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A novel skeletal rearrangement of the A ring of the immonium salt derived from norditerpenoid alkaloid yunaconitine

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Abstract—Treatment of 3-acetylyunaconitine **2** from yunaconitine **1** with NBS at 40°C for 12 h afforded the 3-acetylyunaconitine azomethine **3** (48%). Reaction of **3** with CH_3I in MeOH at room temperature overnight gave the iminium salt **4** (100%). Unexpectedly, treatment of **4** with 5% NaOH in methanol at room temperature for 20 min produced the rearrangement alkaloid **5** (38%) besides other unidentified compounds. Acetylation of **5** with Ac_2O/pyridine containing a small amount of TsOH gave its two derivatives **6** (28%) and **7** (56%). The structure of **5** was confirmed using 2D NMR spectra and single crystal X-ray analysis of its acetyl derivative **7**.

1. Introduction

Norditerpenoid alkaloids are a group of complex natural products, displaying a lot of interesting chemical perspectives.[1] In the course of our intensive investigation on the chemistry of norditerpenoid alkaloids,[2] a novel skeletal rearrangement of the A ring of the iminium salt from 3-acetylyunaconitine azomethine has fortuitously been observed. Herein, we wish to report the characterization of this novel rearrangement product and its derivatives.

2. Results and discussion

As previously mentioned,[2h] the norditerpenoid alkaloid yunaconitine **1**[3] was chosen as the starting material in the synthesis of *N*-19-*seco* norditerpenoid alkaloids, as part of our structural modification project of the norditerpenoid alkaloids. Acetylation of **1** using a general method (Scheme 1) gave 3-acetylyunaconitine **2**[3] in high yield (97%). Treatment of **2** with NBS (6.0 mmol) at room temperature overnight using a method developed by us[2c] afforded the 3-acetylyunaconitine azomethine **3**[4] in moderate yield (50%). The ^1H (^{13}C) NMR spectra of **3** showed the distinctive signals at δ_H 7.37 (1H, brs, H-19) and δ_C 163.2 (d) for the imine group. Its structure was ascertained by comparison of the ^1H (^{13}C) NMR with the authentic sample. Reaction of **3** with CH_3I in methanol at room temperature overnight easily obtained the immonium salt **4**, quantitatively. The IR and NMR spectra of **4** displayed the characteristic signals at 1610 cm^{-1}, δ_{H_+} 9.62 (brs) and δ_C179.3 (d) for the immonium group, N⁺=C(19)H. Meanwhile, the signal for the N–CH_3 in the NMR spectra of **4** also moved downfield to δ_H 4.20 and δ_C 47.6, respectively, due to the strong electron-withdrawing effect of the immonium ion. Treatment of **4** with 5% NaOH in methanol in an attempt to prepare the *N*-19-*seco* norditerpenoid alkaloid via hydrolysis mainly produced the rearrangement product **5** (38%) (Scheme 1). The FAB HRMS of **5** showed the pseudomolecular ion ($M^+ + 1$) at *m/z* 404.2089 corresponding to the formula $C_{22}H_{30}NO_6$. The IR and ^1H (^{13}C) NMR spectra of **5** exhibited characteristic signals at 1675 cm^{-1}, δ_H 6.13 (d, J=1.6 Hz), 9.48 (s), δ_C 148.2 (d), 148.4 (s) and 187.4 (d) for an α,β-unsaturated aldehyde, composed of H-1, C(3)HO, C-1, C-2 and C-3, and the presence of the multi-bond ^1H–^{13}C correlations between H-1 and (C-1, C-11, C-19); as well as H-3 and (C-1, C-19) in the HMBC spectrum (Table 1). Comparison between the NMR spectra of compound **4** and those of compound **5** showed the disappearance of the signals of the ester groups and the appearance of one exocyclic double bond $\Delta^{4(18)}$ in addition to an extra α,β-unsaturated aldehyde moiety. It is important to note that the chemical shifts of the C-13 signals attributing to the A ring for compounds **4** and **5** show great differences. These observations suggest that **4** has rearranged to **5**. The formation of compound **5** from **4** can be explained by the mechanism depicted in Scheme 2. Compound **4** first undergoes hydrolysis, followed by a double Grob fragmentation (**A**→**B**→**C**). Then, compound **D** with ring A newly formed from **C** through attack of C-2 on C-19 via aldol-type condensation, is further accompanied by the elimination of a molecule of methanol, leading to **E** (compound **5**). Finally, our proposed structure of **5** was confirmed by its

Keywords: norditerpenoid alkaloid; yunaconitine; immonium salt; rearrangement.

