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Syntheses and Potato Tuber-inducing Activity of Coronafacic Acid Analogues

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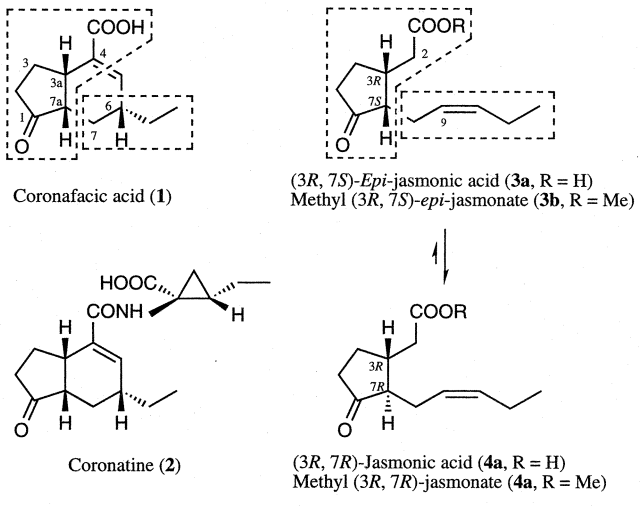
Coronafacic acid (1) is an acid component of coronatine, and has been isolated from several pathovars of *Pseudomonas syringae*. Syntheses of C_6-non- and C_6-alkyl-substituted analogues of 1 were accomplished *via* intramolecular 1,6-conjugate addition as the key step. Among them, 1 and four C_6-alkyl-substituted analogues exhibited potato tuber-inducing activity, but the C_6-non-substituted analogue did not. It was revealed that a certain length of the C_6-alkyl group was necessary to exhibit activity.

Key words: coronafacic acid; coronatine; jasmonic acid; 1,6-conjugate addition; tuber-inducing activity

Coronafacic acid (**1**) is an acid component of the phytotoxin, coronatine (**2**), and has been isolated from several pathovars of 2-producing *Pseudomonas syringae*.[1] There has been strong interest recently shown in **1** and **2** for their unique biological activities, similar to those of (3*R*, 7*S*)-*epi*-jasmonic acid (**3a**),[2] as a kind of plant hormone.[3] It is likely that the structural similarity of **1** and **2** to **3a** would be the cause for their common biological activities. In particular, their cyclopentanone moieties with two stereogenic centers and a carboxyl group are closely similar. Furthermore, the C_4-unit of **1** might correspond to the (*Z*)-2-pentenyl group (C_5-unit) of **3a**. The bicyclic structure of **1** contributes to the retention of C_{3a}- and C_{7a}-stereogenic centers as *cis*-relationship; however, monocyclic compound **3a** readily undergoes epimerization to provide the thermodynamically stable *trans*-isomer, (3*R*, 7*R*)-jasmonic acid (**4a**). Therefore, naturally occurring **1** might be regarded as a configurationally and conformationally restricted bicyclic analogue of **3a** (Fig. 1). From the fact that natural **1** exhibited equal or slightly weak **3a**-like activities in several bioassays characteristic for **3a** and **4a** [sometimes used as an equilibrium mixture of minor (±)-**3a** and major (±)-**4a**; or of minor (±)-**3b** and major (±)-**4b**],[2e] **1** is a useful probe to investigate plant physiological effects relating to jasmonoids. Under the mentioned background, in connection with the construction of a functional 1-hydrindanone framework *via* intramolecular 1,6-conjugate addition as the key step, C_6-non- and C_6-alkyl-substituted analogues of **1** have been synthesized,[4] and their biological activities have been examined. We have already synthesized **1** in both its racemic and optically active form.[5]

A commercially available starting material, 2-cyclopenten-1-one, was converted to racemic ester **5** *via* Michael addition of the acetic acid-ester synthon[6] and subsequent acetalization with ethyleneglycol (Scheme).[5b] The desired precursors ($\alpha,\beta,\gamma,\delta$-unsaturated esters; **8a**, **8b**, **8c** and **8d**) of the intramolecular 1,6-conjugate addition were obtained by the following four-step manipulation: (1) aldol condensation between the lithium enolate of **5** and acrolein derivatives, (2) mesylation of the resulting β-hydroxyl group with mesyl chloride, (3) subsequent β-elimination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and (4) acidic deacetalization.[5b] Only in the case of using acrolein, aldol condensation gave a mixture of hydroxy esters **6a** and **6e**, each as a mixture of two diastereomers, in a 90% yield (**6a**:**6e**=*ca.* 4:1), which could be separated by column chromatography. Since the relative sterochemistry between the ethoxycarbonyl and hydroxyl groups could not be determined at this stage, major **6a** was converted into unsaturated ester **7a**, and minor **6e** into **7e**, each as the sole product. It was deduced that the elimination of the mesyloxy group would proceed *via* the E2 mechanism under the conditions used. The geometries of **7a** and **7e** were determined from their ^{1}H-^{1}H-NOE difference spectra (Fig. 2). The observed NOE enhancements were indicative of **7a** and **7e** being (*E*)- and (*Z*)-isomers, respectively. Therefore, *syn*- and *anti*-relationships of **6a** and **6e** were respectively proved. Deacetalization of **7a** gave desired (*E*)-isomer **8a**. In the cases of using 2-alkylacroleins possessing methyl-, ethyl- and *n*-butyl groups, *syn*-hydroxy esters **6b**, **6c** and **6d**, each as a mixture of two diastereomers, were obtained. Their relative stereochemis-



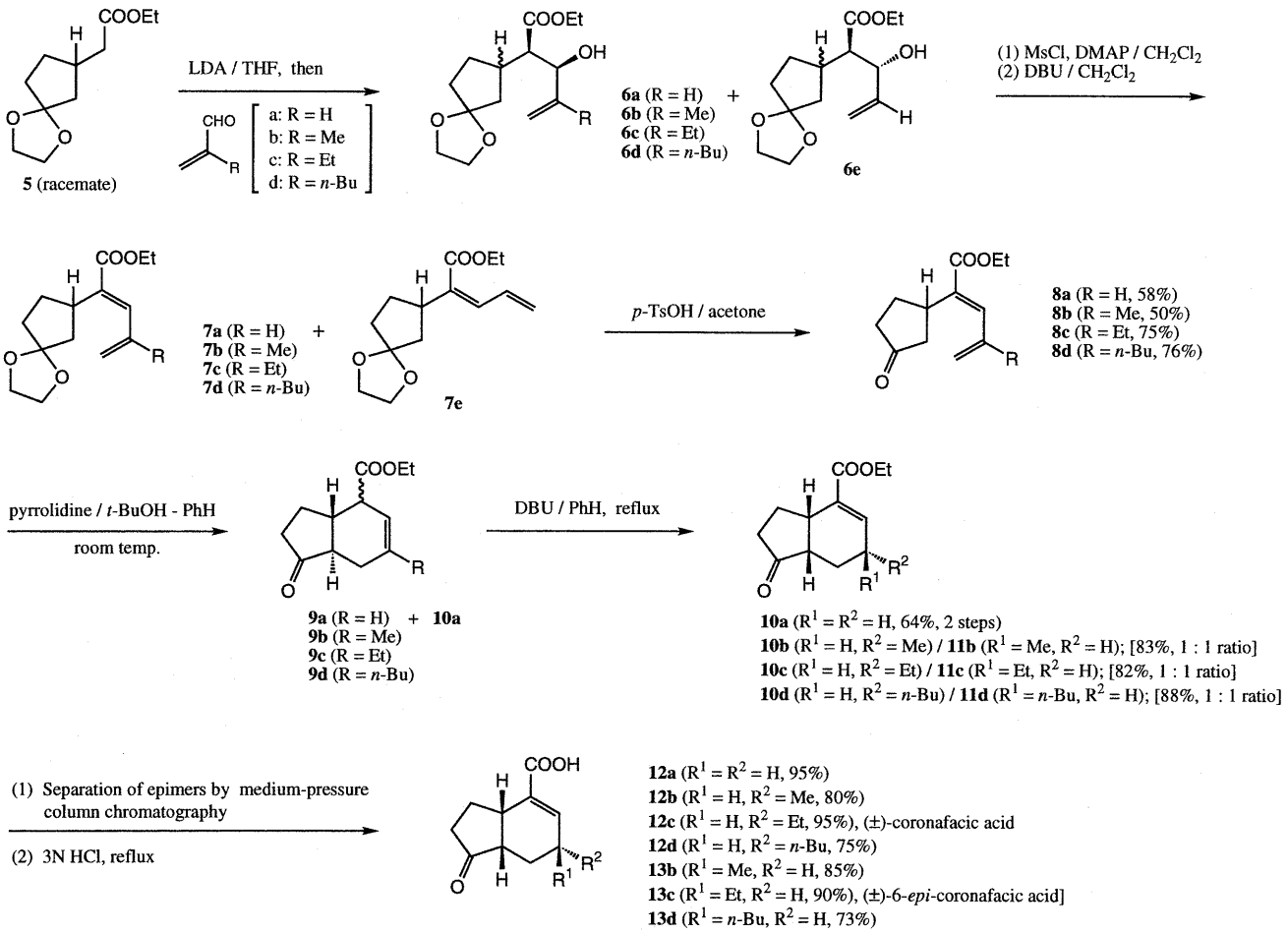
Coronafacic acid (**1**)

