

A novel asymmetric synthesis of highly enantiomerically enriched norbornane-type diamine derivatives

Carsten Bolm,* Ingo Schiffrers, Iuliana Atodiresei, Salih Ozcubukcu and Gerhard Raabe

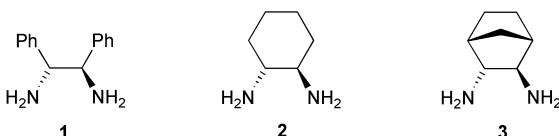
Institut für Organische Chemie der RWTH Aachen, Prof.-Pirlet-Str. 1, 52056, Aachen, Germany. E-mail: Carsten.Bolm@oc.rwth-aachen.de; Fax: +49 241 809 2391

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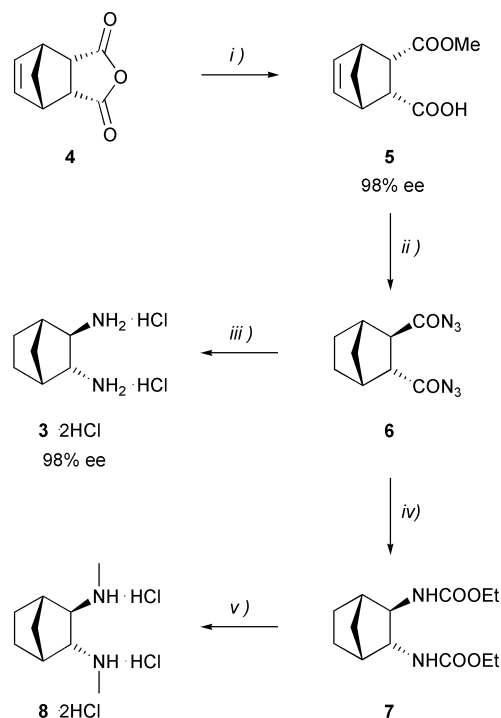
The simple and highly enantioselective methanolysis of norbornene dicarboxylic acid anhydride mediated by quinidine leads to the corresponding *cis*-monomethyl ester with 98% ee. By means of selective ester epimerization, followed by Curtius degradation of the intermediate *trans*-diacyl azide, two optically active norbornane-type diamines are obtained as their hydrochloric salts. Liberating the amine with an excess of triethylamine *in situ* and subsequent derivatization affords potential C_1 -symmetric ligands for asymmetric catalysis in excellent yields.

In recent years, the interest in the development of stereocontrolled syntheses of chiral 1,2-diamines has increased considerably.¹ Vicinal diamines have become important synthetic targets, in particular due to their use as intermediates in the preparation of important biologically active compounds such as biotin,² balanol,³ a broad range of κ -opioid receptor agonists,⁴ which are pharmacologically used as analgesic agents without the clinically side effects that characterize morphine, and 1,2-diamino platinum complexes, which serve as cytostatic remedies in chemotherapy with increased antitumoral activity and less toxicity as compared to cisplatin.⁵ Furthermore, vicinal diamines have found applications in the resolution of racemates,⁶ as chiral auxiliaries in enantio- and diastereoselective syntheses,¹ and in the preparation of a large number of ligands for asymmetric catalysis, including epoxidation,⁷ alkene aziridination,⁸ epoxide ring-opening,⁹ Diels-Alder reactions,¹⁰ and transfer hydrogenation.¹¹ In the light of their synthetic significance it is surprising that most of these studies have been focussed on the use of only a very few diamines. The most widely applied ones are *trans*-1,2-diphenylethylene diamine (**1**) and *trans*-1,2-diaminocyclohexane (**2**). They are readily accessible, and their large-scale preparations have been described in full detail.¹² Interestingly, the related *trans*-diamine **3**, having a more rigid norbornane backbone, has remained almost unnoticed. Since in contrast to **1** and **2**, diamine **3** is C_1 -symmetric, special effects could result when ligands stemming from **3** are used in asymmetric catalysis. Only a few years ago, enantiopure **3** was first isolated by resolution of its racemate with *O,O'*-dibenzoyltartaric acid.¹³ Unsatisfyingly, however, this approach afforded the tartaric salt of *ent*-**3** in only 16% yield, based on the racemate. So, a more efficient preparation, which would allow a broader application of this interesting 1,2-diamine, appeared desirable.



