Application of 1,3-Azomethine Ylides Derived from α-Dicarbonyl Compounds and L-Proline to the Synthesis of Pyrrolizidines

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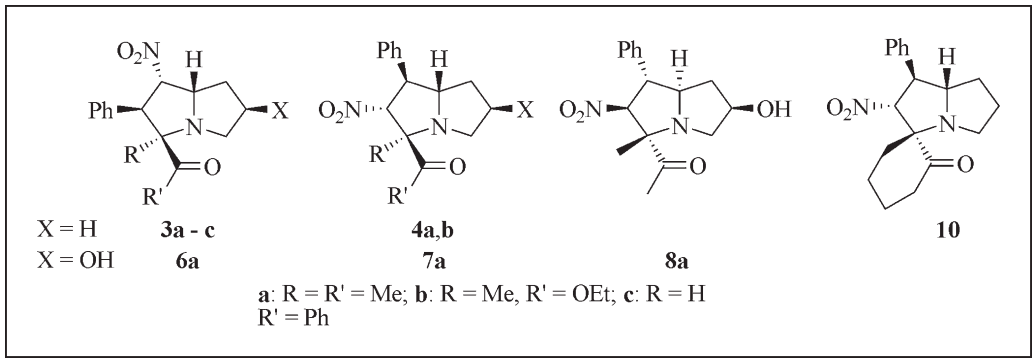

The reaction of 2,3-butanedione, ethyl pyruvate, and phenylglyoxal with β-nitrostyrene and L-proline in isopropanol at room temperature gives substituted pyrrolizidines, as a result of one-pot three component reaction. On the contrary, a spiropyrrolizidine is formed from 1,2-cyclohexanedione only when the reaction is carried out in refluxing isopropanol, whereas at room temperature, incorporation of the amine component into the products is not observed and bicyclo[3.2.1]octanones are formed, as a result of a tandem Michael-Henry reaction. In this latter case, L-proline acts as an organocatalyst, although with modest enantioselectivity. The stereochemistry of the products is given and the mechanism of formation of products is postulated, on the basis of stereochemical arguments.

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INTRODUCTION

The 1-azabicyclo[3.3.0]octane ring is part of naturally occurring and biologically active pyrrolizidine alkaloids, which are studied for their interesting diverse physiological properties [1]. Construction, also asymmetric, of the pyrrolizidine ring are usually made through multistep reactions [2] and also [3+2]cycloadditions between 1,3-azomethine ylides and activated olefins are widely used [3]. A possible source of 1,3-azomethine ylides is derived from activated carbonyl compounds and L-proline, which can loose carbon dioxide when heated. The resulting 1,3-dipoles can react with aldehydes, to give bicyclic 1,3-oxazolidines [4], or with α,β-unsaturated esters [3(a,e,f)], or nitroolefins [3(b)] to give pyrrolizidine derivatives.

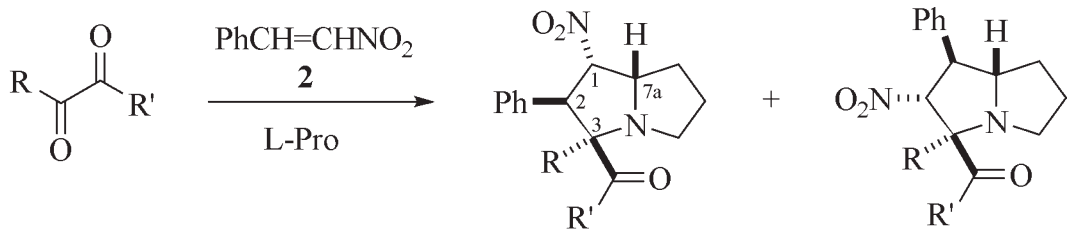
In this work, we report the application of 1,3-azomethine ylides derived from α-dicarbonyl compounds and L-proline to the synthesis of pyrrolizidines by means of 1,3-dipolar cycloaddition reactions to β-nitrostyrene. The use of (2*S*,4*R*)-4-hydroxyproline gave enantiopure polysubstituted pyrrolizidines.

RESULTS AND DISCUSSION

The α-dicarbonyl compounds examined in this study have been 2,3-butanedione **1a**, ethyl pyruvate **1b**, phenylglyoxal **1c** (Scheme 1), and 1,2-cyclohexanedione **9** (Scheme 3), which were reacted with β-nitrostyrene **2** in isopropanol at room temperature, in the presence of an equimolar amount of L-proline. The reaction of 2,3-butanedione **1a** with β-nitrostyrene **2** in isopropanol at room temperature for 3 days gave two regioisomeric cycloadducts in 3:2 ratio, which were assigned the structures **3a** and **4a**, respectively, on the basis of difference NOE measurements (Table 1). The analogous cycloaddition of ethyl pyruvate **1b** to **2** gave two adducts **3b** and **4b** in 9:1 ratio (Scheme 1), with structural assignments based on analogy and difference NOE measurements (Table 1), while the addition of phenylglyoxal **1c** to **2** furnished a single regioisomer **3c**.

To determine the mechanism of formation of the pyrrolizidines, a reaction was carried out between 2,3-butanedione **1a**, β-nitrostyrene **2** and (2*S*,4*R*)-4-hydroxyproline **5** in isopropanol, so to take advantage of the

Scheme 1



R = R' = Me	**1a**	87% (3:2)	**3a**	**4a**
R = Me, R' = OEt	**1b**	90% (9:1)	**3b**	**4b**
R = H, R' = Ph	**1c**	80%	**3c**	

presence of a stereocenter of known configuration. The reaction was much slower, owing to solubility problems, and gentle warming was necessary to drive the reaction to completion. The reaction products isolated were the pyrrolizidines **6a** and **7a**, analogous to **3a** and **4a**, together with a third isomer **8a**, whose formation can be surely ascribed to the higher temperature used. The relative ratio of compounds **6a–8a** was 1:4:1 (Scheme 2).

