Tetrahedron Vol. 39, No. 5, pp. 805 to 810, 1983
Printed in Great Britain

0040-4020/83/050805-06$03.00/0

THE SYNTHESIS OF 3-DEOXY-DL-STREPTOSE

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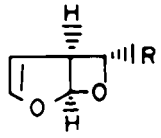
(*Received in UK 20 April 1982*)

Abstract—$KMnO_4$-hydroxylation of 6-methyl-2,7-dioxabicyclo[3.2.0]hept-3-ene (**2**) occurs from the *exo* side and leads—after reorganization of the hemiacetal systems—to 3-deoxy-DL-streptose (isolated as the 1,2-O-isopropylidene derivative **11**). The structure of **11** was proved by conversion to 3,5-dideoxy-1,2-O-isopropylidene-3-C-methyl-β-DL-*arabino*-pentofuranose.

Evidence is presented that a spontaneous epimerization at the formyl group-bearing C atom must occur during hydroxylation of **2**.

Photochemical cycloaddition between furan and aldehydes furnishes with remarkably high regio- and stereoselectivity 6-*exo* substituted derivatives of 2,7-dioxabicyclo [3.2.0]hept-3-ene[1-3] (**1**). Exploring the utility of these highly functionalized compound for the synthesis of natural products[3,4] we became interested in

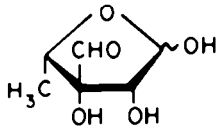


1

R = alkyl, aryl, CO_2R, etc.

elaboration of a simple access to 3-C-formyl-pentose (**7**) system. In fact, hydroxylation of the double bond in **2** would provide a diol (**3**) which after reorganization of the hemiacetal groupings (Scheme 1) should give **7**.

The best known representative of this class of branched-chain sugars is L-streptose (**8**), a component of streptomycin. Although the structure of **8** was deter-



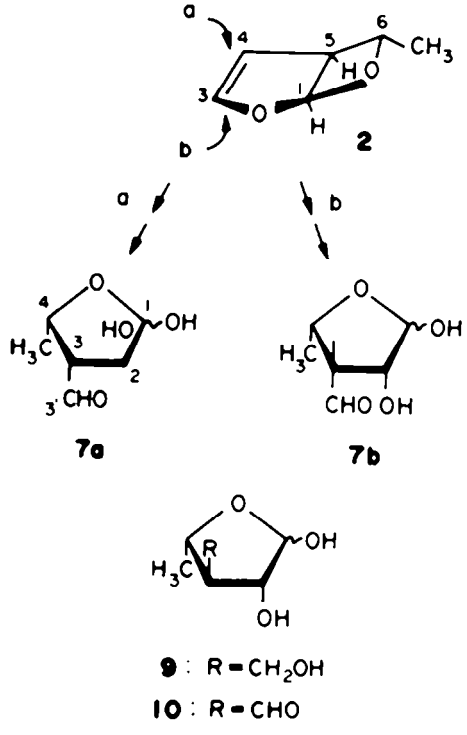
8

mined in 1948,[5] the first successful synthesis of **8** was performed only 17 years later by Dyer.[6] This certainly gives a measure of difficulties connected with the preparation of this little stable monosaccharide. The second systhesis of **8** has been accomplished by Paulsen *et al.*[7] in 1972. Two approaches to similarly branched sugars have been proposed by Tronchet[8] and by (the late) Dyong.[9]

Successful synthesis of **7** would create an access to 3-deoxy-DL-streptose-type compounds.† It is interesting to note that 3-deoxy-dihydro-L-streptose (**9**) is a constituent of dihydrodeoxy-streptomycin, a highly active, chemical modification of the parent antibiotic.[10]

RESULTS AND DISCUSSION

Assuming the attack of the hydroxylating agent on the double bond of **2** from the *endo* side (direction **a**) one would expect the formation of **7** having the 2SR, 3RS, 4SR configuration (**7a**), whereas the attack from the *exo* side (direction **b**) would furnish **7b** with the 2RS, 3RS, 4SR configuration.‡ 3-Deoxy-L-streptose has 2R, 3S, 4S configuration (**10**). Thus, only diastereoisomers of **10** are expected from the hydroxylation of **2**.



