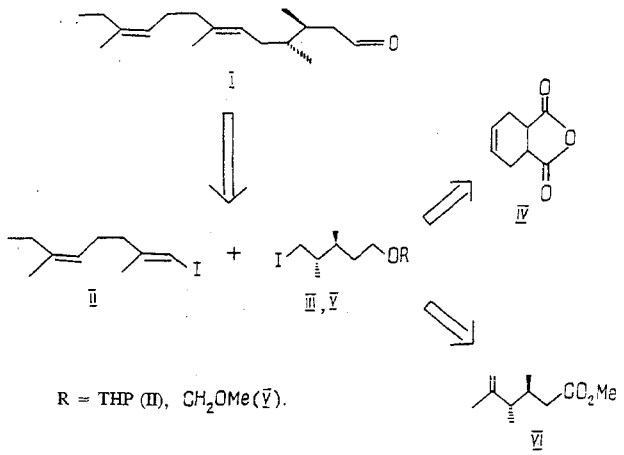
STEREOSPECIFIC SYNTHESIS OF A KEY SYNTHON FOR FARANAL — THE TRAIL PHEROMONE OF THE ANT *Monomorium pharaonis*

A. N. Kasatkin, T. Yu. Romanova, I. P. Podlipchuk, and G. A. Tolstikov

UDC 547.257.1+547.391.3+547.9

An effective scheme is proposed for the synthesis of the methoxymethyl derivative of racemic (erythro)-5-iodo-3,4-dimethylpentan-1-ol (a for obtaining faranal) from methyl (erythro)-3,4,5-trimethylhex-5-enoate — the product of the diastereospecific 1,4-addition of 2,3,-dimethylallylmanganese chloride to methyl crotonate.

At the present time, the synthesis of faranal — (3,4-erythro)-3,4,7,11-tetramethyltrideca-6E,10Z-dienal (I), the trail pheromone of the ant *Monomorium pharaonis* — in the form of a racemate [1-3] or as the natural (3S, 4R)-enantiomer [4-6] is of both scientific and practical interest. The most effective method of obtaining the racemic aldehyde (I) includes the cross-coupling of the alkenyllithium reagent, prepared in situ by treating the iodide (II) with tert-butyllithium, with the erythro-isomeric THP-(tetrahydropyran-2-yl)-protected iodohydrin (III) [2, 3]. The latter was synthesized in 10 stages from the bicyclic anhydride (IV) (the product of the cycloaddition of maleic anhydride to butadiene) with an overall yield of 13.3%.



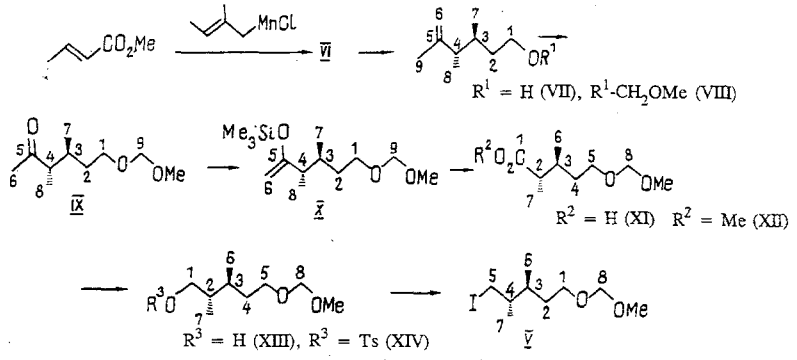
We have shown previously that the interaction of the β,γ-disubstituted σ-allyl complexes of manganese with esters of α,β-unsaturated carboxylic acids is accompanied by the formation of the products of 1,4-addition with a high erythro-diastereoselectivity [7, 8]. In the present work this reaction has been used to obtain the methoxymethyl derivative of racemic (erythro)-5-iodo-3,4,-dimethylpentan-1-ol (V), which is equivalent (from the point of view of the synthesis of the desired pheromone) to the THP derivative (III) [6].

