

Chiral Synthons for the Total Synthesis of Macrolide Antibiotics

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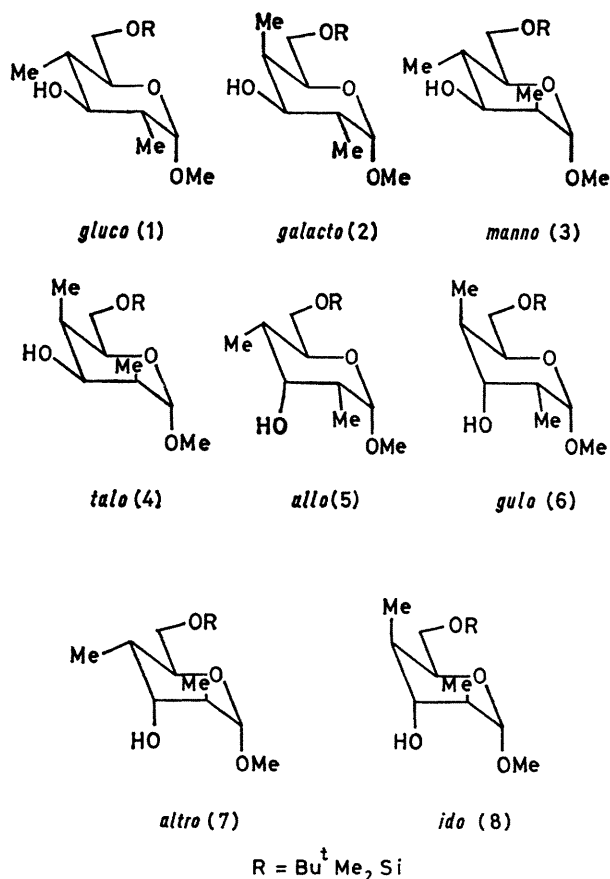
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Summary All the methyl 2,4-dideoxy-2,4-di-*C*-methyl-6-*O*-dimethyl-*t*-butylsilyl- α -D-hexopyranosides, chiral intermediates in the total synthesis of many biologically important natural products have been prepared.

THE elaboration of the chiral, polyfunctional framework of the aglycones of macrolide antibiotics presents a formidable challenge to the synthetic chemist.¹ Considerable effort has been recently directed towards the chiral synthesis of these medically important compounds.²

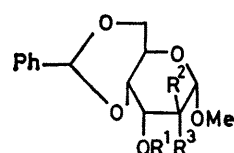
The partial structural unit $R^1\text{-CH(Me)-CH(OR}^3\text{)-CH(Me)-CH(OR}^3\text{)-R}^4$ is present in many biogenetically propionate derived macrolides,¹ ansamycin³ and polyether antibiotics.⁴ The four asymmetric centres of this unit give rise to sixteen possible diastereoisomers. We have been interested in developing methods for the chiral synthesis of these units and report here the preparation of eight of the diastereoisomers, compounds (1) to (8). Recently, stereo- and regio-selective methods were reported by Kishi for the preparation from an acyclic precursor of the four diastereoisomers corresponding to the partial structural unit $R\text{-CH(Me)-CH(OH)-CH(Me)-R}'$.⁵



Benzylation of (9)⁶ in the presence of sodium hydride afforded (10) (m.p. 106 °C, $[\alpha]_D + 37^\circ$)[†] in 85% yield. The benzylidene acetal group of (10) was cleaved with a 1% ethanolic HCl solution and the resulting product (11) was transformed into the silyl ether (12) (syrup, $[\alpha]_D + 80^\circ$) in 92% overall yield.⁷ Oxidation of (12) with pyridinium chlorochromate in benzene⁸ gave (13) (syrup, $[\alpha]_D + 74^\circ$) (yield 80%). Treatment of (13) with methylene triphenylphosphorane (ether, 22 °C) furnished the olefinic derivative (14) (yield 50%) (syrup, $[\alpha]_D + 48^\circ$). Catalytic hydrogenation of (14) overnight (10% Pd-C, H₂, EtAc) gave a mixture of (8)[‡] (syrup, $[\alpha]_D + 58^\circ$) (75%) and (7) (syrup, $[\alpha]_D + 85^\circ$) (25%) which could be separated easily by chromatography [hexane:ether = 1:1; (8) R_f 0.33; (7) R_f 0.56].

