Vilsmeier Formylation of Limonene. A New Method for the Synthesis of α-Atlantone

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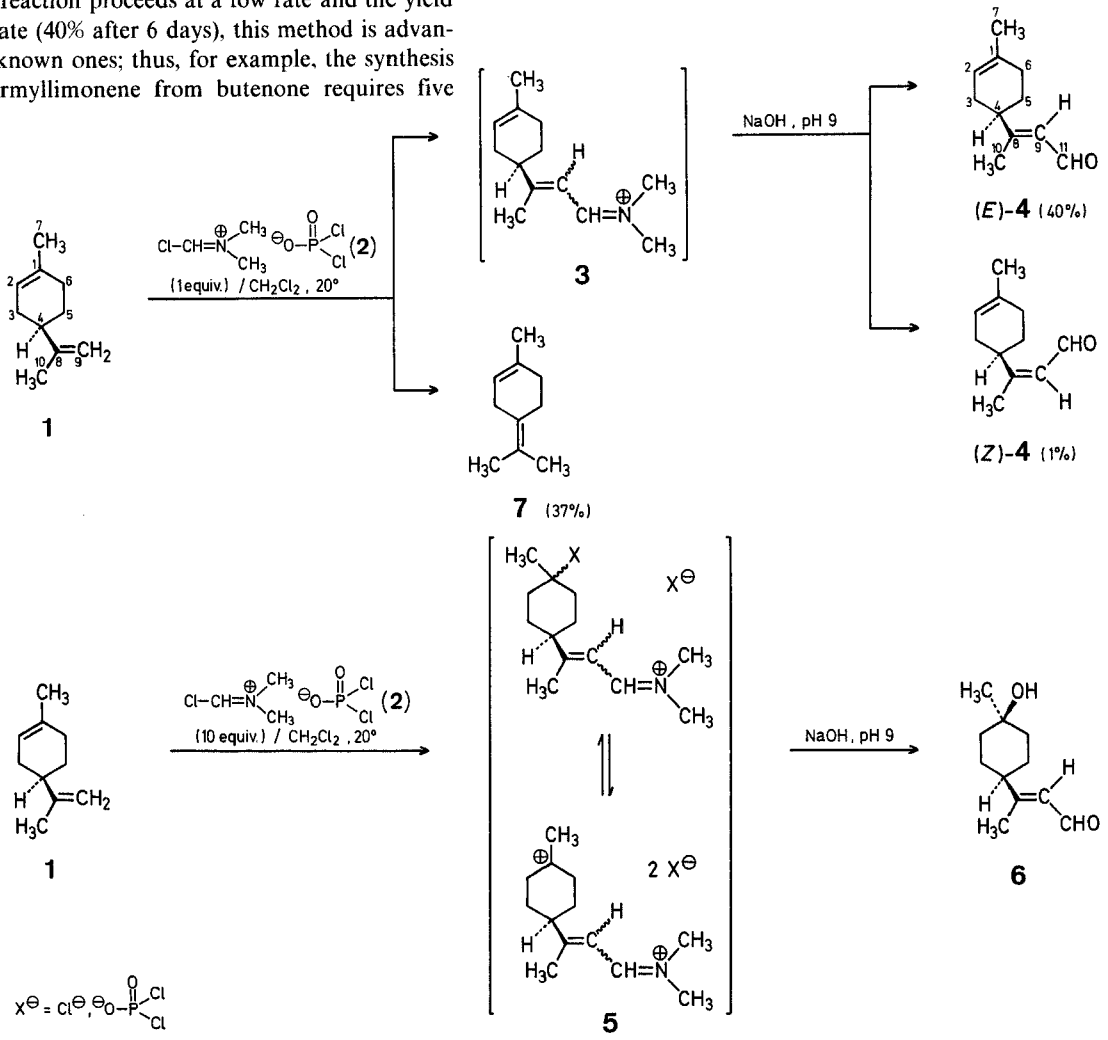
Among the methods used for the preparation of α,β-unsaturated aldehydes[1,2], the Vilsmeier-Haack-Arnold formylation of alkenes by chloromethaniminium salts, a simple and cheap reaction, has not been extensively studied[3]. The only formylations of this type were reported for some terpenes and steroids having an exocyclic methylene group[4,5,6]. Polyformylation may also occur[4], in particular, when the methylene group is not exocyclic, as with isobutene[7]. In a previous investigation, we obtained either formylation or tris-formylation of 17-methylene steroids depending on the reaction conditions[8]. We describe here the preparation of (+)-(4*R*)(*E*)-9-formyllimonene, the first example of the Vilsmeier formylation of a non-exocyclic methylene compound.

