# ISOLATION OF TWO UNUSUAL TETRAHYDROISOQUINOLINE-MONOTERPENE GLUCOSIDES FROM *ALANGIUM LAMARCKII* AS POSSIBLE INTERMEDIATES IN THE NON-ENZYMATIC FORMATION OF ALANGIMARINE FROM ALANGISIDE

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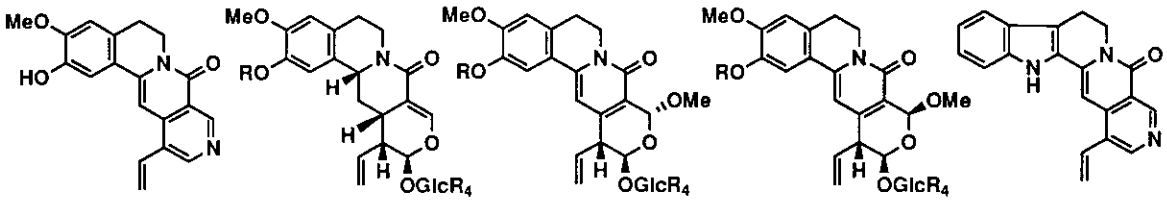
**Abstract**- From the fruits of *Alangium lamarckii*, two new glucosides (**3**) and (**4**), which possessed unusual structures different from any known tetrahydroisoquinoline-monoterpene glucosides, have been isolated. Their structures were determined on the basis of spectroscopic and chemical methods. These same glucosides were also obtained by storage of alangiside (**2**) in MeOH for a prolonged period and glucoside (**4**) was further converted to alangimarine (**1**), a benzopyridoquinolizine alkaloid from this plant, by the usual treatment for isolation of alkaloids, suggesting the possibility of non-enzymatic formation of alangimarine (**1**) from alangiside (**2**) *via* the isolated glucosides (**3**) and (**4**).

*Alangium lamarckii* Thwaites (Alangiaceae) is a traditional medicinal plant in India. The decoction from the root barks has been used as anthelmintic, purgative, emetic and febrifuge and for the treatment of leprosy and other skin diseases.[1] From this plant the isolation of such alkaloids including ipecac alkaloids, e.g. emetine and cephaeline, and benzo[*a*]pyrido[3,4-*g*]quinolizine alkaloids such as alangimarine (**1**) has been reported.[1-3] This plant is also known to be a rich source of alangiside (**2**), a tetrahydroisoquinoline-monoterpene glucoside, the structure of which is closely related to these alkaloids.[4] From our interests in the biosynthesis of the *Alangium* alkaloids, we have investigated the constituents of the fruits of *A. lamarckii*, isolated a variety of nitrogenous glucosides and characterized eighteen of them.[5-9] In continuation of this study, we report here the structure elucidation of two more unusual tetrahydroisoquinoline-monoterpene glucosides (**3**) and (**4**), and the possibility of artificial formation of alangimarine (**1**) from alangiside (**2**) *via* these isolated glucosides.

Compound (**3**), a pale yellow powder, $[\alpha]_D$ +8.5°, and compound (**4**), pale yellow needles, mp 219-220°, $[\alpha]_D$ -105°, have the same molecular formula, $C_{26}H_{31}NO_{11}$, from their HR-SIMS. Their IR spectra showed adsorption bands due to the hydroxyl and lactam carbonyl groups. Conventional acetylation of **3** and **4** gave pentaacetates (**5**) and (**6**), respectively. Their $^1$H NMR spectra showed a signal for a phenolic acetyl group (**5**: δ 2.35; **6**: δ 2.34), indicating the presence of one phenolic hydroxyl group in each glucoside.



