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SYNTHESIS OF OPTICALLY ACTIVE O-PROTECTED (S)- AND (R)-3-HYDROXYALDEHYDES

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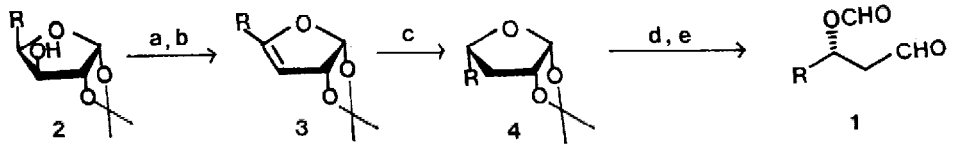
Summary: (S)-3-Formyloxyaldehydes, chiral synthons for natural product synthesis were synthesized *via* highly stereoselective hydrogenation of the unsaturated furanose ring system derived from D-glucose or D-xylose. Alternatively, (R)-3-formyloxyaldehydes were prepared *via* deoxygenation of 3-hydroxyfuranoses derived from D-glucose or D-xylose.

In connection with our current programs on the synthesis of chiral insect pheromones from carbohydrates, we needed the appropriately protected β-hydroxyaldehydes, (S)-**1** and (R)-**1** (Scheme 1, 2). (S)-3-Hydroxybutanoate and (S)- or (R)-3-hydroxypentanoate and their corresponding aldehydes or alcohols were prepared *via* enantioselective microbial reduction of the corresponding β-keto ester.[1] (R)-3-Hydroxybutanoate was available by depolymerization of natural polyhydroxybutyrate[2] and (R)-3-hydroxypentanoate was obtained by microbial β-oxidation[3] of pentanoic acid. Recently, some (R)- or (S)-3-hydroxyalkanoates were prepared by Ru-(R)- or (S)-BINAP catalyzed asymmetric hydrogenation of β-keto ester developed by R. Noyori.[4] We report here a stereocontrolled synthesis of the optically active enantiomers (S)-**1** and (R)-**1** by chemical modification of the α-D-glucofuranose or α-D-xylofuranose, derived from readily available D-glucose or D-xylose.

α-D-Hexofuranose **2c**[5] derived from D-glucose was converted to the triflate with triflic anhydride at -10°C, which was subjected to smooth elimination by treatment of DBU in ether at room temperature to provide hex-3-enofuranose **3c** in 70% overall yield. Catalytic hydrogenation of the hexenofuranose **3c** on Rh/Al_2O_3 at atmospheric pressure in ethyl acetate afforded 3-deoxy-β-L-threo-hexofuranose **4c**(TLC:SiO_2, CH_2Cl_2, R_f=0.25), $[\alpha]_D^{24}$ -11.0°(c=3.0, $CHCl_3$) exclusively as the only isolated product[6] in 84% yield after column chromatographic separation. Orientation of the ethyl substituent of **4c** and excellent stereoselectivity(>99%)[6] were

confirmed by the comparison of the ^{1}H- and ^{13}C-NMR spectra and capillary GLC data of **4c**[7](Scheme 1) and **5c**[7] (Scheme 2). Remarkably, by GLC analysis, only one isomer was detected before and after column chromatographic separation. However, in our hands, catalytic hydrogenation of **3c** on Pd/C at high pressure (50 psi) gave a mixture of two isomers with low selectivity. Removal of the isopropylidene group in **4c** with 2N HCl yielded the hemiacetal, which was subjected to oxidative cleavage with sodium periodate to afford the (S)-3-formyloxy-1-butanal **1c** (TLC:SiO_2, EtOAc, R_f=0.78), $[\alpha]_D^{24}$ -10.8°(c=1.4, $CHCl_3$)(Scheme 1). The reaction sequence was also applied to prepare **1b** and **1d**, which is shown in Scheme 1.

