C_{19} and C_{20} Diterpene Alkaloids from *Aconitum toxicum* RCHB.

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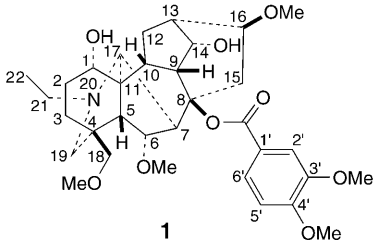
Acotoxinine (**1**), a new norditerpene alkaloid, was isolated from the roots of *Aconitum toxicum* RCHB., together with the structurally related C_{19} diterpene alkaloids neoline (**2**) and aconitine (**3**) and C_{20} diterpene alkaloids songorine (**4**) and songoramine (**5**). The structures were elucidated by HR-MS and advanced NMR methods, including ^{1}H-NMR, JMOD, ^{1}H,^{1}H-COSY, HSQC, and HMBC experiments. This is the first report of C_{20} diterpenoid alkaloids in *Aconitum toxicum*.

Introduction. – *Aconitum toxicum* RCHB. is a known toxic plant native to Romania and the former Yugoslavia [1]. The chemical composition of several *Aconitum* species has been largely studied, and the diterpene alkaloids typical of the genus were identified as the toxic constituents of the plants. Presumably, these extremely toxic compounds protect the plants against different pests since recent reports on the antifeedant and insect-repellent activity of diterpene alkaloids verified this hypothesis [2][3]. Due to their significant physiological effects, diterpene alkaloids command interest as models for drug development, or as tools in drug discovery. According to their structures, diterpene alkaloids act as agonists or as antagonists on voltage-gated Na^+ channels, hence are in the focus of the development of antiarrhythmic drugs [4]. Allapinin, a novel antiarrhythmic drug, has been developed from the Na^+-channel antagonist norditerpene alkaloid lappaconitine [5]. Due to the experimentally demonstrated antiepileptoform effect (*e.g.*, of aconitine, lappaconitine, and 6-benzoylheteratisine) [6] and selective antagonistic effect on the α-bungarotoxin-selective acetylcholine receptor (*e.g.*, of methyllycaconitine) [7], *Aconitum* alkaloids are also promising candidates in the development of drugs acting on the central nervous system.

As a part of our current studies on diterpene alkaloids of the Ranunculaceae species native to the Carpathian basin [8][9], we now report the isolation and structure elucidation of acotoxinine (**1**), a new norditerpene alkaloid, together with neoline (**2**), aconitine (**3**), songorine (**4**) and songoramine (**5**) from the roots of *A. toxicum*. The structures were determined by means of HR-ESI-MS, ^{1}H-NMR, JMOD, ^{1}H,^{1}H-COSY, NOESY, HSQC, and HMBC experiments. The ^{1}H- and ^{13}C-NMR data of songorine (**4**) and songoramine (**5**) were reinvestigated, and complete, unambiguous ^{1}H- and ^{13}C-NMR chemical-shift assignments were determined, including a revision of some δ(C) assignments.



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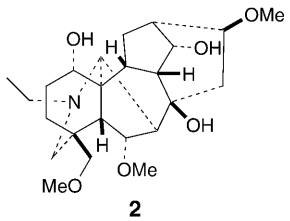

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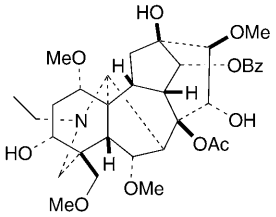

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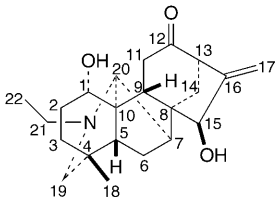
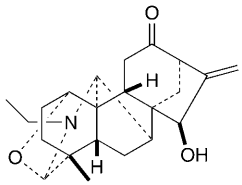


4 [1])



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Results and Discussion. – Multiple chromatographic purification of the $CHCl_3$/MeOH extract of the roots of *A. toxicum* resulted in the isolation of compounds **1**–**5**[1].