Recently, we described a simple and highly enantioselective methanolysis of *meso*-anhydrides such as **4**, mediated by cinchona alkaloids to give optically active monomethylesters of type **5**. Either enantiomer of ester **5** can be prepared in excellent yield with up to 99% ee by using inexpensive and quantitatively recoverable quinine or quinidine as the directing additive.¹⁴ As an extension of our work in this field, we reported on the synthesis and polymerization of both *cis*- and *trans*- β -amino acid methylesters starting from the same monomethylester **5**.¹⁵ On the basis of these findings, we wish to demonstrate herein that **5** is also a valuable intermediate for the preparation of highly enantiomerically enriched norbornane diamine derivatives.

As shown in Scheme 1, the overall reaction sequence involves the asymmetric desymmetrization of *meso*-anhydride **4**, followed by selective epimerization of the *cis*-hemiester **5** to its *trans*-isomer,¹⁶ which is then converted to the

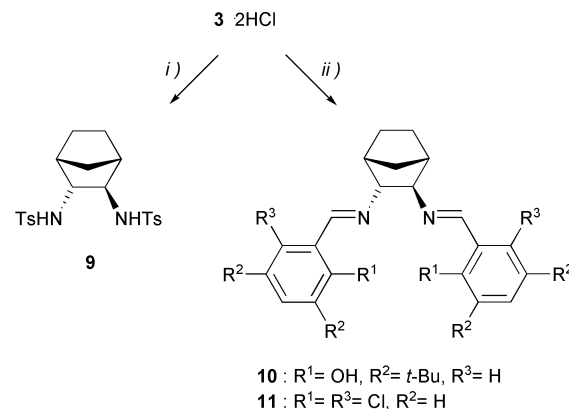


Scheme 1 Synthesis of the diamine dihydrochloric salts **3**·2HCl and **8**·2HCl. Reagents and conditions: (i) quinidine, methanol, -55°C , 98%; (ii) (a) LDA, THF, -78°C , 81%; (b) 1 N NaOH, methanol; (c) H_2 , Pd/C, THF, 88% (2 steps); (d) ClCOOEt , Et_3N , THF, -20°C ; (e) aq. NaN_3 , -10°C to r.t.; (iii) (a) benzene, 80°C ; (b) 8 N HCl, 70% (3 steps); (iv) ethanol, 79°C , 65% (3 steps); (v) LiAlH_4 , THF, 71%.

corresponding saturated diacid by saponification and hydrogenation.¹⁷ For the synthesis of the key intermediate **6**, the diacid is activated by treatment with ethyl chloroformate and triethylamine. Addition of an aqueous solution of sodium azide affords dicarboxylic diazide **6**, which is subjected to thermal rearrangement without further purification. Curtius degradation of the crude diazide in benzene, followed by acidic hydrolysis of the resulting isocyanate, leads to the dihydrochloric salt of diamine **3** in 70% yield. Direct alcoholysis of the intermediate isocyanate by performing the rearrangement in ethanol delivers the corresponding dicarbamate **7**, which is converted into the dihydrochloric salt of diamine **8** by reduction and acidic work-up in 71% yield. The absolute configuration of **3**·2HCl was determined by comparison of its sense of optical rotation with that reported in the literature¹³ and found to be in accordance with the proposed structure in Scheme 1, which was based on the uniform stereochemical outcome of the asymmetric anhydride opening. Since the value of the optical rotation differed strongly from the published data, the enantiomer ratio of 99:1 was confirmed by HPLC analysis of the corresponding ditosylate **9**, using a racemic sample of this compound as reference. As a consequence of the stereospecificity of the epimerization and the Curtius degradation, the enantiomeric excess was identical with that of the starting material **5**. In addition, our findings were verified by the X-ray crystal structure analysis of **8**·2HCl, shown in Fig. 1.¹⁸

