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Synthetic studies towards 1,5-benzodiazocines

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ABSTRACT

Anthranilonitrile reacted with phenylmagnesium bromide to yield a dianion, which when heated (~120 °C) yielded the condensation product 2-(2-aminophenyl)-2,4-diphenyl-1,2-dihydroquinazoline **8**. This heterocycle, when treated with palladium acetate, was converted into 6,12-diphenyldibenzo[*b*,*f*][1,5]diazocine **9**. Methylmagnesium bromide and anthranilonitrile, under similar conditions directly gave a nitrogen-bridged diazocine, whose structure was determined by X-ray crystallography and also proven to be an analogue of Tröger's base. Acid-induced condensation of 2-amino-3-methoxybenzaldehyde gave the trimeric product **45** rather than a dibenzo[*b*,*f*][1,5]diazocine.

1. Introduction

Several benzo[*b*,*f*][1,5]diazocines have shown pharmacologically useful properties such as antiviral, cholesterol-lowering and hormone-like activity.[1,2] Additionally, some members of the diazocine system have found applications as homologues of benzodiazepine drugs and as reversal agents in multidrug resistance.[3,4] In recent years, material chemists have explored the electrochemical properties of diaryldibenzo[*b*,*f*][1,5]diazocines (**1**), which were found to be useful as a basis for molecular machines and artificial muscles (Fig. 1).[5,6] Moreover, a bridged variant of a dibenzo[*b*,*f*][1,5]diazocine, Tröger's base (**2**), has a chiral aromatic cleft structure with a unique ability to host guests and as a result act as a supramolecular receptor.[7] Although most applications of Tröger's base are within the field of supramolecular chemistry, pharmacological applications have also been reported.[8] More recently, the interest in Tröger's bases has extended to iminodibenzodiazocines **3** containing an additional nitrogen, available for further interactions and modifications.[9]

In the context with Tröger's base we will in this paper describe the synthesis and structural determination of the dimeric product **4** obtained from 2-aminobenzonitrile and methylmagnesium bromide.

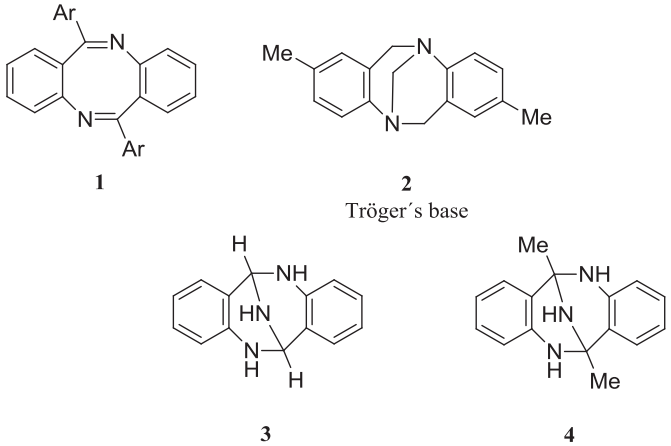

Fig. 1. Examples of benzo[*b*,*f*][1,5]diazocine structures (**1**–**4**).

2. Results and discussion

2-Aminobenzonitrile (**5**) is a readily available and versatile starting material for the synthesis of various heterocyclic systems.[10] This molecule (**5**) will react with Grignard reagents (e.g., C_6H_5MgBr) to produce intermediates of type **6**, which subsequently can be converted into nitrogen heterocycles, e.g., substituted quinazolines (**7**), as illustrated in Scheme 1.[11–15]

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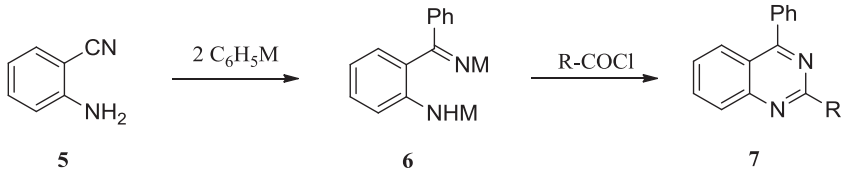
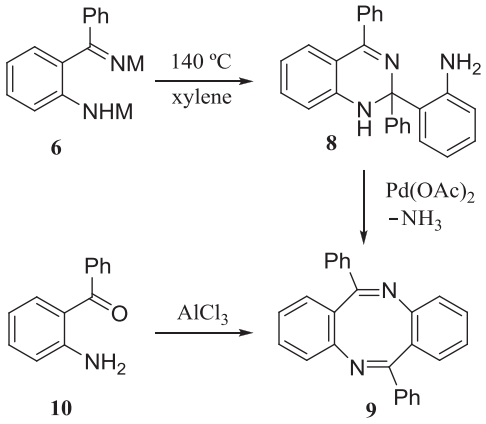
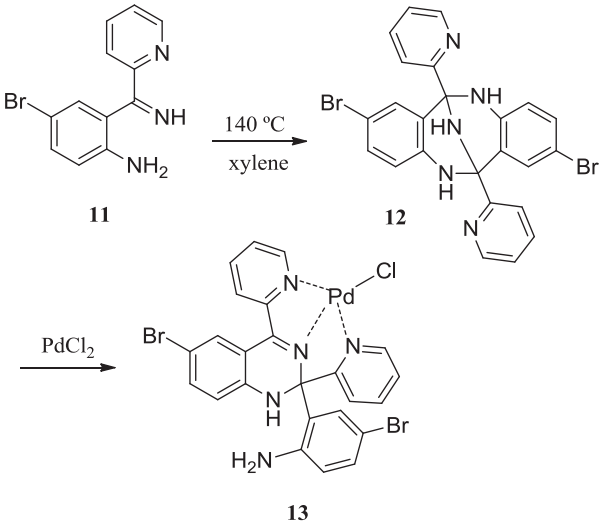


Scheme 1. (R=phenyl, alkyl, M=MgBr).

However, when the intermediate **6** was heated at higher temperatures (typically 140 °C) it underwent self-condensation to give **8**, the structure of which has been corroborated by X-ray crystallography (Scheme 2).[16] The preparation and NMR spectroscopic data for this molecule are now given for the first time.



Scheme 2. (M=MgBr).



Scheme 3.

