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# Biomimetic Synthesis of Quinolizidine Alkaloids

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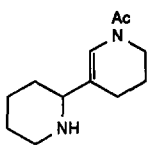
*Key Words: Glutarimide; Biomimetic; Lupine alkaloids; Enantioselective; Quinolizidine;*

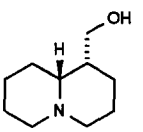
*Abstract: Quinolizidine alkaloids are synthesized from glutarimide ylides via a piperidine ring transformation that is based on the lupinine biosynthesis. A short enantioselective bispiperidine synthesis using R-phenylglycinol as a chiral precursor is described.*

## INTRODUCTION

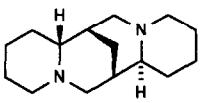
The biosynthesis of the bispiperidine, quinolizidine (lupinine) and the more complex tri- and tetrameric piperidine alkaloids (sparteine, ormosanine) is known for many years to be based on L-lysine[1]. The last questions concerning the lupinine biosynthesis were answered more recently by Golebiewski and Spenser[2], excluding a general, symmetric intermediate. Their tracer experiments in Lupinus luteus with $^{15}N$ and $^{13}C$ labelled cadaverine showed that the stereochemistry of the quinolizidine alkaloids was determined during the piperideine (**1**) dimerization reaction (scheme 1).



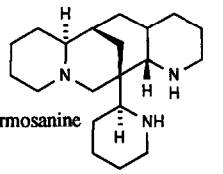
ammodendrine



lupinine



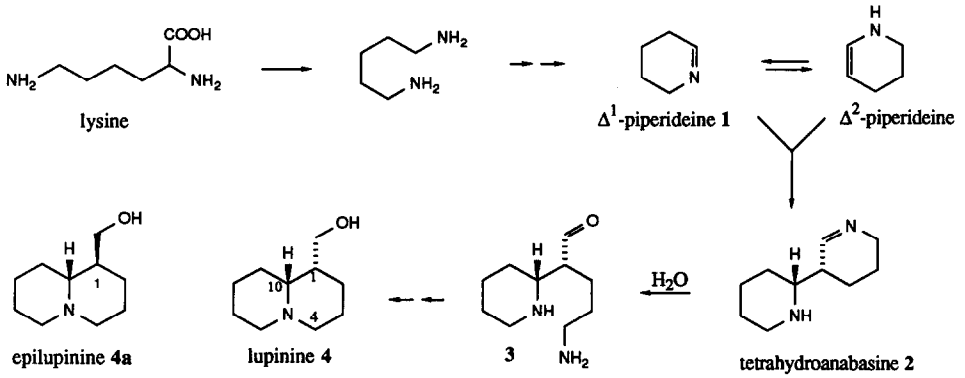
sparteine



ormosanine

The sterically more favoured bispiperidine **2** (tetrahydroanabasine) is formed and after rotation around the central bond, **2** is transformed by ring opening/ring closure into lupinine **4**, possessing the less favourable $C_1$-$C_{10}$ cis stereochemistry with the hydroxymethyl substituent in axial position. Direct transformations of lupinine **4** into 1-epilupinine **4a**, which is also found as a natural product, are described in the literature.

Based on the biosynthetic scheme, we were interested in the question whether the chemical synthesis of these alkaloids could also be realized using stabilized piperidein-like starting materials.




**Scheme 1**

## CHEMISTRY

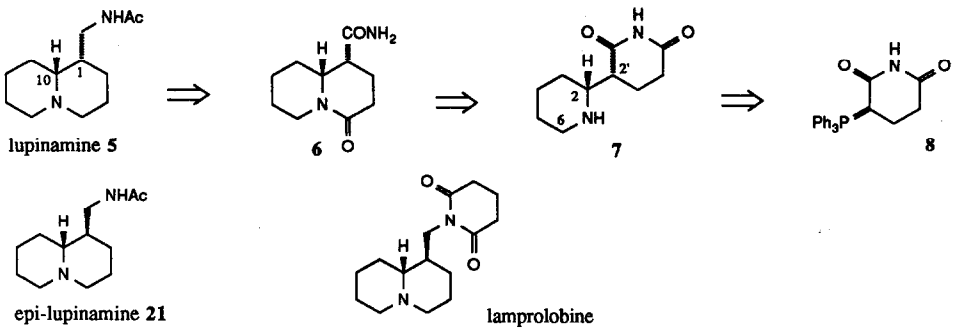
Most of the (epi)lupinine syntheses published, are examples of applications of new synthetic methods[3,4]. When the quinolizidine $C_1$-$C_{10}$ bond is formed in the reaction step that determines the ultimate stereochemistry, the diastereomer with the thermodynamically favoured epilupinine stereochemistry (**4a**, $H_1$-$H_{10}$ trans) will predominate. Preference for lupinine-stereochemistry was observed during hydrogenation reactions[5] of for instance $C_1$-$C_{10}$ double bonds (cis-addition). Nitrone cycloaddition followed by rearrangement[6] and acyclic ester anion alkylation[4] also showed lupinine-selectivity.

*Synthetic scheme.*

The quinolizidine synthesis we describe here follows the biosynthetic bispiperidine ring opening/ring closure sequence from scheme 1, leaving the stereochemistry at the connective bond in the bispiperidine **7** intact (retrosynthetic scheme 2). The glutarimide nitrogen is not removed from the quinolizidine, leading to aminolupinane **5**. The $C_1$-epimer of **5** is a useful lupinine analog in the synthesis of for instance lamprolobine[7]. The easy accessible glutarimide ylid **8**[8] was in all examples our starting material. Instead of an oxidative/hydrolytic piperidine-ring opening, a glutarimide-ring opening catalyzed by nucleophiles was used. The quinolizidine $C_1$-$C_{10}$ stereochemistry is determined in an intramolecular Michael reaction[9].

