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Enantiomerically pure chiral phenazino-crown ethers: synthesis, preliminary circular dichroism spectroscopic studies and complexes with the enantiomers of 1-arethyl ammonium salts

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Abstract

Enantiomerically pure chiral crown ethers containing the phenazine unit [(*R*,*R*)-**2**–(*S*,*S*)-**8**] were prepared by two types of cyclization reactions. Ligands (*R*,*R*)-**2**, (*R*,*R*)-**3**, (*S*,*S*)-**4**, (*R*,*R*)-**5**, (*R*,*R*)-**6** and (*R*,*R*)-**7** were prepared from phenazine-1,9-diol **9** and the appropriate ditosylates (*S*,*S*)-**10**–(*S*,*S*)-**15** in weak basic conditions with complete inversion of configuration. Ligands (*S*,*S*)-**2**, (*S*,*S*)-**7** and (*S*,*S*)-**8**, however, were prepared from 1,9-dichlorophenazine **19** and the appropriate diols (*S*,*S*)-**16**–(*S*,*S*)-**18** in strong basic conditions with retention of configuration. Enantiomeric recognition of most of the chiral ligands with α-(1-naphthyl)ethylammonium perchlorate (NEA) and α-phenylethylammonium perchlorate (PEA) has been studied by CD spectroscopy.

1. Introduction

Since the first synthesis of crown ethers more than three decades ago[1] the field of host–guest chemistry[2] has developed into the very active research area of supramolecular chemistry.[3,4] Inside this area, much effort has been devoted to the design, synthesis and study of synthetic chiral receptors capable of enantioselective recognition of chiral guests.[3,5]

As model systems of enantiomeric recognition, such synthetic chiral receptors not only provide a controlled means for studying the fundamentals of non-covalent intermolecular forces in nature, but also open new routes for the development of novel pharmaceuticals, enantiomer-selective sensors, catalysts, selectors and other molecular devices.[3]

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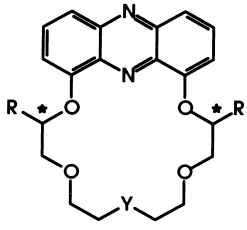
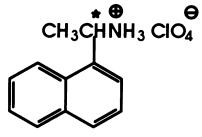
Our interest in enantiomeric recognition has focused on the interaction of chiral synthetic macrocycles with chiral organic ammonium salts.[6–10] Among the chiral macrocycles a number of enantiomerically pure crown ethers containing pyridine[6–8] pyrimidine[9] and phenanthroline[10] subcyclic units have been studied. These studies have shown that hydrogen bonding, aromatic stacking (π–π interaction) and steric repulsion are the three fundamental non-covalent intermolecular forces which are responsible for enantiomeric recognition.[6–10]

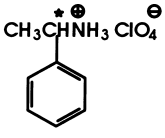
Very recently, we described the preparation of the simplest phenazino-18-crown-6 ligand **1** and its enantiomerically pure dimethyl-substituted analogue (*R*,*R*)-**2** (Fig. 1) as the first two representatives of a crown ether containing the phenazine unit.[11]



1: Y = O; R = H
(*R*,*R*)-2: Y = O; R = Me
(*S*,*S*)-2: Y = O; R = Me
(*R*,*R*)-3: Y = O; R = *i*-Bu
(*S*,*S*)-4: Y = O; R = *s*-Bu
(*R*,*R*)-5: Y = $CHCH_2CH{=}CH_2$; R = Me
(*R*,*R*)-6: Y = $C(CH_2CH{=}CH_2)_2$; R = Me
(*R*,*R*)-7: Y = $CHCH_2CH{=}CH_2$; R = *i*-Bu
(*S*,*S*)-7: Y = $CHCH_2CH{=}CH_2$; R = *i*-Bu
(*S*,*S*)-8: Y = $C(CH_2CH{=}CH_2)_2$; R = *i*-Bu



(*R*)- or (*S*)-NEA



(*R*)- or (*S*)-PEA

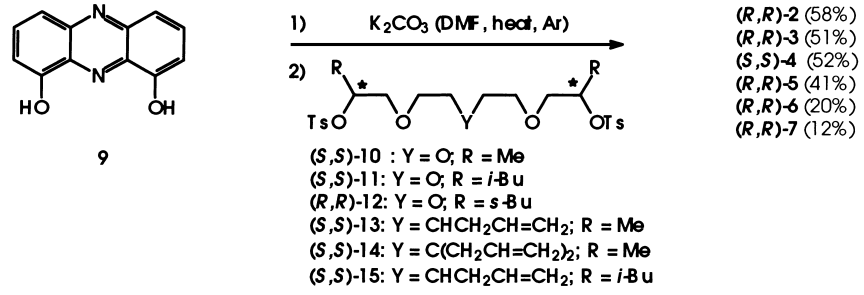
Figure 1. Structures of the phenazino-crown ethers and the ammonium salts

Optically active ligand (*R*,*R*)-**2** has a tricyclic ring system which gives high rigidity to the portions of the macro ring containing the stereogenic centers. Also, the extended π-system of the phenazine ring provides a large area for π–π interactions with the chiral ammonium salts containing an aromatic moiety, so a strong and tight association of the complexes can take place where the difference in steric repulsion becomes more pronounced. Both features assist enantioselectivity.[6–8,10] Our first studies on enantiomeric recognition of α-(1-naphthyl)ethylammonium perchlorate (NEA) by enantiomerically pure dimethylphenazino-18-crown-6 ligand (*R*,*R*)-**2** in the solid state and in the gas phase (molecular modeling) have shown high enantioselectivity of (*R*,*R*)-**2** toward (*S*)-NEA over (*R*)-NEA in complex formation.[12] Our extensive studies on enantiomeric recognition of chiral organic ammonium salts by chiral pyridino-18-crown-6 type ligands have also shown that the bulkiness of the substituents at the stereogenic centers paralleled very well the enantioselectivity.[6–8] Therefore, we designed and prepared chiral phenazino-ligands (*R*,*R*)-**3** and (*S*,*S*)-**4** with bulky substituents. The intention of preparing chiral crown ethers (*R*,*R*)-**5**–(*S*,*S*)-**8** with side chains containing terminal double bonds was that these ligands can be attached covalently to silica gel and the chiral stationary phase (CSP) so that, once obtained, they can be used for enantioseparation of organic ammonium salts by chromatography as we reported in the case of chiral pyridino-crown ethers.[13–15]

Besides the synthesis of chiral crown ethers shown in Fig. 1, we also report our preliminary circular dichroism (CD) spectroscopic studies on enantiomeric recognition of most of them with the enantiomers of NEA and α-phenylethylammonium perchlorate (PEA). These studies clearly show that the chiral ligands containing the phenazine ring have high enantioselectivity for NEA and PEA.

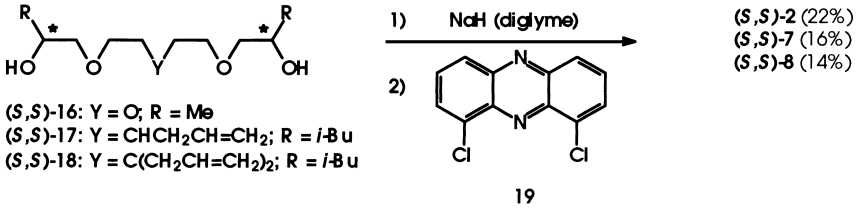
2. Results and discussion

Ligand (*R*,*R*)-**2** was prepared by a modification of our procedure described in the literature,[11] the main difference being that the crude potassium tosylate complex of (*R*,*R*)-**2** was not purified by recrystallization as reported, but subjected directly to chromatography on alumina. This modification not only simplified the purification and increased the yield of (*R*,*R*)-**2**, but also gave a general method for preparation of other chiral phenazino-crown ligands (*R*,*R*)-**3**–(*R*,*R*)-**7** (see Scheme 1).



Scheme 1. Preparation of chiral phenazino-crown ethers using phenazine-1,9-diol and chiral ditosylates

The cyclization reaction of phenazine-1,9-diol **9** and chiral ditosylate (*S*,*S*)-**10** under the conditions outlined in Scheme 1 resulted in complete inversion of configuration as proved indirectly earlier.[11] Here we present direct proof for the total inversion of configuration of both stereogenic centers during the cyclization reactions shown in Scheme 1. When diols (*S*,*S*)-**16**[16] and (*S*,*S*)-**17** were reacted with 1,9-dichlorophenazine **19**[17] in strong basic conditions (see Scheme 2), we measured for products (*S*,*S*)-**2** and (*S*,*S*)-**7** which had the same magnitude, but opposite signs, of specific rotation as for products (*R*,*R*)-**2** and (*R*,*R*)-**7** formed from the ditosylates of (*S*,*S*)-**16** and (*S*,*S*)-**17** in the reaction shown in Scheme 1.

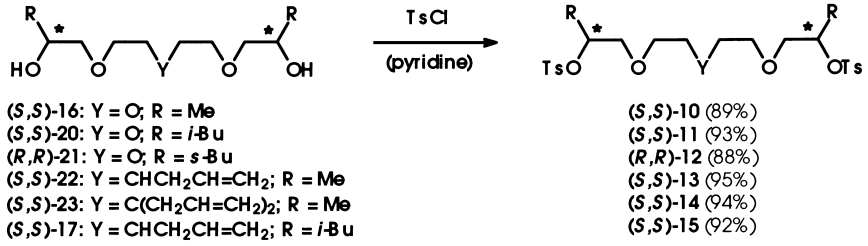


Scheme 2. Preparation of chiral phenazino-crown ethers using 1,9-dichlorophenazine and chiral diols

Since the reactions shown in Scheme 2 do not involve the stereogenic centers, retention of configuration is assured. Since the rotations are of opposite signs, these results clearly demonstrate that the cyclization outlined in Scheme 1 proceeds with complete inversion of configuration. Comparing the yields of the two methods for obtaining chiral ligands (see Schemes 1 and 2) we can conclude that the cyclization reactions shown in Scheme 1 give better yields when the chiral ditosylates contain no side chain, and about the same yields when they do have a side chain.

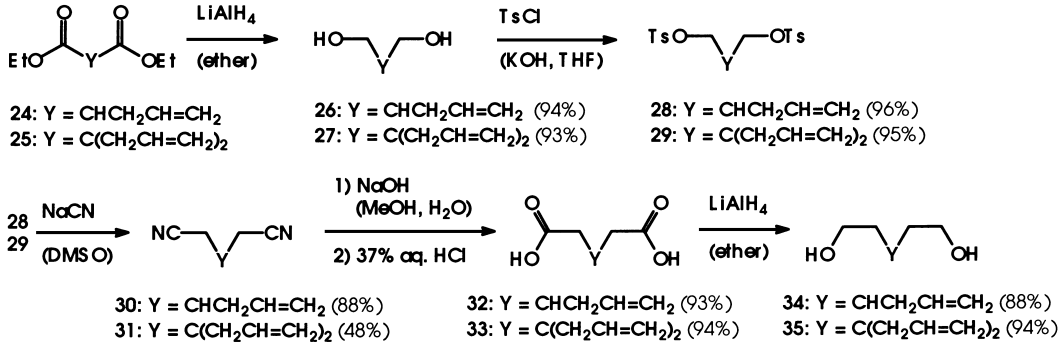
Chiral ditosylates (*S*,*S*)-**10**–(*S*,*S*)-**15** were prepared from the appropriate diols using tosyl chloride (TsCl) in pyridine as both a base and a solvent (see Scheme 3). Tetraethylene glycols (*S*,*S*)-**16**[16] and (*R*,*R*)-**21**[18] were prepared as reported. Tetraethylene glycol (*S*,*S*)-**20** was prepared starting from (*R*)-(−)-leucine [D-leucine] in the same way as reported for its enantiomer (*R*,*R*)-**20** starting from (*S*)-(+)-leucine [L-leucine].[18]

Diols (*S*,*S*)-**17**, (*S*,*S*)-**18**, (*S*,*S*)-**22** and (*S*,*S*)-**23** are novel compounds and their syntheses are shown in Schemes 4 and 5. Diethyl allylmalonate **24** and diethyl diallylmalonate **25**, respectively, were reduced with $LiAlH_4$ to produce diols **26**[19] and **27**, respectively.



