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STEREOSELECTIVE SYNTHESIS OF THE MAJOR COMPONENT OF A MOSQUITO OVIPOSITION ATTRACTANT PHEROMONE FROM A ß-LITHIOPROPIONATE EQUIVALENT [1]

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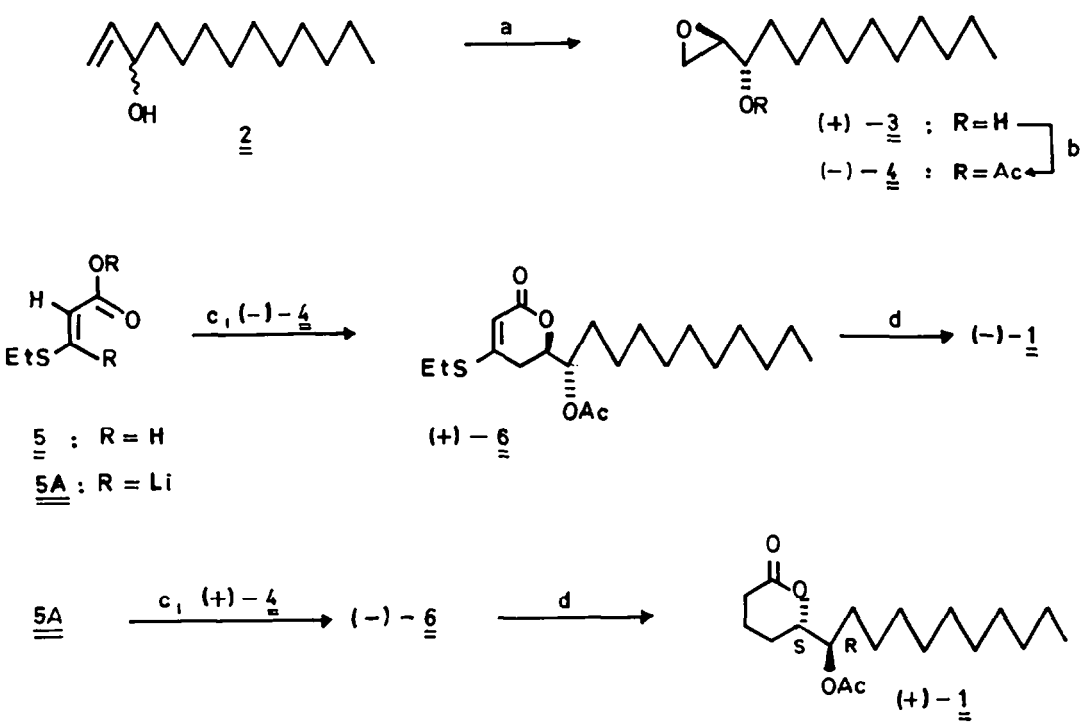
Abstract - ß-Lithiated ß-ethylthioacrylate 5A is a versatile ß-lithiopropionate equivalent. Reaction with enantiomerically pure epoxide (-)-4 and subsequent Raney nickel treatment gives the natural oviposition attractant pheromone of the mosquito Culex pipiens fatigans (-)-1. From epoxide (+)-4 the enantiomer (+)-1 is synthesized.

ß-Lithiated ß-aryl- and ß-alkylthiosubstituted acrylates are versatile ß-lithioacrylate and ß-lithiopropionate equivalents. This is exemplified in short γ- and δ-lactone syntheses with carbonyl compounds and epoxides, respectively, as the required electrophilic nucleophilic species. [2-6] Reaction with enantiomerically pure epoxides should give an easy entry into a variety of natural produtcs. This is demonstrated here in an essentially two step synthesis of the major oviposition attractant pheromone of the mosquito Culex pipiens fatigans (5R, 6S)-(-)-6-acetoxy-5-hexadecanolide (-)-1, [7] which was synthesized already independently. [8,9]

