COMMUNICATION

ChemComm
www.rsc.org/chemcomm

The synthesis and crystallographic structures of novel bora-oxazino-oxazolidine derivatives of resorcarene†

Waldemar Iwanek,*[ab] Roland Fröhlich,[c] Pia Schwab[c] and Volker Schurig[a]

[a] *University of Tübingen, Institute of Organic Chemistry, Auf der Morgenstelle 18, 72076 Tübingen, Germany. E-mail: waldemar.iwanek@uni-tuebingen.de; Fax: +49 7071 295538*

[b] *Pedagogical University, Institute of Chemistry, Chęcińska 5, 25020 Kielce, Poland*

[c] *University of Münster, Institute of Organic Chemistry, Corrensstrasse 40, 48149 Münster, Germany. E-mail: frohlic@nwz.uni-muenster.de*

Received (in Cambridge, UK) 27th June 2002, Accepted 28th August 2002
First published as an Advance Article on the web 25th September 2002

The diastereoselective synthesis and crystallographic structures of novel chiral bora-oxazino-oxazolidine derivatives obtained from resorcarene and L-prolinol are described.

The synthesis of chiral resorcarenes is interesting not only for the preparation of novel chiral supramolecular ligands but also for their potential use in the study of chiral discrimination as well as their application as chiral catalysts for asymmetric reactions.

At present, several examples of chiral resorcarenes are known.[1] One of them concerns the diastereoselective ring closure in the resorcarene molecule resulting in oxazine derivatives.[2] The oxazine ring closure in the resorcarene molecule, in the absence of chiral auxiliaries, affords a mixture of enantiomers having C_4 symmetry. These have been separated chromatographically on a Whelk-01 column, containing 3,5-dinitrobenzamidotetrahydrophenanthrene.[3]

Here we report on the diastereoselective synthesis of novel bora-oxazino-oxazolidine derivatives of resorcarene (Scheme 1).

The Mannich reaction initially afforded the chiral amino-methylene derivatives of resorcarene (**2**) in which the free hydroxy groups and the nitrogen electron pair are subsequently linked to the boron atom *via* phenylboronic acid to give (**3**). The reaction was conducted without isolation of the amino-methylene derivative of resorcarene (**2**), using 4 equivalents of formaldehyde and 4 equivalents of chiral L-prolinol. The reaction was carried out in methanol. The solvent was evaporated after 24 hours. Toluene and 5 equivalents of $PhB(OH)_2$ were added to the residue, followed by azeotropic removal of water for 4 hours. The thus obtained product was crystallized from ethanol, yield 65%.

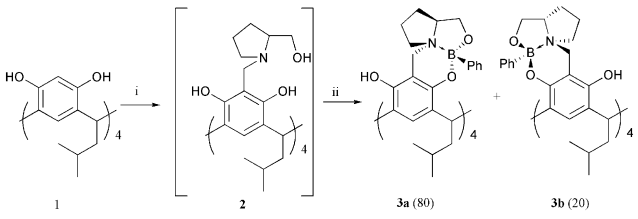
The reaction produces only two diastereoisomers in a ratio of 80 (**3a**) : 20 (**3b**) for the L-prolinol derivative. These diastereoisomers can be separated by multiple crystallization from ethanol. The diastereoisomeric ratio has been determined from the ^{1}H NMR spectra.

The crystallographic structures of both diastereoisomers of the L-prolinol derivative have been resolved. The crystallographic structure of the major diastereoisomer (**3a**) is shown in Fig. 1. The chirality of L-prolinol and the rigid structure of the bora-oxazino-oxazolidine moiety determine the formation of an excess of the diastereoisomer, wherein all the resorcinol units in the resorcarene molecule undergo synchronous clockwise closure (P) of the bora-oxazine rings when viewed from inside the cavity. The bora-oxazino-oxazilidine rings are oriented outwards from the resorcarene cavity, whereas the phenyl groups on boron are oriented towards the cavity. This diastereoisomer (**3a**), when crystallized from acetone, contains one acetone molecule within the cavity, with its methyl group pointing toward the π-basic socket of the resorcarene as a result of CH-π interactions with the resorcinol rings.

