DAEHAN HWAHAK HWOEJEE
(*Journal of the Korean Chemical Society*)
Vol. 26, No. 4, 1982
Printed in the Republic of Korea

단 신

Abscisic Acid의 입체특이적 합성에 관한 연구 (제 1 보). Abscisic Acid의 합성 중간체

李禹永† · 朴外淑* · 朴在鑌
서울대학교 자연과학대학 화학과
*충북대학교 자연과학대학 화학과

(1982. 5. 21 접수)

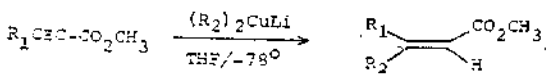
Studies on the Stereospecific Synthesis of Abscisic Acid (I). A Synthetic Precursor of Abscisic Acid

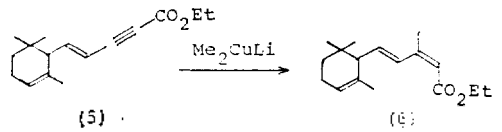
Woo Young Lee†, Oee Sook Park* and **Jae Chan Park**
Department of Chemistry, Seoul National University, Seoul 151, Korea
**Department of Chemistry, Chungbuk National University, Cheongju 310, Korea*

(Received May 21, 1982)

Although the syntheses of abscisic acid (ABA)[1~20] (1) had been accomplished during the past two decades, there were few methods which are favourable and specific. In fact, *cis, trans*-ionylideneacetate (6) is a key intermediate compound in the synthesis of ABA. In the synthesis of the compound (6), however, the investigators applied unfavourable routine reactions such as Wittig or Reformatsky reaction which are not stereoselective. So that, it could not be possible to avoid the formation of its geometrical isomer, decreasing the yield of (6).

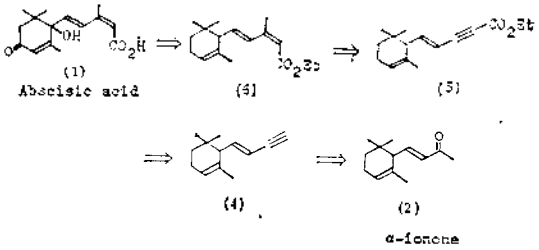
The authors are providing a new synthetic route of a abscisic acid precursor, avoiding the formation of geometrical isomer to get only desired product. If the α,β-acetylenic ester (5) could be synthesized quantitatively, it might be possible to prepare stereospecifically the ABA precursor (6) by the conjugate addition of dialkylcopper lithium[21].





(5) (6)

The authors, thus, provide a simple and convenient synthetic design in which every step goes in one-pot reaction.

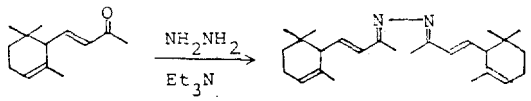


(1) Abscisic acid (6) (5) (4) (2) α-ionone

This design involves firstly the conversion of α-ionone into an enyne (4). The conversion of methyl ketone into a terminal acetylene has been worked out by many investigators. Fringuelli *et al.*[22,23] carried out the conversion by treating a methyl ketone with PCl_5/benzene, followed by sodamide in liquid ammonia. Si-

milar work was made by Corey *et al.*[24] using PCl_5/2,6-lutidine and then $NaNH_2/NH_3$. We tested these syntheses a lot of times, recognizing that they were not applicable in our material, α-ionone.

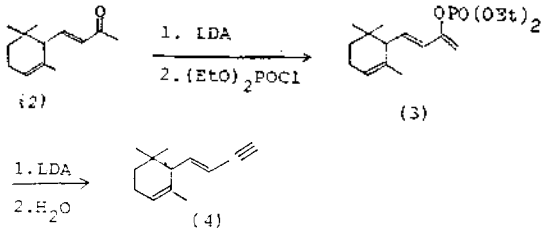
A. Krumbiner et al[25] carried out methyl ketone-acetylene conversion via hydrazone[26,27], which was treated with iodine and then KOH/EtOH. This experiment was also tried with α-ionone. However, it did not give hydrazone of ionone, but there was formed a yellow crystalline azine during the separation.



