Chemistry of Fijian Plants. 13.[1] Floribundal, a Nonglycosidic Bisiridoid, and Six Novel Fatty Esters of δ-Amyrin from *Scaevola floribunda*

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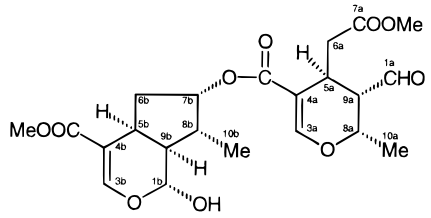
Floribundal (**1**), the first example of a nonglycosidic bisiridoid has been isolated from the heartwood of *Scaevola floribunda* and its structure and relative stereochemistry determined by NMR spectroscopy and molecular modeling. The aglycon **2** of loganin was also isolated. A mixture of six novel δ-amyrin fatty esters with C_{20}−C_{30} acid moieties (**7**−**12**) were isolated from the bark of *S. floribunda* and their structures elucidated by NMR and HRMS of the parent compounds and their hydrolysis products. The bark also contains the triterpenes δ-amyrin (**13**) and δ-amyrin acetate (**14**), and ursolic acid acetate, betulinic acid, and betulin.

Genera of the family Goodeniaceae are known for the high occurrence of iridoids, and this has been considered by Dahlgren et al.[2] to be of chemotaxonomic significance. Iridoids have been isolated from two species of the genus *Scaevola: S. racemigera*[3] and *S. montana*.[4] *Scaevola floribunda* A. Gray (family Goodeniaceae; Fijian names "durubi", "veveduvanua") is an endemic Fijian shrub that grows at elevations from sea level to 1200 m in dense or open forest.[5] A MeOH extract of the heartwood was partitioned between H_2O and EtOAc, and a portion of the crude EtOAc fraction was subjected to gradient elution vacuum liquid chromatography followed by PLC to yield the aglycon of loganin (**2**)[6] and the new bisiridoid floribundal (**1**).



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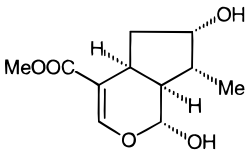
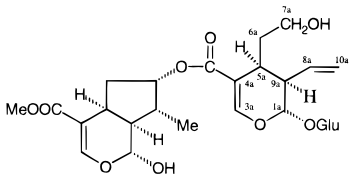


2

Accurate mass measurements (HREIMS) of the molecular ion (452.1682) and of the base peak of **1** (225.0766) gave a molecular formula of $C_{22}H_{28}O_{10}$ and suggested a compound giving rise to two fragments of similar mass on electron impact. The IR spectrum showed absorptions indicative of a hydrogen-bonded hydroxyl group (3418 cm^{-1}), an ester (1740, 1283, 1195 cm^{-1}), and an aldehyde (1634, 2935 cm^{-1}). In the lowfield region of the ^{1}H-NMR spectrum (Table 1), signals at δ 7.41 and 5.29 bore close resemblance to the respective olefinic and C_{7b} proton signals of the iridoid moiety of bisiridoids isolated from the related plant *S. racemigera*.[3] Signals indicative of an olefinic proton of a secoiridoid moiety (δ 7.64) and of an aldehydic proton (δ 9.64) also appeared in the lowfield region of the spectrum. The lack of signals in the spectrum that could be attributed to a sugar unit, indicated that **1** was a nonglycosidic bisiridoid. Comparison of the ^{1}H-NMR data with those published for laciniatoside V (**3**)[7] showed that the iridoid unit was identical with the loganin aglycon moiety of this compound. Two methyl doublets at δ 1.08 and 1.59 in the highfield region of the spectrum, together with the lack of exocyclic olefinic proton signals, suggested that the secoiridoid moiety was a rearranged form of the secoiridoid unit of **3**.

The ^{13}C-NMR spectrum of **1** showed 22 carbon signals, 11 of which matched those of the esterified loganin aglycon unit of **3**. DEPT 135 and DEPT 90 experiments showed that, of the remaining 11 signals, two corresponded with methyl carbons, one with a methylene carbon, five with methine carbons, and three with quaternary carbons. One of the methine signals at δ 199.4 confirmed the presence of an aldehyde group.



