

Mimicking the Reaction of Phenylalanine Ammonia Lyase by a Synthetic Model

by Martin Rettig¹⁾, Andreas Sigrist, and János Rétey*

Institut für Organische Chemie, Lehrstuhl Biochemie der Universität, Richard-Willstätter-Allee,
D-76128 Karlsruhe

Dedicated to Professor *Albert Eschenmoser* on the occasion of his 75th birthday

Phenylalanine and histidine ammonia lyases (PAL and HAL) catalyze the reversible conversion of α -amino acids to the corresponding acrylic acids by elimination of ammonia. The prosthetic group 3,5-dihydro-5-methylidene-4*H*-imidazol-4-one (MIO) at the active site of both enzymes supposedly undergoes an electrophilic attack at the aromatic nucleus in the first step of the mechanism of action. Since no chemical analogy existed for such an electrophile-assisted elimination, we synthesized model compounds, some portion of which mimicked the essentials of the substrate phenylalanine and another portion the electrophilic *Michael* acceptor in a sterically appropriate distance. The first model, ($\pm$)-*rel*-(1*R*,2*S*,3*S*)-3-[1-methylidene-2-oxo-2-(pyrrolidin-1-yl)ethyl]-2-phenylcyclohexanamine (**7**) did not react under *Friedel-Crafts* conditions in the expected way (*Scheme 2*). The second model compound ($\pm$)-2-*rel*-(1*R*,2*S*,3*S*)-3-(dimethylamino)-2-(3-methoxyphenyl)cyclohexyl]prop-2-enal (**12**) with a more nucleophilic methoxyphenyl and a more electrophilic α,β -unsaturated carbonyl moiety, underwent an intramolecular *Friedel-Crafts*-type substitution, but no elimination of the dimethylamino group (*Scheme 4*). The third model compound, ($\pm$)- γ -[(dimethylamino)methyl]-3-methoxy-2,4,6-trimethyl- α -methylidenebenzenebutanal (**25**) eliminated dimethylamine upon treatment with *Lewis* acids and subsequent hydrolysis of the intermediate (*Scheme 6*). When the 3-methoxy-2,4,6-trimethylphenyl moiety of **25** was replaced by the 2,4,6-trimethyl-3-nitrophenyl group, no elimination product could be observed (*Scheme 7*).

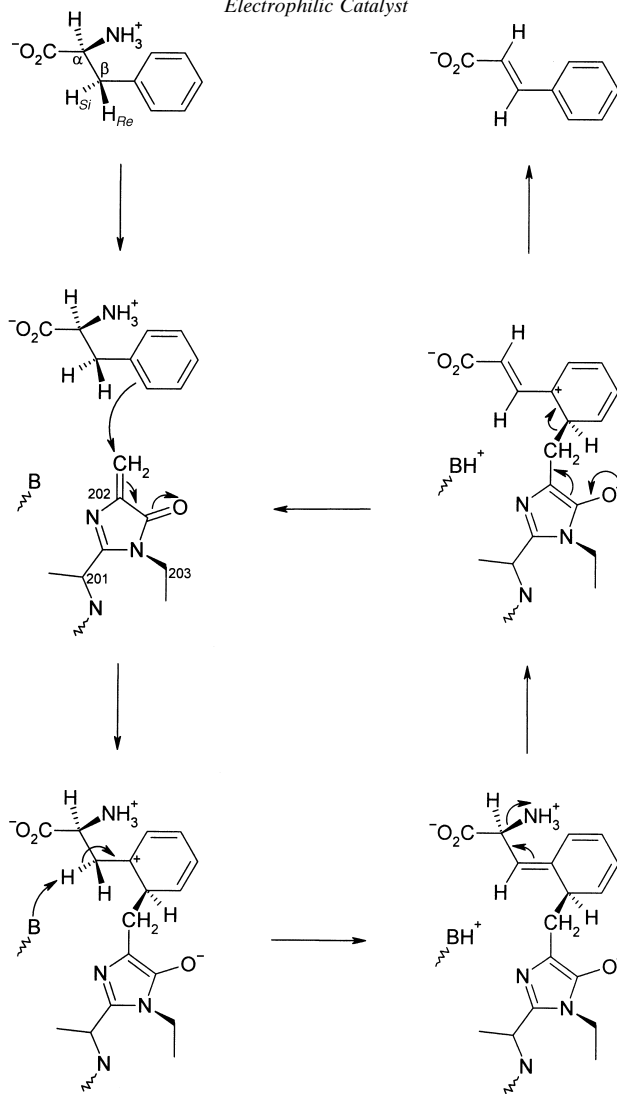
Introduction. – The most common degradation pathway of amino acids begins with transamination to form the corresponding α -keto acids. A notable exception is the non-oxidative ammonia elimination by two ammonia lyases acting on histidine and phenylalanine as substrates. The products of these reactions are the corresponding substituted acrylates *trans*-urocanate and *trans*-cinnamate, respectively. Urocanate is further degraded to glutamate in most organisms, including humans (for a review, see [2]), while cinnamate is the precursor of important ingredients of plants, like lignin, flavonoids, and coumarins (for a review, see [3]). Beside their considerable sequence homology, both ammonia lyases have a common electrophilic prosthetic group that is necessary for catalysis. Based on biochemical evidence, the prosthetic group was long believed to be dehydroalanine [4–6]. After some contradictory results [7], it has been shown that the prosthetic group is formed autocatalytically from a specific serine residue of the precursor proteins [8][9]. More recently, the X-ray structure of histidine ammonia lyase was solved at 2.1-Å resolution, revealing the nature of the prosthetic group [10]. Surprisingly, it is not simply dehydroalanine, but 3,5-dihydro-5-methylidene-4*H*-imidazol-4-one (MIO), which is formed by cyclization of the internal tripeptide Ala¹⁴²-Ser¹⁴³-Gly¹⁴⁴. MIO can be regarded as a modified dehydroalanine the

¹⁾ Part of the Dissertation.

electrophilicity of which is enhanced by preventing delocalization of the N-lone pairs into the α,β -unsaturated system [10]. A precedence for a similar cyclization yielding a substituted methyldeneimidazolone is the transformation of the fluorophore of the green fluorescent protein [11][12].

Proposals for the role of the catalytic electrophile, now known as MIO, included the *Michael* addition of the substrate α -amino group [4][6] and, more recently, a *Friedel-Crafts*-like electrophilic attack at the aromatic ring [13][14]. In the intermediate σ -complex, the acidity of the substrate H-C(β) atoms would be enhanced, facilitating their abstraction by an enzymic base (see *Scheme 1*). Ammonia elimination from the

Scheme 1. *Proposed Mechanism of Action of Phenylalanine Ammonia Lyase: Involvement of MIO as Electrophilic Catalyst*

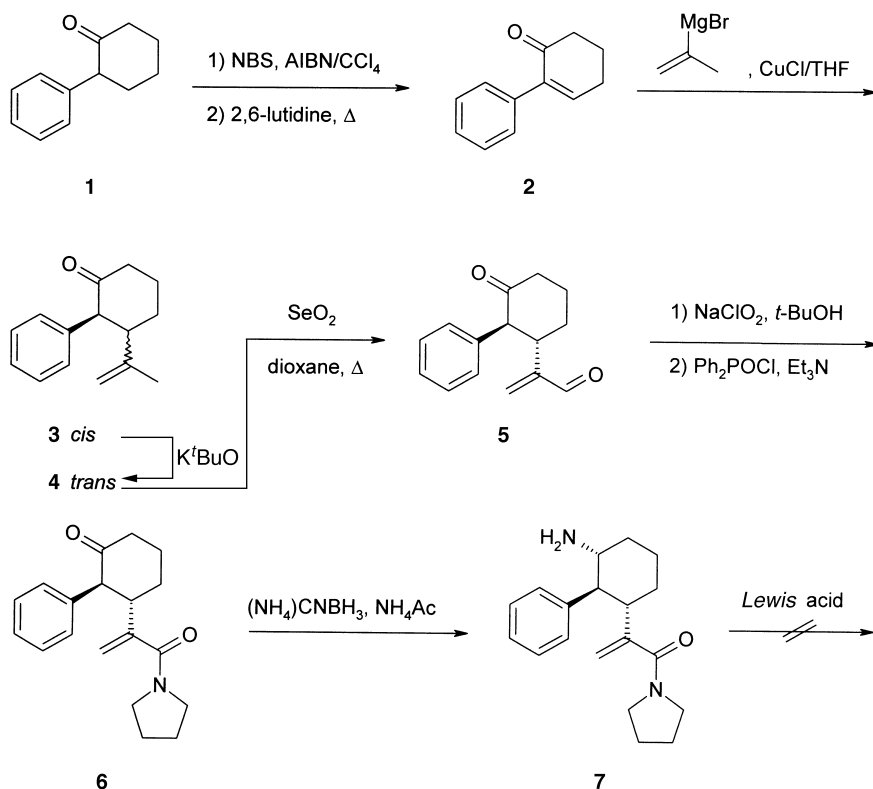


delocalized zwitterion would be driven by restoration of the aromaticity to form the product and to reform the original electrophile (*Scheme 1*).

Here we report on the feasibility of the latter mechanism in a synthetic model that mimicks the essentials of the enzyme-substrate complex.

Results. – *Synthesis of Model 7* (*Scheme 2*): Model **7** comprised a cyclohexanamine substituted with a Ph group in position 2 and an α,β -unsaturated amide moiety in position 3. The starting material for its synthesis was ($\pm$)-2-phenylcyclohexanone (**1**) which was prepared from commercial ($\pm$)-2-chlorocyclohexanone and phenylmagnesium bromide by a modified method of *Newman* and *Farbman* [15][16] (*Scheme 2*). Bromination of **1** by *N*-bromosuccinimide (NBS) followed by heating with 2,6-lutidine (2,6-dimethylpyridine) gave 2-phenylcyclohex-2-en-1-one (**2**) [17]. Treatment of **2** with isopropenylmagnesium bromide in the presence of CuCl resulted in the 1,4-addition of the isopropenyl group [18]. A *cis/trans* mixture **3/4** was obtained and could be chromatographically separated and characterized by $^1\text{H-NMR}$ spectroscopy. However, for further work, the crude *cis/trans* mixture was treated with K^tBuO to transform the *cis*-isomer **3** into the thermodynamically more stable *trans*-isomer **4**. By simple recrystallization of the equilibrated mixture (*cis/trans* 1:5, by $^1\text{H-NMR}$), pure **4** was

Scheme 2. Synthesis of Model Compound **7**



obtained in 74% yield (starting from **2**). Oxidation of **4** with SeO_2 in dioxane gave, after chromatography, ($\pm$)-*trans*-2-(3-oxo-2-phenylcyclohexyl)prop-2-enal (**5**) in 49% yield [19–21]. It is interesting to note that the *cis*-isomer **3**, under identical reaction conditions, afforded a different product, namely, 3-hydroxy-3-isopropenyl-2-phenylcyclohexanone (for possible reasons of the different regioselectivity, see *Discussion*).

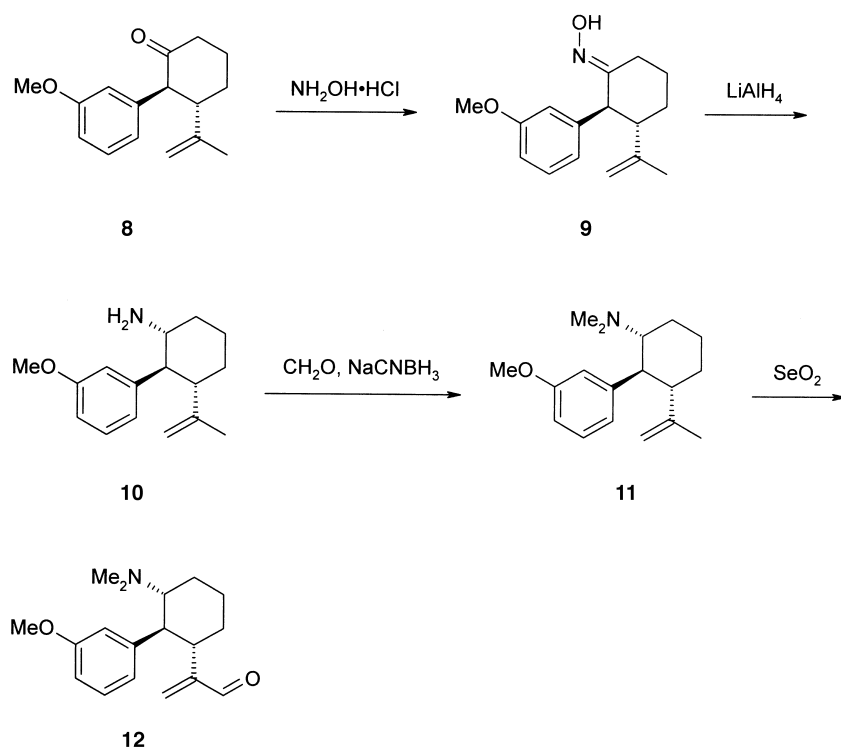
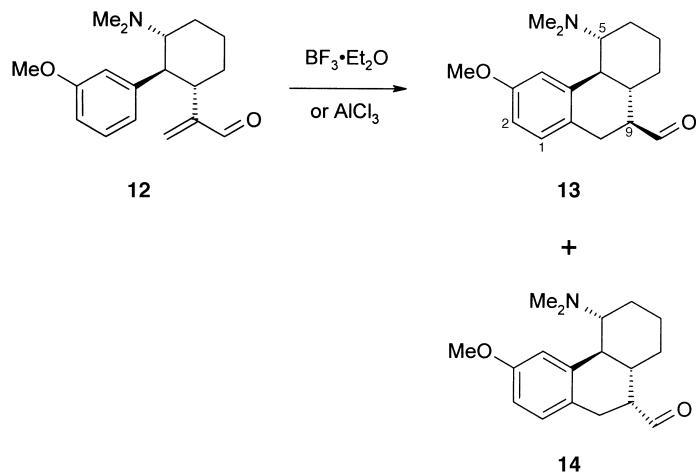
To make the model as similar as possible to the putative active site, **5** was converted to the amide **6** in two steps. First the aldehyde function was oxidized to the corresponding acid by NaClO_2 as oxidant [22][23]. An excess of 2-methylbut-2-ene was added to protect the substrate $\text{C}=\text{C}$ bond from oxidation. This acid was then transformed with pyrrolidine into amide **6** by applying $\text{Ph}_2\text{POCl}/\text{Et}_3\text{N}$ as activating agent [24][25]. In a final step, the amino group had to be introduced. This was achieved with ammonium cyanoborohydride by the method of *Danheiser et al.* [26] which is an improved variant described in a former work [27]. In this reaction, model compound **7** was generated in 81% yield. The main product was all-*trans* **7**, but ^1H -NMR spectroscopy revealed the presence of *ca.* 15% of a product in which the NH_2 and Ph groups were *cis*. This epimer-containing product was used to see whether model compound **7** could mimic the enzymic ammonia elimination.

