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Note

Asymmetric induction in acid-catalysed condensations of sugar aldehydes with furan and 2-methylfuran*

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Recently[1], we reported on the acid-catalysed condensation of furan with 2,3-*O*-isopropylidene-D-glyceraldehyde (**1**) to yield (1*RS*,2*R*)-1-*C*-(2-furyl)-2,3-*O*-isopropylideneglycerol (**2**). This reaction was stereoselective, the ratio of *R* and *S* isomers at the new asymmetric centre being 85:15. Alcohol **2***R* was converted[2] into D-*glycero*-D-*manno*-heptose.

We have now examined the condensation of furan and 2-methylfuran with 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose[3] (**3a**), methyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside[4] (**4a**), 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose[5] (**5a**), benzyl 2,3,4-tri-*O*-benzyl-α-D-*manno*-hexodialdo-1,5-pyranoside (**6a**), methyl 2,3-di-*O*-benzyl-α- (**7a**) and -β-D-*ribo*-pentodialdo-1,4-furanoside (**8a**).

Condensation of **3a–8a** with furan was performed in the presence of chloroacetic acid. When other protic or Lewis acids were employed (*e.g.*, dichloroacetic acid, toluene-*p*-sulfonic acid, zinc chloride, tin tetrachloride, boron trifluoride etherate), formation of bis(2-furyl) products or decomposition of substrates was observed. Aldehydes **3a–5a** reacted with furan to afford the furyl derivatives **3b–5b**, respectively, in moderate to good yields (Table I). Aldehydes **6a–8a** did not react with furan under these conditions but, with 2-methylfuran, the reaction proceeded readily and furnished **6b–8b**, respectively. Acid-catalysed reaction of **1** with 2-methylfuran yielded 62% of **9**.

All the condensations were stereoselective, the ratio of products varied from 3:1 to >19:1, and the individual diastereoisomers could be isolated by column chromatography. The assignment of the *S* configuration to the new asymmetric centre in the crystalline major diastereoisomer of **3b** was effected by X-ray crystallography[6], and the major diastereoisomers of **4b–6b** were converted into compounds of known absolute configuration [*S*-(−)-**10**, **11**, and **12** (see Experimental)]. Thus, it was shown that the *S* configuration at the α-carbon atom induced the *S*

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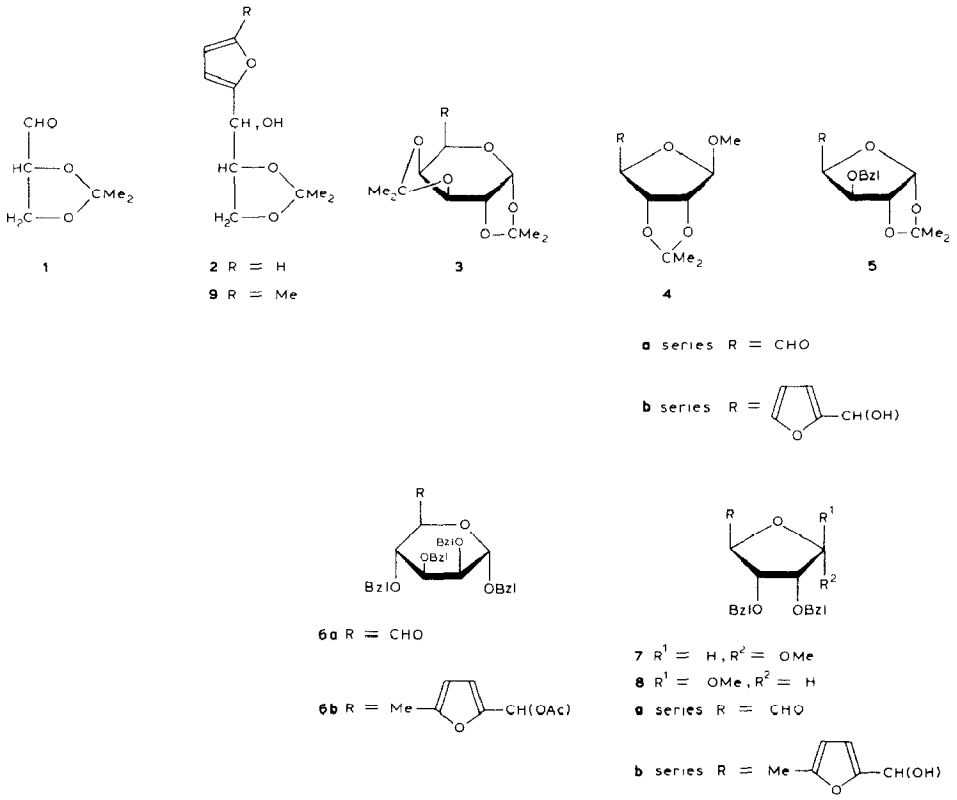


