Pergamon

Tetrahedron Letters 42 (2001) 465–468

TETRAHEDRON LETTERS

# Inside and outside *N*-bridged cavity systems: evidence for *syn*- and *anti*-atropisomers in scaffolds containing two *N*-benzoyl 7-azanorbornane units

Ronald N. Warrener* and Guangxing Sun

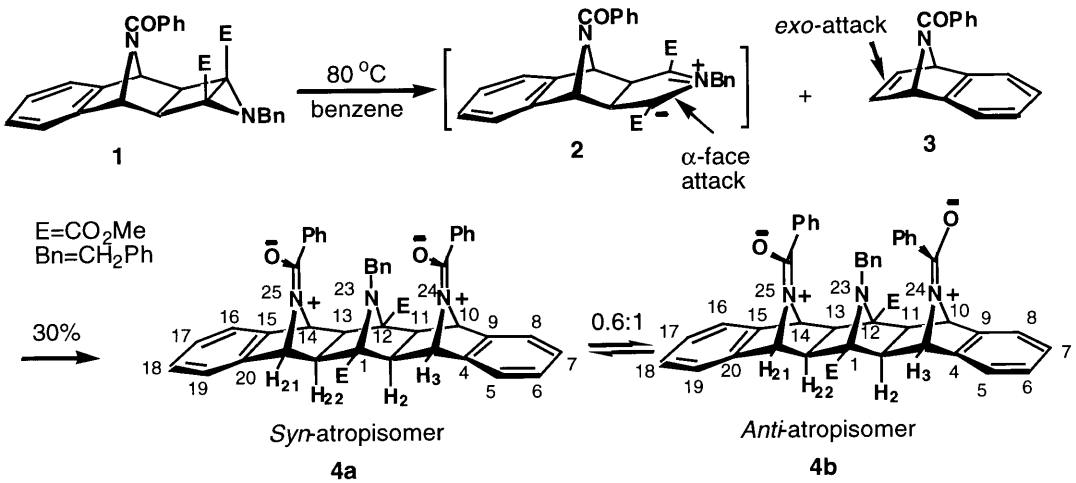
*Centre for Molecular Architecture, Central Queensland University, Rockhampton, Queensland 4702, Australia*

Received 13 October 2000; accepted 2 November 2000

**Abstract**—Alkene and aziridine reagents containing *N*-benzoyl 7-azanorbornane components have been prepared and used to construct [*n*]polynorbornanes in a block building protocol. The presence of *syn*- and *anti*-atropisomers involving the restricted rotation of the *N*-COPh bridge was established by $^1$H NMR spectroscopy in an NNN-[3]polynorbornane **4** (outside bridges) whereas the *anti*-conformer dominated in a cavity NCOCOCN-[7]isopolynorbornane **8** (inside bridges, X-ray confirmation) prepared by a dual 1,3-dipolar addition of an acute-angled norbornene **6** with a hexacyclic bis-epoxide **7**. © 2001 Published by Elsevier Science Ltd.

The development of block coupling protocols for the preparation of [*n*]polynorbornane scaffolds has been explored in some detail by our research group.[1–4] Those involving 1,3-dipolar reagents formed by the thermal ring-opening of ester-activated cyclobutane epoxides[2] and aziridines[3] and their coupling with norbornene dipolarophiles have been especially valuable, not least because of the high stereoselectivity of the coupling process. In this communication, we describe the synthesis of novel [*n*]polynorbornanes containing *N*-benzoyl 7-azanorbornane subunits and report a special type of atropisomerism in an NNN-[3]polynorbornane system having two such subunits.

While the objective of the present study was to establish a new route to cavity systems with inside *N*-bridge functionality (see later), once again the [*n*]polynorbornane frame provided the medium by which an




**Scheme 1.**

*Keywords*: atropisomerism; 7-azanorbornanes; X-ray crystallography; restricted rotation; amides.

* Corresponding author. Tel.: 61 7 4930 9845; fax: 61 7 4930 9917; e-mail: r.warrener@cqu.edu.au

0040-4039/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0040-4039(00)01939-0

unusual aspect of bridge nitrogen chemistry could be identified. We recently reported[4] that *N*-benzyl XNY-[3]polynorbornanes could be used to study nitrogen hybridisation where it was shown that significant compression towards planar nitrogen could be achieved by through-space effects involving the proximal X and Y bridges. Further, in cases where X = Y, dynamic invertomerisation occurred and individual invertomers could not be identified, even at low temperatures.

