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1,3-Diphenylpropan-1,3-diamines IX [1]. Reaction of α-Chlorooxime Ethers with α-Lithiobenzylamines[#]

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Summary. The carbanions of the benzylamine derivatives **1**–**4** have been reacted with α-chlorooxime ether **5** in order to get precursors of 1,3-diphenylpropane-1,3-diamines. Isonitrile **1** afforded the expected result, whereas lithiated benzamide **2** underwent oxidative dimerization and transmetallated chlorooxime derivative **5**. Isoxazolidine **3** gave the condensation product **21** as a mixture of diastereomers; treatment of imine **4** led to the desired amine-oxime **15** in low yield.

Keywords. 1,3-Diphenylpropane-1,3-diamines; Benzylamine carbanions; α-Chloroacetophenone-oxime *O*-methyl ether.

1,3-Diphenylpropan-1,3-diamine, 9. Mitt. Reaktion von α-Chloroximethern mit α-Lithiobenzylaminen

Zusammenfassung. Die Carbanionen der Benzylaminderivate **1**–**4** wurden mit Chloroximether **5** umgesetzt, um Vorstufen von 1,3-Diphenylpropan-1,3-diaminen zu erhalten. Isonitril **1** lieferte die erwartete Verbindung, während das lithiierte Benzamid **2** oxidativ dimerisiert und das Chloroxim **5** ummetallierte. Das Isoxazolidin **3** reagierte zu der gewünschten Verbindung **21** (Diastereomerengemisch), während das Imin **4** in niedriger Ausbeute zum Aminoxim **15** führte.

Introduction

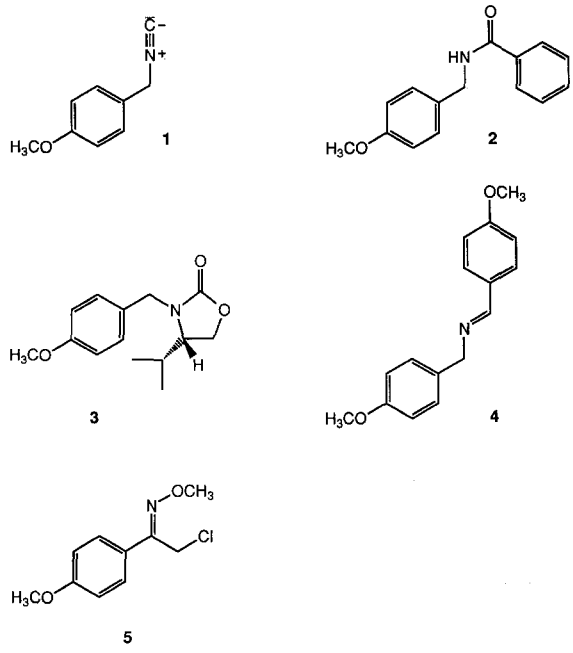
In part VIII of this series [1], we have described the reaction of 4-methoxyacetophenone oxime dianion and that of the monoanion of O-substituted oxime derivatives with C=N-electrophiles, mainly derived from benzaldehydes, affording precursors of the desired 1,3-diphenylpropane-1,3-diamines. This publication deals with the reaction of the α-lithiated amine equivalents **1**–**4** with (*Z*)-α-chloro-oxime O-methyl ether **5** (Scheme 1).

Results and Discussion

Carbanions of benzylamine derivatives **1**–**4**

Isonitrile **1** [2] was obtained by dehydration of N-(4-methoxyphenyl)-formamide with CCl_4/triphenylphosphine. **1** was lithiated with *n*-BuLi in *THF*. Benzamide

[#] Dedicated with warm regards to Prof. Dr. *J. Knabe*, Saarbrücken, Germany, on the occasion of his 75th birthday



