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STEREOSELECTIVE SYNTHESIS OF METHYL β-DL-NOVIOSIDE

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Abstract—Stereoselective synthesis of an antibiotic sugar, methyl β-DL-novioside from 2-(2-furyl)propan-2-ol is described. The key step involved transformation of 2,5-dimethoxy-2,5-dihydrofuran derivative into 2,3-unsaturated pyranos-4-ulose. Its glycosidation followed by reduction, methylation and hydroxylation afforded β-DL-novioside.

It has been demonstrated that anomeric configuration of methyl noviosides and novobiocin are opposite to that reported in the literature.

In the course of acidic degradation of the antibiotic novobiocin[1] a sugar component was isolated as an anomeric mixture of methyl or ethyl glycosides.[2]

The structure of this monosaccharide, which was named noviose, was established as 4-O-methyl-5,5-dimethyl-L-lyxose.[3] The L-lyxo configuration followed from the degradation of the noviose to the (−)α,β-dihydroisovaleric acid and has been confirmed by the synthesis of 2,3-isopropylidene-5-O-methylnovionic acid from L-rhamnose.[4]

Assignment of the anomers' configuration was based on the rules of isorotation. Methyl novioside with positive rotation ($[\alpha]_D^{27}+106°$) was recognized as β-L-lyxo, whereas that with negative ($[\alpha]_D^{25}-45°$) as α-L-lyxo anomer.[5] Later Vaterlaus *et al.*[6] have obtained noviose and subsequently methyl-3-O-carbamoyl-α-L-novioside in multi-stage synthesis from D-glucose.

In the present paper we describe an efficient stereoselective synthesis of racemic methyl β-novioside from a non-sugar precursor. Moreover, result of the synthesis reverses an earlier assignment[5] of the anomeric configuration of methyl noviosides.

RESULTS AND DISCUSSION

Synthesis of methyl β-novioside was based on the previously developed general method of the total synthesis of monosaccharides from substituted furfuryl alcohols.[7] Accordingly, 2-(2-furyl)propan-2-ol (**2**), readily available from Grignard reaction of 2-acetylfuran (**1**) with methyl magnesium bromide, was treated with bromine in methanol to yield 2,5-dimethoxy-2,5-dihydro derivative **3**, as a mixture of *cis* and *trans* isomers (Scheme 1). These were hydrolyzed, without separation, to give ulose **4**, which in turn was converted into methyl glycoside **5** by treatment with methyl orthoformate in the presence of boron trifluoride. Compounds **4** and **5** had analytical and spectral data consistent with their structures. Both showed UV absorption and IR bands characteristic of α,β-unsaturated ketone and MS fragmentation those of 2,3-unsaturated-4-keto sugars[8] (Experimental); in ^{1}H NMR spectra, besides signals corresponding to two Me groups and hydroxy (**4**) or methoxy (**5**) group, there appeared an ABX system with chemical shifts and coupling constants (Table 1) typical for 2,3-unsaturated 4-ulose or 4-uloside.[7]

LAH reduction of uloside **5** gave two carbinols **6** and **9** in the ratio 9:1. Their structure followed from analytical data and configurations were deduced from the values of the methine protons coupling constants. Studies on the 2,3-unsaturated sugars indicate that the conformation of the pyranoid ring is essentially half-chair.[9] In compounds of this type vicinal (J_{12}, J_{34}) and allylic (J_{13}, J_{24}) coupling constants are related to the dihedral angle[10] in a manner described by Garbisch[11] equation and pseudoequatorial or pseudoaxial position of H-1 and H-4 protons could be inferred from their ^{1}H NMR data. These coupling constants (Table 1) indicate that in the main reduction product of uloside **5** both hydrogens H-1 and H-4 are in

