Synthesis of the First Chiral, Functionalised-Bridged Resorcinarenes in Asymmetric Catalysis: Evidence for Intracavity Asymmetric Catalysis

Gareth Arnott,[a] Harry Heaney,[b] Roger Hunter,*[a] and Philip C. B. Page[b]

Keywords: Bridged resorcinarenes / Chiral resorcinarenes / Diethylzinc addition / Asymmetric catalysis / Intracavity catalysis

Methodology is presented for synthesis of the first examples of chiral, bridged resorcinarenes with functionality in the bridge as possible sites for intracavity asymmetric catalysis. A preliminary study comparing unfunctionalised with functionalised lines using the enantioselective addition of diethylzinc to benzaldehyde as a probe reaction, provides compelling evidence for intracavity catalysis.

Introduction

Nature has set a supreme ideal before the synthetic chemist in the form of enzymes that can efficiently, regio- and stereoselectively catalyse a vast array of organic transformations under mild conditions. A synthetic example has yet to be produced that can match or even rival enzymes in their rate acceleration, turnover and specificity.[1] Chiral calixarenes and resorcinarenes offer intriguing possibilities as potential enzyme mimics, but these frameworks have been developed in mainly chiral recognition and discrimination studies.[2] Although the literature contains examples of calixarenes and resorcinarenes that are used as catalysts,[3] very few papers describe asymmetric catalysis. Indeed, an example of an asymmetric reaction occurring on or in the bowl of resorcinarenes has yet to be reported. Matt has shown that a lower-rim, inherently chiral calixarene scaffold can be used in allylic alkylation (palladium) and hydrogenation (rhodium), though low *ee*s were obtained.[4] Others have shown that cooperative effects may potentially be provided by supramolecular interactions involving the concave bowl.[5] However, a comprehensive picture has yet to emerge regarding application of directing effects in the bowl towards designing superior asymmetric catalysts for carrying out reactions rather than purely for recognition phenomenon.

Our research in the area of asymmetric catalysis has focused on developing chiral bridged resorcinarenes[6] in conjunction with cooperative effects in the bowl. In this paper, we report on methodology for successful synthesis of the first examples of chiral bridged resorcinarenes with functionality in the bridge that provides sites for intracavity catalysis, particularly through transition-metal coordination. The methodology extends the use of Mannich technology for attaching a line across the cavity,[6,7] and by using the addition of diethylzinc to benzaldehyde as a probe reaction, we provide compelling evidence for intracavity reactions involving functionality in the line.

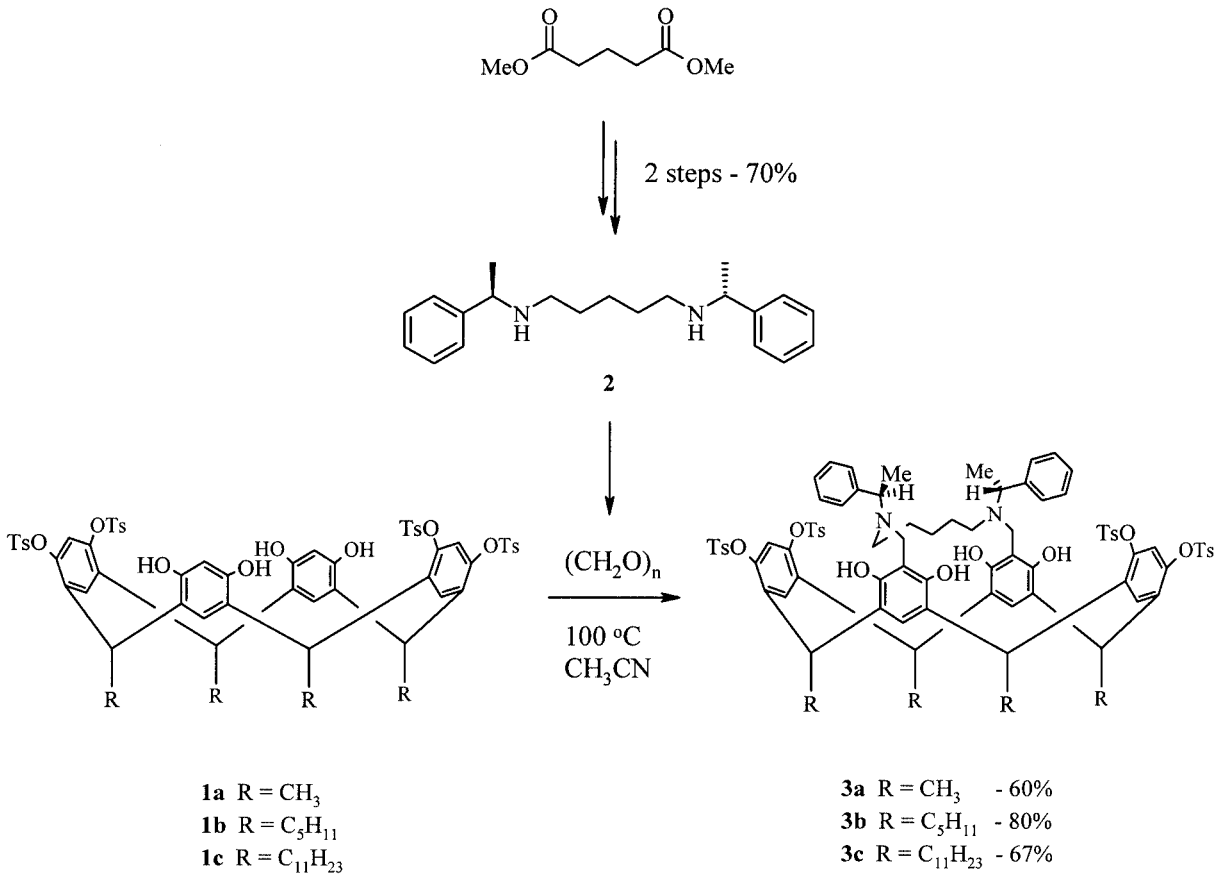
Results and Discussion

Our preliminary studies[6] were conducted on bridged resorcinarene tetratosylates **3a**−**c** involving an unfunctionalised line. These could be synthesized by the double Mannich reaction between resorcinarene tetratosylates **1a**−**c**, chiral diamine **2** and excess paraformaldehyde in moderate to good yields (Scheme 1). Resorcinarene tetratosylates **1a**−**c** were prepared by modification of the methodology reported by Shivanyuk and Böhmer,[8] using tosyl chloride (4 equiv.) with triethylamine (4 equiv.) in THF.

The mechanism of the catalysed enantioselective addition reaction of diethylzinc to benzaldehyde (aldehydes) has been exhaustively studied in recent years, with many catalysts now able to achieve *ee*s in excess of 95%.[9] A comprehensive mechanistic picture has emerged in which amino alcohols are postulated to form zincoxazine intermediates that act as templates for catalysis.[10] In view of the presence of hydroxyamine functionality in **3a**−**c**, we decided to explore the use of the diethylzinc addition reaction as a possible mechanistic probe for attempting to develop the bridged compounds as asymmetric catalysts. Indeed, in our preliminary communication we established catalytic activity

[a] Department of Chemistry, University of Cape Town, Rondebosch 7701, South Africa
Fax: (internat.) +27-21-689-7499
E-mail: roger@science.uct.ac.za
[b] Department of Chemistry, Loughborough University, Leicestershire, LE11 3TU, United Kingdom
Fax: (internat.) +44-1509-222555
E-mail: H.Heaney@lboro.ac.uk

  DOI: 10.1002/ejoc.200400615



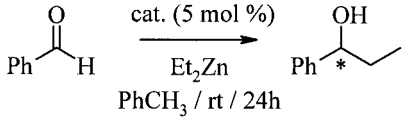
1a R = CH_3
1b R = C_5H_{11}
1c R = $C_{11}H_{23}$

3a R = CH_3 - 60%
3b R = C_5H_{11} - 80%
3c R = $C_{11}H_{23}$ - 67%

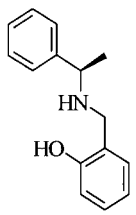
Scheme 1. General synthesis of bridged resorcinarenes

at a modest level of *ee* with a 5% loading of catalyst.[6] In this paper we now report that varying the length of the pendent R group, while keeping the bridge length constant (5 carbon atoms), reveals a significant influence on the enantioselectivity. Table 1 compares these results with those from **4**, an *o*-hydroxybenzylamine with structural characteristics similar to our catalysts, that has been investigated by Palmieri,[11] and which returned only a modest enantioselectivity for the same reaction.