2 **7a** **7b**

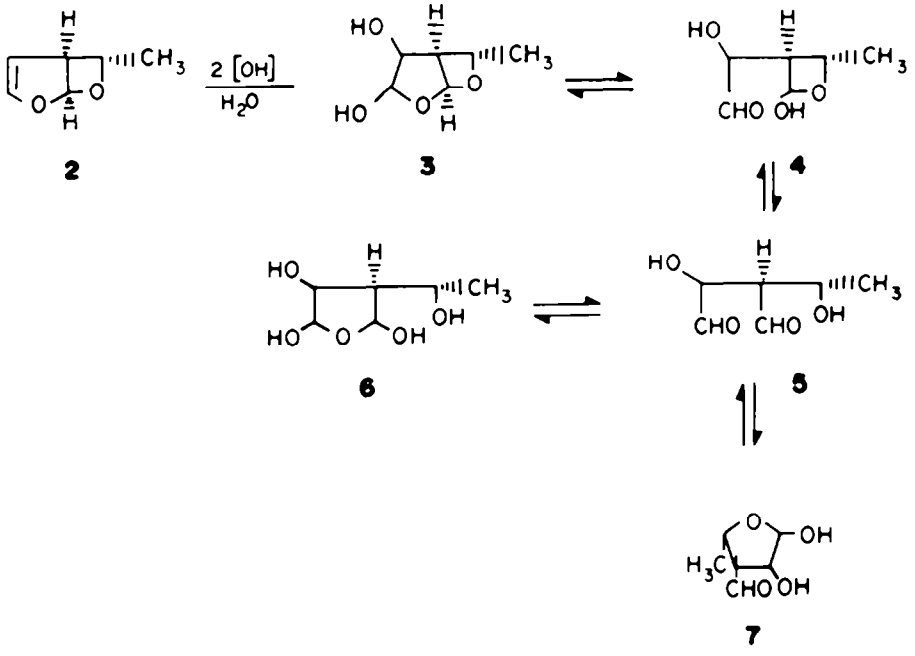
9: R = CH_2OH

10: R = CHO

Hydroxylation of **2** with osmium tetraoxide or with the Milas reagent (6% H_2O_2 in t-BuOH containing catalytic amount of OsO_4) led to a complex mixture of products from which isolation of defined compounds failed. Hydroxylation with $KMnO_4$ in acetone–water solution gave a single-spot (TLC) product. ^1H NMR spectrum

†All compounds obtained during the course of this work were, in fact, racemates. However, in order to facilitate the comparison with L-streptose the formulae drawn in this paper represent only the L forms.

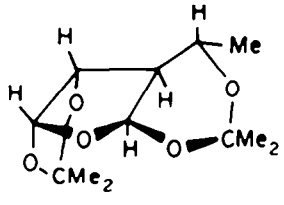
‡Note the change in numbering when passing from 2,7-dioxabicyclo [3.2.0]hept-3-ene system to furanose: carbon atoms Nos. 1, 3, 4, 5 and 6 of the former become Nos. 3', 1, 2, 3 and 4 in the carbohydrate ring.



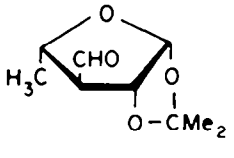
Scheme 1.

(D_2O) of that product revealed the presence of a mixture of compounds; in the anometric proton region, δ 5.2–5.5, at least 5 signals could be discerned. The internal proportion of these signals varied with time. The proton decoupled ^{13}C NMR spectrum displayed 30 lines, again pointing at a mixture of at least 5 compounds being in a state of dynamic equliibrium.

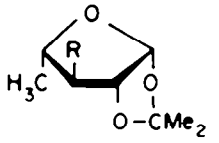
Reaction of the hydroxylation product with acetone in the presence of sulfuric acid led to two isopropylidene derivatives which could be readily separated by column chromatography. The TLC-faster-moving product, formed in *ca* 15% yield, gave a first-order ^1H NMR spectrum which permitted the assignment of structure **11** to it.