1 2: R=H 7: R=Ac 3: R=H 5: R=Ac 4: R=H 6: R=Ac 8

The $^1$H NMR spectrum of **3** showed a singlet for an aromatic methoxyl group at δ 3.92, signals for a terminal vinyl group at δ 5.20 (br d, $J$=10.5 Hz), 5.24 (dt, $J$=17.0, 1.0 Hz), 5.83 (ddd, $J$=17.0, 10.5, 8.0 Hz), a doublet for an acetal proton at δ 5.53 ($J$=1.0 Hz), and signals for a glucosyl moiety at δ 3.17-4.78, implying its structural similarity to alangiside (**2**). However, the $^1$H NMR of **3** lacked an olefinic proton signal for H-9 and a methin proton signal for H-13a, but alternatively exhibited three singlets in the aromatic region (δ 6.61, 6.89 and 7.23), a signal for a methoxyl group (δ 3.66) and a singlet for an acetal proton (δ 5.46). This acetal proton signal was correlated with the methoxyl singlet (δ 3.66) in the ROESY spectrum, and showed a long-range correlation with C-11 (δ 96.9) in the HMBC spectrum. From these results, the signal at δ 5.46 was assigned to H-9 and the methoxyl was located at C-9. On the other hand, the singlet at δ 6.61 was assigned to H-13 by ROESY correlation with H-12 [δ 3.49 (br d, $J$=8.0 Hz)]. Further correlations in ROESY and HMBC spectra (Figure 1) revealed the planar structure of **3**.

The $^1$H and $^{13}$C NMR spectral features of **4** (Table 1) were closely related to those of **3**. Moreover, its HMBC and ROESY spectra suggested that **4** possessed the same structure as **3** except for the configuration of C-9.

These proposed structures were confirmed by preparation of **3** and **4** from alangiside pentaacetate (**7**).[4] Oxidation of **7** with DDQ[10] followed by Zemplen deacetylation afforded two isomeric products which were identified with **3** and **4**.

The stereochemistry at C-9 of **3** and **4** was determined by a detailed comparison of NMR data for **3** and **4** which showed a remarkable difference in the coupling constant between H-11 and H-12. The coupling constant ($J_{11,12}$ =1.0 Hz) of **3** required that both H-11 and H-12 adopted quasi-equatorial positions similar to those of **2**,[5] while the coupling constant ($J_{11,12}$ =7.5 Hz) of **4** suggested that both H-11 and H-12 adopted

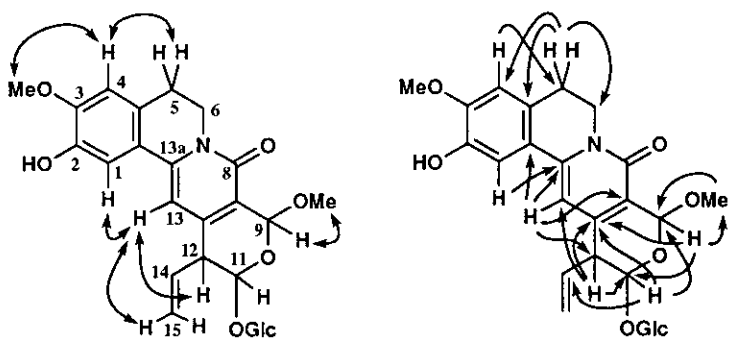


Figure 1. Correlations of ROESY (⟷) and HMBC (⟶) of **3**

quasi-axial positions (Figure 2). This conformation was also supported by the ROESY correlation between H-9 and H-11 in both **4** and **6**. Accordingly, the absolute structures of compounds (**3**) and (**4**) were deduced as shown.

