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A NEW HIGHLY DIASTEREOSELECTIVE SYNTHESIS OF 2,5-DISUBSTITUTED-1,3-DIOXOLAN-4-ONES FROM α-HYDROXYACIDS

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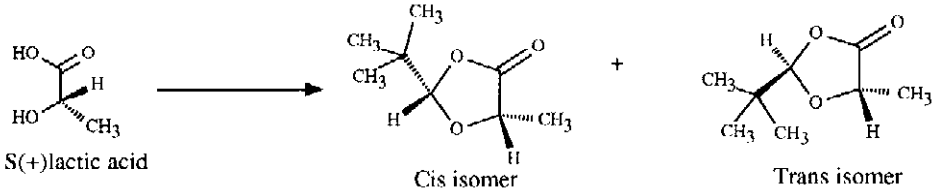
SUMMARY : *Reaction of α-hydroxyacids with acetals under weak acid catalysis gave the corresponding dioxolanones with a better diastereomeric ratio than the usual strong acid catalyzed synthesis from aldehydes.*

Chiral dioxolanones, versatile tools in stereoselective synthesis, have been used in recent years for numerous applications[1,2]. Stereocontrol is first achieved by the diastereoselective dioxolanone formation[3], and for this, pivalaldehyde has been used extensively. To isolate an enantiomerically pure compound, the diastereomeric mixture of oily dioxolanones obtained with α-hydroxyacids and aldehydes, has to be purified by low temperature selective crystallization.

Following our recent observation that excellent control of stereochemistry is achieved by reaction of lactic acid with ketone acetals under weak acid catalysis[4], we investigated the corresponding aldehyde acetals under these conditions with a variety of α-hydroxyacids. The pivalaldehyde/lactic acid case was chosen first, as the crude reaction product obtained by the known procedure usually contains some pivalaldehyde trimer, which impairs the low temperature selective crystallization of the major cis isomer. As a preliminary control experiment, the pyridinium p-toluenesulfonate (PPTS) catalyzed reaction of pivalaldehyde was shown to yield the same diastereomeric ratio (83/17) as the strong acid catalysis. Under PPTS catalysis, the pivalaldehyde dimethylacetal reacted with lactic acid to give a gratifying diastereomeric cis/trans ratio of 97:3.

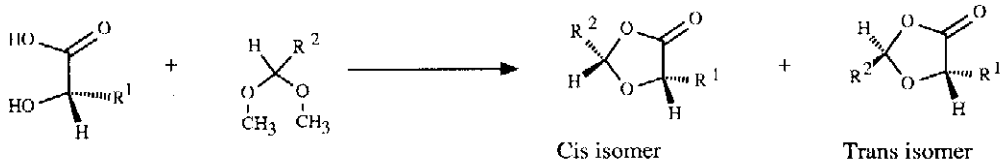


S(+)lactic acid — Cis isomer — Trans isomer

Reaction conditions:

TsOH, pivalaldehyde, pentane, reflux ===> *Cis / Trans = 83 : 17 (ref. 1)*
PPTS, pivalaldehyde, cyclohexane/ethylacetate, reflux ===> *Cis / Trans = 83 : 17 (this work)*
PPTS, pivalaldehyde dimethylacetal, cyclohexane/ethylacetate, reflux ===> *Cis / Trans = **97 : 3** (this work)*

This excellent result led us to investigate the scope of this reaction by changing the size of the aldehyde and hydroxyacid chains (racemic acids were used). The results clearly show that the acetal exchange method gives a kinetic ratio of isomers different from the strong acid catalyzed condensation with aldehydes[6]. The selectivity of this method is an improvement compared to literature results with aldehydes. Excellent results are obtained with the pivalaldehyde dimethylacetal (entries 1, 6, 7, 8, 9) and from mandelic acid (entries 6, 10).



Cis isomer Trans isomer

entry	R^1	R^2	Cis / Trans ratio (yield)	Cis / Trans ratio from aldehyde / comments	
1	*methyl*	*t-butyl*	*97 : 3 (47 - 59%)*	*83 : 17*	*thermodynamic ratio : ref.3*
2	*methyl*	*phenyl*	*70 : 30 (n . d)*	*70 : 30*	*thermodynamic ratio : ref.5*
3	*methyl*	*methyl*	*75 : 25 (20%)*	*69 : 31*	*thermodynamic ratio : ref.6*
4	*methyl*	*cyclohexyl*	*90 : 10 (44%)*	*93 : 7*	*our result with PPTS*
5	*methyl*	*i-propyl*	*90 : 10 (n . d)*	*64 : 36*	*thermodynamic ratio : ref.6*
6	*phenyl*	*t-butyl*	*97 : 3 (25%)*	*97 : 3*	*thermodynamic ratio : ref.5*
7	*benzyl*	*t-butyl*	*95 : 5 (41%)*	*83 : 17*	*thermodynamic ratio : ref.5*
8	*n-butyl*	*t-butyl*	*95 : 5 (62%)*	-	
9	*i-butyl*	*t-butyl*	*>99 : 1 (40%)*	-	*see ref.8 for cis isomer*
10	*phenyl*	*methyl*	*95 : 5 (39%)*	*90 : 10*	*thermodynamic ratio : ref.7*

If both substituents of the resulting dioxolanone have a small steric hindrance, the selectivity is low (entry 3). The 2- and 5- substituents seem to have a different contribution to the ratio of cis / trans isomers obtained, as can be seen by exchanging the methyl and phenyl groups (entries 2 and 10). Another explanation for the poor selectivity in entry 2, identical to the thermodynamic ratio[5], may be the fast epimerization of 2-aryldioxolanones at the acetal center, even in neutral medium[10]. The result in entry 10 is especially useful for the synthesis of optically active secondary alcohols from dioxolanones[2,11]. Despite the moderate yields obtained by our method, it compares favorably with the previous method[3,5], and has been applied in our laboratory for the large scale preparation of enantiomerically pure (2S,5S) and (2R,5R) 2-t-butyl-5-methyl-1,3-dioxolan-4-one **1**.

The chirality-controlling step of this diastereoselective reaction is under investigation.

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Typical procedure: **2-*t*-butyl-5-methyl-1,3-dioxolan-4-one 1**

S(+)lactic acid (85%, 5.4 g, 0.05 mole) dissolved in ethyl acetate (10 ml) is dried by reaction with methyl orthoformate (6 ml) overnight. This mixture is added dropwise over 6 hrs to a solution of pivalaldehyde dimethylacetal (5.0 g, 0.038 mole) in cyclohexane (30 ml) / ethyl acetate (15 ml) containing PPTS[9] (20 mg) heated at 80°C. During this addition, a total of 15 ml of volatile material is collected in a Dean-Stark trap. The reaction mixture is refluxed for 30 hrs (until all starting acetal disappears by GLC) cooled, diluted with pentane, washed with a saturated $NaHCO_3$ solution and dried over Na_2SO_4. Distillation gives 2-t-butyl-5 methyl-1,3-dioxolan-4-one **1**(3.3 g, 55% yield, Bp_{20}= 78°C) as a 97:3 mixture of cis and trans isomers (by 250 MHz ^1H NMR).

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11. identical selectivity is obtained with acetaldehyde diethylacetal (97/3).

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