Tetrahedron Letters 50 (2009) 799–801

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis and isolation of a monoamine having a thermodynamically stabilized pseudo-chirotopic nitrogen

Yuka Kobayashi †, Kentaro Sano, Kazuhiko Saigo *

Department of Chemistry and Biotechnology, Graduate School of Engineering, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-8656, Japan

ARTICLE INFO

Article history:
Received 31 October 2008
Revised 26 November 2008
Accepted 1 December 2008
Available online 6 December 2008

ABSTRACT

We have synthesized a tricyclic monoamine, (1*S*,4*R*)-(*E*)-7,3′-heptenylene-2,3:5,6-dibenzo-7-azabicyclo[2.2.1]heptane (**1**), by applying a ring-closing metathesis reaction in the key step of the synthetic route and by using preparative chiral HPLC for the separation. The X-ray crystallographic analysis of its salt with (1*R*)-camphor-10-sulfonic acid showed that the geometry and absolute configuration are (*E*) and (1*S*,4*R*), respectively. The theoretical calculations revealed that the inversion of the nitrogen atom at the 7-position of (1*S*,4*R*)-(*E*)-**1** thus isolated takes place through a very slow process and that the configuration of the N(7) is highly biased to (*R*), indicating that (1*S*,4*R*)-(*E*)-**1** is a thermodynamically controlled N-pseudo-chirotopic compound ((1*S*,4*R*,7*R*): (1*S*,4*R*,7*S*) = 99.68:0.32 at 120 °C).

© 2008 Elsevier Ltd. All rights reserved.

Amines containing a chirotopic nitrogen have a characteristic that a 'lone pair' exists on their stereogenic center. Accordingly, they are drawing much attention not only from a synthetic point of view but also from the view point of application, for example, as ligands in metal catalysts for asymmetric synthesis, selectors for chirality-recognition, and so on. In order to fix the chirality of a nitrogen atom, nitrogen inversion should be avoided. For this purpose, a structural restriction has been imposed in molecular design; molecules having two nitrogen atoms linked with each other by a methylene bridge are highly attractive for the fixation of N-chirality, as is realized by sparteine and the Tröger base. In contrast, the chirality of the nitrogen of a monoamine is relatively difficult to be fixed, so that a more direct synthetic strategy is required to avoid nitrogen inversion; the synthesis of monoamines with large strain around a nitrogen atom such as aziridine derivatives[1] or with bulky substituents on a nitrogen atom[2] has been tried. Because unique properties and functions are expected for amines with a chirotopic nitrogen, steady researches have been carried out.[3] In this Letter, we report a novel strategy for the synthesis and isolation of a monoamine, having a thermodynamically stabilized pseudo-chirotopic nitrogen, with a simple tricyclic structure.

When a pair of nitrogen-inverted isomers (invertomers) of a monoamine is not enantiomeric but diastereomeric, one of the invertomers might be energetically stable more than the other. If the difference in potential energy between the diastereomeric invertomers is large enough and the equilibrium between the invertomers is sufficiently slow, one of the invertomers would be isolated. On the other hand, 7-azabicyclo[2.2.1]heptane (7-azanorbornane) derivatives are well known to show rather slow nitrogen inversion, which was firstly called in terms of 'bicyclic effect' by Lehn in 1977,[4a] and their stereodynamics has been investigated up to now.[4] On the basis of these consideration and fact, we designed the tertiary amine **1**, which has a 2,3:5,6-dibenzo-7-azabicyclo[2.2.1]heptane skeleton, and is dissymmetrized by introducing a strap between the nitrogen atom and one of the phenylene groups (Fig. 1). Although there are three stereogenic centers at the C(1)-, C(4)-, and N(7)-positions of **1**, only four stereo-isomers are possible to exist for **1** even if the inversion of the nitrogen atom at the 7-position takes place; the chiralities of the two carbons at the 1- and 4-positions are unequivocally determined without any relation to the chirality of the nitrogen atom.

