Phytochemistry, Vol. 31, No. 10, pp. 3609–3612, 1992
Printed in Great Britain.

0031-9422/92 $5.00+0.00

PIPERIDINE ALKALOIDS FROM *PIPER RETROFRACTUM* FRUITS

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(*Received* 25 *November* 1991)

Key Word Index—*Piper retrofractum*; Piperaceae; fruits; piperidine alkaloids; piperoctadecalidine; pipereicosalidine.

Abstract—Two new piperidine alkaloids, piperoctadecalidine and pipereicosalidine have been isolated from the fruits of *Piper retrofractum* (Piperaceae) along with two known piperidine alkaloids piperine and pipernonaline. The structures of the new compounds were determined to be (2*E*,4*E*,14*Z*)-*N*-(2,4,14-octadecatrienoyl)piperidine and (2*E*,4*E*,16*Z*)-*N*-(2,4,16-eicosatrienoyl)piperidine, respectively, by spectral and synthetic methods.

INTRODUCTION

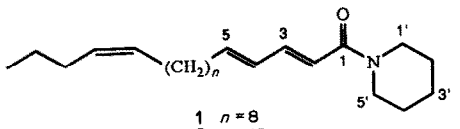
The fruits of Piperaceae species have recently received much attention because they have many physiologically active principles [1, 2]. Among these components, unsaturated amides constitute a major group of secondary metabolites. In continuing our studies on the chemical components of *Piper* fruits, we have isolated two new piperidides named piperoctadecalidine (**1**) and pipereicosalidine (**2**) from *P. retrofractum*, together with two known piperidides, piperine (**3**) and pipernonaline (**4**). We describe the structural elucidation of the two new compounds.

RESULTS AND DISCUSSION

A hexane extract of the fruits of *P. retrofractum* was fractionated by a combination of CC on silica gel and a Lobar column and finally purified by recycling prep. HPLC to afford compounds **1** and **2**.

Compound **1** had the molecular formular $C_{23}H_{39}NO$ (*m/z* 345.3014) indicating five degrees of unsaturation. The alkaloidal nature of the compound was indicated by a positive Dragendorff reaction. The absorption bands at 1651 (conjugated carbonyl group), 1624 (conjugated double bond) and 999 (*trans*-double bond) cm^{-1} in the FT-IR spectrum and λ_{max} at 265 nm in the UV spectrum suggested the presence of a conjugated system related to 2*E*,4*E*-dienamide as observed in those of **5** [3]. The ^1H and ^{13}C NMR spectra indicated signals due to one methyl [δ0.90 (3H, *t*)], three allylic methylenes [δ2.14 (2H, *m*), 2.0 (4H, *m*)], a conjugated diene [δ7.24 (1H, *dd*, *J* = 14.8, 10.6 Hz). 6.27 (1H, *d*, *J* = 14.8 Hz), 6.16 (1H, *dd*, *J* = 15.1, 10.6 Hz), 6.04 (1H, *m*)], an isolated double bond [δ5.35 (2H, *m*)], an amide carbonyl group (δ165.3) being characteristic of a piperidine ring moiety [4].

In the ^1H NMR spectrum (300 MHz), a doublet at δ6.27 (H-2) and a double doublet at δ7.24 (H-3) were assigned to *trans* α- and β-olefinic protons, respectively, conjugated to the amide carbonyl group. The multiplet centred at 5.35 (2H) was assigned to the protons on the isolated *cis*-double bond. The geometry of this double bond was based on the coupling constants of these olefinic protons ($W_{1/2}$ ~9 Hz). The location of this double bond in the molecule was deduced by detailed analysis of its 2D ^1H–^1H COSY and ^{13}C–^1H heterocorrelation. The *cis*-olefinic protons at δ5.35 (2H, *m*), which showed correlation peaks with the carbon signals of δ129.7 and 129.3 in the ^{13}C–^1H heterocorrelation spectrum, were coupled to the two allylic methylene protons centred at δ2.0 (4H, *m*). This latter signal was also correlated with the poorly resolved methylene proton around δ1.28 (H_2-17) which was coupled with the methyl proton at δ0.90 (Me-18). In addition, another allylic methylene proton at δ2.14 (H_2-6) was coupled with a *trans*-olefinic proton at δ6.04 (H-5).



