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Synthesis of 2,6,7-trideoxy-7-*C*-(2,4-dichlorophenyl)-D-*xylo*-heptonic acid and 6-(2,4-dichlorophenyl)-D-*xylo*-2,3,4-trihydroxyhexanesulfonic acid*

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ABSTRACT

2,4-*O*-Benzylidene-L-xylose was converted *via* a Wittig reaction into *Z*-2,4-*O*-benzylidene-5,6-dideoxy-6-*C*-(2,4-dichlorophenyl)-D-*xylo*-hex-5-enitol (**17**), which, on hydrogenation, gave 5,6-dideoxy-6-*C*-(2,4-dichlorophenyl)-D-*xylo*-hexitol (**33**). *tert*-Butyldimethylsililation of the primary hydroxyl group of **33**, followed by 4-methoxybenzylation, and desilylation afforded 5,6-dideoxy-6-*C*-(2,4-dichlorophenyl)-2,3,4-tri-*O*-(4-methoxybenzyl)-D-*xylo*-hexitol (**54**). A Mitsunobu-type reaction of **54** replaced HO-1 by cyanide to give, after hydrolysis and hydrogenolysis, 2,6,7-trideoxy-7-*C*-(2,4-dichlorophenyl)-D-*xylo*-heptono-1,4-lactone (**55**). Mesylation of **33** and then acetylation gave 2,3,4-tri-*O*-acetyl-5,6-dideoxy-6-*C*-(2,4-dichlorophenyl)-1-*O*-methanesulfonyl-D-*xylo*-hexitol (**63**), which was converted *via* its 1-thiobenzoate into bis[1,5,6-trideoxy-6-*C*-(2,4-dichlorophenyl)-D-*xylo*-hexitol] 1,1'-disulfide (**65**). Acetylation of **65**, followed by permanganate oxidation and deacetylation, afforded sodium 6-(2,4-dichlorophenyl)-D-*xylo*-2,3,4-trihydroxyhexanesulfonate (**67**). Both **57** (obtained from **55** by hydrolysis with NaOH) and **67** are weak inhibitors of HMG-CoA reductase.

INTRODUCTION

The significance of the fungal metabolites compactin (**1**) and mevinolin (**2**) as inhibitors of HMG-CoA reductase is well documented[1,2]. Since the isolation of **1** in 1976[3,4] and **2** in 1979[5], many attempts to establish structure–activity relationships have been described[1,6–8]. In most of these studies, the lactone moiety was retained and only the apolar moiety was modified. The lactone moiety can be considered as a 7-*C*-substituted 2,4,6,7-tetradeoxy-D-*erythro*-heptono-1,5-lactone and the free acid is required for biological activity. Modification of the lactone moiety was not pursued intensively probably because the 5*S* diastereomer of mevinolin (**2**) had shown only 10^{-4} times the activity of the natural compound having the 5*R* configuration[9]. In model compounds of type **3**, in which the 2,4-dichlorophenyl group was the apolar moiety, the importance of the absolute configuration of both chiral centers of the lactone was proved[10]. Introduction of an additional methyl group at C-3 (→**4**) diminished the activity further[10], even when the original D-*erythro* configuration was preserved. Exchange of HO-3 for amino (**5**) or thio substituents (**6**) also drastically decreased the activity[11]. However, no

* Potential Inhibitors of HMG-CoA Reductase. Part I.
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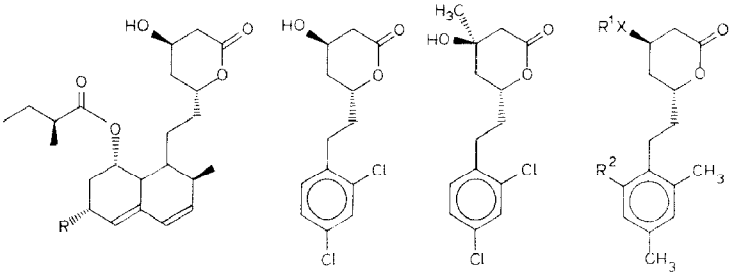
data have been published on analogues that possess an additional hydroxyl group in the lactone moiety. Therefore, we have synthesised and evaluated model compounds having the 2,4-dichlorophenyl group as the apolar moiety and an additional hydroxyl group at C-4.

Most of the published syntheses[12] of compactin and its analogues started from D-glucose (**7**) in order to obtain the lactone moiety **8**. The activated C-6 of **8** was then coupled with the apolar moiety. In this approach, only the chirality of C-5 in **7** was preserved. In our strategy, D-glucitol (**9**) was used as the starting material since the D-*erythro* relationship of HO-2,4 can be preserved when the C-5–C-6 bond is cleaved by periodate oxidation to afford the activated terminal position of **8**, which is necessary for coupling with the apolar moiety. The carboxylate group then has to be introduced by chain elongation, *e.g.*, by an exchange of HO-1 with cyanide. This approach would lead to **10**, which differs from **8** in having an additional hydroxyl group at C-4. Acidic groups, other than carboxyl, *e.g.*, SO_3H (**11**), can be introduced also by this approach.

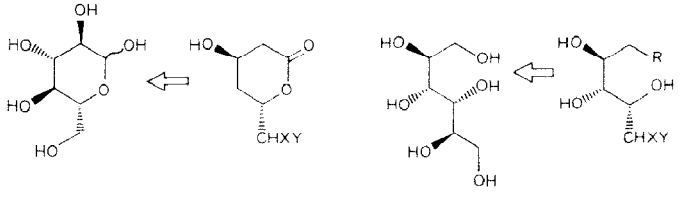


1 R = H
2 R = CH_3

3

4

5 X = N
6 X = S



7

8

9

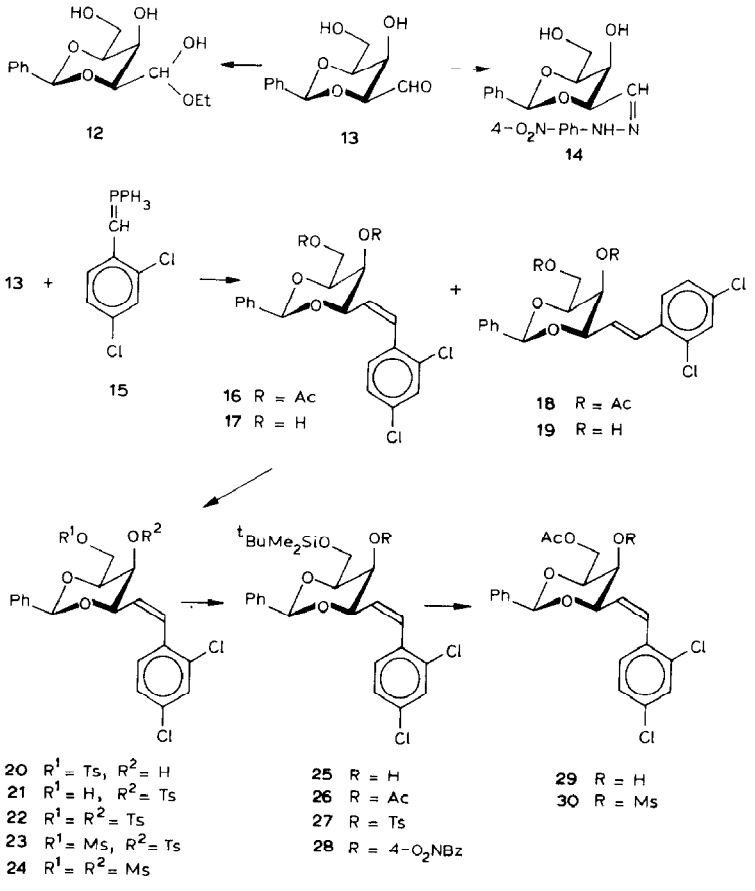
10 R = COOH
11 R = SO_3H

RESULTS AND DISCUSSION

The synthon **10** was obtained from 2,4-*O*-benzylidene-L-xylose[13] (**13**), which can be prepared easily from 2,4-*O*-benzylidene-D-glucitol.

Crude **13** was coupled with the ylid **15** (prepared *in situ* from 2,4-dichlorophenyltriphenylphosphonium chloride and potassium *tert*-butoxide) in tetrahydrofuran–*N,N*-dimethylformamide to yield, after acetylation, the corresponding *Z* (**16**) and *E* (**18**) isomers in the ratio 10:1, which were isolated by column chromatography. The structures of **16** and **18** were established by the ^{1}H-n.m.r. data ($J_{5,6}$ 11.6 and 16.0 Hz, respectively). Zemplén deacetylation of **16** and **18** gave the highly insoluble dihydroxy derivatives **17** and **19**, respectively. Theoretically, **17** is an ideal candidate for the planned chain-elongation process. However, when **17** was treated with pyridine–tosyl chloride (1.5 equiv.), a mixture of the 1- (**20**), and 3-tosylate (**21**), together with the 1,3-ditosylate (**22**), was obtained in the ratios 1:1:2. When the proportion of tosyl chloride was diminished, the ratios of **20**:**21**:**22** were not influenced significantly, and some **17** remained. The structure of **21** was proved by n.O.e. experiments and by the fact that it could be obtained by desilylation of **27**. Compounds **20** and **22** formed an inseparable mixture, but pure **22** was obtained when an excess of tosyl chloride was used.

Thus, there is almost no difference in the reactivity of HO-1 and HO-3 in **17** towards tosylation. This situation contrasts with the behaviour of pyranosides where the primary hydroxyl group can be substituted selectively.