Table 1. Results for the asymmetric addition of diethylzinc using bridged resorcinarenes as ligands



cat.	R	*ee*	*R/S*
3a	CH_3	12%	*R*
3b	C_5H_{11}	41%	*R*
3c	$C_{11}H_{23}$	52%	*R*
4	.	16%	*S*

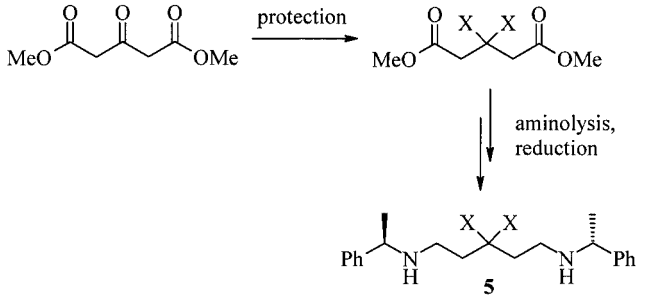


4

Two things were immediately evident from these results. Firstly, the absolute configuration of the major product was reversed, i.e. (*R,R*)-bridged resorcinarenes **3a**−**c** gave (*R*)-1-phenylpropanol, whereas Palmieri's (*R*)-*o*-hydroxybenzylamine **4** gave (*S*)-1-phenylpropanol. Secondly, the enantioselectivity increased with lengthening of the resorcinarene pendant R groups. These initial results drew attention to the possible involvement of the cavity in influencing the stereochemical outcome of the reaction. ^{1}H NMR studies on resorcinarenes **3a**−**c** reveal small (about 0.2 ppm), but significant upfield shifts of the signals for the central bridge methylene protons of **3b** and **3c**. Such shifts indicate that the line resides deeper within the cavity for **3b** and **3c**, and this results in a change in the available space in the bowl,[12] which in turn seems likely to have a bearing on the *ee* values observed. Encouraged by these results, it was decided to turn our attention to the synthesis of a more complex bridged resorcinarene with functionality in the line, for possible coordination to zinc in the addition reaction.

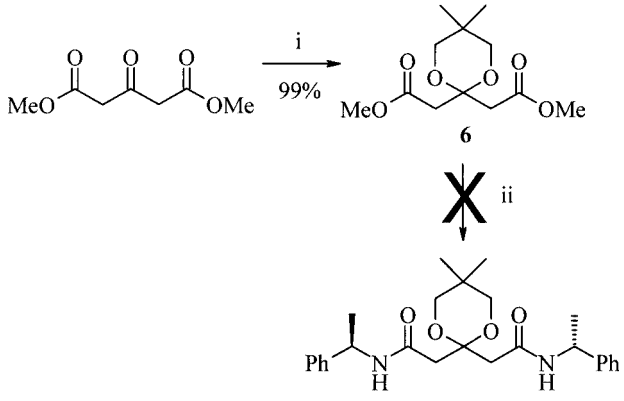
Initially, a synthetic strategy similar to that for the formation of the model line **2** was envisaged. It was hoped that by starting with dimethyl 3-oxopentanedioate, the desired intermediate **5** would be available in a few, short steps, as shown in Scheme 2. Protection of the ketone to form a ketal would provide possible donor sites, hopefully for coordination of a transition-metal to the bridge in the final product.

Protection of dimethyl 3-oxopentanedioate by standard methods,[13] however, failed in our hands. Eventually, ketalisation was realised using Noyori's powerful protocol[14]



Scheme 2. Envisaged synthesis of protected functionalised diamine

involving neopentyl glycol disilyl ether with TMSOTf (cat) at low temperature to afford **6** in essentially quantitative yield, Scheme 3. Unfortunately, the thermal aminolysis of diester **6** using α-methylbenzylamine failed, giving a plethora of product spots on the TLC plate.

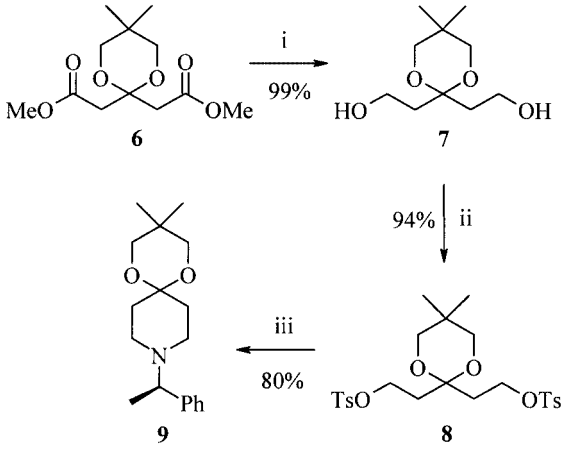


Scheme 3. Reagents and conditions: i) neopentylglycol disilyl ether, TMSOTf (cat), DCM, −20 °C to room temp.; ii) α-methylbenzylamine, 100 °C

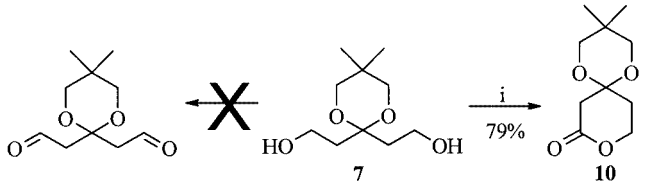
It was hoped that introduction of the chiral auxiliaries could be achieved by a double S_N2 reaction on diol **7** with α-methylbenzylamine (Scheme 4), even though α-methylbenzylamine is known to be a poor nucleophile and requires vigorous reaction conditions for alkylation.[15] To this end, ketal diester **6** was successfully reduced using lithium aluminium hydride, and then converted into its bis-tosylate in the usual manner. Unfortunately, S_N2 displacement with excess α-methylbenzylamine resulted in a high yield of the cyclized piperidine product **9**, with no trace of the desired product.[16]

We next considered a sequence involving double oxidation of diol **7** to the dialdehyde, followed by treatment with α-methylbenzylamine under reductive amination conditions.[17] Unfortunately, this proved to be unsuccessful under standard Swern conditions, while TPAP oxidation[18] gave only lactone **10** (Scheme 5).

It was therefore necessary to opt for a longer reaction sequence, which involved the introduction of the α-methylbenzylamine in a stepwise fashion. Thus, the diol was protected as its benzoate to give **11** in moderate yield (Scheme 6). The resultant alcohol was oxidised under



Scheme 4. Reagents and conditions: i) $LiAlH_4$, THF, 0 °C; ii) TsCl, Et_3N, DCM, room temp.; iii) α-methylbenzylamine, CH_3CN, 50 °C



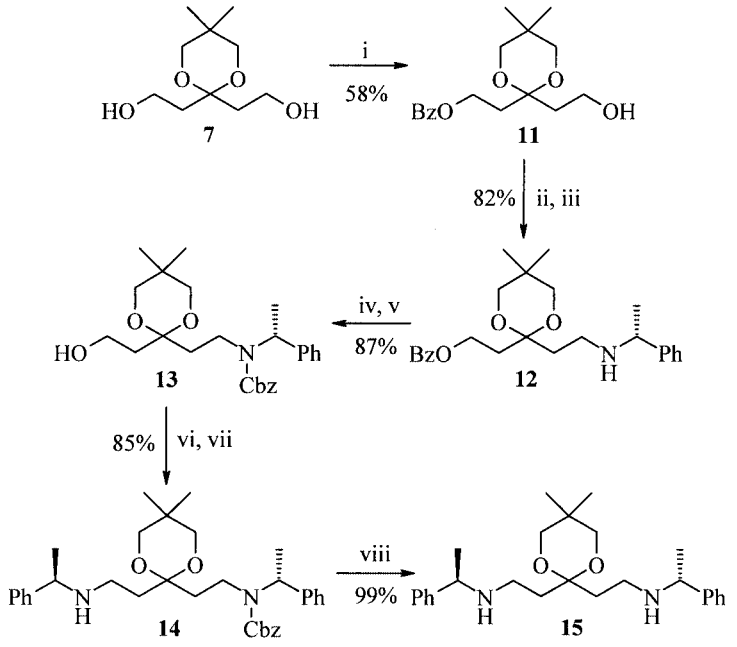
Scheme 5. Reagents and conditions: i) TPAP (5%), NMO, 4-Å sieves, DCM, room temp.

Swern conditions to give the aldehyde, which underwent reductive amination with α-methylbenzylamine and sodium borohydride to furnish monoamine **12** in a high overall yield.

