Synthesis and Physiological Activity of Monodemethyl Absciscic Acids and Methyl 5-(1',6'-Epoxy-2',2'-dimethylcyclohexyl)-3-methyl-(2*Z*,4*E*)-2,4-pentadienoate†

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For the elucidation of the role of methyl substituents on cyclohexene ring of abscisic acid (ABA, I) on the physiological activity, 2'-demethyl-ABA (II), the two stereoisomers (III and IV) of 6'-demethyl-ABA and methyl 5-(1',6'-epoxy-2',2'-dimethylcyclohexyl)-3-methyl-(2*Z*,4*E*)-2,4-pentadienoate (VI) were synthesized. From the result of rice seedling assay, it was concluded that 2'-methyl group of ABA was indispensable for strong growth inhibitory activities and that at least one of the 6'-gem-dimethyl groups was unnecessary for growth inhibition.

Many investigations concerning syntheses and structure-activity relationships in analogs of ABA were already reported.¹⁾ But the effect of methyl substituents on cyclohexene ring on the activity is still obscure. Previously, in view of the fact that methyl 5-(1',2'-epoxy-2',6',6'-trimethylcyclohexyl)-3-methyl-(2*Z*,4*E*)-2,4-pentadienoate (V) is metabolized to ABA in plant tissues,¹⁾ we synthesized two stereoisomers (VII and VIII) of 6'-demethyl analog of V and reported that both VII and VIII showed only weak growth inhibition on rice seedling.²⁾ Now, for further elucidation of the effect of these three methyl groups on the cyclohexene ring of ABA on physiological activity, we synthesized 2'-demethyl-ABA (II), two stereoisomers (III and IV) of 6'-demethyl-ABA and the 2'-demethyl analog (VI) of V.

The activities of these analogs are also interesting in relation to the possible metabolic pathway of demethyl analogs of V to the corresponding demethyl analogs of ABA and the possible explanation of the potent biological activity of the antipode of natural ABA.¹⁾

For the synthesis of 2'-demethyl-ABA (II) and VI, we prepared 2,2-dimethylcyclohexanone as follows. To methylate C-2 position of 2-methylcyclohexanone regiospecifically, C-6 position was protected by N-methylanilinomethylene group during methylation. In spite of inactivation of carbonyl function by this protective group, C-2 position was effectively methylated by the use of potassium *tert*-butoxide in tetrahydrofuran (THF). Removal of the protective group gave 2,2-

FIG. 1.

† Studies on Absciscic Acid. Part XI. Part X see Reference 2).

SCHEME I.

SCHEME II.

SCHEME III.

SCHEME IV.

dimethylcyclohexanone (X) in 56% overall yield from 2-methylcyclohexanone. This method is more facile than those described by S. Boatman *et al.*³⁾ and R. E. Ireland *et al.*⁴⁾

The synthetic route of VI was shown in Scheme I.

The reaction of Grignard reagent prepared from 1-methyl-2-propynyl tetrahydropyranyl (THP) ether with X in THF gave hydroxy THP ether in 98% yield. Removal of protective group and acetylation of secondary hydroxyl group afforded acetylenic monoacetate XI. Dehydration of XI with phosphorous oxychloride in pyridine afforded enyne acetate XII in 51% yield. Reduction of triple bond of XII to (*E*)-double bond and removal of acetate with excess lithium aluminum hydride in refluxing THF gave dienol XIII in 95% yield. The dienol XIII was oxidized with active manganese dioxide in methylene chloride to give 2'-demethyl- β -ionone (XIV) as an oil in 83% yield. The Wittig reaction of XIV with carboethoxymethylenetriphenylphosphorane afforded the mixture of (2*Z*)-isomer XV and (2*E*)-isomer XVI in the ratio of *ca.* 1:1. (2*Z*)-Isomer XV was separated by silica gel column chromatography and was converted to its methyl ester. Epoxidation of the methyl ester with perbenzoic acid in methylene chloride in the presence of 5% aqueous sodium bicarbonate solution as a buffer under vigorous stirring afforded VI as an oil in 58% yield. Other reaction systems such as perbenzoic acid in methylene chloride with or without powdery sodium bicarbonate were unsuccessful.

2'-Demethyl-ABA (II) was synthesized as shown in Scheme II. The mixture of XV and XVI was brominated with NBS, followed by dehydrobromination with quinoline to give ethyl 2'-demethyl-dehydro- β -ionylideneacetate according to the method described by Schwieter *et al.*⁵⁾ Addition of the singlet oxygen gave epidioxide which was rearranged to the keto alcohol (XVII) by basic alumina. Hydrolysis of XVII followed by esterification with diazomethane gave the methyl ester, which crystallized on standing. After separation of

(2*Z*)-isomer (XVIII) and (2*E*)-isomer (XX) by recrystallization from benzene-hexane, alkaline hydrolysis of each isomer gave 2'-demethyl-ABA (II) and (2*E*)-2'-demethyl-ABA (XIX) respectively. In the NMR spectra of XVIII and XX, 3-methyl protons were observed at 2.02 and 2.31 ppm respectively, and the (2*Z*)-structure of XVIII was confirmed.