Attempts with cupric cyanide or sodium iodide in *N,N*-dimethylformamide at 100° to substitute selectively the primary tosyloxy or mesyloxy groups in the corresponding 1,3-disubstituted derivatives **22**–**24** (which were obtained by using an excess of the acylating agents) failed; no reaction took place at 100° and decomposition occurred at 150°. Direct exchange reactions of the primary hydroxyl group in **17** by cyanide, using Me_3SiCl/sodium iodide in acetonitrile and *N,N*-dimethylformamide[14] or carbon tetrachloride, and Ph_3P and subsequently sodium cyanide in *N,N*-dimethylformamide[15], also gave negative results.

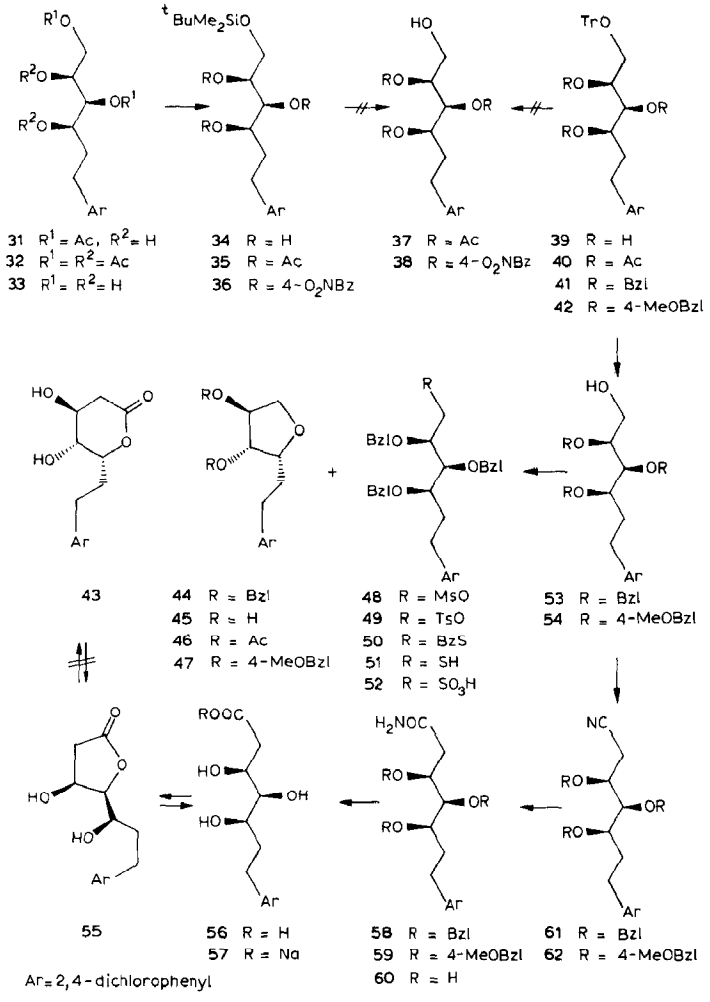
In further attempts, and indirect route was investigated. First, HO-1 of **17** was blocked to give the $^tBuMe_2Si$ ether **25** and then HO-3 was acetylated to give **26**. However, when Bu_4NF in tetrahydrofuran was used to desilylate **26**, an acetyl migration took place, affording the 1-acetate **29** instead of the expected 3-acetate. The structure of **29** was evident from the n.m.r. data, and was proved chemically by conversion into the crystalline 3-mesylate **30**. When methanolic H_2SO_4 was used to desilylate **26**, only **17** could be isolated.

4-Nitrobenzoates are relatively resistant towards migration under acidic conditions[16]; hence, the 3-(4-nitrobenzoate) **28** was synthesised, but its desilylation also afforded **17**. The only compound in which the 3-substituent remained intact during desilylation was the tosylate **27** which, on treatment with methanolic H_2SO_4, afforded the 3-tosylate **21** (89%).

The unusually small difference in the reactivity of the primary and secondary hydroxyl groups of **17** might be attributed to conformational rigidity imposed by the benzylidene group. Therefore, this group was removed by catalytic hydrogenation (Pd/C) of the 1,3-diacetate **16** instead of the rather insoluble **17**. Under the conditions used (ethyl acetate, normal pressure, 2.5 h, room temperature), the double bond was saturated also but, instead of yielding the 1,3-diacetate **31**, a mixture of isomers was formed which reflected the occurrence of partial acetyl migration. Acetylation of this mixture afforded the crystalline tetraacetate **32**, which was deacetylated to give **33**.

In order to ensure the selective activation of HO-1 in **33**, this group was silylated temporarily by reaction with $^tBuMe_2SiCl$ in pyridine (→**34**) to give, after acetylation, the triacetate **35**. When desilylation of **35** was carried out with methanolic H_2SO_4, acetyl migration again occurred to afford a mixture of acetates instead of **37**. The corresponding tri(4-nitrobenzoate) **36** showed a similar behaviour, thus preventing the synthesis of **38**.

In order to avoid the migration of the protecting groups, ethers instead of esters were used. Treatment of **34** with benzyl chloride in the presence of sodium hydroxide gave a mixture of partially benzylated derivatives. When sodium hydride was used as the base in tetrahydrofuran, the silyl group was lost[17]. Finally, HO-1 of **33** was tritylated to yield **39**, which could be purified only by repeated column chromatography. However, purification was not necessary since crude **39** could be converted into its triacetate **40** in excellent yield (92%). Detritylation of **40** under mild conditions (MeOH, 0.01M HCl, room temperature) did not give **37** because of partial acetyl migration.



Treatment of crude **39** in methyl sulfoxide with benzyl chloride and sodium hydride afforded **41**, which was detritylated with methanolic HCl to give the 2,3,4-tri-*O*-benzyl derivative **53** (72%). Mesylation of HO-1 gave **48**, which was unstable and could not be purified by column chromatography. On storage at room temperature, **48** was transformed gradually into the 1,4-anhydride **44**. When freshly prepared **48** was treated with sodium cyanide in *N,N*-dimethylformamide, **44** was formed exclusively (90%) instead of the cyanide **61**. Thus, intramolecular attack of the 4-*O*-benzyl group is much more favoured[18,19] than intermolecular attack by the weak nucleophile. Only such strong nucleophiles as the thiobenzoate ion can compete effectively with anhydro-ring formation, and the thiobenzoate **50** and **44** were formed in the ratio 4:1. The 1-tosylate **49** was even less stable than the mesylate **48** and was converted into the anhydride **44** during recording of the n.m.r. spectrum.

The cyanide **61** was obtained from **53** *via* a Mitsunobu-type reaction[20,21] (diethyl

azodicarboxylate, triphenyl phosphine, and hydrogen cyanide) which gave **61** and anhydride **44** in nearly equal proportions and with similar R_f values. However, the isolation of **61** was unnecessary since, on treatment[22] of the mixture with H_2O_2 in methyl sulfoxide in the presence of K_2CO_3, **61** was converted into the amide **58**, which could be separated easily from unchanged **44**. Catalytic hydrogenation (Pd/C) of **58** removed the benzyl groups and also, according to n.m.r. and f.a.b.-m.s. data, effected dechlorination to give the 2- and 4-chlorophenyl as well as the completely dehalogenated derivative under the conditions applied for the reductive cleavage of the 2,4-*O*-benzylidene group and saturation of the double bond (**16** → **31**).

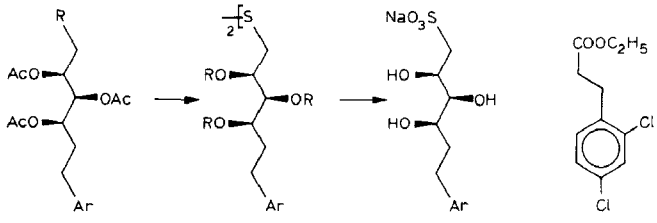
Application of methanolic formic acid[23] or ammonium formate[24] in the presence of Pd/C gave no better results and attempts to remove the *O*-benzyl groups by $Br_2/h\nu$[25] or BBr_3[26] also failed. In order to overcome this problem, 4-methoxybenzyl groups were used to protect the secondary hydroxyl groups of **39**. The product (**42**) was detritylated to give **54**, which was converted by a Mitsunobu-type reaction into the cyanide **62** which could be separated easily from the anhydride **47** formed as a by-product. Hydrogenolysis of the 4-methoxybenzyl groups of the amide **59** (obtained from **62** as described for **58**) also led to partial loss of the chloride substituents. Removal of the protecting groups by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[27] met with difficulties since the DDQH formed and the deprotected amide **60** were insoluble in most solvents, which prevented their separation. The problem was solved by hydrogenolysis of the protecting groups in the presence of methanolic HCl, when the amide **60**, formed as intermediate, was hydrolysed to the free acid **56** which gave the crystalline 1,4-lactone **55** on evaporation of the solvents. The i.r. (ν_{CO} 1780 cm^{-1}) and n.m.r. data indicated that the 1,5-lactone **43** was not formed and confirmed the presence of structure **55**. Treatment of **55** with 1 equiv. of NaOH afforded **57**.

In order to establish the effect of the carboxyl group in **56** on the biological activity, the corresponding sulfonic acid analogue **67** was synthesised. Deacylation of the thiobenzoate **50** required at least 1.1 equiv. of sodium methoxide because of the acidity of the resulting thiol **51**, but attempts to oxidise **51** to the corresponding sulfonic acid (**52**) failed, and a mixture, arising from partial oxidation of the benzyl groups, was obtained.