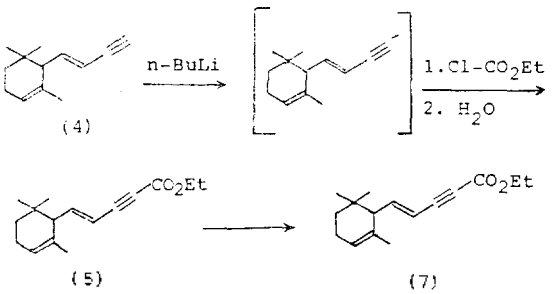
Rosenblum *et al.*[28] made the conversion by treating a methyl ketone with $POCl_3$ in DMF and then NaOH. Hargrove[29] obtained a terminal acetylene by treating a methyl ketone with $(CF_3SO_2)_2O/CCl_4$/pyridine followed by heat. Craig and Moyle[30] converted a methyl ketone, by treating with diethyl phosphochloridate and then $NaNH_2/NH_3$, into a terminal acetylene.

The previous communications concerning with methyl ketone-to-acetylene conversion involve those methyl ketones which do not contain α-methylene or α-methine hydrogens. It has been known that methyl ketones conatining α-hydrogens yield little terminal acetylene, and isomeric allens are major products.

In a recent paper[20] a convenient method in the conversion of methyl ketone-to-acetylene was reported, in which methyl ketones were transformed into a terminal acetylene by treating with LDA and then diethyl chlorophosphate. The LDA procdure was tested with α-ionone and got an excellent result. The LDA was prepared near 0°C by adding *n*-butyl lithium/hexane to a THF solution of equivalent amount of diisopropylamine. By the reaction, at −78°, of LDA with α-ionone followed by diethyl chlorophosphate, an enol phosphate (3) was formed which underwent elimination by the reaction of LDA, to give a terminal acetylene (4).



In the ir spectrum of the enyne (4), a carbonyl absorption at 1680 cm^{-1} disappeared, instead sharp and strong peaks at 3320 cm^{-1} (≡C—H) and 2100 cm^{-1} (C≡C) came out, suggesting the formation of acetylene bond. The other ir bands were almost identical with the starting material, α-ionone. In the nmr spectrum, a signal (doublet) at δ2.8 (1H) was appeared instead of a signal at δ2.1 (3H, $COCH_3$), showing the formation of terminal acetylene (4). For the synthesis of ABA precursor (5), the enyne (4) was converted into an α,β-acetylenic ester by treating the enyne, at −78°, with *n*-butyl lithium and then ethyl chloroformate, followed by quenching with water.



In the spectrum of the α,β-acetylenic ester (5), a strong C=O frequency at 1710cm^{-1} and two strong C—O absorptions at 1100 and 1250 cm^{-1} were observed. The nmr spectrum gave

a quartet at δ4.45 (2H) and a triplet at δ1.34 (3H), which means the production of ethyl ester (5).

The α,β-acetylenic ester could easily be hydrolysed, by saponifying with alkali followed by acidification, to an α,β-acetylenic acid (7), 5-(2, 6, 6-trimethyl-2-cyclohexen-1-yl)-*trans*-4-penten-2-ynoic acid. In the ir spectrum of the acid, carboxylic vibrations were recognized by broad absorption at 3300~2500 cm^{-1} and a strong absorption at 1680 cm^{-1}. In the nmr spectrum, a broad signal of carboxylic proton was observed at δ9.78.

Now it is interesting to achieve a stereospecific synthesis of ethyl 3-methyl-5-(2, 6, 6-trimethyl-2-cyclohexen-1-yl)-*cis*, *trans*-2, 4-pentadienoate (6) by conjugate addition of the α,β-acetylenic ester (5) with dimethylcopper lithium. And then the plant hormone ABA might be obtained by the oxidation of allylic positions of the compound (6) with appropriate oxidizing agent. The investgations are being continued.

EXPERIMENTAL

1-(*trans*-1-Buten-3-ynyl)-2, 6, 6-trimethyl-2-cyclohexene (4). The conversion of methyl keto group of α-ionone into a terminal acetylene could effectively be carried out by LDA procedure[20].

