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Myrioneurinol: a novel alkaloid skeleton from *Myrioneuron nutans*

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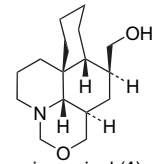
Abstract—A new alkaloid, myrioneurinol (**1**), was isolated from the leaves of *Myrioneuron nutans* and its structure determined from spectral analysis, including mass spectrometry and 2D NMR. Myrioneurinol (**1**) presented an unprecedented fused tetracyclic skeleton. The absolute configuration was established by the modified Mosher's method, using (*R*)- and (*S*)-9-anthrylmethoxyacetic acid (9-AMAA). A plausible biosynthetic pathway starting from L-lysine via Δ-piperideine was proposed for **1** in comparison with nitraramine biosynthesis and related alkaloids.

1. Introduction

The *Myrioneuron* genus is a small one comprising about 15 species, which is distributed over south-east Asia and belongs to the Rubiaceae.[1] The Rubiaceae is a large plant family known to biosynthesize a great variety of alkaloids with important pharmacological interests exemplified by quinine[2a–d] and camptothecin.[3a–c] *Myrioneuron nutans*, a small tree native in North-Viet Nam, was selected in the course of a screening program of plants for their cytotoxicity against tumor cells and also for the high content of alkaloids depicted in this species. Furthermore, there was no previous chemical study on this genus. The alkaloid extract showed cytotoxic activity against KB cells with IC_{50} of 50 μg/mL. Herein, we describe the isolation from *M. nutans* and the structural determination, including absolute configuration of a new alkaloid with a tetracyclic skeleton, myrioneurinol (**1**) containing a 1,3-oxazine ring system. We previously reported the isolation from *M. nutans*, the structure, and the synthesis of two epimeric tricyclic 1,3-oxazines, myrioxazines A and B.[4] Finally, a plausible biosynthetic pathway for myrioneurinol (**1**) is proposed in comparison with related alkaloids derived from lysine.



myrioneurinol (**1**)

2. Results and discussion

2.1. Isolation and structure determination

The dried and ground leaves (5 kg) of *M. nutans* were extracted with CH_2Cl_2 at pH 9 (NH_4OH) and the crude alkaloid obtained by acid–base purification of this extract was separated by a combination of column chromatography to yield myrioneurinol (**1**, 32 mg). Myrioneurinol **1** was obtained as an optically active colorless solid, $[\alpha]_D^{20}$ +63 (*c* 1, MeOH). In its ESI-MS, the protonated molecular ion was observed at *m/z* 266.2149 (calcd 266.2120 for $C_{16}H_{28}NO_2$, $[M+H]^+$), indicating the molecular formula $C_{16}H_{27}NO_2$. IR absorptions implied the presence of a hydroxyl group (ν 3400 cm^{-1}). The 1D NMR (^1H and ^{13}C) spectra showed 11 methylenes, four methines, and one quaternary carbon, in agreement with the molecular formula. The four degrees of unsaturation were thus assigned to four rings.

In the ^1H–^1H COSY spectrum of **1**, correlations between CH_2-3 (δ_H 1.50 and 1.72) and both CH_2-2 (δ_H 2.61 and 3.22) and CH_2-4 (δ_H 1.32 and 1.63) revealed the partial

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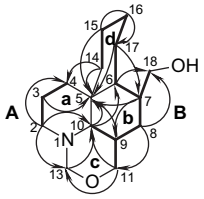


Figure 1. ^{1}H–^{1}H COSY (▬) and selected ^{1}H–^{13}C HBMC correlations (H⌒C) for **1**.

structure **A** drawn with bold bonds in Figure 1. The ^{13}C chemical shifts of CH_2-2 (δ_C 44.9) suggested its linkage to the nitrogen atom. An other set of connectivities determined the partial structure **B**: on one hand, CH_2-14 (δ_H 0.80 and 2.44) was correlated to CH_2-15 (δ_H 1.32 and 1.45), then CH_2-17 (δ_H 1.12 and 1.55) to CH_2-16 (δ_H 1.20 and 1.72) and finally CH_2-15 and 16 were correlated between themselves, forming a $-(CH_2)_4-$ spin system. On the other hand, CH-9 (δ_H 2.40) had correlations with CH_2-11 (δ_H 3.15 and 3.86), CH-10 (δ_H 2.22), and CH_2-8 (δ_H 0.74 and 1.50). This one (CH_2-8) was correlated to CH-7 (δ_H 1.45), which was further correlated to both CH_2-18 (δ_H 3.42 and 3.59) and CH-6 (δ_H 1.11) and finally this latter showed correlation with CH_2-17. The ^{13}C chemical shifts of CH_2-11 (δ_C 73.4) and CH_2-18 (δ_C 65.1) suggested their direct linkage to an oxygen atom, and those of CH-10 (δ_H 2.22 and δ_C 69.5) to a nitrogen atom. A 'W' coupling (^{4}J=1 Hz) was depicted between H-11_{eq} and H-13_{eq}. The chemical shifts of CH_2-13 (δ_C 86.7) indicated it was linked to both nitrogen and oxygen atoms.

