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Trifunctional Chiral Synthons via Stereocontrolled Yeast Reduction. Preparation of Chiral Pentane-1,3,5-triol Derivatives

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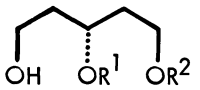
Easy access to pentane-1,3,5-triol derivatives of high optical purity, trifunctional chiral synthons of fundamental importance in the synthesis of various natural products is described, as well as the stereocontrol of baker's yeast reduction of 5-substituted 3-oxopentanoates.

Asymmetrically protected pentane-1,3,5-triol (1) and the related compounds of high optical purity, such as 3,5-dihydroxypentanoate (2) and methyl hydrogen 3-hydroxyglutarate (3), are particularly useful synthons in the synthesis of polyfunctional natural products. Consequently several synthetic sequences have been developed, utilizing such biochemical transformations as asymmetric hydrolysis of prochiral diesters[1,2] or asymmetric reduction of prochiral ketones.[3] However, the former method is sometimes difficult to control and does not necessarily achieve the high enantioselectivity[1,2] or needs some specific microorganisms not commonly available,[1c] while the latter on dialkyl 3-oxoglutarates suffers from low stereoselectivity.[3] As a part of our effort to synthesize biologically active natural products of polyketide origin, such as anthelmintic avermectins,[4] we found ready access of 1 and 2a of high optical purity utilizing baker's yeast reduction of β-keto acid derivatives. The result is described herein.



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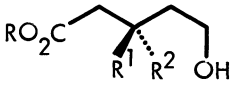
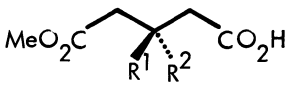


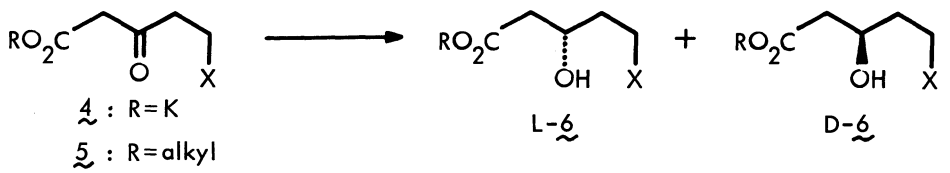
2a : R^1=H; R^2=OH
2b : R^1=OH; R^2=H



3 : R^1=OH; R^2=H
or
R^1=H; R^2=OH

Potassium 5-hydroxy- or 5-mercapto-3-oxopentanoates (4) with hydrophobic protecting group on the C-5 substituent were envisaged as the most proper substrate for the baker's yeast reduction to synthesize chiral 2b from our own result on potassium 3-oxo-alkenoates.[5] However, alkaline hydrolysis of the corresponding ester 5 gave the salt 4 in only poor yield probably because of the elimination of the C-5 substituent.[6] Methyl ester, our second choice,[5a] shows only low selectivity when a large functional group is substituted on C-5

Table 1. Enantioselectivity of baker's yeast reduction of 3-oxopentanoate with C_5-substituent



4 : R=K
5 : R=alkyl

L-6 D-6

	Substrate (5)		Product (6)		
	R	X	Yield /%	Ratio L-6 : D-6	$[\alpha]_D$ in $CHCl_3$
5a	-Me	$-O(CH_2)_2SiMe_3$	41	1 : 2[a]	-4.0°
5b	-Me	$-OCH_2Ph$	58	1 : 4.0[a]	-4.7°
5c	-Me	$-S(CH_2)_2Me$	71	1 : 1.2[a]	+1.1°
5d	-Me	-SMe	28	1 : 1.5[a]	+3.1°
5e[b]	-Me	-SPh	88	2.4 : 1[b]	-1.25°
5f	-Me	-OMe	11	2 : 1[c]	+4.1°
5g	-Et	-OMe	41	4.9 : 1[c]	+8.2°
5h	$-(CH_2)_2Me$	-OMe	40	9.0 : 1[c]	+12.2°
5i	$-(CH_2)_3Me$	-OMe	48	10.2 : 1[c]	+11.4°
5j	$-(CH_2)_4Me$	-OMe	26	9.1 : 1[c]	+10.7°
5k	$-(CH_2)_5Me$	-OMe	15	7.6 : 1[c]	+8.5°
5l	$-(CH_2)_6Me$	-OMe	9	6 : 1[c]	+7.4°
5m	$-(CH_2)_3Me$	-OH	33	8.9 : 1[d]	+16.7°
5n	$-(CH_2)_4Me$	-OH	59	14.0 : 1[d]	+16.9°
5o	$-(CH_2)_5Me$	-OH	3	8 : 1[d]	+16.2°

a) The enantiomer ratio was determined by 200 MHz ^{1}H-NMR chiral shift studies of the ester methyl signal using $Eu(tfc)_3$: the signal of L-alcohol shows a larger down-field shift than that of the corresponding D-alcohol.[5a,8)]

b) From Ref. 6.

