Synthesis of the First Axially Dissymmetric, $C^{\alpha,\alpha}$-Disubstituted Glycine Containing a Crown Ether Receptor, and the Conformational Preferences of a Model Peptide

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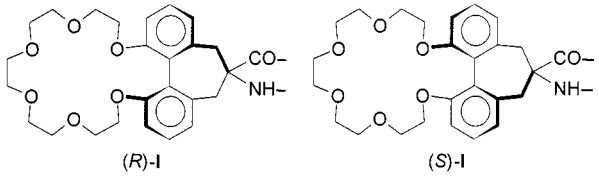
Keywords: Atropoisomeric amino acids / Axial chirality / $C^{\alpha,\alpha}$-disubstituted glycine / Crown compounds / Side-chain modified amino acids

Racemic and enantiomerically enriched N^{α}-protected methyl 6-amino-1,11-(20-crown-6)-6,7-dihydro-5*H*-dibenzo[*a*,*c*]-cycloheptene-6-carboxylates (Boc-[20-C-6]-Bip-OMe) (*RS*)-**Ia**, (*R*)-**Ia** and (*S*)-**Ia** have been synthesized by phase-transfer dialkylation of the 4-chlorobenzylidene derivative of glycine *tert*-butyl ester, with both racemic and resolved (both enantiomers) 2,2′-bis(bromomethyl)-6,6′-dimethoxy-1,1′-biphenyl being used as alkylating agents. Demethylation of the resulting (*RS*)-, (*R*)- and (*S*)-H-[MeO]$_2$-Bip-O*t*Bu, followed by esterification and N^{α}-Boc protection, gave (*RS*)-, (*R*)- and (*S*)-Boc-[HO]$_2$-Bip-OMe. Cyclization with Cs_2CO_3/DMF and pentaethylene glycol ditosylate afforded the crown-carrier $C^{\alpha,\alpha}$-disubstituted glycines (*RS*)-**Ia**, (*R*)-**Ia** and (*S*)-**Ia**, possessing only axial dissymmetry. Although (*R*)-**Ia** and (*S*)-**Ia** are enantiomerically stable in solution at 110 °C, they were obtained with only 64% *ee* and 48% *ee*, respectively, because of racemization occurring both at the demethylation/esterification and at the crown formation stages of the synthesis. Solution synthesis provided access to: (*i*) a number of [20-C-6]-Bip/Gly peptides up to the pentapeptide Boc-[20-C-6]-Bip-Gly-Gly-[20-C-6]-Bip-Gly-OMe (*RR*,*SS*)- and (*RS*,*SR*)-**Va** as a mixture of two racemic isomers, and (*ii*) the heptapeptide Boc-[20-C-6]-Bip-(Aib)$_6$-O*t*Bu (*S*)-**VI**. Conformational analysis of (*S*)-**VI** by FT-IR absorption and ^{1}H NMR indicated a high degree of folding, with spectral patterns typical of a 3_{10}-helical peptide. The absolute configuration of the [20-C-6]-Bip residue was correlated with the CD pattern in the 200–300 nm region.

Introduction

Synthetic α-amino acids bearing crown ether moieties are of great interest for the preparation of ion-selective molecular receptors, since they can easily be assembled in supramolecular architectures of both bis(crown) and polymeric crown compounds with a peptide framework.[1,2] For that purpose, crown-carrier derivatives of L-DOPA,[1−12] lysine[13] and glutamic acid[14] have been exploited in the past few years. However, this concept had not yet been applied to $C^{\alpha,\alpha}$-disubstituted glycines,[15] in spite of their known ability to induce predictable secondary structures by stabilizing either fully extended or folded (turn and helical) conformations in polypeptides,[16−23] which makes them attractive building blocks for the construction of supramolecular devices with peptides as framework. We have recently shown that new cyclic, axially chiral, C^{α}-tetrasubstituted α-amino acids of the 1-aminocycloheptane-1-carboxylic acid (Ac_7c) type, Bip and Bin − 1,1′-biphenyl- and 1,1′-binaphthyl-substituted analogues of Aib − behave as helix inducers in short-chain peptides.[24−27]

In this paper we report our detailed experimental procedure for the synthesis of the 6-amino-1,11-(20-crown-6)-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene-6-carboxylic acid residue ([20-C-6]-Bip) both in racemic and in enantiomerically enriched forms, (*R*)-**I** and (*S*)-**I** (Figure 1).[28,29] This compound represents the first example of a crown-carrier $C^{\alpha,\alpha}$-disubstituted glycine with axial dissymmetry. Selected peptides based on the [20-C-6]-Bip residue have also been synthesized by solution methods.



(*R*)-**I** (*S*)-**I**

Figure 1. Chemical structure of the enantiomeric crown-carrier, axially dissymmetric, $C^{\alpha,\alpha}$-disubstituted glycyl residue [20-C-6]-Bip (*R*)-**I** and (*S*)-**I**

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Results and Discussion

Synthesis and Characterization of Amino Acid Derivatives

Racemic 6,6′-dimethoxy-1,1′-biphenyl-2,2′-dicarboxylic acid [(*R*,*S*)-**1**; Figure 2] was first prepared from 2-amino-3-methoxybenzoic acid,[30] and resolved through its diquinine salt as previously described.[31−33] In our hands, however, the described resolution procedure could not be reproduced well and we ended up with enantiomerically enriched but not enantiomerically pure samples of each enantiomer, (−)-(*R*)-**1** (76% yield; 91 ± 5% *ee*) (*ee*: enantiomeric excess) and (+)-(*S*)-**1** (88% yield; 75 ± 5% *ee*). To avoid racemization, known to occur relatively easily for the diacid, its sodium salt and its methyl ester, it has been recommended (by Hall et al.[32]) that the subsequent steps be carried out at temperatures below ca. 50 °C, with diazomethane in diethyl ether/ethanol at 0 °C for esterification and $LiAlH_4$ in refluxing diethyl ether for reduction of the diester to the corresponding diol. As an improvement on such a two-step procedure, we were able to perform one-step reductions of (−)-(*R*)-**1** and (+)-(*S*)-**1** to the corresponding diols under mild conditions and in high yields − giving (−)-(*R*)-**2** (88% yield; 95 ± 5% *ee*) and (+)-(*S*)-**2** (77% yield; 71 ± 5% *ee*) (Figure 2) − with BH_3/THF (tetrahydrofuran) at room temperature. The racemic diacid (*R*,*S*)-**1** was also successfully reduced to (*R*,*S*)-**2** (92% yield) by that method. The crude samples of diol **2** were then treated with PBr_3 in toluene[32] to give the dibromides (−)-(*R*)-**3** (63% yield; 99 ± 5% *ee*), (+)-(*S*)-**3** (77% yield; 74 ± 5% *ee*) and (*R*,*S*)-**3** (56% yield).

The dibromides (*R*,*S*)-**3**, (*R*)-**3** and (*S*)-**3** were used as alkylating agents in the solid-liquid phase-transfer dialkylation of (4-chlorobenzylidene)glycine *tert*-butyl ester,[34,35] prepared as previously described for (4-chlorobenzylidene)alanine ethyl ester,[36] with tetrabutylammonium bromide as catalyst and the mixed base KOH/K_2CO_3 in dichloromethane, according to O'Donnell et al.[35−37] Deprotection of the amino group of the resulting $C^{\alpha,\alpha}$-dialkylated glycine ester Schiff base, performed variously by transimination,[38,39] acidic cleavage on silica gel or, more conveniently, by hydrolysis of the crude reaction product with 0.5 M citric acid in THF, gave H-$[MeO]_2$-Bip-O*t*Bu (*R*,*S*)-**4** in 64% yield. The corresponding amino esters (*R*)-**4** (61%) and (*S*)-**4** (48%) were obtained in somewhat lower yields, with side products arising from a further *N*,*N*-dialkylation of **4** being isolated: (*RR*)-**5** (21%) and (*SS*)-**5** (35%), respectively (Figure 3). We suspect partial degradation of the starting (4-chlorobenzylidene)glycine *tert*-butyl ester during storage, resulting in the presence of unchanged dibromide **3**, which, after hydrolysis of the reaction mixture, could alkylate the amino function of **4**.

Treatment of aliquots of samples of (*R*)-**4** and of (*S*)-**4** with (−)-(*S*)-α-methoxy-α-trifluoromethyl-α-phenylacetic anhydride, produced by treatment of Mosher's acid[40] with 0.5 equiv. of DCC (*N*,*N*′-dicyclohexylcarbodiimide) in acetonitrile as previously described,[25] provided the diastereoisomeric amido esters (*S*)-Ph(OCH_3)(CF_3)C-CO-(*R*)-$[MeO]_2$-Bip-O*t*Bu with 98 ± 2% *de* (*de*: diastereoisomeric excess) and (*S*)-Ph(OCH_3)(CF_3)C-CO-(*S*)-$[MeO]_2$-Bip-O*t*Bu with 64 ± 5% *de*, respectively, as determined by ^1H NMR and ^{19}F NMR. These *de* values were very similar, within experimental error, to the enantiomeric excesses of the starting dibromides (−)-(*R*)-**3** (99 ± 5% *ee*) and (+)-

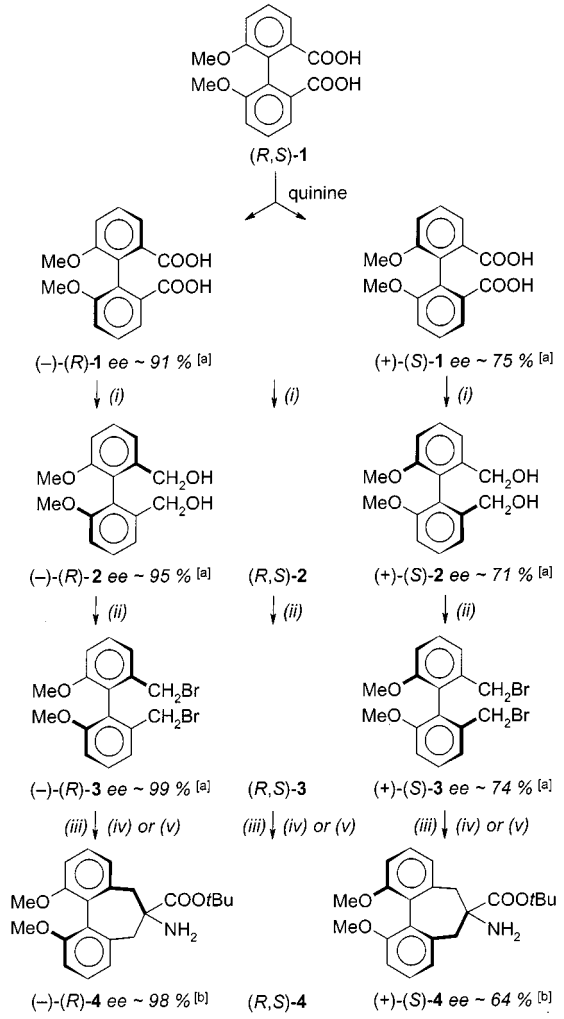

Figure 2. Synthesis of racemic and chirally resolved H-$[MeO]_2$-Bip-O*t*Bu (**4**): (*i*) BH_3, THF, 0 to 25 °C, 5 h; (*ii*) PBr_3, toluene, 0 to 45 °C; (*iii*) (4-chlorobenzylidene)glycine *tert*-butyl ester, KOH powder, K_2CO_3, CH_2Cl_2, room temp.; (*iv*) $NH_2OH{\cdot}HCl$, AcONa, 95% EtOH, room temp.; (*v*) 0.5 M citric acid, THF, room temp.; [a] enantiomeric excess (optical purity) determined by comparison of the optical rotation with the maximum value from literature (see text and Exp. Sect.); [b] determined by ^{19}F NMR of the corresponding Mosher amide (see text and Exp. Sect.)

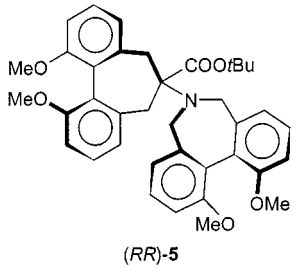

Figure 3. Chemical structure of the side product (*RR*)-**5**

(*S*)-**3** (74 ± 5% *ee*), thus demonstrating *absence of racemization in the phase-transfer dialkylation reaction*.

Demethylation of the 6,6′-methoxy groups of (*RS*)-**4**, (*R*)-**4** and (*S*)-**4** by boron tribromide[41] in dichloromethane was accompanied by cleavage of the *tert*-butyl ester function, to give H-[HO]$_2$-Bip-OH·HBr, which was not isolated but directly esterified in methanol and 98% H_2SO_4 (catalyst) at 50−55 °C to afford the corresponding methyl 6-amino-1,11-dihydroxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene-6-carboxylates (H-[HO]$_2$-Bip-OMe) (*RS*)-**6** (73%), (*R*)-**6** (55%) and (*S*)-**6** (75%) (Figure 4). The enantiomeric purities of (*R*)-**6** (56 ± 5% *ee*) and (*S*)-**6** (37 ± 5% *ee*) were determined by comparison of their optical rotations: $[\alpha]^{25}_{436} = -74.4$, $[\alpha]^{25}_{365} = -343.0$ ($c = 0.1$; MeOH) for (*R*)-**6** and $[\alpha]^{25}_{436} = +51.1$, $[\alpha]^{25}_{365} = +225.8$ ($c = 0.25$; MeOH) for (*S*)-**6**, with the maximum values $[\alpha]^{25}_{436} = -136.7$, $[\alpha]^{25}_{365} = -610.2$ ($c = 0.1$; MeOH) and $[\alpha]^{25}_{436} = +130.5$, $[\alpha]^{25}_{365} = +602.1$ ($c = 0.1$; MeOH), respectively, extrapolated from the optical rotations of samples of known enantiomeric excess (see Table 1), determined from the ^{19}F NMR spectra of the corresponding Mosher's amide/half phenyl ester isomers (vide infra).

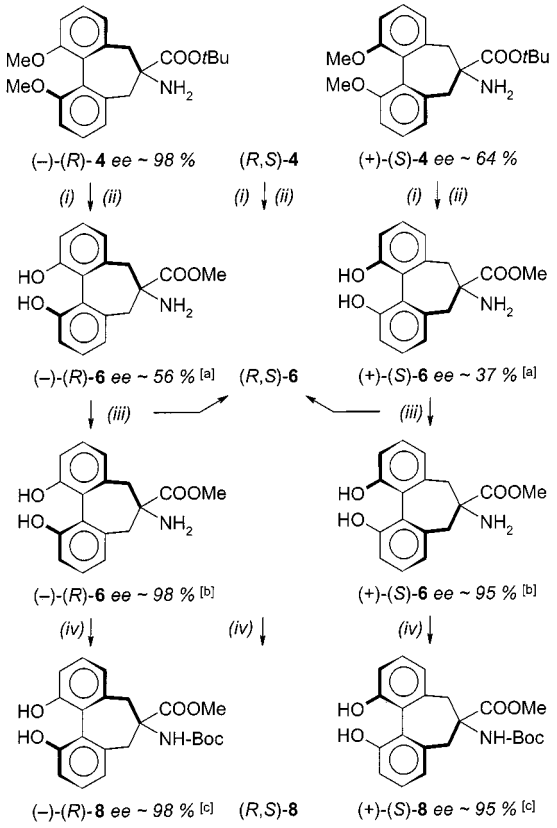

Figure 4. Synthesis of racemic and chirally resolved H-[HO]$_2$-Bip-OMe (**6**) and Boc-[HO]$_2$-Bip-OMe (**8**); (*i*) BBr_3, CH_2Cl_2, room temp.; (*ii*) MeOH, 98% H_2SO_4 (cat.), reflux; (*iii*) fractional crystallization of (*R*,*S*)-**6**; (*iv*) Boc_2O, CH_3CN, room temp. or 75 °C (for racemic); [a] enantiomeric excess (optical purity), determined by comparison of the optical rotation with the calculated maximum value (see text and Exp. Sect.); [b] determined by ^{19}F NMR of the corresponding Mosher amides/half phenyl ester isomers (see text and Exp. Sect.); [c] assumed (see text)

The observed decreases in the enantiomeric purity of (*R*)-**6** (56 ± 5% *ee*) relative to its precursor (*R*)-**4** (98 ± 2% *ee*) and in that of (*S*)-**6** (37 ± 5% *ee*) relative to its precursor (*S*)-**4** (64 ± 5% *ee*), demonstrates the *occurrence of extensive racemization during the demethylation/re-esterification steps*.

