Synthesis of Xyloketals, Natural Products from the Mangrove Fungus *Xylaria* sp

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The xyloketal family of compounds was synthesized by condensation of phloroglucinol (**7**) or 2,4-dihydroxyacetophenone (**15**) with the enone **8a** or **14** in multistep, one-pot, domino reactions, leading to the xyloketals and 5-demethylxyloketals, respectively. In the case of condensation with phloroglucinol (**7**), the mono-, bis, and tris adducts **6**/**18**, **2**/**19**, **1**/**20** are formed; their ratios depend on the ratio of stating materials and reaction time. The ring junction of the pyran and furan rings B and C (at C-2 and C-6) is always *cis*. The *cis* orientation of the methyl groups at C-2 and C-5 is also predominant (8.5:1.5), as found in the natural products. In the bis and tris adducts (**2**/**19**, **1**/**20**), the relative orientation of the rings B and C can be *syn* and *anti*, with the sterically less demanding *anti* orientation slightly favored statistically. Xyloketal D (**4a**) was obtained in the condensation of **15** with enantiomerically enriched enone **8a**, confirming the absolute configuration of the natural product.

Introduction

The xyloketal group of natural products was recently isolated from the mangrove fungus *Xylaria* sp., found on the South China Sea coast.[1] This group of related ketals (see Scheme 1) is structurally unique.[2] Xyloketal A (**1a**) has C_3 symmetry with a *cis*-junction between the tetrahydropyran and tetrahydrofuran rings, whereas the other members are missing axial symmetry. The methyl groups at C-5 of the C-rings are also oriented *syn* to the other methyl groups at C-2 placed between the oxygens of the spiroketal functions. The angular skeleton of xyloketal B (**2a**), evidently a bis adduct analogue of the tris adduct **1a**, is more stable than the linearly condensed xyloketal C (**3**), which spontaneously rearranges in solution to the more stable angular structure **2a**. Xyloketal D (**4a**) is an acetylated mono adduct structure, and xyloketal E (**5**) is a tetrahydrofuran-linked angular bis adduct related to **2a**. Their relative structures were secured by NMR spectroscopic data and, in part, X-ray structure analysis. The absolute configurations of xyloketals A (**1a**) and D (**4a**) were elucidated by quantum mechanical calculation of their CD spectra.[1]

Xyloketal A (**1a**), highlighted as a structurally remarkable C_3-symmetric natural product,[2] is a potent inhibitor of acetylcholine esterase with inhibition at 1.5×10^{-6} mol/L, which makes it an interesting lead compound in the treatment of Alzheimer's disease.[3]

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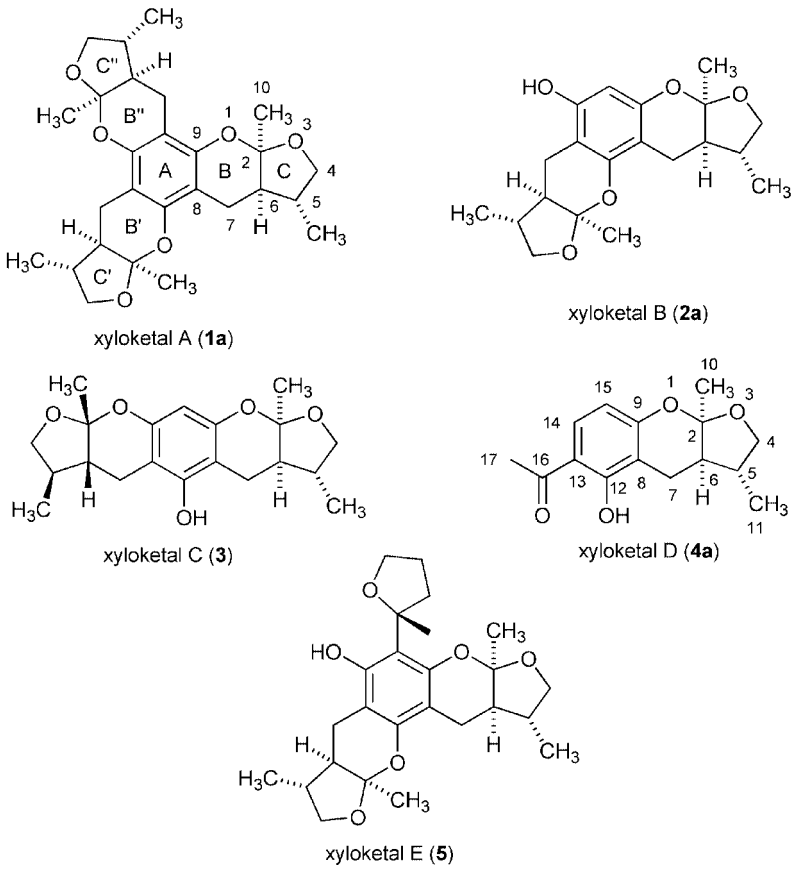
We now report a short and high yielding synthesis of the racemic xyloketals A (**1a**), B (**2a**), and D (**4a**) and the 5-demethyl analogues **16**−**20** and the enantioselective synthesis of xyloketal D (**4a**) in full detail.[3]

Results and Discussion

The retrosynthetic analysis, shown in Scheme 2, leads to only two fragments: phloroglucinol **7** and enone **8a**, available from the α-methylenebutyrolactone **9**. The monoadduct **6** can then be further condensed with **8a** to afford the bis adduct **2a** and, finally, the tris adduct **1a**.

Mechanistically, the two fragments **7** and **8a** may be combined in a Michael addition, followed by spontaneous intramolecular ketal formation via intermediates **A** and **B**, involving the phenolic and the primary aliphatic hydroxy groups and the keto function of the side chain in the ketal formation, as depicted in Scheme 3. The functionalized enone **8a**, which may be in equilibrium with the cyclic hemiacetal **8b**, can be derived from the α-methylenebutyrolactone **9** and further from the γ-lactone **10**. In these one pot, multistep, domino reactions, repetition of the first anellation steps would ultimately lead to the bis adducts **2a** and the tris adducts **1a** in a very short way.

However, two major questions arise from the retrosynthetic scheme. The first concerns the feasibility of the anticipated Michael addition. In principle, addition of the nucleophilic phenolic oxygen to the carbonyl group (1,2-addition) or to the activated double bond (1,4-addition) might also occur. We reasoned that these reactions should be reversible, ultimately leading to the formation of the thermodynamically more stable C−C bond formation shown in



Scheme 1. Structures of xyloketals A (**1a**), B (**2a**), and D (**4a**)[1]

intermediate **A**. This is supported by literature precedence in which α,β-unsaturated acids[4a] or ketones[4b] were successfully added to in a Michael-type reaction with phenols, leading to benzopyrans.

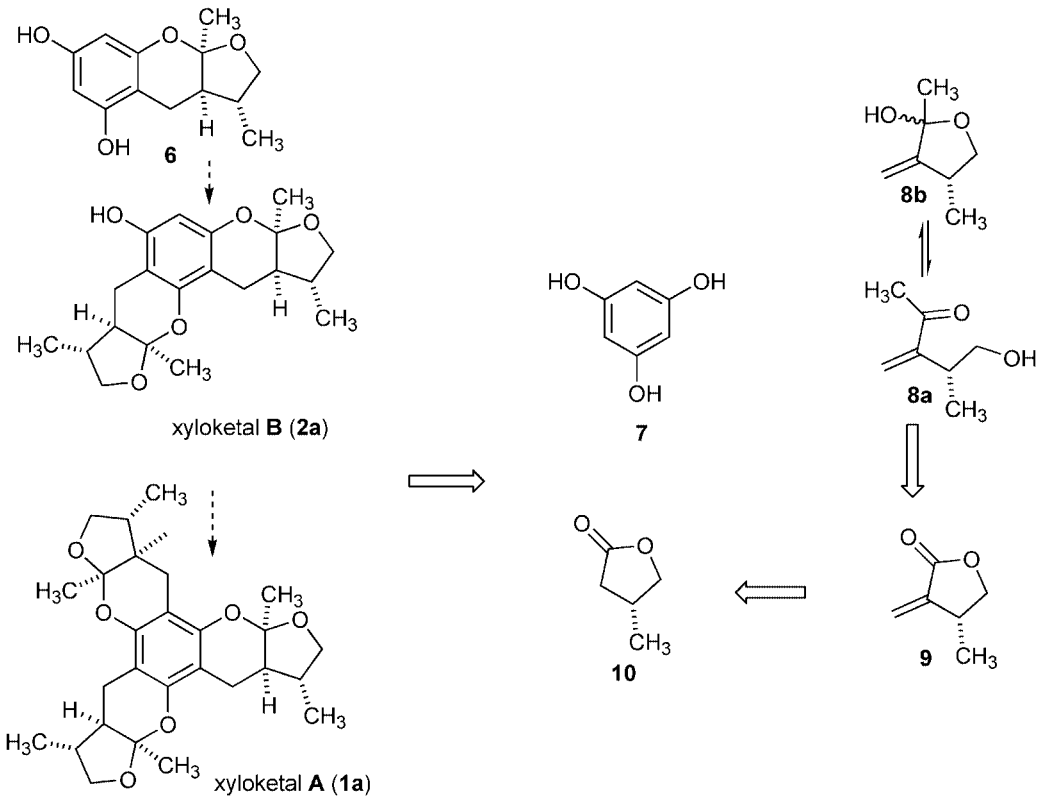
The second problem concerns the stereochemical outcome of the intramolecular ketal formation, which is difficult to predict. In principle, the two oxygen-containing pyran and furan rings B and C can be connected in a *cis* or *trans* fashion. Also, the orientation of these stereogenic centers at the ring-junction positions C-2 and C-6 with respect to the methyl group at C-5 is an open question. Another question concerns the relative orientation of the stereocenters of rings B and C with respect to the remote centers at rings B′,C′ and B′′,C′′ (see Scheme 1).

