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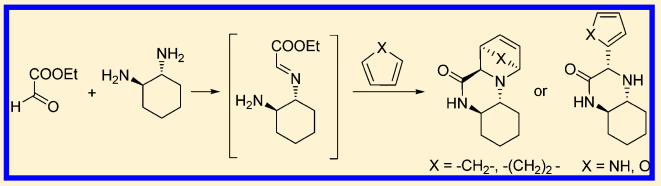
Monoimine Derived from *trans*-1,2-Diaminocyclohexane and Ethyl Glyoxylate: An Intermediate in Aza-Diels–Alder and Mannich Reactions

Elżbieta Wojaczyńska,* Julia Bąkowicz, Mateusz Dorsz, and Jacek Skarżewski

Department of Organic Chemistry, Faculty of Chemistry, Wrocław University of Technology, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław, Poland

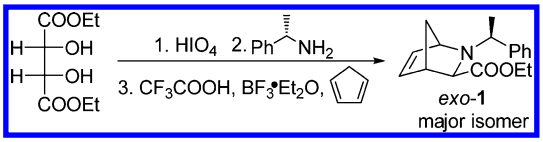
Supporting Information

ABSTRACT: Novel enantiopure policyclic nitrogen heterocycles have been obtained in the diastereoselective *aza*-Diels–Alder or Mannich reaction of dienes with imine formed *in situ* from ethyl glyoxylate and (1*R*,2*R*)-diaminocyclohexane.



The stereoselective aza-Diels–Alder reaction serves as an effective method for the preparation of chiral heterocyclic compounds.[1] The *exo*-ester (1*S*,3*R*,4*R*)-**1** containing a 2-azanorbornene (2-azabicyclo[2.2.1]heptene) skeleton was easily obtained as the main product of the cycloaddition of cyclopentadiene to iminium ion formed *in situ* from ethyl glyoxylate and (*S*)-1-phenylethylamine (Scheme 1).[2] This bicyclic system has proved to be an attractive precursor of chiral ligands useful in asymmetric synthesis.[3−5]

Scheme 1



In our quest for versatile ligands for asymmetric catalysis based on the 2-azanorbornane framework, we focused on the possibility of introducing an additional donor atom to the molecule. The endocyclic nitrogen donor as a tertiary amine is already present in the structure of 2-azanorbornyl derivatives. Another one, of different character, can be introduced *via* an appropriate modification of the exocyclic group as described by Andersson et al.[6]

One can also imagine an alternative synthetic pathway comprising the use of chiral diamine as a starting material for the preparation of the dienophile for aza-Diels–Alder reaction. In order to examine this possibility we reacted enantiopure *trans*-1,2-diaminocyclohexane (DACH) with 1 equiv of ethyl glyoxylate. The dienophile intermediate **2** was treated with freshly distilled cyclopentadiene or 1,3-cyclohexadiene. In both cases the reaction proceeded smoothly, leading to the single aza-Diels–Alder adducts **3** and **4**, respectively, in very high yields (Scheme 2). The reaction generating three new stereogenic centers furnished one diastereomer only. Even in the case of unsymmetrical 1-methoxy-1,3-butadiene, high regio- and stereoselectivity was observed, and despite the lower yield, the major isomer **5** was obtained in 90:10 dr, which is comparable with the diastereomeric composition of the starting diene (*Z*:*E* = ca. 92:8).

Chiral tetracyclic nitrogen heterocycles can be found among biologically active molecules, including alkaloids (e.g., sparteine, asperlicin, benzo[*a*]quinolizidine derivatives[7]), azasteroids[8] (e.g., finasteride, chandonium), and various drugs (e.g., antidepressants mianserin and mirtazapine). Compounds from this class, sparteine and Tröger's base, are also widely used in organic synthesis and as chiral discrimination compounds.[9]

