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Biomimetic Synthesis of Nitraria Alkaloids: Stereoselective Spirocyclization Reactions

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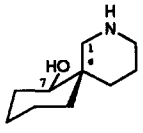
Key Words: nitramine, nitraramine; glutarimide; biomimetic; spirocyclization; Michael addition; biosynthesis

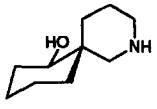
Abstract: *The Michael-induced spirocyclization of 2-alkylidene glutarimides offers a highly stereoselective method for a biomimetic synthesis of nitramine and for the construction of the nitraramine carbon-nitrogen framework.*

1. INTRODUCTION

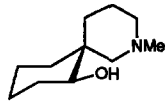
The piperidine alkaloids nitramine, iso-nitramine and sibirine have received considerable synthetic attention[1] since their isolation from *Nitraria schoberi* L. and *Nitraria sibirica* Pall.[2a]. Although X-ray analysis[2b] elucidated the unusual spiro-structure of these isomeric compounds, the absolute configuration had to be established via enantioselective total syntheses of both antipodes by Schultz et al.[1a] and Husson et al.[1b], confirming the relative and absolute stereochemistry as is shown in scheme 1. Several racemic and enantioselective syntheses of one ore more of these alkaloids have appeared since then. Some new alkaloids with a similar spiro-skeleton have been isolated recently from the same Nitraria species, from which nitraramine[3] certainly is the most interesting.



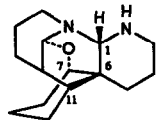
Nitramine
6S,7R



Isonitramine
6R,7R



Sibirine
6S,7S



Nitraramine
(racemic)

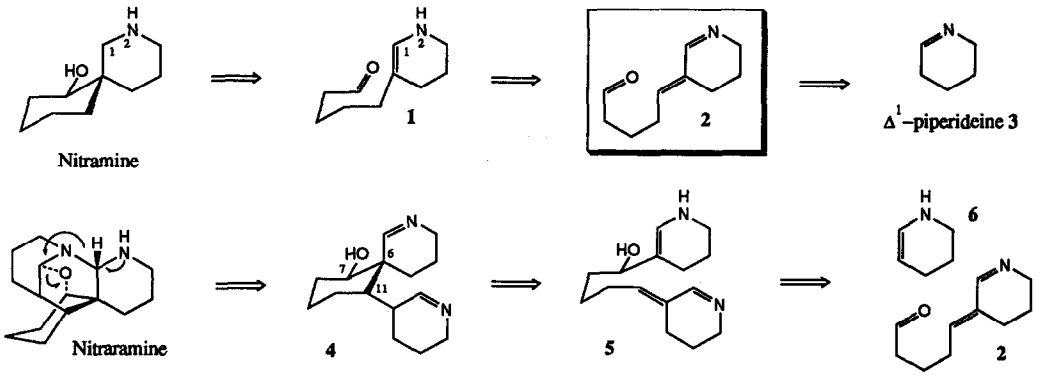
scheme 1

Its stereostructure was established by X-ray analysis[3b], revealing the spiro-part of the molecule to posses the nitramine relative configuration, with a second piperidine ring connected to the 7- and 11-position of the cyclohexane moiety of nitramine, and attached via an aminal bond to the 1-position of the piperidine-part. In contrast to

the simple piperidin spiroalkaloids, the C_7-hydroxyl substituent in nitraramine occupies an axial position, which enables the formation of the two aminal bonds. Additional information about the conformation of these spiroalkaloids was obtained from extended NMR-studies[3c]. While most of the Nitraria spiro alkaloids are optically active, nitraramine shows no rotation, which is in agreement with the centrosymmetric spacegroup in which the alkaloid crystallized according to the X-ray analysis. The occurence of this and several other Nitraria alkaloids as racemates[4] may be a consequence of non-enzymatic cyclization steps during the biosynthesis in Nitraria species.

2. RETROSYNTHETIC ANALYSIS

Although the spiro Nitraria alkaloids are obvious lysine-derived alkaloids, the normal "Lupine" pathway[5] cannot explain the formation of these structures. Biosynthetic retro-analysis of nitramine makes it likely that dehydronitramine is directly formed in a spirocyclization step, proceeding via enamine/aldehyde intermediate **1**, a deaminated dimer of piperideine **3**. The hypothetical aldehydic precursor **2** can be considered as an important general biosynthetic intermediate[6] for most of the Nitraria alkaloids (spiro[2,3], tripiperidine[4c] and tryptamine[7,8] alkaloids) that have been characterized until now.



scheme 2

Retroanalysis of nitraramine starts with breaking of the two aminal bonds, greatly simplifying the molecule to piperideine substituted nitramine **4**. Similarity with lupin alkaloids is found here again, since most of the lupin alkaloids are trimers of piperideine (for instance sparteine and aloperine). The Michael precursor **5** can be constructed from aldehyde **2** and a third molecule piperideine (in its enamine form **6**). It is remarkable that, starting from **2**, no oxidation or reduction steps are required. As stated before, the isolation of nitraramine and several other Nitraria alkaloids[4a] as racemates supports the assumption that enzymes are not involved in crucial steps of their biosynthesis.