Reaction of *N*-benzoyl 7-azabenzonorbornadiene **3**[5] with the *N*-benzoyl bridged aziridine **1**[6] formed the NNN-[3]polynorbornane **4** (Scheme 1) in a 1,3-dipolar reaction which involved the attack of **3** onto dipole **2**. The unusual feature of adduct **4** was evident in the $^1$H NMR spectrum which was not only unsymmetrical owing to the slow rotation of the amide bond[7] but exhibited a dual set of resonances (Fig. 1). The *N*-benzyl group in **4** should be compressed by the flanking *N*-benzoyl groups and was expected to exhibit rapid invertomerisation at room temperature (see above) and this ruled out *N*-benzyl invertomerisation being the cause of the spectral duality. It was significant that the proportion of products was not equal and that we were dealing with two different species. We propose that an equilibrium between two atropisomers was involved owing to slow, restricted rotation of the *N*-COPh bridges,[8] which in **4** gave rise to a mixture of *syn*-atropisomer **4a** and *anti*-atropisomer **4b**, products which differed only in the relative orientation of the two *N*-COPh conformers. This proposal was supported by $^1$H NMR spectroscopy where the complex spectrum at room temperature was attributed to a mixture (ratio 0.6:1) of *syn*-atropisomer **4a** and *anti*-atropisomer **4b** (assignments shown in Fig. 1). The minor *syn*-isomer **4a** had a mirror plane through the central *N*-bridge and the two ester groups at the bridgehead were different (singlets $\delta$ 3.67, 4.05) whereas the *N*-benzylic methylene protons were equivalent (singlet, $\delta$ 4.30). The major *anti*-isomer **4b** had an axis of symmetry through the central *N*-bridge and the ester groups at the bridgehead were equivalent (singlet, $\delta$ 3.85) while the *N*-benzylic methylene protons were diastereotropic (doublet, $\delta$ 4.08, 4.51 $J = 16.3$ Hz). VT-NMR showed that the spectrum broadened on heating yet retained asymmetry to ca. 90°C and coalesced at around 110°C to yield a broad but symmetrical spectrum consistent with a product with $C_{2v}$-symmetry. Further support for the involvement of restricted rotation of the *N*-benzoyl group was forthcoming from the starting reagents **1** and **3** which each exhibited unsymmetrical, broadened $^1$H NMR spectra at room temperature that became symmetrical at higher temperatures. To the best of our knowledge, the detection of **4a** and **4b** is a new form of atropisomerism in *N*-bridged alicyclic systems.[9,10]

Turning next to the formation of a cavity system with inner-surface *N*-bridges, we approached this by the retrosynthetic analysis shown in the box in Scheme 2. This block approach used an alternative 1,3-dipolar coupling technique (ACE coupling)[2] and was applied twice-over to bis-epoxide **7**. The reaction depended on the *exo*,*exo*-specific coupling protocol established for norbornenes and employed the dipolarophilic norbornene **6** that was produced in a stereoselective *exo*,*endo*-fashion by addition of cyclopentadiene **5** to the 7-azabenzonorbornadiene **3**.[11] The asymmetry of the $^1$H NMR spectrum of **6** reinforced the fact that restricted rotation was again in effect and this was especially evident in the wide shift separation of the olefinic protons Hd, He ($\Delta\delta = 0.43$) owing to their proximity to the planar *N*-benzoyl group. This stereochemistry was further reinforced by the lack of vicinal coupling between protons Hb and either Ha or Hc. Addition of **6** to **7** was achieved by heating ($CHCl_3$, 140°C, sealed tube, 12 h) and the cavity product **8** isolated by chromatography in 30% yield, following recrystallisation from chloroform, mp >350°C. The $^1$H NMR spectrum of **8** displayed spectral broadening of some signals, however the presence of distinct atropisomers was not apparent. An X-ray crystal structure of **8** (Fig. 2)[12] confirmed the cavity structure and the attendant curvature of the frame which brought the nitrogen bridges within 9.4 Å of each other. Further, it showed that the *N*-benzoyl groups were essentially planar and had adopted the *anti*-conformation in the solid state. The *anti*-conformation of the *N*-benzoyl group may also dominate in solution since molecular modelling indicated that the phenyl groups in the *syn*-atropisomer are capable of spatial overlap in some conformations. Such proximity would make this conformer much higher in energy than the well-separated *anti*-atropisomer, thereby accounting for the lack of separate atropisomers being observed in the $^1$H NMR spectrum for **8**.

