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Short and efficient Syntheses of (-) -Isocitric acid lactone and (-) -Homoisocitric acid. Conversion of Alkynylsilanes into the corresponding Carboxylic acids

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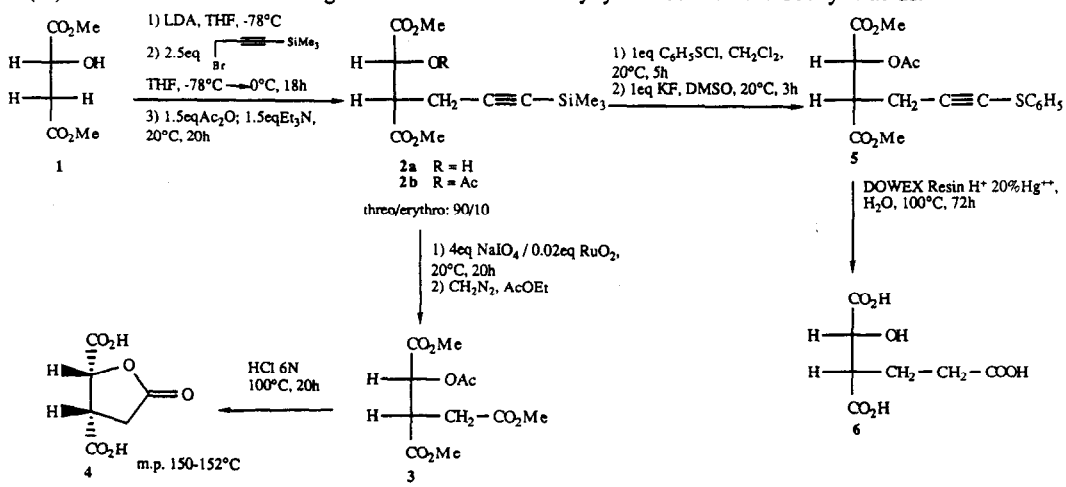
***Keywords**: Isocitric acid lactone; homoisocitric acid; D-malic acid; conversion of alkynylsilane to carboxylic acid*

***Abstract:** We describe a simple synthesis of natural isocitric and homoisocitric acids from a common intermediate 2. A new method of conversion from a silylated triple bond to the carboxylic acid of the same chain length has been formulated.*

The conversion of isocitric acid into α-ketoglutaric acid, catalyzed by isocitric acid dehydrogenase, is a step of the Krebs cycle[1]. The absolute configuration of isocitric acid lactone has been established by a stereoselective synthesis[2]. A stereoselective synthesis of isocitric acid lactone from L-malic acid has been reported[3].

Homoisocitric acid is involved in the α-aminoadipate pathway of lysine biosynthesis in yeasts and certain fungi. The enzymatic conversion of homoisocitric acid into α-ketoadipic acid has been demonstrated[4] and racemic homoisocitric acid was first synthesized by Yamashita[5]. The absolute configuration of the four isomers of homoisocitric acid has been established[6] and only the *threo* D isomer of homoisocitric acid is a substrate for homoisocitric acid dehydrogenase [7]. Here we present a facile, stereoselective synthesis of isocitric acid lactone and homoisocitric acid starting from D-malic acid. This synthesis makes use of a common alkynylsilane **2b**, transformations of which gives isocitric acid lactone and homoisocitric acid. Thus, this synthesis is also a correlation of the stereochemistry of isocitric and homoisocitric acids, and constitutes the first chiral synthesis of (-) -homoisocitric acid utilizing a novel conversion of alkynylsilanes to their carboxylic acids.



The first step of our synthesis was the stereoselective alkylation of the dianion[3] derived from dimethyl ester **1** of D-malic acid with trimethylsilylpropargyl bromide[8,9]. Trimethylsilylpropyne 3-dimethylmalate (*threo* **2a**/*erythro* :90/10) was isolated in 51% yield. After acetylation, the two isomers at C-3 could be separated by silica gel chromatography using hexane/ethyl acetate : 95/5. The major isomer (2R, 3S) has the stereochemistry indicated in formula **2b**, as shown by the correlation with isocitric acid. The silylated triple bond of product **2b** was oxidized by ruthenium tetroxide[10] to the corresponding carboxylic acid with loss of one carbon. Methylation gave isocitric acid trimethylester **3** in 76% yield. Acid hydrolysis of compound **3** afforded isocitric acid lactone **4** in 61% yield. Its properties corresponded to the isomer in the Krebs cycle [α]$_D$ - 60 (c 1.03; H_2O); [lit.[3] : [α]$_D$ + 61.7 (c 0.985 ; H_2O)].

Various methods for the preparation of carboxylic acids from acetylenes without loss of a carbon have been described[11-15]. However we encountered difficulties using these methods for the transformation of compound **2b** to the corresponding acid (yield less than 7 %). Indeed these methods have only been used on aliphatic or aromatic acetylenes devoid of other functional groups. Thus we had to develop an alternative method for the preparation of carboxylic acid from a silylated triple bond. Product **2b** was converted into the acetylenic thioether **5** by addition of phenylsulfenylchloride[16], followed by β-elimination with potassium fluoride in dimethylsulfoxide[17]. The total yield for these two steps was 89%. Acid hydrolysis of thioether **5** was performed in water by using ion exchange resin DOWEX 50 impregnated with 20% mercuric sulfate[18,19]. After filtration of the resin and evaporation of the solvent natural homoisocitric acid **6** was isolated as an oil (yield: 75 %) [α]$_D$ - 10 (c 2.05; acetone) ; [lit.[6] [α]$_D$ - 8 to - 13 (c 1.22 ; acetone)].

Other alkynylsilanes such as phenyl 2-(trimethylsilyl)ethyne, 1-(trimethylsilyl)octyne, 6-hydroxy 1-(trimethylsilyl)hexyne, have been transformed into their corresponding carboxylic acids in an overall yield of 59%, 47% and 31%, respectively, by the same method.

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