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SYNTHESES OF 3,7-DIMETHYLPENTADECAN-2-OLS FROM INTERMEDIATES FORMED FROM CO-OLIGOMERISATION REACTIONS OF BUTADIENE WITH DIETHYL MALONATE AND ACETALDEHYDE

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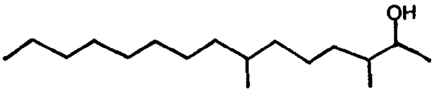
ABSTRACT: The products of the reaction of butadiene with diethyl malonate catalysed by a palladium complex and of butadiene with acetaldehyde catalysed by a nickel(0) complex have been used in two syntheses of 3,7-dimethylpentadecan-2-ol.

The pine sawflies are ubiquitous in various parts of the world and particularly in North America and Sweden. Many species are among the worst defoliants of spruce and pine forests as a result of feeding by the caterpillar-like larvae on coniferous needles. Females of many species of sawfly use either the acetic or propionic ester of 3,7-dimethylpentadecan-2-ol (1) as the pheromone to attract the males[1]. The racemic propionate, which consists of eight enantiomers, has been shown to attract the males of *Neodiprion swainei* but although the racemic acetate attracts males of *N. lecontei* it is less active than the natural pheromone. Information has been obtained that the natural pheromone of *N. lecontei* has an *erythro* arrangement of two hydrogens at C-2 and C-3[2]. It is clear that this, and other species, respond maximally to individual enantiomers of the overall structure.



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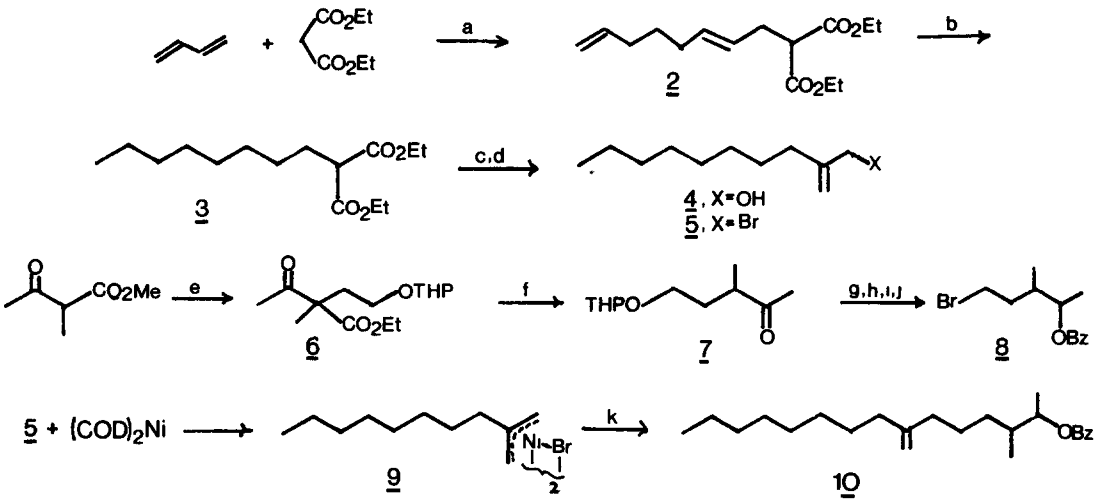
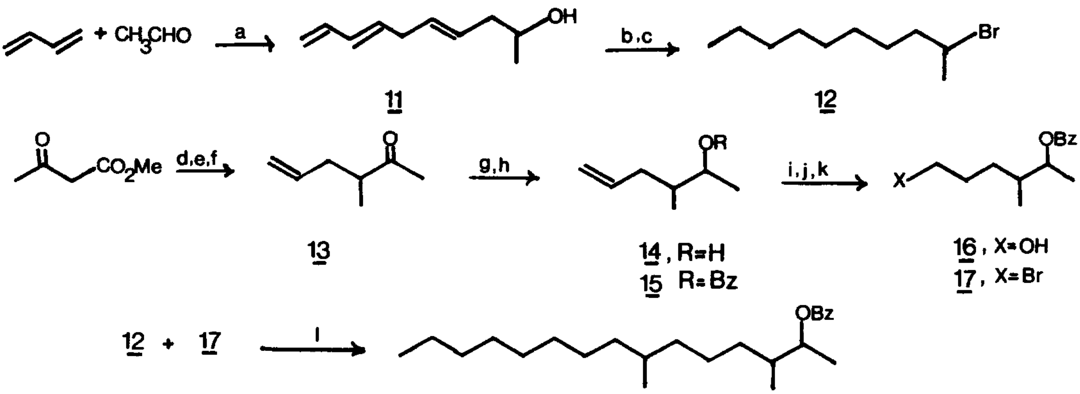
For *N. lecontei* the (-)-*erythro* configuration (2S,3S) has the highest biological activity. In the case of *N. sertifer* the males are attracted specifically to the (+)-2R,3R,7S *erythro*-enantiomer of the acetate[3] and, in contrast, the British population of *Diprion similis* responds comparably to both the (+)-2R,3R,7R and (-)-2S,3S,7S enantiomers of *erythro*-3,7-dimethylpentadecan-2-yl propionate[4]. In spite of the evident enantiomer specificity in the pheromones of some species, syntheses of the racemic compound[5] are still of value due to its possible use in control systems. For example, mating disruption by permeation of the atmosphere with the pheromone[6] could still be successful with racemic material. In the present communication we report two syntheses of 3,7-dimethylpentadecan-2-ol which begin with a metal complex co-oligomerisation of 1,3-butadiene and involve either the coupling of a π-allylnickel halide with an alkyl halide or a coupling of two halides in presence of lithium tetrachlorocuprate.



