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Synthesis of Modified Methyl Furanosides by Intramolecular Oxa-Michael Reaction followed by Pummerer Rearrangement

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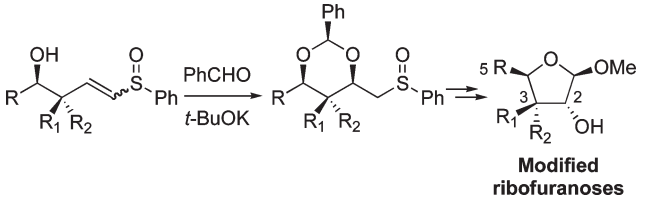


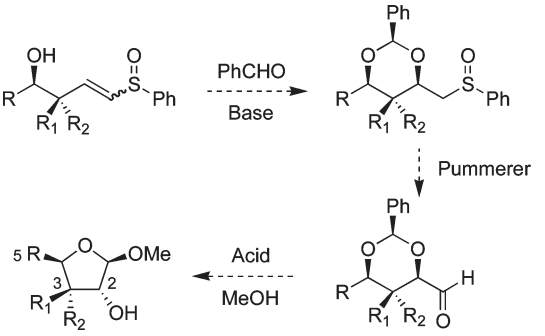
A new method is described for the synthesis of ribofuranoses modified at the C3 and C5 positions. The key step is an intramolecular oxa-Michael reaction on a vinyl sulfoxide to install the C2 hydroxy group. The methyl furanosides are obtained by Pummerer rearrangement of the sulfoxide into the corresponding aldehyde, acidic deprotection of the benzylidene acetal, and cyclization.

Viral infections and cancers constitute major health problems worldwide. With the emergence of new viruses and the development of drug resistance, the need for new therapeutic agents is continuously increasing. Nucleoside analogues play an extremely important role in the fight against viruses, especially human immunodeficiency virus (HIV), hepatitis C virus (HCV), or herpes simplex virus (HSV). So far, more than 40 antiviral drugs belong to this class of compounds, including 24 for the therapy of HIV infections,[1] so their synthesis has attracted the attention of numerous chemists.[2] In addition, nucleoside analogues have been successfully used in the treatment of various tumors.[3] The most common access to these compounds involves modifications of naturally occurring nucleosides.[4]

We report here a new method for the construction of ribofuranoses with modifications at the 3- and 5-positions (Scheme 1) that could be converted to original nucleoside analogues not readily available by classical synthetic routes.

(1) De Clercq, E. *Nat. Rev. Drug. Discov.* **2007**, *6*, 1001.
(2) Ichikawa, E.; Kato, K. *Curr. Med. Chem.* **2001**, *8*, 385.
(3) Matsuda, A.; Sasaki, T. *Cancer Sci.* **2004**, *95*, 105.
(4) Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745.

SCHEME 1. Synthesis of Methyl Furanosides from Vinyl Sulfoxides



The hydroxy group at C2 would be installed diastereoselectively by an intramolecular conjugate addition of a hemiketal alkoxide, made in situ from a homoallylic alcohol in the presence of base and excess benzaldehyde, to a vinyl sulfoxide.[5] The sulfoxide moiety would then be converted to the corresponding aldehyde by Pummerer rearrangement and the unnatural methyl furanoside obtained by acidic deprotection of the benzylidene acetal and cyclization in methanol.

We first embarked on the synthesis of 3-deoxyribofuranoses ($R_1 = R_2 = H$, Scheme 1). The required substrates for the oxa-Michael key step could not be prepared efficiently by cross-metathesis of the corresponding homoallylic alcohols with phenyl vinyl sulfoxide, as described by Grela and co-workers.[6] Cross-metathesis of the homoallylic alcohols with phenyl vinyl sulfide was also unsuccessful.[7] We thus resorted to a two-step sequence from homopropargylic alcohols **1a**−**c** (Scheme 2). Radical addition of thiophenol to these compounds,[8] followed by oxidation of the resulting sulfides with sodium periodate,[9] furnished sulfoxides **2a**−**c** in good overall yields.[10]