During the course of our investigations, Trost *et al.* reported on the application of the diphenylphosphinobenzoyl substituted diamine **3** as ligand in asymmetric allylic alkylations.²⁰ Their synthesis involved a Diels–Alder reaction between (+)-dimethyl fumarate and cyclopentadiene,²¹ followed by saponification of the resulting diester and subsequent degradation similar to that shown in Scheme 1. A direct comparison of the two methods in view of their preparative advantages on a large scale remains difficult at the present time. However, the need for an efficient synthetic access to enantiopure diamine **3** is further emphasized by this catalysis work.

In contrast to the free diamines,²² the corresponding dihydrochloric salts are stable in air and easy to handle. Since treatment of **3**·2HCl with KOH and distillation under reduced pressure led to the free diamine in only moderate yield,¹³ the preferred method was to liberate **3** *in situ* by addition of an excess of triethylamine before further derivatization. As shown in Scheme 2, this protocol afforded ditosylate **9** as well as salenes **10** and **11** in excellent yields. Selective mono-*N*-tosylation by adding dropwise one equivalent of tosylchloride to a methylene chloride solution of **3**·2HCl and triethylamine failed, even at low temperature. However, enantiopure mono-*N*-substituted *cis*- and *trans*-norbornane diamines could finally be prepared by sequential introduction of the two amino



Scheme 2 Synthesis of the ditosylate **9** and the salenes **10** and **11**. Reagents and conditions: (i) TsCl, Et₃N, CH₂Cl₂, 92%; (ii) methanol, Et₃N, for salene **10**: 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde, for salene **11**: 2,6-dichlorobenzaldehyde.

moieties.²³ Details of these syntheses will be described in due course.

In conclusion, we have described the transformation of a norbornane-type *cis*-dicarboxylic acid monoester, which is readily obtained from a quinidine mediated methanolysis of the anhydride, into optically active *trans*-norbornane diamine. All synthetic steps are easy to perform, giving highly enantiomerically enriched diamine derivatives in good yields. Currently, we are focusing our efforts on the application of these new compounds as ligands in asymmetric catalysis.

Experimental

Unless otherwise specified all reagents were purchased from commercial suppliers and used without further purification. All reactions were performed under argon using standard Schlenk and vacuum line techniques. THF was distilled from sodium/benzophenone ketyl radical, CH₂Cl₂ from CaH₂, ethanol from sodium and stored over 4 Å molecular sieves. All other solvents were reagent grade and used as received. ¹H NMR and ¹³C NMR spectra were obtained on an Inova 400 spectrometer and were recorded relative to TMS as internal standard. HPLC analysis was performed using a Chiracel OD-H column, 4.6 × 250 mm, λ = 254 nm. Mass spectra were measured on a Finnigan SSQ 7000 instrument or on a Hewlett Packard GCMS apparatus-system (column HP-5 MS, 30 m × 0.25 mm × 0.25 μm; Mass Selective Detector 5973). Melting points were measured in open glass capillaries with a Büchi apparatus and are uncorrected. Optical rotation values were determined on a Perkin–Elmer P241 instrument at room temperature using solvents of Merck UVASOL-quality. Infrared spectra were recorded on a Perkin–Elmer 1760 FT apparatus. All microanalyses were obtained with a Heraeus CHN-O-RAPID element analyzer at the Institut für Organische Chemie der RWTH Aachen. Preparative column chromatography: Merck silica gel 60, particle size 0.040–0.063 mm (230–400 mesh, flash). Analytical TLC: silica gel 60 F₂₅₄ plates, Merck, Darmstadt.