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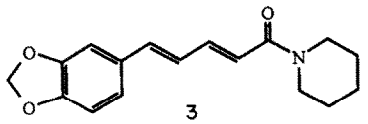
2 *n* = 10



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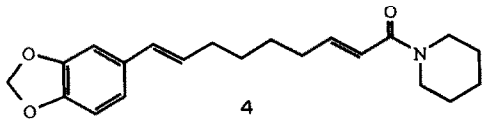

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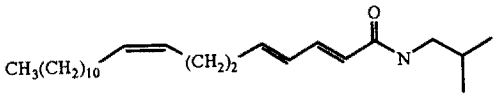

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*Author to whom correspondence should be addressed.

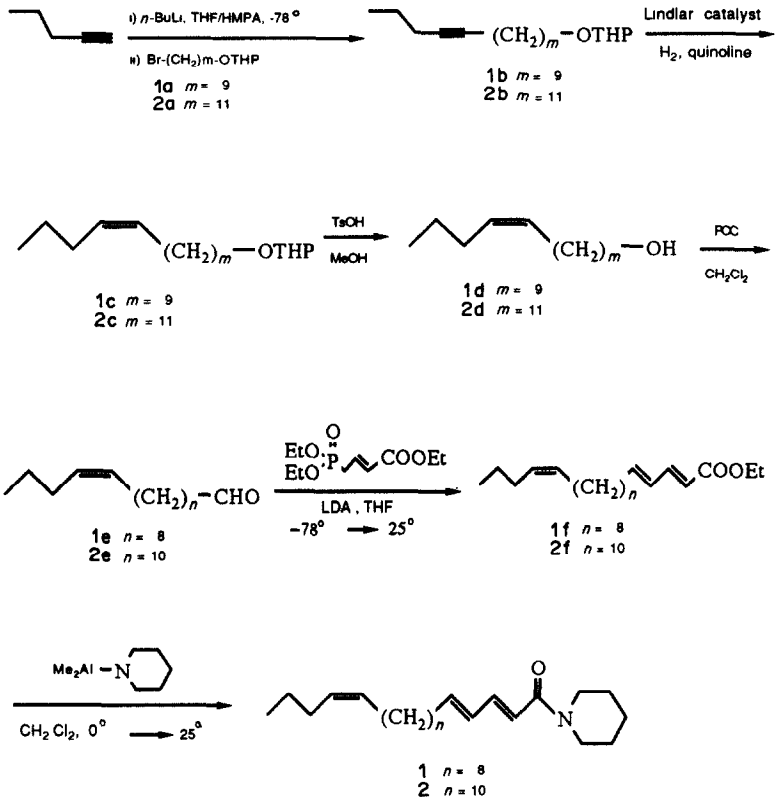

Fig. 1. Synthetic scheme of compounds **1** and **2**.

On the basis of the above spectral data and 2D COSY experiments, the structure of **1** was established to be (2*E*,4*E*,14*Z*)-*N*-(2,4,14-octadecatrienoyl)piperidine, and confirmed by the following synthesis. 1-Pentyne was reacted with *n*-BuLi in THF and then treated with bromoalcohol THP ether (**1a**) in the presence of hexamethylphosphoramide (HMPA) as a cosolvent to afford **1b**. The triple bond in **1b** was selectively hydrogenated to the *cis*-olefin (**1c**) with Lindlar catalyst (Pd-C on $CaCO_3$). Depyrenylation [5] of **1c** followed by oxidation and Wadsworth–Emmons reaction [6] with triethyl phosphonocrotonate gave a triene ester **1f**. Finally, treatment of **1f** with dimethylaluminium piperidide [7] in CH_2Cl_2 gave (2*E*,4*E*,14*Z*)-*N*-(2,4,14-octadecatrienoyl)piperidine (**1**) which was identical with the natural product (chromatographic behaviour and spectral data).

Compound **2** was identified as (2*E*,4*E*,16*Z*)-*N*-(2,4,16-eicosatrienoyl)piperidine. It gave spectral features almost identical to those of **1**, but the EI mass spectrum showed a $[M]^+$ at *m/z* 373, which exceeded that of **1** by 28 mu. In addition, it had additional signals at δ29.2–29.8 of methylene carbons compared with **1** in the ^{13}C NMR spectrum (126 MHz). The structure was also confirmed by synthesis in a similar way to that of **1**.