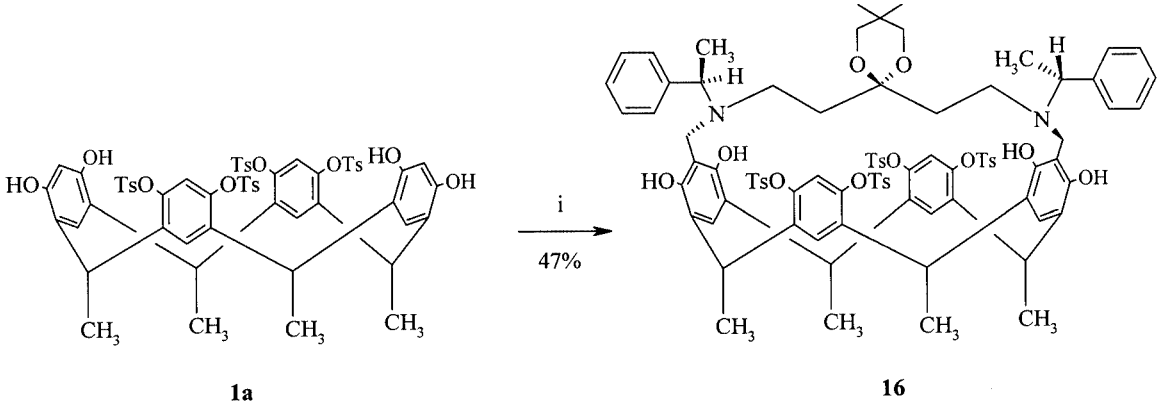
With one auxiliary in place, the process needed to be repeated at the other end of the molecule. Protection of **12** was carried out because it was anticipated that its secondary amino group would cyclize by addition to the aldehyde formed. Protection was successfully achieved with benzyl chloroformate, to afford the *N*-CBz derivative, which was chemoselectively deprotected using potassium hydroxide at room temperature to give alcohol **13** (Scheme 6). Oxidation of **13** to the aldehyde followed by reductive amination with α-methylbenzylamine then gave amine **14**, which on hydrogenolysis of the protecting group over palladium, quantitatively furnished the desired ketal diamine **15** (Scheme 6).

Ketal-protected diamine **15** was now used to bridge the resorcinarene tetratosylate **1a**. Using the same reaction conditions developed for the model system gave the desired bridged product **16**, albeit in a low overall yield of 22%. The reaction yield could be optimised by reducing the temperature to 85 °C and increasing the reaction time to one hour to return a best yield of 47% after column chromatography. (Scheme 7).

In view of the large steric bulk of the dioxane ketal, it was decided to compare catalysis using the smaller dimethoxy ketal group in which the space in the bowl would be increased while retaining coordination possibilities. The relevant ketal diamine for Mannich coupling could be



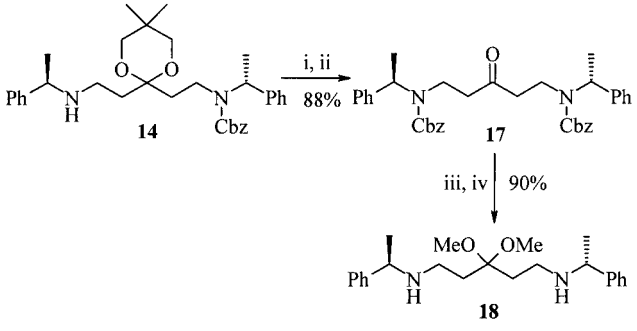
Scheme 6. Reagents and conditions: i) BzCl, Et_3N, DCM, 0 °C to room temp.; ii) DMSO, oxalyl chloride, Et_3N, −78 °C; iii) α-methylbenzylamine, $NaBH_4$, 3-Å sieves, MeOH, 0 °C to room temp.; iv) Benzyl chloroformate, iPr_2NEt, DCM, 0 °C; v) KOH, EtOH, room temp.; vi) oxalyl chloride, DMSO, Et_3N, DCM, −78 °C; vii) α-methylbenzylamine, $NaBH_4$, 3Å sieves, MeOH, 0 °C to room temp.; viii) Pd/C, H_2, EtOH, room temp.



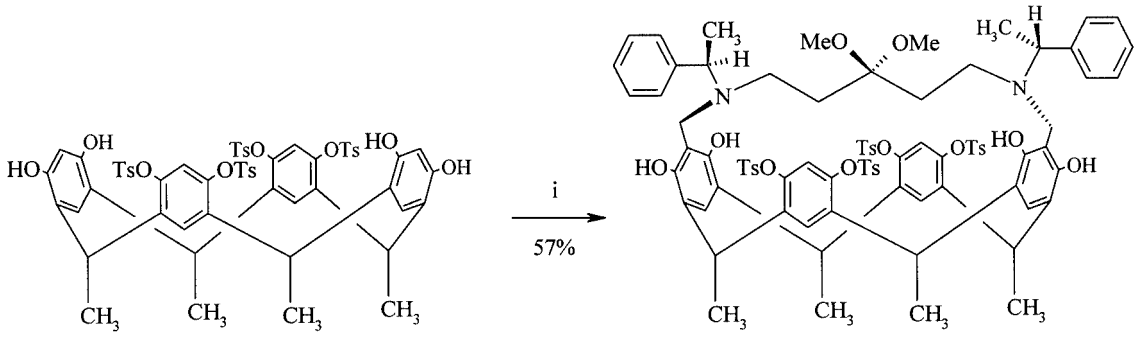
Scheme 7. Reagents and conditions: i) diamine **15**, $(CH_2O)_n$, CH_3CN, 85 °C

accessed from the advanced amine intermediate **14** (Scheme 8), by protection of the secondary amino group with benzyl chloroformate followed by deprotection of the ketal product under acidic conditions to give ketone **17**. This was reprotected as a dimethoxy ketal using Noyori's ketalisation methodology followed by deprotection of the carboxybenzyl group by hydrogenolysis over palladium to give the desired diamine **18** in good overall yield.

Exposure of the diamine **18** to the bridging reaction conditions used before resulted in the formation of the desired bridged resorcinarene **19** in low yield (approximately 20%). TLC shows a complex mixture of polar products, which were inseparable and could not be identified, although NMR spectroscopic evidence suggested resorcinarene derivatives. Heating the bridged-product **19** in acetonitrile at



Scheme 8. Reagents and conditions: i) benzyl chloroformate, iPr_2NEt, DCM, 0 °C; ii) TsOH (cat), acetone, room temp.; iii) TMSOMe, TMSOTf (cat.), DCM, −20 °C; iv) Pd/C (10%), H_2, EtOH, room temp.



1a **19**

Scheme 9. Reagents and conditions: i) diamine **18**, $(CH_2O)_n$, CH_3CN, 85 °C

100 °C, resulted in rapid decomposition to the more polar spots seen on the reaction TLC. Thus, a detailed study was carried out to identify reaction conditions that would optimise product formation with minimal product degradation. Optimal conditions were established that involved heating in acetonitrile at 85 °C for one hour with excess diamine (1.6 equiv.), to return an acceptable yield of 57%.

With the bridged resorcinarene ketals in hand, attention was turned to testing for intracavity catalysis using the diethylzinc reaction as a mechanistic probe. Reactions using individual bridged ketals as catalysts at a 5% loading and under the same conditions of solvent (toluene) and temperature (room temperature) as the unfunctionalised bridged compounds returned an extremely interesting set of results, which are presented in Table 2.

Table 2. Results for diethylzinc probe reactions

Catalyst	Ketal	% Product	*ee*	*R*/*S*
3a	[none]	91	12%	*R*
16	dioxane	85	34%	*R*
19	dimethoxy	85	51%	*S*

The results are striking in that the smaller dimethoxy ketal **19** brought about a complete reversal in enantioselectivity bias from 34% (*R*) to 51% (*S*). This important result strongly suggests direct involvement of the ketal group as a coordination site to the zinc, and this implies intracavity catalysis in view of the position of the ketal in the middle of the line. A simplistic model for explaining the reversal of enantioselectivity bias involves extracavity versus intracavity delivery of the ethyl group in which face selectivity on the aldehyde is reversed.

Conclusion

The results in this paper demonstrate two important features of interest to the application of chiral resorcinarenes. Firstly, methodology is presented for the synthesis of chiral, bridged resorcinarenes with functionality in the line, and hence over the middle of the cavity. Secondly, this is considered to provide a platform for transition-metal coordination of relevance to catalysis, and this principle is demonstrated by the dimethoxy ketal bridged case in the enantioselective addition of diethylzinc to benzaldehyde. This is considered to be the first reported example of using the bowl of an asymmetrically functionalised resorcinarene for promoting asymmetric catalysis, as suggested recently by Iwanek.[19] As such, it establishes a platform for the introduction of many structural modifications that may fine tune this principle of developing the bowl for processes of enzyme mimicry.

