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CATALYTIC REDUCTIVE β-METALLOETHYLATION IN THE SYNTHESIS OF 6-METHYLNONAN-3-ONE AND 3-METHYLHEPTANOIC ACID, RACEMIC ANALOGS OF *Hesperophylax occidentalis* AND *Coleoptera scarabaeidae* PHEROMONES

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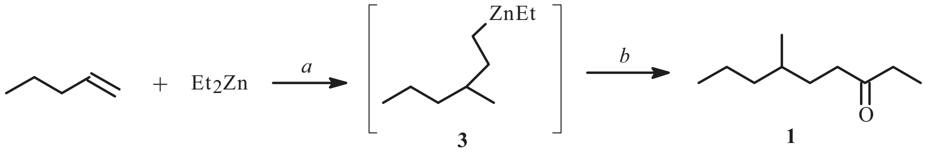
Previously, the syntheses of 4-methyloctanoic acid, an aggregation pheromone component of an *Oryctes* rhinoceros beetle [1], and 6-methyloctan-3-one, a racemic analog of an alarm pheromone of a *Crematogaster* ant [2], were used as examples to demonstrate the potential of the reductive β-metalloethylation of 1-alkenes in the presence of tantalum (Ta) complexes that was discovered by us [3–7].

Herein, this synthetic approach is expanded to the syntheses of 6-methylnonan-3-one (**1**), a racemic analog of the sex pheromone of the caddisfly *Hesperophylax occidentalis*, and 3-methylheptanoic acid (**2**), a racemic analog of the aggregation pheromone of the beetle *Coleoptera scarabaeidae*. The sex pheromone of *H. occidentalis* was first isolated by Bjostad et al. [8] and identified as 6-methylnonan-3-one. Multistep syntheses of this compound as a racemate and enantiomers are known [8–10].

An effective synthetic pathway to the racemic analog of pheromone **1** was based on the new regioselective reductive β-zinc-ethylation of 1-alkenes using Et_2Zn and $TaCl_5$ as a catalyst that was recently discovered by us [4].

Thus, the reaction of pent-1-ene with Et_2Zn in the presence of $TaCl_5$ (Et_2Zn–pent-1-ene–$TaCl_5$, 110:100:5, 20°C, 5 h) formed organozinc compound **3**. For this, pent-1-ene (1.4 mL, 20 mmol) was added to hexane (20 mL) cooled to 0°C, treated with Et_2Zn (22 mmol, 22.0 mL) and $TaCl_5$ (0.4 g, 1 mmol), heated gradually to room temperature, stirred for 5 h, cooled to –5°C, and treated dropwise with propionyl chloride (**4**, 1.74 mL, 20 mmol) in hexane (10 mL). All these manipulations were performed under dry Ar. After **4** was added, the mixture was stirred for 2 h at room temperature and treated with HCl solution (10%). The resulting **1** was extracted with Et_2O (3 × 50 mL), dried over anhydrous $MgSO_4$, and evaporated. The solid was chromatographed (SiO_2, hexane–Et_2O, 6:1) to afford **1** (2.95 g, 99% pure by GC) in 95% yield from **4** (Scheme 1).



a. $TaCl_5$, hexane, 5 h; *b.* 1. C_2H_5COCl (**4**), 2. HCl/H_2O

Scheme 1

Catalytic β-metalloethylation was used in the key step of a synthesis of 3-methylheptanoic acid (**2**).

The reaction of hex-1-ene with EtMgCl in the presence of $TaCl_5$–Ph_3P (1:1) catalyst (EtMgCl–hex-1-ene–$TaCl_5$+Ph_3P, 150:100:5, 1 mM EtMgCl, THF, 20°C, 4 h) formed organomagnesium compound **5** (Scheme 2). For this, a solution of EtMgCl (37.5 mL, 37.5 mmol) in THF (37.5 mL) at 0°C was stirred and treated with hex-1-ene (2.1 g, 25 mmol), Ph_3P (0.33 g, 1.25 mmol), and $TaCl_5$ (0.45 g, 1.25 mmol). The temperature was increased to 20°C. Stirring continued for 4 h. The mixture was oxidized in a glass thermostatted reactor by passing pure O_2 through the reaction mixture at 8–10°C for 2 h. Then, the mixture was poured into HCl solution (5%). The resulting alcohol **6** was extracted with Et_2O (3 × 70 mL). The extract was dried over $MgSO_4$ and evaporated *in vacuo* to isolate 3-methylheptan-1-ol (**6**, 2.93 g, 99% pure by GC, based on starting hex-1-ene), which had the reported spectral characteristics [11].

