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Stereoselective Synthesis of Sitophilate and Sitophilure†

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Abstract: Synthesis of sitophilate **6**, the male-produced aggregation pheromone of the granary weevil, has been achieved with an overall yield of 46% from **1** in high enantiomeric and diastereomeric purity. From sitophilate, sitophilure **8**, aggregation pheromone of the rice weevil and maize weevil, was prepared in a four-step synthesis without any racemization.

The granary weevil *Sitophilus granarius* is a pest which causes commercially important damage to stored cereal grains. Its male-produced aggregation pheromone was isolated, named sitophilate, and identified by Phillips et al.[1] as (R^*,S^*)-1-Ethylpropyl 2-methyl-3-hydroxypentanoate. A synthesis of both enantiomers employing Sharpless asymmetric epoxidation with overall yield of 22% was reported by Chong[2]. Bioassays by Phillips et al.[3] revealed the (2S,3R) enantiomer as the active form of the pheromone. Mori[4] reported another synthesis of sitophilate starting from (S)-methyl 3-hydroxypentanoate, available by biochemical methods[5]; the yield of pheromone obtained in this case was 10%. To the best of our knowledge, no other synthesis of sitophilate has been described since then in the literature, involving chemical asymmetric reactions as key step. In this paper we wish to report on the stereoselective synthesis of sitophilate in enantiomerically pure form with an overall yield of 46% from methyl 3-oxopentanoate **1** , commercially available. Furthermore, sitophilure has been prepared from sitophilate **6** with an overall yield of 58% and unaltered enantiomeric purity, proof that the sequence proceeds with no racemization.

The first step in the synthesis of sitophilate (Scheme 1) was transesterification of **1** with 3-pentanol following Taber's procedure for the preparation of β-keto esters[6] with a modification: an excess of alcohol was used instead of ester. The keto ester **2** was obtained in 85% yield. This procedure is suitable for large scale application and the excess alcohol was easily recovered. Interestingly, this compound has been described as a minor product in Chong's synthesis[2].

The next step, key in the synthesis, was asymmetric reduction of the keto ester to yield chiral hydroxyester **3**. Noyori's asymmetric hydrogenation of 3-oxo carboxylates (methyl or ethyl, mainly) using BINAP-Ru complexes[7] was used due to its high efficiency: substrate to catalyst mole ratio >1000, high chemical yield, and enantiomeric excess and simple isolation of products. Although the original method[7a] employed drastic experimental conditions, hydrogen pressure of 100 atm and long reaction times, recently[7c] much lower pressures and shorter reaction times have been employed. In our case, the reaction proceeded smoothly under 4 atm in a simple Parr hydrogenation apparatus provided with a heating mantle instead of the stainless steel autoclave used by Noyori. Thus, the hydroxyester **3** was obtained with 98%

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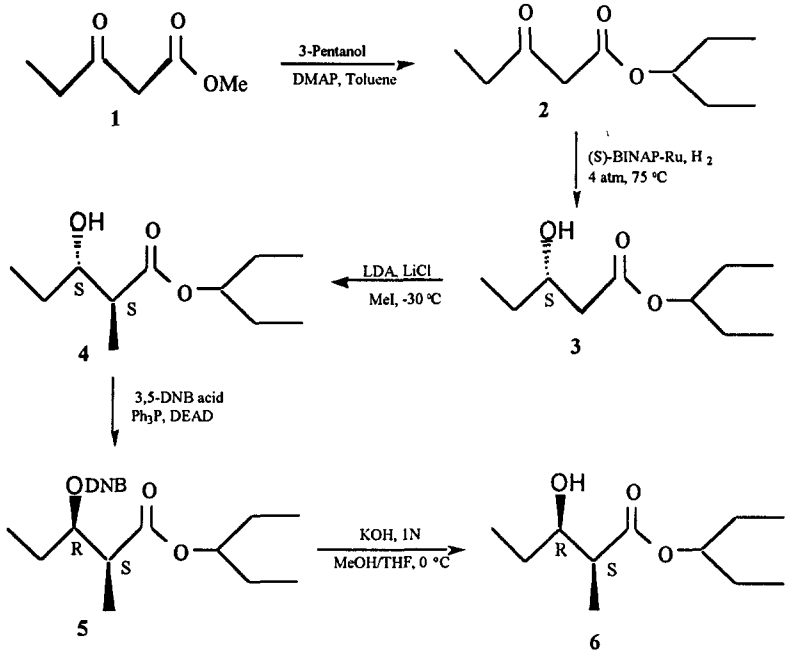
yield and enantiomeric excess near 100% as showed by GC analysis on Cyclodex-β capillary column (racemic **3** was obtained as a reference by reduction of **2** with $NaBH_4$).