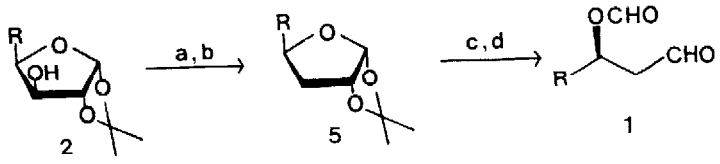


2a R=	**3a** 86% **4a** 82% -80.5°(c=4)		
2b[8] R= Me-	**3b** 66% **4b** 72% -21.1°(c=0.3)	(S)-**1b** 75% -40.1°(c=0.8)	
2c R=Et-	**3c** 69% **4c** 84% -11.0°(c=3)	(S)-**1c** 78% -10.8° (c=1.4)	
2d[9] R=n-Pentyl-	**3d** 82% **4d**[10]83% -8.5°(c=2)	(S)-**1d** 85% -9.1°(c=1.2)	
	$[\alpha]_D^{24}$in $CHCl_3$	$[\alpha]_D^{24}$in $CHCl_3$	

a)Tf_2O, pyridine, CH_2Cl_2, -10°C; b) DBU, ether, rt; c) H_2, Rh/Al_2O_3, atmospheric pressure, EtOAc; d) 2N HCl, DME, rt; e) $NaIO_4$, $MeOH/H_2O$ (5:1), rt

Scheme 1

Alternatively, the enantiomers (R)-**1b-d**, were prepared from the corresponding furanoses **2b-d** via classical Barton-McCombie deoxygenation reaction[11] of the corresponding C-3 hydroxyfuranoses. The furanose **2c** was subjected to deoxygenation reaction [(1) NaH, CS_2, THF, MeI, rt (2) $n\text{-}Bu_3SnH$,AIBN, toluene, 130°C] to provide **5c** (TLC:SiO_2,CH_2Cl_2, R_f =0.42), $[\alpha]_D^{24}$-19.5°(c=0.1, $CHCl_3$), which in turn was converted to (R)-**1c**(TLC:-SiO_2,EtOAc, R_f=0.80), $[\alpha]_D^{24}$+11.2° (c=2.5, $CHCl_3$), by the following reactions (1) 2N HCl, DME, rt, 12h (2) $NaIO_4$, $MeOH/H_2O$(5:1), rt, 2h (Scheme 2). The reaction sequence was also applied to prepare (R)-**1b** and (R)-**1d**, which is shown in Scheme 2.



5a	53%	+9.0°(c=2.0)			
5b	52%	-22.7°(c=3.0)	(R)-**1b**	72%	+43.4°(c=0.8)
5c	50%	-19.5°(c=2.1)	(R)-**1c**	73%	+11.2°(c=3.5)
5d	64%	-1.90°(c=2.6)	(R)-**1d**	87%	+8.5°(c=2.0)
		$[\alpha]_D^{24}$ in $CHCl_3$			$[\alpha]_D^{24}$ in $CHCl_3$

a) CS_2, THF, MeI, rt; b) n-Bu_3SnH, AIBN, toluene, 130°C; c) 2N HCl, DME, rt; d) $NaIO_4$, MeOH/H_2O(5:1), rt

Scheme 2

In summary, the optically active (S)- and (R)-3-hydroxyaldehydes, versatile chiral building blocks were synthesized from D-glucose or D-xylose.

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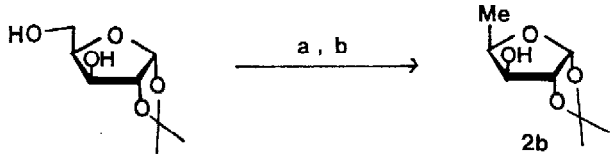
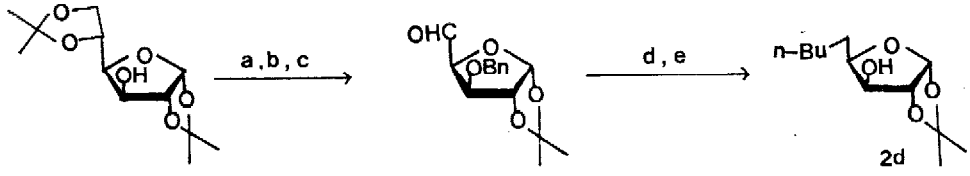
References and Notes