(3*R*, 7*S*)-*Epi*-jasmonic acid (**3a**, R = H)
Methyl (3*R*, 7*S*)-*epi*-jasmonate (**3b**, R = Me)

Coronatine (**2**)

(3*R*, 7*R*)-Jasmonic acid (**4a**, R = H)
Methyl (3*R*, 7*R*)-jasmonate (**4a**, R = Me)

Fig. 1. Structures of Coronafacic Acid and Related Compounds.



Scheme. Syntheses of Coronafacic Acid Analogues.

try was also revealed by converting to unsaturated esters **7b**, **7c** and **7d**, each as the sole product. In a ^{1}H-^{1}H-NOE experiment on **7c**, NOE enhancement was observed between the $C_{7'}$- and C_5-protons indicating that **7c** possessed (*E*)-geometry and *s-cis* conformation. In contrast to **7a** and **7e** existing in the *s-trans* conformation, the ethyl group at the C_4-position in **7c** would contribute to maintaining the *s-cis* conformation, which is more favorable for intramolecular cyclization than the *s-trans* one. In the ^{1}H-NMR spectra of **7b** and **7d**, the signals of C_3-H, C_5-H_a and C_5-H_b were closely similar to those of **7c** (C_3-H, δ 7.03 ppm; C_5-H_a, δ 4.88 ppm; C_5-H_b, δ 5.08 ppm), respectively. Furthermore, the mechanism for the aldol condensation between the lithium enolate of **5** and acrolein derivatives is reasonably explicable for producing predominantly or exclusively *syn*-hydroxy esters (Fig. 2). The (*E*)-geometry of the lithium enolate was proved from that of corresponding silyl enol ether **5a**, which had been obtained from **5** by treating with LDA and then TMSCl in THF, exhibiting NOE-enhancement of the olefinic proton by irradiating the methyl protons. In two possible 6-membered transition states (**T1** and **T2**), **T1** predominates over **T2** due to steric hindrance between the bulky cyclopentane moiety of the enolate of **5** and the alkenyl moiety of an aldehyde in **T2**. When acrolein lacking an alkyl group was used, the aldol condensation would proceed to some extent *via* **T2** to give **6a** and **6e**, because of the relaxation of steric hindrance. When 2-alkylacroleins were used, the aldol condensation would proceed exclusively *via* **T1** to give *syn*-hydroxy esters **6b**, **6c** and **6d**, and further E2 elimination could explain the (*E*)-geometry of **7b**, **7c** and **7d**. Deacetalization of **7b**, **7c** and **7d** gave desired (*E*)-isomers **8b**, **8c** and **8d**, respectively.

Intramolecular 1,6-conjugate addition of **8a** with pyrrolidine gave a mixture of β,γ-unsaturated ester **9a**, itself as a mixture of two diastereomers (*ca.* 5:1 ratio), and α,β-unsaturated ester **10a** in a 7:1 ratio (based on integration of the ^{1}H-NMR spectrum), which was further treated with DBU to give only **10a**. In the ^{1}H-NMR spectrum of C_{7a}-*epi*-coronafacic acid, whose relative stereochemistry has been determined by an X-ray analysis,[1a] C_{3a}-H and C_{7a}-H were observed at δ 2.75 and 2.25 ppm, respectively. However, in the ^{1}H-NMR spectrum of **10a**, C_{3a}-H and C_{7a}-H were observed at δ 3.22 and 2.33–2.47 ppm, similar to those of natural **1** (δ 3.08 and 2.37 ppm),[5b] respectively. Therefore, the juncture of **10a** is considered to be *cis*-relationship. Treatment of **8b** with pyrrolidine exclusively gave β,γ-unsaturated ester **9b** as a mixture of two diastereomers (*ca.* 5:1 ratio), which could be isomerized to a mixture of α,β-unsaturated esters (**10b** and **11b**, 1:1 ratio) with DBU. In the same two-step manner, **8c** and **8d** were also converted to α,β-unsaturated esters (**10c**/**11c** and **10d**/**11d**, each in a 1:1

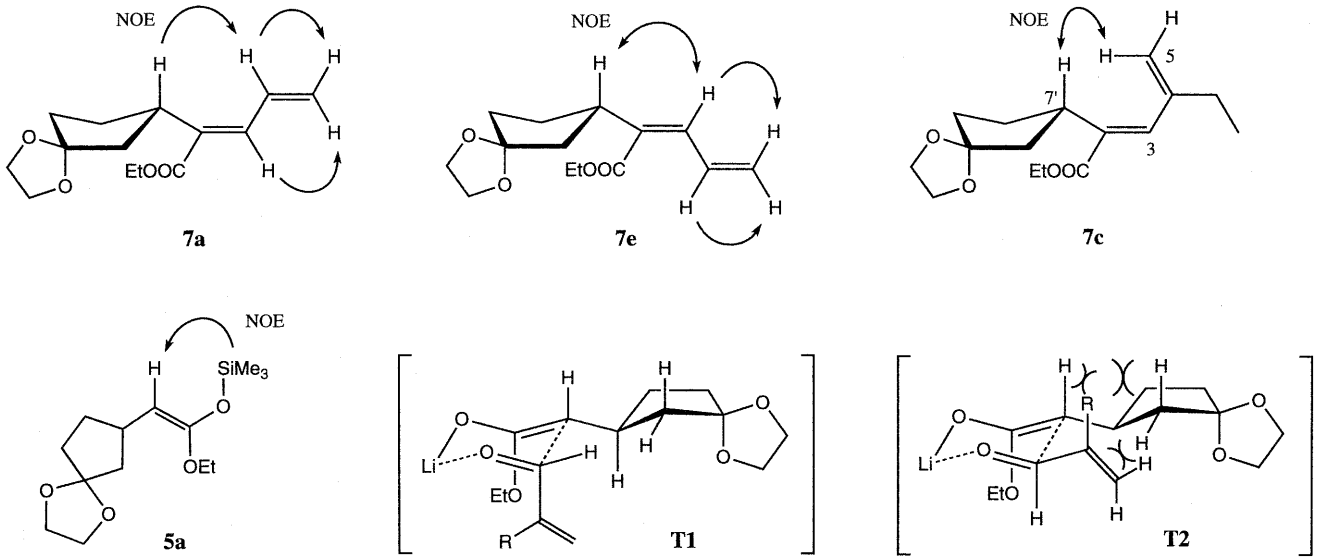


Fig. 2. Observed NOEs of **7a**, **7e**, **7c** and **5a**; and Two Possible Transision States of Aldol Condensation.