In the presence of Pd(II)-compounds (or Hg-compounds) the dimer **8** undergoes a ring expansion with elimination of NH_3. This series of events probably starts with complexation of the metal ion with the nitrogen atom of the imine group. Subsequently the amino group will attack the now activated imine function and the scene is now set for elimination of ammonia, thus forming the well-known eight-membered ring system **9**.[17–19] This compound is readily prepared in excellent yields by condensation of 2-aminobenzophenone (**10**) using $AlCl_3$. Recently, more sophisticated methods, albeit more complex, have been developed.[20] A similar study has been published by Leganza et al.[9a] wherein the more complex imine **11** was heated in xylene to yield **12**, which could rearrange to give a sister compound to **8**, namely **13** (also confirmed by X-ray crystallography),[9a] but still containing palladium as illustrated in Scheme 3.

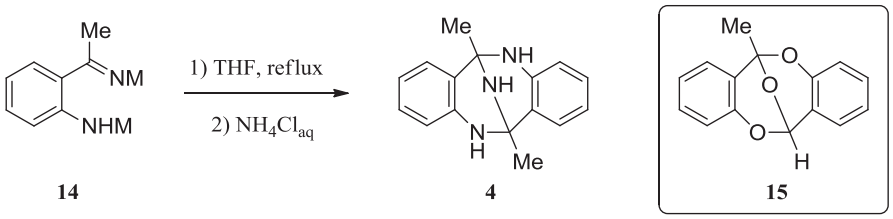
In contrast to the events discussed in Scheme 2 the intermediate **14**, prepared from 2-aminobenzonitrile and methylmagnesium bromide, when heated gave no dimeric product of type **8**. However, a crystalline product with the composition $C_{16}H_{17}N_3$ was isolated and the ^{13}C NMR spectrum of this compound featured a diagnostic singlet at 63.4 ppm, indicating the presence of an *N,N*-substituted aliphatic carbon atom. The ^1H NMR spectrum featured an NH singlet at 2.96 (1H) ppm and another one at 6.36 (2H) ppm. The suggested structure **4** could be corroborated by an X-ray crystallographic study (vide infra) (Scheme 4.). The somewhat related oxygen heterocycle **15** featured two signals at 91.0 and 95.5 ppm, respectively, from the aliphatic carbon atoms in the eight-membered ring.[21]

Interestingly, formation of oxygen-bridged dibenzo[*b*,*f*][1,5] diazocines (e.g., **17** and **18**) had previously been reported by Stefanovic et al. (Scheme 5).[22] The acid corresponding to **17** is unstable and isatin **19** will quickly be formed.

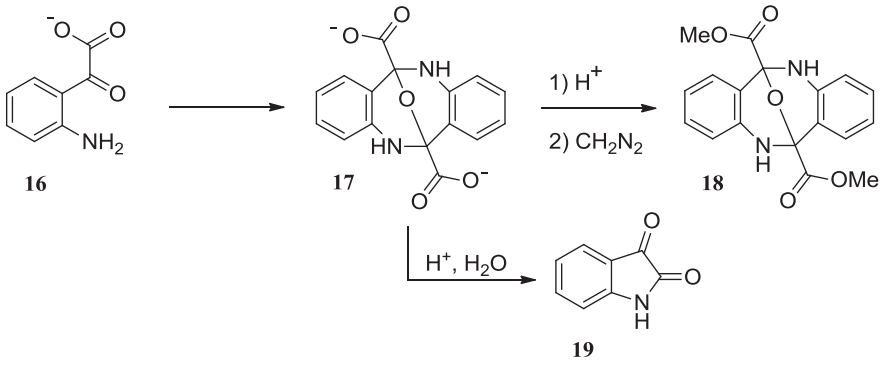
In the presence of even weak acids (e.g., acetic acid) the diazocine **4** underwent ring-opening and hydrolysis (Scheme 6) to the symmetrical dihydroxy derivative **20**, which is stabilized by hydrogen bonds. The aliphatic carbon atoms in **20** resonated at 66.4 ppm. Compound **20** featured only one set of signals in the ^{13}C NMR spectrum and it is assumed to have trans stereochemistry. Attempts to eliminate two molecules of water to yield **21** failed. One can assume that this molecule is suffering from the absence of stabilizing phenyl rings (as in **9**). In some experiments NMR spectroscopic evidence for the formation of **22a** or its chain tautomer **22b** was obtained but this unstable molecule decomposed rather than eliminated water to **21**. The unsuccessful formation of **21** and its parent molecule is precedented in the literature.[9d,37]

In this context we became interested in the recently reported acid-induced condensation of 2-aminoacetophenone **23** as outlined in Scheme 7.[23,24] However, no eight-membered products are formed under these conditions. The real structure of the purported molecule **24** is in fact that of **25**. Actually, it was shown already in 1883 that 2-aminoacetophenone readily undergoes self-condensation to 2-(2-aminophenyl) 4-methylquinoline.[25–27] Attempts to similarly condense 2-aminopropiophenone failed, presumably due to steric hindrance. In a hot medium of hydrogen chloride in acetic acid only the hydrochloride salt of the starting material could be isolated.

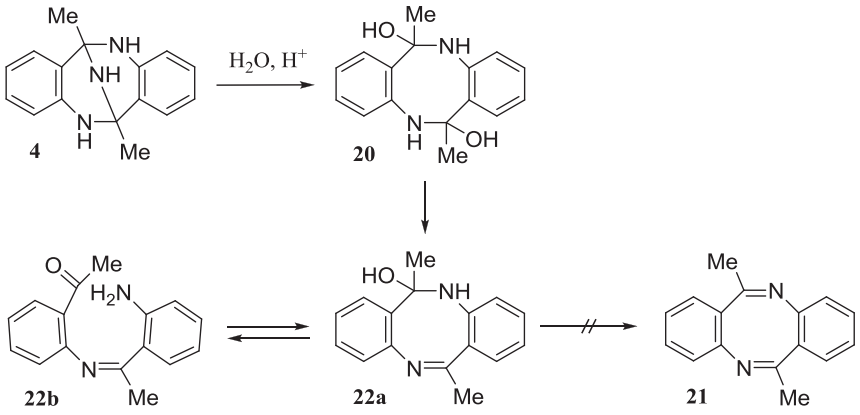
The unsubstituted diazocine **26** has been reported to be formed by hydrogenation of the nitrobenzene derivative **27** (Scheme 8).[28] However, in our hands, the simple 1,5-benzodiazocine **26** could not be obtained and the predominating product was identified as the acetamide derivative **28**. In addition to **28** small amounts of a molecule, which tentatively has been assigned structure **29**, were also isolated. In addition to eight aromatic CH signals and two acetoxy singlets at 17.6 and 21.9 ppm molecule **29** featured a diagnostic CH signal at 88.9 ppm in the ^{13}C NMR spectrum. The similarities between **22** and **29** are evident. Paudler[29] has in a preliminary communication reported that compound **37** upon treatment with cupric acetate was converted into **26**. In our hands this



