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TRANSFORMATIONS OF TARTARIC ACID: A FACILE SYNTHESIS OF DERIVATIVES OF OPTICALLY ACTIVE α-HYDROHYALDEHYDES

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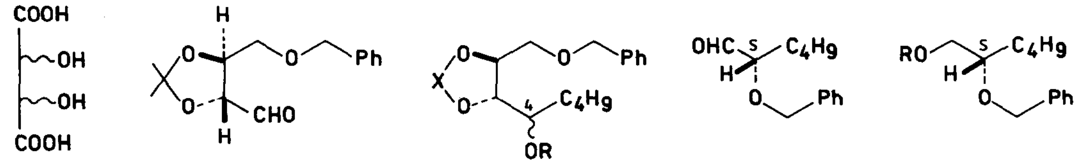
Summary. Methods for synthesis of (R)-and (S)-2-benzyloxy- and 2-(t-butyldiphenylsilyloxy)-aldehydes from optically active tartaric acids are described.

α-Hydroxyaldehydes are useful precursors of an oxirane, an allylic alcohol, a 1,2-diol and other structural units in syntheses of various natural products. Novel methods of preparation of enantiomerically pure α-hydroxyaldehydes consist in transformations with the use of enzymes[1], as well as chiral auxiliaries[2], or chiral starting materials[3]. However, the chiral starting materials hitherto utilized for such purposes are limited to D-mannitol[3a,b] and isopropylidene glyceraldehyde[3c] (derived from mannitol). Now, we describe two alternative methods of synthesis of (S)- and (R)-2-hydroxyaldehydes derivatives, based upon the cheapest chiral starting materials - tartaric acids[4]. The methods are exemplified by the preparation of 2-hydroxyhexanal and 2-hydroxyheptanal derivatives.

Chart 1



1a (R,R)
1b (S,S)

2

3a (4S); X=CMe$_2$; R=H
3b (4R); X=CMe$_2$; R=H
3c (4S); X=CMe$_2$; R=CH$_2$Ph
3d (4S); X=H,H ; R=CH$_2$Ph

4

5a R=H
5b $R=\overset{O}{\overset{\|}{C}}-NH-\underset{Me}{\underset{|}{C}}H-Ph$

Synthetic sequence
$1a \dashrightarrow 2 \longrightarrow 3a \longrightarrow 3c \longrightarrow 3d \longrightarrow 4$

The aldehyde 2 (Chart 1), prepared from L(+) tartaric acid (1a) according to the known procedure[5,6], was treated with 2.0 equivalents of BuLi and 1.3 equivalents of $ZnBr_2$ (THF, -78°C, 0.5 h) to give[7], after chromatography, the 4(S) carbinol 3a in 79% yield and a small amount of its epimer 3b (8%). Lower yields of compound 3a, 72%, were obtained when no $ZnBr_2$ was added to the reaction mixture. Suprisingly[3c,8], the reaction of the aldehyde 2 and $BuTi(OiPr)_3$ gave the adduct in a low yield (15%) and with poor diastereoselectivity (isomer ratio, 3a/3b 2:1). The carbinol 3a was benzylated (NaH, BzlBr, DMF, 85%) to protect the hydroxy group. The acetonide group in compound 3c was cleaved with 80% aqueous AcOH and the diol 3d was oxidized by means of $Pb(OAc)_4$ in benzene solution. Chromatography of the crude product gave the required (S)-2-benzyloxyhexanal 4 (60% from 3c, b.p. 50°C/0.1 mmHg).

The following experiments were carried out to confirm the purity of the product. Reduction of 4 with $LiAlH_4$ furnished the diol 5a which was allowed to react with (R)-1-phenylethylisocyanate. Compound 5b, formed nearly quantitatively, was proved homogeneous by HPLC (RP 18 µm, 72% methanol-water) and NMR measurements (^1H and ^{13}C). It is noteworthy that the $[\alpha]_D$ values of compounds 4 and 5a differ from those reported[3c] [found -88° and +23° (c2, $CHCl_3$), reported -66° and +16.9°, respectively].

In the synthesis involving the aldehyde 2, only two carbon atoms of tartaric acid are incorporated into the product. It was tempting to develop a procedure which would employ the both halfs of the starting material molecule and, therefore allow, at least theoretically, to prepare two equivalents of the product from an equivalent of starting material. Our initial attempts to prepare the dialdehyde 6a (Chart 2) failed. However, the related 1,4-diketones can be obtained[9] from the easily accessible diamide 6b and alkylmagnesium halides. Accordingly, the diketone 6c was prepared from the diamide 6b (L-series) and pentylmagnesium bromide (yields 50-70%). It was gratifying to find that the reduction of the diketone 6c with potassium tri-sec-butylborohydride (K-Selectride) affords efficiently the diol 6d (80% after chromatography) having the same configuration (R) on the both newly formed chiral centers. Reduction of compound 6c with other reducing agents examined were much less selective and, generally, the isomer 6d was the minor reaction product. Some of the results are presented below (a complete report will be given in the full paper).