Experimental Section

General Remarks: All reactions were carried out under nitrogen using dry solvents. Nuclear Magnetic Resonance spectra were recorded with a Varian Unity 400 (100 MHz for ^{13}C) or Varian Mercury 300 MHz (75 MHz for ^{13}C), and were carried out in [D_1]chloroform. Optical rotations were obtained using a Perkin−Elmer 141 polarimeter at 20 °C. Melting points were obtained using a Reichert Jung Thermovar hot-stage microscope and are uncorrected. Elemental analyses were performed using a Fisons EA 1108 CHN elemental analyser. Infrared spectra were recorded with a Perkin−Elmer Paragon 1000 FT-IR spectrometer in either dichloromethane or chloroform. Enantiomeric excesses were determined by chiral GC with a Hewlett Packard HP 5890 Gas Chromatograph, using a modified β-cyclodextrin glass capillary column (heptakis-2,3-di-*O*-acetyl-6-O-TMBMS-β-CD) and helium as a carrier gas.

General Procedure for the Synthesis of 1-Phenylpropanol: To a predried Schlenk tube was added catalyst (0.025 mmol) and 1 M diethylzinc in toluene (1 mmol, 1 mL) at −20 °C. The solution was stirred for 15 minutes followed by the addition of 1 M benzaldehyde in toluene (0.5 mmol, 0.5 mL). The reaction vessel was then sealed and warmed slowly to room temperature. After 16 h, the reaction was checked (TLC) for complete consumption of benzaldehyde. On completion, the reaction was cooled to 0 °C and quenched by the slow addition of 1 M HCl (1 mL), and then extracted from water (20 mL) with dichloromethane (3 × 20 mL). The organic extracts were dried with magnesium sulfate and reduced in the usual manner. Flash chromatography (5 g SiO_2, eluting with ethyl acetate/

petroleum ether, 3:17) afforded 1-phenylpropanol as a clear oil. The enantiomeric excess was determined by chiral GC.

Dimethyl 3-(5,5-Dimethyl-1,3-dioxan-2-yl)pentanedioate (6): TMS triflate (0.1 mL, 0.4 mmol) was added to dry dichloromethane (5 mL), and then cooled to −20 °C. 2,2-Dimethyl-1,3-bis(trimethylsilyloxy)propane (8.87 g, 36 mmol) was added slowly, followed by dimethyl acetonedicarboxylate (5.39 g, 30 mmol) in dichloromethane (5 mL). The reaction was warmed to room temperature, and stirred for 18 h. On completion (TLC), the reaction was cooled to 0 °C and quenched with pyridine (0.8 mL). The quenched reaction was then added to saturated sodium carbonate (100 mL) and extracted three times with ethyl acetate (100 mL). The organic phase was dried with magnesium sulfate and the solvent removed under reduced pressure. The crude oil obtained was then subjected to column chromatography (200 g silica gel, eluting with ethyl acetate/petroleum ether, 3:7), to give **6** (7.74 g, 99%) as a clear oil. IR (CH_2Cl_2, cm^{-1}): $\tilde{\nu}$ = 2955 s and 2873 s (−CH_3), 1737 s (C=O, ester), 1438 s, 1365 m, 1354 m. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 0.93 (s, 6 H, −CH_3 × 2), 3.05 (s, 4 H, H-2,4), 3.53 (s, 4 H, H-1′), 3.66 (s, 6 H, −OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 22.6 (−CH_3), 29.9 (C-2′), 39.4 (C-2,4), 51.8 (−OCH_3), 70.7 (C-1′), 97.0 (C-3), 169.8 (C-1,5). HRMS: *m*/*z* (rel. int.) = 261.1335 (0.3) [M^+ + H]; $C_{12}H_{21}O_6$ requires 261.1338; , 187 (100), 143 (58), 101 (98), 69 (73).

3-(5,5-Dimethyl-1,3-dioxan-2-yl)pentane-1,5-diol (7): Diester **6** (7.59 g, 29 mmol) was dissolved in dry THF (300 mL) and the solution cooled to 0 °C. Lithium aluminium hydride (2.27 g, 60 mmol) was then added very slowly so as to prevent excessive foaming. After five minutes the reaction was quenched by the slow addition of water (2.3 mL), then 1 M sodium hydroxide (4.6 mL) and finally water (4.6 mL). The mixture was stirred at room temperature for one hour to completely decompose the lithium salts. The solid material was filtered off through Celite® and washed with dichloromethane (250 mL). The organic solvents were then removed under reduced pressure to give diol **7** (5.72 g, 97%) as a clear oil. IR (CH_2Cl_2, cm^{-1}): $\tilde{\nu}$ = 3531 s (−O−H), 2961 s, 2874 s (−CH_3), 1472 s, 1367 m, 1352 m. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 0.94 (s, 6 H, −CH_3 × 2), 2.01 (t, *J* = 5.9 Hz, 4 H, H-2,4), 2.91 (br., 2 H, OH), 3.52 (s, 4 H, H-1′), 3.75 (t, *J* = 5.9 Hz, 4 H, H-1,5). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 22.7 (−CH_3), 29.8 (C-2′), 36.2 (C-2,4), 58.5 (C-1,5), 70.3 (C-1′), 101.1 (C-3). HRMS: *m*/*z* (rel. int.) = 203.1275 (0.01) [M^+ − H]; $C_{10}H_{19}O_4$ requires 203.1283; 159 [M^+ − C_2H_5O] (100), 73 (96), 69 (75).

3-(5,5-Dimethyl-1,3-dioxan-2-yl)-5-hydroxypentyl Benzoate (11): Diol **7** (3.04 g, 15 mmol) and triethylamine (2.5 mL, 18 mmol) were added to dichloromethane (100 mL) and the solution cooled to 0 °C. A solution of benzoyl chloride (1.73 mL, 15 mmol) in dichloromethane (100 mL) was then added slowly over 3−4 h. The reaction was warmed to room temperature and stirred under nitrogen for a further 12 h. On completion (TLC), the reaction was washed with water (3 × 75 mL) and dried with magnesium sulfate. The dichloromethane was removed under reduced pressure to yield a yellow oil containing mono- and bis-acylated products. The desired monoester product was obtained by chromatographic separation (100 g silica gel, eluting with ethyl acetate/petroleum ether, 3:7) resulting in **11** (2.69 g, 58%) as a clear oil. IR (CH_2Cl_2, cm^{-1}): $\tilde{\nu}$ = 3524 m (−O−H), 2961 s, 2872 s (−CH_3), 1715 (C=O, ester), 1602 w (C−H, aromatic), 1368 m, 1353 m. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 0.86 (s, 3 H, −CH_3), 1.11 (s, 3 H, −CH_3), 2.02 (t, *J* = 5.5 Hz, 2 H, H-4), 2.32 (t, *J* = 7.3 Hz, 2 H, H-2), 3.48 and 3.65 (d, J_{AB} = 11.4 Hz, 4 H, H-4′, H-6′), 3.88 (t, *J* = 5.5 Hz, 2 H, H-5), 4.40 (t, *J* = 7.3 Hz, 2 H, H-1), 7.42 (t, *J* = 7.7 Hz, 2 H, Ph), 7.54 (t, *J* = 7.7 Hz, 1 H, Ph), 8.02 (d, *J* = 7.7 Hz, 2 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 22.4 (−CH_3), 22.8 (−CH_3), 29.6 (C-5′), 30.8 (C-2), 38.6 (C-4), 58.4 (C-5), 60.8 (C-1), 70.2 (C-4′, C-6′), 100.0 (C-3), 128.3 and 129.5 and 130.1 and 132.9 (Ph), 166.5 (C=O). HRMS: *m*/*z* (rel. int.): = 263.1289 (19) [M^+ − CH_2CH_2OH]; $C_{15}H_{19}O_4$ requires 263.1283;, 159 (100), 141 (68), 105 (59), 77 (23), 69 (43)