Thus, in order to better address the chemical and stereochemical questions, we decided to start our experiments with the synthesis of the simpler 5-demethylxyloketal D (**16**) with 2,4-dihydroxyacetophenone (**15**) as the nucleophilic reaction component and the enone **14** as the Michael acceptor.

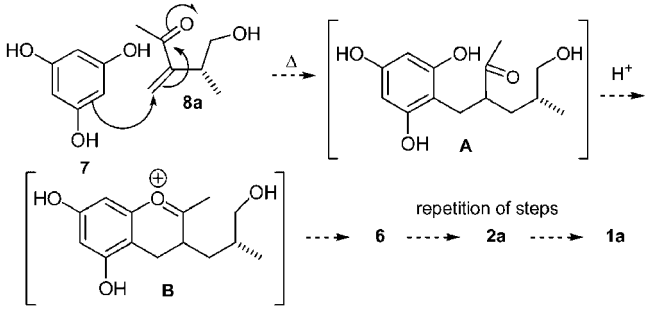
Model Studies on 5-Demethylxyloketals

The required, previously unknown, enone building block **14** was prepared by 1,2-addition of methyllithium to α-methylenebutyrolactone (**12**), easily available by sequential treatment of the γ-butyrolactone (**11**) sodium salt with formic ester and formaldehyde.[5] The addition of methyllithium to yield the tertiary alcohol **13** was largely suppressed at low temperatures (−30 °C) and the desired enone **14** was isolated in 55% yield (Scheme 4). Upon heating of the two components **14** and **15** (1:1) in toluene, a smooth conversion into two less polar compounds was observed. In a series of experiments it was found that the addition of acids was not required and the phenol was sufficiently acidic to promote the reaction autocatalytically. Separation of the two reaction products gave 83% of the less-polar major compound *rac*-5-demethylxyloketal D (**16**) (addition at C-3) and 8% of the polar regioisomer *rac*-5-demethylisoxyloketal D **17** (addition at C-5). Their respective gross structures were easily assigned by ^{1}H NMR spectroscopy, showing two doublets for **16** and two singlets for **17** in the aromatic area. A third possible regioisomer involving the chelated phenolic hydroxy group in its ketal form was not isolated, probably due to the diminished nucleophilicity of the chelated hydroxy group.

The remaining question concerned the stereochemistry of the ring B/C connections in **16** and **17**. The *cis*-arrangement of the pyran and furan rings B and C was secured by a strong nuclear Overhauser effect (66%, see **16** Scheme 4) of the *cis*-oriented proton H-6 with the protons of the methyl group at C-2. The major isomer **16** was thus identified as *rac*-2-demethyl-xyloketal D. *As a rule, in all subsequent condensations leading to xyloketal derivatives, rings B and C were always cis orientated*, as independently confirmed by



Scheme 2. Retrosynthetic analysis leading to the xyloketal family of fungal natural products

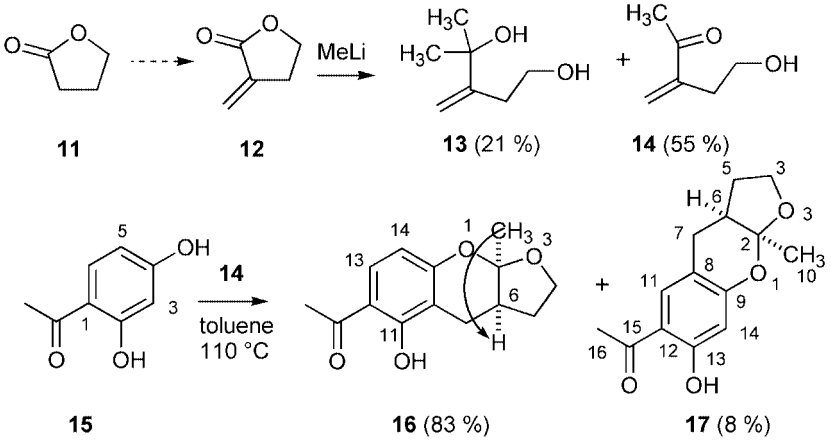


Scheme 3. Domino reactions leading to xyloketal mono, bis and tris adducts **6**, **2a**, and **1a** via intermediates **A** and **B**

X-ray structure analysis of a tris adduct **20b** (see below). All of the isolated naturally occurring xyloketals also show this kind of 2,6-*cis* stereochemistry (see Scheme 1).

The condensation of phloroglucinol (**7**) with the enone **14** was studied next. In this reaction, two points have to be noted. Firstly, in addition to mono adducts related to **16**, the bis and tris adducts can also be formed. As expected, the ratio of the mono, bis, and tris adducts (5-demethylxyloketals **18**, **19a**,**b**, and **20a**,**b**) depended on the ratio of the starting materials **7** and **14** and the reaction time, as shown in Table 1. Secondly, the respective orientation of the *cis*-fused heterocyclic rings B and C in the bis and tris adducts can be *syn* or *anti* with respect to the rings B′,C′ and B″,C″, as shown in structures **19a**,**b** and **20a**,**b** (Scheme 5). Only the more stable angularly fused isomers were isolated, in agreement with the fact that the linearly condensed xyloketal C (**3**) spontaneously rearranges to the angular structure **2a** in solution.[1] Statistically, a 1:1 ratio of **19a**/**19b** can be expected if the relatively remote stereogenic centers are generated independently during the thermodynamically controlled ketal formation. Assuming the same premises, the ratio of the tris adducts **20a**/**20b** must be 1:3 since there is a threefold probability of one ring system to be *anti* to the other two. In agreement with these assumptions, only one mono adduct **18** was isolated from the most polar fraction of three different reactions. The oily compound **18** is stable at −20 °C but slowly decomposes in solution. Interestingly, a mono adduct of phloroglucinol (**7**) was not isolated as a natural product, probably also due to similar instability as observed for the synthetic compound **18**.

The mixture of the bis adducts **19a** and **19b** was easily isolated by crystallization (diethyl ether) from the evaporated reaction mixture. It was not possible to separate the isomers **19a** and **19b** or their respective acetates **19c** and **19d** by chromatography or crystallization. The very close relationship of the isomers was also evident in both the ^{1}H and ^{13}C NMR spectra, with overlapping of nearly identical sets of signals. The ^{13}C NMR spectra were most instructive. Whereas the aromatic carbon atoms resonate as singlets, the methyl (C-10 and C-10′) or methylene groups (C-4,4′, C-7,7′) give rise to very closely resonating quadruplets, triplets or doublets. This is in agreement with expectation. None of



Scheme 4. Preparation of enone **14** and condensation with the acetophenone **15** to yield the 5-demethylxyloketal **16** and the regioisomer **17**

Table 1. Ratio of mono, bis, and tris adducts **18**, **19a**,**b** and **20a**,**b** depending on the ratio of the starting materials and reaction time

No.	Reactants		Products			Yield	Time
	Enone **14**	**7**	mono-**18**	bis-**19a**,**b**	tris-**20a**,**b**		
1	1 mmol	2 mmol	49.5%	27%	6%	82.5%	4 h
2	3 mmol	1 mmol	18.5%	63%	7.3%	88.8%	4 h
3	6 mmol	1 mmol	6.8%	22%	57.5%	86.3%	20 h