3

A COSY experiment gave a spectrum that displayed two distinct spin systems. As expected, the loganin aglycon unit gave rise to a 10-spin system involving signals (δ 5.02, 2.00, 3.12, 2.36, 1.70, 5.30, 2.10, 1.08) already attributed to the iridoid moiety. The secoiridoid moiety produced a 9-spin system corresponding to the fragment $CH_2CHCH(CHO)CHCH_3$. An HMQC experiment permitted unequivocal assignment of all proton-bearing carbons (Table 1), while an HMBC experiment permitted assignment of the structure of the secoiridoid unit and thus of the whole molecule. In the latter spectrum, C_{4a} showed coupling to three protons, H_{9a} (δ 2.64), H_{5a} (δ 3.37), and H_{3a} (δ 7.64), which indicated that it was directly bonded to C_{5a}. Both C_{8a} (δ 69.6) and C_{5a} (δ 28.3) were coupled to the olefinic proton H_{3a}, thus locating C_{3a} (δ 156.6) adjacent to C_{4a}. The relatively lowfield chemical shifts of C_{8a} and H_{8a} (δ 4.21) were

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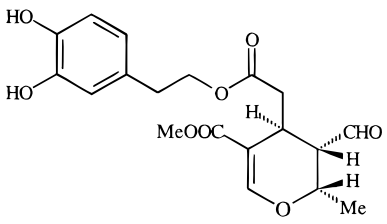
Table 1. ^{1}H-, ^{13}C-, COSY, and HMBC NMR Data for **1** (in $CDCl_3$)

position	δ_C	δ_H (mult, *J* in Hz)[a]	COSY	HMBC
C-1a	199.4	9.64 (dd, 3.4, 1.4)	2.64	2.64, 4.21
C-3a	156.6	7.64 (s)		
C-4a	106.8			2.64, 3.37, 7.64
*C*OO-C7b	165.9			7.64
C-5a	28.3	3.37 (m, 11.1, 2.7, 1.3)	2.27, 2.64, 2.90	2.27, 2.64, 2.90, 7.64
C-6a	38.6	2.27 (dd, 16.0, 11.1)	3.37	2.64
		2.90 (dd, 16.0, 3.0)	2.27, 3.37	
C-7a	171.1			2.27, 3.70, 2.90
COO*Me*	51.9	3.70 (s)		*b*
C-8a	69.6	4.21 (dq, 6.7, 2.4)	1.58, 2.64	1.58, 7.64
C-9a	51.0	2.64 (br s)	3.37, 4.21, 9.64	1.58, 2.90, 9.64
C-10a	18.0	1.58 (d, 6.7)	4.21	*b*
C-1b	94.9	5.04 (d, 5.2)	2.00	2.10, 3.11, 7.41
C-3b	151.1	7.41 (d, 1.1)		5.04, 3.11
C-4b	111.4			1.71, 3.11, 7.41
*C*OOMe	167.5			3.72, 7.41
COO*Me*	51.3	3.72 (s)		*b*
C-5b	31.4	3.11 (dddd, 8.2)	1.71, 2.00, 2.37	1.71, 5.04, 5.29, 7.41
C-6b	39.6	1.71 (ddd, 13.9, 8.0, 5.0)	2.37, 3.11, 5.29	3.11
		2.37 (ddd, 14.7, 7.8, 1.6)	1.71, 3.11, 5.29	
C-7b	76.7	5.29 (dt, 5.4, 1.6)	1.71, 2.10, 2.37	1.08, 2.37
C-8b	40.1	2.10 (m, 6.8, 0.7)	1.08, 5.29	1.08, 2.00, 2.37, 3.11
C-9b	47.1	2.00 (ddd, 8.6, 8.6, 5.1)	3.11, 5.04	1.08, 2.10, 2.37, 3.11, 5.29
C-10b	13.6	1.08 (d, 6.8)	2.10	*b*

[a] Coupling constants are in Hertz. [b] These long-range ^{13}C−^{1}H couplings were obscured by T_1 noise.