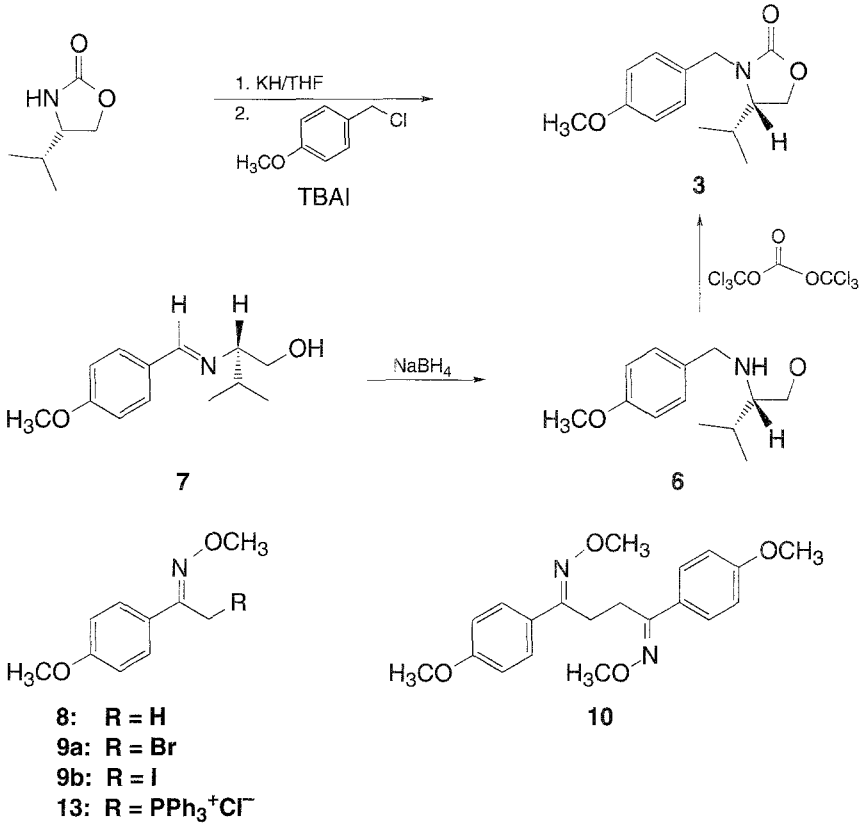
Scheme 1

2 was lithiated by *LDA*, because *n*-BuLi – successfully used by *Tischler* [3] for metallation of N-benzylbenzamide – did not lithiate the 4-methoxy derivative **2** as indicated by D_2O quenching (mass spectrometry). Most probably, the corresponding benzyl anion of **2** is destabilized by the electron donating methoxy group. (*S*)-4-Isopropyl-3-(4-methoxybenzyl)-oxazolidin-2-one (**3**) was obtained from the corresponding 4-isopropyloxazolidin-2-one [4] and 4-methoxybenzyl-chloride, using *Gawley*'s procedure [5]. Alternatively, (*S*)-N-(4-methoxylbenzyl)- valinol (**6**) can be cyclized by *bis*-(trichloromethyl)-carbonate. Aminoalcohol **6** was obtained by $NaBH_4$ reduction of the corresponding imine **7**. This procedure turned out to be more useful than direct reductive amination of anisaldehyde and valinol with $NaBH_3CN$ (cf. Ref. [6]) or twofold $LiAlH_4$ reduction of (*S*)-N-(4- methoxybenzoyl)-valine [7] (data not shown).

In spite of the methoxy substitution, *Gawley*'s method [5] led to complete metallation of **3**, but subsequent protonation occurred with only low diastereoselectivity as indicated by quenching with CD_3OD compared with that afforded by *DMSO*-d_6 which shows a *de* of >90% in tetrahydroisoquinolines [8]. Here both deuterium sources revealed about 60% *de*. The ^1H NMR spectrum shows the collapsed peaks of the AB system of the benzylic CH_2 group at $\delta = 4.80$ and 3.90 ppm, respectively, with 1:4 intensity. Imine **4** and its metallation are known [9].

α-Halogenated oxime ethers

These compounds can be obtained either by bromination of O-alkyl- or O-silylketoximes with N-bromosuccinimide (*NBS*) [10, 11] or by halogenation of lithiated ketoxime methylethers according to *Shatzmiller* [10, 12]. In part VIII [1], we have mentioned an oxidative dimerization of a pertinent anion [1]. This reaction,



Scheme 2

however, can be avoided by addition of the anion to an excess of halogen. This halogenation works with O-alkylated oximes only, because O-silylated oxime carbanions show an equilibrium with the C-silylated C=N–O$^-$-ion [13]. Alternatively, α-halogenated ketones can be reacted with O-alkylated [14] or O-silylated [15] hydroxylamines, respectively.

Shatzmiller-bromination [12] of (*E*)-1-(4-methoxyphenyl)-1-ethanone O-methyloxime (**8**) led to a useless 1:1 mixture of (*Z*)-2-bromo-1-(4-methoxyphenyl)-ethanone O-methyloxime (**9a**)[a] with the dimer **10** originating from **8**-anion. So this procedure was avoided. Attempted iodination of **8** afforded **10** exclusively, chlorination by N-chlorosuccinimide (*NCS*) produced a moderate yield of **5** with only about 10% of **10** which could be removed by column chromatography (CC). There are 10–20% of another impurity of unknown structure as indicated by the CH_2-integral (^{1}H NMR) which could not be eliminated. Therefore, we prepared **5** by condensation of 2-chloro-1-(4-methoxyphenyl)-ethanone [16] with O-methylhydroxylamine. This oximation led to a *Z*/*E*-mixture of **5** (85:15), the components of which were separated by CC. Reaction of 8-anion with *NBS* resulted in a 1:1 mixture of **9a** and **10**. N-iodoscuccinimide (*NIS*) afforded **10** only, but the desired iodoketone oxime ether was obtained by halide exchange of **5**. Treatment of 2-bromo-2-(4-methoxyphenyl)-

[a] The stereochemistry is not changed, but the priorities according to *Cahn-Ingold-Prelog* have been inverted.

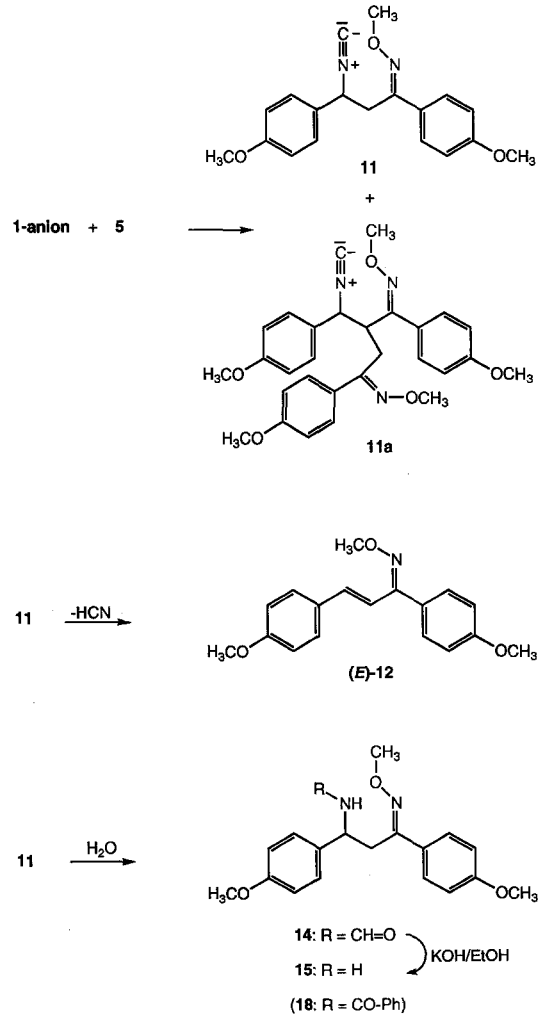
ethanone with $H_2NOCH_3 \cdot HCl$ in MeOH produced a nonseparable mixture of **9a** and (*E*/*Z*)-**5**. This is analogous to *Masaki*'s findings [17] concerning the oximation of α-bromoacetophenone. This halogen exchange can be circumvented by using the hydrobromide of H_2NOCH_3 [18], the preparation of which, however, is cumbersome. Because **5** works nicely, we did not use this route.

