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SYNTHESIS OF 2-FLUOROABSCISIC ACID: A POTENTIAL PHOTO-STABLE ABSCISIC ACID

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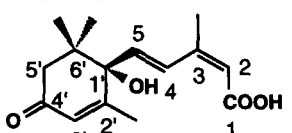
Abstract: Novel fluorinated abscisic acid (ABA) analogs were synthesized by introducing fluorine through the Wittig reaction of α-ionone derivatives with triethyl phosphono-2-fluoroacetate. Molecular orbital calculations showed that the introduction of fluorine at the 2 position stabilized the configuration of the side chain. © 1997 Elsevier Science Ltd. All rights reserved.

Abscisic acid (ABA, **1**) is a plant hormone which regulates physiological processes[1] such as the acceleration of abscission, induction of dormancy, inhibition of rooting, and stimulation of stomatal closure. In addition to these hormonal activities, ABA has attracted considerable attention due to the role it plays in the response to environmental stress such as drought[2] and cold.[3] The geometry (2Z, 4E) of the 2,4-pentadienoic acid moiety of ABA is essential for its hormonal activities. However, the side chain easily isomerizes by light to (2E, 4E) isomer **2**.[4] This isomerization is a significant drawback for its application to crops.[5] It may be possible to obtain compounds with ABA-like activities by blocking the light-induced isomerization of the side chain of ABA. Despite several attempts to synthesize such compounds, few compounds have shown ABA-like activity at the same level as ABA itself, probably because of drastic structural modification of the side chain. Therefore, we considered if we could stabilize the side chain of ABA through minor structural modifications, the resulting ABA analogs should exhibit strong and prolonged ABA-like activities.



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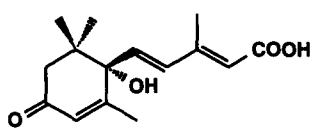

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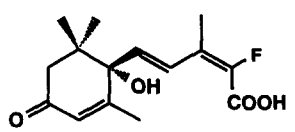

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In recent years, the fluorine atom has been increasingly used as a label for obtaining structural information and mechanistic details regarding bioorganic molecules and their associated processes.[7] Substitution of hydrogen with fluorine changes not only the molecule's size and shape slightly, but also the electronic nature of the molecule greatly due to the strong electronegativity of fluorine. For example, a pyrethric acid analog in which fluorine is introduced into the double bond becomes quite photo-stable and shows strong insecticidal activity.[8] In this study, we introduced a fluorine atom into the C-2 position of abscisic acid (compound **3**) in an attempt to suppress the isomerization of the side chain and thus to enhance the hormonal activities (Fig.1). To determine the effect of the fluorine in the side chain of ABA, the energy barrier of isomerization from the *cis* form to the *trans* form was calculated by performing *ab intio* molecular orbital calculations.