indicative of an adjacent oxygen atom. No coupling was observed between C_{4a} and H_{8a} or between C_{9a} and H_{3a}, and thus an ether oxygen completed the ring. The quaternary carbon at δ 171.7 was assigned as C_{7a} through observed couplings to the C_{6a} methylene protons (δ 2.26, 2.90) and the methoxy protons (δ 3.70). The remaining carbon signal at δ 165.9 showed coupling only to H_{3a}, permitting it to be assigned as the ester carbonyl joining the iridoid and secoiridoid units. The gross structure **1** could therefore be assigned to floribundal. Assuming that the iridoid moiety of floribundal has the same absolute configuration as that of loganin and of other related bisiridoids (a reasonable assumption in the light of the isolation of **2** from *S. floribunda*), two stereoisomers are possible for floribundal. Two secoiridoid diastereomers (**4** and **5**) that have the same gross secoiridoid structures as that of the secoiridoid moiety of floribundal have been reported as constituents of *Olea europa*,[8] and the relative stereochemistry of **4** as 5*S*,8*S*,9*S* has been assigned from comparison of the ^{1}H-NMR data with those recorded for elonolic acid (**6**). The absolute stereochemistry of **6** had been determined as 5*S*,8*S*,9*S* by a stereorational conversion of **6** to (−)-ajmalacine of known absolute configuration.[9] The closer agreement of the ^{1}H-NMR data of the secoiridoid moiety of floribundal with **4** rather than **5** suggested that it also possessed a 5*S*,8*S*,9*S* configuration, and this was supported from NOE data, molecular modeling, and biosynthetic considerations.



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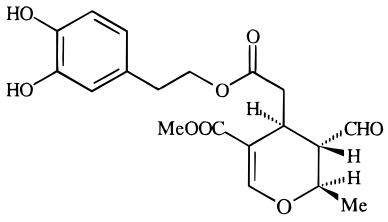

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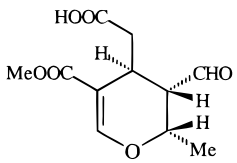

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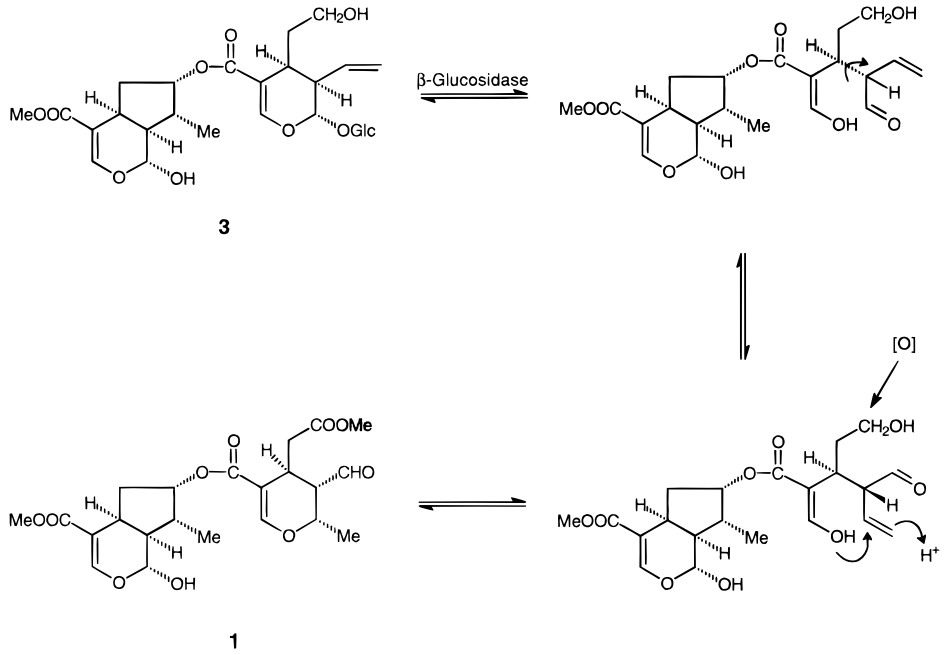
In the phase-sensitive NOESY spectrum, H_{1a} showed NOE correlations with H_{5a} and the methyl protons H_{10a} (δ 1.58), while H_{8a} showed a NOE correlation with the C_{6a} methylene protons. Both the methyl and the aldehyde groups were therefore assigned α-configurations and the ester side chain a β-configuration. As the pyran ring can exist in two conformations, that is, an α-half chair or a β-half chair, the total number of possible conformations doubles. In the ^{1}H-NMR spectrum of **1**, H_{9a} appeared as a broad singlet at δ 2.64, and thus the coupling constants J_{9a-5a} and J_{9a-8a} must be approaching 0 Hz. Using this as a guideline, all of the possible stereochemical configurations and conformations of the secoiridoid moiety were examined by molecular modeling (PCMODEL utilizing the MMX force field) and compared to see if they gave a corresponding result. Of the 16 possible forms, four (i.e., the β-chair 5a*S*,8a*S*,9a*S*, α-chair 5a*R*,8a*R*,9a*R*, β-chair 5a*S*,8a*R*,9a*S*, and α-chair 5a*R*,8a*S*,9a*R* diastereomers) gave small coupling constants. The latter two configurations were ignored because they possessed a relative stereochemistry different from that deduced from the NOESY experiment. A possible biosynthetic route to **1** from laciniatoside V of established configuration **3**, is given in Scheme 1. From this it is probable that floribundal exists as the β-chair 5a*S*,8a*S*,9a*S* diastereoisomer. Floribundal (**1**) was inactive in a brine shrimp assay for cytotoxicity.

