Tetrahedron Vol. 45, No. 5, pp. 1475 to 1490, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00

CHIRAL PRECURSORS FOR SYNTHESES OF FURANOTERPENES

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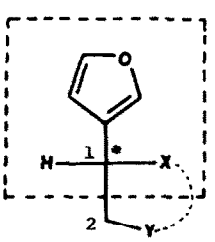
(*Received in UK* 26 *September* 1988)

Abstract.- The synthesis of (2S,4R,5R) and (2R,4R,5R)-2-(3-furyl)-4,5-isopropylidenedioxytetrahydrofuran (4 and 5) and (2S,4R,5S)-5-ethoxy-2-(3-furyl)-4-hydroxytetrahydrofuran (37) from "diacetone glucose" (6) is described. A new approach to 1-(R) and 1-(S)-(3-furyl)-1,2-dihydroxyethane from L-serine and D-mannitol, respectively, is described. These compounds are convenient chiral precursors for syntheses of furanoterpenes.

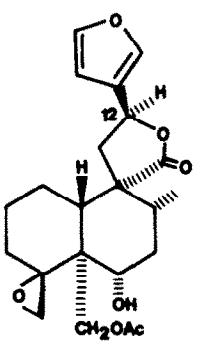
INTRODUCTION

The β-substituted furan ring is a very common structural feature of many natural products.[1] Although some methods have been reported for the synthesis of β-substituted furans,[2] the synthesis of enantiomerically pure compounds of type A (X,Y= OH, OH protecting group, O-functionalization, good leaving group, C-alkyl substitution, etc, in cyclic or acyclic form), having a stereocenter contiguous to the aromatic ring, has been almost neglected. It is evident that



A

1 X, Y = OH



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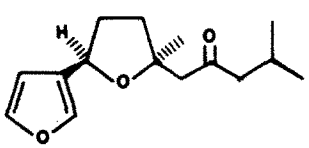

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these compounds are important and critical "chirons" for the asymmetric synthesis of natural products containing this structural and functional moiety [see for example teupolin I, (2)[3]].

Not surprisingly no chiral approach up to now has been reported for the synthesis of this kind of furanoterpenes.[4]

To our knowledge, the only reported synthetic approach in this area has been described by Zamojski and Jarosz.[5a] They prepared 1-(R) and the methyl ester of the corresponding carboxylic acid in a very low e.e.(~7%) by asymmetric photocycloaddition between furan and chiral alkyl glyoxylates. Kato and coworkers[5b] have also described the reaction of L-(-)-carvone with lithium di(3-furyl)cuprate, but the stereochemical course of this process was not studied.

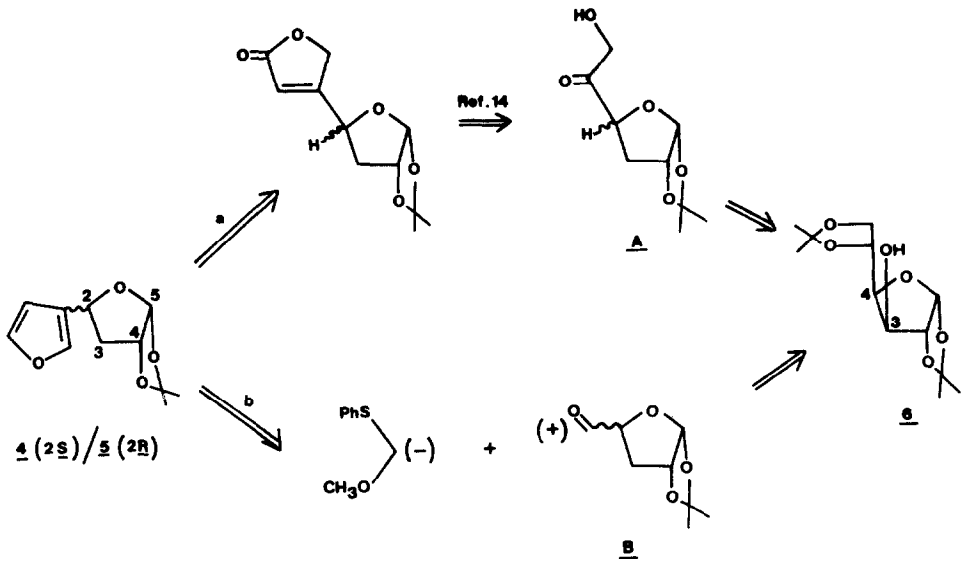
The lack of a general and efficient method for the synthesis of these "β-furochirons" prompted us to explore this subjet. In this communication we describe the synthesis of (2S,4R,5R) and (2R,4R,5R)-2-(3-furyl)-4,5-isopropylidenedioxytetrahydrofuran (4 and 5) and (2S,4R,5R)-5-ethoxy-2-(3-furyl)-4-hydroxytetrahydrofuran (37), as potentially useful and key chiral intermediates in the synthesis of 2,[3] (+)-ipomeamarone 3,[6] fraxinellone[4a] or ancistrofuran[4c], some furanoterpenes with interesting biological activities. Otherwise the synthesis of 4, 5, 37, compounds with a defined absolute stereochemistry at C-2 (see Scheme 1), could help the structural analysis of natural products related to 2, where some difficulties have been claimed in the establishment of the stereochemistry at C-12.[7] Even more, these compounds represent a new class of higher-carbon sugars.[8] In addition, a new approach to (R) and (S)-(3-furyl)-1,2-dihydroxyethane 1 is described.

RESULTS AND DISCUSSION

In our retrosynthetic analysis (see Scheme 1), compounds 4 or 5 could arise from "diacetone glucose" 6, following the routes a or b. In the route a the key intermediate is the α-hydroxyketone A, in principle accessible by simple operations from 6. In the route b, the critical intermediate is the aldehyde B; the final steps leading to the β-furan synthesis should follow the method described by Otera.[9] The merits of 6[10] as common starting material are obvious: it can be obtained in large quantities, deoxygenation at C-3 and epimerization at C-4 are well documented in the literature and it contains the basic framework and functionalization of 4 and 5.

In the route a the steps are: deoxygenation at C-3 in 6,[11,12] selective hydrolysis[13], protection at C-6, oxidation and deprotection.

Due to problems of solubility (see Scheme 2), the silylation[14] of 7[11-13] gave a low yield (20%) of 8. Oxidation [15](PDC,methylene chloride, molecular sieves) gave 9 (61% yield). Treatment of 9 with tetra n-butylammonium fluoride[16] resulted in a complex mixture and we could not isolate the desired com-

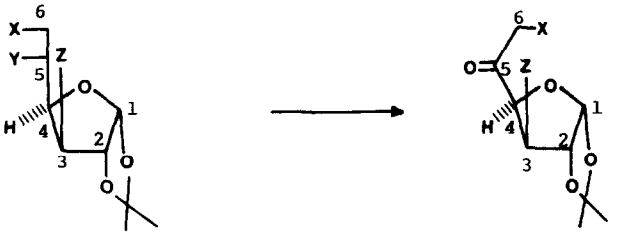


Scheme 1

pound 10. In view of this, we decided to carry out this process with the xanthate group at C-3 and deoxygenate in the last step. With this analysis in mind compound 11[11] was easily silylated.[16] Oxidation again as before, gave 13 (80% yield from 12). Deprotection of 13 was troublesome and we could not isolate 14. Using the pivaloyl group and repetition of the sequence (15 ⟶ 16 ⟶ 17 ⟶ 10) failed again in the last step.

