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New Chirons from D-Glucose. Regio- and Diastereoselective C–C Bond Forming Reactions Exploiting Novel Aldotetrafuranose Acetates as Chiral Synthetic Equivalents of Tartaric Aldehydes

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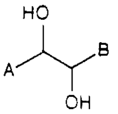
Two differentially protected tetrafuranose acetates **5** and **6** have been prepared from diacetone D-glucose in parallel short routes. They clearly act as chiral synthetic equivalents of D- and *meso*-tartaric aldehydes when exploited in Lewis acid promoted reactions with silicon-based nucleophiles. The synthesis of immediate precursors of 2-deoxy-L-hexoses is presented as an application.

Introduction

The synthesis of enantiomerically pure target molecules is an important goal in organic chemistry. To achieve it, optically active compounds available from the biosphere are indispensable. They can be used (i) as resolving agents for the separation of racemates, (ii) as chiral reagents or catalysts for asymmetric synthesis, (iii) as chiral auxiliaries temporarily added to a prochiral substrate, (iv) as chiral building blocks that will be incorporated in the target molecule. The last strategy relies on the identification of enantiomerically pure chiral synthons possessing the proper skeleton and functionality group pattern that match with those of the paper-drawn fragments coming from a retrosynthetic analysis of the target molecule.[1]

In this paper we will deal with chiral tetrafunctional C-4 synthons related to the general structure A, where A and B represent oxygenated carbons at any oxydation level, namely CH_2OH, CHO, and COOH.



A

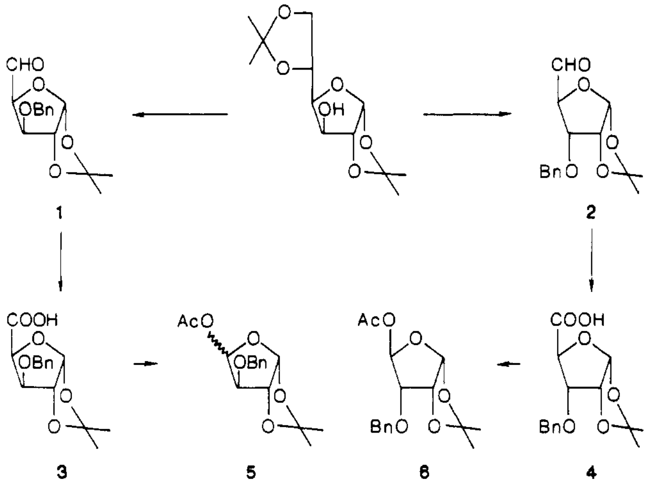
Threose and erythrose derivatives (A = CH_2OH, B = CHO), threo- and erythruronic acids (A = CHO, B = COOH), threonic and erithronic acids (A = COOH, B = CH_2OH), tartaric acids (A = B = COOH), and threitols and erythritols (A = B = CH_2OH) are all available. Only a combination is missing, namely A = B = CHO, as it turns out by scrutinizing the most common catalogues and chemical literature.[1,2]

We want to describe here a simple access to chiral synthetic equivalents of (*R*,*R*)- and *meso*-tartaric dialdehydes starting from diacetone D-glucose and some selective manipulations on one of the two masked carbonyls groups.

Results and Discussion

The acetates **5** and **6**, which represent the pivots of our work, are both prepared in parallel short routes, as depicted in Scheme I. Starting from aldehydes **1**[3] and **2**[4] (whose preparation is reported in the literature from the cheapest and most popular aldofuranose starting material 1,2:5,6-bis-*O*-(methylethylidene)-α-D-glucofuranose), we got the xylofuranuronic acid **3** and ribofuranuronic acid **4** in very high yields with $NaClO_2/H_2O_2$ in buffered aqueous/acetonitrile media.[5] Oxidative decarboxylation of **3** and **4** with 1.3 equiv of lead tetraacetate in dry acetonitrile in the presence of pyridine (1.1 equiv) affords acetates **5** and **6**. Compound **5** was obtained in 83% yield as a 3:1 mixture of epimers upon GC analysis, while any attempt of column chromatographic separation failed. Moreover, the assignment of the α configuration at C-5[6] to the major isomer was made on the basis of NMR properties: a proton coupling constant $J_{5,6}$ = 0 Hz (200 MHz) was observed for the major isomer while a $J_{5,6}$ = 4.2 Hz was measured for the minor. This last value is in agreement with the values reported for similar compounds having a 5-H, 6-H cis relationship.[7] In the ^{13}C NMR spectra the peaks of C-5 and C-6 of the major isomer resulted in downfield shifts of 4.9 and 0.8 ppm, respectively, with respect to the corresponding signals of the epimer. This effect is a probe of a trans relationship according to data reported by several authors.[7,8]

Scheme I



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(1) Hanessian, S. *Total Synthesis of Natural Products: The "Chiron Approach"*; Pergamon Press: Oxford, 1983.

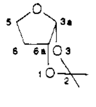
(2) Vasella, A. Chiral Building Blocks in Enantiomer Synthesis –ex Sugars In *Modern Synthetic Methods*; Sheffold, R., Ed.; Otto Salle Verlag: Frankfurt Am Main, 1980; Vol. 2.

(3) Anderson, R. C.; Fraser-Reid, B. *J. Org. Chem.* **1985**, *50*, 4781.

(4) Birmacombe, J. S. *Carbohydr. Res.* **1968**, *8*, 82.

(5) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567.

(6) According to IUPAC nomenclature, the following numbering for the 2,2-dimethylfuro[2,3-*d*]-1,3-dioxole system is used:



(7) Dais, P.; Perlin, A. S. *Carbohydr. Res.* **1986**, *146*, 177.

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Table I. Reactions of Acetate 5 with Different Nucleophiles[a]

nucleophile	Lewis acid (molar equiv)	solvent	time, h	7/8[b]	overall yield,[c] %
CH_2=$CHCH_2SiMe_3$	$MgBr_2$ (2.5)	CH_2Cl_2	15	82/18	91
CH_2=$CHCH_2SiMe_3$	$MgBr_2$ (2.5)	CH_3CN	9	72/28	79
CH_2=$CHCH_2SiMe_3$	$MgBr_2$ (2.5)	CH_3NO_2	5	67/33	75
CH_2=$CHCH_2SiMe_3$	$ZnBr_2$ (2.5)	CH_2Cl_2	15	15/85	66
$CH_3C(OSiMe_3)$=CH_2	$MgBr_2$ (3)	CH_2Cl_2	15	85/15	85
$CH_3C(OSiMe_3)$=CH_2	$ZnBr_2$ (3)	CH_2Cl_2	15	33/67	75
$PhC(OSiMe_3)$=CH_2	$MgBr_2$ (3)	CH_2Cl_2	15	>95/5[d]	65

[a] All reactions were performed on 1 mmol of 5 and 4 mmol of nucleophiles in 7 mL of solvent at 15 °C. [b] Ratio determined by GC. [c] Yields refer to purified compounds. Satisfactory analytical data (±0.4% for C and H) were obtained for all new compounds reported in the table. [d] Ratio determined by integration of signals in ^{1}H NMR spectrum of the crude reaction mixture.

