Norditerpenoid Alkaloids from *Consolida orientalis* and Complete ^{1}H and ^{13}C NMR Signal Assignments of Some Lycoctonine-Type Alkaloids

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A new norditerpene alkaloid was isolated, 18-demethylpubescenine (**1**), in addition to four known compounds, 14-demethyltuguaconitine (**2**), takaosamine (**3**), gigactonine (**4**), and delcosine (**5**), from fresh, whole plants of *Consolida orientalis*. The structure of **1** was established by spectroscopic methods, including various 2D NMR techniques and HRESIMS. As a result of a detailed NMR study, complete ^{1}H NMR chemical shift assignments for alkaloids **1**−**5** are presented herein, and some ^{13}C NMR signal assignments for **2**−**4** have been revised.

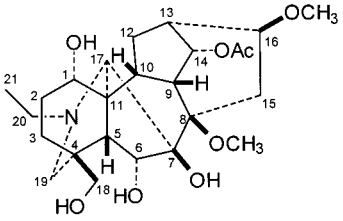
Diterpene alkaloids have attracted considerable interest because of their complex structure, interesting chemistry, and noteworthy physiological effects. This specific type of alkaloids occurs in certain species of the families Ranunculaceae, Garryaceae, Compositae, Saxifragaceae, and Rosaceae. Structurally, two categories of compounds can be differentiated: the highly functionalized C_{19} norditerpenoid alkaloids, and the C_{20} diterpene alkaloids with two or three oxygen functions. A small group of C_{18} bisnorditerpene alkaloids has also been isolated from *Delphinium* and *Aconitum* species.[1] Norditerpene alkaloids have been found to exert antiinflammatory, analgesic, and various cardiovascular effects, and also inhibitory activity against acetylcholinesterase.[2−4]

In the course of a search for biologically active compounds from Hungarian Ranunculaceae species, we have examined the alkaloidal constituents of *Consolida orientalis* (Gay) Schrödinger, a species widely distributed in the Iberian peninsula and in southeastern parts of Europe and occurring abundantly in southeastern Hungary. Previous phytochemical studies demonstrated the occurrence of gigactonine (**4**), delcosine (**5**), delsoline, 18-methoxygadesine, and 18-hydroxy-14-*O*-methylgadesine in *C. orientalis* collected in Spain.[5,6] The recent investigation of this species when collected in Turkey led to the isolation of a new C_{20} diterpene alkaloid, colsorientaline, together with takaosamine (**3**), gigactonine (**4**), delcosine (**5**), and delsoline.[7]

The present paper reports the isolation and structure elucidation of a new norditerpene alkaloid, 18-demethylpubescenine (**1**), together with four known compounds, 14-demethyltuguaconitine (**2**), takaosamine (**3**), gigactonine (**4**), and delcosine (**5**), obtained from a Hungarian population of *C. orientalis*. Extensive NMR studies, including $^{1}H-^{1}H$ COSY, HSQC, HMBC, and NOESY experiments, resulted in complete and unambiguous ^{1}H assignments for **1**−**5** and the reassignment of some ^{13}C NMR chemical shifts for **2**−**4**.

Fresh whole plants of *C. orientalis*, collected in the flowering period, were extracted with MeOH. The extract was subjected to solvent partitioning and then to multiple chromatographic separations, affording compounds **1**−**5**.

The HRESIMS data suggested the molecular formula $C_{25}H_{39}O_8N$ for compound **1** from the *m/z* 482.2769 (M + H)$^+$ ion (calcd *m/z* 482.2754, Δ −3.1 ppm). The ^{1}H NMR and JMOD (*J*-modulated spin−echo experiment) spectra of **1** indicated the presence of two methoxy groups (δ_H 3.42 and 3.39 s; δ_C 52.9 and 56.5), one acetoxy group (δ_H 2.05 s; δ_C 21.2 and 171.0), and one *N*-ethyl group [δ_H 3.02 dq, 2.91 dq (CH_2), and 1.13 t (CH_3); δ_C 50.7 and 13.7] in the molecule. Additionally, the JMOD spectrum, supported by HSQC and HMBC correlations, revealed the presence of a C_{19} diterpene alkaloid core, composed of four sp^3 quaternary carbons, nine sp^3 methines, and six methylene groups (Table 1). The primary $^{1}H-^{13}C$ correlations were identified on the basis of a HSQC experiment. The proton−proton connectivities in the $^{1}H-^{1}H$ COSY spectrum indicated two



