Synthesis of (*R*)-Lactic Acid and (2*R*,5*R*)-2-*t*-Butyl-5-methyl-1,3-dioxolan-4-one

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Abstract: A convenient procedure for synthesis of the very expensive (*R*)-lactic acid from relatively inexpensive (*R*)-alanine is described. Its subsequent conversion into a chiral dioxolanone can be carried out using an inexpensive pivalaldehyde/*t*-butanol mixture.

Key words: chiral pool, stereoselective synthesis, (*R*)-lactic acid, (*R*)-alanine, diazotisation, 1,3-dioxolan-4-one
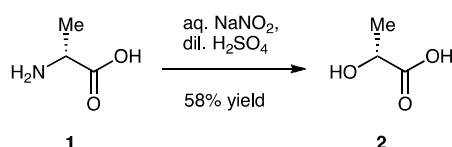
Scheme 1

In the appropriate section of a prestigious reference work published in 1996,[1] the following statement appears: "Both enantiomers of lactic acid (2-hydroxypropanoic acid) are natural products and easily obtained by biotechnological methods, so there is no need for their synthesis in the laboratory". While this may be true of the natural (*S*)-enantiomer, it is certainly not the case for the (*R*)-enantiomer with major chemical suppliers currently offering (*R*)-lactic acid at up to 10^4 times the price of the (*S*)-enantiomer. Thus, while (*S*)-lactic acid has found widespread application as a chiral building block and auxiliary for asymmetric synthesis,[2] extension of these methods to obtain products of the opposite enantiomeric series using the commercially available (*R*)-lactic acid is completely uneconomic. Fortunately, diazotisation of alanine in an aqueous medium proceeds with complete retention of absolute configuration,[3] and since the two enantiomers of alanine differ in cost by a factor of only 2–3, diazotisation of (*R*)-alanine **1** is the method of choice to obtain (*R*)-lactic acid **2**. We were therefore surprised to discover that a detailed experimental procedure for this process does not appear to have been published. The optimised method described here produces (*R*)-lactic **2** acid directly in 58% yield on a multi-gram scale and in a purity comparable to the commercially available (*S*)-enantiomer (Scheme 1).

The diazotisation of alanine is one of the oldest reactions in organic chemistry and was first reported in 1850 by Strecker in the same paper in which he first prepared and named the (racemic) amino acid alanine.[4] Once chiral amino acids were obtained from natural sources, their conversion into the corresponding chiral α-hydroxy acids emerged as a useful general method. Reaction with sodium nitrite in dilute acetic, hydrochloric or sulfuric acid is followed by a range of different work-up procedures to separate the product from the inorganic salts present. However, as recently noted by Ley and coworkers in the course of adapting the process to flow chemistry,[5] lactic acid is exceptionally water soluble, so general methods described for a range of hydroxy acids may not be suitable for this particular case. The reports of conventional (i.e. non-flow) lactic acid synthesis from alanine may be divided into those where formation of (*R*)-lactic acid,[6,7] or (*S*)-lactic acid[8,9] has been carried out but the detailed procedure reported is either general or for another amino acid, and those where (*R*)-lactic acid[10,11] or (*S*)-lactic acid[10,12] has been prepared but no detailed procedure is given at all. After considerable experimentation we have been able to combine certain features of these procedures to come up with a convenient and reliable method that has been used to produce over 100 g of the product.

