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Enzymatic Synthesis of Nonracemic Inherently Chiral Calix[4]arenes by Lipase-Catalysed Transesterification

Julie K. Browne, M. Anthony McKervey,* Miguel Pitarch, and Julie A. Russell
School of Chemistry, The Queen's University of Belfast, Belfast BT9 5AG, Northern Ireland

Jeffrey S. Millership
School of Pharmacy, The Queen's University of Belfast, Belfast BT9 7BL, Northern Ireland

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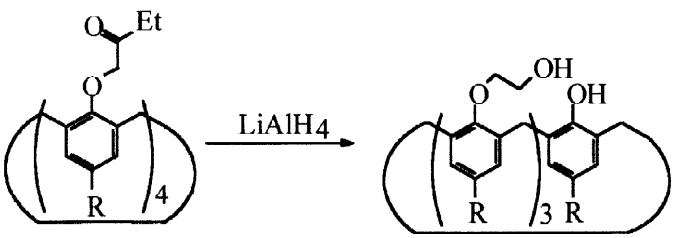
Abstract: A lipase-catalysed transesterification to effect a desymmetrisation has been used to produce chiral calix[4]arene derivatives with enantiomer excesses (ee) of up to 100%.

There are two general approaches to the synthesis of chiral calixarenes, the simpler of which involves the direct attachment of independently chiral substituents to either the upper[1] or lower rim.[2] Of much greater interest, and difficulty, has been the use of achiral subunits or substituents to produce 'inherently' chiral calixarenes whose molecular asymmetry derives from the non-planar nature of the calixarene structure. Inherently chiral calix[4]arenes result if the molecule has four different achiral substituents (ABCD), e.g. on the *para* positions on the upper rim, (or three in the order AABC[3]), or if it incorporates a *meta*-substituted phenolic subunit.[4] Calix[4]arenes showing an AABB substitution pattern are chiral when in the partial cone conformation. Implicit in attempts to separate the enantiomers of inherently chiral calixarenes is the need to suppress ring inversion which would otherwise amount to racemization. There are several examples of chiral calix[4]arenes in fixed conformations where enantiomer separation was achieved by semi-preparative scale chiral HPLC[5]. We now report the first examples of non-racemic inherently chiral calix[4]arenes produced by lipase-catalysed transesterification of achiral alcohols.



R = t-Butyl **1**
R = H **3**

R = t-Butyl **2**
R = H **4**

Scheme 1: Synthesis of Enzyme Substrates

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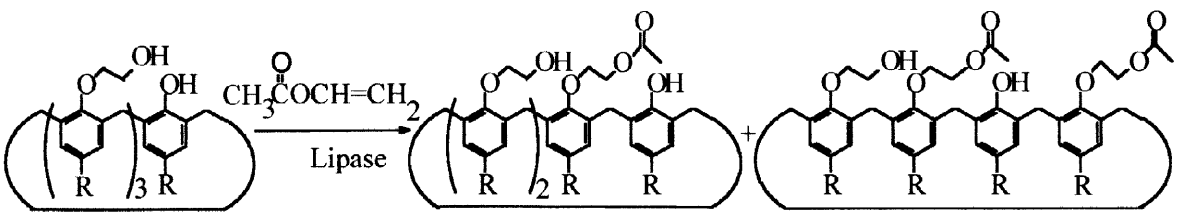
The triethyl alcohol monophenol **2**, prepared by lithium aluminium hydride reduction of p-*tert*-butylcalix[4]arene tetraester **1** in THF, is an achiral calix[4]arene in a stable cone conformation containing two distal enantiotopic hydroxyl groups (**Scheme 1**).[6] Replacement of one or other of these two groups by a new substituent, e.g. *via* esterification, produces enantiomers. Under standard chemical conditions (acetyl chloride and pyridine in THF) triethyl alcohol monophenol **2** could be acetylated to form (±)-monoacetate **5**, m. p. 184-186°C, in 51% yield. The structure of **5** was established by ^{1}H NMR analysis,[7] which also confirmed the presence of the cone conformation. A number of crystals of compound **5** were examined by X-ray analysis but they all exhibited poor diffraction. However, a data set was collected for one of these crystals which allowed confirmation of the atom connectivity. Monoacetate **5** with the substituent pattern AABC is chiral and the individual enantiomers could be detected by HPLC analysis (Chiralcel OD, hexane:2-propanol 90:10 v/v, 0.5 mlmin^{-1}, 280nm).



Scheme 2: Enzyme-catalysed transesterification reaction

The acetylation of **2** could also be achieved enzymatically using various lipases as catalysts and vinyl acetate as the acylating agent (**Scheme 2**). In a typical experiment compound **2** was stirred at room temperature in toluene containing vinyl acetate and a suspension of the lipase, monitoring the reaction progress by TLC. Use of *Candida cylindracea* lipase produced monoacetate **5** (18%) and diacetate **6** (18%). HPLC analysis revealed that **5** was racemic. In further experiments, however, the effect of using cross-linked enzyme crystals[8] (CLECs) on the acetylation of **2** was studied. Of the various lipase CLECs screened, *Mucor miehei* and *Aspergillus niger* lipases were found to catalyse the reaction with the results shown in **Table 1**.

