Total synthesis of (–)-xyloketal D and its enantiomer — Confirmation of absolute stereochemistry

Jeremy D. Pettigrew, Rebecca P. Freeman, and Peter D. Wilson

Abstract: The total synthesis of (–)-xyloketal D and its enantiomer have been achieved by the reaction of an *ortho*-quinone methide with (4*R*)- and (4*S*)-4,5-dihydro-2,4-dimethylfuran via a diastereoselective inverse electron demand Diels–Alder reaction. This total synthesis confirmed the absolute stereochemistry of the natural product. The *ortho*-quinone methide was generated by reaction of an appropriately functionalized Mannich base with methyl iodide. The Mannich base was prepared in one step from 2,4-dihydroxyacetophenone, formaldehyde, and morpholine. The enantiomeric dihydrofurans were prepared from (2*R*)- and (2*S*)-2-methylpent-4-ynoic acid via a three-step reaction sequence. These chiral nonracemic synthetic precursors were prepared from the corresponding (*R*)-phenylglycinol-derived diastereomeric amides of the readily available racemic carboxylic acid. The absolute stereochemistry of these carboxylic acids was firmly established by conversion to a known compound that had been previously prepared from a chiral pool starting material.

Key words: xyloketal D, inverse electron demand Diels–Alder reaction, *ortho*-quinone methide, dihydrofuran.

Résumé : Faisant appel à une réaction de Diels–Alder diastéréosélective, avec une demande d'électron inversée, on a réalisé une synthèse totale de (–)-xylocétal D et de son énantiomère par réaction d'une *ortho*-quinone méthide avec les (4*R*)- et (4*S*)-4,5-dihydro-2,5-diméthyfurane. Cette synthèse totale confirme la stéréochimie absolue du produit naturel. L'*ortho*-quinone méthide a été générée par réaction de l'iodure de méthyle avec une base de Mannich portant une fonctionnalisation appropriée. La base de Mannich a été préparée en une étape à partir de la 2,4-dihydroxyacétophénone, du formaldéhyde et de la morpholine. On a préparé les dihydrofuranes énantiomères en trois étapes par une série de réactions à partir des acides (2*R*)- et (2*S*)-2-méthylpent-4-ynoïque. On a préparé ces précurseurs de synthèse chiraux non racémiques à partir des amides diastéréomères correspondants dérivés du (*R*)-phénylglycinol et de l'acide carboxylique racémique commercialement disponible. La configuration absolue de ces acides carboxyliques a été fermement établie par conversion en un composé connu qui avait précédemment été préparé à partir d'un produit appartenant à un ensemble chiral.

Mots clés : xylocétal D, réaction de Diels–Alder avec demande d'électron inversée, *ortho*-quinone méthide, dihydrofurane.

[Traduit par la Rédaction]

Introduction

The natural products xyloketal A (**1**), B (**2**), C (**3**), D (**4**), and E (**5**) were isolated from a mangrove fungus of the *Xylaria* species (Fig. 1) (1). The molecular structures of these novel secondary metabolites were determined by extensive spectroscopic methods and by X-ray crystallography. In addition, the absolute stereochemistry of xyloketal A (**1**) and D (**4**) were determined by interpretation of their CD spectra. Xyloketal A (**1**) has a unique chiral, C_3-symmetric molecular structure and was shown to be an inhibitor of acetylcholine esterase (1, 2). Xyloketal D (**4**) is the simplest member of this family of natural products. We have previously reported the synthesis of (±)-11-norxyloketal D, the first total synthesis of (±)-xyloketal D (±)-**4** and model studies towards the total synthesis of xyloketal A (**1**) (3).[2] These syntheses featured the cycloaddition reactions of appropriately functionalized *ortho*-quinone methides and dihydrofurans as a key step (4).

The synthesis of (±)-11-norxyloketal D (**10**) (43% yield), via the *ortho*-quinone methide **9**, was achieved by heating the Mannich base **7** and commercially available 4,5-dihydro-2-methylfuran (**8**) (3 equiv.) with methyl iodide (1.05 equiv.) in benzene at reflux for 5 days (Fig. 2) (4–6). The Mannich

Received 25 May 2004. Published on the NRC Research Press Web site at http://canjchem.nrc.ca on 21 December 2004.

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[2]The numbering scheme provided for (–)-xyloketal D (**4**) by Lin and co-workers is employed throughout this paper. See ref. 1.

 doi: 10.1139/V04-138

Fig. 1. Molecular structures of xyloketal A (**1**), B (**2**), C (**3**), D (**4**), and E (**5**).

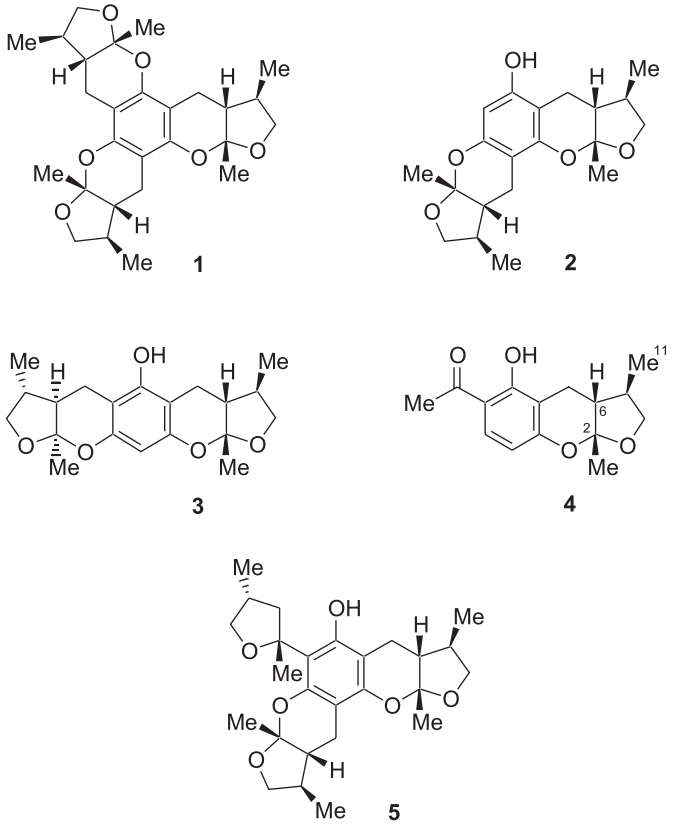
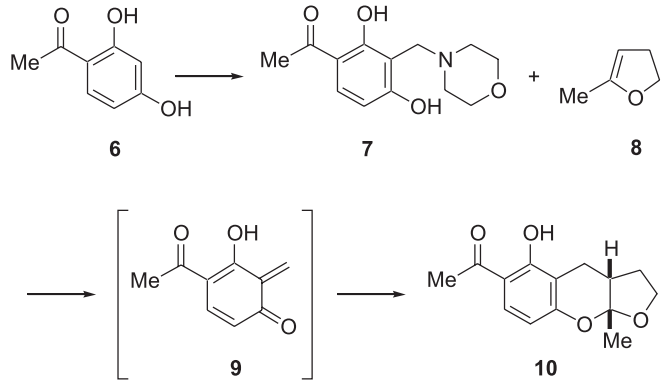


