Chiral, Non-racemic, Distally-bridged Resorcin[4]arenes as Models for Use in Asymmetric Processes

Gareth Arnott,[a] Philip C. Bulman Page,[b] Harry Heaney,[b] Roger Hunter,*[a] Edward P. Sampler[b]

[a] Department of Chemistry, University of Cape Town, Rondebosch, 7701, South Africa

Fax +27(21)6897499; E-mail: Roger@psipsy.uct.ac.za

[b] Department of Chemistry, Loughborough University, Loughborough, Leicestershire, LE11 3TU, UK.

Fax +44(1509)223926; E-mail: h.heaney@lboro.ac.uk

Received 4 January 2001

Abstract: The synthesis of enantiomerically pure, distally-bridged resorcinarenes **3** with various R groups (CH_3, C_5H_{11}, $C_{11}H_{23}$) is reported. The key step makes use of the Mannich reaction for attachment of a chiral diamine-line **2** across the cavity. Yields for this step are good to excellent. One of the bridged compounds exhibits modest activity (27% ee) as an enantioselective catalyst in the addition of diethylzinc to benzaldehyde.

Key words: bridged resorcin[4]arene, chiral resorcin[4]arene, Mannich reaction, enantioselective catalyst, C_{2v}-symmetric diamine chiral auxiliary

Recent interest in the development of resorcinarenes[1] as molecular receptors[2] has focused on attachment of appropriate groups to the upper rim, and in this regard the Mannich reaction has emerged as a versatile methodology. Use of primary amines with aqueous formaldehyde results in benzoxazine[3] formation involving participation of phenolic hydroxyl groups. Interestingly, reaction to the tetrakis(benzoxazine) level is highly regioselective to afford the C_{4v} product, and completely diastereoselective[4] when using α-chiral amines such as α-methylbenzylamine. The latter discovery has been used to prepare the first[5] inherently chiral enantiomerically pure resorcin[4]arenes as a new class of asymmetric receptor. Extension of the benzoxazine approach to afford distally-bridged benzoxazine derivatives with C_{2v} symmetry by using primary diamines has been reported by Böhmer.[6] Our interest in distally-bridged[7] chiral resorcinarenes, centres on developing the asymmetric environment in the line to catalytic and other processes. In this communication, we report on the synthesis of the first chiral, non-racemic, distally-bridged resorcin[4]arenes based on α-methylbenzylamine as the chiral source, and the application of one of them to the enantioselective addition of diethylzinc to benzaldehyde.

In designing the target it was decided to place a chiral auxiliary on each nitrogen of the line bridging the cavity in order to generate a C_{2v}-symmetric target, and an α-methylbenzyl group from α-methylbenzylamine was chosen for this purpose. Such a choice precluded the possibility of using a benzoxazine formation / hydrolysis sequence as used by Böhmer.[6,8] However, our choice was felt to be justified since secondary amines had been shown by Matsushita[9] to aminomethylate the upper rim of resorcinarenes under standard Mannich conditions (aqueous formaldehyde / sec amine). In the event, however, these conditions failed to give the desired-bridged compound and a new set of reaction conditions were developed. A second crucial feature was the necessity to produce quantities of an appropriate C_{2v}-symmetric tetra-substituted resorcinarene with distal rings available for Mannich functionalisation. Tetra-tosylation of C-methyl and C-pentyl resorcinarenes as reported in the literature[10] using tosyl chloride (4 eq) and triethylamine (4 eq) in acetonitrile, and with precipitation of the products, produced tetra-tosylates **1a** and **1b**. By comparison, formation of the tetra-tosylate of C-undecyl resorcinarene required changing the solvent to tetrahydrofuran and the use of column chromatography (no precipitation) to produce **1c** in 41% yield. Protection in the undecyl series with benzyl chloroformate similarly required THF as solvent and column chromatography for isolation, but the resultant tetra-carbonate proved to be unsuitable for further elaboration in view of competing base-catalysed migrations around the ring during Mannich functionalisation (Figure 1).