X-ray analysis of compound **6a** (Fig. 1) showed the geometry of the substituents and the *cis* fusion of the rings. To validate the use of NOE measurements to determine the geometry of the other pyrrolizidines, difference NOE experiments (Table 1) were carried out also on **6a**, whose results were in complete accordance with the X-ray determination. The ring junction in all pyrrolizidines was determined by an analysis of their IR spectra. The Bohlmann bands [5] between 2800 and 2600 cm^{-1}, which are correlated with the presence of a C—H bond antiperiplanar to the nitrogen lone pair, were present only for compound **8a** (2724 and 2671 cm^{-1}), which was therefore assigned the *trans* fusion, whereas pyrrolizidines **3a–c**, **4a**,**b** and **6a**, **7a** which lack these bands, were assigned the *cis* fusion.

1,2-Cyclohexanedione **9** has been chosen as another candidate for synthesizing pyrrolizidine target compounds. Indeed, the reaction of the substrate **9** with β-nitrostyrene **2**, carried out in refluxing isopropanol for 2 h gave as the main reaction product (90%) the nitrospiro pyrrolizidine **10** (Scheme 3, right side). Its stereochemistry was assigned as depicted in Scheme 3. The relative configuration of the spiro carbon atom C-3′ was confirmed by the resonance value found for the axial proton

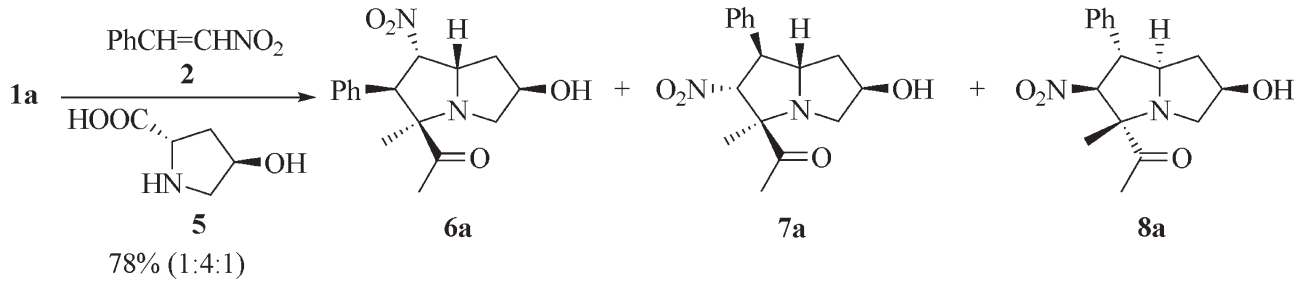
Table 1

Difference NOE experiments carried out on the pyrrolizidines.

	Irradiated protons					
Compound	H-1 (H-1′ for **10**)	H-2 (H-2′ for **10**)	H-3	H-6	H-7a (H-7′a for **10**)	Me
3a	*o*-Ph (8), H-7a (9)	Me (4), H-5 at 2.91 (6), H-7 at 1.33 (2)			H-1 (9), H-7 at 2.04 (5)	H-2 (4)
3b	*o*-Ph (10), H-7a (10)	Me (9), H-5 at 2.90 (4)			H-1 (10), H-7 at 2.07 (6)	H-2 (9)
3c	*o*-Ph (7), H-7a (11)	H-3 (7), H-5 at 2.81 (4)	H-2 (9), H-5 at 2.81 (6)		H-1 (10), *o*-Ph (7), H-7 at 2.06 (8)	
4a	Me (6), H-5 at 3.19 (5), H-7 at 1.75 (4)	*o*-Ph (5), H-7a (3)			*o*-Ph (6), H-2 (3), MeCO (2)	H-1 (6), H-5 at 3.19 (5)
4b	H-5 at 3.13 (3), H-7 at 1.72 (4), Me (3)	*o*-Ph (8), H-7a (4)			Me (4), *o*-Ph (11), H-2 (4), H-5 at 3.13 (3)	H-7a (4), H-5 at 3.13 (3)
6a	*o*-Ph (11), H-7a (8)	Me (7), H-5 at 3.12 (5), H-6 (4)		H-2 (4), H-5 at 3.12 (3), H-7 at 1.63 (4)	H-1 (8), H-7 at 2.15 (3)	H-2 (4)
7a	H-5 at 3.37 (6), H-7 at 2.18 (6)	*o*-Ph (5), H-7a (5), H-7 at 2.03 (4)		H-5 at 3.37 (5), H-7 at 2.18 (8)	*o*-Ph (4), MeCO (2), H-7 at 2.03 (3)	H-5 at 3.37 (2), MeCO (2)
8a	H-5 at 3.21 (3), H-7 at 1.74 (6), Me (1)	*o*-Ph (8)		H-5 at 3.34 (5), H-7 at 2.32 (4)	*o*-Ph (5)	H-5 at 3.21 (6)
10	H-7 at 3.20 (2)	*o*-Ph (7), H-5 at 1.64 (2)			*o*-Ph (5)	

η Values (%) in parenthesis for enhanced protons.

Scheme 2



at C-2 which is strongly deshielded with respect to its geminal equatorial one (3.20 *vs*. 2.39 ppm) by the anisotropic effect of the nitro group that is spatially close to it.

Interestingly, when the same reaction was carried out at room temperature, even under solvent-free conditions, two adducts were obtained in 9:1 ratio (Scheme 3, left side). These compounds were assigned the structures **11** and **12**, on the basis of ^{1}H NMR spectra and X-ray analysis carried out on compound **12**. The two isomers were separated by flash chromatography and they proved weakly optically active ($[\alpha]_D^{25} = +0.05$ (*c* 2.65, MeOH) for **11** and $[\alpha]_D^{25} = -2.6$ (*c* 0.15, MeOH) for **12**, 14% e.e., determined by HPLC on chiral column), thus demonstrating the organocatalytic capability of L-proline, albeit modest, in this particular case.

X-ray analysis of compound **12** (Fig. 2) showed that the geometry of phenyl and the nitro group was *cis,* both groups being *exo* oriented. The stereochemistry of its diastereomer **11** was determined by ^{1}H NMR analysis. In fact, in **12,** the coupling constant between H-6 and H-7 was larger than in **11** ($J_{6,7} = J_{endo,exo} = 5.8$ Hz for **11**, $J_{6,7} = J_{endo,endo} = 9.5$ Hz for **12**), thus demonstrating the *trans* relationship between the phenyl group and the nitro group in **11** [6]. The orientation of the phenyl group was assigned as *exo* also in **11**. In fact, the coupling constant between H-5 and the benzylic proton H-6 was zero, thus indicating a dihedral angle of 90° between them, which is only consistent with the *endo* orientation of the benzylic proton itself.