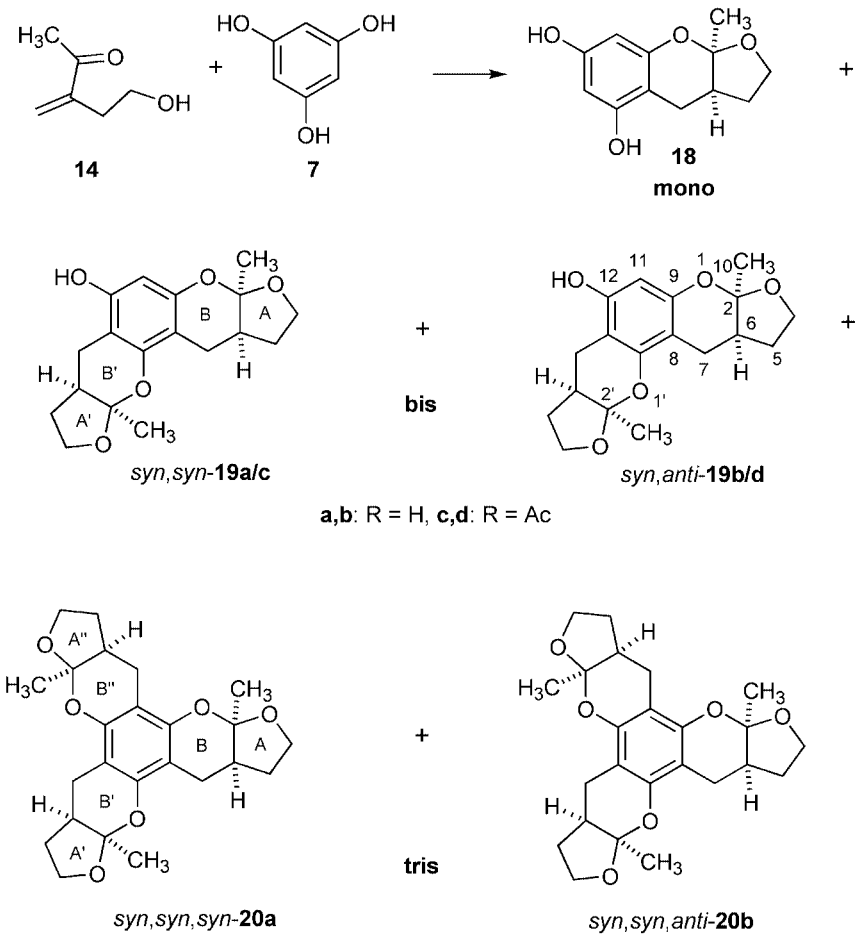
the isomers **19a** or **19b** has C_2 symmetry and all signals could, in principle, have different chemical shifts. This is most evident for the carbon atoms of the methyl groups at C-2 and C-2′. The four signals for C-10 and 10′, visible in both the mixture of the phenols **19a** and **19b** and the acetates **19c** and **19d**, show an approximate ratio of 1.5: 1 in favor of the *anti* isomers **19b** or **19d**, thus deviating from the statistically expected value of 1:1 (for copies of the extended spectra see supporting information, for Supporting Information see also the footnote on the first page of this article).

A slightly different picture was seen with the tris adducts **20a** and **20b**, isolated from the least-polar fraction of the condensation reaction. The all-*syn*-tris(ketal) **20a**, corresponding in stereochemistry to the natural xyloketal A (**1a**), has C_3 symmetry, and only one set of signals is to be expected. In contrast, symmetry is missing in the *syn*,*syn*,*anti* isomer **20b**, and three different sets of signals are possible. In fact, the benzylic carbon atoms C-7, C-7′ and C-7′′ (δ = 20.6 and 20.5) resonate as two very close signals, whereas the methyl groups at C-2, C-2′ and C-2′′ (δ = 107.0, 106.9, 106.8, and 106.7) are four well-separated singlets (one for **20a** and three for **20b**). From the integral of the methyl carbon atoms in **20a** and **20b**, a ratio of the isomers of approximately 1:4 can be deduced, again deviating slightly from the statistically expected 1:3 ratio. Again, the two isomers **20a** and **20b** are chromatographically homogeneous and could also not be separated by crystallization on a preparative scale. Fortunately, from the crystalline conglomerate, one single crystal was appropriate for X-ray crystal analysis. The structure is depicted in Figure 1, showing the major *syn*,*syn*,*anti* isomer **20b**.

Synthesis of the Racemic Xyloketals

Our investigation with the 5-demethyl compounds gave valuable insight into the stereochemical result of the ring B/C connection (e.g. rings B and C are always *cis*) and the possible ratio of the isomers. In the condensation reactions of **7** or **15** with the methylated enone **8a**, the formation of additional isomers is possible because the relative orientation of the new methyl group at C-5 can be *cis* or *trans* with respect to the stereogenic centers at the ring junction at C-2 and C-6. The requisite enone *rac*-**8a** was prepared from citraconic acid anhydride (**21**) by LAH reduction to the mixture of lactones **22** and **23** in a ca. 8.5:1.5 ratio, followed by hydrogenation to *rac*-**10** as described in the literature[6] (Scheme 6). In the subsequent methylenation,[5] only the saturated lactone derived from the regioisomer **23** can be converted into the α-methylenebutyrolactone *rac*-**9**. Gratifyingly, in the subsequent methylation step using MeLi, the yield of unsaturated ketone **8a** was even better (75%) than in the case of the demethyl α-methylenebutyrolactone **12**, probably due to the increased steric hindrance in the formation of the unwanted dimethylation of lactone *rac*-**9**.

The acetophenone **15** was first allowed to react with **8a** because only mono adducts can be formed, thus reducing the number of possible isomers. In agreement with expectation from the previous reaction with **15** (see, **16**/**17**), four compounds were isolated from this condensation. The mixture of stereoisomers *rac*-**4a** and *rac*-**4b** (ratio 8.5 to 1.5) and the mixture of their regioisomers *rac*-**24a**/*rac*-**24b** could be separated chromatographically, both as homogeneous fractions (Scheme 5). From the mixture of the major regioisomers *rac*-**4a** and *rac*-**4b**, the main product *rac*-**4a** could be crystallized as a pure stereoisomer in 64% overall yield. The stereochemistry was again verified by NOE experiments as shown by the arrows in structure **4a** (Scheme 5). The data of this synthetic product perfectly



Scheme 5. Construction of the 5-demethylxyloketals **19a**,**b** and **20a**,**b** by condensation of **7** and **14**.

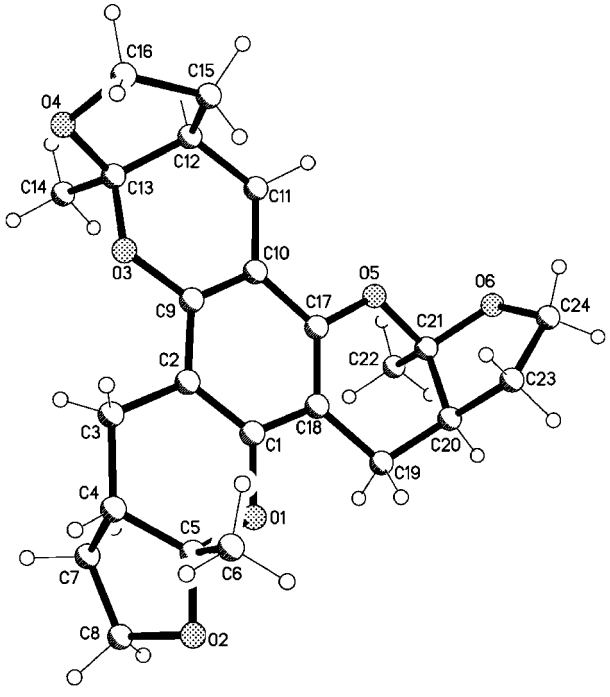
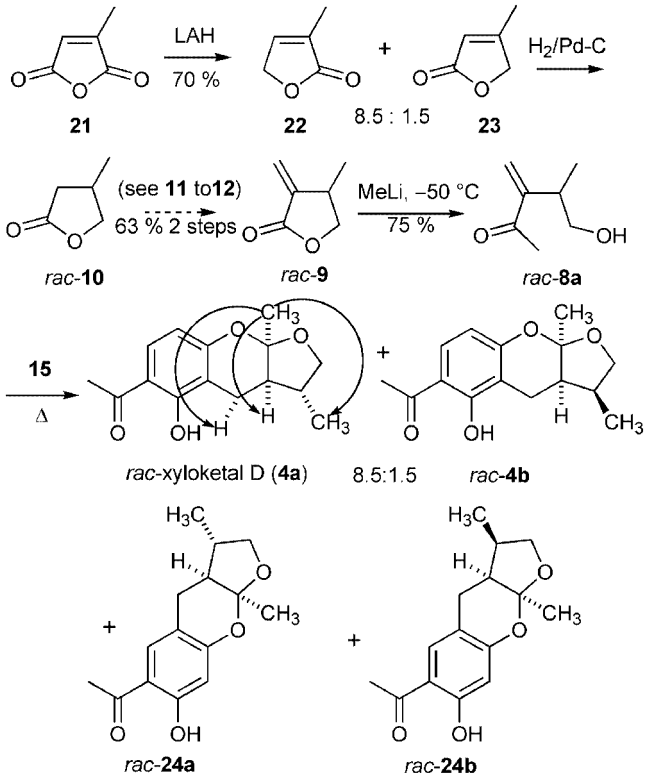


