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Letter

Short-route synthesis of (3*E*,5*Z*)-tetradecadienoic acid (megatomic acid), the sex attractant of the black carpet beetle†

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A new and expeditious route to (3*E*,5*Z*)-3,5-tetradecadienoic acid (megatomic acid), the sex attractant of the black carpet beetle *Attagenus megatoma* (*Fabricius*), is reported which proceeds with 97% stereoselectivity; Cadiot–Chodkiewicz cross-coupling of 1-decyne and 4-bromo-3-butyn-1-ol in the presence of CuCl, followed by stereoselective reductions and Jones oxidation, gives the target molecule, with the synthetic pheromone showing a positive electrophysiological response.

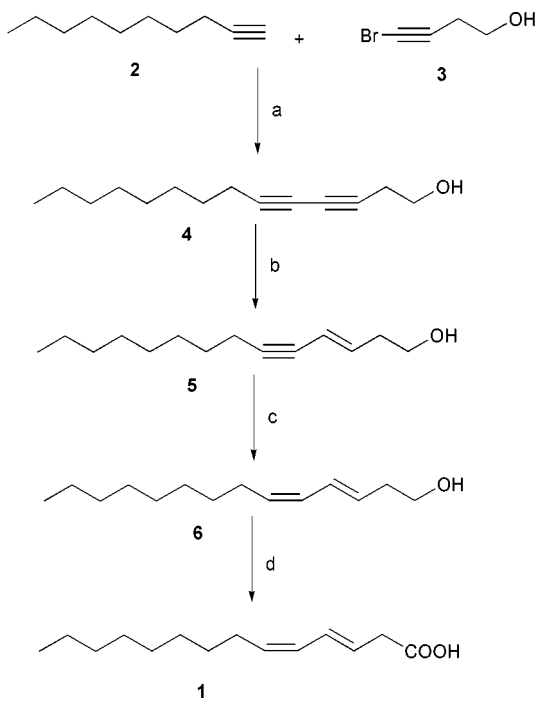
The principle component of the sex attractant of the black carpet beetle *Attagenus megatoma* (*Fabricius*) was identified as (3*E*,5*Z*)-3,5-tetradecadienoic acid (**1**) and was given the trivial name megatomic acid. Different approaches have been reported for the synthesis of megatomic acid. Silverstein and coworkers[1,2] condensed 1-decynylmagnesium bromide with acrolein to afford an allyl alcohol, which was transformed with phosphorus tribromide into a mixture of 2*E* and 2*Z* allyl bromides in a 2 : 1 ratio. One-carbon homologation and other routine transformations afforded megatomic acid. Abrams reported[3] a one-step transformation of 5-tetradecynoic acid with the sodium salt of 1,2-diaminoethane to afford a 1 : 1 mixture of (3*E*,5*Z*)- and (3*Z*,5*Z*)-tetradecadienoic acid in 67% yield. Tsuboi *et al.*[4] prepared (2*E*,4*Z*)-2,4-tridecadienoate from 3,4-tridecadienoate stereoselectively, by a rearrangement promoted by alumina. One-carbon homologation employing a six-step sequence afforded megatomic acid. The same group[5] reported another approach to megatomic acid in which lithium diisopropylamide promoted isomerization of (2*E*,4*E*)-2,4-tetradecadienoate to give a mixture of (3*E*,5*Z*)- and (3*Z*,5*Z*)-tetradecadienoate in a 7.5 : 1.9 ratio. Finally De Jarlais and Emken[6] have reported the condensation of decynylmagnesium bromide with 4-bromo-2-butenoic acid, followed by base-catalyzed isomerization of the unsaturated acid to afford a mixture of 3*E*- and 3*Z*-tetradeca-5-ynoic acid in a 1 : 1 ratio. Further reduction of the triple bond afforded megatomic acid.