In order to overcome this problem, the tetraol **33** was treated with pyridine–mesyl chloride (1.3 equiv.) at −30°. According to t.l.c. [detection with 4-(4-nitrobenzyl)-pyridine–M NaOH[28,29]], a monomesylate was the main product, but attempted isolation resulted in its conversion into the 1,4-anhydride **45**. Therefore, the products were acetylated and this allowed the acetylated 1,4-anhydride **46**, formed only as a by-product (4%), and the crystalline mesylate **63** (42%) to be separated in addition to the tetraacetate **32** (37%). Treatment of **63** with potassium thiobenzoate gave **64** (89%). The thiol, formed on deacylation of **64**, was sensitive to air oxidation and was isolated as the disulfide **65**.

Oxidation of **65** with potassium permanganate[30] afforded 3-(2,4-dichlorophenyl)-propionic acid as the only product, isolated as the ethyl ester **68**. In order to protect the free hydroxyl groups, **65** was converted into the triacetate **66**, oxidation of which with

potassium permanganate and subsequent deacetylation with sodium methoxide afforded **67**.



63 R = MsO
64 R = BzS

65 R = H
66 R = Ac

67

68

Ar = 2,4-dichlorophenyl

BIOLOGICAL RESULTS

The assay for inhibition of HMG-CoA reductase was carried out as described[10] for the model compound **3**. Instead of racemic **3**, the D-*erythro* (3*R*,5*R*) isomer[31] was used. The following activities were recorded, compared to that of compactin (**1**): **3** (10^{-5}M) 82% (*cf.* 80% for the racemate[10]), **57** (10^{-5}M) 17%, and **67** (10^{-4}M) 13%.

Thus, the introduction of an additional hydroxyl group at C-4 (→**57**) markedly decreased the activity and replacement of the carboxyl group of **57** by a sulfonic acid (→**67**) resulted in a further marked decrease in activity.

EXPERIMENTAL

General methods. — Organic solutions were dried with Na_2SO_4 and concentrated under diminished pressure. Reactions were carried out at room temperature (20°) and optical rotations were determined on 1% solutions in $CHCl_3$ at 20° unless stated otherwise. T.l.c. was performed on Kieselgel G with *A*, EtOAc; EtOAc–hexane mixtures (*B* 3:1, *C* 2:1, *D* 1:1, *E* 1:2, *F* 1:3, *G* 1:4, *H* 1:5, *I* 1:6, and *J* 1:9); and *K*, 9:1 EtOAc–EtOH; with detection using 1:1 0.1M $KMnO_4$–M H_2SO_4 at 200°. N.m.r. spectra were recorded with a Bruker AC 250 spectrometer at 250 (^{1}H) and 62.9 MHz (^{13}C) on solutions in $CDCl_3$ (internal Me_4Si) unless stated otherwise. The ^{1}H-n.m.r. data are given in Tables I–III. Mass spectra were recorded with a Finnigan MAT 8430 mass spectrometer/SS300 data system, using an Ion Tech FAB gun (8 kV), and a 4:1 glycerol–*m*-nitrobenzyl alcohol matrix.

*2,4-O-Benzylidene-*L*-xylose* (**13**). — To a stirred slurry of 2,4-*O*-benzylidene-D-glucitol[13] (13.5 g, 50 mmol) and $NaHCO_3$ (0.2 g) in 1,4-dioxane (140 mL) was added a warm (40°) solution of $NaIO_4$ (12.5 g, 58 mmol) in water (25 mL). The mixture was kept for 30 min at room temperature, and the inorganic salts were collected and washed with EtOH (100 mL). The combined filtrate and washings were concentrated, the residue was extracted with EtOH (50 mL), the extract was filtered, the solvent was evaporated, and

TABLE I

^{1}H-N.m.r. data[a] for the 2,4-*O*-benzylidene derivatives **16–30**

Compound	*H-1a*	*H-1b*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*PhCH*	$J_{4,5}$	*Other protons*
16	——4.30–4.05m——			5.04t	4.62dd	5.81dd	6.73d	5.63s	8.4	2.05s (3 H), 2.22s (3 H)
17[b]	——3.57m——		3.84t	3.47d	4.51d	6.13dd	6.69d	5.61s	8.7	4.68t (1 H), 4.88d (1 H)
18	——4.23m——		4.40t	5.14t	4.77ddd	6.08dd	7.08dd	5.78s	4.8	2.08s (3 H), 2.09s (3 H)
19[b]	——3.60m——		3.95t	3.60m	4.68m[c]	6.47dd	6.91d	5.72s	5.3	4.68m[c] (2 H)
20	——4.30–4.05m——			3.52s	4.46d	6.14dd	6.79d	5.56s	8.6	2.42s (3 H)
21	3.87dd	3.77dd	4.07dd	4.73s	4.56d	5.64dd	6.45d	5.58s	8.8	2.48s (3 H), 2.25bs (1 H)
22	——4.12m——		4.25m	4.65t	4.54d	5.66dd	6.51d	5.52s	8.7	2.45s (3 H), 2.41s (3 H)
23	——4.45–4.30m——			4.73s	4.59d	5.63dd	6.52d	5.61s	8.7	3.01s (3 H), 2.48s (3 H)
24	——4.52–4.30m——			4.76s	4.67d	6.04dd	6.84d	5.66s	8.2	3.04s (3 H), 3.24s (3 H)
25	——4.58–3.75m——			3.62d	4.46d	6.24dd	6.78d	5.61s	8.6	0.89s (9 H), 0.08s (3 H), 0.07s (3 H)
26	——3.73m——		4.05t	5.16s	4.61d	5.83dd	6.70d	5.62s	8.2	2.20s (3 H), 0.89s (9 H), 0.05s (6 H)
27	——3.64d——		3.96td	4.83t	4.55dd	5.83dd	6.62d	5.58s	8.6	2.45s (3 H), 0.88s (9 H), 0.03s (6 H)
28	3.78dd	3.69dd	4.17ddd	5.43t	4.73dd	5.81dd	6.69d	5.71s	8.3	8.34s (4 H), 0.82s (9 H), −0.07s (6 H)
29	——4.31m——		4.06t	3.52d	4.48d	6.21dd	6.80d	5.62s	8.7	2.59d (1 H), 2.07s (3 H)
30	——4.40–4.20m——			4.76s	4.63d	6.10dd	6.84d	5.64s	8.5	3.20s (3 H), 2.07s (3 H)

[a] The signals of the protons of the 2,4-dichlorophenyl ring appeared in the range 7.55–7.18 p.p.m. The $J_{2,3}$ and $J_{3,4}$ values were in the range 0–1.5 Hz for all derivatives. $J_{5,6}$ for **18** and **19** was 16.0 Hz; for all other compounds, it was within the range 11.6–11.8 Hz. [b] Me_2SO-d_6 solution. [c] Overlapping multiplets.

TABLE II

^{1}H-N.m.r. data[a] for acyclic derivatives **32–36**, **39**, **40**, **42**, **48**, **50**, **51**, **53**, **54**, **57–59**, and **61–67**

Compound	*H-1a*	*H-1b*	*H-2*	*H-3*	*H-4*	*H-5a,5b*	*H-6a,6b*	*Other protons*
32	4.35dd	3.96dd	5.14m	——5.30 m——		1.86m	2.70m	2.12s (3 H), 2.11s (3 H), 2.05s (6 H)
33[b]	——3.60–3.25m——					1.68m	2.70m	
34	——3.70m——		5.05q	5.46t	5.18q	1.86m	2.70m	2.10s (6 H), 2.06s (3 H), 0.88s (9 H), 0.04s (6 H)
35[b]	——3.75–3.30m——					1.73m	2.70m	0.90s (9 H), 0.08 (6 H)
36	3.98dd	3.88d	5.53q	6.07t	5.66q	2.17m	2.83m	0.87s (9 H), 0.03s (3 H), 0.00s (3 H)
39	——3.27m——		3.42m	3.81m	3.65m	1.79m	2.70m	7.50–7.20m (15 H)
40	3.19dd	3.12dd	4.98q	5.54t	5.18q	1.83m	2.70m	7.45–7.15m (15 H), 2.06s (3 H), 1.99s (6 H)
42	——3.95–3.25m——					1.70m	2.60m	3.80s (3 H), 3.79s (6 H)
48	4.43dd	4.20dd	——3.60m——		3.90m	1.85m	2.65m	4.75–4.50m (6 H), 2.82s (3 H)
50	——3.36m——		——3.82–3.63m——			1.75m	2.65m	4.90–4.50m (6 H)
51	——2.75m——		——3.90–3.60m——			1.75m	2.70m	4.80–4.40m (6 H)
53	——3.80–3.50m——					1.90m	2.70m	4.80–4.45m (6 H), 2.25bs (1 H)
54	——3.80–3.40m——					1.70m	2.55m	6.76m (6 H), 3.70s (6 H), 3.69s (3 H)
57[b]	——2.10m——		3.75m	3.08t	3.50m	1.70m	2.75m	
58	2.60dd	2.36dd	4.11m	——3.65m——		1.80m	2.70m	5.57bs (1 H), 5.30bs (1 H), 4.75–4.50m (6 H)
59	2.56dd	2.32dd	4.06m	——3.60m——		1.75m	2.60m	5.64bs (1 H), 5.18bs (1 H), 4.70–4.40m (6 H), 3.80s (3 H), 3.79s (3 H), 3.77s (3 H)
61	——2.65m[c]——		3.88m	3.66t	3.56m	1.85m	2.65m[c]	4.80–4.45m (6 H)
62	——2.55m[c]——		3.85m	3.57t	3.48m	1.75m	2.55m[c]	4.70–4.35m (6 H), 3.80s (6 H), 3.78s (3 H)
63	4.38dd	4.27dd	5.24ddd	5.35dd	5.14m	1.85m	2.70m	3.04s (3 H), 2.12s (6 H), 2.08s (3 H)
64	3.44dd	3.14dd	——5.30m——		5.21m	1.85m	2.70m	2.15s (3 H), 2.13s (3 H), 2.04s (3 H)
65[b]	——2.75m[c]——		3.77m	3.33m	3.56m	1.70m	2.75m[c]	4.76d (1 H), 4.54d (1 H), 4.48d (1 H)
66	——2.75m[c]——		——5.30m——		5.13m	1.86m	2.75m[c]	2.10s (6 H), 2.05s (3 H)
67[b]	——2.75m[c]——		3.96m	3.28m	3.55m	1.70m	2.75m[c]	

[a] The signals of the protons of the 2,4-dichlorophenyl ring appeared in the range 7.53–6.81 p.p.m. [b] Me_2SO-d_6 solution. [c] Overlapping multiplets.