a, $Pd(PPh_3)_4$, NaOPh, THF; b, 5% Pd/C, H_2, EtOH; c, NaH, $LiAlH_4$, DME; d, PBr_3, Et_2O; e, NaH, $BrCH_2CH_2OTHP$, DMF; f, NaCN, HMPA, 110°; g, $LiAlH_4$, Et_2O; h, NaH, BzCl, DMSO; i, *p*-TsOH, MeOH; j, CBr_4, PPh_3; k, (8), Et_2O.

For the first method the starting material required was the diester (2). This was formed from the reaction of butadiene (180 mmol) with diethylmalonate (30 mmol) in the presence of tetrakis(triphenylphosphine)palladium (0.3 mmol) with sodium phenoxide (1 mmol) as co-catalyst. Fractional distillation gave (2) (79% yield), b.p. 88°/0.2 Torr[7]. Hydrogenation of (2) in presence of a suspension of palladium on charcoal in ethanol yielded (3) (96%). The formation of 2-methylenedecan-1-ol (4) was achieved following the method of Marshall *et al*[8]. Sodium hydride (80.4 mmol, 80% suspension in oil) was added to a stirred solution of (3) (72 mmol) in dimethoxyethane (300 ml) under a nitrogen atmosphere and the mixture heated at reflux temperature for 4h, when lithium aluminium hydride was added to the cooled solution. After the initial reaction had subsided the mixture was heated at reflux temperature for 4h. Ethyl formate (242 mmol) was added to the cooled reaction mixture followed by sodium hydroxide (100 ml, 5% aqueous solution) and after filtration, distillation gave (4) (55%), b.p. 124-6°C/20 Torr[9]. The required allyl bromide (5) was formed in 71% yield on reaction of (4) with phosphorus tribromide in diethyl ether.