Figure 1. X-ray analysis of the *syn*,*syn*,*anti* isomer **20b**

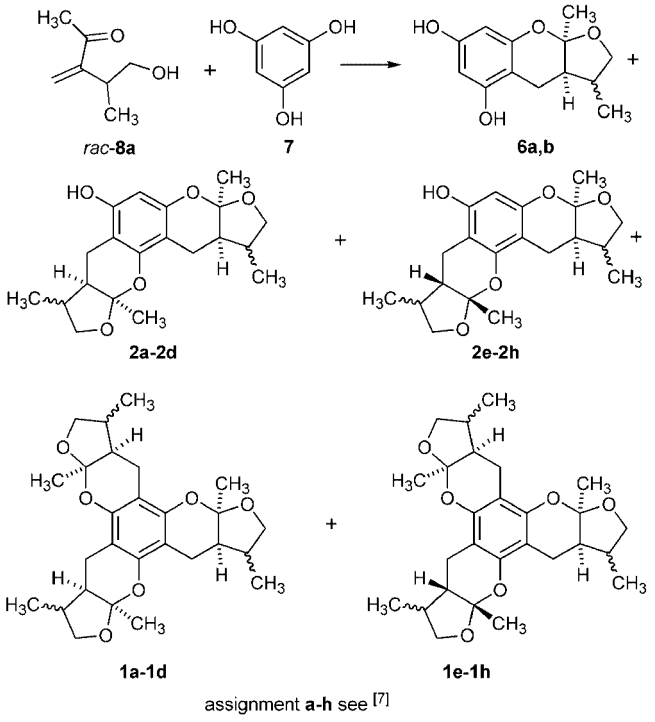
match those of the natural product and the structure can be assigned as *rac*-xyloketal D (**4a**). Interestingly, the natural xyloketals have an all-*cis* configuration at C-2, C-5, and C-6, similar to the major synthetic products resulting from the thermodynamically controlled ketal formation.

To complete the set of reactions, although mixtures of stereoisomers were to be expected, phloroglucinol (**7**) was next reacted with enone *rac*-**8a**. Again, three chromatographically different sets of compounds were formed, corresponding to the mono, bis and tris adducts **6**, **2**, and **1**, respectively. The chemical shifts in both the ^{1}H and the ^{13}C NMR spectra of the mixture of bis and tris adducts were all in close agreement with the respective data published for **1a** and **2a**,[1] although the signals were slightly broadened by overlapping.

The formation of only two stereoisomers is possible in the mono adducts **6**. In fact, the NMR spectra of the most polar fraction show only two sets of overlapping signals, indicating a ca. 8.5 to 1.5 ratio, similar to that found for **4a**,**b**. Two sets of stereoisomers can be formed for the bis adducts: *syn*,*syn* (**2a**−**2d**) or *syn*,*anti* (**2e**−**2h**; Scheme 7). One pure isomer, probably the major isomer **2e**, crystallized from the mixture. Two sets of stereoisomers are also to be expected for the tris adducts: *syn*,*syn*,*syn* (**1a**−**1d**) or



Scheme 6. Preparation of enone *rac*-**8a** from citraconic acid anhydride (**21**)[6] and condensation with **15** to yield *rac*-xyloketal D (**4a**); arrows show NOE correlations



Sdheme 7. Synthesis of xyloketal A and B stereoisomers by condensation of *rac*-**8a** and **7**

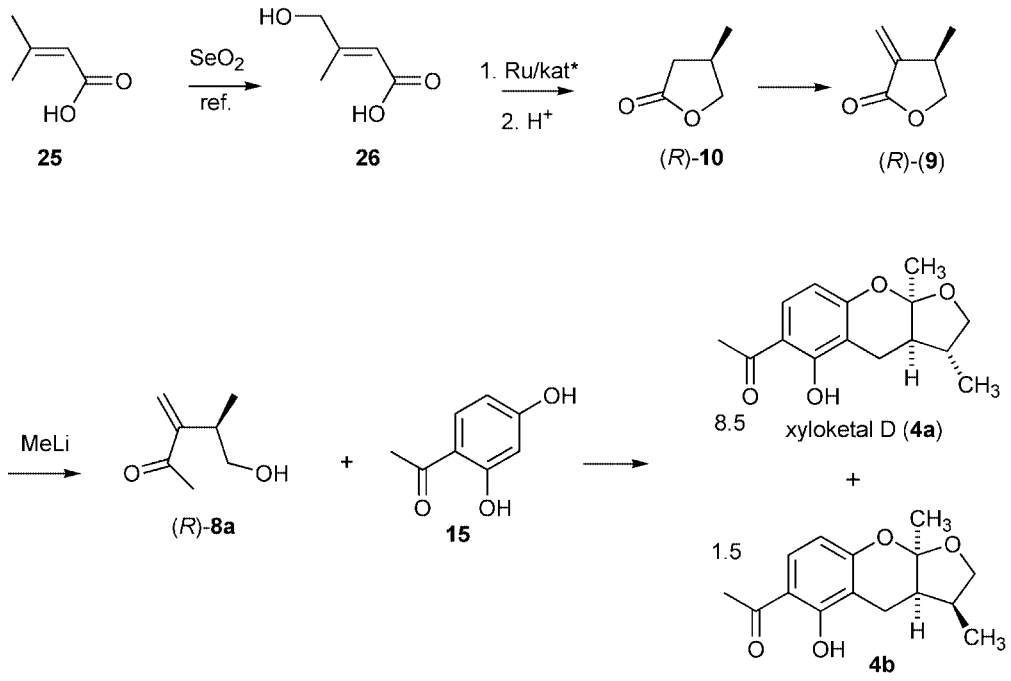
syn,*syn*,*anti*. (**1e**−**1d**). In each set, the C-5 methyl group can be oriented *cis* or *trans* to the respective methyl group at C-2. A calculation of the probable occurrence of the individual stereoisomers in the reaction mixtures, based on NMR spectroscopic data of related model compounds, see ref.[7] In spite of quite good stereochemical control (100% *cis* orientation of rings B,C; 8.5:1.5 ratio of C-2/C-5 methyl groups), the mixture contained only about 29% of the *syn*-*syn* isomer **2a** and 12% of the racemic C_3-symmetrical *syn*,*syn*,*syn* xyloketal (**1a**).[7] These results raise the intriguing question of stereochemical control in chemical ketal formation (missing at present) and possible enzymatic involvement during ketal formation in biosyntheses.

Synthesis of Enantiomerically Pure Xyloketal D (4a)

Our previous investigations showed that rather complex mixtures were to be expected with the bis or tris adducts obtainable from phloroglucinol (**7**). Thus, starting from acetophenone **15**, we wanted to prepare the enantiomerically pure xyloketal D (**4a**), to confirm our previous quantum-mechanical assignment of absolute configuration.[1] To be able to do this, the absolute configuration of the enantiomerically pure starting material had to be known for sure. It was prepared from hydroxy acid **26** (available by SeO_2 oxidation of **25**[8]) and enantioselective homogeneous catalytic Noyori hydrogenation using BINAP as the chiral ligand[9] (93% *ee* by optical rotation), followed by acid-catalyzed cyclization to the lactone (*R*)-**10** (Scheme 8). Methylenation to (*R*)-**9** and methylation to (*R*)-**8a** proceeded similarly as for the racemic models. Not unexpectedly, the usual condensation of (*R*)-**8a** with the acetophenone **15** gave a chromatographically homogeneous mixture of two stereoisomers **4a** and **4b** (as detected by NMR spectroscopy), again in an approximate 8.5 to 1.5 ratio. Fortunately, the major isomer crystallized from diethyl ether/pentane to afford the pure xyloketal D (**4a**). The spectroscopic data of the synthetic material are in perfect agreement with those of the natural product, and the optical purity could be upgraded to almost 100% by recrystallization, confirming the previously assigned absolute configuration.[1]

Conclusion

In conclusion, we have developed a one-pot, domino condensation procedure involving the phenols **7** and **15** and the enones **8a** and **14** to prepare the xyloketal family of natural products and their 5-demethyl analogues. The absolute configuration of xyloketals D (**4a**) was confirmed, starting from (*R*)-**10** of known absolute configuration. However, the occurrence of stereoisomers during the thermodynamically controlled ketal formation showed the need for methodology to control the stereochemistry of this process. Also, the question of involvement of enzymes in ketal formation is raised and how the stereochemistry is controlled.



Scheme 8. Enantioselective synthesis of xyloketal D (**4a**) by condensation of (*R*)-**8a** with the acetophenone **15**

Experimental Section

General Methods and Instrumentation: NMR spectra were recorded with a Bruker ARX 300 MHz spectrometer and the 2D HMQC spectra with a Bruker ARX 200 NMR spectrometer. Chemical shifts are referenced to internal TMS (δ = 0.00 ppm) and coupling constants *J* are reported in Hz; assignment is based on 2D spectra. Optical spectra were recorded with a Nicolet 510P FT-IR spectrophotometer, a UV-2101PC spectrophotometer, and a Perkin−Elmer 241 polarimeter.