Compound **1** was obtained as an amorphous, optically active solid with the molecular formula $C_{33}H_{47}NO_9$, as deduced from the HR-ESI-MS experiment. From the analysis of the ^{1}H- and ^{13}C-NMR spectra (*Table*) and 2D-NMR experiments, the structure was identified as **1**, and the trivial name acotoxinine was chosen (for the systematic name, see the *Exper. Part*).

The ^{1}H-NMR spectrum of **1** (*Table*) exhibited resonances of three aromatic protons at δ(H) 6.85 (*d*), 7.54 (*d*), and 7.66 (*dd*), typical of an *ABX* spin system, which, together with those of two MeO groups at δ(H) 3.91 (*s*), and 3.92 (*s*) was assigned to a veratroyl (=3,4-dimethoxybenzoyl) group. Additionally, in the ^{1}H-NMR spectrum, three MeO (δ(H) 3.04, 3.29, and 3.35 (3*s*)) and an *N*-Et group (δ(H) 1.20 (*t*), 2.65 (*m*), and 2.74 (*m*)) were identified. The JMOD spectrum (*J*-modulated spin-echo experiment) confirmed the presence of a 19 C-atoms containing norditerpene skeleton, besides the signals of the veratroyl, MeO, and *N*-Et groups.

The HSQC plot of **1** allowed the assignment of 6 CH_2 (δ(C) 29.2, 29.5, 29.9, 38.6, 79.9, and 56.9) and 10 CH groups (δ(C) 40.8, 43.9, 44.4, 46.4, 48.6, 63.4, 72.1, 75.3, 82.1, and 84.0) and 3 quaternary C-atoms (δ(C) 38.2, 85.6, and 49.9) of the norditerpene core. ^{1}H,^{1}H-Connectivities detectable in the ^{1}H,^{1}H-COSY plot revealed the presence of four structural fragments: $CH(OR)CH_2CH_2$ (fragment A), CHCH(OR)CH (fragment B), $CHCHCH_2CHCH(OR)$ (fragment C), and $CHCH_2$ (fragment D) (R = H or Me) (*Fig.*). Long-range HMBC correlations between the quaternary C(11) and H–C(1) and between the quaternary C(4) and H–C(3) identified fragment A as the C(1)–C(3) part of the molecule (*Fig.* and *Table*). Similarly, two-bond correlations between H–C(5) and the quaternary C(4) and C(11), and between H–C(7) and C(8) and C(17) confirmed that fragment B is identical to the C(5)–C(7) part of the norditerpene core. The HMBC correlations H–C(10)/C(11), H–C(10)/(17), H–C(9)/C(8), and H–C(10)/C(8) verified that fragment C constitutes the five-membered C ring of the carbon-skeleton. According to the C(8)/CH_2(15), C(16)/CH_2(12), and C(16)/H–C(14) long-range ^{13}C,^{1}H-correlations, fragment D could be identified as the C(15)–C(16) part of the molecule. Additionally, the two isolated CH_2 groups

[1]) Trivial atom numbering.

Table. *NMR Data* ($CDCl_3$) *of* **1**[a]). δ in ppm, J in Hz.