6'-Demethyl-ABA (III) was synthesized as shown in Scheme III. Starting from 2,6-dimethylcyclohexanone (XXI) after several steps similar to that of Scheme I, 6'-demethyl- β -ionone (XXII) was obtained in 32% overall yield from XXI. The Wittig reaction of XXII with carbomethoxymethylenetriphenylphosphorane afforded the mixture of (2*Z*)- and (2*E*) ester XXIII in the ratio of *ca.* 1:1 containing a little impurity produced by isomerization of double bonds. Bromination of XXIII followed by dehydrobromination, addition of the singlet oxygen and rearrangement of the produced epidioxide with alumina gave the mixture of (2*Z*)-keto alcohol (XXIV) and (2*E*)-ketoalcohol (XXV). The esters XXIV and XXV were separated by Florisil column chromatography and were hydrolyzed to give 6'-demethyl-ABA (III) and (2*E*)-6'-demethyl-ABA (XXVI) respectively. However, the compound obtained here was only one of the two possible diastereomers of 6'-demethyl-ABA. It was suggested that singlet oxygen added stereoselectively from the opposite side of 6'-methyl group. In the NMR spectrum of XXIV 6'-methyl protons were observed as broad doublet coupled with 6 Hz due to virtual coupling with 5'-methylene protons.

Another 6'-demethyl-ABA (IV) was synthesized by the following route (Scheme IV). The ethylenedioxyalcohol (XXVII) was easily prepared by the condensation of acetaldehyde and ethyl acetoacetate,⁶⁾ followed by ketalization and reduction of the ester with lithium aluminum hydride. Collins oxidation of XXVII followed by aldol condensation with acetone afforded 6'-demethyl- β -ionone derivative XXVIII. By the removal of the protective group of XXVIII with *p*-TsOH/acetone, the two double bonds migrated to a position of con-

jugation with the ketone of cyclohexane ring. Therefore direct epoxidation of XXVIII with *m*-chloroperbenzoic acid was attempted to obtain the epoxide XXIX. Treatment of XXIX with *p*-TsOH/acetone to remove protecting group opened the epoxide ring simultaneously to give keto alcohol XXX. This reaction was also applicable to methyl 6'-demethyl-epoxyacetates (XXXII, XXXIII and XXXIV), which were prepared after Wittig reaction of XXVIII with carbomethoxymethylenetriphenylphosphorane and subsequent epoxidation with perbenzoic acid. These three stereo-isomers were separated by Florisil column chromatography to give XXXII, XXXIII and XXXIV in the ratio of *ca.* 4: 2: 1. The stereochemistry of these epoxides was deduced by the comparison of NMR spectral data with those of VII and VIII. Spectral pattern of all the assignable protons were almost identical between XXXII and VIII, and also between XXXIV and VII. The stereochemistry of the epoxide ring of XXXII, XXXIII and XXXIV is to be retained in the producing tertiary alcohol.⁷⁾ In fact, treatment of XXXII and XXXIV with *p*-TsOH/acetone afforded XXXV and XXIV respectively, though isomerization of (2*Z*)-double bond of XXXV and XXIV to (2*E*)-double bond was in part brought about during the treatment. The same treatment of XXXIII afforded XXXVI. Though XXXV was unstable in Florisil column, very small amount of pure XXXV was obtained after purification with preparative thin layer chromatography of

alumina. Alkaline hydrolysis of XXXV gave 6'-demethyl-ABA (IV) which was diastereoisomer of III. Although the stereochemistry of III and IV was deduced from the direction of addition of singlet oxygen and the stereochemistry of the epoxides XXXIV and XXXII, further proof was obtained from the results of the lanthanoid induced shifts of IV, XXXV and ABA methyl ester by Eu(fod)₃ in NMR spectra (Table I). Tendency of coordination to oxygen atom of Eu(fod)₃ is in general R-OH > RCO-R' > RCO₂R'. The paramagnetic shifts observed in 6'-methyl group of the three compounds are mainly due to the Eu(fod)₃ coordinated with tertiary hydroxyl group and the configuration of the 6'-methyl group of XXIV and XXXV were clearly identified. The paramagnetic shift of the 6'-methyl group of XXIV was about 1.4 times as much as that of the 6'-methyl group of XXXV, whereas those of the 2'-methyl group of XXIV, XXXV and ABA methyl ester are almost the same. And the paramagnetic shifts of the 6'-methyl group of XXIV and that of XXXV were similar to those of *cis*-6'- and *trans*-6'-methyl group of ABA methyl ester respectively. From these results, it was concluded that the configuration of 6'-methyl group and the side chain of XXIV was *cis* and that of 6'-methyl group and the side chain of XXXV was *trans*. This conclusion is consistent with both the presumption of direction of singlet oxygen addition to 1',4'-carbon and the estimation of the stereochemistry of the epoxides XXXII and XXXIV.

TABLE I. CHEMICAL SHIFTS OF XXIV, XXXV AND ABA METHYL ESTER MEASURED WITH OR WITHOUT Eu(fod)₃

Compound		XXIV		XXXV		ABA methyl ester		
		6'-Me	2'-Me	6'-Me	2'-Me	6'-Me	6'-Me	2'-Me
A	δ^a	1.04	1.98	1.07	1.91	1.03	1.12	1.94
B	δ	1.46	2.58	1.67	2.56	1.47	1.83	2.55
	$\Delta\delta^b$	0.42	0.60	0.60	0.65	0.44	0.71	0.61
C	δ	1.96	3.23	2.30	3.19	1.92	2.52	3.16
	$\Delta\delta$	0.87	1.25	1.23	1.28	0.89	1.40	1.22

^{a)} Chemical shift (ppm) from TMS. A, 42 μ mole of compound in 0.18 ml of CDCl₃; B, A plus 0.2 mole ratio of Eu(fod)₃; C, A plus 0.4 mole ratio of Eu(fod)₃.

^{b)} Paramagnetic shift expressed as Hz.

TABLE II. THE GROWTH INHIBITORY ACTIVITY OF DEMETHYL ANALOGS OF ABA ON RICE SEEDLINGS

Com-pounds	Concentration (Mole/liter)				
	2×10^{-3}	10^{-3}	10^{-4}	10^{-5}	10^{-6}
II	—	22 ^{a)}	81	91	98
III	—	0	0	0	76
IV	—	0	0	0	79
I	—	0	0	0	53
VI	59	67	88	94	—
V	0	0	0	0	—

^{a)} Percentage of control growth. After growing at 28°C (2000 lux) for 6 days, the lengths of the second leaf sheaths of the seedlings were measured (*Oryza sativa* L. var. Honen-Wase).