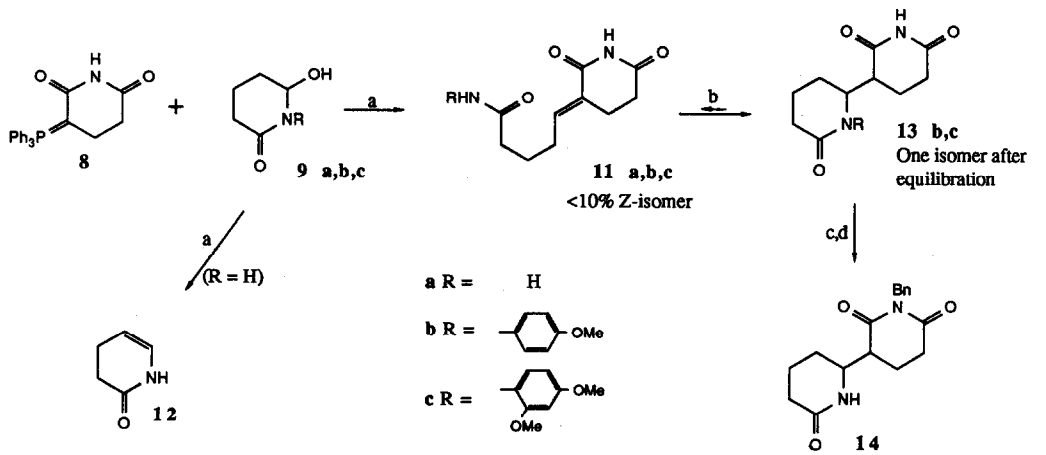
*Via Wittig reaction with hydroxypiperidones.*

Stabilized glutarimide ylide **8** was used in Wittig reactions with several aldehydic $C_5N$-fragments[10], giving α,β–unsaturated imides[8] as Michael acceptors[11,12]. The most simple hydroxypiperidone **9a**[13] however, gave




**Scheme 2**

only small amounts of the desired alkene, the unsaturated piperidone **12** being the main product (scheme 3). N-methoxyphenyl substituted hydroxypiperidone **9b** gave better results in a Wittig reaction with diethylisopropyl amine as a ring opening catalyst. The aromatic N-substituent was also favourable for the Michael reaction: after refluxing **11b** during two days with diazabicyclo-undecene in dichloromethane, a 4 : 1 mixture of two diastereomers **13b** was formed, from which the main isomer was isolated by crystallization. Recycling the mother liquor twice (DBU/dichloromethane) gave a total yield of 92.5% of one isomer. Elucidation of the stereochemistry of this single bonded bispiperidine **13b** proved to be difficult with NMR techniques, but was expected to be easier after ring transformation of **13b** to a quinolizidine ring system.




**Scheme 3**

a) 1,2-dichloroethane, excess diethylisopropylamine, 40 hours reflux;

b) diazabicycloundecene (cat), dichloromethane, 44 hours reflux, 92% (one isomer after 3 cycles);

c) benzyl alcohol, triphenylphosphine, diethyl azodicarboxylate, dichloromethane, 86%;

d) 2 eq. ceric ammonium nitrate, acetonitrile, 28%.

Removal of the methoxyphenyl protecting group from **13b** with ceric ammonium nitrate, according to a literature procedure for β-lactams[14], gave several unidentified, water soluble products and almost no unprotected amide. After substituting the imide N-H by a benzyl group under Mitsunobu conditions, reaction with ceric ammonium nitrate gave **14** with a maximum yield of 28%. The same sequence of reactions was performed with the 2,4-dimethoxyphenyl protecting group, leading to **13c** via **11c**. Attempts to remove this aromatic substituent via oxidation (ceric ammonium nitrate or DDQ) however did not lead to the desired product. An alternative protective group is the (di)-methoxybenzyl, which is easier to remove, but has less favourable properties during the Wittig and Michael reaction. Since no quinolizidines have been synthesized via this sequence, the stereochemistry of the bispiperidines **13** could not be determined.

*Via Wittig reaction with glutaric aldehyde.*

Meanwhile we started a more direct bispiperidine synthesis with glutaric aldehyde **10** as a $C_5$-fragment, followed by introduction of the nitrogen via reductive amination (scheme 4). Wittig reaction of glutarimide ylide **8** with 3 equivalents of glutaric aldehyde (25% in water) gave 76% aldehyde **15** and ca 10% of the bis-glutarimide (resulting from double Wittig reaction). Introduction of the nitrogen atom by standard reductive amination procedures was not very successful. Better results were obtained with benzylamine and tetrabutylammonium cyanoborohydride[15] in dichloromethane at 0°. After completion of the reductive amination exess triethylamine was added to decompose the secondary amine/borane complex, which resulted in ring closure to give a 4.4 : 1 mixture of diastereomers (±)**16a** and (±)**17a**[16].

After debenzylation ($Pd/H_2$) the crucial ring opening/ring closure was tested with the main isomer (±)**16b**[16]. Important is the use of a nucleophile that gives carbonyl-attack with good regioselectivity, *or* a nucleophile that can form back the glutarimide (via **20**).

a,b) The use of anilines and alcohol/tertiary amine combinations (via **19a, b**) as nucleophiles gave low regioselectivity and irreversible glutarimide opening;

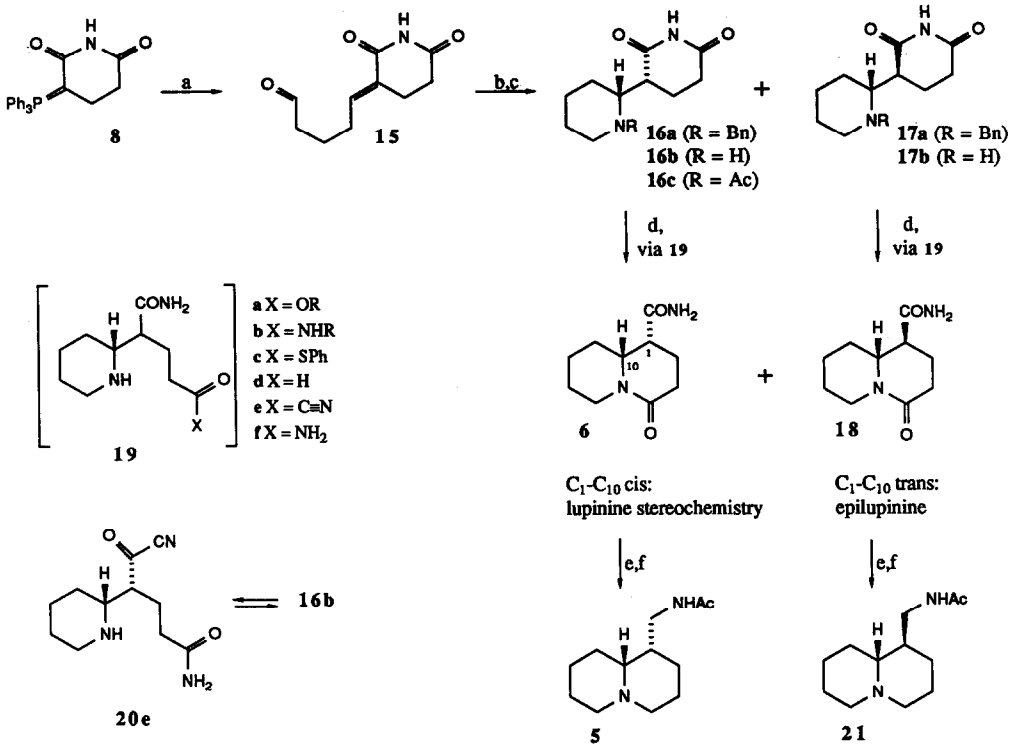
c) Sodium thiophenoxide in THF (reacting via **19c**) resulted in extensive isomerization of the starting material **16b** to **17b** (scheme 6); no rearranged product was observed;