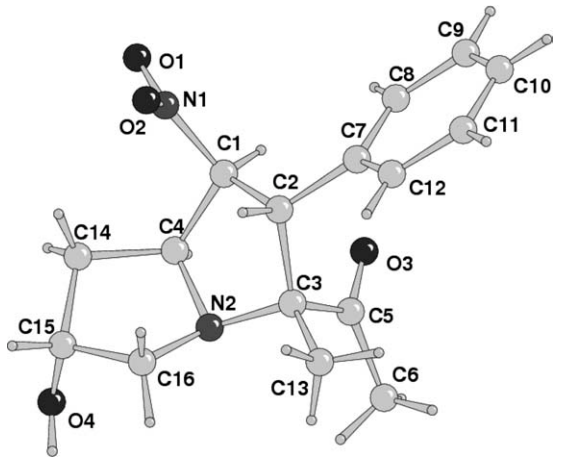


Figure 1. Molecular structure of compound **6a.**

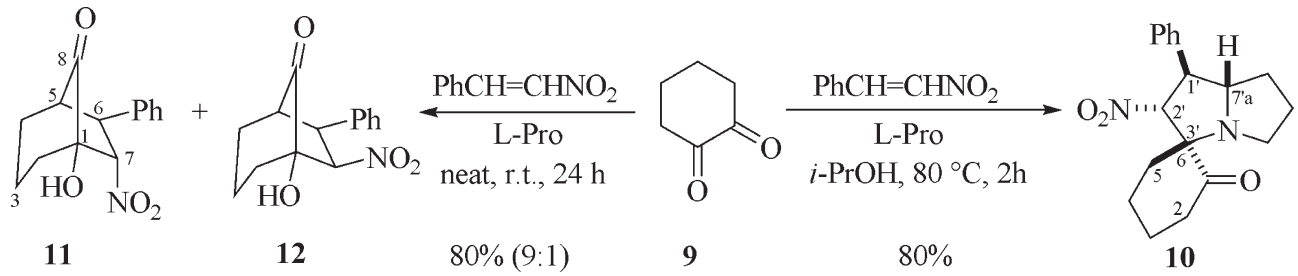
MECHANISM OF THE REACTIONS

The mechanism of pyrrolizidine formation can be inferred from the stereochemistry of the products and in particular from compounds **6a** and **7a**, whose absolute configurations are known, given the *R* absolute configuration of the carbinol carbon atom. Since the majority of the pyrrolizidines in this work are *cis* fused [7], the first formed carbon—carbon bond (C1-C7a) occupies the same position as the carboxy group in the original pyrrolidine ring. Therefore, it seems reasonable to postulate that formation of the intermediate **13** (Scheme 4, illustrated for 2,3-butanedione **1a** as the substrate) is immediately followed by elimination of carbon dioxide with the creation of the 1,3-dipole **14**, existing in two resonance structures **a** and **b**. Both regioisomeric adducts **6a** and **7a** derived from the less encumbered *exo-anti* transition states, while adduct **8a** arose from the *exo-syn* transition state. The same reaction mechanism may be invoked for the formation of the other pyrrolizidines **3a–c**, **4a**,**b** derived from linear 1,2,-dicarbonyl compounds and **10** derived from 1,2-cyclohexanedione.

In the reaction of 1,2-cyclohexanedione **9** with β-nitrostyrene **2** performed at room temperature, L-proline initially reacts with the substrate **9** to give the corresponding cross-conjugated enaminone **15** (Scheme 5) which reacts with the nitroolefin in a Michael-type addition, through a two step mechanism, with subsequent ring closure in **16**, by collapse of the carbanion onto the carbonyl carbon atom. The consequent zwitterion **17** is hydrolysed *in situ* to afford eventually the two diastereomers **11** and **12**.

The easier loss of carbon dioxide observed for the adduct between L-proline and 2,3-butanedione with respect to the analogous intermediate from 1,2-cyclohexanedione could be ascribed to the s-*trans* geometry

Scheme 3



between the carbonyl group and the iminium group in the former which would facilitate the expulsion of carbon dioxide in the former compound.

EXPERIMENTAL

IR spectra were recorded on a Jasco FT/IR 200 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were run on a Jeol EX-400 spectrometer (400 MHz for proton, 100.1 MHz for carbon), and on a Jeol EX-270 spectrometer (270 MHz for proton, 68 MHz for carbon) using deuteriochloroform as the solvent and tetramethylsilane as the internal standard. Chemical shifts are expressed in parts per million (δ). Coupling constants are given in Hz. Optical rotations were determined on a Perkin Elmer Model 241 polarimeter. Mass spectra were recorded on a ion trap instrument Finnigan GCQ (70 eV). HPLC analysis were run on a Hewlett Packard Series 1100 instrument the chiral column being a Lux 5 μm Cellulose-2 (Phenomenex) with a Cellulose tris(3-chloro-4-methylphenylcarbammate) chiral stationary phase, eluent: *n*-hexane/isopropanol 75:25, detector UV 220 nm; TLC's were performed on Polygram® Sil G/UV$_{254}$ silica gel pre-coated plastic sheets. Flash chromatography was run on silica gel for flash-chromatography (BDH). Elemental analyses were determined on a Carlo Erba 1106 instrument, at the Department of Chemical Sciences and Technologies of the University of Udine, Italy. Light petroleum refers to the fraction with b.p. 40–70°C and ether to diethyl ether. 2,3-Butanedione, L-proline, (2*S*,4*R*)-4-hydroxyproline, and β-nitrostyrene were purchased from Sigma-Aldrich and 1,2-cyclohexanedione was purchased from Lancaster.