In an attempt to initiate the postulated *Friedel-Crafts* attack, **7** was treated with a number of *Lewis* acids under various conditions: AlCl_3 in CH_2Cl_2 at various temperatures, AlCl_3 in MeNO_2 under reflux, $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at various temperatures, FeCl_3 in CH_2Cl_2 at various temperatures, $(\text{CF}_3\text{SO}_2)_2\text{O}$ in $\text{C}_2\text{H}_4\text{Cl}_2$ under reflux, POCl_3 at room temperature, conc. H_2SO_4 , or TiCl_4 in CH_2Cl_2 . Under most of these conditions, model compound **7** was inert. In some cases, partial hydrolysis of the amide group could be observed, but not the expected *Friedel-Crafts*-type cyclization or elimination of the amino group.

Synthesis of Model 12 (Scheme 3). The inert behavior of model **7** suggested that both the nucleophilicity of the Ph group and the electrophilicity of the α,β -unsaturated carbonyl system should be enhanced to facilitate a *Friedel-Crafts*-type attack. These requirements could be fulfilled by model compound **12**.

The synthesis was analogous to that of model **7**, except that (3-methoxyphenyl)-magnesium bromide was used to substitute the Cl-atom in ($\pm$)-2-chlorocyclohexanone. The reaction sequence proceeded smoothly in the expected manner up to the intermediate ($\pm$)-*trans*-3-isopropenyl-2-(3-methoxyphenyl)cyclohexanone (**8**) (*Scheme 3*). For the introduction of the dimethylamino group, the strategy had to be changed. First **8** was converted to oxime **9** which was then reduced with LiAlH_4 to amine **10** [28]. Subsequently, the amino group of **10** was dimethylated by formaldehyde and NaCNBH_3 as reagents [29][30]. The intermediate **11** thus obtained was finally oxidized with SeO_2 as described in the synthesis of model **7**. In model **12**, now all prerequisites were met for an intramolecular *Friedel-Crafts*-type attack of the more electrophilic α,β -unsaturated aldehyde portion.

Also compound **12** was inert to mild *Lewis* acids like FeCl_3 , SnCl_4 , as well as HCl and H_2SO_4 , it reacted with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to afford the tricyclic product **13** in 81% yield after chromatography (*Scheme 4*). Compound **13** was fully characterized by its FT-IR, ^1H - and ^{13}C -NMR, and mass spectra (see *Fig. 1* and *Exper. Part*). The analogous reaction of **12** with AlCl_3 as *Lewis* acid gave the tricyclic product in only 46% yield. Moreover, ^1H -NMR spectroscopy showed that *ca.* 12% of the product was the epimeric

Scheme 3. *Synthesis of Model Compound 12*Scheme 4. *Intramolecular Friedel-Crafts Substitution in Model Compound 12*

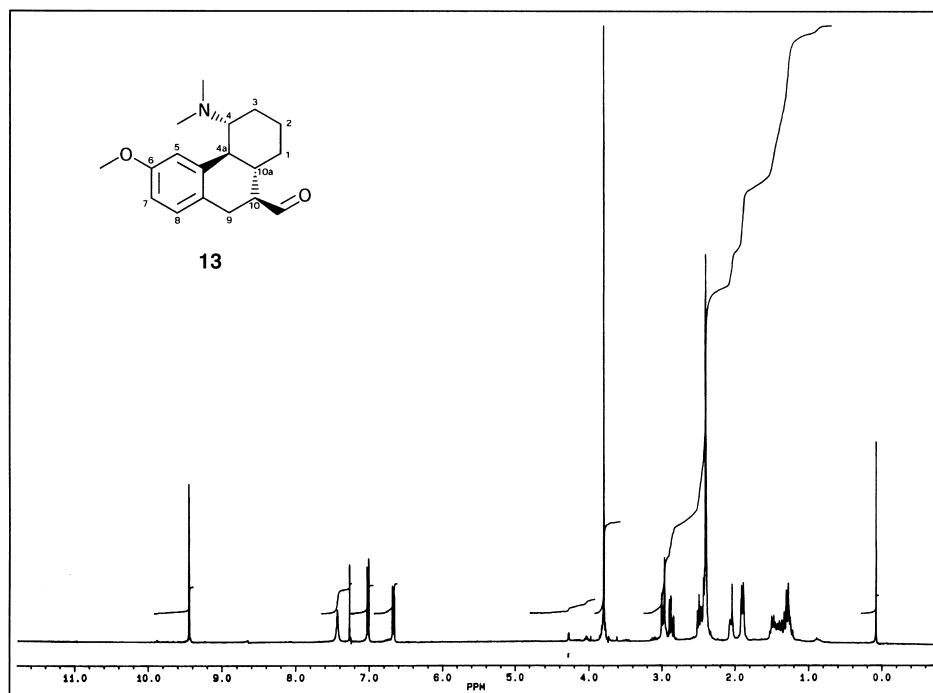
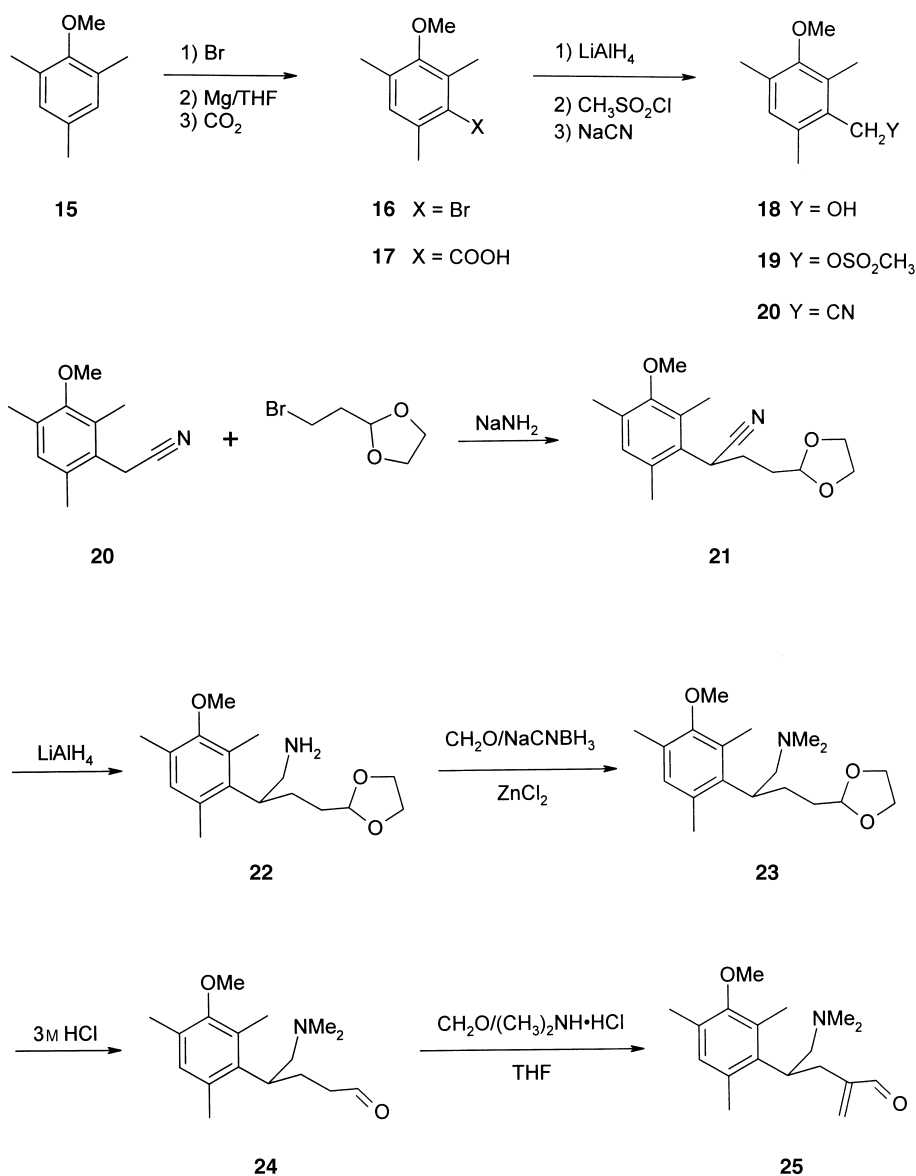


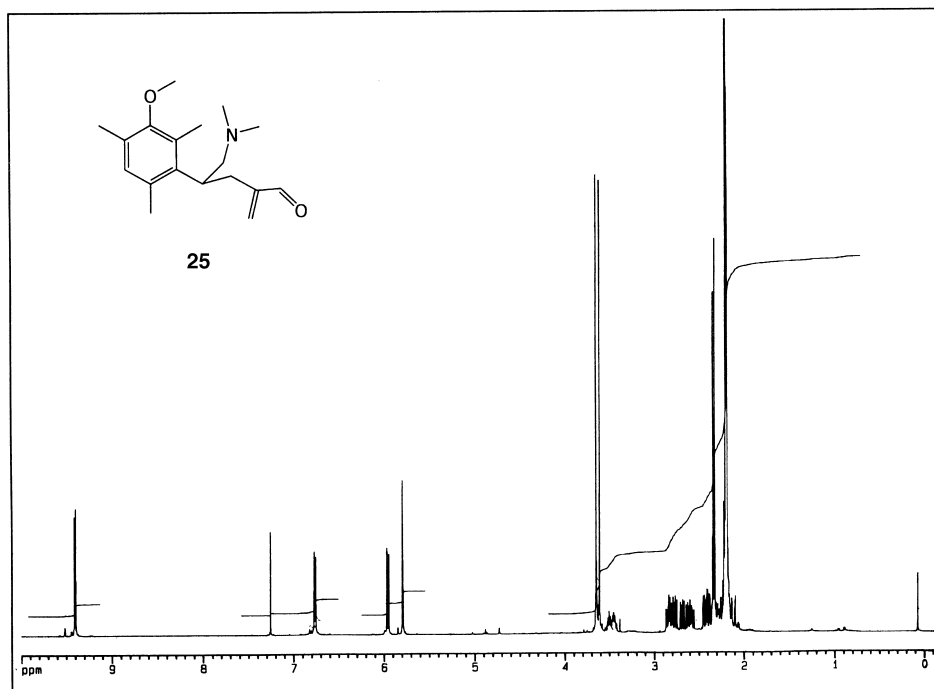
Fig. 1. ^1H -NMR Spectrum of phenanthrenecarbaldehyde **13** obtained by Friedel-Crafts substitution of the model compound **12**

compound **14**. Neither in the reaction with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ nor in that with AlCl_3 could products arising from the elimination of the dimethylamino group be detected.

Synthesis of Model 25 (Scheme 5). Learning from the behavior of model **12** in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as *Lewis* acid, we decided to synthesize model **25** in which the intramolecular *Friedel-Crafts*-type substitution but not the electrophilic attack at the aryl moiety would be prevented by appropriately placed Me groups. Retrosynthetic analysis suggested a strategy different from that applied in the synthesis of models **7** and **12**. Thus, 2,4,6-trimethylanisole **15** was obtained by methylation of commercial 2,4,6-trimethylphenol with Me_2SO_4 [31]. Monobromination of **15** ($\rightarrow$ **16**) was followed by preparation of the corresponding *Grignard* compound, which readily reacted with CO_2 to afford the carboxylic acid **17** (Scheme 5). The corresponding alcohol **18** was obtained by reduction with LiAlH_4 [32] and then converted *via* mesylate **19** to nitrile **20** [33]. The α -acidifying effect of the nitrile group was exploited to substitute one of the methylene protons by the acetal-protected 3-bromopropanal, thus generating intermediate **21** [34]. Reduction by LiAlH_4 resulted in amine **22**, which was dimethylated by $\text{CH}_2\text{O}/\text{NaCNBH}_3$ [35][36]. Removal of the protecting acetal group in **23** by acid resulted in aldehyde **24**. Finally, introduction of the methylene group to form the α,β -unsaturated aldehyde **25** was achieved in almost quantitative yield by applying the *Eschenmoser* salt ($\text{Me}_2\text{N}^+=\text{CH}_2\text{Cl}^-$) generated *in situ* from dimethylamine hydrochloride and formaldehyde [37][38]. The ^1H - and ^{13}C -NMR, FT-IR, and mass spectra

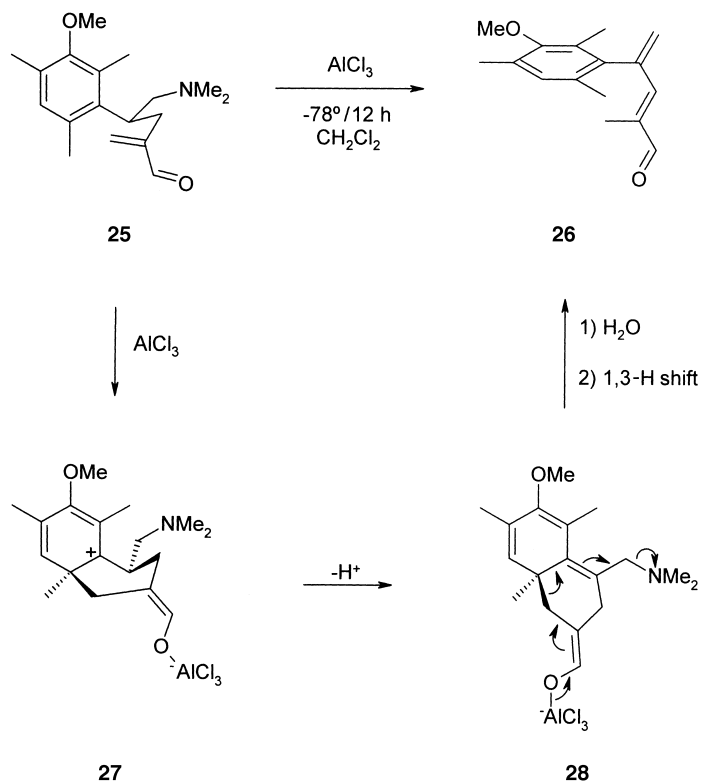
Scheme 5. *Synthesis of Model Compound 25*

were consistent with the structure of the model compound **25** (see also *Fig. 2* and *Exper. Part*). It is noteworthy that certain NMR signals appeared doubly, representing two conformers. This phenomenon was also observed in the NMR spectra of compounds **21–24** due to hindered rotation around the bond connecting the aromatic ring to the stereogenic C-atom.

