Structure Elucidation of Sesbanimide using High-field N.M.R. Spectroscopy

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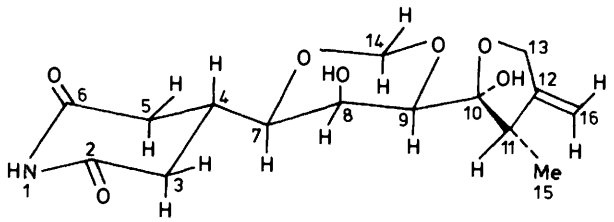
The structure elucidation of sesbanimide, a novel cytotoxic compound isolated from *Sesbania punicea* seeds, is based on a detailed study of its high-field ^1H and ^{13}C n.m.r. spectra. The conformation and relative configuration of sesbanimide were deduced from the observed proton–proton nuclear Overhauser effects (n.O.e.s) and the magnitude of the proton–proton coupling constants. In solution a solvent-dependent equilibrium exists between the tautomeric ring-closed hemiacetal (**1**) and the ring-opened γ-hydroxyketone (**5**) forms of sesbanimide.

Sesbania punicea, a deciduous shrub found throughout the southern United States and South America, is an introduced noxious weed in Southern Africa with a history of toxicity to livestock and fowl.[1,2] Investigations of the related *Sesbania drummondii* resulted in the isolation and structure elucidation of two cytotoxic metabolites, sesbanine[3] and drummondol,[4] and most recently the potent anti-tumour agent sesbanimide (**1**).[5] The single-crystal *X*-ray crystallographic study of compound (**1**) by Powell *et al.*[5] prompted us to report our results on the structure elucidation of sesbanimide by the application of high-field ^1H and ^{13}C n.m.r. spectroscopy.



(**1**)

Sesbanimide (**1**) was obtained from the aqueous ethanol extract of *S. punicea* seeds by treatment with basic lead acetate followed by purification by silica gel column chromatography. The fractionation was monitored by bioassay of all the fractions for acute toxicity in 1 day-old chickens. The crystalline metabolite, m.p. 155—156 °C, analysed for $C_{15}H_{21}NO_7$ and had u.v. and i.r. spectral characteristics (see Experimental section) in accordance with structure (**1**).

The 500.13 MHz ^1H n.m.r. spectrum of sesbanimide showed signals corresponding to 21 protons (see Table 1). The resonances at δ 3.623 (d, *J* 7.2 Hz), 4.254, and 7.795, which are absent from the ^1H n.m.r. spectrum after the addition of deuterium oxide to the sample, are ascribed to three exchangeable protons; the last is assigned to the NH proton of an amide moiety. The remainder of the ^1H n.m.r. spectrum exhibited extensive fine structure. First-order analyses of these multiplets yielded the values of the proton chemical shifts and the proton–proton coupling constants. From the values of the coupling constants, as corroborated by extensive ^1H-{^1H} homonuclear decoupling experiments, three fragments A, B, and C of the sesbanimide molecule could be constituted as shown in structures (**2**)—(**4**) (Figure 1).

Fragment A (**2**).—This fragment is characterized by the number of protons which are located on oxygen-bearing carbon atoms. The doublet at δ 3.570 (*J* 1.2 Hz), assigned to 9-H served as the starting point in the analysis of this spin system. The location of a hydroxy group at C-8 follows from the observation that a proton–proton coupling of 7.2 Hz is absent from the resonance at δ 3.994 (8-H) after the addition of deuterium oxide to the sample. The small coupling constants of 1.2 and 1.3 Hz observed for 8-H must arise from coupling with its neighbours 9-H and 7-H, respectively, and indicate that these protons could be part of a six-membered ring in a chair conformation. The chemical shift values and the magnitude of the geminal and vicinal coupling constants of the protons of the CH_2CHCH_2 grouping, 3-H, 4-H, and 5-H, are consistent with their location in a 4-substituted glutarimide ring in a chair conformation, as in the glutarimide antibiotics, *e.g.* cycloheximide.[6] The magnitude of the geminal coupling constants observed for 3-H and 5-H, 17.0 and 17.3 Hz, respectively, can be explained by the presence of carbonyl functions linked to C-3 and C-5 (see below).[7] A chair conformation for the glutarimide ring would explain the proton–proton coupling of 1.5 Hz exhibited by the equatorial 3-H (δ 2.889) and 5-H (δ 7.743) protons, as appreciable long-range coupling is observed along a W-path in saturated systems.[8] The coupling constant of 8.7 Hz recorded for 7-H arises through interaction with 4-H and is indicative of an anti-periplanar arrangement of these protons.

