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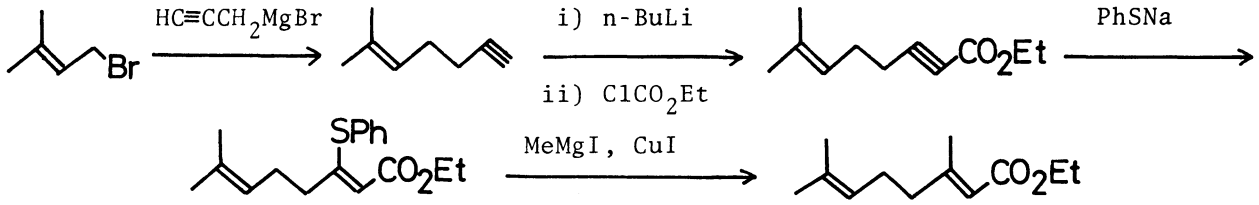
THE STEREOSPECIFIC PREPARATION OF METHYL FARNESOATE AND SYNTHETIC PRECURSORS OF C_{18}- AND C_{17} JUVENILE HORMONES

Susumu KOBAYASHI* and Teruaki MUKAIYAMA
Department of Chemistry, Faculty of Science, The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113

The new method for the stereospecific preparation of 1,5-diene units was successfully applied to the syntheses of methyl farnesoate and the synthetic precursors of C_{18}- and C_{17} juvenile hormones, 15 and 20.

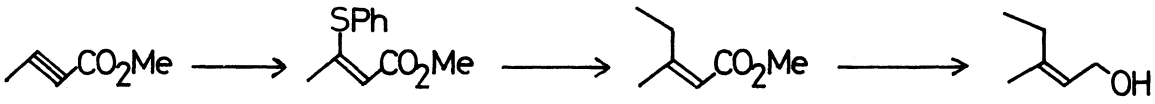
We have recently reported a stereospecific preparation of ethyl geranate from 3-methyl-2-butenyl bromide according to the following scheme.[1] The key steps of this sequence are (1) the trans addition of benzenethiol to the α,β-acetylenic



ester,[2] and (2) the stereospecific replacement of the phenylthio group by methyl group.[3] This method, formally an overall trans addition of methylmagnesium iodide to the α,β-acetylenic ester, is expected to provide a general route to the stereospecific synthesis of trans 1,5-diene units which represent structural moiety found in many naturally occurring products. In this communication we wish to describe the stereospecific preparation of synthetic precursors of C_{18}- and C_{17} juvenile hormones, 15 and 20, and methyl farnesoate by the repetitive application of the above sequence.

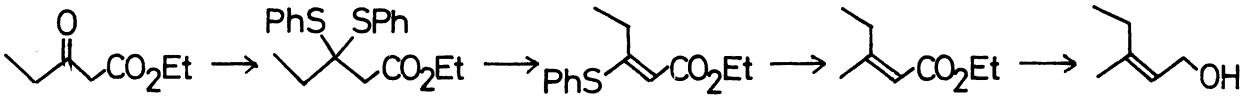
When methyl 2-butynoate was allowed to react with sodium benzenethiolate in methanol-water (4 : 1), the trans addition took place predominantly and methyl (Z)-3-phenylthio-2-butenoate, 1,[4] (bp 128 ∿ 130°C/3mmHg), was isolated in 77%

yield. The stereospecific conversion of 1 to the ester 2 was carried in 73% yield by the coupled use of ethylmagnesium bromide and cuprous iodide in tetrahydrofuran



1 2 3

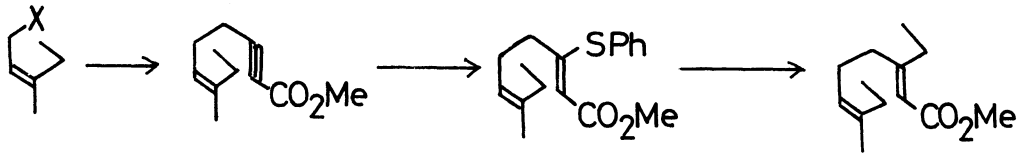
at -78°C. Aluminum hydride reduction of 2 in ether afforded the allylic alcohol 3, bp 79 ∿ 81°C/40mmHg, in 65% yield (purity > 99%). By the separate route, the same alcohol 3 was prepared stereospecifically by the following sequence consisting of (1) thioacetalization of ethyl 3-oxopentanoate, (2) base-catalyzed elimination of



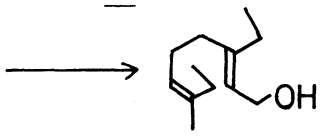
4 5 6 3

benzenethiol from the thioacetal 4, (3) methylation of 5 with methylmagnesium bromide and cuprous iodide, and (4) aluminum hydride reduction of the ester 6.

