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SYNTHESIS OF THE AGLYCON OF PENTALINONSIDE

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Abstract – The aglycon of pentalinonside (**2**), a novel *seco*-pregnane with cage-like DEF-rings, was synthesized. Polyoxygenated DEF-rings were constructed using a known 14,20(16),21(15)-triol derivative via 5-*exo*-cyclization for the F-ring annulation, followed by C14–21(15) oxidative cleavage and intramolecular acetalization.

A native Mexican plant called *Pentalinon andrieuxii* Mueller-Itrgoviensis, which grows in the Yucatan Peninsula, is a Mayan folk medicine for the treatment of cutaneous leishmaniasis lesions. Recent biological studies of extracts of this plant have revealed anti-atherogenic,[1] anti-inflammatory,[2] anti-leishmania,[3] and anti-depressant activities.[4] As part of the discovery of naturally occurring anti-leishmania agents from *P. andrieuxii*, pentalinonside (**1**, Figure 1), a novel polyoxygenated 14,15-*seco*-pregnane with a β-diginosyl group at C3 and cage-like DEF-rings, was isolated from the hexane-soluble extract of its roots in 2012.[5] Although isolated from bioactive extracts, pentalinonside (**1**) does not exhibit anti-leishmania activity.

Velutinol A (**3**), a *seco*-pregnane with cage-like DEF-rings, was also isolated[6] and revealed to be an antagonist of the bradykinin B1 receptor (B1R).[7] As part of our efforts to elucidate the mechanism of action of B1R, a preliminary complex structural model of velutinol A (**3**) bound to the B1R was constructed, which indicated that three oxygen atoms in the cage-like structure of the DEF-rings of velutinol A (**3**) are important for binding.[8] Therefore, we anticipated that *seco*-pregnane derivatives bearing cage-like DEF-rings might exhibit similar bioactivities. We have also accomplished the syntheses of velutinol A (**3**)[8] and the *seco*-pregnane derivatives argeloside aglycon (**4**)[9] and illustrol (**5**),[10] which share similar cage-like DEF-rings, to study the structure-activity relationship. Due to its structural similarity to velutinol A (**3**), our main goal is the synthesis of the pentalinonside aglycon (**2**), even though the biological activities of pentalinonside (**1**) have not yet been specified.

