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New eremophilanes from *Farfugium japonicum*

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ABSTRACT

Eighteen new eremophilanes (dimeric lactones, lactams, carboxylic acid, methyl ester, tetranor- and dinor-ketones, furanoeremophilane, enoleremophilanolide, epoxyeremophilanolide, and hydroxy- or methoxyeremophilanolides) have been isolated from the methanol extract of fresh rhizomes of *Farfugium japonicum* (Compositae), and their structures have been determined on the basis of high-resolution 2D NMR and X-ray crystallographic analyses as well as by chemical transformations.

1. Introduction

Four epoxyeremophilanes from the fresh rhizomes of *Petasites japonicus* have been reported[1] and, more recently, two new lactones with an enol lactone unit and an epoxide at C-7 and C-8 positions have been reported from the fresh rhizomes of the closely related *Farfugium japonicum*.[2] In continuation of these study on the chemical constituents from the same plant, further eighteen new eremophilanes (including nor-type) have been isolated, and their structures determined on the basis of extensive spectroscopic analyses as well as X-ray crystallography and by chemical transformations. The first report of the eremophilane dimer was made by Bohlmann in 2004.[3] Since then, seven dimers of eremophilane-type sesquiterpenes have been reported.[4–10] Recently advances in isolation and detection, predominately through high-resolution 2D NMR methodologies have made possible the identification of dimeric compounds. There are now three examples of eudesmane-type sesquiterpene dimers.[11–13] Baldwin studied the mechanism of formation of such dimers in detail to clarify the radical mechanism.[14] We have been studying the chemical constituents of *Farfugium*,[2] *Petasites*,[1] *Eupatorium*,[15] and *Ligularia*,[16] belonging to Compositae and have found various compounds described in Baldwin's report.[14] Now, recent reports[4–10] have prompted us to report three new dimeric eremophilanolides, one of which has been characterized by X-ray crystallography, lactams, norketones, and other eremophilanolides.

2. Results and discussion

The EtOAc soluble part of the MeOH extract from fresh *F. japonicum* rhizomes collected in Tokushima Prefecture was fractionated by silica gel column chromatography, followed by Sephadex LH-20 and HPLC to isolate eremodimers A (**1**), B (**2**), and C (**3**), eremolactams A (**4**) and B (**5**), eremofarfuginoic acid (**6**), and methyl eremofarfuginoate (**7**), noreremophilanes **8** and **9**, furanoeremophilane **10**, six lactones **11**–**16**, eremopharfugin A (**17**),[2] and eremopetasitenin B_3 (**18**)[2] (Fig. 1), as well as 15 known compounds **19**–**33** (Fig. 2).

In eremodimer A (**1**), $C_{40}H_{50}O_8$, the angeloyl moiety was rapidly identified from the ^{1}H NMR spectrum, because the signals of a proton at δ 6.07 (qq, J=7.1, 1.6 Hz, H-3′) and two methyl groups at δ 1.90 (quint, J=1.6 Hz, H-5′) and δ 2.02 (dq, J=7.1, 1.6 Hz, H-4′) were observed. The presence of the double bond between C-9 and C-10 was inferred from the HMBC spectrum as shown in Figure 3. The connectivity between H-3 and C-1′ was also revealed in the HMBC spectrum. The ^{1}H NMR spectrum of **1** was highly similar to that of known compound **19**[17] except that the proton at δ 5.62 in **19** is shifted to δ 5.73 in **1**, and that the coupling pattern changed from triplet (J=1.9 Hz) to doublet (J=1.4 Hz). A further difference in **1** was seen in the absence of the proton attributable to H-8 at δ 5.17 in **19**. Therefore, the carbon at C-8 must be quaternary, while no functional group appeared to be connected to C-8. The FABMS spectrum clearly showed a quasi-molecular ion peak at m/z 659 $[M+H]^+$, as well as 681 $[M+Na]^+$. Therefore, it should be the symmetric dimer of compound **19** connected at C-8. The ^{13}C NMR spectrum of **1** showed C-8 at δ 86.6 as a singlet, while C-8 of **19** appeared at δ 78.2

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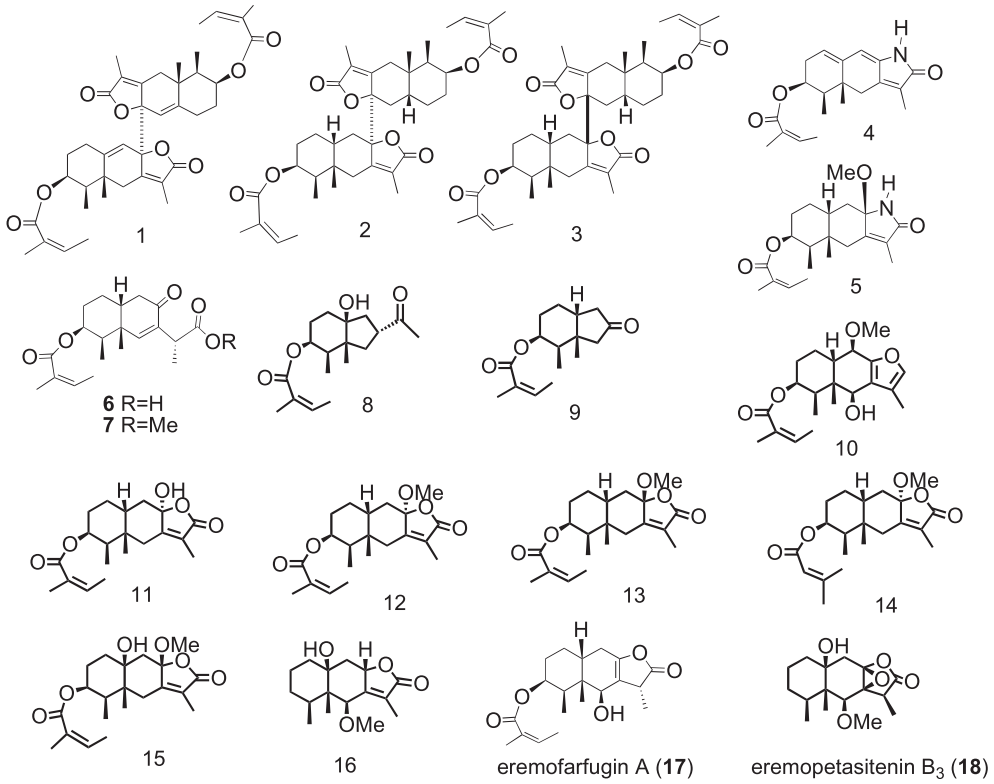

Figure 1. New compounds isolated from *F. japonicum*.

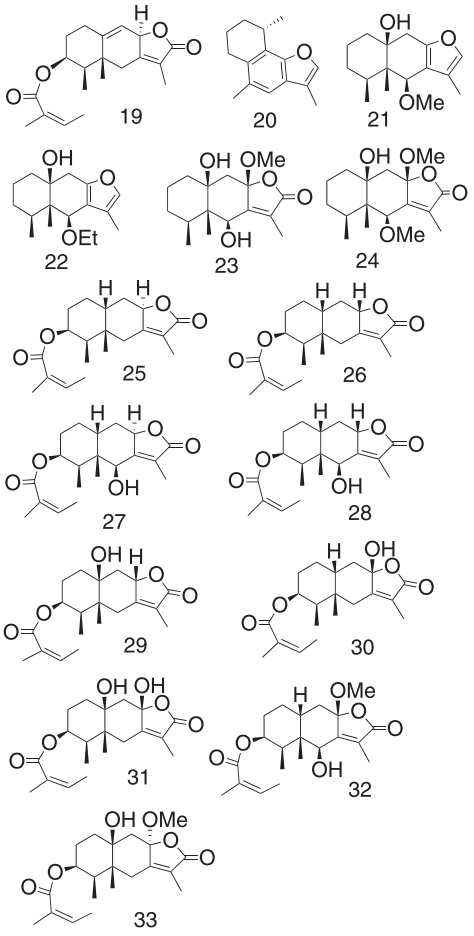

Figure 2. Known compounds isolated from *F. japonicum*.

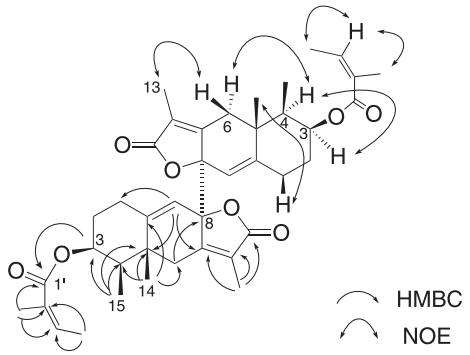

Figure 3. Major HMBC and NOE correlations detected for eremodimer A (**1**).

(Table 1). The stereochemistry was established from the NOESY spectrum (Fig. 3). The cis arrangement of the two methyl groups and the angeloyl moiety was determined by the presence of NOEs between H-3 and H-4, H-4 and H-6α, H-6 β and H-13, H-14 and H-1β, H-3′ and H-4′, and H-3′ and H-5′. Although the NOE between the monomeric units was not observed, the configuration at the C-8 position should be α. If the C-8 position is β,[1,2] the NOEs should not have been observed as indicated in Figure 3. Thus, the total structure was established as depicted in the formula.