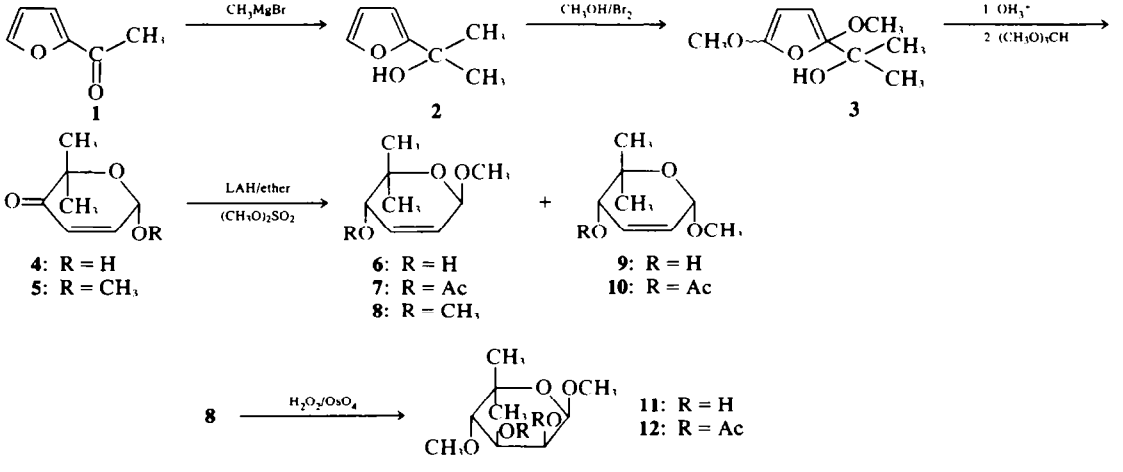
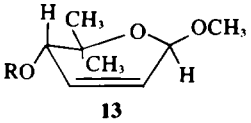


Table 1. 100 MHz ^{1}H NMR data for compounds **4–12**. (a) Could not be obtained from the spectrum. (b) DSS was used as internal standard.

Compound	^{13}C chemical shifts[a] (ppm, TMS=0)								
	C-1	C-2[b]	C-3[b]	C-4	C-5	1-OCH_3	4-OCH_3	eq.-CH_3	ax.-CH_3
Dextro methyl novioside	97.10	70.88	69.15	84.04	71.10	55.78	61.22	28.54	18.66
Laevo methyl novioside	102.33	68.02	71.53	84.04	76.81	54.70	61.12	28.86	22.66
α-Noviose[c]	89.97	71.31	68.67	84.69	72.61	-	61.49	28.21	18.45
β-Noviose[c]	94.18	72.28	74.17	84.15	76.38	-	61.79	28.80	24.92

pseudoaxial position. Consequently carbinol **6** has β-configuration and exists predominantly in $^0H_5$ conformation **13**. Similarly, coupling constants of the LAH reduction minor product acetate **10** show that it has α-configuration and appears in $^5H_0$ conformation **14**.



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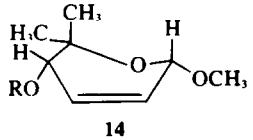

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Compound **6** treated with dimethyl sulphate in the presence of sodium hydroxide in DMF gave methyl ether **8**. Subsequent cis-hydroxylation with Milas' reagent afforded only one diol **11**, which was fully characterized as its diacetate **12**. Since stereoselectivity of hydroxylation of the double bond with Milas' reagent depends on steric hindrance, attack from the side opposite to the axial C_5–Me group should prevail and the formation of β-lyxo compound could be expected. In fact, coupling constant $J_{34} = 10.2$ Hz measured for diacetate **12** revealed axial–axial relation of H-3 and H-4 protons, which proved its β-lyxo configuration. Thus compound **11** is methyl β-DL-novioside.

Synthetic methyl β-DL-novioside (**11**) and its diacetate **12** were compared directly (TLC, GLC, ^{1}H NMR) with both methyl noviosides and their diacetates of natural origin. Surprisingly the identity of relative configurations of synthetic compound **11** and laevorotatory methyl novioside, which have been previously assigned[5] α-configuration, was discovered.

Since the structure of the racemic novioside has been unambigously established by the course of the synthesis, change in anomeric configuration assignment, reported[5] for methyl noviosides, had to be taken into account. It was demonstrated that of the two anomers β-noviose and β-novioside should be thermodynamically more stable,[12] because of 1,3-diaxial interaction present in $^1C_4$† conformation of α-anomer. When both methyl noviosides were taken separately and subjected to equilibration in acidic aqueous methanol the mixture comprising 1 part of dextro- and 2 parts of laevorotatory anomer (GLC of trimethylsilyl ethers) was obtained. Hence laevorotatory anomer should have β-configuration contrary to the earlier assignment.[5] The same conclusion can be drawn from the ^{13}C NMR spectra of methyl noviosides (Table 2).

†The values of J_{34} coupling constant indicate the prevalence of the $^1C_4$ conformation in both anomers of noviose or methyl novioside.[12,13]

Table 2. ^{13}C NMR spectra of noviose and methyl novioside anomers. (a) Mixture of $CDCl_3$ and $(CD_3)SO$ was used as a solvent. (b) Assignment of C-2 and C-3 signals is tentative. (c) Data for α- and β-noviose are taken from the spectrum of the equilibrium mixture of anomers.