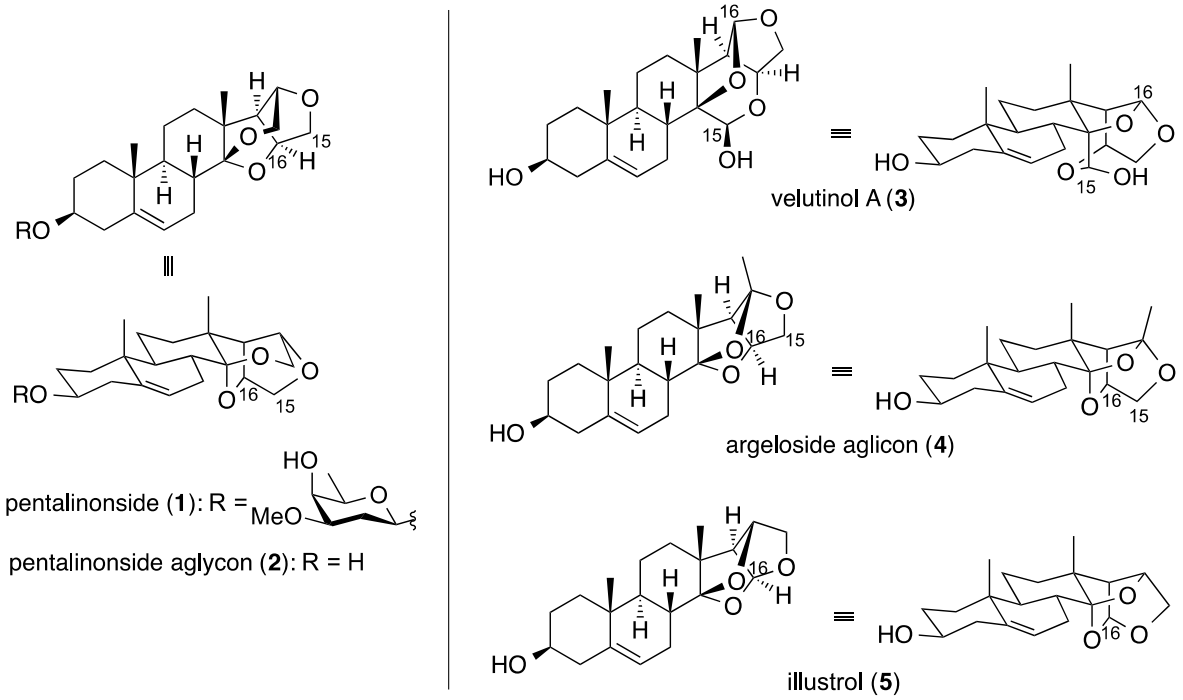
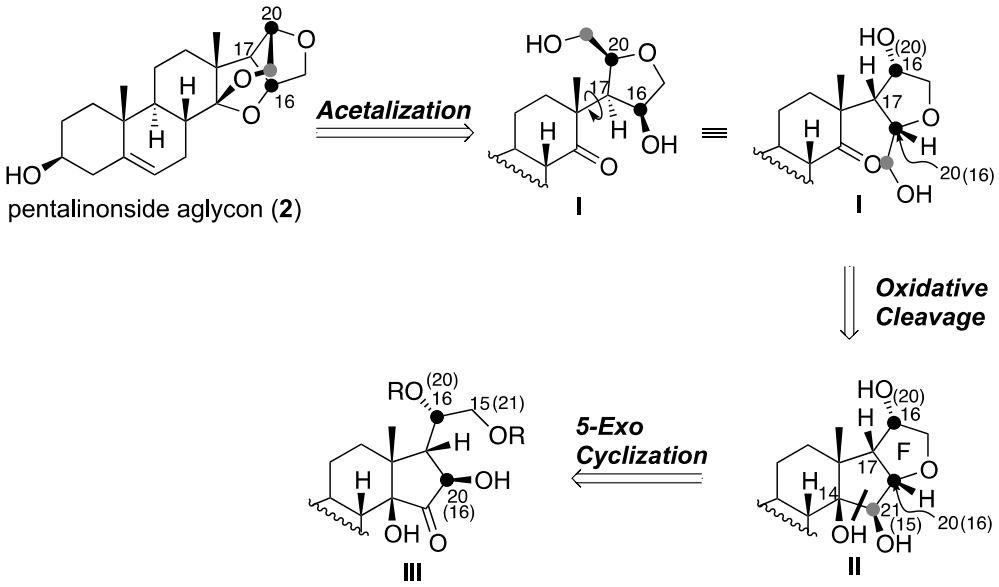


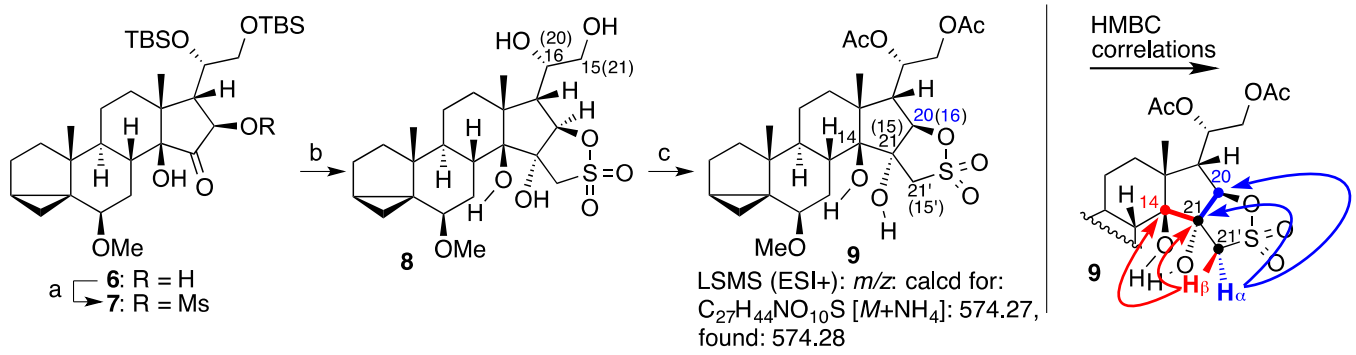
Figure 1. Structures of *seco*-pregnanes with cage-like DEF-rings