Fragment B (**3**).—The terminus of this spin system is formed by a doublet at δ 1.180 (*J* 6.8 Hz) which was assigned to the protons of a methyl group (15-H). The chemical shifts and coupling constants of the protons resonating at δ 4.995 and 4.938, 16a-H and 16b-H, are characteristic of the protons of an exocyclic methylene group. The values of the coupling constants between these protons and those resonating at δ 2.592 (11-H), 4.538 (12a-H), and 4.455 (12b-H) are in the range reported for allylic proton–proton coupling constants.[9]

Fragment C (**4**).—Although the coupling constant of 6.2 Hz for the two protons of this fragment is indicative of either a two- or three-bond (H,H) connectivity pattern, the chemical shift values (δ 5.203 and 4.764) suggest the former, *i.e.* a methylenedioxy moiety. This possibility was confirmed by the ^{13}C n.m.r. data (see below).

The ^{13}C n.m.r. data for sesbanimide (**1**), collated in Table 1, were obtained from broad-band proton-decoupled and single frequency nuclear Overhauser enhanced (n.O.e.) ^{13}C n.m.r. spectra. The reported deuterium isotope shifts[10,11] are the separations between doubled signals in the broad-band proton-decoupled ^{13}C n.m.r. spectrum when the exchangeable protons were partially exchanged with deuterium upon addition of D_2O–H_2O (1:1).

Single frequency n.O.e. and off-resonance proton-decoupled

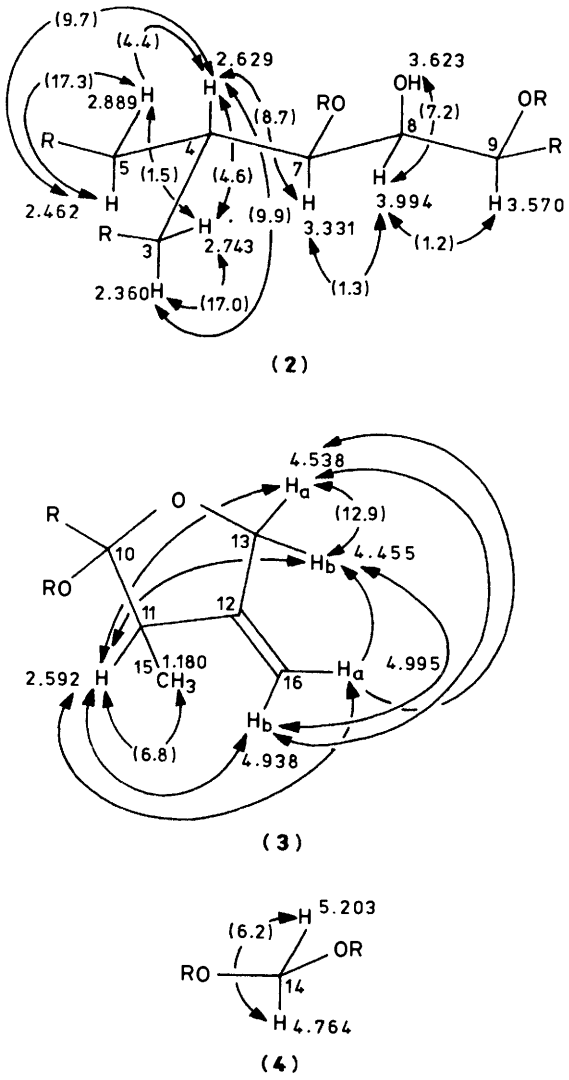


Figure 1. The ^1H chemical shifts and coupling constants (Hz) for fragments A (**2**), B (**3**), and C (**4**) of sesbanimide (**1**). The (^1H,^1H) connectivity pattern as indicated was determined by homonuclear ^1H-{^1H} decoupling experiments. Those cases where effects were observed during decoupling experiments, although no splittings were measured, are indicated by arrows with no coupling constants

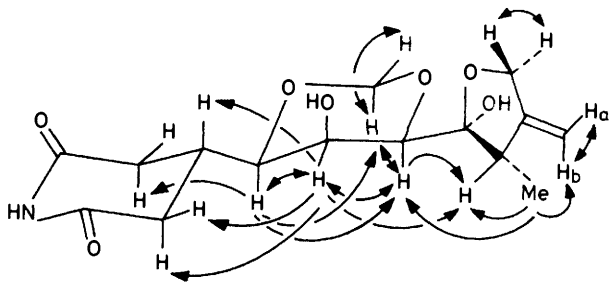


Figure 2. The (^1H,^1H) n.O.e. connectivity pattern observed for sesbanimide (**1**). Arrowheads show enhanced signals. Double-headed arrows denote that n.O.e.s are observed in both directions