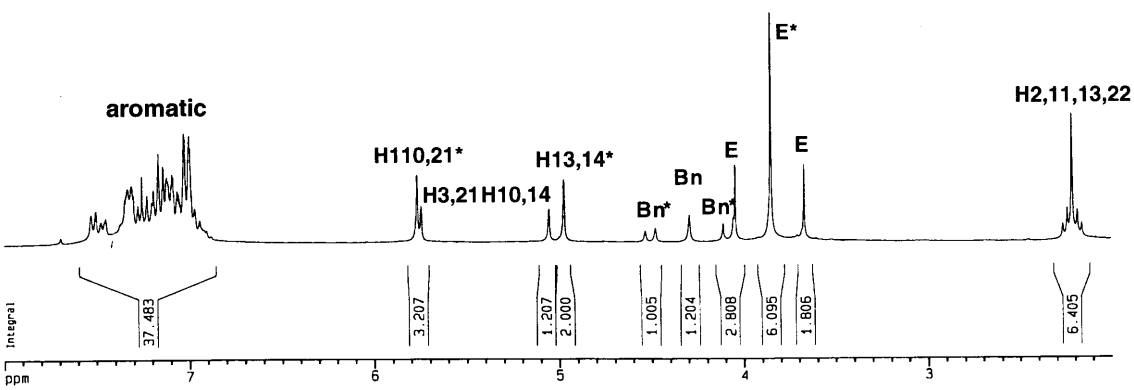
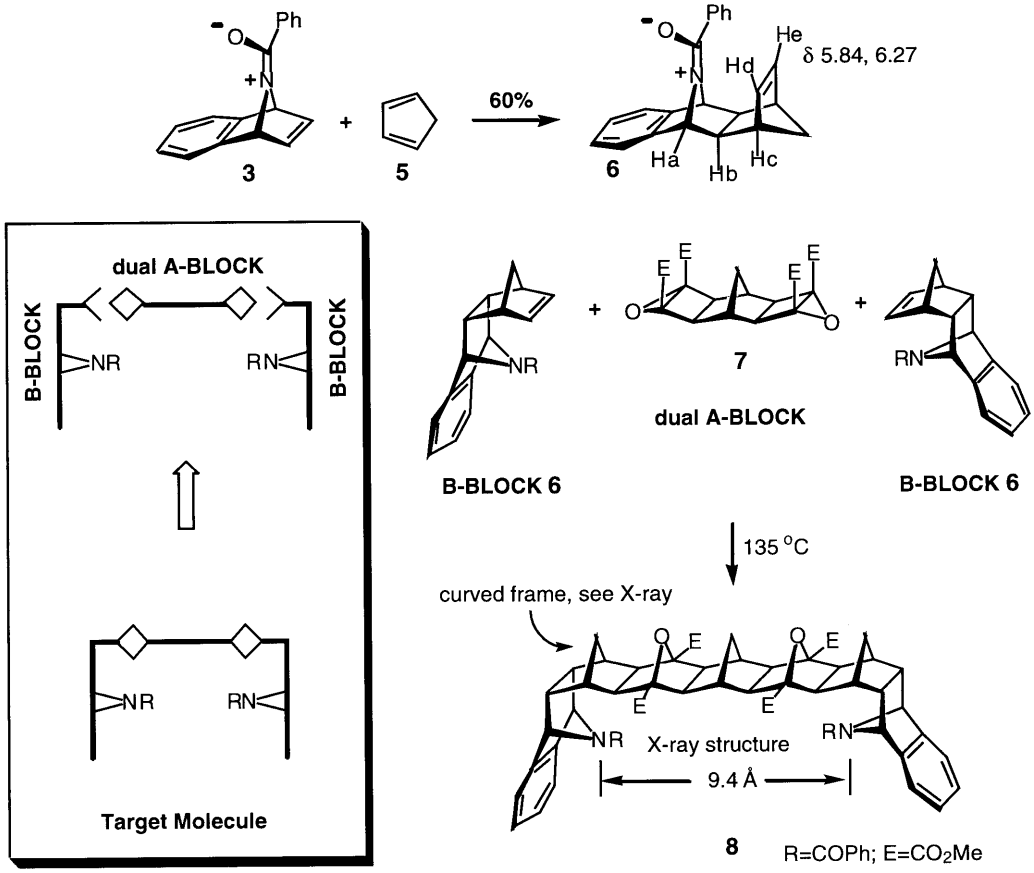