Table II. Reaction of Acetate 6 with Different Nucleophiles[a]

nucleophile	Lewis acid (molar equiv)	solvent	time, h	9/10[b]	overall yield,[c] %
CH_2=$CHCH_2SiMe_3$	$BF_3{\cdot}Et_2O$ (1.5)	CH_2Cl_2	3.5	92/8	82
CH_2=$CHCH_2SiMe_3$	$BF_3{\cdot}Et_2O$ (1.5)	CH_3CN	2.5	95/5	80
CH_2=$CHCH_2SiMe_3$	$BF_3{\cdot}Et_2O$ (1.5)	CH_3NO_2	2	98/2	82
CH_2=$CHCH_2SiMe_3$	$MgBr_2$ (2.5)	CH_2Cl_2	5	20/80	85
$CH_3C(OSiMe_3)$=CH_2	$MgBr_2$ (3)	CH_3NO_2	3	18/82	85
$PhC(OSiMe_3)$=CH_2	$BF_3{\cdot}Et_2O$ (3)	CH_2Cl_2	1.5	85/15[d]	84
$PhC(OSiMe_3)$=CH_2	$MgBr_2$ (3)	CH_2Cl_2	10	30/70[d]	84

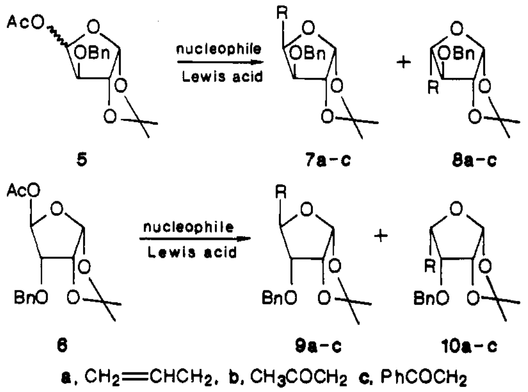
[a] All the reactions were performed on 1 mmol of 5 and 4 mmol of nucleophile at −20 °C in the case of $BF_3{\cdot}Et_2O$ and at 0 °C in the case of $MgBr_2$. [b] Ratio determined by GC. [c] Yields refer to purified compounds. Satisfactory analytical data (±0.4% for C and H) were obtained for all new compounds reported in the table. [d] Ratio determined by integration of signals in ^{1}H NMR spectrum of the crude reaction mixture.

On the contrary, the lead tetraacetate oxidative acetoxylation of acid 4 gave rise only to a single acetate 6 as carefully tested through GC and NMR analyses. To ascertain its configuration we epimerized a sample of 6 with catalytic amounts of $BF_3{\cdot}Et_2O$ and acetic anhydride in CH_2Cl_2 at 20 °C for 1 h. In the ^{13}C NMR spectrum of compound 6, C-5 was 5.3-ppm downfield shifted and C-6 was 0.5-ppm downfield shifted with respect to its epimer indicating a trans relationship of the substituents at C-5 and C-6. The H–H coupling constants in the case of 6 are less revealing about the configuration at C-5 ($J_{5,6}$ = 4.8 Hz was observed for 6, while its epimer showed a $J_{5,6}$ = 5.0 Hz).

The main features of our synthons 5 and 6 are (i) the presence of two differentially protected and stereochemically defined hydroxylated carbons and (ii) the presence of two different acetal functions. From these features directly derives the aim of our research; that is (a) to find out the conditions for regioselective manipulations at one acetal group and (b) to form a new sterogenic center in the most stereoselective way and, possibly, to find the conditions allowing the selective formation of both the stereoisomers. Concerning the first goal we have recently described the regioselective reduction of 5 and 6 with triethylsilane in the presence of Lewis acids.[9]

Here we report the Lewis acid promoted reactions of 5 and 6 with silicon containing nucleophiles.[10]

Scheme II



The reactions of acetate 5 (Scheme II) with three nucleophilic partners (e.g. allyltrimethylsilane and the trimethylsilyl enol ethers of acetone and acetophenone) with various Lewis acids and solvents are reported in Table I.[11] Good yields and stereoselectivity are achieved by using 2.5–3 equiv of $MgBr_2$ in anhydrous CH_2Cl_2 at 15 °C, the major product always being the 7 isomer. Surprisingly no significant effects were observed when increasing the polarity of the solvent going from CH_2Cl_2 to CH_3CN and CH_3NO_2.[12] On the contrary the replacement of $MgBr_2$ with $ZnBr_2$ led to a change in the stereochemical course of the reaction, since the 8 isomer became predominant with the latter catalyst both in the reactions with allylsilane and (2-propenyloxy)silane. Such a trend is not obvious for similar divalent metal halides. Other Lewis acids tested (e.g. $BF_3{\cdot}Et_2O$, $TiCl_4$, triethylsilyl triflate) afforded only decomposition products by reacting at 15 °C, probably because of 1,3-dioxolane ring opening, while at lower temperatures (−20 °C) no reaction occurred. The reactions of acetate 6 with the same nucleophilic partners (Scheme II) are collected in Table II.

Also in this case good yields and excellent stereoselectivity were achieved; with $MgBr_2$ at 0 °C in dichloromethane or nitromethane, the major isomer obtained was 10. As in the case of 5, the $MgBr_2$-promoted substitution reaction leads mainly to the 5,6-cis product with a formal

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[8] Ritchie, R. G. S.; Cyr, N.; Korsch, B.; Koch, H. J.; Perlin, A. S. *Can. J. Chem.* **1975**, *53*, 1424. Urban, J.; Marek, M.; Jary, J.; Sedmera, P. *Collect. Czech. Chem. Commun.* **1980**, *45*, 2779. Ohuri, H.; Jones, G. H.; Moffat, J. G.; Maddox, M. L.; Christensen, A. T.; Byram, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 4602. Nicotra, F.; Panza, L.; Russo, G. *J. Org. Chem.* **1987**, *52*, 5627. Delaseras, F. G.; Fernandez-Resa, P. *J. Chem. Soc., Perkin Trans. 1* **1982**, 903.

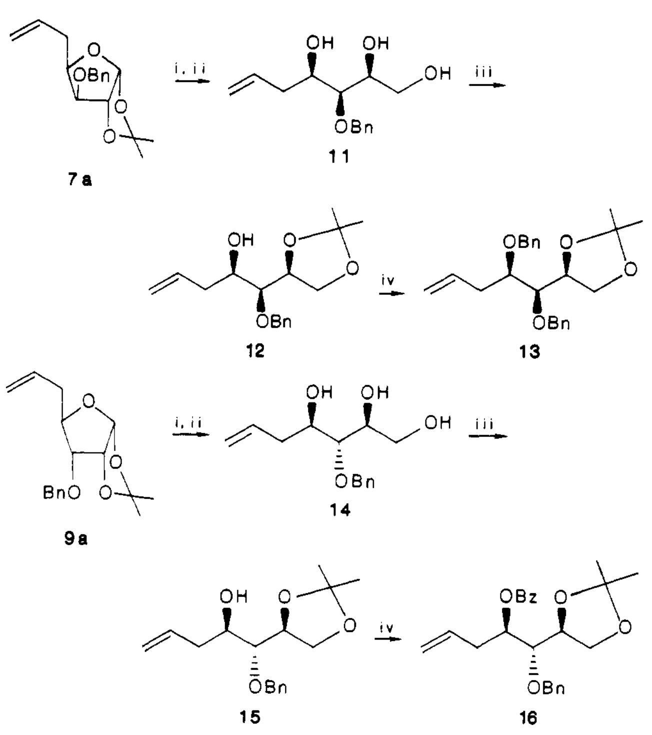
[9] Dhavale, D. D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *Tetrahedron Lett.* **1988**, *47*, 6163.

[10] Mukaiyama, T. *Org. React.* **1982**, *28*, 203.

[11] Monitoring the reactions by GC shows that the less abundant 5α isomer is more reactive and disappears earlier than 5β.

[12] Solvent effects in increasing stereoselectivity of related reactions have been reported: Wilcox, C. S.; Otoski, R. M. *Tetrahedron Lett.* **1986**, *27*, 1011. Kozikowski, A.; Sorgi, K. L.; Wang, B. C.; Xu, Z. *Tetrahedron Lett.* **1983**, *24*, 1563. Giannis, A.; Sandhoff, K. *Tetrahedron Lett.* **1985**, *26*, 1497.