Fig. 2. ^1H -NMR Spectrum of the model compound **25**

Behavior of Model 25 in the Presence of Lewis Acids. In contrast to models **7** and **12**, model **25** gave, upon reaction with the strong *Lewis* acids $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and AlCl_3 , a neutral product **26**, *i.e.*, elimination of dimethylamine occurred presumably *via* **27** and **28** (Scheme 6). The best result with respect to the model reaction was obtained by treatment of **25** with AlCl_3 in CH_2Cl_2 for 12 h at -78° . After aqueous workup and column chromatography, 5% of a neutral compound **26** could be isolated, besides 50% of recovered starting material. Increasing the reaction temperature and time did not raise the yield of the neutral product. Examination of **26** by ^1H - and ^{13}C -NMR, UV, FT-IR, and mass spectrometry corroborated its structure as 4-(3-methoxy-2,4,6-trimethylphenyl)-2-methylpenta-2,4-dienal. Noteworthy is the unusually highfield shift (1.16 ppm) of the 2-methyl group (see also Fig. 3) suggesting a conformation in which the aromatic ring is perpendicular to the $\alpha,\beta,\gamma,\delta$ -unsaturated system with the 2-methyl group close to the plane of the aromatic ring. The UV-absorption maximum (λ_{max} 267 nm) is also in agreement with the value (λ_{max} 265 nm) calculated according to the extended Woodward rules [39].

Synthesis of Less-Active Variants of Model 25. To explore the role of the 3-methoxy-2,4,6-trimethylphenyl moiety of model **25** in the elimination of dimethylamine, variants **30** and **34** of model **25** were also synthesized (Scheme 7). The starting material was, in both cases, commercially available 2,4,6-trimethylbenzeneacetonitrile **29**. Variant **30** was obtained directly from **29** by the same reaction sequence as described for model **25**. Alternatively, **29** was first converted to 2,4,6-trimethyl-3-nitrobenzeneacetonitrile (**31**)

Scheme 6. Reaction of Model Compound **25** with AlCl_3 ; Proposed Mechanism of the Electrophile-Assisted Elimination of Dimethylamine

[40], which was substituted to give **32**. The subsequent reduction of the nitrile group to the amine function by LiAlH_4 had to be modified: $\text{BH}_3 \cdot \text{THF}$ specifically reduced the nitrile group of **32** but not the NO_2 group [41]. Thus, **33** was obtained and transformed to **34** as usual.

Treatment of both variants **30** and **34** of model **25** with AlCl_3 or $\text{BF}_3 \cdot \text{Et}_2\text{O}$ gave product mixtures. All attempts to show elimination of dimethylamine failed.

Discussion. – The elimination of ammonia from histidine and phenylalanine by the corresponding lyases is remarkable, and its understanding represents a challenge. In particular, the abstraction of the non-acidic benzylic proton ($\text{p}K_a \approx 43$ for toluene [42]) by an enzymic base without touching the more acidic α -ammonium group ($\text{p}K_a \approx 9$) poses a chemical problem. To circumvent this obstacle, it was suggested that the catalytically important electrophilic group of these ammonia lyases attacks the aromatic ring to form a *Friedel-Crafts*-type σ -complex, in which the benzylic proton is activated for abstraction. Although this mechanism has been supported by biochemical results [14][43], there existed no chemical analogy for it. When we decided to mimic the lyase reaction in a model system, the electrophilic group was believed to be dehydroalanine [6]. Therefore, our first model had to fulfill the following require-

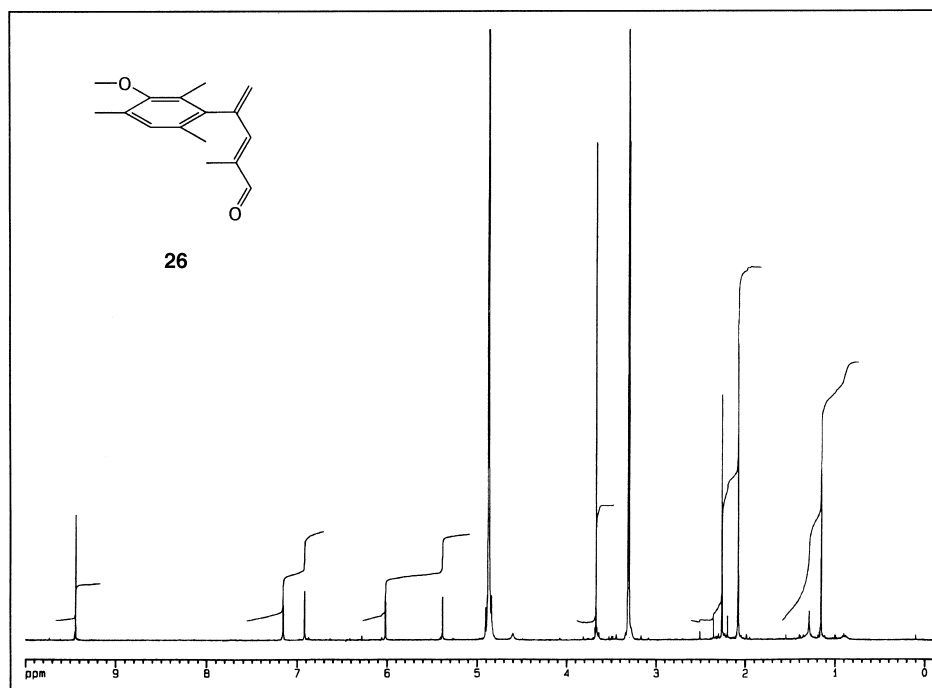
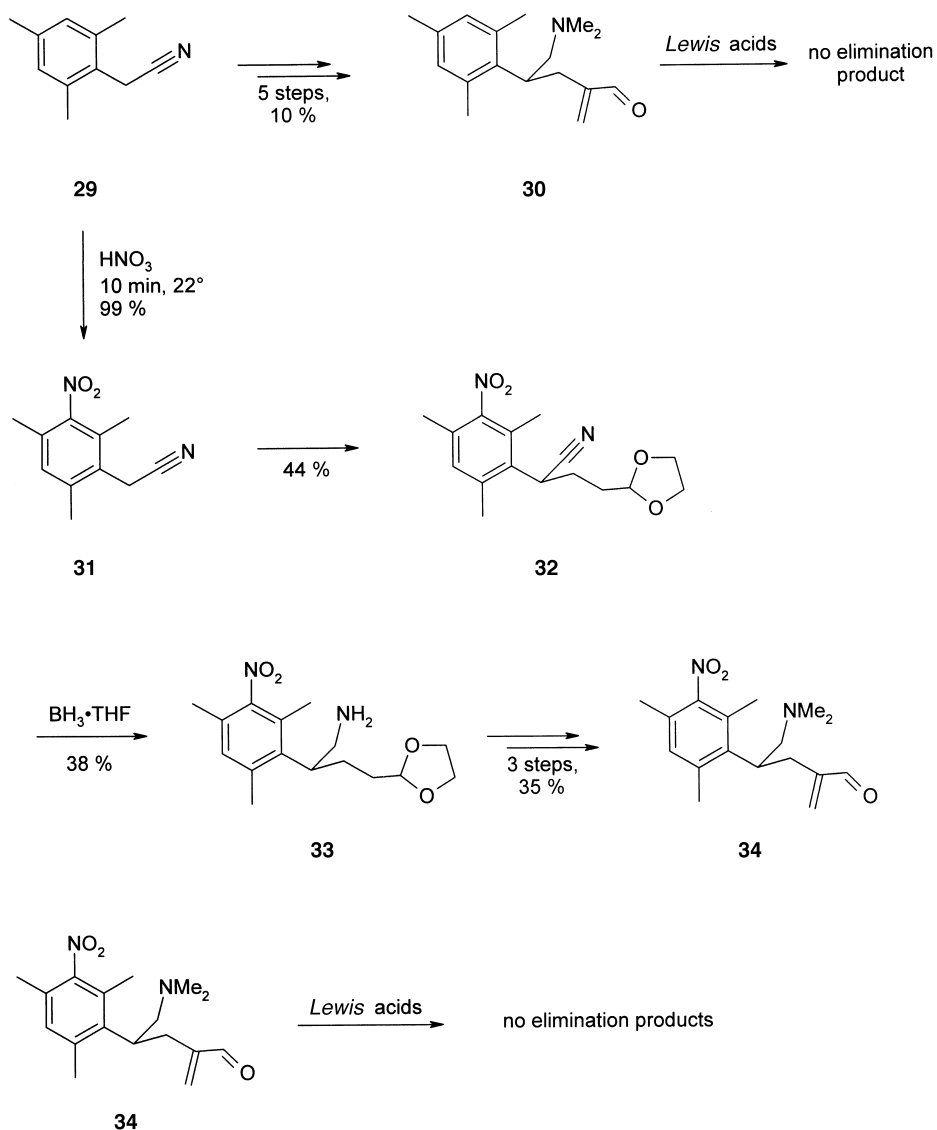


Fig. 3. ^1H -NMR Spectrum of the dienal **26** obtained from the model compound **25** by elimination of dimethylamine in the presence of AlCl_3

ments: It should incorporate an amide of dehydroalanine placed suitably for a favorable intramolecular electrophilic attack at a phenyl ring that is also connected to a cyclohexane moiety carrying an amino group in the correct position (*trans* to the phenyl ring; see model **7**).

The preparation of 2-phenylcyclohex-2-en-1-one, an early intermediate in our synthetic route to model **7** (Scheme 2), has been described [17]. We followed this method, except for the use of commercial ($\pm$)-2-chlorocyclohexanone instead of ($\pm$)-2-bromocyclohexanone, in the preparation of ($\pm$)-2-phenylcyclohexanone (**1**). The high yield (58%) in this step claimed by the original authors [15] could not be confirmed either by us or by other workers [44] even by exactly following the original procedure [15]. The stereoselectivity of the 1,4-addition of the isopropenylmagnesium bromide to form the key intermediate **4** from **2** deserves comment. The kinetically controlled *cis*-product **3** was formed first in excess. Equilibration with K^tBuO transformed it into the thermodynamically more stable *trans*-form **4**. The two diastereoisomers exhibited different regioselectivity in the oxidation by SeO_2 . While the *trans*-isomer **4** gave the desired α,β -unsaturated aldehyde **5**, an OH group was introduced at the alternative allylic position in the same reaction of its *cis*-counterpart **3**. An explanation for the observed regioselectivity may be that, in the *trans*-form **4**, both the phenyl and the isopropenyl group may occupy the equatorial position, whereas in the *cis*-form **3**, the latter is forced into the axial position. In the case of **4**, involvement of the axial ring

Scheme 7. Synthesis of the Variants of Model Compound **25** with a Less-Nucleophilic Aryl Moiety

H-atom in the ene reaction with SeO_2 is stereoelectronically disfavored, in the case of **3**, it is, however, favored.

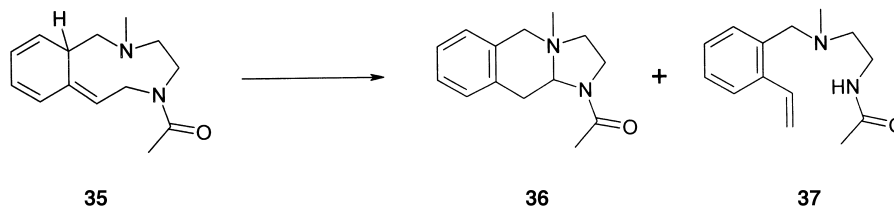
The inertness of model **7** in presence of various *Lewis* acids and under various conditions prompted the synthesis of model **12** (Scheme 3). Introduction of the MeO function enhanced the nucleophilicity of the aryl group. On the other hand, the electrophilicity of the α,β -unsaturated carbonyl moiety could be easily enhanced by omitting the transformation of the aldehyde to the amide, as it was done in the last two

steps of the synthesis of model **7**. A further modification was made by dimethylation of the amino group, thus enhancing its basicity.

Model **12** underwent an intramolecular *Friedel-Crafts* substitution on treatment with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at -78° to afford in good yield the tricyclic product **13** (*Scheme 4*). The analogous reaction with AlCl_3 was less efficient and stereoselective. In no case, elimination of dimethylamine could be detected. Obviously, in the σ -complex intermediate of the electrophilic substitution, abstraction of the ring proton was favored leading directly to rearomatization. To give a chance to the formation of an exocyclic double bond followed by elimination of the amino group, this direct rearomatization had to be prevented. Therefore, model **25** was synthesized (*Scheme 5*) in which the relevant aromatic ring protons were replaced by Me groups. Furthermore, the cyclohexane ring of models **7** and **12**, was replaced by an analogous open-chain system. The last measure makes the system more flexible and facilitates the abstraction of the activated benzylic proton by the possible presence of a conformation with favorable stereoelectronics. It should be noted that model **25** was a racemate, as were also models **7** and **12**.

The generation of **26** on treatment of model **25** with AlCl_3 or $\text{BF}_3 \cdot \text{Et}_2\text{O}$, albeit in a yield of only 5%, by the elimination mechanism shown in *Scheme 6* can be regarded as a chemical model for the reaction catalyzed by the enzyme PAL (see *Scheme 1*). We now know that the catalytic group of PAL is MIO whose electrophilicity equals that of an α,β -unsaturated aldehyde. The enzyme can also prevent the direct re-aromatization of the *Friedel-Crafts* σ -complex by excluding a base in the hydrophobic pocket while it harbors the phenyl group of the phenylalanine substrate. In our model **26**, this protecting function is taken over by the ring Me groups. Survey of the literature revealed that the postulated final step in the PAL reaction, namely the elimination of an N-function coupled with the aromatization of a dehydrobenzene moiety carrying an exocyclic double bond, had already a chemical model [45] (see *Scheme 8*). Indeed, **35** in dimethylformamide was transformed under CsF catalysis to the aromatic products **36** (84%) and **37** (16%), while in the presence of stronger bases, like diazabicyclo[5.4.0]undec-7-ene (DBU), only **36** was observed.

Scheme 8. CsF-Catalyzed Aromatization of a Dihydrophenyl Moiety with an Exocyclic Double Bond May Eliminate a β -Amino Function [45]



Against the reaction sequence postulated for model **25** (see *Scheme 6*), one can argue that elimination would occur also without the help of the 3-methoxy-2,4,6-trimethylphenyl moiety. Although this is unlikely in view of the behavior of models **7** and **12**, we synthesized the two variants **30** and **34** of model **25**, in which the MeO group was replaced by an H-atom or a NO_2 group, respectively (*Scheme 7*). The failure of

these variants with less-nucleophilic aryl moieties to produce elimination products supports the involvement of the 3-methoxy-2,4,6-trimethyl group in the elimination mechanism as outlined in *Scheme 6*.