Scheme 1 shows our retrosynthetic analysis of pentalinonside aglycon (**2**), which began with the deacetalization of the target to 14-keto-16(20),21(15)-dihydroxy derivative **I**. By assuming that ketone **I** would presumably be obtained from diol **II** via oxidative cleavage of the C14–C21(15) bond, diol **II** was established as the precursor. To construct the F-ring in **II**, we envisioned 5-*exo*-cyclization via intramolecular S_N2 addition of the C15(21) hydroxy group to the C20(16) position of the known α,α-dihydroketone **III**.[8]



Scheme 1. Retrosynthetic analysis

As shown in the retrosynthetic analysis, the synthesis begins from α,α'-dihydroxyketone **6** (Scheme 2).[8] First, we chose a mesylate as the leaving group of C20(16). Thus, after sulfonylation of the C20(16)-hydroxy group using methanesulfonyl chloride (MsCl) in pyridine, the TBS groups of the resulting ketone **7** were removed via *n*Bu$_4$NF, which unfortunately resulted in the formation of an oxatholanedioxide ring to give **8** in 45% yield.[11] The structure of **8** was established by heteronuclear multiple bond correlations (HMBC) experiments of diacetate **9**, easily accessible from compound **8**. Thus, after the protection of the 15(21),16(20)-dihydroxy groups as acetyl groups (86%), the HMBC correlations of the resulting compound **9** were measured (Figure 2).



Scheme 2. Unsuccessful route for F-ring formation. *Reagents and conditions*: a) MsCl, pyridine, rt, 2.5 h, 88%; b) *n*Bu$_4$NF, THF, rt, 12 h, 45%; c) pyridine, Ac$_2$O, 86%. Ms = methanesulfonyl

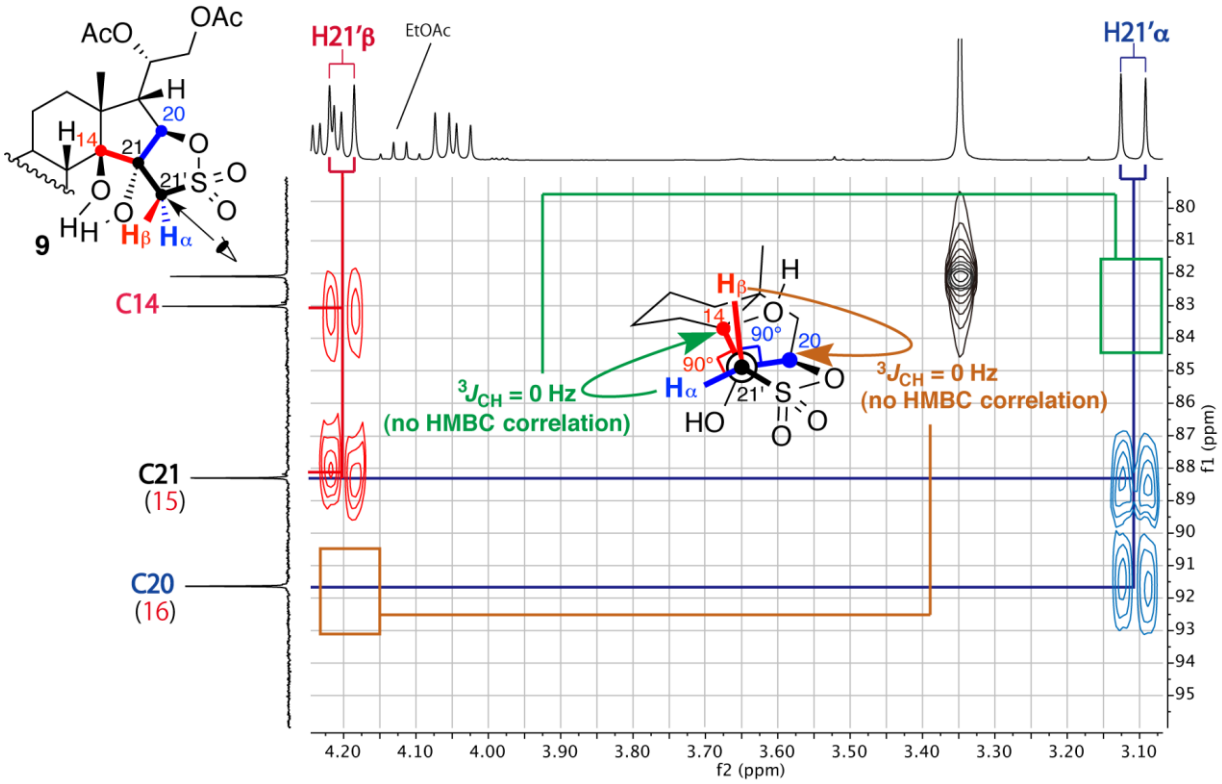
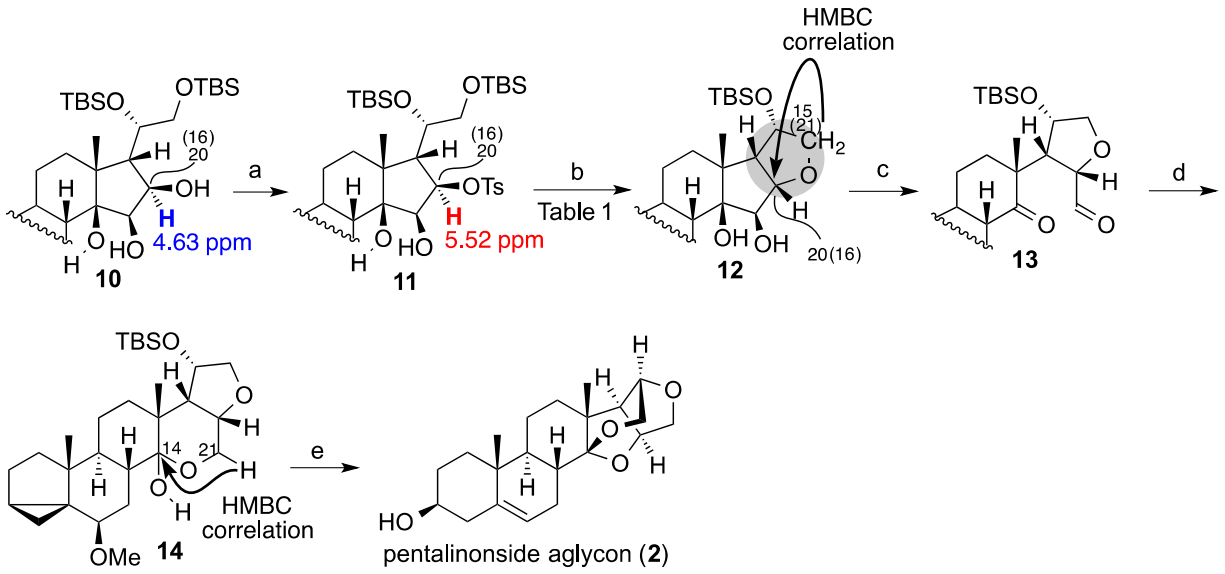