ratio). The ratios of the two diastereomers in **9c** and **9d** were *ca.* 5:1, as well as those in **9a** and **9b**. The relative stereochemistry of the major diastereomers of **9a–9d** would probably be similar and useful for considering the reaction mechanism. However, the two diastereomers of **9a–9d** were inseparable and were subjected to the next isomerization to give α,β-unsaturated esters (**10a–10d** and **11b–11d**). A possible mechanism for intramolecular 1,6-conjugate addition is illustrated in Fig. 3. When pyrrolidine was used, an enamine (**IM1**) generated *in situ* would act as an electron donor. The resulting dienolate (**IM2**) would undergo kinetically controlled protonation at the α-position to give β,γ-unsaturated esters. The stereochemistry at the C_{7a}-position would be controlled thermodynamically *via* an enamine (**IM3**) to give **9a–9d**. The presence of alkyl substituent at the C_6-position might also contribute to keeping the β,γ-position of the double bond in **9b–9d**. In practice, **8a** only gave **9a** and **10a** under the same conditions. Pyrrolidine cannot deprotonate from **IM3** or **9a–9d** to provide a dienolate. DBU acts as base for **9a–9d** to provide a bisenolate. The dienolate part would undergo protonation at the γ-position to give α,β-unsaturated esters (**10** and **11**). In **10** and **11**, deprotonation at the C_6-position with DBU is also possible to give thermodynamically stable α,β-unsaturated esters **10** and **11** as a 1:1 equilibrium mixture. The position of the double bond influences the relative stereochemistry of the juncture. Based on the chemical shifts (C_{3a}-H and C_{7a}-H) in the ^{1}H-NMR spectra already described, all the β,γ-unsaturated esters existed as the *trans*-1-hydrindanone, and all the α,β-unsaturated esters as the *cis*-1-hydrindanone. Three pairs of epimers (**10b/11b**, **10c/11c** and **10d/11d**) with respect to the C_6-position could be separated by column chromatography. The relative stereochemistry of **11c** was determined from ^{1}H-^{1}H-NOESY spectra at 500 MHz (Fig. 4). The observed NOESY correlations could reasonably explain its stereochemistry. The correlation between C_{3a}-H and C_{7a}-H revealed the *cis*-1-hidrindanone framework. The correlations between C_{7a}-H and the methylene protons of the C_6-ethyl group and between C_{7a}-H and C_7-H$_\beta$ resulted from the preferential half-chair-like conformation in **11c**. These observations mean that the relationship between C_6-H and C_{7a}-H would be *trans*. Furthermore, acidic hydrolysis (3 N HCl, reflux) of **10c** gave (±)-coronafacic acid (**12c**) in a 95% yield, whose spectral data were identical with those of natural **1**.[5b] Therefore, **11c** was the C_6-epimer of **10c**. In the ^{1}H-NMR spectra of **10b** and **10d**, the characteristic signals of C_{3a}-H (each of δ 3.07 ppm) were closely similar to those of **10c** (δ 3.08 ppm), while the other corresponding signals were slightly similar. In the ^{1}H-NMR spectra of **11b** and **11d**, the characteristic signals of C_{3a}-H (δ 3.23 and 3.27 ppm) were closely similar to those of **11c** (δ 3.26 ppm), while the other corresponding signals were slightly similar. In this way, the relative stereochemistry of **10b–10d** and **11b–11d** was unequivocally determined. The final acidic hydrolysis of ethyl esters **10a**, **10b**, **10d**, **11b**, **11c** and **11d** gave the analogues of **1**: C_6-non-substituted analogue **12a** and C_6-alkyl-substituted analogues **12b**, **12d**, **13b**, **13c** and **13d**, respectively. In this way, we obtained six new analogues of **1** with respect to the C_6-position.

In addition to the weak potato cell expansion-inducing activity of natural **1** ($>10^{-5}$ M), the potato tuber-inducing activity[8] of natural **1** and of the positive standard [a mixture of minor (±)-**3a** (*ca.* 7%) and major (±)-**4a**], were almost equivalent ($>10^{-7}$ M) with respect to the rate of tuberization.[2e] These results suggested that a tuber-inducing assay would be more sensitive than a cell expansion-inducing assay for **1** and its analogues. Therefore, the tuber-inducing activity was examined, and the results (except for **12b** and **13b**) are shown in the Table. We used a racemic positive standard and analogues in the tuber-inducing assay and assumed the following background information: the tuber-inducing activities of **3a** and **3b** were almost equivalent,[9] and (3*R*, 7*S*)-**3b** exhibited the strongest tuber-inducing activity

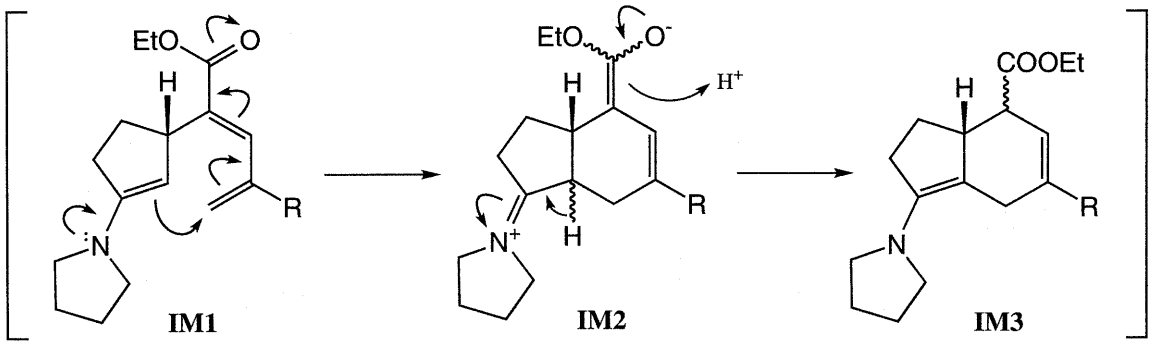


Fig. 3. Possible Mechanism for Intramolecular 1,6-Conjugate Addition.