Scheme III[a]



[a] (i) 2 N HCl, THF, 60 °C, 4 h; (ii) $NaBH_4$, EtOH, 20 °C, 2 h; (iii) PPTS (10% mol), acetone, 20 °C, 5 h; (iv) BzCl, Py, CH_2Cl_2, 20 °C, 15 h.

inversion of configuration at the C-5 center. On the contrary BF_3·Et_2O, which proved to be a very effective catalyst at −20 °C, showed a reversed stereoselectivity with respect to $MgBr_2$ in the reactions of acetate **6** with allyltrimethylsilane and acetophenone silyl enol ether. Particularly in CH_3NO_2 the **9a** allylated product is virtually the only isomer obtained in 82% yield. $ZnBr_2$ was unsuccessful with this substrate.

The assignment of the configuration at the C-5 centers was made mostly on the basis of NMR evidences. In the **7** and **8** products this typical trend was observed: (i) in the ^1H NMR spectrum the $J_{5,6}$ coupling constant is small for a trans relationship, ranging from a 0 Hz value for **5α**, and **8a** to 2 Hz for **8b**, while larger values of 4.2, 3.3, 3.4, and 3 Hz were measured for the corresponding cis products **5β**, **7a**, **7b**, and **7c**; these values are in agreement with those reported for related systems.[7] Furthermore in ^{13}C NMR spectrum a large shielding effect of 5–6 ppm on the carbon bonded to C-5 was always observed for the **7** isomer, probably due to the presence of a cis benzyl group.[7,8]

In the **9** and **10** products the larger $J_{5,6}$ coupling constant of 9 Hz was assigned to **9**, while the 5,6-cis products **10** showed values closed to 7 Hz, in agreement to Perlin.[7] In ^{13}C NMR spectrum a deshielding effect on CH_2, similar but inferior (~1 ppm) to what was observed for the other series, is present for the 5,6-cis products.

Considering that similar NMR properties and chemical trends are observed for homogeneous sets of products, we looked for a support to our stereochemical assignment by correlating one product of series **7** and **9** to known compounds. The transformations depicted in Scheme III allowed us to get the known products **13** and **16** respectively from **7a** and **9a**. These products show identical spectroscopic and chirooptical properties with the reported ones.[13] It is worth mentioning that this correlation also represents a formal route to 2-deoxy-L-*xylo*-hexose and 2-deoxy-L-*ribo*-hexose from **7a** and **9a**, via ozonolysis of the intermediates **11** and **14**, respectively.

The Lewis acid dependent stereoselectivity is the main mechanistic feature of our reactions. To summarize the results, the reactions of silicon nucleophiles in the presence of $MgBr_2$ give, with both acetates **5** and **6**, predominant alkylation on the diastereotopic face of the tetrahydrofuran ring which contains the benzyloxy substituent. On the contrary the same reaction promoted by BF_3·Et_2O in the case of **6**, and $ZnBr_2$ in the case of **5**, leads to alkylation on the less hindered face and formation of products **8** and **9**. While the latter behavior can be easily accounted for by steric factors, a rationale for the $MgBr_2$-induced reaction stereoelectronics does not come out from data in our hands.[14]

In conclusion, we have reported here the preparation of new optically active synthons formally corresponding to tartaric aldehydes equivalents and we have shown their potentialities in regio- and stereoselective substitution reactions.

Compounds **7–10** prepared by this route could find applications as intermediates in the synthesis of many natural products, due to their highly functionalized skeleton and to their stereochemical characteristics. A straightforward application is given by an easy access to the four possible 4-*O*-(phenylmethyl)-2-deoxy L-sugars via acidic hydrolysis and $NaBH_4$ reduction as exemplified in Scheme II in the case of **7a** and **9a**, followed by ozonization of the terminal C–C double bond.

Experimental Section

General. ^1H NMR spectra were measured at 200 MHz on a Varian Gemini 200 instrument. Chemical shifts are reported in δ units relative to internal standard Me_4Si. ^{13}C NMR spectra were obtained at 20 MHz on a Varian FT 80 A instrument; carbon resonances are reported in δ units with reference to internal Me_4Si. Infrared spectra were recorded on a Perkin-Elmer Model 682 and are reported in cm^{-1}. Mass spectra were measured at 70 eV on a VG 7070 double-focusing mass spectrometer. Melting points are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Reactions were conducted in oven-dried (120 °C) or flame-dried glassware under an atmosphere of dry argon. All solvents were purified before use: ether and THF were distilled from sodium benzophenone ketyl; CH_3CN, CH_2Cl_2, and CH_3NO_2 were distilled from P_2O_5.

Analytical GC was performed on a Carlo Erba HRGC 5160 Mega Series chromatograph equipped with a fused silica capillary Supelcowax column (0.5 μm film thickness, 30-m length) with a hydrogen flow of 2 mL/min. The temperature was programmed from 80 to 220 °C at 10 °C/min and held at 220 °C for 20 min. Retention times (t_R) are given in minutes. HPLC analyses were carried out with a Hewlett-Packard Model HP 1090 liquid chromatograph using a ODS column (5 μm particle size, 15-cm length) with H_2O/MeOH, 25:75, mixture as eluting solvent.

TLC analyses were performed on Kieselgel 60 F_{254} plates, and flash column chromatography was carried out with Kieselgel 60 (230–400 mesh) purchased from Merck with cyclohexane–ethyl acetate mixtures as eluents.

Allyltrimethylsilane, boron trifluoride etherate, zinc bromide, diacetone D-glucose were purchased from Aldrich. Lead tetraacetate (95%, Janssen) was washed three times with anhydrous CH_3CN under argon, dried under vacuum, and weighted under argon. (Isopropyloxy)trimethylsilane (70% in HMDSO) was obtained from Fluka. Magnesium bromide[15] (from magnesium

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[13] Williams, D. R.; Klingler, F. D. *Tetrahedron Lett.* **1987**, *28*, 869.

[14] The behavior of $MgBr_2$-promoted reactions could be the result of the chelating properties of magnesium cation that could result in a multiple interaction with the different oxygen atoms of the substrates. An analogous trend has been claimed to explain the reversed selectivity exhibited by BF_3·Et_2O versus $TiCl_4$ in similar condensation reactions: Danishefsky, S. J.; DeNinno, M. P. *Tetrahedron Lett.* **1985**, *26*, 823. Danishefsky, S. J.; DeNinno, M. P.; Phillips, G. P.; Zeelle, R. E.; Lartey, P. A. *Tetrahedron* **1986**, *42*, 2809.

and 1,2-dibromoethane) and (phenylethyloxy)trimethylsilane[16] were prepared according to literature procedures. 1,2-*O*-(Methylethylidene)-3-*O*-(methylphenyl)-α-D-*xylo*-pentodialdo-1,4-furanose (1)[3] and 1,2-*O*-(methylethylidene)-3-*O*-(methylphenyl)-α-D-*ribo*-pentodialdo-1,4-furanose (2) were prepared from diacetone D-glucose. All other chemicals were commercial pure products (98% or better) and were used as purchased.

1,2-*O*-(Methylethylidene)-3-*O*-(phenylmethyl)-α-D-xylofuranuronic Acid (3). To a solution of 1,2-*O*-(methylethylidene)-3-*O*-(phenylmethyl)-α-D-*xylo*-pentodialdo-1,4-furanose (1) (8.9 g, 32 mmol) in acetonitrile (35 mL) was added in turn NaH_2PO_4 (1.03 g) in water (13 mL) and H_2O_2 (35%, 3.4 mL, 35 mmol); to this mixture, stirred and cooled at 0–10 °C was added a solution of $NaClO_2$ (4.5 g, 50 mmol) in water (56 mL) dropwise over 2 h. The reaction mixture was then stirred at 15 °C, and oxygen evolved from the solution was monitored until the end of the reaction (about 10 h) with a bubbler connected to the apparatus. A small amount of Na_2SO_3 (0.4 g) was added, the solution was made acidic to pH 2 by 3 N HCl, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layers were evaporated, the residue was dissolved in 10% $NaHCO_3$ solution (50 mL), and bicarbonate layer was washed with ethyl acetate (25 mL). Bicarbonate solution was then made acidic to pH 2 and extracted with ethyl acetate (100 mL). The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and evaporated to give 3 (8.2 g, 87%) as a crystalline solid, mp 141–2 °C (lit.[17] mp 141.5–142 °C).

