SHORT PAPER

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An efficient synthesis of the plant hormone abscisic acid†

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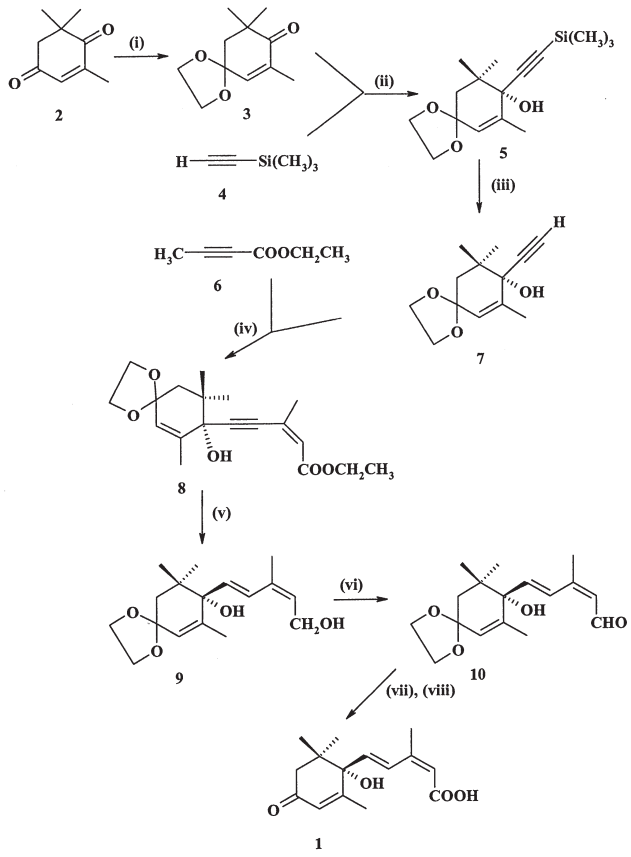
An efficient stereospecific synthesis of the plant hormone (*RS*)-abscisic acid from the readily available 4-oxoisophorone, trimethylsilylacetylene and ethyl but-2-ynoate, is described.

Keywords: plant hormone, abscisic acid

The plant hormone abscisic acid (**1**) induces a number of responses in plants including leaf fall and dormancy.[1] It is only formed in small amounts and it is not readily available from plant sources. Consequently there have been a number of syntheses of abscisic acid and its analogues in order to assess its biological activity.[2] The major objectives of these syntheses have been to create the side chain double bonds [2(*Z*),4(*E*)] in a stereospecific manner. However, not all the syntheses achieve this and a number utilise components that are not readily available. In this paper we describe a simple stereospecific synthesis utilising readily available starting materials.

4-Oxoisophorone (**2**) which has been used in a number of previous syntheses, formed a readily available starting material. The more exposed carbonyl group was selectively protected as its ethylene ketal **3**.[3] A previous synthesis had used a condensation between the ketal **3** and an acetylene, methyl (*Z*)-3-methylpent-2-en-4-ynoate.[2d] However, the starting material for the preparation of this acetylenic ester was no longer commercially available. Consequently we carried out the construction of the side chain in stages.

The ketal **3** reacted easily with lithium salt of trimethylsilylacetylene (**4**) to give after deprotection, the ethynyl alcohol **7**. Ethyl but-2-ynoate (**6**) was prepared in high yield by pyrolysis of the β-ketophosphorane obtained from the reaction of ethyl acetoacetate with triphenylphosphine dichloride.[4,5] The ethynyl alcohol **7** underwent a conjugate addition to ethyl but-2-ynoate (**6**) in the presence of a catalytic amount of palladium(II) acetate[6] to give stereospecifically and in high yield the (*Z*)-isomer of ethyl 3-methyl-5-[1′-hydroxy-2′,6′,6′-trimethyl-4′,4′-ethylenedioxycyclohex-2′, enyl]-pent-2-en-4-ynoate (**8**). The alkene proton resonance (δ_H 6.03) was that of a single isomer**.** The previous synthesis[2d] had utilised chromium(II) sulfate to reduce the ethynyl alcohol[8]. However, in order to avoid the use of toxic chromium salts which could present problems of residues, the reduction of the ethynyl alcohol was carried out with lithium aluminium hydride rather than with chromium(II) chloride. This reduction gave the *trans* isomer (δ_H 5.70 and 6.63, *J* 14.5Hz).[7,8] In order to avoid isomerisation of the (*Z*)-double bond, the oxidation of the primary alcohol **9** was carried out in a stepwise manner. Oxidation with a catalytic amount of tetrapropylammonium perruthenate and *N*-morpholine oxide[9] gave the unsaturated aldehyde **10** which was then oxidised with silver oxide[10] and simultaneously deprotected in the acidic work-up to give (*RS*)-abscisic acid (**1**) in *ca* 25% overall yield from **4**-oxoisophorone (**2**). In conclusion we have developed an efficient stereospecific synthesis of (*RS*)-abscisic acid using readily available starting materials.