Conclusion. – It is shown that model systems containing a nucleophilic methoxyaryl moiety and an electrophilic α,β -unsaturated aldehyde function undergo intramolecular *Friedel-Crafts*-type reactions upon *Lewis* acid catalysis. When the direct aromatization of the intermediate σ -complex is prevented by Me substituents at the aryl moiety like in model **25**, then a benzylic proton can be abstracted leading to an exocyclic C=C bond. Re-aromatization finally occurs with simultaneous elimination of a β -amino group. The above reaction sequence represents a model for the recently postulated mechanism of the enzymic ammonia elimination from phenylalanine.

Experimental Part

1. *General.* $\pm$ -2-Chlorocyclohexanone, isopropenyl bromide, *t*BuOH, MnO₂ (activated), *N,N*-dimethylpyridin-4-amine, 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), CaOCl, CuCl, BF₃·Et₂O, *m*-bromoanisole, 2,4,6-trimethylphenol, and 2-bromo-1,3-dioxolane were products of *Fluka*, 2,4,6-trimethylbenzeneacetonitrile (= mesitylacetonitrile) was from *Lancaster*, BH₃·THF from *Acros*, and 2-methylbut-2-ene, NaOCl₂, 2,6-dimethylpyridine, Ph₂POCl, NaCNBH₃, NaOEt, SeO₂, mesyl chloride (MeSO₂Cl), and K⁺tBuO from *Aldrich*. Column chromatography (CC): silica gel 60 from *Merck* (Darmstadt) and aluminium oxide (Alox type 507c, neutral) from *Fluka*. TLC: plates of the types *Alugram SIL G/UV₂₅₄* and *Alox N/UV₂₅₄* from *Macherey-Nagel* (Düren). UV Spectra: *Perkin-Elmer Lambda-2* spectrophotometer; $\lambda_{\max}$ (ϵ) in nm. IR Spectra: *Bruker-IFS-88-FT-IR* spectrometer; KBr pellet or film on KBr; only *s* and *m* signals given; $\tilde{\nu}$ in cm⁻¹. ¹H- and ¹³C-NMR Spectra: CDCl₃ or CD₃OD solns., *Bruker-WH-250*, *-AM-400*, or *-DRX-500* spectrometer; conventional *Fourier-transform* methods as in our previous studies [46][47]; values in ppm rel. to the CHCl₃ signal, coupling constants *J* in Hz; H_a and H_e = axial and equatorial H-atoms, resp.; compounds **21–25**, **30**, **33**, and **34** having two stable rotamers gave rise to some doubled signals, marked by a*. High resolution MS (HR-MS): *Finnigan MAT 90* spectrometer, ionization potential 70 eV; *m/z* (rel. intensity %).

2. ($\pm$)-2-Phenylcyclohexanone (**1**). Phenylmagnesium bromide, prepared from Mg (0.73 g, 30 mmol) and bromobenzene (4.71 g, 30 mmol) in dry THF (10 ml), was treated at –25° with ($\pm$)-2-chlorocyclohexanone (4 g, 30 mmol) in benzene (60 ml; thiophene-free): **1** (1.5 g, 29%). M.p. 49°, after recrystallization from hexane. Both yield and m.p. were lower than the literature values [15]. ¹H-NMR (250 MHz, CDCl₃): 2.02–2.52 (*m*, CH₂(3), CH₂(4), CH₂(5)); 3.87 (*dd*, CH(2)); 7.35–7.45 (*m*, 2 H_a); 7.47–7.65 (*m*, 2 H_m, H_o).

3. 2-Phenylcyclohex-2-en-1-one (**2**). A soln. of **2** (1.746 g, 10 mmol), *N*-bromosuccinimide (1.783 g, 10 mmol), and 10 mg AIBN (2,2'-azabis[isobutyronitrile]) in CCl₄ (40 ml) was heated under reflux for 1 h. After it was allowed to cool to r.t., the precipitated succinimide was removed by filtration and the solvent by distillation: crude ($\pm$)-2-bromo-2-phenylcyclohexanone (1.53 g, 100%). ¹H-NMR (250 MHz, CDCl₃): 1.72–1.99 (*m*, CH₂(4), CH₂(5)); 2.35–2.62 (*m*, CH₂(3)); 2.82–3.03 (*m*, CH₂(6)); 7.17–7.39 (*m*, Ph).

The crude 2-bromo-2-phenylcyclohexanone was dissolved in 2,6-dimethylpyridine (20 ml) and heated to reflux for 30 min. After allowing to cool to r.t. the pH of the soln. was brought to 2 by adding dil. HCl soln. The mixture was extracted with Et₂O (2 × 20 ml), the extract washed with H₂O (3 ×); dried (MgSO₄), and evaporated, and the crystalline residue recrystallized from hexane/AcOEt 1:1: **2** (1.204 g, 70%). Colorless needles. M.p. 78°. ¹H-NMR (250 MHz, CDCl₃): 1.96–2.01 (*m*, CH₂(5)); 2.45–2.58 (*m*, CH₂(4), CH₂(6)); 7.05 (*t*, CH(3)); 7.21–7.80 (*m*, Ph).

4. ($\pm$)-cis-2-Phenyl-3-(prop-2-enyl)cyclohexanone (**3**). To a stirred suspension of Mg (0.243 g, 10 mmol) in dry THF (10 ml) under Ar, 2-bromoprop-2-ene (1.21 g, 10 mmol) was added and heated to reflux for 30 min. After cooling to r.t., CuCl (60 mg, 6 mol-%) was added. Then **2** (0.516 g, 3 mmol) was dropwise introduced at 0°. After stirring at 0° for 15 min, the mixture was heated under reflux for 1.5 h, then cooled, and added to ice-cold dil. HCl soln. The aq. layer was extracted with Et₂O (3 × 10 ml) and the org. phase washed with H₂O (3 × 10 ml), dried (MgSO₄), and evaporated to give a reddish oil (0.49 g, 76%), which was used in the next step. For characterization, a sample was purified by CC (silica gel, hexane/AcOEt 10:1): **3**. FT-IR (film): 3387*m*, 3056*m*, 3037*m*, 2943*s*, 1701*s*, 1643*m*, 1607*m*, 503*m*, 1456*m*, 1380*m*, 1337*m*, 1282*m*, 1254*m*, 1232*m*, 1209*m*, 1168*s*, 1108*m*,

1021*m*, 895*s*, 841*m*, 791*m*, 759*s*, 651*s*. ¹H-NMR (250 MHz, CDCl₃): 1.60 (*s*, Me); 1.79 (*m*, H_a–C(4)); 1.96 (*m*, H_{ev}–C(5)); 2.15 (H_a–C(4), H_a–C(5)); 2.83 (*m*, H–C(3)); 2.56 (*m*, H_e–C(6)); 2.83 (*m*, H_a–C(6)); 4.08 (*d*, ³J_{ae} = 5.7, H–C(2)); 4.75 (*s*, 1 H, CH₂=C); 4.83 (*s*, 1 H, CH₂=C); 7.15–7.40 (*m*, Ph). ¹³C-NMR (62.5 MHz, CDCl₃): 22.5 (Me); 24.4 (C(4)); 26.0 (C(5)); 39.3 (C(6)); 48.2 (C(3)); 58.8 (C(2)); 112.4 (CH₂=C); 126.8 (C_o); 128.2 (C_o); 129.2 (C_m); 136.6 (C_{ipso}); 144.9 (CH₂=C); 210.4 (C=O). HR-MS: 214.3056 (C₁₅H₁₈O⁺; calc. 214.3063).

5. (±)-trans-2-Phenyl-3-(prop-2-enyl)cyclohexanone (**4**). The crude reddish oil of *Exper. 4* was dissolved in EtOH (20 ml) and cooled to –78°. Addition of K^tBuO (1.122 g, 10 mmol) and stirring for 1 h at –78° were followed by hydrolysis with dil. HCl soln. by adjusting the pH to 2. The soln. was then extracted with Et₂O (2 × 20 ml) the org. layer washed with H₂O (2 × 10 ml), dried (MgSO₄), and evaporated, and the yellowish solid recrystallized from hexane/AcOEt 10:1: to 0.476 g (74% rel. to **2** of **4**). Colorless crystals. M.p. 108°. FT-IR (film): 3391*m*, 3066*m*, 3037*m*, 2944*s*, 1703*s*, 1646*m*, 1605*m*, 1501*m*, 1458*m*, 1382*m*, 1337*m*, 1314*m*, 1282*m*, 1257*m*, 1223*m*, 1207*m*, 1170*s*, 1105*m*, 1079*m*, 1023*m*, 892*s*, 845*m*, 795*m*, 753*s*, 659*s*. ¹H-NMR (250 MHz, CDCl₃): 1.59 (*s*, Me); 1.92–2.02 (*m*, CH₂(4), H₂–C(5)); 2.20 (*m*, H_a–C(5)); 2.43–2.61 (*m*, CH₂(6)); 2.83 (*m*, H_a–C(3)); 3.61 (*d*, ³J_{ap} = 12.2, H_a–C(2)); 4.59 (*s*, 1 H, CH₂=C); 4.61 (*s*, 1 H, CH₂=C); 7.04–7.49 (*m*, Ph). ¹³C-NMR (62.5 MHz, CDCl₃): 18.9 (Me); 26.1 (C(4)); 31.7 (C(5)); 42.0 (C(6)); 53.3 (C(3)); 61.3 (C(2)); 112.8 (CH₂=C); 126.8 (C_p); 128.0 (C_o); 129.3 (C_m); 136.9 (C_{ipso}); 145.6 (CH₂=C); 209.7 (C=O). HR-MS: 214.3057 (C₁₅H₁₈O⁺; calc. 214.3063).

6. (±)-trans-2-(3-Oxo-2-phenylcyclohexyl)prop-2-enal (**5**). To a soln. of **4** (0.86 g, 4 mmol) in abs. dioxane (20 ml), SeO₂ (0.444 g, 4 mmol) was added and the mixture heated under reflux for 2 h. The product, still warm, was filtered and the pellet washed with Et₂O. The filtrate was evaporated, the residue dissolved in Et₂O, the soln. washed with H₂O (2 × 10 ml), dried (MgSO₄), and evaporated, and the residue purified by CC (silica gel, hexane/AcOEt 10:1): **5** (0.443 g, 49%). Colorless oil. FT-IR (film): 2967*s*, 1713*s*, 1645*m*, 1556*s*, 1489*m*, 1454*s*, 1367*m*, 1253*s*, 1200*m*, 1156*m*, 1063*s*, 896*s*, 776*s*, 692*s*. ¹H-NMR (250 MHz, CDCl₃): 1.92–2.05 (*m*, H_e–C(5), CH₂(6)); 2.18 (*m*, H_a–C(5)); 2.58 (*m*, CH₂(4)); 3.25 (*m*, H_a–C(1)); 3.97 (*d*, ³J_{aa} = 12.4, H_a–C(2)); 5.86 (*s*, 1 H, CH₂=C); 6.14 (*s*, 1 H, CH₂=C); 6.96–7.34 (*m*, Ph). ¹³C-NMR (62.5 MHz, CDCl₃): 26.1 (C(5)); 3.19 (C(6)); 41.9 (C(4)); 45.0 (C(1)); 60.4 (C(2)); 127.0 (C_p); 128.3 (C_o); 129.3 (C_m); 136.3 (CH₂=C); 136.4 (C_{ipso}); 150.6 (CH₂=C); 194.0 (CHO); 208.7 (C=O). HR-MS: 228.2896 (C₁₅H₁₆O₂⁺; calc. 228.2903).

7. (±)-trans-3-[1-Methylidene-2-oxo-2-(pyrrolidin-1-yl)ethyl]-2-phenylcyclohexanone (**6**). To a soln. of **5** (100 mg, 0.432 mmol) in ^tBuOH (10 ml), an excess of 2-methylbut-2-ene (2 ml) was added. A soln. of NaClO₂ (300 mg, 3.3 mmol) and NaH₂PO₄·H₂O (300 mg, 2.49 mmol) in H₂O (10 ml) was then dropwise introduced during 10 min. The mixture was stirred under Ar for 2 h at r.t. After adjusting the pH to 4 by adding NaH₂PO₄, the soln. was stirred for further 12 h. Evaporation and dissolution of the residue in H₂O (30 ml) were followed by further decreasing the pH of 2 by dil. HCl soln. The product was then extracted with Et₂O (3 × 10 ml), the combined org. layer washed with H₂O (10 ml) and dried (MgSO₄) and the residue submitted to CC (silica gel, hexane/AcOEt 1:1): crystals of (±)-trans-2-(3-oxo-2-phenylcyclohexyl)propenoic acid (79 mg, 74%). Colorless crystals. M.p. 105°. FT-IR (drift): 3198*s*, 2951*s*, 1712*s*, 1501*m*, 1458*m*, 1100*s*, 964*s*, 834*m*, 702*s*, 667*m*. ¹H-NMR (500 MHz, CDCl₃): 1.89 (*m*, H_e–C(6)); 2.06–2.13 (*m*, H_e–C(5), H_a–C(6)); 2.18 (H_a–C(5)); 2.53–2.64 (*m*, CH₂(4)); 3.25 (*m*, H_a–C(1)); 3.99 (*d*, ³J_{aa} = 12.3, H_a–C(2)); 5.57 (*s*, 1 H, CH₂=C); 6.21 (*s*, 1 H, CH₂=C); 7.03–7.31 (*m*, Ph); 10.5 (*s*, OH). ¹³C-NMR (125 MHz, CDCl₃): 25.8 (C(5)); 32.2 (C(6)); 41.8 (C(4)); 47.7 (C(1)); 60.9 (C(2)); 127.0 (C_p); 128.3 (C_o); 129.0 (CH₂=C); 129.3 (C_m); 136.4 (C_{ipso}); 140.7 (CH₂=C); 171.6 (COOH); 209.3 (C=O). HR-MS: 244.1109 (C₁₅H₁₆O₃⁺; calc. 244.1099).

