenced by the addition of acids, vide infra) and in view of the isolation of xyloketal E (**5**). However, the potentially biogenic route described by Krohn and co-workers cannot be discounted at this time.

(16) (a) Korte, F.; Machleidt, H. *Chem. Ber.* **1957**, *90*, 2137. (b) Gollnick, K.; Knutzen-Mies, K. *J. Org. Chem.* **1991**, *56*, 4017.

(17) The preparation of the alcohol **20** by direct reaction of commercially available 2-methyl-4,5-dihydrofuran **13** with formaldehyde or related synthetic equivalents, under various reaction conditions, was unsuccessful.

(18) Razdan, R. K.; Dalzell, H. C.; Handrick, G. R. *J. Am. Chem. Soc.* **1974**, *96*, 5860. Of note, the cosolvent, dichloromethane, was not used in these studies because of the poor solubility of phloroglucinol **15** in chlorinated solvents.

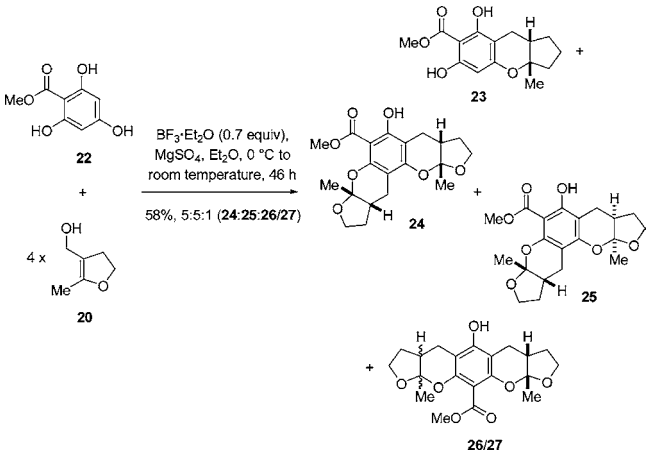
(19) Boron trifluoride diethyl etherate has also been employed as a Lewis acid in the electrophilic aromatic substitution reaction of phloroglucinol **15** and 2-methylbut-3-en-2-ol, see: (a) Collins, E.; John, G. D.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 96. In addition, a key step in a total synthesis of the natural product, alboatrin, has involved a boron trifluoride diethyl etherate-promoted electrophilic aromatic substitution reaction of orcinol with 2,4-dimethyl-3-hydroxymethylfuran, see: (b) Ichiara, A.; Nonaka, M.; Sakamura, S.; Sato, R.; Tajimi, A. *Chem. Lett.* **1988**, 27.

and the limiting starting material, phloroglucinol **15**, was consumed in less than 15 min.[7,10b] These compounds were isolated, in pure form and in reasonable yield (36%), as an inseparable mixture of two diastereoisomers (2:7, respectively). The corresponding mono- and bis-adducts were not isolated from this reaction. In addition, no evidence for the formation of these intermediates (by thin-layer chromatography) was observed during the course of the reaction. It would be expected that these more substituted and electron-rich intermediates would react at a faster rate than the limiting starting material, phloroglucinol **15**.

To improve the efficiency of this new reaction, it was repeated at a lower temperature (−78 °C) (Table 1, entry 2). However, the desired products were isolated in essentially the same yield and diastereoselectivity after 15 min. In this instance, as in the initial experiment, phloroglucinol **15** was completely consumed and highly polar or polymeric reaction byproducts were also formed. Thus, it was decided to systematically decrease the number of equivalents of boron trifluoride diethyl etherate and explore the use of different acid promoters. On employing boron trifluoride diethyl etherate (1.3 equiv), at 0 °C, a dramatic improvement in the isolated yield of the xyloketal A analogues **9** and **10** (69%) was recorded (Table 1, entry 3). Moreover, the use of boron trifluoride diethyl etherate (1.0 equiv, ∼0.3 equiv per phenolic reaction site) led to an exceptionally clean synthetic transformation and the isolation of the xyloketal A analogues **9** and **10** in excellent yield (93%) (Table 1, entry 4). The isolated yield of these reaction products is truly remarkable in view of the fact that this transformation involves, minimally, six individual reactions. Decreasing the number of equivalents of boron trifluoride diethyl etherate further resulted in the isolation of the desired reaction products in lower yield (Table 1, entries 5 and 6). However, it was found that concentrated hydrofluoric acid (which could have been involved in the reactions described above) and *p*-toluenesulfonic acid also promoted this reaction in good yield (Table 1, entries 7 and 8).[20] Of note, the desired C_3-symmetric diastereoisomer [that has the same relative stereochemistry as xyloketal A (**1**)] was the minor component in all of these reactions. However, we anticipate that the stereochemistry of the C4-methyl substituent of the chiral nonracemic alcohol **16** will correctly direct the diastereoselectivity of the triple condensation reactions (in an absolute sense) on attempting the total synthesis of xyloketal A (**1**).