In view of these unexpected facts, we analyzed the route b (Scheme 1).

Before, we examined this chemistry in a simple model[17] (see Scheme 3) using compound 18[18] as the chiral template, readily available in enantiomerically pure form from L-serine. One carbon homologation with lithium methoxymethyl phenyl sulfide[19] gave 19[3-(S)] as a mixture of diastereomers in a 1:1.75 ratio, as it was deduced integrating the areas corresponding to H_1 (s, δ 5.37 and 5.45). Compound 19[3-(S)] is an interesting C_4-chiral building block with a plethora of versatile functional groups and defined stereochemistry at C-3. Following the method described by Otera,[19] we obtained easily and in good yield 20a and 20b. Compounds 19[3-(S)]-20b were obtained pure by simple chromatography and we did not try to separate isomers.[19] Finally treating 20b in benzene at



Ref. 11-13

6 ⟹ 7 X = Y = OH , Z = H

8 X = OSi(CH$_3$)$_2$ t-Bu, Y = OH , Z = H

11 X = Y = OH, Z = OC(S)SCH$_3$

12 X = OSi(CH$_3$)$_2$ t Bu, Y = OH, Z = OC(S)SCH$_3$

15 X = OCO t Bu, Y = OH, Z = OC(S)SCH$_3$

9 X = OSi(CH$_3$)$_2$ t Bu , Z = H

10 X = OH , Z = H

13 X = OSi(CH$_3$)$_2$ t Bu, Z = OC(S)SCH$_3$

14 X = H, Z = OC(S)SCH$_3$

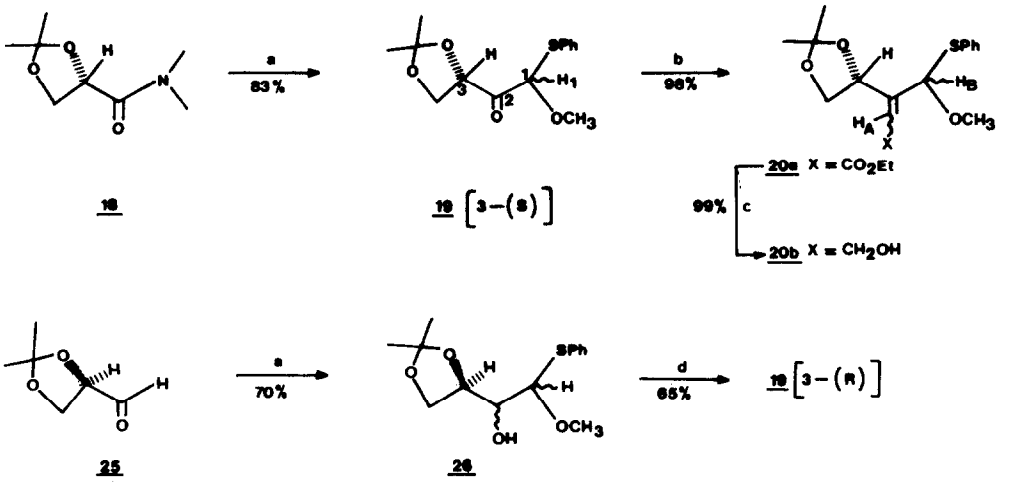
16 X = OCO t Bu, Z = OC(S)SCH$_3$

17 X = OCO t Bu, Z = H

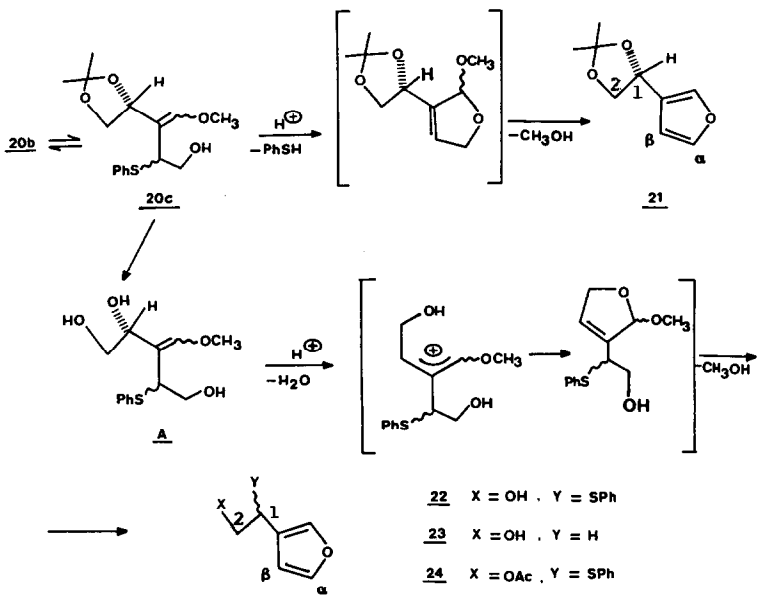
Scheme 2

room temperature with p-toluenesulfonic acid, we obtained 21 (~20% yield) and 22 (65% yield) (see Scheme 4). The formation of 21 is explained following the mechanism proposed by Otera.[19] The unexpected side product 22, whose structure has been inequivocally established transformating it into 23 and 24 (see Experimental Part), could arise by an acid catalyzed thioallylic rearrangement[20] (20b ⟶ 20c) (Scheme 4), acid hydrolysis of the acetonide group in 20c to give A, which in the acidic medium should be transformed into 22[21], after dehydration, ring closure and aromatization with loss of methanol.

Compound 21, contaminated with an unseparable aromatic impurity, was converted into 1-(R) by acid hydrolysis (CF_3COOH, CH_3CN, H_2O, room temperature,



Scheme 3. a: n-BuLi, $PhSCH_2OCH_3$, THF, -78°C, 1 h. b: $(EtO)_2POCH_2CO_2Et$, NaH, THF, r.t., overnight. c: DIBAL, Et_2O, -30°C, 1 h. d: PDC, CH_2Cl_2, powdered molecular sieves (4Å), r.t., overnight.



Scheme 4

overnight, 90%). Compound 1-(R) showed spectroscopic and analytical data in good agreement with its structure, but its physical data [mp 82-84°C; $[\alpha]_D^{25}$ -19.0° (c 0.55, $CHCl_3$)] are different from the previously described[5a] [mp 55°C; $[\alpha]_D^{25}$ +15° (c 1.6, EtOH)].

To clarify this question, we undertook the synthesis of 1-(S) by the same method. As chiral template we used the easily available aldehyde 25.[22] Reaction with lithium methoxymethyl phenyl sulfide gave a complex mixture of diastereomers 26 (see Scheme 3), that without separation and after oxidation gave 19 [3-(R)] , as a mixture of two diastereomers, similar to 19 [3-(S)] (t.l.c. analysis with different solvents, spectroscopic data). The microanalysis confirmed the structure. It was then clear that no overoxidation at the sulfur atom took place. Following the same methodology : 19[3-(R)] ⟶ 20a [3-(S)] ⟶ 20b [3-(S)] ⟶ 21-(S), we obtained 1-(S) [mp 79-81°C; $[\alpha]_D^{25}$ +21° (c 0.2, $CHCl_3$)]. In view of these results, we think that the previously reported physical data for 1-(R) should be reanalyzed.[5a]

With the experience obtained with the simple chiral templates 18 and 25, we directed our attention to a more complicated system in order to obtain the desired compounds 4 and 5.