SCHEME 1

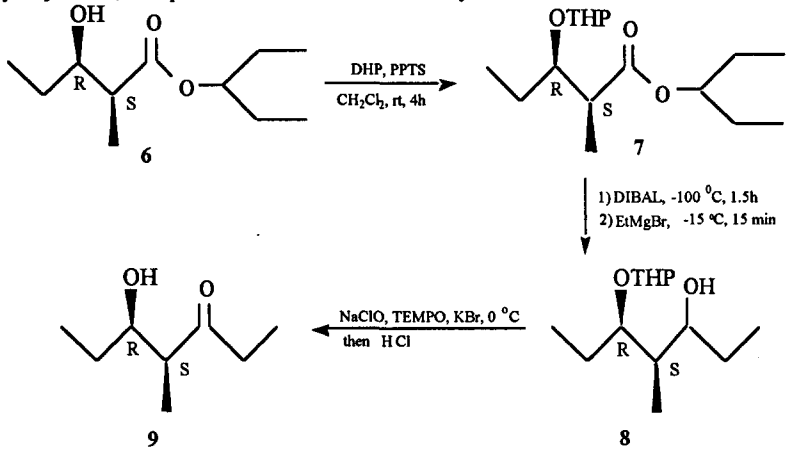
Data for compound **3** was not available in the literature. In order to check the absolute configuration of the new stereocenter, it was hydrolyzed to obtain (S)-3-hydroxypentanoic acid. Comparison with data existing in the literature for the R enantiomer[8] showed the enantiomeric excess of the acid to be >99% ee, in agreement with GC data for the hydroxyester **3**.

The next step was asymmetric alkylation to obtain compound **4**, a reaction that gives rise to the anti diastereomer as a major product[9]. Thus, dianion of compound **3** was generated with LDA using an excess of n-BuLi[10]. When the deprotonation was carried out in the presence of LiCl, the conversion increased in agreement with the work of Myers et al.[11] illustrating the synthetic potential of metal salts (instead of carcinogenic HMPA) in reactions of enolates[12]. Subsequent reaction of the dianion with MeI at -30°C afforded compound **4** in almost quantitative yield and 80% diastereomeric excess based on GC and ^{13}C NMR. Due to the difficulty in the separation of diastereomers at this stage, the mixture was used for next step. Mitsunobu inversion[13] of the hydroxy group of **4** using 3,5- dinitrobenzoic acid, Ph_3P and DEAD yielded a residue which upon column chromatography afforded diastereomerically pure **5** in 61% yield. Physical and spectroscopical data are in agreement with those reported[4] but without the tedious recrystallizations. Finally, removal of ODNB group under mild basic conditions furnished sitophilate **6** in 90% yield, diastereomerically pure by GC and ^{13}C NMR. Its enantiomeric purity was estimated as >98% by comparison of its specific rotation with literature[4].

Concerning sitophilure **9**, this pheromone common to the rice weevil *Sitophilus oryzae* and the maize weevil *S. zeamais* was identified by Schmuff et al.[14] as (R^*,S^*)-4-Methyl-5-hydroxy-3-heptanone. A synthesis of the four possible stereoisomers was reported by Mori[15] to clarify the stereochemistry-bioactivity relationship, starting from a single chiral source, (R)- methyl 3-hydroxypentanoate of microbial origin[16].

Bioassay of Mori's samples by Walgenbach et al.[17] revealed (4S,5R) stereoisomer to be the pheromone. Since then, several syntheses of sitophilure have been reported based on aldol reaction starting from chiral α-trialkylsilyl ketones[18] or cyclic bromoboranes[19], addition of organolithium to homochiral acylketene acetals[20] or reduction of 3-acyltetrahydrothiopyran-4-ones with Bakers' yeast[21].

Here we report the preparation of sitophilure **9** through a four-step synthesis from enantiomerically pure sitophilate **6** (Scheme 2). Thus, after protection of the hydroxy group as tetrahydropyranyl ether, compound **7** was obtained in 96% yield.