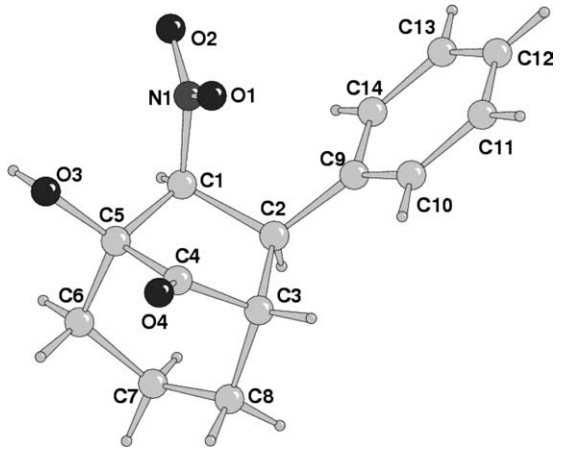


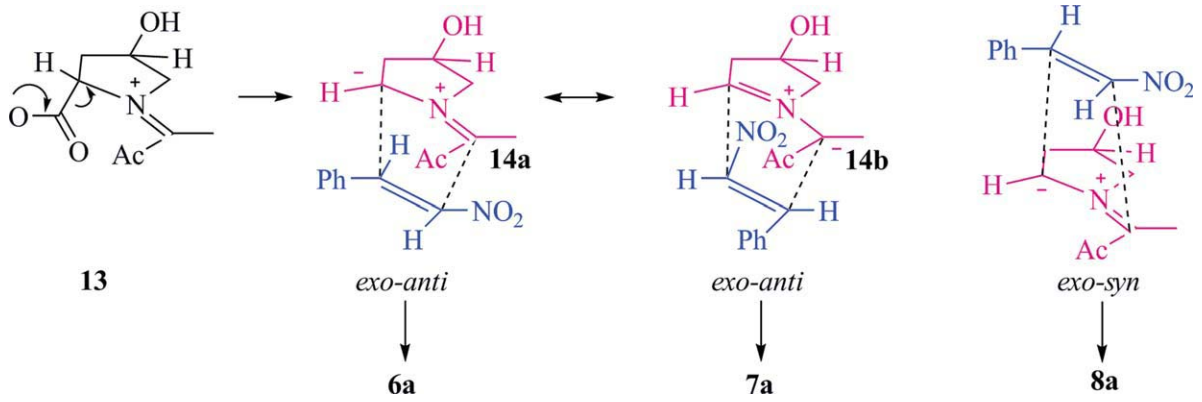
Figure 2. Molecular structure of compound **12**.

General procedure for the reactions between α-dicarbonyl compounds 1a–c and 9, β-nitrostyrene 2 and L-proline or (2*S*,4*R*)-4-hydroxyproline 5. To the α-dicarbonyl compound (1.0 mmol) in isopropanol (10 mL), β-nitrostyrene (1.0 mmol) and the appropriate proline derivative (1.0 mmol) were added. The mixture was set aside at room temperature until completion of the reaction, which needed different times depending on the substrate (96 h for diacetyl and 24 h for 1,2-cyclohexanedione). The solvent was eliminated and the crude reaction mixture was chromatographed on silica gel (eluent: *n*-heptane–ethyl acetate, gradient).

(1S*,2S*,3R*,7aS*)-3-Acetyl-3-methyl-1-nitro-2-phenylazabicyclo[3.3.0]octane (3a). Oil, 52% yield, after purification. R_f 0.15 (eluent: light petroleum–ethyl acetate 4:1). IR (neat) 3050, 3032, 1603, 1498, 761, 733, 702 (Ph), 1708 (C=O), 1545, 1375, 1352 (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (m, 5H, Ph), 5.95 (dd, J_1 = 10.6 Hz, J_2 = 9.1 Hz, 1H, H-1), 4.30 (dt, J_1 = 9.1 Hz, J_2 = J_3 = 7.8 Hz, 1H, H-7a), 3.85 (d, J = 10.6 Hz, 1H, H-2), 3.04 (m, 1H, H-5), 2.93 (ddd, J_1 = 11.2 Hz, J_2 = 8.1 Hz, J_3 = 5.3 Hz, 1H, H-5), 2.05 (m, 1H, H-7), 1.94 (m, 1H, H-6), 1.91 (s, 3H, CH_3CO), 1.83 (m, 1H, H-6), 1.38 (s, 3H, CH_3), 1.33 (m, 1H, H-7); ^{13}C NMR (100.1 MHz, $CDCl_3$): δ 207.7 (s), 133.8 (s), 129.0 (2d), 128.6 (2d), 127.7 (d), 93.1 (d, C-1), 74.5 (s, C-3), 64.0 (d, C-7a), 55.2 (d, C-2), 48.9 (t, C-5), 27.7 (t, C-7), 27.1 (q, CH_3CO), 25.6 (t, C-6), 19.2 (q, CH_3); *m/z* 289 (2, M+1), 245 (45, M+1—CH_3CO), 199 (100, 245—NO_2), 184 (56, 199—CH_3). Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72; Found: C, 66.82; H, 7.12; N, 9.88.

(1S*,2R*,3R*,7aS*)-3-Acetyl-3-methyl-2-nitro-1-phenylazabicyclo[3.3.0]octane (4a). Oil, 35% yield, after purification. R_f 0.65 (eluent: light petroleum–ethyl acetate 4:1). IR (neat) 3063, 3030, 1603, 1496, 742, 700 (Ph), 1714 (C=O), 1548, 1361 (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (m, 3H, Ph), 7.25 (bd, 2H, Ph), 6.09 (d, J = 8.4 Hz, 1H, H-2), 3.84 (dd, J_1 = 8.4 Hz, J_2 = 9.6 Hz, 1H, H-1), 3.22 (m, 1H, H-7a), 3.19 (dd, J_1 = 8.8 Hz, J_2 = 6.9 Hz, 1H, H-5), 3.01 (m, 1H, H-5), 2.46 (s, 3H, CH_3CO), 2.10 (m, 1H, H-6), 2.05 (m, 2H, H-6, H-7), 1.76 (m, 1H, H-7), 1.46 (s, 3H, CH_3); ^{13}C NMR (100.1 MHz, $CDCl_3$): δ 207.6 (s), 137.8 (s), 128.9 (2d), 127.8 (2d), 127.5 (d), 98.4 (d, C-2), 76.4 (s, C-3), 70.8 (d, C-7a), 56.7 (d, C-1), 46.4 (t, C-5), 28.2 (t, C-7), 24.4 (t, C-6), 24.1 (q, CH_3CO), 16.1 (q, CH_3); *m/z* 289 (5, M+1), 245 (40, M+1—CH_3CO), 199 (100, 245—NO_2), 184 (60, 199—CH_3). Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72; Found: C, 66.91; H, 6.80; N, 9.56.