A structure of the obtained cycloadducts was determined by NMR (^{1}H, ^{13}C) spectroscopy and high resolution mass spectrometry. In particular, 2D NMR spectra (^{1}H–^{1}H COSY and NOESY, ^{1}H–^{13}C HMQC/HSQC and HMBC) made it possible to assign spectral resonances and revealed signal correlations that further confirmed formation of tetracyclic (tricyclic in the case of **5**) products and the assigned configurations of the newly created stereogenic centers ((1*S*,11*R*,12*R*) for compounds **3** and **4**, (10*R*,14*R*) for adduct **5**). For example, the observed connectivities in the NOESY map of compound **3** are in a good agreement with the expected interproton contacts (H_3 and H_{14}; H_{11} and H_{15} of -CH_2-bridge) found in the DFT optimized structure of **3** (Figure 1). Also the configuration ascribed to the remaining aza-Diels–Alder adducts corroborated their 2D ^{1}H and ^{13}C NMR spectra. Moreover, the product structures are in agreement with the previously observed general stereochemical outcome of the cycloaddition, i.e., formation of mainly *exo*-2-azanorbornyl derivatives.[2]

The described aza-Diels–Alder procedure offers an easy access to enantiopure tri- or tetracyclic systems possessing up to five stereogenic carbon centers. Chiral imine **2** (Scheme 2)

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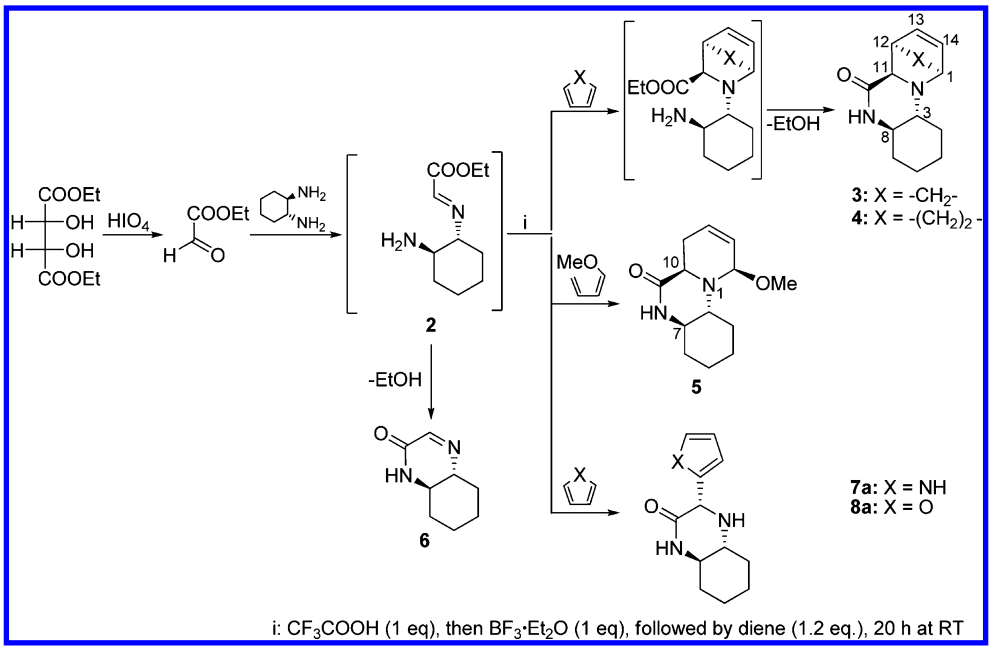
Scheme 2



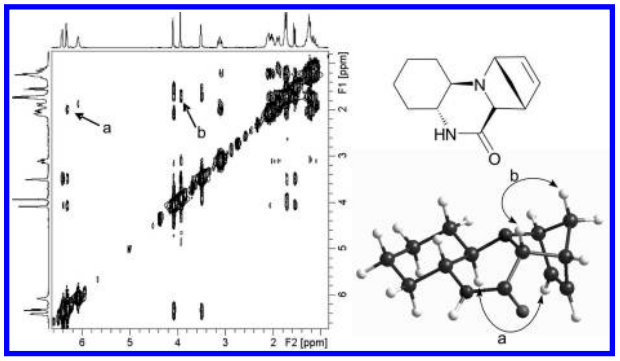


Figure 1. Part of NOESY map of compound **3** showing cross-peaks derived from interproton contacts indicated in the DFT optimized structure.

was prepared *in situ* in a one-pot procedure, starting from the easily available starting materials. Furthermore, other chiral 1,2-diamines may be also used, and glyoxylate can be replaced with pyruvate derivatives;[10] these possibilities together with the diversity of available dienes show the potential of the proposed synthetic route. The presence of several functional groups in the resulting cycloadducts opens the possibility of their further modification.