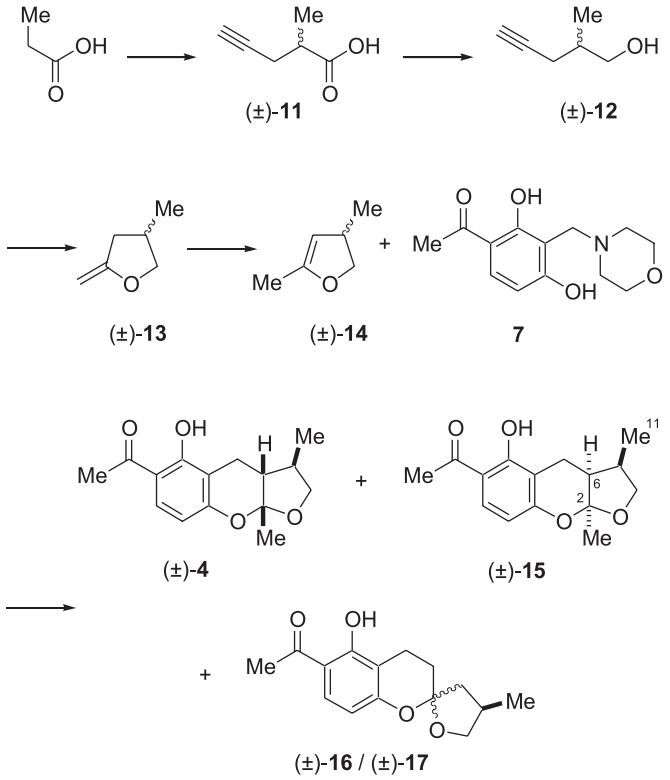
Fig. 2. Synthesis of (±)-11-norxyloketal D ((±)-**10**) (3).



base **7** was prepared as a single regioisomeric product from 2,4-dihydroxyacetophenone (**6**), formaldehyde, and morpholine in 83% yield (7).

The total synthesis of (±)-xyloketal D ((±)-**4**) involved a new synthesis of the known racemic dihydrofuran (±)-**14** (Fig. 3) (8). The racemic carboxylic acid (±)-**11** was prepared by alkylation of propionic acid with propargyl bromide, which in turn was reduced with lithium aluminum hydride to afford the racemic alcohol (±)-**12** (9, 10). Heating this alcohol with a sub-stoichiometric amount of sodium amide afforded the exocyclic dihydrofuran (±)-**13**, which was isomerized thermally to afford the required dihydrofuran (±)-**14** (8). The cycloaddition reaction of the Mannich base **7** with the dihydrofuran (±)-**14** (3 equiv.), under the reaction

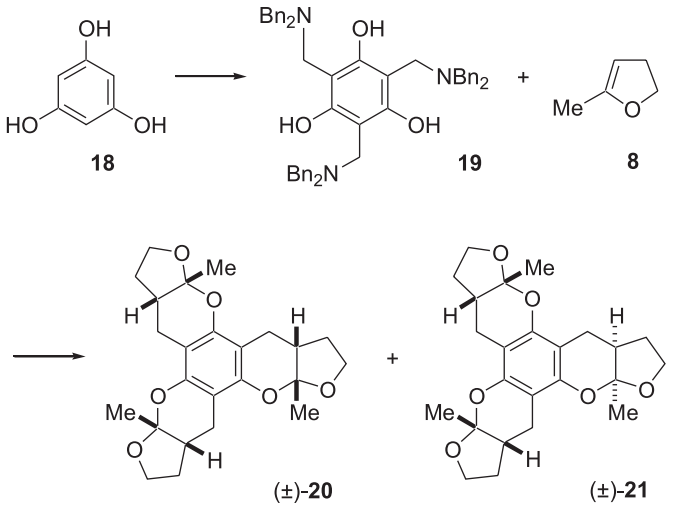
Fig. 3. Total synthesis of (±)-xyloketal D ((±)-**4**), (±)-2,6-*epi*-xyloketal D ((±)-**15**), and the diastereomeric spiroacetals (±)-**16** and (±)-**17** (3).



conditions described above, afforded (±)-xyloketal D ((±)-**4**), (±)-2,6-*epi*-xyloketal D ((±)-**15**), and the diastereomeric spiroacetals (±)-**16** and (±)-**17** as a mixture of products (11:1:3:3) in a combined yield of 54%. The spectral data for synthetic (±)-xyloketal D ((±)-**4**) were in agreement with those reported for the natural product (1). This diastereoselective cycloaddition reaction (11:1 dr) was controlled by the C4-methyl substituent of the dihydrofuran (±)-**14**. We attributed the formation of the isomeric spiroacetal reaction products (±)-**16** and (±)-**17** to the isomerization and subsequent cycloaddition reaction of the corresponding exocyclic dihydrofuran (±)-**13**. Of note, related spiroacetal reaction products were not isolated from the cycloaddition reaction of the dihydrofuran **8** that was employed in the synthesis of (±)-11-norxyloketal D (**10**). We concluded that the additional methyl substituent of dihydrofuran (±)-**14** decreased the reactivity of this endocyclic dihydrofuran in the cycloaddition reaction.

The preliminary model studies towards the total synthesis of (±)-xyloketal A ((±)-**1**) involved the reaction of the Mannich base **19**, the dihydrofuran **8** (9 equiv.), and methyl iodide (3 equiv.) (Fig. 4). This afforded a mixture (1:4) of the desired C_3-symmetric xyloketal A analogue (±)-**20** and the diastereoisomer (±)-**21** in 19% combined yield. This unprecedented and direct synthetic process involved nine individual reactions (three alkylation reactions, three elimination reactions, and three subsequent cycloaddition reactions). Of additional note, the Mannich base **19** was prepared in one step by adaptation of a literature procedure from phloro-

Fig. 4. Synthesis of xyloketal A analogues (±)-**20** and (±)-**21** (3).



glucinol (**18**), *N*,*N*-dibenzylamine, and formaldehyde (11, 12).

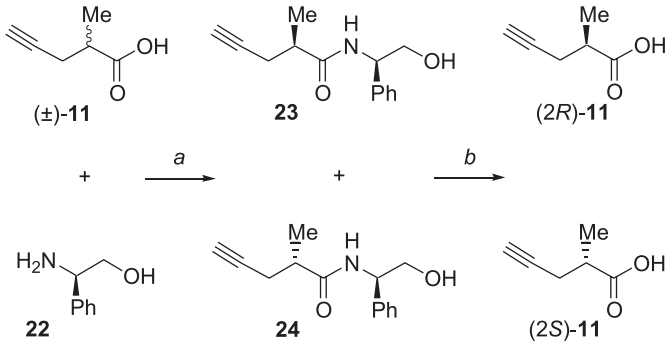
We have subsequently attempted to prepare (±)-xyloketal A ((±)-**1**) from the dihydrofuran (±)-**14** and the Mannich base **19**. However, it was not possible to isolate the desired target compound from a complex mixture of reaction products. Presumably, this process was complicated by the formation of diastereomeric as well as spirocyclic reaction by-products.