Luckily, racemic (*RS*)-**6** appeared to be only sparingly soluble in organic solvents and could be removed almost completely from samples enriched in either one of the more soluble (*R*)-**6** or (*S*)-**6** enantiomers by fractional crystallization. Indeed, crystallization of the sample of (*R*)-**6** (55% yield; 56 ± 5% *ee*) from CH_2Cl_2 provided separated crystals of nearly racemic (*RS*)-**6** (27% yield) and nearly enantiomerically pure (*R*)-**6** (26% yield; 98 ± 2% *ee*). In the same manner, crystals of nearly racemic (*RS*)-**6** (37% yield) and nearly enantiomerically pure (*S*)-**6** (27% yield; 95 ± 5% *ee*) were obtained from the sample of (*S*)-**6** (75% yield; 37 ± 5% *ee*). For determination of the enantiomeric excesses, aliquots of the thus obtained (*R*)-**6** and (*S*)-**6** were treated with excesses of Mosher's anhydride produced by treatment of (*S*)-Ph(OCH$_3$)(CF$_3$)C-COOH with 0.5 equiv. of EDC [*N*-ethyl-*N*′-(dimethylaminopropyl)carbodiimide hydrochloride] in acetonitrile. In these cases, however, acylation not only of the amino group, but also of one of the phenolic hydroxy groups took place, resulting in two amide/half phenyl ester isomers: (*S*)-Ph(OCH$_3$)(CF$_3$)C-CO-(*R*)-[HO; (*S*)-Ph(OCH$_3$)(CF$_3$)C-COO]-Bip-OMe: (*SRS*)-**7A** + (*SRS*)-**7B** from (*R*)-**6** and (*S*)-Ph(OCH$_3$) (CF$_3$)C-CO-(*S*)-[HO; (*S*)-Ph(OCH$_3$)(CF$_3$)C-COO]-Bip-OMe: (*SSS*)-**7A** + (*SSS*)-**7B** from (*S*)-**6** (Figure 5). The isomer pairs (*SRS*)-**7A** and (*SRS*)-**7B** and also (*SSS*)-**7A** and (*SSS*)-**7B** could easily be separated on preparative TLC (thin layer chromatography) silica gel plates. On the other hand, the isomer pairs (*SRS*)-**7A** and (*SSS*)-**7A** and also (*SRS*)-**7B** and (*SSS*)-**7B**, with close R_f values, remained inseparable, but the diastereoisomeric excess could be determined by ^{19}F NMR. Similar values were obtained both in series **7A** and in series **7B**: the (*SRS*)-**7A** and (*SRS*)-**7B** isomers were obtained from (*R*)-**6** with 98 ± 2% *de* over the (*SSS*)-**7A** and (*SSS*)-**7B** isomers, respectively, while the (*SSS*)-**7A** and (*SSS*)-**7B** isomers were obtained from (*S*)-**6** with 95 ± 5% *de* over the (*SRS*)-**7A** and (*SRS*)-**7B** isomers, respectively.[42]

Treatment of the samples of H-[HO]$_2$-Bip-OMe (*R*)-**6** and (*S*)-**6** with di-*tert*-butyl dicarbonate (Boc_2O) in acetonitrile,[43,44] at room temperature to prevent any racemization, afforded the corresponding N^{α}-protected α-amino esters Boc-[HO]$_2$-Bip-OMe (*R*)-**8** (88%) and (*S*)-**8** (87%), respectively (Figure 4). Enantiomeric excesses identical to those of the starting materials (*R*)-**6** and (*S*)-**6** can be assumed for the corresponding samples of (*R*)-**8** (98 ± 2% *ee*) and (*S*)-**8** (95 ± 2% *ee*) with a high degree of confidence, because of the relatively low temperature and neutral reaction conditions. In a control experiment, a solution of (*S*)-**6** in MeOH presented complete optical stability after 24 h at 50 °C (only at 110 °C in DMF did racemization occur, with a half-life of ca. 2 h). In a similar manner, the sparingly soluble racemic α-amino ester (*RS*)-**6** was treated with Boc_2O in acetonitrile at 75 °C to give (*RS*)-**8** (93%).

Table 1. Optical rotations of the different samples of 6,6′-disubstituted-2,2′-bridged biphenyl (Bip) derivatives **4**, **6**, **8** and **Ia** of known enantiomeric excess (*ee*), extrapolated to their maximum values (bold/italic characters)

	$[\alpha]^{25}_{589}$	$[\alpha]^{25}_{578}$	$[\alpha]^{25}_{546}$	$[\alpha]^{25}_{436}$	$[\alpha]^{25}_{365}$	*c* (MeOH)
(*R*)-**4** *ee* 98 ± 2%	+19.8	+18.8	+14.7	−7.6	−132.0	0.1
$[\alpha]_{max}$	***+20.2***	***+19.2***	***+15.0***	***−7.7***	***−134.7***	
(*S*)-**4** *ee* 64 ± 5%	−17.2	−17.7	−17.9	+3.2	+83.8	0.5
$[\alpha]_{max}$	***−26.8***	***−27.6***	***−27.9***	***+5.0***	***+130.9***	
(*R*)-**6** *ee* 98 ± 2%	−3.0	−7.6	−15.2	−134.0	−598.0	0.1
$[\alpha]_{max}$	***−3.1***	***−7.7***	***−15.5***	***−136.7***	***−610.2***	
(*S*)-**6** *ee* 95 ± 2%	+7.0	+7.9	+15.7	+124.0	+572.0	0.1
$[\alpha]_{max}$**x**	***+7.4***	***+8.3***	***+16.5***	***+130.5***	***+602.1***	
(*R*)-**8** *ee* 98 ± 2%	−137.7	−145.5	−174.1	−386.4	−905.0	0.1
$[\alpha]_{max}$	***−140.5***	***−148.5***	***−177.6***	***−394.3***	***−923.5***	
(*S*)-**8** *ee* 95 ± 2%	+137.8	+146.8	+173.0	+382.9	+917.6	0.1
$[\alpha]_{max}$	***+145.0***	***+154.5***	***+182.1***	***+403.0***	***+965.9***	
(*R*)-**Ia** *ee* 64 ± 5%	−89.0	−94.0	−109.0	−210.0	−399.0	0.1
$[\alpha]_{max}$	***−139.1***	***−146.9***	***−170.3***	***−328.1***	***−623.4***	
(*S*)-**Ia** *ee* 48 ± 5%	+72.0	+74.0	+85.0	+162.0	+318.0	0.1
$[\alpha]_{max}$	***+150.0***	***+154.2***	***+177.1***	***+337.5***	***+662.5***	

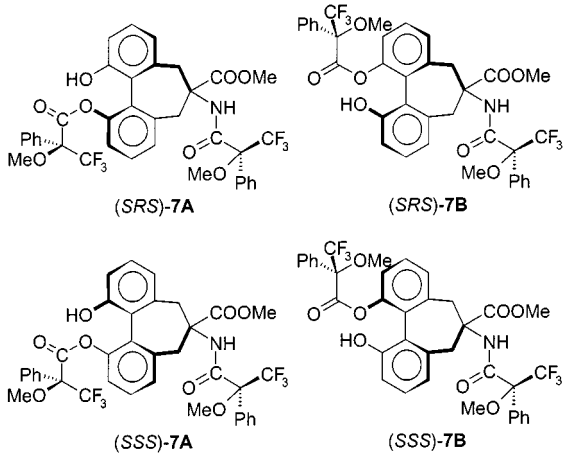

Figure 5. Chemical structures of the four diastereoisomeric Mosher amides/half phenyl esters **7A** and **7B**; note: position of the phenyl ester function in **7A** and **7B** has been arbitrarily assigned

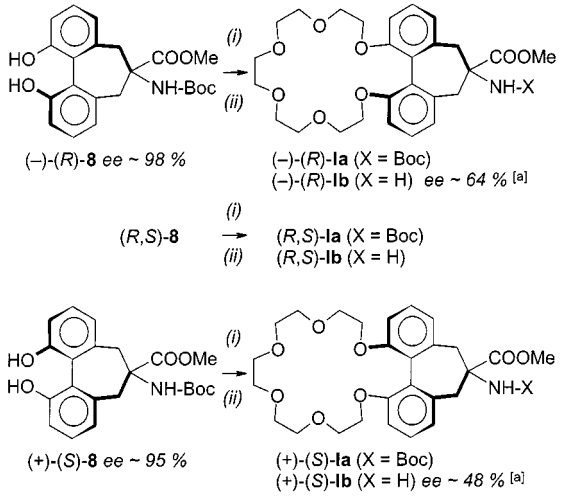

Figure 6. Synthesis of racemic and chirally resolved Boc-[20-C-6]-Bip-OMe (**Ia**) and H-[20-C-6]-Bip-OMe (**Ib**): (*i*) Cs_2CO_3, TsO-CH_2-$(CH_2$-O-$CH_2)_4$-CH_2-OTs, DMF, 60 °C; (*ii*) TFA/CH_2Cl_2 (1:3), room temp.; [a] enantiomeric excess determined by ^{19}F NMR of the corresponding Mosher amide (see text and Exp. Sect.)

The dicesium salts of (*RS*)-**8**, (*R*)-**8** and (*S*)-**8** were treated with pentaethylene glycol ditosylate in DMF (*N*,*N*-dimethylformamide) at 60 °C under high-dilution conditions, in a manner similar to that previously reported by Voyer et al.,[7] to give the expected fully protected crown-carrier α-amino acid residues Boc-[20-C-6]-Bip-OMe (*RS*)-**Ia** (38%), (*R*)-**Ia** (49%) and (*S*)-**Ia** (49%), respectively (Figure 6).

Cleavage of the Boc protecting group of (*RS*)-**Ia** in TFA (trifluoroacetic acid)/CH_2Cl_2 (1:3) at room temperature afforded the free α-amino ester H-[20-C-6]-Bip-OMe (*RS*)-**Ib** (91%). Aliquots of (*R*)-**Ia** and (*S*)-**Ia** were also *N*-deprotected in the same manner, and the resulting crude samples of (*R*)-**Ib** and (*S*)-**Ib** were converted into the corresponding Mosher's amides as above for analysis of their diastereoisomeric excess by ^{19}F NMR. It was found that (*S*)-Ph(OCH_3)(CF_3)C-CO-(*R*)-[20-C-6]-Bip-OMe was obtained from (*R*)-**Ib** with a *de* of only 64 ± 5%, while (*S*)-Ph(OCH_3)(CF_3)C-CO-(*S*)-[20−C-6]-Bip-OMe was obtained from (*S*)-**Ib** with a *de* of only 48 ± 5%. Assuming the absence of any racemization during the conversion of **Ia** to **Ib**, it appears that (*R*)-**Ia** and (*R*)-**Ib** (64 ± 5% *ee*) resulted from (*R*)-**8** (98 ± 2% *ee*) and that (*S*)-**Ia** and (*S*)-**Ib** (48 ± 5% *ee*) resulted from (*S*)-**8** (95 ± 2% *ee*), demonstrating the *occurrence of extensive racemization during the cyclisation step with crown ether formation*.

No decrease in *de* was observed by ^{19}F NMR in a control experiment in which a solution of (*S*)-Ph(OCH_3)(CF_3)C-CO-(*S*)-[20-C-6]-Bip-OMe (48 ± 5% *de*) in [D_8]toluene was kept for one week at 110 °C, reflecting a *very high enantiomeric stability of the [20-C-6]-Bip residue*, as would be expected from racemization studies on related compounds in

the literature.[45,46] Altogether, it appears that racemization only occurred in two steps of the synthesis, in both of which a 6,6′-*dihydroxy*-2,2′-bridged biphenyl was being treated in either an acidic or a basic medium: (*i*) H-[HO]$_2$-Bip-OH·HBr and H-[HO]$_2$-Bip-OMe in the demethylation (BBr_3/CH_2Cl_2/room temp.) and esterification (MeOH/H_2SO_4/50 °C) steps, and (*ii*) Boc-[HO]$_2$-Bip-OMe in the cyclization step (Cs_2CO_3/DMF/60 °C). This result concurs with both the acid-catalysed and the base-catalysed racemization of 2,2′-*dihydroxy*-1,1′-binaphthyl, previously observed and interpreted by Cram et al.[47] Racemization is even probably enhanced in the present case, because of the lower configurational stability of 2,2′,6,6′-tetrasubstituted biphenyls relative to the related 2,2′-disubstituted 1,1′-binaphthyls.

It is noteworthy that, in addition to the absolute configuration of the new series of compounds **4**, **6**, **8** and **Ia**, readily established by chemical correlation with the known starting diacid **1**, diol **2** and dibromide **3** − all [(−)-(*R*); (+)-(*S*)][33] − their maximum optical rotations can be estimated with a high degree of confidence by extrapolation from the optical rotation values of samples of known *ee*, deduced from the *de* values of their Mosher derivatives (Table 1).

Synthesis of Peptides Based on the [20-C-6]-Bip Residue

The synthesis of a few peptides **II**−**VI** based on the [20-C-6]-Bip residue **I** (Figure 7) was performed in order to find suitable coupling conditions in solution for such an unusual $C^{\alpha,\alpha}$-disubstituted glycine.

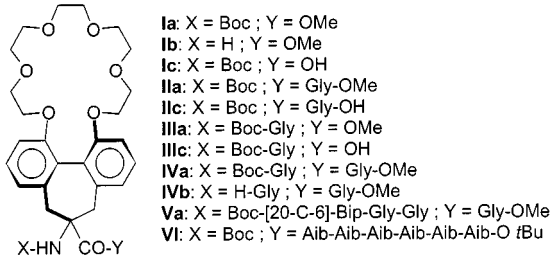

Figure 7. Chemical structures of the peptides **I**−**VI** based on the [20-C-6]-Bip residue

The EDC/HOBt (1-hydroxy-1,2,3-benzotriazole) method[48] had previously been shown to be efficient for the coupling of Ala at the C-termini of $C^{\alpha,\alpha}$-diphenylglycine (Dph),[49] Bip[26] and Bin,[27] but to proceed with low yield for the coupling of Ala at the N-terminus of Dph.[49] It was chosen by us for coupling of H-Gly-OMe at the C-terminus of racemic Boc-[20-C-6]-Bip-OH (*R*,*S*)-**Ic**, obtained in 96% yield after saponification of (*R*,*S*)-**Ia** with 1 N NaOH in MeOH at 50 °C (Figure 8), to give the dipeptide Boc-[20-C-6]-Bip-Gly-OMe (*R*,*S*)-**IIa** (82%). The symmetrical anhydride (Boc-Gly)$_2$O method was used for coupling at the N-terminus of (*R*,*S*)-**Ib**, to give Boc-Gly-[20-C-6]-Bip-OMe (*R*,*S*)-**IIIa** (70%).

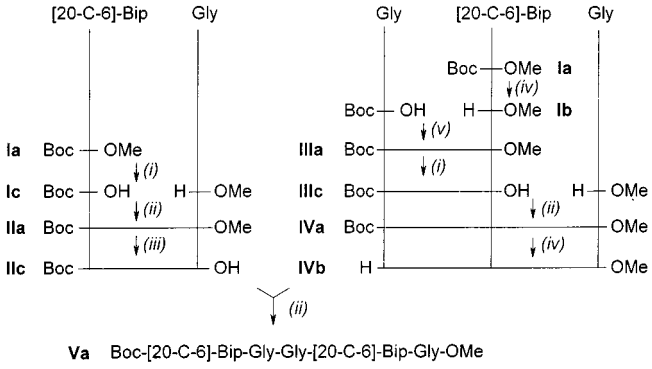

Figure 8. Solution synthesis of peptides **I**−**V**: (*i*) 1 N NaOH, MeOH, 50 °C, 2 h; (*ii*) EDC, HOBt; (*iii*) 1 N NaOH, MeOH, room temp., 2 h; (*iv*) TFA/CH_2Cl_2 (1:3), room temp., 2.5 h; (*v*) (1) Boc-Gly-OH (2 equiv.), EDC, CH_3CN, room temp., 1 h; (2) H-[20-C-6]-Bip-OMe

In the same manner, coupling of H-Gly-OMe by the EDC/HOBt method at the C-terminus of Boc-Gly-[20-C-6]-Bip-OH (*R*,*S*)-**IIIc** (84%), obtained after saponification of (*R*,*S*)-**IIIa**, afforded the tripeptide Boc-Gly-[20-C-6]-Bip-Gly-OMe (*R*,*S*)-**IVa** (82%). Finally, segment coupling of H-Gly-[20-C-6]-Bip-Gly-OMe (*R*,*S*)-**IVb** (100%), resulting from N^{α}-deprotection of (*R*,*S*)-**IVa**, with Boc-[20-C-6]-Bip-Gly-OH (*R*,*S*)-**IIc** (54%), resulting from saponification of (*R*,*S*)-**IIa**, by the EDC/HOBt method afforded the pentapeptide Boc-[20-C-6]-Bip-Gly-Gly-[20-C-6]-Bip-Gly-OMe **Va** (55%) as a mixture of two racemic isomers [(*RR*,*SS*) and (*RS*,*SR*)], which could not be separated by chromatography.

We succeeded in the synthesis of only a single peptide from the corresponding enantiomerically enriched [20-C-6]-Bip residue; coupling of (*S*)-**Ic**, resulting from saponification of (*S*)-**Ia** (48 ± 5% *ee*), with H-(Aib)$_6$-O*t*Bu, obtained by N^{α}-deprotection of the corresponding Z (benzyloxycarbonyl) precursor[50] with H_2 in the presence of Pd/C in MeOH, by the EDC/HOAt (1-hydroxy-7-aza-1,2,3-benzotriazole) method[51] afforded the heptapeptide Boc-[20-C-6]-Bip-(Aib)$_6$-O*t*Bu (*S*)-**VI** (19% yield; assumed 48 ± 5% *ee*).

Conformational Characterization of Boc-[20-C-6]-Bip-(Aib)$_6$-OtBu (S)-VI

The preferred conformation of the terminally protected [20-C-6]-Bip/Aib heptapeptide was determined in a structure-supporting solvent ($CDCl_3$) by FT-IR absorption and ^{1}H NMR at 1 mM concentration, at which self association is absent (results not shown). Figure 9 illustrates the FT-IR absorption spectrum (N−H stretching region), which is characterized by a weak band at 3424 cm^{-1} (free, solvated NH groups) and an intense band at 3324 cm^{-1} (H-bonded NH groups).[52,53]

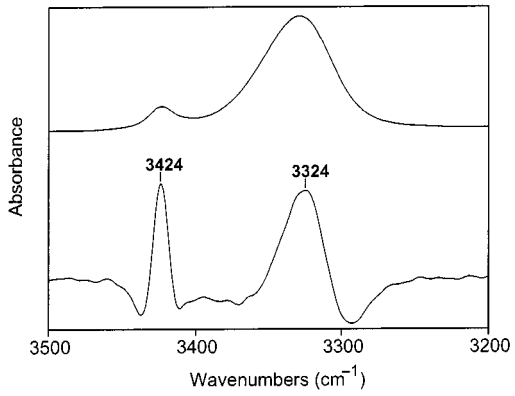

Figure 9. FT-IR absorption and inverted second derivative spectrum of Boc-(*S*)-[20-C-6]-Bip-(Aib)$_6$-O*t*Bu in $CDCl_3$ solution; peptide concentration 1 mM

This analysis provided convincing evidence that intramolecular H-bonding is a factor of paramount importance in supporting a folded conformation of the heptapeptide in $CDCl_3$ solution. The ratio of the intensity of the low-frequency band (A_H) relative to the high-intensity band (A_F) was that expected for an almost fully developed 3_{10}-helical conformation,[54] in which the NH groups near the N-terminus are free and all other NH groups are intramolecularly H-bonded.

The assignment of inaccessible (or intramolecularly H-bonded) NH groups of the heptapeptide by ^{1}H NMR was performed by using the solvent dependence of NH chemical shifts, through addition of increasing amounts of the strong H-bonding acceptor solvent dimethylsulfoxide (DMSO) [55] to the $CDCl_3$ solution (Figure 10).