The stereospecific condensation of methyl crotonate and 2,3-dimethylallylmanganese chloride gave the unsaturated ester (VI) with the anti- arrangement of the β- and γ- groups (yield 69%) [7, 8]. Reduction of the ester (VI) with diisobutylaluminum hydride led to the alcohol (VII), which was converted into the methoxymethyl derivative (VIII). The ozonolysis of compound (VIII) in CH_2Cl_2 in the presence of pyridine [9] was accompanied by the formation of the erythro-isomeric ketone (IX). We may note that the same reaction in a mixture of CH_2Cl_2 and MeOH in the absence of pyridine, followed by the treatment of

Institute of Organic Chemistry, Urals Branch, Russian Academy of Sciences, Ufa. Translated from Khimiya Prirodnykh Soedinenii, No. 3, pp. 459-463, May-June, 1993. Original article submitted November 2, 1992.

0009-3130/93/2903-0397$12.50

the oxidation products with dimethyl sulfide, gave the ketone (IX) in the form of a mixture ($\approx$70:30) of the erythro- and threo-isomers. The lithiation of product (IX) with lithium diisopropylamide under kinetically controlled conditions and the interaction of the enolate with the complex $Me_3SiCl \cdot Et_3N$ [10] led to the enolic silane (X). Ozonolysis of the latter was accompanied by the formation of the acid (XI), which, without isolation, was converted into the methyl ester (XII) by treatment with diazomethane. Reduction of the ester (XII) to the alcohol (XIII) with lithium tetrahydroaluminate the preparation of the tosylate (XIV), and the replacement of the TsO group by iodine under the action of NaI in acetone [11] gave the isomerically pure iodide (V) (^{1}H NMR and ^{13}C spectra). The overall yield of compound (V) calculated on the substrate (VI) was 41.8%.



EXPERIMENTAL

Chromatographic analysis was conducted on a Chrom-5 chromatograph with a flame-ionization detector in a current of helium (50 ml/min; column 3 mm $\times$ 1.2 m, 5% of SE-30 on Inerton-super. PMR spectra were recorded on Tesla BS-567 (100 MHz) and Bruker AM-300 (300 MHz) spectrometers, and ^{13}C NMR spectra on a Jeol FX-90Q spectrometer, the solvent being $CDCl_3$ and the internal standard TMS. IR spectra were recorded on a UR-20 instrument from thin layers of the substances.

Methyl (erythro)-3,4,5-trimethylhex-5-enoate (VI) was obtained from methyl crotonate and 2,3-dimethylallylmagnesium chloride as in [7].

(erythro)-3,4,5-Trimethylhex-5-en-1-ol (VII). With stirring and cooling to 0°C, a solution of 1065 mg (7.5 mmole) of diisobutylaluminum hydride in 5 ml of pentane was added to a solution of 510 mg (3 mmole) of the ester (VI) in 2 ml of pentane. The reaction mixture was kept at 20°C for 1 h, diluted with 5 ml of ether, hydrolyzed with 1 ml of water and then with 7 ml of 2 N HCl, and extracted with ether (3 $\times$ 5 ml). The organic layer was washed with water, dried with $MgSO_4$, and concentrated. With the aid of column chromatography (SiO_2 L 40/100; hexane–ether (3:1)), 392 mg (92%) of compound (VII) was isolated.

IR spectrum (ν, cm^{-1}): 34350, 3080, 1640, 1070, 895. PMR spectrum (δ, ppm): 0.85 (3H, d, J = 7 Hz, CH_3), 1.00 (3H, d, J = 7 Hz, CH_3), 1.20-1.85 (4H, m, CH_2 + CH + OH), 1.66 (3H, s, CH_3C=), 2.00 (1H, dq, $J_1 = J_2 = 7$ Hz, CHC=), 3.69 (2H, m, CH_2OH), 4.68 (2H, m, CH_2=). ^{13}C NMR spectrum (δ, ppm): 61.30 t (C-1), 32.05 t (C-2), 35.90 d (C-3), 46.80 d (C-4), 149.29 s (C-5), 110.38 t (C-6), 18.21 q (C-7), 16.06 q (C-8), 19.84 q (C-9).