TABLE III

^{1}H-N.m.r. data[a] for 1,4-anhydro derivatives **44**–**47**

Compound	*H-1a*	*H-1b*	*H-2*	*H-3*	*H-4*	*H-5a,5b*	*H-6a,6b*	*Other protons*
44	3.76dd	4.20–3.80m				1.95m	2.60m	4.58d (1 H), 4.49s (2 H), 4.43d (1 H)
45[b]	3.62dd	4.30–3.85m				1.92m	2.85m	
46	3.60ddd	4.31dd	5.11ddd	5.25dd	3.98m	1.85m	2.80m	2.10s (3 H), 2.09s (3 H)
47	3.74dd	4.20–3.80m				1.85m	2.80m	4.55d (1 H), 4.44s (2 H), 4.37d (1 H), 3.82s (3 H), 3.80s (3 H)

[a] The signals of the protons of the 2,4-dichlorophenyl ring appeared in the range 7.40–7.12 p.p.m. [b] $CDCl_3$–Me_2SO-d_6 solution.

the residue was treated with ether to give crude **13** (11.6 g, 97.5%), m.p. 124° (dec.), $[\alpha]_D$ −7.5°, R_F 0.4 (solvent *A*), which was used for the further reactions. In the literature[13], $Pb(OAc)_4$ was applied for the synthesis of **13**, but it was more convenient to use $NaIO_4$. When the crude **13** was recrystallised from EtOH–water, the ethyl hemiacetal **12** was obtained, which had m.p. 132–134° (dec.), $[\alpha]_D$ −32° (Me_2SO). N.m.r. data: ^1H, δ 7.60–7.30 (m, 5 H, Ph), 6.05 (bs, 1 H, OH), 5.53 (s, PhC*H*), 4.67 (d, 1 H, $J_{1,2}$ 7.2 Hz, H-1), 4.35 (bs, 1 H, OH), 3.80–3.25 (m, 7 H, H-2,3,4,5a,5b and OCH_2CH_3), and 1.12 (t, 3 t, *J* 7 Hz, OCH_2CH_3); ^{13}C, δ 138.9 (s), 129.0 (d), 128.1 (d), 127.0 (d), 100.9 (d), 94.3 (d), 82.0 (d), 80.8 (d), 62.5 (d), 62.0 (t), 61.0 (t), and 15.5 (q).

Anal. Calc. for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.18; H, 7.14.

A solution of crude **13** (1.1 g) and 4-nitrophenylhydrazine (0.8 g) in MeOH (25 mL) was boiled for 10 min, then concentrated. The residue was treated with ether to give 2,4-*O*-benzylidene-L-xylose 4-nitrophenylhydrazone (**14**; 1.5 g, 87%), m.p. 162° (dec.). N.m.r. data (Me_2SO-d_6): ^1H, δ 11.11 (s, NH), 8.14 (d, 2 H, aromatic), 7.62–7.52 (m, 2 H, aromatic), 7.48 (d, 1 H, $J_{1,2}$ 6 Hz, H-1), 7.45–7.35 (m, 2 H, aromatic), 7.07 (d, 2 H, aromatic), 5.76 (s, PhC*H*), 5.03 (d, 1 H, $J_{OH,3}$ 8.3 Hz, HO-3), 4.79 (t, 1 H, $J_{OH.5a.5b}$ 5.5 Hz, HO-5), 4.63 (d, 1 H, $J_{1,2}$ 6 Hz, H-2), 4.01 (m, H-3), and 3.75–3.55 (m, 2 H, H-3,5).

Anal. Calc. for $C_{18}H_{19}N_3O_6$: C, 57.90; H, 5.13: N, 11.26. Found: C, 57.83; H, 5.22; N, 11.14.

Z- (**16**) *and* E-*1,3-Di*-O-*acetyl-2,4*-O-*benzylidene-5,6-dideoxy-6*-C-*(2,4-dichlorophenyl)*-D-xylo-*hex-5-enitol* (**18**). — To a stirred slurry of [(2,4-dichlorophenyl)methyl]triphenylphosphonium chloride (50.35 g, 0.11 mol) in dry tetrahydrofuran (600 mL) and *N,N*-dimethylformamide (120 mL) was added potassium *tert*-butoxide (15.4 g). The orange solution was stirred for 1 h at room temperature, and then crude **13** (23.8 g, 0.1 mol) was added. T.l.c. (solvent *A*) indicated that the reaction was complete in 10 min. After 30 min, the mixture was diluted with water (800 mL) and extracted with EtOAc (5 × 200 mL), the combined extracts were washed with brine and dried, and the solvent was evaporated. The residue was dissolved in pyridine (80 mL) and acetic anhydride (40 mL) was added. After 20 h, the mixture was processed in the usual way. The product was crystallised from MeOH (60 mL) to give **16** (15.2 g, 32.7%) as needles.

Column chromatography (solvent *G*) of the material in the mother liquor gave **16** (9.18 g, 19.7%; combined yield, 52.4%), m.p. 116–117° (from MeOH), $[\alpha]_D$ +91°, R_F 0.40 (solvent *F*).

Eluted second was **18** (2.5 g, 5.4%), m.p. 109–111° (from MeOH), $[\alpha]_D$ −9°, R_F 0.30.

Anal. Calc. for $C_{23}H_{22}Cl_2O_6$: C, 59.36; H, 4.76; Cl, 15.22. Found: **16**, C, 59.24; H, 4.68; Cl, 15.30; **18**, C, 59.30; H, 4.75; Cl, 15.32.

Z-*2,4*-O-*Benzylidene-5,6-dideoxy-6*-C-*(2,4-dichlorophenyl)*-D-xylo-*hex-5-enitol* (**17**). — To a solution of **16** (7.5 g) in $CHCl_3$ (20 mL) and MeOH (20 mL) was added methanolic 4M sodium methoxide (0.1 mL). After 30 min, the solid was collected and washed with water to give **17** (5.6 g, 91.2%), m.p. 202–204°, $[\alpha]_D$ +180° (Me_2SO), R_F 0.2 (solvent *D*). ^{13}C-N.m.r. data (Me_2SO-d_6): δ 138.9 (s), 129.0 (d), 128.1 (d), 127.0 (d), 100.9 (d), 94.3 (d), 82.0 (d), 80.8 (d), 62.5 (d), 62.0 (t), 61.0 (t), and 15.5 (q).

Anal. Calc. for $C_{19}H_{18}Cl_2O_4$: C, 59.85; H, 4.75; Cl, 18.59. Found: C, 59.66; H, 4.76; Cl, 18.70.

E-*2,4*-O-*Benzylidene-5,6-dideoxy-6*-C-*(2,4-dichlorophenyl)*-D-xylo-*hex-5-enitol* (**19**). — A solution of **18** (0.23 g) in $CHCl_3$ (1 mL) and MeOH (5 mL) was deacetylated, as described for **17**, to give **19** (0.14 g, 73%), m.p. 170–172°, $[\alpha]_D$ −15° (Me_2SO), R_F 0.2 (solvent *D*).

Anal. Calc. for $C_{19}H_{18}Cl_2O_4$: C, 59.85; H, 4.75; Cl, 18.59. Found: C, 59.70; H, 4.79; Cl, 18.68.

Z-*2,4*-O-*Benzylidene-5,6-dideoxy-6*-C-*(2,4-dichlorophenyl)-1*-O-p-*tolylsulfonyl*- (**20**), -*3*-O-p-*tolylsulfonyl*- (**21**), and -*1,3-di*-O-p-*tolylsulfonyl*-D-xylo-*hex-5-enitol* (**22**). — To a solution of **17** (0.8 g) in pyridine (5 mL) was added tosyl chloride (0.6 g, 1.5 equiv.) at 0°. The mixture was processed after 1 h in the usual way. Treatment of the product with EtOAc gave **17** (0.1 g). Column chromatography (solvent *C*) of the material in the mother liquor and concentration of the appropriate fractions gave the following products.

An amorphous 1:2 mixture (0.8 g) of **20** and **22**, R_F 0.3.

Amorphous **21** (0.25 g, 22%), R_F 0.2, $[\alpha]_D$ +64°.

Anal. Calc. for $C_{26}H_{24}Cl_2O_6S$: C, 58.31; H, 4.51; Cl, 13.24; S, 5.98. Found: C, 58.25; H, 4.54; Cl, 13.18; S, 6.05.

The amorphous ditosylate **22** (1.4 g, 97%), obtained when the amount of tosyl chloride was increased to 3 equiv. (1.2 g) and the reaction time was prolonged to 24 h, had $[\alpha]_D$ +52°.

Anal. Calc. for $C_{33}H_{30}Cl_2O_8S_2$: C, 57.47; H, 4.38; Cl, 10.28; S, 9.29. Found: C, 57.32; H, 4.44; Cl, 10.21; S, 9.35.

