Tetrahedron Letters No. 41, pp 3937 - 3940.

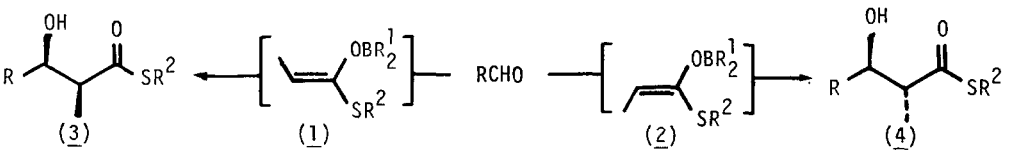
0040-4039/79/1008-3937$02.00/0

USE OF THE E-VINYLOXYBORANE DERIVED FROM S-PHENYL PROPANETHIOATE FOR STEREOSPECIFIC ALDOL-TYPE CONDENSATION. A SIMPLIFIED SYNTHESIS OF THE PRELOG-DJERASSI LACTONIC ACID

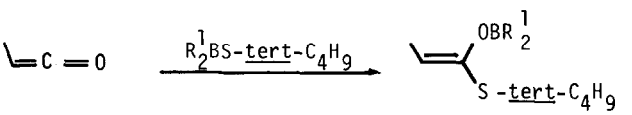
Masahiro Hirama, David S. Garvey, Linda D.-L. Lu, and Satoru Masamune*
Department of Chemistry, Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

The E-vinyloxyborane (5), prepared from S-phenyl propanethioate, 9-BBN triflate, and diisopropylethylamine, reacts stereoselectively with aldehydes to provide erythro-β-hydroxy-α-methylcarboxylic acid thiol esters. This reaction has been applied to a synthesis of Prelog-Djerassi lactonic acid (6).

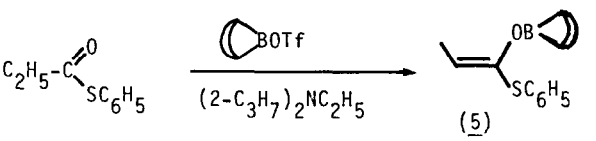
A recent note has clearly demonstrated that the E- and Z-vinyloxyboranes (1) and (2) formally derived from S-tert-butyl propanethioate condense with an aldehyde to provide erythro- and threo-β-hydroxy-α-methylcarboxylic acid thiol esters (3 and 4), respectively.[1] Both the stereoselection and yield of this reaction are exceedingly high. However, the preparation of the E-isomer (1) requires the use of reactive (monomeric) methylketene (equation 1) and the generation of this gaseous reagent has been found to be operationally rather inconvenient. This technical problem has now been obviated in a convenient manner. Of several propanethioates examined, the benzenethiol (but not alkanethiol[2]) ester apparently forms the E-vinyloxyborane 5 exclusively with 9-borabicyclo[3.3.1]non-9-yl trifluoromethanesulfonate (9-BBN triflate) and diisopropylethylamine (equation 2) in a manner similar to that observed earlier for cyclohexyl ethyl ketone.[3] This note



(3) (1) (2) (4)



equation 1

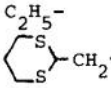


(5)

equation 2

outlines the use of 5, (a) for the preparation of several simple thiol esters of structure 3 (R^2=C_6H_5) and (b) for a practical, simplified synthesis of the Prelog-Djerassi lactonic acid (6),[4] an important intermediate which was earlier utilized in the synthesis of methymycin (7),[5] and since then has attracted synthetic interest of several laboratories.[6]