Scheme 1 (i) $HOCH_2CH_2OH$, *p*TsOH; (ii) LDA/THF; (iii) K_2CO_3, MeOH; (iv) $Pd(OAc)_2$, PPh_3THF; (v) $LiAlH_4$, THF; (vi) TPAP, NMO, 4A Molc.Siev., CH_2Cl_2; (vii) Ag_2O, NaOH, H_2O; (viii) HCl, H_2O.

Experimental

Light petroleum refers to the fraction b.p. 60–80°C. Silica for chromatography was Merck 9385. Extracts were dried over anhydrous sodium sulfate. IR spectra were determined as thin films or as nujol mulls.[1] H NMR spectra were determined at 300MHz for solutions in deuteriochloroform.

4,4-(Ethylenedioxy)-2,6,6-trimethylcyclohex-2-en-1-one (**3**): 4-Oxoisophorone (**2**) (100g, 0.657 mol), ethane-1,2-diol (54 cm^3) and toluene-*p*-sulfonic acid (2.7g) in benzene (500 cm^3) were heated under reflex for 10h. with a Dean and Starke trap to remove the water in a well ventilated fume cupboard. The solution was cooled and poured into aqueous sodium hydrogen carbonate. The organic layer

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was separated and the aqueous phase was extracted with ether. The combined organic extracts were washed with water and dried. The solvents were evaporated and the residue was distilled in vacuo to give 4,4-(ethylenedioxy)-2,6,6-trimethylcyclohex-2-en-1-one (**3**) (94g,73%), b.p. 44–52°C/0.02mmHg (lit.,[3] 76–80°C/0.5mmHg), ν_{max}/cm^{-1} 1680; δ_H 1.16 (6H, s, 6-Me$_2$), 1.75 (3H s, 2-Me), 2.04 (2H, s, 5-H), 3.97 (4H, m, OCH$_2$CH$_2$O), 6.27 (1H, s, 3-H).

4,4-(Ethylenedioxy)-2,6,6-trimethyl-1-trimethylsilanylethynylcyclohex-2-en-1-ol (**5**): Trimethylsilylacetylene (5g, 51 mmol) in tetrahydrofuran (75 cm^3) was added to a 10% solution of lithium diisopropylamide in hexane (54.6 cm^3, 51mmol) in tetrahydrofuran (50 cm^3) at –78°C under nitrogen. The mixture was stirred for 15 min and then a solution of the above ketal (5g, 25.5mmol) in tetrahydrofuran (75 cm^3) was added dropwise. The mixture was allowed to attain room temperature over 1h. Saturated ammonium chloride (250 cm^3) was added and the product was extracted with ether. The organic phase was washed with water, brine and dried. The solvent was evaporated to afford 4,4-(ethylenedioxy)-2,6,6-trimethyl-1-(trimethylsilanylethynyl) cyclohex-2-en-1-ol (**5**) (6.75g, 90%) as an oil, (Found: M$^+$ 317.153 $C_{16}H_{26}O_3SiNa^+$ requires 317.154), ν_{max}/cm^{-1} 3385; δ_H 0.12 (9H, s, SiMe$_3$), 1.05 and 1.11 (each 3H, s, 6-Me), 1.87 (5H**,** overlapping multiplet, 5-H and 2-Me), 3.90 (4H, m. OCH$_2$CH$_2$O), 5.32 (1H, s, 3-H).

Hydrolysis of the silane (**5**): The above silylketal (**5**) (6.5g) in methanol (150 cm^3) was treated with solid potassium carbonate (20g) at room temperature for 2h. The mixture was filtered and the solution concentrated. The product was recovered in ether, washed with water, dried and the solvent evaporated to give 4,4-(ethylenedioxy)-l-ethynyl-2,6,6-trimethylcyclohex-2-en-l-ol (**7**) (4.5g, 91%) which crystallised from acetone as needles, m.p. 78–80°C, (Found: C, 70.2; H, 8.2. $C_{13}H_{18}O_3$ requires C,70.2; H,8.2%), ν_{max}/cm^{-1} 3400; δ_H 1.10 and 1.15 (each 3H, s, 6-Me), 1.92 (5H, overlapping multiplet, 5-H and 2-Me), 3.92 (4H, m, OCH$_2$CH$_2$O), 5.37 (1H, s, 3-H).

Ethyl (Z)-5-[4′,4′-(ethylenedioxy)-1′-hydroxy-2′,6′,6′-trimethylcyclohex-2′-enyl)-3-methylpent-2-en-4-ynoate (**8**): A mixture of palladium(II) acetate (91mg, 0.4mmol) and triphenylphosphine (105mg, 0.40mmol) in tetrahydrofuran (90cm^3) was stirred for 15 min. at room temperature under nitrogen. Ethyl but-2-ynoate (**6**)(3.5cm^3, 30mmol) was added and the mixture was stirred for 5 min. A solution of the above acetylene (4.5g, 20.2 mmol) in tetrahydrofuran (90cm^3) was added dropwise and the mixture was then stirred at room temperature for 20h. The solvent was evaporated and the residue was chromatographed on silica. Elution with 10-20% ether in light petroleum gave ethyl (*Z*)-5-[4′,4′-(ethylenedioxy)-l′-hydroxy-2′,6′,6′-trimethylcyclohex-2′-enyl]-3-methylpent-2-en-4-ynoate (**8**)(5.7g) as an oil, (Found: M$^+$ 335.183, $C_{19}H_{26}O_5$+H$^+$ requires 335.185), ν_{max}/cm^{-1} 3340, 1713; δ_H 1.09 and 1.13 (each 3H, s, 6′-Me), 1.26 (3H, t, *J* 7 Hz, OEt), 1.89 (3H, s, 2′-Me), 1.97 and 2.03 (each 1H, d, *J* 16 Hz, 5′-H), 2.26 (3H, s, 3-Me), 3.92 (4H, m, OCH$_2$CH$_2$O), 4.15 (2H,q, *J* 7 Hz, OEt), 5.38 (1H, s, 3′-H), 6.03 (1H, s, 2-H).