Growth inhibitory activities of the II, III, IV and VIII were tested on rice seedlings and the results were summarized in Table II. 2'-Demethyl-ABA (II) showed weak inhibition, but two diastereomeric 6'-demethyl-ABA (III and IV) showed strong inhibition comparable to ABA. The mode of activity of III and IV resembled ABA as follows: i) at a concentration of 10^{-4} and 10^{-5} mole/liter, the germs retain vivid green in spite that the growth was inhibited. ii) inhibition of root elongation was less than that of germ growth. 2'-Demethyl-epoxide VI showed weaker inhibition than II. From the above data it was revealed that the 2'-methyl group of ABA was indispensable to show the strong growth inhibitory activity, but at least one of the 6'-gem-dimethyl groups did not have so great role to show the activity. Moreover, all the monodemethyl epoxides VI, VII, VIII showed weaker inhibitory activity than those of the corresponding analogs of ABA. Therefore it is clear that the three demethyl analogs of epoxides VI, VII and VIII were not converted into the corresponding analogs of ABA in rice seedling.

Milborrow suggested the possible explanation of the potent biological activity of unnatural (—) ABA as follows: 1) the (—)-enantiomer occupies the same position in an active site as that of the (+)-isomer if the cyclohexene ring lies on its other face and C-6' and C-2' are interchangeable. 2) the tertiary hydroxyl group does not interact with

active site. From the above results, as 6'-gem-dimethyl groups do not have a great role for the activity in contrast with a great role of 2'-methyl group, the former interpretation will be unsuitable in rice seedling. The similar inhibitory activity of 1'-deoxy-ABA methyl ester, in comparison with methyl abscisate,¹⁾ favors also Milborrow's latter explanation and 1'-hydroxylation of 1'-deoxy-ABA to ABA within the *Hordeum distichon*⁸⁾ has recently excluded.

These results suggest that the carbon skeleton of 3-methyl-(2Z,4E)-2,4-pentadienoic acid and the 2'-methyl group and their relative steric location is very important for the biological activity of ABA, and that the 6'-gem-dimethyl groups do not interact with the active site but have a role to fix the side chain of ABA by prohibiting the free rotation of σ -bond between C-5 and C-1.

EXPERIMENTAL

All mp's and bp's are uncorrected. IR spectra were recorded on a IRA-1 spectrophotometer of Japan Spectroscopic Co., Ltd. NMR spectra were recorded at 60 MHz with TMS as an internal standard (JEOL Model JM-MH-60-II). Gas-liquid chromatography was carried out on a JEOL JGC-1100. Mass spectra were obtained at 20 eV utilizing a JEOL JM6-06 mass spectrometer by direct injection. All the reactions except photosensitized oxygenation were carried out under nitrogen atmosphere.

1) 2, 2-Dimethylcyclohexanone (X)

2-(N-Methylanilinomethylene)-6-methylcyclohexanone (IX) was prepared according to the procedure described by R. B. Woodward *et al.*⁶⁾ Potassium *t*-butoxide freed from *t*-butyl alcohol prepared from 9.6 g of metallic potassium was suspended in 200 ml of dry THF and to the stirred mixture, a solution of 52 g of IX in 50 ml of dry THF was added dropwise under ice cooling and stirring was continued for 40 min until potassium *t*-butoxide dissolved. A solution of 62.5 g of methyl iodide in 30 ml of dry THF was added dropwise to the solution during 3 hr with stirring and ice cooling. The mixture was stirred for 15 min in an ice bath, for an additional 1.5 hr at room temperature, refluxed for 1 hr and then allowed to stand overnight. The reaction mixture was poured into ice-water and aqueous layer was saturated with NaCl and extracted four times with ether. The com-

bined organic layer was washed twice with brine, dried over anhyd. MgSO_4 , and evaporated. To the residue, 80 ml of 10% hydrochloric acid was added in one portion and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water and extracted thrice with ether. The combined extracts were washed with brine and were extracted five times with 5% aqueous NaOH solution. The aqueous layers were combined and washed with ether and then was refluxed for 6 hr until an enol test was no longer obtained. The basic aqueous solution was steam distilled until no further organic material distilled. The steam distillate was extracted with ether, and the ether extract was dried over anhyd. MgSO_4 . After evaporation of the solvent the residue was distilled under reduced pressure to give 24.2 g of X, bp 90°C (70 mmHg) as an oil. IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 1720. NMR (CCl_4): 1.10 (6H, s), 1.53~2.08 (4H), 2.08~2.55 (2H). Gas chromatographic analysis using a $1\text{ m} \times 3\text{ mm}$ column packed with 30% silicone SE 30 on celite 545, column temperature: 130°C , FID, N_2 flow rate: 20 ml/min, $t_R=3.0\text{ min}$ (96% purity). X formed a semicarbazone, mp $193\sim 194^\circ\text{C}$ (reported $194\sim 195^\circ\text{C}$).⁴⁾ Anal. Found: C, 59.16; H, 9.49; N, 22.67. Calcd. for $\text{C}_9\text{H}_{17}\text{ON}_3$: C, 58.98; H, 9.35; N, 22.93%.