In this paper, we report an efficient resolution procedure for the racemic carboxylic acid (±)-**11**, a proof of the absolute stereochemistry, and the asymmetric synthesis of (–)-xyloketal D (**4**) as well as its enantiomer. This study was also undertaken to confirm the absolute stereochemistry of the natural product. Recently, Krohn and co-workers (13) have reported an alternative asymmetric synthesis of (–)-xyloketal D (**4**) and the C2,C6-epimer (8.5:1.5 dr) from (3*R*)-3-methylbutyrolactone (93% ee) and 2,4-dihydroxyacetophenone (**6**), as well as model studies towards the total synthesis of xyloketal A (**1**).

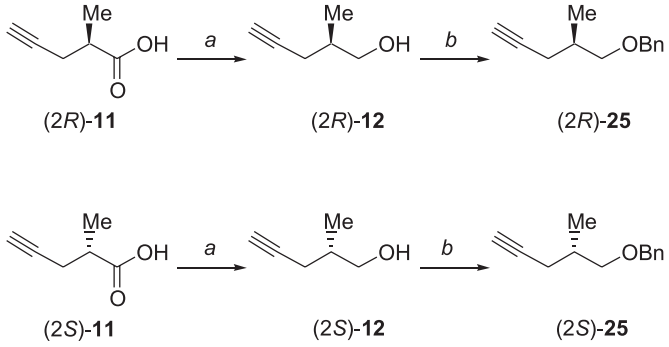
Results and discussion

A variety of methods were investigated to identify an efficient resolution procedure for the racemic carboxylic acid (±)-**11** (3).[3] It was not possible to separate the diastereomeric salts that were formed between the carboxylic acid and (*R*)-methylbenzylamine or (*R*)-(1-naphthyl)-ethylamine by fractional recrystallization. The racemic carboxylic acid (±)-**11** was also converted to the corresponding acid chloride and condensed with a series of commercially available chiral nonracemic alcohols.[4] All of the diastereomeric esters that were prepared could not be separated by fractional recrystallization or by chromatographic methods. The corresponding acid chloride of the carboxylic acid was also condensed with an extensive series of chiral nonracemic amines.[5] It was found that the diastereomeric amides **23** and **24** prepared from (*R*)-phenylglycinol (**22**) could be separated readily by flash chromatography on a multigram scale (Scheme 1) (14, 15).[6,7] The chiral nonracemic carboxylic acids (2*R*)-**11** and (2*S*)-**11** were then prepared by hydrolysis of the diastereomeric amides **23** and **24** under acidic reaction conditions (14, 16).

Scheme 1. Resolution of (±)-2-methylpent-4-ynoic acid ((±)-**11**). Reagents and conditions: (*a*) $(COCl)_2$, CH_2Cl_2, DMF (cat.), 0 °C to room temperature, 2 h; (*R*)-phenylglycinol (**22**), NEt_3, CH_2Cl_2, 0 °C to room temperature, 16 h, 36% (**23**), 34% (**24**); (*b*) 3 mol L^{-1} H_2SO_4, *p*-dioxane, reflux, 7 h, 76% ((2*R*)-**11**), 86% ((2*S*)-**11**).



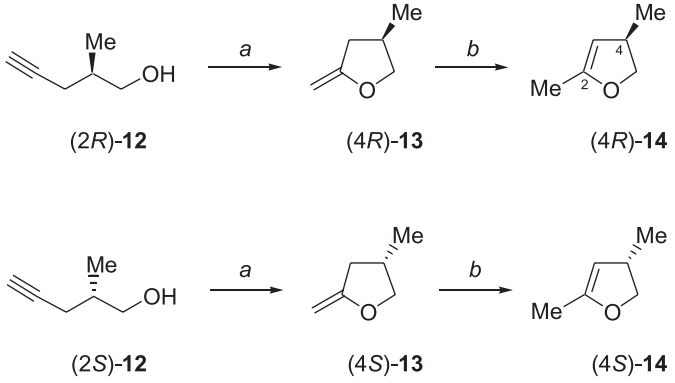
Scheme 2. Synthesis of (2*R*)-2-methylpent-4-yn-1-ol ((2*R*)-**12**) and (2*S*)-2-methylpent-4-yn-1-ol ((2*S*)-**12**): confirmation of absolute stereochemistry. Reagents and conditions: (*a*) $LiAlH_4$, THF, 0 °C to room temperature, 16 h, 89% ((2*R*)-**12**), 85% ((2*S*)-**12**); (*b*) NaH, BnBr, DMF, THF, 6 h, 90% ((2*R*)-**25**), 90% ((2*S*)-**25**).



The chiral nonracemic carboxylic acid (2*R*)-**11** was reduced with lithium aluminum hydride to afford the corresponding alcohol (2*R*)-**12** (Scheme 2) (17). A sample of this alcohol was then converted to the benzyl ether (2*R*)-**25**. The latter compound has been prepared previously from an expensive chiral pool starting material and the optical rotation

[3] A full experimental procedure for the preparation of the racemic carboxylic acid (±)-**11** is provided in the supplementary material.[10]
[4] For example, the diastereomeric esters prepared from menthol, isomenthol, and (2*R*)-butan-2-ol were copolar by TLC.
[5] The chiral nonracemic amines that were employed in these reactions included: (*R*)-methylbenzylamine and (*R*)-(1-naphthyl)-ethylamine, the methyl esters of (*S*)-alanine, isoleucine, leucine, phenylalanine, proline, tryptophan, and (*R*)-phenylglycine, as well as (*S*)-valinol and (1*S*,2*R*)-norephedrine.
[6] The diastereomeric amides that were prepared from (*S*)-valinol were also chromatographically separable.
[7] Attempts, albeit unsuccessful, were also made to resolve the racemic alcohol (±)-**12** on condensation with a series of commercially available chiral nonracemic carboxylic acids and sulfonyl chlorides.

Scheme 3. Synthesis of (4*R*)-4,5-dihydro-2,4-dimethylfuran ((4*R*)-**14**) and (4*S*)-4,5-dihydro-2,4-dimethylfuran ((4*S*)-**14**). Reagents and conditions: (*a*) $NaNH_2$, reflux, 2 h; (*b*) reflux, 2 h, 44% (over two steps) ((4*R*)-**14**), 36% (over two steps) ((4*R*)-**14**).