Z-*2,4*-O-*Benzylidene-5,6-dideoxy-6*-C-*(2,4-dichlorophenyl)-1*-O-*methanesulfonyl-3*-O-p-*tolylsulfonyl*-D-xylo-*hex-5-enitol* (**23**). — To a solution of **21** (0.75 g) in pyridine (5 mL) was added mesyl chloride (0.5 mL), and, after 2 h, the mixture was processed in the usual way to give amorphous **23** (0.8 g, 93%), $[\alpha]_D$ +41°, R_F 0.6 (solvent *D*).

Anal. Calc. for $C_{27}H_{26}Cl_2O_8S_2$: C, 52.85; H, 4.27; Cl, 11.55; S, 10.45. Found: C, 52.73; H, 4.36; Cl, 11.38; S, 10.55.

Z-*2,4*-O-*Benzylidene-5,6-dideoxy-6*-C-*(2,4-dichlorophenyl)-1,3-di*-O-*methanesulfonyl*-D-xylo-hex-5-enitol (**24**). — Treatment of **17** (1 g) in pyridine (10 mL) with mesyl chloride (1 mL) in the usual manner, with recrystallisation of the product from EtOH (30 mL), gave **24** (1.3 g, 93%), m.p. 135–137°, $[\alpha]_D$ +94°, R_F 0.75 (solvent *D*).

Anal. Calc. for $C_{21}H_{22}Cl_2O_8S_2$: C, 46.93; H, 4.13; Cl, 13.19; S, 11.93. Found: C, 47.02; H, 4.26; Cl, 13.00; S, 12.03.

Z-*2,4*-O-*Benzylidene-1*-O-tert-*butyldimethylsilyl-5,6-dideoxy-6*-C-*(2,4-dichlorophenyl)*-D-xylo-hex-5-enitol (**25**). — ^{t}BuMe$_2$SiCl (0.4 g) and imidazole (0.4 g) were added to a solution of **17** (0.8 g) in *N,N*-dimethylformamide (5 mL). After 45 min, the mixture was poured into water, and the precipitate was collected, washed with water, and dried. Column chromatography (solvent *G*) then gave **25** (0.93 g, 89.4%), m.p. 104–106° (from ether–hexane), $[\alpha]_D$ +184°, R_F 0.6 (solvent *I*).

Anal. Calc. for $C_{25}H_{32}Cl_{24}O_4Si$: C, 60.59; H, 6.51; Cl, 14.35. Found: C, 60.62; H, 6.52; Cl, 14.30.

Z-3-O-Acetyl-2,4-O-benzylidene-1-O-tert-butyldimethylsilyl-5,6-dideoxy-6-C-(2,4-dichlorophenyl)-D-xylo-hex-5-enitol (**26**). — (*a*) ^{t}BuMe$_2$SiCl (0.4 g) was added to a solution of **17** (0.8 g) in pyridine (5 mL). After 1 h, t.l.c. (solvent *E*) indicated that the reaction was complete, and acetic anhydride (0.5 mL) was added. The mixture was processed after 20 h in the usual way to give, after column chromatography (solvent *H*), **26** (1.07 g, 95%), isolated as a syrup, $[\alpha]_D$ +80°, R_F 0.6 (solvent *J*).

(*b*) A solution of **25** (2 g) in pyridine (5 mL) and acetic anhydride (1 mL) was processed after 24 h, in the usual way, to give **26** (2.7 g, 97%).

Anal. Calc. for $C_{27}H_{34}Cl_2O_5Si$: C, 60.32; H, 6.37; Cl, 13.19. Found: C, 60.15; H, 6.45; Cl, 13.02.

Z-2,4-O-Benzylidene-1-O-tert-butyldimethylsilyl-5,6-dideoxy-6-C-(2,4-dichlorophenyl)-3-O-p-tolylsulfonyl)-D-xylo-hex-5-enitol (**27**). — ^{t}BuMe$_2$SiCl (0.4 g) was added to a solution of **17** (0.8 g) in pyridine (5 mL). After 1 h, tosyl chloride (0.6 g) was added and, after 36 h, the mixture was processed in the usual way. Column chromatography (solvent *I*) of the product gave **27** (1.5 g, 100%), isolated as a syrup, $[\alpha]_D$ +47°, R_F 0.75 (solvent *G*).

Anal. Calc. for $C_{32}H_{38}Cl_2O_6SSi$: C, 59.15; H, 5.92; Cl, 10.91; S, 4.93. Found: C, 59.31; H, 6.04; Cl, 10.77; S, 4.75.

Desilylation of **27** (1.3 g) in MeOH (40 mL) containing M H_2SO_4 (1.2 mL) was complete in 75 min. The mixture was neutralised with $NaHCO_3$ and the solvent was evaporated. Column chromatography (solvent *C*) of the residue gave **21** (0.95 g, 88.8%) identical with the product described above.

Z-2,4-O-Benzylidene-1-O-tert-butyldimethylsilyl-5,6-dideoxy-6-C-(2,4-dichlorophenyl)-3-O-(4-nitrobenzoyl)-D-xylo-hex-5-enitol (**28**). — To a solution of **17** (0.8 g) in pyridine (5 mL) was added ^{t}BuMe$_2$SiCl (0.4 g) followed, after 1 h, by 4-nitrobenzoyl chloride (0.4 g). After 2 h, the mixture was processed in the usual way. Column chromatography (solvent *I*) of the product gave amorphous **28** (1.3 g, 96%), $[\alpha]_D$ +21°, R_F 0.5 (solvent *I*).

Anal. Calc. for $C_{32}H_{35}Cl_2O_7Si$: C, 59.62; H, 5.47; Cl, 11.00; N, 2.17. Found: C, 59.50; H, 5.52; Cl, 11.13; N, 2.06.

Hydrolysis of **28** (1.1 g) in MeOH (40 mL) containing M H_2SO_4 (1.2 mL) was complete in 45 min. Neutralisation of the mixture with $NaHCO_3$, evaporation of the solvent, and column chromatography of the residue gave **17** (0.5 g, 77%), identical with the product described above.

Z-1-O-Acetyl-2,4-O-benzylidene-5,6-dideoxy-6-C-(2,4-dichlorophenyl)-D-xylo-hex-5-enitol (**29**). — Tetrabutylammonium fluoride (0.6 g) was added to a solution of **26** (0.8 g) in tetrahydrofuran (10 mL). After 20 min, t.l.c. (solvent *H*) indicated that the reaction was complete, and solid CO_2 was added. The solvent was evaporated, a solution of the residue in $CHCl_3$ was washed with water and dried, and the solvent was evaporated. Column chromatography (solvent *E*) of the residue gave **29** (0.35 g, 55.5%), m.p. 136–138° (from ether–hexane), $[\alpha]_D$ +220°, R_F 0.5 (solvent *E*).

Anal. Calc. for $C_{21}H_{20}Cl_2O_5$: C, 59.59; H, 4.76; Cl, 16.75. Found: C, 59.50; H, 4.88; Cl, 16.61.

Z-1-O-Acetyl-2,4-O-benzylidene-5,6-dideoxy-6-C-(2,4-dichlorophenyl)-3-O-methanesulfonyl-D-xylo-*hex-5-enitol* (**30**). — To a solution of **29** (0.2 g) in pyridine (1 mL) was added mesyl chloride (0.1 mL). After 2 h, the mixture was poured into water, and the precipitate was recrystallised from MeOH (6 mL) to give **30** (0.23 g, 86%), m.p. 90–92°, $[\alpha]_D$ + 112°, R_F 0.6 (solvent *C*).

Anal. Calc. for $C_{22}H_{22}Cl_2O_7S$: C, 52.70; H, 4.42; Cl, 14.14; S, 6.39. Found: C, 52.68; H, 4.50; Cl, 14.09; S, 6.45.

1,2,3,4-Tetra-O-acetyl-5,6-dideoxy-6-C-(2,4-dichlorophenyl)-D-xylo-*hexitol* (**32**). — A solution of **16** (2 g) in EtOAc (20 mL) was hydrogenated in the presence of 10% Pd/C (0.15 g) for 2.5 h, then filtered, and the solvent was evaporated. Column chromatography (solvent *A*) of the residue gave a syrupy 4:3 mixture (1.6 g) of two isomeric diacetates, R_F 0.6. ^{1}H-N.m.r. data: δ 2.11 and 2.05, and 2.09 and 2.08 (4 OAc). This syrup was dissolved in pyridine (7 mL), acetic anhydride (5 mL) was added, and, after 20 h, the mixture was poured into water. The precipitate (1.65 g) was recrystallised from MeOH–water to give **32** (1.55 g, 78.3%), m.p. 89–91°, $[\alpha]_D$ − 7°, R_F 0.75 (solvent *D*).

Anal. Calc. for $C_{20}H_{22}Cl_2O_8$: C, 52.07; H, 4.80; Cl, 15.37. Found: C, 52.04; H, 4.87; Cl, 15.30.

5,6-Dideoxy-6-C-(2,4-dichlorophenyl)-D-xylo-*hexitol* (**33**). — A solution of **16** (9.5 g) was hydrogenated, as described for **32**. To a solution of the syrupy product in MeOH (50 mL) was added methanolic 4M sodium methoxide (0.2 mL). After 1 h, the solution was neutralised with solid CO_2, the solvent was evaporated, and the residue was recrystallised from EtOAc–hexane to give **33** (4.9 g, 81.7%), m.p. 112–114°, $[\alpha]_D$ + 27° (MeOH), R_F 0.25 (solvent *A*). Mass spectrum: *m/z* 295/297/299 $[M + H]^+$.

Anal. Calc. for $C_{12}H_{16}Cl_2O_4$: C, 48.82; H, 5.46; Cl, 24.02. Found: C, 48.76; H, 5.58; Cl, 23.94.