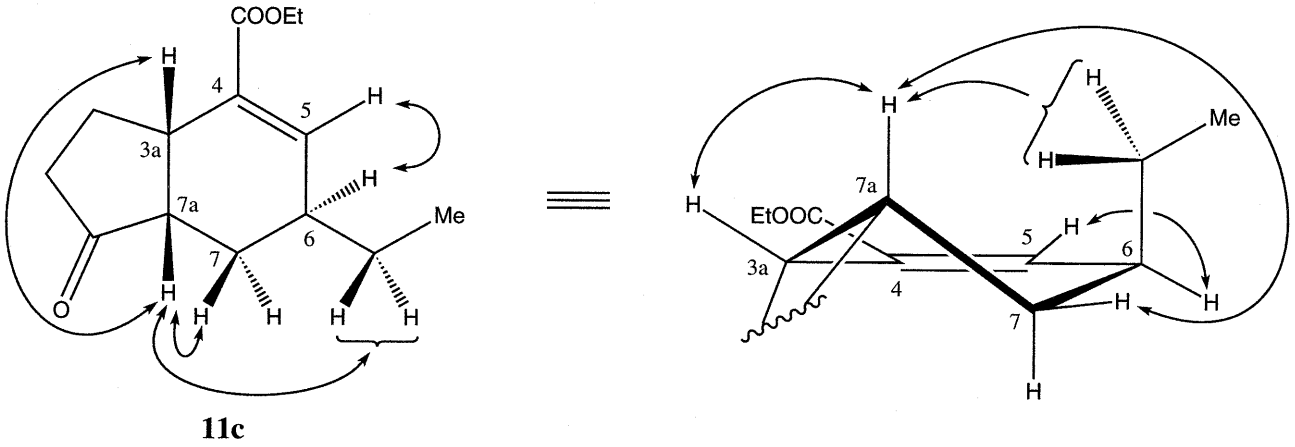


Fig. 4. Selected NOESY Correlations of **11c** Around the Cyclohexene Ring.

among the four stereoisomers of **3b** and **4b**, while the other three stereoisomers also exhibited this activity.[10] Isomerization by enolization was not evaluated in the assay. However, even the positive standard exhibited reasonably similar activity to that of **3b** in the range from 10^{-7} to 10^{-5} M concentration. Sessile tubers are usually induced by the positive standard at a 10^{-5} M concentration with 80–100% rate of tuberization (strong induction), and tubers are induced at the end of elongated lateral shoots below 10^{-6} M concentration (weak induction) from our experience. The racemic analogues of **1** might also be considered to exhibit tuber-inducing activity without competitive inhibition. Only the C_6-non-substituted analogue (**12a**) exhibited no tuber-inducing activity; however, **12c** and three other analogues (**12d**, **13c** and **13d**) each exhibited tuber-inducing activity in the range from 10^{-6} to 10^{-4} M concentration (weak induction). For such an example, tuberonic acid[11] [12-hydroxyl-jasmonic acid that was used as a synthetic mixture of major (3*R**, 7*R**)- and minor (3*R**, 7*S**)-isomers] did not exhibit cell expansion-inducing activity and showed only strong tuber-inducing activity (H. Matsuura, T. Yoshihara, and Y. Koda, unpublished result). The tuber-inducing activities of **12c** and **12d** were almost equivalent to each other at all attempted concentrations, and about one-half that of the positive standard at a 10^{-5} M concentration. By considering the tuber-inducing activity of natural **1**, unnatural enantiomers in **12c** and **12d** might be regarded as exhibiting no activity. However, there is the possibility that unnatural enantiomers in **12c** and **12d** exhibited tuber-inducing activity, because all four stereoisomers of **3b** exhibited this activity.[10] The tuber-inducing activities of **13c** and **13d** (corresponding to C_6-epimers of **12c** and **12d**, respectively) were weaker than those of **12c** and **12d** themselves. The syntheses of C_6-methyl analogues **12b** and **13b** were carried out at different times, so all the analogues could not be subjected to this bioassay at the same time. Since 11-month old tubers were used for the bioassay of **12b** and **13b**, spontaneous tuberization occurred even with the control (20%) on White's medium,[8] and the results were judged after **2** weeks. In such a preliminary assay, although C_6-epimer **13b** exhibited no tuber-inducing activity, **12b** exhibited tuber-inducing activity (60%) at a rather high concentration (10^{-4} M). By considering the control result (20%), the tuber-inducing activity of **12b** was weakest among all the analogues exhibited this activity.

In conclusion, a certain length of the alkyl group (ethyl or *n*-butyl) attached at the C_6-position was essential for exhibiting **3a**-like activity in tuber-inducing assay. The activities of C_6-epimers **13b**, **13c** and **13d** were weaker than those of **12b**, **12c** and **12d**, respectively. The C_4-unit of **12c**/**13c** and the C_6-units of **12d**/**13d**, including the two carbons at the C_6- and C_7-positions, are mimics of the (*Z*)-2-pentenyl group (C_5-unit) of **3a**. Therefore, **1** and its homologue **12d** might have been configurationally also conformationally restricted analogues of **3a**. These compounds would be useful for analyzing the active conformation of **3a** in plant regula-

Table Effect of Coronafacic Acid and Its Analogues on Potato Tuber-inducing Activity *in vitro*

Compound	Rate of tuberization at each concentration (%)[a]		
	10^{-6} M	10^{-5} M	10^{-4} M
control		0	
positive standard[b]		92[c]	
12a	0	0	0
12c	12	42	65
13c	0	12	51
12d	15	46	65
13d	0	12	30

[a] The bioassay was carried out by following the method in ref. 8. The results were judged after 3 weeks.
[b] A mixture of minor (±)-**3a** (*ca.* 7%) and major (±)-**4a** was used.
[c] Tuber-inducing activity of the positive standard at a 10^{-5} M concentration was only examined at this time. The sessile tubers were induced.

tory processes. Design and syntheses of the other analogues of **3a** are in progress.

Experimental

General Methods. ^{1}H- and ^{13}C-NMR spectra were recorded with a JEOL JNM-EX-270 (^{1}H, 270 MHz; ^{13}C, 67.5 MHz) or Brucker AM-500 spectrometer (^{1}H, 500 MHz; ^{13}C, 125 MHz), and chemical shift values are reported in δ (ppm) relative to internal tetramethylsilane or the residual proton of the deuterated solvent. IR spectra were measured with a Perkin Elmer System 2000 FT-IR spectrometer, and mass spectra were recorded with a JEOL JMS-AX500 or JEOL JMS-SX102A spectrometer. Melting point values were obtained with Yanaco micro-melting point apparatus and are uncorrected. Column chromatography was carried out with Silica gel 60 (spherical, 70–140 mesh ASTM, Kanto Chemical). Medium-pressure column chromatography was carried out with a pre-packed glass column, Lobar® (LiChroprep® Si 60, 40–63 μm, Merck). All chemical yields are summarized in the Scheme.

α,β,γ,δ-Unsaturated esters (**7a–7e**, and **8a–8d**). The synthetic manner has been described as the typical procedure for preparing **8c**.[5b] In the case of preparing **8a**, desired *syn*-hydroxyester **6a** was separated by medium-pressure column chromatography (hexane:EtOAc=7:3) after aldol condensation. The spectral data for **7a–7e** and **8a–8d** are described next.

Ethyl (2E)-{1,4-dioxaspiro[4.4]non-7-yl}-2,4-pentadienoate (**7a**). IR ν_{max} (film) cm^{-1}: 3082, 2980, 1707, 1626, 1587, 1463, 1368, 1328, 1255, 1170, 1119, 1029, 1024, 947, 775; ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7.3 Hz, CO_2CH_2*Me*), 1.73–1.83 (2H, m, $C_{8'}$-H, $C_{9'}$-H), 1.87 (1H, dd, J=7.9, 12.2 Hz, $C_{6'}$-H), 1.90–2.16 (2H, m, $C_{8'}$-H, $C_{9'}$-H), 2.23 (1H, t, J=12.2 Hz, $C_{6'}$-H), 3.35 (1H, dq., J=7.9, 12.2 Hz, $C_{7'}$-H), 3.85–3.96 (4H, m, OCH_2CH_2O), 4.21 (2H, q, J=7.3 Hz, CO_2CH_2Me), 5.45 (1H, br.d, J=10.2 Hz, C_5-H), 5.57 (1H, br.d, J=16.5 Hz, C_5-H), 6.79 (1H, ddd, J=10.2, 11.2, 16.5 Hz, C_4-H), 7.11 (1H, d, J=11.2 Hz, C_3-H); ^{13}C-NMR ($CDCl_3$) δ: 14.25, 28.57, 35.64, 35.78, 40.54, 60.41, 64.03, 64.55, 117.75, 124.76, 131.57, 134.02, 139.10, 166.54; EIMS m/z: 253 (6, MH^+), 252 (36, M^+), 99 (66), 86 (100); HRMS m/z (M^+): calcd. for $C_{14}H_{20}O_4$, 252.1361; found, 252.1380.