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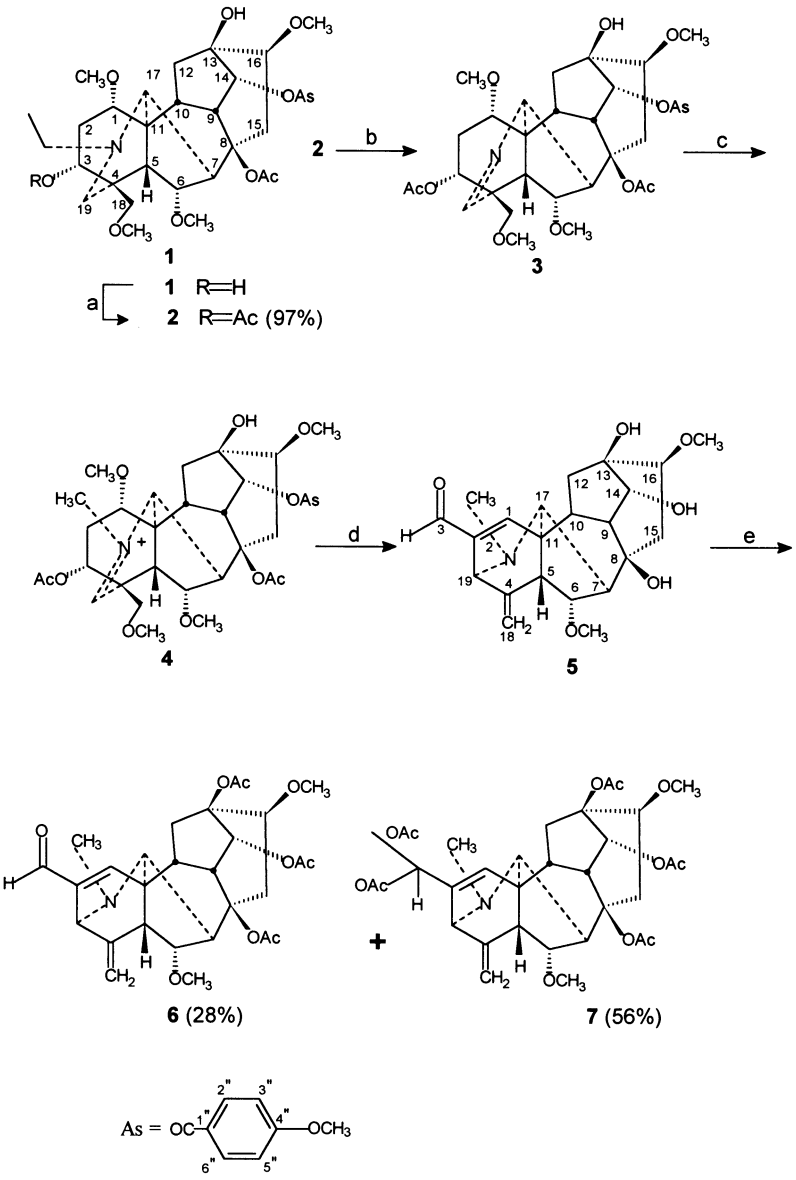


Scheme 1. (a) Ac_2O/pyridine, room temperature; (b) NBS, acetone, 40°C, 12 h (48%); (c) CH_3I, in MeOH (100%); (d) 5% NaOH in MeOH, room temperature, (38%); (e) Ac_2O/pyridine, TsOH.

2D NMR (Table 1), as well as the 2D NMR (Table 2) and single crystal X-ray analysis (Fig. 1) of the derivative **7**.

It was interesting to find that the treatment of compounds such as **2** not containing the immonium group under similar conditions (5% NaOH) did not produce rearrangement products such as **5**, indicating that the immonium group [N=*C*(19)] is the key structural moiety for this rearrangement. This is the first reported novel skeletal rearrangement of the A ring of the immonium salt derived from norditerpenoid alkaloid yunaconitine.