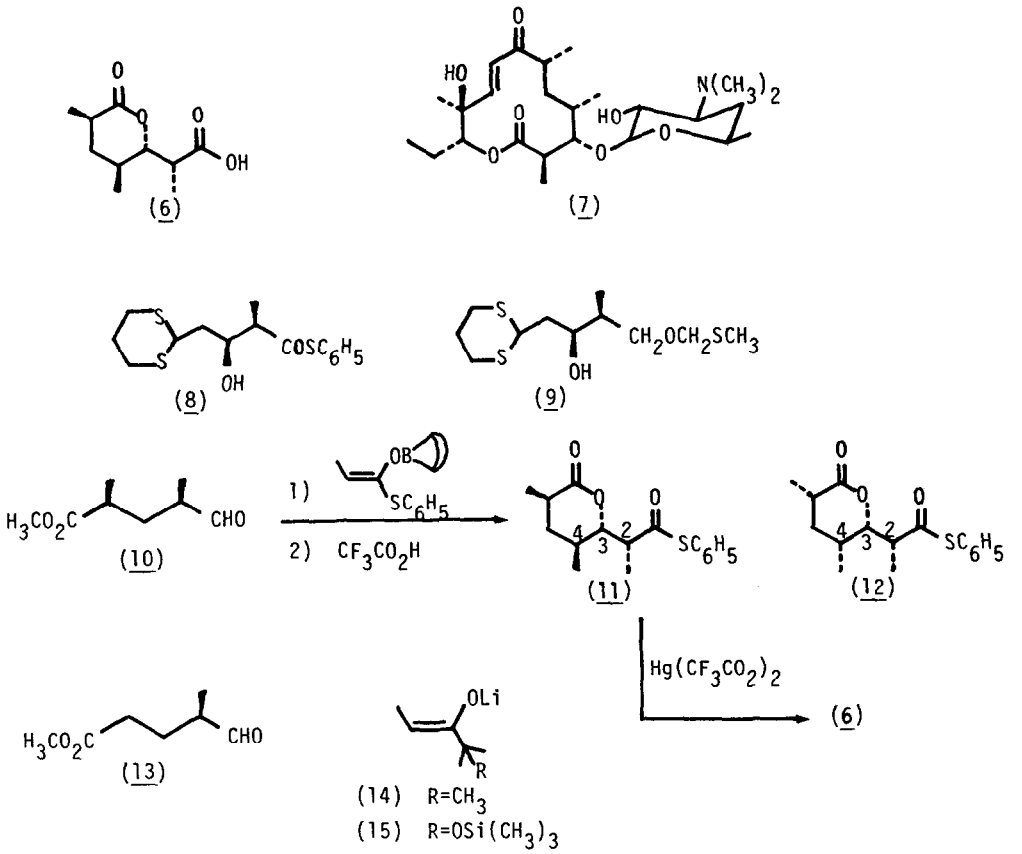
The following procedure for the synthesis of 3 (R^2=C_6H_5) is representative and has been applied to a variety of aldehydes. To a stirred suspension of 9-BBN triflate (1.5 mmol) in cold (0°) ether (3 ml) under nitrogen was added over 5 min a solution of S-phenyl propanethioate (1.5 mmol) and diisopropylethylamine (1.5 mmol) in ice-cooled ether (3 ml). The resulting pale-yellow mixture was stirred at 25°C for 15 min, an aldehyde (1 mmol) added, and stirring continued for an additional 30 min. The mixture was hydrolyzed with a solution of pH 7 phosphate buffer (10.5 ml), methanol (12 ml), and aqueous 30% H_2O_2 (1.8 ml) (30 min at r.t.). Removal of most of the organic solvents, extraction with ether, and finally preparative TLC provided the results summarized below. The stereochemical assignment of the final products, (3) and (4) (R^2=C_6H_5), is

entry	Starting Material	Products	
	Aldehyde RCHO R	erythro (3)/threo (4) ratio (R=C_6H_5)	Combined yield (%)
1	C_6H_5-	97:3	90
2	2-C_3H_7-	97:3	79
3	C_6H_5-CH_2CH_2-	>97:<3	75
4	cyclo-C_6H_{11}-	>97:<3	77
5	C_2H_5-	>97:<3	75
6		exclusively 8	72[a]

[a] $(C_4H_9)_4NF$ was used to liberate the β-hydroxy functionality.

based on the spectral comparison with the corresponding S-tert-butyl propanethioates prepared earlier[1] and compound 8 appearing in entry 6 has been converted in a standard fashion to a known diol derivative (9) with established stereochemistry.[7] The superb stereoselection and operational simplicity of the present method are evident, and the synthetic process required to construct two chiral centers of a β-hydroxy-α-methylcarboxylic acid moiety often found in macrolide natural products is now substantially simplified. Indeed, the recorded synthesis of 9 involved several steps, and also the following example is revealing.