Compound	Solvent	Chemical shifts δ (ppm, TMS=0)								Coupling constants (Hz)					
		H-1	H-2	H-3	H-4	Me	Me	OMe (4-OMe)	Ac	J_{12}	J_{13}	J_{14}	J_{23}	J_{24}	J_{34}
4	$CDCl_3$	5.80	6.99	6.16	-	1.53	1.44	-	-	2.3	1.3	-	10.5	-	-
5	$CDCl_3$	5.24	6.92	6.12	-	1.52	1.41	3.57	-	3.0	1.2	-	10.4	-	-
	C_6D_6	4.84	6.43	5.90	-	1.44	1.34	3.27	-	3.0	1.2	-	10.4	-	-
6	$CDCl_3$	4.87	5.72	5.89	3.88	1.40	1.39	3.46	-	1.5	1.2	2.0	10.3	1.8	2.5
7	C_6D_6	4.77	5.78		5.26	1.77	1.40	3.38	1.77	a	a	a	a	a	a
8	C_6D_6	4.79	4.95	5.04	3.44	1.35	1.29	3.44 (3.16)	-	a	a	a	10.5	a	a
9	$CDCl_3$	4.94	5.85	6.12	3.63	1.27		3.41	-	2.2	1.3	0	10.0	0	4.2
10	$CDCl_3$	5.05	6.07		5.02	1.36	1.28	3.50	2.12	a	a	a	a	a	a
11	D_2O[b]	4.67	3.86	3.95	3.37	1.38	1.30	3.61 (3.47)	-	2.2	-	-	3.4	-	9.0
12	$CDCl_3$	4.67	5.31	5.43	3.44	1.49		3.58 (3.47)	2.18 2.09	1.8	-	-	3.4	-	10.2

The C-5† signal in dextrorotatory anomer is shifted upfield (Table 2) relatively to the corresponding signal in laevorotatory anomer, indicating β-configuration of the latter.[14] Also ^{13}C chemical shifts of the C-5 Me groups are consistent with the above assignment.

The foregoing results demonstrate that dextrorotatory methyl novioside has α- and laevorotatory anomer β-configuration. The configuration of the glycoside link in novobiocin was deduced, on the basis of Hudson's rules of isorotation, from molecular rotations of methyl noviosides.[5] Since the configuration of the anomers ought to be reversed this also applied to the glycoside center in the antibiotic itself, e.g. the glycoside link of novobiocin has β-L-configuration.

EXPERIMENTAL

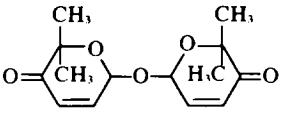
M.ps and b.ps are uncorrected. Optical rotations were measured with a Perkin–Elmer Model 141 automatic polarimeter. IR spectra were recorded on a Unicam SP-200 Spectrophotometer (films or KBr discs). NMR spectra were recorded on a JEOL JMN-4H-100 at 100 MHz for protons and Bruker F.T., 22.63 MHz for ^{13}C. Mass spectra were obtained with LKB-9002 spectrometer (70 eV). GLC was carried on W.Giede 18.3 gas chromatograph equipped with flame ionization detector and 3 m Reoplex column. Silica gel G (Merck) was used for TLC.

Acetylations were carried out with Ac_2O–pyridine 1:1 mixture at room temp followed by usual work up. Trimethylsilyl ethers were obtained according to standard procedure.[17] 2-(2-Furyl)propan-2-ol **2** was prepared according to literature.[18]

2-[2-(2,5-*Dimethoxy*-2,5-*dihydrofuryl*)]*propan*-2-*ol* **3**. To the soln of **2** (1.26 g, 10 mmol) in a mixture of anhyd ether (20 ml) and abs MeOH (60 ml) stirred at −35° Br_2 (1.92 g, 12 mmol) in 10 ml MeOH was added dropwisely. Then mixture was neutralized with gaseous NH_3, allowed to warm up and evaporated. Benzene was added to the residue, NH_4Br filtered off, the filtrate washed with water and dried with $MgSO_4$. Evaporation of the solvent afforded **3** (1.86 g, 97%) b.p. 57–64°/1.3 torr; IR 3500 (OH), 1630 (C=C), 1100, 1030 cm^{-1} (C–O); ^1H NMR (δ) 1.19, 1.28 (CH_3), 2.25 (OH), 3.19, 3.26, 3.60 (OMe_3), 5.54 (H-5 *cis*), 5.81 (H-5 *trans*), 6.40 (CH=CH); mass *m/e* (% of the base peak) 187 (1) M-1, 157 (9), 141 (7), 129 (100), 125 (7), 115 (22), 101 (29), 99 (35), 98 (53), 83 (29), 71 (16), 59 (42), 55 (10), 43 (36).‡ (Found: C, 57.2; H, 8.6. Calc. for $C_9H_{16}O_4$: C, 57.4; H, 8.6%).