SCHEME 2

Diisobutylaluminum hydride reduction at low temperatures[22] was used for conversion of **7** to the corresponding aldehyde. The reaction proceeded in quantitative yield (as shown by GC) at -100°C and shorter reaction times. Due to its unstability, the aldehyde was treated, without further purification, with ethylmagnesium bromide to give **8** in 84% yield after column chromatography.

In the last step, oxidation of secondary alcohol to ketone group, reaction with sodium hypochlorite was considered the most suitable because of its mild reaction conditions and short reaction times. Thus, the procedure described by Anelli et al.[23] for the oxidation of primary alcohols to aldehydes was applied to compound **8**. Under the acidic work-up conditions, the OTHP ether was simultaneously cleaved and sitophilure **9** was isolated in 72% yield. The pheromone was obtained in an overall yield of 58% from sitophilate **6**, had physical and spectroscopical data in agreement with those reported by Mori[15], and had an enantiomeric excess higher than 98%. The yield of sitophilure in Mori's synthesis was 4.3% in 15 steps from (R)-methyl 3-hydroxypentanoate.

In summary, an efficient stereoselective synthesis of sitophilate in high enantiomeric excess has been achieved and is suitable for large scale application. Also sitophilure has been prepared from sitophilate through a four-step synthesis without loss of enantiomeric excess.

Experimental: ^1H and ^1C NMR spectra were obtained in $CDCl_3$ solutions on a Varian Gemini 200. Gas chromatography analysis were conducted in a Shimazu GC-14B, equipped with a FID detector using helium as carrier gas; capillary columns were used: TRB-1 (30m x 0.25mm) and β-DEX 110 (30m x 0.25mm). Elemental analyses were performed in a Carlo Erba EA 1108 Analyzer. Infrared spectra were recorded on a Nicolet 510M FT-IR. Optical rotations were measured in a JASCO-DIP-370 polarimeter. Hydrogenations were conducted in a Parr 3911 shaker-type hydrogenation apparatus.

1-Ethylpropyl 3-oxopentanoate 2. To a solution of 28.7 ml (260 mmol) of 3-pentanol containing 1.6 g (13 mmol) of 4-DMAP in 50 ml of anhydrous toluene was added 16.8 ml (130 mmol) of methyl 3-oxopentanoate. The mixture was refluxed for 2.5 days and cooled to 0°C. After treatment with 250 ml of saturated NH_4Cl solution and extraction with ether, the organic layer was washed with 1N HCl and dried (Na_2SO_4). The solvent was removed and the crude liquid distilled to give 20.7 g (85%)[24] of pure **2**, b.p. 155-157°C (26 mm Hg); IR (film): 1737 (C=O, ester), 1716 (C=O, ketone) cm^{-1}; ^{1}H-NMR: δ 0.81(t, J=7.4 Hz, 6H), 1.00 (t, J=7.3 Hz, 3H), 1.40-1.60 (m,4H), 2.50 (q, J=7.2 Hz, 2H), 3.38 (s, 2H), 4.72 (quintet, J=6.2 Hz, 1H); ^{13}C-NMR: δ 7.51, 9.52, 26.31, 36.23, 49.21, 77.89, 166.93, 203.14.

(S)-1-Ethylpropyl 3-hydroxypentanoate 3. A 25 ml flask was charged with benzeneruthenium (II) chloride dimer (8.54 mg, 0.017 mmol), (S)-BINAP (22.31 mg, 0.036 mmol) and 1ml of dry DMF under nitrogen. The resulting suspension was stirred at 100°C for 10 min, DMF was then eliminated yielding a reddish solid which was taken up in dry MeOH (10 ml). The solution was transferred to a 250 ml Parr bottle containing 1-ethylpropyl 3-oxopentanoate (13.9 g, 75.6 mmol) and methanol (15 ml), previously degassed.The bottle, provided with a heating mantle, was assembled in the Parr apparatus. After flushing several times with hydrogen, this was pressurized to 4 atm. The solution was heated at 75°C for 8 h with magnetic stirring and continuous hydrogen supply. After cooling, the excess hydrogen was removed and the apparatus disassembled. The orange solution was concentrated and the residue purified by distillation to afford 13.84 g (98%) of **3** as a colourless liquid. GC: capillary column β-DEX 110, temp. 190°C, R_t= 24.96 min. single peak (determined as acetate derivative); b.p. 114-116°C (1.4 mm Hg); $[\alpha]^{22}_D$ +26.55 (c 0.52, $CHCl_3$); IR (film) : 3455 (OH) , 1732(C=O) cm^{-1}; ^{1}H-NMR: δ 0.83 (t, J=7.5 Hz, 6H), 0.90 (t, J=7.4 Hz, 3H), 1.38-1.59 (m, 6H), 2.33 (dd, J=16.1 and 8.4 Hz, 1H), 2.47 (dd, J=16.1 and 3.6 Hz, 1H), 3.09 (br s, 1H), 3.81-3.91 (m, 1H), 4.75 (quintet, J=6.2 Hz, 1H); ^{13}C-NMR: δ 9.55, 9.79, 26.36, 29.35, 41.04, 69.28, 77.00, 172.71.