The key intramolecular conjugate addition required four additions of 1.1 equiv of benzaldehyde and a substoichiometric amount of potassium *tert*-butoxide (0.1 equiv) for complete conversion (Scheme 3).[11] Benzylidene acetals **3a**−**c** were formed with excellent diastereoselectivity in favor of the *syn* isomer[12] (R being linear, branched, or oxygenated). The

(5) For a similar reaction with unsaturated esters, see: Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446. With vinyl sulfones, see: (a) Grimaud, L.; Rotulo, D.; Ros-Perez, R.; Guitry-Azam, L.; Prunet, J. *Tetrahedron Lett.* **2002**, *43*, 7477. (b) Rotulo-Sims, D.; Prunet, J. *Org. Lett.* **2007**, *9*, 4147.
(6) Michrowska, A.; Bieniek, M.; Kim, M.; Klajn, R.; Grela, K. *Tetrahedron* **2003**, *59*, 4525. The best yield for the cross-metathesis leading to **2a** was 18% in the presence of 2 mol % of Grubbs 2 catalyst and 0.3 equiv of titanium tetraisopropoxide. Complete conversion for this reaction was only observed with a full equivalent of the ruthenium catalyst.
(7) For a successful ROM/CM cascade with phenyl vinyl sulfide, see: Katayama, H.; Urushima, H.; Nishioka, T.; Wada, C.; Nagao, M.; Ozawa, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 4513.
(8) Griesbaum, K. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 273.
(9) Leonard, N. J.; Johnson, C. R. *J. Org. Chem.* **1962**, *27*, 282.
(10) Throughout this study, sulfoxides were obtained as a 1:1 mixture of *E*/*Z* isomers and a 1:1 mixture of diastereomers at the sulfur center.
(11) Oxa-Michael reaction of sulfoxide **2a** with benzaldehyde and KHMDS furnished **3a** in 55% yield.
(12) The *syn* stereochemistry was proven by NOE experiments performed on benzylidene acetal **3c**.

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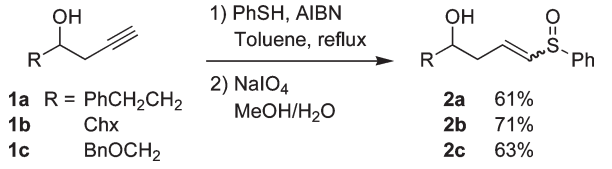
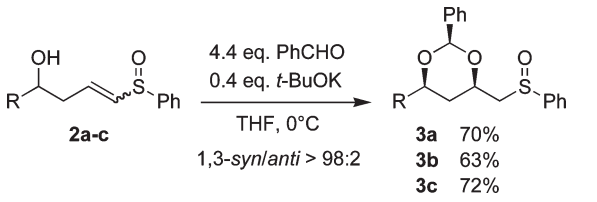
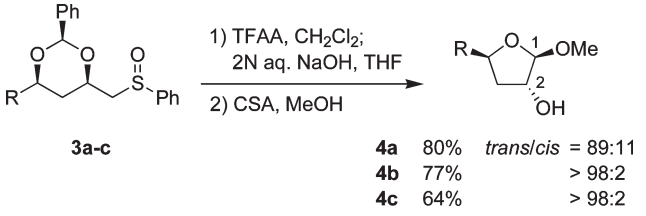
SCHEME 2. Synthesis of Vinyl Sulfoxides 2a−c



SCHEME 3. Oxa-Michael Reaction of Vinyl Sulfoxides 2a−c



SCHEME 4. Synthesis of Methyl 3-Deoxyfuranosides 4a−c

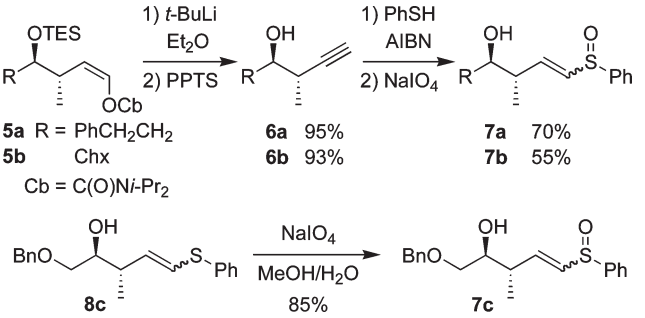


stereogenicity of the sulfoxide has no notable influence on the selectivity of the oxa-Michael reaction, but the *Z* sulfoxides react slower than the *E* isomers.[13]