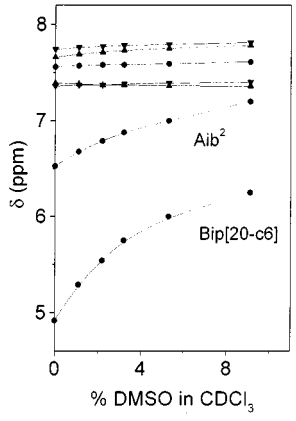

Figure 10. Plot of NH chemical shifts in the ^{1}H NMR spectrum of Boc-(*S*)-[20-C-6]-Bip-(Aib)$_6$-O*t*Bu as a function of increasing percentages of DMSO (v/v) added to the $CDCl_3$ solution; peptide concentration 1 mM

The upfield resonance in $CDCl_3$ solution was unambiguously attributable to the urethane N(1)H proton.[53] By analogy with a variety of model peptides we were also able to assign the resonance at immediately lower field to the N(2)H proton.[54] All other proton resonances fell downfield in a relatively narrow spectral range. In $CDCl_3$/DMSO mixtures, two classes of NH protons were observed. Class (i) [N(1)H and N(2)H protons] contained protons with chemical shifts sensitive to the addition of DMSO. Interestingly, the sensitivity of the N(1)H proton was higher than that of the N(2)H proton. Class (ii) [N(3)H to N(7)H protons] contained those displaying behaviour characteristic of shielded protons (relative insensitivity of chemical shifts to solvent composition). In summary, the ^{1}H NMR results allowed us to conclude that, in $CDCl_3$ solution, the N(3)H to N(7)H protons of the heptapeptide were almost inaccessible to the perturbing agent and so were most probably intramolecularly H-bonded. In view of these findings it was reasonable to conclude that the most populated structure adopted by the *N*- and *C*-protected heptapeptide in $CDCl_3$ solution is the 3_{10}-helix. This conclusion is in excellent agreement with that derived from the FT-IR absorption investigation discussed above.

The CD spectra of the (*S*)-[20-C-6]-Bip heptapeptide **VI** and the (*R*)-[20-C-6]-Bip N^{α}-protected amino acid derivative **Ic** in the 200−300 nm region are shown in Figure 11. The consistently positive Cotton effects at longer wavelengths and negative Cotton effect at shorter wavelengths are typical of the (*S*) compound, whereas an opposite CD pattern is exhibited by the (*R*) compound.[56] Therefore, as in the related Bin derivatives and peptides,[27] the CD spectrum reflects the configurational properties of the [20-C-6]-Bip residue, but does not provide any conformational information.

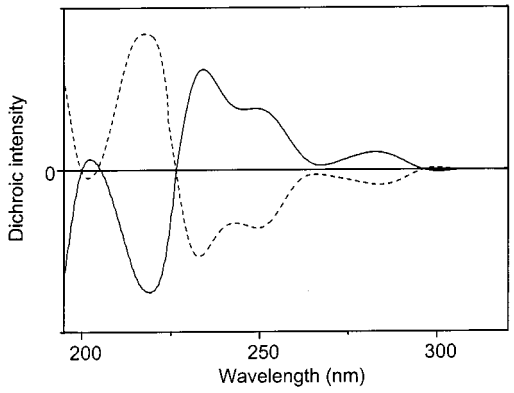

Figure 11. CD spectra of Boc-(*S*)-[20-C-6]-Bip-(Aib)$_6$-O*t*Bu **VI** (−−−−−) and the model compound Boc-(*R*)-[20-C-6]-Bip-OH **Ic** (----) in MeOH solution

Conclusions

In this study we have introduced the new $C^{\alpha,\alpha}$-disubstituted amino acid residue [20-C-6]-Bip, characterized by 2,2′,6,6′-tetrasubstituted biphenyl and crown-ether receptor architectures, and proposed a route for the synthesis of both racemic and optically enriched forms.

In the racemic series, the fully protected α-amino ester Boc-[20-C-6]-Bip-OMe (*R*,*S*)-**Ia** was readily obtained in ca. 10% (not optimised) overall yield from 6,6′-dimethoxy-1,1′-biphenyl-2,2′-dicarboxylic acid. However, when resolved samples of this diacid were used, only enantiomerically enriched − not pure − (*R*)-**Ia** and (*S*)-**Ia** could be obtained,

although their immediate 6,6′-dihydroxy precursors Boc-[HO]$_2$-Bip-OMe (*R*)-**8** and (*S*)-**8** were enantiomerically pure or nearly so; this was because of racemization occurring under the basic conditions needed for the cyclisation step with crown-ether formation. A better way to proceed would therefore be to carry out the resolution after the final stage of the synthesis of [20-C-6]-Bip instead of at an early stage. We are currently investigating such procedures. In spite of that failure, a variety of (*R*) and (*S*) enantiomerically enriched new structures of established absolute configuration, enantiomeric excess and optical rotation − **4**, **6**, **8** and **I** − have been prepared. Short peptides have also been synthesized in order to determine appropriate coupling conditions for the racemic [20-C-6]-Bip residue in solution, as well as to probe the postulated 3_{10}-helical conformation of the heptapeptide Boc-[20-C-6]-Bip-(Aib)$_6$-O*t*Bu (*S*)-**VI** by FT-IR absorption and ^{1}H NMR.

The [20-C-6]-Bip residue presents interesting new features: (*i*) the receptor site is in a *totally rigid and controlled spatial disposition* relative to the C$^\alpha$ atom, in contrast with the previously described *flexible* crown-carrier α-amino acids,[1−14] (*ii*) as emphasized earlier, it belongs to the class of *C*$^{\alpha,\alpha}$-disubstituted glycines, well known for their very high tendency to induce β-bends and α/3_{10}-helices in peptides,[16−23] which would be expected to allow control over the spatial organisation of these receptors in short peptide structures. Indeed, the parent 6,6′-unsubstituted Bip residue itself behaves as helix inducer in short-chain peptides,[26] (*iii*) [20-C-6]-Bip is the *lead compound for new crown-carrier α-amino acids with only axial dissymmetry* related to the 1,1′-binaphthyl/crown ether series developed by Cram et al.,[57] in which the opportunity to incorporate *steric* and *chiral barriers* is of great interest for the design of complementary binding features in host-guest chemistry.

Experimental Section

General: Melting points were determined by means of a capillary tube immersed in an oil bath (Tottoli apparatus, Büchi) with a final temperature increase of 3 °C/min and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, with the $CDCl_3$ solvent being used as internal standard (δ = 7.27 for ^{1}H and δ = 77.00 for ^{13}C). Splitting patterns are abbreviated as follows: (s) singlet, (d) doublet, (t) triplet, (q) quadruplet, (m) multiplet. The optical rotations were measured with an accuracy of 0.3%, in a 1-dm thermostatted cell. Analytical TLC and preparative column chromatography were performed on F 254 Kieselgel and on 60 Kieselgel (0.040−0.063 mm) (Merck), respectively, with the following eluent systems: 2.5% MeOH/97.5% CH_2Cl_2 (I); 5% MeOH/95% CH_2Cl_2 (II); 10% MeOH/90% CH_2Cl_2 (III); 20% MeOH/80% CH_2Cl_2 (IV). UV light (254 nm) allowed viewing of the spots after thin layer chromatography (TLC) runs for all compounds.

Infrared Absorption: FT-IR absorption spectra were recorded with a Perkin−Elmer model 1720X spectrophotometer, nitrogen-flushed, equipped with a sample-shuttle device, at 2 cm^{-1} nominal resolution, averaging 100 scans. Cells with path lengths of 0.1, 1.0 and 10 mm (with CaF_2 windows) were used. Spectrograde deuteriochloroform (99.8% D) was purchased from Merck. Solvent (base line) spectra were recorded under the same conditions.

^{1}H Nuclear Magnetic Resonance: ^{1}H NMR spectra for conformational analysis were obtained with a Bruker model AM 400 spectrometer. Measurements were carried out in deuteriochloroform (99.96% D; Aldrich) and deuterated DMSO (99.96% D_6; Acros Organics) with tetramethylsilane as the internal standard.

Circular Dichroism: CD spectra were obtained with a Jasco model J-710 spectropolarimeter. Cylindrical fused quartz cells with path lengths of 10, 1, 0.2 and 0.1 mm (Hellma) were used. Spectrograde methanol (Acros Organics) was used as solvent.

Resolution of 6,6′-Dimethoxy-1,1′-biphenyl-2,2′-dicarboxylic Acid (*R*,*S*)-1: According to a previously described procedure,[31] a solution of racemic diacid (*R*,*S*)-**1** (4.146 g, 13.73 mmol), prepared from 2-amino-3-methoxybenzoic acid,[30] and anhydrous quinine (8.896 g, 27.46 mmol) in MeOH (100 mL), was concentrated to dryness in vacuo at 60 °C. The residue was solubilized in boiling acetone (100 mL) and the solution was concentrated to ca. 40 mL, and then left at room temperature. Crystallization of white crystals rapidly occurred. The mixture was kept at +4 °C in a refrigerator overnight, and the crystals were filtered, washed with cold acetone and dried in vacuo at 25 °C (crystals C_1; yield 6.138 g). The combined acetone solution of supernatant and washings (filtrate F_1) was heated to reflux and concentrated to ca. 20 mL. After 1 d at room temperature followed by a few days in a refrigerator, the crystals were collected and dried as above (crystals C_{11}; yield 0.854 g). The combined acetone solution of the corresponding filtrate F_2 was heated to reflux and concentrated to ca. 15 mL. No crystallization occurred after several days at +4 °C. The solution was concentrated to dryness in vacuo at 25 °C, to give 6.500 g (100%) of the more soluble diquinine salt (filtrate F_2) as a white, amorphous solid. M.p. 105 °C; $[\alpha]_D^{25} = -41.0$, $[\alpha]_{578}^{25} = -44.6$, $[\alpha]_{546}^{25} = -52.5$, $[\alpha]_{436}^{25} = -127.9$, $[\alpha]_{365}^{25} = -675.3$ (*c* = 0.8; $CHCl_3$); ref.[31] m.p. 98−100 °C; $[\alpha]_D^{20} = -60$ (*c* = 0.8; $CHCl_3$). The crystals C_1 (6.14 g) were recrystallized from acetone (30 mL) as above, to give crystals C_2 {3.691 g; m.p. 179 °C; $[\alpha]_D^{25} = +111$, $[\alpha]_{578}^{25} = +116$, $[\alpha]_{546}^{25} = +138$, $[\alpha]_{436}^{25} = +215$, $[\alpha]_{365}^{25} = +507$ (*c* = 1; $CHCl_3$); ref.[31] m.p. 178−179 °C; $[\alpha]_D^{20} = +111.0$ (*c* = 1; $CHCl_3$); ref.[33] m.p. 176−178 °C; $[\alpha]_D = +110$ (*c* = 2.6; $CHCl_3$)}, and a filtrate F_{11}. From the concentrated acetone solution of combined C_{11} and F_{11} we obtained crystals C_{12} (2.70 g), which were recrystallized from acetone to give crystals C_{13} {2.126 g; m.p. 176 °C; $[\alpha]_D^{25} = +113.0$ (*c* = 1; $CHCl_3$)}, for a total $C_2 + C_{13}$ of 5.817 g (89%) of pure less soluble diquinine salt. The crystals of the less soluble salt (5.817 g) were triturated in the presence of 1.25 N NaOH (90 mL). Et_2O (100 mL) was added to the obtained suspension, and the mixture was magnetically stirred at room temperature until two clear, colourless phases were obtained (ca. 3 h). The separated aqueous phase was extracted with several portions of Et_2O, and then with cold $CHCl_3$ and then again with Et_2O. [***Note:*** In our hands, direct extraction of the suspension of the less soluble salt with cold $CHCl_3$ as in the literature[31] resulted in *extraction of both quinine and the disodium salt of the diacid enantiomer* (−)-(*R*)-**1** in the organic phase. Et_2O, as opposed to $CHCl_3$, was found to be the solvent of choice for extraction of quinine alone, with final salt decomposition indicated by complete solubilization of the initial suspension. On the other hand, no particular problem was encountered in the $CHCl_3$ extraction of quinine from the decomposed more soluble salt, probably because of much weaker interactions between quinine and the diacid enantiomer (+)-(*S*)-**1**]. The resulting clear, colourless, aqueous basic solution was cooled to ca. 0 °C and acidified with an excess of ice-cold 6 N HCl (25 mL), to afford a gel-like precipitate that

turned into a white solid suspension upon trituration. The solid was filtered, abundantly washed with water and air-dried to afford 0.995 g of pure (−)-(*R*)-**1** as a white powder {m.p. 294 °C; $[\alpha]_D^{21}$ = −105.0, $[\alpha]_{578}^{21}$ = −111.4, $[\alpha]_{546}^{21}$ = −133.4, $[\alpha]_{436}^{21}$ = −267.9, $[\alpha]_{365}^{21}$ = −539.2 (*c* = 0.38; acetone), corresponding to 89% optical purity (estimated experimental error: ±5%); ref.[31] m.p. 291−292 °C; $[\alpha]_D^{20}$ = −114.9 (*c* = 0.38; acetone); ref.[32] m.p. 291−292 °C; $[\alpha]_D^{20.5}$ = −117.8 (*c* = 0.88; acetone); ref.[33] m.p. 288−290 °C; $[\alpha]_D$ = −105 (*c* = 2.75; acetone)}. The aqueous acidic solution of filtrate was extracted with several portions of CH_2Cl_2 (total ca. 500 mL) until the diacid spot was no longer detectable by UV in the extracts. The combined organic phases were washed with water, dried ($MgSO_4$) and filtered, and the solvents were evaporated in vacuo at 30 °C to give 0.576 g of pure (−)-(*R*)-**1** as a white solid {m.p. 297 °C; $[\alpha]_D^{21}$ = −107.6, $[\alpha]_{578}^{21}$ = −115.6, $[\alpha]_{546}^{21}$ = −136.5, $[\alpha]_{436}^{21}$ = −275.8, $[\alpha]_{365}^{21}$ = −555.1 (*c* = 0.39; acetone), corresponding to 91 ± 5% optical purity}, for a total yield of 1.571 g (76%). Decomposition of the more soluble salt (6.500 g) by trituration in the presence of NaOH (1.25 N, 90 mL) and extraction of quinine by four portions of cold $CHCl_3$ (total 200 mL), followed by acidification with cold 6 N HCl (25 mL), trituration of the gel-like precipitate, filtration of the resulting white solid, washing with water and drying gave 1.466 g of a white powder. Extraction of the acidic aqueous filtrate by several portions of CH_2Cl_2 (total ca. 500 mL), washing of the combined organic phases with water, drying ($MgSO_4$), filtration and concentration in vacuo at 30 °C gave 0.392 g of a white solid, which was combined with the former sample to give a total of 1.858 g (90%) of pure (+)-(*S*)-**1** {m.p. ca. 300 °C; $[\alpha]_D^{21}$ = +87.9, $[\alpha]_{578}^{21}$ = +94.0, $[\alpha]_{546}^{21}$ = +111.6, $[\alpha]_{436}^{21}$ = +225.0, $[\alpha]_{365}^{21}$ = +451.8 (*c* = 0.36; acetone), corresponding to 75 ± 5% optical purity; ref.[31] m.p. 291−292 °C; $[\alpha]_D^{20}$ = +108.5 (*c* = 0.37; acetone); ref.[32] m.p. 290−292 °C; $[\alpha]_D^{23}$ = +116.8 (*c* = 0.96; acetone)}.

2,2′-Bis(hydroxymethyl)-6,6′-dimethoxy-1,1′-biphenyl [(*R*,*S*)-2]:[32] The racemic diacid (*RS*)-**1** (4.187 g, 13.8 mmol) was solubilized in THF (175 mL). The resulting solution was stirred under argon for 20 min at 0 °C (ice/water bath) and a 1 M solution of BH_3 in THF was slowly added by syringe. The cooling bath was removed, and the resulting turbid mixture clarified after a few minutes to give a clear, colourless solution, which was stirred at room temperature overnight. The solution was again cooled to 0 °C and hydrolysed under a stream of argon by slow addition of water followed by 0.5 M HCl. The acidic mixture was extracted with EtOAc (3 × 150 mL), and the clear, colourless organic phase was washed with water (2 × 150 mL), dried ($MgSO_4$) and filtered. The solvents were evaporated in vacuo to give 3.498 g (92%) of crude (*R*,*S*)-**2** as a white solid, pure by NMR and TLC, which was used without further purification in the next step. R_f = 0.10 (I). ^{1}H NMR ($CDCl_3$): δ = 7.39 [dd (t-like), *J* ≈ 7.7 Hz, 2 H, $ArH^{4,4'}$], 7.15 (dd, *J* ≈ 7.7 and 1.0 Hz, 2 H, $ArH^{5,5'}$), 6.96 (dd, *J* ≈ 8.3 and 1.0 Hz, 2 H, $ArH^{3,3'}$), 4.24 and 4.18 (d, *J* ≈ 11.6 Hz and d, *J* ≈ 11.6 Hz, 4 H, $ArCH_2$), 3.70 (s, 6 H, OMe).

2,2′-Bis(hydroxymethyl)-6,6′-dimethoxy-1,1′-biphenyl [(−)-(*R*)-2]:[32,33] The same experimental and workup conditions as above, when applied to (−)-(*R*)-**1** (0.943 g, 3.12 mmol, 91 ± 5% *ee*), gave crude (−)-(*R*)-**2** (0.707 g, 83%) as a white solid with $[\alpha]_D^{21}$ = −94.1, $[\alpha]_{578}^{21}$ = −98.7, $[\alpha]_{546}^{21}$ = −113.8, $[\alpha]_{436}^{21}$ = −206.5, $[\alpha]_{365}^{21}$ = −351.8 (*c* = 1.24; acetone), corresponding to 95 ± 5% optical purity; ref.[32] $[\alpha]_D^{19.5}$ = −98.7 (*c* = 1.02; acetone); ref.[33] $[\alpha]_D$ = −63.5 (*c* = 2.0; EtOH). Duplicate runs starting from (−)-(*R*)-**1** (0.491 g, 1.62 mmol, 91 ± 5% *ee* and 0.395 g, 1.31 mmol, 91 ± 5% *ee*) gave crude (−)-(*R*)-**2** {0.390 g (88%); $[\alpha]_D^{21}$ = −92.1, $[\alpha]_{578}^{21}$ = −96.6, $[\alpha]_{546}^{21}$ = −111.3, $[\alpha]_{436}^{21}$ = −202.4, $[\alpha]_{365}^{21}$ = −346.5 (*c* = 0.98; acetone), corresponding to 93 ± 5% optical purity; and 0.271 g (76%); $[\alpha]_D^{21}$ = −90.0, $[\alpha]_{578}^{21}$ = −94.5, $[\alpha]_{546}^{21}$ = −108.9, $[\alpha]_{436}^{21}$ = −198.2, $[\alpha]_{365}^{21}$ = −337.1 (*c* = 1.10; acetone), corresponding to 91 ± 5% optical purity, respectively}.