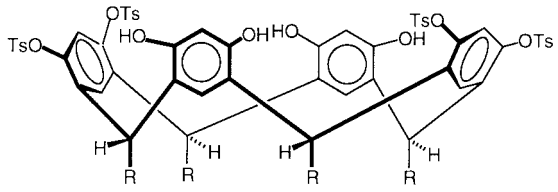
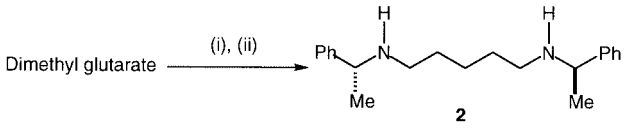


Figure 1 **1a**, R = CH_3; **1b**, R = n-C_5H_{11}; **1c**, R = $C_{11}H_{23}$

Synthesis of the chiral diamine bridging group was straightforward involving thermal amide formation using α-methylbenzylamine and dimethyl glutarate to the diamide followed by reduction ($LiAlH_4$/ THF / Δ) and isolation using salt precipitation following addition of a triethylamine / water mixture. Conventional column chromatography furnished the pure diamine **2** in around 50% overall yield for the two steps. Compound **2** gave satisfactory NMR data and could be unambiguously characterised as its crystalline *bis*-hydrochloride salt or *bis*-toluene-*p*-sulfonamide.[11] Both enantiomers of **2** were prepared in identical optical purity.

Heating the diamine **2** under reflux with the resorcin[4]arene **1c** using the Matsushita conditions of aqueous formaldehyde in ethanol with a catalytic amount of glacial acetic acid only succeeded in substituting the non-

Downloaded by: National University of Singapore. Copyrighted material.



Scheme (i) (*R*)-α-methylbenzylamine (3 eq.) / Δ; (ii) $LiAlH_4$ / THF / Δ

protected phenolic rings of **1c** with ethoxymethyl groups. The participation of ethanol as nucleophile under these conditions suggested that a set of conditions needed to be developed in which the possibility of competing nucleophilic interception was minimised. Gratifyingly, on heating **1c** under reflux with the diamine **2** in a 1:1.2 ratio in the presence of an excess of paraformaldehyde in 1,4-dioxane at moderate dilution (0.02M of tosylate) furnished the desired bridged compound **3c** in about 40% yield after column chromatography. Repeating the same reaction in acetonitrile at 100 ºC in a sealed tube for 30 minutes succeeded in raising the yield to a reproducible 56-67% over several runs. Similarly, using the same conditions, bridged compounds **3a**[12] (58-61% over three runs), and **3b** (75% over two runs) could also be synthesised (Figure 2).

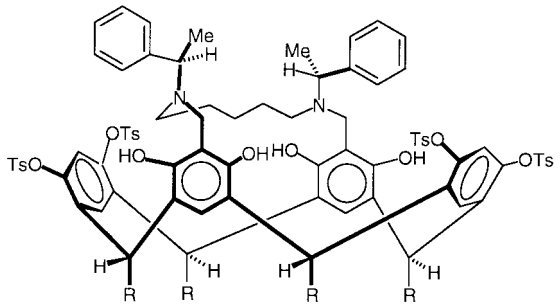


Figure 2 **3a**, R = CH_3; **3b**, R = n-C_5H_{11}; **3c**, R = $C_{11}H_{23}$

Compounds **3a-c** displayed extremely non-polar chromatographic characteristics for diamines, running on TLC in ethyl acetate/light petroleum systems depending on the nature of R (e.g. R_f = 0.6 for **3c** in ethyl acatate:light petroleum = 3:7). Compounds **3b** and **3c** with the larger R groups proved more difficult to purify chromatographically than **3a**, always eluting with traces (<5%) of a marginally less polar contaminant that prevented correct combustion analysis and optical rotation data being obtained. By comparison, the bridged compound **3a** was crystalline and returned excellent spectroscopic and microanalytical data,[12] as well as parity in the specific rotations of the (*R, R*) and (*S, S*) antipodes. The ^{1}H NMR spectra of compounds **3a-c** required being recorded at 50 ºC to avoid line broadening, and revealed a stoichiometric ratio of 1:1 between the diamine-line and the resorcinarene. Three singlets for two sets of aromatic rings, confirmed that distal aromatic substitution had taken place, while only **3a** revealed the diastereotopicity of the benzylic methylene protons as an AB pair of doublets. Evidence that the line lies over the cavity in compounds **3a-c** was provided by NMR chemical shifts. Thus, in their ^{1}H spectra, upfield shifts occurred in the methylene group resonances going from diamine **2** to bridged compounds **3a-c**. Such shifts increased on passing from the α- to the β- and γ-carbons, and with increasing size of R group (Table).

