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Isolation and Structure of Striatenic Acid from Liverwort *Cheilolejeunea serpentina* and the Absolute Configuration by Synthesis

Motoo Tori,* Akihito Aiba, Hiroki Koyama, Toshihiro Hashimoto, Katsuyuki Nakashima, Masakazu Sono and Yoshinori Asakawa

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770-8514, Japan

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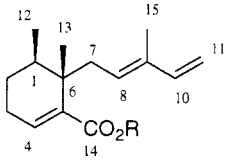
Abstract—Striatenic acid has been isolated from the liverwort *Cheilolejeunea serpentina* collected in Malaysia and its structure was determined on the basis of extensive 2D NMR techniques. The absolute configuration was established by synthesis of the optically active methyl ester.

Introduction

Liverworts are rich sources of terpenoids, which very often show cytotoxic, anti-inflamatory, anti-fungal, or anti-microbial activities.[1–3] We have been studying the chemical constituents of various liverworts collected in all over the world. We have previously reported the metabolites of *Cheilolejeunea trifaria*, i.e. trifarienols A–E (trifarane-type sesquiterpenoids) having a bicyclo[3.3.1]nonane skeleton, which are very rare in the nature.[4,5] We have collected closely related Malaysian species *Cheilolejeunea serpentina* and isolated a new striatane-type sesquiterpene. Now we report the isolation, structure determination, and the absolute configuration[6] of striatenic acid (**1**) by synthesis of the optically active methyl ester **2**.



1 R=H
2 R=Me

Results and Discussion

Isolation and structure

An ether extract of *C. serpentina* was subjected to silica gel column chromatography to isolate striatenic acid (**1**). Because it has a carboxyl group (3200–2500, 1682 cm^{-1}), it was converted to a corresponding methyl ester (1720 cm^{-1}) by treatment with diazomethane.[7] The ester **2** exhibited a molecular ion peak at *m*/*z* 248, whose molecular formula was determined by HRMS to be $C_{16}H_{24}O_2$. The ^1H NMR spectrum showed the existence of five olefinic protons. The presence of a vinyl group was obvious from the signals at δ_H 6.38 (1H, dd, *J*=17.4, 10.4 Hz), 5.04 (1H, d, *J*=17.4 Hz), and 4.89 (1H, d, *J*=10.4 Hz). The ^{13}C NMR showed seven sp^2 carbons, one of which was due to an ester (δ_C 167.9). Therefore, there are three double bonds, two of which were trisubstituted olefins (Table 1). Since the degree

Table 1. The ^1H and ^{13}C NMR data of acid **1** and ester **2** ($CDCl_3$)

	1 (400 MHz)		**2** (600 MHz)	
No.	H	C	H	C
1	1.67 (m)	34.6	1.67 (m)	34.5
2a	1.42 (m)	25.9	1.42 (m)	25.9
2b	1.52 (m)	–	1.52 (m)	–
3	2.16 (m)	25.8	2.16 (m)	25.6
4	7.15 (t, 4.2)	144.0	6.91 (t, 4.2)	140.8
5	–	135.2	–	135.1
6	–	39.9	–	40.0
7a	2.41 (dd, 15.9, 9.0)	34.8	2.41 (dd, 15.4, 8.0)	35.0
7b	2.82 (dd, 15.9, 6.0)	–	2.73 (dd, 15.4, 6.0)	–
8	5.29 (dd, 9.0, 6.0)	130.1	5.26 (dd, 8.0, 6.0)	130.1
9	–	137.4	–	137.4
10	6.34 (dd, 17.2, 10.8)	141.8	6.38 (dd, 17.4, 10.4)	141.8
11a	4.89 (d, 10.8)	110.3	4.89 (d, 10.4)	110.3
11b	5.04 (d, 17.2)	–	5.04 (d, 17.4)	–
12	0.90 (d, 6.8)	15.7	0.89 (d, 6.6)	15.7
13	1.16 (s)	20.8	1.16 (s)	21.0
14	–	172.6	–	167.9
15	1.73 (br s)	11.9	1.72 (br s)	11.9
OMe	–	–	3.68 (s)	51.3

Keywords: carboxylic acids and derivatives; natural products; plants; terpenes and terpenoids.

* Corresponding author. Tel.: +81-88-622-9611 (ext. 5631); fax: +81-88-655-3051; e-mail: tori@ph.bunri-u.ac.jp

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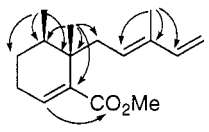


Figure 1. The HMBC correlations for ester **2**.