The ^{2}J and ^{3}J HMBC correlations of the C-5 quaternary carbon (δ_C 36.2) with, on one hand, the protons of CH_2-17, CH_2-15, CH_2-14, CH-10, CH-9, CH-7, and CH-6 of the **B**-fragment and, on the other hand, with the protons at CH_2-4, and CH_2-3 of **A**-fragment provided the connection between the two substructures. Quaternary carbon C-5 was linked to C-6, C-10, and C-14 of **B**-fragment, as well as to C-4 of **A**-fragment (Fig. 1).

This structure was supported by the correlations of both CH-10 (δ_H 2.22) and CH_2-4 (δ_H 1.32 and 1.63) protons with C-14 carbon (δ_C 34.2). Cross peaks of CH_2-2 (δ_H 2.61 and 3.22) with C-10 carbon (δ_C 69.5) indicated their linkage through a nitrogen atom, resulting in a decahydroquinoline moiety. Finally, C-13 (δ_C 86.7) was correlated to CH_2-11 (δ_H 3.15 and 3.86), CH-10 (δ_H 2.22), and CH_2-2 (δ_H 2.61 and 3.22) protons, indicating its direct linkage to N-1 nitrogen and O-12 oxygen, and closing thus an 1,3-oxazine ring. Taking into account the molecular formula, the methylene at CH_2-18 was connected to a hydroxyl group and the gross planar structure of **1** was thus established as indicated in Figure 1.

The relative stereochemistry of **1** was deduced from the NOE correlations and the values of the ^{1}H–^{1}H vicinal coupling constants: H-10 and H-9 presented a large reciprocal coupling constant (J=11.0 Hz), indicative of their trans-diaxial disposition on the cyclohexane **b**-ring in the chair form (Table 1). Moreover, H-9 showed two other trans-diaxial coupling constants (J=10.6 and 12.0 Hz with H-11_{ax} and H-8_{ax}, respectively) and two small couplings (J=4.2 and 4.0 Hz with H-11_{eq} and H-8_{eq}, respectively).

Table 1. NMR data for myrioneurinol (**1**) ($CDCl_3$, 298 K), ^{1}H NMR (400.13 MHz), ^{13}C NMR (75.47 MHz)

Position	δ_C	δ_H	m	J (Hz)
2	44.9	3.22	ddd	12.2; 11.0; 4.0
	—	2.61	ddd	11.0; 4.8; 0.5
3	20.4	1.72	m	
	—	1.50	m	
4	19.7	1.63	ddd	13.3; 13.3; 3.0
	—	1.32	br d	13.3
5	36.2	—		
6	47.6	1.11	ddd	10.5; 10.5; 3.0
7	37.0	1.45	ddddd	12.1; 10.5; 6.0; 3.5; 3.5
8	31.0	1.50	ddd	12.1; 4.0; 3.5
	—	0.74	ddd	12.1; 12.0; 12.0
9	27.1	2.40	ddddd	12.0; 11.0; 10.6; 4.2; 4.0
10	69.5	2.22	d	11.0
11	73.4	3.86	ddd	10.8; 4.2; 1.0
	—	3.15	dd	10.8; 10.6
13	86.7	4.41	dd	10.3; 1.0
	—	4.36	d	10.3
14	34.2	2.44	br d	13.2
	—	0.80	dddd	13.2; 13.2; 4.1; 1.0
15	20.4	1.45	m	
	—	1.32	m	
16	26.6	1.72	m	
	—	1.20	m	
17	23.0	1.55	m	
	—	1.12	dddd	10.5; 10.4; 9.8; 3.5
18	65.1	3.59	dd	10.6; 3.5
	—	3.42	dd	10.6; 6.0

Thus, H-9 was axial on both **b**- and **c**-rings, indicating the trans junctions of these two rings (Fig. 2). The proton H-6 showed two trans-diaxial coupling constants with H-7 (10.5 Hz) and H-17_{ax} (10.5 Hz) and one cis coupling (3.0 Hz with H-17_{eq}), indicating its axial position on both **b**- and **d**-rings and the axial position of H-7 on the **b**-ring. Hence, the oxymethylene CH_2-18 was equatorial on the **b**-ring. Strong NOEs observed on the NOESY spectrum between H-10 and H-14_{ax}, H-13_{ax}, H-11_{ax}, H-8_{ax}, and H-6 and between this latter one (H-6) and H-14_{ax}, H-8_{ax}, and H-16_{ax} allowed to determine their disposition on the same face of **1**. In addition, the correlation of H-3_{ax} with H-14_{eq} and of H-7 with both H-4_{ax} and H-9_{ax} was observed. Complete NOE analysis indicated the chair conformation for the four rings (**a**–**d**) of **1** and the relative configuration shown in Figure 2. Myrioneurinol (**1**) was characterized by a new alkaloid tetracyclic skeleton, including an 1,3-oxazine ring, which can be compared to the tricyclic alkaloid myrioxazine A, as they have in common the tricyclic **a**-, **b**-, and **c**-ring system.[4]

