A Stereoselective Synthesis of (3*E*,5*Z*)-3,5-Tetradecadienoic Acid (Megatomoic Acid), the Sex Attractant of the Black Carpet Beetle†

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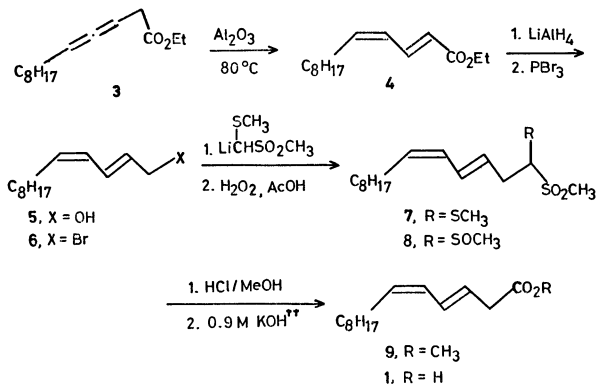
Synopsis. The total synthesis of (3*E*,5*Z*)-3,5-tetradecadienoic acid (megatomoic acid) is accomplished with 74% stereoselectivity through the use of stereoselective rearrangement of ethyl 3,4-tridecadienoate to ethyl (2*E*,4*Z*)-2,4-tridecadienoate with alumina and the extension of the carbon chain with methyl methylthiomethyl sulfone.

The sex attractant of the black carpet beetle, *Attagenus megatoma* (*Fabricius*), was identified as (3*E*,5*Z*)-3,5-tetradecadienoic acid (**1**) by Silverstein *et al.*,[1] to which they assigned the trivial name, megatomoic acid. The total synthesis of **1** has been reported by two groups.[2,3] In spite of reasonable overall yields, their sequences produce a significant amount of stereoisomers.[4] We present here a convenient and stereoselective synthesis of **1** starting with 1-undecyn-3-ol (**2**), which is superior to others[2,3] in its stereoselectivity (74%). The synthetic plan outlined in Scheme 1 was conceived with two strategic aspects: (1) to construct (2*E*,4*Z*)-2,4-dienoic ester (*e.g.*, ester **4**) from readily available materials, (2) to extend its carbon chain with the retention of the geometry. Ethyl (2*E*,4*Z*)-2,4-tridecadienoate (**4**), a key intermediate which fulfills these requirements was prepared in good yield by the highly stereoselective synthesis of (2*E*,4*Z*)-2,4-dienoates with alumina catalyst, as recently described by us.[5]

3,4-Dienoate **3** was prepared in 85% yield by the modified Claisen rearrangement of **2** with triethyl orthoacetate.[5] The thermal rearrangement of **3** with alumina gave 88% yield of (2*E*,4*Z*)-2,4-dienoate **4** of 97% purity.[6] A minor component was suggested to be (2*E*,4*E*)-isomer by comparison of the retention time of GLC.[5] Reduction of **4** with lithium aluminium hydride gave the corresponding alcohol **5** in 95% yield. The reaction of the allylic alcohol **5** with PBr_3 in petroleum ether afforded the desired bromide **6** in a reasonable yield. The conversion of **6** to carboxylate was attempted by various methods. The reactions of the Grignard reagent derived from **6** followed by carbonation resulted in the recovery of the starting material, or in the formation of unidentified materials. The reaction of **6** with sodium cyanide gave 3,5-tridecadienenitrile (**10**) in poor yields as stereoisomeric mixtures. The hydrolysis of **10** to the corresponding carboxylic acid, however, gave a trace of a carboxylic acid. On the other hand, the reaction of **6** with methyl methylthiomethyl sulfone[7] in the presence of butyllithium gave the corresponding product (**7**) with 81% purity in 46% yield,[8] while the reaction using a phase-transfer catalyst (PTC) resulted in poor yields of **7**. Compound **7** was oxidized with peracetic acid under mild conditions to give the sulfinyl sulfone **8**