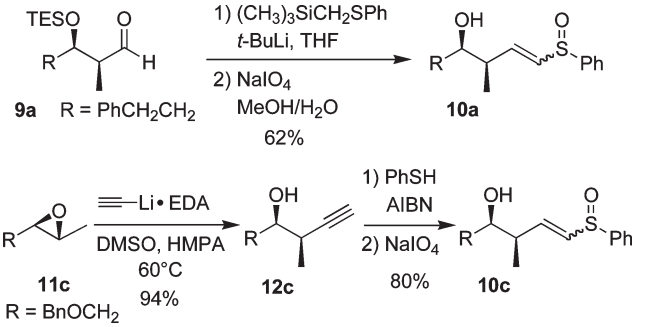
For the conversion of protected diols **3a−c** into the ribofuranose derivatives **4a−c** (Scheme 4), Pummerer rearrangement[14] must be performed prior to the hydrolysis of the benzylidene acetal. This rearrangement was not effective on the sulfoxide compounds bearing the free diol. Acidic cyclization in methanol of the unpurified aldehyde intermediates then led to methyl 3-deoxyfuranosides **4a−c** in good yields and good to excellent selectivity in favor of the 1,2-*trans* isomer.[15] Compound **4c** (R = $BnOCH_2$), a protected form of 3-deoxyribofuranose, is a precursor of cordycepin (3′-deoxyadenosine), which has been reported to present antitumoral[16] and antiviral activities.[17]

Once this new method had been validated for the construction of 3-deoxyribofuranose analogues, we turned our attention to the synthesis of 3-substituted sugar derivatives (R_1 or R_2 = Me, Scheme 1). The required vinyl sulfoxide precursors of these furanoses bear a substituent at the allylic position, and we first prepared 1,2-*anti* alcohols **7**

SCHEME 5. Synthesis of 1,2-*Anti* Alcohols 7a−c



SCHEME 6. Synthesis of 1,2-*Syn* Alcohols 10a,c



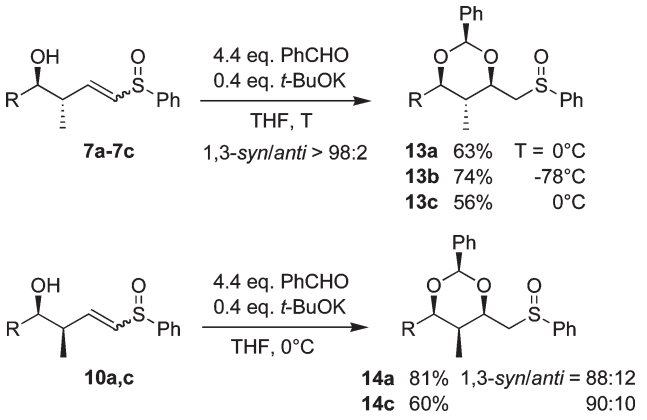
(Scheme 5). Silyl ethers **5a**,**b** were obtained by protection of the corresponding known Hoppe homoaldol adducts.[18] Fritsch−Buttenberg−Wiechel[19] rearrangement of the resulting vinyl carbamates to the alkynes followed by hydrolysis of the triethylsilyl ethers by pyridinium *p*-toluenesulfonate in MeOH/water gave homopropargylic alcohols **6a**,**b** in excellent overall yields. Finally, sulfoxides **7a**,**b** were obtained as before by radical addition of thiophenol to **6a**,**b** and sodium periodate oxidation of the resulting sulfides.[10] Fritsch−Buttenberg−Wiechel rearrangement of compound **6c** (R = $BnOCH_2$) only led to decomposition products, so sulfoxide **7c** was prepared by $NaIO_4$ oxidation of known alcohol **8c**.[20,10]