1,2-*O*-(Methylethylidene)-3-*O*-(phenylmethyl)-α-D-ribofuranuronic Acid (4). 1,2-*O*-(Methylethylidene)-3-*O*-(phenylmethyl)-α-D-*ribo*-pentodialdo-1,4-furanose (2) (8.9 g, 32 mmol) was oxidized according to the same procedure reported for 1 to give 4 (8.3 g, 88%) as a crystalline solid: mp 115–8 °C; $[\alpha]^{23}_D$ +68.2° (*c* 1, $CHCl_3$); IR (Nujol) 1730, 1710, 1120, 1090, 1040, 1000, 760, 710; ^1H NMR δ 1.36 (3 H, s, CH_3), 1.60 (3 H, s, CH_3), 4.01 (1 H, dd, *J* = 4.5 and *J* = 9 Hz, H-3), 4.46–4.93 (4 H, m, CH_2, H-2 and H-4), 5.85 (1 H, d, *J* = 3.75 Hz, H-1), 7.33 (5 H, s, Ar-H), 8.93 (1 H, b s, CO_2H); ^{13}C NMR δ 26.6, 26.9, 72.7, 76.8, 78.0, 80.2, 104.7, 113.9, 128.0, 128.1, 128.5, 137.0, 174.5; MS *m*/*e* (rel intensity) 294 (M^+, traces), 279 (10), 219 (5), 161 (6), 129 (10), 123 (11), 107 (7), 91 (100), 65 (10).

[3a*R*(3aα,6β,6aα)]-Tetrahydro-2,2-dimethyl-5-acetoxy-6-(phenylmethoxy)furo[2,3-*d*]-1,3-dioxole (5). To a stirred solution of acid 3 (2.94 g, 10 mmol) and pyridine (0.87 mL, 11 mmol) in dry acetonitrile (30 mL) was added $Pb(OAc)_4$ (5.76 g, 13 mmol).[18] The mixture, with argon bubbled through the solution, was stirred at 15 °C for 5 h (after 4 h the precipitation of white lead diacetate occurred) and decomposed with brine. The mixture was filtered through Celite, the precipitate was washed with acetone, and the filtrate was concentrated in vacuo. The oil was extracted with ether (50 mL), and the ether layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of ether left an oil, which was chromatographed with cyclohexane–ethyl acetate (95:5) to yield acetate 5 (2.50 g, 81%) as a colorless oil in the epimeric mixture 5α:5β = 3:1 on the basis of the ratio of the corresponding GC peaks. The 5α isomer has a t_R of 22.2 min, the 5β isomer has t_R = 21.7. This mixture was used, without separation of the isomers, for further reactions: IR 1750, 1380, 1230, 1100, 860, 750, 705; ^1H NMR (5α isomer) δ 1.32 (3 H, s, CH_3), 1.57 (3 H, s, CH_3), 2.08 (3 H, s, CH_3), 4.12 (1 H, s, H-6), 4.4–4.9 (3 H, m, CH_2 and H-6a), 6.04 (1 H, d, *J* = 4 Hz, H-3a), 6.29 (1 H, s, H-5), 7.34 (5 H, s, Ar-H); (5β isomer) δ 1.38 (3 H, s, CH_3), 1.49 (3 H, s, CH_3), 2.09 (3 H, s, CH_3), 4.20 (dd, 1 H, *J* = 2.2 Hz and *J* = 4.2 Hz, 6-H), 4.40–4.90 (m, 3 H, CH_2 and 6a-H), 6.00 (d, 1 H, *J* = 4 Hz, 3a-H), 6.44 (d, 1 H, *J* = 4.2 Hz, 5-H), 7.34 (s, 5 H, Ar-H); ^{13}C NMR (5α isomer) δ 21.2, 26.5, 72.1, 82.8, 84.5, 101.3, 108.0, 113.8, 127.9, 128.1, 128.6, 136.9, 169.7; (5β isomer) δ 21.0, 27.3, 27.7, 73.0, 82.4, 83.7, 96.4, 104.9, 114.4, 127.8, 128.0, 128.5, 137.2, 170.0; MS *m*/*e* (relative intensity) 293 ($M^+ - CH_3$, 2), 249 (1), 162 (3), 149 (5), 142 (3), 129 (5), 113 (8), 92 (8), 91 (100), 65 (6), 59 (5), 43 (31).

[3a*R*(3aα,5β,6α,6aα)]-Tetrahydro-2,2-dimethyl-5-acetoxy-6-(phenylmethoxy)furo[2,3-*d*]-1,3-dioxole (6). To a stirred solution of acid 4 (2.94 g, 10 mmol) and pyridine (0.87 mL, 11 mmol) in dry acetonitrile (30 mL) was added $Pb(OAc)_4$ (5.76 g, 13 mmol) portionwise. The mixture, with argon bubbled through the solution, was stirred at 20 °C for 2.5 h (after 1.5 h the white lead diacetate separated out) and decomposed with brine. The mixture was filtered through Celite, the precipitate residue was washed with acetone (three times), and the combined filtrate was concentrated in vacuo. The oil was extracted with ether (50 mL), and the ether layer was washed with brine and dried over Na_2SO_4. GC analysis revealed a single peak at t_R = 23.2 min. Evaporation of ether followed by column chromatography with cyclohexane–ethyl acetate (93:7) gave acetate 6 as a white solid (2.52 g, 83%): mp 72–3 °C; $[\alpha]^{25}_D$ +82.3° (*c* 1.03, MeOH); IR 1750, 1470, 1460, 1380, 1225, 1030, 870, 750, 705; ^1H NMR δ 1.41 (3 H, s, CH_3), 1.62 (3 H, s, CH_3), 2.06 (3 H, s, CH_3), 3.97 (1 H, t, *J* = 4.8 Hz, H-6), 4.50–4.85 (3 H, m, CH_2-Ph and H-6a), 5.86 (1 H, d, *J* = 3.3 Hz, H-3a), 6.24 (1 H, d, *J* = 4.8 Hz, H-5), 7.36 (5 H, s, Ar-H); ^{13}C NMR δ 21.0, 27.1, 27.3, 72.6, 78.2, 80.9, 99.3, 104.7, 114.8, 128.0, 128.1, 128.5, 137.3, 169.4; MS *m*/*e* (relative intensity) 293 ($M^+ - CH_3$, 3), 190 (3), 173 (2), 162 (2), 149 (3), 142 (4), 129 (7), 113 (15), 92 (21), 91 (77), 65 (15), 59 (11), 43 (100).