Figure 2. HMBC correlations of compound **9** (400 MHz, $CDCl_3$)

HMBC correlations from H21'α to C20(16)/C21(15) and from H21'(15')β to C14/C21(15) indicated the formation of an oxatholanedioxide ring. There was no HMBC correlation from H21'α to C14 nor from H21'β to C20(16) because of the dihedral angles (approximately 90°) of each of the protons and carbon atoms [H21'(15')α/C14 and H21'(15')β/C20(16)], as shown in the Figure 2, which is the characteristic conformation of bicycle[3. 3. 0]octane skeletons. The occurrence of the oxatholanedioxide ring is also supported by mass spectrometry.

To prevent annulation, we planned to use triol **10**[8] as the starting material and attach the *p*-toluenesulfonyl (Ts) group to the C20(16) hydroxy group. Thus, the important point of the first step is the regioselective installation of the tosyl group because there are two secondary alcohols at C20(16) and C21(15) in triol **10**. We anticipated that the small difference in steric hindrance around the C20(16) and C21(15) hydroxy groups might achieve the regioselective installation of the Ts group on the C20 hydroxy group. Thus, triol **10** was treated with TsCl in the presence of 4-dimethylaminopyridine (DMAP) in CH_2Cl_2, which, as expected, gave tosylate **11** for F-ring annulation as the sole product in a 93% yield. The structural confirmation of compound **11** was achieved by comparing the ^{1}H NMR values of H20(16) in compounds **10** and **11**. The ^{1}H NMR value assigned to H20(16) was shifted from 4.63 ppm to 5.52 ppm after tosylation, confirming the installation of the Ts group at the C20(16) hydroxy group.