The reaction of O-trimethylsilylated α-chloro-4-methoxyacetophenone oxime, prepared from the chlorooximes with $ClSi(CH_3)_3/NEt_3$ as described for (non-halogenated) oximes [11, 19], with 2-lithiated 2-(4-methoxybenzyl)-1,3-dithiane [7] will be reported in a forthcoming paper.

Reactions of α*-chlorooxime ether* **5** *with* α*-lithio-amine equivalents* **1**–**4**

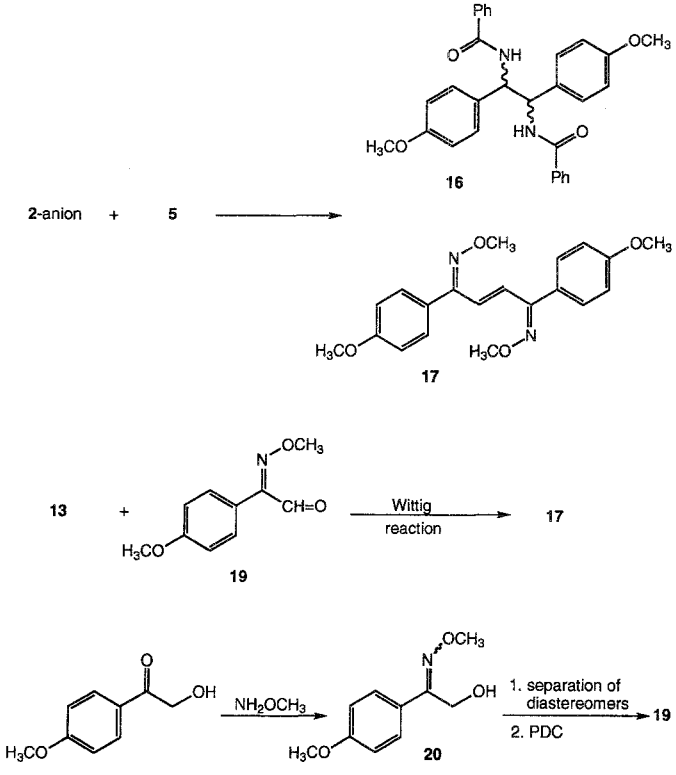
a) With **1***-anion*

Abrupt addition of a cold solution of **5** (−78°) to a cold solution of lithiated isonitrile **1** (−78°) affords (*E*)-3-isocyano-oxime ether **11**. If **5** is slowly added within 10 min,



Scheme 3

the 2 + 1 product **11a** arises in addition to **11** (1:3). When added slowly, lithiated isonitrile **1** probably deprotonates already generated compound **11** which in turn is alkylated at C-2, affording **11a**. This assumption is corroborated by treatment of **11** with *n*-BuLi affording the chalcone oxime **12** probably by a *E1cB* mechanism [7, 20]. **12** was identified as a by-product of the reaction of **5** with **1**-anion. *β*-Elimination of HCN from isonitriles is known [21]. Up to now, this procedure seems to be the only one suitable for the preparation of stereochemically pure (*E*)-**12**: the reaction of 1,3-*bis*-(4-methoxyphenyl)-3-propen-1-one with $H_2NOCH_3 \cdot HCl$ in pyridine as well as *Wittig* reaction of stereochemically pure **5** with triphenylphosphine, followed by treatment of **13** (Scheme 2) with anisaldehyde, afforded (*E*/*Z*)-**12**, *E*-**12** being the dominant component. Because **13** is stereochemically homogeneous (^1H NMR), isomerization during the *Wittig* reaction is likely. This reaction could be brought about with K_2CO_3/DMF (cf. Ref. [22]) only; *n*-BuLi did not work. CC separation of (*E*/*Z*)-**12**, however, was unsuccessful. Addition of water to the isonitrile increment of **11** afforded formamide **14** which was hydrolyzed to benzylamine **15**.



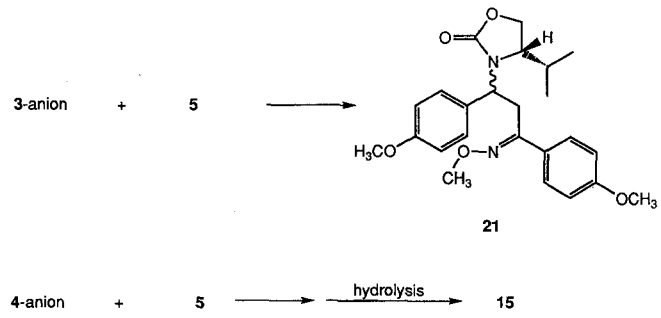
Scheme 4

b) With twofold lithiated **2**

The reaction of **2**-dianion with chlorooxime ether **5** led to the unexpected compounds **16** and **17** instead of the desired precursor **18** (Scheme 3) of a 1,3-diphenylpropane-1,3-diamine. Most likely, **16** – generated by oxidative dimerization of **2**-dianion – is a mixture of diastereomers as indicated by correct elemental analysis,

broad signals in its ^{1}H NMR spectrum, and its broad melting range (see Experimental). The formation of the unsaturated dioxime ether **17** can be explained by transmetallation of **5** at the CH_2–Cl group by **2**-dianion, followed by attack of **5**-anion at non-ionized **5** and subsequent elimination of HCl. A somewhat similar procedure is used in the synthesis of imipramine by base-catalyzed condensation of two molecules of 2-nitrobenzylchloride [23]. Compound **17** was independently synthesized by *Wittig* reaction of **13** with (*Z*)-2-methoxyimino-2-(4-methoxyphenyl)acetaldehyde (**19**), obtained from α- hydroxy-4-methoxyacetophenone [24], its oximation with $H_2NOCH_3 \cdot HCl$ (affording oxime ether **20**), and oxidation of the primary carbinol to aldehyde **19**. Oxime ether **20** resulted as a *E*/*Z*-mixture which was separated by CC. The *E*-configuration is unusually labile: at room temperature, partial isomerization to the *Z*-isomer occurs.

c) With **3***-anion*



Scheme 5

3-Anion reacted with **5** affording the expected isoxazolidine-oxime ether **21** as an oil which could be purified by CC, but the diastereomers could not be separated. NMR spectra did not enable us to determine the ratio of diastereomers.

d) With **4***-anion*

Deprotonation of **4** was achieved by *LDA*, but **4**-anion yielded only 8% of amine-oxime **15** after hydrolysis of the pertinent intermediate [1]. Because **15** had been obtained in higher yield by another procedure [1], we did not follow this route any longer.

