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Fe-CATALYZED SYNTHESIS OF (13*Z*)-EICOS-13-EN-10-ONE, THE MAIN SEX PHEROMONE COMPONENT OF *Carposina niponensis*

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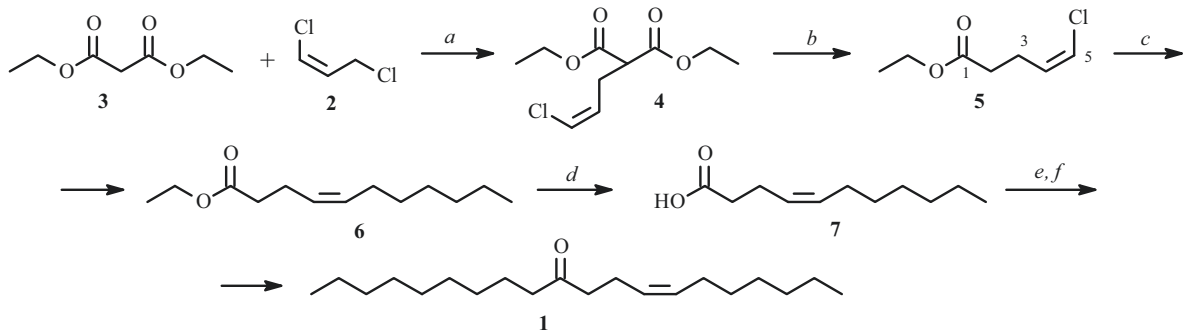
(13Z)-Eicos-13-en-10-one, the main sex pheromone component of Carposina niponensis*, was synthesized stereoselectively via Fe-catalyzed cross-coupling of ethyl (4Z)-5-chloropent-4-enoate with hexylmagnesiumbromide to give ethyl (4Z)-undec-4-enoate and repeated Fe-catalyzed cross-coupling of its acid chloride with nonylmagnesiumbromide.*

Keywords: (13*Z*)-eicos-13-en-10-one, cross-coupling, Fe-catalyzed, pheromone, *Carposina niponensis*, peach fruit moth.

(13*Z*)-Eicos-13-en-10-one (**1**) mixed with the minor component (12*Z*)-nonadec-12-en-9-one in a 20:1 ratio was identified as the sex pheromone of *Carposina niponensis*, a dangerous fruit pest [1], the caterpillars of which infest pear, apple, apricot, peach, plum, quince, and many other cultured and wild stone- and seed-fruit trees.

Many syntheses of **1** are known in which the *Z*-configured double bond was created by partial stereoselective hydrogenation of the corresponding acetylene precursors [1–7], Wittig reactions [8–12], Negishi reactions [13], and also by using (*Z*)-vinylcuprates [14, 15] and various transformations of relatively available (*Z*)-1-bromo-2-nonene [16, 17]. Nevertheless, the development of a convenient and effective synthetic method for the pheromone of this dangerous pest remains as before crucial because of the many steps in these syntheses and the use of difficultly accessible reagents and (or) the low stereoselectivity.

The present work reports a stereoselective method developed by us for building the carbon skeleton of (13*Z*)-eicos-13-en-10-one using two successive Fe-catalyzed cross-coupling reactions of vinyl- and acylchlorides with Grignard reagents. Examples of the successful use of Fe-catalysis to form C–C bonds [18–20], including for the synthesis of natural compounds and drugs [21–23], have recently appeared. The principal advantages of the iron salts [$Fe(acac)_3$, $FeCl_3$] that are usually used in cross-coupling reactions over the traditional platinum-group metal compounds are the low cost, availability, high catalytic rate, the ability to use aryl- and vinylchlorides as electrophilic partners, the lack of ligands, low toxicity, and ecological safety [18, 24].



a. K_2CO_3, 18-crown-6, CH_3CN; *b*. LiCl, H_2O, NMP, 140–150°C; *c*. $C_6H_{13}MgBr$, $Fe(acac)_3$, NMP, THF; *d*. KOH, C_2H_5OH; *e*. $SOCl_2$, DMF; *f*. $C_9H_{19}MgBr$, $Fe(acac)_3$, THF

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The starting compound was (*Z*)-1,3-dichloropropene (**2**), an available multi-ton byproduct of allylchloride production [25]. The (*Z*)- and (*E*)-isomers of 1,3-dichloropropene contain in the allyl and vinyl positions two Cl atoms of different reactivities that are responsible for the unique synthetic potential of this compound [26, 27]. A strategy based on functionalization of the (*Z*)-isomer at the allyl position by various nucleophiles and stereoselective cross-coupling at the vinyl position is highly promising for synthesizing stereochemically pure (*Z*)-unsaturated compounds.

