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# Synthesis of calix[4]arene derivatives bearing chiral pendant groups as ligands for enantioselective catalysis

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**Abstract**—New chiral calix[4]arene derivatives have been synthesized by appending at the lower rim amino acid (L-tyrosine, L-aspartic acid, L-valine, and L-tryptophan) or pinene-like (myrtenyl and homomyrtenyl) units or by distal intrabridging with a binaphthyl amine scaffold. The application of these derivatives in enantioselective catalysis was studied by testing the catalytic activities of the corresponding Ti(IV)/calixarene complexes, prepared in situ, in the asymmetric aldol reaction of Chan's silyloxydiene with *p*-nitrobenzaldehyde.

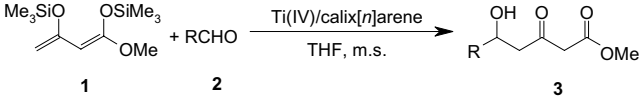

## 1. Introduction

Chiral calixarenes[1] have attracted increasing research interest because of their potential in enantiodiscrimination processes. They can be obtained either by attaching chiral moieties at one of the calix rims (upper or lower)[2] or by synthesizing 'inherently' chiral derivatives[3] in which an asymmetric substitution of the macrocycle is associated to its intrinsic three-dimensional nature. From a practical point of view, the first approach appears to be preferable because inherent chirality always requires a difficult resolution on an appropriate scale.[4] Therefore, a large number of chiral calixarenes have been prepared by using chiral units, such as single amino acids,[5] peptides,[6] amino alcohols,[7] sugars,[8] tartaric acid esters,[9] binaphthyl,[10] glycidyl,[11] menthone,[12] and guanidinium groups.[13]

Many of these derivatives have exhibited significant recognition properties toward achiral cations,[5d,10b] and anions,[5g] but, more interestingly, some of them have shown remarkable enantiodiscrimination abilities.[7,10a,14] Thus, for example, calix[4]arenes bearing chiral amino alcohol groups at lower rim exhibited enantioselective recognition versus racemic carboxylic acids,[7] while a colorimetric enantiodiscrimination of chiral amines has been shown by calix[4]arenes derivatized with a binaphthyl group at the lower rim.[10a]

Another area of application of chiral calixarenes is their use in enantioselective catalysis, which still remains largely less studied. In fact, only a very few examples[15] have been reported, in which chiral calix[4]arenes have been used as ligands for the enantioselective catalysis of hydroformylation,[16a] allylic alkylation, and hydrogenation.[16b]

As a contribution in this area, herein, we report on the synthesis of some new chiral calix[4]arene derivatives and on their use as ligands in an enantioselective Ti(IV)-catalyzed aldol reaction. In fact, very recently we have reported that Ti(IV)/calix[*n*]arene complexes, formed in situ or previously prepared with standard procedures, efficiently catalyze the aldol condensation of Chan's silyloxydiene **1** with several aldehydes **2** affording, in satisfactory yields, aldol adducts **3** (Scheme 1),[17] which are key-intermediates in the synthesis of important bio-active compounds.[18] Obviously, it can




**Scheme 1.**

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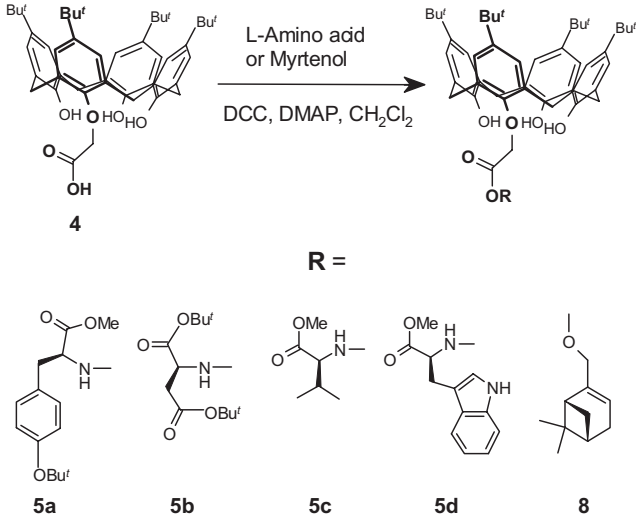
be expected that the use of chiral calixarene ligands may give rise to an efficient enantioselective catalysis for this reaction.[19]

## 2. Results and discussion

### 2.1. Synthesis and characterization of chiral calixarenes

The previous observation that the presence of three contiguous phenolic OH groups in the calixarene ligand appeared as an important requirement in order to strongly tricoordinate the Ti(IV) cation,[17a] induced us to initially synthesize chiral calixarenes by linkage of a single L-amino acid unit at the lower rim. These amino acid derivatives were prepared by coupling of the known *p-tert*-butylcalix[4]arene monoacetic acid **4**[20] with L-amino acids, in the presence of DCC and DMAP, in dry $CH_2Cl_2$ (Scheme 2). The use of appropriately protected L-tyrosine, L-aspartic acid, L-valine, and L-tryptophan, gave the corresponding amino acid conjugated **5a–d** in 47–69% yield (see Section 4).

The structure of compounds **5a–d** were confirmed by elemental analysis and ESI(+) MS, while $^1$H NMR spectra were consistent with an asymmetric calix[4]arene structure. Thus, for example, five and six *t*-Bu singlets were observed for **5a** and **5b**, respectively, whereas **5c** and **5d** gave four signals for the same groups. Interestingly, three OH singlets were observed for **5a–d** at low field (9.07–10.03 ppm), while the NH doublets resonate in the 9.23–9.52 ppm range. These strong downfield shifts for both OH and NH protons are indicative of a circular hydrogen bond at the lower rim of these derivatives, in agreement with the results reported by Frkanec et al.[5e] The presence of an H-bond-stabilized cone conformation was also reflected in the significant chemical shift separation of diastereotopic $OCH_aH_b$ protons ($\Delta\delta$ = 0.10–0.27).