2,2′-Bis(hydroxymethyl)-6,6′-dimethoxy-1,1′-biphenyl [(+)-(*S*)-2]:[32] The same experimental and workup conditions as above, when applied to (+)-(*S*)-**1** (1.829 g, 6.05 mmol, 75 ± 5% *ee*) gave crude (+)-(*S*)-**2** (1.280 g, 77%) as a white solid, with $[\alpha]_D^{21}$ = +70.3, $[\alpha]_{578}^{21}$ = +73.3, $[\alpha]_{546}^{21}$ = +84.6, $[\alpha]_{436}^{21}$ = +153.7, $[\alpha]_{365}^{21}$ = +261.8 (*c* = 1.08; acetone), corresponding to 71 ± 5% optical purity; ref.[32] $[\alpha]_D^{18}$ = +98.0 (*c* = 0.95; acetone).

2,2′-Bis(bromomethyl)-6,6′-dimethoxy-1,1′-biphenyl [(*R*,*S*)-3]:[32] According to a previously described procedure,[32] a solution of phosphorous tribromide (9 mL) in toluene (11 mL) was added dropwise over 30 min to a magnetically well-stirred, ice-cooled milky suspension of the racemic diol (*RS*)-**2** (3.591 g, 13.10 mmol) in toluene (50 mL) [***Note:*** benzene was used in the literature procedure] under argon. The resulting clarified, but still turbid, solution was stirred at room temperature for 1 h and at 40 °C for 1 h, and was then poured onto ice. The cold mixture was magnetically stirred and made basic by addition of a large excess of solid $NaHCO_3$ in small portions, and was then extracted with EtOAc (2 × 150 mL). The organic phase was washed with H_2O (4 × 150 mL), dried ($MgSO_4$) and filtered, and the solvents were evaporated in vacuo to give 2.471 g of crude (*R*,*S*)-**3** as a white solid. A duplicate run starting from (*RS*)-**2** (3.498 g, 12.76 mmol) gave 3.637 g of crude (*R*,*S*)-**3** as a yellowish solid. These combined samples were solubilized in CH_2Cl_2, and absolute EtOH (50 mL) was added. The resulting clear solution was concentrated to ca. 10 mL and left at room temperature. Crystallization rapidly occurred. The mixture was kept at + 4 °C in a refrigerator overnight, the crystals were filtered, washed with cold abs. EtOH and air-dried (yield 5.397 g). More crystals (0.378 g) were obtained after concentration of the mother liquor, to give a total of 5.775 g (56%) of pure (*R*,*S*)-**3** as white, shiny crystals. R_f = 0.85 (I). ^{1}H NMR ($CDCl_3$): δ = 7.49 [dd (t-like), *J* ≈ 7.9 and 8.1 Hz, 2 H, $ArH^{4,4'}$], 7.31 (dd, *J* ≈ 7.7 and 1.0 Hz, 2 H, $ArH^{5,5'}$), 7.03 (dd, *J* ≈ 8.2 and 1.0 Hz, 2 H, $ArH^{3,3'}$), 4.33 and 4.29 (d, *J* ≈ 10.3 Hz and d, *J* ≈ 10.3 Hz, 4 H, $ArCH_2$), 3.78 (s, 6 H, OMe). ^{13}C NMR ($CDCl_3$): δ = 156.6 (C_{Ar}−O), 137.4, 129.2, 123.9, 122.3, 100.5 (C_{Ar}), 55.5 ($ArOCH_3$), 31.8 ($ArCH_2Br$).

2,2′-Bis(bromomethyl)-6,6′-dimethoxy-1,1′-biphenyl [(−)-(*R*)-3]:[32] The same experimental and workup conditions as for the synthesis of (*R*,*S*)-**3**, when applied to (−)-(*R*)-**2** (0.696 g, 2.54 mmol, 95 ± 5% *ee*) gave, after solubilization of the crude product in CH_2Cl_2/abs.EtOH, concentration of the solution (all CH_2Cl_2 off) to a very small volume (ca. 0.5 mL) in vacuo at < 35 °C (resulting in crystallization at room temperature) and then at +4 °C overnight, elimination of the cold supernatant and drying of the crystals in vacuo, pure (−)-(*R*)-**3** (0.635 g, 63%) as a white crystalline powder. {m.p. 114 °C; $[\alpha]_D^{21}$ = −79.9, $[\alpha]_{578}^{21}$ = −84.3, $[\alpha]_{546}^{21}$ = −98.7, $[\alpha]_{436}^{21}$ = −198.6, $[\alpha]_{365}^{21}$ = −408.1 (*c* = 0.98; acetone), corresponding to 99 ± 5% optical purity; ref.[32] m.p. 116−117 °C; $[\alpha]_D^{22}$ = −80.7 (*c* = 1.02; acetone)}. Duplicate runs starting from (−)-(*R*)-**2** (0.378 g, 1.38 mmol, 93 ± 5% *ee* and 0.287 g, 1.05 mmol; 91 ± 5% *ee*), gave pure (−)-(*R*)-**3** as a white crystalline powder {0.338 g (61%); m.p. 115 °C; $[\alpha]_D^{21}$ = −80.3, $[\alpha]_{578}^{21}$ = −84.7, $[\alpha]_{546}^{21}$ = −99.2, $[\alpha]_{436}^{21}$ = −199.7, $[\alpha]_{365}^{21}$ = −410.3 (*c* = 0.98; acetone), corresponding to 99 ± 5% optical purity; and 0.172 g (41%); m.p. 115 °C; $[\alpha]_D^{21}$ = −80.1, $[\alpha]_{578}^{21}$ = −84.5, $[\alpha]_{546}^{21}$ = −98.8, $[\alpha]_{436}^{21}$ = −198.8, $[\alpha]_{365}^{21}$ = −408.7

(c = 0.91; acetone), corresponding to 99 ± 5% optical purity, respectively}.

2,2′-Bis(bromomethyl)-6,6′-dimethoxy-1,1′-biphenyl [(+)-(*S*)-3]:[32] The same experimental and workup conditions as for the synthesis of (−)-(*R*)-**3**, when applied to (+)-(*S*)-**2** (1.268 g, 4.63 mmol; 71 ± 5% *ee*), gave pure (+)-(*S*)-**3** (1.425 g, 77%) as a white crystalline powder, with m.p. 109 °C; $[\alpha]_D^{21}$ = +60.0, $[\alpha]_{578}^{21}$ = +62.5, $[\alpha]_{546}^{21}$ = +73.1, $[\alpha]_{436}^{21}$ = +147.1, $[\alpha]_{365}^{21}$ = +303.1 (c = 1.01; acetone), corresponding to 74 ± 5% optical purity; ref.[32] m.p. 117−118.5 °C; $[\alpha]_D^{20}$ = +80.6 (c = 1.05; acetone).

(4-Chlorobenzylidene)glycine *tert*-Butyl Ester:[34,35] According to a previously described procedure,[36] a suspension of glycine *tert*-butyl ester hydrochloride (16.75 g, 100 mmol) and $MgSO_4$ (18 g, 150 mmol) in a solution of 4-chlorobenzaldehyde (14.05 g, 100 mmol) and CH_2Cl_2 (350 mL) was stirred at room temperature under argon while a solution of Et_3N (27.8 mL, 200 mmol) in CH_2Cl_2 (50 mL) was added dropwise over 1.5 h. The reaction mixture was stirred for 20 h and filtered through fritted glass, and the solvents were evaporated in vacuo at 40 °C. The resulting white solid residue was triturated in Et_2O (400 mL) and the mixture was filtered through fritted glass, the white solid precipitate of Et_3N·HCl being washed several times with Et_2O (3 × 100 mL). The clear, colourless ether filtrate was successively washed with 5% $NaHCO_3$ (2 × 100 mL), a solution of 2 N NaOH containing 2 g/100 mL of NH_2OH·HCl (2 × 200 mL) and 1% $NaHCO_3$ (2 × 200 mL), dried ($MgSO_4$) and filtered. The solvents were evaporated in vacuo to give 24.15 g (95%) of crude (4-chlorobenzylidene)glycine *tert*-butyl ester as a colourless glassy oil, pure by NMR, which was used in the next step without further purification. This sample crystallized upon cooling to give a white solid that could be stored for months at ca. −20 °C. ^{1}H NMR ($CDCl_3$): δ = 8.23 (s, 1 H, ArCH=N), 7.72 (d, $J \approx$ 8.5 Hz, 2 H, ArH), 7.39 (d, $J \approx$ 8.4 Hz, 2 H, ArH), 4.31 (s, 2 H, NCH_2CO), 1.50 (s, 9 H, $OCMe_3$).

***tert*-Butyl 6-Amino-1,11-dimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene-6-carboxylate [(*RS*)-4]:** CH_2Cl_2 (20 mL) was added to a mixture of (*RS*)-**3** (0.492 g, 1.23 mmol), (4-chlorobenzylidene)glycine *tert*-butyl ester (0.374 g, 1.47 mmol), tetrabutylammonium bromide (0.080 g, 0.248 mmol), anhydrous potassium carbonate (1.70 g, 12.3 mmol) and freshly ground KOH pellets (0.69 g, 12.3 mmol). The suspension was magnetically stirred at ca. 1000 rev/min at room temperature for 21 h. The reaction mixture was then concentrated in vacuo and the residue was solubilized in H_2O/Et_2O. The separated Et_2O solution (150 mL) was washed with H_2O (2 × 100 mL), dried ($MgSO_4$) and filtered, and the solvents were evaporated in vacuo. Silica gel (5 g of 60 Kieselgel, 0.063−0.2 mm) and a solution of CH_2Cl_2/MeOH (50 mL) were added to the resulting crude product (orange solid foam, 0.642 g). The mixture was stirred in a water bath at 50 °C for several hours and the solvents were evaporated in vacuo. The resulting mixture of crude product and silica gel was chromatographed on a 21 × 3.3 cm column of silica gel with eluent I to give 0.248 g of a pure fraction and 0.055 g of a fraction that was further purified by preparative TLC on silica gel with eluent I, to afford in total 0.290 g (64%) of analytically pure H-[MeO]$_2$-Bip-O*t*Bu (*RS*)-**4**. R_f = 0.25 (I). ^{1}H NMR ($CDCl_3$): δ = 7.32 [dd (t-like), $J \approx$ 8 Hz, 1 H, ArH], 7.25 [dd (t-like), $J \approx$ 8 Hz, 1 H, ArH], 6.98 (d, $J \approx$ 8 Hz, 1 H, ArH), 6.93 (two superimposed d, $J \approx$ 8 Hz, 2 H, ArH), 6.90 (d, $J \approx$ 8 Hz, 1 H, ArH), 3.82 (s, 6 H, $ArOCH_3$), 2.95 and 2.45 (d, J = 13.2 Hz, 1 H and d, J = 13.2 Hz, 1 H, $ArCH_2\beta$), 2.95 and 2.24 (d, J = 13.2 Hz, 1 H and d, J = 13.2 Hz, 1 H, $ArCH_2\beta'$), 1.46 (s, 9 H, $OCMe_3$). ^{13}C NMR ($CDCl_3$): δ = 174.4 (C=O), 156.8, 156.6 (C_{Ar}−O), 138.4, 137.0, 128.4, 127.9, 124.8, 124.4, 122.2, 122.1, 110.1, 109.8 (C_{Ar}), 81.2 ($OCMe_3$), 67.1 (Cα), 55.73, 55.71 ($ArOCH_3$), 43.4 (Cβ), 42.2 (Cβ′), 27.9 ($OCMe_3$). $C_{22}H_{27}NO_4$·0.25H_2O (373.948): calcd. C 70.66, H 7.41, N 3.75; found C 70.73, H 7.36, N 3.91. In duplicate experiments, crude NMR-pure (*RS*)-**4** could be obtained in higher yields with no chromatography needed. For example, a mixture of (*RS*)-**3** (2.698 g, 6.75 mmol), (4-chlorobenzylidene)glycine *tert*-butyl ester (2.565 g, 10.12 mmol), tetrabutylammonium bromide (0.435 g, 1.35 mmol), anhydrous potassium carbonate (9.31 g, 67.5 mmol) and freshly ground KOH pellets (3.78 g, 67.5 mmol) in CH_2Cl_2 (100 mL) was magnetically stirred at room temperature for 24 h, and then concentrated in vacuo. The residue was solubilized in H_2O/Et_2O and extracted as above. The resulting orange solid foam was solubilized in THF (60 mL), and aqueous citric acid (0.5 M, 150 mL) was added. The mixture was magnetically stirred at room temperature for 16 h and then concentrated in vacuo at 25 °C to ca. 50 mL, diluted with H_2O (ca. 150 mL) and extracted with Et_2O (2 × 200 mL). *The clear, colourless acidic aqueous phase was retained*. The combined, dark orange ethereal phase was washed with 5% $NaHCO_3$ (100 mL) and then H_2O (2 × 200 mL), dried ($MgSO_4$), filtered and concentrated. Analytical TLC of this neutral extract showed the presence of a main UV-positive spot corresponding to 4-chlorobenzaldehyde and only traces of other unidentified spots, but none corresponding to (*RS*)-**4**. The initial acidic aqueous phase obtained after extraction with Et_2O was made basic by addition of a large excess of solid $NaHCO_3$ in small portions, and then extracted with EtOAc (3 × 100 mL). The combined organic phasees were washed with H_2O (3 × 200 mL), dried ($MgSO_4$) and filtered, and the solvents were evaporated in vacuo to give a basic extract consisting of crude (*R*,*S*)-**4** (2.108 g, 85%) as a pale yellow glass, pure by NMR and TLC, which was used in the next step without further purification.

***tert*-Butyl 6-Amino-1,11-dimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene-6-carboxylate [(*R*)-4]:** A mixture of (−)-(*R*)-**3** of 99 ± 5% *ee* (1.135 g, 2.84 mmol), (4-chlorobenzylidene)glycine *tert*-butyl ester (0.863 g, 3.40 mmol), tetrabutylammonium bromide (0.183 g, 0.57 mmol), anhydrous potassium carbonate (3.92 g, 28.4 mmol) and freshly ground KOH pellets (1.59 g, 28.4 mmol) in CH_2Cl_2 (50 mL) was magnetically stirred at room temperature for 20 h and then concentrated in vacuo. Extraction with Et_2O/H_2O as above for (*RS*)-**4** provided a crude product, which was solubilized in CH_2Cl_2/MeOH (50 mL). Silica gel (9 g) was added, and the mixture was stirred at room temperature for one week and then concentrated in vacuo at 30 °C. The resulting mixture of crude product and silica gel was chromatographed on a 14 ×3 cm silica gel column. Elution with CH_2Cl_2 and then with eluent I gave 3 fractions: *Fraction 1:* 0.336 g of 4-chlorobenzaldehyde with minor unidentified impurities. *Fraction 2:* 0.300 g (35%) of a side product identified as (*RR*)-**5**. R_f = 0.45 (CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 7.5−6.9 (m, 12 H, ArH), 3.90 (m, 12 H, $ArOCH_3$), 4.22 and 3.57 (d, J = 12.6 Hz, 2 H and d, J = 12.6 Hz, 2 H, $ArCH_2N$), 3.51 and 2.44 (d, J = 11.9 Hz, 1 H and d, J = 11.9 Hz, 1 H, $ArCH_2\beta$), 3.43 and 2.62 (d, J = 14.5 Hz, 1 H and d, J = 14.5 Hz, 1 H, $ArCH_2\beta'$), 1.39 (s, 9 H, $OCMe_3$). ESI$^+$ MS m/z (%): 608 (100) $[MH]^+$. $C_{38}H_{41}NO_6$·H_2O (625.732): calcd. C 72.93, H 6.92, N 2.24; found C 73.19, H 6.87, N 2.08. *Fraction 3:* 0.590 g of the desired amino ester (*R*)-**4**, which was further purified by column chromatography on silica gel with eluent I to afford 0.502 g (48%) of pure (*R*)-**4** as a pale orange glass, identified by ^{1}H NMR [see (*RS*)-**4**], with $[\alpha]_D^{25}$ = +19.8, $[\alpha]_{578}^{25}$ = +18.8, $[\alpha]_{546}^{25}$ = +14.7, $[\alpha]_{436}^{25}$ = −7.6, $[\alpha]_{365}^{25}$ = −132.0 (c = 0.1; MeOH), corresponding to 98 ± 2% *ee* as determined by ^{19}F NMR of the corresponding Mosher amides (vide infra).

***tert*-Butyl 6-Amino-1,11-dimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene-6-carboxylate [(*S*)-4]:** A mixture of (+)-(*S*)-**3** of 74 ±

5% *ee* (1.409 g, 3.52 mmol), (4-chlorobenzylidene)glycine *tert*-butyl ester (1.072 g, 4.22 mmol), tetrabutylammonium bromide (0.227 g, 0.70 mmol), anhydrous potassium carbonate (4.86 g, 35.2 mmol) and freshly ground KOH pellets (1.97 g, 35.2 mmol) in CH_2Cl_2 (60 mL) was magnetically stirred at room temperature for 20 h and then concentrated in vacuo. Extraction with Et_2O/H_2O afforded a crude product, which was treated with silica gel (10 g) in CH_2Cl_2/MeOH (50 mL) at room temperature for one week, as for (*R*)-**4**. Chromatography on a 14 × 3 cm silica gel column, with CH_2Cl_2 and then with eluent I, gave 3 fractions. *Fraction 1:* 0.504 g of a mixture of 4-chlorobenzaldehyde and a small proportion of remaining $C^{\alpha,\alpha}$-dialkylated glycine ester Schiff base precursor of (*S*)-**4** (incomplete hydrolysis on silica gel). This fraction was dissolved in 95% ethanol (20 mL) and stirred at room temperature for 3 d in the presence of $NH_2OH{\cdot}HCl$ (0.695 g, 10 mmol) and sodium acetate (0.820 g, 10 mmol). Transimination was complete after 3 d. Ethanol was evaporated and the residue was extracted with Et_2O (75 mL) in the presence of 5% $NaHCO_3$ (75 mL). The ethereal solution was dried ($MgSO_4$) and filtered, and the solvents were evaporated in vacuo. The residue was chromatographed on preparative TLC plates with eluent I to afford 0.126 g of (*S*)-**4** containing minor impurities. *Fraction 2:* 0.228 g (21%) of the side product (*SS*)-**5**, identified by ^{1}H NMR (see (*RR*)-**5**). *Fraction 3:* 0.882 g of impure amino ester (*S*)-**4**. This fraction and the sample of (*S*)-**4** obtained from Fraction 1 (0.126 g) were combined and further purified by column chromatography on silica gel with eluent I to afford 0.790 g (61%) of pure (*S*)-**4** as a pale orange glass, identified by ^{1}H NMR [see (*RS*)-**4**], with $[\alpha]_D^{25} = -17.2$, $[\alpha]_{578}^{25} = -17.7$, $[\alpha]_{546}^{25} = -17.9$, $[\alpha]_{436}^{25} = +3.2$, $[\alpha]_{365}^{25} = +83.8$ ($c = 0.5$; MeOH), corresponding to 64 ± 5% *ee* as determined by ^{19}F NMR of the corresponding Mosher amides (vide infra).