We started by using a literature method,[6] involving treatment of alanine in 1 M sulfuric acid with 6 equiv. of aqueous $NaNO_2$ which claimed a yield of 82–92%. At the end of the reaction the pH was adjusted first to 6 with $NaHCO_3$ then to 3 with HCl before freeze-drying. A sequence of extraction with acetone, evaporation and extraction with Et_2O, drying and evaporation was used.[6,9] In our hands this gave a maximum yield of 37% and the product contained up to 20% of the cyclic dimer. On scaling up the same procedure, various unidentified contaminants were formed and separation of the product from the large amount of inorganic salts became increasingly problematic. Attempted purification by vacuum distillation led to increased formation of cyclic dimer and polymer and replacement of acetone in the procedure by THF was also ineffective. With many of the problems being caused by the excess of inorganic salts, we reduced the amount of $NaNO_2$ to 1.5 equiv. but retained the pH adjustment sequence from before. After this, the solution was reduced in volume by evaporation under reduced pressure with the minimum of heating to minimise formation of dimer and polymer. The residual aqueous phase was then extracted exhaustively with ethyl acetate, following the method reported for norleucine,[7] and also based upon the use of isopropyl acetate in the large scale formation of phenyllactic acid.[13] This was successful in separating the product from the inorganic salts which remained in the aqueous phase, and drying and evaporation of the combined extracts gave the prod-

uct. The use of diethyl ether for this extraction as reported for lactic acid[8,10] and other hydroxy acids[8] was not effective in our hands as it proved to be too weak a solvent to extract the highly polar lactic acid from water.

The final product obtained was a very pale green or yellow liquid, which was suitable to be used directly for further transformations. Two very small impurities visible by ^{1}H NMR spectroscopy were the cyclic dimer, (*R*,*R*)-lactide or 3,6-dimethyl-1,4-dioxane-2,5-dione [^{1}H NMR: δ = 1.62 (d, *J* = 7.0 Hz, 3 H, Me), 5.29 (q, *J* = 7.0 Hz, 1 H, C*H*Me)[14] (<3%) and polylactic acid [^{1}H NMR: δ = 1.55 (d, *J* = 7.0 Hz, 3 H, Me), 5.11 (q, *J* = 7.0 Hz, 1 H, C*H*Me)[15] (<2%) but neither of these were detrimental to its use in further reactions and their concentrations were similar to those present in all commercial samples of lactic acid.

One of the most useful applications of lactic acid as a chiral auxiliary is in the formation of the 1,3-dioxolan-4-one by condensation with pivalaldehyde. This was first described in 1984 by Seebach and coworkers,[16] and the two enantiomeric dioxolanones **3** and **4**, derived respectively from (*R*)- and (*S*)-lactic acid, have been used in the synthesis of various natural products,[17,18] as well as in developing new asymmetric synthetic methodology including their use as chiral acyl anion equivalents.[19] In order to demonstrate the purity of the (*R*)-lactic acid formed by our method, it was converted into the dioxolanone **3** using the literature procedure,[16] and the resulting product showed good agreement in terms of yield, NMR spectra and optical rotation both with literature values,[17] and with the enantiomeric product **4** made using commercially available (*S*)-lactic acid.
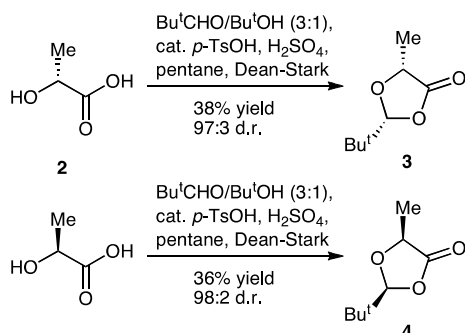
Scheme 2

Pure pivalaldehyde is rather expensive but fortunately we were able to source a mixture of 75% pivalaldehyde/25% *t*-butanol at less than 1/8 of the cost and found that it can be used just as well in the preparation of **3** and **4**. The *t*-butanol does not affect the condensation process and is removed in the aqueous wash.

Experimental

NMR data were recorded in CDCl$_3$ on a Bruker instrument at 400 MHz (^{1}H) and 100 MHz (^{13}C) and are referenced to internal Me$_4$Si. (*R*)-Alanine, (*S*)-lactic acid (85–90% aq. solution) and pivalaldehyde (75% in *t*-butanol) were obtained from Alfa Aesar.