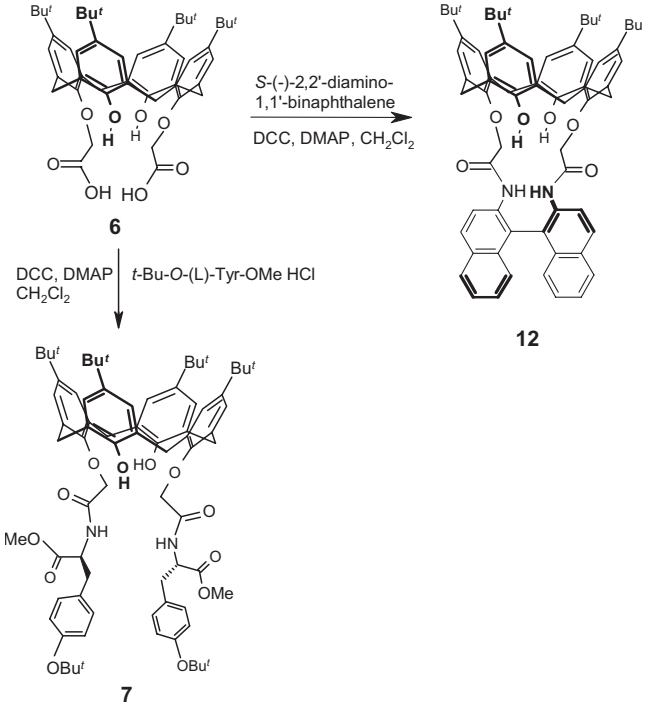



Scheme 2.

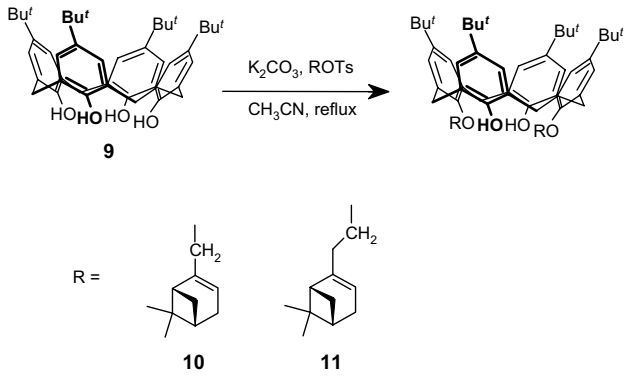
In order to verify the possible influence of a lower number of phenolic OH groups, we decided to synthesize a disubstituted amino acid–calixarene derivative. Thus, calixarene diacetic acid **6**[21] was coupled with L-Tyr-OMe hydrochloride, in the presence of DCC and DMAP to give **7** in 79% yield (Scheme 3). In accordance with the $C_2$-symmetry of the structure, the $^1$H NMR spectrum of **7** contained three *t*-Bu singlets (1.04, 1.27, and 1.28 ppm), one OMe singlet (3.54 ppm), and two AX systems for $ArCH_2Ar$ groups. The equivalence of the two chiral pendant moieties was confirmed by the $^{13}$C NMR spectrum of **7**, which showed a single resonance for $OCH_2$ (75.2 ppm), –COOMe (170.2 ppm), and –CONH– (168.1 ppm) groups. Also in this instance, the presence in the $^1$H NMR spectrum of **7** of a strongly downfield shifted NH resonance (9.61 ppm) was indicative of a circular H-bond at the lower rim involving NH···O interactions.[5e]

A useful complement to the above calixarenes bearing amino acid units could be the use of chiral pendant groups having a lower number of potentially coordinating oxygen atoms. Therefore, we directed our attention to the synthesis of 2-pinen-10-yl (myrtenyl) monoester derivative **8** (Scheme 2). As in the previous instances, this compound was obtained, in 70% yield, by coupling *p-tert*-butylcalix[4]arene monoacetic acid **4** with (−)-myrtenol, in the presence of DCC and DMAP. The $^1$H NMR spectrum of **8** was fully consistent with its asymmetric structure as indicated by the presence of four AX systems for $ArCH_2Ar$ groups.

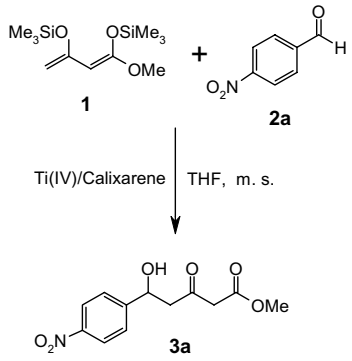
In order to bring the stereogenic moiety closer to the coordinating calixarene OH groups, we devised a simple




Scheme 3.




Scheme 4.




Scheme 5.

variation of the above synthesis. Thus, *p-tert*-butylcalix[4]arene **9** was directly alkylated with myrtenyl[22] or homomyrtenyl (nopyl)[23] *p*-toluensulfonate in the presence of $K_2CO_3$, in refluxing $CH_3CN$ (Scheme 4) to give, after column chromatography on silica gel, 1,3-dimyrtenyl-calix[4]arene **10** (62% yield) and 1,3-dinopyl-calix[4]arene **11** (46% yield). The *syn*-distal disubstitution and the dissymmetry of these derivatives was readily confirmed by $^1H$ and $^{13}C$ NMR spectra. In fact, in both instances, two 1:1 resonances for *tert*-butyl groups, two AX systems for $ArCH_2Ar$ groups, and one broad singlet for vinylic proton were clearly observed in their $^1H$ NMR spectra. $^{13}C$ NMR spectra were also in full agreement by showing, inter alia, two $ArCH_2Ar$ signals in the 30–32 ppm range indicative of a cone conformation.[24]