As is clear from the above discussion, the reported syntheses of megatomic acid suffer from either a lack of stereoselectivity, poor yields or both. Also, these approaches make use of precursors that are not readily available, expensive reagents and/or harsh reaction conditions. In a continuation of our ongoing research program involving the synthesis of insect sex pheromones,[7–9] we wish to report herein a highly practical and efficient straightforward route to the synthesis of (3*E*,5*Z*)-3,5-tetradecadienoic acid employing very mild reaction conditions.

Megatomic acid has been prepared with 97% stereoselectivity by a new expeditious route involving a copper-catalyzed carbon–carbon bond-forming reaction. The key step involves a Cadiot–Chodkiewiez cross-coupling reaction between 1-decyne and (*E*)-4-bromo-3-butyn-1-ol using Cu(I) chloride, $NH_2 \cdot OH \cdot HCl$ and aqueous ethylamine to give 3,5-tetradecadiyn-1-ol, which upon stereoselective reductions, followed by Jones oxidation, affords the target pheromone.

Results and discussion

The route shown in Scheme 1 was envisaged as a viable one to the desired compound. Our synthetic strategy is based on cross-coupling C_{10} and C_4 fragments,[10,11] using 1-decyne (**2**) and 3-butyn-1-ol (homopropargyl alcohol) as the starting materials. 4-Bromo-3-butyn-1-ol (**3**) can be prepared from 3-butyn-1-ol following standard literature procedure.[12] Cadiot–Chodkiewiez cross-coupling[13] of **2** with **3**, using CuCl, $NH_2 \cdot OH \cdot HCl$ and ethylamine, afforded 3,5-tetradecadiyn-1-ol (**4**) in 90% yield. Reduction of **4** with lithium aluminum hydride[14,15] gave (*E*)-tetradeca-3-en-5-yn-1-ol (**5**) with 97% stereoselectivity and 70% yield. Stereoselective hydrogenation with a freshly prepared solution of disiamylborane[15] yielded the dienol **6** with 99% stereoselectivity and 85% yield. Oxidation of dienol **6** with Jones reagent[17] gave megatomic acid (**1**) in 83% yield. The synthetic pheromone showed a positive electrophysiological response.[18]



Scheme 1 (a) CuCl, $NH_2 \cdot OH \cdot HCl$, ethylamine, MeOH, H_2O; (b) lithium aluminum hydride, diethyl ether; (c) disiamylborane, THF, 30% H_2O_2; (d) Jones oxidation, CrO_3–H_2SO_4.

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In conclusion, we have developed a novel protocol for the efficient synthesis of megatomic acid in overall 45% yield with 97% stereoselectivity (as determined by GC analysis) and this new method appears to be an alternative to previously reported methods.

Experimental

General procedures

IR spectra were measured as films with a Nicolet FT/IR-740 spectrometer and ^{1}H-NMR spectra were recorded with TMS as an internal standard in $CDCl_3$ with a Varian Gemini 200 MHz instrument. High-resolution mass spectra (70 eV) were measured with a VG Micromass 7070 H apparatus. Gas chromatography was performed with a Shimadzu GC-17A instrument, using a Neutrabond-1 capillary column (0.25 mm × 15 m; GL Sciences) operated with a temperature program of 2 min at 80 °C, then ramping from 80 to 220 °C at 6 °C min^{-1}; splint vent closed for 1 min, injection at 250 °C; N_2 gas at 1.0 kg cm^{-2} at inlet and recorded as t_R. The olfactory sensitivity was recorded on an EAG, Syntech (Hillversum, The Netherlands).