3. CHEMISTRY

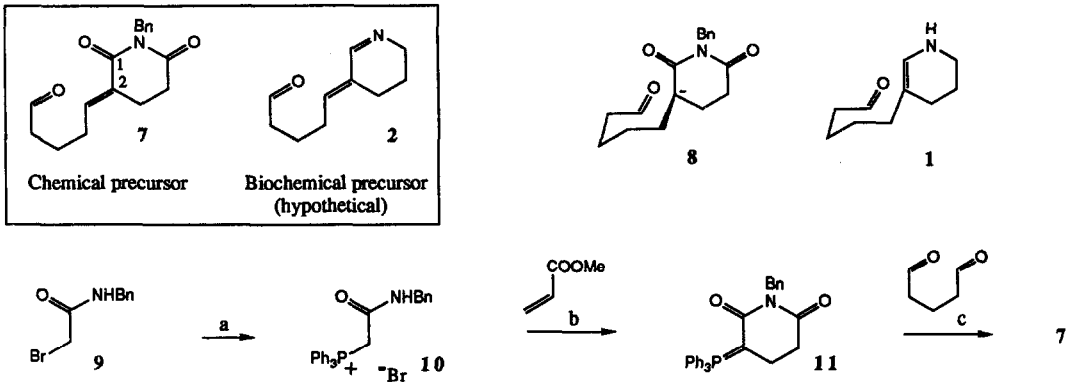
Several racemic and enantioselective syntheses of the "dimeric" alkaloids nitramine, iso-nitramine and sibirine have appeared in the literature, applying a variety of methods[1]. The stereoselectivity of these approaches shows a large variation between completely nitramine[1f,h] (C1-N/C7-OH syn) or isonitramine[1b,d,j,k] (C1-N/C7-OH anti) selectivity depending on the method used. In some approaches the possibility exists to direct this selectivity by reduction of a C7 carbonyl precursor[1a,f].

The retroanalysis we suggest in scheme 2, provides a synthetical strategy for the construction of the (iso)-

nitramine as well as for the nitraramine skeleton, via 2-substituted glutarimides as equivalents of piperideine. These substituted glutarimides have already proven their value in the synthesis of bispiperidines and quinolizidines[9], the advantages of a biomimetic ringopening/ringclosure sequence being demonstrated. The prochiral glutarimide aldehyde **7** (scheme 3) is expected to be an efficient alternative for intermediate **2**, the hypothetical biosynthetic precursor of the Nitraria alkaloids.
Some biosynthetic aspects are present in the enantioselective synthesis of isonitramine by Husson et al.[1b], based on the reaction of glutaric dialdehyde with (-)-phenylglycinol.

3a. Synthesis of (±)-nitramine.

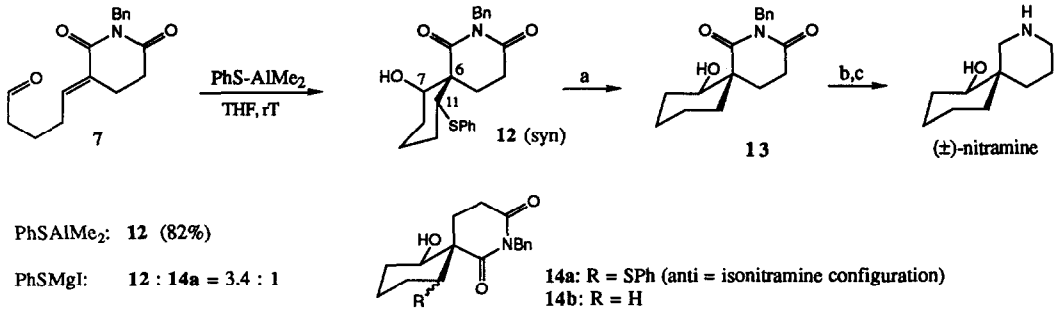
Aldehyde **7** can be obtained easily by Wittig reaction of glutarimide ylide **11**[10] with excess aqueous glutaric dialdehyde[9]. A possibility to create a nucleophilic α-position in **7** for the intramolecular aldol reaction, is hydrogenation of the double bond followed by simple deprotonation leading to anion **8**. The existence however of several protons that are more acidic then the α-hydrogen anticipated, combined with the sensivity of the glutarimidering towards nucleophilic opening, prohibited base catalyzed aldol reactions. A more regioselective method to solve this problem, is 1,4-reduction of the α,β-unsaturated glutarimide thus generating anion **8**. Special reductors for this purpose are complex hydride donors, that are based on copper(I) such as bis(triphenylphosphine)copper(I)borohydride or the methylcopper/DIBAH/HMPA system, efficiently used in an reduction/alkylation sequence for α,β-unsaturated carbonyl compounds[11].



