CHEMISTRY LETTERS, pp.1361-1364, 1979. © The Chemical Society of Japan 1979

SYNTHETIC UTILITY OF ALLYLIC THIOLCARBAMATES. STEREOSELECTIVE SYNTHESIS OF SIMPLE NATURAL PRODUCTS INCLUDING OPTICALLY ACTIVE MANICONE AND β-SINENSAL1)

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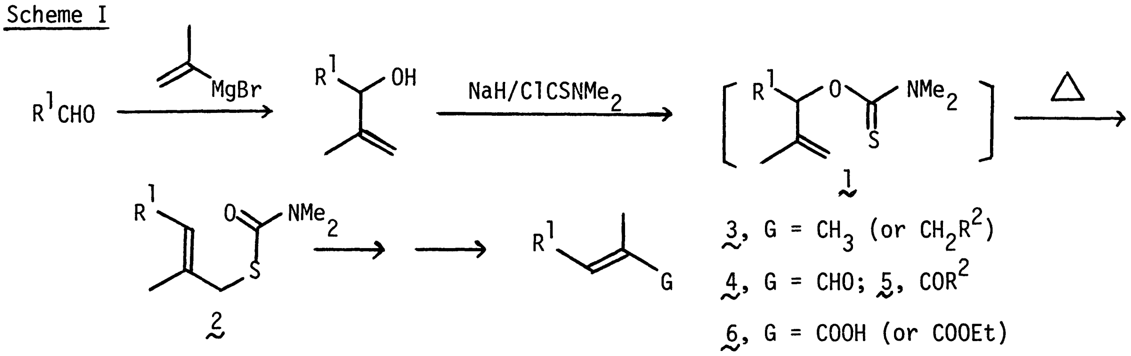
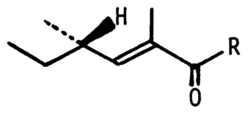
Stereoselective syntheses of the two optically active pheromones of ants, (+)-(*E*)-4,6-dimethyl-4-octen-3-one (manicone) and (+)-(*E*)-2,4-dimethyl-2-hexenoic acid, and of β-sinensal and (*E*)-β-farnesene are described in which allylic thiolcarbamates readily derived from allylic alcohols via the [3,3]sigmatropic rearrangement were used as the key intermediates.

In our continuing investigation of the synthetic utilities of the [3,3]sigmatropic rearrangement of allylic thion-esters,2) we have recently reported3,4) that allylic thiolcarbamates (2), available from allylic alcohols via the in situ rearrangement of the thioncarbamates (1), can serve as key intermediates for the stereoselective synthesis of trisubstituted olefins (3) and all types of α,β-unsaturated carbonyl systems, i.e., aldehydes (4), ketones (5), and acids (or esters) (6) (Scheme I). The remarkable flexibility of such methodology should find unique applications in the area of natural product synthesis since these structural features (3-6) are commonly found in many naturally occurring substances.

Scheme I

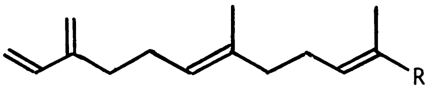


Herein we wish to report successful applications of these synthetic procedures to the stereoselective synthesis of the two pairs of simple natural products (7-10). Both (*E*)-4,6-dimethyl-4-octen-3-one, so-called manicone (7), and (*E*)-2,4-dimethyl-2-hexenoic acid (8) are mandibular gland secretions of Manica and Componotus ants, respectively, which have been identified as components



