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A stereoselective synthesis of asymmetrically substituted calix[4]arenecarbamates

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Abstract—Calix[4]arenes bearing a methoxy and an *R* or *S* α-phenylethylacetamido group at the narrow rim of macrocycles are stereoselectively acylated with 1 equiv of trichloroacetyl isocyanate to give chiral asymmetrically substituted calix[4]arenecarbamates in preparative yields and high diastereomeric excess.

Calixarenes[1] are versatile molecular scaffolds for the design of highly efficient and selective receptors,[2] as well as self-assembling molecular capsules[3] and well-defined functional nanostructures.[4] Over the last few years considerable research has been dedicated to the design and synthesis of chiral calixarenes,[5] which are promising molecular platforms for the construction of enantioselective catalysts[6] and receptors.[7] Of particular interest are inherently chiral calixarenes whose chirality originates from the asymmetric arrangements of functional groups attached to the wide and/or narrow rim of macrocycles. Generating inherent chirality without the use of chiral reagents results in racemic mixtures of both enantiomers, which in some cases have been separated through chromatography on chiral stationary phases.[8] The use of chiral auxiliary groups (α-phenylethyl, amino acid ester, BINOL, menthyl, etc.) generally affords 1:1 mixtures of diastereomers, few of which have been separated by conventional HPLC or crystallization.[9] The diastereomers thus obtained contain an asymmetric center attached to the asymmetrically substituted calixarene fragment. Removal of the chiral auxiliary groups has been shown to afford individual enantiomers of inherently chiral calixarenes.

Herein we report the first easy diastereoselective synthesis of chiral calix[4]arenecarbamates, which is based upon the chiral induction of an α-phenylethylacetamide group attached to the narrow rim of the macrocycle.

The selective reaction of *tert*-butylcalix[4]arene monomethyl ether with 1 equiv of individual *S* or *R* isomers of *N*-(α-phenylethyl)bromoacetamide gave enantiomeric calixarenes **1**(***S***) and **1**(***R***), respectively (Scheme 1).[10] In order to generate an asymmetric pattern of the functional groups at the narrow rim of the calix[4]arene, compounds **1**(***S***) or **1**(***R***) were subjected to the recently developed monoacylation with acylisocyanates.[11] The mild, selective reaction of enantiomers **1**(***S***) or **1**(***R***) with trichloroacetyl isocyanate (ether, Et_3N, 5 °C) gave diastereomeric calix[4]arenecarbamates **2** and **3**.[12]

Diastereomers **2** and **3** were formed in a 4:1[13] ratio, which corresponds to a 60% diastereomeric excess of **2**(***S***) or **2**(***R***). Trituration of the crude mixtures with methanol removed the minor diastereomer along with an equivalent amount of the major product affording enantiomer **2**(***S***) or **2**(***R***) in 85% diastereomeric excess and an overall yield of 53%.[14] Crystallization from a mixture of hexane and CH_2Cl_2 afforded the analytically pure enantiomers.

Although the substitution pattern at the narrow rim of compounds **2** and **3** could be inferred from the NMR spectra, the determination of their absolute structure required X-ray crystallography.

Keywords: Calixarenes; Chirality; Asymmetric synthesis.
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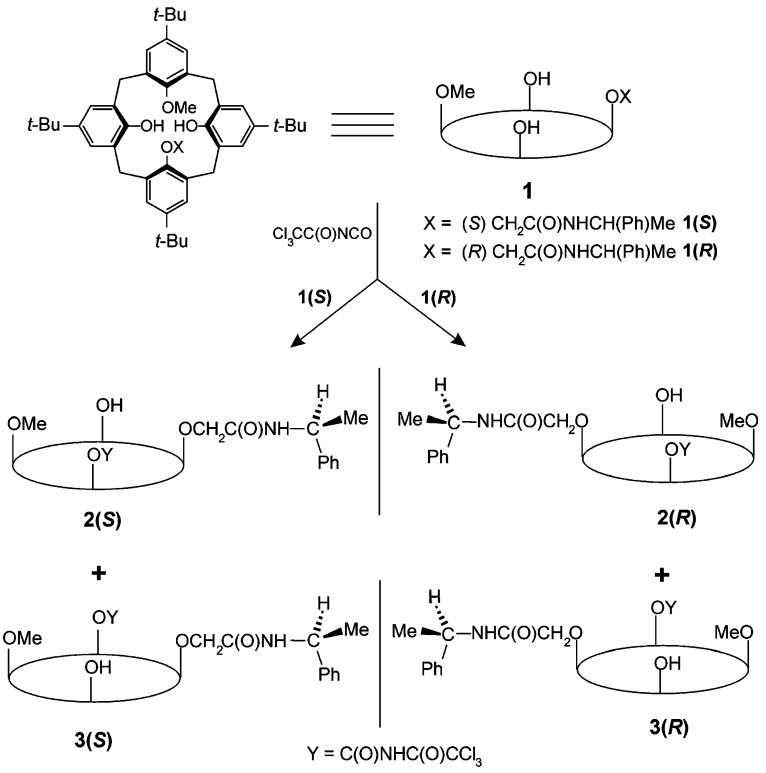

Scheme 1.