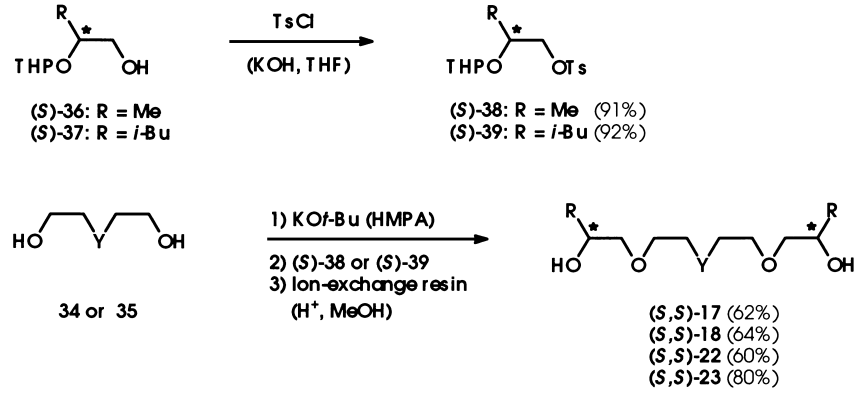
Scheme 3. Preparation of chiral ditosylates from chiral diols

The latter compounds were transformed into ditosylates **28** and **29**, respectively, using TsCl and powdered KOH in THF, a well established method used in our laboratories[11,13,14,18,20,21] for the preparation of primary tosylates in excellent yields (see Scheme 4).



Scheme 4. Preparation of mono- and diallyl-substituted pentane-1,5-diols

Ditosylates **28** and **29** were treated with NaCN in DMSO to give dinitriles **30** and **31**, respectively, which were hydrolyzed under basic conditions followed by acidification with aqueous HCl to give diacids **32** and **33**, respectively. Reduction of diacids **32** and **33** with $LiAlH_4$ in ether afforded substituted pentane-1,5-diols **34** and **35**, respectively. Diols **34** and **35** and tosylates (*S*)-**38** and (*S*)-**39** (see Scheme 5) were the direct precursors of diols (*S*,*S*)-**17**, (*S*,*S*)-**18**, (*S*,*S*)-**22** and (*S*,*S*)-**23**. Tosylate (*S*)-**38** was prepared from alcohol (*S*)-**36** using TsCl and powdered KOH in THF as reported,[21] except that since **34** and **35** are sensitive to any impurities, it was purified instead of using the crude product. Tosylate (*S*)-**39** was obtained in a similar manner from alcohol (*S*)-**37**. Diols **34** and **35** were treated first with KO*t*-Bu in HMPA, then ditosylate (*S*)-**38** or (*S*)-**39** was added to perform a Williamson-type ether formation, and



Scheme 5. Preparation of mono- and diallyl-substituted chiral diols

finally the tetrahydropyranyl (THP) protecting groups were removed with strong acidic ion-exchange resin in MeOH to give diols (*S*,*S*)-**17**, (*S*,*S*)-**18**, (*S*,*S*)-**22** and (*S*,*S*)-**23**.

The UV/vis and CD spectral parameters of crown compounds containing the phenazine unit [**1**-(*R*,*R*)-**7**] are summarized in Tables 1 and 2, respectively. The UV/vis spectrum of the parent achiral crown molecule **1** shows three bands at 420, 362 and 268 nm. The broad long-wavelength band is composed of two overlapping components between 430–390 and 390–310 nm.

Table 1
UV/vis spectral parameters of crown compounds [**1**–(*R*,*R*)-**7**] containing the phenazine unit, and of aralkyl ammonium salts (NEA and PEA) in acetonitrile

Compound	λ_{max} [nm] ($\varepsilon x10^{-4}$)			
1	268 (7.15)	362 (0.43)	420 (0.32)	
(*R*,*R*)-**2**	269 (6.97)	363 (0.45)	423 (0.32)	
(*R*,*R*)-**3**	271 (7.53)	365 (0.48)	428 (0.34)	
(*S*,*S*)-**4**	270 (6.28)	364 (0.42)	428 (0.29)	
(*R*,*R*)-**5**	269 (7.30)	363 (0.49)	426 (0.33)	
(*R*,*R*)-**6**	269 (5.59)	363 (0.38)	424 (0.26)	
(*R*,*R*)-**7**	269 (4.53)	363 (0.32)	426 (0.21)	
(*R*)-NEA		222 (7.43)	280 (0.53)	312 (0.028)
(*S*)-NEA		222 (7.50)	280 (0.53)	312 (0.025)
(*R*)-PEA	205 (0.79)		256 (0.017)	
(*S*)-PEA	205 (0.75)		256 (0.016)	

The former component contributes to the n→π* transition while the latter one centered between 365–362 nm mainly belongs to the ^1L_a transition.[22] The ^1L_a band is split but the fine structure is less expressed than in the spectra of 9-anthroates which have three well-separated ^1L_a UV bands.[23b] The ^1L_b band is covered by the more intense ^1L_a band system. The strongest band in the UV/vis spectrum between 271 and 268 nm is assigned to the ^1B_b band of the substituted phenazine chromophore.[22] The shoulder below 240 nm probably belongs to a transition which corresponds to the less intense ^1C_b band of anthracene derivatives having no center of symmetry. The Platt notations and polarization diagrams are generally used for polyacene chromophores.[23] In the case of phenazine the double replacement of N for CH does not change the D_{2h} symmetry of anthracene, the polarization directions of which are established both experimentally and theoretically.[23b]

In the symmetrically substituted phenazino-crown host molecules the polarization directions of the parent chromophore are not seriously affected. Therefore, the polarization diagram shown in Fig. 6 can be used for determining the chirality of the coupled transition moments. Substituents in positions 3 and 13 or the allyl linker group(s) attached at C8 of the carba-analogue of the parent crown do not result in marked shifts of the position or intensity of the bands in the UV/vis spectrum of **1** (Table 1). The CD spectrum of the most simple chiral phenazino-crown ether compound (*R*,*R*)-**2** shows a negative n→π* band at 430 nm and a positive band at 358 nm due to the spectral contributions of the ^1L_a and ^1L_b transitions (Table 2). The most interesting feature of the CD spectrum of (*R*,*R*)-**2** (and other chiral derivatives of **1**) is the appearance of a negative and a positive band at about 280 and 265 nm, respectively (Figs. 2 and 3). The crossover point at ~270 nm corresponds to the λ_{max} value of the ^1B_b band in the UV/vis spectrum (Table 1). The strongest positive band, accompanied by a short-wavelength shoulder, appears at 232 nm, and the last measurable band at 202 nm in the spectrum of (*R*,*R*)-**2** (Table 2) is again negative.

The same sign pattern is characteristic of the compounds (*R*,*R*)-**3** and (*S*,*S*)-**4** (having an additional stereogenic center in the side chains). Compared to the bands measured in the case of (*R*,*R*)-**2**, the intensity of the positive band at 268 nm in the spectra of (*R*,*R*)-**3** and (*S*,*S*)-**4** increases while that of the

Table 2
CD data of crown compounds containing phenazine chromophores **1**–(*R*,*R*)-**7** and of aralkyl ammonium salts (NEA and PEA), as well as CD spectra of their 1:1 complexes in acetonitrile

Host	Guest	λ_{max} [nm] ($\Delta\varepsilon$)					
1	*(R)*-NEA	211 (40.6)	225 (-155)	271 (77.1)	293 (-2.43)	346 (-0.31)	434 (0.61)
	(S)-NEA	210 (-40.5)	225 (156)	271 (-77.9)	293 (2.79)	346 (0.30)	434 (-0.62)
	(R)-PEA	205 (-3.16)	227 (-0.40)	254 (0.29)	276 (-2.40)	366 (-0.30)	431 (0.18)
		218 (0.65)	241 (0.42)				
	(S)-PEA	206 (3.25)	225 (0.38)		277 (1.98)	357 (0.26)	429 (-0.24)
		217 (-0.56)	244 (0.17)				
(*R*,*R*)-**2**	-	202 (-4.19)	232 (6.80)	265 (5.22)	278 (-6.87)	358 (0.42)	430 (-0.86)
	(R)-NEA	212 (28.1)	225 (-101)	268 (43.6)	284 (-6.76)	368 (1.13)	436 (-1.11)
	(S)-NEA	211 (-50.1)	225 (179)	273 (-73.7)	294 (4.61)	359 (0.70)	437 (-2.10)
	(R)-PEA		236 (6.22)	255 (4.67)	276 (-5.97)	361 (0.60)	436 (-0.84)
	(S)-PEA	214 (-3.68)	233 (7.23)	264 (11.7)	279 (-3.74)	359 (1.08)	436 (-1.74)
	BAP		232 (5.51)	264 (3.25)	278 (-3.25)	362 (0.72)	436 (-0.58)
(*R*,*R*)-**3**	-	211 (-4.15)	232 (4.62)	268 (10.3)	280 (-3.72)	371 (0.51)	436 (-0.54)
	(R)-NEA	211 (19.5)	226 (-60.6)	268 (36.0)	286 (-5.51)	367 (1.48)	440 (-0.91)
	(S)-NEA	211 (-46.1)	225 (163)	273 (-50.3)	294 (3.31)	360 (1.16)	438 (-1.64)
	(R)-PEA	206 (1.03)	236 (8.55)	266 (12.0)	281 (-2.51)	361 (1.16)	439 (-0.83)
	(S)-PEA	213 (-4.27)	236 (9.32)	267 (20.2)	285 (-0.39)	362 (1.58)	438 (-1.47)
	BAP	212 (-2.05)	233 (8.15)	268 (15.3)	282 (-2.13)	363 (1.26)	438 (-0.72)
(*S*,*S*)-**4**	-		230 (-2.51)	268 (6.27)	284 (-0.09)	340 (0.33)	424 (-0.35)
	(R)-NEA	212 (40.6)	226 (-129)	273 (41.6)	292 (-3.76)	352 (-0.81)	442 (2.16)
	(S)-NEA	209 (-7.72)	225 (34.5)	267 (-16.5)	289 (1.56)	370 (-0.84)	441 (0.79)
	(R)-PEA	213 (5.58)	237 (-9.78)	265 (-18.0)	281 (3.53)	348 (-0.77)	441 (1.81)
	(S)-PEA	214 (2.82)	235 (-7.38)	264 (-9.47)	279 (5.81)	338 (-0.31)	442 (0.86)
						383 (-0.41)	
	BAP	213 (1.91)	233 (-8.16)	264 (-11.9)	279 (7.23)	383 (-0.51)	442 (0.80)
(*R*,*R*)-**5**	-	208 (-3.23)	233 (3.84)	266 (5.25)	279 (-4.37)	362 (0.46)	431 (-0.63)
	(R)-NEA	210 (10.6)	225 (-44.5)	269 (17.9)	285 (-2.78)	371 (1.03)	446 (-0.21)
	(S)-NEA	210 (-12.6)	226 (56.9)	269 (-17.3)	293 (1.02)	361 (1.07)	435 (-0.98)
	(R)-PEA	218v (2.36)	232 (3.70)	260 (-0.87)	280 (-1.59)	361 (0.77)	433 (-0.29)
				269 (0.69)			
	(S)-PEA		232 (4.98)	269 (4.93)	282 (-0.78)	362 (1.00)	435 (-0.65)
	BAP	208 (-1.03)	222v (2.18)	268 (1.56)	281 (-2.76)	360 (0.56)	429 (-0.55)
			235 (3.67)				
(*R*,*R*)-**6**	-	203 (-2.61)	234 (1.82)	266 (4.22)	279 (-3.81)	339 (0.23)	430 (-0.60)
	(R)-NEA		223 (-15.9)	267 (5.67)	280 (-2.50)	354 (0.25)	432 (-0.50)
	(S)-NEA	206 (-3.65)	223 (16.9)	264 (0.65)	278 (-4.83)	355 (0.28)	432 (-0.59)
	(R)-PEA	209 (-1.89)	236 (1.41)	267 (3.40)	279 (-2.92)	339 (0.24)	428 (-0.49)
	(S)-PEA	209 (-2.52)	240 (1.04)	267 (3.62)	279 (-2.85)	354 (0.26)	434 (-0.48)
	BAP	209 (-2.72)	236 (0.39)	268 (3.09)	280 (-2.48)	356 (0.25)	430 (-0.41)
(*R*,*R*)-**7**	-	213 (-2.51)		269 (8.50)	283 (-1.33)	345 (0.33)	426 (-0.45)
	(R)-NEA	208 (1.37)	225 (-21.9)	269 (14.1)	285 (-1.57)	364 (0.74)	437 (-0.34)
	(S)-NEA	210 (-9.94)	226 (35.6)	276 (-2.72)	291 (0.60)	360 (0.88)	436 (-0.77)
	(R)-PEA	213 (-1.93)	239 (1.81)	269 (8.12)	284 (-0.87)	360 (0.65)	435 (-0.37)
	(S)-PEA	211 (-3.83)	239 (2.51)	269 (10.4)	285 (-0.49)	359 (0.77)	437 (-0.55)
	BAP	212 (–3.55)	244 (0.75)	269 (9.62)	284 (-1.15)	357 (0.53)	432 (-0.42)