3-(2-Hydroxyethyl)but-3-en-2-one (14): A solution of methyllithium (31 mL, 51 mmol) in Et_2O was added dropwise at −30 °C within 1 h to a stirred solution of α-methylene-γ-butyrolactone (**12**) in Et_2O (20 mL, 5.0 g, 51 mmol, prepared from γ-butyrolactone **11**[5]). The mixture was stirred for 30 min and then warmed slowly to 0 °C over 1 h. The reaction was quenched by addition of a saturated NH_4Cl solution (35 mL) and the mixture was extracted three times with Et_2O (each 20 mL). The combined organic phases were dried ($MgSO_4$), the solvent was removed under reduced pressure, and the pale-yellow, oily residue separated by column chromatography on silica gel (CH_2Cl_2/EtOAc, 96:4) to afford the unsaturated methyl ketone **14** (3.2 g, 55%) from the less-polar fraction and the tertiary alcohol **13** (1.4 g, 21%) from the polar fraction, in addition to small amounts of unchanged starting material **12**.

Data for 14: ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 6.19, 5.95 (each s and each 1 H, CH_2), 3.74 (t, *J* = 6.1 Hz, 2 H, H-4), 2.39 (t, *J* = 7.04 Hz, 2 H, H-3), 2.42 (s, 3 H, H-6) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 201.1 (C-2), 146.7 (C-3), 128.2 (C-4), 62.4 (C-2′), 35.0 (C-1′), 26.2 (C-1) ppm. **Data for 13:** ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.93, 4.71 (each s, 1 H, CH_2), 3.60 (t, *J* = 6.3 Hz, 2 H, H-1), 2.29 (t, *J* = 5.5 Hz, 2 H, H-2), 1.24 (s, CH_3, 6 H) ppm. ^{13}C NMR, ($CDCl_3$, 50 MHz): δ = 153.6 (C-3), 110.1 (CH_2), 72.8 (C-4), 63.0 (C-1), 34.8 (C-2), 29.5 (2 CH_3) ppm.

Condensation of Enone 14 with 2,4-Dihydroxyacetophenone (15): The enone **14** (114 mg, 1 mmol) was added to 2,4-dihydroxyacetophenone (152 mg, 1 mmol) in toluene [10 mL; with or without catalytic amounts (10 mg) of *meta*-chlorobenzoic acid]. The mixture was stirred at 90−100 °C for 4 h, removing traces of water by azeotropic distillation with toluene (3 mL). The reaction mixture was neutralized by addition of $NaHCO_3$ (15 mg, in case of *meta*-chlorobenzoic acid addition), filtered and the solvent removed under reduced pressure. The residue was separated by column chromatography (CH_2Cl_2/hexane, 60:40) to afford **16** (206 mg, 83%) from the less polar fraction and **17** (20 mg, 8%) from the polar fraction (over all yield 91%).

***rac*-5-Demethylxyloketal D 16:** White crystals (diethyl ether/pentane), m.p. 114−116 °C. IR (KBr, cm^{-1}): ṽ = 2981, 2893, 1750, 1620, 1600, 1481, 1382, 1212. UV (MeOH): $\lambda_{max.}$ (log ε) = 269 (4.80) 259 (4.51), 255.8 (4.49), 203 (3.75) nm. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 13.05 (s, 1 H, OH), 7.49 (d, *J* = 9.0 Hz, 1 H, H-13) 6.34 (d, *J* = 8.8 Hz, 1 H, H-14), 4.01 (m, 2 H, H-4), 2.98 (d, *J* = 15.0 Hz, 1 H, H-7a), 2.72 (dd, *J* = 6.4, 18.0 Hz, 1 H, H-7b), 2.51 (s, 1 H, H-16), 2.45 (m, 1 H, H-6), 2.05 (m, 1 H, H-5a), 1.71 (m, 1 H, H-5b), 1.51 (s, 3 H, H-10) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 202.8 (C-15), 163.2 (C-11), 159.9 (C-9), 130.3 (C-13), 113.4 (C-12), 108.9 (C-14), 107.6 (C-2), 106.2 (C-8), 67.1 (C-4), 39.8 (C-6), 29.2 (C-5), 26.3 (C-16), 22.4 (C-10), 19.6 (C-7) ppm. MS (EI, 80 eV): *m*/*z* (%) = 248 (81) [$C_{14}H_{16}O_4$, M^+] , 230 (12), 215 (9), 203 (19), 177 (23), 165 (28), 137 (13), 121 (11), 97 (7), 83 (77), 57 (43), 43 (100). $C_{14}H_{16}O_4$ (248.3): calcd. C 67.73, H 6.53; found C 67.10, H 6.53.

***rac*-5-Demethylisoxyloketal 17:** White crystals (diethyl ether/pentane), m.p. 134−135 °C. IR (KBr, cm^{-1}): ṽ = 2981, 2893, 1750, 1620, 1600, 1481, 1382, 1212. UV (MeOH): $\lambda_{max.}$ (log ε) = 269.2 (4.82), 259.2 (4.51), 203 (3.86) nm. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.48 (s, 1 H, H-11), 6.40 (s, 1 H, H-12), 3.98 (m, 1 H, H-4), 2.99, 2.88, (m, 2 H, H-7), 2.52 (s, 3 H, H-16), 2.48 (m, 1 H, H-6), 2.20 and 1.98 (m, 2 H, H-5), 1.64 (s, 3 H, H-10), 12.40 (s, 1 H, OH) ppm. ^{13}C NMR ($CDCl_3$,75 MHz): δ = 202.7 (C-15), 163.7 (C-13), 160.8 (C-9), 132.5 (C-11), 114.9, (C-12), 110.8 (C-8), 108.5

(C-2), 104.9 (C-14), 67.3 (C-4), 41.1 (C-6), 28.4 (C-5), 26.7 (C-16), 25.7 (C-16), 23.4 (C-7) ppm. MS (EI, 80 eV): *m*/*z* (%) = 248 (67) [$C_{14}H_{16}O_4$, M^+], 230 (8), 215 (11), 203 (18), 177 (19), 165 (79), 137 (22), 83 (39). $C_{14}H_{16}O_4$ (248.3): calcd. C 67.73, H 6.53; found C 67.50, H 6.77.

Reaction of Enone 14 with Phloroglucinol (7). Synthesis of 5-Demethylxyloketals 18, 19a,b, and 20a,b: Three experiments of condensation of enone **13** with phloroglucinol (**7**) were performed, as described for **16/17**, to afford the mono, bis, and tris adducts **18**, **19a**,**b**, and **20a**,**b**, respectively, in different ratios, depending on the proportion of the reactants and reaction time, as shown in Table 1. The major part of the bis adducts **19a**,**b** were precipitated with pentane/EtOAc (3:7) whereas the mono ketal **18** and the tris(ketals) **20a**,**b** were purified by column chromatography on silica gel (CH_2Cl_2/Et_2O, 99:1). The mono ketal **18** was isolated from the polar fraction, the bis adducts **19a**,**b** from the intermediate fraction, and the tris(ketals) **20a**,**b** from the least polar fraction.

Data for Monoketal 18: Resin. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3423 br., 2983, 2923, 2847, 1629, 1520, 1460, 1384, 1286, 1177, 1161, 1150, 1112, 1079, 1003. UV (MeOH): $\lambda_{max.}$ (log ε) = 269.2 (4.65), 240.8 (3.39), 207 (3.25) nm. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.94 (d, *J* = 2.8 Hz, 1 H, H-12), 5.86 (d, *J* = 2.3 Hz, 1 H, H-14), 3.94 (m, 2 H, H-4), 2.86 (d, *J* = 18.0 Hz, 1 H, H-7a), 2.65 (dd, *J* = 6.0, 18.0 Hz, 1 H, H-7b), 2.43 (m, 1 H, H-6), 2.06 (m, 1 H, H-5a), 1.74 (m, 1 H, H-5b), 1.47 (s, 3 H, H-7b, H-10) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 158.4 (C-9), 156.5 (C-11), 156.4 (C-13), 108.6 (C-2), 99.8 (C-8), 97.2 (C-12), 96.7 (C-14), 68.4 (C-4), 42.4 (C-9), 30.7 (C-5), 23.6 (C-10), 21.6 (C-7) ppm. MS (EI, 80 eV): *m*/*z* (%) = 222 (9) [$C_{12}H_{14}O_4$, M^+], 167 (11), 139 (31), 97 (16), 83 (39), 57 (14), 43 (100), 31 (96).