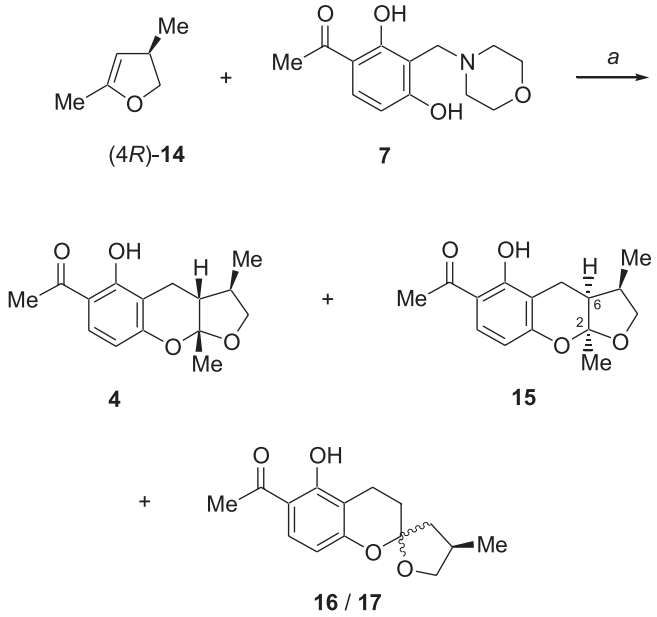


has been reported (18). Thus, the absolute stereochemistry and high optical purity of the resolved carboxylic acid (2*R*)-**11** was firmly established (see Experimental section). To complete the total synthesis of (–)-xyloketal D (**4**) and its nonnatural enantiomer, the carboxylic acid (2*S*)-**11** was reduced with lithium aluminum hydride to afford the alcohol (2*S*)-**12**. A sample of this compound was also converted to the corresponding benzyl ether (2*S*)-**25**, which proved to be the enantiomer of a known compound (18).

The chiral nonracemic alcohol (2*R*)-**12** was then used to prepare the dihydrofuran (4*R*)-**14** as described earlier for the racemic compound (Scheme 3).[8] This compound would serve as the precursor of (–)-xyloketal D (**4**) and would allow for the confirmation of the absolute stereochemistry of the natural product. In an identical fashion, the alcohol (2*S*)-**12** was used to prepare the dihydrofuran (4*S*)-**14**. This compound would serve as the precursor of the nonnatural enantiomer of xyloketal D.

The chiral nonracemic dihydrofuran (4*R*)-**14** (3 equiv.) and the Mannich base **7** were heated in benzene at reflux with methyl iodide (1 equiv.) (Scheme 4).[9] This reaction afforded a mixture (8:1:2:2) of (–)-xyloketal D (**4**), 2,6-*epi*-xyloketal D (**15**), and the diastereomeric spiroacetals **16** and **17** in a combined yield of 40%. The reaction was also repeated using dimethyl sulfate instead of methyl iodide. This reaction proceeded at a faster rate and afforded a mixture of reaction products (16:1:4:4) in a similar combined yield. A diastereomerically and analytically pure sample of the synthetic natural product, (–)-xyloketal D (**4**), was obtained by repeated chromatography and recrystallization. An analytically pure sample of the diastereomeric spiroacetals **16** and **17** was also isolated as a mixture (4:5) by repeated chromatography and recrystallization.

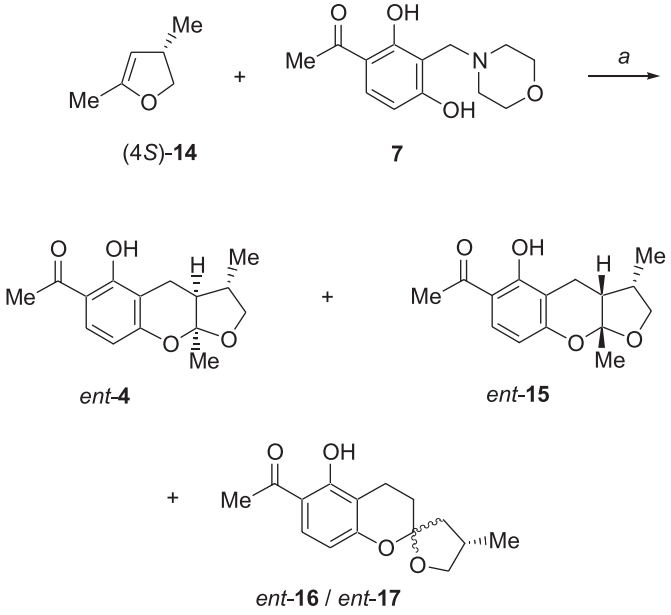
Scheme 4. Synthesis of (–)-xyloketal D (**4**), 2,6-*epi*-xyloketal D (**15**), and the diastereomeric spiroacetals **16** and **17**. Reagents and conditions: (*a*) dihydrofuran (4*R*)-**14** (3 equiv.), MeI (1 equiv), benzene, reflux, 8 days, 40% (**4**, **15**, **16**, and **17** (8:1:2:2)) *or* dihydrofuran (4*R*)-**14** (3 equiv.), Me_2SO_4 (1 equiv.), benzene, reflux, 3 days, 37% (**4**, **15**, **16**, and **17** (16:1:4:4)).



The ^1H NMR spectrum and ^{13}C NMR data of synthetic (–)-xyloketal D (**4**) were identical to those of the natural product[10] (1).[11] The sign of the optical rotation of synthetic (–)-xyloketal D (**4**) was in agreement with that reported for the natural product. This confirmed the absolute stereochemistry of the natural product that had been assigned previously by the interpretation of CD data (1, 13). However, the magnitude of the rotation was slightly lower than reported for the natural product (92% ee based on the optical rotation of the natural product) (1). To determine the enantiomeric purity of synthetic (–)-xyloketal D (**4**), efforts were also made to separate the enantiomers of a sample of racemic xyloketal D ((±)-**4**) (3). This was not possible by analytical chiral HPLC (Daicel Chiracel OD column) or by GC (Cyclosil-B column). Similarly, ^1H NMR spectroscopy using a chiral shift reagent ($Eu(hfc)_3$) was unsuccessful. Derivatization of the phenol moiety of racemic xyloketal D ((±)-**4**) with (*S*)-(+)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride afforded the corresponding Mosher's esters (19). The ^1H NMR (600 MHz) signals of the methoxy substituents were clearly resolved.[12] Subsequent derivatization of synthetic (–)-xyloketal D (**4**) afforded the corresponding Mosher's ester as a single diastereoisomer. This confirmed

[8] The lower yield for the preparation of the chiral nonracemic dihydrofuran (4*R*)-**14** than that reported for the racemic compound is reflective of the smaller scale that this reaction was performed on. See ref. 3.
[9] We have previously reported full experimental procedures for the preparation of Mannich base **7**. See ref. 3.
[10] Detailed experimental procedures and complete product characterization data for all of the additional compounds synthesized, as well as ^1H and ^{13}C NMR spectra for compounds (±)-**11**, **23**, **24**, (2*R*)-**12**, (2*R*)-**25**, (4*R*)-**14**, **4**, **16**, **17**, and the Mosher's ester derivatives of (±)-xyloketal D ((±)-**4**) and synthetic (–)-xyloketal D (**4**) may be purchased from the Directory of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0S2, Canada (http://www.nrc.ca/cisti/irm/unpub_e.shtml for information on ordering electronically).
[11] Of note, the ^1H NMR signal of natural (–)-xyloketal D (**4**) centred at 2.15 ppm should have been reported at 2.08 ppm.
[12] The ^{19}F NMR (470 MHz) signals of the Mosher's ester derivatives were separate but poorly resolved.