The ^{1}H NMR spectra of eremodimers B (**2**), $C_{40}H_{50}O_8$ (HRMS), and C (**3**), $C_{40}H_{50}O_8$ (HRMS), were very similar to each other. Both have an angeloyl moiety (δ 6.04 (H-3′) for **2**, δ 6.05 (H-3′) for **3**) and an oxymethine proton at δ 5.04 and 5.01 (H-3), respectively. The singlet and doublet methyl groups for **2** appeared at δ 1.02 and 1.00, while those for **3** appeared at δ 1.25 and 0.85, respectively. The IR spectra for both compounds showed the presence of lactone and ester groups. However, the oxymethine proton at C-8 was not found, instead the ^{13}C NMR signals appeared at δ 90.7 and 88.1 in **2**

Table 1
^{13}C NMR data for compounds **1**–**7** and **19** (150 MHz, in $CDCl_3$)

No.	19	1	2	3	4	5	6	7
1	27.3	27.9	21.9	21.6	124.2	21.9	24.6	24.7
2	31.2	31.4	25.2	24.8	32.0	25.4	25.9	26.0
3	72.7	73.0	73.0	73.0	71.6	73.0	72.7	72.9
4	45.8	45.2	40.1	32.6	41.2	32.2	41.3	41. 6
5	44.8	45.4	41.4	40.7	37.1	39.4	40.0	39.9
6	38.2	38.5	38.9	36.6	35.5	35.5	154.8	153.8
7	158.5	160.4	164.1	162.7	140.0	151.4	136.5	137.1
8	78.2	86.6	90.7	88.1	135.2	88.6	198.2	197.4
9	117.7	117.2	33.0	37.8	109.8	39.2	39.9	39.9
10	148.8	151.5	36.2	37.8	140.2	37.5	36.2	36.0
11	121.7	123.7	124.8	123.9	125.8	128.7	38.6	38.2
12	174.3	172.6	173.1	172.8	173.2	172.6	176.9	174.9
13	8.2	8.6	8.8	8.8	8.2	8.6	15.8	16.1
14	20.7	21.1	24.7	24.5	20.6	24.1	24.6	24.7
15	11.8	11.8	12.4	12.1	12.2	12.8	8.8	8.6
1′	167.3	167.3	167.3	167.3	167.9	167.3	167.3	167.2
2′	127.6	127.7	127.8	127.8	127.9	127.7	127.9	128.0
3′	138.8	138.8	138.4	138.4	138.2	138.8	138.1	137.8
4′	15.7	15.7	15.7	15.6	15.7	15.7	15.8	15.7
5′	20.8	20.8	20.8	20.9	20.9	20.8	20.7	20.7
OMe	—	—	—	—	—	49.4	—	52.1

and **3**, respectively, as singlets. These values were rather down field compared with that of **1** (δ 78.2). From the careful analysis of 2D NMR spectra, it was concluded that these two compounds should be dimers of the corresponding monomeric eremophilanolides at the C-8 position (Figs. 4 and 6). In each case the NOESY spectrum

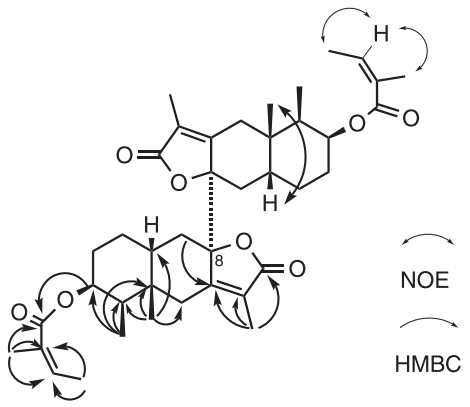

Figure 4. Major HMBC and NOE correlations detected for eremodimer B (**2**).

indicated that rings A and B were in a cis arrangement. Other NOE's from the monomeric parts only suggest the connection at C-8 to be in the β orientation. This may be because the conformation of either compound is distorted due to steric hindrance, and thus no correlation, indicating the correct stereochemistry was seen. Fortunately, eremodimer B (**2**) crystallized form EtOAc and its structure was solved by X-ray crystallography[18] to show α-orientation at the C-8 position as depicted in Figures 4 and 5. Therefore, eremodimer C (**3**) should be substituted at C-8 in the β-orientation (Fig. 6). The conformation of this compound was deduced to be as shown in Figure 7, as calculated by CONFLEX.[19] The angeloyl moiety also adopted the β-orientation in compound **3**. The H-3 appeared at 5.01 ppm with the coupling pattern of a triplet of doublets (J=3.7, 3.0 Hz), indicating it is the equatorial proton. While in compound **2**, ring A was distorted and the H-3 appeared at δ 5.04 as a quartet (J=3.0 Hz), also indicating it to be the equatorial proton. Owing to this phenomenon, it was not easy to distinguish the geometry of these compounds only by the NOESY spectrum.

These compounds may be formed by coupling of the corresponding monomeric counterpart as proposed by Baldwin et al.[14] and thus both isomers **2** and **3** indirectly support this hypothesis as the biogenetic sequence. Furthermore, Baldwin described a monoepoxy-lactone[1,2] and an enol-lactone,[1,2] both of which were isolated from the plants studied by us as mentioned above.

The nitrogen atom of eremolactam A (**4**), $C_{20}H_{25}O_3N$ (determined by HRMS), was attributed to an amide (3500, 3200, 1680 cm^{-1}). The molecule was deduced to be tricyclic, because there were four double bonds and an ester as well as an amide bond in the molecule from the ^{1}H and ^{13}C NMR spectra (Table 1) giving a degree of unsaturation of nine. The amide proton had correlations between the C-7, 8, 9, 11, and 12 in the HMBC spectrum as shown in Figure 8. The presence of an angeloyl group was revealed by the ^{1}H NMR spectrum and the position of substitution was indicated at C-3 by the HMBC spectrum. The H-3 proton appeared at δ 5.21 and its coupling pattern was not clearly axial or equatorial. The pattern was ddd with J=5.8, 1.6, and 1.1 Hz. The most stable conformation was calculated using CONFLEX[19] and the result is shown in Figure 9. Ring A is slightly distorted and the proton at the C-3 position is not equatorial. However, the NOE correlations are shown in Figure 9 and the stereochemistry has been assigned as indicated.

The characteristics of the ^{1}H NMR spectrum of eremolactam B (**5**), $C_{21}H_{31}O_4N$, are similar to known eremophilanes. However, the ^{13}C chemical shift of the C-8 position (δ 88.7) is at a higher field than a typical carbon which is attached to two oxygen atoms (Table 1).

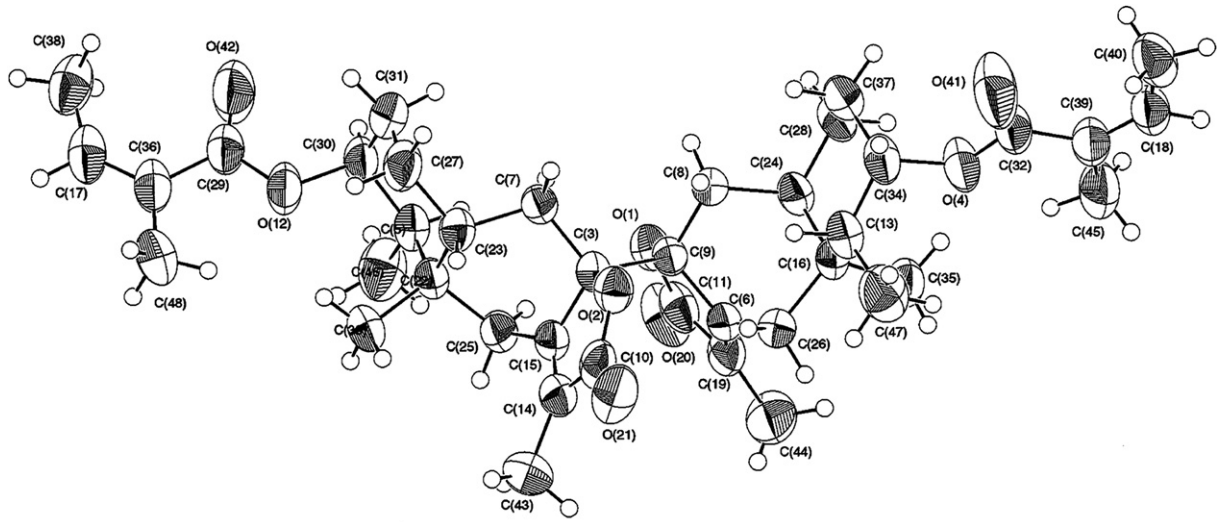

Figure 5. ORTEP drawing of eremodimer B (**2**).

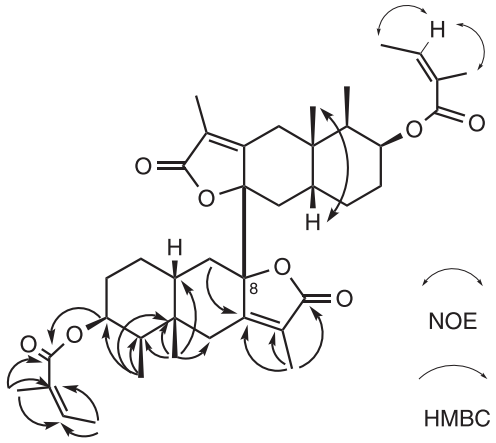

Figure 6. Major HMBC and NOE correlations detected for eremodimer C (**3**).

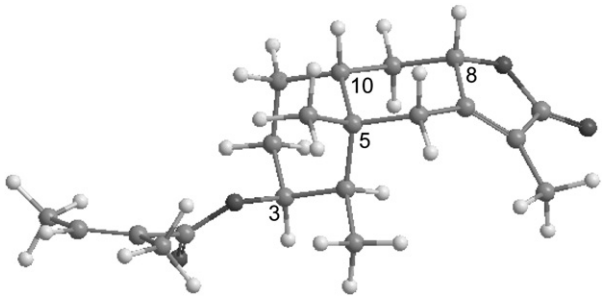

Figure 7. The conformation of eremodimer C (**3**). The C-8 atom has been replaced with H for clarity.

