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AN ENZYMATIC ENANTIOSELECTIVE ROUTE TO METHYL CARBOXYLATE 2,3 - METHANOHOMOSERINE γ – LACTONE ; A PRECURSOR OF CHIRAL 2,3 - METHANOHOMOSERINE.

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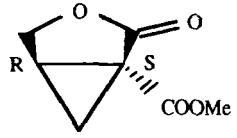
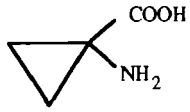
Abstract : Enzymatic hydrolysis of Dimethyl 2 - (tetrahydropyranyl) hydroxymethyl cyclopropane 1,1 - dicarboxylate **6** with an industrial esterase, followed by a deprotection of tetrahydropyranyl ether affords the title compound in 20% yield.

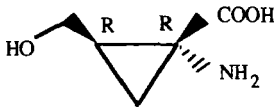
Methyl carboxylate 2,3 - methanohomoserine γ - lactone **1** is an interesting precursor for the synthesis of (2S, 3R) - methanohomoserine **2 a** or **2 b**, a molecule related in structure to aminocyclopropane carboxylic acid (Acc) **3** [1].



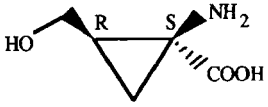
(-) **1**



3



2a



2b

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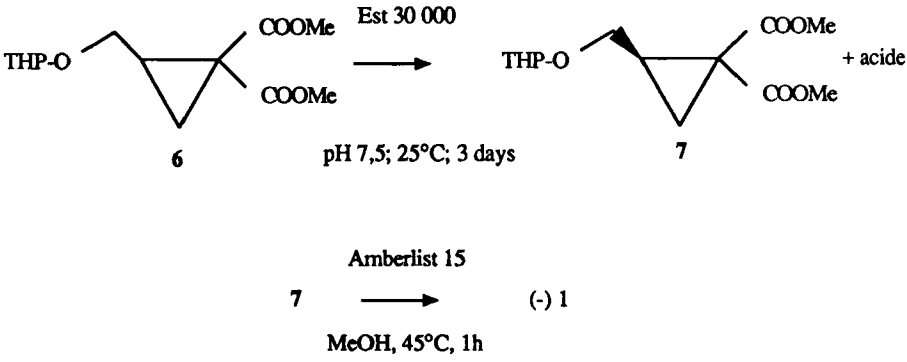
2 can behave as an inhibitor of ACC synthase and therefore induce some physiological effect in plants. It also can behave as a substrate of the enzyme and produce allylic alcohol which can be oxidized into acrolein by some deshydrogenase. Under these circumstances, this molecule would behave as a "proinhibitor" of ACC synthase and also have dramatic effects on plant survival.

We report here an easy synthesis of **1** from commercially available 2,3 - dibromopropanol **4**. After protection of the hydroxyl function by a tetrahydropyranyl residue, the dibromo derivative obtained **5** is submitted to a double malonic synthesis with dimethyl malonate [2]. This leads to **6** in 45% yield.

$$\underset{\mathbf{4}}{HOCH_2\text{-}CHBr\text{-}CH_2Br} \text{ --------> } \underset{\mathbf{5}}{THPOCH_2\text{-}CHBr\text{-}CH_2Br} \text{ --------> } \mathbf{6}$$

This prochiral diester **6**, which possesses two asymetric carbon atoms is submitted to the action of an industrial esterase in a biphasic system until 60% of an ester function is hydrolysed. By classical chemical extractions, an acid fraction and a neutral fraction **7** are obtained. The last one is purified by distillation and submitted to a deprotection in acidic medium with Amberlist 15 for 1 hour at 45°C [3]. The resulting molecule produced has structure **1** as demonstrated by NMR spectroscopy.



This molecule leads by methods already described to aminocyclopropane carboxylic acids **2a** and **2b**.

The overall yield from 2,3 - dibromopropanol to **1** is about 20%.

EXPERIMENTAL SECTION:

2,3 - dibromo 1- (tetrahydropyranyl) hydroxymethyl propane **5**.