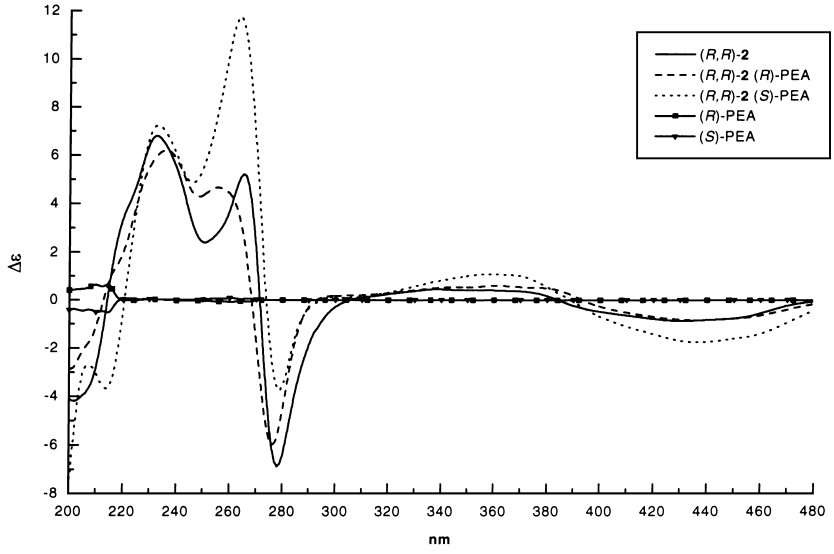


Figure 2. CD spectrum of crown ether host (*R*,*R*)-**2**, (*R*)- and (*S*)-PEA and the homo- and heterochiral complexes measured at a host:guest molar ratio of 1:1 in acetonitrile

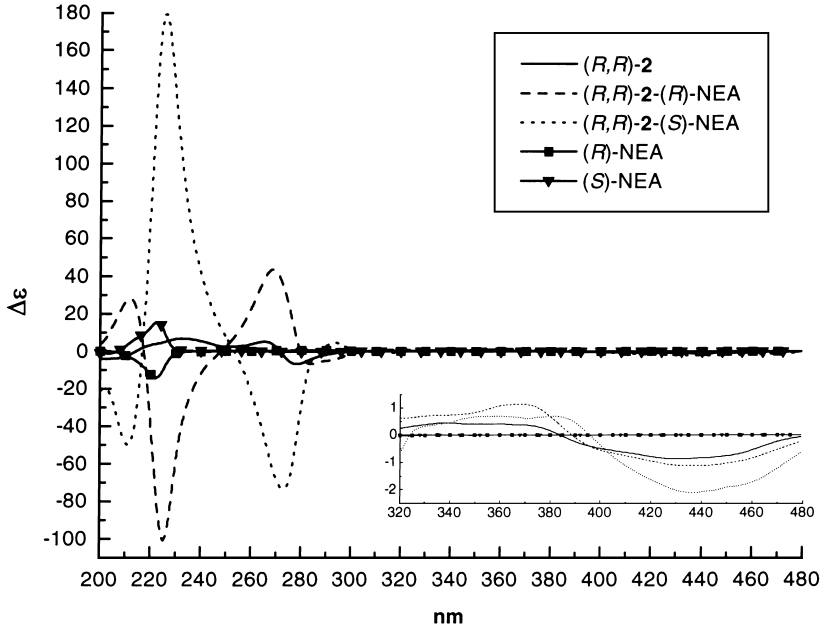


Figure 3. CD spectrum of crown ether host (*R*,*R*)-**2**, (*R*)- and (*S*)-NEA, and the 1:1 homo- and heterochiral complexes in acetonitrile

negative band at 280 and 284 nm, respectively, decreases. (Note the negligible intensity of the negative band in the spectrum of (*S*,*S*)-**4**.)

The replacement of O8 by carbon and the attachment of one or two allyl groups [crowns (*R*,*R*)-**5** and (*R*,*R*)-**6**] do not have a significant influence upon the CD spectrum of the parent molecule (*R*,*R*)-**2** (Table 2). The CD spectra are still dominated by a strong negative and a strong positive band in the ^1B_b region of the phenazine chromophore but the absolute intensity of the negative band decreases more than that of the positive band. The allyl linker group in position C8 of (*R*,*R*)-**7** has a stronger spectral effect

than in (*R*,*R*)-**5** (Table 2 and Fig. 4). The UV and CD spectra of (*R*)- and (*S*)-forms of PEA and NEA have been discussed earlier.[24] CD spectra of the host–guest complexes were measured at a molar ratio of 1:1 (Table 2). The stability constants (K_s) of complexes for similar systems are greater than 10^4 in acetonitrile.[7] Thus, due to their low concentrations, the contribution of the free host and guest molecules to the CD spectrum of the complex can be neglected.[24]

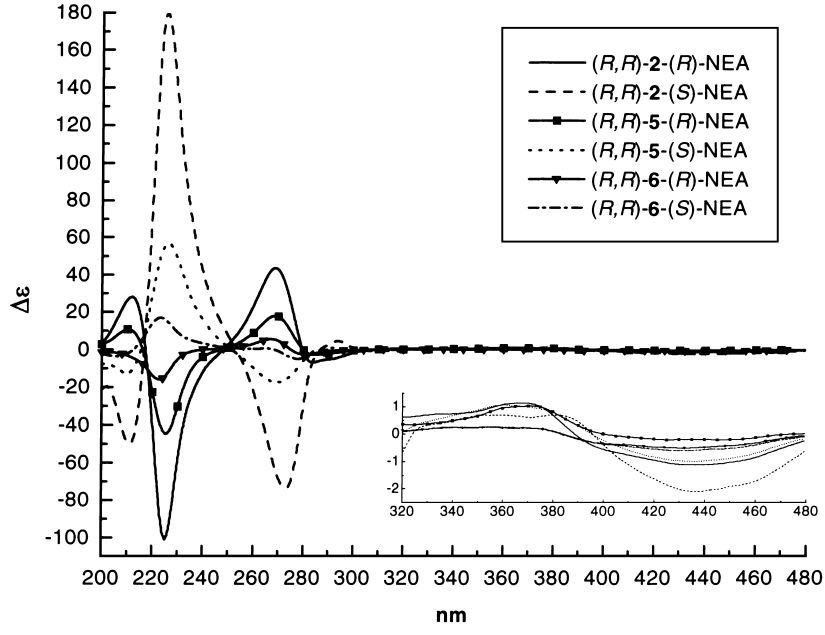


Figure 4. Comparison of the CD spectra of the 1:1 homo- and heterochiral NEA complexes of crown ether hosts (*R*,*R*)-**2**, (*R*,*R*)-**5**, and (*R*,*R*)-**6**, in acetonitrile

The enantiomeric recognition ability of chiral ligands (*R*,*R*)-**2**–(*R*,*R*)-**7** towards aralkyl ammonium salts NEA and PEA was evaluated: (i) by inspection of the spectra, i.e. comparing the spectral responses measured for the heterochiral [(*R*,*R*)-crown/(*S*)-guest or (*S*,*S*)-crown/(*R*)-guest] and homochiral [(*R*,*R*)-crown/(*R*)-guest or (*S*,*S*)-crown/(*S*)-guest] complexes; (ii) by comparing the difference spectra, $\Delta\Delta\varepsilon=\Delta\varepsilon_{complex}-(\Delta\varepsilon_{host}+\Delta\varepsilon_{guest})$; and (iii) by comparing the CD spectra (or difference spectra) of the 1:1 complexes of the aralkyl ammonium salts to those of the achiral complexing agent butylammonium perchlorate (BAP). CD spectra of BAP complexes also served as references for separating the chiral effects of H-bonding from those of aromatic interactions. Spectral additivity, i.e. a difference spectrum close to zero over the whole spectral range, was regarded as the sign of no or weak attractive interactions and therefore the lack of complex formation. In the majority of cases heterochiral or homochiral preference was clearly reflected by the shape of the CD spectra (or difference spectra) of the diastereomeric complexes (Fig. 3). Some of the complexes, however, showed different chiroptical behavior above and below ~300 nm. The same or a similar spectral responses above ~300 nm but significant changes in the ^1B_b or ^1C_b spectral regions were considered as an indication of strong π–π interaction between the host and guest molecules without a significant effect of H-bonding on the chromophoric system of the crown ether. Contrary to this, a whole range similarity of the CD spectra of the BAP complex and the complex of one of the enantiomeric aralkyl ammonium salts clearly indicated the dominance of H-bond formation.

CD data on the enantiomeric recognition ability of chiral ligands (*R*,*R*)-**2**–(*R*,*R*)-**7** towards PEA showed an almost general heterochiral preference in the whole spectral range. Except for the crowded crown

host (*R*,*R*)-**6** having two allyl side chains, analogues (*R*,*R*)-**5** and (*R*,*R*)-**7** with one linker showed a discriminating power comparable to that of the parent host molecules (*R*,*R*)-**2** and (*R*,*R*)-**3**.

Phenazino-crown ether hosts formed stable complexes with both enantiomers of NEA. The CD spectra of the 1:1 complexes showed bands with exceedingly high amplitude (Table 2). The most intense positive band at 225 nm ($\Delta\varepsilon$=179) appeared in the spectrum of the (*R*,*R*)-**2**/(*S*)-NEA complex (Fig. 3). Based on the band positions, signs and intensities, the CD spectra, in general, are marked by a short-wavelength asymmetric exciton couplet.[23b] It is only the CD spectra of the NEA complexes of crown (*R*,*R*)-**6** featuring two allyl linker groups, which showed bands with significantly lower intensity (Table 2, Fig. 4).

The short-wavelength (<310 nm) region of the CD spectra and the corresponding difference spectra (not shown) clearly showed heterochiral preference of the host molecules. Crown (*S*,*S*)-**4**, having (*S*)-*sec*-butyl groups attached to carbons 3 and 13, showed, as expected, couplets of opposite signs with less intense bands (Fig. 5).