Ethyl (2E)-{1,4-dioxaspiro[4.4]non-7-yl}-4-methyl-2,4-pentadienoate (**7b**). IR ν_{max} (film) cm^{-1}: 3082, 2955, 2877, 1715, 1622, 1456, 1435, 1310, 1241, 1160, 1113, 1075, 1036, 949, 910, 771; ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7.3 Hz, CO_2CH_2*Me*), 1.75–1.83 (3H, m, $C_{6'}$-H, $C_{8'}$-H, $C_{9'}$-H), 1.88 (3H, s, *Me*), 1.90–2.15 (2H, m, $C_{8'}$-H, $C_{9'}$-H), 2.27 (1H, t, J=12.4 Hz, $C_{6'}$-H), 3.44 (1H, m, $C_{7'}$-H), 3.87–3.95 (4H, m, OCH_2CH_2O), 4.22 (2H, q, J=7.3 Hz, CO_2CH_2Me), 4.94 (1H, br.s, C_5-H), 5.12 (1H, br.s, C_5-H), 7.01 (1H, s, C_3-H); ^{13}C-NMR ($CDCl_3$) δ: 14.23, 22.82, 28.93, 35.58, 35.94, 40.88, 60.38, 63.99, 64.55, 117.05, 117.86, 134.18, 140.41, 141.58, 167.55; EIMS m/z: 266 (13, M^+), 99 (97), 86 (100); HRMS m/z (M^+): calcd. for $C_{15}H_{22}O_4$, 266.1518; found, 266.1523.

Ethyl (2E)-{1,4-dioxaspiro[4.4]non-7-yl}-4-ethyl-2,4-pentadienoate (**7c**). The spectral data for **7c** have been described elsewhere.[5b]

Ethyl (2E)-4-butyl-{1,4-dioxaspiro[4.4]non-7-yl}-2,4-pentadienoate (**7d**). IR ν_{max} (film) cm^{-1}: 3082, 2957, 2875, 1715, 1623, 1464, 1324, 1238, 1118, 1028, 901, 773; ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=6.9 Hz, $CH_2CH_2CH_2$*Me*), 1.32 (3H, t, J=7.3 Hz, CO_2CH_2*Me*), 1.24–1.43 (4H, m, $CH_2CH_2CH_2$Me), 1.73–1.83 (3H, m, $C_{6'}$-H, $C_{8'}$-H, $C_{9'}$-H), 1.94–2.16 (4H, m, $C_{8'}$-H, $C_{9'}$-H, $CH_2CH_2CH_2$Me), 2.26 (1H, t, J=12.4 Hz, $C_{6'}$-H), 3.44 (1H, m, $C_{7'}$-H), 3.87–3.95 (4H, m, OCH_2CH_2O), 4.22 (2H, q, J=7.3 Hz, CO_2CH_2Me), 4.89 (1H, br.s, C_5-H), 5.08 (1H, br.s, C_5-H), 7.02 (1H, s, C_3-H); ^{13}C-NMR ($CDCl_3$) δ: 13.87, 14.23, 22.23, 28.93, 30.26, 35.62, 35.99, 36.37, 40.86, 60.36, 63.99, 64.51, 114.70, 117.92, 134.81, 141.58, 144.92, 167.37; EIMS m/z: 309 (3, MH^+), 308 (17, M^+), 99 (100), 86 (74); HRMS m/z (M^+): calcd. for $C_{18}H_{28}O_4$, 308.1987; found, 308.1988.

Ethyl (2Z)-{1,4-dioxaspiro[4.4]non-7-yl}-2,4-pentadienoate (**7e**). ^{1}H-NMR (C_6D_6) δ: 1.02 (3H, t, J=7.3 Hz, CO_2CH_2*Me*), 1.73 (1H, m, $C_{8'}$-H), 1.89–2.37 (4H, m, $C_{6'}$-H, $C_{8'}$-H, $C_{9'}$-H_2), 2.25 (1H, ddd, J=1.4, 7.3, 11.9 Hz, $C_{6'}$-H), 3.26 (1H, m, $C_{7'}$-H), 3.51–3.62 (4H, m, OCH_2CH_2O), 4.07 (2H, q, J=7.3 Hz, CO_2CH_2Me), 5.20 (1H, dd, J=2.0, 10.9 Hz, C_5-H), 5.26 (1H, dd, J=2.0, 16.9 Hz, C_5-H), 6.35 (1H, d, J=9.9 Hz, C_3-H), 7.52 (1H, ddd, J=9.9, 10.9, 16.9 Hz, C_4-H); ^{13}C-NMR (C_6D_6) δ: 14.17, 29.93, 36.39, 41.62, 42.34, 60.24, 64.14, 64.37, 117.38, 121.98, 134.31, 135.60, 136.00, 167.37.

Ethyl (2E)-2-(3-oxocyclopent-1-yl)-2,4-pentadienoate (**8a**). Colorless oil (888 mg); IR ν_{max} (film) cm^{-1}: 3082, 2980, 1741, 1702, 1626, 1588, 1463, 1422, 1404, 1370, 1257, 1179, 1086, 1024, 990, 934, 777, 757; ^{1}H-NMR (C_6D_6) δ: 1.01 (3H, t, J=7.9 Hz, CO_2CH_2*Me*), 1.69 (1H, q, J=8.9 Hz, $C_{5'}$-H), 1.90 (1H, dd, J=8.9, 16.5 Hz, $C_{4'}$-H), 2.08–2.31 (3H, m, $C_{2'}$-H, $C_{4'}$-H, $C_{5'}$-H), 2.78 (1H, dd, J=8.9, 17.5 Hz, $C_{2'}$-H), 3.11 (1H, quint.,

J=8.9 Hz, $C_{7'}$-H), 4.02 (2H, q, J=7.9 Hz, CO_2CH_2Me), 5.20 (1H, br.d, J=10.2 Hz, C_5-H), 5.30 (1H, br.d, J=16.8 Hz, C_5-H), 6.42 (1H, ddd, J=10.2, 11.6, 16.8 Hz, C_4-H), 7.30 (1H, d, J=11.6 Hz, C_3-H); ^{13}C-NMR (C_6D_6) δ: 14.12, 27.97, 35.51, 38.23, 42.43, 60.42, 124.95, 131.52, 133.62, 139.46, 166.54, 215.58; EIMS m/z: 208 (100, M^+), 209 (18, M^++H); HRMS m/z (M^+): calcd. for $C_{12}H_{16}O_3$, 208.1099; found, 208.1082.

Ethyl (2E)-4-methyl-2-(3-oxocyclopent-1-yl)-2,4-pentadienoate (**8b**). Colorless oil (901 mg); IR ν_{max} (film) cm^{-1}: 3082, 2979, 1744, 1714, 1627, 1456, 1404, 1368, 1242, 1157, 1096, 1026, 903, 775; ^{1}H-NMR (C_6D_6) δ: 1.01 (3H, t, J=7.3 Hz, CO_2CH_2*Me*), 1.64 (3H, s, *Me*), 1.70–1.93 (2H, m, $C_{4'}$-H, $C_{5'}$-H), 2.16 (1H, dd, J=9.9, 17.5 Hz, $C_{2'}$-H), 2.20–2.35 (2H, m, $C_{4'}$-H, $C_{5'}$-H), 2.81 (1H, dd, J=9.9, 17.5 Hz, $C_{2'}$-H), 3.52 (1H, quint., J=9.9 Hz, $C_{7'}$-H), 4.02 (2H, q, J=7.3 Hz, CO_2CH_2Me), 4.84 (1H, br.s, C_5-H), 4.96 (1H, br.s, C_5-H), 7.25 (1H, s, C_3-H); ^{13}C-NMR (C_6D_6) δ: 14.11, 22.61, 28.45, 35.60, 38.23, 42.97, 60.47, 117.18, 134.04, 140.65, 142.05, 166.62, 215.94; EIMS m/z: 223 (17, M^++H), 222 (100, M^+), 221 (16, M^+-H); HRMS m/z (M^+): calcd. for $C_{13}H_{18}O_3$, 222.1256; found, 222.1239.