Moreover, when the initial imine intermediate **2** formed in the reaction of glyoxylate and DACH was left without the usually added diene, it converted into a bicyclic chiral imine **6** in >90% yield (Scheme 2). Racemic compound **6** has already been prepared and applied as a phenol-alkylating agent by Minakawa et al.[11] Similar bicyclic imines were also obtained in the reaction of pyruvate derivatives with various 1,2-diamines.[10]

Since compound **6** remains an activated chiral imine, we decided to test it as a dienophile in aza-Diels–Alder reaction with CF_3COOH, $BF_3{\cdot}Et_2O$, and freshly distilled cyclopentadiene. Surprisingly, there was no reaction, and the substrate was recovered. Thus clearly iminoglyoxylate **2** is an active dienophile and its internal cyclization halts the Diels–Alder reaction. It seems that an ester activates the imine double bond effectively, while the lactam functionality in structure **6** does not.

When pyrrole or furan and **2** were used in the attempted Diels–Alder reaction, only the ring-alkylation product was isolated as a single diastereomer in 15% and 80% yield, respectively (Scheme 2). The structures of pyrrole **7a** and furan **8a** adducts were deduced from 1D and 2D NMR spectra and, in the case of **7a**, confirmed by X-ray measurement, which showed *S* configuration of the newly created stereogenic center (Figure S1, Supporting Information). The pyrrole ring is almost perpendicular to the mean plane of 10 atoms of the bicyclic system (interplane angle equals 84.8°). Pyrrolic NH fragment is engaged in a hydrogen bond with carbonyl oxygen atom of the neighboring molecule with O–N distance of 2.96 Å.

Since under Diels–Alder conditions a product of nucleophilic addition of pyrrole to imine was obtained, we decided to carry out the reaction using conditions applied by Minakawa et al. to the addition of racemic **6** to phenols (phosphate buffer, pH = 8).[11] This time the conversion of chiral **6** was quantitative, and the two diastereomeric adducts **7a** and **7b** were isolated in 1.4:1 ratio (Scheme 3). After chromatographic separation, diastereomers were identified by comparison with compound **7a** obtained in the course of the attempted Diels–Alder reaction. As can be seen, a significant increase of reaction yield under modified conditions was accompanied by the loss of stereoselectivity.

With an enantiopure compound **6** in hand, we decided to explore the possibility of chiral induction in its reaction with phenols. Addition of *p*-cresol or *p*-(*tert*-butyl)phenol to **6** performed in phosphate buffer at pH = 8 resulted in a mixture of diastereomers (**9a**/**9b** and **10a**/**10b**, respectively). Identity of products was confirmed by high resolution mass spectrometry (see Experimental Section).

The overall yield of adducts and reaction diastereoselectivity were rather modest (40% yield, dr 1.7:1 for **9a**/**9b**, and 29% yield, dr 1.6:1 for **10a**/**10b**) and comparable with values obtained for preparation of racemic compounds **9a** and **9b**.[11] We were able to isolate the enantiomerically pure major isomer (1*R*,4*S*,6*R*)-**9a** by column chromatography.