In the case of the other diastereoisomer obtained from L-prolinol (**3b**, Fig. 2), the crystallographic analysis showed that the closure of all the resorcinol rings to the bora-oxazine derivative is anticlockwise (M) when viewed from inside the cavity and the bora-oxazino-oxazolidine system is reversed by 180°. The bora-oxazino-oxazilidine rings are oriented in this case towards the resorcarene cavity, whereas the phenyl groups on boron are oriented outward from the cavity. This diastereoisomer (**3b**), when crystallized from CH_2Cl_2–MeOH, contains one dichloromethane molecule within the cavity as a result of CH-π interactions of the methylene group and of *n*-π interactions of the chlorine atom with the resorcinol rings.

In both cases the direction of the bora-oxazine ring closure is determined on the basis of the known chirality of the stereogenic carbon atom in L-prolinol.

The molecules of **3a** and **3b** adopt in the crystalline state a crown conformation stabilized by four intramolecular hydrogen bonds between the oxygen atom in the bora-oxazine ring and neighboring hydroxyl groups. The selected crystallographic



Scheme 1 *Reagents and conditions*: (i) L-prolinol, formaldehyde, MeOH, rt, 24 h; (ii) $PhB(OH)_2$, toluene, reflux, 4 h, 65%.

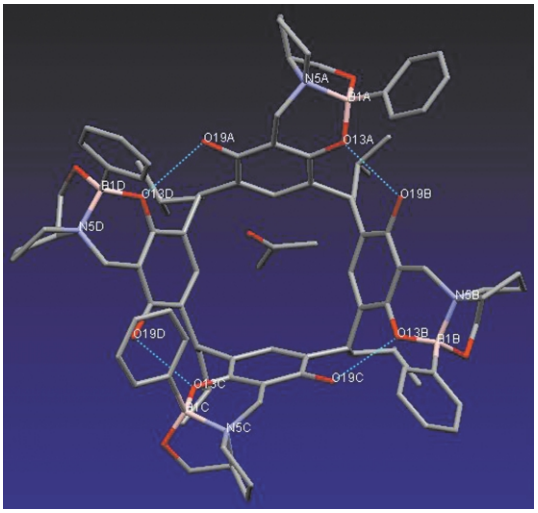


Fig. 1 The crystallographic structure of the bora-oxazino-oxazolidine derivative of resorcarene and L-prolinol (**3a**) with acetone residing within the cavity. The hydrogen bonds are indicated by dotted lines. Hydrogen atoms are omitted for clarity.

† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b2/b206188k/

DOI: 10.1039/b206188k

data, the distances between the oxygen atoms and the bond lengths between nitrogen–boron atoms are listed in Table 1.

During the reaction two new stereocenters are created per unit at the N- and B-atoms. In both derivatives, nitrogen adopts the *S* configuration, whereas the boron adopts the *R* configuration.

The juxtaposition of the bora-oxazino-oxazolidine rings outside or inside of the resorcarene cavity influence the chemical shift of diastereotopic signals of the aminomethylene (Ar–CH_2–N–) and hydroxy (–OH) protons in the ^{1}H NMR spectra. In the case of derivative **3a**,[4] the methylene protons are located deeper inside the cavity than in derivative **3b**.[5] The proton signals of derivative **3a** displayed more upfields shifts (δ = 3.64 and 4.03 ppm) than for derivative **3b** (δ = 3.81 and 4.28 ppm). Furthermore the position of the hydroxy proton in the ^{1}H NMR spectra for derivative **3a** indicated stronger hydrogen bonds than for derivative **3b**. Signals of the hydroxy protons are at δ: 8.62 (**3a**) and 7.31 ppm (**3b**), respectively.

Chemical shifts of the above mentioned protons in the ^{1}H NMR spectra can be used to determine the direction of the oxazine ring closure in bora-oxazino-oxazolidine derivatives of resorcarenes, formed with other chiral aminoalcohols, still under investigation.

In summary, new bora-oxazino-oxazolidine derivatives of resorcarenes from L-prolinol were synthesized by linking hydroxyl groups and the nitrogen electron pair of the aminomethylene derivative of resorcarene (**2**) by $PhB(OH)_2$. As a result, two diasteroisomers of bora-derivatives in a ratio of 80 (**3a**) : 20 (**3b**) are formed. Their crystal structures were described demonstrating that the direction of the bora-oxazine ring closure was governed by the stereogenic carbon atom of L-prolinol.