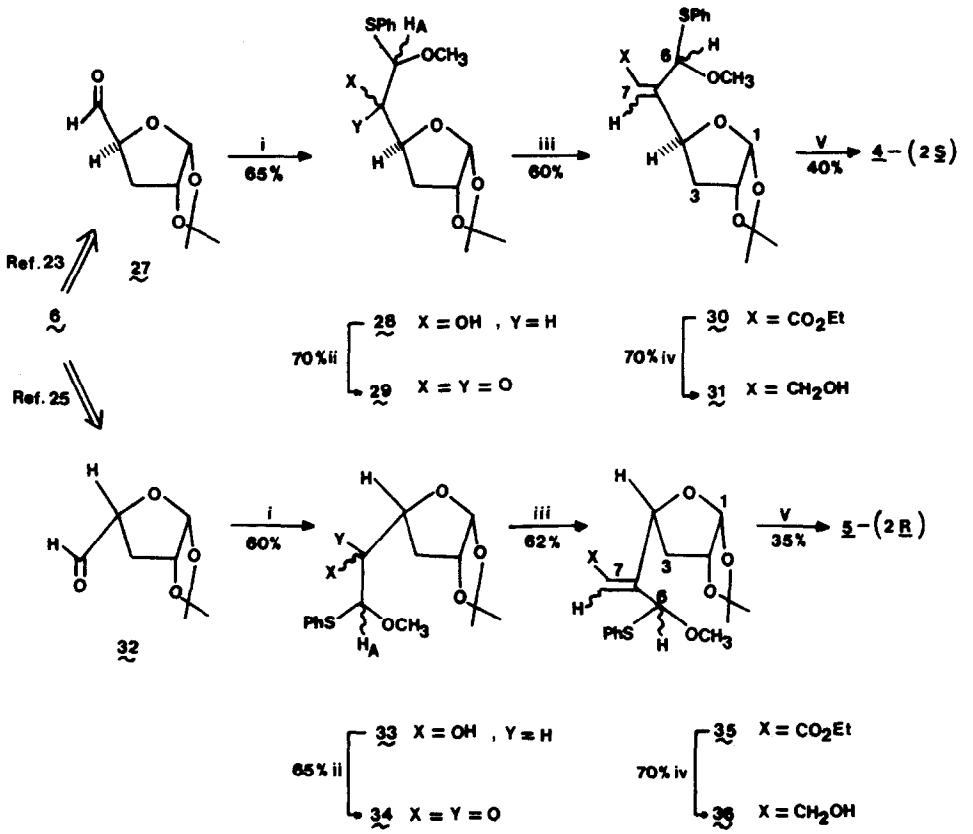
Starting with compound 6 and following methods well documented in the literature,[23] the aldehyde 27 was easily obtained (Scheme 5). One carbon homologation with lithium methoxymethyl phenyl sulfide afforded 28 as a mixture of diastereomers that, after purification, without separation and oxidation[13] gave cleanly ketone 29.[24] Compounds 30 and 31 were obtained following the standard methods.[19]

The epimer at C-4, 32 (see Scheme 5)was easily synthesized from 6.[25] Following the same methodology compound 36 was obtained in good yield from 32.

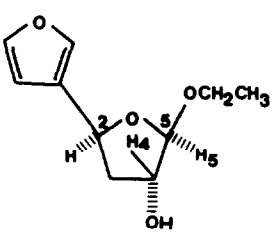
With 31 and 36 in hand, we affronted the last step. Treating 31 in benzene, at room temperature, with a catalytic amount of p-toluenesulfonic acid, we obtained 4 [mp 60-63°C; $[\alpha]_D^{25}$ -19.3° (c, 1.1, $CHCl_3$)] . Using 36, under the same conditions, we prepared 5 in 35% yield [mp 59-62°C; $[\alpha]_D^{25}$ -17° (c, 0.49, $CHCl_3$)].

In the ^1H NMR (200 MHz) spectrum of 4, besides the furanic protons (δ 7.43, 1H, m; 7.39, 1H, t, J=1.7 Hz; 6.40, 1H, dd, J=1.7 and 0.9 Hz), H_5 appears at δ 5.95 (d, $J_{4,5}$=4.3 Hz), H_4 at δ 4.82 (t, $J_{4,5}$=4.3 Hz, $J_{4,3\beta}$=4.3 Hz), $H_{3\beta}$ at δ 1.82 (ddd, $J_{3\alpha,3\beta}$=14 Hz, $J_{3\beta,4}$=4.3 Hz, $J_{3\beta,2}$=11 Hz), $H_{3\alpha}$ at 2.32 (dd, $J_{3\alpha,3\beta}$=14 Hz, $J_{3\alpha,2}$=4.3 Hz) and H_2 at δ 5.14 (dd, $J_{2,3\alpha}$=4.3 Hz, $J_{2,3\beta}$=11 Hz). This is in accordance with the observed values in 3-deoxy furanose compounds.[23] Compound 5 , the epimer at C-2, showed similar chemical shifts, coupling constants and physical data to the observed for 4. This is not surprising and has been pointed out by some authors[7] in connection with the establishment of the absolute configuration at C-12 in the large family of diterpenoids related to 2, where epimers at C-12 have been isolated and analyzed.

Finally, compound 4 was submitted to acid hydrolysis (EtOH, HCl). We only obtained one compound, 37, whose structure was established by careful ana-



Scheme 5. i: n-BuLi, $PhSCH_2OCH_3$, THF, -78°C, 1 h. ii: PDC, CH_2Cl_2, powdered molecular sieve 4 Å, r.t., overnight. iii: NaH, $(EtO)_2POCH_2CO_2Et$, THF, r.t., overnight. iv: DIBAL, Et_2O, -30°C, 1 h. v: p-TsOH, benzene, r.t., 15 min.



37

lysis of its ^{1}H NMR spectrum. The ethoxy group at C-5 is cis respect to the furan ring at C-2, as it is evident from the analysis of H_5 (δ 4.97 ppm, s, $J_{4,5}$=0 Hz). This is in agreement with the coupling constants ($J_{4,5}$) recorded in the literature for α and β glicosides in related compounds.[26]

We have not found an easy explanation for the stereospecific formation of the β-glucoside. F. Fraser-Reid reported the formation of mixtures of the α,β-anomers (1:1) in related 5-deoxy-α-D-xylofuranones[26a] but it is also known the exclusive formation of the β-glicoside in the hydrolysis of analogous 3,5-dideoxy-α-D-ribofuranoses.[26e] It has been pointed out[27] that in furanoses two hydroxyl groups on adjacent carbon atoms are more stable when trans rather than cis; in equilibrium, therefore, the anomer having O-1 and O-2 trans predominates (β for xyloses and riboses, as it is the case in 37).

In summary we have described for the first time and using the "chiron" approach,[28] the synthesis of some furan type higher-carbon sugars and chiral precursors for syntheses of some natural furanoterpenes.