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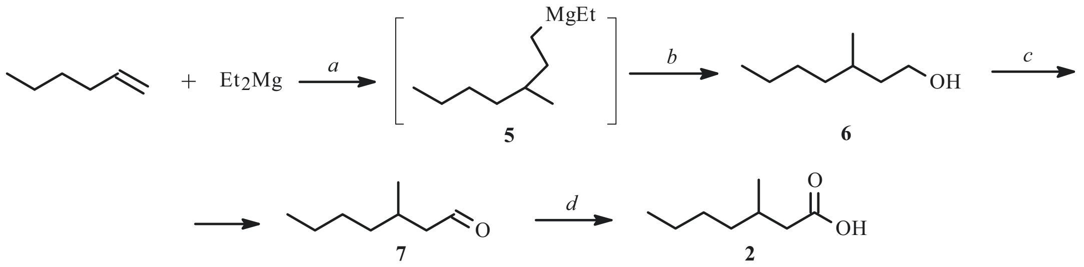

a. $TaCl_5$-PhP_3, THF, 4 h; *b.* O_2, HCl/H_2O; *c.* PCC, CH_2Cl_2; *d.* H_2O–$AgNO_3$ (catalyst), MeCN

Scheme 2

Alcohol **6** was oxidized to aldehyde **7** as follows. A suspension of pyridinium chlorochromate (PCC, 5.9 g, 27.5 mmol) in anhydrous CH_2Cl_2 (35 mL) was stirred (20°C, Ar), treated in one portion with a solution of **6** (2.93 g, 22.5 mmol) in CH_2Cl_2 (10 mL), stirred for 1.5 h, diluted with anhydrous Et_2O (35 mL), and filtered through a layer of Al_2O_3 (5 cm). The solid was rinsed with anhydrous Et_2O (50 mL). The solvents were evaporated to afford **7** (2.51 g, 87.7%). IR spectrum (ν, cm^{-1}): 2730, 2950, 1725, 1470, 1390. Aldehyde **7** was oxidized to acid **2** as follows. A solution of $AgNO_3$ (0.32 g, 0.19 mmol) and **7** (2.51 g, 19.6 mmol) in MeCN (40 mL) was stirred, treated dropwise with H_2O_2 (11.2 mL, 98 mmol, 30%), heated to 50°C and held there for 10 h, decomposed at 5°C by $Na_2S_2O_3$ solution (10%, 10 mL), and extracted with CH_2Cl_2 (2 × 50 mL). The solvent was evaporated. The solid was chromatographed over SiO_2 ($CHCl_3$) to isolate **2** (2.83 g, 63% based on starting hex-1-ene, Scheme 2), which was >98% pure by GC [12].

The structures of **1** and **2** were confirmed by IR, PMR, and ^{13}C NMR spectra, mass spectrometry, and comparisons with the literature [8, 9, 13, 14].

Thus, new synthetic capabilities of catalytic reductive β-metalloethylation were demonstrated.

The isolated products were analyzed on a Shimadzu GC-2014 chromatograph in a He stream using a column (2,000 × 3 mm, 5% SE-30 on Chromaton N-AW-HMDS, 0.125–0.160 mm) at operating temperature 50–300°C. One- (PMR, ^{13}C NMR) and two-dimensional (COSY, HSQC, HMBC) NMR spectra were recorded in $CDCl_3$ on a Bruker Avance-400 spectrometer (100 MHz for ^{13}C, 400 MHz for ^1H) at 25°C. Chemical shifts were given vs. TMS. Mass spectra were measured on a Shimadzu GCMS-QP 2010 (Supelco SLB™-5ms, glass capillary column, 60,000 × 0.25 mm × 0.25 μm, He carrier gas, temperature programmed from 50 to 260°C at 5°C/min, ion-source temperature 260°C, 70 eV). Elemental analyses were determined on a Carlo Erba Model No. 1106 analyzer. Chromatograms of reaction mixtures were calculated using an internal standard. IR spectra were taken on a Bruker VERTEX 70V spectrometer.

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