Synthesis of Xyloketal B and C Analogues. It was considered that analogues of xyloketal B and C could be prepared by decreasing the number of equivalents of the alcohol **20** employed in the above optimized reaction with phloroglucinol **15**. However, given the relative instability of this alcohol and the observed propensity for the preferential formation of the tris-adducts **9** and **10** (as well as to prepare the xyloketal B and C analogues in acceptable yield), it was decided to temporarily block one of the reaction sites of phloroglucinol **15**. For this purpose, a methyl ester blocking group was selected because it was expected that this substituent could be removed by a decarboxylative saponification reaction.[21] Thus, methyl 2,4,6-trihydroxybenzoate **22** was prepared from the corresponding commercially available carboxylic acid, 2,4,6-trihydroxybenzoic acid **21**.[22] In the first instance, the methyl ester **22** (1 equiv) was reacted with the alcohol **20** (4 equiv), boron trifluoride diethyl etherate (1 equiv), and magnesium sulfate in ether and the resultant mixture was allowed to warm from 0 °C to room temperature over 4 h (Scheme 2). On subsequent purification of the crude reaction mixture by flash chromatography, the mono-adduct **23** (6%) and a mixture (3:3:1) of the substituted xyloketal B analogues **24** and **25** as well as the substituted xyloketal C analogues **26** and **27** (50%, combined yield) were isolated. The latter *minor* components were formed as a mixture of diastereoisomers (∼1:1).[5]

SCHEME 2. Synthesis of Substituted Analogues of Xyloketal B (24 and 25) and Xyloketal C (26 and 27)



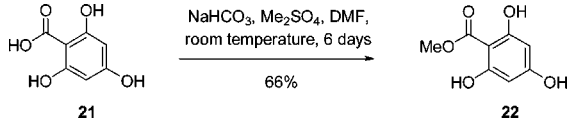
On performing the above reaction for an extended period of time (36 h), a mixture (5:5:1) of the substituted xyloketal B analogues **24** and **25** as well as the substituted xyloketal C analogues **26** and **27** was isolated (51%, combined yield). In this instance, none of the monoadduct **23** was present in the crude reaction mixture and less of the unstable xyloketal C analogues **26** and **27** were isolated as they were presumably converted to the substituted xyloketal B analogues **24** and **25** during the extended reaction time.[5] The substituted xyloketal B analogues **24** and **25** could also be separated from the substituted xyloketal C analogues **26**/**27**, in this instance, following further purification by flash chromatography. It was subsequently found that the above products could be prepared in improved yield (58%) on decreasing the amount of boron trifluoride diethyl etherate employed in the process (0.7 equiv, ∼0.3 equiv per phenolic reaction site) and on performing the reaction for 46 h. Of note, the slower rate and lower isolated yields of these latter reactions reflect the decreased reactivity of the less electron-rich phenol **22** (as compared to phloroglucinol **15**).

The synthesis of the known bis-demethyl analogues of xyloketal B (**28** and **29**) was subsequently accomplished on

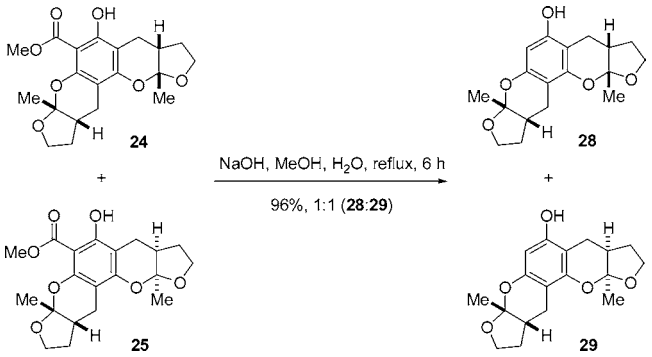
(20) None of the desired products were formed on performing the reactions at room temperature in the absence of an acid promoter or in the presence of acetic acid.