EXPERIMENTAL

Melting points are uncorrected and were determined in a Kofler apparatus. Optical rotations were measured with a Perkin-Elmer 141 polarimeter with a 1-dm cell. Elemental analyses were carried out in Madrid with the help of a Perkin-Elmer 240 analyzer. IR spectra were determined on a Perkin-Elmer 257 spectrometer. ^{1}H NMR spectra were measured on a Varian EM 390, Varian XL-300 or a Bruker AM-200 spectrometer using tetramethylsilane as internal standard. Mass spectra were obtained with a AEI MS 50 spectrometer. For column chromatography, the flash-chromatography technique on silica gel was used.[29]

6-O-(tert-Butyldimethylsilyl)-3-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (8). To a suspension of 3-deoxy-1,2-O-isoprpopylidene-D-glucopfuranose[13] (7) (1.6 g, 8.1 mmol) in dry pyridine (30 mL) was added tert-butyldimethylsilyl chloride (1.2 g, 8.1 mmol). The reaction mixture was stirred for 24 h, diluted with methylene chloride, washed with cold 0.5 N hydrochloric acid and brine, dried and concentrated. Flash-chromatography (90:10 hexane-ethyl acetate) gave 508 mg (20%) of (8) as a viscous oil: $[\alpha]_D^{25}$ -9.4° (c 1.1, $CHCl_3$); IR υ_{max}(film): 3600-3100, 2980, 1460, 1370, 1365, 1075; ^{1}H NMR (90 MHz, $CDCl_3$) δ: 5.70 (d,1H, J=4 Hz, H-1), 4.65 (t, 1H, J=4 Hz, H-2), 4.15 (m, 1H, H-4), 3.55-3.70 (m, 3H, 2H-6, H-5), 2.40 (br s, 1H, OH), 1.80-2.20 (m, 2H, 2H-3), 1.40, 1.25 [s, s, 6H, $C(CH_3)_2$], 0.80 [s, 9H, $(CH_3)_3Si$]; MS m/e: 303 (M-15, 30), 269 (17), 267 (12), 243 (16), 204 (12), 203 (82), 185 (47), 173 (14), 159 (17), 143 (36), 117 (87), 89 (49), 75 (100), 59 (61), 43 (71).

Anal. Calcd. for $C_{15}H_{30}SiO_5$: C, 56.54; H, 9.49. Found: C, 56.20; H, 9.31.

6-O-(tert-Butyldimethylsilyl)-3-deoxy-1,2-O-isopropilidene -α-D-xylo-hexofuran-5-ulose (9). To a suspension of PDC[30] (413 mg, 1.1 mmol) and 1.0 g of powdered molecular sieves (4 Å) in dry methylene chloride (10 mL) was added a solution of 8 (240 mg, 0.75 mmol) in 7 mL of dry methylene chloride. After stirring overnight at room temperature, ether was added and the mixture was filtered over Celite 545. Evaporation and flash-chromatography afforded 148 mg (61%) of 9: mp 74-75°C; $[\alpha]_D^{25}$ -57° (c 0.5, $CHCl_3$); IR υ_{max}(KBr): 2960, 1730, 1385, 1370, 1255, 1140, 1030, 840; ^{1}H NMR (90 MHz, $CDCl_3$) δ: 5.85 (d, 1H, J=4 Hz, H-1), 4.65-4.90 (m, 2H, H-2, H-4), 4.45 (s, 2H, 2 H-6), 2.40 (dd, 1H, J=14 and 5 Hz, H-3α), 1.80 (m, 1H, H-3β), 1.55, 1.35 [s, s, 6H, $C(CH_3)_2$], 0.95 [s, 9H, $(CH_3)_3Si$]; MS m/e: 301 (M-15, 11), 259 (12), 201 (71), 171 (12), 155 (12), 117 (100), 85 (66), 43 (37).

Anal. Calcd. for $C_{15}H_{28}SiO_5$: C, 56.90; H, 8.92. Found: C, 57.02; H, 9.00.

Xanthate of 6-O-(tert-butyldimethylsilyl)-1,2-O-isopropylidene -α-D-glucofuranose (12). To a solution of xanthate (11)[11] (1.1 g, 3.5 mmol) in dry dimethylformamide (20 mL) was added under argon tert-butyldimethylsilyl chloride (572 mg, 3.8 mmol) and imidazole (516 mg, 7.6 mmol). The reaction mixture was stirred at room temperature for 24 h. Water was added and the product extracted with ether (3x100 mL); the combined ether extracts were washed with water, dried (Na_2SO_4), evaporated and purified by flash-chromatography (80:20 hexane-ethyl acetate) to give 1.2 g (80%) of 12: Oil; $[\alpha]_D^{25}$-17.3° (c 1.1, $CHCl_3$); IR υ_{max}(film):3550-3200, 2950, 1465, 1385, 1375, 1200, 1175, 840; ^{1}H NMR (90 MHz, $CDCl_3$) δ: 6.05 (d, 1H, J=3 Hz, H-1), 5.95 (d, 1H, J=4 Hz, H-3), 4.65 (d, 1H, J=3 Hz, H-2), 4.30 (m, 1H, H-4), 3.70-3.90 (m, 3H, 2 H-6, H-5), 2.60 [s, 3H, $OC(S)SCH_3$], 2.50 (br s, 1H, OH), 1.55, 1.30 [s, s, 6H, $C(CH_3)_2$], 0.95 [s, 9H, $(CH_3)_3Si$]; MS m/e: 309 (31), 201 (17), 171 (12), 117 (100), 91 (35), 75 (91), 43 (33).

Anal. Calcd. for $C_{17}H_{32}S_2SiO_6$: C, 48.11; H, 7.54; S, 15.09. Found: C, 48.30; H, 7.79; S, 14.80.

Xanthate of 6-O-(tert-butyldimethylsilyl)-1,2-O-isopropylidene-α-D-xylo-hexofuran-5-ulose (13). Oxidation of 12 to 13 was carried out as described for the preparation of 9. For 13 (82%): Viscous oil; $[\alpha]_D^{25}$-15.8° (c 5.6, $CHCl_3$); IR υ_{max}(film): 2940, 1740, 1470, 1385, 1375, 1190, 1070, 840; ^{1}H NMR (90 MHz, $CDCl_3$) δ: 6.30 (d, 1H, J=4 Hz, H-1), 6.10 (d, 1H, J=3 Hz, H-3), 5.20 (d, 1H, J=3 Hz, H-4), 4.75 (d, 1H, J=4 Hz, H-2), 4.45 (s, 2H, 2 H-6), 2.55 [s, 3H, $OC(S)SCH_3$], 1.55, 1.35 [s, s, 6H, $C(CH_3)_2$], 0.90 [s, 9H, $(CH_3)_3Si$]; MS m/e: 423 (M+1, 10), 365 (65), 257 (13), 211 (17), 199 (45), 190 (12), 186 (11), 171 (56), 159 (13), 117 (26), 91 (86), 75 (100), 43 (55).

Anal. Calcd. for $C_{17}H_{30}S_2SiO_6$: C, 48.34; H, 7.10; S, 15.16. Found: C, 48.01; H, 6.85; S, 14.99.

