New Synthesis of cis-3,cis-5- and trans-3,cis-5-Tetradecadienoic Acids, Pheromone Constituents of Attagenus elongatulus and A. megatoma

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A new method for the synthesis of cis-3,cis-5- and trans-3,cis-5-tetradecadienoic acids, pheromone constituents of the dermestid beetles Attagenus elongatulus and A. megatoma, was developed. The syntheses are based upon the formation of trans-2-tetradecen-5-ynoic acid by reaction of 4-bromo-2-butenoic acid with 1-decynylmagnesium bromide. The enynoic acid undergoes alkali-induced isomerization to yield a mixture of acids from which cis-3- and trans-3-tetradecen-5-ynoic acids were separated in 31% and 34% yields, respectively. Methyl trans-2-tetradecen-5-ynoate was similarly prepared and isomerized to furnish methyl cis-3-tetradecen-5-ynoate in 8% yield. Reduction of the tetradecenynoic acids with dicyclohexylborane gave cis-3,cis-5- and trans-3,cis-5-tetradecadienoic acids in 4% and 39% yields, respectively. A better yield (49%) in the reduction of cis-3-tetradecen-5-ynoic acid to cis-3,cis-5-tetradecadienoic acid was obtained by hydrogenation over Lindlar's catalyst. Similarly, reduction of methyl cis-3-tetradecynoic acid with disiamylborane gave 22% methyl cis-3,cis-5-tetradecadienoate.

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Heslinga et al. (1) reported the synthesis of trans-2-alken-5-ynoic acids by coupling 4-bromo-trans-2-butenolic acid (4-bromocrotonic acid) and 1-alkyn-1-ylmagnesium bromides. The report noted that when the coupling reaction was heated mixtures of cis- and trans-3-alken-5-ynoic acids were formed. This last reaction could constitute a convenient synthesis of cis- and trans-3-tetradecen-5-ynoic acids (c3,a5-14:2 and t3,a5-14:2, respectively), which are pheromone constituents of the dermestid beetles Attagenus elongatulus (Casey) and A. megatoma (Fabricius), respectively.

The pheromones of these beetles were shown to contain c3,c5- and t3,c5-14:2 as principal if not sole constituents. The beetles are destructive pests of stored foodstuffs, and investigations have been made of t3,c5-14:2 as bait for monitoring studies (2). Rather complicated syntheses of these acids have been developed, which depend upon gas chromatographic (GC) separation of isomers (3-5). An extraordinarily simple synthesis was accidently discovered (6). Recently, a new synthesis of t3,c5-14:2 with many steps and low yield was reported (7).

We report here syntheses of c3,c5- and t3,c5-14:2 by a short reaction sequence that started with the reactions described by Heslinga et al. (1) and can provide gram quantities of these pheromones.

EXPERIMENTAL PROCEDURES

Methods. GC analyses were carried out with a Packard Model 428 instrument fitted with a 0.3 × 300-cm glass column packed with 3% EGSS-X or a 50-m 007-CPS-2 (J & S Scientific Inc., Crystal Lake, Illinois) glass capillary column. Also used were a 25-m OV 275 (Chrompack, Bridgewater, New Jersey) and a 100-m SP 2560 (Supelco Inc., Bellefonte, Pennsylvania) glass capillary column.

Liquid chromatographic separations were carried out on 35 × 3.7-cm or 45 × 4.7-cm glass columns (Michel-Miller type, Ace Glass Co., Vineland, New Jersey) packed with ca. 200 or 400 g, respectively, of 30 μm silica or AgNO3 on silica (20:100, w/w). Columns of this type, packed by ordinary tap-fill procedure, tested ca. 200 plates. When particularly crude samples were separated, a small column (13 × 1 cm, Michel-Miller) was connected as precolumn in series with the larger columns. A 35 × 3.7-cm column of the same type but packed with air-elutriated silver ion-saturated XN1010 exchange resin (8) was also used. A Schoeffel model GM 770 UV detector was employed. The columns were pumped with a Metering Pumps Ltd. type SII/100 unit with two variable stroke no. 3 heads 180 degrees out of phase to minimize flow fluctuations. Samples were applied with a Chromatonix slider valve with a 2-ml loop.

Proton and 13C nuclear magnetic resonance (1H-NMR and 13C-NMR) spectra were determined on a Bruker spectrometer. Tetramethylsilane was used as internal standard with samples in DCCI3 solution.

Mass spectral data were obtained with a Finnigan GC/MS spectrometer with butane as ionizing gas for chemical ionization (CI) technique.

Infrared (IR) determinations were made with a Perkin-Elmer model 621.