2) 3-(1'-Hydroxy-2', 2'-dimethylcyclohexyl)-1-methyl-2-propynyl acetate (XI)

A solution of 38.5 g of 1-methyl-2-propynyl THP ether in 40 ml of dry THF was added dropwise during 1 hr to a stirred solution of ethyl magnesium bromide prepared from 6.3 g of magnesium and 34.0 g of ethyl bromide in THF under ice cooling. After refluxing for 1 hr, to the stirred mixture a solution of 25.2 g of X in 40 ml of dry THF was added dropwise during 1 hr under water cooling. The mixture was stirred for 1 hr at room temperature and then allowed to stand overnight. After the addition of saturated ammonium chloride solution the mixture was filtered and the organic layer was separated. The aqueous layer was saturated with NaCl and extracted with ether. The organic layer and extracts were combined, dried over anhyd. K_2CO_3 , and the solvent was evaporated. Chromatography of the residual oil on alumina (eluted with benzene-ethyl acetate=10:1) gave the hydroxy THP ether as an oil (55 g, 98% yield). IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 3340, 2240. The hydroxy THP ether (50 g) was hydrolyzed with 0.3% ethanolic sulfuric acid at room temperature and the product was chromatographed with alumina (eluted with benzene-ethyl acetate=5:2) to give acetylenic diol as an oil quantitatively. IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 3400. Acetylenic diol (34 g) was acetylated with pyridine-acetic anhydride at room temperature to give monoacetate XI quantitatively as an oil. IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 3460, 2240, 1750. NMR (CCl_4) δ : 0.97 (3H, s), 1.05 (3H, s), 1.46 (3H, d, $J=6.5\text{ Hz}$), 2.00 (3H,

s), 2.98 (1H, exchangeable), 5.46 (1H, q, $J=6.5\text{ Hz}$).

3) 3-(6', 6'-Dimethyl-1'-cyclohexenyl)-1-methyl-2-propynyl acetate (XII)

To a stirred solution of 39 g of XI in 200 ml of pyridine, a mixture of 61.2 g of phosphorous oxychloride and 60 g of pyridine was added dropwise at room temperature during 2 hr and then heated at 80°C for 4 hr. The mixture was cooled, and then cautiously poured into ice-water. The resultant mixture was extracted with ether, the extract was washed with dil. hydrochloric acid, aq. NaHCO_3 solution and water successively, dried over anhyd. MgSO_4 , and ether was evaporated. The residue was passed through a short column of alumina (eluted with benzene-ethyl acetate=10:1) and distilled under reduced pressure to give 18.4 g of enyne-acetate XII as an oil, bp $109\sim 111^\circ\text{C}$ (3.5 mmHg). IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 2240, 1750, 1620. NMR (CCl_4) δ : 1.06 (6H, s), 1.46 (3H, d, $J=6.5\text{ Hz}$), 2.00 (3H, s), 6.49 (1H, q, $J=6.5\text{ Hz}$), 5.97 (1H, t, $J=4\text{ Hz}$). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 228.5 (7900).

4) 4-(6', 6'-Dimethyl-1'-cyclohexenyl)-3-(E)-buten-2-ol (XIII)

To a stirred mixture of 11.5 g of LiAlH_4 and 250 ml of dry THF, a solution of 18 g of XII in 50 ml of dry THF was added dropwise during 1.5 hr under water cooling. The mixture was heated under reflux for 8 hr, and the excess of reagent was decomposed by dropwise addition of 20% aq. potassium sodium tartarate solution. The mixture was saturated with salt and extracted with ether exhaustively. The extracts were dried over anhyd. MgSO_4 and evaporated and passed through a short column of alumina (eluted with benzene-ethyl acetate=5:1) to give 14 g of dienol XIII as an oil in 95% yield. IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 3360, 1590, 1585. NMR (CCl_4) δ : 1.03 (6H, s), 1.23 (3H, d, $J=6.5\text{ Hz}$), 3.70 (1H, exchangeable), 4.24 (1H, dq, $J=6.5, 6.5\text{ Hz}$), 5.67 (1H, t, $J=4\text{ Hz}$), 5.74 (1H, dd, $J=6.5, 16\text{ Hz}$), 6.10 (1H, d, $J=16\text{ Hz}$), UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 233 (6700).

5) 4-(6', 6'-Dimethyl-1'-cyclohexenyl)-3-buten-2-one (XIV)

Active manganese dioxide (120 g) was added to a solution of 13.5 g of XIII in 200 ml of CH_2Cl_2 and the mixture was shaken at room temperature for 2 days. The reaction mixture was then filtered and the filtrate was concentrated. Chromatography of the residue on short alumina column (eluted with benzene) and distillation under reduced pressure gave 11 g of 2'-demethyl β -ionone (XIV), as an oil, bp $115\sim 116^\circ\text{C}$ (3.5 mmHg). IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 1715, 1695, 1665, 1595. NMR (CCl_4) δ : 1.10 (6H, s), 2.13 (3H, s), 6.22 (1H, d, $J=16\text{ Hz}$), 7.08 (1H, d, $J=16\text{ Hz}$). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 284.5 (6000), 226 (3600). XIV formed semicarbazone mp

186~188°C (lit⁹) mp 191°C). *Anal.* Found: C, 66.56; H, 9.13; N, 17.66. *Calcd.* for $C_{18}H_{21}ON_3$: C, 66.35; H, 9.06; N, 17.86%.