Xanthate of 1,2-O-isopropylidene-6-O-(pivaloyl)-α-D-glucofuranose (15). To a solution of xanthate 11 (1.95 g, 6.2 mmol) in dry pyridine, cooled at -10°C, under argon, was added recently distilled pivaloyl chloride (0.82 mL, 6.8 mmol). The reaction mixture was warmed to room temperature and stirred

for 16 h, diluted with ether and washed with ice-cold 0.5N hydrochloric acid and brine, dried (Na_2SO_4) and evaporated. The residue was submitted to flash-chromatography (20:80 hexane-ethyl acetate) to afford 2 g of 15 (80%): Oil; $[\alpha]_D^{25}$ + 13.9° (c 6.0, $CHCl_3$); IR υ_{max}(film): 3600-3200, 1730, 1715, 1480, 1380, 1375, 1200, 1070; ^{1}H NMR (90 MHz, $CDCl_3$) δ: 6.15 (d, 1H, J=3 Hz, H-1), 5.95 (d, 1H, J=3.5 Hz, H-3), 4.70 (d, 1H, J=3 Hz, H-2), 4.20-4.40 (m, 4H, 2 H-6, H-5, H-4), 2.90 (br s, 1H, OH), 2.60 [s, 3H, OC(S)SCH_3], 1.55, 1.35 [s, s, 6H, $C(CH_3)_2$], 1.25 [s, 9H, $(CH_3)_3Si$]; MS m/e: 361 (1), 347 (1), 129 (7), 88 (13), 84 (100), 57 (51), 43 (26).

Anal. Calcd. for $C_{16}H_{26}S_2O_7$: C, 48.72; H, 6.64; S, 16.12. Found: C,48.40; H, 6.31; S, 15.89.

Xanthate of 1,2-O-isopropylidene-6-O-(pivaloyl)-α-D-xylo-hexofuran-5-ulose (16). Oxidation of 15 to 16 was performed as described for the preparation of 9. For 16: Viscous oil; $[\alpha]_D^{25}$-68.1° (c 5.6, $CHCl_3$); IR υ_{max}(film): 2900,1740, 1385, 1375, 1150-1200, 1080, 1020; ^{1}H NMR (90 MHz, $CDCl_3$) δ: 6.20 (d, 1H, J=3 Hz, H-1), 6.10 (d, 1H, J=3.5 Hz, H-3), 4.95-5.05 (m, 3H, 2 H-6, H-4), 4.75 (d, 1H, J=3 Hz, H-2), 2.55 [s, 3H, OC(S)SCH_3], 1.55, 1.35 [s, s, 6H, $C(CH_3)_2$], 1.25 [s, 9H, $OC(O)C(CH_3)_3$]; MS m/e: 347 (1), 331 (2), 249 (12), 226 (8), 191 (15), 143 (55), 85 (64), 57 (100).

Anal. Calcd. for $C_{16}H_{24}S_2O_7$: C, 48.98; H, 6.17; S, 16.31. Found: C, 48.68; H, 5.99; S, 15.85.

3-Deoxy-1,2-O-isopropylidene-6-O-(pivaloyl)-α-D-xylo-hexofuran-5-ulose (17). To tributyltin hydride (1.4 mL, 5.5 mmol) in dry refluxing toluene (15 mL) under argon, was added over 1 h the xanthate 16 (1.46 g, 3.7 mmol) in toluene (30 mL). The solution was refluxed for 16 h to effect complete reduction. The solvent was then removed at reduced pressure. Flash-chromatography of the residue gave 771 mg (70%) of 17: mp 87-90°C; $[\alpha]_D^{25}$ -61.5° (c 1.2, $CHCl_3$); IR υ_{max}(KBr): 2900, 1725, 1140, 1030; ^{1}H NMR (90 MHz, $CDCl_3$) δ: 5.95 (d, 1H, J=3.5 Hz, H-1), 5.00-4.60 (m, 4H, 2 H-6, H-4, H-2), 2.45 (dd, 1H, J=15 and 5.5 Hz, H-3β), 2.05 (m, 1H, H-3α), 1.55, 1.40 [s, s, 6H, $C(CH_3)_2$], 1.30 [s, 9H, $OC(O)C(CH_3)_3$]; MS m/e: 271 (M-15, 10), 143 (100), 85 (73), 59 (35), 43 (27).

Anal. Calcd. for $C_{14}H_{22}O_6$: C, 58.73; H, 7.75. Found: C, 58.57; H, 7.37.

(1RS,3S)-3,4-Isopropylidenedioxy-1-methoxy-1-phenylthio-butan-2-one 19[3-(S)]. To a solution of methoxymethyl phenyl sulfide (3.7 mL, 25 mmol) in dry tetrahydrofuran (30 mL), cooled at -78°C, under argon and stirring, n-BuLi (18.7 mL, 30 mmol, 1.6 M in hexane) was added dropwise. After 1 h a solution of 18[18] (4.4 g, 25 mmol) in dry tetrahydrofuran (20 mL) was added slowly. After 1 h, at -78°C, sat. aqueous solution of ammonium chloride (20 mL) was added and extracted with ether (3x50 mL). The organic extract was washed with brine, dried (Na_2SO_4) and evaporated. The oily residue was purified by flash-chromatography (95:5 hexane-ethyl acetate) to give 5.6 g (83%) of 19[3-(S)]: Oil;IR υ_{max} (film): 3060, 2990, 1735, 1580, 1385, 1375, 1220, 1070, 850, 750; MS m/e: 282 (M^+, 1), 232 (5), 231 (5), 153 (100), 110 (12), 109 (20), 101 (10), 73 (14), 45 (13), 43 (24).

Anal. Calcd. for $C_{14}H_{18}SO_4$: C, 59.56; H, 6.43; S, 11.33. Found: C, 59.52; H, 6.40; S, 11.50.

Ethyl (Z,E)-(4R)-4,5-Isopropylidenedioxy-3-[(RS)-(methoxy)(phenylthio)methyl]-2-pentenoate (20a). To a suspension of sodium hydride (400 mg,10 mmol, 60% dispersion in mineral oil) in dry tetrahydrofuran (8 mL) was added under argon a solution of ethyl diethylphosphonoacetate (2 mL, 10 mmol) in dry tetrahydrofuran (10 mL) at 0°C. After stirring 1 h, a solution of 19[3-(S)] (1.9 g, 6.7 mmol) in dry trtrahydrofuran (15 mL) was added at room temperature. After 12 h the reaction was diluted with ether, washed with water, dried (Na_2SO_4) and evaporated. Flash-chromatography (98:2 hexane-ethyl acetate) gave 2.2 g (98%) of 20a: Oil; IR υ_{max}(film): 2990, 1720, 1655, 1585, 1440, 1385, 1375, 1200-1250, 1150, 970, 750; MS m/e: 337 (M-15, 4), 277 (4), 243 (100), 185 (41), 157 (23), 153 (89), 139 (80), 125 (67), 111 (23), 97 (57), 69 (26), 43 (57).

Anal. Calcd. for $C_{18}H_{24}SO_5$: C, 61.35; H, 6.86; S, 9.08. Found: C, 61.50; H, 7.09; S, 8.80.