^{13}C n.m.r. spectra revealed that the 15 carbon resonances observed in the broad-band proton-decoupled ^{13}C n.m.r. spectrum of sesbanimide are due to one methyl, five methylene, five methine, and four quaternary carbon atoms. The residual splittings observed in off-resonance proton-decoupled ^{13}C n.m.r. experiments enabled us to correlate the signals of a number of proton-bearing carbon atoms, *viz.* C-4, C-7, C-8, C-9, C-11, C-13, and C-16, with specific proton resonances [12] and in addition allowed the assignment of the proton-bearing carbon atoms in fragments A (**2**), B (**3**), and C (**4**) (see Table 1). The magnitudes of the observed directly bonded (C,H) coupling constants (Table 1) support these assignments.

Chemical-shift criteria dictate that the resonance at δ 150.02 p.p.m. must be attributed to C-12, the sp^2 quaternary carbon atom of the exocyclic double bond.[11] The two singlet resonances at δ 171.48 and 170.96 p.p.m., both of which exhibit two-bond deuterium isotope shifts (Δδ −0.065 and −0.063 p.p.m., respectively) are assigned to the two carbonyl carbon atoms, C-2 and C-6, of an imide moiety. The linkage of this moiety to C-3 and C-5 of fragment A (**2**) to form the 4-substituted glutarimide ring follows from the ^{13}C chemical-shift values of C-3 and C-5, which correspond closely with the values reported for the corresponding carbon atoms in cycloheximide.[6]

The location of a hydroxy group at C-8, as indicated by the ^1H n.m.r. spectrum of sesbanimide (see above), was confirmed by the two-bond deuterium isotope shift observed for the resonance at δ 64.67 p.p.m. (Δδ −0.115 p.p.m.).[11] This result implies that the oxygen atoms at C-7 and C-9 are present as ether functions and are common to fragments A (**2**) and C (**4**). The carbon chemical shift of C-14, δ 93.94 p.p.m., is in good agreement with the value for the corresponding carbon atom in various substituted 1,3-dioxane systems.[13] The geminal (H,H) coupling constant for the C-14 protons (^2J 6.2 Hz) provides additional evidence for the presence of a 1,3-dioxane moiety in sesbanimide (**1**).[7]

Only one quaternary carbon atom remains unassigned. The chemical shift of this carbon atom, C-10, δ 105.02 p.p.m. as well as the observed two-bond deuterium isotope shift (Δδ −0.089 p.p.m.), indicate that it is substituted by two oxygen atoms present as a hemiacetal moiety. This result allows the final linkage between C-9 in fragment A (**2**) and C-10 in fragment B (**3**) to give the constitution of sesbanimide as shown in formula (**1**).

The conformation and relative configuration of sesbanimide (**1**) were deduced from the proton–proton coupling constants, as well as the results obtained from a series of homonuclear ^1H-{^1H} n.O.e. experiments.[14] The n.O.e. connectivity pattern is shown in Figure 2.

For the basis of the discussion, it is assumed that C-8 has the (*S*) configuration, *i.e.* the hydroxy group is axial in the chair conformation of the 1,3-dioxane. The magnitude of the vicinal proton–proton coupling constants of 1.3 and 1.2 Hz between 8-H, and 7-H and 9-H, respectively, requires that 7-H and 9-H occupy axial positions. This stereochemical requirement is borne out by the n.O.e. observed between 7-H, 9-H, and 14-H_{ax}. The n.O.e. connectivity pattern oberved between 11-H and 9-H, and 8-H shows that 11-H is *cis* to the C-10 1,3-dioxane moiety. This stereochemical arrangement would also explain why an n.O.e. is observed between the protons of the C-11 methyl group and 9-H, but not with 8-H. On the basis of the n.O.e. evidence, the relative configuration shown in structure (**1**) *i.e.* (7*R*,8*S*,9*R*,10*S*,11*S*)† or the enantiomer, is assigned to sesbanimide. The enantiomeric configuration would result if the (8*R*) configuration is used in the discussion. The same relative stereochemistry was obtained by Powell *et al.*[5] from an *X*-ray crystallographic analysis of sesbanimide.†

An interesting phenomenon observed in both the ^1H and ^{13}C n.m.r. spectra of sesbanimide is the existence of a solvent dependent equilibrium between the tautomeric ring-closed

† The (*R*) descriptor is assigned in error to C-10 in ref. 5.

