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# CHIRALITY TRANSFER FROM LACTIC ACID SELECTIVE SYNTHESIS OF 2,2-DISUBSTITUTED-1,3-DIOXOLAN-4-ONES FROM KETONES AND ACETALS

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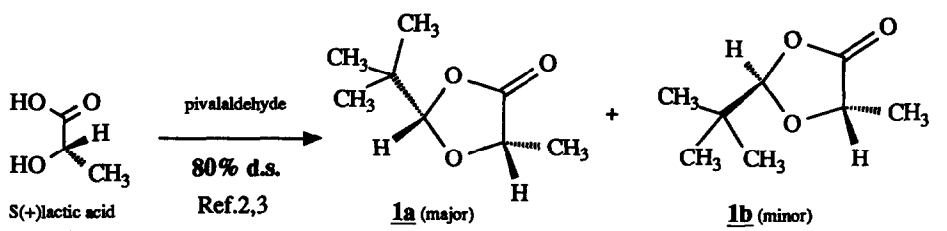
*SUMMARY : Diastereomeric 2,2-disubstituted-5-methyl-1,3-dioxolan-4-ones were prepared from lactic acid and ketones or their acetals with excellent control of stereochemistry under kinetic or thermodynamic reaction conditions.*

One of the approaches to enantioselective and/or diastereoselective carbon-carbon bond formation is the use of a chiral building block, from which new chiral centers may be created by adapted reaction sequences. Lactic acid, available in both enantiomeric forms, is one of the simplest chiral building blocks, and has therefore been used in numerous applications. One of these is part of the more general 1,3 chirality transfer[1] by diastereoselective dioxolanone formation , allowing to obtain very useful chiral enolates, easy to convert to more elaborated compounds with an excellent diastereoselection control[3]. In the optimized case of aldehydes and strong acid catalysis, pivalaldehyde[2] is the most satisfactory reaction partner for lactic acid.



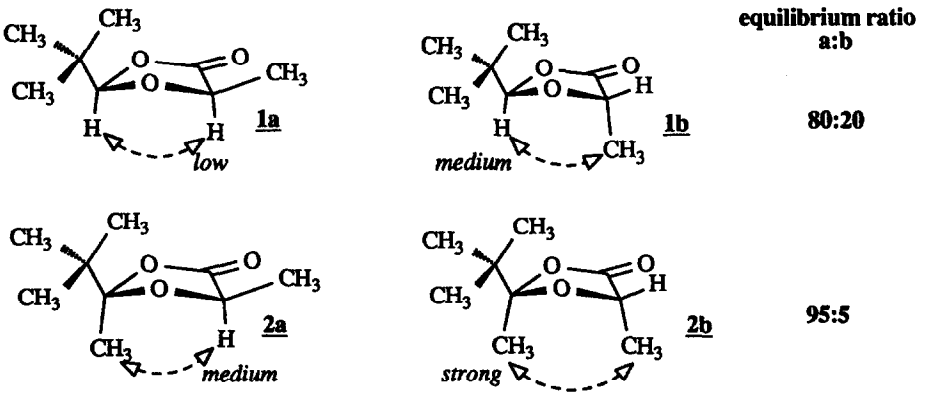

S(+)lactic acid — **1a** (major) — **1b** (minor)

The only weak point in this scheme is the diastereoselective dioxolanone formation giving rise to a 80:20 mixture of oily products **1a** and **1b**, which may be purified by low temperature fractional crystallization[3].

A better way of preparing 1,3-dioxolan-4-ones with a higher degree of chirality transfer was still needed and led us to investigate the selective formation of 2,2-disubstituted-1,3-dioxolan-4-ones.

Introduction of an extra substituent, even as small as a methyl group, would increase the 1,3-pseudodiaxial interactions and thus provide a higher selectivity.