Slow crystallization of calixarene **2**(***S***) from a mixture of hexane and CH_2Cl_2 furnished stable crystals, which were suitable for single crystal X-ray diffraction studies. In the crystalline state, **2**(***S***) adopts *a pinched cone* conformation (Fig. 1) with aromatic rings **B** and **D** being nearly parallel (dihedral angle 11.3°) and rings **A** and **C** oriented almost orthogonally (dihedral angle 84.0°). Hydroxyl O1–H forms an intramolecular hydrogen bond with the oxygen atom of the methoxy group, while the NH-group of the trichloroacetamide fragment is involved in bifurcated hydrogen bonding with O1 and O2. As indicated by intermolecular distances, the (*S*)-α-phenylacetamido group does not form strong hydrogen bonds but rather weak intermolecular attractions with the carbon and chlorine atoms of the neighboring molecule **2a**. It is noteworthy that the equatorial proton of one methylene bridge faces the phenyl ring of the (*S*)-α-phenylacetamido group (ring **E**), which is nearly perpendicular to the main plane of the macrocycle (dihedral angle 83.4°). The distance between the center of ring **E** and the carbon atom of the closest methylene bridge (3.74 Å) indicates C–H···π attractions.

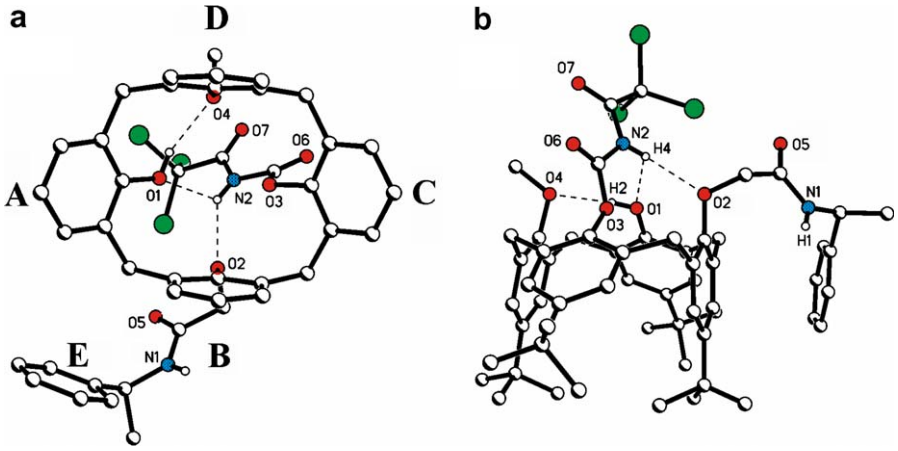

Figure 1. Molecular structure of compound **2**(***S***). (a) Top view: *tert*-Bu groups are omitted for clarity. (b) Side view: characteristic distances and angles for hydrogen bonds: d(O1 O4) = 2.825(1) Å, ∠(O1 H2 O4) = 162(2)°; d(N2 O1) = 2.915(1) Å, ∠(N2 H4 O1) = 117(1)°; d(N2 O2) = 2.903(1) Å, ∠(N2 H4 O2) = 142(1)°.

The ^{1}H NMR spectra of calixarenes **1** (Fig. 2a) contain four well resolved AB doublets for the axial protons of the methylene bridges and a pair of AB doublets for the methylene protons of the acetamide fragment. The AB doublets for the equatorial protons of the methylene bridges strongly overlap to give a compact multiplet centered at 3.4 ppm.

The ^{1}H NMR spectra of enantiomers **2**(***S***) and **2**(***R***) contain two AB doublets for the methylene protons of the acetamido fragments and four well-resolved doublets for the protons of the methylene bridges (Fig. 2b). The stronger shielding of one equatorial proton of the methylene bridge is consistent with the solid state conformation (Fig. 1) in which one equatorial proton is facing the phenyl ring of the α-phenylethyl fragment. In agreement with the crystal structure is also the fact that the NH proton of the acetamide residue emerges at $\delta = 6.74$ ppm most probably due to weak hydrogen bonding compared to compounds **1** ($\delta = 9.05$ ppm). Thus, the solid state conformation of calixarene **2**(***S***) may be considered as a realistic snapshot for the time averaged structure in $CDCl_3$.