Experimental

For general remarks, see part VIII [1]; brine: saturated aqueous solution of NaCl; "x ml BuLi":x ml of a 1.6 molar solution of *n*-butyllithium in hexane; all temperatures in °C; *PE*: petroleum ether 40–60°.

4-Methoxybenzylisonitrile (**1**)

N-(4-Methoxybenzyl)-formamide (16.52 g, 100 mmol) is heated for 3 h at 60° with 15.6 g (101 mmol) of absol. CCl_4, 10.22 g (101 mmol) of absol. NEt_3, and 29.14 g (111 mmo) of PPh_3 in 105 ml absol. $CHCl_3$. $CHCl_3$ ist distilled off, the residue is thoroughly mixed with 150 ml of *PE*, and filtered by suction.

Extraction with *PE* is repeated three times. The filtrates are stored at 4° overnight, filtered again, and evaporated at normal pressure. The remaining oil is distilled (b.p. 94°/0.1 torr). Pale yellow oil of unpleasant smell; 10.11 g (69%); analytical data: Ref. [2]; for metallation, cf. Ref. [2].

N-(4-Methoxybenzyl)-benzamide (**2**)

Synthesized from 4-methoxybenzylamine and benzoylchloride according to Ref. [25].

(S)-(+)-4-Isopropyl-3-(4-methoxybenzyl)-oxazolidin-2-one (**3**)

19.0 g of a 20% suspension of KH in paraffin oil (about 95 mmol) are slowly added to 9.64 g (74.6 mmol) of (*S*)-4-isopropyloxazolidin-2-one ([4]; from (*S*)-valinol [5] and diethylcarbonate/K_2CO_3) dissolved in 350 ml of absol. *THF*. This mixture is refluxed for 20 min. After cooling, 13.45 g (86 mmol) of 4-methoxybenzylchloride (Fluka) in 20 ml of absol. *THF* and 2.76 g (7.47 mmol) of $(n\text{-Bu})_4N^+I^-$ are added under stirring. Stirring is continued for 24 h, 70 ml of a half-satd. NaCl solution are carefully added, the *THF* phase is separated, the aqueous layer is extracted with 350 ml of ether, the combined organic phases are washed with brine, dried, evaporated, and the residue is dried at the oil pump. The resulting two phases are separated; paraffin oil is discarded, and the other phase is purified by CC (CH_2Cl_2/EtOAc 9:1), evaporated, and the solid material (16.2 g) is dissolved in 80 ml of ether. Then, 200 ml of *PE* are slowly added. After standing first at room temp., then at −20°, crystals of **3** separate and are filtered off. 15.53 g (83%); m.p.: 56° (for ring closure with *bis*-(trichloromethyl) carbonate see below).

IR (KBr): $\nu = 1727\,cm^{-1}$ (C=O); ^1H NMR ($CDCl_3$): $\delta = 0.82$ (d; $J = 7.5$ Hz, 3H, $CHCH_3$), 0.85 (d; $J = 7.5$ Hz, 3H, $CHCH_3$), 1.80–2.27 (m; 1H, $CH(CH_3)_2$), 3.37–3.67 (m; 1H, $NCHCH_2O$), 3.77 (s; 3H, OCH_3), 3.93, 4.79 (AB, $J_{AB} = 16$ Hz, 2H, $ArCH_2N$), 4.02–4.18 (m; 2H, $NCHCH_2O$), 6.85, 7.21 (AA'BB', $J_{AB} = 9$ Hz, 4H arom) ppm; $[\alpha]_D^{20} = 29.8°$ ($c = 1$ in $CHCl_3$); $C_{14}H_{19}NO_3$ (243.3); calcd.: C 67.45, H 7.68, N 5.62; found: C 67.37, H 7.69, N 5.64.

(E)-(S)-(−)-2-(4-Methoxybenzylidenamino)-3-methylbutan-1-ol (**7**)

Synthesized from *L*-valinol and 4-methoxybenzaldehyde according to Ref. [26].

(S)-(+)-2-(4-Methoxybenzylamino)-3-methylbutan-1-ol (**6**)

At 0°, 1.0 g (26.4 mmol) of $NaBH_4$ is added in portions to 4.43 g (20 mmol) of **7** dissolved in 40 ml of absol. MeOH. After stirring for 30 min at 0° and 15 min at room temp., MeOH is distilled off. 40 ml of 5 *N* NaOH are added, the mixture is extracted with ether (3 × 100 ml), the ether phase is washed with brine, dried, and evaporated. Pale yellow oil which is dried at the oil pump; 4.30 g (96%); an analytical sample is purified by CC (CH_2Cl_2/MeOH 9:1).

IR (film): $\nu = 3363\,cm^{-1}$ (br, OH and NH); ^1H NMR ($CDCl_3$): $\delta = 0.9$ (d; $J = 7.5$ Hz, 3H, $CHCH_3$), 0.95 (d; $J = 7.5$ Hz, 3H, $CHCH_3$), 1.50–2.07 (m; 1H, $CH(CH_3)_2$), 2.23–2.53 (m; 3H, $NCHCH_2O$, OH and NH, exch.), 3.22–3.83 (m; 4H, $NCHCH_2O$, NCH_2Ar, partial overlap with OCH_3), 3.77 (s; 3H, OCH_3), 6.84, 7.27 (AA'BB', $J_{AB} = 9$ Hz, 4H arom) ppm; $[\alpha]_D^{20} = 5.6°$ ($c = 1$ in $CHCl_3$); $C_{13}H_{21}NO_2$ (223.3); calcd.: C 69.90, H 9.48, N 6.27; found: C 69.92, H 9.74, N 6.39.