3. Experimental

3.1. General

Melting points were determined on a Kofler block (uncorrected); optical rotations were measured in a 1.0 dm cell with a PE-314 polarimeter at 20±1°C; IR spectra were recorded on a Nicolet 200 SXV spectrometer; MS spectra were obtained with a Spec-3000 VG 7070 E GC/MS/DES instrument; ^1H and ^{13}C NMR spectra were acquired on a Bruker AC-E 200 or Varian INOVA-400/54 spectrometer, in $CDCl_3$ with TMS as internal standard; Silica gel GF_{254} and H (10–40 μm, Qingdao Sea Chemical Factory, China) were used for TLC, Chromatotron and CC. Spots on chromatograms were detected with modified Dragendorff's reagent. Only key signals in the ^1H NMR spectra for compounds **4** and **6** are reported.

3.1.1. Compound 2. To a solution of yunaconitine (200 mg, 0.3 mmol) in pyridine (5 ml), Ac_2O (0.5 ml) was added and the solution was stirred at room temperature overnight. Evaporation in vacuo, basifying with 10% Na_2CO_3 (pH=10), extraction with $CHCl_3$ (15 ml×3), drying (anhydrous Na_2SO_4) and removal of solvent afforded 3-acetylyunaconitine **2** (198 mg, 97% yield, mp 152–154°C; R_f

Table 1. ^{1}H and ^{13}C NMR data of compound **5** ($CDCl_3$, 400 MHz for ^{1}H; 100 MHz for ^{13}C)

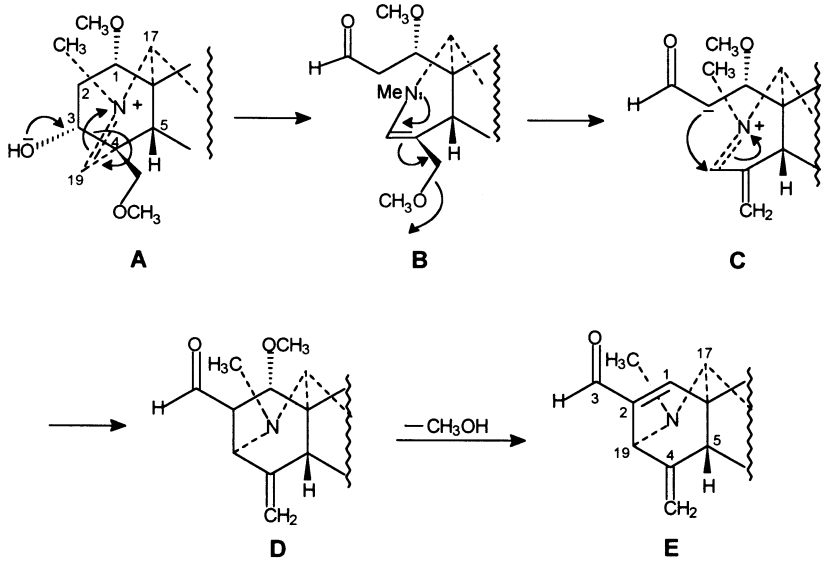
No.	δ_H	Mult (*J* in Hz)	δ_C	HMBC (H→C)
1	6.73	d (1.6)	148.2d	C-3, C-10, C-11, C-19
2	–	–	148.4s	–
3	9.48	s	187.4d	C-1, C-19
4	–	–	146.0s	–
5	2.71	d (6.4)	50.8d	C-4, C-7, C-17, C-18
6	4.06	d (6.4)	81.6d	C-4, C-8, C-6′, C-17
7	2.18	s	59.2d	C-6, C-8, C-9, C-11, C-15
8	–	–	73.0s	–
9	2.31	Hidden	47.5d	C-8, C-10, C-12, C-13, C-14, C-15, C-16
10	2.50	m	34.6d	C-8, C-9, C-11, C-17
11	–	–	53.4s	–
12	1.41	dd (15.8, 6.0)	37.2t	C-10, C-11, C-13, C-14, C-16
	2.26	m		C-16
13	–	–	77.1s	–
14	4.15	d (5.2)	79.3d	C-8, C-13, C-16
15	2.36	dd (16.0, 4.4)	42.5t	C-7, C-13, C-16
	2.58	dd (16.0, 8.8)		C-7, C-8, C-9, C-13, C-16
16	3.29	m	82.9d	C-9, C-13, C-14, C-16′
17	1.88	brs	66.8d	C-5, C-6, N–CH_3
18	4.57	s	109.1t	C-4, C-5, C-19
	5.00	s		C-4, C-5, C-19
19	4.29	d (1.6)	57.9d	C-1, C-2, C-3, C-4, C-5, C-17, NCH_3
6′	3.37	S	58.2q	C-6
16′	3.44	S	58.0q	C-16
NCH_3	2.19	S	43.0q	C-17, C-19