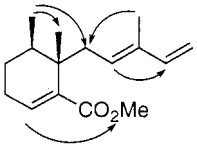
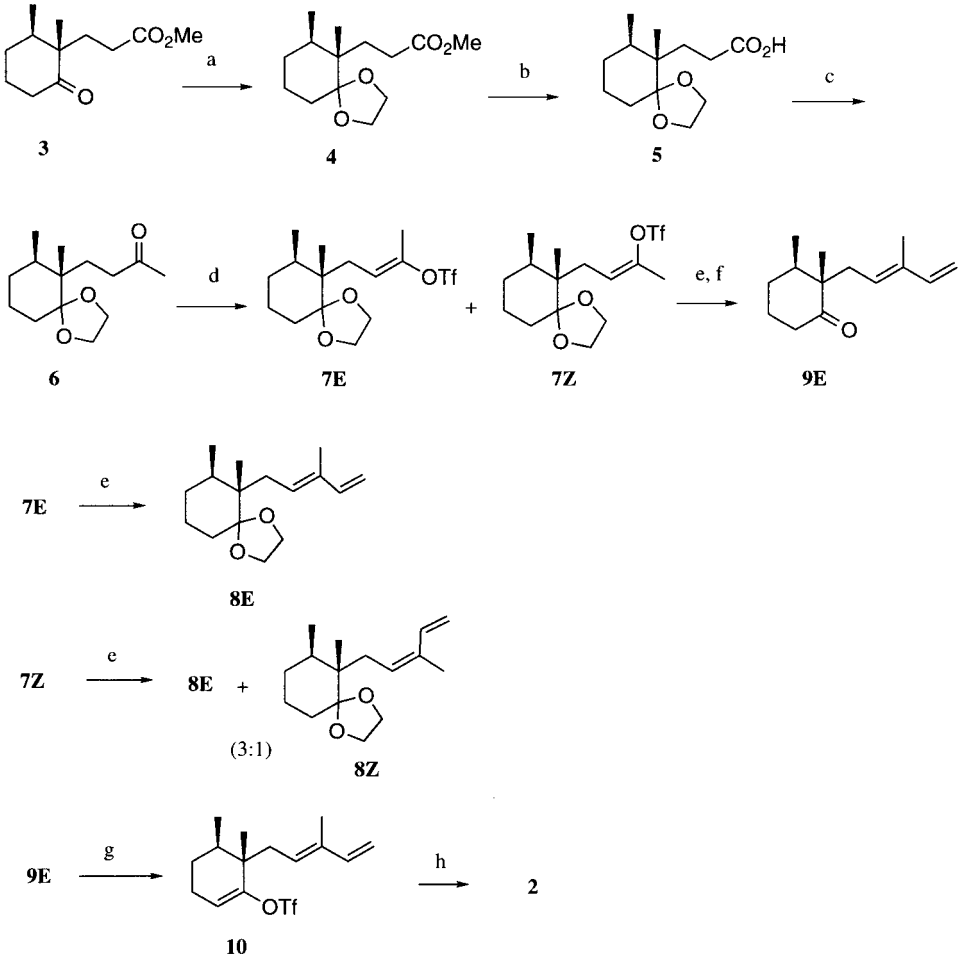


Figure 2. The selected NOE's for ester **2**.

of unsaturation was five, the ester **2** must be a monocyclic compound. The HMQC spectrum showed that the proton at δ_H 5.26 (1H, dd, J=8, 6 Hz) was attached to the carbon at δ_C 130.1 and that at δ_H 6.91 (1H, t, J=4.2 Hz) to δ_C 140.8. The HMBC spectrum indicated the carbon connectivities between H-15 and C-8, C-9, C-10; H-12 and C-1, C-2, C-6; H-13 and C-1, C-6, C-7, C-5; H-4 and C-14 (Fig. 1). Therefore, compound **2** was determined to be the striatane-type sesquiterpene methyl ester as depicted in the formula. The stereochemistry was determined by the NOESY spectrum (Fig. 2). Because H-15 had an NOE into H-7, and H-8 into H-10, the geometry of the double bond at C-8 and C-9 should be *E*. The NOE's between H-12 and H-13 and between H-1 and H-7 were observed to suggest the *cis* orientation of H-12 and H-13. Thus, the stereostructure was established as depicted in the formula **2**. The absolute configuration was left undetermined.