Ethyl (2E)-4-ethyl-2-(3-oxocyclopent-1-yl)-2,4-pentadienoate (**8c**). Colorless oil (420 mg). The spectral data for **8c** have been described elsewhere.[5b]

Ethyl (2E)-4-butyl-2-(3-oxocyclopent-1-yl)-2,4-pentadienoate (**8d**). Colorless oil (674 mg); IR ν_{max} (film) cm^{-1}: 3082, 2959, 1747, 1714, 1623, 1464, 1404, 1367, 1337, 1294, 1243, 1156, 1094, 1026, 903, 776; ^{1}H-NMR (C_6D_6) δ: 0.88 (3H, t, J=7.3 Hz, $CH_2CH_2CH_2$*Me*), 1.01 (3H, t, J=7.3 Hz, CO_2CH_2*Me*), 1.15–1.37 (4H, m, $CH_2CH_2CH_2$Me), 1.70–1.95 (2H, m, $C_{4'}$-H, $C_{5'}$-H), 2.00 (2H, t, J=7.3 Hz, $CH_2CH_2CH_2$Me), 2.21 (1H, dd, J=8.9, 18.1 Hz, $C_{2'}$-H), 2.20–2.36 (2H, m, $C_{4'}$-H, $C_{5'}$-H), 2.84 (1H, dd, J=8.9, 18.1 Hz, $C_{2'}$-H), 3.52 (1H, quint., J=8.9 Hz, $C_{7'}$-H), 4.02 (2H, q, J=7.3 Hz, CO_2CH_2Me), 4.84 (1H, br.s, C_5-H), 5.00 (1H, br.s, C_5-H), 7.30 (1H,s, C_3-H); ^{13}C-NMR (C_6D_6) δ: 13.93, 14.08, 22.45, 28.42, 30.48, 35.71, 36.54, 38.21, 43.04, 60.47, 114.85, 134.90, 141.91, 145.21, 166.44, 215.76; EIMS m/z: 264 (100, M^+); HRMS m/z (M^+): calcd. for $C_{16}H_{24}O_4$, 264.1725; found, 264.1724.

Typical procedure for intramolecular 1,6-conjugate addition with pyrrolidine and subsquent isomerization with DBU. A solution of **8c** (2.10 g, 8.92 mmol) and pyrrolidine (0.07 ml, 0.89 mmol) in benzene (40 ml)/*tert*-BuOH (2.6 ml) was stirred at room temperature for 10 h. The reaction mixture was acidified with 2 N HCl and extracted with EtOAc (3 times). The combined extracts were successively washed with sat. aq. $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography (hexane:EtOAc=9:1) to give a mixture of β,γ-unsaturated esters **9c** (1.97 g) as a colorless oil which was used for the next reaction.

A solution of β,γ-unsaturated esters (39 mg, 0.165 mmol) and DBU (0.05 ml, 0.33 mmol) in benzene (2.0 ml) was refluxed for 64 h. The same work-up and purification as that just described gave a mixture of α,β-unsaturated esters (**10c** and **11c**, 34 mg, 1:1 ratio) as a colorless oil, which was further separated by medium-pressure column chromatography (hexane:EtOAc=96:4).

Ethyl (3aS,7aS*)-2,3,3a,6,7,7a-hexahydro-1-oxo-1H-indene-4-carboxylate* (**10a**). According to the typical procedure, **10a** (360 mg) was obtained as a colorless oil; IR ν_{max} (film) cm^{-1}: 2981, 1739, 1715, 1645, 1465, 1447, 1428, 1381, 1253, 1202, 1147, 1089, 1058, 1023, 901, 750, 725; ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7.3 Hz, CH_2*Me*), 1.17 (2H, q, J=6.3 Hz, C_7-H_2), 1.83 (1H, dq, J=12.5, 7.9 Hz, C_3-H), 2.15–2.24 (2H, m, C_6-H_2), 2.26 (2H, t, J=7.9 Hz, C_2-H_2), 2.33–2.47 (2H, m, C_3-H, C_{7a}-H), 3.22 (1H, dq, J=1.3, 7.9 Hz, C_{3a}-H), 4.23 (2H, m, CH_2Me), 7.07 (1H, dt, J=1.3, 4.3 Hz, C_5-H); ^{13}C-NMR ($CDCl_3$) δ: 14.22, 19.50, 23.85, 27.35, 35.71, 37.07, 46.60, 60.38, 131.81, 140.20, 166.68, 220.59; EIMS m/z: 209 (28, M^++H), 208 (100, M^+); HRMS m/z (M^+): calcd. for $C_{12}H_{16}O_3$, 208.1099; found, 208.1106.

Ethyl (3aS,6R*,7aS*)-2,3,3a,6,7,7a-hexahydro-6-methyl-1-oxo-1H-indene-4-carboxylate and ethyl (3aS*, 6S*, 7aS*)-2,3,3a,6,7,7a-hexahydro-6-methyl-1-oxo-1H-indene-4-carboxylate* (**10b** and **10b**). According to the typical procedure, a mixture of **10b** and **11b** (120 mg, 1:1 ratio) was obtained as a colorless oil, which was further separated by medium-pressure column chromatography (hexane:EtOAc=96:4).

10b: IR ν_{max} (film) cm^{-1}: 2961, 1739, 1713, 1643, 1456, 1376, 1251, 1095, 1057, 905, 752; ^{1}H-NMR ($CDCl_3$) δ: 1.06 (1H, q, J=13.2 Hz, C_7-H), 1.11 (3H, d, J=7.3 Hz, *Me*), 1.31 (3H, t, J=7.3 Hz, CO_2CH_2*Me*), 1.57 (1H, dt, J=8.5, 11.6 Hz, C_3-H), 1.82 (1H, dt, J=13.2, 4.8 Hz, C_7-H), 2.20–2.46 (4H, m, C_2-H_2, C_6-H, C_{7a}-H), 2.56 (1H, dt, J=11.6, 6.9 Hz, C_3-H), 3.07 (1H, dt, J=11.6, 6.9 Hz, C_{3a}-H), 4.17–4.26 (2H, m, CO_2CH_2Me), 6.84 (1H, s, C_5-H); ^{13}C-NMR ($CDCl_3$) δ: 14.25, 20.43, 28.14, 28.36, 31.09, 35.87, 38.12, 46.79, 60.45, 131.28, 145.01, 166.77, 220.32; EIMS m/z: 223 (20, M^++H), 222 (94, M^+), 105 (100); HRMS m/z (M^+): calcd. for $C_{13}H_{18}O_3$, 222.1256; found, 222.1256.