d) Reduction of the glutarimide with DIBAH or Super hydride[18] (via **19d**) not only showed low regioselectivity, but also overreduction to the corresponding alcohol;

e) Potassium cyanide in dimethylformamide at 110° was an effective catalyst, giving a high yield of quinolizidines **6** and **18**. High regioselectivity was expected via reversible formation of acyl cyanide **20e**. The major product was the isomerized, more stable quinolizidine isomer **18** (**6** : **18** ≈ 1 : 4);

f) Ammonia in methanol was the best of the nucleophiles tested, giving a **6** : **18** ratio better then 2 : 1. Bisamide **19f** as a symmetric intermediate solved the problem of regioselectivity. Surprisingly, the starting material **16b**[17] was more stable towards isomerization in ammonia/methanol (at 0°) then in neutral solution. Deprotonation of the glutarimide N-H obviously decreases the acidity of the α-hydrogens, without preventing nucleophilic attack of ammonia on one of the carbonyls (scheme 6).

To check the base-catalyzed equilibration of the end products, isomerization experiments were performed with the quinolizidine **6**. Under basic conditions (DBU or sodium methoxide in THF, reflux) a ratio of **6** : **18** ≈ 1 : 4 was found, in favour of the trans-isomer.




**Scheme 4**

a) 3 eq. glutaric aldehyde, tetrahydrofuran, reflux, 1 hour, 76%;

b) benzylamine, tetrabutylammonium cyanoborohydride, dichloromethane, 0°, 5 hours, then excess triethylamine, room temperature, 16 hours 70%;

c) $H_2$, Pd/C, methanol/acetic acid, 100%; d) 62- 84%, see text;

e) lithium aluminium hydride, tetrahydrofurane;

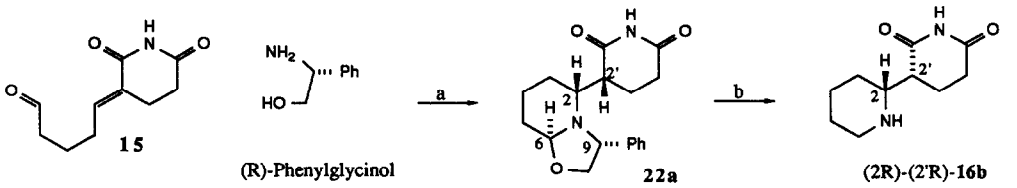
f) acetic anhydride, reflux 50-55% (two steps).

The isomers **6** and **18** were separated by chromatography and crystallization and reduced to the resulting air-sensitive amines with lithium aluminium hydride. Acetylation of **18** gave the corresponding N-acetyl-(±)-epi-lupinamine **21** and acetylation of isomer **6** gave N-acetyl-(±)-lupinamine **5**.

## ENANTIOSELECTIVE SYNTHESIS

For an enantioselective synthesis a chiral source of nitrogen had to be used instead of benzylamine. The use of (+)-α-phenylethylamine in the reductive amination step gave, via the imine, the corresponding secondary amine, but ring closure required long reaction times and resulted in a complex mixture of isomers[19].

An efficient method for enantioselective piperidine synthesis developed by H-P.Husson et al.[20] applies (R)-phenylglycinol and glutaric aldehyde. In our case, reaction of aldehyde-alkene **15** with (R)-phenylglycinol and triethylamine in refluxing acetonitril directly gave a mixture of 2-(2-glutaryl)-6-oxazolopiperidines (-)-**22a** and **22b**[21], without isolation of intermediates (scheme 5). This mixture consisted of two not crystalline isomers at the glutarimide carbon, which were difficult to separate (81%, ratio **22a** : **22b** = 2.5:1) and ca 5% of two minor isomers that could be easily removed.




**Scheme 5**

a) Acetonitrile, triethylamine, reflux, 8 hours, 81%;

b) $H_2$, $Pd(OH)_2$, methanol/acetic acid, 100%.

The first step of the Michael addition is face-selective and, as expected, independent of the geometry of the double bond. The second step, protonation of the stabilized carbanion at the 2-position of the glutarimidering is clearly far less selective. This is also shown in the (racemic) N-benzyl-3-piperidylglutarimide synthesis (**15** → **16a** + **17a**, scheme 3) and in the Michael addition towards glutarimides nucleosides [11,12] (an almost 1 : 1 mixture of diastereomers was formed). Equilibrium experiments were performed with pure (-)-**22a**: under the same reaction conditions an identical mixture of (-)-**22a** : **22b** = 2.5:1 was formed. With diazabicycloundecene in dichloromethane at room temperature, a complex mixture of at least 4 isomers was formed, indicating a reverse Michael reaction.

Hydrogenolysis of pure (-)-**22a** with Pearlman's catalyst in methanol/acetic acid at 60 psi gave (+)-**16b**, while hydrogenolysis of a 2.5 : 1 mixture of isomeric oxazolidines 3-piperidylglutarimides **22** under the same conditions, gave (+)-**16b** and **17b** in the same ratio.This confirms the origin of the diastereomers **22a** and **22b** as glutarimide $C_{2'}$-isomers.

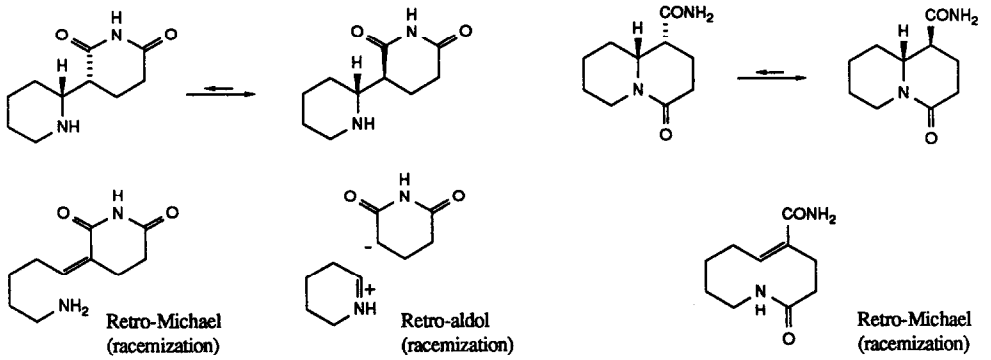
In the next crucial ring transformation step, potassium cyanide in dimethylformamide at 110° gave almost completely racemized quinolizidines **6** and **18**[22,23] (optical rotations < 2°). Ammonia in methanol also resulted in racemization, but to a smaller extent[23]. The isomerization that was observed during the racemic synthesis (scheme 4), obvious proceeds partially via a retro-reaction (scheme 6). We are currently looking for a nucleophile, that will be able to perform this reaction without racemization.