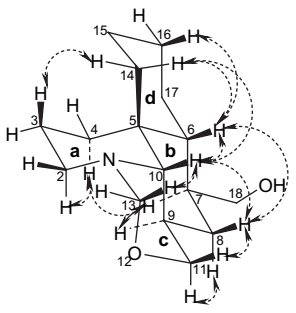


Figure 2. Selected NOE interactions for **1**.

2.1.1. Determination of absolute configuration of myrioneurinol (1) by derivation with (*R*)- and (*S*)-9-anthrylmethoxyacetic acid (9-AMAA). If the absolute stereochemistry of chiral secondary alcohols could be determined by MTPA or MPA (Mosher's method),[5a–h] they are not recommended for β-chiral primary alcohols. However, Reguera and co-workers have demonstrated that absolute configuration of such β-chiral primary alcohol can be established by using 9-anthrylmethoxyacetic acid (9-AMAA) instead of MTPA.[6a–e]

According to this regard, (*R*)- and (*S*)-9-AMAA were prepared by a modified method of the previously reported paper.[6b] Compound **4** was obtained in 65% yield from anthracene (**2**) by reaction with ethyl oxalyl chloride following with $NaBH_4$. Methylation of **4** with MeI and Ag_2O afforded **5**, which was hydrolyzed to yield the free acid **6**. Racemic resolution of 9-AMAA **6** was performed by its derivation with (−)-menthol to afford **7** and **8**. These two diastereoisomers (*S*)-9-AMAA-(−)-menthyl (**7**) and (*R*)-9-AMAA-(−)-menthyl (**8**) were separated by column chromatography and their structure were determined from comparison of their NMR data and optical rotations with those reported in the literature.[6b] (*S*)-AMAA (**9**) and (*R*)-AMAA (**10**) obtained from hydrolysis of the corresponding menthyl esters (**7** and **8**) in basic conditions were esterified with myrioneurinol (**1**) to yield two diastereoisomers **11** and **12**, respectively (Scheme 1).

The resulting esters **11** and **12** were analyzed by NMR and the $\Delta\delta_{R-S}$ ($\delta_{(R)\text{-9-AMA-myrioneurinol}}-\delta_{(S)\text{-9-AMA-myrioneurinol}}$) values were calculated. These values were positive on the upside of the molecule whereas they were negative on the other side, except for H-8_{eq} (Fig. 3). By using Mosher's model,[5a–c,6b] the absolute configuration of the chiral carbon C-7 was determined as *S*. According to the relative configuration established from $^3J_{H-H}$ coupling constants and NOE interactions, the absolute configuration of myrioneurinol (**1**) was determined as 5*R*,6*R*,7*S*,9*R*,10*S*.

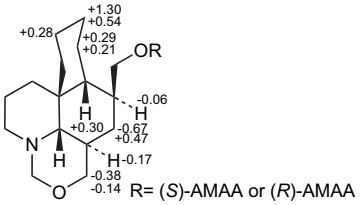
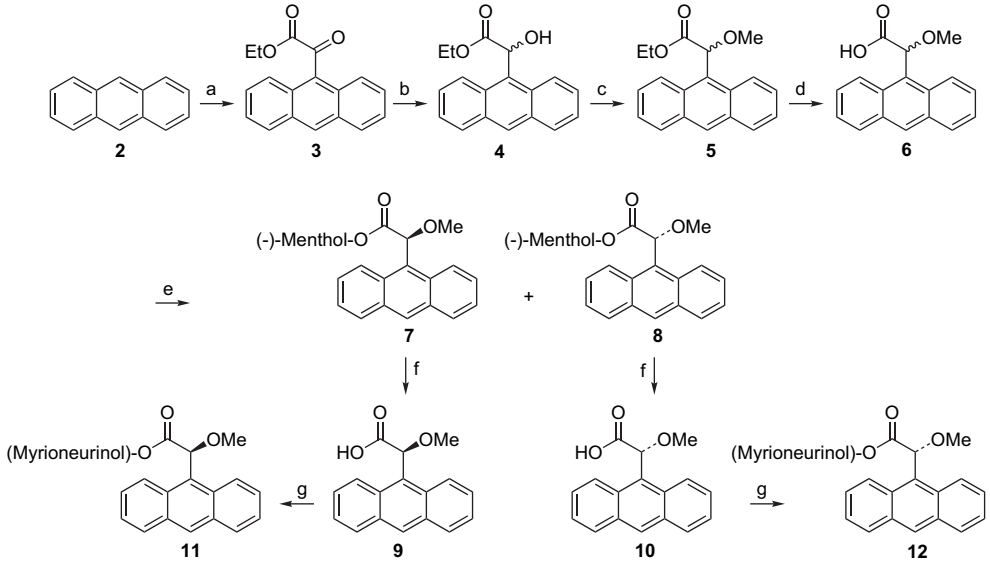