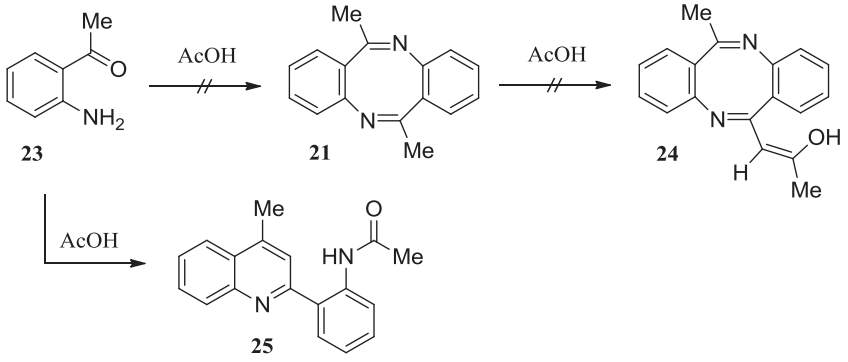
Scheme 4. (M=MgBr).



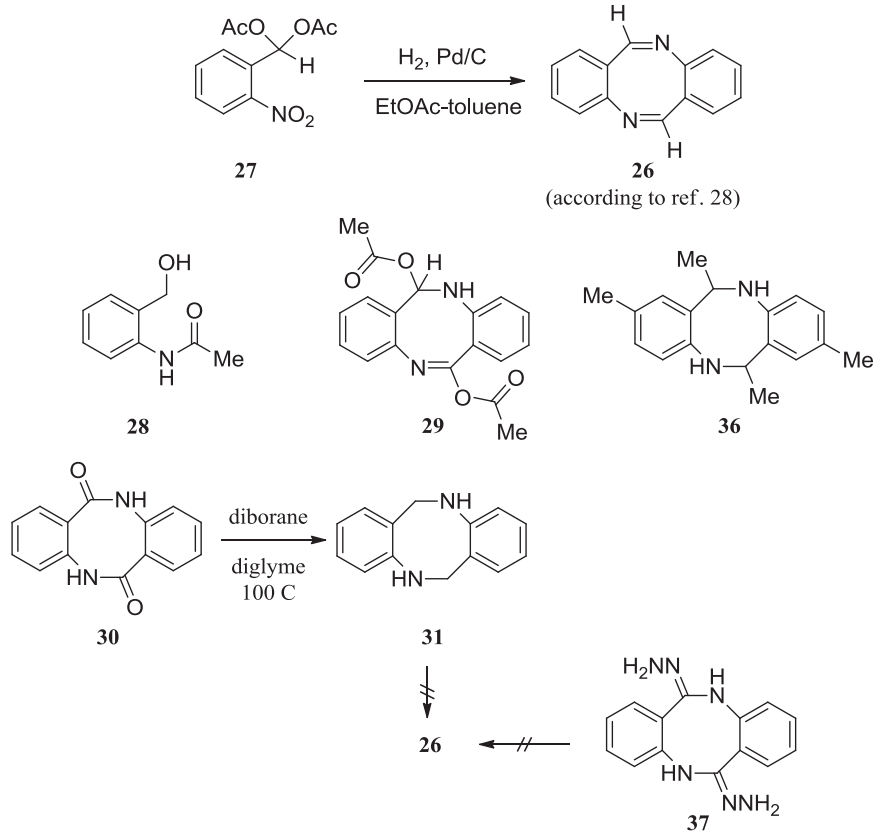
Scheme 5.



Scheme 6.



Scheme 7.



Scheme 8.

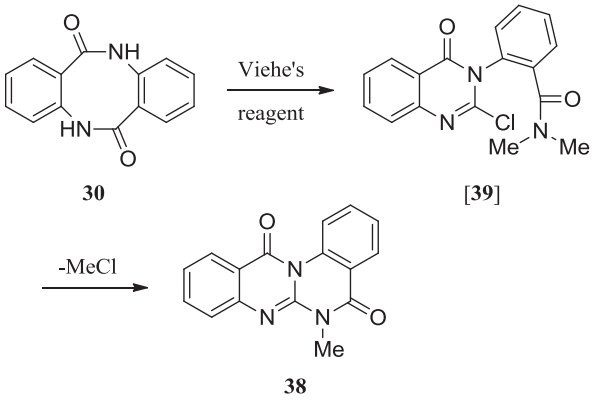
operation gave the cycloamide **30**. In this context the cyclodiamide **30** was converted into the known cyclodiamine **31** by reduction with diborane in hot diglyme. However, all attempts to dehydrogenate **31** to **26** failed. Recently, Harmata et al. have converted Tröger's base (**2**) (Fig. 1) in a multi-step reaction to a tetramethylderivative of **31** namely **36** (Scheme 8).[30]

At this point we decided to synthesize the diazocines **33** and **34** from the diamide **30**,[31–33] and then allow them into react with methylmagnesium bromide. Although the dichloro compound **33** was described as early as 1919, and it has also been resynthesized a few times over the years, we found that the conditions are quite critical and trichloroethylene was found to be the solvent of choice.[32]

Because of the difficulties in making **33**, alternative methods were explored and in this context it was found that Viehe's reagent, $Cl_2C{=}NMe_2Cl$, readily reacted with the diamide **30** to yield **38**, a known compound, that previously had been prepared in a multi-step operation starting with 2-(2-azidophenyl)-4*H*-3,1-benzoxazin-4-one.[40] However the dichloro compound **33** was not obtained.

It is assumed that the transformation of **30** into **38** is initiated by an attack of the reagent on the two nitrogen atoms in the eight-membered ring followed by a ring-opening induced by attack of the dimethylammonium ion leading to the intermediate **39**. The next step features a displacement of the chlorine atom after attack by the nitrogen atom in the dimethylamino function. Finally, the chloride ion generated will attack one of the methyl groups in the now positively charged amide and thereby generate chloromethane and the observed product **38** (Scheme 9).