A soln. of the above acid (137 mg, 0.473 mmol) in dry AcOEt (5 ml) under Ar was cooled to –10° and treated first with Et₃N (48 mg, 0.473 mmol) and then dropwise with diphenylphosphinic chloride (112 mg, 0.52 mmol). After 1 h, pyrrolidine (34 mg, 0.473 mmol) and additional Et₃N (48 mg, 0.473 mmol) were dropwise introduced. After stirring overnight the mixture was filtered and the clear soln. washed first with 3.5*M* HCl (10 ml), then with 10% Na₂CO₃ soln. (20 ml) and finally with H₂O (10 ml). After drying (MgSO₄) and evaporation, the residue was purified by CC (silica gel, hexane/AcOEt 1:1): 111 mg (79%) of **6**. M.p. 98°. FT-IR (drift): 2863*s*, 1715*m*, 1630*m*, 1596*s*, 1445*m*, 1340*m*, 1246*m*, 1168*m*, 1102*m*, 1071*m*, 1036*m*, 927*m*, 876*m*, 838*m*, 786*m*, 752*m*, 709*s*, 670*m*. ¹H-NMR (500 MHz, CDCl₃): 1.40 (*m*, CH₂(β) (pyr)); 1.75 (*m*, CH₂(β') (pyr)); 1.83 (*m*, H_e–C(6)); 2.06–2.18 (*m*, H_e–C(5), H_a–C(6)); 2.29–2.43 (*m*, H_a–C(5), H_e–C(4)); 2.46–2.50 (*m*, CH₂(α) (pyr)); 2.66 (*m*, H_a–C(4)); 3.05 (*m*, H_a–C(1)); 3.30 (*t*, ³J = 7.1, CH₂(α') (pyr)); 3.87 (*d*, ³J_{aa} = 12.5, H_a–C(2)); 5.06 (*s*, 1 H, CH₂=C); 5.23 (*s*, 1 H, CH₂=C); 7.00–7.26 (*m*, Ph). ¹³C-NMR (125 MHz, CDCl₃): 24.1 (C(5)); 25.9 (C(β) (pyr)); 26.2 (C(β') (pyr)); 33.9 (C(6)); 41.8 (C(4)); 45.5 (C(α) (pyr)); 48.6 (C(α') (pyr)); 50.4 (C(1)); 61.0 (C(2)); 118.1 (CH₂=C); 127.0 (C_p); 128.1 (C_o); 129.6 (C_m); 137.1 (C_{ipso}); 146.3 (CH₂=C); 168.7 (CON); 209.4 (C=O). HR-MS: 297.1741 (C₁₉H₂₃NO₂⁺; calc. 297.1729).

8. ($\pm$)-rel-(1*R*,2*S*,3*S*)-3-[1-Methylidene-2-oxo-2-(pyrrolidin-1-yl)ethyl]-2-phenylcyclohexanamine (**7**). A soln. of **6** (271 mg, 0.913 mmol) in abs. MeOH (5 ml) under Ar was cooled to -78° and the following was added: NH_4Ac (835 mg, 10.84 mmol), $(\text{NH}_4)\text{CNBH}_3$ (57 mg, 0.913 mmol), and 3-Å molecular sieves (1 g). After 2 h at -78° , the cooling bath was removed and the mixture kept at r.t. for 10 h. After filtration and removal of the solvent under reduced pressure, the residue was dissolved in Et_2O (20 ml) and extracted with 5% HCl soln. (3×10 ml). The combined aq. layer was brought to pH 12 by addition of 2*N* NaOH and extracted with Et_2O (3×10 ml). After drying (MgSO_4), the solvent was evaporated and the yellowish oil chromatographed (Alox, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1): **7** (221 mg, 81%). Colorless oil. FT-IR (drift): 3332*m*, 2928*s*, 1599*s*, 1445*s*, 1355*m*, 1164*m*, 940*m*, 791*m*, 759*s*, 703*s*, 639*m*. $^1\text{H-NMR}$ (250 MHz, CDCl_3): 1.18–1.82 (*m*, $\text{CH}_2(\beta)$, $\text{CH}_2(\beta')$ (pyr), $\text{H}-\text{C}(4)$, $\text{H}-\text{C}(5)$, $\text{H}-\text{C}(6)$); 1.89–1.93 (*s*, NH_2); 2.31 (*m*, $^3J_{\text{a,a}} = 10.3$, $\text{H}_\text{a}-\text{C}(3)$); 2.43–2.56 (*m*, $\text{CH}_2(\alpha)$ (pyr)); 2.68–2.80 (*m*, $\text{H}_\text{a}-\text{C}(1)$, $\text{H}_\text{a}-\text{C}(2)$); 3.14–3.26 (*m*, $\text{CH}_2(\alpha')$ (pyr)); 4.97 (*s*, 1 H, $\text{CH}_2=\text{C}$); 5.16 (*s*, 1 H, $\text{CH}_2=\text{C}$); 7.06–7.26 (*m*, Ph). $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3): 24.1 (C(5)); 25.1 (C(β) (pyr)); 26.0 (C(β) (pyr)); 34.5 (C(6)); 35.2 (C(4)); 45.4 (C(α) (pyr)); 46.1 (C(3)); 48.5 (C(α') (pyr)); 50.4 (C(1)); 56.2 (C(2)); 116.5 ($\text{CH}=\text{C}$); 126.2 (C_{*p*}); 128.2 (C_{*o*}); 128.8 (C_{*m*}); 142.3 (C_{*ipso*}); 148.4 ($\text{CH}_2=\text{C}$); 170.0 (CONH₂). HR-MS: 298.2032 (C₁₉H₂₆N₂O⁺; calc. 298.2045).

9. ($\pm$)-trans-2-(3-Methoxyphenyl)-3-(prop-2-enyl)cyclohexanone (**8**). The synthesis of **8** was carried out as described for **4**, except that 1-bromo-3-methoxybenzene was used as starting material in the first step (Grignard reaction). The 3-methoxy derivative of **1** ($\pm$)-2-(3-methoxyphenyl)cyclohexanone, was obtained in 31% yield. $^1\text{H-NMR}$ (250 MHz, CDCl_3): 2.04–2.54 (*m*, $\text{CH}_2(3)$, $\text{CH}_2(4)$, $\text{CH}_2(5)$); 2.63–2.87 (*m*, $\text{CH}_2(6)$); 3.74 (*s*, MeO); 3.97 (*dd*, $\text{H}-\text{C}(2)$); 6.43–6.53 (*m*, 2 H_{*o*}); 6.55 (*m*, H_{*p*}); 7.09 (*m*, H_{*m*}).

Bromination according to *Exper. 3* gave ($\pm$)-2-bromo-2-(3-methoxyphenyl)cyclohexanone in 98% yield. $^1\text{H-NMR}$ (250 MHz, CDCl_3): 1.70–1.86 (*m*, $\text{CH}_2(4)$, $\text{CH}_2(5)$); 2.30–2.68 (*m*, $\text{CH}_2(3)$); 2.87–3.09 (*m*, $\text{CH}_2(6)$); 3.72 (*s*, MeO); 6.48 (*m*, H_{*o*}, H_{*o*}); 6.59 (*m*, H_{*p*}); 7.15 (*m*, H_{*m*}).

Elimination according to *Exper. 2* furnished 2-(3-methoxyphenyl)cyclohex-2-en-1-one in 79% yield. $^1\text{H-NMR}$ (250 MHz, CDCl_3): 1.97–2.09 (*m*, $\text{CH}_2(5)$); 2.42–2.57 (*m*, $\text{CH}_2(4)$, $\text{CH}_2(6)$); 3.73 (*s*, MeO); 6.78 (*m*, 2 H_{*o*}, $\text{H}-\text{C}(3)$); 6.94 (*m*, H_{*p*}); 7.15 (*m*, H_{*m*}).

The methoxy derivative of **3** ($\pm$)-*cis*-3-(prop-2-enyl)-2-(3-methoxyphenyl)cyclohexanone was synthesized according to *Exper. 4*. The crude product (*cis/trans* 4:1 by $^1\text{H-NMR}$) was obtained in 80% yield. $^1\text{H-NMR}$ (250 MHz, CDCl_3 ; *cis*-isomer): 1.59 (*s*, Me); 1.77 (*m*, $\text{H}_\text{e}-\text{C}(4)$); 1.99 (*m*, $\text{H}_\text{e}-\text{C}(5)$); 2.14 (*m*, $\text{H}_\text{a}-\text{C}(4)$, $\text{H}_\text{a}-\text{C}(5)$); 2.35 (*m*, $\text{H}_\text{e}-\text{C}(3)$); 2.56 (*m*, $\text{H}_\text{e}-\text{C}(6)$); 2.83 (*m*, $\text{H}_\text{a}-\text{C}(6)$); 3.76 (*s*, MeO); 3.95 (*d*, $^3J_{\text{a,e}} = 5.6$, $\text{H}_\text{a}-\text{C}(2)$); 4.68 (*s*, 1 H, $\text{CH}_2=\text{C}$); 4.78 (*s*, 1 H, $\text{CH}_2=\text{C}$); 6.80 (*m*, H_{*o*}, H_{*o*}); 6.93 (*m*, H_{*o*}); 7.14 (*m*, H_{*m*}).

Equilibration of the crude *cis/trans* mixture according to *Exper. 5* and CC (silica gel, hexane/AcOEt 10:1) gave pure **8** (60% yield, including the last two steps). Colorless oil. FT-IR (film): 2938*s*, 1714*s*, 1646*m*, 1586*s*, 1492*m*, 1455*s*, 1376*m*, 1257*s*, 1168*s*, 1104*m*, 1049*s*, 892*s*, 778*s*, 697*s*. $^1\text{H-NMR}$ (250 MHz, CDCl_3): 1.61 (*s*, Me); 1.80–2.01 (*m*, $\text{CH}_2(4)$, $\text{H}_\text{e}-\text{C}(5)$); 2.17 (*m*, $\text{H}_\text{a}-\text{C}(5)$); 2.44–2.57 (*m*, $\text{CH}_2(6)$); 2.82 (*m*, $\text{H}_\text{a}-\text{C}(3)$); 3.64 (*d*, $^3J_{\text{a,a}} = 10.3$, $\text{H}_\text{a}-\text{C}(2)$); 3.76 (*s*, MeO); 4.61 (*s*, 1 H, $\text{CH}_2=\text{C}$); 4.64 (*s*, 1 H, $\text{CH}_2=\text{C}$); 6.63 (*m*, H_{*o*}, H_{*o*}); 6.79 (*m*, H_{*p*}); 7.22 (*m*, H_{*m*}). $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3): 19.0 (Me); 26.0 (C(4)); 31.7 (C(5)); 42.0 (C(6)); 53.1 (C(3)); 55.0 (MeO); 61.2 (C(2)); 111.9 (C_{*p*}); 112.7 ($\text{CH}_2=\text{C}$); 115.5 (C_{*o*}); 121.8 (C_{*o*}); 128.9 (C_{*m*}); 138.6 (C_{*ipso*}); 145.6 ($\text{CH}_2=\text{C}$); 159.3 (MeO–C_{*m*}); 209.5 (C=O). HR-MS: 244.1448 (C₁₆H₂₀O₂⁺; calc. 244.1463).

10. ($\pm$)-trans-2-(3-Methoxyphenyl)-3-(prop-2-enyl)cyclohexanone Oxime (**9**). To a soln. of **8** (161 mg, 0.66 mmol) in abs. MeOH (10 ml), $\text{NH}_2\text{OH} \cdot \text{HCl}$ (2.9 g, 3 mmol) was added under stirring, and subsequently the pH was adjusted to 5 by addition of *N,N*-dimethylpyridin-4-amine (DMAP). Heating to reflux for 2 h followed, while keeping the pH at 5 by further addition of DMAP. After solvent removal under reduced pressure, Et_2O (20 ml) and H_2O (10 ml) were added, the aq. layer was further extracted with Et_2O (2×10 ml), the combined org. layer washed with sat. NaHCO_3 soln. (10 ml) and brine (10 ml) dried (MgSO_4), and evaporated and the residue chromatographed (silica gel, hexane/AcOEt 5:1): 123 mg (72%) of **9** (*E/Z* mixture). Colorless oil. $^1\text{H-NMR}$ (250 MHz, CDCl_3): 1.61 (*s*, Me); 1.75–2.04 (*m*, $\text{CH}_2(4)$, $\text{H}_\text{e}-\text{C}(5)$); 2.12 (*m*, $\text{H}_\text{a}-\text{C}(5)$); 2.23–2.56 (*m*, $\text{CH}_2(6)$); 2.80 (*m*, $\text{H}_\text{a}-\text{C}(3)$); 3.19 (*m*, $\text{H}_\text{a}-\text{C}(2)$); 3.76 (*s*, MeO); 4.60 (*s*, 1 H, $\text{CH}_2=\text{C}$); 4.67 (*s*, 1 H, $\text{CH}_2=\text{C}$); 6.64 (*m*, 2 H_{*o*}); 6.72 (*m*, H_{*p*}); 7.15 (*m*, H_{*m*}).

11. ($\pm$)-rel-(1*R*,2*S*,3*S*)-2-(3-Methoxyphenyl)-3-(prop-2-enyl)cyclohexanamine (**10**). To a vigorously stirred suspension of LiAlH_4 (38 mg, 1 mmol) in abs. THF (10 ml), a soln. of **9** (107 mg, 0.413 mmol) in abs. THF (5 ml) was dropwise added under Ar at r.t. Reflux (2 h) and cooling were followed by careful addition of AcOEt (30 ml) and then of 2*N* NaOH (5 ml). The org. layer was washed with H_2O (10 ml), dried (MgSO_4), and evaporated and the remaining colorless oil purified by CC (silica gel, hexane/AcOEt 1:1): 77 mg (76%) of **10**. FT-IR (film): 2924*s*, 1601*s*, 1486*m*, 1375*m*, 1262*m*, 1156*m*, 1048*m*, 886*m*, 781*m*, 734*m*, 701*m*. $^1\text{H-NMR}$ (500 MHz, CDCl_3): 1.49 (*s*, Me); 1.50 (*m*, $\text{H}_\text{e}-\text{C}(4)$, $\text{CH}_2(5)$); 1.73 (*m*, $\text{H}_\text{a}-\text{C}(4)$); 1.86 (*m*, $\text{H}_\text{e}-\text{C}(6)$); 2.07

(*m*, H_a –C(6)); 2.31 (*m*, $^3J_{a,a} = 11.3$, 11.1, $^3J_{a,e} = 3.2$, H_a –C(3)); 2.38 (*dd*, $^3J_{a,a} = 11.3$, 10.0, H_a –C(2)); 2.88 (*m*, $^3J_{a,a} = 10.0$, $^3J = 10.2$, $^3J_{a,e} = 3.2$, H_a –C(1)); 3.35 (*s*, NH_2); 3.77 (*s*, MeO); 4.47 (*d*, $^2J = 1.4$, 1 H, $CH_2=C$); 4.49 (*s*, 1 H, $CH_2=C$); 6.73 (*m*, H_o , H_o' , H_p); 7.17 (*dd*, $^3J = 8.5$, 7.6, H_m). ^{13}C -NMR (125 MHz, $CDCl_3$): 19.5 (Me); 24.6 (C(5)); 32.1 (C(4)); 33.9 (C(6)); 50.8 (C(3)); 55.1 (MeO); 55.2 (C(1)); 55.8 (C(2)); 111.8 (C(4)); 111.8 ($CH_2=C$); 111.9 (C_o); 129.4 (C_m); 129.4 (C_o); 143.0 (C_{ipso}); 147.0 ($CH_2=C$); 159.6 (MeO–C_m). HR-MS: 245.1841 (C₁₆H₂₃NO⁺; calc. 245.1835).