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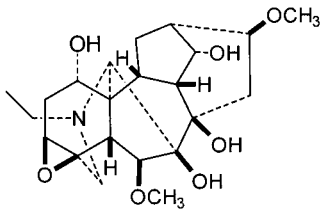

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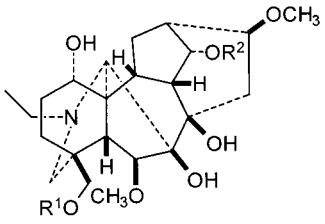

	R^1	R^2
3	H	H
4	H	CH_3
5	CH_3	H

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Table 1. NMR Data of 18-Demethylpubescenine (**1**) [500 MHz (^{1}H), 125 MHz (^{13}C), $CDCl_3$, δ (ppm) (J = Hz)]

position	^{1}H[a]	^{13}C	HMBC (C no.)	NOESY
1	3.66 brs	72.2	2, 3, 10, 11, 17	2β, 2α, 10, 12α, 12β
2α	1.60 m	29.5	4	1
2β	1.49 m			1, 5
3α	1.62 m	29.5		19b
3β	1.66 m			18a, 18b
4		39.1		
5	2.16 d (6.9)	40.6	4, 7, 10, 11, 17, 18, 19	2β, 6, 10, 18a, 18b
6	4.48 d (6.9)	70.3	4, 7, 8, 17	5, 9, OMe-8
7		85.2		
8		80.8		
9	2.30 t (6.0)	43.8	8, 12, 13, 14	6, 10, 14
10	1.92 m	43.2	8, 9, 11, 12, 17	1, 5, 9, 14
11		47.5		
12α	1.81 dd (14.3, 4.6)	29.6	9, 11, 13, 14, 16	1, 13, 16
12β	2.07 m		9, 11, 13	1, 13, 14
13	2.48 dd (7.2, 4.6)	38.0	9, 14, 16	12α, 12β, 14, 16, OMe-16
14	4.76 t (4.5)	75.7	8, 9, 13, 16, AcCO	9, 10, 12β, 13
15α	2.64 dd (14.6, 8.5)	28.6	7, 8, 9, 13, 16	16, 17
15β	1.97 dd (14.6, 8.1)		7, 8, 16	OMe-8
16	3.45 t (8.5)	82.8	14, 15, OMe-16	12α, 13, 15α, 17
17	2.75 s	63.5	6, 7, 8, 10, 11, 19, 20	15α, 16, 19a, 21
18a	3.89 d (10.6)	70.4	3, 4, 11, 19	3β, 5, 18b, 19a
18b	3.54 d (10.6)		3, 5, 11, 19	3β, 5, 18a
19a	2.80 d (11.0)	56.2	3, 4, 18, 20	17, 18a
19b	2.35 d (11.0)		3, 4, 17	3α, 20b, 21
20a	3.02 dq (12.7, 7.3)	50.7	17, 19, 21	
20b	2.91 dq (12.7, 7.3)		17, 19, 21	19b
21	1.13 t (7.2)	13.7	20	17, 19b
OMe-8	3.42 s	52.9	8	6, 15β, OAc-14
OMe-16	3.39 s	56.5	16	13
acetyl				
Me	2.05 s	21.2	AcCO	OMe-8
CO		171.0		

[a] OH signals: 2.72 s, 2.18 s, 2.03 brs.

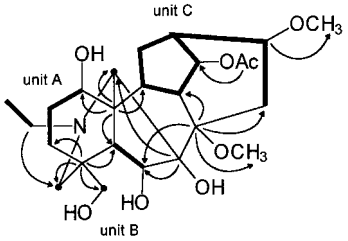

Figure 1. Selected ^{1}H−^{1}H COSY (—) and HMBC (C → H) correlations for **1**.