6) *Ethyl 5-(6', 6'-dimethyl-1'-cyclohexenyl)-3-methyl-(2Z, 4E and 2E, 4E)-2, 4-pentadienoate (XV) and (XVI)*

A solution of 7.1 g of XIV and 20.9 g of carboethoxymethylenetriphenylphosphorane in 100 ml of dry xylene was refluxed for 50 hr. Evaporation of xylene, removal of deposited triphenylphosphine oxide by filtration and purification by chromatography on 150 g of silica gel (eluted with benzene) afforded 2.1 g of triene ester XV, 0.9 g of triene ester XVI and 4.5 g of a mixture of XV and XVI as an oil. XV: IR $\nu_{\max}^{film}$ cm^{-1} : 1715, 1610. NMR (CCl_4) δ : 1.12 (6H, s), 1.25 (3H, t, $J=7$ Hz), 1.99 (3H, d, $J=1$ Hz), 4.06 (2H, q, $J=7$ Hz), 5.48 (1H), 5.92 (1H, d, $J=4$ Hz), 6.36 (1H, d, $J=16$ Hz), 7.84 (1H, d, $J=16$ Hz). UV $\lambda_{\max}^{EtOH}$ nm (ϵ): 308 (15,100) 224 (7200). XVI: IR $\nu_{\max}^{film}$ cm^{-1} : 1715, 1605. NMR (CCl_4) δ : 1.06 (6H, s), 1.25 (3H, t, $J=7$ Hz), 2.24 (3H, d, $J=1$ Hz), 4.08 (2H, q, $J=7$ Hz), 5.64 (1H), 5.78 (1H, t, $J=4$ Hz), 6.25 (1H, d, $J=16$ Hz), 6.45 (1H, d, $J=16$ Hz).

7) *Methyl 5-(1', 6'-epoxy-2', 2'-dimethylcyclohexyl)-3-methyl-(2Z, 4E)-2, 4-pentadienoate (VI)*

XV (1.9 g) was hydrolyzed to give 1.3 g of crystalline acid which was recrystallized from hexane, IR $\nu_{\max}^{KBr}$ cm^{-1} : 1680, 1660, 1600, 1590. NMR ($CDCl_3$) δ : 1.12 (6H, s), 2.07 (3H, d, $J=1$ Hz), 5.67 (1H, s), 6.07 (1H, t, $J=4$ Hz), 6.61 (1H, d, $J=16$ Hz), 7.93 (1H, d, $J=16$ Hz), 11.63 (1H, exchangeable). UV $\lambda_{\max}^{EtOH}$ nm (ϵ): 223 (7600), 303 (16,000). *Anal.* Found: C, 76.23; H, 9.17. *Calcd.* for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15%. Esterification of the acid with diazomethane afforded methyl ester as an oil quantitatively. A solution of 0.55 g of perbenzoic acid in CH_2Cl_2 was added to a stirred mixture of 0.89 g of foregoing methylester in 50 ml of CH_2Cl_2 and 15 ml of 0.5 M aq. $NaHCO_3$. The mixture was stirred under ice cooling for 4 hr and the organic phase was separated, washed with 1 N NaOH solution and water successively, and dried over anhyd. Na_2SO_4 . The CH_2Cl_2 was evaporated and the residue was chromatographed on 10 g of alumina (eluted with hexane-ether=5:1) to give 550 mg of epoxyster VI as an oil in 58% yield. IR $\nu_{\max}^{film}$ cm^{-1} : 1715, 1630, 1600. NMR (CCl_4) δ : 0.99 (3H, s), 1.10 (3H, s), 1.96 (3H, d, $J=1$ Hz), 2.60 (3H, s), 2.94 (1H, t, $J=2$ Hz), 5.55 (1H, s), 6.27 (1H, d, $J=16$ Hz), 7.59 (1H, d, $J=16$ Hz). UV $\lambda_{\max}^{EtOH}$ nm (ϵ): 266.5 (14,800). MS m/e (%): 250 (M^+ , 14).

8) *2'-Demethyl-ABA (II) and its (2E) isomer (XIX)*

According to the method described by Schwieter *et al.* 5.0 g of XV and XVI was converted to 3.2 g of ethyl 2'-

demethyl-dehydro- β -ionylideneacetates by bromination with NBS in CH_2Cl_2 at room temperature followed by dehydrobromination with quinoline at 100°C for 1 hr and chromatography on alumina (eluted with hexane). A solution of 3.2 g of 2'-demethyl-dehydro-ionylideneacetates and 400 mg of rose bengal in 400 ml of methanol was shaken under oxygen while illuminated with a 20 W fluorescent lamp at room temperature for 2 days. After evaporation of methanol, the residue was dissolved in hexane and shaken with 20 g of basic alumina (Merk) at room temperature for 2 hr and chromatographed on an additional 20 g of alumina. Elution with ether gave 900 mg of crude keto alcohol XVII. The crude XVII was rechromatographed on silica gel (elution with benzene-ethyl acetate=6:1) to give 380 mg of XVII as an oil. Hydrolysis of XVII with 5% methanolic NaOH gave a mixture of II and XIX. The mixture of II and XIX was again methylated with cold ethereal diazomethane to give mixture of XVIII and XX as crystals. Isomeric esters XVIII and XX were separated by recrystallization from benzene-hexane. XVIII and XX were hydrolyzed to give II and XIX as crystals respectively. XVIII: mp 118~118.5°C. IR $\nu_{\max}^{KBr}$ cm^{-1} : 3360, 1705, 1660, 1625, 1595. NMR ($CDCl_3$) δ : 1.01 (3H, s), 1.13 (3H, s), 2.02 (3H, d, $J=1$ Hz), 2.39 (2H), 2.99 (1H, exchangeable), 3.65 (3H, s), 5.69 (1H), 5.96 (1H, d, $J=10$ Hz), 6.52 (1H, d, $J=10$ Hz), 6.17 (1H, d, $J=16$ Hz), 7.73 (1H, d, $J=16$ Hz). UV $\lambda_{\max}^{EtOH}$ nm (ϵ): 265.5 (21,300). *Anal.* Found: C, 67.98; H, 7.83. *Calcd.* for $C_{16}H_{20}O_4$: C, 68.16; H, 7.63%. XX: mp 105~106°C. IR $\nu_{\max}^{KBr}$ cm^{-1} : 3400, 1705, 1660, 1630, 1610. NMR ($CDCl_3$) δ : 1.03 (3H, s), 1.14 (3H, s), 2.31 (3H, d, $J=1$ Hz), 2.42 (2H), 2.74 (1H, exchangeable), 3.74 (3H, s), 5.86 (1H), 6.03 (1H, d, $J=10$ Hz), 6.55 (1H, d, $J=10$ Hz), 6.14 (1H, d, $J=16$ Hz), 6.54 (1H, d, $J=16$ Hz). UV $\lambda_{\max}^{EtOH}$ nm (ϵ): 267 (24,600). *Anal.* Found: C, 68.09; H, 7.86. *Calcd.* for $C_{16}H_{20}O_4$: C, 68.16; H, 7.63%. II: mp 156~157°C. IR $\nu_{\max}^{KBr}$ cm^{-1} : 3380, 1675, 1660, 1625, 1600. UV $\lambda_{\max}^{EtOH}$ nm (ϵ): 246 (20,700). *Anal.* Found: C, 67.14; H, 7.27. *Calcd.* for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25%. XIX: mp 185~186°C. IR $\nu_{\max}^{KBr}$ cm^{-1} : 3400, 1685, 1660, 1630, 1610. UV $\lambda_{\max}^{EtOH}$ nm (ϵ): 249 (19,100). *Anal.* Found: C, 67.16; H, 7.38. *Calcd.* for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25%.