5-C-*Methyl*-2,3,6-*trideoxyhex*-2-*eno*-DL-*pyranos*-4-*ulose* **4**. Carbinol **3** (1.69 g, 9 mmol) was dissolved in 1% H_2SO_4 aq (10 ml) and left for 2 hr at room temp. The mixture was then adjusted to pH 5 with solid $NaHCO_3$ and water evaporated under vacuum below 30°. The residue was triturated with ether, ether soln filtered and dried with $MgSO_4$. Removal of the solvent left **4** (1.39 g, 98%) b.p. 100°/0.5 torr; UV 207 nm (7200); IR 3430 (OH), 1690 (α,β-unsaturated ketone), 1630 (C=C), 1100 cm^{-1} (C–O); mass *m/e* (% of the base peak) 142 (1) M$^+$, 125 (3), 97 (7), 84 (100), 69 (3), 59 (22), 55 (44), 43 (21).§ (Found: C, 59.3; H, 7.3. Calc. for $C_7H_{10}O_3$: C, 59.1; H, 7.1%).

Methyl 5-C-*methyl*-2,3,6-*trideoxyhex*-2-*eno*-DL-*pyranosid*-4-*ulose* **5**. To the soln of **4** (1.14 g, 8 mmol) in abs ether (50 ml) methyl orthoformate (1 g) was added at 0–5° followed by BF_3Et_2O (0.2 ml) and the soln was left at room temp. When the reaction was completed (TLC) the mixture was washed quickly with ice-water, dried with $MgSO_4$ and the solvent evaporated. Column chromatography of the crude product (petr. ether–EtOAc 4:1) yielded at first small quantity of diuloside **15** m.p. 104°, IR 1690 (α,β-unsaturated ketone), 1650 (C=C), 1100 cm^{-1} (C–O); mass *m/e* (% of the base peak) 208 (1) M$^+$, 183 (1), 149 (1), 125 (96), 97 (100), 81 (15), 79 (16), 69 (14), 55 (24), 43 (42). (Found: C, 63.1; H, 7.0.



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Calc. for $C_{14}H_{18}O_4$: C, 63.1; H, 6.8%). Further elution with the same solvent gave **5** (1.10 g, 70%) b.p. 48–50°/1.3 torr; UV 204 (6950), 208 (6300), 214 nm (5400); IR 1690 (α,β-unsaturated ketone), 1640 (C=C), 1100, 1050 cm^{-1} (C–O); mass *m/e* (% of base peak) 156 (1) M$^+$, 125 (16), 113 (3), 98 (100), 83 (33), 70 (33), 55 (18), 49 (20), 43 (40). (Found: C, 61.5; H, 8.0. Calc. for $C_8H_{12}O_3$: C, 61.5; H, 7.8%).

Methyl 5-C-*methyl*-2,3,6-*trideoxyhex*-2-*eno*-DL-*pyranosides* β-(**6**) *and* α-(**9**). To a stirred soln of **5** (1.0 g, 6.4 mmol) in abs ether (60 ml) LAH was added (0.2 g). The mixture was worked up as usual to give residue which was chromatographed on a silica gel column. Elution with petr. ether–EtOAc 4:1 gave **6** (0.90 g, 88%) b.p. 75°/1 torr; IR 3400 (OH), 1640 (C=C), 1060 cm^{-1} (C–O). (Found: C, 60.3; H, 8.9. Calc. for $C_8H_{14}O_3$: C, 60.7; H, 8.9%) and subsequently **9** (0.10 g, 9%) b.p. 75°/1 torr; IR 3400 (OH), 1640 (C=C), 1060 cm^{-1} (C–O). (Found: C, 60.9; H, 9.1. Calc. for $C_8H_{14}O_3$: C, 60.7; H, 8.9%).

