

## The Stereospecific Synthesis of Abscisic Acid

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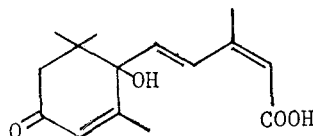
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**Abstract**—A stereospecific synthesis of 3-methyl-5-(1-hydroxy-4-oxo-2,6,6-trimethyl-2-cyclohexen-1-yl)-cis, trans-2,4-pentadienoic acid (abscisic acid) from  $\alpha$ -ionone has been investigated. Ethyl 5-(2,6,6-trimethyl-2-cyclohexen-1-yl)-trans-4-penten-2-ynoate ( $\alpha, \beta$ -acetylenic ester), which was synthesized from  $\alpha$ -ionone in two steps, was stereospecifically converted in good yield into ethyl 3-methyl-5-(2,6,6-trimethyl-2-cyclohexen-1-yl)-cis, trans-2,4-pentadienoate ( $\alpha$ -ionylideneacetate) by the conjugate addition of lithium dimethylcuprate at  $-78^\circ\text{C}$ . Basic hydrolysis of the ethyl  $\alpha$ -ionylideneacetate gave an abscisic acid precursor, 3-methyl-5-(2,6,6-trimethyl-2-cyclohexen-1-yl)-cis, trans-2,4-pentadienoic acid, which can be oxidized to yield abscisic acid.

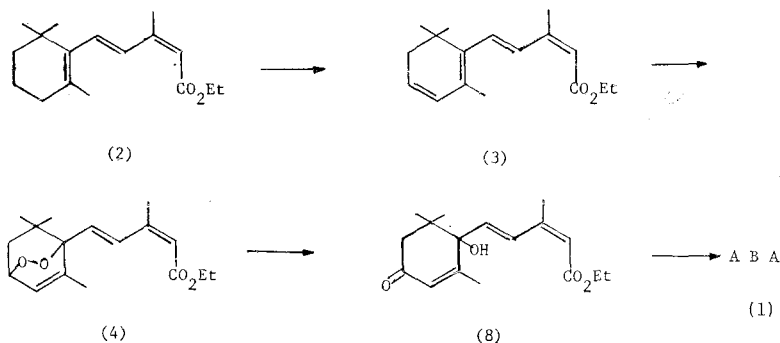
**Keywords**—Stereospecific synthesis • conjugate addition • lithium dimethylcuprate

Abscisic acid (ABA), also known as abscisin II or dormine, has been shown to exhibit hormonal activity related to leaf and flower growth or dormancy.<sup>1-9)</sup> To facilitate the investigation of its botanical activity in addition to confirming the proposed structure, gram quantities of ABA were required. So some organic chemists began to show their concern about the synthesis of ABA, and many synthetic methods have been developed.

The structure<sup>2,9-11)</sup> and absolute configuration<sup>12-14)</sup> have been worked out and known as the sesquiterpene (+)-3-methyl-5-(1-hydroxy-



(1)



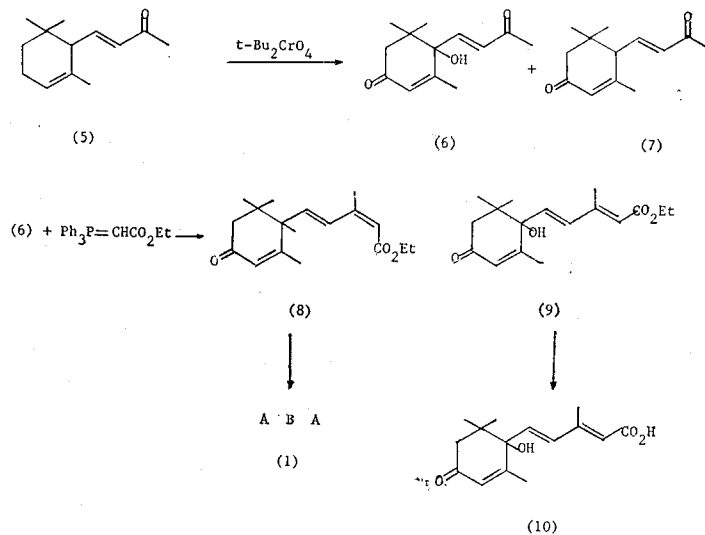
Scheme 1

4-oxo-2, 6, 6-trimethyl-2-cyclohexen-1-yl)-cis, trans-2, 4-pentadienoic acid of the structure (1).