As expected, the ^{1}H NMR spectrum of the equimolar mixture of **2**(***S***) and **2**(***R***) was identical to the sum of the spectra of the individual components. Addition of the Pirkle reagent resulted in the splitting of all the signals likely due to the formation of the diastereomeric complexes (Fig. 2c).

In order to evaluate the relative stability of diastereomers **2**(***S***) and **3**(***S***) the structures of both molecules were optimized using the B3LYP/6-31G(d, p) method employing the structure of **2**(***S***) in the crystalline state as the starting point. The energy of both the diastereomers was calculated at the MP2/6-31G(d, p) level of theory for the DFT optimized geometry. Compound **2**(***S***) was predicted to be about 2 kcal/mol more stable than its diastereomer **3**(***S***). This energy gain can be attributed mostly to the subtle differences in the strength of intramolecular hydrogen bonds and van der Waals interactions. The observed diastereomeric excess implies a lower energy for the transition states leading to the major diastereomers. The $\Delta\Delta G^{\#}$ value for such stabilization is estimated to be 0.75 kcal/mol.[15] Thus, the above results suggest that the diastereomeric transition state of lower energy transforms into the more stable diastereomer.

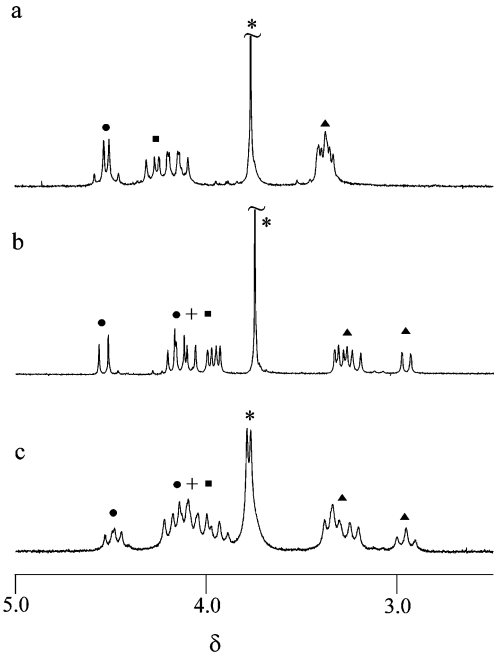

Figure 2. A portion of the ^{1}H NMR spectrum (295 K, 300 MHz, $CDCl_3$) of: **1**(***S***) or **1**(***R***) (a), **2**(***S***) or **2**(***R***) (b) and **2**(***S***) + **2**(***R***) in the presence of the Pirkle reagent (c). ●: $-CH_2CO$; ■ and ▲: axial and equatorial protons of the methylene bridges, respectively; ∗: $-CH_3O$.

In conclusion, a simple synthetic approach has been developed for the asymmetric synthesis of chiral calix[4]-arenes bearing three types of functional groups at the narrow rim of the macrocycle. Although the exact cause for the selectivity remains unclear it seems plausible that it is related to the mild reaction conditions as well as the proximity of the chiral auxiliary group to the reacting hydroxyls. Alkylations of the OH groups followed by the hydrolytic cleavage of the amido and carbamate functions would generate a virtually unlimited structural and functional diversity of inherently chiral calixarenes. These synthetic methodologies are currently being developed and will be published in due course.

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Supplementary data

Spectral characteristics and crystallographic details for the reported compounds have been deposited as supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.08.095.