Scheme 4

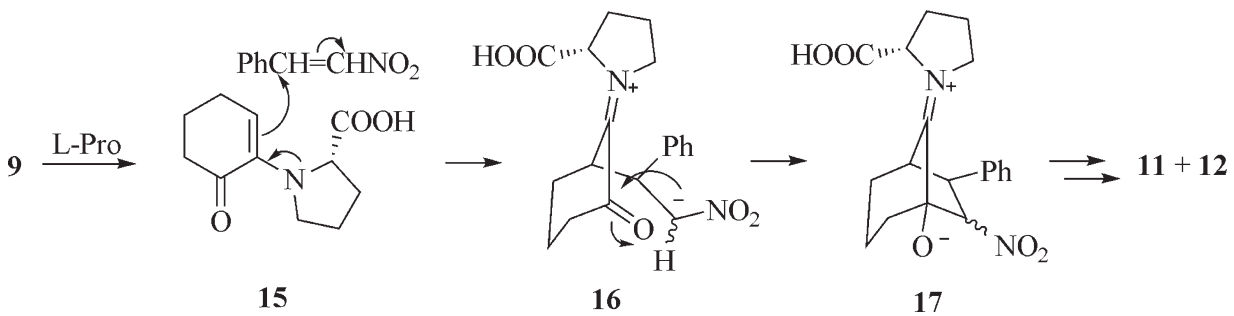


(1S*,2S*,3R*,7aS*)-3-Methyl-1-nitro-2-phenylazabicyclo[3.3.0] octane-3-carboxylic acid ethyl ester (3b). Mp 101–102°C, 85% yield, after purification. R_f 0.30 (eluent: *n*-heptane–ethyl acetate 4:1). IR ($CHCl_3$) 3080, 3060, 1598, 1498, 770, 701, 669 (Ph), 1686 (C=O), 1549, 1376 (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (m, 3H, Ph), 7.19 (m, 2H, *o*-Ph), 5.90 (dd, J_1 = 10.6 Hz, J_2 = 9.1 Hz, 1H, H-1), 4.64 (bq, J = 9.1 Hz, 1H, H-7a), 3.99 (dq, 2H, CH_2O), 3.90 (d, J = 10.6 Hz, 1H, H-2), 3.04 (m, 1H, H-5 *cis* to H-7a), 2.90 (m, 1H, H-5 *trans* to H-7a), 2.07 (m, 1H, H-7 *cis* to H-7a), 1.93 (m, 1H, H-6), 1.85 (m, 1H, H-6), 1.48 (s, 3H, CH_3), 1.35 (m, 1H, H-7), 1.08 (t, 3H, CH_3CH_2O); ^{13}C NMR (100.1 MHz, $CDCl_3$): δ 172.6 (s), 133.7 (s), 128.6 (2d), 128.1 (2d), 128.0 (d), 93.3 (d, C-1), 72.4 (s, C-3), 65.0 (d, C-7a), 61.0 (t, CH_2O), 55.8 (d, C-2), 49.5 (t, C-5), 27.9 (t, C-7), 25.5 (t, C-6), 18.5 (q, CH_3), 13.8 (q, CH_3CH_2O); *m/z* 319 (12, M+1), 272 (38, M—NO_2), 245 (50, M—COOEt), 199 (30, M—COOEt—NO_2), 198 (100, M—COOEt—HNO_2), 183 (15), 170 (20). Anal. Calcd. for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80; Found: C, 63.85; H, 6.83; N, 8.73.

(1S*,2R*,3R*,7aS*)-3-Methyl-2-nitro-1-phenylazabicyclo[3.3.0] octane-3-carboxylic acid ethyl ester (4b). Oil, 5% yield, after purification. R_f 0.50 (eluent: *n*-heptane–ethyl acetate 4:1). IR (neat) 3064, 3031, 1603, 1498, 752, 701 (Ph), 1723 (C=O), 1550, 1367 (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, 5H, Ph), 5.92 (d, J = 9.6 Hz, 1H, H-2), 4.30 (dq, 2H, CH_2O), 3.72 (q, 1H, H-7a), 3.69 (dd, J_1 = 8.4 Hz, J_2 = 9.6 Hz, 1H, H-1), 3.13 (dd, J_1 = 9.0 Hz, J_2 = 6.8 Hz, 1H, H-5 *trans* to H-7a), 2.93 (m, 1H, H-5 *cis* to H-7a), 2.00 (3H, m, 2 H-6, H-7), 1.76 (m, 1H, H-7), 1.45 (s, 3H, CH_3), 1.34 (t, 3H, CH_3CH_2O); ^{1}H NMR (400 MHz, CD_3OH): δ 7.30 (m, 5H, Ph), 5.90 (d, J = 9.9 Hz, 1H, H-2), 4.29 (dq, 2H, CH_2O), 3.71 (t, J_1 = 9.9 Hz, J_2 = 10.1 Hz, 1H, H-1), 3.63 (m, 1H, H-7a), 3.17 (m, 1H, H-5 *trans* to H-7a), 2.88 (m, 1H, H-5 *cis* to H-7a), 2.04 (m, 1H, H-6), 1.91 (m, 2H, H-6, H-7), 1.73 (m, 1H, H-7), 1.42 (s, 3H, CH_3), 1.32 (t, 3H, CH_3CH_2O); ^{13}C NMR (100.1 MHz, $CDCl_3$): δ 172.5 (s), 137.8 (s), 128.9 (2d), 127.7 (2d), 127.6 (d), 99.2 (d, C-2), 70.6 (s, C-3), 70.2 (d, C-7a), 62.2 (t, CH_2O), 54.8 (d, C-1), 46.6 (t, C-5), 29.0 (t, C-7), 25.2 (t, C-6), 16.0 (q, CH_3), 14.0 (q, CH_3CH_2O); *m/z* 319 (10, M+1), 272 (40, M—NO_2), 245 (90, M—COOEt), 199 (100, M—COOEt—NO_2), 198 (80, M—COOEt—HNO_2), 184 (80, 199—CH_3). Anal. Calcd. for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80; Found: C, 64.86; H, 6.74; N, 8.68.