	δ(H)	δ(C)	^{1}H,^{1}H-COSY	HMBC (C → H)
H–C(1)	3.71 (br. *s*)	72.1	CH_2(2)	CH_2(3), H–C(10), OH–C(1)
CH_2(2)	1.65 (*m*, H_α)	29.9	H–C(1), CH_2(3)	–
	1.53 (*m*, H_β)		H–C(1), H_α–C(3)	
CH_2(3)	1.90 (*dd*, *J* = 13.7, 5.6, H_α)	29.5	CH_2(2)	CH_2(18), H_a–C(19)
	1.70 (*dd*, *J* = 13.7, 4.6, H_β)		H_α–C(2)	
C(4)	–	38.2	–	H_β–C(3), H–C(5), H–C(6), CH_2(18), H_a–C(19)
H–C(5)	2.28 (*d*, *J* = 6.4)	44.4	H–C(6)	H–C(17), CH_2(18)
H–C(6)	4.20 (*m*)	84.0	H–C(5), H–C(7)	H–C(7), H–C(17), MeO
H–C(7)	3.31 (*s*)	48.6	H–C(6)	H–C(5), CH_2(15)
C(8)	–	85.6	–	H–C(6), H–C(7), H–C(9), H–C(10), CH_2(15)
H–C(9)	2.52 (*t*, *J* = 5.9)	46.4	H–C(10), H–C(14)	H–C(7), H–C(10), CH_2(15)
H–C(10)	2.00 (*m*)	43.9	H–C(9), CH_2(12)	H–C(1), H–C(5), H–C(9), CH_2(12), H–C(13)
C(11)	–	49.9	–	H–C(1), H–C(5), H–C(7), H–C(10), H_α–C(12)
CH_2(12)	2.10 (*m*, H_β)	29.2	H–C(10), H_α–C(12)	H–C(9), H–C(10), H–C(13), H–C(16)
	1.82 (*dd*, *J* = 14.4, 4.6, H_α)		H–C(10), H_β–C(12)	
H–C(13)	2.36 (*m*)	40.8	H_β–C(12), H–C(14)	H–C(9), CH_2(12), H–C(14), H_α–C(15)
H–C(14)	4.20 (*m*)	75.3	H–C(9), H–C(13)	H–C(9), H_α–C(12), H–C(13), H–C(16)
CH_2(15)	3.00 (*dd*, *J* = 16.2 8.9, H_α)	38.6	H_β–C(15), H–C(16)	H–C(7), H–C(9)
	2.38 (*m*, H_β)		H_α–C(15), H–C(16)	
H–C(16)	3.42 (*t*, *J* = 8.3, 6.8)	82.1	CH_2(15)	CH_2(12), H–C(14), CH_2(15), MeO
H–C(17)	2.81 (*s*)	63.4	–	H–C(5), H–C(6), H–C(7), H–C(10), H_a–C(19)
CH_2(18)	3.59 (*d*, *J* = 8.1, H_a)	79.9	H_b–C(18)	H–C(5), H_a–C(19), MeO
	3.12 (*d*, *J* = 8.1, H_b)		H_a–C(18)	
CH_2(19)	2.71 (*d*, *J* = 11.0, H_a)	56.9	H_b–C(19)	H–C(5), H–C(17), CH_2(18)
	2.41 (*m*, H_b)		H_a–C(19)	
CH_2(21)	2.74 (*m*, H_a)	48.5	H_b–C(21), Me(22)	H_a–C(19), Me(22)
	2.65 (*m*, H_b)		H_a–C(21), Me(22)	
Me(22)	1.20 (*t*, *J* = 7.2)	12.7	CH_2(21)	CH_2(21)
C(1′)	–	124.1	–	H–C(5′)
H–C(2′)	7.54 (*d*, *J* = 1.7)	112.1	H–C(6′)	H–C(6′)
C(3′)	–	148.7	–	H–C(2′), H–C(5′), MeO
C(4′)	–	153.0	–	H–C(2′), H–C(5′), H–C(6′), MeO
H–C(5′)	6.85 (*d*, *J* = 8.4)	110.3	H–C(6′)	–
H–C(6′)	7.66 (*dd*, *J* = 8.4, 1.7)	123.4	H–C(2′), H–C(5′)	H–C(2′)

Table (cont.)

	δ(H)	δ(C)	^{1}H,^{1}H-COSY	HMBC (C → H)
COO	–	165.5	–	H–C(2′), H–C(5′), H–C(6′)
OH–C(1)	3.38 (*s*)	–	–	–
*Me*O–C(3′)	3.91 (*s*)	56.0	–	–
*Me*O–C(4′)	3.92 (*s*)	56.0	–	–
*Me*O–C(6)	3.04 (*s*)	58.2	–	H–C(6)
*Me*O–C(16)	3.35 (*s*)	56.6	–	H–C(16)
*Me*O–C(18)	3.29 (*s*)	59.1	–	CH_2(18)

[a]) Measured at 500 MHz (^{1}H) and 125 MHz (^{13}C).

were identified as C(18) and C(19) by the ^{13}C,^{1}H-correlations C(4)/CH_2(18), C(4)/H_a–C(19), and C(17)/H_a–C(19). The positions of the MeO groups were established by means of HMBC correlations observed between the MeO protons (δ(H) 3.04, 3.35, and 3.29) and C(6), C(16), and C(18). The presence of an OH group at C(1) could be determined by a long-range correlation between C(1) and the OH group (δ(H) 3.38 (*s*)). Substitution of C(8) and C(14) with a veratroyl and an OH group, respectively, could not be determined by HMBC correlations. However, the chemical shift of H–C(14) at δ(H) 4.20 indicated a 14-OH,8-*O*-veratroyl substitution since H–C(14) should resonate in the range δ(H) 4–4.2 in the case of an OH group at C(14) but in the range δ(H) 4.8–5.8 in the case of an acyl substitution at C(14) [10].