3-(5,5-Dimethyl-1,3-dioxan-2-yl)-5-(1-phenylethylamino)pentyl Benzoate (12): A solution of dimethyl sulfoxide (1.33 mL, 18.7 mmol) in dry dichloromethane (50 mL) was cooled to −78 °C. Oxalyl chloride (0.81 mL, 9.3 mmol) was added slowly and the reagent formed within 10 min. Then a solution of alcohol **11** (2.4 g, 7.8 mmol) in dichloromethane (10 mL) was added slowly and the reaction stirred for a further 15 min. Triethylamine (5.4 mL, 38.9 mmol) was added slowly, and then the reaction was allowed to warm to room temperature. The crude material was then poured into saturated sodium hydrogen carbonate (100 mL) and extracted with dichloromethane (3 × 50 mL). The organic phase was dried with magnesium sulfate, and the solvent was removed under reduced pressure to give a yellow oil. The product was purified by column chromatography (60 g silica gel, eluting with ethyl acetate/petroleum ether, 3:7) to give the aldehyde (2.32 g, 97%) as a clear oil. The aldehyde (1.48 g, 4.8 mmol) was dissolved in dry methanol (25 mL), and activated 3-Å molecular sieves (1 g) were added. (*R*)-α-methylbenzylamine (1.24 mL, 9.7 mmol) was added, and the reaction was stirred for two hours at room temperature. The solution was then cooled to 0 °C, and sodium borohydride (454 mg, 12 mmol) was added in small portions to prevent excessive foaming. The reaction mixture was then warmed to room temperature and stirred for a further hour until the reaction was complete (TLC). The molecular sieves were removed by filtration through Celite®, and the solvent evaporated under reduced pressure. The crude material was then added to a saturated sodium carbonate solution (50 mL), and the organic material extracted with ethyl acetate (3 × 30 mL). The organic phase was dried with magnesium sulfate and the solvent removed under reduced pressure to give a crude oil. The product was purified by column chromatography (50 g silica gel, eluting with dichloromethane/methanol, 95:5) to give **12** (1.68 g, 85%) as a clear oil. $[\alpha]_D$ = +23.6 [*c* = 1.15, $CHCl_3$; (*R,R*)-enantiomer], −22.2 [*c* = 1.86, $CHCl_3$, (*S,S*)-enantiomer]. IR (CH_2Cl_2, cm^{-1}): $\tilde{\nu}$ = 2960 m and 2870 m (−CH_3), 1715 s (C=O, ester), 1602 w (C−H, aromatic), 1365 w, 1353 w. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = 0.93 (s, 3 H, −CH_3), 0.94 (s, 3 H,−CH_3), 1.34 (d, *J* = 6.6 Hz, 3 H, H-2′), 1.78 (br., 1 H, NH), 1.98 (t, *J* = 7.2 Hz, 2 H, H-4), 2.16 (t, *J* = 7.2 Hz, 2 H, H-2), 2.59 and 2.69 (dt, J_{AB} = 12.0, 7.2 Hz, 2 H, H-5), 3.49 (s, 4 H, H-4′′, H-6′′), 3.74 (q, *J* = 6.6 Hz, 1 H, H-1′), 4.43 (t, *J* = 7.2 Hz, 2 H, H-1), 7.17−7.58 (m, 8 H, Ph), 8.02 (m, 2 H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 22.6 (−CH_3), 24.1 (C-2′), 29.6 (C-5′), 32.9 (C-2), 34.6 (C-4), 42.6 (C-5), 58.6 (C-1′), 61.0 (C-1), 70.1 (C-4′′, C-6′′), 99.0 (C-3), 126.6 and 126.8 and 128.3 and 128.4 and 129.5 and 130.4 and 132.8 and 145.7 (Ph), 166.5 (C=O). HRMS: *m*/*z* (rel. int.) = 411.2417 (2) [M^+]; $C_{25}H_{33}NO_4$ requires 411.2410; 326 (50), 274 (63), 188 (35), 105 (100), 91 (7), 77 (16).

Benzyl *N*-[3-(5,5-Dimethyl-1,3-dioxan-2-yl)-5-hydroxypentyl]-*N*′-(1-phenylethyl)carbamate (13): Amine **12** (1.66 g, 4 mmol) was dissolved in dry dichloromethane (8 mL) with diisopropylethylamine (2.09 mL, 12 mmol). The solution was cooled to 0 °C, and benzyl chloroformate (0.75 mL, 5.2 mmol) dripped in slowly. After 5 minutes the reaction was complete (TLC control). The solution was then added to a saturated sodium hydrogen carbonate solution (50 mL), and the product extracted into dichloromethane (3 ×

50 mL). The organic phase was dried with magnesium sulfate, and the solvents evaporated to afford a crude oil, which was purified by column chromatography (50 g silica gel, eluting with ethyl acetate/petroleum ether, 3:7) to give the protected amine (2.02 g, 92%) as a clear oil. The amine (1.83 g, 3.3 mmol) was dissolved in absolute ethanol (10 mL), followed by the addition of solid potassium hydroxide (188 mg, 3.3 mmol). The solution was stirred at room temperature for 45 min until hydrolysis was complete (TLC). The solution was then added to water (50 mL), and the product extracted with ethyl acetate (3 × 30 mL). The organic fractions were dried and reduced to give a crude oil, which was purified by column chromatography (50 g silica gel, eluting with ethyl acetate/petroleum ether, 4:6). In this way, alcohol **13** (1.39 g, 95%) was obtained as a colourless oil. $[\alpha]_D = +48.2$ [*c* = 1.48, $CHCl_3$, (*R,R*)-enantiomer], −50.2 [*c* = 1.61, $CHCl_3$, (*S,S*)-enantiomer]. IR (CH_2Cl_2, cm^{-1}): $\tilde{\nu}$ = 3518 w, 2960 m and 2873 m (−CH_3), 1685 s (C=O, carbamate), 1602 w (C−H, aromatic), 1419 s, 1221 s. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = 0.61 (br. s, 3 H, −CH_3), 1.04 (br. s, 3 H, −CH_3), 1.55 (d, *J* = 7.4 Hz, 3 H, H-2′), 1.66−1.88 (br., 4 H, H-2, H-4), 2.66 (br., 1 H, −OH), 2.86−3.36 (br. m, 6 H, H-4′′, H-6′′, H-1), 3.66 (br. s, 2 H, H-5), 5.21 (s, 2 H, H-4′), 5.54 (br., 1 H, H-1′), 7.22−7.41 (m, 10 H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 16.9 (C-2′), 22.1 (−CH_3), 22.9 (−CH_3), 29.4 (C-5′), 30.4 (C-2), 38.9 (C-1, C-4), 53.9 (C-1′), 58.3 (C-5), 67.4 (C-4′), 69.9 and 70.0 (C-4′′ C-6′′), 100.3 (C-3), 127.4 and 127.5 and 127.9 and 128.3 and 136.6 and 140.8 (Ph), 156.0 (C-3′). HRMS: *m*/*z* (rel. int.) = 441.2526 (1) [M^+]; $C_{26}H_{35}NO_5$ requires 441.2515; , 396 (12), 159 (100), 141 (5), 105 (26), 91 (45), 77 (2).

Benzyl *N*-[3-(5,5-Dimethyl-1,3-dioxan-2-yl)-5-(1-phenylethylamino)-pentyl]-*N*′-(1-phenylethyl)carbamate (14): Dimethyl sulfoxide (2.41 mL, 34 mmol) was added to dry dichloromethane (120 mL), and the solution cooled to −78 °C. Oxalyl chloride (1.48 mmol, 17 mmol) was added slowly, and the reaction mixture was stirred for 15 min. A solution of alcohol **13** (6.22 g, 14 mmol) in dichloromethane (30 mL) was added slowly, and the reaction mixture was stirred for a further 25 min. Triethylamine (9.8 mL, 70 mmol) was added and the solution allowed to warm to room temperature. The reaction was then poured into saturated sodium hydrogen carbonate (100 mL) and extracted with dichloromethane (3 × 75 mL). The organic phase was dried with magnesium sulfate and the solvent removed under reduced pressure to yield a crude yellow oil. This oil was then dissolved in dry methanol (100 mL) with activated 3Å molecular sieves (4 g). (*R*)-α-Methylbenzylamine (2.7 mL, 21 mmol) was added, and the reaction mixture was stirred for one hour at room temperature. The solution was then cooled to 0 °C, and sodium borohydride (1.32 g, 35 mmol) added in small portions. The reaction mixture was warmed to room temperature and stirred for a further hour. The molecular sieves were removed by filtration, and the solvent evaporated under reduced pressure. The crude material was then added to a saturated sodium carbonate solution (100 mL), and the organic material extracted with ethyl acetate (3 × 100 mL). The organic phase was dried with magnesium sulfate, and the solvent removed under reduced pressure to give a crude oil. The product was purified by column chromatography (150 g silica gel, eluting with ethyl acetate) to give 6.52 g (85%) of **14** as a clear oil. $[\alpha]_D = +56.7$ [*c* = 1.02, $CHCl_3$ − (*R,R*)-enantiomer], −59.1 [*c* = 1.20, $CHCl_3$ − (*S,S*)-enantiomer]. IR ($CHCl_3$, cm^{-1}): $\tilde{\nu}$ = 2960s and 2871s (−C−H, aliphatic), 1687s (C=O, carbamate), 1604 w and 1496 m (C−H, aromatic), 1262 s, 1258 s, 1090 s (C−O−C, ether). ^1H NMR (300 MHz, $CDCl_3$, ppm): δ = 0.67 (br. s, 3 H, Me), 0.91 (br. s, 3 H, Me), 1.31 (d, *J* = 6.8 Hz, 3 H, H-6′), 1.51 (d, *J* = 7.3 Hz, 3 H, H-2′), 1.58−1.80 (br., 5 H, H-2, H-4, NH), 2.51 (m, 2 H, H-5), 2.95−3.38 (m, 6 H, H-1, H-4′′, H-6′′), 3.67 (q, *J* = 6.8 Hz,1 H, H-5′), 5.18 (s, 2 H, H-4′), 5.50 (br., 1 H, H-1′), 7.16−7.38 (m, 15 H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 16.9 (C-2′), 22.3 (Me), 22.7 (Me), 24.0 (C-6′), 29.0 (C-5̈), 31.8 (C-2), 35.7 (C-4), 38.8 (C-1), 42.3 (C-5) 53.9 (C-1′), 58.4 (C-5′), 67.1 (C-4′), 69.8 (C-4′′, C-6̈), 99.1 (C-3), 126.6 and 126.7 and 127.3 and 127.4 and 127.8 and 128.2 and 128.3 and 128.4 and 136.8 and 141.1 and 145.6 (Ph), 156.2 (C=O). HRMS: *m*/*z* (rel. int.) = 544.3290 (0.5) [M^+]; $C_{34}H_{44}O_2N_2$ requires 544.3301; , 529.3 [M^+ − CH_3] (2), 396.2 [M^+ − $CH_2CH_2N(H)CH(CH_3)Ph$] (45), 134.1 [$PhCH(CH_3)NHCH_2$] (30), 120.1 [$PhCH(CH_3)NH$] (39), 105.1 [$PhCH(CH_3)$] (100).