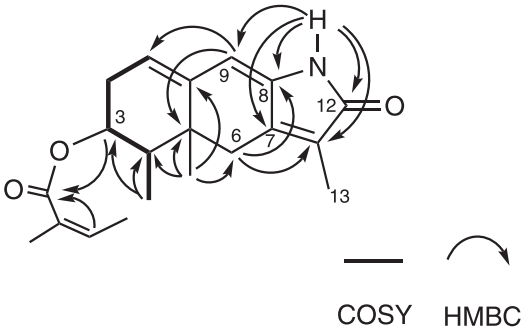

Figure 8. Major HMBC and COSY correlations detected for eremolactam A (**4**).

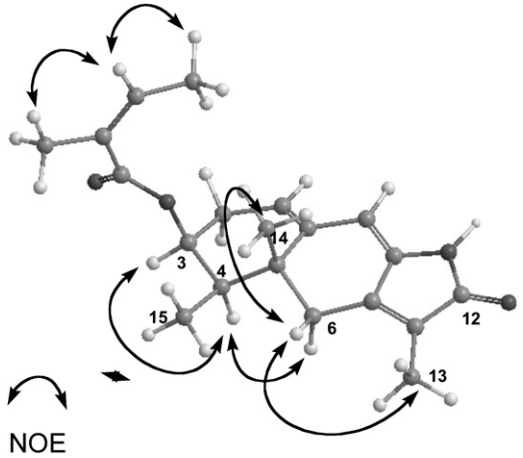

Figure 9. Major NOE correlations detected for eremolactam A (**4**).

From this observation and other 2D NMR evidence, it was determined to be a lactam as depicted in Figure 10. The angeloyl moiety was substituted at the C-3 position indicated by the HMBC spectrum. The stereochemistry was established by the NOESY spectrum to have the A/B cis ring system (Fig. 11). The CD spectrum showed the positive Cotton effect at 254 nm ($\Delta\epsilon$ +5.1), which was similar to those of known 8βH- or 8β-OMe substituted eremophilenolides.[20] Therefore, the absolute configuration of **5** was established as depicted in Figure 11.

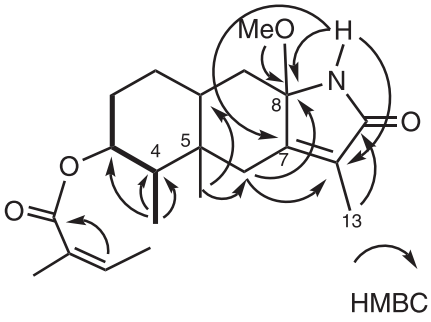

Figure 10. Major HMBC correlations detected for eremolactam B (**5**).

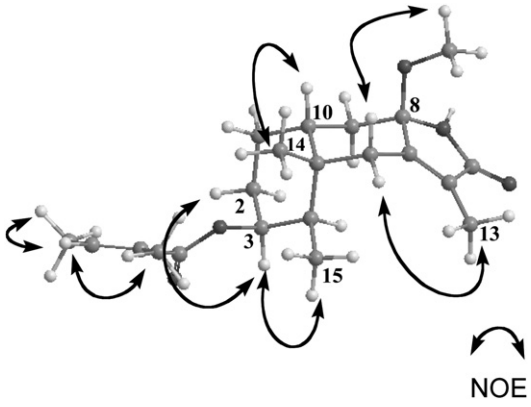

Figure 11. Major NOE correlations detected for eremolactam B (**5**).

The IR spectrum of the eremofarfuginoic acid (**6**), $C_{20}H_{28}O_5$, showed the presence of carboxyl (3600–2600 cm^{-1}), ester (1730 cm^{-1}), and enone (1710 and 1680 cm^{-1}) groups. Methyl eremofarfuginoate (**7**), $C_{21}H_{30}O_5$ (by HRMS), exhibited absorptions at 1740, 1710, and 1680 cm^{-1} in the IR spectrum. The ^1H NMR spectra of **6** and **7** were very similar to each other. Therefore, the acid **6** was treated with TMS diazomethane in ether/methanol to afford methyl ester **7**, the spectral data of which were identical to the natural product. The HMBC spectrum of **7** showed the connectivities as shown in Figure 12. Although the long-range connectivity between H-3 and C-1′ was not indicated in the HMBC spectrum, it does suggest that the angeloyl group is attached at the C-3 position, because it indicates the oxygen function is attached at

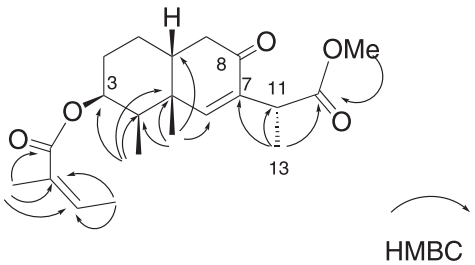

Figure 12. Major HMBC correlations detected for methyl eremofarfuginoate (**7**).

C-3. The configuration of the doublet methyl group at the C-11 position, however, cannot be determined from these data.

Eremopetasitenin A (**17**),[2] one of the new compounds isolated in this plant, must be biogenetically closely related with compound **7**. Therefore, eremopetasitenin A (**17**) was treated with TsOH to hydrolyze the enol-lactone. The compound produced was treated with diazomethane to afford the methyl ester, whose spectral data were identical with those of methyl eremofarfuginoate (**7**) (Fig. 13). The configuration at the C-11 position was established to be *R*. Fortunately, compound **7** crystallized and this stereochemistry was confirmed by X-ray crystallography (Fig. 14).[18]

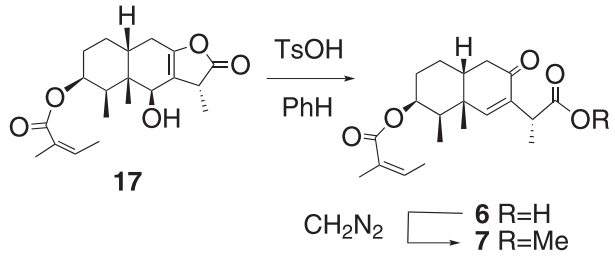

Figure 13. Chemical correlation of compound **17** with eremofarfuginoic acid (**6**) and methyl eremofarfuginoate (**7**).

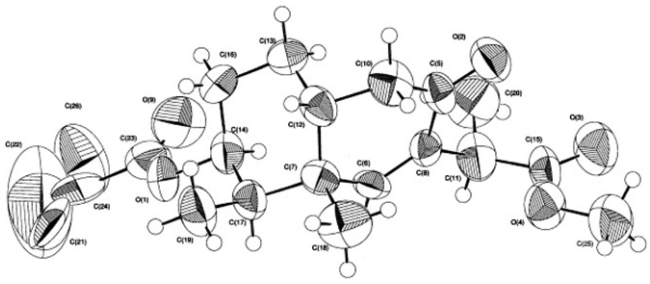

Figure 14. ORTEP drawing of methyl eremofarfuginoate (**7**).

The MS spectrum of compound **8** showed a molecular ion peak at *m*/*z* 302 and its molecular formula was determined to be $C_{18}H_{28}O_4$. The ^{13}C NMR spectrum exhibited only 18 peaks, among them an angeloyl moiety as well as a carbonyl group. This gave a degree of unsaturation of five, and thus has a bicyclic nor type skeleton. The HMBC spectrum indicated the six and five-membered skeleton as shown in Figure 15. The stereochemistry was deduced from the NOESY spectrum (Fig. 15). Similar compounds have been reported previously (vide infra).

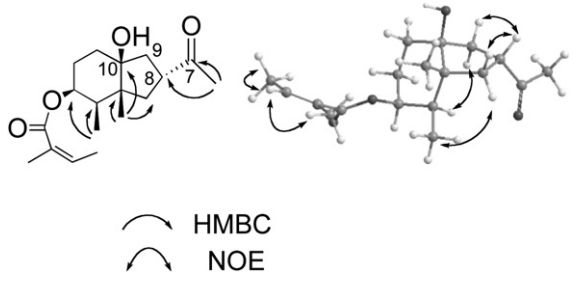

Figure 15. Major HMBC and NOE correlations detected for compound **8**.

Compound **9** had a quasi-molecular ion peak at *m*/*z* 265. The molecular formula has two carbons less than compound **8**. Namely, there is no acetyl group in this compound. The 2D NMR spectra indicated the structure shown in Figure 16. The bicyclic hydrindanone is fused in a cis arrangement. It is worth mentioning that for compounds **8** and **9** some of the carbon signals are quite broad in

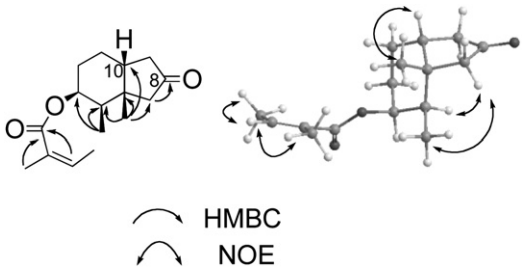

Figure 16. Major HMBC and NOE correlations detected for compound **9**.

$CDCl_3$. Assigning these signals revealed that C-1, 5, 9, 10, and 14 were broadening for both compounds. This is presumably due to slow inversion of the five-membered ring, although the NOEs were clearly observed between H-10 and H-14, H-4α and 6α, as well as H-15 and 6α (for compound **9**). These phenomena are sometimes observed in similar compounds. Because the CD spectrum showed the negative Cotton effect at 297 nm ($\Delta\epsilon$ −1.7), the absolute configuration of **9** was established as depicted in Figure 16.

Compound **10** has a furan, an angeloyl and a methoxyl group as judged by the ^1H and ^{13}C NMR spectra as well as the IR spectrum. The HMBC spectrum suggested the position of the methoxyl group to be at C-9, and the hydroxy group at C-6 (Fig. 17). Rings A and B are cis to each other, and the configurations of the hydroxy and methoxyl groups were both determined to have a β orientation as indicated in Figure 17.