This was indeed observed by going from pivalaldehyde to pinacolone where 2a was obtained with a 95:5 selectivity. In this latter case, the usual experimental procedure[3] had to be modified to allow the reaction to proceed without self-condensation of lactic acid, the major reaction pathway with any ketone and a strong acid in known procedures[4]. Excess pinacolone was used as a solvent for the dropwise addition of the 85% lactic acid aqueous solution and to ensure a homogenous reaction medium, a major point to prevent self-condensation of lactic acid. Continuous water removal was achieved with a Dean-Stark trap using refluxing cyclohexane as a solvent. (Method A).



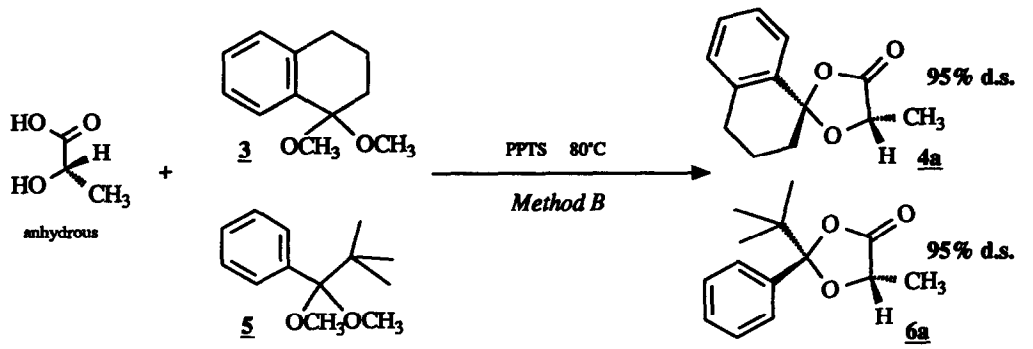

**1,3 pseudodiaxial interaction in substituted 1,3-dioxolan-4-ones**

When acetophenone was reacted under these conditions, a disappointing low yield (<10% conversion) and an equally poor selectivity of 45:55[5] (7a:7b) were obtained. The siloxane method[6] improved the yield but the same ratio of diastereomers was obtained[7]. An interesting observation was made during purification, where selective hydrolysis of one diastereomer occurred on silicagel, thus leading to a highly selective formation of the trans isomer 7b (97:3) but at the expense of yield (25%).

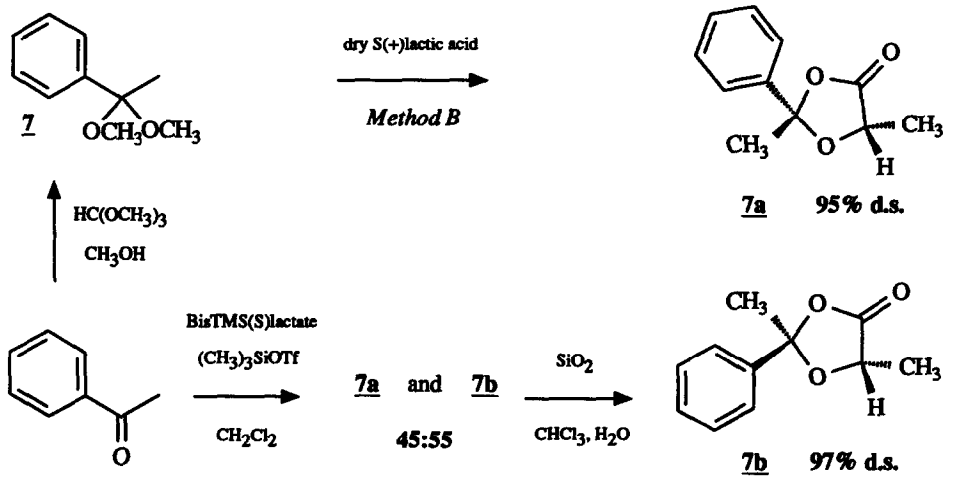
At this point, another reaction sequence was devised to obtain the expected products under mild conditions, namely acetal exchange from the corresponding ketone dimethyl acetal. As a preliminary experiment, dried lactic acid[8] was reacted with 1,1-dimethoxyindan in ethyl acetate at 0° together with a catalytic amount of pyridinium paratoluenesulfonate (PPTS)[9]. Dioxolanone formation occurred readily to yield a 50:50 mixture of the two diastereomers. This result is not surprising as the five membered ring removes phenyl and $CH_2$ groups away from the steric interaction, as shown on a molecular model. In the case of dimethyl acetal of 1-tetralone 3, a high degree of selectivity (95:5 in favor of cis isomer 4a) was obtained under the same conditions, even at 100°C. Slow distillation of the reaction medium allows continuous removal of methanol as an azeotropic mixture with cyclohexane or toluene. (Method B).