EXPERIMENTAL

General. Recycling prep. HPLC (JAI, LC-20) was used for sepn of the mixt. The column employed was JAIGEL GS-320 (20 mm i.d. × 500 mm). MPLC was carried out on silica gel (Merck 9390). NMR spectra were recorded at 300 Mz (^1H) and 126 MHz (^{13}C) with TMS as int. std. All 2D and DEPT spectra were recorded using pulse programs supplied by Bruker. The fruits were collected in Jawa, Indonesia by I.K. in March 1989.

Exraction and isolation. Ripe fruits (450 g) were extd with *n*-hexane to give 20 g of crude ext. Part of the ext (8 g) was fractionated by CC using EtOAc–CH_2Cl_2 solvent system to give 4 frs, I (CH_2Cl_2) 5.2 g, II (EtOAc–CH_2Cl_2, 1:9) 1.5 g. III (EtOAc–CH_2Cl_2, 1:4) 0.2 g, IV (EtOAc) 0.1 g. Sepn of fr. II by MPLC (silica gel; EtOAc–*n*-hexane, 1:4), prep. TLC (silica gel; Me_2CO–*n*-hexane, 1:4) and finally by recycling prep. HPLC with MeOH gave **1** (40 mg) and **2** (45 mg). Rechromatography of fr. III by prep. TLC (silica gel; EtOAc–*n*-hexane, 3:7) gave piperine (**3**) (R_f 0.32, 60 mg) and pipernonaline (**4**) (R_f 0.40, 120 mg) identified by comparison of their spectroscopic properties with lit. values [8, 9].

Piperoctadecalidine (**1**). Oil. IR ν_{max}^{KBr} cm^{-1}: 1651, 1624, 1435, 1257, 1134, 999. UV λ_{max}^{MeOH} nm (ε): 265 (28 700). EIMS (70 eV) *m/z* (% rel. int.): 345 $[M]^+$ (100), 316 $[M-C_2H_5]^+$ (20), 302 (15), 248 (18), 192 (63), 178 (27), 164 (61), 138 (65), 112 $[C_6H_{10}NO]^+$ (33), 84 $[C_5H_{10}N]^+$ (84); HRMS: observed 345.3014, $C_{23}H_{39}NO$ requires 345.3032. ^1H NMR ($CDCl_3$, 300 MHz): δ7.24 (1H, *dd*, *J* = 14.7, 10.7 Hz, H-3), 6.27 (1H, *d*, *J* = 14.7 Hz, H-2), 6.18 (1H, *dd*, *J* = 15.2, 10.7 Hz, H-4), 6.04 (1H, *m*, H-5), 5.35 (2H, *m*, H-14 and H-15), 3.61, 3.49 (each 2H, *br s*, H_2-1′ and H_2-5′), 2.14 (2H, *q*, J = 7.0 Hz, H_2-6), 2.03–1.94 (4H, *m*, H_2-13 and H_2-16), 1.65–1.56 (6H, *m*, H_2-2′, H_2-3′ and H_2-4′), 1.42–1.28 (14H, *m*, methylenes), 0.90 (3H, *t*, *J* = 7.3 Hz, Me-18). ^{13}C NMR: see Table 1.

Pipereicosalidine (**2**). Oil. IR ν_{max}^{KBr} cm^{-1}: 1647, 1624, 1442, 1261, 1133, 1018. UV λ_{max}^{MeOH} nm (ε): 263 (26 500). EIMS (70 eV) *m/z* (% rel. int.): 373 $[M]^+$ (100), 344 $[M-C_2H_5]^+$ (20), 330 (20), 276 (12), 192 (42), 178 (20), 164 (50), 138 (65), 127 (45), 112 (25), 84 (50). ^1H NMR ($CDCl_3$, 500.13 MHz): δ.7.20 (1H, *dd*, *J* = 14.8, 10.8 Hz, H-3), 6.22 (1H, *d*, *J* = 14.8 Hz, H-2), 6.15 (1H, *dd*, *J* = 15.1,