The bishydrazone **37** was prepared by nucleophilic displacement of the dichloro derivative **33** with hydrazine. Initially this reaction was fraught with problems and therefore displacement with dimethylamine was studied in order to broaden the



Scheme 9.

knowledge of this type of substitution, which gave the known molecule **40**.[39] At room temperature this molecule features restricted rotation of the dimethylamino groups. The barrier is, however, of low energy as the point of coalescence was determined to be 34.8 °C.

Thionation of **30** as described in the literature,[34] gave **41**, which upon methylation gave **34**. Treatment of **34** with methylmagnesium bromide in the presence of Ni^{2+} salts under conditions originally developed by Wenkert[35] gave a product in obvious disagreement with **4**, **20** and **21**, because the two aromatic rings gave 4+4 signals from the methine carbon atoms. Treatment of the dichloro derivative **33** with methylmagnesium bromide in hot tetrahydrofuran (in the absence of Ni^{2+}) and a work-up procedure involving treatment with aq ammonium chloride gave the identical

product. Somewhat surprisingly both reactants gave the same product, namely the monomethyl-substituted hydrated molecule **22a**. Perhaps again, an illustration of the importance of hydrogen bonds.

To this end, no established methods exist for the preparation of either dibenzo[*b*,*f*][1,5]diazocines with aliphatic substituents in positions 6 and 12 or the parent compound **26** (Scheme 8.). The *tert*-butyl derivative **42** (Fig. 2), however, seems to be an exception.[36] Recently, compound **43** (Fig. 3) has been reported as a side-product when 2-amino-4-methoxybenzonitrile was allowed to react with ethylmagnesium bromide. In this context also a condensation product of 2-amino-3-methoxybenzaldehyde prepared a long time ago by Tröger et al.[41,42] was of interest as this molecule after several assignments was given structure **44**. If correct this would have been the first example of the elusive system **26**. This work has now been reinvestigated and as excellent NMR spectroscopic data could be obtained. This condensation product has now been re-assigned as the trimeric molecule **45**. Useful diagnostic signals (CH doublets) in the ^{13}C NMR spectrum appeared at 80.5, 63.5, 63.3 ppm. The parent molecule **46** had previously been correctly assigned by McGeachin[37] in 1966 after detailed studies of its chemical transformations as well as ^{1}H NMR spectroscopic data. McGeachin also established that if the condensation between 2-aminobenzaldehyde was performed in presence of Ni^{2+} the tetrameric product **47** was formed. Later similar condensations have been studied by a wide range of research workers.[38]

Finally it should be added that Friedländer was the first (1884) to study the condensation of 2-aminobenzaldehyde and structure **48** was given rather than its ring tautomer **49**.[43,44] Over the years a considerable amount of wrong structures were introduced in the literature until 1966 when McGeachin clarified the situation.[37]

The structure of **4** was confirmed by X-ray analysis, the details of which are given in the Experimental section, and an ORTEP representation of the molecular structure is shown in Fig. 4. The molecules are linked together via hydrogen bonds and CH–π stacking interactions to form a 3D network. The packing coefficient (percent filled van der Waals space in the unit-cell) is 68.8%, indicating an efficient molecular framework in the solid state.

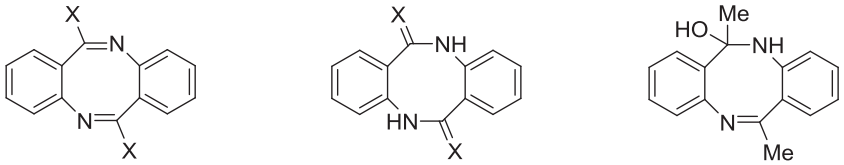
3. Conclusions

The dianion, formed by addition of Grignard reagents to anthranilonitrile is a versatile synthon that can be converted into quinazolines and benzodiazepines but also into NH-bridged 1,5-benzodiazocines.

4. Experimental section

4.1. General techniques and apparatus

All starting materials and solvents were obtained from commercial sources and used without further purification. THF was

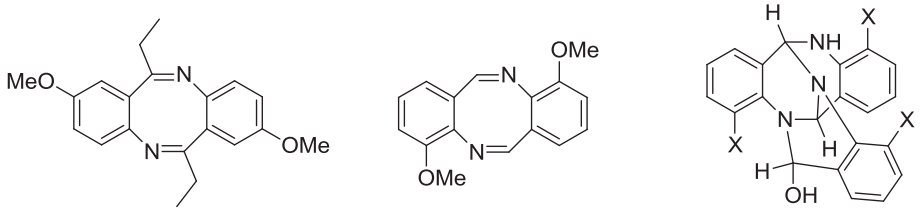


33 X = Cl
34 X = SMe
37 X = $NHNH_2$
40 X = NMe_2
42 X = *t*Bu

30 X = O
41 X = S

23

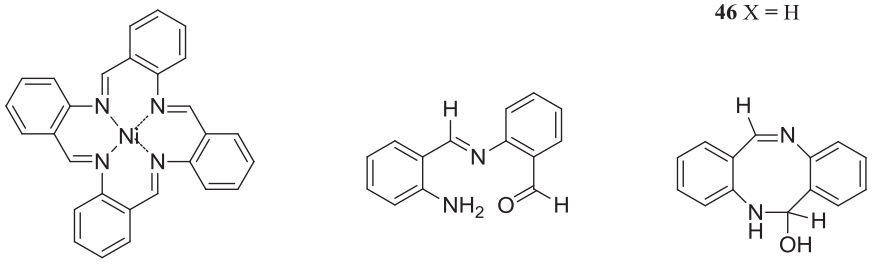
Fig. 2. Structures of additional benzo[*b*,*f*][1,5]diazocines.



43

44

45 X = OMe
46 X = H



47

48

49

Fig. 3. Additional benzo[*b*,*f*][1,5]diazocines and some related molecules.