1-O-tert-Butyldimethylsilyl-5,6-dideoxy-6-C-(2,4-dichlorophenyl)-D-xylo-*hexitol* (**34**). — Deacetylation of **35** (2.1 g) in MeOH (10 mL) and methanolic M sodium methoxide (0.1 mL) gave, after column chromatography (solvent *D*), **34** (1.15 g, 72%), m.p. 114–115° (from ether–hexane), $[\alpha]_D$ + 10°, R_F 0.45 (solvent *D*).

Anal. Calc. for $C_{18}H_{30}Cl_2O_4Si$: C, 52.80; H, 7.39; Cl, 17.31. Found: C, 52.68; H, 7.72; Cl, 17.15.

2,3,4-Tri-O-acetyl-1-O-tert-butyldimethylsilyl-5,6-dideoxy-6-C-(2,4-dichlorophenyl)-D-xylo-*hexitol* (**35**). — To a solution of **33** (1.5 g) in pyridine (10 mL) was added ^{t}BuMe$_2$SiCl (1 g) followed, after 1 h, by acetic anhydride (5 mL). After the usual processing and column chromatography (solvent *F*), **35** (2.45 g, 91%) was obtained; m.p. 68–70°, $[\alpha]_D$ + 10°, R_F 0.6 (solvent *E*).

Anal. Calc. for $C_{24}H_{36}Cl_2O_7Si$: C, 53.82; H, 6.77; Cl, 13.24. Found: C, 53.85; H, 6.80; Cl, 13.14.

1-O-tert-Butyldimethylsilyl-5,6-dideoxy-6-C-(2,4-dichlorophenyl)-2,3,4-tri-O-(4-nitrobenzoyl)-D-xylo-*hexitol* (**36**). — ^{t}BuMe$_2$SiCl (0.2 g) was added to a stirred solution of **33** (0.3 g) in pyridine (2 mL). After 1 h, the solution was cooled with ice and

4-nitrobenzoyl chloride (0.6 g) was added. After storage for 1 h at room temperature, the mixture was processed in the usual way to give, after column chromatography (solvent *H*) and crystallisation from EtOH, **36** (0.58 g, 68%), m.p. 68–71°, $[\alpha]_D$ +40°, R_F 0.8 (solvent *E*).

Anal. Calc. for $C_{39}H_{39}Cl_2N_3O_{13}Si$: C, 54.67; H, 4.58; Cl, 8.27; N, 4.90. Found: C, 54.55; H, 4.62; Cl, 8.21; N, 4.83.

*5,6-Dideoxy-6-*C*-(2,4-dichlorophenyl)-1-*O*-trityl-*D*-xylo-hexitol* (**39**). — Trityl chloride (4 g) was added to a solution of **33** (3 g) in pyridine (15 mL). After 3 days, the solution was processed in the usual way to give, after column chromatography (solvent *E*), crude amorphous **39** (5.1 g, 93%) contaminated with trityl alcohol (n.m.r. data) which could be removed by repeated column chromatography to give **39**, $[\alpha]_D$ 0°, R_F 0.5 (solvent *D*).

Anal. Calc. for $C_{31}H_{30}Cl_2O_4$: C, 69.27; H, 5.62; Cl, 13.19. Found: C, 69.33; H, 5.78; Cl, 13.03.

For further experiments, crude **39** was used.

Acetylation of **39** (0.54 g) with pyridine (3 mL) and acetic anhydride (2 mL) for 2 days, followed by the usual processing and column chromatography (solvent *F*), gave the amorphous triacetate **40** (0.62 g, 92%), $[\alpha]_D$ +22°, R_F 0.4 (solvent *F*).

Anal. Calc. for $C_{37}H_{36}Cl_2O_7$: C, 66.96; H, 5.46; Cl, 10.68. Found: C, 66.92; H, 5.52; Cl, 10.61.

*5,6-Dideoxy-6-*C*-(2,4-dichlorophenyl)-2,3,4-tri-*O*-(4-methoxybenzyl)-1-*O*-triphenylmethyl-*D*-xylo-hexitol* (**42**). — Sodium hydride (50%, 3 g) was reacted with Me_2SO (30 mL), a solution of **39** (6 g) in Me_2SO (30 mL) was added, followed, after 30 min, by a solution of 4-methoxybenzyl chloride (7.2 mL) in Me_2SO (10 mL). The mixture was stored for 2 h, then poured into water, and extracted with $CHCl_3$, and the extract was concentrated. Column chromatography (solvent *H*) of the residue gave **42** (9.4 g, 97%), isolated as a syrup, $[\alpha]_D$ +13°, R_F 0.45 (solvent *G*).

Anal. Calc. for $C_{55}H_{54}Cl_2O_7$: C, 73.56; H, 6.06; Cl, 7.89. Found: C, 72.38; H, 6.12; Cl, 7.79.

*1,4-Anhydro-2,3-di-*O*-benzyl-5,6-dideoxy-6-*C*-(2,4-dichlorophenyl)-*D*-xylo-hexitol* (**44**). — Sodium cyanide (0.5 g, 5 equiv.) was added to a solution of freshly prepared **48** (1.1 g) in *N,N*-dimethylformamide (10 mL) and water (2 mL). The solution was heated for 1 h at 100°; to give, after the usual processing and column chromatography (solvent *J*), **44**, isolated as syrup (0.7 g, 90%), $[\alpha]_D$ −11°, R_F 0.4 (solvent *H*). ^{13}C-N.m.r. data: δ 138.2, 137.8–137.7, 134.5, 132.1, 131.2, 128.5–127.6, 129.1, 127.0, 82.4, 82.2, 80.0, 71.7, 71.5, 71.3, 29.8, and 28.3.

Anal. Calc. for $C_{26}H_{26}Cl_2O_3$: C, 68.27; H, 5.73; Cl, 15.50. Found: C, 68.12; H, 5.80; Cl, 15.26.

*1,4-Anhydro-5,6-dideoxy-6-*C*-(2,4-dichlorophenyl)-*D*-xylo-hexitol* (**45**). — (*a*) A solution of **44** (1.2 g) in EtOH (25 mL) was hydrogenated in the presence of 10% Pd/C (0.1 g) for 6 h. More 10% Pd/C (0.1 g) was added, hydrogenation was continued for 3 h, the solution was then filtered, and the solvent was evaporated. The residue was extracted with MeOH–water and then recrystallised from ether–hexane to give **45** (0.59 g, 82%), m.p. 118–120°, $[\alpha]_D$ −6°, R_F 0.5 (solvent *A*).

(*b*) Methanolic M sodium methoxide (0.01 mL) was added to a solution of **46** (0.23 g) in MeOH (2 mL). After 20 h, sodium ions were removed by Varion KS (H^+) resin, the solvent was evaporated, and the residue was recrystallised from ether–hexane to give **45** (0.15 g, 85.2%) identical with the product in (*a*).

(*c*) Compound **47** (2 g) was treated with boiling methanolic 2M HCl (20 mL) for 30 min, the solution was cooled, neutralised with solid $NaHCO_3$, and filtered, and the solvent was evaporated. Column chromatography (solvent *A*) of the residue and recrystallisation from ether–hexane gave **45** (0.8 g, 72%), identical with the product in (*a*).

Anal. Calc. for $C_{12}H_{14}Cl_2O_3$: C, 52.03; H, 5.09; Cl, 25.60. Found: C, 51.98; H, 5.21; Cl, 25.52.

2,3,4-Tri-O-*benzyl-5,6-dideoxy-6*-C-*(2,4-dichlorophenyl)-1*-O-*methanesulfonyl*-D-xylo-*hexitol* (**48**). — Mesyl chloride (0.25 mL) was added to a solution of **53** (1.1 g) in pyridine (10 mL) at 0°. After 15 min, more mesyl chloride (0.12 mL) was added and, after 20 min, the mixture was processed in the usual way to give crude **48** (1.26 g, 97%) as a syrup. T.l.c. (solvent *F*) revealed **48** (R_F 0.5) and ~ 5% of the anhydride **44** (R_F 0.7) which was formed only on the plate (n.m.r. data). On detection with 4-(4-nitrobenzyl)-pyridine–NaOH, **48** gave a single blue spot (R_F 0.5), characteristic of alkylating agents[28,29]. Because of its instability, **48** could not be purified by column chromatography, and was used immediately. It had $[\alpha]_D$ − 5°.

The corresponding 1-tosylate **49** (0.3 g, 94%), obtained from **53** (0.25 g) by reaction with tosyl chloride (0.25 g) in pyridine (5 mL), decomposed rapidly to give **44** (R_F 0.6 → 0.7, solvent *F*) and the n.m.r. spectrum could not be recorded.

1-S-*Benzoyl-2,3,4-tri*-O-*benzyl-5,6-dideoxy-6*-C-*(2,4-dichlorophenyl)-1-thio*-D-xylo-*hexitol* (**50**) *and 1,4-anhydro-2,3-di*-O-*benzyl-5,6-dideoxy-6*-C-*(2,4-dichlorophenyl)*-D-xylo-*hexitol* (**44**). — Potassium thiobenzoate (1.8 g) was added to a solution of **48** (2.5 g, freshly prepared from 2.2 g of **53**) in acetone (40 mL). The solution was boiled under reflux for 1 h, then cooled, and filtered. More potassium thiobenzoate (0.9 g) was added and boiling under reflux was continued for 2 h. The solvent was evaporated, a solution of the residue in $CHCl_3$ was washed with aq. $NaHCO_3$ and dried, and the solvent was evaporated. Column chromatography (solvent *J*) of the residue gave **50**, isolated as a syrup (1.80 g, 77%), R_F 0.5 (solvent *H*), $[\alpha]_D$ + 24°. ^{13}C-N.m.r. data: δ 191.4, 138.4–138.1, 138.0, 134.4, 132.0, 130.9, 129.0, 128.6–127.6, 126.8, 80.0, 78.7, 77.6, 30.1, 28.9, and 28.6.