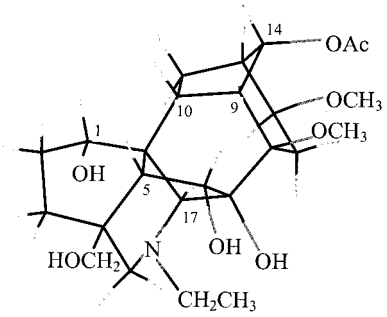

Figure 2. Calculated conformation of 18-demethylpubescenine (**1**).

isolated methylenes [δ_H 3.89 and 3.54 d (CH_2-18), 2.80 and 2.35 d (CH_2-19)] and three structural fragments: δ_H 3.66 brs, 1.60 m, 1.49, 1.62, and 1.66 m (unit A: H-1−H-3), δ_H 2.16 and 4.48 d (unit B: H-5−H-6), and δ_H 4.76 t, 2.30 t, 1.92 m, 1.81 dd, 2.07 m, 2.48 dd, 3.45 t, 2.64 dd, and 1.97 dd (unit C: H-14−H-9−H-10−H-12−H-13−H-16−H-15) (Figure 1). The overall structure of **1** was determined by interpretation of the long-range ^{1}H−^{13}C correlations observed in the HMBC spectrum (Table 1). Most informative were the correlations of the quaternary carbons, which led to the connection of partial structures and quaternary carbons, resulting in the *N*-ethyl norditerpene skeleton formed by six rings (Figure 1), typical for Ranunculaceae species. The ^{13}C NMR chemical shifts of C-1, C-6, C-7, C-8, C-14, C-16, and C-18 showed that this compound has seven oxygen functions: two methoxy, one acetoxy, and four hydroxy groups. The positions of the methoxy groups were evident from the three-bond correlations between the methoxy protons and the skeletal carbons (C-8 and C-16). The location of the acetoxy group at C-14 was concluded from the correlation of the carbonyl carbon and the skeletal proton at δ_H 4.76 (H-14).

The stereochemistry of **1** was elucidated by analyzing a Dreiding model with respect to Overhauser effects detected in a NOESY spectrum. Starting from the β position of the proton at the ring junction (H-5), it was found that the β-oriented H-1, H-9, H-10, H-14, and CH_2-18 protons were present from the diagnostic cross-peaks between H-5 and H-10, H-5 and H-18a,b, H-10 and H-9, H-10 and H-1, H-10 and H-14, and H-14 and H-13. The correlative signals of H-19 and H-17 and the ethyl methyl protons were in accordance with the fact that the heterocyclic bridge is directed below the plane of ring A, as is usual in norditerpene alkaloids (Figure 2). The stereochemistry of H-16 was concluded to be α from its NOESY cross-peak with H-17. Further important NOE interactions were observed between H-9 and H-6, H-6 and H-5, and H-6 and OMe-8, proving their β configuration. Moreover, the 6.9 Hz coupling constant between H-5 and H-6 was consistent with a β-oriented H-6, in contrast with compounds **2**−**5**, which all have an α-oriented H-6 and exhibit singlet H-6 signals. Additionally, on the basis of the NOESY spectrum, the methylene protons could also be differentiated concerning their stereochemistry. Thus, NOE correlations between H-5 and the proton at δ_H 1.49, between H-18a,b and the proton at δ_H 1.66, and between H-14 and the proton at δ_H 2.07

Table 2. ^{1}H NMR Data of Compounds **2**−**5** [500 MHz, $CDCl_3$, δ (ppm) (J = Hz)]