A ring-closing metathesis (RCM) reaction using the Grubbs' catalyst of the second generation[5] was adopted for the synthesis of the tertiary amine **1**. Although we tried the RCM reactions of the analogues of the diene **2** with shorter alkenyl chain(s) at the 7- and/or 3′-position, no desired products were isolated. In contrast, when **2** was used as the substrate, the RCM reaction took

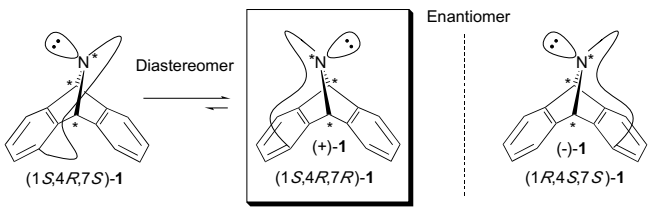
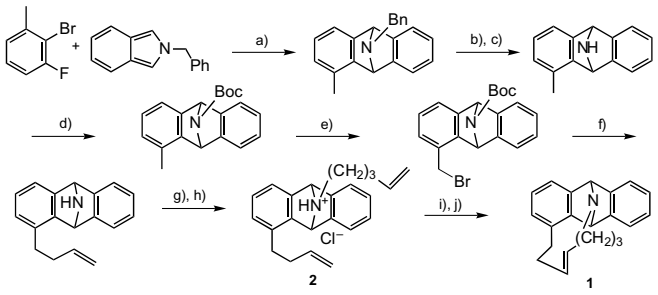


Figure 1. Design of a N-pseudo chiral monoamine (**1**).

* Corresponding author. Tel.: +81 3 5841 7266; fax: +81 3 5802 3348.
E-mail address: saigo@chiral.t.u-tokyo.ac.jp (K. Saigo).
† Present address: Waseda Institute for Advanced Study (WIAS), Waseda University, Nishiwaseda, Shinjyuku-ku, Tokyo 169-8050, Japan.

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.12.004



Scheme 1. Synthesis of (1*S*,4*R*)-(*E*)-**1**. Reagents and conditions: (a) Mg activated with $BrCH_2CH_2Br$, THF, reflux, 1.5 h, 76%;[6] (b) NBS, 1,4-dioxane/H_2O, rt, 3 days; (c) quenching with KOH aq, 69% (overall yield for 2 steps); (d) $(Boc)_2O$, Et_3N, MeOH, reflux, 1 h, 92%; (e) NBS, BPO, *h*n, CCl_4, reflux, 3 h, 81%; (f) $CH_2{=}CHCH_2MgCl$, THF, reflux, 2 h, 69%; (g) $CH_2{=}CH(CH_2)_3Br$, K_2CO_3, CH_3CN, reflux, 8 h; (h) quenching with HCl, Et_2O, 80% (overall yield for 2 steps); (i) the Grubbs' catalyst (the second generation), CH_2Cl_2, reflux, 3 days, 75%; (j) separation on a Daicel Chiralcel OD column, 44%.

place very smoothly to give the corresponding ring-closed product in 75% yield, as shown in Scheme 1. However, spectroscopic analyses revealed that the product was a mixture of some stereo-isomers. In order to isolate one isomer from the mixture, preparative chiral high performance liquid chromatography (HPLC) was carried out by means of a Daicel Chiralcel OD column with an eluent of hexane/2-propanol (95:5, v/v); **1** diastereopure in a ^{1}H NMR level was obtained from the mixture in 44% yield as a singly separable product. The geometry of the alkynylene of the strap and the absolute configuration of the three stereogenic centers (C(1), C(4), and N(7)) in **1** thus obtained were determined to be (*E*) and (1*S*,4*R*,7*R*), respectively, by the X-ray crystallographic analysis of its salt with (1*R*)-camphor-10-sulfonic acid.[7] The crystal structure of the salt is shown in Figure 2.

The C(1)–N(7)–C(4) angle has been often pointed out to be an important factor for the suppression of the nitrogen inversion of 7-azanorbornane derivatives.[4] However, the angle of (1*S*,4*R*,7*R*)-(*E*)-**1** (the abbreviation (7*R*)-**1** is used for simplicity hereafter) in the salt crystal determined by the X-ray crystallographic analysis is 94.9°, which is the same as that reported for 7-methyl-7-azanorbornane,[4c] and all of the bond lengths and angles are in usual ranges.