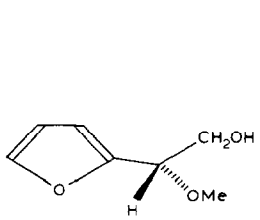
configuration at the new centre of chirality in the major diastereoisomeric products. The absolute configurations at C-5 of the major diastereoisomers of **7b** and **8b** were not determined but are probably *S*.

The condensations described above are new examples of the well-known 1,2-asymmetric induction. However, the formation of the new centre of chirality occurs in a carbocation-mediated substitution reaction and not in a typical nucleophilic

TABLE I

REACTION OF SUGAR ALDEHYDES WITH FURAN AND 2-METHYLFURAN

Reaction	*Product*	*Yield (%)*	*Ratio of isomers*	*Configuration of new asymmetric centre of the major stereoisomer*
1 + furan	**2**	42	85:15	*R*
1 + 2-methylfuran	**9**	62	95:5	*R*
3a + furan	**3b**	45	87:13	*S*
4a + furan	**4b**	68	95.5	*S*
5a + furan	**5b**	45	86:14	*S*
6a + 2-methylfuran	**6b**	35	75:25	*S*
7a + 2-methylfuran	**7b**	36	73:27	*S*
8a + 2-methylfuran	**8b**	62	76:24	*S*



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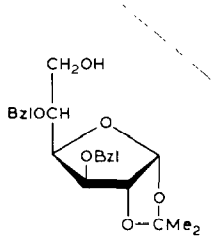

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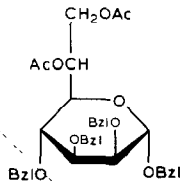

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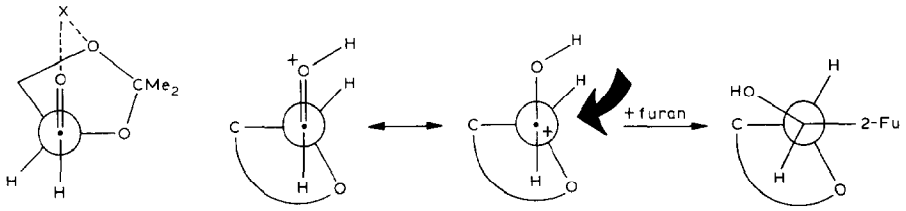
addition of a reagent to the carbonyl group. The stereochemical outcome of these reactions may be due to intramolecular hydrogen-bonding of the carbocations to the α-, β-, and γ-oxygen atoms. Mukaiyama *et al.*[7] postulated the transient formation of a complex **13** involving the β-oxygen atom when 2-lithiofuran reacted with **1** in the presence of magnesium or zinc halides. The formation of similar complexes (**13**, X = H^+) could explain the results described above for **3a** and **5a**. Hydrogen bonding to the α- or γ-oxygen atoms can be excluded since this should lead to preponderance of the alternative diastereoisomer. The results may be explained on the basis of the Felkin model[8] of 1,2-asymmetric induction. Thus, if carbocation **14** is chosen as the minimum-energy rotamer of the six potentially possible structures, it predicts correctly the structure of the major diastereoisomers.

The exploitation of **3a–8a** and **9** for the stereocontrolled synthesis of higher sugars will be reported elsewhere.



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EXPERIMENTAL

Melting points were determined on a Kofler apparatus and were not corrected. Optical rotations were measured with a Perkin–Elmer 141 polarimeter. ^{1}H-N.m.r. spectra were recorded with a JEOL JNM-4H-100 spectrometer for solutions in $CDCl_3$ (internal Me_4Si). I.r. spectra were recorded with a Unicam SP 200 spectrophotometer. All aldehydes used, except **1**[9] and **5a**[5], were prepared by oxidation of the appropriate alcohols with methyl sulfoxide–oxalyl chloride[10].