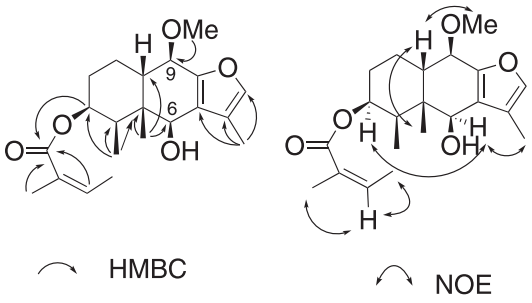

Figure 17. Major HMBC and NOE correlations detected for compound **10**.

Lactones **11**–**16** were all A/B cis and either 8α or 8β configuration. As already discussed, these compounds, tend to adopt the conformation indicated in Figures 18 and 19, which was supported by the NOEs as indicated by the arrows. Therefore, compounds **11**–**16** were easily identified as 8α-OH for **11**, 8α-OMe for **12**, 8β-OMe for **13**, 8α-OMe for **14**, 8β-OMe for **15**, and 8β-H for **16**. Compound **16** has no oxygen function at the C-3 position, but there is an angeloyl group at the C-3 position for all the others except for compound **14**. Compound **14** had a senecioyl group[21] at the C-3 position, which has two methyl groups with long-range coupling attached to the sp^2 carbon as well as an olefinic proton with long-range coupling.

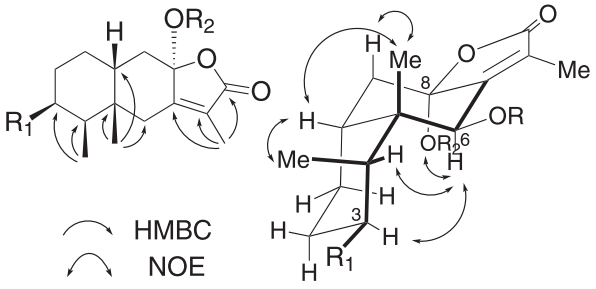

Figure 18. Major HMBC and NOE correlations detected for compounds **11**, **12**, and **14**.

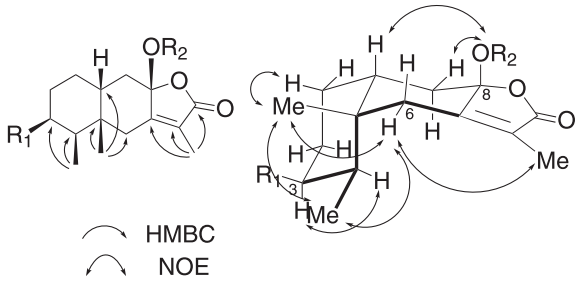

Figure 19. Major HMBC and NOE correlations detected for compounds **13**, **15**, and **16**.

Compound **15** crystallized from a EtOAc/hexane mixture, and the structure was solved by X-ray analysis. An ORTEP drawing is shown in Figure 20.[18] The CD spectrum shows the positive Cotton effect at 253 nm ($\Delta\epsilon$ +7.6), which is similar to those of known compounds, 8β-hydroxyeremophil-7(11)-en-12,8α-olide (242 nm, $\Delta\epsilon$ +9), and 8βH-eremophil-7(11)-en-12,8α-olide (227 nm, $\Delta\epsilon$ +5).[20] Therefore, the absolute configuration was the same as those of known compounds.

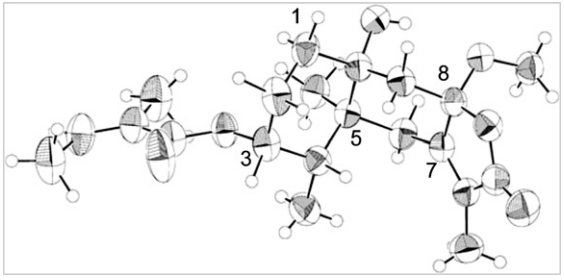

Figure 20. ORTEP drawing of compound **15**.

Preliminary reports on compounds **17** and **18** have already been published.[2] The known compounds **19**–**33**[17,22–30] were also identified in this extract (Fig. 2).

3. Conclusion

In conclusion, 18 new eremophilanes have been isolated: eremodimers A (**1**), B (**2**), and C (**3**) are examples of dimers of eremophilane-type sesquiterpenes, although dimeric compounds with eremophilane skeleton have been reported previously.[3–10] Two lactams, eremolactams A (**4**) and B (**5**) are only the fourth and fifth examples of lactams in eremophilane-type sesquiterpenes.[31–33] The seco-type of eremophilanes has previously been reported,[34–37] but the stereochemistry at the C-11 position was left undetermined. We have established the whole structure of the eremofarfuginoic acid (**6**) and methyl eremofarfuginoate (**7**) by use of X-ray crystallographic analysis and chemical transformation. Several dinor- and tetranor-type sesquiterpenoids are known[37–39] and they are biosynthetically related to compounds **6** and **7**. Various lactones were isolated as well as one example of a furanoeremophilane. *F. japonicum* is a rich source of eremophilane sesquiterpenoids, including seco-, dimeric-, and lactam-type compounds, all of which are genuine natural products found in this plant. Our discovery of the symmetrical dimers supports the Baldwin hypothesis as the biogenetic sequence. The absolute configurations of some new compounds were determined using the CD spectra by comparing with those of known compounds. The eremophilane sesquiterpenoids isolated from higher plants are believed to have the absolute configuration with *vic*-methyl groups in the β configuration as depicted in the formula.[16e,20,40]

4. Experimental

4.1. General procedure

Specific rotations and CD spectra were measured on a JASCO DIP-1000 and a JASCO J-725 auto recording polarimeter; IR spectra, on a JASCO FT/IR-5300 spectrophotometer; ^{1}H and ^{13}C NMR spectra, on a Varian Unity 600 (600 MHz and 150 MHz, respectively) and a JEOL ECP 400 (400 MHz and 100 MHz, respectively) spectrometer. Mass spectra, including high-resolution data, were recorded on a JEOL JMS-700 MStation. X-ray crystallographic analysis was carried out on a Mac Science MXC 18 diffractometer using a DIP image plate. Chemcopak Nucleosil 50–5 (4.6×250 mm) with a solvent system of hexane/ethyl acetate was used for HPLC (JASCO pump system). Silica gel 60 (70–230 mesh, Fuji Silysia) was used for column chromatography. Silica gel 60 F_{254} plates (Merck) were used for TLC.

4.2. Extraction and isolation

The EtOAc soluble fraction (52 g) of the MeOH extract (279 g) from the fresh rhizomes of *F. japonicum* (8.05 kg) collected in Tokushima Prefecture was separated by silica gel column chromatography, followed by Sephadex LH-20 ($CHCl_3$/MeOH, 1:1) and HPLC (Nucleosil 50–5, hexane/EtOAc or $CHCl_3$/EtOAc) to isolate eremodimers A (**1**) (9.9 mg), B (**2**) (1.4 mg), and C (**3**) (4.4 mg), eremolactams A (**4**) (19.0 mg) and B (**5**) (6.5 mg), eremofarfuginoic acid (**6**) (14.9 mg), and methyl eremofarfuginoate (**7**) (19.9 mg), **8** (1.5 mg), **9** (12.5 mg), **10** (66.4 mg), **11** (47.3 mg), **12** (10.3 mg), **13** (5.7 mg), **14** (1.4 mg), **15** (4.4 mg), **16** (2.4 mg), **17** (5.6 mg), **18** (30.1 mg), **19**[17] (25.3 mg), **20**[21] (9.4 mg), **21**[22] (902.3 mg), **22**[23] (20.3 mg), **23**[24] (11.0 mg), **24**[25] (49.6 mg), **25**[26] (406.1 mg), **26**[27] (20.9 mg), **27**[26] (375.7 mg), **28**[27] (172.2 mg), **29**[25] (19.8 mg), **30**[27] (78.3 mg), **31**[28] (10.3 mg), **32**[29] (1.9 mg), and **33**[24] (44.6 mg).

*4.2.1. Compound **1**.* Solid. $[\alpha]_D^{21}$ +88.4 (*c* 0.93, $CHCl_3$); FABMS *m*/*z* 681 $[M+Na]^+$, 659 $[M+H]^+$; HRFABMS obsd *m*/*z* 659.3592 $[M+H]^+$ (calcd for $C_{40}H_{51}O_8$: 659.3584); IR (KBr) cm^{-1}: 1760, 1710, 1650; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.01 (3H, d, *J*=7.1 Hz, 15-H), 1.04 (3H, s, 14-H), 1.79 (3H, d, *J*=1.1 Hz, 13-H), 1.80 (1H, m, 2α-H), 1.90 (3H, quint, *J*=1.6 Hz, 5′-H), 2.02 (3H, dq, *J*=7.1, 1.6 Hz, 4′-H), 2.04 (1H, m, 4-H), 2.08 (1H, m, 2β-H), 2.11 (1H, m, 1α-H), 2.47 (1H, td, *J*=14.3, 3.3 Hz, 1β-H), 2.30 (1H, br d, *J*=12.9 Hz, 6α-H), 5.15 (1H, q, *J*=2.7 Hz, 3-H), 5.73 (1H, d, *J*=1.4 Hz, 9-H), 6.07 (1H, qq, *J*=7.1, 1.6 Hz, 3′-H); ^{13}C NMR ($CDCl_3$) in Table 1.