Anal. Calc. for $C_{40}H_{38}Cl_2O_4S$: C, 70.06; H, 5.58; Cl, 10.34; S, 4.67. Found: C, 69.92; H, 5.63; Cl, 10.21; S, 4.60.

Eluted second was **44** (0.3 g, 19%), R_F 0.4, identical with the product described above.

Compound **50** (1.8 g) was debenzoylated in tetrahydrofuran (10 mL) and MeOH (5 mL) with methanolic 4M sodium methoxide (1 mL, 1.5 equiv.) for 30 min. The solution was neutralised with solid CO_2 and processed in the usual way. Column chromatography (solvent *J*) of the product gave 2,3,4-tri-*O*-benzyl-5,6-dideoxy-6-*C*-(2,4-dichlorophenyl)-D-*xylo*-hexitol (**51**; 1.25 g, 82.2%), isolated as a syrup, $[\alpha]_D$ + 67°,

R_F 0.6 (solvent *H*). ^{13}C-N.m.r. data: δ 138.4–138.2, 137.9, 134.5, 132.2, 131.1, 129.2, 128.4–127.7, 127.0, 79.4, 78.7, 77.6, 38.3, 30.4, and 28.9.

Anal. Calc. for $C_{33}H_{34}Cl_2O_3S$: C, 68.14; H, 5.89; Cl, 12.19; S, 5.51. Found: C, 68.02; H, 5.72; Cl, 12.04; S, 5.67.

*2,3,4-Tri-*O*-benzyl-5,6-dideoxy-6-*C*-(2,4-dichlorophenyl)-*D*-xylo-hexitol* (**53**). — Sodium hydride (50%, 6 g) was reacted with Me_2SO (60 mL) and a solution of crude **39** (12.3 g) in Me_2SO (60 mL) was added at a rate to keep the temperature at $< 30°$. After 30 min, a solution of benzyl chloride (12 mL) in Me_2SO (20 mL) was added during 30 min. The excess of benzyl chloride was decomposed after 3 h by slowly adding MeOH (5 mL) to the cooled (0°) solution. After storage for 30 min at room temperature, the mixture was poured into water and extracted with $CHCl_3$ and the extract was dried and concentrated to afford **41** (20 g) as a syrup (R_F 0.6, solvent *I*). To a solution of this syrup in $CHCl_3$ (200 mL) and MeOH (100 mL) was added methanolic 2M HCl (5 mL). After 35 min, t.l.c. indicated the reaction to be complete (R_F 0.95 → 0.5, solvent *E*). The solution was neutralised with solid $NaHCO_3$ and filtered, and the solvent was evaporated. Column chromatography (solvent *G*) of the residue gave **53** (9.2 g, 72%), isolated as syrup, $[\alpha]_D$ + 10°.

Anal. Calc. for $C_{33}H_{34}Cl_2O_4$: C, 70.08; H, 6.06; Cl, 12.53. Found: C, 70.01; H, 6.10; Cl, 12.48.

*5,6-Dideoxy-6-*C*-(2,4-dichlorophenyl)-2,3,4-tri-*O*-(4-methoxybenzyl)-*D*-xylo-hexitol* (**54**). — A solution of **42** (8.3 g) in $CHCl_3$ (40 mL), MeOH (20 mL), and methanolic 2M HCl (0.5 mL) was kept for 48 h at 4°, then neutralised with solid $NaHCO_3$, and filtered, and the solvent was evaporated. Column chromatography (solvent *E*) of the residue gave **54** (4.7 g, 78%), isolated as a syrup, $[\alpha]_D$ + 9°, R_F 0.3.

Anal. Calc. for $C_{36}H_{40}Cl_2O_7$: C, 65.94; H, 6.15; Cl, 10.81. Found: C, 65.80; H, 6.22; Cl, 10.74.

*2,6,7-Trideoxy-7-*C*-(2,4-dichlorophenyl)-*D*-xylo-heptono-1,4-lactone* (**55**). — A solution of **59** (340 mg) in EtOAc (10 mL) and methanolic 2M HCl (10 mL) was hydrogenated in the presence of 10% Pd/C (100 mg) for 4 h, then filtered, and concentrated, and EtOH was evaporated from the residue three times. The semisolid residue was extracted with EtOAc, the extract was concentrated, and the residue was crystallised from ether–hexane to give **55** (108 mg, 72%), m.p. 132–134°, $[\alpha]_D$ + 7° (*c* 0.5, MeOH), R_F 0.5 (solvent *C*). N.m.r. data (CD_3OD): ^{1}H, δ 7.39, 7.23, and 7.32 (d, dd, and d, 3 H, aromatic), 4.52 (ddd, $J_{2a,3}$ 6.0, $J_{3,4}$ 4.2, $J_{2b,3}$ 1.3 Hz, H-3), 4.30 (dd, $J_{4,5}$ 6.9, $J_{3,4}$ 4.2 Hz, H-4), 4.00 (ddd, $J_{5,6a}$ 9.6, $J_{4,5}$ 6.9, $J_{5,6b}$ 3.1 Hz, H-5), 3.10–2.75 (m, 3 H, H-2a,7a,7b), 2.46 (dd, $J_{2a,2b}$ 17.5, $J_{2b,3}$ 1.3 Hz, H-2b), and 2.05–1.65 (m, 2 H, H-6a,6b); ^{13}C, δ 178.4, 139.7, 135.7, 132.7, 129.9, 128.2, 88.6, 70.1, 69.1, 40.6, 33.1, and 28.9.

Anal. Calc. for $C_{13}H_{14}Cl_2O_4$: C, 51.19; H, 4.63; Cl, 23.24. Found: C, 51.27; H, 4.62; Cl, 23.20.

*Sodium 2,6,7-trideoxy-7-*C*-(2,4-dichlorophenyl)-*D*-xylo-heptonate* (**57**). — 0.1M NaOH (3 mL) was added to a solution of **55** (91.5 mg, 0.3 mmol) in MeOH (10 mL). After 20 h, the solution was concentrated, and EtOH was evaporated from the residue which was filtered with EtOH–ether to give amorphous **57** (100 mg, 97%), m.p. 198–205°, $[\alpha]_D$ + 11° (1:1 MeOH–water).

Anal. Calc. for $C_{13}H_{15}Cl_2NaO_5$: C, 45.23; H, 4.38; Cl, 20.55. Found: C, 45.18; H, 4.42; Cl, 20.47.

*3,4,5-Tri-O-benzyl-2,6,7-trideoxy-7-C-(2,4-dichlorophenyl)-*D*-xylo-heptonamide* (**58**). — To a stirred solution of **61** (1.15 g) in Me_2SO (5 mL) were added K_2CO_3 (0.2 g) and aq. 30% H_2O_2 (0.5 mL) at 0°. Stirring was continued for 20 h at room temperature, when more aq. 30% H_2O_2 (0.5 mL) and Me_2SO (1 mL) were added. After 4 h, the mixture was diluted with water, the pH was adjusted to ~ 2 with 5M HCl, the precipitate was collected, a solution in EtOAc was washed with water and dried, and the solvent was evaporated. The residue was treated with hexane to give **58** (0.75 g, 63%), m.p. 93–95°, $[\alpha]_D$ +9°, R_F 0.4 (solvent *C*).

Anal. Calc. for $C_{34}H_{35}Cl_2NO_4$: C, 68.91; H, 5.95; Cl, 11.97; N, 2.36. Found: C, 68.90; H, 5.97; Cl, 11.92; N, 2.22.

When a crude mixture of **61** + **44** (2.1 g) was used [obtained in the Mitsunobu reaction of **53** (1.9 g)] as starting material, **58** (1.1 g, 55%) was obtained.

Concentration of the hexane filtrate and column chromatography (solvent *J*) of the residue gave **44** (0.58 g, 38%).

*2,6,7-Trideoxy-7-C-(2,4-dichlorophenyl)-3,4,5-tri-O-(4-methoxybenzyl)-*D*-xylo-heptonamide* (**59**). — Treatment of **62** (0.92 g), as described above for **58**, gave **59** (0.65 g, 68.8%), m.p. 102–104°, $[\alpha]_D$ +7°, R_F 0.4 (solvent *B*).

Anal. Calc. for $C_{37}H_{41}Cl_2NO_7$: C, 65.09; H, 6.05; Cl, 10.38; N, 2.05. Found: C, 64.98; H, 5.97; Cl, 10.41; N, 2.00.

*3,4,5-Tri-O-benzyl-2,6,7-trideoxy-7-C-(2,4-dichlorophenyl)-*D*-xylo-heptononitrile* (**61**). — Triphenylphosphine (2.25 g, 8.5 mmol), diethyl azodicarboxylate (1.65 mL, 8.6 mmol), and M HCN in benzene (7 mL) were added to a stirred solution of **53** (4 g, 7 mmol) in benzene (50 mL) at 0°. Stirring was continued at room temperature and, after 1 h, more triphenylphosphine (1.1 g), diethyl azodicarboxylate (0.8 mL), and M HCN in benzene (3.5 mL) were added. After 2 h, saturated aq. NH_4Cl (5 mL) was added, the organic solution was washed with water, the solvent was evaporated, and the residue was subjected to repeated column chromatography (solvent *I*) to give **61** (1.15 g, 28%), R_F 0.45 (solvent *H*), $[\alpha]_D$ 0°. F.a.b.-m.s.: *m/z* 574/576/578 $[M + H]^+$.

