Chemistry of Natural Compounds, Bioorganic, and Biomolecular Chemistry

New synthesis of serricornin, the sex pheromone of the cigarette beetle (*Lasioderma serricorne*)

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A new approach to the total synthesis of serricornin, the sex pheromone of the cigarette beetle, based on readily available (4*S*,5*E*)-4-methyhept-5-enenitrile was implemented.

Key words: (4*S*,6*S*,7*S*)-7-acetoxy-4,6-dimethylnonan-3-one, (*S*)-ethyl lactate, (4*S*,5*E*)-4-methylhept-5-enenitrile, (4*S*,5*E*)-4-methylhept-5-enoic acid, iodolactonization, serricornin, pheromones, cigarette beetle (*Lasioderma serricorne*).

The sex pheromone of the females of the cigarette beetle (*Lasioderma serricorne*), a pest for stored plant products including tobacco goods, has been identified as (4*S*,6*S*,7*S*)-7-hydroxy-4,6-dimethylnonan-3-one (**1a**) and its structure has been confirmed by a number of multisep syntheses.[1] Here we report one more approach to the synthesis of this compound, based on the transformation of (4*S*,5*E*)-4-methylhept-5-enenitrile (**2**),[2] which we prepared previously from (*S*)-ethyl lactate.

According to the chosen strategy, nitrile **2** was hydrolyzed almost quantitatively to give the corresponding heptenoic acid **3** (Scheme 1). Unfortunately, the stereoselectivity of iodolactonization of this acid under kinetic control conditions recommended[3] for this procedure proved to be rather low. Indeed, on treatment with NIS in DMF, acid **3** is converted into a mixture of isomeric lactones **4** and **5** (~3 : 2). When the acid is treated first with a saturated solution of $NaHCO_3$ and then with aqueous I_2 in the presence of KI (see Ref. 4), iodolactonization is actually not stereoselective.

The mixture of stereoisomers **4** and **5** was, nevertheless, quantitatively resolved into components by column chromatography. Subsequently, iodides **4** and **5** were dehalogenated by treatment with Bu^n_3SnH (see Ref. 4) to give lactones **6** and **7**, respectively. The former compound, whose stereochemistry was adequate to the given task, was subjected to *C*-methylation. The trisubstituted pentanolide **8** obtained in this stereospecific reaction[6] was made to condense with EtMgBr.[6] The target hydroxy ketone **1a** thus obtained, existing as an equilibrium mixture of the open and hemiketal forms,[7] was converted into acetate **1b**, which is traditionally used for

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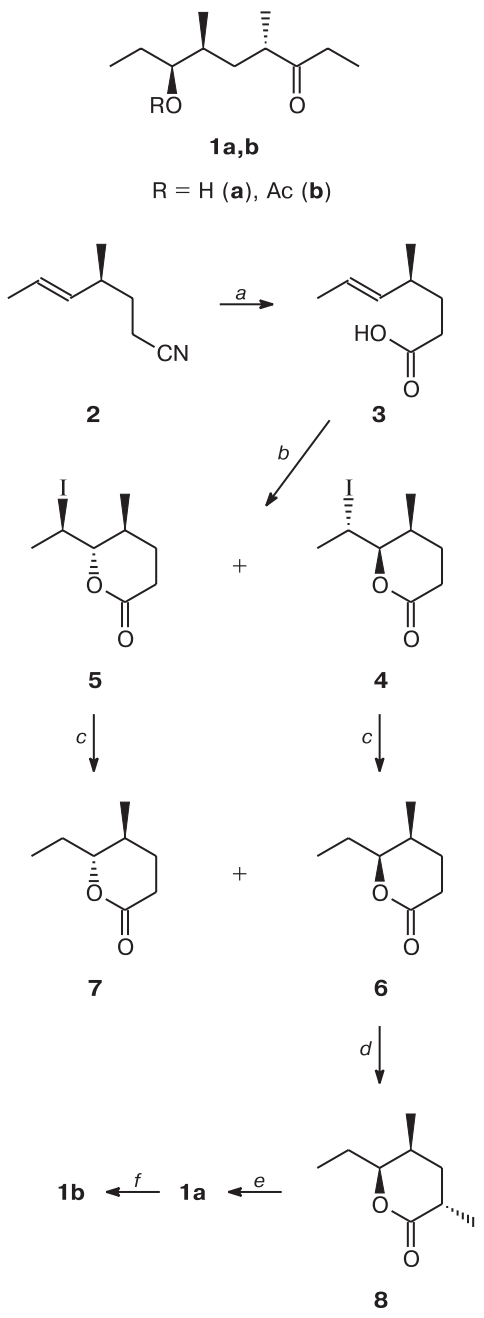
Scheme 1



