#### Tetrahedron Letters 53 (2012) 345-348

Contents lists available at SciVerse ScienceDirect

## **Tetrahedron Letters**

journal homepage: www.elsevier.com/locate/tetlet



# New cyclic aminals derived from *rac-trans*-1,2-diaminocyclohexane: synthesis and crystal structure of racemic 1,8,10,12-tetraazatetracyclo[8.3.1.1.<sup>8,12</sup>0<sup>2,7</sup>] pentadecane and a route to its enantiomerically pure (R,R) and (S,S) isomers

Augusto Rivera<sup>a,\*</sup>, Diego Quiroga<sup>a</sup>, Leonardo Jiménez-Cruz<sup>a</sup>, Karla Fejfarová<sup>b</sup>, Michal Dušek<sup>b</sup>

<sup>a</sup> Departamento de Química, Universidad Nacional de Colombia, Ciudad Universitaria, Carrera 30 No. 45-03, Bogotá, D.C., Colombia <sup>b</sup> Institute of Physics ASCR, v.v.i., Na Slovance 2, 182 21 Praha 8, Czech Republic

#### ARTICLE INFO

Article history: Received 26 September 2011 Revised 7 November 2011 Accepted 10 November 2011 Available online 18 November 2011

Keywords: 1,2-Diaminocyclohexane Cyclic aminal Chiral cyclic aminal X-ray diffraction Benzotriazole derivative

### ABSTRACT

New enantiomerically pure macrocyclic aminals (2R,7R)- and (2S,7S)-1,8,10,12-tetraazatetracyclo[8.3.1.1.<sup>8.12</sup>0<sup>2.7</sup>]pentadecane (**4a** and **4b**) were obtained by a three component reaction between their respective pure enantiomer of *trans*-1,2-diaminocyclohexane, ammonia, and formaldehyde. Additionally, the X-ray structure of the racemic compound **4** and the specific rotations of the racemic and optically pure compounds were determined. To further understand the synthetic utilities of enantiomers **4a** and **4b**, Mannich-type reactions with 1*H*-benzotriazole were performed, affording (3a*R*,7a*R*)- and (3a*S*,7a*S*)-1, 1'-{[2,3,3a,4,5,6,7,7a-octahydro-1*H*-1,3-benzimidazole-1,3-diyl]bis(methylene)}bis-1*H*-benzotriazole (**9** and **10**) and allowing for new possibilities related to the preparation of chiral ligands for asymmetric catalysis.

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Cyclic aminals for instance 1,3,6,8-tetraazatricyclo[4.4.1.1<sup>3,8</sup>] dodecane **1** are compounds with interesting electrophilic and nucleophilic behavior.<sup>1</sup> As part of our ongoing interest in the chemistry of cyclic aminals, we started a detailed study with the macrocyclic aminal (2R,7R,115,165)-1,8,10,17-tetraazapentacyclo [8.8.1.1<sup>8,17</sup>,0<sup>2,7</sup>,0<sup>11,16</sup>]icosane **2**, which was obtained via a known condensation reaction procedure<sup>2,3</sup> between racemic *trans*-1,2-diaminocyclohexane and formaldehyde.



<sup>\*</sup> Corresponding author. Tel.: +57 1 3165000; fax: +57 1 3165220. *E-mail address:* ariverau@unal.edu.co (A. Rivera).

We have previously reported that aminal 1,3,6,8-tetraazatricyclo[4.3.1.1<sup>3,8</sup>]undecane (TATU) **3** can be readily obtained by the simple reaction of **1** with ammonium fluoride at room temperature.<sup>4</sup> Therefore, compound **2** was reacted with ammonium fluoride to afford racemic 1,8,10,12-tetraazatetracyclo[8.3.1.1.<sup>8,12</sup>0<sup>2,7</sup>] pentadecane **4** as a white solid in good yield.<sup>5a</sup> Interestingly, by using ammonium chloride, we were also able to obtain similar results. Based on these results, we presume the reaction must elapse in a similar manner as that observed for aminal **1**, which we have previously described in the literature.<sup>4b</sup>

To assign the structure of product **4**, detailed NMR studies, including COSY, NOESY, and HSQC experiments were performed. Efforts were made to crystallize this compound and X-ray crystallography of a single crystal of **4** not only confirmed the expected structure but also revealed that the crystal consists of a racemic pair of enantiomers namely (2R,7R) and (2S,7S)-1,8,10,12-tetraazatetracyclo[8.3.1.1.<sup>8.12</sup>0<sup>2.7</sup>]pentadecane (**4a**, **4b**).