12. (±)-rel-(1*R*,2*S*,3*S*)-2-(3-Methoxyphenyl)-N,N-dimethyl-3-(prop-2-enyl)cyclohexanamine (**11**). To a soln. of **10** (392 mg, 1.6 mmol) in abs. MeOH (10 ml) under Ar, first a 37% aq. formaldehyde soln. (0.4 ml, 5 mmol) was added. Then, at r.t. and under vigorous stirring, a soln. of NaCNBH₃ (101 mg, 1.6 mmol) and ZnCl₂ (109 mg, 0.8 mmol) in abs. MeOH (5 ml) was dropwise and slowly introduced. After 10 h, the mixture was treated with 0.5M aq. NaOH (10 ml), and most of the MeOH was distilled off *in vacuo*. After extraction with Et₂O (3 × 20 ml), washing with H₂O, and drying (MgSO₄), the product was purified by CC (silica gel, hexane/AcOEt 1:1): 376 mg (86%) of **11**. Colorless oil. FT-IR (film): 2928s, 2777m, 1645m, 1608s, 1585m, 1487s, 1453s, 1373m, 1262s, 1154s, 1084s, 886s, 804s, 772s, 698s. 1H -NMR (500 MHz, $CDCl_3$): 1.47 (*s*, Me); 1.34–1.48 (*m*, H_c –C(4), $CH_2(5)$); 1.68 (*m*, H_a –C(4)); 1.94 (*m*, $CH_2(6)$); 2.14 (*s*, Me₂N); 2.25 (*m*, H_a –C(3)); 2.56 (*m*, H_a –C(1)); 2.75 (*m*, H_a –C(2)); 3.76 (MeO); 4.43 (*s*, 1 H, $CH_2=C$); 4.44 (*s*, 1 H, $CH_2=C$); 6.71 (*m*, H_o , H_o' , H_p); 7.16 (*m*, H_m). ^{13}C -NMR (125 MHz, $CDCl_3$): 19.6 (Me); 23.9 (C(5)); 25.0 (C(4)); 32.4 (C(6)); 40.2 (Me₂N); 51.2 (C(3)); 53.0 (C(2)); 54.9 (MeO); 67.2 (C(1)); 110.3 (C(4)); 111.2 ($CH_2=C$); 114.3 (C_o); 120.5 (C_o); 128.5 (C_m); 145.2 (C_{ipso}); 147.5 ($CH_2=C$); 159.0 (MeO–C_m). HR-MS 273.2083 C₁₈H₂₇NO⁺; calc. 273.2093).

13. (±)-2-rel-(1*R*,2*S*,3*S*)-3-(Dimethylamino)-2-(3-methoxyphenyl)cyclohexylprop-2-enal (**12**). Oxidation of **11** with SeO₂ according to *Exper. 6* and CC (silica gel, hexane/AcOEt 1:1) gave **12** in 54% yield. Colorless oil. FT-IR (film): 2931s, 1689s, 1601m, 1453m, 1262s, 1155m, 1046s, 953m, 781m, 700m. 1H -NMR (500 MHz, $CDCl_3$): 1.41–1.58 (*m*, H_c –C(4), $CH_2(5)$); 1.67 (*m*, H_a –C(4)); 1.93 (*m*, H_c –C(6)); 2.00 (*m*, H_a –C(6)); 2.14 (*s*, Me₂N); 2.88 (*m*, $^3J_a = 10.2$, $^3J_{a,e} = 9.3$, H_a –C(3)); 2.97 (*m*, H_a –C(1), H_a –C(2)); 3.73 (*s*, MeO); 5.87 (*s*, 1 H, $CH_2=C$); 6.27 (*s*, 1 H, $CH_2=C$); 6.69 (*m*, 2 H_o , H_p); 7.10 (*dd*, $^3J = 8.4$, $^3J = 7.5$, H_m). ^{13}C -NMR (125 MHz, $CDCl_3$): 24.4 (C(5)); 25.1 (C(4)); 32.7 (C(6)); 40.4 (Me₂N); 44.4 (C(1)); 50.8 (C(2)); 55.1 (MeO); 67.5 (C(3)); 111.1 (C(4)); 114.3 (C(2)); 120.6 (C(6)); 129.0 (C_m); 135.6 ($CH_2=C$); 144.1 (C_{ipso}); 152.1 ($CH_2=C$); 159.4 (MeO–C_m); 194.1 (CHO). EI-MS (70 eV, 25°): 47.0(8), 49.0(6), 58.1(5), 71.1(22), 83.9(84), 85.1(3), 85.9(31), 121.1(3), 138.1(7), 166.1(100), 167.1(9), 287.2(12), 288.2(2). HR-MS: 287.1904 (C₁₈H₂₅NO₂⁺; calc. 287.1885).

14. (±)-rel-(4*bS*,5*R*,8*aS*,9*S*)-5-(Dimethylamino)-4*b*,5,6,7,8,9,10-octahydro-3-methoxyphenanthrene-9-carbaldehyde (**13**). A soln. of **12** (100 mg, 0.35 mmol) in CH_2Cl_2 (5 ml) was cooled to –78° under Ar. BF₃·Et₂O (248 mg, 1.75 mmol) was then added and stirred for 12 h at –78°. After removing the cooling bath and reaching r.t., 0.5N aq. NaOH (10 ml) was added. The aq. layer was extracted with CH_2Cl_2 (3 × 10 ml), the combined org. layer washed with H₂O (5 ml), dried (MgSO₄), and evaporated, and the residue submitted to CC (silica gel, hexane/AcOEt 1:1): 81 mg (81%) of **13**. Colorless oil. 1H -NMR (400 MHz, $CDCl_3$): 1.21–1.53 (*m*, $CH_2(7)$, $CH_2(8)$); 1.90 (*m*, $CH_2(6)$); 2.05 (*m*, H –C(8a)); 2.40 (*s*, NMe₂); 2.48 (*m*, H –C(9), 1 H –C(10)); 2.87 (*m*, H –C(5)); 2.98 (*m*, H –C(4b), 1 H –C(10)); 3.79 (*s*, MeO); 6.68 (*m*, H –C(2)); 7.01 (*d*, $^3J = 8.2$, H –C(1)); 7.43 (*s*, H –C(4)); 9.44 (*d*, $^3J = 2.2$, CHO). ^{13}C -NMR (100.6 MHz, $CDCl_3$): 21.6 (C(7)); 24.3 (C(8)); 26.9 (C(6)); 33.7 (C(10)); 39.6 (C(8a)); 40.0 (Me₂N); 42.0 (C(9)); 53.8 (C(4b)); 55.1 (MeO); 63.6 (C(5)); 110.5 (C(2)); 112.7 (C(4)); 127.7 (C(1)); 128.3 (C(10a)); 144.1 (C(4a)); 158.2 (C(3)); 203.2 (CHO). FT-IR (film): 2927s, 1722s, 1580m, 1491s, 1264m, 1155m, 857m, 732s. EI-MS (70 eV, 25°): 47.0 (12), 49.0 (9), 56.0 (4), 58.1 (38), 83.9 (100), 85.1 (4), 85.9 (38), 87.9 (5), 99.0 (9), 115.1 (4), 128.1 (4), 129.1 (3), 144.1 (3), 159.1 (6), 171.1 (10), 174.1 (4), 213.1 (11), 214.3 (14), 216.2 (4), 258.2 (50), 259.2 (27), 260.2 (4), 286.2 (7), 287.2 (31), 288.2 (5). HR-MS: 287.1905 (C₁₈H₂₅NO₂⁺; calc. 287.1885).

15. 1-Methoxy-2,4,6-trimethylbenzene (**15**). A suspension of 2,4,6-trimethylphenol (10 g, 73.42 mmol) in H₂O (20 ml) placed in an ice bath was vigorously stirred and rapidly treated with KOH (5.14 g, 91.18 mmol) in H₂O (50 ml). Under continuous cooling, Me₂SO₄ (9.26 g, 73.42 mmol) was added. Then the ice bath was replaced by an oil bath and the mixture heated to 60° for 2 h. After cooling to r.t., the mixture was diluted with Et₂O (50 ml) and the org. layer washed with 20% aq. KOH (4 × 20 ml) and H₂O (2 × 20 ml), dried (MgSO₄), and evaporated: 9.815 g (89%) of **15**. Colorless liquid. 1H -NMR (250 MHz, $CDCl_3$): 2.12 (*s*, Me–C(4)); 2.13 (*s*, Me–C(2), Me–C(6)); 3.60 (*s*, MeO); 6.72 (*s*, 2 arom. H).

16. 2-Bromo-4-methoxy-1,3,5-trimethylbenzene (**16**). To a soln. of **15** (10 g, 66.6 mmol) in CCl₄ (100 ml), cooled to 0° and vigorously stirred, a soln. of Br₂ (10.65 g, 66.6 mmol) in CCl₄ (20 ml) was slowly added. After the addition, the mixture was heated to 60° for 2 h until no vapor of Br₂ was observed. Usual workup and distillation *in vacuo* afforded 8.694 g (57%) of **16**. Colorless liquid. B.p. 79°/1 mbar. 1H -NMR (250 MHz, $CDCl_3$): 2.12 (*s*, Me–C(5)); 2.25 (*s*, Me–C(3)); 2.27 (*s*, Me–C(1)); 3.60 (*s*, MeO); 6.85 (*s*, arom. H).

17. *3-Methoxy-2,4,6-trimethylbenzoic Acid (17)*. To a suspension of Mg (0.53 g, 21.8 mmol) in abs. THF (20 ml), a soln. of **16** (5 g, 21.8 mmol) in abs. THF (20 ml) was added in portions at r.t. To complete the reaction, the mixture was gently boiled for further 30 min. The *Grignard* reagent thus prepared was poured on dry ice (100 g). After the excess CO₂ had sublimed, H₂O (10 ml) was added, the THF evaporated, Et₂O (30 ml) added, and the org. phase extracted with 2N NaOH (5 ml) and 1N NaOH (20 ml). The pH of the combined aq. layer was brought to 2 by addition of dil. HCl soln., the acid soln. extracted with Et₂O (2 × 20 ml), and the combined org. layer dried (MgSO₄) and evaporated: 3.175 g (75%) of **17**. Colorless solid. ¹H-NMR (250 MHz, CDCl₃): 2.20 (s, Me–C(4)); 2.30 (s, Me–C(2), Me–C(6)); 3.62 (s, MeO); 6.83 (s, 1 arom. H); 10.6 (s, COOH).

18. *3-Methoxy-2,4,6-trimethylbenzenemethanol (18)*. To a suspension of LiAlH₄ (1.17 g, 30.9 mmol) in abs. THF (20 ml) a soln. of **17** (6 g, 30.9 mmol) in abs. THF (20 ml) was dropwise added at a rate that kept the mixture gently boiling. Subsequent heating to reflux for 4 h was followed by careful addition of H₂O (10 ml) and then of 1N HCl (5 ml). Most of the THF was removed by distillation *in vacuo* and the residue diluted with Et₂O (50 ml). Adjustment of the pH to 10 by 0.5N NaOH, extraction with Et₂O (2 × 20 ml), washing of the combined org. layers with brine, followed by the usual workup and distillation afforded 4.73 g (85%) of **18**. Colorless liquid. FT-IR (drift): 3308s, 2916m, 1479s, 1307m, 1230s, 1099s, 1008s, 984m, 865s, 736m. ¹H-NMR (250 MHz, CDCl₃): 1.89 (s, OH); 2.26 (s, Me–C(4)); 2.35 (s, Me–C(2), Me–C(6)); 3.68 (s, MeO); 4.65 (s, CH₂OH); 6.87 (s, arom. H). ¹³C-NMR (100.6 MHz, CDCl₃): 11.8 (Me–C(4)); 16.0, 19.0 (Me–C(2), Me–C(6)); 59.9 (MeO); 130.4 (arom. C); 130.4 (arom. C); 130.5 (C(5)); 132.6 (C(4)); 135.6 (C(1)); 155.1 (C(3)). HR-MS: 180.1144 (C₁₁H₁₆O₂⁺; calc. 180.1150).

19. *3-Methoxy-2,4,6-trimethylbenzyl Methanesulfonate (19)*. To a soln. of **18** (2 g, 7.14 mmol) and Et₃N (1.98 ml, 14.28 mmol) in abs. CH₂Cl₂ (10 ml), a soln. of MeSO₂Cl (0.84 ml, 10.71 mmol) in abs. CH₂Cl₂ (5 ml) was added dropwise at –25°, and within 10 min, the mixture was allowed to warm to 10° and then stirred at 10° for 2 h. The reaction was terminated by addition of H₂O (5 ml), the aq. layer separated and extracted with CH₂Cl₂ (2 × 10 ml), and the combined org. layer washed with ice-cold H₂O (2 × 10 ml), dried (MgSO₄), and evaporated at 0°: 2.48 g (97%) of **19**. Colorless oil. ¹H-NMR (250 MHz, CDCl₃): 2.28 (s, Me–C(4)); 2.38 (s, Me–C(2), Me–C(6)); 3.43 (s, MeSO₃); 3.67 (s, MeO); 4.87 (s, CH₂); 6.88 (s, arom. H).

20. *3-Methoxy-2,4,6-trimethylacetoneitrile (20)*. To a soln. of **19** (2.48 g, 6.93 mmol) in abs. DMF at 0°, KCN (451 mg, 6.93 mmol) was added in portions. After stirring for 24 h, Et₂O (100 ml) and 1N NaOH (20 ml) were added. The org. layer was washed with 0.1N NaOH (4 × 10 ml) and H₂O (2 × 10 ml); dried (MgSO₄), and evaporated, and the product purified by CC (silica gel, hexane/AcOEt 10:1): 0.917 g (70%) of **20**. Colorless solid. FT-IR (drift): 2952s, 2246m, 1480s, 1309m, 1236s, 1219m, 1088s, 1000s, 869s, 734m. ¹H-NMR (250 MHz, CDCl₃): 2.27 (s, Me–C(4)); 2.32, (2s, Me–C(2), Me–C(6)); 3.61 (s, CH₂CN); 3.69 (s, MeO); 6.92 (s, arom. H). ¹³C-NMR (100.6 MHz, CDCl₃): 12.4 (Me–C(4)); 16.0, 18.0 (Me–C(2), Me–C(6)); 19.62 (CH₂); 60.1 (MeO); 117.5 (CN); 126.3 (arom. C); 129.8 (arom. C); 130.8 (C(5)); 131.8 (C(1)); 155.5 (C(3)). HR-MS: 189.1141 (C₁₂H₁₅NO⁺; calc. 189.1153).

