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Synthesis of a new chiral cyclic aminal derived from *rac*-1,2-propanediamine

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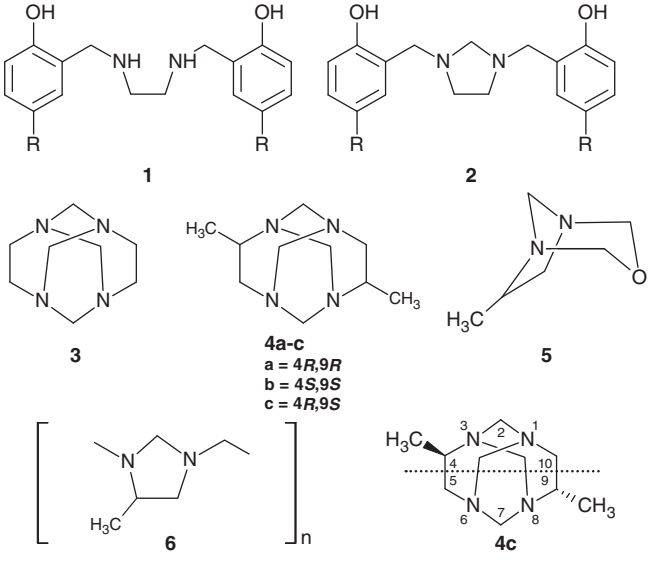
ABSTRACT

The cyclic aminal 4,9-dimethyl-1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane **4c** was synthesized by the reaction of commercial *rac*-1,2-propanediamine with paraformaldehyde in an aqueous solution. ^{1}H NMR analysis clearly revealed that the compound is chiral and racemic with an axis of chirality. To our knowledge, this is the first example of an azaadamantane derivative having axial chirality. This aminal was used in a Mannich type reaction with *p*-chlorophenol yielding 2,2′-[(4-methylimidazolidine-1,3-diyl)dimethanediyl]bis(4-chlorophenol) **7** as a racemic mixture. The crystal structure of **7** was determined by single X-ray diffraction analysis.

Introduction

1,2-Propanediamine is the simplest chiral diamine. 1,2-Propanediamine is a useful intermediate in the preparation of *N*,*N*′-disalicylidene-1,2-propanediamine, the active ingredient of the additive approved for use by military specification MIL-T-5624 and ASTM specification D1655.[1] This amine attracts interest as a useful precursor for the synthesis of non-symmetrical tetradentate di-Schiff base ligands.[2] Metal-templated Mannich reactions involving 1,2-propanediamine and formaldehyde have been employed in the preparation of saturated polyazamacrocyclic complexes.[3] Our group has been interested in synthesizing novel N-containing heterocycles using cyclic aminals for some time. We previously prepared cyclic aminals by the condensation of formaldehyde with 1,2-diamines.[4] Some of these cyclic aminal products have been successfully used in the synthesis of compounds such as **1** and **2**. In fact, in a previous work,[5] we reported the successful synthesis of *N*,*N*′-bis(2-hydroxybenzyl)ethylenediamine compounds **1** (salans) by the hydrolysis of 4,4′-disubstituted-2,2′-[imidazolidine-1,3-diylbis(methylene)]diphenols **2**. Compounds such as **2** are easily synthesized by a Mannich-type condensation of a phenol and the cyclic aminal 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (TATD) **3**,[6] which is a product of the condensation of ethylenediamine with formaldehyde. Additionally, chiral salens are one of the most popular and widely used ligands in asymmetric synthesis, and their metal complexes are now used as catalysts for various stereoselective processes.[7] Salen has been extensively used as catalyst in many enantioselective reactions.[8] Salan ligands (H2[H4]salen, tetrahydrosalen, and *N*,*N*′-bis(2-hydroxybenzyl)-1,2-diaminoethane) are present in a number of metal coordination complexes, including complexes containing elements located in groups 12, 13, and 14.[9] These facts prompted us to synthesize the aminal cage 4,9-dimethyl-1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (DMTATD, **4**), the closest analogue of cyclic aminal **3.** An extensive literature search revealed that the synthesis of this molecule has not been reported to date.