The occurrence of the unusual glucosides (**3**) and (**4**) gave an important clue to the genesis of the benzo[*a*]pyrido[3,4-*g*]quinolizine alkaloids of the plant. Although Pakrashi *et al.* have claimed that these alkaloids were natural products biosynthesized from alangiside (**2**),[3] we could assume that alangimarine (**1**) would be an artifact, as in the same case as for angustine (**8**), a related pyridino-indolo-quinolizidinone alkaloid, which was proposed to be formed during extraction procedures by the action of ammonia on the lactam compound.[11] Alangimarine (**1**) might possibly arise by reaction with AcOH and/or HCl and then with ammonia of the isolated glucosides (**3**) and (**4**), both of which were non-enzymatically derived from alangiside (**2**) by oxidation processes followed by addition of methanol during extraction. To prove this assumption, the following reactions were performed. On heating in MeOH for a short period, alangiside (**2**) was converted neither to **3** nor to **4**. On the other hand, when a methanolic solution of alangiside (**2**) was

Table 1. $^1$H and $^{13}$C NMR spectral data of compounds **3** and **4** in $CD_3OD$ (500 and 125 MHz).

| | **3** | | | | **4** | | | |
|---|---|---|---|---|---|---|---|---|
| C | $\delta_H$ | | | $\delta_C$ | $\delta_H$ | | | $\delta_C$ |
| 1 | 7.23 | s | | 113.1 | 7.14 | s | | 112.8 |
| 2 | - | | | 147.2[a] | - | | | 147.4 |
| 3 | - | | | 151.8 | - | | | 151.8 |
| 4 | 6.89 | s | | 111.7 | 6.88 | s | | 111.8 |
| 4a | - | | | 129.5 | - | | | 129.4 |
| 5 | 2.92 | t | (6.5) | 28.1 | 2.90 | t | (6.5) | 28.1 |
| 5 | 2.92 | t | (6.5) | - | 2.90 | t | (6.5) | - |
| 6 | 4.17 | dt | (13.0, 6.5) | 41.0 | 4.17 | dt | (13.0, 6.5) | 40.9 |
| 6 | 4.24 | dt | (13.0, 6.5) | - | 4.21 | dt | (13.0, 6.5) | - |
| 8 | - | | | 161.6 | - | | | 161.7 |
| 8a | - | | | 119.2 | - | | | 120.5 |
| 9 | 5.46 | s | | 96.3 | 5.63 | s | | 97.6 |
| 11 | 5.53 | d | (1.0) | 96.9 | 5.49 | d | (7.5) | 93.9 |
| 12 | 3.49 | br d | (8.0) | 48.1 | 3.41 | br t | (8.5) | n.d.[b] |
| 12a | - | | | 147.4[a] | - | | | 149.0 |
| 13 | 6.61 | s | | 104.5 | 6.57 | s | | 103.6 |
| 13a | - | | | 145.2 | - | | | 145.1 |
| 13b | - | | | 122.3 | - | | | 122.3 |
| 14 | 5.83 | ddd | (17.0, 10.5, 8.0) | 137.0 | 5.78 | dt | (17.5, 9.5) | 135.6 |
| 15 | 5.20 | br d | (10.5) | 119.0 | 5.39-5.44 m | | | 121.6 |
| 15 | 5.24 | dt | (17.0, 1.0) | - | 5.39-5.44 m | | | - |
| 1' | 4.78 | d | (8.0) | 99.5 | 4.80 | d | (8.0) | 99.6 |
| 2' | 3.17 | dd | (9.0, 8.0) | 75.0 | 3.23 | dd | (9.0, 8.0) | 74.8 |
| 3' | 3.42 | t | (9.0) | 78.3 | 3.41 | t | (9.0) | 78.3 |
| 4' | 3.26 | dd | (9.5, 9.0) | 71.5 | n.d.[b] | | | 71.7 |
| 5' | 3.37 | ddd | (9.5, 6.0, 2.0) | 78.5 | n.d.[b] | | | 78.6 |
| 6' | 3.67 | dd | (12.0, 6.0) | 62.8 | 3.68 | dd | (12.0, 5.5) | 62.8 |
| 6' | 3.91 | dd | (12.0, 2.0) | - | 3.87 | dd | (12.0, 2.0) | - |
| OMe | 3.66 | s | | 56.6 | 3.57 | s | | 56.3 |
| OMe | 3.92 | s | | 57.9 | 3.91 | s | | 56.6 |

[a] Values are interchangeable.
[b] Not determined.