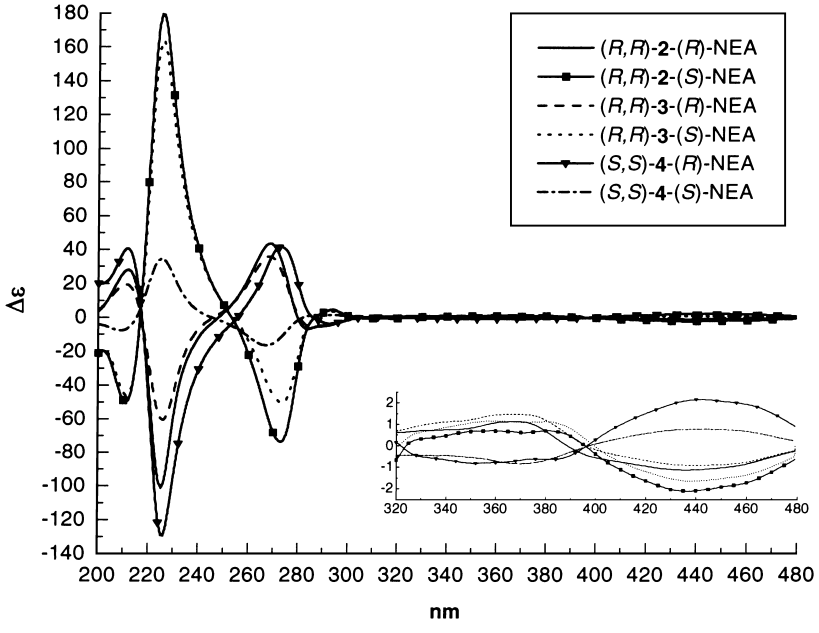


Figure 5. Comparison of the CD spectra of the 1:1 homo- and heterochiral NEA complexes of crown ether hosts (*R*,*R*)-**2**, (*R*,*R*)-**3**, and (*S*,*S*)-**4**, in acetonitrile

In the region above ~310 nm, the CD spectra featuring a negative longer-wavelength and a positive shorter-wavelength band also reflected heterochiral preference of the host molecules (Table 2). Only the band centered near 360 nm showed comparable intensity or higher amplitude for the homochiral complex.

The sign of the exciton couplet allowed determination of the relative orientation of the phenazine and naphthalene chromophores in the complexes. All (*R*,*R*)-crown/(*S*)-NEA exciton spectra showed the following sign and intensity pattern of bands below ~310 nm: $+I_w$, $-I_s$, sh, $+I_{vs}$, $-I_{m,s}$. Considering the λ_{max} values of bands in the UV/vis spectrum, the above sign pattern of extremely and moderately intense bands can be explained by multiple coupling of the ^1C_b and ^1B_b transitions of the phanazine and ^1B_b and ^1L_a transitions of the naphthalene chromophores. Multiple coupling is well known in the literature of CD spectroscopy[25] but has not yet been observed in the field of aromatic crown complexes. The chiroptical behavior of crown ether complexes resembles that of 4-substituted [2.2]paracyclophanes which show complex CD spectra comprising three exciton couplets in the ^1L_b, ^1L_a and ^1B_b spectral regions.[26] Fig. 6a

shows the transition dipole directions of the phanazine and naphthalene chromophores.[22] The short-wavelength couplet with bands at ~210 and ~225 nm is positive for all heterochiral NEA complexes of (*R*,*R*)-hosts. On the basis of the λ_{max} values of the naphthalene and phenazine transitions in the UV spectrum, the intense positive couplet reflects the interaction of the naphthalene ^1B_b and phenazine ^1C_b transitions.

The exciton chirality rule[23] predicts a negative torsion or projection angle between the long axes of the chromophores in the heterochiral complex (Fig. 6b). (The ^1B_b electric transition moment vectors roughly parallel the long axes of the rings.[22]) This corresponds to a positive sign of the dominant short-wavelength couplet in the spectra of the heterochiral complexes. The homochiral complex[25] also results in a strong dominant couplet but with opposite (negative) sign and decreased band intensities. This suggests a positive projection angle between the long axes (Fig. 6c). This orientation also allows an extended π–π interaction between the electron-rich naphthalene ring and the electron-poor parts of the phenazine ring. However, the repulsion between the hydrogens attached in positions 2 and 3 at the naphthalene ring and the upwardly oriented substituent in position 13 of the crown ether macro ring (Fig. 6d) loosens the complex giving rise to less intense bands in the CD spectrum. In the heterochiral case the larger distance between the side chain at C3 of the crown and the closest atoms of the naphthalene ring (Fig. 6b) are favorable for both H-bonding and π–π interaction explaining the extremely intense exciton couplets in the CD spectrum. The suggested geometry of the heterochiral (Fig. 6b) and homochiral complexes (Fig. 6d) is strongly supported by a comparison of the CD spectra of the NEA complexes of crowns (*R*,*R*)-**2**, (*R*,*R*)-**3** and (*S*,*S*)-**4** (Fig. 5).

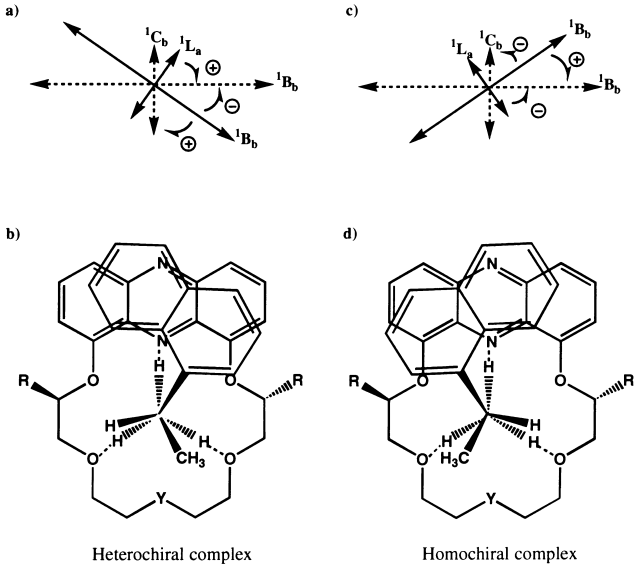


Figure 6. Polarization directions (a, c) and relative orientation of the aromatic ring systems (b, d) in the NEA complexes of (*R*,*R*)-phenazino-crown ether hosts

The band amplitudes decrease more in the homochiral than in the heterochiral case upon the increase of the bulkiness of the crown substituents at C3 and C13. The opposite, (*S*,*S*)-configuration of crown (*S*,*S*)-**4**, leads to negative instead of positive couplets in the spectrum of the heterochiral complex. The band intensities in the CD spectrum of the homochiral (*S*,*S*)-**4**/(*S*)-NEA complex are at the borderline of the requirements of exciton chirality (Table 2).

The high amplitude of the band near ~270 nm [$\Delta\varepsilon$=−73.7 for the (*R*,*R*)-**2**/(*S*)-NEA complex] and the long-wavelength shoulder of the strongest band of the complexes suggest exciton interaction between

the naphthalene ^1L_a and phenazine ^1B_b transitions and/or ^1B_b transitions of both chromophores. Theoretical calculations to analyze the long-wavelength region of the spectra are in progress. Recent X-ray crystallographic data[12] on the heterochiral and homochiral complexes of (*R*,*R*)-**2** with (*S*)- and (*R*)-NEA show negative and positive projection angles between the long axes in the heterochiral and homochiral complex, respectively. This is in agreement with the positive sign of the short-wavelength couplet due to exciton interaction between the naphthalene ^1B_b and phenazine ^1C_b transitions in the heterochiral NEA complexes (Fig. 6). Notably, the positive sign of the possible $^1L_a/^1B_b$ and the negative sign of the $^1B_b/^1B_b$ exciton couplets also predict a geometry which agrees with the X-ray crystallography-based structure of the heterochiral complex (Fig. 6b).[12]

Attachment of one allyl linker group at C8 of the carba-analogues of (*R*,*R*)-**5** and (*R*,*R*)-**7** also results in couplets (positive–positive in the heterochiral and negative–negative in the homochiral cases) with decreased band intensities when complexing with the NEA enantiomers. Notably, the longer-wavelength couplet is practically not present in the spectrum of the NEA complexes of crown (*R*,*R*)-**7**, while the low band intensities and other spectral features suggest only negligible exciton interaction and chiral discriminating power of crown (*R*,*R*)-**6** with two allyl groups at C8 (Table 2).

Results of the CD studies discussed above clearly show that chiral crown compounds (*R*,*R*)-**2**–(*R*,*R*)-**7** containing the phenazine unit are superior to pyridino-18-crown-6 ligands[24] as chiral selectors. CD spectroscopy revealed an almost general heterochiral preference of ligands (*R*,*R*)-**2**–(*R*,*R*)-**7** for NEA and PEA.

More importantly, the presence of one allyl linker at C8 of the carba-analogues (*R*,*R*)-**5** and (*R*,*R*)-**7** does not result in a significant decrease of the discriminating power.

3. Experimental

Infrared spectra were obtained on a Zeiss Specord IR 75 spectrometer. Optical rotations were taken on a Perkin–Elmer 241 polarimeter that was calibrated by measuring the optical rotations of both enantiomers of menthol.

^1H (500 MHz) and ^{13}C (125 MHz) NMR spectra were taken on a Bruker DRX-500 Avance spectrometer and ^1H (80 MHz) NMR spectra were obtained on a Bruker AW-80 spectrometer in $CDCl_3$ unless otherwise indicated. Molecular weights were determined by a VG-ZAB-2 SEQ reverse geometry mass spectrometer. Elemental analyses were performed in the Microanalytical Laboratory of the Department of Organic Chemistry, L. Eötvös University, Budapest, Hungary. Melting points were taken on a Boetius micro melting point apparatus and were uncorrected. Starting materials were purchased from Aldrich Chemical Company unless otherwise noted. Silica gel 60 F_{254} (Merck) and aluminum oxide 60 F_{254} neutral type E (Merck) plates were used for TLC. Aluminum oxide (neutral, activated, Brockman I) and silica gel 60 (70–230 mesh, Merck) were used for column chromatography. Solvents were dried and purified according to well established methods.[27] Evaporations were carried out under reduced pressure unless otherwise stated.

CD spectra were recorded on a Jobin–Yvon Mark VI dichrograph (calibrated with epiandrosterone) at room temperature using a 0.02 cm cell for measurements between 195 and 240 nm and 0.1, 0.2 or 0.5 cm cells above 240 nm. Acetonitrile (Merck, for chromatography) was used as solvent and the concentration ranged from 0.5 to 5 mmol dm^{-3}, depending on the absorption.

3.1. (3R,13R)-(−)-3,13-Dimethyl-2,5,8,11,14-pentaoxa-20,26-diazatetracyclo[13.9.3.0^{19,27}.0^{21,25}]-heptacosa-1(25),15,17,19,21,23,26-heptaene (R,R)-**2**

A mixture of phenazine-1,9-diol **9**[11] (424 mg, 2 mmol), ditosylate (*S*,*S*)-**10** (1.06 g, 2 mmol), finely powdered anhydrous K_2CO_3 (2.76 g, 20 mmol) and DMF (50 mL) was stirred under Ar at room temperature for 10 min then at 50°C for 5 days. The solvent was removed at 50°C and the residue was taken up in a mixture of ice-water (30 mL) and EtOAc (60 mL). The aqueous phase was extracted with EtOAc (3×30 mL). The combined organic phase was dried over $MgSO_4$, filtered, and the solvent evaporated. Chromatography on alumina using 2% EtOH in toluene as an eluent, then recrystallization from EtOH, gave (*R*,*R*)-**2** (462 mg, 58%) as yellow crystals identical in every aspect to that reported.[11]

3.2. (3S,13S)-(+)-3,13-Dimethyl-2,5,8,11,14-pentaoxa-20,26-diazatetracyclo[13.9.3.0^{19,27}.0^{21,25}]-heptacosa-1(25),15,17,19,21,23,26-heptaene (S,S)-**2**

A mixture of NaH (112 mg, 2.8 mmol, 60% dispersion in mineral oil), (2*S*,12*S*)-(+)-4,7,10-trioxatridecane-2,12-diol (*S*,*S*)-**16**[16] (222 mg, 1 mmol) and diglyme (12 mL) was stirred under Ar at room temperature for 10 min then at 90°C for 1 h. The reaction mixture was cooled to room temperature and 1,9-dichlorophenazine **19**[17] (249 mg, 1 mmol) was added, then it was stirred at 90°C for 3 days. The solvent was evaporated (0.2 mmHg) and the residue was taken up in ice-water (28 mL) and EtOAc (50 mL). The aqueous phase was extracted with EtOAc (3×25 mL). The combined organic phase was shaken with distilled water (50 mL), dried over $MgSO_4$, filtered and the solvent evaporated. Chromatography on alumina using 2% EtOH in toluene as an eluent, then recrystallization from EtOH gave (*S*,*S*)-**2** (88 mg, 22%) as yellow crystals. $[\alpha]_D^{25}$=+121.4 (*c* 0.210, CH_2Cl_2); lit.[11] $[\alpha]_D^{25}$=−121.5 (*c* 0.521, CH_2Cl_2) for the other enantiomer (*R*,*R*)-**2**. All other physical and spectral data were identical to those reported[11] for (*R*,*R*)-**2**.