(erythro)-1-Methoxymethoxy-3,4,5-trimethylhex-5-ene (VIII). With cooling to 0°C, 285 mg (3.54 mmole) of chloromethyl methyl ether and 671 mg (5.2 mmole) of diisopropylethylamine were added to a solution of 327 mg (2.3 mmole) of the alcohol (VII) in 3.5 ml of CH_2Cl_2. The reaction mixture was stirred at 20°C for 20 h, and then 3 ml of 2 N HCl was added and the products were extracted with ether (3 $\times$ 4 ml). The organic layer was washed with water to a neutral reaction, dried with $MgSO_4$, and concentrated. With the aid of column chromatography (SiO_2 L 40/100; hexane–ether (10:1)), 402 mg (94%) of compound (VIII) was isolated.

IR spectrum (ν, cm^{-1}): 3080, 1640, 1170, 1130, 1080, 1050, 985. PMR spectrum (δ, ppm): 0.85 (3H, d, J = 7 Hz, CH_3), 0.98 (3H, d, J = 7 Hz, CH_3), 1.23-1.75 (3H, m, CH_2 + CH), 1.63 (3H, s, CH_3C=), 1.90 (1H, dq, $J_1 = J_2 = 7$ Hz, CHC=), 3.33 (3H, s, CH_3O), 3.50 (2 H, m, CH_2O), 4.53 (2H, s, OCH_2O), 4.70 (2H, m, CH_2=). ^{13}C NMR spectrum (δ, ppm): 66.24 t (C-1), 32.25 t (C-2), 33.20 d (C-3), 45.92 d (C-4), 148.40 s (C-5), 110.65 t (C-6), 17.89 q (C-7), 16.53 q (C-8), 18.92 q (C-9), 96.55 t (OCH_2O), 55.18 q (OCH_3).

(erythrol)-1-Methoxymethoxy-3,4-dimethylhexan-5-one (IX). A mixture of ozone and oxygen was passed through a solution of 595 mg (3.2 mmole) of the ester (VIII) and 0.9 ml of pyridine in 15 ml of CH_2Cl_2 at –78°C until the substrate

had disappeared (19 min, monitoring by TLC); then the ozone was displaced with argon. The reaction mixture was heated to 20°C, and it was diluted with 20 ml of ether, washed with 10% H_2SO_4 (10 ml), with water (10 ml), and with saturated $NaHCO_3$ solution (10 ml), dried with $MgSO_4$, and concentrated. This gave 559 mg (95%) of the ketone (IX).

IR spectrum (ν, cm^{-1}): 1715, 1170, 1130, 1080, 1050. PMR spectrum (δ, ppm): 0.93 (3H, d, J = 7 Hz, CH_3), 1.04 (3H, d, J = 7 Hz, CH_3), 1.30 (1H, m, CH_2), 1.70 (1H, m, CH_2), 1.99 (1H, m, CH), 2.13 (3H, s, CH_3CO), 2.41 (1H, dq, $J_1 = J_2 = 7$ Hz, CHCO), 3.34 (3H, s, CH_3O), 3.54 (2H, m, CH_2O), 4.59 (2H, s, OCH_2O). ^{13}C NMR spectrum (δ, ppm): 65.80 t (C-1), 32.10 t (C-2), 32.70 d (C-3), 52.75 d (C-4), 212.19 s (C-5), 28.86 q (C-6), 17.89 q (C-7), 12.58 q (C-8), 96.57 t (C-9), 55.24 q (OCH_3).

(erythrol)-1-Methoxymethoxy-3,4-dimethyl-5-trimethylsiloxyhex-5-en-ol (X). With cooling to 0°C, 1.89 ml (5 mmole) of a 2.65 M solution of BuLi in hexane was added to a solution of 505 mg (5 mmole) of diisopropylamine in 7 ml of THF, and the mixture was stirred for 1 h. After the addition of 470 mg (2.5 mmole) of the ketone (IX), the reaction mixture was kept at 0°C for 1 h and then a mixture of 614 mg (5.66 mmole) of trimethylchlorosilane and 300 mg (2.97 mmole) of triethylamine was added and the new reaction mixture was stirred for 0.5 h and was then hydrolyzed with 0.1 ml of water. The solvent was distilled off under reduced pressure, and the residue was carefully washed with pentane. The organic layer was dried with $MgSO_4$ and concentrated. This gave 617 mg (95%) of the O-silylenol (X).