The structures of **4a** and **4b** in the racemic mixture were determined by X-ray crystallography (Figs. 1 and 2).<sup>6</sup> The packing of **4** in the crystal lattice shows that each enantiomer links by intermolecular hydrogen bond interactions between the nitrogen atoms and H<sub>2</sub>O molecules, and the molecules are connected into trimers by interacting with the diamine moiety. The water and aminal molecules of **4** are alternately linked. Overall, these results show a new example of the formation of hydrates in amine cages. New hydrates are of particular interest because they allow for further morphological studies of water clusters, and they can be utilized as

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versatile, cage-like building blocks for the construction of coordination polymers due to their behaviors as N-donor ligands.<sup>7</sup>

With this racemic mixture in hand, we attempted to separate the two isomers, but all of our attempts were unsuccessful. In the meantime, Kuznetsov et al. reported<sup>8</sup> that condensation of a mixture of formaldehyde, ammonia, and aromatic 1, 2-diamines yielded not only hexamethylenetetramine and condensation products from formaldehyde and diamines but also products similar to 1,5:3,7-dimethano-1,3,5,7-benzotetrazonine **5**. Because the previous reports have shown that reacting optically active *trans*-1,2diaminocyclohexane with four molecules of formaldehyde does not form the respective diastereomers for **2**,<sup>2,3</sup> simple analogy suggests that a similar three-component reaction between formaldehyde, ammonia, and (*R*,*R*) or (*S*,*S*)-*trans*-1,2-diaminocyclohexane should obtain enantiomerically pure **4a** and **4b**, respectively, in a one pot reaction.

It is known that the enantiomers of trans-(rac)-1,2-diaminocyclohexane can be separated by resolution via diastereomeric tartrates.<sup>9</sup> Based on the protocol in the literature, the desired resolution of relatively inexpensive trans-(rac)-1,2-diaminocyclohexane was accomplished with L-(+)-tartaric acid. Furthermore, we successfully separated the (*R*,*R*)- and (*S*,*S*)-isomers of trans-



Scheme 1. Three component condensations for the synthesis of 4a and 4b.

1,2-diaminocyclohexane using the method described by Larrow and Jacobsen (L-(+)-tartaric acid in a mixture of water and acetic acid).

According to the method above, pure trans-(R,R)-1,2-diaminocyclohexane [L-(+) tartrate] salt precipitated which was isolated in a 43% yield by filtration. Additionally, after the addition of a large excess of L-(+)-tartaric acid, the removal of water under reduced pressure and the addition of concentrated HCl and acetone to the filtrate, the *trans-(S,S)*-diamino cyclohexane enantiomer was obtained as a hydrochloride salt in a 28% yield after filtration. We next focused on the use of these enantiomerically pure diamines in syntheses of the desired enantiomerically pure 4a and 4b. To our satisfaction, we found that the application of the aforementioned method<sup>8</sup> gave the expected condensation products **4a** and **4b** in moderate yields (Scheme 1). The major impurity found was urotropine in low yields (10% yield) <sup>5b</sup> and as desired, aminal 2 was not afforded. Unfortunately, to date, it has not been possible to grow suitable, single crystals of 4a or 4b for X-ray structural analysis.

Although the mechanism of this reaction remains speculative, our studies on the reaction between the diamines and formaldehyde allowed us to propose that the pathway of the reaction involves the formation of methylolamines and not imines.<sup>10</sup> A plausible pathway involving methylolamines intermediates is depicted in Scheme 2. In this scheme, we proposed that (R,R)-1,2diaminocyclohexane is liberated in the basic media employed



Figure 2. Invisible hydrogen bond interactions between water molecules and enantiomers 4a,b.