a. Triphenyl phosphine, acetonitrile, reflux, 69%; b. Methyl acrylate, sodium methoxide, methanol, rT, 18h, 80%; c. Glutaric dialdehyde, tetrahydrofuran, reflux, 4h, 58%.

scheme 3

Although the glutarimide carbonyl groups were not reduced upon applying these methods to **7**, the unconjugated aldehyde could not resist reduction. A third possibility, a Michael induced aldol reaction with thiophenolate as nucleophile looked very promising, and has as the sole drawback the necessity to remove the nucleophile afterwards. Two different derivatives of thiophenol, the dimethylaluminium complex[12] and the iodomagnesium salt[13], are described in the literature as nucleophiles in tandem-difunctionalization reactions[14], with especially the former having very favourable properties in a comparable cyclization reaction[12]. Two equivalents of this complex prepared from trimethyl aluminium and thiophenol in tetrahydrofuran reacted cleanly with **7** at room temperature to give spiro-glutarimide **12** as a single isomer in 82% yield (scheme 4).

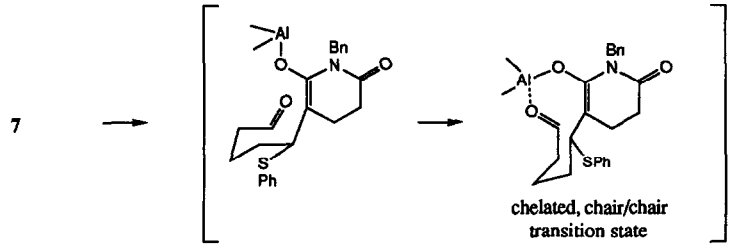


a. Raney Ni, tetrahydrofuran, rT, 30 min, 81%; b. Lithium aluminium hydride, diethyl ether, rT (18h) and reflux (2h), 71%; c. H_2, $Pd(OH)_2/C$, methanol + acetic acid, 4 h, 1 atm. 96%.

scheme 4

The configuration around the C-6/C-7 bond in **12** was confirmed to be the nitramine-syn, by conversion via two reductive steps into N-benzyl nitramine[1g], which could be hydrogenated quantitavely to (±)-nitramine[1i]. When the iodomagnesiumcomplex of thiophenol was used, the formation of a small amount of a second isomer was observed (**12** : **14a** = 3.4 : 1), which after desulfurization could be identified by NMR as spiro glutar-imide **14b**. This compound was identical with the product possessing the isonitramine configuration, obtained via Diels Alder reactions[1i].

An explanation for the high stereoselectivity may be found in the highly substituted nature of the intermediate thiophenolate adduct (scheme 5). This aluminium enolate is formed by an initial thiophenol 1,4-addition to methylene glutarimide[15] **7**. If in the next cyclization step the aldehyde oxygen of the side chain chelates to the aluminium, a transition state can be formed with the aluminiumchelate in a favourable chairlike 6-membered ring[16, 17].

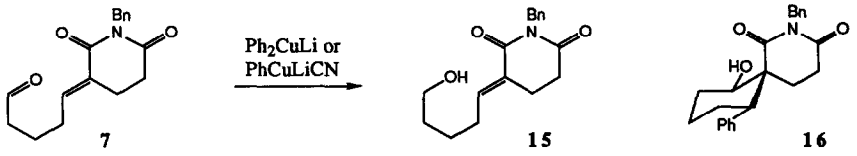


scheme 5

This leads to **12** with C1-N/C7-OH syn simple diastereoselectivity, which is also present in nitramine. The cyclohexane ring in the product prefers a conformation with the steric demanding phenylthio substituent in an equatorial, and the C7-OH in an axial position (see NMR-analysis). After reductive removal of the phenylthio substituent with Raney Ni, compound **13** was obtained, with the normal nitramine conformation: the C7-OH changed from axial to an equatorial position[18].

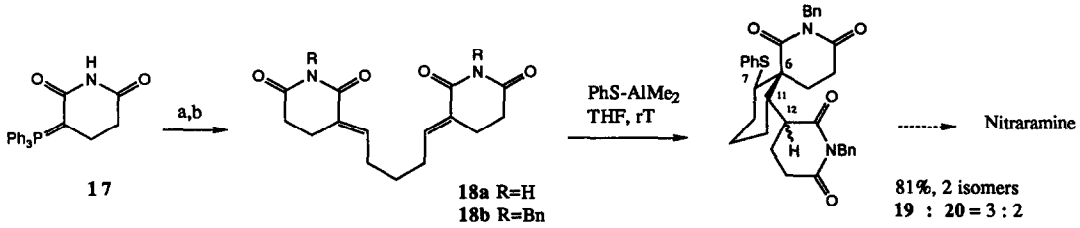
3b. Approach to (±)-nitraramine

The second piperidine ring that is present in nitraramine requires a C_5N-fragment as a nucleophile instead of the thiophenolate anion, to add to methylene glutarimide **7**. It should be noted that Michael addition of thiophenolate anion to **7** (scheme 5) is a reversible proces, which will not be the case with C-nucleophiles. Favourable properties with respect to 1,4-addition were expected to be found in Cu(I) derived nucleophiles, so phenyllithium derived cuprates were used in the Michael-induced cyclization reactions. None of the desired products was formed however; the only product that could be identified was **15**, the reduction product of the aldehydic part of **7**.



