Synthesis of Compounds Containing the Isoprene Unit; a Stereospecific Synthesis of β-Ionilideneacetic Acid and Dehydro-β-ionilideneacetic Acid, a Key Intermediate to Abscisic Acid

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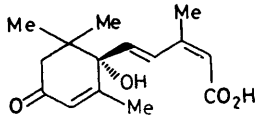
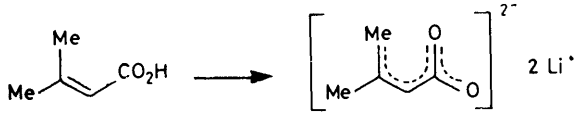
A stereospecific synthesis of dehydro-β-ionilideneacetic acid (7b), a key intermediate to the abscisic acid (1), starting from the dianion of 3-methylbut-2-enoic acid (2) and safranal (3b) is described. Dehydrobromination to the bromoaldehyde (11) was achieved by treatment of (10) with the resin Amberlyst A 26 in the F^- form. In the same way, treatment of β-cyclocitral (3a) with (2) gives β-ionilideneacetic acid (7a) in good yield.

ABSCISIC acid (1) has been shown to exhibit an hormonal activity related to leaf and flower growth or dormancy.[1] This plant hormone is thought to be involved in the regulation on transpiration through its effect on the stomatal aperture; it was observed that synthetic (1) causes stomatal closure in whole plants, shoots and leaves.[2] Our interest in the stereospecific synthesis



(1)

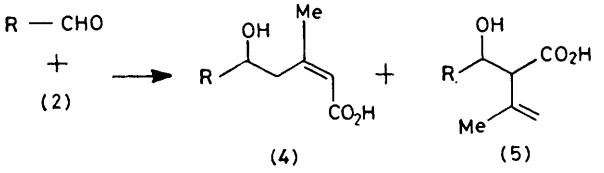
of double bonds prompts this report on the stereospecific introduction of an $\alpha\beta(Z),\gamma\delta(E)$ conjugated system by a one-step addition of the synthon (2), the dianion of the 3-methylbut-2-enoic acid.[3]



(2)

The chain of abscisic acid comprises a substituted (2*Z*),(4*E*)-pentadienoic acid, a typical configuration that we have already realized in a new synthesis of (2*Z*)-vitamin A and dehydronerol isovalerate.[4]

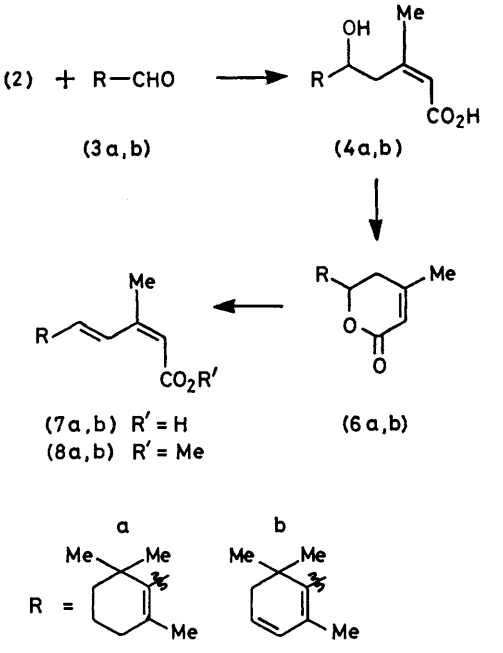
The synthon (2) is easily obtained by metallation of 3-methylbut-2-enoic acid by means of lithium di-isopropylamide, and permits direct addition to an aldehyde without going through the halogeno-derivative of the Reformatsky reaction. The behaviour of the key reagent (2) is extensively described in our previous



(4) (5)

papers: electrophilic attack at the α or γ position, leading to (4) and (5), respectively, depends upon the nature of the counter ion and the solvent, and can be regioselectively directed to the γ position by adding a small amount of HMPA.

However, the most important property of the synthon (2) lies in its ability to introduce the prenyl unit stereospecifically, leading exclusively to the (2*Z*)-isomer; in no case are mixtures of configurational isomers observed.