Table 1. ^{13}C NMR spectral data of compounds **1** and **2***

C	1†	2‡
1	165.3 *s*	165.6 *s*
2	118.3 *d*	118.4 *d*
3	142.5 *d*	142.8 *d*
4	128.6 *d*	128.7 *d*
5	142.1 *d*	142.5 *d*
6	32.7 *t*	32.8 *t*
7–12	28.9–29.5 *t*§	—
7–14	—	29.1–29.7 *t*§
13	26.9 *t*[a]	—
14	129.7 *d*[b]	—
15	129.3 *d*[b]	27.1 *t*[a]
16	28.6 *t*[a]	130.0 *d*[b]
17	22.6 *t*	129.5 *d*[b]
18	15.5 *q*	28.7 *t*[a]
19	—	22.8 *t*
20	—	13.7 *q*
1′	46.5 *t*[c]	46.8 *t*[c]
2′	26.4 *t*[d]	26.6 *t*[d]
3′	24.4 *t*	24.6 *t*
4′	25.4 *t*[d]	25.5 *t*[d]
5′	42.9 *t*[c]	43.1 *t*[c]

*Multiplicities established by DEPT pulse sequence.

†Measured in $CDCl_3$ at 76 MHz.

‡Measured in $CDCl_3$ at 126 MHz.

§Overlapped.

[a–d]These assignments may be reversed in each column.

10.8 Hz, H-4), 6.03 (1H, *m*, H-5), 5.33 (2H, *m*, H-16 and H-17), 3.58, 3.46 (each 2H, *br s*, H_2-1′ and H_2-5′) 2.10 (2H, *q*, $J = 7.0$ Hz, H_2-6), 2.00–1.96 (4H, *m*, H_2-15 and H_2-18), 1.65–1.54 (6H, *m*, H_2-2′, H_2-3′ and H_2-4′), 1.42–1.25 (18H, *m*, methylenes), 0.87 (3H, *t*, $J = 7.2$ Hz, Me-20). ^{13}C NMR: see Table 1.

9-Bromononanol THP ether (**1a**). To a mixt. of 9-bromononaol (4.3 g, 19.5 mmol) and *p*-toluenesulphonic acid monohydrate (370 mg, 1.9 mmol) in CH_2Cl_2 (20 ml) was added dropwise dihydropyran (2.5 g, 29.3 mmol) with stirring at 25° under N_2. Stirring was continued for 3 hr. The mixt. was then poured into satd $NaHCO_3$ soln and extd with Et_2O. The organic ext. was washed with brine and dried over $MgSO_4$. The crude product obtained on removal of solvent was purified by CC on silica gel (EtOAc–*n*-hexane, 1:10) to give **1a** (5.5 g, 91%) as an oil. IR (neat) ν_{max} cm^{-1}: 1432, 1340, 1244, 1195, 1026, 981, 901. ^{1}H NMR ($CDCl_3$): δ4.58 (1H, *m*), 3.87 (1H, *m*), 3.72 (1H, *m*), 3.50 (1H, *m*), 3.42 (3H, *m*), 1.90–1.28 (20H, *m*).

11-Bromoundecanol THP ether (**2a**). Yield 93%. IR (neat) ν_{max} cm^{-1}: 1432, 1343, 1250, 1195, 1027. ^{1}H NMR ($CDCl_3$): δ4.58 (1H, *m*), 3.87 (1H, *m*), 3.73 (1H, *m*), 3.50 (1H, *m*), 3.42 (3H, *m*), 1.89–1.28 (24H, *m*).

10-Tetradecyn-1-ol THP ether (**1b**). To a stirred soln of 1-pentyne (691 mg, 10.1 mmol) in THF (3 ml) was added dropwise *n*-BuLi (6.3 ml, 10.1 mmol) at −78°. The reaction mixt. was allowed to warm to 0° and HMPA (3 ml) was added with stirring. After 10 min, the bromide **1a** (3.1 g, 10.1 mmol) was added to the mixt. Stirring was continued overnight at room temp. The reaction mixt. was extd with Et_2O and washed. The Et_2O ext. was concd and subjected to CC over silica gel (EtOAc–*n*-hexane, 1:20) to afford **1b** (2.8 g, 93%) as an oil. IR (neat) ν_{max} cm^{-1}: 1427, 1337, 1194, 1153, 1026, 981, 901. ^{1}H NMR ($CDCl_3$): δ4.58 (1H, *m*), 3.87 (1H, *m*), 3.72 (1H, *m*), 3.50 (1H, *m*), 3.39 (1H, *m*), 2.13 (2H, *m*), 1.82–1.27 (24H, *m*), 0.96 (3H, *t*, $J = 7.3$ Hz).