Synthesis of the optically active methyl ester 2

In order to establish the absolute configuration of striatenic acid (**1**), we have planned to synthesize the optically active methyl ester **2**. We have previously reported the total synthesis of trifarienols A and B starting from the optically active keto ester **3**, which was prepared from (*R*)-pulegone through the chiral Michael addition reaction using (*S*)-(−)-phenylethylamine with high de and ee.[8] Thus, this compound is easily accessed as a starting material. The ketone **3**[8] was protected as an acetal, and the side chain was elongated with one carbon to afford ketone **6** by addition of MeLi to the corresponding carboxylic acid **5**. The triflate was derived from ketone **6** with KHMDS and triflic imide at rt for 5 days.[9–13] The mixture of *E* and *Z* enol triflate, **7*E*** and **7*Z*** (1:10), which could be separated by HPLC, was obtained in 46% yield. The *E*/*Z* isomers were



Scheme 1. (a) $HOCH_2CH_2OH$, TsOH, PhH, reflux, 1 day, 83%; (b) 10% aq. KOH, MeOH, rt, 1 h, 90%; (c) MeLi, Et_2O, 0°C, 1 h, 74%; (d) KHMDS, $PhNTf_2$, THF, rt, 5 days, 46% (*E*:*Z*=1:10); (e) $^nBu_3SnCH{=}CH_2$, $Pd(PPh_3)_4$, LiCl, THF, reflux, overnight; (f) TsOH, acetone–H_2O (5:1), rt, overnight; then SiO_2–$AgNO_3$; (g) ^{t}BuLi, $PhNTf_2$, THF, −20°C, 14 days; (h) CO, $Pd(OAc)_2$, PPh_3, NEt_3, DMF, MeOH, rt, 1 day, 21% (2 steps).

determined by the NOE experiments. The *E*/*Z* mixture was treated with $Pd(PPh_3)_4$, LiCl, and $^nBu_3SnCH{=}CH_2$ in THF under reflux to afford a mixture of dienes **8*E*** and **8*Z*** (3:1) in 95% yield. The acetal in the dienes **8*E*** and **8*Z*** was deprotected with TsOH in acetone–H_2O (5:1) to afford a mixture of ketones **9*E*** and **9*Z***, which was purified by $AgNO_3$-impregnated silica gel column chromatography to give pure **9*E*** (Scheme 1). It was very interesting to note that the pure *E*-triflate **7*E*** gave the pure *E*-diene **8*E***, while the pure *Z*-triflate **7*Z*** afforded a mixture of *E*- and *Z*-dienes, **8*E*** and **8*Z*** (*E*:*Z*=3:1, from the ^{1}H NMR spectrum). These results are presumably explained by the the isomerization of **8*Z*** into **8*E*** owing to Pd present in the mixture after the C–C bond formation. When ketone **9*E*** was treated with LDA and triflic imide in THF overnight, complete recovery of the starting ketone was observed. Thus, the triflate was derived from ketone **9*E*** by treatment with ^{t}BuLi and triflic imide in THF for 14 days. Although the yield was very low (judging from the ^{1}H NMR spectrum), the final carbonylation was carried out with $Pd(OAc)_2$, PPh_3, NEt_3, CO, and MeOH in DMF to afford ester **2** in 21% in two steps.[9–13] The spectral data of ester **2** was completely identical with those of the natural product. The specific rotation of the synthetic ester **2** was $[\alpha]_D$=+45.7 (natural one $[\alpha]_D$=+49.9). Therefore, the absolute configuration of ester **2** was established as depicted in the formula.

As a conclusion, we have isolated striatenic acid (**1**) from the liverwort *C. serpentina* and the structure was determined to have a striatane-type, a rearranged monocyclofarnesane, on the basis of 2D NMR data. Furthermore, the absolute configuration was established by synthesis of the optically active ester **2** starting from the easily accessible ketone **3**.

Experimental

General

The IR spectra were measured with a JASCO FT/IR-5300 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were taken with a Varian Unity 200 (200 MHz), a Unity 600 (600 MHz), or a JEOL JNM GX400 (400 MHz) spectrometer. The mass spectra including high resolution mass spectra were taken with a JEOL JMS AX-500 spectrometer. Chemcopak Nucleosil 50-5 (10×250 mm) was used for HPLC (JASCO pump system). Silica gel 60 (70–230 mesh, Merck) was used for column chromatography and silica gel 60 F_{254} plates (Merck) were used for TLC.