Table ^{1}H NMR[a] shifts in line[b] of compounds **3a-c**

C-H [c]	*R = CH₃*	*R = C₅*	*R = C₁₁*
Benzylic	+0.08	+0.08	+0.06
α	-0.25	-0.31	-0.33
β	-0.40	-0.65	-0.63
γ	-0.41	-0.59	-0.61

[a] recorded on a 400 MHz instrument
[b] in ppm relative to diamine **2** and with negative values = upfield
[c] H on line relative to nitrogen

In conclusion, we have synthesised the first chiral, non-racemic, distally-bridged resorcinarenes as models for a number of processes that use chiral materials. As an example, reaction of **3c** with diethylzinc[13] and benzaldehyde in THF at room temperature afforded 1-phenyl-1-propanol in 27% ee.[14] Further studies will focus on elaborating the bridged resorcinarenes into more effective reagents.

Typical experimental procedure

The tetra-tosylate (0.5 mmol), paraformaldehyde (10 mmol, 10 eq), and the diamine (**2**) (0.6 mmol, 1.2 eq) were heated together in dry acetonitrile (25 ml, 0.02 M in tosylate) in a sealed tube (thick glass wall with teflon pressure screw-tap) for 30 minutes. On cooling, the vessel was opened, the contents filtered (to remove unreacted paraformaldehyde) and solvent evaporated to afford a crude residue which was subjected to column chromatography directly without work-up. Eluent ethyl acetate: light petroleum (bp 60-80 °C) = 2:1 to 1:1 depending on the R group present in the resorcinarene; yields 60-80% of bridged compounds.

Acknowledgement

This work was initiated at Loughborough (by R.H.) during a period of study leave. We thank the National Research Foundation, Pretoria, Fine Chemicals Corporation, Cape Town, and the EPSRC (UK), for financial support.

References and Notes

(1) (a) Timmerman, P.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1996**, *52*, 2663-2704; (b) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995,** *34*, 713-745; (c) Mclldowie, M.; Mocerino, M.; Skelton, B. W.; White, A. H. *Org. Lett.* **2000**, *2*, 3869-3871.
(2) (a) Higler, I.; Boerrigter, H.; Verboom, W.; Kooijman, H.; Spek, A. I.; Reinhoudt, D. N. *Eur. J. Org. Chem.* **1998**, 1597-1607; (b) Shivanyuk, A.; Spaniol, T. P.; Rissanen, K.; Kolehmainen, W.; Böhmer, V. *Angew. Chem., Int. Ed.* **2000**, *39*, 3497-3500.
(3) Airola, K.; Böhmer, V.; Paulus, E. F.; Rissanen, K.; Schmidt, C.; Thondorf, I.; Vogt, W. *Tetrahedron* **1997**, *53*, 10709-10724.

Downloaded by: National University of Singapore. Copyrighted material.

(4) (a) El Gihani, M. T.; Heaney, H. *Tetrahedron Lett*. **1995**, *36*, 4905-4909; (b) Iwanek, W.; Mattay, J. *Liebigs Ann*. **1995**, 1463-1466; (c) Arnecke, R.; Böhmer, V.; Friebe, S.; Gebauer, S.; Krauss, G. J.; Thondorf, I.; Vogt, W. *Tetrahedron Lett*. **1995**, *36*, 6221-6224; (d) Iwanek, W. *Tetrahedron: Asymmetry* **1998**, *9*, 4289-4290.

(5) Bulman Page, P. C.; Heaney, H.; Sampler, E. P. *J. Am. Chem. Soc*. **1999**, *121*, 6751-6752.

(6) Shivanyuk, A.; Schmidt, C.; Böhmer, V.; Paulus, E. F.; Lukin, O.; Vogt, W. *J. Am. Chem. Soc*. **1998**, *120*, 4319-4326.

(7) For cases of both upper and lower-rim, distally-bridged calix[4]arenes: (a) Wieser- Jeunesse, C.; Matt, D.; De Cian A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2861-2864; (b) Ross, H.; Lüning, U. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 2555-2557; (c) Sharma, S. K.; Gutsche, C. D. *J. Org. Chem*. **1999**, *64*, 998-1003; (d) Saiki, T.; Goto, K.; Okazaki, R. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2223-2224; (e) Morikawa, O.; Nakanishi, K.; Miyashiro, M.; Kobayashi K.; Konishi, H. *Synthesis* **2000**, *233*; (f) Ito, K.; Yamamori, Y.; Ohba, Y.; Sone, T. *Synth. Commun*. **2000,** *30*, 4343-4351.

(8) Schmidt, C.; Airola, K.; Böhmer, V.; Vogt, W.; Rissanen, K. *Tetrahedron* **1997**, *53*, 17691-17698.