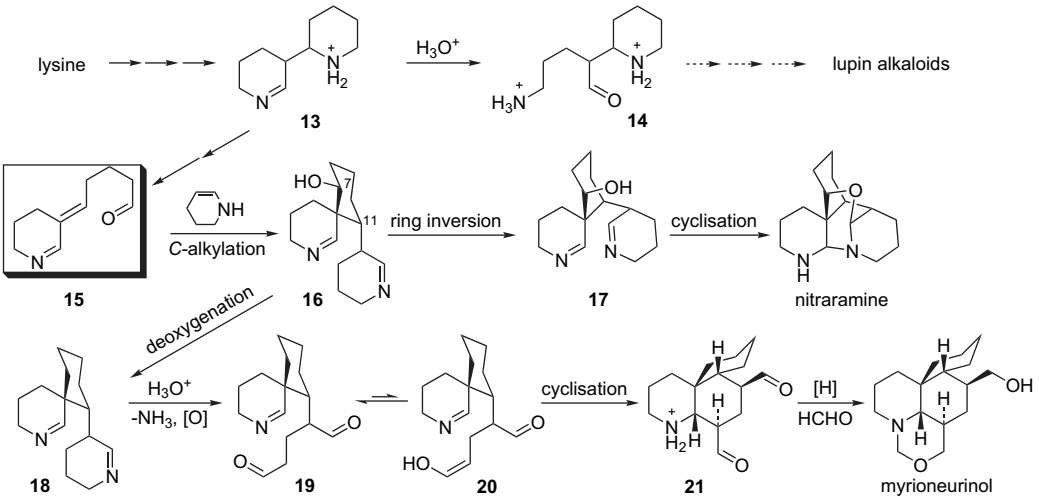
Figure 3. Some significant $\Delta(\delta_{(R)\text{-9-AMAA-myrioneurinol}}-\delta_{(S)\text{-9-AMAA-myrioneurinol}})$ values of the two esters **11** and **12**.

2.2. Biosynthesis of myrioneurinol (1)

Retroanalysis of myrioneurinol (**1**) shows piperidine ring substitutions, which are characteristic for Δ-piperideine derived (from lysine) polycyclic alkaloids. Nitraria alkaloids such as nitramine and sibirine, and also lupin alkaloids such as lupinine, sparteine, and matrine, are good examples for products derived from Δ-piperideine. A hypothetical biosynthetic pathway for lupin alkaloids was previously reported, in which the amino enamine **13** resulting from lysine could be immediately hydrolyzed to afford the intermediate **14**. From this intermediate, a number of lupin alkaloids such as lupinine and sparteine are biosynthesized. However, the amino enamine **13** could be also transformed to the key intermediate **15**.[7a–d] Addition of a third Δ^2-piperideine unit to **15**, followed by cyclisation leads to intermediate **16** (Scheme 2). Compound **16** could be, on one hand, transformed to nitraramine with ring inversion leading to a ring conformation (**17**) where the hydroxyl at C-7 and the piperideine ring at C-11 are in a 1,3-diaxial disposition. This facilitates the formation of the two successive aminal bonds by cyclisation process. On the other hand, compound **16** could be deoxygenated to afford the diimine **18**, which could be hydrolyzed and oxidized into the dialdehyde **19**. The enol form of **19** could cyclise to afford the amino dialdehyde **21**. In the last step, **21** is reduced and condensed with formaldehyde to complete the myrioneurinol biosynthesis (Scheme 2). Note that no ring inversion of the intermediate **14** is needed for the myrioneurinol (**1**)



Scheme 1. (a) Ethyl oxalyl chloride, CH_2Cl_2, 25 °C, 12 h, 86%; (b) $NaBH_4$, MeOH, 0 °C, 12 h, 85%; (c) MeI, Ag_2O, CH_2Cl_2, 25 °C, 24 h, 67%; (d) LiOH, THF/MeOH/H_2O (3:1:1), 0–25 °C, 4 h, 71%; (e) (−)-menthol, DCC, DMAP, CH_2Cl_2, 25 °C, 24 h, 32% for **7** and 29% for **8**; (f) 2 N NaOH, EtOH, 25 °C, 12 h, 62% for **9** and 51% for **10**; (g) myrioneurinol (**1**), DCC, DMAP, CH_2Cl_2, 25 °C, 24 h, 38% for **11** and 31% for **12**.