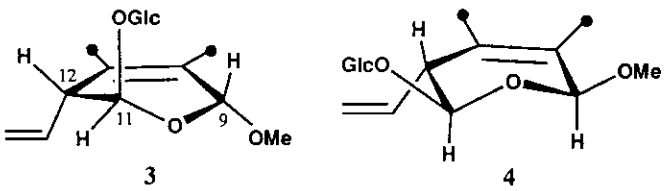



Figure 2. Conformations of dihydropyran ring in **3** and **4** from $^1$H NMR analysis.

kept for a prolonged period, **3** and **4** were formed in a small quantity. Glucosides with the same 2-methoxy dihydropyran ring have already been reported as artifacts of iridoid glucosides and the mechanism of their formation was proposed.[12] Formation of compounds (**3**) and (**4**) should also involve oxidation processes and an addition of MeOH.

Furthermore, glucoside (**4**) was treated with *dil.* HCl and then with 14% ammonia to give alangimarine (**1**) in 19% yield. From these results, we concluded that the isolated glucosides (**3**) and (**4**) could be artifacts derived from alangiside (**2**) through reactions during exposure to air and the separation procedure. We assume that part of alangimarine (**1**) could be non-enzymatically formed, although the possibility of its being a natural alkaloid could not be ruled out.

## EXPERIMENTAL

Melting points were measured on a Büchi melting point apparatus and are reported uncorrected. UV spectra were recorded on a Shimadzu UV-240 spectrophotometer and IR spectra on a Shimadzu FTIR-8200 spectrophotometer. Optical rotations were measured on a Jasco DIP-370 digital polarimeter. MS and HR-MS were obtained with a Hitachi M-4100 mass spectrometer. For SIMS, glycerol was used as the matrix. The NMR experiments were performed with Varian VXR-500 and Varian Gemini-200 spectrometers, with TMS as internal standard. HPLC was performed using a Waters system (600E multisolvent delivery system, 486 tunable absorbance detector). CC was carried out with Silica gel 60 (70-230 mesh, Nacalai Tesque). TLC was performed on precoated Kieselgel 60$F_{254}$ plates (Merck).

### Plant material and isolation of glucosides.

The source of plant material and isolation of glucosides were as described in a previous paper.[7] Compound E and H in ref. 7 correspond to **4** and **3**, respectively.

### Compound (3)

Pale yellow powder. $[\alpha]_D^{27}$ +8.5° (*c*=1.0, MeOH). UV $\lambda_{max}^{MeOH}$nm (log ε): 221 (4.32), 226 (4.32), 243sh (4.02), 258sh (3.79), 267 (3.84), 351 (4.33), 366sh (4.24). IR $\nu_{max}^{KBr}$cm$^{-1}$ : 3385 (OH), 1647 (NCO), 1591 (Ar), 1558 (Ar), 1512 (Ar). $^1$H NMR: Table 1. $^{13}$C NMR: Table 1. SIMS *m/z*: 556 [M+Na]$^+$, 502, 340. HR-SIMS *m/z*: [M+Na]$^+$ Calcd for $C_{26}H_{31}NO_{11}Na$ : 556.1796. Found: 556.1783.