7, R = C_2H_5

8, R = OH



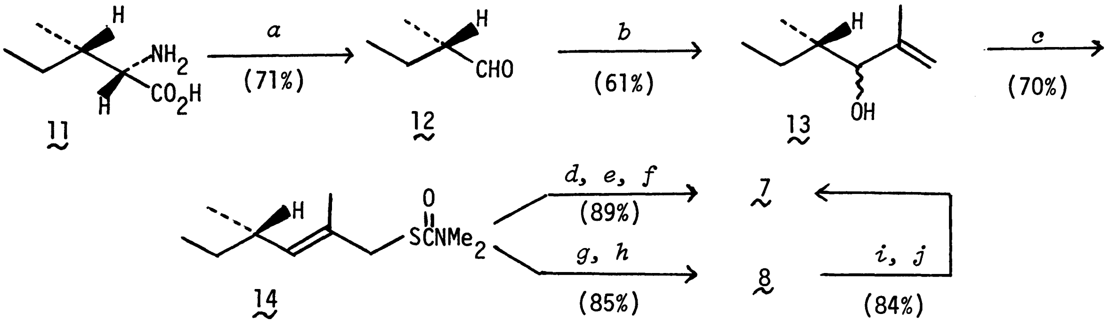
9, R = CHO

10, R = CH_3

of alarm pheromones.[5,6] However, the absolute configurations of biologically active species have not been determined yet. Thus the syntheses of 7 and 8 using a chiral intermediate were attempted in this work. On the other hand, β-sinensal (9) is a fragrant of the Chinese orange oil which exhibits juvenile hormone activities[7,8] and (*E*)-β-farnesene (10) is a constituent of various essential oils which has been identified an alarm pheromone of several aphid species.[9,10]

Scheme II outlines the synthetic sequence of the pair, (*S*)-7 and (*S*)-8. In order to obtain the requisite chiral aldehyde (12), we chose L-isoleucine (11) as the chiral starting material since the attempted oxidation of commercial (-)-2-methyl-1-butanol with pyridinium chlorochromate led to considerable racemization.[11] Thus oxidative decarboxylation of 11 with silver (II) picolinate[12] afforded optically pure (*S*)-2-methylbutanal (12): $[\alpha]_D^{25}$ +35.2° (neat) (lit.[13] $[\alpha]_D^{25}$ +32.2° (neat)). Addition of the vinylic Grignard reagent to 12 afforded a diastereomeric mixture of the allylic alcohol (13) (bp 47-49°C/6 mmHg)[14] which was then treated with sodium hydride followed by N,N-dimethylthiocarbamoyl chloride to produce, after distillation, the requisite (*E*)-allylic thiolcarbamate (14): bp 85-90°C/0.04 mmHg; $[\alpha]_D^{25}$ +25.9° (*c* 1.75, THF).[14] The monosulfenylation-alkylation (with ethyl iodide)-hydrolysis sequence[4] performed on 14 afforded (*S*)-manicone (7): bp ca. 87°C/18 mmHg; $[\alpha]_D^{20}$ +39.6° (*c* 0.85, CH_2Cl_2).[15] The optical purity of this sample was found to be ca. 85% based on the literature value.[16, 17] On the other hand, the bissulfenylation-hydrolysis sequence[4] performed on 14 afforded the desired (*S*)-acid (8): bp 110-115°C/0.01 mmHg; $[\alpha]_D^{25}$ +44.4° (*c* 1.05, CH_2Cl_2).[15] In order to determine the optical purity of 8 thus obtained, 8 was converted to 7 via the reaction of the acid chloride of 8 with diethyllithium cuprate.[6a]