(21) For recent references regarding the facile decarboxylative saponification reactions of ortho-phenolic esters, see: (a) Hu, H.; Harrison, T. J.; Wilson, P. D. *J. Org. Chem.* **2004**, *69*, 3782. (b) Kang, Y.; Mei, Y.; Du, Y.; Jin, Z. *Org. Lett.* **2003**, *5*, 4481. (c) Kurdyumov, A. V.; Hsung, R. P.; Ihlen, K.; Wang, J. *Org. Lett.* **2003**, *5*, 3935.

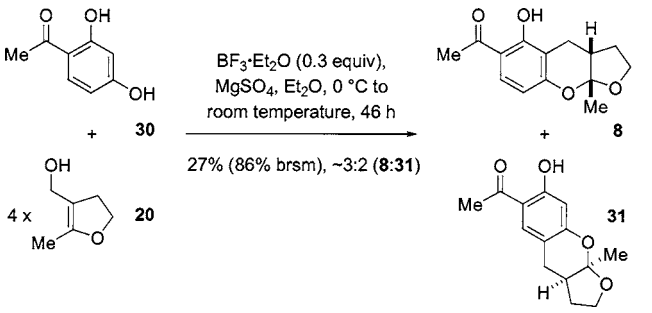
(22) Methyl 2,4,6-trihydroxybenzoate **22** was prepared from the carboxylic acid **21**, on reaction with dimethyl sulfate and sodium bicarbonate, according to a literature procedure, see: Carvalho, C. F.; Russo, A. V.; Sargent, M. V. *Aust. J. Chem.* **1985**, *38*, 777.



SCHEME 3. Synthesis of Analogues of Xyloketal B (28 and 29)



SCHEME 4. Synthesis of Analogues of Xyloketal D (8) and Xyloketal G (31)



executing a facile and high yielding decarboxylative saponification reaction (96%) of a mixture (1:1) of the substituted xyloketal B analogues **24** and **25** (Scheme 3).[10b,21]

Synthesis of Xyloketal D and G Analogues. In a similar way to that described above, the synthesis of the xyloketal D and G analogues **8** and **31** was undertaken from the corresponding commercially available phenol, 2,4-dihydroxyacetophenone **30** (Scheme 4). Accordingly, the acetophenone **30** (1 equiv) was reacted with the alcohol **20** (2 equiv), boron trifluoride diethyl etherate (0.3 equiv), and magnesium sulfate in ether. On allowing the reaction mixture to warm from 0 °C to room temperature over 46 h and following purification of the crude reaction mixture by flash chromatography, the known xyloketal D analogue **8** [13% (41% brsm)] and the xyloketal G analogue **31** [11% (34% brsm)] were isolated.[7,10b] A substantial quantity of the unreacted acetophenone **30** (62%) was also recovered.

In view of the relatively poor reactivity of this particularly less electron-rich phenol, the above reaction was repeated with an increased amount of alcohol **20** (4 equiv). In this instance, the xyloketal D analogue **8** [17% (54% brsm)] and the xyloketal G analogue **31** [10% (32% brsm)] were isolated in slightly improved combined yield. In addition, the unreacted acetophenone **30** (68%) was also recovered from the crude reaction mixture. No further attempts were made to improve the yield of this less facile and nonregioselective reaction in view of the fact that xyloketal D (**4**) and G (**7**) are minor metabolites and that no biological activity has been reported for these natural products.