The homologation of the C_6-alcohol 3 to the C_{12}-alcohol 12 was achieved by the same procedure described in the preparation of ethyl geranate. The alcohol 3 was converted to the bromide 7, which was in turn treated with propargylmagnesium bromide in ether at 0°C to give the terminal acetylene 8 accompanying a small amount of the allenic isomer. A tetrahydrofuran solution of 8 was injected with calculated amount of n-butyllithium at 0°C, followed by the addition of methyl



9 10 11



12

3 X = OH

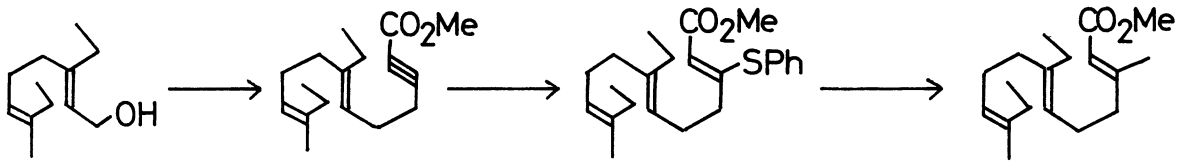
7 X = Br

8 X = $CH_2C{\equiv}CH$

chloroformate at -78°C. After the reaction mixture was stirred at that temperature for 1 hr and at room temperature for 3 hr, the acetylenic ester 9 was obtained in 50% yield based on the alcohol 3. The vinyl sulfide 10,[4] produced in 78% yield from the reaction of 9 with benzenethiol under basic condition, was alkylated

stereospecifically by ethylmagnesium bromide and cuprous iodide to form the dienic ester 11, bp 80 ∿ 81°C/0.4mmHg, in 90% yield (purity 97%), and further converted to the C_{12}-alcohol 12 quantitatively (purity 94%) by the treatment with aluminum hydride in ether at room temperature.

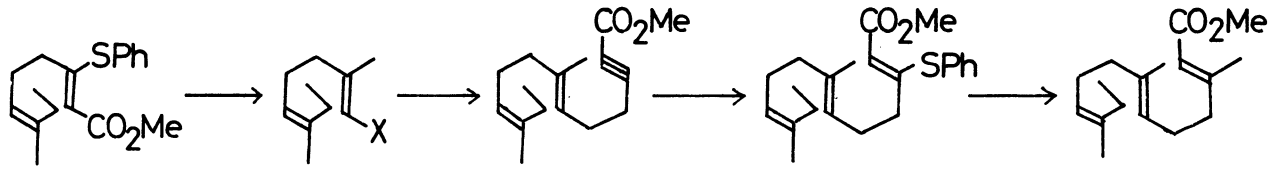
A repetitive application of the above mentioned procedure resulted in the formation of the acetylenic ester 13 in 57% overall yield from the C_{12}-alcohol 12, and gave the vinyl sulfide 14[4] in 75% yield on treating of 13 with benzenethiol. The stereospecific methylation of 14 was effected by the reaction with the mixture



12 13 14 15

of methylmagnesium bromide and cuprous iodide in tetrahydrofuran at -78°C for 2 hr to give 87% yield of the desired trienic ester 15, synthetic precursor of C_{18} juvenile hormone, and the product so obtained was 93% pure by gas chromatographic analysis and exhibited fully consistent of n.m.r. and infrared spectra[5] with the structure 15.

The synthesis of the trienic ester 20, precursor of C_{17} juvenile hormone, was also achieved by the same reaction sequence from 10; (1) methylation to 16 (90% yield, purity 97%, bp 76-7°C/0.4mmHg), (2) reduction to 17 (99% yield), (3) propynylation followed by methoxycarbonylation to the ester 18 (45% yield from 17), (4) addition of benzenethiol (78% yield), and (5) methylation to the desired trienic ester 20[6] in 69% yield (purity 94%).



10 16 X = CO_2Me 17 X = CH_2OH 18 19 20

Further, methyl farnesoate was also synthesized in 38% overall yield (purity 95%) starting from geraniol.

The noteworthy feature of this sequence is the high stereospecificity and that wide variety of alkyl side chains could be introduced by the selective use of

various readily available Grignard reagents.

References

* Laboratory of Organic Chemistry, Tokyo Institute of Technology, Ookayama Meguro-ku, Tokyo 152.

1) S. Kobayashi and T. Mukaiyama, Chem. Lett., 705 (1974).

2) S. B. Bowlus and J. A. Katzenellenbogen, Tetrahedron Lett., 1277 (1973).

3) S. Kobayashi and T. Mukaiyama, Chem. Lett., 1097 (1973).

4) The configuration of β-phenylthio-α,β-ethylenic ester was determined by the chemical shift of the olefinic proton α to the methoxy-or ethoxycarbonyl group, since we have preliminary observed that α olefinic protons of Z-isomers absorb around δ 5.6 ∿ 5.9, and those of E- isomers around δ 5.1 ∿ 5.3, respectively.

5) n.m.r.; δ 0.97 (t, J = 7Hz, 6H), δ 1.66 (s, 3H), δ 1.8 ∿ 2.3 (m, 12H), δ 2.15 (s, 3H), δ 3.62 (s, 3H), δ 5.03 (m, 2H), δ 5.60 (bs, 1H)
i.r.: $\nu_{C=O}$ 1720 cm^{-1}, $\nu_{C=C}$ 1650 cm^{-1}.

6) n.m.r.; δ 0.97 (t, J = 7Hz, 3H), δ 1.60 (s, 3H), δ 1.64 (s 3H), δ 1.8 ∿ 2.30 (m, 10H), δ 2.13 (s, 3H), δ 3.60 (s, 3H), δ 5.05 (m, 2H), δ 5.58 (bs, 1H)
i.r.; $\nu_{C=O}$ 1720 cm^{-1}, $\nu_{C=C}$ 1650 cm^{-1}.

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