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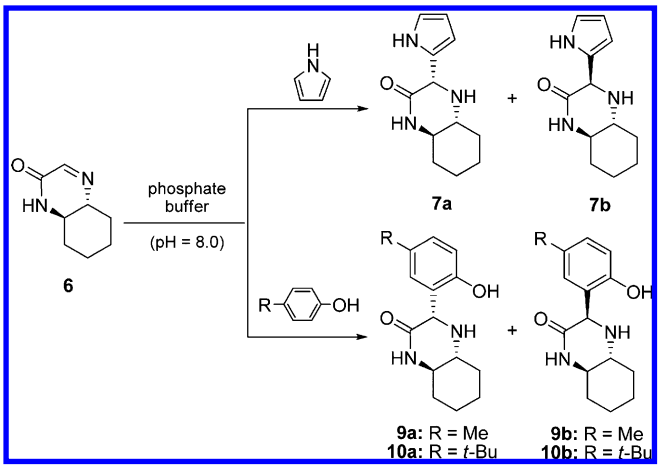
Scheme 3



Among rare reports on 2-furyl-substituted bicyclic diaza-compounds, racemic hexa- and decahydroquinoxaline derivatives have been described.[12] Quinoxalinones, imines containing a lactam functionality closely related to **6**, were applied in the Friedel–Crafts reaction to yield indolyl derivatives.[13] Asymmetric induction was observed in the reaction of various azinones with nucleophiles.[14] Diastereoselective Barbier allylation of dihydropyrazinones followed by cyclization afforded chiral bicyclic and tricyclic piperazinones.[15] In conclusion, the stereoselective addition of pyrrole and furan to bicyclic imine under Diels–Alder conditions described herein (see Scheme 2) provides an interesting route to new chiral heterocyclic compounds, which will be tested as (N,X)-donating ligands for asymmetric catalysis.

EXPERIMENTAL SECTION

Synthesis of Cycloadducts 3–5 and Adducts 7a, 8a. Aza-Diels–Alder reaction of dienes and an iminium ion derived from ethyl glyoxylate and (1*R*,2*R*)-*trans*-diaminocyclohexane (DACH) was performed according to the modified literature procedure.[2c] In a typical synthesis, 1.39 g (6.12 mmol) of $HIO_4{\cdot}2H_2O$ was added stepwise to a stirred solution of 1.26 g (6.12 mmol) of diethyl tartrate in 30 mL of diethyl ether at 0 °C during 0.5 h, and the stirring was continued for 0.5 h at room temperature. The precipitate was filtered off, and solvent was evaporated. The solid residue was dissolved in 40 mL of CH_2Cl_2, and 1.39 g (12.25 mmol, 1 equiv) of DACH was added to the solution, which was stirred over molecular sieves 4Å for 2 h at room temperature. CF_3COOH (0.94 mL, 12.25 mmol), 1.50 mL of $BF_3{\cdot}Et_2O$ (12.25 mmol), and freshly distilled diene (1.2 equiv) were then introduced in 10 min intervals. The reaction mixture was stirred for 20 h at room temperature. Reaction was quenched by stirring with aqueous Na_2CO_3 for 2 h. The reaction mixture was filtered through a bed of cellite, and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over Na_2SO_4, filtered, and evaporated. Chromatography on silica column (5% CH_3OH in $CHCl_3$ was used as eluent) was then performed, yielding cycloadducts (**3**–**5**) or adducts (**7a**, **8a**).

Chiral imine **6** was isolated from the reaction mixture before the acidification step.

(1*S*,3*R*,8*R*,11*R*,12*R*)-10-Oxo-2,9-diazatetracyclo-[10.2.1.0^{2,11}.0^{3,8}] pentadec-13-ene (3). Yield 2.4 g (90%), mp 149–150 °C. $[\alpha]^{20}_D$ +24.2 (*c* 1.22, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20–1.30 (m, 4H), 1.53–1.57 (dt, 1H, J_1 = 8.4 Hz, J_2 = 1.5 Hz), 1.71–1.74 (m, 3H), 1.86–1.92 (m, 1H), 1.98–2.12 (m, 2H), 3.09–3.12 (m, 1H), 3.51 (d, 1H, *J* = 1.5 Hz), 3.95 (d, 1H, *J* = 6.0 Hz), 4.09 (d, 1H, *J* = 1.5 Hz), 6.08 (bs, 1H, NH), 6.31–6.34 (m, 1H), 6.42–6.50 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.9, 24.2, 30.7, 31.1, 46.8, 48.0, 54.1, 61.3, 61.8, 62.4, 136.3, 137.7, 172.4 ppm. IR (KBr): 747, 1294, 1370, 1670, 2858, 2935, 2978, 3195 cm^{-1}. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $(C_{13}H_{19}N_2O)^+$ 219.1497; found 219.1514.