**Figure 1.** $^1$H NMR spectrum of atropisomers **4a** and **4b** (resonances starred).




**Scheme 2.**

In conclusion, we have demonstrated the role of 1,3-dipolar coupling techniques to produce *N*-benzoyl bridged scaffolds and cavity systems, and shown for the first time that compounds containing two such bridges are capable of existing as atropisomeric pairs owing to the restricted rotation of the amide N–CO bond. We are currently seeking ways to stabilise atropisomers of this type so that individual atropisomers are capable of isolation.

**Acknowledgements**

G.S. thanks Central Queensland University for the provision of a CQU Ph.D. scholarship. We thank Dr. A. Lough (University of Toronto) for conducting the X-ray structure of **8**.

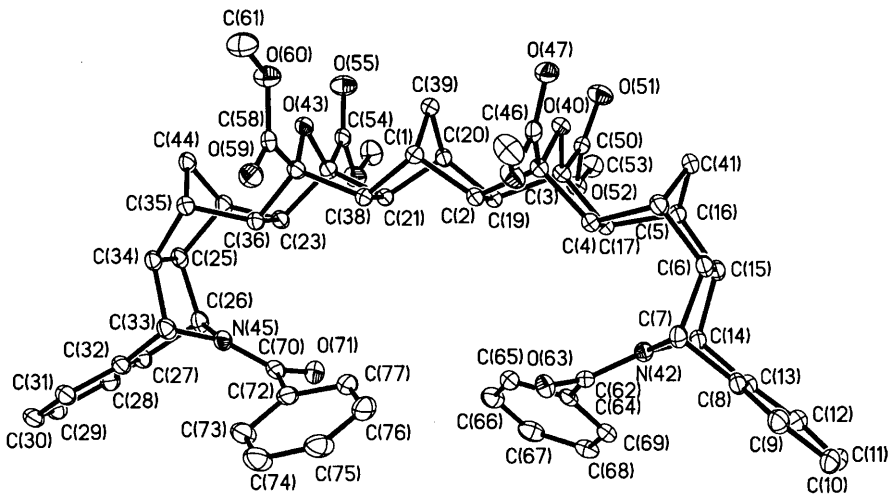



**Figure 2.** X-Ray structure[12] of cavity system **8**.

## References


1. Applications of 1,3-dipolar coupling to form [*n*]polynorbornane scaffolds: (a) Warrener, R. N.; Butler, D. N.; Margetic, D.; Pfeffer, F. M.; Russell, R. A. *Tetrahedron Lett*. **2000**, *41*, 4671–4675. (b) Schultz, A. C.; Kelso, L. S.; Johnston, M. R.; Warrener, R. N.; Keene, F. R. *Inorg. Chem*. **1999**, *38*, 4906. (c) Warrener, R. N.; Schultz, A. C.; Johnston, M. R.; Gunter, M. J. *J. Org. Chem*. **1999**, *64*, 4218. (d) Warrener, R. N.; Margetic, D.; Amarasekara, A. S.; Russell, R. A. *Org. Lett*. **1999**, *1*, 203. (e) Review: Warrener, R. N.; Butler, D. N.; Russell, R. A. *Synlett* **1998**, 556–573. (f) Warrener, R. N.; Margetic, D.; Amarasekara, A. S.; Foley, P.; Butler, D. N.; Russell, R. A. *Tetrahedron Lett*. **1999**, *40*, 4111–4114. (g) Review: Warrener, R. N.; Margetic, D.; Russell, R. A. Article 014, *Electronic Conference on Heterocyclic Chemistry '98*; Rzepa, H. S.; Kappe, O., Eds.; Imperial College Press, 1998. (h) Sun, G.; Butler, D. N.; Warrener, R. N.; Margetic, D.; Malpass, J. R. Article 062, *Electronic Conference on Heterocyclic Chemistry '98*; (http://www.ch.ic.ac.uk/ectoc/echet98/pub/062/index.htm); Rzepa, H. S.; Kappe, O., Eds.; Imperial College Press, 1998.
2. Warrener, R. N.; Schultz, A. C.; Butler, D. N.; Wang, S.; Mahadevan, I. B.; Russell, R. A. *Chem. Commun*. **1997**, 1023–1024.
3. Butler, D. N.; Malpass, J. R.; Margetic, D.; Russell, R. A.; Sun, G.; Warrener, R. N. *Synlett* **1998**, 588.
4. (a) 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. (b) Malpass, J. R.; Butler, D. N.; Johnston, M. R.; Hammond, M. L. A.; Warrener, R. N. *Org. Lett*. **2000**, *2*, 725–728.