Coupling of Acetate 5 with Allyltrimethylsilane Promoted by $MgBr_2$. To $MgBr_2$ (0.46 g, 2.5 mmol) in dry CH_2Cl_2 (7 mL) stirred at 0 °C were added in turn allyltrimethylsilane (0.46 g, 4 mmol) and acetate 5 (0.308 g, 1 mmol) in dry dichloromethane (10 mL). The reaction mixture was warmed to 15 °C, stirred for 15 h, and decomposed with 10% solution of $NaHCO_3$ (15 mL). The aqueous layer was extracted with ether (60 mL), and the ether layer was washed with water and brine and dried over Na_2SO_4. GC analysis of the crude reaction mixture showed two peaks having t_R 15.9 and 16.6 in the ratio 18/82. From column chromatography (cyclohexane–ethyl acetate, 92:8) only partial enrichment of the isomeric composition was obtained in some fractions, but no complete separation was achieved; the overall amount of 7a and 8a resulted to be 0.26 g (91%). A 90% pure sample (based on GC) of the major product **[(3a*R*-(3aα,5β,6β,6aα)]-tetrahydro-2,2-dimethyl-5-(2-propen-1-yl)-6-(phenylmethoxy)furo[2,3-*d*]-1,3-dioxole (7a)** was obtained by iterative (3 runs) column chromatography (cyclohexane–ethyl acetate, 92:8): IR (neat) 3060, 3030, 2980, 2940, 1640, 1500, 1460, 1380, 1370, 1080, 1030, 920, 890, 860, 740, 700; ^1H NMR δ 1.33 (3 H, s, CH_3), 1.50 (3 H, s, CH_3), 2.50 (2 H, dt, *J* = 1.5 and 7.2 Hz, CH_2), 3.85 (1 H, d, *J* = 3 Hz, H-6), 4.23 (1 H, dt, *J* = 3 and 7.2 Hz, H-5), 4.50 (1 H, d, *J* = 12 Hz, CH_2Ph), 4.63 (1 H, d, *J* = 3.7 Hz, H-6a), 4.70 (1 H, d, *J* = 12 Hz, CH_2Ph), 4.9–5.3 (2 H, m, $=CH_2$), 5.5–6.1 (1 H, m, $=CH$), 5.93 (1 H, d, *J* = 3.7 Hz, H-3a), 7.35 (5 H, s, Ar-H); ^{13}C NMR δ 26.2, 26.7, 32.5, 71.9, 79.8, 82.0, 82.2, 104.8, 111.3, 117.2, 127.7, 127.9, 128.4, 134.3, 137.6; MS *m*/*e* (relative intensity) 275 ($M^+ - CH_3$, 3), 249 (28), 162 (5), 149 (8), 129 (11), 105 (5), 92 (22), 91 (100), 65 (20), 43 (51).

Coupling of Acetate 5 with (Isopropenyloxy)trimethylsilane Promoted by $MgBr_2$. According to the same procedure reported for the allylation of 5 to give 7a and 8a, to $MgBr_2$ (0.55 g, 3 mmol) in CH_2Cl_2 (7 mL) were added in turn a 70% solution in hexamethyldisiloxane of (isopropenyloxy)trimethylsilane (0.95 mL, 4 mmol) and acetate 5 (0.308 g, 1 mmol) in CH_2Cl_2 (10 mL) at 0 °C. GC analysis after 15 h indicates two peaks at t_R 24.1 and 25.0 in the 85/15 ratio corresponding to 7b and 8b, respectively. Column chromatography (cyclohexane–ethyl acetate, 93:7) gave 0.26 g (85%) of a mixture of 7b and 8b. Iterative column chromatography allowed to get 0.05 g of 98% pure (based on GC) of the major isomer corresponding to **[3a*R*(3aα,5β,6β,6aα)]-tetrahydro-2,2-dimethyl-5-(2-oxopropyl)-6-(phenylmethoxy)furo[2,3-*d*]-1,3-dioxole (7b)**: $[\alpha]^{25}_D$ −55° (*c* 1.2, $CHCl_3$); IR 3070, 3030, 2995, 2930, 1720, 1500, 1455, 1385, 1375, 1220, 1170, 1080, 1020, 860, 745, 705; ^1H NMR δ 1.32 (3 H, s, CH_3) 1.60 (3 H, s, CH_3), 2.13 (3 H, s, CH_3), 2.83 (1 H, dd, *J* = 17.4 and 7.4 Hz, $COCH_2$), 2.93 (1 H, dd, *J* = 17.4 and 6.4 Hz, $COCH_2$), 4.04 (1 H, d, *J* = 3.4 Hz, H-6), 4.41 (1 H, d, *J* = 11.6 Hz, CH_2Ph), 4.57 (1 H, ddd, *J* = 7.4, 6.4, and 3.4 Hz, H-5), 4.61 (1 H, d, *J* = 3.8 Hz, H-6a), 4.65 (1 H, d, *J* = 11.6 Hz, CH_2Ph), 5.87 (1 H, d, *J* = 3.8

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Hz, H-3a), 7.22–7.42 (5 H, m, Ar-H); ^{13}C NMR δ 26.2, 26.8, 30.5, 42.2, 72.1, 76.3, 82.3, 104.5, 111.6, 127.7, 128.5, 137.5, 206.3; MS *m/e* (relative intensity) 291 ($M^+ - CH_3$, 1) 245 (4), 169 (3), 141 (10), 100 (3), 99 (3), 92 (8), 91 (100), 65 (7), 43 (33).

Coupling of Acetate 5 with [(1-Phenylethenyl)oxy]trimethylsilane Promoted by $MgBr_2$. According to the same procedure reported for the coupling with (isopropenyloxy)trimethylsilane, by using $MgBr_2$ (0.55 g, 3 mmol), [(1-phenylethenyl)oxy]trimethylsilane (0.768 g, 4 mmol), and acetate **5** (0.308 g, 1 mmol) at 15 °C for 15 h we obtained **7c** containing less than 5% of **8c** on the basis of NMR spectra. Column chromatography (cyclohexane–ethyl acetate, 92:8) gave 0.24 g (65%) of **7c**: IR (Nujol) 3085, 3060, 3030, 1680, 1455, 1450, 1380, 765, 750, 725, 700, 690; ^{1}H NMR δ 1.34 (3 H, s, CH_3), 1.54 (3 H, s, CH_3), 2.08 (3 H, s, CH_3), 342 (1 H, dd, J = 17.7 and 5.5 Hz $COCH_2$), 3.53 (1 H, dd, J = 17.7 and 8.4 Hz, $COCH_2$), 4.20 (1 H, d, J = 3.3 Hz, H-6), 4.39 (1 H, d, J = 11.7 Hz, CH_2Ph), 4.62 (1 H, d, J = 11.7 Hz, CH_2Ph), 4.6–4.72 (1 H, m, H-6a), 4.75–4.90 (1 H, m, H-5), 5.94 (1 H, d, J = 4 Hz, H-3a), 7.1–8.05 (10 H, m, Ar-H); ^{13}C NMR δ 26.4, 26.9, 37.4, 72.2, 77.1, 82.3, 82.6, 104.5, 111.7, 127.8, 128.1, 128.3, 128.6, 133.2, 136.8, 137.4, 197.7; MS *m/e* (relative intensity) 353 ($M^+ - CH_3$, 2), 310 (2), 292 (2), 277 (3), 245 (3), 231 (14), 103 (10), 165 (6), 105 (46), 92 (8), 91 (100), 77 (10), 43 (10).

Coupling of Acetate 5 with Allyltrimethylsilane Promoted by $ZnBr_2$. To $ZnBr_2$ (0.56 g, 2.5 mmol), in CH_2Cl_2 (7 mL) were added in turn at 0 °C allyltrimethylsilane (0.46 g, 4 mmol) and acetate **5** (0.308 g, 1 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at 15 °C for 15 h and quenched with 10% aqueous $NaHCO_3$. Column chromatography afforded 0.19 g (66%) of a mixture of **8a** (t_R 15.9) and **7a** (t_R 16.6) in the 85/15 ratio. An analytical sample of 95% pure **8a** (major product) gave the following spectra: ^{1}H NMR δ 1.36 (3 H, s, CH_3), 1.54 (3 H, s, CH_3), 2.27–2.67 (2 H, m, CH_2), 3.84 (1 H, dd, J = 3.5 and 0.5 Hz, H-6), 4.07 (1 H, dt, J = 3.5 and 7 Hz, H-5), 4.43–4.83 (3 H, m, CH_2Ph and H-6a), 4.9–5.3 (2 H, m, $=CH_2$), 5.5–6.2 (1 H, m, $=CH$), 5.86 (1 H, d, J = 3.9 Hz, H-3a), 7.33 (5 H, s, Ar-H); ^{13}C NMR δ 26.5, 27.2, 38.4, 71.8, 83.9, 84.9, 85.3, 105.6, 113.5, 117.7, 127.7, 127.8, 128.5, 133.9, 137.6; MS *m/e* (relative intensity) 353 ($M^+ - CH_3$, 1), 292 (2), 264 (2), 248 (7), 231 (4), 203 (14), 161 (5), 121 (5), 120 (4), 105 (62), 100 (5), 92 (8), 91 (100), 77 (18), 65 (7).