Coupling of (*R*)-4 and (*S*)-4 with (−)-(*S*)-α-Methoxy-α-phenyl-α-trifluoromethylacetic Acid: DCC (0.0148 g, 0.071 mmol) was added to a solution of (−)-(*S*)-MTPA (α-methoxy-α-trifluoromethyl-α-phenylacetic acid; Aldrich, 99%; 0.0336 g, 0.143 mmol) in acetonitrile (1.1 mL), which immediately resulted in the formation of a white precipitate of DCU (*N*,*N*′-dicyclohexylurea). After this had stirred at room temperature for 15 min, the resulting solution of the MTPA anhydride was filtered through a pipette capped with cotton wool, and divided into two portions of 0.5 mL each, which were added to samples of (*R*)-**4** (0.0053 g, 0.014 mmol) and (*S*)-**4** (0.0052 g, 0.014 mmol). The resulting clear, colourless solutions were stirred at room temperature for 16 h and then diluted with Et_2O (100 mL each). The organic phases from both procedures were successively extracted with 5% $NaHCO_3$ (2 × 50 mL) and then water (2 × 100 mL), dried ($MgSO_4$) and filtered, and the solvents were evaporated in vacuo. The residues were chromatographed on preparative TLC plates of silica gel with CH_2Cl_2 as eluent, care being taken not to exercise a mechanical separation of one of the diastereoisomers over the other. From (*R*)-**4**, the amido ester (*S*)-Ph(OCH_3)(CF_3)C-CO-(*R*)-[MeO]$_2$-Bip-O*t*Bu (0.0076 g, 91%) was obtained with > 98% *de* (estimated experimental error: ±2%). ^{1}H NMR ($CDCl_3$): δ = 7.56 (m, 2 H, ArH MTPA), 7.40 (m, 3 H, ArH MTPA), δ = 7.30 [dd (t-like), $J \approx 8$ Hz, 1 H, ArH], 7.25 [dd (t-like), $J \approx 8$ Hz, 1 H, ArH], 7.07 (s, 1 H, NH), 6.98 (d, $J = 7.9$ Hz, 1 H, ArH), 6.95 (d, $J = 7.9$ Hz, 1 H, ArH), 6.86 (d, $J = 7.4$ Hz, 1 H, ArH), 6.85 (d, $J = 7.4$ Hz, 1 H, ArH), 3.83 (s, 3 H, $ArOCH_3$), 3.81 (s, 3 H, $ArOCH_3$), 3.30 (m, 3 H, OCH_3 MTPA), 3.18 and 2.39 (d, $J = 12.8$ Hz, 1 H and d, $J = 12.8$ Hz, 1 H, $ArCH_2\beta$), 3.07 and 3.02 (d, $J \approx 14$ Hz, 1 H and d, $J \approx 14$ Hz, 1 H, $ArCH_2\beta'$), 1.49 [s (< 1%), $OCMe_3$ of the (*SS*) isomer] and 1.40 [s (> 99%), 9 H, $OCMe_3$]. ^{13}C NMR ($CDCl_3$): δ = 170.0 (C=O), 165.0 (C=O MTPA), 156.8, 156.7 (C_{Ar}−O), 137.2, 135.7, 131.9, 129.4, 128.6, 128.43, 128.37, 128.29, 125.8, 124.9, 122.2, 121.9, 110.6, 110.3 (C_{Ar}), 83.8 (CF_3), 81.7 ($OCMe_3$), 68.2 (Cα), 55.8 ($ArOCH_3$), 54.8 (OCH_3 MTPA), 41.3 (Cβ), 37.0 (Cβ′), 27.8 ($OCMe_3$). ^{19}F NMR ($CDCl_3$): −68.85 [s (< 1%), CF_3 of the (*SS*) isomer], −69.17 [s (> 99%), CF_3]. From (*S*)-**4**, the amido ester (*S*)-Ph(OCH_3)(CF_3)C-CO-(*S*)-[MeO]$_2$-Bip-O*t*Bu (0.0081 g, 97%) was obtained with 64% *de* (estimated experimental error: ±5%). ^{1}H NMR ($CDCl_3$): δ = 7.67 (m, 2 H, ArH MTPA), 7.47 (m, 3 H, ArH MTPA), 7.25 [dd (t-like), $J \approx 8$ Hz, 1 H, ArH], 7.09 [dd (t-like), $J \approx 8$ Hz, 1 H, ArH], 6.94 (d, $J = 8.2$ Hz, 1 H, ArH), 6.90 (d, $J = 8.0$ Hz, 1 H, ArH), 6.81 (d, $J = 7.7$ Hz, 1 H, ArH), 6.74 (s, 1 H, NH), 6.41 (d, $J = 7.1$ Hz, 1 H, ArH), 3.80 (s, 3 H, $ArOCH_3$), 3.79 (s, 3 H, $ArOCH_3$), 3.48 (m, 3 H, OCH_3 MTPA), 3.14 and 2.34 (d, $J = 12.6$ Hz, 1 H and d, $J = 12.8$ Hz, 1 H, $ArCH_2\beta$), 3.01 and 2.88 (d, $J = 13.9$ Hz, 1 H and d, $J = 14.2$ Hz, 1 H, $ArCH_2\beta'$), 1.49 (s, 9 H, $OCMe_3$) all signals corresponding to the (*SR*) isomer (vide supra) also present in the proportion of ca. 20%. ^{13}C NMR ($CDCl_3$): δ = 169.8 (C=O), 165.0 (C=O MTPA), 156.8, 156.7 (C_{Ar}−O), 137.2, 135.5, 132.6, 129.5, 128.4, 128.3, 127.5, 124.9, 124.7, 122.0, 121.8, 110.7, 110.3 (ca. 20%), 110.1 (C_{Ar}), 83.6 (CF_3), 81.8 ($OCMe_3$), 68.0 (Cα), 55.8 ($ArOCH_3$), 55.0 (OCH_3 MTPA), 41.2 (Cβ), 37.0 (ca. 20%), 36.7 (Cβ′), 27.8 ($OCMe_3$). ^{19}F NMR ($CDCl_3$): δ = −68.84 [s (ca. 82%), CF_3], −69.17 [s (ca. 18%), CF_3 of the (*SR*) isomer].

Methyl 6-Amino-1,11-dihydroxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene-6-carboxylate [(*RS*)-6]: A solution of BBr_3 (1 M in CH_2Cl_2, 5 mL, 5 mmol) was slowly added by syringe to a solution of (*RS*)-**4** (0.205 g, 0.55 mmol) in CH_2Cl_2 (25 mL), cooled to −10 °C (ice/salt bath) and magnetically stirred under argon. The resulting orange-brown suspension was stirred under argon between −10 °C and 0 °C for 3 h and then at room temperature for 3 d. Addition of MeOH (40 mL) afforded a clear orange-brown solution of the free amino acid H-[HO]$_2$-Bip-OH·HBr, which was concentrated to ca. 20 mL (CH_2Cl_2 off) in vacuo at 30 °C, and then diluted to ca. 70 mL with more MeOH and stirred at room temperature while 98% H_2SO_4 (2.5 mL) was added dropwise. The solution was heated under reflux under argon for 48 h, and then cooled to room temperature and poured onto ice. The obtained cold, pale orange, acidic, clear solution (ca. 300 mL) was made basic by slow addition of a very large excess of solid $NaHCO_3$ in small portions and then extracted with EtOAc (2 × 125 mL). The organic phase was washed with water (100 mL), dried ($MgSO_4$) and filtered, and the solvents were evaporated in vacuo. The crude product (0.156 g) was solubilized in ca. 5 mL of EtOAc/CH_2Cl_2 (1:1) (sparingly soluble in CH_2Cl_2) and chromatographed on a 37 × 1.5 cm silica gel column with eluent I to afford 0.121 g (73%) of pure H-[HO]$_2$-Bip-OMe (*RS*)-**6** as a white solid. Crystallization from CH_2Cl_2 gave an analytical sample (white crystals). M.p. 217 °C. $R_f = 0.20$ (II). ^{1}H NMR ($CDCl_3$): δ = 7.29 [dd (t-like), $J \approx 7.4$ Hz, 1 H, ArH], 7.23 [dd (t-like), $J \approx 7.7$ Hz, 1 H, ArH], 7.02 (dd, $J = 8.2$ Hz and 1.1 Hz, 1 H, ArH), 6.99 (dd, $J = 7.9$ Hz and 1.1 Hz, 1 H, ArH), 6.97 [d (broad), $J \approx 8$ Hz, 1 H, ArH], 6.92 [d (broad), $J \approx 8$ Hz, 1 H, ArH], 3.74 (s, 3 H, OCH_3), 3.05 and 2.53 (d, $J = 13.2$ Hz, 1 H and d, $J = 13.2$ Hz, 1 H, $ArCH_2\beta$), 2.91 and 2.20 (d, $J = 13.2$ Hz, 1 H and d, $J = 13.2$ Hz, 1 H, $ArCH_2\beta'$]. ^{1}H NMR ($CDCl_3$ + 10% CD_3OD): δ = 7.14 [dd (t-like), $J \approx 7.5$ Hz, 1 H, ArH], 7.07 [dd (t-like), $J \approx 7.5$ Hz, 1 H, ArH], 6.91 (dd, $J = 8.1$ Hz and 1.1 Hz, 1 H, ArH), 6.85 (dd, $J = 8.3$ Hz and 1.1 Hz, 1 H, ArH), 6.78 (dd, $J = 7.4$ Hz and 1.1 Hz, 1 H, ArH), 6.73 (dd, $J = 7.4$ Hz and 1.1 Hz, 1 H, ArH), 3.64 (s, 3 H, OCH_3), 2.90 and 2.39 (d, $J = 13.2$ Hz, 1 H and d, $J = 13.1$ Hz, 1 H, $ArCH_2\beta$), 2.83 and 2.09 (d, $J = 13.2$ Hz, 1 H and d, $J = 13.2$ Hz, 1 H, $ArCH_2\beta'$). ^{13}C NMR ($CDCl_3$ + 10% CD_3OD): δ = 175.1 (C=O), 153.0, 152.6 (C_{Ar}−O), 138.2, 136.7,

128.6, 128.3, 123.7, 123.2, 122.4, 122.1, 116.2, 115.7 (C_{Ar}), 66.7 (Cα), 52.1 (OCH_3), 43.3 (Cβ), 41.8 (Cβ′). $C_{17}H_{17}NO_4 \cdot 0.25\ H_2O$ (303.818): calcd. C 67.20, H 5.81, N 4.61; found C 66.76, H 5.68, N 4.66. In duplicate experiments under the same experimental conditions, starting from (*i*) 2.330 g (6.31 mmol) and (*ii*) 2.562 g (6.94 mmol) of crude NMR-pure (*RS*)-**4** (vide supra), samples of (*i*) 1.009 g (53%) and (*ii*) 1.037 g (50%) of pure (*RS*)-**6** were obtained after chromatography.

Methyl 6-Amino-1,11-dihydroxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene-6-carboxylate [(*R*)-6]: A solution of (*R*)-**4** of 98 ± 2% *ee* (0.490 g, 1.33 mmol) in CH_2Cl_2 (50 mL) was treated with a solution of BBr_3 (1 M in CH_2Cl_2, 10 mL, 10 mmol) and the obtained free amino acid H-[HO]$_2$-Bip-OH·HBr was stirred under argon at 50−55 °C for 48 h in MeOH (90 mL) containing 98% H_2SO_4 (2.5 mL), under the same experimental and workup conditions as for the preparation of (*RS*)-**6**. Chromatography on a 37 × 1.5 cm silica gel column with eluents I and then II afforded 0.218 g (55%) of pure (*R*)-**6** as a white solid, with $[\alpha]_D^{25} = -2.4$, $[\alpha]_{578}^{25} = -4.3$, $[\alpha]_{546}^{25} = -9.7$, $[\alpha]_{436}^{25} = -74.4$, $[\alpha]_{365}^{25} = -343.0$ (*c* = 0.1; MeOH), corresponding to 56 ± 5% optical purity by comparison with the extrapolated maximum values $[\alpha]_{436}^{25} = -136.7$, $[\alpha]_{365}^{25} = -610.2$ (*c* = 0.1; MeOH) (see text and Table 1). This sample was solubilized in CH_2Cl_2 (ca. 50 mL) and the solution was concentrated to ca. 4−5 mL in vacuo at 30 °C, and then allowed to cool to room temperature. The resulting mixture of white crystals and clear, pale yellow supernatant was stored in a freezer for 3 weeks, diluted with cold Et_2O (ca. 100 mL), filtered through a Büchner funnel, rapidly washed with cold Et_2O and air-dried, to afford 0.108 g (27%) of almost racemic (*RS*)-**6** as white crystals, with $[\alpha]_D^{25} = 0$, $[\alpha]_{578}^{25} = 0$, $[\alpha]_{546}^{25} = -1.9$, $[\alpha]_{436}^{25} = -13.4$, $[\alpha]_{365}^{25} = -65.1$ (*c* = 0.1; MeOH). The filtrate from the crystallization was concentrated in vacuo at 30 °C, to afford 0.104 g (26%) of analytically pure (*R*)-**6** as a white, amorphous solid. M.p. 208 °C. ^{1}H NMR ($CDCl_3$): see (*RS*)-**6**. $[\alpha]_D^{25} = -3.0$, $[\alpha]_{578}^{25} = -7.6$, $[\alpha]_{546}^{25} = -15.2$, $[\alpha]_{436}^{25} = -134.0$, $[\alpha]_{365}^{25} = -598.0$ (*c* = 0.1; MeOH), corresponding to 98 ± 2% *ee* as determined by ^{19}F NMR of the corresponding Mosher amide/half phenyl ester isomers (vide infra). $C_{17}H_{17}NO_4 \cdot 0.25H_2O$ (303.818): calcd. C 67.20, H 5.81, N 4.61; found C 67.25, H 5.64, N 4.47.

Methyl 6-Amino-1,11-dihydroxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene-6-carboxylate [(*S*)-6]: A solution of (*S*)-**4** of 64 ± 5% *ee* (0.506 g, 1.37 mmol) in CH_2Cl_2 (50 mL) was treated with a solution of BBr_3 (1 M in CH_2Cl_2, 10 mL, 10 mmol), and the obtained free amino acid H-[HO]$_2$-Bip-OH·HBr was stirred under argon at 50−55 °C for 48 h in MeOH (100 mL) containing 98% H_2SO_4 (2.5 mL), under the same experimental and workup conditions as for the preparation of (*RS*)-**6**. Chromatography on a 41 × 1.5 cm silica gel column with eluents I and then II afforded 0.308 g (75%) of pure (*S*)-**6** as a white solid, with $[\alpha]_D^{25} = +2.3$, $[\alpha]_{578}^{25} = +2.7$, $[\alpha]_{546}^{25} = +6.9$, $[\alpha]_{436}^{25} = +51.1$, $[\alpha]_{365}^{25} = +225.8$ (*c* = 0.25; MeOH), corresponding to 37 ± 5% optical purity by comparison with the extrapolated maximum values $[\alpha]_{436}^{25} = +130.5$, $[\alpha]_{365}^{25} = +602.1$ (*c* = 0.1; MeOH) (see text and Table 1). This sample was crystallized from CH_2Cl_2 (concentrated solution), stored for a few days in a freezer, diluted with cold Et_2O and filtered through a Büchner funnel as above for (*R*)-**6**, to afford 0.141 g of almost racemic (*RS*)-**6** as white crystals, with $[\alpha]_D^{25} = 0$, $[\alpha]_{578}^{25} = 0$, $[\alpha]_{546}^{25} = 0$, $[\alpha]_{436}^{25} = 0$, $[\alpha]_{365}^{25} = +6.7$ (*c* = 0.1; MeOH). More crystals (0.011 g) of almost racemic (*RS*)-**6** were obtained from the concentrated filtrate by the same operations, to provide a total of 0.152 g (37%). Finally, the new filtrate was concentrated in vacuo at 30 °C, to afford 0.109 g (27%) of analytically pure (*S*)-**6** as a white amorphous solid. ^{1}H NMR ($CDCl_3$): see (*RS*)-**6**. $[\alpha]_D^{25} = +7.0$, $[\alpha]_{578}^{25} = +7.9$, $[\alpha]_{546}^{25} = +15.7$, $[\alpha]_{436}^{25} = +124.0$, $[\alpha]_{365}^{25} = +572.0$ (*c* = 0.1; MeOH), corresponding to 95 ± 5% enantiomeric excess as determined by ^{19}F NMR of the corresponding Mosher amide/half phenyl ester isomers (vide infra). $C_{17}H_{17}NO_4 \cdot 0.5H_2O$ (308.322): calcd. C 66.22, H 5.88, N 4.54; found C 66.62, H 5.55, N 4.47. A duplicate run starting from (*S*)-**4** of 64 ± 5% *ee* (0.238 g, 0.645 mmol), carried out under identical experimental and workup conditions, afforded 0.104 g (54%) of (*S*)-**6** after chromatography, and then after fractional crystallization, 0.025 g (13%) of almost racemic (*RS*)-**6** and 0.041 g (21%) of enantiomerically enriched (*S*)-**6** with $[\alpha]_D^{25} = +10.0$, $[\alpha]_{578}^{25} = +11.0$, $[\alpha]_{546}^{25} = +18.1$, $[\alpha]_{436}^{25} = +130.6$, $[\alpha]_{365}^{25} = +584.4$ (*c* = 0.1; MeOH), corresponding to 97 ± 5% optical purity by comparison with the extrapolated maximum value $[\alpha]_{365}^{25} = +602.1$ (*c* = 0.1; MeOH) (see Table 1).