To a solution of 1.06 g (10.5 mmole) of diisopropylamine in 10 m*l* of dry THF was added with stirring, under nitrogen, 6.6 m*l* (1.6*M*, 10.5 mmole) of *n*-butyl lithium in hexane, at a temperature of ice-salt mixture. The resultant solution was cooled to −78° after stirring for 20 miuutes. To this LDA solution was added dropwise a solution of 1.9 g (10 mmole) of α-ionone in 5 ml of THF under nitrogen. After stirring 1 h 1.9 g(11 mmole) of diethyl chlorophosphate was added showly to the anionic solution at −78°. The resultant mixture was gradually warmed to room temperature and it was added dropwise at −78° to a solution of LDA (22.5 mmole) in THF prepared described above. The mixture was warmed to room temperature, stirred for 3 h, and quenched with 10 m*l* of water. The reaction mixture was extracted with *n*-hexane, washed the organic layer with 1 *N* HCl, water and aqueous sodium bicarbonate successively. After dried over magnesium sulfate, evaporated the solvent, and chromatographed by silica gel column, using hexane as an eluent, an acetylenic product (4) was obtained as a pale yellow liquid. The yield was almost quantitative. H-NMR ($CDCl_3$, TMS); δ2.80 (*d*, 1H, ≡CH), δ0.90 (*d*, 6H, CH_3), δ1.60(*d*, 3H, =C-CH_3), δ6.08 (*q*, 1H, =CH), δ5.34 (*q*, 1H, =CH), δ5.40 (*m*, 1H, =CH), δ2.1 (*m*, 2H, =C-CH_2-), δ1.3 (*t*, 2H, −CH_2-), δ2.2 (*s*, 1H, *tert.*). IR (neat); 3320(*s*, ≡CH), 3030 (*m*, =C-H), 2100 (C≡C, sharp), 1620 (*w*, C=C), 1370, 1390, 1450, 2955, 2930, 2866cm^{-1}. Mass spectrum (*m/e*); 174 (M^+, 4.4), 118 (97.5), 117(100), 115(15.4), 103(34.0), 91(31.2).

Ethyl 5-(2, 6, 6-trimethyl-2-cyclohexen-1-yl)-*trans*-4-penten-2-ynoate (5). The conversion of the acetylenic compound (4) into an α,β-acetylenic ester (5) was accomplished by following way. To a solution of 1.0 g(5.7 mmole) of 1-(*trans*-1-buten-3-ynyl)-2, 6, 6-trimethyl-2-cyclohexene (4) in 20 m*l* of THF was added, under nitrogen, 5.76 mmole of n-butyl lithium in hexane (1.6 *M*, 3.6 m*l*) at −78°. The reaction mixture was gradually warmed to 0°C. After half an hour, it was cooled again to −78°. To this resultant mixture was added dropwise a solution of 0.7 g (6 mmole) of ethyl chloroformate in 10m*l* THF under nitrogen. After stirred the resultant

mixture for 3 h at room temperature, 100 m*l* of water was added and stirred for 1 h. The organic product was extracted with ether, washed with water, and dried over magnesium sulfate, to give a brown liquid. The crude product was chromatographed with silica gel-hexane, giving quantitatively a yellowish liquid, the α,β-acetylenic ester (5). H-NMR ($CDCl_3$, TMS); δ 4.45 (*q*, 2H in Et), δ 1.34 (*t*, 3H in Et), δ 0.9 (*d*, 6H), δ1.6 (*s*, 3H) δ 6.65 (*q*, 1H), δ 5.75 (*d*, 1H), δ 5.70 (*m*, 1H), δ 2.25 (*m*, 2H), δ 1.34 (*t*, 2H), δ 2.4 (*s*, 1H). IR (neat); 3030 (*w*), 2955, 2930, 2866 (*s*), 2220 (*s*, C≡C), 1710 (*s*, C=O), 1620 (*m*, C=C), 1100 and 1250 (*s*, C-O), 1370, 1450 cm^{-1}. Mass spectrum (*m/e*); 246 (M^+, 4.3), 201 (15.8), 190 (100), 161 (40.9), 118 (49.8), 117 (87.6), 115 (30.9), 91 (32.7).