These structural informations indicate that no structural strain exists in (7*R*)-**1**. Moreover, the X-ray crystallographic analysis shows that the invertomer (1*S*,4*R*,7*S*)-(*E*)-**1** (the abbreviation (7*S*)-**1** is used for simplicity hereafter) molecules do not exist at all in the salt crystal.

The observations, however, do not necessarily guarantee the fixation of the chirality of the nitrogen atom in (1*S*,4*R*)-(*E*)-**1** in a solution. Therefore, the stereodynamics of (1*S*,4*R*)-(*E*)-**1** in a solution was investigated; dynamic ^{1}H NMR measurements were carried out for (1*S*,4*R*)-(*E*)-**1** at a temperature range of −95 to 120 °C (solvent, $CDCl_3$ at lower temperatures and DMSO-d_6 at higher temperatures). As a result, no coalescence of the ^{1}H NMR signals was observed in the temperature range. The result made us to expect the fixation of the chirality of the nitrogen atom even at a high temperature, because the coalescence temperature was reported to be 1 °C for a 7-azanorbornane derivative.[4c] However, the possibility of the fast inversion of the nitrogen atom even at a low temperature would not be excluded only on the basis of the dynamic ^{1}H NMR phenomenon. Thus, the dynamic ^{1}H NMR was incompetent for clarifying the behavior of (1*S*,4*R*)-(*E*)-**1** in a solution.

Then, in order to know the thermodynamic property of (1*S*,4*R*)-(*E*)-**1**, we performed theoretical calculations for the potential energy profile of (7*R*)-**1**/(7*S*)-**1** using the GAUSSIAN 03 package.[8] Geometries were optimized with RHF/6-31g*, and single point energies were evaluated with CASSCF(10,10)/6-31G*, which is recognized to be appropriate for the accurate representation of complicated π-bonding systems.[9] An active space, which consists of 10 electrons distributing among 10 orbitals, includes the orbital of the nitrogen lone pair, the π orbitals of the alkenylene part, a part of the π orbitals of the two phenylene parts, and the s orbitals of C(1)–N(7)–C(4). All components in the active space were made to be consistent through the calculations. Figure 3 shows the calculated potential energy profile of (7*R*)-**1**/(7*S*)-**1**; the activation energy ($\Delta H^{\ddagger}$) for the nitrogen inversion of (7*R*)-**1** was evaluated to be 15.1 kcal/mol.[10] This value is almost equal to that of a 7-azanorbornane derivative (15.3 kcal/mol) calculated on the basis of its dynamic NMR analysis.[4c] This means that the $\Delta H^{\ddagger}$ for (7*R*)-**1** is not large enough to completely prevent nitrogen inversion.

Taking account of a static electron correlation effect, the electronic states of (7*R*)- and (7*S*)-**1** were also estimated with CASSCF. As a result, the energy difference (ΔH^0) between the invertomers (7*R*)- and (7*S*)-**1** was evaluated to be 4.3 kcal/mol, meaning that the ratios of (7*R*)- and (7*S*)-**1** are calculated to be 99.92:0.08 at room temperature and 99.68:0.32 even at 120 °C, taking into account the Boltzmann distribution. These results indicate that (7*R*)-**1** is highly stable, compared with (7*S*)-**1**, from the view point of thermodynamics; the invertomer (7*S*)-**1** only can exist in an extremely low ratio under the dynamic NMR measurement condi-

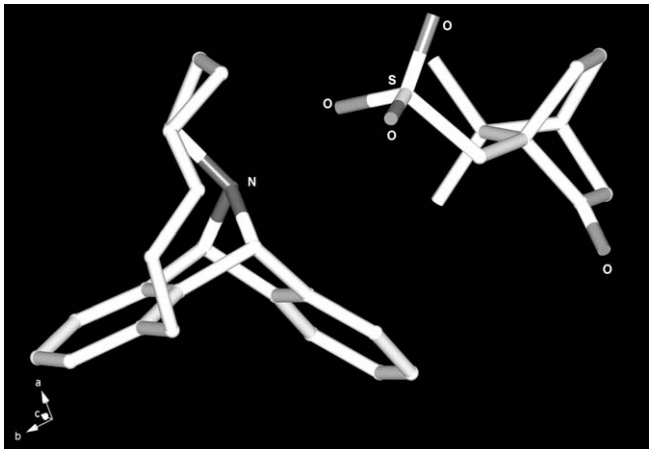


Figure 2. X-ray crystal structure of (1*S*,4*R*,7*R*)-(*E*)-**1**·(1*R*)-camphor-10-sulfonic acid.