Racemization Tests on (*S*)-6: A solution of (*S*)-**6** of 37 ± 5% *ee* (0.00109 g) in MeOH (1.0 mL) was kept at 50 °C in the thermostatted cell of a polarimeter and the following optical rotations $[\alpha]_{365}^{50}$ (*c* = 0.1; MeOH) were recorded at the time intervals stated: +279.8 (initial), +279.8 (1 h), +281.7 (2 h), +280.7 (3 h), +285.3 (19 h), +281.7 (21 h), +283.5 (24 h). In a similar manner, a solution of (*S*)-**6** of 37 ± 5% *ee* (0.00248 g) in DMF (2.0 mL) presenting an initial optical rotation $[\alpha]_{436}^{25} = +84.7$ was kept in an oil bath at 110 °C for 1 h, allowed to cool to room temperature and transferred to the thermostatted cell of a polarimeter. Its optical rotation was recorded, and it was transferred back to the initial flask, kept again at 110 °C for a second cycle of 1 h and so on, with the following results: $[\alpha]_{436}^{25}$ (*c* = 0.12; DMF) = +84.7 (initial), +63.7 (1 h), +41.9 (2 h), +31.4 (3 h), +19.3 (4 h).

Coupling of (*R*)-6 and (*S*)-6 with (−)-(*S*)-α-Methoxy-α-phenyl-α-(trifluoromethyl)acetic Acid: EDC (0.0073 g, 0.038 mmol) was added to a solution of (−)-(*S*)-MTPA (0.0176 g, 0.075 mmol) in acetonitrile (1 mL). The solution was stirred at room temperature for 1 h and divided into two portions of 0.5 mL each, which were added to aliquots of samples of (*R*)-**6** (0.0019 g, 0.006 mmol) and (*S*)-**6** (0.0023 g, 0.007 mmol), obtained after removal of most (*RS*)-**6** by crystallization (vide supra). The resulting clear, colourless solutions were stirred at room temperature for 16 h and then diluted with Et_2O (100 mL each). The organic phases from both experiments were washed with 0.5 N HCl (50 mL) and then water (2 × 100 mL), dried ($MgSO_4$) and filtered, and the solvents were evaporated in vacuo. The residues, which presented two main well-separated, UV-positive spots (R_f = 0.65 and 0.50) on analytical TLC with eluent I, were chromatographed on preparative TLC plates of silica gel with eluent I/CH_2Cl_2 (1:1). The two corresponding bands were separated, providing after workup two compounds arbitrarily designated as **7A** and **7B** (Figure 5), readily identified as the two expected (*S*)-MTPA amide/half ester isomers of **6** by ^{1}H NMR and ^{19}F NMR. From (*R*)-**6** there were obtained the following isomers: (*SRS*)-**7A**: R_f = 0.65 (I). ^{1}H NMR ($CDCl_3$): δ = 7.5−6.7 (several m, 16 H, 6 ArH and 10 ArH MTPAc, 5.00 (s, 1 H, NH), 3.69 (s, 3 H, OCH_3), 3.43 (m, 3 H, OCH_3 MTPA ester), 3.33 (m, 3 H, OCH_3 MTPA amide), 3.37 and 2.39 (d, *J* = 13.1 Hz, 1 H and d, *J* = 13.0 Hz, 1 H, $ArCH_2\beta$), 3.05 [s (broad), 2 H, $ArCH_2\beta'$]. ^{19}F NMR ($CDCl_3$): δ = −70.2058 [s (100%), CF_3 MTPA amide], signal of CF_3 MTPA amide of isomer (*SSS*)-**7A** at δ = −70.1158 not seen, −73.0830 [s (99.07%), CF_3 MTPA ester], −72.7903 [s (0.93%), CF_3 MTPA ester of isomer (*SSS*)-**7A**], corresponding to > 98% *de*. (*SRS*)-**7B**: R_f = 0.50 (I). ^{1}H NMR ($CDCl_3$): δ = 7.5−6.7 (several m, 16 H, 6 ArH and 10 ArH MTPA), 4.93 (s, 1 H, NH), 3.68 (s, 3 H, OCH_3), 3.45 (m, 3 H, OCH_3 MTPA ester), 3.27 (m, 3 H, OCH_3 MTPA amide), 3.28 and 3.11 (d, *J* = 13.9 Hz, 1 H and d, *J* =

13.8 Hz, 1 H, $ArCH_2\beta$), 3.07 and 2.58 (d, J = 13.0 Hz, 1 H and d, J = 13.0 Hz, 1 H, $ArCH_2\beta'$]. ^{19}F NMR ($CDCl_3$): δ = −70.0302 (s (100%), CF_3 MTPA amide], signal of CF_3 MTPA amide of isomer (*SSS*)-**7B** at δ = −69.8006 not seen, −73.1775 [s (99.3%), CF_3 MTPA ester], −72.7903 [s (0.7%), CF_3 MTPA ester of isomer (*SSS*)-**7B**], corresponding to > 98% *de*. From (*S*)-**6** were obtained the following isomers: **(*SSS*)-7A:** R_f = 0.65 (I). ^1H NMR ($CDCl_3$): δ = 7.6−6.6 (several m, 16 H, 6 ArH and 10 ArH MTPA), 4.94 (s, 1 H, NH), 3.74 (s, 3 H, OCH_3), 3.40 (m, 3 H, OCH_3 MTPA ester), 3.36 (m, 3 H, OCH_3 MTPA amide), 3.57 and 2.33 (d, J = 13.4 Hz, 1 H and d, J = 13.1 Hz, 1 H, $ArCH_2\beta$), 3.00 and 2.87 (d, J = 14.1 Hz, 1 H and d, J = 14.3 Hz, 1 H, $ArCH_2\beta'$). ^{19}F NMR ($CDCl_3$): δ = −70.1158 [s (100%), CF_3 MTPA amide], signal of CF_3 MTPA amide of isomer (*SRS*)-**7A** at δ = −70.2058 not seen, −72.7903 [s (95.7%), CF_3 MTPA ester], −73.0830 [s (4.3%), CF_3 MTPA ester of isomer (*SRS*)-**7A**], corresponding to ca. 92% *de*. **(*SSS*)-7B:** R_f = 0.50 (I). ^1H NMR ($CDCl_3$): δ = 7.6−6.7 (several m, 16 H, 6 ArH and 10 ArH MTPA), 4.87 (s, 1 H, NH), 3.76 (s, 3 H, OCH_3), 3.52 (m, 3 H, OCH_3 MTPA ester), 3.34 (m, 3 H, OCH_3 MTPA amide), 3.12 and 2.45 (d, J = 13.0 Hz, 1 H and d, J = 13.1 Hz, 1 H, $ArCH_2\beta$), 3.07 [s (broad), 2 H, $ArCH_2\beta'$]. ^{19}F NMR ($CDCl_3$): δ = −69.8006 [s (98.1%), CF_3 MTPA amide], −70.0347 [s (1.9%), CF_3 MTPA ester of isomer (*SRS*)-**7B**], −72.7903 [s (99.1%), CF_3 MTPA ester], −73.1730 [s (0.9%), CF_3 MTPA ester of isomer (*SRS*)-**7B**], corresponding to ca. 96−98% *de*.

Methyl 6-*tert*-Butyloxycarbonylamino-1,11-dihydroxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene-6-carboxylate [(*RS*)-8]: A suspension of (*RS*)-**6** (0.149 g, 0.50 mmol) and Boc_2O (0.218 g, 1.00 mmol) in acetonitrile (20 mL) was stirred at 75 °C for 1 h, and the resulting clear solution was stirred at room temperature for 10 d and then concentrated in vacuo. The crude product was chromatographed on a 40 × 1.5 cm silica gel column with eluent II to give 0.184 g (93%) of analytically pure Boc-[HO]$_2$-Bip-OMe (*RS*)-**8** as a white, crystalline powder. M.p. 156 °C. R_f = 0.30 (II). ^1H NMR ($CDCl_3$): δ = 7.72 [s (broad), 2 H, ArOH], 7.20 [s (broad), 1 H, ArH], 7.13 [dd (t-like), J = 7.8 Hz, 1 H, ArH], 7.02 [dd (t-like), $J \approx$ 8 Hz, 2 H, ArH], 6.78 (d, J = 7.4 Hz, 2 H, ArH), 5.01 [s (broad), 1 H, NH], 3.72 (s, 3 H, OCH_3), 3.05 and 2.21 (d, J = 12.9 Hz, 1 H and d, J = 12.8 Hz, 1 H, $ArCH_2\beta$), 2.92 [m (broad), 2 H, $ArCH_2\beta'$], 1.46 (s, 9 H, CMe_3 Boc). ^{13}C NMR ($CDCl_3$): δ = 173.5 (C=O), 154.8 (C=O Boc), 152.6, 152.2 (C_{Ar}−O), 137.3, 136.6, 129.0, 128.8, 123.5, 123.2, 122.9, 122.6, 116.6, 116.5 (C_{Ar}), 80.6 (O−C Boc), 68.1 (Cα), 52.6 (OCH_3), 41.5 (Cβ), 37.8 (Cβ′), 28.2 (CH_3 Boc). $C_{22}H_{25}NO_6$·0.5 H_2O (408.436): calcd. C 64.69, H 6.42, N 3.43; found C 64.94, H 6.21, N 3.59.

Methyl 6-*tert*-Butyloxycarbonylamino-1,11-dihydroxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene-6-carboxylate (*R*)-8: A solution of (*R*)-**6** of 98 ± 2% *ee* (0.097 g, 0.32 mmol) and Boc_2O (0.142 g, 0.65 mmol) in acetonitrile (25 mL) was stirred at room temperature for 10 d and then concentrated in vacuo. The crude product was chromatographed on a 41 × 1.5 cm silica gel column with eluent II to give 0.115 g (88%) of analytically pure (*R*)-**8** as a white, amorphous solid. ^1H NMR ($CDCl_3$): see (*RS*)-**8**. $[\alpha]_D^{25}$ = −137.7, $[\alpha]_{578}^{25}$ = −145.5, $[\alpha]_{546}^{25}$ = −174.1, $[\alpha]_{436}^{25}$ = −386.4, $[\alpha]_{365}^{25}$ = −905.0 (c = 0.1; MeOH), corresponding to 98 ± 2% (assumed) enantiomeric excess. $C_{22}H_{25}NO_6$·0.25H_2O (403.932): calcd. C 65.41, H 6.36, N 3.47; found C 65.21, H 6.24, N 3.34.

Methyl 6-*tert*-Butyloxycarbonylamino-1,11-dihydroxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene-6-carboxylate [(*S*)-8]: A solution of (*S*)-**6** of 95 ± 5% *ee* (0.147 g, 0.49 mmol) and Boc_2O (0.215 g, 0.98 mmol) in acetonitrile (25 mL) was stirred at room temperature for 10 d and then concentrated in vacuo. The crude product was chromatographed on a 41 × 1.5 cm silica gel column with eluent II to give 0.171 g (87%) of analytically pure (*S*)-**8** as a white, amorphous solid. ^1H NMR ($CDCl_3$): see (*RS*)-**8**. $[\alpha]_D^{25}$ = +137.8, $[\alpha]_{578}^{25}$ = +146.8, $[\alpha]_{546}^{25}$ = +173.0, $[\alpha]_{436}^{25}$ = +382.9, $[\alpha]_{365}^{25}$ = +917.6 (c = 0.1; MeOH), corresponding to 95 ± 5% (assumed) enantiomeric excess. $C_{22}H_{25}NO_6$·0.25H_2O (403.932): calcd. C 65.41, H 6.36, N 3.47; found C 65.25, H 5.94, N 3.34.

Methyl 6-*tert*-Butyloxycarbonylamino-1,11-(20-crown-6)-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene-6-carboxylate [(*RS*)-Ia]: Experimental conditions as previously reported by Voyer et al.[7] were applied: A solution of (*RS*)-**8** (0.040 g, 0.10 mmol) and Cs_2CO_3 (0.038 g, 0.11 mmol) in degassed MeOH (2 mL) was stirred under argon at 45 °C for 15 min and then concentrated to dryness in vacuo. DMF (2 mL) was added to the residue under a stream of argon, and the resulting solution was concentrated under high vacuum at 45 °C to remove the residual methanol. Again, DMF (5 mL) was added to the residue, generating a greenish-orange solution that was magnetically stirred under argon at 60 °C while a solution of pentaethylene glycol ditosylate (Aldrich, 95%) (0.056 g, 0.10 mmol) in DMF (3 mL) was added dropwise over a 1 h period. The solution was stirred at 60 °C overnight and the solvents were evaporated to dryness under high vacuum. The residue was solubilized in CH_2Cl_2 (100 mL) and 5% $NaHCO_3$ (50 mL). The decanted CH_2Cl_2 solution was washed with 5% $NaHCO_3$ (2 × 50 mL) and then with H_2O (2 × 100 mL), dried ($MgSO_4$) and filtered, and the solvents were evaporated in vacuo. The crude product (0.055 g) was chromatographed on preparative silica gel TLC plates with eluent I (two elutions) to afford 0.023 g (38%) of analytically pure Boc-[20-C-6]-Bip-OMe (*RS*)-**Ia** as a pale yellow glass. R_f = 0.20 (II); 0.50 (III). ^1H NMR ($CDCl_3$): δ = 7.28 (dd, J = 8.3 Hz and 7.5 Hz, 1 H, ArH), 7.21 (dd, J = 8.3 Hz and 7.5 Hz, 1 H, ArH), 6.96 (dd, J = 8.8 Hz and 1.1 Hz, 1 H, ArH) 6.91 (dd, J = 8.8 Hz and 1.1 Hz, 1 H, ArH), 6.84 (dd, J = 7.4 Hz and 1.1 Hz, 1 H, ArH), 6.83 (dd, J = 7.4 Hz and 1.1 Hz, 1 H, ArH), 4.79 (s, 1 H, NH), 4.17 (m, 2 H, OCH_2), 4.06 (m, 2 H, OCH_2), 3.79−3.75 (m, 4 H, OCH_2), 3.75−3.60 (m, 12 H, OCH_2), 3.74 (s, 3 H, OCH_3), 3.15 and 2.24 (d, J = 13.1 Hz, 1 H and d, J = 13.1 Hz, 1 H, $ArCH_2\beta$), 2.94 [m (broad), 2 H, $ArCH_2\beta'$], 1.45 (s, 9 H, CMe_3 Boc). ^{13}C NMR ($CDCl_3$): δ = 173.2 (C=O), 156.4, 156.1 (C_{Ar}−O), 154.5 (C=O Boc), 136.3, 128.4, 128.2, 125.3, 125.1, 122.0, 121.9, 111.3 (C_{Ar}), 80.1 (O−C Boc), 70.8, 70.7, 70.6, 70.5, 69.8, 69.7, 67.9, 67.8 (OCH_2 and Cα), 52.3 (OCH_3), 41.5 (Cβ), 38.0 (Cβ′), 28.2 (CH_3 Boc). ESI^+ MS: m/z (%) = 640 (9) $[MK]^+$, 624 (100) $[MNa]^+$, 602 (3) $[MH]^+$. $C_{32}H_{43}NO_{10}$·0.5H_2O (610.680): calcd. C 62.93, H 7.26, N 2.29; found C 62.96, H 7.24, N 2.14. In a duplicate run, treatment of (*RS*)-**8** (0.327 g, 0.82 mmol) and Cs_2CO_3 (0.320 g, 0.98 mmol) in DMF (50 mL) with pentaethylene glycol ditosylate (0.477 g, 0.87 mmol) under the same experimental and workup conditions as above afforded 0.189 g (38%) of (*RS*)-**Ia** after chromatography.

Methyl 6-*tert*-Butyloxycarbonylamino-1,11-(20-crown-6)-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene-6-carboxylate [(*R*)-Ia]: Treatment of (*R*)-**8** of 98 ± 2% assumed *ee* (0.113 g, 0.28 mmol) with Cs_2CO_3 (0.111 g, 0.34 mmol) and pentaethylene glycol ditosylate (0.171 g, 0.31 mmol) in DMF (23 mL), under the same experimental and workup conditions as for the preparation of (*RS*)-**Ia**, afforded 0.084 g (49%) of (*R*)-**Ia** after chromatography, as a pale yellow glass. ^1H NMR ($CDCl_3$): see (*RS*)-**Ia**. $[\alpha]_D^{25}$ = −89.0, $[\alpha]_{578}^{25}$ = −94.0, $[\alpha]_{546}^{25}$ = −109.0, $[\alpha]_{436}^{25}$ = −210.0, $[\alpha]_{365}^{25}$ = −399.0 (c = 0.1; MeOH), corresponding to 64 ± 5% *ee* as determined by ^{19}F NMR of the Mosher amides of the N^{α}-deprotected amino ester (*R*)-**Ib** (vide infra). $C_{32}H_{43}NO_{10}$·0.25H_2O (606.176): calcd. C 63.40, H 7.23, N 2.31; found C 63.32, H 7.34, N 2.30.

Methyl 6-*tert*-Butyloxycarbonylamino-1,11-(20-crown-6)-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene-6-carboxylate [(*S*)-Ia]: Treatment of (*S*)-**8** of 95 ± 5% assumed *ee* (0.169 g, 0.42 mmol) with Cs_2CO_3 (0.111 g, 0.34 mmol) and pentaethylene glycol ditosylate (0.171 g, 0.31 mmol) in DMF (23 mL), under the same experimental and workup conditions as for the preparation of (*RS*)-**Ia**, afforded 0.126 g (49%) of (*S*)-**Ia** after chromatography, as a pale yellow glass. ^{1}H NMR ($CDCl_3$): see (*RS*)-**Ia**. $[\alpha]_D^{25} = +72.0$, $[\alpha]_{578}^{25} = +74.0$, $[\alpha]_{546}^{25} = +83.0$, $[\alpha]_{436}^{25} = +162.0$, $[\alpha]_{365}^{25} = +318.0$ (*c* = 0.1; MeOH), corresponding to 48 ± 5% *ee* as determined by ^{19}F NMR of the Mosher amides of the corresponding N^{α}-deprotected amino ester (*S*)-**Ib** (vide infra). $C_{32}H_{43}NO_{10}\cdot 0.25H_2O$ (606.176): calcd. C 63.40, H 7.23, N 2.31; found C 63.41, H 7.45, N 2.17.