Scheme 2. Proposed mechanism for forming compounds 4a or 4b.



Scheme 3. Synthesis of (3aR,7aR)-and (3aS,7aS)-enantiomers (9 and 10).

and then reacts with 2 equiv of formaldehyde to afford *N*,*N*′-dime-thylol-(*R*,*R*)-1,2-diamino cyclohexane **7**.

As is known, methanediamine **6** is an intermediate commonly observed during the reaction between ammonia and formaldehyde in the formation of cyclotrimethylenetriamine because during the condensation reaction with formaldehyde and ammonia, urotropine is formed.<sup>11</sup> Fortunately; this urotropine formation is likely inhibited by the condensation reaction between **6** and **7**. Specifically, condensation occurs with 2 equiv of formaldehyde affording the intermediate **8**. The latter then undergoes an intramolecular condensation to eliminate 2 equiv of water, leading to the aminal **4a**.

Notably, the aminals that are derived from a chiral vicinal diamine have the potential to serve as privileged structural elements in the search for chiral catalysts and other relevant compounds.<sup>12</sup> Therefore, to further explore the reactivity of aminals **4a** and **4b**, they were used in a Mannich reaction with 1*H*-benzotriazole (Scheme 3). A simple addition of the aminal ((*R*,*R*)-**4a** or (*S*,*S*)-**4b**) to a stirred solution of 1*H*-benzotriazole in dioxane/water (3:2) followed by refluxing for 8 h and cooling to ambient temperature, gave (3a*R*,7a*R*)- and (3a*S*,7a*S*)-1,1'-{[2,3,3a,4,5,6,7,7a-octahydro-1*H*-1,3-benzimidazole-1,3-diyl]bis (methylene)}bis-1*H*-benzotriazole (**9** and **10**) in a 65% and a 60% yields, respectively.<sup>13</sup>

In summary, we have synthesized a new aminal cage **4** by two different methodologies. Both afforded **4** as a racemic mixture with a difficult resolution. X-ray crystallography of a single crystal of **4** confirmed the structure as a racemic pair of enantiomers ((R,R)-**4a** and (S,S)-**4b**). We also have identified a new one-pot three component synthesis for preparing enantiomerically pure aminals (R,R)-**4a** and (S,S)-**4b**. The synthesis of aminals (R,R)-**4a** and (S,S)-**4b**.

**4b** have not only opened avenues related to the preparation of chiral ligands for asymmetric catalysis i.e. salans but they have also allowed for the obtention of other chiral complexes through the developed benzotriazole methodology.

#### Acknowledgments

We acknowledge the Dirección de Investigaciones, Sede Bogotá (DIB) de la Universidad Nacional de Colombia for the financial support of this work, as well as the Institutional Research Plan No. AVOZ10100521 of the Institute of Physics and the Praemium Academiae Project of the Academy of Sciences of the Czech Republic. D.Q. and L.J-C. also acknowledge the Vicerrectoría Académica de la Universidad Nacional de Colombia for the fellowships provided.