Anal. Calc. for $C_{34}H_{33}Cl_2NO_3$: C, 71.08; H, 5.78; Cl, 12.34; N, 2.43. Found: C, 71.01; H, 5.60; Cl, 12.51; N, 2.25.

For the conversion of **61** into the amide **58**, it was not necessary to separate **61** from **44** (see preparation of **58**).

*2,6,7-Trideoxy-7-C-(2,4-dichlorophenyl)-3,4,5-tri-*O*-(4-methoxybenzyl)-*D*-xylo-heptononitrile* (**62**) *and 1,4-Anhydro-5,6-dideoxy-6-C-(2,4-dichlorophenyl)-2,3-di-O-(4-methoxybenzyl)-*D*-xylo-hexitol* (**47**). — A solution of **54** (3.2 g) in benzene (30 mL) was treated as described above for **61**. Column chromatography (solvent *H*) of the products gave **47** (0.57 g, 22.6%), R_F 0.6 (solvent *F*), $[\alpha]_D$ −18°.

Anal. Calc. for $C_{28}H_{30}Cl_2O_5$: C, 64.99; H, 5.84; Cl, 13.70. Found: C, 64.88; H, 5.90; Cl, 13.62.

Eluted second was **62** (1.2 g, 37%), R_F 0.45, $[\alpha]_D$ 0°. ^{13}C-N.m.r. data: δ 159.5–159.4 (s), 137.9 (s), 134.4 (s), 132.2 (s), 130.9 (d), 130 129.8 (d), 129.9 129.4 (s), 129.1 (d),

126.9 (d), 118.1 (s), 78.9 (d), 76.8 (d), 74.5 (d), 74.1 (t), 73.1 (t), 71.8 (t), 55.2 (q), 29.5 (t), 29.1 (t), and 20.1 (t).

Anal. Calc. for $C_{37}H_{39}Cl_2NO_6$: C, 66.86; H, 5.91; Cl, 10.67; N, 2.10. Found: C, 66.69; H, 5.98; Cl, 10.57; N, 2.02.

*2,3,4-Tri-O-acetyl-5,6-dideoxy-6-C-(2,4-dichlorophenyl)-1-O-methanesulfonyl-*D-xylo-*hexitol* (**63**) *and 2,3-di-O-acetyl-1,4-anhydro-5,6-dideoxy-6-C-(2,4-dichlorophenyl)-*D-xylo-*hexitol* (**46**). — Mesyl chloride (0.5 mL, 1.3 equiv.) was added to a stirred solution of **33** (1.5 g) in pyridine (10 mL) at −30°. Stirring was continued for 1 h at 0°, acetic anhydride (3 mL, 6 equiv.) was added, and the solution was kept for 2 h at room temperature. After usual processing and column chromatography (solvent *D*) of the product, **46** (70 mg, 3.9%) was isolated as a syrup, R_F 0.8, $[\alpha]_D$ +35°. ^{13}C-N.m.r. data: δ 159.4 (s), 138.3 (s), 132.4 (s), 131.2 (d), 130.0–129.9 (s), 129.4–129.2 (d), 129.1 (d), 127.0 (d), 82.2 (d), 82.1 (d), 80.0 (d), 74.1 (t), 73.1 (t), 71.8 (t), 55.3 (q), 29.8 (t), and 28.3 (t).

Anal. Calc. for $C_{16}H_{18}Cl_2O_5$: C, 53.19; H, 5.02; Cl, 19.64. Found: C, 53.03; H, 5.15; Cl, 19.52.

Eluted next was **32** (0.5 g, 37.3%), R_F 0.7.

Eluted last was **63** (1.06 g, 42%), R_F 0.35, m.p. 83–85° (from MeOH–water), $[\alpha]_D$ 0°. ^{13}C-N.m.r. data: δ 170.3, 169.8, 169.6, 136.6, 134.3, 132.6, 131.1, 129.2, 127.1, 70.5, 70.4, 69.0, 66.4, 37.6, 30.3, 28.6, 20.7, 20.5, and 20.4.

Anal. Calc. for $C_{19}H_{24}Cl_2O_9S$: C, 45.69; H, 4.84; Cl, 14.20; S, 6.42. Found: C, 45.65; H, 4.92; Cl, 14.14; S, 6.53.

*2,3,4-Tri-O-acetyl-1-S-benzoyl-5,6-dideoxy-6-C-(2,4-dichlorophenyl)-1-thio-*D-xylo-*hexitol* (**64**). — A solution of potassium thiobenzoate (1.5 g, 1.4 equiv.) and **63** (3 g) in acetone (50 mL) was boiled under reflux for 2 h, then cooled, and filtered. More potassium thiobenzoate (0.75 g) was added to the filtrate and boiling under reflux was continued for 2 h. The solution was concentrated, a solution of the residue in $CHCl_3$ was washed with aq. $NaHCO_3$ and dried, and the solvent was evaporated. The residue was filtered with ether–hexane to give **64** (2.9 g, 89%), m.p. 112–114°, $[\alpha]_D$ −33°, R_F 0.7 (solvent *D*).

Anal. Calc. for $C_{25}H_{26}Cl_2O_7S$: C, 55.45; H, 4.84; Cl, 13.09; S, 5.92. Found: C, 55.44; H, 4.82; Cl, 13.14; S, 5.89.

*Bis[1,5,6-trideoxy-6-C-(2,4-dichlorophenyl)-*D-xylo-*hexitol] 1,1'-disulfide* (**65**). — Methanolic 4M sodium methoxide (3 mL) was added to a solution of **64** (2.9 g) in MeOH (50 mL). After 2 h, the solution was neutralised with solid CO_2, then concentrated, the residue was extracted with EtOAc, and the extract was concentrated. Column chromatography (solvent *K*) of the residue and treatment with ether gave **65** (1.22 g, 73%), m.p. 126–128°, R_F 0.4, $[\alpha]_D$ −13° (Me_2SO): F.a.b.-mass spectrum: *m/z* 619/621/623 $[M + H]^+$. The product did not react with sodium 4-nitroprusside, characteristic for SH compounds.

Anal. Calc. for $C_{24}H_{30}Cl_4O_6S_2$: C, 46.46; H, 4.87; Cl, 22.86; S, 10.34. Found: C, 46.32; H, 4.92; Cl, 22.77; S, 10.23.

*Bis[2,3,4-Tri-O-acetyl-1,5,6-trideoxy-6-C-(2,4-dichlorophenyl)-*D-xylo-*hexitol] 1,1'-disulfide* (**66**). — A solution of **65** (0.4 g) in pyridine (10 mL) and acetic anhydride (6

mL) was kept for 20 h at room temperature, then concentrated. Column chromatography (solvent *E*) and recrystallisation from MeOH gave **66** (0.5 g, 89%), R_F 0.25, m.p. 114–115°.

Anal. Calc. for $C_{36}H_{42}Cl_4O_{12}S_2$: C, 49.54; H, 4.85; Cl, 16.25; S, 7.34. Found: C, 49.51; H, 4.90; Cl, 16.18; S, 7.31.

Sodium 6-(2,4-dichlorophenyl)-D-xylo-*2,3,4-trihydroxyhexanesulfonate* (**67**). — $KMnO_4$ (50 mg) was added to a stirred solution of **66** (100 mg) in acetic acid (10 mL) and water (1 mL). Stirring was continued overnight, the mixture was concentrated, toluene (2 × 10 mL) was evaporated from the residue, which was then dissolved in MeOH (10 mL), and methanolic 4M sodium methoxide (0.1 mL) was added. After 4 h, water (10 mL) was added, and the mixture was filtered with carbon and then eluted from a column of Varion KS (H^+) resin (10 mL) with 1:1 MeOH–water (20 mL). The appropriate fractions were combined and concentrated, and toluene (2 × 10 mL) was evaporated from the residue to remove traces of acetic acid. The pH of a solution of the residue in MeOH (10 mL) was adjusted to 7 with 0.1M NaOH, the solution was concentrated, and a solution of the residue in water (1 mL) was freeze-dried to give amorphous **67** (70 mg, 78%), $[\alpha]_D$ +8° (*c* 0.7, water). ^{13}C-N.m.r. data: δ 139.1, 133.7, 131.7, 130.9, 128.3, 127.1, 74.7, 70.3, 68.6, 54.2, 33.0, and 28.7.

Anal. Calc. for $C_{12}H_{15}Cl_2NaO_6 \cdot H_2O$: C, 36.07; H, 4.29; Cl, 17.76; S, 8.03. Found: C, 36.01; H, 4.42; Cl, 17.69; S, 7.92.

Ethyl 3-(2,4-dichlorophenyl)propionate (**68**). — A solution of $KMnO_4$ (300 mg) in water (1 mL) was added to a solution of **65** (300 mg) in acetone (30 mL). The mixture was stirred for 30 min at 50°, then cooled, and filtered through charcoal. The filtrate was acidified with 5M HCl and then concentrated, the residue was extracted with EtOH, and the extract was concentrated to give **68** (110 mg, 46%) as a liquid. ^{1}H-N.m.r. data: δ 7.37 (s, 1 H, aromatic), 7.18 (s, 2 H, aromatic), 4.14 (q, 2 H, *J* 7 Hz, OCH_2CH_3), 3.04 (t, 2 H, $J_{2,3}$ 7 Hz, H-3a,3b), 2.62 (t, 2 H, $J_{2,3}$ 7 Hz, H-2a,2b), and 1.23 (t, 3 H, *J* 7 Hz, OCH_2CH_3).

Anal. Calc. for $C_{11}H_{12}Cl_2O_2$: C, 53.46; H, 4.90; Cl, 12.95. Found: C, 53.30; H, 5.02; Cl, 12.83.

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