(9) Matsushita, Y.; Matsui, T. *Tetrahedron Lett*. **1993**, *34*, 7433-7436.

(10) (a) Shivanyuk, A.; Paulus, E. F.; Böhmer, V.; Vogt, W. *J. Org. Chem*. **1998,** *63*, 6448-6449; (b) Lukin, O.; Shivanyuk, A.; Pirozhenko, V. V.; Tsymbal, I. F.; Kalchenko, V. I. *J. Org. Chem*. **1998**, *63*, 9510-9516.

(11) Data for the bis(*p*-toluenesulfonamide) of **2**: mp 106-108 ºC (ether) (Found: C, 67.92; H, 6.91; N, 4.60; S, 10.04. $C_{35}H_{42}N_2O_4S$ requires C, 67.93; H, 6.84; N, 4.53, S, 10.36%); $[\alpha]_D$ for (*R*,*R*) = +19.4 (c 1.15 in $CHCl_3$), for (*S*,*S*) = -19.1 (c 1.19 in $CHCl_3$); ^1H (300 MHz, $CDCl_3$) 0.80 (2H, m, γ-CH_2), 0.95 (2H, m, β-CH_2), 1.20 (2H, m, β-CH_2), 1.32 (6H, d, *J* 7.2 Hz, CH_3), 2.43 (6H, s, CH_3), 2.84 (4H, m, α-CH_2), 5.13 (2H, q, *J* 7.2 Hz, CH), 7.23 (10H, m, Ar), 7.28 (4H, m, Ar), 7.71 (4H, m, Ar); ^{13}C (75.5 MHz, $CDCl_3$) 16.55, 21.47, 24.14, 29.94, 43.89, 55.18, 127.09, 127.50, 127.53, 128.25, 129.60, 138.39, 140.35, 142.95

(12) Data for **3a**: mp 150-157 ºC (ether / CH_2Cl_2) (Found: C, 66.70; H, 5.83; N, 1.92; S, 8.32. $C_{83}H_{86}N_2O_{16}S_4$ requires C, 66.64; H, 5.79; N, 1.87; S, 8.57%); [α[$_D$ for (*R*,*R*) = +8.3 (c 1.14 in $CHCl_3$), for (*S*,*S*) = -8.8 (c 1.06 in $CHCl_3$); ^1H (400 MHz, $CDCl_3$) 0.89 (2H, m, γ-CH_2), 1.04 (4H, m, β-CH_2), 1.36 (12H, d, *J* 6.8 Hz, CH_3), 1.42 (6H, d, *J* 6.8 Hz, CH_3), 2.10 (2H, m, α-CH_2), 2.26 (2H, m, α-CH_2), 2.48 (12H, s, CH_3), 3.71 (2H, d, J_{AB} 16.4 Hz, CH_2 benzylic), 3.78 (2H, d, J_{AB} 16.4 Hz, CH_2 benzylic), 3.84 (2H, q, *J* 6.8 Hz, CH benzylic$_N$), 4.54 (4H, m, CH benzylic$_C$), 6.79 (2H, s, Ar), 6.83 (br s, Ar), 7.11 (2H, s, Ar), 7.26 (10H, m), 7.39 (8H, m), 7.96 (8H, m); ^{13}C (100.6 MHz, $CDCl_3$) selected resonances: 16.96 (CH_3), 21.66, 21.77 (2 × CH_3 of Ts), 25.28, 25.36 (β- and γ- CH_2), 30.93, 31.04 (CH benzylic$_C$), 49.13 (CH_2 benzylic$_N$), 51.08 (α-CH_2), 61.49 (CH benzylic$_N$), 115.18 (resorc C-H), 123.11 (resorc C-H), 127.68 (resorc C-H).

(13) (a) Näslund, J.; Welch, C. J. *Tetrahedron: Asymmetry* **1991**, *2*, 1123-1126; (b) Soai, K.; Hirose, Y.; Sakata, S. *Bull. Chem. Soc. Jpn*. **1992**, *65*, 1734-1735.

(14) The reaction was carried out in toluene at RT according to conditions described in ref. 13 (a) using 0.05 eq of catalyst. The ee was ascertained using chiral HPLC on a Chiralcel OD column and eluting with hexane:isopropanol = 98:2. The major isomer had the *(R)*-configuration.

Article Identifier:
1437-2096,E;2001,0,03,0412,0414,ftx,en;L21900ST.pdf

Downloaded by: National University of Singapore. Copyrighted material.