Syntheses

(2*R*,3*R*)-Bicyclo[2.2.1]heptane-2-endo-3-exo-diamine dihydrochloric salt (3**·2HCl).** Ethyl chloroformate (3.82 ml, 40.0 mmol, 4.0 equiv) was added to a mixture of (2*R*,3*R*)-bicyclo[2.2.1]heptane-2-endo-3-exo-dicarboxylic acid^{17,24} (1.84 g, 10.0 mmol) and Et₃N (8.36 ml, 60.0 mmol, 6.0 equiv) in THF (16.0 ml) at –20 °C and the reaction mixture was stirred at this temperature for 1 h. A solution of NaN₃ (3.9 g, 60.0 mmol, 6.0 equiv) in H₂O (24 ml) was added at –10 °C. The

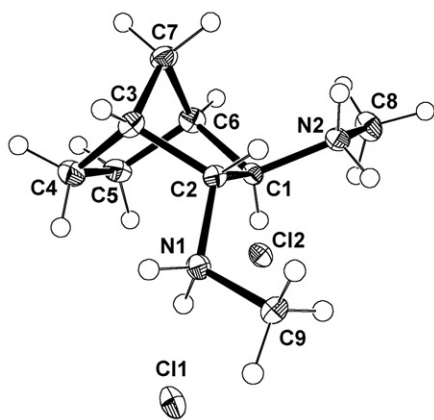


Fig. 1 Molecular structure of **8**·2HCl in the solid state as determined by X-ray crystal structure analysis.

temperature was gradually increased to r.t. and stirring continued for 2 h. The mixture was diluted with water, extracted with EtOAc and the organic phase was washed with NaHCO₃, dried over MgSO₄, filtered and concentrated to provide the corresponding acyl azide **6**, which was dissolved in benzene (16 ml) and heated under reflux for 2 h. To the cooled isocyanate solution conc. aq. HCl (30 ml) was added and the resulting mixture was refluxed for 4 h. The reaction mixture was extracted with Et₂O and the aqueous layer was concentrated to give a solid that was washed with THF and dried under high vacuum to give 1.4 g (7.05 mmol, 70%) of the title compound as a colorless solid. Mp: > 250 °C (rac, en), lit.²² mp: > 350 °C (rac). $[\alpha]_D = -9.3$ ($c = 1.52$, MeOH), $[\alpha]_D = -16.4$ ($c = 1.18$, H₂O), lit.¹³ for *ent*-**3-2HCl**: $[\alpha]_D = +26.0$ ($c = 2.0$, MeOH). ¹H NMR (DMSO-*d*⁶): $\delta = 1.22$ (d, $J = 10.2$ Hz, 1H), 1.30–1.39 (m, 2H), 1.49–1.59 (m, 2H), 1.98 (d, $J = 10.2$ Hz, 1H), 2.3 (s, 1H), 2.95 (s, 1H), 3.30 (s, 1H), 3.46 (s, 1H), 8.54 (s, 3H), 8.59 (s, 3H). ¹³C NMR: $\delta = 21.0$, 27.5, 35.3, 39.8, 40.9, 57.2, 58.0. MS (EI, 70 eV): $m/z = 126$ (44), 108 (16), 97 (20), 92 (18), 85 (25), 70 (43), 56 (100). IR (KBr): $\tilde{\nu} = 2970$, 2614, 1604, 1565, 1496, 1120, 1061 cm⁻¹. Anal. calcd. for C₇H₁₆Cl₂N₂ (199.12): C, 42.22%; H, 8.10%; N, 14.07%; found: C, 42.22%; H, 8.19%; N, 14.00%.