5-(2, 6, 6-Trimethyl-2-cyclohexen-1-yl)-*trans*-4-penten-2-ynoic Acid (7). The α,β-acetylenic ester (5) was converted into an acetylenic acid (7) by saponification. 0.5g (2 mmole) of ethyl 5-(2, 6, 6-trimethyl-2-cyclohexen-1-yl)-*trans*-4-penten-2-ynoate (5) was refluxed with 1.6 g of potassium hydroxide and 20 m*l* of methanol for 3 h. After evaporated the solvent (methanol), 50 m*l* of 1*N* HCl was added, followed by stirring for several minutes. The hydrolysis product was extracted with ether, washed with brine, and dried over magnesium sulfate. The crude product was chromatographed with a silica gel-ethyl acetate column, to give a yellowish liquid product, 5-(2,6,6-trimethyl-2-cyclohexen-1-yl)-*trans*-4-penten-2-ynoic acid (yield ~60%). H-NMR ($CDCl_3$, TMS); δ 9.78, (broad, 1H, COOH), δ 0.9 (*d*, 6H), δ 1.63 (*s*, 3H), δ6.45 (*q*, 1H), δ 5.55 (*d*, 1H), δ 5.48 (*m*, 1H), δ 2.05 (*m*, 2H), δ 1.3 (*m*, 2H), δ 2.32 (*m*, 1H). IR (neat); 3300~2500 (broad, OH), 3030 (*w*), 2190 (*s*, C≡C), 1680 (*s*, C=O), 1615 (*m*, C=C), 1410, 1365, 1275, 1100 cm^{-1}.

ACKNOWLEDGEMENT

The Writers are indebted to The Korean Traders Scholarship Foundation for generous financial support.

REFERENCES

1. F. T. Addicott *et al.*, *Science*, **159**, 1493 (1968).
2. K. Ohkuma *et al.*, *Tet. Lett.*, **29**, 2529 (1965).
3. J. W. Cornforth *et al.*, *Nature*, 205 (1965).
4. J. W. Cornforth et al., *Nature*, 210, 627 (1966).
5. K. Dörthing, *Naturwissenschaften*, **54**, 23 (1969).
6. K. Ohkuma, *J. Agr. Chem. Soc., Japan.*, **40**, 45 (1966).
7. H. El-Antably *et al.*, *Planta*, **73**, 74 (1967).
8. B. V. Milborrow, *Planta*, **70**, 155 (1966).
9. J. W. Cornforth, B. Milborrow and G. Ryback, *Nature*, **206**, 715 (1965).
10. Kenji Mori, *Tet. Lett.*, **28**, 2635 (1973).
11. M. Neil Galbraith and Denis H.S. Horn, *JCS. Comm.*, 566 (1973).
12. J. Cornforth, W. Draber, B. Milborrow and G. Ryback, *Chem. Comm.*, **3**, 114 (1967).
13. M. Koreeda *et al.*, *J. Amer. Chem. Soc.*, **95**, 239 (1973).
14. G. Ryback, *JCS Chem. Comm.*, 1190 (1972).
15. D. L. Roberts, R. A. Heckman, B. P. Hege, S. A. Bellin, *J. Org. Chem.*, **33**, 3566 (1968).
16. K. B. Wiberg, "Oxidation in Org. Chem.," Part A, P. 106, Academic Press, New York, N. Y., 1965.
17. J. A. Findlay and W. D. Mackay, *Can. J. Chem.*, **49**, 2369 (1971).
18. H. B. Henbest, *Nature*, **161**, 481 (1948).
19. T. Oritani and K. Yamashita, *Agr. Biol. Chem.*, **34**, 1821 (1970).
20. E. Negishi, A. King, W. Klima, W. Patterson and A. Silveria, *J. Org. Chem.*, **45**, 2526 (1980).
21. E. J. Corey and J. A. Katzenellenbogen, *J. Amer. Chem. Soc.*, **91**, 1851 (1969).
22. F. Fringuelle, V. Maneini and A. Taticchi,

Tetrahedron, **25**, 4249 (1969).
23. R. S. Sweet and C. S. Marvel, *J. Amer. Chem. Soc.*, **54**, 1184 (1932).
24. E. J. Corey *et al.*, *J. Amer. Chem. Soc.*, **89**, 4245 (1967).
25. A. M. Krumbiner, N. Gottfried and E. F. Oliveto, *J. Org. Chem.*, 3502 (1969).
26. R. A. Sneen and N. P. Matheny, *J. Amer. Chem. Soc.*, **86**, 5503 (1964).
27. G. R. Newkome and D. L. Fishel, *J. Org. Chem.*, **31**, 677 (1966).
28. M. Rosenblum, N. Brawn, J. Papenmeier and M. Appelbaum, *J. Organomet. Chem.*, **6**, 173 (1966).
29. R. J. Hargrove and P. J. Stang, *J. Org. Chem.*, **39**, 581 (1974).
30. J. C. Craig and M. Moyle, *J. Chem. Soc.*, 3712 (1963).