(1*S*,3*R*,8*R*,11*R*,12*R*)-10-Oxo-2,9-diazatetracyclo-[10.2.2.0^{2,11}.0^{3,8}]hexadec-13-ene (4). Yield 2.7 g (95%), mp 152–153 °C. $[\alpha]^{20}_D$ −21.4 (*c* 0.55, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22–1.39 (m, 6H), 1.64–1.90 (m, 5H), 2.15–2.20 (m, 2H), 3.00–3.14 (m, 1H), 3.34–3.36 (m, 1H), 3.69–3.71 (m, 2H), 6.15 (bs, 1H, NH), 6.36–6.43 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.5, 23.9, 24.4, 26.4, 30.4, 31.5, 32,5, 48.6, 52.8, 62.4, 62.9, 134.0, 134.4, 172.0. IR (KBr): 705, 1373, 1668, 2856, 2929, 3066, 3185 cm^{-1}. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $(C_{14}H_{21}N_2O)^+$ 233.1654; found 233.1645.

(2*R*,7*R*,10*R*,14*R*)-14-Methoxy-9-oxo-1,8-diazatricyclo-[8.4.0.0^{2,7}]tetradec-12-ene (5). Yield 0.92 g (32%), de 80%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.20–1.36 (m, 4H), 1.73–1.80 (m, 4H), 2.46–2.55 (m, 2H), 2.64–2.68 (m, 1H), 2.97–3.02 (m, 1H), 3.0 (s, 3H, OMe), 3.55 (dd, 1H, J_1 = 10.3 Hz, J_2 = 3.4 Hz), 4.81 (d, 1H, *J* = 5.2 Hz), 5.55 (dd, 1H, J_1 = 15.6 Hz, J_2 = 5.2 Hz), 5.80–5.85 (m, 1H), 6.18 (bs, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.8, 24.7, 30.7, 31.3, 35.5, 52.6, 53.2, 57.5, 58.4, 102.0, 130.9, 131.4, 172.2. IR (film): 838, 995, 1055, 1128, 1355, 1448, 1657, 2859, 2932, 3183, 3303 cm^{-1}. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $(C_{13}H_{21}N_2O_2)^+$ 237.1603; found 237.1591.

(1*R*,6*R*)-3-Oxo-2,5-diazabicyclo[4.4.0]decane (6). $[\alpha]^{20}_D$ −234.7 (*c* 1.11, CH_2Cl_2), spectral characteristics of this compound was in agreement with literature data for racemic imine.[11]

(1*R*,4*S*,6*R*)-3-Oxo-4-(2-pyrrolyl)-2,5-diazabicyclo[4.4.0]-decane (7a). Yield 0.40 g (15%, de 100%, attempted Diels–Alder reaction)/0.25 g (55%, de 58%, Mannich conditions), mp 193–194 °C. $[\alpha]^{20}_D$ +35.3 (*c* 0.39, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30–1.40 (m, 4H), 1.63–1.97 (m, 5H), 2.66 (td, 1H, J_1 = 10.1 Hz, J_2 = 3,5 Hz), 3.05–3.09 (m, 1H), 4.76 (s, 1H), 5.93 (bs, 1H, NH), 6.16–6.20 (m, 2H), 6.75–6.77 (m, 1H), 9.38 (bs, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.8, 24.7, 30.7, 31.6, 57.3, 58.2, 58.4, 105.5, 108.1, 117.5, 128.3, 170.4. IR (film): 717, 1083, 1451, 1648, 1746, 2925, 3362 cm^{-1}. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $(C_{12}H_{18}N_3O)^+$ 220.1450; found 220.1457. R_f (ethyl acetate) 0.18.