Table 1. N.m.r. data for sesbanimide (**1**)

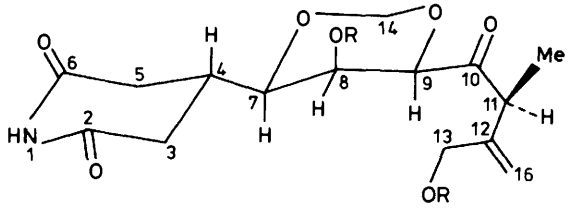
Carbon atom	δ_C[a]	^1J(C,H) (Hz)	Proton	δ_H[d,e]	J(H,H) (Hz)
2	171.48 S[b]				
3	33.16 T[c]	129.5	3-*ax*	2.360 dd	17.0, 9.9
			3-*eq*	2.743 ddd	17.0, 4.6, 1.5
4	30.84 D	131.8	4	2.629 m	
5	33.83 T[c]	131.1	5-*ax*	2.462 dd	17.3, 9.7
			5-*eq*	2.889 ddd	17.3, 4.4, 1.5
6	170.96 S[b]				
7	81.32 D	136.4	7	3.331 dd	8.7, 1.3
8	64.67 D	146.4	8	3.994 ddd	7.2, 1.3, 1.2
9	80.93 D	136.5	9	3.570 d	1.2
10	105.02 S				
11	45.56 D	128.4	11	2.592 m	
12	150.02 S				
13	69.52 T	149.5	13	4.538 dddd	12.9, 2.2, 2.2, 2.2
				4.455 dddd	12.9, 2.2, 2.2, 2.2
14	93.94 DD	171.2,	14-*ax*	4.764 d	6.2
		160.0	14-*eq*	5.203 d	6.2
15	11.78 Q	127.7	15	1.180 d	6.8
16	104.33 T	159.8	16a	4.995 ddd	2.9, 2.1, 2.1
			16b	4.938 ddd	2.5, 2.5, 2.5

[a] In p.p.m. relative to Me_4Si; solvent $CDCl_3$. Capital letters refer to the pattern resulting from directly bonded (C,H) couplings [^1J(C,H)]. S = singlet, D = doublet, T = triplet, and Q = quartet. [b,c] May be interchanged. [d] In p.p.m. relative to Me_4Si; solvent $CDCl_3$. [e] Resonances of exchangeable protons: δ 7.795 (s, NH), 4.254 (s, 10-OH), and 3.623 (d, J 7.2 Hz, 8-OH). The chemical shift values are concentration- and temperature-dependent.

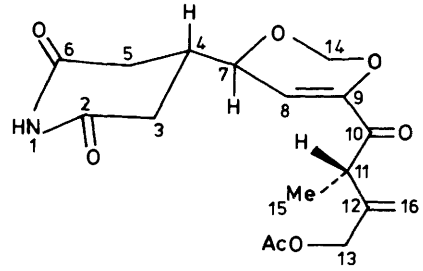
Table 2. ^{13}C N.m.r. data for sesbanimide (**1**) using [$^2H_6$]dimethyl sulphoxide as solvent

Carbon atom	δ_C[a]	Δδ[b]	δ_C[a]	Δδ[b]
2	172.69 S	−0.090	172.69 S	−0.090
3	33.57 S		33.57 S	
4	30.36 D[c]		30.04 D[c]	
5	32.58 S		32.58 S	
6	172.36 S	−0.087	172.36 S	−0.087
7	80.80 D[d]		80.77 D[d]	
8	64.22 D[e]	−0.109	63.61 D[e]	−0.105
9	83.15 D		80.59 D[d]	
10	208.35 S		105.35 S	−0.103
11	43.56 D[f]		44.97 D[f]	
12	148.90 S	−0.032	152.41 S	
13	63.28 T	−0.116	68.20 T	
14	92.56 DD[g]		91.90 DD[g]	
15	15.65 Q		12.50 Q	
16	108.65 T		102.66 T	

[a] In p.p.m. relative to Me_4Si. Multiplicities as in Table 1. [b] Deuterium isotope shifts in p.p.m. observed upon addition of D_2O–H_2O (1:1) to the sample. [c–g] May be interchanged.