(S)-(+)-4-Isopropyl-3-(4-methoxybenzyl)-oxazolidin-2-one (**3**) *from aminoalcohol* **6**

At 0°, 1.60 g (5.39 mmol) of *bis*-(trichloromethyl) carbonate in 35 ml of absol. ether are added dropwise to a solution of 3.27 g (14.64 mmol) **6** and 3.44 g (34 mmol) NEt_3 in 50 ml of absol. ether. After stirring for 10 min at 0°, refluxing for 20 min, cooling to 0°, filtration and washing of the residue (3 × 40 ml of ether),

the combined filtrate is washed twice with 15 ml of 2 *N* HCl and with 30 ml of brine, dried, concentrated, and purified by CC (CH_2Cl_2/EtOAc 9:1). After evaporation, the residue is dissolved in 10 ml of ether; 30 ml of *PE* are added in portions. Storage first at 4°, then at −20° affords 2.62 g (72%) crystals. Data: see above.

N-(4-Methoxybenzylidene)-4-methoxybenzylamine (**4**)

Synthesized from 4-methoxybenzylamine and anisaldehyde according to Ref. [9].

(E,E)-1,4-bis-(4-Methoxyphenyl)-1,4-butandione-bis-(o-methyloxime) (**10**)

At −78°, 3.5 ml BuLi are dropped to 0.9 g (5 mmol) **8** [1] in 10 ml of absol. *THF* within 3 min under N_2. After stirring for 40 min at −78° this solution is added dropwise to a solution of 5.1 g (20 mmol) I_2 in 20 ml of absol. *THF* at −78° within 30 min. Excess of I_2 is eliminated by conc. $Na_2S_2O_3$ solution, the organic phase is separated, the aqueous phase is extracted with ether (2 × 30 ml), the combined organic phase is washed with dil. $Na_2S_2O_3$ solution and brine, dried, and evaporated. Pale-yellow solid; 0.80 g (90%); crystallization from 2-propanol affords colourless crystals; m.p.: 123°.

IR (KBr): $\nu = 1605\,cm^{-1}$ (C=N and C=C); ^1H NMR ($CDCl_3$): $\delta = 2.90$ (s; 4H, 2 CH_2), 3.80 (s; 6H, 2 OCH_3), 4.00 (s, 6H, 2 $NOCH_3$), 6.87, 7.63 (AA'BB', $J_{AB} = 9$ Hz, 8H arom) ppm; $C_{20}H_{24}N_2O_4$ (356.4); calcd.: C 67.39, H 6.78, N 7.86; found: C 67.67, H 6.85, N 7.90.

(E) and (Z)-2-Chloro-1-(4-methoxyphenyl)-ethanone O-methyloxime (**5**)

9.23 g (50 mmol) of 2-chloro-1-(4-methoxyphenyl)-ethanone [16] and 8.35 g (100 mmol) of $H_2NOCH_3 \cdot HCl$ in 50 ml of MeOH are stirred for 24 h at room temp. MeOH is evaporated, the residue is mixed with 100 ml of water, and extracted with ether (3 × 70 ml). The ether solution is washed with 40 ml of water and 40 ml of brine, dried, and concentrated, followed by CC-separation (*PE*/ether 8:2). In addition to 3.1 g (29%) *E*/*Z*-mixture there are obtained:

(*Z*)-**5**: colourless oil; 6.46 g (60%); IR (film): $\nu = 1609\,cm^{-1}$ (C=N and C=C); ^1H NMR ($CDCl_3$): $\delta = 3.83$ (s; 3H, OCH_3), 4.05 (s; 3H, $NOCH_3$), 4.50 (s; 2H, CH_3), 6.90, 7.65 (AA'BB', $J_{AB} = 9$ Hz, 4H arom) ppm; $C_{10}H_{12}ClNO_2$ (213.7); calcd.: C 56.21, H 5.66, N 6.56; found: C 56.32, H 5.57, N 6.57.

(*E*)-**5**: colourless oil; 87 mg (0.8%); IR (film): $\nu = 1607\,cm^{-1}$ (C=N and C=C); ^1H NMR ($CDCl_3$): $\delta = 3.83$ (s; 3H, OCH_3), 3.93 (s; 3H, $NOCH_3$), 4.43 (s; 2H, CH_2), 6.93, 7.60 (AA'BB', $J_{AB} = 9$ Hz, 4H arom) ppm; $C_{10}H_{12}ClNO_2$ (213.7); calcd.: C 56.21, H 5.66, N 6.56; found: C 56.20, H 5.68, N 6.56.

(Z)-2-Iodo-1-(4-methoxyphenyl)-ethanone O-methylhydroxylamine (**9b**)

A solution of 0.64 g (3 mmol) **5** and 2.5 g NaI in 10 ml of acetone is stirred for 2 h at room temp. After filtration and concentration, 20 ml of water are added. This solution is extracted with ether (3 × 20 ml), the ether phase is washed with $Na_2S_2O_3$ solution and brine, dried, and evaporated to dryness. The residue is crystallized from 2 ml of petroleum ether (50–70°) at 4°. Faint yellow crystals; m.p.: 64°; 0.84 g (92%).

IR (KBr): $\nu = 1609\,cm^{-1}$ (C=N and C=C); ^1H NMR ($CDCl_3$): $\delta = 3.80$ (s; 3H, OCH_3), 4.05 (s; 3H, $NOCH_3$), 4.18 (s; 2H, CH_2), 6.88, 7.63 (AA'BB', $J_{AB} = 9$ Hz, 4H arom) ppm; $C_{10}H_{12}INO_2$ (305.1); calcd.: C 39.37, H 3.96, N 4.59; found: C 39.52, H 3.85, N 4.64.