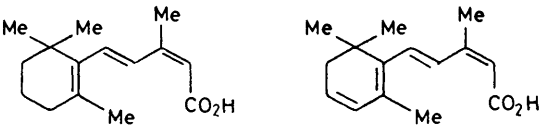


(3a,b) (4a,b) (6a,b) (7a,b) R′ = H (8a,b) R′ = Me

SCHEME 1

The hydroxy-acid (4a, b) obtained converts quantitatively to the lactone (6a, b) on acidification, and by treatment with base easily and stereospecifically gives the $\alpha\beta(Z),\gamma\delta(E)$ doubly unsaturated acid (7a, b), with the same configuration as required for (1).

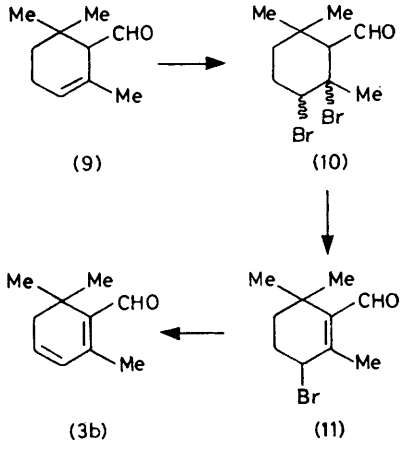
In this paper we wish to describe the stereospecific synthesis, following Scheme 1, of β-ionilideneacetic acid (7a)[5] and dehydro-β-ionilideneacetic acid (7b), a key intermediate in the synthesis of abscisic acid (1).[6]



(7a) (7b)

RESULTS AND DISCUSSION

Addition of a solution of β-cyclocitral (3a) in THF to an equimolar amount of the prenylating reagent (2) in THF–HMPA at −78 °C, followed by acidification and work-up gives the lactone (6a) in 78% yield. Our method seems to be superior to the alternative Reformatsky reaction which requires a bromo-derivative and gives a much lower yield.[7] Pentenolides have been shown to intramolecularly eliminate under the action of bases yielding $\alpha\beta(Z),\gamma\delta(E)$ doubly unsaturated acids almost quantitatively. Treatment of (6a) with sodium hydride in THF containing a small amount of HMPA gives rise in fact to the expected β-ionilideneacetic acid (7a) in 92% yield. Following the same procedure dehydro-β-ionilideneacetic acid (7b) was obtained in an overall yield of 56%, starting from safranal (3b). β-Cyclocitral (3a) was synthesized from citral following a slightly modified standard procedure as reported in the Experimental section.



SCHEME 2

The major problem in the synthesis of (7b) was the preparation of pure safranal (3b). The literature reports several synthetic routes,[8] but none of these seems to have much practical value. The synthesis of Könst *et al.*,[9] the only suitable one, has been followed introducing some modifications (Scheme 2).

The dibromide (10) obtained by direct bromination with bromine of α-cyclocitral was dehydrobrominated by refluxing for 45 min in toluene in the presence of the resin Amberlyst A 26 in the F^- form[10] to give the bromoaldehyde (11) in quantitative yield. The use of the resin greatly simplifies the work-up of the reaction, which is simply performed by filtering off the resin and removing the solvent *in vacuo*. To our knowledge, this is the first application of this polymeric reagent to perform a dehydrobromination reaction. The bromoaldehyde (11) was further dehydrobrominated to safranal (3b) on addition to boiling collidine and refluxing for 15 min. The reaction conditions are critical: warming a solution of (11) in collidine from room temperature to reflux temperature, as reported in the literature, causes partial reductive debromination to β-cyclocitral.

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer 710B spectrometer. N.m.r. spectra were recorded on an R12B Perkin-Elmer instrument with $SiMe_4$ as internal reference. Mass spectra were measured on a Hitachi–Perkin-Elmer RMU6D (single focus) spectrometer at 60 eV. T.l.c. was performed on silica gel HF_{254} (Merck) and column chromatography on silica gel 0.05—0.20 mesh (Merck), with hexane–ether as a solvent. THF was obtained dry and oxygen-free by distillation over sodium benzophenone ketyl under argon. Di-isopropylamine was distilled from calcium hydride and stored over molecular sieves. Hexamethylphosphoramide (HMPA) was distilled from molecular sieves under argon. n-Butyl-lithium was purchased from Roth (Karlsruhe) as a 2.2M solution in n-heptane.