Data for Bis(ketals) 19a,b: White crystals, m.p. 244−245 °C (dec.). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3363, 2975, 2955, 2893, 2846, 1615, 1505, 1450, 1382, 1108, 1082, 994. UV (MeOH): $\lambda_{max.}$ (log ε) = 269.1 (4.54), 259.2 (4.18) nm. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.48 (s, 1 H, H-12), 3.97 (m, 2 H, H-4a, H-4a′,), 3.81 (m, 2 H, H-4b, H-4b′), 3.29 (m, 2 H, H-7a, H-7a′), 3.02 (m, 2 H,H-7b, H-7b′), 2.92 (m, 1 H, H-6), 2.79 (m, 1 H, H-6′), 1.79 (m, 4 H, H-5, H-5′), 1.55, 1.53, 1.51, 1.49 (each s, 6 H, H-10, H-10′) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 156.5, 156.4 (C-11), 153.5, 153.4, 153.3, 153.1 (C-9, C-9′), 107.6, 107.4, 106.9, 106.8 (C-2, C-2′), 100.2, 100.0, 99.2, 98.6 (C-8, C-8′), 96.5, 96.4 (C-12, C-12′), 66.96, 66.90, 66.79 (C-4, C-4′), 41.0, 40.9 (C-6, C-6′), 29.6, 29.4 (C-5, C-5′), 23.4, 23.1, 23.0, 22.9 (C-10, C-10′), 21.2, 21.1, 20.8 (C-7, C-7′) ppm. MS (EI, 80 eV): *m*/*z* (%) = 318 (72) [$C_{18}H_{22}O_5$, M^+], 234 (88), 219 (68), 191 (28), 152 (35), 139 (57), 111 (19), 84 (81), 69 (21), 43 (100). $C_{18}H_{22}O_5$ (318.3): calcd. C 67.91, H 6.97; found C 67.26, H 6.96.

Acetates 19c,d: The bis(ketals) **19a**,**b** (100 mg) were acetylated with acetic anhydride (0.2 mL) in pyridine (1 mL) and catalytic amounts of DMAP to obtain the acetylated demethylxyloketals **19c**,**d** as white crystals after usual workup, m.p. 169−170 °C. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3446, 2981, 2939, 2893, 1746, 1605, 1496, 1424, 1367. (MeOH): UV $\lambda_{max.}$ (log ε) = 269.2 (4.53), 256.2 (4.20), 203 (2.99) nm. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.18 (s, 1 H, H-12), 4.00 (m, 4 H, H-4a, H-4a′, H-4b, H-4b′), 2.89 (d, *J* = 18.0 Hz, 2 H, H-7a, H-7a′), 2.65 (ddd, *J* = 6.0, 18.0, 24.0 Hz, 2 H, H-7b, H-7b′), 2.36 (m, 2 H, H-6, H-6′), 2.25 (s, 3 H, H-14), 2.00 (m, 2 H, H-5a, H-5a′), 1.75, (m, 2 H, H-5b, H-5b′), 1.51, 1.49, 1.48, 1.47 (each s, 6 H, H-10, H-10′,) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 201.4, 169.4 (C-13), 152.6, 152.2 (C11), 150.0, 149.6, 149.3, 148.4 (C-9, C-9′) 107.7, 107.4, 106.7 (C-2, C-2′), 105.1, 104.3, 104.0 (C-8, C-8′), 103.1, 103.1 (C-12), 67.0 (C-4, C-4′), 40.4, 40.3, 40.1, 40.0 (C-6, C-6′), 29.2, 29.1, 29.0 (C-5, C-5′), 23.4, 23.1 (C-14), 23.1, 22.6, 22.5, 22.4 (C-10, C-10′), 21.1 (C-14) 20.6 (C-7, C-7′) ppm. MS (EI, 80 eV): *m*/*z* (%) = 360 ($C_{20}H_{24}O_6$, M^+, 88), 330 (8), 317 (17), 276 (37), 234 (42), 219 (27), 191 (21), 152 (36), 84 (49), 43 (100). $C_{20}H_{24}O_6$ (360.4): calcd. C 66.65, H 6.71; found C 65.98, H 6.78.

Data for Tris(ketals) 20a,b: White crystals, m.p. 155−157 °C. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3560−3301, 2986, 2934, 2887, 2846, 1620, 1470, 1382, 1196, 1113, 989, 855. UV (MeOH): $\lambda_{max.}$ (log ε) = 269.2 (4.84), 259.4 (4.51) nm. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.07−3.88 (m, 2 H, H-4), 2.88 (m, 1 H, H-7a), 2.69 (m, 1 H, H-7b), 2.38 (m, 1 H, H-6), 2.04 (m, 1 H, H-5a), 1.77 (m, 1 H, H-5b), 1.52, 1.50, 1.49 (each s, 3 H, H-10) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 150.2, 150.2, 150.1, 150, 1 (C-9), 107.0, 106.9, 106.8, 106.7 (C-2), 99.6, 99.5, 99.4, 99.3 (C-8), 66.9 (C-4), 40.5, 40.4, 40.4 (C-6), 29.5, 29.4 (C-5), 23.2, 23.1, 22.9, 22.8 (C-10), 20.6, 20.5 (C-7) ppm. MS (EI, 80 eV): *m*/*z* (%) = 414 (36) [$C_{24}H_{30}O_6$, M^+], 330 (57), 246 (43), 203 (18), 85 (95), 83 (100), 43 (46). $C_{24}H_{30}O_6$ (414.5): calcd. C 69.54, H 7.30; found C 69.47, H 7.45.

Crystal Structure Determination of 20b:[10] $C_{24}H_{30}O_6$, M_r = 414.5, monoclinic, space group $P2_1/c$, *a* = 6.8219(11), *b* = 26.234(4), *c* = 11.6881(19) Å, β = 92.775(3)°, *V* = 2089.3(6) Å^3, *Z* = 4, $D_{calcd.}$ = 1.318 g/cm^3, *F*(000) = 888, *T* = 173(2) K. Bruker-AXS SMART APEX, graphite-monochromated, λ(Mo-K_α) = 0.71073 Å, μ = 0.09 mm^{-1}, poorly diffracting colorless crystal, size 0.45 × 0.20 × 0.20 mm^3, 8459 intensities collected $3 < 2\theta < 49.4°$, $-8 < h < 8$, $-30 < k < 30$, $-8 < l < 13$. Structure solved by direct methods, full-matrix least-squares refinement based on F^2 and 271 parameters, all but H atoms refined anisotropically, H atoms refined with riding model on idealized positions with U = 1.5 U_{iso}(O) and 1.2 U_{iso}(C). Refinement converged at $R1(F)$ = 0.086, $wR2(F^2$, all data) = 0.268, S = 0.93, max.(δ/σ) < 0.001, min./max. height in final ΔF map −0.42/0.55 e/Å^3. Figure 1 shows the molecular structure. Programs used: SHELXTL.[11]

Reduction of Citraconic Anhydride (21) with $LiAlH_4$, and Hydrogenation: Citraconic anhydride (**21**) was reduced with $LiAlH_4$ as described in the literature[6] to obtain the mixture of unsaturated isomeric lactones **22** and **23** in a 8.5:1.5 ratio and in 70% yield. Subsequent hydrogenation of this mixture was carried out using 10% Pd on charcoal to afford 3-methyl-γ-butyrolactone *rac*-**10** (as a crude mixture with the isomer corresponding to **23**) in 72% yield.

4-Methyl-3-methylenedihydrofuran-2-one (*rac*-9): Absolute EtOH (3 mL) was slowly added under nitrogen to a suspension of NaH (9.6 g, 0.4 mol) in dry diethyl ether (200 mL). A mixture of ethyl formate (32.9 mL, 0.4 mol) and crude *rac*-**10**[5] (35.2 mL, 0.4 mol) was then slowly added to the mixture over a period of 1.3 h (compare procedure in ref.[5b]). The rate of addition was controlled to give a steady reflux and evolution of hydrogen gas. After complete addition, the mixture was stirred for a further 30 min at 20 °C. The solid precipitate formed was filtered off, washed with dry diethyl ether, and dried under vacuum to give the light yellow α-formyl-γ-butyrolactone sodium salt (59.43 g, 99%). Part of this salt (27.2 g, 0.2 mol) was added to a stirred suspension of paraformaldehyde (27.0 g, 0.2 mol) in dry diethyl ether (200 mL) and the mixture was immediately refluxed for 1 h. The mixture was cooled to 10 °C and treated with a saturated aqueous solution of potassium carbonate (25 mL) and diethyl ether (100 mL). The organic layer was separated, dried and the solvents evaporated to dryness to afford a pale yellow oil (14.8 g, 66%). **Data for (*rac*-9):** ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 6.01(d, *J* = 3.0 Hz 1 H, H-7a), 5.58 (d, *J* = 3.0 Hz 1 H, H-7b), 4.8−4.5 (m, 2 H, H-5), 2.85 (m, 1 H, H-4), 1.50 (m, 3 H, H-6) ppm. ^{13}C NMR, ($CDCl_3$, 50 MHz): δ = 170.7 (C-2), 140.3 (C-3), 120.7 (C-7), 72.4 (C-5), 33.9 (C-4), 17.7 (C-6) ppm.