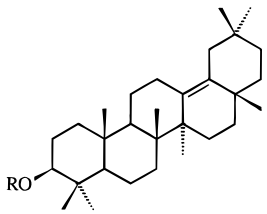
A hexane extract of the bark of *S. floribunda* afforded a mixture of six novel long-chain esters of δ-amyrin (**7**−**12**) as well as δ-amyrin (**13**) itself and δ-amyrin acetate (**14**). The EIMS of the mixture showed a series of six peaks (*m*/*z* 861, 833, 805, 777, 749, 721), each separated by 28 mass units. This finding is indicative of a mixture

Scheme 1. Possible Biosynthetic Route to **1** from **3**



3 **1**

Table 2. Mass Spectral Analysis for **7**−**12**



7 R=$COC_{19}H_{39}$
8 R=$COC_{21}H_{43}$
9 R=$COC_{23}H_{47}$
10 R=$COC_{25}H_{51}$
11 R=$COC_{27}H_{55}$
12 R=$COC_{29}H_{59}$
13 R=H
14 R=$COCH_3$

compound	*m/z*	HREIMS	formula	ratio
7	721	720.6783	$C_{50}H_{88}O_2$	5
8	749	748.7095	$C_{52}H_{92}O_2$	27
9	777	776.7411	$C_{54}H_{96}O_2$	17
10	805	804.7708	$C_{56}H_{100}O_2$	48
11	833	832.8051	$C_{58}H_{104}O_2$	7
12	861	860.8361	$C_{60}H_{108}O_2$	1

of compounds, as a repetitive loss of a fragment of 28 mass units is unusual. HREIMS of the six peaks gave molecular formulas (see Table 2) and a strong fragment (52%) at *m/z* 409 corresponding to a formula $C_{30}H_{49}$, which confirmed that the mixture was composed of long-chain fatty esters of a triterpene alcohol. The ^{1}H-NMR spectrum of **7**−**12** was very similar to that of **14**, exhibiting eight tertiary methyl group singlets at δ 1.15, 1.00, 0.92, 0.87, 0.84, 0.84, 0.83, and 0.69. The deshielding of an unresolved doublet of doublets at δ 4.49 due to the C-3 proton suggested that the ester linkage occurred at C-3. A large broad singlet at δ 1.24 and a two proton triplet at δ 2.28 (J = 7.0 Hz) was indicative of the long hydrocarbon chain of a fatty acid esterified at the C-3 β-hydroxyl of δ-amyrin. Hydrolysis of the mixture gave δ-amyrin (**13**) and a mixture of fatty acids, the mass spectrum of which showed six distinct peaks (*m/z* 452, 424, 396, 368, 340, and 312) separated by 28 mass units. Accurate mass measurement of the four peaks of higher mass gave molecular formulas $C_{30}H_{60}O_2$ (triacontanoic acid), $C_{28}H_{56}O_2$ (octacosanoic acid), $C_{26}H_{52}O_2$ (hexacosanoic acid), and $C_{24}H_{48}O_2$ (tetracosanoic acid), respectively.

Ursolic acid acetate, betulinic acid, and betulin were also isolated from the bark and identified either by direct comparison with authentic samples or by extensive spectroscopic examination.

Experimental Section

General Experimental Procedures. MS were determined on a Varian VG 70-SE mass spectrometer. ^{1}H- and ^{13}C-NMR spectra at highfield were recorded on either a Bruker AM-400 or a DRX-400 MHz NMR spectrometer in $CDCl_3$, unless otherwise stated. All 1D and 2D spectra of **1** (phase-sensitive DQF−COSY, HMQC, HMBC, NOESY) were recorded on the DRX-400 spectrometer using UXNMR software. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer, and optical rotations were measured with a Perkin-Elmer 141 polarimeter on $CHCl_3$ solutions. Si gel (type 60, Merck) was used for column chromatography and aluminum-backed plates coated with Si gel F_{254} (Merck) were used for TLC. PLC plates (1 mm) were prepared using Si gel 60 $PF_{254\,+\,366}$ on 25 × 25-cm glass plates. All solvents were distilled prior to use.