9) *4-(2', 6'-Dimethyl-1'-cyclohexenyl)-3-(E)-buten-2-one (XXII)*

XXII was prepared from XXI by the same procedure used for the preparation of XIV in 32% overall yield as an oil, bp 105~107°C (2.0 mmHg). IR $\nu_{\max}^{film}$ cm^{-1} : 1685, 1660, 1610, 1580. NMR (CCl_4) δ : 1.04 (3H, d, $J=7$ Hz), 1.88 (3H, s), 2.18 (3H, s), 5.99 (1H, d, $J=16$ Hz), 7.43 (1H, d, $J=16$ Hz). UV $\lambda_{\max}^{EtOH}$ nm: 298, 224.

10) *Methyl 5-(2', 6'-dimethyl-1'-cyclohexenyl)-3-methyl-(2Z and E, 4E)-2, 4-pentadienoate (XXIII)*

A solution of 8.9 g of XXII and 23.3 g of carbomethoxymethylenetriphenylphosphorane in 120 ml of dry xylene was refluxed for 77 hr. The reaction was worked up by the same procedure described for the preparation of XV and XVI from XIV to give 1.5 g of (2Z)-isomer and 8.2 g of the mixture of (2Z) and (2E)-isomer as an oil in 82% yield. The spectral data of (2Z)-isomer were as follows. IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 1720, 1610, 1585. NMR (CCl_4) δ : 1.14 (3H, d, $J=7$ Hz), 1.81 (3H, s), 2.04 (3H, d, $J=1$ Hz), 3.63 (3H, s), 5.57 (1H), 6.84 (1H, d, $J=16$ Hz), 7.78 (1H, d, $J=16$ Hz). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 321 (22,300). Alkaline hydrolysis of (2Z)-isomer afforded 5-(2', 6'-dimethyl-1'-cyclohexenyl)-3-methyl-(2Z, 2E)-2, 4-pentadienoic acid as crystals, mp 160~161°C (from acetonitrile). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1670, 1595, 1580. NMR (CDCl_3) δ : 1.10 (3H, d, $J=7$ Hz), 1.83 (3H, s), 2.09 (3H, d, $J=1$ Hz), 2.69 (1H), 5.64 (1H), 7.04 (1H, d, $J=16$ Hz), 7.75 (1H, d, $J=16$ Hz). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 312 (21,700), 222 (4400). Anal. Found: C, 76.09; H, 9.26. Calcd. for $\text{C}_{14}\text{H}_{20}\text{O}_2$: C, 76.30; H, 9.26%.

11) *Methyl 5-(1'-hydroxy-2', 6'-cis-dimethyl-4'-oxo-2'-cyclohexen-r-1'-yl)-3-methyl-(2Z, 4E and 2E, 4E)-2, 4-pentadienoate (XXIV and XXV)*

According to the method described by Schwieter *et al.* 9.40 g of XXIII was converted to 3.8 g of methyl 6'-demethyldehydro- β -ionylideneacetates by bromination with NBS in CH_2Cl_2 at $-15 \sim -20^\circ\text{C}$ followed by dehydrobromination with quinoline at room temperature for 1 hr and chromatography on alumina (eluted with hexane). A solution of 3.8 g of foregoing ionylideneacetates and 500 mg of rose bengal in 500 ml of methanol was shaken under oxygen while illuminated with a 20 W fluorescent lamp at room temperature for 2 days. After evaporation of methanol the residue was chromatographed on 20 g of alumina (eluted with ether) to give 2.0 g of crude mixture of XXIV and XXV. The mixture was chromatographed on Florisil which was eluted with benzene-ethylacetate (10:1) to give XXIV (150 mg), mixture of XXIV and XXV (350 mg), and XXV (200 mg). The separated esters XXIV and XXV were recrystallized respectively from benzene-hexane. XXIV: mp 132~133°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3420, 1710, 1645, 1620, 1595. NMR (CDCl_3) δ : 1.04 (3H, d, $J=6$ Hz), 1.98 (3H, d, $J=1$ Hz), 2.01 (3H, d, $J=1.5$ Hz), 2.38 (2H), 2.42 (6'-methine proton, revealed by decoupling at 100 MHz), 2.79 (1H, s, exchangeable), 3.59 (3H, s), 5.75 (1H), 5.90 (1H), 6.03 (1H, d, $J=16$ Hz), 7.80 (1H, d, $J=16$ Hz). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 264 (20,200). Anal. Found: C, 67.93; H, 7.79. Calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_4$: C, 68.18; H, 7.63%. XXV: mp 138~139°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3430, 1715, 1655, 1630, 610. NMR (CDCl_3) δ : 1.06 (3H, d, $J=6$ Hz), 1.99 (3H, d, $J=1$ Hz), 2.33 (3H, d, $J=1$ Hz),

2.71 (1H, exchangeable), 3.80 (3H, s), 6.00 (1H), 6.08 (1H), 6.17 (1H, d, $J=16$ Hz), 6.55 (1H, d, $J=16$ Hz). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 264 (23,300). Anal. Found: C, 67.87; H, 7.70. Calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_4$: C, 68.16; H, 7.63%.