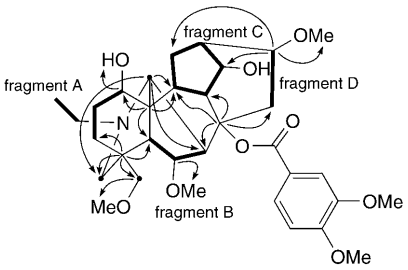

Figure. *Significant ^{1}H,^{1}H-COSY* (▬) *and HMBC Correlations* (→) *for Acotoxinine* (**1**)

The configuration of **1** was studied by means of NOESY experiments. The NOEs H–C(1)/H–C(10), H–C(10)/H–C(14), H–C(14)/H–C(9), and H–C(9)/H–C(10) indicated β-oriented protons at these locations. The coupling constant between H–C(5) and H–C(6) (J = 6.4 Hz) confirmed the β-position of H–C(6), and NOE H–C(6)/H–C(7) established the β-orientation of these protons. Further, the NOEs H–C(17)/$H_α$–C(15) and $H_α$–C(15)/H–C(16) demonstrated the α-position of H–C(16). The NOEs H–C(16)/$H_α$–C(15), H–C(17)/$H_α$–C(12), H–C(5)/$H_β$–C(2), and $H_α$–C(2)/$H_α$–C(3) allowed the steric differentiation of the protons of CH_2(2), CH_2(3), CH_2(12), and CH_2(15), as shown in the *Table*.

From *A. toxicum*, the known neoline (**2**) [11], aconitine (**3**) [12], songorine (**4**) [13], and songoramine (**5**) [14][15] were also isolated and identified by comparison of their spectral data with those published in the literature. The NMR chemical shifts of songorine (**4**) and songoramine (**5**) were identical to those described earlier, but our two-dimensional NMR investigations, including ^{1}H,^{1}H-COSY, NOESY, HSQC, and HMBC experiments, permitted the revision of some ^{13}C-NMR assignments and complete ^{1}H-NMR assignments for **4** and **5** for the first time (see the *Exper. Part*).

Conclusions. – The chemical composition of *A. toxicum* has been poorly studied earlier, only one alkaloid, talatisamine has been identified so far from the plant [16]. In the present study of *A. toxicum,* apart from the new compound acotoxinine (**1**), four known alkaloids, neoline (**2**), aconitine (**3**), songorine (**4**), and songoramine (**5**), were identified. Acotoxinine (**1**), neoline (**2**), and aconitine (**3**) are biogenetically related lycoctonine-type C_{19} diterpene alkaloids, which differ in the positions and presence of ester and OH groups. The presence of C_{20} diterpene alkaloids (songorine (**4**) and songoramine (**5**)) in *A. toxicum* is reported here for the first time. The C_{20} alkaloid songoramine (**5**) can be regarded as the product of an oxirane-ring formation in songorine (**4**).

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Experimental Part

General. Column chromatography (CC): polyamide for CC (*ICN*), and neutral aluminium oxide (*Brockmann II*, *Reanal*); vacuum liquid CC with aluminium oxide *G* (type *E*; *Merck*); gel CC with *Sephadex LH-20* (25–100 μm, *Pharmacia Fine Chemicals*) and MeOH as eluent. Prep. TLC: 20×20 cm plates coated with silica gel *60 F_{254}* (*Merck*) or aluminium oxide *60 F_{254}* (neutral; *Merck*). Centrifugal planar chromatography (CPC): *Chromatotron* model *8924* (*Harrison Research*); manually prepared plates coated with 2 mm of silica gel *60 GF_{254}* (*Merck*) or aluminium oxide *G* (type *E*; *Merck*). Anal. TLC: silica gel (*Merck 5715*); detection by spraying with *Dragendorff* reagent or conc. H_2SO_4 soln. followed by heating. $[\alpha]_D$: *Perkin-Elmer 341* polarimeter. NMR Spectra: *Bruker-Avance DRX-500* spectrometer at 500 (^{1}H) or 125 MHz (^{13}C); in $CDCl_3$, with the signals of the deuterated solvent as the reference; 2D data were acquired and processed with standard *Bruker* software; for ^{1}H,^{1}H-COSY, HSQC, and HMBC experiments, gradient-enhanced versions were used. HR-MS: *VG-ZAB-SEQ* hybrid mass spectrometer equipped with a *Cs-SIMS* ion source; resolution 10000; sample in MeOH soln.; glycerol as matrix, using its cluster peak at *m*/*z* 645 in peak-matching experiments, in *m*/*z*.