*NMR*

The main isomer (-)-**22a** was examined by NMR. Alerted by a recent publication[24] concerning NMR-measurements on oxazolidines, careful proton assignments were made by $^1H$-$^{13}C$ correlation and doubleresonance techniques. nOe-experiments showed a H-2, H-9 cis-relationship; trans-relations were observed between H-2, H-6 and H-6, H-9.

The configuration of $C_{2'}$ of the glutarimide ring could not be determined with certainty by NMR, but is proven by conversion to **16b** (see above).

Since $C_9$ is derived from (R)-phenylglycinol, the configuration of (-)**22a** is 2R,2'R,6S,9R, as is shown in scheme 5.




**Scheme 6**

*Conclusion.*

For the synthesis of bispiperidines and their biomimetic rearrangement into quinolizidines, glutarimides have the appropriate stability and functionality. During the intramolecular Michael reaction the bispiperidines with "lupinine"-stereochemistry were formed predominantly. The acidity of the glutarimide α-protons however requires less basic nucleophiles to realize the bispiperidine/quinolizidine ring conversion without concommitant isomerization.

The asymmetric bispiperidine synthesis base on (R)-(-)-phenylglycinol is very short, and effectively gives the correct relative and absolute stereochemistry that is present in lupinine. The isomerization observed in the racemic syntheses, appears to be a more complicated retro-Michael or retro-aldol reaction,which in this case results in the formation of partial racemized quinolizidines.

## EXPERIMENTAL

All melting points are uncorrected. Melting points were recorded on a Perkin Elmer 1310 spectrophotometer. The absorptions are given in $cm^{-1}$. NMR spectra were run on Bruker 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. Optical rotations were measured on a Perkin Elmer 241 polarimeter. Flash chromatography was performed on silica gel 60 (230 - 400 mesh). Thin-layer chromatography was carried out with F 254 plates.

*Triphenylphosphoranylidene glutarimide* ***8***.

Methyl acrylate (31.7 ml, 0.35 mol) was added to a stirred suspension of triphenylphosphoranylidene acetamide[25] (95.7 g, 0.3 mol) in 350 ml dry methanol. After stirring for 24 hours the thick suspension was stirred at 30° for 2 hours and cooled in the refrigerator overnight. The product was isolated by filtration and washed with cold methanol (twice) and with ether. Air-drying gave **8**[8] as a white solid in 79% yield (88.1 g, 0.236 mol).

Mp: 262-263° (dichloromethane/ether); IR: 3400, 1685, 1600. $^1$H-NMR: 2.0-2.6 (m, 4H); 7.6 (M, 16H). Anal.: $C_{23}H_{20}N\,O_2P$ = 373.39; calc. C: 73.98; H: 5.40; N: 3.75; Found: C: 73.84; H: 5.35; N: 3.83.

*N-Methoxyphenyl-6-hydroxy-2-piperidone* **9b**.
Glutaric anhydride (5.7 g, 50 mmol) and p-anisidine (6.15 g, 50 mmol) were heated with stirring at 250 - 260° during 30 minutes. The reaction mixture was cooled to ca 100° and refluxed with acetic anhydride (50 ml) during 3 hours. Evaporation of the excess reagent and crystallization the residu twice from methanol gave 4.3 g (39%) *N-Methoxyphenyl-glutarimide*. Mp 168-171°; IR: 1730, 1680, 1600, 1510; $^1$H-NMR: 2.09 (quintet, 2H, J = 6.7); 2.81 (t, 4H, J = 6.6); 3.82 (s, 3H); 6.99 (m, 4H, Ar).
Lithium triethylborohydride[18], (Superhydride, 10.5 ml of a 1N solution in toluene, 10.5 mmol) was added dropwise to a solution of N-methoxyphenyl-glutarimide (2.19 g, 10 mmol) in 50 ml dichloromethane at -78°, during 45 min. TLC showed both starting material and overreduced alcohol as side products. After 30 minutes at this temperature ammonium chloride in water (50 ml, semi-saturated) was added and the mixture was stirred at room temperature for 2 hours. The organic layer was washed with water and dried over sodium sulfate. Crystallization from ethyl acetate and chromatography of the filtrate (2% methanol in ethyl acetate) gave a combined yield of 1.35 g *N-Methoxyphenyl-6-hydroxy-2-piperidone* **9b** (61%). mp 125-129°. IR: 3590 and 3200-3500 (OH), 1640, 1600, 1510. $^1$H-NMR: 1.75 - 2.75 (m, 7H), 3.82 (s, 3H), 5.23 (m, 1H, $H_6$); 6.92 - 7.18 (AB- pattern, 4H, J = 9.0).

*N-(2,4-dimethoxyphenyl)-6-hydroxy-2-piperidone* **9c**.
Glutaric anhydride (5.7 g, 50 mmol) and 2,4-dimethoxyaniline (7.65 g, 50 mmol) were reacted as described for **9b**. Crystallization of the product (active carbon treatment) from ethyl acetate/hexanes gave 4.55 g slightly coloured product. Chromatography of the filtrate gave a combined yield of 5.66 g (45.5%) *N-2,4-dimethoxyphenyl-glutarimide*. Mp 122-124.5 °; IR: 1730, 1680, 1610, 1590, 1510; $^1$H-NMR: 2.08 (quintet, 2H, J = ca 6.5); 2.80 (t, 4H, J = ca 6.5); 3.75 (s, 3H); 3.81 (s, 3H); 6.55 (m, 2H, Ar); 6.96 (m, 1H, Ar).
Lithium triethylborohydride reduction of N-2,4-dimethoxyphenyl-glutarimide (2.49 g, 10 mmol) was performed as described for **9b**, giving a total yield of 0.82 g **9c** (32.5%) Crystallization was possible after chromatography. Mp 109-112°; IR: 3590 and 3200-3500 (OH), 1640, 1610, 1590 and 1510; $^1$H-NMR: 1.75 - 2.75 (m, 7H), 3.81 (s, 6H), 5.08 (m, 1H, $H_6$); 6.52 (m, 2H); 7.05 (m, 1H).