*4.2.2. Compound **2**.* Colorless crystals; mp 258–262 (EtOAc); $[\alpha]_D^{21}$ +54.9 (*c* 0.43, $CHCl_3$); CIMS *m*/*z* 663 $[M+H]^+$, 333, 233 (base); HRCIMS obsd *m*/*z* 663.3880 (calcd for $C_{40}H_{55}O_8$: 663.3897); IR (KBr) cm^{-1}: 1760, 1710, 1680, 1650; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.00 (3H, d, *J*=6.9 Hz, 15-H_3), 1.02 (3H, s, 14-H_3), 1.20 (1H, br d, *J*=14.4 Hz, 10-H), 1.30 (1H, m, 1α-H), 1.66 (1H, tt, *J*=14, 2.8 Hz, 2α-H), 1.76 (3H, d, *J*=0.6 Hz, 13-H_3), 1.77 (1H, br d, *J*=14 Hz, 2β-H), 1.88 (3H, quint., *J*=1.5 Hz, 5′-H), 1.92 (1H, m, 1β-H), 1.93 (1H, dd, *J*=14, 3.3 Hz, 9β-H), 2.00 (3H, dq, *J*=7.1, 1.5, 0.6 Hz, 4′-H), 2.06 (1H, qd, *J*=6.9, 3.0 Hz, 4-H), 2.28 (1H, br d, *J*=13.2 Hz, 6α-H), 2.41 (1H, d, *J*=13.2 Hz, 6β-H), 2.69 (1H, t, *J*=14 Hz, 9α-H), 5.04 (1H, q, *J*=3.0 Hz, 3-H), 6.04 (1H, qq, *J*=7.1, 1.5 Hz, 3′-H); ^{13}C NMR ($CDCl_3$) in Table 1.

*4.2.3. Compound **3**.* Solid. $[\alpha]_D^{21}$ +90.0 (*c* 0.19, $CHCl_3$); CIMS *m*/*z* 663 $[M+H]^+$, 391, 279, 57 (base); HRCIMS obsd *m*/*z* 663.3901 (calcd for $C_{40}H_{55}O_8$: 663.3897); IR (KBr) cm^{-1}: 1760, 1710, 1680, 1650; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.85 (3H, d, *J*=7.0 Hz, 15-H_3), 1.25 (3H, s, 14-H_3), 1.28 (1H, m, 1α-H), 1.40 (1H, qd, *J*=7.0, 3.7 Hz, 4-H), 1.63 (1H, m, 2-H), 1.66 (1H, m, 2-H), 1.68 (1H, m, 6β-H), 1.70 (1H, m, 9α-H), 1.78 (3H, d, *J*=1.0 Hz, 13-H_3), 1.90 (3H, quint., *J*=1.4 Hz, 5′-H), 1.99

(3H, dq, J=7.1, 1.4 Hz, 4′-H), 2.06 (1H, tt, J=13.5, 3.7 Hz, 1β-H), 2.52 (1H, m, 9β-H), 2.71 (1H, d, J=13.7 Hz, 6α-H), 5.01 (1H, td, J=3.7, 3.0 Hz, 3-H), 6.05 (1H, qq, J=7.4, 1.4 Hz, 3′-H); ^{13}C NMR ($CDCl_3$) in Table 1.

4.2.4. Compound ***4***. Oil; $[\alpha]_D^{22}$ +58.1 (*c* 1.3, $CHCl_3$); CIMS (CH_4) *m/z* 328 $[M+H]^+$, 256, 244, 228 (base); HRCIMS (CH_4) obsd *m/z* 328.1898 $[M+H]^+$ (calcd for $C_{20}H_{26}O_3N$: 328.1912); IR (KBr) cm^{-1}: 3500, 3200, 1710, 1680; ^{1}H NMR ($CDCl_3$) δ 1.12 (3H, d, J=7.1 Hz, 15-H_3), 1.16 (3H, s, 14-H_3), 1.87 (3H, quint, J=1.4 Hz, 5′-H_3), 1.89 (3H, d, J=1.9 Hz, 13-H_3), 1.96 (1H, qd, J=7.1, 2.7 Hz, 4α-H), 1.99 (3H, dq, J=7.4, 1.4, 4′-H_3), 2.18 (1H, br d, J=15.9 Hz, 6α-H), 2.43 (1H, dd, J=20.9, 4.8 Hz, 2β-H), 2.66 (1H, ddd, J=20.9, 5.5, 3.3 Hz, 2α-H), 2.82 (1H, d, J=15.9 Hz, 6β-H), 5.21 (1H, ddd, J=5.8, 1.7, 1.1 Hz, 3α-H), 5.63 (1H, t, J=4.1 Hz, 1-H), 5.86 (1H, s, 19-H), 6.04 (1H, qq, J=7.4, 1.4 Hz, 3′-H), 7.93 (1H, br s, NH); CD ($CHCl_3$) [θ] +7400 (257 nm), −4400 (308 nm); ^{13}C NMR ($CDCl_3$) in Table 1.

4.2.5. Compound ***5***. Oil; $[\alpha]_D^{26}$ +146.6 (*c* 0.35, $CHCl_3$); CIMS (CH_4) *m/z* 362 $[M+H]^+$, 330, 262, 230 (base), 83; HRCIMS (CH_4) obsd *m/z* 362.2343 $[M+H]^+$ (calcd for $C_{21}H_{32}O_4N$: 362.2331); IR (KBr) cm^{-1}: 3500, 3200, 1720, 1690; ^{1}H NMR ($CDCl_3$) δ 0.91 (3H, d, J=6.9 Hz, 15-H_3), 1.25 (3H, s, 14-H_3), 1.57 (1H, qd, J=7.1, 3.3 Hz, 4α-H), 1.65 (1H, m, 2-Hα), 1.67 (1H, m, 2β-H), 1.71 (1H, dq, J=13.7, 1.5 Hz, 6β-H), 1.81 (1H, t, J=7.7 Hz, 9α-H), 1.83 (3H, d, J=1.5 Hz, 13-H_3), 1.92 (3H, quint, J=1.4 Hz, 5′-H_3), 1.96 (1H, m, 10β-H), 1.97 (1H, m, 9β-H), 2.00 (3H, dq, J=7.1, 1.4 Hz, 4′-H_3), 2.06 (1H, tt, J=14.0, 4.7 Hz, 1β-H), 2.73 (1H, d, J=13.7 Hz, 6α-H), 3.01 (3H, s, OMe), 5.03 (1H, td, J=3.3, 2.7 Hz, 3α-H), 5.80 (1H, br s, NH), 6.05 (1H, qq, J=7.1, 1.4 Hz, 3′-H); CD ($CHCl_3$) Δε +5.1 (254 nm); ^{13}C NMR ($CDCl_3$) in Table 1.

4.2.6. Compound ***6***. Oil; $[\alpha]_D^{21}$ +2.9 (*c* 0.37, $CHCl_3$); CIMS (NH_3) *m/z* 366 $[M+NH_3+H]^+$, 349 $[M+H]^+$, 248, 204, 83 (base); HRCIMS obsd *m/z* 349.2027 $[M+H]^+$ (calcd for $C_{20}H_{29}O_5$: 349.2015); IR (KBr) cm^{-1}: 3600–2600, 1730, 1710, 1680; ^{1}H NMR ($CDCl_3$) δ 1.01 (3H, d, J=7.1 Hz, 15-H_3), 1.25 (3H, s, 14-H_3), 1.34 (3H, d, J=7.1 Hz, 13-H_3), 1.52 (2H, m, 1β-H, 2α-H), 1.71 (2H, m, 1α-H, 2β-H), 1.90 (3H, quint, J=1.6 Hz, 5′-H_3), 1.99 (3H, dq, J=7.3, 1.5 Hz, 4′-H_3), 2.05 (1H, m, 4-H), 2.10 (1H, m, 10-H), 2.39 (1H, dd, J=17.3, 4.4 Hz, 9α-H), 2.65 (1H, dd, J=17.3, 3.6 Hz, 9β-H), 3.61 (1H, q, J=7.1 Hz, 11-H), 4.90 (1H, dt, J=6.3, 4.1 Hz, 3-H), 6.07 (1H, qq, J=7.4, 1.6 Hz, 3′-H), 6.64 (1H, s, 6-H); ^{13}C NMR ($CDCl_3$) in Table 1.

4.2.7. Compound ***7***. Colorless needles; mp 90–92 °C (hexane/$CHCl_3$); $[\alpha]_D^{22}$ +14.7 (*c* 1.5, $CHCl_3$); CIMS (CH_4) *m/z* 391 $[M+C_2H_5]^+$, 363 $[M+H]^+$, 331, 263, 231, 83 (base); HRCIMS (CH_4) obsd *m/z* 363.2152 $[M+H]^+$ (calcd for $C_{21}H_{31}O_5$: 363.2171); IR (KBr) cm^{-1}: 1740, 1710, 1680; ^{1}H NMR ($CDCl_3$) δ 1.00 (3H, d, J=6.9 Hz, 15-H_3), 1.24 (3H, s, 14-H_3), 1.30 (3H, d, J=7.4 Hz, 13-H_3), 1.53 (1H, m. 2α-H), 1.68 (1H, m, 1β-H), 1.71 (1H, m, 1α-H), 1.72 (1H, m, 2β-H), 1.90 (3H, quint, J=1.4 Hz, 5′-H_3), 1.98 (3H, dq, J=7.1, 1.4 Hz, 4′-H_3), 2.09 (1H, m, 4-H), 2.10 (1H, m, 10-H), 2.35 (1H, dd, J=17.9, 4.1 Hz, 9α-H), 2.64 (1H, dd, J=17.0, 4.1 Hz, 9β-H), 3.68 (3H, s, OMe), 4.89 (1H, m, 3-H), 6.06 (1H, qq, J=7.1, 1.4 Hz, 3′-H), 6.57 (1H, s, 6-H); CD ($CHCl_3$) [θ] −1300 (256 nm); ^{13}C NMR ($CDCl_3$) in Table 1.