An identical reaction sequence from (15)^{6b} gave in four steps the unstable (16) in 70% overall yield. A Wittig reaction transformed (16) into (17) (yield 50%) (syrup, $[\alpha]_D + 59^\circ$) and the latter was hydrogenated catalytically (10% Pd-C, H₂, EtAc) for a short time affording a mixture of the 3-*O*-benzyl derivatives of (5) (50%) and (6) (50%)

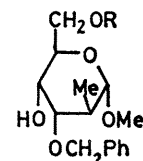
which were separated [hexane:EtAc = 13:1; 3-*O*-benzyl (5) R_f 0.35; 3-*O*-benzyl (6) R_f 0.30]. Removal of the benzyl group (10% Pd-C, H₂, EtAc) of each isomer led to (5) (syrup, $[\alpha]_D + 91^\circ$) and (6) (syrup, $[\alpha]_D + 71^\circ$) in quantitative yield.[§]



(9) $R^1 = R^3 = \text{H}; R^2 = \text{Me}$

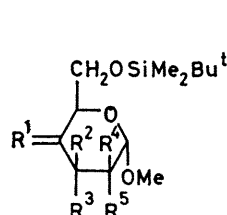
(10) $R^1 = \text{PhCH}_2; R^2 = \text{Me}; R^3 = \text{H}$

(15) $R^1 = R^2 = \text{H}; R^3 = \text{Me}$



(11) $R = \text{H}$

(12) $R = \text{Bu}^t \text{Me}_2 \text{Si}$



(13) $R^1 = \text{O}; R^2 = R^5 = \text{H}; R^3 = \text{OCH}_2 \text{Ph}; R^4 = \text{Me}$

(14) $R^1 = \text{CH}_2; R^2 = R^5 = \text{H}; R^3 = \text{OCH}_2 \text{Ph}; R^4 = \text{Me}$

(16) $R^1 = \text{O}; R^2 = R^4 = \text{H}; R^3 = \text{OCH}_2 \text{Ph}; R^5 = \text{Me}$

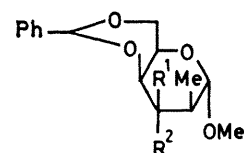
(17) $R^1 = \text{CH}_2; R^2 = R^4 = \text{H}; R^3 = \text{OCH}_2 \text{Ph}; R^5 = \text{Me}$

(18) $R^1 = \text{O}; R^2 = \text{OCH}_2 \text{Ph}; R^3 = R^4 = \text{H}; R^5 = \text{Me}$

(19) $R^1 = \text{CH}_2; R^2 = \text{OCH}_2 \text{Ph}; R^3 = R^4 = \text{H}; R^5 = \text{Me}$

(23) $R^1 = \text{O}; R^2 = \text{OCH}_2 \text{Ph}; R^3 = R^5 = \text{H}; R^4 = \text{Me}$

(24) $R^1 = \text{CH}_2; R^2 = \text{OCH}_2 \text{Ph}; R^3 = R^5 = \text{H}; R^4 = \text{Me}$



(20) $R^1 = \text{H}; R^2 = \text{OH}$

(21) $R^1 R^2 = \text{O}$

(22) $R^1 = \text{OH}; R^2 = \text{H}$

Upon treatment of (16) with a solution of sodium methoxide in methanol epimerisation took place^{6b} at C-3 to give the unstable (18) (yield 70%). The Wittig reaction on (18) led to (19) (syrup, $[\alpha]_D + 91^\circ$) (yield 50%) and catalytic hydrogenation overnight (10% Pd-C, H₂, EtAc) afforded a mixture of 65% of (2) and 35% of (1) which were separated in the form of their 3-acetates [hexane:EtAc = 13:1; 3-acetate of (1) R_f 0.55; 3-acetate of (2) R_f 0.62]. Deacetylation furnished (1) (syrup, $[\alpha]_D + 85^\circ$) and the very important methyl 2,4-dideoxy-2,4-di-*C*-methyl-6-*O*-dimethyl-*t*-butylsilyl- α -D-galactopyranoside (2) (syrup, $[\alpha]_D + 114^\circ$), which encompasses four asymmetric centres (C-10, C-11, C-12, and C-13) of the aglycones of the 14-membered macrolide

[†] $[\alpha]_D$ values were measured in CHCl₃ solution at room temperature ($c = 1$).