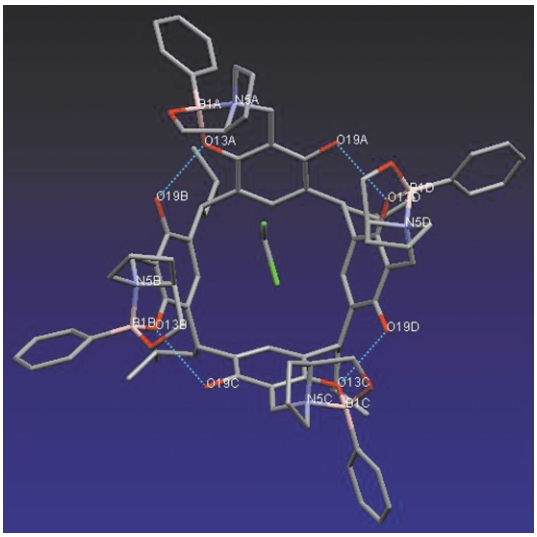


Fig. 2 The crystallographic structure of the bora-oxazino-oxazolidine derivative of resorcarene and L-prolinol (**3b**) with dichloromethane residing within the cavity. The hydrogen bonds are indicated by dotted lines. Hydrogen atoms are omitted for clarity.

Table 1 Selected crystallographic data and bond lengths (Å) for derivatives **3a** and **3b**[a]

	3a	**3b**
Formula	$C_{92}H_{112}B_4N_4O_{12}\cdot 4C_3H_6O$	$C_{92}H_{112}B_4N_4O_{12}\cdot 2CH_3OH\cdot 3CH_2Cl_2$
M	1741.41	1827.96
a/Å	15.381(1)	19.536(1)
b/Å	23.282(1)	19.536(1)
c/Å	29.512(1)	21.881(1)
α/deg	90.00	90.00
β/deg	90.00	90.00
γ/deg	90.00	120.00
V/Å^3	10568.3(9)	7232.2(6)
D_{calc}/g cm^{-3}	1.094	1.259
Z	4	3
Cryst. syst.	Orthorhombic	Trigonal
Space group	$P2_12_12_1$	$P3_1$
R	0.130	0.078
O19A–O13D	2.677	2.806
O19B–O13A	2.701	2.704
O19C–O13B	2.714	2.794
O19D–O13A	2.827	2.665
N5A–B1A	1.670	1.631
N5B–B1B	1.635	1.622
N5C–B1C	1.655	1.655
N5D–B1D	1.585	1.607

[a] CCDC 183052 and 183053. See http://www.rsc.org/suppdata/cc/b2/b206188k/ for crystallographic data in CIF or other electronic format.

Notes and references

1 (*a*) W. Iwanek, Ch. Wolff and J. Mattay, *Tetrahedron Lett.*, 1995, **36**, 8969; (*b*) Ch. Schmidt, T. Straub, D. Falrbu, E. F. Paulus, E. Wegelius, E. Kolehmainen, V. Böhmer, K. Rissanen and W. Vogt, *Eur. J. Org. Chem.*, 2000, 3937; (*c*) W. Iwanek, *Polish J. Chem.*, 1999, **73**, 1777; (*d*) P. C. B. Page, H. Heaney and E. P. Sampler, *J. Am. Chem. Soc.*, 1999, **121**, 6751; (*e*) W. Iwanek, *Tetrahedron: Asymmetry*, 1998, **9**, 3171; (*f*) J. Pfeiffer and V. Schurig, *J. Chromatogr. A*, 1999, **840**, 145; (*g*) M. M. Mocerino, B. W. Skelton and A. H. White, *Org. Lett.*, 2000, **2**, 3869; (*h*) A. D. M. Curtis, *Tetrahedron. Lett.*, 1997, 4295; (*i*) B. Botta, G. D. Monache, M. C. De Rosa, C. Seri, E. Benedetti, R. Iacovino, M. Botta, F. Corelli, V. Masignani, A. Tafi, E. Gacs-Baitz, A. Santini and D. Misiti, *J. Org. Chem.*, 1997, **63**, 1788; (*j*) A. Shivanyuk, Ch. Schmidt, V. Böhmer, E. F. Paulus, O. Lukin and W. Vogt, *J. Am. Chem. Soc.*, 1998, **120**, 4319; (*k*) H. Konishi, T. Tamura, H. Ohkub, K. Kobayashi and O. Morikawa, *Chem. Lett.*, 1996, 685; (*l*) C. Agena, Ch. Wolff and J. Mattay, *Eur. J. Org. Chem.*, 2001, 2977; (*m*) G. Arnott, P. C. B. Page, H. Heaney, R. Hunter and E. Sampler, *Synthesis*, 2001, **3**, 412.