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10. A mixture of 25,26,27-trihydroxy-28-methoxy-*p*-*tert*-butylcalix[4]arene (1.43 g, 2.15 mmol) and K_2CO_3 (0.16 g, 1.15 mmol) in dry acetonitrile (150 mL) was stirred at 65 °C for 2 h. Then *N*-((*S*)-1-phenylethyl)bromoacetamide (0.55 g 2.26 mmol) for the synthesis of **1**(***S***) or *N*-((*R*)-1-phenylethyl)bromoacetamide (0.55 g 2.26 mmol) for the synthesis of **1**(***R***) was added and the reaction mixture was stirred at reflux for 6 h. After cooling, the solvent was removed under reduced pressure, the solid residue was triturated with HCl (50 mL, 1 N) and extracted with $CHCl_3$ (3×20 mL). The organic layer was separated, dried over Na_2SO_4, and evaporated in vacuo to give, quantitatively, compound **1**(***S***) or **1**(***R***), which was used in subsequent reactions without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 0.99 (s, 9H), 1.01 (s, 9H), 1.29 (s, 18H), 1.68 (d, $J = 7.1$ Hz, 3H), 3.36 (d, $J = 12.9$ Hz, 1H), 3.38 (d, $J = 13.2$ Hz, 1H), 3.39 (d, $J = 13.2$ Hz, 1H), 3.40 (d, $J = 12.9$ Hz, 1H), 3.77 (s, 3H), 4.12 (d, $J = 13.2$ Hz, 1H), 4.17 (d, $J = 13.2$ Hz, 1H), 4.22 (d, $J = 12.9$ Hz, 1H), 4.29 (d, $J = 12.9$ Hz, 1H), 4.48 (d, $J = 14.7$ Hz, 1H), 4.56 (d, $J = 14.7$ Hz, 1H), 5.33 (m, 1H), 6.85 (d, $J = 2.4$ Hz, 2H), 6.88 (d, $J = 2.4$ Hz, 1H), 6.90 (d, $J = 2.4$ Hz, 1H), 7.05 (d, $J = 2.4$ Hz, 1H), 7.07 (d, $J = 2.4$ Hz, 1H), 7.10 (d, $J = 2.4$ Hz, 2H), 7.34 (m, 3H), 7.49 (s, 1H), 7.54 (m, 2H), 7.57 (s, 1H), 9.05 (d, $J = 8.2$ Hz, 1H).
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12. To a solution of **1**(***S***) or **1**(***R***) in diethyl ether (5 mL), trichloroacetyl isocyanate (0.51 g, 2.69 mmol) dissolved in dry diethyl ether (10 mL) was added at 5 °C followed by one drop of Et_3N. The reaction mixture was stirred for 100 h at 5 °C, after which the solvent was removed under reduced pressure and the residue was triturated with boiling methanol (12 mL), resulting in precipitation. After 24 h at 0 °C the colorless precipitate of **2**(***S***) or **2**(***R***) was filtered off and washed with cold methanol. Yield 1.15 g, 53%, $[\alpha]_D^{20}$ −42.86 (*c* 0.504, $CHCl_3$) for **2**(***S***) and $[\alpha]_D^{20}$ 42.54 (*c* 0.496, $CHCl_3$) for **2**(***R***). Mp 221–223 °C (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 0.63 (s, 9H), 0.82 (s, 9H), 1.27 (s, 9H), 1.31 (s, 9H), 1.52 (d, $J = 7.1$ Hz, 3H), 2.96 (d, $J = 13.4$ Hz, 1H), 3.22 (d, $J = 13.1$ Hz, 1H), 3.29 (d, $J = 13.4$ Hz, 1H), 3.31 (d, $J = 13.8$ Hz, 1H), 3.75 (s, 3H), 3.95 (d, $J = 13.4$ Hz, 1H), 3.98 (d, $J = 13.8$ Hz, 1H), 4.08 (d, $J = 13.4$ Hz, 1H), 4.14 (d, $J = 14.7$ Hz, 1H), 4.18 (d, $J = 13.1$ Hz, 1H),4.55 (d, $J = 14.7$ Hz, 1H), 5.12 (m, 1H), 6.27 (d, $J = 2.5$ Hz, 1H), 6.37 (d, $J = 2.5$ Hz, 1H), 6.59–6.62 (m, 3H), 6.74 (d, $J = 8.5$ Hz, 1H), 7.02 (d, $J = 2.4$ Hz, 1H), 7.06 (dd, $J = 2.4$, 2.3 Hz, 2H), 7.17–7.29 (m, 6H), 10.39 (s, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ ppm: 167.21, 159.39, 152.06, 150.76, 149.91, 149.63, 148.86, 147.20, 146.33, 144.03, 142.91, 142.17, 135.05, 134.78, 131.31, 131.26, 131.15, 128.71, 128.61, 128.18, 127.28, 127.02, 126.43, 126.00, 125.79, 125.68, 125.59, 125.34, 125.17, 124.95, 92.15, 75.30, 63.72, 48.91, 34.38, 33.90, 33.81, 33.56, 31.67, 31.46, 30.87, 30.72, 21.47. Anal. Calcd for $C_{58}H_{69}Cl_3N_2O_7$: C 68.80, H 6.87, Cl 10.50, N 2.77. Found: C 69.01, H 6.75, Cl 10.42, N 2.86.
13. This was determined via integration of the corresponding signals in the ^{1}H NMR spectra of the crude products.
14. The yield was calculated for two steps on the basis of the amount of *tert*-butylcalix[4]arene monomethyl ether used in the synthesis.
15. $\Delta\Delta G^{\#} = RT \ln 4$, where 4 is the observed diastereomeric ratio.