Reagents and conditions: *a*. NaOH/EtOH, sealed tube, 200 °C. *b*. aq. $NaHCO_3$, then I_2/KI, H_2O, 20 °C (*A*); NIS, DMF, 20 °C (*B*). *c*. Bu^n_3SnH/AIBN, PhH, 80 °C. *d*. $(TMS)_2NLi$, THF/HMPA, −78→10 °C, then MeI, −78 °C. *e*. EtMgBr, THF, −40 °C. *f*. Ac_2O/Py, 20 °C.

determining the authenticity of this pheromone. It is also noteworthy that lactone **7**, which has not found application in this study, deserves attention as a starting compound in the synthesis of macrolide antibiotics of the milbemycin and avermectin series (see, for example, Ref. 8).

The structures of the previously unknown compounds **3—5** were confirmed by the combination of data from elemental and spectroscopic analyses. In particular, the *cis*-configuration of the substituents in lactone **4** is indicated by the smaller (2.6 Hz) spin-spin coupling constant of the C(4)H and C(5)H protons compared to this value for the *trans*-isomer **5** (8.8 Hz). The configuration of the MeCHI fragment in lactones **4**, **5** was identified taking into account the known *anti*-diastereospecificity of iodolactonization, reported previously for related compounds.[3]

The ^1H and ^{13}C NMR spectra of lactones **6**,[6] **7**,[9] and **8**[6] and acetate **1b**[7,10] virtually coincided with the spectra reported previously. Note that the specific optical rotation of lactone **6** reported in two publications ($[\alpha]_D^{24}$ −65.82 (*c* 1.024, $CHCl_3$),[8] $[\alpha]_D$ −63.90 (*c* 1.0, $CHCl_3$)[11]) differs from the value found for the compound we prepared ($[\alpha]_D^{21}$ −86.7 (*c* 1.01, $CHCl_3$)). Moreover, the specific optical rotation of lactone **8** ($[\alpha]_D^{20}$ −74.3 (*c* 0.96, $CHCl_3$)), which was then synthesized from compound **6** by a known procedure,[6] differs just as appreciably ($[\alpha]_D^{25}$ −45.82 (*c* 0.875, $CHCl_3$),[6] $[\alpha]_D^{24}$ −59.58 (*c* 0.876, $CHCl_3$)[8]). The reasons for this discrepancy are not entirely clear, the more so, because for the final product, acetate **1b**, this parameter ($[\alpha]_D^{22}$ −18.2 (*c* 0.61, $CHCl_3$)) was almost identical to the value reported for enantiomerically pure semisynthetic (prepared by acetylation of the natural pheromone **1a**) ($[\alpha]_D^{23}$ −17.7 (*c* 0.155, hexane)[10]) and synthetic specimens ($[\alpha]_D^{23}$ −17.9 (*c* 0.168, $CHCl_3$),[6] $[\alpha]_D^{21.5}$ −18.2 (*c* 0.58, hexane),[7] $[\alpha]_D^{25}$ −18.4 (*c* 0.07, hexane)[12]).

Experimental

IR spectra were recorded on a Specord M-80 instrument. ^1H and ^{13}C NMR spectra were measured on a Bruker AC-200 spectrometer (200.13 and 50.32 MHz, respectively) in $CDCl_3$. The chemical shifts are referred to the solvent signals (7.27 (^1H) and 77.0 (^{13}C)). Mass spectra (EI) were run on a Varian MAT-311A instrument (70 eV). Optical rotation ($[\alpha]_D$) was measured on a Jasco DIP-360 polarimeter. Column chromatography was performed using Silica gel 60 (≤0.063 mm, Fluka).

All solvents were purified and dried by standard procedures. The commercial reagents NIS, Bu^n_3SnH, AIBN, and $(TMS)_2NH$ (Fluka) were used as received.