(2R,3R)-2-endo-3-exo-Di(ethoxycarbonylamino)bicyclo[2.2.1]heptane (7). Analogously prepared, the crude acyl azide **6** was dissolved in ethanol and heated under reflux for 4 h. After removal of the solvent, the residue was purified by column chromatography (pentane–ethyl acetate, 1:1) delivering 1.757 g (6.5 mmol, 65%) of **7** as a white solid. Mp: 136.5 °C (en). $[\alpha]_D = 0$ ($c = 1.07$, CHCl₃), $[\alpha]_D = 0$ ($c = 1.28$, MeOH). ¹H NMR (CDCl₃): $\delta = 1.22$ (t, $J = 7.1$ Hz, 6H), 1.29–1.42 (m, 3H), 1.45–1.61 (m, 3H), 2.19 (d, $J = 3.3$ Hz, 1H), 2.47 (s, 1H), 3.18 (s, 1H), 3.65 (s, 1H), 4.11 (q, $J = 7.1$ Hz, 4H), 5.35 (s, 1H), 5.43 (s, 1H). ¹³C NMR: $\delta = 14.6$, 20.5, 27.4, 35.0, 40.2, 43.1, 60.8, 61.2, 61.8, 156.3, 156.7. MS (EI, 70 eV): $m/z = 225$ (3), 181 (37), 153 (100), 128 (5), 108 (6), 81 (7). IR (KBr): $\tilde{\nu} = 3293$, 2976, 1681, 1552, 1325, 1308, 1279, 1235, 1110 cm⁻¹. Anal. calcd. for C₁₃H₂₂N₂O₄ (270.32): C, 57.76%; H, 8.20%; N, 10.36%; found: C, 57.42%; H, 8.27%; N, 10.58%.

(2R,3R)-N,N'-Dimethylbicyclo[2.2.1]heptane-2-endo-3-exo-diamine dihydrochloric salt (8·2HCl). A solution of diethylcarbamate **7** (1.5 g, 5.5 mmol) in THF (15.0 ml) was added to a suspension of LiAlH₄ (760.0 mg, 20 mmol, 3.6 equiv) in THF (10.0 ml) at 0 °C. After being stirred for 16 h at r.t. the reaction mixture was refluxed for 3 h, hydrolyzed with 1 N aq. NaOH, filtered; the filtrate was washed with Et₂O. The organic phase was extracted with 1 N aq. HCl and the resulting aqueous layer was concentrated and dried *in vacuo* to give a solid that was recrystallized from methanol to provide 895.0 mg (3.94 mmol, 71%) of the title compound as colorless crystals. Mp: > 250 °C (en). $[\alpha]_D = -23.2$ ($c = 1.62$, MeOH). ¹H NMR (CD₃OD): $\delta = 1.46$ –1.72 (m, 5H), 1.8–1.93 (m, 2H), 2.65 (d, $J = 4.7$ Hz, 1H), 2.79 (s, 3H), 2.81 (s, 3H), 3.18 (dd, $J = 2.2$, 3.6 Hz, 1H), 3.67 (t, $J = 3.6$ Hz, 1H), 4.83 (br s, 4H). ¹³C NMR: $\delta = 20.2$, 26.1, 32.0, 32.1, 34.8, 38.3, 39.5, 64.6, 65.2. MS (EI, 70 eV): $m/z = 139$ (5), 124 (100), 113 (6), 96 (10), 84 (21), 70 (76), 57 (9). IR (KBr): $\tilde{\nu} = 2965$, 2887, 2805, 2672, 2561, 2483, 2455, 2397, 2344, 1586, 1478, 1427, 1057 cm⁻¹. Anal. calcd. for C₉H₂₀Cl₂N₂ (227.17): C, 47.58%; H, 8.87%; N, 12.33%; found: C, 47.25%; H, 9.09%; N, 12.16%.