Plant Material. The roots of *Aconitum toxicum* RCHB. were collected near Maroshévíz, Romania, in August 2002, and were identified by Prof. *Károly Csedő* (University of Medicine and Pharmacy, Targu Mures, Romania). Roots of the plants were dried, ground, and stored at r.t. until processing. A voucher specimen (No. 655) has been deposited in the Herbarium of the Department of Pharmacognosy, University of Szeged, Szeged, Hungary.

Extraction and Isolation. The ground, dry roots (950 g) were extracted with $CHCl_3$/MeOH 9:1 (15 l). After evaporation, the dry residue (47 g) was subjected to CC (polyamide, 20 and 40% MeOH). After evaporation, the 20%-MeOH fraction was further fractionated by CC (Al_2O_3 (*CCI*), cyclohexane/$CHCl_3$/MeOH of increasing polarity. *Frs. CCI.26–37*, eluted with cyclohexane/$CHCl_3$ 5:2, were purified by gel CC (*Sephadex LH-20* (*CCII*)). *Frs. CCII.4* and *5* were further fractionated by prep. TLC (silica gel, CH_2Cl_2/MeOH 19:1): pure **1** (5 mg). From *Frs. CCII.10–20*, **4** (40 mg) was crystallized. The combined *Frs. CCI.47–78*, eluted with cyclohexane/$CHCl_3$ 5:2 and 5:3, were subjected to gel CC (*Sephadex LH-20* (*CCIII*)). *Frs. CCIII.6–10* contained a high amount of a complex alkaloid mixture, which was fractionated by vacuum liquid CC (Al_2O_3 (*CCIV*), gradient cyclohexane/AcOEt/MeOH/H_2O). *Frs. CCIV.3* and *4*, eluted with cyclohexane/AcOEt 7:3, contained pure **5** (4 mg). *Frs. CCIV.24–33*, eluted with cyclohexane/AcOEt/MeOH 4:4:5 and AcOEt//MeOH/H_2O 400:5:3 and 200:5:3, were purified by prep. TLC (Al_2O_3, AcOEt/MeOH/H_2O 50:3:2): **2** (18.3 mg). *Frs. CCI.10–19*, eluted with cyclohexane/$CHCl_3$ 5:2, were subjected in multiple steps to CPC (silica gel and Al_2O_3, cyclohexane/AcOEt/EtOH of increasing polarity): **3** (98 mg).

Acotoxinine (*=(1α,6α,14α,16β)-20-Ethyl-1,14-dihydroxy-6,16-dimethoxy-4-(methoxymethyl)aconitan-8-yl 3,4-Dimethoxybenzoate*; **1**): Amorphous solid. $[\alpha]_D^{25} = +32$ ($c = 0.05$, $CHCl_3$). ^{1}H- and ^{13}C-NMR: *Table*. HR-ESI-MS: 602.3329 ($[M+H]^+$, $C_{33}H_{48}NO_9^+$; calc. 602.3329).

Neoline (**2**): Amorphous solid. $[\alpha]_D^{25} = +29$ ($c = 0.1$, $CHCl_3$). ^{1}H- and ^{13}C-NMR ($CDCl_3$): data identical with those published in [11].

Aconitine (**3**): Amorphous solid. $[\alpha]_D^{25} = +16$ ($c = 0.2$, $CHCl_3$). ^{1}H- and ^{13}C-NMR ($CDCl_3$): data identical with those published in [12].