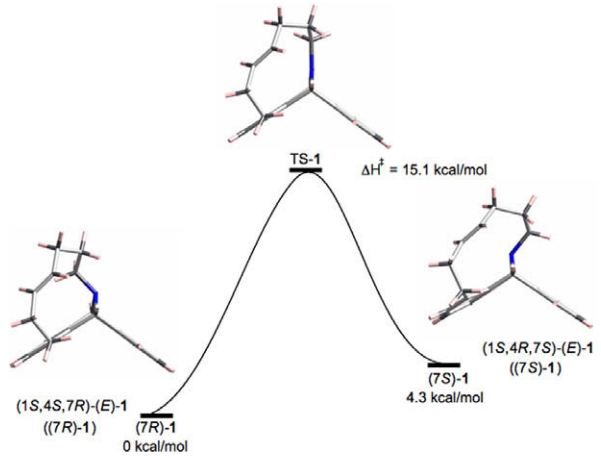


Figure 3. Potential energy surface of (1*S*,4*R*)-(*E*)-**1** evaluated with CASSCF(10,10)/6-31G*.

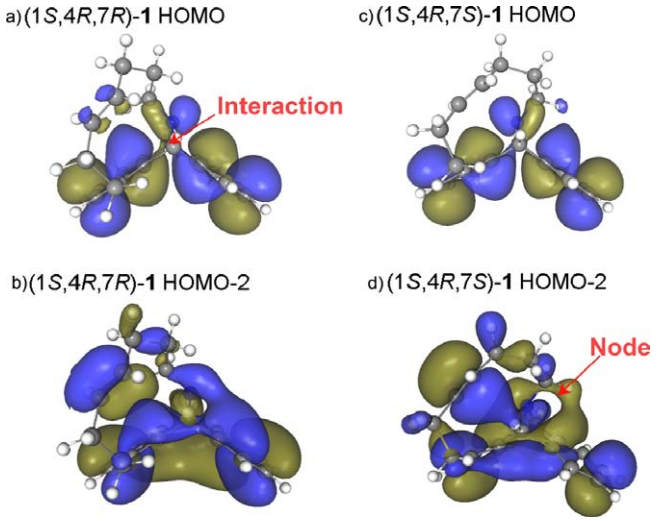


Figure 4. Molecular orbitals of HOMO and HOMO-2 of (1*S*,4*R*,7*R*)- and (1*S*,4*R*,7*S*)-**1**.

tions mentioned above, which resulted in apparently no observation of the coalescence of its ^{1}H NMR signals.

The ΔH^0 between (7*R*)- and (7*S*)-**1** could be qualitatively elucidated on the basis of their molecular orbitals. Figure 4 shows the molecular orbitals of HOMO and HOMO-2 for (7*R*)- and (7*S*)-**1**. The HOMO of (7*R*)-**1** shows that there exists orbital interaction between the N(7)–C(chain) s orbital and the π orbital of the phenylene ring, while such interaction is not observed in (7*S*)-**1**. Moreover, the HOMO-2 of (7*R*)-**1** indicates that the orbital of the N(7) lone pair interacts with the π orbital of the phenylene ring to stabilize (7*R*)-**1** whereas the corresponding orbital in (7*S*)-**1** has a node to destabilize (7*S*)-**1**. These calculations strongly indicate that (7*R*)-**1** is obviously more stable than (7*S*)-**1** owing to the advantageous intramolecular orbital interactions.

In conclusion, we have succeeded in the synthesis and isolation of a tricyclic monoamine, (1*S*,4*R*)-(*E*)-7,3′-heptenylene-2,3:5,6-dibenzo-7-azabicyclo[2.2.1]heptane (**1**), which exists as a thermodynamically stabilized pseudo-single diastereomer even at 120 °C. Although the inversion of the nitrogen atom at the 7-position of (1*S*,4*R*)-(*E*)-**1** takes place somewhat, we would be able to expect some function of the chirality of the N(7). The functions of (1*S*,4*R*)-(*E*)-**1** are under investigation.

