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STEREOSELECTIVE SYNTHESIS OF β-HYDROXY-α-METHYLCARBOXYLIC ACID THIOL ESTERS VIA VINYLOXYBORANES

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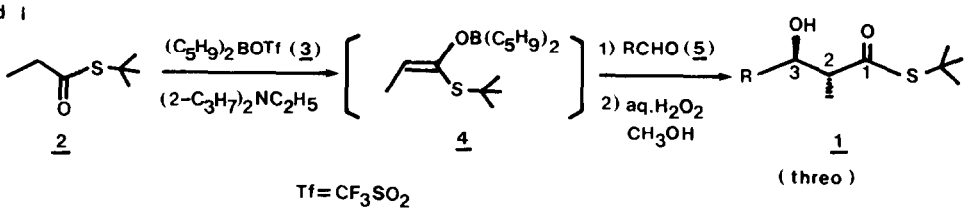
Both threo- and erythro-β-hydroxy-α-methylcarboxylic acid thiol esters are stereoselectively synthesized through an aldol-type condensation of vinyloxyboranes derived formally from S-tert-butyl propanethioate.

The basic carbon skeletons of many macrolide antibiotics are biosynthesized through a series of condensations of acetyl- and propionyl-CoA units and are rich in chirality.[1] Methods to achieve stereoselective construction of the β-hydroxy-α-methylcarbonyl system,[2] therefore, are highly useful for, and sometimes essential to, the synthesis of these antibiotics. We have recently demonstrated that Z- and E-vinyloxyboranes can be prepared stereoselectively and that the Z- and E-isomers react with aldehydes to yield mainly the erythro and threo aldol products, respectively.[3] We have extended this work and wish to describe in this note an efficient and stereoselective aldol-type condensation of vinyloxyboranes derived formally from thiol esters.

Close examination of Mukaiyama's procedures[4] for the generation of vinyloxyboranes and judicial choice of several reaction parameters has led to the following preparations of β-hydroxy-α-methylcarboxylic acid thiol esters, method I for the threo isomers and method II for the erythro series.

Method I

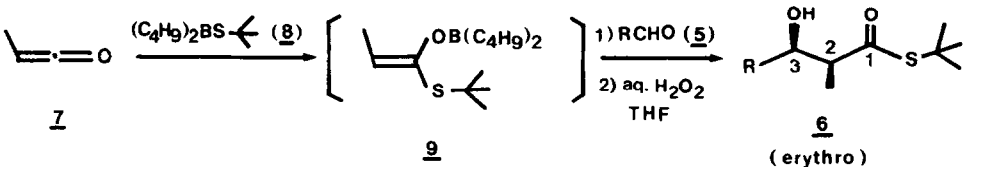


2 4 1 (threo)

Tf = CF_3SO_2

The preparation of the threo thiol esters (1) was accomplished by reaction of S-tert-butyl propanethioate (2) with dicyclopentylboron trifluoromethanesulfonate (dicyclopentylborinic trifluoromethanesulfonic anhydride) (3)[5] and N,N-diisopropylethylamine to give the intermediate vinyloxyborane (4)[6] which was condensed with aldehydes (5), followed by aqueous H_2O_2 mediated hydrolysis (see Table 1).

Method II



7 9 6 (erythro)

The erythro thiol esters (6) were prepared by reaction of methylketene (7) with a mixture of tert-butyl di-n-butylthioborinate (8) and an aldehyde (5), followed by aqueous H_2O_2 mediated hydrolysis (see Table 1). The stereoselective condensation reaction in this case likely proceeds via the E-vinyloxyborane (9).[7] The stereochemical assignments of 1 and 6 are based on the well-established observation that the coupling constants ($J_{2,3}$) between the two protons at C(2) and C(3) of threo isomers are normally larger than those of the corresponding erythro isomers.[2a]

Table 1. Stereoselective β-hydroxy-α-methylcarboxylic acid thiol ester formation.

Method	Aldehyde	threo(1)/erythro(6) ratio	Combined Yield
I	5a R=C_6H_5	>95:5[a]	83
	5b R=2-C_3H_7	>95:5[b]	79
	5c R=$CH_2CH_2C_6H_5$	>95:5[b]	68
II	5a	7:93[a]	78
	5b	5:>95[b]	75
	5c	5:>95[b]	65

[a]The ratio was determined by NMR spectroscopy. $J_{2,3}$(Hz): 1a, 7.9; 1b, 5.8; 1c,~6; 6a, 4.3; 6b, 3.7; 6c, 3.5.

[b]Each isomer was isolated by ptlc.

Two comments are in order. 1) The behavior of vinyloxyboranes sharply contrasts with that of the lithium enolate (generated from 2 with lithium diisopropylamide at -78°C) which reacted virtually non-stereoselectively with aldehyde 5a. 2) The stereo-isomer ratio of the product obtained by Method I is extremely sensitive to the alkyl substituents of both the boron reagent and base, and use of the combination specified above is essential in order to attain satisfactory results. The aldol condensations described herein have three definite advantages: the high degree of stereoselectivity, the mildness of the conditions and the flexibility of selective

transformations of thiol esters into other functional groups. We intend to apply these methods to the synthesis of complex natural products, such as the macrolide antibiotics where the stereoselective incorporation of a propionate unit is required.

Procedure for 1:[8] To a cold (-78°) suspension of 3 (0.65 mmole) in ether (1 ml) was added diisopropylethylamine (0.65 mmole) and a solution of 2 (0.65 mmole) in ether (1 ml). The mixture was stirred at r.t. for 1 h, then 5a (0.50 mmole) in ether (1 ml) was added slowly over 10 min, and finally stirred at r.t. for 1.5 h. The mixture was hydrolyzed with a solution of pH 7 phosphate buffer (4 ml), methanol (5 ml), and aqueous 30% H_2O_2 (1 ml) (2 h at r.t.) to give after ptlc (silica gel) a mixture of 1a and 6a (98:2) in 83% yield.

Procedure for 6:[8] A solution of methylketene (7) in THF was prepared by the method of Ward[9] and redistilled (-25°C/1-2 mm Hg). A mixture of 8 (0.68 mmole) and 5a (0.57 mmole) in THF (1 ml) was stirred at r.t. for 1 h, cooled to -25°, and then a freshly prepared cold (-78°) solution of 7 (~1.0 mmole) in THF was added dropwise. The mixture was stirred at r.t. for 2 h and then hydrolyzed with a solution of 30% H_2O_2 (0.4 ml) and THF (2 ml) in water (2 ml) (16 h at r.t.) to give after ptlc (silica gel) a mixture of 1a and 6a (7:93) in 78% yield.

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References and Footnotes

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5. Dicyclopentylboron triflate (3) was prepared by stirring a mixture of tricyclopentylborane and trifluoromethanesulfonic acid (equivalent amounts) at r.t. overnight, followed by distillation (bp. 78.0-79.5°/1 mm).

6. The structure of 4 is tentatively assigned as Z and one isomer is predominantly formed as shown by NMR.

7. In this case the intermediate vinyloxyborane (9) could not be examined by NMR spectroscopy because the pretreatment of 8 with an aldehyde (5) prior to the addition of 7 was necessary to achieve the high degree of stereoselectivity in this reaction. When 8 was treated with 7 in the absence of 5 a complex mixture of vinyloxyboranes was observed by NMR and gave a mixture of condensation products 1 and 6 (>1.5:1 respectively, <40% yield) and other unidentified products.

8. The procedures essentially follow those of Mukaiyama and coworkers.[4]

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