(-)-1

The epoxide (+)-3 was obtained by Sharpless epoxidation of the vinylmagnesium bromide adduct 2 as described by Mori and Otsuka. [8] Acetylation gave the required acetoxyepoxide (-)-4. ß-Ethylthioacrylic acid 5 was converted with two equivalents tert.-butyllithium into the corresponding dilithiated species 5A. [10] Addition of acetoxyepoxide (-)-4 in presence of borontrifluoride ether [3] and subsequent acid addition afforded the δ-lactone (+)-6 in 78% yield. This compound furnished upon treatment with Raney nickel in tetrahydrofuran almost exclusively the desired natural pheromone (-)-1, thus demonstrating the ß-lithiopropionate character of ß-lithiated acrylate 5A. The unnatural enantiomer (+)-1 was obtained via the same route from 5A and acetoxyepoxide (+)-4. Both enantiomers (-)-1 and (+)-1, respectively, had otpical rotation in agreement within experimental error with reported values. [8,9]



a. $Ti(OiPr)_4$, diisopropyl L-(+)-tartrate, t-BuOOH, CH_2Cl_2, -20°C, 20 h, b. Ac_2O, pyridine, RT, 12 h. c. (i) 2 eq t-BuLi, THF, -80°C, 2 h; (ii) 1 eq $BF_3 \cdot OEt_2O$, 1 eq (-)-4, -80°C, 10 min; (iii) p-TsOH, benzene, reflux, 15 min. d. Raney-Ni, THF, 10 min.

EXPERIMENTAL

Preparation of (2R,3S)- and (2S,3R)-1,2-Epoxi-3-tridecanol (+)-3 and (-)-3

Compound (+)- and (-)-3 are prepared by Sharpless asymmetric epoxidation according to the procedure described by Mori et al. [8] $[\alpha]_{589}^{RT}$ = +17.5° (c=1, $CHCl_3$), for (+)-3 reported $[\alpha]_D^{20}$ = +16.2° (c=1.01, $CHCl_3$); $[\alpha]_{589}^{RT}$ = -16.8° (c=1, $CHCl_3$), for (-)-3 reported $[\alpha]_D^{20}$ = -16.6° (c=1.12, $CHCl_3$).

(2R,3S)-3-Acetoxy-1,2-epoxytridecane (-)-4

To a solution of 2.5 g of (-)-3 in 1 ml pyridine is added 2 ml of acetic anhydride and the solution is allowed to stand overnight at room temperature. The reaction mixture is mixed with toluene (100 ml) and evaporated under reduced pressure to yield a gum which showed a single spot on t.l.c. (R_F 0.5, 1:5, ethyl acetate : petroleum ether 60°-80°). Flash chromatography of the crude yielded 2.6 g (99 %) of (-)-4 as a gum. $[\alpha]_{589}^{RT}$ = -10.8° (c=1, $CHCl_3$). - ^1H n.m.r. (400 MHz, $CDCl_3$): δ = 4.73 (dd, 1H, H-3, J = 5.6 and 12.7 Hz), 2.95 (m, 1H, H-2), 2.72 (m, 2H, H-1), 2.06 (s, 3H, acetate), 1.66 (m, 2H, H-4), 1.25 br, 16H, $-CH_2-$), 0.88 (t, 3H, $-CH_2-\underline{CH}_3$, J = 6.5 Hz).

(2S,3R)-3-Acetoxy-1,2-epoxytridecane (+)-4

With the same procedure as above but using acetoxyepoxide (+)-3 in place of epoxide (-)-3, compound (+)-4 was isolated in 95% yield as a gum; $[\alpha]_{589}^{RT}$ = +10.5° (c=1, $CHCl_3$).

(E)-3-Ethylthioacrylic Acid 5

Ethyl 3-ethylthioacrylate [11] (6.5 g, 44.5 mmol) was suspended in a mixture of methanol (20 ml) and water (20 ml). After addition of potassium hydroxide (2.74 g, 48.95 mmol) the mixture was refluxed for 2 h. Then the alcohol was evaporated under reduced pressure and the remaining solution diluted with ice water (50 ml) and acidified with concentrated hydrochloric acid to pH 1. Extraction with ether (4 x 50 ml) and subsequent evaporation afforded a crystalline product which was recrystallized from ether/petroleum ether, 1:1. Yield 4.94 g (84 %), colorless crystals, m.p. 82-83°C, reported [12] 83-84°C; - t.l.c. (chloroform/methanol, 9:1) R_F 0.66. - ^{1}H n.m.r. (80 MHz, $CDCl_3$) δ = 12.15 (sb, 1H, COOH), 8.05 (d, 1H, H-3, $J_{2,3}$ = 16.0 Hz), 5.85 (d, 1H, H-2, $J_{2,3}$ = 16.0 Hz), 2.90 (q, 2H, S-CH_2), 1.35 (t, 3H, CH_3).

This material was used for the synthesis of compound 6.