The observation that in all the above chiral calixarene derivatives, the dangling chiral moieties are freely swinging with respect to the putative catalytic center induced us to synthesize an additional derivative bearing a rigid chiral bridge at the lower rim. Therefore, calix[4]arene diacetic acid **6** was condensed with binaphthyl amine (slowly added dropwise) in the presence of DCC and DMAP in dry $CH_2Cl_2$, to give **12** in 30% yield (Scheme 3). $^1H$ and $^{13}C$ NMR spectra of compound **12** confirmed the $C_2$-symmetry of the structure. In particular, two *t*-Bu singlets (1.19 and 1.29 ppm), one AX (3.55/4.48 ppm, $J = 12.6$ Hz, 4H), and one AB (3.52/3.84 ppm, $J = 13.8$ Hz, 4H) systems for $ArCH_2Ar$ groups, and one AB system for $OCH_2$ protons (4.13/4.40 ppm, $J = 14.8$ Hz, 4H) were observed in its $^1H$ NMR spectrum. The presence of an AB system for one of the two $ArCH_2Ar$ groups indicate a $C_2$ flattened-cone conformation for compound **12**.[25]

## 2.2. Application of chiral calixarene derivatives in aldol reaction

In order to evaluate the catalytic properties of the synthesized chiral calixarenes in the above mentioned aldol reaction, we decided to consider the reaction between Chan's diene **1** with *p*-nitrobenzaldehyde **2a**, chosen as a representative substrate, in the presence of a Ti(IV)/calixarene complex formed in situ by addition of 1 equiv of Ti(O-*i*-Pr)$_4$ (Scheme 5). The reaction was carried out in THF under conditions similar to those previously optimized for the Ti(IV)/*p-tert*-butylcalix[4]arene system.[17b] Table 1 summarizes chemical yields and ees experimentally observed.

When the reaction was carried out in the presence of 8% mol of the Ti(IV)/**5a** complex[17b] (entry 1), aldol adduct **3a** was obtained only in 12% yield. A more satisfactory chemical yield (80%) was obtained by increasing the catalyst loading to 16 mol % (entry 2) but the enantioselectivity was very poor (7%).

By using derivative **7**, bearing two distal tyrosine substituents, as a ligand of the Ti(IV)-complex a negligible ee was obtained, in addition to a significant decreasing of the catalytic activity (40%, entry 3) with respect to the related monosubstituted derivative **5a**. This result is in accordance with our previous conclusion that three contiguous phenolic OH groups are very likely a minimal requirement in order to strongly coordinate Ti(IV) cation.[17a]

A similar trend can also be observed when the catalytic activity of myrtenyl monoester derivative **8** (68%, entry 4) is compared with that of 1,3-dimyrtenyl ether **10** (27%, entry 5). In both instances, the observed enantioselectivity was very low.

In the attempt to increase the enantioselectivity, we studied the influence of the reaction temperature in the aldol reaction catalyzed by Ti(IV)/**5a** complex. By performing the reaction for 16 h at 0 °C, after the 2 h step at −78 °C (entry 6), a very high chemical yield (90%) was obtained, but only a slight increase of the ee (12%) was detected. Interestingly, a further decrease in temperature to −20 °C (entry 7) resulted in a beneficial effect on enantioselectivity (27%) with an acceptable drop in efficiency (64%). However, no further improvement in ee could be observed by running the reaction at a lower temperature (−40 °C for 16 h; entry 8).

The low ees observed for ligands **5a** and **7** suggest that the presence of asymmetric carbon atoms on the pendant group has a scarce influence on the enantioselectivity probably due to an excessive mobility of this moiety which is not geometrically fixed with respect to the Ti-catalytic center determined by the coordinating calixarene OH groups. Therefore, on this basis it could

**Table 1.** Efficiency of Ti(IV)/chiral-calixarene complexes in aldol reaction of diene **1** with *p*-nitrobenzaldehyde **2a**[a]

| Entry | Ligand | Temperature (time) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1[a] | **5a** | −78 °C (2 h) + rt (16 h) | 12 | — |
| 2 | **5a** | −78 °C (2 h) + rt (16 h) | 80 | 7 |
| 3 | **7** | −78 °C (2 h) + rt (16 h) | 40 | 3 |
| 4 | **8** | −78 °C (2 h) + rt (16 h) | 68 | 4 |
| 5 | **10** | −78 °C (2 h) + rt (16 h) | 27 | 1 |
| 6 | **5a** | −78 °C (2 h) + 0 °C (16 h) | 90 | 12 |
| 7 | **5a** | −78 °C (2 h) + −20 °C (16 h) | 64 | 27 |
| 8 | **5a** | −78 °C (2 h) + −40 °C (16 h) | 70 | 28 |
| 9 | **12** | −78 °C (2 h) + rt (16 h) | 56 | 11 |
| 10 | **12** | −78 °C (2 h) + −20 °C (16 h) | 40 | 11 |

[a] The reactions were performed by using 1 mmol of aldehyde and 16 mol % of Ti(IV)/calixarene complex. An exception is given by the reaction of entry 1, which was performed in the presence of 8 mol % of Ti(IV)/**5a** complex.

[b] Yields refer to isolated, chromatographically pure compound whose structure was confirmed by comparison with the literature data.[19]

[c] Determined by HPLC on a Chiralpak AD column. The preferred absolute configuration of the aldol product **3a** was (*S*), as determined by comparison of the HPLC retention times with the literature values.[19]

be expected that calix[4]arene **12**, rigidified by the sterically demanding binaphthyl-bridge, should give better results. Unfortunately, only low ees (11%) with a decreased efficiency (40–56%) were obtained by performing the reaction either at room temperature (entry 9) as well as at −20 °C (entry 10). These disappointing results can be rationalized in terms of the general low catalytic efficiency observed for 1,3-disubstitued calix[4]arenes, which is attributable to the weaker Ti-coordination by only two calixarene OH groups. In addition, the relatively large distance between the stereogenic and catalytic centers could account for the limited chiral induction.