position	2	3[a]	4	5
1	3.94 t (2.0)	3.68 brs	3.71 brs	3.67 brd (8.7)
2α	2.22 ddd (14.2, 5.5, 2.0)	1.67 m	1.64 m	1.61 m
2β	1.23 ddd (14.2, 7.1, 2.0)	1.51 m	1.48 ddt (15.3, 7.6, 2.4)	1.49 dddd (14.6, 13.7, 7.3, 3.0)
3α	3.12 dd (7.1, 5.5)	1.70 m	1.67 m	1.65 m
3β	-	1.94 m	1.98 m	1.98 m
5	1.42 d (2.0)	1.88 d (1.8)	1.88 d (2.0)	1.88 d (1.7)
6	4.43 s	4.00 s	3.99 s	4.02 s
9	2.89 t (6.0, 5.0)	2.96 t (6.1)	2.96 m	2.95 m
10	1.96 ddd (11.9, 6.0, 5.1)	1.94 m	1.96 m	1.92 m
12α	1.52 dd (14.3, 5.1)	1.61 m	1.69 dd (14.2, 4.6)	1.61 m
12β	2.10 ddd (14.3, 11.9, 7.6)	2.10 m	2.05 m	2.08 ddd (14.4, 11.5, 7.9)
13	2.38 dd (7.6, 5.0)	2.37 dd (7.5, 4.8)	2.42 dd (7.6, 4.6)	2.37 dd (7.4, 5.1)
14	4.13 t (5.0)	4.12 q (4.8)	3.63 m	4.11 dd (10.2, 5.1)
15α	2.80 dd (16.1, 9.2)	2.77 dd (16.3, 9.2)	2.62 dd (14.6, 8.6)	2.77 dd (16.0, 9.3)
15β	1.70 dd (16.1, 6.3)	1.68 m	1.74 dd (14.6, 8.6)	1.67 dd (16.0, 5.5)
16	3.35 m	3.37 m	3.30 t (8.6)	3.37 m
17	2.95 d (2.0)	2.89 d (1.8)	2.82 d (2.0)	2.87 d (1.7)
18a	3.45 d (10.0)	3.66 d (10.4)	3.65 d (13.2)	3.39 d (9.0)
18b	2.54 d (10.0)	3.39 m	3.38 d (13.2)	3.01 d (9.0)
19	−	2.46 ABq (11.5)	2.44 s	2.45 s
20a	3.03 m	2.98 dq (12.8, 7.2)	2.97 m	2.95 dq (12.9, 7.1)
20b	3.03 m	2.84 dq (12.8, 7.2)	2.83 dq (12.7, 7.1)	2.83 dq (12.9, 7.1)
21	1.08 t (7.2)	1.10 t (7.2)	1.10 t (7.1)	1.10 t (7.1)
OMe-6	3.42 s	3.41 s	3.40 s	3.36 s
OMe-14			3.42 s	
OMe-16	3.37 s	3.37 s	3.36 s	3.37 s
OMe-18				3.33 s
OH-1	n.a.[b]	7.20 brs	7.65 brs	7.15 d (8.7)
OH-7	n.a.[b]	3.28 s	3.38 s	3.24 s
OH-8	3.84 brs	3.93 s	4.07 s	3.96 s

[a] 2×OH: 3.48 s. [b] n.a. = not assigned.

led to the assignment of these signals as those of the β-oriented H-2, H-3, and H-12, respectively. NOESY cross-peaks between the signal at δ_H 2.64 and H-16 and H-17 allowed its assignment to H-15α. By interpretation of these NMR data, the structure of compound **1** was elucidated as 18-demethylpubescenine. This compound is a new natural product belonging to the rare group of 6-*epi*-lycoctonine-type alkaloids. Compound **1** with a 6-*epi* oxygen function is structurally dissimilar from alkaloids **2**−**5**, also isolated from the same plant as presented below, but is analogous to pubescenine and consolidine, obtained earlier from *Consolida pubescens* and *C. oliveriana*.[8,9]

Detailed NMR studies permitted the assignment of compound **2** as 14-demethyltuguaconitine. This is the second isolation of this compound: it was first obtained from *Delphinium stapeliosum* by Shrestha et al.[10] We found ^{13}C NMR chemical shifts identical to those described earlier,[10] but our two-dimensional NMR investigations, including ^{1}H−^{1}H COSY, HSQC, and HMBC experiments, permitted some revised assignments for **2**. The ^{13}C NMR assignments of 14-demethyltuguaconitine (**2**) should be corrected similarly as proposed earlier by Lao et al. for tuguaconitine,[11] in consequence of the following long-range correlations observed in the HMBC spectrum of **2**: the signal at δ_C 48.7 (C-5) with H-6, H-10, H-17, and H-18b; the signal at δ_C 45.4 (C-9) with H-10, H-12a, H-13, H-15, and OH-8; the signal at δ_C 42.8 (C-10) with H-1, H-5, H-9, H-12a, and H-13; and the signal at δ_C 39.7 (C-13) with H-9, H-12a, and H-15. Consequently, the correct assignments for C-5, C-9, C-10, and C-13 are δ_C 48.7, 45,4, 42.8, and 39.7, respectively. The ^{1}H chemical shift assignment of **2** was also reinvestigated by the interpretation of the ^{1}H−^{1}H COSY and HSQC spectra and corrected as listed in Table 2. The NOESY spectrum of 14-demethyltuguaconitine corroborated the stereostructure of the molecule as depicted in formula **2**. Moreover, the boat conformation of ring A, which generally occurs in 3,4-epoxy-substituted bisnorditerpene alkaloids,[12,13] was also demonstrated in **2** by the NOESY correlations observed between the β-oriented, equatorial H-1 and both equatorial and axial H-2.