Scheme II

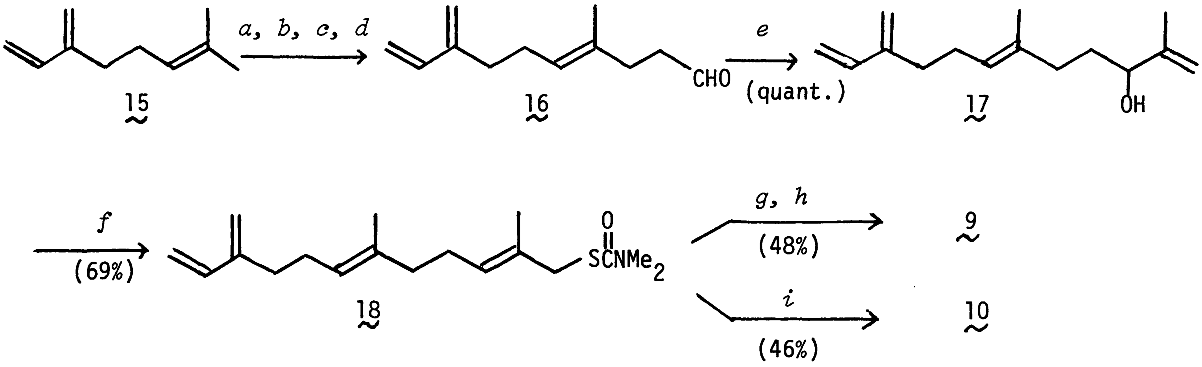


a: $Ag(II)Pic_2$, H_2O, *b*: $CH_2{=}C(CH_3)MgBr$, THF, *c*: NaH, $ClCSNMe_2$, THF→distillation,
d: $LiN(i\text{-}Pr)_2$(1 equiv), CH_3SSCH_3(1 equiv), THF, -78°C, *e*: $LiN(i\text{-}Pr)_2$, C_2H_5I, THF, -78°C,
f: HgO/BF_3OEt_2, aq.THF, *g*: $LiN(i\text{-}Pr)_2$(2 equiv), CH_3SSCH_3(2 equiv), THF, -78°C,
h: $HgCl_2$, aq. CH_3CN, *i*: $SOCl_2$, *j*: $(C_2H_5)_2LiCu$ (excess), Et_2O, -78°C.

The specific rotation ($[\alpha]_D^{20}$ +38.8° (c 1.02, CH_2Cl_2)) for 7 obtained from 8 indicated that the optical purity of 8 was at least 83%. The (+)-7 and (+)-8 prepared in this work have been sent out for bioassays.

Scheme III illustrates the synthetic sequence of the other pair, 9 and 10, starting with easily available myrcene (15). The requisite trienal (16) (bp 69-79°C/0.03 mmHg)[14] was obtained according to the literature procedures.[8b] Addition of the vinylic Grignard reagent to 16 afforded the allylic alcohol (17) (bp 100-107°C/0.02 mmHg)[14] which was then converted in one operation to the requisite (E)-allylic thiolcarbamate (18) as described above: bp 160-170°C/0·009 mmHg.[14] The monosulfenylation-hydrolysis sequence[3] performed on 18 afforded β-sinensal (9)[15] in 48% yield. The relatively low yield apparently arises from the great instability of 9 which led to cyclization and/or isomerization.[8] On the other hand, reductive desulfurization of 18 should provide the desired tetraene (10). However, we encountered a serious, but somewhat expected problem because reductive desulfurizations with the conventional methods such as deactivated Raney Ni,[3,18] $NaBH_4$-$NiCl_2$ system,[18] and Li-amines[19] were accompanied by partial or complete reduction of the terminal conjugated diene moiety of 18. The best result (48% yield of 10[15]) was obtained by the reduction with $LiAlH_4$-$CuCl_2$ system[20] in which little over-reduction products were detected, although the yield was only moderate.

Scheme III



a: SeO_2, EtOH, b: $NaBH_4$, MeOH, c: PBr_3, pyr., n-hexane, d: $LiCH_2CH{=}NBu\text{-}t$, Et_2O, -20°C $\longrightarrow H_3O^+$, e: $CH_2{=}C(CH_3)MgBr$, THF, f: NaH, $ClCSNMe_2$, THF $\longrightarrow$ distillation, g: $LiN(i\text{-}Pr)_2$, CH_3SSCH_3(1 equiv), THF, -78°C, h: $HgCl_2$, aq. CH_3CN, i: $LiAlH_4$-$CuCl_2$ (4 : 2), THF

In summary, this work presents examples demonstrating that allylic thiolcarbamates, readily accessible from various allylic alcohols via the [3,3]sigmatropic rearrangement, have the great flexibility for synthetic elaborations which allows the creation of a number of functional groups for constructing complex molecules.

Acknowledgments. We thank Professor Keiji Yamamoto of this Department for the use of an automatic polarimeter. Thanks are also due to Kyowa Hakko Kogyo Co. Ltd. for the generous gift of L-isoleucine and to the Ministry of Education for the partial support of this research through a Grant-in-Aid for Scientific Research (No. 255320).

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11) Oxidation of (*S*)-2-methyl-1-butanol ($[\alpha]_D^{25}$ -5.73°(neat)) with pyridinium chlorochromate in dichloromethane produced **12** with $[\alpha]_D^{25}$ +14.1°(neat) (optical purity, ca. 50%).

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13) E. J. Badin and E. Pacsu, *J. Am. Chem. Soc.*, 67, 1352 (1945).

14) These intermediates exhibited spectral (IR and NMR) data in accord with the assigned structures.

15) These products exhibited spectral (IR and NMR) data in accord with the reported literature values.

16) Professor Mukaiyama (ref 6c) reported that (*S*)-manicone with $[\alpha]_D^{20}$ +45.45° (*c* 1.00,CH_2Cl_2) was of the optical purity of 97%.

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(Received September 7, 1979)