11



12

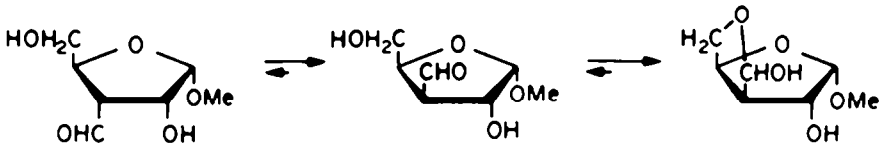


13 : R = CH_2OH
14 : R = CH_2Cl
15 : R = $CH_2\gamma$
16 : R = CH_3

The second product was more abundant (*ca* 33%) and here again a simple ^1H NMR spectrum made possible the direct assignment of structure **12**, i.e. of 3-deoxy-1,2-O-isopropylidene-β-DL-streptose to it. An independent proof of the constitution and configuration was obtained from a sequence of reactions transforming the formyl group in **12** via the hydroxymethyl (**13**), chloromethyl (**14**), iodomethyl (**15**) into 3-C-Me group of **16**. Optically active compound **16** (of the D configuration) was obtained by Tronchet and Graf[11] in an independent manner from 5-deoxy-1,2-O-isopropylidene-β-D-*threo*-furanos-3-ulose. The ^1H NMR data of DL-**16** and of Tronchet and Graf's compound are practically identical.

It is conceivable that both isopropylidene derivatives, **11** and **12**, were formed from the products present in the equilibrium mixture (Scheme 1). Compound **11** was certainly formed by di-isopropylidenation of **6**. The configuration at C-2 of **11** confirms that the attack of the hydroxylating agent occurred from the more readily accessible *exo* side of the bicyclic substrate **2**. The configuration of both remaining chiral centers at C-3 and C-4 is the same as in the substrate, i.e. 3RS,4SR.

The other product **12** stemmed from the same *exo*-face attack of the hydroxylating agent, because the configuration of the secondary alcoholic center at C-2 is the same as in **11**. However, the configuration at C-3 is different from that expected. It must be assumed that a spontaneous epimerization of the formyl group occurred during the reaction. There is a report in literature indicating such a possibility. Williams *et al.*[12] observed that methyl 3-deoxy-3-C-formyl-α-D-*ribo*-furanoside (**17**) epimerized during isolation to the *xylo* stereoisomer (**18**);

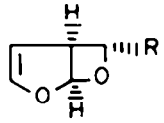


17 18

This product was stabilized due to the formation of an additional hemiacetal ring.

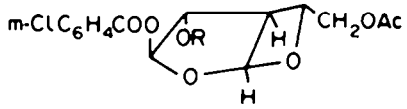
If the formation of a hemiacetal ring stabilizes configuration of the compound, then having a hydroxymethyl and an OH group *cis*-positioned in the primary hydroxylation product, one would expect the retention of the original configuration.

Photochemical cycloaddition between furan and *n*-butyl glyoxylate furnished a bicyclic adduct **19** of the same constitution and configuration as **2**.[3] Careful

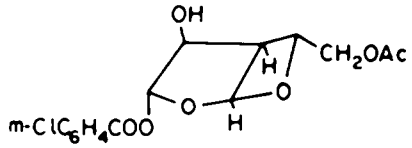


19 : R = CO_2Bu
20 : R = CH_2OH
21 : R = CH_2OAc

reduction of **19** with LAH gave the primary alcohol **20**. For hydroxylation experiment the acetyl derivative **21** was taken. Reaction of **21** with *m*-chloro-peroxybenzoic acid (MCPBA) gave two products, **22** and **24**, formed in 64 and 19% and yields, respectively. A readable ^{1}H NMR spectrum permitted the assignment of structure to **22**. According to expectation the preponderant product stemmed from the *exo* attack of the hydroxylation reagent on **21**. Configuration of the minor product **24** could also be determined from the ^{1}H NMR data as resulting from the *endo* attack.