(+)-(4*R*)-Limonene (**1**) reacts with an equimolar amount of Vilsmeier reagent **2** (*N*,*N*-dimethylchloromethaniminium phosphorodichloridate, obtained from dimethylformamide and phosphoryl chloride) to give (+)-(4*R*)-(*E*)-9-formyllimonene [(*E*)-**4**] and dimethylamine via the iminium ion **3** and hydrolysis. The reaction is highly stereoselective, the *E*/*Z* ratio of the product aldehydes **4** being 98/2. Although the reaction proceeds at a low rate and the yield is only moderate (40% after 6 days), this method is advantageous over known ones; thus, for example, the synthesis of *dl*-(*E*)-9-formyllimonene from butenone requires five steps[9]. The high stereoselectivity of our reaction may be rationalized by the assumption that the *E*/*Z* ratio of the iminium ion **3** increases with time and that the thermodynamic equilibrium (98/2) is reached after 6 days. An analogous equilibration in favor of the *E* isomer was observed with 9-formyl-β-pinene[10]. The enantiomeric purity of the 9-formyllimonenes (*E*)-**4** and (*Z*)-**4** decreases with time. However, the decrease in optical rotation is small during the first hours of the reaction: a value of $[\alpha]_{578}^{25}$: +106° is obtained for (*E*)-**4** after 15 min and a similar value is found after 2 h. The enantiomeric purities of (*E*)-**4** and the starting limonene (**1**) may therefore be assumed to be the same[11]. During the reaction, isomerization of limonene (**1**) to terpinolene (**7**) competes with racemization and substitution to **3**. The endocyclic double bond of limonene (**1**) is not attacked by reagent **2** due to steric effects[3].

The reaction of (+)-limonene (**1**) with 10 equiv of Vilsmeier reagent **2** leads to substitution at C-9 and addition of hydrogen chloride or phosphorodichloridic acid to the endocyclic double bond to afford the iminium salt **5** which is then hydrolyzed to give (*E*)-3-(4-hydroxy-4-methylcyclohexyl)-2-butenal (**6**) in 35% yield.

The dienamines corresponding to the iminium salts **3** and **5** (conjugated bases) do not undergo electrophilic substitution with the reagent **2**; thus, polyformylation is not observed in our reaction.

(+)-(4*R*)-(*E*)-9-Formyllimonene (**4a**) is an interesting intermediate for the synthesis of natural products, in particular sesquiterpenoids. We used it for a synthesis of (+)-



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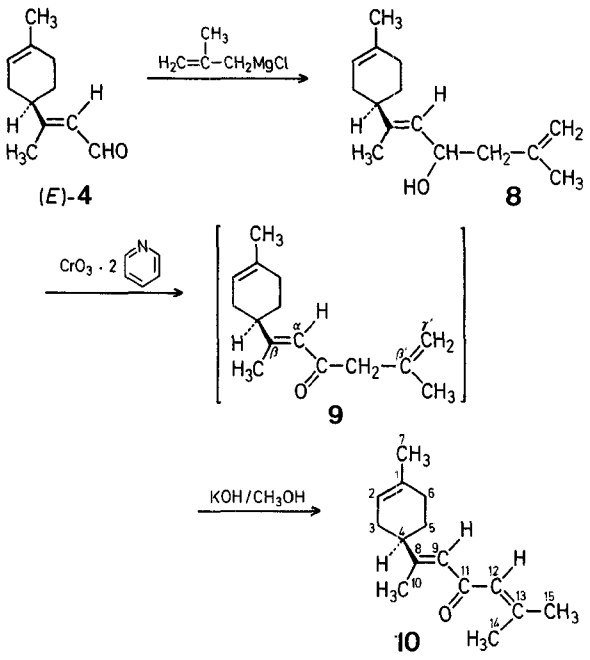
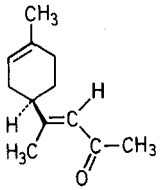
(4*R*)-(*E*)-α-atlantone[13] (**10**), an odor constituent of *Cedrus* oils: reaction of methallylmagnesium chloride with aldehyde (*E*)-**4** ($[\alpha]_{578}^{25}$: +106°) according to Babler[9] gives the alcohol **8** in 99% yield; oxidation of **8** with chromium(VI) oxide-pyridine complex[14] gives the α,β;β′,γ′-di-unsaturated ketone **9** which is isomerized to the conjugated dienone **10**, (+)-(4*R*)-(*E*)-α-atlantone ($[\alpha]_{578}^{25}$: +75°) in 80% yield using methanolic potassium hydroxide[15].



This three-step synthesis of **10** compares favorably with the syntheses reported in Ref. [15,16] and the optical rotation of our product **10** is comparable to the value given in Ref. [16] ($[\alpha]_D^{30}$: +77°) for a product obtained from limonene of the same optical rotation as that used by us. A further constituent of *Cedrus* oils, (+)-(4*R*)-(*E*)-9-acetyllimonene[17] (**11**), can be obtained by an analogous method.