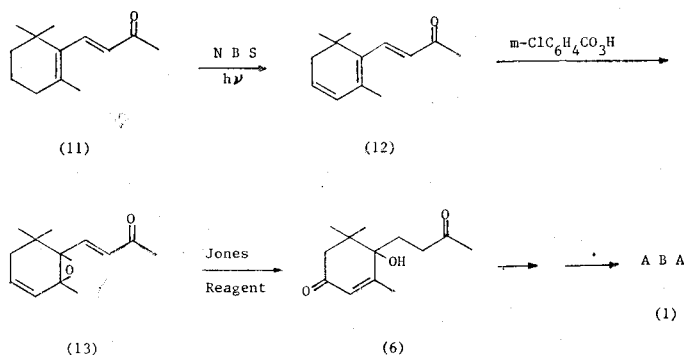
Conforth, Milborrow, and Ryback<sup>9</sup> verified the structure by the synthesis shown in scheme 1. This synthesis involves the conversion of ethyl 3-methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-cis, trans-2, 4-pentadienoate (2) into (RS)-abscisic acid (1) in approximately 7% yield.

Synthetic investigations on abscisic acid have been communicated since 1960s. Robert et al.<sup>15</sup> reported a synthesis of (RS)-abscisic acid starting from  $\alpha$ -ionone (Scheme 2). In this method, they oxidized the allylic positions of  $\alpha$ -ionone (5) with *t*-butyl chromate, obtaining approximately 25% of 1-hydroxy-4-oxo- $\alpha$ -ionone (6)

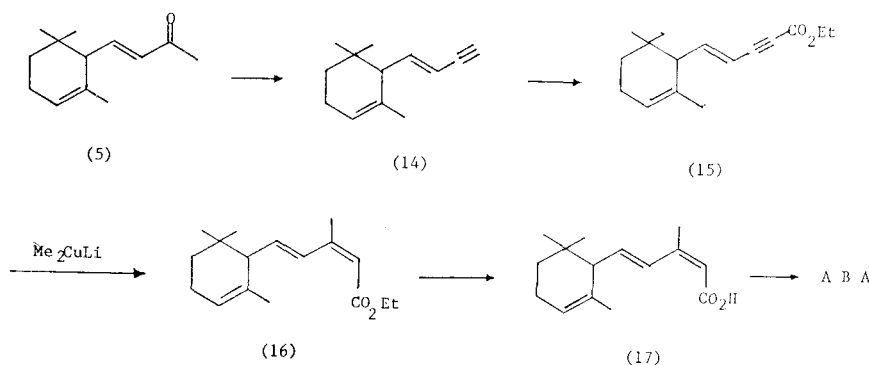
in addition to 4-oxo- $\alpha$ -ionone (7).<sup>16</sup> The racemic bis-enone (6) was treated with carboethoxymethylenetriphenylphosphorane to give esters of abscisic acid and its trans, trans-isomer (8, 9). The Wittig reaction gave equal amounts of cis, trans- and trans, trans-esters. By saponification and acidification of the isomeric esters, abscisic acid (1) and the trans, trans-isomer (10) were obtained. The two isomer's were separated by slow crystallization from the other, giving nearly pure abscisic acid. The combined yield of the Wittig reaction and hydrolysis was 83%, thus the overall yield of abscisic acid and its trans, trans-isomer based on  $\alpha$ -ionone was approximately 22%. The overall yield of (RS)-abscisic



Scheme 2



Scheme 3



Scheme 4

acid, therefore, was nearly 11% as a result of equal amounts of isomeric acid produced.

The key intermediate 1-hydroxy-4-oxo- $\alpha$ -ionone(6) was also prepared from  $\beta$ -ionone by Findlay and Mackay<sup>17)</sup> providing an alternate route to (RS)-abscisic acid. This synthesis, shown as scheme 3, involves tungsten lamp irradiation of  $\text{CCl}_4$  solution containing  $\beta$ -ionone (11) and NBS to give 3,4-dehydro- $\beta$ -ionone (12) in 91% yield.<sup>18)</sup> This compound(12) was oxidized with *m*-chloroperbenzoic acid to an epoxide(13) which was treated with Jones reagent to give crystalline abscisic acid precursor (6) in 43% yield from  $\beta$ -ionone(11).<sup>19)</sup>

The key step of the syntheses mentioned above was Wittig reaction. The Wittig reaction was not stereoselective and gave equal amounts of *cis*, *trans*- and *trans, trans*-isomers. Therefore, the synthetic methods previously reported were not stereospecific in the synthesis of (RS)-abscisic acid.

