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ENANTIOSELECTIVE SYNTHESIS OF THE METHYLENECYCLOPROPANE DERIVATIVE RELATED TO HYPOGLYCINE, STARTING FROM MALIC ACID

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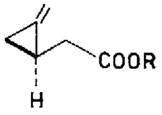
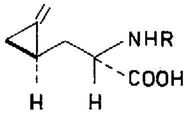
Abstract: The methylenecyclopropane derivative 11 was synthesized from (S) malic acid *via* epoxide 5 and β-trimethylsilyl sulfone 6.

(R) (Methylenecyclopropyl)acetyl-CoA 1 is the active metabolite of amino acids hypoglycines A and B (3 and 4), which have first been isolated from Jamaican ackee tree and which attracted a great deal of attention owing to their pronounced hypoglycemic effect in animals[1,2]. Recently, the key intermediate for preparation of thioester 1, methylenecyclopropylacetic acid 2 has been synthesized in the racemic form[3]. We now report an enantioselective synthesis of (S) 2-methylenecyclopropaneethanol 11 and its 3,5-dinitrobenzoate 12, starting from (S) malic acid. A method for efficient oxidation of alcohol 11 to acid 2 is known[3c].



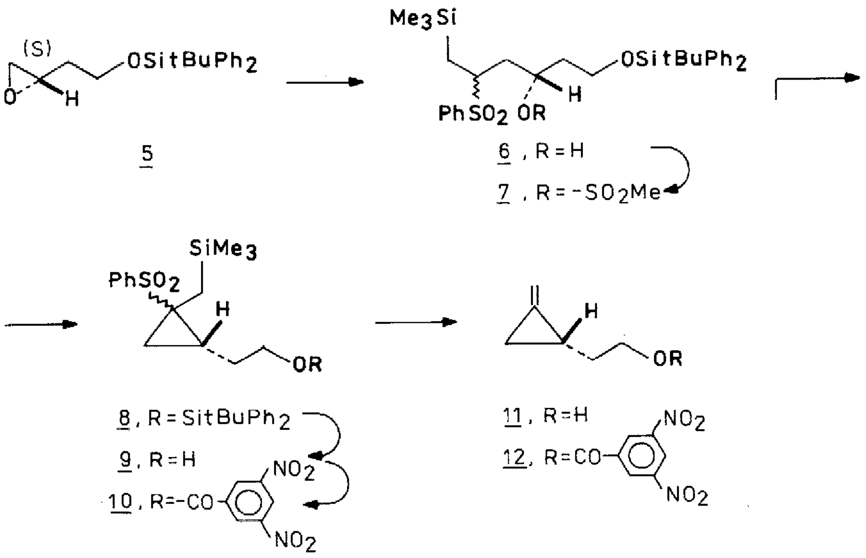
1, R=SCoA
2, R=H



3, R=H
4, R=γ-glutaminyl

Epoxide 5 easily accessible[4] from (S) malic acid, was treated with the anion derived from 2-trimethylsilylethyl phenyl sulfone[5,6] and n-butyllithium. Adduct 6 (87% yield, diastereomers in a 1:3 ratio) was esterified with methanesulfonyl chloride in pyridine to give mesylate 7 (97% yield). Intramolecular cyclization[6] of compound 7 by means of lithium diisopropylamide (1.5 molequivalent) in tetrahydrofuran (THF) at -78°C afforded the cyclopropane derivative 8 in a 89% yield.

The reaction of silyl sulfone 8 with tetra-n-butylammonium fluoride[7] (TBAF) trihydrate in THF at room temperature resulted in alcohol 9 (97% yield). Upon the use of anhyd. TBAF in THF at reflux temperature both silyl groups were, however, removed and the required methylenecyclopropaneethanol 11 was formed (volatile liquid, isolated in a 41% yield) together with t-butyldiphenylfluorosilane (93% yield). Alternatively, alcohol 9 was esterified with 3,5-dinitrobenzoyl chloride, and the derivative 10 (86% yield, m. p. 134-137°) was treated with anhyd. TBAF in THF under reflux. Dinitrobenzoate 12 was obtained in a 59% yield { 37% yield from epoxide 5, m. p. 83-86.5°C, $[\alpha]_D^{25}$=+3.09° ($CHCl_3$)}. Since malic acid is available in both enantiomeric forms, the presented method offers a simple approach to both enantiomers of methylenecyclopropaneacetic acid (2)[8,9].



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8. All new compounds and mixtures of epimeric compounds gave satisfactory spectral (^1H and ^{13}C n. m. r., i. r.), analytical and/or high resolution mass spectral data.
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