## 3. Conclusion

In conclusion, we have described the synthesis of some new optically active calix[4]arene derivatives bearing chiral pendant units, which include amino acids, pinene-like, and binaphthyl groups. The application of these derivatives in enantioselective catalysis was studied by testing the catalytic activities of the corresponding Ti(IV)/calixarene complexes, prepared in situ, in an asymmetric aldol reaction. Unfortunately, only limited enantioselectivities were observed probably due to one or more key factors which include: (i) eccessive flexibility of the dangling chiral moieties; (ii) large spatial separation between the Ti-catalytic site and the stereogenic center, and (iii) ineffective coordination of the Ti cation by a nonsufficient number of calixarene OH groups. The extension of this work to the design of improved chiral calixarenes ligands may include the use of short chiral bridging moieties containing additional OH coordination sites or the exploitation of inherent chirality which, in accordance with recent reports,[16b] could be effectively transferred to the metal catalytic center. Both approaches are currently under study in our laboratory.

## 4. Experimental

ESI(+) MS measurements were performed on a BIO-Q triple quadrupole mass spectrometer (MICROMASS) equipped with an electrospray ion source, using $CH_2Cl_2$ and 5% HCOOH as solvent. All NMR spectra were recorded at 400 ($^1$H) and 100 ($^{13}$C) MHz on a Bruker Avance-400 spectrometer. Chemical shifts are reported relative to the residual solvent peak ($CHCl_3$: $\delta = 7.26$, $CDCl_3$: $\delta = 77.2$). Optical rotations were measured on an JASCO DIP-1000 polarimeter at the wavelength of 589.3 nm. Flash chromatography was performed using silica gel (Kieselgel-60, 0.040–0.063 mm, Merck). All reagents were of reagent grade quality and used without further purification. Dichloromethane was distilled over $CaH_2$. Compounds **4**,[20] **6**,[21] myrtenyl *p*-toluensulfonate,[22] nopyl *p*-toluensulfonate,[23] and *p*-*tert*-butylcalix[4]arene[26] were prepared according to a literature procedure. Reactions were monitored by TLC on Merck silica gel plate (0.25 mm) and visualized by UV light and spraying with $H_2SO_4$–$Ce(SO_4)_2$.

### 4.1. General method for coupling *p*-*tert*-butylcalix[4]arene monoacetic acid 4 with amino acids. Compounds 5a–d

A mixture of *p*-*tert*-butylcalix[4]arene monoacetic acid **4** (0.2 g, 0.3 mmol), DMAP (0.034 g, 0.3 mmol), and DCC (0.12 g, 0.61 mmol) in dry $CH_2Cl_2$ (30 mL) was stirred at 25 °C for 10 min and then L-amino acid was added (0.6 mmol). The solution was stirred for 3 h at room temperature. Then dicyclohexylurea was filtered off, and $CH_2Cl_2$ washed with 1 M HCl and brine. The organic phase was dried over $Na_2SO_4$ and concentrated in vacuo. The crude product was subjected to flash chromatography on silica gel, using $CH_2Cl_2$ as eluent, to give the isolated compounds.

**4.1.1. 5,11,17,23-Tetra-*tert*-butyl-25-[*O*-methyl-*O*′-*tert*-butyl-(*S*)-tyrosinyl-carbonylmethoxy]calix[4]aren-26,27,28-triol 5a.** 0.16 g (58%), $[\alpha]_D^{25} = -36$ (*c* 3.91, $CHCl_3$); $^1$H NMR ($CDCl_3$, 298 K): $\delta$ 1.19 [s, $C(CH_3)_3$, 9H], 1.25 [s, $C(CH_3)_3$, 9H], 1.26 [s, $C(CH_3)_3$, 18H], 1.33 [s, $C(CH_3)_3$, 9H], 3.20 (dd, Tyr-H$^\beta$, $J = 14.0$, 10.5 Hz, 1H), 3.35 (d, $ArCH_2Ar$, $J = 13.1$ Hz, 1H), 3.45 (dd, Tyr-H$^\beta$, $J = 14.0$, 5.4 Hz, 1H), 3.52 (br d, $ArCH_2Ar$, 3H), 3.84 (s, $OCH_3$, 3H), 4.09 (d, $ArCH_2Ar$, $J = 13.1$ Hz, 1H), 4.20 (d, $ArCH_2Ar$, $J = 13.5$ Hz, 1H), 4.27 (d, $ArCH_2Ar$, $J = 13.8$ Hz, 1H), 4.28 (d, $ArCH_2Ar$, $J = 13.8$ Hz, 1H), 4.35 and 4.62 (AB, $OCH_2CO$, $J = 14.7$ Hz, 2H), 5.17 (m, Tyr-H$^\alpha$, 1H) 6.89–7.21 (AB, ArH, $J = 8.4$ Hz, 4H),

7.03–7.12 (overlapping, ArH, 8H), 9.18 (s, OH, 1H), 9.52 (d, NH, $J = 8.9$ Hz, 1H), 9.64 (s, OH, 1H), 10.04 (s, OH, 1H); $^{13}$C NMR ($CDCl_3$, 298 K): $\delta$ 28.52 (q), 30.78 (q), 31.11 (q), 31.17 (q, 6C), 31.62 (t), 31.88 (t), 32.55 (t), 32.69 (t), 33.63 (s, 2C), 33.78 (s), 33.97 (s), 36.84 (t), 52.22 (d), 53.06 (q), 74.78 (t), 77.95 (s), 123.85 (d, 3C), 125.52 (s), 125.61 (d, 3C), 125.85 (d), 126.22 (d), 126.61 (s), 126.70 (s), 126.86 (d), 127.34 (s), 127.53 (s), 128.10 (s), 129.25 (d, 3C), 131.29 (s), 132.14 (s), 132.68 (s), 143.23 (s), 143.61 (s), 143.81 (s), 146.75 (s), 147.65 (s), 147.89 (s), 148.29 (s), 148.84 (s), 153.80 (s), 167.50 (s), 171.67 (s); ESI(+) MS *m/z* 962 ($MNa^+$). Anal. Calcd for $C_{60}H_{77}NO_8$: C, 76.64; H, 8.25; N, 1.49. Found: C, 76.60; H, 8.30; N, 1.41.