Plant Material. The wood and bark of *Scaevola floribunda* were collected from the forest of Wailoku, inland of Suva, Fiji, and authenticated by Dr. J. Ash, former Curator, Fiji National Herbarium, Suva (voucher no. S. V. 1023).

Extraction and Isolation. Dried and milled heartwood (375 g) was exhaustively extracted (Soxhlet) with hexane and then MeOH to yield 0.65 g (0.17%) and 28.4 g (7.6%) of the crude extracts, respectively. The MeOH

extract (15.1 g) was partitioned between H_2O and EtOAc, and the EtOAc solubles were dried and concentrated *in vacuo* to yield 1.95 g of crude extract. A portion (1.0 g) was partitioned by gradient-elution vacuum liquid chromatography using EtOAc−hexane mixtures. The fraction eluted with EtOAc−hexane (3:2) was purified further via PLC (EtOAc−hexane 9:11) to yield **1** (4 mg, 0.002%) and **2** (2 mg, 0.001%); correct IR, ^{1}H and ^{13}C NMR and MS;[6] HRDEIMS $[M]^+$ 228.0999, ($C_{11}H_{16}O_5$ requires 228.0998).

Dried and milled bark (136.2 g) was exhaustively extracted (Soxhlet) with hexane and then CH_2Cl_2 to yield 5.76 g (4.2%) and 2.61 g (1.9%) of the crude extracts, respectively. A portion of the hexane extract (1.15 g) was partitioned by flash column chromatography using hexane−CH_2Cl_2−EtOAc mixtures to yield *δ*-amyrin acetate (**14**) (0.24 g, 0.86%), a mixture of *δ*-amyrin eicosanoate (**7**), *δ*-amyrin docosanoate (**8**), *δ*-amyrin tetracosanoate (**9**), *δ*-amyrin hexacosanoate (**10**), *δ*-amyrin octacosanoate (**11**), and *δ*-amyrin triacotanoate (**12**) (37 mg, 0.14%), as well as *δ*-amyrin (**13**) (23 mg, 0.08%); semicrystalline solid; mp 193−197 °C, (lit.[10] 213.5−215 °C); $[\alpha]_D$ −54° (*c* 0.21, $CHCl_3$), (lit.[10] −54.8°); correct IR, ^{1}H NMR, and MS[10,11] and ursolic acid acetate (18 mg, 0.07%); amorphous solid; mp 187−190 °C, (lit.[12] 286 °C); correct IR, ^{1}H and ^{13}C NMR, and MS.[13] The CH_2Cl_2 extract (0.99 g) was partitioned by flash column chromatography using hexane−CH_2Cl_2−EtOAc mixtures to yield betulinic acid (0.16 g, 0.30%); clear needles; mp 290−292 °C (dec), [lit.[14] 290−293 °C (dec)]; $[\alpha]_D$ +6.1° (*c* 0.84, $CHCl_3$), (lit.[14] +7.5°); correct IR, ^{1}H NMR, ^{13}C NMR, and MS,[15] and betulin (20 mg, 0.04%); clear needles; mp 258−259 °C, (lit.[16] 255−256 °C); $[\alpha]_D$ +21° (*c* 0.17, $CHCl_3$), (lit.[16] +20.1°); correct IR, ^{1}H and ^{13}C NMR, and MS.[16]

Floribundal (1): colorless amorphous solid; mp 60−65 °C; $[\alpha]_D$ −21° (*c* 0.30, $CHCl_3$); IR (film) ν_{max} 3418, 2935, 1740, 1634, 1436, 1283, 1195, 1097, 768 cm^{-1}; ^{1}H- and ^{13}C-NMR data, see Table 1; LRDEIMS *m/z* (rel int) $[M]^+$ 452 (4), 243 (20), 225 (100), 211 (35), 210 (14), 193 (18), 192 (21), 183 (21), 182 (20), 179 (28), 161 (12), 160 (11), 151 (19), 150 (32), 149 (27), 139 (33), 123 (16), 109 (16), 81 (50), 41 (23); HRDEIMS $[M]^+$ 452.1682, ($C_{22}H_{28}H_{10}$ requires 452.1683), *m/z* 225.0766 ($C_{11}H_{13}O_5$ requires 225.0763).

