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CHIRAL SYNTHESIS OF 3,4-DISUBSTITUTED 2-AZETIDINONES FROM (R,R)-(+)-TARTARIC ACID

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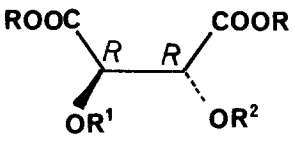
Summary: A novel route is described for the enantioselective synthesis of 2-azetidinones 24 and 25 from (R,R)-(+)-tartaric acid. Monomethylation, monobenzylation of 2 and the use of site specific pig liver esterase (PLE) to produce 6 and 7 are the key steps in the sequence.

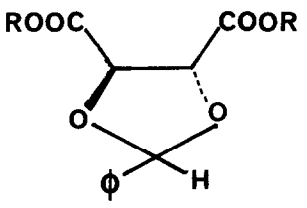
Since 1970 there has been renewed interest in the development of efficient routes for the preparation of bicyclic and monocyclic β-lactams, as they constitute the most important class of antibacterial agents known at the present time.[1-4]

It is now widely accepted that a suitably activated monocyclic β-lactam ring might be the minimum structural entity required for biological activity. We therefore focused our efforts on the construction of 2-azetidinones with nonclassical substitution at positions 3 and 4, using the readily accessible and cheap natural (R,R)-(+)-tartaric acid 1, and we now wish to report the synthesis of 2-azetidinones 24 and 25. The synthetic strategy described here is based on the presence of a C_2 axis of symmetry in (R,R)-(+)-tartaric acid. The symmetry of this system - which has equivalent hydroxyls - should allow (1) convenient preparation of monosubstituted benzyl and methyl ethers 3, 4; (2) chemoselective cleavage of the diesters 3, 4 to the required β-hydroxy-half esters 6, 7; and (3) N-C_4 ring closure of the O-benzylhydroxamates 12, 13 (derived from β-hydroxy acids 6, 7) to the 2-azetidinones 20 and 21.

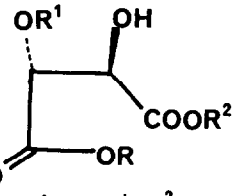
We investigated first the possibility of using reductive opening of the O-benzylidene tartrate 5. Treatment of 5 with sodium cyanoborohydride in acetonitrile in the



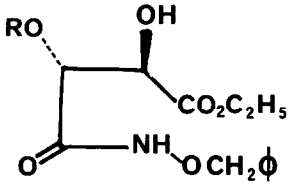
1 R = R^1 = R^2 = H
2 R = C_2H_5 R^1 = R^2 = H
3 R = C_2H_5 R^1 = $CH_2\phi$ R^2 = H
4 R = C_2H_5 R^1 = CH_3 R^2 = H



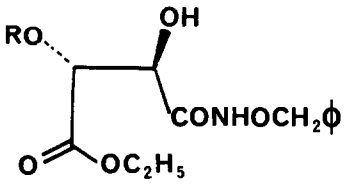
5 R = C_2H_5



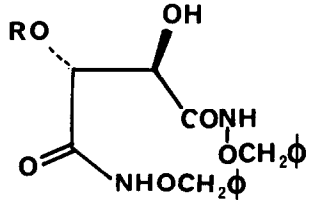
6 R = H R^1 = $CH_2\phi$ R^2 = C_2H_5
7 R = H R^1 = CH_3 R^2 = C_2H_5
8 R = C_2H_5 R^1 = $CH_2\phi$ R^2 = H
9 R = C_2H_5 R^1 = CH_3 R^2 = H
10 R = R^2 = H R^1 = $CH_2\phi$
11 R = R^2 = H R^1 = CH_3



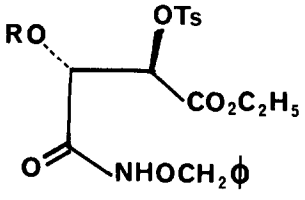
12 R = $CH_2\phi$
13 R = CH_3



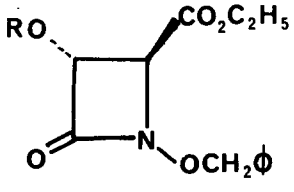
14 R = $CH_2\phi$
15 R = CH_3



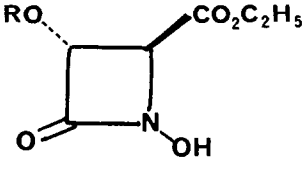
16 R = $CH_2\phi$
17 R = CH_3



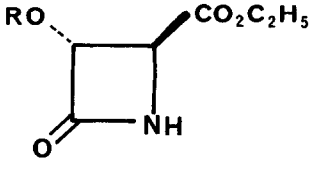
18 R = $CH_2\phi$
19 R = CH_3



20 R = $CH_2\phi$
21 R = CH_3



22 R = $CH_2\phi$
23 R = CH_3



24 R = $CH_2\phi$
25 R = CH_3

in the presence of hydrogen chloride in diethyl ether at room temperature during 1 hr proceeded efficiently and afforded monobenzyl ether 3 in 85% yield. $\{[\alpha]_D^{25}$ + 73°, (c = 1.35, $CHCl_3$)$\}$.