Methyl 6-Amino-1,11-(20-crown-6)-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene-6-carboxylate [(*RS*)-Ib]: TFA (2.5 mL) was added to a solution of (*RS*)-**Ia** (0.130 g, 0.22 mmol) in CH_2Cl_2 (7.5 mL). The solution was stirred at room temperature for 1 h and the solvents were evaporated to dryness in vacuo. The residue was solubilized in CH_2Cl_2 (100 mL). The solution was washed with 5% $NaHCO_3$ (100 mL) and then H_2O (2 × 100 mL), dried ($MgSO_4$) and filtered, and the solvents were evaporated in vacuo, to afford 0.099 g (91%) of crude H-[20-C-6]-Bip-OMe (*RS*)-**Ib**, which was used without further purification in the next step. R_f = 0.30 (III). ^{1}H NMR ($CDCl_3$): δ = 7.28 (dd, *J* = 8.3 Hz and 7.4 Hz, 1 H, ArH), 7.22 (dd, *J* = 8.3 Hz and 7.5 Hz, 1 H, ArH), 6.96 [d (broad), *J* = 8.3 Hz, 1 H, ArH], 6.91 [d (broad), *J* = 7.4 Hz, 1 H, ArH], 6.90 (dd, *J* = 8.4 Hz and 1.0 Hz, 1 H, ArH), 6.87 (dd, *J* = 7.4 Hz and 1.0 Hz, 1 H, ArH), 4.17 (m, 2 H, OCH_2), 4.05 (m, 2 H, OCH_2), 3.83−3.71 (m, 8 H, OCH_2), 3.71−3.59 (m, 8 H, OCH_2), 3.72 (s, 3 H, OCH_3), 3.00 and 2.24 (d, *J* = 13.1 Hz, 1 H and d, *J* = 13.2 Hz, 1 H, $ArCH_2\beta$), 2.93 and 2.51 [d (broad), *J* ≈ 13 Hz, 1 H and d, *J* = 13.4 Hz, 1 H, $ArCH_2\beta'$].

Methyl 6-Amino-1,11-(20-crown-6)-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene-6-carboxylate [(*R*)-Ib]: A solution of (*R*)-**Ia** (0.0074 g, 0.012 mmol) in CH_2Cl_2 (3 mL) was treated with TFA (1 mL) under the same experimental and workup conditions as for the preparation of (*RS*)-**Ib** to afford 0.0058 g (94%) of crude (*R*)-**Ib**, pure by ^{1}H NMR and TLC (see (*RS*)-**Ib**). An aliquot of that sample was used without further purification for the preparation of the corresponding Mosher amide (vide infra).

Methyl 6-Amino-1,11-(20-crown-6)-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene-6-carboxylate [(*S*)-Ib]: A solution of (*S*)-**Ia** (0.0098 g, 0.016 mmol) in CH_2Cl_2 (3 mL) was treated with TFA (1 mL) under the same experimental and workup conditions as for the preparation of (*RS*)-**Ib** to afford 0.0080 g (98%) of crude (*S*)-**Ib**, pure by ^{1}H NMR and TLC (see (*RS*)-**Ib**). An aliquot of that sample was used without further purification for the preparation of the corresponding Mosher amide (vide infra).

Coupling of (*R*)-Ib and (*S*)-Ib with (−)-(*S*)-α-Methoxy-α-phenyl-α-(trifluoromethyl)acetic Acid: EDC (0.0123 g, 0.064 mmol) was added to a solution of (−)-(*S*)-MTPA (0.0300 g, 0.128 mmol) in acetonitrile (2 mL). The solution was stirred at room temperature for 1 h and divided in two portions of 1 mL each, which were added to aliquots of crude (*R*)-**Ib** (0.0035 g, 0.007 mmol) and crude (*S*)-**Ib** (0.0060 g, 0.012 mmol) (vide supra). The resulting clear, colourless solutions were stirred at room temperature for 48 h and then diluted with EtOAc (100 mL each). The organic phases from both procedures were washed with 0.5 N HCl (50 mL) and then water (2 × 100 mL), dried ($MgSO_4$) and filtered, and the solvents were evaporated in vacuo. The residues were chromatographed on preparative silica gel TLC plates with eluent II, care being taken not to exercise a mechanical separation of one of the diastereoisomers over the other. From (*R*)-**Ib** the amido ester (*S*)-Ph(OCH_3)(CF_3)C-CO-(*R*)-[20-C-6]-Bip-OMe was obtained with 64% *de* (estimated experimental error: ±5%). ^{1}H NMR ($CDCl_3$): δ = 7.54 (m, 2 H, ArH MTPA), 7.41 (m, 3 H, ArH MTPA), 7.27 [dd (t-like), *J* ≈ 8 Hz, 1 H, ArH], 7.22 [dd (t-like), *J* ≈ 8 Hz, 1 H, ArH], 7.09 (s, 1 H, NH), 6.98 (d, *J* ≈ 8 Hz, 1 H, ArH), 6.95 (d, *J* ≈ 8 Hz, 1 H, ArH), 6.83 (d, *J* ≈ 7.5 Hz, 1 H, ArH), 6.78 (d, *J* ≈ 7.5 Hz, 1 H, ArH), 4.18 (m, 2 H, OCH_2), 4.07 (m, 2 H, OCH_2), 3.8−3.6 (m, 16 H, OCH_2), 3.68 (s, 3 H, OCH_3), 3.32 (m, 3 H, OCH_3 MTPA), 3.12 and 2.43 (d, *J* = 13.2 Hz, 1 H and d, *J* = 12.9 Hz, 1 H, $ArCH_2\beta$), 3.10 and 3.05 (d, *J* = 13.8 Hz, 1 H and d, *J* = 13.8 Hz, 1 H, $ArCH_2\beta'$), all signals corresponding to the (*SS*) isomer (vide infra) also present in a proportion of ca. 20%. ^{19}F NMR ($CDCl_3$): δ = −69.0245 [s (ca. 18.5%), CF_3 of the (*SS*) isomer], −69.0695 [s (ca. 81.5%), CF_3]; for better separation of the 2 signals: ^{19}F NMR ([D_8]toluene): δ = −68.9948 [s (ca. 18%), CF_3 of the (*SS*) isomer], −69.1479 [s (ca. 82%), CF_3]. From (*S*)-**Ib**, the amido ester (*S*)-Ph(OCH_3)(CF_3)C-CO-(*S*)-[20-C-6]-Bip-OMe was obtained with 48 ± 5% *de*. ^{1}H NMR ($CDCl_3$): δ = 7.63 (m, 2 H, ArH MTPA), 7.47 (m, 3 H, ArH MTPA), 7.23 [dd (t-like), *J* = 8.0 Hz, 1 H, ArH], 7.13 [dd (t-like), *J* = 7.9 Hz, 1 H, ArH], 6.92 (d, *J* ≈ 8 Hz, 2 H, ArH), 6.88 (d, *J* = 8.1 Hz, 1 H, ArH), 6.85 (s, 1 H, NH), 6.52 (d, *J* = 7.0 Hz, 1 H, ArH), 4.16 (m, 2 H, OCH_2), 4.05 (m, 2 H, OCH_2), 3.8−3.6 (m, 16 H, OCH_2), 3.73 (s, 3 H, OCH_3), 3.43 (m, 3 H, OCH_3 MTPA), 3.28 and 2.34 (d, *J* = 12.9 Hz, 1 H and d, *J* = 12.9 Hz, 1 H, $ArCH_2\beta$), 2.99 and 2.88 (d, *J* = 14.0 Hz, 1 H and d, *J* = 14.0 Hz, 1 H, $ArCH_2\beta'$), all signals corresponding to the (*SR*) isomer (vide supra) also present in a proportion of ca. 25%. ^{19}F NMR ($CDCl_3$): δ = −69.0245 [s (ca. 73.5%), CF_3], −69.0695 [s (ca. 26.5%), CF_3 of the (*SR*) isomer]; for better separation of the two signals: ^{19}F NMR ([D_8]toluene): δ = −68.9948 [s (ca. 74%), CF_3], −69.1479 [s (ca. 26%), CF_3 of the (*SR*) isomer]. This ratio of the CF_3 signals of the two diastereoisomers (ca. 74:26) remained unchanged when the ^{19}F NMR spectrum was recorded again after the NMR tube containing the [D_8]toluene solution had been introduced into an oil bath kept at 110 °C for 24 h and 8 d.

6-*tert*-Butyloxycarbonylamino-1,11-(20-crown-6)-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene-6-carboxylic Acid [(*RS*)-Ic]: NaOH (1 N, 10 mL) was added to a solution of (*RS*)-**Ia** (0.060 g, 0.10 mmol) in MeOH (10 mL). The solution was stirred at room temperature for 17 h and then at 50 °C for further 2 h, in order to complete the saponification reaction, its progress being monitored by TLC on silica gel with eluent III. Methanol was evaporated in vacuo at 40 °C. The resulting aqueous basic solution was cooled by addition of ice and then acidified by addition of a large excess of 0.5 N HCl and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with H_2O (2 × 100 mL), dried ($MgSO_4$) and filtered, and the solvents were evaporated in vacuo to afford 0.056 g (96%) of crude Boc-[20-C-6]-Bip-OH (*RS*)-**Ic** as a white, amorphous solid, which was used in the next step without further purification. R_f = 0.30 (III). ^{1}H NMR ($CDCl_3$): δ = 7.27 [dd (t-like), *J* ≈ 8 Hz, 1 H, ArH], 7.22 [dd (t-like), *J* = 7.9 Hz, 1 H, ArH], 6.97 (d, *J* = 8.1 Hz, 1 H, ArH), 6.93 [d (broad), *J* ≈ 7.5 Hz, 1 H, ArH], 6.92 [d (broad), *J* = 8.3 Hz, 1 H, ArH], 6.83 (d, *J* = 7.4 Hz, 1 H, ArH), 4.87 [s (broad), 1 H, NH], 4.22−4.00 (m, 4 H, OCH_2), 3.85−3.61 (m, 16 H, OCH_2), 3.23 and 2.25 (d, *J* = 12.9 Hz, 1 H and d, *J* = 13.1 Hz, 1 H, $ArCH_2\beta$), 3.01 and 2.92 [d (broad), *J* ≈ 13 Hz, 1 H and d, *J* = 12.9 Hz, 1 H, $ArCH_2\beta'$], 1.47 (s, 9 H, CMe_3 Boc). ^{13}C NMR ($CDCl_3$): δ = 176.5 (C=O), 156.3, 155.9 (C_{Ar}−O), 155.2 (C=O Boc), 137.1, 128.2, 128.1, 125.6, 125.5, 122.7, 122.3, 111.8, 111.7 (C_{Ar}), 80.0 (O−C Boc), 70.6, 70.4, 69.7, 68.5, 68.0 (OCH_2 and Cα), 41.4 (Cβ), 38.0 (Cβ′), 28.3 (CH_3 Boc).

6-*tert*-Butyloxycarbonylamino-1,11-(20-crown-6)-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene-6-carboxylic Acid [(*R*)-Ic]: A solution of (*R*)-**Ia** (0.079 g, 0.13 mmol) in MeOH (20 mL) and NaOH (1 N, 20 mL) was stirred at 50 °C for 4 h. The crude product obtained after the same workup procedure as for the preparation of (*RS*)-**Ic** was triturated in hexane. The supernatant hexane solution was discarded, and the decanted solid was dried in vacuo at 40 °C to afford 0.0057 g (74%) of pure (*R*)-**Ic** as a white, amorphous solid. ^{1}H NMR ($CDCl_3$): see (*RS*)-**Ic**. $[\alpha]_D^{25} = -94.3$, $[\alpha]_{578}^{25} = -99.5$, $[\alpha]_{546}^{25} = -116.0$, $[\alpha]_{436}^{25} = -223.2$, $[\alpha]_{365}^{25} = -424.7$ (c = 0.1; MeOH), corresponding to 64 ± 5% *ee* (assumed). $C_{31}H_{41}NO_{10}\cdot 0.5H_2O$ (596.654): calcd. C 62.40, H 7.09, N 2.35; found C 62.14, H 7.28, N 2.19.

6-*tert*-Butyloxycarbonylamino-1,11-(20-crown-6)-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptene-6-carboxylic Acid [(*S*)-Ic]: A solution of (*S*)-**Ia** (0.114 g, 0.19 mmol) in MeOH (25 mL) and NaOH (1 N, 25 mL) was stirred at 50 °C for 4 h. The same workup procedure as for the preparation of (*R*)-**Ic** was applied, to afford 0.0064 g (57%) of pure (*S*)-**Ic** as a white, amorphous solid. ^{1}H NMR ($CDCl_3$): see (*RS*)-**Ic**. $[\alpha]_D^{25} = +91.7$, $[\alpha]_{578}^{25} = +93.5$, $[\alpha]_{546}^{25} = +114.3$, $[\alpha]_{436}^{25} = -220.0$, $[\alpha]_{365}^{25} = +432.2$ (c = 0.1; MeOH), corresponding to 48 ± 5% *ee* (assumed). [*Note*: The recorded optical rotations of (*S*)-**Ic** with an assumed *ee* of 48 ± 5% are ca. 20−25% too high relative to those of (*R*)-**Ic** with 64 ± 5% assumed *ee*. Slight differences in the purification processes for the two samples by trituration/precipitation from hexane may account for this discrepancy, since either an increase or a decrease of enantiomeric purity might result from solubility differences between racemic and enantiomerically pure **Ic**]. $C_{31}H_{41}NO_{10}$ (587.646): calcd. C 63.36, H 7.03, N 2.38; found C 63.11, H 7.48, N 2.07.

Boc-[20-C-6]-Bip-Gly-OMe (*RS*)-IIa: Et_3N (triethylamine, 0.034 mL, 0.24 mmol) was added to a suspension of (*RS*)-**Ic** (0.0474 g, 0.08 mmol), HCl·H-Gly-OMe (0.0304 g, 0.24 mmol) and HOBt (0.022 g, 0.16 mmol) in THF (tetrahydrofuran) (2 mL) and CH_2Cl_2 (3 mL), followed by a solution of EDC (0.0230 g, 0.12 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at room temperature overnight, and the solvents were evaporated to dryness in vacuo. The residue was solubilized in EtOAc (100 mL) and HCl (0.5 N, 50 mL) with stirring. The separated organic phase was extracted with HCl (0.5 N, 50 mL), H_2O (100 mL), 5% $NaHCO_3$ (2 × 50 mL) and H_2O (2 × 100 mL), dried ($MgSO_4$) and filtered, and the solvents were evaporated in vacuo. The crude product was chromatographed on a 35 × 1.5 cm silica gel column with eluents II and then III, to give 0.0435 g (82%) of analytically pure (*RS*)-**IIa** as a pale yellow, glassy solid. R_f = 0.40 (III). ^{1}H NMR ($CDCl_3$): δ = 7.27 [dd (t-like), $J \approx 8$ Hz, 1 H, ArH], 7.23 [dd (t-like), $J \approx 8$ Hz, 1 H, ArH], 7.00 [m (broad), 1 H, NH Gly], 6.97 (d, J = 7.7 Hz, 2 H, ArH), 6.90 (d, J = 8.3 Hz, 1 H, ArH), 6.82 (d, J = 6.8 Hz, 1 H, ArH), 4.74 [s, 1 H, NH (20-C-6)-Bip], 4.22−3.95 (m, 4 H, OCH_2), 4.15 and 3.99 [dd (partly masked), J = 18.4 Hz and 5.5 Hz, 1 H and dd, J = 18.4 Hz and 5.0 Hz, 1 H, CH_2 Gly], 3.79−3.60 (m, 16 H, OCH_2), 3.76 (s, 3 H, OCH_3), 3.28 and 2.21 (d, J = 12.9 Hz, 1 H and d, J = 13.0 Hz, 1 H, $ArCH_2\beta$), 3.06 and 2.95 [d (broad), $J \approx 13$ Hz, 1 H and d, J = 13.2 Hz, 1 H, $ArCH_2\beta'$], 1.46 (s, 9 H, CMe_3 Boc). ^{13}C NMR ($CDCl_3$): δ = 172.8, 170.4 (C=O Gly and [20-C-6]-Bip), 156.4, 156.0 (C_{Ar}-O), 154.7 (C=O Boc), 136.8, 136.6, 128.3, 125.4, 125.0, 122.6, 121.8, 111.3 (C_{Ar}), 80.4 (O−C Boc), 70.8, 70.7, 70.6, 70.5, 69.8, 68.5, 67.8 (OCH_2 and Cα [20-C-6]-Bip), 52.2 (OCH_3), 41.9 (CH_2 Gly), 41.4 (Cβ [20-C-6]-Bip), 36.9 (Cβ′ [20-C-6]-Bip), 28.2 (CH_3 Boc). $C_{34}H_{46}N_2O_{11}\cdot 0.5H_2O$ (667.732): calcd. C 61.15, H 7.10, N 4.20; found C 61.16, H 7.14, N 4.55.

Boc-[20-C-6]-Bip-Gly-OH (*RS*)-IIc: A solution of (*RS*)-**IIa** (0.039 g, 0.06 mmol) in MeOH (10 mL) and NaOH (1 N, 10 mL) was stirred at room temperature for 2 h, the reaction progress being monitored by TLC on silica gel with eluent III. The same workup procedure as for the preparation of (*RS*)-**Ic** was applied, to afford 0.021 g (55%) of crude (*RS*)-**IIc** as a white, amorphous solid, pure by TLC, which was used in the next step without further purification. R_f = 0.05 (III); 0.10 (IV).