Now, the authors wish to provide a stereospecific synthesis of (RS)-abscisic acid by a procedure shown in Scheme 4. The key steps of this synthetic design are conversion of methyl ketone to terminal acetylene, and stereospecific alkylation of  $\alpha, \beta$ -acetylenic ester with lithium dimethylcuprate to give only desired *cis*, *trans*-isomer.

## Experimental

### 1. Conversion of $\alpha$ -Ionone to Enyne(14)

To a LDA solution, prepared from 1.069 g (10.5 mmole) of diisopropylamine and 6.6 ml (1.6 M, 10.5 mmole) of *n*-butyl lithium, was added dropwise, at  $-78^\circ\text{C}$ , a solution of 1.9 g (10 mmole) of  $\alpha$ -ionone in THF under nitrogen. Stirred for 1 hr, 1.9 g (11 mmole) of diethyl chlorophosphate was added at  $-78^\circ\text{C}$  and the mixture was gradually warmed to rt. The resultant mixture was cooled to  $-78^\circ\text{C}$  and added to a LDA solution(22.5 mole) in THF. After stirring for 3hr at rt, the reaction mixture was quenched with water. Working up and chromatographing the mixture, an acetylenic product(14), 1-(*trans*-1-buten-3-ynyl)-2,6,6-trimethyl-2-cyclohexene, was obtained almost quantitatively as a pale yellow liquid.  $\text{ir}(\text{neat})$ ,  $\nu_{\text{max}}$  3320, 3030, 2100, 1620, 1370, 1390, and 1450  $\text{cm}^{-1}$ ,  $\text{H}'\text{-nmr}$  ( $\text{CDCl}_3$ , TMS),  $\delta$  6.08(1H, q, =CH), 5.40(1H, m, =CH), 5.34(1H, q, =CH), 2.80(1H, d,  $\equiv\text{CH}$ ), 2.2(1H, s, tert.), 2.1(2H, m, =CH- $\text{CH}_2$ -), 1.60(3H, d, =C- $\text{CH}_3$ ), 1.30(2H, t, - $\text{CH}_2$ -), 0.90(6H, s, two  $\text{CH}_3$ ).

### 2. Preparation of an $\alpha, \beta$ -Acetylenic Ester(15)

To a THF solution of 1.0 g(5.7 mmole) of the enyne(14) was added, at  $-78^\circ$ , 5.76 mmole

of *n*-butyl lithium (1.6 M, 3.6 ml) under nitrogen. This mixture was treated with a THF solution of 0.7 g (6 mmole) of ethyl chloroformate under nitrogen. After stirring for 3 hr at rt, the reaction mixture was quenched with water and worked up. Separation of the crude product on silica gel gave almost quantitatively the  $\alpha, \beta$ -acetylenic ester, ethyl 5-(2,6,6-trimethyl-2-cyclohexen-1-yl)-trans-4-penten-2-ynoate (15). *ir*(neat),  $\nu_{\max}$  3030, 2220, 1710, 1100, 1250, and 1370  $\text{cm}^{-1}$ ,  $^1\text{H}$ -nmr( $\text{CDCl}_3$ , TMS),  $\delta$  6.65 (1H, q,  $J=16, 10$  Hz), 5.75 (1H, d,  $J=16$  Hz), 5.70 (1H, m), 4.45 (2H, q.), 2.4 (1H, s), 2.25 (2H, m), 1.6 (3H, s), 1.34 (2H, t), 1.34 (3H, t), 0.9 (6H, s, two  $\text{CH}_3$ ).

### 3. Ethyl 3-Methyl-5-(2,6,6-trimethyl-2-cyclohexen-1-yl)-cis, trans-2,4-pentadienoate (16)

Stereospecific alkylation of  $\alpha, \beta$ -acetylenic ester (15) into ethyl  $\alpha$ -ionylidenacetate (16) was carried out by modifying the procedure reported by Corey et al.<sup>20)</sup>