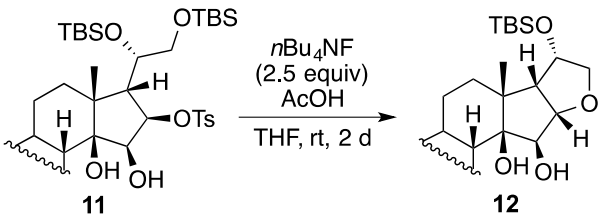


Scheme 3. Synthesis of the pentalinonside aglycon (**2**). *Reagents and conditions*: a) TsCl, DMAP, CH_2Cl_2, rt, 2 h, 93%; b) *n*Bu_4NF/AcOH (1:2), THF, reflux, 2 h, 62%, for yields and conditions see Table 1; c) $NaIO_4$, THF/H_2O (1:1), rt, 5 h, 81%; d) $NaBH_4$, MeOH, 0 °C, 10 min, 71%; e) $HClO_4$, 1,4-dioxane/H_2O (5:4), rt, 2 h, 95%. Ts = *p*-toluenesulfonyl, DMAP = 4-dimethylaminopyridine

For the key 5-*exo*-cyclization to annulate the F-ring, *n*Bu_4NF was used not only to remove the TBS groups but also as a weak base for the intramolecular S_N2-type reaction (Table 1, entry 1). Despite

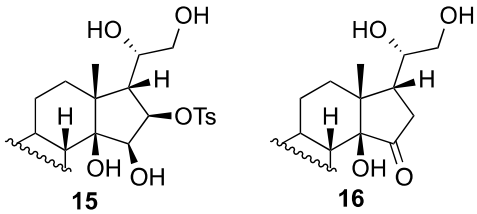
quantitative conversion of **11**, the major product was the unfavorable ketone **16** (89%), generated by the E2 elimination of TsOH and tautomerization of the resulting enol, along with tetrol **15** (9%). This result suggested that basic conditions would not be adequate for the F-ring annulation of **11** because the basicity of the reaction, even with the distinctly weak base *n*Bu$_4$NF, triggered the E2 elimination of **11**. To prevent E2 elimination, diol **11** was treated with 2.5 equivalents of *n*Bu$_4$NF in the presence of 1.3 equivalents of AcOH for 2 d (entry 2). Under these conditions, the desired product **12** was obtained in 35% yield concomitant with the recovery of the starting material in 15% yield. Increasing the equivalents of AcOH from 1.3 to 2.5 increased the recovery (35%, entry 3). The product was obtained in 46% yield when 5.0 equivalents of AcOH were added to the reaction (entry 4). The reaction was ultimately performed at 60 °C for 2 h in the presence of 5.0 equivalents of AcOH to afford **12** in 71% yield (entry 5). We elucidated the structure of compound **12** based on HMBC correlations between H15(21) and C20(16), which indicated the formation of the F-ring.

Table 1. 5-*exo*-Cyclization



Entry	AcOH/equiv	Yield/%	
		12	**11**
1[a]	—	—	—
2	1.3	35	15
3	2.5	32	35
4	5.0	46	35
5[b]	5.0	71	—

[a] Tetrol **15** and triol **16** were obtained in 9% and 89% yield, respectively. [b] The reaction was performed at 60 °C for 6 h.



The C14–21(15) bond of cyclized compound **12** was then oxidatively cleaved using $NaIO_4$ to give keto–aldehyde **13** in 81% yield (Scheme 2). Selective reduction of the C20(16)-oxo group in **13** was achieved via $NaBH_4$ at 0 °C to afford hemi-ketal **14** [71%, confirmed by HMBC correlation between H21(15) and C14]. Treatment of **14** with $HClO_4$ achieved the conversion of the AB rings, detachment of the TBS group, and intramolecular ketalization to give pentalinonside aglycon (**2**) in 95% yield. The structure of **2** was confirmed by comparing the ^{1}H-NMR and ^{13}C-NMR spectra[12] of the synthetic aglycon and authentic pentalinonside.[5] As shown in Figure 3, the ^{13}C-NMR peaks of **2** were nearly identical to those of pentalinonside (**1**), with the exception of those peaks assigned as C2–C4 from the $\Delta\delta$C value (authentic – synthetic/ppm), which are the positions adjacent to the glycoside bond.