We also synthesized 1,2-*syn* alcohols **10a**,**c** (Scheme 6). Vinyl sulfoxide **10a** was made by Peterson olefination[21] of known aldehyde **9a**,[22] followed by $NaIO_4$ oxidation of the resulting vinyl sulfide.[10] Compound **10c** was more conveniently prepared via alkyne **12c** (Scheme 6). Known epoxide **11c**[23] was opened by lithium−acetylide complex in a mixture of DMSO and HMPA to furnish homopropargylic alcohol **12c** in excellent yield and with total regioselectivity.[24] Subsequent transformation of **12c** into **10c** was effected as previously shown in Schemes 2 and 5.[10]

The oxa-Michael reaction was then studied with substrates **7a−c** (Scheme 7). Benzylidene acetals **13a−c** were produced with excellent diastereoselectivity in favor of the 1,3-*syn* diastereomers. In the case of vinyl sulfoxide **7b**, when

(13) Recovered vinyl sulfoxides from incomplete conjugate addition reactions were enriched in *Z* diasteromers.
(14) Feldman, K. S. *Tetrahedron* **2006**, *62*, 5003.
(15) The trans stereochemistry was assigned by comparison of the ^1H NMR spectrum of **4c** (known compound) with the literature data: Jones, M. F.; Noble, S. A.; Robertson, C. A.; Storer, R.; Highcock, R. M.; Lamont, R. B. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1427.
(16) Nakamura, K.; Yoshikawa, N.; Yamaguchi, K; Kagota, S.; Shinozuka, K.; Kinutomo, M. *Anticancer Res.* **2006**, *26*, 43.
(17) Luo, G. X.; Hamatake, R. K.; Racela, J.; Rigat, K. L.; Lemm, J.; Colonno, R. J. *J. Virol.* **2000**, 851.
(18) (a) Kalkofen, R.; Brandau, S.; Wibbeling, B.; Hoppe, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 6667. (b) Risatti, C. A.; Taylor, R. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 6671.
(19) Férézou, J.-P.; Julia, M.; Li, Y.; Liu, L. W.; Pancrazi, A. *Bull. Soc. Chim. Fr.* **1995**, *132*, 428.
(20) This alcohol was synthesized by regio- and diastereoselective addition of the anion of crotyl phenyl sulfide to benzyloxyacetaldehyde; see: Gamba-Sanchez, D.; Oriez, R.; Prunet, J. *Tetrahedron Lett.* **2009**, *50*, 883.
(21) Chen, F.; Mudryk, B.; Cohen, T. *Tetrahedron* **1999**, *55*, 3291.
(22) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1999**, *64*, 5201.
(23) Fuganti, C.; Grasseli, P.; Sevi, S.; Zirotti, C. *Tetrahedron Lett.* **1982**, *23*, 4269.
(24) Parker, K. A.; Chang, W. *Org. Lett.* **2005**, *7*, 1785.

SCHEME 7. Oxa-Michael Reaction of Vinyl Sulfoxides 7a−c and 10a,c



the reaction was performed at 0 °C, only decomposition was observed. However, we were pleased to see that at −78 °C, **13b** was obtained in good yield with the same selectivity.

The same reaction conditions were applied to **10a** and **10c** (Scheme 7). In this case, the 1,3-*syn* selectivity for **14a** and **14c** is slightly eroded because the methyl group in the 1,3-*syn* isomer occupies an axial position and is equatorial in the 1,3-*anti* isomer, which lowers the energy difference between these two isomers.

Benzylidene acetals **13** and **14** were converted to the corresponding methyl furanosides **15** and **16** by Pummerer rearrangement to the corresponding aldehydes followed by acidic treatment in the presence of methanol (Table 1), under the conditions described in Scheme 4. The 1,2-*trans* product is the major diastereomer for compounds **15** (R_1 = H, R_2 = Me), with the methoxy substituent *trans* to both the OH at C2 and the Me group at C3. In the case of acetals **16** (R_1 = Me, R_2 = H), the OH and the Me groups are on opposite faces, so these products are formed as 1:1 mixtures of 1,2-*trans* and 1,2-*cis* isomers.