0.5, $CHCl_3$–MeOH 95:5) that was identified by comparison of TLC (silica gel FG_{254}, $CHCl_3$–MeOH 95:5; ether–acetone 9:1) with the authentic sample.

3.1.2. Compound 3. To a solution of 3-acetylyunaconitine **2** (700 mg, 1.00 mmol) in $(CH_3)_2CO$–H_2O (2:1) (20 ml), NBS (1.06 g, 6 mmol) was added and the solution was heated at 40°C overnight. Evaporation in vacuum afforded a residue that was diluted with water (10 ml), and basified with conc. NH_4OH (pH=11) and extracted with $CHCl_3$ (20 ml×3). The combined chloroform solutions were dried over anhydrous Na_2SO_4. After removal of solvent followed by column chromatography (silica gel H, 30 g; $CHCl_3$–CH_3OH 99:1 and Chromatotron purification (silica gel G, 1 mm, $CHCl_3$–CH_3OH 98.5:1.5), 3-acetylyunaconitine azomethine (**3**) (320 mg, 48% yield) was obtained as a white amorphous powder that was identified by comparison of TLC (silica gel GF_{254}, R_f 0.54, $CHCl_3$–MeOH 95:5) and ^{1}H (^{13}C) NMR data with the authentic sample.

3.1.3. Compound 4. To a solution of 3-acetylyunaconitine azomethine (**3**) (300 mg, 0.45 mmol) in MeOH (5 ml), CH_3I (0.5 ml) was added and the solution was stirred at room temperature overnight. Removal of solvent afforded compound **4** (363 mg, 100% yield) as white amorphous powder; mp 185–186°C; R_f 0.55 ($CHCl_3$–MeOH 9:1); $[\alpha]_D^{20}=+29.0$ (*c* 1.66, $CHCl_3$); ν_{max} (KBr) 3451 (OH), 2940, 2830, 1724 (COO), 1610 (C=N), 1284, 1233, 1105 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.36 (3H, s, OAc-8), 2.31 (3H, s, OAc-3), 3.12, 3.24, 3.33, 3.65 (each 3H, s, OCH_3×4), 3.88 (3H, s, Ar–OCH_3), 4.20 (3H, s, NCH_3), 4.88 (1H, d, *J*=4.8 Hz, H-14β), 5.57 (1H, d, *J*=6.0 Hz, H-3β), 6.49, 7.98 (each 2H, AA′BB′ system, *J*=8.6 Hz, Ar-H), 9.62 (1H, brs, H-19); δ_C (100 MHz, $CDCl_3$) 81.5 (C-1), 26.4 (C-2), 74.4 (C-3), 54.3 (C-4), 41.8 (C-5), 78.0 (C-6), 54.3 (C-7), 82.1 (C-8), 41.8 (C-9), 37.7 (C-10), 53.0 (C-11), 35.4 (C-12), 74.5 (C-13), 77.7 (C-14), 38.6 (C-15), 81.5 (C-16), 69.3 (C-17), 72.7 (C-18), 179.3 (C-19), 47.6 (NCH_3), 56.9 (C-1′), 57.9 (C-6′), 59.1 (C-16′), 59.1 (C-18′), 169.6, 170.6; 21.2, 21.9 (OAc×2), 165.7 [O*C*–C_6H_4–OCH_3(*p*)], 121.8 (C-1″), 131.6 (C-2″, C-6″), 113.9 (C-3″, C-5″), 163.7 C-4″), 55.4 (OCH_3-4″); *m/z* (FAB) 687 (100, M^++1), 627 (55, M^+−OAc); HRMS (FAB): 686.3174, $C_{36}H_{48}NO_{12}$ requires 686.3176.