Compound 20a is a mixture of Z ans E isomers (1:1); each isomer appears as a mixture of two diastereomers (1:1.5) due to the stereocenter supporting the methoxy group {[δH_A: E (s, 6.75; 6.65); Z (s, 6.15; 6.05)]; [δH_B: E (s, 5.65; 5.50); Z (s, 5.55; 5.35)] (the assigned pair of values in E/Z for H_A or H_B can be interchanged)} as could be observed in the ^1H NMR (90 MHz) spectrum.

We did not try to separate these isomers and proceeded with this mixture.

(Z,E)-(4R)-4,5-Isopropylidenedioxy-3-[(RS)-(methoxy)(phenylthio)methyl]-2-penten-1-ol (20b). To a solution of 20a (1.87 g, 5.3 mmol) in dry ether (30 mL), was added, under argon and at -30°C, DIBAL (22 mL, 22 mmol, 1.0M in hexane). After stirring 2 h at this temperature, methanol (10 mL) was added. The reaction was warmed to room temperature, filtered through Celite 545 and evaporated. Flash-chromatography (90:10 hexane-ethyl acetate) gave 1.6 g of 20b (99%): Oil; IR υ_{max}(film): 3600-3100, 1590, 1010-1070, 880; MS m/e: 220 (35), 218 (52), 189 (18), 154 (12), 128 (33), 111 (100), 110 (76), 109 (69), 97 (65), 83 (22), 69 (63), 55 (49), 41 (33).

Anal. Calcd. for $C_{16}H_{22}SO_5$: C, 61.92; H, 7.15; S, 10.31. Found: C, 61.67; H, 7.43; S, 10.18.

Acid treatment of 20b. To a solution of 20b (1.2 g, 3.8 mmol) in dry benzene (10 mL) was added a catalytic amount of p-toluenesulfonic acid. After stirring for 12 h at room temperature, the reaction was diluted with ether, washed with ice-cold 5% aqueous bicarbonate solution, brine, dried (Na_2SO_4) and evaporated. Flash-chromatography (95:5 hexane-ethyl acetate) gave 130 mg (~20%) of 21 [oil; ^1H NMR (90 MHz, $CDCl_3$) δ: 7.40 (m, 2H, $H_{\alpha'}$, $H_{\alpha'}$), 6.40 (m, 1H, H_β), 5.05 (dd, 1H, J=6 and 7.5 Hz, H-1), 4.20 (dd, 1H, J=6 and 7.5 Hz, H-2), 3.75 (t, 1H, J=7.5 Hz, H-2'), 1.48, 1.43 [s, s, 6H, $C(CH_3)_2$]; and 551 mg (65%) of 22 [oil; IR ν_{max} (film): 3600-3200, 1590, 1510, 1485, 1440, 1160, 1070, 1030, 880, 745; ^1H NMR (90 MHz, $CDCl_3$) δ: 7.50-7.20 (m, 7H, S-C_6H_5, $H_{\alpha'}$, $H_{\alpha'}$), 6.40 (m, 1H, H_β), 4.25 (t, 1H, J=6 Hz, H-1), 3.80 (d, 2H, J=6Hz, 2H-2), 2.10 (s, 1H, OH); MS m/e: 220 (M^+, 25), 189 (16), 128 (11), 111 (100), 110 (83), 109 (26), 83 (31), 69 (42), 55 (42), 39 (19). Anal. Calcd. for $C_{12}H_{12}SO_2$: C, 65.44; H, 5.49; S, 14.53. Found: C, 65.64; H, 5.55; S, 14.34].

Treatment of 22 (100 mg, 0.45 mmol) with Raney nickel in ethanol at reflux

for 1 h, gave after filtration, evaporation and flash-chromatography (80:20 hexane-ethyl acetate) 25 mg (50%) of 2-(3-furyl)-1-ethanol (23) [IR υ_{max} (film): 3600-3100, 2940, 1510, 1043, 880; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.32 (m, 1H, H_α), 7.25 (m, 1H, $H_{\alpha'}$), 6.25 (m, 1H, H_β), 3.72 (m, 2H, 2 H-2), 2.61 (t, 2H, J=6.5 Hz, 2 H-1), 1.39 (br s, 1H, OH).

Anal. Calcd. for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.00; H, 7.32].

Acetylation of 22 (100 mg, 0.45 mmol) (2 mL of acetic anhydride, 4 mL of pyridine, room temperature, 24 h) gave quantitatively, after flash-chromatography (hexane) 24 [oil; IR υ_{max} (film): 2930, 1745, 1585, 1510, 1240, 1030, 875; ^{1}H NMR (90 MHz, $CDCl_3$) δ: 7.50-7.25 (m, 7H, S-C_6H_5, H_α, $H_{\alpha'}$), 6.40 (m, 1H, H_β), 4.35 (m, 3H, 2 H-2, H-1), 2.00 (s, 3H, CH_3COO); MS m/e: 262 (M^+, 2), 202 (8), 153 (40), 111 (60), 43 (100). Anal. Calcd. for $C_{14}H_{14}SO_3$: C, 64.11; H, 5.38; S, 12.20. Found: C, 63.80; H, 5.20; S, 12.42].

(R)-(3-furyl)-1,2-dihydroxyethane 1-(R). 100 mg (0.58 mmol) of 21 (contaminated with a small , unseparable aromatic impurity) was treated with acetonitrile (4 mL), water (1 mL) and three drops of trifluoroacetic acid, at room temperature for 20 h. The mixture was treated with solid sodium bicarbonate up to pH 7, diluted with methylene chloride, dried (Na_2SO_4), filtered and evaporated. Flash-chromatography (60:40 hexane-ethyl acetate) gave 69 mg (90%) of 1-(R): mp 82-84°C; $[\alpha]_D^{25}$ -19.0° (c 0.55, $CHCl_3$); IR υ_{max} (Nujol): 3600-3100, 1510, 1470, 1155, 1100, 1040, 870; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.45 (m, 1H, H_α), 7.40 m, 1H, $H_{\alpha'}$), 6.40 (m, 1H, H_β), 4.77 (dd, 1H, J=7.3 and 3.9 Hz, H-1), 3.79 (dd, 1H, J=12 and 3.9 Hz, H-2), 3.70 (dd, 1H, J=12 and 7.3 Hz, H-2'), 2.09 (br s, 2H, OH); MS m/e: 128 (M^+, 24), 97 (100), 69 (33), 41 (41).

Anal. Calcd. for $C_6H_8O_3$: C, 56.24; H, 6.29. Found: C, 56.43; H, 6.59.

(1RS,2RS,3R)-3,4-O-Isopropylidene-1-methoxy-1-phenylthio-2,3,4-butanetriol (26). Following the same method as described for the preparation of 19 [3-(S)], but using the aldehyde 25,[22] we prepared 26 (70%): Oil; IR υ_{max} (film): 3600-3100, 1590, 1470, 1385, 1375, 1220, 1070, 850; MS m/e: 284 (M^+,3), 175 (10), 153 (32), 143 (12), 117 (20), 110 (42), 101 (93), 85 (14), 75 (50), 61 (23), 43 (100).

Anal. Calcd. for $C_{14}H_{20}SO_4$: C, 59.14; H, 7.09; S, 11.25. Found: C, 58.86; H, 8.80; S, 10.94.