3-(5,5-Dimethyl-1,3-dioxan-2-yl)-*N*,*N*′-bis(1-phenylethyl)pentane-1,5-diamine (15): Mono-Cbz-diamine **14** (783 mg, 1.4 mmol) was dissolved in absolute ethanol (10 mL), and palladium on carbon (149 mg, 0.14 mmol) was added. The suspension was then stirred for one hour under positive hydrogen pressure. After the reaction was complete (TLC control), the solution was filtered through Celite® and washed with ethanol. Removal of the ethanol under reduced pressure quantitatively afforded diamine **15** (574 mg). The product was characterised as the bis-tosylate. M.p. 136−137 °C (from ethyl acetate/petroleum ether). $[\alpha]_D = -22.5$ (*c* = 1.06, $CHCl_3$). IR ($CHCl_3$, cm^{-1}): $\tilde{\nu}$ = 2959 m and 2871 m (−C−H, aliphatic), 1599 w and 1495 m (C−H, aromatic), 1328 s and 1162 s (−SO_2−N⟨), 1220 s, 1214 s, 1086 s (C−O−C, ether). ^1H NMR (400 MHz, $CDCl_3$, ppm): δ = 0.70 (6 H, s, 2 × Me), 1.25 (d, *J* = 7.0 Hz, 6 H, H-2′), 1.30 and 1.69 (2 × ddd, *J* = 13.6, 12.4, 4.8 Hz, 4 H, H-2, H-4), 2.41 (s, Ts-CH_3,6 H), 2.86 and 3.19 (2 × ddd, *J* = 14.6, 12.4 and 4.8, 4 H, H-1, H-5), 2.92 and 3.07 (2 × d, *J* = 11.0 Hz, 4 H, H-4′′, H-6′′), 5.17 (q, *J* = 7.0 Hz, 2 H, H-1′), 7.17−7.30 (m, 10 H, Ph), 7.32 and 7.80 (2 × d, *J* = 8.4 Hz, 8 H, Ts). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 15.8 (C-2′), 21.6 (Ts-*C*H_3) 22.6 (Me), 29.5 (C-5′′), 34.9 (C-2,4), 39.0 (C-1,5), 55.4 (C-1′), 69.6 (C-4′′,6′′), 98.0 (C-3), 127.3, 127.7, 127.9, 128.4, 129.8, 138.4, 140.6 and 143.1 (Ph and Ts). HRMS: *m*/*z* (rel. int) = 703.2872 (0.5) [M^+ − CH_3]; $C_{39}H_{47}O_6N_2S_2$ requires 703.2877;, 563.3 [M^+ − Tos] (13), 416.2 [M^+ − $PhCH(CH_3)N(Tos)CH_2CH_2$] (95), 288.1 [$CH_2N(Tos)CH(CH_3)Ph$] (22), 105.1 [$PhCH(CH_3)$] (100). $C_{40}H_{50}N_2O_6S_4$ (783.1): calcd. C 66.82, H 7.01, N 3.90, S 8.92; found C 66.74, H 7.06, N 3.91, S 8.84.

(*R,R*)-1^2,1^4,11^2,11^4-Tetrahydroxy-6-(5,5-dimethyl-1,3-dioxan-2-yl)-12,14,15,17-tetramethyl-3,9-bis(1-phenylethyl)-13^4,13^6,16^4,16^6-tetra-(*p*-tolylsulfonyloxy)-3,9-diaza-1,11(1,3,5),13,16(1,3)-tetrabenzenabicyclo[9.3.3]heptadecaphane (16): (Tetratosyl)resorcinarene **1a** (580 mg, 0.5 mmol), diamine **15** (320 mg, 0.8 mmol) and paraformaldehyde (300 mg, 10 mmol) were added to a high-pressure glass reaction vessel with a screw top. Acetonitrile (40 mL) was added and the vessel sealed and placed in an oil bath at 85 °C. After one hour, the reaction was checked by TLC for complete consumption of **4**. Silica gel (2−3 g) was then added, and the solvent removed under reduced pressure. The solid-supported crude material was then finely ground and subjected to column chromatography (40 g silica gel eluting with ethyl acetate/petroleum ether, 2:3). In this manner, bridged resorcinarene **16** (378 mg, 47%) was obtained as a white powder. M.p. 143−146 °C (diisopropyl ether/dichloromethane). $[\alpha]_D = +6.0$ (*c* = 1.93, $CHCl_3$). IR (CH_2Cl_2, cm^{-1}): $\tilde{\nu}$ = 3526 m (O−H, H-bonded), 2956 m and 2931 m (C−H, aliphatic), 1599 s (aryl stretch), 1371 s and 1178 s (−SO_2−O−), 1093 s (C−O−C, ether). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.78 and 1.28 (2 × s, 6 H, >C(CH_3)$_2$], 1.33 (2 × d, *J* = 7.2 Hz, 12 H, −CH_3), 1.41 (d, *J* = 6.6 Hz, 6 H, NCHCH_3), 1.56 (m, 4 H, H-5,7), 2.28 and 2.42 (m, 4 H, H-4,8), 2.48 (2 × s, 12 H, H-7′) 2.97 and 3.04 (2 × d, *J* = 11.4 Hz, 4 H, H-4′′, 6′′), 3.74 (s, 4 H, H-2,10), 3.83 (q, *J* =

6.6 Hz, 2 H, H-α), 4.52 and 4.55 (2 × q, J = 7.2 Hz, 4 H, H-12,14,15,17), 6.69 (s, 2 H, H-13^2,16^2), 6.87 (s, 2 H, H-13^5,16^5), 7.08 (s, 2 H, H-1^6,11^6), 7.18−7.32 (m, 10 H, Ph), 7.40 (2 × d, J = 8.4 Hz, 8 H, H-3′,5′), 7.96 (2 × d, J = 8.4 Hz, 8 H, H-2′,6′). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 17.9 (NCH*C*H$_3$), 21.4 and 21.5 (C-7′), 21.7 (−CH*C*H$_3$), 22.4 [−C(*C*H$_3$)$_2$], 28.8 (C-5,7), 29.4 (C-5̃), 29.3 [−C(*C*H$_3$)$_2$], 31.1 (C-12,14,15,17), 44.8 (C-4,8), 48.7 (C-2,10), 60.8 (N*C*HCH$_3$), 69.6 (C-4′′,6′′), 98.9 (C-6), 108.6 (C-1^3,11^3), 114.9 (C-13^5,16^5), 119.1 (C-1^1,1^5,11^1,11^5), 123.5 (C-1^6,11^6), 127.4 (C-13^2,16^2), 128.1 and 128.4 and 128.5 (C-2′,6′, Ph), 130.1 (C-3′,5′), 133.5 (C-1′), 139.7 (C-13^1,13^3,16^1,16^3), 141.8 (Ph), 144.7 (C-13^4,13^6,16^4,16^6), 145.5 (C-4′), 153.5 (C-1^2,1^4,11^2,11^4). HRMS: *m*/*z* (rel. int) = 1595.7 (9) [M$^+$] , 1490.6 (3) [M$^+$ − PhCHCH$_3$], 1441.7 (3), 1185.3 (4), 1031.4 (2), 875.3 (2), 547.2 (2), 411.3 (23), 276.2 (29), 175.1 (39), 134.2 (100),105.1 [PhCHCH$_3$] (100). $C_{88}H_{94}N_2O_{18}S_4$ (1596.0): calcd. C 66.23, H 5.94, N 1.76, S 8.04; found C 66.33, H 6.06, N 1.76, S 8.17.