12-Hexadecyn-1-ol THP ether (**2b**). Yield 73%. IR (neat) ν_{max} cm^{-1}: 1454, 1342, 1195, 1020, 979. ^{1}H NMR ($CDCl_3$): δ4.58 (1H, *m*), 3.86 (1H, *m*), 3.73 (1H, *m*), 3.50 (1H, *m*), 3.38 (1H, *m*), 2.12 (2H, *m*), 1.87–1.27 (28H, *m*), 0.99 (3H, *t*, $J = 7.3$ Hz).

cis-10-Tetradecen-1-ol THP ether (**1c**). Compound **1b** (2.8 g, 9.5 mmol) in *n*-hexane (5 ml) was hydrogenated at atmos. pres. over Lindlar catalyst. After uptake of H_2 was complete, the reaction of mixt. was filtered and washed with 0.1 M HCl. The crude product was purified by flash CC (EtOAc–*n*-hexane, 1:40) to give the *cis*-olefin **1c** (2.6 g, 93%) as an oil. IR (neat) ν_{max} cm^{-1}: 1453, 1357, 1195, 1130, 1020, 982. ^{1}H NMR ($CDCl_3$): δ5.35 (2H, *m*), 4.58 (1H, *m*), 3.87 (1H, *m*), 3.74 (1H, *m*), 3.50 (1H, *m*), 3.38 (1H, *m*), 2.0 (4H, *m*), 1.84–1.29 (22H, *m*), 0.90 (3H, *t*, $J = 7.3$ Hz).

cis-12-Hexadecen-1-ol THP ether (**2c**). Yield 79%. IR (neat) ν_{max} cm^{-1}: 1453, 1358, 1195, 1129, 1073, 1020, 981. ^{1}H NMR ($CDCl_3$): δ5.35 (2H, *m*), 4.57 (1H, *m*), 3.86 (1H, *m*), 3.73 (1H, *m*), 3.49 (1H, *m*), 3.36 (1H, *m*), 2.01 (4H, *m*), 1.86–1.27 (26H, *m*), 0.90 (3H, *t*, $J = 7.3$ Hz).

cis-10-Tetradecen-1-ol (**1d**). A mixt. of THP ether **1c** (2.6 g, 8.9 mmol) and *p*-toluenesulphonic acid monohydrate (168 mg, 0.9 mmol) inMeOH was stirred for 2 hr at room temp. The reaction mixt. was concd *in vacuo* and subjected to CC on silica gel (EtOAc–*n*-hexane, 1:6) to give alcohol **1d** (1.5 g, 77%) as an oil. IR (neat) ν_{max} cm^{-1}: 3302, 1443, 1051. ^{1}H NMR ($CDCl_3$): δ5.36 (2H, *m*), 3.62 (2H, *t*, $J = 6.7$ Hz), 2.01 (5H, *m*), 1.55 (2H, *m*), 1.43–1.29 (14H, *m*), 0.90 (3H, *t*, $J = 7.3$ Hz).

cis-12-Hexadecen-1-ol (**2d**). Yield 76%. IR (neat) ν_{max} cm^{-1}: 3294, 1453, 1050. ^{1}H NMR ($CDCl_3$): δ5.36 (2H, *m*), 3.63 (2H, *t*, $J = 6.5$ Hz), 2.01 (4H, *m*), 1.56 (3H, *m*), 1.43–1.27 (18H, *m*), 0.90 (3H, *t*, $J = 7.3$ Hz).

cis-10-Tetradecen-1-yl aldehyde (**1e**). To a stirred suspension of pyridinium chlorochromate (2.1 g, 9.9 mmol) [10] in CH_2Cl_2 was added a soln of alcohol **1d** (1.4 g, 6,6 mmol) in CH_2Cl_2 and the mixt. stirred for 1.5 hr at room temp. Et_2O was added and the supernatant liquid decanted off. The residue was washed with Et_2O (3 × 10 ml). The combined organic exts were filtered through a short pad of Florisil and the solvent removed. The crude product obtained was purified by CC on silica gel (EtOAc–*n*-hexane, 1:15) to produce the aldehyde **1e** (1.1 g, 88%) as an oil. IR (neat) ν_{max} cm^{-1}: 1719, 1453. ^{1}H NMR ($CDCl_3$): δ9.76 (1H, *t*, $J = 0.9$ Hz), 5.36 (2H, *m*), 2.42 (2H, *dt*, $J = 7.3$, 1.2 Hz), 2.01 (4H, *m*), 1.62 (2H, *m*), 1.43–1.30 (12H, *m*), 0.90 (3H, *t*, $J = 7.4$ Hz).