Scheme 1.

as an oil. The subsequent treatment of **8** with concentrated hydrochloric acid in methanol gave methyl (3*E*,5*Z*)-3,5-tetradecadienoate (**9**) with 74% purity, in 30% yield from **7**. The desired product, megatomoic acid **1**, was obtained in 89% yield by the hydrolysis of **9** with 0.9 M potassium hydroxide. The spectral properties of the synthesized **1** were identical with those reported for the natural product.[1]

Experimental

The boiling points are uncorrected. Elemental analyses were carried out by Mr. Eiichiro Amano of our laboratory. Analytical determinations by GLC were performed on a Hitachi Model 163 gas chromatograph fitted with 10% Silicone SE-30 on Chromosorb W column (3 mm o.d. × 1 m). IR spectra were taken on a Hitachi Model EPI-S2 or a JASCO Model A-102 spectrometer. ^{1}H NMR spectra (60 MHz) were recorded with a Hitachi R-24 apparatus. ^{13}C NMR spectra (25 MHz) were obtained with JEOL LTD. JNM-FX 100 apparatus equipped with FT facilities, using $CDCl_3$ as solvent. 1-Undecyn-3-ol (**2**) was prepared by a method in the literature:[5b,9] bp 89 °C (5 mm); 71% yield, improved over the previously reported value.[5b]

(2E,4Z)-2,4-Tridecadien-1-ol (5). To a stirred mixture of 160 mg (4.2 mmol) of lithium aluminium hydride and 10 ml of dry ether was added dropwise a solution of 1.0 g (4.2 mmol) of **4** in 10 ml of dry ether at −40 °C. After 1.5 h, the reaction mixture was quenched with 400 mg of ethyl acetate, and neutralized with 10% HCl. The organic layer was extracted with ether, and the combined ethereal layers were washed with water and dried over $MgSO_4$. Removal of the solvent gave 780 mg (95%) of **5** containing 9% (2*E*,4*E*)-isomer by ^{13}C NMR: IR (neat) 3350 (OH), 1640 cm^{-1} (C=C); ^{1}H NMR (CCl_4) δ=0.92 (broad t, 3 H, J=4 Hz, CH_3), 1.27 (broad s, 12 H, $(CH_2)_6$), 2.13 (m, 2H, $=CHC\underline{H}_2C_7H_{15}$), 3.64 (s, 1H, OH), 4.09 (d, 2H, J=5.5 Hz, $C\underline{H}_2OH$), 5.10—6.08 (m, 3H, $C\underline{H}=C\underline{H}CH=C\underline{H}CH_2OH$), 6.45 (dd, 1H, J=10 and 15 Hz, $C\underline{H}=CHCH_2OH$); ^{13}C NMR

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†† 1 M = 1 mol dm^{-3}.

($CDCl_3$) δ=14.1 (d, CH_3), 22.8 (t, C_{12}), 27.9 (t, C_6), 29.4 (t), 29.6 (t), 29.8 (t), 32.0 (t, C_{11}), 63.0 (t, C_1), 126.6 (d, C_3), 128.0 (d, C_4), 132.0 (d, C_2), 132.6 (d, C_5). Found: C, 79.76; H, 12.08%. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32%.

