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THE HIGHLY STEREOSELECTIVE SYNTHESIS OF ETHYL GERANATE

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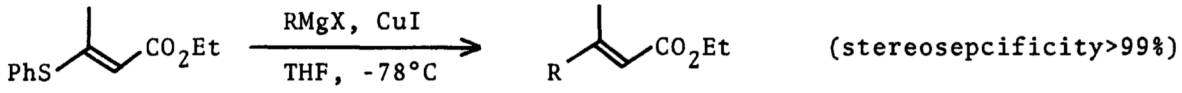
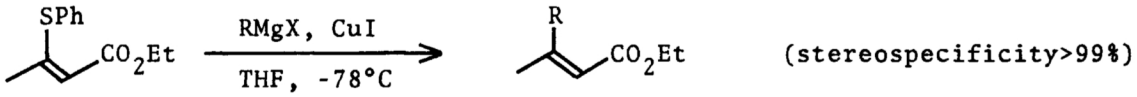
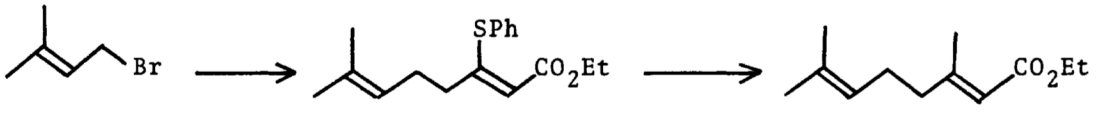
The new method for the stereospecific synthesis of trisubstituted olefin was successfully applied to a highly stereoselective synthesis of 1,5-diene unit, demonstrating the preparation of ethyl geranate [3] starting from 3-methyl-2-butenyl bromide [1].

In the previous paper[1] dealing with the reaction of β-phenylthio-α,β-ethylenic esters with Grignard reagents in the presence of cuprous iodide, it was shown that phenylthio group was replaced by an alkyl group with complete stereospecificity.





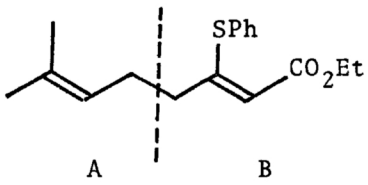
We describe in this communication the highly stereoselective synthesis of ethyl geranate [3] from 3-methyl-2-butenyl bromide [1] as shown in the following scheme.



1 2 3

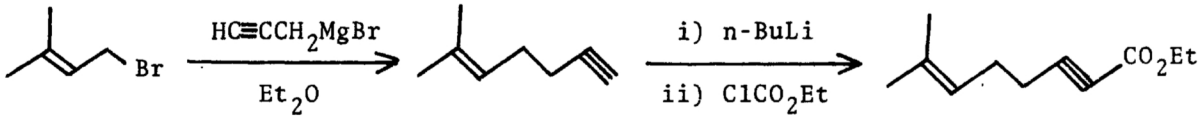
This stereoselective synthesis of ethyl geranate requires two synthetic processes: (1) the stereospecific or stereoselective preparation of Z-β-phenylthio-α,β-ethylenic ester 2 from 3-methyl-2-butenyl bromide [1], and (2) the stereospecific alkylation of 2 to ethyl geranate.

The attempts to prepare the key intermediate 2 by the combination of the two



units, A and B, of 2 were unsuccessful due to the lack of stereospecificity and/or regiospecificity.

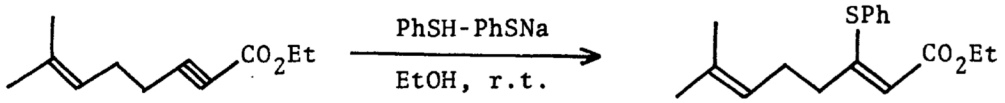
In the base catalyzed addition of a thiol to an α,β-acetylenic ester it has been known that the Z-isomer of β-phenylthio-α,β-ethylenic ester is formed predominantly when protic solvents are employed. Consequently the preparation of 2 via α,β-acetylenic ester 5 was examined according to the following method; reaction of 3-methyl-2-butenyl bromide [1] with propargylmagnesium bromide[2] in ether afforded enyne 4 accompanying a small amount of allenic isomer. A tetrahydrofuran solution of 4 was treated with calculated amount of n-butyllithium at 0°C, followed by the addition of two equivalents of ethyl chloroformate at -78°C. After the reaction



1 4 5

mixture was stirred overnight at room temperature, α,β-acetylenic ester 5 was obtained in 66% yield based on 3-methyl-2-butenyl bromide [1].

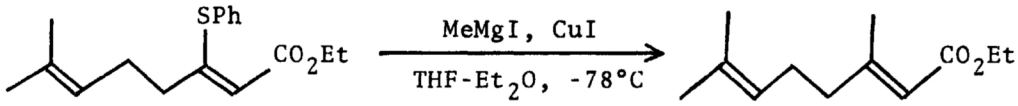
The desired Z-isomer of β-phenylthio-α,β-ethylenic ester 2[3] was produced exclusively in 88% yield, as expected, on treating 5 with sodium thiophenolate in ethanol at room temperature for 4 hr. The Z configuration of 2 was determined by the chemical shift (δ 5.90) of the olefinic proton α to the ethoxycarbonyl group, since we have preliminary observed that α olefinic protons of Z-β-phenylthio-α,β-



5 2

ethylenic esters absorb around δ 5.7∿5.9, and those of E-isomers around δ 5.1∿5.3, respectively.

The stereospecific conversion of 2 to ethyl geranate [3] was accomplished in 99% yield by the coupled use of methylmagnesium iodide and cuprous iodide.[1] The structure of 3 was confirmed by spectroscopic (i.r., n.m.r.) and gas chromatographic comparison with the authentic sample.[4]



2 3

This method provides a general method for the stereoselective synthesis of trans substituted 1,5-diene units[5] which represent structural moiety found in many naturally occurring products (e.g., farnesol and juvenile hormones). Further noteworthy feature of this sequence is that a wide variety of alkyl side chains could be introduced by the selective use of various readily available Grignard reagents. Investigations are continuing on the syntheses of cecropia juvenile hormones and related compounds.

REFERENCES and NOTES

1) S. Kobayashi, H. Takei, and T. Mukaiyama, Chem. Lett., 1097 (1973).

2) F. Sondheimer, R. Wolovsky, and D. A. Ben-Efraim, J. Amer. Chem. Soc., 83, 1686 (1961).

3) n.m.r.; δ 1.38 (t, J = 7Hz, 3H), δ 1.44 (s, 3H), δ 1.60 (s, 3H), δ 1.9∿2.2 (bs, 4H), δ 4.25 (q, J = 7Hz, 2H), δ 4.7∿5.1 (m, 1H), δ 5.90 (s, 1H), δ 7.18∿7.86 (m, 5H).

4) Authentic sample 3 was directly prepared by the reaction of ethyl E-3-phenylthio-2-butenoate and 4-methyl-3-pentenylmagnesium bromide in the presence of cuprous iodide.

5) Corey and Siddall have independently reported[6] a highly stereoselective cis addition of an organocopper reagent to an α,β-acetylenic ester. Our method described here is formally an overall trans addition of a Grignard reagent to an α,β-acetylenic ester. Therefore the preparation of various 1,5-diene units becomes realizable by the proper choice of these types of methods.

6) E. J. Corey and J. A. Katzenellenbogen, J. Amer. Chem. Soc., 91, 1851 (1969), J. B. Siddall, M. Biskup, and J. H. Fried, ibid., 91, 1853 (1969).

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