scheme 6

After considering the existence of 1,2-bispiperidyl pentane **5** (scheme 2) as a possible intermediate in the nitraramine biosynthesis, the thiophenol induced spirocyclization method (nitramine synthesis, scheme 4) was applied here succesfully. The symmetric bisglutarylidene pentane **18a** could be obtained conveniently from triphenylphosphoranylidene glutarimide **17**, by simply using stoichiometric amounts of the phosphonium ylid and glutaric dialdehyde in stead of excess aldehyde. Protection of the glutarimide N-H's with benzyl bromide produced the prochiral bisenone **18b**, which was directly suitable for spirocyclization with dimethylaluminium benzenethiolate (tetrahydrofuran, rT, 18h) giving a clean conversion into two isomeric products **19** and **20** in a ratio of 3 : 2.



a. Glutaric dialdehyde (0.5 eq.), tetrahydrofuran, reflux, 32h, 76%; b. Benzyl bromide, potassium carbonate, dimethyl formamide, rT, 20 h, 82,5%.

scheme 7

The stereostructure of both isomers **19** and **20** was analyzed by NMR (see below), which showed only differences in configuration at carbon atom 12. The C6-C7 anti-selectivity, directed by the phenylthio substituent, is the same as in the nitramine spirocyclization (scheme 4). The C6-C11 configuration we observed in both isomers is also anti, which is unsuitable for the nitraramine synthesis. Predictions about conformational preference in the transition state are difficult to make. Chelation of the aluminium enolate with the carbonyl requires an 8-membered ring, and will be less favourable in comparison with the nitramine synthesis.

4. NMR-ANALYSIS

Nitramine precursor 12.

The C6-C7 syn relationship in **12** was already proven by conversion into nitramine (scheme 4). Proton assignments were made from ^1H - ^1H and ^1H -^{13}C correlation spectra. The equatorial position of the phenylthio substituent at C11 was immediately clear from NMR (H-11: dxd, J=11.3, J= 4.1). To determine the relation between H11 and H7, NOE experiments had to be performed. Suitable chemical shift differences were obtained by changing the solvent from $CDCl_3$ to C_6D_6, containing 5% d-TFA to exchange the C7-OH, which had the same chemical shift as H7. Irradiation of H7 resulted in enhancement of the signals for H4 and H5.
Irradiation of H11 showed only enhancement of the cyclohexane protons $H_{eq}10$ and $H_{ax}8$.
The same NOE's were observed after acetylation of **12**, confirming the relationships to be: H11 and H7 anti, H7 and C=O anti, H11 and C=O syn.

Nitraramine precursors 19 and 20.

H7, the proton next to the phenylthio substituent and H11 are situated in a 1,3-diaxial position, as appeared from NOE-experiments. Since no enhancements were observed for the signals of the C4 and C5 glutarimide protons upon irradiation of H7 and H11, the C6-C7 as well as the C6-C11 configuration is assumed to be anti. The configuration of C12 in the second glutarimide ring, could not be established from NOE experiments.

CONCLUSIONS

An effective, nucleophile induced spiro-cyclization method is developed by adapting biosynthetic routes. The correct nitramine stereochemistry is obtained via an aluminium chelated transition state. Extention of this reaction may be possible by using a non-chelating thiophenolate complex, to obtain the corresponding isonitramine-configuration. Enantioselective spirocyclization by variation of the aluminium substituents needs further investigation.
The nucleophile induced spiro-cyclization is also succesful in the nitraramine synthesis. The unavailability however of a chelating aldehyde oxygen, directs the cyclization to anti (= isonitramine) selectivity, which is not suitable for nitraramine. Effects of the thiophenolate nucleophile upon the stereochemical coarse of the reaction will be examined by replacing dimethylaluminium benzenethiolate for e.g. diethylaluminium iodide in the cyclization step.

EXPERIMENTAL.

All melting points are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1310 spectrophotometer. The absorptions are given in cm^{-1}. NMR spectra were run on Bruker AMX 300, WM 250 and AC 200 instruments. Unless otherwise stated, IR and NMR spectra were take in $CHCl_3$ and $CDCl_3$ respectively. Mass spectra were obtained with a Varian Matt-711 spectrometer. Flash chromatography was performed on silica gel 60 (230 - 400 mesh). Thin-layer chromatography was carried out with F 254 plates.