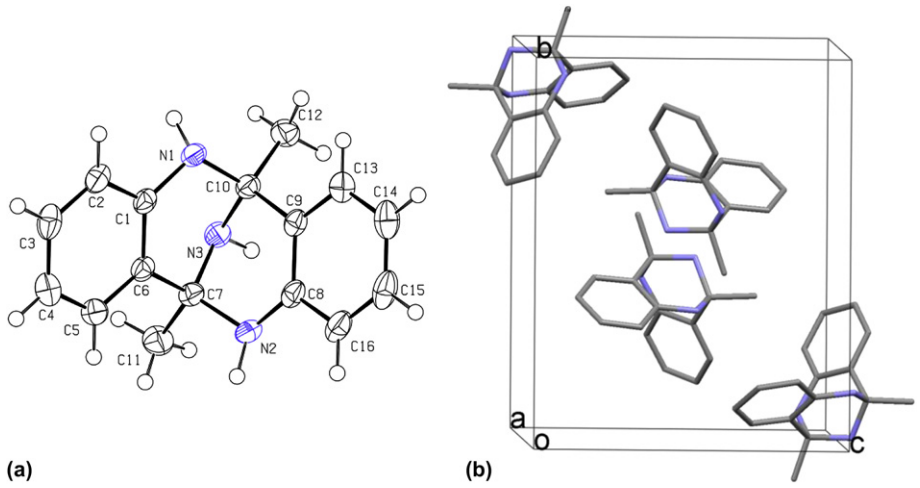


Fig. 4. (a) Molecular and (b) crystal structure (H-atoms omitted) of **4**.

distilled from sodium and benzophenone. Chromatography was performed using silica gel (40–63 μm). Melting points were determined in open capillary tubes on a Büchi-B545 melting point apparatus. IR spectra were recorded on Thermo Nicolet Avatar 330 FT-IR instrument. NMR spectra were recorded on a Bruker DPX 300 operating at 300.1 MHz for ^{1}H and 75.5 MHz for ^{13}C in DMSO-d_6. Chemical shifts are reported downfield to TMS. The elemental analyses were performed by H. Kolbe Microanalytisches Laboratorium, Mülheim an der Ruhr, Germany.

4.2. Methods and analysis

*4.2.1. 6,12-Dimethyl-6,12-imino-5,6,11,12-tetrahydrodibenzo[b,f][1,5] diazocine (**4**).* To a THF-solution (20 mL) of anthranilonitrile (2.36 g, 20 mmol), MeMgBr (23.3 mL, 70 mmol) was added-drop wise at room temperature. After stirring for 30 min, the mixture was heated at reflux for 23 h and then quenched with NH_4Cl (40 mL, 20% aq). EtOAc (20 mL) was added to the mixture and the organic layer was separated, washed with water (3×50 mL) and dried (Na_2SO_4). Evaporation of the solvent gave a yellow oil that was purified by flash chromatography (MeOH/toluene, 1:6) to afford **4** 1.0 g (41%) as a white solid, mp 151–152 °C. An analytically pure version (as colourless prisms) of **4**, suitable for X-ray crystallography, was obtained by recrystallization from 2-propanol; IR ν_{max}: 3345, 3287, 3236, 3026, 1601, 1469, 1134, 934, 829, 751 cm^{-1}; ^{1}H NMR (DMSO-d_6): 1.62 (s, 6H), 6.32 (s, 2H), 6.39 (d, 2H, *J* 7.5 Hz), 6.49 (t, 2H, *J* 7.5 Hz), 6.82 (t, 2H, *J* 7.5 Hz), 7.13 (d, 2H, *J* 7.5 Hz); ^{13}C NMR (DMSO-d_6): 26.6 (q), 63.4 (s), 114.5 (d), 115.9 (d), 124.8 (d), 126.8 (d), 128.6 (s), 143.9 (s). Anal. Calcd C, 76.46; H, 6.82; N, 16.72. Found: C, 76.30; H, 6.86; N, 16.56.

*Crystal data for **4***: $C_{16}H_{17}N_3$, M_r=251.33 g/mol, monoclinic, space group $P2_1/c$ (No 14), a=9.1320(6) Å, b=13.3771(8) Å, c=10.7692(7) Å, β=96.689(3)°, V=1306.61(14) Å^3, Z=4, D_{calcd}=1.278 g cm^{-3}, μ(Mo Kα)=0.78 cm^{-1}, R=0.035, wR^2=0.094, GOF=1.08. The data were collected at 200 K on a Bruker APEX-II CCD with graphite monochromatized Mo Kα radiation (λ=0.71073 Å) and employing a 0.08 mm×0.12 mm×0.18 mm crystal (R_{int}=0.03). CCDC-886046 contains the supplementary crystallographic data for **4**, respectively. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

*4.2.2. 2-(2-Aminophenyl)-2,4-diphenyl-1,2-dihydroquinazoline (**8**).* 2-Aminobenzonitrile (5.9 g, 50 mmol) was added in portions to a solution of phenylmagnesium bromide (prepared from bromobenzene (16.0 g, 0.1 mol and magnesium 2.7 g)) in ether (200 mL) at reflux. After a reflux period of 4 h, toluene (200 mL) was added whereupon most of the ether was distilled off and the residue heated at reflux for 4 h. The mixture was allowed to cool and ammonium chloride (aq 5%, 2×200 mL) was added. The organic phase was separated, dried and evaporated. Treatment of the residue with isopropyl ether/isopropanol (2:1) gave after a lag of ~1 h crystals of the title compound **8** (9.6 g, 51%), mp 185–187 °C; IR ν_{max}: 3437, 3378, 3322, 3045, 1606, 1450, 1332, 1156, 966, 754, 740, 697 cm^{-1}; ^{1}H NMR (DMSO-d_6): 5.32 (s, 2H), 6.53–6.59 (m, 3H), 6.92–7.05 (m, 3H), 7.26–7.41 (m, 7H), 7.50–7.56 (m, 6H); ^{13}C NMR (DMSO-d_6): 77.1 (s), 114.4 (d), 114.6 (d), 114.7 (s), 116.0 (d), 116.3 (d), 126.9 (d), 127.0 (d), 127.1 (d), 127.5 (s), 127.6 (d), 127.9 (d), 128.1 (2d), 129.0 (d), 129.3 (d), 133.1 (d), 138.3 (s), 145.6 (s), 145.7 (s), 146.2 (s), 163.2 (s). Anal. Calcd C, 83.17; H, 5.64;, N, 11.19. Found: C, 82.90; H, 5.77; N, 11.02. The structure of **8** has been confirmed by X-ray crystallography.[16] The crystals used at the time (1988) emanated from our laboratory.