α-Cyclocitral (*2,6,6-Trimethylcyclohex-2-ene-1-carbaldehyde*) (9).—A solution of citral (15.2 g; 100 mmol) and pyrrolidine (14.2 g; 200 mmol) in dry benzene (100 ml) in the presence of molecular sieve (10 g) was refluxed for 1 h; the molecular sieve was then filtered off and the filtrate was evaporated *in vacuo*, to give pyrrolidine enamine as a brown oil in quantitative yield. This product was added dropwise to 90% H_2SO_4 (60 ml) at −20 °C under an inert atmosphere during 30 min and stirred for a further 45 min at −15 °C. The reaction mixture was added to ice (100 g) and extracted with $CHCl_3$. The extracts were dried (Na_2SO_4) and concentrated, and the residue was distilled *in vacuo* to yield α-cyclocitral (9), b.p. 85—93 °C at 15 mmHg (8.5 g; 56% yield); $\nu_{max.}$ (neat) 1 720 (C=O) cm^{-1}; δ(CCl_4) 0.9 and 1.0 (2 s, 6 H, CMe_2), 1.4 (m, 2 H, CH_2), 1.6 (dd, 3 H, Me, *J* 2 Hz), 2.15 (m, 2 H, CH_2–C=), 2.3 (d, 1 H, C*H*–CHO, *J* 6 Hz), 5.72 (br s, 1 H, CH=C), and 9.50 (d, 1 H, CHO, *J* 6 Hz).

β-Cyclocitral (*2,6,6-Trimethylcyclohex-1-ene-1-carbaldehyde*) (3a).—To a suspension of Bu^tOK (3.36 g; 30 mmol) in dry THF (50 ml) was added α-cyclocitral (4.56 g; 30 mmol) in dry THF (20 ml) dropwise at 0 °C. After stirring for 15 min at 0 °C the mixture was diluted with water and ether and acidified with 2N HCl. After extraction with ether, the organic layer was washed with 10% aqueous $NaHCO_3$ and water and then dried (Na_2SO_4). The organic layer was evaporated to dryness and the residue chromatographed on silica gel to yield β-cyclocitral (3a) (4.3 g; 94% yield) (eluant hexane); $\nu_{max.}$ (neat) 1 700 (C=O) cm^{-1}; δ(CCl_4) 1.15 (s, 6 H, CMe_2), 1.5 (m, 4 H, CH_2), 2.1 (s, 3 H, =C–Me), 2.2 (m, 2 H, CH_2–C=), and 10.05 (s, 1 H, CHO).

3-Methyl-5-(2,6,6-trimethylcyclohex-1-enyl)pent-2-en-5-olide (6a).—To a solution of di-isopropylamine (3 g; 30 mmol) in dry THF (20 ml) at 0 °C under argon, was slowly added a 2.2M Bu^nLi (13.7 ml; 30 mmol) n-heptane solution. The mixture was stirred at 0 °C for 1 h and at room temperature for 2 h. 3-Methylbut-2-enoic acid (1.5 g; 15 mmol) in dry THF (10 ml) was then added at 0 °C. The mixture was stirred for 0.5 h, then heated and stirred successively for 1.5 h at 45 °C. After cooling to −78 °C HMPA (7 ml) was added, and then β-cyclocitral (2.3 g; 15 mmol) in THF (10 ml) was added during 20 min and the mixture was stirred at −60 °C overnight. The mixture was then diluted with ether and water and acidified with 2N HCl. After extraction with ether the organic layer was washed with water, dried (Na_2SO_4), and the solvent removed *in vacuo*. Chromatography of the residue on silica gel gave (6a) (2.75 g, 78% yield), eluant hexane–ether (6 : 4); $\nu_{max.}$ (neat) 1 720 (C=O) and 1 650 (C=C) cm^{-1}; δ(CCl_4) 1.0 and 1.10 (2 s, 6 H, CMe_2), 1.55 (m, 4 H, CH_2), 1.8 (s, 3 H, Me–C=C),

2.05 (s, 3 H, *Me*–C=CH–C=O), 2.20 [m, 2 H, $-CH_2-C=C$ (ring)], 2.3 (m, 2 H, $-CH_2-CH-O-$), 5.05 (dd, 1 H, –CH–O–), and 5.9 (s, 1 H, C=CH–C=O); *m/e* 234 (M^+) (Found: C, 76.80; H, 9.75. $C_{15}H_{22}O_2$ requires C, 76.88; H, 9.46%).