3.1.4. Compound 5. A solution of compound **3** (150 mg, 0.17 mmol) in 5% NaOH solution in MeOH (5 ml) was heated at 40°C for 20 min, and evaporated in vacuo to give a residue that was diluted with H_2O (10 ml), and extracted with $CHCl_3$ (10 ml×4). The combined chloroform solutions were dried over anhydrous Na_2SO_4. Removal of solvent and column chromatography (silica gel H, 5 g; $CHCl_3$–CH_3OH 95:5) afforded compound **5** (30 mg, 38% yield) as a white amorphous powder.



Scheme 2. A plausible mechanism for rearrangement from **4** to **5**.

Table 2. ^{1}H and ^{13}C NMR data of compounds **6** and **7** ($CDCl_3$, 400 MHz for ^{1}H; 100 MHz for ^{13}C)

No.	**6**	**7**			
	δ_C	δ_H	Mult (*J*in Hz)	δ_C	HMBC (H→C)
1	147.5d	5.91	brs	129.2d	C-3, C-5, C-10, C-11, C-17, C-19
2	148.5s	–	–	142.1s	–
3	187.3d	7.17	s	87.3 d	C-1, C-19, *C*OOAc
4	145.3s	–	–	146.9s	–
5	50.3d	2.60	brd (6.8)	49.7d	C-4, C-7, C-10, C-17, C-19
6	81.7d	3.85	brd (6.8)	81.6d	C-4, C-6′, C-7, C-8
7	54.6d	3.11	s	54.3d	C-5, C-6, C-8, C-9, C-11, C-16, C-17
8	84.1s	–	–	84.3s	–
9	40.5d	2.66	dd (7.6, 5.6)	40.5d	C-8, C-10, C-12, C-13, C-14, C-15
10	34.6d	2.54	m	34.8d	C-8, C-11, C-12, C-17, C-19
11	53.3s	–	–	51.2s	–
12	37.8t	2.16	m	37.3t	C-10, C-11, C-13,
		2.16	m		C-14, C-16
13	81.3s	–	–	81.3s	–
14	77.0d	4.95	d (5.2)	77.0d	C-8, C-9, C-13, C-16, *C*OOAc
15	39.6t	2.35	dd (15.2, 7.2)	39.6t	C-7, C-8, C-16
		3.15	dd (15.2, 8.8)		C-7, C-8, C-9, C-13, C-16
16	79.8d	3.81	m	79.7d	C-12, C-13, C-14, C-16′
17	66.3d	1.79	brs	65.7d	C-5, C-6, C-11, NCH_3
18	109.7t	4.51	s	108.0t	C-4, C-5, C-19
		4.91	s		C-4, C-5, C-19
19	57.6d	3.82	brs	60.2d	C-1, C-2, C-3, C-4, C-5, C-17, C-18
NCH_3	43.0q	2.30	s	43.1q	C-17, C-19
6′	58.1q	3.26	s	57.9q	C-6
16′	58.2q	3.33	s	58.1q	C-16
OAc	21.1q	1.99	s	22.1q	
	170.6s			170.5s	
	21.1q	2.03	s	20.6q	
	169.0s			170.5s	
	21.1q	2.06	s	20.7q	
	169.0s			169.0s	
		2.12	s	21.0q	
				168.4s	
		2.13	s	21.1q	
				168.4s	

Mp 153–155°C; R_f 0.44 (*n*-hexane–acetone 2:1); $[\alpha]_D^{20}=+42.90$ (*c* 0.45, CH_3OH); ν_{max} (KBr) 3387 (OH), 2935, 1675 (C=C–*CHO*), 1192, 1092 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; *m/z* (FAB) 404 (100, $M^+ +1$), 386 (14, $M^+ -OH$); HRMS (FAB): 404.2089, $C_{22}H_{30}NO_6$ requires 404.2073.