*4.2.3. 6,12-Diphenyldibenzo[b,f][1,5]diazocine (**9**).* The condensation dimer **8** (374 mg, 1 mmol) was dissolved in DMF (50 mL) and palladium acetate (5 mg, 0.020 mmol) was added and the mixture heated at 140 °C for 1 h. After filtration and concentration the residue was crystallized from ethanol to give the title compound as bright-yellow needles (210 mg, 52%), mp 190–192 °C (lit.[18] mp 191–193 °C); ^{1}H NMR (DMSO-d_6): 7.01–7.10 (m, 6H), 7.36–7.44 (m, 6H), 7.49–7.50 (m, 2H), 7.66–7.68 (m, 4H); ^{13}C NMR (DMSO-d_6): 120.6 (d), 124.1 (d), 126.6 (s), 127.8 (d), 129.0 (d), 129.3 (d), 130.4 (d), 131.9 (d), 137.6 (s), 151.8 (s), 169.1 (s). These data are in good agreement with those in the literature.[46] There are several methods available in the literature for compound **9**, which has been known[45] since 1896. The by far synthetically most useful method is due to Sternbach.[17] This excellent procedure was repeated and the material obtained was identical with the product obtained above. The analytical sample was recrystallized from acetonitrile, mp 190–192 °C. In a recent paper by Wang et al.[20] a considerably higher range, 226–227 °C was reported, which might be due to polymorphism.

*4.2.4. Sodium-6,12-oxido-5,6,11,12-tetrahydrodibenzo[b,f][1,5]diazocine-6,12-dicarboxylate (**17**).* This compound was prepared according to Stefanovic et al.[22] Yield: 80%, mp 170–175 °C (lit.[22] mp 176 °C); ^{1}H NMR: 4.72 (br s, 4H), 6.56 (t, 2H, *J*=7.5 Hz), 6.75 (d, 2H, *J* 7.5 Hz), 6.93 (t, 2H, *J* 7.5 Hz), 7.32 (d, 2H *J* 7.5 Hz); ^{13}C NMR: 82.9 (s), 116.4 (d), 117.6 (d), 124.5 (s), 126.0 (d), 128.4 (d), 142.3 (s), 171.5 (s).

*4.2.5. Dimethyl-6,12-oxido-5,6,11,12-tetrahydrodibenzo[b,f][1,5]diazocine-6,12-dicarboxylate (**18**).* The acid **17** was treated with

diazomethane as described by Stefanovic et al.[22] Yield 95%, mp 236–237 °C (lit.[22] mp 238 °C); ^{1}H NMR: 3.79 (s, 6H, 2OCH$_3$), 6.68 (dd, 2H, *J*=7.8), 6.85 (d, 2H, *J*=7.8), 7.01–7.08 (m, 4H), 7.57 (s, 2H, 2NH); ^{13}C NMR: 53.2 (q), 82.9 (s), 117.0 (d), 118.4 (d), 122.3 (s), 124.0 (d), 128.8 (d), 140.8 (s), 168.6 (s).

*4.2.6. 6,12-Dimethyl-5,6,11,12-tetrahydrodibenzo[b,f][1,5]diazocine-6,12-diol (**20**).* The transannular amine **4** (252 mg, 1.0 mmol) was dissolved in acetic acid (1.5 mL) at 25 °C and after 2 min diluted with water containing two drops of hydrochloric acid. The white solid formed was collected and dried. Yield (243 mg, 90%), mp 190–195 °C dec; IR ν_{max}: 3240 (w), 2940, 1611, 1559, 1493, 1249, 749, 582 cm^{-1}; ^{1}H NMR (DMSO-d_6): 1.97 (s, 6H), 6.62 (d, 2H, *J* 7.7 Hz), 6.75 (t, 2H, *J* 7.7 Hz), 7.07 (t, 2H, *J* 7.7 Hz), 7.29 (d, 2H, *J* 7.7 Hz), 7.53 (s, 2H), 10.36 (br s, 2H); ^{13}C NMR (DMSO-d_6); 23.8 (q), 66.5 (s), 115.3 (d), 118.7 (d), 123.5 (s), 125.6 (d), 129.0 (d), 141.0 (s). Anal. Calcd C, 71.09; H, 6.71; N, 10.36. Found: C, 70.88; H, 6.70; N, 10.22.

*4.2.7. 6,12-Dimethyl-5,6-dihydrodibenzo[b,f][1,5]diazocin-6-ol (**22a**).* The experiment just described was repeated but at the end hydrochloric acid (0.1 mL, 1.0% in H_2O) was added. The unstable solid formed was collected, dried and studied with NMR-spectroscopy yield (204 mg, 80%), mp 220–230 dec; ^{1}H NMR (DMSO-d_6): 2.23 (s, 3H), 2.43 (s, 3H), 7.22 (t, 1H, *J* 6.9 Hz), 7.46–7.51 (m, 1H), 7.73 (t, 1H, *J* 7.1 Hz), 7.99–8.04 (m, 2H), 8.42 (d, 1H, *J* 7.1 Hz), 8.49–8.56 (m, 2H), 10.99 (s, 1H), 12.04 (s, 1H); ^{13}C NMR (DMSO-d_6): 24.7 (q), 25.1 (q), 114.2 (s), 121.6 (d), 122.8 (d), 124.1 (d), 124.3 (s), 127.3 (d), 127.9 (d), 130.7 (d), 131.0 (d), 134.7 (d), 139.1 (s), 150.4 (s), 156.3 (s), 159.4 (s), 168.7 (s), 170.2 (s).

No good elemental analysis data could be obtained.

