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Synthesis of Methyl-branched 2,3,4,5-Tetrahydroxycyclohexanone Derivatives via 6-Deoxyhex-5-enopyranosides

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Seven novel methyl-branched 2,3,4,5-tetrahydroxycyclohexanone derivatives were prepared in good yields by Ferrier reaction via corresponding key intermediates: 6-deoxyhex-5-enopyranosides.

C-Methylcyclitols such as laminitol and mitilitol are characteristic components of various algaes[1] and, in general, can be prepared by introduction of methyl-branch into the corresponding cyclitol. However, this method has difficulties in availability of required starting cyclitols, selective protection of the desired hydroxyl group, and stereoselective introduction of methyl-branch. In order to overcome these difficulties, we examined preparation of methyl-branched cyclitol derivatives using Ferrier's method.[2] This communication describes a convenient synthesis of protected novel methyl-branched 2,3,4,5-tetrahydroxycyclohexanone derivatives (**9-12**, **17**, **18**, and **21**) from the corresponding branched-chain 6-deoxyhex-5-enopyranosides (**5-8**, **15**, **16**, and **20**). Key intermediates (**5-8**, **15**, **16**, and **20**)[3] were newly prepared in one-pot procedure from corresponding 6-bromo-6-deoxy- (**1-4**, **13**, and **14**)[4] or 6-p-tolylsulfonylhexopyranoside **19**[4] by successive treatment with iodide anion and 1,8-diazabicyclo(5,4,0)undec-7-ene (DBU) in dimethyl sulfoxide (DMSO) at 80-120 °C.[5] The favorable procedure for this elimination reaction were as follows: A

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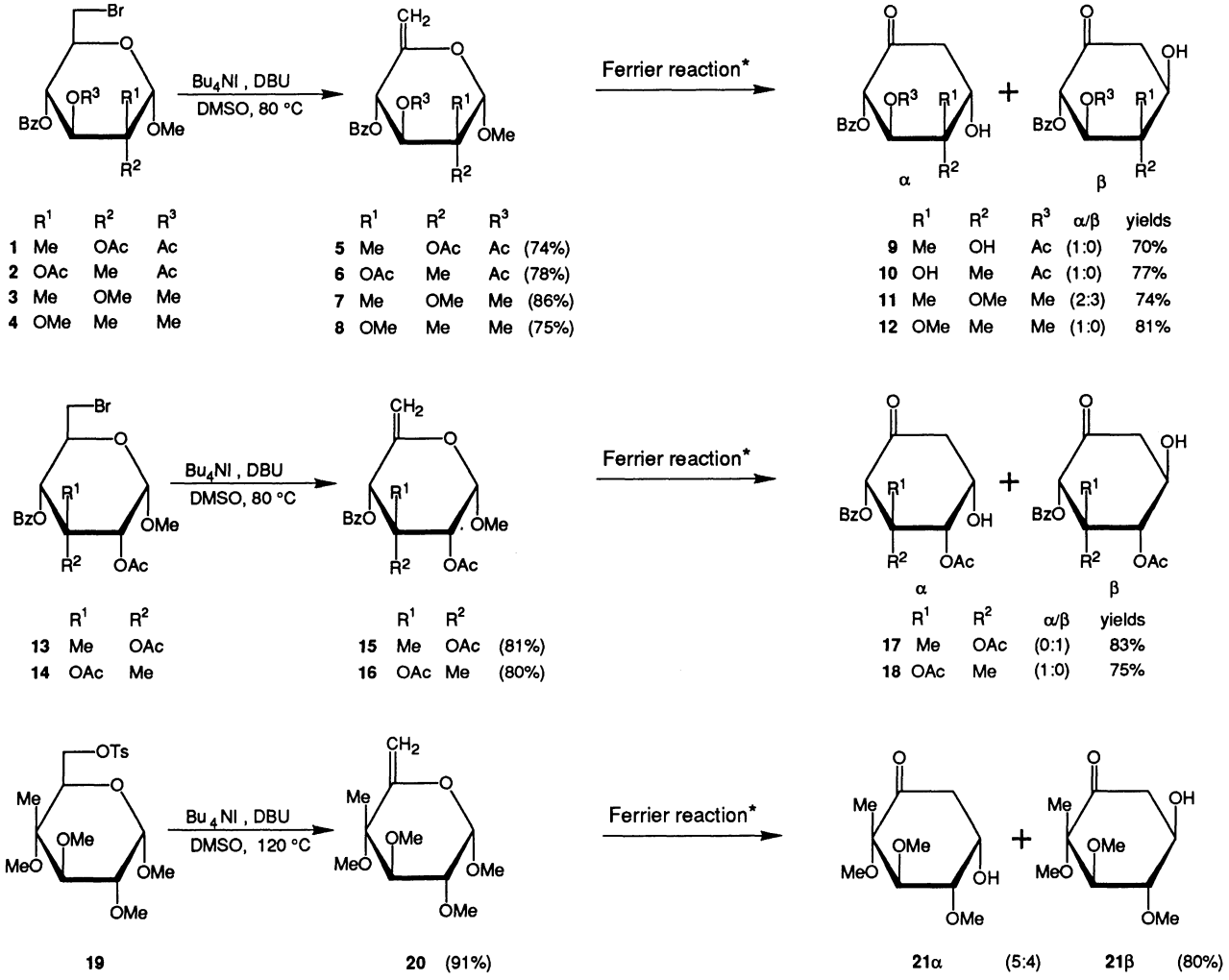
mixture of branched-chain 6-bromo-6-deoxy- or 6-p-tolylsulfonylhexopyranoside (1.27 mmol), sodium iodide (6.35 mmol), tetrabutylammonium iodide (6.35 mmol), and molecular sieves 4A in DMSO (5 ml) was stirred at 80-120 °C until the starting hexose disappeared on TLC. After DBU (6.35 mmol) was added, the mixture was stirred at the same temperature until the intermediary 6-deoxy-6-iodo derivative disappeared. The reaction mixture was directly treated on silica-gel column (Kieselgel 60, hexane-ethyl acetate, 2:1) to give expected 6-deoxyhex-5-enopyranoside. Using this procedure, methyl 6-bromo-6-deoxy-α-D-hexopyranosides (**1-4**, **13**, and **14**) and 6-O-p-tolylsulfonyl-α-D-hexopyranoside **19** could be converted into the corresponding 6-deoxyhex-5-enopyranosides (**5-8**, **15**, **16**, and **20**) in 74-91% yield.