Isolation procedure

The liverwort (20.2 g) was collected at Langkawi Island, Malaysia in 1992 and was identified by Dr M. Mizutani. The voucher specimen was deposited in the herbarium of Faculty of Pharmaceutical Sciences, Tokushima Bunri University. The liverwort was pulverized and was extracted with ether to afford the extract (490.5 mg), which was separated by silica gel column chromatography (hexane–EtOAc, in gradient) to yield 5 fractions. The second fraction was further separated by silica gel chromatography (hexane–EtOAc, gradient) to afford striatenic acid (**1**) (53.2 mg). A solution of acid **1** (20 mg) in ether (2 mL) was treated with diazomethane for 1 h at 0°C. The excess diazomethane was decomposed by AcOH (0.5 mL). The reaction mixture was evaporated to give a residue (25 mg), which was purified by preparative TLC (hexane–EtOAc, 20%) to afford ester **2** (12.2 mg). **1**: $[\alpha]_D^{20}$=+43.5 (*c*=2.7, $CHCl_3$); MS (EI) *m*/*z* 234 (M^+), 153 (base), 135, 125, 107. HRMS Obs. *m*/*z* 234.1603; Calcd for $C_{15}H_{22}O_2$ 234.1620; UV (EtOH) λ_{max} nm (log ϵ): 216 (4.08), 233 (4.38); IR (FT) 3200–2500, 1682, 1634, 1271 cm^{-1}. **2**: $[\alpha]_D^{20}$=+49.9 (*c*=0.77, $CHCl_3$); MS *m*/*z* 248 (M^+), 167 (base); HRMS Obs. *m*/*z* 248.1758; Calcd for $C_{16}H_{24}O_2$ 248.1776; IR (FT) 1720 cm^{-1}.

Acetalization of keto ester 3

A mixture of keto ester **3** (2.8 g, 13 mmol), TsOH (370 mg), and ethyleneglycol (8.0 mL, 130 mmol) in PhH (310 mL) was refluxed overnight with the aid of the Dean–Stark water separator. The mixture was washed with sat. $NaHCO_3$ and brine, dried ($MgSO_4$), and was evaporated to give a residue, which was purified by silica gel column chromatography (elution with hexane–EtOAc, 20%) to afford acetal **4** (2.8 g, 83%); oil; $[\alpha]_D^{23}$=−25 (*c*=0.3, $CHCl_3$); IR (FT) 1740 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.84 (3H, d, *J*=7 Hz), 0.91 (3H, s), 3.65 (3H, s), 3.92 (4H, br s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.9 (CH_3), 16.2 (CH_3), 22.4 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 30.4 (CH_2), 30.7 (CH_2), 35.4 (CH_2), 43.3 (C), 51.4 (CH_3), 54.1 (CH_2), 113.8 (CH_2), 175.4 (C); MS (CI-CH_4) *m*/*z* 257 $(M+H)^+$, 241, 225, 195, 183, 141, 113, 99 (base); HRMS Obs. 257.1769 $(M+H)^+$. Calcd for $C_{14}H_{25}O_4$ 257.1752.

Hydrolysis of ester 4

A solution of methyl ester **4** (3.1 g, 12 mmol) in MeOH (30 mL) was treated with 10% aqueous KOH (90 mL) at rt for 1 h. Methanol was removed and the residue was extracted with ether. The aqueous layer was acidified with 1 M HCl at 0°C and the mixture was extracted with ether. The ethereal solution was washed with brine, dried ($MgSO_4$), and evaporated to afford acid **5** (2.6 g, 90%); oil; IR (FT) 3400–2400, 1700 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.84 (3H, d, *J*=6.8 Hz), 0.92 (3H, s), 3.92 (4H, br s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.8 (CH_3), 16.1 (CH_3), 22.3 (CH_2), 29.3 (CH_2), 29.7 (CH_2), 30.2 (CH_2), 30.6 (CH_2), 35.3 (CH_2), 43.3 (C), 64.0 (CH_2), 113.8 (CH_2), 181.4 (C); MS (CI-CH_4) *m*/*z* 243 $(M+H)^+$, 225, 181, 171, 141, 127, 113, 99 (base), 86; HRMS Obs. 243.1591 $(M+H)^+$, Calcd for $C_{13}H_{23}O_4$ 243.1596.