1-Decyne and 3-butyn-1-ol were commercially available and used without further purification. Diethyl ether and THF were dried and distilled according to literature procedures.[19]

Syntheses

3,5-Tetradecadiyn-1-ol (4). A solution of hydroxylamine hydrochloride (1.25 g, 18 mmol) in water (5 ml), 70% aqueous ethylamine (10 ml), and copper(I) chloride (187 mg, 1.7 mmol) in methanol (12 ml) were placed in a round-bottom flask. Air was completely replaced by nitrogen and, while stirring, 1-decyne (**2**, 3.5 g, 25 mmol) was added in one portion. To the resulting yellow suspension, 4-bromo-3-butyn-1-ol (**3**, 3.75 g, 25 mmol) was added over a period of 30 min while maintaining the temperature between 30–35 °C. After an additional 15 min at 40 °C, a solution of KCN (0.65 g, 10 mmol) and NH_4Cl (2.5 g, 46.7 mmol) in water (40 ml) was added and the mixture stirred for 20 min. The product was isolated by extraction with diethyl ether (3 × 100 mL). The combined organic extracts were washed with aqueous NH_4Cl solution, dried over Na_2SO_4 and evaporated to afford the crude compound, which was purified by column chromatography on silica gel, using hexane–ethyl acetate (90 : 10) as the eluent to afford 4.6 g of compound **4** (92%). IR (film) ν_{max}/cm^{-1}: 3345 (OH), 2930 (C–H), 2160 (C≡C). ^{1}H NMR ($CDCl_3$) δ: 0.90 (3H, distorted t, J = 7.0), 1.20–1.60 (12H, mult), 1.80–1.90 (1H, OH), 2.10 (2H, t, J = 6.0), 2.50 (2H, t, J = 6.0), 3.30 (2H, t, J = 6.0 Hz). HR-MS: m/z [M]$^+$: calc. for $C_{14}H_{22}O$: 206.1670, found: 206.1663.

(*E*)-Tetradeca-3-en-5-yn-1-ol (5). To a suspension of lithium aluminum hydride (210 mg, 5.5 mmol) in diethyl ether (15 ml) at −5 °C under nitrogen, was added a solution of **4** (2.30 g, 11.15 mmol) in diethyl ether (10 ml) dropwise over a period of 15 min. The reaction mixture was stirred for 2 h at 35 °C and then cooled to 0 °C. The reaction mixture was diluted with diethyl ether (20 ml) and quenched with 2 N HCl. The layers were separated and the aqueous layer was extracted with ether; the combined organic layers were washed with saturated brine and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*. The product was purified by column chromatography using hexane–ethyl acetate (90 : 10) as the eluent to afford 1.6 g of **5** (70%). IR (film) ν_{max}/cm^{-1}: 3345 (OH), 2930 (C–H), 2160 (C≡C), 1660 (C=C), *trans* def. 975 (C–H). ^{1}H NMR ($CDCl_3$) δ: 0.95 (3H, distorted t, J = 7.0), 1.20–1.60 (13H, mult), 2.25 (2H, quart, J = 6.8), 2.50 (2H, t, J = 6.8), 3.65 (2H, t, J = 6.8, 5.55 (1H, d, J = 15.9), 6.00 (1H, dt, J = 15.9, 6.82 Hz). HR-MS m/z [M]$^+$: calc. for $C_{14}H_{24}O$: 208.1827, found: 208.1815.