4.2.8. Compound ***8***. Oil; $[\alpha]_D^{19}$ −54.7 (*c* 0.06, $CHCl_3$); MS (CI) *m/z* 308 $[M]^+$ 291, 209, 191 (base), 167, 147, 120, 83, 55; HRCIMS obsd *m/z* 308.1991 $[M]^+$ calcd for $C_{18}H_{28}O_4$ 308.1988; FTIR (KBr) 3500, 1730, 1710, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92 (3H, d, J=6.9 Hz, 15-H_3), 1.04 (3H, s, 14-H_3), 1.56 (1H, m, 4-H), 1.69 (1H, m, 1-H), 1.70 (1H, m, 2-H), 1.73 (1H, m, 2-H), 1.74 (1H, dd, J=13.7, 1.7 Hz, 9β-H), 1.82 (1H, dd, J=13.4, 11.8 Hz, 6β-H), 1.88 (1H, m, 1-H), 1.91 (3H, quint, J=1.2 Hz, 5′-H_3), 2.00 (3H, dq, J=7.2, 1.2 Hz, 4′-H_3), 2.02 (1H, m, 6α-H), 2.17 (3H, s, 11-H_3), 2.43 (1H, dd, J=13.7, 9.6 Hz, 9α-H), 3.27 (1H, m, 8-H), 4.99 (1H, q, J=3.0 Hz, 3-H), 6.04 (1H, qq, J=7.2, 1.2 Hz, 3′-H); ^{13}C NMR ($CDCl_3$) in Table 2.

Table 2
^{13}C NMR data for compounds **8**–**16** (150 MHz, in $CDCl_3$)

No.	8	9	10	11	12	13[a]	14	15	16[a]
1	28.4[b]	19.8	25.4	27.1	26.7	21.6	26.8	29.9	34.5
2	27.6[b]	24.3	25.4	25.6	25.7	25.1	25.7	27.5	22.0
3	72.4	72.2	71.7	71.6	71.8	73.1	71.0	72.0	29.7
4	38.9	36.2	36.2	42.0	42.1	32.9	42.1	36.6	33.4
5	48.1	41.4	42.3	41.7	42.0	39.9	42.0	46.3	46.9
6	39.1	53.3	67.9	32.4	32.7	35.9	32.7	31.4	81.3
7	210.7	—	120.8	156.3	157.9	156.8	158.0	155.6	158.1
8	47.4	218.7	148.9	108.6	105.9	106.4	105.9	105.5	77.3
9	37.4	40.4	76.0	35.2	37.6	37.9	37.6	42.4	41.7
10	83.2	41.0	41.5	34.5	34.9	38.7	34.9	73.3	75.4
11	29.4	—	120.2	126.9	126.7	125.0	126.6	125.9	125.8
12	—	—	140.4	171.7	171.6	171.7	171.6	171.1	174.0
13	—	—	9.0	8.2	8.2	8.4	8.2	8.6	8.7
14	15.8	22.8	20.2	24.1	24.0	24.5	24.1	18.2	10.9
15	12.5	11.9	8.5	8.9	9.0	12.0	8.8	12.4	16.3
1′	167.4	167.4	167.5	167.4	167.5	167.3	166.2	167.2	—
2′	127.9	127.9	128.1	128.0	128.0	127.9	116.3	127.7	—
3′	138.2	138.3	137.8	137.9	138.0	138.4	157.0	138.8	—
4′	15.7	15.7	15.7	15.8	15.7	15.7	27.5	15.7	—
5′	20.9	20.9	20.7	20.6	20.6	20.9	20.2	20.8	—
OMe	—	—	57.5	—	50.0	50.2	50.0	50.3	57.8

[a] Measured at 100 MHz.
[b] Assignment may be reversed.

4.2.9. Compound ***9***. Solid. $[\alpha]_D^{21}$ −5.6 (c 1.5, $CHCl_3$); MS (CI) *m/z* 265 $[M+H]^+$, 247, 165 (base), 101, 83; HRMS (CI) HRCIMS obsd *m/z* 264.1725 $[M]^+$ calcd for $C_{16}H_{24}O_3$ 264.1725. FTIR 1745, 1718, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (3H, d, J=7.1 Hz, 15-H_3), 1.22 (3H, s, 14-H_3), 1.49 (1H, dq, J=14.6, 3.6 Hz, 1α-H), 1.59 (1H, m, 4α-H), 1.72 (1H, ddt, J=16.5, 12.4, 3.9 Hz, 2β-H), 1.82 (1H, dq, J=14.8, 4.4 Hz, 2α-H), 1.93 (3H, quint, J=1.4 Hz, 5′-H_3), 1.93 (1H, d, J=18.1 Hz, 6β-H), 1.97 (1H, m, 1β-H), 2.01 (3H, dq, J=7.1, 1.4 Hz, 4′-H_3), 2.28 (2H, m, 9-H_2), 2.30 (1H, m, 10β-H), 2.46 (1H, d, J=18.1 Hz, 6α-H), 5.08 (1H, q, J=3.9 Hz, 3α-H), 6.07 (1H, qq, J=7.1, 1.4 Hz, 3′-H); CD ($CHCl_3$) Δε −1.7 (297 nm); ^{13}C NMR ($CDCl_3$) in Table 2.

4.2.10. Compound ***10***. Solid. $[\alpha]_D^{23}$ −1.9 (*c* 1.0, $CHCl_3$); MS (CI) *m/z* 363 $[M+H]^+$, 345, 312, 263, 231 (base), 213, 154, 83; HRCIMS obsd *m/z* 363.2155 $[M+H]^+$ calcd for $C_{21}H_{31}O_5$ 363.2172. FTIR 3450, 1715, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00 (3H, d, J=7.1 Hz, 15-H_3), 1.08 (3H, s, 14-H_3), 1.23 (1H, m, 1α-H), 1.60 (1H, m, 1β-H), 1.73 (1H, m, 2β-H), 1.82 (1H, m, 2α-H), 1.91 (3H, quint, J=1.4 Hz, 5′-H_3), 2.00 (3H, dq, J=7.1, 1.4 Hz, 4′-H_3), 2.10 (3H, d, J=1.1 Hz, 13-H_3), 2.21 (1H, ddd, J=12.9, 4.1, 1.9 Hz, 10-H), 2.30 (1H, m, 4α-H), 3.48 (3H, s, OMe), 3.90 (1H, br s, 9α-H), 5.00 (1H, br s, 6α-H), 5.28 (1H, dt, J=11.3, 4.1 Hz, 3α-H), 6.07 (1H, qq, J=7.1, 1.4 Hz, 3′-H), 7.16 (1H, q, J=1.0 Hz, 12-H); ^{13}C NMR ($CDCl_3$) in Table 2.

4.2.11. Compound ***11***. Solid. $[\alpha]_D^{22}$ −46.2 (*c* 0.3, $CHCl_3$); MS (CI) *m/z* 348 $[M]^+$, 330, 265, 248, 230, 174, 124, 107, 83 (base), 55; HRCIMS obsd *m/z* 348.1922 $[M]^+$ calcd for $C_{20}H_{28}O_5$ 348.1936. FTIR 3330, 1770, 1715, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.86 (3H, s, 14-H_3), 1.00 (3H, d, J=7.1 Hz, 15-H_3), 1.57 (1H, m, 1β-H), 1.64 (1H, m, 2β-H), 1.76 (1H, m, 10β-H), 1.78 (1H, m, 2α-H), 1.85 (3H, d, J=1.6 Hz, 13-H_3), 1.90 (3H, quint, J=1.6 Hz, 5′-H_3), 1.93 (1H, m, 4α-H), 1.97 (1H, m, 9β-H), 2.00 (3H, dq, J=7.4, 1.6 Hz, 4′-H_3), 2.16 (1H, m, 1α-H), 2.19 (1H, m, 9α-H), 2.20 (1H, d, J=13.7 Hz, 6β-H), 2.98 (1H, d, J=13.7 Hz, 6α-H), 5.27 (1H, dt, J=12.4, 4.4 Hz, 3α-H), 6.07 (1H, qq, J=7.1, 1.4 Hz, 3′-H), 8.55 (1H, s, OH); ^{13}C NMR ($CDCl_3$) in Table 2.

4.2.12. Compound ***12***. Solid. $[\alpha]_D^{22}$ −83.0 (c 1.4, $CHCl_3$); MS (CI) *m/z* 362 $[M]^+$, 331, 263, 231, 83 (base); HRCIMS obsd *m/z* 363.2148 $[M+H]^+$ calcd for $C_{21}H_{31}O_5$ 363.2172. FTIR 1765, 1710, 1645 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 0.84 (3H, s, 14-H_3), 1.01 (3H, d, J=7.1 Hz, 15-H_3), 1.58 (1H, m, 1β-H), 1.67 (1H, td, J=12.4, 4.1 Hz, 2β-H), 1.75 (1H, m, 10β-H), 1.76 (1H, m, 2α-H), 1.85 (3H, d, J=1.4 Hz, 13-H_3), 1.87 (1H, dd, J=14.0, 5.8 Hz, 9β-H), 1.90 (3H, quint, J=1.4 Hz, 5′-H_3), 1.92 (1H, m, 4α-H), 2.00 (3H, dq, J=7.1, 1.4 Hz, 4′-H_3), 2.16 (1H, m, 9α-H), 2.17 (1H, dd, J=13.2, 1.4 Hz, 6β-H), 2.21 (1H, td, J=14.0, 4.4 Hz, 1α-H), 2.82 (1H, d, J=13.2 Hz, 6α-H), 3.13 (3H, s, OMe), 5.25 (1H, dt, J=12.4, 4.4, 3α-H), 6.08 (1H, qq, J=7.1, 1.4 Hz, 3′-H); ^{13}C NMR ($CDCl_3$) in Table 2.