Scheme 2. Plausible biosynthetic pathway for myrioneurinol (**1**) and related alkaloids.

formation. This is a difference in the biosynthetic pathways of myrioneurinol (**1**) and nitraramine.

2.3. Biological activities' evaluation

When evaluated for its cytotoxic and antimalarial activities, myrioneurinol (**1**) induced weak inhibition on KB cell proliferation with IC_{50} of 26 μg/mL. However, it showed a stronger activity in antimalarial assay on *Plasmodium falciparum* (IC_{50}: 11 μg/mL), suggesting that its moderate antimalarial activity was not due to its cytotoxicity.

3. Conclusion

This paper describes the isolation and absolute structure determination of the tetracyclic alkaloid, myrioneurinol (**1**) showing a new skeleton. The absolute configuration was established by analysis of its derivatives with (*R*)- and (*S*)-9-AMAA, which were resolved from racemic form through their esters with (−)-menthol. Retroanalysis of structure of **1** allows to suggest its biosynthesis from Δ-piperideine derived from lysine.

4. Experimental section

4.1. General

Melting points were determined on a Reichert microscope and were uncorrected. Optical rotations were measured on a Perkin Elmer 341 Kontron spectrophotometer. ESI-mass spectra were performed on an API Q-STAR PULSAR i of Applied Biosystems. ^{13}C spectra were recorded on a Bruker AC 300 spectrometer operating at 300.13 and 75.43 MHz. ^{1}H 1D and 2D NMR spectra were recorded on a Bruker Avance 400 spectrometer operating at 400.13 MHz. For HMBC experiments the delay (1/2*J*) was 70 ms and for the NOESY experiments the mixing time was 150 ms.

4.2. Plant material and extraction

M. nutans Drake was collected in North-Viet Nam in June 2000 and a specimen (VN 700) was deposited in the Institute of Botany, VAST, Viet Nam. The dried and ground leaves (5 kg) were alkalinized with aqueous NH_4OH (10%) and extracted with CH_2Cl_2. After evaporation to dryness, the CH_2Cl_2 crude extract was suspended in an aqueous 5% HCl solution and then extracted with CH_2Cl_2. The crude alkaloid extract obtained after solvent removing under reduced pressure was chromatographed over silica gel column and eluted with a gradient of CH_2Cl_2/MeOH (from 1/0 to 0/1) to provide myrioneurinol (**1**, 32 mg).

4.3. Natural compound characterization

4.3.1. Myrioneurinol (1). $C_{16}H_{27}NO_2$; colorless microcrystalline solid (Et_2O/EtOH); mp: 145–146 °C; $[\alpha]_D^{20}$ +63.2 (*c* 1, MeOH); IR (KBr) ν_{max} (cm^{-1}): 3400, 2929, 2859, 1468, 1450, 1380, 1280, 1180, 1166, 1134, 1032, 742, 704; ESI-MS (TOF), *m/z*: 266.2149 $[M+H]^+$ (calcd 266.2120 for $C_{16}H_{28}NO_2$); ESI-MSMS (TOF) on $[M+H]^+$ ion, *m/z*: 266 $[M+H]^+$, 236, 218, 206, 187, 176, 173, 159, 145, 131, 119, 110, 107, 105, 93, 79, 70, 67, 56, 44.

4.4. Procedures for preparation of compounds 3–12

4.4.1. Ethyl (9-anthryl)glyoxylate (3). To a solution of anthracene (8 g, 44 mmol) in anhydrous CH_2Cl_2 (150 mL) was added ethyl oxalyl chloride (5.1 mL, 49 mmol) at 0 °C. The resulting solution was stirred for 1 h and then warmed to 25 °C for 12 h. Water (100 mL) was added and the organic layer was separated. The aqueous solution was extracted with CH_2Cl_2 (2×100 mL). The combined extracts were washed with 5% $NaHCO_3$ and water, and dried over $MgSO_4$. The solvent was removed under diminished pressure and the crude was purified by silica gel column chromatography (*n*-hexane/EtOAc) to afford **3** (10.5 g, 86% yield). ESI-MS *m/z* 279 $[M+H]^+$.