Preparation of (*R*)-lactic acid 2

A solution of sodium nitrite (23.35 g, 338 mmol) in water (200 mL) was added to a stirred solution of (*R*)-alanine **1** (20.0 g, 225 mmol) in 0.5 M H$_2$SO$_4$ (344 mL, 172 mmol) over a 2 h period, with the temperature kept at 0–5 ^{o}C. The reaction mixture was then left to stir and warm up to RT overnight. Solid NaHCO$_3$ was then added to the reaction mixture to achieve pH 6 and then conc. HCl was added until pH 3 was reached. The solution was then concentrated to roughly a fifth of its original volume (120 mL) under reduced pressure and then extracted with ethyl acetate (9 × 100 mL). The combined organic extracts were dried with MgSO$_4$ and the solvent was removed under reduced pressure to give (*R*)-lactic acid as a pale yellow oil (11.83 g, 58%)

^{1}H NMR: δ = 1.49 (d, *J* = 7.0 Hz, 3 H, Me), 4.40 (q, *J* = 7.0 Hz, 1 H, C*H*Me) [Lit.[5] δ = 1.48 (d, *J* = 6.8 Hz, 3 H), 4.38 (q, *J* = 6.8 Hz, 1 H)].

^{13}C NMR: δ = 20.0, 66.6, 179.9 (Lit.[20] δ = 20.5, 66.9, 180.0)

[α]$_D$ = +14.6 (*c* 2.5, 1.5 M NaOH) [Lit.[21] for (*S*)-lactic acid [α]$_D$ = −14.3 (*c* 2.5, 1.5 M NaOH)].

Preparation of (2*R*,5*R*)-2-*t*-butyl-5-methyl-1,3-dioxolan-4-one 3

A solution of (*R*)-lactic acid (8.49 g, 95 mmol), pivalaldehyde (75% in *t*-butanol, 20.3 g, 177 mmol), *p*-toluenesulfonic acid monohydrate (0.005 g, 0.0025 mmol) and conc. H$_2$SO$_4$ (0.25 mL) in pentane (85 mL) was heated under reflux with azeotropic removal of water under Dean-Stark conditions for 24 h. The mixture was then washed with water, dried over MgSO$_4$ and the solvent was removed under reduced pressure without heating to afford the crude product. Kugelrohr distillation at 20 Torr followed by recrystallisation from pentane at −78 ^{o}C with collection of the crystalline product in a cooled filtration funnel gave the product as colourless crystals, which melted to a colourless liquid below RT (5.67 g, 38%)

^{1}H NMR: δ = 0.98 (s, 9H, Bu^t), 1.49 (d, *J* = 6.7 Hz, 3 H, Me), 4.37 (qd, *J* = 6.7, 1.2 Hz, 1 H, C*H*Me), 5.15 (d, *J* = 1.2 Hz, C*H*Bu^t) (Lit.[17] δ = 0.98, 1.48, 4.36, 5.15).

[α]$_D$ = −41.5 (*c* 1.87, CHCl$_3$) [Lit.[17] −44.7 (*c* 1.89, CHCl$_3$].

Preparation of (2*S*,5*S*)-2-*t*-butyl-5-methyl-1,3-dioxolan-4-one 4

The method above but using commercially available (*S*)-lactic acid gave the enantiomeric product **4** (36%)

mp 5–6 ^{o}C (Lit.[16] mp 5 ^{o}C)

^{1}H NMR: δ = 0.98 (s, 9H, Bu^t), 1.48 (d, *J* = 6.6 Hz, 3 H, Me), 4.36 (qd, *J* = 6.6, 1.2 Hz, 1 H, C*H*Me), 5.15 (d, *J* = 1.2 Hz, C*H*Bu^t) (Lit.[16] δ = 0.98, 1.48, 4.45, 5.14).

$[\alpha]_D = +46.8$ (*c* 1.82, CHCl$_3$) [Lit.[16] +44.8 (*c* 1.83, CHCl$_3$)].

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(short title)

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(Graphical abstract)