4.2.13. Compound ***13****.* Solid. $[\alpha]_D^{23}$ +136.2 (*c* 0.8, $CHCl_3$); MS (CI) *m*/*z* 362 $[M]^+$, 331, 279, 263 (base), 231, 83; HRCIMS obsd *m*/*z* 362.2091 $[M]^+$ calcd for $C_{21}H_{30}O_5$ 362.2094; FTIR 1765, 1718, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92 (3H, d,. J=7.0 Hz, 15-H_3), 1.27 (1H, m, 1-H), 1.27 (3H, s, 14-H_3), 1.53 (1H, m, 1-H), 1.55 (1H, m, 4-H), 1.64 (1H, m, 2-H), 1.68 (1H, m, 2-H), 1.81 (1H, m, 6β-H), 1.86 (1H, m, 9β-H), 1.87 (3H, d, J=1.5 Hz, 13-H_3), 1.92 (3H, quint, J=1.5 Hz, 5′-H_3), 1.96 (1H, m, 10β-H), 2.00 (3H, dq, J=7.3, 1.5 Hz, 4′-H_3), 2.05 (1H, m, 1-H), 2.13 (1H, td, J=13.2, 3.7 Hz, 9α-H), 2.80 (1H, d, J=13.5 Hz, 6α-H), 3.12 (3H, s, OMe), 5.05 (1H, q, J=3.3 Hz, 3α-H), 6.06 (1H, qq, J=7.3, 1.5 Hz, 3′-H); ^{13}C NMR ($CDCl_3$) in Table 2.

4.2.14. Compound ***14****.* Solid. $[\alpha]_D^{22}$ −64.6 (*c* 0.3, $CHCl_3$); MS (CI) *m*/*z* 362 $[M]^+$, 331, 263, 231, 83 (base); HRCIMS obsd *m*/*z* 362.2108 $[M]^+$ calcd for $C_{21}H_{30}O_5$ 362.2093; FTIR 1760, 1710, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.83 (3H, s, 14-H_3), 0.98 (3H, d, J=7.1 Hz, 15-H_3), 1.56 (1H, m, 1-H), 1.60 (1H, m, 2-H), 1.52 (1H, m, 2-H), 1.71 (1H, m, 10-H), 1.84 (3H, d, J=1.4 Hz, 13-H_3), 1.85 (1H, m, 9-H), 1.90 (1H, m, 4α-H), 1.91 (3H, quint, J=1.1 Hz, 5′-H_3), 2.16 (1H, m, 9-H), 2.18 (1H, m, 6β-H), 2.18 (3H, quint, J=1.1 Hz, 4′-H_3), 2.20 (1H, m, 1-H), 2.82 (1H, d, J=13.2 Hz, 6α-H), 3.12 (3H, s, OMe), 5.19 (1H, dt, J=12.4, 4.4 Hz, 3α-H), 5.69 (1H, septet, J=1.1 Hz, 2′-H); ^{13}C NMR ($CDCl_3$) in Table 2.

4.2.15. Compound ***15****.* Mp 161–163.5 °C (hexane/AcOEt); $[\alpha]_D^{20}$ +100.3 (*c* 0.13, $CHCl_3$); MS (CI) *m*/*z* 407 $[M+C_2H_5]^+$, 379 $[M+H]^+$, 361, 347, 329, 278, 261, 247 (base), 223, 195, 95, 83; HRCIMS obsd *m*/*z* 407.2434 $[M+C_2H_5]^+$ calcd for $C_{23}H_{35}O_6$ 407.2434; FTIR 3520, 1770, 1715, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.96 (3H, d, J=7.1 Hz, 15-H_3), 1.27 (3H, s, 14-H_3), 1.36 (1H, ddd, J=14.4, 4.4, 2.5 Hz, 1α-H), 1.49 (1H, dq, J=7.1, 3.3 Hz, 4α-H), 1.61 (1H, tt, J=14.4, 4.4 Hz, 2α-H), 1.84 (1H, ddt, J=14.4, 4.4, 2.5 Hz, 2β-H), 1.91 (3H, quint, J=1.6 Hz, 5′-H_3), 1.91 (3H, d, J=1.4 Hz, 13-H_3), 2.01 (3H, dq, J=7.3, 1.6 Hz, 4′-H_3), 2.05 (1H, td, J=14.4, 4.4 Hz, 1β-H), 2.19 (1H, dq, J=14.2, 1.4 Hz, 6β-H), 2.20 (1H, d, J=14.3 Hz, 9α-H), 2.24 (1H, J=14.3 Hz, 9β-H), 2.64 (1H, d, J=14.2 Hz, 6α-H), 3.18 (3H, s, OMe), 3.80 (1H, s, OH), 5.01 (1H, q, J=3.3 Hz, 3α-H), 6.07 (1H, qq, J=7.3, 1.6 Hz, 3′-H); CD ($CHCl_3$) Δϵ +7.6 (253 nm); ^{13}C NMR ($CDCl_3$) in Table 2.

4.2.16. Compound ***16****.* Solid. $[\alpha]_D^{23}$ +81.6 (*c* 0.3, $CHCl_3$); MS (CI) *m*/*z* 281 $[M+H]^+$ (base), 263, 248, 231, 206, 155, 140; HRCIMS obsd *m*/*z* 281.1754 $[M+H]^+$ calcd for $C_{16}H_{25}O_4$ 281.1753; FTIR 3500, 1760, 1708, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.83 (3H, d, J=6.0 Hz, 15-H_3), 1.16 (3H, s, 14-H_3), 1.25 (1H, m), 1.30 (1H, m), 1.32 (1H, m), 1.36 (1H, m), 1.38 (1H, m), 1.40 (1H, m), 1.66 (1H, m), 1.91 (3H, d, J=1.8 Hz, 13-H_3), 1.96 (1H, dd, J=12.8, 11.0 Hz, 9β-H), 2.30 (1H, dd, J=12.8, 7.0 Hz, 9α-H), 3.31 (3H, s, OMe), 4.16 (1H, s, OH), 4.30 (1H, s, 6α-H), 5.16 (1H, dd, J=11.0, 7.0 Hz,, 8β-H); ^{13}C NMR ($CDCl_3$) in Table 2.

4.2.17. Compound ***19****.* Oil; ^{1}H NMR (600 MHz. $CDCl_3$) δ 1.05 (3H, d, J=7.1 Hz, 15-H_3), 1.07 (3H, s, 14-H_3), 1.64 (1H, tdd, J=14.6, 2.7, 1.6 Hz, 2α-H), 1.82 (1H, qd, J=7.1, 3.0 Hz, 4-H), 1.85 (3H, t, J=1.6 Hz, 13-H_3), 1.91 (3H, quint, J=1.6 Hz, 5′-H_3), 2.02 (3H, dq, J=7.4, 1.6 Hz, 4′-H_3), 2.04 (1H, m, 2β-H), 2.07 (1H, m, 1α-H), 2.18 (1H, br d, J=12.9, 6α-H), 2.42 (1H, tdt, J=14.6, 2.3, 1.9 Hz, 1β-H), 2.84 (1H, d, J=12.9 Hz, 6β-H), 5.14 (1H, dt, J=3.0, 2.7 Hz, 3-H), 5.17 (1H, br s, 8-H), 5.62 (1H, t, J=1.9 Hz, 9-H), 6.08 (1H, qq, J=7.4, 1.6 Hz, 3′-H); ^{13}C NMR ($CDCl_3$) in Table 1.

4.3. X-ray crystallography

All diagrams and calculations were performed using maXus (Bruker Nonius, Delft & Mac Science, Japan). Mo Kα radiation, λ=0.71073 Å. Data collection: DIP Image plate, Program(s) used to refine structure: *SHELXL*-97 (Sheldrick, 1997). Crystallographic data for compounds **2**, **7**, and **15** have been deposited at the Cambridge Crystallographic Data Center with supplementary publication numbers below. Copies of the data can be obtained, free of charge, via www.ccdc.cam.ac.uk/data_request/cif, or by mailing to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: data_request@ccdc.cam.ac.uk].

For compound **2**: 7231 measured reflections, 7207 independent reflections, 5227 observed reflections, crystal data: orthorhombic, $P2_12_12_1$, a=10.4490 (4) Å, b=10.4490 (4) Å, c=34.7480 (11) Å, α=90.00°, β=90.00°, γ=90.00°, V=3793.8 (2) Å^3, R=0.0631. CCDC 767923.

For compound **7**: 2088 measured reflections, 2072 independent reflections, 1389 observed reflections, crystal data: orthorhombic, $P2_12_12_1$, a=7.716000 (0) Å, b=13.300000 (0) Å, c=19.974001 (0) Å, α=90.00°, β=90.00°, γ=90.00°, V=2049.899902 (0) Å^3, R=0.0807. CCDC 767924.

For compound **15**: 2971 measured reflections, 2778 independent reflections, 2157 observed reflections, crystal data: orthorhombic, $C222_1$, a=11.908000 (0) Å, b=8.096000 (0) Å, c=43.157001 (0) Å, α=90.00°, β=90.00°, γ=90.00°, V=4161.000000 (0) Å^3, R=0.047. CCDC 767925.

4.4. Conversion of compound 17 to methyl farfuginoate (7)

A stirred solution of compound **17** (5.6 mg) in benzene (1 mL) was treated with TsOH (1 mg) at rt for 2 h. Ether was added and the organic layer was washed with an aqueous $NaHCO_3$ solution followed by brine. The solvent was evaporated to give a residue. The residue was directly methylated with diazomethane in ether to afford compound **7** (4.9 mg) after purification (SiO_2 column chromatography).

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Supplementary data

^{1}H NMR spectra of the new compounds **1**–**18**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.04.079.