From *C. orientalis*, the known takaosamine (**3**), gigactonine (**4**), and delcosine (**5**) were also isolated and identified by NMR investigations. As a result of ^{1}H NMR, JMOD, ^{1}H−^{1}H COSY, NOESY, HSQC, and HMBC experiments, unambiguous and complete chemical shift assignments for all protons of alkaloids **3** and **4** were determined and are reported in Table 2. In the case of delcosine (**5**), previously published ^{1}H NMR data[14] were supplemented with the exact assignments of the overlapping ^{1}H NMR signals in the range 1.4−3.4 ppm (Table 2). The ^{13}C NMR assignments for takaosamine (**3**) and gigactonine (**4**) were also revised on the basis of HMBC spectra; the corrected data are listed in the Experimental Section. Stereochemical investigation of alkaloids **3**−**5** was performed by means of NOESY measurements. The detected Overhauser effects prove the configuration of all the stereogenic centers as illustrated in formulas **3**−**5** and suggest that ring A possesses a boat conformation, which is best manifested by the NOE correlation between the β-oriented axial H-2 and H-5 protons. For all three compounds a downfield-shifted OH signal (δ_H 7.1−7.7) was observed, supporting the presence of an intramolecular N- - -H−O hydrogen bond between the N atom and the α-oriented axial OH-1 group.

Experimental Section

General Experimental Procedures. Melting points are uncorrected. The optical rotations were determined with a Perkin-Elmer 341 polarimeter. The UV spectrum was recorded on a Shimadzu UV-2101 PC spectrometer. NMR spectra were recorded in $CDCl_3$ on a Bruker Avance DRX 500 spectrometer, at 500 MHz (^{1}H) and 125 MHz (^{13}C), with TMS as internal standard. Two-dimensional data were acquired and processed with standard Bruker software. HRESIMS measurements were carried out on a Perkin-Elmer Q-STAR Pulsar Q-TOF mass spectrometer equipped with an electrospray ion source. For vacuum-liquid chromatography (VLC), silica gel (Kieselgel

GF_{254} 15 μm, Merck) and aluminum oxide G (Type E) (Merck) were used. Preparative TLC was performed on silica gel plates (Merck 5715). Chromatographic fractions were monitored by TLC, visualized by spraying with concentrated sulfuric acid, followed by heating or with Dragendorff's reagent.

Plant Material. *C. orientalis* was collected in the flowering period in June 1999, from wild stock growing near Hódmezővásárhely, Hungary. A voucher specimen (No. 520) has been deposited in the Herbarium of the Department of Pharmacognosy, University of Szeged, Szeged, Hungary.

Extraction and Isolation. The fresh whole plants of *C. orientalis* (20 kg) were crushed in a blender and then extracted exhaustively with MeOH (80 L). The methanolic extract was concentrated to 2 L and acidified with 2 L of 4% H_2SO_4. After the removal of neutral materials with 9 × 4 L of $CHCl_3$, the acidic solution was adjusted to pH 9.0 with 5% NaOH. The solution was extracted with 10 × 2 L of $CHCl_3$ to yield the crude alkaloid fraction (8.14 g). The $CHCl_3$ extract was fractionated by vacuum liquid chromatography (VLC-1) on silica gel using a gradient solvent system of cyclohexane−EtOAc−EtOH (80:20:2, 70:30:5, 6:4:1, 6:4:2, and 4:6:3), and finally 100% EtOH. Fractions 52−76 obtained with cyclohexane−EtOAc−EtOH (6:4:2) were rechromatographed by subsequent VLC (VLC-2), with elution with mixtures of petroleum ether−Et_2O−MeOH of increasing polarity. Fractions 25−30 in VLC-2 were crystallized from acetone to yield delcosine (**5**) (21 mg), and fractions 31−37 afforded the crystalline gigactonine (**4**) (92 mg). Fractions 77−87 in VLC-1, obtained with cyclohexane−EtOAc−EtOH (4:6:3), were subjected to VLC-3 on aluminum oxide, using the same gradient system as for VLC-2. Fractions 28−37 and 38−41 in VLC-3, after preparative TLC purification on silica gel with petroleum ether−Et_2O−MeOH (50:50:7), furnished 14-demethyltuguaconitine (**2**) (7 mg) and 18-demethylpubescenine (**1**) (3 mg), respectively. Upon standing, fractions 42−45 in VLC-3 afforded takaosamine (**3**) as a crystalline material.