Lithium dimethylcuprate solution was prepared in the following way. 32.5 ml of MeLi (0.53 M, 17.2 mmole) was added at 0°C to 1.66 g (8.7 mmole) of CuI in 130 ml THF under nitrogen. After stirred 20~30 min, the reaction mixture was cooled to -78°C to give lithium dimethylcuprate soln. To a soln of 2.1 g (8.54 mmole) of  $\alpha, \beta$ -acetylenic ester in 100 ml THF, 8.6 mmole of lithium dimethylcuprate soln. was added at -78°C with a syringe. After 3 hr, the reaction was quenched by adding 100 ml ethanol at -78°C and the reaction mixture was gradually warmed to rt. After evaporated the solvent, the organic product was extracted with ether, washed with water and brine, dried over magnesium sulfate to give a yellow liquid. The crude product was chromatographed with a silica gel to give a pale yellow liquid (16) in 65.1% yield. *ir*(neat),  $\nu_{\max}$  3050, 2940, 2800, 1710, and 1628  $\text{cm}^{-1}$ ,  $^1\text{H}$ -nmr ( $\text{CDCl}_3$ , TMS),  $\delta$  7.52 (1H, d,  $J=16$  Hz), 5.89

(1H, q,  $J=16, 10$  Hz)), 5.59d (1H, s), 5.39 (1H, s), 4.23 (2H, q), 2.00 (3H, d), 1.59 (3H, d), 1.26 (3H, m), 0.88 (6H, two  $\text{CH}_3$ ).

### 4. 3-Methyl-5-(2,6,6-trimethyl-2-cyclohexen-1-yl)-cis, trans-2,4-pentadienoic acid (17)

1.2 g (4.58 mmole) of ethyl  $\alpha$ -ionylidenacetate in 60 ml ethanol was refluxed with 2.0 g of potassium hydroxide and 60 ml of ethanol for 4hr. After the solvent (ethanol) evaporated, 40 ml of 1 N HCl was added, followed by stirring for several min. The hydrolysis product was extracted with ether, washed with brine and dried over magnesium sulfate. The crude product was chromatographed with silica gel-dichloromethane column to give the product (17) in 90.5% yield. *ir*(neat),  $\nu_{\max}$  3300-2500, 3010, 1670, 1620, 1589, 1260 and 1230  $\text{cm}^{-1}$ ,  $^1\text{H}$ -nmr( $\text{CDCl}_3$ , TMS),  $\delta$  11.4 (1H,  $-\text{CO}_2\text{H}$ ), 7.53 (1H, d,  $J=16$  Hz), 5.93 (1H, q,  $J=16, 10$  Hz), 5.63 (1H, s), 5.43 (1H, s), 2.33 (1H, d,  $J=10$  Hz), 2.00 (3H, s), 1.56 (3H, s), 0.97 (3H, s), 0.83 (3H, s).

## Result and Discussion

In previous communications, the synthesis of (RS) abscisic acid (ABA) involves the preparation of ionylideneacetate (2) or 1-hydroxy-4-keto- $\alpha$ -ionylideneacetate (8) which are the key precursors of (RS)-ABA. The investigators, however, applied Wittig or Reformatsky reaction which are not stereoselective, and are not able to avoid the formation of geometrical isomer, decreasing the yield of desired product.

We are providing a new synthetic route of abscisic acid, avoiding the formation of geometrical isomer. Since the  $\alpha, \beta$ -acetylenic ester (15) could be synthesized quantitatively, it might be possible to prepare stereospecifically the ABA precursor (16) by the conjugate addition of lithium dimethylcuprate.<sup>20)</sup>

We, thus, provide a simple and convenient

synthetic design, scheme 4, in which every step goes in one-pot reaction.

The previous communications<sup>21-27</sup> concerning with methyl ketone-to-acetylene conversion involve those methyl ketones which do not contain  $\alpha$ -methylene or  $\alpha$ -methine hydrogens. It has been known that methyl ketones containing  $\alpha$ -hydrogens yield little terminal acetylene, and isomeric allenes are major products.

$\alpha$ -Ionone could be transformed into a terminal acetylene(14) by treating with LDA and then diethyl chlorophosphate.

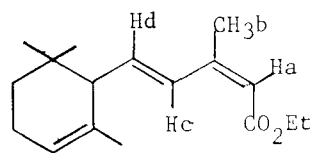
In the ir spectrum of the enyne(14), a carbonyl absorption at  $1680\text{ cm}^{-1}$  disappeared, instead sharp and strong peaks at  $3320\text{ cm}^{-1}$  ( $\text{C}\equiv\text{C}-\text{H}$ ) and  $2100\text{ cm}^{-1}$  ( $\text{C}\equiv\text{C}$ ) came out, suggesting the formation of acetylenic bond. In the nmr spectrum, a signal(doublet) at 2.8(d, 1H) was appeared instead of a signal at 2.1(3H,  $\text{COCH}_3$ ), showing the formation of terminal acetylene(14). For the synthesis of  $\alpha, \beta$ -acetylenic ester(15), the enyne(14) was treated, at  $-78^\circ\text{C}$ , with *n*-butyl lithium and then ethyl chloroformate, followed by quenching with water. In this reaction the same equivalent amount of *n*-Buli, enyne (14) and ethyl chloroformate were required to avoid further substitution.