*4.2.8. N-(2-(4-Methylquinolin-2-yl)phenyl)acetamide (**25**).* 2-Aminoacetophenone (1.35 g, 10.0 mmol) was dissolved in acetic acid (12 mL) containing sulfuric acid (0.1 mL) and the solution was heated at reflux for 3 h, whereupon acetic anhydride (3 mL) was added and the heating was continued for 1 h. The cooled mixture was poured in to water and the semi-solid formed was crystallized from ethanol to give the title compound (0.80 g, 40%), mp 115–116 °C (lit.[27] mp 116 °C); IR ν_{max}: 3058 (w), 2922, 1682, 1001, 1583, 1533, 1440, 1307, 1122, 1109, 851, 760, 735 cm^{-1}; ^{1}H NMR (DMSO-d_6): 2.15 (s, 3H, CH$_3$), 2.73 (s, 3H, CH$_3$), 7.20 (dd, 1H, J_1 7.7 Hz, J_2 7.3 Hz), 7.41 (dd, 1H, J_1 7.7 Hz, J_2 7.3 Hz), 7.64 (dd, 1H, J_1 7.7 Hz, J_2 7.3 Hz), 7.82 (dd, 1H, J_1 7.7 Hz, J_2 7.3 Hz), 7.93 (s, 1H), 7.98–8.09 (m, 3H), 8.44 (d, 1H, *J* 7.3 Hz), 12.8 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): 18.4 (q), 24.8 (q), 121.1 (d), 121.2 (d), 123.3 (d), 124.1 (d), 124.9 (s), 126.2 (s), 126.8 (d), 128.7 (d), 129.6 (d), 156.9 (s), 168.0 (s), 130.1 (d), 130.2 (d), 138.2 (s), 145.3 (s), 146.1 (s).

4.2.9. Acetylation of 2-(4-methylquinolin-2-yl)aniline. 2-(2-Aminophenyl)-4-methylquinoline (2.34 g, 10 mmol) was dissolved in acetic anhydride (5 mL). After 30 min at 60 °C the solvent was evaporated and the residue crystallized from ethanol to give the title compound (2.67 g, 95%). This material was identical with that obtained in the previous experiment.

*4.2.10. N-(2-(Hydroxymethyl-phenyl))acetamide (**28**).* Palladium (5% on carbon, 1.0 g) was added to a solution of **27** (5.06 g, 20 mmol) in ethanol (100 mL) and toluene (60 mL). After 6 h at room temperature, the catalyst was removed by filtration and washed with a small amount of toluene. Evaporation gave a white solid that was purified by column chromatography ($CHCl_3$). Compound **28** was obtained as a white solid (1.8 g, 53%), mp 115–116 °C (lit.[47] mp 116 °C); IR ν_{max}: 3271, 3195, 1653, 1530, 1454, 1367, 1295, 1036, 983, 760, 534 cm^{-1}; ^{1}H NMR: 2.16 (s, 3H), 4.67 (s, 2H), 7.06–7.10 (m, 1H), 7.18 (d, 1H), 7.27–7.33 (m, 1H), 7.97 (d, 1H), 8.65 (s, 1H); ^{13}C NMR: 24.8 (q), 64.4 (t), 122.9 (d), 124.6 (d), 129.1 (d), 129.2 (d), 135.4 (s), 139.4 (s), 169.3 (s). The spectroscopic data are in good agreement with those in the literature.[47]

Compound **29** was obtained as a minor product from the chromatographic procedure described above and isolated as a white crystalline solid, 259 mg, 8.0%, ^{1}H NMR ($CDCl_3$): 1.94 (s, 3H), 2.01 (s, 3H), 4.31 (d, 1H), 6.65–6.70 (m, 2H), 6.87 (d, 1H), 6.93 (d, 1H), 6.98–7.04 (m, 1H), 7.16 (d, 1H), 7.20 (t, 1H), 7.67 (d, 1H); ^{13}C NMR ($CDCl_3$): 17.6 (q), 21.9 (q), 88.9 (d), 113.1 (d), 114.6 (d), 120.5 (d), 123.2 (d), 124.1 (s), 124.8 (d), 124.9 (s), 126.8 (d), 127.3 (d), 130.5 (d), 130.7 (d), 137.6 (s), 142.0 (s), 167.0 (s). No good elemental analysis data could be obtained for this unstable compound.

*4.2.11. 5,11-Dihydro-6,12-dioxodibenzo[b,f][1,5]diazocine (**30**).* Methyl anthranilate (45.3 g, 0.30 mol) was dissolved in THF (450 mL) under an atmosphere of dry nitrogen. Sodium hydride (19.3 g, 60% in oil) was then intermittently added over 0.5 h to the stirred mixture at 30 °C. This mixture was worked-up after 76 h at 25–30 °C by addition of water (1.5 L), filtration and acidification with acetic acid gave a precipitate of the title compound (28.9 g, 81%), which was collected after 1 h at room temperature, mp 344 °C (lit.[31] mp 333 °C); IR ν_{max}: 3035, 1654, 1640, 1603, 1378, 1262, 783, 752, 609, 535 cm^{-1}; ^{1}H NMR (DMSO-d_6): 7.1–7.4 (m, 8H), 10.2 (s, 2H, NH); ^{13}C NMR (DMSO-d_6): 125.7 (d), 127.3 (d), 128.2 (d), 130.5 (d), 133.6 (s), 134.8 (s), 169.3 (s).

*4.2.12. 5,6,11,12-Tetrahydrodibenzo[b,f][1,5]diazocine (**31**).* The diamide **30** (4.76 g, 20 mmol) was heated under nitrogen, to 135 °C in diglyme (150 mL). After cooling to 70–80 °C sodium borohydride (2.40 g, 6.0 mmol) was added followed by boron trifluoride etherate (5.0 mL). After 45 min at this temperature it was increased to 90–110 °C during 45 min whereupon the reaction mixture was allowed to cool and the solvent distilled off. The residue was treated with water (100 mL) and concd HCl (30 mL) at 35 °C and stirred for 3 h. After filtration the filtrate was treated with concd ammonia until pH 8–9 was reached and after a stirring period of 2 h the white solid was collected and dried to give the title compound (2.8 g, 65%), mp 138.5–139.5 °C (lit.[32d] mp 137.8 °C); ^{1}H NMR (DMSO-d_6): 4.42 (d, 2H), 4.86 (d, 2H), 7.26 (d, 2H), 7.41 (m, 2H), 7.49 (m, 2H), 7.59 (m, 2H), 10.48 (br s, 2H); ^{13}C NMR (DMSO-d_6): 57.2 (t), 124.7 (d), 126.4 (s), 128.5 (d), 128.9 (d), 129.0 (d), 137.6 (s).