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- 5. (a) Reaction of (2R,7R,11S,16S)-1,8,10,17-tetraazapentacyclo [8.8.1.1<sup>8,17</sup>.0<sup>2,7</sup>.0<sup>11,16</sup>] icosane 2 with ammonium fluoride: A solution of ammonium fluoride (74 mg, 2 mmol) in water (5.0 mL) was added to a solution of (2*R*,7*R*,11*S*,165)-1,8,10,17-tetrazapentacyclo[8.8.1.1.<sup>8,17</sup>0.<sup>2,7</sup>0<sup>11,16</sup>]icosane **2** (276 mg, 1 mmol) in ethanol (10.0 mL). The reaction mixture was stirred at room temperature for 8 h, after which the solvent was slowly evaporated at room temperature over a period of about 1 week, and the solid residue was extracted with chloroform  $(3 \times 5.0 \text{ mL})$ . The organic layer was dried over anhydrous sodium sulfate, filtered, and the solvent was evaporated under reduced pressure. The crude reaction product was purified by column chromatography on Silica gel, eluting with a chloroform-methanol (7:3) to afford racemic compound 4 (mp 78-80 °C, an 85% yield): <sup>1</sup>H NMR (400.1 MHz, CDCl<sub>3</sub>): δ 1.31 (m, 2H), 1.40 (m, 2H), 1.80 (*m*, 2H), 1.85 (*m*, 2H), 2.60 (d, J = 8.8 Hz, 2H), 3.84 (dd,  ${}^{2}J_{gem} = 13.4$  Hz,  ${}^{4}J_{w} = 1.2$  Hz, 2H), 4.01 (dd,  ${}^{2}J_{gem} = 14.0$  Hz,  ${}^{4}J_{w} = 1.2$  Hz, 2H), 4.57 (dd,  ${}^{2}J_{gem} = 14.0$  Hz,  ${}^{4}J_{w} = 1.6$  Hz, 2H), 4.59 (dd,  ${}^{2}J_{gem} = 13.4$  Hz,  ${}^{4}J_{w} = 1.6$  Hz, 2H).  ${}^{13}$ C NMR (100.6 MHz, CDCl<sub>3</sub>): δ 26.27, 34.06, 65.59, 75.12, 78.29. The sign of the optical rotation was determined with a polarimeter model ADP440+ from Bellingham and Stanley (Bogotá, Colombia) and the value is the average of ten measures,  $[\alpha]_D^{20}$ =-12.0 (c 0.6; CH<sub>2</sub>Cl<sub>2</sub>). (b) Reaction of trans-(R,R)-1,2diaminocyclohexane[1-(+)-tartrate]salt, ammonia, and formaldehyde: trans-(R,R)-1,2-diaminocyclohexane [L-(+)-tartrate] salt (264 mg, 1.0 mmol) was mixed with a 25% aqueous solution of ammonia (1.1 mL, 7 mmol) and paraformaldehyde (150 mg, 5 mmol) was added in small portions with vigorous stirring for 1 h. The reaction mixture was stirred at room temperature for 8 h, and the product was extracted with  $CHCl_3$  (4 × 5 mL). The extract was concentrated under reduced pressure and the residue was purified by column chromatography on Silica gel and eluted with a chloroform–methanol (7:3) mixture, to afford (2*R*,7*R*)-1,8,10,12-tetraazatetracyclo[8.3.1.1.<sup>8.12</sup>0<sup>2,7</sup>]penta decane **4a** (mp 68–70 °C, a 60% yield): HR-ESI-MS in its positive mode m/z: [M+H]<sup>+</sup>calcd for C<sub>11</sub>H<sub>21</sub>N<sub>4</sub>: 209.1766, found: 209.1756; The sign of the optical rotation was determined with a polarimeter model ADP440+ from Bellingham and Stanley (Bogotá, Colombia) and the value is the average of ten measures,  $[\alpha]_D^{20}$ =-51.9 (c 0.6; CH<sub>2</sub>Cl<sub>2</sub>). (c) Reaction of trans-(S,S)-1,2-diaminocyclohexane dihydrochloride salt, ammonia, and formaldehyde: trans-(S,S)-1,2-diaminocyclohexane dihydro chloride salt (187 mg, 1.0 mmol) was mixed with 25% aqueous solution of ammonia (1.1 mL, 7 mmol) and paraformaldehyde (150 mg, 5 mmol) was added in small portions with vigorous stirring for 1 h. The reaction mixture was stirred at room temperature for 8 h, and the product was extracted with  $CHCl_3$  (4  $\times$  5 mL). The extract was concentrated under reduced pressure, and the residue was purified by column chromatography on Silica gel and eluted with a chloroform-methanol (7:3) mixture, to afford (25,75)-1,8,10,12-tetraazatetracyclo [8.3.1.1.<sup>8,12</sup>0<sup>2,7</sup>]penta decane **4b** (mp 68–70 °C, a 55% yield): HR-ESI-MS in its positive mode m/z:  $[M+H]^+$  calcd for  $C_{11}H_{21}N_4$ : 209.1766, found: 209.1756; The sign of the optical rotation was determined with a polarimeter model ADP440+ from Bellingham and Stanley (Bogotá, Colombia) and the value is the average of ten measures,  $[\alpha]_{D}^{20} = +52.0$  (*c* 0.6; CH<sub>2</sub>Cl<sub>2</sub>).