Benzyl {5-[Benzyloxycarbonyl-(1-phenylethyl)amino]-3-oxopentyl}-(1-phenylethyl)carbamate (17): Amine **14** (4.32 g, 7.9 mmol) was dissolved in dry dichloromethane (40 mL) with diisopropylethylamine (2.09 mL, 12 mmol). The solution was cooled to 0 °C, and benzyl chloroformate (1.47 mL, 10.3 mmol) dripped in slowly. After 5 min, the reaction was complete (TLC control). The solution was then added to a saturated sodium hydrogen carbonate solution (50 mL), and the product extracted into dichloromethane (3 × 50 mL). The organic phase was dried with magnesium sulfate, and the solvents evaporated to afford a crude oil, which was purified by column chromatography (50 g silica gel, eluting with ethyl acetate/petroleum ether, 2:8) to give the bis-Cbz protected diamine (5.09 g, 95%) as a clear oil. The protected diamine (3.86 g, 5.7 mmol) was dissolved in acetone (30 mL), and *p*-toluenesulfonic acid (100 mg, 0.5 mmol) was added. The reaction mixture was allowed to stir at room temperature until the hydrolysis was complete (TLC control), typically overnight. Saturated sodium hydrogen carbonate (100 mL) was then added, and the acetone removed under reduced pressure. The product was extracted three times into ethyl acetate (3 × 75 mL), dried with magnesium sulfate, and the solvent reduced. The crude oil formed in this manner was further purified by column chromatography (100 g silica gel, eluting with ethyl acetate/petroleum ether, 2:8), to furnish ketone **17** (3.14 g, 93%) as a clear oil. [α]$_D$ = +82.9 [*c* = 1.01, $CHCl_3$, (*R,R*)-enantiomer], −87.9 [*c* = 1.04, $CHCl_3$, (*S,S*)-enantiomer]. IR (CH_2Cl_2, cm^{-1}): ν̃ = 2980 m (C−H, aliphatic), 1690 s (C=O, carbamate and ketone), 1496 w (C−H, aromatic). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 (d, J = 6.9 Hz, 6 H, H-2′ × 2), 2.17 and 2.36 (br., 4 H, H-2,4), 3.21 (t, J = 7.4 Hz, 4 H, H-1,5), 5.14 and 5.19 (AB d, J = 12.2 Hz, 4 H, −CH$_2$Ph), 5.44 (br., 2 H, H-1′), 7.19−7.38 (m, 20 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ = 17.0 (C-2′), 37.6 (C-1,5), 42.7 (C-2,4), 53.9 (C-1′), 67.2 (C-4′), 127.2, 127.5, 127.8, 128.0, 128.4, 128.5, 136.7 and 140.8 (Ph), 156.0 (C-3′), 207.4 (C-3). HRMS: *m*/*z* (rel. int.) = 592.2926 (0.1) [M$^+$]; $C_{37}H_{40}N_2O_5$ requires 592.2937; 487.2 (9) [M$^+$ − PhCHCH$_3$] , 457.2 (5) [M$^+$ − PhCH$_2$OC=O], 383.2 (6) [M$^+$ − 2 × PhCHCH$_3$], 353.2 (7), 202.1 (26), 120.1 (8), 105.1 [PhCHCH$_3^+$] (64), 91.1 [PhCH$_2^+$] (100).

3,3-Dimethoxy-*N,N′*-bis(1-phenylethyl)pentane-1,5-diamine (18): TMS triflate (0.1 mL, 0.4 mmol) was added to dry dichloromethane (2 mL), and the solution cooled to −78 °C. Methoxytrimethylsilane (4.14 g, 40 mmol) was added slowly, followed by ketone **17** (7.47 g, 12.6 mmol) in dichloromethane (8 mL). The reaction mixture was warmed to −20 °C and stirred for 6 h. On completion (TLC), the reaction was quenched with triethylamine (0.5 mL). The quenched reaction was then added to saturated sodium carbonate (100 mL) and extracted with dichloromethane (3 × 70 mL). The organic phase was dried with magnesium sulfate, and the solvent removed under reduced pressure. The crude oil obtained was then subjected to column chromatography (100 g silica gel, eluting with ethyl acetate/petroleum ether, 3:17), to give the dimethoxy ketal (7.27 g, 90%) as a clear oil. The dicarbamate (3.4 g, 5.3 mmol) was dissolved in absolute ethanol (50 mL), and palladium on carbon (1.06 g, 0.5 mmol) was added. The suspension was then stirred for one hour under positive hydrogen pressure. After the reaction was complete (TLC control), the solution was filtered through Celite® and washed with ethanol. Removal of the ethanol under reduced pressure afforded dimethoxy diamine **18** (1.9 g) quantitatively. [α]$_D$ = +52.0 [*c* = 1.50, $CHCl_3$, (*R,R*)-enantiomer], −53.4 [*c* = 1.26, $CHCl_3$, (*S,S*)-enantiomer]. IR ($CHCl_3$, cm^{-1}): ν̃ = 3315 m (N−H), 3024 s (aromatic C−H), 2962 s and 2832 s (aliphatic C−H), 1602w (aryl ring), 1192 m (C−N), 1124 s (C−O−C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (d, J = 6.6 Hz, 6 H, −C*H*$_3$), 1.58 (br s, 2 H, NH × 2), 1.68 (t, J = 7.3 Hz, 4 H, H-2,4), 2.38 and 2.44 (2 × dt, J = 11.7, 7.3 Hz, 4 H, H-1,5), 3.08 (s, 6 H, OC*H*$_3$), 3.68 (q, J = 6.6 Hz, 2 H, NC*H*CH$_3$), 7.12−7.34 (m, 10 H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 24.2 (*C*H$_3$), 33.2 (C-2,4), 42.7 (C-1,5), 47.5 (O*C*H$_3$), 58.2 (N*C*HCH$_3$), 102.1 (C-3), 126.4, 126.7, 128.3 and 145.5 (Ph). MS: *m*/*z* (rel. int.) = 371 (49) [M$^+$ + H]; $C_{23}H_{35}N_2O_2$ requires 371.