	R^1	R^2	R^3
1	Me	OAc	Ac
2	OAc	Me	Ac
3	Me	OMe	Me
4	OMe	Me	Me

	R^1	R^2	R^3	
5	Me	OAc	Ac	(74%)
6	OAc	Me	Ac	(78%)
7	Me	OMe	Me	(86%)
8	OMe	Me	Me	(75%)

	R^1	R^2	R^3	α/β	yields
9	Me	OH	Ac	(1:0)	70%
10	OH	Me	Ac	(1:0)	77%
11	Me	OMe	Me	(2:3)	74%
12	OMe	Me	Me	(1:0)	81%

	R^1	R^2
13	Me	OAc
14	OAc	Me

	R^1	R^2	
15	Me	OAc	(81%)
16	OAc	Me	(80%)

	R^1	R^2	α/β	yields
17	Me	OAc	(0:1)	83%
18	OAc	Me	(1:0)	75%

Ferrier reaction of branched-chain 6-deoxyhex-5-enopyranosides was carried out under modified conditions as follows: Methyl 2,3-di-O-acetyl-4-O-benzoyl-6-deoxy-2-C-methyl-α-D-xylo-hex-5-enopyranoside (**5**, 1.0 mmol) and mercury(II) acetate (4.3 mmol) were refluxed in acetone-H_2O (20 ml, 5:2) containing 1% acetic acid until starting material disappeared. The acetone was removed and the residue was extracted with ethyl acetate (3 times), and the extracts were dried and evaporated to give crude deacetylated methyl-branched 2,3,4,5-tetrahydroxycyclohexanone derivative **9α**, which was purified on silica-gel column (Kieselgel 60, hexane-ethyl acetate, 3:1). Under these conditions cyclohexanone derivatives were obtained in 70-83% yields. 2-C-Methyl-5-enopyranosides (**5**, **6**, and **8**) irrespective of the configuration of the branching carbon gave pseudo-α-anomers (**9α**, **10α**, and **12α**, respectively) exclusively. However, only **7** gave a mixture of α-anomer (**11α**) and β-anomer (**11**) with a ratio of 2:3. On the contrary, in the cases of 3-C-methyl-5-enopyranosides (**15** and **16**), β-anomer **17β** and α-anomer **18α** were obtained exclusively depending on the configuration of the branching carbon. Further, 4-C-methyl-5-enopyranoside **20** gave a mixture of both anomers (**21α** and **21β**) in a ratio of 5:4.

Lukacs et al.[6] pointed out that the configuration on C-5 of the cyclohexanone derivatives formed by Ferrier reaction depends on the conformation of starting 5-enopyranosides, that is, those adopting C1 and 1C conformations gave preferentially pseudo-α-anomer (axially oriented hydroxyl group on C-5) and pseudo-β-anomer (equatorially oriented one), respectively. As a whole this tendency was also observed in the cases of branched-chain 6-deoxyhex-5-enopyranosides. However, it is noteworthy that unexpected isomers were obtained in the cases of **7** and **15** and that deacetylation of tertiary acetoxy group occurred in the cases of **5** and **6**. For the former, the reversed selectivity was observed between methyl and acetyl groups. Further investigation should be necessary for explanation of the stereoselectivity in Ferrier reaction.