(3*E*,5*Z*)-Tetradecadien-1-ol (6). To a solution of **5** (1.0 g, 4.8 mmol) in THF (40 ml) at −10 °C was added over a period of 30 min a solution of disiamylborane (23.4 mmol) [prepared from 2-methyl-2-butene (2.98 ml, 28.2 mmol), THF (100 ml), BH_3 · THF (1.0 M in THF, 23.4 ml, 23.4 mmol), 0 °C, 30 min]. The reaction mixture was stirred for 20 min at −10 °C, then warmed up to 0 °C and left for 4 h. Acetic acid (6.2 ml) was added and the reaction was heated at 60 °C for 6 h, then cooled to room temperature and stirred for an additional 12 h. The reaction was quenched by the addition of NaOH (6 M, 20 ml) at −5 °C, followed by dropwise addition of hydrogen peroxide (30% aq, 5 ml) and warmed to 40 °C for 30 min. The reaction was cooled to room temperature and diluted with diethyl ether (30 ml) and water (30 ml). The layers were separated and the aqueous layer was extracted with diethyl ether; the combined organic layers were washed with saturated brine (2 × 30 ml) and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* at reduced pressure; the residual product was purified by column chromatography on silica gel using hexane–ethyl acetate (90 : 10) as the eluent, to afford 850 mg of **6** (85%). IR (film) ν_{max}/cm^{-1}: 3345 (OH), 2980 (C–H), 2960 (C–H), 1640 (C=C), *trans* def. 980 (C–H), *cis* def. 723 (C–H). ^{1}H NMR ($CDCl_3$) δ: 0.90 (3H, distorted t, J = 7.0), 1.10–1.55 (13H, mult), 2.15 (2H, quart, J = 6.9), 2.35 (2H, quart, J = 6.9), 3.70 (2H, t, J = 6.8), 5.35 (1H, dt, J = 10.9, 7.6), 5.60 (1H, dt, J = 15.0, 7.5), 5.90 (1H, dd, J = 11.0, 10.9), 6.35 (1H, ddd, J = 15.3, 11.0, 1.3 Hz). HR-MS m/z [M]$^+$: calc. for $C_{14}H_{26}O$: 210.1984, found: 210.1973.

(3*E*,5*Z*)-Tetradecadienoic acid (1). To a stirred solution of chromium trioxide (190 mg, 1.90 mmol) in 1.5 M H_2SO_4 (1.25 ml), maintained between 5 and 10 °C, was added a solution of **6** (400 mg, 1.90 mmol) in acetone (23 ml) over a period of 30 min. The mixture was stirred for another 2 h at room temperature; isopropanol (2 ml) and diethyl ether (100 ml) were then added. The organic layer was decanted, washed with brine (3 × 50 ml) and solvent removed *in vacuo*. The residue was diluted with diethyl ether and treated with 1 M NaOH (2 × 10 ml). The layers were separated and the aqueous layer acidified with 6 M H_2SO_4 and back-extracted with diethyl ether (3 × 10 ml). The organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. Final purification was accomplished by column chromatography on silica gel, using hexane–ethyl acetate (2 : 1) as the eluent to afford 350 mg of megatomic acid (**1**) as an oily liquid (83%). The retention time by GC analysis matched that of an authentic sample.[5] IR (film) ν_{max}/cm^{-1}: 3450 (COOH), 2980 (C–H), 2960 (C–H), 1640 (C=C), *trans* def. 980 (C–H), *cis* def. 723 (C–H). ^{1}H NMR ($CDCl_3$) δ: 0.90 (3H, distorted t, J = 7.0), 1.25 (12H, mult), 2.05 (2H, distorted quart, J = 6.9), 3.00 (2H, d, J = 6.9), 5.35 (1H, dt, J = 10.9, 7.6), 5.60 (1H, dt, J = 15.0, 7.5), 5.90 (1H, dd, J = 11.0, 10.9), 6.35 (1H, ddd, J = 15.3, 11.0, 1.3 Hz). HR-MS m/z [M]$^+$: calc. for $C_{14}H_{24}O_2$: 224.1776, found; 224.1768.

EAG recording

The olfactory sensitivity of a male black carpet beetle to (3*E*, 5*Z*)-tetradecadienoic acid was recorded by the electro-antennegram recording technique. 10 µl of a 0.1% solution of the synthetic compound in hexane were placed on a filter paper (8 × 60 mm); after complete evaporation of the solvent the filter paper was carefully inserted into a Pasteur pipette and air puffed onto a beetle antenna fixed between two silver electrodes. At the same time, air from a pipette with a filter paper of the same size treated with 10 µl of hexane was puffed

onto the antenna as a control. The male antennal preparation gave a response to the synthetic compound, showing up to 0.7 mV depolarization.

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