5-Hydroxy-4-methyl-3-methylenepentan-2-one (*rac*-8a). Methylation of α-Methylene-γ-butyrolactone (*rac*-9): A solution of MeLi (21 mL, 32.9 mmol) in diethyl ether (30 mL) was added slowly to a stirring solution of *rac*-**9** (14 mL, 32.9 mmol). The mixture was stirred for 30 min and was then warmed up to 0 °C over a period of 1 h. The reaction was quenched by addition of aqueous NH_4Cl solution (20 mL) and the mixture was extracted three times with diethyl ether (each 20 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was removed under reduced pressure to afford a yellowish oil. The residue was separated by column chromatography over silica gel (CH_2Cl_2/EtOAc, 95:5) to afford methyl ketone *rac*-**8** (75% yield) from the less-polar fraction. The ratio between the desired ketone *rac*-**8a** and the dimethylated side product related to **13** was found to be 86:14. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 6.14 (d, *J* = 1.7 Hz, 1 H, H-4a), 5.70 (d, *J* = 1.7 Hz, 2 H, H-7b), 3.74 (m, 2 H, H-2′), 2.96 (m, 1 H, H-1′), 2.36 (s, 3 H, H-1) 1.35 (d, *J* = 6.0 Hz, 3 H, H-6) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 200.7 (C-2), 151.4 (C-3), 125.5 (C-4), 66.0 (C-2′), 36.2 (C-1′), 26.6 (C-1) 15.4 (C-1′′) ppm.

Condensation of Enone *rac*-8a with 2,4-Dihydroxyacetophenone (15). Formation of *rac*-Xyloketal D (*rac*-4a): Enone *rac*-**8a** and 2,4-dihydroxyacetophenone (**15**, 578 mg, 3.8 mmol) were heated in toluene as described for **16**. The mixture was separated by column chromatography on silica gel (hexane/dichloromethane, 12:88) to afford a mixture of **4a** and **4b** (800 mg, 3.05 mmol, 80.3%) from the less-polar fraction and **24a**,**b** (89.7 mg, 9%) from the polar fraction (overall yield 89.3%). The ^{1}H NMR spectra showed the mixture of **4a** and **4b** in a ca. 8.5 to 1.5 ratio. Crystallization from diethyl ether gave pure *rac*-xyloketal D **(4a)** (637 mg, 64%).

Data for *rac*-Xyloketal D 4a: White crystals, m.p. 82 °C. IR (KBr, cm^{-1}): ṽ = 2965, 2929, 2887, 2841, 1765, 1615, 1491, 1424, 1387, 1341, 1206, 1108, 1072. UV ($CHCl_3$): $\lambda_{max.}$ (log ε) = 315 (5.7) 283 (4.2), 266 (4.5), 223 (5.50), 219 (5.4), 211 (5.47) nm. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 13.1, (m, 1 H, OH), 7.5 (d, *J* = 8.9 Hz, 1 H, H-14), 6.34 (d, *J* = 8.9 Hz, 1 H, H-15), 4.22 (t, *J* = 8.1 Hz, 1 H, H-4a), 3.6 (t, *J* = 8.1 Hz, 1 H, H-4b), 3.01 (d, *J* = 18 Hz, 1 H, H-7a), 2.76 (dd, *J* = 5.6, 18.0 Hz, 1 H, H-7b), 2.57 (s, 3 H, H-17), 2.28−1.94 (m, 2 H, H-5 and H-6), 1.57 (s, 3 H, H-10), 1.11 (d, *J* = 6.1 Hz, 3 H, H-11) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 203.0 (C-16), 163.3 (C-12), 159.8 (C-9), 130.3 (C-14), 113.4 (C-13), 109.1 (C-15), 108.6 (C-2), 106.5 (C-8), 74.6 (C-4), 47.3 (C-6), 35.4 (C-5), 26.5 (C-17), 23.0 (C-10), 18.3 (C-7), 16.1 (C-11) ppm. MS (EI, 80 eV): *m*/*z* (%) = 248 (47) [$C_{14}H_{16}O_4$, M^+], 219 (8), 203 (12), 177 (14), 165 (100), 137 (100), 121 (10), 97 (67), 83 (38), 43 (40). $C_{15}H_{18}O_4$ (262.3): calcd. C 68.68, H 6.92; found C 68.56, H 6.73.

Data for *iso*-Xyloketals D 24a,b: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 12.35, (m, 1 H, OH), 6.33 (d, *J* = 2.4 Hz, 1 H, H-15), 5.25 (d, *J* = 2.4 Hz, 1 H, H-12), 4.15 (t, *J* = 8.1 Hz, 1 H, H-4a), 3.53 (t, *J* = 8.1 Hz, 1 H, H-4b), 2.97 (d, *J* = 16.3 Hz, 1 H, H-7a), 2.7 (m, 1 H, H-7b), 2.53 (s, 3 H, H-17), 2.19−1.82 (m, 2 H, H-5 and H-6), 1.53 (s, 3 H, H-10), 1.06 (d, *J* = 6.2 Hz, 3 H, H-11) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 202.7 (C-16), 163.7 (C-13), 160.2 (C-9), 132.5 (C-15), 116.3 (C-14), 110.7 (C-8), 109.3 (C-2), 105.0 (C-12), 74.6 (C-4), 48.5 (C-6), 35.4, 35.0 (C-5), 26.7 (C-17), 23.9 (C-10), 18.4 (C-7), 16.4 (C-11) ppm. MS (EI, 80 eV): *m*/*z* (%) = 262 (43) [$C_{15}H_{18}O_4$, M^+], 219 (3), 203 (12), 165 (100), 147 (15), 97 (57), 83 (33), 43 (41). $C_{15}H_{18}O_4$ (262.3): calcd. C 68.68, H 6.92; found C 68.50, H 6.71.

Condensation of Enone *rac*-8 with Phloroglucinol (7). Synthesis of *rac*-Xyloketals A (1a−h), B (2a−h), and (6a,b): Enone *rac*-**8a** (256 mg, 2 mmol) was condensed with phloroglucinol (**7**) (252 mg, 2 mmol) in boiling toluene as described for **16**. The mixture was separated by column chromatography on silica gel (hexane/dichloromethane, 12:88) into three fractions. The least-polar fraction contained stereoisomers of the tris adducts xyloketals A (**1a**−**1h**; 50 mg, 5.5%) was further purified by repeated preparative TLC on silica gel. The fraction of medium polarity contained the stereoisomeric bis adducts of xyloketals **B** (**2a**−**2h**; 211 mg, 30.5%). Colorless plates separated from fraction two in diethyl ether, showing only one isomer (probably **2e**) in the NMR spectra. The monoadducts (**6a**,**b**; 235 mg, 50.0%) were isolated from the polar fraction as an amorphous powder. The overall yield of the condensation was found to be 86%. The NMR spectrum showed a ca. 8.5 to 1.5 mixture of stereoisomers, similar to that found in the related reaction of *rac*-**8** with 2,4-dihydroxyacetophenone (**15**).

Data for Xyloketal A (1a−1h, mixture): ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.19 = (m, 2 H, H-4a), 3.52 (m, 2 H, H-4b), 3.1−2.42 (m, 4 H, H-7a, H-7b), 2.21−1.81 (m, 4 H, H-5, H-6), 1.4 (s, 3 H, H-10), 1.1 (d, *J* = 6.3 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$,75 MHz): δ = 152.6, 152.2, 151.8 (C-9), 108.3, 108.1, 107.9 (C-2), 99.9, 99.8, 99.6 (C-8), 74.4, 74.1 (C-4), 48.0 (C-6), 35.8, 35.7, 35.5, 35.2 (C-5), 24.0, 23.7, 23.5, 23.1 (C-10), 19.5, 19.3, 19.2, 19.1 (C-7), 16.6, 16.5, 16.4 (C-11) ppm. MS (EI, 80 eV): *m*/*z* (%) = 456 (5) [$C_{27}H_{36}O_6$, M^+], 396 (35), 300 (42), 163 (12), 83 (100), 43 (84). $C_{27}H_{36}O_6$: (456.58) calcd. C 71.03, H 7.95; found C 70.90, H 7.28.