*(2E,4Z)-1-Bromo-2,4-tridecadiene (**6**).* To a stirred solution of 600 mg (3.06 mmol) of **5** in 1.5 ml of petroleum ether was added dropwise a solution of 580 mg (2.15 mmol) of PBr_3 in 1.5 ml of petroleum ether at −15 °C for a period of 15 min. The mixture was stirred for 2 h at −15 °C and then overnight at room temperature. The reaction mixture was diluted with ice water (50 ml) and neutralized with dilute $NaHCO_3$. The organic layer was extracted with petroleum ether. The combined extracts were washed with water, and dried over $MgSO_4$. Removal of the solvent gave 624 mg (79%) of **6** as a clean oil: IR (neat) 1645 cm^{-1} (C=C); ^1H NMR (CCl_4) δ=0.92 (broad t, 3 H, J=4 Hz, CH_3), 1.25 (broad s, 12H, $(CH_2)_6$), 2.13 (m, 2H, =CH-C<u>H</u>$_2C_7H_{15}$), 3.91 (d, J=7.4 Hz, 2H, CH_2Br), 5.29—6.11 (m, 3H, C<u>H</u>=C<u>H</u>CH=C<u>H</u>CH_2Br), 6.47 (dd, 1H, J=10 and 15 Hz, C<u>H</u>=CHCH_2Br). Found: C, 60.47; H, 8.90 %. Calcd for $C_{13}H_{23}Br$: C, 60.23; H, 8.94%.

*(3E,5Z)-1-Methylsulfonyl-1-methylthio-3,5-tetradecadiene (**7**).* To a stirred solution of 342 mg (2.44 mmol) of methyl methylthiomethyl sulfone in 5 ml of dry THF was added dropwise 1.57 ml (2.43 mmol) of 1.55 M butyllithium (hexane) at −20 °C under a static N_2 atmosphere. The mixture was stirred for 90 min and then cooled at −65 °C. After gradual addition of 600 mg (2.32 mmol) of **6**, the mixture was stirred for 1 h at −65 °C and then for 12 h at 0 °C. It was poured into water (*ca.* 30 ml) and the organic layer extracted with ether. The dried ($MgSO_4$) ethereal layer was concentrated *in vacuo* to yield 765 mg of an oil. Column chromatography on silica gel (30 g) with hexane–ethyl acetate gave 337 mg (46%) of **7** as a clean, viscous oil containing 19% (3*E*,5*E*)-isomer by ^{13}C NMR:[10] IR (neat) 2910, 1300, 1160 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ=0.92 (broad t, 3 H, J=5 Hz, CH_3), 1.30 (broad s, 12H, $(CH_2)_6$), 1.9—2.5 (m, 2H, =CHC<u>H</u>$_2C_7H_{15}$), 2.33 (s, 3H, SCH_3), 2.60 (dd, 2H, J= 7 and 10 Hz, =CHC<u>H</u>$_2$CH<), 3.01 (s, 3H, SO_2CH_3), 3.62 (dd, 1H, J=4 and 10 Hz, >C<u>H</u>SO_2), 5.26—6.20 (m, 3H, C<u>H</u>=C<u>H</u>CH=C<u>H</u>CH_2CH<), 6.59 (dd, 1H, J=10 and 15 Hz, C<u>H</u>=CHCH_2CH<); ^{13}C NMR ($CDCl_3$) δ=14.1 (q, CH_3), 14.2 (q, CH_3), 22.7 (t, C_{13}), 27.8 (t, C_7), 29.2 (t), 29.4 (t), 29.6 (t), 30.3 (t, C_2), 31.9 (t, C_{12}), 36.7 (q, SO_2CH_3), 126.3 (d), 127.5 (d), 130.0 (d), 133.0(d). Found: C, 60.12; H, 9.54%. Calcd for $C_{16}H_{30}O_2S_2$: C, 60.33; H, 9.49%.

*Methyl (3E,5Z)-3,5-Tetradecadienoate (**9**).* A mixture of **7** (270 mg, 0.85 mmol), acetic acid (1.5 ml), and 35% hydrogen peroxide (0.1 ml, 1.1 mmol) was stirred for 2 d at room temperature in a dark room. The mixture was dissolved in CH_2Cl_2 and then treated with 3 g of potassium carbonate. After fitration, the filtrate was dried over $MgSO_4$. Removal of the solvents gave 254 mg of an oil, which was assumed to be (3*E*,5*Z*)-1-methylsulfonyl-1-methylsulfinyl-3,5-tetradecadiene (**8**).