Allylation of malonic ester (**3**) by (*Z*)-1,3-dichloropropene (**2**) in the presence of K_2CO_3 and a catalytic amount of 18-crown-6 gave diethyl[(2*Z*)-3-chloroprop-2-en-1-yl]propanedioate (**4**) in good yield with full retention of the configuration of the double-bond substituents [27]. Decarbalkoxylation of **4** under optimized Krapcho conditions [28] using LiCl and H_2O in *N*-methylpyrrolidone (NMP) proceeded smoothly to (4*Z*)-5-chloropent-4-enoate (**5**). Fe-catalyzed cross-coupling of vinylchloride **5** with hexylmagnesiumbromide in the presence of a catalytic amount of $Fe(acac)_3$ and NMP in THF at room temperature formed in good yield (78%) ethyl (4*Z*)-undec-4-enoate (**6**), which then was converted by alkaline hydrolysis into corresponding acid **7**, transformation of which into the acid chloride by $SOCl_2$/DMF and a second Fe-catalyzed cross-coupling of it with nonylmagnesiumbromide gave target pheromone **1** of isomeric purity >98%.

The structures, stereochemical configurations, and isomeric purities of the synthesized compounds were confirmed by high-efficiency GC analysis, IR and NMR spectroscopy, and GC-MS. Chemical shifts of allyl C atoms in **1** and **5**–**7** that were displaced by ~4–5 ppm to strong field as compared with the corresponding C atoms of the (4*E*)-isomer provided reliable proof that the substituents on the double bond had the (*Z*)-configuration [20].

The advantages of the developed synthesis of the pheromone were the use of the industrially available (*Z*)-isomer of 1,3-dichloropropene (byproduct of allylchloride production), the few steps, the high yield and isomeric purity of the target product, and the low cost of the Fe-catalyst that was used in two successive cross-coupling reactions.

EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS standard for ^1H and solvent resonances as standards for ^{13}C (δ_C 77.0 ppm) on a Bruker AM-300 instrument (300 and 75 MHz operating frequencies, respectively). IR spectra were recorded from thin layers on an IR Prestige-21 FTIR spectrophotometer (Shimadzu) (the ten strongest absorption bands are given). GC-MS analysis used a Shimadzu GCMS-QP2010S instrument [electron-impact ionization at 70 eV, detected mass range 33–350 Da, HP-1ms capillary column (30 m × 0.25 mm × 0.25 μm), vaporizer temperature 280°C, ionization chamber 200°C, temperature programmed from 50 to 300°C at 10°C/min, He carrier gas (1.1 mL/min)]. The ten strongest peaks for fragment ions and the molecular ion are given for the mass spectra.

Ethyl (4*Z*)-5-Chloropent-4-enoate (5). A mixture of malonic ester (**3**, 1.92 g, 0.012 mol), (*Z*)-1,3-dichloropropene (**2**, 1.11 g, 0.01 mol), 18-crown-6 (0.05 g), and K_2CO_3 (1.38 g, 0.01 mol) in MeCN (10 mL) was stirred and refluxed for 6 h until **2** was fully converted (GC monitoring) and then filtered. The precipitate was rinsed with EtOAc. The combined organic layers were concentrated to afford crude diethyl [(2*Z*)-3-chloroprop-2-en-1-yl]propanedioate (**4**, 2.42 g) that was used without further purification.

A mixture of **4**, H_2O (0.36 g, 0.02 mol), and LiCl (1.27 g, 0.03 mol) in NMP (12 mL) was stirred at 140–150°C until the substrate was fully converted (4–5 h, GC monitoring) and treated with H_2O (30 mL) and EtOAc (30 mL). The organic layer was separated. The aqueous layer was worked up with EtOAc (2 × 20 mL). The combined organic phases were washed with H_2O, dried over $MgSO_4$, and concentrated at atmospheric pressure. The product was isolated by column chromatography (SiO_2, hexane–Et_2O, 9:1→8:2), yield 0.91 g (56%) in two steps, oily compound. IR spectrum (ν, cm^{-1}): 2984, 1730, 1373, 1333, 1304, 1258, 1211, 1184, 1161, 735. ^1H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.26 (3H, t, J = 7, CH_3), 2.42 (2H, t, J = 7.3, H-2), 2.52–2.57 (2H, m, H-3), 4.14 (2H, q, J = 7, CH_2O), 5.80 (1H, q, J_{cis} = 7, H-4), 6.07 (1H, d, J_{cis} = 7, H-5). ^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 14.08 (CH_3), 22.42 (C-3), 32.77 (C-2), 60.42 (CH_2O), 119.27 (C-5), 129.60 (C-4), 172.59 (C-1). Mass spectrum, *m/z* (I_{rel}, %): 127 ($[M - Cl]^+$, 70), 117 (28), 99 (92), 91 (25), 89 (47), 88 (33), 53 (100), 51 (25), 43 (32), 42 (22).