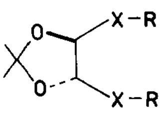
Entry	Reagent	Yield (%)	Product composition (%)[11] RRRR (9)	SRRR (7)	SRRS (8)
1	K-Selectride, THF, -78°C, 2h	95	94	6	0
2	$Ce(BH_4)_3$, ethanol-water, -5°C, 2h	98	17	50	33
3	$NaBH_4$, ethanol, -30°C, 0.5h	98	17	33	50
4	$Zn(BH_4)_2$, ether, -78°C, 1h	95	13	62	25

The synthesis of (R)-2-benzyloxyheptanal 10 from 1a via 6d was completed by means of the following consecutive reactions. The diol 6d was benzylated. the dibenzyloxy acetonide 6e was hydrolyzed (CF_3COOH - $CHCl_3$), and the dibenzyloxy diol 9 was oxidized with $Pb(OAc)_4$. The product (10) was obtained in 73% yield from 6d.

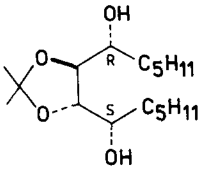
The diketone route (Chart 2) is complementary to the aldehyde route (Chart 1), since starting from the same enantiomer of tartaric acid it leads to a hydroxyaldehyde derivative of the opposite configuration.

The described above methods provide α-hydroxyaldehydes having the hydroxy group protected as benzyl ether. For the planned syntheses[10] in the eicosanoid field we needed also the corresponding alkyl (aryl) silyloxy derivatives. The replacement of the benzyl group with a trialkylsilyl group in the synthetic sequence was complicated by susceptbility of the silyl ethers to the hydrolysis upon the conditions of the acetonide cleavage. After considerable experimentation these difficulties were solved in the way presented on the following example. Starting from D(-) tartaric acid (1b) the diamide 11a, then the diketone 11b and the isopropylidene tetraol 11c (accompanied by small amount of its isomer 12) were prepared. The diol 11c was transformed to di-t-butyldiphenylsilyl derivative 11d (t-BuPh$_2$SiCl, imidazol, DMF, 80°C, 2h, 90% yield). For the removal of the acetonide group, compound 11d was exposed to the action of I$_2$ in methanol[12]; when the reaction was stopped at 40% of the conversion of the starting material, the diol 13 was isolated as the exclusive product and the unchanged acetonide 11d was recovered. Although this procedure requires the recycling of the acetonide 11d, the losses of the material are relatively low[13]. With the higher rate of the conversion of 11d side products appeared. Compound 13 was oxidized with Pb(OAc)$_4$ to give (S)-2-(t-butyldiphenylsilyloxy)-heptanal 14 (80% from 11c, $[\alpha]_D$ -6.0°, c 2, benzene, b.p. $130^\circ C/10^{-3}$ mmHg).

Chart 2



6a X=CO ; R=H
6b X=CO ; R=NMe$_2$
6c X=CO ; R=C_5H_{11}
6d X=(R) CH(OH) ; R=C_5H_{11}
6e X=(R) CH(OCH$_2$Ph) ; R=C_5H_{11}



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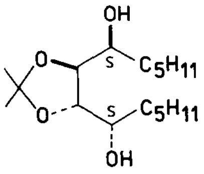

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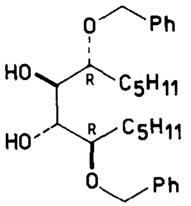

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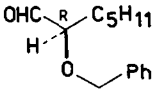
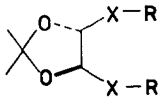


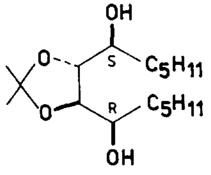
10

Synthetic sequence

1a ------> 6b → 6c → 6d → 6e → 9 → 10



11a X=CO ; R=NMe$_2$
11b X=CO ; R=C_5H_{11}
11c X=(S) CH(OH) ; R=C_5H_{11}
11d X=(S) CH(OSitBuPh$_2$) ; R=C_5H_{11}



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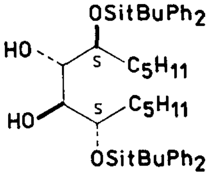

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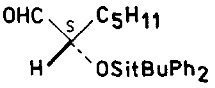

14

Synthetic sequence

1b ----> 11a → 11b → 11c → 11d → 13 → 14

In conclusion, the aldehyde 2, derived from optically active tartaric acid, reacts with selected organometallic reagents with high degree of diastereoselectivity, giving the main product in accord with the Cram's rule. The same steric course was noted for K-Selectride reduction of diketone 6c. These reactions were used for a facile preparation of enantiomerically pure derivatives of (S)- and (R)-2-hydroxyaldehydes.

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