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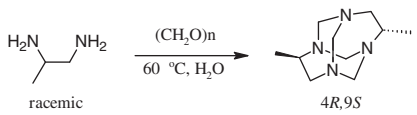


Scheme 1. Synthesis of chiral cyclic aminal (**4c**).

To the best of our knowledge, there is only one study in the literature describing the reaction between 1,2-propanediamine and formaldehyde.[10] According to that study, this reaction does not produce the expected aminal cage but instead affords a mixture of liquid products composed of the oxygenated bicycle 6-methyl-3-oxa-1,5-diazabicyclo[3.2.1]octane **5** and oligomers of type **6**, for which molecular weight determinations indicate that $n = 4$ or 5. On the other hand, the reaction of ethylenediamine with paraformaldehyde at 80 °C in *N,N*-dimethylformamide as the solvent has been reported to produce the cyclic aminal **3**.[11] Accordingly, we considered this procedure to be a potential route to obtain the desired aminal cage. These observations influenced us to prepare the aminal cages (4*R*,9*R*)-4,9-dimethyl-1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (**4a**) and (4*S*,9*S*)-4,9-dimethyl-1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (**4b**) by reacting enantiopure *R*- and *S*-1,2-propanediamine with formaldehyde in *N,N*-dimethylformamide. To our disappointment, all efforts to obtain the aminal cages were unsuccessful. Instead, in agreement with Hocker and Wendish,[10] only resinous products were obtained. Thus, the cyclization of two molecules of diamine with the same absolute configuration to a polycyclic structure failed, which also occurs with *trans*-1,2-cyclohexanediamine.[12] Interestingly, when experiments were carried out with *rac*-1,2-propanediamine and paraformaldehyde in *N,N*-dimethylformamide, it was apparent that the reaction followed a different initial condensation pathway. Accordingly, we designed a series of experiments to optimize these reaction conditions. During our optimization experiments, we found that the condensation of *rac*-1,2-propanediamine with paraformaldehyde in water at 60 °C for 4 h yielded a mixture of liquid products from which the target aminal cage **4c** was isolated as a single (*R*,S) stereoisomer in 54% yield (Scheme 1). Next, we carried out several experiments to confirm the chemical structure of this new aminal cage.

Results and discussion

For the reaction of *rac*-1,2-propanediamine with paraformaldehyde, we chose to use water over *N,N*-dimethylformamide because water is known to play the role of a catalyst in many such reactions.[13] It is worth mentioning that the complex nature of formal-

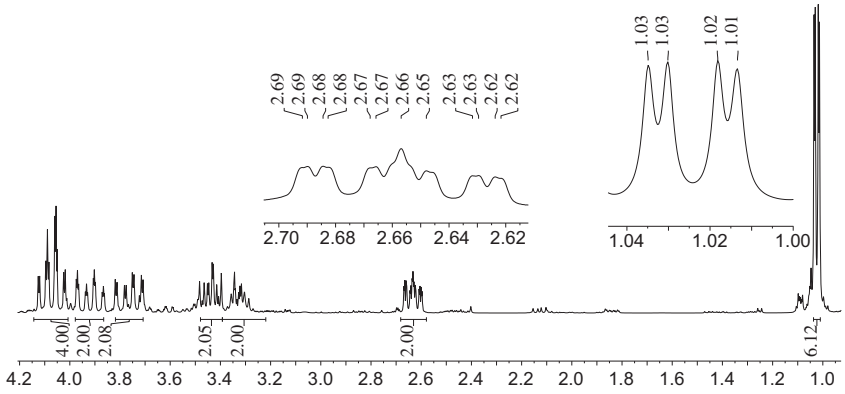


Figure 1. ^{1}H NMR spectrum of **4c**.