3.3. (3R,13R)-(−)-3,13-Diisobutyl-2,5,8,11,14-pentaoxa-20,26-diazatetracyclo[13.9.3.0^{19,27}.0^{21,25}]-heptacosa-1(25),15,17,19,21,23,26-heptaene (R,R)-**3**

Macrocycle (*R*,*R*)-**3** was prepared as described above for macrocycle (*R*,*R*)-**2** starting from phenazine-1,9-diol **9** (424 mg, 2 mmol) and ditosylate (*S*,*S*)-**11** (1.23 g, 2 mmol). The reaction was completed at 50°C in 10 days. Chromatography on alumina using 1% EtOH in toluene as an eluent, then recrystallization from EtOH gave (*R*,*R*)-**3** (492 mg, 51%) as yellow crystals. Mp 83°C (EtOH); R_f=0.31 (alumina TLC, 2% EtOH in toluene); $[\alpha]_D^{25}$=−36.4 (*c* 1.04, CH_2Cl_2); IR (KBr) 2960, 2920, 2870, 1610, 1560, 1480, 1410, 1330, 1260, 1100, 930, 900, 820, 750 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.93 (d, *J*=6 Hz, 6H), 0.99 (d, *J*=6 Hz, 6H), 1.69–1.74 (m, 2H), 1.80–1.91 (m, 4H), 3.67–3.74 (m, 6H), 3.87–3.96 (m, 4H), 4.23 (d, *J*=2 Hz, 1H), 4.26 (d, *J*=2 Hz, 1H), 5.18–5.23 (m, 2H), 7.15 (d, *J*=8 Hz, 2H), 7.72 (t, *J*=8 Hz, 2H), 7.80 (d, *J*=8 Hz, 2H); ^{13}C NMR (125 MHz) δ 23.04, 23.31, 25.13, 39.67, 71.63, 71.72, 73.19, 78.69, 112.03, 121.79, 131.07, 136.78, 144.46, 154.62; HRMS (EI) calcd for $C_{28}H_{38}N_2O_5$: 482.2781; found: 482.2804; anal. calcd for $C_{28}H_{38}N_2O_5$: C, 69.67; H, 7.94; N, 5.81; found: C, 69.65; H, 7.94; N, 5.68.

3.4. (3S,13S)-(−)-3.13-Di-[(S)-sec-butyl]-2,5,8,11,14-pentaoxa-20,26-diazatetracyclo-[13.9.3.0^{19,27}.0^{21,25}]heptacosa-1(25),15,17,19,21,23,26-heptaene (S,S)-**4**

Macrocycle (*S*,*S*)-**4** was prepared as described above for macrocycle (*R*,*R*)-**2** starting from phenazine-1,9-diol **9** (424 mg, 2 mmol) and ditosylate (*R*,*R*)-**12** (1.23 g, 2 mmol). The reaction was completed at

50°C in 15 days. Chromatography on alumina using 1% EtOH in toluene as an eluent, then recrystallization from EtOH gave (*S*,*S*)-**4** (502 mg, 52%) as yellow crystals. Mp 68°C (EtOH); R_f=0.36 (alumina TLC, 2% EtOH in toluene); $[\alpha]_D^{25}$=−6.6 (*c* 1.32, CH_2Cl_2); IR (KBr) 2970, 2930, 2900, 2870, 1610, 1560, 1490, 1460, 1410, 1320, 1280, 1110, 1040, 910, 830, 760 cm^{-1}; ^1H NMR (500 MHz) δ 0.90 (t, *J*=7 Hz, 6H), 1.02 (d, *J*=7 Hz, 6H), 1.26–1.32 (m, 2H), 1.64–1.72 (m, 2H), 2.08–2.13 (m, 2H), 3.66–3.79 (m, 8H), 4.13–4.16 (m, 2H), 4.21–4.23 (m, 2H), 5.25–5.28 (m, 2H), 7.20 (d, *J*=8 Hz, 2H), 7.71 (t, *J*=8 Hz, 2H), 7.81 (d, *J*=8 Hz, 2H); ^{13}C NMR (125 MHz) δ 12.02, 14.79, 26.08, 36.12, 71.40, 71.59, 72.31, 83.88, 113.56, 122.03, 131.35, 136.86, 144.53, 154.96; HRMS (EI) calcd for $C_{28}H_{38}N_2O_5$: 482.2781; found: 482.2790; anal. calcd for $C_{28}H_{38}N_2O_5$: C, 69.67; H, 7.94; N, 5.81; found: C, 69.53; H, 7.97; N, 5.53.

*3.5. (3*R,*13*R*)-(−)-3,13-Dimethyl-8-(2-propenyl)-2,5,11,14-tetraoxa-20,26-diazatetracyclo-[13.9.3.0^{19,27}.0^{21,25}]heptacosa-1(25),15,17,19,21,23,26-heptaene (*R,R*)-**5**

Macrocycle (*R*,*R*)-**5** was prepared as described above for macrocycle (*R*,*R*)-**2** starting from phenazine-1,9-diol **9** (424 mg, 2 mmol) and ditosylate (*S*,*S*)-**13** (1.14 g, 2 mmol). The reaction was completed at 50°C in 6 days. Chromatography on alumina using 1% EtOH in toluene as an eluent, then recrystallization from EtOH gave (*R*,*R*)-**5** (320 mg, 41%) as yellow crystals. Mp 102°C (EtOH); R_f=0.38 (alumina TLC, 2% EtOH in toluene); $[\alpha]_D^{25}$=−86.4 (*c* 1.04, CH_2Cl_2); IR (KBr) 3080, 3070, 3060, 2970, 2930, 2910, 2850, 1640, 1590, 1560, 1480, 1450, 1410, 1330, 1310, 1290, 1260, 1150, 1110, 1050, 900, 820, 740 cm^{-1}; ^1H NMR (500 MHz) δ 1.47 (d, *J*=7 Hz, 3H), 1.49 (d, *J*=7 Hz, 3H), 1.57–1.70 (m, 4H), 1.85–1.90 (m, 1H), 2.04 (t, *J*=7 Hz, 2H), 3.63–3.99 (m, 8H), 4.93–4.97 (m, 2H), 5.12–5.18 (m, 2H), 5.66–5.75 (m, 1H), 7.10 (d, *J*=8 Hz, 1H), 7.11 (d, *J*=8 Hz, 1H), 7.72 (t, *J*=8 Hz, 2H), 7.79 (d, *J*=8 Hz, 1H), 7.80 (d, *J*=8 Hz, 1H); ^{13}C NMR (125 MHz) δ 15.70, 16.02, 31.33, 33.36, 33.83, 39.77, 69.63, 70.15, 73.62, 73.73, 75.19, 75.54, 110.72, 111.11, 116.06, 121.41, 121.55, 130.83, 130.86, 136.63, 136.68, 137.14, 144.24, 144.29, 153.91, 153.96; HRMS (EI) calcd for $C_{26}H_{32}N_2O_4$: 436.2362; found: 436.2363; anal. calcd for $C_{26}H_{32}N_2O_4$: C, 71.52; H, 7.39; N, 6.42; found: C, 71.31; H, 7.51; N, 6.40.

*3.6. (3*R,*13*R*)-(−)-3,13-Dimethyl-8,8-bis(2-propenyl)-2,5,11,14-tetraoxa-20,26-diazatetracyclo-[13.9.3.0^{19,27}.0^{21,25}]heptacosa-1(25),15,17,19,21,23,26-heptaene (*R,R*)-**6**

Macrocycle (*R*,*R*)-**6** was prepared as described above for macrocycle (*R*,*R*)-**2** starting from phenazine-1,9-diol **9** (212 mg, 1 mmol) and ditosylate (*S*,*S*)-**14** (609 mg, 1 mmol). The reaction was completed at 50°C in 10 days. Chromatography on alumina using 2% EtOH in toluene as an eluent, then recrystallization from EtOH gave (*R*,*R*)-**6** (95 mg, 20%) as yellow crystals. Mp 63°C (EtOH); R_f=0.44 (alumina TLC, 2% EtOH in toluene); $[\alpha]_D^{25}$=−64.2 (*c* 1.63, CH_2Cl_2); IR (KBr) 3080, 2970, 2930, 2840, 1640, 1600, 1560, 1540, 1480, 1450, 1410, 1330, 1310, 1270, 1150, 1120, 1080, 900, 830, 740 cm^{-1}; ^1H NMR (500 MHz) δ 1.51 (d, *J*=6 Hz, 6H), 1.61–1.67 (m, 4H), 2.01 (d, *J*=7 Hz, 4H), 3.67–3.89 (m, 8H), 4.97–5.03 (m, 4H), 5.22–5.27 (m, 2H), 5.75–5.83 (m, 2H), 7.12 (d, *J*=8 Hz, 2H), 7.72 (t, *J*=8 Hz, 2H), 7.81 (d, *J*=8 Hz, 2H); ^{13}C NMR (125 MHz) δ 16.64, 36.66, 38.10, 42.30, 68.73, 74.60, 76.00, 111.79, 117.99, 121.96, 131.35, 135.01, 136.97, 144.60, 154.59; HRMS (EI) calcd for $C_{29}H_{36}N_2O_4$: 476.2675; found: 476.2682; anal. calcd for $C_{29}H_{36}N_2O_4$: C, 73.07; H, 7.62; N, 5.88; found: C, 72.90; H, 7.84; N, 5.81.

3.7. (3R,13R)-(−)-3,13-Diisobutyl-8-(2-propenyl)-2,5,11,14-tetraoxa-20,26-diazatetracyclo-[13.9.3.0^{19,27}.0^{21,25}]heptacosa-1(25),15,17,19,21,23,26-heptaene (R,R)-**7**

Macrocycle (*R*,*R*)-**7** was prepared as described above for macrocycle (*R*,*R*)-**2** starting from phenazine-1,9-diol **9** (212 mg, 1 mmol) and ditosylate (*S*,*S*)-**15** (653 mg, 1 mmol). The reaction was completed at 50°C in 10 days. The crude product was purified by chromatography first on alumina using 0.5% EtOH in toluene, then on silica gel using 4% EtOH in toluene as eluent to give (*R*,*R*)-**7** (52 mg, 10%) as a yellow oil. R_f=0.52 (alumina TLC, 2% EtOH in toluene); $[\alpha]_D^{25}$=−27.3 (*c* 0.460, CH_2Cl_2); IR (KBr) 3080, 2960, 2920, 2870, 1640, 1580, 1490, 1480, 1400, 1320, 1280, 1100, 830, 770, 680 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.98 (d, *J*=8 Hz, 3H), 1.01 (d, *J*=8 Hz, 3H), 1.03 (d, *J*=8 Hz, 3H), 1.04 (d, *J*=8 Hz, 3H), 1.42–1.47 (m, 2H), 1.49–1.55 (m, 4H), 1.66–1.71 (m, 2H), 1.84–1.90 (m, 2H), 1.91–1.96 (m, 1H), 2.15–2.20 (m, 2H), 3.47–3.75 (m, 6H), 3.92–4.02 (m, 2H), 4.84–4.90 (m, 2H), 5.18–5.23 (m, 1H), 5.53–5.59 (m, 1H), 5.59–5.64 (m, 1H), 7.17 (d, *J*=8 Hz, 1H), 7.18 (d, *J*=8 Hz, 1H), 7.72 (t, *J*=8 Hz, 1H), 7.73 (t, *J*=8 Hz, 1H), 7.82 (d, *J*=8 Hz, 1H), 7.84 (d, *J*=8 Hz, 1H); ^{13}C NMR (125 MHz) δ 23.09, 23.12, 23.19, 23.26, 25.03, 25.10, 31.56, 33.14, 33.79, 39.91, 40.12, 40.48, 69.85, 69.88, 72.49, 72.79, 78.12, 78.20, 111.76, 113.15, 116.08, 121.65, 122.06, 131.01, 131.03, 136.80, 137.13, 137.24, 144.35, 144.41, 154.60, 154.92; HRMS (EI) calcd for $C_{32}H_{44}N_2O_4$: 520.3301; found: 520.3287; anal. calcd for $C_{32}H_{44}N_2O_4$: C, 73.80; H, 8.52; N, 5.38; found: C, 73.65; H, 8.41; N, 5.22.