**4.1.2. 5,11,17,23-Tetra-*tert*-butyl-25-[bis(*O*-*tert*-butyl)-(*S*)-aspartyl-carbonylmethoxy)]calix[4]aren-26,27,28-triol 5b.** 0.17 g (55%), $[\alpha]_D^{25} = -5.1$ (*c* 0.4, $CHCl_3$); $^1$H NMR ($CDCl_3$, 298 K): $\delta$ 1.20 [s, $C(CH_3)_3$, 9H], 1.24 [s, $C(CH_3)_3$, 9H], 1.25 [s, $C(CH_3)_3$, 9H], 1.26 [s, $C(CH_3)_3$, 9H], 1.46 [s, $C(CH_3)_3$, 9H], 1.52 [s, $C(CH_3)_3$, 9H], 2.92 (dd, Asp-H$^\beta$, $J = 16.3$, 8.3 Hz, 1H), 3.03 (dd, Asp-H$^\beta$, $J = 16.3$, 5.3 Hz, 1H), 3.45–3.54 (overlapping, $ArCH_2$-Ar, 4H), 4.23–4.30 (overlapping, $ArCH_2Ar$, 4H), 4.57 and 4.70 (AB, $OCH_2CO$, $J = 14.7$ Hz, 2H), 5.07 (m, Asp-H$^\alpha$, 1H), 7.03–7.10 (overlapping, ArH, 8H), 9.26 (s, OH, 1H), 9.48 (d, NH, $J = 9.9$ Hz, 1H), 9.49 (s, OH, 1H), 9.96 (s, OH, 1H); $^{13}$C NMR ($CDCl_3$, 298 K): $\delta$ 28.18 (q, 6C), 31.30 (q), 31.67 (q, 9C), 32.27 (t), 32.43 (t), 33.04 (t), 33.10 (t), 34.12 (s, 2C), 34.24 (s), 34.47 (s), 37.81 (t), 50.00 (d), 75.42 (t), 81.31 (s), 82.33 (s), 125.93 (d, 4C), 125.99 (s), 126.12 (d), 126.22 (d), 126.90 (s), 127.22 (d, 2C), 127.32 (s), 127.62 (s), 128.16 (s), 128.39 (s), 132.91 (s), 133.07 (s), 143.65 (s), 143.82 (s), 144.02 (s), 147.30 (s), 148.25 (s), 148.50 (s), 149.04 (s), 149.23 (s), 167.89 (s), 169.60 (s), 169.83 (s); ESI(+) MS *m/z* 956 ($MNa^+$). Anal. Calcd for $C_{58}H_{79}NO_9$: C, 74.57; H, 8.52; N, 1.50. Found: C, 74.62; H, 8.49; N, 1.45.

**4.1.3. 5,11,17,23-Tetra-*tert*-butyl-25-[*O*-methyl-(*S*)-valinyl-carbonylmethoxy]calix[4]aren-26,27,28-triol 5c.** 0.11 g (47%). $[\alpha]_D^{25} = -1.5$ (*c* 0.83, $CHCl_3$); $^1$H NMR ($CDCl_3$, 298 K): $\delta$ 1.09 (d, $CH(CH_3)_3$, $J = 6.7$ Hz, 3H), 1.13 (d, $CH(CH_3)_3$, $J = 6.8$ Hz, 3H), 1.17 [s, $C(CH_3)_3$, 9H], 1.21 [s, $C(CH_3)_3$, 9H], 1.22 [s, $C(CH_3)_3$, 18H], 2.42 (m, Val-H$^\beta$, 1H), 3.45–3.52 (overlapping, $ArCH_2Ar$, 4H), 3.83 (s, $OCH_3$, 3H), 4.19–4.27 (overlapping, $ArCH_2Ar$, 4H), 4.56 and 4.66 (AB, $OCH_2CO$, $J = 15.2$ Hz, 2H), 4.75 (dd, Val-H$^\alpha$, $J = 8.9$, 6.7 Hz, 1H), 6.99–7.09 (overlapping, ArH, 8H), 9.16 (s, OH, 1H), 9.23 (d, NH, $J = 9.5$ Hz, 1H), 9.50 (s, OH, 1H), 10.03 (s, OH, 1H); $^{13}$C NMR ($CDCl_3$, 298 K): $\delta$ 18.89 (q), 19.38 (q), 30.78 (d), 31.09 (q), 31.41 (q), 31.49 (q, 6C), 31.86 (t), 32.14 (t), 32.91 (t), 32.96 (t), 33.93 (s, 2C), 34.09 (s), 34.29 (s), 52.28 (d), 57.94 (q), 75.37 (t), 125.75 (d, 4C), 125.84 (d), 125.97 (d), 126.13 (d), 126.73 (d), 126.78 (s), 126.95 (s), 127.11 (s), 127.46 (s), 127.92 (s), 128.40 (s), 132.49 (s), 132.87 (s), 143.41 (s), 143.70 (s), 144.02 (s), 146.99 (s), 148.00 (s), 148.33 (s), 148.59 (s), 149.13 (s), 168.11 (s), 171.87 (s); ESI(+) MS *m/z* 842 ($MNa^+$). Anal. Calcd for $C_{52}H_{69}NO_7$: C, 76.16; H, 8.48; N, 1.71. Found: C, 76.22; H, 8.40; N, 1.65.