(**5**) R = H
(**6**) R = Ac



(**7**)

hemiacetal (**1**) and the ring-opened γ-hydroxyketone (**5**). The ^1H and ^{13}C n.m.r. spectra of sesbanimide in [^2H]chloroform reveal the presence of the hemiacetal form (**1**) alone, whereas in the ^1H n.m.r. spectrum in [$^2H_4$]methanol both forms, (**1**) and (**5**), are present, in the ratio 2:1, respectively, as shown by the integral ratio of the methyl proton resonance. With [$^2H_5$]pyridine as solvent, this ratio changes to 3:1, whereas in [$^2H_6$]dimethyl sulphoxide it is 1:1. Removal of the different solvents and re-examination of the ^1H n.m.r. spectrum in [^2H]chloroform shows in each case the presence of the hemiacetal form (**1**) alone.

Unambiguous proof for the presence of the ring-opened γ-hydroxyketone (**5**) in solution was provided by the chemical shift of the C-10 resonance in the ^{13}C n.m.r. spectrum of sesbanimide in a [$^2H_6$]dimethyl sulphoxide solution. The resonance at δ 208.35 p.p.m. is assigned to the sp^2 carbon atom of the carbonyl group of (**5**), whereas the resonance at δ 105.35 p.p.m., which exhibits a two-bond deuterium isotope shift (Δδ −0.103 p.p.m.), is assigned to the hemiacetal carbon atom of (**1**) (see Table 2). Ring closure of the γ-hydroxyketone (**5**) proceeds by stereospecific attack of the C-13 hydroxy group on the *SiR* face[15] of the carbonyl group to give the hemiacetal (**1**).

Chemical evidence for the presence of the ring-opened form (**5**) of sesbanimide in solution was provided by acetylation with acetic anhydride in pyridine to give the diacetate (**6**) and the α,β-unsaturated ketone (**7**), $\lambda_{max.}$ 259 nm (ε 4 370). In the ^1H n.m.r. spectrum of (**6**), the 13-H's appear as an AB spin system (J 13.8 Hz) at δ 4.609 and 4.575, whereas 8-H appears at δ 4.935 as a double doublet (J 1.2 and 1.8 Hz). The presence of two acetate groups in the compound was evident from the three-proton resonances at δ 2.067 and 2.063. In contrast, only one acetate group (δ 2.063) is present in the α,β-unsaturated ketone (**7**) and

8-H now appears as a doublet (J 2.0 Hz) at δ 5.863 in the ^{1}H n.m.r. spectrum.

Experimental

M.p.s were determined on a Kofler hot-stage apparatus. U.v. absorptions were measured for solutions in methanol on a Unicam SP 8-100 spectrometer and i.r. spectra in chloroform on a Perkin-Elmer 257 spectrometer. ^{1}H (500.13 MHz) and ^{13}C (125.76 MHz) n.m.r. spectra were recorded on a Bruker WM-500 spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. T.l.c. was carried out on Merck precoated silica gel plates (thickness 0.25 mm). For column chromatography Merck silica gel, particle size 0.063—0.200 mm, was used.

Isolation of Sesbanimide (**1**).—*Sesbania punicea* seeds (4.5 kg) were ground in a mill to pass through a 50 mesh sieve. The ground seeds were extracted with ethanol (70%; 6 × 1 l) for 6 h at room temperature, filtered, and the combined filtrates concentrated under reduced pressure to give an aqueous residue (500 ml). This solution was treated with an excess of basic lead acetate, filtered, and the filtrate saturated with hydrogen sulphide gas. After filtration, the filtrate was concentrated under reduced pressure to *ca.* 250 ml and continuously extracted with chloroform under reflux for 48 h. The chloroform solution was dried (Na_2SO_4) and the solvent removed under reduced pressure to leave a brown gum (1.1 g). Purification on silica gel (200 g), eluting with ethyl acetate–n-hexane (1:1 v/v), gave sesbanimide (**1**) (102 mg), which crystallized from methanol–dichloromethane as white plates, m.p. 155—156 °C (lit.,[5] m.p. 158—159 °C); $[\alpha]_D^{20}$ +54.7° (*c* 0.17, $CHCl_3$) and −3.8° (*c* 0.28, MeOH) {lit.,[5] $[\alpha]_D^{23}$ −5.6° (MeOH)}; $\lambda_{max.}$ end absorption only; $\nu_{max.}$ 3 530, 3 360, 3 000, 2 860, 1 710, 1 360, and 1 060 cm^{-1}; *m/z* [electron impact (e.i.)] 309 ($M^+ - H_2O$), *m/z* (FAB) 350 $[M + Na]^+$ (Found: C, 55.0; H, 6.6; N, 4.15. Calc. for $C_{15}H_{21}NO_7$: C, 55.06; H, 6.42; N, 4.28%).