Acknowledgments

The present work was supported by the Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan (No. 17750033 and No. 19350064). Y.K. acknowledges financial supports from Kurata Memorial, Hitachi Science and Technology Foundation, and Sumitomo Foundation.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.12.004.

References and notes

1. Jennings, W. B.; Boyd, D. R. In *Cyclic Organonitrogen Stereodynamics*; Lambert, J. B., Takeuchi, Y., Eds.; VCH: New York, 1992.
2. Kostyanovsky, R. G.; Kadorkina, G. K.; Kostyanovsky, V. R.; Schurig, V.; Trapp, O. *Angew. Chem., Int. Ed.* **2000**, *39*, 2938–2940.
3. (a) Uozumi, Y.; Mizutani, K.; Nagai, S. *Tetrahedron Lett.* **2001**, *42*, 407–410; (b) Arnold, M. A.; Durón, S. G.; Gin, D. Y. *J. Am. Chem. Soc.* **2005**, *127*, 6924–6925; (c) Kamikawa, K.; Kinoshita, S.; Matsuzaka, H.; Uemura, M. *Org. Lett.* **2006**, *8*, 1097–1100.
4. (a) Lehn, J.-M. *Fortschr. Chem. Forsch.* **1970**, *15*, 311–377; (b) Gribble, G. W.; Easton, N. R., Jr.; Eaton, J. T. *Tetrahedron Lett.* **1970**, *13*, 1075–1078; (c) Nelsen, S. F.; Ippoliti, J. T.; Frigo, T. B.; Petillo, P. A. *J. Am. Chem. Soc.* **1989**, *111*, 1776–1781; (d) Davies, J. W.; Durrant, M. L.; Walker, M. P.; Belkacemi, D.; Malpass, J. R. *Tetrahedron* **1992**, *48*, 861–8844; (e) Belostotskii, A. M.; Gottlieb, H. E.; Hassner, A. *J. Am. Chem. Soc.* **1996**, *118*, 7783–7789; (f) Butler, D. N.; Hammond, M. L. A.; Johnston, M. R.; Sun, G.; Malpass, J. R.; Fawcett, J.; Warrener, R. N. *Org. Lett.* **2000**, *2*, 721–724; (g) Malpass, J. R.; Butler, D. N.; Johnston, M. R.; Hammond, M. L. A.; Warrener, R. N. *Org. Lett.* **2000**, *2*, 725–728; (h) Belostotskii, A. M.; Gottlieb, H. E.; Shokhen, M. *J. Org. Chem.* **2002**, *67*, 9257–9266.
5. (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426–5427; (b) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856–9857.
6. Carpino, L. A.; Padykula, R. E.; Barr, D. E.; Hall, F. H.; Krause, J. G.; Dufresne, R. F.; Thoman, C. J. *J. Org. Chem.* **1988**, *53*, 2565–2572.
7. The X-ray intensities were collected with a Rigaku Mercury CCD system by using Mo Kα radiation (l = 0.71073 Å). The crystal structure was solved by the direct method with the SHELXL-97 program and refined by the full-matrix least-squares procedure for all non-hydrogen atoms anisotropically. All hydrogen atoms were generated geometrically. The absolute configuration of 1 was determined on the basis of the known absolute configuration of (1*R*)-(−)-camphor-10-sulfonic acid. CCDC 671578 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
8. GAUSSIAN 03, Revision B.05; Gaussian, Inc., Pittsburgh, PA, 2003.
9. (a) Roos, B. O. *Int. J. Quantum Chem.* **1980**, *17*, 175–189; (b) Kobayashi, Y.; Tajima, N.; Nakano, H.; Hirao, K. *J. Phys. Chem. B* **2004**, *108*, 12264–12266.
10. We excluded the term of ΔS in the estimation of the activation energy, because its contribution to the activation energy is known to be generally very small in the cases of 7-zanorbornane derivatives (see Ref. 4c).