Coupling of Acetate 5 with (Isopropenyloxy)trimethylsilane Promoted by $ZnBr_2$. The reaction of acetate **5** (0.308 g, 1 mmol), with (isopropenyloxy)trimethylsilane (0.95 mL of a 70% solution in hexamethyldisiloxane, 4 mmol) in the presence of $ZnBr_2$ (0.67 g, 3 mmol) in CH_2Cl_2 (15 mL), gave after 15 h at 15 °C, followed by the usual workup and chromatography, 0.23 g (75%) of **8b** (t_R 25.0) and **7b** (t_R 24.1) in the 2/1 ratio. The following peaks of the NMR spectra were attributed to **8b**: ^{1}H NMR δ 1.30 (3 H, s, CH_3), 1.53 (3 H, s, CH_3), 2.1 (3 H, s, CH_3), 2.8 (1 H, dd, J = 7 and 17 Hz, $COCH_2$), 2.95 (1 H, dd, J = 6.7 and 17 Hz, $COCH_2$), 3.85 (1 H, br s, H-6), 4.35–4.7 (4 H, m, CH_2Ph, H-6a, and H-5), 5.9 (1 H, d, J = 3.8 Hz, H-3a), 7.2–7.38 (5 H, m, Ar-H); ^{13}C NMR δ 25.9, 26.9, 30.6, 47.5, 71.7, 80.7, 84.9, 105.9, 112.4, 127.9, 128.5, 137.5, 206.3.

Coupling of Acetate 6 with Allyltrimethylsilane Promoted by $BF_3{\cdot}Et_2O$. A solution of $BF_3{\cdot}Et_2O$ (0.23 g, 1.6 mmol) in dry dichloromethane (2 mL) was instilled over 15 min into a stirred, cooled (−20 °C) solution of acetate **6** (0.308 g, 1 mmol) and allyltrimethylsilane (0.63 mL, 4.0 mmol) in dry CH_2Cl_2 (15 mL) under argon. After additional 4 h at −20 °C the reaction mixture was quenched with 10% solution of $NaHCO_3$ (15 mL), stirred for 10 min at 15 °C and extracted with ether (60 mL). The organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and evaporated to give an oil, which, upon GC analysis, showed two peaks at t_R 16.2 and 17.6 in the ratio 92/8. Column chromatography (cyclohexane–ethyl acetate, 92:8) allowed to isolate 0.02 g (7%) of **10a** and 0.22 g (75%) of **[3a*R*-(3aα,5β,6α,6aα)]-tetrahydro-2,2-dimethyl-5-(2-propen-1-yl)-6-(phenylmethoxy)furo[2,3-*d*]-1,3-dioxole (9a)**: $[\alpha]^{25}_{D}$ +109.9° (*c* 1.01, $CHCl_3$) and $[\alpha]^{25}_{D}$ +124.7° (*c* 0.19, MeOH); IR 3075, 3015, 2995, 2950, 1645, 1500, 1460, 1390, 1380, 1220, 1170, 1030, 920, 880, 740, 705; ^{1}H NMR δ 1.36 (3 H, s, CH_3), 1.60 (3 H, s, CH_3), 2.12–2.37 (1 H, m, CH_2), 2.40–2.70 (1 H, m, CH_2), 3.45 (1 H, dd, J = 4.36 and 9.0 Hz, H-6), 4.12 (1 H, ddd, J = 4.1, 6.75, and 9.0 Hz, H-5), 4.54 (1 H, d, J = 12 Hz, CH_2Ph), 4.55 (1 H, dd, J = 4.0 and 4.36 Hz, H-6a), 4.78 (1 H, d, J = 12 Hz, CH_2Ph), 4.95–5.30 (2 H, m, $=CH_2$), 5.70–6.0 (1 H, m, $=CH$), 5.91 (1 H, d, J = 4 Hz, H-3a), 7.36 (5 H, m, Ar-H); ^{13}C NMR δ 26.7, 26.8, 36.0, 72.3, 77.4, 77.5, 81.0, 104.3, 112.7, 117.8, 128.4, 128.5, 128.8, 134.2, 138.1; MS *m/e* (relative intensity) 275 ($M^+ - CH_3$, 3), 232 (2), 191 (10), 125 (4), 92 (8), 91 (100), 77 (4), 65 (7), 59 (6), 43 (20).

Coupling of Acetate 6 with [(1-Phenylethenyl)oxy]trimethylsilane Promoted by $BF_3{\cdot}Et_2O$. The reaction between acetate **6** (0.308 g, 1 mmol) and [(1-phenylethenyl)oxy]trimethylsilane (0.77 g, 4 mmol) in the presence of $BF_3{\cdot}Et_2O$ (0.42 g, 3 mmol) in CH_2Cl_2 (15 mL) gave after 1.5 h at −20 °C a mixture of **9c** and **10c** in the 85/15 ratio determined by HPLC analysis. These products were separated by column chromatography (cyclohexane–ethyl acetate, 95:5) to give **[3a*R*(3aα,5β,6α,6aα)]-tetrahydro-2,2-dimethyl-5-(2-phenyl-2-oxoethyl)-6-(phenylmethoxy)furo[2,3-*d*]-1,3-dioxole (9c)** [(0.26 g, 71%) $[\alpha]^{25}_{D}$ +65° (*c* 0.8, $CHCl_3$); IR 3060, 3020, 2980, 2925, 1685, 1595, 1445, 1380, 1370, 1215, 1020, 870, 750, 700; ^{1}H NMR δ 1.34 (3 H, s, CH_3), 1.60 (3 H, s, CH_3), 3.05 (1 H, dd, J = 15.75 and 7.5 Hz, $COCH_2$), 3.23, (1 H, dd, J = 15.75 and 3.75 Hz, $COCH_2$), 3.69 (1 H, dd, J = 4.3 and 9.05 Hz, H-6), 4.54 (1 H, d, J = 12.1 Hz, CH_2Ph), 4.5–4.65 (2 H, m, H-5 and H-6a), 4.80 (1 H, d, J = 12.1 Hz, CH_2Ph), 5.70 (1 H, d, J = 3.8 Hz, H-3a), 7.25–7.58 (8 H, m, Ar-H), 7.90 (2 H, m, Ar-H); ^{13}C NMR δ 26.8, 40.7, 72.3, 74.8, 77.0, 81.4, 104.2, 113.1, 128.1, 128.5, 133.0, 137.2, 197.2; MS *m/e* (relative intensity) 353 ($M^+ - CH_3$, 3), 310 (3), 292 (6), 264 (10), 248 (31), 231 (17), 203 (50), 190 (13), 161 (13), 120 (15), 105 (90), 92 (18), 91 (100), 77 (31), 43 (12)] and **[3a*R*(3aα,5α,6α,6aα)]-tetrahydro-2,2-dimethyl-5-(2-phenyl-2-oxoethyl)-6-(phenylmethoxy)furo[2,3-*d*]-1,3-dioxole (10c)** (0.05 g, 13%): $[\alpha]^{25}_{365}$ −38° (*c* 1.13, $CHCl_3$); IR 3060, 3025, 2995, 2940, 1690, 1600, 1450, 1385, 1215, 1030, 880, 750, 700; ^{1}H NMR δ 1.37 (3 H, s, CH_3), 1.68 (3 H, s, CH_3), 3.38 (1 H, dd, J = 17.3 and 6.1 Hz, $COCH_2$), 3.75 (1 H, dd, J = 17.3 and 6.8 Hz, $COCH_2$), 4.12 (1 H, dd, J = 6.9 and 5.2 Hz, H-6), 4.52 (1 H, d, J = 12 Hz, CH_2Ph), 4.65 (1 H, dd, J = 4.1 and 5.2 Hz, H-6a), 4.68 (1 H, d, J = 12 Hz, CH_2Ph), 4.91 (1 H, q, J = 6.5 Hz, H-5), 5.74 (1 H, d, J = 4.1 Hz, H-3a), 7.25 (5 H, s, Ar-H), 7.35–7.55 (3 H, m, Ar-H), 7.93 (2 H, m, Ar-H); ^{13}C NMR δ 26.3, 27.0, 39.8, 72.7, 77.0, 79.2, 104.9, 113.7, 127.8, 128.2, 128.4, 128.5, 133.0, 198.1; MS *m/e* (relative intensity) 353 ($M^+ - CH_3$, 3), 310 (1), 292 (2), 231 (14), 204 (12), 186 (4), 161 (5), 117 (4), 133 (4), 120 (5), 105 (73), 92 (9), 91 (100), 77 (13), 65 (5), 43 (7).