21. *(±)-α-(3-Methoxy-2,4,6-trimethylphenyl)-1,3-dioxolane-2-butanenitrile (21)*. To a stirred soln. of **20** (1.89 g, 10 mmol) and 2-(2-bromomethyl)-1,3-dioxolane (1.99 g, 11 mmol) in benzene (10 ml), NaNH₂ (0.43 g, 11 mmol) was added at r.t. After the addition, the mixture was heated to reflux, the cooled soln. diluted with Et₂O (30 ml), and the excess NaNH₂ hydrolyzed by careful addition of H₂O (10 ml). The aq. phase was extracted with Et₂O (2 × 10 ml), the combined org. phase dried (MgSO₄) and evaporated, and the residue chromatographed (silica gel, hexane/AcOEt 10:1): 2.46 g (85%) of **21**. Colorless oil. FT-IR (film): 2950s, 2236m, 1481s, 1305m, 1238m, 1142s, 1002m, 945m, 735m. ¹H-NMR (250 MHz, CDCl₃): 1.76–2.22 (m, (CH₂)₂); 2.22 (s, Me–C(4')); 2.35, 2.36 (2s, Me–C(2'), Me–C(6')); 3.69 (s, MeO); 3.80–3.97 (m, O(CH₂)₂O); 4.25 (dd, ³J = 9.9, 6.0, H–C(α)); 4.90 (m, H–C(2)); 6.86 (s, arom. H). ¹³C-NMR (100.6 MHz, CDCl₃): 12.8 (Me–C(4')); 15.9, 20.1 (Me–C(2'), Me–C(6')); 26.1 (CH₂); 31.1 (CH₂); 31.6 (C(α)); 59.8 (MeO); 64.9 (O(CH₂)₂O); 103.4 (C(2)); 120.5 (CN); 129.4 (arom. C); 130.4 (arom. C); 130.9 (arom. C); 131.3 (C(5')); 131.6 (C(1')); 155.7 (C(3')). HR-MS: 289.1689 (C₁₇H₂₃NO₃⁺; calc. 289.1677).

22. *(±)-β-(3-Methoxy-2,4,6-trimethylphenyl)-1,3-dioxolane-2-butanamine (22)*. To a stirred suspension of LiAlH₄ (132 mg, 3.5 mmol) in abs. THF (5 ml), a soln. of **21** (1 g, 3.5 mmol) in abs. THF (10 ml) was dropwise and slowly added at r.t. After heating to reflux for 5 h, the excess LiAlH₄ was destroyed by addition of H₂O (5 ml) under cooling in an ice bath. Most of the solvent was removed by distillation, and then Et₂O (20 ml) and 0.5N NaOH (5 ml) were added to the residue. The aq. phase was extracted with Et₂O (2 × 20 ml), the combined org. layer dried (MgSO₄) and evaporated, and the residue chromatographed (silica gel, hexane/AcOEt 1:1): 739 mg (72%) of **22**. Colorless oil. FT-IR (film): 2950s, 1572m, 1478m, 1402s, 1301m, 1236m, 1142s, 1032m, 943m, 755m. ¹H-NMR (250 MHz, CDCl₃): 1.55 (m, CH₂); 1.84 (m, CH₂); 2.17 (s, Me–C(4')); 2.25, 2.27 (2s, Me–C(2'), Me–C(6')); 3.02 (m, CH₂NH₂); 3.26 (m, H–C(β)); 3.42 (s, NH₂); 3.62 (3.60)* (s, MeO); 3.85–3.95

(O(CH₂)₂O); 4.74 (*t*, ³*J* = 4.6, H–C(2)); 6.79 (6.73)* (*s*, arom. H). ¹³C-NMR (100.6 MHz, CDCl₃): 13.3 (13.4)* (*Me*–C(6')); 15.8 (*Me*–C(4')); 20.9 (21.8)* (*Me*–C(2')); 25.6 (25.9)* (CH₂); 32.2 (32.4)* (CH₂); 44.7 (44.9)* (CH₂NH₂); 49.9 (C(β)); 59.6 (59.9)* (MeO); 64.8 (O(CH₂)₂O); 104.3 (C(2)); 128.4 (129.4)* (arom. C); 131 (C(4')); 131.4 (133.3)* (C(5')); 132.5 (C(1')); 136.7 (136.8)* (arom. C); 155.0 (156.2)* (C(3')). HR-MS: 293.1976 (C₁₇H₂₇NO₃⁺; calc. 293.1991).

23. (±)-β-(3-Methoxy-2,4,6-trimethylphenyl)-N,N-dimethyl-1,3-dioxolane-2-butanamine (**23**). To a soln. of **22** (469 mg, 1.6 mmol) in abs. MeOH (10 ml), 37% aq. CH₂O soln. 0.4 ml, 5 mmol) was added, and then, under vigorous stirring and at r.t., a soln. of NaCNBH₃ (101 mg, 1.6 mmol) and ZnCl₂ (109 mg, 0.8 mmol) in abs. MeOH (5 ml) was slowly introduced. After 10 h, 0.5*N* aq. NaOH (10 ml) was added, and most of the MeOH was distilled off *in vacuo*. The aq. layer was extracted with Et₂O (3 × 20 ml), the combined org. layer washed with H₂O (2 × 10 ml), dried (MgSO₄), and evaporated, and the concentrated crude product purified by CC (silica gel, hexane/AcOEt 1:1): 416 mg (81%) of **23**. Colorless oil. FT-IR (film): 2944*s*, 2764*m*, 1459*s*, 1220*m*, 1141*s*, 1034*m*. ¹H-NMR (250 MHz, CDCl₃): 1.55 (*m*, CH₂); 1.92 (*m*, CH₂); 2.19 (*s*, *Me*–C(4')); 2.22, 2.23 (2*s*, Me₂N); 2.27, 2.29 (2*s*, *Me*–C(2'), *Me*–C(6')); 2.45 (*m*, 1 H, CH₂N); 2.73 (*m*, 1 H, CH₂N); 3.26 (*m*, H–C(β)); 3.64 (3.62)* (*s*, MeO); 3.85–3.95 (*m*, OCH₂CH₂O); 4.76 (*m*, H–C(2)); 6.80 (6.75)* (*s*, arom. H). ¹³C-NMR (100.6 MHz, CDCl₃): 13.1 (13.6)* (*Me*–C(6')); 15.8 (*Me*–C(4')); 21.3 (21.5)* (*Me*–C(2')); 26.7 (27.0)* (CH₂); 32.4 (32.6)* (CH₂); 39.4 (39.8)* (Me₂N); 46.0 (C(β)); 59.6 (59.9)* (MeO); 64.4 (64.7)* (CH₂N); 64.8 (O(CH₂)₂O); 104.5 (C(2)); 127.9 (C(4')); 129.5 (129.8)* (arom. C); 130.8 (C(5')); 131.6 (132.3)* (arom. C); 139.0 (C(1')); 154.9 (C(3')). HR-MS: 321.2315 (C₁₉H₃₁NO₃⁺; calc. 321.2304).

24. (±)-γ-γ'-(Dimethylamino)methyl]-3-methoxy-2,4,6-trimethylbenzenebutanal (**24**). To a soln. of **23** (418 mg, 1.3 mmol) in THF (5 ml), 3*N* HCl (2 ml) was added under vigorous stirring, and the mixture was allowed to stand for 24 h at r.t. After addition of Et₂O (30 ml) and 0.5*N* NaOH (10 ml), the aq. layer was extracted with Et₂O (2 × 10 ml) and the combined org. layer dried (MgSO₄) and evaporated: 360 mg (100%) of **24**. Colorless oil. FT-IR (film): 2943*s*, 1723*m*, 1460*s*, 1300*m*, 1236*m*, 1009*m*, 866*m*. ¹H-NMR (500 MHz, CDCl₃): 2.04 (*m*, CH₂); 2.19 (*s*, *Me*–C(4)); 2.24 (*s*, Me₂N); 2.26, 2.29 (2*s*, *Me*–C(2), *Me*–C(6)); 2.15–2.45 (*m*, 1 H of CH₂N, CH₂CHO, CH₂); 2.80 (*m*, 1 H of CH₂N); 3.25 (*m*, H–C(γ)); 3.63 (3.64)* (*s*, MeO); 6.76 (6.81)* (*s*, arom. H); 9.48 (9.50)* (*s*, CHO). ¹³C-NMR (125 MHz, CDCl₃): 12.9 (13.7)* (*Me*–C(6')); 15.8 (*Me*–C(4')); 21.3 (*Me*–C(2')); 24.7 (25.0)* (CH₂); 38.7 (39.0)* (Me₂N); 42.0 (42.6)* (CH₂); 45.9 (C(γ)); 59.5 (59.8)* (MeO); 64.1 (64.4)* (CH₂N); 128.4 (C(4)); 129.6 (129.8)* (arom. C); 130.9 (132.4)* (C(5)); 131.6 (132.4)* (arom. C); 138.1 (C(1)); 155.0 (156.2)* (C(3)); 199.2 (CHO). EI-MS (70 eV, 40°): 42.0 (1), 43.0 (3), 57.1 (1), 58.1 (100), 59.1 (4), 84.0 (2), 91.1 (1), 161.1 (1), 176.1 (1), 277.2 (3), 278.2 (1). HR-MS: 277.2054 (C₁₇H₂₇NO₂⁺; calc. 277.2042).

25. (±)-γ-γ'-(Dimethylamino)methyl]-3-methoxy-2,4,6-trimethyl-α-methylidenebenzenebutanal (**25**). A soln. of **24** (277 mg, 1 mmol), Et₃N·HCl (98 mg, 1.2 mmol), and 37% aq. CH₂O (97 mg, 1.2 mmol) in THF (10 ml) was heated under reflux for 3 h. After cooling to r.t., Et₂O (30 ml) and 0.5*N* NaOH (10 ml) were added. The aq. layer was extracted with Et₂O (2 × 20 ml), the combined org. phase dried (MgSO₄), and evaporated, and the crude product chromatographed (silica gel, hexane/AcOEt 1:1): 283 mg (98%) of pure **25**. FT-IR (drift): 2941*s*, 1685*m*, 1458*s*, 1235*m*, 1012*m*, 866*m*. ¹H-NMR (500 MHz, CDCl₃): 2.19 (*m*, *Me*–C(2), *Me*–C(4), *Me*–C(6), 1 MeN); 2.33 (2.34)* (*s*, 1 MeN); 2.10–2.85 (*m*, CH₂N, CH₂); 3.50 (*m*, H–C(γ)); 3.61 (3.65)* (*s*, MeO); 5.80 (*s*, 1 H, CH₂=C); 5.96 (*d*, ³*J* = 9.5, 1 H, CH₂=C); 6.76 (6.78)* (*s*, arom. H); 9.40 (9.42)* (*s*, CHO). ¹³C-NMR (125 MHz, CDCl₃): 12.8 (13.9)* (*Me*–C(6')); 15.8 (*Me*–C(4)); 21.1 (21.3)* (*Me*–C(2')); 30.7 (30.9)* (CH₂); 38.1 (38.4)* (Me₂N); 45.6 (C(γ)); 59.5 (59.8)* (MeO); 63.3 (63.6)* (CH₂N); 128.1 (C(4)); 129.5 (129.9)* (arom. C); 130.8 (132.2)* (C(5)); 131.6 (132.4)* (arom. C); 133.8 (CH₂=C); 138.4 (C(1)); 148.8 (148.9)* (CH₂=C); 154.9 (156.1)* (G(s3)); 194.1 (CHO). EI-MS (70 eV, 90°): 42.0 (1), 44.0 (1), 45.0 (1), 47.0 (2), 57.1 (1), 58.1 (100), 59.1 (3), 82.9 (4), 83.9 (3), 84.9 (2), 85.9 (3), 91.1 (1), 105.1 (1), 163.1 (1), 289.2 (10), 290.2 (3). HR-MS: 289.2058 (C₁₈H₂₇NO₂⁺; calc. 289.2042).

26. (±)-4-(3-Methoxy-2,4,6-trimethylphenyl)-2-methylpenta-2,4-dienal (**26**). To a soln. of **25** (100 mg, 0.36 mmol) in CHCl₃ (5 ml), AlCl₃ (233 mg, 1.75 mmol) was added under Ar at –78°. After 12 h, the cooling bath was removed and the mixture brought to r.t. and poured onto an ice-cold 1*M* AcONa soln. (100 ml). After stirring (1 h), Et₂O (50 ml) was added and the aq. layer further extracted with Et₂O. To the combined org. extract, 0.1*N* NaOH (50 ml) was added, the org. layer further extracted with 0.1*N* NaOH (2 × 20 ml), then washed with H₂O (2 × 20 ml), dried (MgSO₄), and evaporated, and the residue chromatographed (silica gel, hexane/AcOEt 10:1): 4.2 mg (*ca.* 5%) of **26**. UV (6.2 · 10^{–5} *M* MeOH): 267 (31800). FT-IR (drift): 2926*s*, 1687*s*, 1454*m*, 1234*s*, 1087*m*, 1057*m*. Colorless oil. ¹H-NMR (500 MHz, CD₃OD): 1.16 (*s*, Me); 2.08 (*s*, *Me*–C(2')); *Me*–C(6')); 2.26 (*s*, *Me*–C(4')); 3.67 (*s*, MeO); 5.39 (*s*, 1 H, CH₂=C); 6.02 (*s*, 1 H, CH₂=C); 6.92 (*s*, arom. H); 7.16 (*s*, CH=); 9.44 (*s*, CHO). ¹³C-NMR (125 MHz, CD₃OD): 11.2 (Me) 13.5 (*Me*–C(6')); 16.1 (*Me*–C(4'));

20.0 (*Me*–C(2')); 60.2 (*MeO*); 121.3 ($\text{CH}_2=\text{C}$); 128.9 (arom. C); 130.1 (arom. C); 130.8 (C(5')); 131.0 (arom. C); 135.0 ($=\text{CCHO}$); 141.9 (C(1')); 146.7 ($\text{CH}_2=\text{C}$); 151.5 ($\text{CH}=\text{}$); 156.2 (C(3')); 197.8 (*CHO*). EI-MS (70 eV, 45°): 75.0 (16), 78.1 (28), 81.1 (29), 115.1 (7), 118.1 (9), 128.1 (7), 129.6 (8), 131.1 (8), 150.1 (13), 171.1 (7), 173.1 (8), 185.1 (11), 186.1 (16), 187.2 (12), 188.2 (9), 200.2 (15), 201.2 (28), 213.2 (12), 215.2 (28), 227.2 (7), 229.1 (17), 230.2 (4), 243.2 (8), 244.2 (100, M^+), 245.2 (14), 246.2 (5).