*N-benzyl-triphenylphosphoniumacetamide bromide **10***
N-benzylbromoacetamide **9** (34.2 g, 0.15 mol) and triphenylphosphine (39.3 g, 0,15 mol) were refluxed in ethyl acetate (150 ml) during 15 minutes. Upon cooling crystalline N-benzyl-triphenylphosphoniumacetamide bromide **10** (51.0 g, 0.104 mol, 69%) was obtained. Mp: 240-242° C; IR: 3200, 1660, 1550, 1435; ^1H-NMR: 4.27 (d, 2H, J=6.2, CH_2N); 5.08 (d, 2H, J=14.4, CH_2P); 7.18 (s, 5H, Ph); 7.5-7.8 (m, 15H, PPh_3); 9.82 (m, NH).

*N-benzyl-2-triphenylphosphoranylidene glutarimide **11***
N-benzyl-triphenylphosphoniumacetamide bromide **10** (1.962 g, 4 mmol) was added to a solution of sodium (97 mg, 4.2 mmol) in methanol (anhydrous, 20 ml) at room temperature. After stirring during 15 minutes the phosphonium salt had dissolved, and methyl acrylate (0.453 ml, 5 mmol) was added. After stirring during 20 h the reaction was quenched with water. Extractive workup (ether), drying (sodium sulfate) and evaporation of the

solvents gave N-benzyl-2-triphenylphosphoranylidene glutarimide **11** as a sirup (quantitative), which was pure enough for Wittig reactions. To obtain a storable product, the crystalline hydrochloride was formed with concentrated hydrochloric acid from methanol/ether (80%).
11: IR: 1730, 1657, 1580; ^{1}H-NMR: 1.8-2.2 (m, 2H); 2.4 - 2.7 (m, 2H); 5.02 (s, CH_2Ph); 7.1 - 7.8 (m, 20 H);
11.HCl: Mp: 248°C (dec); IR: 3400, 2720, 2450, 1725, 1665, 1435; ^{1}H-NMR: 1.98 (m, 1H, H_{3a}); 2.44 (m, H_{3b}); 2.79 (m, J_{AB}=17.9, H_{4a}); 4.03 (dxdxd, 1H, J=17.9, 13.8, 5.1, H_{4b}); 4.76 (d, 1H, J_{AB}=14.2, CH_2Ph), 4.85 (d, J_{AB}=14.2, CH_2Ph), 6.91 (d, J=7.0, 2H, Ph); 7.10 (m, 3H, Ph); 7,5-7.98 (m, 15H, PPh_3); 8.25 (dxdxd, 1H, J=17.6, 12.8, 4.8, H_2).

N-benzyl-2-(1-pentene-5-al)-glutarimide 7
11 (1.0 g, 2 mmol, hydrochloride) was stirred and refluxed with glutaric dialdehyde (25% in water, 4 ml, 10.6 mmol) and sodium acetate (0.180 g, 2.2 mmol) in tetrahydrofuran (20 ml) under nitrogen, during 1.5 h. Evaporation of the tetrahydrofuran under reduced pressure and at a maximum temperature of 30°C was necessary to avoid co-polymerization of the product with glutaraldehyde, especially at higher concentrations. The residue was divided between water and a 5 : 1 mixture of cyclohexane and ethyl acetate. The aqueous layer was extracted 3 times with the organic solvent and the combined organic fractions were washed twice with water. Drying over sodium sulfate, evaporation and chromatography with dichloromethane containing 10% ethyl acetate, yielded successively **7** Z-isomer (0.044 g, 8%), **7** E-isomer (0.330 g, 58%) and dimer **18b** (0.020 g, 2%).
7-Z: IR: 1720 1670, 1640; ^{1}H-NMR: 1.80 (m, 2H, J=7.6, CH_2); 2.50 (dxt, 2H, J=7.4, J=1.3, CH_2-10); 2.47 - 2.75 (m, 6H, 3x CH_2); 4.98 (s, 2H, CH_2-Ar); 6.08 (t, J=7.4, =CH); 7.25-7.38 (m, 5H, Ph); 9.78 (t, 1H, J=1.3, O=CH);
7-E: IR: 1720, 1670, 1630; ^{1}H-NMR: 1.7-2.0 (m, 2H, CH_2); 2.26 (m, 2H, CH_2); 2.45 - 2.72 (m, 6H, 3x CH_2); 4.99 (s, 2H, CH_2-Ar); 6.93 (t, 1H, J=7.6, =CH); 7.21-7.39 (m, 5H, Ph); 9.76 (t, 1H, J=1.3, O=CH);
18b (dimer): IR: 1715, 1665, 1630; ^{1}H-NMR: 1.67 (quintet, 2H, F=7.2, CH_2); 2.27 (m, 4H, 2xCH_2); 2.58 - 2.71 (m, 8H, 4x CH_2); 5.00 (s, 4H, CH_2-Ar); 6.95 (t, 2H, J=7.6, =CH); 7.23-7.39 (m, 10H, Ph); ^{13}C-NMR: 20.46, 27.38, 27.74, 32.16, 43.33 (5x CH_2); 127.37, 127.68, 128.37, 128.75 (Ar), 137.33 (C_2); 141.81 (C_7); 166.34, 171.88 (C=O).