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(+)-(4*R*)-(*E*)-9-Formyllimonene [(*E*)-4] and (−)-(4*R*)-(*Z*)-9-Formyllimonene [(*Z*)-4]:

Method A: A solution of *N,N*-dimethylchloromethaniminium phosphorodichloridate (**2**) is prepared by adding a solution of phosphoryl chloride (15.3 g, 0.10 mol) in dichloromethane (10 ml) to a stirred solution of dimethylformamide (8.0 g, 0.11 mol) in dichloromethane (20 ml) under nitrogen at 0° and then keeping the temperature below 5° for 2 h. The solution of reagent **2** thus prepared is added, at a temperature below 5°, to a solution of (+)-limonene (**1**; 13.6 g, 0.10 mol; $[\alpha]_{578}^{20}$: −110°, *c* 0.5, ethanol) in dichloromethane (50 ml). The mixture is stirred at room temperature for 6 days and then poured into ice-cold water (200 ml). The lower organic layer is distilled in vacuo to give *terpinolene* (**7**); yield: 5.0 g (37%); b.p. 74°/12 torr (Ref. [18], b.p. 72°/10 torr [this product is identical (G.L.C., ^{1}H-N.M.R.) with a sample prepared according to Ref. [18].] The upper aqueous layer is neutralized to pH 9 with aqueous sodium hydroxide, stirred for 2 h, and extracted with ether. The ether extract is dried with anhydrous sodium sulfate and evaporated to give a mixture of the aldehydes (*E*)-**4** and (*Z*)-**4**; yield: 7.0 g (42%); ratio (*E*)-**4**/(*Z*)-**4**: 98/2 according to ^{1}H-N.M.R. and G.L.C. analyses [retention times: (*Z*)-**4**, 6 min; (*E*)-**4**, 7 min; 2 m column packed with 20% Carbowax 20 M in Chromosorb W, 180°]. The isomers are separated by column chromatography on silica gel using cyclohexane/ethyl acetate (9/1) as eluent.

Aldehyde (*E*)-**4**; yield: 6.6 g (40%); oil; b.p. 74–75°/0.06 torr; $[\alpha]_{578}^{25}$: +29° (*c* 2.34, ethanol).

$C_{11}H_{16}O$	calc.	C 80.44	H 9.83
(164.2)	found	80.40	9.90

^{1}H-N.M.R. (CCl_4): δ = 9.95 (d, H-11, *J* = 7.5 Hz); 5.88 (d, H-9, *J* = 7.5 Hz); 5.45 (s, broad, H-2); 2.18 (d, CH_3-10, *J* = 1.3 Hz); 1.65 ppm (s, CH_3-7).

^{13}C-N.M.R. ($CDCl_3$): δ = 191.7 (C-11); 168.0 (C-8); 134.0 (C-1); 126.0 (C-9); 119.7 (C-2); 43.9 (C-4); 30.1 (C-3); 30.1 (C-6); 27.0 (C-5); 23.4 (C-7); 16.0 ppm (C-10).

Aldehyde (*Z*)-**4**; yield: 0.2 g (1%); oil; $[\alpha]_{578}^{25}$: −4° (*c* 0.31, ethanol).

$C_{11}H_{16}O$	calc.	C 80.44	H 9.83
(164.2)	found	80.30	9.98

^{1}H-N.M.R. (CCl_4): δ = 9.98 (d, H-11, *J* = 7.5 Hz); 5.84 (d, H-9, *J* = 7.5 Hz); 5.45 (s, broad, H-2); 1.88 (d, CH_3-10, *J* = 1.5 Hz); 1.65 ppm (s, CH_3-7).

^{13}C-N.M.R. ($CDCl_3$): δ = 190.2 (C-11); 168.2 (C-8); 134.0 (C-1); 128.3 (C-9); 119.7 (C-2); 36.3 (C-4); 30.1 (C-3); 30.5 (C-6); 27.3 (C-5); 23.4 (C-7); 20.6 ppm (C-10).

Method B: Identical conditions as in method A except for reaction time (24 h). (*E*)-**4**; yield: 2.5 g (15%); $[\alpha]_{578}^{25}$: +68° (*c* 3.08, ethanol).

Method C: Identical conditions as in method A except for reaction time (2 h). (*E*)-**4**: yield: 0.8 g (5%); $[\alpha]_{578}^{25}$: +106° (*c* 0.107, ethanol). (*Z*)-**4**; yield: 0.2 g (1%); $[\alpha]_{578}^{25}$: −15° (*c* 0.090, ethanol).