4.4.2. (±)-Ethyl α-hydroxy-α-(9-anthryl) acetate (4). A solution containing **4** (9.5 g, 34.17 mmol) in MeOH (50 mL) was treated with $NaBH_4$ (1.3 g, 34.17 mmol) at 0 °C. The reaction mixture was stirred for 5 h. Saturated aqueous solution of NH_4Cl (50 mL) was added, and then the mixture solution was warmed to 25 °C and extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts

were washed with water and dried over $MgSO_4$. The solvent was removed under diminished pressure. The crude was chromatographed on silica gel column and eluted with gradient mixture of *n*-hexane/EtOAc to provide **4** (8.1 g, 85% yield): mp 107 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 0.97 (t, 7.1 Hz, 3H), 4.12 (q, 7.1 Hz, 2H), 6.55 (s, 1H), 7.28 (m, 4H), 7.99 (d, 7.8 Hz, 2H), 8.32 (d, 8.7 Hz, 2H), 8.45 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz): 13.8, 62.2, 68.1, 123.8, 124.8, 126.5, 128.5, 129.1, 129.2, 130.3, 131.5, 175.1; ESI-MS *m*/*z* 281 $[M+H]^+$.

4.4.3. (±)-Ethyl α-methoxy-α-(9-anthryl) acetate (5). To a solution containing **4** (6 g, 21.42 mmol) and MeI (6 mL) in anhydrous CH_2Cl_2 (50 mL) was added Ag_2O (5.9 g, 25.4 mmol). The reaction mixture was stirred at 25 °C for 12 h and then water (50 mL) was added. The solution mixture was extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were washed with water and dried over $MgSO_4$. The solvent was evaporated under diminished pressure and the crude was purified over silica gel column chromatography (*n*-hexane/EtOAc), giving **5** (4.2 g, 67% yield): mp 79 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 1.02 (t, 7.1 Hz, 3H), 3.39 (s, 3H), 4.10 (q, 7.1 Hz, 2H), 6.25 (s, 1H), 7.49 (m, 4H), 8.01 (dd, 0.5 and 8.3 Hz, 2H), 8.45 (s, 1H), 8.55 (d, 8.8 Hz); ^{13}C NMR ($CDCl_3$, 75.47 MHz): 13.9, 57.4, 61.3, 77.2, 124.4, 124.9, 126.4, 127.4, 129.1, 129.2, 130.6, 131.5, 171.3; ESI-MS *m*/*z* 295 $[M+H]^+$.

4.4.4. (±)-α-Methoxy-α-(9-anthryl) acetic acid (6). To a solution of **5** (3.5 g, 11.9 mmol) in a mixture of THF/MeOH/H_2O (3:1:1, 30 mL) was added LiOH (0.6 g, 23.8 mmol) at 0 °C. The resulting mixture was stirred for 3 h and then warmed to 25 °C for 1 h. To this solution mixture, 1 N HCl was slowly added until pH 7. The volatile layer was removed under diminished pressure. The mixture solution was extracted with EtOAc (4×50 mL). The combined organic extracts were washed with water and dried over $MgSO_4$. The solvent was removed under diminished pressure, the crude was chromatographed on silica gel column, and eluted with a gradient mixture of CH_2Cl_2/MeOH to afford **6** (2.2 g, 71% yield): mp 188 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 3.36 (s, 3H), 6.28 (s, 1H), 7.49 (m, 4H), 8.01 (dd, 0.5 and 8.2 Hz, 2H), 8.46 (d, 8.8 Hz, 2H), 8.49 (s, 1H); ESI-MS *m*/*z* 267 $[M+H]^+$.

4.4.5. (−)-Menthyl (+)-(*S*)-α-methoxy-α-(9-anthryl) acetate (7) and (−)-menthyl (−)-(*R*)-α-methoxy-α-(9-anthryl) acetate (8). A solution of **7** (1.5 g, 5.6 mmol) and (−)-menthol (1.1 g, 7.0 mmol) in anhydrous CH_2Cl_2 (20 mL) was treated with DCC (1.2 g, 5.6 mmol) and DMAP (0.1 g, 0.8 mmol) at 25 °C. The resulting solution was stirred for 24 h and then 50 mL water was added. The mixture was extracted with CH_2Cl_2 (3×50 mL). The combined extracts were washed with water and dried over $MgSO_4$. The crude obtained after removing the solvent was chromatographed on silica gel column and eluted with a mixture of cyclohexane/CH_2Cl_2 to afford **7** (0.72 g, 32% yield) and **8** (0.65 g, 29% yield).

Compound **7**: $[\alpha]_D^{20}$ −5.8 (*c* 0.002, EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz): 0.44 (q, 9 Hz, 1H), 0.5–2.0 (m, 8H), 0.64 (d, 6.7 Hz, 3H), 0.75 (d, 7.2 Hz, 3H), 0.84 (d, 7.2 Hz, 3H), 3.38 (s, 3H), 4.73 (br dd, 3.1 and 9.8 Hz, 1H), 6.25 (s, 1H), 7.49 (m, 4H), 7.78 (d, 7.7 Hz, 2H), 8.44 (s, 1H), 8.57 (d, 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.47 MHz): 16.5, 20.6, 21.7, 23.4, 26.5, 31.1, 33.9, 39.9, 46.6, 57.4, 75.4, 77.3, 124.5, 124.9, 126.3, 126.9, 129.0, 130.6, 131.4, 170.2; ESI-MS *m*/*z* 405.2365 $[M+H]^+$.