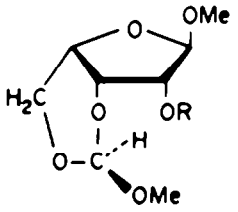
22 : R = H
23 : R = Ac



24

Removal of the ester grouping in **22** with sodium methoxide followed by acidification of the medium *in situ* gave a single di-methoxylated product **25**. Its structure, readily discernible from the ^{1}H NMR spectrum, fully confirmed that after reorganization of the original bicyclic system into a furanose a closure of a second 5-membered hemiacetal ring followed, thus stabilizing the configuration of the primary hydroxylation product.

We regard this result as an evidence confirming that the primary, reorganized product of hydroxylation from the *exo* side of **2** must have the 2RS, 3RS, 4SR configuration. Spontaneous epimerization at C-3 occurs probably at the stage of formation of the furanose ring **7**.



25 : R = H
26 : R = C_6H_5CO

It is obvious that from the synthetic point of view the process of epimerization in that system is very fortunate as it furnishes the desired 3-deoxy-DL-streptose system without any additional operations.

Further modifications of **2** and of its analogs will be described in forthcoming papers.

EXPERIMENTAL

^{1}H NMR spectra were recorded with Jeol JNM-4H-100 spectrometer (δ scale, TMS = 0 ppm). IR spectra were recorded on a UNICAM SP-200 spectrophotometer. Mass spectra were obtained with a LKB 2091 mass spectrometer. For column chromatography silica gel 60 Merck, and for thin layer chromatography silica gel G Merck were employed.

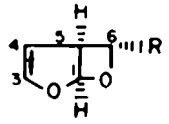
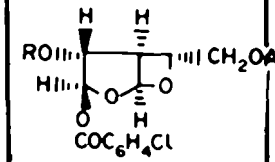
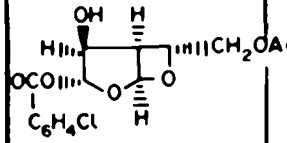
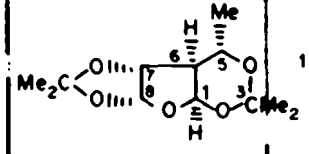
Compound **2** was obtained according to Ref. 1. **19** (^{1}H NMR: Table 1) was prepared by photochemical cycloaddition between furan and butyl glyoxylate.[3] Acetylations were performed with Ac_2O in pyridine soln at ambient temps. The acetyl derivatives were purified by chromatography.

6 - *Hydroxymethyl* - 2, 7 - *dioxabicyclo* [3, 2.0] *hept* - 3 - *ene* (**20**). Ester **19** (9.9 g) was dissolved in oxolane (100 ml) and slowly added to a stirred soln of LAH (3.7 g) in 400 ml anhyd ether. After 2 hr the excess LAH was decomposed with water and 15% NaOHaq. The ether soln was decanted and the ppt was washed with ether. The combined soln was dried ($MgSO_4$) and evaporated to dryness. The residue was distilled at 78–83°/0.2. Colorless liquid, 6.25 g (55%). (Found: C, 56.2; H, 6.6. Calc for $C_6H_8O_3$: C, 56.2; H, 6.3%). IR (film.) 3500, 1610, 1040, 965, 890, 860 cm^{-1}.

6 - *Acetoxymethyl* - 2, 7 - *dioxabicyclo* [3.2.0] *hept* - 3 - *ene* (**21**), dist. at 83–86°/0.2 (air bath). (Found: C, 56.5; H, 6.2. Calc for $C_8H_{10}O_4$: C, 56.4; H, 5.9%). IR (film): 1745, 1605, 1230, 1130, 1045, 960, 892 cm^{-1}. ^{1}HNMR: Table 1.