Aluminium catalyzed cyclization of 7.
Dimethylaluminium benzenethiolate was prepared according to a literature procedure[12]: A solution of thiophenol (0.154 g, 1.5 mmol) in tetrahydrofuran (2 ml) was added to a solution of trimethylaluminium (0.75 ml, 2M in hexane, 1.5 mmol) in tetrahydrofuran (1 ml) at 0° and the mixture was stirred for 20 minutes. A solution of aldehyde **7** (0.143 g, 0.5 mmol, E-isomer) in tetrahydrofuran (1.5 ml) was added and the resulting clear solution was stirred at room temperature for 48 h. After quenching the reaction with acetic acid, and extractive workup (ethyl acetate/water) the residue was purified by chromatography (ethyl acetate : PE 60/80 = 2 : 3), giving **12** (0.162 g, 82%) as an oil and starting material **7-E** (0.012 g, 8.4%).
12: IR: 3400 (broad), 1720, 1660, 1675; ^{1}H-NMR ($CDCl_3$): 1.5 - 2.1 (m, 7H), 2.27 (dxdxd, 1H, J= 14.6, J= 9.2, J= 5.6, H_{5a}); 2.67 (dxdxd, 1H, J= 15.0, J= 9.2, J= 5.6, H_{4a}); 2.89 (dxdxd, 1H, J= 15.0, J= 7.3, J= 5.6, H_{4b}); 3.50 (br, 1H, OH); 3.87 (dxd, 1H, J= 11.3, J= 4.1, H_{11}); 3.94 (br, 1H, H_7); 4.97 (AB-pattern, 2H, J= 14.0, CH_2Ph); 7.25 (m, 10H, Ar); ^{1}H-NMR (C_6D_6): 1.98 (dxdxd, 1H, J= 17.5, J= 10.0, J= 5.6, H_{4a}); 2.40 (dxdxd, 1H, J= 17.5, J= 13.3, J= 5.7, H_{4b}); 3.46 (br, 2H, H_7, OH); 4.06 (dxd, 1H, J= 21.1, J= 4.1, H_{11}); 4.97 (AB, 2H, J= 13.9, CH_2Ph), 6.9 - 7.6 (m, 10H, Ar); the OH at 3.46 ppm disappeares with d-TFA;
NOE: irradiation of H_7 showes enhancement of H_4, H_{5a} and H_8; irradiation of H_{11} showes enhancement of the OH (before deuterium-exchange), and of some cyclohexane protons;
^{13}C-NMR: 19.46, 21.73, 26.76, 29.18, 29.33 (5x CH_2); 43.71 (CH_2Ar); 50.63 C_{11}); 50.68 (C_6, spiro); 70.35 (C_7); 127.36, 128.34, 128.38, 129.03, 132.49, 134.63, 136.86 (Ar); 171.20, 176.62 (C=O);
12-acetate: Obtained from **12** with acetic anhydride in pyridine;
^{1}H-NMR: 1.5 - 2.3 (m, 8H); 1.88 (s, 3H, CH_3); 2.80 (m, 2H, H_4); 3.92 (m, 1H, H_{11}); 4.95 (AB-pattern, 2H, J= 14.3, CH_2Ph); 5.30 (br, 1H, H_7); 7.1 - 7.5 (m, 10H, Ar); NOE: irradiation of H_7 showes enhancement of H_4 and H_{5a}; irradiation of H_{11} showes only enhacement of some cyclohexane protons.
14 (Isonitramine-isomer): IR: 1720, 1660; ^{1}H-NMR: 1.2 - 2.0 (m, 9H); 2.20 (m, 1H) 2.56 - 2.91 (m, 2H, H_4); 4.29 (dxd, J= ca 4, J= ca 11, H_7); 4.96 (s, 2H, CH_2Ar); 7.27 (m, Ar).

Magnesium catalyzed cyclization of 7

Iodomagnesium benzenethiolate (0.4 mmol) was prepared from thiophenol and methyl magnesium iodide according to a literature procedure[13]. A solution of aldehyde **7** (0.057 g, 0.2 mmol, E-isomer) in tetrahydrofuran (0.5 ml) was added at -18°C and after an hour at this temperature the mixture was stirred at room temperature during two hours. Workup of the reaction mixture was performed as described at the preceeding reaction, yielding after chromatographic purification an unseperable mixture of **12** and **14a** (0.41 mg, 0.104 mmol, 52%) in a ratio of 3.4 : 1 (NMR). This mixture was seperated after the next desurfurization step.