Ethyl (4*Z*)-Undec-4-enoate (6). A solution of **5** (0.325 g, 2 mmol) and $Fe(acac)_3$ (14 mg, 0.04 mmol) in a mixture of THF (2 mL) and NMP (1.6 mL) at 0°C under Ar was treated slowly dropwise with a solution (1 M) of *n*-hexylmagnesiumbromide in THF (2.1 mL), stirred at room temperature for 1 h, and worked up with HCl solution (10 mL, 5%) and EtOAc (10 mL). The organic layer was separated. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic phases were

washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated. The product was isolated by column chromatography (SiO_2, hexane–EtOAc, 9:1). Yield 0.332 g (78%), oily compound. IR spectrum (ν, cm^{-1}): 2958, 2927, 2857, 1740, 1466, 1371, 1349, 1250, 1162, 1039. ^1H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.88 (3H, t, J = 7, CH_3-11), 1.22–1.38 (11H, m, $C\underline{H}_3CH_2O$, $4CH_2$), 2.04 (2H, q, J = 6.8, H-6), 2.33–2.43 (4H, m, H-2, 3), 4.13 (2H, q, J = 7.1, $CH_3C\underline{H}_2O$), 5.28–5.46 (2H, m, H-4, 5). ^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 14.03 (C-11), 14.18 ($\underline{C}H_3CH_2O$), 22.60 (C-10), 22.78 (C-3), 27.15 (C-6), 28.92 (CH_2), 29.55 (CH_2), 31.71 (C-9), 34.37 (C-2), 60.22 (CH_2O), 127.30 (C-4), 131.46 (C-5), 173.22 (C-1). Mass spectrum, *m/z* (I_{rel}, %): 212 ($[M]^+$, 3), 124 (75), 96 (72), 88 (93), 84 (54), 81 (53), 69 (64), 67 (65), 55 (100), 43 (65), 41 (86).

(4*Z*)-Undec-4-enoic Acid (7). A solution of **6** (0.3 g, 1.41 mmol) and KOH (0.252 g, 4.5 mmol) in EtOH (95%, 5 mL) was stirred at 70°C for 5 h until the substrate was fully converted (GC monitoring), cooled, and mostly evaporated. The residue was acidified with HCl (5%) and extracted with $CHCl_3$. The organic phase was washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated. Yield 0.246 (95%), oily compound. IR spectrum (ν, cm^{-1}): 2956, 2926, 2855, 1715, 1465, 1457, 1378, 1250, 1164, 723. ^1H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.88 (3H, t, J = 7, CH_3-11), 1.21–1.42 (8H, m, $4CH_2$), 2.04 (2H, q, J = 6.9, H-6), 2.34–2.43 (4H, m, H-2, 3), 5.29–5.48 (2H, m, H-4, 5). ^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 14.03 (C-11), 22.48 (C-3), 22.60 (C-10), 27.18 (C-6), 28.92 (CH_2), 29.55 (CH_2), 31.73 (C-9), 34.19 (C-2), 126.88 (C-4), 131.88 (C-5), 179.81 (C-1). Mass spectrum, *m/z* (I_{rel}, %): 184 ($[M]^+$, 1), 84 (36), 82 (40), 69 (61), 68 (44), 67 (48), 56 (36), 55 (93), 54 (38), 43 (83), 41 (100).

(13*Z*)-Eicos-13-en-10-one (1). A solution of **7** (0.2 g, 1.09 mmol) and DMF (4 μL) in anhydrous toluene (1 mL) was diluted with thionylchloride (0.169 g, 1.42 mmol) and stirred under Ar at room temperature for 4 h until the acid was fully converted (GC monitoring). The solvent and excess of $SOCl_2$ were vacuum distilled. A solution of the acid chloride of **7**, $Fe(acac)_3$ (11 mg, 0.03 mmol) in anhydrous THF (2 mL) under Ar was treated slowly with a solution (1 M) of *n*-nonylmagnesiumbromide in THF (1.1 mL), stirred at room temperature for 1 h, and treated with HCl solution (5 mL, 5%) and hexane (10 mL). The organic layer was separated. The aqueous layer was extracted with hexane (2 × 5 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated. The product was isolated by column chromatography (SiO_2, hexane–EtOAc, 9:1). Yield 0.254 g (79%) in two steps, oily compound. IR spectrum (ν, cm^{-1}): 2956, 2927, 2856, 1716, 1466, 1458, 1368, 1261, 1163, 722. ^1H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.88 (6H, t, J = 7, CH_3-1, 20), 1.19–1.41 (20H, m, $10CH_2$), 1.54–1.59 (2H, m, H-8), 2.00–2.07 (2H, m, H-15), 2.26–2.46 (6H, m, H-9, 11, 12), 5.25–5.43 (2H, m, H-13, 14). ^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 14.02 (C-1, 20), 21.66 (C-8), 22.59 (C-2, 19), 23.79 (C-12), 27.15 (C-15), 28.94 (CH_2), 29.21 ($2CH_2$), 29.39 ($2CH_2$), 29.57 (CH_2), 31.73 (C-3 or C-18), 31.82 (C-3 or C-18), 42.61 (C-9 or C-11), 42.91 (C-9 or C-11), 127.75 (C-13), 131.17 (C-14), 210.86 (C-10). Mass spectrum, *m/z* (I_{rel}, %): 294 ($[M]^+$, 5), 155 (75), 95 (42), 83 (48), 81 (44), 71 (72), 69 (49), 57 (65), 55 (79), 43 (100), 41 (71).

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