11b: IR ν_{max} (film) cm^{-1}: 2961, 1739, 1715, 1645, 1456, 1373, 1249, 1105, 1082, 885, 758; ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, d, J=7.3 Hz, *Me*), 1.29 (4H, t, J=7.3 Hz, C_7-H, CO_2CH_2*Me*), 1.85–2.04 (2H, m, C_3-H, C_7-H), 2.07–2.33 (4H, m, C_2-H_2, C_3-H, C_6-H), 2.46 (1H, dt, J=5.0, 7.3 Hz, C_{7a}-H), 3.23 (1H, q, J=7.3 Hz, C_{3a}-H), 4.20 (2H, q, J=7.3 Hz, CH_2Me), 6.84 (1H, d, J=3.3 Hz, C_5-H); ^{13}C-NMR ($CDCl_3$) δ: 14.20, 20.17, 26.88, 27.78, 28.02, 35.60, 36.73, 45.64, 60.41, 130.85, 146.00, 166.86, 221.15; EIMS m/z: 223 (22, M^++H), 222 (91, M^+), 105 (100); HRMS m/z (M^+): calcd. for $C_{13}H_{18}O_3$, 222.1256; found, 222.1263.

Ethyl (3aS,6R*,7aS*)-6-ethyl-2,3,3a,6,7,7a-hexahydro-1-oxo-1H-indene-4-carboxylate and ethyl (3aS*,*

6S, 7aS*)-6-ethyl-2,3,3a,6,7,7a-hexahydro-1-oxo-1H-indene-4-carboxylate* (**10c** and **11c**). The spectral data for **10c** and **11c** have been described elsewhere.[5b]

Ethyl (3aS,6R*,7aS*)-6-butyl-2,3,3a,6,7,7a-hexahydro-1-oxo-1H-indene-4-carboxylate and ethyl (3aS*, 6S*, 7aS*)-6-butyl-2,3,3a,6,7,7a-hexahydro-1-oxo-1H-indene-4-carboxylate* (**10d** and **11d**). According to the typical procedure, a mixture of **10d** and **11d** (579 mg, 1:1 ratio) was obtained as a colorless oil, which was further separated by medium-pressure column chromatography (hexane:EtOAc=96:4).

10d: IR ν_{max} (film) cm^{-1}: 2930, 1744, 1715, 1645, 1467, 1381, 1301, 1255, 1143, 1102, 1075, 1029, 752; ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7.3 Hz, $CH_2CH_2CH_2$*Me*), 1.06 (1H, dt, J=11.2, 13.2 Hz, C_7-H), 1.31 (3H, t, J=7.3 Hz, CO_2CH_2*Me*), 1.28–1.55 (6H, m, $CH_2CH_2CH_2$Me), 1.59 (1H, dt, J=8.6, 12.5 Hz, C_3-H), 1.84 (1H, dt, J=13.2, 4.6 Hz, C_7-H), 2.24 (1H, m, C_6-H), 2.28–2.47 (3H, m, C_2-H_2, C_{7a}-H), 2.56 (1H, dt, J=12.5, 7.3 Hz, C_3-H), 3.07 (1H, dt, J=7.3, 12.5 Hz, C_{3a}-H), 4.13–4.29 (2H, m, CO_2CH_2Me), 6.90 (1H, s, C_5-H); ^{13}C-NMR ($CDCl_3$) δ: 13.93, 14.27, 22.64, 26.26, 28.14, 28.77, 34.68, 36.03, 36.19, 38.11, 46.70, 60.45, 131.36, 144.21, 166.83, 220.54; EI-MS *m/z*: 265 (26, M^++H), 264 (100, M^+), 147 (85); HRMS *m/z* (M^+): calcd. for $C_{16}H_{24}O_4$, 264.1725; found, 264.1741.

11d: IR ν_{max} (film) cm^{-1}: 2930, 1744, 1716, 1645, 1464, 1381, 1251, 1144, 1097, 888, 756; ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7.3 Hz, $CH_2CH_2CH_2$*Me*), 1.18–1.42 (7H, m, C_7-H, $CH_2CH_2CH_2$Me), 1.32 (3H, t, J=7.3 Hz, CO_2CH_2*Me*), 1.89–2.05 (2H, m, C_3-H, C_7-H), 2.10 (1H, m, C_6-H), 2.15–2.35 (3H, m, C_2-H_2, C_3-H), 2.47 (1H, q, J=6.0 Hz, C_{7a}-H), 3.27 (1H, q, J=6.0 Hz, C_{3a}-H), 4.19–4.28 (2H, m, CO_2CH_2Me), 6.96 (1H, d, J=3.0 Hz, C_5-H); ^{13}C-NMR ($CDCl_3$) δ: 14.06, 14.37, 22.80, 25.87, 27.11, 29.18, 33.20, 34.57, 35.99, 36.94, 45.82, 60.57, 131.19, 145.26, 167.09, 221.32; EIMS *m/z*: 265 (26, M^++H), 264 (100, M^+), 147 (49); HRMS *m/z* (M^+): calcd. for $C_{16}H_{24}O_4$, 264.1725; found, 264.1724.

(3aS, 7aS*)-2,3,3a,6,7,7a-hexahydro-1-oxo-1H-indene-4-carboxylic acid* (**12a**). By the same method as that described for the synthesis of (±)-**1**,[5b] **12a** (209 mg) was obtained as colorless crystals [crystallized from acetone-H_2O (6:4)]; mp 109–110°C; IR ν_{max} (KBr) cm^{-1}: 2943, 1737, 1673, 1429, 1284, 1246, 1201, 1148, 1093, 930, 722; ^{1}H-NMR ($CDCl_3$) δ: 1.60–1.74 (2H, m, C_7-H_2), 1.83 (1H, dt, J=6.0, 12.2 Hz, C_3-H), 2.21–2.29 (4H, m, C_2-H_2, C_6-H_2), 2.31–2.46 (2H, m, C_3-H, C_{7a}-H), 3.14 (1H, q, J=6.0 Hz, C_{3a}-H), 7.19 (1H, t, J=4.0 Hz, C_5-H), 11.0 (1H, br., COOH); ^{13}C-NMR ($CDCl_3$) δ: 19.36, 24.15, 27.32, 35.46, 37.09, 46.51, 131.05, 143.36, 172.13, 220.68; EIMS *m/z*: 181 (12, M^++H) 180 (100, M^+); HRMS *m/z* (M^+): calcd. for $C_{10}H_{12}O_3$, 180.0786; found, 180.0786.

(3aS,6R*,7aS*)-2,3,3a,6,7,7a-hexahydro-6-methyl-1-oxo-1H-indene-4-carboxylic acid* (**12b**). By the same method,[5b] **12b** (60 mg) was obtained as colorless crystals [crystallized from acetone-H_2O (6:4)]; mp 129–130°C; IR ν_{max} (KBr) cm^{-1}: 2948, 1733, 1683, 1628, 1470, 1425, 1290, 1140, 1058, 946, 727; ^{1}H-NMR ($CDCl_3$) δ: 1.08 (1H, q, J=13.2 Hz, C_7-H), 1.14 (3H, d, J=7.3 Hz, *Me*), 1.57 (1H, ddd, J=8.5, 11.8, 13.2 Hz, C_3-H), 1.87 (1H, dt, J=13.2, 4.9 Hz, C_7-H), 2.23–2.47 (4H, m, C_2-H_2, C_6-H, C_{7a}-H), 2.56 (1H, dt, J=11.8, 6.6 Hz, C_3-H), 3.07 (1H, dt, J=11.8, 7.3 Hz, C_{3a}-H), 7.02 (1H, s, C_5-H), 11.0 (1H, br., COOH); ^{13}C-NMR ($CDCl_3$) δ: 20.29, 28.07, 28.21, 31.36, 35.64, 38.13, 46.70, 130.55, 148.09, 171.97, 220.09; EIMS *m/z*: 195 (13, M^++H), 194 (100, M^+); HRMS *m/z* (M^+): calcd. for $C_{11}H_{14}O_3$, 194.0943; found, 194.0958.