Reduction of the ester (**8**)**:** The above ester (5g, l5mmol) in tetrahydrofuran (50cm^3) was added to a solution of lithium aluminium hydride (1g, 22mmol) in dry tetrahydrofuran (100cm^3) at 0°C. The mixture was then stirred at room temperature for 2h. Water (10cm^3), followed by 15% aqueous sodium hydroxide (10 cm^3) and a further amount of water (30 cm^3) were then added. The mixture was stirred for 30 min and the precipitate filtered and washed with ether. The combined organic phases were dried and the solvent was evaporated to give 5-[4′,4′-(ethylenedioxy)-1′-hydroxy-2′,6′,6′-trimethyl cyclohex-2′-enyl]-3-methylpenta-4(*E*),2(*Z*)-dien-1-ol (**9**) (3.85g, 91%) as an oil, (lit.,[11] oil), ν_{max}/cm^{-1} 3400; δ_H 0.90 and 1.07 (each 3H, s, 6′-Me), 1.66 (3H, s, 2′-Me), 1.79 and 1.92 (each 1H, d, *J* 16 Hz, 5′-H), 1.84 (3H, s, 3-Me), 3.90 (4H, m, OCH$_2$CH$_2$O), 4.30 (2H, d, *J* 6.9 Hz, 1-H), 5.42 (1H, s, 3′-H), 5.57 (1H, d, *J* 6.9Hz, 2-H), 5.70 (1H, d, *J* 14.5 Hz, 4-H), 6.63 (1H, d, *J* 14.5Hz, 5-H).

Oxidation of the alcohol (**9**): Tetrapropylammonium perruthenate [TPAP)(210 mg) was added in one portion to a mixture of the above alcohol (3.5g, 11.9 mmol), *N*-methylmorpholine *N*-oxide (2.lg, 17.85 mmol) and powdered 4A molecular sieves (6.0g) in dichloromethane (25 cm^3) at room temperature under nitrogen. The mixture was stirred for 15 min. and then filtered through a short column of silica. The column was rinsed with dichloromethane and ether. The solvents were evaporated *in vacuo* to afford 5-[4′,4′-(ethylenedioxy)-l′-hydroxy-2′,6′,6′-trimethylcyclohex-2′-enyl)-3-methylpenta-4(*E*),2(*Z*)-dien-1-a1 (10)(2.9g, 83%), m.p.74–76°C, (Found: C, 67.3; H, 8.3. $C_{17}H_{24}O_4.0.5H_2O$ requires C, 67.7, H, 8.4%), ν_{max}/cm^{-1} 3500, 1670; δ_H 0.91 and 1.08 (each 3H, s, 6′-Me), 1.65 (3H, s, 2′-Me), 1.89 (3H, s, 3-Me) 2.03 and 2.26 (each 1H, d, *J* 17 Hz, 5′-H), 3.91 (4H, m, OCH$_2$CH$_2$O), 5.44 (1H, s, 3′-H), 5.84 (1H, d, *J* 8,2 Hz, 2-H), 6.09 and 7.32 (each 1H, d, *J* 15.5 Hz, 4- and 5- H) 10.19 (1H, d, *J*, 8.2Hz, 1-H). The aldehyde (10) (1g) was added to a suspension of silver(I) oxide (1.3g) in 10% aqueous sodium hydroxide (3 cm^3) and water (5cm^3) in a test tube. The mixture was stirred for 30 min. The mixture was then filtered and the filtrate was acidified with conc. hydrochloric acid and allowed to stand for 30min. The product was extracted with ether. The extract was washed with water and dried. The solvent was evaporated to give (*RS*)-abscisic acid (1)(700mg, 78%), m.p.183–185°C (lit.,[1] m.p.188–190°C), ν_{max}/cm^{-1} 3420, 1680, 1643, 1625; δ_H 1.03 and 1.12 (each 3H, s, 6′-Me), 1.93 (3H, s, 2′-Me), 2.05 (3H, s, 3-Me), 2.29 and 2.49 (each 1H, d, *J* 17 Hz, 5′-H), 5.79 (1H, s, 2-H), 5.97 (1H, s, 3′-H), 6.17 (1H, d, *J* 16 Hz, 4-H), 7.79 (1H, d, *J* 16 Hz, 5H).

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