**Compound (4)**

Pale yellow needles. mp 219-220° (MeOH). $[\alpha]_D^{20}$ -105° (*c*=1.0, MeOH). UV $\lambda_{max}^{MeOH}$nm (log ε): 226.5 (4.38), 244sh (4.10), 260sh (3.89), 266.5 (3.91), 334sh (4.21), 351.5 (4.37), 367sh (4.28). IR $\nu_{max}^{KBr}cm^{-1}$: 3448 (OH), 1644 (NCO), 1592 (Ar), 1558 (Ar), 1514 (Ar). $^1$H NMR: Table 1. $^{13}$C NMR: Table 1. ROESY: H-1 / H-13; H-4 / OMe (δ 3.91); H-4 / $H_2$-5; H-9 / OMe (δ 3.57); H-9 / H-11; H-11 / H-14; H-11 / H-1'; H-12 / H-13; H-12 / $H_2$-15; H-13 / $H_2$-15. HMBC: H-1 to C-13a; H-4 to C-5; H-9 to C-8a; H-9 to C-11; H-9 to C-12a; H-9 to OMe (δ 56.3); H-11 to C-14; H-11 to C-1'; H-12 to C-11; H-12 to C-12a; H-12 to C-14; H-13 to C-8a; H-13 to C-13a; H-13 to C-13b; H-2' to C-1'; OMe (δ 3.57) to C-9. SIMS *m/z*: 556 $[M+Na]^+$. HR-SIMS *m/z*: $[M+Na]^+$ Calcd for $C_{26}H_{31}NO_{11}Na$ : 556.1796. Found: 556.1805.

**Acetylation of 3**

Compound (**3**) (12.2 mg) was acetylated with $Ac_2O$ (0.2 mL) in pyridine (0.2 mL) overnight in a refrigerator and the crude acetate was purified by prep. TLC with $CHCl_3$-MeOH (97:3) to afford pentaacetate (**5**) (13.9 mg) as an amorphous powder.

$[\alpha]_D^{32}$ -64°(*c*=1.39, $CHCl_3$). UV $\lambda_{max}^{MeOH}$nm (log ε): 218 (4.43), 242sh (3.79), 259sh (3.90), 266 (3.95), 330sh (4.21), 346 (4.32), 362sh (4.20). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$ : 1755 (OAc), 1655 (NCO), 1593 (Ar), 1562 (Ar), 1508 (Ar). $^1$H NMR (500 MHz, $CDCl_3$) δ: 1.87, 1.99, 2.03, 2.10, 2.35 (15H, each s, 5xAc), 2.94 (2H, t, *J*=6.5 Hz, $H_2$-5), 3.38 (1H, br d, *J*=8.0 Hz, H-12), 3.67 (3H, s, OMe), 3.78 (1H, ddd, *J*=10.0, 5.0, 2.5 Hz, H-5'), 3.89 (3H, s, OMe), 4.16 (1H, dd, *J*=12.5, 2.5 Hz, H-6'), 4.23 (1H, dt, *J*=13.5, 6.5 Hz, H-6), 4.29 (1H, dt, *J*=13.5, 6.5 Hz, H-6), 4.31 (1H, dd, *J*=12.5, 5.0 Hz, H-6'), 4.98 (2H, m, H-1', H-2'), 5.09 (1H, dd, *J*=10.0, 9.5 Hz, H-4'), 5.20 (1H, dt, *J*=17.0, 1.0 Hz, H-15), 5.23 (1H, br d, *J*=10.0 Hz, H-15), 5.24 (1H, m, H-3'), 5.39 (1H, d, *J*=1.5 Hz, H-11), 5.52 (1H, s, H-9), 5.75 (1H, ddd, *J*=17.0, 10.0, 8.5 Hz, H-14), 6.32 (1H, s, H-13), 6.82 (1H, s, H-4), 7.37 (1H, s, H-1). ROESY: H-4 / $H_2$-5; H-4 / OMe (δ 3.89); H-9 / OMe (δ 3.67); H-11 / H-14; H-11 / H-1'; H-12 / H-13; H-12 / H-15 (δ 5.20); H-13 / H-15 (δ 5.23). MS *m/z* (rel. int.): 743 $[M]^+$ (0.01), 713 (0.02), 395 (28), 364 (100), 336 (23), 43 (50). HR-MS *m/z*: $[M]^+$ Calcd for $C_{36}H_{41}NO_{16}$: 743.2427. Found: 743.2430.