(E)-3-Isocyano-1,3-bis-(4-methoxyphenyl)-propan-1-one O-methyloxime (**11**)

Under N_2, 8.4 ml BuLi are added dropwise to a solution of 1.77 g (12 mmol) **1** in 25 ml of absol. *THF* at −78°. After stirring for 40 min at this temp., a cooled solution (−78°) of 2.56 (12 mmol) **5** in 20 ml of

absol. *THF* is added *in a gush.* After 20 min of stirring at −78°, 15 ml of water are added, the organic phase is separated, washed twice with brine, dried, and evaporated. The residue is dried at the oil pump and affords a crystallizing yellow oil (4.0 g) which is dissolved in the minimum amount of CH_2Cl_2, purified by CC (ether/PE 1:1), and crystallized from 5 ml of EtOH. 2.73 g (73%); m.p.: 74°.

IR (KBr): $\nu = 2138$ (NC), 1613 cm^{-1} (C=N and C=C); ^1H NMR ($CDCl_3$): $\delta = 3.10–3.43$ (m; 2H, CH_2), 3.80 (s; 6H, 2 OCH_3), 4.00 (s; 3H, $NOCH_3$), 5.00–5.27 (m; 1H, CH), 6.77–7.00 (m; 4H arom), 7.20–7.60 (m; 4H arom) ppm; $C_{19}H_{20}N_2O_3$ (324.4); calcd.: C 70.35, H 6.21, N 8.64; found: C 70.32, H 6.10, N 8.61.

(E,E)-2-((4-Methoxyphenyl)-isocyanomethyl)-1,4-bis-(4-methoxyphenyl)-1,4-butandione-bis-(O-methyloxime) (**11a**)

As described for **11**, but the solution of **5** is added *slowly* over 10 min. Purification by CC (CH_2Cl_2/EtOAc 9.5:0.5) affords a faint yellow oil. In addition to 1.04 g (35%) **11a**, 1.98 g (51%) **11** are isolated.

11a: IR (film): $\nu = 2134$ (NC), 1611 cm^{-1} (C=N and C=C); ^1H NMR ($CDCl_3$): $\delta = 3.28–3.93$ (m; 19H, 5 OCH_3, CH_2 and 2 CH), 6.63–6.93 (m, 6H arom), 7.15–7.47 (m; 6H arom) ppm; $C_{29}H_{31}N_3O_5$ (501.6); calcd.: C 69.44, H 6.23, N 8.38; found: C 69.22, H 6.23, N 8.30.

(E)-1,3-bis-(4-Methoxyphenyl)-2-propen-1-one O-methyloxime (**12**) *from isonitrile* **11**

Under N_2, 1.4 ml BuLi are added dropwise to 0.65 g (2 mmol) **11** dissolved in 10 ml of absol. *THF* at −78°. After stirring for 30 min, the reaction is terminated by addition of 2 ml of water. The organic phase is washed with brine (2 × 5 ml), dried, and evaporated. The residue is purified (CC; ether/hexane 1:1). Colourless oil (0.28 g, 47%) which crystallizes slowly at the oil pump; m.p.: 59°.

IR (film): $\nu = 1605$ cm^{-1} (C=N and C=C); ^1H NMR ($CDCl_3$): $\delta = 3.80$ (s; 3H, OCH_3), 3.85 (s; 3H, OCH_3), 4.03 (s; 3H, $NOCH_3$), 6.57–7.07 (m; 4H arom and 1H, =CH), 7.25–7.60 (m; 4H arom and 1H, =CH) ppm; $C_{18}H_{19}NO_3$ (297.4); calcd.: C 72.70, H 6.44, N 4.71; found: C 72.73, H 6.55, N 4.80.

(E/Z)-**12** *from 1,3-bis-(4-methoxyphenyl)-2-propen-1-one* [27]

2.698 g (10 mmol) of this propen-1-one and 1.17 g (14 mmol) of $H_2NOCH_3 \cdot HCl$ are refluxed in 10 ml of pyridine for 5 h. After evaporation and usual work-up, (*E/Z*)-**12** is obtained as 2.35 g (79%) colourless oil. The ^1H NMR data (see above) show an additional singlet at $\delta = 3.90$ ppm for $NOCH_3$ of the *Z*-isomer (*E/Z* = 5:2).

(E/Z)-**12** *by Witting reaction*

a) *(Z)-(2-Methoxyimino-2-(4-methoxyphenyl)-ethyl)-triphenylphosphonium chloride* (**13**)

2.14 (10 mmol) **5** and 6.30 g (24 mmol) PPh_3 in 10 ml of toluene are refluxed for 4 h. After standing at 4°, the colourless crystals are sucked off, washed with absol. toluene (2 × 5 ml), and dried. 4.68 g (98%); m.p.: 214° (dec.).

IR (KBr): $\nu = 1605$ (C=N and C=C), 1439 cm^{-1} (P-aryl); ^1H NMR ($CDCl_3$): $\delta = 3.50$ (s; 3H, $NOCH_3$), 3.73 (s; 3H, OCH_3), 5.58 (d; $J = 16.5$ Hz, 2H, CH_2), 6.73 (part of a AA'BB'-system; $J_{AB} = 9$ Hz, 2H arom), 7.43–8.00 (m; 17H arom) ppm; $C_{28}H_{27}NO_2PCl$ (475.9); calcd.: C 70.66, H 5.72, N 2.94; found: C 70.65, H 5.66, N 2.98.

b) *(E/Z)*-**12** *(Wittig reaction)*

A solution of 2.38 g (5 mmol) **13** in 190 ml of absol. *DMF* is stirred for 5 min with 0.76 g (5.5 mmol) thoroughly ground K_2CO_3 at room temp. Stirring is continued with 0.68 g (5 mmol) 4-methoxybenzal-

dehyde for 48 h. Then 100 ml of water are added, the mixture is extracted with ether (3 × 60 ml), the ether phase is washed with water (2 × 50 ml) and brine, dried, evaporated, and purified by CC (ether/hexane 1:1). For application onto the silica, the residue is mixed with ether, leaving Ph_3PO undissolved. 1.06 g (*E/Z*)-**12** (71%), about 10–15% *Z*-isomer (^{1}H NMR).