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3) Partial ^{1}H-NMR data measured in $CDCl_3$: **5**: 5.59(s, H-1), 5.75(d, $J_{3,4}$=10.2 Hz, H-3), 5.64(ddd, $J_{4,6}$=2.0 Hz, $J_{4,6'}$ =1.7 Hz, H-4), 4.77(dd, $J_{6,6'}$ =2.0 Hz, H-6), 4.54(dd, H-6'). **6**: 5.57(s, H-1), 5.58(d, $J_{3,4}$=10.0 Hz, H-3), 5.97(ddd, $J_{4,6}$=$J_{4,6'}$ =1.8 Hz, H-4), 4.77(dd, $J_{6,6'}$ =1.7 Hz, H-6), 4.57(dd, H-6'). **7**: 4.67(s, H-1), 3.82(d, $J_{3,4}$=9.5 Hz, H-3), 5.62(ddd, $J_{4,6}$=$J_{4,6'}$ =2.2 Hz, H-4), 4.50(dd, $J_{6,6'}$ =2.2 Hz, H-6), 4.70(dd, H-6'). **8**: 4.67(s, H-1), 3.61(d, $J_{3,4}$=10.0 Hz, H-3), 6.03(ddd, $J_{4,6}$=$J_{4,6'}$ =2.2 Hz, H-4), 4.67(dd, $J_{6,6'}$ =2.2 Hz, H-6), 4.46(dd, H-6'). **9α**: 5.70(d, $J_{2,3}$=10.3 Hz, H-2), 5.48(d, H-3), 4.08(dd, $J_{5,6}$=3.2 Hz, $J_{5,6'}$ =2.9 Hz, H-5), 2.80(bd, H-6,6'. **10α**: 5.80(d, $J_{2,3}$=10.5 Hz, H-2), 5.65(d, H-3), 4.13(dd, $J_{5,6}$=$J_{5,6}$=3.2 Hz, H-5), 3.32(dd, H-6), 2.59(dd, H-6'). **11α**: 5.45(d, $J_{2,3}$=10.0 Hz, H-2), 4.12(dd, $J_{5,6}$=$J_{5,6'}$ =3.4 Hz, H-5), 3.90(d, H-3), 2.75(dd, H-6), 2.63(dd, H-6'). **11β**: 5.52(d, $J_{2,3}$=8.8 Hz, H-2), 3.83(dd, $J_{5,6}$ =10.5 Hz, $J_{5,6'}$ =5.9 Hz, H-5), 3.61(d, H-3), 2.84(dd, H-6), 2.63(dd, H-6'). **12α**: 5.82(d, $J_{2,3}$ =10.3 Hz, H-2), 4.13(dd, $J_{5,6}$=3.2 Hz, $J_{5,6'}$ =2.9 Hz, H-5), 3.78(d, H-3), 3.18(dd, H-6), 2.48(dd, H-6'). **15**: 4.77(d, $J_{1,2}$=2.4 Hz, H-1), 5.48(d, H-2), 5.92(s, H-4), 4.97(d, $J_{6,6'}$ =1.0 Hz), 4.94(d, H-6'). **16**: 5.03(d, $J_{1,2}$=4.2 Hz), 6.05(d, H-2), 6.52(dd, $J_{4,6}$=$J_{4,6'}$ =1.5 Hz, H-4), 4.82(dd, $J_{6,6'}$ =1.5 Hz, H-6), 4.76(dd, H-6'). **17β**: 5.60(s, H-2), 5.43(d, $J_{4,5}$=9.5 Hz, H-4), 4.25(ddd, $J_{5,6}$=11.2 Hz, $J_{5,6'}$ =3.9 Hz, H-5), 3.01(dd, H-6), 2.73(dd, H-6'). **18α**: 6.81(s, H-2), 6.40(d, $J_{4,5}$=3.7 Hz, H-4), 4.47(ddd, $J_{5,6}$=$J_{5,6'}$ =3.4 Hz, H-5), 2.97(dd, H-6), 2.77(H-6'). **20**: 4.84(d, $J_{1,2}$=3.5 Hz, H-1), 3.34(dd, $J_{2,3}$=9.5 Hz, H-2), 3.88(d, H-3), 4.70(d, $J_{6,6'}$=0.7 Hz, H-6), 4.66(d, H-6'). **21α**: 4.26(ddd, $J_{5,6}$=$J_{5,6'}$ =3.9 Hz, H-5), 3.86(d, $J_{3,4}$=8.8 Hz, H-3), 3.43(dd, $J_{4,5}$=2.7 Hz, H-4), 2.69(dd, H-6), 2.46(dd, H-6'). **21β**: 3.82(ddd, $J_{5,6}$=11.7 Hz, $J_{5,6'}$ =5.9 Hz, H-5), 3.60(d, H-3), 3.38(t, $J_{3,4}$=$J_{4,5}$=9.5 Hz, H-4), 2.75(dd, H-6), 2.55(dd, H-6').

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