12) *5-(1'-Hydroxy-2', 6'-cis-dimethyl-4'-oxo-2'-cyclohexen-r-1'-yl)-3-methyl-(2Z, 4E and 2E, 4E)-2, 4-pentadienoic acid (III and XXVI)*

The ester XXIV and XXV were hydrolyzed with 5% methanolic NaOH at room temperature to give III and XXVI as crystals respectively. III: mp 189~190°C (from ethyl acetate-benzene). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3400, 1680, 1645, 1620, 1600. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 242.5 (23,000). Anal. Found: C, 67.30; H, 7.27. Calcd. for $\text{C}_{14}\text{H}_{18}\text{O}_4$: C, 67.18; H, 7.25%. XXVI: mp 155~156°C (from ethyl acetate-benzene). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3420, 1685, 1635, 1615. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 248 (23,000). Anal. Found: C, 67.17; H, 7.34. Calcd. for $\text{C}_{14}\text{H}_{18}\text{O}_4$: C, 67.18; H, 7.25%.

13) *4-(2, 6-Dimethyl-4-ethylenedioxy-1-cyclohexenyl)-3-(E)-buten-2-one (XXVIII)*

2, 6-Dimethyl-4-ethylenedioxy-1-cyclohexenemethanol^{10,11)} (XXVII 19.8 g) was oxidized with CrO_3 -pyridine complex by the method described by R. Ratcliffe²⁾ with some modifications to give 14.5 g of oily unsaturated aldehyde in 67% yield, bp 107~110°C (1.0 mmHg). IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 1660, 1620. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm: 243. A mixture of 10.0 g of foregoing unsaturated aldehyde, 70 ml of acetone and 10 ml of 10% aq. NaOH was stirred at room temperature overnight. The reaction mixture was poured into water and extracted twice with ether. The combined ethereal layer was washed twice with water, dried over anhyd. K_2CO_3 and evaporated. The residue was purified by chromatography (alumina, eluted with benzene-ethyl acetate=4:1) and distillation to give 8.4 g of oily unsaturated ketone XXVIII in 68% yield. bp 145~160°C (0.5 mmHg). IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1} : 1655, 1610, 1580. NMR (CCl_4) δ : 1.13 (3H, d, $J=7$ Hz), 1.87 (3H, s), 2.16 (3H, s), 2.32 (2H), 2.65 (1H, m), 3.85 (4H, s), 6.01 (1H, d, $J=16$ Hz), 7.45 (1H, d, $J=16$ Hz). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 294 (17,500), 224 (3700).

14) *4-(1', 2'-Epoxy-4'-ethylenedioxy-2', 6'-dimethyl-1'-cyclohexyl)-3-(E)-buten-2-one (XXIX)*

A mixture of 400 mg of XXVIII, 400 mg of *m*-chloroperbenzoic acid and 30 ml of CH_2Cl_2 was stirred under ice cooling and allowed to stand in ice box overnight. White solid was filtered off and the filtrate was poured into 5% aqueous NaOH solution, and the organic layer was separated, washed with 5% aq. NaOH solution, water and brine successively and dried over Na_2SO_4 . After evaporation of CH_2Cl_2 , 400 mg of crude epoxide was obtained. The crude epoxide was

purified by preparative thin layer chromatography (silica gel Merk PF₂₅₄) using benzene-ethyl acetate (3:1) as developing solvent to give crystalline epoxide XXIX, mp 79~80°C (from hexane). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1690, 1620. NMR (CDCl₃) δ : 0.95 (3H, d, $J=7$ Hz), 1.21 (3H, s), 2.26 (3H, s), 3.90 (4H, s), 6.24 (1H, d, $J=16$ Hz), 6.78 (1H, d, $J=16$ Hz). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 233 (13,600). Anal. Found: C, 66.57; H, 8.05. Calcd. for C₁₄H₂₀O₄: C, 66.64; H, 7.99%.

15) 4-(1'-Hydroxy-2', 6'-dimethyl-4'-oxo-2'-cyclohexen-1'-yl)-3-(E)-buten-2-one (XXX)

A mixture of 400 mg of crude epoxide XXIX, 20 mg of *p*-toluenesulfonic acid and 20 ml of acetone was stirred at room temperature overnight. The reaction mixture was poured into aq. NaHCO₃ solution and extracted twice with ether. The ethereal layers were combined and washed with saturated NaHCO₃ solution and water and dried over anhyd. Na₂SO₄. After evaporation of ether, the residue was purified by preparative thin layer chromatography on silica gel (Merk PF₂₅₄) using benzene-ethyl acetate (3:1) as development solvent to give 55 mg of oily hydroxy-diketone XXX. IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 3420, 1710, 1660, 1620. NMR (CDCl₃) δ : 1.03 (3H, d, $J=6.5$ Hz), 1.92 (3H, d, $J=1$ Hz), 2.30 (3H, s), 2.40 (2H), 2.63 (1H, exchangeable), 5.96 (1H), 6.49 (1H, d, $J=16$ Hz), 6.71 (1H, d, $J=16$ Hz). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm: 233.