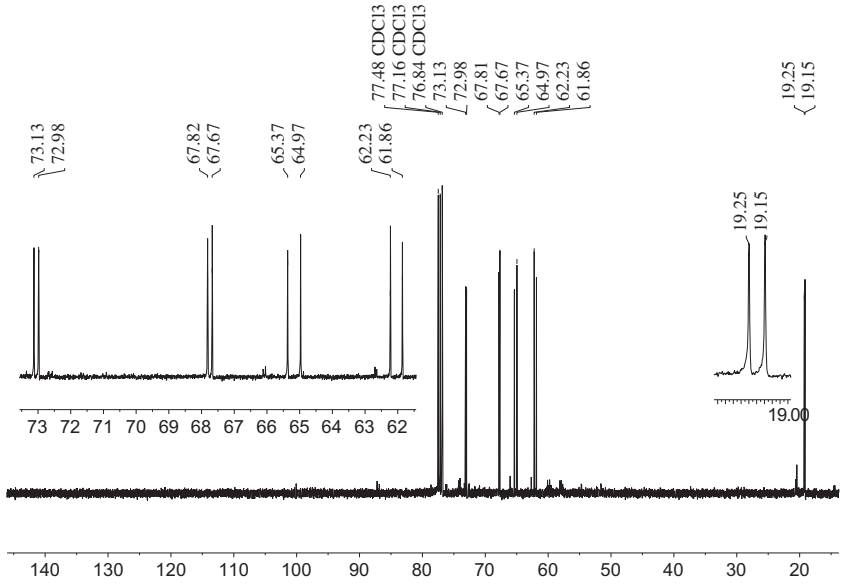


Figure 2. ^{13}C NMR spectrum of **4c**.

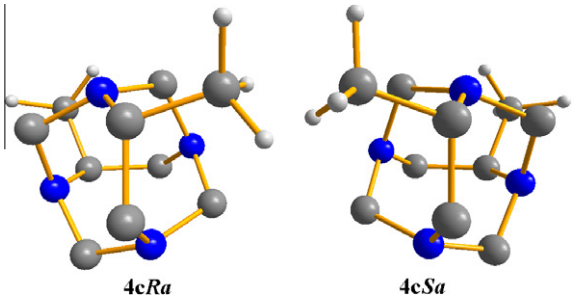


Figure 3. View of the two possible spatial distributions around the chiral axis. For clarity only shows the hydrogens of methyl groups.

dehyde solutions makes it difficult to predict the precise effect of the standard conditions on paraformaldehyde concentration.[14] As such, it was necessary to add a 3-molar excess of paraformaldehyde to drive the reaction to completion.[15] After solvent evaporation at reduced pressure, a very viscous liquid product was recovered by chromatography of the crude product on silica gel (eluent, 8:2 methanol-25% NH_4OH). All efforts to obtain a solid by treating this liquid with different solvents were unsuccessful. Because of the extreme viscosity of this compound, it was irrelevant to measure the boiling point.