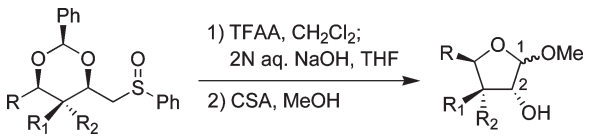
Furanoses similar to **15c** and **16c** (R = $BnOCH_2$) have been synthesized from xylose,[25] but all the other ketals reported here are not readily available by known modifications of natural sugars. Variation of the R, R_1, and R_2 groups would easily lead to a large number of unnatural ribofuranoses (Table 1).

In conclusion, we have developed a short and efficient methodology for the synthesis of ribofuranoses modified at the C3 and C5 positions. A diastereoselective oxa-Michael reaction is employed to install the hydroxy group at C2, and the ribofuranose analogues are then obtained by Pummerer rearrangement followed by cyclization to the methyl furanosides. Although this method has been developed on racemic subsrates, it could easily be transposed to the synthesis of enantiopure furanosides, as vinyl carbamates **5a**,**b**,[18] aldehyde **9a**,[22] and epoxide **11c**[23] have been described as single enantiomers.

In addition to new furanose analogues of therapeutic interest, the intermediate sulfoxides (as well as the corresponding transposed aldehydes) flanked by a protected 1,3-diol motif are useful synthons that could be employed for the construction of highly oxygenated natural products such as the polyene antibiotics.

(25) Couturier, S.; Aljarah, M.; Gosselin, G.; Mathé, C.; Périgaud, C. *Tetrahedron* **2007**, *63*, 11260.

TABLE 1. Synthesis of Methyl Furanosides 15a−c and 16a,c



R_1	R_2	substrate	product	yield (%)	1,2-*trans*/1,2-*cis*
H	CH_3	**13a**	**15a**	75	94:6
H	CH_3	**13b**	**15b**	80	95:5
H	CH_3	**13c**	**15c**	69	84:16
CH_3	H	**14a**	**16a**	60	1:1
CH_3	H	**14c**	**16c**	57	1:1

Experimental Section

Conjugate addition. (2*R,4*R**,6*R**)-4-Phenethyl-2-phenyl-6-(phenylsulfinylmethyl)-1,3-dioxane 3a.** To a solution of vinyl sulfoxide **2a** (213 mg, 0.71 mmol) in THF (7.1 mL) at 0 °C was added *t*-BuOK (8 mg, 0.071 mmol) followed by benzaldehyde (79 μL, 0.78 mmol), and the resulting mixture was stirred for 15 min at 0 °C. A second portion of *t*-BuOK and benzaldehyde was added, after 15 min a third portion was added, and after 15 min a fourth addition was made. The resulting mixture was then stirred at 0 °C for 2 h and quenched with a saturated aqueous NH_4Cl solution. The aqueous phase was extracted three times with Et_2O, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography with AcOEt/petroleum ether (30:70−40:60) to give 199 mg (70%) of the desired ketal **3a** as a pale yellow oil (*syn*/*anti* > 98:2, 1:1 mixture of diastereomers at the sulfur center): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.18−7.66 (m, 15H), 5.67 (s, 0.5H), 5.41 (s, 0.5H), 4.48−4.55 (m, 0.5H), 4.08−4.15 (m, 0.5H), 3.83−3.92 (m, 0.5H), 3.74−3.81 (s, 0.5H), 3.31 (dd, *J* = 13.3, 6.6 Hz, 0.5H), 2.70−2.97 (m, 3.5H), 1.97−2.06 (m, 1H), 1.48−1.87 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.4 (C), 143.3 (C), 141.56 (C), 141.54 (C), 138.1 (C), 138.0 (C), 131.1 (CH), 131.0 (CH), 129.3 (CH), 128.77 (CH), 128.75 (CH), 128.5 (CH), 128.43 (CH), 128.42 (CH), 128.35 (CH), 128.2 (CH), 128.1 (CH), 126.0 (CH), 125.9 (CH), 124.2 (CH), 123.7 (CH), 100.4 (CH), 75.5 (CH), 75.4 (CH), 70.8 (CH_2), 70.4 (CH_2), 64.4 (CH_2), 62.0 (CH_2), 37.3 (CH_2), 37.1 (CH_2), 36.4 (CH_2), 36.2 (CH_2), 31.1 (CH_2), 31.0 (CH_2); IR (CH_2Cl_2, cm^{-1}) 3394, 3058, 3036, 2925, 2860, 1958, 1887, 1813, 1725, 1702, 1494, 1446, 1341, 1276, 1044, 1021, 909; HRMS (EI) M^+ calcd for $C_{25}H_{26}O_3S$ 406.1603, found 406.1608.