(4*S*,5*E*)-4-Methylhept-5-enoic acid (3). A mixture of nitrile **2** (0.28 g, 2.28 mmol), NaOH (0.30 g, 7.34 mmol), EtOH (2.6 mL), and H_2O (0.05 mL) was heated for 5 h at 200 °C in a tube sealed under argon. Then the mixture was cooled to ~20 °C and concentrated *in vacuo* to dryness. The powder residue was washed on a filter with $MeOBu^t$ and dissolved in water. The aqueous solution was acidified with 27% $HClO_4$ to pH ~1 and extracted three times with $MeOBu^t$. The combined ethereal layer was washed three times with brine, dried with Na_2SO_4,

and concentrated *in vacuo*, and the residue was chromatographed on SiO_2. Gradient elution with MeOBu^t—hexane mixtures (1 : 9 to 3 : 17 (v/v)) gave 0.32 g (99%) of acid **3** as a colorless oil. Distillation using a short-path distillation apparatus (~80 °C, 1 Torr) afforded 0.31 g (96%) of acid **3** as a colorless oil, $[\alpha]_D^{24}$ +27.7 (*c* 2.16, MeOH). Found (%): C, 68.02; H, 9.99. $C_8H_{14}O_2$. Calculated (%): C, 67.57; H, 9.92. IR (film), ν/cm^{-1}: 945, 975, 1220, 1250, 1275, 1380, 1417, 1453, 1710, 2880, 2930, 2965. ^{1}H NMR, δ: 0.99 (d, 3 H, C(4)Me, J = 6.6 Hz); 1.45—1.75 (m, 2 H, C(3)H$_2$); 1.65 (dd, 3 H, C(7)H$_3$, J = 6.2 Hz, J = 1.3 Hz); 1.95—2.20 (m, 1 H, C(4)H); 2.20—2.48 (m, 2 H, C(2)H$_2$); 5.22 (ddq, 1 H, C(5)H, J = 15.3 Hz, J = 7.8 Hz, J = 1.3 Hz); 5.42 (dq, 1 H, C(6)H, J = 15.3 Hz, J = 6.2 Hz). ^{13}C NMR, δ: 17.8 (C(7)); 20.8 (MeC(4)); 31.6; 32.1; 36.5 (C(4)); 124.4 (C(6)); 136.0 (C(5)); 180.5 (C(1)).

(1′*S*,5*S*,6*R*)-6-(1′-Iodoethyl)-5-methyltetrahydro-2*H*-pyran-2-one (4) and (1′*R*,5*S*,6*S*)-6-(1′-iodoethyl)-5-methyltetrahydro-2*H*-pyran-2-one (5). ***A.*** A solution of KI (372 mg, 2.24 mmol) and I_2 (474 mg, 1.86 mmol) in 2 mL of H_2O was added at 20 °C (argon) to a solution of acid **3** (176.5 mg, 1.243 mmol) in 1 mL of a saturated solution of $NaHCO_3$. The reaction mixture was stirred for 40 min at 20 °C and diluted 3-fold with H_2O. Sodium thiosulfate was added until the mixture became colorless, and the mixture was extracted three times with MeOBu^t. The combined ethereal layer was washed twice with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The residue (0.31 g, yellow oil) was chromatographed on SiO_2. Elution with a MeOBu^t—hexane mixture (3 : 17 (v/v)) gave 153 mg (46%) of lactone **4**; further gradient elution with MeOBu^t—hexane mixtures (1 : 4 to 3 : 7 (v/v)) furnished 149 mg (45%) of lactone **5**.

Lactone 4. Colorless crystals, m.p. 57—60 °C. Found (%): C, 36.24; H, 4.77; I, 47.27. $C_8H_{13}IO_2$. Calculated (%): C, 35.84; H, 4.89; I, 47.34. IR ($CHCl_3$), ν/cm^{-1}: 540, 625, 914, 995, 1027, 1060, 1070, 1140—1270, 1344, 1353, 1393, 1455, 1736, 2800—3100. ^{1}H NMR, δ: 0.95 (d, 3 H, C(5)Me, J = 7.2 Hz); 1.65—1.82 (m, 1 H, C(4)H$_{ax}$); 2.02—2.22 (m, 1 H, C(4)H$_{eq}$); 2.10 (d, 3 H, H$_3$CCHI, J = 6.5 Hz); 2.48—2.60 (m, 2 H, C(3)H$_2$); 4.02 (dq, 1 H, HCI, J = 10.8 Hz, J = 6.5 Hz); 4.31 (dd, 1 H, C(6)H, J = 10.8 Hz, J = 2.6 Hz). ^{13}C NMR, δ: 10.5; 24.2; 25.4 (superimposition of two signals, DEPT data); 26.3; 29.1 (C(5)); 86.2 (C(6)); 170.3 (C(2)).