Methyl 4-O-*acetyl*-5-C-*methyl*-2,3,6-*trideoxyhex*-2-*eno*-β-DL-*pyranoside* **7**, b.p. 75°/1.3 torr; IR 1740, 1240 (OAc), 1080, 1050 cm^{-1} (C–O). (Found: C, 59·9; H, 8.1. Calc. for $C_{10}H_{16}O_4$: C, 60.0; H, 8.1%).

Methyl 4-O-*methyl*-5-C-*methyl*-2,3,6-*trideoxyhex*-2-*eno*-β-DL-*pyranoside* **8**. Alcohol **6** (0.79 g, 5 mmol) was dissolved in DMSO (10 ml) under N_2, finely powdered NaOH (0.3 g) and Me_2SO_4 (0.8 g) was added, the mixture stirred for 2 hr at room temp, poured into water and the soln extracted with ether. The organic layer was dried and evaporated yielding **8** (0.75 g, 86%) b.p. 55°/0.8 torr; IR 1660 (C=C), 1100, 1070, 1040 cm^{-1} (C–O). (Found: C, 62.5; H, 9.4. Calc. for $C_9H_{16}O_3$: C, 62.8; H, 9.4%).

β-DL-*Novioside* **11**. Ether **8** (0.62 g, 3.6 mmol) was dissolved in 6% H_2O_2 soln in t-BuOH (10 ml) and osmium tetroxide (10 mg) was added. After 2 days solvents were removed under reduced pressure and the remaining syrup was chromatographed on silica gel column. Elution with benzene–ether 1:1 mixture gave **11** (0.38 g, 51%) as colorless crystals m.p. 98.5–100° (from ether); IR 3450 (OH), 1130, 1070, 1050 cm^{-1} (C–O). (Found: C, 52.5; H, 8.8. Calc. for $C_9H_{15}O_5$: C, 52.4; H, 8.8%).

Methyl 2,3-*di*-O-*acetyl*-β-DL-*novioside* **12**, m.p. 68–70° (from petroleum ether); IR 1740, 1240 (OAc), 1100, 1050 cm^{-1} (C–O). (Found: C, 53.7; H, 7.7. Calc. for $C_{13}H_{22}O_7$: C, 53.8; H, 7.6%).

Methyl (+)-*novioside*. To the soln of methyl 3-O-carbamoyl novioside m.p. 118°, $[\alpha]_D^{19}$ + 126.5° (*c* 1.0, EtOH); (0.05 g) in water (5 ml) $Ba(OH)_2$ (0.2 g) was added and the mixture stirred at room temp overnight. Stream of CO_2 was then passed through the soln to precipitate $BaCO_3$. Mixture was filtered, filtrate evaporated, triturated with EtOH and filtered again. Residue after evaporation of the solvent (0.033 g, 82%) had $[\alpha]_D^{22}$ +92.8° (*c* 1.0, EtOH) (lit.[5]) $[\alpha]_D^{27}$ +106° (*c* 0.7, water)).

Methyl 2,3-*di*-O-*acetyl novioside obtained from dextrorotatory novioside*, ^1H NMR (δ): 5.52 (H-2), 5.11 (H-3), 4.72 (H-1), 3.40 (H-4), 3.60, 3.57 (2 × OMe), 2.23, 2.10 (2 × OAc), 1.45, 1.29 (2 × CH_3); J_{12} = 1.5, J_{23} = 3.4, J_{34} = 10.5 Hz.

Methyl (−)-*novioside*. Noviose (0.2 g) m.p. 133–4°, $[\alpha]_D^{22}$ +22° (*c* 1.0, 50% EtOH) was dissolved in 3% methanolic HCl (5 ml) and kept overnight at room temp. The solvent was evaporated under reduced pressure and the residue applied on a silica gel column. Elution with EtOAc afforded glycoside m.p. 69–70°, $[\alpha]_D^{22}$ −66.8° (*c* 1.0, EtOH) in about 60% yield. Further elution gave dextrorotatory glycoside (about 30%) identical with that described in the previous experiment.

Methyl 2,3-di-O-acetyl novioside obtained from laevorotatory glycoside had ^1H NMR spectrum identical with that of racemic diacetate **12**.

†For the pyranosides in which Reeves effect[15] is possible, assignment of the anomeric configuration based on the C-1 chemical shifts difference may prove misleading.[16] In our case however, the rule of an upfield shift of axialy substituted anomeric carbon is valid, in spite of dipoles interaction[16] present in β-novioside, presumably because of strong crowding effect of axial C-5 Me group.

‡For *m/e* assignment cf. ref. 19.

§For *m/e* assignment cf. ref. 7.

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