**4.1.4. 5,11,17,23-Tetra-*tert*-butyl-25-[*O*-methyl-(*S*)-tryptophanyl-carbonylmethoxy]calix[4]aren-26,27,28-triol 5d.** 0.19 g (69%), $[\alpha]_D^{25} = -22$ (*c* 4.1, $CHCl_3$); $^1$H NMR ($CDCl_3$, 298 K): $\delta$ 1.17 [s, $C(CH_3)_3$, 9H], 1.23 [s, $C(CH_3)_3$, 9H], 1.24 [s, $C(CH_3)_3$, 9H], 1.26 [s, $C(CH_3)_3$, 9H], 3.21 (d, $ArCH_2Ar$, $J = 13.1$ Hz, 1H), 3.43–3.60 (overlapping, 5H), 3.84 (s, $OCH_3$, 3H), 4.00 (d, $ArCH_2$-Ar, $J = 13.1$ Hz, 1H), 4.12 (d, $ArCH_2Ar$, $J = 13.8$ Hz, 1H), 4.18 (d, $ArCH_2Ar$, $J = 13.4$ Hz, 1H), 4.20 (d, $ArCH_2Ar$, $J = 13.8$ Hz, 1H), 4.40 and 4.64 (AB, $OCH_2$-CO, $J = 14.7$ Hz, 2H), 5.27 (m, Trp-H$^\alpha$, 1H), 7.01–7.27 (overlapping, ArH, 12H), 7.65 (d, ArH, $J = 7.8$ Hz, 1H) 7.91 (br s, NH, 1H), 9.07 (s, OH, 1H), 9.45 (d, NH, $J = 8.7$ Hz, 1H), 9.49 (s, OH, 1H), 9.96 (s, OH, 1H); $^{13}$C NMR ($CDCl_3$, 298 K): $\delta$ 27.89 (t), 31.25 (q), 31.60 (q), 31.66 (q), 31.72 (q), 32.00 (t), 32.32 (t), 32.99 (t), 33.12 (t), 34.11 (s, 2C), 34.25 (s), 34.43 (s), 52.83 (s), 53.06 (q), 75.44 (t), 111.11 (s), 111.24 (d), 118.93 (d), 119.65 (d), 122.17 (d), 123.07 (d), 125.90 (d, 2C), 126.01 (d, 3C), 126.31 (d), 126.68 (d), 127.10 (s, 2C), 127.29 (d), 127.77 (s, 2C), 128.07 (s), 128.57 (s, 2C), 132.64 (s), 133.08 (s), 136.36 (s), 143.53 (s), 144.04 (s), 144.23 (s), 147.07 (s), 148.01 (s), 148.50 (s), 148.81 (s), 149.23 (s), 168.11 (s), 172.41 (s); ESI(+) MS *m/z* 929 ($MNa^+$). Anal. Calcd for $C_{58}H_{70}N_2O_7$: C, 76.69; H, 7.78; N, 3.09. Found: C, 76.62; H, 7.85; N, 3.15.

### 4.2. 5,11,17,23-Tetra-*tert*-butyl-25,27-bis[*O*-methyl-*O*′-*tert*-butyl-(*S*)-tyrosinyl-carbonylmethoxy]calix[4]aren-26,28-diol 7

*p*-*tert*-Butylcalix[4]arene-diacetic acid **6** (0.08 g, 0.10 mmol) was reacted for 6 h with DMAP (0.02 g, 0.24 mmol), DCC (0.10 g, 0.48 mmol), and *t*-Bu-*O*-(L)-Tyr-OMe·HCl (0.14 g, 0.48 mmol) as described above for compounds **5a**–**d**. The crude product was subjected to flash chromatography on silica gel, using dichloromethane/diethyl ether (95:5, v/v) as eluent, to give **7**: 0.97 g (79%), $[\alpha]_D^{25} = +22$ (*c* 0.7, $CHCl_3$); $^1$H NMR ($CDCl_3$, 298 K): $\delta$ 1.04 [s, $C(CH_3)_3$, 18H], 1.27 [s, $C(CH_3)_3$, 18H], 1.28 [s, $C(CH_3)_3$, 18H], 2.97–3.13 (overlapping, 6H), 3.47 (m, 2H), 3.54 (s, $OCH_3$, 6H), 4.03–4.16 (overlapping, 8H), 5.06 (m, Tyr-H$^\alpha$, 2H), 6.69–7.05 (overlapping, ArH, 16H), 7.92 (s, OH, 2H), 9.61 (d, NH, $J = 8.6$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 298 K): $\delta$ 25.19 (q), 25.84 (q), 29.06 (t), 31.24 (t), 31.91 (t), 34.20 (q), 38.92 (s, 4C), 49.41 (q), 52.99 (d), 75.21 (t), 77.26 (s), 124.35 (d), 125.24 (d), 125.61 (d), 126.13 (d), 126.48 (d), 127.06 (d), 127.68 (d), 129.70 (d), 131.30 (s), 131.70 (s), 132.90 (s), 133.10 (s), 143.00 (s), 148.10 (s), 149.90 (s), 150.05 (s), 154.60 (s), 157.00 (s), 168.10 (s), 170.18 (s); ESI(+) MS *m/z* 1253 ($MNa^+$). Anal. Calcd for $C_{76}H_{98}N_2O_{12}$: C, 74.12; H, 8.02; N, 2.27. Found: C, 74.20; H, 8.00; N, 2.19.