[‡] This compound has recently been prepared by a stereospecific method in connection with the synthesis of (–)- α -multistriatin (ref. 9).

[§] Chromatographic separation of (5) and (6) was unsuccessful.

TABLE^a

	<i>gluco</i> (1)	<i>galacto</i> (2)	<i>manno</i> (3)	<i>talo</i> (4)	<i>allo</i> (5)	<i>gulo</i> (6)	<i>altro</i> (7)	<i>ido</i> (8)
C-1	102.1	102.1	103.7	102.4	102.8	102.7	103.4	103.5
C-2	42.2	36.4 ^b	38.6	37.0	38.4	32.5	38.6	37.6
C-3	74.0	71.0 ^c	71.8	70.7	73.7	75.1	74.2	75.6
C-4	39.3	35.9 ^b	33.6	40.9	36.5	36.8	30.0	40.3
C-5	74.6	71.9 ^c	74.7	75.2	69.8	66.0	69.5	69.3
C-6	64.1	63.6	64.3	64.3	64.2	64.1	64.1	64.0
C-2Me	12.7	12.5	10.6	12.9 ^b	12.9	12.8	14.8	15.1
C-4Me	12.7	4.8	13.3	12.0 ^b	13.9	10.6	13.7	12.5
OMe	54.5	54.7	54.7	56.0	55.1	55.1	54.8	55.2

^a ¹³C N.m.r. chemical shifts (p.p.m.) in CDC₃ solution (Me₄Si=0); Bu^tMe₂Si carbon signals appear for all compounds at 3 × 25.8) ± 0.1, (1 × 18.3) ± 0.1, and (2 × -5.5) ± 0.1. ^{b,c} Assignments can be interchanged.

antibiotics erythromycin B, oleandomycin, and lankamycin¹ with the correct relative and absolute stereochemistry.

Base catalysed epimerisation at C-3 in the case of (13) was not successful. Thus the preparation of the 'manno' and 'talo' derivatives (3) and (4) was attempted from (20).⁹ Oxidation of (20) with dimethyl sulphoxide-acetic anhydride gave the crystalline (21) (m.p. 140°C; [α]_D + 74°) in over 95% yield. Reduction of the carbonyl group of (21) (NaBH₄, MeOH, dimethylformamide) afforded a mixture containing an unexpectedly high proportion (75%) of the desired (22) (m.p. 123 °C [α]_D + 88°) and 25% of (20) which were separated [hexane:EtAc = 6:4; (20) *R*_f 0.6; (22) *R*_f 0.52]. The reaction sequence described above furnished (24) (syrup, [α]_D + 82°) via the unstable (23) in 60% overall yield. Catalytic hydrogenation of (24) (10% Pd-C₂H₅, EtAc) overnight gave a mixture of (3) (syrup, [α]_D + 55°) (17%), the very important methyl 2,4-dideoxy-2,4-di-C-methyl-6-O-dimethyl-t-butylsilyl-α-D-talopyranoside (4) (syrup, [α]_D + 71°) (58%) and a less polar product of

unknown constitution (25%) which were separated [dichloromethane:methanol = 40:1; (3) *R*_f 0.54; (4) *R*_f 0.61]. Compound (4) comprises four asymmetric centres (C-22, C-23, C-24, and C-25) of the chain of the rifamycin antibiotics³ with the correct relative and absolute stereochemistry.

Unambiguous structural differentiation between the various isomers is based on ¹H and mainly ¹³C n.m.r. spectroscopic evidence. Chemical shifts for compounds from (1) to (8) are given in the Table.

The method described here is particularly advantageous when a convergent synthetic scheme requires both epimers at C-4.

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