2 (*a*) W. Iwanek and J. Mattay, *Liebigs Ann. Chem.*, 1995, 1463; (*b*) M. T. El Gihani, H. Heaney and A. M. Slavin, *Tetrahedron Lett.*, 1995, **36**, 4905; (*c*) R. Arnecke, V. Boehmer, S. Friebe, S. Gebauer, G. Krauss, I. Thondorf and W. Vogt, *Tetrahedron Lett.*, 1995, **36**, 6221; (*d*) K. Airola, V. Böhmer, E. Paulus, K. Rissanen, Ch. Schmidt, I. Thondorf and W. Vogt, *Tetrahedron*, 1997, **53**, 10709.

3 V. Boehmer, S. Caccamese, G. Prinzipato and Ch. Schmidt, *Tetrahedron Lett.*, 1999, **40**, 5927.

4 *Spectroscopic data for* **3a**: Mp > 300 °C; $[\alpha]^{20}_D$ = +102.0 (*c* = 1.02, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (d, ^3J (H,H) = 3.7 Hz, 12H), 1.08 (d, ^3J (H,H) = 13.7 Hz, 12H), 1.51 (m, 4H), 1.73 (m, 8H), 1.89 (m, 8H), 2.13 (m, 8H), 3.02 (m, 4H), 3.42 (m, 4H), 3.56 (d, ^3J (H,H) = 3 Hz, 4H), 3.64 (d, ^3J (H,H) = 13.7 Hz, 4H), 3.83 (dd, ^3J (H,H) = 6.7 Hz, 4H), 4.03 (d, ^3J (H,H) = 13.7 Hz, 4H), 4.54 (q, ^3J (H,H) = 6.7 Hz, 4H), 7.23 (m, 20H), 7.59 (m, 4H), 8.62 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.27, 23.50, 24.40, 26.32, 30.83, 31.19, 31.74, 42.47, 51.63, 59.79, 67.42, 69.10, 107.05, 123.23, 124.26, 125.33, 127.12, 127.45, 129.00, 133.00, 149.97, 151.89. MS (FAB): *m*/*z* 1508.9 (M^+), 1322.7 ($M^+ - C_{11}H_{14}BNO$), 1134.9 ($M^+ - 2C_{11}H_{14}BNO$), 947.7 ($M^+ - 3C_{11}H_{14}BNO$), 760.3 ($M^+ - 4C_{11}H_{14}BNO$). HR-MS (FAB): *m*/*z* 1508.8967, calc. 1508.8937.

5 *Spectroscopic data for* **3b**: Mp > 300 °C; $[\alpha]^{20}_D$ = +97.3 (*c* = 1.05, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (d, ^3J (H,H) = 6.8 Hz, 12H), 0.93 (d, ^3J (H,H) = 6.8 Hz, 12H), 1.51 (m, 4H), 1.76 (m, 4H), 1.89 (m, 4H), 2.02 (m, 12H), 2.31 (m, 4H), 2.49 (m, 4H), 3.43 (m, 8H), 3.58 (m, 8H), 3.81 (d, ^3J (H,H) = 15.2 Hz), 4H), 4.15 (m, 4H), 4.28 (d, ^3J (H,H) = 15.2 Hz, 4H), 4.51 (q, ^3J (H,H) = 6.8 Hz, 4H), 7.25 (m, 16H), 7.31 (s, 4H), 7.48 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.41, 22,81, 23.47, 23.63, 26.08, 26.18, 26.28, 30.87, 30.91, 42.94, 51.42, 57.95, 66.10, 67.73, 104.06, 123.69, 124.17, 124.67, 127.13, 127.13, 127.34, 127.60, 132.43, 149.67, 150.04. MS (FAB): *m*/*z* 1508.9 (M^+), 1322.6 ($M^+ - C_{11}H_{14}BNO$), 1134.8 ($M^+ - 2C_{11}H_{14}BNO$), 947.8 ($M^+ - 3C_{11}H_{14}BNO$), 760.3 ($M^+ - 4C_{11}H_{14}BNO$). HR-MS (FAB): *m*/*z* 1508.8945, calc. 1508.8937.