The procedure was also applied to the hindered pivalophenone dimethyl acetal 5, resulting in the formation of the trans isomer 6a with a 95% selectivity. In this case, the major isomer is easy to purify by recrystallization and melts at 101°C.

In these two preparations, the thermodynamically favored product is obtained, but the same reaction sequence, performed on 3 in presence of strong acid (PTSA), yields an equilibrium mixture of the two isomers (65:35 in favor of 4a), thus showing that **weak acid catalysis gives a kinetic product ratio.**




The most surprising result of this new method was observed in the case of acetophenone dimethyl acetal where this time a 95:5 ratio in favor of the cis isomer 7a was obtained, in presence or even in absence of PPTS, with apparently no steric reason. On the other hand, strong acid catalysis gave the usual 45:55 isomer mixture. This means that selective dioxolanone formation may be obtained by two ways: thermodynamic control by the reaction product (the usual strong acid catalyzed reversible reaction) or kinetic control by the transition state (in presence of weak acid: PPTS or lactic acid it self).




In these new reaction conditions, lactic acid reacts with several ketones or their derivatives to yield selective formation of 2,2-disubstituted dioxolanones with a high degree of 1,3 chirality transfer[10]. Use of these tools for asymmetric synthesis is in progress[11] and results will be published in due time.

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Typical procedures:

**Method A**: Ketone and Lactic acid under strong acid catalysis
**2-*t*-butyl-2,5-dimethyl-1,3-dioxolan-4-one 2**
A mixture of cyclohexane (350 ml), pinacolone (130 ml), and paratoluenesulfonic acid (1.5 g) is refluxed while a solution of 85% (+) lactic acid (74.1 g, 0.7 mole) in pinacolone (110 ml, 0.9 mole) is added dropwise over 15 hrs. A total volume of 26 ml of water is collected. After cooling, the organic layer is washed with a saturated $NaHCO_3$ solution, dried and distilled to give 2-*t*-butyl-2,5-dimethyl-1,3-dioxolan-4-one **2**(64.4 g, 54% yield, $Bp_{18}$= 86°C) as a 95:5 mixture of cis and trans isomers **2a** and **2b** (by NMR).The reaction solvent mixture may be recycled.

**Method B**: Ketone acetal and Lactic acid without added acid catalysis
**(2S,5S) 2-phenyl-2,5-dimethyl-1,3-dioxolan-4-one 7**
S(+)lactic acid (85%, 80 g, 0.89 mole) dissolved in ethyl acetate (400 ml) is dried by reaction with methyl orthoformate (71 g) overnight. This mixture is added dropwise over 8 hrs to a solution of acetophenone dimethyl acetal (100 g, 0.6 mole) in toluene (700 ml) heated at 95°C. During addition, a total of 300 ml of volatile material is distilled. After one more hour at 105°C, the reaction is stopped by addition of pyridine (50 ml). The reaction mixture is washed with water, a saturated $NaHCO_3$ solution, dried and concentrated. The crude product (115 g) is purified by vacuum distillation to give 2-phenyl-2,5-dimethyl-1,3-dioxolan-4-one (75 g, 65% yield, $Bp_{0.18}$= 66°C) as a 95:5 mixture of cis and trans isomers **7a** and **7b** (by NMR). A sample of pure (2S,5S) 2-phenyl-2,5-dimethyl-1,3-dioxolan-4-one **7a** is obtained with a 74% recovery by low temperature crystallization from pentane/diisopropyl oxide.