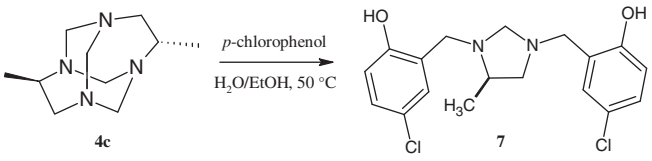
The spectroscopic evidence showed that the product obtained was the desired cyclic aminal (**4c**). The HR-ESI-MS of **4c**[15] exhibited a quasi-molecular-ion peak ($[M+H]^+$) at m/z 197.1733 (calculated 197.1761), corresponding to the molecular formula $C_{10}H_{21}N_4$. In the ^1H and ^{13}C NMR spectra of compound **4c**, all of the signals could be assigned and were as expected. One striking feature in both the ^1H and ^{13}C spectra was the presence of duplicated signals (Figs. 1 and 2). In our experience, this doubled-signal pattern had not been observed in other ^1H NMR spectra of aminal cages that we previously synthesized. The ^1H NMR spectrum showed two distinct resonances at δ 1.02 (J = 1.8 Hz) and 1.03 (J = 1.7 Hz) assigned to the methyl protons, which displayed two close signals at 19.15 and 19.25 ppm in the ^{13}C NMR spectrum. Due to the geometrical rigidity and non-planar structure of **4c**, a chiral environment is created for any pair of geminal protons, resulting in diastereotopy, as observed by chemical no-equivalence of these hydrogens. The ^1H NMR spectrum also contained signals characteristic of the NCH_2N protons between 3.7 and 4.2 ppm. In detail, the proton spectrum displayed the expected AB splitting pattern for hydrogens 2, 7, 11, and 12 (diastereotopic geminal protons), with an additional splitting into doublets imposed by a long range W-coupling constant similar to that observed in 1,3,6,8-tetraazatricyclo-[4.3.1.1^{3,8}]undecane (TATU), an aminal cage previously synthesized in our laboratory.[16] In theory, this condensation reaction can result in several stereoisomers due to the possibility of each possible pair of the enantiomers reacting. Taking into account the NMR data, it was possible that at least two possible diastereoisomers were present, namely (4*R*,9*S*)-4,9-dimethyl-1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (**4c**) and (4*R*,9*R*) or (4*S*,9*S*)-4,9-dimethyl-1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (**4a–b**). However, it was reasonable to assume that if each of the enantiomerically pure (*R*)- and (*S*)-diamines did not afford the respective aminal cage in the self-condensation reactions, the configuration of **4c** should be (4*R*,9*S*).

The question of the duplicated signals observed in the ^1H NMR spectrum, which suggested the existence of two configurational isomers, was addressed by considering the existence of a hypothetical chiral axis. It is well known that adamantane and twistane structures may be chiral compounds due to the presence of a chiral axis.[17,18] Similarly, the incorporation of two methyls in the structure of TATD (**3**) broke the symmetry, and consequently, the methylene groups of the aminal cage were in different environments. This process resulted in two axially diastereomeric aminal cages displaying different NMR signals.

The imaginary chiral axis passes through the mid-point of the ethylene moieties of aminal cage (**4c**), and two possible spatial distributions can be obtained: *Ra*-(4*R*,9*S*)-4,9-dimethyl-1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (**4c*Ra***) and *Sa*-(4*R*,9*S*)-4,9-dimethyl-1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (**4c*Sa***) (Fig. 3).

To confirm the structure of the product inferred from the spectroscopic analysis above, we carried out a Mannich-type reaction between **4c** and *p*-chlorophenol following the protocol described previously,[6] which afforded 4,4′-disubstituted-2,2′-[imidazolidine-1,3-diylbis(methylene)]diphenol **2** as the major product. Based on a similar reaction, we expected to observe *ortho*-aminomethylation to yield the bis-2-hydroxybencilimida-zolidine derivative (**2**). When we carried out this Mannich-type reaction, (Scheme 2) the expected product, 2,2′-[(4-methylimidazolidine-1,3-diyl)dimethanediyl]bis(4-chlorophenol) **7** was formed and was completely characterized by NMR, IR, and MS.[19] The structure of **7** was also determined by X-ray analysis. In the IR spectrum of Mannich base **7**, the absorption band at 3300–2200 cm^{-1} was attributed to the O–H stretching vibration, suggesting possible hydrogen bond interactions between the N atom of heterocyclic ring and the H atom of phenol residue, which was confirmed by X-ray analysis. The ^1H NMR spectrum showed that all of the methylene protons were diastereotopic due to the presence of a chiral carbon atom. Methylene protons adjacent to the chiral center of heterocyclic ring appeared as two double doublets: one at δ = 2.43 ppm (J = 10, 7.8 Hz) and the other at δ = 3.25 ppm (J = 9.9, 7.0 Hz). Both aminalic hydrogens (δ = 3.42 ppm, J = 7.1 Hz/δ = 3.63 ppm, J = 7.2 Hz) and benzylic hydrogens (δ = 3.58 ppm, J = 14 Hz/δ = 4.11 ppm, J = 13.9 Hz, δ = 3.84 ppm, J = 13.8 Hz/δ = 3.77 ppm, J = 13.8 Hz) appeared as doublets due to geminal coupling.