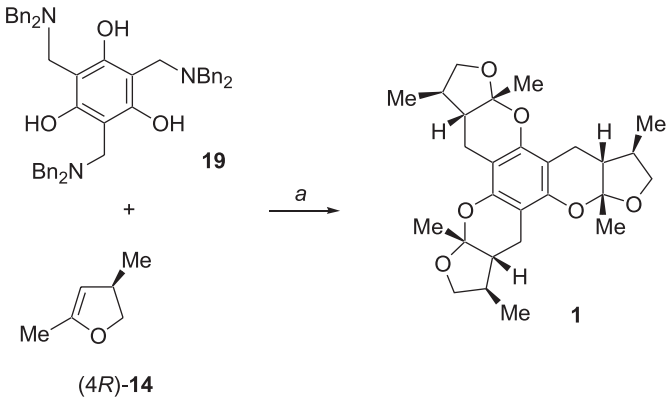
Scheme 5. Synthesis of (+)-xyloketal D (*ent*-**4**), *ent*-2,6-*epi*-xyloketal D (*ent*-**15**), and the diastereomeric spiroacetals *ent*-**16** and *ent*-**17**. Reagents and conditions: (*a*) dihydrofuran (4*S*)-**14** (3 equiv.), MeI (1 equiv.), benzene, reflux, 6 days, 46% (*ent*-**4**, *ent*-**15**, *ent*-**16** and *ent*-**17** (13:1:3:3)) *or* dihydrofuran (4*S*)-**14** (3 equiv.), Me_2SO_4 (1 equiv.), benzene, reflux, 3 days, 36% (*ent*-**4**, *ent*-**15**, *ent*-**16**, and *ent*-**17** (20:1:3:3)).



that the synthetic material was enantiomerically pure.[10] The melting point of synthetic (–)-xyloketal D (**4**) (71–73 °C) was, however, significantly lower than that reported for the natural product (111–113 °C). We were unable to increase the melting point of our synthetic material by repeated recrystallization from petroleum ether. Krohn et al. (13*b*) have reported that synthetic (–)-xyloketal D (**4**) (93% ee calculated from optical rotation and 93% ee based on the enantiomeric purity of a synthetic precursor) also had a lower melting point (87 °C, ether–pentane). They also reported that subsequent recrystallization from ether–pentane afforded the natural product, which had a melting point of 110 to 111 °C. We have also recrystallized our synthetic material from this solvent system. However, in our hands this procedure did not increase the melting point. We have concluded that our sample is either contaminated with a trace amount of the enantiomer, which has significantly depressed the melting point, or that we have isolated the natural product in a different crystal form.[13]

The Mannich base **7** was also reacted with the chiral nonracemic dihydrofuran (4*S*)-**14** using the two procedures described previously (Scheme 5). These reactions afforded mixtures of (+)-xyloketal D (*ent*-**4**), *ent*-2,6-*epi*-xyloketal D (*ent*-**15**), and the diastereomeric spiroacetals *ent*-**16** and *ent*-**17**. A diastereomerically and analytically pure sample of the enantiomeric natural product, (+)-xyloketal D (*ent*-**4**), was also prepared and fully characterized following repeated chromatography and recrystallization.

Scheme 6. Attempted synthesis of (–)-xyloketal A (**1**). Reagents and conditions: (*a*) dihydrofuran (4*R*)-**14** (9 equiv.), MeI (3 equiv.), benzene, reflux, or dihydrofuran (4*R*)-**14** (9 equiv.), Me_2SO_4 (3 equiv.), benzene, reflux.



The total synthesis of (–)-xyloketal A (**1**) was also attempted (Scheme 6). The Mannich base **19** and a large excess of the chiral nonracemic dihydrofuran (4*R*)-**14** were heated in benzene at reflux with methyl iodide and with dimethyl sulfate.[14] The natural product was not isolated from the complex mixtures of products that were produced in these reactions.

It was anticipated that the stereochemistry of this attempted cycloaddition reaction would have been directed efficiently by the C4-methyl substituent of the chiral nonracemic dihydrofuran (4*R*)-**14**. However, it appears that the competing isomerization reaction of the dihydrofuran (4*R*)-**14** and the subsequent nonstereoselective cycloaddition reaction of the exocyclic dihydrofuran (4*R*)-**13** is a dominant complicating factor.

Conclusions

The racemic carboxylic acid (±)-**11** was resolved by the chromatographic separation of the corresponding diastereomeric amides **23** and **24** that were prepared from (*R*)-phenylglycinol (**22**). The absolute stereochemistry and the enantiomeric purity of the chiral nonracemic carboxylic acid (2*R*)-**11** were determined by conversion to the benzyl ether (2*R*)-**25**, which had been prepared previously from a chiral pool starting material. The total synthesis of (–)-xyloketal D (**4**) and its enantiomer were completed from the chiral nonracemic dihydrofurans (4*R*)-**14** and (4*S*)-**14**. These dihydrofurans, which were prepared in three steps from the carboxylic acids (2*R*)-**11** and (2*S*)-**11**, were reacted with an appropriately functionalized *ortho*-quinone methide **9** that was generated from the Mannich base **7**. These results confirmed the absolute stereochemistry of the natural product that was reported by Lin and co-workers (1, 13). The synthesis of (–)-xyloketal A (**1**) from the chiral nonracemic dihydrofuran (4*R*)-**14** and the Mannich base **19** was unsuccessful. Thus, alternative synthetic routes are actively being

[13]Professor Krohn has informed us that he has recently checked the melting point of a sample of natural (–)-xyloketal D (**4**), which was kindly provided by Professor Lin, and found it to be 107 to 108 °C (Büchi SMP-20 melting point apparatus).
[14]We have previously reported full experimental procedures for the preparation of Mannich base **19**. See ref. 3.

pursued to complete the total synthesis of this unique and biologically relevant natural product.

