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FACILE ROUTES TO NATURAL ACYCLIC POLYENES
SYNTHESES OF SPILANTHOL AND TRAIL PHEROMONE FOR TERMITE

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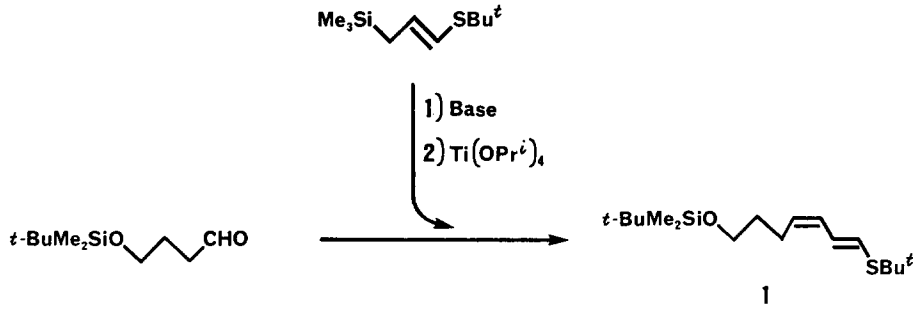
Summary: The synthetic procedures for spilanthol and trail-following pheromone for a southern subterranean termite were described. The syntheses heavily depend on the new diene synthesis using titanium reagent.

The preceding communication describes a general and stereoselective synthetic route to 1,4-dialkyl 1,3-diene which takes advantage of the ready availability of the (E,Z)-alkylthio-1,3-diene, prepared in a single step by sequential reaction of t-butyl 3-trimethylsilyl-1-propenyl sulfide with t-butyllithium and titanium tetraisopropoxide followed by aldehyde.[1] The stereochemical control and the flexibility inherent in our approach to the construction of the 1,3-diene system suggested the application of the method to the synthesis of numerous biologically and biogenetically interesting structures of acyclic polyenes.[2] In this paper this utility is illustrated by application to the syntheses of spilanthol(3), a naturally occurring insecticide from Spilanthes oleranceae,[3] and trail pheromone for a southern subterranean termite(7)[4] and these syntheses document the effectiveness of our new synthetic tactics.

Reaction of t-butyl 3-trimethylsilyl-1-propenyl sulfide[1] with 1 equiv of t-butyllithium in THF-HMPA at -78°C for 10 min and at 0°C for 1 h followed by 1 equiv of titanium tetraisopropoxide at -78°C for 40 min generated allylic titanium derivative which upon reaction with 4-(t-butyldimethylsiloxy)butanal[5]



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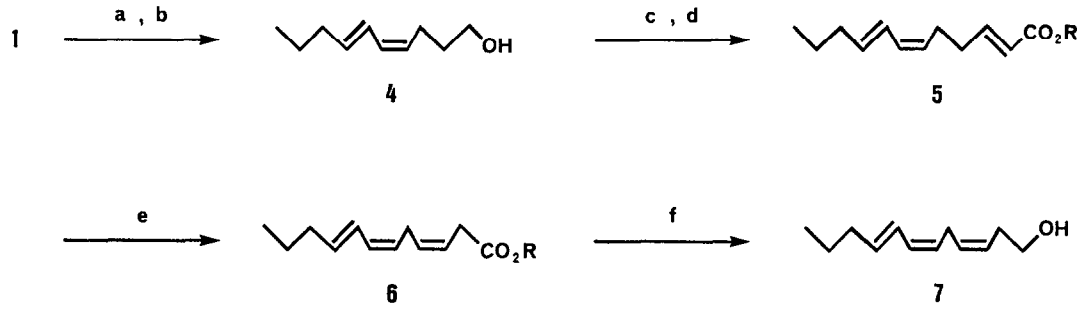
afforded the E,Z-diene **1** in 53% yield after extractive isolation.[6] The diene **1** is a possible starting point for the synthesis of a number of acyclic polyenes.