2,3 - dibromopropanol (109g, 0.5 mol) was added dropwise to dihydropyran (45g, 0.5 mol) and 1,3mg of PTSA. The mixture was stirred at 30°C for 2 hours. 150ml of methylene chloride was added to the mixture, and the organic phase was washed with potassium hydrogenocarbonate (1M, 3 x 100ml). The organic phase was dried on $MgSO_4$ and evaporated. The crude product was chromatographied from silica gel using cyclohexane as eluent, to give **5** in 75% yield.

Dimethyl 2 - (tetrahydropyranyl) hydroxymethyl cyclopropane 1,1 - dicarboxylate **6**.

The dibromoderivative **5** (66.87g, 0.22 mol), dimethyl malonate (14.62g, 0.11 mol), potassium carbonate (61.12g, 0.44 mol) and 93ml of DMSO were stirred vigourously for 5 days at room temperature.The mixture was then treated with 200ml of water and extracted with ether (3 x 100ml). The organic extracts to which was added 50ml of pentane were then washed with water and dried on $MgSO_4$. Evaporation of the organic phase left a residue which was distilled to give **6** in 45% yield.^{1}H NMR (250 MHz - $CDCl_3$) : 4.59 ppm (bt, 3.2Hz, 1H, O-C<u>H</u>-O) ; 4.53 ppm (bt, 3.2Hz, 1H, O-C<u>H</u>-O) ; 3.8 to 3.46 ppm (2H, CH_2-C<u>H</u>$_2$-O ; 6H, O-C<u>H</u>$_3$; 2H, O-C<u>H</u>$_2$-CH) ; 1.43 to 1.87 ppm (6H THP and 2H cyclopropane).

Enzymatic hydrolysis of **6** : Dimethyl 2 R- (tetrahydropyranyl) hydroxymethyl cyclopropane 1,1 - dicarboxylate

In a typical experiment, 2.4g of esterase 30 000 were suspended in 15ml of 0.1M phosphate buffer pH 7.5 and added to a mixture of 5g (18 mmol) of diester **6** in 5ml of cyclohexane and 15ml of buffer. The heterogeneous mixture was stirred vigourously and pH of the medium was maintained constant by addition of 1N NaOH solution with a pHstat. The reaction was performed at 25°C and stopped by addition of hydrochloric acid (6M) until pH 4. The aqueous solution was added to 150ml of ethyl acetate and stirred. The organic phase was dried by slow addition of $MgSO_4$, filtered then evaporated. 50ml of ether were then added to the crude product and the organic phase was washed with a potassium hydrogenocarbonate solution (1M, 4 x 25ml). It was dried on Na_2SO_4 and the solvent was evaporated. The residue was distilled by a Kugelrohr apparatus to give **7** in 85% yield. $[\alpha]_D$ = - 25.8° ± 0.2° (c = 10, $CHCl_3$).

Deprotection of 7 : Methyl carboxylate 2,3 - methanohomoserine γ - lactone 1.

To 7 (500mg, 1.8 mmol) dissolved in methanol (10ml), amberlist H-15 (55mg, 0.185 meq) was added and the mixture was heated at 45°C for 1 hour. The resin was then filtered off and the solvent evaporated to yield 1 as an oil. Crystallisation and recrystallisation of 1 from ether at - 78°C gave white plates (170mg); mp 45.8°C, $[\alpha]_D$ = -158 ± 0,2 (c = 0.97, CH_2Cl_2) ; ref. litt. [1b] (mp = 46-47°C, $[\alpha]_D$ = - 163 ±0.2°).^{1}H NMR (250 MHz, $CDCl_3$) : 4.38 (dd ; 9.5Hz, 4.7Hz ; 1H; C<u>H</u>-O) ; 4.20 (d ; 9.5Hz; 1H ; C<u>H</u>-O) ; 3.82 (s ; 3H ; O-C<u>H</u>$_3$) ; 2.76 (m ; 1H ; CH_2-C<u>H</u>-CH_2) ; 2.1 (dd ; 8.15Hz, 4.8Hz ; 1H; CH-C<u>H</u>$_2$-C) ; 1.42 ; (t5.16Hz ; 1H ; CH-C<u>H</u>$_2$-C).

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