18-Demethylpubescenine (1): amorphous solid; $[\alpha]_D^{23}$ +8° (*c* 0.1, $CHCl_3$); UV λ_{max} (log ϵ) (MeOH) 202 (3.72), 287 (2.93), 321sh (2.75); ^{1}H and ^{13}C NMR data, see Table 1; HRESIMS *m/z* 482.2769 $[M + H]^+$ (calcd for $C_{25}H_{40}O_8N$ *m/z* 482.2754, Δ −3.1 ppm).

14-Demethyltuguaconitine (2): amorphous solid; $[\alpha]_D^{23}$ +59.6° (*c* 0.4, $CHCl_3$), lit.[10] +59.5° (*c* 0.337, $CHCl_3$); ^{1}H NMR, see Table 2; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 77.9 (C-1), 31.5 (C-2), 58.7 (C-3), 58.6 (C-4), 48.7 (C-5), 90.0 (C-6), 89.6 (C-7), 78.1 (C-8), 45.4 (C-9), 42.8 (C-10), 53.5 (C-11), 29.6 (C-12), 39.7 (C-13), 75.6 (C-14), 34.4 (C-15), 81.9 (C-16), 67.5 (C-17), 54.3 (C-18), 50.1 (C-20), 14.1 (C-21), 58.9 (OMe-6), 56.4 (OMe-16).

Takaosamine (3): colorless crystals; mp 178−180 °C; $[\alpha]_D^{23}$ +61.3° (*c* 0.2, $CHCl_3$), lit.[15] 61.6° (*c* 0.19, $CHCl_3$); ^{1}H NMR, see Table 2; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 72.6 (C-1), 29.4 (C-2), 27.0 (C-3), 38.3 (C-4), 45.0 (C-5), 90.2 (C-6), 87.9 (C-7), 78.0 (C-8), 45.3 (C-9), 44.1 (C-10), 48.9 (C-11), 29.2 (C-12), 39.3 (C-13), 75.7 (C-14), 34.5 (C-15), 82.0 (C-16), 66.3 (C-17), 67.0 (C-18), 57.0 (C-19), 50.4 (C-20), 13.7 (C-21), 57.8 (OMe-6), 56.3 (OMe-16).

Gigactonine (4): colorless crystals; mp 166−168 °C; $[\alpha]_D^{23}$ +45.1° (*c* 0.5, $CHCl_3$), lit.[1] +49° (EtOH); ^{1}H NMR, see Table 2; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 72.6 (C-1), 29.3 (C-2), 26.6 (C-3), 38.1 (C-4), 44.6 (C-5), 90.5 (C-6), 87.7 (C-7), 78.5 (C-8), 43.3 (C-9), 43.9 (C-10), 49.3 (C-11), 30.5 (C-12), 37.7 (C-13), 84.5 (C-14), 33.5 (C-15), 82.9 (C-16), 66.0 (C-17), 66.7 (C-18), 57.2 (C-19), 50.2 (C-20), 13.5 (C-21), 57.7 (OMe-6), 57.7 (OMe-14), 56.2 (OMe-16).

Delcosine (5): colorless crystals; mp 204−205 °C; $[\alpha]_D^{23}$ +54.1° (*c* 0.8, $CHCl_3$), lit.[1] +57° ($CHCl_3$); ^{1}H NMR, see Table 2; ^{13}C NMR, data agreed with the literature values.[14]

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