The other derivative required was 2-benzyloxy-5-bromo-3-methylpentane (8). Methyl 2-methylacetoacetate was added to a suspension of sodium hydride in a mixture of benzene and dimethylformamide followed by the addition of the tetrahydropyranyl ether of bromoethanol; (6) (46%) was isolated by fractional distillation, b.p. 136-142°C/1 Torr. Treatment of (6) with sodium cyanide in hexamethylphosphoramide at 110°C for 4h gave (7) in 56% isolated yield. Formation of (8) then followed the sequence, reduction with lithium aluminium hydride, benzylation, hydrolysis of the tetrapyranyl ether and bromination.



a, $(COD)_2Ni$, PPh_3, Et_2O; b, Pd/C, H_2, EtOH; c, PBr_3, Et_2O; d, NaH, $CH_2{=}CHCH_2Br$, THF; e, NaH, MeI, THF; f, NaCN, HMPA; g, $LiAlH_4$, Et_2O; h, NaH, BzCl, DMSO; i, $(BH_3)_2$; j, H_2O_2, NaOH; k, PBr_3, Et_2O; l, Mg, Li_2CuCl_4, THF.

The coupling of the allylic bromide (5) with (8) was achieved by the method of Corey and Semmelhack[10]. Addition of (5) (4.3 mmol) to bis(1,5-cyclooctadiene)nickel (4.4 mmol)[11] in dry ether (20 ml) at -15°C under an argon atmosphere gave, after stirring for 3h, a red solution of the bis- π-allyl halide complex (9). After evaporation of the ether and trituration with pentane the red solid was dissolved in dry DMF under argon and (8) (4.4 mmol) added. The solution was stirred overnight and, after ether extraction, 2-benzyloxy-3-methyl-7-methylenepentadecane (10) was isolated by silica column chromatography in 56% yield. Hydrogenation with 5% Pd/C yielded 3,7-dimethylpentadecan-2-ol.

In a second method for the formation of 3,7-dimethylpentadecan-2-ol the important intermediate was 4,7,9-decatrien-2-ol (11), which was formed from the nickel catalysed co-oligomerisation of 1,3-butadiene and acetaldehyde[12]. Butadiene (1.043 mol) was distilled into a solution of bis(1,5-cyclooctadiene)nickel (51 mmol) and triphenylphosphine (51 mmol) in benzene (400 ml) and a red solution was obtained. After 30 min, freshly distilled acetaldehyde (179 mmol) was added and the solution stirred at 0°C for 16 h. Aqueous potassium cyanide (210 mmol) was added and the products extracted with ether. Distillation gave (11) (239% with respect to nickel), b.p. 115-120/15 Torr. Hydrogenation of the triene in presence of Pd/C led to decan-2-ol and treatment with phosphorus tribromide in ether gave 2-bromodecane (12).

The other intermediate required for this synthesis was 2-benzyloxy-6-bromo-3-methylhexane (17) and this again originated from disubstitution of methyl acetoacetate. Addition of allyl bromide to the anion of methyl acetoacetate (57%) followed by reaction with methyl iodide (71%) and decarboxymethylation in the presence of sodium cyanide in HMPA proceeded smoothly to give the ketone (13) in 43% yield. Reduction with lithium aluminium hydride gave (14) and the alcohol function was protected by benzylation. Hydroboration of (15) yielded (16) and treatment with phosphorus tribromide produced (17).[†]

The Grignard reagent of 2-bromodecane (4.5 mmol) was formed in THF and (17) (1.75 mmol) added. Following cooling to 0°C, dilithium tetrachlorocuprate (0.04 mmol) was added and the reaction mixture stirred at 0°C for 3h and room temperature overnight[13]. After extraction and silica gel chromatography a 40% yield of 2-benzyloxy-3,7-dimethylpentadecane was obtained which was converted to 3,7-dimethylpentadecan-2-ol.

Both of these methods provide satisfactory syntheses of 3,7-dimethylpentadecan-2-ol and exemplify the versatility of carbon-carbon bond forming reactions utilising organo-palladium and -nickel complexes.

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[†] (14), (15), (16) and (17) were diastereomeric mixtures.

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