(6R,7S)-6-(1-Acetoxyundecanyl)-4-ethylthio-5,6-dihydro-pyran-2-one (+)-6

tert.-Butyllithium (4.5 ml of a 1.5 molar solution in hexane, 6.8 mmol) is added dropwise with stirring to a solution of trans-β-ethylthio-acrylic acid (5, 3.12 mmol) in dry THF (30 ml) at -80° under nitrogen. [3] The mixture is stirred for further 2 h at the same temperature and then $BF_3 \cdot OEt_2$ (3.12 mmol), distilled over CaH_2) is introduced into the reaction flask with a syringe. Immediately after the addition of $BF_3 \cdot OEt_2$ the acetoxyepoxide (-)-4 (0.8 g, 3.12 mmol) is added to the reaction mixture. After 10 min stirring at -80°, the reaction is stopped by adding a saturated solution of sodium hydrogen carbonate (15 ml) and the reaction mixture is allowed to reach room temperature. The reaction mixture is poured into water (200 ml), acidified to pH 1 with concentrated HCl and extracted with methylene chloride (4 x 100 ml). The organic phase is washed with water (100 ml), dried over anhydrous sodium sulfate, and evaporated. The residue is subjected to ring closure without further purification by refluxing in dry benzene for 15-20 min with a catalytic amount of p-toluene sulfonic acid. The reaction mixture is diluted with methylene chloride (200 ml), washed successively with a saturated solution of sodium hydrogencarbonate (50 ml) and water (50 ml), dried over sodium sulfate and evaporated to yield a gum which was homogenous on t.l.c. (R_F 0.5, ethyl acetate : petroleum ether, 1:1). The crude gum is further purified by flash chromatography to yield 0.88 g (76 %) of (+)-4 as a gum; $[\alpha]_{589}^{RT}$ = +55.0° (c=1, $CHCl_3$). - ^{1}H n.m.r., (400 MHz, $CDCl_3$) δ = 5.67 (d, 1H, H-3, J = 1.3 Hz), 5.07 (dd, 1H, H-7, J = 5.4 and 13 Hz), 4.44 (ddd, 1H, H-6, J = 3.4, 5.3, and 12.2 Hz), 2.89 (q, 2H, -S-$\underline{CH_2}$-CH_3, J = 7.3 Hz), 2.65 (dd, 1H, H-5a, J = 12.2 and 17.1 Hz), 2.3 (dd, 1H, H-5b, J = 3.4 and 17 Hz), 2.09 (s, 3H, acetate), 1.7 (m, 2H, H-8), 1.35 (t, 3H, -S-CH_2-$\underline{CH_3}$, J = 7.3 Hz), 1.25 (br, 16 H, H-9 to H-16), 0.85 (t, 3H, -$CH_2\underline{CH_3}$, J = 6.4 Hz). (Found: C, 64.84; H, 9.19. Calc. for $C_{20}H_{34}O_4S$: C, 64.83; H, 9.25%).

(6S, 7R)-6-(1-Acetoxyundecanyl)-4-ethylthio-5,6-dihydro-pyran-2-one (-)-6

With the same procedure as above but using acetoxyepoxide (+)-4 in place of acetoxyepoxide (-)-4, compound (-)-6 was isolated in 80% yield; $[\alpha]_{589}^{RT}$ =-54.3° (c=1, $CHCl_3$).

(5R,6S)-6-(6-Acetoxy-5-hexadecanolide (-)-1

A solution of (+)-6 (0.6 g, 1.62 mmol) in dry THF (20 ml) was stirred at room temperature with 2.0 g of Raney nickel while monitoring the reaction on t.l.c. After 10 min. when the t.l.c. indicated that no more of the starting material is present, the catalyst is filtered off and washed with THF (2 x 50 ml). The combined organic phase is evaporated under reduced pressure to yield (-)-1, as a gum

which was further purified by flash chromatography. Yield 0.43 g (85%). - $[\alpha]_{589}^{RT}$ =-35.2° (c=0.7, $CHCl_3$), reported [8] $[\alpha]_D^{21.5}$ = -38.5° (c=0.51, $CHCl_3$).

(5S,6R)-6-(6-Acetoxy-5-hexadecanolide (+)-1

Using the same method but using (-)-6 in place of (+)-6 compound (5S,6R)-6-acetoxy-5-hexadecanolide (+)-1 was obtained in 90% yield. - $[\alpha]_{589}^{RT}$ = +36.1° (c=1, $CHCl_3$), reported [8] $[\alpha]_D^{21.5}$ = +38.8° (c=1.21, $CHCl_3$). - ^1H n.m.r. (400 MHz) spectral data of (+)-1 were in accordance with the reported values.

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