The pathway of the synthesis of spilanthol (**3**) is as follows: The t-butylthio group of **1** was cleanly replaced by methyl with methyl Grignard reagent in the presence of $Ni(DPPP)Cl_2$ in 83% yield.[7] Gc analysis revealed the compound was >97% pure. Removal of t-butyldimethylsilyl protecting group could be effected cleanly by reaction with tetrabutylammonium fluoride in THF for 30 min at room temperature.[8] Oxidation of the resulting alcohol with oxalyl chloride-DMSO and triethylamine in methylene chloride[9] afforded after short path column chromatography on silica gel the unstable aldehyde in 54% yield.[10] This aldehyde was transformed into spilanthol(**3**) by reaction with the corresponding Wittig reagent which in turn was prepared in situ from isobutyl triphenylphosphonium acetamide[11] and LDA in THF at 0°C for 10 min.[12] The yield of spilanthol(**3**), spectroscopically identical with an autherntic specimen,[13] was 61% from the aldehyde; ca. 18% of the Δ3-isomer, which was easily separated by column chromatography on silica gel, was also formed in this Wittig reaction.

a) MeMgI, Ni cat. 0.5-1 h; b) $n\text{-}Bu_4NF$; c) $(COCl)_2\text{-}Me_2S{=}O$, Et_3N; d) $Ph_3P{=}CHCONHBu^i$

The conversion of the intermediate **1** to the trail-following pheromone for a southern subterranean termite[4] was also accomplished by a sequence of straightforward steps. Propylation of **1** with excess propyl Griganard reagent (10 equiv) in benzene-ether in the presence of $Ni(DPPP)Cl_2$ (0.1 equiv)[14] at reflux for 1 h gave the diene (71% yield) which was quantitatively converted to the alcohol **4** in >90% yield using tetrabutylammonium fluoride in THF.[8] Purification of the alcohol **4** and the intermediate silyl ether was effected by careful column chromatography on silica gel, and the product **4** so obtained was >96% pure by gc analysis and exhibited fully consistent spectral data.[15] Oxidation of **4** with Me_2S-NCS complex at -78°C in toluene and treatment with triethylamine at -23°C yielded the unstable aldehyde[16] which was transformed by reaction with sodium salt of 2,4-dimethyl-3-pentyl phosphonoacetate[17] in THF-HMPA at 0°C for 30 min into the ester **5** in 78% over-all yield (95% pure by gc analysis).[18] the stereoselective rearrangement of the ester **5** to the Z-3-

isomer **6** was carried out in 70% yield by a new procedure[17] in one step which involves stirring of **5** with excess potassium hexamethyldisilazide in THF at -78°C for 2.5 h to generate the corresponding enolate which was then quenched with saturated NH_4Cl. After usual workup the product was purified by column chromatography on silica gel to give the ester **6** in 70% yield. Exposure of the ester to excess lithium alumnium hydride in ether at 0°C for 0.5 h resulted in formation of the desired alcohol **7**,[19] in 86% yield.



a) n-PrMgI, Ni cat. 0.5-1 h; b) n-Bu_4NF; c) NCS-Me_2S, Et_3N
d) $(EtO)_2P(O)CH(Na)CO_2CH(Pr^i)_2$; e) $KN(SiMe_3)_2$; f) $LiAlH_4$

References and Notes

1 J. Ukai, Y. Ikeda, N. Ikeda, and H. Yamamoto, Tetrahedron Lett., in press.

2 "Aliphatic and Related Natural Product Chemistry", ed. F. D. Gunstone (Specialist Periodical Reports), The Chemical Society, London, Chapter 1 of Volumes 1-3.

3 Spilanthol was also found to be the same as affinin, see M. Jacobson, Chem. and Ind., 50 (1957); Structure and synthesis: L. Crombie, A. H. A. Krasinski, and M. Manzoor-i-Khuda, J. Chem. Soc., 4970 (1963).

4 Structure: F. Matsumura, H. C. Coppel, and A. Tai, Nature, 219, 963 (1968); Synthesis: A. Tai, F. Matsumura, and H. C. Coppel, J. Org. Chem., **34**, 2180 (1969).