***δ*-Amyrin acetate (14):** colorless plates, mp 209−210 °C, (lit.[10] 207−209 °C); $[\alpha]_D$ −31° (*c* 0.17, $CHCl_3$), (lit.[10] −36.5°); correct IR, ^{1}H NMR, and ^{13}C NMR;[10] correct MS.[10,11]

Mixture of *δ*-Amyrin eicosanoate (7), *δ*-amyrin docosanoate (8), *δ*-amyrin tetracosanoate (9), *δ*-amyrin hexacosanoate (10), *δ*-amyrin octacosanoate (11), and *δ*-amyrin triacotanoate (12): semicrystalline white solid; mp 78.5−80 °C; IR (film) ν_{max} 2916, 2850, 1713, 1472, 1377, 1262, 1172, 1098, 1013, 971, 803, 717 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 0.69 (3H, s, 20α-CH_3), 0.83 (3H, s, 4α-CH_3), 0.84 (6H, s, 4*β*-CH_3, 8*β*-CH_3), 0.87 (3H, s, 10*β*-CH_3), 0.92 (3H, s, 20*β*-CH_3), 1.00 (3H, s, 17*β*-CH_3), 1.15 (3H, s, 14α-CH_3), 2.24 (1H, dd, *J* = 13.9, 2.0 Hz, H-19a), 2.28 (2H, t, *J* = 7.0 Hz, OOCCH_2), 2.64 (1H, ddd, *J* = 14.8, 4.9, 1.9 Hz, H-12a), 4.49 (1H, dd, *J* = 10.0, 6.3 Hz, H-3α), 1.24 (2nH, br s, $(CH_2)_n$); HRDEIMS, H-triazine for calibration, $[M]^+$ 721 (5), found 720.6783 ($C_{50}H_{88}O_2$ requires 720.6784), $[M]^+$ 749 (27), found 748.7095 ($C_{52}H_{92}O_2$ requires 748.7097), $[M]^+$ 777 (17), found 776.7411 ($C_{54}H_{96}O_2$ requires 776.7410); $[M]^+$ 805 (48), found 804.7708 ($C_{56}H_{100}O_2$ requires 804.7723), $[M]^+$ 833 (7), found 832.8051 ($C_{58}H_{104}O_2$ requires 832.8036), $[M]^+$ 861 (1), found 860.8361, ($C_{60}H_{108}O_2$ requires 860.8349).

Hydrolysis of 7−12. The mixture of *δ*-amyrin esters (**7**−**12**) (17 mg) was refluxed with 5% KOH in MeOH (2 mL) and C_6H_6 (20 mL) for 24 h. The resulting clear solution was concentrated *in vacuo*, H_2O (25 mL) was added, and the solution was extracted with $CHCl_3$ (5 × 20 mL). The organic layer was concentrated in vacuo to yield *δ*-amyrin (**13**); mp and mixed mp 193−197 °C. The aqueous layer was acidified with dilute HCl, extracted with EtOAc (5 × 20 mL), and the EtOAc extract was concentrated *in vacuo* to yield a mixture of tetracosanoic acid, hexacosanoic acid, octacosanoic acid, and triacontanoic acid (8.8 mg) as a white semicrystalline solid; mp 76.5−77.5 °C; IR (film) ν_{max} 3500−2500 (br), 2921, 2850, 1713, 1459, 1376, 720 cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 0.88 (3H, t, *J* = 6.1 Hz, $(CH_2)_n$-CH_3), 1.25 (2nH, br s, $(CH_2)_n$), 1.63 (2H, m, CH_2CH_2O), 2.35 (2H, t, *J* = 7.3 Hz, CH_2CH_2O); LRDEIMS *m/z* (rel int.) $[M]^+$ 452 (2), $[M]^+$ 424 (23), $[M]^+$ 396 (88), $[M]^+$ 368 (8), 353 (12), 185 (12), 129 (39), 111 (12), 97 (25), 83 (31), 73 (66), 57 (100), 43 (100); HRDEIMS $[M]^+$ 452.4587, ($C_{30}H_{60}O_2$ requires 452.4593); found $[M]^+$ 424.4280, ($C_{28}H_{56}O_2$ requires 424.4280).

References and Notes

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