Methyl (2Z,4E)-β-*Ionilideneacetate* [*Methyl* (2Z,4E)-3-*Methyl*-5-(2,6,6-*trimethylcyclohex*-1-*enyl*)*penta*-2,4-*dienoate*] (8a).—A solution of (6a) (1.2 g, 5 mmol) in dry THF (10 ml) was added to a suspension of NaH (150 mg dispersion 80% in oil) in dry THF (15 ml) and HMPA (1 ml), and stirred for 20 min at 0 °C. The mixture was then diluted with ether and water and acidified with 2N HCl. The organic layer, after extraction with ether, was washed with water, dried (Na_2SO_4), and the solvent removed *in vacuo* to give (7a) (1.07 g, 92% yield) which was esterified with diazomethane to give quantitatively (8a); $\nu_{max.}$ (neat) 1 705 (C=O) and 1 610 (C=C) cm^{-1}; δ(CCl_4) 1.1 (s, 6 H, CMe_2), 1.55 (m, 4 H, $-CH_2-$), 1.8 (s, 3 H, Me–C=C), 2.05 (s, 3 H, *Me*–C=CH–CO_2Me), 2.05 [m, 2 H, $-CH_2-C=C$ (ring)], 3.65 (s, 3 H, OMe), 5.65 (s, 1 H, C=C*H*–CO_2Me), 6.55 (d, 1 H, –C*H*=CH–C=CH–CO_2Me, *J* 18 Hz), and 7.75 (d, 1 H, –CH=C*H*–C=CH–CO_2Me, *J* 18 Hz); $\lambda_{max.}$ (MeOH) 312 nm (ε 15 450); *m/e* 248 (M^+) (Found: C, 77.25; H, 9.75. $C_{16}H_{24}O_2$ requires C, 77.37; H, 9.74%).

3-*Bromo*-2,6,6-*trimethylcyclohex*-2-*ene*-1-*carbaldehyde* (11).—To a mixture of α-cyclocitral (4.5 g; 30 mmol) and $CaCO_3$ (1 g) in CH_2Cl_2 (40 ml) at −60 °C bromine (4.8 g; 30 mmol) in CH_2Cl_2 (30 ml) was added dropwise during 15 min. After allowing the reaction mixture to warm to room temperature, $CaCO_3$ was filtered off and the solvent was evaporated off *in vacuo*. The residue was then dissolved in toluene (80 ml) and dry resin Amberlyst A 26 (12 g, F^- form) were added. The mixture was refluxed for 45 min and then the resin was filtered off. After evaporation of the solvent, the residue was chromatographed on silica gel (eluant hexane) to give (11) in quantitative yield; $\nu_{max.}$ (neat) 1 680 (C=O) cm^{-1}; δ(CCl_4) 1.20, 1.25 (2 s, 6 H, CMe_2), 2.10 (m, 4 H, CH_2), 2.3 (s, 3 H, Me), 4.65 (br s, 1 H, CH–Br), and 10.15 (s, 1 H, CHO).

Safranal (2,6,6-*Trimethylcyclohexa*-1,3-*diene*-1-*carbaldehyde*) (3b).—Compound (11) (6.9 g, 30 mmol) was added to boiling collidine (40 ml) and the mixture was refluxed under argon for 15 min. The reaction mixture was then poured into ice–water and extracted with ether; the organic layer was then washed with 2N HCl, aqueous $NaHCO_3$, and water, and dried (Na_2SO_4). After removal of solvent *in vacuo*, the residue was steam-distilled. The distillate was extracted twice with ether, dried (Na_2SO_4), and the solvent was removed *in vacuo*. Chromatography on silica gel eluting with hexane–ether (9 : 1) yielded (3b) (2.34 g; 52% yield); $\nu_{max.}$ (neat) 1 665 (C=O) cm^{-1}; δ(CCl_4) 1.15 (s, 6 H, CMe_2), 2.1 (m, 2 H, CH_2), 2.15 (s, 3 H, Me), 5.70—6.35 (m, 2 H, CH=CH), and 10.10 (s, 1 H, CHO); $\lambda_{max.}$ (MeOH) 312 nm (ε 8 200).