(2R,3R)-2-endo-3-exo-Bis(*p*-toluenesulfonamide)bicyclo[2.2.1]heptane (9). A suspension of **3-2HCl** (176.0 mg, 0.88 mmol) in CH₂Cl₂ (5.0 ml) was treated with Et₃N (0.5 ml, 3.59 mmol, 4.0 eq) and TsCl (337 mg, 2.0 eq). After stirring for 16 h at r.t., the mixture was acidified with 1 N aq. HCl,

extracted with CH₂Cl₂, dried over MgSO₄, filtered and concentrated to give 352.0 mg (0.81 mmol, 92%) of the title compound as a colorless solid. Mp: 179 °C (en). $[\alpha]_D = +41.3$ ($c = 1.57$, CHCl₃). ee = 98% [HPLC analysis: Chiracel OD-H, *n*-Heptane–2-Propanol = 95:5, 0.7 ml min⁻¹, 254 nm, $t_1 = 45.5$ (major), $t_2 = 56.9$ (minor)]. ¹H NMR (CDCl₃): $\delta = 1.00$ –1.09 (m, 1H), 1.16–1.32 (m, 3H), 1.41–1.52 (m, 2H), 2.13 (d, $J = 3.8$ Hz, 1H), 2.23 (s, 1H), 2.42 (s, 6H), 2.61 (s, 1H), 3.06 (d, $J = 3.3$ Hz, 1H), 5.02 (d, $J = 4.1$ Hz, 1H), 5.21 (d, $J = 4.4$ Hz, 1H), 7.29 (d, $J = 8.0$ Hz, 4H), 7.72 (t, $J = 8.5$ Hz, 4H). ¹³C NMR: $\delta = 20.4$, 21.6, 27.1, 34.9, 40.3, 41.9, 64.1, 64.6, 127.2, 127.3, 129.8, 136.5, 136.7, 143.7. MS (EI, 70 eV): $m/z = 279$ (100), 182 (4), 155 (18), 108 (24), 91 (57), 81 (15). IR (KBr): $\tilde{\nu} = 3272$, 2959, 1446, 1325, 1305, 1290, 1161, 1093 cm⁻¹. Anal. calcd. for C₂₁H₂₆N₂O₄S₂ (434.57): C, 58.04%; H, 6.03%; N, 6.45%; found: C, 57.79%; H, 5.95%; N, 6.27%.

(2R,3R)-N,N'-Bis(3,5-di-*tert*-butylsalicyliden)bicyclo[2.2.1]heptane-2-endo-3-exo-diamine (10). To a solution of **3-2HCl** (382.0 mg, 1.92 mmol) and 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (900.0 mg, 2.84 mmol, 2.0 equiv) in MeOH was added Et₃N (4.0 ml, 28.8 mmol, 15.0 equiv), and the mixture was stirred for 16 h at r.t. The solvent was removed *in vacuo* to give a yellow solid that was dissolved in CH₂Cl₂, washed with water, dried over MgSO₄ and concentrated to provide 1.019 g (1.82 mmol, 95%) of the title compound as a yellow solid. Mp: > 250 °C (rac), 196.5 °C (en). $[\alpha]_D = -356.0$ ($c = 1.51$, CHCl₃). ¹H NMR (CDCl₃): $\delta = 1.28$ (s, 18H), 1.46 (s, 9H), 1.47 (s, 9H), 1.50–1.57 (m, 3H), 1.73–1.78 (m, 1H), 1.81–2.05 (m, 1H), 2.14 (d, $J = 10.2$ Hz, 1H), 2.32 (d, $J = 4.1$ Hz, 1H), 2.44 (s, 1H), 3.17 (s, 1H), 3.57 (s, 1H), 7.06 (t, $J = 2.5$ Hz, 2H), 7.38 (s, 2H), 8.26 (s, 1H), 8.34 (s, 1H), 13.63 (s, 1H), 13.69 (s, 1H). ¹³C NMR: $\delta = 22.5$, 27.7, 29.8, 31.9, 34.5, 35.4, 36.7, 43.7, 45.6, 80.2, 80.7, 118.0, 118.2, 126.3, 127.1, 127.2, 136.8, 140.4, 158.0, 158.1, 164.4, 166.2. MS (EI, 70 eV): $m/z = 558$ (M⁺, 19), 325 (100), 296 (14), 264 (32), 244 (12), 219 (7), 84 (7). IR (KBr): $\tilde{\nu} = 2955$, 2873, 1624, 1595, 1473, 1440, 1362, 1248, 1175, 1057 cm⁻¹. Anal. calcd. for C₃₇H₅₄N₂O₂ (558.84): C, 79.52%; H, 9.74%; N, 5.01%; found: C, 79.47%; H, 9.92%; N, 5.13%.