Determination of the absolute configuration of 3: under standard conditions, compound 3 was hydrolyzed to give (S)-3-hydroxypentanoic acid: $[\alpha]^{25}_D$ + 37.7 (c 1, chloroform), (lit.[8] for the enantiomer R: $[\alpha]^{25}_D$ - 37.2°, c 1, chloroform); b.p. 135-140°C (1.4 mm Hg); IR (film): 3500-2500 (COOH), 1713 (C=O) cm^{-1}; ^{1}H-NMR: δ 0.93 (t, J=7.4 Hz, 3H), 1.44-1.60 (m, 2H), 2.42 (dd, J=16.4 and 8.6 Hz, 1H), 2.55 (dd, J=16.4 and 3.7 Hz, 1H), 3.89-4.01 (m, 1H), 7.10 (br s, 1H).

(2S,3S)-1-Ethylpropyl 3-hydroxy-2-methylpentanoate 4. To a suspension of LiCl (8.14 g, 192 mmol) in anhyd. THF (40 ml), 11.4 ml (80 mmol) of diisopropylamine were added. After cooling at -78°C, 2.5 M n-BuLi solution in hexane (32 ml, 80 mmol) was added dropwise under nitrogen. After stirring for 1 h at 0°C, the LDA solution was cooled to -78°C and compound **3** (6 g, 32 mmol) in THF (15 ml) was added dropwise. The reaction mixture was then stirred at -30°C[25] for 2 h. Then another 32 ml (80 mmol) of n-BuLi were added at -78°C and the mixture was allowed to react for 2 more hours at -30°C. The dianion thus formed was cooled to -78°C and MeI (10.2 ml, 160 mmol) in 5 ml of THF was added, keeping the mixture at -30°C for 1.5 days. The reaction was quenched by addition of saturated NH_4Cl aqueous solution. The aqueous layer was extracted with ether and the organic layer washed with brine and dried ($MgSO_4$). The solvent was removed and 6.87 g of compound **4** were obtained. GC analysis showed that conversion was >99% and diastereomeric excess 80%. GC: capillary column TRB-1, temp 190°C, R_t= 7.91 min (anti), R_t= 8.07 min (syn); ^{13}C-NMR: δ 14.29 (10.99 syn), 27.40 (26.80 syn), 44.99 (44.25 syn), 74.37 (73.06 syn).

(2S,3R)-1-Ethylpropyl 3-(3,5-dinitrobenzoyloxy)-2-methylpentanoate 5. A mixture of **4** (5.26 g, 26.56 mmol), triphenylphosphine (21.14 g, 79.68 mmol), and 3,5-dinitrobenzoic acid (17.10 g, 79.68 mmol) in dry THF (90 ml) was stirred and cooled to 0°C under nitrogen. To the mixture was added dropwise DEAD (12.5 ml, 79.69 mmol) and stirred for 2 days at room temperature. Changes in colour was a good manner of monitoring the reaction: yellow, blue-greenish, dark blue, red, orange and finally yellow again. Hexane (100 ml) and ether (40 ml) were added to the reaction mixture, and the stirring was continued for 1 h. After filtration and concentration of the filtrate in vacuo, the residue was chromatographed on silica gel. Elution with hexane/ethyl acetate (15/1) afforded 6.47 g (61%) of **5** as a single diastereomer. M.p. 32-33°C; $[\alpha]^{24}_D$ -6.56° (c 1.11, $CHCl_3$) (lit[4] : $[\alpha]^{23}_D$ -6.52, c 0.97, $CHCl_3$), IR (KBr): 1732 (C=O), 1549, 1344 (NO_2) cm^{-1}; ^{1}H-NMR: δ 0.79 (t, J=7.3 Hz, 6H), 0.94 (t, J=7.4 Hz, 3H), 1.25 (d, J=7.1 Hz, 3H), 1.49 (quint., J=7.4 Hz, 4H),