Only two peaks could be observed at 5.67 and 5.41 ppm (1:1 ratio) for the acetal protons, corresponding to the two diastereomers at the sulfur center. No trace of the *anti* isomers could be detected.

(2*R,4*R**,5*R**,6*R**)-5-Methyl-4-phenethyl-2-phenyl-6-(phenylsulfinylmethyl)-1,3-dioxane 13a.** The above procedure was used with vinyl sulfoxide **7a** (230 mg, 0.732 mmol). The crude residue was purified by silica gel column chromatography with AcOEt/petroleum ether (30:70−40:60) to give 193 mg (63%) of the desired ketal **13a** as a pale yellow oil (*syn*/*anti* > 98:2, 1:1 mixture of diastereomers at the sulfur center): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66−7.68 (m, 2H), 7.60−7.62 (m, 1H), 7.49−7.52 (m, 3H), 7.35−7.43 (m, 4H), 7.26−7.31 (m, 2H), 7.18−7.23 (m, 3H), 5.73 (s, 0.5H), 5.36 (s, 0.5H), 4.15 (td, *J* = 10.3, 1.6 Hz, 0.5H), 3.54 (td, *J* = 7.5, 2.6 Hz, 1H), 3.32−3.37 (m, 1H), 3.14 (dd, *J* = 13.4, 2.9 Hz, 0.5H), 3.08 (dd, *J* = 13.1, 1.9 Hz,

0.5H), 2.88−3.00 (m, 1H), 2.84 (dd, J = 13.2, 10.8 Hz, 0.5H), 2.68−2.79 (m, 1H), 1.97−2.10 (m, 1H), 1.74−1.91 (m, 1.5H), 1.59−1.63 (m, 0.5H), 0.83 (d, J = 6.6 Hz, 1.5H), 0.76 (d, J = 6.7 Hz, 1.5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.6 (C), 143.4 (C), 141.9 (C), 141.8 (C), 138.2 (C), 138.0 (C), 131.1 (CH), 130.9 (CH), 129.3 (CH), 129.2 (CH), 128.7 (CH), 128.5 (CH), 128.46 (CH), 128.40 (CH), 128.37 (CH), 128.2 (CH), 128.1 (CH), 125.9 (CH), 125.86 (CH), 125.84 (CH), 124.4 (CH), 123.7 (CH), 99.9 (CH), 99.8 (CH), 80.9 (CH), 80.8 (CH), 76.3 (CH), 75.7 (CH), 62.9 (CH_2), 60.4 (CH_2), 38.5 (CH), 38.0 (CH), 34.6 (CH_2), 34.2 (CH_2), 31.2 (CH_2), 31.0 (CH_2), 12.0 (CH_3), 11.8 (CH_3); IR (CH_2Cl_2, cm^{-1}) 3424, 3034, 2963, 2927, 2251, 1957, 1889, 1814, 1731, 1602, 1491, 1449, 1403, 1343, 1265, 1253, 1215, 1130, 1080, 1063, 1047, 929; HRMS (EI) M^+ calcd for $C_{26}H_{28}O_3S$ 420.1759, found 420.1761.

Only two peaks could be observed at 5.73 and 5.36 ppm (1:1 ratio) for the acetal protons, corresponding to the two diastereomers at the sulfur center. No trace of the *anti* isomers could be detected.