Boc-Gly-[20-C-6]-Bip-OMe (*RS*)-IIIa: EDC (0.076 g, 0.40 mmol) was added to a solution of Boc-Gly-OH (0.141 g, 0.80 mmol) in acetonitrile (5 mL). The solution was stirred at room temperature for 1 h [complete formation of the symmetrical anhydride (Boc-Gly)$_2$O assumed] and then transferred by pipette into a flask containing (*RS*)-**Ib** (0.099 g, 0.20 mmol). The resulting clear, colourless solution was stirred at room temperature for 20 h, and the solvents were evaporated in vacuo. The residue was solubilized in EtOAc (100 mL) and HCl (0.5 N, 50 mL) with stirring. The separated organic phase was extracted with HCl (0.5 N, 50 mL), H_2O (100 mL), 5% $NaHCO_3$ (2 × 50 mL) and H_2O (2 × 100 mL), dried ($MgSO_4$) and filtered, and the solvents were evaporated in vacuo. The crude product was chromatographed on a 1.5 × 36 cm silica gel column with eluents II and then III, to afford 0.091 g (70%) of analytically pure (*RS*)-**IIIa** as a white, amorphous solid. R_f = 0.45 (III). ^{1}H NMR ($CDCl_3$): δ = 7.24 [dd (t-like), J = 7.5 Hz, 1 H, ArH], 7.21 [dd (t-like), J = 7.5 Hz, 1 H, ArH], 6.94 (d, J = 7.7 Hz, 1 H, ArH), 6.91 (d, J = 7.7 Hz, 1 H, ArH), 6.85 (d, J = 7.5 Hz, 1 H, ArH), 6.81 (d, J = 7.4 Hz, 1 H, ArH), 6.49 [s, 1 H, NH (20-C-6)-Bip], 5.21 [m (broad), 1 H, NH Gly], 4.15 (m, 2 H, OCH_2), 4.03 (m, 2 H, OCH_2), 4.15 and 3.99 [dd (partly masked), J = 18.4 Hz and 5.5 Hz, 1 H and dd, J = 18.4 Hz and 5.0 Hz, 1 H, CH_2 Gly], 3.77−3.59 (m, 18 H, OCH_2 and masked CH_2 Gly), 3.69 (s, 3 H, OCH_3), 3.20 and 2.29 (d, J = 13.0 Hz, 1 H and d, J = 12.8 Hz, 1 H, $ArCH_2\beta$), 2.94 and 2.89 (d, J = 13.8 Hz, 1 H and d, J = 13.9 Hz, 1 H, $ArCH_2\beta'$), 1.42 (s, 9 H, CMe_3 Boc). ^{13}C NMR ($CDCl_3$): δ = 172.6, 168.9 (C=O Gly and [20-C-6]-Bip), 156.4, 156.1 (C_{Ar}−O and C=O Boc), 136.4, 136.0, 128.6, 128.3, 125.3, 125.1, 121.9, 121.8, 111.4 (C_{Ar}), 80.2 (O−C Boc), 70.8, 70.7, 70.6, 70.5, 69.8, 69.7, 67.8, 67.5 (OCH_2 and Cα [20-C-6]-Bip), 52.4 (OCH_3), 44.3 (CH_2 Gly), 41.0 (Cβ [20-C-6]-Bip), 37.9 (Cβ′ [20-C-6]-Bip), 28.2 (CH_3 Boc). $C_{34}H_{46}N_2O_{11}\cdot 0.5H_2O$ (667.732): calcd. C 61.15, H 7.10, N 4.20; found C 60.91, H 7.31, N 4.51.

Boc-Gly-[20-C-6]-Bip-OH (*RS*)-IIIc: A solution of (*RS*)-**IIIa** (0.087 g, 0.13 mmol) in MeOH (10 mL) and NaOH (1 N, 10 mL) was stirred at 50 °C for 2 h, the reaction progress being monitored by TLC on silica gel with eluent III. The same workup procedure as for the preparation of (*RS*)-**Ic** was applied, to afford 0.071 g (84%) of crude (*RS*)-**IIIc** as a white, amorphous solid, pure by TLC, which was used in the next step without further purification. R_f = 0.05 (III); 0.15 (IV).

Boc-Gly-[20-C-6]-Bip-Gly-OMe (*RS*)-IVa: A mixture of (*RS*)-**IIIc** (0.071 g, 0.11 mmol), HCl·H-Gly-OMe (0.042 g, 0.33 mmol), HOBt (0.030 g, 0.22 mmol), Et_3N (0.046 mL, 0.33 mmol) and EDC (0.032 g, 0.17 mmol) in THF (3 mL) and CH_2Cl_2 (4 mL), was treated at room temperature for 24 h under the same experimental and workup conditions as for the preparation of (*RS*)-**IIa**. The crude product was chromatographed on a 36 × 1.5 cm silica gel column with eluents III and then IV, to afford 0.065 g (82%) of analytically pure (*RS*)-**IVa** as a white, amorphous solid. R_f = 0.15 (II); 0.40 (III); 0.60 (IV). ^{1}H NMR ($CDCl_3$, Boc-Gly^1-[20-C-6]-Bip^2-Gly^3-OMe): δ = 7.36 (t, J = 5.3 Hz, 1 H, NH Gly^3), 7.23 [dd (t-like), J = 7.9 Hz, 2 H, ArH], 6.98 (d, J = 7.4 Hz, 1 H, ArH), 6.94 (d, J = 7.9 Hz, 1 H, ArH), 6.91 (d, J = 8.3 Hz, 1 H, ArH),

6.80 (d, J = 7.2 Hz, 1 H, ArH), 6.51 [s, 1 H, NH (20-C-6)-Bip^2], 5.37 [m (broad), 1 H, NH Gly^1], 4.20−3.94 (m, 4 H, OCH_2 and masked dd, 1 H, CH Gly^3), 3.90 (dd, J = 18.0 Hz and 5.3 Hz, 1 H, CH Gly^3), 3.80−3.59 (m, 18 H, OCH_2 and masked CH_2 Gly^1), 3.72 (s, 3 H, OCH_3), 3.35 and 2.29 [d (broad), $J \approx$ 12.5 Hz, 1 H and d, J = 12.9 Hz, 1 H, $ArCH_2\beta$], 3.09 and 2.98 (d, J = 13.8 Hz, 1 H and d, J = 13.6 Hz, 1 H, $ArCH_2\beta'$), 1.42 (s, 9 H, CMe_3 Boc). ^{13}C NMR ($CDCl_3$): δ = 172.3, 170.4, 169.7 (C=O Gly^1, [20-C-6]-Bip^2 and Gly^3), 156.4, 156.0 (C_{Ar}−O and C=O Boc), 136.7, 136.4, 128.4, 125.5, 125.1, 122.7, 121.8, 111.7 (C_{Ar}), 80.6 (O−C Boc), 70.7, 70.6, 70.51, 70.46, 69.8, 69.7, 68.8, 68.0 (OCH_2 and Cα [20-C-6]-Bip^2), 52.1 (OCH_3), 45.1, 41.6 (CH_2 Gly^1 and Gly^3), 41.3 (Cβ [20-C-6]-Bip^2), 37.0 (Cβ′ [20-C-6]-Bip^2), 28.2 (CH_3 Boc). ESI$^+$ MS: m/z (%) = 754 (9) $[MK]^+$, 738 (100) $[MNa]^+$, 716 (3) $[MH]^+$, 381 (15) $[MNa_2]^{++}$. $C_{36}H_{49}N_3O_{12}$ (715.776): calcd. C 60.40, H 6.90, N 5.87; found C 60.32, H 6.68, N 5.59.

H-Gly-[20-C-6]-Bip-Gly-OMe (*RS*)-IVb: A solution of (*RS*)-**IVa** (0.039 g, 0.054 mmol) in CH_2Cl_2 (6 mL) was treated with TFA (2 mL) at room temperature for 3 h under the same experimental and workup conditions as for the preparation of (*RS*)-**Ib**, to afford 0.034 g (100%) of crude (*RS*)-**IVb**, which was used in the next step without further purification. R_f = 0.05 (III); 0.10 (IV). ^{1}H NMR ($CDCl_3$, H-Gly^1-[20-C-6]-Bip^2-Gly^3-OMe): δ = 7.81 (broad t, 1 H, NH Gly^3), 7.74 [broad s, 1 H, NH (20-C-6)-Bip^2], 7.24 [dd (t-like), J = 7.7 Hz, 2 H, ArH], 7.05 (d, J = 7.2 Hz, 1 H, ArH), 6.95 (d, J = 8.8 Hz, 1 H, ArH), 6.92 (d, J = 8.4 Hz, 1 H, ArH), 6.85 (d, J = 7.0 Hz, 1 H, ArH), 4.23−4.01 (m, 4 H, OCH_2 and masked dd, 1 H, CH Gly^3), 3.97 (dd, J = 18.2 Hz and 5.1 Hz, 1 H, CH Gly^3), 3.80−3.59 (m, 18 H, OCH_2 and masked CH_2 Gly^1), 3.75 (s, 3 H, OCH_3), 3.34 (broad s, 2 H, NH_2 Gly^1), 3.65 and 2.29 [d (masked), 1 H and d, J = 13.4 Hz, 1 H, $ArCH_2\beta$], 3.15 and 2.95 (d, J = 14.0 Hz, 1 H and d, J = 13.8 Hz, 1 H, $ArCH_2\beta'$).

Boc-[20-C-6]-Bip-Gly-Gly-[20-C-6]-Bip-Gly-OMe (*RR*,*SS*)- + (*RS*,*SR*)-Va: A mixture of Boc-[20-C-6]-Bip-Gly-OH (*RS*)-**IIc** (0.020 g, 0.031 mmol), H-Gly-[20-C-6]-Bip-Gly-OMe (*RS*)-**IVb** (0.032 g, 0.052 mmol), HOBt (0.010 g, 0.074 mmol) and EDC (0.012 g, 0.062 mmol) in THF (2 mL) and CH_2Cl_2 (3 mL) was treated at room temperature for 24 h under the same experimental and workup conditions as for the preparation of (*RS*)-**IIa**. The crude product was chromatographed on a 35 × 1.5 cm silica gel column with eluents III and then IV, to afford 0.021 g (55%) of an analytically pure ca. 1:1 mixture (by ^{1}H NMR) of diastereoisomers (*RR*,*SS*)- + (*RS*,*SR*)-**Va** as a white amorphous solid. R_f = 0.10 (III); 0.45 (IV). ^{1}H NMR ($CDCl_3$): δ = 8.08 (broad t, 1 H, NH Gly of 2 isomers), 7.32−6.62 (m, 15 H, 12 ArH, 2 masked NH Gly and masked NH Bip of 2 isomers), 5.05 [s, 1 H, (Boc) NH (20-C-6)-Bip of 2 isomers], 4.18−3.58 (m, 46 H, 20 OCH_2 and 3 masked CH_2 Gly of 2 isomers), 3.71 and 3.68 (s, 3 H, OCH_3 of 2 isomers), 3.28 and 2.54 (d, J = 12.3 Hz, 0.5 H and d, J = 13.2 Hz, 0.5 H), 3.24 and 2.37 (d, J = 12.5 Hz, 0.5 H and d, J = 13.0 Hz, 0.5 H), 3.17 and 3.09 (d, J = 13.8 Hz, 0.5 H and d, J = 13.6 Hz, 0.5 H), 3.10 and 3.01 (d, J = 13.6 Hz, 0.5 H and d, J = 13.6 Hz, 0.5 H), 3.05 and 2.08 (d, J = 13.6 Hz, 0.5 H and d, J = 13.2 Hz, 0.5 H), 3.01 and 2.18 (d, J = 13.6 Hz, 0.5 H and d, J = 13.0 Hz, 0.5 H), 2.91 and 2.73 (d, J = 13.6 Hz, 0.5 H and d, J = 13.6 Hz, 0.5 H), 2.80 and 2.63 (d, J = 13.6 Hz, 0.5 H and d, J = 14.3 Hz, 0.5 H) ($ArCH_2\beta$ and $ArCH_2\beta'$ of 2 [20-C-6]-Bip residues of 2 isomers), 1.43 and 1.42 [s and s (ratio ca. 1:1), 9 H, Boc of 2 isomers]. ^{13}C NMR ($CDCl_3$): δ = 173.8, 173.3, 172.6, 170.8, 170.7, 170.6, 169.0, 168.9 (C=O from 3 Gly and 2 [20-C-6]-Bip residues of 2 isomers), 156.6, 156.5, 156.2, 156.1, 155.93, 155.91, 155.8, 152.2 (C_{Ar}−O and C=O Boc of 2 isomers), 137.4, 136.7, 136.6, 136.5, 136.0, 135.7, 135.5, 128.6, 128.5, 128.1, 125.5, 125.44, 125.36, 125.3, 125.0, 124.7, 124.5, 122.8, 122.7, 122.4, 122.1, 121.7, 121.4, 111.7, 111.6, 111.4, 111.2, 110.7 (C_{Ar} of 2 isomers), 81.7, 81.6 (O−C Boc of 2 isomers), 70.8, 70.7, 70.5, 69.8, 69.7, 69.1, 68.9, 68.3, 68.1, 67.7, 67.5 (OCH_2 and Cα [20-C-6]-Bip of two isomers), 52.0 (OCH_3 of two isomers), 44.2, 43.7, 42.1, 41.8, 41.6 (CH_2 Gly of two isomers), 41.4, 41.3 (Cβ [20-C-6]-Bip of two isomers), 38.4, 36.8, 36.3, 36.2 (Cβ′ [20-C-6]-Bip of two isomers), 28.2 (CH_3 Boc of two isomers). ESI$^+$ MS: m/z (%) = 1280 (3) $[MK]^+$, 1264 (35) $[MNa]^+$, 1242 (3) $[MH]^+$, 652 (17) $[MKNa]^{++}$, 644 (100) $[MNa_2]^{++}$, 633 (13) $[MHNa]^{++}$, 437 (4) $[MNa_3]^{+++}$. $C_{64}H_{83}N_5O_{20}\cdot 2H_2O$ (1278.376): calcd. C 60.13, H 6.86, N 5.48; found C 60.05, H 6.75, N 5.81.

Boc-[20-C-6]-Bip-Aib-Aib-Aib-Aib-Aib-Aib-O*t*Bu (*S*)-VI: Pd/C (10%, 0.025 g) was added to a solution of Z-$(Aib)_6$-O*t*Bu[50] (0.055 g, 0.076 mmol) in MeOH (40 mL). The mixture was hydrogenated in a Parr apparatus at room temperature for 5 h and filtered through paper, and the solvents were evaporated in vacuo at 40 °C to give 0.045 g (100%) of crude H-$(Aib)_6$-O*t*Bu. A mixture of this sample (0.045 g, 0.076 mmol), crude Boc-[20-C-6]-Bip-OH (*S*)-**Ic** of 48 ± 5% assumed *ee* (vide supra) (0.054 g, 0.092 mmol), HOAt (0.018 g, 0.132 mmol) and EDC (0.025 g, 0.131 mmol) in CH_2Cl_2 (5 mL), was treated at room temperature for 4 weeks under the same experimental and workup conditions as for the preparation of (*RS*)-**IIa**. The crude product was chromatographed on a preparative TLC plate of silica gel with eluent III, and the collected fraction of the desired product was purified by further TLC on silica gel with eluent EtOAc (6 consecutive elutions), to afford 0.017 g (19%) of analytically pure (*S*)-**VI** of 48 ± 5% assumed *ee*, as a pale yellow, amorphous solid after trituration in hexane and concentration to dryness in vacuo. R_f = 0.40 (III); 0.10 (EtOAc). ^{1}H NMR ($CDCl_3$): δ = 7.77 (s, 1 H, NH Aib), 7.69 (s, 1 H, NH Aib), 7.58 (s, 1 H, NH Aib), 7.39 (s, 2 H, 2 NH Aib), 7.32 [dd (t-like), J = 7.5 Hz, 1 H, ArH], 7.20 [dd (t-like), J = 7.7 Hz, 1 H, ArH], 7.01 (d, J = 8.1 Hz, 1 H, ArH), 6.93 (d, J = 8.3 Hz, 1 H, ArH), 6.77 (d, J = 7.0 Hz, 1 H, ArH), 6.75 (d, $J \approx$ 7 Hz, 1 H, ArH), 6.60 (s, 1 H, NH Aib), 5.03 [s, 1 H, NH (20-C-6)-Bip], 4.23−4.06 (m, 4 H, OCH_2), 3.86−3.60 (m, 16 H, OCH_2), 3.07 and 2.27 (d, J = 13.8 Hz, 1 H and d, J = 13.2 Hz, 1 H, $ArCH_2\beta$), 3.01 and 2.71 [d (broad), $J \approx$ 13 Hz, 1 H and d, J = 14.0 Hz, 1 H, $ArCH_2\beta'$], 1.64−1.48 (m, 36 H, CH_3 of 6 Aib), 1.44 (s, 18 H, CMe_3 Boc and CMe_3 COO*t*Bu). ^{13}C NMR ($CDCl_3$): δ = 175.3, 174.7, 174.2, 174.0, 172.2 (C=O Aib and [20-C-6]-Bip), 156.6, 156.1, 155.6 (C_{Ar}−O and C=O Boc), 136.1, 135.7, 128.7, 128.1, 125.3, 124.7, 122.3, 121.5, 111.6 (C_{Ar}), 81.6, 79.7 (O−C Boc and COO*t*Bu), 70.9, 70.8, 70.6, 70.6, 70.5, 69.9, 68.4, 68.0 (OCH_2 and Cα [20-C-6]-Bip), 56.8, 56.7, 56.6, 56.5 (Cα Aib), 42.0 (Cβ [20-C-6]-Bip), 37.3 (Cβ′ [20-C-6]-Bip), 28.2, 27.9 (CH_3 Boc and COO*t*Bu), 26.1 (broad), 25.5, 25.1, 24.8, 24.5 (broad) (CH_3 Aib). $[\alpha]_D^{25}$ = +69.7, $[\alpha]_{578}^{25}$ = +71.3, $[\alpha]_{546}^{25}$ = +80.9, $[\alpha]_{436}^{25}$ = +153.9, $[\alpha]_{365}^{25}$ = +293.0 (c = 0.1; MeOH). ESI$^+$ MS: m/z (%) = 1176 (12) $[MNa]^+$, 599.9 (100) $[MNa_2]^{++}$. $C_{59}H_{91}N_7O_{16}$ (1154.374): calcd. C 61.38, H 7.95, N 8.49; found C 61.31, H 8.07, N 7.77.

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Received October 19, 2001
[O01509]