Reaction of sugar aldehydes with furan and 2-methylfuran. — To a 10% solution of aldehyde (**1**, **3a–8a**) in furan or 2-methylfuran was added chloroacetic acid (1 equiv.). The mixture was kept until the substrate was consumed (t.l.c.), then

diluted with ether, neutralised with triethylamine, filtered through a short column of neutral alumina, and concentrated, and the crude product was purified by column chromatography.

*6-C-(2-Furyl)-1,2:3,4-di-O-isopropylidene-α-*D- (D-**3b**) *and* -L-glycero-D-galacto-*hexopyranose* (L-**3b**). — The crude product (obtained from 666 mg of **3a** and furan) was fractionated by column chromatography (benzene–methanol, 97:3) to yield D-**3b** as the faster-moving compound (325 mg), m.p. 176–178° (from light petroleum–ethyl acetate, 3:1), $[\alpha]_D^{25}$ −53° (*c* 1, chloroform); ν_{max}^{KBr} 3550 and 870 cm^{-1}. ^{1}H-N.m.r. data: δ 7.37 and 6.36 (protons of the furan ring), 5.50 (d, 1 H, $J_{1,2}$ 4.8 Hz, H-1), 4.90 (d, 1 H, $J_{5,6}$ 7.8 Hz, H-6), 4.66–4.51 (ABq, 2 H, $J_{2,3}$ 2.25, $J_{3,4}$ 7.8 Hz, H-3,4), 4.31 (dd, 1 H, H-2), 4.12 (dd, 1 H, $J_{4,5}$ 1.5 Hz, H-5), 1.60, 1.52, 1.41, and 1.35 (4 s, 2 CMe_2).

Anal. Calc. for $C_{16}H_{22}O_7$: C, 58.9; H, 6.8. Found: C, 58.7; H, 7.1.

Eluted second was L-**3b** (49 mg), m.p. 98–102° (from light petroleum–ethyl acetate, 3:1), $[\alpha]_D^{25}$ −84° (*c* 1.4, chloroform); ν_{max}^{KBr} 3550 and 870 cm^{-1}. ^{1}H-N.m.r. data: δ 7.42 and 6.41 (protons of the furan ring), 5.46 (d, 1 H, $J_{1,2}$ 4.9 Hz, H-1), 4.81 (d, 1 H, $J_{5,6}$ 8.75 Hz, H-6), 4.66–4.54 (ABq, 2 H, $J_{2,3}$ 2.0, $J_{3,4}$ 7.9 Hz, H-3,4), 4.10 (d, 1 H, $J_{4,5}$ <1.0 Hz, H-5), 1.63, 1.51, 1.41, and 1.35 (4 s, 2 CMe_2).

Anal. Found: C, 59.5; H, 7.1.

*Methyl 5-C-(2-furyl)-2,3-O-isopropylidene-β-*D-allo-*pentofuranoside* (D-**4b**). — The crude product, obtained from **4a** (554 mg) and furan, was subjected to column chromatography (benzene–methanol, 97:3) to afford D-**4b** (265 mg) as an oil, $[\alpha]_D^{20}$ −73° (*c* 1.1, chloroform); ν_{max}^{film} 3550 and 875 cm^{-1}. ^{1}H-N.m.r. data: δ 7.40 and 6.30 (protons of the furan ring), 3.30 (s, 3 H, OMe), 1.35 and 1.25 (2 s, CMe_2).

Anal. Calc. for $C_{13}H_{18}O_6$: C, 57.8; H, 6.7. Found: C, 57.7; H, 6.9.

Unreacted **4a** (260 mg) was also recovered.