PMR spectrum (δ, ppm): 0.19 (9H, s, CH_3Si), 0.92 (3H, d, J = 7 Hz, CH_3), 1.02 (3H, d, J = 7 Hz, CH_3), 1.37 (1H, m, CH_2), 1.75 (1H, m, CH_2), 1.88 (1H, m, CH), 2.35 (1H, dq, $J_1 = J_2 = 7$ Hz, CH — C=), 3.36 (3H, s, CH_3O), 3.58 (2H, m, CH_2O), 4.02 (2H, m, CH_2=), 4.62 (2H, s, OCH_2O). ^{13}C NMR spectrum (δ, ppm): 66.59 t (C-1), 32.36 t (C-2), 33.22 d (C-3), 45.36 d (C-4), 162.25 s (C-5), 89.00 t (C-6), 17.51 q (C-7), 15.31 q (C-8), 96.51 t (C-9), 55.14 q (OCH_3), 0.18 q ($SiCH_3$).

Methyl (erythro)-5-Methoxymethoxy-2,3-dimethylpentanoate (XII). A mixture of ozone and oxygen was passed through a solution of 416 mg (1.6 mmole) of the O-silylenol (X) in a mixture of 20 ml of CH_2Cl_2 and 4 ml of methanol at −78°C until the substrate had disappeared (11 min, monitoring by TLC). The ozone was displaced with argon, and after the addition of 0.35 ml of dimethyl sulfide the mixture was heated to 20°C for 20 h. The solvent was distilled off under reduced pressure, and the residue was treated with 5 ml (5 mmole) of a 1 M ethereal solution of diazomethane, and the reaction mixture was allowed to stand for 30 min. Then it was washed with water (3 × 2 ml), dried with $MgSO_4$, and concentrated. With the aid of column chromatography (SiO_2 L 40/100, hexane−ether (5:1)), 242 mg (74%) of compound (XII) was isolated.

IR spectrum (ν, cm^{-1}): 1745, 1270, 1210, 1170, 1130, 1080, 1055. PMR spectrum (δ, ppm): 0.92 (3H, d, J = 7 Hz, CH_3), 1.14 (3H, d, J = 7 Hz, CH_3), 1.40 (1H, m, CH_2), 1.75 (1H, m, CH_2), 1.90 (1H, m, CH), 2.41 (1H, dq, $J_1 = J_2 =$ 7 Hz, $CHCO_2$), 3.36 (3H, s, CH_3O), 3.56 (2H, m, CH_2O), 3.67 (3H, s, CH_3OC=O), 4.61 (2H, s, OCH_2O). ^{13}C NMR spectrum (δ, ppm): 176.40 s (C-1), 44.63 d (C-2), 33.43 d (C-3), 33.17 t (C-4), 65.78 t (C-5), 16.93 q (C-6), 14.11 q (C-7), 96.48 t (C-8), 55.26 q (OCH_3), 51.40 q (CH_3OC=O).

(erythro)-5-Methoxymethoxy-2,3-dimethylpentan-1-ol (XIII). With stirring and cooling to 0°C, a solution of 306 mg (1.5 mmole) of compound (XII) in 1.5 ml of ether was added to a suspension of 76 mg (2 mmole) of lithium tetrahydroaluminate in 3 ml of ether. The reaction mixture was stirred at 20°C for 2 h and was hydrolyzed with 0.2 ml of water and then with 3 ml of 2 N HCl and was extracted with ether (3 × 5 ml). The organic layer was dried with $MgSO_4$ and concentrated. With the aid of column chromatography (SiO_2 L 40/100, hexane−ether (3:1)), 222 mg (84%) of the alcohol (XIII) was isolated.

IR spectrum (ν, cm^{-1}): 3440, 1170, 1125, 1070, 1050. PMR spectrum (δ, ppm): 0.88 (1H, d, J = 7 Hz, CH_3), 0.94 (3H, d, J = 7 Hz, CH_3), 1.31 (1H, m, CH_2), 1.71 (3H, m, CH_2 + CH + CH), 1.99 (1H, br.s, OH), 3.37 (3H, s, CH_3O), 3.47 (1H, dd, $J_1 = 10.8$ Hz, $J_2 = 6.7$ Hz, CH_2OH), 3.56 (2H, m, CH_2O), 3.59 (1H, dd, $J_1 = 10.8$ Hz, $J_2 = 6.6$ Hz, CH_2OH), 4.62 (2H, s, OCH_2O). ^{13}C NMR spectrum (δ, ppm): 66.74 t, 67.47 t (C-1, C-5), 41.36 d (C-2), 33.00 d (C-3), 31.91 t (C-4), 18.13 q (C-6), 13.83 q (C-7), 97.39 t (C-8), 56.13 q (OCH_3).