Experimental section

For general experimental details refer to the supplementary material.[10]

(2*R*)-*N*-[(1*R*)-1-Phenyl-2-hydroxyethyl]-2-methyl-4-pentynamide (23) and (2*S*)-*N*-[(1*R*)-1-phenyl-2-hydroxyethyl]-2-methyl-4-pentynamide (24)

To a solution of the racemic carboxylic acid (±)-**11** (3) (5.40 g, 48.2 mmol) in dichloromethane (100 mL) at 0 °C were added oxalyl chloride (5.5 mL, 58 mmol) and *N*,*N*-dimethylformamide (2 drops). The resultant solution was allowed to warm to room temperature over 2 h and then was concentrated in vacuo to afford the corresponding acid chloride. A solution of this acid chloride in dichloromethane (50 mL) was then added to a stirred solution of (*R*)-phenylglycinol (**22**) (6.60 g, 48.2 mmol) and triethylamine (8.0 mL, 58 mmol) in dichloromethane (150 mL) at 0 °C. The resultant solution was allowed to warm to room temperature over 16 h and then water (50 mL) was added. The reaction mixture was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. Purification by flash chromatography using petroleum ether – ethyl acetate (1:2) as the eluant afforded the title compounds **23** (4.01 g, 36%) and **24** (3.82 g, 34%) as white solids. Amide **23**: R_f = 0.37 (petroleum ether – ethyl acetate, 1:2), mp 78–82 °C, petroleum ether – ethyl acetate. $[\alpha]_D^{24}$ = –63 (*c* 1.31, $CHCl_3$). IR (ef, cm^{-1}): 3314, 3286, 2936, 1650, 1544, 1052, 758, 702. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.25 (d, *J* = 6.5 Hz, 3H), 2.07 (t, *J* = 2.6 Hz, 1H), 2.30 (broad s, 1H), 2.38 (m, 1H), 2.51 (m, 2H), 3.91 (d, *J* = 4.6 Hz, 2H), 5.10 (dt, *J* = 7.0, 4.8 Hz, 1H), 6.32 (broad d, *J* = 4.9 Hz, 1H), 7.34 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 17.1, 23.1, 40.4, 55.6, 66.2, 70.2, 82.1, 126.6, 127.7, 128.7, 138.9, 175.0. MS (CI) *m*/*z* (rel. intensity): 232 (M + H, 100). Anal. calcd. for $C_{14}H_{17}NO_2$: C 72.70, H 7.41, N 6.06; found: C 72.86, H 7.35, N 5.87. Amide **24**: R_f = 0.27 (petroleum ether – ethyl acetate, 1:2), mp 90–93 °C, petroleum ether – ethyl acetate. $[\alpha]_D^{23}$ = –33 (*c* 0.80, $CHCl_3$). IR (ef, cm^{-1}): 3282, 2938, 1645, 1545, 1038, 699. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.29 (d, *J* = 6.7 Hz, 3H), 2.01 (t, *J* = 2.7 Hz, 1H), 2.25 (broad s, 1H), 2.39 (ddd, *J* = 15.8, 6.2, 2.8 Hz, 1H), 2.51 (m, 2H), 3.90 (m, 2H), 5.08 (dt, *J* = 6.8, 4.8 Hz, 1H), 6.37 (d, *J* = 4.3 Hz, 1H), 7.32 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 17.2, 23.1, 40.4, 55.8, 66.4, 70.4, 82.0, 126.7, 127.8, 128.8, 138.8, 175.1. MS (CI) *m*/*z* (rel. intensity): 232 (M + H, 100). Anal. calcd. for $C_{14}H_{17}NO_2$: C 72.70, H 7.41, N 6.06; found: C 72.45, H 7.54, N 5.77.

(2*R*)-2-Methylpent-4-ynoic acid ((2*R*)-11)

To a solution of the amide **23** (5.44 g, 23.5 mmol) in *p*-dioxane (60 mL) at room temperature was added sulfuric acid (3 mol L^{-1}, 60 mL). The resultant solution was heated at reflux for 7 h and then was cooled to 0 °C. The reaction mixture was basified to pH ~10 with an aqueous solution of sodium hydroxide (50 wt. %), then diluted with water (50 mL) and extracted with dichloromethane (3 × 50 mL). The aqueous layer was acidified to pH ~2 with sulfuric acid (3 mol L^{-1}) and then extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by distillation at reduced pressure afforded the title compound (2*R*)-**11** (2.01 g, 76%) as a colourless oil. R_f = 0.48 (hexanes – ethyl acetate, 1:2), bp 103–106 °C, 5 mmHg (1 mmHg = 133.322 Pa) (lit. value (9) bp 106.5–109.5 °C, 14–15 mmHg (1 mmHg = 133.322 4 Pa)) for the racemic carboxylic acid (±)-**11**)). $[\alpha]_D^{20}$ = +6.5 (*c* 1.50, $CHCl_3$). All other spectroscopic data were identical to those reported for the racemic carboxylic acid (±)-**11**.[10]

(2*S*)-2-Methylpent-4-ynoic acid ((2*S*)-11)

The title compound (2*S*)-**11** (1.91 g, 86%) as a colourless oil was also prepared from the corresponding amide **24** (4.56 g, 19.7 mmol). $[\alpha]_D^{20}$ = –6.1 (*c* 1.52, $CHCl_3$). All other spectroscopic data were identical to those reported for the racemic carboxylic acid (±)-**11**.[10]

(2*R*)-2-Methylpent-4-yn-1-ol ((2*R*)-12)

To a suspension of lithium aluminum hydride (0.79 g, 20.8 mmol) in tetrahydrofuran (35 mL) at 0 °C was added a solution of the carboxylic acid (2*R*)-**11** (1.17 g, 10.4 mmol) in tetrahydrofuran (10 mL) and the resultant suspension was stirred at room temperature for 16 h. Water (0.8 mL), an aqueous solution of sodium hydroxide (2 mol L^{-1}, 0.8 mL), and water (2.4 mL) were then added in succession and the resultant mixture was filtered. The filter cake was rinsed with ether (100 mL) and the combined organic filtrates were concentrated in vacuo. Purification by distillation at reduced pressure afforded the title compound (2*R*)-**12** (0.91 g, 89%) as a colourless oil. R_f = 0.55 (hexanes – ethyl acetate, 1:2), bp 61–66 °C, ~20 mmHg (1 mmHg = 133.322 4 Pa) (lit. value (9) bp 64–64.5 °C, 10 mmHg (1 mmHg = 133.322 4 Pa) (for the racemic alcohol (±)-**12**)). $[\alpha]_D^{20}$ = +10.9 (*c* 1.10, $CHCl_3$). IR (ef, cm^{-1}): 3409, 2961, 2922, 1641, 2117, 1461, 1430, 1037, 651. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.01 (d, *J* = 6.9 Hz, 3H), 1.56 (broad s, 1H), 1.90 (m, 1H), 1.98 (t, *J* = 2.7 Hz, 1H), 2.21 (ddd, *J* = 16.8, 6.4, 2.7 Hz, 1H), 2.29 (ddd, *J* = 16.8, 6.2, 2.7 Hz, 1H), 3.59 (d, *J* = 6.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 16.0, 22.2, 34.8, 66.8, 69.6, 82.6. MS (CI) *m*/*z* (rel. intensity): 99 (M + H, 100).