Conclusions

A potentially biomimetic synthesis of analogues of the xyloketal natural products has been demonstrated. A series of demethyl analogues of xyloketal A, B, C, D, and G were prepared in a notably direct manner from 3-hydroxymethyl-2-methyl-4,5-dihydrofuran and a series of corresponding phenols via electrophilic aromatic substitution reactions that were promoted by boron trifluoride diethyl etherate. In the case of the synthesis of analogues of xyloketal A, the process was found to be highly efficient (up to 93% yield). This remarkable transformation involves six individual reactions (i.e., three electrophilic aromatic substitution reactions and three subsequent acetal formation reactions). Analogues of xyloketal B and C were prepared from methyl 2,4,6-trihydroxybenzoate and analogues of xyloketal D and G were also prepared from 2,4-dihydroxyacetophenone. The lower isolated yields of the desired analogues, in these instances, reflected the decreased reactivity of these phenolic substrates toward electrophilic aromatic substitution reactions. Although all of these syntheses were nondiastereoselective, it would be expected that the stereochemistry of the acetal formation reactions would be controlled by the C4-methyl substituent of the corresponding chiral nonracemic alcohol that is required for the total synthesis of the xyloketal natural products. The results of our studies toward this ultimate objective will be reported in due course.

Experimental Section

(±)-11-Trinorxyloketal A (9) and (±)-2,6-*epi*-11,11′,11″-Trinorxyloketal A (10).[7,10b] To a suspension of phloroglucinol **15** (38 mg, 0.30 mmol, 1 equiv), a solution of alcohol **20** in ether [(3.0 mL, 1.8 mmol, 6 equiv) prepared from the corresponding ester **19** (854 mg, 6.01 mmol) in ether (10 mL)], and anhydrous magnesium sulfate (0.25 g) in ether (2 mL) at 0 °C was added boron trifluoride diethyl etherate (38 μL, 0.30 mmol, 1 equiv). The resultant mixture was stirred at 0 °C for 15 min. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. Purification by flash chromatography with ether:hexanes (3:1) as the eluant afforded a mixture (2:7) of the title compounds **9** and **10** (115 mg, 93%) as a solid white foam. Recrystallization of the title compounds **9** and **10** from petroleum ether, on slow evaporation of the solvent afforded an analytically pure mixture (2:7) of the title compounds **9** and **10** as a white solid. R_f 0.32, ether:hexanes (3:1); mp 139−143 °C, petroleum ether [lit.[7] mp 144−145 °C, petroleum ether for a mixture (1:4) of the title compounds **9** and **10** and lit.[10b] mp 155−157 °C, for a mixture (1:4) of the title compounds **9** and **10**]; ^{1}H NMR (400 MHz, C_6D_6) δ 1.44 (s, 3H), 1.45 (s, 3H), 1.47 (s, 3H), 1.48 (s, 9H, corresponding to the symmetrical minor isomer **9**), 1.51 (m, 3H), 1.65 (m, 3H), 1.94 (m, 3H), 2.74 (m, 3H), 3.05 (m, 3H), 3.62 (m, 3H), 3.90 (m, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 20.8, 20.9, 22.9, 23.0, 23.2, 23.3, 29.4, 29.5, 66.57, 66.59, 99.7, 99.8, 106.9, 107.0, 107.1, 107.2, 150.86, 150.93, 151.0, 151.1; IR (ef) 2981, 2936, 2885, 2852, 1617, 1455, 1371, 1179, 1105, 1003 cm^{-1}; MS (CI) *m*/*z* (rel intensity) 415 (M + H, 31), 414 (M, 15), 373 (10), 331 (100), 97 (9), 43 (32). Anal. Calcd. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.34; H, 7.48.

(±)-11,11′-Dinorxyloketal B 13-Methylcarboxylate (24), (±)-2,6-*epi*-11,11′-Dinorxyloketal B 13-Methylcarboxylate (25), and the (±)-11,11′-Dinorxyloketal C 13-Methylcarboxylates (26/27). To a suspension of the methyl ester **22** (139 mg, 0.76 mmol, 1 equiv), a solution of alcohol **20** [(4 mL, 3.0 mmol, 4 equiv) prepared from the corresponding ester **19** (1.07 g, 7.5 mmol) in ether (10 mL)], and anhydrous magnesium sulfate (0.75 g) in ether (10 mL) at 0 °C was added boron trifluoride diethyl etherate (63 μL, 0.50 mmol, 0.7 equiv). The resultant mixture was allowed to warm to room temperature and was stirred for 46 h. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 15 mL). The combined filtrates were washed with water (3 × 20 mL), dried over anhydrous magnesium sulfate, and concentrated