3.8. (3S,13S)-(+)-3,13-Diisobutyl-8-(2-propenyl)-2,5,11,14-tetraoxa-20,26-diazatetracyclo-[13.9.3.0^{19,27}.0^{21,25}]heptacosa-1(25),15,17,19,21,23,26-heptaene (S,S)-**7**

Macrocycle (*S*,*S*)-**7** was prepared as described above for macrocycle (*S*,*S*)-**2** starting from diol (*S*,*S*)-**17** (172 mg, 0.5 mmol) and 1,9-dichlorophenazine **19** (125 mg, 0.5 mmol). The reaction was completed at 90°C in 6 days. The crude product was purified by chromatography first on alumina using 0.5% EtOH in toluene, then on silica gel using 4% EtOH in toluene as eluent to give (*S*,*S*)-**7** (42 mg, 16%) as a yellow oil. $[\alpha]_D^{25}$=+27.35 (*c* 0.200, CH_2Cl_2). All other physical and spectral data were identical to (*R*,*R*)-**7** described above.

3.9. (3R,13R)-(+)-3,13-Diisobutyl-8,8-bis(2-propenyl)-2,5,11,14-tetraoxa-20,26-diazatetracyclo-[13.9.3.0^{19,27}.0^{21,25}]heptacosa-1(25),15,17,19,21,23,26-heptaene (S,S)-***8***

Macrocycle (*S*,*S*)-**8** was prepared as described above for macrocycle (*S*,*S*)-**2** starting from diol (*S*,*S*)-**18** (192 mg, 0.5 mmol) and 1,9-dichlorophenazine **19** (125 mg, 0.5 mmol). The reaction was completed at 90°C in 10 days. The crude product was purified by chromatography first on alumina using 0.3% EtOH in toluene, then on silica gel using 2.5% EtOH in toluene as eluent to give (*R*,*R*)-**8** (39 mg, 14%) as a yellow oil. R_f=0.61 (alumina TLC, 2% EtOH in toluene); $[\alpha]_D^{25}$=+22.35 (*c* 0.680, CH_2Cl_2); IR (KBr) 3080, 2970, 2940, 2880, 1640, 1620, 1600, 1560, 1470, 1460, 1370, 1320, 1260, 1110, 830, 750, 660 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.01 (d, *J*=6 Hz, 6H), 1.02 (d, *J*=6 Hz, 6H), 1.45–1.51 (m, 4H), 1.65–1.69 (m, 2H), 1.89 (d, *J*=7 Hz, 4H), 1.91–1.99 (m, 4H), 3.51–3.56 (m, 2H), 3.62–3.71 (m, 4H), 4.00–4.03 (m, 2H), 4.91–4.98 (m, 4H), 5.33–5.38 (m, 2H), 5.66–5.74 (m, 2H), 7.18 (d, *J*=8 Hz, 2H), 7.72 (t, *J*=8 Hz, 2H), 7.82 (d, *J*=8 Hz, 2H); ^{13}C NMR (125 MHz) δ 23.13, 23.35, 25.08, 36.06, 37.55, 40.83, 41.91, 68.20, 73.01, 78.24, 112.82, 117.75, 122.02, 131.09, 134.56, 136.90, 144.43, 154.95; HRMS (EI) calcd for $C_{35}H_{48}N_2O_4$: 560.3614; found: 560.3618; anal. calcd for $C_{35}H_{48}N_2O_4$: C, 74.95; H, 8.63; N, 5.00; found: C, 75.11; H, 8.54; N, 5.16.

3.10. (2S,12S)-(−)-4,7,10-Trioxatridecane-2,12-diol di-p-tosylate (S,S)-10

To a stirred solution of (2*S*,12*S*)-(+)-4,7,10-trioxatridecane-2,12-diol (*S*,*S*)-**16**[16] (2.22 g, 10 mmol) in pyridine (10 mL) at 0°C and under Ar was added tosyl chloride (4.19 g, 22 mmol) dissolved in pyridine (20 mL). The reaction mixture was stirred at 0°C for 10 min, and at room temperature for 1 day, then it was poured into ice-water (150 mL). This stirred mixture was made weakly acidic (pH=3) with 37% aqueous HCl at 0°C then extracted with ether (1×400, 3×200 mL). The combined organic phase was shaken with 3% aqueous HCl (1×150 mL), distilled water (1×500 mL), and saturated brine (2×300 mL), then dried over $MgSO_4$ and filtered, and the solvent evaporated. The crude product was purified by chromatography on silica gel using 9% EtOAc in toluene as an eluent to give (*S*,*S*)-**10** (4.72 g, 89%) as a colorless oil identical in every aspect to that prepared by the literature procedure.[11]

3.11. (4S,14S)-(−)-2,16-Dimethyl-6,9,12-trioxaheptadecane-4,14-diol di-p-tosylate (S,S)-11

Ditosylate (*S*,*S*)-**11** was prepared as described above for ditosylate (*S*,*S*)-**10** using (4*S*,14*S*)-(−)-2,16-dimethyl-6,9,12-trioxaheptadecane-4,14-diol [(*S*,*S*)-**20**, see above in results and discussion] (3.06 g, 10 mmol). This time the reaction was completed in 2 days. The crude product was purified by chromatography on silica gel using 9% EtOAc in toluene as an eluent to give (*S*,*S*)-**11** (5.72 g, 93%) as a colorless oil. R_f=0.48 (silica gel TLC, 20% EtOAc in toluene); $[\alpha]_D^{25}$=−2.2 (*c* 4.72, CH_2Cl_2); IR (film) 3080, 3050, 3030, 2970, 2930, 2910, 2870, 1590, 1490, 1470, 1370, 1190, 1180, 1110, 1090, 910, 810, 770, 660 cm^{-1}; ^1H NMR (500 MHz) δ 0.79 (d, *J*=6 Hz, 6H), 0.86 (d, *J*=6 Hz, 6H), 1.40–1.45 (m, 2H), 1.55–1.63 (m, 4H), 2.45 (s, 6H), 3.48–3.59 (m, 12H), 4.69–4.73 (m, 2H), 7.33 (d, *J*=8 Hz, 4H), 7.81 (d, *J*=8 Hz, 4H); ^{13}C NMR (125 MHz) δ 21.75, 21.99, 23.15, 24.22, 40.64, 70.59, 70.96, 72.68, 80.62, 127.97, 129.76, 134.69, 144.58.

3.12. (3S,4R,14R,15S)-(−)-3,15-Dimethyl-6,9,12-trioxaheptadecane-4,14-diol di-p-tosylate (R,R)-12

Ditosylate (*R*,*R*)-**12** was prepared as described above for ditosylate (*S*,*S*)-**10** using (3*S*,4*R*,14*R*,15*S*)-(−)-3,15-dimethyl-6,9,12-trioxaheptadecane-4,14-diol [(*R*,*R*)-**21**][16] (3.06 g, 10 mmol). This time the reaction was completed in 2 days. The crude product was purified by chromatography on silica gel using 9% EtOAc in toluene as an eluent to give (*R*,*R*)-**12** (5.41 g, 88%) as a colorless oil. R_f=0.53 (silica gel TLC, 20% EtOAc in toluene); $[\alpha]_D^{25}$=−13.4 (*c* 4.79, CH_2Cl_2); IR (film) 3080, 3050, 3030, 2980, 2950, 2910, 2890, 1600, 1500, 1480, 1380, 1200, 1190, 1120, 1100, 910, 810, 790, 680 cm^{-1}; ^1H NMR (500 MHz) δ 0.82 (t, *J*=7 Hz, 6H), 0.85 (d, *J*=7 Hz, 6H), 1.06–1.12 (m, 2H), 1.34–1.40 (m, 2H), 1.72–1.76 (m, 2H), 2.43 (s, 6H), 3.43–3.60 (m, 12H), 4.61–4.64 (m, 2H), 7.30 (d, *J*=8 Hz, 4H), 7.79 (d, *J*=8 Hz, 4H); ^{13}C NMR (125 MHz) δ 11.57, 13.86, 21.62, 25.31, 36.11, 70.40, 70.43, 70.68, 84.80, 127.83, 129.55, 134.73, 144.30.

3.13. (2S,12S)-(−)-7-(2-Propenyl)-4,10-dioxatridecane-2,12-diol di-p-tosylate (S,S)-13

Ditosylate (*S*,*S*)-**13** was prepared as described above for ditosylate (*S*,*S*)-**10** using diol (*S*,*S*)-**22** (2.60 g, 10 mmol). The crude product was purified by chromatography on silica gel using 9% EtOAc in toluene as an eluent to give (*S*,*S*)-**13** (5.40 g, 95%) as a colorless oil. R_f=0.60 (silica gel TLC, 20% EtOAc in toluene); $[\alpha]_D^{25}$=−8.5 (*c* 1.04, CH_2Cl_2); IR (film) 3080, 3050, 3030, 2980, 2920, 2860, 1640, 1590, 1480, 1450, 1350, 1190, 1180, 1110, 1090, 910, 900, 800, 760, 660 cm^{-1}; ^1H NMR (500 MHz) δ 1.25 (d, *J*=6 Hz, 6H), 1.36–1.46 (m, 4H), 1.51–1.56 (m, 1H), 1.97 (t, *J*=7 Hz, 2H), 2.42 (s, 6H), 3.32–3.45

(m, 8H), 4.64–4.69 (m, 2H), 4.97–5.00 (m, 2H), 5.64–5.72 (m, 1H), 7.31 (d, *J*=8 Hz, 4H), 7.78 (d, *J*=8 Hz, 4H); ^{13}C NMR (125 MHz) δ 17.69, 21.63, 31.49, 33.18, 38.08, 69.54, 72.98, 78.13, 116.43, 127.81, 129.69, 134.39, 136.48, 144.47.

3.14. (2S,12S)-(−)-7,7-Bis(2-propenyl)-4,10-dioxatridecane-2,12-diol di-p-*tosylate (*S,S*)-**14**

Ditosylate (*S,S*)-**14** was prepared as described above for ditosylate (*S,S*)-**10** using diol (*S,S*)-**23** (3 g, 10 mmol). The crude product was purified by chromatography on silica gel using 6% EtOAc in toluene as an eluent to give (*S,S*)-**14** (5.72 g, 94%) as a colorless oil. R_f=0.69 (silica gel TLC, 20% EtOAc in toluene); $[\alpha]_D^{25}$=−8.5 (*c* 1.258, CH_2Cl_2); IR (film) 3080, 3050, 3030, 2970, 2930, 2910, 2870, 1640, 1600, 1500, 1460, 1380, 1200, 1190, 1110, 1090, 1000, 930, 820, 780, 680 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.25 (d, *J*=6 Hz, 6H), 1.39 (t, *J*=7 Hz, 4H), 1.93 (d, *J*=7 Hz, 4H), 2.43 (s, 6H), 3.35–3.43 (m, 8H), 4.64–4.70 (m, 2H), 5.00–5.07 (m, 4H), 5.70–5.78 (m, 2H), 7.31 (d, *J*=8 Hz, 4H), 7.79 (d, *J*=8 Hz, 4H); ^{13}C NMR (125 MHz) δ 18.10, 22.04, 36.29, 37.33, 42.09, 67.97, 73.50, 78.52, 118.23, 128.22, 130.10, 134.63, 134.78, 144.88.