To unambiguously define their structures and to establish the conformational influence of the methyl substituent, we attempted to obtain a crystal of **7** suitable for X-ray analysis. Attempts to crystallize **7** from several solvents always resulted in the recovery of amorphous material. Fortunately, crystals were grown in chloroform–methanol using the slow evaporation method. The molecular structure of **7** (Fig. 4) indicates that the heterocyclic ring adopts a



Scheme 2. Mannich-type reaction leading to **7** from **4c** and *p*-chlorophenol.

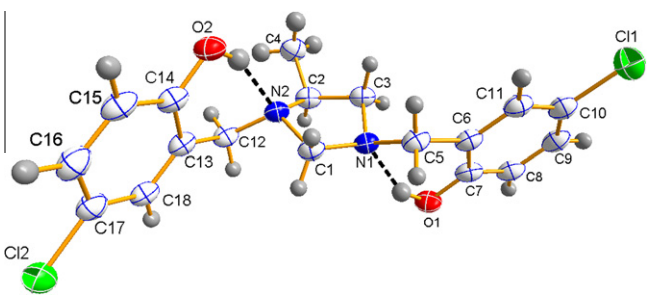


Figure 4. The molecular structure of **7**. Displacement ellipsoids are drawn at the 50% probability level, and H atoms are shown as small spheres.

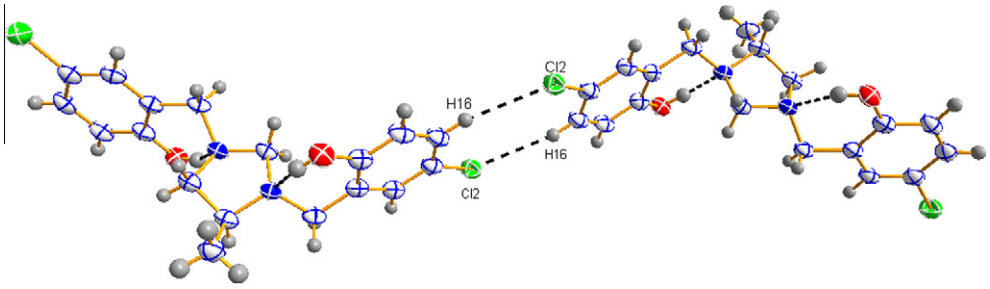


Figure 5. Non-conventional hydrogen bonds linking the pair of enantiomers in the crystal lattice.

twisted conformation on C2—C3, (Q(2) = 0.3721 (17) Å, φ = 126.8 (3)°),[20] whereas a related structure has a twist conformation on C—N.[21] This finding could indicate that the conformational change of the ethylene bridge is a consequence of methyl substitution on the heterocyclic ring. Additionally, it was determined that compound **7** crystallized as a racemic mixture, which unequivocally proves that the configuration of aminal cage **4c** is (4*R*,9*S*). In the crystal lattice, a pair of enantiomers was bonded together by non-classical intermolecular interactions C—H···Cl between H16 and Cl2 (Fig. 5). The crystal structure of **7** confirms the presence of two intramolecular hydrogen bond interactions. However, no significant differences in the values observed in a related structure are observed.

The synthesis of this new bisbenzylimidazolidine derivative represents an expansion of our previous work regarding the use of cyclic aminals as preformed electrophiles in Mannich condensations to prepare new ligands with imidazolidinic cores and potential uses in homogeneous catalysis.[22–24]

In summary, we report the first synthesis of the cyclic aminal 4,9-dimethyl-1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (DMTATD, **4c**). We probed its existence through an *ortho*-aminomethylation reaction to form the di-Mannich base **7**. This finding could be exploited to produce a range of unprecedented chiral salans.