- 6. (a) Crystal data for compound **4**,  $3(C_{11}H_{20}N_4)\cdot 2(H_2O)$ , were collected using an Xcalibur Atlas Gemini ultra diffractometer using the following parameters: Oxford Diffraction at 120 K,  $M_r = 661$ , monoclinic, C2/c, a = 25.985(3) Å, b = 11.9676(13) Å, c = 12.2514(15) Å, V = 3441.9(8) Å<sup>3</sup>, Z = 4, Dx = 1.275 Mg m<sup>-3</sup>, CuK $\alpha$  X-ray source (radiation),  $\lambda = 1.5418$  Å, and F(000) = 1448 colorless prism  $0.39 \times 0.03 \times 0.01$  mm. All non-hydrogen atoms were refined with anisotropic thermal parameters using full-matrix least squares procedures on  $F^2$  to give R = 0.074, wR = 0.187 for 2282 independently observed reflections and 220 parameters. Crystallographic data (excluding structural factors) for the given structure in this LETTER have been deposited at the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication number CCDC 844994. Copies of these data can be obtained, free of charge, upon request to the CCDC at 12 Union Road, Cambridge. CB2 IEZ, UK. Fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk. Program used to refine structure: (b) Petříček, V.; Dusěk, M.; Palatinus, L. JANA2006. Institute of Physics, Praha, Czech Republic. 2006.
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- 13. Preparations of (3aR,7aR) and (3aS,7aS)-1,1'-{[2,3,3a,4,5,6,7,7a-octahydro-1H-1,3-benzimidazole-1,3-diyl]bis(methylene)]bis-1H-benzotriazole (9 and 10): A solution of the respective aminal (208 mg, 1,00 mmol) (2R,7R) or (2S,7S)-1,8,10,12-tetraazatetracyclo [8.3.1.1.<sup>8,12</sup>0<sup>2,7</sup>]pentadecane (4a, 4b), in dioxane (3 mL) and water (4 mL) was added dropwise into a dioxane solution (3 mL) containing 2 equiv of 1H-benzotriazole (238 mg, 2,00 mmol) in a two-necked round-bottomed flask. The mixture was refluxed for approximately 8 h or until the precipitation of a colorless solid. The resulting solid was collected by filtration, washed with cold methanol, and dried under vacuum to give the product 9 or 10 (mp 123–124 °C, a 60–65% yield): <sup>1</sup>H NMR (400.1 MHz, CDCl<sub>3</sub>):  $\delta$  1. 17 (m, 2H), 1.27 (m, 2H), 1.82 (m, 2H), 2.18 (m, 2H), 2.39 (m, 2H), 4.03 (s, 2H), 5.42 (d, <sup>2</sup>J<sub>gem</sub> = 14.0 Hz, 2H), 5.47 (d, <sup>2</sup>J<sub>gem</sub> = 14.0 Hz, 2H), 7.36 (dd, <sup>3</sup>J<sub>H,H</sub> = 8.4 Hz, <sup>4</sup>J<sub>H,H</sub> = 1.6 Hz, 2H), 7.46 (m, 4H), 8.04 (dd, <sup>3</sup>J<sub>H,H</sub> = 8.4 Hz, <sup>4</sup>J<sub>H,H</sub> = 1.6 Hz, 2H). <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta$  23.86, 28.18, 61.62, 64.85, 69.32, 109.37, 119.92, 123.96, 127.66, 133.74, 145.80. The sign of the optical rotation was determined with a polarimeter model ADP440+ from Bellingham and Stanley (Bogotá, Colombia) and the value is the average of ten measures: for the (3aR,7aR) enantiomer 9: [a]<sub>D</sub><sup>0</sup> =-42.6 (c 0.3; CH<sub>2</sub>Cl<sub>2</sub>); for the (3aS,7aS) enantiomer 10: [a]<sub>1</sub><sup>20</sup> =+45.5 (c 0.5; CH<sub>2</sub>Cl<sub>2</sub>).