(2*R*)-Benzyl-(2-methylpent-4-ynyl) ether ((2*R*)-25)

To a suspension of sodium hydride (60 wt. % in mineral oil, 81.3 mg, 2.03 mmol, prewashed with hexanes) in *N*,*N*-dimethylformamide (4.0 mL) at 0 °C were added a solution of the alcohol (2*R*)-**12** (181 mg, 1.85 mmol) in tetrahydrofuran (1 mL) and benzyl bromide (230 µL, 1.93 mmol). The resultant mixture was stirred at room temperature for 6 h. The reaction mixture was then diluted with ether (10 mL) and washed with water (3 × 10 mL) and brine (10 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes–ether (50:1) as the eluant afforded the title compound (2*R*)-**25** (313 mg, 90%) as a colourless oil. R_f = 0.77 (hexanes–ether, 4:1). $[\alpha]_D^{20}$ = +16.1 (*c* 1.40, $CHCl_3$) (lit. value (18*a*) $[\alpha]_D^{20}$ = +16 (*c* 1.20,

$CHCl_3$) and lit. value (18*b*) $[\alpha]_D^{20}$ = +16.3 (*c* 0.95, $CHCl_3$)). IR (ef, cm^{-1}): 3289, 3031, 2857, 2117, 1609, 1496, 1454, 1112, 749. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.03 (d, *J* = 6.8 Hz, 3H), 1.95 (t, *J* = 2.6 Hz, 1H), 2.02 (m, 1H), 2.21 (ddd, *J* = 16.7, 6.9, 2.6 Hz, 1H), 2.35 (ddd, *J* = 16.7, 5.5, 2.7 Hz, 1H), 3.39 (d, *J* = 6.5 Hz, 2H), 4.52 (s, 2H), 7.33 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 16.3, 22.5, 32.8, 69.3, 73.0, 74.1, 82.7, 127.48, 127.51, 128.3, 138.5. MS (CI) *m*/*z* (rel. intensity): 189 (M + H, 78), 171 (17), 111 (M – Ph, 100).

(2*S*)-2-Methylpent-4-yn-1-ol ((2*S*)-12)

The title compound (2*S*)-**12** (1.17 g, 85%) as a colourless oil was also prepared from the corresponding carboxylic acid (2*S*)-**11** (1.57 g, 14.0 mmol). $[\alpha]_D^{20}$ = –11.1 (*c* 1.83, $CHCl_3$). All other spectroscopic data were identical to those reported for the enantiomeric alcohol (2*R*)-**12**.

(2*S*)-Benzyl-(2-methylpent-4-ynyl) ether ((2*S*)-25)

The title compound (2*S*)-**25** (248 mg, 90%) as a colourless oil was also prepared from the corresponding alcohol (2*S*)-**12** (144 mg, 1.47 mmol). $[\alpha]_D^{20}$ = –15.9 (*c* 1.05, $CHCl_3$). All other spectroscopic data were identical to those reported for the enantiomeric ether (2*R*)-**25**.

(4*R*)-4,5-Dihydro-2,4-dimethylfuran ((4*R*)-14)

The alcohol (2*S*)-**12** (0.91 g, 9.28 mmol) and sodium amide (50 mg, 1.28 mmol) were heated, without solvent, at reflux for 2 h. Direct distillation of the reaction mixture at atmospheric pressure afforded the exocyclic dihydrofuran (4*R*)-**13** and a small amount of the endocyclic dihydrofuran (4*R*)-**14** as a colourless oil. ^1H NMR (500 MHz, C_6D_6, ~90% pure) δ: 0.58 (d, *J* = 6.2 Hz, 3H), 1.80 (m, 2H), 2.27 (m, 1H), 3.27 (dd, *J* = 8.1, 6.5 Hz, 1H), 3.77 (dd, *J* = 8.1, 6.0 Hz, 1H), 3.92 (m, 1H), 5.46 (m, 1H). This material was heated at reflux for 2 h and then distilled at atmospheric pressure to afford the title compound (4*R*)-**14** (0.40 g, 44%) as a colourless oil, bp 97–103 °C, ~760 mmHg (1 mmHg = 133.322 4 Pa) (lit. value (3) bp ~100 °C, ~760 mmHg (1 mmHg = 133.322 4 Pa) for the racemic dihydrofuran (±)-**14**)). $[\alpha]_D^{24}$ = +11.8 (*c* 0.82, $CHCl_3$). IR (ef, cm^{-1}): 2961, 2875, 1674, 1453, 1383, 1243, 1043, 1008, 886. ^1H NMR (400 MHz, C_6D_6) δ: 0.86 (d, *J* = 6.6 Hz, 3H), 1.68 (apparent t, *J* = 1.5 Hz, 3H), 2.76 (m, 1H), 3.71 (dd, *J* = 8.7, 6.5 Hz, 1H), 4.21 (dd, *J* = 9.5, 8.6 Hz, 1H), 4.43 (m, 1H). ^{13}C NMR (101 MHz, C_6D_6) δ: 13.6, 20.9, 37.9, 77.2, 101.4, 155.0. MS (CI) *m*/*z* (rel. intensity): 99 (M + H, 100).

(4*S*)-4,5-Dihydro-2,4-dimethylfuran ((4*S*)-14)

The title compound (4*S*)-**14** (0.42 g, 36%) as a colourless oil was also prepared from the corresponding alcohol (2*S*)-**12** (1.17 g, 11.9 mmol). $[\alpha]_D^{20}$ = –12 (*c* 0.44, $CHCl_3$). All other spectroscopic data were identical to those reported for the enantiomeric dihydrofuran (4*R*)-**14**.

(–)-Xyloketal D (4), 2,6-*epi*-xyloketal D (15), and the diastereomeric spiroacetals (16) and (17)

Method A

To a solution of the dihydrofuran (4*R*)-**14** (295 mg, 3.01 mmol) in benzene (10 mL) at room temperature were added the Mannich base **7** (251 mg, 1.00 mmol) and methyl iodide (65.0 μL, 1.05 mmol). The resultant solution was then heated at reflux until the Mannich base **7** had completely reacted (8 days, TLC analysis). The reaction mixture was then cooled to room temperature, filtered, and concentrated in vacuo. Purification by flash chromatography using dichloromethane as the eluant afforded a mixture (8:1:2:2) of (–)-xyloketal D (**4**), 2,6-*epi*-xyloketal D (**15**), and the diastereomeric spiroacetals **16** and **17** (105 mg, 40%) as a yellow solid. Repeated flash chromatography using hexanes–ether (4:1) as the eluant on TLC grade silica gel (5–25 μm) afforded a mixture (20:1) of (–)-xyloketal D (**4**) and 2,6-*epi*-xyloketal D (**15**) as a pale cream solid and a separate mixture (4:5) of the two diastereomeric spiroacetals **16** and **17** as a pale cream solid. An analytically pure sample of synthetic (–)-xyloketal D (**4**), as pale pink prisms, was prepared by recrystallization from petroleum ether. An analytically pure sample of a mixture (4:5) of the diastereomeric spiroacetals **16** and **17**, as white needles, was also prepared by recrystallization from petroleum ether.