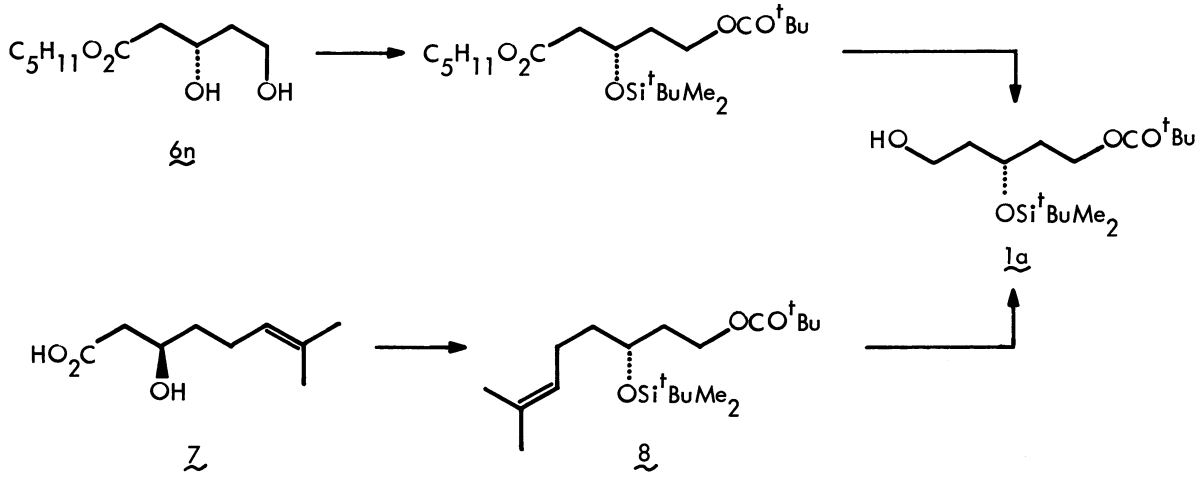
c) Determined by ^{1}H-NMR chiral shift studies of methyl ether signal using $Eu(tfc)_3$: the signal of D-alcohol shows a larger down-field shift contrary to the ester methyl signal.[9)]

d) Determined by ^{1}H-NMR chiral shift studies after the selective protection of C_5-hydroxy group as a t-butyldimethylsilyl ether[10)] and the conversion of the corresponding methyl ester.[8)]

(Table 1, 5a-5e). Therefore, we turned our attention to the alkyl 3-oxopentanoates (5) which possess a large hydrophobic R group[7] and small hydrophilic X group.

While ethyl 3-oxopentanoate was reported to give 3R-hydroxypentanoate (D-6, X=H) in 40% e.e.,[11] ethyl 5-methoxy-3-oxopentanoate (5g), easily prepared by the coupling of the dianion of ethyl acetoacetate with methyl chloromethyl ether, was found to yield the (3S)-alcohol, L-6g, with the opposite chirality[9] in 66% e.e. Encourated by this we examined the effect of the size of ester alkyl group.[5a,7] All substrates examined (5f-5l) in this context afforded L-6 as major enantiomer in ratios indicated in Table 1. Interestingly, both enantiomer ratio and chemical yield increased on going from methyl ester 5f to butyl ester 5i reaching to 82% e.e. and 48% yield, and then fell off toward heptyl ester 5l. The esters 5m-5o[12] with yet smaller and more hydrophilic OH group exhibited the similar trend, but in this series the maximum (87% e.e., 59% yield) was obtained in the reaction of pentyl ester 5n. These are in striking contrast to the previous result reported by Sih et al.[7] on the reduction of alkyl 4-chloro-3-oxobutanoates where they found higher selectivity for larger ester alkyl group, although the preferred enantiomer has the same L-configuration when R is sufficiently larger in both series.

L-6n (2a) thus obtained was converted to the compound 1a (1: R^1=Si^{t}BuMe$_2$, R^2=CO^{t}Bu) of $[\alpha]_D$ -4.4°(c 1.0, $CHCl_3$) in four steps: i) ^{t}BuCOCl, pyridine; ii) ^{t}BuMe$_2$SiCl, imidazole, DMF; iii) LiOH (1.0 molar equiv.), THF-EtOH-H_2O (3:1:1); iv) $BH_3\cdot SMe_2$ (1.0 molar equiv., r.t.; 50% overall yield).



We have developed an alternative reaction sequence to the optically pure 1a, $[\alpha]_D$ -5.6°(c 1.0, $CHCl_3$) utilizing again yeast reduction. Starting from the hydroxy acid 7,[5] $LiAlH_4$ reduction followed by the selective and sequential protections with ^{t}BuCOCl[5b] and ^{t}BuMe$_2$SiCl gave the compound 8, $[\alpha]_D$ -17.5° (c 1.1, $CHCl_3$), in 63% yield. Ozonolysis (-78 °C, CH_2Cl_2; Me_2S), enol acetylation of the resulting aldehyde (Ac_2O, DMAP, Et_3N)[13] and second ozonolysis

(-78 °C, MeOH) followed by the reduction with $NaBH_4$ (-78 °C to r.t.) afforded 1a in 59% yield from 8.

The chiral pentane-1,3,5-triol derivative 1a should be a versatile synthon for the synthesis of complex natural products of polyketide origin. The synthetic study towards avermectins[4] will be reported in due course.

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