*3-O-Benzyl-5-C-(2-furyl)-1,2-O-isopropylidene-α-*D-gluco- (D-**5b**) *and -β-*L-ido-*pentofuranose* (L-**5b**). — The crude product obtained from **5a** (630 mg) and furan was subjected to column chromatography (light petroleum–ethyl acetate, 7:3) to yield D-**5b** (305 mg) as an oil, $[\alpha]_D^{22}$ −68° (*c* 2.6, chloroform); ν_{max}^{film} 3520 and 860 cm^{-1}. ^{1}H-N.m.r. data: δ 7.44 and 6.30 (protons of the furan ring), 5.99 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 5.06 (d, 1 H, $J_{4,5}$ 7.0 Hz, H-5), 4.67–4.58 (ABq, CH_2Ph), 4.62 (d, 1 H, $J_{2,3}$ 1.0 Hz, H-2), 4.46 (dd, 1 H, $J_{3,4}$ 3.25 Hz, H-4), 4.17 (d, 1 H, H-3), 1.49 and 1.31 (CMe_2).

Anal. Calc. for $C_{19}H_{22}O_6$: C, 65.9; H, 6.4. Found: C, 65.6; H, 6.5.

Eluted second was L-**5b** (50 mg), m.p. 60–63° (from light petroleum–ethyl acetate, 3:1), $[\alpha]_D^{22}$ −68° (*c* 3.6, chloroform); ν_{max} 3520 and 860 cm^{-1}. ^{1}H-N.m.r. data: δ 7.41 and 6.30 (protons of the furan ring), 5.95 (d, 1 H, $J_{1,2}$ 3.75 Hz, H-1), 5.03 (d, 1 H, $J_{4,5}$ 6.75 Hz, H-5), 4.76–4.55 (3 H, H-2 and CH_2Ph), 4.46 (dd, 1 H, $J_{3,4}$ 3.25 Hz, H-4), 4.16 (d, 1 H, $J_{2,3}$ 1.0 Hz, H-3), 1.50 and 1.31 (CMe_2).

*Benzyl 6-O-acetyl-2,3,4-tri-O-benzyl-6-C-[2-(5-methylfuryl)]-α-*D- (D-**6b**) *and* -L-glycero-D-manno-*hexopyranoside* (L-**6b**). — The crude product obtained from **6a** (1.73 g) and 2-methylfuran was acetylated (Ac_2O, pyridine, 4-dimethylamino-

pyridine, room temperature). The ^{1}H-n.m.r. spectrum of the crude mixture of acetates indicated the ratio of D-**6b** and L-**6b** to be 3:1 (signals at δ 6.52 and 6.31, and 6.41 and 6.28). Column chromatography of the mixture afforded D-**6b** (547 mg) as an oil, $[\alpha]_D^{25}$ +38° (*c* 1, chloroform).

Anal. Calc. for $C_{41}H_{42}O_7$: C, 76.1; H, 6.5. Found: C, 75.6; H, 6.3.

Eluted second was a mixture (110 mg) of D-**6b** and L-**6b**.

Eluted third was L-**6b** (150 mg), which was identified by conversion into L-*glycero*-D-*manno*-heptose as described for D-**6b** (see below).

*Methyl 2,3-di-*O*-benzyl-5-*C*-[2-(5-methylfuryl)]-α-*D-allo- (D-**7b**) *and* -β-*L-talo-*pentofuranoside* (L-**7b**). — Column chromatography (light petroleum–ether, 3:1) of the crude product obtained from **7a** (234 mg) and 2-methylfuran afforded, first, D-**7b** (80 mg) as an oil, $[\alpha]_D$ +18° (*c* 1.7, chloroform). ^{1}H-N.m.r. data: δ 7.22 (10 H, 2 Ph), 6.16, 5.96, and 2.20 (protons of 2-methylfuran), 4.87–4.40 (6 H, H-4,5 and 2 CH_2Ph), 4.10 (dd, 1 H, $J_{3,4}$ 2.5, $J_{2,3}$ 6.5 Hz, H-3), 3.70 (dd, 1 H, H-2), 3.46 (s, 3 H, OMe).

Anal. Calc. for $C_{25}H_{28}O_6$: C, 70.7; H, 6.7. Found: C, 70.9; H, 7.5.

Eluted second was L-**7b** (30 mg) as an oil, $[\alpha]_D$ +59° (*c* 1.1, chloroform). ^{1}H-N.m.r. data: δ 7.24 (10 H, 2 Ph), 6.24, 5.97, and 2.30 (protons of 2-methylfuran), 4.90 (d, 1 H, $J_{1,2}$ 4.5 Hz, H-1), 4.81–4.43 (m, 6 H, H-4,5 and 2 CH_2Ph), 4.01–3.60 (m, 2 H, $J_{2,3}$ 6.7 Hz, H-2,3), 3.35 (s, 3 H, OMe).