1.74-1.97 (m, 2H), 2.83 (dq, J=7.7 and 5.5 Hz, 1H), 4.69 (quint., J=6.2 Hz, 1H), 5.40 (dt, J=5.7 and 5.4 Hz, 1H), 9.07 D, J=2.1 Hz, 2H), 9.16 (t, J=2.2 Hz, 1H); ^{13}C-NMR: δ 9.50, 9.90, 12.33, 24.87, 26.22, 42.91, 77.21, 78.37, 122.19, 129.16, 133.77, 148.42, 161.77, 172.85; anal. calc. for $C_{18}H_{24}N_2O_8$: C 54.54, H 6.10, N 7.07; found: C 54.52, H 6.13, N 7.10.

(2S,3R)-1-Ethylpropyl 3-hydroxy-2-methylpentanoate 6. To a solution of **5** (3.93 g, 9.92 mmol) in THF/MeOH 1/1 (30 ml) was added dropwise aqueous 1N KOH solution (9 ml, 9 mmol) at 0°C. The purple solution thus obtained was kept for 2 h at the same temperature. After that, the reaction was quenched with saturated ammonium chloride solution, the aqueous layer extracted with ether, the organic layer washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give a liquid which was purified by distillation yielding 1.80 g (90%) of **6** (Sitophilate) as a colourless liquid. B.p. 120-123°C (1.4 mm Hg); $[\alpha]^{24}_D$ -4.16° (c 1.7, $CHCl_3$) (lit.[4]: $[\alpha]^{24}_D$ -3.9, c 1.74, $CHCl_3$); IR (film): 3477 (OH), 1728 (C=O) cm^{-1}; ^{1}H-NMR: δ 0.75 (t, J=7.6 Hz, 6H), 0.83 (t, J=7.3 Hz, 3H), 1.06 (d, J=7.2 Hz, 3H), 1.27-1.52 (m, 6H), 2.39 (dq, J=7.2 and 4.4 Hz, 1H), 2.91 (br s, 1H), 3.65 (dt, J=7.3 and 5.3 Hz, 1H), 4.65 (quint., J=6.2 Hz, 1H); ^{13}C-NMR: δ 9.42, 10.17, 11.06, 26.27, 26.83, 44.31, 73.07, 76.59, 175.73.

(2S,3R)-1-Ethylpropyl 2-methyl-3-tetrahydropyranyloxypentanoate 7. To a solution of **6** (0.55 g, 2.72 mmol) and DHP (0.52 ml, 5.44 mmol) in dry dichloromethane (10 ml), 0.26 g (1.1 mmol) of PPTS were added. After stirring 4 hours at room temperature, the reaction mixture was extracted with ether; the organic layer washed with aqueous saturated sodium bicarbonate, then brine and dried. Upon concentration under vacuum, a liquid was obtained that was purified by distillation to give 0.76 g (96%) of **7**. B.p. 148-150°C (1.4 mm Hg); $[\alpha]^{22}_D$ +14.72 (c 1, $CHCl_3$); IR (film): 1730 (C=O) cm^{-1}; ^{1}H-NMR: δ 0.67-0.82 (m, 9H), 0.97-1.12 (2d, J=7 Hz, 3H), 1.12-1.75 (m, 12H, containing 6H from THP), 2.40-2.60 (m, 1H), 3.20-3.33 (m, 1H from THP), 3.60-3.80 (m, 2H, containing 1H from THP), 4.49 (m, 1H from THP), 4.58 (quintet, J=6.2 Hz, 1H).