Preparations. 4-Bromocrotonic acid was prepared in 42% yield as described by Heslinga (1). Methyl 4-bromocrotonate was prepared as described by Vogel (9).

Trans-2-tetradecen-5-ynoic acid (t2,a5-14:2) was prepared by Heslinga's method (1) in 22% yield as off-white crystals (98% pure by GC). The structure was confirmed by NMR: 1H-NMR δ 8.8 (t, 2H, CH=CH2) (J = 15 Hz), 2.17 (m, 2H, CH2) (J = 15 Hz). Also used were a 25-m OV 275 (Chrompack, Bridgewater, New Jersey) and a 100-m SP 2560 (Supelco Inc., Bellefonte, Pennsylvania) glass capillary column.
METHODS

The preparation of methyl ester of t2,a5-14:2 from methyl 4-bromocrotonate was carried out by reaction with a molar equivalent of 1-decynylmagnesium bromide per the preparation of the acid just described. By GC analysis, the crude product contained 66% of the expected isomer together with 5% of c3,a5-14:2 and 3% of t3,a5-14:2 (as methyl esters). A peak with a longer retention amounting to 23% was identified as 9,11-eicosadiyne. The crude mixture was separated by vacuum distillation through a 15-cm indented column to yield 13.5 g (bp 25–40°C/0.5 mm), 12.7 g (bp 100–140°C/0.6 mm) and 1.6 g (bp 140–170°C/0.7 mm). The last fraction, which contained 93% of 9,11-eicosadiyne, was recrystallized from acetone to give a pure GC sample of 9,11-eicosadiyne: MS-CI m/e (rel int) 276 (m, 100); 10C-NMR: 140.0-C1 and 20.27.7-C2 and 9.31.9-C3 and 18.29.2, 28.9-C4-6 and 17-15; 28.4-C7 and 14; 19.2-C8 and 13; 77.4-C9 and 12; 65.4-C10 and 11.

Tetradecynoic acid mixtures and their methyl esters were isomerized by various methods to attain high conversions to c3,a5- and t3,a5-14:2. Method 1: the second distillation fraction above (12.7 g of methyl esters of t2,a5-[71%], c3,a5- [13%] and t3,a5-14:2 [6%] as well as 5% of 9,11-eicosadiyne) was treated with 70 mg sodium methoxide in 50 ml methanol at room temperature under N2 for 24 hr. The reaction mixture was poured into 400 ml ice and saline (saturated NaCl solution), and the resultant mixture was extracted with three 100-ml portions (3×100 ml) PE. The combined extracts were washed with 2×400-ml portions of saline and 1×400 ml H2O and dried over MgSO4. Isolation gave 12.6 g yellow oil that by GC on the 007-CPS-2 capillary (decomposed on SP 2560): 88% c3,c5-14:2 of 98% purity by GC.

Another portion (3.28 g) of c3,c5-14:2 was reduced over Lindlar’s catalyst in 50 ml PE containing 0.25 g quinoline at 10°C and 760 mm. The H2 uptake leveled out after 83% of the theoretical uptake. The mixture was filtered through a pad of filter aid. The filter aid was washed with 50 ml PE. The combined PE solutions were washed with 300 ml 2.5 N H2SO4 and 300 ml saline and dried with MgSO4. Filtration and solvent evaporation gave 2.81 g of solid. The product was recrystallized at low temperature from PE to give 1.61 g (49%) c3,c5-14:2 of 98% purity by GC.

Reduction of Me c3,a5-14:2 to c3,c5-14:2 was carried out by adapting the procedure of Svirskaya for the reduction of a conjugated diyne with dicyclohexylborane (10). Thus, 2.61 g (11.8 mmol) c3,a5-14:2 was treated with 35.4 mmol dicyclohexylborane in THF and subjected to acetolysis overnight at room temperature and then at 40–50°C for 1 hr. The crude product (9.0 g), which also contained boron compounds, was separated on a 35-cm silica column using 2-propanol/acetone/hexane (5:1:1000, v/v/v). Two large partially resolved peaks (UV detection at 260 nm) were collected. This material was analyzed by GC on the Ag resin 35-cm column with eluent methanol/ether (5:100, v/v), an excellent separation was achieved to yield 0.11 g (4%) of c3,c5-14:2 of 98% purity by GC.

Reduction of t3,a5-14:2 (2.89 g, 13 mmol) with dicyclobenzylborane gave 2.65 g t3,c5-14:2 (all as methyl esters; t2,a5-14:14 was not significant) 1 hr, 71, 5, 24; 3 hr, 65, 7, 28; 22 hr, 46, 18, 36; and 43 hr, 51, 23, 34, respectively. After 43 hr, the solution was poured into 800 ml saline, acidified to pH 3 and extracted with 3×150 ml ether. The combined ether extracts were washed with 600 ml saline, dried over MgSO4, and filtered. The filtrate

hexane (PE) in 22% yield. Because the total tetradecynoic acids is ca. 75% in these mixtures, the whole crude mixture was subjected to isomerization.