Table 1. Enantiomer Ratios and % Yield of Products

Starting Material	Enzyme	Products		
		Monoacetate		Diacetate
		Ratio of Enantiomers	% Yield	% Yield
2	Chemical	50:50	51	---
	Candida cylindracea Lipase	50:50	18	18
	Mucor miehei Lipase	82:18	13	---
	Aspergillus niger Lipase	93: 7	8	---
4	Chemical	50:50	62	---
	Candida cylindracea Lipase	7:93	14	12
	Mucor miehei Lipase	50:50	25	33
	Aspergillus niger Lipase	100:0	19	---

The monoacetylated products from these reactions were again resolved by chiral HPLC. In both cases there was a large excess of the first eluted isomer. Peak areas indicated the enantiomer ratios of **5** to be 82:18 (observed $[\alpha]^{25}_{D}$ = + 6.2°, c=1.3, $CHCl_3$) for *Mucor miehei* lipase and 93:7 (observed $[\alpha]^{25}_{D}$ = + 8.1°, c=1.5, $CHCl_3$) for *Aspergillus niger* lipase (**Table 1**).

Transesterification was repeated with the dealkylated trialcohol monophenol calix[4]arene derivative **4**, as the substrate.[9] Chemical acetylation afforded the racemic monoacetate **7** as a standard for comparison. Lipase from *Aspergillus niger* halted the acetylation at the first stage, giving **7** in 19% yield (29% based on conversion of **4**, m. p. 76-78°C). *Candida cylindracea* and *Mucor miehei* lipases allowed transesterification to proceed further, producing a mixture of mono **7** and diacetylated **8** products.

HPLC analyses of these products were performed (Chiralcel OD, hexane:2-propanol 97.5:2.5 v/v, 0.5 $mlmin^{-1}$, 220nm). The lipases screened showed remarkable enantioselectivity. *Aspergillus niger* lipase gave an enantiomer ratio of 100:0, whilst lipase from *Candida cylindracea* showed a very high reversed enantioselectivity of 7:93. Lipase from *Mucor miehei* however, gave a racemic mixture of enantiomers (**Table 1**).

Polarimetry measurements carried out on the pure enantiomer of **7** from *Aspergillus niger* lipase, gave an $[\alpha]^{25}_{D}$ = -4.5° (c = 2.0, $CHCl_3$), while the optical rotation of the mixture of enantiomers obtained using *Candida cylindracea* lipase was in accordance with this value.

These results demonstrate the importance of enzymes as a means to effect enantioselective syntheses of large, inherently chiral calix[4]arenes. They also reveal the very subtle long range effect of calix[4]arene constitution on the enzymic selectivity. For example, *Candida cylindracea* lipase exhibits no enantioselectivity with p-*tert*-butylcalixarene derivative **2**. However when the p-*tert*-butyl groups are replaced by hydrogen the lipase shows a distinct preference for one of the distal prochiral alcohol groups. The scope of these reactions can be extended by suitable functionalisation of the free phenolic position in **2** and **4**, thereby allowing further 'fine-tuning' of the enantioselective behaviour of the lipase catalysts.

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6. Satisfactory elemental analyses, ^{1}H NMR spectra, electrospray and FAB mass spectra were obtained for all new compounds.
7. Selected ^{1}H NMR data: Compound **5**: δ_H ($CDCl_3$, 500MHz) 0.82 (9H, s, $C(CH_3)_3$), 0.84 (9H, s, $C(CH_3)_3$), 1.33 (9H, s, $C(CH_3)_3$), 1.35 (9H, s, $C(CH_3)_3$), 2.10 (3H, s, CH_3), 3.22 (1H, d, $H_{B'''}$, $J_{A'''B'''}$ = 12.58 Hz, $ArCH_2Ar$), 3.27 (2H, two overlapping d's, $H_{B'}$, $H_{B''}$, J = 12.92 Hz, $ArCH_2Ar$), 3.32 (1H, d, H_B, J_{AB} = 13.61Hz, $ArCH_2Ar$), 3.75 - 4.45 (12H, m, OCH_2CH_2), 4.26 (1H, d, $H_{A''}$, $J_{A''B''}$ = 13.27 Hz, $ArCH_2Ar$), 4.27 (1H, d, $H_{A'}$, $ArCH_2Ar$), 4.32 (1H, d, $H_{A'''}$, $ArCH_2Ar$), 4.40 (1H, d, $H_{A'}$, $ArCH_2Ar$), 4.62 (1H, t, OH), 5.99 (1H, s, OH), 6.54 (1H, s, ArH), 6.55 (1H, s, ArH), 6.57 (1H, s, ArH), 6.58 (1H, s, ArH), 7.08 (2H, two overlapping s's, ArH), 7.18 (2H, two overlapping s's, ArH).
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9. Typical Experimental Procedure: To a solution of the corresponding alcohol (**2** or **4**) (100mg), dissolved in toluene was added vinyl acetate (15 eq.) and the lipase CLEC (30mg). The resulting mixture was stirred magnetically at room temperature until TLC (6:4 ethyl acetate:hexane) showed no further progress in the reaction. The lipase catalyst was filtered off and the filtrate concentrated to give the crude mixture of products. Purification by column chromatography (flash silica gel, 1:1 ethyl acetate:hexane) furnished the pure products.