(*E*)-3-(4-*cis*-Hydroxy-4-methylcyclohexyl)-2-butenal (6):

A solution of reagent **2** [prepared from dimethylformamide (80 g, 1.1 mol) and phosphoryl chloride (153 g, 1 mol) in dichloromethane (150 ml)] is added to a solution of (+)-limonene (**1**; 13.6 g, 0.10 mol) in dichloromethane (50 ml) at a temperature below 5°. Performance of the reaction and work-up is as described for the preparation of (*E*)-**4**, Method A, except for the reaction time (4 days); yield: 6.4 g (35%); oil; b.p. 80–84°/0.06 torr. [The configuration at C-1 was determined by comparison of the ^{13}C-N.M.R. spectrum of **6** with those of *cis*- and *trans*-4-*t*-butyl-1-methylcyclohexanol[19].]

$C_{11}H_{18}O_2$	calc	C 72.49	H 9.96
(182.2)	found	72.38	11.01

^{1}H-N.M.R. (CCl_4): δ = 9.93 (d, H-11, *J* = 8.0 Hz); 5.83 (d, H-9, *J* = 8.0 Hz); 3.0 (s, OH); 2.18 (d, CH_3-10, *J* = 1.3 Hz); 1.20 ppm (s, CH_3-7).

^{13}C-N.M.R. ($CDCl_3$): δ = 191.9 (C-11); 168.7 (C-8); 126.0 (C-9); 68.6 (C-1); 47.7 (C-4); 38.5 (C-6); 38.5 (C-2); 31.4 (C-7); 26.1 (C-5); 26.1 (C-3); 16.0 ppm (C-10).

(+)-(4*R*)-(*E*)-α-Atlantone (10):

4-(RS)-Hydroxy-2-methyl-6-[4-methyl-3-cyclohexen-1(R)-yl]-(E)-1,5-heptadiene (**8**): Prepared from methallylmagnesium chloride [from 3-chloro-2-methylpropene (7.57 g, 0.084 mol) and magnesium (5.0 g, 0.206 g-atom) in ether (100 ml)] and the aldehyde (*E*)-**4** (3.3 g, 0.02 mol; $[\alpha]_{578}^{25}$: +106°, *c* 0.107, ethanol) under the conditions given in Ref. [9]: yield: 4.3 g (99%); b.p. 85–95°/0.05 torr (Ref. [9], b.p. 90–102°/0.07 torr). The I.R. and ^{1}H-N.M.R. spectra are identical with those reported in Ref. [9].

(+)-(4R)-(E)-α-Atlantone (**10**): The alcohol **8** (4.3 g, 0.02 mol) is oxidized with chromium(VI) oxide-pyridine complex under the conditions given in Ref. [14]. The resultant crude ketone **9** is added to a stirred solution of potassium hydroxide (1.8 g) in methanol/water (80/20; 45 ml) at 0°. Stirring is continued at 0° for 45 min, the mixture then neutralized with 10% sulfuric acid (5 ml), and extracted

with ether. The extract is dried with anhydrous sodium sulfate the ether evaporated in vacuo, and the crude product purified by column chromatography on silica gel using cyclohexane/ethyl acetate (96/4) as eluent; yield of **10**: 3.4 g (80%); oil; n_D^{20}: 1.5376; $[\alpha]_{578}^{25}$ +75° (*c* 0.047, ethanol). [The ^{1}H-N.M.R., I.R. and U.V. spectral properties are identical with those previously reported for (*E*)-α-atlantone[15, 16, 20].]

$C_{15}H_{22}O$	calc.	C 82.51	H 10.16
(218.3)	found	82.10	10.32

^{13}C-N.M.R. ($CDCl_3$): δ = 192.1 (C-11); 161.8 (C-8)[a]; 154.0 (C-13)[b]; 133.8 (C-1); 126.5 (C-9); 124.3 (C-12)[b]; 120.2 (C-2); 44.6 (C-4); 30.3 (C-3); 30.3 (C-6); 27.7 (C-15)[c]; 27.5 (C-5); 23.4 (C-7); 20.6 (C-14)[c]; 17.5 ppm (C-10).

[a] Assignment C-8 made by comparison with C-8 of (*E*)-**4**, α,β-unsaturated aldehyde : corresponding α,β-unsaturated methyl ketone, Δδ for β-C being about −10 ppm (*cf.* J. B. Stothers, *Carbon-13 NMR Spectroscopy*, Academic Press, New York, 1972, p. 190, 193).

[b] Assignment C-12 and C-13 made by comparison with corresponding carbon of mesityl oxide [*cf.* D. H. Marr, J. B. Stothers, *Can. J. Chem.* **43**, 596 (1965)].

[c] Assignment C-14 and C-15 made by comparison with C-10 of (*E*)-**4**, (*Z*)-**4**, and (*E*)-α-atlantone **(10)**, the predominant conformation of **10** being symmetric *s-cis s-cis*[15].

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