*Methyl 2,3-di-*O*-benzyl-5-*C*-[2-(5-methylfuryl)]-β-*D-allo- (D-**8b**) *and* -α-*L-talo-*pentofuranoside* (L-**8b**). — Column chromatography (light petroleum–ether, 3:1) of the crude product obtained from **8a** (625 mg) and 2-methylfuran afforded, first, D-**8b** (322 mg) as an oil, $[\alpha]_D$ −32° (*c* 1.1, chloroform). ^{1}H-N.m.r. data: δ 7.20 (10 H, 2 Ph), 6.10, 5.85, and 2.21 (protons of 2-methylfuran), 4.87 (d, 1 H, $J_{1,2}$ 1.8 Hz, H-1), 4.57 (d, 1 H, $J_{4,5}$ 4.3 Hz, H-5), 4.52 (s, 2 H, CH_2Ph), 4.37 (dd, 1 H, $J_{3,4}$ 4.8 Hz, H-4), 4.35 (s, 2 H, CH_2Ph), 4.15 (m, 1 H, $J_{2,3}$ 5.0 Hz, H-3), 3.35 (s, 3 H, OMe).

Anal. Calc. for $C_{25}H_{28}O_6$: C, 70.7; H, 6.7. Found: C, 70.5; H, 6.7.

Eluted second was a mixture (180 mg) of D-**8b** and L-**8b**.

Eluted third was L-**8b** (102 mg) as an oil. ^{1}H-N.m.r. data: δ 7.20 (10 H, 2 Ph), 6.10, 5.82, and 2.31 (protons of 2-methylfuran), 4.67 (s, 1 H, H-1), 4.65–4.25 (m, 6 H, H-4,5 and 2 CH_2Ph), 4.21–3.94 (m, 1 H, $J_{3,4}$ 5.0 Hz, H-3), 3.71 (d, 1 H, $J_{2,3}$ 4.4 Hz, H-2).

*2,3-*O*-Isopropylidene-1-[2-(5-methylfuryl)]-*D-*glycerol* (**9**). — Column chromatography (light petroleum–ether) of the crude product obtained from **1** (650 mg) and 2-methylfuran afforded **9** (650 mg), m.p. 66–67° (from ethyl acetate–hexane, 1:3). ^{1}H-N.m.r. data: δ 6.25, 6.00, and 2.30 (protons of 2-methylfuran), 4.80 (d, 1 H, $J_{1,2}$ 4.7 Hz, H-1), 4.41 (m, 1 H, H-2), 4.10 (m, 2 H, H-3,3′), 1.48 and 1.40 (CMe_2).

Anal. Calc. for $C_{11}H_{16}O_4$: C, 62.3; H, 7.6. Found: C, 62.1; H, 7.5.

Determination of the configuration of D-**4b**. — To a solution of D-**4b** (400 mg) in chloroform (5 mL) was added methyl iodide (1 mL) followed by freshly prepared

silver oxide (2 g). The mixture was boiled under reflux for 16 h, the crude product was isolated as usual, and a solution in tetrahydrofuran–H_2O–AcOH (5 mL, 1:1:2.5) was boiled under reflux for 16 h. The mixture was concentrated, and a solution of the residue in water (5 mL) was poured into a solution of sodium periodate (4 g) and sodium hydrogencarbonate (0.5 g) in water (50 mL). After the addition of ether (40 mL), the mixture was stirred for 20 min, the organic layer was separated, and the aqueous layer was extracted with ether. Evaporation of the solvent left an oily residue which was reduced with lithium aluminium hydride (50 mg) in tetrahydrofuran (5 mL). The usual work-up gave 2-(2-furyl)-2-methoxyethanol [*S*-(−)-**10**, 30 mg] isolated as an oil, $[\alpha]_D$ −8.4° (*c* 2.5, ethyl acetate). ^{1}H-N.m.r. data: δ 7.35 and 6.27 (1 H and 2 H, protons of the furan ring), 4.20 [dd, 1 H, *J* 7.4 and 5.2 Hz, C*H*(OH)–CH_2OH], 3.65 (m, 2 H, CH_2OH), and 3.27 (s, 3 H, OMe). Compound *S*-(−)-**10** was prepared independently from optically active menthyl (2-furyl)glycolate[11] (methylation followed by reduction).