Acknowledgments

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References and notes

1. Chusuei, C. C.; Morris, R. E.; Schreifels, J. A. *Ind. Eng. Chem. Res.* **1998**, *37*, 3610–3617.
2. Chattopadhyay, S.; Drew, M. G. B.; Ghosh, A. *Polyhedron* **2007**, *26*, 3513–3522.
3. Sujatha, S.; Balasubramanian, S.; Varghese, B. *Polyhedron* **2009**, *28*, 3723–3730.
4. Rivera, A.; Quiroga, D.; Jiménez-Cruz, L.; Fejfarová, K.; Dušek, M. *Tetrahedron Lett.* **2012**, *53*, 345–348.
5. Rivera, A.; Quevedo, R.; Maldonado, M.; Navarro, M. A. *Synth. Commun.* **2004**, *34*, 2479–2485.
6. Rivera, A.; Gallo, G. I.; Gayón, M. E.; Joseph-Nathan, P. *Synth. Commun.* **1993**, *23*, 2921–2929.
7. Danilova, T. I.; Rozenberg, V. I.; Vorontsov, E. V.; Starikova, Z. A.; Hopf, H. *Tetrahedron: Asymmetry* **2003**, *14*, 1375–1383.
8. Jacobsen, E. N.; Yoon, T. P. *Science* **2003**, *299*, 1691–1693.
9. Atwood, D. A. *Coord. Chem. Rev.* **1997**, *165*, 267–296.
10. Hocker, J.; Wendish, D. J. *J. Chem. Res., Synop.* **1977**, 236.
11. Peori, M. B.; Vaughan, K.; Hooper, D. L. *J. Org. Chem.* **1998**, *63*, 7437–7444.
12. Murray-Rust, P.; Riddell, F. G. *Can. J. Chem.* **1975**, *53*, 1933–1935.
13. Hammam, E.; Lee, E. P. F.; Dyke, J. M. *J. Phys. Chem. A* **2000**, *104*, 4571.
14. Norris, C. B.; Joseph, P. R.; Mackiewicz, M. R.; Reed, S. M. *Chem. Mater.* **2010**, *22*, 3637–3645.
15. *Reaction of rac-1,2-propanediamine with paraformaldehyde*: Paraformaldehyde (1026 mg, 34.2 mmol) was added in small portions to a solution of *rac*-1,2-propanediamine (1 mL, 11.4 mmol) in water (20.0 mL) with vigorous stirring for 10 min, at 60 °C. The reaction mixture was stirred for 4 h, and the product was extracted with $CHCl_3$ (4 × 5 mL). The organic layer was dried over anhydrous sodium sulfate and filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel and eluted with methanol–25% NH_4OH (8:2) mixture to afford (4*R*,9*S*)-4,9-dimethyl-1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane **4c** (54% yield) as a viscous liquid: ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 1.02 (d, 3H), 1.03 (d, 3H), 2.63 (m, 2H), 3.33 (m, 2H), 3.44 (m, 2H), 3.71–4.13 (m, 8H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.15, 19.25, 61.86, 62.23, 64.97, 65.37, 67.67, 67.82, 72.98, 73.13. HR-ESI-MS in its positive mode *m*/*z*: $[M+H]^+$ calcd for $C_{10}H_{21}N_4$: 197.1761, found: 197.1733.
16. Rivera, A.; Núñez, M. E.; Morales-Rios, M. S.; Joseph-Nathan, P. *Tetrahedron Lett.* **2004**, *45*, 7563–7565.
17. Shibuya, M.; Taniguchi, T.; Takahashi, M.; Ogasawara, K. *Tetrahedron Lett.* **2002**, *43*, 4145–4147.
18. Geivandov, R. Ch.; Goncharova, I. V.; Titov, V. V. *Mol. Cryst. Liq. Cryst.* **1989**, *166*, 101–103.