*Wittig reaction with N-Methoxyphenyl-6-hydroxy-2-piperidone* **9b**.
Triphenylphosphoranylidene glutarimide **8** (1.12 g, 3 mmol) and N-methoxyphenyl-6-hydroxy-2-piperidone **9b** (0.442 g, 2 mmol) were refluxed with N,N-di-isopropylethylamine (0.2 ml, 0.8 mmol) and 5 mg radical inhibitor (3-tert-butyl-4-hydroxy-5-methylphenyl-sulfide[25]) in 1,2-dichloro-ethane (20 ml) for 70 hours. The blue reaction mixture was evaporated and dissolved in methanol, from which 0.145 g crystalline starting ylide **8** was recovered. Chromatography of the mother liquor (ethyl acetate) gave resp. 0.553 g **11b** (E-isomer) and 0.040 g **11b** (Z-isomer). Total yield: 0.597 g, 94%.
**11b**(E): mp 150-151.5 ° (ethyl acetate); IR: 3420 (amide-NH), 3360 (imide-NH), 1715, 1680, 1630, 1500; $^1$H-NMR: 1.92 (quintet, J=7.2, 2H); 2.37 (m, 4H); 2.63 (m, 4H); 3.79 (s, 3H); 6.85 (d, 2H, J=9.0, Ar); 6.99 (t, 1H, J=7.7, C=CH); 7.32 (s, amide-NH); 7.40 (d, 2H, J=9.0, Ar); 8.13 (s, imide-NH); Acc Mass: Calc. for $C_{17}H_{20}N_2O_4$: 316.1423; found: 316.1419;
**11b**(Z): mp 128-132 °; IR: 3430, 3370, 1715, 1700, 1680, 1640, 1510; $^1$H-NMR: 1.90 (quintet, 2H, J=7.2); 2.37 (m, 2H); 2.58 (s, 4H); 2.69 (m, 2H); 3.77 (s, 3H); 6.21 (t, 1H, J=7.8, C=CH); 6.82 (d, 2H, J=9.0, Ar); 7.43 (d, 2H, J=9, Ar); 7.71 (s, NH); 8.25 (s, NH).

*N-(4-methoxyphenyl)-6-(2-glutaryl)-2-piperidone* **13b**.
α,β-unsaturated imide **11a** (0.158 g, 0.5 mmol) was stirred with diazabicycloundecene (90 mg, 0.6 mmol) in dichloromethane (8 ml, distilled from $P_2O_5$) during 70 hours. The solution was diluted with hexanes and filtered over silicagel. The products were eluted with 5% methanol in ethyl acetate. Evaporation and crystallization from ethyl acetate with a small amount of hexanes (seeding with pure **13b** was necessary) gave, after recrystallization from dichloromethane/hexanes, a first crop of 0.082 g. The filtrates were collected and reacted again with diazabicycloundecene in dichloromethane. After 3 cycles a total yield of 0.146 g (92.4%) **13b** was obtained.
Mp: 185-187°; IR: 3365, 1720, 1705, 1640, 1600, 1505; $^1$H-NMR: 1.5-2.9 (m, 11H); 3.81 (s, 3H); 4.68 (m, 1H, CH-N); 6.93 (d, 2H, J=8.9); 7.13 (d, 2H, J=8.9); 7.93 (s, NH); $^{13}$C-NMR: 17.53; 19.34; 22.85; 31.68; 33.07 (5x $CH_2$); 43.60 (2'); 55,18 ($CH_3O$); 58.41 ($C_2$); 114.64; 127.98; 156.50; 158.40 (Ar); 171.54; 172.26 (C=O). Acc Mass: Calc. for $C_{17}H_{20}N_2O_4$: 316.1423; found: 316.1431;
The minor isomer was not isolated in pure form, but only detected by NMR in crude reaction mixtures: 4.27 (m, $C_2$H-N); 7.83 (s, NH).

*N-benzylation of* **13b**.
Diethyl azodicarboxylate (0.079 ml) was added dropwise to a solution of **13b** (0.095 g, 0.3 mmol), triphenylphosphine (0.11 g, 0.5 mmol) and benzylalcohol (0.054 g, 0.5 mmol) in a mixture of tetrahydrofuran (3 ml) and dichloromethane (3 ml) at 0°. After stirring at room temperature for 3 hours the reaction mixture was evaporated and chromatographed with ethyl acetate. 0.105 g *N-4-methoxyphenyl-6-(2-N-benzyl-glutaryl)-2-*

*piperidone* (85%) was obtained as a glass.
IR: 1725, 1670, 1640, 1600, 1508; $^1$H-NMR: 1.5-2.7 (m, 11H); 2.82 (t.t, 1H, J=17.2, J=3); 3.79 (s, 3H); 4.68 (m, 1H); 4.86 (AB-system, 2H, J=13.9); 6.91 (d, 2H, J=8.9, Ar); 7.12 (d, 2H, J=8.9, Ar); 7.27 (s, 5H).

*6-[2-(N-benzyl-glutaryl)]-2-piperidone* **14**.
An icecold solution of ceric ammonium nitrate (CAN, 0.160 g, 0.3 mmol) in water (1 ml) was added to a solution of N-4-methoxyphenyl-6-(2-N-benzyl-glutaryl)-2-piperidone (40.6 mg, 0.1 mmol) in acetonitrile (1 ml) at 0°. After stirring for 30 min. the reaction mixture was quenched with a sodium bisulfite solution, followed by aqueous $NH_4OAc$. Extraction with ethyl acetate containing 5% methanol and chromatography (ethyl acetate/methanol) yielded 4 mg **14** (27%) as a glass. Scaling up the reaction did not give any improvement.
IR: 3380. 1722, 1670, 1645; $^1$H-NMR: 1.3-2.7 (m, 10H); 2.88 (dxdxd, 1H, J=3.1, J=4.5, J=17.6); 3.85 (m, 1H); 4.94 (s, 2H); 7.06 (s, N-H); 7.3 (m, 5H, Ar).