Desulfurization of ***12***
Thio-ether **12** (0.090 g, 0.228 mmol) in tetrahydrofuran (3 ml) was stirred vigorously with excess Raney Ni (washed with tetrahydrofuran) for 30 minutes. Filtration and evaporation of the solvent gave **13** as a glass (0.053 g, 81%). IR: 1720, 1660; ^{1}H-NMR: 1.3 - 2.3 (m, 10 H); 2.75 (m, 2H, H_4); 3.35 (br, 1H, OH); 3.58 (dxd, after D_2O-exchange; J=3.5, J=7.3, H_7); 4.93 (AB-pattern, J=14, CH_2Ar); 7.30 (m, Ar); ^{13}C-NMR: 20.56, 21.71, 26.42, 28.69, 29.82 (5x CH_2); 43.06 (CH_2Ar); 45.94 C_6, spiro); 73.78 (C_7); 127.28, 128.11, 128.35, 137.27 (Ph), 171.66, 177.67 (C=O).

Isonitramine isomer ***14a***
The mixture of thioethers **12** and **14a** (0.41 mg, 0.104 mmol) was desulfurized as described above. Chromatographic seperation of the product gave **13** and **14b**.
14b: IR: 1720, 1660; ^{1}H-NMR: 1.2 - 1.9 (m, 10 H); 2.22 (dxdxd, 1H, J= 12.3, J= 6.0, J= 5.9 H_{5eq}); 2.65 (dxdxd, 1H, J= 17.9, J= 12.3, J= 5.8, H_{4ax}); 2.84 (dxdxd, 1H, J= 17.9, J= 5.7, J= 4.1, H_{4eq}); 4.29 (dxd, J=11.3, J=4.2, H_7); 4.9 (s, 2H, CH_2Ar); 7.30 (m, Ar).

N-benzyl-nitramine
Glutarimide **13** (0.053g, 0.185 mmol) was stirred with lithium aluminium hydride (0.038 g, 1 mmol) in anhydrous ether (2 ml) during 18 hours at room temperature, and an additional 2 hours at reflux temperature. Excess reducting agent was destroyed with methanol and the resulting mixture was worked up with N NaOH and extracted with dichloromethane containing 5% methanol. Chromatography with 3% methanol in dichloromethane (saturated with concentrated ammonia) over silicagel (pretreated with the same eluent) gave N-benzyl-nitramine[1g] as a sirup (0.034 g, 71%). ^{1}H-NMR: 1.0-1.8 (m, 12H); 1.91-2.33 (m, $2H_3$); 2.88 (d, 1H, J_{AB}=11.3, H_{1a}); 3.25 (d, J_{AB}=11.5, H_{1b}); 3.40 (AB-pattern, J=12.9, CH_2Ph), 3.47 (m, 1H, H_7); 7.2-7.4 (m, $5H_{Ar}$); ^{13}C-NMR: 21.02, 23.83, 24.51, 32.75, 36.80, 38.02, 38.82 (6 x CH_2 + spiro-C); 54.34, 59.16, 63.51 (3 x CH_2); 79.08 (C_7); 127.29, 128.37, 129.09, 137.57 (Ar).

E,E-1,5-di-(glutarylidene)pentane ***18a***
Triphenylphosphoranylidene glutarimide **17**[10] (0.746 g, 2 mmol) and glutaric dialdehyde (25% in water, 0.377 ml, 1 mmol) were refluxed in tetrahydrofurane (8 ml) under nitrogen during 32 h. The solvent was removed by evaporation, and the residu was coevaporated with methanol. Trituration of the residu with methanol yielded **18a** as a white solid (0.216 g, 0.76 mmol, 76%) Mp: 200-205° (recrystallized from chloroform/methanol); IR (KBr): 3190, 3090, 1710, 1675, 1635; ^{1}H-NMR (DMSO-d_6): 1.53 (quintet, J=7.2, 2H); 2.20 (m, 4H); 2.49 (m, 8H); 6.67 (t, 2H, J=7.3, =CH); 10.63 (s, 2H, N-H); According to the NMR-spectra, a small amount of the mixed, E,Z-alkene was present (=CH at 6.1 and 6.67 ppm), which was removed by chromatography after the next benzylation step.

E,E-1,5-di-(N-benzyl-2-glutarylidene)pentane ***18b***
E,E-1,5-di-(glutarylidene)pentane **18a** (0.145 g, 0.5 mmol) was stirred with potassium carbonate (anhydrous, 0.346 g, 2.5 mmol) and benzylbromide (0.143 ml, 1.2 mmol) in DMF (1.5 ml, dest. from calcium hydride) under N_2 during 20 h. Di-ethylether/water workup and flashchromatography (ethyl acetate/PE = 1/2) gave **18b** as a sirup (0.194 g, 0.413 mmol, 82.5%) and a small amount of the E/Z-isomer (0.01 g, 2%).
For spectral data, see preparation of **7**.