Lactone 5. Colorless crystals, m.p. 56—59 °C. Found (%): C, 36.07; H, 5.02; I, 46.76. $C_8H_{13}IO_2$. Calculated (%): C, 35.84; H, 4.89; I, 47.34. IR ($CHCl_3$), ν/cm^{-1}: 595, 914, 991, 1020, 1039, 1067, 1118, 1140—1270, 1334, 1353, 1388, 1463, 1736, 2800—3100. ^{1}H NMR, δ: 1.08 (d, 3 H, C(5)Me, J = 6.5 Hz); 1.48—1.70 (m, 1 H, C(4)H$_{ax}$); 1.80—2.10 (m, 2 H, C(4)H$_{eq}$ and C(5)H); 1.85 (d, 3 H, H$_3$CCHI, J = 7.2 Hz); 2.40—2.73 (m, 2 H, C(3)H$_2$); 4.12 (dd, 1 H, C(6)H, J = 8.8 Hz, J = 2.9 Hz); 4.45 (dq, 1 H, HCI, J = 7.2 Hz, J = 2.9 Hz). ^{13}C NMR, δ: 17.6; 21.4; 25.0; 27.0; 29.2; 30.9 (C(5)); 89.0 (C(6)); 170.7 (C(2)).

B. A solution of acid **3** (14.2 mg, 0.1 mmol) and NIS (30 mg, 0.13 mmol) in 0.5 mL of DMF was stirred under argon for 20 h at 20 °C, diluted with water, and extracted with MeOBu^t. The extract was washed twice with water and with brine, dried with Na_2SO_4, and concentrated *in vacuo* to give 20 mg (75%) of a mixture of iodolactones **4**, **5** (~3 : 2, ^{1}H NMR data).

(5*S*,6*S*)-6-Ethyl-5-methyltetrahydro-2*H*-pyran-2-one (6). Bu$^n{}_3$SnH (0.78 g, 2.67 mmol) and AIBN (10 mg) were added under argon to a solution of lactone **4** (0.55 g, 2.05 mmol) in 5 mL of PhH. The reaction mixture was refluxed for 2 h, cooled to 20 °C, diluted twofold with MeOBu^t, and filtered through a short SiO_2 layer. The filtrate was concentrated *in vacuo* and the residue was chromatographed on SiO_2. Gradient elution with MeOBu^t—hexane mixtures (1 : 4 to 3 : 7 (v/v)) afforded 0.28 g (97%) of lactone **6** as a colorless oil, b.p. 76 °C (1 Torr). MS, m/z (I_{rel} (%)): 142 [M]$^+$ (2), 113 [M – Et]$^+$ (33), 85 (23), 84 (26), 57 (25), 56 (100), 55 (46). ^{1}H NMR, δ: 0.91 (d, 3 H, C(5)Me, J = 7.2 Hz); 0.96 (t, 3 H, MeCH$_2$, J = 7.2 Hz); 1.38—2.13 (m, 5 H, C(4)H$_2$, C(5)H, MeCH$_2$); 2.46—2.58 (m, 2 H, C(3)H$_2$); 4.17 (ddd, 1 H, C(6)H, J = 8.5 Hz, J = 5.5 Hz, J = 2.9 Hz). ^{13}C NMR, δ: 10.0 (MeCH$_2$); 12.2 (MeC(5)); 24.9; 26.0; 26.6; 28.8 (C(5)); 84.4 (C(6)); 171.9 (C(2)).

(5*S*,6*R*)-6-Ethyl-5-methyltetrahydro-2*H*-pyran-2-one (7) was prepared in a similar way from iodolactone **5**. The product was a colorless oil, b.p. 76 °C (1 Torr), $[\alpha]_D^{20}$ +53.3 (*c* 0.99, $CHCl_3$) (*cf.* Ref. 8: $[\alpha]_D^{26}$ +49.32 (*c* 1.034, $CHCl_3$)). MS, m/z (I_{rel} (%)): 142 [M]$^+$ (2), 113 [M – Et]$^+$ (47), 85 (35), 84 (28), 57 (30), 56 (100), 55 (54). ^{1}H NMR, δ: 1.00 (d, 3 H, C(5)Me, J = 6.5 Hz); 1.02 (t, 3 H, MeCH$_2$, J = 7.2 Hz); 1.45—2.00 (m, 5 H, C(4)H$_2$, C(5)H, MeCH$_2$); 2.36—2.72 (m, 2 H, C(3)H$_2$); 3.90 (ddd, 1 H, C(6)H, J = 9.5 Hz, J = 7.5 Hz, J = 3.3 Hz). ^{13}C NMR, δ: 8.7 (MeCH$_2$); 17.3 (MeC(5)); 26.1; 27.7; 29.5; 31.6 (C(5)); 86.8 (C(6)); 172.0 (C(2)).