Compound 26 appears in t.l.c. and ^{1}H NMR as a complex mixture of anti and syn isomers. We did not try to separate them. Oxidation of this mixture as described for the preparation of 9 gave 19[3-(R)] (65%) as a mixture of diastereomers, similar in its spectroscopic and analytical data to 19[3-(S)]. From 19 [3-(R)] and following the method described for the preparation of 20a,b[3-(R)] we obtained 20a,b[3-(S)]. The reaction with p-toluenesulfonic acid in benzene, as for 20b[3-(R)] afforded 21-(S), which was submitted to hydrolysis in the same conditions giving finally 1-(S) [mp 79-81°C; $[\alpha]_D^{25}$ +21° (c 0.2,$CHCl_3$)] identical to 1-(R) in its spectroscopic and analytical data.

(6RS)-3-Deoxy-1,2-O-isopropylidene-6-O-(methyl)-6-C-(phenylthio)-α-D-glucofuranose + (6RS)-3-deoxy-1,2-O-isopropylidene-6-O-(methyl)-6-C-(phenylthio)-β-L-idofuranose (28). The reaction between 27[23] and lithium methoxymethyl phenyl sul

fide, carried out as described for the synthesis of 19, gave 28 (65%) as a mixture of α-D-gluco and β-L-idofuranose isomers (ratio not established) that without separation, was submitted to further reaction. For 28: Oil; IR υ_{max}(film): 3600-3200, 3040, 2990, 1585, 1440, 1385, 1375, 1080; MS m/e: 326 (M^+,2), 278 (3), 245 (4), 159 (10), 157 (15), 143 (65), 109 (10), 101 (13), 85 (73), 73 (11), 43 (100).

Anal. Calcd. for $C_{16}H_{22}SO_5$: C, 58.88; H, 6.80; S, 9.80. Found: C, 58.54; H, 6.54; S, 9.43.

(6RS)-3-Deoxy-1,2-O-isopropylidene-6-O-(methyl)-6-C-(phenylthio)-α-D-xylo-hexofuran-5-ulose (29). Oxidation of 28 as described for the preparation of 9 gave 29 (70%) as a mixture of two diastereomers (1:1)(δH_A: s, 5.50 and 5.45) that we did not try to separate. For 29: Oil; IR υ_{max}(film): 3060, 2990, 1735, 1590, 1385, 1375, 1220, 1070, 1020, 850; MS m/e: 324 (M^+, 2), 217 (7), 187 (26), 153 (100), 143 (23), 129 (15), 85 (34), 59 (26), 43 (27).

Anal. Calcd. for $C_{16}H_{20}SO_5$: C, 59.25; H, 6.22; S, 9.86. Found: C, 59.16; H, 6.54; S, 9.55.

Ethyl (6RS)-3,5-Dideoxy-1,2-O-isopropylidene-5-C-[(methoxy)(phenylthio)methyl]-α-D-xylo-hept-5-(Z,E)-enofuranuronate (30). Following the method previously described for the preparation of 20a, 29 was transformed into 30 (60% yield), a mixture of isomers Z and E (1:1; see compound 20a). For 30: Oil; IR υ_{max}(film): 3040, 2990, 1715, 1650, 1580, 1440, 1385, 1375, 1220, 1150, 1080, 1020, 860; MS m/e: 379 (M^+-15, 2), 363 (2), 285 (100), 227 (34), 211 (28), 197 (29), 165 (23), 139 (18), 109 (18), 85 (46), 59 (43), 43 (89).

Anal. Calcd. for $C_{20}H_{26}SO_6$: C, 60.90; H, 6.64; S, 8.11. Found: C, 60.67; H, 6.68; S, 8.48.

(6RS)-3,5-Dideoxy-7-hydroxymethyl-1,2-O-isopropylidene-5-C-[(methoxy)(phenylthio)methyl]-α-D-xylo-hept-5-(Z,E)-enofuranose (31). Following the method previously described for the preparation of 20b, 30 was converted into 31 (70%): Oil; IR υ_{max}(film): 3600-3200, 3060, 2940, 1650, 1585, 1440, 1380, 1370, 1215, 1070, 1020, 850; MS m/e: 320 (3), 304 (5), 261 (4), 242 (14), 211 (39), 185 (9), 167 (13), 153 (100), 135 (24), 109 (22), 85 (20), 79 (14), 69 (20), 59 (30), 43 (23).

Anal. Calcd. for $C_{18}H_{24}SO_5$: C, 61.35; H, 6.86; S, 9.08. Found: C, 61.21; H, 7.03; S, 9.10.

(2S,4R,5R)-2-(3-Furyl)-4,5-isopropylidenedioxytetrahydrofuran (4). To a solution of 31 (151 mg, 0.42 mmol) in dry benzene (5 mL) was added a catalytic amount of p-toluenesulfonic acid. After 15 min at room temperature, solid sodium bicarbonate was added and filtered. Evaporation and flash-chromatography (95:5 hexane - ethyl acetate) gave 4 (34 mg, 40% yield): mp 60-64°C; $[\alpha]_D^{25}$-19.3° (c 1.1, $CHCl_3$); IR υ_{max}(KBr): 3215, 3090, 3040, 3000, 1490, 1420, 1340, 1210, 1100, 910, 850; ^1H NMR (see the text); MS m/e: 210 (M^+, 11), 195 (47), 152 (59), 135 (87), 107 (50), 95 (53), 85 (19), 79 (22), 77 (12), 59 (54), 43 (100).

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.99; H, 6.36.

(2S,4R,5S)-5-Ethoxy-2-(3-furyl)-4-hydroxytetrahydrofuran (37). Compound 4 (15 mg, 0.04 mmol) was treated with HCl/EtOH (3 mL) for 2 h. Neutralization with silver carbonate, filtration, evaporation and flash-chromatography (85:15 exane - ethyl acetate) gave 37 (9 mg, 64% yield) as the only detected compound. For 37: Oil; $[\alpha]_D^{25}$-88.4º (c 0.79, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40-7.38 (m, 2H, H_α, $H_{\alpha'}$),6.39 (m, 1H, H_β), 5.30 (dd, 1H, J=7 and 8.5 Hz, H-2), 4.97 (s, 1H, H-5), 4.35 (dd, 1H, J=1.5 and 3.8 Hz, H-4), 3.75, 3.46 (dq, 2H, J=7 and 10 Hz, $-OCH_2CH_3$), 2.24-2.19 (m, 2H, 2 H-3), 1.79 (br s, 1H, OH), 1.19 (t, 3H, J=7 Hz, $-OCH_2-CH_3$); MS m/e: 198 (M^+, 2), 153 (25), 138 (4), 134 (8), 124 (14), 123 (11), 95 (100), 82 (55), 81 (64), 68 (15), 67 (23), 65 (10), 47 (14), 41 (15).

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.32; H, 6.88.

(6RS)-3-Deoxy-1,2-O-isopropylidene-6-O-(methyl)-6-C-(phenylthio)-α-D-galactofuranose + (6RS)-3-deoxy-1,2-O-isopropylidene-6-O-(methyl)-6-C-(phenylthio)-β-L-altrofuranose (33). This compound was prepared by the same method as described for the synthesis of 28, but using in this case the aldehyde 32.[25] Compound 33 showed similar spectroscopic and analytical data as reported (see above) for 28.