3-*Methyl*-5-(2,6,6-*trimethylcyclohexa*-1,3-*dien*-1-*yl*)*pent*-2-*en*-5-*olide* (6b).—To a solution of di-isopropylamine (1.68 g; 16 mmol) in dry THF (20 ml) at 0 °C under argon, was slowly added a 2.2M n-BuLi (7.7 ml; 16 mmol) n-heptane solution. The mixture was stirred at 0 °C for 1 h and at room temperature for 2 h. Then 3-methylbut-2-enoic acid (0.8 g; 8 mmol) in THF (5 ml) was added at 0 °C. The mixture was stirred for 0.5 h, heated and then stirred for 1.5 h at 45 °C. After cooling to −78 °C, HMPA (5 ml) was added during 20 min and then safranal (1.2 g; 8 mmol) in THF (10 ml) was added during 20 min and the mixture was stirred at −60 °C overnight. The mixture was then diluted with ether and water and acidified with 6N HCl. After extraction with ether the organic layer was washed with water, dried (Na_2SO_4), and the solvent removed *in vacuo*. Chromatography on silica gel then gave (6b) (1.2 g, 61% yield), eluant [hexane–ether (7 : 3)]; $\nu_{max.}$ (neat) 1 720 (C=O) and 1 640 (C=C) cm^{-1}; δ(CCl_4) 1.1 (s, 6 H, CMe_2), 1.85 (s, 3 H, Me–C=C), 2.00 (s, 3 H, $CH_3-C=C-C=O$), 2.1—2.4 (m, 4 H, CH_2), 5.25 (dd, 1 H, –CH–O–), and 5.8 (m, 3 olefinic H); *m/e* 232 (M^+) (Found: C, 78.0; H, 8.85. $C_{15}H_{20}O_2$ requires C, 77.55; H, 8.68%).

Methyl (2Z,4E)-*Dehydro*-β-*ionilideneacetate* [*Methyl* (2Z,4E)-3-*Methyl*-5-(2,6,6-*trimethylcyclohexa*-1,3-*dienyl*)-*penta*-2,4-*dienoate* (8b).—A solution of (6b) (700 mg; 3 mmol) in dry THF (10 ml) was added to a suspension of NaH (70 mg of dispersion, 80% in oil) in dry THF (10 ml) and HMPA (1 ml), and stirred for 30 min at 0 °C. The mixture was then diluted with ether and water and acidified with 2N HCl. The organic layer, after extraction with ether, was washed with water, dried (Na_2SO_4), and the solvent removed *in vacuo* to give acid (7b) (620 mg, 93%) which was esterified with diazomethane to give (8b) quantitatively; $\nu_{max.}$ (neat) 1 705 (C=O) and 1 605 (C=C) cm^{-1}; δ(CCl_4) 1.10 (s, 6 H, CMe_2), 1.95 (s, 3 H, Me–C=C), 2.1 (s, 3 H, *Me*–C=CH–CO_2Me), 2.15 (m, 2 H, CH_2), 3.75 (s, 3 H, OMe), 5.7 (s, 1 H, C=C*H*–CO_2Me), 5.9 (br s, 2 H, CH=CH ring), 6.65 (d, 1 H, C*H*=CH–C=CH–CO_2Me, *J* 18 Hz), and 7.95 (d, 1 H, CH=C*H*–C=CH–CO_2Me, *J* 18 Hz); $\lambda_{max.}$ (MeOH) 356 nm (ε 12 200); *m/e* 246 (M^+) (Found: C, 77.30; H, 9.0. $C_{16}H_{22}O_2$ requires C, 78.01; H, 9.00%).

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