(erythro)-5-Iodo-1-methoxymethoxy-3,4-dimethylpentane (V). With cooling to 5°C, 380 mg (2 mmole) of tosyl chloride was added to a solution of 352 mg (2 mmole) of the alcohol (XIII) in 1 ml of pyridine, and the mixture was stirred at 5°C for 20 min and at 20°C for 20 min. The resulting solution was treated with 4 ml of 3 N H_2SO_4, and extracted with ether (3 × 5 ml). The organic layer was washed with water (5 ml) and with saturated NaCl solution (5 ml), dried with $MgSO_4$, and concentrated. The residue was dissolved in 2.5 ml of acetone containing 690 mg (4.6 mmole) of NaI. The reaction mixture was boiled for 2 h, the solvent was distilled off under reduced pressure, and the residue was treated with 3 ml of water and 10 ml of pentane. The organic layer was washed with 3 ml of saturated NaCl solution, dried with $MgSO_4$, and concentrated. With the aid of column chromatography (SiO_2 L 40/100; hexane−ether (10:1)) 480 mg (88%) of the iodide (V) was isolated.

PMR spectrum (δ, ppm): 0.92 (3H, d, J = 7 Hz, CH_3), 1.02 (3H, d, J = 7 Hz CH_3), 1.36 (1H, m, CH_2), 1.50-1.78 (3H, m, CH_2 + CH + CH), 3.13 (1H, dd, J_1 = 9.6 Hz, J_2 = 7.7 Hz, CH_2I), 3.30 (1H, dd, J_1 = 9.6 Hz, J_2 = 4.5 Hz, CH_2I), 3.37 (3H, s, OCH_3), 3.58 (2H, m, CH_2O), 4.63 (2H, s, OCH_2O). ^{13}C NMR spectrum (δ, ppm): 66.18 t (C-1), 32.42 t (C-2), 34.44 d (C-3), 40.59 d (C-4), 14.78 t (C-5), 17.49 q (C-6), 16.71 q (C-7), 96.53 t (C-8), 55.32 q (CH_3O).

REFERENCES

1. D. W. Knight and B. Ojhara, J. Chem., Soc. Perkin Trans. I, 955 (1983).
2. R. Baker, D. C. Billington, and N. Ekanyake, J. Chem. Soc., Chem. Commun, 1234 (1981).
3. R. Baker, D. C. Billington, and N. Ekanayake, J. Chem. Soc., Perkin Trans. I, 1387 (1981).
4. K. Mori and H. Ueda, Tetrahedron Lett., **22**, 461 (1981).
5. K. Mori and H. Ueda, Tetrahedron Lett., **38**, 1227 (1982).
6. L. Poppe, L. Novak, P. Kolonits, A. Bata, and C. Szantay, Tetrahedron Lett., **27**, 5769 (1986).
7. A. N. Kasatkin, O. Yu. Tsypyshev, T. Yu. Romanova, and G. A. Tolstikov, Izv. Akad. Nauk SSSR, Ser. Khim., 1154 (1990).
8. A. N. Kasatkin, O. Yu. Tsypyshev, T. Yu. Romanova, G. A. Tolstikov, and O. V. Shitikova, Metalloorgan. Khim., **4**, 200 (1991).
9. G. A. Tolstikov, F. Z. Galin, V. K. Ignatyuk, F. Z. Makaev, N.A. Yulmukhametova, S. A. Abdrakhimova, L. M. Khalilov, and V. S. Sultanova, Zh. Org. Khim., **27**, 335 (1991).
10. S. E. Kelly and B. C. Vanderplas, J. Org. Chem., **56**, 1325 (1991).
11. K. Mori, M. Ohki, A. Sato, and M. Matsui, Tetrahedron, **28**, 3739 (1972).