Selective monomethylation of diethyl tartrate was based on the regioselective enhancement of the nucleophilicity of hydroxyl groups in 2 by complexation with tin (II) chloride prior to methylation with diazomethane. Thus reaction of diethyl tartrate in acetonitrile with diazomethane in diethyl ether solution provided the syrupy monomethyl ether 4 in 75% yield. $\{[\alpha]_D^{25}$ + 37°, (c = 1.09, $CHCl_3$)$\}$.

We examined next the monosaponification of 3 and 4, the second crucial step in our synthetic strategy. Treatment of the mono-ethers 3, 4 with 2.5 equivalents of potassium carbonate in dioxane-water (1:1) solution resulted in the formation of the required β-hydroxy-half esters 6, 7. In addition, some undesired monoesters 8, 9 and also dicarboxylic acids 10, 11 were produced. The crude products derived from the chemoselective base hydrolysis of the monoethers 6, 7 were treated with O-benzyl-hydroxylamine hydrochloride and 1-ethyl-3-(dimethylamino)propylcarbodiimide hydrochloride in water-tetrahydrofuran at pH 4.5 at room temperature for 1 hr. Careful chromatography gave fractions containing the monohydroxamates 12, 13 (55-65%), and dihydroxamates 16, 17 (6-10%) as determined by ^{1}H N.M.R. Repeated chromatography on silica gel, did not separate the monohydroxamate half-esters 12, 13 from the undesired positional isomers 14, 15. Due to the lack of selectivity experienced in the chemical hydrolysis of 3 and 4, a chemo-enzymatic approach was considered.

We were curious to know whether or not a cofactor independent hydrolase such as pig liver esterase (PLE)[5,6] could be exploited for the preparation of β-hydroxy half esters 6 and 7.

When the diethyl esters 3 and 4 in 0.1 M phosphate buffer (pH 8.0), were incubated with pig liver esterase (Sigma), half-esters 6 and 7 were exclusively formed, which were transformed to the β-hydroxy hydroxamates 12 and 13 required for β-lactam formation.

It has been firmly established that β-hydroxy-hydroxamates can be efficiently transformed into monocyclic β-lactams either by the Miller methodology[7-9] using diethyl azodicarboxylate-triphenylphosphine (DEAD/TPP) or by mesylation followed by cyclization (MsCl-pyridine/K_2CO_3-acetone).

Cyclization of the hydroxamates 12, 13 to the β-lactams was effected either by the DEAD/TPP reagent or by mesylation followed by treatment with potassium carbonate in acetone. The 2-azetidinones 20, 21 were thus obtained in yields of 20-35%. These and other cyclization procedures tried were inefficient.

Tosylation in pyridine of the monohydroxamates 12 and 13 furnished the sulphonate esters 18 {80%, m.p. 83-84°C, $[\alpha]_D^{25}$ + 20°, (c = 0.87 $CHCl_3$)} and 19 {80%, m.p. 101-102°C, $[\alpha]_D^{25}$ + 12°, (c = 1.03, $CHCl_3$)}. Treatment of tosylates 18 and 19 with K_2CO_3-acetone provided the 2-azetidinones 20 and 21 in almost quantitative yields, $\{[\alpha]_D^{25}$ + 40°, (c = 0.63; $CHCl_3$) and $[\alpha]_D^{25}$ + 37°, (c = 1.6, $CHCl_3$) respectively$\}$.

Selective catalytic hydrogenation of 20 and 21 led to the N-hydroxy β-lactams 22, 23 and $TiCl_3$ mediated reduction of the N-O bonds in 22, 23 provided the target

3,4-disubstituted chiral 2-azetidinones 24, 25 {$[\alpha]_D^{25}$ + 30°, (c = 1.1, $CHCl_3$), $[\alpha]_D^{25}$ + 15°, (c = 1.3, $CHCl_3$) respectively}.

The extension of these findings by systematic chemical modifications of the systems described[10] here should allow the synthesis of methoxylated and non-methoxylated monocyclic and bicyclic enantiomerically pure β-lactams. Studies along these lines are in progress.

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10. The same sequence of reactions was repeated starting from (R,R)-dimethyl tartrate. For all new compounds the spectral data (IR, ^1H, ^{13}C and Mass) were in agreement with the assigned structure. Satisfactory microanalyses were obtained for key products.

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