(3*S*,5*S*,6*S*)-6-Ethyl-3,5-dimethyltetrahydro-2*H*-pyran-2-one (8). A 1.71 *M* hexane solution of Bu^{n}Li (0.74 mL, 1.26 mmol) was added at −78 °C under argon to a stirred solution of (TMS)$_2$NH (0.32 g, 1.49 mmol) in 2 mL of THF and 0.5 mL of HMPA. After 15 min, a solution of lactone **6** (163 mg, 1.148 mmol) in 0.5 mL of THF was added to the resulting (TMS)$_2$NLi at the same temperature. The reaction mixture was stirred for 30 min at −78 °C and for 1 h at −10 °C, and cooled again to −78 °C. Methyl iodide (0.29 mL, 4.59 mmol) was added and the mixture was kept for 1 h at −78 °C and quenched with a saturated solution of NH_4Cl. The aqueous layer was separated and extracted three times with MeOBu^t. The combined organic phase was washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*, and the residue was chromatographed on SiO_2. Gradient elution with MeOBu^t—hexane mixtures (1 : 4 to 3 : 7 (v/v)) gave 149 mg (83%) of lactone **8** as a colorless oil. MS, m/z (I_{rel} (%)): 156 [M]$^+$ (1), 127 [M – Et]$^+$ (12), 84 (21), 70 (56), 56 (100). ^{1}H NMR, δ: 1.00 (d, 3 H, C(5)Me, J = 6.9 Hz); 1.00 (t, 3 H, MeCH$_2$, J = 7.3 Hz); 1.25 (d, 3 H, C(3)Me, J = 7.2 Hz); 1.40—2.15 (m, 5 H, C(4)H$_2$, C(5)H, MeCH$_2$); 2.50—2.75 (m, 1 H, C(3)H); 4.24 (ddd, 1 H, C(6)H, J = 8.5 Hz, J = 5.8 Hz, J = 2.9 Hz). ^{13}C NMR, δ: 7.1; 8.4; 15.1 (MeC(5)); 22.7; 26.5; 28.5; 33.1 (C(5)); 82.6 (C(6)); 174.5 (C(2)).

(4*S*,6*S*,7*S*)-7-Actoxy-4,6-dimethylnonan-3-one (serricornin acetate) (1a). A 0.87 *M* solution of EtMgBr (0.73 mL, 0.63 mmol) in THF was added to a solution of lactone **8** (90 mg, 0.58 mmol) in 3 mL of THF stirred under argon at −40 °C. The reaction mixture was stirred for an additional 2 h at the same temperature and for 2 h at 20 °C and quenched with a saturated solution of NH_4Cl. The aqueous layer was separated and extracted 3 times with pentane. The combined organic phase was dried with Na_2SO_4 and concentrated and the resulting hydroxy ketone **1** was acetylated, without further purification, with a mixture of 0.5 mL Ac_2O and 0.5 mL of Py for 10 h at 20 °C.

The reaction mixture was diluted with $MeOBu^t$, washed with water, 5% HCl, a saturated solution of $NaHCO_3$, and brine, dried with Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on SiO_2. Gradient elution with $MeOBu^t$—hexane mixtures (1 : 9 to 3 : 17 (v/v)) afforded 85 mg (65%) of acetate **1a** as a colorless oil. MS, m/z (I_{rel} (%)): 168 $[M - AcOH]^+$ (14), 157 (8), 140 (2), 139 (20), 128 (5), 127 (5), 125 (4), 117 (4), 112 (5), 111 (27), 101 (2), 99 (13), 97 (5), 91 (2), 87(6), 86 (65), 84 (5), 83 (33), 82 (6), 70 (22), 69 (53), 57 (78), 56 (9), 55 (30), 43 (100). ^{1}H NMR, δ: 0.85 (t, 3 H, C(9)H_3, J = 7.2 Hz); 0.87 (d, 3 H, C(6)Me, J = 6.5 Hz); 1.03 (d, 3 H, C(4)Me, J = 6.5 Hz); 1.04 (t, 3 H, C(1)H_3, J = 7.2 Hz); 1.14—1.78 (m, 5 H, C(5)H_2, C(6)H, C(8)H_2); 2.05 (s, 3 H, COMe); 2.40—2.74 (m, 3 H, C(2)H_2 and C(4)H); 4.80 (m, 1 H, C(7)H). ^{13}C NMR, δ: 7.8, 10.1, 14.4, 16.6, 21.1, 24.1, 33.6, 34.3, 35.8, 43.4, 79.0, 171.0, 215.2.

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