Method B

To a solution of the dihydrofuran (4*R*)-**14** (121 mg, 1.23 mmol) in benzene (5 mL) at room temperature were added the Mannich base **7** (103 mg, 0.41 mmol) and dimethyl sulfate (41 μL, 0.43 mmol). The resultant solution was heated at reflux until the Mannich base **7** had completely reacted (3 days, TLC analysis). The reaction mixture was then cooled to room temperature and decanted. The remaining solid residue was extracted with dichloromethane (3 × 5 mL) and the combined organic extracts were concentrated in vacuo. Purification by flash chromatography using dichloromethane–ether (19:1) as the eluant afforded a mixture (16:1:4:4) of (–)-xyloketal D (**4**), 2,6-*epi*-xyloketal D (**15**), and the diastereomeric spiroacetals **16** and **17** (40 mg, 37%) as a yellow solid. (–)-Xyloketal D **4**: R_f = 0.24 (hexanes–ether, 4:1), mp 71–73 °C as pale pink prisms from petroleum ether (lit. value (1) mp 111–113 °C) and mp 68–70 °C as white crystals on recrystallization from ether–pentane (lit. value (13) mp 110 to 111 °C, ether–pentane). $[\alpha]_D^{20}$ = –110.1 (*c* 0.102, $CHCl_3$) (lit. value (1) $[\alpha]_D^{25}$ = –119.5 (*c* 0.113, $CHCl_3$)). IR (ef, cm^{-1}): 3399, 2967, 2927, 2884, 1620, 1491, 1421, 1382, 1370, 1332, 1272, 1117, 1070, 1006. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.07 (d, *J* = 6.5 Hz, 3H), 1.53 (s, 3H), 1.98 (ddd, *J* = 11.3, 6.5, 1.1 Hz, 1H), 2.08 (m, 1H), 2.55 (s, 3H), 2.72 (dd, *J* = 17.9, 6.5 Hz, 1H), 2.97 (d, *J* = 18.0, 1H), 3.57 (apparent t, *J* = 8.4 Hz, 1H), 4.20 (apparent t, *J* = 8.3 Hz, 1H), 6.36 (d, *J* = 8.9 Hz, 1H), 7.52 (d, *J* = 8.9 Hz, 1H), 13.12 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 15.8, 18.0, 22.7, 26.1, 35.1, 47.0, 74.3, 106.2, 108.3, 108.8, 113.1, 130.0, 159.5, 162.9, 202.6. MS (CI) *m*/*z* (rel. intensity): 263 (M + H, 100). Anal. calcd. for $C_{15}H_{18}O_4$: C 68.68, H 6.92; found: C 68.52, H 6.98. Diastereomeric spiroacetals **16** and **17** (4:5 mixture): R_f = 0.32 (hexanes–ether, 4:1), mp 60 to 61 °C, petroleum ether. $[\alpha]_D^{20}$ = +26.9 (*c* 0.71, $CHCl_3$). IR (ef, cm^{-1}): 3423, 2958, 2878, 1626, 1488, 1419, 1369, 1331, 1270, 1247, 1136, 1060, 1018, 853. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.10 (d, *J* = 6.6 Hz, 3H), 1.18 (d, *J* = 6.6 Hz, 3H), 1.55 (dd, *J* = 12.8, 9.5 Hz, 1H), 2.00 (m, 5H), 2.27 (dd, *J* = 13.4, 9.4, 1H), 2.36 (dd, *J* = 12.9, 7.3, 1H), 2.46 (m, 1H), 2.54 (s, 3H), 2.55 (s, 3H), 2.78 (m, 5H),

3.54 (t, *J* = 7.7 Hz, 1H), 3.64 (t, *J* = 8.4 Hz, 1H), 4.09 (t, *J* = 7.9 Hz, 1H), 4.21 (t, *J* = 7.9 Hz, 1H), 6.34 (d, *J* = 8.9 Hz, 1H), 6.37 (d, *J* = 9.0 Hz, 1H), 7.50 (d, *J* = 8.9 Hz, 1H), 7.51 (d, *J* = 8.9 Hz, 1H), 13.01 (s, 1H), 13.02 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 16.3, 16.5, 17.6, 18.0, 26.2, 29.3, 29.6, 31.9, 33.0, 45.2, 45.3, 75.0, 75.4, 108.1, 108.9, 109.0, 110.0, 110.1, 113.16, 113.24, 129.58, 129.62, 159.6, 162.2, 202.7, 202.8. MS (CI) *m/z* (rel. intensity): 263 (M + H, 100), 111 (12). Anal. calcd. for $C_{15}H_{18}O_4$: C 68.68, H 6.92; found: C 68.58, H 6.99.

ent-Xyloketal D (*ent*-4), *ent*-2,6-*epi*-xyloketal D (*ent*-15), and the diastereomeric spiroacetals (*ent*-16) and (*ent*-17)

Method A

A solution of the dihydrofuran (4*S*)-**14** (237 mg, 2.42 mmol), the Mannich base **7** (202 mg, 0.804 mmol), and methyl iodide (52 µL, 0.84 mmol) in benzene (8 mL) was heated at reflux for 6 days. Isolation and purification of the reaction products, as described previously, afforded a mixture (13:1:3:3) of *ent*-xyloketal D (*ent*-**4**), *ent*-2,6-*epi*-xyloketal D (*ent*-**15**), and the diastereomeric spiroacetals *ent*-**16** and *ent*-**17** (96 mg, 46%) as a yellow solid. Additional purification and recrystallization of these reaction products, as described previously, afforded an analytically pure sample of *ent*-xyloketal D (*ent*-**4**) as pale pink prisms and an analytically pure mixture (4:5) of the diastereomeric spiroacetals *ent*-**16** and ent-**17** as white needles.

Method B

The procedure described in the previous section was also used to prepare a mixture (20:1:3:3) of *ent*-xyloketal D (*ent*-**4**), *ent*-2,6-*epi*-xyloketal D (*ent*-**15**), and the diastereomeric spiroacetals *ent*-**16** and *ent*-**17** (64 mg, 36%) as a yellow solid. *ent*-Xyloketal D (*ent*-**4**): mp 70 to 71 °C as pale pink crystals from petroleum ether and mp 68–71 °C as white crystals from ether–pentane. $[\alpha]_D^{20}$ = +113.1 (*c* 0.122, $CHCl_3$). All other spectroscopic data were identical to those reported previously for (–)-xyoketal D (**4**). Diastereomeric spiroacetals *ent*-**16** and *ent*-**17** (4:5): mp 59–61 °C, petroleum ether. $[\alpha]_D^{20}$ = –26.7 (*c* 1.05, $CHCl_3$). All other spectroscopic data were consistent with that reported for the diastereomeric spiroacetals **16** and **17**.

Acknowledgments

We are grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC) and Simon Fraser University (SFU) for financial support. We also wish to acknowledge the Canadian Foundation for Innovation (CFI) and AstraZeneca Canada Inc. for support of our research program. J.D.P. thanks SFU for an entrance scholarship and NSERC for a PGSA award. We thank Mr. Jason A. Bexrud for preliminary investigations. We are also grateful to Professor Yongcheng Lin for kindly providing a copy of the ^{1}H NMR spectrum of xyloketal D (**4**) for comparison purposes.

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