Compound **8**: $[\alpha]_D^{20}$ −55.1 (*c* 0.002, EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz): −0.08 (d, 5.9 Hz, 3H), 0.05 (d, 2.5 Hz, 3H), 0.09 (m, 1H), 0.5–2.1 (m, 8H), 3.48 (s, 3H), 4.53 (br dd, 3.3 and 10.6 Hz, 1H), 6.25 (s, 1H), 7.49 (m, 4H), 8.01 (d, 7.6 Hz, 2H), 8.45 (s, 1H), 8.59 (d, 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.47 MHz): 14.3, 16.4, 21.3, 22.0, 23.1, 25.9, 31.8, 34.7, 45.2, 50.8, 57.9, 61.4, 71.8, 77.4, 124.8, 125.0, 126.8, 127.1, 130.2, 130.8, 131.4, 171.2; ESI-MS *m*/*z* 405.2378 $[M+H]^+$.

4.4.6. (+)-(*S*)-α-Methoxy-α-(9-anthryl) acetic acid—(*S*)-AMAA (9). To a solution of **7** (0.5 g, 1.2 mmol) in 3 mL of a mixture of EtOH/H_2O (1:1) was treated with NaOH (96 mg, 2.4 mmol) at 25 °C. The reaction mixture was stirred for 12 h and then 1 N HCl was slowly added until pH 7. The mixture was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were washed with water and dried over $MgSO_4$. The solvent was removed under diminished pressure and the crude was chromatographed on silica gel column (CH_2Cl_2/MeOH) to provide **9** (197 mg, 62% yield): $[\alpha]_D^{20}$ +131.2 (*c* 0.001, EtOH).

4.4.7. (−)-(*R*)-α-Methoxy-α-(9-anthryl) acetic acid—(*R*)-AMAA (10). Compound **10** (176 mg, 51% yield) was obtained from **8** (0.55 g, 1.3 mmol) according to the procedure for **9**: $[\alpha]_D^{20}$ −128.2 (*c* 0.001, EtOH).

4.4.8. Myrioneurinol-(*S*)-AMAA (11). A solution of myrioneurinol (**1**, 5 mg, 0.019 mmol) and (*S*)-AMAA (**9**, 10 mg, 0.038 mmol) in anhydrous CH_2Cl_2 (1 mL) was treated with DCC (5.9 mg, 0.028 mmol) and a small crystal of DMAP. The resulting solution was stirred at 25 °C for 24 h. The solvent was removed and the crude was purified by prep. TLC to afford **11** (3.7 mg, 38% yield): $[\alpha]_D^{20}$ +76.4 (*c* 0.01, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz): −0.28 (ddd, 12.9, 11.7, 3.8 Hz, H-6), −0.17 (m, H-16_{ax}), −0.07 (ddd, 13.2, 13.2, 4.3 Hz, H-14_{ax}), 0.05 (ddd, 12.6, 12.6, 12.6 Hz, H-8_{ax}), 0.50 (m, H-17_{ax}), 0.75 (ddd, 12.6, 3.8, 3.8 Hz, H-8_{eq}), 0.79 (m, H-17_{eq}), 0.89 (m, H-4_{ax}), 1.01 (m, CH_2-15), −1.05 (m, H-16_{eq}), 1.14 (ddddd, 12.6, 11.7, 4.3, 3.8, 3.2 Hz, H-7), 1.25 (m, H-4_{eq}), 1.29 (d, 11.1 Hz), 1.31 (m, H-3_{eq}), 1.50 (m, H-3_{ax}), 1.98 (m, H-9), 2.03 (m, H-14_{eq}), 2.47 (br dd, 11.7, 4.3 Hz, H-2_{eq}), 2.65 (dd, 10.7, 10.7 Hz, H-11_{ax}), 3.00 (ddd, 11.7, 11.7, 3.9 Hz, H-2_{ax}), 3.44 (s, OMe), 3.48 (dd, 10.7, 3.7 Hz, H-11_{eq}), 3.59 (dd, 11.0, 3.2 Hz, H-18_a), 4.17 (d, 10.2 Hz, H-13_{ax}), 4.25 (dd, 11.0, 4.3 Hz, H-18_b), 4.31 (d, 10.2, H-13_{eq}), 6.28 (s, 1H), 7.49 (m, 2H), 7.53 (m, 2H), 8.02 (br d, 8.3 Hz, 2H), 8.48 (s, 1H), 8.60 (br d, 8.3 Hz, 2H).