1. For excellent reviews, see: a) Mori, K., in : *Studies in Natural Products Chemistry*, Vol. 1, Stereoselective Synthesis (Part A), A-u-Rahman,(ed.) Elsevier, **1988**, p677-712. b) Mori, K., in : *Organic Synthesis: Modern Trends*, O.Chizhov, (ed.) Blackwell, **1987**, p293-304. c) Servi, S. *Synthesis*, **1990**, 1.
2. a) Sugai, T.; Fujita, M.; Mori, K. *Nippon Kagaku Kaishi(J. Chem. Soc. Jpn.)*, **1983**, 1315. b) Seebach, D.; Zuger, M. *Helv. Chim. Acta*, **1982**, *65*, 495.
3. Hasegawa, J.; Hamaguchi, S.; Ogura, M.; Watanabe, K. *J. Ferment. Technol*, **1981**, *59*, 257.
4. Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856.
5. Pougny, J-R. *Tetrahedron Lett.* **1984**, *25*, 2363. We have prepared this compound from diacetone D-glucose in four steps: (a) NaH,BnCl, THF,rt,24h(98%) (b) 50% HOAc,rt,24h(99%) (c) $Me_2NCH(OMe)_2$, CH_2Cl_2,rt,1h, then Ac_2O,160°C,3h(79%) (d) H_2,Pd/C,EtOAc,rt,atmospheric pressure, 24h(97%).

6. Capillary GC analyses were performed for **4a-d** and **5a-d** by using Hewlett-Packard 5890 GC system (column: HP-20M, 0.2mmX25m, 100°C, N_2, 1.0ml/min). The values of the retention time for each compounds were as follows: **4a**: 12.26 min, **4b**: 2.85 min, **4c**: 2.36 min, **4d**: 8.06 min, **5a**: 6.78 min, **5b**: 2.60 min, **5c**: 2.27 min, **5d**: 7.07 min.
7. All new compounds gave spectral data (IR, ^{1}H and ^{13}C NMR, and mass) in accord with the assigned structure.
8. The compound **2b** was prepared from 1,2-O-isopropylidene-D-xylofuranose in two steps (a) p-TsCl, pyridine, $CHCl_3$,0°C,12h(79%) (b) $LiAlH_4$,THF, reflux,12h(99%).



9. The **2d** was prepared conventionally from diacetone-D-glucose by the following reaction sequence (a) NaH, BnCl,THF,rt, 24h (98%) (b) 50% HOAc, rt,24h (99%) (c) $NaIO_4$, SiO_2, CH_2Cl_2, rt, 1 h (99%) (d) $(C_6H_5)_3P{=}CHCH_2CH_2CH_3$(from n-BuLi and n-butyltriphenylphosphonium bromide),THF,rt,2h(75%) (e) H_2,Pd/C,EtOAc,rt,atmospheric pressure, 24h(88%).



10. Physical and spectroscopic data of **4d** and **5d**: **4d**; ^{1}H NMR(80MHz, $CDCl_3$)δ 0.88(t,3H,-CH_3), 1.10-1.80(m, 8H, -$(CH_2)_4$-), 1.37,1.56 (s, each 3H, acetonide) ,1.85-2.30 (m,2H,H-3), 4.07(m,1H,H-4),4.73(m,1H,H-2), 5.74 (d,1H,H-I,J=4.0Hz). ^{13}C-NMR(22.6MHz,$CDCl_3$) δ 112.4, 106.3, 81.2, 80.9, 36.8, 36.5,27.3, 26.4, 26.0, 22.6, 14.0. $[\alpha]_D^{24}$ -8.5° (c=2.0,$CHCl_3$). TLC;SiO_2,CH_2Cl_2,R=0.69. **5d**: H-NMR (80MHz,$CDCl_3$) δ 0.88(t,3H,-CH_3), 1.05-1.80 (m,9H,-$(CH_2)_4$,H-3),1.32, 1.53(s,each 3H,acetonide), 2.10 (dd,1H,H-3, J=14.0Hz,5.0Hz), 4.14 (m,1H,H-4), 4.70 (dd,1H,H-2,J=4.8Hz, 4.0Hz), 5.75 (d,1H,H-1,J=4.0Hz). ^{13}C-NMR(22.6MHz,$CDCl_3$)δ 111.3, 105.3, 80.6, 78.0, 39.1, 34.3, 31.8,26.6, 26.1, 25.7, 22.5, 13.9. $[\alpha]_D^{24}$ -1.90° (c=2.6, $CHCl_3$). TLC;SiO_2, Rf=0.75(CH_2Cl_2).
11. Barton, D.H.R.; McCombie, S.W. *J. Chem. Soc. Perkin Trans 1*, **1975**, 1574.

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