Songorine (**4**): Amorphous solid. $[\alpha]_D^{27} = -111$ ($c = 0.2$, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$)[1]): 3.81 (*dd*, *J* = 9.2, 6.8, H–C(1)); 1.90 (*m*, H_α–C(2)); 2.11 (*m*, H_β–C(2)); 1.31 (*m*, H_α–C(3)); 1.58 (*dt*, *J* = 13.4, 3.1, H_β–C(3)); 1.30 (*m*, H–C(5)); 1.33 (*dd*, *J* = 14.2, 5.0, H_α–C(6)); 2.45 (*m*, H_β–C(6)), 2.20 (*m*, H–C(7)); 1.73 (*dd*, *J* = 11.2, 7.2, H–C(9)); 3.28 (*dd*, *J* = 17.2, 11.3, H_α–C(11)); 2.29 (*dd*, *J* = 17.2, 7.1, H_β–C(11)); 3.05 (*d*, *J* = 3.0, H–C(13)); 2.08 (*d*, *J* = 12.4, H_α–C(14)); 1.43 (*dd*, *J* = 12.4, 3.8, H_β–C(14)); 4.32 (br. *s*, H–C(15)); 5.25, 5.17 (2 br. *s*, CH_2(17)); 0.74 (*s*, Me(18)); 2.50 (*m*, H_α–C(19)); 2.20 (*m*, H_β–C(19)); 3.41 (br. *s*, H–C(20)); 2.55, 2.40 (2 *m*, CH_2(21)); 1.03 (*t*, *J* = 7.1, Me(22)). ^{13}C-NMR (125 MHz, $CDCl_3$)[1]): 70.3 (C(1)); 32.0 (C(2)); 37.3 (C(3)); 34.1 (C(4)); 49.2 (C(5)); 23.1 (C(6)); 43.6 (C(7)); 49.9 (C(8)); 35.2 (C(9)); 52.3 (C(10)); 38.1 (C(11)); 210.1 (C(12)); 53.8 (C(13)); 31.6 (C(14)); 77.2 (C(15)); 150.8 (C(16)); 111.4 (C(17)); 26.0 (C(18)); 57.4 (C(19)); 65.9 (C(20)); 50.9 (C(21)); 13.4 (C(22)).

Songoramine (**5**): Amorphous solid. $[\alpha]_D^{27} = -26$ ($c = 0.05$, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$)[1]): 3.99 (*d*, *J* = 5.3, H–C(1)); 2.19, 1.76 (2*m*, CH_2(2)); 1.56 (*m*, H_α–C(3)); 1.27 (*m*, H_β–C(3)); 1.29 (*m*, H–C(5)); 1.82, 1.44 (2*m*, CH_2(6)); 2.00 (*m*, H–C(7)); 1.79 (*m*, H–C(9)); 2.37 (*dd*, *J* = 16.3, 12.6, H_α–C(11)); 2.13 (*dd*, *J* = 16.3, 6.4, H_β–C(11)); 3.16 (*d*, *J* = 4.2, H–C(13)); 2.03 (*dd*, *J* = 17.2, 4.2, H_α–C(14)); 1.57 (*m*, H_β–C(14)); 4.40 (*d*, H–C(15)); 5.32, 5.20 (2*s*, CH_2(17)); 0.85 (*s*, Me(18)); 3.71 (*s*, CH_2(19)); 2.85 (*s*, H–C(20)); 2.72, 2.68 (2*dq*, *J* = 14.0, 7.2, CH_2(21)); 1.04 (*t*, *J* = 7.2, Me(22)). ^{13}C-NMR (125 MHz, $CDCl_3$)[1]): 67.9 (C(1)); 24.3 (C(2)); 29.7 (C(3)); 37.8 (C(4)); 46.0 (C(5)); 24.0 (C(6)); 48.5 (C(7)); 50.2 (C(8)); 31.4 (C(9)); 51.8 (C(10)); 37.4 (C(11)); 208.5 (C(12)); 53.1 (C(13)); 31.3 (C(14)); 77.0 (C(15)); 149.8 (C(16)); 111.9 (C(17)); 18.9 (C(18)); 92.9 (C(19)); 66.2 (C(20)); 48.5 (C(21)); 14.2 (C(22)).

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