## References and notes.


1.D.SEEBACH, R.IMWINKELRIED, T.WEBER "Modern Synthetic Methods 1986", *SPRINGER-VERLAG*, Berlin Heidelberg 1986
2.G.FRÄTER, U.MÜLLER, W.GÜNTER Tetrahedron Lett. (1981) **22**, 4221
3.D.SEEBACH, R.NAEF, G.CALDERARI Tetrahedron (1984) **40**, 1313
4.N.G.GAYLORD, J.R.BENZINGER J.Org.Chem. (1954) **19**, 1991
M.FARINES, J.SOULIER, Bull.Soc.Chim.Fr. (1970) 332
5.Benzaldehyde leads to a 70:30 mixture of isomers by strong acid catalysis[3].
6.T.R.HOYE, B.H.PETERSON, J.D.MILLER J.Org.Chem. (1987) **52**, 1351
W.H.PEARSON, M.C.CHENG J.Org.Chem. (1987) **52**, 1353
7.In these conditions, ortho substituted acetophenones gave good yields of products as a mixture of isomers in favor of the trans isomer.
8.Water from commercial lactic acid may be removed by physical (freeze drying or adsorption by molecular sieves) or chemical methods (reaction with an ortho ester). This latter method seems to be the most convenient. Dry lactic acid polymerizes slowly on standing and should be used rapidly.
9.M. MIYASHITA, A. YOSHIKOSHI, P.A. GRIECO J.Org.Chem. (1977) **42**, 3772
10.Physical data of diastereomerically pure products: (all structure assignments are made by NOE)
**(2R,5S) 2-*t*-Butyl-2,5-dimethyl-1,3-dioxolan-4-one 2a:** $Bp_{18}$= 86°C $[\alpha]_D^{27}$= +48° (c=2,0 $CHCl_3$) IR (KBr) : 1790 $cm^{-1}$. $^1H$ NMR ($CDCl_3$):δ 4,50( q , J=7Hz , 1H ) 1,49( s , 3H ) 1,46( d , J=7Hz , 3H ) 1,02( s , 9H ). $^{13}C$ NMR ($CDCl_3$):δ 173,94 115,22 70,15 37,90 24,36 19,34 16,40 .
**(2R,5S) 2-phenyl,2-*t*-butyl-5-methyl-1,3-dioxolan-4-one 6a:** Mp= 101°C $[\alpha]_D^{21}$= +15° (c=1,62 $CHCl_3$) $^1H$ NMR ($CDCl_3$):δ 7,27-7,48( m , 5H ) 4,09( q , J= 6 Hz , 1H ) 1,50( d , J= 6 Hz , 3H ) 1,01( s ,9H ) $^{13}C$ NMR ($CDCl_3$):δ 174,00 136,93 128,77 127,84 127,53 114,35 70,47 38,23 24,43 15,87 .
**(2S,5S) 2-phenyl-2,5-dimethyl-1,3-dioxolan-4-one 7a:** $Bp_{0.2}$=70°C $[\alpha]_D^{23}$= +69° (c=1,52 $CHCl_3$) IR (KBr): 1785 $cm^{-1}$ $^1H$ NMR ($CDCl_3$):δ 7,36-7,55( m, 5H ) 4,65( q , J=6,9Hz , 1H ) 1,83( s , 3H ) 1,39( d , J=6,9Hz , 3H ). $^{13}C$ NMR ($CDCl_3$):δ 173,47 141,11 129,08 128,36 124,77 110,23 70,95 27,65 17,22 .
11.Preliminary results on alkylation of enolates with benzyl bromide show a 95:5 selectivity from **2a** and a 75:25 selectivity from **7a** (by NMR).


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