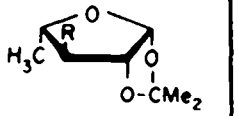
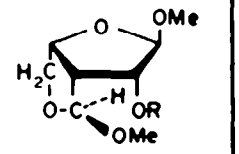
Hydroxylation of **2** *with* $KMnO_4$. To a soln of $KMnO_4$ (3.0 g) in 300 ml water–acetone (1:1) v/v) containing 3.0 g $MgSO_4$ 2.0 g of **2** were added at −10°. After 4 hr the MnO_2 was filtered off and washed with 100 ml water. The aqueous soln was concentrated to dryness under reduced pressure and the residue was purified on a silica gel column with benzene–ether–methanol 6:6:1 v/v/v used for elution. Colorless oil (1.35 g) soluble in H_2O and acetone. ^{1}H NMR spectrum (D_2O) of the product was complex: in the region δ 5.2–5.6 four doublets and a singlet were discernible. The proportion of these signals varied with time. ^{13}C NMR spectrum (D_2O) displayed in the anomeric C atom region (90–105 ppm) four distinct signals of approximately equal intensity at 95.5, 97.7, 98.1 and 101.1 ppm and two minor signals at 96.3 and 103.8 ppm.

Table 1. ^{1}H NMR data of compounds 2, 11, and 19–24 (100 MHz, $CDCl_3$ soln)[a]

	Compd No / R	H-1	H-3	H-4	H-5	H-6		$J_{1,5}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	
	2 / CH_3	6.09	6.45	5.17	3.29	4.50	CH_3:1.42	4.5	2.8	2.8	3.2	J_{6,CH_3} = 8.0
	19 / CO_2Bu	6.34	6.59	5.34	3.69	4.50	OCH_2:4.13 $(CH_2)_2$:1.2–1.8 CH_3 : 1.13	4.2	3.0	3.0	2.9	
	20 / CH_2OH	6.31	6.63	5.31	3.63	4.63	CH_2OH:3.76	4.5	2.8	2.8	3.0	J_{6,CH_2OH} = 3.0
	21 / CH_2OAc	6.05	6.65	5.34	3.57	4.60	CH_2OAc:4.23, 2.08	4.4	3.0	3.0	2.9	J_{6,CH_2OAc} = 4.0
	22 / H	6.12	6.66	4.55	3.31	4.68	CH_2OAc:4.33, 2.10	4.0	0	0	4.0	J_{6,CH_2OAc} = 4.2
	23 / Ac	6.11	6.74	5.43	3.39	4.76		4.0	0	0	4.0	
	24	5.95	6.53	4.45	3.53	5.04	CH_2OAc : 4.33, 2.11	3.6	4.0	8.5	3.6	J_{6,CH_2OAc} = 3.6
		H-1	H-8	H-7	H-6	H-5		$J_{1,6}$	$J_{7,8}$	$J_{6,7}$	$J_{5,6}$	
	11	5.83	5.61	4.28	2.09	3.64	CMe_2:1.33(6H) 1.41 (3H) 1.50 (3H)	4.5	3.9	0	11.1	J_{5,CH_3} = 6.0

Chemical shifts in δ, coupling constants in Hz.

Table 2. ^{1}H NMR data of furanoses 12–16 and 25, 26 (100 MHz, $CDCl_3$ soln)[a]

	compd No / R	H-1	H-2	H-3	H-3'	H-4	H-5	CMe_2	$J_{1,2}$	$J_{2,3}$	$J_{3,3'}$	$J_{3,4}$	$J_{4,5}$	
	12 / CHO	5.72	4.95	2.95	9.62	4.40	1.50	1.35 1.56	4.1	1.9	0	4.7	6.3	
	13 / CH_2OH	5.61	4.53	2.18	3.96	3.96	1.43	1.35 1.58	4.0	1.6	6.2	4.3	6.4	
	14 / CH_2Cl	5.64	4.53	2.38	3.48	4.00	1.45	1.33 1.70	4.0	1.7	6.2	4.3	6.2	
	15 / CH_2J	5.67	4.42	2.30	3.12	3.92	1.43	1.34 1.56	4.0	1.6	5.9	3.6	6.1	
	16 / CH_3	5.74	4.31	2.07	1.06	3.78	1.38	1.38 1.58	4.0	2.1	7.5	4.8	6.2	
	25 / H	5.17	4.14	2.96	4.76	4.51	3.71 3.87	3.04[b] 3.09[b]	0	7.0	0	7.2	4.0 8.2	$J_{5,5'}$ = 10
	26 / Bz	5.10	5.58	3.10	5.02	4.65	3.79 4.12	3.10[b]	0	7.4	0	7.4	4.4 7.4	$J_{5,5'}$ = 10

a. Chemical shifts in δ, coupling constants in Hz.

b. OCH_3.