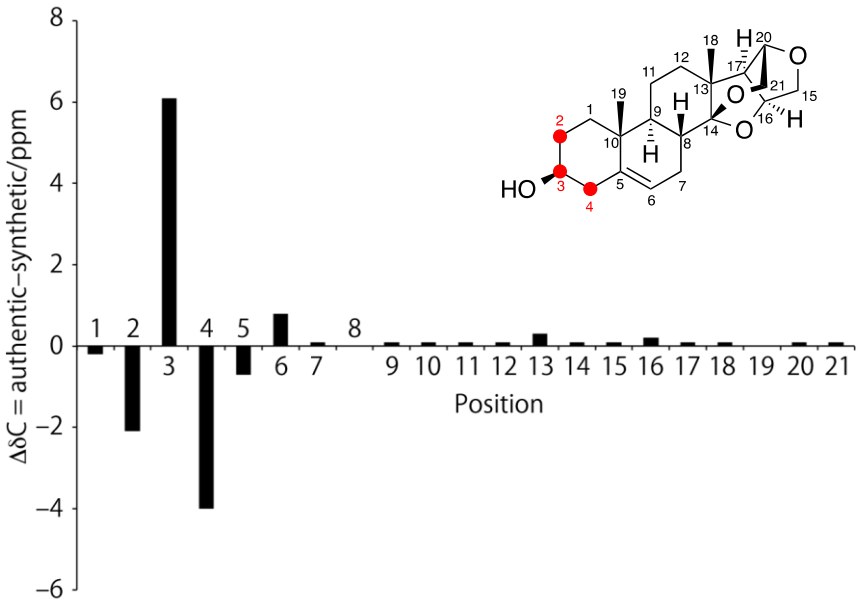


Figure 3. ΔδC values of the authentic pentalinonside aglycon and synthetic aglycon

In summary, we have accomplished the concise synthesis of pentalinonside aglycon (**2**) in 5 steps by utilizing compound **10**, the intermediate in velutinol A (**3**) synthesis. The stereoselective glycosylation of 2,6-dideoxy saccharide for the total synthesis of pentalinonside (**1**) is now under investigation.

ACKNOWLEDGEMENTS

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12. Chemical data of **2**: solid, mp 206.2–206.4 °C; $[\alpha]_D^{20}$ –37.19 (*c* 0.32, MeOH); ^{1}H NMR (500 MHz, pyridine-d_5): δ = 5.49–5.45 (m, 1H, H-6), 4.57 (t, 1H, *J* = 4.6 Hz, H-16), 4.49 (ddd, 1H, *J* = 8.0, 5.8, 1.2 Hz, H-20), 4.23 (d, 1H, *J* = 10.1 Hz, H-15b), 4.06 (dd, 1H, *J* = 12.6, 5.8 Hz, H-21a), 4.03 (dd, 1H, *J* = 10.1, 4.6 Hz, H-15a), 3.89–3.81 (m, 1H, H-3), 3.80 (dd, 1H, *J* = 12.6, 1.2 Hz, H-21b), 2.66–2.60 (m, 1H, H-7), 2.63–2.58 (m, 1H, H-4), 2.61 (dd, 1H, *J* = 8.0, 4.6 Hz, H-17), 2.52–2.44 (m, 1H, H-7), 2.13–2.06 (m, 1H, H-2a), 1.90–1.83 (m, 1H, H-1b), 1.89–1.84 (m, 1H, H-8), 1.83–1.73 (m, 1H, H-2b), 1.52–1.46 (m, 1H, H-11), 1.49–1.43 (m, 1H, H-12b), 1.45–1.40 (m, 1H, H-9), 1.38–1.32 (m, 1H, H-12a), 1.34–1.28 (m, 1H, H-11), 1.18–1.10 (m, 1H, H-1a), 1.1 (s, 3H, H-18), 1.02 (s, 3H, H-19) ppm; ^{13}C NMR (125 MHz, pyridine-d_5): δ = 140.4 (C-5), 121.8 (C-6), 108.1 (C-14), 80.7 (C-16), 76.2 (C-20), 74.2 (C-15), 71.2 (C-3), 66.1 (C-21), 54.5 (C-17), 46.0 (C-9), 43.4 (C-4), 41.3 (C-10), 37.7 (C-1), 36.8 (C-13), 36.2 (C-8), 34.8 (C-12), 32.5 (C-2), 25.4 (C-79, 20.5 (C-11), 19.6 (C-19), 17.2 (C-18) ppm; IR (ATR): *v* = 3309, 2927, 1439, 1381, 1364, 1269, 1202, 1169, 1133, 1101, 1052, 1019, 986, 972, 954 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{21}H_{30}O_4$ [*M*+*H*]: 302.2217, found: 302.2223.