### 4.3. 5,11,17,23-Tetra-*tert*-butyl-25-[(*R*,*R*)-6,6-dimethyl-bicyclo[3.1.1]hept-2-ene-2-methoxy-carbonylmethoxy]-calix[4]aren-26,27,28-triol 8

*p*-*tert*-Butylcalix[4]arene monoacetic acid **4** (0.30 g, 0.42 mmol), was reacted with (−)-myrtenol (0.15 g, 0.97 mmol), DMAP (0.10 g, 0.84 mmol), and DCC (0.20 g, 0.97 mmol) in dry $CH_2Cl_2$ (40 mL), as described

above for compounds **5a**–**d**. The crude product was subjected to flash chromatography on silica gel, using $CH_2Cl_2$ as eluent, to give **8**: 0.25 g, (70%), $[\alpha]_D^{25} = -8.0$ (*c* 2.8, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 298 K): $\delta$ 0.93 [s, $CH_3$, 3H], 1.27 [s, $C(CH_3)_3$, 9H], 1.28 [s, $C(CH_3)_3$, 18H], 1.30 [s, $C(CH_3)_3$, 9H], 1.38 [s, $CH_3$, 3H], 2.19–2.51 (overlapping 6H), 3.49 (d, $ArCH_2Ar$, $J = 13.0$ Hz, 2H), 3.50 (d, $ArCH_2Ar$, $J = 13.7$ Hz, 2H), 4.38 (d, $ArCH_2Ar$, $J = 13.6$ Hz, 2H), 4.56 (d, $ArCH_2Ar$, $J = 13.0$ Hz, 1H), 4.59 (d, $ArCH_2Ar$, $J = 13.0$ Hz, 1H), 4.75 and 4.81 (AB, $OCH_2$, $J = 12.2$ Hz, 2H), 4.95 and 4.99 (AB, $OCH_2$, $J = 15.9$ Hz, 2H), 5.77 (br s, C=CH, 1H), 7.05 (br s, ArH, 1H), 7.06 (br s, ArH, 1H), 7.12 (br s, ArH, 4H), 7.16 (br s, ArH, 2H), 9.33 (br s, OH, 2H), 10.30 (br s, OH, 1H); $^{13}C$ NMR ($CDCl_3$, 298 K): $\delta$ 21.09 (q), 22.64 (s), 26.07 (q), 31.20 (q), 31.32 (t, 2C), 31.45 (q, 9C), 32.51 (t, 2C), 32.96 (t, 2C), 33.89 (s, 2C), 34.18 (s), 38.06 (s), 40.58 (d), 43.60 (d), 68.39 (t), 71.91 (t), 123.15 (d), 125.58 (d, 2C), 125.73 (d, 4C), 126.58 (d, 2C), 127.65 (s, 3C), 127.97 (s, 4C), 133.22 (s), 133.28 (s), 142.18 (s), 143.02 (s, 2C), 143.30 (s), 148.22 (s, 3C), 150.16 (s), 169.67 (s); ESI(+) MS *m*/*z* 863 ($MNa^+$). Anal. Calcd for $C_{56}H_{72}O_6$: C, 79.96; H, 8.63. Found: C, 79.88; H, 8.70.

### 4.4. 5,11,17,23-Tetra-*tert*-butyl-25,27-bis[(*R*,*R*)-6,6-dimethyl-bicyclo[3.1.1]hept-2-ene-2-methoxy]calix[4]aren-26,28-diol 10

A mixture of *p*-*tert*-butylcalix[4]arene **9** (0.04 g, 0.07 mmol), $K_2CO_3$ (0.02 g, 0.17 mmol) and myrtenyl *p*-toluensulfonate (0.20 g, 0.66 mmol) in 5 mL of $CH_3CN$, was refluxed for 36 h. After concentration under vacuum, the residue was dissolved in $CH_2Cl_2$ and washed with 1 M HCl (10 mL) and brine (10 mL). The organic phase was dried over $Na_2SO_4$ and concentrated in vacuo. The crude product was subjected to flash chromatography on silica gel, using petroleum ether/dichloromethane (95:5, v/v) as eluent, to give **10**: 40 mg (62%), $[\alpha]_D^{25} = +2.6$ (*c* 1.9, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 298 K): $\delta$ 0.92 [s, $C(CH_3)_3$, 18H], 0.95 [s, $CH_3$, 6H], 1.27 [s, $CH_3$, 6H], 1.32 [s, $C(CH_3)_3$, 18H], 1.87–2.18 (overlapping, 10H), 2.66 (m, 2H), 3.28 and 4.28 (AX, $ArCH_2Ar$, $J = 12.9$ Hz, 4H), 3.29 and 4.33 (AX, $ArCH_2$-Ar, $J = 13.0$ Hz, 4H), 3.78 (br t, $OCH_2$, 4H), 5.11 (br s, C=CH, 2H), 6.75 (br s, ArH, 4H), 7.07 (br s, ArH, 4H), 7.27 (s, OH, 2H); $^{13}C$ NMR ($CDCl_3$, 298 K): $\delta$ 19.38 (t), 20.47 (q), 24.22 (t), 24.48 (t), 26.26 (q), 31.20 (q), 31.69 (t), 31.95 (q), 34.00 (s), 34.05 (s), 39.84 (s), 41.14 (d), 43.45 (d), 81.86 (t), 124.16 (d, 4C), 125.45 (d, 3C), 125.62 (d, 3C), 127.86 (s), 127.94 (s), 132.52 (s), 132.58 (s), 141.31 (s), 146.72 (s), 150.23 (s), 151.18 (s, 4C); ESI(+) MS *m*/*z* 939 ($MNa^+$). Anal. Calcd for $C_{64}H_{84}O_4$: C, 83.79; H, 9.23. Found: C, 83.85; H, 9.16.