5. (a) Davies, J. W.; Durrant, M. L.; Walker, M. P.; Belkacemi, D.; Malpass, J. R. *Tetrahedron* **1992**, *48*, 861–884. (b) Gribble, G. W.; Allen, R. W.; LeHouiller, C. S.; Eaton, J. T.; Easton, N. R.; Slayton, R. I.; Sibi, M. P. *J. Org. Chem*. **1981**, *46*, 1025–1026. (c) Gribble, G. W.; LeHoullier, C. S. *Tetrahedron Lett*. **1981**, *22*, 903–906. (d) Underwood, G. R.; Friedman, H. S. *J. Am. Chem. Soc*. **1977**, *99*, 27–32.
6. Aziridine **1** was formed from **3** by conversion to the related cyclobutene-1,2-diester by ruthenium-catalysed [2+2] cycloaddition of dimethyl acetylenedicarboxylate (62%), followed by addition of benzyl azide (high pressure 14 kbar, 4 days, 92%) and deazetisation (benzene, 300 nm, 96%).
7. It has recently been reported that the *N*-acyl derivatives of some aza-alicyclic compounds, in particular 7-azanorbornanes, are substantially non-planar (Ohwada, T.; Achiwa, T.; Okamoto, I.; Shudo, K. *Tetrahedron Lett*. **1998**, *39*, 865–868); however, the X-ray structure of **9** supports the planarity of the present systems.
8. (a) Drew, M. G. B.; George, A. V.: Isaacs, N. S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1277–1284. (b) Deloughry, W. J.; Sutherland, I. O. *J. Chem. Soc., D* **1971**, 1104–1105. (c) Chow, T. J.; Hwang, J.-J.; Wen, Y.-S.; Lin, S.-C. *J. Chem. Soc., Dalton Trans*. **1994**, 937–942. (d) Cho, B. P.; Zhou, L. *Biochemistry* **1999**, *38*, 7572–7583. (e) Ikeura, Y.; Natsugari, H. *Takeda Kenkyushohu* **1999**, *58*, 1–51. (f) Kanemasa, S.; Ueno, K.; Onimura, K.; Kikukawa, T.; Yamamoto, Y. *Tetrahedron* **1995**, *51*, 10453–10462.
9. For examples of amide participation in atropisomerism involving restricted rotation about the $C_{Ar}$–$CONR_2$ bond, see: (a) Clayden, J.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett*. **1999**, *40*, 7883–7887. (b) Ahmed, A.; Bragg, R. A.; Claydon, J.; Lai, L. W.; McCarthy, C.; Pink, J. H.; Westlund, N.; Yasin, S. A. *Tetrahedron* **1998**, *54*, 13277–13294. (c) Hughes, A. D.; Simpkins, N. S. *Synlett* **1998**, 967–968. (d) Fujita, M.; Kitagawa, O.; Izawa, H.; Dobashi, A.; Fukaya, H.; Taguchi, T. *Tetrahedron Lett*. **1999**, *40*, 1949–1952.
10. For restricted rotation about the $C_{Ar}$–NRCOR′ bond, see: Curran, D. P.; Qi, H.; Geib, S. J.; DeMellow, N. C. *J. Am. Chem. Soc*. **1994**, *116*, 3131–3132.
11. Margetic, D.; Warrener, R. N.; Malpass, J. R. In: *Fifth Electronic Conference on Computational Chemistry*; Bachrach, S., Ed.; 1998.
12. Archival crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 12233 336 033; e-mail: deposit@ccdc.cam.ac.uk).