1^2,1^4,11^2,11^4-Tetrahydroxy-6,6-dimethoxy-12,14,15,17-tetramethyl-3,9-bis(1-phenylethyl)-13^4,13^6,16^4,16^6-tetra(*p*-tolylsulfonyloxy)-3,9-diaza-1,11(1,3,5),13,16(1,3)tetrabenzena-bicyclo[9.3.3]heptadecaphane (19): Resorcinarene tetratosylate **1a** (580 mg, 0.5 mmol), diamine **18** (300 mg, 0.8 mmol) and paraformaldehyde (300 mg, 10 mmol) were added to a high-pressure glass reaction vessel with a screw top. Acetonitrile (40 mL) was added, and the vessel sealed and placed in an oil bath at 85 °C. After one hour, the reaction was checked by TLC for complete consumption of **1a**. Silica gel (2−3 g) was then added, and the solvent removed under reduced pressure. The solid-supported crude material was then finely ground and subjected to column chromatography (40 g silica gel eluting with ethyl acetate/petroleum ether, 2:3) to afford bridged resorcinarene **19** (450 mg, 57%) as a white powder. M.p. 153−155 °C (acetone/diethyl ether). [α]$_D$ = −45.4 [*c* = 2.20, $CHCl_3$, (*R,R*) enantiomer], +45.1 [*c* = 1.46, $CHCl_3$, (*S,S*) enantiomer). IR ($CHCl_3$, cm^{-1}): ν̃ = 3524 s (O−H, H-bonded), 2974 m and 2935 m (C−H, aliphatic), 1598 s (aryl stretch), 1371 s and 1176 s (−SO$_2$−O−), 1093 s (C−O−C, ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (m, 18 H, −C*H*$_3$, NCHC*H*$_3$), 1.59 (m, 4 H, H-5,7), 2.43 (m, 4 H, H-4,8), 2.45 and 2.50 (2 × s, 12 H, H-7′), 2.71 (s, 6 H, OC*H*$_3$), 3.78 and 3.90 (2 × d, J_{AB} = 16.0 Hz, 4 H, H-2,10), 3.78 (q, J = 6.5 Hz, 2 H, H-α), 4.50 and 4.53 (2 × q, J = 7.3 Hz, 4 H, H-12,14,15,17), 6.54 (s, 2 H, H-13^2,16^2), 6.89 (s, 2 H, 13^5,16^5), 7.03 (s, 2 H, H-1^6,11^6), 7.20−7.34 (m, 10 H, Ph), 7.38 and 7.42 (2 × d, J = 8.4 Hz, 8 H, H-3′,5′), 7.98 and 7.99 (2 × d, J = 8.4 Hz, 8 H, H-2′,6′). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ = 19.4 (NCH*C*H$_3$), 20.9 and 21.0 (C-7′), 21.7 (−*C*H$_3$), 26.6 (C-5,7), 31.4 and 31.7 (C-12,14,15,17), 45.7 (C-4,8), 47.4 (OCH$_3$), 49.4 (C-2,10), 61.0 (C-α), 101.7 (C-6), 109.1 (C-1^3,11^3), 114.8 (C-13^5,16^5), 118.6 and 119.3 (C-1^1,1^5,11^1,11^5), 123.8 (C-1^6,11^6), 127.3 (C-13^2,16^2), 127.6, 127.8, 128.5, 128.6, 128.7 (C-2′,6′, Ph), 130.0 and 130.2 (C-3′,5′), 133.3 and 133.7 (C-1′), 139.4 and 140.0 (C-13^1,13^3,16^1,16^3), 141.6 (Ph), 145.0 and 145.4, (C-13^4,13^6,16^4,16^6), 145.5 and 145.7 (C-4′), 152.4 and 154.4 (C-1^2,1^4,11^2,11^4). MS: *m*/*z* (rel. int.) = 1556.0 (28) [M$^+$], 1525.0 (10) [M$^+$ − OCH$_3$], 1318.7 (49), 1185.5 (52), 1029.5 (25), 875.5 (28), 719.4 (19), 307.2 (31), 204.2 (96), 105.1 [PhCHCH$_3$] (100). $C_{85}H_{90}N_2O_{18}S_4{\cdot}H_2O$ (1573.9): calcd. C 64.87, H 5.89, N 1.78, S 8.15; found C 64.85, H 5.91, N 1.84, S 7.96.

Acknowledgments

We would like to thank the National Research Foundation and Fine Chemicals Corporation, Cape Town for financial support.

[1] For reviews see: [1a] W. B. Motherwell, M. J. Bingham, Y. Six, *Tetrahedron* **2001**, *57*, 4663−4686. [1b] R. Breslow, S. D. Dong, *Chem. Reviews* **1998**, *98*, 1997−2001.

[2] [2a] Y. Tanaka, Y. Aoyama, *Bull. Chem. Soc., Jpn.* **1990**, *63*, 3343−3344. [2b] K. Kobayashi, Y. Asakawa, Y. Kikushi, H. Toi, Y. Aoyama, *J. Am. Chem. Soc.* **1993**, *115*, 2648−2654. [2c] S. Pappalardo, M. F. Parisi, *Tetrahedron Lett.* **1996**, *37*, 1493−1496. [2d] F. Arnaud−Neu, S. Caccamese, S. Fuangswasdi, S. Pappalardo, M. F. Parisi, A. Petringa, G. Principato, *J. Org. Chem.* **1997**, *62*, 8041−8048. [2e] M. A. Tairov, M. O. Vysotsky, O. I. Kalchenko, V. V. Pirozhenko, V. I. Kalchenko, *J. Chem. Soc., Perkin 1* **2002**, *11*, 1405−1411. [2f] Y. He, Y. Xiao, L. Meng, Z. Zeng, X. Wu, C.-T. Wu, *Tetrahedron Lett.* **2002**, *43*, 6249−6253.

[3] [3a] S. Steyer, C. Jeunesse, D. Matt, R. Welter, M. Wesolek, *J. Chem. Soc., Dalton Trans.* **2002**, *22*, 4264−4274. [3b] C. J. Cobley, D. D. Ellis, A. G. Orpen, P. G. Pringle, *J. Chem. Soc., Dalton Trans.* **2000**, *20*, 1109−1112. [3c] F. J. Parlevliet, C. Kiener, J. Fraanje, K. Goubitz, M. Lutz, A. L. Spek, P. C. J. Kamer, P. W. N. M. van Leeuwen, *J. Chem. Soc., Dalton Trans.* **2000**, *20*, 1113−1122. [3d] S. Shimizu, S. Shirakawa, Y. Sasaki, C. Hirai, *Angew. Chem. Int. Ed.* **2000**, *39*, 1256−1259. [3e] L. Baldini, C. Bracchini, R. Cacciapaglia, A. Casnati, L. Mandolini, R. Ungaro, *Chem. Eur. J.* **2000**, *6*, 1322−1330. [3f] G. Dospil, J. Schatz, *Tetrahedron Lett.* **2001**, *42*, 7837−7840. [3g] M. Frank, G. Maas, J. Schatz, *Eur. J. Org. Chem.* **2004**, *3*, 607−613

[4] C. Dieleman, S. Steyer, C. Jeunesse, D. Matt, *J. Chem. Soc., Dalton Trans.* **2001**, 2508−2517

[5] For examples see: [5a] F. Löffler, M. Hagen, U. Lüning, *Synlett* **1999**, *11*, 1826−1828. [5b] C. Gibson, J. Rebek, *Organic Letters* **2002**, *4*, 1887−1890.

[6] G. Arnott, P. C. B. Page, H. Heaney, R. Hunter, E. Sampler, *Synlett* **2001**, 412−414

[7] A. Shivanyuk, C. Schmidt, V. Böhmer, E. F. Paulus, O. Lukin, W. Vogt, *J. Am. Chem. Soc.* **1998**, *120*, 4319−4326.

[8] [8a] O. V. Lukin, V. V. Pirozhenko, A. N. Shivanyuk, *Tetrahedron Lett.* **1995**, *36*, 7725−7728. [8b] A. Shivanyuk, E. F. Paulus, V. Böhmer, W. Vogt, *J. Org. Chem.* **1998**, *63*, 6448−6449

[9] For recent reviews of the asymmetric addition of dialkylzincs, see: [9a] L. Pu, H.-B. Yu, *Chem. Rev.* **2001**, *101*, 757−824. [9b] L. Pu, *Tetrahedron* **2003**, *59*, 9873−9886. For a recent paper see: M. T. Barros, C. D. Maycock, A. M. F. Phillips, *Eur. J. Org. Chem.* **2004**, *8*, 1820−1829.

[10] [10a] R. Noyori, S. K. Kawai, S. Okada, M. Kitamura, *Pure Appl. Chem.* **1988**, *60*, 1597−1606. [10b] M. Yamakawa, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 6327−6335. [10c] M. Yamakawa, R. Noyori, *Organometallics* **1999**, *18*, 128−133.

[11] G. Palmieri, *Tetrahedron: Asymmetry* **2000**, *11*, 3361−3373

[12] For a similar case, see: O. Morikawa, K. Nakanishi, M. Miyashiro, K. Kobayashi, H. Konishi, *Synthesis* **2000**, *2*, 233−236 for an analogous system.

[13] For other ketalisations of dimethyl 3-oxopentanedioate, see: [13a] R. J. Davenport, A. C. Regan, *Tetrahedron Lett.* **2000**, *41*, 7619−7622. [13b] J. S. Yadav, A. Bandyopadhyay, A. C. Kunwar, *Tetrahedron Lett.* **2001**, *42*, 4907−4911

[14] T. Tsunoda, M. Suzuki, R. Noyori, *Tetrahedron Lett.* **1980**, *21*, 1357−1358

[15] For examples of alkylations using α-methylbenzylamine, see: [15a] N. Demirel, Y. Bulut, *Tetrahedron: Asymmetry* **2003**, *14*, 2633−2637. [15b] O. Muñoz-Muñiz, E. Juaristi, *J. Org. Chem.* **2003**, *68*, 3781−3785.

[16] S. Najdi, M. J. Kurth, *Tetrahedron Lett.* **1990**, *31*, 3279−3282.

[17] Imine formation is known to be facile. See: [17a] G. Demailly, G. Solladie, *J. Org. Chem.* **1981**, *46*, 3102−3108. [17b] S. Sakane, K. Maruoka, H. Yamamoto, *Tetrahedron* **1986**, *42*, 2203−2209

[18] S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* **1994**, *7*, 639−666

[19] W. Iwanek, M. Urbaniak, B. Grawdzik, V. Schurig, *Tetrahedron: Asymmetry* **2003**, *14*, 2787−2792

Received August 31, 2004