in vacuo. Purification by flash chromatography with dichloromethane:ether (12:1) as the eluant afforded a mixture (5:5:1) of the title compounds **24**, **25**, and **26**/**27** (165 mg, 58%) as a solid white foam. Further purification by flash chromatography with dichloromethane:ether (19:1) as the eluant afforded a mixture (1:1) of the analytically pure title compounds **24** and **25** as a solid white foam. Title compounds **24** and **25** (1:1): R_f 0.21, dichloromethane:ether (19:1); mp 137−138 °C, dichloromethane:ether; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51 (s, 3H), 1.52 (s, 3H), 1.53 (s, 6H), 1.73 (m, 4H), 2.05 (m, 4H), 2.41 (m, 4H), 2.63 (apparent dt, J = 17.0, 7.0 Hz, 2H), 2.70 (apparent dt, J = 17.3, 7.0 Hz, 2H), 2.83 (apparent ddd, J = 17.0, 8.1, 2.2 Hz, 2H), 2.93 (apparent ddd, J = 17.3, 3.6, 1.5 Hz, 2H), 3.90 (s, 2 × 3H), 3.98 (m, 8H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.7, 19.8, 20.26, 20.30, 22.5, 22.6, 22.8, 22.9, 28.58, 28.62, 29.4, 29.5, 39.8, 40.07, 40.14, 52.1, 66.81, 66.84, 96.18, 96.22, 98.3, 98.4, 99.5, 107.5, 107.6, 107.76, 107.83, 153.7, 153.8, 156.3, 156.4, 160.79, 160.81, 172.1; IR (ef) 3425 (br), 2981, 2898, 2852, 1648, 1615, 1338, 1227, 1177, 1105, 1002 cm^{-1}; MS (CI) *m*/*z* (rel intensity) 377 (M + H, 8), 376 (M, 4), 345 (15), 293 (100), 85 (11), 43 (17). Anal. Calcd. for $C_{20}H_{24}O_7$: C, 63.82; H, 6.43. Found: C, 63.93; H, 6.54. Title compounds **24**, **25**, and **26**/**27** (5:5:1): mp 48−51 °C, dichloromethane:ether; ^{1}H NMR [500 MHz, $CDCl_3$ (additional signals observed for the title compounds **26**/**27**)] δ 1.20 (s, 3H), 1.22 (s, 3H), 1.59 (m), 1.87 (m), 3.56 (m). Anal. Calcd for $C_{20}H_{24}O_7$: C, 63.82; H, 6.43. Found: C, 63.58; H, 6.60.

(±)-11,11′-Dinorxyloketal B (28) and (±)-2,6-*epi*-11,11′-Dinorxyloketal B (29).[10b] To a suspension of the esters **24** and **25** (1:1, 57 mg, 0.15 mmol) in methanol (2 mL) and water (2 mL) was added an aqueous solution of sodium hydroxide (2 M, 0.75 mL). The resultant mixture was heated at reflux for 6 h and then allowed to cool to room temperature. The reaction mixture was then diluted with ethyl acetate (30 mL). The resultant solution was washed with a saturated aqueous solution of ammonium chloride (2 × 8 mL) and brine (8 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. Purification by flash chromatography with dichloromethane:ether (17:3) as the eluant afforded a mixture (1:1) of the title compounds **28** and **29** (46 mg, 96%) as a white solid. R_f 0.29, ether:hexanes (17:3); mp 236 °C dec, dichloromethane:ether [lit.[10b] mp 244−245 °C dec, for a mixture (1:1) of the title compounds **28** and **29**]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52 (s, 3H), 1.53 [2 × (s, 3H)], 1.54 (s, 3H), 1.79 (m, 4H), 2.04 (m, 4H), 2.42 (m, 4H), 2.64 (dd, J = 17.1, 6.3 Hz, 2H), 2.73 (m, 2H), 2.88 (m, 4H), 3.94 (m, 4H), 4.03 (m, 4H), 5.88 (s, 1H), 5.92 (s, 1H), 6.16 (s, 1H), 6.17 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.0, 20.08, 20.12, 22.5, 22.6, 22.8, 28.9, 29.00, 29.04, 40.0, 40.1, 40.3, 66.69, 66.71, 66.8, 95.91, 95.94, 98.5, 98.7, 99.4, 99.5, 106.67 106.72, 106.8, 106.9, 151.9, 152.13, 152.16, 152.2, 153.2, 153.3; IR (ef) 3364 (br), 2981, 2933, 2896, 2848, 1618, 1509, 1453, 1381, 1175, 1131, 1106, 1082, 1002 cm^{-1}; MS (CI) *m*/*z* (rel intensity) 319 (M + H, 15), 318 (M, 30), 277 (32), 235 (5), 180 (8), 85 (18), 43 (100). Anal. Calcd. for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.55; H, 7.09.