*Wittig reaction with N-(2,4-dimethoxyphenyl)-6-hydroxy-2-piperidone* **9c**.
Triphenylphosphoranylidene glutarimide **8** (1.12 g, 3 mmol) and N-(2,4-dimethoxyphenyl)-6-hydroxy-2-piperidone **9c** (0.502 g, 2 mmol) were refluxed with N,N-di-isopropylethylamine (0.2 ml, 0.8 mmol) and 5 mg radical inhibitor (see **9b**) in dichloroethane (20 ml) for 70 hours. The reaction mixture was evaporated and dissolved in methanol, from which 0.1 g crystalline starting ylide **8** was recovered. Chromatography of the mother liquor was performed with ethyl acetate/hexanes/methanol 50/50/1 instead of ethyl acetate, to improve the separation from triphenylphosphinoxide.The total yield of the alkenes **11c** was 0.607 g, 88% (E : Z ≈ 9 : 1).
**11c**(E): mp 159-163° (ethyl acetate); IR: 3420 (amide-NH), 3370 (imide-NH), 1715, 1690, 1640, 1520; $^1$H-NMR: 1.93 (quintet, J=7.2, 2H); 2.41 (m, 4H); 2.62 (m, 4H); 3.78 (s, 3H); 3.84 (s, 3H); 6.5 (m, 2H, Ar); 6.99 (t, 1H, J=7.6, C=CH); 7.53 (s, amide-NH); 8.20 (m, 2H, HAr and imide N-H);
**11c**(Z): IR: 3430, 3370, 1715, 1700, 1680, 1640, 1510; $^1$H-NMR: 1.8-2.8 (m, 10H); 3.79 (s, 3H); 3.85 (s, 3H); 6.3 (t, 1H, J=7.8, C=CH).

*N-(2,4-dimethoxyphenyl)-6-(2-glutaryl)-2-piperidone* **13c**.
**11c** (E/Z-mixture, 0.173 g, 0.5 mmol) was stirred with diazabicycloundecene (0.09 g, 0.6 mmol) in dichloromethane (7 ml) at room temperature during 2 days. Chromatography using ethyl acetate gave 0.111g of the main isomer **13c**, 0.042 g of a 1/1 mixture of two isomers and 0.021 g starting material (100% recovery). The reaction was not recycled as described for **13b**.
Mp: 176-179°; IR: 3370, 1720, 1700, 1640, 1605, 1580, 1505; $^1$H-NMR: 1.5-2.6 (m, 10H); 2.76 (d, broad, 1H, J=17.3); 3.80 (s, 6H); 4.61 (m, 1H); 6.51 (m, 3H, Ar); 7.0 (m, 1H, Ar); 8.09 (s, N-H); minor isomer: 3.77 (m, 1H); 8.35 (s, N-H); Acc Mass: Calc. for $C_{18}H_{22}N_2O_5$: 346.1529; found: 346.1531.

*Glutarimide aldehyde* **15**.
A mixture of triphenylphosphoranylidene glutarimide **8** (3.73 g, 10 mmol) and glutaric dialdehyde (11.32 ml of a 25 wt.%-solution in water, 30 mmol) was refluxed for 1 hour in tetrahydrofurane (50 ml, distilled from sodium/benzophenone). The solvents were evaporated and the residue was stirred with ca 80 ml water of 30°. After a night in the refrigerator the solid, consisting mainly of triphenylphosphine oxide and bis-Wittig product, was removed by filtration. The water was evaporated from the filtrate (co-evaporation with toluene) and the residu was purified by chromatography (ethyl acetate/hexanes). Glutaric dialdehyde was difficult to separate from the Z-isomer.
**15**(E) was recrystallized from ethyl acetate/hexanes at -20 ° yielding 1.48 g product (76%). mp 65-67° (ethyl acetate); IR: 3380, 1720, 1690, 1640; $^1$H-NMR: 1.83 (quintet, 2H, J=7.3); 2.29 (q, 2H, J=7.4); 2.50 (dxt, 2H, J=7.0, J=1.1); 2.64 (s, 4H); 6.95 (t, 1H, J=7.6, C=CH); 8.24 (s, N-H); 9.78 (s, 1H, CH=O); Acc Mass: Calc. for $C_{10}H_{13}N_1O_3$: 195.0895; found: 195.0891;
**15**(Z): $^1$H-NMR: 6.15 (t, J=7.4, C=CH).
Bis-glutarimide [1,6-bis-(2-glutarylidene)-hexane]: mp 195-198°; $^1$H-NMR (dmso-$d_6$): 1.61 (m, 2H); 2.25 (m, 4H); 2.6 (m, 8H); 6.75 (t, J=7.4, C=CH); 10.71 (N-H).

*N-benzyl-2-(2-glutaryl)-piperidines* **16a** *and* **17a**.
Benzylamine (0.235 ml, 2.2 mmol) was added dropwise to a solution of glutarimide aldehyde **15** (0.39 g, 2 mmol) in dichloromethane (15 ml, dest. from calcium hydride) at -18°. The mixture was allowed to warm to room temperature, and after 30 minutes tetrabutylammonium cyanoborohydride[15] (0.677 g, 2.4 mmol) was added. After stirring for 5 hours triethylamine (0.32 ml, 2.5 mmol) was added and stirring was continued overnight. The reaction was quenched with M HCl (12 ml) and after stirring during 1 hour the organic layer was separated and washed twice with M hydrogen chloride. The combined aqueous solutions were washed with dichloromethane and saturated with solid sodium carbonate. Extraction with dichloromethane and

chromatography (1% MeOH in dichloromethane, saturated with ammonia) gave a 1 : 4.4 mixture of diastereomers **16a** and **17a** (0.40 g, 70%), from which the main isomer **16a** was obtained in pure form by crystallization from ethyl acetate/hexanes: mp 156-159° (needles). IR: 3370, 1720, 1700; $^1$H-NMR: 1.2-2.9 (m, 6H); 12.1 (m, 3H); 2.4-2.6 (m, 2H); 2.75 (m, 1H); 3.15 (m, 1H); 3.17 (d, 1H, J=13.6); 3.61 (d, 1H, J=13.6); 7.3 (m, 5H Ar); 7.94 (s, N-H); $^{13}$C-NMR: 17.78; 23.96; 25.60; 26.42; 31.56 (5x $CH_2$); 43.09 ($C_2$'); 54.43; 58.61 (2x $CH_2$); 61.22 ($C_2$); 126.7; 128.04; 128.14; 139.40 (Ar); 172.13; 173.61 (C=O); Acc Mass: Calc. for $C_{17}H_{22}N_2O_2$: 286.1681; Found: 286.1679;
**17a**: IR: 3370, 1720, 1705; $^1$H-NMR: 1.2-2.3 (m, 10H); 2.58 (d, broad,1H, J=17.1); 3.21 (d, 1H, J=13.7); 3.89 (d, 1H, J=13,7); $^{13}$C-NMR: 18.44; 23.55; 23.70; 28.95; 31.05 (5x $CH_2$); 45.74 ($C_2$'); 50.95 ($CH_2$); 57.52 ($C_2$); 58.32 ($CH_2$); 127.03; 128.31; 128.36; 139.38 (Ar); 172.36; 174.30 (C=O); Anal: Calc. for $C_{17}H_{22}N_2O_2$: C 71.30; H 7.74; N 9.78; Found: C 70.76; H 7.76; N 9.86.