5 4-(t-Butyldimethylsiloxy)butanal was prepared as follows: To a solution of butanediol (4 equiv), Et_3N (1.3 equiv), and 4-N,N-dimethylamino-pyridine (cat.) in CH_2Cl_2 was added a solution of t-butyl chlorodimethyl-silane (1 equiv) in CH_2Cl_2 over a period of 4 h at room temperature and the mixture was stirred for an additional hour. After usual workup the crude product was purified by column chromatography on silica gel to give mono silylated butanediol (>88%). Oxidation of the resulting alcohol with oxalyl chloride-DMSO and Et_3N in CH_2Cl_2 afforded the desired

aldehyde in >90% yield.

6 IR (neat) 2970, 2870, 1260, 1105, 840 cm^{-1}; PMR ($CDCl_3$) δ 6.58 (1H, dd, J = 13.8 and 10.4 Hz), 6.20 (1H, d, J = 13.8 Hz), 5.97 (1H, dd, J = 10.4 Hz), 5.33 (1H, dt, J = 10.4 and 6.0 Hz), 3.55 (2H, t, J = 6 Hz), 2.43-1.37 (4H, m), 1.28 (9H, s), 0.83 (9H, s), 0.08 (6H, s); Rf 0.25 (hexane-ether, 60:1); Anal. Found: C, 65.0; H, 10.7%.

7 H. Okamura, M. Miura, H. Takei, Tetrahedron Lett., 43 (1979); E. Wenkert, T. W. Ferreira, E. L. Michelotti, J. Chem. Soc., Chem. Commun., 637 (1979).

8 E. J. Corey and A. Venkaeswarlu, J. Am. Chem. Soc., 94, 6190 (1972).

9 A. J. Mancuso and D. Swern, Synthesis 165 (1981) and references cited therein.

10 IR (CCl_4) 3050, 2940, 1740, 1460, 995 cm_{-1}; PMR ($CDCl_3$) δ 9.71 (1H, s); 6.60-5.13 (4H, m), 2.63-2.40 (4H, m), 1.80 (3H, d, J = 6 Hz); Rf 0.42 (ether-hexane 1:5).

11 Wittig reagent was prepared as follows: N-Isobutyl α-bromoacetamide, prepared according to W. E. Weaver and W. M. Whaley, J. Am. Chem. Soc., **69**, 515 (1947), (0.97g, 5.0 mmol) and triphenylphosphine (1.31 g, 5.0 mmol) in benzene was heated at reflux for 7 h. The solvent was removed in vacuo and the product was purifed by recrystallization from benzene-hexane (1.70 g, 86%): mp 191.5-192.3 ^{o}C.

12 Attempted preparation of the Wittig reagent under the standard conditions (NaOH as the base) was totally unsuccessful.

13 J. Correa, S. Roquet, and E. Diaz, Organic Magnetic Resonance, **3**, 1 (1971).

14 Under standared conditions using $Ni(PPh_3)_2Cl_2$ and propyl Grignard reagent, the yield of the cross coupling product was found to be exceedingly low, see ref. 7.

15 IR (neat) 3320, 2930, 1450, 1060, 980, 950 cm^{-1}; PMR (CCl_4) δ 5.00-6.53 (4H, m), 3.56 (2H, t, J = 6.0 Hz), 0.67-2.47 (12H, m); Rf 0.35 (ether-hexane, 1:1); Anal. Found: C, 77.9; H, 11.8%.

16 The same aldehyde may be also prepared by the method of Swern oxidation (ref. 9) in 50-60% yield. After NCS oxidation, the solution of the aldehyde, without any extractive workup, was introduced directly to the Wittig reagent.

17 Y. Ikeda and H. Yamamoto, Tetrahedron Lett., in press.

18 IR (CCl_4) 2960, 1720, 1650, 1455, 1255, 1190, 980 cm^{-1}; PMR (CCl_4) δ 6.85 (1H, d, J = 15.8 Hz), 6.29 (1H, dd, J = 9.8 and 13.6 Hz), 4.91-5.96 (4H, m), 4.56 (1H, dd, J = 6.0 Hz), 2.29 (2H, m); Rf 0.27 (ether-hexane, 1:20); Anal. Found: C, 77.9; H, 11.1%.

19 IR and PMR spectra were identical with the reported values, see ref. 4. Careful gc analysis (25-m PEG-HT capillary column) showed, however, our product is containing with a maximum of 12% of unidentified impurities.

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