(E)-N-(3-Methoxyimino-1,3-bis-(4-methoxyphenyl)-1-propyl)-formamide (**14**)

At 0°, 0.8 ml of conc. HCl are mixed with 3.24 g (10 mmol) isonitrile **11** in 70 ml of ether. After reaching room temp., the mixture is shaken for 5 min, mixed with 20 ml of satd. $NaHCO_3$ solution, and cooled to −20°. After 3 h the solid is allowed to melt, the crystals are sucked off, washed with water (3 × 10 ml), dried, and recrystallized from 8 ml of EtOH. Faint grey solid; 3.02 g (88%); m.p.: 118°.

IR (KBr): ν = 3249 (NH), 1655 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ = 2.80–3.10 (m; 1H, *H*CH), 3.27–3.62 (m; 1H, HC*H*), 3.78 (s; 3H, OCH_3), 3.83 (s; 3H, OCH_3), 3.98 (s; 3H, $NOCH_3$), 5.00–5.30 (m; 1H, CH), 6.43 (s; br, 1H, NH, exch.), 6.78–7.00 (m; 4H arom), 7.17–7.37 (m; 2H arom), 7.47–7.70 (m; 2H arom), 8.10 (s; 1H, NCHO) ppm; $C_{19}H_{22}N_2O_4$ (342.4); calcd.: C 66.65, H 6.48, N 8.18; found: C 66.53, H 6.56, N 8.19.

(E)-3-Amino-1,3-bis-(4-methoxyphenyl)-1-propanone O-methyloxime (**15**)

a) *Hydrolysis of* **14**

At 50°, 1.71 g (5 mmol) **14** are stirred in 50 ml of 10% ethanolic KOH for 24 h. EtOH is evaporated, 30 ml of water are added, the mixture is extracted with EtOAc (3 × 50 ml), the EtOAc phase is washed with brine, dried, and purified (CC; CH_2Cl_2/MeOH 9:1). Yellow oil; 1.40 g (89%); analytical data: Ref. [1].

b) *From benzyliden-benzylamine* **4**

LDA is prepared from 0.47 g (0.65 ml; 4.62 mmol) of absol. diisopropylamine in 18 ml of absol. *THF* and 3.5 ml BuLi at −78° under N_2. To this solution, 1.28 g (5 mmol) **4** in 5 ml of absol. *THF* are added with stirring. After stirring for 90 min at −78°, 1.07 g (5 mmol) **5** in 5 ml of absol. *THF* are added. After 10 min of stirring the cooling bath is removed, stirring is continued for 20 min, 6 ml of satd. NH_4Cl solution are added, the solvents are distilled off, the residue is stirred for 20 min with 15 ml of EtOH and 2 ml of conc. HCl, EtOH is removed *in vacuo*, 100 ml of 2 *N* HCl are added, the mixture is extracted with ether (2 × 50 ml), the HCl phase is alkalized with solid Na_2CO_3, and extracted with EtOAc. For work-up, cf. a); 0.126 g (8%) **15** [1].

1,2-bis-Benzamido-1,2-bis-(4-methoxyphenyl)-ethane (**16**) and
(E,E,E)-1,3-bis-(4-Methoxyphenyl)-2-butene-1,4-dione-bis-(O-methyloxime) (**17**)

At −78°, 8.7 ml BuLi are added dropwise under N_2 to a stirred solution of 1.20 g (5 mmol) **2** and 0.76 g (7.5 mmol) of absol. diisopropylamine in 17 ml of absol. diglyme. After 3 h of stirring at −78°, 1.07 g (5 mmol) **5** in 5 ml of absol. diglyme are added. After stirring for 30 min at −78° the mixture is poured onto 60 ml water. After stirring for 5 min the mixture is filtrated. The dried residue (1.8 g) is extracted by boiling MeOH (12 ml); after cooling, the mixture is filtered. This extraction is repeated with 5 ml of MeOH (the MeOH solutions contain **2** and little **5**). Then the residue is boiled twice with 5 ml of EtOAc. Bisoxime ether **17** crystallizes from the combined EtOAc phase. 73 mg (8%); m.p.: 171–172°.

IR (KBr): ν = 1608 cm^{-1} (C=N and C=C); ^{1}H NMR (*DMSO*-d_6): δ = 3.83 (s; 6H, 2 OCH_3), 3.90 (s; 6H, 2 $NOCH_3$), 6.97 (s; 2H, CH=CH), 7.00, 7.45 (AA'BB', J_{AB} = 9 Hz, 8H arom) ppm; MS (70eV): m/z = 354 (100%, $M^{+\cdot}$); $C_{20}H_{22}N_2O_4$ (354.4); calcd.: C 67.78, H 6.26, N 7.91; found: C 67.68, H 6.19, N 7.98.

1,2-bis-Benzamido-1,2-bis-(4-methoxyphenyl)-ethane (**16**; *mixture of diastereomers*)

The residue of the EtOAc extraction (see above) is recrystallized from nitromethane. 0.23 g (11%); melting range: 260–270°.

IR (KBr): $\nu = 3332$ (NH), 1632 cm^{-1} (C=O); ^1H NMR (*DMSO*-d_6): δ (ppm) = 3.70 (s; 6H, 2 OCH_3), 5.43–5.73 (m; 2H, 2 CH), 6.70–6.90 (m; 4H arom), 7.20–7.78 (m; 14H arom), 8.77 (s; br, 2H, 2 NH, exch.) ppm; MS (70eV): *m/z* (%) = 359 (1; *McLafferty*), 240 (100; 359-PhNCO)), 105 (86; PhCO); $C_{30}H_{28}N_2O_4$ (480.6); calcd.: C 74.98, H 5.87, N 5.83; found: C 74.87, H 5.84, N 5.93.