*4.2.13. 6,12-Dichlorodibenzo[b,f][1,5]diazocine (**33**).* A mixture of 5,11-dihydro-6,12-dioxodibenzo[*b,f*][1,5]diazocine (11.9 g, 50 mmol) and phosphorous pentachloride (25.0 g) in trichloroethylene (220 mL) was heated at reflux for 3 h. After filtration the filtrate was concentrated to ca. 100 mL and the solution was allowed to stand for 24 h. Big crystals of **33** had now deposited (10.5 g, 77%), mp 219–221 °C (lit.[32a] mp 220 °C); IR ν_{max}: 3063, 1649, 1593, 1477, 1212, 1119, 944, 924, 866, 816, 757, 696, 644 cm^{-1}; ^{1}H NMR (C_2Cl_4): 6.95–7.35 (m, 8H); ^{13}C NMR (C_2Cl_4): 121.5 (s), 124.6 (d), 125.8 (d), 126.6 (d), 130.8 (d), 145.0 (s), 155.5 (s). This molecule has been prepared on several occasions in the past and no ^{13}C NMR data have been published until now.

*4.2.14. 6,12-Dithiomethoxydibenzo[b,f][1,5]diazocine (**34**).* Thione **36**[33,34] (2.70 g, 10.0 mmol) was dissolved in dimethylformamide (40 mL) and dimethyl sulfate (2.77 g, 21.0 mmol) was added to the stirred solution at 40 °C. A precipitate was quickly formed, which was collected and treated with a solution of sodium carbonate (4.0 g) in water (100 mL) and ethanol (10) mL. The yellow solid formed was collected and dried to give the title compound (2.70 g, 90%), mp 212–216 °C; IR ν_{max}: 3149, 2920, 1606, 1592, 1508, 1474, 1374, 1216, 1017, 966, 760, 703 cm^{-1}; ^{1}H NMR (DMSO-d_6): 2.50 (6H, s, 2SMe), 6.88 (d, 2H), 4.05 (t, 2H, *J* 7.5 Hz), 7.19 (d, 2H, *J* 7.5 Hz), 7.32 (t, 2H, *J* 7.5 Hz); ^{13}C NMR (DMSO-d_6): 14.0 (q), 121.9 (d), 123.8 (d),

127.0 (s), 127.2 (d), 130.9 (d), 148.9 (s), 169.8 (s). Anal. Calcd C, 64.35; H, 4.04; N, 4.69. Found: C, 64.26; H, 3.99; N, 4.49.

*4.2.15. 6-Methyl-12H-quinazolino[3,2-a]-quinazoline-5[6H]-12-dione (**38**).* Dibenzo[*b*,*f*][1,5]diazocine-6,12-dione (2.38 g, 10.0 mmol) and dichloromethylene–dimethyl-iminium chloride, Viehe's reagent (3.25 g, 20.0 mmol) were heated at reflux temperature in acetonitrile (50 mL) for 2 h. After concentration methanol (35 mL) was added, which soon resulted in crystallization of the product (2.20g, 79%), mp 180–181 °C (lit.[40] mp 177–178 °C); ^{13}C NMR (DMSO-d_6): 29.9 (q), 118.3 (s), 118.5 (s), 120.8 (d), 125.1 (d), 125.6 (d), 126.7 (d), 127.0 (d), 127.3 (d), 133.6 (d), 135.3 (d), 135.6 (s), 145.4 (s), 159.2 (s), 161.5 (s).

The ^{1}H NMR data were in agreement with data reported in the literature.[40]

*4.2.16. 6,12-Bis-Dimethylaminodibenzo[b,f][1,5]diazocine (**40**).* The dichloro compound **33** (550 mg, 2.0 mmol) was dissolved in dioxane (25 mL) at 80 °C and a stream of dimethylamine was introduced. After the reaction had gone to completion, evaporation of the solvent gave a residue, which was treated with water to remove salts. The remaining solid was treated with 2-propanol and diisopropylether and the solid formed was collected to give the title compound (535 mg, 91%), mp 144–145 °C (lit.[39] mp 144–145 °C); IR ν_{max}: 3073 (w), 2953 (w), 1705, 1693, 1600, 1590, 1559, 1465, 1423, 1359, 1287, 1159, 1051, 1015, 953, 767, 681 cm^{-1}; ^{1}H NMR (35 °C) ($CDCl_3$): 2.96 (br s, 12H), 6.84–7.35 (m, 8H); ^{1}H NMR (25 °C): 2.96 (d, $\Delta\nu$=151.0 Hz); ^{13}C NMR ($CDCl_3$): 37.9 (q), 120.6 (d), 124.5 (d), 125.9 (d), 126.0 (s), 129.5 (s), 130.5 (d), 147.5 (s), 158.5 (s). The IR spectral data are in good agreement with those in the literature (obtained in Nujol).[39]

*4.2.17. Bisanhydro trimer (**45**).* 2-Amino-3-methoxybenzaldehyde (1.51 g, 10.0 mmol) was dissolved in acetic acid (30 mL) and heated at reflux temperature for 1 h. The product has low solubility in the medium and starts to precipitate within 5 min. Filtration gave the title compound (1.40 g, 95%), mp 280–282 °C; IR ν_{max}: 3268, 2932, 1592, 1576, 1477, 1437, 1254, 1212, 1054, 1035, 750 cm^{-1}; ^{1}H NMR (DMSO-d_6): 3.74 (s, 3H), 3.75 (s, 3H), 3.85 (s, 3H), 5.42–5.44 (m, 2H), 5.47 (s, 1H), 6.38 (d, 1H), 6.61–6.65 (m, 1H), 6.69–6.72 (m, 2H), 6.80–6.88 (m, 5H), 6.97–6.99 (m, 1H); ^{13}C NMR (DMSO-d_6): 55.3 (q), 55.4 (q), 55.7 (q), 63.3 (d), 63.5 (d), 80.5 (d), 109.3 (d), 110.2 (d), 110.3 (d), 116.5 (d), 120.4 (d), 120.9 (s), 121.0 (d), 121.5 (d), 123.6 (d), 123.7 (d), 130.3 (s), 130.6 (s), 131.0 (s), 132.2 (s), 132.7 (s), 146.7 (s), 151.8 (s), 152.1 (s). Anal. Calcd C, 69.05; H, 5.55; N, 10.07. Found: C, 68.97; H, 5.36; N, 9.87. This molecule had a long time ago been prepared by the Tröger group[41,42] on several occasions, however with incorrect assignments.

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