7, 8 - *O* - *Isopropylidene* - 3, 3, 5*SR*-*trimethyl*-1*RS*, 6*RS* - 2, 4, 9 - *trioxabicyclo*-[4.3.0] *nona*-7*RS*, 8*RS*-*diol* (**11**) *and* 3, 5 - *dideoxy* 3 *C* - *formyl* - 1, 2 *O* - *isopropylidene* - β-DL-arabino-*pentofuranose* (**12**). $KMnO_4$-Hydroxylation product (1.35 g) from the previous experiment was dissolved in anhyd acetone (20 ml) and treated with conc H_2SO_4 (*ca* 0.5 ml). After 12 hr TLC showed the presence of two new products. Neutralization of the soln with Et_3N and evaporation to dryness gave a residue which was separated on a silica gel column with benzene–ether 4:1 v/v.

Product **11** was eluted first (0.293 g, 14.5%, m.p. 55–56°). (Found: C, 59.5; H, 8.8. Calc for $C_{12}H_{20}O_5$: C, 59.0; H, 8.3%). IR (KBr): 1400, 1385, 1275, 1220, 1180, 1050, 995, 880 cm^{-1}. ^{1}H NMR: Table 1.

Product **12** (1.06 g, 69.1%, dist. at 80–90°/0.2). (Found: C, 58.1; H, 7.6. Calc for $C_9H_{14}O_4$: C, 58.1; H, 7.6%). IR (film): 1720, 1686, 1385, 1205, 1160, 1105, 1020, 875 cm^{-1}. MS–EI (70 eV), m/z (%): 186 (M^+), 171 (M^+ – 15.94), 129 (21), 111(21), 43 (100). ^{1}H NMR: Table 2.

3,5-*Dideoxy* - 3 - *C* - *hydroxymethyl* - 1, 2 - *O* - *isopropylidene* - β - DL - arabino-*pentofuranose* (**13**). To a suspension of LAH (0.635 g) in ether (30 ml) a soln of **12** (3.1 g) in 10 ml ether was added dropwise at −5°. After 1 hr the excess of LAH was destroyed by careful addition of water (2 ml) followed by 15% NaOHaq. The ether soln was decanted and the ppt was washed several times with ether. Combined ether extracts were dried and evaporated to dryness. The residue was distilled at 90°/0.2. colorless oil (2.8 g, 89%). (Found: C, 57.0; H, 8.4. Calc for $C_9H_{16}O_4$: C, 57.4; H, 8.6%). IR (film): 3500, 1390, 1210, 1160, 1060, 1020, 880 cm^{-1}. ^{1}H NMR: Table 2.

3 - *C* - *Chloromethyl* - 3, 5 - *dideoxy* - 1, 2 - *O* - *isopropylidene* - β - DL - arabino-*pentofuranose* (**14**). Compound **13** (0.22 g) and triphenylphosphine (0.579 g) were refluxed in 25 ml CCl_4. After 36 hr the soln was filtered and evaporated to dryness. The product was distilled at 70–75°/0.2. Colorless oil (0.257 g, 73%). (Found: C, 52.2; H, 7.4. Calc for $C_9H_{15}ClO_3$: C, 52.3; H, 7.3%). MS–EI (15 eV), m/z (%): 193–191 (M^+–15, 22.5 and 67.1), 135–133 (M^+–58, 2.3 and 8.3), 43 (100). ^{1}H NMR: Table 2.

3, 5 - *Dideoxy* - 3 - *C* - *iodomethyl* - (—) - 1, 2 - *O* - *isopropylidene* - β - DL - arabino-*pentofuranose* (**15**). A soln of **14** (0.18 g) and KI (0.3 g) in 3 ml acetone was sealed in a glass tube and heated at 80°. After 12 hr the tube was opened, the content was diluted with 80 ml ether and filtered. The soln was evaporated and the remaining product was distilled at 85–90°/0.2 (0.24 g, 93%). (Found: C, 36.4; H, 5.2. Calc for $C_9H_{15}IO_3$: C, 36.3; H, 5.1%). IR (film): 1390, 1380, 1210, 1165, 1070, 1020, 870 cm^{-1}. ^{1}H NMR: Table 2.