(1S*,2S*,3R*,7aS*)-3-Benzoyl-1-nitro-2-phenylazabicyclo[3.3.0] octane (3c). Oil, 80% yield, after purification. R_f 0.15 (eluent: light petroleum–ethyl acetate 4:1). IR (neat) 3088, 3065, 1598, 1581, 1496, 754, 698 (Ph), 1686 (C=O), 1545, 1375 (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (bd, 2H, *o*-PhCO), 7.45 (bt, 1H, *p*-PhCO), 7.32 (bt, 2H, *m*-PhCO), 7.09 (m, 5H, Ph), 5.48 (dd, J_1 = 7.8 Hz, J_2 = 5.3 Hz, 1H, H-1), 5.32 (d, J = 7.3 Hz, 1H, H-3), 4.49 (m, 2H, H-2, H-7a), 3.42 (m, 1H, H-5), 2.81 (m, 1H, H-5), 2.06 (m, 3H, 2 H-6, H-7), 1.49 (m, 1H, H-7); ^{1}H NMR (400 MHz, CD_3OH): δ 8.05 (bd, 2H, *o*-PhCO), 7.70 (bd, 2H, *o*-Ph), 7.55 (bt, 1H, *p*-PhCO), 7.32 (bt, 2H, *m*-PhCO), 7.10 (m, 3H, Ph), 5.50 (t, J = 7.8 Hz, 9.5 Hz, 1H, H-1), 5.18 (d, J = 7.7 Hz, 1H, H-3), 4.51 (dd, J_1 = 9.5 Hz, J_2 = 7.7 Hz, 1H, H-2), 4.31 (dt, J_1 = 9.5 Hz, J_2 = 7.7 Hz, 1H, H-7a), 3.35 (m, 1H, H-5), 2.89 (m, 1H, H-5), 2.30 (m, 3H, 2 H-6, H-7), 2.15 (m, 1H, H-7); ^{13}C NMR (100.1

Scheme 5



MHz, $CDCl_3$): δ 198.2 (s), 136.8 (s), 135.1 (s), 133.0 (d, *p*-PhCO), 128.8 (2d, Ph), 128.5 (2d, *m*-PhCO), 128.1 (d, Ph), 127.9 (2d, Ph), 127.9 (2d, *o*-PhCO), 92.6 (d, C-1), 73.5 (s, C-3), 67.0 (d, C-7a), 55.6 (t, C-5), 53.3 (d, C-2), 28.2 (t, C-7), 27.4 (t, C-6); *m*/*z* 317 (2, M+1), 286 (20), 231 (95, M—PhCO), 184 (100, M—PhCO—HNO_2), 156 (45). Anal. Calcd. for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33; Found: C, 71.02; H, 5.72; N, 8.40.

(1S,2S,3R,6R,7aS)-3-Acetyl-6-hydroxy-3-methyl-1-nitro-2-phenylazabicyclo[3.3.0]octane (6a). Colorless solid, mp 118–119°C, 48% yield, after purification. R_f 0.10 (eluent: *n*-heptane: ethyl acetate 1:3). IR ($CDCl_3$) 3399 (OH), 3051, 3032, 1590, 1501, 734, 702 (Ph), 1706 (C=O), 1546, 1376 (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (m, 5H, Ph), 5.95 (dd, J_1 = 10.2 Hz, J_2 = 9.1 Hz, 1H, H-1), 4.51 (bq, J = 8.2 Hz, 1H, H-7a), 4.49 (b signal, 1H, H-6), 3.87 (d, J = 10.2 Hz, 1H, H-2), 3.13, 3.06 (part AB of an ABX system, J_{AB} = 9.5 Hz, J_{AX} = 3.3 Hz, J_{BX} = 1.2 Hz, 2H, 2 H-5), 2.12 (dd, J_1 = 8.2 Hz, J_2 = 14.3 Hz, 1H, H-7), 2.06 (bs, 1H, OH), 1.91 (s, 3H, CH_3CO), 1.65 (ddd, J_1 = 14.3 Hz, J_2 = 7.9 Hz, J_3 = 5.3 Hz, 1H, H-7), 1.56 (s, 3H, CH_3); ^{13}C NMR (100.1 MHz, $CDCl_3$): δ 207.6 (s), 133.5 (s), 129.0 (2d), 128.7 (2d), 127.9 (d), 93.4 (d, C-1), 74.5 (s, C-3), 72.0 (d, C-6), 62.8 (d, C-7a), 56.2 (t, C-5), 55.9 (d, C-2), 36.9 (t, C-7), 27.3 (q, CH_3CO), 19.4 (q, CH_3); *m*/*z* 304 (<1, $M^{+\bullet}$), 261 (56, M—CH_3CO), 215 (28, M—CH_3CO—NO_2), 214 (100, M—CH_3CO—HNO_2), 196 (25, 214—H_2O), 170 (10); Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 63.14; H, 6.62; N, 9.20; Found: C, 63.27; H, 6.80; N, 9.09; $[\alpha]_D^{25}$ = –120.5 (*c* 0.36, $CHCl_3$).