(4S,5R)-4-Methyl-5-tetrahydropyranyloxy-3-heptanol 8. A solution of **7** (0.75 g, 2.62 mmol) in anhydrous ether (10 ml) was cooled to -100°C and a 1M dichloromethane solution of DIBAL (4 ml, 4 mmol) was added dropwise. The reaction mixture was stirred for 1 h at the same temperature and then, 2 ml of methanol were added. The reaction was allowed to warm to room temperature and it was poured into a saturated solution of Rochelle salts. After stirring for 1 h, the aqueous layer was extracted with ether and the organic layer was dried ($MgSO_4$) and concentrated in vacuo to give crude aldehyde: (2S,3R)-2-methyl-3-tetrahydropyranyloxypentanal (quantitative yield by GC) that was used for the next step without further purification[26]. To a solution of the aldehyde in ether (7 ml), 1M solution of EtMgBr in THF (5 ml, 5 mmol) was added dropwise at -15°C, the mixture was stirred for 15 min. and then quenched with saturated NH_4Cl. After extraction with ether, the solution was dried and concentrated to give a liquid that was purified by chromatography. Elution with hexane/ethyl acetate (10/1) afforded **8** (0.5 g, 84%). B.p. 122-124°C (1.9 mm Hg); $[\alpha]^{22}_D$ +14.1 (c 1, $CHCl_3$); IR (film): 3457 (OH) cm^{-1}; ^{1}H-NMR: δ 0.62-1.00 (m, 9H), 1.20-1.90 (m, 11H, containing 6H from THP), 2.95 (br s, 1H), 3.30-3.70 (m, 3H, 1H from THP), 3.75-3.95 (m, 1H from THP), 4.35-4.80 (m, 1H from THP).

(4S,5R)-5-Hydroxy-4-methyl-3-heptanone 9. To a solution of **8** (0.21 g, 0.92 mmol) and TEMPO (1.43 mg, 0.0092 mmol) in dichloromethane (5 ml), a solution of KBr (11 mg, 0.092 mmol) in 0.3 ml of water was added. The mixture was cooled to 0°C and vigorously stirred. Then 4.2 ml (5.5 mmol) of 1.34 M aqueous sodium hypochlorite at pH 9.5 was added. After 20 min., the organic phase was separated and the aqueous phase was extracted with dichloromethane. The organic extract was washed with 20 ml of 6% aqueous HCl containing 0.32 g of KI by stirring the biphasic system for 20 min. The organic phase was treated with 30 ml of 10% aqueous sodium thiosulfate, then with water and finally dried over anhydrous sodium sulphate. After concentration in vacuo, a liquid was obtained that was purified by column chromatography (hexane/ethyl acetate, 10/1) yielding 95 mg (72%) of **9** (Sitophilure) as a colourless liquid. B.p. 66-68° C (1.4 mm Hg); $[\alpha]^{22}_D$ +27.0 (c 1.1, ether) (lit.[15]: $[\alpha]^{20}_D$ +27.0 , c 1.24, ether); IR (film): 3465 (OH), 1711 (C=O) cm^{-1}; ^{1}H-NMR: δ 0.92 (t, J=7.4 Hz, 3H), 1.02 (t, J=7.3 Hz, 3H), 1.09 (d, J=7.2 Hz,

3H), 1.25-1.60 (m, 2H), 2.35-2.68 (m, 3H), 2.80 (br s, 1H), 3.74-3.82 (m, 1H); ^{13}C-NMR: δ 7.67, 9.94, 10.47, 26.89, 35.11, 49.27, 72.56, 216.49.

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24. Higher yield of keto ester **2** (89%) (which would lead to 48% overall yield of sitophilate) was obtained when an excess of methyl 3-oxopentanoate instead of 3-pentanol was used. However, the advantage of using an excess of alcohol, besides its lower price, is that it is easier to recover.
25. Whenever -30°C was needed, the reaction mixture was kept in a freezer, instead of using a cryogenic bath.
26. Spectroscopic data for an analytical sample of (2S,3R)-2-methyl-3-tetrahydropyranyloxypentanal: IR (film): 1727 (C=O) cm^{-1}; ^{1}H-NMR: δ 0.80 (t, J=7.1 Hz, 3H), 0.92-0.97 (2d, J=7 Hz, 3H), 1.20-1.75 (m, 8H, 6H from THP), 2.30-2.50 (m, 1H), 3.20-3.40 (m, 1H from THP), 3.55-3.92 (m, 2H, 1H from THP), 4.40-4.60 (m, 1H from THP), 9.62 (d, J=0.7 Hz, 1H).

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