3.1.5. Compounds 6 and 7. A mixture of compound **5**

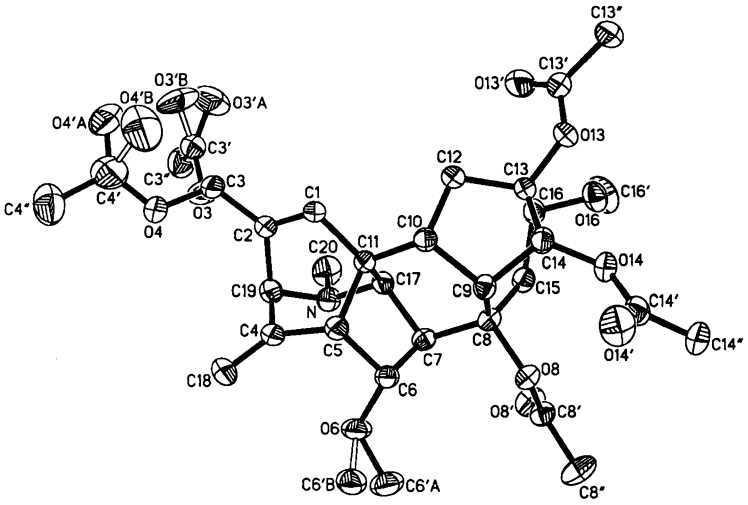


Figure 1. ORTEP crystal structure of compound **7**.

(200 mg, 0.25 mmol) and Ac_2O (5 ml) with TsOH (100 mg) was heated at 50°C for 4 h. After cooling with ice water, the reaction solution was diluted with water (5 ml), basified with conc. NH_4OH (pH=9) and extracted with $CHCl_3$ (10 ml×3). The combined chloroform solutions were dried over anhydrous Na_2SO_4. Removal of solvent and column chromatography (silica gel H, 5 g; *n*-hexane–acetone 3:1) afforded compounds **6** (34 mg) and **7** (97 mg) in 26 and 62% yield, respectively.

Compound ***6***. White amorphous powder; mp 108–109°C; R_f 0.42 (*n*-hexane–acetone 2:1); $[\alpha]_D^{20}=+61.3$ (*c* 0.83, $CHCl_3$); ν_{max} (KBr) 2930, 1736 (COO), 1699 (C=C–*CO*), 1371, 1256, 1235, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), 2.07, 2.17, 2.20 (each 3H, s, OAc×3), 2.30 (3H, s, NCH_3), 3.34, 3.40 (each 3H, s, OCH_3×2), 3.98 (1H, d, *J*=7.2 Hz, H-6β), 4.35 (1H, d, *J*=1.2 Hz, H-19), 4.63 (1H, s, H-18), 5.05 (1H, d, *J*=4.8 Hz, H-14β), 5.08 (1H, s, H-18), 6.78 (1H, brs, H-1), 9.51 (1H, s, H-3); ^{13}C NMR, see Table 2; *m/z* (FAB) 530 (100, M^++1), 470 (30); HRMS (FAB): 530.2384, $C_{28}H_{36}NO_9$ requires 530.2390.

Compound ***7***. Colorless orthorhombic crystals; mp 208–209°C; R_f 0.54 (*n*-hexane–acetone 2:1); $[\alpha]_D^{20}=+63.2$ (*c* 0.96, $CHCl_3$); ν_{max} (KBr) 2980, 2930, 2850, 2815, 1763 (COO), 1739 (COO), 1370, 1236, 1250, 1108, 1043 cm^{-1}; ^1H and ^{13}C NMR, see Table 2; *m/z* 632 (100, M^++1), 574 (34); HRMS (FAB): 632.2699, $C_{32}H_{42}NO_{12}$ requires 632.2707; crystal structure for **7**: a colorless orthorhombic crystal from *n*-hexane–acetone was mounted on a P_4 four circle diffractometer and exposed to graphite-monochromated Mo Kα irradiation. The unit cell parameters are *a*=8.442 (10) Å, *b*=14.712 (2) Å, *c*=12.984 (2) Å in space group $P2_12_12_1$, of the 4053 measured with $1.57<Q<27.48°$ scan, 3661 were independently observed at the level of $F_0>4\sigma(F_0)$. The structure was solved by the direct method using the program SHELXTL and the atomic squares on F^2 method. The final *R* indexes [$I>2\sigma(I)$] was $R^1=0.0402$, $wR2=0.0860$.

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