(2*R,4*R**,5*S**,6*R**)-5-Methyl-4-phenethyl-2-phenyl-6-(phenylsulfinylmethyl)-1,3-dioxane 14a.** The above procedure was used with vinyl sulfoxide **10a** (120 mg, 0.38 mmol). The crude residue was purified by silica gel column chromatography with AcOEt/petroleum ether (30:70−40:60) to give 130 mg (81%) of the desired ketal **14a** as a pale yellow oil. The product is a 88:12 mixture of isomers (*syn*/*anti*) and a 1:1 mixture of diastereomers at the sulfur center for the *syn* isomer. Only the two *syn* diastereomers are described: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.10−7.68 (m, 15H), 5.68, 5.37 (2s, 1H), 4.57 (dt, J = 10.6, 2.0 Hz, 0.5H), 4.22−4.26 (m, 0.5H), 3.92−3.96 (m, 0.5H), 3.83−3.87 (m, 0.5H), 3.28 (dd, J = 13.4, 7.6 Hz, 0.5H), 2.92−2.97 (m, 1H), 2.63−2.83 (m, 2.5H), 1.99−2.09 (m, 1H), 1.66−1.77 (m, 1.5H), 1.50−1.55 (m, 0.5H), 1.05, 0.97, 0.76 (3d, J = 6.7, 7.0, 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ144.7 (C), 143.2 (C), 141.6 (C), 141.5 (C), 138.3 (C), 138.1 (C), 131.1 (CH), 131.0 (CH), 129.3 (CH), 129.2 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.0 (CH), 126.1 (CH), 126.0 (CH), 125.9 (CH), 124.1 (CH), 123.7 (CH), 101.5 (CH), 101.2 (CH), 79.7 (CH), 79.6 (CH), 74.3 (CH), 73.9 (CH), 62.7 (CH_2), 58.9 (CH_2), 35.3 (CH), 34.7 (CH), 34.2 (CH_2), 34.1 (CH_2), 31.6 (CH_2), 31.5 (CH_2), 6.4 (CH_3), 6.3 (CH_3); IR (CH_2Cl_2, cm^{-1}) 2979, 2953, 2861, 1959, 1889, 1814, 1603, 1584, 1496, 1478, 1454, 1444, 1407, 1389, 1347, 1312, 1215, 1177, 1135, 1123, 1087, 1042, 1028; HRMS (EI) M^+ calcd for $C_{26}H_{28}O_3S$ 420.1759, found 420.1761.

The *syn*/*anti* ratio was determined by the relative integrations of the peaks for the acetal protons at 5.68 and 5.37 ppm (*syn* isomers) and at 6.01 (*anti* isomer).

Pummerer Reaction and Acidic Cyclization. (2*R,3*R**,5*R**)-2-Methoxy-5-phenethyltetrahydrofuran-3-ol 4a.** TFAA (1.71 g, 11.3 mmol) was added to a solution of ketal **3a** (1.15 g, 2.83 mmol) in CH_2Cl_2 (30 mL) at 0 °C. The mixture was stirred for about 30 min at this temperature. Then a 2 N aqueous NaOH solution (30 mL) and 15 mL of THF was added, and the mixture was warmed and stirred for 90 min at 20 °C. The organic phase was extracted three times with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was dissolved in MeOH (115 mL), camphorsulfonic acid (CSA) (130 mg, 0.56 mmol) was added, and the mixture was stirred overnight. The reaction mixture was quenched with Et_3N (pH ~8) and diluted with saturated aqueous $NaHCO_3$. The aqueous phase was extracted three times with AcOEt, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography with AcOEt/petroleum ether (30:70−50:50) to give 503 mg (80%) of the desired tetrahydrofuran **4a** as a pale yellow oil and a *trans*/*cis* (89:11) mixture. Only the NMR data for the *trans* isomer is described: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.17−7.30 (m, 5H), 4.79 (s, 1H), 4.30−4.37 (m, 1H), 4.24 (bs, 1H), 3.36 (s, 3H), 2.64−2.83 (m, 2H), 1.79−2.01 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.8 (C), 128.38 (CH), 128.36 (CH), 125.8 (CH), 108.8 (CH), 78.7 (CH), 76.2 (CH), 54.2 (CH_3), 39.5 (CH_2), 38.0 (CH_2), 32.5 (CH_2); IR (CH_2Cl_2, cm^{-1}) 3602, 3047, 3033, 2991, 2939, 1952, 1879, 1810, 1753, 1690, 1602, 1494, 1446, 1378, 1346, 1312, 1191, 1157, 1099, 1040, 971; HRMS (EI) M^+ calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1251.