3.15. (4S,14S)-(−)-2,16-Dimethyl-9-(2-propenyl)-6,12-dioxaheptadecane-4,14-diol di-p-*tosylate (*S,S*)-**15**

Ditosylate (*S,S*)-**15** was prepared as described above for ditosylate (*S,S*)-**10** using diol (*S,S*)-**17** (3.06 g, 10 mmol). This time the reaction was completed in 2 days. The crude product was purified by chromatography on silica gel using 5% EtOAc in toluene as an eluent to give (*S,S*)-**15** (6.20 g, 95%) as a colorless oil. R_f=0.75 (silica gel TLC, 20% EtOAc in toluene); $[\alpha]_D^{25}$=−15.2 (*c* 1.279, CH_2Cl_2); IR (film) 3080, 2960, 2920, 2870, 1640, 1590, 1500, 1470, 1370, 1200, 1180, 1120, 1100, 910, 810, 780, 680 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.78 (d, *J*=6 Hz, 6H), 0.85 (d, *J*=6 Hz, 6H), 1.38–1.46 (m, 6H), 1.54–1.62 (m, 5H), 1.99 (t, *J*=7 Hz, 2H), 2.44 (s, 6H), 3.31–3.46 (m, 8H), 4.65–4.69 (m, 2H), 4.98–5.03 (m, 2H), 5.66–5.75 (m, 1H), 7.32 (d, *J*=8 Hz, 4H), 7.80 (d, *J*=8 Hz, 4H); ^{13}C NMR (125 MHz) δ 21.80, 22.03, 23.18, 24.26, 31.71, 33.30, 38.18, 40.75, 69.74, 72.16, 80.64, 116.60, 127.98, 129.79, 134.70, 136.66, 144.59.

*3.16. (4S,14S)-(+)-2,16-Dimethyl-9-(2-propenyl)-6,12-dioxaheptadecane-4,14-diol (*S,S*)-**17**

To a well-stirred mixture of KO*t*-Bu (5.38 g, 0.048 mol) and HMPA (40 mL) was added in an ice-water bath and under Ar 3-(2-propenyl)-pentan-1,5-diol (**34**) (1.73 g, 0.012 mol). The reaction mixture was stirred in the ice-water bath for 5 min then (*S*)-(−)-4-methyl-2[(tetrahydro-2*H*-pyran-2-yl)oxy]-pentan-1-ol *p*-tosylate [(*S*)-**39**, see later] (11.11 g, 0.031 mol) was added and stirring was continued in the ice-water bath for 20 min and at room temperature for 1 day. The resulting mixture was taken up in ice-water (150 mL) and ether (200 mL). The aqueous phase was extracted with ether (3×120 mL). The combined organic phase was shaken with ice-cold water (500 mL), saturated brine (250 mL), dried over $MgSO_4$, filtered and evaporated. The residue was dissolved in MeOH (100 mL) and Amberlite® IR-120 ion-exchange resin (H^+ form) (1 g) was added to this solution. After stirring the mixture at room temperature for 1 day, the resin was filtered off and washed with MeOH (3×5 mL). The filtrate and washings were combined and the solvent evaporated. The residue was dissolved in toluene and the solvent was removed. The latter procedure was repeated twice to remove traces of water. The crude product was purified by chromatography on silica gel using 6% acetone in CH_2Cl_2 as an eluent to give (*S,S*)-**17** (2.56 g, 62%) as a colorless oil. R_f=0.58 (silica gel TLC, 14% acetone in CH_2Cl_2); $[\alpha]_D^{25}$=+1.9 (*c* 2.040, CH_2Cl_2); IR

(film) 3600–3100 (broad), 3080, 2960, 2920, 2870, 1640, 1480, 1380, 1100, 1000, 910, 850 cm^{-1}; ^1H NMR (500 MHz) δ 0.89 (d, *J*=7 Hz, 6H), 0.91 (d, *J*=7 Hz, 6H), 1.07–1.15 (m, 2H), 1.35–1.42 (m, 2H), 1.56–1.61 (m, 4H), 1.74–1.81 (m, 3H), 2.05 (t, *J*=7 Hz, 2H), 3.07 (broad s, 2H), 3.16–3.56 (m, 8H), 3.79–3.85 (m, 2H), 4.97–5.02 (m, 2H), 5.70–5.78 (m, 1H); ^{13}C NMR (125 MHz) δ 22.22, 22.26, 23.55, 23.56, 24.56, 24.59, 31.60, 33.19, 33.32, 38.74, 42.02, 42.11, 68.46, 68.50, 69.25, 69.43, 75.96, 76.19, 116.59, 136.76.

*3.17. (4S,14S)-(+)-2,16-Dimethyl-9,9-bis(2-propenyl)-6,12-dioxaheptadecane-4,14-diol (S,S)-**18***

Diol (*S,S*)-**18** was prepared as described above for diol (*S,S*)-**17** starting from diol **35** (2.21 g, 12 mmol) and tosylate (*S*)-**39** (11.11 g, 31 mmol). The crude product was purified by chromatography on silica gel using 5% acetone in CH_2Cl_2 as an eluent to give (*S,S*)-**18** (1.87 g, 60%) as a colorless oil. R_f=0.68 (silica gel TLC, 14% acetone in CH_2Cl_2); $[\alpha]_D^{25}$=+0.15 (*c* 4.660, CH_2Cl_2); IR (film) 3600–3100 (broad), 3080, 2960, 2920, 2870, 1640, 1480, 1380, 1100, 1000, 910, 860 cm^{-1}; ^1H NMR (500 MHz) δ 0.91 (d, *J*=7 Hz, 6H), 0.92 (d, *J*=7 Hz, 6H), 1.10–1.15 (m, 2H), 1.36–1.42 (m, 2H), 1.61 (t, *J*=7 Hz, 4H), 1.77–1.81 (m, 2H), 1.96–2.03 (m, 4H), 3.01 (broad s, 2H), 3.19–3.55 (m, 8H), 3.82–3.85 (m, 2H), 5.03–5.09 (m, 4H), 5.75–5.83 (m, 2H); ^{13}C NMR (125 MHz) δ 22.31, 23.60, 24.61, 36.10, 37.71, 41.73, 42.13, 67.70, 68.62, 76.46, 118.10, 134.26.

*3.18. 1,9-Dichlorophenazine **19***

Compound **19** was prepared as reported.[17] Mp 212°C (toluene); lit.[17] mp 208–209°C (MeOH); R_f=0.20 (silica gel TLC, 14% EtOAc in hexane); IR (KBr) 3750, 3660, 3100, 1690, 1620, 1540, 1500, 1470, 1420, 1300, 960, 880, 830, 760, 660 cm^{-1}; ^1H NMR (500 MHz) δ 7.80 (t, *J*=8 Hz, 2H), 8.00 (d, *J*=8 Hz, 2H), 8.18 (d, *J*=8 Hz, 2H); ^{13}C NMR (125 MHz) δ 128.77, 130.59, 130.88, 134.12, 140.15, 144.32.

*3.19. (2S,12S)-(+)-7-(2-Propenyl)-4,10-dioxatridecane-2,12-diol (S,S)-**22***

Diol (*S,S*)-**22** was prepared as described above for diol (*S,S*)-**17** starting from diol **34** (1.73 g, 12 mmol) and tosylate (*S*)-**38** (9.8 g, 31 mmol). The crude product was purified by chromatography on silica gel using 14% acetone in CH_2Cl_2 as an eluent to give (*S,S*)-**22** (1.87 g, 60%) as a colorless oil. R_f=0.18 (silica gel TLC, 14% acetone in CH_2Cl_2); $[\alpha]_D^{25}$=+24.2 (*c* 4.082, CH_2Cl_2); IR (film) 3600–3100 (broad), 3080, 2990, 2950, 2890, 2880, 1640, 1470, 1450, 1380, 1330, 1100, 1000, 910, 860 cm^{-1}; ^1H NMR (500 MHz) δ 1.13 (d, *J*=6 Hz, 3H), 1.14 (d, *J*=6 Hz, 3H), 1.56–1.61 (m, 4H), 1.76–1.78 (m, 1H), 2.07 (t, *J*=7 Hz, 2H), 3.00 (broad s, 2H), 3.20–3.57 (m, 8H), 3.94–3.97 (m, 2H), 5.01–5.04 (m, 2H), 5.74–5.79 (m, 1H); ^{13}C NMR (125 MHz) δ 18.52, 31.52, 33.14, 33.17, 38.55, 66.22, 66.29, 69.10, 69.26, 76.51, 76.74, 116.43, 136.59.

*3.20. (2S,12S)-(+)-7,7-Bis(2-propenyl)-4,10-dioxatridecane-2,12-diol (S,S)-**23***

Diol (*S,S*)-**23** was prepared as described above for diol (*S,S*)-**17** starting from diol **35** (2.21 g, 12 mmol) and tosylate (*S*)-**38** (9.8 g, 31 mmol). The crude product was purified by chromatography on silica gel using 14% acetone in CH_2Cl_2 as an eluent to give (*S,S*)-**23** (2.88 g, 80%) as a colorless oil. R_f=0.22 (silica gel TLC, 14% acetone in CH_2Cl_2); $[\alpha]_D^{25}$=+20.2 (*c* 2.021, CH_2Cl_2); IR (film) 3600–3100 (broad), 3080, 2980, 2920, 2900, 2870, 1640, 1480, 1450, 1370, 1320, 1100, 1000, 910, 840 cm^{-1}; ^1H NMR (500 MHz) δ 1.11 (d, *J*=6 Hz, 6H), 1.60 (t, *J*=7 Hz, 4H), 1.92–2.03 (m, 4H), 3.17–3.55 (m, 8H), 3.24 (broad

s, 2H), 3.92–3.95 (m, 2H), 5.02–5.08 (m, 4H), 5.75–5.82 (m, 2H); ^{13}C NMR (125 MHz) δ 18.64, 36.08, 37.68, 41.70, 66.53, 67.64, 77.15, 118.08, 134.22.

3.21. 2,2-Bis(2-propenyl)-propane-1,3-diol ***27***

To a well-stirred mixture of $LiAlH_4$ (9.1 g, 0.24 mol) in dry and pure ether (140 mL) was added dropwise at 0°C and under Ar diethyl diallylmalonate **25** (24 g, 0.1 mol) dissolved in ether (150 mL). The reaction mixture was stirred at 0°C for 30 min, at room temperature for 30 min, and at reflux temperature for 12 h, then it was cooled down to 0°C and aqueous saturated NH_4Cl (9 mL) followed by 5% aqueous NaOH (18 mL) were added very slowly. The resulting mixture was stirred at room temperature for 30 min, then at reflux temperature for 14 h. The white precipitate was filtered off and washed thoroughly with ether (5×50 mL). Filtrate and washings were combined and this ethereal solution was dried over $MgSO_4$, filtered and the solvent was evaporated. Traces of water from the residue were removed as described above for (*S*,*S*)-**17** using toluene. The crude product was purified by distillation to give **27** (14.5 g, 93%) as a clear oil. Bp 88–89°C (0.1 mmHg). All other physical properties and spectroscopic data were identical to diol **27** prepared by a different procedure described in the literature.[28]

*3.22. 2-(2-Propenyl)-propane-1,3-diol di-*p*-tosylate* ***28***

To a well-stirred mixture of finely powdered KOH (26.4 g, 85%, 0.4 mol) in THF (40 mL) was added dropwise at 0°C and under Ar diol **26** (5.81 g, 0.05 mol) and tosyl chloride (26.7 g, 0.14 mol) dissolved together in THF (160 mL). The resulting mixture was stirred at 0°C for 2 h, then it was allowed to warm up to room temperature and stirring was continued at room temperature for 4 h. The solvent was evaporated at room temperature, and the residue was taken up in ice-water (300 mL) and CH_2Cl_2 (800 mL). The aqueous phase was extracted with CH_2Cl_2 (3×200 mL). The combined organic phase was shaken with distilled water (400 mL), dried over $MgSO_4$, filtered and evaporated. The crude product was recrystallized from EtOH to give **28** (20.1 g, 97%) as white crystals identical in every aspect to tosylate **28** prepared by the reported procedure.[29] R_f=0.50 (silica gel TLC, 33% EtOAc in hexane); IR (KBr) 3080, 3050, 3030, 3000, 2970, 2920, 1640, 1610, 1500, 1480, 1460, 1400, 1380, 1210, 1190, 1100, 1030, 990, 930, 860, 830, 800, 690, 600, 570 cm^{-1}; ^{1}H NMR (80 MHz) δ 1.88–2.18 (m, 3H), 2.45 (s, 6H), 3.92 (d, *J*=6 Hz, 4H), 4.78–5.05 (m, 2H), 5.28–5.81 (m, 1H), 7.30 (d, *J*=8 Hz, 4H), 7.73 (d, *J*=8 Hz, 4H).