19. *Synthesis of 2,2′-[(4-methylimidazolidine-1,3-diyl)dimethane-diyl]bis(4-chlorophenol)* **7**: A solution of *p*-chlorophenol (182 mg, 1,4 mmol) in ethanol (1 mL) was added dropwise into a solution of (4*R*,9*S*)-4,9-dimethyl-1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dode-cane **4c** (140 mg, 0.7 mmol) in water (1 mL). The mixture was stirred for 4 days at 50 °C. The resulting product was purified by column chromatography on silica gel using gradient elution with benzene/ethyl acetate to afford the product **7** (mp 117.5–118 °C, 39 % yield): ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 1.26 (d, ^3J = 6.2 Hz, 3H), 2.43 (dd, $^2J_{gem}$ = 10.0, ^3J = 7.8 Hz, 1H), 3.10–2.92 (m, 1H), 3.25 (dd, $^2J_{gem}$ = 9.9, ^3J = 7.0 Hz, 1H), 3.42 (d, ^3J = 7.1 Hz, 1H), 3.58 (d, $^2J_{gem}$ = 14.0 Hz, 1H), 3.63 (d, ^3J = 7.2 Hz, 1H), 3.77 (d, $^2J_{gem}$ = 13.8 Hz, 1H), 3.84 (d, $^2J_{gem}$ = 13.8 Hz, 1H), 4.11 (d, $^2J_{gem}$ = 13.9 Hz, 1H), 6.77 (d, ^3J = 8.7 Hz, 2H), 6.95 (dd, ^3J = 6.6, ^4J = 2.5 Hz, 2H), 7.13 (dd, ^3J = 8.7, ^4J = 2.0 Hz 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): d 18.57, 29.85, 56.64, 57.72, 59.48, 59.64, 74.90, 116.81, 117.75, 117.81, 122.65, 123.07, 124.07, 124.10, 128.11, 128.11, 129.13, 129.62, 156.20, 156.26. FT-IR (KBr) (ν, cm^{-1}): 3300–2200 (O–H, broad, st), 2956 (CH_3 asym, st), 2924 (CH_2 asym, st), 2865 (CH_3 sym, st), 2851 (CH_2 sym, st), 1607(–C=C, st), 1308 (C–N, st), 643 (C–Cl, st); HR-ESI-MS in its positive mode *m*/*z*: $[M+H]^+$ calcd for $C_{18}H_{21}Cl_2N_2O_2$: 367.0981, found: 367.0971.
20. *Crystal data for compound* **7**, $C_{18}H_{20}Cl_2N_2O_2$, *were collected using a goniometer Xcalibur detector*: Atlas (Gemini ultra Cu) diffractometer, *M* = 367.3, monoclinic, $P2_1/c$, *a* = 18.3098(7) Å, *b* = 6.0252(3) Å, *c* = 16.1039(8) Å, *V* = 1758.01(14) Å^3, *Z* = 4, X-ray source Cu Kα (radiation), λ = 1.54180 Å, F(0 0 0) = 768, colorless prism 0.26 × 0.13 × 0.07 mm. The refinement was carried out against all reflections. The conventional *R*-factor is always based on *F*. The goodness of fit as well as the weighted *R*-factor are based on *F* and F^2 for refinement carried out on *F* and F^2, respectively. The threshold expression is used only for calculating *R*-factors etc. and it is not relevant to the choice of reflections for refinement. Crystallographic data (excluding structure factors) for the given structure in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 894271. Copies of these data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or email: deposit@ccdc.cam.ac.uk).
21. Rivera, A.; Sadat-Bernal, J.; Rios-Motta, J.; Pojarova, M.; Dusek, M. *Acta Crystallogr., Sect. E* **2011**, *67*, o2581.
22. Zhang, Z.; Xu, X.; Li, W.; Yao, Y.; Zhang, Y.; Shen, Q.; Luo, Y. *Inorg. Chem.* **2009**, *48*, 5715–5724.
23. Song, F.; Yan, C.; Sun, H.; Yao, Y.; Shen, Q.; Zhang, Y. *Chin. Sci. Bull.* **2009**, *54*, 3231–3236.
24. Bera, M.; Nanda, P.; Mukhopadhyay, U.; Ray, D. *J. Chem. Sci.* **2004**, *116*, 151–158.