A GC program of 160°C for 11 rain followed by temperature rise to 190°C at 10°C per min was used to detect the formation of substances with long retention times. The GC results were (reaction time, GC percent-

ages for c3,a5-14:2, 2,4,5-14:3 and t3,a5-14:2 [all as methyl esters; t2,a5-14:14 was not significant]) 1 hr, 71, 5, 24; 3 hr, 65, 7, 28; 22 hr, 46, 18, 36; and 43 hr, 51, 23, 34, respectively. After 43 hr, the solution was poured into 800 ml saline, acidified to pH 3 and extracted with 3×150 ml ether. The combined ether extracts were washed with 600 ml saline, dried over MgSO4, and filtered. The filtrate

freed of ether on the rotary evaporator yielded 4.2 g orange oil. The oil was applied in ca. 0.5-g portions to a 35×3.7-cm silica and eluted with 2-propanol/acetic acid/hexane (5:1:1000, v/v/v). The last eluted peak yielded 0.98 g t3,a5-14:2. The two first large peaks were collected together to yield 2.51 g of a mixture that consisted of c3,a5-14:2 (77%), 2,4,5-14:3 (19%) and t3,a5-14:2 (2%) by GC of methyl esters. To obtain a higher conversion to t3,a5-14:2, the last collected fraction was isomerized in a solution of 2.8 g KOH in aqueous methanol (1:1, v/v). After 100 hr, a mixture having 53% c3,a5-14:2, 16% 2,4,5-14:3 and 31% t3,a5-14:2 was found. To this solution was added 20 ml dimethylsulfoxide (DMSO). After seven days, the mixture contained 48% c3,a5- and 37% t3,a5-14:2.

As a result of these isomerization reactions followed by separation on the silica columns, 2.61 g of c3,a5-14:2 and 2.89 g of t3,a5-14:2 (both 98% pure by GC) were obtained. Yields were 31% and 34%, respectively, based on bromo- crotonic acid. A typical silica separation is shown in Figure 1.

Reduction of c3,a5-14:2 to c3,c5-14:2 was carried out by adapting the procedure of Svirskaya for the reduction of a conjugated diyne with dicyclohexylborane (10). Thus, 2.61 g (11.8 mmol) c3,a5-14:2 was treated with 35.4 mmol dicyclohexylborane in THF and subjected to acetolysis overnight at room temperature and then at 40–50°C for 1 hr. The crude product (9.0 g), which also contained boron compounds, was separated on a 35-cm silica column using 2-propanol/acetone/hexane (5:1:1000, v/v/v). Two large partially resolved peaks (UV detection at 260 nm) were collected. This material was analyzed by GC on the 007-CPS-2 capillary (decomposed on SP 2560): 88% c3,c5-14:2 of 98% purity by GC.

Another portion (3.28 g) of c3,c5-14:2 was reduced over 1.2 g Lindlar’s catalyst in 50 ml PE containing 0.25 g quinoline at 10°C and 760 mm. The H2 uptake leveled out after 83% of the theoretical uptake. The mixture was filtered through a pad of filter aid. The filter aid was washed with 50 ml PE. The combined PE solutions were washed with 300 ml 2.5 N H2SO4 and 300 ml saline and dried with MgSO4. Filtration and solvent evaporation gave 2.81 g of solid. The product was recrystallized at low temperature from PE to give 1.61 g (49%) c3,c5-14:2 (98% pure by GC).

Reduction of t3,a5-14:2 (2.89 g, 13 mmol) with dicyclobenzylborane gave 5.5 g t3,c5-14:2 (1.16 g, 39%) of 98% purity by GC following separation on the Ag resin column using eluent THF/hexane (1:2, v/v). The last fraction was collected to yield 2.89 g t3,a5-14:2.

Reduction of Me c3,a5-14:2 (2.97 g, 12.6 mmol) with 2 mol disiamylborane in the same manner as the above reductions with dicyclobenzylborane gave a crude product of 8.58 g. This material was separated by passage through a 45-cm column packed with AgNO3/silica (20:100, w/w) in portions of 0.5 to 1.5 ml using eluent ACN/hexane (4:1000, v/v). A typical separation is shown in Figure 2. There were obtained 0.66 g (22%) of Me c3,c5-14:2, 94% pure by GC on 007-CPS-2.