**Acetylation of 4**

Conventional acetylation of **4** (15.1 mg) and subsequent purification by prep. TLC with $CHCl_3$-MeOH (97:3) afforded pentaacetate (**6**) (15.4 mg) as an amorphous powder.

$[\alpha]_D^{27}$ -61°(*c*=0.85, $CHCl_3$). UV $\lambda_{max}^{MeOH}$nm (log ε): 217 (4.40), 243sh (3.79), 258sh (3.84), 266 (3.91), 334sh (4.24), 348 (4.33), 364sh (4.19). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$ : 1757 (OAc), 1651 (NCO), 1591 (Ar), 1558 (Ar), 1508 (Ar). $^1$H NMR (500 MHz, $CDCl_3$) δ: 2.01, 2.03, 2.04, 2.08, 2.34 (15H, each s, 5xAc), 2.93 (2H, t, *J*=6.5 Hz, $H_2$-5), 3.29 (1H, br t, *J*=8.0 Hz, H-12), 3.65 (3H, s, OMe), 3.75 (1H, ddd, *J*=10.0, 5.5, 2.5 Hz, H-5'), 3.88 (3H, s, OMe), 4.13 (1H, dd, *J*=12.0, 2.5 Hz, H-6'), 4.14 (1H, dt, *J*=14.0, 6.5 Hz, H-6), 4.27 (1H, dd, *J*=12.0, 5.5 Hz, H-6'), 4.37 (1H, dt, *J*=14.0, 6.5 Hz, H-6), 5.00 (1H, d, *J*=7.5 Hz, H-1'), 5.04 (1H, br t, *J*=8.5 Hz, H-2'), 5.10 (1H, t, *J*=9.0 Hz, H-4'), 5.27 (1H, t, *J*=9.0 Hz, H-3'), 5.33 (1H, d, *J*=7.0 Hz, H-11), 5.39 (1H, br d, *J*=17.0 Hz, H-15), 5.42 (1H, dd, *J*=10.0, 1.5 Hz, H-15), 5.68 (1H, s, H-9), 5.72 (1H, ddd, *J*=17.0, 10.0, 9.0 Hz, H-14), 6.38 (1H, s, H-13), 6.81 (1H, s, H-4), 7.34 (1H, s, H-1). ROESY: H-1 / H-13; H-4 / $H_2$-5; H-4 / OMe (δ 3.88); H-9 / OMe (δ 3.65); H-9 / H-11; H-11 / H-1'; H-11 / H-14; H-12 / H-13, H-12 / H-15

(δ 5.39); H-12 / OMe (δ 3.65); H-13 / H-14; H-13 / H-15 (δ 5.39). MS *m/z* (rel. int.): 743 $[M]^+$ (4.8), 713 (4.7), 396 (26), 382 (20), 364 (55), 336 (38), 331 (11), 43 (100). HR-MS *m/z*: $[M]^+$ Calcd for $C_{36}H_{41}NO_{16}$ : 743.2427. Found: 743.2425.

**Preparation of 3 and 4 from alangiside pentaacetate (7)**

Alangiside pentaacetate (**7**) (200 mg, 0.28 mmol) was treated with DDQ (200 mg, 0.88 mmol) in toluene-MeOH (1:1, 10 mL) at 50° for 1 h. The reaction mixture was diluted with toluene (90 mL), the solution was chromatographed on a silica gel column with toluene-MeOH (19:1) as eluent and the product was further purified by prep. TLC (toluene-MeOH, 3:1) to afford a mixture of **5** and **6** (212.2 mg). To a solution of the mixture in MeOH (10 mL) was added a solution of 0.1 N NaOMe (2.0 mL) and the whole stirred at rt for 4 h. The reaction mixture was neutralized by Amberlite IR-120B ($H^+$ form) and evaporated *in vacuo*. The resulting residue was subjected to prep. TLC ($CHCl_3$-MeOH, 4:1) to afford **3** (22.4 mg, 15% from **7**) and **4** (104.2 mg, 70% from **7**).