Synthesis and optical resolution of 2-fluoroabscisic acid

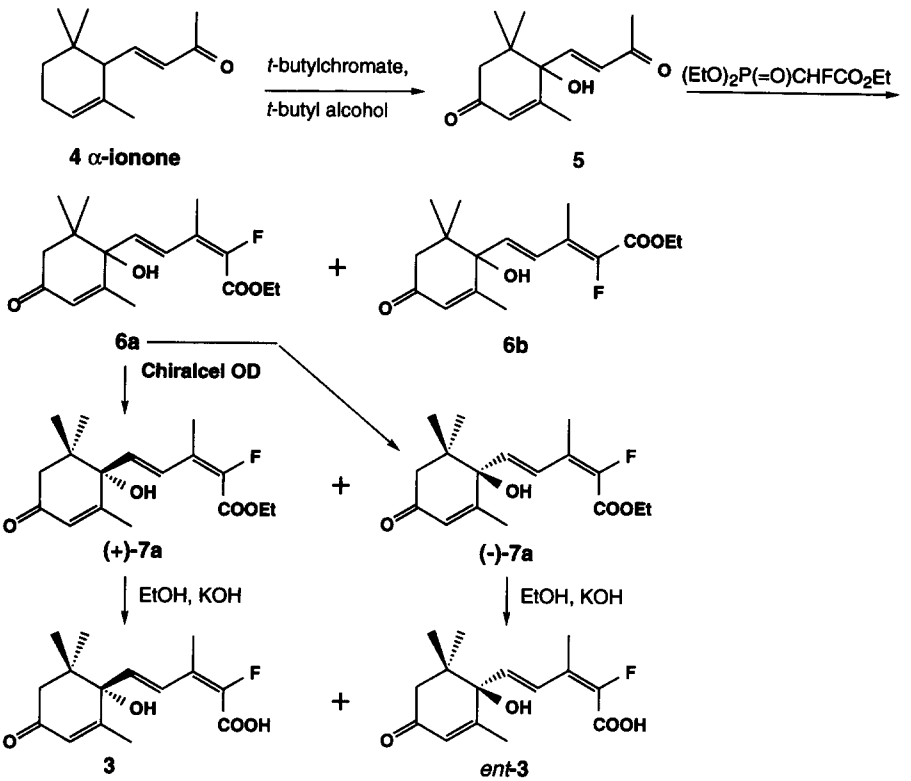

Fig. 1

Compound **5** (1'-hydroxy-4'-oxo group) was obtained in moderate yield from the direct oxidation of α-ionone (**4**) with t-butyl chromate.[10] **5** was converted into 2-fluoroabscisic acid ethyl ester analogs **6a** and **6b** by the Wittig-Horner reaction with triethylphosphono-2-fluoroacetate,[9] which was prepared by the Arbusov reaction of ethyl bromofluoroacetate with triethylphosphite. The Wittig-Horner reaction gave an isomeric mixture of **6a** and **6b** which were separated on a silica-gel column (hexane : ethyl acetate = 4 : 1) to give an enantiomeric mixture of (2*E* ,4*E*)-**6a** (41% yield; mp 120-122 °C; ^{1}H-NMR(200MHz, $CDCl_3$) δ 1.00 (s, 3H), 1.09 (s, 3H), 1.33 (t, 3H), 1.90 (d, 3H, J = 1.3 Hz), 1.97 (d, 3H, J = 4.03 Hz), 2.25 (d, 1H, J = 17.1 Hz), 2.41(s, 1H, OH), 2.45 (d, 1H, J = 16.9 Hz), 4.27 (q, 2H), 5.92 (s, 1H), 6.07 (d, 1H, J = 15.9 Hz), 7.59 (d, 1H, J = 15.2 Hz); ^{19}F-NMR (100MHz, $CFCl_3$) -121.0ppm(d, J = 3.4 Hz); MS *m/z*(rel intensity) : 310 (M^+, 9), 292 (19), 254 (100), 234 (38), 208 (100), 205 (16), 180 (100), 165 (8), 161 (31), 157 (36), 152 (24), 129 (10); HR-MS *m/z*: 310.1575. Calcd. for $C_{17}H_{23}FO_4$: 310.3688) and (2*Z*, 4*E*)-**6b** (42% yield; mp 114-115 °C; ^{1}H-NMR (200MHz, $CDCl_3$) δ 1.01 (s, 3H), 1.11 (s, 3H), 1.36 (t, 3H), 1.90 (d, 3H, J = 1.4 Hz), 2.21(d, 3H, J = 3.3 Hz), 2.30 (d, 1H, J = 17.2 Hz), 2.33 (s, 1H, OH), 2.48 (d, 1H, J = 17.2 Hz), 4.31 (q, 2H), 5.94 (d, 1H, J = 1.2 Hz), 6.12 (d, 1H, J = 15.8 Hz), 6.95 (d, 1H, J = 15.8 Hz); ^{19}F-NMR (100MHz, $CFCl_3$) -124.4ppm; MS *m/z*(rel intensity): 310 (M^+, 46), 254 (30), 208 (57), 180 (100), 161 (39), 152 (43), 137 (11), 133 (15), 123 (14), 109 (29), 83 (16), 56 (44).) in a 1:1 ratio. The enantiomeric mixture of (2*E*, 4*E*)-ethyl-2-fluoroabscisate (**6a**) was resolved by HPLC with a Chiralcel OD column (hexane: *i*-PrOH = 98:2), and subsequent hydrolysis of the (+)- and (-)-enantiomers with KOH in refluxing MeOH and acidification with aqueous HCl gave (+)-2-fluoroabscisic acid **3** ($[\alpha]_D^{25}$ +210.3° (MeOH, *c* 0.282)) and (-)-2-fluoroabscisic acid *ent*-**3** ($[\alpha]_D^{25}$ -185.8°

(MeOH, *c* 0.282)) with an optical purity of more than 99%. The CD spectra of the (+)-enatiomer showed the same positive first and negative second Cotton effect, i. e. the positive excitation chirality, as those of **1**.[10] Therefore, the absolute configuration at C-1' of **3** was assigned as in Fig. 1.