Determination of the configuration of D-**5b**. — The alcohol D-**5b** was benzylated (KOH, Me_2SO, benzyl bromide, room temp.) and the crude benzyl ether (500 mg) was subjected to ozonolyzis (chloroform, −60°, 12 min). The ozonide was decomposed (0°, 1 h) with triphenylphosphine (500 mg) in chloroform (30 mL). Solvent was evaporated, and to a solution of the crude product in dry benzene (4 mL) was added dry ether (30 mL). The triphenylphosphine oxide was removed, the filtrate was concentrated to dryness, and a solution of the residue in tetrahydrofuran (5 mL) was added dropwise to a mixture of lithium aluminium hydride (80 mg) in tetrahydrofuran (10 mL). T.l.c. (light petroleum–ethyl acetate, 1:1) revealed several products. 3,5-Di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (52 mg) was isolated by column chromatography (light petroleum–ethyl acetate, 3:1); $[\alpha]_D$ −53° (*c* 1.1, chloroform). ^{1}H-N.m.r. data: δ 7.30 (5 H, Ph), 5.85 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 1.47 and 1.27 (2 s, 6 H, CMe_2). This product was identical (^{1}H-n.m.r., $[\alpha]_D$) with authentic material[12,13].

Determination of the configuration of D-**6b**. — A solution of D-**6b** (547 mg) in dichloromethane (30 mL) was ozonolysed (−78°, 4 min). The crude ozonide was reduced as described above, and then acetylated to give benzyl 6,7-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-*glycero*-D-*manno*-heptopyranoside (**12**), which was identified (t.l.c., i.r.) by comparison with an authentic sampale. The synthesis of **12** {oil, $[\alpha]_D$ +38° (*c* 2.1, chloroform)} will be described elsewhere.

ACKNOWLEDGMENT

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REFERENCES

1 K. DZIEWISZEK, M. CHMIELEWSKI, AND A. ZAMOJSKI, *Carbohydr Res.*, 104 (1982) c1–c3

2 O. ACHMATOWICZ, JR., P. BUKOWSKI, B. SZECHNER, Z. ZWIERZCHOWSKA, AND A. ZAMOJSKI, *Tetrahedron*, 27 (1971) 1793–1996.
3 R. E. ARRICK, D. C. BAKER, AND D. HORTON, *Carbohydr. Res.*, 26 (1973) 441–447.
4 G. H. JONES AND J. G. MOFFATT, *Methods Carbohydr. Chem.*, 6 (1972) 315–322.
5 M. L. WOLFROM AND S. HANESSIAN, *J. Org. Chem.*, 27 (1962) 1800–1804.
6 J. W. KRAJEWSKI, P. GLUZIŃSKI, Z URBAŃCZYK-LIPKOWSKA, A ZAMOJSKI, AND P. LUGER, *Carbohydr. Res.*, 139 (1985) 55–63.
7 K. SUZUKI, Y. YUKI, AND T. MUKAIYAMA, *Chem Lett.*, (1981) 1529–1532.
8 M. CHEREST, H. FELKIN, AND N. PRUDENT, *Tetrahedron Lett.*, (1968) 2199–2204; M. CHEREST AND H. FELKIN, *ibid.*, (1968) 2205–2208.
9 B. BAER AND H. O. L. FISHER, *J. Biol. Chem.*, 128 (1939) 463–473.
10 A. J. MANCUSO, SH.-L. HUANG, AND D. SWERN, *J. Org. Chem.*, 43 (1978) 2480–2482.
11 O. ACHMATOWICZ, JR., AND P. BUKOWSKI, *Bull. Acad. Polon. Sci., Ser. Sci. Chim.*, 19 (1971) 305–308.
12 K. DAX, W. WOLFLEHNER, AND H. WEIDMANN, *Carbohydr. Res.*, 65 (1978) 132–138.
13 A. ROSSI, S. Afr. Pat. 68 05,705 (1968), *Chem. Abstr.*, 73 (1970) 4156k.