References and notes

1. (a) Tori, M.; Kawahara, M.; Sono, M. *Tetrahedron Lett.* **1997**, *38*, 1965; (b) Tori, M.; Kawahara, M.; Sono, M. *Phytochemistry* **1998**, *47*, 401.
2. Tori, M.; Shiotani, Y.; Tanaka, M.; Nakashima, K.; Sono, M. *Tetrahedron Lett.* **2000**, *41*, 1797.
3. Bohlmann, F.; Van, N. L. *Phytochemistry* **1978**, *17*, 1173.
4. Zhao, Y.; Jiang, H.; MacLeod, M.; Parsons, S.; Rankin, D. W. H.; Wang, P.; Cheng, C. H. K.; Shi, H.; Hao, X.; Gueritte, F. *Chem. Biodiv.* **2004**, *1*, 1546.
5. Wu, Q.-H.; Wang, C.-M.; Cheng, S.-G.; Gao, K. *Tetrahedron Lett.* **2004**, *45*, 8855.
6. Wu, Q.-X.; Yang, A.-M.; Shi, Y.-P. *Tetrahedron* **2005**, *61*, 10529.
7. Li, Y.-S.; Li, S.-S.; Wang, Z.-T.; Luo, S.-D.; Zhu, D.-Y. *Nat. Prod. Res.* **2006**, *20*, 1241.

8. Liu, J.-Q.; Zhang, M.; Zhang, C.-F.; Qi, H.-Y.; Bashall, A.; Bligh, S. W. A.; Wang, Z.-T. *Phytochemistry* **2008**, *69*, 2231.
9. Zhang, Z.-X.; Wang, C.-M.; Fei, D.-Q.; Jia, Z.-J. *Chem. Lett.* **2008**, *37*, 346.
10. Wang, X.; Sun, L.; Huang, K.; Shi, S.; Zhang, L.; Xu, J.; Peng, H.; Sun, X.; Wang, L.; Wu, X.; Zhao, Y.; Li, X.; Stockigt, J.; Qu, J. *Chem. Biodiv.* **2009**, *6*, 1053.
11. Lin, Y.; Jin, T.; Wu, X.; Huang, Z.; Fan, J. *J. Nat. Prod.* **1997**, *60*, 27.
12. Kouno, I.; Hirai, A.; Jiang, Z.; Tanaka, T. *Phytochemistry* **1997**, *46*, 1283.
13. Rosquete, C.; Olmo, E. D.; Sanz, F.; San Feliciano, A. *Chem. Pharm. Bull.* **2002**, *50*, 964.
14. (a) Bagal, S. K.; Adlington, R. M.; Marquez, R.; Cowley, A. R.; Baldwin, J. E. *Tetrahedron Lett.* **2003**, *44*, 4993; (b) Bagal, S. K.; Adlington, R. M.; Baldwin, J. E.; Marquez, R. *J. Org. Chem.* **2004**, *69*, 9100; (c) Bagal, S. K.; Adlington, R. M.; Brown, R. A. B.; Baldwin, J. E. *Tetrahedron Lett.* **2005**, *46*, 4633.
15. (a) Tori, M.; Takeichi, Y.; Kuga, H.; Nakashima, K.; Sono, M. *Heterocycles* **2000**, *52*, 1075; (b) Tori, M.; Morishita, N.; Hirota, N.; Saito, Y.; Nakashima, K.; Sono, M.; Tanaka, M.; Utagawa, A.; Hiroshi, H. *Chem. Pharm. Bull.* **2008**, *56*, 677.
16. (a) Hanai, R.; Gong, X.; Tori, M.; Kondo, S.; Otose, K.; Okamoto, Y.; Nishihama, T.; Murota, A.; Shen, Y.; Wu, S.; Kuroda, C. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1302; (b) Tori, M.; Honda, K.; Nakamizo, H.; Okamoto, Y.; Sakaoku, M.; Takaoka, S.; Gong, X.; Shen, Y.; Kuroda, C.; Hanai, R. *Tetrahedron* **2006**, *62*, 4988; (c) Tori, M.; Fujiwara, M.; Okamoto, Y.; Tanaka, M.; Gong, X.; Shen, Y.; Hanai, R.; Kuroda, C. *Nat. Prod. Commun.* **2007**, *2*, 357; (d) Tori, M.; Okamoto, Y.; Tachikawa, K.; Mihara, K.; Watanabe, A.; Sakaoku, M.; Takaoka, S.; Tanaka, M.; Gong, X.; Kuroda, C.; Hattori, M.; Hanai, R. *Tetrahedron* **2008**, *64*, 9136; (e) Tori, M.; Watanabe, A.; Matsuo, S.; Okamoto, Y.; Tachikawa, K.; Takaoka, S.; Gong, X.; Kuroda, C.; Hanai, R. *Tetrahedron* **2008**, *64*, 4486; (f) Tori, M.; Nakamizo, H.; Mihara, K.; Sato, M.; Okamoto, Y.; Nakashima, K.; Tanaka, M.; Saito, Y.; Gong, X.; Shen, Y.; Hanai, R.; Kuroda, C. *Phytochemistry* **2008**, *69*, 1158; (g) Torihata, A.; Hanai, R.; Matsushima, M.; Nagano, H.; Saito, Y.; Baba, M.; Tanio, Y.; Okamoto, Y.; Takashima, Y.; Ichihara, M.; Gong, X.; Kuroda, C.; Tori, M. *Helv. Chim. Acta* **2009**, *92*, 2071.
17. Kurihara, T.; Suzuki, S. *Yakugaku Zasshi* **1980**, *100*, 681.
18. Crystallographic data for the structure of this compound have been deposited (see Experimental).
19. (a) Goto, H.; Ohta, K.; Kamakura, T.; Obata, S.; Nakayama, N.; Matsumoto, T.; Osawa, E. Conflex corp: Tokyo, Japan, 2004. (b) Goto, H.; Osawa, E. *J. Am. Chem. Soc.* **1989**, *111*, 8950; (c) Goto, H.; Osawa, E. *J. Chem. Soc., Perkin Trans. 2* **1993**, 187.
20. (a) Bodensieck, A.; Fabian, W. M. F.; Kunert, O.; Belaj, F.; Jahangir, S.; Schühly, W.; Bauer, R. *Chirality* **2010**, *22*, 308; (b) Naya, K.; Shimizu, M.; Nishio, H.; Takeda, M.; Oka, S.; Hirota, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1071; (c) Sugama, K.; Hayashi, K.; Mitsuhashi, H. *Phytochemistry* **1985**, *24*, 1531; (d) Naya, K.; Kanazawa, R.; Sawada, M. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3220.
21. Asahina, Y. *Arch. Pharm.* **1914**, *251*, 355.
22. For compound **20**: Nagano, H.; Moriyama, T.; Tanahashi, Y.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1994.
23. For compound **21**: Tada, M.; Moriyama, Y.; Tanahashi, Y.; Takahashi, T. *Chem. Lett.* **1971**, 4007.
24. For compound **22**: See Ref. 16e.
25. For compound **23** and **33**: Massiot, G.; Nuzillard, J.-M.; Le Men-Olivier, L.; Aclinou, P.; Benkouider, A.; Khelifa, A. *Phytochemistry* **1990**, *29*, 2207.
26. For compounds **24** and **29**: Ito, K.; Iida, T.; Takeichi, C. *Yakugaku Zasshi* **1978**, *98*, 1592.
27. For compounds **25** and **27**: Ito, K.; Iida, T.; Funatani, T. *Yakugaku Zasshi* **1979**, *99*, 349.
28. For compounds **26**, **28**, and **30**: *Yakugaku Zasshi* **1977**, *97*, 863.
29. For compound **31**: Ito, K.; Iida, T.; Funatani, T. *Yakugaku Zasshi* **1980**, *100*, 69.
30. For compound **32**: Nakatani, M.; Maeda, S.; Higashi, K.; Kurawaki, J.; Okamura, H.; Iwagawa, T. *Heterocycles* **2003**, *60*, 373.
31. Jizba, J.; Samek, Z.; Novotný, L. *Coll. Czech. Chem. Chem.* **1977**, *42*, 2438.
32. Torres, P.; Ayala, J.; Grande, C.; Anaya, J.; Grande, M. *Phytochemistry* **1999**, *52*, 1507.
33. Mohamed, A. E. H.; Ahmed, A. A. *J. Nat. Prod.* **2005**, *68*, 439.
34. Zhao, Y.; Jia, Z.; Peng, H. *J. Nat. Prod.* **1995**, *58*, 1358.
35. Yaoita, Y.; Kikuchi, M. *Chem. Pharm. Bull.* **1995**, *43*, 1738.
36. Mao, M.; Jia, Z. *Planta Med.* **2002**, *68*, 55.
37. Fei, D.-Q.; Li, S.-G.; Wu, G.; Gao, K. *J. Nat. Prod.* **2007**, *70*, 241.
38. Yaoita, Y.; Kikuchi, M. *Chem. Pharm. Bull.* **1996**, *44*, 1731.
39. Zhang, Z.-X.; Lin, C.-J.; Li, P.-L.; Jia, Z.-J. *Planta Med.* **2007**, *73*, 585.
40. For example: (a) Singh, S. B.; Zink, D.; Polishook, J.; Valentino, D.; Shafiee, A.; Silverman, K.; Felock, P.; Teran, A.; Villela, D.; Hazuda, D. J.; Lingham, R. B. *Tetrahedron Lett.* **1999**, *40*, 8775; (b) Kim, S.; Hatori, M.; Ojika, M.; Sakagami, Y.; Marumo, S. *Bioorg. Med. Chem.* **1998**, *6*, 1975; (c) Stillman, M. J.; Stothers, J. B. *Can. J. Chem.* **1981**, *59*, 2303.