(1S,2R,3R,6R,7aS)-3-Acetyl-6-hydroxy-3-methyl-2-nitro-1-phenylazabicyclo[3.3.0]octane (7a). Semisolid material, 15% yield, after purification, R_f 0.23 (eluent: *n*-heptane: ethyl acetate 1:3). IR ($CDCl_3$) 3406 (OH), 3050, 3032, 1603, 1496, 731, 701 (Ph), 1713 (C=O), 1549, 1359 (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.25 (m, 3H, Ph), 7.15 (bd, 2H, Ph), 6.10 (d, J = 8.1 Hz, 1H, H-2), 4.57 (b signal, 1H, H-6), 3.83 (dd, J_1 = 8.1 Hz, J_2 = 10.6 Hz, 1H, H-1), 3.39, 3.37 (m + dd, J_1 = 4.0 Hz, J_2 = 9.9 Hz, 2H, H-7a, H-5), 3.05 (bd, J = 9.9 Hz, 1H, H-5), 2.42 (s, 3H, CH_3CO), 2.18 (ddd, J_1 = 3.3 Hz, J_2 = 5.9 Hz, J_3 = 14.6 Hz, 1H, H-7), 2.06 (s + ddt, J_1 = 14.6 Hz, J_2 = 7.5 Hz, J_3 = 1.2 Hz, 2H, OH + H-7), 1.39 (s, 3H, CH_3); ^{1}H NMR (400 MHz, CD_3OH): δ 7.30 (m, 5H, Ph), 6.00 (d, J = 8.8 Hz, 1H, H-2), 4.55 (b signal, 1H, H-6), 3.82 (dd, J_1 = 8.8 Hz, J_2 = 9.9 Hz, 1H, H-1), 3.46 (ddd, 1H, H-7a), 3.36 (dd, J_1 = 4.6 Hz, J_2 = 10.1 Hz, 1H, H-5), 2.99 (d, J = 10.1 Hz, 1H, H-5), 2.43 (s, 3H, CH_3CO), 2.14 (ddd, 1H, H-7), 1.91 (ddt, 1H, H-7), 1.34 (s, 3H, CH_3); ^{13}C NMR (100.1 MHz, $CDCl_3$): δ 207.0 (s), 137.2 (s), 129.1 (2d), 127.8 (2d), 127.7 (d), 98.5 (d, C-2), 76.1 (s, C-3), 72.3 (d, C-6), 69.1 (d, C-7a), 57.1 (d, C-1), 55.1 (t, C-5), 39.7 (t, C-7), 24.2 (q, CH_3CO), 16.2 (q, CH_3); *m*/*z* 304 (<1, $M^{+\bullet}$), 261 (58, M—CH_3CO), 215 (100, M—CH_3CO—NO_2), 214 (18, M—CH_3CO—HNO_2), 200 (28), 170 (15). Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 63.14; H, 6.62; N, 9.20; Found: C, 63.32; H, 6.85; N, 9.02; $[\alpha]_D^{25}$ = +71.8 (*c* 0.87, $CHCl_3$).

(1R,2S,3S,6R,7aR)-3-Acetyl-6-hydroxy-3-methyl-2-nitro-1-phenylazabicyclo[3.3.0]octane (8a). Colorless solid, mp 166–167°C, 15% yield, after purification, R_f 0.27 (eluent: *n*-heptane: ethyl acetate 1:3). IR (nujol) 3181 (OH), 2724, 2671 (CH), 1713 (C=O), 1602, 1493, 701 (Ph), 1549, 1359 (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (m, 3H, Ph), 7.25 (bd, 2H, Ph), 6.10 (d, J = 8.4 Hz, 1H, H-2), 4.59 (b signal, 1H, H-6), 4.18 (dd, J_1 = 8.4 Hz, J_2 = 10.5 Hz, 1H, H-1), 3.35 (dd, J_1 = 9.0 Hz, J_2 = 6.4 Hz, 1H, H-5), 3.22 (dd, J_1 = 9.0 Hz, J_2 = 7.3 Hz, 1H, H-5), 3.20 (ddd, J_1 = 2.9 Hz, J_2 = 7.7 Hz, J_3 = 10.5 Hz, 1H, H-7a), 2.34 (s + m, 4H, CH_3CO, H-7), 1.84 (bd, 1H, OH), 1.78 (ddd, J_1 = 2.9 Hz, J_2 = 5.1 Hz, J_3 = 13.7 Hz, 1H, H-7), 1.38 (s, 3H, CH_3); ^{13}C NMR (100.1 MHz, $CDCl_3$): δ 207.0 (s), 137.4 (s), 129.0 (2d), 127.8 (2d), 127.7 (d), 98.0 (d, C-2), 77.2 (s, C-3), 72.3 (d, C-6), 69.8 (d, C-7a), 57.1 (d, C-1), 54.4 (t, C-5), 38.0 (t, C-7), 24.1 (q, CH_3CO), 16.2 (q, CH_3); *m*/*z* 304 (<1, $M^{+\bullet}$), 261 (56, M—CH_3CO), 215 (30, M—CH_3CO—NO_2), 214 (100, M—CH_3CO—HNO_2), 196 (32, 214—H_2O), 170 (12). Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 63.14; H, 6.62; N, 9.20; Found: C, 63.22; H, 6.74; N, 9.13; $[\alpha]_D^{25}$ = –83.3 (*c* 0.09, $CHCl_3$).

(1′S*,2′R*,3′S*,7′aS*)-2′-Nitro-1′-phenylspiro[cyclohexanone-6,3′-pyrrolizidine (10). Colorless oil, 70% yield, after purification. IR (neat) 3063, 3029, 1603, 1497, 757, 701 (Ph), 1713 (CO), 1545, 1361 (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, 5H, Ph), 6.16 (d, J = 7.7 Hz, 1H, H-2′), 3.81 (dd, J_1 = 10.6 Hz, J_2 = 7.7 Hz, 1H, H-1′), 3.28–3.15 (m, 3H, H-2, H-5′, H-7′a) [The three overlapping signals are as follows: 3.20 (dt, J_1 = J_2 = 14.0 Hz, J_3 = 6.0 Hz, 1H, H-2), 3.20 (m, 2H, H-5′), 3.18 (m, 1H, H-7′a)], 3.12 (dt, 1H, H-5′), 2.39 (bd, J = 14.0 Hz, 1H, H-2), 2.20–2.05 (m, 3H, H-5, H-6′, H-7′), 2.00–1.77 (m, 4H, H-3, H-4, H-6′, H-7′), 1.77–1.58 (m + dt, 2H, H-3, H-5); ^{13}C NMR (100.1 MHz, $CDCl_3$): δ 207.8 (s), 138.2 (s), 128.9 (2d), 128.1 (2d), 127.4 (d), 98.3 (d, C-2′), 76.9 (s, C-3′), 70.7 (d, C-7′a), 56.8 (d, C-1′), 45.0 (t, C-5′), 37.9 (t, C-2), 30.9 (t, C-5), 27.0 (t, C-7′), 26.9 (t, C-3), 23.4 (t, C-6′), 22.2 (t, C-4); *m*/*z* 315 (10, M+1), 268 (78, M+1—NO_2), 240 (45, 268—CO), 171 (100), 143 (30), 129 (92), 70 (65). Anal. Calcd. for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91; Found: C, 68.91; H, 7.25; N, 8.75.