16) Methyl 5-(4'-ethylenedioxy-2', 6'-dimethyl-1'-cyclohexenyl)-3-methyl-(2Z and E, 4E)-2, 4-pentadienoate (XXXI)

A solution of 4.0 g of XXVIII and 10.0 g of carbomethoxymethylenetriphenylphosphorane in 60 ml of xylene was refluxed for 81 hr. The reaction was worked up by the same procedure as described for the preparation of XV and XVI from XIV to give 2.8 g of the oily mixture of (2Z) and (2E)-isomer in 56% yield. IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 1710, 1600.

17) Methyl 5-(1', 2'-epoxy-4'-ethylenedioxy-2'-cis-6'-trans-dimethyl-*r*-1'-cyclohexyl)-3-methyl (2Z, 4E and 2E, 4E)-2, 4-penta-dienoate (XXXII and XXXIII) and methyl 5-(1', 2'-epoxy-4'-ethylene-dioxy-2'-cis, 6'-cis-dimethyl-*r*-1'-cyclohexyl)-3-methyl-(2Z, 4E)-2, 4-pentadienoate (XXXIV)

The ketal-ester XXXI (1.7 g) was epoxidized with perbenzoic acid by the same procedure used for the preparation of VI. The product was chromatographed on 50 g of Florisil. Elution with benzene-ethyl acetate (20:1) afforded 50 mg of XXXI, 120 mg of XXXIII, 90 mg of a mixture of XXXIII, (2E)-isomer of XXXIV, 350 mg of XXXII, 70 mg of a mixture of XXXII and XXXIV, 80 mg of XXXIV, as an oil respectively. XXXII: IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 1715, 1630, 1600. NMR (CCl₄) δ : 0.96 (3H, d, $J=6.5$ Hz), 1.20 (3H, s), 2.02

(3H, d, $J=1$ Hz), 3.66 (3H, s), 3.87 (4H, s), 5.67 (1H), 6.07 (1H, d, $J=16$ Hz), 7.71 (1H, d, $J=16$ Hz). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 267 (17,300). XXXIII: IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 1710, 1605, NMR (CCl₄) δ : 0.96 (3H, d, $J=6.5$ Hz), 1.14 (3H, s), 2.27 (3H, d, $J=1$ Hz), 3.64 (3H, s), 3.83 (4H, s), 5.78 (1H), 6.01 (1H, d, $J=16$ Hz), 6.33 (1H, d, $J=16$ Hz). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 266 (22,900). XXXIV: IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 1720, 1640, 1605. NMR (CCl₄) δ : 1.17 (3H, s), 1.21 (3H, d, $J=7$ Hz), 1.99, 3.62 (3H, s), 3.70 (4H, s), 5.58 (1H), 6.19 (1H, d, $J=16$ Hz), 7.63 (1H, d, $J=16$ Hz). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 266.5 (12,200).

18) Methyl 5-(1'-hydroxy-2', 6'-trans-dimethyl-4'-oxo-2'-cyclohexen-*r*-1'-yl)-3-methyl-(2Z, 4E and 2E, 4E)-2, 4-pentadienoate (XXXV and XXXVI)

The epoxy-ketal XXXII (300 mg) was converted to keto-alcohol XXXV by the same procedure used for the preparation of XXX from XXIX though a part of (2E) double bond was isomerized. The product was chromatographed on 15 g of Florisil (elution with benzene-ethyl acetate=10:1) to give 40 mg of crude XXXV which was separated from XXXVI. As XXXV was so unstable in Florisil that only a small amount of impure XXXV was recovered after chromatography. Crude XXXV was purified by preparative TLC (alumina, developed with benzene-ethyl acetate=3:1) giving 11.2 mg of XXXV as an oil. Epoxy-ketal XXXIII and XXXIV were converted to XXXVI and XXIV by the same procedure described for the preparation of XXXV. XXXV: IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 3420, 1715, 1660, 1630, 1600. NMR (CDCl₃) δ : 1.06 (3H, d, $J=6.5$ Hz), 1.93 (3H, d, $J=1$ Hz), 2.03 (3H, d, $J=1$ Hz), 2.32 (6'-methyne proton, revealed by decoupling at 100 MHz), 2.43 (2H), 2.66 (1H, exchangeable), 3.69 (3H, s), 5.76 (1H), 5.93 (1H), 6.08 (1H, d, $J=16$ Hz), 7.84 (1H, d, $J=16$ Hz). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 236.5 (15,400), 260 (14,400). MS *m/e* (%): 264 (M⁺, 2), 246 (3), 232 (5), 190 (32), 162 (25), 134 (30), 125 (100). XXXVI: IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 3480, 1730, 1670, 1610. NMR (CDCl₃) δ : 1.04 (3H, d, $J=6.5$ Hz), 1.93 (3H, d, $J=1$ Hz), 2.30 (3H, d, $J=1$ Hz), 2.43 (2H), 2.85 (1H, exchangeable), 3.75 (3H, s), 5.90 (1H), 5.95 (1H), 6.05 (1H), 6.05 (1H, d, $J=16$ Hz), 6.48 (1H, d, $J=16$ Hz). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 262 (24,800). MS *m/e* (%): 264 (M⁺, 0.3).

19) 5-(1'-Hydroxy-2', 6'-trans-dimethyl-4'-oxo-2'-cyclohexen-*r*-1'-yl)-3-methyl-(2Z, 4E)-2, 4-pentadienoic acid (IV)

Hydrolysis of XXXV with 5% methanolic NaOH at room temperature gave 2 mg of carboxylic acid IV as an gummy oil. IR $\nu_{\text{max}}^{\text{CCl}_4}$ cm⁻¹: 3400, 1715, 1660, 1600. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm: 234.

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