Coupling of Acetate 6 with Allyltrimethylsilane Promoted by $MgBr_2$. Via the analogous procedure described for the $MgBr_2$-promoted allylation of acetate **5**, we stirred at 0 °C for 5 h allyltrimethylsilane (0.46 g, 4 mmol) and acetate **6** (0.308 g, 1 mmol) in CH_2Cl_2 (10 mL) in the presence of $MgBr_2$ (0.46 g, 2.5 mmol). GC analysis of the crude reaction mixture gave two peaks at t_R 16.2 and 17.6 in the 1/4 ratio. After the usual workup we obtained the allylated products **9a** (0.05 g, 17%) and **10a** (0.19 g, 65%): $[\alpha]^{25}_{D}$ −5.1° (*c*, 0.72, $CHCl_3$); IR 3075, 3030, 2990, 2940, 1645, 1500, 1460, 1385, 1375, 1215, 1160, 1025, 920, 880, 740, 705; ^{1}H NMR δ 1.28 (3 H, s, CH_3), 1.56 (3 H, s, CH_3), 2.35–2.55 (1 H, m, CH_2), 2.55–2.80 (1 H, m, CH_2), 3.92 (1 H, dd, J = 4.9 and 6.85 Hz, H-6), 3.95–4.08 (1 H, m, H-5), 4.52 (1 H, d, J = 12.1 Hz, CH_2Ph), 4.56 (1 H, dd, J = 4.9 and 4.2 Hz, H-6a), 4.68 (1 H, d, J = 12.1 Hz, CH_2Ph), 4.9–5.2 (2 H, m, $=CH_2$), 5.64 (1 H, d, J = 4.2 Hz, H-3a), 5.82 (1 H, ddt, J = 17.2, 10.2 and 7.0 Hz, $=CH$), 7.32 (5 H, m, Ar-H); ^{13}C NMR δ 26.3, 26.7, 35.0, 72.6, 77.5, 79.0, 80.6, 104.7, 113.7, 116.7, 127.8, 128.5, 135.5, 137.2; MS *m/e* (relative intensity) 290 (M^+, tr), 275 (0.5), 263 (1), 205 (1.5), 191 (3), 105 (8), 92 (8), 91 (100), 77 (8), 65 (12), 59 (10), 55 (8), 43 (32).

Coupling of Acetate 6 with [(1-Phenylethenyl)oxy]trimethylsilane Promoted by $MgBr_2$. The reaction between acetate **6** (0.308 g, 1 mmol) and [(1-phenylethenyl)oxy]trimethylsilane (0.77 g, 4 mmol) in the presence of $MgBr_2$ (0.55 g, 3 mmol) in CH_2Cl_2 (15 mL) gave after 10 h at 0 °C a mixture of **9c** and **10c** in the 30/70 ratio in the 84% overall yield.

Coupling of Acetate 6 with (Isopropenyloxy)trimethylsilane Promoted by $MgBr_2$. The reaction between acetate **6** (0.308 g, 1 mmol) and [(isopropenyl)oxy]trimethylsilane (0.95 mL of a 70% solution in hexamethyldisiloxane, 4 mmol) in the presence of $MgBr_2$ (0.55 g, 3 mmol) in CH_3NO_2 (15 mL) gave, after 3 h at 0 °C, a mixture of **10b** (t_R 26.2) and **9b** (t_R 25.4) in the 82/18 ratio. Column chromatography (cyclohexane–ethyl acetate, 94:6) allowed to separate **[3a*R*(3aα,5α,6α,6aα)]-tetrahydro-2,2-dimethyl-5-(2-oxoprop-1-yl)-6-(phenylmethoxy)furo[2,3-*d*]-**

1,3-dioxole (10b) [(0.21 g, 70%) $[\alpha]^{25}_D$ +17° (*c* 0.73, $CHCl_3$); IR 3060, 3040, 2980, 2940, 1710, 1500, 1460, 1380, 1370, 1050, 1030, 880, 740, 700; ^1H NMR δ 1.34 (3 H, s, CH_3), 1.64 (3 H, s, CH_3), 2.14 (3 H, s, CH_3), 2.93 (1 H, dd, *J* = 16.8 and 7.05 Hz, $COCH_2$), 3.06 (1 H, dd, *J* = 16.8 and 6.6, $COCH_2$), 4.03 (1 H, dd, *J* = 7.1 and 5.1 Hz, H-6), 4.53 (1 H, d, *J* = 12 Hz, CH_2Ph), 4.59 (1 H, dd, *J* = 5.1 and 4.0 Hz, H-6a), 4.67 (1 H, q, *J* = 6.7 Hz, H-5), 4.68 (1 H, d, *J* = 12 Hz, CH_2Ph), 5.68 (1 H, d, *J* = 4 Hz, H-3a), 7.34 (5 H, s, Ar-H); ^{13}C NMR δ 26.1, 26.8, 31.0, 44.5, 72.6, 76.5, 77.1, 78.8, 104.8, 113.5, 127.9, 128.0, 128.5, 137.5, 206.9; MS *m/e* (relative intensity) 291 ($M^+ - CH_3$, 2), 248 (1), 230 (1), 190 (3), 169 (5), 147 (4), 142 (9), 141 (9), 105 (6), 99 (6), 92 (15), 91 (100), 65 (8), 59 (5), 43 (41)] and **[3a*R*(3aα,5β,6α,6aα)]-tetrahydro-2,2-dimethyl-5-(2-oxoprop-1-yl)-6-(phenylmethoxy)furo[2,3-*d*]-1,3-dioxole (9b)** (0.05 g, 90% pure on the basis of GC): IR 3060, 3040, 2980, 1710, 1500, 1460, 1380, 1370, 1050, 1030, 880, 740, 700; ^1H NMR δ 1.35 (3 H, s, CH_3), 1.61 (3 H, s, CH_3), 2.17 (3 H, s, CH_3), 2.50 (1 H, dd, *J* = 15.2 and 8.0 Hz, $COCH_2$), 2.72 (1 H, dd, *J* = 15.2 and 4.0 Hz, $COCH_2$), 3.53 (1 H, dd, *J* = 9.0 and 4.2 Hz, H-6), 4.41 (1 H, ddd, *J* = 9.0, 8.0, and 4.0 Hz, H-5), 4.53 (1 H, d, *J* = 11.8, CH_2Ph), 4.54 (1 H, dd, *J* = 4.2 and 3.7 Hz, H-6a), 4.78 (1 H, d, *J* = 11.8 Hz, CH_2Ph), 5.71 (1 H, d, *J* = 3.7, H-3a), 7.35 (5 H, s, Ar-H); ^{13}C NMR δ 26.6, 26.8, 31.3, 45.9, 72.5, 74.6, 77.2, 81.4, 104.4, 112.8, 128.4, 128.5, 128.9, 137.7, 206.5.