Preparation of ketone 6

A solution of acid **5** (1.5 g, 6.2 mmol) in ether (100 mL) was treated with MeLi (1.09 M in ether, 12.5 mL, 14 mmol) at 0°C for 1 h. Wet ether was added and the ether layer was separated. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to give a residue, which was purified by silica gel column chromatography (elution with hexane–EtOAc, in gradient) to afford ketone **6** (1.1 g, 74%); oil; $[\alpha]_D^{23}$=−24.2 (*c*=1.6, $CHCl_3$); IR (FT) 1710 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.84 (3H, d, *J*=6.8 Hz), 0.91 (3H, s), 2.13 (3H, s), 3.91 (4H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.8 (CH_3), 16.3 (CH_3), 22.3

(CH_2), 27.9 (CH_2), 29.7 (CH_2), 30.0 (CH_2), 30.2 (CH_2), 35.4 (CH), 40.1 (CH_3), 43.1 (C), 64.0 (C), 113.8 (CH_2), 209.9 (C); MS (CI-CH_4) *m*/*z* 241 $(M+H)^+$, 223, 209, 183 (base), 161, 141, 113, 99, 86; HRMS Obs. 241.1788 $(M+H)^+$. Calcd. for $C_{14}H_{25}O_3$ 241.1804.

Preparation of ketone 9

A mixture of ketone **6** (1.2 g, 5.0 mmol), KHMDS (0.5 M in toluene, 14.5 mL, 7 mmol), Tf_2NPh (5 g, 14 mmol), and THF (50 mL) was stirred at rt for 5 days. Aqueous NaOH solution (10%) was added at 0°C and the solvent was removed. The residue was extracted with ether and the organic layer was washed with brine, dried ($MgSO_4$), and was evaporated to give a residue, which was purified by silica gel column chromatography (elution with hexane–EtOA, 1%) to afford a mixture of **7*E*** and **7*Z*** (840 mg, 46%, 1:10); **7*E***: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.82 (3H, d, *J*=6.8 Hz), 0.95 (3H, s), 2.03 (3H, br s), 3.92 (4H, m), 5.89 (1H, t, *J*=7.4 Hz). **7*Z***: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (3H, d, *J*=7 Hz), 0.94 (3H, s), 2.05 (3H, br s), 3.90 (4H, m), 5.62 (1H, t, *J*=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8 (CH_3×2), 19.8 (CH_3), 22.5 (CH_2), 29.9 (CH_2), 30.2 (CH_2), 30.6 (CH_2), 36.2 (CH), 44.4 (C), 64.1 (CH_2), 64.2 (CH_2), 113.3 (C), 120.7 (CH), 143.9 (C). A solution of a mixture of triflates **7*E*** and **7*Z*** (657 mg, 1.9 mmol) in THF (50 mL) was treated with LiCl (240 mg, 6.0 mmol), $Pd(PPh_3)_4$ (2 mol%), and ^{n}$Bu_3SnCH{=}CH_2$ (0.72 mL, 2.6 mmol) under reflux overnight. Aqueous ammonia (28%) was added and the solvent was removed. The residue was extracted with ether and the organic layer was washed with brine, dried ($MgSO_4$), and was evaporated to give a residue, which was purified by silica gel column chromatography (elution with hexane–EtOAc, 2%) to afford dienes **8*E*** and **8*Z*** (450 mg, 95%, 3:1). The mixture of dienes **8*E*** and **8*Z*** (400 mg) was treated with TsOH (10 mg) in acetone (50 mL) and H_2O (10 mL) at rt overnight. The solvent was evaporated and the residue was extracted with ether. The organic layer was washed with sat. $NaHCO_3$ and brine, dried ($MgSO_4$), and was evaporated to give a residue, which was purified by silica gel column chromatography to afford dienes (263 mg). This sample was further purified by $AgNO_3$-impregnated silica gel column chromatography (elution with hexane–EtOAc, 0–15%) to give pure **9*E*** (37.2 mg, 12%) and a mixture of **9*E*** and **9*Z*** (39.9 mg).[14]

9*E*: $[\alpha]_D^{20}=-12.2$ (*c*=1.0, $CHCl_3$); IR (FT) 1720 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91 (3H, d, *J*=6.8 Hz), 1.02 (3H, s), 1.76 (3H, br s), 4.93 (1H, d, *J*=10 Hz), 5.08 (1H, d, *J*=18 Hz), 5.40 (1H, t, *J*=6 Hz), 6.35 (1H, dd, *J*=18 Hz, 10); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.0, 15.7, 19.1, 24.2, 29.2, 34.8, 38.4, 38.6, 52.7, 110.6, 135.2, 138.5, 141.5, 215.3; MS (EI) *m*/*z* 206 (M^+), 191, 163, 149, 135, 126, 111, 93, 81 (base), 69, 55; HRMS Obs. 206.1653 (M^+). Calcd for $C_{14}H_{22}O$ 206.1670.