(1S*,5S*,6R*,7R)-1-Hydroxy-7-nitro-6-phenylbicyclo[3.2.1]octan-8-one (11). Semisolid material, 73% yield, after purification, R_f 0.40 (eluent: light petroleum–ethyl acetate 4:1). IR (CCl_4) 3454 (OH), 3050, 3030, 1498, 788, 754, 700 (Ph), 1764 (C=O), 1549, 1370 (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (m, 3H, Ph), 7.15 (bd, 2H, Ph), 4.81 (d, J = 5.8 Hz, 1H, H-7), 4.18 (d, J = 5.8 Hz, 1H, H-6), 3.36 (bs, 1H, OH), 2.78 (dd, J_1 = 4.4 Hz, J_2 = 1.8 Hz, 1H, H-5), 2.35 (m, 2H, CH_2), 2.11 (m, 1H, ring CH), 2.00 (s, 2H, CH_2), 1.75 (m, 1H, ring CH); ^{13}C NMR (100.1 MHz, $CDCl_3$): δ 212.5 (s), 142.3 (s), 129.4 (2d), 127.8 (d), 126.7 (2d), 93.6 (d, C-7), 81.6 (s, C-1), 51.6 (d, C-5), 43.9 (d, C-6), 39.8 (t, C-2), 36.0 (t, C-4), 17.9 (t, C-3); *m*/*z* 261 (11, $M^{+\bullet}$), 229 (20, M—NO—H_2), 197 (10, M—NO_2—H_2O), 169 (100, 197–28), 141 (48, 169–28). Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36; Found: C, 64.40; H, 5.87; N, 5.40.

(1S*,5S*,6R*,7S)]-1-Hydroxy-7-nitro-6-phenylbicyclo[3.2.1]octan-8-one (12). Mp 146–147°C, from cyclohexane, 7% yield, after purification. R_f 0.30 (eluent: light petroleum–ethyl acetate 4:1). IR (nujol) 3425 (OH), 3050, 3030, 1496, 743, 721, 695 (Ph), 1752 (C=O), 1553 (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (m, 3H, Ph), 7.16 (bd, 2H, Ph), 5.29 (d, J = 9.5 Hz, 1H, H-7), 3.92 (d, J = 9.5 Hz, 1H, H-6), 3.22 (bs, 1H, OH), 3.05 (b signal, W_H = 9.2 Hz, 1H, H-5), 2.41 (m, 1H), 2.20–2.05 (m, 3H, ring CH), 2.02–1.83 (m, 2H); ^{13}C NMR (100.1 MHz, $CDCl_3$): δ 213.9 (s), 136.3 (s), 128.7 (2d), 128.5 (2d), 127.8 (d), 91.0 (d, C-7), 80.0 (s, C-1), 47.1 (d, C-5), 44.3 (d, C-6), 41.2 (t, C-2), 35.9 (t, C-4), 17.6 (t, C-3). Anal. Calcd.

for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36; Found: C, 64.42; H, 5.93; N, 5.50.

Crystal structure determinations. Diffraction data for the structures reported were collected at room temperature on a Nonius DIP-1030H system (Mo-Kα radiation, $\lambda = 0.71073$ Å). Both the structures were solved by direct methods and refined by the full-matrix least-squares method based on F^2 with all observed reflections [8]. The calculations were performed using the WinGX System, Ver 1.80.05 [9].

Crystal data for 6a. $C_{16}{\cdot}H_{20}{\cdot}N_2{\cdot}O_4$, fw = 304.34 g/mol; Tetragonal, $P\ 4_1$, $a = 13.640(3)$, $c = 8.299(2)$ Å, $V = 1544.0(6)$ Å^3, $Z = 4$, $D_{calcd} = 1.309$ g/cm^3, μ(Mo-Kα) = 0.095 mm^{-1}, $F(000) = 648$, $\theta = 24.71°$. Final $R_1 = 0.0426$, $wR_2 = 0.0996$, GOF = 0.850 for 132 parameters and 1370 unique reflections, of which 815 with $I > 2\sigma(I)$, residuals in ΔF map 0.186, –0.181 e. Å^{-3}.

Crystal data for 12. $C_{14}{\cdot}H_{15}{\cdot}NO_4$, fw = 261.27 g/mol; Monoclinic, $P\ 2_1$, $a = 8.323(2)$, $b = 6.309(2)$, $c = 12.535(3)$ Å, $\beta = 104.31(3)°$, $V = 637.8(3)$ Å^3, $Z = 2$, $D_{calcd} = 1.361$ g/cm^3, μ(Mo-Kα) = 0.100 mm^{-1}, $F(000) = 276$, $\theta = 24.69°$. Final $R_1 = 0.0341$, $wR_2 = 0.0890$, GOF = 0.889 for 173 parameters and 1107 unique reflections, of which 717 with $I > 2\sigma(I)$, residuals in ΔF map 0.101, –0.156 e. Å^{-3}.

CONCLUSION

Although [3+2]cycloadditions between 1,3-azomethine ylides and activated olefins are known, the easy access to these polyfunctionalized pyrrolizidines is interesting, in particular, as far as the formation of the nitro spiro pyrrolizidine is concerned. In fact, a similar spiro pyrrolizidine of terpenoid nature, the (+)-nitropolyzonamine [10], extracted from a millipede, has been studied as a potential allomone to deter predators [11].

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