Correlation of Products 7a and 9a to Known Compounds. Acidic hydrolysis of a sample of **7a** containing 10% of **7b** (0.75 g, 2.6 mmol) was carried out in THF (10 mL) with 2 N HCl (10 mL) at 60 °C for 4 h. After cooling to 20 °C, neutralization with 10% $NaHCO_3$ and extraction with ethyl acetate gave 0.63 g of crude product, which was dissolved in EtOH (10 mL), cooled at 0 °C, and treated with 0.1 g (2.76 mmol) of $NaBH_4$. The reaction mixture was stirred at 20 °C for 2 h and then decomposed with brine (2 mL). Ethanol was evaporated under vacuum, and oil obtained was extracted with EtOAc (4 × 15 mL). The organic layer was washed with brine, dried over Na_2SO_4, and chromatographed (cyclohexane–ethyl acetate, 25:75) to give 0.58 g (89%) of **(2*S*,3*S*,4*R*)-3-(phenylmethoxy)-6-heptene-1,2,4-triol (11)** (containing 6% of its 4*S* epimer): IR 3450, 1640, 1090, 1080, 1020, 750, 700; ^1H NMR δ 2.35 (2 H, t, *J* = 7 Hz, H-5), 3.15 (2 H, br s, OH), 3.47 (1 H, dd, *J* = 2 and 4.8 Hz, H-3), 3.6–4.0 (4 H, m, H-1, H-2 and H-4), 4.66 (2 H, s, CH_2Ph), 4.9–5.3 (2 H, m, H-7), 5.4–6.2 (1 H, m, H-6), 7.33 (5 H, s, Ar-H); ^{13}C NMR δ 38.8, 62.5, 70.1, 71.1, 74.6, 80.3, 118.0, 128.2, 128.6, 134.5, 137.7; MS *m/e* (relative intensity) 203 ($M^+ - H_2O$ and $-CH_2OH$, 2.5), 164 (15), 146 (3), 133 (3), 118 (3), 107 (7), 92 (20), 91 (100), 65 (7).

The triol 11 (0.3 g, 1.2 mmol) dissolved in dry acetone (10 mL) was stirred at 20 °C in the presence of pyridinium *p*-toluenesulfonate (10% mol), for 5 h. Water (3 mL) was added, acetone was evaporated, and the aqueous layer was extracted with ethyl acetate. The residue, after solvent evaporation, was dissolved in CH_2Cl_2 (10 mL), treated with pyridine (0.12 mL, 1.6 mmol) and benzoyl chloride (0.14 mL, 1.2 mmol) at room temperature, and stirred overnight. The reaction was decomposed with 10% $NaHCO_3$ and extracted with ether. The ether layer was washed quickly with cold 0.5 N HCl (three times), and then with water, 10% $NaHCO_3$, and brine. Column chromatography (cyclohexane–ethyl acetate, 96:4) gave 0.26 g (80%) of pure **(4*S*)-4-[(1*S*,2*R*)-1-(phenylmethoxy)-2-(benzoyloxy)-4-penten-1-yl]-2,2-dimethyl-1,3-dioxole (13)**, which was identical on the basis of optical rotation and ^1H NMR with the product reported by Williams et al.[13] The same synthetic sequence was repeated starting from pure **9a** to get first **(2*S*,3*R*,4*R*)-3-(phenylmethoxy)-6-heptene-1,2,4-triol (14)** as a solid: mp 54–56 °C; $[\alpha]^{25}_D$ +5.5° (*c* 0.95, $CHCl_3$); IR (Nujol) 3440, 3340, 1640, 1090, 1080, 1025, 755, 705; ^1H NMR (after D_2O exchange) δ 2.15–2.35 (1 H, m, H-5), 2.45–2.65 (1 H, m, H-5), 3.4 (1 H, t, *J* = 6 Hz, H-3), 3.6–4.0 (4 H, m, H-1, H-2, and H-4), 4.6 (1 H, d, *J* = 12 Hz, CH_2Ph), 4.65 (1 H, d, *J* = 12 Hz, CH_2Ph), 5.05–5.25 (2 H, m, H-7), 5.7–6.0 (1 H, m, H-6), 7.35 (5 H, s, Ar-H); ^{13}C NMR δ 38.0, 63.3, 71.5, 72.6, 74.0, 81.7, 118.6, 128.0, 128.4, 128.6, 134.5, 137.8; MS *m/e* (relative intensity) 203 ($M^+ - H_2O$ and $-CH_2OH$, 2.5), 164 (15), 146 (3), 133 (3), 118 (3), 107 (7), 92 (20), 91 (100), 65 (7). The triol **14** was subjected to the previously described acetonation and benzoylation reaction to afford **(4*S*)-4-[(1*R*,2*R*)-1-(phenylmethoxy)-2-(benzoyloxy)-4-penten-1-yl]-2,2-dimethyl-1,3-dioxole (16)** identical with the product described by Williams.[13]

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Registry No. **1**, 23558-05-6; **2**, 63593-02-2; **3**, 39682-04-7; **4**, 120417-90-5; 5α-**5**, 120417-91-6; 5β-**5**, 120520-93-6; **6**, 120520-94-7; **7a**, 89755-56-6; **7b**, 120417-93-8; **7c**, 120417-95-0; **8a**, 120417-92-7; **8b**, 120417-94-9; **9a**, 120417-96-1; **9b**, 120418-00-0; **9c**, 120417-98-3; **10a**, 120417-97-2; **10b**, 120418-01-1; **10c**, 120417-99-4; **11**, 120520-95-8; **13**, 111555-40-9; **14**, 120418-02-2; **16**, 111611-84-8; $H_2C{=}CHCH_2SiMe_3$, 762-72-1; $H_2C{=}C(CH_3)OSiMe_3$, 1833-53-0; $H_2C{=}C(Ph)OSiMe_3$, 13735-81-4; D-glucose, 50-99-7; (*R*,*R*)-tartaric dialdehyde, 66213-22-7; *meso*-tartaric dialdehyde, 58066-70-9.

Isolation, Structure, and Synthesis of Combretastatin C-1[1]

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A new cell growth inhibitory (PS ED_{50} 2.2 μg/mL) phenanthraquinone designated combretastatin C-1 (**2**) has been isolated from the African tree *Combretum caffrum*. The structure (**2**) assigned combretastatin C-1 was based on high-resolution mass and NMR spectral analyses and confirmed by total syntheses. Synthetic routes **5b** → **6b** → **2** and especially **5c** → **6c** → **2** proved to be quite practical.

The Cape bush willow *Combretum caffrum* (Eckl. and Zeyh.) Kuntz (Combretaceae) is a deciduous African tree found principally in the Eastern Cape and Transki (to Natal). In autumn, these trees become quite prominent with displays of reddish-brown fruit and leaves that turn bright red prior to falling.[2] Previously, we summarized[3a] the significance of this plant to the Zulu, application of closely related species in primitive medicine, and isolation of a series of cell growth inhibitory *cis*-stilbenes,[3a,b] bibenzyls,[3c] phenanthrenes,[3d] and dihydrophenanthrenes.[3d]

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(1) Antineoplastic Agents series contribution 166. For part 165 refer to *Can. J. Chem.*, in press.

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