cis-12-Hexadecen-1-yl aldehyde (**2e**). Yield 88%. IR (neat) ν_{max} cm^{-1}: 1702, 1453. ^{1}H NMR ($CDCl_3$): δ9.76 (1H, *t*, $J = 1.8$ Hz), 5.36 (2H, *m*), 2.42 (2H, *dt*, $J = 7.3$, 1.8 Hz), 2.01 (4H, *m*), 1.62 (2H, *m*), 1.42–1.21 (16H, *m*), 0.90 (3H, *t*, $J = 7.3$ Hz).

(2*E*,4*E*,14*Z*)-2,4,14-*Octadecatrienoic acid ethyl ester* (**1f**). To a soln of lithium diisopropylamide (LDA), which was prepd from diisopropylamine (622 mg, 6.2 mmol) and *n*-BuLi in THF, was added triethyl phosphonocrotonate (1.4 g, 5.6 mmol) at −10°. After stirring for 10 min, the mixt. was cooled to −78°. Aldehyde **1e** (980 mg, 4.7 mmol) was then added slowly, the mixt. stirred and then allowed to warm to 25°. This was then poured into satd Na_2SO_4 soln (25 ml) and extd with Et_2O. The Et_2O ext was dried and concd. The residue was purified by flash CC (EtOAc–*n*-hexane, 1:15) to give the trienoic acid Et ester **1f** (934 mg, 65%) as an oil. IR (neat) ν_{max} cm^{-1}: 1714, 1612, 1441, 1361, 1290, 1252, 1170, 1030, 994. ^{1}H NMR ($CDCl_3$): δ7.20 (1H, *m*), 6.15 (2H, *m*), 5.78 (1H, *d*, $J = 1.5.4$ Hz), 5.35 (2H, *m*), 4.19 (2H, *q*, $J = 7.2$ Hz), 2.17 (2H, *m*), 2.01 (4H, *m*), 1.44–1.26 (17H, *m*), 0.90 (3H, *t*, $J = 7.3$ Hz).

(2E,4E,16Z)-2,4,16-*Eicosatrienoic acid ethyl ester* (**2f**). Yield 64%. IR (neat) ν_{max} cm^{-1}: 1714, 1612, 1442, 1361, 1252, 1170, 1030, 995. ^1H NMR ($CDCl_3$): δ7.26 (1H, *m*), 6.14 (2H, *m*), 5.78 (1H, *d*, $J=15.3$ Hz), 5.36 (2H, *m*), 4.19 (2H, *q*, $J=7.1$ Hz), 2.15 (2H, *m*), 2.00 (4H, *m*), 1.44–1.27 (21H, *m*), 0.90 (3H, *t*, $J=7.3$ Hz).

(2E,4E,14Z)-N-(2,4,14-*octadecatrienoyl*)*Piperidine* (**1**). To a coold soln of piperidine (744 mg, 8.7 mmol) in CH_2Cl_2 at $-40°$ was added trimethyl aluminium and the mixt. allowed to warm to 0° during a period of 20 min. A soln of ester **1f** (535 mg, 1.8 mmol) in CH_2Cl_2 was then added and the mixt. stirred overnight at room temp. The reaction mixt. was poured into satd sodium potassium tartrate soln (10 ml) and extd with CH_2Cl_2 (3 × 10 ml). The combined exts were dried over $MgSO_4$ and filtered. The solvent was evapd *in vacuo* and the crude product purified by flash CC (EtOAc–*n*-hexane, 1:4) to give the desired product **1** (332 mg, 55%) as an oil, which was identical with the natural product. In a similar way, (2*E*,4*E*,16*Z*)-*N*-(2,4,16-eicosatrienoyl)piperidine (**2**) was synthesized and was also obtained as an oil in 62% yield.

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