The *trans*/*cis* ratio was determined by the relative integrations of the peaks for the acetal protons at 4.79 (s, *trans* isomer) and 4.94 ppm (d, J = 4.4 Hz, *cis* isomer).

(2*R,3*R**,4*R**,5*R**)-2-Methoxy-4-methyl-5-phenethyltetrahydrofuran-3-ol 15a.** The above procedure was applied to ketal **13a** (225 mg, 0.535 mmol). The crude residue was purified by silica gel column chromatography with AcOEt/EP (30:70−50:50) to afford tetrahydrofuran **15a** (95 mg, 75%) as a pale yellow oil and a *trans*/*cis* (94:6) mixture. Only the NMR data for the *trans* isomer are described: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.16−7.30 (m, 5H), 4.78 (s, 1H), 3.98 (d, J = 4.3 Hz, 1H), 3.85(td, J = 8.8, 3.6 Hz, 1H), 3.37 (s, 3H), 2.84−2.91 (m, 1H), 2.66−2.74 (m, 1H), 2.07−2.14 (m, 1H), 1.87−1.97 (m, 1H), 1.71−1.81 (s, 1H), 1.04 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.1 (C), 128.3 (CH), 125.7 (CH), 108.8 (CH), 84.1 (CH), 78.2 (CH), 54.3 (CH_3), 40.9 (CH), 37.7 (CH_2), 32.5 (CH_2), 9.8 (CH_3); IR (CH_2Cl_2, cm^{-1}) 3611, 3086, 3071, 3044, 3029, 2992, 2934, 2831, 1949, 1876, 1811, 1603, 1583, 1496, 1455, 1381, 1315, 1283, 1255, 1193, 1154, 1104, 1032; HRMS (EI) M^+ calcd for $C_{14}H_{20}O_3$ 236.1413, found 236.1410.

(2*R,3*R**,4*S**,5*R**)-2-Methoxy-4-methyl-5-phenethyltetrahydrofuran-3-ol 16a.** The above procedure was applied to ketal **14a** (300 mg, 0.71 mmol). The crude residue was purified by silica gel column chromatography with AcOEt/EP (30:70−70:30) to afford tetrahydrofuran **16a** (101 mg, 60%) as a pale yellow oil and a *trans*/*cis* (50:50) mixture: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.16−7.30 (m, 5H), 4.88 (d, J = 4.4 Hz, 0.5H), 4.78 (d, J = 1.7 Hz, 0.5H), 4.15−4.26 (m, 1H), 3.90−3.92 (m, 0.5H), 3.78−3.84 (m, 0.5H), 3.48 (s, 1.5H), 3.42 (s, 1.5H), 2.78−2.91 (m, 1H), 2.58−2.68 (m, 1H), 2.09−2.21 (m, 1H), 1.65−1.90 (m, 2H), 1.03 (d, J = 7.3 Hz, 1H), 0.97 (d, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.1 (C), 141.9 (C), 128.44 (CH), 128.42 (CH), 128.3 (CH), 125.8 (CH), 125.7 (CH), 110.4 (CH), 101.7 (CH), 83.2 (CH), 81.3 (CH), 78.5 (CH), 55.4 (CH_3), 55.3 (CH_3), 43.2 (CH), 41.7 (CH), 33.6 (CH_2), 33.2 (CH_2), 32.8 (CH_2), 32.6 (CH_2), 12.0 (CH_3), 11.9 (CH_3); IR (CH_2Cl_2, cm^{-1}) 3604, 3526, 3085, 3068, 3055, 3048, 1995, 2937, 2661, 2254, 1950, 1877, 1810, 1733, 1603, 2583, 1496, 1479, 1454, 1411, 1380, 1304, 1283, 1221, 1191, 1154, 1105, 1081, 1049; HRMS (EI) M^+ calcd for $C_{14}H_{20}O_3$ 236.1413, found 236.1420.

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Supporting Information Available: Experimental procedures and full characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.