(±)-11-Norxyloketal D (8) and (±)-10-Norxyloketal G (31).[7,10] To a suspension of the 2,4-dihydroxyacetophenone **30** (230 mg, 1.51 mmol, 1 equiv), a solution of the alcohol **20** [(7.5 mL, 6.0 mmol, 4 equiv) prepared from the corresponding ester **19** (1.14 g, 8.03 mmol) in ether (10 mL)], and anhydrous magnesium sulfate (1.0 g) in ether (10 mL) at 0 °C was added boron trifluoride diethyl etherate (63 μL, 0.50 mmol, 0.3 equiv). The resultant mixture was allowed to warm to room temperature and was stirred for 46 h. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 15 mL). The combined filtrates were washed with water (3 × 20 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. Purification by flash chromatography with a gradient of dichloromethane:ether (99:1 to 98:2) as the eluant afforded the title compound **8** [63 mg, 17% (54% brsm)] as a white solid (on evaporation from petroleum ether), the title compound **31** [37 mg, 10% (32% brsm)] as a white solid (also on evaporation from petroleum ether), and the unreacted acetophenone **30** (158 mg, 68%). Title compound **8**: R_f 0.48, dichloromethane:ether (99:1); mp 103−105 °C, petroleum ether [lit.[7] mp 104−105 °C, hexanes:ether and lit.[10b] mp 114−116 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (s, 3H), 1.74 (m, 1H), 2.08 (m, 1H), 2.47 (m, 1H), 2.54 (s, 3H), 2.75 (dd, J = 17.9, 6.4 Hz, 1H), 3.02 (dd, J = 17.9, 1.1 Hz, 1H), 3.98 (apparent q, J = 8.5 Hz, 1H), 4.06 (apparent td, J = 9.5, 2.9 Hz, 1H), 6.37 (d, J = 8.9 Hz, 1H), 7.52 (d, J = 8.9 Hz, 1H), 13.10 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 19.4, 22.2, 26.1, 28.5, 39.6, 66.9, 106.1, 107.4, 108.7, 113.1, 130.0, 159.6, 162.9, 202.6; IR (ef) 3232 (br), 2987, 2930, 2897, 1622, 1491, 1420, 1370, 1330, 1271, 1177, 1107, 1085, 1004, 852 cm^{-1}; MS (CI) *m*/*z* (rel intensity) 249 (M + H, 100), 231 (30). Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.38; H, 6.81. Title compound **31**: R_f 0.35, dichloromethane:hexanes (99:1); mp 131−133 °C, petroleum ether [lit.[10b] mp 134−135 °C]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.58 (s, 3H), 1.73 (m, 1H), 2.05 (m, 1H), 2.48 (m, 1H), 2.54 (s, 3H), 2.77 (dd, J = 16.3, 1.2 Hz, 1H), 3.00 (dd, J = 16.3, 5.4 Hz, 1H), 3.97 (m, 2H), 6.36 (s, 1H), 7.44 (s, 1H), 12.37 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.0, 25.3, 26.2, 28.0, 40.7, 66.9, 104.5, 108.1, 110.4, 114.4, 132.2, 160.4, 163.3, 202.3; IR (ef) 3399 (br), 2988, 2927, 2899, 1650, 1615, 1494, 1390, 1364, 1284, 1160, 1099, 1074, 1000 cm^{-1}; MS (CI) *m*/*z* (rel intensity) 249 (M + H, 100), 248 (M, 26), 231 (30), 165 (7), 43 (59). Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.60; H, 6.65.

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Supporting Information Available: General experimental details, experimental procedures, and full product characterization data for all of the compounds synthesized, ^{1}H and ^{13}C NMR spectra for compounds **19**, **20**, **9**, **10**, **22**−**25**, **28**, **29**, **8**, and **31**, as well as selected COSY and HMQC spectra for compounds **24**, **25**, **28**, **29**, and **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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