27. ($\pm$)- γ -[*(Dimethylamino)methyl*]-2,4,6-trimethyl- α -methylidenebenzenebutanal (**30**). According to *Exper.* 21–25 (preparation of **25**), with 2,4,6-trimethylbenzeneacetonitrile (**29**; 5.17 g, 32.5 mmol): 1 g (10% over 5 steps) of **30**. Yellow oil. FT-IR (film): 2966s, 2931s, 2856s, 2817s, 2765s, 1688s, 1612m, 1458s, 1374m, 1262m, 1097m, 1033s, 943m, 852s, 804m, 757m, 734m. ^1H -NMR (500 MHz, CDCl_3): 2.20 (*s*, *Me*–C(2)); 2.21 (*s*, *Me*–C(4)); 2.24 (*s*, *Me*–C(6)); 2.38 (*s*, Me_2N); 2.14–2.86 (*m*, CH_2 , CH_2N); 3.50 (*m*, *H*–C(γ)); 5.81 (*s*, 1 H, $\text{CH}_2=\text{C}$); 5.97 (*s*, 1 H, $\text{CH}_2=\text{C}$); 6.77 (*s*, arom. H); 9.43 (*s*, *CHO*). ^{13}C -NMR (125 MHz, CDCl_3): 20.6 (*Me*–C(6')); 21.5 (*Me*–C(4)); 21.7 (*Me*–C(2')); 30.8 (CH_2); 37.6 (C(γ)); 45.6 (Me_2N); 63.5 (CH_2N); 129.3 (C(3)); 131.2 (C(5)); 133.8 ($\text{CH}_2=\text{C}$); 135.4 (arom. C); 136.2 (arom. C); 136.3 (arom. C); 136.9 (C(1)); 149.0 ($\text{CH}_2=\text{C}$); 194.2 (*CHO*). EI-MS (70 eV, 30°): 42.1 (2), 43.1 (2), 44.1 (1), 57.1 (1), 58.1 (100), 59.1 (2), 84.1 (1), 86.1 (16), 91.1 (1), 129.1 (1), 131.1 (1), 133.1 (1), 205.2 (4), 217.2 (5), 220.2 (1), 259.3 (3). HR-MS: 259.1931 ($\text{C}_{17}\text{H}_{25}\text{NO}^+$; calc. 259.1936).

28. 2,4,6-Trimethyl-3-nitrobenzeneacetonitrile (**31**). To **29** (5 g, 31.4 mmol), fuming nitric acid (5 ml) was added dropwise under stirring. After the soln. had turned orange, it was heated to 40° for 5 min. Then H_2O (10 ml) was added slowly, the mixture extracted with Et_2O (3×5 ml), and the combined org. layer washed with sat. NaHCO_3 soln. (20 ml), dried (MgSO_4), and evaporated: 633 g (99%) of **31**. Yellow solid. M.p. 85° ([40]: 90°). FT-IR (drift): 3181m, 2981s, 2942s, 2882s, 2740m, 2254s, 1525s, 1369s, 1033s, 882s, 843s, 803s. ^1H -NMR (500 MHz, CDCl_3): 2.26 (*s*, *Me*–C(2)); 2.30 (*s*, *Me*–C(4)); 2.41 (*s*, *Me*–C(6)); 3.66 (*s*, CH_2); 7.04 (*s*, *H*–C(5)). ^{13}C -NMR (125 MHz, CDCl_3): 14.7 (*Me*–C(4)); 17.1 (*Me*–C(6')); 17.9 (CH_2); 20.2 (*Me*–C(2')); 116.2 (arom. C); 126.8 (arom. C); 128.1 (arom. C); 129.3 (arom. C); 131.1 (G(5)); 138.9 (C $\equiv\text{N}$); 151.3 (C(3)). EI-MS (70 eV, 90°): 39.0 (4), 77.1 (9), 91.1 (19), 105.1 (7), 115.1 (22), 116.1 (16), 119.1 (11), 131.1 (21), 132.1 (23), 147.1 (8), 160.1 (100), 161.1 (10), 187.1 (49), 204.1 (59), 205.1 (9). HR-MS: 204.0901 ($\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_2^+$; calc. 204.0899).

29. ($\pm$)- β -(2,4,6-Trimethyl-3-nitrophenyl)-1,3-dioxolane-2-butanamine (**33**). ($\pm$)- α -(2,4,6-Trimethyl-3-nitrophenyl)-1,3-dioxolane-2-butanenitrile (**32**; prepared from **31** as described for **21** in *Exper.* 21; 2.597 g, 8.53 mmol) was dissolved in 1M $\text{BH}_3 \cdot \text{THF}$ (12.8 ml, 12.8 mmol) under Ar at r.t. The stirred soln. was refluxed (1 h) and, after cooling, H_2O (10 ml) was added carefully. The soln. was extracted with Et_2O (3×10 ml) and the combined org. phase dried (MgSO_4) and evaporated: 1 g (38%) of **33**. FT-IR (film): 3371m, 2957s, 2883s, 1527s, 1370s, 1142s, 1036s, 913s, 843s, 734s. ^1H -NMR (500 MHz, CDCl_3): 1.46–1.64 (*m*, CH_2); 1.84–1.94 (*m*, CH_2); 2.19 (*s*, *Me*–C(4')); 2.26 (2.24)* (*s*, *Me*–C(2')); 2.37 (2.39)* (*s*, *Me*–C(6')); 3.04–3.12 (*m*, CH_2NH_2); 3.30–3.34 (*m*, *H*–C(β)); 3.80–3.93 (*m*, $\text{O}(\text{CH}_2)_2\text{O}$); 4.78–4.80 (*m*, *H*–C(2)); 6.94 (6.89)* (*s*, *H*–C(5')). ^{13}C -NMR (125 MHz, CDCl_3): 15.0 (16.9)* (*Me*–C(6')); 16.8 (*Me*–C(4')); 22.4 (21.5)* (*Me*–C(2')); 25.9 (25.4)* (CH_2); 32.5 (32.2)* (CH_2); 44.4 (C(β)); 64.9 ($\text{O}(\text{CH}_2)_2\text{O}$); 104.1 (C(2)); 127.1 (126.6)* (arom. C); 128.6 (C(4')); 131.0 (132.6)* (C(5')); 138.0 (C(1')); 140.2 (138.4)* (arom. C); 152.8 (151.7)* (C(3')). EI-MS (70 eV, 75°): 43.0 (19), 45.0 (11), 47.0 (15), 49.0 (12), 73.1 (17), 84.0 (100), 86.0 (63), 88.0 (10), 119.0 (3), 174.1 (3), 191.1 (4), 262.2 (14), 308.2 (2). HR-MS: 308.1740 ($\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_4^+$; calc. 308.1736).

30. ($\pm$)- γ -[*(Dimethylamino)methyl*]-2,4,6-trimethyl- α -methylidene-3-nitrobenzenebutanal (**34**). According to *Exper.* 25, with **33** (989 mg, 3.21 mmol): 343 mg (35% over 3 steps of **34**). Yellow oil. ^1H -NMR (500 MHz, CDCl_3): 2.09–2.79 (*m*, *Me*, CH_2 , CH_2N); 3.47 (*m*, *H*–C(γ)); 5.86 (*s*, 1 H, $\text{CH}_2=\text{C}$); 6.04 (*s*, 1 H, $\text{CH}_2=\text{C}$); 6.82 (*s*, *H*–C(5)); 9.42 (*s*, *CHO*). ^{13}C -NMR (125 MHz, CDCl_3): 15.3 (*Me*–C(6')); 16.7 (*Me*–C(4)); 21.6 (*Me*–C(2')); 30.9 (CH_2); 37.9 (C(γ)); 45.7 (Me_2N); 63.4 (CH_2N); 126.6 (126.2)* (arom. C); 127.1 (C(4)); 127.6 (127.4)* (C(5)); 130.8 (132.4)* (arom. C); 134.5 ($\text{CH}_2=\text{C}$); 139.4 (arom. C); 148.3 ($\text{CH}_2=\text{C}$); 151.5 (151.7) (C(3)); 194.1 (*CHO*). EI-MS (70 eV, 150°): 43.0 (3), 58.1 (100), 71.1 (2), 86.1 (2), 105.1 (1), 115.1 (2), 128.1 (2), 129.1 (2), 141.1 (1), 174.1 (1), 247.2 (1), 262.2 (5), 304.2 (1). HR-MS: 304.1791 ($\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_3^+$; calc. 304.1787).

REFERENCES

- [1] M. Rettig, Ph.D. Thesis, University of Karlsruhe, 1998.
- [2] J. Rétey, *Naturwissenschaften* **1996**, 83, 439.
- [3] K. Hahlbrock, D. Scheel, *Annu. Rev. Plant. Physiol. Mol. Biol.* **1989**, 40, 347.
- [4] I. L. Givot, T. A. Smith, R. H. Abeles, *J. Biol. Chem.* **1969**, 244, 6341.
- [5] R. B. Wickner, *J. Biol. Chem.* **1969**, 244, 6550.

- [6] K. R. Hanson, E. A. Havir, *Arch. Biochem. Biophys.* **1970**, *141*, 1.
- [7] M. W. Consevage, A. T. Phillips, *Biochemistry* **1985**, *24*, 301.
- [8] M. Langer, G. Reck, J. Reed, J. Rétey, *Biochemistry* **1994**, *33*, 6462.
- [9] B. Schuster, J. Rétey, *FEBS Lett.* **1994**, *349*, 252.
- [10] T. Schwede, J. Rétey, G. E. Schulz, *Biochemistry* **1999**, *38*, 5355.
- [11] M. Ormö, A. B. Cubitt, K. Kallio, L. A. Gross, R. Y. Tsien, S. J. Remington, *Science (Washington, D.C.)* **1996**, *273*, 1392.
- [12] B. G. Reid, G. C. Flynn, *Biochemistry* **1997**, *36*, 6786.
- [13] M. Langer, A. Pauling, J. Rétey, *Angew. Chem.* **1995**, *107*, 1585; *Angew. Chem., Int. Ed.* **1995**, *34*, 1464.
- [14] B. Schuster, J. Rétey, *Proc. Natl. Acad. Sci. U.S.A.* **1995**, 8433.
- [15] M. S. Newman, M. D. Farbman, *J. Am. Chem. Soc.* **1944**, *66*, 1550.
- [16] W. E. Bachmann, G. I. Fujimoto, L. B. Wick, *J. Am. Chem. Soc.* **1950**, *72*, 1995.
- [17] W. E. Bachmann, L. B. Wick, *J. Am. Chem. Soc.* **1950**, *72*, 3388.
- [18] J. P. Marino, J. S. Farina, *Tetrahedron Lett.* **1975**, 3901.
- [19] N. Rabjohn, *Org. React.* **1976**, *24*, 261.
- [20] H. L. Pan, C. A. Cole, T. L. Fletcher, *Synthesis* **1980**, 1324.
- [21] S. Manna, P. Yadagiri, J. R. Falck, *J. Chem. Soc., Chem. Commun.* **1987**, 1324.
- [22] B. O. Lindgren, T. Nilsson, *Acta Chem. Scand.* **1973**, *27*, 888.
- [23] B. S. Bal, W. E. Childers, H. Pinnick, *Tetrahedron* **1981**, *37*, 2091.
- [24] A. G. Jackson, G. W. Kenner, G. A. Moore, R. Ramage, W. D. Thorpe, *Tetrahedron Lett.* **1976**, 3627.
- [25] S. Bernasconi, A. Comini, A. Corbella, P. Gariboldi, M. Sisti, *Synthesis* **1980**, 385.
- [26] R. L. Danheiser, J. M. Morin, E. J. Salaski, *J. Am. Chem. Soc.* **1985**, *107*, 8066.
- [27] R. F. Borch, M. D. Bernstein, H. D. Durst, *J. Am. Chem. Soc.* **1971**, *93*, 2897.
- [28] K. Kawada, T. Tsushima, *Heterocycles* **1989**, *28*, 573.
- [29] W. S. Emerson, *Org. React.* **1940**, *4*, 174.
- [30] P. Möller, R. Schröter, in 'Methoden der Organischen Chemie (Houben-Weyl)', Thieme Verlag, Stuttgart, 1952, Vol. 11/1, p. 602.
- [31] W. Q. Beard, *J. Org. Chem.* **1961**, *26*, 2310.
- [32] F. Fuson, J. Corse, P. Welldon, *J. Am. Chem. Soc.* **1941**, *63*, 2645.
- [33] M. E. Maier, D. Langenbacher, F. Rebien, *Liebigs Ann. Chem.* **1995**, 1843.
- [34] J. A. Moore, M. Rahm, *J. Org. Chem.* **1961**, *26*, 1109.
- [35] R. M. Moriarty, R. Lin, H. Zhuang, D. Lenz, *Synth. Commun.* **1995**, *18*, 2763.
- [36] B. Bhattacharya, *Synth. Commun.* **1995**, *25*, 2061.
- [37] C. S. Marvel, R. L. Myers, J. H. Saunders, *J. Am. Chem. Soc.* **1948**, *70*, 1694.
- [38] Y. Nakatsugi, T. Nakamura, M. Yonetani, H. Yuya, M. Okahara, *J. Am. Chem. Soc.* **1988**, *110*, 531.
- [39] M. Hesse, H. Meier, B. Zeeh, 'Spektroskopische Methoden in der organischen Chemie', Thieme Verlag, Stuttgart, 1991, p. 18.
- [40] F. W. Küster, A. Stallberg, *Justus Liebigs Ann. Chem.* **1894**, 278, 213.
- [41] J. S. Fowler, R. R. MacGregor, A. N. Ansari, H. L. Atkins, A. P. Wolf, *J. Med. Chem.* **1974**, *17*, 245.
- [42] F. G. Bordwell, Y. Zhao, *J. Org. Chem.* **1995**, *60*, 6348.
- [43] A. Gloge, B. Langer, L. Poppe, J. Rétey, *Arch. Biochem. Biophys.* **1998**, *359*, 1.
- [44] N. Nobuto, S. Kazuhiro, H. Hisashi, H. Hasihiro, *J. Chem. Res. (Miniprint)* **1984**, *12*, 3501.
- [45] T. Kitano, N. Shirai, M. Motoi, Y. Sato, *J. Chem. Soc., Perkin Trans. 1* **1992**, 2581.
- [46] L. Poppe, E. Stupperich, W. E. Hull, T. Buckel, J. Rétey, *Eur. J. Biochem.* **1997**, *250*, 303.
- [47] L. Poppe, W. E. Hull, R. Nitsche, T. Graf, E. Stupperich, J. Rétey, *Helv. Chim. Acta* **1999**, *82*, 1250.

Received May 19, 2000