*(±)-2-(2-glutaryl)-piperidine **16b**.*
N-benzylpiperidine **16a** (0.286 g, 1 mmol) was hydrogenated with Pearlmans catalyst ($Pd(OH)_2$, 50 mg) in methanol (35 ml) containing acetic acid (0.5 ml) at 60 psi during 5 hours. The catalyst was removed by filtration and the residu was coëvaporated three times with ethyl acetate, giving **16b** as a slowly solidifying syrup (acetic acid salt, quantitative) with mp 155-161°(ethyl acetate/methanol). IR (KBr): 3100-2000, 1715, 1690, 1620, 1560; $^1$H-NMR ($D_2O$): 1.5-2.3 (m, 8H); 1.95 (s, 3H, $CH_3COO^-$); 2.75 (m, 2H); 2.99 (dxdxd, 1H, J=5.1, J=7.6, J=12.8)3.12 (d, broad, 1H, J=12.4); 3.52 (d, broad, 1H, J=12.5), 3.69 (m, 1H); $^{13}$C-NMR ($D_2O$): 2.29; 24.43; 24.5926.97; 33.69 (5x $CH_2$); 45.72 ($C_2$'); 48.76 ($C_6$); 59.49 ($C_2$); 177.69; 178.61 (C=O);
**17b**: $^{13}$C-NMR ($D_2O$): from mixtures with **16b**: 22.06; 24.18; 24.43; 28.00; 33.29 (5x $CH_2$); 45.24 ($C_2$'); 48.03 ($C_6$); 59.39 ($C_2$); 177.69; 178.47 (C=O);

*(±)-N-acetyl-2-(2-glutaryl)-piperidine **16c**.*
**16b** (acetic acid salt, 25.6 mg, 0.1 mmol) was acetylated with excess acetic anhydride and N,N-diisopropylethylamine in dichloromethane overnight. Chromatography (1% methanol in ethyl acetate) and crystallization from ethyl acetate/hexanes gave **16c** (12.5 mg, 52%).
Mp: 133-134°; IR: 3360, 1720, 1700, 1620; $^1$H-NMR (proton assignments after cosy-experiments:)1.3-2.15 (m, 8H); 2.04 (s, 3H); 2.54 (dxt, 1H, J=17.8, J=4.0); 2.81 (dxdxd, 1H, J=17.8, J=5.7, J=13.1); 3.01 (dxdxd, 1H, $J_{H_2}$-$J_{H_2}$'=10.3, J=4.8, J=3.2, $H_2$'); 3.42 (m, 1H); 3.65 (d, broad, 1H, J=13.7); 5.03 (d, broad, 1H, J≈10, $H_2$); 8.16 (s, N-H); $^{13}$C-NMR: 18.74; 20.81; 25.28; 25.72; 27.63 (5x $CH_2$); 21.77 (Me); 39.39 ( $C_2$'); 42.77 ( $C_6$); 46.86 ($C_2$); 170.44; 171.64; 172.83 (C=O); Acc Mass: Calc. for $C_{12}H_{18}N_2O_3$: 238.1317; found: 238.1321;

*Ringconversion of (±)16 to (±)6 and (±)18.*
a) With potassium cyanide in dimethyl formamide:
2-(2-glutaryl)-piperidine **16b** (acetic acid salt, 0.347 g, 1.357 mmol) and potassium cyanide (0.275 g, 5 mmol) were dissolved in dimethyl formamide (distilled over calcium hydride, 10 ml) and the solution was concentrated in vacuo to ca 5 ml to remove traces of water. The resulting mixture was stirred under nitrogen at 110° (bath temperature) for 5 hours. The dimethyl formamide was evaporated and the residue stirred with dichloromethane (25 ml) containing 20% methanol and filtered to remove potassium salts. Chromatography with methanol in dichloromethane (gradient, 8% -> 16%) gave a total yield of 0.244 g (84%) of a mixture of **6** and **18**. Complete separation of the diastereomers by chromatography was not possible, but after several crystallizations **6** and **18** were obtained in pure form. The products were recrystallized by dissolving them in small amounts of hot methanol, followed by dilution with ethyl acetate and cooling.
(±)**6**. 0.0295 g (11%); mp 216-218°; IR (KBr): 3340, 3160, 1680, 1605; $^1$H-NMR ($CDCl_3$ + 10% $CD_3OD$): 1.2-2.5 (m, 11H); 2.77 (dxdxd, 1H, J=12,0, J=6,0, J=3.7); 3.56 (dxd, broad, 1H, J=11.1, J= 6.0); 4.60 (d, broad, 1H, J=12.5); $^{13}$C-NMR ($CDCl_3$ + 10% $CD_3OD$): 19.27; 24.55; 25.12; 27.58; 30.94 (5x $CH_2$) ; 43.69 ($C_1$); 44.44 ($C_6$); 58.47 ($C_{10}$); 167.93; 173.51; Acc Mass: Calc. for $C_{10}H_{16}N_2O_2$: 196.1212; found: 196.1208; nOe: Irradiation on the signal of $H_{10}$ gave a nOe of $H_1$ and $H_{6ax}$.
(±)**18**. 0.136 g (51%); mp 160-165°; IR: 3520, 3410, 1680, 1620, 1585; $^1$H-NMR: 1.0-2.0 (m, 7H); 2.1-2.6 (m, 5H); 3.54 (dxdxd, 1H, J=9.1, J=8.9, J=2.4);4.75 (d, broad, J=13.8); 6.11 (s, 1H, N-H); 6.24 (s, 1H, N-H); $^{13}$C-NMR: 23.89; 23.90; 24.94; 31.47; 33.00 (5x $CH_2$); 42.28 ($C_6$); 48.04 ($C_1$); 57.93 ($C_{10}$); 168.11; 175.01; Acc Mass: Calc. for $C_{10}H_{16}N_2O_2$: 196.1212; found: 196.1221;
nOe: Irradiation on the signal of $H_{10}$ gave a nOe of the $NH_2$-signals at 6.22 and 6.44 ppm.

b) With ammonia in methanol.
2-(2-glutaryl)-piperidine **16b** (acetic acid salt, 0.050 g, 0.195 mmol) was stirred with a saturated solution of ammonia in methanol (2 ml) at room temperature. After 4 hours the solvent was evaporated and the residu refluxed with methanol for 2 hours. Workup as described under **a**) gave 0.017 g (±)**6** and 0.009 g (±)**18** (68%).