*3.23. 2,2-Bis(2-propenyl)-propane-1,3-diol di-*p*-tosylate* ***29***

Ditosylate **29** was prepared as described above for ditosylate **28** using diol **27** (7.8 g, 0.05 mol). The crude product was recrystallized from MeOH to give **29** (21.6 g, 97%) as white crystals. Mp 71°C (MeOH); R_f=0.55 (silica gel TLC, 33% EtOAc in hexane); IR (KBr) 3080, 3050, 3030, 2980, 2950, 2910, 2840, 1640, 1590, 1490, 1470, 1380, 1180, 1090, 960, 930, 830, 810, 790, 670, 550 cm^{-1}; ^{1}H NMR (80 MHz) δ 1.98 (d, *J*=7 Hz, 4H), 2.45 (s, 6H), 3.78 (s, 4H), 4.81–5.18 (m, 4H), 5.28–5.84 (m, 2H), 7.31 (d, *J*=8 Hz, 4H), 7.75 (d, *J*=8 Hz, 4H).

3.24. 3-(2-Propenyl)-glutaronitrile ***30***

A mixture of 2-(2-propenyl)-propan-1,3-diol di-*p*-tosylate **28** (25.5 g, 0.06 mol), NaCN (11.7 g, 0.24 mol) and DMSO (160 mL) was stirred at room temperature for 10 min then at 75°C for 18 h. The reaction was cooled to room temperature and was taken up in ice-water (300 mL) and ether (500 mL). The aqueous

phase was extracted with ether (2×300 mL). The aqueous phase containing NaCN was treated with an excess of 20% aqueous $FeSO_4$ solution to cease its toxicity. The combined organic phase was shaken with ice-cold water (500 mL), and saturated brine (250 mL), dried over $MgSO_4$, filtered and evaporated. Traces of water from the residue were removed as described above for (*S*,*S*)-**17** using toluene. The crude product was purified by fractional distillation to give **30** (7.1 g, 88%) as a colorless oil. Bp 76°C (0.2 mmHg); R_f=0.44 (silica gel TLC, 9% 2-butanone in toluene); IR (film) 3080, 3050, 3030, 2990, 2940, 2850, 2240, 1640, 1440, 1420, 990, 920, 840 cm^{-1}; ^1H NMR (80 MHz) δ 2.18–2.40 (m, 3H), 2.55 (d, *J*=6 Hz, 4H), 5.00–5.32 (m, 2H), 5.42–5.96 (m, 1H).

*3.25. 3,3-Bis(2-propenyl)-glutaronitrile **31***

Dinitrile **31** was prepared as described above for dinitrile **30** using ditosylate **29** (27.3 g, 0.06 mol). Chromatography on silica gel using 20% acetone in hexane as an eluent, then triturating the product with hexane gave **31** (5.0 g, 48%) as white crystals. Mp 37°C (hexane); R_f=0.18 (silica gel TLC, 20% acetone in hexane); IR (KBr) 3080, 3050, 3030, 3000, 2980, 2950, 2930, 2920, 2870, 2850, 2240, 1640, 1440, 1420, 1000, 930, 840, 630 cm^{-1}; ^1H NMR (80 MHz) δ 2.26 (d, *J*=7 Hz, 4H), 2.34 (s, 4H), 5.05–5.41 (m, 4H), 5.48–6.04 (m, 2H).

*3.26. 3-(2-Propenyl)-glutaric acid **32***

A mixture of nitrile **30** (13.4 g, 0.1 mol), MeOH (600 mL) and 35% (w/w) aqueous NaOH (250 g) was stirred at reflux temperature for 10 h. Most of the MeOH was removed by distillation at atmospheric pressure and the resulting aqueous mixture was refluxed for 4 h, then cooled to 0°C and it was made acidic with 37% aqueous HCl (pH=2). Diacid **32** was extracted with EtOAc (3×400 mL). The combined organic phase was dried over $MgSO_4$, filtered and evaporated. Traces of water from the residue were removed as described above for (*S*,*S*)-**17** using toluene. The crude product was purified by distillation to give pure **32** (16.2 g, 94%) which solidified after standing. Bp 150–152°C (0.2 mmHg); mp 28–30°C; R_f=0.35 (silica gel TLC, 8% acetic acid and 8% acetone in toluene); IR (KBr) 3600–2300 (broad), 1700, 1640, 1440, 1410, 1290, 1230, 990, 910, 860 cm^{-1}; ^1H NMR (80 MHz) δ 2.05–2.28 (m, 3H), 2.30–2.52 (m, 4H), 4.84–5.22 (m, 2H), 5.42–6.02 (m, 1H), 10.92 (broad s, 2H).

*3.27. 3,3-Bis(2-propenyl)-glutaric acid **33***

Diacid **33** was prepared as described above for diacid **32** starting from dinitrile **31** (5.22 g, 0.03 mol). The crude product was purified by crystallization from toluene to give **33** (6.1 g, 96%) as white crystals. Mp 111°C (toluene); R_f=0.44 (silica gel TLC, 8% acetic acid and 8% acetone in toluene); IR (KBr) 3600–2300 (broad), 1700, 1640, 1440, 1400, 1320, 1280, 1210, 1180, 990, 930, 910, 620 cm^{-1}; ^1H NMR (80 MHz, DMSO-d_6) δ 2.16 (d, *J*=7 Hz, 4H), 2.32 (s, 4H), 4.84–5.21 (m, 4H), 5.57–6.18 (m, 2H), 11.95 (broad s, 2H).

*3.28. 3-(2-Propenyl)-pentane-1,5-diol **34***

To a well-stirred mixture of $LiAlH_4$ (5.7 g, 0.15 mol) in dry and pure ether (200 mL) was added dropwise at 0°C and under Ar diacid **32** (8.60 g, 0.05 mol) dissolved in ether (250 mL). The reaction mixture was stirred at 0°C for 30 min, at room temperature for 30 min, then at reflux temperature for 24 h. The reaction mixture was cooled down to 0°C and aqueous saturated NH_4Cl (6 mL) then 5% aqueous

NaOH (12 mL) were added very slowly. The resulting mixture was stirred at room temperature for 30 min, then at reflux temperature for 10 h. The white precipitate was filtered off and washed throughly with ether (5×50 mL). Filtrate and washings were combined and this ethereal solution was dried over $MgSO_4$, filtered and the solvent was evaporated. Traces of water from the residue were removed as described above for (*S*,*S*)-**17** using toluene. The crude product was purified by distillation to give **34** (6.34 g, 88%) as a clear oil. Bp 96–98°C (0.2 mmHg); R_f=0.25 (silica gel TLC, 14% EtOH in toluene); IR (film) 3650–3100 (broad), 3080, 3030, 2980, 2940, 2870, 2850, 1640, 1440, 1060, 1000, 900 cm^{-1}; ^1H NMR (80 MHz) δ 1.55 (t, *J*=7 Hz, 4H), 1.58–1.98 (m, 1H), 2.09 (t, *J*=7 Hz, 2H), 3.41 (broad s, 2H), 3.61 (t, *J*=7 Hz, 4H), 4.82–5.18 (m, 2H), 5.52–6.03 (m, 1H).

3.29. 3,3-Bis(2-propenyl)-pentane-1,5-diol ***35***

Diol **35** was prepared as described above for diol **34** using diacid **33** (10.6 g, 0.05 mol). Chromatography on silica gel using 9% EtOH in toluene as an eluent, then triturating the product with hexane gave **35** (8.65 g, 94%) as white crystals. Mp 40°C (hexane); R_f=0.30 (silica gel TLC, 14% EtOH in toluene); IR (KBr) 3650–3100 (broad), 3080, 3030, 2950, 2940, 2920, 2870, 1640, 1440, 1050, 1020, 1000, 900 cm^{-1}; ^1H NMR (80 MHz) δ 1.58 (t, *J*=7 Hz, 4H), 2.05 (d, *J*=7 Hz, 4H), 2.72 (broad s, 2H), 3.71 (t, *J*=7 Hz, 4H), 4.83–5.18 (m, 4H), 5.51–6.08 (m, 2H).

*3.30. (*S*)-(−)-2[(Tetrahydro-2*H*-pyran-2-yl)oxy]-propan-1-ol* p-*tosylate (*S*)-**38***

Tosylate (*S*)-**38** was prepared as reported[21] starting from alcohol (*S*)-**36** (16.0 g, 0.1 mol). The crude product was purified by chromatography on silica gel using 2% acetone in toluene as an eluent to give (*S*)-**38** (28.6 g, 91%) as a mixture of two diastereomers. R_f=0.25 (silica gel TLC, 3% acetone in toluene); $[\alpha]_D^{25}$=−3.0 (*c* 2.90, CH_2Cl_2); IR (film) 3080, 3050, 3030, 2980, 2950, 2930, 2900, 2870, 1600, 1500, 1460, 1360, 1180, 1170, 1120, 1070, 1030, 1010, 970, 800, 660 cm^{-1}; ^1H NMR (80 MHz) δ 1.08 and 1.18 (d, *J*=6 Hz, 3H), 1.32–1.94 (m, 6H), 2.43 (s, 3H), 3.22–4.15 (m, 5H), 4.52–4.68 (m, 1H), 7.29 (d, *J*=8 Hz, 2H), 7.79 (d, *J*=8 Hz, 2H).

*3.31. (*S*)-(−)-4-Methyl-2[(tetrahydro-2*H*-pyran-2-yl)oxy]-pentan-1-ol* p-*tosylate (*S*)-**39***

Tosylate (*S*)-**39** was prepared in the same way as described for tosylate (*S*)-**38** in the literature[21] starting from alcohol (*S*)-**37**[30] (20.2 g, 0.1 mol). The crude product was purified by chromatography on silica gel using 1% acetone in toluene as an eluent to give (*S*)-**39** (32.8 g, 92%) as a mixture of two diastereomers. R_f=0.40 (silica gel TLC, 3% acetone in toluene); $[\alpha]_D^{25}$=−25.0 (*c* 1.353, CH_2Cl_2); IR (film) 3080, 3050, 3030, 2970, 2940, 2880, 1600, 1500, 1480, 1470, 1370, 1200, 1190, 1140, 1100, 1080, 1040, 990, 810, 670 cm^{-1}; ^1H NMR (80 MHz) δ 0.92 (d, *J*=6 Hz, 6H), 1.16–1.83 (m, 9 H), 2.45 (s, 3H), 3.21–4.27 (m, 5H), 4.52–4.72 (m, 1H), 7.32 (d, *J*=8 Hz, 2H), 7.81 (d, *J*=8 Hz, 2H).

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