Xyloketal B 2a−2h: ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 6.14 = (1 H, OH), 6.12 (s, 1 H, H-13), 4.14 (dd, *J* = 8.3, 17.3 Hz, 2 H, H-4a, H-4a′), 3.47 (m, 2 H, H-ba, H-4b′), 2.86 (d, *J* = 17.1 Hz, 2 H, H-7a, H-7a′), 2.58 (m, 2 H, H-7b, H-7b′), 2.13 (m, 2 H, H-6, H-6′), 1.88 (m, 2 H, H-5, H-5′), 1.51 (s, 6 H, H-10, H-10′), 1.03 (d, *J* = 6.6, 6 H, H-11, H-11′) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 154.0, 153.9 (C-12), 152.3, 152.2, (C-9′) 152.1, 151.9 (C-9), 108.0, 107.9 (C-2′) 107.7 (C-2), 99.4, 99.2 (C-8), 98.9, 98.2 (C-8′), 96.2, 96.1 (C-13), 74.2, 74.1, (C-2, C-2′), 48.1, 48.0 (C-6) 47.8 (C-6′), 35.6 (C-5 and C-5′), 23.5, 23.3 (C-10′), 23.1, 23.0 (C-10), 19.0, 18.9 (C-7′), 18.8, 18.7 (C-7), 16.5, 16.3 (C-11′), 16.2, 16.0 (C-11) ppm.

Isoxyloketal B (probably 2e): White crystals, m.p. 231−234 °C (dec.). IR (KBr, cm^{-1}): ṽ = 3394, 2950, 2929, 2887, 1620, 1512, 1455, 1387, 1341, 1206, 1118. UV ($CHCl_3$): $\lambda_{max.}$ (log ε) = 303 (5.1), 297 (5.2), 282 (5.2), 264 (4.6), 259 (4.53), 219 (4.51), 212 (4.53), 208 (4.5) nm. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 6.13 (s, 1 H, OH), 6.12 (s, 1 H, H-13), 4.17 (dd, *J* = 7.6, 17.5 Hz, 2 H, H-4a, H-4a′), 3.47 (m, 2 H, H-4b, H-4b′), 2.89 (d, *J* = 17.0 Hz, 2 H, H-7a, H-7a′), 2.65 (, m, 2 H, H-7b, H-7b′), 2.15 (m, 2 H, H-5, H-5′), 1.91 (m, 2 H, H-6, H-6′,), 1.55 (s, 6 H, H-10, H-10′), 1.08 (d, *J* = 6.0, 6 H, H-11, H-11′) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 153.6 (C-12), 152.2, (C-9′) 152.1, 152.0 (C-9), 107.9 (C-2′) 107.8 (C-2), 99.5 (C-8′), 98.8 (C-8), 96.1 (C-13), 74.2 (C-2, C-2′), 48.0, 48.2 (C-6′) 47.8 (C-6), 35.7, 35.5 (C-5′ and C-5), 23.3 (C-10′), 23.2 (C-10), 16.3 (C-11′), 16.0 (C-11) ppm. MS (EI, 80 eV): *m*/*z* (%) = 346 (65) [$C_{20}H_{26}O_5$, M^+], 250 (20), 249 (33), 249 (63), 233 (20), 205 (57), 83 (33), 43 (41). $C_{20}H_{26}O_5$ (346.4): calcd. C 69.34, H 7.56; found C 69.47, H 7.28.

Monoadducts 6a,b: White amorphous powder, IR (KBr, cm^{-1}): ṽ = 3374 br, 2955, 2924, 2847, 1625, 1527, 1465, 1393, 1279, 1155. UV ($CHCl_3$): $\lambda_{max.}$ (log ε) = 297 (4.7), 263 (3.9), 259 (3.8), 224 (3.9), 220 (3.87), 208 (3.9) nm. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 6.00 (d, *J* = 2.2 Hz, 1 H, H-12), 5.92 (d, *J* = 2.2 Hz, 1 H, H-14), 4.17 (t, *J* = 8.3 Hz, 1 H, H-4a), 3.52 (dd, *J* = 8.3 Hz, 1 H, H-4b), 2.79 (d, *J* = 17.1 Hz, 1 H, H-7a), 2.68 (dd, *J* = 5.8, 16.9 Hz, 1 H, H-7b), 2.13 (m, 1 H, H-5), 1.91 (m, 1 H, H-6), 1.49 (s, 3 H, H-10), 1.04 (d, *J* = 6.5 Hz, 3 H, H-11) ppm. ^{13}C NMR ($CDCl_3$ 75 MHz):

δ = 155.6 (C-9), 154.5 (C-15, C-13), 108.2 (C-2), 99.1 (C-8), 96.8 (C-12) 96.3 (C-14), 74.4 (C-4), 47.8 (C-6), 35.5 (C-5), 23.1 (C-10), 18.6 (C-7), 16.0 (C-11) ppm. MS (EI, 80 eV): *m/z* (%) = 236 (50) [$C_{13}H_{16}O_4$, M^+], 221 (16), 139 (100), 98 (16), 97 (43), 83 (54), 69 (15), 55 (12). $C_{13}H_{16}O_4$ (236.26): calcd. C 66.09, H 6.83; found C 65.32, H 7.19.

Synthesis of Enantiomerically Enriched Xyloketal D (*R*)-(4a). 3-(Hydroxymethyl)isocrotonic Acid (26): A mixture of 3,3-dimethylacrylic acid (**25**) (50 g, 0.5 mol), SeO_2 (28 g, 0.25 mol), and glacial acetic (50 mL) was refluxed for 4 h as describe in the literature.[8] The fractional distillation afforded unchanged acid **25**, 3-(hydroxymethyl)isocrotonic acid (**26**) (45%) and 3-(acetoxymethyl)isocrotonic acid (37%).

(*R*)-3-Methylbutyrolactone (10): 3-(Hydroxymethyl)isocrotonic acid (**26**) was enantioselectively hydrogenated in 93% *ee* and 100% conversion as described by Noyori et al.[9] using (*R*)-BINAP-Ru(OAc)$_2$ as the catalyst. The intermediate saturated acid (750 mg, 6.4 mmol) was not purified but lactonized quantitatively into the required (*R*)-3-methylbutyrolactone (**10**; 477 mg, 4.8 mmol) by refluxing in a mixture of $CHCl_3$ (5 mL) and concd. HCl (1 mL) (74.5% yield).[12]

Xyloketal D (*R*)-4a: The methylenation of the enantiomerically enriched lactone (*R*)-**10** (477 mg, 4.77 mmol) and the methylation to the enone (*R*)-**8a** (330 mg, 2.6 mmol, yield: 54%) was performed as described for the racemic material. The unsaturated ketone (*R*)-**8a** (150 mg, 1.17 mmol) was then condensed with 2,4-dihydroxyacetophenone (**15**), as described previously, to yield a mixture of xyloketal D (**4a**) and the stereoisomer **4b** in a ca. 8.5:1.5 ratio (by NMR spectroscopy). The crude mixture was crystallized from diethyl ether/pentane to afford the major isomer as white crystals m.p. 87 °C (120 mg, 0.95 mmol, 81%, 93% *ee* calculated from optical rotation). After one recrystallization (diethyl ether/pentane) the product had m.p. 110−111 °C and $[\alpha]_D^{25} = -118$, (c = 0.10 $CHCl_3$). The data were in agreement with those of xyloketal D (**4a**), (ref.[1] m.p. 111−113 °C. $[\alpha]_D^{25} = -119.5$). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2965, 2929, 2887, 1781, 1620, 1495, 1420, 1385, 1341, 1209. UV (MeOH): $\lambda_{max.}$ (log ε) 263 = (4.3) 254 (4.1), 250.3 (4.6), 206 (3.34) nm. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 13.15, (m, 1 H, OH), 7.54 (d, J = 8.9 Hz, 1 H, H-14) 6.39 (d, J = 8.9 Hz, 1 H, H-15), 4.22 (t, J = 8.0 Hz, 1 H, H-4a), 3.59 (dd, J = 8.26, 16.6 Hz, 1 H, H-4b), 2.99 (d, J = 17.6 Hz, 1 H, H-7a), 2.74 (dd, J = 5.9, 18.0 Hz, 1 H, H-7b), 2.57 (s, 3 H, H-17), 2.20−1.93 (m, 2 H, H-5 and H-6), 1.56 (s, 3 H, H-10), 1.1 (d, J = 6.07 Hz, 3 H, H-11) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 202.9 (C-16), 163.1 (C-12), 159.7 (C-9), 130.3, (C-14), 113.3, (C-13), 109.0 (C-15), 108.5 (C-2), 106.3 (C-8), 74.5 (C-4), 47.1 (C-6), 35.3 (C-5), 26.3 (C-17), 22.9 (C-10), 18.2 (C-7), 16.0 (C-11) ppm. MS (EI, 80 eV): *m/z* (%) = 262 (39) [$C_{15}H_{18}O_4$, M^+], 247 (8), 203 (11), 177 (14), 166 (11), 165 (100), 97 (69), 83 (38). $C_{15}H_{18}O_4$ (262.3): calcd. C 68.68, H 6.92; found C 68.56, H 6.73.

Supporting Information: Detailed probability calculations (ref.[7] and extended ^{13}C NMR spectra of compounds **17**; and **18**. This material is available free of charge via the Internet (see also the footnote on the first page of this article).

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