Preparation of **17** *by Wittig reaction*

1.50 g (3.15 mmol) **13**, 0.61 g (3.15 mmol) **19** (see below), and 0.65 g (4.7 mmol) finely ground K_2CO_3 in 17 ml of *DMF* are stirred for 14 h at room temp. Then the mixture is stirred with 60 ml of water for 30 min, filtered, and the residue is washed with MeOH (2 × 2 ml), dried, and crystallized from 2.6 ml of toluene. 1.01 g (90%); for data, see above.

(E)- and (Z)-2-Hydroxy-1-(4-methoxyphenyl)-ethanone-O-methyloxime (**20**)

8.31 g (50 mmol) α-hydroxy-4-methoxyacetophenone [31] and 6.26 (75 mmol) $H_2NOCH_3 \cdot HCl$ are stirred in 7 ml of pyridine for 7 h at room temp. and refluxed for 5 min. Pyridine is distilled off *in vacuo*; 50 ml of ice cold *N* HCl are added, followed by extraction with EtOAc (3 × 50 ml). The EtOAc phase is washed with satd. $NaHCO_3$ solution and brine, dried, and concentrated. CC (Et_2O/*PE* 7:3) is used for the separation of *E*/*Z*-**20**.

Z-**20**: colourless crystals; 5.49 g (57%); m.p.: 69° (ether); IR (KBr): $\nu = 3282$ (OH), 1607 cm^{-1} (C=N and C=C); ^1H NMR ($CDCl_3$): $\delta = 2.93$ (s; 1H, OH, exch.), 3.80 (s; 3H, OCH_3), 3.97 (s; 3H, $NOCH_3$), 4.60 (s; 2H, CH_2), 6.87, 7.57 (AA'BB', $J_{AB} = 9$ Hz, 4H arom) ppm; $C_{10}H_{13}NO_3$ (195.2); calcd.: C 61.52, H 6.71, N 7.18; found: C 61.44, H 6.67, N 7.25.

E-**20**: faint yellow oil; 0.77 g (8%); IR (film): $\nu = 3407$ (OH), 1607 cm^{-1} (C=N and C=C); ^1H NMR ($CDCl_3$): $\delta = 2.97$ (s; 1H, OH, exch.), 3.82 (s; 3H, OCH_3), 3.90 (s; 3H, $NOCH_3$), 4.47 (s; 2H, CH_2), 6.90, 7.55 (AA'BB', $J_{AB} = 9$ Hz, 4H arom) ppm; $C_{10}H_{13}NO_3$ (195.2); calcd.: C 61.52, H 6.71, N 7.18; found: C 61.48, H 6.95, N 7.23.

(Z)-2-Methoxyimino-2-(4-methoxyphenyl)-acetaldehyde (**19**)

3.0 g (15 mmol) *Z*-**20** and 11.3 g (30 mmol) pyridinium dichromate (*PDC*) in 50 ml of absol. CH_2Cl_2 are stirred for 24 h at room temp. The solvent is decanted, the remaining tarry black material is extracted with CH_2Cl_2 (3 × 30 ml), the CH_2Cl_2 phase is evaporated, the gummy residue is mixed with ether (3 × 30 ml), and kneaded with a glass rod. The ether phase is washed with a small quantity of water, 2 *N* HCl (10 ml), satd. $NaHCO_3$ solution (2 × 20 ml), and brine, dried, concentrated, and purified by CC (*PE*/ether 8:2). Yellow oil; crystalline only in the refrigerator; 1.66 g (57%).

IR (film): $\nu = 1702$ (C=O), 1609 cm^{-1} (C=N and C=C); ^1H NMR ($CDCl_3$): $\delta = 3.80$ (s; 3H, OCH_3), 4.08 (s; 3H, $NOCH_3$), 6.93, 7.62 (AA'BB', $J_{AB} = 9$ Hz, 4H arom), 10.55 (s; 1H, CHO); $C_{10}H_{11}NO_3$ (193.2); calcd.: C 62.17, H 5.74, N 7.25; found: C 62.03, H 5.73, N 7.24.

(E)-(1'RS,4S)-3-(3-Methoxyimino-1,3-bis-(4-methoxyphenyl)-propyl)-4-isopropyl-oxazolidin-2-one (**21**)

Under N_2, 2.49 g (10 mmol) **3** in 30 ml of absol. *THF* are deprotonated by 7.0 ml BuLi at −78°. After stirring at this temp. for 30 min, the mixture is cooled to −100° and 2.14 g (10 mmol) **5** in 20 ml of absol.

THF are added. During 7 h the mixture is allowed to reach 0°. Then 10 ml of half-satd. NH_4Cl solution are added, the organic phase is separated, the aqueous phase is extracted with ether (2 × 40 ml), the combined organic phase is washed with brine, dried, concentrated, and purified by CC (CH_2Cl_2/EtOAc 9.5:0.5, then 9:1). Colourless oil; 3.73 g (87%).

IR (film): $\nu = 1748$ (C=O), 1611 cm^{-1} (C=N and C=C); ^1H NMR ($CDCl_3$): $\delta = 0.70$ („t"; $J = 6$ Hz, 6H, $CH(CH_3)_2$), 1.40–1.78 (m; 1H, $CH(CH_3)_2$), 3.52–3.95 (m; 3H, $NCHCH_2O$, partial overlap with OCH_3), 3.78 (s, 6H, 2 OCH_3), 3.97 (s; 3H, $NOCH_3$), 4.98 (t; $J = 7.5$ Hz, 1H, CHN), 6.70–6.93 (m; 4H arom), 7.23–7.57 (m; 4H arom) ppm; $C_{24}H_{30}N_2O_5$ (426.5); calcd.: C 67.58, H 7.09, N 6.57; found: C 67.44, H 7.19, N 6.67.

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