(3aS,6R*,7aS*)-6-ethyl-2,3,3a,6,7,7a-1-oxo-1H-indene-4-carboxylic acid* [(±)-coronafacic acid; **12c**]. Colorless crystals (140 mg). The synthesis and spectral data for **12c** have been described elsewhere.[5b]

(3aS, 6R*, 7aS*)-6-butyl-2,3,3a,6,7,7a-hexahydro-1-oxo-1H-indene-4-carboxylic acid* (**12d**). By the same method,[5b] **12d** (153 mg) was obtained as colorless crystals [crystallized from acetone-H_2O (6:4)]; mp 145–146°C; IR ν_{max} (KBr) cm^{-1}: 2955, 1736, 1683, 1627, 1468, 1430, 1284, 1141, 1075, 950, 728; ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7.3 Hz, $CH_2CH_2CH_2$*Me*), 1.09 (1H, dt, J=11.2, 12.9 Hz, C_7-H), 1.24–1.68 (7H, m, C_3-H, $CH_2CH_2CH_2$Me), 1.88 (1H, dt, J=12.9, 5.0 Hz, C_7-H), 2.22–2.47 (4H, m, C_2-H_2, C_6-H, C_{7a}-H), 2.60 (1H, dt, J=13.1, 6.3 Hz, C_3-H), 3.07 (1H, dt, J=12.2, 6.3 Hz, C_{3a}-H), 7.06 (1H, s, C_5-H), 11.0 (1H, br., COOH); ^{13}C-NMR ($CDCl_3$) δ: 13.95, 22.64, 26.09, 28.05, 28.75, 34.50, 35.94, 36.26, 38.12, 46.60, 130.69, 147.15, 172.11, 220.34; EIMS *m/z*: 237 (18, M^++H), 236 (100, M^+); HRMS *m/z* (M^+): calcd. for $C_{14}H_{20}O_3$, 236.1412; found, 236.1380.

(3aS,6S*,7aS*)-2,3,3a,6,7,7a-hexahydro-6-methyl-1-oxo-1H-indene-4-carboxylic acid* (**13b**). By the same method,[5b] **13b** (33 mg) was obtained as a colorless oil; IR ν_{max} (film) cm^{-1}: 2961, 1733, 1682, 1635, 1456, 1404, 1274, 1146, 1036, 885, 760; ^{1}H-NMR (270 MHz) δ: 1.06 (3H, d, J=6.9 Hz, *Me*), 1.34 (1H, ddd, J=5.0, 7.9, 13.2 Hz, C_7-H), 1.96–2.10 (2H, m, C_3-H, C_7-H), 2.12–2.35 (4H, m, C_2-H_2, C_3-H, C_6-H), 2.51 (1H, dt, J=5.0, 7.9 Hz, C_{7a}-H), 3.25 (1H, q, J=5.0 Hz, C_{3a}-H), 7.07 (1H, d, J=2.6 Hz, C_5-H), 11.0 (1H, br., COOH); ^{13}C-NMR ($CDCl_3$) δ: 20.04, 26.88, 27.64, 28.34, 35.38, 36.77, 45.59, 130.15, 149.07, 172.31, 221.17; EIMS *m/z*: 195 (12, M^++H), 194 (100, M^+); HRMS *m/z* (M^+): calcd. for $C_{11}H_{14}O_3$, 194.0943; found, 194.0938.

(3aS,6S*,7aS*)-6-ethyl-2,3,3a,6,7,7a-1-oxo-1H-indene-4-carboxylic acid* [(±)-6-*epi*-coronafacic acid; **13c**]. By the same method,[5b] **13c** (100 mg) was obtained as a colorless oil; IR ν_{max} (film) cm^{-1}: 2963, 2633, 1733, 1683, 1464, 1418, 1277, 1146, 1054, 929, 891, 758; ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J=7.3 Hz, CH_2*Me*), 1.25–1.44 (3H, m, C_7-H, CH_2Me), 1.89–2.30 (6H, m, C_2-H_2, C_3-H_2, C_6-H, C_7-H), 2.44 (1H, q, J=6.0 Hz, C_{7a}-H), 3.20 (1H, q, J=6.0 Hz, C_{3a}-H), 7.08 (1H, d, J=2.3 Hz, C_5-H), 11.0 (1H, br., COOH); ^{13}C-NMR ($CDCl_3$) δ: 11.38,

25.27, 26.87, 27.48, 34.86, 35.62, 36.73, 45.73, 130.49, 147.89, 172.25, 221.2; EIMS *m/z*: 209 (14, $M^+ + H$), 208 (100, M^+); HRMS *m/z* (M^+): calcd. for $C_{12}H_{16}O_3$, 208.1099; found, 208.1083.

(3aS,6S*,7aS*)-6-butyl-2,3,3a,6,7,7a-hexahydro-1-oxo-1H-indene-4-carboxylic acid* (**13d**). By the same method,[5b] **13d** (40 mg) was obtained as a colorless oil; IR ν_{max} (film) cm^{-1}: 2930, 2632, 1740, 1683, 1635, 1458, 1419, 1275, 1145, 1066, 887; ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.3 Hz, $CH_2CH_2CH_2$*Me*), 1.24–1.43 (7H, m, C_7-H, $CH_2CH_2CH_2$Me), 1.92–2.04 (2H, m, C_3-H, C_7-H), 2.09–2.37 (4H, m, C_2-H_2, C_3-H, C_6-H), 2.49 (1H, dt, J=5.6, 7.3 Hz, C_{7a}-H), 3.24 (1H, q, J=5.6 Hz, C_{3a}-H), 7.12 (1H, d, J=2.0 Hz, C_5-H), 11.0 (1H, br., COOH); ^{13}C-NMR ($CDCl_3$) δ: 13.93, 22.64, 25.55, 26.90, 29.00, 33.30, 34.25, 35.60, 36.77, 45.61, 130.33, 148.12, 172.34, 221.22; EIMS *m/z*: 237 (22, $M^+ + H$), 236 (100, M^+); HRMS *m/z* (M^+): calcd. for $C_{14}H_{20}O_3$, 236.1412; found, 236.1418.

(3aS, 6R, 7aR)-6-ethyl-2,3,3a,6,7,7a-1-oxo-1H-indene-4-carboxylic acid (C_{7a}-*epi*-coronafacic acid). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.02 (3H, t, J=7.4 Hz, CH_2*Me*), 1.36 (1H, m, CH_2Me), 1.49–1.65 (3H, m, CH_2Me, C_3-H, C_7-H), 1.94 (1H, dt, J=3.0, 13.0 Hz, C_2-H), 2.05 (1H, dd, J=3.8, 13.0 Hz, C_2-H), 2.25 (1H, ddd, J=8.3, 9.5, 18.0 Hz, C_{7a}-H), 2.39–2.46 (2H, m, C_3-H, C_6-H), 2.49 (1H, dd, J=9.5, 18.0 Hz, C_7-H), 2.75 (1H, ddd, J=5.0, 8.3, 13.5 Hz, C_{3a}-H), 7.05 (1H, br.s, C_5-H), 11.0 (1H, br., COOH).

Bioassays. Cell expansion-inducing activity was examined with cultures of tissue discs of potato tubers (*Solanum tuberosum* L. cv. Irish Cobbler) *in vitro*, as reported previously.[7] In the range from 10^{-6} to 10^{-4} M concentration, all analogues of **1**, as well as **12c** (each as a racemate), exhibited almost no activity.

Tuber-inducing activity was examined with cultures of single-node segments of potato stems *in vitro*, as reported previously.[8] The positive standard, a mixture of minor (±)-**3a** (*ca.* 7%) and major (±)-**4a**, was prepared from a commercially available mixture of minor (±)-**3b** and major (±)-**4b**.[2e]

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