3, 5 - *Dideoxy* - 1, 2 - *o* - *isopropylidene* - 3 - *C* - *methyl* - β-DL-arabino-*pentofuranose* (**16**). A soln of **15** (0.3 g) in MeOH (100 ml) containing 0.22 g KOH was hydrogenated in a Parr apparatus at 5 atm in the presence of Raney Ni (1 g). After 10 hr the mixture was filtered and the solvent was removed under reduced pressure. The residue was distilled at 80–100° 100, colorless oil (0.16 g, 92%). IR (film) 1460, 1365, 1350, 1250, 1215, 1170, 1136, 1067, 1023, 880 cm^{-1}. MS–EI (15 eV), m/z (%): 157 (M^+–15, 82), 97 (25), 59 (100). ^{1}H NMR chemical shifts and coupling constants of **16** (Table 2) were identical with those described by Tronchet and Graf[11] for D-enantiomer of the compound of identical constitution and configuration.

6*RS*-*Acetoxymethyl* - 3*SR* - (*m*-*chlorobenzoyloxy*) - 4*RS* - *hydroxy*- *and* 6*RS* - *acetoxymethyl* - 3*RS* - (*m*-*chlorobenzoyloxy*) -4*SR* - *hydroxy*- 1*SR*:5*RS* - 2, 7 - *dioxabicyclo* [3.2.0] *heptanes* (**22** and **24**). In a soln of **21** (1.68 g) in CH_2Cl_2 (80 ml) $NaHCO_3$ (4.2 g) was suspended and 1.9 g *m*-chloroperoxybenzoic acid in 20 ml CH_2Cl_2 was gradually added at 0°. After 6 hr the mixture was filtered and the filtrate was evaporated to dryness. The mixture of **22** and **24** was separated on a silica gel column with benzene ether 1:1 v/v.

Product **24**, 0.033 g ^{1}H NMR: Table 1.

Product **22** (2.79 g, 63%). IR (film): 3520, 1740, 1580, 1435, 1380, 1250, 1090, 980, 925, 745 cm^{-1}. ^{1}H NMR: Table 1. Monoacetyl derivative **23**. (Found: C, 52.7; H, 4.6. Calc for $C_{17}H_{17}ClO_8$: C, 53.1; H, 4.5%). IR ($CHCl_3$): 1738, 1575, 1370, 1235, 1050, 982 cm^{-1}. ^{1}H NMR: Table 1.

3 *RS*: 6 *SR*-*Dimethoxy*-4 *RS*-*hydroxy* - 1 *RS*: 5 *SR* - 2, 7 - *dioxabicyclo* [3.3.0] *octane* (**25**). Compound **22** (0.34 g) was deesterified at room temp. with 2% NaOMe in MeOH (5 ml). After completion of the reaction (tlc) *ca* 2 g of IR120 (H-form) resin was added. After 24 hr the resin was filtered off and washed with MeOH. Combined methanolic solns were evaporated to dryness. The residue was purified on a silica gel column (eluent: benzene–ether 4:1 v/v). Colorless crystals (0.12 g, 63%, m.p. 93–94°). (Found: C, 50.0; H, 7.6. Calc for $C_8H_{14}O_5$: C, 50.5; H, 7.4%). IR (KBr): 3550, 1370, 1280, 1207, 1195, 1105, 1030, 920, 745 cm^{-1}. ^{1}H NMR: Table 2.

Benzoate **26**, colorless oil. (Found: C, 61.7; H, 6.9. Calc. for $C_{15}H_{18}O_6$: C, 61.2; H, 6.1%). IR (film): 1730, 1607, 1370, 1275, 1110, 1045, 985, 710 cm^{-1}. ^{1}H NMR: Table 2.

Acknowledgement—This investigation was financed by the grant No. MR-I.12.1.7.4.

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