Molecular Orbital Calculations

With 2-fluorine-substituted abscisic acid in hand, isomerization of the C_2-C_3 bond of **3** was investigated through molecular orbital calculations of model compounds 3-methyl-2,4-pentadienoic acid and its 2-fluoro derivative (Fig. 2) in order to verify the photo-stability of the side chain of this abscisic acid analog. All of the geometrical parameters were fully optimized with the 4-31G basis set using the GAUSSIAN-90 program.[11] Diffused orbitals were not used in this calculation, because the rotational energy

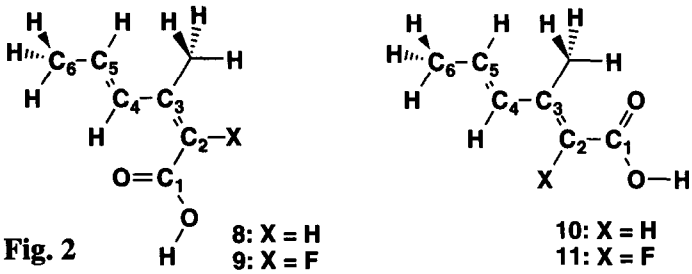

Fig. 2

associated with the formation of covalent bonds between 2nd-row elements is not influenced very much by the orbitals. Hydrogen bonds were included in this model. The minimum energy path (MEP) for the *cis-trans* (or *trans-cis*) transition was calculated. During the calculation, all of the geometrical parameters were also optimized at every dihedral angle C_1-C_2-C_3-C_4. The dihedral angle C_1-C_2-C_3-C_4 was increased in 10 degree increments. As shown in Fig. 3, the energy difference between the *trans*- and *cis*-conformations is negligibly

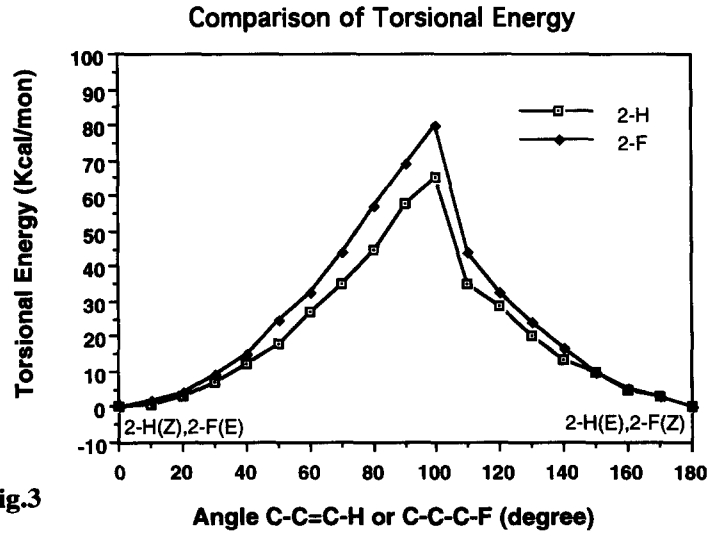

Fig.3

small for both X = H and X = F. The *trans*-isomer is 0.067 and 0.033 kcal/mol more stable than the *cis*-isomer for the hydrogen- and fluorine-substituted compounds, respectively. In Fig. 3, the energy of the *trans*-isomer of each substituted molecule is considered to be zero. The resulting energy barriers of the

hydrogen- and fluorine-substituted compounds were 65 and 78.7 kcal/mol, respectively. Thus, the geometrical isomerization of (2*E*, 4*E*)-2-fluoro-3-methyl-2,4-pentadienoic acid (**9**) to the (2*Z*, 4*E*) isomer (**11**) requires about 14 kcal/mol more energy than that of (2*Z*, 4*E*)-3-methyl-2,4-pentadienoic acid (**8**) to the (2*E*, 4*E*) isomer (**10**). This result suggests that **3** is more stable than **1** with regard to light-induced isomerization of the side chain. Since these calculations indicate that **3** is more stable than the parent compound, the stability and activity of 2-fluoroabscisic acid should be tested in the field.

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