A simplified synthesis of the Prelog-Djerassi lactonic acid (6). Although three syntheses of this lactonic acid (6) have appeared recently,[5,6] all of them are rather laborious and involve ten steps or more. The following scheme that has been examined provides a means of preparing 6 expediently and in reasonably abundant quantities. Methanolysis of meso-2,4-dimethylglutaric acid anhydride afforded the corresponding half methyl ester which was in turn converted to the aldehydic ester 10 in a standard fashion.[8,9] Reaction of 10 with 5 (1.5 equiv) at r.t. for 1.5 h was performed in the manner described above, and the resulting δ-hydroxyesters[10] were treated with trifluoroacetic acid in methylene chloride to afford, in 56% overall yield, only two (rather than four[11]) lactonic acid thiol esters (11) and (12), which were readily separated through SiO_2 column



chromatography[12] (see below for the stereochemical assignment of 12 and the ratio of the two products, 11 and 12).[13] The thiol ester hydrolysis of 11 with $Hg(CF_3CO_2)_2$ provided 6, mp 116-117°, in 72% yield after recrystallization.

The reaction course of 5 with aldehydes amply demonstrated above, almost secures the relative stereochemistry at the 2 and 3 positions of compounds 11 and 12 as indicated, and therefore it is safely assumed that these compounds are stereochemically isomeric at the 3 and 4 positions. The ratio of 11 and 12 is 55:45 and contrasts to that (26:74) reported earlier for a similar reaction of 13 with the lithium enolate 14.[14] The fact that 11 predominates in the present case, although only slightly, is unexpected and noteworthy in that the condensation proceeds formally in violation of the Cram rule,[14,15] an observation that provides a clue for the elucidation of possible factors influencing the stereochemical course of reaction. Data now accumulating in these laboratories suggest that the conformation of the reacting aldehyde plays a crucial role. While the problem concerning the 2,3-stereochemistry of the aldol-type products has been largely solved, the stereochemical control of the 3,4-position is currently a central issue of our concern.

Acknowledgments

This work was supported by the Sloan Basic Research Funds (M.I.T.) and National Institutes of Health Grant 1R01 AI15403.

References and Notes

1. M. Hirama and S. Masamune, Tetrahedron Lett., 2225 (1979). Also see T. Mukaiyama and T. Inoue, Chem. Lett., 559 (1976).
2. All attempts to prepare 3 (R^2=CH_3, C_2H_5, 2-C_3H_7 and tert-C_4H_9) stereoselectively and in reasonable yields have failed.
3. D. E. Van Horn and S. Masamune, Tetrahedron Lett., 2229 (1979).
4. R. Anliker, D. Dvornik, K. Gubler, H. Heusser, and V. Prelog, Helv. Chim. Acta, 39, 1785 (1956); C. Djerassi and J. A. Zderic, J. Am. Chem. Soc., 78, 6390 (1956).
5. S. Masamune, C. U. Kim, K. E. Wilson, G. O. Spessard, P. E. Georghiou, and G. S. Bates, J. Am. Chem. Soc., 97, 3512 (1975).
6. J. D. White and Y. Fukuyama, J. Am. Chem. Soc., 101, 228 (1979); G. Stork and V. Nair, ibid., 101, 1314 (1979).
7. E. J. Corey and M. G. Bock, Tetrahedron Lett., 2643 (1975). We thank Professor Corey for providing us with an NMR spectrum of 9.
8. S. Masamune, Aldrichimica Acta, 11, No. 2, 23 (1978).
9. P. A. Bartlett and J. Myerson, J. Org. Chem., 44, 1625 (1979).
10. The δ-hydroxyester corresponding to 11 can be utilized directly (rather than via 6) for further synthetic transformations leading to 7 and potentially other macrolides. Thus, use of this aldol-type reaction would further simplify the synthesis of these antibiotics.
11. Note that this condensation creates three (rather than two) chiral centers in the products.
12. Solvent, pentane/ether (1:1); R_f, 0.20 for 11 and 0.46 for 12.
13. The reaction of 10 with the lithium enolate 15 has already been described. See reference 8.
14. C. T. Buse and C. H. Heathcock, J. Am. Chem. Soc., 99, 8109 (1977).
15. D. J. Cram and F. A. Abd El Hafez, J. Am. Chem. Soc., 74, 5828 (1952); H. B. Kagan and J. C. Fiand in "Topics in Stereochemistry", Ed., E. L. Eliel and N. L. Allinger, Vol. 10, John Wiley and Sons, New York, N.Y., 1978, pp. 175-285.

(Received in USA 9 July 1979)