In the ir spectrum of the  $\alpha, \beta$  acetylenic ester (15), a strong  $\text{C}=\text{O}$  frequency at  $1710\text{ cm}^{-1}$  and two strong  $\text{C}-\text{O}$  absorptions at  $1100$  and  $1250\text{ cm}^{-1}$  were observed. The nmr spectrum gave a quartet at  $\delta 4.45$  (2H) and a triplet at  $\delta 1.34$  (3H), which means the production of ethyl ester (15).

The stereospecific alkylation of  $\alpha, \beta$ -acetylenic ester(15) to ethyl 3-methyl-5-(2,6,6-trimethyl-2-cyclohexen-1-yl)-*cis, trans*-2,4-pentadienoate (16) was accomplished by conjugate addition of lithium dimethylcuprate at  $-78^\circ\text{C}$ .

In the ir spectrum of the *cis, trans*-ionylideneacetate(16), a strong  $\text{C}\equiv\text{C}$  frequency at  $2220\text{ cm}^{-1}$  was disappeared, instead two strong  $\text{C}=\text{C}$  absorp-

tions at  $1628, 1595\text{ cm}^{-1}$  were observed, showing the formation of unsymmetrical conjugated dienes. A strong  $\text{C}=\text{O}$  frequency at  $1710\text{ cm}^{-1}$  still remained. In the nmr spectrum, a doublet at  $\delta 2.00$  (3H<sub>b</sub>,  $J_{\text{HaHb}}=2\text{ Hz}$ ) and a doublet at  $\delta 5.59$  (1H<sub>a</sub>) was appeared. And a doublet at  $\delta 5.75$  (H<sub>c</sub>,  $J=16\text{ Hz}$ ) in the  $\alpha, \beta$ -acetylenic ester was shifted downfield to  $\delta 7.52$  ( $J=16\text{ Hz}$ ), meanwhile, a quartet at  $\delta 6.65$  (H<sub>d</sub>,  $J=16, 10\text{ Hz}$ ) in the  $\alpha, \beta$ -acetylenic ester was shifted upfield to  $\delta 5.89$  ( $J=16, 10\text{ Hz}$ ).



In this conjugate addition, the stereochemistry of the products is highly dependent upon the reaction temperature and the nature of the solvent. When the reaction is conducted at  $-78^\circ\text{C}$  in THF, usually *syn* addition takes place exclusively, the stereoisomer can be observed when the reaction is done in diethyl ether at  $-78^\circ\text{C}$  or in THF at somewhat higher temperature than  $-78^\circ\text{C}$ .<sup>20</sup>

The *cis, trans*-ionylideneacetate could easily be hydrolyzed by saponification to corresponding acid(17), 3-methyl-5-(2,6,6-trimethyl-2-cyclohexen-1-yl)-*cis, trans*-pentadienoic acid. In the ir spectrum of the acid, carboxylic-OH vibrations were recognized by broad absorption at  $3300\sim 2500\text{ cm}^{-1}$  and a strong carbonyl absorption at  $1670\text{ cm}^{-1}$ . The nmr spectrum gave a broad signal of carboxylic proton at  $\delta 11.4$ .

Conformation of the structure of *cis, trans*-ionylideneacetate(16) was made by matching the nmr data of its basic hydrolysis product, 3-methyl-5-(2,6,6-trimethyl-2-cyclohexen-1-yl)-*cis, trans*-2,4-pentadienoic acid, with the previously reported data.

The authors have discussed so for the stereospecific synthesis of *cis, trans*-ionylideneacetate (16) and corresponding acid(17) as synthetic

precursors of (RS)-abscisic acid. Since Roberts et al.<sup>15</sup> reported the oxidation of allyl positions of cis, trans-ionylideneacetate(16), using t-butyl chromate, to give (RS)-abscisic acid, this stereospecific synthesis of cis, trans-ionylideneacetate (16) is, practically, a formal total synthesis of ABA.

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