A mixture of the above oil **8** (123 mg, 0.368 mmol), methanol (2 ml), and a catalytic amount of conc HCl was heated at reflux temperature for 6 h, and then poured into water (*ca.* 25 ml). The resulting mixture was extracted with ether, and the organic layer washed with water and dried over $MgSO_4$. Removal of the solvents yielded 100 mg of an oil which was purified by column chromatography on silica gel (4 g) with hexane–AcOEt as an eluent, giving 29 mg (30% from **7**, 32% from consumed **7**) of **9** (74% pure by ^{13}C NMR): ^{13}C NMR ($CDCl_3$) δ=14.0 (q, C_{14}), 22.6 (t, C_{13}), 27.7 (t, C_7), 29.2 (t), 29.4 (t), 29.5 (t), 31.8 (t, C_{12}), 38.0 (t, C_2), 51.8 (q, CO_2CH_3), 124.3 (d), 127.5 (d), 129.2 (d), 132.4 (d), 172.0 (s, <u>C</u>O_2CH_3). GLPC analysis [column temp, 150 °C; carrier gas, N_2 (1.0 kg/cm^2)] indicated that it consisted of two components with the retention times, 10.5 min (**9**, 74 parts) and 12.3 min (the (3*E*,5*E*)-isomer,[2] 26 parts). IR and ^1H NMR data of pure **9** obtained by preparative GLPC were identical with those in the literature.[2,3] Another fraction gave 15 mg of **7**, the spectral data of which were identical with those of the sample prepared above.

*(3E,5Z)-3,5-Tetradecadienoic Acid (**1**).* A mixture of 20 mg (0.084 mmol) of **9** purified by preparative GLPC and 0.3 ml of 0.9 M KOH in 90% MeOH was stirred at 25 °C for 5 h, and poured into cooled water. The mixture was acidified with 10% HCl, and the organic layer extracted with ether. The combined ethereal layers were washed with water and dried over $MgSO_4$. Removal of the solvent gave 17 mg (89%) of **1** as a viscous oil. IR and ^1H NMR data were identical with those of the authentic sample.[1]

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References

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3) K. Yokoi and Y. Matsubara, *Kinki Daigaku Rikogakubu Kenkyu Hokoku*, **1979**, 65.

4) It is reported that the ratios of **1** to the isomers were 50/22 and 1/18, respectively. See Refs. 2 and 3.

5) a) S. Tsuboi, T. Masuka, H. Makino, and A. Takeda, *Tetrahedron Lett.*, **23**, 209 (1982); b) S. Tsuboi, T. Masuda, and A. Takeda, *J. Org. Chem.*, **47**, 4478 (1982).

6) The purity of **4** was improved over that reported in the previous paper (Ref. 5).

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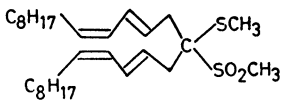
8) The reaction was accompanied with the compound supposed to be a disubstituted product (**11**) (30% yield).



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9) L. Brandsma, "Preparative Acetylenic Chemistry," Elsevier, Amsterdam (1971), p. 71.

10) Another fraction eluted earlier provided 180 mg (30%) of **11** as an oil: IR (neat) 1650, 1605, 1460, 1300, 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.99 (broad t, 6 H, J=5 Hz, 2 CH_3), 1.26 (broad s, 28 H, 2 $(CH_2)_7$), 1.8—2.4 (m, 4H, 2 $C_7H_{15}C$<u>H</u>$_2$CH=), 2.29 (s, 3H, SCH_3), 2.6—3.0 (m, 4H, 2 =CHC<u>H</u>$_2$C<), 3.03 (s, 3H, SO_2CH_3), 5.2—6.8 (m, 8H, olefin protons). Found: C, 70.11; H, 10.58%. Calcd for $C_{29}H_{52}O_2S_2$: C, 70.10; 10.55%.