Following the same methodology we effected the epimeric sequence 33 ⟶ 34 ⟶ 35 ⟶ 36. Each one of these compounds gave satisfactory spectroscopic and analytical data,in full agreement with the described for the corresponding C-4 epimers. As before, the mixtures of isomers were processed without separation.

(2R,4R,5R)-2-(3-Furyl)-4,5-isopropylidenedioxytetrahydrofuran (5). Following the same method for the preparation of 4, we obtained 5 (35% yield) from 36. For 5: mp 59-62ºC; $[\alpha]_D^{25}$-17.0º (c 0.49, $CHCl_3$); IR υ_{max}(film): 3100, 3050, 1485, 1430, 1210, 1100, 910, 850; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43 (m, 1H, H_α) 7.40 (m, 1H, $H_{\alpha'}$), 6.41 (m, 1H, H_β), 5.91 (d, 1H, J=4.2 Hz, H-5), 5.15 (dd, 1H, J=4.3 and 11 Hz, H-2), 4.82 (t, 1H, J=4.2 Hz, H-4), 2.32 (dd, 1H, J=4.3 and 14 Hz, H-3_α), 1.84 (ddd, 1H, J=4.2, 11 and 14 Hz, H-3_β), 1.56, 1.35 [s, s, 6H, $C(CH_3)_2$]; MS m/e: 210 (M^+, 17), 195 (74), 152 (64), 135 (100), 107 (66), 95 (65), 85 (23), 79 (32), 77 (19), 67 (15), 59 (67), 43 (85).

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.70; H, 6.52.

ACKNOWLEDGMENTS

I thank Miss M.D. Casado and Mrs. M. Plaza for recording the ^{1}H NMR spectra; Mr. N. de la Hoz for a generous supply of "diacetone glucose" and Dr. Rodríguez for helpful discussions.

REFERENCES AND NOTES

1. P. Crews and S. Naylor, Prog. Chem. Org. Nat. Prod., 1985, 48, 203.
2. S.R. Buxton, K.H. Holm and L. Skatebøl, Tetrahedron Lett., 1987, 28, 2167 and references cited therein.
3. J.L. Marco, B. Rodríguez, G. Savona and F. Piozzi, Phytochemistry, 1982, 21, 2567.
4. For some examples of syntheses of racemic compounds in this series see: a) Fraxinellone: Y. Fukuyama, T. Tokoroyama and T. Kubota, Tetrahedron Lett., 1973, 4869. b) Ipomeamarone: L.T. Burka, B.J. Wilson and T.M. Harris, J.Org.Chem., 1974, 39, 2212. c) Ancistrofuran: T.R. Hoye and A.J. Caruso, J.Org.Chem., 1981, 46, 1198; R. Baker, I.F. Cottrell, P.D. Ravenscroft and C.J. Swain, J.Chem.Soc. Perkin Trans I, 1985, 2463; A. Saito, H. Matsuhita and H. Kaneko, Agric.Biol.Chem., 1986, 50, 1309. d) 5-(3-furyl)-8-methyloctahydroindolizine: J.J. Tufariello and A.D. Dyszlewski, J.Chem. Soc.,Chem.Commun., 1987, 1138. e) Pyroangolensolide: T. Tokoroyama, Y. Fukuyama and (in part) Y. Kotsuji, J.Chem.Soc. Perkin Trans. I, 1988, 445.
5. a) S. Jarosz and A. Zamojski, Tetrahedron, 1982, 38, 1447. b) Y. Kojima, S. Wakita and N. Kato, Tetrahedron Lett., 1979, 4577.
6. J.A. Schneider, K. Yosihara and K. Nakanishi, J.Chem.Soc. Chem.Commun., 1983, 352.
7. F. Piozzi, B. Rodríguez and G. Savona, Heterocycles, 1987, 25, 807.
8. K.S. Kim, J.-K. Sohng, S.B. Ha, C.S. Cheong, D.I. Jung and C.S. Hahn, Tetrahedron Lett., 1988, 29, 2847 and references cited therein.
9. J. Otera, Synthesis, 1988, 95.
10. O.T. Schmidt, Methods Carbohydr.Chem., 1965, 2, 320.
11. G. Just and C. Luthe, Can. J. Chem., 1980, 58, 1799.
12. H.R. Barton and S.W. McCombie, J.Chem.Soc. Perkin Trans I, 1975, 1574.
13. E. J. Hedgley, W.G. Overend and R.A.C. Rennie, J.Chem.Soc., 1963, 4701.
14. M. Georges, T.-F. Tam and B.Fraser-Reid, J.Org.Chem., 1985, 50, 5747.
15. J. Herscovici and K. Antoniakis, J.Chem.Soc.Chem.Commun., 1980, 561.
16. E.J. Corey and A. Venkateswarlu, J.Am.Chem.Soc., 1972, 94, 6190.
17. For a preliminary communication: J.L. Marco and J.A. Hueso-Rodríguez, Tetrahedron Lett., 1988, 29, 2459.
18. M. Larchevêque and Y. Petit, Synthesis, 1986, 60.
19. T. Mandai, M. Takeshita, K. Mori, M. Kawada and J. Otera, Chem.Lett., 1983, 1909.
20. P. Brownbridge and S. Warren, J.Chem.Soc. Perkin Trans. I, 1976, 2125.
21. Compound 22 can be an enriched mixture of enantiomers. The optical yield and the absolute configuration has not been determined. 22: $[\alpha]_D^{25}$ -5.1° (c 0.8, $CHCl_3$).
22. J. Jurzak, S. Pikul and T. Bauer, Tetrahedron, 1986, 42, 447.
23. R.E. Ireland, D.W. Norbeck, G.S. Mandel and N.S. Mandel, J.Am.Chem.Soc., 1985, 107, 3285.

24. Compounds 28 and 33/ 29 and 34 are, in principle, excellent "carbohydrate nucleophiles" for carbon-carbon bond formation with appropriate "carbohydrate electrophiles" in the synthesis of higher-carbon sugars. See reference 8 for analogous systems.
25. B.M. Trost and T.P. Klun, J.Am.Chem.Soc., 1981, 103, 1864.
26. a) R.C. Anderson and B. Fraser-Reid, J.Org.Chem., 1985, 50, 4786. b) K.C. Nicolaou, M.R. Pavia and S.P. Seitz, Tetrahedron Lett., 1979, 2327. c) M. Rudrun and D.F. Shaw, J.Chem.Soc., 1965, 52. d) S.J.F. Mcdonald, W.B. Huizinga and T.C. McKenzie, J.Org.Chem., 1988, 53, 3371. e) J. Mulzer et al., J.Am.Chem.Soc., 1988, 110, 4640.
27. S.J. Angyal: "Conformation of Sugars", pg 195, in "The Carbohydrates: Chemistry and Biochemistry", second Edition. Ed. Pigman and Horton, Academic Press, New York, 1972.
28. S. Hanessian, 'Total Synthesis of Natural Products. The "Chiron" Approach', Pergamon Press, 1983.
29. W.C. Still, M. Kahn and A. Mitra, J.Org.Chem., 1978, 43, 2923.
30. E.J. Corey and G. Schmidt, Tetrahedron Lett., 1979, 399.