*(±)-N-acetyllupinamine* **5**.
Quinolizidinamide **6** (19.6 mg, 0.1 mmol) was stirred with lithium aluminium hydride (0.038 g, 3 mmol) in tetrahydrofuran (3 ml) for 20 hours at room temperature. After 2 hours reflux the reaction was quenched with methanol. Workup with M sodium hydroxide and extraction with 10% methanol in dichloromethane gave lupinamine, which was immediately acetylated with acetic anhydride (1 ml) during 3 hours at 130°. The acetic anhydride was evaporated and the residue was dissolved in dilute ammonium hydroxide to hydrolyse any N,N-bisacetate that was formed during the reaction. Chromatography (15% methanol in dichloromethane, saturated with concentrated ammonia) gave **5** (11 mg, 52%) as colourless needles with mp. 144-146° (ethyl acetate, hexanes); IR: 3460, 2800, 2760, 1650, 1520; $^1$H-NMR: 1.1 - 2.2 (m, 14H); 1.96 (s, $CH_3$), 2.84 (m, 2H) 3.44 (m, $CH_2$-NH); 7.47 (broad, N-H); $^{13}$C-NMR: 21.78; 24.56; 25.48; 26.48; 29.76 (5x $CH_2$); 23.24 ($CH_3$); 35.80 ($C_1$); 41.13 ($C_{11}$); 56.69 ($C_4$/$C_6$); 57.07 ($C_4$/$C_6$); 64.52 ($C_{10}$); Acc Mass: Calc. for $C_{10}H_{16}N_2O_2$: 210.1732; found: 210.1719;

*(±)-N-acetyl-epilupinamine* **21**.
Quinolizidinamide **18** (39.3 mg, 0.2 mmol) was reduced with lithium aluminium hydride (0.114 g, 3 mmol) in tetrahydrofuran (3 ml) as described for **5**. (±)-N-acetyl-epilupinamine **21** (22.3 mg, 53%) was isolated as an oil. IR: 3450, 2800, 2760, 1660, 1510; $^1$H-NMR: 1.0 - 2.2 (m, 14H); 1.97 (s, $CH_3$), 2.2.79 (m, 2H) 3.13 (dxdxd, $J_{AB}$=13.5; $J_{1,10}$=6.9; $J_{NH,11}$=6.9; $H_{11a}$; 3.33 (dxdxd, $J_{AB}$=13.5; $J_{1,10}$=4.2; $J_{NH,11}$=5.2; $H_{11b}$); 5.56 (broad, N-H).

*(-)-2-(2-glutaryl)-6-oxazolopiperidine* **22**.
A solution of glutarimide aldehyde **15** (0.293 g, 1.5 mmol), R-(-)-phenylglycinol (0.233 g, 1.7 mmol) and zinc(II)chloride (28 mg, 0.2 mmol) in acetonitril (12 ml, distilled from $P_2O_5$) containing triethylamine (0.5 ml, 4 mmol) was refluxed under nitrogen during 8 hours. The solvent was evaporated and the residu was chromatographed with ethyl acetate/hexanes 1/1. First 20 mg of a mixture of two unidentified isomers was eluted, followed by 0.111 g of the main isomer **22a** (containing ca 5% **22b**). Finally 0.251 g of a ≈ 2 : 1 mixture of **22a** and **22b** was eluted, giving a combined yield of 81%. All attempts to crystallize one of the isomers failed.
**22a** (57%): IR: 3370, 1720, 1700; $^1$H-NMR: 1.5-2.3 (m, 10H); 2.52 (dxdxd, J=8.8, J=5.2, J=5.2, $H_2$'); 3.42 (m, $H_2$); 3.70 (dxd, J=7.6, J=5.4, $H_{8a}$); 4.24 (dxd, J=7.5, J=5.4, $H_9$); 4.39 (dxd, J=7.6, J=7.6, $H_{8b}$); 4.66 (m, $H_6$); 7.29 (m, 5H); 7.84 (broad, N-H); $^{13}$C-NMR: 18.01; 19.46; 27.03; 30.55 (5x $CH_2$); 45.73 ($C_2$'); 53.13 ($C_2$); 64.47 ($C_9$); 71.51 ($C_8$); 89.00 ($C_6$); 127.22; 127.53; 128.64; 141.34; 172.49; 174.40; Acc Mass: Calc. for $C_{18}H_{22}N_2O_3$: 314.1630; found: 314.1636; $[a]_D$ = -54.5° (c = 1.0, methanol).
**21b** (20%), spectra taken from mixtures with isomer **22a**: IR: 3370, 1720, 1700; $^1$H-NMR: 1.5-2.3 (m, 10H); 3.6 (m, $H_{8/9}$); 3.82 (m, $H_{8/9}$); 4.13 (dxd, J=8.6, J=8.0, $H_{8/9}$); 7.81 (broad, N-H); $^{13}$C-NMR: 18.31; 20.30; 22.34; 29.53; 31.38 (5x $CH_2$); 46.45 ($C_2$'); 58.65 ($C_2$); 75.32 ($C_8$); 96.76 ($C_6$); 127.77; 128.23; 128.85; 142.33; 171.46; 174.33.

*Hydrogenation of* **21a** *to 2R,2'S-2-(2-glutaryl)-piperidine* **16b**.
A solution of **21a** (0.46 g, 1.465 mmol) in a mixture of methanol (10 ml) and acetic acid (0.5 ml) was hydrogenated with $Pd(OH)_2$ (Pearlman's catalyst, 0.065 g ) at 60 psi during 5 hours. The catalyst was removed by filtration, and the filtrate was concentrated at reduced pressure untill a volume of ca 2ml. The residue was divided between water and ethyl acetate and the water layer was extracted three times to remove the phenylethanol. The organic layers were washed with water, containing some acetic acid. The water layer was lyophilized, yielding a slightly coloured, glassy residue (0.403 g, quantitative). Normal evaporation of the water results in (partial) loss of acetic acid, and isomerization to a mixture of **16b** and **17b** (TLC-control with silica gel and 15% methanol in dichloromethane, saturated with concentrated ammonia).

*Ringconversion of 2R,2'S-2-(2-glutaryl)-piperidine* **16b**.
a) The reaction with potassium cyanide in dimethyl formamide was performed as is described for racemic **16b**. Crystallization of the diastereomeric mixture of 6 and 18 gave several crystalfractions, with large melting ranges, indicating the presence of enantiomers. The optical rotations varied between -2° for **18** and 0° for the lupinine-isomer **6**.
b) With ammonia in methanol compound **6** was isolated in moderate yield, with a melting point of 198-209°, compared to 216-218° for the racemate. $[\alpha]_D$ = + 4.7° (c = 0.68 in methanol).

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