**3**. $[\alpha]_D^{26}$ +8.0° (*c*=1.0, MeOH). SIMS *m/z*: 556 $[M+Na]^+$, 534 $[M+H]^+$, 502, 340.

UV, IR and $^1H$ NMR spectra of this compound were identical with those of **3** from natural source.

**4**. $[\alpha]_D^{27}$ -110° (*c*=1.0, MeOH). SIMS *m/z*: 556 $[M+Na]^+$, 534 $[M+H]^+$, 502, 340.

UV, IR and $^1H$ NMR spectra of this compound were identical with those of **4** from natural source.

**Conversion of alangiside (2) into 3 and 4**

A solution of alangiside (**2**) (100 mg) in MeOH (5 mL) was allowed to stand at rt for 9 months. After evaporation of the solvent, the resulting residue was purified by prep. HPLC (MeOH-$H_2O$, 1:1) to give **3** (1.8 mg) and **4** (4.9 mg) along with the recovered **2** (75.6 mg).

A MeOH solution (2 mL) of **2** (10.0 mg) was then refluxed for 18 h, but neither **3** nor **4** was detected in the reaction mixture by HPLC analysis.

**Preparation of alangimarine (1) from 4**

To a solution of **4** (60 mg) in THF (3 mL) was added 1N HCl (3.0 mL) and the whole stirred at rt for 1 h. The reaction mixture was basified with 14% $NH_4OH$ at 0° and stirred at rt for 1 h. The mixture was then extracted with $CHCl_3$ and the organic layer was washed and dried over $MgSO_4$, and the solvent removed under reduced pressure. The resulting residue was purified by prep. TLC with $CHCl_3$-MeOH (93:7) to afford **1** (7.0 mg, 19%).

UV $\lambda_{max}^{MeOH}$ nm (log ε): 220sh (4.40), 247 (4.11), 260 (4.14), 290sh (3.85), 364 (4.41), 377sh (4.37). IR $\nu_{max}^{KBr}$ $cm^{-1}$ : 1645 (NCO), 1599 (Ar), 1510 (Ar). $^1H$ NMR (200 MHz, $CDCl_3$) δ: 2.95 (2H, t, *J*=6.0 Hz, $H_2$-5), 3.98 (3H, s, OMe), 4.35 (2H, t, *J*=6.0 Hz, $H_2$-6), 5.58 (1H, dd, *J*=11.0, 1.0 Hz, H-15), 5.84 (1H, dd, *J*=17.5, 1.0 Hz, H-15), 6.75 (1H, s, H-4), 6.98 (1H, s, H-1), 7.13 (1H, dd, *J*=17.5, 11.0 Hz, H-14), 7.42 (1H, s, H-13), 8.76 (1H, s, H-11), 9.51 (1H, s, H-9). (200 MHz, $C_5D_5N$) δ: 2.82 (2H, t, *J*=6.0 Hz, $H_2$-5), 3.83 (3H, s, OMe), 4.35 (2H, t, *J*=6.0 Hz, $H_2$-6), 5.48 (1H, dd, *J*=11.0, 1.0 Hz, H-15), 5.86 (1H, dd, *J*=17.5, 1.0 Hz, H-15), 6.84 (1H, s, H-4), 7.06 (1H, s, H-1), 7.19 (1H, dd, *J*=17.5, 11.0 Hz, H-14), 7.80 (1H, s, H-13), 8.97 (1H, s, H-11), 9.84 (1H, s, H-9). MS *m/z* (rel. int.): 320 $[M]^+$ (100), 305 (59). HR-MS *m/z*: $[M]^+$ Calcd for $C_{19}H_{16}N_2O_3$ : 320.1162. Found: 320.1169.

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