(2R,3R)-N,N'-Bis(2,6-dichlorobenzyliden)bicyclo[2.2.1]heptane-2-endo-3-exo-diamine (11). As described above, **3-2HCl** was treated with 2,6-dichlorobenzaldehyde in MeOH in the presence of Et₃N, delivering diimine **11** as a white solid in 92% yield. Mp: 85.0 °C (en). $[\alpha]_D = -128.0$ ($c = 1.0$, CHCl₃). ¹H NMR (CDCl₃): $\delta = 1.48$ –1.60 (m, 3H), 1.70–1.79 (m, 1H), 2.16–2.23 (m, 2H), 2.40 (d, $J = 4.1$ Hz, 1H), 2.51 (br s, 1H), 3.41 (t, $J = 2.2$ Hz, 1H), 3.75 (br s, 1H), 7.20 (dd, $J = 7.4$, 8.5 Hz, 2H), 7.31 (d, $J = 3.1$ Hz, 2H), 7.33 (d, $J = 3.0$ Hz, 2H), 8.32 (s, 1H), 8.48 (s, 1H). ¹³C NMR: $\delta = 22.3$, 28.0, 36.8, 44.3, 45.2, 80.8, 81.6, 128.7, 128.8, 130.3, 130.4, 133.6, 133.8, 134.8, 134.8, 155.3, 156.9. MS (EI, 70 eV): $m/z = 267$ (100), 239 (40), 174 (39), 156 (24), 123 (24), 66 (22). IR (KBr): $\tilde{\nu} = 2954$, 2870, 1642, 1579, 1557, 1429, 1375, 1189, 1094, 781 cm⁻¹. Anal. calcd. for C₂₁H₁₈N₂Cl₄ (440.19): C, 57.30%; H, 4.12%; N, 6.36%; found: C, 57.26%; H, 3.91%; N, 6.35%.

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- X-Ray crystal structure analysis of 8·2HCl: formula $C_9H_{20}N_2Cl_2$; $M = 227.18$, colorless crystal, $0.06 \times 0.06 \times 0.17 \text{ mm}^3$, $a = 6.9118(2)$, $b = 8.1756(2)$, $c = 21.0256(5) \text{ Å}$, $V = 1188.12 \text{ Å}^3$, $\rho_{\text{calcd}} = 1.270 \text{ g cm}^{-3}$, $\mu = 0.509 \text{ mm}^{-1}$, $Z = 4$, orthorhombic, space group $P2_12_12_1$ (No. 19), $\lambda = 0.71073 \text{ Å}$, $T = 120 \text{ K}$, ω scans, 18496 reflections collected, 4544 independent and 3827 observed reflections [$I \geq 4\sigma(I)$], 198 refined parameters, $R = 0.043$, $wR = 0.048$, ($w = [\sigma^2(F) + 0.0004 \cdot F^2]^{-1}$), $S = 1.076$, residual electron density $-1.12/0.76 \text{ e Å}^{-3}$, hydrogens located and refined isotropically. The structure has been solved by direct methods as implemented in the Xtal3.7 set of crystallographic routines,^{19a} employing GENSIN^{19b} for the generation of structure invariant relationships and GENTAN^{19c} for the general tangent phasing procedure. CCDC reference number 189661. See <http://www.rsc.org/suppdata/nj/b2/b206943c/> for crystallographic files in CIF or other electronic format.
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