4.4.9. Myrioneurinol-(*R*)-AMAA (12). Compound **12** (2.1 mg, 31% yield) was obtained from (*R*)-AMAA (**10**, 3.5 mg): $[\alpha]_D^{20}$ +8.6 (*c* 0.01, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz): −0.62 (ddd, 12.2, 12.2, 12.2 Hz, H-8_{ax}), 0.02 (m, H-6), 0.71 (m, H-17_{ax}), 0.95 (m, H-4_{ax}), 1.01 (m, H-3_{ax}), 1.08 (m, H-7), 1.13 (m, H-16_{ax}), 1.15 (m, H-10), 1.21 (m, H-3_{eq}), 1.22 (m, H-8_{eq}), 1.29 (m, CH_2-15), 1.81

(m, H-9), 2.27 (dd, 11.0, 11.0 Hz, H-11_{ax}), 3.34 (br d, 11.0 Hz, H-11_{eq}), 3.45 (m, CH_2-2), 3.56 (dd, 11.1, 4.1 Hz, H-18_a), 4.09 (m, H-18_b), 4.24 (m, CH_2-13), 6.29 (s, 1H), 7.51 (m, 4H), 8.13 (m, 2H), 8.58 (m, 3H).

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References and notes

1. Mabberley, D. J. *The Plant Book*, 2nd ed.; Cambridge University Press, Port Chester: Cambridge, New York, NY, Melbourne, Sydney, 2002.
2. (a) Woodward, R. B.; Doering, W. E. *J. Am. Chem. Soc.* **1945**, *67*, 860; (b) Lyle, G. G.; Keefer, L. K. *Tetrahedron* **1967**, *23*, 3253; (c) Moreland, C. G.; Philip, A.; Caroll, F. I. *J. Org. Chem.* **1974**, *39*, 2413; (d) Bruneton, J. *Pharmacognosy Phytochemistry Medicinal Plants*; Lavoisier—Technic and Documentation: London, Paris, New York, NY, 1995.
3. (a) Kitajima, M.; Masumoto, S.; Takayama, H.; Aimi, N. *Tetrahedron Lett.* **1997**, *38*, 4255; (b) Aimi, N.; Ueno, M.; Hoshino, H.; Sakai, S. I. *Tetrahedron Lett.* **1992**, *33*, 5403; (c) Aimi, N.; Nishimura, M.; Miwa, A.; Hoshino, H.; Sakai, S. I.; Haginiwa, J. *Tetrahedron Lett.* **1989**, *54*, 4991.
4. Pham, V. C.; Jossang, A.; Chiaroni, A.; Sévenet, T.; Bodo, B. *Tetrahedron Lett.* **2002**, *43*, 7565.
5. (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543; (b) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *38*, 2143; (c) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512; (d) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M. *J. Org. Chem.* **1986**, *51*, 2370; (e) Latypov, S. K.; Seco, J. M.; Quinoa, E.; Riguera, R. *J. Org. Chem.* **1996**, *61*, 8569; (f) Seco, J. M.; Latypov, S. K.; Quinoa, E.; Riguera, R. *J. Org. Chem.* **1997**, *62*, 7569; (g) Xiao, L.; Yamazaki, T.; Kitazume, T.; Yonezawa, T.; Sakamoto, Y.; Nogawa, K. *J. Fluorine Chem.* **1997**, *84*, 19; (h) Takahashi, H.; Iwashima, M.; Iguchi, K. *Tetrahedron Lett.* **1999**, *40*, 333.
6. (a) Seco, J. M.; Latypov, S. K.; Quinoa, E.; Riguera, R. *Tetrahedron: Asymmetry* **1995**, *6*, 107; (b) Latypov, S. K.; Seco, J. M.; Quinoa, E.; Riguera, R. *J. Org. Chem.* **1995**, *60*, 504; (c) Ferreiro, M. J.; Latypov, S. K.; Quinoa, E.; Riguera, R. *Tetrahedron: Asymmetry* **1996**, *7*, 2195; (d) Latypov, S. K.; Ferreiro, M. J.; Quinoa, E.; Riguera, R. *J. Am. Chem. Soc.* **1998**, *120*, 4741; (e) Seco, J. M.; Quinoa, E.; Riguera, R. *Tetrahedron* **1999**, *55*, 569.
7. (a) Golebiewski, W. M.; Spenser, I. D. *J. Am. Chem. Soc.* **1984**, *106*, 7925; (b) Wanner, M. J.; Koomen, G. J. *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; 1994; Vol. 14, p 731; (c) Leete, E. *J. Am. Chem. Soc.* **1969**, *91*, 1697; (d) Gravel, E.; Poupon, E.; Hocmiller, R. *Tetrahedron* **2006**, *62*, 5248.