(1*R*,4*S*,6*R*)-3-Oxo-4-(2-furyl)-2,5-diazabicyclo[4.4.0]decane (8a). Yield 2.2 g (80%), mp 146–147 °C. $[\alpha]^{20}_D$ +61.8 (*c* 0.18, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19–1.33 (m, 5H), 1.60–1.81 (m, 4H), 2.65–2.72 (m, 1H), 3.06–3.13 (m, 1H), 4.79 (s, 1H), 6.20 (bs, 1H, NH), 6.29–6.35 (m, 2H), 7.38 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.8, 24.6, 30.6, 31.4, 53,1, 57.0, 58.5, 107.8, 110.5, 142.2, 153.5, 167.8. IR (KBr): 755, 808, 1050, 1352, 1671, 2933, 3184 cm^{-1}. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $(C_{12}H_{17}N_2O_2)^+$ 221.1290; found 221.1296.

Mannich Reaction of Imine 6 with Nucleophiles. Addition of pyrrole and phenols (*p*-cresol or *p*-(*tert*-butyl)phenol) to imine **7** (0.31 g, 2 mmol) was performed according to the literature procedure (24 h at rt in pH = 8.0 phosphate buffer containing 5% of DMSO).[11] Diastereomer ratio was assigned from ^{1}H NMR measurement. Pyrrolic adducts **7a**,**7b** were separated by chromatography on silica using ethyl acetate as eluent. Major diastereomer from cresol addition, **9a** was isolated in an enantiopure form using column chromatography with *t*-BuOMe/$CHCl_3$ (2:1 v/v).

(1*R*,4*R*,6*R*)-3-Oxo-4-(2-pyrrolyl)-2,5-diazabicyclo[4.4.0]-decane (7b). Yield 0.18 g (40%), mp 175–177 °C. $[\alpha]^{20}_D$ +45.7 (*c* 0.14, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26–1.42 (m, 4H), 1.61 (bs, 1H), 1.77–1.81 (m, 2H), 1.84–1.90 (m, 1H), 1.93–1.96 (m, 1H), 2.65–2.69 (m, 1H), 3.07–3.12 (m, 1H), 4.76 (s, 1H), 5.74 (bs, 1H, NH), 6.16 (dd, 1H, J_1 = 6.0 Hz, J_2 = 2.7 Hz), 6.18–6.20 (m, 1H), 6.76 (dd, 1H, J_1 = 4.1 Hz, J_2 = 2.5 Hz), 9.38 (bs, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.8, 24.7, 30.7, 31.6, 57.3, 58.2, 58.5, 105.5, 108.1, 117.6, 128.2, 170.3. IR (film): 717, 803, 1083, 1308, 1572, 1655, 2857, 2926, 3239, 3365 cm^{-1}. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $(C_{12}H_{18}N_3O)^+$ 220.1450; found 220.1458. R_f (ethyl acetate) 0.24.

(1*R*,4*S*,6*R*)-3-Oxo-4-(2-hydroxy-5-methylphenyl)-2,5-diazabicyclo[4.4.0]decane (9a). Yield 0.2 g (25%), $[\alpha]^{20}_D$ +155.8 (*c*

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0.2, CH_2Cl_2); spectral characteristics were in agreement with literature data for the racemic adduct.[11] R_f (ethyl acetate) 0.50; for **9b** R_f (ethyl acetate) 0.58.

9a/**9b** HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $(C_{15}H_{21}N_2O_2)^+$ 261.1603; found 261.1590. **10a**/**10b** HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $(C_{18}H_{27}N_2O_2)^+$ 303.2072; found 303.2080.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C spectra and selected 2D NMR maps, DFT optimized structure of compound **3**, and ORTEP view of compound **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: elzbieta.wojaczynska@pwr.wroc.pl.

Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Jacek Gawroński on the occasion of his seventieth birthday.

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