Reaction of pure 7*E*

A solution of pure **7*E*** (24 mg, 0.06 mmol), ^{n}$Bu_3SnCH{=}CH_2$ (0.025 mL, 1.3 equiv.), $Pd(PPh_3)_4$ (1.3 mg, 2 mol%), and LiBr (7.6 mg, 3 equiv.) in THF (2 mL) was heated under reflux overnight. Work-up as above afforded a residue (49.8 mg), which was purified by silica gel chromatography (hexane–EtOAc, 2%) to give pure **8*E*** (12 mg, 80%).

Reaction of pure 7*Z*

A solution of **7*Z*** (50 mg, 0.16 mmol), ^{n}$Bu_3SnCH{=}CH_2$ (0.08 mL, 0.24 mmol, 1.5 equiv.), $Pd(PPh_3)_4$ (10 mg, 5 mol%), and LiBr (20 mg, 0.48 mmol, 3 equiv.) in THF (5 mL) was heated under reflux overnight. Work-up as above afforded a residue, which was purified by silica gel chromatography (hexane–EtOAc, 2%) to give a mixture of **8*E*** and **8*Z*** (38.1 mg, 95%, 3:1).

Preparation of methyl striatenate 2

A solution of ketone **9*E*** (37 mg, 0.18 mmol) in THF (3.5 mL) was treated with *t*BuLi (1.6 M, 0.4 mL, 0.54 mmol) and Tf_2NPh (190 mg, 0.54 mmol) at −20°C for 14 days. After 10% NaOH aq. was added, the solvent was evaporated and the residue was extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$), and was evaporated to give crude triflate **10** (149.3 mg); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92 (3H, d, *J*=7 Hz), 1.04 (3H, s), 1.55 (3H, br s), 4.97 (1H, d, *J*=10 Hz), 5.12 (1H, d, *J*=18 Hz), 5.36 (1H, t, *J*=6 Hz), 5.79 (1H, t, *J*=4 Hz), 6.38 (1H, dd, *J*=18, 10 Hz). A mixture of crude triflate **10** (166 mg), PPh_3 (180 mg, 0.7 mmol), $Pd(OAc)_2$ (70 mg, 0.3 mmol), DMF (1 mL), NEt_3 (0.2 mL, 1.4 mmol), and MeOH (2 mL) was stirred at rt under CO atmosphere overnight. Water was added and the mixture was extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$), and was evaporated to give a residue. The residue was purified by silica gel column chromatography (elution with hexane–EtOAc, 2%) to afford a crude product (149.3 mg), which was further purified by HPLC (Nucleosil 50-5, 10×250 mm, hexane–EtOAc 10%) to afford pure methyl striatenate (**2**) (9.2 mg, 21% from **9*E***); $[\alpha]_D^{25}=+45.7$ (*c*=0.9, $CHCl_3$); IR (FT) 1720 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89 (3H, d, *J*=6.8 Hz), 1.16 (3H, s), 1.72 (3H, s), 2.15 (2H, m), 2.40 (1H, dd, *J*=14.6, 8.3 Hz), 2.75 (1H, dd, *J*=14.6, 6.3 Hz), 3.68 (3H, s), 4.89 (1H, d, *J*=10.6 Hz), 5.04 (1H, d, *J*=17.2 Hz), 5.26 (1H, t, *J*=6.3 Hz), 6.34 (1H, dd, *J*=17.2, 10.6 Hz), 6.91 (1H, t, *J*=4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.9, 15.7, 21.0, 25.6, 25.9, 34.6, 35.0, 40.1, 51.2, 110.3, 130.1, 135.1, 137.4, 140.8, 141.9, 167.9; MS (EI) *m*/*z* 248 (M^+), 217, 189, 167, 135 (base), 107, 93, 79.

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