Spirocyclization of ***18b***
Dimethylaluminium benzenethiolate was prepared according to the literature procedure (described for **17**), from thiophenol (41 µl, 0.4 mmol) in tetrahydrofuran (0.5 ml) and trimethylaluminium (0.2 ml, 2M in hexane, 0.4 mmol) in tetrahydrofuran (0.5 ml) at 0°. A solution of 1,5-di-(N-benzyl-2-glutarylidene)pentane **18b** (0.094 g, 0.2 mmol, E,E-isomer) in tetrahydrofuran (0.3 ml) was added and the resulting clear solution was stirred at room

temperature for 20 h, during which time an aluminiumcomplex had precipitated. After quenching the reaction with acetic acid, extractive workup (ethyl acetate/water) and evaporation, the residue was triturated with ethyl acetate. Filtration yielded isomer **20** as a white solid (0.0386 g, 0.067 mmol, 33.5%). The filtrate was purified by chromatography (7 → 12% ethyl acetate in dichloromethane), giving isomer **19** (0.055 g, 0.096 mmol, 48%) as a white foam.

19: IR: 1715, 1668, 1575; ^{1}H-NMR (CDCl3): 1.17 (dxdxd, 1H, J= 13, J= 13, J= 3.6, $H_{9\text{-}ax}$); 1.4 - 2.1 (m, 10H); 2.19 (dxdxd, 1H, J= 14.8, J= 6.7, J= 4.5, H_{5a}); 2.55 (m, 1H, J_{AB}= 17.7, H_{14a}); 2.73 (dxdxd, 1H, J= 17.1, J= 6.0, J= 4.4, H_{4a}); 3.18 (dxdxd, 1H, J= 17.3, 12.2, 6.8, H_{4b}); 3.20 (m, 1H, J_{ax}= 10.5, H_{11}); 3.64 (dxd, 1H, J= 12.5, J= 3.7, H_7); 4.77 (AB-pattern, 2H, J= 13.8, CH_2Ph); 4.83 (d, 1H, J_{AB}= 13.4, CH_2Ph); 5.03 (d, 1H, J= 13.4, CH_2Ph); 7.0 (m, 2H, Ar); 7.2 - 7.5 (m, 13H, Ar); ^{1}H-NMR (C_6D_6); ^{13}C-NMR: 18.63, 20.43, 22.88, 26.01, 29.37, 30.91, 32.09 (7 x CH_2); 43.36, 43.54 (2 x CH_2-Ph); 44.04, 45.60 (C_{11}/C_{12}); 51.41 (spiro-C_6); 58.19 (C_7); 127.47, 127.58, 127.76, 128.22, 128.31, 129.03, 129.16, 129.63, 132.58, 134.23, 137.21, 137.38 (3 x Ph), 171.07, 171.67, 172.58, 175.83 (4 x C=O);
NOE: irradiation of H_7 showed enhancement of the H_{11} signal; irradiation of H_{11} showed enhancement of H_7; no effect was observed on the glutarimide CH_2-4 and CH_2-5 (see **12**).

20: Mp: 227-230°C; IR (KBr): 3440, 1718, 1605, 1575; ; ^{1}H-NMR ($CDCl_3$ + 10% CD_3OD): 1.1 - 2.2 (m, (m, 12H); 2.58 (dxdxd, 1H, J= 2.2, 6.3 and 16.5, H_{4a}); 2.67 (dxd, 1H, J= 3.3 and 12.9, H_{11}); 3.10 (dxdxd, 1H, J= 6.7, 13.1 and 18.3, H_{4b}); 3.24 (d, 1H, J= 15.6, CH_2Ph); 3.70 (dxd, 1H, J= 4.5 and13.0, H_7); 4.77 (d, 1H, J= 13.9, CH_2Ph); 4.79 (d, 1H, J= 15.6, CH_2Ph); 5.03 (d, 1H, J= 13.9, CH_2Ph); 6.95 (d, 2H, J= 6.8, CH_2Ph, ortho-H's); 7.0 - 7.5 (m, 11H, Ar); 7.64 (dxd, 2H, J= 1.5 and 8.2, SPh, ortho-H's); ^{13}C-NMR ($CDCl_3$ + 10% CD_3OD): 16.55, 22.92, 23.51, 25.67, 29.96, 30.60, 32.23 (7 x CH_2); 42.91, 44.32 (2 x CH_2-Ph); 43.54 (C_{11}); 50.90 (C_7); 51.80 (spiro-C_6); 126.50, 127.09, 127.34, 128.12, 128.16, 128.23, 128.30, 128.62, 128.72, 129.03, 129.31, 132.52, 133.03 ($\underline{C}H_{Ar}$); 135.43, 137.05, 139.99 (3x $\underline{C}_{Ar}$); 172.39, 173.45, 173.67 (C=O). NOE: irradiation of H_7 showed a strong enhancement of the H_{11} signal, and weaker enhancements of H_{8eq} and $H_{9\text{-}ax}$. No relation between $H_{4/5}$ and resp. H_7 and H_{11} was observed.

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