### 4.5. 5,11,17,23-Tetra-*tert*-butyl-25,27-bis[(*R*,*R*)-6,6-dimethyl-bicyclo[3.1.1]hept-2-ene-2-ethoxy]calix[4]aren-26,28-diol 11

*p*-*tert*-Butylcalix[4]arene **9** (0.2 g, 0.3 mmol), was reacted for 16 h with homomyrtenyl *p*-toluensulfonate (1.0 g, 3.3 mmol) and $K_2CO_3$ (0.12 g, 0.86 mmol) in 15 mL of $CH_3CN$ as described above for compound **10**. The crude product was subjected to flash chromatography on silica gel, using petroleum ether/dichloromethane (99:1, v/v) as eluent, to give **11**: 0.13 g (46%), $[\alpha]_D^{25} = -15$ (*c* 1.5, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 298 K): $\delta$ 0.85 [s, $CH_3$, 6H], 0.97 [s, $C(CH_3)_3$, 18H], 1.27 [s, $C(CH_3)_3$, 18H], 1.28 [s, $CH_3$, 6H], 2.08–2.39 (overlapping, 8H), 2.70–2.80 (overlapping, 8H), 3.30 (d, $ArCH_2$- Ar, $J = 12.9$ Hz, 4H), 3.98 (t, $OCH_2$, $J = 8.0$ Hz, 4H), 4.27 (d, $ArCH_2Ar$, $J = 12.9$ Hz, 2H), 4.29 (d, $ArCH_2Ar$, $J = 12.9$ Hz, 2H), 5.40 (br s, CH=C, 2H), 6.80 (br s, ArH, 4H), 7.03 (br s, ArH, 4H), 7.57 (s, OH, 2H); $^{13}C$ NMR ($CDCl_3$, 298 K): 21.42 (q), 26.53 (q), 31.27 (q), 31.62 (t), 31.85 (t), 31.90 (q), 32.11 (t), 32.14 (t), 34.02 (s), 34.15 (s), 37.62 (t), 38.29 (s), 40.94 (d), 46.19 (d), 74.89 (t), 118.87 (d), 125.23 (d, 4C), 125.60 (d), 125.68 (d), 128.07 (s), 128.16 (s), 132.97 (s), 133.02 (s), 141.47 (s), 144.11 (s), 146.85 (s), 150.32 (s), 150.84 (s); ESI(+) MS *m*/*z* 967 ($MNa^+$). Anal. Calcd for $C_{66}H_{88}O_4$: C, 83.85; H, 9.38. Found: C, 83.79; H, 9.46.

### 4.6. 5,11,17,23-Tetra-*tert*-butyl-25,27-[(*S*)-binaphthyl-2,2′-bis(aminocarbonylmethoxy]calix[4]aren-26,28-diol 12

A mixture of *p*-*tert*-butylcalix[4]arene diacetic acid **6** (0.3 g, 0.4 mmol), DCC (0.24 g, 1.2 mmol), and DMAP (0.14 g, 1.7 mmol) in dry $CH_2Cl_2$ (24 mL) was stirred at 25 °C for 30 min. Then, a solution of (*S*)-(−)-2,2′-diamino-1,1′-binaphthalene (0.11 g, 0.4 mmol) in $CH_2Cl_2$ (24 mL), was added dropwise over 1 h. The resulting solution was stirred for 90 min at room temperature and then dicyclohexylurea was filtered off. The $CH_2Cl_2$ phase was washed with 1 M HCl, brine, dried over $Na_2SO_4$, and concentrated in vacuo. The crude product was subjected to flash chromatography on silica gel, using dichloromethane/petroleum ether (98:2, v/v) as eluent, to give **12**: 0.12 g (30%), $[\alpha]_D^{25} = -89$ (*c* 2.5 $CHCl_3$); $^1H$ NMR ($CDCl_3$, 298 K): 1.19 [s, $C(CH_3)_3$, 18H], 1.29 [s, $C(CH_3)_3$, 18H], 3.52 and 3.84 (AB, $ArCH_2Ar$, $J = 13.8$ Hz, 4H), 4.13 and 4.40 (AB, $OCH_2$, $J = 14.8$ Hz, 4H), 3.55 and 4.48 (AX, $ArCH_2Ar$, $J = 12.6$ Hz, 4H), 7.02–8.13 (overlapping, ArH, 20H), 8.85 (OH, 2H) 10.9 (NH, 2H); $^{13}C$ NMR ($CDCl_3$, 298 K): $\delta$ 31.07 (q), 31.56 (q), 31.95 (t), 32.86 (t), 33.94 (s), 34.31 (s), 74.09 (t), 125.06 (d), 125.68 (d, 3C), 125.98 (d, 3C), 126.30 (d), 127.33 (d), 127.52 (s, 6C), 127.62 (d), 128.08 (d), 129.54 (d, 4C), 131.41 (s), 132.37 (s), 132.61 (s), 132.95 (s), 133.70 (s), 143.40 (s), 148.12 (s), 148.96 (s), 149.42 (s), 164.86 (s); ESI(+) MS *m*/*z* 1035 ($MNa^+$). Anal. Calcd for $C_{68}H_{72}N_2O_6$: C, 80.60; H, 7.16; N, 2.76. Found: C, 80.54; H, 7.24; N, 2.70.

### 4.7. General procedure for asymmetric aldol reaction catalyzed by Ti(IV)/chiral-calix[4]arene complex

A mixture of $Ti(O\text{-}i\text{-}Pr)_4$ (0.16 mmol), chiral *p*-*tert*-butylcalix[4]arene derivative (0.16 mmol), and molecular sieves (680 mg) in dry THF (4 mL) was stirred at rt for 1 h. The mixture was cooled at −78 °C, then aldehyde **2a** (1 mmol) was added followed, after 30 min, by a solution of the Chan's diene **1** (2 mmol) in THF (2 mL). The mixture was stirred at −78 °C for 2 h and at rt overnight (16 h). The mixture was cooled to −78 °C and TFA (0.8 mL) added. After stirring at rt

for 1 h, desilylation was complete and the reaction mixture diluted with ether and a saturated aqueous $NaHCO_3$ solution (4 mL) was added dropwise. The mixture was stirred until the evolution of gas ceased (30 min), then the organic layer was separated and washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The pure aldol product was obtained by the usual purification procedures and enantiomeric excesses were determined by HPLC analysis on Chiralpak AD column as reported in the literature.[19]

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