Acetylation of Sesbanimide (**1**).—Sesbanimide (**1**) (20 mg) in pyridine (1 ml) and acetic anhydride (0.5 ml) was kept at 20 °C for 16 h. After addition of water (10 ml), the mixture was acidified (2M-HCl) and extracted with chloroform (2 × 5 ml). The combined organic extracts were dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. Purification on silica (15 g), eluting with methanol–chloroform (5:95 v/v), gave the α,β-unsaturated ketone (**7**) (3.2 mg) as a colourless oil, $\nu_{max.}$ 259 nm (ε 4 370); $\delta_H(CDCl_3)$ 7.842 (NH), 5.863 (d, 8-H, $J_{7,8}$ 2.0 Hz), 5.218 (d, 14-H, J_{gem} 5.7 Hz), 5.132 (m, 16-H), 4.901 (m, 16-H), 4.899 (d, 14-H, J_{gem} 5.7 Hz), 4.603 (m, 13-H, J_{gem} 13.7 Hz), 4.578 (m, 13-H, J_{gem} 13.7 Hz), 4.489 (dd, 7-H, $J_{7,8}$ 2.0, $J_{4,7}$ 3.7 Hz), 3.637 (q, 11-H, $J_{11,15}$ 6.9 Hz), 2.718 [ddd, 3-H$_{eq}$ (or 5-H$_{eq}$), J_{gem} 17.2, $J_{3,4}$ 5.0, $J_{3,5}$ 1.4 Hz], 2.624 [dd,3-H$_{ax}$ (or 5-H$_{ax}$), J_{gem} 17.2, $J_{3,4}$ 10.0 Hz), 2.621 (ddd, 5-H$_{eq}$ (or 3-H$_{eq}$), J_{gem} 17.2, $J_{3,4}$ 5.0, $J_{3,5}$ 1.4 Hz], 2.516 [dd, 5-H$_{ax}$ (or 3-H$_{ax}$), J_{gem} 17.2, $J_{4,5}$ 10.0 Hz], 2.390 (m, 4-H), 2.063 (acetate CH_3), and 1.240 (d, CH_3, $J_{11,15}$ 6.9 Hz); *m/z* 351 (M^+) ($C_{17}H_{21}NO_7$ requires *M*, 351).

Continued elution gave the *diacetate* (**6**) (6.5 mg) as a colourless oil, $\delta_H(CDCl_3)$ 7.885 (NH), 5.410 (m, 16-H), 5.259 (d, 14-H, J_{gem} 6.4 Hz), 5.143 (m, 16-H), 4.935 (dd, 8-H, $J_{7,8}$ 1.2, $J_{8,9}$ 1.8 Hz), 4.780 (d, 14-H, J_{gem} 6.4 Hz), 4.609 (m, 13-H, J_{gem} 13.8 Hz), 4.575 (m, 13-H, J_{gem} 13.8 Hz), 4.274 (d, 9-H, $J_{8,9}$ 1.8 Hz), 3.686 (q, 11-H, $J_{11,15}$ 6.9 Hz), 3.488 (dd, 7-H, $J_{4,7}$ 8.6, $J_{7,8}$ 1.2 Hz), 2.862 [ddd, 3-H$_{eq}$ (or 5-H$_{eq}$), J_{gem} 17.2, $J_{3,4}$ 4.6, $J_{3,5}$ 1.4 Hz], 2.764 [ddd, 5-H$_{eq}$ (or 3-H$_{eq}$), J_{gem} 17.4, $J_{4,5}$ 4.6, $J_{3,5}$ 1.4 Hz], 2.499 [dd, 3-H$_{ax}$ (or 5-H$_{ax}$), J_{gem} 17.4, $J_{3,4}$ 9.2 Hz], 2.434 [dd, 5-H$_{ax}$ (or 3-H$_{ax}$), J_{gem} 17.2, $J_{4,5}$ 9.4 Hz], 2.263 (m, 4-H), 2.067 and 2.063 (2 × acetate CH_3), and 1.202 (d, CH_3, $J_{11,15}$ 6.9 Hz); *m/z* 411 (M^+) ($C_{19}H_{25}NO_9$ requires *M*, 411).

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